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# Application of differential reactivity towards synthesis of lamellarin and 8-oxoprotoberberine derivatives: Study of photochemical properties of aryl-substituted benzofuran-8-oxoprotoberberines

Sameer Vyasamudri, Ding-Yah Yang*

*Department of Chemistry, Tunghai University, No. 1727, Sec. 4, Taiwan Boulevard, Xitun District, Taichung, 40704, Taiwan*

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ABSTRACT

A unique differential reactivity between dihydroisoquinolines and 3-nitrocoumarins was observed and was exploited for the efficient construction of lamellarins and their isomeric benzofuran-8-oxoprotoberberine derivatives under acid-catalyzed or base-promoted conditions. Further, these prepared aryl-substituted benzofuran-8-oxoprotoberberine derivatives bearing electron-donating substituents on benzofuran moiety are found to be benchtop stable but light-sensitive, and can undergo oxidative ring-opening reaction to give the corresponding keto products when exposed to visible light under aerobic conditions.



## 1. Introduction

Lamellarins[1] are a diverse family of marine alkaloids. Ever since their first discovery by Faulkner and co-workers[2] in 1985, more than 70 lamellarins and structurally-related pyrrole alkaloids have been isolated from mollusks, ascidians, and sponges so far. Most of lamellarins share a common pyrrolo[2,1-*a*]isoquinoline- and coumarin-fused pentacyclic core structure but differ on their peripheral functional groups. These lamellarin alkaloids have been found to exhibit a variety of biological activities such as antitumor activity,[3] reversal of multidrug resistance,[4] and HIV-1 integrase inhibition activity.[5] Owing to their novel molecular structures and intriguing biological properties, the synthesis of lamellarins and their analogues has continued to attract considerable interest to organic and medicinal chemists. Among these alkaloids, lamellarin D[3a] has received the most attention of all, since it can not only inhibit DNA topoisomerase I (topo I) activity at nanomolar concentration but also exhibit potent anticancer activity against multidrug-resistant cell lines.[6] Previous studies have demonstrated that lamellarin D is capable of promoting DNA cleavage through stabilization of topo I–DNA covalent complexes,[6b-c] a mode of action similar to that of anticancer drug camptothecin[7] and berberines.[8] Camptothecin is a cytotoxic quinoline alkaloid that contains a crucial pyridone moiety, whereas berberines represent a large family of alkaloids that bear an isoquinoline ring-fused system with various biological activities. By comparing the molecular structures of lamellarin D, camptothecin, and berberine (Fig. 1), we speculate that the replacement of the original lamellarin core with its isomeric benzofuran-8-oxoprotoberberine skeleton might potentially provide a new scaffold mimicking the critical interactions of lamellarins with the topo I-DNA complex.

Protoberberines are alkaloids constituting many families of natural products that share similar molecular skeletons such as berberines, tetrahydroprotoberberines, and 8-oxoprotoberberines. Most protoberberines exhibit a wide spectrum of biological activities.[9–12] Mainly due to their potential biological importance, the synthesis of 8-oxoprotoberberines and their derivatives has been well studied by synthetic and medicinal chemists in the past.[13] While previous efforts have been primarily focused on synthesis, biological and therapeutic applications of 8-oxoprotoberberines, their intrinsic photochemical properties,[14] especially visible-light-sensitive properties, were much less explored. Photosensitizer-free, visible-light-mediated organic reactions have recently received increasing attention owing to their simplicity and sustainability.[15] Thus, as a part of our ongoing

* Corresponding author.
*E-mail address:* yang@thu.edu.tw (D.-Y. Yang).

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research in pursuit of novel strategy for efficient construction of lamellarin analogues so as to facilitate the process to the development of lamellarin-derived anticancer drugs, here we describe a concise synthesis of lamellarins and their isomeric benzofuran- and pyridone-fused derivatives by acid-catalyzed or base-promoted coupling of dihydroisoquinoline hydrochlorides and 3-nitrocoumarins. The photochemical properties of the benzofuran-8-oxoprotoberberines are then investigated. Some are found to be light-insensitive, whereas others are light-sensitive and can undergo oxidative ring-opening reaction when exposed to visible light under aerobic conditions. A possible mechanism for this photooxygenation is also proposed on the basis of experimental data.

## 2. Results and discussion

Recently, we have reported[16] the synthesis of lamellarin type II derivatives by Grob-type coupling[17] of 3-nitrocoumarins and papaverine under sealed tube conditions. Success of this coupling reaction serves as a good reference for the current investigation of lamellarin type I synthesis. Scheme 1 outlines the optimized preparation of lamellarin G trimethyl ether (**1a**) by $SnCl_2$-catalyzed direct coupling of **2a** and **3a** in toluene in sealed tube at 140 °C for 8 h (Route I). To the best of our knowledge, this synthetic scheme represents the shortest route for lamellarin G trimethyl ether (**1a**) preparation ever reported in the literature[18] (two steps only with overall yield of 29.7% from commercial 2-hydroxy-4,5-dimethoxybenzaldedyde). Alternatively, **1a** can also be prepared via a stepwise process (Route II) by coupling (**2a**) with 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline (**3b**) to afford the pentacycle **4**. Bromination of **4** with NBS generated the bromo-substituted pentacycle **5**. Finally, Suzuki coupling between **5** and 3,4-dimethoxyphenylboronic acid afforded **1a**.[19] While Route I is shorter and gives higher overall yields, Route II has the advantage of introducing different aryl groups onto the pentacyclic skeleton. Fig. 2 lists the structures and yields for the prepared lamellarin derivatives **1a**–**f** via Route I. Since substituted 3-nitrocoumarins and 3,4-dihydropapaverines are readily available, this Grob-type coupling reaction provides an easy and rapid access to the biologically important lamellarin type I derivatives.

Similarly, Scheme 2 shows the two synthetic routes for the preparation of benzofuran-8-oxoprotoberberine **6a**. In Route I, **6a** was synthesized by $Cs_2CO_3$-mediated coupling reaction between 6,7-dimethoxy-3-nitrocoumarin (**2a**, prepared from condensation of 2-hydroxy-4,5-dimethoxybenzaldedyde with ethyl nitroacetate) and 3,4-dihydropapaverine hydrochloride (**3a**) in sealed tube in 18% yield (27% of **3a** was recovered). Alternatively, compound **6a** can also be prepared via a stepwise process (Route II, Scheme 2) by first coupling of **2a** with 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline hydrochloride (**3b**) in sealed tube to afford the pentacycle **7**. The subsequent bromination of **7** with NBS generated the bromo-substituted pentacycle **8**. Final Suzuki coupling of **8** with 3,4-dimethoxyphenylboronic acid afforded the target **6a**.[13] While Route I is shorter and gives a higher overall yield, Route II is capable of incorporating different aryl groups onto the pentacyclic skeleton.

In order to prove that the formation of this oxoprotoberberine scaffold is not a random process but follows a pattern that can be applied to a large substrate scope, we have prepared a series of 3-nitrocomarin and 3,4-dihydropapaverine derivatives with electron-donating ($N(Et)_2$, OMe) and electron-withdrawing (Cl, $NO_2$) substituents as the substrates. Fig. 3 lists the structures and

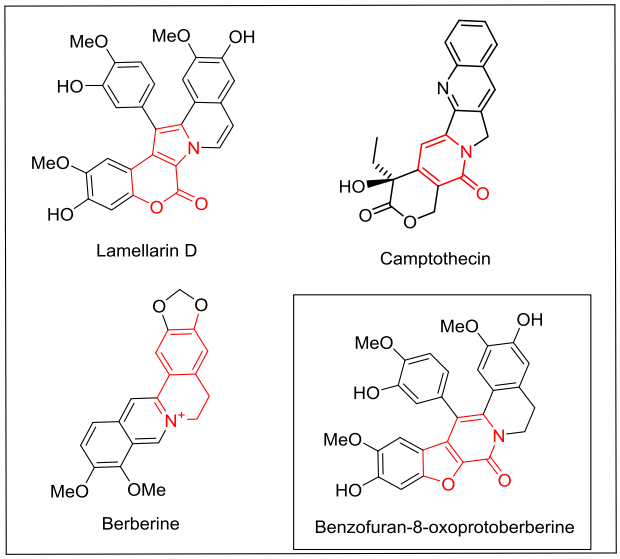
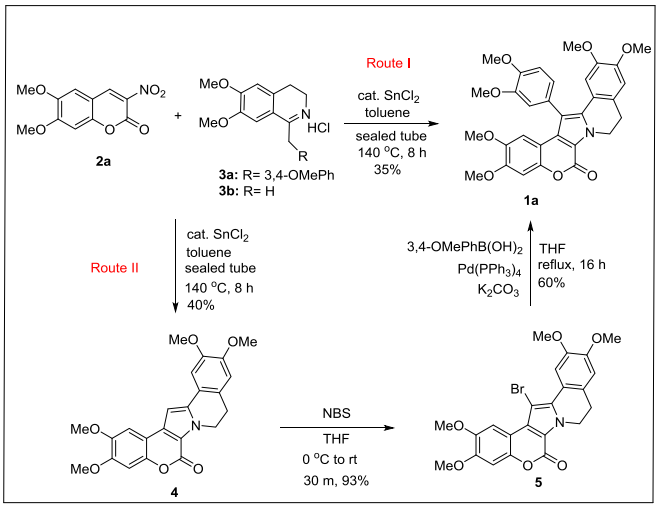



**Fig. 1.** Structures of lamellarin D, camptothecin, berberine, and benzofuran-8-oxoprotoberberine.




**Scheme 1.** Synthesis of lamellarin **1a**.

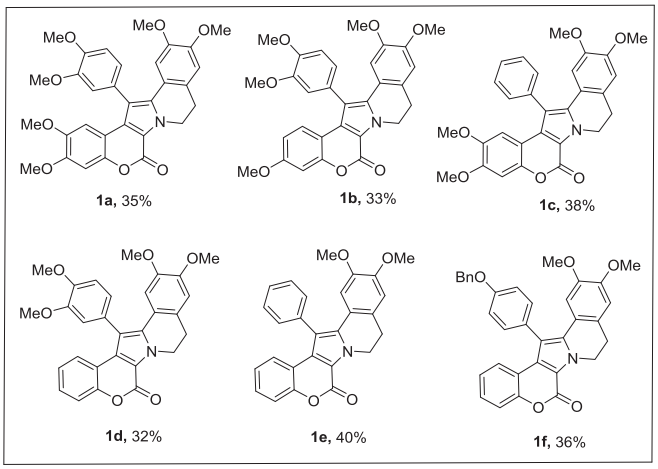



**Fig. 2.** Structures of the prepared lamellarins **1a**–**f**.

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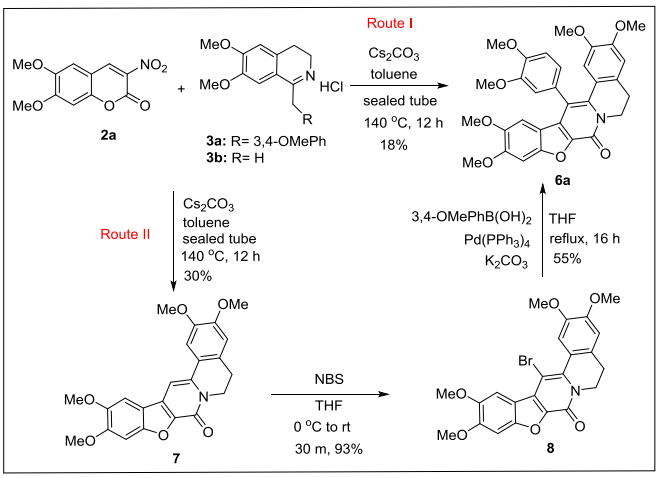



**Scheme 2.** Synthesis of benzofuran-8-oxoprotoberberine **6a**.

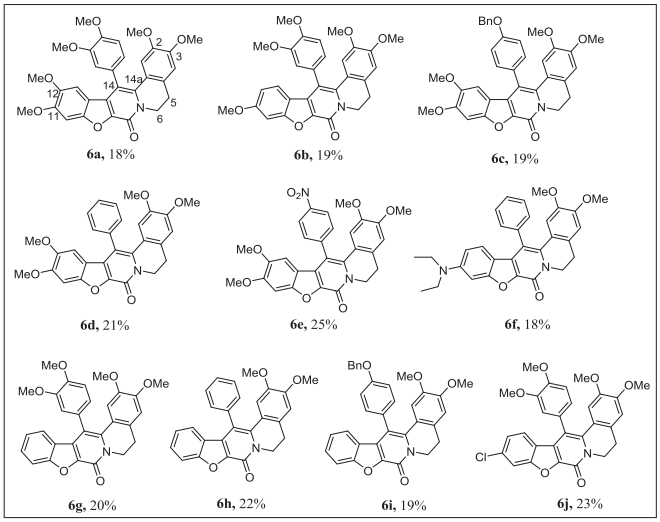



**Fig. 3.** Structures of the prepared **6a**–**j**.

yields for the synthesized benzofuran-8-oxoprotoberberine derivatives **6a**–**j** via direct coupling of 3-nitrocoumarins and 3,4-dihydropapaverines. The electronic nature of the substituents on both substrates seems to have little effect on the yield of the coupling reaction. Some of the molecular structures such as **1e** and **6h** were further confirmed by X-ray crystal analysis as shown in Fig. 4.

Schemes 3 and 4 depict the proposed mechanism for the formation of **1a** and **6a**, respectively. We envisioned that the mechanism for the coupling of **2a** and **3a** under acidic conditions (Scheme 3) presumably involves $SnCl_2$-catalyzed formation of Michael adduct **9** which further undergoes isomerization to generate the enamine **10**. The intramolecular cyclization of **10** via nucleophilic addition of the amine nitrogen to the iminium carbon generates the cyclized dihydroxyamine **11**. Final elimination of water and hyponitrous acid from **11** gives the aromatized phenyl-substituted pentacyclic lamellarin **1a**.[20]

While Michael addition (1,4-addition) between **2a** and **3a** is the major process when the coupling reaction is carried out under acidic conditions, we found that the nucleophilic acyl substitution to open up the coumarin lactone ring becomes the dominant reaction when the coupling was performed under basic conditions.

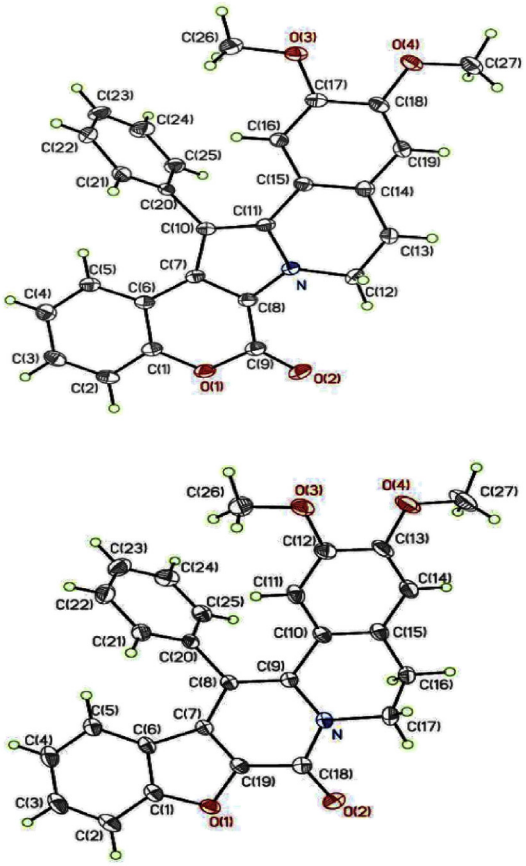
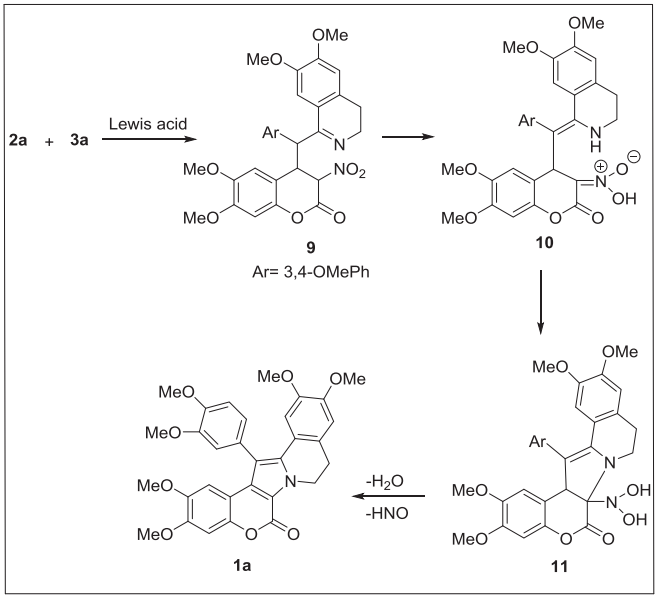



**Fig. 4.** ORTEP crystal structures of **1e** (top) and **6h** (bottom).




**Scheme 3.** The proposed mechanism for the formation of **1a**.

We speculate that the formation of **6a** presumably begins with the nucleophilic enamine nitrogen of **3a** attacks coumarin carbonyl carbon of **2a** to give the enamide **12**. The subsequent enamine-mediated intramolecular conjugate addition of **12** affords the cyclized **13**. The second intramolecular cyclization of **13** via

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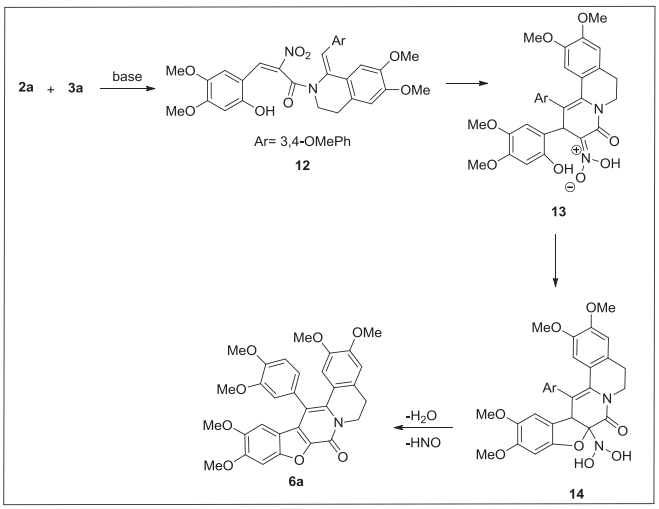



**Scheme 4.** The proposed mechanism for the formation of **6a**.

nucleophilic addition of the phenolic oxygen to the iminium carbon generates the cyclized dihydroxyamine **14**. Final elimination of water and hyponitrous acid[21] from **14** gives the aromatized aryl-substituted benzofuran-8-oxoprotoberberine **6a**. The differential reactivity between dihydroisoquinolines and 3-nitrocoumarins under different conditions is likely due to the intrinsic property of 3-nitrocoumarins, that is, prone to undergo ring-opening of the coumarin lactone in the presence of nitrogen nucleophiles under basic conditions.[22]

With compounds **6a**–**i** in hand, their photochemical properties were then evaluated. Some of the prepared benzofuran-8-oxoprotoberberine derivatives were found to be benchtop stable but light-sensitive. After exposed to visible light (a 23 W fluorescence light bulb or blue LED) in the absence of any external sensitizers under aerobic conditions in methylene chloride overnight, compounds **6a**–**f** were converted to the oxidized ring-opened products, quantitatively, except **6e**. The nitro-substituted **6d** gave relatively lower yield (32%) of the oxidized product **13e**, suggesting that the presence of an electron-withdrawing group on the 14-aryl moiety of **6e** hampers its photochemical reaction. Figs. 5 and 6 show the structures of the photogenerated products **13a**–**f** and the X-ray crystal structure of **13f**, respectively. Only the compounds bearing electron-donating group on benzofuran moiety **(6a**–**e)** were found to be sensitive to light and undergo oxidative ring-opening reaction upon visible light irradiation. Compounds with no substituents (**6g**–**i**) or bearing electron-withdrawing groups such as chloro (**6j**) are light-insensitive, and no oxidized products were observed even after prolonged visible light irradiation.

Scheme 5 depicts the proposed mechanism for this visible-light-mediated reaction. We envision that, upon visible light irradiation, the oxygen molecule in solvent was trapped by double bond at C-14 and C-14a of benzofuran-8-oxoprotoberberine **6a** (see Scheme 5 for atom-numbering) to give the dioxetane **14** which further undergoes ring-opening to afford the corresponding oxidized product **13a**.

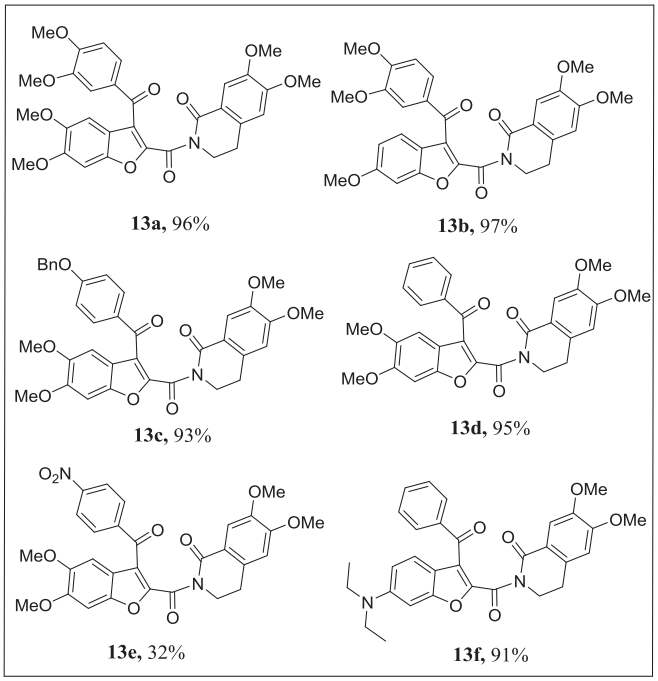



**Fig. 5.** Structures and yields of the photogenerated products **13a**–**f**.

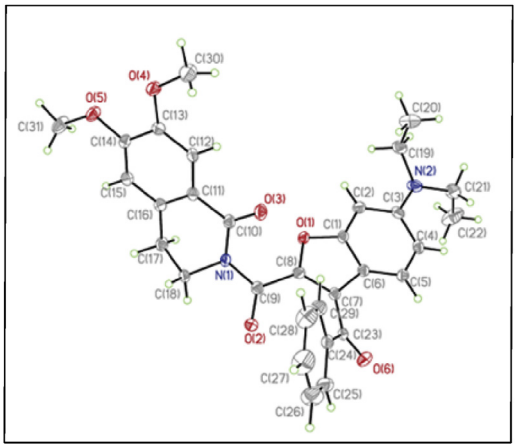
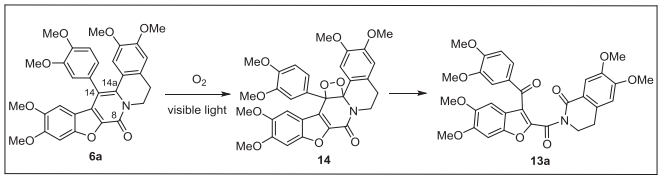


**Fig. 6.** ORTEP X-ray crystal structure of **13f**.




**Scheme 5.** Proposed photochemical mechanism of **6a** to **13a**.

## 3. Conclusions

In summary, we have established that the aryl-substituted pentacyclic lamellarins and their benzofuran-8-oxoprotoberberine isomers can be prepared via $SnCl_2$-catalyzed or $Cs_2CO_3$-mediated coupling of dihydroisoquinoline hydrochlorides and 3-nitrocoumarins in sealed tube. The scope of these two reactions was illustrated by the preparation of six lamellarin derivatives **1a**–**f** and ten benzofuran-8-oxoprotoberberines **6a**–**j**. Although the yields of the reactions remain to be improved, this synthetic approach not only demonstrates the feasibility of construction of isomeric pentacyclic skeletons via differential coupling reactions but also provides an easy and quick access to biologically important lamellarins and 8-oxoprotoberberines. Moreover, the

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prepared aryl-substituted benzofuran-8-oxoprotoberberine derivatives **6a**–**f** bearing electron-donating substituents on benzofuran moiety were found to be light-sensitive and undergo aerobic oxidative ring-opening to generate the products **13a**–**f** when exposed to visible light. The biological activities of the prepared **6a**–**j** and their derivatives are currently under investigation and will be reported in due course.

## 4. Experimental section

### 4.1. Instrumentation

Melting points were determined on a Mel-Temp melting point apparatus in open capillaries and are uncorrected. Infrared (IR) spectra were recorded using 1725XFT-IR spectrophotometer. High resolution mass spectra (HRMS) were obtained on a Thermo Fisher Scientific Finnigan MAT95XL spectrometer using magnetic sector analyzer $^1$H NMR (400 MHz) and $^{13}$C NMR (100 or 150 MHz) spectra were recorded on a Varian VXR300 or Bruker 400/600 spectrometer. Chemical shifts were reported in parts per million on the δ scale relative to an internal standard (tetramethylsilane, or appropriate solvent peaks) with coupling constants given in hertz. $^1$H NMR multiplicity data are denoted by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Analytical thin-layer chromatography (TLC) was carried out on Merck silica gel 60G-254 plates (25 mm) and developed with the solvents mentioned. Visualization was accomplished by using portable UV light, ninhydrin spray, or iodine chamber. Flash chromatography was performed in columns of various diameters with Merck silica gel (230–400 mesh ASTM 9385 kieselgel 60H) by elution with the solvent systems. Solvents, unless otherwise specified, were reagent grade and distilled once prior to use. All new compounds exhibited satisfactory spectroscopic and analytical data.

### 4.2. Synthesis of 4, 5 and 1a (Route-II)

#### 4.2.1. 2,3,11,12-Tetramethoxy-8,9-dihydro-6H-chromeno[4′,3′:4,5] pyrrolo[2,1-a]isoquinolin-6-one (*4*)

A flame-dried 50 mL sealed tube fitted with Teflon ring screw cap was charged with **2a** (100 mg, 0.39 mmol), 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline (98 mg, 0.47 mmol, 1.2 equiv), $SnCl_2$ (15 mg, 0.08 mmol, 0.2 equiv) in toluene (10 mL) under argon atmosphere. The resulting mixture was then heated to 140 °C in the sealed tube for 12 h. Once the reaction mixture was cooled down to room temperature, the solvent was evaporated *in vacuo*. The crude mixture was purified by column chromatography to give an off-white solid **4**. $R_f$ = 0.50 (40% EtOAc/hexanes); 65 mg; yield 40%; mp 250–252 °C (Lit.[23] 249–252 °C); $^1$H NMR ($CDCl_3$, 400 MHz) δ 7.19 (s, 1H), 7.18 (s, 1H), 6.93 (s, 1H), 6.80 (s, 2H), 4.72 (t, *J* = 6.8 Hz, 2H), 4.0 (s, 3H), 3.99 (s, 3H), 3.94 (s, 3H), 3.93 (s, 3H), 3.11 (t, *J* = 6.8 Hz, 2H).

#### 4.2.2. 14-Bromo-2,3,11,12-tetramethoxy-8,9-dihydro-6H-chromeno [4′,3′:4,5]pyrrolo[2,1-a]isoquinolin-6-one (*5*)

To a solution of **4** (50 mg, 0.122 mmol) in THF (25 mL) was added *N*-bromosuccinimide (NBS, 32.7 mg, 0.18 mmol, 1.5 equiv) at 0 °C. The resulting mixture was stirred at room temperature for 30 min. The precipitate was then filtered-off, washed with hexanes (3 × 5 mL), and dried *in vacuo* to yield the compound **5**. $R_f$ = 0.55 (40% EtOAc/hexanes); pale-yellow solid; 55.5 mg; yield 93%; mp 225–228 °C (Lit.[23] 227–230 °C); $^1$H NMR ($CDCl_3$, 400 MHz) δ 8.27 (s, 1H), 8.16 (s, 1H), 6.94 (s, 1H), 6.82 (s, 1H), 4.78 (t, *J* = 6.8 Hz, 2H), 4.00 (s, 3H), 3.99 (s, 3H), 3.95 (s, 3H), 3.94 (s, 3H), 3.07 (t, *J* = 6.8 Hz, 2H).

#### 4.2.3. 14-(3,4-dimethoxyphenyl)-2,3,11,12-tetramethoxy-8,9-dihydro-6H-chromeno[4′,3′:4,5]pyrrolo[2,1-a]isoquinolin-6-one (***1a***)

A sealed tube with Teflon screw-stopper (flame dried and cooled under a stream of nitrogen) was charged with **5** (50 mg, 0.10 mmol), 3,4-dimethoxy phenylboronic acid (22.5 mg, 0.12 mmol, 1.2 equiv), $Pd(PPh_3)_4$ (23 mg, 0.02 mmol, 0.2 equiv), and $K_2CO_3$ (21 mg, 0.15 mmol, 1.5 equiv) in THF (20 mL). The sealed mixture was refluxed for 12 h. After cooled down to room temperature, the green colored solution was evaporated *in vacuo* and the crude product was subjected to column chromatography to give the compound **1a** (60%).

### 4.3. General procedure for synthesis of type-I lamellerins 1a-1f (Route-I)

A flame-dried 50 mL sealed tube fitted with Teflon ring screw cap was charged with 3-nitrocoumarin (0.15 mmol, 1 equiv), dihydroisoquinoline hydrochlorides (0.18 mmol, 1.2 equiv), $SnCl_2$ (0.03 mmol, 0.2 equiv) in toluene (10 mL) under argon atmosphere. The resulting mixture was then heated to 140 °C in the sealed tube for 12 h. Once the reaction mixture was cooled down to room temperature, the solvent was evaporated *in vacuo*. The crude mixture was purified by column chromatography to get the pure compound.

#### 4.3.1. 14-(3,4-dimethoxyphenyl)-2,3,11,12-tetramethoxy-8,9-dihydro-6H-chromeno[4′,3′:4,5]pyrrolo[2,1-a]isoquinolin-6-one (***1a***)

Off-white solid. $R_f$ = 0.55 (40% EtOAc/hexanes); 28 mg; yield 35%; mp 236–238 °C (Lit.[24] 235 °C); $^1$H NMR ($CDCl_3$, 400 MHz) δ 7.12 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.08 (d, *J* = 8.0 Hz, 1H), 7.05 (d, *J* = 1.6 Hz, 1H), 6.91 (s, 1H), 6.76 (s, 1H), 6.72 (s, 1H), 6.67 (s, 1H), 4.83–4.75 (m, 2H), 3.95 (s, 3H), 3.89 (s, 3H), 3.88 (s, 3H), 3.86 (s, 3H), 3.46 (s, 3H), 3.37 (s, 3H), 3.12 (t, *J* = 6.8 Hz, 2H).

#### 4.3.2. Synthesis of 14-(3,4-dimethoxyphenyl)-3,11,12-trimethoxy-8,9-dihydro-6H-chromeno[4′,3′:4,5]pyrrolo[2,1-a]isoquinolin-6-one (***1b***)

Off-white solid. $R_f$ = 0.58 (40% EtOAc/hexanes) 30 mg; yield 32%; mp 248–250 °C; $^1$H NMR ($CDCl_3$, 400 MHz) δ 7.11 (d, *J* = 8.8 Hz, 1H), 7.06 (s, 2H), 6.99 (s, 1H), 6.90 (d, *J* = 2.4 Hz, 1H), 6.75 (s, 1H), 6.65 (s, 1H), 6.61 (dd, *J* = 8.8, 2.4 Hz, 1H), 4.81–4.76 (m, 2H), 3.98 (s, 3H), 3.89 (s, 3H), 3.85 (s, 3H), 3.81 (s, 3H), 3.36 (s, 3H), 3.11 (t, *J* = 6.8 Hz, 2H); $^{13}$C NMR ($CDCl_3$, 150 MHz) δ 159.2, 155.4, 152.6, 149.8, 148.9, 148.8, 147.4, 136.1, 128.1, 127.9, 126.6, 124.1, 123.3, 120.0, 115.1, 113.8, 113.3, 111.9, 111.5, 111.4, 110.9, 108.7, 101.5, 56.1, 55.9, 55.5, 55.2, 42.4, 28.7; IR $\nu_{max}$ 2945, 1708, 1610, 1402, 1321, 1256, 1132, 1038, 951, 771, 693 cm$^{-1}$; HRMS (EI) *m*/*z* calcd for $C_{30}H_{27}NO_7$ [M$^+$] 513.1788, found 513.1790.

#### 4.3.3. Synthesis of 2,3,11,12-tetramethoxy-14-phenyl-8,9-dihydro-6H-chromeno[4′,3′:4,5]pyrrolo[2,1-a]isoquinolin-6-one (***1c***)

White solid. $R_f$ = 0.60 (40% EtOAc/hexanes); 29 mg; yield 38%; mp 250–252 °C; $^1$H NMR ($CDCl_3$, 400 MHz) δ 7.59–7.54 (m, 4H), 7.49–7.45 (m, 1H), 6.90 (s, 1H), 6.76 (s, 1H), 6.60 (s, 1H), 6.56 (s, 1H), 4.80 (t, *J* = 6.8 Hz, 2H), 3.88 (s, 6H), 3.39 (s, 3H), 3.29 (s, 3H), 3.12 (t, *J* = 6.8 Hz, 2H); $^{13}$C NMR ($CDCl_3$, 150 MHz) δ 155.6, 148.9, 148.7, 147.5, 146.0, 145.5, 135.8, 135.8, 131.4, 129.3, 128.1, 128.0, 126.6, 120.0, 115.0, 113.9, 111.0, 110.3, 108.7, 104.4, 100.5, 56.0, 55.9, 55.3, 55.0, 42.4, 28.7; IR $\nu_{max}$ 2998, 2832, 1702, 1517, 1414, 1341, 1214, 1165, 1043, 863 cm$^{-1}$; HRMS (EI) *m*/*z* calcd for $C_{29}H_{25}NO_6$ [M$^+$] 483.1682, found 483.1678.

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*4.3.4. Synthesis of 14-(3,4-dimethoxyphenyl)-11,12-dimethoxy-8,9-dihydro-6H-chromeno[4′,3′:4,5]pyrrolo[2,1-a]isoquinolin-6-one **(1d)***

Off-white solid. $R_f = 0.63$ (40% EtOAc/hexanes); 30 mg; yield 32%; mp 240–243 °C (Lit.[25] 235–239 °C); $^1$H NMR ($CDCl_3$, 400 MHz) δ 7.38 (d, $J = 8.0$ Hz, 1H), 7.30–7.22 (m, 2H), 7.10–7.07 (m, 2H), 7.03–6.99 (m, 2H), 6.76 (s, 1H), 6.65 (s, 1H), 4.85–4.80 (m, 2H), 3.99 (s, 3H), 3.89 (s, 3H), 3.85 (s, 3H), 3.36 (s, 3H), 3.12 (t, $J = 6.4$ Hz, 2H).

*4.3.5. Synthesis of 11,12-dimethoxy-14-phenyl-8,9-dihydro-6H-chromeno[4′,3′:4,5]pyrrolo[2,1-a]isoquinolin-6-one **(1e)***

Off-white solid. $R_f = 0.65$ (40% EtOAc/hexanes); 25 mg; yield 38%; mp 274–276 °C; $^1$H NMR ($CDCl_3$, 400 MHz) δ 7.57–7.50 (m, 5H), 7.37 (dd, $J = 8.4$, 1.2 Hz, 1H), 7.26 (td, $J = 7.2$, 1.2 Hz, 1H), 7.16 (dd, $J = 8.0$, 1.6 Hz, 1H), 6.96 (td, $J = 8.0$, 1.2 Hz, 1H) 6.75 (s, 1H), 6.49 (s, 1H), 4.83 (t, $J = 6.8$ Hz, 2H), 3.88 (s, 3H), 3.28 (s, 3H), 3.12 (t, $J = 6.8$ Hz, 2H); $^{13}$C NMR ($CDCl_3$, 150 MHz) δ 155.3, 151.2, 148.9, 147.4, 136.0, 135.7, 131.1, 129.5, 128.1, 127.3, 127.2, 126.6, 123.7, 123.3, 119.9, 118.3, 117.1, 116.1, 114.6, 110.9, 108.7, 55.9, 55.0, 42.5, 28.7; IR $\nu_{max}$ 2934, 2837, 1667, 1494, 1446, 1245, 1139, 1019, 926, 815 cm$^{-1}$; HRMS (EI) *m/z* calcd for $C_{27}H_{21}NO_4$ [M$^+$] 423.1471, found 423.1474.

*4.3.6. Synthesis of 14-(4-(benzyloxy)phenyl)-11,12-dimethoxy-8,9-dihydro-6H-chromeno[4′,3′:4,5]pyrrolo[2,1-a]isoquinolin-6-one **(1f)***

Off-white solid. $R_f = 0.60$ (40% EtOAc/hexanes); 26.5 mg; yield 32%; mp 220–222 °C; $^1$H NMR ($CDCl_3$, 400 MHz) δ 7.49 (d, $J = 8.4$ Hz, 2H), 7.44–7.36 (m, 6H), 7.27 (td, $J = 8.0$, 1.2 Hz, 1H), 7.21 (dd, $J = 8.0$, 1.2 Hz, 1H), 7.16 (d, $J = 8.0$ Hz, 2H), 6.99 (td, $J = 8.0$, 1.2 Hz, 1H), 6.74 (s, 1H), 6.56 (s, 1H), 5.19 (s, 2H), 4.81 (t, $J = 6.4$ Hz, 2H), 3.88 (s, 3H), 3.26 (s, 3H), 3.11 (t, $J = 6.4$ Hz, 2H); $^{13}$C NMR ($CDCl_3$, 150 MHz) δ 158.6, 155.3, 151.3, 148.9, 147.4, 136.8, 132.2, 128.7, 128.1, 127.8, 127.5, 127.34, 127.29, 126.6, 123.7, 123.3, 120.0, 118.4, 117.1, 115.9, 115.6, 114.5, 110.9, 108.7, 70.0, 55.9, 55.1, 42.5, 28.7; IR $\nu_{max}$ 2933, 2858, 1695, 1610, 1454, 1402, 1220, 1168, 1044, 753 cm$^{-1}$; HRMS (EI) *m/z* calcd for $C_{34}H_{27}NO_5$ [M$^+$] 529.1889, found 529.1886.

*4.4. General procedure for synthesis 7, 8 and 6a (Route-II)*

*4.4.1. 2,3,11,12-Tetramethoxy-5,6-dihydro-8H-benzofuro[3′,2′:4,5] pyrido[2,1-a]isoquinolin-8-one **(7)***

A flame-dried 50 mL sealed tube fitted with Teflon ring screw cap was charged with **2a** (100 mg, 0.39 mmol), 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline (98 mg, 0.47 mmol, 1.2 equiv), $Cs_2CO_3$ (259 mg, 0.79 mmol, 2.0 equiv) in toluene (10 mL) under argon atmosphere. The resulting mixture was then heated to 140 °C in the sealed tube for 12 h. Once the reaction mixture was cooled down to room temperature, the solvent was evaporated *in vacuo*. The crude mixture was purified by column chromatography to give an off-white solid **7**. $R_f = 0.50$ (80% EtOAc/hexanes); 52 mg; yield 32%; mp 264–266 °C; $^1$H NMR ($CDCl_3$, 400 MHz) δ 7.32 (s, 1H), 7.30 (s, 1H), 7.17 (s, 1H), 7.06 (s, 1H), 6.77 (s, 1H), 4.43 (t, $J = 6.4$ Hz, 2H), 4.03 (s, 3H), 4.02 (s, 3H), 3.99 (s, 3H), 3.96 (s, 3H), 2.96 (t, $J = 6.4$ Hz, 2H); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 153.5, 152.5, 151.5, 150.5, 148.6, 147.2, 142.5, 138.8, 129.3, 128.5, 122.5, 114.7, 110.5, 108.1, 102.0, 95.8, 94.6, 56.6, 56.5, 56.3, 56.2, 39.7, 28.0; IR $\nu_{max}$ 2923, 2848, 1659, 1514, 1476, 1334, 1209, 1116, 1017, 928 cm$^{-1}$; HRMS (EI) *m/z* calcd for $C_{23}H_{21}NO_6$ [M$^+$] 407.1369, found 407.1371.

*4.4.2. 14-Bromo-2,3,11,12-tetramethoxy-5,6-dihydro-8H-benzofuro [3′,2′:4,5] pyrido[2,1-a]isoquinolin-8-one **(8)***

To a solution of **7** (50 mg, 0.26 mmol) in THF (25 mL) was added *N*-bromosuccinimide (NBS, 61 mg, 0.34 mmol, 1.3 equiv) at 0 °C. The resulting mixture was stirred at room temperature for 30 min. The precipitate was then filtered-off, washed with hexanes (3 × 5 mL), and dried *in vacuo* to yield the compound **14**. White solid; $R_f = 0.53$ (80% EtOAc/hexanes); 54.3 mg; yield 91%; mp 223–225 °C; $^1$H NMR ($CDCl_3$, 400 MHz) δ 7.95 (s, 1H), 7.92 (s, 1H), 7.20 (s, 1H), 6.81 (s, 1H), 4.36 (bs, 2H) 2.89 (t, $J = 6.0$ Hz, 2H); $^{13}$C NMR ($CDCl_3$, 150 MHz) δ 152.6, 152.5, 151.8, 150.2, 146.7, 146.6, 141.7, 136.5, 132.0, 129.7, 121.4, 115.5, 113.8, 109.9, 104.0, 95.5, 91.6, 56.5, 56.30, 56.25, 56.0, 41.8, 29.1; IR $\nu_{max}$ 2928, 2852, 1652, 1512, 1463, 1332, 1262, 1210, 1110, 1029, 930 cm$^{-1}$; HRMS (EI) *m/z* calcd for $C_{23}H_{20}BrNO_6$ [M$^+$] 485.0474, found 485.0483.

*4.4.3. 14-(3,4-dimethoxyphenyl)-2,3,11,12-tetramethoxy-5,6-dihydro-8H-benzofuro[3′,2′:4,5]pyrido[2,1-a]isoquinolin-8-one **(6a)***

A sealed tube with Teflon screw-stopper (flame dried and cooled under a stream of nitrogen) was charged with **8** (50 mg, 0.10 mmol), 3,4-dimethoxyphenylboronic acid (22 mg, 0.12 mmol, 1.2 equiv), $Pd(PPh_3)_4$ (24 mg, 0.02 mmol, 0.2 equiv), and $K_2CO_3$ (21 mg, 0.15 mmol, 1.5 equiv) in THF (20 mL). The sealed mixture was refluxed for 12 h. After cooled down to room temperature, the green colored solution was evaporated *in vacuo* and the crude product was subjected to column chromatography to give the compound **6a**; 31 mg; yield 55%.

*4.5. General procedure for synthesis of benzofurane-8-oxoprotoberberines (**6a-6j**, Route-I)*

A flame-dried 50 mL sealed tube fitted with Teflon ring screw cap was charged with appropriately substituted 3-nitrocoumarins, (0.15 mmol), appropriately substituted dihydroisoquinoline hydrochlorides (0.18 mmol, 1.2 equiv), $Cs_2CO_3$ (0.30 mmol, 2.0 equiv) in toluene (10 mL) under argon atmosphere. The resulting mixture was then heated to 140 °C in the sealed tube for 12 h. Once the reaction mixture was cooled down to room temperature, the solvent was evaporated *in vacuo*. The crude mixture was purified by column chromatography.

*4.5.1. 14-(3,4-dimethoxyphenyl)-2,3,11,12-tetramethoxy-5,6-dihydro-8H-benzofuro[3′,2′:4,5]pyrido[2,1-a]isoquinolin-8-one **(6a)***

Off-white solid. $R_f = 0.50$ (80% EtOAc/hexanes); 15 mg; yield 18%; mp 254–256 °C; $^1$H NMR ($CDCl_3$, 400 MHz) δ 7.14 (s, 1H), 7.01 (d, $J = 8.0$ Hz, 1H), 6.99 (d, $J = 1.6$ Hz, 1H), 6.95 (dd, $J = 8.0$, 1.6 Hz, 1H), 6.75 (s, 1H), 6.72 (s, 1H), 6.22 (s, 1H), 4.60–4.54 (m, 1H), 4.57, 4.31 (dt, $J = 14.0$, 5.6 Hz, 1H each), 3.95 (s, 3H), 3.94 (s, 3H), 3.90 (s, 3H), 3.82 (s, 3H), 3.59 (s, 3H), 3.28 (s, 3H), 2.93 (t, $J = 5.6$ Hz, 2H); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 153.2, 152.7, 151.3, 150.1, 149.2, 149.0, 146.6, 146.5, 141.9, 135.5, 131.1, 130.5, 129.8, 123.5, 122.2, 115.2, 114.2, 113.6, 112.9, 112.1, 109.9, 103.8, 95.6, 56.3, 56.1, 55.9, 55.4, 41.2, 28.9; IR $\nu_{max}$ 2922, 2851, 1668, 1599, 1455, 1270, 1134, 1001, 926, 770 cm$^{-1}$; HRMS (EI) *m/z* calcd for $C_{31}H_{29}NO_8$ [M$^+$] 543.1893, found 543.1884.

*4.5.2. 14-(3,4-dimethoxyphenyl)-2,3,11-trimethoxy-5,6-dihydro-8H-benzofuro[3′,2′:4,5]pyrido[2,1-a]isoquinolin-8-one **(6b)***

Off-white solid. $R_f = 0.50$ (80% EtOAc/hexanes); 14.5 mg; yield 19%; mp 254–256 °C; $^1$H NMR ($CDCl_3$, 400 MHz) δ 7.13 (d, $J = 1.6$ Hz, 1H), 7.00 (d, $J = 8.4$ Hz, 1H), 6.95 (d, $J = 1.6$ Hz, 1H), 6.92 (dd, $J = 8.0$, 1.6 Hz, 1H), 6.75–6.72 (m, 2H), 6.71 (s, 1H), 6.70 (s, 1H), 4.57, 4.31 (dt, $J = 14.0$, 5.6 Hz, 1H each), 3.97 (s, 3H), 3.90 (s, 3H), 3.86 (s, 3H), 3.79 (s, 3H), 3.27 (s, 3H), 2.93 (t, $J = 5.6$ Hz, 2H); $^{13}$C NMR ($CDCl_3$, 150 MHz) δ 160.9, 158.6, 153.1, 149.9, 149.0, 148.9, 146.5, 141.9, 135.6, 130.9, 130.3, 129.6, 123.6, 123.2, 122.0, 116.6, 113.9, 113.4, 112.9, 112.6, 112.0, 109.7, 96.3, 56.2, 56.1, 55.8, 55.7, 55.2, 41.2, 28.8; IR $\nu_{max}$ 2934, 2837, 2251, 1662, 1586, 1494, 1227, 1139, 1013, 815, 728 cm$^{-1}$; HRMS (EI) *m/z* calcd for $C_{30}H_{27}NO_7$ [M$^+$] 513.1788, found 513.1796.

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*4.5.3. 14-(4-(benzyloxy)phenyl)-2,3,11,12-tetramethoxy-5,6-dihydro-8H-benzofuro[3′,2′:4,5]pyrido[2,1-a]isoquinolin-8-one* ***(6c)***

Off-white solid, $R_f = 0.50$ (80% EtOAc/hexanes); 14 mg; yield 19%; mp 234–236 °C; $^1$H NMR ($CDCl_3$, 400 MHz) δ 7.46–7.36 (m, 4H), 7.35–7.32 (m, 3H), 7.13–7.11 (m, 3H), 6.71 (s, 1H), 6.66 (s, 1H), 6.18 (s, 1H), 5.15 (s, 2H), 4.43 (dt, $J = 6.0$ Hz, 2H), 3.94 (s, 3H), 3.89 (s, 3H), 3.53 (s, 3H), 3.21 (s, 3H), 2.92 (t, $J = 6.0$ Hz, 2H); $^{13}$C NMR ($CDCl_3$, 150 MHz) δ 158.4, 153.0, 152.5, 151.0, 148.9, 146.3, 146.2, 141.8, 136.6, 135.3, 132.3, 130.9, 130.2, 129.7, 128.7, 128.2, 127.2, 122.0, 115.6, 115.0, 113.6, 112.7, 109.6, 103.6, 95.4, 70.0, 56.2, 55.8, 55.2, 41.1, 28.8; IR $\nu_{max}$ 2922, 2851, 1668, 1599, 1455, 1270, 1134, 1001, 926, 770 cm$^{-1}$; HRMS (EI) *m/z* calcd for $C_{36}H_{31}NO_7$ [M$^+$] 589.2101, found 589.2104.

*4.5.4. 2,3,11,12-Tetramethoxy-14-phenyl-5,6-dihydro-8H-benzofuro[3′,2′:4,5]pyrido[2,1-a]isoquinolin-8-one* ***(6d)***

White solid, $R_f = 0.60$ (80% EtOAc/hexanes); 16 mg; yield 21%; mp 264–266 °C; $^1$H NMR ($CDCl_3$, 400 MHz) δ 7.55–7.45 (m, 5H), 7.13 (s, 1H), 6.72 (s, 1H), 6.65 (s, 1H), 6.06 (s, 1H), 4.46 (t, $J = 6.0$ Hz, 2H), 3.94 (s, 3H), 3.89 (s, 3H), 3.53 (s, 1H), 3.18 (s, 3H), 2.94 (t, $J = 6.0$ Hz, 2H); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 153.2, 152.7, 151.2, 149.2, 146.6, 146.5, 142.0, 138.2, 135.2, 131.3, 131.1, 129.6, 129.5, 128.1, 122.0, 115.1, 113.9, 113.2, 109.9, 103.6, 95.5, 56.3, 56.0, 55.9, 55.3, 41.2, 29.0; IR $\nu_{max}$ 2943, 2836, 1660, 1471, 1261, 1212, 1110, 1011, 927, 826, 726 cm$^{-1}$; HRMS (EI) *m/z* calcd for $C_{29}H_{25}NO_6$ [M$^+$] 483.1682, found 483.1684.

*4.5.5. 2,3,11,12-Tetramethoxy-14-(4-nitrophenyl)-5,6-dihydro-8H-benzofuro[3′,2′:4,5]pyrido[2,1-a]isoquinolin-8-one* ***(6e)***

Yellow solid, $R_f = 0.45$ (80% EtOAc/hexanes); 21 mg; yield 25%; mp 308–310 °C; $^1$H NMR ($CDCl_3$, 400 MHz) δ 8.40 (d, $J = 8.8$ Hz, 2H), 7.68 (d, $J = 8.8$ Hz, 2H), 7.15 (s, 1H), 6.75 (s, 1H), 6.34 (s, 1H), 6.14 (s, 1H), 4.41 (t, $J = 6.0$ Hz, 2H) 3.95 (s, 3H), 3.90 (s, 3H), 3.57 (s, 3H), 3.18 (s, 3H), 2.95 (t, $J = 6.0$ Hz, 2H); $^{13}$C NMR ($CDCl_3$, 150 MHz) δ 152.8, 152.6, 151.4, 149.7, 147.3, 146.6, 145.2, 142.0, 136.0, 132.7, 131.6, 128.0, 124.1, 120.9, 114.0, 113.9, 110.6, 110.1, 103.0, 95.5, 56.2, 56.0, 55.9, 55.3, 41.0, 28.7; IR $\nu_{max}$ 2930, 2852, 1666, 1590, 1488, 1344, 1212, 1171, 1036, 837, cm$^{-1}$; HRMS (EI) *m/z* calcd for $C_{29}H_{24}N_2O_8$ [M$^+$] 528.1533, found 528.1539.

*4.5.6. 11-(diethylamino)-2,3-dimethoxy-14-phenyl-5,6-dihydro-8H-benzofuro[3′,2′:4,5]pyrido[2,1-a]isoquinolin-8-one* ***(6f)***

Brown solid. $R_f = 0.50$ (80% EtOAc/hexanes); 13.3 mg; yield 18%; mp 264–266 °C; $^1$H NMR ($CDCl_3$, 400 MHz) δ 7.51–7.44 (m, 3H), 7.42–7.40 (m, 2H), 6.82 (d, $J = 2.0$ Hz, 1H), 6.70 (s, 1H), 6.57 (s, 1H), 6.53 (d, $J = 8.8$ Hz, 1H), 6.46 (dd, $J = 8.8$, 2.0 Hz, 1H), 4.44 (t, $J = 6.0$ Hz, 2H), 3.39 (q, $J = 7.2$ Hz, 4H), 2.91 (t, $J = 6.0$ Hz, 2H), 1.17 (t, $J = 7.2$ Hz, 6H); $^{13}$C NMR ($CDCl_3$, 150 MHz) δ 160.0, 152.9, 148.9, 148.8, 146.3, 140.8, 138.4, 135.1, 131.0, 130.9, 130.0, 129.3, 127.8, 123.4, 122.1, 113.7, 113.2, 111.7, 109.6, 109.2, 93.5, 55.9, 55.2, 44.9, 41.0, 28.9, 12.4; IR $\nu_{max}$ 2974, 2834, 1626, 1505, 1342, 1254, 1105, 1027, 875, 797 cm$^{-1}$; HRMS (EI) *m/z* calcd for $C_{31}H_{30}N_2O_4$ [M$^+$] 494.2206, found 494.2203.

*4.5.7. 14-(3,4-dimethoxyphenyl)-2,3-dimethoxy-5,6-dihydro-8H-benzofuro[3′,2′:4,5]pyrido[2,1-a]isoquinolin-8-one* ***(6g)***

White solid, $R_f = 0.55$ (80% EtOAc/hexanes); 14.6 mg; yield 20%; mp 308–310 °C; $^1$H NMR ($CDCl_3$, 400 MHz) δ 7.67 (d, $J = 8.4$ Hz, 1H), 7.46 (td, $J = 7.6$, 1.2 Hz, 1H), 7.11 (t, $J = 7.6$ Hz, 1H), 7.01 (d, $J = 8.0$ Hz, 1H), 6.97 (d, $J = 2.0$ Hz, 1H), 6.94 (dd, $J = 8.0$, 2.0 Hz, 1H), 6.88 (d, $J = 7.6$ Hz, 1H), 6.72 (s, 2H), 4.59, 4.32 (dt, 14.0, 6.0 Hz, 1H each), 3.98 (s, 3H), 3.90 (s, 3H), 3.80 (s, 3H), 3.28 (s, 3H), 2.94 (t, $J = 6.0$ Hz, 2H); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 157.1, 153.6, 150.0, 149.2, 149.1, 146.6, 142.3, 135.7, 131.0, 130.2, 129.2, 128.5, 123.7, 123.4, 123.3, 123.2, 123.1, 122.1, 114.0, 113.5, 113.4, 112.8, 112.2, 109.8, 56.3, 56.2, 56.0, 55.4, 41.5, 28.9; IR $\nu_{max}$ 2944, 2836, 1658, 1506, 1251, 1142, 1024, 876, 746 cm$^{-1}$; HRMS (EI) *m/z* calcd for $C_{29}H_{25}NO_6$ [M$^+$] 483.1682, found 483.1690.

*4.5.8. 2,3-Dimethoxy-14-phenyl-5,6-dihydro-8H-benzofuro[3′,2′:4,5]pyrido[2,1-a]isoquinolin-8-one* ***(6h)***

Off-white solid. $R_f = 0.65$ (80% EtOAc/hexanes); 14 mg; yield 22%; mp 288–290 °C; $^1$H NMR ($CDCl_3$, 400 MHz) δ 7.67 (d, $J = 8.0$ Hz, 1H), 7.53–7.48 (m, 3H), 7.47–7.42 (m, 3H), 7.08 (t, $J = 8.0$ Hz, 1H), 6.76 (d, $J = 8.0$ Hz, 1H), 6.72 (s, 1H), 6.58 (s, 1H), 4.47 (t, $J = 6.0$ Hz, 2H), 3.89 (s, 3H), 3.18 (s, 3H), 2.94 (t, $J = 6.0$ Hz, 2H); $^{13}$C NMR ($CDCl_3$, 150 MHz) δ 157.0, 153.5, 149.0, 146.4, 142.3, 137.8, 135.4, 131.0, 130.9, 129.5, 128.8, 128.4, 128.1, 123.5, 123.2, 123.1, 121.8, 113.7, 113.5, 112.7, 109.7, 55.8, 55.2, 41.3, 28.8; IR $\nu_{max}$ 2947, 2834, 1667, 1506, 1275, 1209, 1107, 1037, 877, 723 cm$^{-1}$; HRMS (EI) *m/z* calcd for $C_{27}H_{21}NO_4$ [M$^+$] 423.1479, found 423.1479.

*4.5.9. 14-(4-(benzyloxy)phenyl)-2,3-dimethoxy-5,6-dihydro-8H-benzofuro[3′,2′:4,5]pyrido[2,1-a]isoquinolin-8-one* ***(6i)***

Off white solid. $R_f = 0.65$ (80% EtOAc/hexanes); 15.2 mg; yield 19%; mp 218–220 °C; $^1$H NMR ($CDCl_3$, 400 MHz) δ 7.67 (d, $J = 8.4$ Hz, 1H), 7.49–7.41 (m, 5H), 7.38 (d, $J = 6.8$ Hz, 1H), 7.32 (d, $J = 8.8$ Hz, 2H), 7.12 (d, $J = 8.8$ Hz, 2H), 7.14–7.10 (m, 1H), 6.86 (d, $J = 7.6$ Hz, 1H), 6.71 (s, 1H), 6.61 (s, 1H), 5.17 (s, 2H), 4.45 (t, $J = 6.0$ Hz, 2H), 3.90 (s, 3H), 3.20 (s, 3H), 2.93 (t, $J = 6.0$ Hz, 2H); $^{13}$C NMR ($CDCl_3$, 150 MHz) δ 158.5, 157.0, 153.5, 149.0, 146.4, 142.3, 136.6, 135.6, 132.1, 130.9, 130.1, 129.1, 128.7, 128.4, 128.2, 127.4, 123.6, 123.3, 123.1, 121.9, 115.9, 113.6, 113.2, 112.7, 109.6, 70.1, 55.8, 55.2, 41.3, 28.8; IR $\nu_{max}$ 3048, 2835, 1668, 1505, 1219, 1104, 1032, 837, 732 cm$^{-1}$; HRMS (EI) *m/z* calcd for $C_{34}H_{27}NO_5$ [M$^+$] 529.1889, found 529.1883.

*4.5.10. 11-Chloro-14-(3,4-dimethoxyphenyl)-2,3-dimethoxy-5,6-dihydro-8H-benzofuro[3′,2′:4,5]pyrido[2,1-a]isoquinolin-8-one* ***(6j)***

Pale-yellow solid. $R_f = 0.60$ (80% EtOAc/hexanes); 18 mg; yield 23%; mp 244–246 °C; $^1$H NMR ($CDCl_3$, 400 MHz) δ 7.66 (d, $J = 1.6$ Hz, 1H), 7.09 (dd, $J = 8.4$, 1.6 Hz, 1H), 7.00 (d, $J = 8.4$ Hz, 1H), 6.93 (s, 1H), 6.92 (d, $J = 8.4$ Hz, 1H), 6.77 (d, $J = 8.4$ Hz, 1H), 6.72 (s, 1H), 6.70 (s, 1H), 4.56, 4.33 (dt, $J = 14.0$, 5.6 Hz, 1H each), 3.97 (s, 3H), 3.90 (s, 3H), 3.80 (s, 3H), 3.28 (s, 3H), 2.93 (t, $J = 5.6$ Hz, 2H); $^{13}$C NMR ($CDCl_3$, 150 MHz) δ 157.1, 153.2, 150.0, 149.2, 149.0, 146.5, 142.6, 136.1, 134.4, 130.9, 129.8, 128.8, 124.1, 123.9, 123.1, 122.3, 121.7, 113.7, 113.3, 113.1, 112.8, 112.1, 109.7, 56.2, 56.1, 55.9, 55.2, 41.4, 28.8; IR $\nu_{max}$ 2989, 2839, 1665, 1506, 1460, 1231, 1141, 1023, 805, 727 cm$^{-1}$; HRMS (EI) *m/z* calcd for $C_{29}H_{24}ClNO_6$ [M$^+$] 517.1292, found 517.1293.

*4.6. General procedure for the photochemical reaction: synthesis of compounds* ***13a-13f***

Compound (**6a**–**j**, 0.02 mmol) was dissolved in dichloromethane (5 mL) and was kept the solution for stirring near a visible light source (10 cm away from a 23 W fluorescence light bulb or blue LED). The reaction was stirred for 8–18 h, and the reaction was monitored by TLC. Once completed, the solution was concentrated and the crude product was purified by column chromatography to give the pure compound.

*4.6.1. 2-(3-(3,4-dimethoxybenzoyl)-5,6-dimethoxybenzofuran-2-carbonyl)-7,8-dimethoxy-3,4-dihydroisoquinolin-1(2H)-one* ***(13a)***

Yellow solid; $R_f = 0.55$ (50% EtOAc/hexanes); 10.2 mg; yield 96%; mp 196–198 °C; $^1$H NMR ($CDCl_3$, 400 MHz) δ 7.66 (dd, $J = 8.4$, 2.0 Hz, 1H), 7.57 (s, 1H), 7.52 (d, $J = 2.0$ Hz, 1H), 7.20 (s, 1H), 7.04 (s, 1H), 6.85 (d, $J = 8.4$ Hz, 1H), 6.70 (s, 1H), 3.96 (s, 3H), 3.96–3.94 (m, 2H), 3.93 (s, 3H), 3.92 (s, 3H), 3.89 (s, 3H), 3.84 (s, 3H), 2.81 (t,

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$J = 6.4$ Hz, 2H); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 189.3, 165.0, 162.9, 154.0, 153.6, 151.0, 149.4, 149.1, 148.9, 148.6, 148.2, 135.1, 131.4, 124.9, 122.7, 120.0, 119.2, 111.2, 111.0, 110.3, 109.6, 102.3, 95.1, 56.5, 56.4, 56.2, 56.2, 56.1, 44.2, 27.9; IR $\nu_{max}$ 2925, 2852, 1668, 1599, 1512, 1339, 1267, 1133, 1020, 837, 770 $cm^{-1}$; HRMS (EI) *m/z* calcd for $C_{31}H_{29}NO_{10}$ [$M^+$] 575.1791, found 575.1785.

*4.6.2. 2-(3-(3,4-dimethoxybenzoyl)-6-methoxybenzofuran-2-carbonyl)-7,8-dimethoxy-3,4-dihydroisoquinolin-1(2H)-one* ***(13b)***

Light brown solid **13b**. $R_f = 0.60$ (50% EtOAc/hexanes); 9.8 mg; yield 97%; mp 192–194 °C; $^1$H NMR ($CDCl_3$, 400 MHz) δ 7.63 (dd, $J = 8.8$, 2.0 Hz, 1H), 7.62 (d, $J = 8.8$ Hz, 1H), 7.54 (s, 1H), 7.51 (d, $J = 2.0$ Hz, 1H), 7.02 (d, $J = 2.0$ Hz, 1H), 6.96 (dd, $J = 8.8$, 2.0 Hz, 1H), 6.84 (d, $J = 8.8$ Hz, 1H), 6.70 (s, 1H), 3.98–3.95 (m, 2H), 3.97 (s, 3H), 3.92 (s, 3H), 3.88 (s, 3H), 3.86 (s, 3H), 3.84 (s, 3H), 2.91 (t, $J = 6.0$ Hz, 2H); $^{13}$C NMR ($CDCl_3$, 150 MHz) δ 188.8, 164.8, 162.9, 160.3, 155.3, 153.9, 153.5, 149.03, 148.97, 148.4, 134.9, 131.2, 124.7, 122.8, 122.4, 120.1, 119.9, 114.4, 111.1, 110.9, 110.1, 109.5, 95.6, 56.2, 56.1, 56.0, 55.7, 44.0, 27.7; IR $\nu_{max}$ 2921, 2851, 1667, 1514, 1338, 1264, 1116, 1021, 818, 768 $cm^{-1}$; HRMS (EI) *m/z* calcd for $C_{30}H_{27}NO_9$ [$M^+$] 545.1686, found 545.1689.

*4.6.3. 2-(3-(4-(benzyloxy)benzoyl)-5,6-dimethoxybenzofuran-2-carbonyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-1(2H)-one* ***(13c)***

Off white solid; 1 $R_f = 0.55$ (50% EtOAc/hexanes); 10.2 mg; yield 93%; mp 210–213 °C; $^1$H NMR ($CDCl_3$, 400 MHz) δ 7.97 (d, $J = 8.8$ Hz, 2H), 7.55 (s, 1H), 7.43–7.35 (m, 5H), 7.16 (s, 1H), 7.04 (s, 1H), 6.97 (d, $J = 8.8$ Hz, 2H), 6.67 (s, 1H), 5.11 (s, 2H), 3.97 (s, 3H), 3.94–3.91 (m, 2H), 3.92 (s, 3H), 3.89 (s, 3H), 3.88 (s, 3H), 2.88 (t, $J = 6.4$ Hz, 2H); $^{13}$C NMR ($CDCl_3$, 150 MHz) δ 189.1, 164.7, 162.9, 153.9, 150.7, 149.2, 149.1, 148.4, 148.0, 148.2, 136.1, 134.9, 131.9, 131.4, 128.7, 128.2, 127.5, 122.6, 119.9, 118.9, 114.6, 111.0, 109.5, 102.3, 95.0, 70.1, 56.33, 56.26, 56.24, 56.1, 44.0, 27.7; IR $\nu_{max}$ 2932, 2859, 1672, 1589, 1521, 1332, 1272, 1131, 1025, 835, 760 $cm^{-1}$; HRMS (EI) *m/z* calcd for $C_{36}H_{31}NO_9$ [$M^+$] 621.1999, found 621.1994.

*4.6.4. 2-(3-Benzoyl-5,6-dimethoxybenzofuran-2-carbonyl)-7,8-dimethoxy-3,4-dihydroisoquinolin-1(2H)-one* ***(13d)***

Light yellow solid; $R_f = 0.62$ (50% EtOAc/hexanes); 10.2 mg; yield 95%; mp 200–203 °C; $^1$H NMR ($CDCl_3$, 400 MHz) δ 7.96 (d, $J = 8.0$ Hz, 2H), 7.57–7.30 (m, 1H), 7.56 (s, 1H), 7.41 (t, $J = 8.0$ Hz, 2H), 7.22 (s, 1H), 7.05 (s, 1H), 6.68 (s, 1H), 3.97 (s, 3H), 3.93 (s, 3H), 3.93–3.91 (m, 2H), 3.89 (s, 6H), 2.86 (t, $J = 6.4$ Hz, 2H); $^{13}$C NMR ($CDCl_3$, 150 MHz) δ 190.6, 164.6, 162.6, 153.9, 150.6, 150.1, 149.2, 148.4, 148.1, 138.5, 134.9, 133.0, 129.4, 128.6, 128.4, 121.7, 119.8, 118.7, 111.0, 109.4, 102.5, 95.0, 56.32, 56.26, 56.22, 56.1, 43.9, 27.6; IR $\nu_{max}$ 2922, 2851, 1668, 1468, 1338, 1265, 1144, 1037, 891, 727 $cm^{-1}$; HRMS (EI) *m/z* calcd for $C_{29}H_{25}NO_8$ [$M^+$] 515.1580, found 515.1582.

*4.6.5. 2-(5,6-Dimethoxy-3-(4-nitrobenzoyl)benzofuran-2-carbonyl)-7,8-dimethoxy-3,4-dihydroisoquinolin-1(2H)-one* ***(13e)***

Yellow solid; $R_f = 0.65$ (50% EtOAc/hexanes); 3.4 mg; yield 32%; mp 189–192 °C; $^1$H NMR ($CDCl_3$, 400 MHz) δ 8.37 (d, $J = 8.8$ Hz, 1H), 8.18 (d, $J = 8.8$ Hz, 1H), 7.61 (s, 1H), 7.33 (s, 1H), 7.03 (s, 1H), 6.73 (s, 1H), 3.99 (s, 3H), 3.94 (s, 3H), 3.93 (s, 3H), 3.92 (s, 3H), 3.91–3.90 (m, 2H), 3.03 (t, $J = 6.4$ Hz, 2H); $^{13}$C NMR ($CDCl_3$, 150 MHz) δ 189.2, 164.8, 162.5, 154.2, 151.2, 151.0, 150.0, 149.2, 148.6, 148.5, 143.5, 135.0, 130.2, 123.7, 121.1, 119.5, 118.4, 111.0, 109.6, 102.2, 95.0, 56.4, 56.3, 56.1, 44.0, 27.8; IR $\nu_{max}$ 2920, 2851, 1667, 1515, 1464, 1339, 1265, 1144, 1036, 849 $cm^{-1}$; HRMS (EI) *m/z* calcd for $C_{29}H_{24}N_2O_{10}$ [$M^+$] 560.1431, found 560.1434.

*4.6.6. 2-(3-Benzoyl-6-(diethylamino)benzofuran-2-carbonyl)-7,8-dimethoxy-3,4-dihydroisoquinolin-1(2H)-one* ***(13f)***

Brown solid; $R_f = 0.55$ (50% EtOAc/hexanes); 9.6 mg; yield 91%; mp 205–208 °C; $^1$H NMR ($CDCl_3$, 400 MHz) δ 7.95 (d, $J = 8.4$ Hz, 1H), 7.55–7.51 (m, 2H), 7.46 (d, $J = 8.4$ Hz, 1H), 7.40 (t, $J = 8.4$ Hz, 2H), 6.74 (dd, $J = 8.4$, 2.0 Hz, 1H) 6.70 (d, $J = 2.0$ Hz, 1H), 6.67 (s, 1H), 3.96 (s, 3H), 3.92 (t, $J = 6.4$ Hz, 2H), 3.87 (s, 3H), 3.40 (q, $J = 6.4$ Hz, 1H), 2.90 (t, $J = 6.4$ Hz, 2H), 1.18 (t, $J = 6.4$ Hz, 6H); $^{13}$C NMR ($CDCl_3$, 150 MHz) δ 190.9, 164.7, 163.1, 156.9, 153.6, 148.6, 148.3, 147.7, 138.3, 134.8, 132.9, 129.5, 128.4, 123.2, 122.6, 120.1, 115.8, 111.4, 110.9, 109.4, 93.0, 56.2, 56.1, 44.9, 44.1, 27.7, 12.5; IR $\nu_{max}$ 2922, 2851, 1645, 1514, 1360, 1262, 1164, 1035, 889, 804 $cm^{-1}$; HRMS (EI) *m/z* calcd for $C_{31}H_{30}N_2O_6$ [$M^+$] 526.2104, found 526.2114.

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## Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.tet.2018.01.042.

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