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From Phenylacetylphenylacetic Acids and 1-Benzylisoquinolines to 6,11-Dihydrobenzo[*b*]naphtho[2,3-*d*]furan-6,11-diones, 6*H*-Dibenzo[*c,h*]chroman-6-ones and 7,12-Dihydro-5*H*-dibenzo[*c,g*]chroman-5,7,12-triones via 2-Phenyl-3-hydroxy-1,4-dihydro-1,4-naphthalenediones or 2-Phenyl-1-naphthols

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Abstract—We describe the synthesis of 6,11-dihydrobenzo[*b*]naphtho[2,3-*d*]furane-6,11-diones, 6*H*-Dibenzo[*c,h*]chroman-6-ones and 7,12-dihydro-5*H*-dibenzo[*c,g*]chroman-5,7,12-triones from 2-(2′-phenyl)-3-hydroxy-1,4-dihydro-1,4-naphthalenediones or 2-phenyl-1-naphthols obtained from 2-(2′-bromophenylacetyl)-phenylacetic acids or 1-benzylisoquinolines.

The pharmacological activities of the anticoccidial antibiotic WS-5995A (**1a**) (Fig. 1),[1] a natural dibenzochromanone isolated from *S. auranticolor*, and ravidomycin (**2a**),[2] a natural dibenzochromanone from *S. ravidus* which exhibits significant antibiotic and antitumor activity, have been attributed to their embedded planar 2-phenyl-1,4-naphthoquinone subunit,[3] the planarity of which is ensured by the lactone bridge. This structure is also present in related biologically and pharmacologically active compounds, including benzofuronaphthoquinones **3**,[4,5] which also have industrial applications.

In most syntheses of **1**,[6] **2**[7] and **3**,[8] the key step is the linkage of appropriately functionalized naphthalenes and benzenes, which is followed by completion of the heterocyclic ring. However, in one approach to **1a**, the intermediate phenylnaphthoquinone **6a** is obtained from ketoacid **4a** (Scheme 1).[9] Our interest in synthetic applications of phenylacetylphenylacetic acids **4**[10] has led us to study the extension of this latter method to the preparation of other naphthoquinone-based compounds.[11,12] We describe here the synthesis of benzofuronaphthoquinones **3** by intramolecular Ullmann coupling reaction of bromophenylnaphthoquinones

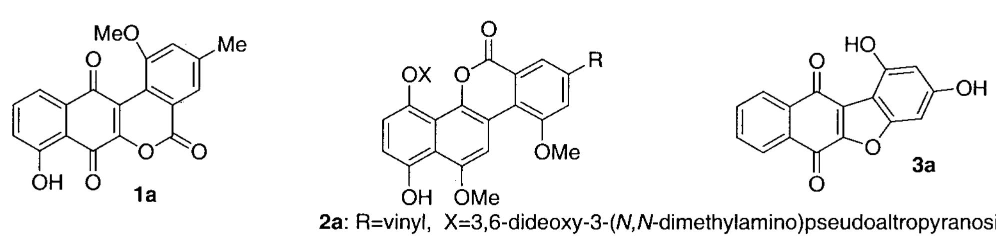

Figure 1.

Keywords: antitumour compounds; chromones; furans; quinones; Ullmann reactions.

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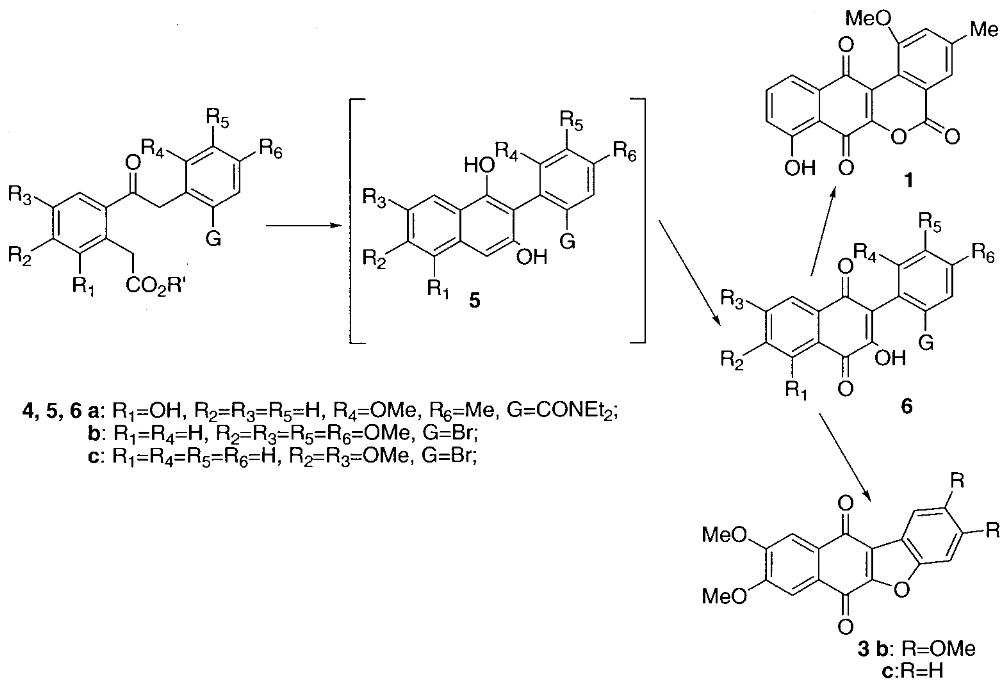


Scheme 1.

6 obtained from either bromophenylacetylphenylacetic acids **4**[10] or 1-benzylisoquinolines **8**, and related synthesis of **1b** and **2b**.

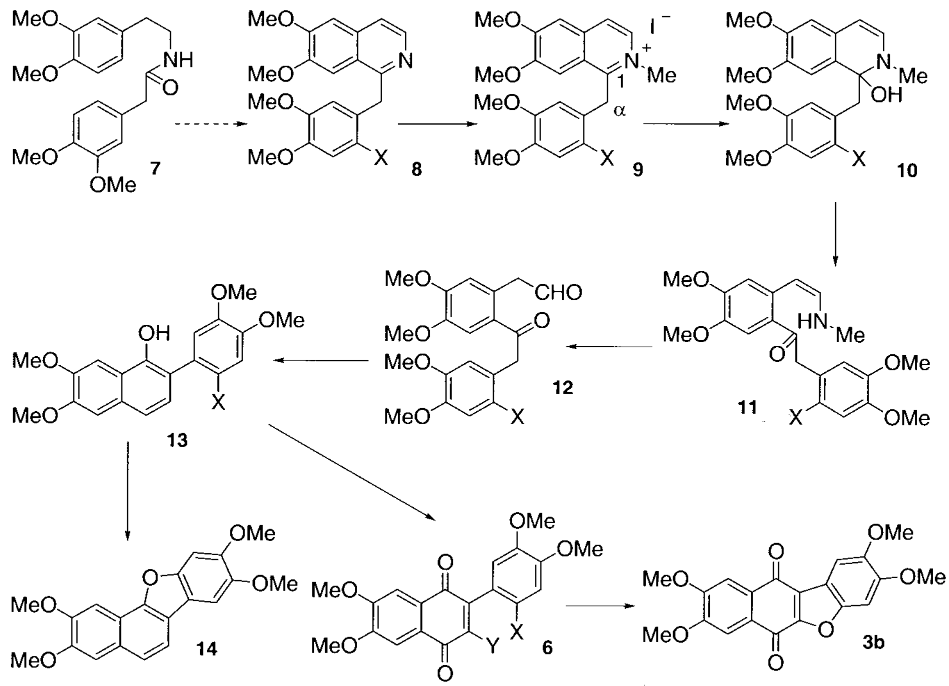
Bromoketoester **4b** (R′=Me) was prepared by esterification of the corresponding bromoketoacid[10a] (R′=H) and was refluxed for 30 min in a solution of KOH in water/ethanol affording the red bromophenylnaphthoquinone **6b** by intramolecular Dieckmann condensation followed by oxidation of the cyclization product **5b** in the reaction medium. Refluxing a solution of **6b**, cuprous oxide, potassium carbonate and pyridine under argon for 2 h, gave a 92% yield of benzofuronaphthoquinone **3b**,[12] which was identified from its analytical and spectroscopic data. Its ^{1}H NMR spectrum shows four singlets at 3.99, 4.02, 4.06 and 4.07 ppm due to the four methoxyl groups, and four singlets at 7.11, 7.58, 7.62 and 7.64 corresponding to the four aromatic protons. The same strategy transformed bromoketoester **4c**[10b] (R′=Me) almost quantitatively into dimethoxy-benzofuronaphthoquinone **3c** via naphthoquinone **6c**. Compound **3c** is a red solid of mp 260–261°C; its ^{1}H NMR spectrum shows two singlets at 4.05 and 4.06 ppm due to the two methoxyl groups, a multiplet at 7.45–7.69 ppm due to three aromatic protons, two singlets at 7.63 and 7.64 ppm due to two aromatic protons, and a multiplet at 8.25 ppm due to the remaining aromatic proton.

Unfortunately, this short, efficient new route to benzofuronaphthoquinones **3** is of limited scope because the range of ketoacids **4** is restricted by the limitations of the Friedel–Crafts acylation reactions by which they are obtained.[10] In order to avoid this problem we developed an alternative closely related route to phenylnaphthoquinones **6** starting from readily available 1-benzylisoquinolines **8** (Scheme 2).

Commercially available papaverine (**8a**)[13] was treated with methyl iodide at room temperature, to give a 92% yield of *N*-methyl-1-benzylisoquinolinium iodide (**9a**), which was then heated in a refluxing solution of NaOH in water/methanol to afford 2-phenyl-1-naphthol **13a** in 85% yield. The formation of **13a** may be explained as follows: in the basic media the salt **9a** is in equilibrium with carbinolamine **10a**, which is in turn in equilibrium with ketoenamine **11a**; hydrolysis of **11a** gives ketoaldehyde **12a** (similar to ketoacids **4**), and in the basic reaction conditions **12a** undergoes intramolecular aldol condensation followed by dehydration to **13a**.[14] Subsequent oxidation[15] of **13a** with Fremy's salt furnished phenylnaphthoquinone **6d** in 80% yield, and heating[16] of **6d** in a solution of NaOH in water/methanol solution gave hydroxyphenylnaphthoquinone **6e** in almost quantitative yield.

Note that as papaverine (**8a**) is obtained from *N*-phenylacetylphenylethylamine **7**,[13] the above synthesis involves regiospecific transfer of a phenylacetyl group from the nitrogen atom of phenylethylamide **7** to the desired position of **11a** by a four step sequence that includes a Bischler–Napieralski cyclization. This method of acylation of aromatic rings is less dependent than Friedel–Crafts acylations on the electronic properties of substituents.[10]

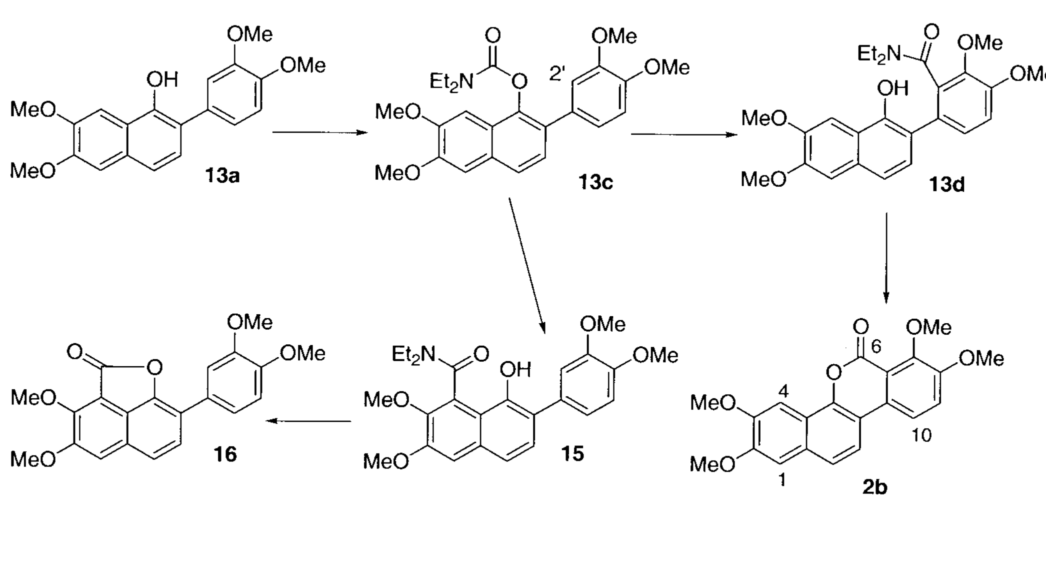
We next applied this new route to naphthoquinones **6** to the synthesis of benzofuronaphthoquinones **3**. Bromination of papaverine (**8a**) followed by treatment with methyl iodide and final heating of the resulting bromobenzylisoquinolinium salt **9b** in a refluxing solution of NaOH in water/methanol, led us to the expected 2-phenyl-1-naphthol **13b**, in albeit only 45% yield, the competitive formation of isoquinoline by cleavage of C_1–C_α bond under the basic reaction conditions being favoured by the electron-withdrawing bromine atom.[17] Subsequent oxidation of **13b** with Fremy's salt furnished an 80% yield of bromophenylnaphthoquinone **6f**, which was heated in a solution of NaOH in water/methanol to give hydroxyphenylnaphthoquinone



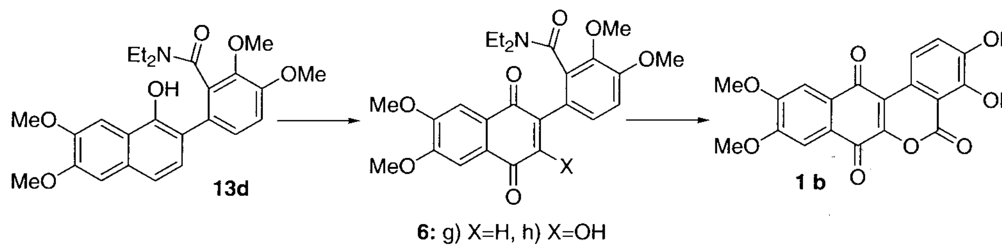
Scheme 2. **6**: **b** X=Br, Y=OH; **d** X=Y=H; **e** X=H, Y=OH; **f** X=Br, Y=H; **8**, **9**, **10**, **11**, **12**, **13**: **a** X=H, **b** X=Br.

6b. Ullmann reaction of **6b** as above afforded tetramethoxybenzofuronaphthoquione **3b**; additionally, Ullmann reaction of **13b** under the same conditions afforded benzonaphthofuran **14**.

The above route from papaverine (**8a**) to 2-phenyl-1-naphthol **13a** was next combined with directed ortho metalation and subsequent remote acyl transfer[18] to achieve a new regiocontrolled synthesis of dibenzochromanones **1** and **2**. Heating a solution of naphthol **13a** and *N*,*N*-diethylcarbamoyl chloride in dry pyridine at 100°C under argon for 4.5 days gave the expected carbamate **13c** as a white solid of mp 118–120°C (Et_2O) (Scheme 3). Reaction of **13c** with LDA gave a solid identified as compound **13d** on the basis of its analytical and spectroscopic data; the mass spectrum confirmed the molecular formula $C_{27}H_{29}NO_6$ and its ^1H NMR spectrum showed three singlets at 3.91, 3.98 and 4.01 ppm for the four methoxyl groups (the 4.01 ppm signal corresponding to deshielded methoxyl group contiguous to the carbonyl group), signals at 6.99–7.72 ppm for the six aromatic protons, and a broad singlet at 8.65 due to the hydroxyl group. The formation of **13d** may be attributed to metalation of position C-2′ (a process facilitated by the contiguous methoxyl group) followed by transfer of the amide group to the phenyl substituent. Refluxing a solution of **13d** in acetic acid for 6 h gave the chromanone **2b**, identified from its analytical and spectroscopic data; the mass spectrum showed the expected peak for the molecular ion at *m*/*z*=366 and the IR exhibited a carbonyl band at 1732 cm^{-1}, while the ^1H NMR spectrum included two singlets for aromatic protons at 7.12 and 7.76 ppm, and two AB systems at 7.42 and 7.87 ppm and at 7.55 and



Scheme 3.



Scheme 4.

7.82 ppm; the possibility of **16** having been obtained via **15** was ruled out by an HMBC study that showed correlation between δ 7.77 (H4) and δ 106.4 (C1) and between δ 7.12 (H1) and δ 100.9 (C4), (Additionally, correlation between δ 157.8 (C6) and δ 7.87 (H10) indicated that the carbonyl is attached to C(6a).)

Finally, dibenzochromanone **1b** was obtained as follows. Naphthol **13d** (Scheme 4) was easily and efficiently oxidized to naphthoquinone **6g** by stirring for 9 h at room temperature in a solution of Fremy's salt and potassium bisulfate in acetone. Addition of an excess of NaOH to a solution of **6g** in 80:20 methanol/water, and heating at 50°C for 7 h then gave hydroxynaphthoquinone **6h** as a red solid of mp 233–235°C. Refluxing a solution of **6h** in acetic acid for 6 h gave the cyclized dibenzochromanone **1b**, identified from its spectroscopic data.

To sum up, we have confirmed the utility of ketoacids **4** as starting materials for the preparation of condensed naphthoquinones by using them as the basis of a new total synthesis of benzofuronaphthoquinones **3**. Additionally, we have developed an alternative route to 2-phenyl-3-hydroxy-1,4-naphthoquinones **6** starting from 1-benzylisoquinolines, and have used its end-products or intermediates to synthesize benzofuronaphthoquinones and dibenzochromanones **1** and **2**. This new route to **6** avoids having to start from ketoacids **4** prepared by Friedel–Crafts acylations, a process of well-known limitations.

Experimental

Melting points were determined on a Kofler Thermogerate apparatus and are uncorrected. Infrared spectra were recorded on a MIDAC FTIR spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Bruker WM-250 apparatus, using deuteriochloroform solutions containing tetramethylsilane as an internal standard. Mass spectra were obtained on a Kratos MS 50 TC mass spectrometer. Thin layer chromatography (TLC) was performed using Merck GF-254 type 60 silica gel and Cl_2CH_2/MeOH mixtures as eluant; the TLC spots were visualized with ultraviolet light or iodine vapor. Column chromatography was carried out using Merck type 9385 silica gel. Solvents were purified as per Ref. 19. Solutions of extracts in organic solvents were dried with anhydrous sodium sulfate.

2-(2′-Bromo-4′,5′-dimethoxyphenyl)-6,7-dimethoxy-1,4-dihydro-3-hydroxy-1,4-naphthalenedione (6b). *Procedure A:* A mixture of bromoketoester **4b** (R′=Me) (1 g, 2.1 mmol), EtOH (30 mL) and 20% aqueous NaOH solution (30 mL) was refluxed for 30 min. The EtOH was then evaporated in vacuo, the residue was suspended in water (250 mL), and this mixture was acidified with 10% aqueous HCl and extracted with Cl_2H_2 (3×50 mL). The organic layers were dried, filtered and concentrated in vacuo to give quinone **6b** (0.92 g, 96%) as a red solid, mp 222–224°C (MeOH). IR (ν, cm^{-1}, KBr): 3335 (–OH), 1617 (C=O). ^1H NMR (δ, ppm): 3.83 (s, 3H, $-OCH_3$), 3.88 (s, 3H, $-OCH_3$), 4.01 (s, 6H, 2×$-OCH_3$), 6.75 (s, 1H, Ar–H), 7.12 (s, 1H, Ar–H), 7.52 (s, 1H, Ar–H), 7.55 (s, 1H, –OH), 7.58 (s, 1H, Ar–H). ^{13}C NMR (δ, ppm): 56.0 ($-OCH_3$), 56.1 ($-OCH_3$), 56.5 ($-OCH_3$), 56.6 ($-OCH_3$), 107.8 (CH), 109.0 (CH), 114.1 (CH), 114.5 (C), 115.5 (CH), 121.6 (C), 123.6 (C), 123.9 (C), 128.1 (C), 148.3 (C), 149.8 (C), 152.9 (C), 153.1 (C), 154.8 (C), 180.8 (C=O), 182.8 (C=O). Ms (*m/z*, %): 450 (M^+, 0.05), 448 (M^+, 0.05), 369 (100). Anal. Calcd for $C_{20}H_{17}BrO_7$: C, 53.47; H, 3.81. Found: C, 53.63; H, 3.56.

Procedure B: A solution of compound **6f** (316 mg, 0.73 mmol) and NaOH (146 mg, 3.65 mmol) in deoxygenated 4:1 MeOH/water (20 mL) was heated at 50°C for 4.5 h under argon. Water (50 mL) was added, the resulting suspension was acidified with 10% aqueous HCl solution, the precipitate was filtered out and the filtrate was extracted with Cl_2CH_2 (3×30 mL). The pooled organic layers were dried, filtered and concentrated in vacuo to give a solid identical to the filtration residue. The pooled solids were crystallized from MeOH to give compound **6b** (320 mg, 98% yield).

2,3,8,9-Tetramethoxy-6,11-dihydrobenzo[*b*]naphtho[2,3-*d*]-furan-6,11-dione (3b). A mixture of compound **6b** (100 mg, 0.2 mmol), CuO (56 mg, 0.7 mmol) and K_2CO_3 (159 mg, 1.15 mmol) in dry deoxygenated pyridine (3 mL) was refluxed under argon for 2 h. The mixture was then added to 20% aqueous HCl solution (40 mL) and the resulting suspension was extracted with Cl_2CH_2 (3×25 mL). The pooled organic layers were then washed with 10% aqueous NaOH solution, dried, filtered and concentrated in vacuo to give compound **3b** (75 mg, 92% yield), mp 282–284°C (MeOH). IR (ν, cm^{-1}, KBr): 1665 (C=O). ^1H NMR (δ, ppm): 3.99 (s, 3H, $-OCH_3$), 4.02 (s, 3H, $-OCH_3$), 4.06 (s, 3H, $-OCH_3$), 4.07 (s, 3H, $-OCH_3$), 7.11 (s, 1H, Ar–H), 7.58 (s, 1H, Ar–H), 7.62 (s, 1H, Ar–H), 7.64 (s, 1H, Ar–H). ^{13}C NMR (δ, ppm): 56.8 ($-OCH_3$), 56.9 (3×$-OCH_3$), 95.7 (CH), 103.1 (CH), 108.8 (CH), 108.9 (CH), 115.6 (C), 124.7 (C), 127.5 (C), 128.2 (C), 149.8 (2×C), 152.6 (C), 153.1 (C), 153.5 (2×C), 174.5 (C=O), 181.9 (C=O). Ms (*m/z*, %): 368 (M^+, 100), 325 (13), 69 (18). Anal. Calcd for $C_{20}H_{16}O_7$: C, 65.22; H, 4.38. Found: C, 65.01; H, 4.39.

2-(2′-Bromophenyl)-6,7-dimethoxy-1,4-dihydro-3-hydroxy-1,4-naphthalenedione (6c). Compound **6c** was obtained in 99% yield from compound **4c** (R′=Me) (1 g, 2.46 mmol) following the same procedure as for compound **6b** (Procedure A), mp 224–225° C (MeOH). IR (ν, cm^{-1}, KBr): 3350 (–OH), 1649 (C=O). ^{1}H NMR (δ, ppm): 4.05 (s, 6H, 2×OCH_3), 7.30 (m, 2H, 2×Ar–H), 7.42 (m, 1H, Ar–H), 7.51 (s, 1H, –OH), 7.57 (s, 1H, Ar–H), 7.62 (s, 1H, Ar–H), 7.69 (m, 1H, Ar–H). ^{13}C NMR (δ, ppm): 56.9 (–OCH_3), 57.0 (–OCH_3), 108.2 (CH), 109.5 (CH), 122.0 (C), 123.8 (C), 124.5 (C), 127.6 (CH), 128.5 (C), 130.5 (CH), 132.0 (CH), 132.5 (C), 133.1 (CH), 153.0 (C), 153.2 (C), 155.3 (C), 181.1 (C=O), 182.9 (C=O). Ms (*m/z*, %): 310 (21), 309 (100). Anal. Calcd for $C_{18}H_{13}BrO_5$: C, 55.55; H, 3.37. Found: C, 55.81; H, 3.18.

8,9-Dimethoxy-6,11-dihydrobenzo[*b*]naphtho[2,3-*d*]furan-6,11-dione (3c). Compound **3c** was prepared in 99% yield from compound **6c** (123 mg, 0.3 mmol) by the procedure described above for compound **3b**, mp 260–261°C (MeOH). IR (ν, cm^{-1}, KBr): 1665 (C=O). ^{1}H NMR (δ, ppm): 4.05 (s, 3H, –OCH_3), 4.06 (s, 3H, –OCH_3), 7.45–7.69 (m, 3H, 3×Ar–H), 7.63 (s, 1H, Ar–H), 7.64 (s, 1H, Ar–H), 8.25 (m, 1H, Ar–H). ^{13}C NMR (δ, ppm): 57.0 (–OCH_3), 57.1 (–OCH_3), 109.0 (2×CH), 113.2 (CH), 123.3 (C), 124.2 (CH), 126.3 (CH), 127.1 (C), 128.4 (C), 129.6 (CH), 153.5 (2×C), 153.9 (C), 154.0 (C), 156.6 (C), 175.6 (C=O), 181.5 (C=O). Ms (*m/z*, %): 308 (M^+, 100), 237 (13), 194 (13). Anal. Calcd for $C_{18}H_{12}O_5$: C, 70.13; H, 3.92. Found: C, 70.01; H, 3.76.

1-(3′,4′-Dimethoxybenzyl)-6,7-dimethoxy-2-methylisoquinolinium iodide (9a). A mixture of papaverine hydrochloride (4.7 g, 12.5 mmol) and 20% aqueous NaOH solution (100 ml) was stirred at rt for 30 min and then extracted with Cl_2CH_2 (3×50 mL). The pooled organic layers were dried, filtered and concentrated in vacuo to give 4.1 g (12.1 mmol) of pure paraverine, which was dissolved with MeI (4.14 mL, 66.4 mmol) in dry acetone (20 mL). This solution was stirred at rt, more MeI (0.83 mL, 13.30 mmol) being added every 12 h until, after 3 days, TLC showed no starting material. The white solid formed was filtered out and washed with dry acetone to give compound **9a** (5.36 g, 92% yield), mp 152–154°C (acetone). IR (ν, cm^{-1}, NaCl): 1645 (C=N). ^{1}H NMR (δ, ppm): 3.76 (s, 3H, –OCH_3), 3.82 (s, 3H, –OCH_3), 3.98 (s, 3H, –OCH_3), 4.12 (s, 3H, –OCH_3), 4.51 (s, 3H, –NCH_3), 5.08 (s, 2H, –CH_2–), 6.20 (dd, *J*=8.3 Hz, *J*=1.8 Hz, 1H, Ar–H), 6.65 (d, *J*=8.3 Hz, 1H, Ar–H), 6.99 (d, *J*=1.8 Hz, 1H, Ar–H), 7.48 (s, 1H, Ar–H), 7.66 (s, 1H, Ar–H), 8.27 (d, *J*=6.8 Hz, 1H, Ar–H), 8.71 (d, *J*=6.8 Hz, 1H, Ar–H). ^{13}C NMR (δ, ppm): 35.2 (CH_2), 47.2 (CH_3), 55.9 (–OCH_3), 56.5 (–OCH_3), 57.0 (–OCH_3), 57.7 (–OCH_3), 105.1 (CH), 106.7 (CH), 111.8 (CH), 112.2 (CH), 119.5 (CH), 123.1 (CH), 124.6 (C), 126.1 (C), 136.1 (CH), 136.3 (C), 148.7 (C), 149.8 (C), 153.5 (C), 155.0 (C), 157.5 (C). Ms (*m/z*, %): 454 (M^+, 8), 142 (100).

2-(3′,4′-Dimethoxyphenyl)-6,7-dimethoxy-1-naphthol (13a). A solution of compound **9a** (0.15 g, 0.31 mmol) and NaOH (0.7 g, 17.5 mmol) in deoxygenated MeOH (15 mL) was refluxed under argon for 20 h. Water (50 mL) was then added, and the reaction mixture was then acidified to pH 3 with 10% aqueous HCl solution, and extracted with Cl_2CH_2 (3×15 mL). The pooled organic layers were dried, filtered and concentrated in vacuo to give a residue that was purified by flash column chromatography (1:1 EtOAc/hexane) to afford compound **13a** (93 mg, 85% yield) as a white solid, mp 165–167°C (MeOH/Et_2O). IR (ν, cm^{-1}, NaCl): 3443 (–OH). ^{1}H NMR (δ, ppm): 3.91 (s, 3H, –OCH_3), 3.93 (s, 3H, –OCH_3), 4.01 (s, 3H, –OCH_3), 4.03 (s, 3H, –OCH_3), 5.87 (s, 1H, –OH), 6.98–7.09 (m, 3H, 3×Ar–H), 7.11 (s, 1H, Ar–H), 7.21 (d, *J*=8.3 Hz, 1H, Ar–H), 7.32 (d, *J*=8.3 Hz, 1H, Ar–H), 7.55 (s, 1H, Ar–H). ^{13}C NMR (δ, ppm): 56.2 (–OCH_3), 56.3 (–OCH_3), 56.4 (2×–OCH_3), 101.6 (CH), 106.6 (CH), 112.4 (CH), 112.9 (CH), 119.0 (CH), 119.7 (C), 120.4 (C), 121.7 (CH), 126.3 (CH), 130.4 (C), 130.5 (C), 147.3 (C), 149.1 (C), 149.7 (C), 150.2 (C), 150.3 (C). Ms (*m/z*, %): 340 (M^+, 100), 325 (14). Anal. Calcd for $C_{20}H_{20}O_5$: C, 70.57; H, 5.92. Found: C, 70.62; H, 6.11.

2-(3′,4′-Dimethoxyphenyl)-6,7-dimethoxy-1,4-dihydro-1,4-naphthalenedione (6d). A solution of Fremy's salt (456 mg, 1.7 mmol) and KH_2PO_4 (44 mg, 0.32 mmol) in water (4 mL) was added to a solution of compound **13a** (340 mg, 1 mmol) in acetone (4 mL) and the resulting mixture was stirred at rt for 2 h. The acetone was evaporated in vacuo, the resulting precipitate was filtered out and the filtrate was extracted with Cl_2CH_2 (3×50 mL). The pooled organic layers were dried, filtered and concentrated in vacuo to give a solid identical to the filtration residue. The pooled solids were crystallized from MeOH to give compound **6d** (283 mg, 80% yield) as an orange solid, mp 192–194°C. IR (ν, cm^{-1}, NaCl): 1651 (C=O). ^{1}H NMR (δ, ppm): 3.92 (s, 6H, 2×–OCH_3), 3.99 (s, 6H, 2×–OCH_3), 6.90 (s, 1H, Ar–H), 6.93 (s, 1H, Ar–H), 7.12–7.19 (m, 2H, 2×Ar–H), 7.45 (s, 1H, Ar–H), 7.52 (s, 1H, Ar–H). ^{13}C NMR (δ, ppm): 55.9 (2×–OCH_3), 56.4 (2×–OCH_3), 107.3 (CH), 108.5 (CH), 111.0 (CH), 112.6 (CH), 122.8 (CH), 126.2 (C), 126.9 (C), 127.3 (C), 133.6 (CH), 147.1 (C), 148.8 (C), 150.9 (C), 153.5 (C), 153.6 (C), 184.3 (C=O), 184.8 (C=O). Ms (*m/z*, %): 354 (M^+, 74), 338 (28), 323 (100). Anal. Calcd for $C_{20}H_{18}O_6$: C, 67.79; H, 5.12. Found: C, 67.64; H, 5.02.

2-(3′,4′-Dimethoxyphenyl)-6,7-dimethoxy-3-hydroxy-1,4-dihydro-1,4-naphthalenedione (6e). Starting from compound **6d** (40 mg, 0.11 mmol), compound **6e** was obtained in 90% yield following the same procedure as for compound **6b** (Procedure B), mp 234–236°C (MeOH). IR (ν, cm^{-1}, NaCl): 3327 (–OH), 1645 (C=O). ^{1}H NMR (δ, ppm): 3.98 (s, 3H, –OCH_3), 3.99 (s, 3H, –OCH_3), 4.01 (s, 3H, –OCH_3), 4.02 (s, 3H, –OCH_3), 7.00 (d, *J*=8.0 Hz, 1H, Ar–H), 7.08 (s, 1H, –OH), 7.18 (d, *J*=8.0 Hz, 1H, Ar–H), 7.51 (s, 1H, Ar–H), 7.60 (s, 2H, 2×Ar–H). ^{13}C NMR (δ, ppm): 55.8 (–OCH_3), 55.9 (–OCH_3), 56.5 (–OCH_3), 56.6 (–OCH_3), 107.5 (CH), 109.0 (CH), 110.6 (CH), 114.1 (CH), 120.8 (C), 122.6 (C), 123.4 (C), 123.9 (CH), 128.1 (C), 148.3 (C), 149.3 (C), 151.8 (C), 152.8 (C), 154.6 (C), 180.9 (C=O), 183.7 (C=O). Ms (*m/z*, %): 370 (M^+, 100), 355 (14), 339 (42). Anal. Calcd for $C_{20}H_{18}O_7$: C, 64.86; H, 4.90. Found: C, 64.59; H, 4.93.

1-(2′-Bromo-4′,5′-dimethoxybenzyl)-6,7-dimethoxyisoquinoline (8b). A solution of bromine (1.8 mL, 31 mmol) in

AcOH (17 mL) was added dropwise, over 30 min, to a solution of papaverine (4.55 g, 13.42 mmol) in 1:1 AcOH/water (100 mL) maintained at 10°C with an ice/water bath. The mixture was then stirred at rt for 3.5 h and added to water (100 mL). After extraction with Cl_2CH_2 (3×50 mL), the pooled organic layers were washed with saturated aqueous $Na_2S_2O_3$ solution, 10% aqueous $NaHCO_3$ solution and water, dried, filtered and concentrated in vacuo to give bromopapaverine (**8b**; 4.57 g, 88% yield), mp 168–170°C (MeOH). IR (ν, cm^{-1}, NaCl): 1618 (C=N). ^{1}H NMR (δ, ppm): 3.59 (s, 3H, –OCH$_3$), 3.83 (s, 3H, –OCH$_3$), 3.97 (s, 3H, –OCH$_3$), 3.99 (s, 3H, –OCH$_3$), 4.64 (s, 2H, –CH$_2$–), 6.66 (s, 1H, Ar–H), 7.03 (s, 1H, Ar–H), 7.04 (s, 1H, Ar–H), 7.33 (s, 1H, Ar–H), 7.44 (d, J=5.7 Hz, 1H, Ar–H), 8.37 (d, J=5.7 Hz, 1H, Ar–H). ^{13}C NMR (δ, ppm): 41.3 (CH$_2$), 55.8 (–OCH$_3$), 55.9 (–OCH$_3$), 56.0 (–OCH$_3$), 56.3 (–OCH$_3$), 104.3 (CH), 105.2 (CH), 113.0 (CH), 113.7 (C), 115.1 (CH), 118.9 (CH), 123.0 (C), 131.0 (C), 133.4 (C), 140.8 (CH), 148.3 (C), 148.7 (C), 150.2 (C), 152.7 (C), 157.5 (C). Anal. Calcd for $C_{20}H_{20}BrNO_4$: C, 57.43; H, 4.82; N, 3.35. Found: C, 57.61; H, 4.90; N, 3.10.

1-(2′-Bromo-4′,5′-dimethoxybenzyl)-6,7-dimethoxy-2-methylisoquinolinium iodide (9b). Compound **9b** was prepared in 92% yield from compound **8b** (2 g, 4.78 mmol) by the same procedure as for compound **9a**, mp 234–236°C (acetone). IR (ν, cm^{-1}, NaCl): 1700 (C=N). ^{1}H NMR (δ, ppm, CDCl$_3$/DMSO): 3.60 (s, 3H, –OCH$_3$), 3.83 (s, 3H, –OCH$_3$), 3.94 (s, 3H, –OCH$_3$), 4.12 (s, 3H, –OCH$_3$), 4.58 (s, 3H, –NCH$_3$), 5.02 (s, 2H, –CH$_2$–), 6.39 (s, 1H, Ar–H), 7.03 (s, 1H, Ar–H), 7.37 (s, 1H, Ar–H), 7.72 (s, 1H, Ar–H), 8.38 (d, J=6.8 Hz, 1H, Ar–H), 8.85 (d, J=6.8 Hz, 1H, Ar–H). ^{13}C NMR (δ, ppm, CDCl$_3$/DMSO): 35.4 (CH$_2$), 46.7 (CH$_3$), 56.0 (–OCH$_3$), 56.4 (–OCH$_3$), 56.5 (–OCH$_3$), 57.1 (–OCH$_3$), 104.6 (CH), 106.3 (CH), 112.0 (CH), 114.1 (C), 116.2 (CH), 123.3 (CH), 124.5 (C), 125.4 (C), 136.1 (CH), 136.4 (C), 149.3 (C), 149.5 (C), 153.5 (C), 154.0 (C), 157.7 (C). Ms (m/z, %): 434 ((M+1)$^+$, 5), 432 ((M+1)$^+$, 5), 433 (M$^+$, 20), 431 (M$^+$, 20), 418 (20), 416 (20), 91 (100). Anal. Calcd for $C_{21}H_{23}BrINO_4$: C, 45.02; H, 4.14; N, 2.50. Found: C, 45.15; H, 4.02; N, 2.77.

2-(2′-Bromo-4′,5′-dimethoxyphenyl)-6,7-dimethoxy-1-naphthol (13b). Following the procedure described for compound **13a**, compound **13b** was obtained from compound **9b** (1 g, 1.78 mmol) in 45% yield, mp 142–144°C (MeOH). IR (ν, cm^{-1}, NaCl): 3377 (–OH). ^{1}H NMR (δ, ppm): 3.84 (s, 3H, –OCH$_3$), 3.92 (s, 3H, –OCH$_3$), 4.01 (s, 3H, –OCH$_3$), 4.03 (s, 3H, –OCH$_3$), 5.44 (s, 1H, –OH), 6.88 (s, 1H, Ar–H), 7.12 (d, J=8.5 Hz, 1H, Ar–H), 7.13 (s, 1H, Ar–H), 7.17 (s, 1H, Ar–H), 7.33 (d, J=8.5 Hz, 1H, Ar–H), 7.57 (s, 1H, Ar–H). ^{13}C NMR (δ, ppm): 55.8 (–OCH$_3$), 55.9 (–OCH$_3$), 56.1 (–OCH$_3$), 56.3 (–OCH$_3$), 101.4 (CH), 106.3 (CH), 114.5 (CH), 114.9 (C), 115.9 (CH), 118.4 (CH), 119.3 (C), 119.8 (C), 126.2 (CH), 129.6 (C), 130.5 (C), 147.1 (C), 149.0 (C), 149.4 (C), 149.7 (C), 150.2 (C). Ms (m/z, %): 420 (M$^+$, 27), 418 (M$^+$, 27), 308 (100). Anal. Calcd for $C_{20}H_{19}BrO_5$: C, 57.29; H, 4.57. Found: C, 57.03; H, 4.60.

2-(2′-Bromo-4′,5′-dimethoxyphenyl)-6,7-dimethoxy-1,4-dihydro-1,4-naphthalenedione (6f). Compound **6f** was prepared from **13b** (90 mg, 0.21 mmol) in 80% yield using the same procedure as for compound **6d**, mp 166–168°C (MeOH). IR (ν, cm^{-1}, NaCl): 1656 (C=O). ^{1}H NMR (δ, ppm, CDCl$_3$/DMSO): 3.85 (s, 3H, –OCH$_3$), 3.90 (s, 3H, –OCH$_3$), 4.01 (s, 3H, –OCH$_3$), 4.02 (s, 3H, –OCH$_3$), 6.76 (s, 1H, Ar–H), 6.84 (s, 1H, Ar–H), 7.10 (s, 1H, Ar–H), 7.49 (s, 1H, Ar–H), 7.52 (s, 1H, Ar–H). ^{13}C NMR (δ, ppm, CDCl$_3$/DMSO): 57.8 (–OCH$_3$), 57.9 (–OCH$_3$), 58.0 (2×–OCH$_3$), 109.2 (CH), 110.2 (CH), 115.0 (C), 115.4 (CH), 117.5 (CH), 128.5 (C), 128.6 (C), 128.9 (C), 138.7 (CH), 150.0 (C), 150.9 (C), 152.0 (C), 155.4 (C), 155.5 (C), 184.5 (C=O), 186.5 (C=O). Ms (m/z, %): 434 (M$^+$, 0.6), 432 (M$^+$, 0.6), 353 (100). Anal. Calcd for $C_{20}H_{17}BrO_6$: C, 55.44; H, 3.95. Found: C, 55.38; H, 3.97.

2,3,8,9-Tetramethoxybenzo[*b*]naphtho[2,1-*d*]furan (14). A mixture of compound **13b** (68 mg, 0.16 mmol), CuO (41 mg, 0.51 mmol) and K_2CO_3 (116 mg, 0.84 mmol) in dry deoxygenated pyridine (5 mL) was refluxed under argon for 2 h and then added over 20% aqueous HCl solution (40 mL). The resulting suspension was extracted with Cl_2CH_2 (325 mL), and the pooled organic layers were washed with 10% aqueous NaOH solution, dried, filtered and concentrated in vacuo to give compound **14** (35 mg, 64% yield), mp 208–210°C (MeOH). ^{1}H NMR (δ, ppm): 4.00 (s, 3H, –OCH$_3$), 4.02 (s, 3H, –OCH$_3$), 4.04 (s, 3H, –OCH$_3$), 4.11 (s, 3H, –OCH$_3$), 7.24 (s, 1H, Ar–H), 7.27 (s, 1H, Ar–H), 7.39 (s, 1H, Ar–H), 7.59 (d, J=8.4 Hz, 1H, Ar–H), 7.63 (s, 1H, Ar–H), 7.76 (d, J=8.4 Hz, 1H, Ar–H). ^{13}C NMR (δ, ppm): 55.9 (–OCH$_3$), 56.0 (–OCH$_3$), 56.3 (–OCH$_3$), 56.6 (–OCH$_3$), 95.9 (CH), 99.6 (CH), 102.0 (CH), 107.5 (CH), 116.1 (CH), 116.6 (C), 117.0 (C), 118.7 (C), 121.6 (CH), 127.9 (C), 146.5 (C), 149.0 (C), 149.3 (C), 150.0 (C), 150.7 (C), 151.6 (C). Ms (m/z, %): 338 (M$^+$, 100), 323 (34). Anal. Calcd for $C_{20}H_{18}O_5$: C, 70.99; H, 5.36. Found: C, 70.73; H, 5.21.

***N,N*-Diethylamino-2-(3′,4′-dimethoxyphenyl)-6,7-dimethoxy-1-naphthyloxymethanone (13c).** A solution of naphthol **13a** (0.7 g, 2.02 mmol) and *N,N*-diethylcarbamoyl chloride (1.53 mL, 12 mmol) in dry pyridine (3 mL) was heated at 110°C in a sealed tube for 4.5 days. The reaction mixture was then added to ice/water, and after extraction with Et_2O (3×75 mL), the pooled organic layers were washed (first with 10% aqueous HCl solution (3×75 mL) and then with saturated aqueous $NaHCO_3$ solution (75 mL), dried, filtered and concentrated in vacuo to give a residue which was purified by flash column chromatography (1:1 EtOAc/hexene) to afford compound **13c** (0.66 g, 75% yield), mp 118–120°C (Et_2O). IR (ν, cm^{-1}, NaCl): 1714 (C=O). ^{1}H NMR (δ, ppm): 1.04–1.08 (m, 3H, –CH$_3$), 1.17–1.22 (m, 3H, –CH$_3$), 3.27–3.34 (m, 2H, –CH$_2$–), 3.40–3.45 (m, 2H, –CH$_2$–), 3.89 (s, 3H, –OCH$_3$), 3.91 (s, 3H, –OCH$_3$), 3.97 (s, 3H, –OCH$_3$), 4.00 (s, 3H, –OCH$_3$), 6.92 (d, J=7.8 Hz, 1H, Ar–H), 7.04–7.07 (m, 2H, 2×Ar–H), 7.12 (s, 1H, Ar–H), 7.15 (s, 1H, Ar–H), 7.35 (d, J=8.4 Hz, 1H, Ar–H), 7.59 (d, J=8.4 Hz, 1H, Ar–H). ^{13}C NMR (δ, ppm): 13.7 (CH$_3$), 14.7 (CH$_3$), 42.3 (CH$_2$), 42.5 (CH$_2$), 56.0 (–OCH$_3$), 56.2 (–OCH$_3$), 56.3 (–OCH$_3$), 56.4 (–OCH$_3$), 100.9 (CH), 106.8 (CH), 111.4 (CH), 112.9 (CH), 121.9 (CH), 124.1 (C), 124.3 (CH), 126.9 (CH), 130.2 (C), 130.3 (C), 131.9 (C), 143.4 (C), 148.5 (C), 148.9 (C), 150.1 (C), 150.5 (C), 154.2 (C=O).

Ms (*m/z*, %): 439 (M^+, 15), 100 (100). Anal. Calcd for $C_{25}H_{29}NO_6$: C, 68.32; H, 6.65; N, 3.19. Found: C, 68.09; H, 6.53; N, 3.36.

***N,N*-Diethyl-6-(1′-hydroxy-6′,7′-dimethoxy-2′-naphthyl)-2,3-dimethoxybenzamide (13d).** A solution of LDA in THF (1.14 mmol) was added dropwise to a solution of urethane **13c** (0.2 g, 0.45 mmol) in dry THF (1.5 mL) kept at −78°C with an acetone/dry ice bath. The resulting mixture was first stirred at −78°C for 30 min, then at rt for 1 h and finally at 80°C for 15 h. The THF was evaporated off and the residue suspended in water. After extraction with Et_2O (3×75 mL), the pooled organic layers were dried, filtered and concentrated in vacuo, and the resulting residue was purified by flash column chromatography (6:4 EtOAc/cyclohexane) to give compound **13d** (82 mg, 41% yield) as a yellow solid, mp 186–194°C (Et_2O, decomposition). IR (ν, cm^{-1}, NaCl): 3417 (–OH), 1708 (C=O). ^1H NMR (δ, ppm): 0.79–0.92 (m, 6H, 2×–CH_3), 2.98–3.08 (m, 2H, –CH_2–), 3.11–3.45 (m, 2H, –CH_2–), 3.91 (s, 6H, 2×–OCH_3), 3.98 (s, 3H, –OCH_3), 4.01 (s, 3H, –OCH_3), 6.99 (s, 2H, 2×Ar–H), 7.03 (d, *J*=8.5 Hz, 1H, Ar–H), 7.06 (s, 1H, Ar–H), 7.25 (d, *J*=8.5 Hz, 1H, Ar–H), 7.72 (s, 1H, Ar–H), 8.65 (bs, 1H, –OH). ^{13}C NMR (δ, ppm): 11.7 (CH_3), 13.5 (CH_3), 39.1 (CH_2), 43.1 (CH_2), 55.8 (–OCH_3), 55.9 (2×–OCH_3), 61.6 (–OCH_3), 102.7 (CH), 105.8 (CH), 113.1 (CH), 118.7 (CH), 121.5 (C), 122.5 (C), 126.7 (CH), 127.7 (CH), 129.5 (C), 130.4 (C), 131.6 (C), 144.0 (C), 148.9 (C), 149.2 (C), 149.9 (C), 151.8 (C), 169.9 (C=O). Ms (*m/z*, %): 439 (M^+, 2.5), 366 (100).

2,3,7,8-Tetramethoxy-6*H*-dibenzo[*c,h*]chroman-6-one (2b). A solution of compound **13d** (115 mg, 0.26 mmol) in AcOH (5 mL) was refluxed under a calcium chloride tube for 6 h. The reaction mixture was then concentrated in vacuo and the resulting residue was crystallized from Et_2O to give compound 15 (74 mg, 77% yield) as a solid, mp 218–220°C. IR (ν, cm^{-1}, NaCl): 1732 (C=O). ^1H NMR (δ, ppm): 3.98 (s, 3H, –OCH_3), 4.03 (s, 6H, 2×–OCH_3), 4.10 (s, 3H, –OCH_3) 7.12 (s, 1H, Ar–H), 7.42 (d, *J*=9 Hz, 1H, Ar–H), 7.55 (d, *J*=8.8 Hz, 1H, Ar–H), 7.76 (s, 1H, Ar–H), 7.82 (d, *J*=8.8 Hz, 1H, Ar–H), 7.87 (d, *J*=9 Hz, 1H, Ar–H). ^{13}C NMR (δ, ppm): 55.8 (–OCH_3), 56.3 (–OCH_3), 56.4 (–OCH_3), 61.4 (–OCH_3), 100.9 (CH), 106.4 (CH), 111.5 (C), 115.1 (C), 117.4 (CH), 117.6 (CH), 118.8 (C), 119.5 (CH), 122.5 (CH), 129.8 (2×C), 145.4 (C), 150.1 (C), 150.5 (C), 151.5 (C), 152.9 (C), 157.8 (C=O). Ms (*m/z*, %): 366 (M^+, 100). Anal. Calcd for $C_{21}H_{18}O_6$: C, 68.85; H, 4.95. Found: C, 69.03; H, 4.79.

***N,N*-Diethyl-6-(6′,7′-dimethoxy-1′,4′-dioxo-1′,4′-dihydro-2′-naphthalenyl)-2,3-dimethoxy-benzamide (6g).** A solution of Fremy's salt (229 mg, 0.85 mmol) and KH_2PO_4 (23.5 mg, 0.13 mmol) in water (5 mL) was added to a solution of compound **13d** (75 mg, 0.17 mmol) in acetone (3.5 mL) and the resulting mixture was stirred at rt for 9 h. The acetone was then evaporated in vacuo, the precipitate was filtered out and the filtrate was extracted with Cl_2CH_2 (3×25 mL). The pooled organic layers were dried, filtered and concentrated in vacuo to give a solid identical to the filtration residue. Crystallization of the pooled solids from MeOH gave compound **6g** (68 mg, 88% yield) as an orange solid, mp 231–232°C. IR (ν, cm^{-1}, NaCl): 1660 (C=O). ^1H NMR (δ, ppm): 0.96–1.07 (m, 6H, 2×–CH_3), 3.07–3.21 (m, 4 H, 2×–CH_2–), 3.82 (s, 3H, –OCH_3), 3.90 (s, 3H, –OCH_3), 3.97 (s, 3H, –OCH_3), 3.98 (s, 3H, –OCH_3), 6.94 (s, 1H, Ar–H), 7.05 (d, *J*=8.4 Hz, 1H, Ar–H), 7.06 (d, *J*=8.4 Hz, 1H, Ar–H), 7.44 (s, 2H, 2×Ar–H). ^{13}C NMR (δ, ppm): 12.3 (–CH_3), 13.5 (–CH_3), 38.3 (–CH_2–), 43.1 (–CH_2–), 55.9 (–OCH_3), 56.4 (–OCH_3), 56.5 (–OCH_3), 61.6 (–OCH_3), 107.5 (CH), 108.3 (CH), 111.9 (CH), 124.2 (C), 126.8 (CH), 127.1 (C), 132.2 (C), 135.9 (CH), 145.2 (C), 146.8 (C), 153.4 (2×C), 153.6 (2×C), 166.5 (C=O), 183.8 (C=O), 184.4 (C=O). Ms (*m/z*, %): 453 (M^+, 5), 382 (100). Anal. Calcd for $C_{25}H_{27}NO_7$: C, 66.21; H, 6.00; N, 3.09. Found: C, 66.38; H, 6.15, N, 3.31.

***N,N*-Diethyl-6-(3′-hydroxy-6′,7′-dimethoxy-1′,4′-dioxo-1′,4′-dihydro-2′-naphthalenyl)-2,3-dimethoxybenzamide (6h).** A solution of compound **6d** (67 mg, 1.48 mmol) and NaOH (325 mg, 8.13 mmol) was transformed into compound **6h** (79%) following the same procedure as for **6b**, mp 227–235°C (MeOH, decomposition). IR (ν, cm^{-1}, NaCl): 3391 (–OH), 1660 (C=O). ^1H NMR (δ, ppm): 0.83–1.09 (m, 6H, 2×–CH_3), 3.11–3.35 (m, 4H, 2×–CH_2–), 3.84–3.85 (bs, 3H, –OCH_3), 3.90–3.92 (bs, 3H, –OCH_3), 3.99 (s, 3H, –OCH_3), 4.00 (bs, 3H, –OCH_3), 6.98 (s, 1H, Ar–H), 6.99 (s, 1H, Ar–H), 7.49 (s, 2H, 2×Ar–H). ^{13}C NMR (δ, ppm, CD_3OD): 12.6 (CH_3), 13.6 (CH_3), 39.3 (CH_2), 44.3 (CH_2), 56.4 (–OCH_3), 56.7 (–OCH_3), 56.8 (–OCH_3), 61.7 (–OCH_3), 109.4 (CH), 114.3 (CH), 125.8 (C), 126.8 (C), 127.1 (C), 129.6 (CH), 129.9 (CH), 131.2 (C), 132.9 (C), 146.0 (C), 152.8 (2×C), 153.0 (C), 156.3 (C), 171.0 (C=O), 185.0 (C=O), 190.0 (C=O). Ms (*m/z*, %): 469 (M^+, 12), 368 (100).

3,4,9,10-Tetramethoxy-7,12-dihydro-5*H*-dibenzo[c,g]-chroman-5,7,12-trione (1b). A solution of compound **6h** (48 mg, 0.1 mmol) in AcOH (4 mL) was refluxed under a calcium chloride tube for 6 h. The reaction mixture was then concentrated in vacuo and the residue was precipitated from Cl_2CH_2 as amorphous solid **1b** (33 mg, 82% yield). IR (ν, cm^{-1}, KBr): 1753 (C=O), 1667 (C=O). ^{13}C NMR (δ, ppm, CF_3CO_2D): 54.7 (–OCH_3), 54.9 (–OCH_3), 55.0 (–OCH_3), 60.8 (–OCH_3), 107.5 (CH), 108.5 (CH), 116.0 (C), 120.2 (CH), 122.0 (C), 123.0 (C), 126.2 (CH), 127.1 (C), 147.0 (C), 148.0 (C), 152.7 (C), 154.0 (C), 154.9 (C), 161.5 (C), 177.0 (C=O), 184.0 (2×C=O). Ms (*m/z*, %): 396 (M^+, 100). HRMS Calcd for $C_{21}H_{16}O_8$: 396.0845. Found: 396.0839.

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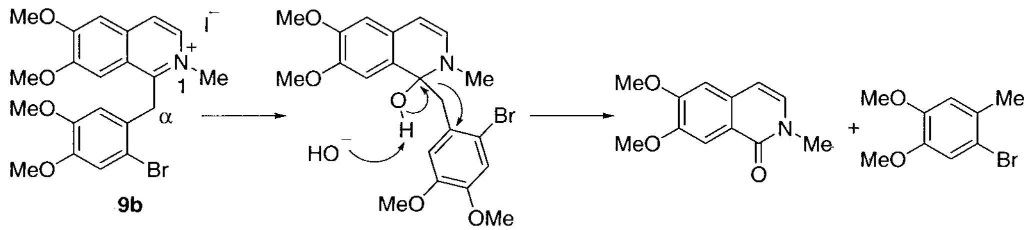

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