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Short synthesis of functionalized pentalongin derivatives using pyridinium ylid chemistry

Pieter Claes, Jan Jacobs, Sven Claessens, Norbert De Kimpe *

Department of Organic Chemistry, Faculty of Bioscience Engineering, Ghent University, Coupure Links 653, B-9000 Ghent, Belgium

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ABSTRACT

3-Substituted pentalongin derivatives possessing an acetal function at C-1 were synthesized by cyclization of acylmethylnaphthoquinones. The latter naphthoquinones were prepared starting from 2-dioxolanylnaphthoquinone by means of both a stoichiometric and a catalytic method deploying various pyridinium ylids.

1. Introduction

Natural products are an important source of lead compounds toward drug discovery. For instance, anticancer drugs, such as daunorubicin, doxorubicin, mitomycin, mitoxantrones, and saintopin are all quinones derived from natural products or are natural products themselves. Pentalongin **1** was isolated from the roots of the Central East-African woody herb *Pentas longiflora* Oliv.[1] The roots of this herb are used in the Kenyan traditional medicine as a cure against tapeworm, itchy rash, and acne. A decoction of the roots is mixed with milk and used as a cure for malaria, but causes acute diarrhea and acts as a purgative. In Rwanda the plant is known as Isagara and it is mixed with butter as an ointment to treat scabies and the skin disease Pityriasis versicolor.[2] Multiple syntheses are known for this natural product applying a lot of different strategies to construct the heterocyclic pyran ring.[3] In previous synthetic studies, Aldersley et al. and more recently Kobayashi et al. synthesized 3-substituted pentalongin derivatives **2** by a pyridinium ylid and an enamine strategy, respectively.[4,5] An important factor influencing drug distribution is the octanol/water partition coefficient (log *P*). In order to have a broad range of compounds, having different log *P* values, we envisaged the synthesis of 3-substituted benzo[*g*]chromenediones **3** bearing an acetal function at C-1 (Fig. 1). This acetal can serve as a point of attachment for further functionalization, such as the addition of a sugar side chain to alter the solubility. Table 1 gives an overview of the calculated

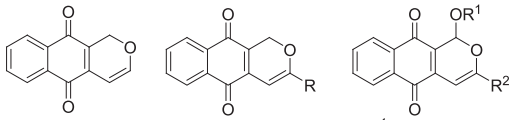
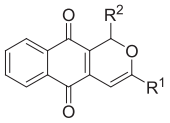


Figure 1. Proposed elaboration of the basic scaffold of pentalongin.

Table 1
Calculated log *P* values for the elaboration of the pentalongin basic skeleton using ChemDraw Ultra 7.0 (σ=0.43–0.83 log *P* units)



R^1	R^2			
	OCH_2CH_2OH	OH	H	OMe
Me	−0.07	0.08	0.16	0.44
H	0.30	0.46	**0.53**	0.82
i-Pr	0.81	0.97	1.04	1.33
t-Bu	1.35	1.51	1.58	1.87
2,5-$(MeO)_2C_6H_3$	1.75	1.90	1.98	2.26
4-$MeOC_6H_4$	1.87	2.03	2.10	2.39
C_6H_5	2.00	2.15	2.23	2.52
4-FC_6H_4	2.16	2.31	2.39	2.67
4-MeC_6H_4	2.49	2.64	2.72	3.00
4-ClC_6H_4	2.56	2.71	2.79	3.07
4-BrC_6H_4	2.83	2.98	3.06	3.35

* Corresponding author. Tel.: +32 9 264 59 51; fax: +32 9 264 62 43; e-mail address: norbert.dekimpe@UGent.be (N. De Kimpe).

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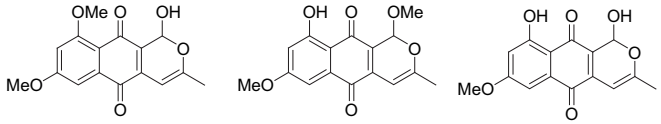
log *P* values of our target compounds using ChemDraw Ultra 7.0 (σ=0.43–0.83 log *P* units). Pentalongin has a log *P* value of 0.53. The hydroxyethoxy and the hydroxyl substituents at C-1 lower the log *P*, while a methoxy group at C-1 increases the log *P*. Bulky substituents at C-3 increase the log *P*.

Moreover, these benzo[*g*]chromenediones with an acetal function at C-1 are also found in nature. 1-Hydroxydehydroherbarin **4** was isolated from a *Corynespora* species occurring in the cavern beard lichen *Usnea cavernosa*.[6] Ascomycone A **5** and B **6** were isolated from an unidentified Ascomycete and exhibit activity against the phytopathogens *Magnaporthe grisea* (rice blast fungus) and *Fusarium graminearum* (wheat head blight fungus) (Fig. 2).[7]



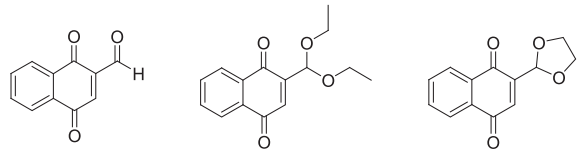
4 1-hydroxydehydroherbarin **5** ascomycone A **6** ascomycone B

Figure 2. Benzo[*g*]chomenedione natural products bearing an acetal function at C-1.

2. Results and discussion

Pyridinium ylids are versatile tools in organic synthesis, giving rise to different heterocycles, for instance pyridines, furans, azepines, etc.[8] More specifically, in quinone chemistry, pyridinium ylids proved to be very useful to introduce acetonyl side chains onto quinone moieties.[5] After introduction of the acetonyl side chain, further elaboration toward the natural product isagarin,[9] anthraquinones, pyranonaphthoquinones,[5,10] 2-azaanthraquinones,[11] and indolizines[12] has been reported.

Initially, three quinones were considered as suitable Michael acceptors for pyridinium ylid chemistry, namely 2-formyl-1,4-naphthoquinone **7**, 2-diethoxymethyl-1,4-naphthoquinone **8**, and 2-(1,3-dioxolan-2-yl)-1,4-naphthoquinone **9** (Fig. 3). 2-Formyl-1,4-naphthoquinone **7** was prepared by means of an oxidative demethylation of 1,4-dimethoxy-2-formylnaphthalene **10** with cerium (IV) ammonium nitrate (CAN). However, this aldehyde **7** was not a suitable candidate for further elaboration since it decomposed within minutes after synthesis. Reports in literature confirm this observation and solve the instability issue by in situ generation of 2-formyl-1,4-naphthoquinone **7**.[13] However, this in situ protocol did not produce satisfying results under the conditions presented in this report. Therefore, 2-diethoxymethyl-1,4-naphthoquinone **8** was evaluated as a potential starting material, but this quinone **8** was an oily substance, very prone to hydrolysis. Finally, 2-(1,3-dioxolan-2-yl)-1,4-naphthoquinone **9** was the quinone of choice since it is a powder, which, upon storage under nitrogen, is stable



7 **8** **9**

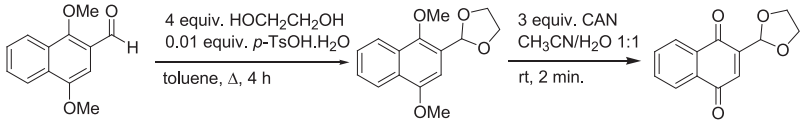
Figure 3. Proposed starting materials for the synthesis of pentalongin derivatives **3**.

for over a month. The synthesis of 2-(1,3-dioxolan-2-yl)-1,4-naphthoquinone **9** was achieved starting from the acetal formation under Dean–Stark conditions of the known 1,4-dimethoxy-2-formylnaphthalene **10**,[14] resulting in 2-(1,3-dioxolan-2-yl)-1,4-dimethoxynaphthalene **11** in a 74% yield. Two reports on the oxidation of 2-(1,3-dioxolan-2-yl)-1,4-dimethoxynaphthalene **11** toward 2-(1,3-dioxolan-2-yl)-1,4-naphthoquinone **9** with silver(II) dipicolinate,[15] silver(I) oxide,[16] cobalt(III) fluoride,[16] and CAN[16] as oxidants are known in the literature. We herein report a procedure using CAN minimizing the reaction time to two minutes in order to reduce acetal hydrolysis to obtain 2-(1,3-dioxolan-2-yl)-1,4-naphthoquinone **9** in 86% yield (Scheme 1).

Next, 2-(1,3-dioxolan-2-yl)-1,4-naphthoquinone **9** was reacted with a wide variety of pyridinium ylids, which were generated in situ by means of deprotonation of the corresponding pyridinium salts **12** with triethylamine. Interestingly, the addition of 1 equiv of triethylamine to the reaction mixture led to the formation of acylmethyl substituted quinones **13** together with trace amounts of 1-hydroxyethoxy-pyranonaphthoquinones **14**. Addition of 1.5 equiv of triethylamine led to full conversion of the acylmethyl substituted naphthoquinones **13** to the 1-(hydroxyethoxy)pyranonaphthoquinones **14** in moderate to good yields (Scheme 2). In case of acylmethyl substituted naphthoquinones **13f** and **13g**, ring closure failed under the given reaction conditions. However, using an excess of Na_2CO_3 in CH_3CN at 60 °C, ring closure of acylmethyl substituted naphthoquinones **13f** and **13g** could finally be performed (Scheme 2).

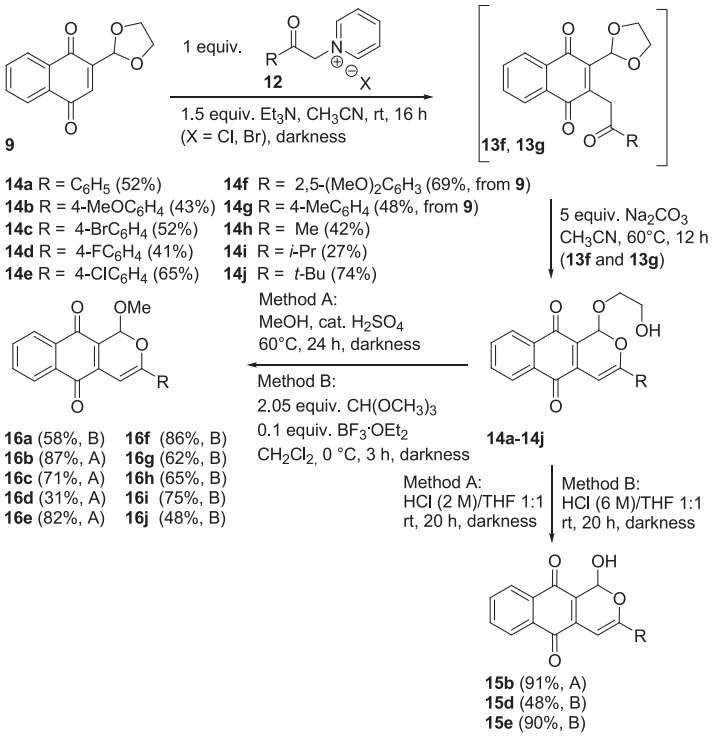
Since all 1-(hydroxyethoxy)pyranonaphthoquinones **14** showed moderate sensitivity to light, all reactions were shielded from daylight by means of aluminum foil. 1-Hydroxyethoxypyranonaphthoquinones **14** could be deprotected under acidic conditions (aqueous HCl in HPLC grade solvent or acetic acid/H_2O 1:1) to yield the target 1-hydroxypyranonaphthoquinones **15**. Nevertheless, these compounds were highly unstable and decomposed readily upon exposure to light. This decomposition involves more than likely radicals, since it is known that quinones are prone to radical reactions.[17,18] As a result, only three 1-hydroxypyranonaphthoquinones **15** could be isolated in 48–91% yield (Scheme 2). Therefore, it was decided to prepare the 1-methoxypyranonaphthoquinones **16** as an alternative, more stable target. These derivatives were initially prepared by means of an acid catalyzed acetalisation of 1-(hydroxyethoxy)pyranonaphthoquinones **14** in methanol. However, this method only provided 1-methoxypyranonaphthoquinones **16b–e** in 31–87% yield (Scheme 2). For all the other derivatives, a boron(III) fluoride catalyzed acetalisation with trimethyl orthoformate furnished the target compounds **16** in moderate to good yields (Scheme 2). In contrast to 1-hydroxypyranonaphthoquinones **15**, the corresponding 1-methoxy analogues proved to be easy to handle crystalline compounds, which were only slightly sensitive to light. Therefore, these compounds are ideal intermediates for further functionalisation at C-1.

Recently, a catalytic version of pyridinium ylid chemistry was published by Yadav and Garima to synthesize aziridines.[19] In this paper, a one-pot reaction of phenacyl bromides and *N*-tosyl imines catalyzed by 1,4-diazabicyclo[2.2.2]octane (DABCO), yielding the corresponding aziridines is described. Benefits of this method are the catalytic use of organic base and the in situ preparation of pyridinium salts as well as the corresponding ylids. However, in our case, the use of DABCO as the catalytic tertiary amine under



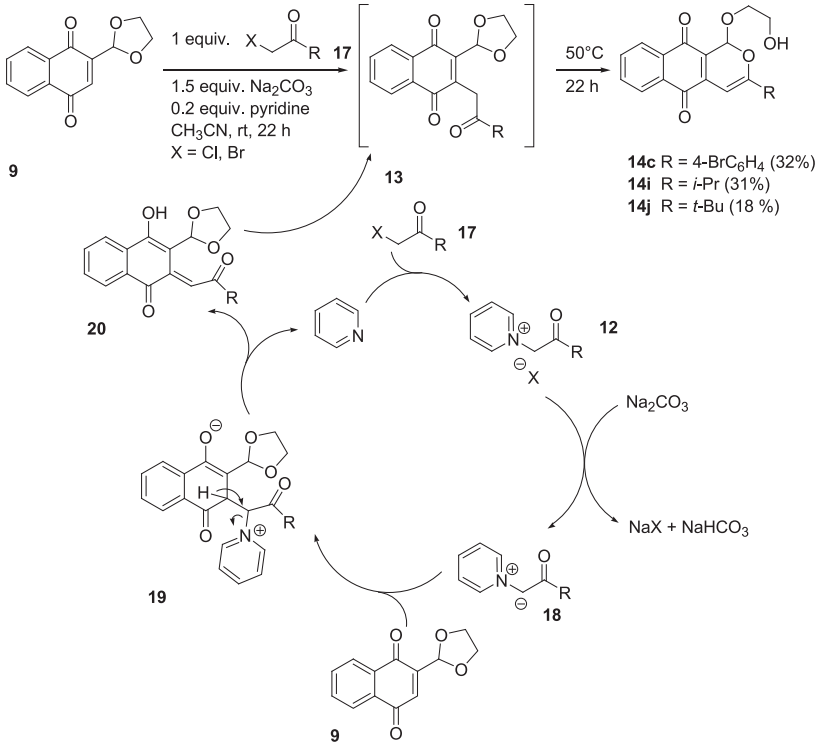
10 **11** (74%) **9** (86%)

Scheme 1.



Scheme 2.

the described conditions with 1-bromo-3-methylbutan-2-one **17i** and 2-(1,3-dioxolan-2-yl)-1,4-naphthoquinone **9** gave no reaction, most probably due to the formation of a charge transfer complex of the quinone moiety with DABCO. Repeating the same reaction with a catalytic amount of pyridine instead of DABCO yielded 1-(2-hydroxyethoxy)-3-isopropyl-1*H*-benzo[*g*]isochromene-5,10-dione **14i** in 31% yield. In the optimal reaction conditions, 1.5 equiv Na_2CO_3, 1 equiv α-halogenated ketone **17**, 1 equiv 2-(1,3-dioxolan-2-yl)-1,4-naphthoquinone **9**, and 0.2 equiv pyridine were reacted overnight at room temperature to form the acylmethyl substituted quinone **13** and subsequently heated at 60 °C for 20 h to induce cyclization toward 1-(hydroxyethoxy)pyranonaphthoquinones **14** (Scheme 3). The catalytic version of the reaction proved to give similar results in the synthesis of 1-(hydroxyethoxy)pyranonaphthoquinones **14** in comparison to the equimolar method (Table 2).



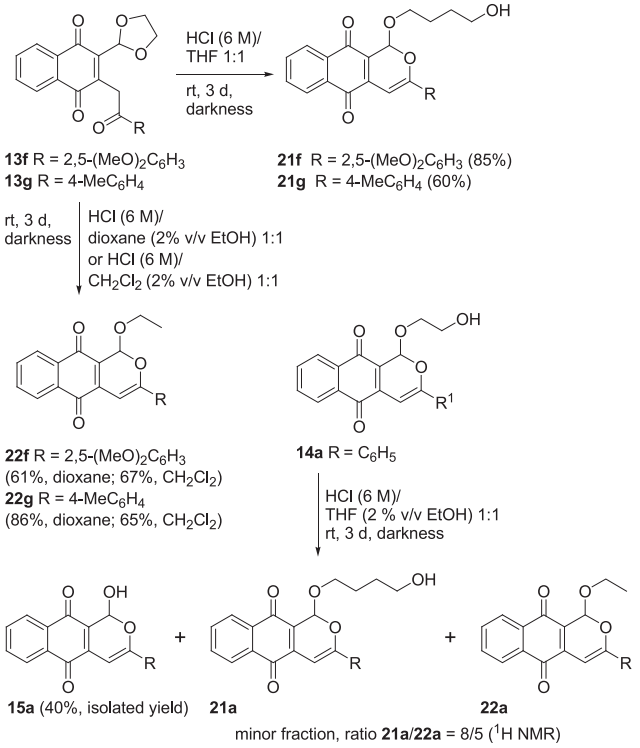
Scheme 3. Catalytic version of the synthesis of 1-(hydroxyethoxy)pyranonaphthoquinones **14**.

Table 2
Comparison between the equimolar and catalytical synthesis of 1-(hydroxyethoxy) pyranonaphthoquinones **14**

Compound	R	Equimolar method (%)		Catalytic method (%)	
		Crude[c]	Isolated Yield	Crude[c]	Isolated yield
14a	C_6H_5	57	52	24	—
14b	4-$MeOC_6H_4$	47	43	72	—
14c	4-BrC_6H_4	55	52	53	32
14d	4-FC_6H_4	44	41	77	—
14e	4-ClC_6H_4	68	65	57	—
14f	4-MeC_6H_4	70[b]	69	52	—
14g	2,5-$(MeO)_2C_6H_3$	72[b]	48	57	—
14h	Me	64	42	70[a]	—
14i	*i*-Pr	51	27	60	31
14j	*t*-Bu	81	74	42[a]	18

[a] Notes: for X=Cl, the reaction only occurred upon the addition of 10 mol % of KI and heating for 2 days at 60 °C.
[b] Reaction under the given reaction conditions yielded a mixture of **13** and **14** and the reaction mixture was heated at 50 °C for 12 h in the presence of 5 equiv Na_2CO_3 to obtain complete conversion.
[c] Occurrence in the reaction crude after workup as determined by means of LC.

During the synthesis of 1-(hydroxyethoxy)pyranonaphthoquinones **14**, some remarkable side reactions were observed. Attempts to ring close acylmethyl substituted naphthoquinones **13f** and **13g** using HCl (6 M)/THF, yielded 1-(4-hydroxybutoxy)pyranonaphthoquinones **21** due to ring opening of THF in acidic medium. Upon the use of HCl (6 M)/dioxane or CH_2Cl_2, attempts to ring close acylmethyl substituted naphthoquinones **13f** and **13g** yielded 1-ethoxypyranonaphthoquinones **22**, ascribed to the presence of minor solvent impurities of ethanol in reagent grade dichloromethane and dioxane (Scheme 4). Moreover, upon deprotection of 1-hydroxyethoxypyranonaphthoquinone **14a** by means of HCl (6 M)/THF, both phenomenons were observed (Scheme 4) and, as a consequence, only HPLC grade solvents were used to avoid such artifacts.



Scheme 4.

3. Conclusion

A new methodology toward the synthesis of substituted pentalongin derivatives bearing an acetal function at C-1 is described. This methodology is based on the addition of pyridinium ylids to introduce the necessary acylmethyl side chain. Both a catalytic and a stoichiometric version of this reaction were investigated. 1-(Hydroxyethoxy)pyranonaphthoquinones **14** proved to be key intermediates for the synthesis of 1-hydroxypyranonaphthoquinones **15** and 1-methoxypyranonaphthoquinones **16**.

4. Experimental section

4.1. General experimental methods

Spectroscopic data were recorded as follows: ^{1}H NMR spectra were recorded at 300 MHz, ^{13}C NMR spectra were recorded at 75 MHz and ^{19}F NMR spectra were recorded at 282 MHz. Peak assignments were performed with the aid of 2D-COSY and HSQC spectra. Mass spectra were recorded using a direct inlet system (70 eV) with a VL detector (ES, 4000 V). Elemental analyses were executed with a Perkin–Elmer Series II CHNS/O Analyzer 2400. The reported melting points are not corrected. Flash chromatography was carried out using a glass column with silica gel (particle size 0.035–0.07 mm, pore diameter ca. 6 nm). Solvent systems were determined via initial TLC analysis (silica gel). Reaction progress was monitored by means of LC-analysis. All solvents used were HPLC grade, all chemicals were used without further purification with the exception of trimethyl orthoformate, which was purified by means of a vacuum distillation. All pyridinium salts were prepared by dropwise addition of pyridine (1 equiv) to a solution of commercially available halomethylketones in anhydrous ethyl acetate. After overnight reaction the salts were filtered off, dried under high vacuum, and stored under nitrogen. 1-Bromo-3-methyl-2-butanone **17i** was not commercially available and was prepared according to a literature procedure.[20]

4.2. Synthesis of 2-(1,3-dioxolan-2-yl)-1,4-dimethoxynaphthalene 11

To a solution of 2-formyl-1,4-dimethoxynaphthalene **10** (5 g, 23.12 mmol) in toluene (50 ml), ethylene glycol (5.74 g, 92.49 mmol, 4 equiv) and *para*-toluenesulphonic acid (0.044 g; 0.23 mmol; 0.01 equiv) were added. The reaction was heated under reflux for 4 h using a Dean–Stark apparatus. Subsequently, the reaction mixture was washed once with aq satd $NaHCO_3$ (30 ml) and twice with brine (2×20 ml). Drying over $MgSO_4$ and evaporation of the solvent in vacuo yielded 2-(1,3-dioxolan-2-yl)-1,4-dimethoxynaphthalene **11**, which was sufficiently pure (97%, LC-MS) to be used in the next step without further purification.

4.2.1. 2-(1,3-Dioxolan-2-yl)-1,4-dimethoxynaphthalene ***11***. Yield 74%, mp 109.2 °C, brown crystals. ^{1}H NMR ($CDCl_3$): δ 3.97 (3H, s, OCH_3), 4.01 (3H, s, OCH_3), 4.10–4.11 (2H, m, OCH_2CH_2O), 4.24–4.26 (2H, m, OCH_2CH_2O), 6.29 (1H, s, $CH(OCH_2CH_2O)$), 6.91 (1H, s, CH-3), 7.45–7.59 (2H, m, CH-6, and CH-7), 8.07–8.09 (1H, m, CH_{Ar}), 8.07–8.09 (1H, m, CH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 55.64 (OCH_3), 63.40 (OCH_3), 65.48 (OCH_2CH_2O), 99.33 ($CH(OCH_2CH_2O)$), 100.62 (CH-3), 122.11 (CH-6 or CH-7), 122.45 (CH-6 of CH-7), 125.16 (C_{quat}), 126.24 (CH-5 of CH-8), 126.75 (CH-5 or CH-8), 127.38 (C_{quat}), 128.51 (C_{quat}), 148.97 ($COCH_3$), 152.14 ($COCH_3$). IR (cm^{-1}): ν_{max} 1371. MS (ES^+) m/z (%): 261 ($M+H^+$, 100).

4.3. Synthesis of 2-(1,3-dioxolan-2-yl)-1,4-naphthoquinone 9

2-(1,3-Dioxolan-2-yl)-1,4-dimethoxynaphthalene **11** (1.47 g, 5.63 mmol) was dissolved in CH_3CN (20 ml), and a solution of CAN

(9.26 g, 16.89 mmol, 3 equiv) in water (20 ml) was added in one portion. The reaction mixture was stirred for 2 min at room temperature and subsequently poured in a mixture of 20 ml of ethyl acetate and 20 ml of brine. The organic layer was washed with brine (20 ml) and the solvent was evaporated in vacuo, yielding the crude 2-(1,3-dioxolane-2-yl)-1,4-naphthoquinone **9**, which was sufficiently pure to be used without further purification (98%, LC-MS).

*4.3.1. 2-(1,3-Dioxolan-2-yl)-1,4-naphthoquinone **9**.* Yield 86%, mp 120.0 °C, yellow powder, spectral data in accordance with the literature.[16] ^{1}H NMR ($CDCl_3$): δ 4.08 (4H, s, OCH_2CH_2O), 6.08 (1H, s, C*H*(OCH_2CH_2O)), 7.11 (1H, s, CH-3), 7.75–7.78 (2H, m, CH-6, and CH-7), 8.16–8.22 (2H, m, CH-5, and CH-8). ^{13}C NMR ($CDCl_3$): δ 65.62 (OCH_2CH_2O), 98.23 (*C*H(OCH_2CH_2O)), 126.31 (CH_{Ar}), 126.64 (CH_{Ar}), 132.03 (C_{quat}), 134.09 (2×CH_{Ar}), 134.17 (CH-3), 138.78 (C_{quat}), 144.98 (C_{quat}), 184.48 (C=O), 185.52 (C=O). IR (cm^{-1}): ν_{max} 1662. MS (ES^+) *m*/*z* (%): 231 ($M+H^+$, 100).

4.4. Synthesis of 3-substituted 1-(2-hydroxyethoxy)-1*H*-benzo[*g*]isochromene-5,10-diones 14

4.4.1. Method A. Et_3N was added dropwise (1.31 mmol, 0.183 ml, 1.5 equiv) to a solution of 2-(1,3-dioxolan-2-yl)-1,4-naphthoquinone **9** (0.2 g, 0.873 mmol) and the desired pyridinium salt **12** (0.873 mmol; 1 equiv) in CH_3CN (2 ml). The reaction mixture was stirred for 14 h, shielded from light by means of aluminum foil, and subsequently poured in brine (8 ml). The aqueous phase was extracted with chloroform (3×4 ml). Evaporation of the solvent in vacuo yielded the product, which was further purified by means of column chromatography on silica gel (petroleum ether/ethyl acetate). 3-Acylmethyl-2-(1,3-dioxolan-2-yl)-1,4-naphthoquinones **13f** and **13g** did not cyclize spontaneously and were stirred in CH_3CN in the presence of 5 equiv of Na_2CO_3 for 12 h at 60 °C. Filtration of the solids followed by evaporation of the solvent in vacuo yielded the crude 1-(2-hydroxyethoxy)-1*H*-benzo[*g*]isochromene-5,10-diones **14f** and **14g**, which were further purified by means of column chromatography on silica gel (petroleum ether/ethyl acetate).

4.4.2. Method B. Pyridine (0.174 mmol, 19 μl, 0.2 equiv) was added dropwise to a solution of 2-(1,3-dioxolan-2-yl)-1,4-naphthoquinone **9** (0.2 g, 0.873 mmol), the desired halomethylketone **17** (0.873 mmol, 1.0 equiv), and Na_2CO_3 (1.31 mmol, 129 mg, 1.5 equiv) in CH_3CN (3.5 ml). The reaction mixture was stirred at room temperature for 22 h and subsequently heated at 60 °C for 22 h. Extraction and purification were executed as described under method A. For chloromethylketones **17h** and **17j**, KI (0.087 mmol, 14.4 mg, 0.1 equiv) was added and the reaction mixture was heated for two days at 60 °C.

The yields, which are reported below, are the ones obtained with method A.

*4.4.3. 1-(2-Hydroxyethoxy)-3-phenyl-1H-benzo[g]isochromene-5,10-dione **14a**.* Yield 52%, mp 161.1 °C, R_f 0.13 (petroleum ether/ethyl acetate 7/3), orange crystals. ^{1}H NMR ($CDCl_3$): δ 3.06 (1H, t, *J*=6.6 Hz, OH), 3.78–3.84 (2H, m, CH_2OH), 4.01–4.08 (1H, m, CH_aH_bO), 4.13–4.20 (1H, ddd, *J*=3.9 Hz, 6.6 Hz, 11.1 Hz, CH_aH_bO), 6.74 (1H, s, CH-1), 6.94 (1H, s, CH-4), 7.45–7.51 (3H, m, 3×CH_{Ar}), 7.74–7.80 (2H, m, CH-7, and CH-8), 7.86–7.92 (2H, m, 2×CH_{Ar}), 8.13–8.20 (2H, m, CH-6, and CH-9). ^{13}C NMR ($CDCl_3$): δ 62.24 (CH_2O), 70.76 (CH_2O), 93.02 (CH-4), 95.24 (CH-1), 121.91 (C_{quat}), 126.29 (2×CH_{Ar}), 126.35 (CH-6 of CH-9), 126.86 (CH-6 or CH-9), 128.92 (2×CH_{Ar}), 131.16 (CH_{Ar}), 131.91 (C_{quat}), 132.77 (C_{quat}), 133.13 (C_{quat}), 133.70 (CH-7 or CH-8), 134.44 (CH-7 or CH-8), 137.21 (C_{quat}), 159.26 (C_{quat}), 182.89 (C=O), 183.01 (C=O). IR (cm^{-1}): ν_{OH}=3483, $\nu_{C=O}$=1671, 1650, ν_{CHAr}=1545. MS (ES^+) *m*/*z* (%): 287 ($M-OCH_2CH_2OH$, 100). Anal. Calcd for $C_{21}H_{16}O_5$: C, 72.41, H, 4.63, obtained: C, 72.26, H, 4.29.

*4.4.4. 1-(2-Hydroxyethoxy)-3-(4-methoxyphenyl)-1H-benzo[g]isochromene-5,10-dione **14b**.* Yield 43%, mp 223.7 °C, R_f 0.10 (petroleum ether/ethyl acetate 4/1), red crystals. ^{1}H NMR ($CDCl_3$): δ 3.78–3.84 (2H, m, CH_2O), 3.88 (3H, s, OCH_3), 4.01–4.08 (1H, m, CH_aH_bO), 4.13–4.20 (1H, m, CH_aH_bO), 6.72 (1H, s, CH-1), 6.83 (1H, s, CH-4), 6.99 (2H, d, *J*=8.8 Hz, 2×CH_{Ar}), 7.70–7.86 (2H, m, CH-7, and CH-8), 7.86 (2H, d, *J*=8,8 Hz, 2×CH_{Ar}), 8.05–8.19 (2H, m, CH-6, and CH-9). ^{13}C NMR ($CDCl_3$): δ 55.85 (OCH_3); 70.65 (2×CH_2), 91.57 (CH-4), 95.37 (CH-1), 114.37 (2×CH_{Ar}), 120.90 (C_{quat}), 125.68 (C_{quat}), 126.31 (CH-6 or CH-9), 126.81 (CH-6 of CH-9), 128.12 (2×CH_{Ar}), 131.96 (C_{quat}), 132.90 (C_{quat}), 133.51 (CH-7 or CH-8), 134.40 (CH-7 or CH-8), 137.56 (C_{quat}), 159.52 (C_{quat}), 162.19 (C_{quat}), 182.69 (C=O), 183.24 (C=O). IR (cm^{-1}): ν_{OH}=3746, $\nu_{C=O}$=1671, 1647, ν_{CHAr}=1507. MS (ES^-) *m*/*z* (%): 333 ($M-H^+$, 100). Anal. Calcd for $C_{22}H_{18}O_6$: C, 69.83, H, 4.79, obtained: C, 70.04, H, 4.91.

*4.4.5. 3-(4-Bromophenyl)-1-(2-hydroxyethoxy)-1H-benzo[g]isochromene-5,10-dione **14c**.* Yield 52%, mp 187.5 °C, R_f 0.10 (petroleum ether/ethyl acetate 7:3), red crystals. ^{1}H NMR ($CDCl_3$): δ 3.09 (1H, br s, CH_2OH), 3.67–3.81 (2H, m, CH_2O), 3.99–4.06 (1H, m, CH_aCH_bO), 4.10–4.17 (1H, m, CH_aCH_bO), 6.68 (1H, s, CH-1), 6.89 (1H, s, CH-4), 7.59 (2H, d, *J*=8.3 Hz, 2×CH_{Ar}), 7.71 (2H, d, *J*=8.3 Hz, 2×CH_{Ar}), 7.71–7.83 (2H, m, 2×CH_{Ar}), 8.10–8.18 (2H, m, 2×CH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 62.20 (CH_2O), 70.85 (CH_2O), 93. 31 (CH-4), 95.25 (CH-1), 122.26 (C_{quat}), 125.68 (C_{quat}), 126.38 (CH_{Ar}), 126.89 (CH_{Ar}), 127.64 (2×CH_{Ar}), 131.82 (C_{quat}), 132.02 (C_{quat}), 132.15 (2×CH_{Ar}), 132.69 (C_{quat}), 133.77 (CH_{Ar}), 134.49 (CH_{Ar}), 136.90 (C_{quat}), 157.97 (C_{quat}), 182.81 (2×C=O). IR (cm^{-1}): ν_{OH}=3472, $\nu_{C=O}$=1673, 1649, ν_{CHAr}=1543, 1484, ν_{C-O}=1270, 1306. MS (ES^-) *m*/*z* (%): 425/427 ($M-H^+$, 100/98). Anal. Calcd for $C_{21}H_{15}BrO_5$: C, 59.04, H, 3.54, obtained: C, 59.35, H, 3.26.

*4.4.6. 3-(4-Fluorophenyl)-1-(2-hydroxyethoxy)-1H-benzo[g]isochromene-5,10-dione **14d**.* Yield 41%, mp 136.1 °C, R_f 0.16 (petroleum ether/ethyl acetate 7/3), red crystals. ^{1}H NMR ($CDCl_3$): δ 3.78–3.84 (2H, m, CH_2OH), 4.01–4.06 (1H, m, $CH_aH_bCH_2OH$), 4.12–4.20 (1H, m, C$H_aH_bCH_2OH$), 6.72 (1H, s, CH-1), 6.87 (1H, s, CH-4), 7.16 (2H, m, 2×CH_{Ar}), 7.70–7.78 (2H, m, CH-7, and CH-8), 7.82–7.93 (2H, m, 2×CH_{Ar}), 8.12–8.21 (2H, m, CH-6, and CH-9). ^{13}C NMR ($CDCl_3$): 62.23 (CH_2OH), 70.79 (CH_2CH_2OH), 92.73 (CH-4), 95.33 (CH-1), 116.12 (2×CH_{Ar}, J_{C-F}=21.9 Hz), 121.85 (C_{quat}), 126.38 (CH-6 or CH-9), 126.89 (CH-6 or CH-9), 128.43 (2×CH_{Ar}, J_{C-F}=9.2 Hz), 129.38 (C_{quat}, J_{C-F}=3.5 Hz), 131.86 (C_{quat}), 132.73 (C_{quat}), 133.74 (CH-7 or CH-8), 134.49 (CH-7 or CH-8), 137.13 (C_{quat}), 158.25 (C-3), 164.51 (C_{quat}, J_{C-F}=251.5 Hz), 182.95 (2×C=O). ^{19}F NMR ($CDCl_3$): −107.98 to −108.09 (1F, m, F). IR (cm^{-1}): ν_{OH}=3073, $\nu_{C=O}$=1672, 1650, ν_{CHAr}=1505. MS (ES^+) *m*/*z* (%): 305 ($M-OCH_2CH_2OH$, 100). Anal. Calcd for $C_{21}H_{15}FO_5$: C, 68.85, H, 4.13, obtained: C, 68.54, H, 4.24.

*4.4.7. 3-(4-Chlorophenyl)-1-(2-hydroxyethoxy)-1H-benzo[g]isochromene-5,10-dione **14e**.* Yield 65%, mp 166.9 °C, R_f 0.10 (petroleum ether/ethyl acetate 7/3), red crystals. ^{1}H NMR ($CDCl_3$): δ 3.08 (1H, br s, OH), 3.78–3.84 (2H, m, CH_2O), 4.01–4.06 (1H, m, CH_aH_bO), 4.12–4.20 (1H, m, CH_aH_bO), 6.71 (1H, s, CH-1), 6.90 (1H, s, CH-4), 7.43 (2H, d, *J*=8.8 Hz, 2×CH_{Ar}), 7.70–7.86 (2H, m, CH-7, and CH-8), 7.83 (2H, d, *J*=8.8 Hz, 2×CH_{Ar}), 8.10–8.21 (2H, m, CH-6, and CH-9). ^{13}C NMR ($CDCl_3$): δ 62.20 (CH_2OH), 70.84 (CH_2CH_2OH), 93.27 (CH-4), 95.25 (CH-1), 122.18 (C_{quat}), 126.38 (CH-6 or CH-9), 126.87 (CH-6 or CH-9), 127.47 (2×CH_{Ar}), 129.19 (2×CH_{Ar}), 131.57 (C_{quat}), 131.82 (C_{quat}), 132.69 (C_{quat}), 133.76 (CH-7 or CH-8), 134.49 (CH-7 or CH-8), 136.92 (C_{quat}), 137.22 (C_{quat}), 157.93 (C-3), 182.81 (2×C=O). IR (cm^{-1}): ν_{OH}=3446, $\nu_{C=O}$=1654, ν_{CHAr}=1490. MS (ES^+) *m*/*z* (%): 321/

323 (M−OCH_2CH_2OH, 100/32). Anal. Calcd for $C_{21}H_{15}ClO_5$: C, 65.89, H, 3.95, obtained: C, 65.63, H, 3.67.

4.4.8. 2-[2-(2,5-Dimethoxyphenyl)-2-oxoethyl]-3-(1,3-dioxolan-2-yl)-1,4-naphthoquinone ***13f***. Yield 95%, mp 153.3 °C, R_f 0.17 (petroleum ether/ethyl acetate 7/3), purple crystals. ^{1}H NMR ($CDCl_3$): δ 3.79 (3H, s, OCH_3), 3.89–4.08 (3 and 4H, s and m, OCH_3, and OCH_2CH_2O), 4.63 (2H, s, CH_2C=O), 6.16 (1H, s, C*H*(OCH_2CH_2O)), 6.95 (1H, d, J=9.1 Hz, CH-3′), 7.08 (1H, dd, J=9.1 Hz, 3.3 Hz, CH-4′), 7.37 (1H, d, J=3.3 Hz, CH-6′), 7.70–7.78 (2H, m, CH-6, and CH-7), 8.04–8.14 (2H, m, CH-5, and CH-8). ^{13}C NMR ($CDCl_3$): δ 41.22 (*C*H_2C=O), 55.89 (OCH_3), 56.24 (OCH_3), 65.31 (2×OCH_2), 98.23 (O–CH–O), 113.30 (CH-3′), 114.11 (CH-6′), 121.09 (CH-4′), 126.47 (CH-5 or CH-8), 126.75 (CH-5 or CH-8), 127.27 (C_{quat}), 131.80 (C_{quat}), 132.06 (C_{quat}), 133.80 (CH-6 or CH-7), 134.02 (CH-6 or CH-7), 139.48 (C_{quat}), 146.57 (C_{quat}), 153.56 (C_{quat}), 153.65 (C_{quat}), 184.13 (C=O), 184.83 (C=O), 196.48 (C=O). IR (cm^{-1}): $\nu_{C=O}$=1654. MS (ES^+) m/z (%): 409 (M+H^+, 100).

4.4.9. 3-(2,5-Dimethoxyphenyl)-1-(2-hydroxyethoxy)-1H-benzo[g] isochromene-5,10-dione ***14f***. Yield 69% (from **9**), mp 152.2 °C, R_f 0.25 (petroleum ether/ethyl acetate 1/1), dark red crystals. ^{1}H NMR ($CDCl_3$): δ 3.15 (1H, t, J=6.9 Hz, CH_2OH), 3.80 (2H+3H, m+s, CH_2O+CH_3O), 3.93 (3H, s, CH_3O), 3.95–4.07 (1H, m, C*H*$_a$C*H*$_b$O), 4.10–4.17 (1H, m, C*H*$_a$C*H*$_b$O), 6.67 (1H, s, CH-1), 6.93 (1H, d, J=9.4 Hz, CH-3′), 6.98 (dd, J=9.4, 2.8 Hz, CH-4′), 7.35 (1H, s, CH-4), 7.41 (1H, d, J=2.8 Hz, CH-6′), 7.70–7.80 (2H, m, 2×CH_{Ar}), 8.12–8.16 (2H, m, 2×CH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 55.91 (CH_3O), 56.23 (CH_3O), 62.27 (CH_2O), 70.72 (CH_2O), 94.81 (CH-1), 98.47 (CH-4), 112.76 (CH-3′), 114.02 (CH-6′), 117.18 (CH-4′), 121.78 (C_{quat}), 122.58 (C_{quat}), 126.25 (CH_{Ar}), 126.78 (CH_{Ar}), 132.03 (C_{quat}), 132.81 (C_{quat}), 133.59 (CH_{Ar}), 134.28 (CH_{Ar}), 137.32 (C_{quat}), 152.92 (C_{quat}), 153.45 (C_{quat}), 156.11 (C_{quat}), 182.92 (C=O), 183.18 (C=O). IR (cm^{-1}): ν_{OH}=3423, $\nu_{C=O}$=1670, 1643, ν_{CHAr}=1531, 1497, ν_{C-O}=1298. MS (ES^-) m/z (%): 407 (M−H^+, 100). Anal. Calcd for $C_{23}H_{20}O_7$: C, 67.64, H, 4.94, obtained: C, 67.41, H, 4.78.

4.4.10. 3-(1,3-Dioxolan-2-yl)-2-(2-oxo-2-(4-methylphenyl)ethyl)-1,4-naphthoquinone ***13g***. Since this compound could not be purified by recrystallization or column chromatography, it was used as such in the next step. ^{1}H NMR ($CDCl_3$): δ 2.42 (3H, s, CH_3), 3.92 (4H, m, OCH_2CH_2O), 4.60 (2H, s, CH_2C=O), 6.14 (1H, s, C*H*(OCH_2CH_2O)), 7.30 (2H, d, J=8.3 Hz, 2×CH_{Ar}), 7.72–7.78 (2H, m, CH-6, and CH-7), 7.93 (2H, d, J=8.3 Hz, 2×CH_{Ar}), 8.08–8.17 (2H, m, CH-5, and CH-8).

4.4.11. 1-(2-Hydroxyethoxy)-3-(4-methylphenyl)-1H-benzo[g]isochromene-5,10-dione ***14g***. Yield 48% (from **9**), mp 153.5 °C, R_f 0.28 (petroleum ether/ethyl acetate 4/1), red crystals. ^{1}H NMR ($CDCl_3$): δ 2.46 (3H, s, CH_3), 3.10 (1H, t, J=7.0 Hz, CH_2OH), 3.68–3.81 (2H, m, CH_2O), 3.99–4.06 (1H, m, C*H*$_a$C*H*$_b$O), 4.10–4.17 (1H, m, C*H*$_a$C*H*$_b$O), 6.71 (1H, s, CH-1), 6.89 (1H, s, CH-4), 7.27 (2H, d, J=8.3 Hz, 2×CH_{Ar}), 7.71–7.81 (2H, m, 2×CH_{Ar}), 7.77 (2H, d, J=8.3 Hz, 2×CH_{Ar}), 8.10–8.18 (2H, m, 2×CH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 21.64 (CH_3), 62.20 (CH_2O), 70.67 (CH_2O), 92.37 (CH-4), 95.21 (CH-1), 121.45 (C_{quat}), 126.26 (3×CH_{Ar}), 126.78 (CH_{Ar}), 129.64 (2×CH_{Ar}), 130.34 (C_{quat}), 131.88 (C_{quat}), 132.78 (C_{quat}), 133.53 (CH_{Ar}), 134.34 (CH_{Ar}), 137.30 (C_{quat}), 141.76 (C_{quat}), 182.69 (C=O), 183.03 (C=O). IR (cm^{-1}): ν_{OH}=3447, $\nu_{C=O}$=1674, 1646, ν_{CHAr}=1540, 1507, ν_{C-O}=1270. MS (ES^+) m/z (%): 301 (M−$HOCH_2CH_2O$, 100). Anal. Calcd for $C_{22}H_{18}O_5$: C, 72.92, H, 5.01, obtained: C, 72.66, H, 4.80.

4.4.12. 1-(2-Hydroxyethoxy)-3-methyl-1H-benzo[g]isochromene-5,10-dione ***14h***. Yield 42%, mp 108.6 °C, R_f 0.10 (petroleum ether/ethyl acetate 7/3), brown crystals. ^{1}H NMR ($CDCl_3$): δ 2.17 (3H, s, CH_3), 3.17 (1H, br s, OH), 3.68–3.83 (2H, m, CH_2OH), 3.93–4.06 (2H, m, CH_2CH_2OH), 6.13 (1H, s, CH-1), 6.50 (1H, s, CH-4), 7.68–7.77 (2H, m, CH-7, and CH-8), 8.07–8.11 (2H, m, CH-6, and CH-9). ^{13}C NMR ($CDCl_3$): δ 21.05 (CH_3), 62.13 (CH_2O), 70.65 (CH_2O), 94.10 (CH-4), 95.04 (CH-1), 120.83 (C_{quat}), 126.16 (CH-6 or CH-9), 126.62 (CH-6 or CH-9), 131.69 (C_{quat}), 132.48 (C_{quat}), 133.52 (CH-7 or CH-8), 134.22 (CH-7 or CH-8), 136.90 (C_{quat}), 162.60 (C_{quat}); 182.91 (C=O), 182.96 (C=O). IR (cm^{-1}): ν_{OH}=3461, $\nu_{C=O}$=1671, 1656, ν_{CHAr}=1556. MS (ES^+) m/z (%): 309 (M+Na^+, 100). Anal. Calcd for $C_{16}H_{14}O_5$: C, 67.13, H, 4.93, obtained: C, 67.38, H, 5.03.

4.4.13. 1-(2-Hydroxyethoxy)-3-isopropyl-1H-benzo[g]isochromene-5,10-dione ***14i***. Yield 31%, mp 89.6 °C, R_f 0.13 (petroleum ether/ethyl acetate 7/3), brown crystals. ^{1}H NMR ($CDCl_3$): δ 1.24 (6H, d, J=7.2 Hz, CH(C*H*$_3$)$_2$), 2.67 (1H, septet, J=7.2 Hz, C*H*(CH_3)$_2$), 3.10 (1H, m, CH_2OH), 3.80 (2H, m, CH_2O), 3.92–3.99 (1H, m, C*H*$_a$CH$_b$O), 4.02–4.14 (1H, m, CH$_a$C*H*$_b$O), 6.17 (1H, s, CH-4), 6.53 (1H, s, CH-1), 7.70–7.89 (2H, m, 2×CH_{Ar}), 8.10–8.14 (2H, m, 2×CH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 19.96 (CH(*C*H$_3$)$_2$), 20.21 (CH(*C*H$_3$)$_2$), 33.71 (*C*H(CH_3)$_2$), 62.17 (CH_2O), 70.61 (CH_2O), 91.40 (CH-4), 94.82 (CH-1), 121.22 (C_q), 126.20 (CH_{Ar}), 126.69 (CH_{Ar}), 131.82 (C_q), 132.55 (C_q), 133.56 (CH_{Ar}), 134.26 (CH_{Ar}), 137.13 (C_q), 170.65 (C_q), 183.01 (C=O), 183.15 (C=O). IR (cm^{-1}): ν_{OH}=3542, $\nu_{C=O}$=1669, 1652, ν_{CHAr}=1582, 1560, ν_{C-O}=1297. MS (ES^-) m/z (%): 313 (M−H^+, 100). Anal. Calcd for $C_{18}H_{18}O_5$: C, 68.78; H, 5.77, obtained: C, 68.49, H, 5.51.

4.4.14. 3-tert-Butyl-1-(2-hydroxyethoxy)-1H-benzo[g]isochromene-5,10-dione ***14j***. Yield 74%, mp 83.9, R_f 0.39 (petroleum ether/ethyl acetate 4/1), orange crystals. ^{1}H NMR ($CDCl_3$): δ 1.27 (9H, s, C(CH_3)$_3$), 4.00–4.03 (2H, m, CH_2OH), 4.11–4.13 (2H, m, CH_2CH_2OH), 6.26 (1H, s, CH- 4), 6.74 (1H, s, CH-1), 7.72–7.74 (2H, m, CH-7, and CH-8), 8.10–8.13 (2H, m, CH-6, and CH-9). ^{13}C NMR ($CDCl_3$): δ 27.86 (C(*C*H$_3$)$_3$), 36.91 (*C*(CH$_3$)$_3$), 62.23 (CH_2O), 70.61 (CH_2O), 90.47 (CH-4), 94.79 (CH-1), 121.22 (C_{quat}), 126.23 (CH_{Ar}), 126.75 (CH_{Ar}), 131.91 (C_{quat}), 132.58 (C_{quat}), 133.61 (CH_{Ar}), 134.28 (CH_{Ar}), 137.24 (C_{quat}), 172.68 (C_{quat}), 183.12 (C=O), 183.27 (C=O). IR (cm^{-1}): ν_{OH}=3466, $\nu_{C=O}$=1666, 1651, ν_{CHAr}=1582, 1552, ν_{C-O}=1267. MS (ES^-) m/z (%): 327 (M−H^+, 100). Anal. Calcd for $C_{19}H_{20}O_5$: C, 69.50; H, 6.14, obtained: C, 69.16, H, 5.78.

4.5. Synthesis of 3-aryl-1-hydroxy-1*H*-benzo[*g*]isochromene-5,10-diones 15a, 15d, and 15e

3-(4-Halophenyl)-1-(2-hydroxyethoxy)-1*H*-benzo[*g*]isochromene-5,10-diones**14a**, **14d**, and **14e** (2.18 mmol) were dissolved in THF (5 ml), to which aqueous HCl (6 M, 5 ml) was cautiously added. The reaction mixture was stirred for 20 h at room temperature, shielded from light by means of aluminum foil, and poured in brine (10 ml), after which it was extracted with chloroform (3×5 ml). Drying over $MgSO_4$ and evaporation of the solvent in vacuo yielded the crude 3-(4-halophenyl)-1-hydroxy-1*H*-benzo [*g*]isochromene-5,10-diones **15d** and **15e**. These compounds were further purified by means of trituration with diethyl ether. For 1-hydroxy-3-phenyl-1*H*-benzo[*g*]isochromene-5,10-dione **15a** the reaction was stirred for three days and a mixture was obtained in which 1-hydroxy-3-phenyl-1*H*-benzo[*g*]isochromene-5,10-dione **15a** was the major compound together with 1-(4-hydroxy-butoxy)-3-phenyl-1*H*-benzo[*g*]isochromene-5,10-dione **21a** 1-ethoxy-3-phenyl-1*H*-benzo[*g*]isochromene-5,10-dione **22a**. 1-Hydroxy-3-phenyl-1*H*-benzo[*g*]isochromene-5,10-dione **15a** was isolated by means of preparative TLC on silica gel (petroleum ether/ethyl acetate 7/3). Due to the unstable nature of hydroxypyranonapthoquinones **15**, elementary analysis could not be performed.

4.5.1. 1-Hydroxy-3-phenyl-1H-benzo[g]isochromene-5,10-dione ***15a***. Yield 40%, mp 154.0 °C, R_f 0.26 (petroleum ether/ethyl acetate 7/3), orange red crystals. ^{1}H NMR ($CDCl_3$): δ 3.99 (1H, br s, OH), 6.92 (1H, s, CH-1), 6.93 (1H, s, CH-4), 7.43–7.50 (m, 3×CH_{Ar}), 7.69–7.79 (2H, m, CH-7, and CH-8), 7.87–7.91 (2H, m, 2×CH_{Ar}), 8.12–8.15 (2H, m, CH-6, and

CH-9). ^{13}C NMR ($CDCl_3$): δ 88.72 (CH-1), 92.72 (CH-4), 122.56 (C_{quat}), 126.22 (CH-6 or CH-9), 126.33 (2×CH_{Ar}), 126.68 (CH-6 or CH-9), 128.73 (2×CH_{Ar}), 131.03 (CH_{Ar}), 131.81 (C_{quat}), 132.70 (C_{quat}), 133.05 (C_{quat}), 133.44 (CH-7 or CH-8), 134.31 (CH-7 or CH-8), 136.50 (C_{quat}), 158.94 (C-3), 182.15 (C=O), 183.14 (C=O). IR (cm^{-1}): ν_{OH}=3331. $\nu_{C=O}$=1670, 1640. ν_{CHAr}=1535. MS (ES^-) *m*/*z* (%): 303 ($M-H^+$, 100).

4.5.2. 3-(4-Fluorophenyl)-1-hydroxy-1H-benzo[g]isochromene-5,10-dione ***15d***. Yield 48%, mp 221.2 °C, R_f 0.21 (petroleum ether/ethyl acetate 4/1), red crystals. ^{1}H NMR ($CDCl_3$): δ 3.80 (1H, br s, OH), 6.82 (1H, s, CH-1), 6.87 (1H, s, CH-4), 7.11–7.17 (2H, m, 2×CH_{Ar}), 7.70–7.75 (2H, m, CH-7, and CH-8), 7.86–7.91 (2H, m, 2×CH_{Ar}), 8.05–8.15 (2H, m, CH-6, and CH-9). ^{13}C NMR (DMSO-d_6): δ 88.82 (CH-1), 92.84 (CH-4), 116.57 (2×CH_{Ar}, J_{C-F}=21.9 Hz), 123.80 (C_{quat}), 126.18 (CH_{Ar}), 126.81 (CH_{Ar}), 129.09 (2×CH_{Ar}, J_{C-F}=8.1 Hz), 130.28 (C_{quat}, J_{C-F}=3.5 Hz), 131.90 (C_{quat}), 132.73 (C_{quat}), 133.51 (CH_{Ar}), 134.41 (CH_{Ar}), 135.27 (C_{quat}), 136.12 (C_{quat}), 164.14 (C_{quat}, J_{C-F}=249.2 Hz), 182.11 (C=O), 183.35 (C=O). ^{19}F NMR (DMSO-d_6): −109.14 to −109.19 (1F, m, F). IR (cm^{-1}): ν_{OH}=3287, $\nu_{C=O}$=1672, 1646. ν_{CHAr}=1502. MS (ES^-) *m*/*z* (%): 321 ($M-H^+$, 100).

4.5.3. 3-(4-Chlorophenyl)-1-hydroxy-1H-benzo[g]isochromene-5,10-dione ***15e***. Yield 90%, mp 236.4 °C, R_f 0.23 (petroleum ether/ethyl acetate 4/1), red crystals. ^{1}H NMR (DMSO-d_6): δ 6.60 (1H, d, *J*=5.0 Hz, CH-1), 6.88 (1H, s, CH-4), 7.58 (2H, d, *J*=8.8 Hz, 2×CH_{Ar}), 7.83–7.95 (2H, m, CH-7, and CH-8), 7.83–7.95 (2H, d, *J*=8.8 Hz, 2×CH_{Ar}), 8.01–8.09 (2H, m, CH-6, and CH-9). ^{13}C NMR (DMSO-d_6): δ 88.78 (CH-1), 93.40 (CH-4), 124.15 (C_{quat}), 126.18 (CH-6 or CH-9), 126.81 (CH-6 or CH-9), 128.29 (2×CH_{Ar}), 129.56 (2×CH_{Ar}), 131.85 (C_{quat}), 132.51 (C_{quat}), 132.70 (C_{quat}), 133.44 (CH-7 or CH-8), 135.25 (CH-7 and CH-8), 135.94 (C_{quat}), 136.06 (C_{quat}), 157.16 (C-3), 182.11 (C=O), 183.23 (C=O). IR (cm^{-1}): ν_{OH}=3278, $\nu_{C=O}$=1673, 1640. ν_{CHAr}=1529. MS (ES^-) *m*/*z* (%) 337/339 ($M-H^+$, 100/32).

4.6. Synthesis of 1-hydroxy-3-(4-methoxyphenyl)-1*H*-benzo[*g*]isochromene-5,10-dione 15b

1-(2-Hydroxyethoxy)-3-(4-methoxyphenyl)-1*H*-benzo[*g*]isochromene-5,10-dione **14b** (825 mg, 2.18 mmol) was dissolved in THF (5 ml) to which aqueous HCl (2 M, 5 ml) was added and the reaction mixture was stirred for 20 h at room temperature, shielded from light by means of aluminum foil. The reaction mixture was poured in brine (10 ml) and extracted with chloroform (3×5 ml). Drying over $MgSO_4$ and evaporation of the solvent in vacuo yielded the crude 1-hydroxy-3-(4-methoxyphenyl)-1*H*-benzo[*g*]isochromene-5,10-dione **15b**. This compound was found to be too unstable to record a ^{13}C NMR spectrum.

4.6.1. 1-Hydroxy-3-(4-methoxyphenyl)-1H-benzo[g]isochromene-5,10-dione ***15b***. Yield 91%, mp 223.7 °C, purple crystals. ^{1}H NMR (acetone-d_6): δ 3.87 (3H, s, CH_3O), 6.83 (1H, s, CH-1), 6.88 (1H, s, CH-4), 7.07 (d, *J*=8.8 Hz, 2×CHAr), 7.83–7.95 (2H, m, CH-6, and CH-7), 7.90 (d, *J*=8.8 Hz, 2×CHAr), 8.10–8.21 (2H, m, CH-5, and CH-8). IR (cm^{-1}): ν_{OH}=3382, $\nu_{C=O}$=1669, 1640, ν_{CHAr}=1535, 1501. MS (ES^-) *m*/*z* (%): 333 ($M-H^+$, 100).

4.7. Synthesis of 1-methoxy-1*H*-benzo[*g*]isochromene-5,10-diones 16b–e

3-Aryl-1-(2-hydroxyethoxy)-1*H*-benzo[*g*]isochromene-5,10-diones **14b–e** (0.27 mmol) were dissolved in methanol (2 ml), to which one drop of concentrated sulfuric acid was added. The reaction mixture was stirred for 24 h at 60 °C, shielded from light by means of aluminum foil, and poured in brine (10 ml). Extraction with chloroform (3×5 ml), drying over $MgSO_4$, and evaporation of the solvent in vacuo yielded the crude 3-aryl-1-methoxy-1*H*-benzo[*g*]isochromene-5,10-diones **16b–e**, which were further purified by means of recrystallization from methanol.

4.7.1. 1-Methoxy-3-(4-methoxyphenyl)-1H-benzo[g]isochromene-5,10-dione ***16b***. Yield 87%, mp 173.6 °C, R_f 0.33 (petroleum ether/ethyl acetate 7/3), purple crystals. ^{1}H NMR ($CDCl_3$): δ 3.68 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 6.50 (1H, s, CH-1), 6.84 (1H, s, CH-4), 6.97 (2H, d, *J*=8.8 Hz, 2×CH_{Ar}), 7.69–7.82 (2H, m, CH-7, and CH-8), 7.86 (2H, d, *J*=8.8 Hz, 2×CH_{Ar}), 8.11–8.16 (2H, m, CH-6, and CH-9). ^{13}C NMR ($CDCl_3$): δ 55.57 (OCH_3), 56.00 (OCH_3), 91.90 (CH-4), 95.80 (CH-1), 114.32 (2×CH_{Ar}), 121.05 (C_{quat}), 125.74 (C_{quat}), 126.18 (CH-6 or CH-9), 126.69 (CH-6 or CH-9), 128.06 (2×CH_{Ar}), 131.96 (C_{quat}), 132.93 (C_{quat}), 133.30 (CH-7 or CH-8), 134.29 (CH-7 or CH-8), 137.25 (C_{quat}), 159.16 (C_{quat}), 162.05 (C_{quat}), 181.94 (C=O), 183.41 (C=O). IR (cm^{-1}): $\nu_{C=O}$=1672, 1645. ν_{CHAr}=1538, 1506. MS (ES^+) *m*/*z* (%): 317 ($M-CH_3O$, 100). Anal. Calcd for $C_{21}H_{16}O_5$: C, 72.41, H, 4.63, obtained: C, 72.03, H, 4.47.

4.7.2. 3-(4-Bromophenyl)-1-methoxy-1H-benzo[g]isochromene-5,10-dione ***16c***. Yield 71%, mp 172.1–178.1 °C, R_f 0.17 (petroleum ether/ethyl acetate 19/1), red crystals. ^{1}H NMR ($CDCl_3$): δ 3.68 (3H, s, CH_3), 6.51 (1H, s, CH-1), 6.93 (1H, s, CH-4), 7.59 (2H, d, *J*=8.3 Hz, 2×CH_{Ar}), 7.71 (2H, d, *J*=8.3 Hz, 2×CH_{Ar}), 7.71–7.83 (2H, m, 2×CH_{Ar}), 8.10–8.18 (2H, m, 2×CH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 56.23 (CH_3O), 93.65 (CH-1), 95.76 (CH-4), 122.38 (C_{quat}), 125.47 (C_{quat}), 126.25 (CH_{Ar}), 126.75 (CH_{Ar}), 127.56 (2×CH_{Ar}), 131.82 (C_{quat}), 132.11 (2×CH_{Ar}), 132.72 (C_{quat}), 133.51 (CH_{Ar}), 134.37 (CH_{Ar}), 136.57 (C_{quat}), 157.62 (C_{quat}), 182.04 (C=O), 182.92. IR (cm^{-1}): $\nu_{C=O}$=1671, 1656, ν_{CHAr}=1586, 1566, 1551, 1487 ν_{C-O}=1305, 1269. MS (ES^+) *m*/*z* (%): 365.0/367.0 ($M-CH_3O$, 100). Anal. Calcd for $C_{2O}H_{13}BrO_4$: C, 60.47, H, 3.30, obtained: C, 60.12, H, 3.14.

4.7.3. 3-(4-Fluorophenyl)-1-methoxy-1H-benzo[g]isochromene-5,10-dione ***16d***. Yield 34%, mp 162.8 °C, R_f 0.45 (petroleum ether/ethyl acetate 4/1), red crystals. ^{1}H NMR ($CDCl_3$): δ 3.66 (3H, s, OCH_3), 6.50 (1H, s, CH-1), 6.89 (1H, s, CH-4), 7.10–7.17 (2H, m, 2×CH_{Ar}), 7.70–7.75 (2H, m, CH-7, and CH-8), 7.86–7.91 (2H, m, 2×CH_{Ar}), 8.05–8.15 (2H, m, CH-6, and CH-9). ^{13}C NMR ($CDCl_3$): δ 56.23 (OCH_3), 93.09 (CH-4), 95.82 (CH-1), 116.08 (2×CH_{Ar}, J_{C-F}=21.9 Hz), 121.10 (C_{quat}), 126.26 (CH-6 or CH-9), 126.77 (CH-6 or CH-9), 128.35 (2×CH_{Ar}, J_{C-F}=9.2 Hz), 129.44 (C_{quat}, J_{C-F}=3.5 Hz), 131.88 (C_{quat}), 132.78 (C_{quat}), 133.51 (CH-7 or CH-8), 134.40 (CH-7 or CH-8), 136.81 (C_{quat}), 157.91 (C-3), 164.43 (C_{quat}, J_{C-F}=251.5 Hz), 182.11 (C=O), 183.13 (C=O). IR (cm^{-1}): $\nu_{C=O}$=1676, 1652, ν_{CHAr}=1551, 1503. MS (ES^+) *m*/*z* (%) 305 ($M-CH_3O$. 100). Anal. Calcd for $C_{2O}H_{13}FO_4$: C, 71.43, H, 3.90, obtained: C, 71.67, H, 4.06.

4.7.4. 3-(4-Chlorophenyl)-1-methoxy-1H-benzo[g]isochromene-5,10-dione ***16e***. Yield 82%, mp 164.3 °C, R_f 0.40 (petroleum ether/ethyl acetate 4/1), red crystals. ^{1}H NMR ($CDCl_3$): δ 3.68 (3H, s, OCH_3), 6.49 (1H, s, CH-1), 6.92 (1H, s, CH-4), 7.43 (2H, d, *J*=8.8 Hz, 2×CH_{Ar}), 7.69–7.82 (2H, m, CH-7, and CH-8), 7.43 (2H, d, *J*=8.8 Hz. 2×CH_{Ar}), 8.05–8.15 (2H, m, CH-6, and CH-9). ^{13}C NMR ($CDCl_3$): δ 56.24 (OCH_3), 93.62 (CH-4), 95.76 (CH-1), 122.32 (C_{quat}), 126.28 (CH-6 or CH-9), 126.78 (CH-6 or CH-9), 127.42 (2×CH_{Ar}), 129.18 (2×CH_{Ar}), 131.66 (C_{quat}), 131.85 (C_{quat}), 132.75 (C_{quat}), 133.54 (CH-7 or CH-8), 134.40 (CH-7 or CH-8), 136.64 (C_{quat}), 137.06 (C_{quat}), 157.64 (C-3), 182.08 (C=O), 183.01 (C=O). IR (cm^{-1}): $\nu_{C=O}$=1670, 1654. ν_{CHAr}=1542. MS (ES^+) *m*/*z* (%) 321/323 ($M-CH_3O$, 100/32). Anal. Calcd for $C_{20}H_{13}ClO_4$: C: 68.09, H: 3.71, obtained: C: 67.92, H: 3.46.

4.8. Synthesis of 1-methoxy-1*H*-benzo[*g*]isochromene-5,10-diones 16a and 16f–j

General procedure. The 1-(2-hydroxyethoxy)-1*H*-benzo[*g*]isochromene-5,10-dione **14** (0.27 mmol) of choice and trimethyl

orthoformate (59 mg, 0.58 mmol, 2.05 equiv) were dissolved in dry dichloromethane (5 ml). Subsequently $BF_3 \cdot OEt_2$ (0.01 ml, 0.03 mmol, 0.1 equiv) was added dropwise under a nitrogen atmosphere at 0 °C. The reaction mixture, shielded from light by means of aluminum foil, reacted for 3 h at 0 °C and was subsequently quenched with satd aq $NaHCO_3$ (10 ml) and extracted with chloroform (3×5 ml). Evaporation of the solvent in vacuo yielded the crude 1-methoxy-1*H*-benzo[*g*] isochromene-5,10-diones **16**, which were further purified by means of preparative TLC on silica gel (petroleum ether/ethyl acetate 9/1).

4.8.1. 3-Phenyl-1-methoxy-1H-benzo[g]isochromene-5,10-dione ***16a***. Yield 58%, mp 141.4 °C, R_f 0.18 (petroleum ether/ethyl acetate 9/1), orange crystals. ^{1}H NMR ($CDCl_3$): δ 3.65 (3H, s, OCH_3), 6.51 (1H, s, CH-1), 6.96 (1H, s, CH-4), 7.46–7.48 (3H, m, 3×CH_{Ar}), 7.70–7.77 (2H, m, CH-7, and CH-8), 7.88–7.93 (2H, m, 2×CH_{Ar}), 8.13–8.18 (2H, m, CH-6, and CH-9). ^{13}C NMR ($CDCl_3$): δ 56.15 (OCH_3), 93.37 (CH-4), 95.71 (CH-1), 122.03 (C_{quat}), 126.25 (2×CH_{Ar} and CH-6 or CH-9), 126.75 (CH-6 or CH-9), 128.89 (2×CH_{Ar}), 131.02 (CH_{Ar}), 131.93 (C_{quat}), 132.83 (C_{quat}), 133.18 (C_{quat}), 133.45 (CH-7 or CH-8), 134.34 (CH-7 or CH-8), 136.90 (C_{quat}), 158.92 (C_{quat}), 182.13 (C=O), 183.20 (C=O). IR (cm^{-1}): $\nu_{C=O}$=1674, 1650. ν_{CHAr}=1540. MS (ES^+) *m*/*z* (%): 287 (M−CH_3O, 100). Anal. Calcd for $C_{20}H_{14}O_4$: C, 75.46, H, 4.43, obtained: C, 75.15, H, 4.22.

4.8.2. 3-(2,5-Dimethoxyphenyl)-1-methoxy-1H-benzo[g]isochromene-5,10-dione ***16f***. Yield 86%, mp 153.2 °C, R_f 0.26 (petroleum ether/ethyl acetate 4/1), purple crystals. ^{1}H NMR ($CDCl_3$): δ 3.68 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.94 (3H, s, OCH_3), 6.46 (1H, s, CH-1), 6.94–6.98 (2H, m, 2×CH_{Ar}), 7.39 (1H, s, CH-4), 7.44 (1H, d, *J*=3.3 Hz, CH-3′), 7.69–7.78 (2H, m, CH-7, and CH-8), 8.12–8.16 (2H, m, CH-6, and CH-9). ^{13}C NMR ($CDCl_3$): δ 55.84 (OCH_3), 56.02 (OCH_3), 56.11 (OCH_3), 95.18 (CH-1), 98.78 (CH-4), 112.65 (CH-3′), 113.85 (CH-6′), 116.92 (CH-4′), 121.78 (C_{quat}), 122.53 (C_{quat}), 126.07 (CH-6 or CH-9), 126.75 (CH-6 or CH-9), 131.96 (C_{quat}), 132.77 (C_{quat}), 133.28 (CH-7 or CH-8), 134.10 (CH-7 or CH-8), 137.00 (C_{quat}), 152.58 (*C*OCH_3), 153.35 (*C*OCH_3), 155.67 (C_{quat}), 182.10 (C=O), 183.29 (C=O). IR (cm^{-1}): $\nu_{C=O}$=1666 en 1655. ν_{CHAr}=1542. MS (ES^+) *m*/*z* (%): 347 (M−CH_3O, 100). Anal. Calcd for $C_{22}H_{18}O_6$: C, 69.83, H, 4.79, obtained: C, 69.95, H, 5.03.

4.8.3. 1-Methoxy-3-(4-methylphenyl)-1H-benzo[g]isochromene-5,10-dione ***16g***. Yield 62%, mp 165.2 °C; R_f 0.08 (petroleum ether/ethyl acetate 19/1); red crystals. ^{1}H NMR ($CDCl_3$): δ 2.39 (3H, s, CH_3), 3.67 (3H, s, CH_3O), 6.47 (1H, s, CH-1), 6.88 (1H, s, CH-4), 7.25 (2H, d, *J*=8.3 Hz, 2×CH_{Ar}), 7.71–7.81 (2H, m, 2×CH_{Ar}), 7.77 (2H, d, *J*=8.3 Hz, 2×CH_{Ar}), 8.10–8.18 (2H, m, 2×CH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 21.63 (CH_3), 56.03 (CH_3O), 92.72 (CH-4), 95.69 (CH-1), 121.60 (C_{quat}), 126.18 (CH_{Ar}), 126.23 (2×CH_{Ar}), 129.62 (2×CH_{Ar}), 130.41 (C_{quat}), 131.93 (C_{quat}), 132.86 (C_{quat}), 133.35 (CH_{Ar}), 134.28 (CH_{Ar}), 137.06 (C_{quat}), 141.59 (C_{quat}), 159.19 (C_{quat}), 182.01 (C=O), 183.24 (C=O). IR (cm^{-1}): $\nu_{C=O}$=1671, 1649, ν_{CHAr}=1593, 1539, 1507, ν_{C-O}=1029. MS (ES^+) *m*/*z* (%): 301 (M−CH_3O, 100). Anal. Calcd for $C_{21}H_{16}O_4$: C, 75.89, H, 4.85, obtained: C, 75.58, H, 4.66.

4.8.4. 1-Methoxy-3-methyl-1H-benzo[g]isochromene-5,10-dione ***16h***. Yield 65%, mp 123.6 °C, R_f 0.09 (petroleum ether/ethyl acetate 19/1), orange crystals. ^{1}H NMR ($CDCl_3$): δ 2.19 (3H, s, CH_3), 3.61 (CH_3O), 6.18 (1H, s, CH-4), 6.30 (1H, s, CH-1), 7.68–7.77 (2H, m, 2×CH_{Ar}), 8.10–8.15 (2H, m, 2×CH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 20.98 (CH_3), 55.98 (CH_3O), 94.52 (CH-4), 95.60 (CH-1), 121.04 (C_{quat}), 126.12 (CH_{Ar}), 126.58 (CH_{Ar}), 131.80 (C_{quat}), 132.63 (C_{quat}), 133.36 (CH_{Ar}), 134.20 (CH_{Ar}), 136.64 (C_{quat}), 162.26 (C_{quat}), 182.30 (C=O), 183.18 (C=O). IR (cm^{-1}): $\nu_{C=O}$=1669, 1658, ν_{CHAr}=1592, 1582, 1557, ν_{C-O}=1302. MS (ES^+) *m*/*z* (%): 225 (M−CH_3O, 100). Anal. Calcd for $C_{15}H_{12}O_4$: C, 70.31, H, 4.72, obtained: C, 70.48, H, 4.93.

4.8.5. 3-Isopropyl-1-methoxy-1H-benzo[g]isochromene-5,10-dione ***16i***. Yield 75%, mp 84.5 °C, R_f 0.24 (petroleum ether/ethyl acetate 19/1), orange crystals. ^{1}H NMR ($CDCl_3$): δ 1.25 (6H, d, *J*=7.2 Hz, CH(*C*H_3)$_2$), 2.68 (1H, septet, *J*=7.2 Hz, *C*H(CH_3)$_2$), 3.62 (CH_3O), 6.18 (1H, s, CH-4), 6.31 (1H, s, CH-1), 7.67–7.76 (2H, m, 2×CH_{Ar}), 8.08–8.12 (2H, m, 2×CH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 20.16 (CH(*C*H_3)$_2$), 20.27 (CH(*C*H_3)$_2$), 33.71 (*C*H(CH_3)$_2$), 56.20 (CH_3O), 91.76 (CH-4), 95.39 (CH-1), 121.25 (C_{quat}), 126.12 (CH_{Ar}), 126.61 (CH_{Ar}), 131.88 (C_{quat}), 132.66 (C_{quat}), 133.35 (CH_{Ar}), 134.19 (CH_{Ar}), 136.87 (C_{quat}), 170.36 (C_{quat}), 182.33 (C=O), 183.41 (C=O). IR (cm^{-1}): $\nu_{C=O}$=1668, 1653, ν_{CHAr}=1582, 1552, ν_{C-O}=1299. MS (ES^+) *m*/*z* (%): 253 (M−CH_3O, 100). Anal. Calcd for $C_{17}H_{16}O_4$: C, 71.82, H, 5.67, obtained: C, 72.16, H, 5.85.

4.8.6. 3-tert-Butyl-1-methoxy-1H-benzo[g]isochromene-5,10-dione ***16j***. Yield 48%, mp 64.2 °C, R_f 0.56 (petroleum ether/ethyl acetate 7/3), brown crystals. ^{1}H NMR ($CDCl_3$): δ 1.28 (9H, s, C(CH_3)$_3$), 3.63 (3H, s, OCH_3), 6.24 (1H, s, CH-1), 6.32 (1H, s, CH-4), 7.66–7.76 (2H, m, CH-7, and CH-8), 8.07–8.12 (2H, m, CH-6, and CH-9). ^{13}C NMR ($CDCl_3$): δ 28.00 (3×CH_3), 36.90 (*C*(CH_3)$_3$), 56.36 (OCH_3), 90.75 (CH-4), 95.40 (CH-1), 121.17 (C_{quat}), 126.09 (CH-6 or CH-9), 126.60 (CH-6 or CH-9), 131.88 (C_{quat}), 132.86 (C_{quat}),133.35 (CH-7 or CH-8), 134.19 (CH-7 or CH-8), 136.90 (C_{quat}), 172.39 (C_{quat}), 182.30 (C=O), 183.46 (C=O). IR (cm^{-1}): $\nu_{C=O}$=1655, 1672. ν_{CHAr}=1557. MS (ES^+) *m*/*z* (%): 267 (M−CH_3O. 100). Anal. Calcd for $C_{18}H_{18}O_4$: C, 72.47, H, 6.08, obtained: C, 72.27, H, 5.92.

4.9. Synthesis of 3-aryl-1-(4-hydroxybutoxy)-1*H*-benzo[*g*] isochromene-5,10-diones 21f and 21g

2-Acylmethyl-3-(1,3-dioxolan-2-yl)-1,4-naphthoquinones **13f** and **13g** (2.18 mmol) were dissolved in THF (5 ml), to which aqueous HCl (6 M, 5 ml) was added cautiously. The reaction mixture was stirred for three days at room temperature, shielded from light by means of aluminum foil, poured in brine (10 ml) and extracted with chloroform (3×5 ml). Drying over $MgSO_4$ and evaporation of the solvent in vacuo yielded the crude 3-aryl-1-(4-hydroxybutoxy)-1*H*-benzo[*g*]isochromene-5,10-diones **21f** and **21g**, which were further purified by means of column chromatography or preparative TLC on silica gel (petroleum ether/ethyl acetate 4/1).

4.9.1. 1-(4-Hydroxybutoxy)-3-(4-methylphenyl)-1H-benzo[g]isochromene-5,10-dione ***21f***. Yield 85%, mp 125.9 °C, R_f 0.26 (petroleum ether/ethyl acetate 7/3), red crystals. ^{1}H NMR ($CDCl_3$): δ 1.75–1.82 (4H, m, 2×CH_2), 2.42 (3H, s, CH_3), 3.46–3.52 (2H, m, CH_2O), 3.91–3.95 (1H, m, CH_aH_bO), 4.05–4.14 (1H, m, *C*H_aH_bO), 6.57 (1H, s, CH-1), 6.91 (1H, s, CH-4), 7.28 (2H, d, *J*=8.3 Hz, 2×CH_{Ar}), 7.70–7.76 (2H, m, CH-7, and CH-8), 7.79 (2H, d, *J*=8.3 Hz, 2×CH_{Ar}), 8.12–8.17 (2H, m, CH-6, and CH-9). ^{13}C NMR ($CDCl_3$): δ 21.53 (CH_3), 26.87 (CH_2), 28.98 (CH_2), 44.74 (CH_2O), 68.03 (CH_2O), 92.52 (CH-4), 94.54 (CH-1), 121.50 (C_{quat}), 126.05 (2×CH_{Ar}), 126.57 (CH-6 and CH-9), 129.52 (2×CH_{Ar}), 130.33 (C_{quat}), 131.84 (C_{quat}), 132.73 (C_{quat}), 133.23 (CH-7 or CH-8), 134.13 (CH-7 or CH-8), 136.89 (C_{quat}), 141.47 (C_{quat}), 158.99 (C_{quat}), 181.86 (C=O), 183.16 (C=O). IR (cm^{-1}): ν_{OH}=2930. $\nu_{C=O}$=1675, 1649, ν_{CHAr}=1544. MS (ES^+) *m*/*z* (%): 301 (M−O(CH_2)$_4$OH, 100). Anal. Calcd for $C_{24}H_{22}O_5$: C, 73.83, H, 5.68, obtained: C, 74.05, H, 5.88.

4.9.2. 3-(2,5-Dimethoxyphenyl)-1-(4-hydroxybutoxy)-1H-benzo[g]isochromene-5,10-dione ***21g***. Yield 60%, R_f 0.26 (petroleum ether/ethyl acetate 7/3), purple amorphous crystals. ^{1}H NMR ($CDCl_3$): δ 1.78–1.83 (4H, m, 2×CH_2), 3.36–3.49 (2H, m, CH_2O), 3.84 (1H, s, OCH_3), 3.86–3.91 (1H, m, CH_aH_bO), 3,94 (1H, s, OCH_3), 3.96–4.08 (1H, m, *C*H_aH_bO), 6.53 (1H, s, CH-1), 6.92–6.96 (2H, m, 2×CH_{Ar}), 7.39 (1H, s, CH-4), 7.42–7.45 (1H, m, CH_{Ar}), 7.72–7.79 (2H, m, CH-7, and CH-8), 8.12–8.17 (2H, m, CH-6, and CH-9). ^{13}C NMR ($CDCl_3$): δ 15.34 (CH_2), 29.14 (CH_2), 44.87 (CH_2O), 55.92 (OCH_3), 56.19 (OCH_3), 68.12 (CH_2O), 94.17 (CH-1), 98.87 (CH-4), 112.73 (CH_{Ar}), 113.86 (CH_{Ar}), 116.90 (CH_{Ar}), 121.88 (C_{quat}), 122.60 (C_{quat}), 126.11 (CH-6 or CH-9), 126.66 (CH-6 or CH-9), 132.06 (C_{quat}), 132.83 (C_{quat}),

133.36 (CH-7 or CH-8), 134.15 (CH-7 or CH-8), 137.03 (C_{quat}), 152.89 (C_{quat}), 153.41 (C_{quat}), 155.56 (C_{quat}), 182.13 (C=O), 183.38 (C=O). IR (cm^{-1}): ν_{OH}=2946, $\nu_{C=O}$=1672, 1649, ν_{CHAr}=1533. MS (ES^+) *m*/*z* (%): 347 (M−O(CH_2)$_4$OH, 100). Anal. Calcd for $C_{25}H_{24}O_7$: C, 68.80, H, 5.54, obtained: C, 69.06, H, 5.68.

4.10. Synthesis of 3-aryl-1-ethoxy-1*H*-benzo[*g*]isochromene-5,10-diones 22a, f, g

2-Acylmethyl-3-(1,3-dioxolan-2-yl)-1,4-naphthoquinones **13f** and **13g** or 3-phenyl-1-(2-hydroxyethoxy)-1*H*-benzo[*g*]isochromene-5,10-dione **14a** (1.22 mmol) were dissolved in reagent grade CH_2Cl_2 (5 ml), to which HCl (6 M, 5 ml) was added. The reaction mixture, shielded from light by means of aluminum foil, was vigorously stirred for 3 days at room temperature, poured in brine (10 ml) and extracted with chloroform (3×5 ml). Evaporation of the solvent in vacuo yielded the crude 3-aryl-1-ethoxy-1*H*-benzo[*g*]isochromene-5,10-diones **22a**, **f**, and **g**. 1-Ethoxy-3-(4-methylphenyl)-1*H*-benzo[*g*]isochromene-5,10-dione **22g** was recrystallized from ethanol, while 3-aryl-1-ethoxy-1*H*-benzo[*g*]isochromene-5,10-diones **22a** and **22f** were purified by means of column chromatography on silica gel (petroleum ether/ethyl acetate 4/1).

*4.10.1. 1-Ethoxy-3-phenyl-1H-benzo[g]isochromene-5,10-dione **22a**.* Yield 98%, mp 144.6 °C, R_f 0.14 (petroleum ether/ethyl acetate 4/1), orange crystals. ^{1}H NMR ($CDCl_3$): δ 1.26 (3H, t, *J*=7.2 Hz, OCH_2CH_3), 3.93 (1H, dq, *J*=9.6 Hz, 7.2 Hz, OCH_aH_b), 4.10 (1H, dq, *J*=9.6, 7.2 Hz, OCH_aH_b), 6.57 (1H, s, CH-1), 6.91 (1H, s, CH-4), 7.29–7.43 (3H, m, 3×CH_{Ar}), 7.69–7.74 (2H, m, CH-7, and CH-8), 7.83–7.90 (2H, m, 2×CH_{Ar}), 8.08–8.13 (2H, m, CH-6, and CH-9). ^{13}C NMR ($CDCl_3$): δ 15.34 (CH_3), 64.85 (OCH_2), 93.30 (CH-4), 94.46 (CH-1), 122.12 (C_{quat}), 126.17 (CH_{Ar}), 126.22 (2×CH_{Ar}), 126.67 (C_{quat}), 128.84 (2×CH_{Ar}), 130.90 (CH_{Ar}), 131.94 (C_{quat}), 132.84 (C_{quat}), 133.33 (CH_{Ar}), 133.36 (CH_{Ar}), 134.23 (CH_{Ar}), 136.81 (C-3), 182.07 (C=O), 183.17 (C=O). IR (cm^{-1}): $\nu_{C=O}$=1673, 1652. ν_{CHAr}=1548. MS (ES^+) *m*/*z* (%) 287 (M−CH_2CH_3O, 100). Anal. Calcd for $C_{21}H_{16}O_4$: C: 75.89, H: 4.85, obtained: C: 75.58, H: 4.72.

*4.10.2. 3-(2,5-Dimethoxyphenyl)-1-ethoxy-1H-benzo[g]isochromene-5,10-dione **22f**.* Yield 67%, decomposition at 181.6 °C, R_f 0.30 (petroleum ether/ethyl acetate 7/3), purple crystals. ^{1}H NMR ($CDCl_3$): δ 1.26 (3H, t, *J*=7.2 Hz, OCH_2CH_3), 3.83 (3H, s, OCH_3), 3.94 (3H, s, OCH_3), 3.94 (1H, dq, *J*=9.6, 7.2 Hz, OCH_aH_b), 4.09 (1H, dq, *J*=9.6, 7.2 Hz, OCH_aH_b), 6.56 (1H, s, CH-1), 6.93 (1H, d, *J*=9.2 Hz, CH-3′), 6.97 (1H, dd, *J*=9.2, 2.8 Hz, CH-4′), 7.39 (1H, s, CH-4), 7.44 (1H, d, *J*=2.8 Hz, CH-6′), 7.69–7.78 (2H, m, CH-7, and CH-8), 8.12–8.16 (2H, m, CH-6, and CH-9). ^{13}C NMR ($CDCl_3$): δ 15.32 (CH_3), 55.94 (OCH_3), 56.23 (OCH_3), 64.73 (OCH_2), 93.98 (CH-1), 98.87 (CH-4), 112.76 (CH-3′), 114.03 (CH-6′), 116.92 (CH-4′), 121.78 (C_{quat}), 122.02 (C_{quat}), 122.83 (C_{quat}), 126.12 (CH-6 of CH-9), 126.64 (CH-6 of CH-9), 132.12 (C_{quat}), 132.93 (C_{quat}), 133.33 (CH-7 of CH-8), 134.14 (CH-7 of CH-8), 137.07 (C_{quat}), 152.97 ($COCH_3$). 153.44 ($COCH_3$), 155.71 (C-3), 182.23 (C=O), 183.49 (C=O). IR (cm^{-1}): $\nu_{C=O}$=1666, 1648, ν_{CHAr}=1528, 1498. MS (ES^+) *m*/*z* (%): 347 (M−CH_2CH_3O, 100). Anal. Calcd for $C_{23}H_{20}O_6$: C: 70.40, H: 5.14, obtained: C: 70.15, H: 4.82.

*4.10.3. 1-Ethoxy-1H-3-(4-methylphenyl)-benzo[g]isochromene-5,10-dione **22g**.* Yield 86%, mp 159.6 °C, R_f 0.30 (petroleum ether/ethyl acetate 7/3), orange crystals. ^{1}H NMR ($CDCl_3$): δ 1.26 (3H, t, *J*=7.2 Hz, OCH_2CH_3), 2.42 (3H, s, CH_3), 3.94 (1H, dq, *J*=9.6, 7.2 Hz, OCH_aH_b), 4.09 (1H, dq, *J*=9.6 Hz, 7.2 Hz, OCH_aH_b), 6.60 (1H, s, CH-1), 6.91 (1H, s, CH-4), 7.27 (2H, d, *J*=8.3 Hz, 2×CH_{Ar}), 7.79 (2H, d, *J*=8.3 Hz, 2×CH_{Ar}), 7.69–7.78 (2H, m, CH-7, and CH-8), 8.12–8.17 (2H, m, CH-6, and CH-9). ^{13}C NMR ($CDCl_3$): δ 15.36 (CH_3), 21.63 (CH_3), 64.75 (OCH_2), 92.67 (CH-1), 94.44 (CH-4), 121.70 (C_{quat}), 126.14 (CH-6 of CH-9), 126.23 (2×CH_{Ar}), 126.64 (CH-6 of CH-9), 129.59 (2×CH_{Ar}), 130.57 (C_{quat}), 131.96 (C_{quat}), 132.89 (C_{quat}), 133.30 (CH-7 of CH-8), 134.22 (CH-7 of CH-8), 137.03 (C_{quat}), 141.50 (C-3), 182.02 (C=O), 183.32 (C=O). IR (cm^{-1}): $\nu_{C=O}$=1673 en 1641. ν_{CHAr}=1538, 1530, 1504. MS (ES^+) *m*/*z* (%): 301 (M−CH_2CH_3O, 100). Anal. Calcd for $C_{21}H_{16}O_4$: C: 75.89, H: 4.85, obtained: C: 75.65, H: 4.55.

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.07.012.

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