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Investigation towards an efficient synthesis of benzo[g]isoquinoline-1,5,10(2*H*)-triones

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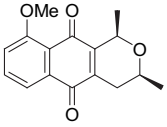
Nenitzescu reaction

ABSTRACT

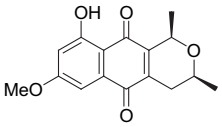
As part of our research on 2-aza analogues of pentalongin, the active principle of *Pentas longiflora* Oliv., the first synthesis of 2,3-disubstituted benzo[g]isoquinoline-1,5,10(2*H*)-triones via 3,4-disubstituted 6-hydroxybenzo[g]furo[4,3,2-*de*]isoquinoline-2,5(4*H*)-diones as the key intermediates is reported. The latter compounds have been prepared by treating 2-methoxycarbonyl-1,4-naphthoquinone with *N*-substituted enaminoesters under acidic conditions. These reagents are easily accessible from readily available 1,4-dihydroxy-2-naphthoic acid, β-ketoesters and primary amines. Finally, a short synthesis of substituted benzo[g]isoquinoline-1,5,10(2*H*)-triones is achieved by an oxidative addition of *N*-substituted enaminoesters onto methyl 1,4-dihydroxynaphthalene-2-carboxylate.

1. Introduction

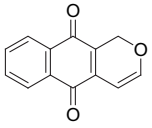
2-Azaanthraquinones can be considered as 2-aza analogues of pyranonaphthoquinones to which belong eleutherin **1**,[1] ventiloquinone L **2**[2] and pentalongin **3**,[3] the naturally occurring pyranonaphthoquinone and active principle of *Pentas longiflora* Oliv,[3] which suggests their potential value as lead structures for the development of new pharmaceuticals and agrochemicals.



1 eleutherin

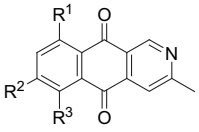


2 ventiloquinone L

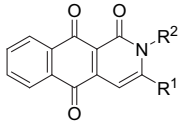


3 pentalongin

Unlike pyranonaphthoquinones, their nitrogen analogues are scarcely found in nature and are reported to exhibit several interesting bioactivities, including antimicrobial, cytotoxic and insecticidal activities.[4] Examples of naturally occurring 2-azaanthraquinones include bostrycoidin **4**,[5,7] tolypocladin **5**[6] and scorpinone **6**.[5f,7] Several research groups[8] including ours, disclosed different synthetic strategies for the preparation of 2-azaanthraquinone derivatives, such as *N*-substituted benzo[g]isoquinoline-5,10-diones,[9] *N*-substituted benzo[g]isoquinoline-3,5,10(2*H*)-triones[10] and 2,4-disubstituted benzo[g]isoquinoline-3,5,10(2*H*)-triones.[11]

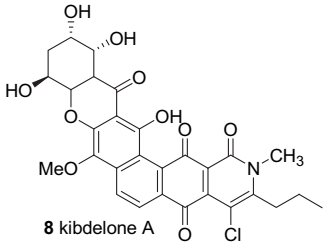


4 $R^1 = R^3 = OH$, $R^2 = OMe$ (bostrycoidin)
5 $R^1 = R^2 = R^3 = OH$ (tolypocladin)
6 $R^1 = R^2 = OMe$, $R^2 = H$ (scorpinone)



7

However, the synthesis of 2,3-disubstituted benzo[g]isoquinoline-1,5,10(2*H*)-triones **7**, the partial structural pattern found in kibdelone A **8**, has only been synthesized to a very limited extend.[12a] Kibdelone A **8** belongs to a novel family of bioactive heterocyclic polyketides produced by a rare soil actinomycete *Kibdelosporangium* sp. (MST-108465) and exhibits potent selective cytotoxicity against a panel of human tumour cell lines as well as significant antibiotic and nematocidal activity.[12]



8 kibdelone A

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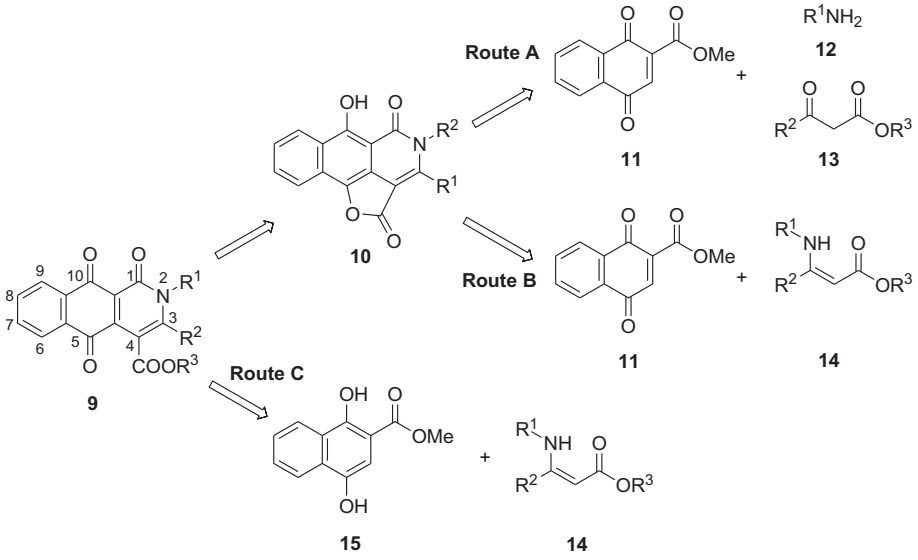
In this manuscript, an investigation towards the first synthesis of substituted benzo[*g*]isoquinoline-1,5,10(2*H*)-triones **9** is reported. Retrosynthetic analysis suggested that three possible routes could lead to the synthesis of the targeted alkyl 2,3-dialkylbenzo[*g*]isoquinoline-1,5,10(2*H*)-trione-4-carboxylates **9** (Scheme 1). Two routes rely on the synthesis of 3,4-dialkyl-6-hydroxybenzo[*g*]furo[4,3,2-*de*] isoquinoline-2,5(4*H*)-diones **10** as key intermediates, which may most likely be prepared by treating 2-methoxycarbonyl-1,4-naphthoquinone **11** with either β-ketoesters **13** and primary amines **12** (Scheme 1, route A) or ready-made *N*-alkyl enaminoesters **14** (Scheme 1, route B). A third route, which will be investigated, concerns the oxidative addition reaction of *N*-alkyl enaminoesters **14** with methyl 1,4-dihydroxynaphthalene-2-carboxylate **15** (Scheme 1, route C) as entries towards the synthesis of substituted benzo[*g*] isoquinoline-1,5,10(2*H*)-triones **9**.



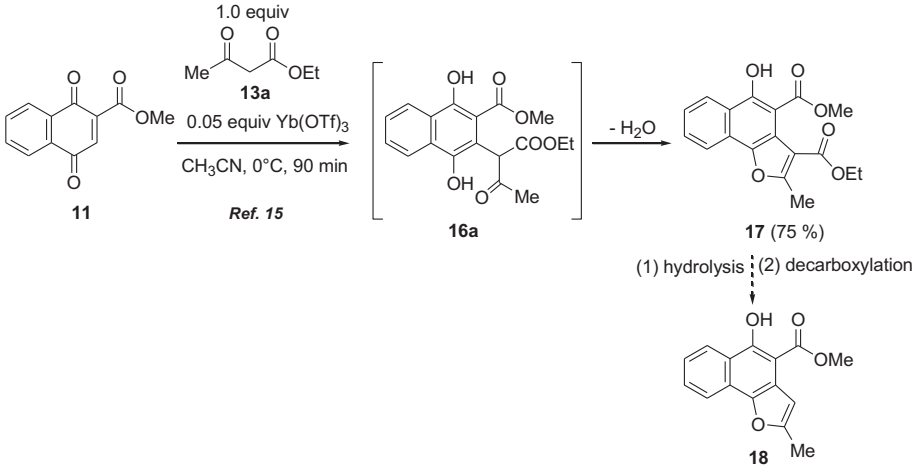
Scheme 1.

2. Results and discussion

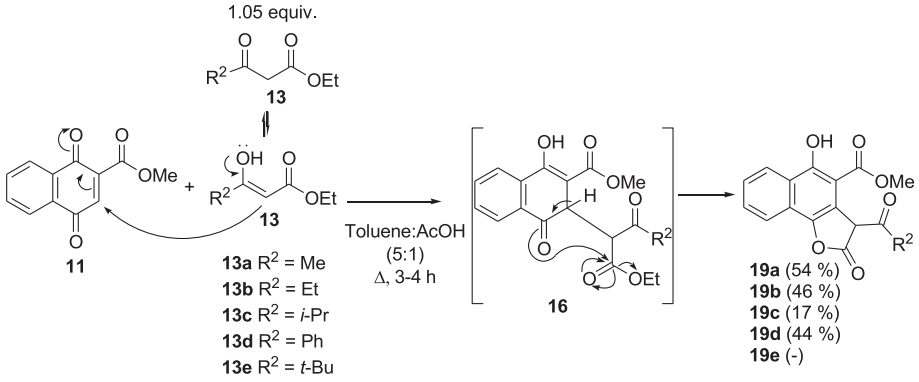
2.1. Route A

The addition of β-ketoesters to quinones under basic[13] and radical[14] conditions has been well described, but few reports are disclosed on this addition reaction under acidic conditions[15] despite the fact that experiments[14,15] and ab initio calculations[16] showed that quinones behave better as electrophiles under acidic conditions. Therefore, the addition of β-ketoesters **13** to 2-methoxycarbonyl-1,4-naphthoquinone **11**[17] was conducted under acidic conditions in order to avoid the formation of the kinetic product of the reaction, i.e., ethyl 5-hydroxy-4-methoxycarbonyl-2-methylnaphtho[1,2-*b*]furan-3-carboxylate **17** and its subsequent decarboxylated derivative **18**, which would divert the course of the synthesis.[15] The naphtho[1,2-*b*]furan **17** arises from the intramolecular nucleophilic attack of the intermediate phenol of the adduct **16a** across the ketone function of the acetonyl moiety (Scheme 2). Therefore, test reactions were conducted under different reaction conditions treating the activated naphthoquinone **11** with ethyl acetoacetate **13a**. The desired naphtho[1,2-*b*]furan-2(3*H*)-one **19a** was obtained in 54% yield when using a mixture of toluene and acetic acid (5:1) under reflux for 4 h (Scheme 3).

Extending the optimized reaction conditions for the synthesis of other derivatives **19b**–**d** from 2-methoxycarbonyl-1,4-naphthoquinone **11** and higher β-ketoesters **13** was successful in low (17%) to moderate yield (54%) except for compound **19e** due to the steric hindrance of the bulky *tert*-butyl group, which afforded



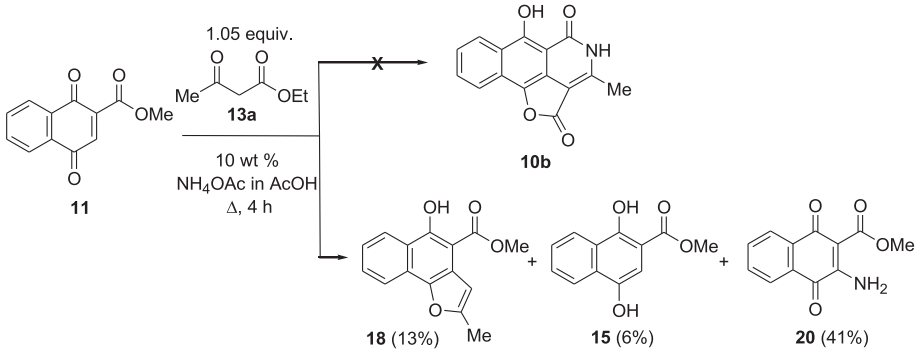
Scheme 2.



Scheme 3.

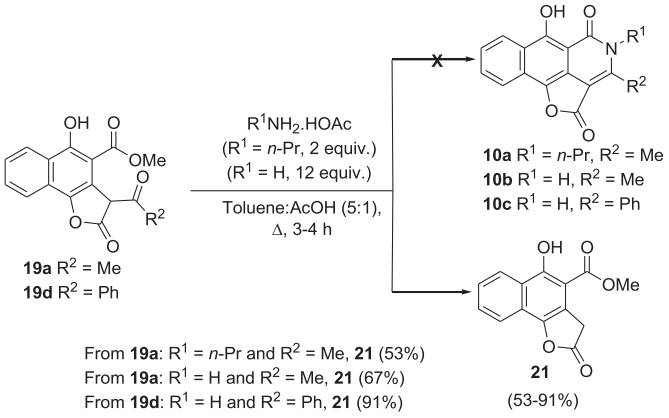
a very complex mixture without a trace of the targeted compound **19e** as checked by NMR and LC–MS analysis.

In a following part, a one-pot synthesis of benzo[*g*]furo[4,3,2-*de*] isoquinoline-2,5(4*H*)-diones **10** was investigated by reaction of the activated naphthoquinone **11** with ethyl acetoacetate **13a** and ammonium acetate in boiling acetic acid. However, no trace of compound **10b** was observed while the naphtho[1,2-*b*]furan **18** was isolated in 13% yield together with methyl 1,4-dihydroxynaphthalene-2-carboxylate **15** and 3-amino-2-methoxycarbonyl-1,4-naphthoquinone **20** in 6% and 41% yield, respectively (Scheme 4).



Scheme 4.

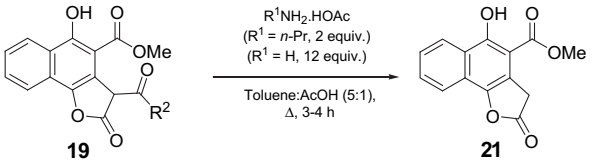
The formation of the tricyclic compound **18** arose from a condensation reaction outlined in Scheme 2. The formation of methyl 1,4-dihydroxynaphthalene-2-carboxylate **15** and 3-amino-2-methoxycarbonyl-1,4-naphthoquinone **20** was also observed recently by the reaction of the activated naphthoquinone **11** with an excess of ammonium acetate in boiling acetic acid.[9a] Therefore, the outcome of the competitive addition of ammonia and of the enolate of ethyl acetoacetate **13a** to 2-methoxycarbonyl-1,4-naphthoquinone **11** led favourably towards the facile ammonia addition compared to that of the ethyl acetoacetate **13a**. Under these conditions, the ammonia adduct **20** is formed preferentially in comparison with compound **18**, which is supported by the respective isolated yields of each addition product, and as a consequence, treatment of the activated naphthoquinone **11** with β-ketoesters **13** and ammonium acetate in boiling acetic acid did not appear to be the right condition to set an efficient one-pot synthesis of benzo[*g*]furo[4,3,2-*de*]isoquinoline-2,5(4*H*)-diones **10**. Thus, an alternative synthesis was to be envisaged in order to prepare the target intermediates **10** from methyl 3-acyl-2,3-dihydro-5-hydroxy-2-oxonaphtho[1,2-*b*]furan-4-carboxylates **19** and primary amines **12**. Unfortunately, treatment of methyl 3-acetyl-2,3-dihydro-5-hydroxy-2-oxonaphtho[1,2-*b*]furan-4-carboxylate **19a** with 2 equiv of *n*-propylammonium acetate, which was generated in situ by the reaction of *n*-propylamine and acetic acid at 0 °C for 30 min, in boiling toluene-acetic acid (5:1) resulted in the formation of methyl 2,3-dihydro-5-hydroxy-2-oxonaphtho[1,2-*b*]furan-4-carboxylate **21** in 53% yield instead of the targeted 2,3-dialkylbenzo[*g*]furo[4,3,2-*de*]isoquinoline-2,5(4*H*)-dione **10a** (Scheme 5). Facing this drawback, different attempts were made to insert the nitrogen atom using an excess of ammonium acetate in different solvents in order to reduce the eventual steric effect that might be exhibited by an alkyl group.



Scheme 5.

However, all the attempts failed to afford compound **10a** (Table 1, entries 2–4) and provided the same unexpected methyl 2,3-dihydro-5-hydroxy-2-oxonaphtho[1,2-*b*]furan-4-carboxylate **21** in 46–67% yield. An attempt to increase the substrate electrophilicity of the carbonyl group by substitution of the methyl group in methyl 3-acetyl-2,3-dihydro-5-hydroxy-2-oxonaphtho[1,2-*b*]furan-4-carboxylate **19a** with a phenyl group in methyl 3-benzoyl-2,3-dihydro-5-hydroxy-2-oxonaphtho[1,2-*b*]furan-4-carboxylate **19d** improved the yield of the same product **21** to 91% (Table 1, entry 5), probably by limiting side reactions.

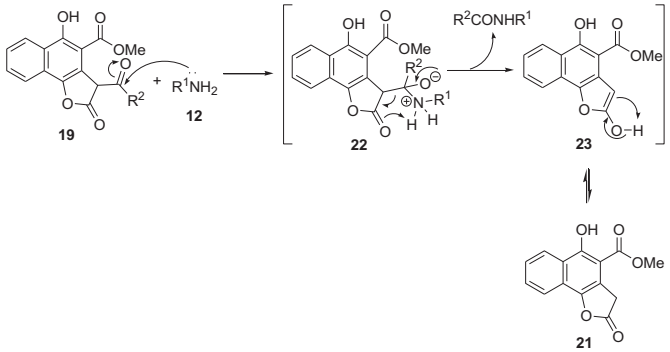
Table 1
Reaction conditions for the conversion of methyl 3-acyl-2,3-dihydro-5-hydroxy-2-oxonaphtho[1,2-*b*]furan-4-carboxylates **19a**,**d** to methyl 2,3-dihydro-5-hydroxy-2-oxonaph-tho[1,2-*b*]furan-4-carboxylate **21**



19 21

Entry	Substrate	Equiv of R^1NH_2 ·HOAc	Solvent and reaction conditions	Isolated yield of **21** (%)
1	**19a**	2 (R^1=*n*-Pr)	Toluene/AcOH (5:1), Δ, 3 h	53
2	**19a**	12 (R^1=H)	Toluene, Δ, 4 h	46
3	**19a**	12 (R^1=H)	AcOH, Δ, 4 h	54
4	**19a**	12 (R^1=H)	Toluene/AcOH (5:1), Δ, 4 h	67
5	**19d**	12 (R^1=Ph)	Toluene/AcOH (5:1), Δ, 4 h	91

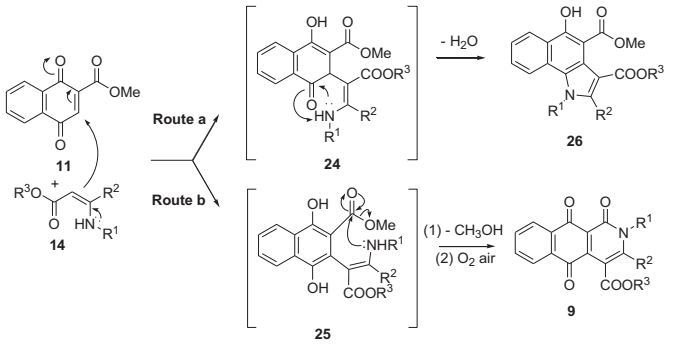
The formation of methyl 2,3-dihydro-5-hydroxy-2-oxonaphtho[1,2-*b*]furan-4-carboxylate **21** can be explained by a nucleofuge group expulsion of intermediate **22**, which is formed after the addition of the amine across the acyl or benzoyl group of naphthofuran derivatives **19**, and subsequent keto-enol tautomerism (Scheme 6). The difficult access to the key intermediates **10** by reaction of naphthofurans **19** with amines put a serious impediment to this first route A towards the targeted benzo[*g*]isoquinoline-1,5,10(2*H*)-triones **9** and prompted us to work out the second route B, which calls upon *N*-substituted enaminoesters **14**.



Scheme 6.

2.2. Route B

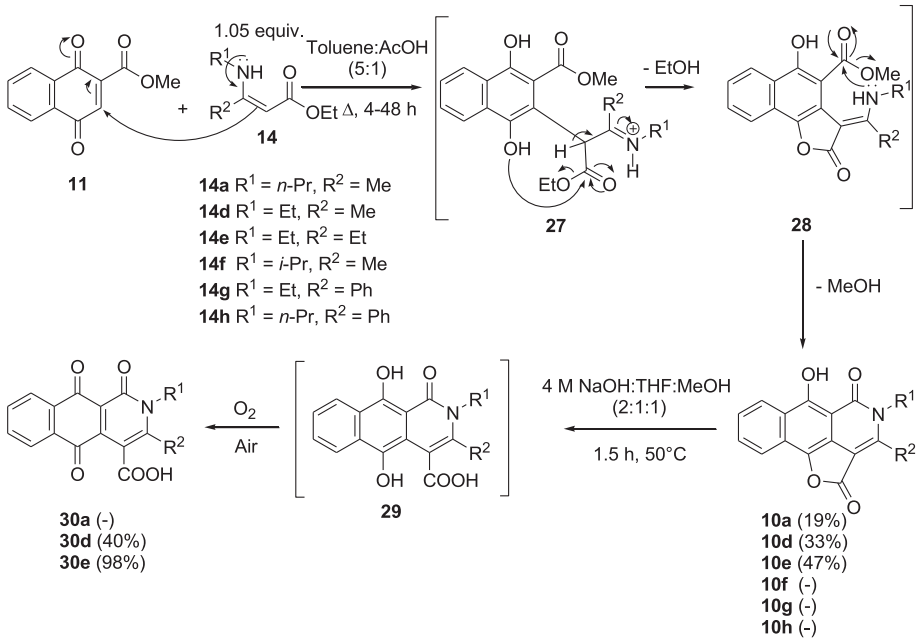
The reaction of enaminoesters with simple quinones is known in the literature as the Nenitzescu reaction.[17] In case of 2-methoxycarbonyl-1,4-naphthoquinone **11** as the substrate, enaminoesters **14**[18] add to this activated quinone to form tautomeric intermediates **24** and **25**, which can cyclize in two modes. The first mode implies a nucleophilic attack of the amino group of compound **24** across the ketone moiety leading to an annelated indole **26**, while the second mode implies a nucleophilic attack of the amino group of intermediate **25** across the ester carbonyl group leading to benzo[*g*]isoquinoline-1,5,10(2*H*)-triones **9** (Scheme 7).



Scheme 7.

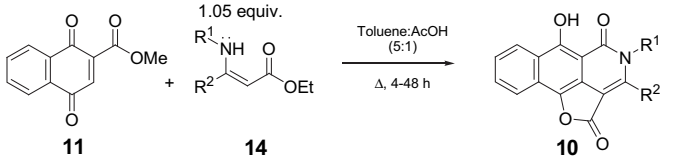
The reaction of the activated naphthoquinone **11** with *N*-*n*-propyl- and *N*-ethylamino-2-butenoates **14a** and **14d** in boiling toluene/acetic acid (5:1), as previously established in the case of β-ketoesters, furnished the hydroquinone adducts **25**, which cyclized to compounds **10** (Scheme 8, Table 2). Structure determination of the compounds, which were isolated from the reaction crudes, excluded annelated indoles **26** as a possible structure for these compounds, since the ^{13}C NMR spectra showed the presence of an amide as well as an ester function (Scheme 7). However, the *para*-quinone system of the alternative compound **9** was not present in the ^{13}C NMR and the IR showed the presence of a hydroxyl group. In this way, the molecular structure of the isolated compounds was determined to be 6-hydroxy-3-methylbenzo[*g*]furo[4,3,2-*de*]isoquinoline-2,5(4*H*)-diones **10**. Amending the above mentioned reactions, the hydroquinone adducts **25** were found to cyclize hardly to 6-hydroxy-4-*n*-propyl-3-methylbenzo[*g*]furo[4,3,2-*de*]isoquinoline-2,5(4*H*)-dione **10a** and 4-ethyl-6-hydroxy-3-methyl-benzo[*g*]furo[4,3,2-*de*]isoquinoline-2,5(4*H*)-dione **10d** (Table 2, entries 1 and 2). Nevertheless, the use of *N*-ethylamino-2-pentenoate **14e** resulted in a spontaneous cyclization to the targeted benzo[*g*]furo[4,3,2-*de*]isoquinoline-2,5(4*H*)-dione **10e** upon boiling in toluene: acetic acid (5:1) for 4 h (Table 2, entry 3). Other substituent combinations utilizing enaminoesters **14f**–**g** gave intractable mixtures of compounds, from which the targeted compounds could not be isolated by column chromatography and/or recrystallization. This can be ascribed to a difficult cyclization of intermediate naphtho[1,2-*b*]furans **28**, even upon prolongation of the reaction time to 48 h, which results in a partial degradation of the compounds (Table 2, Scheme 8).

Finally, 4-ethyl-6-hydroxy-3-methylbenzo[*g*]furo[4,3,2-*de*]isoquinoline-2,5(4*H*)-dione **10d** and 3,4-diethyl-6-hydroxybenzo[*g*]furo[4,3,2-*de*]isoquinoline-2,5(4*H*)-dione **10e** were hydrolyzed to 2-ethyl-3-methyl-1,2,5,10-tetrahydro-1,5,10-trioxobenzo[*g*]isoqui-noline-4-carboxylic acid **30d** and 2,3-diethyl-1,2,5,10-tetrahydro-1,5,10-trioxobenzo[*g*]isoquinoline-4-carboxylic acid **30e** in 40 and 98% of crude yield, respectively, using 4 M NaOH/THF/MeOH (2:1:1) at 50 °C for 1.5 h and subsequent spontaneous air oxygen oxidation. However, hydrolysis of 6-hydroxy-3-methyl-4-*n*-propylbenzo[*g*]furo[4,3,2-*de*]isoquinoline-2,5(4*H*)-dione **10a** under the same conditions gave a complex mixture of reaction products (Scheme 8). All attempts to purify compounds **30d** and **30e** by chromatography and recrystallization techniques failed.

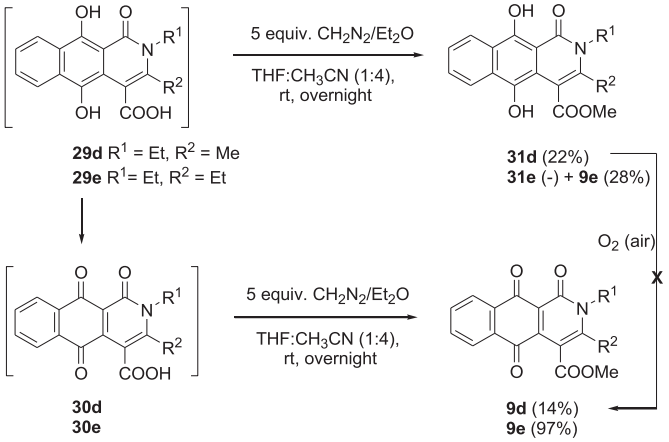


Scheme 8.

Table 2
Reaction of different *N*-substituted enaminoesters **14** with 2-methoxycarbonyl-1,4-naphthoquinone **11** in boiling toluene: acetic acid (5:1) to afford 3,4-dialkyl-6-hydroxybenzo[*g*]furo[4,3,2-*de*]isoquinoline-2,5(4*H*)-diones **10**



Entry	Enaminoester	R^1	R^2	Reaction time (h)	Isolated product	Yield (%)
1	**14a**	*n*-Pr	Me	36	**10a**	19
2	**14d**	Et	Me	36	**10d**	33
3	**14e**	Et	Et	4	**10e**	47
4	**14f**	*i*-Pr	Me	36	—	—
5	**14g**	Et	Ph	48	—	—
6	**14h**	*n*-Pr	Ph	48	—	—



Scheme 9.

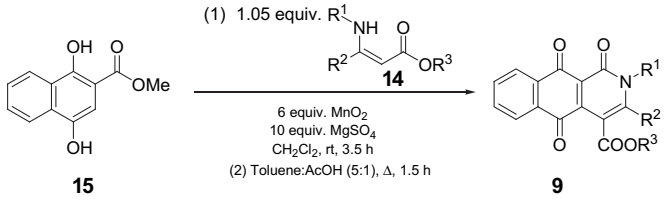
Therefore, the crude extracts of the hydrolysis reactions containing 2-ethyl-3-methyl-1,2,5,10-tetrahydro-1,5,10-trioxobenzo[*g*]isoquinoline-4-carboxylic acid **30d** and 2,3-diethyl-1,2,5,10-tetrahydro-1,5,10-trioxobenzo[*g*]isoquinoline-4-carboxylic acid **30e**, respectively, have been converted to the corresponding methyl esters by treatment with a solution of diazomethane in anhydrous diethyl ether at room temperature (Scheme 9). In the first case, methyl 2-ethyl-3-methyl-1,2,5,10-tetrahydro-1,5,10-trioxobenzo[*g*]isoquinoline-4-carboxylate **9d** was isolated together with methyl 2-ethyl-1,2-dihydro-5,10-dihydroxy-3-methyl-1-oxobenzo[*g*]isoquinoline-4-carboxylate **31d** in 14% and 22% yield, respectively. Different attempts to purify compound **31d** by preparative TLC and recrystallization failed. In order to get full conversion of intermediate hydroquinone **31d** to benzo[*g*]isoquinoline-1,5,10(2*H*)-trione **9d**, the workup extract of the diazomethane reaction was stirred with magnesium sulfate or silica gel for 24 h in the presence of air oxygen. Unfortunately, this operation failed to fully convert the reaction substrate to the targeted benzo[*g*]isoquinoline-1,5,10(2*H*)-trione **9d**. Secondly, methyl 2,3-diethyl-1,2,5,10-tetrahydro-1,5,10-trioxobenzo[*g*]isoquinoline-4-carboxylate **9e** was isolated as the sole product in an excellent yield of 97% directly after the treatment of compound **29e** with diazomethane in the presence of air. An attempt to obtain methyl 2,3-diethyl-1,2-dihydro-5,10-dihydroxy-1-oxobenzo[*g*]isoquinoline-4-carboxylate **31e** by running the reaction with diazomethane under nitrogen atmosphere and quickly performing the workup of the reaction gave methyl 2,3-diethyl-1,2,5,10-tetrahydro-1,5,10-trioxobenzo[*g*]isoquinoline-4-carboxylate **9e** in 28% yield and a complex fraction, which revealed the presence of very minute quantity of methyl 2,3-diethyl-1,2-dihydro-5,10-dihydroxy-1-oxobenzo[*g*]isoquinoline-4-carboxylate **31e** upon LC–MS analysis.

The remarkable differences observed in the chemical behaviour of compound **31d** in comparison with compound **31e** on the one hand and of benzo[*g*]isoquinoline-1,5,10(2*H*)-trione **9d** in comparison with compound **9e** on the other hand, were clues for the development of a short alternative procedure, such as the direct reaction of methyl 1,4-dihydroxynaphthalene-2-carboxylate **15** with enaminoesters **14** under oxidative conditions.

2.3. Route C

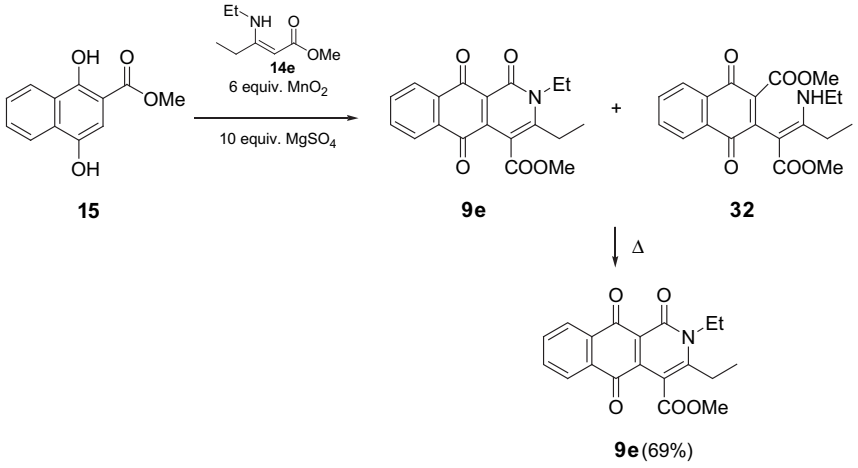
First, the reaction of methyl 1,4-dihydroxynaphthalene-2-carboxylate **15** with enaminoester **14e** was screened in order to optimize the oxidative addition reaction for these reaction substrates. An excess of oxidant was needed to assure the oxidation of hydroquinone **15** before the addition reaction and of the adduct after the addition of enaminoester **14e**. Therefore, methyl 1,4-dihydroxynaphthalene-2-carboxylate **15** and enaminoester **14e** were reacted using manganese oxide as the oxidant of choice. At the end, methyl 2,3-diethyl-1,2,5,10-tetrahydro-1,5,10-trioxobenzo[*g*]isoquinoline-4-carboxylate **9e** was obtained in 69% yield over two steps using 6 equiv of manganese dioxide and 10 equiv of magnesium sulfate in anhydrous dichloromethane for 3.5 h at room temperature to afford a mixture of the targeted benzo[*g*]isoquinoline-1,5,10(2*H*)-trione **9e** and its precursor **32**, which was converted subsequently in the target compound **9e** by boiling in a mixture of toluene/acetic acid (5:1) (Table 3, entry 1). In the absence of acetic acid in the second step, the yield of the reaction was lowered (Table 3, entry 2). The attempts to prepare methyl 2,3-diethyl-1,2,5,10-tetrahydro-1,5,10-trioxobenzo[*g*]isoquinoline-4-carboxylate **9e** in a single step resulted in lower yields (Table 3, entries 3 and 4). It was noticed that the presence of acetic acid was detrimental to this direct one-step procedure.

Table 4
Synthesis of 2,3-disubstituted alkyl 1,2,5,10-tetrahydro-1,5,10-trioxobenzo[*g*]isoquinoline-4-carboxylates **9** by a two-steps procedure involving oxidative addition of enaminoesters **14** to methyl 1,4-dihydroxynaphthalene-2-carboxylate **15**



Entry	Enaminoester	R^1	R^2	R^3	Isolated product	Yield (%)
1	**14a**	*n*-Pr	Me	Me	**9a**	46
2	**14e**	Et	Et	Me	**9e**	69
3	**14g**	Et	Ph	Et	**9g**	32
4	**14h**	*n*-Pr	Ph	Et	**9h**	56
5	**14i**	*n*-Pr	Me	Et	**9i**	29
6	**14j**	*n*-Pr	Et	Me	**9j**	71

Table 3
Test reactions towards the direct synthesis of methyl 2,3-diethyl-1,2,5,10-tetrahydro-1,5,10-trioxobenzo[*g*]isoquinoline-4-carboxylate **9e**



Entry	Scale (mmol)	Reaction conditions	Yield **9e** (%)
1	1.15	(1) CH_2Cl_2, rt, 3.5 h, (2) Δ, Toluene/AcOH (5:1), 1 h	69
2	2.30	(1) CH_2Cl_2, rt, 3.5 h, (2) Δ, Toluene, 1 h	59
3	2.30	Δ, Toluene, 1.5 h	44
4	2.30	Δ, Toluene/AcOH (5:1), 1.5 h	12

Referring to the overall yield of each route, the two-steps procedure appeared to be the best entry towards benzo[*g*]isoquinoline-1,5,10(2*H*)-triones **9** compared to the direct one-step oxidative addition (Table 3, entries 3 and 4) and the multistep procedures previously elaborated and described earlier in this manuscript (routes A and B). Having in hand this two-steps procedure, other derivatives (**9a**,**e**–**j**) were prepared accordingly in 29–71% yields (Table 4).

3. Conclusion

A short and efficient synthesis of 2,3-disubstituted alkyl 1,2,5,10-tetrahydro-1,5,10-trioxobenzo[*g*]isoquinoline-4-carboxylates was achieved in two steps by reacting methyl 1,4-dihydroxynaphthalene-2-carboxylate with enaminoesters in the presence of 6 equiv of manganese dioxide and 10 equiv of magnesium sulfate in anhydrous dichloromethane for 3.5 h and subsequent boiling in a mixture of toluene/acetic acid (5:1).

4. Experimental section

4.1. General experimental methods

^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded with a Jeol NMR spectrometer. Peak assignments were performed with the aid of the DEPT technique, 2D COSY and HSQC

spectra. Mass spectra were recorded using a direct inlet system (70 eV) with a VL detector (ES, 4000 V). IR spectra were recorded with a Perkin Elmer FT-IR spectrometer. Elemental analyses were executed with a Perkin–Elmer Series II CHNS/O Analyzer 2400. Although numerous attempts were executed for the recrystallized compounds, the results were found to be unsatisfactory to date. Therefore, HRMS were recorded using a tandem spectrometer Agilent 6220 TOF-LC/MS. Melting points were recorded on a Buchi melting point B-540 apparatus and are not corrected. Flash chromatography was carried out using a glass column with silica gel (particle size 0.035–0.070 mm, pore diameter ca. 6 nm). Solvent systems for column chromatography were determined via initial TLC analysis (silica gel).

4.2. Synthesis of methyl 3-acyl-2,3-dihydro-5-hydroxy-2-oxonaphtho[1,2-*b*]furan-4-carboxylates 19

General procedure: To a solution of 2-methoxycarbonyl-1,4-naphthoquinone **11** (2.4 mmol, 0.5 g)[9a] in toluene (16.7 ml) were added acetic acid (3.3 ml) and 1.05 equiv of β-ketoesters **13a–e**, respectively. The reaction mixture was subsequently boiled under reflux for 4 h. After cooling to room temperature, the reaction mixture was poured in a saturated aqueous solution of sodium bicarbonate. The organic phase was separated and the remaining aqueous phase was extracted with 3×20 ml of dichloromethane. The combined extracts were dried over magnesium(II) sulfate. Solvent evaporation in vacuo furnished a crude solid, which was recrystallized from ethanol.

*4.2.1. Methyl 3-acetyl-2,3-dihydro-5-hydroxy-2-oxonaphtho[1,2-b]furan-4-carboxylate **19a**.* Green crystals, mp: 180.9–181.8 °C (EtOH). ^{1}H NMR ($CDCl_3$): δ 2.46 (3H, s, CH_3), 3.93 (3H, s, MeO), 5.17 (1H, s, H-3), 7.60–7.67 (1H, m, H-7 or H-8), 7.70–7.77 (1H, m, H-7 or H-8), 7.94 (1H, d, J=8.3 Hz, H-6 or H-9), 8.46 (1H, d, J=8.3 Hz, H-6 or H-9), 11.84 (1H, s, OH). ^{13}C NMR ($CDCl_3$): δ 29.34 (CH_3), 52.49 (C-3), 61.17 (OCH_3), 101.62 (C_{quat}), 114.26 (C_{quat}), 121.10 (CH), 123.51 (C_{quat}), 124.87 (CH), 125.56 (C_{quat}), 127.47 (CH), 130.86 (CH), 143.22 (C_{quat}), 159.07 (=C–O), 169.74 (O=C–O), 170.18 (O=C–O), 197.06 (C=O). IR (ATR): ν_{max} 3099, 1806, 1721, 1667, 1644, 1600 cm^{-1}. MS m/z (%): 301 ([M+H]$^+$, 100). Anal. Calcd for $C_{16}H_{12}O_6$: C 64.00, H 4.03; found: C 63.83, H 3.98. HRMS (ESI) for $C_{16}H_{12}O_6$: 299.0634 [M–H]$^+$, found 299.0563.

*4.2.2. Methyl 2,3-dihydro-5-hydroxy-3-(1-oxo-n-propyl)naphtho[1,2-b]furan-4-carboxylate **19b**.* Green crystals, mp: 154.7–156.0 °C (EtOH). ^{1}H NMR ($CDCl_3$): δ 1.15 (3H, t, J=7.2 Hz, CH_2CH_3), 2.65 (1H, qd, J=7.2, 8.9 Hz, $CH_aH_bCH_3'$), 3.03 (1H, qd, J=7.2, 8.9 Hz, $CH_aH_bCH_3$), 3.91 (3H, s, MeO), 5.17 (1H, s, H-3), 7.60–7.68 (1H, m, H-7 or H-8), 7.75-7.78 (1H, m, H-7 or H-8), 7.95 (1H, d, J=8.3 Hz, H-6 or H-9), 8.47 (1H, d, J=8.3 Hz, H-6 or H-9), 11.86 (1H, s, OH). ^{13}C NMR ($CDCl_3$): δ 7.58 (CH_2CH_3), 35.74 (CH_2), 52.42 (C-3), 60.53 (OCH_3), 101.60 (C_{quat}), 114.41 (C_{quat}), 121.10 (CH), 123.56 (C_{quat}), 124.89 (CH), 125.53 (C_{quat}), 127.40 (CH), 130.86 (CH), 143.28 (C_{quat}), 159.13 (=C–O), 169.76 (O=C–O), 170.48 (O=C–O), 199.85 (C=O). IR (ATR): ν_{max} 3078, 1804, 1745, 1724, 1660, 1646, 1646, 1598 cm^{-1}. MS m/z (%): 313 ([M–H]$^+$, 100). Anal. Calcd for $C_{17}H_{14}O_6$: C 64.97, H 4.49; found: C 64.54, H 4.00. HRMS (ESI) for $C_{17}H_{14}O_6$: 313.0790 [M–H]$^+$, found 313.0715.

*4.2.3. Methyl 2,3-dihydro-5-hydroxy-3-(1-oxoisobutyryl)naphtho[1,2-b]furan-4-carboxylate **19c**.* Green crystals, mp: 178.6–179.4 °C (EtOH). ^{1}H NMR ($CDCl_3$): δ 1.15 (3H, d, J=6.6 Hz, CH(CH_3)(CH_3)), 1.25 (1H, d, J=6.6 Hz, CH(CH_3)(CH_3)), 3.20 (1H, sept, J=6.6 Hz, CH(CH_3)$_2$), 3.91 (3H, s, MeO), 5.30 (1H, s, H-3), 7.64–7.67 (1H, m, H-7 or H-8), 7.72–7.77 (1H, m, H-7 or H-8), 7.96 (1H, d, J=8.3 Hz, H-6 or H-9), 8.48 (1H, d, J=8.3 Hz, H-6 or H-9), 11.96 (1H, s, OH). ^{13}C NMR ($CDCl_3$): δ 17.58 (CH(CH_3)(CH_3)), 19.31 (CH(CH_3)(CH_3)), 39.42 (CH(CH_3)$_2$), 52.47 (C-3), 59.65 (OCH_3), 101.92 (C_{quat}), 114.37 (C_{quat}), 121.12 (CH), 123.51 (C_{quat}), 124.89 (CH), 125.53 (C_{quat}), 127.42 (CH), 130.82 (CH), 143.12 (C_{quat}), 159.13 (=C–O), 170.05 (O=C–O), 170.25 (O=C–O), 202.94 (C=O). IR (ATR): ν_{max} 3790, 2980, 2921, 1798, 1716, 1660, 1598 cm^{-1}. MS m/z (%): 327 ([M–H]$^+$, 100). Anal. Calcd for $C_{18}H_{16}O_6$: C 65.85, H 4.91; found: C 65.60, H 4.26. HRMS (ESI) for $C_{18}H_{18}O_6$: 327.0947 [M–H]$^+$, found 327.0867.

*4.2.4. Methyl 3-benzoyl-2,3-dihydro-5-hydroxy-2-oxo-naphtho[1,2-b]furan-4-carboxylate **19d**.* Green crystals, mp: 219.1–220.3 °C (EtOH). ^{1}H NMR ($CDCl_3$): δ 3.44 (3H, s, MeO), 6.11 (1H, s, H-3), 7.59–7.71 (3H, m, H-3′, H-4′ and H-5′), 7.72–7.77 (1H, m, H-7 or H-8), 7.77–7.99 (1H, m, H-7 or H-8), 8.00 (1H, d, J=8.3 Hz, H-6 or H-9), 8.17–8.20 (2H, m, H-2′ and H-6′), 8.50 (1H, d, J=8.3 Hz, H-6 or H-9), 11.89 (1H, s, OH). ^{13}C NMR ($CDCl_3$): δ 52.10 (C-3), 55.68 (OCH_3), 101.49 (C_{quat}), 115.56 (C_{quat}), 121.15 (CH), 123.62 (C_{quat}), 124.87 (CH), 125.54 (C_{quat}), 127.34 (CH), 129.18 (2× CH), 129.51 (2× CH), 130.83 (CH), 134.31 (CH), 135.77 (C_{quat}), 143.57 (C_{quat}), 159.23 (=C–O), 169.68 (O=C–O), 170.65 (O=C–O), 190.61 (C=O). IR (ATR): ν_{max} 3056, 1798, 1688, 1660, 1649, 1597 cm^{-1}. MS m/z (%): 361 ([M–H]$^+$, 100). Anal. Calcd for $C_{21}H_{14}O_6$: C 69.61, H 3.89; found: C 69.09, H 3.16. HRMS (ESI) for $C_{21}H_{14}O_6$: 361.0790 [M–H]$^+$, found 361.0695.

4.3. Synthesis of methyl 5-hydroxy-2-methylnaphtho[1,2-*b*]furan-4-carboxylate 18

To a 10 wt % solution of ammonium acetate (1.0 g) in acetic acid (10 ml) were added 2-methoxycarbonyl-1,4-naphthoquinone **11** (2.4 mmol, 0.50 g) and ethyl acetoacetate **13a** (2.5 mmol, 0.32 g), and the reaction mixture was subsequently boiled under reflux for 4 h. After cooling to room temperature, the reaction mixture was poured in water. The organic phase was separated and the aqueous phase was extracted twice with 5 ml of dichloromethane. The combined organic extracts were washed with a saturated aqueous solution of sodium bicarbonate and then dried over magnesium(II) sulfate. Solvent evaporation in vacuo furnished a mixture of three compounds. Purification by column chromatography on silica gel with hexane/ethyl acetate (9:1) gave methyl 5-hydroxy-2-methylnaphthofuran-4-carboxylate **18** (0.08 g, 13%), methyl 1,4-dihydroxynaphthalene-2-carboxylate **15** (0.03 g, 6%) and 3-amino-2-methoxycarbonyl-1,4-naphthoquinone **20** (0.23 g, 41%). Spectral data of compounds **15** and **20** correspond to the experimental data in the literature.[9a]

White crystals, mp:136.0–136.9 °C. ^{1}H NMR ($CDCl_3$): δ 2.55 (3H, s, CH_3), 4.07 (3H, s, MeO), 6.82 (1H, s, H-3), 7.47 (1H, m, H-7 or H-8), 7.68 (1H, m, H-7 or H-8), 8.14 (1H, m, H-6 or H-9), 8.44 (1H, m, H-6 or H-9), 12.21 (1H, s, OH). ^{13}C NMR ($CDCl_3$): δ 14.27 (CH_3), 52.28 (CH), 99.50 (C_{quat}), 119.52 (C_{quat}), 120.50 (C_{quat}), 122.20 (C_{quat}), 124.50 (CH), 124.51 (C_{quat}), 124.75 (C_{quat}), 124.99 (CH), 130.00 (CH), 155.09 (C_{quat}), 158.96 (C_{quat}), 172.05 (O=C–O). IR (ATR): ν_{max} 3027, 1638, 1600 cm^{-1}. MS m/z (%): 257 ([M+H]$^+$, 100). Anal. Calcd for $C_{15}H_{12}O_4$: C 70.31, H 4.72, found: C 71.00, H 5.15. HRMS (ESI) for $C_{15}H_{12}O_4$: 257.0736 [M+H]$^+$, found 257.0350.

4.4. Synthesis of methyl 2,3-dihydro-5-hydroxy-2-oxonaphtho[1,2-*b*]furan-4-carboxylate 21

To a solution of compound **19a** or **19d** (0.25 g) in toluene (10 ml) and acetic acid (2 ml) was added 12 equiv of ammonium acetate, and the reaction mixture was heated under reflux for 4 h. After cooling to room temperature, the reaction mixture was poured in water. The organic phase was separated and the aqueous phase was extracted with 3×8 ml of dichloromethane. The combined organic extracts were washed with a saturated solution of sodium bicarbonate, brine and dried over magnesium(II) sulfate. Solvent evaporation in vacuo furnished a solid, which was recrystallized

from ethanol to furnish methyl 2,3-dihydro-5-hydroxy-2-oxonaphtho[1,2-*b*]furan-4-carboxylate **21**.

Brown crystals, mp: 172.5–173.3 °C (EtOH). ^{1}H NMR ($CDCl_3$): δ 4.03 (3H, s, MeO), 4.07 (2H, s, H-3), 7.60 (1H, dd, *J*=7.9, 8.2 Hz, H-7), 7.73 (1H, dd, *J*=7.7, 7.9 Hz, H-8), 7.96 (1H, *J*=7.7 Hz, H-9), 8.45 (1H, d, *J*=8.2 Hz, H-6), 11.93 (1H, s, OH). ^{13}C NMR ($CDCl_3$): δ 36.79 (CH_2), 52.74 (CH), 101.93 (C_{quat}), 114.79 (C_{quat}), 120.90 (CH), 123.71 (C_{quat}), 124.72 (CH), 126.78 (CH), 130.63 (CH), 142.75 (C_{quat}), 158.61 (C_{quat}), 170.78 (O=C–O), 174.86 (O=C–O). IR (ATR): ν_{max} 3566, 3118, 3028, 2958, 1788, 1670, 1644, 1599 cm^{-1}. MS *m*/*z* (%): 257 ([M–H]$^+$, 100). Anal. Calcd for $C_{15}H_{12}O_4$: C 65.12, H 3.90; found: C 64.70, H 2.62. HRMS (ESI) for $C_{15}H_{12}O_4$: 257.0528 [M–H]$^+$, found 257.0450.

4.5. Synthesis of 3,4-dialkyl-6-hydroxybenzo[*g*]furo[4,3,2-*de*] isoquinoline-2,5(4*H*)-diones 10

General procedure: To a solution 2-methoxycarbonyl-1,4-naphthoquinone **11** (2.40 mmol, 0.50 g) in toluene (16.7 ml) were added acetic acid (3.3 ml) and 1.05 equiv of the appropriate enaminoester **14a**–**h**, respectively. The reaction mixture was subsequently boiled under reflux for 4–48 h (Table 2). The reaction was followed to completion by TLC and LC–MS. After cooling to room temperature, the target compounds **10a**, **10d** and **10e** precipitated as yellow-orange solids from the reaction mixture. After filtration of the crystals, the filtrate was poured in a saturated aqueous solution of sodium bicarbonate. The organic phase was separated and the aqueous phase was extracted with 3×20 ml of dichloromethane. The combined organic extracts were dried over magnesium(II) sulfate. Solvent evaporation in vacuo furnished crude solids, which were mixed with the isolated yellow-orange precipitate and were then recrystallized from ethanol.

4.5.1. 6-Hydroxy-3-methyl-4-n-propylbenzo[g]furo[4,3,2-de]isoquinoline-2,5(4H)-dione ***10a***. Orange crystals, mp: 241.7–242.9 °C (EtOH). ^{1}H NMR ($CDCl_3$): δ 1.08 (3H, t, *J*=7.1 Hz, $NCH_2CH_2CH_3$), 1.85–1.75 (2H, m, $NCH_2CH_2CH_3$), 2.86 (3H, s, CH_3), 4.10 (2H, t, *J*=7.2 Hz, $NCH_2CH_2CH_3$), 7.49 (1H, ddd, *J*=1.4, 7.0, 8.8 Hz, H-7 or H-8), 7.68 (1H, ddd, *J*=1.4, 7.0, 8.8 Hz, H-7 or H-8), 7.98–8.01 (1H, dm, *J*=8.8 Hz, H-6 or H-9), 8.42–8.45 (1H, m, H-6 or H-9), 10.26 (1H, s, OH). ^{13}C NMR ($CDCl_3$): δ 11.43 (CH_3), 16.13 (CH_3), 22.84 ($NCH_2CH_2CH_3$), 45.37 (NCH_2), 100.67 (C_{quat}), 101.94 (C_{quat}), 120.31 (CH), 120.63 (C_{quat}), 122.32 (C_{quat}), 122.86 (C_{quat}), 124.44 (CH), 124.67 (CH), 129.82 (CH), 134.13 (C_{quat}), 150.72 (C_{quat}), 153.16 (=C–O), 165.36 (O=C–N), 166.51 (O=C–O). IR (ATR): ν_{max} 3170, 1793, 1754, 1676, 1636, 1610, 1225 cm^{-1}. MS *m*/*z* (%): 310 ([M+H]$^+$, 100). Anal. Calcd for $C_{18}H_{15}NO_4$: C 69.89, H 4.89, N 4.53; found: C 68.89, H 4.30, N 4.36. HRMS (ESI) for $C_{18}H_{15}NO_4$: 308.1001 [M–H]$^+$, found 308.0930.

4.5.2. 4-Ethyl-6-hydroxy-3-methylbenzo[g]furo[4,3,2-de]isoquinoline-2,5(4H)-dione ***10d***. Orange crystals, mp: 243.1–244.6 °C (EtOH). ^{1}H NMR ($CDCl_3$): δ 1.40 (3H, t, *J*=7.1 Hz, NCH_2CH_3), 2.86 (3H, s, CH_3), 4.23 (2H, q, *J*=7.1 Hz, NCH_2CH_3), 7.49 (1H, ddd, *J*=1.4, 7.0, 8.8 Hz, H-7 or H-8), 7.68 (1H, ddd, *J*=1.4, 7.0, 8.8 Hz, H-7 or H-8), 7.98–8.02 (1H, dm, *J*=8.8 Hz, H-6 or H-9), 8.27–8.46 (1H, m, H-6 or H-9), 10.23 (1H, s, OH). ^{13}C NMR ($CDCl_3$): δ 14.27 (CH_3), 16.01 (CH_3), 38.96 (NCH_2), 100.67 (C_{quat}), 101.97 (C_{quat}), 120.32 (CH), 120.32 (C_{quat}), 122.18 (C_{quat}), 122.87 (C_{quat}), 124.46 (CH), 124.69 (CH), 129.84 (CH), 140.35 (C_{quat}), 150.55 (C_{quat}), 153.16 (=C–O), 165.21 (O=C–N), 167.09 (O=C–O). IR (ATR): ν_{max} 3170, 1793, 1754, 1676, 1636, 1610, 1225 cm^{-1}. MS *m*/*z* (%): 296 ([M+H]$^+$, 100). Anal. Calcd for $C_{17}H_{13}NO_4$: C 69.15, H 4.44, N 4.74; found: C 68.16, H 3.54, N 4.49. HRMS (ESI) for $C_{17}H_{13}NO_4$: 294.0845 [M–H]$^+$, found 294.0768.

4.5.3. 3,4-Diethyl-6-hydroxybenzo[g]furo[4,3,2-de]isoquinoline-2,5(4H)-dione ***10e***. Yellow crystals, mp: 200.7–201.6 °C (EtOH). ^{1}H NMR ($CDCl_3$): δ 1.41 (3H, t, *J*=7.2 Hz, CH_2CH_3), 1.49 (3H, t, *J*=7.2 Hz, NCH_2CH_3), 3.22 (2H, q, *J*=7.2 Hz, CH_2CH_3), 4.22 (2H, q, *J*=7.2 Hz, NCH_2CH_3), 7.46 (1H, ddd, *J*=1.4, 7.0, 8.8 Hz, H-7 or H-8), 7.65 (1H, ddd, *J*=1.4, 7.0, 8.8 Hz, H-7 or H-8), 7.94–7.99 (1H, dm, *J*=8.8 Hz, H-6 or H-9), 8.38–8.43 (1H, m, H-6 or H-9), 10.20 (1H, s, OH). ^{13}C NMR ($CDCl_3$): δ 13.91 (CH_3), 14.90 (CH_3), 22.84 (CH_2CH_3), 38.68 (NCH_2), 100.70 (C_{quat}), 100.90 (C_{quat}), 120.18 (CH), 120.76 (C_{quat}), 122.14 (C_{quat}), 122.72 (C_{quat}), 124.35 (CH), 124.58 (CH), 129.73 (CH), 134.37 (C_{quat}), 153.00 (C_{quat}), 156.38 (=C–O), 165.34 (O=C–N), 166.57 (O=C–O). IR (ATR): ν_{max} 3170, 1793, 1754, 1676, 1636, 1610, 1225 cm^{-1}. MS *m*/*z* (%): 310 ([M+H]$^+$, 100). Anal. Calcd for $C_{18}H_{15}NO_4$: C 69.89, H 4.89, N 4.53; found: C 69.39, H 4.47, N 4.40. HRMS (ESI) for $C_{18}H_{15}NO_4$: 308.1001 [M–H]$^+$, found 308.0920.

4.6. Synthesis of 2,3-dialkyl-1,2,5,10-tetrahydro-1,5,10-trioxobenzo[g]isoquinoline-4-carboxylic acids 30

General procedure: 100 mg of 3,4-dialkyl-6-hydroxybenzo[*g*]furo[4,3,2-*de*]isoquinoline-2,5(4*H*)-diones **10d** (0.34 mmol) and **10e** (0.32 mmol) were added to a solution of 2 ml of 4 M NaOH, 1 ml of THF and 1 ml of MeOH. This reaction mixture was stirred for 1.5 h in an oil bath, which was preheated to 50 °C, and then it was cooled to room temperature. The reaction mixture was poured in 8 ml of 1 M HCl and extracted with 3×5 ml of chloroform. The combined organic extracts were washed with brine and concentrated in vacuo to afford the target compounds **30d** and **30e** (purity 81–83%). All attempts to purify the latter compounds by column chromatography and/or recrystallization techniques failed as it resulted in degradation of the products.

4.6.1. 2-Ethyl-3-methyl-1,2,5,10-tetrahydro-1,5,10-trioxobenzo[g]isoquinoline-4-carboxylic acid ***30d***. Brown powder, mp: 190.6–191.8 °C. ^{1}H NMR (DMSO-d_6): δ 1.24–1.28 (3H, t, *J*=7.1 Hz, NCH_2CH_3), 2.51 (3H, s, CH_3), 4.12 (2H, q, *J*=7.1 Hz, NCH_2CH_3), 7.82–7.987 (1H, dd, *J*=6.3 and 7.1 Hz, H-7 or H-8), 7.90–7.95 (1H, dd, *J*=6.6 and 7.1 Hz, H-7 or H-8), 8.02 (1H, d, *J*=7.1 Hz, H-6 or H-9), 8.07 (1H, d, *J*=7.1 Hz, H-6 or H-9). ^{13}C NMR (DMSO): δ 13.40 (CH_3), 18.65 (CH_3), 79.74 (NCH_2), 111.89 (C_{quat}), 116.66 (C_{quat}), 126.58 (CH), 126.72 (CH), 131.8 (C_{quat}), 134.00 (2× CH), 135.80 (C_{quat}), 141.29 (C_{quat}), 153.56 (C_{quat}), 157.56 (C_{quat}), 168.91 (O=C–N and O=C–O), 180.34 (C=O), 183.76 (C=O). IR (ATR): ν_{max} 3352, 3164, 3071, 2922, 2853, 2626, 2360, 2341, 1716, 1682, 1616, 1521, 1285 cm^{-1}. MS *m*/*z* (%): 312 ([M+H]$^+$, 100). Purity (LC–MS): 83%.

4.6.2. 2,3-Diethyl-1,2,5,10-tetrahydro-1,5,10-trioxobenzo[g]isoquinoline-4-carboxylic acid ***30e***. Brown powder, mp: 192.1–193.9 °C. ^{1}H NMR ($CDCl_3$): δ 1.43 (6H, 2×t, *J*=7.1 Hz, CH_2CH_3 and NCH_2CH_3), 2.94 (2H, q, *J*=7.1 Hz, CH_2CH_3), 4.28 (2H, q, *J*=7.1 Hz, NCH_2CH_3), 7.71–7.76 (1H, dd, *J*=7.1 and 7.1 Hz, H-7 or H-8), 7.80–7.85 (1H, dd, *J*=7.7 and 7.7 Hz, H-7 or H-8), 8.10 (1H, d, *J*=7.7 Hz, H-6 or H-9), 8.26 (1H, d, *J*=7.7 Hz, H-6 or H-9). ^{13}C NMR (DMSO-d_6): δ 14.15 (CH_3), 14.39 (CH_3), 25.28 (CH_2CH_3), 79.94 (NCH_2), 111.65 (C_{quat}), 117.10 (C_{quat}), 126.60 (CH), 126.72 (CH), 131.81 (C_{quat}), 134.02 (CH), 134.03 (C_{quat}), 135.82 (CH), 141.52 (C_{quat}), 157.67 (C_{quat}), 157.76 (CH), 168.75 (O=C–N and O=C–O), 180.39 (C=O), 183.76 (C=O). IR (ATR): ν_{max} 3342, 3165, 3073, 3025, 2963, 2700, 1750, 1678, 1606, 1528 cm^{-1}. MS *m*/*z* (%): 326 ([M+H]$^+$, 100). Purity (LC–MS): 81%.

4.7. Synthesis of alkyl 2,3-disubstituted alkyl 1,2,5,10-tetrahydro-1,5,10-trioxobenzo[g]isoquinoline-4-carboxylates 9

Procedure A: To a solution of 2,3-diethyl-1,2,5,10-tetrahydro-1,5,10-trioxobenzogisoquinoline-4-carboxylic acid **30e** (200 mg, 0.62 mmol) in 2 ml of THF and 8 ml of acetonitrile was added a freshly-prepared solution of 5 equiv of diazomethane in

anhydrous diethyl ether at room temperature. The reaction was run to completion after 2 h. Then the reaction mixture was poured in 10 ml of water and extracted with 3×10 ml of ethyl acetate. The combined organic extracts were washed with brine and dried over magnesium sulfate. The filtrate was concentrated under reduced pressure to form a crude solid, which was purified by preparative thin layer chromatography on silica gel using a mixture of hexane/ethyl acetate (1:4) as eluents to afford 203 mg (97%) of the target compound **9e**.

Procedure B, *Oxidative addition*: To a mixture of methyl 1,4-dihydroxynaphthalene-2-carboxylate **15** (0.5 g, 1.15 mmol), manganese oxide (1.34 g, 6.90 mmol) and magnesium(II) sulfate (2.76 g, 11.50 mmol) was added a solution of an appropriate enaminoester **14** (1.05 equiv in 20 ml of anhydrous dichloromethane). The reaction mixture was stirred at room temperature for 3.5 h, after which it was filtered and concentrated in vacuo. The resulting residue was dissolved in 15 ml of toluene and 3 ml of acetic acid, and this mixture was subsequently boiled under reflux for 1–1.5 h. After cooling to room temperature, the reaction mixture was poured in water and extracted with ethyl acetate (3×20 ml). The combined organic extracts were washed with aqueous saturated sodium bicarbonate and brine, after which they were dried ($MgSO_4$) and concentrated in vacuo. The obtained target compounds were recrystallized from methanol for compounds **9a**,**e** and from ethanol for compounds **9g**–**j**.

*4.7.1. Methyl 2-n-propyl-3-methyl-1,2,5,10-tetrahydro-1,5,10-trioxobenzo[g]isoquinoline-4-carboxylate **9a**.* Greenish brown powder, mp: not observed due to compound decomposition at 256 °C. ^{1}H NMR ($CDCl_3$): δ 1.01 (3H, t, J=7.4 Hz, $CH_2CH_2CH_3$), 1.77 (2H, sext, J=7.4 Hz, $NCH_2CH_2CH_3$), 3.19 (3H, s, CH_3), 4.00 (3H, s, OCH_3), 4.11 (2H, br s, $NCH_2CH_2CH_3$), 7.76 (1H, t, J=7.7 Hz, H-7 or H-8), 7.83 (1H, t, J=7.7 Hz, H-7 or H-8), 8.08 (1H, d, J=7.7 Hz, H-6 or H-9), 8.25 (1H, d, J=7.7 Hz, H-6 or H-9). ^{13}C NMR ($CDCl_3$): δ 11.17 ($NCH_2CH_2CH_3$), 22.67 ($NCH_2CH_2CH_3$), 30.73 (CH_3), 47.07 ($NCH_2CH_2CH_3$), 53.91 (OCH_3), 110.75 (C_{quat}), 118.86 (C_{quat}), 126.77 (CH), 127.28 (CH), 131.39 (C_{quat}), 133.59 (C_{quat}), 133.59 (CH), 135.47 (CH), 141.82 (C_{quat}), 151.41 (C_{quat}), 159.06 (O=C–N), 168.40 (O=C–O), 180.20 (C=O), 183.24 (C=O). IR (ATR): ν_{max} 2961, 1717, 1688, 1631, 1592, 1513, 1437, 1415, 1283, 1254, 1164, 969 cm^{-1}. MS m/z (%): 340 ([M+H]$^+$, 10), 699 (100). Anal. Calcd for $C_{19}H_{17}NO_5$: C 67.25, H 5.05, N 4.13; found: C 66.39, H 3.78, N 4.93. HRMS (ESI) for $C_{19}H_{17}O_5$: 340.1107 [M+H]$^+$, found 340.1181.

*4.7.2. Methyl 2-3-diethyl-1,2,5,10-tetrahydro-1,5,10-trioxobenzo[g]isoquinoline-4-carboxylate **9e**.* Red orange crystals, mp: 183.1–184.2 °C (MeOH). ^{1}H NMR ($CDCl_3$): δ 1.37 (3H, t, J=7.0 Hz, CH_2CH_3), 1.41 (3H, t, J=7.0 Hz, NCH_2CH_3), 2.80 (2H, q, J=7.0 Hz, CH_2CH_3), 4.00 (3H, s, OCH_3), 4.28 (2H, q, J=7.0 Hz, NCH_2CH_3), 7.72 (1H, d, J=7.7 Hz, H-7 or H-8), 7.82 (1H, d, J=7.7 Hz, H-7 or H-8), 8.09 (1H, d, J=7.7 Hz, H-6 or H-9), 8.25 (1H, d, J=7.7 Hz, H-6 or H-9). ^{13}C NMR ($CDCl_3$): δ 13.86 (CH_2CH_3), 14.13 (NCH_2CH_3), 25.35 (CH_2CH_3), 40.88 (NCH_2CH_3), 53.28 (OCH_3), 109.01 (C_{quat}), 117.60 (C_{quat}), 126.66 (CH), 127.19 (CH), 131.45 (C_{quat}), 133.36 (C_{quat}), 133.74 (CH), 135.30 (CH), 141.73 (C_{quat}), 157.36 (C_{quat}), 158.29 (O=C–N), 168.28 (O=C–O), 180.46 (C=O), 183.46 (C=O). IR (ATR): ν_{max} 2946, 1731, 1693, 1632, 1514, 1434, 1283, 1260, 1153, 1087, 994, 749 cm^{-1}. MS m/z (%): 340 ([M+H]$^+$, 100). Anal. Calcd for $C_{19}H_{17}NO_5$: C 67.25, H 5.05, N 4.13; found: C 67.04, H 4.47, N 5.53. HRMS (ESI) for $C_{19}H_{17}NO_5$: 340.1107 [M+H]$^+$, found 340.1201.

*4.7.3. Ethyl 2-ethyl-3-phenyl-1,2,5,10-tetrahydro-1,5,10-trioxobenzo[g]isoquinoline-4-carboxylate **9g**.* Yellow-orange crystals, mp: 193.4–194.2 °C (EtOH). ^{1}H NMR ($CDCl_3$): δ 1.00 (3H, t, J=7.1 Hz, NCH_2CH_3), 1.21 (3H, t, J=6.9 Hz, OCH_2CH_3), 3.97 (2H, q, J=7.1 Hz, NCH_2CH_3), 4.02 (2H, q, J=6.9 Hz, OCH_2CH_3), 7.37–7.40 (2H, m, H-2′ and H-5′), 7.49–7.56 (3H, m, H-3′, H-4′ and H-5′), 7.73 (1H, t, J=6.0 Hz, H-7 or H-8), 7.83 (1H, t, J=6.0 Hz, H-7 or H-8), 8.10 (1H, d, J=6.0 Hz, H-6 or H-9), 8.28 (1H, d, J=6.0 Hz, H-6 or H-9). ^{13}C NMR ($CDCl_3$): δ 13.66 (NCH_2CH_3), 13.94 (OCH_2CH_3), 43.13 (NCH_2CH_3), 61.77 (OCH_2CH_3), 111.88 (C_{quat}), 119.02 (C_{quat}), 126.67 (CH), 127.27 (CH), 128.49 (2× CH), 128.75 (2× CH), 130.47 (CH), 131.44 (C_{quat}), 131.57 (C_{quat}), 133.44 (CH), 133.77 (C_{quat}), 135.29 (CH), 141.42 (C_{quat}), 154.69 (C_{quat}), 157.89 (O=C–N), 166.45 (O=C–O), 180.63 (C=O), 183.21 (C=O). IR (ATR): ν_{max} 2991, 1735, 1658, 1628, 1591, 1523, 1488, 1444, 1400, 1327, 1223, 1182, 1150, 1047, 977, 916 cm^{-1}. MS m/z (%): 402 ([M+H]$^+$, 100). Anal. Calcd for $C_{24}H_{19}NO_5$: C 71.81, H 4.77, N 3.49; found: C 71.39, H 4.02, N 3.49. HRMS (ESI) for $C_{24}H_{19}O_5$: 402.1263 [M+H]$^+$, found 402.1344.

*4.7.4. Ethyl 3-phenyl-2-n-propyl-1,2,5,10-tetrahydro-1,5,10-trioxobenzo[g]isoquinoline-4-carboxylate **9h**.* Orange crystals, mp: 169.0–169.4 °C (EtOH). ^{1}H NMR ($CDCl_3$): δ 0.75 (3H, t, J=7.4 Hz, $NCH_2CH_2CH_3$), 1.00 (3H, t, J=7.1 Hz, OCH_2CH_3), 1.66 (2H, sext, J=7.4 Hz, $NCH_2CH_2CH_3$), 3.82 (2H, q, J=7.4 Hz, $NCH_2CH_2CH_3$), 4.02 (2H, q, J=7.1 Hz, OCH_2CH_3), 7.36–7.41 (2H, m, H-2′ and H-5′), 7.49–7.56 (3H, m, H-3′, H-4′ and H-5′), 7.73 (1H, t, J=6.0 Hz, H-7 or H-8), 7.83 (1H, t, J=6.0 Hz, H-7 or H-8), 8.10 (1H, d, J=6.0 Hz, H-6 or H-9), 8.28 (1H, d, J=6.0 Hz, H-6 or H-9). ^{13}C NMR ($CDCl_3$): δ 11.31 ($NCH_2CH_2CH_3$), 13.66 (OCH_2CH_3), 22.09 ($NCH_2CH_2CH_3$), 49.30 ($NCH_2CH_2CH_3$), 61.77 (OCH_2H_3), 111.80 (C_{quat}), 118.98 (C_{quat}), 126.67 (CH), 127.28 (CH), 128.57 (2× CH), 128.67 (2× CH), 130.46 (CH), 131.47 (C_{quat}), 131.57 (C_{quat}), 133.42 (CH), 133.79 (C_{quat}), 135.27 (CH), 141.39 (C_{quat}), 154.66 (C_{quat}), 158.00 (O=C–N), 166.47 (O=C–O), 180.59 (C=O), 183.23 (C=O). IR (ATR): ν_{max} 2980, 1688, 1628, 1593, 1524, 1492, 1446, 1406, 1320, 1285, 1177, 1166, 1024, 977, 928 cm^{-1}. MS m/z (%): 416 ([M+H]$^+$, 100). Anal. Calcd for $C_{25}H_{21}NO_5$: C 72.28, H 5.10, N 3.37; found: C 71.39, H 4.55, N 8.21. HRMS (ESI) for $C_{25}H_{21}NO_5$: 416.1419 [M+H]$^+$, found 416.1502.

*4.7.5. Ethyl 3-methyl-2-n-propyl-1,2,5,10-tetrahydro-1,5,10-trioxobenzo[g]isoquinoline-4-carboxylate **9i**.* Brown crystals, mp: 128.6–129.0 °C (EtOH). ^{1}H NMR ($CDCl_3$): δ 1.12 (3H, t, J=7.4 Hz, $CH_2CH_2CH_3$), 1.40 (3H, J=7.4 Hz, OCH_2CH_3), 1.77 (2H, sext, J=7.4 Hz, $NCH_2CH_2CH_3$), 3.18 (3H, s, CH_3), 4.26 (2H, br s, $NCH_2CH_2CH_3$), 4.48 (2H, q, J=7.4 Hz, OCH_2CH_3), 7.75 (1H, t, J=7.7 Hz, H-7 or H-8), 7.84 (1H, t, J=7.7 Hz, H-7 or H-8), 8.09 (1H, d, J=7.7 Hz, H-6 or H-9), 8.26 (1H, d, J=7.7 Hz, H-6 or H-9). ^{13}C NMR ($CDCl_3$): To date, a decent ^{13}C NMR spectrum of this derivative could not be recorded even upon prolongation of the relaxation delay and increasing the number of recorded scans. IR (ATR) ν_{max}: 2968, 1725, 1688, 1629, 1592, 1511, 1440, 1417, 1415, 1327, 1282, 1254, 1210, 1174, 1058, 1011, 968 cm^{-1}. MS m/z (%): 354 ([M+H]$^+$, 10%), 705 (100%). Anal. Calcd for $C_{20}H_{19}NO_5$: C 67.98, H 5.42, N 3.96; found: C 67.66, H 4.71, N 6.61. HRMS (ESI) for $C_{20}H_{19}NO_5$: 354.1263 [M+H]$^+$, found 354.1326.

*4.7.6. Methyl 3-ethyl-2-n-propyl-1,2,5,10-tetrahydro-1,5,10-trioxobenzo[g]isoquinoline-4-carboxylate **9j**.* Orange crystals, mp: 128.6–129.0 °C (EtOH). ^{1}H NMR ($CDCl_3$): δ 1.05 (3H, t, J=7.4 Hz, $CH_2CH_2CH_3$), 1.36 (3H, J=7.4 Hz, CH_2CH_3), 1.79 (2H, sext, J=7.4 Hz, $NCH_2CH_2CH_3$), 2.80 (2H, q, J=7.4 Hz, CH_2CH_3), 4.00 (3H, s, OCH_3), 4.11 (2H, q, J=7.4 Hz, NCH_2CH_3), 7.72 (1H, t, J=7.7 Hz, H-7 or H-8), 7.81 (1H, t, J=7.7 Hz, H-7 or H-8), 8.09 (1H, d, J=7.7 Hz, H-6 or H-9), 8.25 (1H, d, J=7.7 Hz, H-6 or H-9). ^{13}C NMR ($CDCl_3$): δ 11.52 (CH_3), 13.80 (CH_3), 22.35 (CH_2CH_3), 25.41 ($NCH_2CH_2CH_3$), 47.16 ($NCH_2CH_2CH_3$), 53.26 (OCH_3), 109.96 (C_{quat}), 117.57 (C_{quat}), 126.66 (CH), 127.21 (CH), 131.47 (C_{quat}), 133.35 (C_{quat}), 133.76 (CH), 135.29 (CH), 141.71 (C_{quat}), 157.41 (C_{quat}), 158.42 (O=C–N), 168.29 (O=C–O), 180.43 (C=O), 183.47 (C=O). IR (ATR): ν_{max} 2966, 1728, 1691, 1633, 1593, 1516, 1415, 1330, 1282, 1255, 1148, 1064, 979 cm^{-1}. MS

m/*z* (%): 354 ([M+H]$^+$, 100). Anal. Calcd for $C_{20}H_{19}NO_5$: C 67.98, H 5.42, N 3.96; found: C 67.73, H 4.92, N 12.35. HRMS (ESI) for $C_{20}H_{19}NO_5$: 354.1262 [M+H]$^+$, found 354.1262.

4.8. Synthesis of methyl 1,2-dihydro-5,10-dihydroxy-2-ethyl-3-methyl-1-oxobenzo[g]isoquinoline-4-carboxylate 31d

To a solution of 1,2-dihydro-5,10-dihydroxy-2-ethyl-3-methyl-1-oxobenzo[g]isoquinoline-4-carboxylic acid **29d** (200 mg, 0.64 mmol) in 2 ml of THF and 8 ml of acetonitrile was added a freshly-prepared solution of 5 equiv of diazomethane in anhydrous diethyl ether at room temperature. The reaction was run to completion, after which the reaction mixture was poured in 10 ml of water and extracted with 3×10 ml of ethyl acetate. The combined organic extracts were washed with brine and dried over magnesium(IV) sulfate in a flask, which was open to air and which was stirred vigorously for 1 h. After filtration, the solvent was evaporated in vacuo to form a crude solid, which was purified by preparative thin layer chromatography on silica gel using a mixture of hexane/ethyl acetate (1:4) as eluents to afford compound **31d** and compound **9d** in 22% and 14%, respectively.

*4.8.1. Methyl 1,2-dihydro-5,10-dihydroxy-2-ethyl-3-methyl-1-oxobenzo[g]isoquinoline-4-carboxylate **31d**.* Green sticky solid, ^{1}H NMR ($CDCl_3$): δ 1.40 (3H, t, *J*=7.5 Hz, NCH_2CH_3), 2.90 (3H, s, CH_3), 4.18 (3H, s, OCH_3), 4.25 (2H, q, *J*=7.5 Hz, NCH_2CH_3), 7.53 (1H, t, *J*=9.0 Hz, H-7 or H-8), 7.67 (1H, t, *J*=9.0 Hz, H-7 or H-8), 8.08 (1H, d, *J*=9.0 Hz, H-6 or H-9), 8.45 (1H, d, *J*=9.0 Hz, H-6 or H-9). ^{13}C NMR ($CDCl_3$): δ 14.12 (CH_3), 16.09 (CH_3), 39.65 (NCH_2CH_3), 63.72 (OCH_3), 99.91 (C_{quat}), 109.13 (C_{quat}), 120.58 (CH), 122.00 (C_{quat}), 122.54 (C_{quat}), 125.04 (CH), 125.70 (CH), 128.05 (C_{quat}), 129.27 (CH), 138.31 (C_{quat}), 151.70 (C_{quat}), 153.48 (C_{quat}), 160.13 (O=C–N), 166.95 (O=C–O). IR (ATR): ν_{max} 3347, 2944, 2358, 1751, 1672, 1638, 1440, 1396, 1366, 1237, 1044 cm^{-1}. MS *m*/*z* (%): 328 ([M+H]$^+$, 100).

*4.8.2. Methyl 2-ethyl-3-methyl-1,2,5,10-tetrahydro-1,5,10-trioxobenzo[g]isoquinoline-4-carboxylate **9d**.* Orange red powder, mp: not observed due to decomposition of the compound at 280 °C. ^{1}H NMR ($CDCl_3$): δ 1.42 (3H, t, *J*=7.4 Hz, CH_2CH_3), 3.19 (3H, s, CH_3), 4.09 (3H, s, OCH_3), 4.24 (2H, br s, NCH_2), 7.74 (1H, t, *J*=7.7 Hz, H-7 or H-8), 7.83 (1H, t, *J*=7.7 Hz, H-7 or H-8), 8.09 (1H, d, *J*=7.7 Hz, H-6 or H-9), 8.25 (1H, d, *J*=7.7 Hz, H-6 or H-9). ^{13}C NMR ($CDCl_3$): δ 14.27 (CH_2CH_3), 30.66 (CH_3), 41.32 (NCH_2), 53.79 (OCH_3), 110.74 (C_{quat}), 118.83 (C_{quat}), 126.61 (CH), 127.20 (CH), 131.28 (C_{quat}), 133.23 (C_{quat}), 135.43 (CH), 136.91 (CH), 141.78 (C_{quat}), 151.67 (C_{quat}), 157.94 (O=C–N), 168.33 (O=C–O), 180.36 (C=O), 183.32 (C=O). IR (ATR): ν_{max} 1735, 1687, 1508, 1416, 1281, 1259, 994 cm^{-1}. MS *m*/*z* (%): 326 ([M+H]$^+$, 100).

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