Tetrahedron 64 (2008) 7545–7554

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

First straightforward synthesis of 2,4-disubstituted benz[*g*]isoquinoline-3,5,10(2*H*)-triones, 1,2,3,5-substituted naphtho[3,2,1-*de*]isoquinoline-4,7-diones, and 6-substituted benzo[*h*]pyrido[3,4,5-*kl*]-1,2,3,4-tetrahydroacridine-5,8-diones

Jan Jacobs, Bart Kesteleyn, Norbert De Kimpe *

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

ARTICLE INFO

Article history:
Received 13 February 2008
Received in revised form 21 May 2008
Accepted 23 May 2008
Available online 28 May 2008

Keywords:
Benz[*g*]isoquinoline-3,5,10(2*H*)-triones
2-Azaanthraquinones
Quinones

ABSTRACT

Structural modifications to the benz[*g*]isoquinoline skeleton of *N*-substituted benz[*g*]isoquinoline-3,5,10(2*H*)-triones were envisaged in order to make future SAR studies possible for this type of bioactive compounds. Several *N*-substituted benz[*g*]isoquinoline-3,5,10(2*H*)-triones were converted to novel 2,4-substituted benz[*g*]isoquinoline-3,5,10(2*H*)-triones, new tetracyclic 1,2,3,5-substituted naphtho-[3,2,1-*de*]isoquinoline-4,7-diones, and 6-substituted benzo[*h*]pyrido[3,4,5-*kl*]-1,2,3,4-tetrahydroacridine-5,8-diones. All the synthesized target compounds represent new heterocyclic systems, which were previously undescribed in the literature.

1. Introduction

Naphthoquinones with annelated *N*-heterocycles constitute an important research area in organic synthesis due to the pronounced biological activities of several natural products (Fig. 1). For instance, the unsubstituted benz[*g*]isoquinoline-5,10-dione (**1**) has been isolated from *Psychotria camponutans* and *Mitracarpus scaber*, and is renowned for its strong activity against chloroquine-resistant *Plasmodium falciparum*, which is responsible for malaria.[1] In addition, the 2-azaanthraquinone **1** exhibits growth inhibition against the multi-drug resistant pathogen *Staphylococcus aureus*, and its good activity against *Trypanosoma congolense* has also been described.[1c,2] The naturally occurring bostrycoidin (**2**) and analogues **3**–**7** on the other hand have been isolated from different fungi,[3] and have been shown to possess interesting physiological activities, amongst which is the antibiotic activity against *Mycobacterium tuberculosis* and Gram-positive bacteria.[3a,4]

The naturally occurring 1-azaanthraquinone cleistopholin **10**, isolated from *Cleistopholis patens*, and synthetic analogues **9** and **11** are very strong inhibitors of *Mycobacterium intracellulare* with MIC's equal to or less than that of rifamycin.[5] Ascididemin, a naturally occurring 1-azaanthraquinone related to cleistopholin **10**, and related alkaloids also showed good cytotoxic activity especially against human cell lung carcinoma (A-549) and human melanoma (MEL-28).[6] Finally, benz[*g*]isoquinoline-3,5,10(2*H*)-triones **8** are promising antitumor compounds as cytotoxic activity against murine leukemia cells (L 1210) has been discovered.[7] Therefore, these compounds could be interesting target compounds in the search for new bioactive compounds. As a consequence, structural modifications to the benz[*g*]isoquinoline-3,5,10(2*H*)-trione skeleton are also of great importance for SAR studies. Keeping this in mind, the synthesis of new different substituted benz[*g*]isoquinoline-3,5,10(2*H*)-triones **12** is disclosed in the present article. In addition, the synthesis of different substituted naphtho[3,2,1-*de*]isoquinoline-4,7-diones **13** and benzo[*h*]pyrido[3,4,5-*kl*]-1,2,3,4-tetrahydroacridine-5,8-diones **14** will be discussed (Fig. 2).

2. Results and discussion

Since benz[*g*]isoquinoline-3,5,10(2*H*)-triones **15**[8] posses a good Michael acceptor at C-4, conjugate addition was evaluated in order to modify their molecular skeleton in an easy and straightforward way. After all, addition of the nucleophile followed by aromatization by tautomerization and spontaneous oxidation by air should yield 4-substituted benz[*g*]isoquinoline-3,5,10(2*H*)-triones.

Indeed, treatment of different benz[*g*]isoquinoline-3,5,10(2*H*)-triones **15** with potassium cyanide in refluxing methanol resulted in the isolation of the corresponding 4-cyano substituted compounds **16** in 65–95% yield (Scheme 1). In the same way, 2-alkyl-4-aminoalkylbenz[*g*]isoquinoline-3,5,10(2*H*)-triones **17** were synthesized in 26–95% yield after reaction of the appropriate substrate **15** with different amines in ethanol (Table 1). The position of

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

0040-4020/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2008.05.111

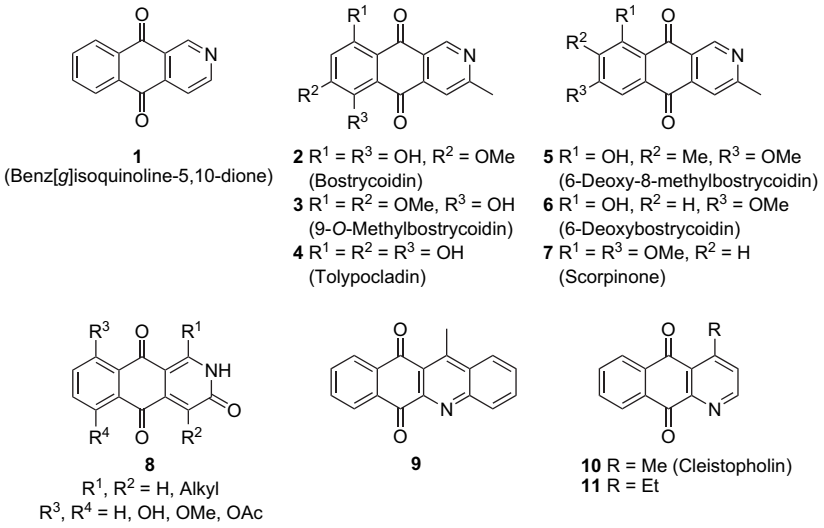
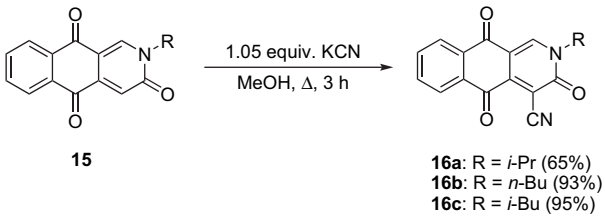


Figure 1.

the isopropylamino group of compound **17a** at C-4 is in accordance with the spectral data since the chemical shift of proton H-1 moved upfield from 8.60 ppm to 7.88 ppm due to the mesomeric electron-donating effect of the alkylamino group at C-4, while the singlet of proton H-4 in 2-isopropylbenz[*g*]isoquinoline-3,5,10(2*H*)-trione (**15a**) had disappeared. Furthermore, irradiation of the proton H-1 of compound **17a** caused a Nuclear Overhauser Effect (NOE) of 7% on the protons of the isopropyl group at C-2, while irradiation of the NH-proton gave only a NOE of 5% on the protons of the isopropylamino moiety at C-4.

However, for performing these reactions the use of absolute ethanol is very important, as the presence of 2-butanone, used in order to denaturate ethanol, gives rise to the formation of compounds **18**. The formation of these new tetracyclic compounds **18** can be explained from the reaction of enamine **20**, which is formed in situ after condensation of 2-butanone and a primary amine, by Michael addition at C-4 to the intermediate **21**, followed by intramolecular condensation with the C-5 carbonyl group, elimination of water, aromatization, and spontaneous oxidation (Scheme 3). Once the formation of these new compounds **18** had been noticed, several attempts were made to optimize their synthesis. First, a higher yield was obtained by adding an excess of 2-butanone and then the effect of the reaction temperature was investigated. However, refluxing the reaction mixture in ethanol or DMF for 1 day resulted in the isolation of a complex mixture of degradation products along with unreacted starting material. Therefore, a set of 5-alkyl-2-aminoalkyl-3-methylnaphtho[3,2,1-*de*]isoquinoline-4,7-diones **18** and **19** was prepared in isolated yields from 25% to 35% by reaction of *N*-substituted benz[*g*]isoquinoline-3,5,10(2*H*)-triones **15** with an excess of different primary amines and 2-butanone in



Scheme 1.

ethanol at room temperature over a period of 3 days (Table 2, Scheme 2). Only traces of the conjugate adducts **17** were isolated under these reaction conditions, except for the synthesis of 5-isopropyl-2-isopropylamino-3-methyl-4*H*-dibenz[*de*,*g*]isoquinoline-4,7(5*H*)-dione (**18a**), which was accompanied with compound **17a**, isolated in a yield of 10%. By observations from NOE experiments of compound **18a**, the structure of compounds **18** was finally confirmed (Fig. 3). Indeed, irradiation of the proton H-1 of compound **18a** caused a NOE on the protons of the isopropyl group at C-2 and on the protons at C-11. Furthermore, irradiation of the protons of the C-3 methyl group gave only a NOE on the 2-aminoalkyl group, while irradiation of the NCH-proton of the 5-aminoalkylgroup gave only a NOE on the proton at C-6.

The extension of 2-butanone to other ketones as co-reagent leads to the synthesis of new tetracyclic derivatives. For instance, reaction of 2-isopropylbenz[*g*]isoquinoline-3,5,10(2*H*)-trione (**15a**) with acetone and isopropylamine resulted in the isolation of both the conjugate adduct (**17a**) and 5-isopropyl-2-isopropylaminonaphtho[3,2,1-*de*]isoquinoline-4,7-dione (**18d**) in 21%

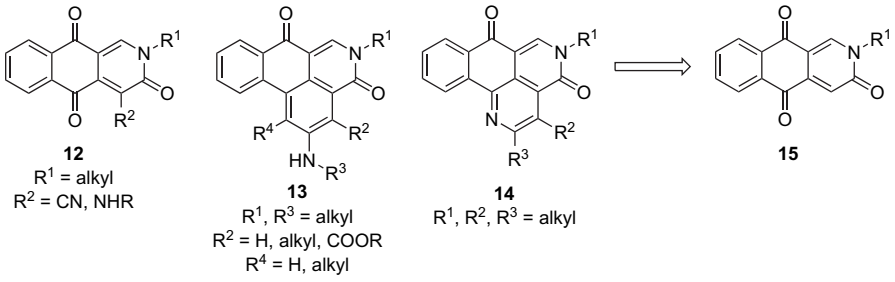
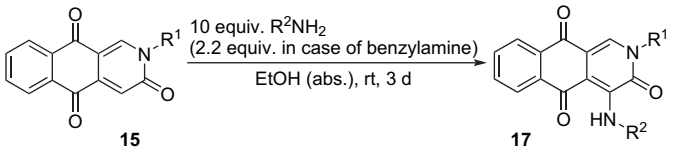


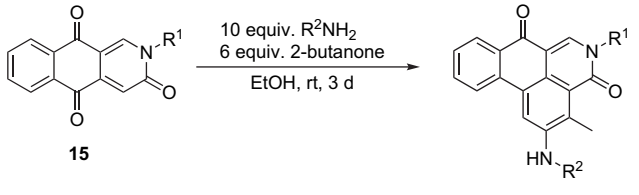
Figure 2.

Table 1
Reaction of *N*-substituted benz[*g*]isoquinoline-3,5,10(2*H*)-triones **15** with different primary amines



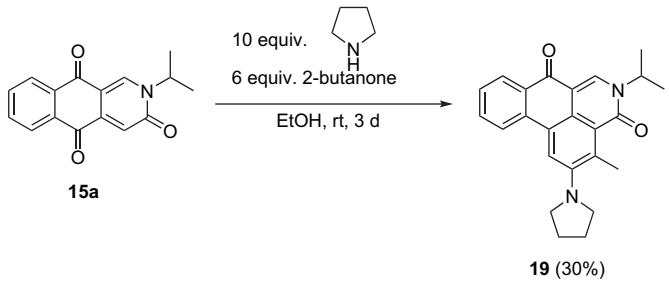
Compound	R^2NH_2	R^1	R^2	Yield (%)
17a	*i*-$PrNH_2$	*i*-Pr	*i*-Pr	44
17b	*n*-$PrNH_2$	*n*-Pr	*n*-Pr	31
17c	NH_3	*i*-Pr	H	95
17d	Allylamine	*i*-Pr	Allyl	26
17e	Benzylamine	*i*-Pr	Bz	56

Table 2
Reaction of *N*-substituted benz[*g*]isoquinoline-3,5,10(2*H*)-triones **15** with different primary amines in the presence of 2-butanone



Compound	R^2NH_2	R^1	R^2	Yield (%)
18a[a]	*i*-$PrNH_2$	*i*-Pr	*i*-Pr	35
18b	*n*-$PrNH_2$	*n*-Pr	*n*-Pr	25
18c	*n*-$PrNH_2$	*i*-Pr	*n*-Pr	26

[a] During this reaction compound **17a** was also isolated in 10% yield.

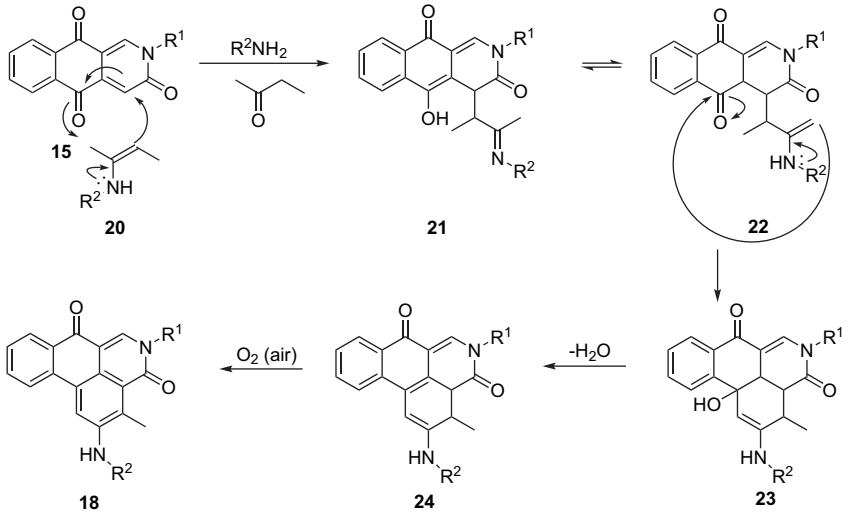


Scheme 2.

and 28% yield, respectively (Scheme 4). The same tendency could be noted upon the use of 2- and 3-pentanone, which resulted in the isolation of the target compounds **18e** and **18f** together with 1,4-adduct **17a** in 36% and 12% (for 2-pentanone) and 16% and 38% yield (for 3-pentanone), respectively (Scheme 4).

Upon treatment of 2-isopropylbenz[*g*]isoquinoline-3,5,10(2*H*)-trione **15a** with an excess of isopropylamine and cyclohexanone a new reaction occurred and as a result 6-isopropylbenzo[*h*]-pyrido[3,4,5-*kl*]-1,2,3,4-tetrahydroacridine-5,8-dione (**25**) was isolated in 2% yield after purification by column chromatography (Scheme 5). However, product **25** was only the minor compound of the reaction mixture as the conjugate adduct (**17a**) was isolated in 64% yield. The mechanism for the formation of compound **25** can be explained by the formation of intermediate **22** (Scheme 3). If the intramolecular ring closure would occur via the carbon atom of enamine **22** across the ketone at position 5, subsequent aromatization would be prevented. Therefore, intramolecular ring closure takes place directly via the nitrogen of enamine **22** across the ketone at position 5. Subsequent elimination of water and dealkylation of the nitrogen will give rise to the formation of the pentacyclic compound (**25**).

In a following step, the reaction conditions were optimized for the synthesis of target compound **25** (Table 3). In order to avoid the formation of the disturbing side-product **17a**, *N*-isopropylcyclohexylideneamine (**26**) was added directly to substrate **15a** in the presence of a weak, non-nucleophilic base, i.e., potassium carbonate. Performing this reaction at room temperature in ethanol as a solvent for 3 days resulted in the isolation of the target compound **25** in 9% yield. However, since this reaction is suitable



Scheme 3.

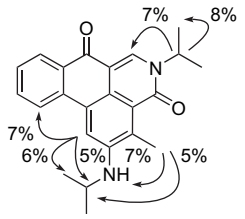
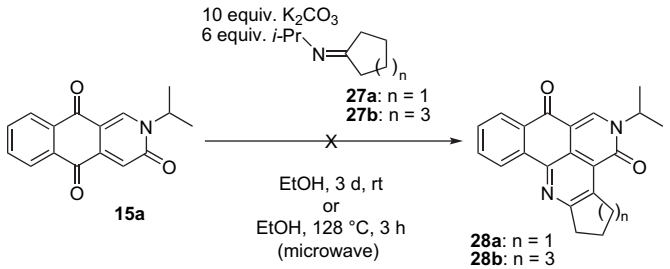


Figure 3. DifNOE analysis of 5-isopropyl-2-isopropylamino-3-methylnaphtho[3,2,1-*de*]isoquinoline-4,7-dione (**18a**).

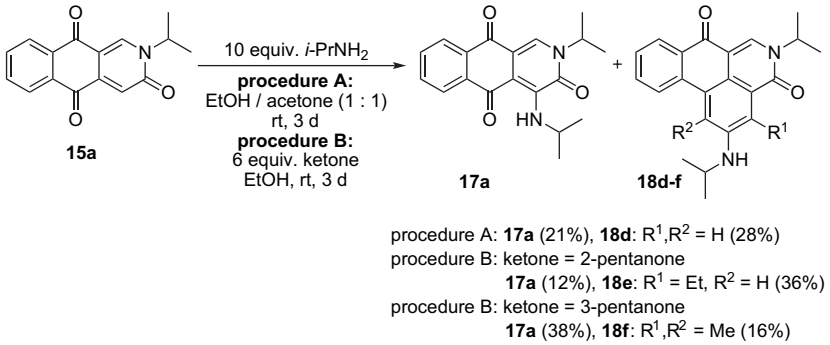
for a microwave mediated synthesis, which proved to be a valuable method for the synthesis of naphtho[3,2,1-*de*]isoquinoline-4,7-diones **30** (vide infra), the reaction was performed in ethanol as a solvent in the microwave at 128 °C for 3 h and eventually compound **25** could be isolated in 16% yield.

However, extension of this reaction to higher and lower ring homologues of compound **25** by treatment of benz[*g*]isoquinoline-3,5,10(2*H*)-trione **15a** with *N*-isopropylcyclopentylideneamine (**27**) and *N*-isopropylcycloheptylideneamine (**27b**) in the presence of a base failed completely as complex reaction mixtures were retrieved (Scheme 6).

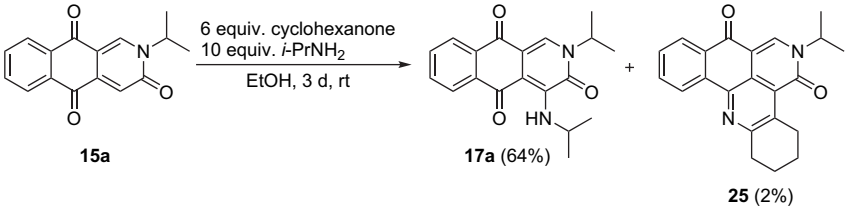


Scheme 6.

In the final part of this research, the synthesis of functionalized naphtho[3,2,1-*de*]isoquinoline-4,7-diones **30** was achieved by reaction of *N*-substituted benz[*g*]isoquinoline-3,5,10(2*H*)-triones **15** with different enaminoesters **29**, which could be easily prepared from the corresponding β-ketoesters and primary amines under Dean–Stark conditions.[9] First, the reaction conditions were optimized for the synthesis of compound **30d** (Table 4). As no reaction occurred in ethanol at room temperature, the reaction mixture was subsequently heated under reflux. However, upon use of these

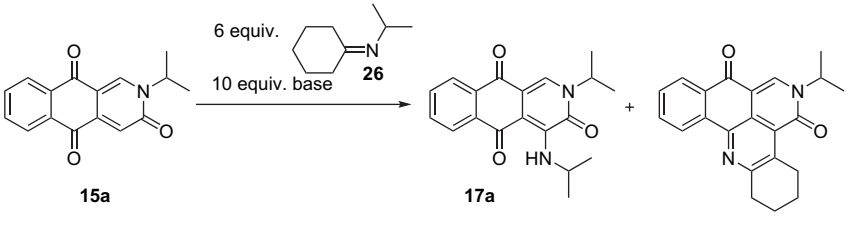


Scheme 4.



Scheme 5.

Table 3
Optimization of reaction conditions for the synthesis of 6-isopropylbenzo[*h*]pyrido[3,4,5-*kl*]-1,2,3,4-tetrahydroacridine-5,8-dione (**25**)



Entry	Base	Solvent	Reaction conditions	Result (%)	
				17a	**25**
1	K_2CO_3	EtOH	rt, 3 days	—	9
2	K_2CO_3	DMF	rt, 3 days	Complex mixture	
3	K_2CO_3	EtOH	128 °C, 3 h (microwave)	—	16

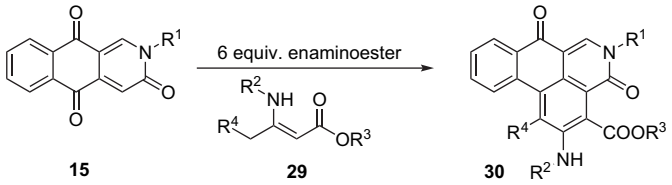
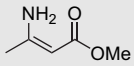
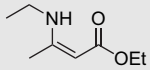
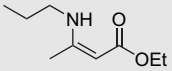
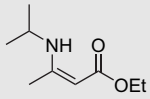
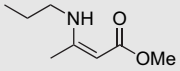
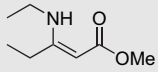


Table 4
Optimization of reaction conditions for the synthesis of 3-ethoxycarbonyl-5-isopropyl-2-isopropylaminonaphtho[3,2,1-*de*]isoquinoline-4,7-dione (**30d**)

Entry	R^1	R^2	R^3	R^4	Reaction conditions	Yield (%)
1	*i*-Pr	*i*-Pr	Et	H	EtOH, Δ, 3 days	22
2	*i*-Pr	*i*-Pr	Et	H	DMF, Δ, 2 days	7
3	*i*-Pr	*i*-Pr	Et	H	EtOH, 128 °C, 3 h (MW)	38
4	*i*-Pr	*i*-Pr	Et	H	DMF, 203 °C, 1 h (MW)	9

MW=microwave.

Table 5
Synthesis of substituted naphtho[3,2,1-*de*]isoquinoline-4,7-diones **30**

Compound	Enaminoester	R^1	R^2	R^3	R^4	Yield (%)
30a		*i*-Pr	H	Me	H	No reaction
30b		*i*-Pr	Et	Et	H	34
30c		*i*-Pr	*n*-Pr	Et	H	42
30d		*i*-Pr	*i*-Pr	Et	H	38
30e		*n*-Bu	*n*-Pr	Me	H	34
30f		*n*-Bu	Et	Me	Me	33

conditions, the reaction took 3 days in order to complete, and as a result a substantial amount of non-identifiable degradation products was formed in the course of the reaction. Therefore, several attempts were made in order to shorten the reaction time. First, *N*,*N*-dimethylformamide (DMF) was used as a solvent instead of ethanol, which allowed a higher reaction temperature. Although the reaction time was decreased to 2 days, the formation of degradation products became even more problematic. Since the investigated reaction concerns the use of polar compounds and a polar solvent, it was performed using a microwave in a final attempt. Indeed, the more polar a reaction mixture is, the greater is its ability to couple with the microwave energy, which leads to a rapid rise in temperature and faster reaction rates in comparison with conventional methods.[10] Two polar solvents, ethanol and DMF, were used in these microwave reactions and gave rise to the formation of the target compound **30d** in 38% and 9% yield, respectively (Table 4). The remarkable difference in results between the use of these two polar solvents can be understood as follows. First, the coupling efficiency of ethanol with the microwave energy is higher than the coupling efficiency of DMF, which means that DMF will require more time and energy to reach the desired temperature.[10,11] Moreover, as the target temperature was set to 50 °C, above the boiling point of the solvent, pressure will built up in the reaction vessel, which is advantageous for the reaction rate. However, the pressure, which is generated while performing the reaction in ethanol is twice as much as when the reaction is performed in DMF.[10] It has to be noted that in the case of DMF, the substrate was not fully converted to the target compound **30d**. However, prolongation of the reaction time under microwave conditions only resulted in the formation of more unidentifiable degradation products. Since the best results were obtained upon the use of ethanol as a solvent in the microwave at 128 °C for 3 h, these reaction conditions were used to synthesize a whole set of different naphtho[3,2,1-*de*]isoquinoline-4,7-diones **30** in 33–42% yield (Table 5). However, the presence of alkyl substituents at the nitrogen of enaminoesters **29** was required for a successful reaction.

In conclusion, it has been proven that benz[*g*]isoquinoline-3,5,10(2*H*)-triones are useful substrates for the synthesis of 2,4-substituted benz[*g*]isoquinoline-3,5,10(2*H*)-triones, 1,2,3,5-substituted naphtho[3,2,1-*de*]isoquinoline-4,7-diones, and 6-substituted benzo[*h*]pyrido[3,4,5-*kl*]-1,2,3,4-tetrahydroacridine-5,8-diones in a one-step reaction.

3. Experimental section

3.1. General experimental methods

Spectroscopic data were recorded as follows: ^{1}H NMR spectra were recorded at 300 or 270 MHz and ^{13}C NMR spectra were recorded at 75 or 68 MHz. Peak assignments were performed with the aid of the DEPT technique, 2D-COSY, and HETCOR 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 PerkinElmer 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 (Merck, silica gel 60F_{254}). Preparative TLC was performed using silica gel plates (silica gel 60F_{254}, thickness 2.0 mm). Microwave reactions were performed in a CEM Discover® microwave.

3.2. Synthesis of 2-substituted 4-cyanobenz[*g*]isoquinoline-3,5,10(2*H*)-triones 16

General procedure: potassium cyanide (1.49 mmol, 100 mg) was added to a solution of 1.42 mmol of benz[*g*]isoquinoline-3,5,10(2*H*)-trione **15** in methanol (16 ml). The reaction mixture was boiled under reflux for 3 h, after which it was cooled to room temperature and poured in an aqueous solution of saturated sodium hydrogen carbonate. The aqueous phase was extracted with small portions of ethyl acetate (three times) and the combined organic extracts were dried ($MgSO_4$). Solvent evaporation in vacuo furnished crude 2-substituted 4-cyanobenz[*g*]isoquinoline-3,5,10(2*H*)-triones **16**.

*3.2.1. 4-Cyano-2-isopropylbenz[g]isoquinoline-3,5,10(2H)-trione (**16a**)*

Flash chromatography on silica gel with ethyl acetate/hexane (1:4) as eluent followed by recrystallization from methanol gave **16a** as yellow crystals (yield 65%), mp 265.6–266.0 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.54 (6H, d, J=6.9 Hz, 2×CH_3), 5.32 (1H, septet, J=6.9 Hz, NCH), 7.85–7.94 (2H, m, H-7 and H-8), 8.31–8.38 (2H, m, H-6 and H-9), 8.80 (1H, s, H-1). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.0 (2×CH_3), 50.7 (NCH), 101.4 (CN), 112.9 (=C_{quat}), 114.0 (=C_{quat}), 127.6 and 128.5 (C-6 and C-9), 133.2 (=C_{quat}), 133.6 (=C_{quat}), 135.1 and 135.7 (C-7 and C-8), 142.4 (C-1), 143.2 (=C_{quat}), 160.0 (N–C=O), 178.5 (C=O), 179.5 (C=O). IR (KBr): ν_{max} 2218, 1692, 1670, 1652, 1587, 1575, 1531 cm^{-1}. MS (ES) m/z (%): 310 ($M+NH_4^+$, 100), 293

($M+H^+$, 95). Anal. Calcd for $C_{17}H_{12}N_2O_3$: C 69.86, H 4.14, N 9.58; found: C 70.01, H 4.29, N 9.46.

3.2.2. 2-n-Butyl-4-cyanobenz[g]isoquinoline-3,5,10(2H)-trione (**16b**)

Recrystallization from diethyl ether gave **16b** as orange crystals (yield 93%), mp 196.7–197.1 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.00 (3H, t, J=7.5 Hz, CH_3), 1.44 (2H, sextet, J=7.5 Hz, CH_2CH_3), 1.80–1.90 (2H, m, NCH_2CH_2), 4.18 (2H, t, J=7.6 Hz, NCH_2), 7.86–7.93 (2H, m, H-7 and H-8), 8.31–8.38 (2H, m, H-6 and H-9), 8.73 (1H, s, H-1). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.6 (CH_3), 19.9 (CH_2CH_3), 31.0 (NCH_2CH_2), 52.3 (NCH_2), 101.6 (CN), 112.5 (=C_{quat}), 113.9 (=C_{quat}), 127.5 and 128.5 (C-6 and C-9), 133.1 (=C_{quat}), 133.5 (=C_{quat}), 135.1 and 135.7 (C-7 and C-8), 143.9 (=C_{quat}), 146.0 (C-1), 160.1 (N–C=O), 178.5 (C=O), 179.5 (C=O). IR (KBr): ν_{max} 2220, 1686, 1663, 1655, 1586, 1527 cm^{-1}. MS (ES) m/z (%): 324 ($M+NH_4^+$, 100), 307 ($M+H^+$, 70). Anal. Calcd for $C_{18}H_{14}N_2O_3$: C 70.58, H 4.61, N 9.15; found: C 70.28, H 4.81, N 8.96.

3.2.3. 4-Cyano-2-isobutylbenz[g]isoquinoline-3,5,10(2H)-trione (**16c**)

Recrystallization from diethyl ether afforded **16c** as yellow crystals (yield 95%), mp 227.4–227.6 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.02 (6H, d, J=6.9 Hz, 2×CH_3), 2.28 (1H, septet, J=6.9 Hz, $CH(CH_3)_2$), 3.99 (2H, d, J=6.9 Hz, NCH_2), 7.86–7.93 (2H, m, H-7 and H-8), 8.31–8.38 (2H, m, H-6 and H-9), 8.67 (1H, s, H-1). ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.82 (2×CH_3), 27.98 ($CH(CH_3)_2$), 59.30 (NCH_2), 101.64 (CN), 112.21 (=C_{quat}), 113.91 (=C_{quat}), 127.50 and 128.46 (C-6 and C-9), 133.12 (=C_{quat}), 133.50 (=C_{quat}), 135.09 and 135.70 (C-7 and C-8), 143.88 (=C_{quat}), 146.32 (C-1), 160.19 (N–C=O), 178.46 (C=O), 179.50 (C=O). IR (KBr): ν_{max} 2229, 1691, 1674, 1643, 1588, 1537 cm^{-1}. MS (ES) m/z (%): 324 ($M+NH_4^+$, 100), 307 ($M+H^+$, 80). Anal. Calcd for $C_{18}H_{14}N_2O_3$: C 70.58, H 4.61, N 9.15; found: C 70.73, H 4.94, N 9.30.

3.3. Synthesis of 2-alkyl-4-aminoalkylbenz[g]isoquinoline-3,5,10(2*H*)-triones 17

General procedure: 18.7 mmol of a primary amine (4.11 mmol in the case of benzylamine) was added to a solution of 1.87 mmol of a *N*-substituted benz[g]isoquinoline-3,5,10(2*H*)-trione **15** in absolute ethanol (20 ml). The reaction mixture was stirred for 3 days in a stoppered flask at room temperature. After solvent evaporation in vacuo, the residue was purified by column chromatography on silica gel.

3.3.1. 2-Isopropyl-4-isopropylaminobenz[g]isoquinoline-3,5,10(2H)-trione (**17a**)

Flash chromatography on silica gel with ethyl acetate/hexane (1:4) as eluent gave **17a** (yield 44%) as red crystals. An analytical sample was purified by recrystallization from methanol and afforded **17a** as fine red needles, mp 190 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.37 (6H, d, J=6.3 Hz, 2×CH_3), 1.44 (6H, d, J=6.9 Hz, 2×CH_3), 5.22 (1H, septet, J=6.9 Hz, NCH), 5.27 (1H, septet, J=6.3 Hz, NCH), 7.68–7.77 (2H, m, H-7 and H-8), 7.88 (1H, s, H-1), 8.26–8.33 (2H, m, H-6 and H-9), 11.22 (1H, br s, NH). ^{13}C NMR (68 MHz, $CDCl_3$): δ 21.6 (2×CH_3), 25.0 (2×CH_3), 46.7 (NCH), 47.9 (NCH), 107.9 (=C_{quat}), 113.8 (=C_{quat}), 123.9 (C-1), 126.6 and 126.7 (C-6 and C-9), 132.8 and 133.8 (C-7 and C-8), 134.0 (2×=C_{quat}), 143.5 (C-4), 158.3 (N–C=O), 181.1 (C=O), 182.5 (C=O). IR (KBr): ν_{max} 1630, 1560, 1325, 1290, 1250 cm^{-1}. MS (70 eV) m/z (%): 324 (M^+, 76), 309 (51), 281 (100), 167 (42). Anal. Calcd for $C_{19}H_{20}N_2O_3$: C 70.35, H 6.21, N 8.64; found: C 70.13, H 6.34, N 8.59.

3.3.2. 2-n-Propyl-4-n-propylaminobenz[g]isoquinoline-3,5,10(2H)-trione (**17b**)

Recrystallization from methanol gave **17b** (yield 31%) as fine red needles, mp 142–144 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.00 (3H, t, J=7.6 Hz, CH_3), 1.06 (3H, t, J=7.3 Hz, CH_3), 1.75 (2H, sextet, J=7.3 Hz, $CH_2CH_2CH_3$), 1.83 (2H, sextet, J=7.6 Hz, $CH_2CH_2CH_3$), 3.93 (2H, t, J=7.6 Hz, NCH_2), 4.09 (2H, q, J=6.6 Hz, $NHCH_2$), 7.67–7.80 (2H, m, H-7 and H-8), 7.75 (1H, s, H-1), 8.25–8.33 (2H, m, H-6 and H-9), 11.23 (1H, br s, NH). ^{13}C NMR (68 MHz, $CDCl_3$): δ 11.2 (CH_3), 11.5 (CH_3), 22.2 ($CH_2CH_2CH_3$), 24.6 ($CH_2CH_2CH_3$), 47.5 ($NHCH_2$), 52.3 (NCH_2), 108.3 (=C_{quat}), 113.4 (=C_{quat}), 126.7 (C-6 and C-9), 128.3 (C-1), 132.8 and 133.8 (C-7 and C-8), 133.7 (=C_{quat}), 135.9 (=C_{quat}), 144.4 (C-4), 158.9 (N–C=O), 181.1 (C=O), 182.5 (C=O). IR (KBr): ν_{max} 3060, 1635, 1570, 1330, 1275 cm^{-1}. MS (70 eV) m/z (%): 324 (M^+, 52), 295 (100), 253 (31). Anal. Calcd for $C_{19}H_{20}N_2O_3$: C 70.35, H 6.21, N 8.64; found: C 70.12, H 6.24, N 8.47.

3.3.3. 4-Amino-2-isopropylaminobenz[g]isoquinoline-3,5,10(2H)-trione (**17c**)

Flash chromatography on silica gel with ethyl acetate/hexane (3:7) as eluent followed by recrystallization from methanol gave **17c** as red crystals (yield 95%), mp 197.4–198.3 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.47 (6H, d, J=6.9 Hz, 2×CH_3), 5.29 (1H, septet, J=6.9 Hz, NCH), 6.52 (1H, br s, NH_2), 7.73–7.82 (2H, m, H-7 and H-8), 7.91 (1H, s, H-1), 8.30–8.33 (2H, m, H-6 and H-9), 9.24 (1H, br s, NH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.8 (2×CH_3), 48.8 (NCH), 107.4 (=C_{quat}), 113.8 (=C_{quat}), 123.2 (C-1), 126.9 and 127.2 (C-6 and C-9), 133.5 and 134.0 (C-7 and C-8), 134.3 (=C_{quat}), 135.4 (=C_{quat}), 141.8 (=C_{quat}), 158.5 (N–C=O), 181.1 (C=O), 184.0 (C=O). IR (KBr): ν_{max} 3383, 3270, 1668, 1636, 1582, 1561, 1295, 1278, 1262 cm^{-1}. MS (ES) m/z (%): 283 ($M+H^+$, 100), 228 (20). Anal. Calcd for $C_{16}H_{14}N_2O_3$: C 68.07, H 5.00, N 9.92; found: C 67.94, H 5.09, N 10.01.

3.3.4. 4-Allylamino-2-isopropylaminobenz[g]isoquinoline-3,5,10(2H)-trione (**17d**)

Flash chromatography on silica gel with ethyl acetate/hexane (1:9) as eluent gave **17d** as red crystals (yield 26%), mp 151.7–152.4 °C. This product was found to degrade rapidly as the crystals turned black over a period of 4 h at room temperature. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.44 (3H, d, J=6.9 Hz, 2×CH_3), 4.77 (2H, m, NCH_2), 5.16–5.25 (2H, m, $CH(CH_3)_2$ and =CH_aH_b), 5.34 (1H, ddt, J=1.4, 3.0, 17.3 Hz, =CH_aH_b), 6.07 (1H, ddt, J=5.2, 10.3, 17.3 Hz, =CH), 7.73 (1H, td, J=1.8, 7.6 Hz, H-7 or H-8), 7.78 (1H, td, J=1.8, 7.6 Hz, H-7 or H-8), 7.90 (1H, s, H-1), 8.29 (1H, dd, J=1.8, 7.6 Hz, H-6 or H-9), 8.33 (1H, dd, J=1.8, 7.6 Hz, H-6 or H-9). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.6 (2×CH_3), 47.8 (NCH_2), 47.9 (NCH), 108.5 (=C_{quat}), 113.7 (=C_{quat}), 116.2 (=CH_2), 124.2 (C-1), 126.7 (C-6 and C-9), 133.0 (C-7 or C-8), 133.8 (C-7 or C-8), 135.4 (=C_{quat}), 135.8 (=C_{quat}), 143.6 (=C_{quat}), 158.7 (N–C=O), 180.9 (C=O), 182.8 (C=O). IR (KBr): ν_{max} 3078, 1667, 1634, 1612 cm^{-1}. MS (ES) m/z (%): 323 ($M+H^+$, 100).

3.3.5. 4-Benzylamino-2-isopropylaminobenz[g]isoquinoline-3,5,10(2H)-trione (**17e**)

Flash chromatography on silica gel with ethyl acetate/hexane (1:9) as eluent followed by recrystallization from methanol gave **17e** as red needles (yield 56%), mp 185.3–185.7 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.44 (6H, d, J=6.9 Hz, 2×CH_3), 5.21 (1H, septet, J=6.9 Hz, NCH), 5.36 (2H, d, J=5.8 Hz, NCH_2), 7.29–7.43 (5H, m, $5CH_{ar}$), 7.69–7.78 (2H, m, H-7 and H-8), 7.90 (1H, s, H-1), 8.27–8.30 (H-6 and H-9), 11.38 (1H, br s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.6 (2×CH_3), 47.9 (NCH_2), 49.4 (NCH), 108.7 (=C_{quat}), 113.7 (=C_{quat}), 124.4 (C-1), 126.7 and 126.8 (C-6 and C-9), 127.5 (CH_{ar}), 127.6 ($2CH_{ar}$), 128.8 ($2CH_{ar}$), 133.0 and 133.8 (C-7 and C-8), 133.7 (=C_{quat}), 135.8 (=C_{quat}), 139.3 (=C_{quat}), 143.5 (=C_{quat}), 158.8 (N–C=O), 180.9 (C=O), 182.9 (C=O). IR (KBr): ν_{max} 3401, 1666, 1636, 1614, 1595, 1567, 1558, 1333, 1292, 1279 cm^{-1}. MS (ES) m/z (%): 373 ($M+H^+$, 100). Anal. Calcd for $C_{23}H_{20}N_2O_3$: C 74.18, H 5.41, N 7.52; found: C 74.30, H 5.33, N 7.67.

3.4. Synthesis of 5-alkyl-2-alkylamino-3-methylnaphtho[3,2,1-*de*]isoquinoline-4,7-diones 18 and 19

General procedure: to a solution of a *N*-substituted benz[*g*]isoquinoline-3,5,10(2*H*)-trione **15** (1.8 mmol) in absolute ethanol (20 ml) and 2-butanone (1 ml) was added a primary or secondary amine (18 mmol; isopropylamine, *n*-propylamine, pyrrolidine), and the reaction mixture was stirred at room temperature for 3 days. The solvent was evaporated in vacuo and the residue was chromatographed on silica gel using ethyl acetate/hexane (1:4) as eluent. First, 2-alkyl-4-alkylaminobenz[*g*]isoquinoline-3,5,10(2*H*)-triones (**17**) eluted from the column as a red coloured band, but they were only isolated in the case of 2-isopropyl-4-isopropylaminobenz[*g*]isoquinoline-3,5,10(2*H*)-trione (**17a**) in a yield of 10%. For physical and spectral data of compound **17a**, vide supra. 5-Alkyl-2-aminoalkyl-3-methylnaphtho[3,2,1-*de*]isoquinoline-4,7-diones **18** and **19** eluted as a yellow colored band and they were isolated in yield of 25–35%.

3.4.1. 5-Isopropyl-2-isopropylamino-3-methylnaphtho-[3,2,1-de]isoquinoline-4,7-dione (**18a**)

Recrystallization from methanol gave **18a** as yellow crystals, mp 178 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.37 (6H, d, J=6.3 Hz, 2×CH_3), 1.49 (6H, d, J=6.9 Hz, 2×CH_3), 3.85 (1H, br s, NH), 2.84 (3H, s, CH_3), 3.95 (1H, septet, J=6.3 Hz, NCH), 5.40 (1H, septet, J=6.9 Hz, NCH), 7.51 (1H, t, J=7.9 Hz, H-9), 7.71 (1H, t, J=7.9 Hz, H-10), 7.87 (1H, s, H-1), 8.21 (1H, d, J=7.9 Hz, H-11), 8.45 (1H, d, J=7.9 Hz, H-8), 8.53 (1H, s, H-6). ^{13}C NMR (68 MHz, $CDCl_3$): δ 14.3 (CH_3), 22.1 (2×CH_3), 23.2 (2×CH_3), 44.8 (NCH), 47.3 (NCH), 111.1 (C-3), 111.6 (C-1), 122.6 (C-11), 123.0 (2=C_{quat}), 123.7 (=C_{quat}), 125.5 (=C_{quat}), 127.7 (C-8 and C-9), 130.7 (=C_{quat}), 133.2 (C-6 and C-10), 136.4 (=C_{quat}), 145.3 (=C_{quat}), 162.9 (N–C=O), 181.9 (C=O). IR (KBr): ν_{max} 3430, 1665, 1630, 1605, 1585, 1290, 1265 cm^{-1}. MS (70 eV) *m*/*z* (%): 360 (M^+, 100), 345 (57), 317 (18), 303 (67), 287 (16), 275 (22). Anal. Calcd for $C_{23}H_{24}N_2O_2$: C 76.64, H 6.71, N 7.77; found: C 76.58, H 6.62, N 7.76.

3.4.2. 5-n-Propyl-2-n-propylamino-3-methylnaphtho-[3,2,1-de]isoquinoline-4,7-dione (**18b**)

Recrystallization from methanol gave **18b** as yellow crystals, mp 222 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.03 (3H, t, J=7.3 Hz, CH_2CH_3), 1.12 (3H, t, J=7.3 Hz, CH_2CH_3), 1.83 (2H, sextet, J=7.3 Hz, $CH_2CH_2CH_3$), 1.89 (2H, sextet, J=7.3 Hz, $CH_2CH_2CH_3$), 2.80 (3H, s, CH_3), 3.35 (2H, t, J=6.9 Hz, $NHCH_2$), 4.08 (2H, t, J=7.3 Hz, NCH_2), 7.52 (1H, t, J=7.9 Hz, H-9), 7.72 (1H, t, J=7.9 Hz, H-10), 7.84 (1H, s, H-1), 8.25 (1H, d, J=7.9 Hz, H-11), 8.43 (1H, s, H-6), 8.44 (1H, d, J=7.9 Hz, H-8). ^{13}C NMR (68 MHz, $CDCl_3$): δ 11.2 (CH_2CH_3), 11.8 (CH_2CH_3), 14.0 (CH_3), 22.6 (CH_2CH_3), 22.8 (CH_2CH_3), 46.2 ($NHCH_2$), 52.4 (NCH_2), 110.5 (C-1), 110.8 (C-3), 122.8 (C-11), 123.1 (=C_{quat}), 123.5 (=C_{quat}), 123.9 (=C_{quat}), 125.2 (=C_{quat}), 127.7 and 127.8 (C-8 and C-9), 130.7 (=C_{quat}), 133.3 (C-10), 136.5 (=C_{quat}), 137.4 (C-6), 146.2 (=C_{quat}), 163.2 (N–C=O), 182.2 (C=O). IR (KBr): ν_{max} 3080, 1665, 1640, 1605, 1580, 1325, 1310 cm^{-1}. MS (70 eV) *m*/*z* (%): 360 (M^+, 100), 331 (73), 317 (10), 289 (34). Anal. Calcd for $C_{23}H_{24}N_2O_2$: C 76.64, H 6.71, N 7.77; found: C 76.50, H 6.40, N 7.49.

3.4.3. 5-Isopropyl-2-n-propylamino-3-methylnaphtho-[3,2,1-de]isoquinoline-4,7-dione (**18c**)

An analytical sample was obtained by recrystallization from methanol to give **18c** as yellow crystals, mp 188.9–190.5 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.11 (3H, t, J=7.2 Hz, CH_2CH_3), 1.50 (6H, d, J=6.6 Hz, 2×CH_3), 1.80 (2H, sextet, J=7.2 Hz, $CH_2CH_2CH_3$), 2.82 (3H, s, CH_3), 3.29 (2H, t, J=7.2 Hz, $NHCH_2$), 3.93 (1H, m, NH), 5.38 (1H, septet, J=6.6 Hz, NCH), 7.49 (1H, t, J=7.1 Hz, H-9), 7.69 (1H, t, J=7.1 Hz, H-10), 7.75 (1H, s, H-1), 8.17 (1H, d, J=7.9 Hz, H-11), 8.43 (1H, d, J=7.6 Hz, H-8), 8.52 (1H, s, H-6). ^{13}C NMR (68 MHz, $CDCl_3$): δ 11.8 (CH_2CH_3), 14.1 (CH_3), 22.1 (2×CH_3), 22.8 (CH_2CH_3), 46.2 (NCH_2), 47.3 (NCH), 110.5 (C-1), 111.1 (C-3), 122.7 (C-11), 123.0 (=C_{quat}), 123.7 (=C_{quat}), 125.2 (=C_{quat}), 127.7 (C-8 and C-9), 130.7 (=C_{quat}), 133.0 (C-10), 133.1 (C-6), 136.4 (=C_{quat}), 146.1 (2×=C_{quat}), 162.9 (N–C=O), 181.9 (C=O). IR (KBr): ν_{max} 1660, 1630, 1580, 1330, 1310, 1255 cm^{-1}. MS (70 eV) *m*/*z* (%): 360 (M^+, 100), 331 (41), 289 (91). Anal. Calcd for $C_{23}H_{24}N_2O_2$: C 76.64, H 6.71, N 7.77; found: C 76.49, H 6.97, N 7.40.

3.4.4. 5-Isopropyl-3-methyl-2-pyrrolidinylnaphtho-[3,2,1-de]isoquinoline-4,7-dione (**19**)

Recrystallization from methanol gave **19** as orange needles, mp 174.3–174.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.50 (6H, d, J=6.9 Hz, 2×CH_3), 2.01–2.06 (4H, m, 2×CH_2), 2.87 (3H, s, CH_3), 3.28–3.32 (4H, m, 2×NCH_2), 5.41 (1H, septet, J=6.9 Hz, NCH), 7.51 (1H, td, J=1.4, 7.8 Hz, H-9), 7.72 (1H, td, J=1.4, 7.8 Hz, H-10), 8.20 (1H, s, H-1), 8.24 (1H, dd, J=1.4, 7.8 Hz, H-8), 8.47 (1H, dd, J=1.4, 7.8 Hz, H-11), 8.63 (1H, s, H-6). ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.2 (CH_3), 22.1 (2×CH_3), 24.9 (2×CH_2), 47.3 (NCH), 51.6 (2×NCH_2), 110.9 (=C_{quat}), 116.9 (C-1), 122.7 (C-11), 123.0 (=C_{quat}), 124.2 (=C_{quat}), 126.2 (=C_{quat}), 127.7 and 127.8 (C-9 and C-10), 130.7 (=C_{quat}), 133.2 (C-8), 134.7 (C-6 and =C_{quat}), 136.4 (=C_{quat}), 149.6 (=C_{quat}), 162.8 (N–C=O), 181.9 (C=O). IR (KBr): ν_{max} 1668, 1638, 1607, 1576, 1369, 1297, 1267, 1189, 1150 cm^{-1}. MS (ES) *m*/*z* (%): 373 ($M+H^+$, 100), 371 (8), 290 (10), 288 (42). Anal. Calcd for $C_{24}H_{24}N_2O_2$: C 77.39, H 6.49, N 7.52; found: C 77.54, H 6.31, N 7.70.

3.5. Reaction of 2-isopropylbenz[*g*]isoquinoline-3,5,10(2*H*)-trione (15a) with acetone and isopropylamine (procedure A) and with 2-pentanone or 3-pentanone and isopropylamine (procedure B)

Procedure A. To a solution of 2-isopropylbenz[*g*]isoquinoline-3,5,10(2*H*)-trione (**15a**) (3.4 mmol, 0.90 g) in acetone (15 ml) was added dropwise a solution of isopropylamine (34 mmol, 2 g) in absolute ethanol (15 ml) and the reaction mixture was stirred at room temperature for 3 days. The solvent was evaporated in vacuo and the residue was chromatographed on silica gel using ethyl acetate/hexane (1:4) as eluent. Elution of a red coloured band gave first 2-isopropyl-4-isopropylaminobenz[*g*]isoquinoline-3,5,10(2*H*)-trione (**17a**) (230 mg, 21%). For spectral data of compound **17a**, vide supra. Using the same solvent combination, a second compound eluted from the column as a yellow coloured band to give 5-isopropyl-2-isopropylaminonaphtho[3,2,1-*de*]isoquinoline-4,7-dione (**18d**) (330 mg, 28%) as a yellow powder. Recrystallization from methanol gave **18d** as yellow crystals, mp 172.6–173.5 °C.

Procedure B. The synthesis of 3-ethyl-5-isopropyl-2-isopropylaminonaphtho[3,2,1-*de*]isoquinoline-4,7-dione (**18e**) and 5-isobutyl-2-isopropyl-1,3-dimethylnaphtho[3,2,1-*de*]isoquinoline-4,7-dione (**18f**) was analogous to the synthesis of 5-alkyl-2-alkylamino-3-methylnaphtho[3,2,1-*de*]isoquinoline-4,7-diones (**18a–c**). Upon the use of 2-pentanone as co-reagent, the reaction gave rise to the isolation of the conjugate adduct **17a** and the target compound **18e** in 12% and 36% yield, respectively. Some of the aromatic quaternary carbons remained in the noise of the ^{13}C NMR spectrum of compound **18e**, even upon prolongation of the pulse delay and raising the number of recorded scans. When 3-pentanone was used as co-reagent, the conjugate adduct **17a** and the target compound **26c** could be isolated after the reaction in 38% and 16% yield, respectively.

3.5.1. 5-Isopropyl-2-isopropylaminonaphtho[3,2,1-de]isoquinoline-4,7-dione (**18d**)

^{1}H NMR (270 MHz, $CDCl_3$): δ 1.32 (6H, d, J=6.3 Hz, 2×CH_3), 1.50 (6H, d, J=6.6 Hz, 2×CH_3), 1.57 (1H, br s, NH), 3.83–3.96 (1H, m, $NHCH$), 5.44 (1H, septet, J=6.6 Hz, NCH), 7.53 (1H, td, J=7.4, 1.0 Hz, H-9), 7.59 (1H, d, J=2.3 Hz, H-3), 7.70 (1H, td, J=1.0, 7.4 Hz, H-10), 7.74

(1H, d, J=2.3 Hz, H-1), 8.16 (1H, d, J=7.9 Hz, H-11), 8.45 (1H, s, H-6), 8.46 (1H, dd, J=1.6, 7.6 Hz, H-8). ^{13}C NMR (68 MHz, $CDCl_3$): δ 22.0 (2×CH_3), 22.8 (2×CH_3), 44.4 (*C*H(CH_3)$_2$), 47.5 (*C*H(CH_3)$_2$), 109.1 and 115.4 (C-1 and C-3), 111.3 (=C_{quat}), 122.03 (=C_{quat}), 122.8 (C-11), 125.7 (=C_{quat}), 126.9 (=C_{quat}), 127.9 and 128.1 (C-8 and C-9), 131.3 (=C_{quat}), 131.9 and 133.1 (C-6 and C-10), 135.7 (=C_{quat}), 147.0 (C-2), 161.8 (N–C=O), 181.7 (C=O). IR (KBr): ν_{max} 1661, 1629, 1608, 1263 cm^{-1}. MS (70 eV) m/z (%): 346 (M$^+$, 100), 331 (77), 289 (65). Anal. Calcd for $C_{22}H_{22}N_2O_2$: C 76.28, H 6.40, N 8.09; found: C 76.09, H 6.09, N 7.73.

3.5.2. 3-Ethyl-5-isopropyl-2-isopropylaminonaphtho-[3,2,1-de]isoquinoline-4,7-dione (**18e**)

Preparative TLC on silica gel with hexane/ethyl acetate (4:1) (solvent elution 4×) afforded **18e** as orange crystals, mp 178.2–179.7 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.34 (3H, t, J=7.4 Hz, CH_2CH_3), 1.37 (6H, d, J=6.4 Hz, 2×CH_3), 1.49 (6H, d, J=6.9 Hz, 2×CH_3), 3.38 (2H, q, J=7.4 Hz, CH_2CH_3), 3.96 (1H, septet, J=6.4 Hz, NHC*H*), 5.40 (1H, septet, J=6.9 Hz, NCH), 7.52 (1H, td, J=1.0, 7.3 Hz, H-9), 7.71 (1H, ddd, J=1.4, 7.3, 8.2 Hz, H-10), 7.91 (1H, s, H-1), 8.22 (1H, d, J=8.2 Hz, H-11), 8.46 (1H, dd, J=1.4, 7.7 Hz, H-8), 8.54 (1H, s, H-6). ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.6 (CH_3), 20.9 (CH_2), 22.1 (2×CH_3), 23.2 (2×CH_3), 44.8 (NCH), 47.1 (NCH), 112.2 (C-1), 122.7 (C-11), 127.8 (C-6 and C-8), 131.3 (=C_{quat}), 133.2 (C-6 and C-10), 144.7 (N–C=O), 162.4 (O–C=O). IR (KBr): ν_{max} 3426, 1667, 1638, 1607, 1584, 1260 cm^{-1}. MS (ES) m/z (%): 375 (M+H$^+$, 100). Anal. Calcd for $C_{24}H_{26}N_2O_2$: C 76.98, H 7.00, N 7.48; found: C 76.62, H 7.27, N 7.29.

3.5.3. 5-Isobutyl-2-isopropylamino-1,3-dimethylnaphtho-[3,2,1-de]isoquinoline-4,7-dione (**18f**)

Flash chromatography on silica gel with ethyl acetate/hexane (1:4) as eluent followed by recrystallization from methanol gave **18f** as orange crystals, mp 150.9–152.6 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.00 (6H, d, J=6.6 Hz, CH(C*H*$_3$)$_2$), 1.22 (6H, d, J=6.3 Hz, NCH(C*H*$_3$)$_2$), 2.28 (1H, m, C*H*(CH_3)$_2$), 2.86 (3H, s, CH_3), 2.92 (3H, s, CH_3), 3.57 (1H, septet, J=6.3 Hz, NC*H*(CH_3)$_2$), 3.90 (1H, d, J=7.4 Hz, NH), 3.92 (2H, d, J=7.4 Hz, NCH_2), 7.50 (1H, td, J=1.3, 7.7 Hz, H-9), 7.67 (1H, td, J=1.3, 7.7 Hz, H-10), 8.07 (1H, d, J=7.7 Hz, H-8), 8.44 (1H, s, H-6), 8.45 (1H, dd, J=1.4, 7.7 Hz, H-11). ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.8 (CH_3), 20.0 (CH(*C*H$_3$)$_2$), 21.7 (CH_3), 23.8 (NCH(*C*H$_3$)$_2$), 28.0 (*C*H(CH_3)$_2$), 49.2 (NHCH), 57.9 (NCH_2), 109.9 (=C_{quat}), 121.4 (=C_{quat}), 125.6 (=C_{quat}), 127.3 and 127.4 (C-9 and C-10), 128.3 (=C_{quat}), 129.3 (C-11), 132.0 (C-8), 132.1 (=C_{quat}), 132.3 (=C_{quat}), 135.1 (=C_{quat}), 137.7 (=C_{quat}), 139.1 (C-6), 147.5 (C-2), 163.1 (N–C=O), 182.3 (C=O). IR (KBr): ν_{max} 3313, 1667, 1643, 1604, 1584, 1271 cm^{-1}. MS (ES) m/z (%): 389 (M+H$^+$, 75), 262 (100), 243 (30). Anal. Calcd for $C_{24}H_{26}N_2O_2$: C 76.98, H 7.00, N 7.48; found: C 77.16, H 7.33, N 7.30.

3.6. Synthesis of 6-isopropylbenzo[*h*]pyrido[3,4,5-*kl*]-1,2,3,4-tetrahydroacridine-5,8-dione (25)

3.6.1. Synthesis of imines **26**, **27a**, and **27b**

The synthesis of *N*-isopropylcyclohexylideneamine (**26**), *N*-isopropylcyclopentylideneamine (**27a**), and *N*-*n*-propylcycloheptylideneamine (**27b**) was accomplished according to a method in the literature utilizing titanium(IV) chloride as a Lewis catalyst for the condensation of the cyclic ketone with the primary amine.[12] Spectral data of *N*-isopropylcyclohexylideneamine (**26**) were in accordance with the literature data.[13] ^{13}C NMR of *N*-isopropylcyclopentylideneamine (**27a**) was in accordance with the literature data.[13a] Other experimental properties are given below.

*3.6.1.1. N-Isopropylcyclopentylideneamine (**27a**).* Distillation (21 °C, 3.0 mmHg) gave **27a** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.12 (6H, d, J=6.3 Hz, 2×CH_3), 1.72 (2H, pentet, J=6.6 Hz, CH_2), 1.81 (2H, pentet, J=6.6 Hz, CH_2), 2.21 (2H, t, J=7.3 Hz, =CCH_2), 2.31 (2H, t, J=7.3 Hz, =CCH_2), 3.45 (1H, septet, J=6.3 Hz, NCH). IR (NaCl): ν_{max} 3331, 1673 cm^{-1}. MS (ES) m/z (%): 126 (M+H$^+$, 100). Anal. Calcd for $C_8H_{15}N$: C 76.74, H 12.07, N 11.19; found: C 76.49, H 11.83, N 11.01.

*3.6.1.2. N-n-Propylcycloheptylideneamine (**27b**).* Distillation (42 °C, 0.01 mmHg) gave **27b** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.94 (3H, t, J=7.4 Hz, CH_3), 1.57–1.74 (10H, m, 5×CH_2), 2.35 (2H, t, J=6.9 Hz, CH_2), 2.55–2.48 (2H, m, CH_2), 3.14 (2H, t, J=7.3 Hz, NCH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.2 (CH_3), 24.3 (CH_2), 25.0 (CH_2), 27.1 (CH_2), 30.1 (CH_2), 30.3 (CH_2), 31.9 (CH_2), 41.1 (CH_2), 52.4 (NCH_2), 175.8 (C=N). IR (NaCl): ν_{max} 3267, 1641 cm^{-1}. MS (ES) m/z (%): 154 (M+H$^+$, 100). Anal. Calcd for $C_{10}H_{19}N$: C 78.37, H 12.50, N 9.14; found: C 78.56, H 12.07, N 8.98.

3.6.2. Microwave mediated synthesis of 6-isopropylbenzo-[h]pyrido[3,4,5-kl]-1,2,3,4-tetrahydroacridine-5,8-dione (**25**)

N-Isopropylcyclohexylideneamine (**26**) (2.22 mmol, 0.31 g) was added to a solution of 2-isopropylbenz[*g*]isoquinoline-3,5,10(2*H*)-trione (**15a**) (0.37 mmol, 100 mg) and potassium carbonate (3.7 mmol, 0.31 g) in absolute ethanol (4 ml). The reaction vessel was introduced in a CEM microwave and the following parameters were used: target temperature 128 °C, reaction time 3 h, and maximal pressure 275 psi. After completion of the reaction, the solvent was removed under reduced pressure and the reaction mixture was purified with the aid of preparative TLC on silica gel using petroleum ether/ethyl acetate (4:1) (solvent elution 3×) in 16% yield.

*3.6.2.1. 6-Isopropylbenzo[h]pyrido[3,4,5-kl]-1,2,3,4-tetrahydroacridine-5,8-dione (**25**).* Recrystallization from methanol gave **25** as orange needles, mp 280.9–282.7 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.50 (6H, d, J=6.9 Hz, 2×CH_3), 1.94 (4H, m, CH_2-2 and CH_2-3), 3.18 (2H, t, J=5.7 Hz, CH_2-4), 3.54 (2H, t, J=5.5 Hz, CH_2-1), 5.35 (1H, septet, J=6.9 Hz, N–CH), 7.61 (1H, td, J=1.4, 7.9 Hz, H-10), 7.78 (1H, td, J=1.4, 7.9 Hz, H-11), 8.39 (1H, dd, J=1.4, 7.9 Hz, H-9), 8.62 (1H, s, H-7), 8.86 (1H, dd, J=1.4, 7.9 Hz, H-12). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.3 (2×CH_3), 22.6 and 23.3 (CH_2-2 and CH_2-3), 28.8 (CH_2-1), 34.6 (CH_2-4), 48.1 (N–CH), 110.5 (=C_{quat}), 124.0 (=C_{quat}), 125.1 (C-12), 126.6 (=C_{quat}), 127.5 (C-9), 129.9 (C-10), 132.2 (=C_{quat}), 134.0 (C-11), 134.1 (=C_{quat}), 136.9 (C-7), 137.2 (=C_{quat}), 142.6 (=C_{quat}), 156.2 (C=N), 162.2 (N–C=O), 181.4 (C=O). IR (KBr): ν_{max} 1671, 1648, 1607, 1589, 1263 cm^{-1}. MS (ES) m/z (%): 345 (M+H$^+$, 100), 247 (25), 235 (45). Anal. Calcd for $C_{22}H_{20}N_2O_2$: C 76.72, H 5.85, N 8.13; found: C 76.47, H 5.71, N 8.24.

3.7. Synthesis of functionalized naphtho[3,2,1-*de*]-isoquinoline-4,7-diones 30

3.7.1. Synthesis of enaminoesters **29**

Enaminoesters **29** were prepared from the corresponding β-ketoesters and primary amines under Dean–Stark conditions following the literature procedures.[9] The spectral data of ethyl 3-isopropylbut-2-enoate (**29d**) were in full accordance with the literature data.[14] The spectral data of methyl 3-aminobut-2-enoate (**29a**) were also in accordance with the literature data,[15] and missing ^{1}H and ^{13}C NMR spectral data are given below.

*3.7.1.1. Methyl 3-aminobut-2-enoate (**29a**).* Yellow crystals, mp 84–85 °C (lit. 89–90 °C,[15a] 83–84 °C[15b]). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.91 (3H, s, CH_3), 3.64 (3H, s, OCH_3), 4.52 (1H, s, =CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.3 (CH_3), 50.1 (OCH_3), 83.6 (=CH), 160.0 (=C_{quat}), 170.6 (C=O).

*3.7.1.2. Ethyl 3-ethylaminobut-2-enoate (**29b**).* Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.22 (3H, t, J=7.3 Hz, $NHCH_2CH_3$), 1.25 (3H, t, J=7.2 Hz, OCH_2CH_3), 1.92 (3H, s, CH_3), 3.25 (2H, qd, J=5.8, 7.3 Hz,

NHCH_2CH$_3$), 4.08 (2H, q, J=7.2 Hz, OCH_2CH$_3$), 4.43 (1H, s, =CH), 8.48 (1H, br s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.8 (OCH$_2$CH_3), 15.8 (NHCH$_2$CH_3), 19.4 (CH$_3$), 37.8 (NHCH_2), 58.4 (OCH_2CH$_3$), 81.9 (=CH), 162.0 (=C$_{quat}$), 170.8 (C=O). IR (NaCl): ν_{max} 3286, 1650, 1615, 1268 cm^{-1}. MS (ES) m/z (%): 158 (M+H$^+$, 100). Anal. Calcd for $C_8H_{15}NO_2$: C 61.12, H 9.62, N 8.91; found: C 61.03, H 9.69, N 8.99.

*3.7.1.3. Ethyl 3-n-propylaminobut-2-enoate (**29c**).* Distillation (78 °C, 1.0 mmHg) gave **29c** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.97 (3H, t, J=7.3 Hz, CH$_2$CH_3), 1.25 (3H, t, J=7.1 Hz, OCH$_2$CH_3), 1.59 (2H, sextet, J=7.3 Hz, NCH$_2$CH_2CH$_3$), 1.91 (3H, s, CH$_3$), 3.17 (2H, m, NHCH_2CH$_2$), 4.08 (2H, q, J=7.1 Hz, OCH_2CH$_3$), 4.43 (1H, s, =CH), 8.58 (1H, br s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.4 (CH$_2$CH$_3$), 14.7 (OCH$_2$CH$_3$), 19.4 (CH$_3$), 23.7 (CH$_2$), 44.8 (NCH$_2$), 58.2 (OCH_2CH$_3$), 88.7 (=CH), 162.0 (=C$_{quat}$), 170.7 (C=O). IR (NaCl): ν_{max} 3286, 1651, 1611, 1268 cm^{-1}. MS (ES) m/z (%): 172 (M+H$^+$, 100). Anal. Calcd for $C_9H_{17}NO_2$: C 63.13, H 10.01, N 8.18; found: C 62.90, H 10.21, N 8.05.

*3.7.1.4. Methyl 3-n-propylbut-2-enoate (**29e**).* Flash chromatography on silica gel using hexane/ethyl acetate (4:1) as eluent gave **29e** as a colorless solid, mp 120–121 °C.[16] ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.98 (3H, t, J=7.3 Hz, CH$_2$CH_3), 1.59 (2H, sextet, J=7.3 Hz, NCH$_2$CH_2CH$_3$), 1.91 (3H, s, CH$_3$), 3.17 (2H, dt, J=6.9, 7.3 Hz, NHCH_2CH$_2$), 3.63 (3H, s, OCH$_3$), 4.44 (1H, s, =CH), 8.56 (1H, br s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.4 (CH$_2$CH$_3$), 19.4 (CH$_3$), 23.7 (CH$_2$), 44.8 (NCH$_2$), 49.9 (OCH$_3$), 81.4 (=CH), 162.2 (=C$_{quat}$), 171.0 (C=O). IR (NaCl): ν_{max} 3290, 1649, 1611, 1238 cm^{-1}. MS (ES) m/z (%): 158 (M+H$^+$, 100). Anal. Calcd for $C_8H_{15}NO_2$: C 61.12, H 9.62, N 8.91; found: C 61.33, H 9.85, N 8.81.

*3.7.1.5. Methyl 3-ethylaminopent-2-enoate (**29f**).* Distillation (72 °C, 0.8 mmHg) gave **29f** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.13 (3H, t, J=7.4 Hz, CH$_3$), 1.23 (3H, t, J=7.3 Hz, NHCH$_2$CH_3), 2.23 (2H, q, J=7.4 Hz, CH_2CH$_3$), 3.25 (2H, qd, J=5.7, 7.3 Hz, NHCH_2CH$_3$), 3.63 (3H, s, OCH$_3$), 4.46 (1H, s, =CH), 8.49 (1H, br s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.3 (NHCH$_2$CH$_3$), 15.7 (CH$_2$CH$_3$), 25.3 (CH$_2$), 37.2 (NHCH$_2$), 49.9 (OCH$_3$), 79.5 (=CH), 167.2 (=C$_{quat}$), 171.4 (C=O). IR (NaCl): ν_{max} 3225, 1689, 1607, 1259 cm^{-1}. MS (ES) m/z (%): 158 (M+H$^+$, 100). Anal. Calcd for $C_8H_{15}NO_2$: C 61.12, H 9.62, N 8.91; found: C 60.95, H 9.66, N 8.93.

*3.7.2. Microwave mediated synthesis of 5-alkyl-2-alkylamino-3-alkyloxycarbonylnaphtho[3,2,1-de]isoquinoline-4,7-diones **30***

General procedure: the enaminoester **29** (2.24 mmol) was added to a solution of an *N*-substituted benz[*g*]isoquinoline-3,5,10(2*H*)-trione **15** (0.36 mmol) in absolute ethanol (4 ml). The reaction vessel was introduced in a CEM microwave and the following parameters were used: target temperature 128 °C, reaction time 3 h, and maximal pressure 275 psi. After completion of the reaction, the solvent was removed under reduced pressure and the reaction mixture was purified with the aid of column chromatography or preparative TLC on silica gel. Some of the aromatic quaternary carbons remained in the noise of the ^{13}C NMR spectrum of compound **30e**, even upon prolongation of the pulse delay and raising the number of recorded scans.

*3.7.2.1. 3-Ethoxycarbonyl-2-ethylamino-5-isopropylnaphtho[3,2,1-de]-isoquinoline-4,7-dione (**30b**).* Preparative TLC analysis on silica gel with ethyl acetate/hexane (1:4) as eluent followed by recrystallization from methanol gave **30b** as orange crystals, mp 194.0–194.6 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.18 (3H, t, J=7.2 Hz, NCH$_2$CH_3), 1.37 (3H, t, J=7.2 Hz, OCH$_2$CH_3), 1.50 (6H, d, J=6.6 Hz, CH(CH_3)$_2$), 3.34 (2H, qd, J=5.2, 7.2 Hz, NCH$_2$), 4.34 (2H, q, J=7.2 Hz, OCH$_2$), 5.33–5.36 (1H, br s, NH), 5.40 (1H, septet, J=6.6 Hz, NCH), 7.53 (1H, td, J=1.4, 7.5 Hz, H-9), 7.60 (1H, td, J=1.6, 7.5 Hz, H-10), 7.69 (1H, s, H-1), 7.76 (1H, dd, J=1.4, 7.5 Hz, H-11), 8.44 (1H, s, H-6), 8.45 (1H, dd, J=1.6, 7.5 Hz, H-8). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.5 (NCH$_2$CH_3), 14.5 (OCH$_2$CH_3), 22.0 (2×CH$_3$), 38.4 (NCH$_2$), 47.7 (NCH), 62.4 (OCH$_2$), 108.7 (C-1), 111.1 (=C$_{quat}$), 120.2 (=C$_{quat}$), 122.1 (=C$_{quat}$), 126.2 (=C$_{quat}$), 127.1 (=C$_{quat}$), 127.3 (C-9), 127.9 (C-11), 128.7 (C-6), 132.2 (C-10), 132.3 (=C$_{quat}$), 132.5 (C-8), 135.6 (=C$_{quat}$), 145.9 (=C$_{quat}$), 161.5 (N–C=O), 170.7 (O–C=O), 181.6 (C=O). IR (KBr): ν_{max} 3352, 1713, 1666, 1637, 1268 cm^{-1}. MS (ES) m/z (%): 405 (M+H$^+$, 100). Anal. Calcd for $C_{24}H_{24}N_2O_4$: C 71.27, H 5.98, N 6.93; found: C 71.48, H 6.21, N 6.88.

*3.7.2.2. 3-Ethoxycarbonyl-5-isopropyl-2-n-propylaminonaphtho[3,2,1-de]isoquinoline-4,7-dione (**30c**).* Preparative TLC analysis on silica gel with ethyl acetate/hexane (1:4) as eluent followed by recrystallization from methanol gave **30c** as orange crystals, mp 144.1–144.4 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.06 (3H, t, J=7.3 Hz, CH$_2$CH$_2$CH_3), 1.18 (3H, t, J=7.2 Hz, OCH$_2$CH_3), 1.50 (6H, d, J=6.9 Hz, 2×CH$_3$), 1.76 (2H, sextet, J=7.3 Hz, CH$_2$CH_2CH$_3$), 3.26 (2H, td, J=5.2, 7.3 Hz, NHCH_2), 4.34 (2H, q, J=7.2 Hz, OCH$_2$), 5.42 (1H, septet, J=6.9 Hz, NCH), 5.45–5.47 (1H, br s, NH), 7.53 (1H, td, J=1.4, 7.5 Hz, H-9), 7.60 (1H, td, J=1.8, 7.5 Hz, H-10), 7.69 (1H, s, H-1), 7.76 (1H, dd, J=1.4, 7.5 Hz, H-11), 8.43 (1H, s, H-6), 8.44 (1H, dd, J=1.4, 7.5 Hz, H-8). ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.7 (CH$_2$CH$_2$CH$_3$), 13.6 (OCH$_2$CH$_3$), 21.9 (2×CH$_3$), 22.3 (CH$_2$CH$_3$), 45.6 (NCH$_2$), 47.7 (NCH), 63.2 (OCH$_2$), 108.8 (C-1), 111.1 (=C$_{quat}$), 120.2 (=C$_{quat}$), 122.0 (=C$_{quat}$), 126.3 (=C$_{quat}$), 127.1 (=C$_{quat}$), 127.4 (C-9), 127.9 (C-11), 128.6 (C-6), 132.2 (C-10), 132.3 (=C$_{quat}$), 132.4 (C-8), 135.6 (=C$_{quat}$), 146.0 (=C$_{quat}$), 161.5 (N–C=O), 170.7 (O–C=O), 181.6 (C=O). IR (KBr): ν_{max} 3414, 1701, 1669, 1643, 1266 cm^{-1}. MS (ES) m/z (%): 419 (M+H$^+$, 100). Anal. Calcd for $C_{25}H_{26}N_2O_4$: C 71.75, H 6.26, N 6.69; found: C 71.91, H 6.37, N 6.60.

*3.7.2.3. 3-Ethoxycarbonyl-5-isopropyl-2-isopropylaminonaphtho[3,2,1-de]isoquinoline-4,7-dione (**30d**).* Flash chromatography on silica gel with ethyl acetate/hexane (1:4) as eluent followed by recrystallization from methanol gave **30d** as orange crystals, mp 276.2–276.8 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.41 (3H, t, J=7.2 Hz, OCH$_2$CH_3), 1.51 (6H, d, J=6.4 Hz, CH(CH_3)$_2$), 1.53 (6H, d, J=6.4 Hz, CH(CH_3)$_2$), 3.30–3.50 (1H, m, NHC*H*), 4.52 (2H, q, J=7.2 Hz, CH_2CH$_3$), 5.31 (1H, septet, J=6.4 Hz, C*H*(CH$_3$)$_2$), 7.61 (1H, td, J=1.5, 7.5 Hz, H-9), 7.75 (1H, td, J=1.6, 7.5 Hz, H-10), 8.09 (1H, s, H-1), 8.18 (1H, dd, J=1.5, 7.5 Hz, H-11), 8.46 (1H, dd, J=1.6, 7.5 Hz, H-8), 8.58 (1H, s, H-6). ^{13}C NMR (75 MHz, DMSO-d_6): δ 13.8 (CH$_3$), 20.9 (2×CH$_3$), 21.1 (2×CH$_3$), 48.2 (NCH), 61.2 (OCH$_2$), 109.9 (C-1), 116.9 (=C$_{quat}$), 121.4 (=C$_{quat}$), 123.1 (=C$_{quat}$), 123.9 (=C$_{quat}$), 127.3 (C-9 and C-11), 129.4 (C-6), 129.5 (=C$_{quat}$), 130.3 (C-10), 134.2 and 134.3 (C-8 and =C$_{quat}$), 135.2 (=C$_{quat}$), 153.6 (=C$_{quat}$), 159.7 (N–C=O), 167.3 (O–C=O), 180.6 (C=O). IR (KBr): ν_{max} 3121, 1729, 1675, 1637, 1273 cm^{-1}. MS (ES) m/z (%): 419 (M+H$^+$, 10), 378 (100). Anal. Calcd for $C_{25}H_{26}N_2O_4$: C 71.75, H 6.26, N 6.69; found: C 71.50, H 6.37, N 6.86.

*3.7.2.4. 5-n-Butyl-3-methoxycarbonyl-2-n-propylaminonaphtho[3,2,1-de]isoquinoline-4,7-dione (**30e**).* Preparative TLC analysis on silica gel with ethyl acetate/hexane (1:4) as eluent followed by recrystallization from methanol gave **30e** as orange crystals, mp 151.8–152.1 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.98 (3H, t, J=7.4 Hz, CH$_3$), 1.06 (3H, t, J=7.4 Hz, CH$_3$), 1.40–1.48 (2H, m, CH$_2$), 1.72–1.86 (4H, m, 2×CH$_2$), 3.23–3.29 (2H, m, NHCH_2), 3.83 (3H, s, OCH$_3$), 4.14 (2H, t, J=7.4 Hz, NCH$_2$), 5.46–5.51 (1H, m, NH), 7.54 (1H, td, J=1.4, 7.3 Hz, H-9), 7.61 (1H, td, J=1.6, 6.9 Hz, H-10), 7.68 (1H, s, H-1), 7.67–7.70 (1H, m, H-11), 8.33 (1H, s, H-6), 8.45 (1H, s, dd, J=1.6, 7.6 Hz, H-8). ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.6 (CH$_3$), 14.1 (CH$_3$), 19.9 (CH$_2$), 22.2 (CH$_2$), 31.4 (NCH$_2$CH$_2$), 45.6 (NCH$_2$), 50.2 (NCH$_2$), 52.9 (OCH$_3$), 108.6 (C-1), 126.4 (=C$_{quat}$), 127.1 (C-9), 127.7 (=C$_{quat}$), 127.9 (C-11), 128.7 (C-6), 129.0 (=C$_{quat}$), 132.2 (=C$_{quat}$), 132.4 (C-8), 136.6 (C-10), 136.7 (=C$_{quat}$), 142.0 (=C$_{quat}$), 146.0 (=C$_{quat}$), 161.7 (N–C=O), 171.1 (O–C=O). IR (KBr): ν_{max} 3350, 1670, 1643, 1609, 1592, 1266 cm^{-1}.

MS (ES) m/z (%): 419 ($M+H^+$, 100). Anal. Calcd for $C_{25}H_{26}N_2O_4$: C 71.75, H 6.26, N 6.69; found: C 71.59, H 6.43, N 6.60.

*3.7.2.5. 5-n-Butyl-2-ethylamino-3-methoxycarbonyl-1-methylnaphtho[3,2,1-de]isoquinoline-4,7-dione (**30f**).* Preparative TLC analysis on silica gel with ethyl acetate/hexane (1:4) as eluent followed by recrystallization from methanol gave **30f** as orange crystals, mp 156.2–157.9 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.99 (3H, t, J=7.3 Hz, $CH_2CH_2CH_3$), 1.13 (3H, t, J=7.1 Hz, NCH_2CH_3), 1.45 (2H, sextet, J=7.3 Hz, $CH_2CH_2CH_3$), 1.79–1.89 (2H, m, NCH_2CH_2), 2.92 (3H, s, CH_3), 3.05 (2H, q, J=7.1 Hz, $NHCH_2CH_3$), 3.87 (3H, s, OCH_3), 4.11 (2H, t, J=7.3 Hz, NCH_2CH_2), 7.53 (1H, td, J=1.1, 7.6 Hz, H-9), 7.63 (1H, td, J=1.6, 7.6 Hz, H-10), 7.81 (1H, dd, J=1.1, 7.6 Hz, H-11), 8.45 (1H, dd, J=1.6, 7.6 Hz, H-8), 8.54 (1H, s, H-6). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.7 ($CH_2CH_2CH_3$), 16.0 (NCH_2CH_3), 18.1 (CH_3), 20.1 (CH_2CH_3), 31.3 (NCH_2CH_2), 44.2 ($NHCH_2$), 50.6 (NCH_2), 53.1 (OCH_3), 110.0 (=C_{quat}), 122.8 (=C_{quat}), 124.5 (=C_{quat}), 126.2 (CH_{ar}), 127.7 (CH_{ar}), 128.3 (CH_{ar}), 128.6 (=C_{quat}), 129.6 (=C_{quat}), 131.4 (=C_{quat}), 132.7 (CH_{ar}), 135.7 (=C_{quat}), 137.4 (=C_{quat}), 139.9 (CH_{ar}), 145.3 (=C_{quat}), 162.4 (N–C=O), 171.5 (O–C=O), 181.4 (C=O). IR (KBr): ν_{max} 3383, 1712, 1670, 1648, 1287 cm^{-1}. MS (ES) m/z (%): 419 ($M+H^+$, 100). Anal. Calcd for $C_{25}H_{26}N_2O_4$: C 71.75, H 6.26, N 6.69; found: C 71.63, H 6.38, N 6.57.

Acknowledgements

The authors are indebted to the 'Research Foundation—Flanders (FWO-Vlaanderen)' for financial support of this research.

References and notes

1. (a) Solis, P. N.; Lang'at, C.; Gupta, M. P.; Kirby, G. C.; Warhurst, D. S.; Phillipson, J. D. *Planta Med.* **1995**, *61*, 62–65; (b) Phillipson, J. D. *Phytochemistry* **1995**, *38*, 1319–1343; (c) Okunade, A. L.; Clark, A. M.; Hufford, C. D.; Oguntimein, B. O. *Planta Med.* **1999**, *65*, 447–448.
2. Nok, A. J. *Cell Biochem. Funct.* **2002**, *20*, 205–212; *Chem. Abstr.* **2002**, 636119.
3. (a) Arsenault, G. P. *Tetrahedron Lett.* **1965**, *6*, 4033–4037 and references therein; (b) Parisot, D.; Devys, M.; Barbier, M. *Z. Naturforsch.* **1989**, *44*, 1473–1474; (c) Parisot, D.; Devys, M.; Barbier, M. Z. *Phytochemistry* **1990**, *29*, 3364–3365; (d) Gräfe, U.; Ihn, W.; Tresselt, D.; Miosga, N.; Kaden, U.; Schlegel, B.; Bormann, E.-J.; Sedmera, P.; Novak, J. *Biol. Met.* **1990**, *3*, 39–44; (e) Miljkovic, A.; Mantle, P. G.; Williams, D. J.; Rassing, B. *J. Nat. Prod.* **2001**, *64*, 1251–1253; (f) Moriyasu, Y. K.; Miyagawa, H.; Hamada, N.; Miyawaki, H.; Ueno, T. *Phytochemistry* **2001**, *58*, 239–241.
4. (a) Parisot, D.; Devys, M.; Barbier, M. *J. Antibiot.* **1989**, *42*, 1189–1190; (b) Steyn, P. S.; Wessels, P. L.; Marasas, W. F. O. *Tetrahedron* **1979**, *35*, 1551–1555; (c) Visconti, A.; Surico, G.; Iacobellis, N. S.; Bottalico, A. *Phytopath. Medit.* **1983**, *22*, 122–156.
5. (a) Waterman, P. G.; Muhammad, I. *Phytochemistry* **1985**, *24*, 523–527; (b) Peterson, J. R.; Zjawiony, J. K.; Liu, S.; Hufford, C. D.; Clark, A. M.; Rogers, R. D. *J. Med. Chem.* **1992**, *35*, 4069–4077.
6. (a) Kobayashi, J.; Cheng, J.; Nakamura, H.; Ohizumi, Y.; Hirata, Y.; Sasaki, T.; Ohta, T.; Nozoe, S. *Tetrahedron Lett.* **1988**, *29*, 1177–1180; (b) Feliu, L.; Ajana, W.; Alvarez, M.; Joule, J. A. *Tetrahedron* **1997**, *53*, 4511–4520; (c) Alvarez, M.; Feliu, L.; Ajana, W.; Joule, J. A.; Fernandez-Puentes, J. L. *Eur. J. Org. Chem.* **2000**, 849–855.
7. Carneiro do Nascimento, S.; Bouammali, B.; Boitard, M.; Pautet, F.; Soufiaoui, M.; Fillion, H. *Pharmazie* **1994**, *49*, 702–703.
8. Jacobs, J.; Claessens, S.; Kesteleyn, B.; Huygen, K.; De Kimpe, N. *Tetrahedron* **2007**, *63*, 2503–2510.
9. Baraldi, P. G.; Simoni, D.; Manfredini, S. *Synthesis* **1983**, 902–903.
10. Hayes, B. L. *Microwave Synthesis, Chemistry at the Speed of Light*; CEM: Matthews, NC, 2002; pp 292.
11. Gabriel, C.; Gabriel, S.; Grant, E. H.; Halstead, B. S. J.; Mingos, D. M. P. *Chem. Soc. Rev.* **1998**, *27*, 213–223.
12. Weingarten, H.; Chupp, J. P.; White, W. A. *J. Org. Chem.* **1967**, *32*, 3246–3249.
13. (a) Fraser, R. R.; Banville, J.; Akiyama, F.; Chuaqui-Offermanns, N. *Can. J. Chem.* **1981**, *59*, 705–709; (b) Liao, S.; Collum, D. B. *J. Am. Chem. Soc.* **2003**, *125*, 15114–15127; (c) Ma, Y.; Lobkovsky, E.; Collum, D. B. *J. Org. Chem.* **2005**, *70*, 2335–2337.
14. (a) Brandt, C. A.; da Silva, A. C. M. P.; Pancote, C. G.; Brito, C. L.; da Silveira, M. A. B. *Synthesis* **2004**, 1557–1559; (b) Zhang, Z.-H.; Song, L. M. *J. Chem. Res.* **2005**, 817–820; (c) Zhang, Z.-H.; Yin, L.; Wang, Y. M. *Adv. Synth. Catal.* **2006**, *348*, 184–190.
15. (a) Iwanami, M.; Shibanuma, T.; Fujimoto, M.; Kawai, R.; Tamazawa, K.; Takenaka, T.; Takahashi, K.; Murakami, M. *Chem. Pharm. Bull.* **1979**, *27*, 1426–1440; (b) Litvic, M.; Filipan, M.; Pogoreli, I.; Cepanec, I. *Green Chem.* **2005**, *7*, 771–774; (c) AIST: Integrated Spectral Database System of Organic Compounds (Japan).
16. Anderson, P. C.; Staskun, B. *J. Org. Chem.* **1965**, *30*, 3033–3037.