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New and highly efficient synthesis of 3-substituted 1-hydroxybenz[*g*]-isoquinoline-5,10-diones

Jan Jacobs [a], Sven Claessens [a], Blaise Mavinga Mbala [a], Kris Huygen [b], Norbert De Kimpe [a,*]

[a] *Department of Organic Chemistry, Faculty of Bioscience Engineering, Ghent University, Coupure links 653, B-9000 Ghent, Belgium*
[b] *Scientific Institute of Public Health, Engelandstraat 642, B-1180 Brussels, Belgium*

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ABSTRACT

A new and efficient strategy for the synthesis of 3-substituted 1-hydroxybenz[*g*]isoquinoline-5,10-diones by reaction of 2-methoxycarbonyl-1,4-naphthoquinone with different pyridinium salts under Kröhnke conditions is disclosed. This one-step reaction was found to be dependent on the substitution pattern of the aromatic nucleus in the pyridinium salts.

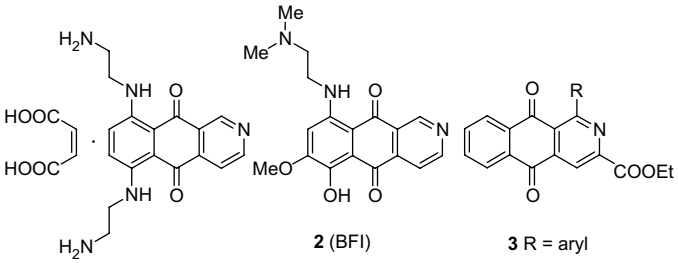
1. Introduction

2-Azaanthraquinones constitute an important research area in organic synthesis due to the pronounced biological activities of these compounds. For instance, 2-azaanthraquinones attract considerable attention in cancer research as intercalating DNA-binding agents, which can interfere with DNA topoisomerases.[1] In this way, the antitumor agent pixantrone (BBR 2778 dimaleate) **1**,[2] and the benzo-fused isoquinolinedione derivative BFI **2** were discovered as potent intercalating agents (Fig. 1).[3] Moreover, pixantrone **1** has also been proposed as a very promising immunosuppressant agent for clinical use in the treatment of multiple sclerosis.[4] Finally, 1-aryl substituted 2-azaanthraquinones **3** were evaluated as potential antitumor agents and inhibition of the proliferation of MT-4 cells at micromolar concentrations.[5]

Since 2-azaanthraquinones display interesting physiological activities, they have been subjected to SAR-studies, which revealed that the presence of hydroxy substituents at the *peri*-carbonyl position enhances antimicrobial activity.[6] Therefore, short and efficient syntheses of various 2-azaanthraquinones become a very interesting target in synthetic organic chemistry.[7] In the present manuscript, a new strategy for the synthesis of functionalized 2-azaanthraquinones will be discussed as it is the purpose to form 3-substituted 1-hydroxybenz[*g*]isoquinoline-5,10-diones **4** from activated quinone **6** with different pyridinium ylids, generated from pyridinium salts **5** under Kröhnke conditions, which refers to the use of ammonium acetate acting simultaneously as a base and as a source of ammonia in the presence of acetic acid (Fig. 2).[8]

2. Results and discussion

After the discovery of pyridinium ylids by F. Kröhnke in 1935,[9] these reagents were gradually incorporated in organic chemistry, giving rise to the synthesis of different heterocycles, for instance pyridines, furans, azepines, etc.[10] However, the reactivity of pyridinium ylids depends very much on the electronic properties of their substituents, the solvent system in which the reaction is performed and the nature of the reactant at which the addition of the pyridinium ylid takes place.[10,11] More specific, in quinone chemistry, pyridinium ylids proved to be very useful to introduce



1 (BBR 2778 dimaleate, Pixantrone) **2** (BFI) **3** R = aryl

Figure 1.

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

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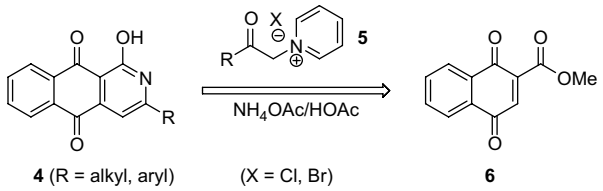
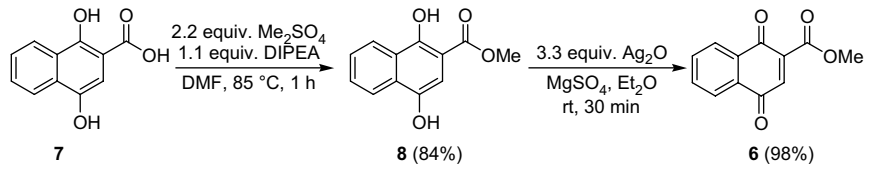


Figure 2.

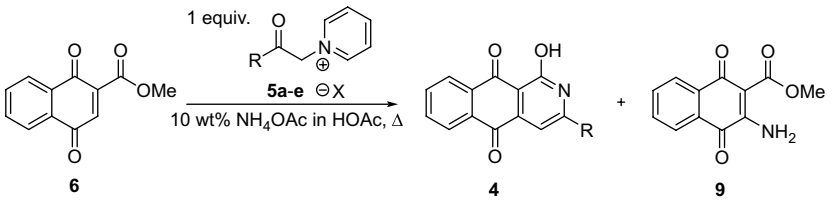
acetonyl side chains onto quinone moieties.[12] After introduction of the acetonyl side chain, further elaboration toward the natural product isagarin,[13] anthraquinones,[14] pyranonaphthoquinones,[12,14,15] 2-azaanthraquinones,[16] and indolizines[17] has been reported. In the present manuscript, a one-step synthesis of 1-hydroxybenz[*g*]-isoquinoline-5,10-diones **4** by conjugate addition of different pyridinium ylids to a quinone was elaborated. This would be possible by treatment of an activated quinone **6** with a pyridinium salt **5** under Kröhnke conditions. These mild reaction conditions have been well studied in the synthesis of mono- and oligopyridines and are renowned to give high yielding syntheses.[10b] A requirement for these mono- and oligopyridine syntheses is the presence of a Michael acceptor in order to allow conjugate addition of the pyridinium ylid and the presence of a carbonyl moiety at δ-position of the ketone function, originating from the pyridinium salt, in order to give heterocyclization after addition of the pyridinium ylid. Since these structural features were also found in activated quinone **6**, it was believed to be a good substrate for the synthesis of 2-azaanthraquinones **4** in one step using the methodology from the Kröhnke pyridine synthesis. Actually, the term activated quinone is defined as a quinone, which bears an electron-withdrawing substituent at the 2-position. The LUMO at position 3 of such an activated quinone is substantially lowered, which makes it highly reactive toward nucleophiles. Although literature reports exist on the synthesis of quinone **6**,[18] the following procedure was found to be much more successful for a large scale synthesis of activated quinone **6** (Scheme 1). The commercially available 1,4-dihydroxy-2-naphthoic acid **7** was treated with Hunig's base and dimethyl sulfate in *N*,*N*-dimethylformamide at 85 °C for 1 h, after which methyl 1,4-dihydroxynaphthalene-2-carboxylate **8** was isolated in 84% yield. Finally, silver(I) oxide mediated oxidation of the naphthalene-1,4-diol **8** afforded the activated quinone **6** in 98% yield.

Next, the activated quinone **6** was reacted with different pyridinium salts **5** in a 10 wt % solution of ammonium acetate in acetic acid (Table 1). As it is clear from Table 1, the reaction was found to be dependent on the electron-donating or electron-withdrawing properties of the substituents of pyridinium salts **5a–e**, since a competition between the addition of the pyridinium ylid and the direct addition of ammonia across the 1,4-naphthoquinone **6** to form 3-amino-2-methoxycarbonyl-1,4-naphthoquinone **9** was observed. For instance, in entries 1–3, 3-(4-fluorophenyl)-1-hydroxybenz[*g*]isoquinoline-5,10-dione **4a** was found in a ratio of 98/2 with respect to 3-amino-2-methoxycarbonyl-1,4-naphthoquinone **9**, which was not isolated by column chromatography due to a strong affinity of the small fraction of compound **9** onto the silica gel.



Scheme 1.

Table 1
Synthesis of 1-hydroxybenz[*g*]isoquinoline-5,10-diones **4** under Kröhnke conditions



Entry	Compound	R	Reaction time (h)	Ratio **4**/**9**[a]	Isolated yield (%)	
					4	**9**
1	**4a**	4-FC_6H_4	1	98/2	68	Not isolated
2			2	97/3		
3			4	96/4		
4	**4b**	4-ClC_6H_4	1	97/3	76	Not isolated
5			2	95/5		
6			4	94/6		
7	**4c**	C_6H_5	1	96/4	45	Not isolated
8			2	95/5		
9			4	95/5		
10	**4d**	*t*-Bu	1	64/36	48	19
11			2	65/35		
12			4	69/31		
13	**4e**	4-$MeOC_6H_4$	1	34/66	50	33
14			2	42/58		
15			4	1/1		

In addition non-identified degradation products were present.
[a] Determined by LC–MS analysis.

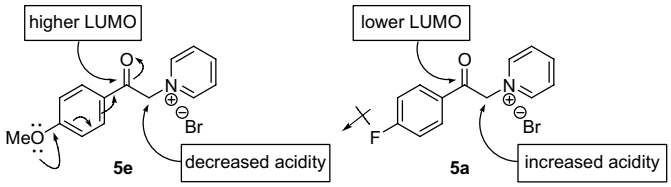
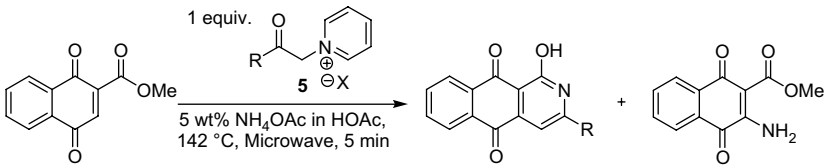


Figure 3.

However, upon use of more electron-rich pyridinium salts **5d**,**e** (Table 1, entries 10–15), the formation of a substantial amount of the side-product 3-amino-2-methoxycarbonyl-1,4-naphthoquinone **9** could not be avoided. These observations can be explained by the fact that in case of the 1-[2-(4-fluorophenyl)-2-oxo-ethyl]-pyridinium bromide **5a**, the carbonyl is more activated by the inductive electron-withdrawing effect of the 4-fluoro-substituent and this results in more acidic protons at the α-position of the carbonyl in comparison with more electron-rich pyridinium salts **5d**,**e** (Fig. 3). Therefore, the electron-poor pyridinium ylids **10a**,**b** are readily formed in the reaction mixture and can immediately add across naphthoquinone **6**, whereas it is more difficult for the electron-rich pyridinium ylids **10d**,**e** to be formed. This competition results in a more significant direct addition of ammonia to activated quinone **6**. In this way, the electron-rich pyridinium salts **5d**,**e** were reacted for 4 h with the naphthoquinone **6**, while the reaction with more electron-poor pyridinium salts **5a**–**c** was finished after 1 h. Finally, the target 1-hydroxybenz[*g*]isoquinoline-5,10-diones **4** were isolated in 48–76% yield.

However, knowing the competition between the addition of electron-rich pyridinium ylids and the direct addition of ammonia, reaction conditions were sought to optimize the synthesis of the target compounds **4** by avoiding the formation of 3-amino-2-methoxycarbonyl-1,4-naphthoquinone **9** as a side-product. In a first attempt, the reactions were performed in a microwave reactor since it was believed that applying more efficient heating would increase the reaction rate toward the target compounds **4**. Therefore, the activated quinone **6** was reacted in a microwave with different pyridinium salts **5** in a 5 wt % solution of ammonium acetate in acetic acid (Table 2). After reaction at 142 °C for 5 min an improvement in the formation of target compounds **4d** and **4e** could be noted upon LC–MS analysis of the crude reaction mixtures. However, the more severe reaction conditions of the microwave-mediated syntheses gave more complex reaction mixtures, which were more difficult to purify by column chromatography. As a result, the isolated yields of the target compounds **4d** and **4e** did not improve significantly in comparison with the above presented method (Table 1). In addition, in case of pyridinium salts **5a**–**c** the side-product 3-amino-2-methoxycarbonyl-1,4-naphthoquinone **9** was formed predominantly and as a result, these reactions were not considered for subsequent purification (Table 2). Subsequently, a microwave reaction was considered using a 5 wt % solution of ammonium acetate in methanol. Methanol is known to perform better as solvent in microwave conditions, resulting in a better

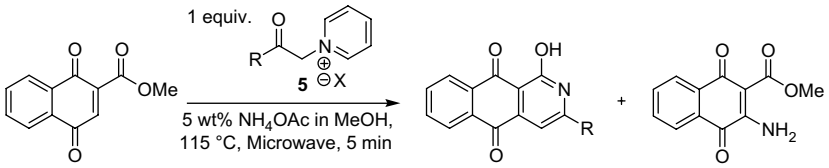
Table 2
Microwave-assisted synthesis of 1-hydroxybenz[*g*]isoquinoline-5,10-diones **4** in a 5 wt % solution of ammonium acetate in acetic acid



Entry	Compound	R	Ratio **4**/**9**[a]	Isolated yield (%)	
				4	**9**
1	**4a**	4-FC_6H_4	20/80	Not purified	
2	**4b**	4-ClC_6H_4	21/79	Not purified	
3	**4c**	C_6H_5	20/80	Not purified	
4	**4d**	*t*-Bu	86/14	51	13
5	**4e**	4-$MeOC_6H_4$	74/26	31	19

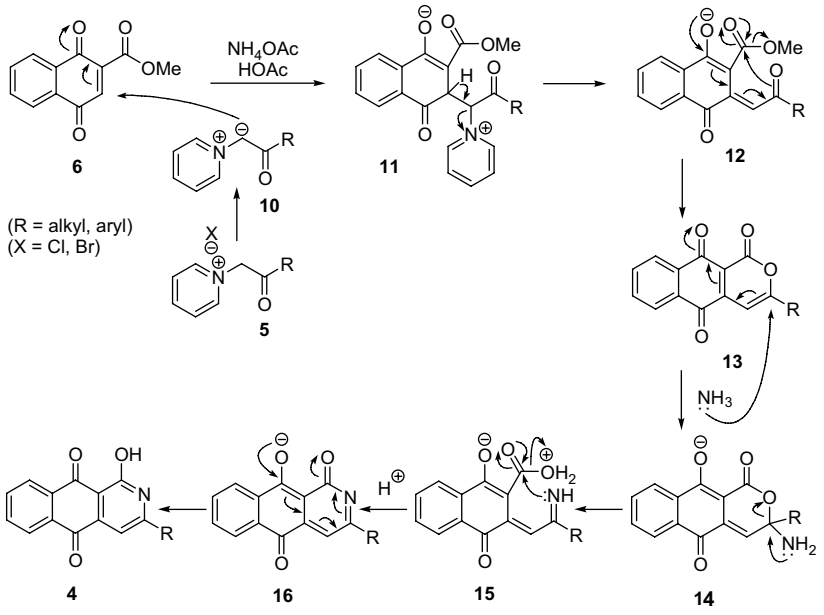
In addition non-identified degradation products were present.
[a] Determined by LC–MS analysis.

Table 3
Microwave-assisted synthesis of 1-hydroxybenz[*g*]isoquinoline-5,10-diones **4** in a 5 wt % solution of ammonium acetate in methanol



Entry	Compound	R	Ratio **4**/**9**[a]	Isolated yield of **4** (%)
1	**4a**	4-FC_6H_4	77/33	51
2	**4b**	4-ClC_6H_4	68/32	61
3	**4c**	C_6H_5	7/3	31
4	**4d**	*t*-Bu	64/36	28
5	**4e**	4-$MeOC_6H_4$	1/1	40

In addition non-identified degradation products were present.
[a] Determined by LC–MS analysis of reaction crude.



Scheme 2.

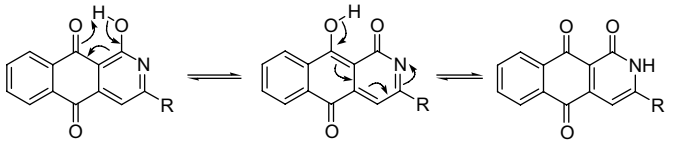
heating efficiency as compared to acetic acid.[19,20] Moreover, it was believed that the target compounds would crystallize after cooling down the reaction mixture to room temperature. In this way the activated naphthoquinone **6** was reacted in a microwave at 115 °C for 5 min with different pyridinium salts **5** in a 5 wt % solution of ammonium acetate in methanol (Table 3). Indeed, after cooling down the reaction mixture to room temperature the target compound **4a**,**b**,**e** could be easily isolated by filtration. After washing with ice-cold methanol the pure 1-hydroxybenz[*g*]isoquinoline-5,10-diones **4a**,**b**,**e** were isolated in 40–61% yield. In case of the synthesis of the target compounds **4c** and **4d**, the solvent had to be evaporated in vacuo after reaction to provoke crystallization.

Thanks to the microwave-assisted synthesis of 1-hydroxybenz[*g*]isoquinoline-5,10-diones **4** in a 5 wt % solution of ammonium acetate in methanol, one can obtain pure 1-hydroxybenz[*g*]isoquinoline-5,10-diones in less than 15 min, including setting up the experiment and performing both the reaction and purification. Taking this into account in combination with the fact that the starting compounds **5** and **6** could be prepared in one or two high yielding steps from commercially available compounds, a very efficient method for the synthesis of 2-azaanthraquinones is presented.

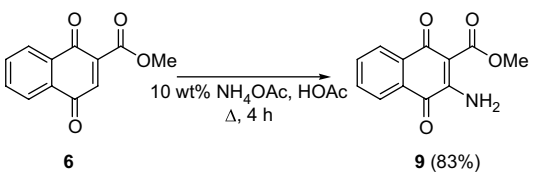
Mechanistically, after conjugate addition of the pyridinium ylid **10**, formed after deprotonation of pyridinium salts **5**, across the 1,4-naphthoquinone **6**, the pyridinium moiety is eliminated in 1,2-fashion due to the presence of an acidic α-hydrogen (Scheme 2). Subsequently, ring closure occurs after the formation of compound **12**. The resulting 1-oxo-3,4-dehydropyranonaphthoquinone **13** contains a novel Michael acceptor, which allows the addition of ammonia. Similar mechanisms were found in the degradation of the natural product pentalongin in alcoholic solvents.[21] In the next step, the pyran moiety is opened with the formation of imine **15**, which can provoke acid-catalyzed ring closure. Tautomerization gives then rise to the formation of the target compounds **4** (Scheme 2).

Concerning the spectral data of the synthesized 3-substituted 1-hydroxybenz[*g*]isoquinoline-5,10-diones **4**, broadening and a decreasing intensity of the ^{1}H and the ^{13}C NMR signals was noted. This can be explained by an equilibrium between the target compounds **4** and 2-azaanthraquinone **18**, which is caused by prototropy. The broadening and decreasing intensity of the ^{1}H and the ^{13}C NMR signals could only be observed for the atoms, which are part of the tautomeric system (Scheme 3).

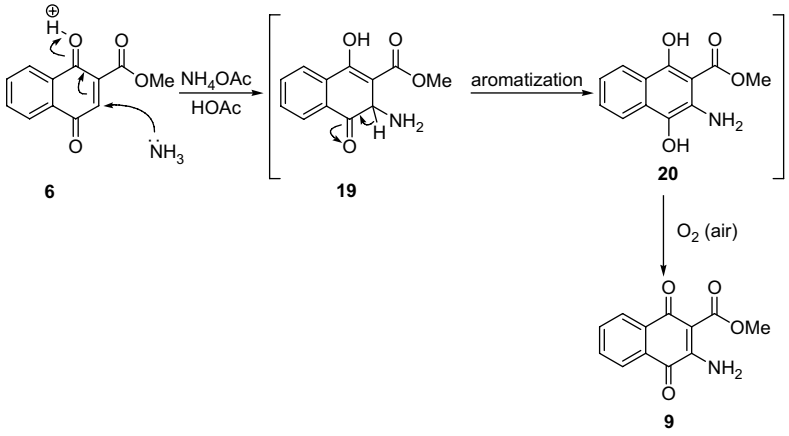
As conjugate addition of ammonia to quinones is not an easy and straightforward process, the isolation of 3-amino-2-methoxycarbonyl-1,4-naphthoquinone **9** as side-product in the synthesis of 1-hydroxybenz[*g*]isoquinoline-5,10-diones **4** is also important. So far, addition-elimination procedures in which ammonia replaces a chloro-[22] or a methoxy-substituent,[23] and addition of azide and subsequent reduction[24] are generally used to obtain 2-amino-1,4-naphthoquinones. It is demonstrated now that reactions of 1,4-naphthoquinones under Kröhnke conditions are a valuable alternative in the synthesis of 2-amino-1,4-naphthoquinones by the synthesis of 3-amino-2-methoxycarbonyl-1,4-naphthoquinone **9**. Since 3-amino-2-methoxycarbonyl-1,4-naphthoquinone **9** promotes the growth of important *Bifidobacteria* at an extremely low concentration, the product is useful for the prevention of intestinal carcinogenesis.[25] Therefore, the reaction of 2-methoxycarbonyl-1,4-naphthoquinone **6** with ammonium acetate in acetic acid was also performed without the presence of a pyridinium salt **5** and resulted in the synthesis 3-amino-2-methoxycarbonyl-1,4-naphthoquinone **9** in 83% yield (Scheme 4). In this way, a new and high yielding entry to useful 2-amino-1,4-naphthoquinones has been described. Mechanistically, after conjugate addition of ammonia across the activated naphthoquinone **6**, 3-amino-1,4-dihydroxy-2-methoxycarbonylnaphthalene **20** is formed as an intermediate. Naphthalene **20** is then oxidized by oxygen in air to the corresponding naphthoquinone **9** (Scheme 5).



Scheme 3.



Scheme 4.



Scheme 5.

3. Conclusion

A new and efficient synthesis of 1-hydroxybenz[*g*]isoquinoline-5,10-diones **4** is disclosed by reaction of 2-methoxycarbonyl-1,4-naphthoquinone **6** with different pyridinium salts **5a**–**e** under Kröhnke conditions. In case of electron-poor pyridinium salts **5a**–**c** the reaction was found to give the target compounds as the sole reaction product, while upon the use of electron-rich pyridinium salts **5d**,**e**, a competition with direct addition of ammonia to the activated quinone resulting in the synthesis of 3-amino-2-methoxycarbonyl-1,4-naphthoquinone **9** took place. Performing the reaction of 2-methoxycarbonyl-1,4-naphthoquinone **6** with different pyridinium salts **5a**–**e** in a 5 wt % solution in ammonium acetate in methanol proved to be the easiest and most efficient method to obtain pure 1-hydroxybenz[*g*]isoquinoline-5,10-diones **4**.

4. Experimental section

4.1. General experimental methods

Spectroscopic data were recorded as follows: ^{1}H NMR spectra were recorded at 300 MHz, ^{13}C NMR spectra were recorded at 75 MHz and ^{19}F NMR spectra were recorded at 282 MHz. Peak assignments were performed with the aid of 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). 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 (silica gel). Microwave reactions were performed in a CEM Discover® microwave.

4.2. Synthesis of 2-methoxycarbonyl-1,4-naphthoquinone 6

*4.2.1. Synthesis of methyl 1,4-dihydroxynaphthalene-2-carboxylate **8***

Dimethyl sulfate (0.22 mol, 27.75 g) and *N*,*N*-diisopropylethylamine (0.11 mol, 14.22 g) were added to a solution of 1,4-dihydroxynaphthoic acid **7** (0.10 mol, 20.4 g) in DMF (140 ml). The reaction mixture was heated for 1 h at 85 °C and after cooling to room temperature, it was poured in a saturated solution of aqueous sodium hydrogencarbonate. The aqueous phase was extracted with small portions of ethyl acetate (3×) and the combined organic phases were washed for an additional time with saturated aqueous sodium bicarbonate and three times with brine. After drying ($MgSO_4$) and solvent evaporation in vacuo, methyl 1,4-dihydroxynaphthalene-2-carboxylate **8** was obtained in 84% yield. The spectral data of methyl 1,4-dihydroxynaphthalene-2-carboxylate **8** were in complete accordance with data in the literature.[26]

4.3. Synthesis of 2-methoxycarbonyl-1,4-naphthoquinone 6

Freshly prepared silver(I) oxide (0.17 mol, 39.39 g)[27] and magnesium(II) sulfate (11 g) were added to a solution of methyl 1,4-dihydroxynaphthalene-2-carboxylate **8** (0.05 mol, 10.91 g) in diethyl ether. The reaction mixture was stirred for 30 min at room temperature, after which it was filtered. Solvent evaporation in vacuo of the filtrate furnished the activated quinone **6**. Chromatography or recrystallization of 2-methoxycarbonyl-1,4-naphthoquinone **6** is not advised, since this compound decomposes on silica gel or upon heating. However, since this oxidation protocol is a high conversion reaction, minor impurities could be removed by washing the crystals with cold diethyl ether and the activated quinone **6** could be isolated in a yield of 98%. The spectral data of methyl 2-methoxycarbonyl-1,4-naphthoquinone **6** were in complete accordance with data in the literature.[18d,26a]

4.4. Synthesis of 3-substituted 1-hydroxybenz[*g*]-isoquinoline-5,10-diones 4

General procedure 1. To a 10 wt % solution of ammonium acetate (1.0 g) in acetic acid (10 ml) were added 2-methoxycarbonyl-1,4-naphthoquinone **6** (1.2 mmol, 0.25 g) and a pyridinium salt **5** (1.2 mmol), and the reaction mixture was subsequently boiled under reflux for 1 and 4 h in case of pyridinium salts **5**,**a**,**b**,**c** and **5d**,**e**, respectively. After cooling to room temperature, the reaction mixture was poured in water and extracted with dichloromethane. The combined organic extracts were washed with a saturated aqueous solution of sodium hydrogencarbonate and dried over magnesium(II) sulfate. After solvent evaporation in vacuo, the crude mixture was purified by column chromatography on silica gel to yield the 3-substituted 1-hydroxybenz[*g*]isoquinoline-5,10-diones **4**.

General procedure 2. 2-Methoxycarbonyl-1,4-naphthoquinone **6** (0.69 mmol, 0.15 g) and a pyridinium salt **5** (0.69 mmol) were added to a previously prepared 5 wt % solution of ammonium acetate in acetic acid (6 ml). The sealed reaction vessel was introduced in a CEM Discover® microwave apparatus (ramp time 5 min, p_{max} 275 psi). After 5 min at 142 °C, the reaction mixture was cooled to room temperature and poured in water, which was extracted with dichloromethane. The combined organic extracts were washed with a saturated aqueous solution of sodium hydrogencarbonate and dried over magnesium(II) sulfate. After

evaporation of the solvent in vacuo, the crude mixture was purified by column chromatography on silica gel to yield the 3-substituted 1-hydroxybenz[*g*]isoquinoline-5,10-diones **4d** and **4e**, along with 3-amino-2-methoxycarbonyl-1,4-naphthoquinone **9**.

General procedure 3. 2-Methoxycarbonyl-1,4-naphthoquinone **6** (1.38 mmol, 0.30 g) and a pyridinium salt **5** (1.38 mmol) were added to a previously prepared 5 wt % solution of ammonium acetate in methanol (6 ml). The sealed reaction vessel was introduced in a CEM Discover® microwave (ramp time 5 min, p_{max} 275 psi). After 5 min at 115 °C, the reaction mixture was cooled to room temperature. Upon use of pyridinium salts **5c** and **5d** solvent evaporation in vacuo was needed until crystallization of the target compounds **4c** and **4d** was achieved. The reaction mixture was filtered and the crystals were washed with ice-cold methanol to yield pure 1-hydroxybenz[*g*]isoquinoline-5,10-diones **4**.

*4.4.1. 3-(4-Fluorophenyl)-1-hydroxybenz[g]isoquinoline-5,10-dione **4a***

Column chromatography on silica gel with dichloromethane/methanol (9:1) afforded **4a** as orange crystals in 68% yield, mp 299–302 °C. ^{1}H NMR ($CDCl_3$): δ 7.21–7.27 (2H, m, H-3′ and H-5′), 7.45 (1H, s, H-4), 7.81 (1H, d×d×d, *J*=1.3, 7.7, 7.7 Hz, H-7 or H-8), 7.89 (1H, d×d×d, *J*=1.3, 7.7, 7.7 Hz, H-7 or H-8), 8.03–8.10 (2H, m, H-2′ and H-6′), 8.22 (1H, d×d, *J*=1.3, 7.7 Hz, H-6 or H-9), 8.30 (1H, d×d, *J*=1.3, 7.7 Hz, H-6 or H-9). ^{13}C NMR ($CDCl_3$): δ 96.5 (C-4), 116.9 (d, *J*=23.0 Hz, C-3′ and C-5′), 127.0 (CH_{ar}), 127.5 (CH_{ar}), 129.4 (d, *J*=9.2 Hz, C-2′ and C-6′), 131.5 (=C_{quat}), 133.4 (=C_{quat}), 133.9 (CH_{ar}), 135.2 (d, *J*=9.2 Hz, =C_{quat}), 135.8 (CH_{ar}), 148.0 (=C_{quat}), 154.9 (d, *J*=211.1 Hz, C-4′), 166.0 (=C_{quat}), 167.4 (=C_{quat}), 178.7 (=C_{quat}), 179.4 (C=O), 182.4 (C=O). ^{19}F NMR ($CDCl_3$): δ −104.1 (1F, br s, =C_{quat}–F). IR (KBr): ν_{max} 1674 cm^{-1}. MS (ES) *m*/*z* (%): 321 (M+2H$^+$, 100). Anal. Calcd for $C_{19}H_{10}FNO_3$: C 71.47, H 3.16, N 4.39, found: C 71.32, H 3.44, N 4.49.

*4.4.2. 3-(4-Chlorophenyl)-1-hydroxybenz[g]isoquinoline-5,10-dione **4b***

Column chromatography on silica gel with dichloromethane/methanol (9:1) afforded **4b** as orange yellowish crystals in 76% yield, mp 277.2–277.9 °C. ^{1}H NMR ($CDCl_3$): δ 7.48–7.57 (3H, m, H-4, H-3′ and H-5′), 7.84–7.94 (2H, m, H-7 and H-8), 8.32–8.39 (2H, m, H-6 and H-9). ^{13}C NMR ($CDCl_3$): δ 109.8 (C-4), 127.3 (CH_{ar}), 127.8 (CH_{ar}), 129.2 (2×CH_{ar}), 129.3 (2×CH_{ar}), 132.8 (=C_{quat}), 133.1 (=C_{quat}), 135.2 (2×CH_{ar}), 135.4 (=C_{quat}), 137.8 (=C_{quat}), 141.9 (=C_{quat}), 162.9 (=C_{quat}), 165.8 (=C_{quat}), 182.0 (C=O), 186.7 (C=O). IR (KBr): ν_{max} 1674, 1634, 1586 cm^{-1}. MS (ES) *m*/*z* (%): 335/337 (M+H$^+$, 40). Anal. Calcd for $C_{19}H_{10}ClNO_3$: C 71.47, H 3.16, N 4.39, found: C 71.39, H 3.40, N 4.27.

*4.4.3. 3-Phenyl-1-hydroxybenz[g]isoquinoline-5,10-dione **4c***

Column chromatography on silica gel with dichloromethane/methanol (9:1) afforded **4c** as brown crystals in 45% yield, mp 192.8 °C. ^{1}H NMR ($CDCl_3$): δ 7.52–7.56 (3H, m, H-3′, H-4′ and H-5′), 7.84–7.94 (2H, m, H-7 and H-8), 8.19 (1H, s, H-4), 8.22–8.27 (2H, m, H-2′ and H-6′), 8.32–8.39 (2H, m, H-6 and H-9). ^{13}C NMR ($CDCl_3$): δ 110.0 (C-4), 127.2 (CH_{ar}), 127.7 (CH_{ar}), 127.9 (2×CH_{ar}), 129.0 (2×CH_{ar}), 131.4 (CH_{ar}), 132.8 (2×=C_{quat}), 133.1 (2×=C_{quat}), 135.0 (CH_{ar}), 135.1 (CH_{ar}), 136.9 (=C_{quat}), 165.8 (=C_{quat}), 182.1 (C=O), 186.7 (C=O). IR (KBr): ν_{max} 1676, 1634 cm^{-1}. MS (ES) *m*/*z* (%): 302 (M+H$^+$, 100). Anal. Calcd for $C_{19}H_{11}NO_3$: C 75.74, H 3.68, N 4.65, found: C 75.50, H 3.86, N 4.58.

*4.4.4. 3-tert-Butyl-1-hydroxybenz[g]isoquinoline-5,10-dione **4d***

Column chromatography on silica gel with petroleum ether/ethyl acetate (4:1) yielded 48% of **4d** as yellowish orange crystals, mp 149.7 °C. ^{1}H NMR ($CDCl_3$): δ 1.44 (9H, s, 3×CH_3), 7.25 (1H, s, H-4), 7.81–7.89 (2H, m, H-7 and H-8), 8.26–8.33 (2H, m, H-6 and H-9). ^{13}C NMR ($CDCl_3$): δ 29.6 (3×CH_3), 38.8 (C_{quat}), 108.8 (C-4), 123.7 (=C_{quat}), 127.2 (CH_{ar}), 127.6 (CH_{ar}), 132.9 (=C_{quat}), 133.1 (=C_{quat}), 134.4 (=C_{quat}), 134.8 (CH_{ar}), 135.1 (CH_{ar}), 141.8 (=C_{quat}), 164.8 (=C_{quat}), 182.7 (C=O), 186.3 (C=O). IR (KBr): ν_{max} 1689, 1674 cm^{-1}. MS (ES) *m*/*z* (%): 280 (M-H$^+$, 100). Anal. Calcd for $C_{17}H_{15}NO_3$: C 72.58, H 5.37, N 4.98, found: C 72.36, H 5.55, N 4.84.

*4.4.5. 3-(4-Methoxyphenyl)-1-hydroxybenz[g]isoquinoline-5,10-dione **4e***

Column chromatography on silica gel with dichloromethane/methanol (9:1) afforded **4e** as reddish orange crystals in 53% yield, mp 192.8 °C. ^{1}H NMR ($CDCl_3$): δ 3.90 (3H, s, OCH_3), 7.03 (2H, d, *J*=8.8 Hz, H-2′ and H-6′), 7.83–7.91 (2H, m, H-7 and H-8), 8.10 (1H, s, H-4), 8.23 (2H, d, *J*=8.8 Hz, H-3′ and H-5′), 8.31–8.37 (2H, m, H-6 and H-9). ^{13}C NMR ($CDCl_3$): δ 55.60 (OCH_3), 107.9 (=C_{quat}), 108.2 (=C_{quat}), 109.3 (C-4), 114.5 (C-3′ and C-5′), 127.2 (CH_{ar}), 127.7 (CH_{ar}), 129.7 (=C_{quat}), 129.8 (C-2′ and C-6′), 133.1 (=C_{quat}), 133.3 (=C_{quat}), 134.9 (CH_{ar}), 135.1 (CH_{ar}), 141.6 (=C_{quat}), 162.6 (=C_{quat}), 166.0 (C=O), 182.3 (C=O). IR (KBr): ν_{max} 3253, 1677 cm^{-1}. MS (ES) *m*/*z* (%): 332 (M+H$^+$, 100). Anal. Calcd for $C_{20}H_{13}NO_4$: C 72.50, H 3.95, N 4.23, found: C 72.67, H 4.10, N 4.13.

4.5. Synthesis of 3-amino-2-methoxycarbonyl-1,4-naphthoquinone 9

To a 10 wt % solution of ammonium acetate (1.0 g) in acetic acid (10 ml) was added 2-methoxycarbonyl-1,4-naphthoquinone **6** (1.2 mmol, 0.25 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 and extracted with dichloromethane. The combined organic extracts were washed with a saturated aqueous solution of sodium hydrogencarbonate and dried over magnesium(II) sulfate. Solvent evaporation in vacuo gave 3-amino-2-methoxycarbonyl-1,4-naphthoquinone **9**, which was purified by column chromatography on silica gel with petroleum ether/ethyl acetate (4:1) in 83% yield.

*4.5.1. 3-Amino-2-methoxycarbonyl-1,4-naphthoquinone **9***

Brown crystals, mp 146 °C (lit. 145–146 °C[28]). ^{1}H NMR ($CDCl_3$): δ 3.92 (3H, s, OCH_3), 7.01 (1H, br s, NH), 7.64–7.70 (1H, m, H-6 or H-7), 7.79–7.85 (1H, m, H-6 or H-7), 8.07–8.10 (1H, m, H-5 or H-8), 8.22–8.24 (1H, m, H-5 or H-8), 9.15 (1H, br s, NH). ^{13}C NMR ($CDCl_3$): δ 52.3 (OCH_3), 101.5 (=C_{quat}), 126.4 (CH_{ar}), 127.5 (CH_{ar}), 129.6 (=C_{quat}), 132.5 (CH_{ar}), 134.1 (=C_{quat}), 136.1 (CH_{ar}), 153.2 (=C_{quat}), 169.5 (=C_{quat}), 179.1 (C=O), 180.7 (C=O). IR (KBr): ν_{max} 1690, 1655 cm^{-1}. MS (ES) *m*/*z* (%): 232 (M+H$^+$, 100). Anal. Calcd for $C_{12}H_9NO_4$: C 62.34, H 3.92, N 6.06, found: C 62.59, H 4.04, N 5.98.

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