Original and Efficient Synthesis of Substituted 3,4-Dihydronaphtho[2,3-*g*]quinoline-2,6,11(1*H*)-triones

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Abstract: We report an original and short synthesis of substituted 3,4-dihydronaphtho[2,3-*g*]quinoline-2,6,11(1*H*)-triones by using the tetrakis(dimethylamino)ethylene or malonate substitution strategies, followed by a one-pot reduction–cyclization reaction.

Key words: quinones, electron transfer, cyclization, malonate, naphthoquinolinetriones

Anthracycline derivatives such as daunomycin and adriamycin (Figure 1) possess high antitumor activity because of their ability to intercalate the DNA double helix, thereby producing dramatic changes in the conformation of the DNA;[1] furthermore, these compounds can inhibit DNA replication and transcription.[2] Unfortunately, their clinical use is limited by dose-related cumulative cardiotoxicity and the development of drug resistance.[3] Several synthesis of heterocyclic anthracycline analogs have been developed in which the cyclohexane ring (A) of anthracycline is replaced by a heterocycle.[4] Interesting activity against drug-resistant cells is obtained by modifying the 4,11-dihydroxynaphtho[2,3-*f*]indole-5,10-dione scaffold (Figure 1).[5]

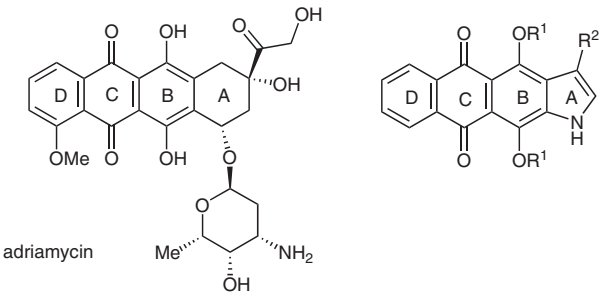

Figure 1 Adriamycin and the 4,11-dihydroxynaphtho[2,3-*f*]indole-5,10-dione scaffold

Since 2003, we have pursued a new program directed at the development of original synthetic methods in medicinal chemistry by using a strategy based on $N^1,N^1,N^1,N^1,N^2,N^2,N^2,N^2$-octamethylethene-1,1,2,2-tetramine [tetrakis(dimethylamino)ethylene; TDAE].[6] We have shown that TDAE can generate a nitrobenzyl carbanion from 2- or 4-nitrobenzyl chloride, which can react with various electrophiles, such as aromatic aldehydes, α-keto esters, keto malonates, α-keto lactams, or α-diketone derivatives. We have recently reported an extension of this reactivity with aromatic aldehydes in the anthraquinone series.[7]

In connection with our program centered on the synthesis of new quinonic compounds by using the single-electron-transfer methodology and on the preparation of new, potentially bioactive, compounds as anticancer agents, we report an original and efficient synthesis of substituted naphtho[2,3-*g*]quinoline-2,6,11-triones by a reduction–cyclization reaction[8] of nitroanthraquinonic ester derivatives prepared by the TDAE or malonate substitution strategies.

In our attempts to apply these strategies in preparing nitroquinonic ester derivatives with nitro and ester groups in the appropriate relative positions, we began by focusing on a retrosynthetic pathway in which TDAE reactions are succeeded by a nitration reaction. We therefore prepared, as previously described,[7] the 2-(bromomethyl)-1,4-dimethoxy-9,10-anthraquinone (**1**).

Reaction of quinone **1** with 3 equivalents of various α-keto esters in *N*,*N*-dimethylformamide containing TDAE at –20 °C for one hour and then at room temperature for two hours gave the corresponding α-hydroxy ester derivatives **2a–c** in good yields (Scheme 1). As described in our previous study,[6b] this reaction is regioselective: only the oxo group of the keto ester reacted with the quinonic anion.

The second step was the nitration of the α-hydroxy ester derivatives **2a–c** with nitric acid in acetic acid at 0 °C. This reaction was accompanied by demethylation of the methoxy group in the 4-position of the anthraquinonic moiety[9] to give the nitro α-hydroxy ester derivatives **3a–c** in moderate yields (Scheme 1).

The last step was the reduction of the nitro aromatic group by iron in acetic acid at 65 °C. This reduction was followed by a cyclization reaction in which nucleophilic attack by the amino group onto the ester carbonyl group led to the corresponding 3,12-dihydroxy-5-methoxy-3,4-dihydronaphtho[2,3-*g*]quinoline-2,6,11(1*H*)-triones **4a–c** in moderate yields (39–63%).

To avoid the demethylation that accompanied the nitration reaction, we modified the synthesis strategy to start from the 1-hydroxy-4-methoxy-3-methyl-2-nitro-9,10-

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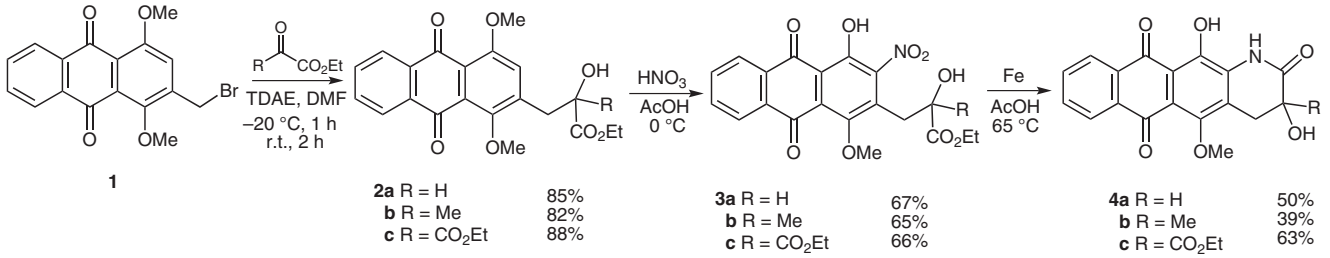


Scheme 1 Synthesis of 3,12-dihydroxy-5-methoxy-3,4-dihydronaphtho[2,3-*g*]quinoline-2,6,11(1*H*)-triones **4a–c**

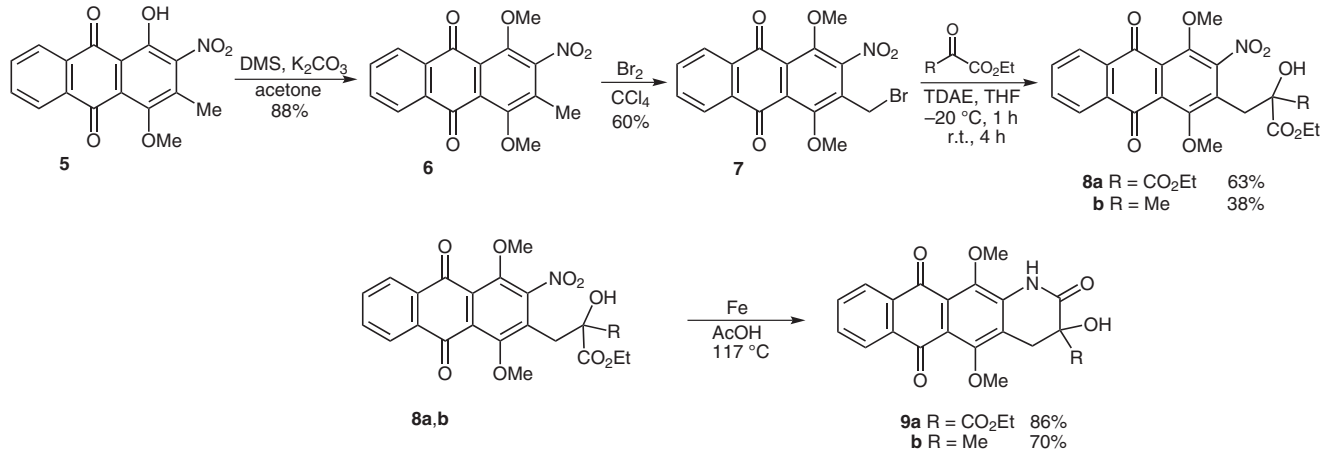
anthraquinone (**5**),[9] which gave, after methylation and bromation, the 2-bromomethyl derivative **7**.

We studied the reactivity of bromide **7** under TDAE conditions with α-keto ester derivatives. The absence of reactivity or poor reactivity of **7** toward α-keto esters in *N*,*N*-dimethylformamide as solvent led us to perform the reaction in tetrahydrofuran (another solvent for TDAE reactions).[10] The reaction of quinone **7** with α-keto ester derivatives in the presence of TDAE in tetrahydrofuran at –20 °C for one hours and then at room temperature for four hours gave the corresponding α-hydroxy ester derivatives **8a** and **8b**. In contrast to the reaction of 2-bromomethyl-1,4-dimethoxy-9,10-anthraquinone (**1**) with α-keto ester derivatives, which gave α-hydroxy esters **2a–c** in good yields (82–88%), 2-bromomethyl-1,4-dimethoxy-3-nitro-9,10-anthraquinone (**7**) gave **8a** and **8b** in moderate yields (38% and 63%, respectively; Scheme 2), probably because the quinonic carbanion is more stabilized by the nitro group. The second step was the reduction of the nitro group with iron in boiling acetic acid, which gave, after cyclization, the 3-hydroxy-5,12-dimethoxy-3,4-dihydronaphtho[2,3-*g*]quinoline-2,6,11(1*H*)-triones **9a** and **9b** in good yields (Scheme 2).

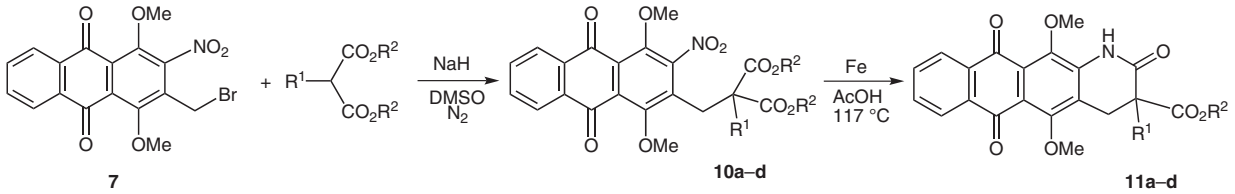
In order to prepare other nitroquinonic ester derivatives, we envisaged the use of the bromide **7** as an electrophile in a nucleophilic substitution reaction with various alkyl malonate anions. The reaction of bromide **7** with alkylmalonate derivatives (3 equiv) and sodium hydride (3 equiv) in dimethyl sulfoxide under an inert atmosphere for 15 minutes gave the corresponding ester derivatives **10a–d** in good yields (60–71%), as shown in Scheme 3 and listed in Table 1.

These substituted products **10a–d** are good candidates for further cyclization reactions. Reduction of the nitro aromatic group with iron under the same conditions as described above led to the corresponding alkyl 5,12-dimethoxy-1,2,3,4,6,11-hexahydro-2,6,11-trioxonaphtho[2,3-*g*]quinoline-3-carboxylates **11a–d** in good yields (73–90%), as shown in Scheme 3 and listed in Table 2.

In conclusion, we developed a synthesis of new substituted nitroanthraquinonic esters or malonates by the TDAE



Scheme 2 Synthesis of 3-hydroxy-5,12-dimethoxy-3,4-dihydronaphtho[2,3-*g*]quinoline-2,6,11(1*H*)-triones **9a** and **9b**



Scheme 3 Synthesis of alkyl 5,12-dimethoxy-1,2,3,4,6,11-hexahydro-2,6,11-trioxonaphtho[2,3-*g*]quinoline-3-carboxylates **11a–d**

Table 1 Reaction of Bromide **7** with Malonate Derivatives

R	R^1	Product[a]	Yield (%)[b]
H	Et	**10a**	76
H	Me	**10b**	69
Me	Et	**10c**	63
Ph	Et	**10d**	71

[a] All reactions were performed at r.t. under N_2 for 15 min using **7** (1 equiv) and malonate (3 equiv) in DMSO.
[b] Yields of chromatographically isolated pure products relative to bromide **7**.

Table 2 Reduction–Cyclization Reactions of **10a–d**

R	R^1	Product[a]	Yield (%)[b]
H	Et	**11a**	90
H	Me	**11b**	87
Me	Et	**11c**	75
Ph	Et	**11d**	73

[a] All the reactions were performed by using Fe (30 equiv) in boiling AcOH for 2 h.
[b] Yields of chromatographically isolated pure products relative to the nitro ester derivatives **10a–d**.

or malonate substitution strategies that involves the reaction of 2-bromomethyl-1,4-dimethoxy-3-nitro-9,10-anthraquinone (**7**) with α-keto ester or malonate derivatives. These two strategies are complementary in that the bromide **7** reacts as a nucleophile in the TDAE method and as an electrophile in the malonate method. Moreover, we present an example of the use of the TDAE strategy to generate a quinonic anion that cannot be generated effectively by the conventional organometallic strategy. Finally, the reduction–cyclization reaction of the nitroquinonic ester derivatives gave new substituted 3,4-dihydronaphtho[2,3-*g*]quinoline-2,6,11(1*H*)-triones. The pharmacological properties of these compounds are under active investigation.

Melting points were determined on a Buchi capillary melting point apparatus and are uncorrected. Elemental analyses were performed by the Centre de Microanalyses of the Spectropole (Aix-Marseille University). Both ^{1}H and ^{13}C NMR spectra were determined on a Bruker AC 200 spectrometer. The ^{1}H chemical shifts are reported as parts per million downfield from TMS whereas the ^{13}C chemical shifts are referenced to the solvents peaks for $CDCl_3$ (76.9 ppm) or DMSO-d_6 (39.6 ppm). Absorptions are reported with the following notations: s, singlet; d, doublet; t, triplet; q, quartet; m, complex multiplet or overlapping multiplets. Column chromatography was performed on silica gel 60 (Merck, particle size 0.063–0.200 mm, 70–230 mesh ASTM). TLC was performed using an appropriate solvent on 5 × 10 cm aluminum plates coated with silica gel 60 F-254 (Merck).

Reaction of 2-Bromomethyl-1,4-dimethoxy-9,10-anthraquinone (1) and α-Keto Ester Derivatives in the Presence of TDAE; General Procedure

A two-necked flask equipped with a drying tube (silica gel) and a N_2 inlet was charged with a soln of anthraquinone **1** (0.4 g, 1.10 mmol) and the appropriate α-keto ester (3 equiv) in anhyd DMF (10 mL) at –20 °C. The soln was stirred and maintained at –20 °C for 30 min and then TDAE (0.22 g, 1.10 mmol) was added dropwise from a syringe. A red color immediately developed with the formation of a fine white precipitate. The soln was stirred vigorously at –20 °C for 1 h and then warmed to r.t. for 2 h, when TLC analysis (CH_2Cl_2) clearly showed that compound **1** was totally consumed. The soln was filtered and H_2O (80 mL) was added. The aq soln was extracted with chloroform (3 × 40 mL) and the combined organic layers were washed with H_2O (2 × 40 mL), dried ($MgSO_4$), and concentrated to give a viscous orange liquid as a crude product. This was purified by chromatography [silica gel (CH_2Cl_2–Et_2O, 95:5)] and recrystallization (EtOH) to give the α-hydroxy ester derivatives **2a–c**.

Ethyl 3-(1,4-Dimethoxy-9,10-dioxo-9,10-dihydroanthracen-2-yl)-2-hydroxypropanoate (2a)

Yellow solid; yield: 85%; mp 154 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.27 (t, *J* = 7.1 Hz, 3 H, CH_3), 3.03 (dd, *J* = 13.9, 8.2 Hz, 1 H, CH_2), 3.12 (br s, 1 H, OH), 3.33 (dd, *J* = 13.9, 5.8 Hz, 1 H, CH_2), 3.90 (s, 3 H, OCH_3), 3.99 (s, 3 H, OCH_3), 4.24 (q, *J* = 7.1 Hz, 2 H, CH_2), 4.51 (dd, *J* = 8.2, 4.2 Hz, 1 H, CH), 7.32 (s, 1 H, Ar-H), 7.68–7.75 (m, 2 H, Ar-H), 7.12–7.18 (m, 2 H, Ar-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.2, 35.6, 56.8, 62.1, 62.2, 70.3, 121.6, 121.7, 126.4, 126.5, 127.0, 133.2, 133.6, 133.8, 134.3, 140.9, 152.7, 156.2, 174.0, 182.8, 183.3.

Anal. Calcd for $C_{21}H_{20}O_7$: C, 65.62; H, 5.24. Found: C, 65.20; H, 5.47.

Ethyl 3-(1,4-Dimethoxy-9,10-dioxo-9,10-dihydroanthracen-2-yl)-2-hydroxy-2-methylpropanoate (2b)

Yellow solid; yield: 82%; mp 142 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.24 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.51 (s, 3 H, CH_3), 3.13 (d, *J* = 13.7, 1 H, CH_2), 3.27 (d, *J* = 13.7 Hz, 1 H, CH_2), 3.45 (br s, 1 H, OH), 3.88 (s, 3 H, OCH_3), 4.00 (s, 3 H, OCH_3), 4.18 (q, *J* = 7.2 Hz, 2 H, CH_2), 7.38 (s, 1 H, Ar-H), 7.69–7.74 (m, 2 H, Ar-H), 8.13–8.19 (m, 2 H, Ar-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.0, 26.1, 39.9, 56.7, 62.1, 62.2, 74.7, 121.8, 122.2, 126.4, 126.5, 126.9, 133.2, 133.5, 133.9, 134.3, 140.1, 152.9, 155.9, 176.0, 182.9, 183.2.

Anal. Calcd for $C_{22}H_{22}O_7$: C, 66.32; H, 5.57. Found: C, 66.11; H, 5.79.

Diethyl [(1,4-Dimethoxy-9,10-dioxo-9,10-dihydroanthracen-2-yl)methyl](hydroxy)malonate (2c)

Yellow solid; yield: 88%; mp 87 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.27 (t, *J* = 7.1 Hz, 6 H, 2 CH_3), 3.56 (s, 2 H, CH_2), 3.89 (s, 3 H, OCH_3), 3.98 (s, 3 H, OCH_3), 4.26 (q, *J* = 7.1 Hz, 4 H, 2 CH_2), 7.44 (s, 1 H, Ar-H), 7.69–7.74 (m, 2 H, Ar-H), 8.12–8.19 (m, 2 H, Ar-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.9 (2 C), 34.6, 56.7, 62.2, 62.9 (2 C), 78.5, 121.9, 122.2, 126.3, 126.5, 126.9, 133.2, 133.5, 133.9, 134.3, 138.8, 152.9, 155.9, 169.8 (2 C), 182.8, 183.1.

Anal. Calcd for $C_{24}H_{24}O_9$: C, 63.15; H, 5.30. Found: C, 62.92; H, 5.58.

Nitration of α-Hydroxy Derivatives 2a–c; General Procedure

Fuming HNO_3 (2.5 mL) was added dropwise to a soln of α-hydroxy derivative **2a–c** (0.4 g, 1 equiv) in glacial AcOH (3 mL) at 0 °C. The soln was maintained at 0 °C for 10 min then poured into crushed ice. The precipitate was filtered off, washed with H_2O, dried, and recrystallized (EtOH) to give the corresponding nitro α-hydroxy ester derivative **3a–c**.

Ethyl 2-Hydroxy-3-(4-hydroxy-1-methoxy-3-nitro-9,10-dioxo-9,10-dihydroanthracen-2-yl)propanoate (3a)

Yellow solid; yield: 67%; mp 181 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.27 (t, *J* = 7.1 Hz, 3 H, CH_3), 1.57 (br s, 1 H, OH), 3.00 (br s, 1 H, OH), 3.07 (dd, *J* = 13.5, 8.9 Hz, 1 H, CH_2), 3.19 (dd, *J* = 13.5, 5.1 Hz, 1 H, CH_2), 3.96 (s, 3 H, OCH_3), 4.26 (q, *J* = 7.1 Hz, 2 H, CH_2), 4.48 (dd, *J* = 8.9, 5.1 Hz, 1 H, CH), 7.83–7.87 (m, 2 H, Ar-H), 8.28–8.32 (m, 2 H, Ar-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.1, 32.2, 62.4, 62.6, 69.3, 116.6, 124.7, 126.9, 127.8, 131.9, 134.2, 134.4, 135.4, 135.6, 145.2, 150.7, 152.8, 173.3, 180.6, 188.0.

Anal. Calcd for $C_{20}H_{17}NO_9$: C, 57.83; H, 4.13; N, 3.37. Found: C, 57.53; H, 4.08; N, 3.48.

Ethyl 2-Hydroxy-3-(4-hydroxy-1-methoxy-3-nitro-9,10-dioxo-9,10-dihydroanthracen-2-yl)-2-methylpropanoate (3b)

Yellow solid; yield: 65%; mp 159 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.32 (t, *J* = 7.1 Hz, 3 H, CH_3), 1.46 (s, 3 H, CH_3), 3.23 (d, *J* = 13.5 Hz, 1 H, CH_2), 3.35 (d, *J* = 13.5 Hz, 1 H, CH_2), 3.89 (s, 3 H, OCH_3), 4.24 (q, *J* = 7.1 Hz, 2 H, CH_2), 7.83–7.87 (m, 2 H, Ar-H), 8.27–8.31 (m, 2 H, Ar-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.0, 25.9, 36.4, 62.3, 62.6, 74.0, 116.6, 124.6, 126.8, 127.7, 131.9, 134.2, 134.3, 135.2, 135.6, 146.0, 151.0, 152.9, 175.4, 180.5, 188.0.

Anal. Calcd for $C_{21}H_{19}NO_9$: C, 58.74; H, 4.46; N, 3.26. Found: C, 58.21; H, 4.42; N, 3.21.

Diethyl Hydroxy[(4-hydroxy-1-methoxy-3-nitro-9,10-dioxo-9,10-dihydroanthracen-2-yl)methyl]malonate (3c)

Yellow solid; yield: 66%; mp 157 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.31 (t, *J* = 7.1 Hz, 6 H, 2 CH_3), 3.68 (s, 2 H, CH_2), 3.79 (br s, 1 H, OH), 3.87 (s, 3 H, OCH_3), 4.28 (q, *J* = 7.1 Hz, 4 H, 2 CH_2), 7.75–7.84 (m, 2 H, Ar-H), 8.20–8.28 (m, 2 H, Ar-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.9 (2 C), 31.1, 62.4, 63.1 (2 C), 77.2, 116.8, 124.6, 126.8, 127.6, 131.9, 134.0, 134.2, 134.3, 135.6, 146.3, 150.9, 152.8, 169.5 (2 C), 180.3, 188.1.

Anal. Calcd for $C_{23}H_{21}NO_{11}$: C, 56.68; H, 4.34; N, 2.87. Found: C, 56.55; H, 4.35; N, 2.79.

Reduction–Cyclization of α-Hydroxy Derivatives 3a–c; General Procedure

Fe powder (6 equiv) was added portionwise to a stirred soln of **3a–c** (0.2 g) in glacial AcOH (40 mL) at 65 °C. The soln was maintained at 65 °C for 30 min then filtered through Celite. The solvent was evaporated under reduced pressure and the residue was extracted with $CHCl_3$ (3 × 40 mL). The combined organic layers were washed with H_2O (2 × 40 mL), dried ($MgSO_4$), and concentrated. The residue was purified by chromatography [silica gel (CH_2Cl_2–Et_2O, 90:10)] and recrystallization (EtOH) to give the corresponding quinoline derivative **4a–c**.

3,12-Dihydroxy-5-methoxy-3,4-dihydronaphtho[2,3-*g*]quinoline-2,6,11(1*H*)-trione (4a)

Yellow solid; yield: 50%; mp 294 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 1.22 (br s, 1 H, OH), 2.90 (dd, *J* = 16.7, 10.3 Hz, 1 H, CH_2), 3.24 (dd, *J* = 16.7, 5.7 Hz, 1 H, CH_2), 3.77 (s, 3 H, OCH_3), 4.20–4.28 (m, 1 *H,* CH), 5.81 (d, *J* = 4.5 Hz, 1 H, OH), 7.88–7.97 (m, 2 H, Ar-H), 8.14–8.22 (m, 2 H, Ar-H), 10.20 (s, 1 H, NH).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 29.2, 61.7, 65.8, 115.1, 118.2, 126.8, 127.0, 127.6, 132.7, 134.6 (2 C), 135.4, 136.2, 147.4, 153.3, 171.4, 180.4, 189.4.

Anal. Calcd for $C_{18}H_{13}NO_6$: C, 63.72; H, 3.86; N, 4.13. Found: C, 62.40; H, 4.04; N, 3.85.

3,12-Dihydroxy-5-methoxy-3-methyl-3,4-dihydronaphtho[2,3-*g*]quinoline-2,6,11(1*H*)-trione (4b)

Yellow solid; yield: 39%; mp 260 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 1.22 (br s, 1 H, OH), 1.30 (t, *J* = 7.1 Hz, 3 H, CH_3), 2.90 (d, *J* = 7.2 Hz, 1 H, CH_2), 3.11 (d, *J* = 7.2 Hz, 1 H, CH_2), 3.75 (s, 3 H, OCH_3), 5.68 (br s, 1 H, OH), 7.80–7.91 (m, 2 H, Ar-H), 8.10–8.20 (m, 2 H, Ar-H), 10.12 (s, 1 H, NH).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 24.7, 34.9, 61.3, 68.2, 114.5, 117.7, 126.5, 127.0, 127.2, 132.3, 134.1 (2 C), 135.0, 135.7, 146.8, 152.9, 172.2, 180.0, 189.0.

Anal. Calcd for $C_{19}H_{15}NO_6$: C, 64.59; H, 4.28; N, 3.96. Found: C, 63.94; H, 4.41; N, 3.84.

Ethyl 3,12-Dihydroxy-5-methoxy-2,6,11-trioxo-1,2,3,4,6,11-hexahydronaphtho[2,3-*g*]quinoline-3-carboxylate (4c)

Yellow solid; yield: 63%; mp 226 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 1.14 (t, *J* = 7.1 Hz, 3 H, CH_3), 3.22 (d, *J* = 17.2, 1 H, CH_2), 3.44 (d, *J* = 17.2 Hz, 1 H, CH_2), 3.76 (s, 3 H, OCH_3), 4.12 (q, *J* = 7.1 Hz, 2 H, CH_2), 6.78 (br s, 1 H, OH), 7.87–7.93 (m, 2 H, Ar-H), 8.10–8.21 (m, 2 H, Ar-H), 10.62 (s, 1 H, NH).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 14.8, 32.0, 61.8, 62.4, 74.5, 115.1, 118.5, 125.9, 126.9, 127.6, 132.5, 133.9, 134.5, 135.2, 136.1, 147.3, 153.1, 168.0, 171.2, 180.3, 189.3.

Anal. Calcd for $C_{21}H_{17}NO_8$: C, 61.31; H, 4.17; N, 3.40. Found: C, 60.81; H, 4.21; N, 3.26.

2-(Bromomethyl)-1,4-dimethoxy-3-nitro-9,10-anthraquinone (7)

A soln of Br_2 (3.28 mL, 64 mmol) in CCl_4 (10 mL) was added dropwise to a soln of nitroanthraquinone **6** (0.7 g, 3 mmol) in CCl_4 (140 mL) at 80 °C. The soln was kept at 80 °C for 4 h and then cooled. The organic layer was washed with sat. aq Na_2SO_3 (100 mL), dried ($MgSO_4$) and concentrated. Purification of the residue by chromatography (silica gel, CH_2Cl_2) and recrystallization (EtOH) gave a yellow solid; yield: 60%; mp 177 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.04 (s, 3 H, OCH_3), 4.12 (s, 3 H, OCH_3), 4.51 (s, 2 H, CH_2Br), 7.79–7.84 (m, 2 H, Ar-H), 8.19–8.27 (m, 2 H, Ar-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 18.9, 63.8, 64.7, 126.8, 126.9, 128.4, 128.8, 131.9, 133.3, 133.4, 134.3, 134.4, 147.8, 150.7, 155.7, 180.7, 181.2.

Anal. Calcd for $C_{17}H_{12}BrNO_6$: C, 50.27; H, 2.98; N, 3.45. Found: C, 50.14; H, 2.96; N, 3.46.

Reaction of 2-(Bromomethyl)-1,4-dimethoxy-3-nitro-9,10-anthraquinone (7) with α-Keto Ester Derivatives in the Presence of TDAE; General Procedure

A two-necked flask equipped with a drying tube (silica gel) and a N_2 inlet was charged with a soln of nitroanthraquinone **7** (0.3 g, 0.73 mmol) and diethyl oxomalonate (1 g, 5.9 mmol) or ethyl 2-oxopro-

panoate (0.68 g, 5.9 mmol) in anhyd THF (3 mL) at –20 °C. The soln was stirred and maintained at –20 °C for 30 min and then TDAE (0.15 g, 0.73 mmol) was added dropwise from a syringe. A red color immediately developed with the formation of a white fine precipitate. The soln was stirred vigorously at –20 °C for 1 h and then warmed to r.t. for 4 h, when TLC (CH_2Cl_2) clearly showed that compound **7** was totally consumed. The soln was filtered to remove the octamethyloxamidinium dibromide, and H_2O (80 mL) was added. The aqueous mixture was extracted with $CHCl_3$ (3 × 40 mL) and the combined organic layers were washed with H_2O (2 × 40 mL), dried ($MgSO_4$), and concentrated. The resulting viscous orange liquid was purified by chromatography [silica gel (CH_2Cl_2–Et_2OH, 95:5)] and recrystallization (EtOH) to give the corresponding nitroquinonic ester **8a** or **8b**.

Diethyl 2-[(1,4-Dimethoxy-3-nitro-9,10-dioxo-9,10-dihydroanthracen-2-yl)methyl](hydroxy)malonate (8a)
Yellow solid; yield: 63%; mp 172 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.30 (t, *J* = 7.1 Hz, 6 H, 2 CH_3), 3.61 (s, 2 H, CH_2), 3.89 (s, 3 H, OCH_3), 3.98 (s, 3 H, OCH_3), 4.27 (q, *J* = 7.1 Hz, 4 H, 2 CH_2), 7.75–7.82 (m, 2 H, Ar-H), 8.13–8.20 (m, 2 H, Ar-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.8 (2 C), 31.1, 62.8, 63.0 (2 C), 64.4, 76.7, 126.7, 126.8, 127.4, 127.8, 130.7, 133.5, 133.6, 134.1, 134.2, 148.1, 152.9, 156.5, 169.5 (2 C), 181.0, 181.4.

Anal. Calcd for $C_{24}H_{23}NO_{11}$: C, 57.49; H, 4.62; N, 2.79. Found: C, 57.21; H, 4.69; N, 2.74.

Ethyl 3-(1,4-Dimethoxy-3-nitro-9,10-dioxo-9,10-dihydroanthracen-2-yl)-2-hydroxy-2-methyl Propanoate (8b)
Yellow solid; yield: 38%; mp 128 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.32 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.46 (s, 3 H, CH_3), 3.15 (d, *J* = 13.8 Hz, 1 H, CH_2), 3.27 (d, *J* = 13.8 Hz, 1 H, CH_2), 3.91 (s, 3 H, OCH_3), 4.00 (s, 3 H, OCH_3), 4.25 (q, *J* = 7.2 Hz, 2 H, CH_2), 7.77–7.82 (m, 2 H, Ar-H), 8.17–8.23 (m, 2 H, Ar-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.0, 26.0, 36.5, 62.6, 62.8, 64.5, 73.8, 126.8, 126.9, 127.5, 127.6, 131.9, 133.5, 133.7, 134.2, 134.3, 148.2, 152.7, 156.6, 175.5, 181.1, 181.6.

Anal. Calcd for $C_{22}H_{21}NO_9$: C, 59.59; H, 4.77; N, 3.16. Found: C, 59.35; H, 4.85; N, 3.15.

Reduction–Cyclisation of α-Hydroxy Derivatives 8a–b; General Procedure
Fe powder (30 equiv) was added over 0.5 h to a stirred soln of **8a** or **8b** (0.1 g) in glacial AcOH (25 mL) at 117 °C. The soln was maintained at 117 °C for 2 h then filtered through Celite. The solvent was evaporated under reduced pressure and the residue was extracted with $CHCl_3$ (3 × 40 mL). The combined organic layers were washed with H_2O (2 × 40 mL), dried ($MgSO_4$), and concentrated. The residue was purified by chromatography [silica gel (CH_2Cl_2–Et_2O, 90:10)] and recrystallization (EtOH) to give the corresponding quinoline derivatives **9a** and **9b**.

Ethyl 3-Hydroxy-5,12-dimethoxy-2,6,11-trioxo-1,2,3,4,6,11-hexahydronaphtho[2,3-*g*]quinoline-3-carboxylate (9a)
Yellow solid; yield: 86%; mp 242 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.22 (t, *J* = 7.1 Hz, 3 H, CH_3), 1.59 (br s, 1 H, OH), 3.24 (d, *J* = 17.3 Hz, 1 H, CH_2), 3.81 (d, *J* = 17.3 Hz, 1 H, CH_2), 3.96 (s, 3 H, OCH_3), 3.97 (s, 3 H, OCH_3), 4.24 (q, *J* = 7.1 Hz, 2 H, CH_2), 7.73–7.78 (m, 2 H, Ar-H), 8.17–8.24 (m, 2 H, Ar-H), 8.36 (s, 1 H, NH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.8, 32.0, 62.2, 62.3, 62.5, 74.5, 121.6, 124.4, 126.6, 126.9, 127.0, 134.3, 134.5 (2 C), 134.9, 139.3, 143.9, 155.5, 168.6, 171.2, 181.7, 182.8.

Anal. Calcd for $C_{22}H_{19}NO_8$: C, 62.12; H, 4.50; N, 3.29. Found: C, 61.57; H, 4.63; N, 3.19.

3-Hydroxy-5,12-dimethoxy-3-methyl-3,4-dihydronaphtho[2,3-*g*]quinoline-2,6,11(1*H*)-trione (9b)
Yellow solid; yield: 70%; mp 240 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.37 (s, 3 H, CH_3), 2.30 (br s, 1 H, OH), 3.04 (d, *J* = 16.8 Hz, 1 H, CH_2), 3.55 (d, *J* = 16.8 Hz, 1 H, CH_2) 3.93 (s, 3 H, OCH_3), 3.97 (s, 3 H, OCH_3), 7.74–7.23 (m, 2 H, Ar-H), 8.17–8.21 (m, 2 H, Ar-H), 8.22 (s, 1 H, NH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 24.8, 34.8, 61.7, 62.1, 68.2, 120.8, 125.6, 125.8, 126.5, 126.6, 133.9, 134.0, 134.2, 134.4, 139.4, 143.3, 155.2, 172.7, 181.3, 182.5.

Anal. Calcd for $C_{20}H_{17}NO_6$: C, 65.39; H, 4.66; N, 3.81. Found: C, 64.50; H, 4.84; N, 3.66.

Reaction of 2-(Bromomethyl)-1,4-dimethoxy-3-nitro-9,10-anthraquinone (7) with Malonate Derivatives; General Procedure
A soln of 60% NaH (3 equiv) in DMSO under an inert atmosphere was treated with the appropriate dialkyl malonate (3 equiv) and stirred for 40 min. A soln of **7** (1 equiv) in DMSO was then added and the mixture was stirred for 15 min. The mixture was poured into cold H_2O (80 mL), and the soln was extracted with $CHCl_3$ (3 × 30 mL). The organic layers were washed with H_2O (50 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Purification by chromatography [silica gel (CH_2Cl_2–Et_2O, 95:5)] and recrystallization (*i*-PrOH) gave the corresponding quinonic malonate derivative **10a–d**.

Diethyl [(1,4-Dimethoxy-3-nitro-9,10-dioxo-9,10-dihydroanthracen-2-yl)methyl]malonate (10a)
Yellow solid; yield: 76%; mp 128 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.22 (t, *J* = 7.1 Hz, 6 H, 2 CH_3), 3.23 (d, *J* = 7.3 Hz, 2 H, CH_2), 3.80 (t, *J* = 7.3 Hz, 1 H, CH), 3.95 (s, 3 H, OCH_3), 3.99 (s, 3 H, OCH_3), 4.18 (q, *J* = 7.1 Hz, 4 H, CH_2), 7.72–7.73 (m, 2 H, Ar-H), 8.16–8.20 (m, 2 H, Ar-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.9 (2 C), 26.1, 50.9, 61.9 (2 C), 62.9, 64.6, 126.8, 126.9, 127.6, 127.7, 133.1, 133.4, 133.6, 134.2, 134.3, 147.8, 151.8, 156.5, 168.0 (2 C), 180.9, 181.6.

Anal. Calcd for $C_{24}H_{23}NO_{10}$: C, 59.38; H, 4.78; N, 2.89. Found: C, 59.47; H, 4.84; N, 2.84.

Dimethyl [(1,4-Dimethoxy-3-nitro-9,10-dioxo-9,10-dihydroanthracen-2-yl)methyl]malonate (10b)
Yellow solid; yield: 69%; mp 137 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.21 (d, *J* = 7.3 Hz, 2 H, CH_2), 3.73 (s, 6 H, 2 CH_3), 3.82 (t, *J* = 7.3 Hz, 1 H, CH), 3.95 (s, 3 H, OCH_3), 3.99 (s, 3 H, OCH_3), 7.77–7.82 (m, 2 H, Ar-H), 8.17–8.21 (m, 2 H, Ar-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 26.2, 50.6, 52.9 (2 C), 63.0, 64.6, 126.8, 126.9, 127.6, 127.7, 132.8, 133.5, 133.6, 134.2, 134.3, 147.8, 151.8, 156.4, 168.4 (2 C), 180.9, 181.6.

Anal. Calcd for $C_{22}H_{19}NO_{10}$: C, 57.77; H, 4.19; N, 3.06. Found: C, 57.51; H, 4.25; N, 2.81.

Diethyl [(1,4-Dimethoxy-3-nitro-9,10-dioxo-9,10-dihydroanthracen-2-yl)methyl](methyl)malonate (10c)
Yellow solid; yield: 63%; mp 133 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.24 (s, 3 H, CH_3), 1.25 (t, *J* = 7.2 Hz, 6 H, 2 CH_3), 3.40 (s, 2 H, CH_2), 3.85 (s, 3 H, OCH_3), 3.97 (s, 3

H, OCH_3), 4.18 (q, *J* = 7.2 Hz, 4 H, 2 CH_2), 7.73–7.82 (m, 2 H, Ar-H), 8.14–8.20 (m, 2 H, Ar-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.9 (2 C), 19.5, 31.5, 53.2, 61.9 (2 C), 62.6, 64.5, 126.7, 126.9, 127.3, 127.6, 132.3, 133.4, 133.6, 134.1, 134.2, 147.7, 152.7, 157.0, 171.2 (2 C), 180.9, 181.4.

Anal. Calcd for $C_{25}H_{25}NO_{10}$: C, 60.12; H, 5.05; N, 2.80. Found: C, 59.87; H, 5.10; N, 2.67.

Diethyl [(1,4-Dimethoxy-3-nitro-9,10-dioxo-9,10-dihydroanthracen-2-yl)methyl](phenyl)malonate (10d)
Yellow solid; yield: 71%; mp 127 °C.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.26 (t, *J* = 7.2 Hz, 6 H, 2 CH_3), 3.80 (s, 3 H, OCH_3), 3.81 (s, 2 H, CH_2), 3.82 (s, 3 H, OCH_3), 4.23 (q, *J* = 7.1 Hz, 4 H, 2 CH_2), 7.05–7.18 (m, 5 H, Ar-H), 7.76–7.81 (m, 2 H, Ar-H), 8.16–8.20 (m, 2 H, Ar-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.8 (2 C), 34.2, 62.3 (2 C), 62.4, 63.1, 64.2, 126.7, 126.8, 126.9, 127.3, 127.7, 127.9 (2 C), 128.3 (2 C), 132.9, 133.5, 133.6, 134.1, 134.2, 135.4, 147.6, 152.1, 157.3, 169.6 (2 C), 180.9, 181.4.

Anal. Calcd for $C_{30}H_{27}NO_{10}$: C, 64.17; H, 4.85; N, 2.49. Found: C, 64.06; H, 4.98; N, 2.37.

Reduction–Cyclization of Quinonic Malonate Derivatives 10a–d; General Procedure
Fe powder (30 equiv) was added over 30 min to a stirred soln of **10a–d** (0.2 g) in glacial AcOH (50 mL) at 117 °C. The soln was maintained at 117 °C for 2 h then filtered through Celite. The solvent was evaporated under reduced pressure and the residue was extracted with $CHCl_3$ (3 × 40 mL). The combined organic layers were washed with H_2O (2 × 40 mL), dried ($MgSO_4$), and concentrated. The residue was purified by chromatography [silica gel (CH_2Cl_2–Et_2O, 90:10)] and recrystallization (EtOH) to give the corresponding quinoline derivatives **11a–d**.

Ethyl 5,12-Dimethoxy-2,6,11-trioxo-1,2,3,4,6,11-hexahydronaphtho[2,3-*g*]quinoline-3-carboxylate (11a)
Yellow solid; yield: 90%; mp 243 °C.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.27 (t, *J* = 7.1 Hz, 3 H, CH_3), 3.33 (dd, *J* = 15.8, 5.6 Hz, 1 H, CH_2), 3.54 (dd, *J* = 15.8, 8.4 Hz, 1 H, CH_2), 3.66 (m, 1 H, CH), 3.95 (s, 6 H, 2 OCH_3), 4.23 (q, *J* = 7.1 Hz, 2 H, CH_2), 7.72–7.73 (m, 2 H, Ar-H), 8.16–8.20 (m, 2 H, Ar-H), 8.34 (s, 1 H, NH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.1, 23.4, 46.3, 62.0, 62.1, 62.2, 121.8, 123.5, 126.2, 126.5, 126.7, 133.5, 133.6, 133.9, 134.0, 137.6, 142.8, 155.3, 165.7, 168.3, 181.6, 182.5.

Anal. Calcd for $C_{22}H_{19}NO_7$: C, 64.54; H, 4.68; N, 3.24. Found: C, 64.48; H, 4.76; N, 3.36.

Methyl 5,12-Dimethoxy-2,6,11-trioxo-1,2,3,4,6,11-hexahydronaphtho[2,3-*g*]quinoline-3-carboxylate (11b)
Yellow solid; yield: 87%; mp 272 °C.

^1H NMR (200 MHz, $CDCl_3$): δ = 3.33 (dd, *J* = 16.4, 7.8 Hz, 1 H, CH_2), 3.68 (dd, *J* = 16.4, 6.1 Hz, 1 H, CH_2), 3.72 (dd, *J* = 7.8 Hz, *J* = 6.1 Hz, 1 H, CH), 3.79 (s, 3 H, OCH_3), 3.95 (s, 3 H, OCH_3), 3.96 (s, 3 H, OCH_3), 7.74–7.81 (m, 2 H, Ar-H), 8.17–8.22 (m, 2 H, Ar-H), 8.33 (s, 1 H, NH).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 23.2, 46.1, 52.9, 61.8, 62.1, 121.1, 124.8, 126.1, 126.5, 126.6, 133.8, 134.1 (2 C), 134.5, 139.3, 143.7, 154.7, 166.7, 169.9, 181.3, 182.4.

Anal. Calcd for $C_{21}H_{17}NO_7$: C, 63.80; H, 4.33; N, 3.54. Found: C, 63.84; H, 4.52; N, 3.44.

Ethyl 5,12-Dimethoxy-3-methyl-2,6,11-trioxo-1,2,3,4,6,11-hexahydronaphtho[2,3-*g*]quinoline-3-carboxylate (11c)
Yellow solid; yield: 75%; mp 169 °C.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.13 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.22 (s, 3 H, CH_3), 2.90 (d, *J* = 16.8 Hz, 1 H, CH_2), 3.74 (d, *J* = 16.8 Hz, 1 H, CH_2), 3.93 (s, 6 H, 2 OCH_3), 4.12 (q, *J* = 7.2 Hz, 2 H, CH_2), 3.69–7.73 (m, 2 H, Ar-H), 8.14–8.16 (m, 2 H, Ar-H), 8.52 (s, 1 H, NH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.9, 20.3, 31.3, 48.5, 61.9, 62.0, 62.1, 121.5, 123.9, 126.1, 126.4, 126.6, 133.4, 133.5, 133.8, 133.9, 137.8, 142.6, 155.1, 169.2, 171.0, 181.5, 182.5.

Anal. Calcd for $C_{23}H_{21}NO_7$: C, 65.24; H, 5.00; N, 3.31. Found: C, 65.14; H, 5.06; N, 3.29.

Ethyl 5,12-Dimethoxy-2,6,11-trioxo-3-phenyl-1,2,3,4,6,11-hexahydronaphtho[2,3-*g*]quinoline-3-carboxylate (11d)
Yellow solid; yield: 73%; mp 250 °C.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.21 (t, *J* = 7.1 Hz, 3 H, CH_3), 3.78 (d, *J* = 16.8 Hz, 1 H, CH_2), 3.88 (s, 3 H, OCH_3), 3.92 (d, *J* = 16.8 Hz, 1 H, CH_2), 3.97 (s, 3 H, OCH_3), 4.24 (q, *J* = 7.1 Hz, 2 H, CH_2), 7.29–7.34 (m, 5 H, Ar-H), 7.70–7.77 (m, 2 H, Ar-H), 8.12–8.20 (m, 2 H, Ar-H), 8.56 (s, 1 H, NH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.9, 29.9, 58.0, 62.0, 62.1, 62.5, 121.7, 124.3, 126.1, 126.4, 126.6, 127.3 (2 C), 128.3, 128.6 (2 C), 133.4, 133.5, 133.8, 133.9, 134.6, 137.2, 142.6, 155.1, 167.8, 169.6, 181.6, 182.5.

Anal. Calcd for $C_{28}H_{23}NO_7$: C, 69.27; H, 4.78; N, 2.89. Found: C, 68.90; H, 4.92; N, 2.84.

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