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New cytotoxic furoquinones obtained from terpenyl-1,4-naphthoquinones and 1,4-anthracenediones

José M. Miguel del Corral,[a,*] M. Angeles Castro,[a] Alaide B. Oliveira,[b] Simone A. Gualberto,[b] Carmen Cuevas[c] and Arturo San Feliciano[a]

[a]*Departamento de Química Farmacéutica, Facultad de Farmacia, Universidad de Salamanca, E-37007 Salamanca, Spain*
[b]*Faculdade de Farmácia, Dpto. Productos Farmacêuticos, Universidade Federal de Minas Gerais, Cep. 30180.112 Belo Horizonte-MG, Brazil*
[c]*PharmaMar S.A. Avda. de los Reyes, 1. P.I. La Mina-Norte, 28770 Colmenar Viejo, Madrid, Spain*

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Abstract—A series of new furoterpenyl-1,4-naphtho(anthra)quinones have been prepared via oxidative cyclization of the corresponding 2-hydroxy-3-butenyl-1,4-naphtho(anthra)quinones. Depending on the reaction conditions the 1,2-quinones or the 1,4-quinones were obtained. Several new furo-1,4-anthraquinones were also obtained by condensation of 2,3-dichloroquinones with 1,3-dicarbonyls. The compounds synthesized have been evaluated for their cytotoxicity against neoplastic cell lines, some of them being effective below the micromolar level.

1. Introduction

Quinones, and particularly 1,4-naphthoquinones (1,4-NQs), are widespread among the secondary metabolites of plants and microorganisms. They can also be prepared synthetically and are widely produced by the chemical industry as organic dyes. The interest of 1,4-NQ is not restricted to the chemistry of dyes; a wide spectrum of biological activities is described for them,[1,2] including antitumour, wound healing, anti-inflammatory, antiparasitic and cytotoxic activities, among others. These biological activities have justified the large number of studies found in the literature aimed at the synthesis and evaluation of either natural quinones or their analogues as potential pharmacological agents.[3] In fact, several clinically important anticancer drugs,[4] such as daunorubicin or mitomycin C (Fig. 1), contain the quinone moiety as a relevant part of their structures.

In most cases, the biological activity is related to the ability of quinones to accept one or two electrons to form highly reactive radical anion intermediates, which

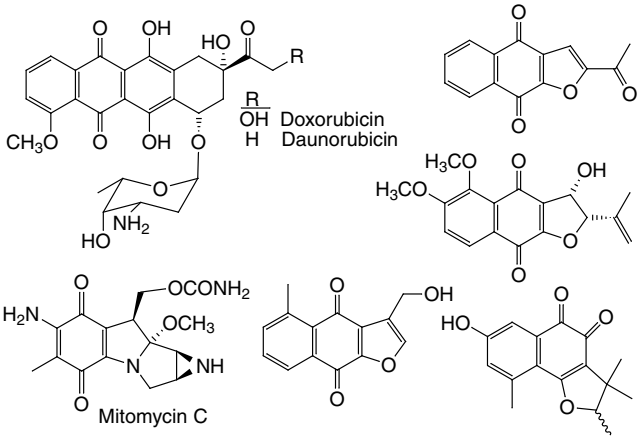

Figure 1. Natural biologically active quinones and several furonaphthoquinones.

are responsible for the oxidative stress observed in the cells.[1] But there are several other mechanisms[5] attributed to quinonoid compounds such as DNA intercalation, alkylation, induction of DNA strand breaks or inhibition of special proteins or enzymes such as topoisomerases.

Among the 1,4-NQs, an important group of heterocyclic quinones are the furonaphthoquinones. A number of

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* Corresponding author. Tel.: +34 923 294528; fax: +34 923 294515; e-mail: jmmcs@usal.es

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biologically interesting natural products and synthetic derivatives having this skeleton have attracted the attention of the scientific community because they have shown significant cytotoxic and antiprotozoan activities.[6] Most of these furonaphthoquinones have no substituents on the benzene ring of the naphthoquinone moiety and, even where such a substituent is present, it is usually something small such as a methoxyl or a methyl group, but not longer carbon chains.[7] Several examples of naturally occurring furonaphthoquinones are illustrated in Figure 1.

A variety of methods for synthesizing this class of molecules[8] have been reported since Hooker, as early as 1896,[8c] described the synthesis of the first representative of this group (2-isopropylnaphtho[2,3-*b*]furane-4,9-dione) by the annelation of lawsone. The synthetic strategies range from the construction of the benzenoid ring to the construction of the quinonoid ring, or to the synthesis of the furan ring on an existing naphthoquinone system. The latter is the most frequently used procedure although the yields described are usually low.[8b]

In the last few years, we have synthesized several monoterpenyl- and diterpenyl-1,4-naphthoquinones via Diels–Alder cycloaddition between natural terpenoids and *p*-benzoquinone (BQ).[9] Further transformations were performed on the side chain, leading to cytotoxic analogues with IC_{50} cytotoxicity values in the micromolar range against several neoplastic cell lines. This fact prompted us to study the effect of the introduction of other substituents, such as hydroxyl groups[10] or amino substituents,[11] onto the naphthoquinone system.

Now we report the synthesis and cytotoxicity evaluation of new furoterpenylnaphthoquinones with the aim of analysing how the presence of an alkyl chain, or a new carbocyclic ring fused to the benzenoid core, would affect the bioactivity of the furoquinone derivatives.

2. Results and discussion

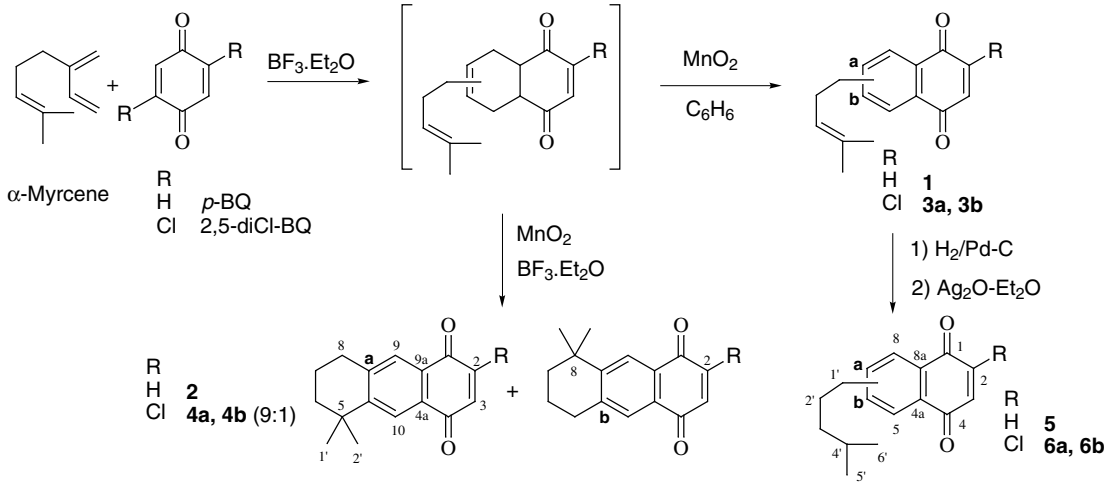
2.1. Chemistry

One of the standard procedures for the synthesis of furonaphthoquinones requires the condensation of a 2-hydroxynaphthoquinone with aldehydes. We have previously described[10] the introduction of the hydroxyl group at C-2 on our terpenylnaphthoquinones applying one of two procedures following the formation of the naphthoquinone: epoxidation and further treatment of the epoxide with acid or via the nucleophilic substitution of a halogen atom.

The terpenylnaphthoquinone precursors of the new furonaphthoquinones were prepared by Diels–Alder addition between commercially available α-myrcene and *p*-BQ in the presence of $BF_3{\cdot}Et_2O$.[9b] Further oxidation with MnO_2 of the cycloadduct obtained from 1,4-BQ yielded NQ **1**. When the MnO_2 oxidation was done without washing out the boron trifluoride, compound **2** was formed, in which the cyclization of the terpenyl side chain occurred[12] (Scheme 1).

When 2,5-dichloro-*p*-BQ was used in the Diels–Alder cycloaddition, the naphthoquinones **3** and **4** were obtained, depending whether the BF_3 was present or not during the oxidation with MnO_2. Compounds **3** and **4** were mixtures of the two possible regioisomers **a/b** in a 9:1 ratio.

Regiospecific cycloadditions have been consistently achieved when haloquinones react with electron-rich dienes, usually oxygenated.[13] Myrcene, although is not oxygenated, is an unsymmetrical diene able to induce a fair regioselectivity when reacts with different dichlorobenzoquinones.[10] As it has been stated,[13a,14] in the presence of the BF_3, such regioselectivity could be explained in terms of the orientation of the diene with the side chain located in front of the unsubstituted carbon of the 2,5-diCl-BQ that is the site with greatest electron deficiency. The major isomer was the one with the chlorine atom at the C-2 position and the alkyl chain at



Scheme 1. Preparation of terpenylnaphthoquinones via Diels–Alder cycloaddition.

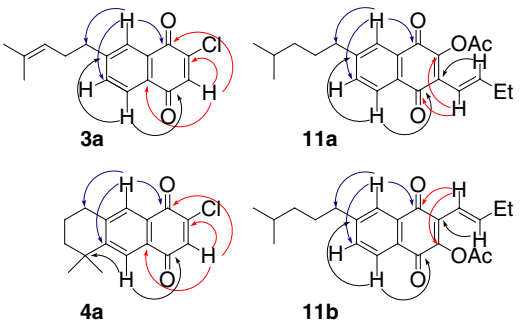


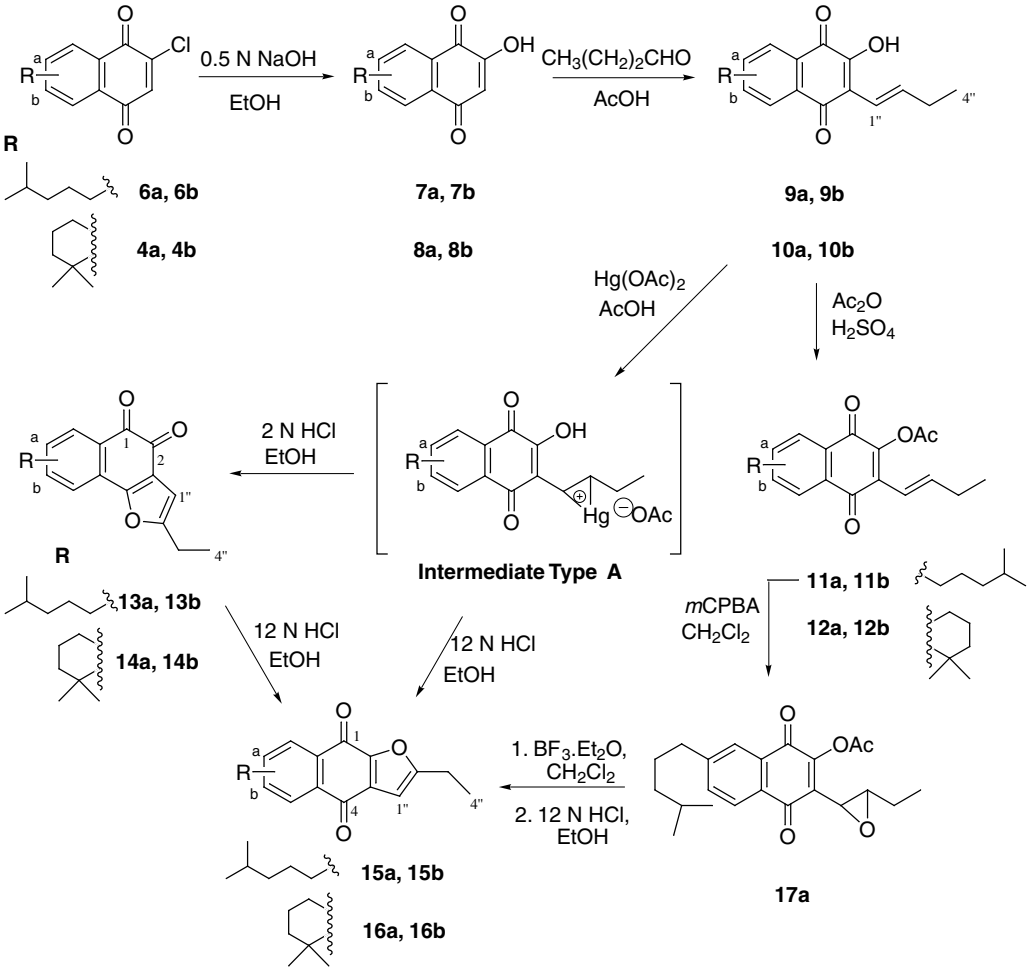
Figure 2. Representative HMBC correlations observed for the quinone pairs **3a/4a** and **11a/11b**.

C-7 (isomer **a**) as confirmed by two-dimensional (HMBC) NMR experiments. The most relevant correlations are shown in Figure 2. Most of the subsequent reactions were carried out with the mixture of the two regioisomers, although a small amount of each compound was isolated and purified by chromatographic techniques, thus allowing us the correct characterisation of isomers **a/b**.

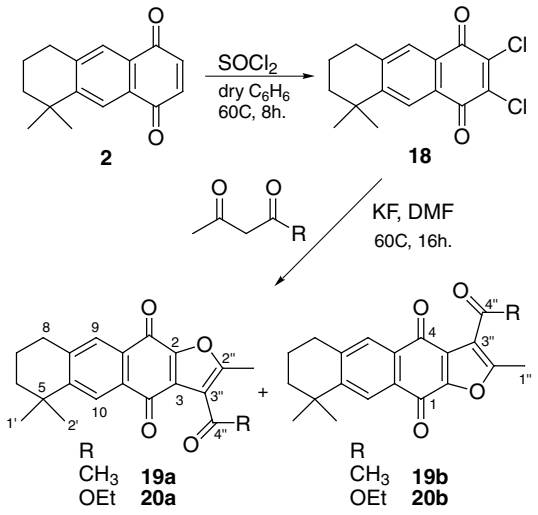
In order to avoid further unwanted side reactions in the formation of the furo-NQ, the side-chain double bond of **1** and **3** was hydrogenated. During hydrogenation a partial reduction of the NQ to the corresponding hydroquinone was observed and the product was treated with Ag_2O to obtain NQs **5** and **6** in quantitative yield.

The chloro derivatives **6** and **4** were transformed into the corresponding 2-hydroxy-NQ by treatment with sodium hydroxide to yield, respectively, **7** and **8** in the same 9:1 ratio as the precursors[10] (Scheme 2). The 2-hydroxy derivatives, without purification, were condensed with *n*-butyraldehyde under acidic conditions[15] to give the butenyl derivatives **9** and **10**. The mixtures of the regioisomers **9a/9b** and **10a/10b** were difficult to resolve; however, their acetyl derivatives **11** and **12** were easily separated by column chromatography on silica gel. Two-dimensional NMR experiments performed with **11a** and **11b** confirmed the locations of the substituents on the NQ system (Fig. 2).

The furonaphthoquinones were prepared via oxidative cyclization of the 2-hydroxy-3-butenyl derivatives **9** and **10** with mercuric acetate.[16] The treatment of the alkenyl-NQ with mercuric acetate led to an intermediate type **A** (Scheme 2), which gave rise to the furo-1,2- or furo-1,4-NQs, depending on the subsequent reaction conditions. With dilute acid and short reaction times,



Scheme 2. Synthesis of terpenylfuronaphthoquinones.



Scheme 3. Synthesis of 2″,3″-disubstituted terpenylfuroquinones.

the 1,2-quinone derivatives **13** and **14**, which are the kinetic reaction products, were obtained; whereas with concentrated acid and longer reaction times, the reaction went towards the thermodynamic products, the furo-1,4-NQs **15** and **16**. If the 1,2-NQs were kept in concentrated hydrochloric acid, isomerisation to the more stable 1,4-NQs took place. These reactions were performed with the mixture of the regioisomers, although a pure sample of each compound was obtained by preparative TLC or column chromatography for proper characterisation. The numbering used for furoquinone derivatives (Schemes 2 and 3) is that derived from the naphthoquinone or the anthraquinone precursors rather than from the systematic names, in order to simplify comparison of NMR data. Nevertheless, names of compounds in the experimental section follow the systematic rules.

In order to confirm the structure of both isomers, **a** and **b**, an alternative procedure based on the facile separation of the acetoxy derivatives **11** and **12** was used. Thus, epoxidation of pure **11a** gave the epoxide **17** and further treatment with BF_3 led to the *p*-furonaphthoquinone **15a**.

The transformations described above led to furonaphthoquinones substituted at position C-2″. In order to analyse the influence of more substituents on the furane ring on the cytotoxicity, we also decided to prepare 1″,2″-disubstituted compounds following the one-pot procedure described by Kuo et al.,[17] by condensation of 2,3-dichloro-NQ and 1,3-dicarbonyl compounds. Thus, the 2,3-dichloroquinone **18** was obtained by treatment of **2** with $SOCl_2$. Further condensation of **18** with acetylacetone and ethyl acetoacetate in dimethylformamide, in the presence of potassium fluoride, yielded the furo-1,4-NQs **19** and **20**, respectively (Scheme 3).

2.2. Biological activities

Most of the furo-NQs prepared were evaluated in vitro to establish their cytotoxicity against neoplastic cell cultures of A-549 human lung carcinoma and HT-29 or H-116 human colon carcinomas.[18] The results are shown in Table 1, expressed as GI_{50} values in micromolars, in which GI_{50} for doxorubicin has also been included as reference.

Table 1. Cytotoxicity of the terpenylquinones against the cancer cell lines A-549, HT-29 and H-116 (GI_{50} μM)

Compound	A-549	HT-29	H-116
1	1.0	1.0	n.d.
2	2.1	0.2	n.d.
3a	>3.6	>3.6	n.d.
3b	>3.6	>3.6	n.d.
5	0.4	0.4	n.d.
11a	1.4	1.4	n.d.
11b	7.0	7.0	n.d.
12a	7.1	n.d.	7.1
12a + **12b** (1:1)	>14.1	n.d.	14.1
13a	3.2	3.2	n.d.
13b	3.2	3.2	n.d.
14a + **14b** (4:1)	0.3	3.2	n.d.
14a + **14b** (1:2)	3.2	3.2	n.d.
15a	>16.1	n.d.	>16.1
15b	>16.1	n.d.	>16.1
16a + **16b** (1:1)	81.2	n.d.	16.2
18	16.2	n.d.	8.1
19a	>14.9	n.d.	>14.9
19b	>14.9	n.d.	>14.9
20a + **20b** (1:1)	<13.7	n.d.	<13.7
Doxorubicin	0.08	0.1	n.d.

n.d., not determined.

From these results, it can be observed that our NQs showed GI_{50} values one or two orders of magnitude less than the reference drug, doxorubicin, although several derivatives maintained the cytotoxicity in the micromolar range. Among the terpenylquinones prepared, the substituted-NQs **3** and **11**–**20** are, in general, less cytotoxic than the unsubstituted precursors **1**, **2** and **5**, regardless of whether the terpenyl side chain is cyclized or not.

Among the asymmetrically substituted NQs, there were no significant differences between the **a** and **b** regioisomers, only it is worth mentioning derivatives **11** and **12** for which isomer **a** was somewhat more potent than **b**, keeping the GI_{50} in the same range as the precursors. However, if the furo-NQs are considered, the furo-1,2-NQs (**13** and **14**) showed higher cytotoxicity than the corresponding furo-1,4-NQs (**15** and **16**). This higher potency of 1,2-quinones is in accordance with the results reported by other authors, not only with respect to their cytotoxicity,[19] but also with that of the trypanocidal activity.[6c,20] These results can be related with their redox potentials. The furo-1,2-NQs are easier to reduce than the furo-1,4-NQs,[20,21] and so that, are able to generate active oxygen species through redox cycling that is one of the mechanisms by which several NQs exhibit their bioactivity.[2] In view that the 1,2-quinone moiety is more relevant for bioactivity, further research is in progress in our laboratory in order to improve the biological profile of this kind of derivatives.

On the other hand, the presence of two different substituents on the furan ring, as in derivatives **19** and **20**, does not improve the cytotoxicity of the compounds, although the exact GI_{50} value for **20** could not be determined.

3. Experimental

3.1. Chemistry

IR spectra were obtained on a Nicolet (Impact 410) spectrophotometer in NaCl film. NMR spectra were recorded at 200 MHz for ^1H and 50 MHz for ^{13}C in deuterochloroform using TMS as internal reference, on a Bruker AC 200. Chemical shift values are expressed in parts per million followed by multiplicity and coupling constants (*J*) in hertz. Column chromatography (CC) was performed on silica gel (Merck No. 9385). HRMS were run in a VG TS-250 spectrometer. TLC was carried out on silica gel 60 F_{254} (Merck, 0.25 mm thick). Solvents and reagents were purified by standard procedures as necessary.

3.1.1. 6-(4-Methyl-3-pentenyl)-1,4-naphthoquinone (1) and 5,5-dimethyl-5,6,7,8-tetrahydroanthracene-1,4-dione (2). Quinones **1** and **2** were obtained as previously described.[12]

3.1.2. 2-Chloro-7(6)-(4-methyl-3-pentenyl)-1,4-naphthoquinones (3a,b). The Diels–Alder cycloaddition between 2,5-dichlorobenzoquinone (893 mg, 5 mmol) and α-myrcene (0.8 mL, 5 mmol) was performed following the described procedure.[12] The reaction product was purified by CC on silica gel to yield a 9:1 mixture (952 mg, 69%) of **3a** and **3b** (eluent: hexane–CH_2Cl_2, 7:3). The isomers were separated by preparative TLC (eluent: hexane–CH_2Cl_2–Et_2O, 7:2:1). Compound **3a**: IR (*v*, cm^{-1}): 3060, 1682, 1665, 1600, 1570, 1060, 820. ^1H NMR: Table 2. ^{13}C NMR: Table 3. HRMS (FAB-POSI, M+1) calcd 275.0839, found 275.0862. Compound **3b**: IR (*v*, cm^{-1}): 3060, 1682, 1665, 1600, 1570, 1060, 820. ^1H NMR: Table 2. ^{13}C NMR: Table 3.

3.1.3. 2-Chloro-5,5(8,8)-dimethyl-5,6,7,8-tetrahydroantracene-1,4-diones (4a,b). The Diels–Alder cycloadditon between 2,5-dichlorobenzoquinone (893 mg, 5 mmol) and α-myrcene (0.8 mL, 5 mmol) was performed as reported.[12] The reaction product was purified by CC on silica gel to yield a 9:1 mixture of **4a** and **4b** (483 mg, 35%) (eluent: hexane–CH_2Cl_2, 7:3). The isomers were separated by preparative TLC (eluent: hexane–CH_2Cl_2–Et_2O, 7:2:1). Compound **4a**: IR (*v*, cm^{-1}): 3060, 1680, 1670, 1600, 1570, 1060, 820. ^1H NMR: Table 2. ^{13}C NMR: Table 3. HRMS (FAB-POSI, M+1) calcd 275.0839, found 275.0824. Compound **4b**: IR (*v*, cm^{-1}): 3060, 1680, 1670, 1600, 1570, 1060, 820. ^1H NMR: Table 2. ^{13}C NMR: Table 3.

3.1.4. 6-(4-Methylpentyl)-1,4-naphthoquinone (5). Compound **1** (240 mg, 1 mmol) was dissolved in EtOAc (20 mL) containing 100 mg of 10% $Pd/CaCO_3$ and kept under hydrogen atmosphere at rt for 24 h. After filtering off the catalyst on Celite, the solvent was evaporated and the reaction product was dissolved in dry Et_2O and Ag_2O (229 mg, 1 mmol) was added and kept at rt under an inert atmosphere overnight. The mixture was filtered on Celite, the solvent evaporated off and the product purified by CC to yield quinone **5** (196 mg, 80% overall yield) (eluent: hexane–CH_2Cl_2, 1:1). IR (*v*, cm^{-1}): 3060, 1675, 1665, 1600, 1140, 1045, 830. Anal. $C_{16}H_{18}O_2$ (C, H). ^1H NMR: Table 2. ^{13}C NMR: Table 3. HRMS (FAB-POSI, M+1) calcd: 243.1385, found: 243.1399.

3.1.5. 2-Chloro-7(6)-(4-methylpentyl)-1,4-naphthoquinones (6a,b). In the same way as described for **5**, a 9:1 mixture of **6a** and **6b** (220 mg, 80% overall yield) was obtained from the mixture of **3a** and **3b**. The isomers were separated by preparative TLC (eluent: hexane–CH_2Cl_2–Et_2O, 7:2:1). Compound **6a**: IR (*v*, cm^{-1}): 1680, 1665, 1600, 1570, 1060, 1022, 825. Anal. $C_{16}H_{17}ClO_2$ (C, H). ^1H NMR: Table 2. ^{13}C NMR: Table 3. HRMS (FAB-POSI, M + 1) calcd 277.0995 found 277.1002. Compound **6b**: IR (*v*, cm^{-1}): 1680, 1665, 1600, 1570, 1060, 1022, 825. ^1H NMR: Table 2. ^{13}C NMR: Table 3.

3.1.6. 2-Hydroxy-7(6)-(4-methylpentyl)-1,4-naphthoquinones (7a,b) and 2-hydroxy-5,5(8,8)-dimethyl-5,6,7,8-tetrahydroantracene-1,4-diones (8a,b). 2-Chloro-1,4-naphthoquinones **6a/6b** and **4a/4b** (1 mmol) were dissolved in boiling MeOH (10 mL) and an aq solution of 0.5 N NaOH (10 mL) was added. The mixtures were heated for 10 min, and then poured into cold water, acidified with 2 N HCl and extracted with EtOAc. Organic layers were washed with brine, dried, filtered and evaporated in vacuo to afford the corresponding 2-hydroxynaphthoquinones **7** and **8**. ^1H NMR: Table 2. They were used for the next step without further purification.

3.1.7. 3-(1*E*-Butenyl)-2-hydroxy-7(6)-(4-methylpentyl)-1,4-naphthoquinones (9a,b) and 3-(1*E*-butenyl)-2-hydroxy-5,5(8,8)-dimethyl-5,6,7,8-tetrahydroantracene-1,4-diones (10a,b). To the crude reaction products of 2-hydroxynaphthoquinones **7a/7b** and **8a/8b** (1 g) in glacial acetic acid (20 mL), a solution of 12 N HCl (1.0 mL) in glacial acetic acid (10 mL) was added in one portion. The solutions were stirred and heated at 80 °C, then butyraldehyde (1.0 mL, 12 mmol) was added, and the mixtures were stirred for 3 h at 80 °C. The solutions were poured into cold water, and extracted with Et_2O. The organic layers were washed with aq solution of 3% NaOH until the aqueous layer became clear. The combined aq layers were acidified with 12 N HCl and extracted with EtOAc. The organic layers were washed with brine, dried, filtered and evaporated in vacuo to afford the corresponding 3-alkenyl-2-hydroxy-terpenylnaphthoquinones **9a/9b** and **10a/10b** which were used without further purification. ^1H NMR: Table 2.

3.1.8. 2-Acetoxy-3-(1*E*-butenyl)-7(6)-(4-methylpentyl)-1,4-naphthoquinones (11a,b). The reaction product **9a/9b** was acetylated by treating it with 20 mL of a solution of sulfuric acid in acetic anhydride (previously prepared with 0.15 mL of 96% H_2SO_4 and 50 mL of Ac_2O). The reaction mixture was stirred at rt and after 1 h, ice was

Table 2. ^{1}H NMR ($CDCl_3$–TMS, δ ppm, (J Hz)) data for compounds **1**–**20**

H	**1**	**3a**	**3b**	**5**	**6a**	**6b**
2	6.93 s			6.93 s		
3	6.93 s	7.17 s	7.19 s	6.93 s	7.18 s	7.18 s
5	7.87 d (1.8)	7.97 d (8.0)	7.89 d (1.8)	7.88 d (1.6)	8.04 d (8.0)	7.92 d (1.8)
6		7.56 dd (8.0;1.8)			7.54 dd (8.0;1.8)	
7	7.55 dd (8.0;1.8)		7.58 dd (8.0;1.8)	7.54 dd (7.6;1.6)		7.56 dd (8.0;1.8)
8	7.97 d (8.0)	7.96 d (1.8)	8.08 d (8.0)	7.98 d (7.6)	7.85 d (1.8)	7.96 d (8.0)
1′	2.76 t (7.3)	2.78 t (7.2)	2.78 t (7.3)	2.73 t (7.3)	2.71 t (7.3)	2.71 t (7.3)
2′	2.33 m	2.34 m	2.35 m	1.67 m	1.69 m	1.69 m
3′	5.11 m	5.11 m	5.12 m	1.23 m	1.22 m	1.22 m
4′				1.57 m	1.60 m	1.60 m
5′/6′	1.66 s/1.52 s	1.66 s/1.52 s	1.67 s/1.52 s	0.88 d (6.8)	0.86 d (6.6)	0.86 d (6.6)

H	**7a/7b**	**9a/9b**	**11a**	**11b**
2				
3	6.28 s/6.29 s			
5	7.96 d (8.0)/7.87 d (1.8)	7.98 d (8.0)/7.89 d (1.8)	8.01 d (8.0)	7.90 d (1.8)
6	7.52 dd (8.0;1.8)/—	7.50 dd (8.0;1.8)/—	7.52 dd (8.0;1.8)	
7	—/7.44 dd (8.0;1.8)	—/7.43 dd (8.0;1.8)		7.51 dd (8.0;1.8)
8	7.84 d (1.8)/7.94 d (8.0)	7.82 d (1.8)/7.92 d (8.0)	7.87 d (1.8)	7.98 d (8.0)
1′	2.67 t (6.6)	2.67 m	2.71 t (7.7)	2.73 t (7.3)
2′	1.62 m	1.64 m	1.66 m	1.66 m
3′	1.22 m	1.24 m	1.22 m	1.22 m
4′	1.53 m	1.56 m	1.57 m	1.57 m
5′/6′	0.84 d (6.6)	0.87 d (6.6)	0.89 d (6.6)	0.88 (6.6)
1″		6.68 d (16.2)	6.40 dt (16.0;1.8)	6.39 dt (16.0;1.5)
2″		7.08 dt (16.2;6.6)	7.04 dt (16.0;7.0)	7.03 dt (16.0;6.9)
3″		2.30 m	2.32 m	2.32 m
4″		1.11 t (7.7)	1.12 t (7.7)	1.12 t (7.3)
Ac			2.42 s	2.42 s

H	**13a**	**13b**	**15a**	**15b**	**17a**
2					
3					
5	7.55 d (7.8)	7.46 d (1.8)	8.06 d (8.0)	7.94 d (1.8)	8.02 d (7.7)
6	7.41 dd (7.8;2.0)		7.51 dd (8.0;1.8)		7.56 dd (7.7;1.8)
7		7.21 dd (8.0;1.8)		7.52 dd (7.8;1.8)	
8	7.86 d (2.0)	7.95 d (8.0)	8.00 d (1.8)	8.08 d (7.8)	7.89 d (1.8)
1′	2.62 t (7.6)	2.67 t (8.0)	2.73 t (7.7)	2.73 t (7.7)	2.72 t (7.7)
2′	1.63 m	1.61 m	1.67 m	1.67 m	1.73 m
3′	1.21 m	1.20 m	1.28 m	1.28 m	1.23 m
4′	1.56 m	1.57 m	1.62 m	1.62 m	1.65 m
5′/6′	0.88 d (6.4)	0.89 d (6.6)	0.88 d (6.6)	0.88 d (6.6)	0.88 d (6.6)
1″	6.41 s	6.44 s	6.61 s	6.60 s	3.74 d (2.2)
2″					3.13 td (5.5;2.2)
3″	2.73 cd (7.6;1.2)	2.76 cd (7.7;1.1)	2.84 c (7.3)	2.84 c (7.3)	1.73 m
4″	1.30 t (7.6)	1.32 t (7.7)	1.36 t (7.3)	1.36 t (7.3)	1.09 t (7.7)
Ac					2.40 s

H	**2**	**4a**	**4b**	**8a/8b**	**10a/10b**	**12a**	**12b**
2	6.90 s						
3	6.90 s	7.16 s	7.14 s	6.29 s/6.27 s			
5			2.90 t (6.2)	—/2.88 t (6.3)	—/2.85 t (6.0)		2.87 m
6	1.71 m	1.86 m	1.87 m	1.72 m/1.83 m	1.70 m/1.80 m	1.72 m	1.83 m
7	1.85 m	1.72 m	1.72 m	1.83 m/1.72 m	1.80 m/1.70 m	1.83 m	1.72 m
8	2.90 t (6.4)	2.90 t (6.2)	—	2.88 t (6.3)/—	2.85 t (6.0)/—	2.87 m	
9	7.73 s	7.82 s	8.11 s	7.76 s/8.04 s	7.71 s/8.071s	7.76 s	8.06 s
10	8.03 s	8.03 s	7.73 s	8.06 s/7.75 s	8.07 s/7.77 s	8.02 s	7.73 s
1′,2′	1.34 s/1.37 s	1.34 s	1.35 s	1.34 s	1.33 s	1.33 s	1.33 s
1″					6.60 dt (16.2;1.1)	6.39 dt (16.1;1.5)	6.39 dt (16.1;1.5)
2″					7.07 dt (16.2;6.6)	7.02 dt (16.1;7.3)	7.02 dt (16.1;7.3)
3″					2.32 m	2.33 m	2.33 m
4″					1.12 t (7.3)	1.11 t (7.7)	1.11 t (7.7)
Ac						2.42 s	2.41 s

Table 2 (*continued*)

H	14a	14b	16a/16b	18	19a	19b	20a/20b
2							
3							
5		2.81 m	—/2.87 t (6.2)			2.91 t (6.0)	—/2.91 t (6.0)
6	1.69 m	1.82 m	1.72 m/1.83 m	1.72 m	1.72 m	1.85 m	1.72 m/1.85 m
7	1.82 m	1.69 m	1.83 m/1.72 m	1.84 m	1.85 m	1.71 m	1.85 m/1.72 m
8	2.84 t (6.2)		2.87 t (6.2)/—	2.88 t (6.0)	2.81 t (6.0)		2.91 t (6.0)/—
9	7.31 s	7.74 s	7.82 s/8.12 s	7.79 s	7.86 s	8.15 s	7.79 s/8.08 s
10	8.02 s	7.56 s	8.08 s/7.76 s	8.08 s	8.14 s	7.84 s	8.14 s/7.86 s
1′,2′	1.35 s	1.36 s	1.34 s	1.33 s	1.36 s	1.36 s	1.35 s
1″	6.42 s	6.43 s	6.58 s/6.56 s		2.79 s	2.78 s	1.88 s
2″							
3″	2.73 c (7.7)	2.72 m	2.72 m				
4″	1.35 t (7.7)	1.31 m	1.31 m				
Others					2.65 s	2.65 s	4.15 c (8.0) 1.15 t (8.0)

added and the mixture extracted with EtOAc. The organic layers were washed with aq satd $NaHCO_3$, then with brine, dried over anhydrous Na_2SO_4 and evaporated to dryness. The reaction product was chromatographed on silica gel (eluent: hexane–CH_2Cl_2, 7:3) yielding: (a) 90 mg (6.5% from **7a/7b**) of **11a**: IR (ν, cm^{-1}): 1780, 1670, 1630, 1600, 1540, 1150, 1020. Anal. $C_{22}H_{26}O_4$ (C, H). ^1H NMR: Table 2. ^{13}C NMR: Table 3. HRMS (FAB-POSI, M+1) calcd: 355.1909, found: 355.1898; (b) 280 mg (20%) of a 9:1 mixture of **11a** and **11b**; (c) 60 mg (4.5%) of **11b**: IR (ν, cm^{-1}): 1780, 1670, 1630, 1600, 1460, 1170, 1010. Anal. $C_{22}H_{26}O_4$ (C, H). ^1H NMR: Table 2. ^{13}C NMR: Table 3. HRMS (FAB-POSI, M+1) calcd 355.1909, found 355.1952.

3.1.9. 2-Acetoxy-3-(1*E*-butenyl)-5,5(8,8)-dimethyl-5,6,7,8-tetrahydroanthracene-1,4-diones (12a,b). Starting from **8a/8b** and following the procedure described above, the CC of the reaction product yielded: (a) 70 mg (5%) of **12a**: IR (ν, cm^{-1}): 1660, 1600, 1460, 1420, 1360, 1170, 750. Anal. $C_{22}H_{24}O_4$ (C, H). ^1H NMR: Table 2. ^{13}C NMR: Table 3; (b) 250 mg (18%) of a 9:1 mixture of **12a** and **12b**; (c) 50 mg (4%) of **12b**: IR (ν, cm^{-1}): 1660, 1600, 1460, 1420, 1360, 1170, 750. Anal. $C_{22}H_{24}O_4$ (C, H). ^1H NMR: Table 2. ^{13}C NMR: Table 3. HRMS (FAB-POSI, M+1) calcd: 353.1753, found: 353.1711.

3.1.10. 2-Ethyl-7(8)-(4-methylpentyl)-naphtho[1,2-*b*]furan-4,5-dione (13a,b). The 2-hydroxy-3-alkenyl-terpenylnaphthoquinones **9a/9b** (1 mmol) were dissolved in glacial acetic acid (20 mL) and a solution of $Hg(OAc)_2$ (2 mmol) in glacial acetic acid (15 mL) was added. The mixture was stirred at rt for 30 min, and 15 min more at 80 °C. After cooling, Et_2O was added and the precipitate formed was filtered off. The solvent was evaporated off, the resulting products (intermediate type A) were dissolved in EtOH (20 mL) and 2 N HCl (20 mL) was added. The mixture was stirred at 80 °C for 15 min, and then poured into cold water and extracted with EtOAc. The organic layers were washed with aq satd $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4 and evaporated off. The product was chromatographed on silica gel (eluent: hexane–CH_2Cl_2, 7:3) to afford a 9:1 mixture of 1,2-terpenylfuronaphthoquinones **13a** and **13b** (217 mg, 70%). The isomers were purified by preparative TLC (eluent: hexane–CH_2Cl_2–Et_2O, 7:2:1). Compound **13a**: IR (ν, cm^{-1}): 1670, 1600, 1580, 1550, 1500, 1230, 1170. Anal. $C_{20}H_{22}O_3$ (C, H). ^1H NMR: Table 2. ^{13}C NMR: Table 3. HRMS (FAB-POSI, M+1) calcd 311.1647, found: 311.1632. Compound **13b**: IR (ν, cm^{-1}): 1670, 1610, 1590, 1560, 1450, 1220, 1190. Anal. $C_{20}H_{22}O_3$ (C, H). ^1H NMR: Table 2. ^{13}C NMR: Table 3. HRMS (FAB-POSI, M+1) calcd: 311.1647, found: 311.1686.

3.1.11. 2-Ethyl-10,10(7,7)-dimethyl-7,8,9,10-tetrahydroanthra[1,2-*b*]furan-4,5-diones (14a,b). Starting from **10a/10b** and following the procedure described above, CC of the reaction product yielded a 9:1 mixture of 1,2-furoanthraquinones **14a** and **14b** (220 mg, 71%). The isomers were purified by preparative TLC (eluent: hexane–CH_2Cl_2–Et_2O, 7:2:1). Compound **14a**: IR (ν, cm^{-1}): 1670, 1590, 1490, 1460, 1220, 1170, 820. ^1H NMR: Table 2. ^{13}C NMR: Table 3. HRMS (ESI, M+Na) calcd: 331.1311, found: 331.1342. Compound **14b**: IR (ν, cm^{-1}): 1670, 1590, 1490, 1460, 1220, 1170, 820. ^1H NMR: Table 2. ^{13}C NMR: Table 3.

3.1.12. 2-Ethyl-7(6)-(4-methylpentyl)-naphtho[2,3-*b*]furan-4,9-diones (15a,b). *Method A.* The intermediate type A obtained from **9a/9b** was dissolved in EtOH (20 mL) and 12 N HCl (20 mL) was added. The mixtures were stirred at 80 °C for 3 h and the reaction was worked up as described above for **13a** and **13b**. The crude reaction mixture was chromatographed on silica gel (eluent: hexane–CH_2Cl_2, 7:3) to afford a 9:1 mixture of 1,4-terpenylfuronaphthoquinones **15a** and **15b** (230 mg, 74%). The isomers were purified by preparative TLC (eluent: hexane–CH_2Cl_2–Et_2O, 7:2:1). Compound **15a**: IR (ν, cm^{-1}): 1670, 1600, 1540, 1460, 1280, 1120. Anal. $C_{20}H_{22}O_3$ (C, H). ^1H NMR: Table 2. ^{13}C NMR: Table 3. HRMS (FAB-POSI, M+1) calcd: 311.1647, found: 311.1640. Compound **15b**: IR (ν, cm^{-1}): 1670, 1600, 1540, 1460, 1280, 1120. Anal. $C_{20}H_{22}O_3$ (C, H). ^1H NMR: Table 2. ^{13}C NMR: Table 3. HRMS (FAB-POSI, M+1) calcd: 311.1647, found: 311.1609.

Method B. To a solution of the 1,4-naphthoquinone **11a** (1.0 mmol), in CH_2Cl_2 (50 mL), mCPBA (1.65 g) and

Table 3. ^{13}C NMR ($CDCl_3$–TMS, δ ppm) data for compounds **1**–**20**

C	**1**	**3a**	**3b**	**5**	**6a**	**6b**	**7a**	**7b**	**9a/9b**
1	184.4	178.1	177.9	184.8	177.6	177.7	181.9	181.7	181.8/181.2
2	138.1	146.0	146.5	138.4	146.0	146.4	148.9	151.8	151.2/151.3
3	138.3	135.9	135.8	138.7	135.9	135.8	110.5	110.5	132.8
4	184.9	182.5	183.1	185.3	182.6	183.1	185.2	185.6	184.4/184.7
5	125.9	127.3	126.7	126.1	127.3	126.5	126.6	126.3	127.3/127.0
6	149.0	134.6	150.3	150.0	134.6	150.9	135.0	156.8	135.0/149.0
7	132.7	149.7	134.4	133.9	150.4	134.2	156.6	135.3	149.0/133.1
8	126.2	126.8	127.7	126.6	127.0	127.8	126.1	126.6	125.7/126.3
4a	131.4	129.7	131.8	131.8	129.7	131.8	129.3	130.3	129.4/129.4
8a	129.5	131.1	129.3	129.1	131.3	129.2	130.4	129.4	130.6/130.6
1′	35.9	36.1	36.3	36.4	36.4	36.4	35.9	36.7	36.2/36.6
2′	29.0	29.2	29.3	28.7	28.8	28.8	28.6	29.8	28.8
3′	122.4	122.4	122.4	38.4	38.3	38.3	38.3	38.5	38.5
4′	133.8	133.2	133.4	27.8	27.9	27.9	27.6	27.9	28.1
5′/6′	25.4/17.6	25.6/17.6	25.7/17.7	22.4	22.6	22.6	22.3	22.6	22.6
1″									118.0
2″									145.2
3″									27.9
4″									13.4

C	**11a**	**11b**	**13a**	**13b**	**15a**	**15b**	**17a**	C	**2**	**4a**	**4b**
1	178.6	178.1	181.1	180.5	173.6	173.4	178.7	1	184.7	178.1	178.0
2	148.5	148.6	174.6	174.9	131.9	131.9	150.4	2	138.2	146.2	146.4
3	132.1	132.2	121.8	122.0	132.6	132.6	133.6	3	138.2	136.0	135.9
4	184.6	184.1	160.1	159.8	181.0	181.2	184.2	4	184.7	182.9	182.9
5	127.0	126.6	122.0	122.1	127.2	126.7	126.5	4a	128.6	129.7	129.6
6	134.1	150.2	135.2	151.8	133.5	149.7	134.5	5	34.3	34.9	31.2
7	149.1	133.9	145.4	130.8	150.0	133.7	150.5	6	38.2	38.4	19.1
8	126.0	126.6	130.5	129.9	126.8	127.1	126.8	7	18.8	19.1	38.4
4a	130.8	128.7	126.4	126.6	131.0	130.4	130.8	8	30.8	31.1	34.8
8a	130.2	132.1	128.7	128.8	128.9	131.0	129.7	8a	143.0	143.9	153.4
1′	36.2	36.4	35.9	36.6	36.4	36.3	36.3	9	127.0	128.6	127.7
2′	28.6	28.7	28.7	28.7	28.9	28.8	28.7	9a	129.5	128.3	129.5
3′	38.4	38.4	38.9	38.5	38.5	38.5	38.4	10	124.7	125.5	126.4
4′	27.8	27.8	27.8	27.9	27.9	27.8	27.8	10a	152.6	153.8	144.3
5′/6′	22.6	22.4	22.5	22.6	22.6	22.6	22.5	1′/2′	31.1	31.4	31.4
1″	117.3	117.2	102.8	103.0	103.6	103.5	60.6	1″			
2″	148.1	147.9	161.0	161.3	165.8	165.6	52.3	2″			
3″	28.0	27.9	21.2	21.4	21.8	21.8	25.3	3″			
4″	12.9	12.9	11.6	11.8	11.7	11.6	9.5	4″			
Others							20.4				
							168.0				

C	**8a**	**8b**	**12a**	**12b**	**14a**	**14b**	**16a/16b**	**18**	**19a**	**19b**	**20a/20b**
1	181.9	181.7	181.4	181.5	180.9	180.6	173.3	176.0	173.8	173.7	178.1
2	152.1	151.9	147.8	147.9	175.1	174.8	151.7	143.5	153.3	153.2	153.8
3	110.5	110.4	132.0	132.1	122.0	122.9	131.7/131.5	143.3	125.5	130.5	128.9
4	185.5	185.4	184.7	184.9	160.3	160.5	181.0	176.0	180.7	180.6	181.8
4a	130.8	130.0	132.0	132.1	125.6	126.3	131.0/130.5	128.8	131.1	131.3	129.7
5	35.0	31.2	34.7	31.0	34.3	29.8	34.6/31.0	34.9	34.8	31.0	34.8/31.1
6	38.5	19.0	38.5	19.1	38.6	19.2	38.6/19.2	38.4	38.5	19.1	38.5/19.1
7	19.1	38.3	19.1	38.5	19.1	38.6	19.2/38.6	19.0	19.1	38.5	19.1/38.5
8	30.9	34.5	31.1	34.7	29.8	34.8	31.0/34.6	31.1	31.0	34.8	31.1/34.8
8a	142.5	156.7	143.7	153.2	145.1	154.6	143.0/152.2	144.5	143.6	153.1	144.3/153.3
9	127.7	127.6	125.1	125.6	129.7	120.5	127.8/125.5	128.8	126.3	126.3	126.1/128.3
9a	130.8	130.0	132.0	132.1	126.9	129.7	129.7/130.2	127.9	128.6	129.5	129.4
10	125.5	125.3	127.8	127.3	122.9	131.9	125.5/127.8	126.7	127.8	127.3	128.3/126.1
10a	154.7	145.1	152.8	143.3	148.4	138.8	152.5/142.8	154.0	153.2	143.6	158.3/143.8
1′/2′	31.4	31.3	31.4	31.4	31.3	31.3	31.3	31.4	31.4	31.4	31.5
1″			117.4	117.4	102.9	102.9	102.2		14.3	14.3	20.0
2″			147.8	147.9	160.9	160.9	169.3		196.0	195.9	175.2
3″			28.0	28.0	21.3	21.3	21.3		121.1	131.5	96.5
4″			12.9	13.0	11.8	11.8	11.8		163.7	163.7	170.4
Others			167.9	167.8					32.0	32.0	61.1
			20.5	20.5							14.1

$NaHCO_3$ (1.0 g) were added. The mixture was stirred at rt for 30 min, then poured on cold water and extracted with EtOAc. The organic layer was washed with aq solutions of 0.05 M $Na_2S_2O_8$, satd $NaHCO_3$, dried over anhydrous Na_2SO_4 and evaporated off. The product was chromatographed on silica gel (eluent: CH_2Cl_2) to afford epoxide **17a** (105 mg, 33%). IR (ν, cm^{-1}): 1780, 1680, 1600, 1470, 1370, 1290, 1170, 1020. ^1H NMR: Table 2. ^{13}C NMR: Table 3. HRMS (ESI, M+Na) calcd: 393.1672, found: 393.1682.

Epoxide **17a** was dissolved in dry CH_2Cl_2 (10 mL), kept at 0 °C and $BF_3{\cdot}Et_2O$ (5 μL) was added. The mixture was stirred at 0 °C for 1 h, then poured into cold water and extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4 and evaporated to dryness. The product was dissolved in EtOH (7.5 mL) and 12 N HCl (7.5 mL) was added. The mixture was stirred at 80 °C for 3 h, then poured into cold water and extracted with EtOAc. The organic layer was washed with aq satd $NaHCO_3$, dried over anhydrous Na_2SO_4 and evaporated to dryness. CC of the product (eluent: hexane–CH_2Cl_2, 7:3) afforded the 1,4-terpenylfuronaphthoquinone **15a** (71 mg, 85% overall yield).

3.1.13. 2-Ethyl-6,6(9,9)-dimethyl-7,8,9,10-tetrahydroanthra[2,3-*b*]furan-4,11-diones (16a,b). Following the Method A described above, CC of the reaction product obtained from **10a/10b** yielded a 9:1 mixture of 1,4-furoanthraquinones **16a** and **16b** (201 mg, 65%). IR (ν, cm^{-1}): 1670, 1590, 1570, 1490, 1460, 1220, 1170, 820. ^1H NMR: Table 2. ^{13}C NMR: Table 3.

3.1.14. 2,3-Dichloro-5,5-dimethyl-5,6,7,8-tetrahydroanthracene-1,4-dione (18). To a solution of **2** (160 mg, 0.67 mmol) in dry benzene (100 mL) at 60 °C, pyridine (6.0 mL, 75 mmol) and recently distilled $SOCl_2$ (4.0 mL, 56 mmol) were added simultaneously. The mixture was stirred at 60 °C for 8 h, and then water was slowly added and extracted with EtOAc. The organic layers were washed with aq satd $NaHCO_3$, dried over anhydrous Na_2SO_4 and evaporated off. The product was chromatographed on silica gel (eluent: CH_2Cl_2–Et_2O, 9:1) to afford **18** (195 mg, 95%). IR (ν, cm^{-1}): 1680, 1600, 1560, 1280, 1010, 850. Anal. $C_{16}H_{14}Cl_2O_2$ (C, H). ^1H NMR: Table 2. ^{13}C NMR: Table 3. HRMS (FAB-POSI, M+1) calcd: 309.0449, found: 309.0473.

3.1.15. 3-Acetyl-2,6,6(2,9,9)-trimethyl-6,7,8,9-tetrahydroanthra[2,3-*b*]furan-4,11-diones (19a,b). The 2,4-pentanedione (0.6 mmol) and KF (2.08 mmol) in dimethylformamide (2.0 mL) were stirred at rt for 10 min, then a solution of **18** (123 mg, 0.4 mmol) in dimethylformamide (5.0 mL) was added in one portion. The mixture was stirred at 60–65 °C for 16 h, poured into cold water and extracted with EtOAc. The organic layers were dried over anhydrous Na_2SO_4 and evaporated off. Products obtained were chromatographed on silica gel (eluent: hexane–CH_2Cl_2, 7:3) to afford a 1:1 mixture of **19a/19b** (72.5 mg, 54%). The isomers were purified by preparative TLC (eluent: hexane–CH_2Cl_2–Et_2O, 7:2:1). Compound **19a**: IR (ν, cm^{-1}): 1670, 1600, 1540, 1290, 1220, 1170. Anal. $C_{21}H_{20}O_4$ (C, H). ^1H NMR: Table 2. ^{13}C NMR: Table 3. HRMS (FAB-POSI, M+1) calcd: 337.1440, found: 337.1438. Compound **19b**: IR (ν, cm^{-1}): 1670, 1600, 1540, 1290, 1220, 1170. Anal. $C_{21}H_{20}O_4$ (C, H). ^1H NMR: Table 2. ^{13}C NMR: Table 3. HRMS (FAB-POSI, M+1) calcd: 337.1440, found: 337.1471.

3.1.16. 2,6,6(2,9,9)-Trimethyl-4,11-dioxo-4,6,7,8,9,11-hexahydroanthra[2,3-*b*]furan-3-carboxylic acid ethyl esters (20a,b). Following the above procedure, a 1:1 mixture of **20a/20b** (73 mg, 50%) was obtained when ethyl acetoacetate was used. IR (ν, cm^{-1}): 1690, 1670, 1600, 1460, 1330, 1290, 1060, 870. Anal. $C_{22}H_{22}O_5$ (C, H). ^1H NMR: Table 2. ^{13}C NMR: Table 3. HRMS (FAB-POSI, M+1) calcd: 367.1559, found: 367.1581

3.2. Bioactivity

A colorimetric assay using sulforhodamine B (SRB) has been adapted for a quantitative measurement of cell growth and viability, following a previously described method.[18] Cells were seeded in 96-well microtitre plates, at 5×10^3 cells per well in aliquots of 195 μL of RPMI medium, and they are allowed to attach to the plate surface by growing in drug-free medium for 18 h. Afterwards, samples are added in aliquots of 5 μL (dissolved in DMSO–H_2O, 3:7). After 72 h exposure, the antitumour effect is measured by the SRB methodology: cells are fixed by adding 50 μL of cold 50% (w/v) trichloroacetic acid (TCA) and incubating for 60 minutes at 4 °C. Plates are washed with deionised water and dried; 100 μL of SRB solution (0.4% w/v in 1% acetic acid) is added to each microtitre well and incubated for 10 min at room temperature. Unbound SRB is removed by washing with 1% acetic acid. Plates are air-dried and bound stain is solubilized with Tris buffer. Optical densities are read on an automated spectrophotometer plate reader at a single wavelength of 490 nm. Data analyses are generated automatically by LIMS implementation. Using control OD values (C), test OD values (T) and time zero OD values (T_0), the drug concentration that causes 50% growth inhibition (GI_{50} value) was calculated from the equation: $100 \times [(T - T_0)/(C - T_0)] = GI_{50}$. All calculations represent the average of three determinations.

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