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# Synthesis and cytotoxicity of new aminoterpenylquinones

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**Abstract**—Several 6(7)-alkyl-1,4-naphthoquinones (NQ) have been prepared by cycloaddition reactions between the monoterpene α-myrcene and *p*-benzoquinones and halogen and nitrogen-containing functional groups have been introduced at the C-2 position of the naphthoquinone ring via nucleophilic addition or substitution reactions. These substituents at positions 2/3 of the NQ clearly influence the cytotoxic potency of this type of compound. Of particular interest is substitution by arylamino, specifically *p*-oxyarylamino, groups, which considerably enhance their bioactivity and selectivity.


## 1. Introduction

The quinone/hydroquinone moiety is a common structural feature in a large number of natural products[1] and it is associated with a wide spectrum of therapeutic applications such as antileishmanial,[2] antimalarial,[3] trypanocidal,[4] fungicidal,[5] etc. and most often as anticancer agents.[6] We can find clinically used anticancer agents derived from anthraquinone (daunorubicin), benzoquinone (mitomycin C) or naphthoquinones (menadione) and there is an enormous body of scientific work oriented towards the search for new analogues as potential therapeutic agents.[7] Examples of biologically active quinones are illustrated in Figure 1.

Several studies have shown that the quinone moiety is essential for their cytotoxic activity. Two mechanisms of action have been proposed.[6] The first requires either the formation of an alkylating intermediate (a quinone methide) or the direct addition of nucleophiles to the quinone ring, resulting in the alkylation of important biomolecules such as nucleic acids and proteins. The second involves repeated bioreductions and spontaneous oxidations (redox cycling) of the quinone, resulting in the formation of toxic oxygen species, such as superoxide ($O_2^-$), hydrogen peroxide ($H_2O_2$) and hydroxyl radical (•OH) that are responsible for oxidative stress in the cell. In fact several studies have found a good correlation between the redox potential of quinones and their cytotoxicity.[4,8]

Among the 1,4-naphthoquinones (NQs), there are numerous interesting biologically active compounds such as atovaquone, lapachol, plumbagin or menadione.[1] In the last few years we have synthesized several monoterpenyl- and diterpenylnaphthoquinones through Diels–Alder addition of natural terpenoids and *p*-benzoquinones.[9] Further transformations on the side chain led to derivatives with $IC_{50}$ values in the micromolar range in several tumour cell lines. Also, some of them showed a moderate selectivity against P-388 and MEL-28 cell lines. All these results prompted us to study the effect of the introduction of other substituents on the naphthoquinone ring. We had already prepared several derivatives with hydroxyl groups at C-2[10] and here we describe the preparation and evaluation of NQs with amino groups at C-2, a group that is present in numerous naturally occurring bioactive quinones, such as mitomycin C, as well as synthetic compounds.[1]

Aminoquinones play an important role in electron transport and oxidative phosphorylation processes and

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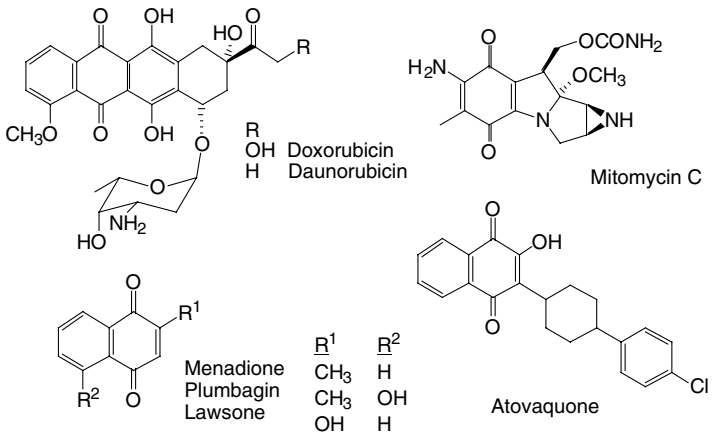



**Figure 1.** Several biologically active quinines.

they are also involved in enzyme inhibition, DNA cross linking, antibacterial, antifungal and anticancer activities.[6] Interestingly, most of the described amino-NQs are not substituted on the benzenoid ring. Our previous work[9,10] has demonstrated that several side chains (alkyl or alkenyl) attached to the benzenoid ring considerably improved the cytotoxicity of the NQ moiety. We present here our work on the design and synthesis of new monoterpenylnaphthoquinones (MTNQs) substituted at C-2 by amino groups, with the aim of analysing the influence of these substituents on the cytotoxicity of those derivatives.

## 2. Results and discussion

### 2.1. Chemistry

NQs substituted at C-2 can be obtained through nucleophilic processes, either addition or substitution reactions.[11] We have used both types of method to prepare the amino-terpenylnaphthoquinones reported here. The NQs used as starting materials are compounds **1** and **2** for the addition reactions and the haloderivatives **3**–**9** for the substitution reactions.

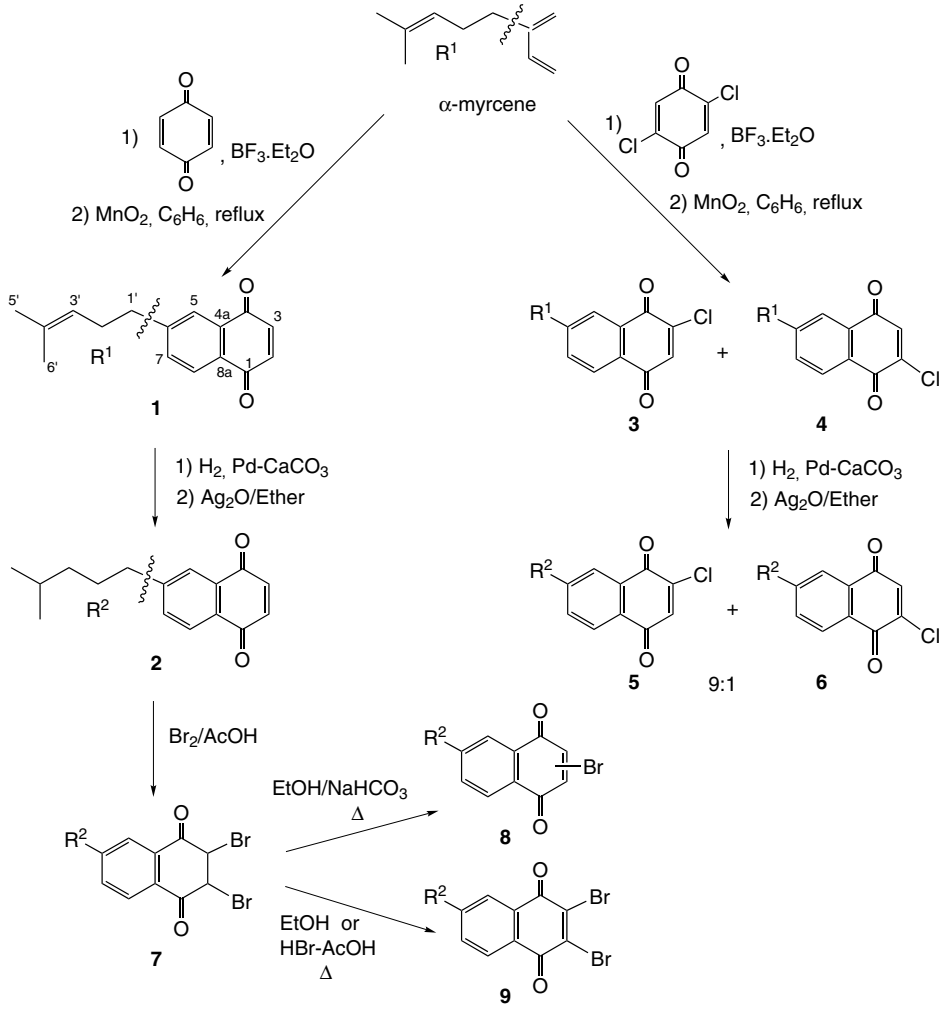
NQs **1**, **2** and the 9:1 mixture of **5/6** were obtained by Diels–Alder cycloaddition between α-myrcene and *p*-benzoquinone or 2,5-dichlorobenzoquinone, respectively, following the procedure previously reported by us[10] (Scheme 1). The bromo derivatives **8** and **9** were obtained by addition of bromine[12] to NQ **2**. The addition product **7** is stable enough to permit its purification and spectroscopic identification. Reflux of **7** in ethanol in the presence of $NaHCO_3$ yielded the 1:1 mixture of regioisomers **8**, while the same reflux conditions in the absence of base or in the presence of additional HBr produced the dibromo derivative **9**.

The procedures applied to obtain 2-amino-MTNQs with a free amino group are summarized in Scheme 2. Several procedures have been described for the preparation of 2-amino-NQs, mainly based on nucleophilic addition of reagents such as azides,[13] hydroxylamines[14] or benzylamines.[15] They yielded the final amino group directly or after a further liberation step such as hydrolysis or hydrogenation.

Thus, treatment of **1** with sodium azide yielded a complex reaction product from which, after acetylation, a small amount of the 1:1 mixture of regioisomers **10/11** was obtained. Thinking that the double bond in the side chain could interfere in the progress of the reaction, the subsequent transformations were done with derivatives that have that double bond hydrogenated. Thus, addition of benzylamine to NQ **2** yielded the 1:1 mixture **12/13**; a small amount of both isomers was obtained after column chromatography of the product. The location of the benzylamino group, with respect the side chain, was established by bidimensional NMR experiments (HMQC, HMBC) of isomer **12**. Hydrogenolysis of **12/13** gave the 2-amino derivatives **14** and **15** that were also separated by chromatographic techniques.

The same amino derivatives **14/15** were prepared through substitution from the halo-NQ **8** and the 9:1 mixture **5/6**. The halogen atoms were substituted with sodium azide.[13] The progress of the reaction was followed by the characteristic IR azide absorption at $2100\,cm^{-1}$, although the crude product was generally used without purification for the hydrogenolysis, to obtain the amino-NQs **14/15** in acceptable yields. In the case of the mixture **5/6**, the reaction product was considerably enriched in the regioisomer **15**, which has the side chain at the same position (C-7) as **5**. This fact seems to indicate that the reaction goes by the substitution of the chlorine and not by a possible addition–elimination process. Treatment of **14/15** with acetic anhydride in sulphuric acid gave the acetamides **16** and **17**.

Once the 2-amino derivatives were obtained, we prepared several alkyl- and arylamino-MTNQs by addition of primary or secondary amines to the NQs **1** and **2**. Thus, the addition of alkylamines to **1** and **2** was performed in ethanolic[16] or methanolic[17] solution at room temperature to produce derivatives **18**–**21** in variable yields (Scheme 3). Addition of various substituted ani-




**Scheme 1.** Synthesis of monoterpenylnaphthoquinones **1**–**9**.

lines was performed in methanol and required longer reaction times than the aliphatic amines. The 1,4-addition to the quinone moiety should lead to the corresponding amino-substituted naphthohydroquinones but they were spontaneously oxidized by molecular oxygen, to allow the regeneration of the quinone final products **18**–**21**.

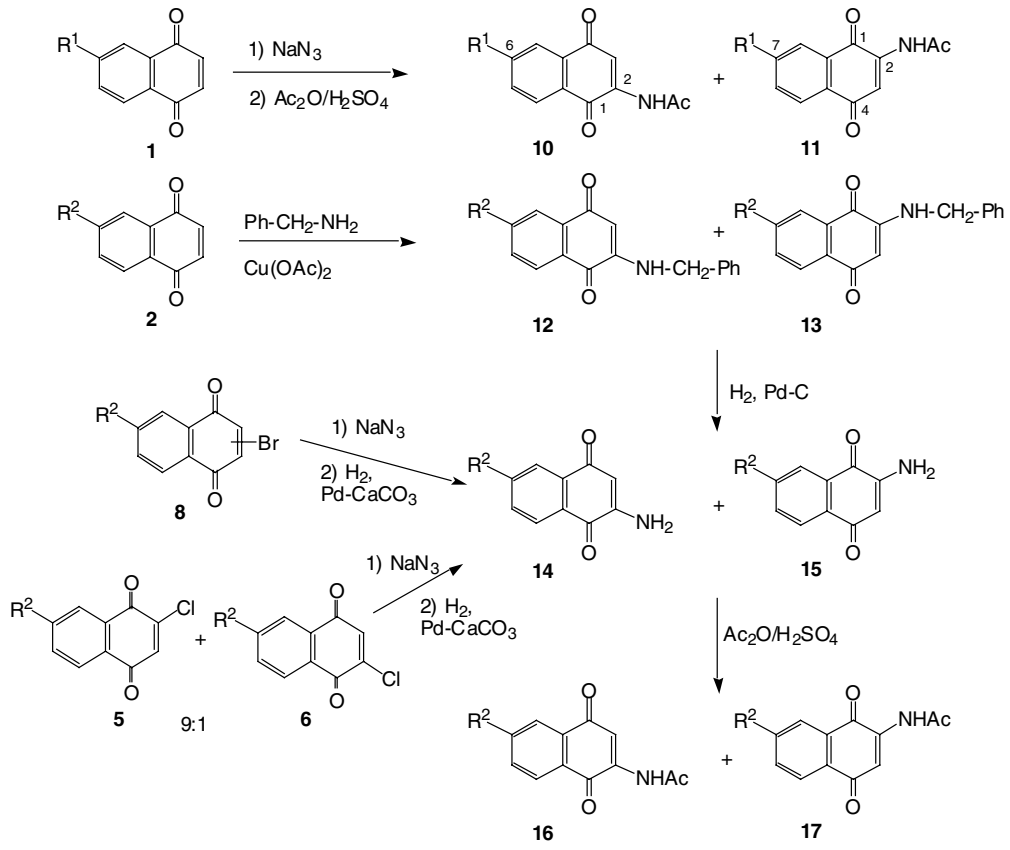
We also prepared 2,3-substituted MTNQs starting from the dibromoderivative **9**. Treatment of **9** with 4-methoxyaniline gave a reaction product in which only a bromine atom was substituted by the aniline, yielding a 1:1 mixture of **22**/**23**, which was resolved by column chromatography.

As the starting MTNQs are asymmetrically substituted, all the reaction products are mixtures of the two regioisomers in a 1:1 ratio, although they were separated by column chromatography in quantities sufficient to permit their spectroscopic characterization and biological evaluation. In fact, for compounds **18h**, **19h**, **20a**, **21a**, **22** and **23** bidimensional NMR experiments were performed in order not only to assign unequivocally all the signals in the spectra, but also to define the position (6 or 7) for the side chain in each isomer. In those experiments, we found that small differences were observed in the benzenoid ring between the chemical shifts due to each isomer, especially for the carbon supporting the side chain (C-6 or C-7) and for the adjacent proton (H-7 or H-6). Thus, $\delta$ for C-6 in the 6-alkyl regioisomers **18** and **20** were greater than those corresponding to C-7 in the 7-alkyl isomers **19** and **21** and the opposite happened with $\delta$ for H-7 and H-6. These differences were consistent across all the MTNQs synthesized, the 6-isomer always being eluted first in the CC separations. These facts allowed the correct identification of both regioisomers.

### 2.2. Biological evaluation

Most of the compounds prepared were evaluated in vitro to establish their cytotoxicity against a panel of ten human tumor cell lines representing diverse tissues and organs such as prostate, ovary, breast, melanoma, lung, leukemia, pancreas, colon and cervix.

The cell lines used are the following: DU-145 prostate carcinoma tumour cells, IGROV ovarian cells, SK-BR-3 breast adenocarcinoma, MEL-28 malignant melanoma, A-549 lung carcinoma NSCL, K-562 chronic




**Scheme 2.** Preparation of 6(7)-alkyl-2-amino-1,4-naphthoquinones **10**–**17**.

myelogenous leukemia, PANC-1 pancreatic epitheloid carcinoma, HT-29 colon adenocarcinoma, LoVo-Dox colon adenocarcinoma resistant to Doxorubicin and HeLa cervix epitheloid carcinoma. A conventional colourimetric assay[18] was set up to estimate $GI_{50}$ values, that is, the drug concentration that causes 50% cell growth inhibition after 72 h continuous exposure to the test molecules. The results obtained are shown in Table 1 expressed in μM. From the data some general observations can be made.

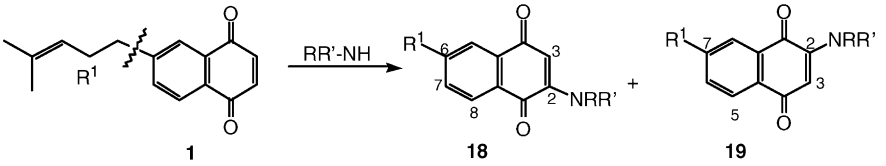
Hydrogenation of the terpenic side chain led to less potent compounds in general (i.e., **2** vs **1**, **20d** vs **18d**) although the presence of an additional substituent at position C-2 had variable effects depending on the regioisomer in question. While for the 6-alkyl isomer, the difference in potency is low (**20d** vs **18d**), for the 7-alkyl isomers **19** and **20**, the saturation of the side chain led to compounds significantly less potent, as can be seen by comparing **21d** and **21e** versus **19d** and **19e**.

The presence of a bromine or chlorine atoms in the quinonic ring has little effect on the potency (**3** and **8** vs **1** and **2**) but the presence of two bromine atoms or a bromine and other substituent, as in **9** and **22**, gives compounds, which are nearly inactive.

Regarding the 2-amino-1,4-NQs, the observed cytotoxicity depends considerably upon the substituent on the nitrogen atom. A free amino group (**14** and **15**) led to compounds much less potent than the parent quinone; but the cytotoxicity was recovered when the acetamide **11** is considered.

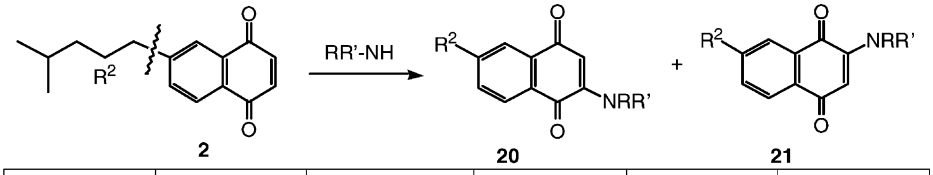
A significant decrease in cytotoxicity was observed for the 2-alkylamino-1,4-naphthoquinones, with no significant differences between secondary and tertiary amines (**18a**–**c** to **21a**–**c** vs **1** and **2**). However the presence of an aromatic ring attached to the 2-amino group led to the most potent compounds of these series. A notable increase in potency was observed with respect to the parent quinones, especially in those compounds retaining the double bond in the side chain (**18d**–**i** vs **1**). These results correlate quite well with the redox potential of some representative derivatives[19] (**1**, **2**, **18e** and **20b**) in the sense that the half-wave redox potential for those naphthoquinones was parallel (**1** > **2** > **18e** > **20b**) to their cytotoxic potency. Additional studies with the rates of oxygen consumption or ferricytochrome c reduction[19] were consistent with a redox cycling mechanism or possible interference of mitochondrial respiration as reported for other naphthoquinone derivatives.[8,20]

It is worth mentioning that the substituent on the aniline ring was important not only for the cytotoxicity, but also for the selectivity. Within the limited number of compounds tested, those having oxygenated functions were the most potent compounds and showed a signifi-



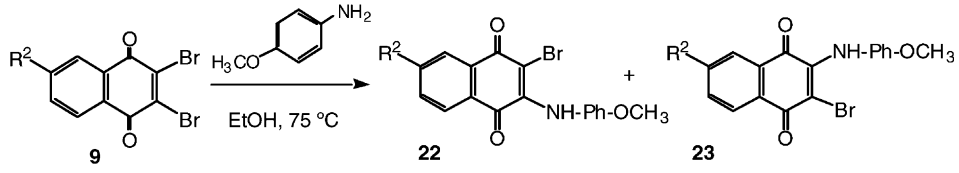

| Method | R | R' | Products | Time | Yield |
|---|---|---|---|---|---|
| A | H | $-C^{(1')}H_2-C^{(2')}H_3$ | **18a + 19a** | 4 h | 54 |
| A | H | $-(CH_2)_5-CH_3$ | **18b + 19b** | 6.5 h | 37 |
| B | $-CH_2-CH_2-CH_2-CH_2-$ | | **18c + 19c** | 1.5 h | 25 |
| B | H | Ph | **18d + 19d** | 4 d | 62 |
| B | H | *p*-$CH_3$-Ph | **18e + 19e** | 1 d | 69 |
| B | H | *p*-OH-Ph | **18f + 19f** | 5 d | 61 |
| * | H | *p*-OAc-Ph | **18g + 19g** | | |
| B | H | *p*-$CH_3O$-Ph | **18h + 19h** | 2.5 d | 72 |
| B | H | 3,4,5-$CH_3O$-Ph | **18i + 19i** | 5 d | 61 |

Method A: EtOH, pyridine, rt; Method B: MeOH, rt; * Acetylation ($Ac_2O$, Py) of **18f + 19f**




| Method | R | R' | Products | Time | Yield |
|---|---|---|---|---|---|
| A | H | $-CH_2-CH_3$ | **20a + 21a** | 4 h | 40 |
| A | H | $-(CH_2)_5-CH_3$ | **20b + 21b** | 6.5 h | 34 |
| A | $-CH_2-CH_2-CH_2-CH_2-$ | | **20c + 21c** | 2 h | 88 |
| B | $-CH_2-CH_2-CH_2-CH_2-$ | | **20c + 21c** | 1 h | 23 |
| B | H | Ph | **20d + 21d** | 8 d | 58 |
| B | H | *p*-$CH_3$-Ph | **20e + 21e** | 4 d | 49 |
| B | H | *p*-OH-Ph | **20f + 21f** | 1 d | 61 |
| * | H | *p*-OAc-Ph | **20g + 21g** | | |

Method A: EtOH, pyridine, rt; Method B: MeOH, rt; * Acetylation ($Ac_2O$, Py) of **20f + 21f**




**Scheme 3.** Preparation of 6(7)-alkyl-2-aminoalkyl(aryl)-1,4-naphthoquinones **18**–**23**.

cant selectivity against colon and cervix cell lines (**19f** and **18g** vs **1**) with $GI_{50}$ values under the μM level.

In summary, we have prepared 6(7)-alkyl-1,4-naphthoquinones by cycloaddition reactions between the monoterpene α-myrcene and *p*-benzoquinones, and we have introduced halogen and nitrogen-containing functions at the C-2 position of the naphthoquinone ring through nucleophilic processes, either addition or substitution reactions. These substituents at positions 2/3 of the NQ clearly influence the cytotoxic potency of these types of compounds.

In this sense and from the biological results reported here, it can be stated that, whereas substitution by bromine, chlorine, amino or alkylamino residues tends to decrease the cytotoxicity of these quinones, substitution by arylamino and particularly *p*-oxyarylamino groups contributes considerably to an enhancement of their bioactivity and selectivity. In addition, it should be mentioned that several of the less cytotoxic derivatives reported here have shown promising results, which will be published shortly, in preliminary assays against *Toxoplasma gondii*.

## 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 50.3 for $^{13}C$ in deuterochloroform using TMS as internal reference, on a Bruker WP 200 SY. Chemical shift values are expressed in ppm followed by multiplicity and coupling constants

**Table 1.** Cytotoxicity data ($GI_{50}$ in μM) for NQs **1**–**22**

| No. | DU-145 | IGROV | SK-BR3 | SKMEL-28 | A549 | K-562 | PANC1 | HT-29 | LOVO-DO | HELA |
|---|---|---|---|---|---|---|---|---|---|---|
| **1** | 7.2 | 4.3 | 7.0 | 5.8 | 10.1 | 9.0 | 5.7 | 6.4 | 4.0 | 4.0 |
| **2** | 11.4 | 7.2 | >12.4 | 12.4 | >12.4 | >12.4 | 7.5 | >12.4 | 8.0 | 8.2 |
| **3** | 10.2 | 3.7 | >10.9 | 8.4 | >10.9 | >10.9 | 5.5 | 10.9 | 6.4 | 10.9 |
| **8** | 7.2 | 7.0 | 6.9 | 5.2 | >9.3 | >9.3 | 8.4 | >9.3 | 7.8 | >9.3 |
| **9** | >7.5 | >7.5 | 6.3 | >7.5 | >7.5 | >7.5 | >7.5 | >7.5 | >7.5 | >7.5 |
| **11** | 6.2 | 4.8 | 8.4 | 6.4 | 9.7 | 5.8 | 5.5 | >10.1 | 3.9 | 4.0 |
| **12** | >8.6 | >8.6 | >8.6 | >8.6 | >8.6 | >8.6 | >8.6 | >8.6 | >8.6 | >8.6 |
| **13** | >8.6 | >8.6 | >8.6 | >8.6 | >8.6 | >8.6 | >8.6 | >8.6 | >8.6 | >8.6 |
| **14** | >11.7 | 7.7 | >11.7 | >11.7 | >11.7 | >11.7 | >11.7 | >11.7 | >11.7 | >11.7 |
| **15** | >11.7 | >11.7 | >11.7 | >11.7 | >11.7 | >11.7 | >11.7 | >11.7 | >11.7 | >11.7 |
| **18a** | >10.6 | >10.6 | >10.6 | >10.6 | >10.6 | >10.6 | >10.6 | >10.6 | >10.6 | 6.8 |
| **19a** | 10.3 | 5.5 | >10.6 | 4.4 | 7.8 | 1.9 | 6.1 | 2.9 | 2.6 | 1.8 |
| **18b** | >8.8 | >8.8 | 5.6 | 6.4 | >8.8 | >8.8 | >8.8 | >8.8 | 5.0 | 5.2 |
| **19b** | >8.8 | >8.8 | >8.8 | >8.8 | >8.8 | >8.8 | >8.8 | >8.8 | >8.8 | >8.8 |
| **18c** | >9.7 | >9.7 | >9.7 | >9.7 | >9.7 | >9.7 | >9.7 | >9.7 | >9.7 | >9.7 |
| **18d** | 4.0 | 2.2 | 1.2 | 1.9 | 2.2 | 1.7 | 3.5 | 2.1 | 1.3 | 0.95 |
| **19d** | 2.0 | 1.8 | 0.26 | 1.7 | 1.7 | 1.5 | 1.8 | 1.7 | 0.81 | 0.91 |
| **18e** | 2.7 | 2.0 | 1.4 | 2.0 | 2.1 | 2.0 | 2.2 | 1.9 | 1.3 | 1.2 |
| **19e** | 1.4 | 1.5 | 1.1 | 1.9 | 2.4 | 1.4 | 2.0 | 1.5 | 1.0 | 1.2 |
| **18f** | 0.20 | 0.20 | >8.6 | 0.23 | 0.35 | 0.17 | 0.19 | 2.5 | 0.16 | 0.14 |
| **19f** | 0.12 | 0.12 | 3.6 | 0.073 | 0.18 | 0.040 | 0.14 | 0.11 | 0.045 | 0.038 |
| **18g** | 0.20 | 0.17 | >7.7 | 0.17 | 7.7 | 0.15 | 0.17 | 2.4 | 0.10 | 0.098 |
| **19g** | 0.22 | 0.34 | 7.7 | 0.17 | 2.8 | 0.14 | 0.39 | 0.17 | 0.13 | 0.10 |
| **18h** | 0.35 | 0.21 | >8.3 | 0.22 | 0.81 | 0.21 | 0.50 | 0.28 | 0.20 | 0.15 |
| **19h** | 0.49 | 0.50 | 4.9 | 0.60 | 2.4 | 0.31 | 0.71 | 0.48 | 0.28 | 0.38 |
| **18i** | 0.29 | 0.34 | 0.33 | 1.3 | 1.3 | 1.2 | 1.4 | 1.1 | 0.52 | 0.72 |
| **19i** | 0.96 | 1.1 | 0.36 | 0.56 | 1.1 | 0.78 | 1.2 | 0.81 | 0.38 | 0.42 |
| **20a** | >10.5 | >10.5 | 9.9 | 7.1 | >10.5 | 9.7 | >10.5 | >10.5 | 4.1 | 4.1 |
| **20b** | >8.8 | >8.8 | >8.8 | >8.8 | >8.8 | >8.8 | >8.8 | >8.8 | >8.8 | >8.8 |
| **21b** | >8.8 | >8.8 | 6.5 | >8.8 | >8.8 | >8.8 | >8.8 | >8.8 | >8.8 | 5.1 |
| **20c** | >9.6 | >9.6 | >9.6 | >9.6 | >9.6 | >9.6 | >9.6 | >9.6 | >9.6 | >9.6 |
| **20d** | 5.1 | 4.6 | >9.0 | 4.3 | 7.5 | 2.9 | 5.1 | 2.1 | 3.4 | 3.0 |
| **21d** | >9.0 | >9.0 | >9.0 | >9.0 | >9.0 | >9.0 | >9.0 | >9.0 | >9.0 | >9.0 |
| **20e** | 4.1 | 3.8 | 1.4 | 1.9 | 3.2 | 2.4 | 3.8 | 3.5 | 1.6 | 1.6 |
| **21e** | >8.6 | >8.6 | >8.6 | >8.6 | >8.6 | >8.6 | >8.6 | >8.6 | >8.6 | >8.6 |
| **21f** | 0.46 | 0.43 | 0.31 | 0.48 | 0.52 | 0.61 | 0.53 | 0.49 | 0.18 | 0.21 |
| **20g** | 4.0 | 3.5 | >7.7 | 1.7 | 7.2 | 1.5 | 2.6 | 5.9 | 1.3 | 1.1 |
| **21g** | 3.8 | 3.5 | 1.5 | 1.9 | 3.9 | 3.4 | 3.3 | 3.6 | >7.7 | 1.3 |
| **22** | >6.8 | >6.8 | >6.8 | >6.8 | >6.8 | >6.8 | >6.8 | >6.8 | >6.8 | >6.8 |

(*J*) in Hz. Column chromatography (CC) was performed on silica gel (Merck No 9385). HRMS were runned in a VG TS-250 spectrometer working at 70 eV. TLC were carried out on silica gel 60 $F_{245}$ (Merck, 0.25 mm thick). Solvents and reagents were purified by standard procedures as necessary.

**3.1.1. [1,4]-Naphthoquinones 1–6.** Compounds **1**–**6** were obtained followed the procedures described before.[10]

**3.1.2. 2-Bromo-6(7)-(4-methylpentyl)-[1,4]-naphthoquinone 8.** Naphthoquinone **2** (280 mg, 1.16 mmol) was dissolved in 2 mL of a solution of bromine in acetic acid (previously prepared with 1 mL of bromine in 33 mL of acetic acid). It was stirred under a nitrogen atmosphere in the dark for 20 min. The reaction mixture was poured onto crushed ice and the whole was stirred for 10 min. The mixture was extracted with ethyl acetate, washed with brine, dried, filtered and evaporated in vacuum to afford **7**. $^1$H NMR Table 2. $^{13}$C NMR Table 3. HRMS (FAB-POSI, M + 1) calcd, 402.9731, found 402.9723.

The crude product **7** was dissolved in EtOH and a small amount of $NaHCO_3$ was added. The mixture was stirred with heating at 80 °C for 4 h, then it was poured into ice-water and extracted with ethyl acetate. The organic layer was washed with brine, dried, filtered and evaporated off to give the bromo derivatives **8** (99%). IR: 3060, 1680, 1660, 1590, 1570, 1050, 800 $cm^{-1}$. $^1$H NMR Table 2 $^{13}$C NMR Table 3. HRMS (FAB-POSI, M + 1) calcd, 321.0490, found 321.0517.

**3.1.3. 2,3-Dibromo-6-(4-methylpentyl)-[1,4]-naphthoquinone 9.** In the presence of hydrogen bromide in acetic acid: The crude product **7** (256 mg, 0.64 mmol) was dissolved in acetic acid (3 mL) and a solution of 33% hydrogen bromide in acetic acid (0.60 mL, 3.31 mmol) was added, under an inert atmosphere. The mixture was refluxed for 5 h, then poured on ice-water, slowly basified with aq satd $NaHCO_3$ and extracted with ether. The combined organic layers were washed with brine, dried, filtered and evaporated off and the product purified by column chromatography (CC) yielding **9** (40 mg, 16%) (eluent: hexane/dichloromethane 7:3). IR:

**Table 2.** $^1$H NMR ($CDCl_3$–TMS, $\delta$ ppm, ($J$ Hz)) data for NQs **1**–**23**

| H | **1** | **2** | **3** | **4** | **5** | **6** | **7** |
|---|---|---|---|---|---|---|---|
| 2 | 6.93 s | 6.93 s | — | — | — | — | 4.97 s |
| 3 | 6.93 s | 6.93 s | 7.17 s | 7.19 s | 7.18 s | 7.18 s | 4.97 s |
| 5 | 7.87 d (1.8) | 7.88 d (1.6) | 7.97 d (8.0) | 7.89 d (1.8) | 8.04 d (8.0) | 7.92 d (1.8) | 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) | 7.54 dd (7.6; 1.6) | — | 7.58 dd (8.0; 1.8) | — | 7.56 dd (8.0; 1.8) | 7.66 dd (8.0; 1.8) |
| 8 | 7.97 d (8.0) | 7.98 d (7.6) | 7.96 d (1.8) | 8.08 d (8.0) | 7.85 d (1.8) | 7.96 d (8.0) | 8.04 d (8.0) |
| 1′ | 2.76 t (7.3) | 2.73 t (7.6) | 2.78 t (7.2) | 2.78 t (7.3) | 2.71 t (7.2) | 2.71 t (7.3) | 2.76 t (7.7) |
| 2′ | 2.30 m | 1.67 m | 2.34 m | 2.35 m | 1.69 m | 1.69 m | 1.69 m |
| 3′ | 5.09 m | 1.23 m | 5.11 m | 5.12 m | 1.22 m | 1.22 m | 1.25 m |
| 4′ | — | 1.57 m | — | — | 1.60 m | 1.60 m | 1.59 m |
| 5′ | 1.66 s | 0.88 d (6.8) | 1.66 s | 1.67 s | 0.86 d (6.6) | 0.86 d (6.6) | 0.85 d (6.6) |
| 6′ | 1.52 s | 0.88 d (6.8) | 1.52 s | 1.52 s | 0.86 d (6.6) | 0.86 d (6.6) | 0.85 d (6.6) |
| Others | | | | | | | |

| H | **9** | **12** | **13** | **14** | **15** | **16** | **17** |
|---|---|---|---|---|---|---|---|
| 2 | | | | | | | |
| 3 | — | 5.76 s | 5.75 s | 5.96 s | 5.96 s | 7.80 s | 7.80 s |
| 5 | 7.90 d (1.8) | 7.91 d (1.7) | 7.99 d (7.9) | 7.88 d (1.8) | 7.97 d (7.8) | 7.88 d (1.8) | 7.99 d (7.8) |
| 6 | — | — | 7.52 dd (7.9; 1.8) | — | 7.52 dd (7.8; 1.8) | — | 7.50 dd (7.8; 1.8) |
| 7 | 7.51 dd (7.9; 1.8) | 7.42 dd (7.8; 1.7) | — | 7.43 dd (7.7; 1.8) | — | 7.56 dd (7.8; 1.8) | — |
| 8 | 8.02 d (7.9) | 7.97 d (7.8) | 7.86 d (1.8) | 7.96 d (7.7) | 7.85 d (1.8) | 7.99 d (7.8) | 7.88 d (1.8) |
| 1′ | 2.69 t (7.7) | 2.70 t (7.8) | 2.69 t (7.7) | 2.70 t (7.8) | 2.69 t (7.7) | 2.71 t (7.7) | 2.71 t (7.7) |
| 2′ | 1.64 m | 1.65 m | 1.66 m | 1.65 m | 1.65 m | 1.69 m | 1.69 m |
| 3′ | 1.21 m | 1.23 m | 1.24 m | 1.23 m | 1.24 m | 1.22 m | 1.22 m |
| 4′ | 1.51 m | 1.56 m | 1.55 m | 1.53 m | 1.55 m | 1.57 m | 1.57 m |
| 5′ | 0.85 d (6.6) | 0.88 d (6.6) | 0.87 d (6.6) | 0.86 d (6.6) | 0.87 d (6.6) | 0.87 d (6.6) | 0.86 d (6.6) |
| 6′ | 0.85 d (6.6) | 0.88 d (6.6) | 0.87 d (6.6) | 0.86 d (6.6) | 0.87 d (6.6) | 0.87 d (6.6) | 0.86 d (6.6) |
| Others | | 4.38 d (5.7)<br>7.30–7.37 m | 4.37 d (5.9)<br>7.30–7.37 m | | | 2.28 s | 2.28 s |

| H | **18a** | **19a** | **18b** | **19b** | **18c** | **19c** | **18d** |
|---|---|---|---|---|---|---|---|
| 2 | | | | | | | |
| 3 | 5.67 s | 5.67 s | 5.67 s | 5.67 s | 5.71 s | 5.68 s | 6.39 s |
| 5 | 7.90 sa | 7.98 d (7.7) | 7.91 d (1.8) | 7.97 d (8.0) | 7.88 d (1.8) | 7.93 d (8.0) | 7.98 d (1.8) |
| 6 | — | 7.50 dd (7.7; 1.8) | — | 7.49 dd (8.0; 1.8) | — | 7.47 dd (8.0; 1.8) | — |
| 7 | 7.38 dd (7.8; 1.8) | — | 7.38 dd (7.8; 1.8) | — | 7.39 dd (7.8; 1.8) | — | 7.44 dd (8.0; 1.8) |
| 8 | 7.92 d (7.8) | 7.83 d (1.8) | 7.93 d (7.8) | 7.82 d (1.8) | 7.90 d (7.8) | 7.79 d (1.8) | 8.00 d (8.0) |
| 1′ | 2.72 t (7.7) | 2.71 t (7.7) | 2.73 t (7.7) | 2.71 t (7.5) | 2.73 t (7.3) | 2.71 t (7.3) | 2.75 t (7.5) |
| 2′ | 2.31 m | 2.31 m | 2.31 m | 2.30 m | 2.32 m | 2.31 m | 2.34 m |
| 3′ | 5.10 m | 5.11 m | 5.11 m | 5.10 m | 5.12 m | 5.12 m | 5.12 m |
| 4′ | — | — | — | — | — | — | — |
| 5′ | 1.65 s | 1.66 m | 1.64 s | 1.65 s | 1.66 s | 1.65 s | 1.67 s |
| 6′ | 1.51 s | 1.51 s | 1.50 s | 1.51 s | 1.52 s | 1.51 s | 1.54 s |
| Others | 3.19 m 1.31 t (7.3) | 3.20 m 1.32 t (7.3) | 3.15 c (6.6)<br>1.29–1.64 m (8H)<br>0.87 t (6.3, 3H) | 3.14 c (6.6)<br>1.32–1.64 m (8H)<br>0.88 t (6.4) | 1.98 m<br>3.2–4.0 m | 1.98 m<br>3.2–4.0 m | 7.15–7.44 m |

| H | **19d** | **18e** | **19e** | **18f** | **19f** | **18g** | **19g** |
|---|---|---|---|---|---|---|---|
| 3 | 6.39 s | 6.33 s | 6.33 s | 6.16 s | 6.13 s | 6.34 s | 6.34 s |
| 5 | 7.99 d (7.8) | 7.92 d (1.8) | 8.00 d (8.0) | 7.94 d (1.8) | 8.02 d (7.8) | 7.92 d (1.8) | 8.00 d (8.0) |
| 6 | 7.55 dd (7.8; 1.8) | — | 7.55 dd (8.0; 1.8) | — | 7.56 dd (7.8; 1.8) | — | 7.56 dd (8.0; 1.8) |
| 7 | — | 7.45 dd (7.8; 1.8) | — | 7.46 dd (8.0; 1.8) | — | 7.46 dd (7.8; 1.8) | — |
| 8 | 7.92 d (1.8) | 8.01 d (7.8) | 7.92 d (1.8) | 8.02 d (8.0) | 7.92 d (1.8) | 8.02 d (7.8) | 7.92 d (1.8) |
| 1′ | 2.75 t (7.7) | 2.76 t (7.6) | 2.76 t (7.3) | 2.77 t (7.3) | 2.76 t (7.3) | 2.56 t (7.3) | 2.77 t (7.3) |
| 2′ | 2.34 m | 2.34 m | 2.32 m | 2.35 m | 2.35 m | 2.35 m | 2.35 m |
| 3′ | 5.14 m | 5.13 m | 5.14 m | 5.13 m | 5.14 m | 5.12 m | 5.14 m |
| 4’ | — | — | — | — | — | — | — |
| 5′ | 1.67 s | 1.67 s | 1.68 s | 1.68 s | 1.69 s | 1.67 s | 1.68 s |
| 6′ | 1.54 s | 1.54 s | 1.54 s | 1.54 s | 1.54 s | 1.53 s | 1.54 s |
| Others | 7.19–7.44 m | 7.19 d (8.8) | 7.19 d (8.8) | 7.11 d (8.6) | 7.07 d (8.8) | 7.29 d (8.9) | 7.28 d (8.9) |

(*continued on next page*)

**Table 2** (*continued*)

| H | 19d | 18e | 19e | 18f | 19f | 18g | 19g |
|---|---|---|---|---|---|---|---|
| | | 7.17 d (8.8)<br>2.36 s | 7.15 d (8.8)<br>2.36 s | 6.89 d (8.6) | 6.89 d (8.8) | 7.15 d (8.9)<br>2.32 s | 7.15 d (8.9)<br>2.32 s |
| H | 18h | 19h | 18i | 19i | 20a | 21a | 20b |
| 3 | 6.20 s | 6.20 s | 6.32 s | 6.32 s | 5.68 s | 5.69 s | 5.67 s |
| 5 | 7.92 d (1.6) | 7.80 d (7.8) | 7.92 d (1.5) | 8.00 d (7.7) | 7.89 d (1.8) | 8.00 d (8.0) | 7.87 sa |
| 6 | — | 7.54 dd (7.8; 1.6) | — | 7.55 dd (7.7; 1.5) | — | 7.52 dd (8.0; 1.8) | — |
| 7 | 7.44 dd (7.8; 1.6) | — | 7.46 dd (8.0; 1.5) | — | 7.38 dd (7.8; 1.8) | — | 7.36 dd (7.8; 1.8) |
| 8 | 8.01 d (7.8) | 7.92 d (1.6) | 8.01 d (8.0) | 7.92 d (1.5) | 7.93 d (7.8) | 7.84 d (1.8) | 7.91 d (7.8) |
| 1′ | 2.76 t (7.5) | 2.76 t (7.5) | 2.76 t (7.3) | 2.76 t (7.7) | 2.68 t (7.8) | 2.69 t (7.7) | 2.66 t (7.7) |
| 2′ | 2.34 m | 2.35 m | 2.33 m | 2.34 m | 1.64 m | 1.66 m | 1.61 m |
| 3′ | 5.13 m | 5.14 m | 5.13 m | 5.13 m | 1.22 m | 1.24 m | 1.21 m |
| 4’ | — | — | — | — | 1.54 m | 1.53 m | 1.55 m |
| 5′ | 1.67 s | 1.68 s | 1.67 s | 1.68 s | 0.85 d (6.6) | 0.87 d (6.6) | 0.84 d (6.6) |
| 6′ | 1.54 s | 1.54 s | 1.53 s | 1.53 s | 0.85 d (6.6) | 0.87 d (6.6) | 0.84 d (6.6) |
| Others | 7.19 d (8.8)<br>6.94 d (8.8)<br><br>3.83 s | 7.19 d (8.8)<br>6.94 d (8.8)<br><br>3.83 s | 6.49 s<br>3.85 s<br><br>3.87 s | 6.49 s<br>3.85 s<br><br>3.87 s | 3.19 m<br>1.31 t (7.3) | 3.22 m<br>1.33 t (7.3) | 3.13 c (6.7)<br>1.29–1.65 m (8H)<br>0.87 t (6.2) |
| H | 21b | 20c | 21c | 20d | 21d | 20e | 21e |
| 3 | 5.68 s | 5.71 s | 5.70 s | 6.38 s | 6.40 s | 6.32 s | 6.31 s |
| 5 | 7.99 d (7.8) | 7.87 d (1.8) | 7.96 d (8.0) | 7.89 d (1.8) | 8.01 d (8.0) | 7.90 d (1.8) | 7.99 d (7.8) |
| 6 | 7.51 dd (7.8; 1.8) | — | 7.49 dd (8.0; 1.8) | — | 7.55 dd (8.0; 1.8) | — | 7.54 dd (7.8; 1.8) |
| 7 | — | 7.38 dd (8.0; 1.8) | — | 7.42 dd (7.8; 1.8) | — | 7.44 dd (7.7; 1.8) | — |
| 8 | 7.82 d (1.8) | 7.91 d (8.0) | 7.80 d (1.8) | 7.98 d (7.8) | 7.91 d (1.8) | 8.00 d (7.7) | 7.90 d (1.8) |
| 1′ | 2.67 t (7.7) | 2.68 t (7.7) | 2.68 t (7.7) | 2.69 t (7.7) | 2.72 t (7.7) | 2.70 t (7.7) | 2.70 t (7.7) |
| 2′ | 1.61 m | 1.65 m | 1.67 m | 1.64 m | 1.66 m | 1.66 m | 1.66 m |
| 3′ | 1.20 m | 1.22 m | 1.22 m | 1.22 m | 1.22 m | 1.24 m | 1.25 m |
| 4′ | 1.55 m | 1.54 m | 1.53 m | 1.53 s | 1.52 s | 1.54 m | 1.55 m |
| 5′ | 0.86 d (6.6) | 0.86 d (6.6) | 0.87 d (6.6) | 0.86 d (6.6) | 0.89 d (6.6) | 0.87 d (6.6) | 0.88 d (6.6) |
| 6′ | 0.86 d (6.6) | 0.86 d (6.6) | 0.87 d (6.6) | 0.86 d (6.6) | 0.89 d (6.6) | 0.87 d (6.6) | 0.88 d (6.6) |
| Others | 3.15 c (6.9)<br>1.29 –1.65 m (8H)<br>0.87 m | 1.98 m<br>3.2–4.0 m | 1.99 m<br>3.2–4.0 m | 7.14–7.43 m | 7.16–7.45 m | 7.20 d (8.4)<br>7.14 d (8.4)<br>2.35 s | 7.21 d (8.6)<br>7.14 d (8.6)<br>2.35 s |

| H | 20f | 21f | 20g | 21g | 22 | 23 | H | 8 | 10/11 |
|---|---|---|---|---|---|---|---|---|---|
| 3 | 5.99 s | 6.14 s | 6.34 s | 6.34 s | — | — | 3 | 7.36 s | 7.75 s |
| 5 | 7.83 sa | 8.03 d (8.0) | 7.91 d (1.8) | 8.00 d (7.8) | 7.99 d (1.6) | 8.09 d (7.9) | 5/8 | 8.08/7.99 d (7.7) | 7.95/7.92 d (7.8) |
| 6 | — | 7.57 dd (8.0; 1.8) | — | 7.56 dd (7.8; 1.6) | — | 7.54 dd (7.9; 1.7) | 6/7 | 7.60/7.56 dd (7.7; 1.8) | 7.51/7.44 dd (7.8; 1.8) |
| 7 | 7.58 d (7.8) | — | 7.46 dd (7.8; 1.8) | — | 7.47 dd (7.9; 1.6) | — | | | |
| 8 | 7.99 d (7.8) | 7.92 d (1.8) | 8.02 d (7.8) | 7.92 d (1.6) | 8.01 d (7.9) | 7.90 d (1.7) | 8/5 | 7.97/7.88 d (1.8) | 7.83/7.82 d (1.8) |
| 1′ | 2.77 t (7.7) | 2.76 t (7.7) | 2.71 t (7.8) | 2.72 t (7.8) | 2.73 t (7.7) | 2.72 t (7.7) | 1′ | 2.74 t (7.3) | 2.71 t (7.7) |
| 2′ | 1.69 m | 1.68 m | 1.65 m | 1.67 m | 1.67 m | 1.67 m | 2′ | 1.66 m | 2.28 m |
| 3′ | 1.25 m | 1.27 m | 1.22 m | 1.24 m | 1.25 m | 1.24 m | 3′ | 1.21 m | 5.07 t (7.3) |
| 4′ | 1.56 m | 1.55 m | 1.55 m | 1.54 s | 1.54 m | 1.57 s | 4′ | 1.57 m | — |
| 5′ | 0.87 d (6.5) | 0.89 d (6.6) | 0.87 d (6.6) | 0.88 d (6.6) | 0.88 d (6.6) | 0.89 d (6.6) | 5′ | 0.88 d (6.6) | 1.62 s |
| 6′ | 0.87 d (6.5) | 0.89 d (6.6) | 0.87 d (6.6) | 0.88 d (6.6) | 0.88 d (6.6) | 0.89 d (6.6) | 6′ | 0.88 d (6.6) | 1.48 s |
| Others | 7.25 d (8.7)<br>6.93 d (8.7) | 7.09 d (8.8)<br>6.90 d (8.8) | 7.28 d (8.9)<br>7.14 d (8.9)<br>2.31 s | 7.28 d (8.9)<br>7.15 d (8.9)<br>2.32 s | 7.06 d (8.8)<br>6.88 d (8.8)<br>3.83 s | 7.06 d (8.9)<br>6.88 d (8.9)<br>3.84 s | NHAc | | 2.25 s |

2953, 2867, 1681, 1599, 1580, 1076, 782 $cm^{-1}$. $^1H$ NMR: Table 2. $^{13}C$ NMR: Table 3. HRMS (FAB-POSI, M + 1) calcd 398.9595, found 398.9622.

In refluxed ethanol: A solution of **7** (425 mg, 1.06 mmol) in ethanol (20 mL) was heated under reflux for 2 h. The mixture was then cooled to room temperature and concentrated leading to a residue, which was redissolved in ethyl acetate and washed with aq satd $NaHCO_3$. The combined organic layers were washed with brine, dried, filtered and evaporated in vacuum affording **9** (363 mg, 86%).

**Table 3.** $^{13}C$ NMR ($CDCl_3$–TMS, $\delta$ ppm) data for NQs **1**–**23**

| C | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **9** | **12** | **13** | **14** | **15** | **16** | **17** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 184.7 | 184.8 | 178.1 | 177.9 | 177.6 | 177.7 | 183.6 | 175.6 | 181.5 | 182.2 | 181.7 | 182.3 | 180.8 | 181.4 |
| 2 | 138.5[a] | 138.4 | 146.0 | 146.5 | 146.0 | 146.4 | 46.1 | 142.3[a] | 147.8 | 147.9 | 148.5 | 148.1[a] | 139.9 | 139.9 |
| 3 | 138.7[a] | 138.7 | 135.9 | 135.8 | 135.9 | 135.8 | 46.1 | 142.7[a] | 101.5 | 101.7 | 104.9 | 105.1 | 117.0 | 117.2 |
| 4 | 185.2 | 185.3 | 182.5 | 183.1 | 182.6 | 183.1 | 186.8 | 176.1 | 183.5 | 183.3 | 184.3 | 184.1 | 185.7 | 185.3 |
| 4a | 132.0 | 131.8 | 129.7 | 131.8 | 129.7 | 131.8 | 130.3 | 130.7 | 133.5 | 131.5 | 133.4 | 131.3 | 132.2 | 130.1 |
| 5 | 126.1 | 126.1 | 127.3 | 126.7 | 127.3 | 126.5 | 127.7 | 128.0 | 126.1 | 126.2 | 126.1 | 126.1 | 126.2 | 126.5 |
| 6 | 149.4 | 150.0 | 134.6 | 150.3 | 134.6 | 150.9 | 151.8 | 150.9 | 151.1 | 134.9 | 151.0 | 134.8 | 151.5 | 135.1 |
| 7 | 134.0 | 133.9 | 149.7 | 134.4 | 150.4 | 134.2 | 135.5 | 134.6 | 132.1 | 147.9 | 132.4 | 148.3[a] | 133.4 | 149.3 |
| 8 | 126.5 | 126.6 | 126.8 | 127.7 | 127.0 | 127.8 | 128.4 | 128.5 | 126.6 | 126.5 | 126.6 | 126.4 | 127.0 | 126.6 |
| 8a | 130.1 | 129.1 | 131.1 | 129.3 | 131.3 | 129.2 | 129.8 | 128.7 | 128.4 | 130.5 | 128.5 | 130.5 | 127.9 | 129.9 |
| 1′ | 36.2 | 36.4 | 36.1 | 36.3 | 36.4 | 36.4 | 36.5 | 36.3 | 36.6 | 36.2 | 36.7 | 36.3 | 36.6 | 36.3 |
| 2′ | 29.2 | 28.7 | 29.2 | 29.3 | 28.8 | 28.8 | 28.7 | 28.7 | 28.7 | 28.9 | 28.9 | 28.9 | 28.8 | 28.8 |
| 3′ | 122.7 | 38.4 | 122.4 | 122.4 | 38.3 | 38.3 | 38.5 | 38.4 | 38.5 | 38.5 | 38.6 | 38.5 | 38.5 | 38.5 |
| 4′ | 133.0 | 27.8 | 133.2 | 133.4 | 27.9 | 27.9 | 27.8 | 27.8 | 27.8 | 27.9 | 27.9 | 27.9 | 27.9 | 27.9 |
| 5′ | 25.5 | 22.4 | 25.6 | 25.7 | 22.6 | 22.6 | 22.6 | 22.6 | 22.5 | 22.6 | 22.6 | 22.6 | 22.6 | 22.6 |
| 6′ | 17.6 | 22.4 | 17.6 | 17.7 | 22.6 | 22.6 | 22.6 | 22.6 | 22.5 | 22.6 | 22.6 | 22.6 | 22.6 | 22.6 |
| 1″ | | | | | | | | | 46.8 | 46.8 | | | | |
| 2″ | | | | | | | | | 135.9 | 136.0 | | | | |
| 3″ | | | | | | | | | 127.6 | 127.7 | | | | |
| 4″ | | | | | | | | | 129.0 | 129.1 | | | | |
| 5″ | | | | | | | | | 128.1 | 128.1 | | | | |
| 6″ | | | | | | | | | 129.0 | 129.1 | | | | |
| 7″ | | | | | | | | | 127.6 | 127.7 | | | | |
| NHAc | | | | | | | | | | | | | 169.5 | 169.5 |
| | | | | | | | | | | | | | 25.1 | 25.1 |

| C | **18a** | **19a** | **18b** | **19b** | **18c** | **19c** | **18d** | **19d** | **18e** | **19e** | **18f** | **19f** | **18g** | **19g** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 181.7 | 182.2 | 181.7 | 182.2 | 182.8 | 182.6 | 181.8 | 182.4 | 181.9 | 182.5 | 181.8 | 182.2 | 181.8 | 182.3 |
| 2 | 148.1 | 147.0 | 148.2 | 146.9 | 149.2 | 146.6 | 144.8 | 144.7 | 145.2 | 145.1 | 146.5 | 146.6 | 145.0 | 144.8 |
| 3 | 100.7 | 100.6 | 100.6 | 100.5 | 104.8 | 104.7 | 103.2 | 103.4 | 102.9 | 103.0 | 101.9 | 101.5 | 103.3 | 103.5 |
| 4 | 183.3 | 183.1 | 183.3 | 183.0 | 183.2 | 183.6 | 184.4 | 184.2 | 184.3 | 184.1 | 184.6 | 184.8 | 184.4 | 184.1 |
| 4a | 133.0 | 131.5 | 133.0 | 131.5 | 133.3 | 131.7 | 133.2[a] | 131.2 | 133.4 | 131.1 | 133.5 | 131.4 | 133.2 | 131.2 |
| 5 | 126.2 | 126.1 | 126.3 | 126.0 | 125.4 | 125.4 | 126.2 | 126.3 | 126.3 | 126.3 | 126.4 | 126.5 | 126.3 | 126.4 |
| 6 | 150.5 | 134.9 | 150.5 | 134.8 | 149.6 | 134.2 | 150.7 | 135.2 | 150.7 | 135.2 | 150.9 | 135.4 | 150.9 | 135.2 |
| 7 | 132.1 | 147.8 | 132.1 | 147.9 | 131.9 | 149.0 | 132.5 | 147.5 | 132.5 | 147.5 | 132.6 | 147.8 | 132.7 | 147.7 |
| 8 | 126.5 | 126.2 | 126.6 | 126.2 | 126.6 | 126.2 | 126.8 | 126.5 | 126.8 | 126.5 | 126.9 | 126.7 | 126.9 | 126.5 |
| 8a | 128.5 | 130.4 | 128.5 | 130.3 | 129.8 | 131.1 | 128.3 | 130.3 | 128.4 | 128.9 | 128.4 | 130.4 | 128.4 | 130.3 |
| 1′ | 36.5 | 35.9 | 36.5 | 35.9 | 36.4 | 36.0 | 36.5 | 36.1 | 36.6 | 36.1 | 36.6 | 36.1 | 36.6 | 36.1 |
| 2′ | 29.4 | 29.4 | 29.4 | 29.3 | 29.5 | 29.4 | 29.4 | 29.5 | 29.4 | 29.5 | 29.5 | 29.5 | 29.4 | 29.5 |
| 3′ | 122.9 | 122.7 | 122.8 | 122.7 | 123.0 | 122.8 | 122.7 | 122.7 | 122.7 | 122.7 | 122.8 | 122.7 | 122.8 | 122.7 |
| 4′ | 133.7 | 132.9 | 133.8 | 132.9 | 132.9 | 132.8 | 133.1[a] | 133.1 | 133.1 | 133.1 | 133.2 | 133.2 | 133.2 | 133.2 |
| 5′ | 25.7 | 25.6 | 25.7 | 25.5 | 25.7 | 25.6 | 25.7 | 25.7 | 25.7 | 25.7 | 25.8 | 25.8 | 25.7 | 25.8 |
| 6′ | 17.7 | 17.6 | 17.8 | 17.6 | 17.7 | 17.6 | 17.7 | 17.8 | 17.8 | 17.7 | 17.8 | 17.8 | 17.8 | 17.8 |
| 1″ | 37.3 | 37.2 | 42.7 | 42.5 | | | 137.6 | 137.6 | 135.6 | 135.6 | — | 129.0 | 135.2 | 135.2 |
| 2″ | 13.6 | 13.5 | 31.5 | 31.3 | 51.0 | 50.8 | 129.7 | 129.7 | 130.3 | 130.3 | 125.3 | 125.4 | 123. 8 | 123.7 |
| 3″ | | | 28.3 | 28.1 | 51.0 | 50.8 | 122.6 | 122.6 | 122.7 | 122.7 | 116.5 | 116.6 | 122.9 | 123.0 |
| 4″ | | | 26.8 | 26.6 | 51.0 | 50.8 | 125.5 | 125.5 | 134.9 | 134.9 | 154.5 | 155.1 | 148.0 | 148.0 |
| 5″ | | | 22.6 | 22.4 | 51.0 | 50.8 | 122.6 | 122.6 | 122.7 | 122.7 | 116.5 | 116.6 | 122.9 | 123.0 |
| 6″ | | | 14.1 | 13.9 | | | 129.7 | 129.7 | 130.3 | 130.3 | 125.3 | 125.4 | 123.8 | 123.7 |
| 7″ | | | | | | | | | 21.0 | 21.0 | | | | |
| NHAc | | | | | | | | | | | | | 169.5 | 169.4 |
| | | | | | | | | | | | | | 21.2 | 21.2 |

| C | **18h** | **19h** | **18i** | **19i** | **20a** | **21a** | **20b** | **21b** | **20c** | **21c** | **20d** | **21d** | **20e** | **21e** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 181.8 | 182.4 | 181.8 | 182.4 | 181.7 | 182.3 | 181.7 | 182.4 | 182.8 | 182.7 | 181.7 | 182.4 | 181.9 | 182.5 |
| 2 | 145.7 | 145.6 | 145.3 | 145.1 | 148.1 | 147.6 | 148.2 | 147.7 | 149.2 | 149.2 | 144.8 | 144.7 | 145.2 | 145.0 |
| 3 | 102.3 | 102.5 | 103.3 | 103.5 | 100.6 | 100.7 | 100.5 | 100.6 | 104.8 | 104.8 | 103.2 | 103.5 | 102.9 | 103.0 |
| 4 | 184.0 | 183.9 | 184.3 | 184.1 | 183.4 | 183.2 | 183.3 | 183.2 | 183.2 | 183.8 | 184.3 | 184.2 | 184.3 | 184.0 |
| 4a | 133.3 | 131.2 | 133.3 | 131.3 | 133.8 | 131.6 | 133.8 | 131.7 | 133.3 | 131.9 | 133.3 | 131.2 | 133.4 | 131.3 |
| 5 | 126.1 | 126.2 | 126.3 | 126.4 | 126.1 | 126.0 | 126.1 | 126.1 | 125.3 | 125.7 | 126.1 | 126.4 | 126.1 | 126.3 |
| 6 | 150.6 | 135.0 | 150.9 | 135.3 | 151.1 | 134.8 | 151.1 | 134.9 | 150.2 | 134.2 | 151.3 | 135.1 | 151.3 | 135.0 |
| 7 | 132.3 | 147.3 | 132.6 | 147.7 | 132.0 | 147.8 | 131.9 | 148.0 | 131.8 | 147.4 | 132.4 | 148.2 | 132.3 | 148.1 |
| 8 | 126.6 | 126.3 | 126.8 | 126.4 | 126.6 | 126.4 | 126.6 | 126.4 | 126.7 | 126.2 | 126.9 | 126.4 | 126.9 | 126.3 |
| 8a | 128.3 | 130.3 | 128.3 | 130.3 | 128.4 | 130.5 | 128.5 | 130.6 | 129.8 | 131.2 | 128.3 | 130.4 | 128.3 | 130.2 |

(*continued on next page*)

**Table 3** (*continued*)

| C | 18h | 19h | 18i | 19i | 20a | 21a | 20b | 21b | 20c | 21c | 20d | 21d | 20e | 21e |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1′ | 36.5 | 35.9 | 36.6 | 36.1 | 36.7 | 36.1 | 36.7 | 36.2 | 36.6 | 36.3 | 36.6 | 36.2 | 36.7 | 36.2 |
| 2′ | 29.4 | 29.4 | 29.4 | 29.5 | 28.8 | 28.8 | 28.8 | 28.9 | 28.9 | 29.0 | 28.8 | 28.9 | 28.8 | 28.9 |
| 3′ | 122.7 | 122.7 | 122.7 | 122.7 | 38.6 | 38.4 | 38.6 | 38.5 | 38.6 | 38.6 | 38.5 | 38.5 | 38.6 | 38.5 |
| 4′ | 132.9 | 133.0 | 133.1 | 133.4 | 27.9 | 27.8 | 27.9 | 27.9 | 27.9 | 27.9 | 27.8 | 27.9 | 27.9 | 27.9 |
| 5′ | 25.6 | 25.6 | 25.7 | 25.7 | 22.6 | 22.5 | 22.6 | 22.6 | 22.6 | 22.6 | 22.6 | 22.6 | 22.6 | 22.6 |
| 6′ | 17.6 | 17.6 | 17.8 | 17.8 | 22.6 | 22.5 | 22.6 | 22.6 | 22.6 | 22.6 | 22.6 | 22.6 | 22.6 | 22.6 |
| 1″ | 130.1 | 130.1 | 136.1 | 136.1 | 37.3 | 37.3 | 42.6 | 42.7 | | | 137.6 | 137.7 | 135.5 | 135.5 |
| 2″ | 124.7 | 124.7 | 100.8 | 100.8 | 13.6 | 13.5 | 31.4 | 31.5 | 51.0 | 51.0 | 129.7 | 129.7 | 130.2 | 130.2 |
| 3″ | 114.8 | 114.9 | 154.0 | 154.0 | | | 28.2 | 28.3 | 51.0 | 51.0 | 122.6 | 122.6 | 122.7 | 122.7 |
| 4″ | 157.6 | 157.6 | 133.3 | 133.3 | | | 26.7 | 26.8 | 51.0 | 51.0 | 125.5 | 125.5 | 134.9 | 135.0 |
| 5″ | 114.8 | 114.9 | 154.0 | 154.0 | | | — | — | 51.0 | 51.0 | 122.6 | 122.6 | 122.7 | 122.7 |
| 6″ | 124.7 | 124.7 | 100.8 | 100.8 | | | 14.0 | 14.1 | | | 129.7 | 129.7 | 130.2 | 130.2 |
| $CH_3$ | | | | | | | | | | | | | 21.0 | 21.0 |
| $OCH_3$ | 55.5 | 55.5 | 61.1 | 61.1 | | | | | | | | | | |
| | | | 56.4 | 56.4 | | | | | | | | | | |

| C | 20f | 21f | 20g | 21g | 22 | 23 | C | 8 | 10/11 |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 182.4 | 182.2 | 181.7 | 182.3 | 179.8 | 180.4 | 1 | 178.2 (177.7) | 180.7 |
| 2 | 147.5 | 146.5 | 144.9 | 144.7 | 144.4 | 144.3 | 2 | 139.9 | 142.6 (144.9) |
| 3 | 102.2 | 101.6 | 103.3 | 103.4 | 105.6 | 106.1 | 3 | 140.4 (140.2) | 117.7 (116.9) |
| 4 | 183.4 | 184.7 | 184.3 | 184.0 | 177.5 | 177.3 | 4 | 182.4 (182.8) | 185.3 (185.7) |
| 4a | 130.5 | 131.3 | 133.2 | 131.1 | 132.5 | 130.4 | 4a | 130.9 (131.8) | — |
| 5 | 126.1 | 126.5 | 126.1 | 126.4 | 127.2 | 127.5 | 5/8 | 127.6 (128.9) | 126.5 (126.3) |
| 6 | 151.5 | 135.1 | 151.4 | 135.0 | 151.4 | 135.0 | 6/7 | 134.6 (134.8) | 135.2 (133.4) |
| 7 | 132.9 | 148.3 | 132.5 | 148.2 | 132.7 | 148.6 | 7/6 | 150.4 (150.8) | 148.7 (150.8) |
| 8 | 127.1 | 126.5 | 126.9 | 126.4 | 127.2 | 126.7 | 8/5 | 129.7 (128.1) | 126.5 (126.9) |
| 8a | 129.5 | 130.4 | 128.2 | 130.3 | 127.6 | 129.7 | 8a | 129.7 (128.9) | — |
| 1′ | 36.9 | 36.2 | 36.7 | 36.2 | 36.5 | 36.1 | 1′ | 36.4 | 36.1 (36.4) |
| 2′ | — | 28.9 | 28.8 | 28.9 | 28.6 | 28.7 | 2′ | 28.8 | 29.2 |
| 3′ | 39.1 | 38.4 | 38.5 | 38.4 | 38.4 | 38.4 | 3′ | 38.5 | 122.5 |
| 4′ | — | 27.9 | 27.8 | 27.9 | 27.8 | 27.8 | 4′ | 27.9 | 133.2 |
| 5′ | 22.7 | 22.5 | 22.6 | 22.5 | 22.5 | 22.5 | 5′ | 22.6 | 25.6 |
| 6′ | 22.7 | 22.5 | 22.6 | 22.5 | 22.5 | 22.5 | 6′ | 22.6 | 17.7 |
| 1″ | 134.3 | 129.0 | 135.1 | 135.0 | 130.4 | 130.4 | NHAc | | 169.6 |
| 2″ | 126.4 | 125.3 | 123.7 | 123.6 | 126.7 | 126.7 | | | 25.0 |
| 3″ | 116.8 | 116.5 | 122.9 | 122.9 | 113.6 | 113.7 | | | |
| 4″ | 156.3 | 154.9 | 147.9 | 147.9 | 157.9 | 157.8 | | | |
| 5″ | 116.8 | 116.5 | 122.9 | 122.9 | 113.6 | 113.7 | | | |
| 6″ | 126.4 | 125.3 | 123.7 | 123.6 | 126.7 | 126.7 | | | |
| OAc | | | 169.4 | 169.3 | | | | | |
| | | | 21.1 | 21.1 | | | | | |
| $OCH_3$ | | | | | 55.4 | 55.4 | | | |

[a] Exchangeable assignments.

**3.1.4. 2-Acetamido-6-(4-methyl-3-pentenyl)-[1,4]-naphthoquinone 10 and 2-acetamido-7-(4-methyl-3-pentenyl)-[1,4]-naphthoquinone 11.** To a stirred solution of **1** (367 mg, 1.53 mmol) in acetone (15 mL) under an inert atmosphere, was added a solution of sodium azide (585 mg, 9.00 mmol) in water (5 mL), acidified to pH 4 (with 1 N HCl). The reaction was stirred at room temperature for 20 h, then the solvent was evaporated off, and the residue was redissolved in ethyl acetate and washed with brine. The combined organic layers were dried, filtered and concentrated. The crude product thus obtained was treated with sulfuric acid in acetic anhydride (9 mL from a solution previously prepared with 0.15 mL of $H_2SO_4$ and 50 mL of $Ac_2O$) and it was stirred at room temperature for 3 h. Then ice was added and the mixture was extracted with ethyl acetate, washed with aq satd $NaHCO_3$ and brine, dried, filtered and evaporated till dryness. After chromatographic purification, a 1:1 mixture of acetylated regioisomers **10** and **11** was obtained (72 mg, 19%) (eluent: hexane/ethyl acetate 7:3). IR: 3326, 2963, 2863, 1713, 1667, 1599, 1504, 888 $cm^{-1}$. $^1H$ NMR: Table 2. $^{13}C$ NMR: Table 3. HRMS (FAB-POSI, M + 1) calcd 298.1443, found 298.1405.

**3.1.5. 2-Benzylamino-6-(4-methylpentyl)-[1,4]-naphthoquinone 12 and 2-benzylamino-7-(4-methylpentyl)-[1,4]-naphthoquinone 13.** A solution of **2** (159 mg, 0.66 mmol) in methanol/chloroform (1:1, 6 mL) at 10 °C, was treated with copper(II) acetate (79 mg, 0.39 mmol) and benzylamine (75 μL, 0.69 mmol). After 2 h stirring at 10 °C, it was added additional benzylamine (35 μL, 0.32 mmol) and the resulting mixture was allowed to warm at room temperature and stirred for an additional 72 h. The solvent was removed and the residue redissolved in ethyl acetate. The organic layer was washed with 2 N HCl and brine, dried, filtered and evaporated off. The reaction product was purified by CC over silica gel (eluent:

dichloromethane), yielding: (a)16 mg (16%) of **12**. IR: 3321, 2951, 2867, 1677, 1586, 1565, 729 $cm^{-1}$. $^1H$ NMR: Table 2. $^{13}C$ NMR: Table 3. HRMS (FAB-POSI, M + 1) calcd 348.1963, found 348.1936. (b) 9 mg (9%) of mixture of **12** and **13**. (c) 15 mg (15%) of **13**. IR: 3318, 2954, 2867, 1679, 1595, 1561, 730 $cm^{-1}$. $^1H$ NMR: Table 2. $^{13}C$ NMR: Table 3. HRMS (FAB-POSI, M + 1) calcd 348.1963, found 348.1921.

**3.1.6. 2-Amino-6-(4-methylpentyl)-[1,4]-naphthoquinone 14 and 2-amino-7-(4-methylpentyl)-[1,4]-naphthoquinone 15.** Via hydrogenolysis: A mixture of **12** and **13** (93 mg, 0.27 mmol) was dissolved in ethyl acetate (20 mL) containing 10% Pd/C (38 mg) and kept under hydrogen atmosphere at room temperature for 4.5 days. After filtering off the catalyst through Celite, the solvent was evaporated and the reaction product was chromatographed over silica gel (eluent: dichloromethane/ethyl acetate 95:5), affording: (a) 6 mg (9%) of **14**. IR: 3416, 3288, 2954, 2868, 1688, 1590, 1556, 798 $cm^{-1}$. $^1H$ NMR: Table 2. $^{13}C$ NMR: Table 3. HRMS (FAB-POSI, M + 1) calcd 258.1494, found 258.1483. (b) 18 mg (27%) of mixture of **14** and **15**. (c) 5 mg (7%) of **15**. IR: 3407, 3284, 2952, 2868, 1687, 1596, 1544, 829 $cm^{-1}$. $^1H$ NMR: Table 2. $^{13}C$ NMR: Table 3. HRMS (FAB-POSI, M + 1) calcd 258.1494 found 258.1526.

Via nucleophilic substitution of an halogen atom: From bromo derivative **8**. A stirred solution of **8** (114 mg, 0.36 mmol) in methanol (12 mL), under an inert atmosphere, was treated with a solution of sodium azide (139 mg, 2.14 mmol) in 3 mL of water, acidified to pH 4 (with 1 N HCl). After 23 h stirring at room temperature the solvent was concentrated and then extracted with ethyl acetate and washed with brine. The organic layer was dried, filtered and evaporated under reduced pressure. The crude product was then dissolved in ethyl acetate (10 mL) containing 10% Pd/$CaCO_3$ (36 mg) and stirred under hydrogen atmosphere at room temperature. After 8 h the catalyst was filtered off through Celite and the solvent was concentrated to yield a 1:1 mixture of **14** and **15** (79 mg, 85%).

From chloro derivatives **5** and **6**. In the same way as described above from bromo derivative **8**, the 9:1 mixture of **5** and **6** (204 mg, 0.74 mmol) gave a 1:9 mixture of **14** and **15** (35%).

**3.1.7. 2-Acetamido-6-(4-methylpentyl)-[1,4]-naphthoquinone 16 and 2-acetamido-7-(4-methylpentyl)-[1,4]-naphthoquinone 17.** With acetyl chloride: A 1:9 mixture of **14** and **15** (35 mg, 0.14 mmol) in dry dichloromethane (2 mL) was treated with acetyl chloride (0.14 mL) and triethylamine (0.14 mL). After 5 days stirring at room temperature, the solvent was removed and the residue was redissolved in ethyl acetate and washed with brine. The combined organic layers were dried, filtered and evaporated off giving a crude product, which was purified by CC leading to a 1:9 mixture of **16** and **17** (25 mg, 60%) (eluent: chloroform:ethyl acetate 96:4). IR: 3324, 2952, 2867, 1712, 1662, 1598, 1512, 858 $cm^{-1}$. $^1H$ NMR: Table 2. $^{13}C$ NMR: Table 3. HRMS (FAB-POSI, M + 1) calcd 300.1599, found 300.1623.

With acetic anhydride: A 1:9 mixture of **14** and **15** (79 mg, 0.31 mmol) was dissolved in 2 mL of a solution of sulfuric acid in acetic anhydride (previously prepared with 0.15 mL of $H_2SO_4$ and 50 mL of $Ac_2O$). The reaction was stirred at room temperature and after 3.5 h ice was added and the mixture was extracted with ethyl acetate. The organic fraction was washed with aq satd $NaHCO_3$ and brine, dried, filtered and evaporated till dryness, yielding a 1:9 mixture of **16** and **17** (83 mg, 90%).

**3.1.8. General procedures for the preparation of 2-alkyl(aryl)amino-6(7)-(4-methyl-3-pentenyl/pentyl)-[1,4]-naphthoquinones 18(a–i), 19(a–i), 20(a–g) and 21(a–g).** Method A: To a stirred solution of naphthoquinones **1** or **2** (1.00 mmol) in absolute ethanol (10 mL) was added pyridine (3 mL, 37.24 mmol) and the alkylamine (1.10 mmol). The reaction was stirred at room temperature and monitored by TLC (the times are depicted in Scheme 3). Then, the solvent was removed and the residue was redissolved in ethyl acetate, was washed with 2 N HCl and brine, dried, filtered and concentrated in vacuum. The crude product was purified by CC over silica gel.

Method B: To a solution of naphthoquinones **1** or **2** (1.00 mmol) in methanol (5 mL), arylamine (1.20 mmol) was added and the reaction mixture was stirred at room temperature and monitored by TLC (the times are depicted in Scheme 3). After removing the solvent, the crude product was purified by CC over silica gel.

**3.1.9. 2-Ethylamino-6-(4-methyl-3-pentenyl)-[1,4]-naphthoquinone 18a and 2-ethylamino-7-(4-methyl-3-pentenyl)-[1,4]-naphthoquinone 19a.** Chromatographic purification of the reaction product (eluent: dichloromethane/ethyl acetate 98:2) between **1** and ethylamine, following method A, gave: (a) 27 mg (9%) of **18a**. IR: 3271, 2966, 2851, 1680, 1589, 1569, 847 $cm^{-1}$. $^1H$ NMR: Table 2. $^{13}C$ NMR: Table 3. HRMS (FAB-POSI, M + 1) calcd 284.1650, found 284.1621. (b) 110 mg (38%) of mixture of **18a** and **19a**. (c) 21 mg (7%) of **19a**. IR: 3351, 2969, 2856, 1674, 1603, 1567, 803 $cm^{-1}$. $^1H$ NMR: Table 2. $^{13}C$ NMR: Table 3. HRMS (FAB-POSI, M + 1) calcd 284.1650, found 284.1645.

**3.1.10. 2-Hexylamino-6-(4-methyl-3-pentenyl)-[1,4]-naphthoquinone 18b and 2-hexylamino-7-(4-methyl-3-pentenyl)-[1,4]-naphthoquinone 19b.** Chromatographic purification of the reaction product (eluent: dichloromethane) between **1** and *n*-hexylamine, following method A, gave: (a) 31 mg (12%) of **18b**. IR: 3341, 2948, 2852, 1673, 1604, 1569 $cm^{-1}$. $^1H$ NMR: Table 2. $^{13}C$ NMR: Table 3. HRMS (FAB-POSI, M + 1) calcd 340.2276, found 340.2253. (b) 42 mg (16%) of mixture of **18b** and **19b**. (c) 24 mg (9%) of **19b**. IR: 3350, 2949, 2857, 1673, 1603, 1565, 838 $cm^{-1}$. $^1H$ NMR: Table 2. $^{13}C$ NMR: Table 3. HRMS (FAB-POSI, M + 1) calcd 340.2276, found 340.2293.

**3.1.11. 2-Ethylamino-6-(4-methylpentyl)-[1,4]-naphthoquinone 20a and 2-ethylamino-7-(4-methylpentyl)-[1,4]-naphthoquinone 21a.** Chromatographic purification of the reaction product (eluent: dichloromethane/ethyl acetate 94:6) between **2** and ethylamine, following method A, gave: (a) 29 mg (11%) of **20a**. IR: 3271, 2953, 2868, 1679, 1589, 1568, 848 $cm^{-1}$. $^1H$ NMR: Table 2. $^{13}C$ NMR: Table 3. HRMS (FAB-POSI, M + 1) calcd 286.1807, found 286.1783. (b) 44 mg (17%) of mixture of **20a** and **21a**. (c) 30 mg (12%) of **21a**. IR: 3349, 2955, 2868, 1674, 1601, 1567, 803 $cm^{-1}$. $^1H$ NMR: Table 2. $^{13}C$ NMR: Table 3. HRMS (FAB-POSI, M + 1) calcd 286.1807, found 286.1813.

**3.1.12. 2-Hexylamino-6-(4-methylpentyl)-[1,4]-naphthoquinone 20b and 2-hexylamino-7-(4-methylpentyl)-[1,4]-naphthoquinone 21b.** Chromatographic purification of the reaction product (eluent: hexane/dichloromethane 1:9) between **2** and *n*-hexylamine, following method A, gave: (a) 57 mg (17%) of **20b**. IR: 3340, 2951, 2866, 1673, 1604, 1568, 1348 $cm^{-1}$. $^1H$ NMR: Table 2. $^{13}C$ NMR: Table 3. HRMS (FAB-POSI, M + 1) calcd 342.2420, found 342.2474. (b) 15 mg (5%) of mixture of **20b** and **21b**. (c) 40 mg (12%) of **21b**. IR: 3354, 2952, 2866, 1674, 1604, 1564, 1358 $cm^{-1}$. $^1H$ NMR: Table 2. $^{13}C$ NMR: Table 3. HRMS (FAB-POSI, M + 1) calcd 342.2420, found 342.2453.

**3.1.13. 6-(4-Methylpentyl)-2-pyrrolidino-[1,4]-naphthoquinone 20c and 7-(4-methyl-pentyl)-2-pyrrolidino-[1,4]-naphthoquinone 21c.** Application of method A, between **2** and pyrrolidine yielded after purification (eluent: dichloromethane/ethyl acetate 94:6): (a) 60 mg (30%) of **20c**. IR: 2953, 2931, 2868, 1674, 1594, 1557, 824 $cm^{-1}$. $^1H$ NMR: Table 2. $^{13}C$ NMR: Table 3. HRMS (FAB-POSI, M + 1) calcd 312.1963, found 312.1965. (b) 85 mg (43%) of mixture of **20c** and **21c**. (c) 30 mg (15%) of **21c**. IR: 2953, 2929, 2868, 1674, 1602, 1555, 823 $cm^{-1}$. $^1H$ NMR: Table 2. $^{13}C$ NMR: Table 3. HRMS (FAB-POSI, M + 1) calcd 312.1963, found 312.1977.

Following the method B, addition of pyrrolidine to **2** gave after purification: (a) 13 mg (8%) of **20c**. (b) 11 mg (7%) of mixture of **20c** and **21c**. (c) 12 mg (8%) of **21c**.

**3.1.14. 6-(4-Methyl-3-pentenyl)-2-pyrrolidino-[1,4]-naphthoquinone 18c and 7-(4-methyl-3-pentenyl)-2-pyrrolidino-[1,4]-naphthoquinone 19c.** Following method B, the treatment of **1** with pyrrolidine gave after CC (eluent: dichloromethane/ethyl acetate 9:1): (a) 13 mg (8%) of **18c**. IR: 2965, 2921, 2856, 1674, 1593, 1562, 825 $cm^{-1}$. $^1H$ NMR: Table 2. $^{13}C$ NMR: Table 3. HRMS (FAB-POSI, M + 1) calcd 310.1807, found 310.1841. (b) 16 mg (9%) of mixture of **18c** and **19c**. (c) 14 mg (8%) of **19c**. IR: 2961, 2927, 2856, 1674, 1602, 1553, 823 $cm^{-1}$. $^1H$ NMR: Table 2. $^{13}C$ NMR: Table 3. HRMS (FAB-POSI, M + 1) calcd 310.1807, found 310.1839.

**3.1.15. 2-Anilino-6-(4-methyl-3-pentenyl)-[1,4]-naphthoquinone 18d and 2-anilino-7-(4-methyl-3-pentenyl)-[1,4]-naphthoquinone 19d.** Following method B, the reaction of **1** with aniline yielded after purification (eluent: dichloromethane): (a) 53 mg (18%) of **18d**. IR: 3316, 2924, 2853, 1672, 1589, 1569, 848 $cm^{-1}$. $^1H$ NMR: Table 2. $^{13}C$ NMR: Table 3. HRMS (FAB-POSI, M + 1) calcd 332.1650, found 332.1669. (b) 117 mg (40%) of mixture of **18d** and **19d**. (c) 10 mg (4%) of **19d**. IR: 3316, 2953, 2849, 1731, 1668, 1591, 1147 $cm^{-1}$. $^1H$ NMR: Table 2. $^{13}C$ NMR: Table 3. HRMS (FAB-POSI, M + 1) calcd 332.1650, found 332.1612.

**3.1.16. 6-(4-Methyl-3-pentenyl)-2-(*p*-tolylamino)-[1,4]-naphthoquinone 18e and 7-(4-methyl-3-pentenyl)-2-(*p*-tolylamino)-[1,4]-naphthoquinone 19e.** Following the method B, the addition of *p*-toluidine to **1** afforded by column chromatography (eluent: dichloromethane): (a) 25 mg (14%) of **18e**. IR: 3290, 2962, 2852, 1674, 1588, 1567, 837 $cm^{-1}$. $^1H$ NMR: Table 2. $^{13}C$ NMR: Table 3. HRMS (FAB-POSI, M + 1) calcd 346.1807, found 346.1804. b) 74 mg (41%) of mixture of **18e** and **19e**. (c) 26 mg (14%) of **19e**. IR: 3315, 2960, 2851, 1669, 1595, 1567, 837 $cm^{-1}$. $^1H$ NMR: Table 2. $^{13}C$ NMR: Table 3. HRMS (FAB-POSI, M + 1) calcd 310.1807, found 310.1781.

**3.1.17. 2-(*p*-Hydroxyanilino)-6-(4-methyl-3-pentenyl)-[1,4]-naphthoquinone 18f and 2-(*p*-hydroxyanilino)-7-(4-methyl-3-pentenyl)-[1,4]-naphthoquinone 19f.** Following the method B, the reaction between **1** and *p*-aminophenol gave after purification (eluent: dichloromethane/ethyl acetate 9:1): (a) 6 mg (3%) of **18f**. IR: 3295, 2958, 2852, 1669, 1587, 1571, 831 $cm^{-1}$. $^1H$ NMR: Table 2. $^{13}C$ NMR: Table 3. HRMS (FAB-POSI, M + 1) calcd 348.1599, found 348.1571. (b) 115 mg (52%) of mixture of **18f** and **19f**. (c) 13 mg (6%) of **19f**. IR: 3302, 2954, 2853, 1673, 1603, 828 $cm^{-1}$. $^1H$ NMR: Table 2. $^{13}C$ NMR: Table 3. HRMS (FAB-POSI, M + 1) calcd 348.1599, found 348.1592.

**3.1.18. 2-(*p*-Methoxyanilino)-6-(4-methyl-3-pentenyl)-[1,4]-naphthoquinone 18h and 2-(*p*-methoxyanilino)-7-(4-methyl-3-pentenyl)-[1,4]-naphthoquinone 19h.** Following method B, treatment of **1** with *p*-anisidine yielded by column chromatography (eluent: dichloromethane): (a) 20 mg (6%) of **18h**. IR: 3271, 2959, 2855, 1680, 1588, 1567, 829 $cm^{-1}$. $^1H$ NMR: Table 2. $^{13}C$ NMR: Table 3. HRMS (FAB-POSI, M + 1) calcd 362.1756, found 362.1783. (b) 181 mg (58%) of mixture of **18h** and **19h**. (c) 25 mg (8%) of **19h**. IR: 3316, 2955, 2854, 1670, 1598, 1566, 830 $cm^{-1}$. $^1H$ NMR: Table 2. $^{13}C$ NMR: Table 3. HRMS (FAB-POSI, M + 1) calcd 362.1756, found 362.1721.

**3.1.19. 6-(4-Methyl-3-pentenyl)-2-(3,4,5-trimethoxyanilino)-[1,4]-naphthoquinone 18i and 7-(4-methyl-3-pentenyl)-2-(3,4,5-trimethoxyanilino)-[1,4]-naphthoquinone 19i.** Application of the method B between **1** and 3,4,5-trimethoxyaniline, followed by purification (eluent: dichloromethane/ethyl acetate 95:5) led to: (a) 30 mg (8%) of **18i**. IR: 3313, 2963, 2853, 1672, 1593, 1571, 799 $cm^{-1}$. $^1H$ NMR: Table 2. $^{13}C$ NMR: Table 3. HRMS (FAB-POSI, M + 1) calcd 422.1967, found 422.2003. (b) 199 mg (50%) of mixture of **18i** and **19i**. (c) 13 mg (3%) of **19i**. IR: 3324, 2955, 2853, 1673, 1596, 1567, 829 $cm^{-1}$. $^1H$ NMR: Table 2. $^{13}C$ NMR: Table 3.

**3.1.20. 2-Anilino-6-(4-methylpentyl)-[1,4]-naphthoquinone 20d and 2-anilino-7-(4-methylpentyl)-[1,4]-naphthoquinone 21d.** Application of method B to naphthoquinone **2** and aniline, followed by column chromatography (eluent: dichloromethane), led to: (a) 95 mg (36%) of **20d**. IR: 3282, 2955, 2868, 1678, 1587, 1568, 850 $cm^{-1}$. $^1H$ NMR: Table 2. $^{13}C$ NMR: Table 3. HRMS (FAB-POSI, M + 1) calcd 334.1807, found 334.1846. b) 10 mg (4%) of mixture of **20d** and **21d**. (c) 47 mg (18%) of **21d**. IR: 3315, 2947, 1667, 1590, 1567, 853 $cm^{-1}$. $^1H$ NMR: Table 2. $^{13}C$ NMR: Table 3. HRMS (FAB-POSI, M + 1) calcd 334.1807, found 334.1823.

**3.1.21. 6-(4-Methylpentyl)-2-(*p*-tolylamino)-[1,4]-naphthoquinone 20e and 7-(4-methylpentyl)-2-(*p*-tolylamino)-[1,4]-naphthoquinone 21e.** Following the method B, the addition of *p*-toluidine to **2** afforded by chromatographic purification (eluent: dichloromethane): (a) 59 mg (22%) of **20e**. IR: 3286, 2952, 2866, 1674, 1588, 1567, 815 $cm^{-1}$. $^1H$ NMR: Table 2. $^{13}C$ NMR: Table 3. HRMS (FAB-POSI, M + 1) calcd 348.1963, found 348.1995. (b) 37 mg (14%) of mixture of **20e** and **21e**. (c) 36 mg (13%) of **21e**. IR: 3316, 2950, 2924, 1674, 1594, 1567 $cm^{-1}$. $^1H$ NMR: Table 2. $^{13}C$ NMR: Table 3. HRMS (FAB-POSI, M + 1) calcd 348.1963, found 348.1901.

**3.1.22. 2-(*p*-Hydroxyanilino)-6-(4-methylpentyl)-[1,4]-naphthoquinone 20f and 2-(*p*-hydroxyanilino)-7-(4-methylpentyl)-[1,4]-naphthoquinone 21f.** Application of the method B, between **2** and *p*-aminophenol gave after column purification (eluent: dichloromethane/ether 95:5): (a) 85 mg (29%) of **20f**. IR: 3293, 2949, 2867, 1669, 1587, 1572, 831 $cm^{-1}$. $^1H$ NMR: Table 2. $^{13}C$ NMR: Table 3. HRMS (FAB-POSI, M + 1) calcd 350.1756, found 350.1807. (b) 20 mg (8%) of mixture of **20f** and **21f**. (c) 70 mg (24%) of **21f**. IR: 3297, 2948, 2862, 1671, 1606, 831 $cm^{-1}$. $^1H$ NMR: Table 2. $^{13}C$ NMR: Table 3. HRMS (FAB-POSI, M + 1) calcd 350.1756, found 350.1721.

**3.1.23. 2-(*p*-Acetoxyanilino)-6-(4-methyl-3-pentenyl)-[1,4]-naphthoquinone 18g and 2-(*p*-acetoxyanilino)-7-(4-methyl-3-pentenyl)-[1,4]-naphthoquinone 19g.** A 1:1 mixture of **18f** and **19f** (115 mg, 0.33 mmol) was treated with acetic anhydride (2 mL) in pyridine (2 mL) and allowed to stand at room temperature in darkness overnight. After addition of ice, the mixture was extracted with ethyl acetate and washed with 2 N HCl, aq satd $NaHCO_3$ and brine. The combined organic layers were dried, filtered and evaporated off giving a crude product, which was purified by column chromatography over silica gel (eluent: dichloromethane/ethyl acetate 95:5), leading to: (a) 6 mg (5%) of **18g**. IR: 3287, 2950, 2850, 1756, 1678, 1589, 1518, 837 $cm^{-1}$. $^1H$ NMR: Table 2. $^{13}C$ NMR: Table 3. HRMS (FAB-POSI, M + 1) calcd 390.1705, found 390.1682. (b) 114 mg (89%) of a mixture of **18g** and **19g**.

Compound **19f** (13 mg, 0.04 mmol) was acetylated as described above with acetic anhydride (1 mL) in pyridine (1 mL), yielding 11 mg (71%) of **19g**. IR: 3314, 2964, 2856, 1765, 1670, 1596, 1519, 833 $cm^{-1}$. $^1H$ NMR: Table 2. $^{13}C$ NMR: Table 3. HRMS (FAB-POSI, M + 1) calcd 390.1705, found 390.1713.

**3.1.24. 2-(*p*-Acetoxyanilino)-6-(4-methylpentyl)-[1,4]-naphthoquinone 20g and 2-(*p*-acetoxyanilino)-7-(4-methylpentyl)-[1,4]-naphthoquinone 21g.** Derivative **20f** (55 mg, 0.16 mmol) was acetylated following the procedure described above affording **20g** (61 mg, 98%). IR: 3289, 2955, 2868, 1759, 1677, 1588, 1518, 838 $cm^{-1}$. $^1H$ NMR: Table 2. $^{13}C$ NMR: Table 3. HRMS (FAB-POSI, M + 1) calcd 392.1862, found 392.1856.

In a similar way, from compound **21f** (50 mg, 0.14 mmol) was obtained **21g** (55 mg, 98%). IR: 3318, 2951, 2866, 1768, 1668, 1596, 1518, 833 $cm^{-1}$. $^1H$ NMR: Table 2. $^{13}C$ NMR: Table 3. HRMS (FAB-POSI, M + 1) calcd 392.1862, found 392.1897.

**3.1.25. 3-Bromo-2-(*p*-methoxyanilino)-6-(4-methylpentyl)-[1,4]-naphthoquinone 22 and 3-bromo-2-(*p*-methoxyanilino)-7-(4-methylpentyl)-[1,4]-naphthoquinone 23.** A solution of **9** (157 mg, 0.39 mmol) and *p*-anisidine (50 mg, 0.41 mmol) in ethanol (15 mL) was refluxed for 6 h. Then, the mixture was concentrated in vacuum and the residue was purified by column chromatography over silica gel (eluent: dichloromethane), yielding: (a) 8 mg (5%) of **22**. IR: 3221, 2954, 1673, 1592, 1558, 1288, 826 $cm^{-1}$. $^1H$ NMR: Table 2. $^{13}C$ NMR: Table 3. HRMS (FAB-POSI, M + 1) calcd 442.1018, found 442.1002. (b) 70 mg (41%) of mixture of **22** and **23**. (c) 7 mg (4%) of **23**. IR: 3301, 2954, 2867, 1671, 1603, 1565, 1292, 827 $cm^{-1}$. $^1H$ NMR: Table 2. $^{13}C$ NMR: Table 3. HRMS (FAB-POSI, M + 1) calcd 442.1018, found 442.1040.

### 3.2. Bioactivity. Cell growth inhibition assay

A colourimetric 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 microtiter plates, at $5 \times 10^3$ 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. Afterward, 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% (wt/vol) trichloroacetic acid (TCA) and incubating for 60 min at 4 °C. Plates are washed with deionized water and dried; 100 μL of SRB solution (0.4% wt/vol in 1% acetic acid) is added to each microtiter 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: $100 \times [(T - T_0)/(C - T_0)] = 50$.

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