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Artigo

Synthesis of New 2-*N,N'*-dialkylamino-1,4-naphthoquinone Derivatives: Concerning the Reactivity of Lapachol with Secondary Amines

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Síntese de Novos Derivados de 2-*N,N'*-dialquilamino-1,4-naftoquinonas: Sobre a Reatividade do Lapachol com Aminas Secundárias

Resumo: A reatividade das 2-metóxi-naftoquinonas com aminas secundárias pode ser modificada de acordo com a presença de substituintes na cadeia lateral de quinonas naturais e sintéticas. Derivados 2-dialquilamino-1,4-naftoquinonas foram sintetizados por substituição nucleofílica com aminas secundárias utilizando-se 2-metóxi-1,4-naftoquinonas derivadas do *nor*-lapachol e lausona. As reações mostraram bons rendimentos em condições experimentais simples. Não foram obtidos produtos de substituição do derivado do 2-metóxi-lapachol com aminas secundárias nas condições estudadas. Os compostos foram caracterizados por RMN de ^{1}H, ^{13}C, HMBC, IV e foram comparados com os dados da literatura.

Palavras-chave: Quinona; 1,4-naftoquinona; lapachol; *nor*-lapachol; lausona; 2-dialquilamino-1,4-naftoquinonas.

Abstract

The reactivity of 2-methoxy-naphthoquinones with secondary amines can be modified by the presence of side-chain substituents in natural and synthetic quinones. We report the synthesis of 2-dialkylamino-1,4-naphthoquinone derivatives by nucleophilic substitution with secondary amines using 2-methoxy-1,4-naphthoquinones derived from *nor*-lapachol and lawsone. The reported reactions show good yields and straightforward experimental conditions. No products were obtained for the reaction of 2-methoxy-lapachol with secondary amines under the studied experimental conditions. The compounds were characterized by ^{1}H, ^{13}C NMR spectroscopy, HMBC, IR and by comparing with literature data.

Keywords: Quinone; 1,4-naphthoquinone; lapachol; *nor*-lapachol; lawsone; 2-dialkylamine-1,4-naphthoquinones.

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Synthesis of New 2-*N,N'*-dialkylamino-1,4-naphthoquinone Derivatives: Concerning the Reactivity of Lapachol with Secondary Amines

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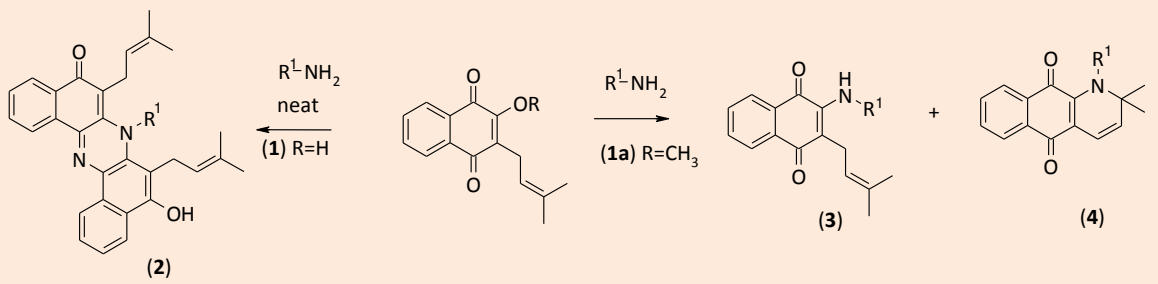
1. Introduction

Naphthoquinones belong to a class of compounds with a wide range of biological activities, and their reactivity and chemical profile is an interesting field of research worldwide.[1] There is a continuous interest to obtain derivatives of new naphthoquinones due to their previously reported bioactivities[2-5] and in special amino-naphthoquinones derived from naturally occurring lapachol **(1)**[6] and related quinones such as β-lapachone.[7] In part because of their improved biological profile as cytotoxic compounds,[8] and also their particular chemistry.[9-13] In our group, we have been found facile acess to lapachol **(1)** by extraction from Brazilian *Tabebuia sp* (ipê) heartwood,[14] allowed us to observe that **(1)** reacts with neat primary amines to yield phenazines[15] **(2)** (Scheme 1), in the so called Strecker degradation oxidation.[16] This behavior contrasts with other previously direct substitution procedure explored by our group[12,17,18] which the 2-methoxy derivative of **(1a)** or synthetic *nor*-lapachol **(5)** smoothly afford the formation of 2-aminoalkyl derivatives and some other interesting unexpected cyclization products (Scheme 1).[17,18] The change in reactivity profile is attributed to the methoxyl's improved leaving group character in compound **(1a)** compared to the hydroxyl group in lapachol. In this paper our interest was to synthesize a series of 2-dialkylamino derivatives obtained by direct displacement of 2-methoxy-lapachol **(1a)**, 2-methoxy-*nor*-lapachol **(5a)** and 2-methoxy-lawsone **(6a)** with suitable secondary amines from an inexpensive source.[12,17,18] The compounds were synthesized in a straightforward procedure

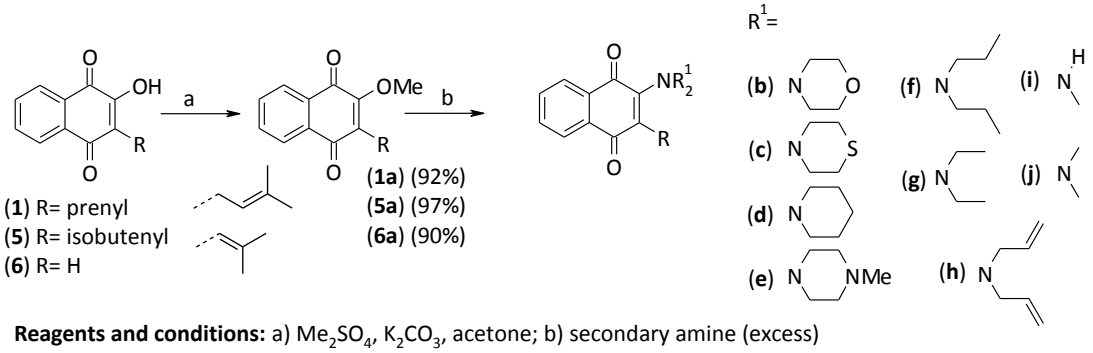
using suitable cyclic and acyclic secondary amines (Scheme 2) and the series obtained had their structure confirmed by usual spectroscopy techniques. In this work we also compared the NMR spectroscopic data of synthesized compounds with data previously reported in the literature, discussing some observed disagreements in previously reported data.



Scheme 1. Divergent products obtained from primary amines and naphthoquinones. The 2-methoxyl-substituted-quinone **(1a)** yields expected 2-aminoalkyl derivatives **(3)** and **(4)** and the unsubstituted hydroxyl **(1)** quinone results in phenazines **(2)**

2. Results and discussion

In order to obtain the expected compounds, we tried to perform nucleophilic substitutions using corresponding suitable secondary amines and 2-methoxy derivatives **(1a, 5a, 6a)** and we were able to achieve good results for the majory of reactions (table 2). Our efforts were unsuccessful to obtain the the expected products **(1b-j)** from 2-methoxy-lapachol **(1a)** and cyclic or acyclic secondary amines **(5f-h)**. Also the products from 2-methoxy-norlapachol **(5a)** with acyclic secondary amines were not obtained under the tested conditions (Scheme 2), while those from the less basic and less crowded cyclic amines react to produce **(5b-e)** with good yields (64-87 %). Several attempts were made to obtain 2-aminoderivative from 2-methoxy-lapachol **(1a)** using morpholine and diethylamine as models in various conditions: reaction in polar, nonpolar, protic or aprotic solvents, use of microwave and conventional heating, but all proved unsuccessful. Under these conditions we observed that the starting material **(1a)** is not satisfactorily consumed and many by-products are formed as revealed by TLC inspection, in a time-dependent degradation manner. It seems plausible that the steric hindrance of the prenyl in C-3 blocks the displacement of the methoxyl by the secondary amine at C-2 in 2-methoxy-lapachol **(1a)**. This effect maybe consistent, because the reactions between **(6a)**, derived from lawsone**,** and the appropriate dialkylamines led to the desired products were obtained in good yields **(6b-h**). Except for **(6f-h)** wich show low yields, longer reaction times and amine excess was required. It is noteworthy to mention the sensitivity of the reaction to steric hindrance at amine and alkenyl side chain of the substrate. This can be observed by comparing the yield of the product from di-*n*-propylamine **(6f)** and di-*n*-allylamine **(6h)** (42 and 30% yield, respectively) with diethylamine **(6g)** (79 %).



Reagents and conditions: a) Me_2SO_4, K_2CO_3, acetone; b) secondary amine (excess)

Scheme 2. Synthesis of 2-dialkylamino-naphthoquinones derivatives.

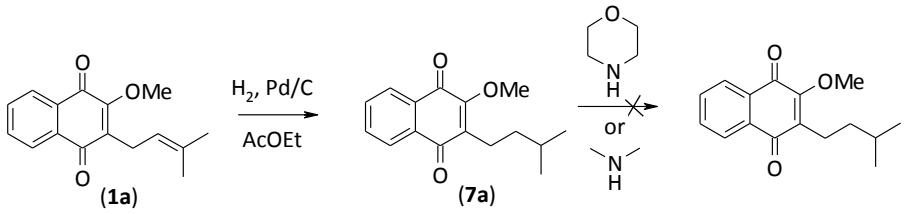
Table 1. Conditions for the reaction of 2-methoxy-[1,4]naphthoquinone and secondary amines

Entry	Compound	Reaction conditions (methoxy-quinone:amine)	Time (h)	Yield (%)
1	**1b-h**	A,B*	-	-
2	**1i**	C	2	94
3	**1j**	C	-	-
4	**5b**	B, 1: 3	18	69
5	**5c**	B, 1: 3	18	64
6	**5d**	B, 1: 3	18	82
7	**5e**	B, 1: 3	18	87
8	**5f-h**	A,B*	-	-
9	**5i**	C	2	92
10	**5j**	C	48	9
11	**6b**	A, 1: 3	18	87
12	**6c**	A, 1: 3	18	71
13	**6d**	A, 1: 3	18	72
14	**6e**	A, 1: 3	18	63
15	**6f**	A, 1: 20	72	42
16	**6g**	A, 1: 20	72	79
17	**6h**	A, 1: 20	72	30
18	**6i**	C	2	80
19	**6j**	C	0,16	95

A – excess amine as solvent at r.t.; B – excess amine in same volume of methanol at r.t.; C – excess methylamine or dimethylamine sol. in methanol at r.t.; * The starting material is not fully consumed and the reaction has many byproducts (see text)

The steric hindrance of the alkenyl side chain of lapachol preventing the nucleophilic attack can indeed be demonstrated since no products could be isolated from the reaction between **(1a)** and morpholine or dimethylamine. Even if **(1a)** was partially hydrogenated at the side chain of 2-methoxy-lapachol yielding **(7a)**[19] no product was formed yet (Scheme **3**). This last compound was used to probe if the basic amines could abstract the poorly acidic allylic hydrogen at C-1' in (1a)[20] thus explaining perhaps the formation of many byproducts in the observed reactions. However, a very similar behavior in TLC was observed from **(1a)** and **(7a)**. At this point, we performed the reaction of methoxyl-derivatives **(1a), (5a)** and **(6a)** with methylamine 40 % in methanol, yielding

94, 92 and 80 % of **(1i)**, **(5i)** and **(6i)**, respectively (Scheme 2). With these results, primary amines were not substantially blocked by the 3-alkenyl- side chain. A very different situation was found when a secondary amine such dimethylamine was employed. In this case, **(1a)** failed to yield the desired product even after very long reaction time, **(5a)** gave the corresponding 2-dimethylamino (**5j**, 9%), while **(6j)** was obtained in 95 % yield (Scheme 2). These results showed that the alkenyl group of **(1a)** and **(5a)** allows nucleophilic substitution primary amines, in constrast secondary amines were not reactive, probably due to the steric hindrance, as alread described.



Scheme 3. Partial hydrogenation of 2-methoxy-lapachol (**1a**) side chain

The characterization of representative 2-*N*-piperidinyl derivative of *nor*-lapachol **(5d)** showed at high resolution mass spectrometry (MALDI) a molecular mass peak in accordance for $C_{19}H_{21}NO_2$ of 295.1553 (calc 295.1572). The ^{1}H NMR ($CDCl_3$, 400 MHz) analysis (table 2; figure S14) showed a very simplified spectrum. Two signals at 1.59 ppm (singlet, 3H) and 1.95 ppm (singlet, 3H) were attributed to diastereotopic methyl groups of the isobutenyl side chain, as well as the singlet in 6.03 ppm (1H) which was attributed to the vinylic hydrogen. Two doublets at 8.02 ppm (1H, *J* = 7.4 Hz) and 7.98 ppm (1H, *J* = 7.4 Hz) were attributed to the 5- and 8-hydrogens *ortho* to the carbonyl. The *meta* hydrogens absorb as a pair of double doublets at 7.59 (1H, J=7.4/8.0 Hz) and 7.64 ppm (1H, J = 7.4/8.0 Hz). The methylene attached to the nitrogen appears at 3.31 ppm (4H) and the other methylenes absorbs at 1.67 ppm (6H) as a multiplet.

The HMBC experiments of **(5d)** (figure S17) showed the $^2J_{CH}$ correlations between H-5, H-8 and C-6, C-7, respectively, as well as the $^2J_{CH}$ and $^3J_{CH}$ correlations between H-6, H-7 and C-5, respectively. The carbon C-2 display a three bond correlation with the vinylic hydrogen and with the nitrogen-attached methylene hydrogens, compatible with the proposed structure.

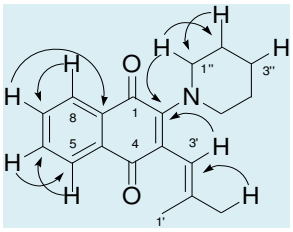
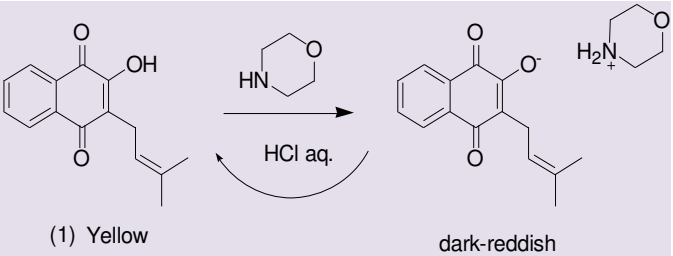


Figure 1. Major correlations of HMBC spectrum ($^2J_{CH}$ and $^3J_{CH}$) of **(5d)**

The ^{13}C NMR chemical shift for C-2 of 2-alkylamino-1,4-naphthoquinones from primary amines ranged from 144.8 ppm to 149.0 ppm,[10,12,17,21-23] and more upfield than those of secondary amines (ranging from 150.6 ppm to 154.0 ppm).[10,23-26] From the data in table 3, it can be observed that the C-2 chemical shift of dialkylamino derivatives ranges from 150.0 ppm to 154.1 ppm **(5b-e**,**5j, 6b-h**, **6j** table 3**)** and the corresponding

values for the *N*-alkylamino derivatives are in the range of 145.7 ppm to 146.3 ppm **(1i, 5i)**, in agreement with the previous literature data. However, the compounds previously obtained by Oliveira *et al* (2002)[27] **(1b,d)** and Wenceslau *et al* (2006)[28] present C2 shifts outside this range: the value for the 2-*N*-ethylamine lapachol derivative from Wenceslau *et al* (2006)[28] is 169.3 ppm (spectra recorded in CD_3OD), and some other similar data shows this particular disagreement. The values for the secondary amines derivatives from Wenceslau *et al* (2006)[28] ranges from 163.6 ppm to 168.8 ppm and finally, the values from Oliveira *et al* (2002)[27] range from 154.7 ppm to 165.9 ppm (both recorded in $CDCl_3$). These data suggest that the compounds obtained by Oliveira *et al* (2002)[27] and Wenceslau *et al* (2006),[28] both using the same methodology, are in reality easily understood if we rationalize they are actually alkyl- and dialkylammonium salts of lapachol and thus are not the result of the claimed substitution reactions. The absence of HMBC correlation between the carbon chain of amine with C-2 further compromises the conclusions put forward by these authors. In this case, as we previously stated,[15] we expect that the amines used[27,28] deprotonates the 2-hydroxy group of lapachol (or hydroxyquinones),[29] according to Scheme 4. The resulting salt of lapachol has a characteristic dark-reddish coloration as described by both Oliveira *et al* (2002)[27] and Wenceslau *et al* (2006),[28] and also noticed by us.[15] As far as we know, there is no precedent in the literature for a direct displacement of a hydroxyl-attached to a quinone nucleus by amines.[12,13,30-32] To prove this conclusion, we repeated the procedure described,[27,28] with lapachol and *nor*-lapachol and morpholine. After 6 hours, the acidification of the reaction mixture results in the precipitation of the intact hydroxyl-naphthoquinones, as revealed by TLC inspection, as also by isolation of the unreacted lapachol after silica gel column chromatography.



Scheme 4. Reaction of obtaining of the 3-(3-methyl-but-2-enyl)-[1,4]naphthoquinone-2-olate morpholin-4-ium and regeneration of lapachol by reaction with HCl 10%

3. Conclusion

The nucleophylic substitution of 2-methoxy-1,4-naphthoquinones derived from lapachol, *nor*-lapachol and lawsone shows distinct reactivity profile with secondary symmetrical dialkylamines. In general the size of 3-alkenyl substituent plays an important role in preventing the substitution reaction when we change from prenyl (from lapachol derivatives), to 2-methyl-propenyl (*nor*-lapachol) and finally to non-substituted lawsone. Even under forced conditions previous literature results aiming at the reaction between lapachol itself with some cyclic and acyclic secondary amines could not be reproduced.

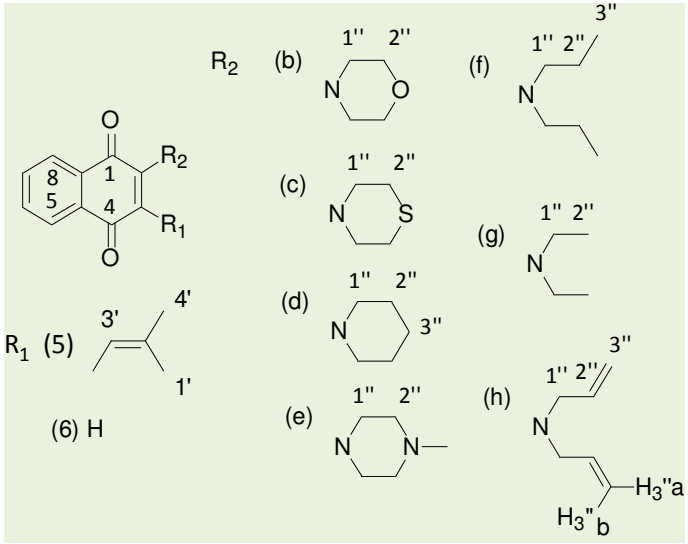
Table 2. ^{1}H NMR spectroscopy data ($CDCl_3$, 400 MHz) of 2-*N,N'*-dialkylamino-1,4-naphthoquinone derivatives

	5b	5c	5d	5e	6b	6c	6d	6e	6f	6g	6h
H-3	-	-	-	-	6.01 (s, 1H)	6.02 (s, 1H)	6.00 (s, 1H)	6.02 (s, 1H)	5.83 (s, 1H)	5.85 (s, 1H)	5.93 (s, 1H)
H-5	8.03 (d, 1H, 7.0)	8.02 (d, 1H, 7.4)	8.02 (d, 1H, 7.4)	8.01 (d, 1H, 7.0)	8.03 (dd, 1H, 7.4; 1.2)	8.03 (dd, 1H, 7.4; 0.8)	8.01 (d, 1H, 7.4)	8.02 (d, 1H, 7.4)	8.00 (d, 1H, 7.8)	8.00 (dd, 1H, 7.6;1.2)	8.01 (dd, 1H, 7.4; 0.8)
H-6	7.64 (m, 1H, 7.4)	7.65 (m, 1H, 7.0)	7.62 (m, 1H, 7.4)	7.62 (m, 1H, 7.0)	7.70 (dt, 1H, 7.4; 1.6)	7.70 (dt, 1H, 7.4; 1.4)	7.66 (dt, 1H, 7.4; 1.0)	7.68 (dt, 1H, 7.4; 1.2)	7.66 (dt, 1H, 7.4; 1.2)	7.65 (dt, 1H, 7.4;1.4)	7.67 (dt, 1H, 7.4; 1.2)
H-7	7.64 (m, 1H, 7.4)	7.65 (m, 1H, 7.0)	7.62 (m, 1H, 7.4)	7.62 (m, 1H, 7.0)	7.64 (dt, 1H, 7.4;1.6)	7.64 (dt, 1H, 7.4; 1.6)	7.60 (dt, 1H, 7.4; 1.2)	7.63 (dt, 1H, 7.4; 1.2)	7.57 (dt, 1H, 7.4; 1.2)	7.56 (dt, 1H, 7.6;1.4)	7.59 (dt, 1H, 7.4; 1.4)
H-8	7.98 (d, 1H, 7.4)	7.99 (d, 1H, 7.0)	7.98 (d, 1H, 7.4)	7.97 (d, 1H, 7.0)	8.0 (d, 1H, 7.8)	8.0 (dd, 1H, 7.4; 1.0)	7.96 (d, 1H, 7.4)	7.98 (dd, 1H, 7.4;1.0)	7.94 (d, 1H, 7.6)	7.93 (dd, 1H, 7.6;1.2)	7.96 (dd, 1H, 7.4; 0.8)
H-1'	1.61 (s, 3H)	1.61 (s, 3H)	1.59 (s, 3H)	1.58 (s, 3H)	-	-	-	-	-	-	-
H-3'	6.03 (s, 1H)	6.02 (s, 1H)	6.03 (s, 1H)	6.04 (s, 1H)	-	-	-	-	-	-	-
H-4'	1.96 (s, 3H)	1.97 (s, 3H)	1.95 (s, 3H)	1.93 (s, 3H)	-	-	-	-	-	-	-
H-1''	3.40 (m, 4H, 3.9)	2.77 (m, 4H, 3.5)	3.31 (m, 4H)	3.40 (m, 4H)	3.49 (m, 4H, 4.7)	2.80 (m, 4H, 5.1)	3.47 (m, 4H, 5.4)	3.52 (m, 4H, 5.0)	3.41 (t, 4H, 7.8)	3.50 (q, 4H, 7.1)	4.05 (d, 4H, 5.5)
H-2''	3.79 (m, 4H, 4.3)	3.55 (m, 4H, 3.9)	1.67 (m, 4H)	2.53 (m, 4H)	3.86 (m, 4H, 4.7)	3.84 (m, 4H, 5.1)	1.72 (m, 4H, 6.2)	2.57 (m, 4H, 5.1)	1.70 (m, 4H, 7.4)	1.27 (t, 6H, 7.0)	5,86-5.91 (m, 2H, 5.1)
H-3''	-	-	1.67 (m, 2H)	-	-	-	1.72 (m, 2H, 6.2)	-	0.94 (t, 6H, 7.6)	-	5.26 (a) (dd, 2H, 10.2; 1.2) 5.20 (b) (dd, 2H, 17.2; 1.2)
N-Me	-	-	-	2.33 (s, 3H)	-	-	-	2.34 (s, 3H)			

For compounds without assignment of **H-3''a H3''b** are equivalent hydrogens

Table 3. ^{13}C NMR spectroscopy data ($CDCl_3$, 100 MHz) of 2-*N,N'*-dialkylamino-1,4-naphthoquinone derivatives

	5b	5c	5d	5e	6b	6c	6d	6e	6f	6g	6h
C-1	184.6	184.8	184.4	184.7	183.7	183.6	183.5	183.6	183.9	183.8	183.4
C-2	150.0	151.3	151.4	150.4	153.6	153.2	154.1	153.7	151.1	150.9	151.3
C-3	124.3	125.6	123.4	124.2	112.0	111.6	110.4	111.7	106.0	105.6	107.9
C-4	183.8	183.9	184.1	183.9	182.9	183.1	183.4	183.0	182.7	182.7	183.1
C-5	126.2	126.2	126.1	126.1	126.7	126.7	126.6	126.6	126.4	126.3	126.5
C-6	132.5	132.6	132.2	132.4	132.6	132.5	132.2	132.4	131.8	131.8	132.0
C-7	133.6	133.6	133.4	133.5	134.0	134.0	133.7	133.8	133.7	133.7	133.8
C-8	125.9	125.9	125.7	125.8	125.6	125.5	125.4	125.5	125.2	125.2	125.3
C-9	132.4	132.3	132.6	132.3	132.7	132.7	132.9	132.8	132.8	132.8	132.6
C-10	138.5	138.5	137.2	138.1	132.2	132.2	132.5	132.3	132.8	132.7	132.5
C-1'	25.8	25.9	25.8	25.8	-	-	-	-	-	-	-
C-2'	132.2	132.2	132.4	132.3	-	-	-	-	-	-	-
C-3'	119.2	119.1	119.7	119.3	-	-	-	-	-	-	-
C-4'	20.4	20.5	20.3	20.3	-	-	-	-	-	-	-
C-1''	51.2	28.2	52.4	55.7	49.1	27.1	50.4	54.6	54.6	46.7	53.9
C-2''	67.6	53.3	26.9	50.6	66.4	51.8	25.7	48.8	20.7	12.6	132.0
C-3''	-	-	24.3	-	-	-	24.3	-	11.3	-	117.9
N-Me	-	-		46.2	-	-	-	46.0	-	-	-



4. Experimental

General

All common reagents and solvents were used as obtained from commercial suppliers (Sigma-Aldrich, Vetec, Dinamica) without further purification. Melting points were determined with an electrically heating metal block apparatus (Quimis) and are uncorrect. FTIR spectra were obtained in a Varian Mercury spectrophotometer using KBr film. Column chromatography (CC) was performed on silica gel G_{60} (70-230 mesh, ASTM, Merck), and thin-layer chromatography was performed on 0.2 mm plates GF_{254} (Merck), visualized with short-wavelength UV light. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 400 MHz and ANASAZI 90 MHz spectrometer with $CDCl_3$ or DMSO-d_6 as solvent. High-resolution mass spectra were obtained on an Autoflex III MALDI-TOF/TOF mass spectrometer (Bruker Daltonics, Billerica, MA, USA) in positive reflection mode. The **(1a)**, **(5a)** and **(6a)** obtention compounds were described previously in literature.[12,17,33]

General procedure for the synthesis of the nitrogenated derivatives of naphthoquinones from 2-methoxy-norlapachol and cyclic secondary amines (5b-e). 2-methoxy-*nor*-lapachol (242 mg, 1 mmol) (**5a**) was added to a stirred mixture of appropriate secondary amine (3 mmol) in methanol (1 ml) at room temperature. The reaction was followed by tlc and, after completion (about 18 hours), the products were precipitate with cold water followed by vacuum filtration and purified by *flash* chromatography on silica gel with hexane/ethyl acetate. ^{1}H and ^{13}C NMR spectroscopy data are in table 2 and 3.

2-(Morpholin-4-yl)-3-(2-methyl-propenyl)-[1,4]naphthoquinone $C_{18}H_{19}NO_3$ (5b). Red crystals (69 %), mp 81-3 °C. IR (KBr) υ_{max}: 3442; 3073; 3017; 2953; 2856; 1663; 1631; 1594; 1550; 1284; 1114. HRMS: calcd: 297.1360; found: 297.1350.

2-(Thiomorpholin-4-yl)-3-(2-methyl-propenyl)-[1,4]naphthoquinone $C_{18}H_{19}NO_2S$ (5c). Red crystals (64 %), mp 89-90 °C. IR (KBr) υ_{max}: 3442; 3070; 2963; 2850; 1666; 1631; 1595; 1551; 1292. HRMS: calcd: 313.1131; found: 313.1137.

2-(Piperidin-1-yl)-3-(2-methyl-propenyl)-[1,4]naphthoquinone $C_{19}H_{21}NO_2$ (5d). Red crystals (82 %), mp 74-5 °C. IR (KBr) υ_{max}: 3434; 3074; 3018; 2930; 2852; 1667; 1626; 1548; 1289. HRMS: calcd: 295.1567; found: 295.1553.

2-(*N*-Methyl-piperazin-1-yl)-3-(2-methyl-propenyl)-[1,4]naphthoquinone $C_{19}H_{22}N_2O_2$ (5e). Red crystals (87 %), mp 114-5 °C. IR (KBr) υ_{max}: 3447; 3013; 2964; 2882; 1665; 1629; 1555; 1290. HRMS: calcd: 310.1676; found: 310.1658.

General procedure for the synthesis of the nitrogenated derivatives of naphthoquinones from 2-methoxy-lawsone and cyclic and acyclic secondary amines (6b-h). 2-methoxy-lawsone (188 mg, 1 mmol) (**6a**) was added to appropriate amine (3 mmol for cyclic secondary amines and 20 mmol for acyclic secondary amines) under magnetic stirring at room temperature. The reaction was followed by tlc and, after completion (about 18 hours for cyclic secondary amines and 72 hours for acyclic secondary amines), the products were precipitate with cold water followed by vacuum filtration and purified by *flash* chromatography on silica gel with hexane/ethyl acetate. ^{1}H and ^{13}C NMR spectroscopy data are in table 2 and 3.

2-(Morpholin-4-yl)-[1,4]naphthoquinone $C_{14}H_{13}NO_3$ (6b). Orange crystals (87 %), mp 146-7 °C (lit. 134-5 °C). [32] IR (KBr) υ_{max}: 3459; 3070; 3037; 2974; 2873; 1677; 1645; 1567; 1305; 1119. HRMS: calcd: 243.0890; found: 243.09077.

2-(Thiomorpholin-4-yl)-[1,4]naphthoquinone $C_{14}H_{13}NO_2S$ (6c). Orange crystals (71 %), mp 125-7 °C. IR (KBr) υ_{max}: 3495; 3066; 3006; 2966; 2843; 1678;

1624; 1590; 1561; 1337; 1305; 1191. HRMS: calcd: 259.0662; found: 259.0692.

2-(Piperidin-1-yl)-[1,4]naphthoquinone $C_{15}H_{15}NO_2$ (6d). Orange crystals (72 %), mp 91-93 °C (lit. 86-8 °C). [23] IR (KBr) υ_{max}: 3451; 3068; 3017; 2936; 2855; 1677; 1628; 1590; 1561; 1242; 1126. HRMS: calcd: 241.1097; found: 241.1119.

2-(*N*-Methyl-piperazin-1-yl)-[1,4]naphthoquinone $C_{15}H_{16}N_2O_2$ (6e). Orange crystals (63 %), mp 118-9 °C (lit. 131.6 °C). [10] IR (KBr) υ_{max}: 3467; 3068; 3042; 2929; 2844; 1673; 1642; 1592; 1562; 1295; 1242; 1208; 1147. HRMS: calcd: 256.1206; found: 256.1205.

2-(*N,N'*-dipropylamino)-[1,4]naphthoquinone $C_{16}H_{19}NO_2$ (6f). Orange solid (42 %), mp 52-5 °C. IR (KBr) υ_{max}: 3450; 3067; 2965; 2873; 1675; 1619; 1592; 1554; 1298; 1243; 1150.

2-(*N,N'*-diethylamino)-[1,4]naphthoquinone $C_{14}H_{15}NO_2$ (6g). Orange solid (79 %), mp 65-6 °C (lit. 76-7 °C). [34] IR (KBr) υ_{max}: 3479; 3064; 3025; 2977; 2936; 1676; 1620; 1587; 1558; 1256; 1145. HRMS: calcd: 229.1097; found: 229.1103.

2-(*N,N'*-diallylamino)-[1,4]naphthoquinone $C_{16}H_{15}NO_2$ (6h). Orange solid (30 %), mp 93-6 °C. IR (KBr) υ_{max}: 3445; 3085; 3060; 2980; 2860; 1670; 1634; 1592; 1560; 1302; 1210. HRMS: calcd: 253.1097; found: 253.1093.

General procedure for the reaction of (1a), (5a) and (6a) with methylamine. To 1 mmol of 2-methoxy derivative of naphthoquinone dissolved in methylamine (excess) in MeOH and the mixture was kept under stirring at room temperature, for two hours. The products were isolated by precipitate with cold water followed by vacuum filtration.

2-(*N*-methylamino)-3-(3-methylbut-2-enyl)-[1,4]naphthoquinone $C_{16}H_{17}NO_2$ (1i). Red solid (94 %), mp 118-120 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 1.70 (d, 3H, *J*=1.2 Hz); 1.76 (s, 3H); 3.22 (d, 3H, *J*=5.9 Hz); 3.45 (d, 2H, *J*=5.9 Hz); 5.13 (m, 1H, *J*=5.1/1.2 Hz); 5.88 (br s, 1H); 7.56 (dt, 1H, *J*=7.6/1.2 Hz); 7.67 (dt, 1H, *J*=7.6/1.2 Hz); 7.98 (dd, 1H, *J*=7.6/1.4 Hz); 8.08 (dd, 1H, *J*=7.8/1.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): 183.0; 183.0; 146.3; 134.3; 133.5; 131.8; 131.7; 130.3; 126.2; 125.9; 123.7; 115.1; 32.4; 25.7; 23.4; 18.1. IR (KBr) υ_{max}: 3333; 3086; 3027; 2954; 2892; 1671; 1598; 1512; 1349; 1276. HRMS: calcd: 255.1254; found: 255.1252.

2-(*N*-methylamino)-3-(2-methylpropenyl)-[1,4]naphthoquinone $C_{15}H_{15}NO_2$ (5i). [36] Dark red solid (92 %), mp 100-3 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 1.51 (s, 3H); 1.95 (s, 3H); 2.88 (d, 3H, *J*=5.9 Hz); 5.98 (brs, 1H); 6.18 (s, 1H); 7.58 (dt, 1H, *J*=7.8/1.0 Hz); 7.68 (dt, 1H, *J*=7.4/1.4 Hz); 8.00 (dd. 1H, *J*=7.2/1.0 Hz); 8.08 (dd, 1H, *J*=1.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): 183.5; 182.9; 145.7; 138.2; 134.4; 133.6; 131.8; 130.4; 126.2; 125.9; 118.1; 113.4; 32.1; 25.4; 20.0. IR (KBr) υ_{max}: 3350; 3068; 2974; 1666; 1624; 1596; 1571; 1514; 1281. HRMS: calcd: 241.1097; found: 241.1101.

2-(*N*-methylamino)-[1,4]naphthoquinone $C_{11}H_9NO_2$ (6i). Orange solid (80 %), mp 215 °C (lit. 218 °C). [37] ^{1}H NMR (90 MHz, DMSO-d_6): 8.06 – 7.71 (m, 5H); 5.62 (s, 1H); 2.83 (d, 3H, *J*=5.1Hz). IR (KBr) υ_{max}: 3346; 3067; 3010; 2924; 2894; 1678; 1608; 1567; 1502.

General procedure for the reaction of (5a) and (6a) with dimethylamine. To 1 mmol of 2-methoxy derivative of naphthoquinone dissolved in dimethylamine (excess) in MeOH and the mixture was kept under stirring at room temperature. The solvent was removed under reduced pressure.

2-(*N,N'*-dimethylamino)-3-(2-methylpropenyl)-[1,4]naphthoquinone $C_{16}H_{17}NO_2$ (5j). Purified by chromatograph with silica gel using hexane/ethyl acetate 95:5 giving red solid (9 %), mp 92-95 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 1.47 (d, 3H, *J*=1.2 Hz); 1.96 (d, 3H, *J*=1.6 Hz); 3.0 (s, 6H); 6.21 (s, 1H); 7.60 (dt, 1H, *J*=7.4/1.6 Hz); 7.64 (dt, 1H, *J*=7.6/1.2 Hz); 7.97 (dd, 1H, *J*=7.6/1.4 Hz); 8.02 (dd, 1H, *J*=7.4/1.2 Hz). ^{13}C NMR (100

MHz, $CDCl_3$): 184.7; 184.5; 151.0; 137.2; 133.5; 132.7; 132.2; 132.1; 125.9; 125.6; 120.6; 120.0; 43.8; 25.7; 19.8. IR (KBr) υ_{max}: 3079; 2961; 2924; 2856; 1670; 1628; 1594; 1554; 1278. HRMS: calcd: 255.1254; found: 255.1206.

2-(*N,N'*-dimethylamino)-[1,4]naphthoquinone $C_{12}H_{11}NO_2$ (6j). Purified by chromatograph with silica gel using hexane/ethyl acetate 50:50 giving orange solid (95 %), mp 112-5 °C (lit. 106-8 °C).[38] ^{1}H NMR (90 MHz, $CDCl_3$): 8.05 – 7.86 (m, 2H); 7.53 - 7.67 (m, 2H); 5.77 (s, 1H); 3.18 (s, 3H); 3.17 (s, 3H). ^{13}C NMR (22.73 MHz, $CDCl_3$): 183.4; 182.5; 152.3; 137.8; 132.8; 132.5; 131.9; 126.4; 125.3; 106.8; 42.5. IR (KBr, cm^{-1}): 3065; 3012; 2929; 2860; 1675; 1619; 1592; 1563; 1299; 1271.

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