Synthesis of some NH- and NH,S- substituted 1,4-quinones

Ayşecik KAÇMAZ*

Department of Chemistry, Faculty of Engineering, Istanbul University-Cerrahpaşa, Istanbul, Turkey

* Correspondence: kacmaz@istanbul.edu.tr

1. Introduction

Quinones are widespread in nature [1,2] (in plants, fungi, bacteria etc.), and many synthetic or natural quinones possess various pharmacological properties including anticancer [3–5], antibacterial [6], antifungal [6], antiinflammatory [7], antitubercular [8], and molluscidal [9] activities. Moreover, substituents such as halogen, amino, thio groups of the synthetic quinone derivatives can increase their pharmacological activities, such as antibacterial, cytotoxic, and antiproliferative [3,10,11]. Quinonoid systems' pharmacological specialties are related to their capacity to produce free radicals or semiquinones in redox reactions [11–13].

Among quinones, 1,4-naphthoquinone scaffold are found in many natural or synthetic products such as menadione, juglone, plumbagin, alkannin, and shikonin [14–16]. In addition, 1,4-naphthoquinone derivatives have received a considerable interest in biological applications with their antibacterial [11], antiatherosclerosis [17], antiinflammatory [18], antitumor [18], and cytoxic [19] activities. Thus, many reports on the reactions of 1,4-naphthoquinones with amines [3,5,13], anilines [11,20], phenols [21], thiols [3,5,22], aminopyridine [23], alcohol [24,25], glycol [25] are available in the literature. In this study, compounds 10, 12, 13, 15, 17, and 19, 20 have NH- and NH,SR- substituted-1,4-naphthoquinone skeleton, respectively.

Abstract: A series of NH-substituted-1,4-quinones, possessing one, two, three or not chlorine, were synthesized by the reaction between different quinones (p-chloranil (1), p-toluquinone (2), or 2,3-dichloro-1,4-naphthoquinone (3)) and (-)-cis-myrtantylamine (5) via nucleophilic reactions. Moreover, 2-bromo,1,4-naphthoquinone (4) was reacted with 2-(methylthio)ethylamine (11) to produce amino-substituted naphthoquinones (12 and 13), bearing with bromine and not bromine. In addition, 2-bromo,1,4-naphthoquinone (4) was reacted with 4'-aminodibenzo-18-crown-6 (14) and 4'-aminobenzo-18-crown-6 (16) to yield crown-containing 1,4-naphthoquinones (15 and 17), respectively. New compounds were characterized, providing ¹H NMR, ¹³C NMR, FTIR, MS-ESI, UV/Vis and elemental analysis.

Key words: Quinones, amines, p-chloranil, p-toluquinone, 2,3-dichloro-1,4-naphthoquinone
substituted)-1,4-benzoquinone structures, respectively, synthesized from \textit{p}-chloranil \textit{1} and primary amine \textit{5}. Moreover, compounds \textit{8} and \textit{9} are di-amination products of methyl-\textit{p}-benzoquinone \textit{2}.

Different research groups from our university have reported some N-, NH- or SR- substituted 1,4-naphtho(benzo)quinones \cite{22,40–45}. Some of these compounds have antifungal, antibacterial, antioxidant, and cytotoxic activities. Recently, our research group have reported some 1,4-quinone derivatives \cite{46–49} with their antifungal, antibacterial activities, electrochemical properties, or antiproliferative effects. Moreover, in the literature, there are many reports regarding biologically important compounds, including benzoquinone or naphthoquinone core \cite{3,30,50}.

The importance of this kind of compounds has motivated this study to synthesize 1,4-naphtho(benzo)quinones \cite{22,40–45}. Some of these compounds have antifungal, antibacterial, antioxidant, and cytotoxic activities.

2. Materials and methods

2.1. Chemistry

All the chemicals used (\textit{1}, \textit{2}, \textit{3}, \textit{4}, \textit{5}, \textit{11}, \textit{14}, \textit{16}, \textit{18}) were commercially purchased and used without further purification. To measure melting points, Buchi B-540 was used. The elemental analyses, IR spectra, and UV-Vis spectra were carried out by using the ThermoFinnigan Flash EA1112, Thermo Scientific Nicolet 6700, and Shimadzu UV/Vis spectrophotometer 2600 (in CHCl\textsubscript{3}), respectively. The UV-Vis spectra were recorded on a Shimadzu UV/Vis spectrophotometer 2600, in CHCl\textsubscript{3}. The mass spectra were performed on a ThermoFinnigan LCQ AdvantageMAX system. \textit{H} and \textit{13}C NMR spectra were performed in CDCl\textsubscript{3} solution on a spectrometer (Varian Unity Inova). Chemical shifts (\textit{\delta}, ppm) are reported by using tetramethylsilane as internal standard. Column chromatography was performed on glass columns by using silica gel (70–230 mesh).

2.2. Synthesis of quinonoid compounds

2.2.1. Synthesis of \textit{2-((6,6-dimethylbicyclo[3.1.1]heptan-2-ylmethyl)amino)-3,5,6-trichlorocyclohexa-2,5-diene-1,4-dione (6)} and \textit{2,5-bis((6,6-dimethylbicyclo[3.1.1]heptan-2-ylmethyl)amino)-3,6-dichlorocyclohexa-2,5-diene-1,4-dione (7)}

The solution of \textit{1} (640 mg, 2.6 mmol) and (-)-\textit{cis}-myrtanylamine \textit{5} (400 mg, 2.6 mmol) in dichloromethane was allowed to stir at room temperature by monitoring the progression of the reaction mixture with Thin-layer chromatography (TLC). Then, the reaction mixture was extracted with water and CHCl\textsubscript{3}. The organics were dried over sodium sulfate and removed under vacuo; thus, the crude mixture was obtained. The crude mixture was then purified by column chromatography (stationary phase) with n-hexane/CH\textsubscript{2}Cl\textsubscript{2} (1/2) (mobil phase) to afford products 6 and 7.

\textbf{2-((6,6-dimethylbicyclo[3.1.1]heptan-2-ylmethyl)amino)-3,5,6-trichlorocyclohexa-2,5-diene-1,4-dione (6):} \textit{R}_f = 0.8 (CH\textsubscript{2}Cl\textsubscript{2}); Yield: 10% (100 mg); Dark purple viscous oil; UV (CHCl\textsubscript{3}), \textit{\lambda} max nm (log \varepsilon): 244 (4.87), 320 (4.71), 529 (4.06); IR (ATR): 3336, 2906, 2870, 1683, 1648, 1606, 1572, 1514, 1459, 1218, 1083; \textit{H} NMR (CDCl\textsubscript{3}) \textit{\delta}: 5.88 (1H, NH, brs), 3.60–3.80 (m, 2H, -CH\textsubscript{2}-NH), 2.20–2.40 (m, 2H), 1.80–2.00 (m, 5H), 0.60–1.40 (m, 8H); \textit{13}C NMR (CDCl\textsubscript{3}) \textit{\delta}: 174.48 (C=O), 173.15, 143.09, 135.59, 129.40, 95.81, 50.63, 43.48, 42.62, 41.23, 38.72, 33.23, 29.71, 27.90, 25.82, 23.22, 19.60; MS \textit{m/z} 360.4 ([M-H], 100%). Anal. calc. for C\textsubscript{16}H\textsubscript{18}Cl\textsubscript{3}NO\textsubscript{2} (362.68): C 52.99, H 5.00, N 3.86; Found: C 53.25, H 5.10, N 3.98.

\textbf{2,5-bis((6,6-dimethylbicyclo[3.1.1]heptan-2-ylmethyl)amino)-3,6-dichlorocyclohexa-2,5-diene-1,4-dione (7):} \textit{R}_f = 0.9 (CH\textsubscript{2}Cl\textsubscript{2}); Yield: 36% (225 mg); Grey solid; m.p. 233–235 °C; UV (CHCl\textsubscript{3}), \textit{\lambda} max nm (log \varepsilon): 361 (4.92), 242 (4.25); IR (ATR): 3244, 2897, 1655, 1567, 1489, 1440, 1330, 1056; \textit{H} NMR (CDCl\textsubscript{3}) \textit{\delta}: 7.18 (brs, 2H, NH), 3.88–3.96 (2H, m), 3.75–3.87 (2H, m), 2.30–2.50 (4H, m), 1.80–2.10 (10H, m), 1.40–1.60 (m, 2H), 1.21 (s, 6H), 1.04 (s, 6H), 0.95 (d, 2H, \textit{J} = 3 Hz), Anal. calc. for C\textsubscript{16}H\textsubscript{21}Cl\textsubscript{2}NO\textsubscript{2} (346.68): C 54.85, H 5.53, N 3.46; Found: C 55.15, H 5.33, N 3.48.

\textbf{Figure.} Quinones used in the present work (\textit{p}-chloranil \textit{1}, methyl-\textit{p}-benzoquinone \textit{2}, 2,3-dichloro-1,4-naphthoquinone \textit{3} and 2-bromo-1,4-naphthoquinone \textit{4}).
2.2.2. Synthesis of 3,5-bis-(6,6-dimethylbicyclo[3.1.1]heptan-2-ylmethylamino)-2-methylcyclohexa-2,5-diene-1,4-dione (8) and 2,5-bis-(6,6-dimethylbicyclo[3.1.1]heptan-2-ylmethylamino)cyclohexa-2,5-diene-1,4-dione (9)

The solution of methyl-p-benzoquinone 2 (398 mg, 3.26 mmol) and (-)-cis-myrtamylamine 5 (500 mg, 3.26 mmol) in EtOH (20 mL) and water (1.5 mL) in the presence of Na$_2$CO$_3$ was allowed to stir at room temperature by monitoring the progression of the reaction mixture with TLC. Then, the reaction mixture was extracted with water and CHCl$_3$. The organics were dried over sodium sulfate and removed under vacuo; thus, the crude mixture was obtained. The crude mixture was then purified by column chromatography on silica gel (stationary phase) with n-hexane/CH$_2$Cl$_2$ (2/1) (mobil phase) to afford products 8 and 9.

2.2.3. Synthesis of 2-(6,6-dimethylbicyclo[3.1.1]heptan-2-ylmethylamino)-3-chloronaphthalene-1,4-dione (10)

The solution of 2,3-dichloro-1,4-naphthoquinone 7 (740 mg, 3.26 mmol) and (-)-cis-myrtamylamine 5 (500 mg, 3.26 mmol) in CH$_2$Cl$_2$ was allowed to stir at room temperature by monitoring the progression of the reaction mixture with TLC. Then, the reaction mixture was extracted with water and CHCl$_3$. The organics were dried over sodium sulfate and removed under vacuo; thus, the crude mixture was obtained. The crude mixture was then purified by column chromatography on silica gel (stationary phase) with n-hexane/CH$_2$Cl$_2$ (1/3) (mobil phase) to afford product 10: R$_f$ = 0.6 (CH$_2$Cl$_2$); Yield: 10% (69 mg); Purple solid; m.p. 198–200 °C; IR (cm$^{-1}$): ν = 3250, 2989, 1637, 1601, 1553, 1458, 1341, 1237, 1088; $^1$H NMR (CDCl$_3$) δ: 6.72 (brs, 2H, NH), 5.25 (s, 1H, CH$_{quinone}$), 3.59 (d, 2H, CH$_{myrt}$, $^J_F$ = 7.80 Hz), 3.07–3.19 (m, 2H, 2×CH$_{myrt}$), 2.25–2.45 (m, 4H, CH$_{myrt}$), 2.07 (s, 3H, CH$_{quinone}$), 1.82–2.05 (10H, m, CH$_3$), 1.41–1.56 (2H, m, CH$_3$), 1.12 (s, 3H), 0.98 (s, 3H);

2.2.4. Synthesis of 2-(2-(methylthio)ethylamino)naphthalene-1,4-dione (11) and 2-(2-(methylthio)ethylamino)naphthalene-1,4-dione (12)

A solution of 4 (1.3 g, 5.48 mmol) and 2-(methylthio)ethylamine 11 (0.5 g, 5.48 mmol) in CH$_2$Cl$_2$ was allowed to stir at room temperature by monitoring the progression of the reaction mixture with TLC. Then, the reaction mixture was extracted with water and CHCl$_3$. The organics were dried over sodium sulfate and removed under vacuo; thus, the crude mixture was obtained. The crude mixture was then purified by column chromatography on silica gel (stationary phase) with n-hexane/CH$_2$Cl$_2$ (1/1) (mobil phase) to afford products 12 and 13.

2-(methylthio)ethylamino)naphthalene-1,4-dione (12): R$_f$ = 0.5(CH$_2$Cl$_2$); Yield: 7% (125 mg); Dark red solid; m.p. 102–104 °C; UV (CHCl$_3$), $\lambda_{max}$ nm (log e): 277 (4.48), 487 (3.42); IR (ATR): 3306, 1673, 1591, 1560, 1513, 1441,1327, 1251, 1123; $^1$C NMR (CDCl$_3$) δ: 8.12 (d, 1H, CH$_{naph}$, $^J_F$ = 7.3 Hz); 8.02 (d, 1H, CH$_{naph}$, $^J_F$ = 7.7 Hz), 7.71 (t, 1H, CH$_{naph}$, $^J_F$ = 7.6 Hz), 7.62 (t, 1H, CH$_{naph}$, $^J_F$ = 7.6 Hz), 6.44 (d, 1H, CH$_{naph}$, $^J_F$ = 6.3 Hz), 2.83 (t, 2H, CH$_3$-S, $^J_F$ = 6.3 Hz); 2.16 (s, 3H, CH$_3$); $^{13}$C NMR (CDCl$_3$) δ: 179.97, 176.37 (C=O=naph); 144.3 (=C=N); 134.9, 132.8, 132.3, 129.7, 126.8 (C$_{naph}$); 50.3, 43.5, 42.7, 41.3, 38.7, 33.3, 27.9, 25.9, 23.2, 19.7; MS/m/z 342.5 ([M$^+$], 100%). Anal. calc. for C$_{16}$H$_{12}$Cl$_2$O$_2$ (343.85): C 69.86, H 6.45, N 4.07; Found: C 69.47, H 6.55, N 3.75.

2.2.5. Synthesis of 2-(2-(methylthio)ethylamino)-3-bromonaphthalene-1,4-dione (13)

A solution of 4 (1.3 g, 5.48 mmol) and 2-(methylthio)ethylamine 11 (0.5 g, 5.48 mmol) in CH$_2$Cl$_2$ was allowed to stir at room temperature by monitoring the progression of the reaction mixture with TLC. Then, the reaction mixture was extracted with water and CHCl$_3$. The organics were dried over sodium sulfate and removed under vacuo; thus, the crude mixture was obtained. The crude mixture was then purified by column chromatography on silica gel (stationary phase) with n-hexane/CH$_2$Cl$_2$ (1/1) (mobil phase) to afford products 12 and 13.

2-(methylthio)ethylamino)naphthalene-1,4-dione (13): R$_f$ = 0.2(CH$_2$Cl$_2$); Yield: 30% (410 mg); Orange solide; m.p 139–141 °C; UV (CHCl$_3$), $\lambda_{max}$ (log e): 271 (4.21), 442 (3.37); IR (ATR): 3360, 3237, 2910, 1664, 1591, 1563, 1498, 1444,
2.2.5. Synthesis of Compound 15
The solution of 4 (63 mg, 0.27 mmol) and 4'-aminodibenzo-18-crown-6 14 (0.1 g, 0.27 mmol) with CH₃COONa in CHCl₃ and ethanol was allowed to stir at room temperature by monitoring the progression the reaction mixture with TLC. Then, the reaction mixture was extracted with water and CHCl₃. The organics were dried over sodium sulfate and removed under vacuo; thus, the crude mixture was obtained. The crude mixture was then purified by column chromatography on silica gel (stationary phase) with ethyl acetate/CHCl₃ (10/1) to afford product 15: Yield: 69% (112 mg); Dark purple solid; m.p. 187–189 °C; IR (ATR): 3277, 2987, 2921, 1669, 1649, 1592, 1566, 1509, 1225; ¹H NMR (CDCl₃) δ: 8.13 (1H, dd, CH₃); 7.81 (1H, d, CH₃); 7.61 (td, 1H, CH₃); δ: 183.0, 181.6 (C=O); 147.7; 134.7; 133.5; 132.1; 130.5; 126.8; 126.6; 126.5; 116.8; 115.4; 108.4 (CH₃); 69.9, 69.7, 68.8, 67.7, 67.5, 58.9 (CH₂); 32.2 (CH₂); 31.9, 29.64, 29.62, 29.60, 29.5, 29.3, 29.1, 28.7, 24.0, 22.7, 19.7 (CH₃); 13.7 (CH₃); MS m/z 682.3 ([M-H]⁻, 100%). Anal. calc. for C₈₅H₆₃BrNO₆ (562.41): C, 55.53; H, 4.62; N, 2.29. Found C, 54.93; H, 4.92; N, 2.49.

2.2.6. Synthesis of compound 17
The solution of 2-bromo-1,4-naphthoquinone 4 (72 mg, 0.30 mmol) and 4'-aminobenzo-18-crown-6 16 (0.1 g, 0.30 mmol) with Na₂CO₃ in CH₂Cl₂ was allowed to stir at reflux temperature by monitoring the progression the reaction mixture with TLC. Then, the reaction mixture was extracted with water and CHCl₃. The organics were dried over sodium sulfate and removed under vacuo; thus, the crude mixture was obtained. The crude mixture was then purified by column chromatography on silica gel (stationary phase) with ethyl acetate/CH₂Cl₂ (10/1) to afford product 17: Yield: 29% (50 mg); Dark purple solid; m.p. 138–141 °C; IR (ATR): 3139, 2957, 2872, 1668, 1649, 1592, 1526, 1509, 1225; ¹H NMR (CDCl₃) δ: 8.09 (dd, 1H, CH₃); 7.72 (td, 1H, CH₃); δ: 181.0, 180.4 (C=O); 147.7; 134.7; 133.6; 132.6; 130.5; 126.3; 126.2; 101.2; 40.8 (NH-CH₂); 32.2 (-CH₂-S); 15.3 (CH₃); MS m/z 247.9 ([M+H]⁺, 100%). Anal. calc. for C₁₅H₁₃NO₇S (247.31): C, 63.13; H, 5.30; N, 6.66; S, 12.97; Found: C, 63.12; H, 5.12; N, 5.58, S, 13.33.

2.2.7. Synthesis of compound 19
The solution of 17 (40 mg, 0.07 mmol) and 1-dodecanethiol 18 (510 mg, 2.52 mmol) in CH₂Cl₂ in the presence of triethylamine (2-3 mL) was allowed to stir at reflux temperature by monitoring the progression the reaction mixture with TLC. Then, the reaction mixture was extracted with water and CHCl₃. The organics were dried over sodium sulfate and removed under vacuo; thus, the crude mixture was obtained. The crude mixture was then purified by column chromatography on silica gel (stationary phase) with ethyl acetate/CH₂Cl₂ (1/1) to afford product 19: Yield: 80% (39mg); Dark purple viscous oil; IR (ATR): 3444, 2957, 2921, 2851, 1665, 1591, 1550, 1430, 1320; ¹H NMR (CDCl₃) δ: 8.07 (1H, dd, CH₃); δ: 7.81 (1H, d, CH₃); 7.71 (td, 1H, CH₃); δ: 7.32 (1H, d, CH₃); 7.24 (td, 1H, CH₃); δ: 1.47 Hz, J = 0.98 Hz); 7.99 (dd, 1H, CH₃); δ: 7.32 Hz, J = 0.98 Hz); 7.74 (brs, 1H, NH); 7.68 (td, 1H, CH₃); δ: 5.75 Hz, J = 1.47 Hz); 7.59 (td, 1H, CH₃); δ: 7.58 Hz, J = 1.31 Hz); 6.71 (1H, CH₢); δ: 8.78 Hz); 6.52 (dd, 1H, CH₢); δ: 8.30 Hz, J = 1.95 Hz); 6.49 (s, 1H, CH₢); δ: 2.44 Hz); 4.00–4.15 (m, 4H, 2CH₂); 3.80–3.95 (m, 4H, 2CH₂); 3.68–3.80 (m, 8H, 4CH₂); 3.21 (t, 2H, S-CH₂); δ: 8.54 Hz), 1.65–0.85 (m, 20H, 10 CH₢); 0.80 (3H, s, CH₢); δ: 7.08 Hz); ¹C NMR (CDCl₃) δ: 181.0, 180.4 (C=O); 147.5, 145.4, 145.3, 134.6, 133.6, 132.6, 132.4, 130.5, 126.8, 126.6, 126.5, 116.8, 115.4, 108.4 (CH₢); δ: 69.9, 69.7, 68.8, 67.7, 67.5, 58.9 (CH₂); 31.9, 29.64, 29.62, 29.60, 29.5, 29.3, 29.1, 28.7, 24.0, 22.7, 19.7 (CH₢); 13.7 (CH₢); MS m/z 682.6 ([M-H]⁻, 20%) and 249.5 (M⁻ - 433). Anal. calc. for C₃₈H₃₅NO₇S (683.89): C, 66.74; H, 7.81; N, 2.05; S, 4.69. Found C, 66.98; H, 7.59; N, 2.35, S, 5.00.

2.2.8. Synthesis of 2-(2-(methylthio)ethylamino)-3-(dodecylthio)naphthalene-1,4-dione (20)
The solution of 13 (46 mg, 0.19 mmol) and 1-dodecanethiol 18 (70 mg, 0.35 mmol) in ethanol and dichloromethane in the presence of triethylamine (1-2 mL) was allowed to stir at reflux temperature by monitoring the progression the reaction mixture with TLC. Then, the reaction mixture was extracted with water and CHCl₃. The organics were dried over sodium...
sulfate and removed under vacuum; thus, the crude mixture was obtained. The crude mixture was then purified by column chromatography on silica gel (stationary phase) with chloroform (mobile phase) to afford product 20: R = 0.4 (CHCl₃); Yield: 60% (51 mg); Dark red viscous oil; IR (ATR): 3305, 2956, 2918, 2849, 1668, 1552, 1498, 1287; ¹H NMR (CDCl₃, δ: 8.15 (1H, dd, CH₃₉), J = 7.81 Hz, J’= 0.98 Hz); 8.04 (1H, dd, CH₃₉, J = 7.81 Hz, J’ = 0.97 Hz); 7.63 (td, 1H, CH₃₉, J = 7.81 Hz, J’ = 0.98 Hz); 7.72 (td, 1H, CH₃₉, J = 7.81 Hz, J’ = 0.98 Hz); 6.70–6.80 (brs, 1H, NH), 4.14 (t, 2H, NH-CH₃), J = 6.36 Hz), 2.84 (t, 4H, 2 x CH₂-S, J = 6.45 Hz), 2.17 (s, 3H, S-CH₃), 1.20–1.35 (m, 20H, CH₂₉), 1.20–1.35 (m, 20H, CH₂₉), 0.75–0.95 (s, 3H, CH₃₉), 35.01, 34.67, 31.91, 29.58, 29.54, 29.34, 28.92, 22.69 (m, CH₂₉), 15.07 (t, S-CH₃), 11.14 (CH₂-S), MS m/z 447.1 ([M⁺], 100%). Anal. calc. for C₁₉H₂₂NO₂S: C, 67.07; H, 8.33; N, 3.13; Found: C, 67.37; H, 8.10; N, 3.38.

3. Results and discussion

Initial investigation began with the reactions of 5 with different 1,4-(benzo/naphtho)quinones (1, 2, and 3) to yield a series of new benzoquinone and naphthoquinone derivatives (6–8, 10) as shown in Scheme. Secondly, 2-bromo-1,4-naphthoquinone 4 reacted with and 2-(methylthio)ethylamine 11 to yield 2-(NH-substituted)-3-bromo-1,4-naphthoquinone 12 and 2-(NH-substituted)-1,4-naphthoquinone 13. The reaction between 13 and 1-dodecanethiol 18 resulted NH-S-substituted naphthoquinone compound 20. In addition, 4 reacted with 14 and 16, respectively, to produce crown-containing 1,4-naphthoquinones 15 and 17. NH-S-substituted- and having crown ether moiety, 1,4-naphthoquinone compound 19, was synthesized the reaction between 17 and 1-dodecanethiol 18.

The reaction between chloranil and primary/secondary amines gives the NH-/N-substituted quinones. Some examples of such reactions have been previously described [51–54]. For example, Singh Gautam BP et al. synthesized and characterized the compound 2,5-dichloro-3,6-bis-(methylamino)-1,4-benzoquinone, which was capable of forming molecular complexes like chloranilic acid [54]. In this work, compounds 6 and 7, having mono-NH-substituted-tri-chloro-1,4-benzoquinone and 2,5-dichloro-3,6-bis(NH-substituted)-1,4-benzoquinone structures, respectively, were synthesized by the reaction of 1:1 molar ratio of p-chloranil 1 with (-)-cis-myrtanylamine 5 in dichloromethane at room temperature. The ¹³C-NMR spectrum of compound 7 shows three symmetric carbon signals at quinone moiety, at 172.12 ppm (C=O), at 145.44 ppm (C-N) and at 99.23 ppm (C-Cl). Moreover, ¹H-NMR spectrum of 7 showed N-H proton at 7.18 ppm (brs) and other protons at 0.9–4.0 ppm region. Mass spectra of 6 and 7 exhibited m/z [M-H] = 360.4 and m/z [M+H]⁺ = 479.1, respectively, as expected.

The reactions between methyl-substituted quinones and amines were studied by Cameron et al. [55,56]. For example, o-Xyloquinone with methylamine gave 2-methyl-3,6-bis(methylamino)-1,4-benzoquinone (39%) yield by displacement of a methyl by an amino-group [56]. Then, Kumaratani et al. carried out the reaction of toluidine with excess n-butylamine [57]. Thus, the results obtained from the study gave the formation of both of 3,6-bis-(n-butylamino)-toluquinone (32%) and 2,5-bis(n-butylamino)-p-benzoquinone (8%, not including methyl group) [57]. Similarly, in the present work, methyl-p-benzoquinone 2 was reacted with primary amine 5 in equimolar ratio in EtOH and water in the presence of Na₂CO₃, to afford 3,5-bis(NH-substituted)-2-methyl-p-benzoquinone 8 (10%) and 2,5-bis(NH-substituted)-p-benzoquinone 9 (78%, not including methyl group). Moreover, compound 9 was synthesized in our previous study [47] but from the reaction between p-benzoquinone and primary amine 5 in equimolar ratio in dichloromethane. While CH₉₉ signals of carbon and signals of 8 could be observed in ¹H and ¹³C-NMR spectra at 2.07 ppm and at 10.44 ppm, respectively, in the ¹H and ¹³C-NMR spectra of 9, the disappearance of CH₉₉ signals supported to the formation of 2,5(NH-substituted)-p-benzoquinone structure 9. Moreover, mass spectra of 8 and 9 exhibited peaks at m/z [M+H]⁺ = 425.3 and m/z [M+H]⁺ = 411.3, respectively.

In the literature, there are some reports on the different location of mono- or bis- (NH) groups on the methyl-1,4-quinine moiety, which including 3,5-bis(NH-substituted)-2-methyl-p-benzoquinone, 3,6-bis(NH-substituted)-2-methyl-p-benzoquinone, 2-(NH-substituted)-6-methyl-1,4-benzoquinone, 2-(NH-substituted)-5-methyl-1,4-benzoquinone derivatives [37,58–60]. In this work, 8 has 3,5-bis(NH-substituted)-2-methyl-p-benzoquinone structure.

Monosubstitution of the 2,3-dichloro-1,4-naphthoquinone 3 with (-)-cis-myrtanylamine 5 was obtained by using dichloromethane as the solvent to yield compound 10. ¹H-NMR spectrum of 10 showed two doublet of doublets due to CH₉₉ (8.07, 7.95 ppm) and two doublet of triplets CH₉₉ (7.64 and 7.53 ppm) with proper splitting patterns. In addition, compound 10 displayed signal due to amine (-NH) at 6.03 ppm.

The reaction of 4 with 11 yielded two new amino-substituted-1,4-naphthoquinones (12 and 13), including bromine and not bromine, respectively. In the ¹H-NMR spectrum of 13, a singlet appeared at 5.75 ppm, which was assignable to the proton presence of 13 instead of bromine. In addition, in the FTIR spectra of these derivatives (12 and 13) the characteristic bands observed at 1673 and 1664 cm⁻¹ were assignable to the C=O stretching vibrations, respectively.
The reactions of 4 with crown ethers (14 and 16, respectively) were studied and the products 15 and 17 were obtained, respectively. The reaction product 15 had four CH$_{napht}$ peaks at 8.21, 8.13, 7.77, 7.70 and sixteen –O-CH$_2$ peaks at 4.13-4.25 (m, 8H), 4.00–4.10 (m, 8H) ppm, in the $^1$H NMR spectrum. In addition, compound 17 exhibited four CH$_{napht}$ peaks at 8.13,
8.04, 7.69, 7.61 and twenty –O-CH\textsubscript{3} peaks at 4.05–4.13 (m, 4H), 3.82–3.90 (m, 4H), 3.68–3.74 (m, 4H), 3.62–3.68 (m, 8H), in the \textsuperscript{1}H NMR spectrum.

Compound 17 was reacted with 1-dodecanethiol 18, in the presence of triethylamine, providing both of NH- and SR-substituted-1,4-naphthoquinone 19, which included crown structure. In the proton NMR spectrum of 19, CH\textsubscript{naph}, CH\textsubscript{1,4}, and CH\textsubscript{rown} exhibited signals in a lower field than in the starting compound 17, because of the bonding S-(CH\textsubscript{2})\textsubscript{naph}, to quinoid structure, instead of bromine.

To produce NH,SR-substituted-1,4-naphthoquinone derivative 20, 1-dodecanethiol 18 were added a reaction mixture of 13 in solution of dichloromethane and ethanol in the presence of triethylamine. \textsuperscript{1}H NMR spectrum of 20 exhibited methyl proton of 1-dodecanethiolate (–S(CH\textsubscript{2})\textsubscript{11}–CH\textsubscript{3}) at 0.89 ppm, methyl proton of –NH-C\textsubscript{rown}, S-CH\textsubscript{2}, and CH\textsubscript{rown} exhibited signals in a lower field than in the starting compound 17, because of the bonding S-(CH\textsubscript{2})\textsubscript{naph}, to quinoid structure, instead of bromine.

4. Conclusion

The main goal of this study is to synthesize NH-substituted-1,4-benzo(naphtho)quinones (6-10, 12, 13, 15, 17) starting from different quinones (1, 2, 3, or 4) with amines (–)-cis-myrtanylamino 5 or 4-tert-butylbenzylamine 11. The formation of both of NH- and SR- substituted-1,4-naphthoquinones (19, 20) were obtained from NH-substituted-1,4-naphthoquinones 17 and 13 with 1-dodecanethiol 18, respectively. Moreover, compounds 15, 17, and 19 included crown-ether moiety. Medium yields (80% and 60%) were observed for NH-S-substituted naphthoquinones (19 and 20), whereas lower yields were generally produced for NH-substituted naphthoquinones. New products were verified by elemental analysis, UV-Vis, FTIR, \textsuperscript{1}H-NMR, \textsuperscript{13}C-NMR, and MS-ESI spectroscopy.

Acknowledgment

Support was received for this work under Project (Project Number: FBA-2017-22046, the Research Fund of İstanbul University-Cerrahpaşa). We would like to thank for the financial support.

References

1. Monks TJ, Hanzlik RP, Cohen GM, Ross D, Graham DG. Quinone chemistry and toxicity. Toxicology and Applied Pharmacology 1992; 112: 2-16. doi: 10.1016/0041-008X(92)90273-U
2. Kutyrev AA. Nucleophilic reactions of quinones. Tetrahedron report number 298, Tetrahedron 1991; 47 (38): 8043-8065. doi: 10.1016/S0040-4020(01)91002-6
3. Delarmelina M, Daltone RD, Cerri MF, Madeira KP, Rangel LBA et al. Synthesis, Antitumor Activity and Docking of 2,3-(Substituted)-1,4-naphthoquinone derivatives containing nitrogen, oxygen and sulfur. Journal of the Brazilian Chemical Society 2015; 26 (9): 1804-1816. doi: 10.5935/0103-5053.20150157
4. Neckers L, Schulte TW, Mimnaugh E. Geldanamycin as a potential anti-cancer agent: its molecular target and biochemical activity. Investigational. New Drugs 1999; 17: 361-373. doi: 10.1023/A:1006382320697
5. Tandon VK, Maurya HK, Kumar S, Rashid A, Panda D. Synthesis and evaluation of 2-Heteroaryl and 2,3-Diheteroaryl-1,4-naphthoquinones that potently induce apoptosis in cancer cells. RSC Advances 2014; 4: 12441-12447. doi: 10.1039/C3RA47720G
6. Gafner S, Wolfender JL, Nianga M, Stoeckli-Evans H, Hostettmann K. Antifungal and antibacterial naphthoquinones from Newbouldia laevis roots. Phytochemistry 1996; 42 (5): 1315-1320. doi: 10.1016/0031-9422(96)00135-5
7. Optiz W, Pelster B, Fruchtmann R, Krupka U, Gauss W et al. 1,4-Naphthoquinone derivatives having anti-inflammatory action. U.S. Patent 4,628,062, Dec. 9, 1986.
8. Tran T, Saheba E, Arcerio AV, Chavez V, Li Q-yi et al. Quinones as antimycobacterial agents. Bioorganic & Medicinal Chemistry 2004; 12: 4809-4813. doi: 10.1016/j.bmc.2004.07.015
9. Silva TMS, Camara CA, Barbosa TP, Soares AZ, Cunha LC da et al. Molluscicidal activity of synthetic lapachol amino and hydrogenated derivatives. Bioorganic & Medicinal Chemistry 2005; 13: 193-196. doi: 10.1016/j.bmc.2004.09.043
10. Ryu, CK, Lee IK, Jung SH, Lee CO. Synthesis and cytotoxic activities of 6-chloro-7-arylamino-5,8-isoquinolinediones. Bioorganic & Medicinal Chemistry Letters 1999; 9: 1075-1080. doi: 10.1016/S0960-894X(99)00152-3
11. Satheshkumar A, Ganesh K, Elango KP. Charge transfer facilitated direct electrophilic substitution in phenylaminonaphthoquinones: experimental, theoretical and electrochemical studies. New Journal of Chemistry 2014; 38: 993-1003. doi: 10.1039/C3NJ01228F
12. Tudor G, Gutierrez P, Aguilera-Gutierrez A, Sausville EA. Cytotoxicity and apoptosis of benzoquinones: redox cycling, cytochrome c release, and BAD protein expression. Biochemical Pharmacology 2003; 65: 1061-1075. doi: 10.1016/S0006-2952(03)00013-3

13. Pal S, Jadhav M, Weyhirmüller T, Patil Y, Nethaji M et al. Molecular structures and antiproliferative activity of side-chain saturated and homologated analogs of 2-chloro-3-(n-alkylamino)-1,4-naphthoquinone. Journal of Molecular Structure 2013; 1049: 355-361. doi: 10.1016/j.molstruc.2013.06.062

14. Bao N, Ou J, Xu M, Guan F, Shi W et al. Novel NO-releasing plumbagin derivatives: design, synthesis and evaluation of antiproliferative activity. European Journal of Medicinal Chemistry 2017; 137: 88-95. doi: 10.1016/j.ejmech.2017.05.046

15. Babula P, Vaverkova V, Poborilova Z, Ballova L, Masarik M et al. Phytotoxic action of naphthoquinone juglone demonstrated on lettuce seedling roots. Plant Physiology and Biochemistry 2014; 84: 78-86. doi: 10.1016/j.plaphy.2014.08.027

16. Papageorgiou VP, Assimopoulou AN, Couladouros E, Hepworth D, Nicolaou KC. The chemistry and biology of alkannin, shikonin, and related naphthazarin natural products. Angewandte. Chemie International Edition 1999; 38: 270-300. doi: 10.1002/(SICI)1521-3773(19990201)38:3<270::AID-ANIE270>3.0.CO;2-0

17. Ding Y, Chen ZJ, Liu S, Che D, Vetter M et al. Inhibition of Nox-4 activity by plumbagin, a plant-derived bioactive naphthoquinone. Journal of Pharmacy and Pharmacology 2005; 57: 111-116. doi: 10.1211/00223570551119

18. Kumagai Y, Shinkai Y, Miura T, Cho AK. The chemical biology of naphthoquinones and its environmental implications. Annual Review of Pharmacology and Toxicology 2012; 52: 221-247. doi: 10.1146/annurev-pharmtox-010611-134517

19. Silva MG, Camara CA, Silva TMS, Feitosa ACS, Meira AS et al. Synthesis of 2,3-Diyne-1,4-naphthoquinone derivatives and evaluation of cytotoxic activity against tumor cell lines. Journal of the Brazilian Chemical Society 2013; 24 (9): 1420-1426. doi: 10.5935/0103-5053.20130180

20. Satheshkumar A, Elango KP. Spectroscopic and theoretical studies on the nucleophilic substitution of 2,3-dichloronaphthoquinone with para-substituted anilinesin solid state via initial charge transfer complexation. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy 2012; 98: 378-383. doi: 10.1016/j.saa.2012.08.056

21. Tandon VK, Maurya HK. Water-promoted unprecedented chemoselective nucleophilic substitution reactions of 1,4-quinones with oxygen nucleophiles in aqueous micelles. Tetrahedron Letters. 2010; 51: 3843-3847. doi: 10.1016/j.tetlet.2010.05.071

22. Deniz NG, Ozurek M, Tufan AN, Apak R. One-pot synthesis, characterization, and antioxidant capacity of sulfur- and oxygen-substituted benzocrown ethers. Russian Chemical Bulletin International Edition 2012; 61 (12): 2282-2294. doi: 10.1007/s11172-012-0323-z

23. Tapia RA, Cantuarias L, Cuellar M, Villena J. Microwave-assisted reaction of 2,3-Dichloronaphthoquinone with aminopyridines. Journal of the Brazilian Chemical Society 2009; 20 (5): 999-1002. doi: 10.1590/S0103-50532009000500027

24. Kadela-Tomanek M, Bebenek E, Chrobak E, Latocha M, Boryczka S. Alkoxy and enediyne derivatives containing 1,4-Benzquinone subunits synthesis and antitumor activity. Molecules 2017; 22: 447. doi: 10.3390/molecules22030447

25. Martyanov TP, Ushakov EN, Savelyev VA, Klimenko LS. Crown-containing naphtho and anthraquinones: synthesis and complexation with alkali and alkaline-earth metal cations. Russian Chemical Bulletin 1994; 43 (3): 410-412. doi: 10.1007/BF01169717

26. Lubenet's EG, Kusov SZ, Ektova LV, Kobriona VN, Kornaukhova LM et al. Synthesis and properties of naphthoquinonylamino-substituted benzocrown ethers. Russian Chemical Bulletin 1994; 43 (3): 410-412. doi: 10.1007/BF01169717

27. Martayanov TP, Ushakov EN, Savelyev VA, Klimenko LS. Crown-containing naphtho and anthraquinones: synthesis and complexation with alkali and alkaline-earth metal cations. Russian Chemical Bulletin International Edition 2012; 61 (12): 2282-2294. doi: 10.1007/s11172-012-0323-z

28. Nishina A, Uchibori T. Antimicrobial activity of 2,6-dimethoxy-p-benzoquinone, isolated from thick-stemmed bamboo, and its analogs. Agricultural and Biological Chemistry 1991; 55 (9): 2395-2398. doi: 10.1080/00021369.1991.10870973

29. Sara EJL, Caraza F, Takahashi JA. Antibacterial evaluation of 1,4-benzoquinone derivatives. Journal of Agricultural and Food Chemistry 2006; 54: 2053-2056. doi: 10.1021/jf052407z

30. Barbosa LCA, Pereira UA, Maltha CRA, Teixeira RR, Valente VMM et al. Synthesis and biological evaluation of 2,5-bis(alkylamino)-1,4-benzoquinones. Molecules 2010; 15: 5629-5643. doi: 10.3390/molecules15085629

31. Leslie Gunatilaka AA, Berger JM, Evans R, Miller JS, Wisse JH et al. Isolation, synthesis, and structure-activity relationships of bioactive benzoquinones from Micrionia lepidota from the suriname rainforest. Journal of Natural Products 2001; 64: 2-5. doi: 10.1021/np000219r

32. Siraki AG, Chan TS, J'O'Brien P. Application of quantitative structure-toxicity relationships for the comparison of the cytotoxicity of 14 p-Benzoquinone congeners in primary cultured rat hepatocytes versus PC12 cells. Toxicological Sciences. 2004; 81: 148-159. doi: 10.1093/toxsci/kfh182
33. You ZL, Xian DM, Zhang M, Cheng XS, Li XF. Synthesis, biological evaluation, and molecular docking studies of 2,5-substituted-1,4-benzoquinone as novel urease inhibitors. Bioorganic & Medicinal Chemistry 2012; 20: 4889-4894. doi: 10.1016/j.bmc.2012.07.002

34. Mori K, Takahashi K, Kishi T, Sayo H. Synthesis and biological activities of 2,3-dimethyl-1,4-benzoquinones having alkylthio and arylthio side chains. Chemical and Pharmaceutical Bulletin 1987; 35 (3): 1270-1274. doi: 10.1248/cpb.35.1270

35. Bayen S, Barooah N, Sarma RJ, Sen TK, Karmakar A et al. Synthesis, structure and electrochemical properties of 2,5-bis(alkyl/aryl ammino)1,4-benzoquinones and 2-arylamino-1,4-naphthoquinones. Dyes and Pigments 2007; 75: 770-775. doi: 10.1016/j.dyepig.2006.07.033

36. Katritzky AR, Fedoseyenko D, Mohapatra PP, Steel PJ. Reactions of p-benzoquinone with sulfur nucleophiles. Synthesis 2008; 5: 777-787. doi: 10.1055/s-2008-1032186

37. Martinez-Cifuentes M, Clavijo-Allancan G, Di Vaggio-Conejeros C, Weiss-Lopez B, Araya-Maturana R. On-Water reactivity and regioselectivity of quinones in C-N coupling with amines: experimental and theoretical study. Australian Journal of Chemistry 2014; 67: 217-224. doi: 10.1071/CH13355

38. Wu H, Zhang D, Zhang G, Zhu D. New substituted tetrathiafulvalene-quinone dyads: the influences of electron accepting abilities of quinone units on the metal ion-promoted electron-transfer processes. The Journal of Organic Chemistry 2008; 73: 4271-4274. doi: 10.1021/jo800581t

39. Singh D, Kushwaha A, Banerjee A, Prasad RL. Synthesis and characterization of multifunctional coordination polymer of the type [Cu(Ni-x)(dedb).2H2O]. In: Solid State Sciences 2015; 45: 35-45. doi: 10.1016/j.solidstatesciences.2015.04.004

40. Yildirim H, Bayrak N, Tuyun AF, Kara Mataraci E, Celik Ozbek B et al. 2,3-disubstituted-1,4-naphthoquinones containing an arylamine with trifluoromethyl group: synthesis, biological evaluation, and computational study. RSC Advances 2017; 7 (41): 25753-25764. doi: 10.1039/C7RA00868F

41. Goksel FS, Bayrak N, Ibis C. Synthesis of novel S,O-Substituted 1,4-benzoquinones. Phosphorus, Sulfur, and Silicon and Related Elements 2014; 189: 113-123. doi: 10.1080/10426507.2013.798787

42. Bayrak N, Yildirim H, Tuyun AF, Kara Mataraci E, Celik Ozbek B et al. Synthesis, computational study, and evaluation of in vitro antimicrobial, antibiofilm, and anticancer activities of new sulfanyl aminonaphthoquinone derivatives. Letters in Drug Design & Discovery 2017; 14 (6): 647-661. doi: 10.2174/157018081406170606155530

43. Bayrak N, Tuyun AF, Yildirim H, Onul N. Spectroscopic and structural aspects of the reactions of 1,4-quinones with sulfur and nitrogen nucleophiles. Comptes Rendus Chimie 2014; 17: 563-569. doi: 10.1016/j.crci.2013.10.022

44. Ibis C, Tuyun AF, Ozoys-Gunes Z, Bahar H, Stasevych MV et al. Synthesis and biological evaluation of novel nitrogen- and sulfur-containing hetero-1,4-naphthoquinones as potent antifungal and antibacterial agents. European Journal of Medicinal Chemistry 2011; 46: 5861-5867. doi: 10.1016/j.ejmech.2011.09.048

45. Deniz NG, Ibis C, Gokmen Z, Stasevych M, Novikov V et al. Design, synthesis, biological evaluation, and antioxidant and cytotoxic activity of heteroatom-substituted 1,4-naphthoquinones. Chemical and Pharmaceutical Bulletin 2015; 63: 1029-1039. doi: 10.1248/cpb.c15-00607

46. Kacmaz A, Turker Acar E, Atun G, Kaya K, Diren Sigirci B et al. Synthesis, electrochemistry, DFT calculations, antimicrobial properties and X-ray crystal structures of some NH- and/or S- substituted-1,4-quinones. Chemistry Select 2018; 3: 8615-8623. doi: 10.1002/slct.201801155

47. Kacmaz A, Hamurcu Z. New NH-substituted 1,4-naphtho- and 1,4-benzo- quinones: synthesis, characterization and potential antiproliferative effect against MDAMB-231 cells. Phosphorus, Sulfur, and Silicon and Related Elements 2018; 193 (12): 831-839. doi: 10.1080/10426507.2018.1514503

48. Kacmaz A, Deniz NG, Aydinli SG, Sayil C, Onay-Ucar E, Mertoglu E, Arda N. Synthesis and antiproliferative evaluation of some 1,4-naphthoquinone derivatives against human cervical cancer cells. Open Chemistry 2019; 17: 337-345. doi: 10.1515/chem-2019-0030

49. Kacmaz A. Some new NH-, NH, S, S- and NH,NH- substituted 1,4-naphtho(benzo)quinones. Phosphorus, Sulfur, and Silicon and Related Elements 2020; 195 (1): 43-49. doi: 10.1080/10426507.2019.1633534

50. Ryu CK, Kim DH. The synthesis and antimicrobial activities of some 1,4-naphthoquinones (II). Archives of Pharmacal Research 1992; 15 (3): 263-268. doi: 10.1007/BF02974067

51. Buckley D, Henbest HB, Slade P. Syntheses of substituted amino-, aminovinyl, and aminobutadienyl-p-quinones. Journal of the Chemical Society 1957; 4891-4900. doi: 10.1039/JR9570004891

52. Tandon VK, Maurya HK. ‘On water’: unprecedented nucleophilic substitution and addition reactions with 1,4-quinones in aqueous suspension. Tetrahedron Letters 2009; 50: 5896-5902. doi: 10.1016/j.tetlet.2009.07.149

53. Smith RE, Davis WR. Spectrophotometric determination of amines with p-chloranil. Analytical Chemistry 1984; 56 (13): 2345-2349. doi: 10.1021/ac00277a019
54. Singh Gautam BP, Srivastava M, Prasad RL, Yadav RA. Synthesis, characterization and quantum chemical investigation of molecular structure and vibrational spectra of 2,5-dichloro-3,6-bis-(methylamino)1,4-benzoquinone. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy 2014; 129: 241-254. doi: 10.1016/j.saa.2014.02.082

55. Cameron DW, Scott PM, Todd. Side-chain Amination: A new reaction of nuclear alkylated quinones. Journal of Chemical Society 1964; 42-48. doi: 10.1039/JR9640000042

56. Cameron DW, Scott PM. Facile loss of C-methyl groups during the amination of quinones. Journal of Chemical Society 1964; 5569-5573. doi: 10.1039/JR9640005569

57. Kumanotani J, Kagawa F, Hikosaka A, Sugita K. Ring-butylamination of toluquinone: isolation of products by TLC and an observation of their reaction course on the basis of molecular reactivity Index, Bulletin of the Chemical Society of Japan 1968; 41 (9): 2118-2123. doi: 10.1246/bcsj.41.2118

58. Norcott P, Spielman C, McErlean CSP. An in-water, on-water domino process for synthesis. Green Chemistry 2012; 14: 605-609. doi: 10.1039/c2gc16259h

59. Yogo M, Ito C, Furukawa H. Synthesis of some carbazolequinone alkaloids and their analogues. Facile palladium-assisted intramolecular ring closure of arylamino-1,4-benzoquinones to carbazole-1,4-quinones. Chemical and Pharmaceutical Bulletin 1991; 39 (2): 328-334. doi: 10.1248/cpb.39.328

60. Yoshihira K, Sakaki S, Ogawa H, Natori S. Hydroxybenzoquinone from Myrsinaceae Plants IV. Further confirmation of structures of ardisiaquinones and some observations on alkylaminobenzoquinone derivatives. Chemical and Pharmaceutical Bulletin. 1968; 16 (12): 2383-2389. doi: 10.1248/cpb.16.2383