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

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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*-myrtanylamine (**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 ^{1}H NMR, ^{13}C NMR, FTIR, MS-ESI, UV/Vis and elemental analysis.

Key words: Quinones, amines, *p*-chloranil, *p*-toluquinone, 2,3-dichloro-1,4-naphthoquinone

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], antimycobacterial [8], and molluscicidal [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 receieved a considerable interest in biological applications with their antibacterial [11], antiatherosclerosis [17], antiinflammatory [18], anticancer [5,18], and cytotoxic [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.

The literature mentions some aminobenzocrown ethers [26,27] similar to **15** and **17**. For example, N-(2-chloro-1,4-naphthoquinon-3-yl)-4'-aminobenzocrown ethers were synthesized from the reaction between 4'-aminobenzocrown ethers and 2,3-dichloro-1,4-naphthoquinone [26], and thus in the present study, synthesis of **15** and **17** contribute to crown-containing naphthoquinones, carrying out the reaction between crown ethers (**14** and **16**) and 2-bromo-1,4-naphthoquinone (**4**). Moreover, crown-containing naphthoquinone **19** was synthesized, including both amino and thio substituents, together.

1,4-benzoquinones, including NH-, methoxy, thio, alkyl or aryl groups, have been the subject of study due to their properties such as antimicrobial [28], antibacterial [29], cytotoxic [30–32], potential urease inhibitor [33], and potent inhibitory activity towards enzyme system [34]. In addition, some of studies on the formation of N(H)-, SR-, alkoxy substituted-1,4-benzoquinones have been reported in the literature [34–38]. Among 1,4-benzoquinones, halogenanils, such as chloranil, with amines yield amination products of quinones. For example, Wu H et al. reported tetrathiafulvalene-quinone dyad, having mono-NH-substituted-tri-chloro-1,4-benzoquinone structure [38]. In another example, Sing and et al. synthesized [39] new coordination polymers, starting from 2,5-dichloro-3,6-bis(ethylamino)-1,4-benzoquinone. In this study, compounds **6** and **7** have mono-NH-substituted-tri-chloro-1,4-benzoquinone and 2,5-dichloro-3,6-bis(NH-

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substituted)-1,4-benzoquinone structures, respectively, synthesized from *p*-chloranil **1** and primary amine **5**. Moreover, compounds **8** and **9** are di-amination products of methyl-*p*-benzoquinone **2**.

Different research groups from our university have reported some N-, NH- or SR- substituted 1,4-naphtho(benzo) quinones [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 [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 [3,30,50].

The importance of this kind of compounds has motivated this study to synthesize 1,4-naphtho(benzo)quinones bearing with amino and/or thio. Thus, *p*-chloranil **1**, methyl-*p*-benzoquinone **2**, dichloro-1,4-naphthoquinone **3** and 2-bromo-1,4-naphthoquinone **4** were used as lead molecules, as shown Figure. Various spectroscopic techniques (UV/Vis, FTIR, ^{1}H NMR, ^{13}C NMR, MS-ESI) have been employed to characterize the synthesized compounds. It is expected that the new synthesized compounds will be useful for pharmacological field with their potential biological activities.

2. Materials and methods

2.1. Chemistry

All the chemicals used (**1**, **2**, **3**, **4**, **5**, **11**, **14**, **16**, **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 $CHCl_3$), respectively. The UV-Vis spectra were recorded on a Shimadzu UV/Vis spectrophotometer 2600, in $CHCl_3$. The mass spectra were performed on a ThermoFinnigan LCQ AdvantageMAX system. ^{1}H and ^{13}C NMR spectra were performed in $CDCl_3$ solution on a spectrometer (Varian Unity Inova). Chemical shifts (δ, 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 2-((6,6-dimethylbicyclo[3.1.1]heptan-2-ylmethyl)amino)-3,5,6-trichlorocyclohexa-2,5-diene-1,4-dione (6) and 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 **1** (640 mg, 2.6 mmol) and (-)-*cis*-myrtanylamine **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 $CHCl_3$. 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_2Cl_2 (1/2) (mobil phase) to afford products **6** and **7**.

2-((6,6-dimethylbicyclo[3.1.1]heptan-2-ylmethyl)amino)-3,5,6-trichlorocyclohexa-2,5-diene-1,4-dione (6): R_f = 0.8 (CH_2Cl_2); Yield: 10% (100 mg); Dark purple viscous oil; UV ($CHCl_3$), λ_{max}, nm (log ε): 244 (4.87), 320 (4.71), 529 (4.06); IR (ATR): 3336, 2906, 2870, 1683, 1648, 1606, 1572, 1514, 1459, 1218, 1083; ^{1}H NMR ($CDCl_3$) δ: 5.88 (1H, NH, brs), 3.60–3.80 (m, 2H, -C<u>H</u>$_2$-NH), 2.20-2.40 (m, 2H), 1.80–2.00 (m, 5H), 0.60–1.40 (m, 8H); ^{13}C NMR ($CDCl_3$) δ: 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 *m/z* 360.4 ([M-H]$^-$, 100%). Anal. calc. for $C_{16}H_{18}Cl_3NO_2$ (362.68): C 52.99, H 5.00, N 3.86; Found: C 53.25, H 5.10, N 3.98.

2,5-bis((6,6-dimethylbicyclo[3.1.1]heptan-2-ylmethyl)amino)-3,6-dichlorocyclohexa-2,5-diene-1,4-dione (7): R_f = 0.9 (CH_2Cl_2); Yield: 36% (225 mg); Grey solid; m.p. 233–235 °C; UV ($CHCl_3$), λ_{max}, nm (log ε): 361 (4.92), 242 (4.25); IR (ATR): 3244, 2897, 1655, 1567, 1489, 1440, 1330, 1056; ^{1}H NMR ($CDCl_3$) δ: 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, ^{3}J =

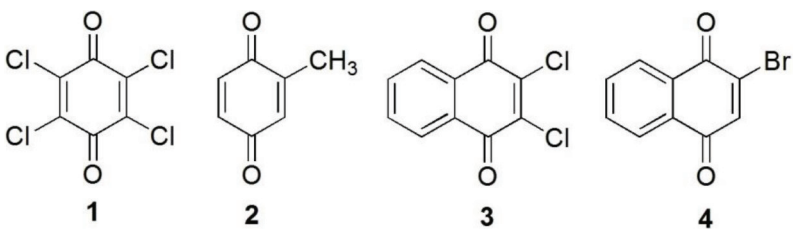


Figure. Quinones used in the present work (*p*-chloranil **1**, methyl-*p*-benzoquinone **2**, 2,3-dichloro-1,4-naphthoquinone **3** and 2-bromo-1,4-naphthoquinone **4**).

9.75 Hz); ^{13}C NMR ($CDCl_3$) δ: 172.12 (C=O), 145.44 (C-N), 99.23 (C-Cl), 50.20, 43.44, 42.56, 41.23, 38.67, 33.21, 33.17, 27.87, 27.84, 25.84, 23.20, 23.19, 19.52; MS *m/z* 479.1 ([M+H]$^+$, 100%). Anal. calc. for $C_{26}H_{36}Cl_2N_2O_2$ (479.48): C 65.13, H 7.57, N 5.84; Found: C 65.43, H 7.85, N 5.99.

2.2.2. Synthesis of 3,5-bis((6,6-dimethylbicyclo[3.1.1]heptan-2-ylmethyl)amino)-2-methylcyclohexa-2,5-diene-1,4-dione (8) and 2,5-bis((6,6-dimethylbicyclo[3.1.1]heptan-2-ylmethyl)amino)cyclohexa-2,5-diene-1,4-dione (9)

The solution of methyl-*p*-benzoquinone **2** (398 mg, 3.26 mmol) and (-)-*cis*-myrtanylamine **5** (500 mg, 3.26 mmol) in EtOH (20 mL) and water (1.5 mL) in the presence of Na_2CO_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_2Cl_2 (2/1) (mobil phase) to afford products **8** and **9**.

3,5-bis((6,6-dimethylbicyclo[3.1.1]heptan-2-ylmethyl)amino)-2-methylcyclohexa-2,5-diene-1,4-dione (8): Rf= 0.6 (CH_2Cl_2); Yield: 10% (69 mg); Purple solid; m.p. 198–200 °C; IR (cm^{-1}): ν = 3250, 2898, 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}, ^3J = 7.80 Hz), 3.07–3.19 (m, 2H, CH_{myrt}), 2.25–2.45 (m, 4H, CH_{myrt}), 2.07 (s, 3H, $CH_{3quinone}$), 1.82–2.05 (10H, m, CH_{myrt}), 1.41–1.56 (2H, m, CH_{myrt}), 1.21 (d, 6H, CH_{myrt}, *J* = 4.39 Hz), 1.03 (d, 6H, CH_{myrt}, *J* = 3.90 Hz), 0.93 (t, 2H, CH_{myrt}, *J* = 7.81 Hz); ^{13}C NMR ($CDCl_3$) δ: 178.98, 178.88 (C=O), 150.91, 148.13, 101.77, 91.71, 50.54, 48.25, 43.77, 43.52, 42.55, 41.27, 41.20, 40.24, 38.69, 38.64, 33.27, 33.14, 27.91, 27.88, 27.85, 25.88, 23.26, 23.23, 19.94, 19.74; 10.44 ($CH_{3quinone}$); MS *m/z* 425.3 ([M+H]$^+$, 100%). Anal. calc. for $C_{27}H_{40}N_2O_2$ (424.62): C, 76.37; H, 9.50; N, 6.60; Found C, 75.97; H, 9.49; N, 6.69.

2,5-bis((6,6-dimethylbicyclo[3.1.1]heptan-2-ylmethyl)amino)cyclohexa-2,5-diene-1,4-dione (9):[47] Light pink solid; m.p 281–282 °C; (lit[47]: 280–282 °C); Yield: 78% (524 mg); ^{1}H NMR ($CDCl_3$) δ: 6.61 (2H, 2×NH, brs), 5.23 (2H, 2×$CH_{quinone}$), 3.02–3.14 (m, 4H, 2 -C<u>H</u>$_2$-NH), 2.26–2.36 (m, 4H); 1.78–1.98 (m, 10H); 1.36–1.46 (m, 2H), 1.13 (s, 6H, 2×CH_3), 0.96 (s, 6H, 2×CH_3), 0.86 (s, H), 0.84 (s, H); ^{13}C NMR ($CDCl_3$) δ: 177.02 (C=O); 150.48 (=C-NH-); 91.62, 91.57 (C-H_{quin}); 47.31, 47.18, 42.79, 40.23, 39.27, 37.66, 32.14, 26.87, 24.87, 22.24, 18.98. MS *m/z* 411.3 ([M+H]$^+$, 100%).

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

The solution of 2,3-dichloro-1,4-naphthoquinone **3** (740 mg, 3.26 mmol) and (-)-*cis*-myrtanylamine **5** (500 mg, 3.26 mmol) in CH_2Cl_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_2Cl_2 (1/3) (mobil phase) to afford product **10**: R_f = 0.6(CH_2Cl_2); Yield: 40% (450 mg); Red solid; m.p. 179–181 °C; UV ($CHCl_3$), λ_{max}, (log ε): 278 (4.48), 474 (3.58); IR (ATR): 3267, 2978, 2908, 1680, 1596, 1554, 1514, 1408, 1294, 1252, 1062; ^{1}H NMR ($CDCl_3$) δ: 8.07 (dd, H, CH_{napht}, ^3J = 7.3 Hz, ^4J = 1.0 Hz); 7.95 (dd, H, CH_{napht}, ^3J = 7.8 Hz, ^4J = 1.0 Hz); 7.64 (td, H, CH_{napht}, ^3J = 7.6 Hz, ^4J = 1.1 Hz); 7.53 (td, H, CH_{napht}, ^3J = 7.3 Hz, ^4J = 1.1 Hz); 6.03 (1H, NH, brs); 3.70–3.90 (m, 2H, -CH_2-NH-); 2.20–2.40 (m, 2H); 1.80–2.00 (m, 4H); 1.40–1.60 (m, H); 1.14 (s, 3H); 0.98 (s, 3H); 0.87 (d, H, ^3J = 9.76 Hz); ^{13}C NMR ($CDCl_3$) δ: 180.5, 176.7 (C=O_{napht}); 144.3(=C-N); 134.9, 132.8, 132.3, 129.7, 126.8 (C_{napht}, C-H_{napht}); 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 $C_{20}H_{22}ClNO_2$ (343.85): C 69.86, H 6.45, N 4.07; Found: C 69.47, H 6.55, N, 3.75.

2.2.4. Synthesis of 2-(2-(methylthio)ethylamino)-3-bromonaphthalene-1,4-dione (12) and 2-(2-(methylthio) ethylamino)naphthalene-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_2Cl_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_2Cl_2 (1/1) (mobil phase) to afford products **12** and **13**.

2-(2-(methylthio)ethylamino)-3-bromonaphthalene-1,4-dione (12): R_f= 0.5(CH_2Cl_2); Yield: 7% (125 mg); Dark red solid; m.p. 102–104 °C; UV ($CHCl_3$), λ_{max}, nm (log ε): 277 (4.48), 487 (3.42); IR (ATR): 3306, 1673, 1591, 1560, 1513, 1441,1327, 1251, 1123; ^{1}H NMR ($CDCl_3$) δ: 8.12 (d, 1H, CH_{napht}, ^3J = 7.3 Hz); 8.02 (d, 1H, CH_{napht}, ^3J = 7.7 Hz), 7.71 (t, 1H, CH_{napht}, ^3J = 7.6 Hz), 7.62 (t, 1H, CH_{napht}, ^3J = 7.6 Hz), 6.44 (brs, 1H, NH), 4.08 (t, 2H, NH-CH_2, ^3J = 6.3 Hz); 2.83 (t, 2H, CH_2-S, ^3J = 6.3 Hz); 2.16 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ: 179.97, 176.37 (C=O); 146.48, 134.79, 132.47, 132.44, 132.22, 129.88, 127.03, 126.87 (C_{napht}, CH_{napht}); 43.00 (NH-CH_2), 34.68 (CH_2-S), 15.06 (CH_3); MS *m/z* 324.0 ([M-H]$^-$, 100%). Anal. calc. for $C_{13}H_{12}BrNO_2S$ (326.21): C 47.86, H 3.71, N 4.29; Found: C 48.28, H 3.64, N 4.04.

2-(2-(methylthio)ethylamino)naphthalene-1,4-dione (13): R_f = 0.2(CH_2Cl_2); Yield: 30% (410 mg); Orange solide; m.p 139–141 °C; UV ($CHCl_3$), λ_{max} (log ε): 271 (4.21), 442 (3.37); IR (ATR): 3360, 3237, 2910, 1664, 1591, 1563, 1498, 1444,

1339, 1227, 1068; ^{1}H NMR ($CDCl_3$) δ: 8.09 (dd, 1H, CH_{napht}, ^3J = 7.7 Hz, ^4J = 1.0 Hz); 8.04 (dd, 1H, CH_{napht}, ^3J = 7.6 Hz, ^4J = 1.1 Hz); 7.72 (td, 1H, CH_{napht}, ^3J = 7.6 Hz, ^4J = 1.3 Hz); 7.61 (td, 1H, CH_{napht}, ^3J = 7.6 Hz, ^4J = 1.3 Hz); 6.25 (brs, 1H, NH); 5.75 (s, 1H, CH_{napht}); 3.40 (q, 2H, -NH-C$\underline{H}_2$, ^3J = 6.3 Hz); 2.81 (t, 2H, -CH_2-, ^3J = 6.3 Hz); 2.15 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ: 183.0, 181.6 (C=O); 147.7; 134.7; 133.5;132.1; 130.5; 126.3; 126.2;101.2; 40.8 (NH-$\underline{C}H_2$); 32.2 (-$\underline{C}H_2$-S); 15.3 (CH_3); MS *m/z* 247.9 ([M+H]$^+$, 100%). Anal. calc. for $C_{13}H_{13}NO_2S$ (247.31): C 63.13, H 5.30, N 5.66, S 12.97; Found: C 63.12; H 5.12; N 5.58, S 13.33.

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 CH_3COONa in $CHCl_3$ 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 $CHCl_3$. 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 ethyl acetate/CH_2Cl_2 (10/1) (mobil phase) 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; ^{1}H NMR ($CDCl_3$) δ: 8.21 (1H, dd, CH_{napth}, ^3J = 7.81 Hz, ^4J =0.98 Hz), 8.13 (1H, dd, CH_{napth}, ^3J = 7.57 Hz, ^4J = 1.21 Hz), 7.77 (td, 1H, CH_{napth}, ^3J = 7.54 Hz, ^4J = 1.38 Hz), 7.70 (td, 1H, CH_{napth}, ^3J = 7.55 Hz, ^4J = 1.31 Hz), 7.74 (brs, 1H, NH), 6.85–6.93 (m, 4H, CH_{arom}), 6.82 (d, 1H, CH_{arom}, ^3J =8.49 Hz), 6.70 (dd,1H, CH_{arom}, ^3J = 8.43 Hz, ^4J = 2.32 Hz), 6.66 (s, 1H, CH_{arom}, ^4J = 2.45 Hz), 4.13–4.25 (m, 8H, 4 x CH_2), 4.00–4.10 (m, 8H, 4 x CH_2); ^{13}C NMR ($CDCl_3$) δ: 180.11, 177.35 (C=O), 144.22, 134.99, 132.77, 132.54, 130.54, 129.74, 127.49, 127.08, 118.02, 113.18, 101.46; 69.88, 68.66 (CH_2); MS *m/z* 608.3 ([M-H]$^-$, 100%). Anal. calc. for $C_{30}H_{28}BrNO_8$ (610.5): C, 59.03; H, 4.62; N, 2.29. Found C, 59.43; 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 Na_2CO_3 in CH_2Cl_2 was allowed to stir at reflux 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 ethyl acetate/CH_2Cl_2 (10/1) (mobil phase) to afford product **17**: R_f = 0.8 (CH_3OH); Yield: 29% (50 mg); Dark purple solid; m.p. 139–141 °C; IR (ATR): 3319, 2927, 2872, 1668, 1642, 1591, 1563, 1506, 1234, 1124; ^{1}H NMR ($CDCl_3$) δ: 8.13 (1H, dd, CH_{napth}, ^3J = 7.81 Hz, ^4J =0.98 Hz), 8.04 (dd, 1H, CH_{napth}, ^3J = 7.81 Hz, ^4J =0.98 Hz), 7.69 (td, 1H, CH_{napth}, ^3J = 7.57 Hz, ^4J =1.46 Hz), 7.65 (brs, NH), 7.61 (td, 1H, CH_{napth}, ^3J = 7.57 Hz, ^4J =1.46 Hz), 6.76 (d, 1H, CH_{arom}, ^3J = 8.29 Hz), 6.62 (dd, 1H, CH_{arom}, ^3J = 8.78 Hz, ^4J =2.44 Hz), 6.59 (s, 1H, CH_{arom}, ^4J =2.44 Hz), 4.05–4.13 (m, 4H, 2 CH_2), 3.82–3.90 (m, 4H, 2 CH_2), 3.68–3.74 (m, 4H, 2 CH_2), 3.62–3.68 (m, 8H, 4 CH_2); ^{13}C NMR ($CDCl_3$) δ: 180.1, 177.3 (C=O), 148.5, 147.4, 144.2, 135.0, 132.8, 132.5, 130.7, 129.7, 127.5, 127.1, 127.0, 118.2, 111.9, 106.1, 70.8, 70.7, 70.6, 69.6, 69.4, 69.3, 69.1, 69.0; MS *m/z* 560.2 ([M-H]$^-$, 100%). Anal. calc. for $C_{26}H_{28}BrNO_8$ (562.41): C, 55.53; H, 5.02; N, 2.49. Found C, 55.13; H, 5.34; N, 2.77.

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 $CHCl_3$ in the presence of triethylamine (2-3 mL) was allowed to stir at reflux 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 ethyl acetate/CH_2Cl_2 (1/1) (mobil phase) to afford product **19**: Yield: 80% (39mg); Dark purple viscous oil; IR (ATR): 3444, 2957, 2921, 2851, 1665, 1591, 1550, 1513, 1230; ^{1}H NMR ($CDCl_3$) δ: 8.07 (1H, dd, CH_{napth}, ^3J = 7.81 Hz, ^4J =0.98 Hz), 7.99 (dd, 1H, CH_{napth}, ^3J = 7.32 Hz, ^4J =0.98 Hz), 7.74 (brs, 1H, NH), 7.68 (td, 1H, CH_{napth}, ^3J = 7.57 Hz, ^4J =1.47 Hz), 7.59 (td, 1H, CH_{napth}, ^3J = 7.58 Hz, ^4J =1.31 Hz), 6.71 (d, 1H, CH_{arom}, ^3J = 8.78 Hz), 6.52 (dd, 1H, CH_{arom}, ^3J = 8.30 Hz, ^4J = 1.95 Hz), 6.49 (s, 1H, CH_{arom}, ^4J = 2.44 Hz), 4.00–4.15 (m, 4H, $2CH_{2crown}$), 3.80–3.95 (m, 4H, $2CH_{2crown}$), 3.68–3.80 (m, 4H, $2CH_{2crown}$), 3.60–3.68 (m, 8H, $4CH_{2crown}$), 3.21 (t, 2H, S-CH_2-, ^3J = 8.54 Hz), 1.65–0.85 (m, 20H, 10 CH_{2aliph}), 0.80 (3H, t, CH_3, ^3J =7.08 Hz); ^{13}C NMR ($CDCl_3$) 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_{napht}, C_{napht}, CH_{arom}); 69.9, 69.7, 68.8, 67.7, 67.5, 58.9 (CH_{2crown}); 31.9, 29.64, 29.62, 29.60, 29.5, 29.3, 29.1, 28.7, 24.0, 22.7, 19.7 (CH_{2aliph}); 13.7 (CH_3); MS *m/z* 682.6 ([M-H]$^-$, 20%) and 249.5 (M^--433). Anal. calc. for $C_{38}H_{53}NO_8S$ (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 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 chloroform (mobil phase) to afford product **20**: R_f = 0.4 ($CHCl_3$); Yield: 60% (51 mg); Dark red viscous oil; IR (ATR): 3305, 2956, 2918, 2849, 1668, 1552, 1498, 1287; ^{1}H NMR ($CDCl_3$) δ: 8.15 (1H, dd, CH_{napht}, ^3J = 7.81 Hz, ^4J =0.98 Hz); 8.04 (1H, dd, CH_{napht}, ^3J = 7.81 Hz, ^4J = 0.97 Hz); 7.63 (td, 1H, CH_{napht}, ^3J = 7.81 Hz, ^4J = 0.98 Hz); 7.72 (td, 1H, CH_{napht}, ^3J = 7.81 Hz, ^4J = 0.98 Hz); 6.70–6.80 (brs, 1H, NH), 4.14 (t, 2H, NH-C$\underline{H}_2$, ^3J = 6.36 Hz), 2.84 (t, 4H, 2 x C$\underline{H}_2$-S, ^3J = 6.45 Hz), 2.17 (s, 3H, S-CH_3), 1.20–1.35 (m, 20H, CH_{2aliph}), 0.75–0.95 (m, 3H, CH_{3aliph}); ^{13}C NMR ($CDCl_3$) δ: 183.05, 181.35 (C=O), 134.54, 133.69, 132.10, 130.78, 128.83, 126.53 (C_{napht}, CH_{napht}), 43.71 (NH-$\underline{C}H_2$); 35.01, 34.67, 31.91, 29.97, 29.58, 29.54, 29.34, 28.92, 22.69 (CH_{2aliph}), 15.07 (-S-CH_3), 14.11 (CH_2-$\underline{C}H_3$); MS *m/z* 447.1 ([M]$^-$, 100%). Anal. calc. for $C_{25}H_{37}NO_2S_2$ (447.7): 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**.

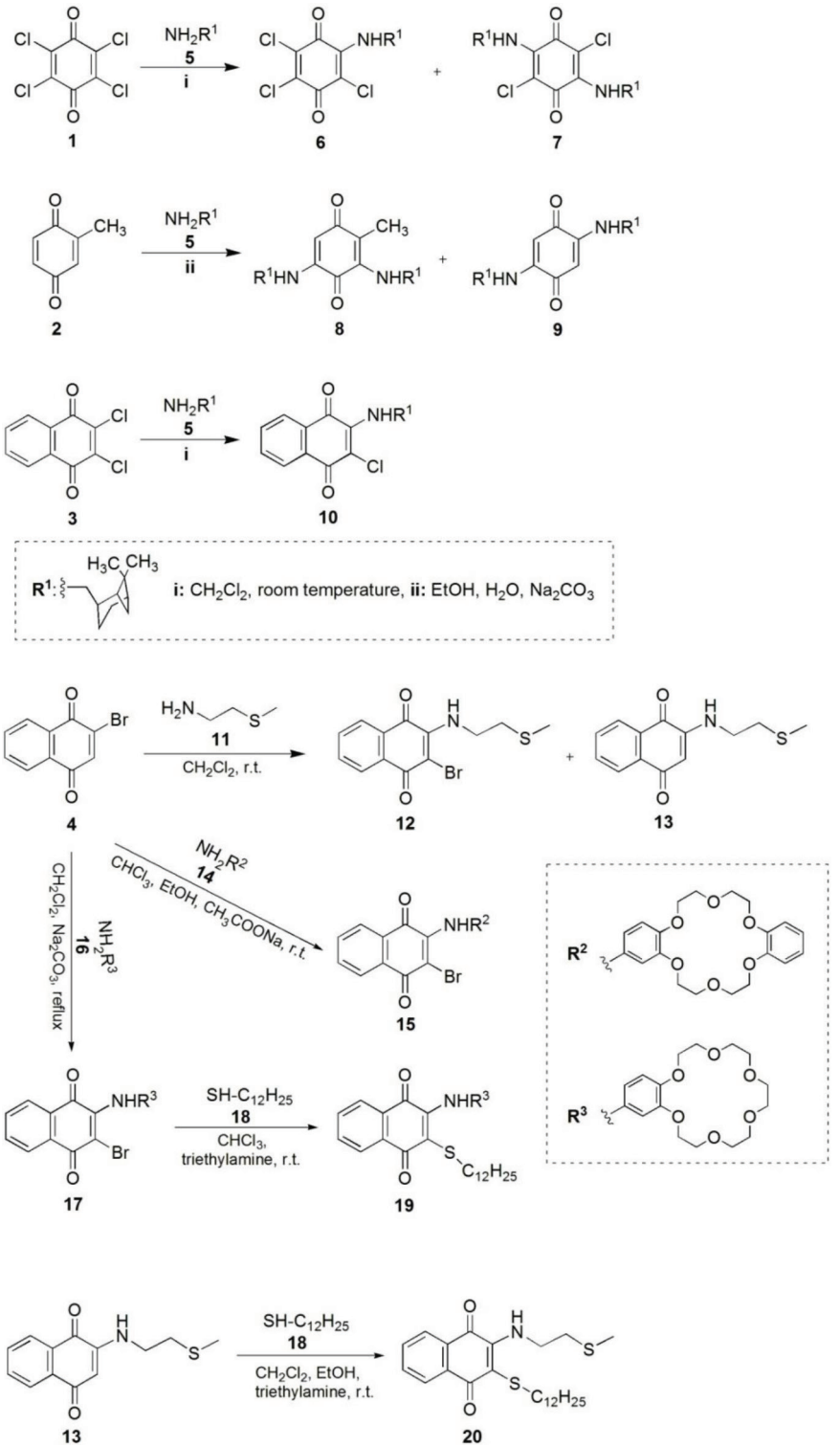
The reaction between chloranil and primary/secondary amines gives the NH-/N-substituted quinones. Some examples of such reactions have been previously described [51–54]. For example, Singh Gautam BP et al. synthesized and characterized the compound 2,5-dichloro-3,6-bis-(methylamino)-1,4-benzoquinone, 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 ^{13}C-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, ^{1}H-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-bismethylamino-1,4-benzoquinone (39% yield) by displacement of a methyl by an amino-group [56]. Then, Kumanotani et al. carried out the reaction of toluquinone 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 Na_2CO_3 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 $CH_{3quinone}$ proton and carbon signals of **8** could be observed in ^{1}H and ^{13}C-NMR spectra at 2.07 ppm and at 10.44 ppm, respectively, in the ^{1}H and ^{13}C-NMR spectra of **9**, the disapperance of $CH_{3quinone}$ 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-quinone 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**. ^{1}H-NMR spectrum of **10** showed two doublet of doublets due to CH_{naphth} (8.07, 7.95 ppm) and two doublet of triplets CH_{naphth} (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 ^{1}H-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.



Scheme. The synthesis of compounds **6**-**10**, **12**, **13**, **15**, **17**, **19**, and **20**.

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_2 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 ^{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 including crown structure. In the proton NMR spectrum of **19,** CH_{napht}, CH_{arom}, and CH_{2crown} exhibited signals in a lower field than in the starting compound **17**, because of the bonding S-$(CH_2)_{11}$-CH_3 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. ^{1}H NMR spectrum of **20** exhibited methyl proton of 1-dodecanethiolate (–S$(CH_2)_{11}$-C$\underline{H}_3$) at 0.89 ppm, methyl proton of –NH-C_2H_4S-C$\underline{H}_3$ at 2.17 ppm and naphthoquinone protons at 8.15, 8.04, 7.63, and 7.72 ppm, together. In the ^{13}C spectra of all synthesized naphthoquinone derivatives (**10**, **12**, **13**, **15**, **17**, **19** and **20**), the characteristic signals appeared in the range of 180.0–183.1 and 176.4–181.6 ppm (quinonic carbonyl carbons). Furthermore, it can be clearly seen that the *m/z* values of these compounds are in ESI mass spectra, as expected.

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*-myrtanylamine **5** or 4-tert-butylbenzylamine **11**. The formation of both of NH- and SR- substituted-1,4-napthoquinones (**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, ^{1}H-NMR, ^{13}C-NMR, and MS-ESI spectroscopy.

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