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SOME AMINO- AND THIO- SUBSTITUTED 1,4-QUINONES: SYNTHESIS AND CHARACTERIZATION

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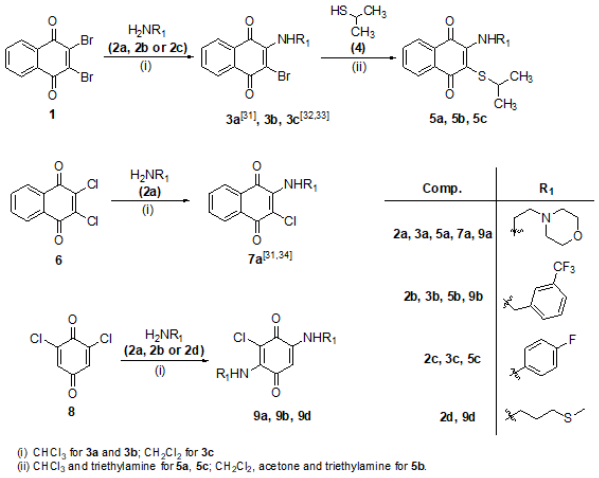
Some bromine/chlorine substituted aminonaphthoquinones (**3a-c**, **7a**) and NH, NH- substituted 1,4-benzoquinones (**9a**, **9b** and **9d**) were synthesized by the reaction of quinones (2,3-dibromo/chloro-1,4-naphthoquinone (**1**, **6**) or 2,6-dichloro-1,4-benzoquinone (**8**)) with amines (**2a-d**). Reaction of aminonaphthoquinones (**3a**, **3b** and **3c**) with sodium 2-propanethiolate (**4**) yielded naphthoquinones with both NH- and S- substituents (**5a**, **5b** and **5c**). All synthesized compounds were characterized, providing ^{1}H-NMR, ^{13}C-NMR, MS(ESI), IR, UV/Vis and elemental analysis.



INTRODUCTION

There is considerable interest in the synthesis of 1,4-naphthoquinone derivatives because of their many properties, such as photosensitizer,[1] dye,[2] anion recognition or chemosensor[3,4] and biological activity etc. Especially, 1,4-naphthoquinone's various bioactivities, such as leishmanicidal[5] anticancer,[6] Hsp90 inhibitor,[7] antifungal,[8] antiproliferative,[9] antimicrobial,[10] antimycobacterial,[11] have been of considerable interest in medical or pharmaceutical areas as potential drug candidates. Notably, the incorporation of different groups (such as methyl, amino and sulfonyl groups) on the 1,4-naphthoquinone scaffold can enhance biological activities due to their redox potentials.[12–14] For example, Prachayasittikul and Pingaew *et al.* reported some phenylamino-1,4-naphthoquinones bearing sulfonamide moiety, which were found to be potential anticancer and antimalarial agents.[14] Yoo *et al*. evaluated the anticancer activity of 1,4-naphthoquinones having both NH- and S-groups on the naphthoquinone scaffold.[6] Therefore, a developing interest to produce 1,4-napthoquinone derivatives with various substituents is highly desirable. And, in literature, there are many reports on reactions of 2,3-dichloro (or dibromo)-1,4-naphthoquinones with 2-aminothiazoles,[15] primary

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amines,[16,17] thiols,[18] aminophenols[19] etc. Also, recently, our research group has reported some 1,4-naphtho (or benzo) quinone derivatives.[20,21] With this background, the present study aims to synthesize bromine/chlorine substituted aminonaphthoquinones (**3a-c** and **7a**) and naphthoquinones with both NH- and S- substituents (**5a**, **5b** and **5c**). Compounds **3a-c** and **7a** were obtained from the reaction of 2,3-dibromo/dichloro-1,4-naphthoquinone and primary amines (**2a-c**) while **5a-c** were newly synthesized from the reaction of (**3a-c**) and sodium 2-propanethiolate (**4**) in the presence of triethylamine.

1,4-Benzoquinone derivatives are a versatile family of quinoid compounds, which play significant role in pharmaceutical, chemistry and material science fields.[22–25] This has motivated many syntheses of 1,4-benzoquinone derivatives, thus, being reported alkoxy-,[26] thio-,[27] (alkyl/aril) amino-,[28] phenyl/benzyl-[29] substituted compounds and polymers containing 1,4-benzoquinones.[30] In this study, three new bis(amino)-substituted-1,4-benzoquinone derivatives (**9a**, **9b** and **9d**) have been synthesized from 2,6-dichloro-1,4-benzoquinone as starting compound. The structures of all 1,4-naphtho/benzo quinones were characterized by spectroscopic techniques (NMR, MS, IR, UV/Vis etc.) and elemental analysis.

MATERIALS AND METHODS

Chemistry

Chemicals (**1, 4, 6, 8** and **2a-d**) were commercially purchased and were used as received. The melting point was determined using Buchi B-540. FTIR (Fourier-Transform Infrared) spectra were recorded on (JASCO, FT/IR 4700). The UV-Visible spectra of compounds were recorded on Perkin Elmer Lambda 35. The masses of compounds were determined from the Electrospray-mass spectrum (MS-ESI) recorded on ThermoFinnigan LCQ AdvantageMAX system. NMR (Nuclear Magnetic Resonance) spectra were acquired on a Varian UnityInova instrument. Tetramethylsilane is used as a reference. The purification was performed by using column chromatography over silica gel (70–230 mesh). Reactions were monitored by analytical thin-layer chromatography (TLC) and visualized using UV light (190–900 Nm).

Synthesis of Quinone Derivatives

Synthesis of 2-(2-morpholinoethylamino)-3-bromonaphthalene-1,4-dione **(3a)**.[31] 1.5 g (4.74 mmol) of 2,3-dibromo-1,4-naphthoquinone (**1**) was dissolved in $CHCl_3$ (100mL). To this solution were added 0.62 g (4.74 mmol) 4-(2-aminoethyl)morpholine (**2a**) and the reaction mixture was stirred at room temperature for about 52 hours (monitored by TLC). After the end of the reaction, water was added to this mixture and the extraction was performed with chloroform (3 × 15 mL). The combined organic layers were dried on anhydrous sodium sulfate and filtered. The filtrate was concentrated in vacuo to give crude mixture which was purified by column chromatography over silica gel in the ethyl acetate : chloroform 1: 4 system to give the pure product **3a**[31]; Rf (EtOAc:CH_2Cl_2 1:1): 0.6; Yield: 1.04 g, 60%; Solid; m.p. 118.0–119.0ºC; UV/vis($CHCl_3$):λ_{max}(log ε)= 280 (3.86), 473 (3.09); IR (ATR, ϒ, cm^{-1}): 3229, 2958, 2938, 2889, 2842, 1679, 1554; ^{1}H-NMR (500MHz,$CDCl_3$): δ 8.11 (dd, 1H, ^3J= 7.6 Hz, ^4J= 1.1 Hz, H_{napht}), 7.98 (dd, 1H, ^3J= 7.6 Hz, ^4J= 1.1 Hz, H_{napht}), 7.68 (td, 1H, ^3J= 7.5 Hz, ^4J= 1.3 Hz, H_{napht}), 7.59 (td, 1H, ^3J= 7.5 Hz, ^4J= 1.3 Hz, H_{napht}), 6.96 (s, 1H, NH), 3.95 (dd, 2H, *J*=11.3 Hz, *J*=5.6 Hz), 3.78-3.70 (m, 4H), 2.66 (t, 2H, *J*=6.0 Hz), 2.53 (s, 4H); ^{13}C-NMR (125MHz, $CDCl_3$): δ 180.2, 176.2 (C=O); 147.0, 134.7, 132.4, 132.3, 130.0, 126.9, 126.7, 67.0, 56.7, 52.9, 41.1; MS(ESI): *m/z* 365.1 ($[M+H]^+$, 26%), 285.2 ($[M-Br]^-$, 100%); Anal. calc. for $C_{16}H_{17}BrN_2O_3$: C, 52.62; H, 4.69; N, 7.67. Found C, 52.56; H, 4.58; N, 7.64. The results are in line with the literature [31].

Synthesis of 2-(2-morpholinoethylamino)-3-(isopropylthio)naphthalene-1,4-dione **(5a).** 0.111 g (0.31 mmol) of (**3a**) was dissolved in $CHCl_3$ (20 mL). And 0.03 g (0.31 mmol) sodium 2-propanethiolate (**4**) was added to this solution, followed by dropwise addition of triethylamine (~2 mL). The reaction mixture was stirred at room temperature for about 50 hours (monitored by TLC). After the end of the reaction, water was added to this mixture and the extraction was performed with chloroform (3 × 15 mL). The combined organic layers were dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated in vacuo to give the crude mixture which was purified by column chromatography over silica gel in the ethyl acetate : chloroform 1: 20 system to give the pure product **5a**. Rf (EtOAc:$CHCl_3$ 1:1): 0.6; Yield: 0.022 g, 20%; Dark red solid; m.p. 94–96 ºC; UV/vis($CHCl_3$):λ_{max}(logε)= 283 (4.57), 492 (3.78);

IR (ATR, ϒ, cm^{-1}): 2961, 2918, 2846, 1670, 1587, 1540, 1262. ^{1}H-NMR (500MHz,$CDCl_3$): δ 8.14 (dd, 1H, ^3J= 7.7 Hz, ^4J= 1.0 Hz, H_{napht}), 8.02 (d, 1H, ^3J= 7.7 Hz, H_{napht}), 7.71 (td, 1H, ^3J= 7.5 Hz, ^4J= 1.1 Hz, H_{napht}),7.60 (td, 1H, ^3J= 7.5 Hz, ^4J= 1.1 Hz, H_{napht}), 7.38 (s, 1H, NH), 3.98 (dd, 2H, *J*=11.1 Hz, *J*=5.5 Hz), 3.80-3.72 (m, 4H), 3.47 (hept, 1H, ^3J=6.7 Hz, -S-C<u>H</u><), 2.65 (t, 2H, ^3J=5.9 Hz), 2.52 (s, 4H), 1.27 (d, 6H, $2CH_3$, ^3J=6.7 Hz); ^{13}C-NMR (125MHz, $CDCl_3$): δ 181.8, 180.1, 134.5, 133.8, 131.9, 130.9, 126.6, 126.3, 67.0, 57.1, 53.1, 42.0, 38.3 (-S-CH<); 23.4. MS(+ESI): *m/z* 361.2 ($[M+H]^+$, 100%), Anal. calc. for $C_{19}H_{24}N_2O_3S$: C, 63.31; H, 6.71; N, 7.77. Found C, 63.36; H, 6.68; N, 7.75.

Synthesis of 2-(3-(trifluoromethyl)benzylamino) -3-bromonaphthalene-1,4-dione **(3b).** 1.2 g (3.8 mmol) of 2,3-dibromo-1,4-naphthoquinone (**1**) was dissolved in $CHCl_3$ (100 mL) in a round bottom flask and 0.67 g (3.8 mmol) 3-(trifluoromethyl) benzylamine (**2b**) was added to this solution, reaction mixture was stirred at room temperature for about 50 hours (monitored by TLC). After the end of the reaction, water was added to this mixture and the extraction was performed with chloroform (3 × 15 mL). The combined organic layers were dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated in vacuo to give the crude mixture which was purified by column chromatography over silica gel in the $CHCl_3$ system to give the pure product **3b**. Rf ($CHCl_3$): 0.4; Yield: 0.31 g, 20%; Orange solid; m.p. 130.0–131.0°C; UV/vis($CHCl_3$):λ_{max}(logε)= 279 (3.91), 458 (3.10); IR (ATR, ϒ, cm^{-1}): 3286, 1681, 1597, 1556, 1508; ^{1}H-NMR (500MHz,$CDCl_3$): δ 8.15 (dd, 1H, ^3J= 7.7 Hz, ^4J= 1.2 Hz, H_{napht}), 8.03 (dd, 1H, ^3J= 7.7 Hz, ^4J= 1.2 Hz, H_{napht}), 7.72 (td, 1H, ^3J= 7.6 Hz, ^4J= 1.3 Hz, H_{napht}), 7.64 (td, 1H, ^3J= 7.6 Hz, ^4J= 1.3 Hz, H_{napht}), 7.59 (d, 2H), 7.56-7.48 (m, 2H), 6.26 (bs, 1H, NH), 5.14 (d, ^3J= 6.0 Hz, 2H, CH_2); ^{13}C-NMR (125MHz, $CDCl_3$): δ 179.9, 176.6 (C=O); 146.2, 139.0, 134.9, 132.7, 132.1, 131.5, 131.2, 130.8, 129.8, 129.5, 127.1, 124.8, 124.3, 122.8, 110.0; 48.5 (CH_2); MS(+ESI): *m/z* 410.2 ($[M+H]^+$); Anal. calc. for $C_{18}H_{11}BrF_3NO_2$: C, 52.71; H, 2.70; N, 3.41; Found C, 52.68; H, 2.74; N, 3.38.

Synthesis of 2-(3-(trifluoromethyl)benzylamino)- 3-(isopropylthio)naphthalene-1,4-dione **(5b).** 0.055 g (0.13 mmol) of (**3b**) was dissolved in CH_2Cl_2 (20 mL) and acetone (10 mL). And, 0.02 g (0.20 mmol) sodium 2-propanethiolate (**4**) was added to this solution, followed by dropwise addition of the triethylamine (~2 mL). The reaction mixture was stirred at room temperature for about 48 hours (monitored by TLC). After the end of the reaction, water was added to this mixture and the extraction was performed on chloroform (3 × 15 mL). The combined organic layers were dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated in vacuo to give the crude mixture which was purified by column chromatography over silica gel in the $CHCl_3$ system to give the pure product **5b**. Rf ($CHCl_3$): 0.5; Yield: 0.012 g, 22%; m.p. 113–115 °C; UV/vis($CHCl_3$):λ_{max}(logε)= 285 (4.31), 482 (3.51); IR (ATR, ϒ, cm^{-1}):); 3329, 2955, 2919, 2849, 1670, 1618, 1592, 1549, 1505, 1422, 1328; ^{1}H-NMR (500MHz, $CDCl_3$): δ 8.13 (dd, 1H, ^3J= 7.7 Hz, ^4J= 1.2 Hz, H_{napht}), 8.03 (dd, 1H, ^3J= 7.7 Hz, ^4J= 1.2 Hz, H_{napht}), 7.72 (td, 1H, ^3J= 7.6 Hz, ^4J= 1.3 Hz, H_{napht}), 7.63 (td, 1H, ^3J= 7.6 Hz, ^4J= 1.3 Hz, H_{napht}), 7.60–7.45 (m, 4H, H_{arom}), 6.75 (bs, 1H, NH), 5.17 (d, ^3J= 6.4 Hz, 2H, CH_2), 3.53 (hept, 1H, ^3J= 6.7 Hz, -S-C<u>H</u><), 1.20 (d, 6H, $2CH_3$, ^3J= 6.7 Hz, 6H); ^{13}C-NMR (125MHz, $CDCl_3$): δ 181.3, 180.3 (C=O); 139.5, 134.7, 133.5, 132.3, 130.8, 129.4, 126.7, 126.5, 124.60, 124.57, 124.31, 124.27; 49.4(CH_2); 38.6 (-S-<u>C</u>H<); 29.7, 23.1; MS(+ESI): *m/z* 406.1 ($[M+H]^+$, 100%); Anal. calc. for $C_{21}H_{18}F_3NO_2S$: C, 62.21; H, 4.47; N, 3.45; Found C, 62.18; H, 4.50; N, 3.48.

Synthesis of 2-(4-fluorophenylamino)-3- (isopropylthio)naphthalene-1,4-dione **(5c).** Compound **5c** was produced starting from **3c**. Compound **3c** is known [32-33], being synthesized with our previously reported method [33]. 0.24 g (0.69) mmol of **3c** was dissolved in $CHCl_3$ (50 mL). And, 0.08 g (0.81 mmol) sodium 2-propanethiolate (**4**) was added to this solution, followed by dropwise addition of triethylamine (~2 mL). The reaction mixture was stirred at room temperature for about 72 hours (monitored by TLC). After the end of the reaction, water was added to this mixture and the extraction was performed with chloroform (3 × 15 mL). The combined organic layers were dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated in vacuo to give the crude mixture which was purified by column chromatography over silica gel in the petroleum ether chloroform 1 : 3 system to give the pure product **5c**. Rf (CH_2Cl_2):0.66; Yield: 0.15 g, 64%; Dark red solid; UV/vis ($CHCl_3$):λ_{max}(logε)= 279 (4.55), 505 (3.53); IR (ATR, ϒ, cm^{-1}): 3259, 2954, 2919, 2849, 1666, 1632, 1591, 1500, 1216; ^{1}H-NMR (500MHz,$CDCl_3$): δ 8.15 (d, ^3J= 7.7 Hz, 1H, H_{napht}), 8.06 (d, ^3J= 7.6 Hz, 1H, H_{napht}), 7.78 (bs, 1H, NH), 7.74 (t, ^3J= 7.6 Hz, 1H, H_{napht}), 7.66 (t, ^3J= 7.5 Hz, 1H, H_{napht}), 7.04–6.99 (m, 4H, H_{arom}), 3.28 (m, -S-

C<u>H</u><), 1.09 (dd, 2 x CH_3, 6H, *J*= 6.7 Hz, *J*= 1.6 Hz); ^{13}C-NMR (125MHz, $CDCl_3$): δ 181.2, 180.6 (C=O); 160.0 (d, $J_{C,F}$= 244.9 Hz), 146.7, 134.7, 133.5, 132.9, 130.9, 127.1, 126.8; 125.1 (d, $J_{C,F}$= 8.5 Hz); 117.1, 115.3 (d, $J_{C,F}$= 23.0 Hz); 38.1 (-S-<u>C</u>H<); 23.2 (CH_3); MS(+ESI) *m/z* 342.0 ([M+H]$^+$, 100%) and MS(-ESI) *m/z* 340.2 ([M-H]$^-$, 100%); Anal. calc. for $C_{19}H_{16}FNO_2S$: C, 66.84; H, 4.72; N, 4.10; Found C, 66.80; H, 4.75; N, 4.14.

Synthesis of 2-(2-morpholinoethylamino)-3-chloronaphthalene-1,4-dione **(7a)** [17,31,34,37]. 1g (4.4 mmol) of 2,3-dichloro-1,4-naphthoquinone (**6**) was dissolved in $CHCl_3$ (100 mL). And, 0.57 g (4.4 mmol) 4-(2-aminoethyl)morpholine (**2a**) was added to this solution. The reaction mixture was stirred at room temperature overnight (monitored by TLC). After the end of the reaction, water was added to this mixture and the extraction was performed with chloroform (3 × 15 mL). The combined organic layers were dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated in vacuo to give the crude mixture which was purified by column chromatography over silica gel in the ethyl acetate : chloroform 1 : 7 system to give the pure product **7a**. Rf (EtOAc:CH_2Cl_2 1:1): 0.7; Yield: 0.7 g (50%); Solid; m.p. 114.5–115.5ºC; UV/vis($CHCl_3$):λ_{max}(log ε)= 277 (3.98), 473 (3.15); IR (ATR, ϒ, cm^{-1}): 3200, 2956, 2884, 2837, 1678, 1589, 1567, 1452; ^{1}H-NMR (500MHz,$CDCl_3$): δ 8.13 (dd, 1H, ^3J= 7.7 Hz, ^4J= 1.1 Hz, H_{napht}), 8.01 (dd, 1H, ^3J= 7.7 Hz, ^4J= 1.1 Hz, H_{napht}),7.71(td, 1H, ^3J= 7.6 Hz, ^4J= 1.3 Hz, H_{napht}), 7.61 (td, 1H, ^3J= 7.6 Hz, ^4J= 1.3 Hz, H_{napht}), 6.89 (bs, NH, 1H), 3.98 (s, 2H), 3.77 (s, 4H), 2.70 (s, 2H), 2.56 (s, 4H); ^{13}C-NMR (125MHz, $CDCl_3$): δ 180.6, 176.6, 144.6, 134.8, 132.7, 132.4, 129.9, 126.73, 126.68, 67.18, 56.86, 53.01, 40.78; MS(ESI): *m/z* 321.1 ([M+H]$^+$, 100%), 285.3 ([M-Cl]$^-$, 56%); Anal. calc. for $C_{16}H_{17}ClN_2O_3$: C, 59.91; H, 5.34; N, 8.73; Found C, 59.88; H, 5.30; N, 8.70. The results are in line with the literature [34].

Synthesis of 2,5-bis(2-morpholinoethylamino)-3-chlorocyclohexa-2,5-diene-1,4-dione **(9a).** 0.75 g (4.23 mmol) of 2,6-dichloro-1,4-benzoquinone (**8**) was dissolved in $CHCl_3$ (30 mL). And, 1.10 g (8.47 mmol) 4-(2-aminoethyl)morpholine (**2a**) was added to this solution, reaction mixture was stirred at room temperature for 96 hours (monitored by TLC). After the end of the reaction, water was added to this mixture and the extraction was performed with chloroform (3 × 15 mL). The combined organic layers were dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated in vacuo to give the crude mixture which was purified by column chromatography over silica gel in the $CHCl_3$ system to give the pure product **9a**. Rf (EtOAc:CH_2Cl_2 1:1): 0.3; Yield: 0.76 g (45%); Lime green solid; Lime green solid; m.p. 172–174 ºC UV/vis($CHCl_3$):λ_{max}(log ε)= 352 (3.62), 515 (1.73); IR (ATR, ϒ, cm^{-1}): 3339, 3286, 3247, 2959, 2936, 2889, 2819, 1650, 1614, 1490, 1455; ^{1}H-NMR (500MHz,$CDCl_3$): δ 7.54 (bs, 1H, NH), 7.14 (bs, 1H, NH), 5.15 (s, 1H, $H_{quinone}$), 3.90 (m, 2H), 3.69-3.62 (m, 8H), 3.13 (m, 2H), 2.63-2.54 (m, 4H), 2.48-2.36 (m, 8H); ^{13}C-NMR (125MHz, $CDCl_3$): δ 176.3, 173.3, 150.3, 145.8, 110.00, 100.4, 91.9, 91.8, 66.9, 66.8, 56.7, 55.3, 53.1, 53.0, 40.5, 38.7; MS(+ESI): *m/z* 399.2 ([M+H]$^+$, 100%); Anal. calc. for $C_{18}H_{27}ClN_4O_4$: C, 54.20; H, 6.82; N, 14.05; Found C, 54.16; H, 6.80; N, 14.00.

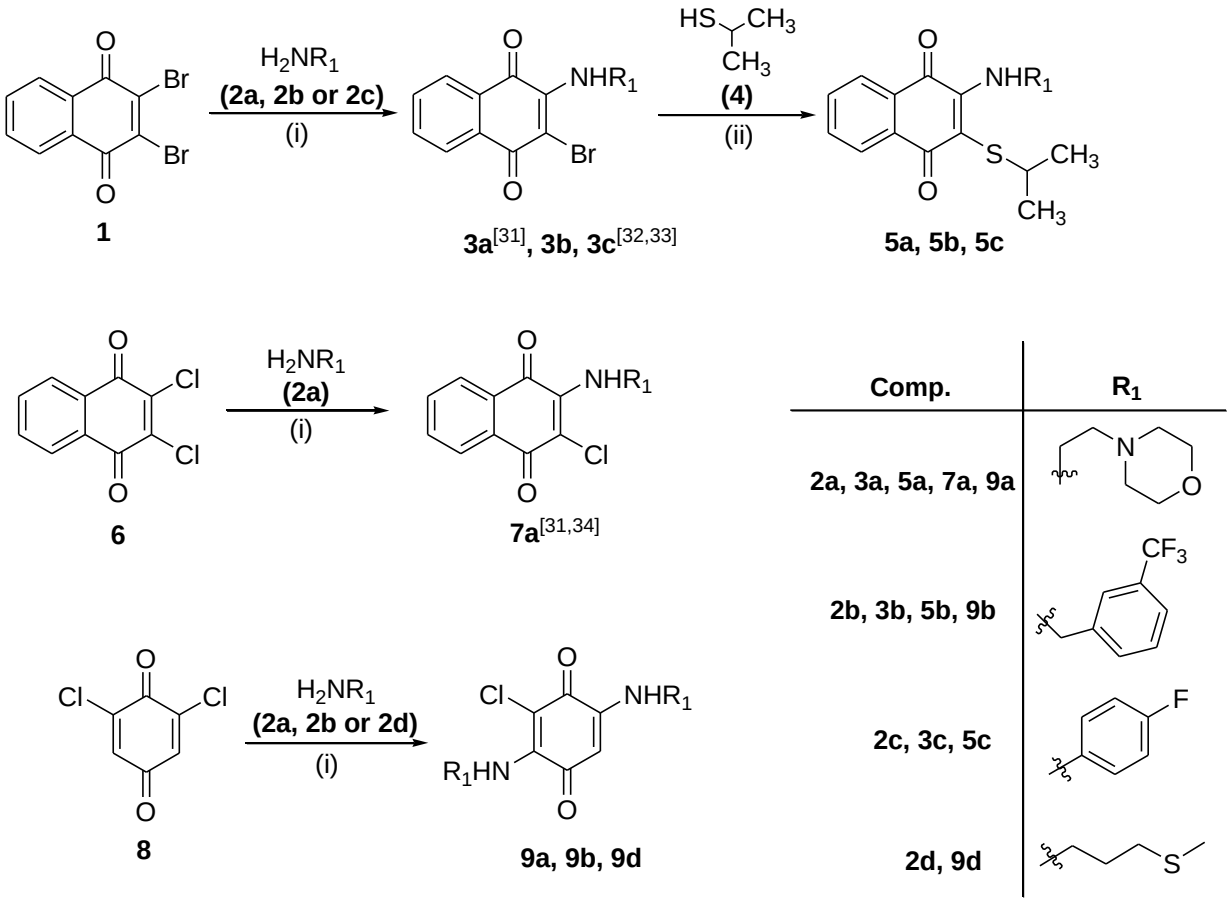
Synthesis of 2,5-bis(3-(trifluoromethyl) benzylamino)-3-chlorocyclohexa-2,5-diene-1,4-dione **(9b).** 0.75 g (4.23 mmol) of 2,6-dichloro-1,4-benzoquinone (**8**) was dissolved in $CHCl_3$ (30 mL). And, 1.48 g (8.47 mmol) 3-(trifluoromethyl) benzylamine (**2b**) was added to this solution, reaction mixture was stirred at room temperature for 96 hours (monitored by TLC). After the end of the reaction, water was added to this mixture and the extraction was performed with chloroform (3 × 15 mL). The combined organic layers were dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated in vacuo to give the crude mixture which was purified by column chromatography over silica gel in the $CHCl_3$ system to give the pure product **9b**. Rf ($CHCl_3$): 0.5; Yield: 0.80 g (39%); Reddish purple solid; m.p. 179.0–180.0 ºC; UV/vis($CHCl_3$):λ_{max}(log ε)= 348 (3.94), 509 (1.96); IR (ATR, ϒ, cm^{-1}): 3286, 3247, 3077, 2956, 1648, 1571, 1485; ^{1}H-NMR (500MHz, $CDCl_3$): δ 7.63-7.43 (m, 8H, H_{arom}), 5.37 (s,1H, $H_{quinone}$), 5.14 (d, 2H, *J*= 6.5 Hz, CH_2), 4.46 (d, *J*= 6.1 Hz, CH_2); ^{13}C-NMR (125MHz, $CDCl_3$): δ 177.0, 174.0, 149.8, 144.9, 138.4, 136.3, 130.8, 130.7, 129.65, 129.58, 125.20, 125.17, 125.01, 124.97, 124.36, 124.33, 124.19, 124.16, 47.90, 46.49; MS(+ESI): *m/z* 489.1 ([M+H]$^+$, 100%); Anal. calc. for $C_{22}H_{15}ClF_6N_2O_2$: C, 54.06; H, 3.09; N, 5.73; Found C, 54.10; H, 3.06; N, 5.77.

Synthesis of 2,5-bis(3-(methylthio)propylamino)-3-chlorocyclohexa-2,5-diene-1,4-dione **(9d)**. A solution of 2,6-dichloro-1,4-benzoquinone (**8**) (0.75 g, 4.23 mmol) and 3(methylthio)propylamine (**2d**) (0.89 g, 8.47 mmol) in $CHCl_3$ (30 mL) was stirred at room temperature for 72 hours. The progress of the reaction was monitored by TLC using $CHCl_3$ as

eluent. After the end of the reaction, water was added to this mixture and the extraction was performed with chloroform (3 × 15 mL). The combined organic layers were dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated in vacuo to give the crude mixture which was purified by column chromatography over silica gel in the $CHCl_3$ system to give the pure product **9d**. Rf (EtOAc:CH_2Cl_2 1:2): 0.9; Yield: 0.89g, 60%; Dark red solid; m.p. 144.0–145.0 °C; UV/vis($CHCl_3$):λ_{max}(log ε)= 347 (3.78), 520 (2.09); IR (ATR, ϒ, cm^{-1}): 3273, 3217, 2950, 2918, 2852, 1650, 1556, 1485, 1453; ^{1}H-NMR (500MHz, $CDCl_3$): δ 7.10 (bs, 1H, NH), 6.82 (bs, 1H, NH), 5.34 (s, $H_{quinone}$,1H), 3.95 (q, 2H, CH_2, ^3J=6.88 Hz), 3.31 (q, *J*= 6.7 Hz, 2H, CH_2), 2.56 (q, 4H, $2CH_2$), 2.10 (s, 3H, CH_3), 2.09 (s, 3H, CH_3), 2.01-1.90 (m, 4H, $2CH_2$); ^{13}C-NMR (125MHz, $CDCl_3$): δ 176.4, 173.5 (C=O), 150.6, 145.6, 100.4, 91, 43.3, 41.6, 31.4, 31.2, 30.0, 27.1 (6 CH_2); 15.6, 15.5 (2 CH_3); MS(+ESI): *m/z* 349.0 ($[M+H]^+$, 100%); Anal. calc. for $C_{14}H_{21}ClN_2O_2S_2$: C, 48.19; H, 6.07; N, 8.03, S, 18.38; Found C, 48.22; H, 6.02; N, 8.00, S, 18.35.

RESULTS AND DISCUSSION

The compounds synthesized here could be divided in three classes: Firstly, bromine/chlorine substituted aminonaphthoquinones **(3a-c**, **7a**), secondly naphthoquinones with both amino- and thio- substituents (**5a-c**) and finally bis(amino)substituted 1,4-benzoquinones (**9a-b**, **9d**), as shown Scheme 1.



(i) $CHCl_3$ for **3a** and **3b**; CH_2Cl_2 for **3c**
(ii) $CHCl_3$ and triethylamine for **5a**, **5c**; CH_2Cl_2, acetone and triethylamine for **5b**.

Scheme 1 – The synthesis of compounds 3a-c, 5a-c, 7a, 9a-b and 9d.

Aminonaphthoquinones are known pharmaceutically active agents[12] and can also serve as chemical sensors.[35,36] For example, Salunke-Gawali et al reported metal ion (such as Cu^{2+}) binding studies of bromine substituted aminonapththoquinones.[35] In the present study,

compounds (**3a-b** and **7a**) have bromine/chlorine substituted aminonaphthoquinone skeleton and they were obtained via the nucleophilic substitution reaction of 2,3-dibromo/dichloro-1,4-naphthoquinone (**1**) by primary amines (**2a-b**) in $CHCl_3/CH_2Cl_2$ medium. Compounds **3a**, **3c** and **7a** were known from literature;[17,31–34,37] Synthesis of compounds **3a** and **7a** was reported in the literature starting from **1** and **6** respectively and gave products in 74% and 86% yields, respectively, in the presence of N, N-diisopropylethylamine (DIEA) and acetonitrile at room temperature.[31] Additionally, compound **7a** was obtained from **6**, in ether in the presence of triethylamine with 59% yield,[34] in ethanol at reflux with 74.5 % yield[17] and in dry dichloromethane and N, N-diisopropylethylamine at room temperature with 96 %yield.[37] Thus, in the present work, compounds **3a** and **7a** were obtained by stirring a chloroform solution of **2a** and naphthoquinone (**1** or **6**) at room temperature, a simpler method compared with the previously reported ones.[17,31,34,37] Also, synthesis of compound **3c** was reported in literature starting from **1** and gave a product in 30% yield, in the presence of ethanol under reflux.[32] In the present work, this compound (**3c**) has been synthesized by our previously reported method,[33] by stirring a dichloromethane solution of **2c** and **1** at room temperature.

Among naphthoquinones, **3a**, **5a** and **7a** have morpholino moiety in naphthoquinone structure. It is known from literature that 1,4-naphthoquinone derivatives having morpholino moiety have biological activities such as antiproliferative, leishmanicidal or trypanocidal activity.[5,17,21,31,34] Compounds **3b** and **9b** have 3-(trifluoromethyl) benzyl)amino moiety in their structure. There are some related works, for example; Langer *et al*.[38] reported the reaction of 2,3-dibromo-1,4-naphthoquinone (**1**) with 3-(trifluoromethyl) benzylamine (**2b**) in palladium catalyzed medium to produce a benzo[b] carbazoledione derivative. And, Varriccihio *et al*.[39] evaluated 2-Aniline-1,4-naphthoquinones as potential drug candidates including 2-Chloro-3-(3-(trifluoromethyl)benzyl) amino)naphthalene-1,4-dione, synthesized starting from 2,3-dichloro-1,4-naphthoquinone (**6**) and 3-(trifluoromethyl)benzylamine (**2b**). In the present work, 2-(3-(trifluoromethyl)benzylamino)-3-bromo naphthalene-1,4-dione (**3b**) was synthesized from the reaction between **1** and **2b** in $CHCl_3$.

The ^{1}H-NMR spectrum of bromine/chlorine substituted aminonaphthoquinones (**3a**, **3b** and **7a**) revealed two dd and two td in the region δ = 7.98-8.15 and δ = 7.59–7.72 ppm, respectively (with *J* values at about 7.6 Hz and 1.2 Hz), indicating the presence of four protons for the 1,4-naphthoquinone moiety, while the broad singlet at δ = 6.96–6.26 ppm resulted from the NH proton. And, in the ^{13}C-NMR spectra of these products (**3a**, **3b** and **7a**), characteristic signals of two carbonyl carbons of naphthoquinone moiety were visible at about δ = 180 and 176 ppm. Also, signals of amino- moiety's protons and carbons in NMR, supported their structure. For example, in the ^{1}H-NMR spectrum of **3b**, the appearance of -CH_2- protons signal at δ = 5.14 ppm and the carbon signal of –CH_2- at δ = 48.5 ppm confirmed the presence of the amino moiety in its structure. IR spectra of (**3a**, **3b** and **7a**) revealed characteristic -NH stretching like that 3229 cm^{-1} (**3a**), 3200 cm^{-1} (**7a**) and 3286 cm^{-1} (**3b**). And, the carbonyl stretching frequency was observed at about 1680 cm^{-1} for compounds **3a**, **3b** and **7a**.

When aminonaphthoquinones (**3a-c**) were subjected to the reaction with thiol (sodium 2-propanethiolate, **4**) in the presence of triethylamine, the corresponding products (**5a-c**) having both of NH- and S- groups, were obtained in 20–64 % yields. Thus, with introduction of a thio moiety at C3 of the 1,4-naphthoquinone ring, the signals (-S-C<u>H</u><) were observed for the reaction products (**5a-c**) between δ = 3.28–3.53 ppm in the ^{1}H-NMR spectrum. And, signals between δ = 38.1-38.6 ppm on the ^{13}C-NMR spectrum were assignable to the S-<u>C</u>H< carbons for (**5a-c**).

In the UV-visible spectrum of the bromine/chlorine substituted aminonaphthol quinones (**3a-b** and **7a**), a broad band centered 473–458 nm was observed in the visible region, which could be stem from charge transfer (CT) band and weak n-π* transitions of the carbonyl of the quinone.[40,41] With the formation of naphthoquinone with both amino- and thio- substituents (**5c**) by adding a thio group to aminoquinone **3c**, the visible absorption band shifted from from 474 nm to 505 nm.

2,6-dichloro-1,4-benzoquinone (**8**) was reacted with primary amines (**2a**, **2b** or **2d**) to obtain bis(amino)substituted 1,4-benzoquinones (**9a-b**, **9d**). In their ^{1}H-NMR spectra, the presence of benzoquinone proton was confirmed between δ= 5.15–5.37 ppm as singlet, which confirmed the binding of the amino moieties in both positions 2 and 5. Also, these compounds (**9a-b** and **9d**) exhibited broad bands at 509–520 nm in the visible region. The synthesized bis(amino)substituted-1,4-

benzoquinones might be regarded as potential bioactive compounds since in literature[42] 2,5-bis[4-(2-aminoethyl) morpholin-1-yl]-3,6-dichloro-1,4-benzoquinone, a similar compound to **9a**, was found to have antioxidant and cytotoxic activity.

Structures of all 1,4-naphtho/benzo- quinone derivatives (**3a-b**, **5a-c**, **7a, 9a-b** and **9d**) were confirmed by mass spectral method MS(ESI). For example, the protonated molecular ion $[M+H]^+$ peak and deprotonated molecular ion $[M-H]^-$ peak of compound **5c** were observed at m/z= 342.0 and at m/z= 340.2, respectively, which were in agreement with the molecular formula of $C_{19}H_{16}FNO_2S$.

CONCLUSION

In conclusion, the synthesis and characterization of bromine/chlorine substituted aminonaphthol quinones (**3a-c**, **7a**), bis(amino)substituted 1,4-benzoquinones (**9a-b, 9d**) and naphthoquinones with both amino- and thio- substituents (**5a-c**) have been reported. Compounds **3a-c**, **7a** and **9a** were prepared by the reaction of different quinone substrates (2,3-dibromo-1,4-naphthoquinone **1**, 2,3-dichloro-1,4-naphthoquinone **6** and 2,6-dichloro-1,4-benzoquinone **8**) with amines (**2a-c**). Compounds **5a-c** were synthesized starting from **3a-c**; Compounds **3a-c** were thiolated in $CHCl_3$ or CH_2Cl_2/acetone with sodium 2-propanethiolate (**4**) in the presence of triethylamine to produce target products (**5a-c**) with 20–64% yields. All the compounds were characterized using IR, NMR, mass spectroscopy, or UV/Vis studies.

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