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# Synthesis of Some Mono-, Bis- NH-substituted-1,4-Benzoquinones

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**Abstract:** The preparation of new mono- and bis- NH-substituted-1,4-benzoquinones, namely 2,5-bis(5,6-dimethylbenzo[d]thiazol-2-ylamino)cyclohexa-2,5-diene-1,4-dione (**3**), 2,5-bis(3-(2-methylpiperidin-1-yl)propylamino)-3-chlorocyclohexa-2,5-diene-1,4-dione (**6**), 2-(4-tert-butylbenzylamino)-3,5,6-trichlorocyclohexa-2,5-diene-1,4-dione (**9**), 2-(4-fluorophenylamino)-6-tert-butylcyclohexa-2,5-diene-1,4-dione (**12**) are reported. The synthesis of new quinone derivatives (**3**, **6**, **9**, **12**) have been carried out from the reactions between quinones (*p*-benzoquinone (**1**), 2,6-dichloro-1,4-benzoquinone (**4**), tetrachloro-1,4-benzoquinone (**7**) or 2-tert-butyl-1,4-benzoquinone (**10**)) and different amines (2-amino-5,6-dimethylbenzothiazole (**2**), N-(3-aminopropyl)-2-pipecoline (**5**), 4-tert-butylbenzylamine (**8**) or 4-fluoroaniline (**11**)). The new compounds were characterized by elemental analysis, mass spectrometry, IR, $^{1}$H-NMR, $^{13}$C-NMR spectroscopy.

**Keywords:** Quinones, NH-substituted-benzoquinones, Amines.

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## INTRODUCTION

Quinones are found in both natural and synthetic products (1-3). And, these compounds are important in many fields including medicinal chemistry, color chemistry, optical data storage, photoconductors, supercapacitors, coordination polymers (4-10). Especially, these compounds are of particular interest because of their biological and chemotherapeutic activities, such as antifungal, antibacterial, anti-tumor, anti-inflammatory, antiplatelet, and antiallergic (11-13). The biological activity of the quinones is related to the redox chemistry of these compounds (14-15).

There are a lot of reports on biological or pharmalogical evaluation of amino or thio substituted 1,4-(naphtho/benzo)quinones (16-19). Also, the presence of different substituent (NH, SR, alkyl, halogen, *etc.*) on the quinoid structure can impact the quinone's capability to accept electrons and thus its biological activities (12, 20, 21), including antifungal, antibacterial, antitumor, and sometimes the substituents improve these activities. Thus, many researchers have centered their studies on the synthesis, characterization, biological activity and redox properties of quinones. In this respect, many quinones were reacted with amines, thiols, alcohols, to produce amino-, azido, hydroxy-, thio-, halogeno- or alkyl- substituted quinones by using different solvents such as EtOH, MeOH, $H_2O$, $CH_3CN$, $CH_2Cl_2$, at room or reflux temperature (22-26). Recently, in our laboratory, some NH-/SR- substituted quinones were synthesized between the reaction of quinones and amines/thiols, and also the antifungal, antibacterial, antioxidant or anticancer activities of these compounds have been evaluated (27-30).

Among quinones, 2,5-diamino-1,4-benzoquinones are obtained the reaction between 1,4-benzoquinones and primary aliphatic amines, which by the addition, isomerization, and oxidation reactions (31, 32). There are some uses these type of compounds. For example, the quinone-containing conducting additive, 2,5-bis((2-(1H-indol-3-yl)ethyl)amino)cyclohexa-2,5-diene-1,4-dione (HBU), was synthesized and used as an additive for application to electrode material for supercapacitors (8). Another example, Barbosa *et al.* synthesized new 2,5-bis(alkylamino)-1,4-benzoquinones and investigated their cytotoxicity (33). They indicated that the some synthesized 2,5-bis(NH-substituted)-1,4-benzoquinone compounds exhibited activity against HL-60 (leukemia), MDA-MB-435 (melanoma), SF-295 (brain) and HCT-8 (colon) human cancer cell lines (33). In this study, compounds **3** and **6** have 2,5-bis(NH-substituted)-1,4-benzoquinone structure, including not halogen and chlorine, respectively.

## MATERIALS AND METHODS

The melting points were obtained on a Buchi B-540 apparatus. The IR spectra were measured using a Jasco FT/IR-4700 instrument. The mass spectra were recorded on a Thermo Finnigan LCQ Advantage MAX system using ion-trap mass analyzer for ESI source. The $^{1}H$ and $^{13}C$ NMR spectra were recorded on a Varian Unity Inova spectrometer (500 and 125 MHz, respectively) using $CDCl_3$ as solvent and TMS an internal standard. Column chromatography was carried out using silica gel (Kieselgel 60, 70–230 mesh, Merck). Kieselgel 60 F-254 plates (Merck) were used for thin-layer chromatography.

**Synthesis of 2,5-bis(5,6-dimethylbenzo[d]thiazol-2-ylamino)cyclohexa-2,5-diene-1,4-dione (3)**: A solution of *p*-benzoquinone **1** (0.8 g, 4.5 mmol) and 2-amino-5,6-dimethylbenzothiazole **2** (0.5 g, 4.5 mmol) in methanol (20 mL) was stirred at reflux temperature. The progress of the reaction was monitored by thin layer chromatography (TLC) using $CH_2Cl_2$ as eluent. Upon the completion of the reaction, the reaction mixture was diluted with water (30 mL) and extracted with chloroform (3×15 mL). The combined organic extract was dried over anhydrous $Na_2SO_4$, concentrated under vacuum and the residue was subjected to column chromatography using silica gel in dichloromethane/ethyl acetate (1:1) to give the pure product **3**: $R_f$ (MeOH): 0.7. Yield: 16 % (165 mg). Brownish solid. M.p= 180-182 $^{o}$C. IR (ATR): 3371, 3289, 2912, 1642, 1531, 1454, 1364, 1314, 1272, 1200, 1108, 859. Mass spectrum (+ESI), m/z $[M-H]^+$= 459.3. $^{1}H$ NMR ($CDCl_3$) δ (ppm): 7.58 (s, $CH_{arom}$, 1H), 7.52 (s, $CH_{arom}$, 1H), 7.40 (bs, 2H, NH), 7.27 (s, $CH_{arom}$, 1H), 7.22 (s, $CH_{arom}$, 1H), 5.83 (s, 1H, $CH_{quinone}$), 5.06 (s, 1H, $CH_{quinone}$), 2.27 (s, 3H, $CH_3$), 2.22 (s, 3H, $CH_3$), 2.21 (s, 3H, $CH_3$), 2.20 (s, 3H, $CH_3$). $^{13}C$ NMR ($CDCl_3$) δ (ppm):182.5 (C=O), 181.7 (C=O), 165.6, 160.9, 157.3, 150.0, 139.7, 135.9, 134.8, 133.9, 132.1, 131.3, 128.6, 127.6, 122.3, 122.3, 121.2, 119.8, 108.0, 103.8, 20.1 ($CH_3$), 20.1 ($CH_3$), 20.1 ($CH_3$), 19.8 ($CH_3$). $C_{24}H_{20}N_4O_2S_2$ calcd. C, 62.59; H, 4.38; N, 12.16; S, 13.92. Found C, 62.60; H, 4.39; N, 12.14; S, 13.90.

**Synthesis of 2,5-bis(3-(2-methylpiperidin-1-yl)propylamino)-3-chlorocyclohexa-2,5-diene-1,4-dione (6)**: A solution of 2,6-dichloro-1,4-benzoquinone **4** (0.75 g, 4.2 mmol) and N-(3-aminopropyl)-2-pipecoline **5** (0.66 g, 4.2 mmol) in dichloromethane (20 mL) was stirred at room temperature. The progress of the reaction was monitored by thin layer chromatography (TLC) using $CH_2Cl_2$ as eluent. Upon the completion of the reaction, the reaction mixture was diluted with water (30 mL) and extracted with chloroform (3×15 mL). The combined organic extract was dried over anhydrous $Na_2SO_4$, concentrated under vacuum and the residue was subjected to column chromatography using silica gel in ethyl acetate to give the pure product **6**: $R_f$ (Ethylacetate): 0.16. Yield: 15% (286 mg). M.p: 126-128 $^{o}$C. Mass spectrum (+ESI), m/z $[M+H]^+$= 451.3, Mass spectrum (-ESI), m/z $[M]^-$=449.5**.** $^{1}H$ NMR ($CDCl_3$) δ (ppm): 5.19 (s, 1H, $CH_{quinone}$), 4.80 (bs, 2H, NH), 3.70-4.0 (m, 2H), 3.08-3.20 (m, 2H), 2.78-2.92 (m, 4H), 2.26-2.46 (m, 4H), 2.06-2.24 (m, 2H), 1.68-1.88 (m, 5H), 1.54-1.64 (m, 7H), 1.38-1.48 (m, 2H), 1.20-1.32 (m, 2H), 1.05 (d, 3H, $CH_3$, $^{3}J$=6.35 Hz), 1.00 (d, 3H, $CH_3$, $^{3}J$=6.35 Hz). $^{13}C$ NMR ($CDCl_3$) δ (ppm): 176.8 (C=O), 176.3 (C=O), 173.5, 151.0, 146.0, 91.4, 56.7, 52.2, 52.1, 51.8, 51.6, 51.2, 47.5, 43.7, 42.9, 33.6, 33.3, 26.1, 25.3, 25.0, 23.9, 23.8, 23.1, 18.0. $C_{24}H_{39}ClN_4O_2$ calcd. C, 63.91; H, 8.72; N, 12.42. Found C, 63.90; H, 8.70; N, 12.42.

**2-(4-*Tert*-butylbenzylamino)-3,5,6-trichlorocyclohexa-2,5-diene-1,4-dione (9):** A solution of tetrachloro-1,4-benzoquinone **7** (1.5 g, 6.1 mmol) and 4-*tert*-butylbenzylamine **8** (1 g, 6.1 mmol) in dichloromethane (20 mL) and ethanol (20 mL) in the presence of $NaHCO_3$ was stirred at 45 $^{o}$C temperature. The progress of the reaction was monitored by thin layer chromatography (TLC) using $CH_2Cl_2$ as eluent. Upon the completion of the reaction, the reaction mixture was diluted with water (30 mL) and extracted with chloroform (3×15 mL). The combined organic extract was dried over anhydrous $Na_2SO_4$,

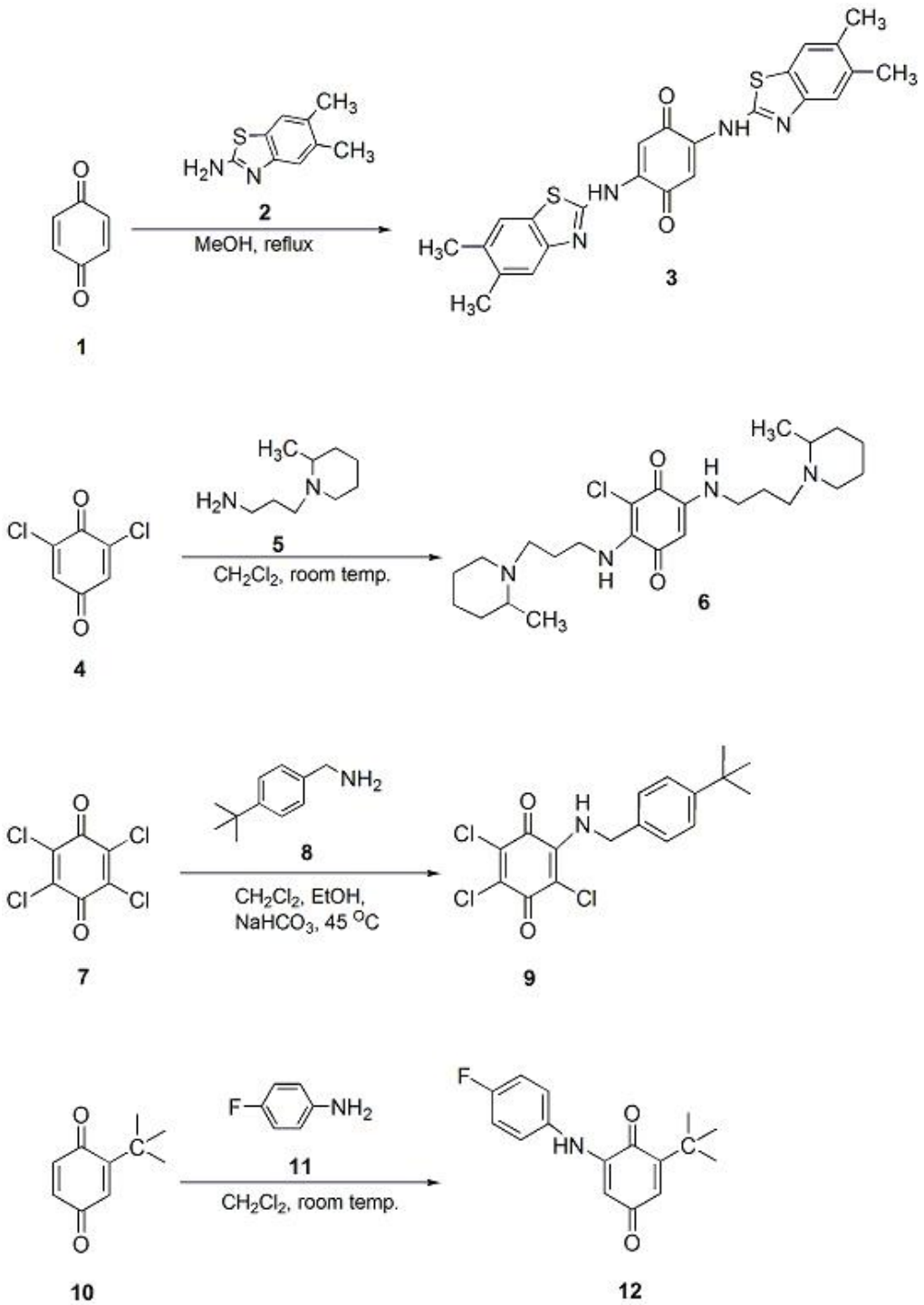
concentrated under vacuum and the residue was subjected to column chromatography using silica gel in hexane/chloroform (3:1) to give the pure product **9**: $R_f$ ($CH_2Cl_2$): 0.66. Dark purple, semi-solid. Yield: 10% (230 mg). IR (ATR): 3299, 2956, 2927, 2861, 1686, 1606, 1572, 1514, 1293, 1085. Mass spectrum (-ESI), m/z $[M-H]^-$= 370.8. $^1$H NMR ($CDCl_3$) δ (ppm): 7.33 (dd, 2H, $CH_{arom}$, $J^3$= 6.35 Hz, $J^4$= 1.95 Hz), 7.15 (d, 2H, $CH_{arom}$, $J^3$= 8.30 Hz), 5.90-6.0 (bs, 1H, NH), 4.86 (d, 2H, $CH_{2ethyl}$, $J^3$= 5.85 Hz), 1.25 (9H, 3x$CH_3$). $^{13}$ C NMR ($CDCl_3$) δ (ppm): 188.9, 182.7 (C=O), 164.9, 158.6, 145.6, 138.1, 130.9, 127.6, 126.13, 47.7, 31.3, 29.7. $C_{17}H_{16}Cl_3NO_2$ calcd. C, 54.79; H, 4.33; N, 3.76. Found C, 54.80; H, 4.31; N, 3.74.

**2-(4-Fluorophenylamino)-6-tert-butylcyclohexa-2,5-diene-1,4-dione (12)** A solution of 2-*tert*-butyl-1,4-benzoquinone **10** (1.5 g, 9.1 mmol) and 4-fluoroaniline **11** (1.2 g, 9.1 mmol) in dichloromethane (20 mL) was stirred at room temperature. The progress of the reaction was monitored by thin layer chromatography (TLC) using $CH_2Cl_2$ as eluent. Upon the completion of the reaction, the reaction mixture was diluted with water (30 mL) and extracted with chloroform (3×15 mL). The combined organic extract was dried over anhydrous $Na_2SO_4$, concentrated under vacuum and the residue was subjected to column chromatography using silica gel in dichloromethane to give the pure product **12**: Brown solid, M.p= 166-168 $^o$C. Yield: 8 % (200 mg). IR (ATR): 3270 (NH), 2959, 2919, 1666, 1623, 1572, 1496, 1404, 1353, 1210, 908. Mass spectrum (+EI), m/z $[M]^+$=273.1. $^1$H NMR ($CDCl_3$) δ (ppm): 7.08-7.14 (m, 3H, $CH_{arom}$ and NH), 7.03 (t, 2H, $^3$J=8.54 Hz, $CH_{arom}$), 6.44 (d, 1H, $CH_{quinone}$, $^4$J= 2.44 Hz), 5.88 (d, 1H, $CH_{quinone}$, $^4$J= 2.44 Hz), 1.23 (s, 9H, 3 x $CH_3$). $^{13}$ C NMR ($CDCl_3$) δ (ppm): 187.0, 183.3, 161.2, 159.2, 151.7, 144.7, 134.4, 134.4, 133.6, 124.6, 116.5, 99.7, 99.5, 35.0, 29.1, 29.0. $^{19}$F NMR ($CDCl_3$) δ (ppm): -115.6. $C_{16}H_{16}FNO_2$ calc. C, 70.31; H, 5.90; N, 5.12. Found C, 70.29; H, 5.87; N, 5.10.

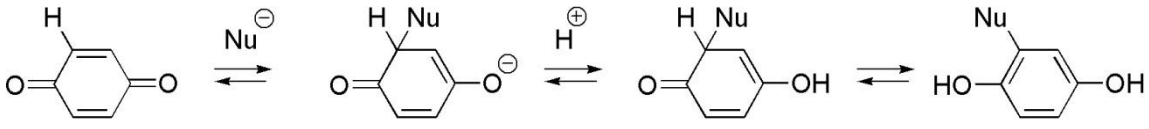
## RESULTS AND DISCUSSION

In this study, 1,4-benzoquinone compounds (**1**, **4**, **7** or **10**), respectively, were reacted with primary amines (**2**, **5**, **8** or **11**) to obtain mono-/bis-(NHsubstituted) 1,4,benzoquinones (**3**, **6**, **9**, **12**) as illustrated in Scheme 1. All compounds were purified by coloumn chromatography. The purity was checked by TLC and chemical structures were confirmed using FTIR, $^1$H-NMR, $^{13}$C-NMR spectroscopies and ESI-MS spectrometry.

Conjugated addition of nucleophiles to *p*-benzoquinone give initially mono-products (34). However, depending on the character of the nucleophile (nitrogen, sulfur, oxygen, *etc*.) may form further nucleophilic reactions to produce bis-, tris- or tetrakis-products. (34). For example, *p*-benzoquinone undergoes a nucleophilic attack by primary aliphatic amine to produce 2,5-diamino-1,4-benzoquinones (31). Furthermore, monoamino-1,4-benzoquinones were not obtained in this reaction. The result of exclusively 2,5-isomer formation can be explained that attack of two amines to 1,4-benzoquinone require the furthest possible distance due to electrostatic reasons (35). According to the explanation of Kutyrev, the reaction mechanism includes firstly by the addition of an amine to a carbon-carbon double bond (the formation of intermediate), after the intermediate isomerize to aminohydroquinone, which is oxidized to monoaminoquinone, and then the reaction of monoaminoquinone and second amine produce diaminoquinone via intermediate (31, 32). Also, the general scheme of the reaction of 1,4-quinones with nucleophilic compounds was given as Scheme 2 (31).




**Scheme 1.** Synthesis of NH-substituted-1,4-benzoquinones.




**Scheme 2.** The general scheme of the reaction of 1,4-quinones with nucleophilic compounds (31).

In this study, it was obtained the reaction between *p*-benzoquinone (**1**) and **2** to obtain bis-NH-substituted compound (**3**), in methanol at reflux temperature. The corresponding $^1$H NMR spectrum of compound **3**, the apperance of $CH_{arom}$ (δ 7.58-7.22 ppm), $CH_{quinone}$ (δ 5.83, 5.06 ppm) and NH- (δ 7.40 ppm) proton signals were a clear evidence for –NHR formation. The stretching vibration of the carbonyl (C=O) group of quinone was

observed at 1642 $cm^{-1}$, in the IR spectra, whereas the ESI mass spectrum of **3** exhibited the molecular ion peak at m/z 459.3, as expected.

The reaction between 2,6-dichloro-1,4-benzoquinone **4** and N-(3-aminopropyl)-2-pipecoline **5** was obtained at room temperature in dichloromethane to obtain 2,5-(bis-NH)-substituted-3-chloro-1,4-benzoquinone derivative **6**. In $^{1}H$ NMR spectra of **6**, the presence of benzoquinone proton was confirmed by one signal at δ 5.19 ppm (s). And, in $^{13}C$ NMR spectrum of **6**, two quinonic carbonyl moieties (C=O) appeared in δ 176.8 and 176.3 ppm, as expected. In the mass spectra (ESI-MS) of this compound (**6**), the protonated $[M+H]^+$ molecular ion peak gave m/z= 451.3 in the positive ion mode and molecular ion peak gave m/z $[M]^-$=449.5 in the negative ion mode, which were agreement with the molecular formula.

It is known that mono- and bis- NH-substituted-1,4-benzoquinones by the reaction between p-chloranil and primary amines (10, 36, 37). In order to prepare mono(NH-substituted)-trichloro-1,4-benzoquinone derivative (**9**), tetrachloro-1,4-benzoquinone (**7**) was treated with 4-tert-butylbenzylamine (**8**) in dichloromethane and ethanol in the presence of $NaHCO_3$ at a temperature of 50 °C. Compound **9** displayed signals due to $CH_{arom}$ groups at 7.33 ppm and 7.15 ppm with proper $^{3}J$ and $^{4}J$ coupling constants. In the mass spectra MS(ESI) of compound **9**, the deprotonated molecular ion peak m/z $[M-H]^-$= 370.8 gave the expected molecular weight.

The reaction between 2-tert-butyl-1,4-benzoquinone (**10**) and 4-fluoroaniline (**11**) in equimolar ratio, using dichloromethane as solvent at room temperature, yielded compound **12**. During structural elucidation of compound **12**, the assignment of the location of the -NHR group (C2 or C3) is determined by the splitting patern ($^{4}J$= 2.44 Hz). In the literature, there are similar situations, including different location of –NHR (38-40). Also, the mass spectrum obtained for **12** and showed a molecular ion peak m/z= 273.1 ($C_{16}H_{16}FNO_2$, 273.3 $g.mol^{-1}$). Also, in the corresponding $^{13}C$ NMR spectrum of **12**, the apperance of C=O and $C_{tert}$ carbon signals at δ= 187.0, 183.3 and 35.0 ppm, respectively, and in the corresponding $^{19}F$ NMR spectrum of **12**, the presence of of signal at δ= -115.6 ppm (belong to F-$C_6H_4$-) is a clear evidence for -NHR formation.

## CONCLUSION

In conclusion, in this study, the synthesis and characterization of mono- or bis- NH-substituted-1,4-benzoquinones (**3**, **6**, **9** and **12**) have been reported. Compounds were prepared by the reaction of *p*-benzoquinone (**1**), 2,6-dichloro-1,4-benzoquinone (**4**), tetrachloro-1,4-benzoquinone (**7**) or 2-tert-butyl-1,4-benzoquinone (**10**), respectively, with amines (2-amino-5,6-dimethylbenzothiazole (**2**), N-(3-aminopropyl)-2-pipecoline (**5**), 4-tert-butylbenzylamine (**8**) or 4-fluoroaniline (**11**) at room temperature to reflux. The new synthesized compounds might have biological activities because of their quinoid skeleton.

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