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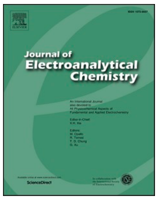

Investigation of electrochemical and spectroelectrochemical properties of some amino-substituted naphthoquinones (NQs)

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ABSTRACT

The class of quinone compounds are excellent representatives of biologically redox-active compounds. Electron transfers such as in quinone compounds play important roles in the bioactivation of redox-active drugs, in their metabolism/catabolism, and targeted release at precise destinations and frequently promote their ligand–target interactions. Owing to the enthralling synthetic importance and pharmacological applications of 1,4-naphthoquinone derivatives, our interest is turned into a detailed electro- and photoelectrochemistry study of these pharmacophoric structures. Firstly, amino(substituted)-1,4-naphthoquinone (NQ) derivatives (**2a-b**, **3**, **4a-b**, **5**, **6**, **7**, **8** and **9**) were synthesized according to Michael addition mechanism. The exact structures of compounds were elucidated by spectroscopic methods such as FT-IR, ^{1}H-/^{13}C NMR, MS and microanalysis. Secondly, the electrochemical behaviors of NQ derivatives are determined with voltammetric and *in situ* UV–Vis spectroelectrochemical measurements. All synthesized NQ derivatives illustrate two reductions and one oxidation processes. Voltammetric analyses of the couples of the molecules indicate electrochemical reversibility of the reductions and electrochemical irreversibility of the oxidation couples. Substituent environments of NQ structure considerably influence the chemical reversibility of the redox processes.

1. Introduction

Quinone-based compounds can exist in many structures, both naturally or synthetically obtained. Naphthoquinone (NQ) are among the important heterocycles due to their rich redox activities in various biological functionalities, such as, antimicrobials [1], antitumor agents [2], antibiotics, and cancer chemotherapy [3–5]. Quinones are electroactive organic molecules that are used by biological systems as electron shuttles, are used by humans as dyes, pharmaceuticals, reactants, and catalysts, and are being investigated for use in energy transduction and organic electronics, all of which have to do with their electrochemistry [1]. In most of these applications, anionic (radicalic $NQ^{\cdot-}$ anion and dianionic NQ^{2-}) or cationic (radicalic $NQ^{\cdot+}$ cation) forms of NQ's play important roles [2]. Thus, it is critical to control the electrochemical activity of the NQ derivatives with appropriate substituents. There are some recent studies on the prediction the relation between the redox activities and their biological functionalities [6–9]. In similar studies, it is well reported that the substituents on the NQ heterocycles play critical role on their activities in various applications [8,10–13]. In order to control the redox activity of NQ heterocycle, we have tried to synthesize different NQ derivatives carrying different substituents. For instance, we have reported electrochemical behaviors of NQ heterocycles substituted with various electron releasing and/or withdrawing moieties [12,14,25–27].

In this study, new NQ with piperazine and alkylamine substituents (**2a-b**, **3**, **4a-b**, **5** and **6**) were synthesized and the structures of these compounds were characterized by spectroscopic methods. Compounds **7**, **8** and **9** were previously synthesized by our team and their structures were elucidated [28]. In addition, in this study, the redox mechanisms of all compounds were analyzed by voltammetric and spectroelectrochemical measurements.

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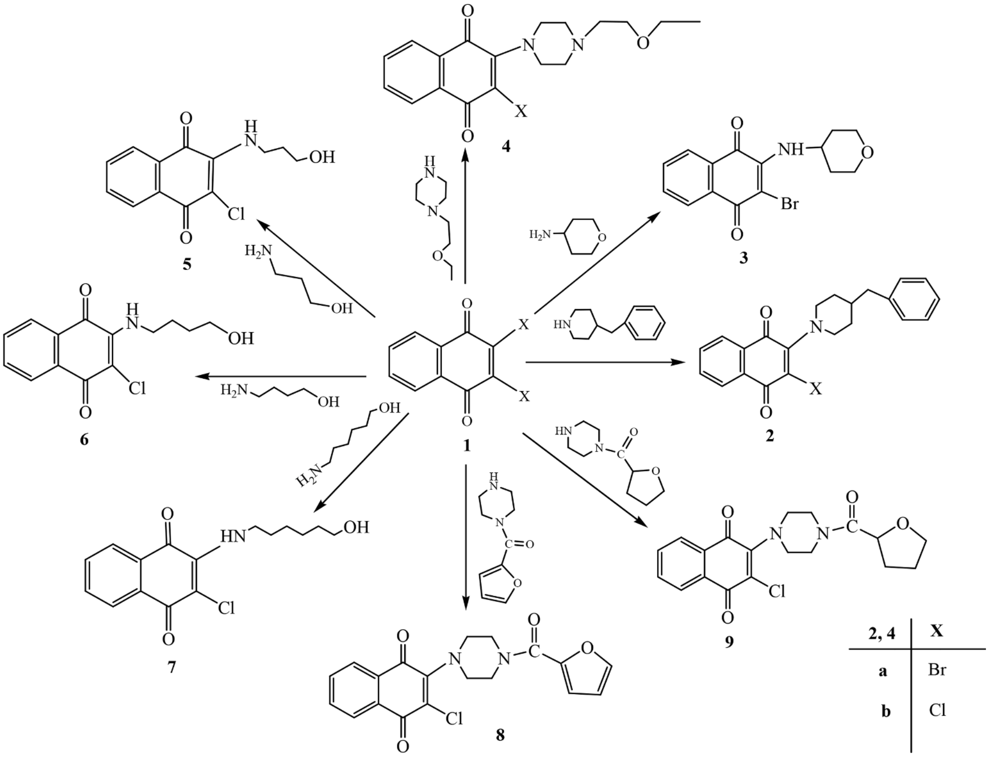

Scheme 1. The synthesis of *N*-substituted-1,4-naphthoquinones (2a-b, 3, 4a-b, 5–9).

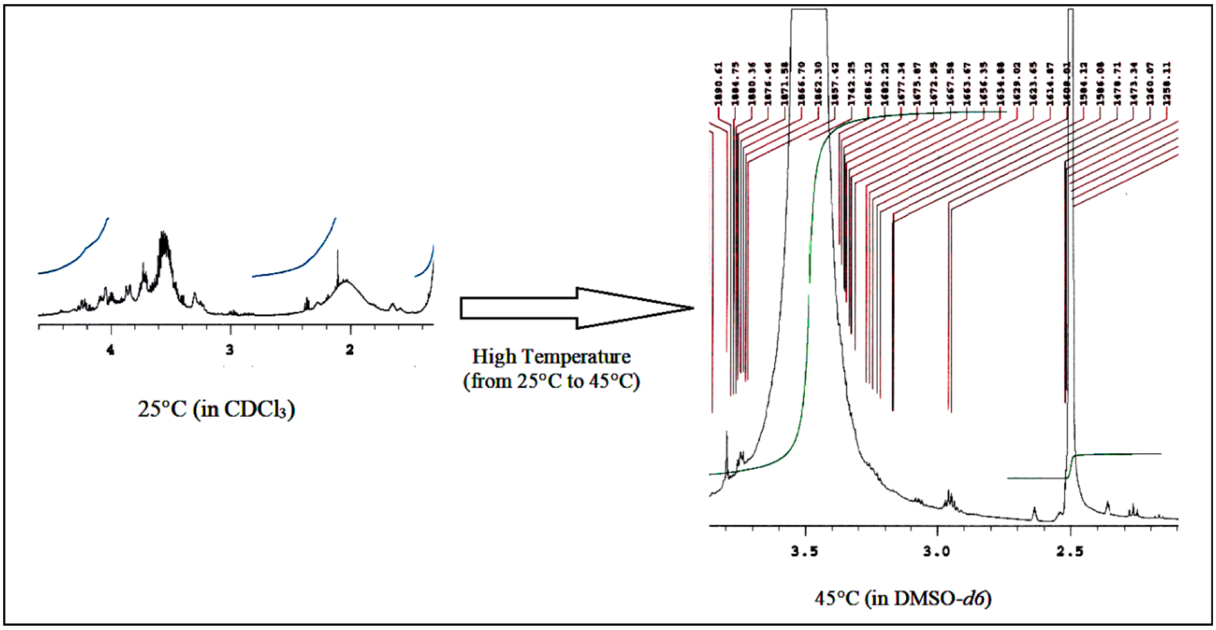

Fig. 1. The proton NMR spectra of piperazine methylene protons of 4b at 25 °C (in $CDCl_3$) and 45 °C (in DMSO-d_6).

2. Materials and methods

2.1. Apparatus

All the chemicals used in the present work were of reagent grade and procured from Sigma Aldrich and Alfa-Aesar. IR spectra were done on Shimadzu IR Prestige 21 model Diamond by ATR method. NMR spectra were performed on a Varian Unity Inova 125 MHz and 500 MHz instruments using solvents $CDCl_3$. Tetramethylsilane (TMS) was used as an internal standard. Chemical shift and coupling constant are provided in Hertz (Hz) and parts per million (ppm), respectively. QTRAP-4000 (hybrid triple quadrupole linear ion trap, ABSciex) using electron spray ionization method was used for recording the mass spectra and provided in *m/z*. Melting points were recorded by using Büchi B-540 apparatus. Elemental analyses were performed on a Thermo Finnigan Flash EA 1112 elemental analyzer.

Gamry Reference 600 Galvolnostat/Potansiostat was used for all voltametric measurements. *In situ* spectroelectrochemical measurements were carried out with a OceanOptic QE65000 diode array spectrophotometer.

Table 1
Voltammetric data of NQ derivatives.

Molecules	Oxidation couple			NQ/NQ$^{\cdot-}$ reduction couple			NQ$^{\cdot-}$/NQ^{2-} reduction couple		
	$^{a}E_{1/2}$	$^{b}\Delta E_p$	I_{pa}/I_{pc}	$E_{1/2}$	$^{b}\Delta E_p$	I_{pa}/I_{pc}	$^{a}E_{1/2}$	$^{b}\Delta E_p$	I_{pa}/I_{pc}
2a	1.34	163	0.36	−0.49	63	0.96	−0.94	65	0.74
2b	1.31	174	0.28	−0.50	65	0.94	−0.96	70	0.71
3	1.28	133	0.65	−0.57	62	0.97	−1.03	68	1.72
4a	1.33	128	0.56	−0.52	80	0.93	−1.04	93	1.22
4b	1.30	143	0.44	−0.53	76	0.90	−1.07	88	1.25
5	1.29	167	0.23	−0.62	200	0.96	−1.10	108	0.93
6	1.32	145	0.24	−0.61	100	0.95	−1.09	123	1.54
7	1.32	120	0.83	−0.63	63	0.99	−1.15	64	1.02
8	1.34	151	0.44	−0.50	66	0.93	−0.98	75	081
9	1.31	132	0.52	−049	67	0.90	−0.96	87	0.85

(^{a}) = $E_{1/2}$ values were derived from the SWVs. ^{b}: $\Delta E_p = |E_{pa} - E_{pc}|$. All potentials were given vs. Ag/AgCl (V) observed in DMSO/TBAP electrolyte.

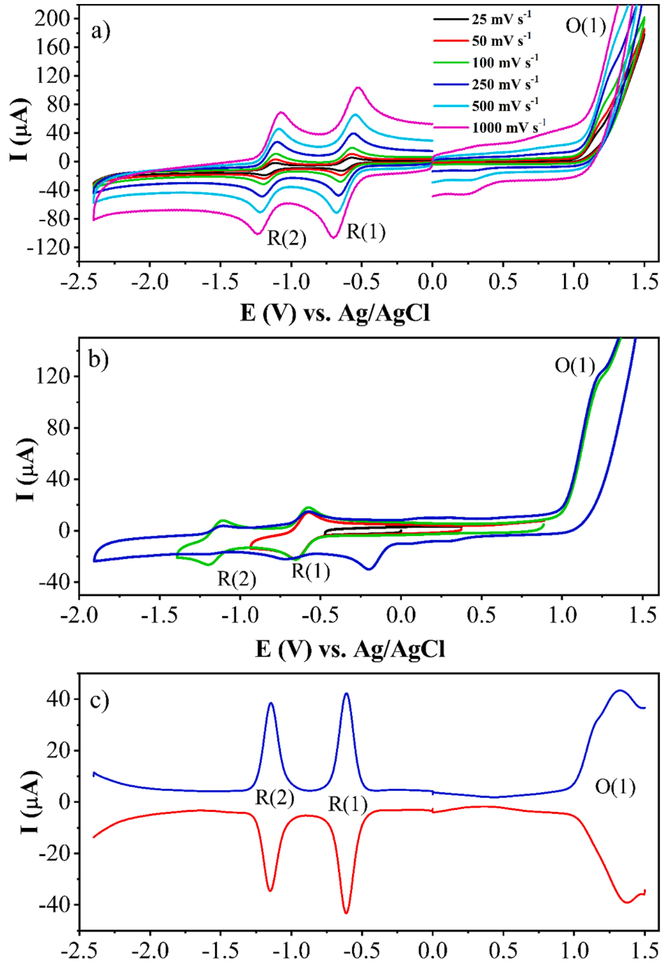

Fig. 2. Voltammetric responses of compound 7 on GCE in DMSO/TBAP. a) CVs at various scan rates, b) CVs recorded with different vertex potentials at 0.100 Vs^{-1} scan rate, and c) SWVs.

2.2. *Electrochemical and in situ spectroelectrochemical measurements*

All electrochemical measurements were carried out by following the procedure conducted in our previous paper [12,14]. Glassy carbon (GCE) working, Pt wire counter, and Ag/AgCl reference electrodes were used in a three electrode cell configurations. *In situ* spectroelectrochemical measurements were carried out by utilizing a Pt tulle working electrode in the three-electrode configuration of thin-layer quartz spectroelectrochemical cell. Voltammetric and *In situ* spectroelectrochemical measurements were carried out in dimethylsulfoxide (DMSO) containing 0.10 mol dm^{-3} tetrabuthylammonium perchlorate (TBAP).

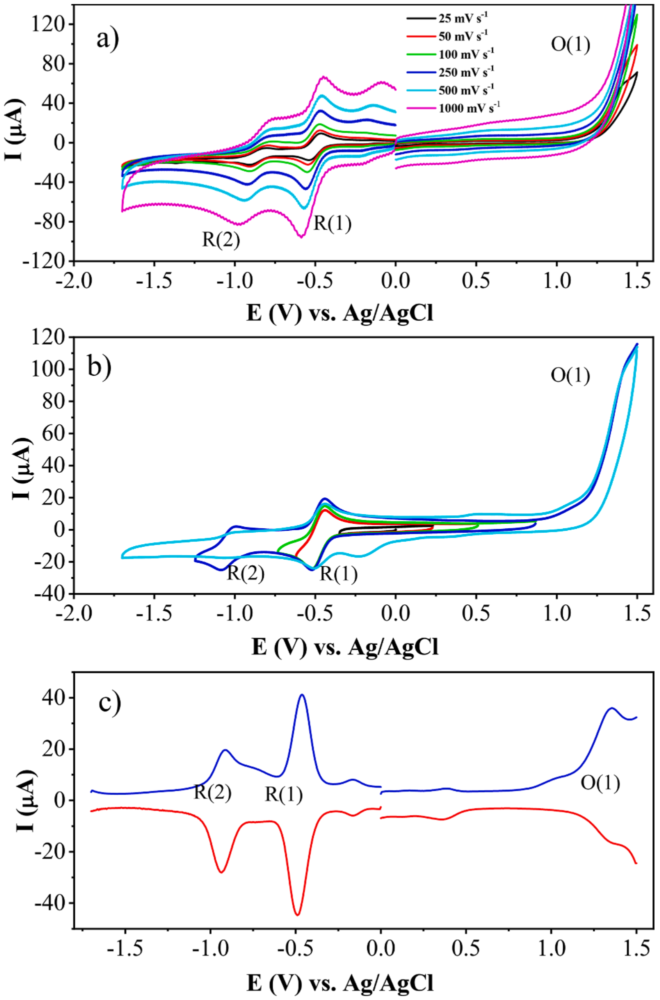

Fig. 3. Voltammetric responses of compound 2a on GCE in DMSO/TBAP. a) CVs at various scan rates, b) CVs recorded with different vertex potentials at 0.100 Vs^{-1} scan rate, and c) SWVs.

2.3. *Preparation of N-substituted-bromo-1,4-naphthoquinones (Procedure 1)*

In a 250 mL round bottom flask, one molar equivalents of 2,3-dibromo-1,4-naphthoquinone (**1a**) and one molar equivalents of amines were stirred in chloroform (50 mL) for 8 h. The progress of the

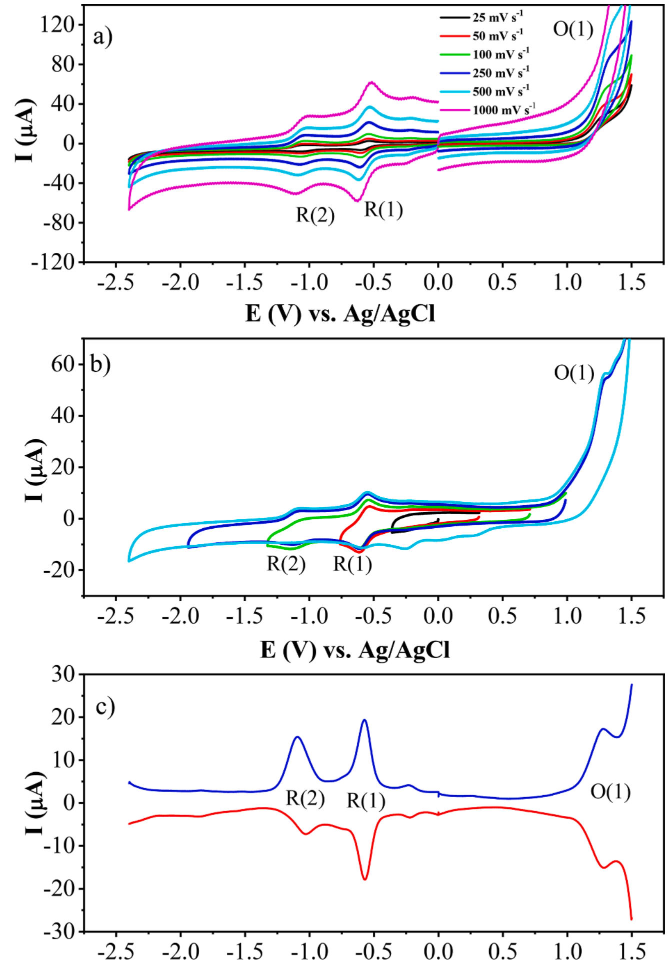

Fig. 4. Voltammetric responses of compound 3 on GCE in DMSO/TBAP. a) CVs at various scan rates, b) CVs recorded with different vertex potentials at 0.100 Vs^{-1} scan rate, and c) SWVs.

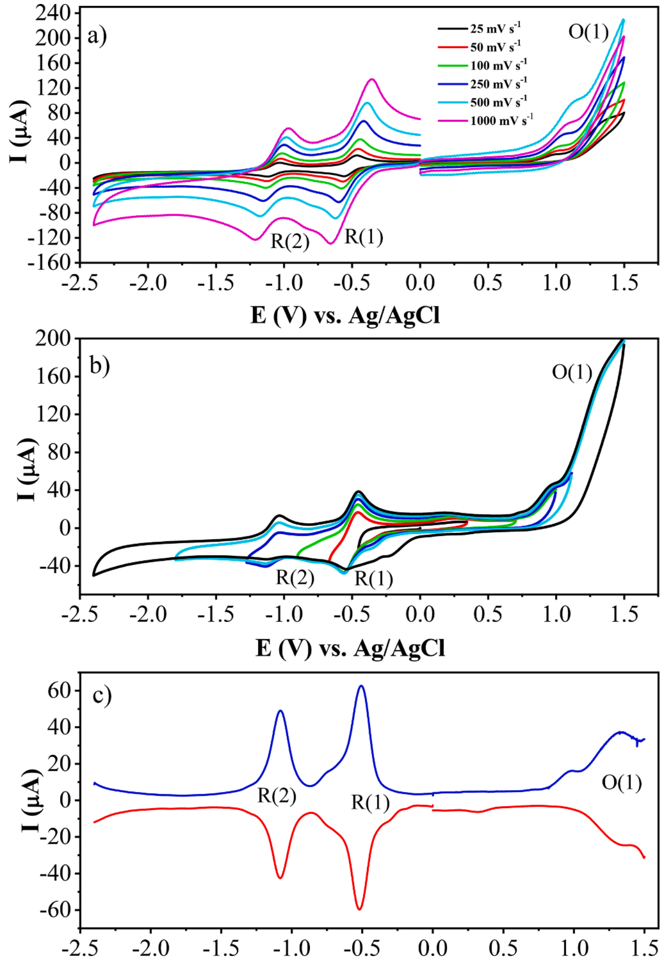

Fig. 5. Voltammetric responses of compound 4a on GCE in DMSO/TBAP. a) CVs at various scan rates, b) CVs recorded with different vertex potentials at 0.100 Vs^{-1} scan rate, and c) SWVs.

reaction was monitored by TLC. Chloroform (4 × 30 mL) was added to the reaction mixture. The organic layer was washed with water (100 mL), and dried with anhydrous sodium sulphate. After the solvent was evaporated the residue was purified by column chromatography with solvents. (**2a**, **3** and **4a**).

2.4. Preparation of N-substituted-chloro-1,4-naphthoquinones (Procedure 2)

One molar equivalents of 2,3-dichloro-1,4-naphthoquinone (**1b**) and one molar equivalents of amines were stirred in chloroform (50 mL) for 8 h in a 250 mL round bottom flask. The progress of the reaction was monitored by TLC. Chloroform (4 × 30 mL) was added to the reaction mixture. The organic layer was washed with water (100 mL), and dried with anhydrous sodium sulphate. After the solvent was evaporated the residue was purified by column chromatography with solvents. (**2b**, **4b**, **5**, **6**, **7**, **8** and **9**).

2.4.1. 2-(4-Benzylpiperidin-1-yl)-3-bromonaphthalene-1,4-dione (2a)

Compound **2a** was synthesized by the reaction of **1a** (1.0 g, 3.17 mmol) with 1-(4-benzyl)piperidinyl (0.55 g, 3.17 mmol) according to procedure 1.

Yield: 0.50 g (92%); Dark red solid; mp: 84.6–84.9 °C; $R_f = 0.69$ in hexane/ethylacetate (3:1) as a developing solvent; IR (ATR, cm^{-1}): 2980, 2898, 1668, 1638, 1588, 1541; ^1H NMR (500 MHz, $CDCl_3$, ppm): $\delta = 1.55–1.68$ (m, 1H, CH), 1.70–2.03 (m, 4H, $2CH_{2piperidinyl}$), 2.80–2.83 (m, 2H, $CH_{2\text{-}Ph}$), 3.60–4.48 (m, 4H, $2CH_{2piperidinyl}$), 7.00–7.50 (m, 5H, $5CH_{benzyl}$), 7.50–7.78 (m, 3H, $3CH_{naphthyl}$), 8.00–8.20 (m, 1H, $CH_{naphthyl}$); ^{13}C NMR (125 MHz, $CDCl_3$, ppm): $\delta = 31.90$ $CH(\underline{CH_2})_2$, 37.8 ($CH_{piperidnyl}$), 49.6 ($\underline{CH_2}$-Ph), 52.6 $N(\underline{C}H_2)_2$, 126.0, 126.1, 126.6, 126.8, 126.9, 128.3, 128.4, 128.5, 129.0 (C_{benzyl}, $C_{naphthyl}$), 153.3, 154.1 (=C-Br), 181.8, 183.6 (C=O); MS [+ESI]: *m/z* (%): (100) 410.2 $[M]^+$; Micro An.: $C_{22}H_{20}BrNO_2$ (M, 410.30 g/mol): Calcd. C, 64.40; H, 4.91; N, 3.41; Found C, 64.65; H, 5.03; N, 3.42%.

2.4.2. 2-(4-Benzylpiperidin-1-yl)-3-chloronaphthalene-1,4-dione (2b)

Compound **2b** was synthesized by the reaction of **1b** (1.0 g, 4.40 mmol) with 1-(4-benzyl)piperidinyl (0.77 g, 4.39 mmol) according to procedure 2.

Yield: 0.87 g (54%); Brown solid; mp: 112.0–112.9 °C; $R_f = 0.45$ in Petrolum ether/$CHCl_3$ (2:1) as a developing solvent; IR (ATR, cm^{-1}): 3018, 2853, 1670, 1631, 1590, 1548; ^1H NMR (500 MHz, $CDCl_3$, ppm): $\delta = 1.40–1.90$ (q, 5H, CH, $2CH_{2piperidinyl}$), 2.47–2.50 (d, 2H, $CH_{2\text{-}Ph}$), 3.10–3.20 (t, 2H, N-$CH_{2piperidinyl}$), 3.70–3.80 (d, 2H, N-$CH_{2piperidinyl}$), 7.04–7.24 (m, 5H, $5CH_{phenyl}$), 7.54–7.62 (m, 2H, $2CH_{naphthyl}$), 7.88–7.92 (d,1H, $CH_{naphthyl}$), 8.00–8.04 (d, 1H, $CH_{naphthyl}$); ^{13}C NMR (125 MHz, $CDCl_3$, ppm): $\delta = 32.3$ $CH(\underline{CH_2})_2$, 37.0 ($CH_{piperidinyl}$), 42.3 ($\underline{CH_2}$-Ph), 51.4 $N(\underline{C}H_2)_2$, 126.0, 127.7, 128.2, 130.7, 132.1, 133.2, 139.3, 149.9 ($C_{arom.}$, $C_{naphthyl}$), 177.3, 181.3 (C=O); MS [+ESI]: *m/z* (%): (100) 366.4 $[M]^+$; Micro An.: $C_{22}H_{20}ClNO_2$ (M, 365.85 g/mol): Calcd. C, 72.22; H, 5.51; N, 3.83; Found. C, 72.29; H, 5.51; N, 3.87%.

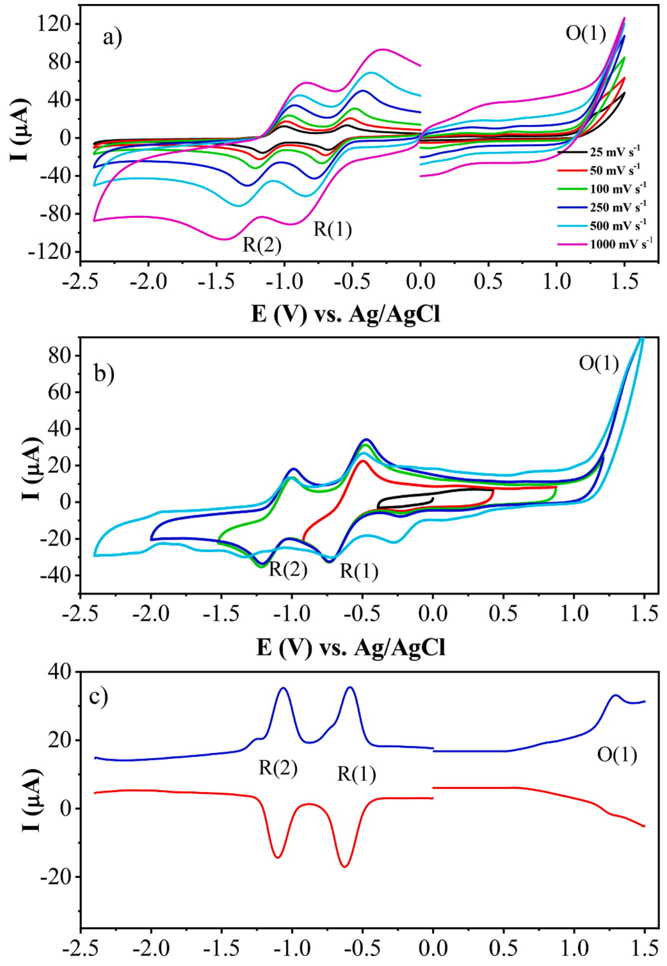

Fig. 6. Voltammetric responses of compound 5 on GCE in DMSO/TBAP. a) CVs at various scan rates, b) CVs recorded with different vertex potentials at 0.100 Vs^{-1} scan rate, and c) SWVs.

$$NQ \overset{O\,(1)}{\Longleftrightarrow} NQ^{\cdot +} + e^{-}$$

$$NQ + e^{-} \overset{R\,(1)}{\Longleftrightarrow} NQ^{\cdot -}$$

$$NQ^{\cdot -} + e^{-} \overset{R\,(2)}{\Longleftrightarrow} NQ^{2-}$$

Scheme 2. The proposed redox mechanism for the NQ derivatives.

2.4.3. 2-Bromo-3-(tetrahydro-2H-pyran-4-ylamino)naphthalene-1,4-dione (3)

Compound **3** was synthesized by the reaction of **1a** (1.0 g, 3.17 mmol) with 4-aminotetrahydropyran (0.32 g, 3.17 mmol) according to procedure 1.

Yield: 0.52 g (50%); Red solid; mp: 130.0–130.5 °C; $R_f = 0.64$ in Ethylacetate/Petroleum ether (1:4) as a developing solvent; IR (ATR, cm^{-1}): 3677, 3294, 2970, 2922, 2844, 2753, 1679, 1629 1596, 1557, 1509; ^{1}H NMR (500 MHz, $CDCl_3$, ppm): $\delta = 1.50$–1.52 (dd, $J = 12.6$, 6.5 Hz, 2H, CH_{2pyran}), 2.04–2.16 (m, 2H, CH_{2pyran}), 3.38–3.50 (m, 2H, CH_{2pyran}), 3.90–4.03 (dd, $J = 7.5$, 4.4 Hz, 2H, CH_{2pyran}), 4.85–4.70 (m, 1H, CH_{pyran}), 5.98 (sbr, 1H, NH), 7.56–7.62 (td, 1H, $C_{naphthyl}$), 7.64–7.70 (td, 1H, $C_{naphthyl.}$), 7.98–8.02 (dd, 1H, $C_{naphthyl.}$), 8.08–8.12 (d, $J = 6.7$ Hz, 1H, $C_{naphthyl.}$); ^{13}C NMR (125 MHz, $CDCl_3$, ppm): $\delta = 34.7$ ($\underline{CH}_{2pyran}$-CH), 49.9 (CH_{pyran}), 66.3 (CH_{2pyran}-O), 126.8, 126.9, 127.1, 127.2, 129.7, 132.3, 132.5, 132.7, 134.9, 145.5 ($CH_{arom.}$, $C_{arom.}$),176.5, 180.1 (C═O); MS [+ESI]: m/z (%) 333.9 (100) $[M-H]^{+}$; Micro An.: $C_{15}H_{14}BrNO_3$ (M, 336.18 g/mol): Calcd. C, 53.59; H, 4.20; N, 4.17; Found C, 53.60; H, 4.21; N, 4.19%.

2.4.4. 2-Bromo-3-(4-(2-etoxyethyl)piperazin-1-yl)naphthalene-1,4-dione (4a)

Compound **4a** was synthesized by the reaction of **1a** (0.75 g, 2.40 mmol) with 1-(2-etoxyethyl)piperazine (0.37 g, 2.40 mmol) according to procedure 1.

Yield: 0.48 g (61%); Red liquid; $R_f = 0.38$ in $CHCl_3$/ethylacetate (1:1) as a developing solvent; IR (ATR, cm^{-1}): 3067, 2969, 2899, 1670, 1643, 1590, 1544; ^{1}H NMR (500 MHz, $CDCl_3$, ppm): $\delta = 1.21$–1.24 (t, 3H, CH_3), 3.15 (sbr, 4H, $2CH_{2piperazine}$), 3.25–3.35 (s, 2H, N-CH_2), 3.53–3.57 (q, 4H, $2CH_{2piperazine}$), 3.92–3.96 (q, 4H, $\underline{CH_2}$-O-$\underline{CH_2}$), 7.65–7.78 (m, 2H, $2CH_{naphthyl}$), 8.02–8.06 (d, 1H, $CH_{naphthyl}$), 8.12–8.15 (d, 1H, $CH_{naphthyl}$); ^{13}C NMR (125 MHz, $CDCl_3$, ppm): $\delta = 15.1$ (CH_3), 48.9, 53.5 ($C_{piperazine}$), 57.6 (N-$\underline{CH_2}$-CH_2-O), 65.6 (O-$\underline{CH_2}$-CH_3), 66.8 (O-CH_2.), 119.9, 127.2, 131.1, 133.5, 133.8, 134.4 ($C_{naphthyl}$), 151.8 (=C-Br), 178.0, 181.4 (C═O); MS [+ESI]: m/z (%): (100) 395.2 $[M + 2H]^{+}$; Micro An. $C_{18}H_{21}BrN_2O_3$ (M, 393.27 g/mol): Calcd. C, 54.97; H, 5.38; N, 7.12; Found C, 54.99; H, 5.36; N, 7.15%.

2.4.5. 2-Chloro-3-(4-(2-etoxyethyl)piperazin-1-yl)naphthalene-1,4-dione (4b)

Compound **4b** was synthesized by the reaction of **1b** (0.72 g, 3.17 mmol) with 1-(2-etoxyethyl)piperazine (0.5 g, 3.16 mmol) according to procedure 2.

Yield: 0.79 g, (72%); Brown oil; $R_f = 0.66$ in petrolumether/ethylacetate (3:1) as a developing solvent; IR (ATR, cm^{-1}): 2973, 2870, 1667, 1608, 1591, 1570; ^{1}H NMR (500 MHz, $CDCl_3$, ppm): $\delta = 1.0$–1.2 (t, 3H, $J = 7.32$ Hz, CH_3), 2.20 (sbr, 4H, $2CH_{2piperazine}$), 3.25–3.35 (s, 2H, N-CH_2), 3.40–3.57 (t, $J = 6.84$ Hz, 4H, $2CH_{2piperazine}$), 3.92–3.96 (q, 4H, $\underline{CH_2}$-O-$\underline{CH_2}$), 7.65–7.78 (m, 2H, $2CH_{naphthyl}$), 8.02–8.06 (d, 1H, $CH_{naphthyl}$), 8.12–8.15 (d, 1H, $CH_{naphthyl}$); ^{13}C NMR (125 MHz, $CDCl_3$, ppm): $\delta = 15.2$ (CH_3), 48.7, 53.2 ($C_{piperazine}$), 57.5 (N-$\underline{CH_2}$-CH_2-O), 65.8 (O-$\underline{CH_2}$-CH_3), 66.4 (O-CH_2.), 119.7, 127.4, 131.0, 133.7, 133.9, 134.5 ($C_{naphthyl}$), 151.4 (=C-Cl), 178.2 181.6 (C═O); MS [+ESI]: m/z (%): (100) 349.2 $[M]^{+}$; Micro An. $C_{18}H_{21}ClN_2O_3$ (M, 348.82 g/mol): Calcd. C, 61.98; H, 6.07; N, 8.03; Found C, 61.95; H, 6.09; N, 8.02%.

2.4.6. 2-Chloro-3-(3-hidroxylpropyl)naphthalene-1,4-dione (5)

Compound **5** was synthesized by the reaction of **1b** (1.0 g, 4.40 mmol) with 3-amino-1-propanol (0.33 g, 4.40 mmol) according to procedure 2.

Yield: 0.67 g, (57%); Red oil; $R_f = 0.54$ in Petrolum ether/Ethylacetate (2:1) as a developing solvent; IR (ATR, cm^{-1}): 3666, 3464, 2978, 2907, 1673, 1643, 1595, 1555, 1499, 1447; ^{1}H NMR (500 MHz, $CDCl_3$, ppm): $\delta = 1.45$–1.55 (s,1H, OH), 1.81–1.85 (q, 2H, $\underline{CH_2}$-CH_2-OH), 3.72–3.74 (t, 2H, NH-$\underline{CH_2}$), 3.89–3.93 (q, 2H, $\underline{CH_2}$-OH), 6.30–6.38 (sbr, 1H, NH), 7.46–7.52 (t, 1H, $CH_{naphthyl}$), 7.56–7.63 (t, 1H, $CH_{naphthyl}$), 7.88–7.92 (t, 1H, $CH_{naphthyl}$), 8.00–8.04 (d, 1H, $CH_{naphthyl}$); ^{13}C NMR (125 MHz, $CDCl_3$, ppm): $\delta = 31.6$ (CH_2-$\underline{CH_2}$-CH_2-OH), 41.7 (NH-CH_2), 59.6 (CH_2-OH), 124.4, 128.5, 128.6, 131.1, 131.5, 133.7, 148.5, 153.2 ($C_{napthtyl}$), 177.7, 178.4 (C═O); MS [+ESI]: m/z (%): (100) 266.1 $[M]^{+}$; Micro An. $C_{13}H_{12}ClNO_3$ (M, 265.69 g/mol): Calcd. C, 58.77; H, 4.55; N, 5.27; Found C, 58.79; H, 4.51; N, 5.24%.

2.4.7. 2-Chloro-3-(4-hidroxylbuthyl)naphthalene-1,4-dione (6)

Compound **6** was synthesized by the reaction of **1b** (1.0 g, 4.40 mmol) with 4-amino-1-butanol (0.39 g, 4.40 mmol) according to procedure 2.

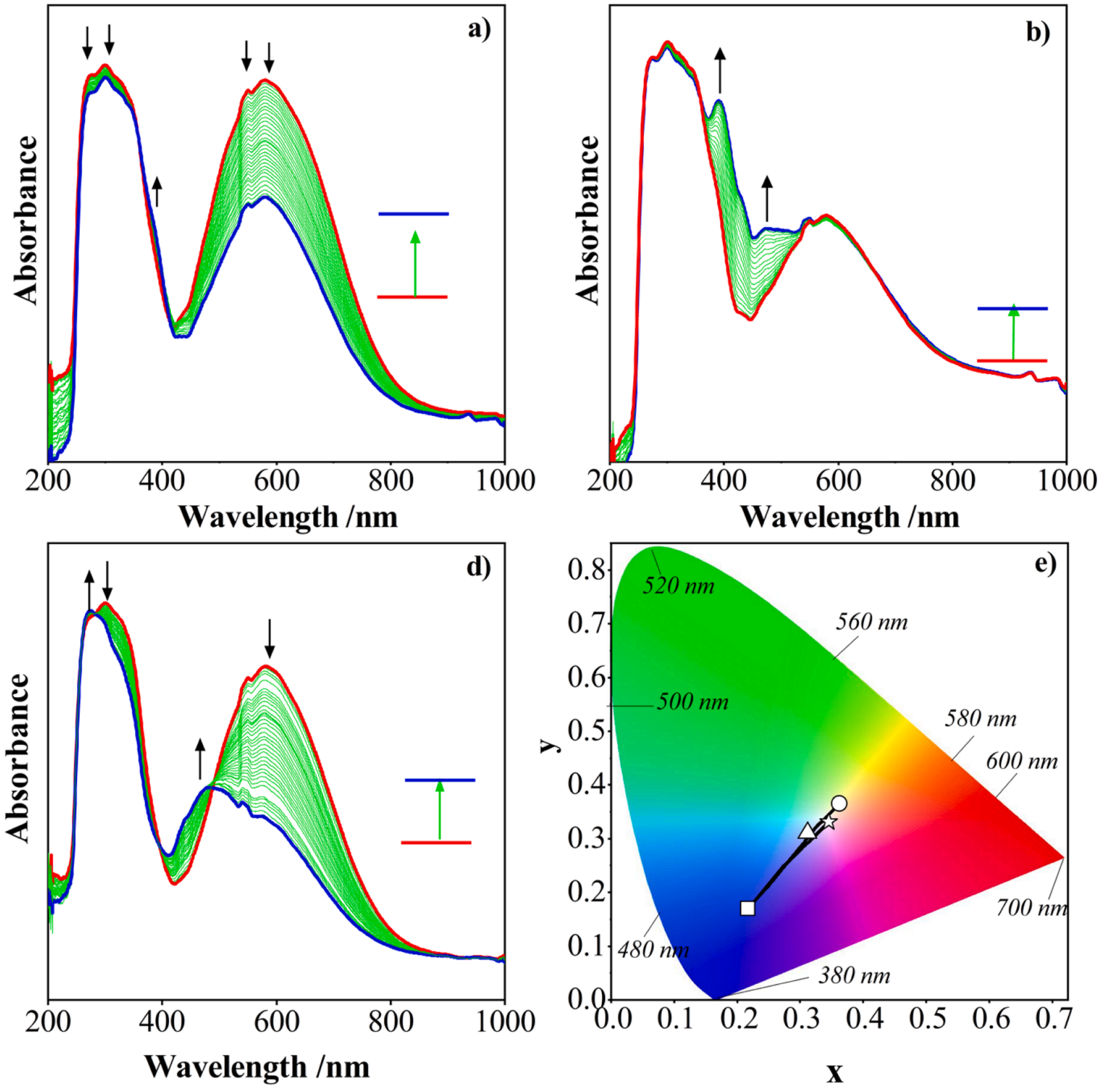

Fig. 7. UV–Vis spectral changes of compound 7 recorded during *in-situ* spectroelectrochemical measurements at applied potentials of a) $E_{app} = -0.75$ V, b) $E_{app} = -1.30$ V, c) $E_{app} = 1.40$ V in DMSO/TBAP electrolyte system (changing of the spectrum during the redox reactions were represented with the arrow directions), and d) color of the species (Neutral 7:; radicalic monoanionic 7:; Dianionic 7:; monocationic 7:).

Yield: 0.46 g, (38%); Red solid; mp: 110.0–110.6 °C; $R_f = 0.41$ in Petrolum ether/Ethylacetate (2:1) as a developing solvent; IR (ATR, cm^{-1}): 3663, 3321, 2984, 2940, 2903, 2886, 1668, 1598, 1568, 1516, 1457; ^1H NMR (500 MHz, $CDCl_3$, ppm): $\delta = 1.45$–1.55 (s,1H, OH), 1.60–1.70 (m, 2H, $\underline{CH_2}$-CH_2-OH), 1.70–1.80 (m, 2H, NH-CH_2-$\underline{CH_2}$), 3.65–3.70 (t, 2H, NH-$\underline{CH_2}$), 3.80–3.90 (q, 2H, $\underline{CH_2}$-OH), 6.10–6.24 (sbr, 1H, NH), 7.54–7.60 (t, 1H, $CH_{naphthyl}$), 7.64–7.70 (t, 1H, $CH_{naphthyl}$), 7.96–8.02 (d, 1H, $CH_{naphthyl}$), 8.08–8.14 (d, 1H, $CH_{naphthyl}$); ^{13}C NMR (125 MHz, $CDCl_3$, ppm): $\delta = 28.6$ (NH-CH_2-$\underline{CH_2}$), 30.9 ($\underline{CH_2}$-CH_2-OH), 43.6 (NH-CH_2), 61.3 (CH_2-OH), 111.2 (C-Cl), 125.8, 127.8, 128.7, 131.4, 131.7, 133.9, 147.4 ($C_{napthtyl}$), 179.5, 181.4 (C=O); MS [+ESI]: *m/z* (%): (1 0 0) 280.1 $[M]^+$; Micro An. $C_{14}H_{14}ClNO_3$ (M, 279.72 g/mol): Calcd. C, 60.11; H, 5.04; N, 5.01; Found C, 60.15; H, 5.06; N, 5.05%.

3. Results and discussion

3.1. Chemistry

This study focused on the synthesis of a series of amino (substituted) derivatives of 1,4-naphthoquinone by substitution of a chlorine or bromine atom in the quinone pharmacophore.

The preparation of amino(substituted)-1,4-naphthoquinones was illustrated in Scheme 1. New *N*-substituted-1,4-naphtoquinone compounds **2a-b, 3**, **4a-b, 5** and **6** were obtained from the reactions of starting compounds **1a** and **1b** with amines in chloroform solution according to general procedures 1 and 2. Compounds **7**, **8** and **9** were previously synthesized by our co-worker [28]. All synthesized compounds were characterized by using FT-IR, ^1H NMR, ^{13}C NMR, MS and micro analysis which were provided in the Supporting Information.

Compounds **2a-b** and **3** were naphthoquinone compounds with a piperidinyl and tetrahydropyran ring. In the ^1H NMR spectra of compounds **2a-b**, methylene protons of benzyl group (–$\underline{CH_2}$–Ph) were observed as a multiplet at 2.80–2.83 ppm for compound **2a**, as a doublet at 2.47–2.50 ppm for compound **2b**. In the ^1H NMR spectrum of compound **3**, amine (–NH) proton was observed as a broad single peak at 5.98 ppm. In addition, in the ^{13}C NMR spectrum of compound **3**, the carbons of the tetrahydrapyran ring at 34.7, 49.9 and 66.3 ppm were also observed.

In this study, the methylene protons of the piperazine ring of the 2-chloro-3-(4-(2-ethoxyethyl)piperazin-1-yl)naphthalene-1,4-dione **4b** in

^{1}H NMR taken at 25 °C (in $CDCl_3$) and at 45 °C (in DMSO-d_6) were shown in the Fig. 1. We saw that the peaks of piperazine methylene groups were broad signals at $\delta = 2.20$ ppm and triplet at $\delta = 3.40–3.57$ ppm at room temperature. In the ^{1}H NMR of **4b**, when the temperature increased the signals were getting sharpened and changed to singlet peaks at $\delta = 2.20$ and triplet at $\delta = 3.40–3.57$ ppm at 45 °C. The molecular ion peaks of compound **4b** were identified at m/z 368.7, 398.1 and 349.2 $[M + H]^+$ in the positive ion mode for ESI technique, respectively.

Compounds **5** and **6** were new compounds obtained from the reaction of 2,3-dichloro-1,4-naphthoquinone with aminoalcohol compounds. The characteristic bands for the hydroxyl group in the IR spectra of these compounds were 3666, 3464 cm^{-1} for compound **5** and 3663, 3321 cm^{-1} for compound **6**. The broad single signal seen in the ^{1}H NMR spectrum at 6.30–6.38 ppm for compound **5** and 6.10–6.24 ppm for compound **6** was a peak specific to the NH group. In addition, the peaks seen in the ^{13}C NMR spectrum at 31.6, 41.7, 59.6 ppm for compound **5** and at 28.6, 30.9, 43.6 and 61.3 ppm for compound **6** were the peaks of aliphatic methylene carbons. Although compounds **7, 8** and **9** were previously synthesized [28], the electrochemical properties of these compounds were investigated for the first time in this study.

3.2. *Electrochemical and in-situ spectroelectrochemical measurements*

Cyclic voltammograms (CVs) and square wave voltammograms (SWVs) conducted in DMSO/TBAP electrolyte on GCE illustrate similar responses. As tabulated in Table 1, all NQs undergo two reduction and one oxidation couple. R(1) and R(2) couples of NQs are assigned to the one electron reduction of neutral NQ to $NQ^{\cdot-}$ radical anion and the reduction of $NQ^{\cdot-}$ radical anion to NQ^{2-} dianion. Similarly, the oxidation couples (O(1)) of all NQs, are assigned to NQ to $NQ^{\cdot+}$ oxidation. Altering the substituents on NQ heterocycle only influence the peak potentials and their reversibility. Reversibility of the processes was evaluated by comparing with the redox responses of the universal reversible ferrocene/ferrocenium (Fc^+/Fc) couples recorded in the same media. Fc^+/Fc couple was recorded at 0.45 V at 100 mVs^{-1} scan rate. While ΔE_p values of this couple deviated from 60 to 89 mV within the scan rates from 25 to 500 mVs^{-1}, I_{pa}/I_{pc} ratio of the couple was observed as 0.98 at all scan rates. It is clearly evaluated by comparing the Fc^+/Fc couple responses that for all NQs (except **5** and **6**), the first reduction couple (R(1)) has electrochemically and chemically reversible characters with respect to ΔE_p and I_{pa}/I_{pc} responses of the redox processes. Altering theΔE_p between 61 and 97 mV by increasing the scan rate from 25 to 500 mVs^{-1} and closeness of the to unity at these scan rates indicate the electrochemical and chemical reversibility of the R(1) of the corresponding compounds. Similarly, comparisons of the peak behaviors of the R(2) and O(1) couples of compounds with that of Fc^+/Fc couple indicate electrochemical reversibility and electrochemical quasi-reversibility of these processes respectively. Deviations of the I_{pa}/I_{pc} responses of R(2) from unity with increasing scan rates are resulted from the following chemical reactions which make this process electrochemically irreversible. Altering the substituents on the compounds generally influence the I_{pa}/I_{pc} responses of R(2) and therefore the rate of the accompanying chemical reactions.

Among the NQs, the compound **7** illustrate more reversible reduction couples as shown in Fig. 2. It illustrates electrochemically and chemically reversible R(1) and R(2) couples at −0.63 and −1.15 V and a quasi-reversible oxidation couple at 1. 32 V vs. Ag/AgCl reference electrodes. The ΔE_p values of them are 63 and 64 mV and I_{pa}/I_{pc} values are 0.99 and 1.02 at 100 mVs^{-1} scan rate respectively and these responses remain in the reversibility range within all scan rates. As shown in Fig. 2a, all CVs recorded at various scan rates show the reversibility of both reduction couples, since ΔE_p values increase up to a maximum of 95 mV when the scan rate was increased upto 250 mVs^{-1} scan rates (Table 1). Reversibility of the reduction couples is influenced from the swept potential windows as shown in Fig. 2b. While the R(1) and R(2) couples are reversible upon only negative potential scans, these couples get irreversible after the positive potential scans. This behavior indicates that the cationic form of the compound is chemically irreversible, which also influenced the reversibility of the reduction processes. SWVs given in Fig. 2 to support the reversibility of the redox processes of the compound **7**.

In Figs. 3-6, voltametric responses of the compounds **2a, 3, 4a**, and **5** were illustrates as examples. Among all compounds, the compound **2a** was shown as the most easily reducible one with −0.49 and −0.94 V reduction potentials. Similarly, the compound **7** was the hardest to reduce with −0.63 V of R(1) couple among all compounds. Although the reduction reactions of **2a** were electrochemically reversible, the R(2) couple get chemically quasi-reversible at the fast scan rates due to the following chemical reactions. While the compounds **2b, 5, 8,** and **9** have similar behaviors with **2a**, the other compounds have high I_{pa}/I_{pc} responses than unity for the R(2) couples, which indicate presence of chemical reactions before the R(2) couple. It was well documented in the literature that electrochemical characters of $NQ/NQ^{\cdot+}$, $NQ/NQ^{\cdot-}$, and $NQ^{\cdot-}/ NQ^{2-}$ processes of NQs could be easily influenced from the electrolyte properties. The NQ structure, the substituents on NQs, type and polarity of the solvent and conducting electrolyte significantly alters the electron transfer features of NQs [15–18]. Within harmony with the literature, here we clearly illustrate that the substituents on the NQs considerably affect the chemical and electrochemical reversibility and peak position of the redox reactions of NQ rings. The well reversible and easily reduction reactions were observed with the compound **2a** having piperazine ring and bromine substituents.

Although there were some differences on the peak potential and the reversibility of the electron transfer reactions of the compounds, voltammetric analyses and *in situ* UV–Vis spectroelectrochemical studies showed that all NQs have the following same redox mechanism [4]. (Scheme 2).

In situ UV–Vis spectroelectrochemical responses of NQ derivatives are rarely studied in the literature. In a few examples in the literature, the spectral changes of NQ moieties and their spectra of the neutral, monoanionic and dianionic forms were reported [19,20]. For example, Záliš, S. et al. reported voltammetric and U-Vis spectroelectrochemical responses of 1,4-naphthoquinone bearing aniline substituent (**2**) [21]. They assigned the absorption in the range from 290 to 380 nm to the local π-π transitions and from 400 to 600 nm to the charge transfer (CT) on NQ. Mono-reduced form of compound **2** is illustrated three intensive bands around 300, 405, and 470 nm. They also reported a broad transition around 406 nm for the electronic spectrum of doubly reduced species. In another study, Dron, P. I. and his coworkers reported the electrochemical and spectroelectrochemical responses of,3-diamino-1,4-naphthoquinone and two of its *N*-alkylated derivatives (1–3) in acetonitrile [20]. They stated that three NQ derivatives indicated characteristic spectral changes between 250 and 500 nm for the monoanionic and dianionic species. Although the UV–Vis spectroelectrochemical analyses of NO derivatives were rare in number, there are some example on the *In situ* FT-IR spectroelectrochemical responses of NQ derivatives [8,22]. It is well illustrated that the structure of these compounds and the electrolyte types considerably influence the optical responses [12,14,20,21]. For instance, in our previous paper we reported *in situ* UV–Vis spectroelectrochemical responses of 3-chloro-2-(mesitylamino)-5-nitro-1,4-naphthoquinone. This compound illustrated distinct spectral changes during the first reduction reaction with the decreasing of the band of neutral compound at 500 nm and observation of a new band at 400 nm [14]. Here, *situ* UV–Vis spectroelectrochemical studies of NQs were investigated to find out the influence of the substituents on the NQ heterocycle. All the NQs studied here gave very similar *in situ* UV–Vis spectroelectrochemical responses with each other and with the previously reported ones. *In situ* UV–Vis spectroelectrochemical responses of the compound **7** was represented as an example in Fig. 7. Without a potential application, compound **7** illustrates distinct bands at 272, 298, 345, 552, and 584 nm. When −0.75 V constant potential is applied (R(1)), all bands of neutral **7** decrease in intensity and a small new band increases at 392 nm. These spectral changes give well resolved isosbestic points at 360 and 407 nm (Fig. 7a). All of these spectral changes were in harmony with the reduction of NO to NQ$^{\cdot-}$ monoanionic radical species [12,14,20,21]. After formation of NQ$^{\cdot-}$ radical anion, the blue color of neutral 7 (point; x = 0.219 and y = 0.167) turns to light yellow (point; x = 0.312 and y = 0.310) as shown in Fig. 7d. During the reduction of NQ$^{\cdot-}$ radical anion to NQ^{2-} dianionic form of **7** at −1.30 V potential application (R(2)), the band observed during R(1) at 392 and a new band at 472 nm increase, while other bands remain as unchanged (Fig. 7b). As shown in the chromaticity diagram in Fig. 7d, a yellow color (point; x = 0.360 and y = 0.399) is observed for the dianionic species. During the oxidation reaction of the compound 7 at 1.40 V (O(1)), while the bands at 298, 345, and 584 nm decrease in intensity, the band at 584 nm shifts towards short wavelengths with decreasing in intensity (Fig. 7c). These spectral changes give light orange color (point; x = 0.347 and y = 0.328) for the cationic species of the compound (Fig. 7d). The profound spectral and color changes during the redox reactions of the NQ compounds show their electrochromic functionality for the display technologies. It is well documented [19,23,24] that the distinct spectral changes in the visible region and profound color changes are two basic parameters for the possible usage of the compounds in electrochromic applications in solution and in solid state.

4. Conclusions

In this paper, we have described the synthesis and characterization of some *N*-substituted-1,4-naphthoquinones. All new compounds were characterized on the basis of nuclear magnetic resonance spectroscopy (^{1}H- and ^{13}C NMR), MS, FT-IR and elemental analysis. All synthesized compounds were stable and obtained in crystalline form with good yields.

The electrochemical behaviors of synthesized compounds (NQ derivatives) were determined with voltammetric and *in situ* UV–Vis spectroelectrochemical measurements. All NQ derivatives illustrate two reductions and one oxidation processes. Voltammetric analyses of the couples of the molecules indicate electrochemical reversibility of the reductions and electrochemical irreversibility of the oxidation couples. Substituent environments of NQ structure considerably influence the chemical reversibility of the redox processes. While the first reduction couples of NQ derivatives (except **5** and **6**) were chemically reversible, the chemical reversibility of the second reduction couples varies with the substituents due to the possible chemical reactions succeeding the redox processes. The most reversible reduction couples were observed with compound **7** bearing hydroxy-alkyl amine substituent. The substituents on the NQ structure also slightly affect the easy of the electron transfer reactions. Among all compounds, **2a** and **9** were the most easily reduced compounds due to the high electron withdrawing ability of bromine and piperazine rings substituents, respectively. Although, slight voltammetric differences were observed with these ten compounds, *in situ* UV–Vis spectroelectrochemical responses of them were almost same with each other. Well resolved optical and color changes were recorded during the spectroelectrochemical measurement, which show their functionality as electro-chromophores in different opto-electrochemical technologies.

All NQ derivatives illustrated very similar redox reactions and *in situ* UV–Vis spectroelectrochemical responses and substituents on the NQ heterocycles only alter the reversibility and peak positions of the electron transfer reactions. Substituents also influenced the eases of the electron trans highly reversible redox responses were observed with the compound **7** bearing hydroxy-alkyl amine substituent. Evident spectral and color changes during the redox reactions indicated functionality of the compounds in optoelectrochemical (OE) applications.

CRediT authorship contribution statement

Zeynep Ozyildiz: . **Dilan Gezer:** . **Nahide Gulsah Deniz:** . **Zeliha Gokmen:** . **Özlem Uğuz Neli:** Methodology, Writing – original draft. **Atıf Koca:** Methodology, Writing – original draft.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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References

[1] V.K. Tandon, D.B. Yadav, R.V. Singh, A.K. Chaturvedi, P.K. Shukla, Synthesis and biological evaluation of novel (L)-α-amino acid methyl ester, heteroalkyl, and aryl substituted 1, 4-naphthoquinone derivatives as antifungal and antibacterial agents, Bioorg. Med. Chem. Lett. 15 (23) (2005) 5324–5328.

[2] Y. Xia, Z.-Y. Yang, P. Xia, T. Hackl, E. Hamel, A. Mauger, J.-H. Wu, K.-H. Lee, Antitumor agents. 211. Fluorinated 2-phenyl-4-quinolone derivatives as antimitotic antitumor agents, J. Med. Chem. 44 (23) (2001) 3932–3936.

[3] J. Tonholo, L.R. Freitas, F.C.d. Abreu, D.C. Azevedo, C.L. Zani, A.B.d. Oliveira, M.O.F. Goulart, Electrochemical properties of biologically active heterocyclic naphthoquinones, J. Braz. Chem. Soc. 9 (2) (1998) 163–169.

[4] E.B. Diogo, G.G. Dias, B.L. Rodrigues, T.T. Guimarães, W.O. Valença, C.A. Camara, R.N. de Oliveira, M.G. da Silva, V.F. Ferreira, Y.G. de Paiva, Synthesis and anti-Trypanosoma cruzi activity of naphthoquinone-containing triazoles: Electrochemical studies on the effects of the quinoidal moiety, Bioorg. Med. Chem. 21 (21) (2013) 6337–6348.

[5] F. Ferreira, S.B. Ferreira, A.J. Araujo, J. Marinho, C. Pessoa, M.O. Moraes, L. V. Costa-Lotufo, R.C. Montenegro, F. da Silva, V.F. Ferreira, Arylated alpha-and beta-dihydrofuran naphthoquinones: Electrochemical parameters, evaluation of antitumor activity and their correlation, Electrochim. Acta 110 (2013) 634–640.

[6] T.L. Silva, S. Maria de Lourdes, F.R. Ferreira, D.C. Santos, C. Amatore, M. O. Goulart, Quinone-based molecular electrochemistry and their contributions to medicinal chemistry: a look at the present and future, Curr. Opin. Electrochem. 24 (2020) 79–87.

[7] M. Elhabiri, P. Sidorov, E. Cesar-Rodo, G. Marcou, D.A. Lanfranchi, E. Davioud-Charvet, D. Horvath, A. Varnek, Electrochemical Properties of Substituted 2-Methyl-1, 4-Naphthoquinones: Redox Behavior Predictions, Chemistry–A, Eur. J. 21 (8) (2015) 3415–3424.

[8] X. Qiao, D. Li, L. Cheng, B. Jin, Mechanism of electrochemical capture of CO2 via redox cycle of chlorinated 1, 4-naphthoquinone in BMIMBF4: An in-situ FT-IR spectroelectrochemical approach, J. Electroanal. Chem. 845 (2019) 126–136.

[9] S.K. Verma, V.K. Singh, Synthesis, electrochemical, fluorescence and antimicrobial studies of 2-chloro-3-amino-1, 4-naphthoquinone bearing mononuclear transition metal dithiocarbamate complexes [M κ 2 S, S-S 2 C–piperazine–C 2 H 4 N (H) ClNQ n], RSC Adv. 5 (65) (2015) 53036–53046.

[10] L. Hou, Z. Hu, H. Wu, X. Wang, Y. Xie, S. Li, F. Ma, C. Zhu, 2-Amino-3-chloro-1, 4-naphthoquinone-covalent modification of graphene nanosheets for efficient electrochemical energy storage, Dalton Trans. 48 (25) (2019) 9234–9242.

[11] L.A. Shundrin, I.G. Irtegova, N.V. Vasilieva, I.A. Khalfina, Benzoquinone and naphthoquinone based redox-active labels for electrochemical detection of modified oligonucleotides on Au electrodes, Tetrahedron Lett. 57 (3) (2016) 392–395.

[12] N.G. Deniz, C. Sayil, D. Akyüz, A. Koca, Synthesis, electrochemistry, in-situ spectroelectrochemistry and molecular structures of 1, 4-naphthoquinone derivatives, J. Mol. Struct. 1224 (2021), 129145.

[13] R. Patil, S. Bhand, V.B. Konkimalla, P. Banerjee, B. Ugale, D. Chadar, S.K. Saha, P. P. Praharaj, C. Nagaraja, D. Chakrovarty, Molecular association of 2-(n-alkylamino)-1, 4-naphthoquinone derivatives: Electrochemical, DFT studies and antiproliferative activity against leukemia cell lines, J. Mol. Struct. 1125 (2016) 272–281.

[14] N.G. Deniz, A.F.S. Abdassalam, C. Sayil, O. Uguz, A. Koca, Regioselective synthesis of novel 5-nitro-naphthoquinone derivatives: Electrochemistry and in-situ

spectroelectrochemistry properties, J. Photochem. Photobiol. A Chem. (2022), 114064.

[15] J.V. Milić, T. Schneeberger, M. Zalibera, F. Diederich, C. Boudon, L. Ruhlmann, Spectro-electrochemical toolbox for monitoring and controlling quinone-mediated redox-driven molecular gripping, Electrochim. Acta 313 (2019) 544–560.

[16] B. Batanero, R. Saez, F. Barba, Electroreduction of quinones under aprotic conditions, Electrochim. Acta 54 (21) (2009) 4872–4879.

[17] V. Glezer, J. Stradins, J. Friemanis, L. Baider, The mechanism of electrochemical reduction of intramolecular charge-transfer complexes derived from 1, 4-naphthoquinone, Electrochim. Acta 28 (1) (1983) 87–95.

[18] Y. Hui, E.L.K. Chng, C.Y.L. Chng, H.L. Poh, R.D. Webster, Hydrogen-bonding interactions between water and the one-and two-electron-reduced forms of vitamin K1: applying quinone electrochemistry to determine the moisture content of non-aqueous solvents, J. Am. Chem. Soc. 131 (4) (2009) 1523–1534.

[19] A. Lücht, S. Sobottka, L.J. Patalag, P.G. Jones, H.U. Reissig, B. Sarkar, D.B. Werz, New Dyes Based on Extended Fulvene Motifs: Synthesis through Redox Reactions of Naphthoquinones with Donor-Acceptor Cyclopropanes and Their Spectroelectrochemical Behavior, Chemistry–A, Eur. J. 25 (44) (2019) 10359–10365.

[20] P.I. Dron, Š. Ramešová, N.P. Holloran, L. Pospíšil, J. Michl, Redox Behavior of 2, 3-Diamino-1, 4-naphthoquinone and its N-Alkylated Derivatives, Electroanalysis 28 (11) (2016) 2855–2860.

[21] S. Záliš, J. Fiedler, L. Pospíšil, N. Fanelli, C. Lanza, L. Lampugnani, Electron transfer in donor–acceptor molecules of substituted naphtoquinones: spectral and redox properties of internal charge transfer complexes, Microchem. J. 54 (4) (1996) 478–486.

[22] D. Li, L. Cheng, B. Jin, Investigation on PCET–accompanied dimerization of 5–hydroxy–1, 4–naphthoquinone in the process of electrochemical reduction by in situ FT–IR spectroelectrochemistry and density functional calculation, Electrochim. Acta 130 (2014) 387–396.

[23] S. Sobottka, M. Nößler, A.L. Ostericher, G. Hermann, N.Z. Subat, J. Beerhues, M. Behr-van Der Meer, L. Suntrup, U. Albold, S. Hohloch, Tuning PtII-Based Donor-Acceptor Systems through Ligand Design: Effects on Frontier Orbitals, Redox Potentials, UV/Vis/NIR Absorptions, Electrochromism, and Photocatalysis, Chemistry–A, Eur. J. 26 (6) (2020) 1314–1327.

[24] R. Tatemura, M. Yasutake, H. Kinoshita, K. Miura, Electrochemical Properties and Electrochromism of 6-Aryl-1, 3-bis (trimethylsilyl) fulvenes and Their Derivatives, J. Org. Chem. 87 (1) (2021) 172–183.

[25] D. Karakas, R.O. Akar, Z. Gokmen, N.G. Deniz, E. Ulukaya, A novel 1,4-naphthoquinone-derived compound induces apoptotic cell death in breast cancer cells, Turkish J. Bio. 43 (4) (2019) 256–263.

[26] Z. Gokmen, H. Alahmad, Novel Amino- and Thio(substituted)-1,4-Naphthoquinone (NQ) Compounds: Synthesis and characterization, Phosphorus Sulfur, Silicon Relat. Element. 195 (9) (2020) 718–725.

[27] A. Kacmaz, N.G. Deniz, S.G. Aydinli, C. Sayil, E. Onay-Ucar, E. Mertoglu, N. Arda, Synthesis and antiproliferative evaluation of some 1,4-naphthoquinone derivatives against human cervical cancer cells, Open Chem. 17 (2019) 337–345.

[28] Z. Gokmen, M.E. Onan, N.G. Deniz, D. Karakas, E. Ulukaya, Synthesis and investigation of cytotoxicity of New N- and S, S-substituted-1,4-Naphthoquinone (NQ) Derivatives on Selected Cancer Lines, Synth. Commun. 49 (21) (2019) 3008–3016.