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ORIGINAL PAPER

Cost-effective electrosynthesis of a series of edaravones through an electrochemical-assisted domino heteroannulation and paired electrochemical process

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Abstract A series of novel edaravone structures was successfully synthesized through the anodic oxidation of catechols in the presence of edaravone in aqueous solution. The cyclic voltammetric results indicate that a one-pot multistep sequential reaction occurs between edaravone and the electrochemically derived *ortho*- and *para*-benzoquinones affording fused poly-heterocyclic compounds. Using controlled potential coulometry, it has been proved that this catalyst-free, tandem reaction occurs via EC, $ECEC_i$, and $ECEC_iC_i$ mechanisms. The paired electrochemical synthesis of compound **5g** has been successfully performed in a one-pot process with carbon rods as working electrodes and RVC as counter electrodes in an undivided cell. In addition, the electrosynthesis of edaravone derivatives has been successfully performed in ambient conditions in an undivided cell using an environmentally friendly method with high atom economy. All of the obtained compounds were fully characterized by spectroscopic methods such as FT-IR, ^{1}H NMR, ^{13}C NMR, and MS.

Keywords Edaravone · Catechol · Hydroquinone · Paired electrochemical synthesis · Cyclic voltammetry

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Introduction

Edaravone chemically known as 3-methyl-1-phenyl-2-pyrazolin-5-one has become the topic of interest due to its different uses. Edaravone and its derivatives are well-known because of their potential application in medicinal chemistry due to their analgesic, antipyretic, and anti-inflammatory properties [1–4]. They are also renowned for their antitumor [5–7] and hypoglycemic activities [8]. Recently, edaravone, a potent hydroxyl radical scavenger, also exhibits antioxidant activity [9].

Although several synthetic strategies are available for the synthesis of edaravones, these have disadvantages including long reaction periods and use of toxic solvents. In organic synthesis, there is an urgent need for the development of environmentally benign oxidations [10]. The series of pyrazolones was synthesized by oxidation with O_2 using laccases as catalysts [11].

Electric current is one of the cleanest tools in the transformation of organic molecules, and accordingly, several electrochemical techniques have provided a variety of highly reactive intermediates affording useful and/or novel organic compounds without the use of any environmentally undesirable catalyst [12]. Also, the paired electrochemical synthesis is a powerful technique for clean reactions without any additional chemical reagents [13]. In paired electrochemical synthesis, the anode and cathode concurrently contribute to the formation of the product(s), and the consumption of energy is reduced when compared to the routine organic and electroorganic syntheses [14].

In continuation of our efforts to develop more versatile and convenient electrochemical and chemical synthesis of highly functionalized heterocyclic compounds [15–21], here we report the electrosynthesis of a series of polycyclic edaravones through a one-pot electrooxidative-coupling

sequential reaction. The present protocol provides an efficient procedure via EC, $ECEC_i$, and $ECEC_iC_i$ electrochemical mechanisms to construct the heterocyclic compounds of type edaravones, a relatively rare fused-ring system.

Experimental

Apparatus and reagents

All experiments were carried out in a conventional electrochemical cell using the traditional three-electrode system. The working electrode used in voltammetry experiments was a glassy carbon disc (1.8 mm in diameter), and platinum wire was used as the counter electrode. The working electrode used in controlled-potential coulometry and bulk electrolysis (using an electronic potentiostat) was an assembly of four rods of graphite electrodes, 6 mm in diameter, and ~10 cm in length, and a reticulated vitreous carbon (RVC electrode) electrode constituted the counter electrode. The working electrode potentials were measured versus Ag/AgCl. ^{1}H and ^{13}C NMR spectra were recorded on a spectrometer operating at 400 and 100 MHz for proton and carbon nuclei. Chemical shifts were recorded as δ values in parts per million (ppm). ^{1}H NMR spectra are reported as follows: chemical shift (δ) [multiplicity (where multiplicity is defined as *br* broad; *s* singlet; *d* doublet; *t* triplet; *q* quartet; *m* multiplet), coupling constant (s), J (Hz), relative integral, and assignment]. Mass spectra and exact masses were recorded on a 5973 Network Mass Selective Detector, Agilent Technology (HP), (EI, 70 eV) mass spectrometer. Infrared spectra were recorded and are reported in wavenumbers (cm^{-1}). All chemicals were of reagent grade, and the solvents and the reagents were of pro-analysis grade. These chemicals were used without further purification.

Electro-organic synthesis of 5a–c, 5f, 3d–e, 3g

In a typical experiment, 100 mL of suitable buffer solution in water/acetonitrile mixture (see Table 1) containing 1.0 mmol of catechol and hydroquinone derivatives and 1.0 mmol of edaravone (**I**) was electrolyzed in an undivided cell equipped with a carbon cathode (an assembly of four rods of graphite electrodes, 6 mm in diameter, and 10 cm in length) and RVC electrode as the counter electrode (anode), at suitable potential (V) versus Ag/AgCl (see Table 1) at ambient condition. The electrolysis was terminated when the current decreased by more than 95 %. The electrolysis process was interrupted and the graphite cathode was washed in acetone in order to reactivate it. At the end of electrolysis, a few drops of acetic acid were added to the solution and the cell was placed in a refrigerator overnight. The precipitated solid was collected by filtration, washed copiously with distilled water and characterized by FT-IR, ^{1}H NMR, ^{13}C NMR, and MS. The final products

Table 1 Electroanalytical and preparative electrolysis data for preparation of synthesized edaravone derivatives

Catechols	Peak potentials (V)[b]		Peak potentials (V)[c]		Applied potential at carbon rods[d]	Product	EE[e]/Yield[f] (%)	Solvent (CH_3CN/H_2O)
	Ep_{ox1}	Ep_{red1}	Ep_{ox1}	Ep_{red1}				
1a	0.2835	0.1858	0.4055	−0.2536	+0.17	**5a**	96/90	10/90
1b	0.2346	0.1370	0.4055	−0.3024	+0.15	**5b**	89/87	20/80
1c	0.2346	0.1370	0.4299	−0.1803	+0.13	**5c**	91/89	20/80
1d	0.2102	0.1370	0.2346	−0.4000	+0.12	**3d**	87/83	20/80
1e	0.2311	0.1614	0.2359	−0.3268	+0.15	**3e**	76/71	30/70
1f	0.1858	0.0881	0.2835	0.0881	+0.22	**5f**	95/92	10/90
1g	0.4019	0.3530	0.4275	0.3180	+0.20	**3g**	61/23	20/80
1g	–	−0.89	–	−1.1	−0.89	**5g**	78/89	20/80
1h	0.3323	0.2346	0.4544	−0.2291	+0.13	**5a**	86/84	10/90
1i	0.3079	0.1614	0.3323	−0.2291	+0.20	**5f**	89/81	10/90

[a] Cyclic voltammetry measurements were performed in phosphate buffer solution (0.2 M, pH 6) and CH_3CN, with glassy carbon (GC) as working electrode; scan rate 100 mV/s. Reference electrode: Ag/AgCl

[b] 1 mM of **1a–i** in the absence

[c] 1 mM of **1a–i** in the presence of 1 mM of **I**

[d] Controlled-potential coulometries were carried out in phosphate buffer solution (0.2 M, pH 6) and CH_3CN, at carbon rods; reference electrode: Ag/AgCl

[e] Calculated using the Faraday's law

[f] Isolated yields

were obtained in a purified form and no extra purification was needed.

Compound (5a)

Light tan solid; m.p = 233 °C; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ (ppm): 2.89 (s, 3H, CH$_3$), 6.56 (s, 1H, aromatic CH), 6.69 (s, 1H, aromatic CH), 7.40 (m, 2H, two aromatic CH), 7.52 (m, 2H, two aromatic CH), 7.82 (m, 1H, aromatic CH), 8.78 (br, OH); ^{13}C NMR (100 MHz, DMSO-d$_6$) δ (ppm): 13.61, 99.82, 106.18, 107.05, 119.13, 120.32, 126.52, 128.22, 129.21, 129.50, 137.47, 144.39, 146.91, 147.35, 148.57, 151.73; IR (neat) ν (cm^{-1}): 3488, 2924, 2853, 1945, 1596, 1457, 1125, 725, 689; MS (EI): *m/z* calcd for $C_{16}H_{12}N_2O_3$: 280.08486; found: 280.

*Compound (**5a**); obtained from the reaction of **1g** and **I***

Light tan solid; m.p = 233 °C; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ (ppm): 2.89 (s, 3H, CH$_3$), 6.29 (s, 1H, aromatic CH), 6.42 (s, 1H, aromatic CH), 7.26 (m, 2H, two aromatic CH), 7.49 (m, 2H, two aromatic CH), 7.86 (m, 1H, aromatic CH), 8.48 (br, OH), 9.16 (br, OH); ^{13}C NMR (100 MHz, DMSO-d$_6$) δ (ppm): 13.64, 99.77, 106.17, 107.08, 118.43, 120.79, 126.26, 128.23, 129.02, 129.63, 136.00, 144.68, 146.93, 148.38, 148.80, 151.89; IR (neat) ν (cm^{-1}): 3069, 2921, 2796, 1950, 1597, 1496, 1303, 756, 690; MS (EI): *m/z* calcd for $C_{16}H_{12}N_2O_3$: 280.08486; found: 280.

*Compound (**5b**)*

Light brown solid; m.p = 242 °C (decomposed); ^{1}H NMR (400 MHz, DMSO-d$_6$) δ (ppm): 1.96 (s, 3H, CH$_3$), 2.26 (s, 3H, CH$_3$), 6.19 (s, 1H, aromatic CH), 7.30 (m, 1H, aromatic CH), 7.50 (m, 1H, aromatic CH), 7.57 (m, 1H, aromatic CH), 7.87 (d, 1H, aromatic CH), 7.92 (d, 1H, aromatic CH), 9.12 (s, OH), 9.58 (s, OH); ^{13}C NMR (100 MHz, DMSO-d$_6$) δ (ppm): 9.19, 13.65, 104.08, 107.82, 113.77, 118.59, 119.96, 125.40, 126.42, 129.21, 129.50, 141.90, 142.79, 144.42, 145.06, 147.40, 157.97; IR (neat) ν (cm^{-1}): 690, 754, 1133, 1497, 1596, 1872, 1950, 2856, 3396; MS (EI): *m/z* calcd for $C_{16}H_{12}N_2O_3$: 294.10052; found: 294.

*Compound (**5c**)*

Amorphous brown solid; m.p = 210 °C (decomposed); ^{1}H NMR (400 MHz, DMSO-d$_6$) δ (ppm): 2.13 (s, 3H, CH$_3$), 3.73 (s, 3H, CH$_3$), 6.44 (s, 1H, aromatic CH), 7.20 (m, 1H, aromatic CH), 7.44 (t, 2H, two aromatic CH), 7.70 (d, 1H, aromatic CH), 7.88 (d, 1H, aromatic CH), 8.50 (br, OH), 9.17 (br, OH); ^{13}C NMR (100 MHz, DMSO-d$_6$) δ (ppm): 14.05, 56.07, 102.96, 109.15, 118.19, 118.43, 124.56, 125.18, 126.28, 128.91, 134.27, 138.12, 139.90, 140.18, 146.02, 148.64; IR (neat) ν (cm^{-1}): 690, 754, 1094, 1225, 1433, 1596, 1872, 1950, 2856, 3396; MS (EI): *m/z* calcd for $C_{17}H_{14}N_2O_4$: 310.09542; found: 310.

*Compound (**5f**)*

Brown solid; m.p = 282 °C (decomposed); ^{1}H NMR (400 MHz, DMSO-d$_6$) δ (ppm): 2.89 (s, 3H, CH$_3$), 7.32 (d, J = 7.2, 1H, aromatic CH), 7.50 (d, J = 7.4, 1H, aromatic CH), 7.70 (m, 2H, two aromatic CH), 7.80 (t, 1H, aromatic CH), 8.69 (br, OH); ^{13}C NMR (100 MHz, DMSO-d$_6$) δ (ppm): 13.90, 107.47, 115.60, 117.77, 119.28, 123.34, 126.38, 140.20, 141.33, 145.01, 146.80, 147.20, 149.69; IR (neat) ν (cm^{-1}): 689, 754, 1158, 1274, 1457, 1596, 2853, 2924, 2952, 3488; MS (EI): *m/z* calcd for $C_{16}H_{12}N_2O_3$: 280.08486; found: 280.

*Compound (**5f**); obtained from the reaction of **1h** and **I***

Brown solid; m.p = 282 °C (decomposed); ^{1}H NMR (400 MHz, DMSO-d$_6$) δ (ppm): 2.89 (s, 3H, CH$_3$), 7.32 (d, J = 7.2, 1H, aromatic CH), 7.52 (d, J = 7.4, 1H, aromatic CH), 7.70 (m, 2H, two aromatic CH), 7.80 (t, 1H, aromatic CH), 8.70 (br, OH); ^{13}C NMR (100 MHz, DMSO-d$_6$) δ (ppm): 13.92, 107.52, 115.59, 117.75, 119.20, 123.40, 126.30, 140.33, 141.34, 144.94, 146.72, 148.15, 149.74; IR (neat) ν (cm^{-1}): 688, 755, 1111, 1303, 1457, 1595, 2802, 2922, 2952, 3068, 3406; MS (EI): *m/z* calcd for $C_{16}H_{12}N_2O_3$: 280.08486; found: 280.

*Compound (**3d**)*

Light gray solid; m.p = 266 °C (decomposed); ^{1}H NMR (400 MHz, DMSO-d$_6$) δ (ppm): 1.97 (s, 3H, CH$_3$), 2.09 (s, 3H, CH$_3$), 6.52 (s, 1H, aromatic CH), 6.66 (s, 1H, aromatic CH), 7.23 (t, 1H, aromatic CH), 7.43 (m, 2H, two aromatic CH), 7.77 (m, 2H, two aromatic CH), 8.68 (s, OH), 10.61 (s, OH), 10.99 (s, OH); ^{13}C NMR (100 MHz, DMSO-d$_6$) δ (ppm): 13.12, 19.00, 117.07, 118.20, 120.03, 120.79, 124.06, 125.04, 128.02, 128.40, 128.78, 131.02, 139.06, 142.66, 144.36, 146.56, 174.57; IR (neat) ν (cm^{-1}): 691, 761, 1112, 1442, 1527, 1881, 1950, 2785, 2920, 3070, 3511; MS (EI): *m/z* calcd for $C_{17}H_{16}N_2O_3$: 296.11618; found: 296.

*Compound (**3e**)*

Light tan solid; m.p = 235 °C (decomposed); ^{1}H NMR (400 MHz, DMSO-d$_6$) δ (ppm): 1.26 (s, 9H, 3CH$_3$), 1.91 (s, 3H, CH$_3$), 6.68 (s, 1H, aromatic CH), 6.82 (s, 1H, aromatic CH), 7.17 (d, 1H, aromatic CH), 7.33 (d, 1H, aromatic CH), 7.44 (t, 1H, aromatic CH), 7.56 (t, 1H, aromatic CH),

7.79 (t, 1H, aromatic CH), 10.83 (br, OH), 12.70 (br, OH); ^{13}C NMR (100 MHz, DMSO-d$_6$) δ (ppm): 12.73, 117.60, 118.76, 120.53, 121.83, 125.41, 126.18, 128.78, 129.20, 130.04, 140.30, 141.57, 144.32, 145.14, 147.06, 148.74; IR (neat) ν (cm^{-1}): 692, 784, 1094, 1498, 1556, 1866, 2960; MS (EI): *m/z* calcd for $C_{17}H_{16}N_2O_3$: 338.16316; found: 338.

Compound (3g)

Dark brown solid; m.p = 279 °C (decomposed); ^{1}H NMR (400 MHz, DMSO-d$_6$) δ (ppm): 1.90 (s, 3H, CH$_3$), 6.37 (s, 1H, aromatic CH), 6.57 (s, 1H, aromatic CH), 7.03 (t, 1H, aromatic CH), 7.28 (t, 1H, aromatic CH), 7.33 (t, 1H, aromatic CH), 8.09 (d, 1H, aromatic CH), 8.27 (d, 1H, aromatic CH), 10.09 (br, OH), 12.12 (br, OH); ^{13}C NMR (100 MHz, DMSO-d$_6$) δ (ppm): 12.53, 117.84, 118.58, 119.78, 120.50, 122.23, 127.76, 128.26, 129.06, 129.51, 137.28, 141.44, 145.47, 146.91, 154.96, 157.53; IR (neat) ν (cm^{-1}): 692, 756, 1077, 1364, 1458, 1564, 1594, 2855, 2926, 3065; HRMS (EI): *m/z* calcd for $C_{16}H_{13}N_3O_5$: 327.08559; found: 327.

The paired electro-organic synthesis of 5g

An aqueous solution of phosphate buffer (50 mL, pH 6.0, 0.2 M) and CH$_3$CN was prepared in 4:1 (V:V) ratio. 1.0 mmol of 4-nitrocatechol (**1p**), 1.0 mmol of edaravone (**I**) and 1 mmol of potassium ferrocyanide were electrolyzed at a working potential of −0.89 V versus Ag/AgCl (see Table 1), in an undivided cell equipped with graphite rods as cathode (an assembly of two rods, 6 mm in diameter, and 10 cm in length) and RVC counter electrode (anode). The electrolysis was terminated when the cathodic peak that corresponds to the reduction of 4-nitrocatechol (C$_1$ in Fig. 4) in cyclic voltammetry disappears (after consumption of 8.5 F/mol). At the end of the electrolysis, cell was placed in the refrigerator overnight. The precipitated solid was collected by filtration and washed with water. After washing, the products were characterized by IR, ^{1}H NMR, ^{13}C NMR, and MS.

*Compound (**5g**)*

Dark brown solid; m.p = 256 °C (decomposed); ^{1}H NMR (400 MHz, DMSO-d$_6$) δ (ppm): 2.08 (s, 3H, CH$_3$), 4.33 (d, NH), 5.74 (s, 1H, aromatic CH), 6.28 (s, 1H, aromatic CH), 6.76 (m, 2H, two aromatic CH), 7.01 (t, 1H, aromatic CH), 7.06 (t, 1H, aromatic CH), 7.12 (t, 1H, aromatic CH), 9.13 (br, OH); ^{13}C NMR (100 MHz, DMSO-d$_6$) δ (ppm): 13.12, 117.07, 118.20, 120.03, 120.79, 124.16, 125.04, 126.02, 128.78, 137.44, 139.08, 142.65, 144.36, 146.56; IR (neat) ν (cm^{-1}): 514, 831, 1262, 1518, 1629, 1858, 1979, 3008, 3200, 3304, 3373; HRMS (EI): *m/z* calcd for $C_{16}H_{15}N_3O_3$: 297.11145; found: 297.

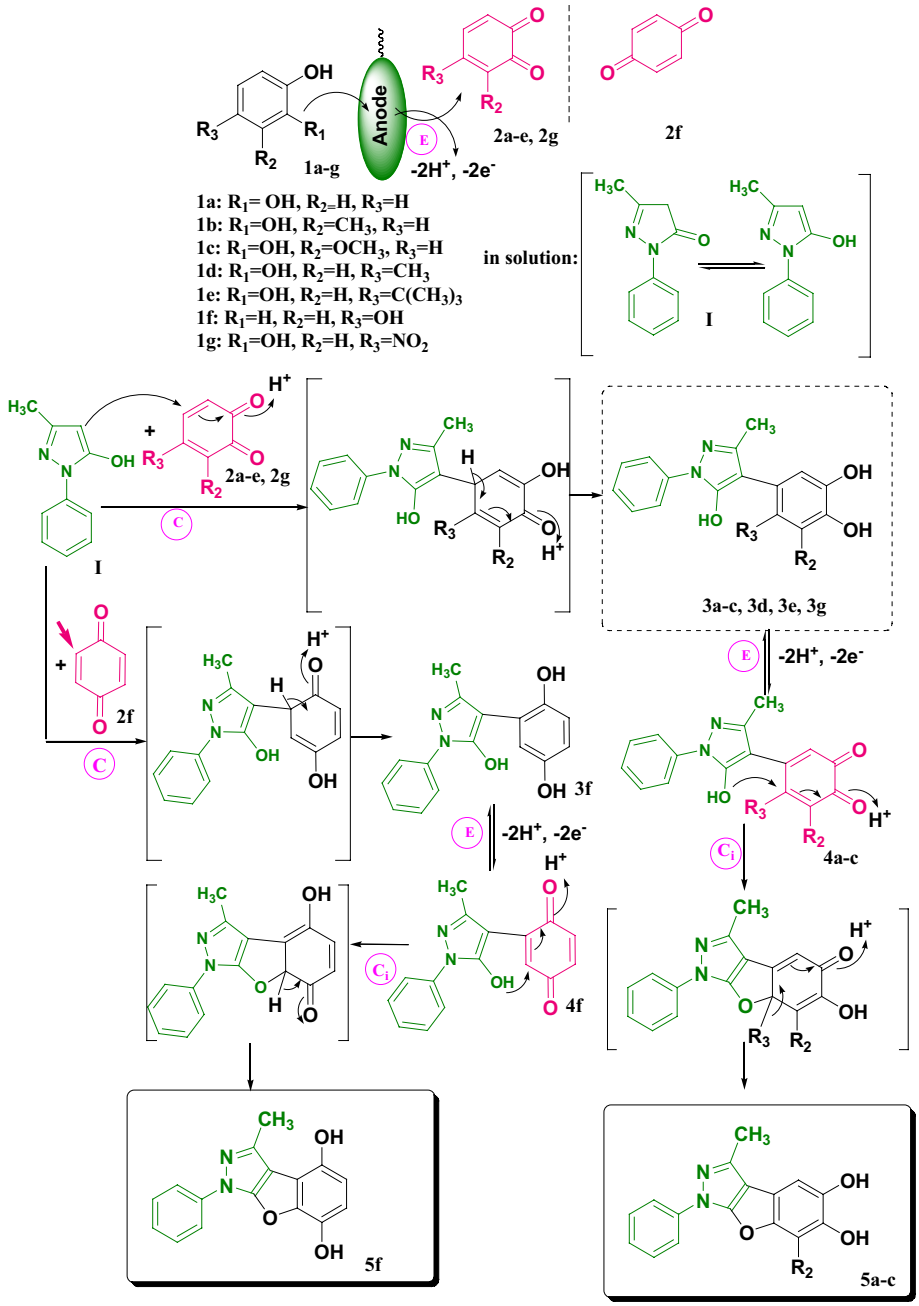
Results and discussion

Electrochemical study of catechols (1a–i) in the presence of edaravone (I)

Initial characterization of the reactions was carried out using cyclic voltammetry technique. Cyclic voltammetric responses of a GC electrode to 1 mM of catechol (**1a**, Scheme 1) in water/acetonitrile (90/10) solution containing 0.2 M sodium phosphate, pH = 6, in the absence and presence of edaravone (**I**, Scheme 1) are outlined in Fig. 1. In this Figure, curve a shows a well-defined oxidative peak (A$_1$) at 0.185 V (vs. Ag/AgCl) consistent with the oxidation of **1a** to *ortho*-benzoquinone (**2a**, Scheme 1). Upon reversal of the scan direction, a corresponding reduction peak (C$_1$) is observed at 0.088 V, which is attributed to reduction of **2a** back to the parent catechol (Scheme 1). A peak current ratio (I_p^{C1}/I_p^{A1}) of nearly unity, especially during the repetitive recycling of the potential, can be observed for **1a** in the absence of **I** and this ratio can be considered as a criterion for the stability of *ortho*-benzoquinone generated at the surface of GC electrode under the applied experimental conditions.

In Fig. 1, curve b shows the cyclic voltammogram obtained for a 1 mM solution of **1a** in the presence of 1 mM of **I**. The voltammogram exhibits three anodic peaks (A$_1$, A$_2$, A$_3$) at 0.234, 0.429 and 0.698 V versus Ag/AgCl respectively, and one decreased cathodic peak (C$_1$) at −0.229 V versus Ag/AgCl. The new anodic peak (A$_3$) is attributed to the electrooxidation of intermediate (**3a**) which is formed at the surface of electrode.

By comparing A$_1$ peak in curves a and b, it was determined that the b voltammogram exhibits a relatively intense decrease in the anodic peak current A$_1$ together with some potential shift in a positive direction, which is not shown here (Fig. S-2) (see supporting information); the positive shift of the A$_1$ peak in the presence of edaravone (**I**) is due to the formation of a thin film of product at the surface of the electrode inhibiting to a certain extent the performance of electrode [22–25]. Also notably, comparison of the cathodic part of curves a and b (peak C$_1$) shows a great decrease in the current density for curve b. This clearly reveals that compared to the reduction of **2a** to **1a**, the intermolecular Michael-type addition of **I** to **2a** is a dominant and fast process, and as a result, the cathodic part of curve b almost disappears. These facts are in good agreement with the high reactivity of electrogenerated orthobenzoquinone **2a** toward **I** and the formation of Michael adduct through an interfacial reaction at the electrode



Scheme 1 A schematic representation of mechanisms for the electro-oxidation of **1a–g** in the presence of **I**

surface [26]. In Figure 1, curve c shows the cyclic voltammogram obtained for a 1 mM solution of **I** in the absence of **1a** and confirms that **I** is electrochemically active (A_2 peak) at 0.429 V versus Ag/AgCl.

Edaravone (**I**) is in appropriate nucleophile, so it seems that a Michael 1, 4-addition of **I** to **2a** can proceed in a quick and simple way leading to the considerable decrease in the height of cathodic peak (C_1). As a result, the reactivity of **2a** towards **I** can be monitored as an increase in the height of the cathodic peak C_1 at higher scan rates. The cyclic voltammetries of **1a** in the presence of **I** in various sweep rates revealed that the height of cathodic and anodic peak currents is increased with the addition of potential sweep rate (see supporting information). Also, a plot of peak current ratio (I_p^{C1}/I_p^{A1}) versus scan rate for a mixture of **1a** and **I**, which is an increase in the height of the cathodic peak C_1 at higher scan rates (see supporting information), confirms the reactivity of **I** towards **1a**. On the other hand, with the increasing scan rate, the current function for the anodic A_1 peak, ($I_p^{A1}/v^{1/2}$), decreased and such behavior is adopted as indicative of an $ECEC_i$ mechanism [27]. It should be emphasized that an increase in the height of peak currents with scan rate is expected even in the absence of a chemical reaction; but a plot of peak current ratio (I_p^{C1}/I_p^{A1})

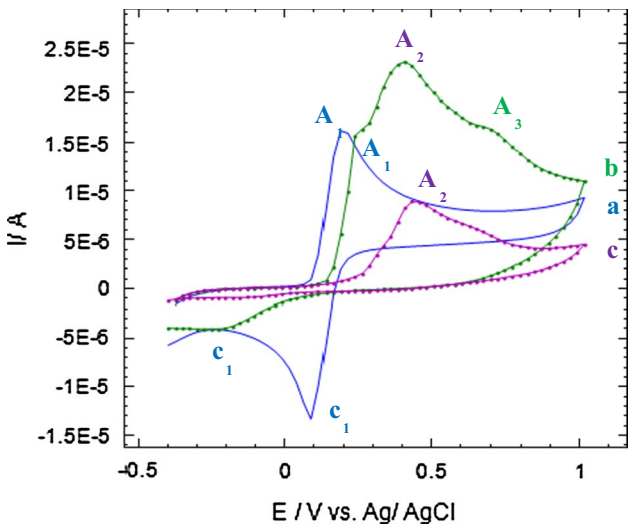


Fig. 1 Cyclic voltammograms of 1 mM of catechol (**1a**): *a* in the absence; *b* in the presence of 1 mM of edaravone (**I**); and *c* 1 mM of edaravone (**I**) in the absence of **1a** using a glassy carbon electrode in sodium phosphate solution (0.2 M, pH 6); scan rate 100 mV/s; $T = 25 \pm 1$ °C

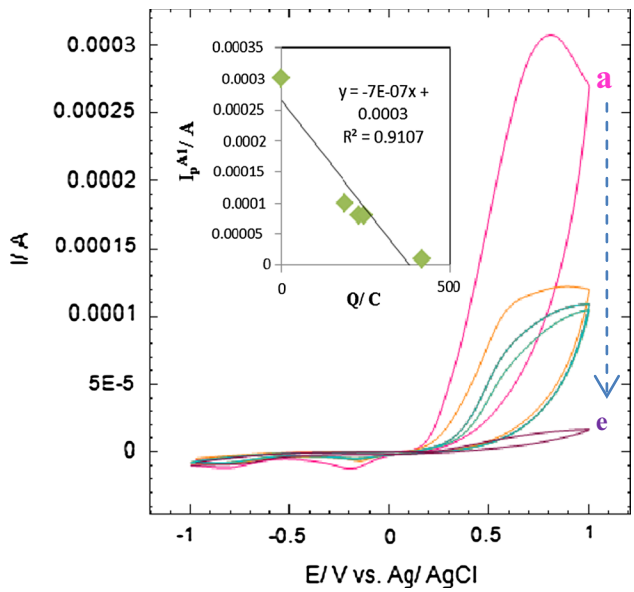


Fig. 2 Cyclic voltammograms of 1.0 mmol of **1a** in the presence of 1.0 mmol of nucleophile **I**, at a glassy carbon electrode during controlled potential coulometry at +0.17 V versus Ag/AgCl after consumption of *a* 0, *b* 190, *c* 230, *d* 247, and *e* 416 C. Scan rate 100 mV/s; $T = 25 \pm 1$ °C; *inset* variation of peak current (Ip^{A1}) versus charge consumed

versus scan rate for a mixture of **1a** and **I** and the current function for the anodic A_1 peak ($I_p^{A1}/v^{1/2}$) are different from a plot of peak current ratio (I_p^{C1}/I_p^{A1}) versus scan rate and the current function for the anodic A_1 peak, ($I_p^{A1}/v^{1/2}$) for **1a**, which indicates the reactivity of **I** and type of electrochemical mechanism for the reaction of **1a** and **I**.

According to the above results, our investigations on the preparative electrolysis of **1a** in the presence of **I** began with the optimization of the reaction conditions. According to the aforementioned cyclic voltammetry studies, we found that the optimum conditions required included an RVC anode, water/acetonitrile (80/20 v/v) as the solvent, and sodium phosphate solution (0.2 M, pH 6) as the supporting electrolyte. In addition, 1.0 equivalent of **1a** and 1.0 equivalent of nucleophile **I** were a good reagent combination for this reaction. In the meantime, the anode potential was maintained at +0.17 V versus Ag/AgCl, which is at a potential for which **1a** could be oxidized to the corresponding *ortho*-benzoquinone form (**2a**) and vice versa within a reversible two-electron process. The continuously low concentration of the electrogenerated *ortho*-benzoquinone (**2a**), together with the large excess of **I**, promotes the Michael-type reaction at the expense of other side reactions and this intermolecular event seems to be much faster than the other side reactions.

The monitoring of electrolysis progress was carried out using cyclic voltammetry and the related voltammograms are shown in Fig. 2. Notably, proportional to the advancement of coulometry, A_1 decreased and its related cathodic peak (C_1) almost disappeared when the charge consumption became about four electrons per molecule of **1a**.

The aforementioned voltammetry and coulometry results allow us to propose the pathways shown in Scheme 1 for the electrooxidation of catechol **1a** in the presence of **I**. According to our results, it seems that following anodic oxidation of **1a** to *ortho*-benzoquinone (**2a**), an *intermolecular* Michael-type reaction of **I** with **2a** occurs and this reaction seems to occur much faster than other side reactions [26], leading to the formation of intermediate **3a**. The oxidation of **3a** is more convenient than the oxidation of the parent-starting molecule **1a** by virtue of the presence of an electron-donating group. Then, following the oxidation of **3a** to **4a**, an *intramolecular* Michael-type reaction occurs in a domino fashion to give **5a**. The over-oxidation of **5a** is precluded, because of insolubility of this compound. This compound is synthesized through an oxidative/*intermolecular* Michael-type addition/oxidative/*intramolecular* Michael-type addition ($ECEC_i$).

The electrochemical efficiency (EE) of this controlled-potential coulometry was simply calculated using the Faraday's law [28] and found to be ~96.0 % ($ECEC_i$ mechanism needs at least four electrons, $n = 4$ and 4F charge consumption per each mol of **1a**) (experimental proofs exist in Table 1). Under these reaction conditions, **5a** was obtained in a purified form with excellent EE and no extra purification was needed.

With a reliable set of conditions in hand, and in order to investigate the scope and generality of the developed procedure, we studied the electrochemically induced reaction

of **I** with some other catechols and hydroquinones bearing electron-withdrawing or electron-donating groups at the C-2, C-3, or C-4 positions. For the electrooxidation of 3-methylcatechol (**1b**), 3-methoxycatechol (**1c**), and hydroquinone (**1f**) in the presence of **I**, except reaction times and yields, other electrochemical investigations, including cyclic voltammetry and controlled potential coulometry, showed a behavior similar to that of **1a** and the reactions proceed in a manner similar to that of **1a** as depicted in Scheme 1. These sequential reactions led to the formation of novel compounds **5b, 5c**, and **5f** through the same one-pot four-step $ECEC_i$ mechanism in high yields and electrochemical efficiencies (Table 1). More interestingly, in contrast to the cases of **3a–c**, no further oxidations and subsequent heteroannulation reaction were observed in the cases of **3d**, **3e,** and **3g**, and these adducts were obtained as the final products in moderate yields. It is seen that, proportional to the increase of potential sweep rate, the height of peak C_1 of **1d** increases (see supporting information). On the other hand, a plot of peak current ratio (I_p^{C1}/I_p^{A1}) versus scan rate and the current function for peak A_1, ($I_p^{A1}/v^{1/2}$) for a mixture of **1d** and **I**, changes only slightly with the increasing scan rate and such behavior is adopted as indicative of an EC mechanism [18]. Monitoring of the progress of electrolysis was carried out by cyclic voltammetry (see supporting information). It is shown that, proportional to the progress of the coulometry, anodic peak A_1 decreases and disappears when the charge consumption becomes about $2e^-$ per molecule of **1d.**

In addition to insolubility of **3d**, **3e**, and **3g** in water/acetonitrile media, one can assume that the presence of a methyl or tert-butyl group at the C-4 position of these adducts would probably cause a steric inhibition of the accessibility of their C-4 position to the nucleophilic oxygen atom of the adjacent edaravone moiety and therefore, there is no possibility for the subsequent heteroannulation reaction to occur. These observations allow us to propose the pathway in Scheme 1 for the electrooxidation of **1d**, **1e**, and **1g** in the presence of **I**. These sequential reactions in Scheme 1 led to the formation of compounds **3d**, **3e**, and **3g** through the same one-pot two-step EC mechanism in yields and high electrochemical efficiencies (Table 1).

As it is clear from Scheme 1, there is an interesting regioselectivity in this one-pot sequential reaction affording a single regioisomer (**3d**, **3e**, **3g, 5b**, and **5c**). Also notably, the existence of a methyl or methoxy group at the C-3 position of **1b** or **1c** and a methyl, tert-butyl or nitro group at the C-4 position of **1d**, **1e**, and **1g** may have subtle effects on the reactivity of their relevant *ortho*-bezoquinones and would probably cause these Michael-type acceptors (**2b**, **2c**, **2d**, **2e,** and **2g** Scheme 1) to be attacked by **I** from the C-3, C-4, C-5, or C-6 positions. Because methyl, methoxy, and tert-butyl groups are electron-donating substituents, it seems that *ortho*-benzoquinones **2b**, **2c**, **2d**, and **2e** are more electropositive at C-5 position and therefore the 1,4-addition exclusively occurs at the more electrophilic carbon atom of the corresponding *ortho*-benzoquinones [11, 29]. So *ortho*-benzoquinones **2b**, **2c**, **2d,** and **2e** can be selectively attacked in all probability only at the C-5 position by **I** leading to the formation of intermediates **3b** and **3c** and final products **3d** and **3e** (Scheme 1), respectively. As depicted in Scheme 1, similar to that of **3a**, further oxidation of these intermediates (**3b**, **3c**) is followed by an *intramolecular* Michael-type reaction, which leads to the final products. Also *ortho*-benzoquinones **2e** is more electropositive at C-5 position and therefore the 1,4-addition exclusively occurs at the more electrophilic carbon atom of the corresponding *ortho*-benzoquinones [11, 29], thus leading to the formation of final product **3g**.

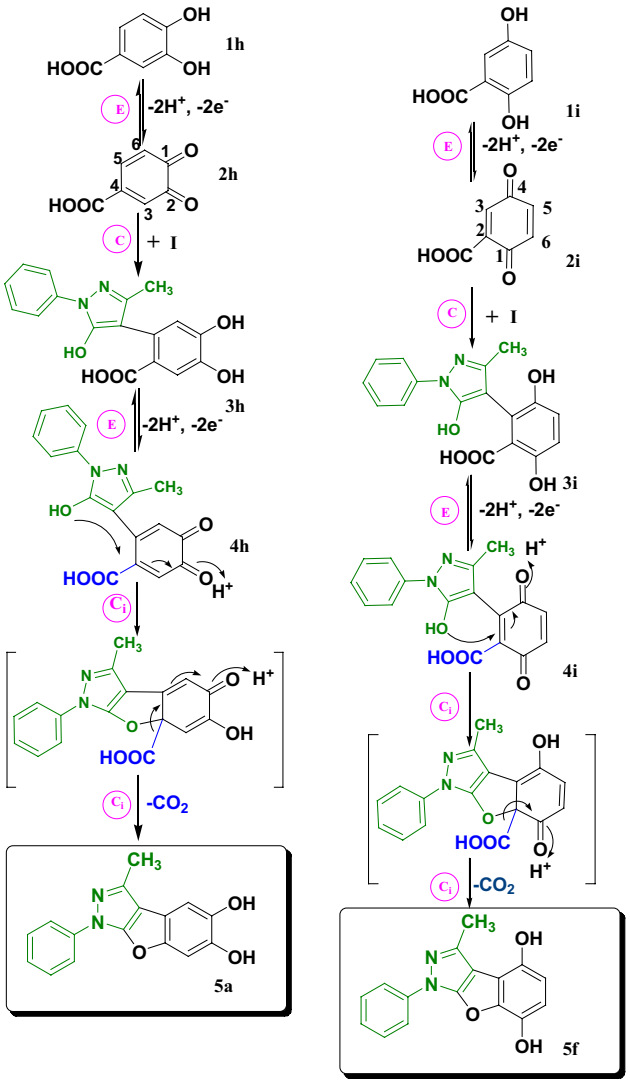
To distinguish the correct structure of single regioisomers, we utilize ^{1}H NMR, ^{13}C NMR, and MS spectroscopic techniques (see supporting information). There are some noticeable differences in the ^{1}H NMR, ^{13}C NMR and MS spectra for the possible structural features of regioisomers which can support the formation of **5b**, **5c**, **3d**, **3e** and **3g** regioisomers.

Oxidation of 3, 4-dihydroxybenzoic acid (**1h**) and 2, 5-dihydroxybenzoic acid (**1i**) with an electron- withdrawing group in the presence of **I** proceeds in a nearly different manner when compared to that of **1a–g**. Oxidation of **1h** to **2h** (Scheme 2), and subsequent *intermolecular* Michael addition reaction of **I** with **2h** (at the more electropositive C-5 position) leads to the formation of an adduct **3h** which is capable of undergoing further oxidation to yield an intermediate **4h**. An *intramolecular* 1, 4-addition (Michael) reaction in **4h** followed by an electro-decarboxylation process [28, 30, 31] can lead to the final product **5a** (Table 1).

As it can be seen, this unique sequential heteroannulation reaction of **1h** with **I** yields the same product **5a** obtained from the reaction of **1a** and **I**, but through a different mechanism $ECEC_iC_i$. In addition, the reaction of **1i** with **I** gives the same product **5f** obtained from the reaction of **1f** and **I.** The overall reactions are presented in Scheme 2.

Paired electrochemical synthesis of new edaravone derivative (5g)

The electrochemical study of 1 mM solution of 4-nitrocatechol (**1g**) in the aqueous phosphate buffer solution (0.2 M, pH 6.0), with a glassy carbon electrode has been conducted using cyclic voltammetry (Fig. 3, I). The voltammogram shows two cathodic peaks (C_1, C_3) and two anodic peaks (A_2, A_3) at −0.89, 0.33, 0.03, and 0.40 V versus Ag/AgCl. C_1 and A_2 peaks correspond to the reduction of



Scheme 2 A schematic representation of mechanisms for the electro-oxidation of **1h–i** in the presence of **I**

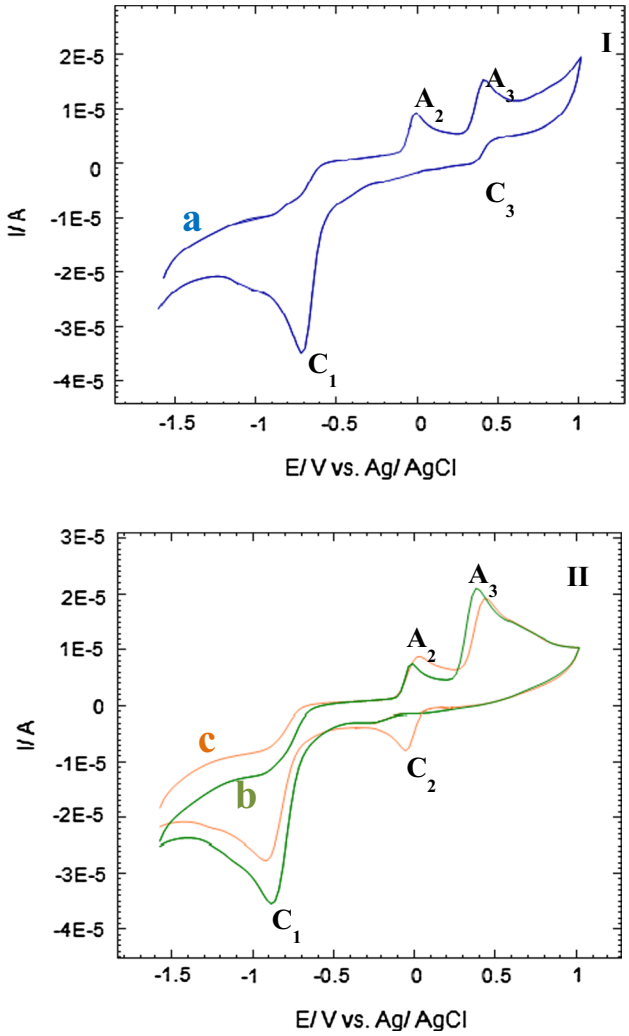
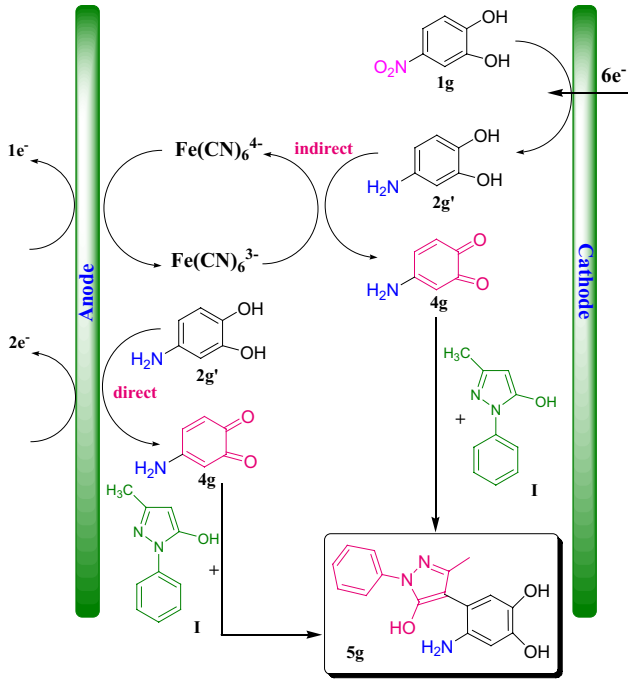


Fig. 3 **I** Cyclic voltammogram of 1 Mm of 4-nitrocatechol (**1g**) at the first scan (*a*); **II** multi-cyclic voltammograms of 1 mM of (**1g**) at the second (*b*) and third scan (*c*) with a glassy carbon electrode in sodium phosphate solution (0.2 M, pH 6); scan rate 100 mV s^{-1}; $T = 25 \pm 1$ °C

4-nitrocatechol (**1g**) to 4-aminocatechol (**2g′**) (Scheme 3) and oxidation of "*cathodically generated 4-aminocatechol* (**2g′**)" to 4-amino-*o*-benzoquinone (**4g**) (Scheme 3), respectively [14]. A_3 and C_3 peaks correspond to the oxidation of 4-nitrocatechol (**1g**) to 4-nitro-*o*-benzoquinone (**2g**) and reduction of 4-nitro-*o*-benzoquinone (**2g**) to 4-nitrocatechol (**1g**), (Scheme 1) (see supporting information), respectively. The multi-cyclic voltammogram (Fig. 3, II) shows that, parallel to the decrease in current of C_1, a new cathodic peak (C_2) appears at less negative potentials (-0.05 V). This new peak is related to the reduction of 4-amino-*o*- A_3 and C_3 peaks corresponding to the oxidation of 4-nitrocatechol (**1g**) to 4-nitro-*o*-benzoquinone (**2g**) and reduction of 4-nitro-*o*-benzoquinone (**2g**) to 4-nitrocatechol (**1g**), (Scheme 1) (see supporting information), respectively. The multi-cyclic voltammogram (Fig. 3, II) shows that, parallel to the decrease in current of C_1, a new cathodic peak (C_2) appears at less negative potentials (−0.05 V). This new peak is related to the reduction of 4-amino-*o*-benzoquinone (**4g**) to 4-aminocatechol (**2g′**). A peak current ratio (I_p^{C2}/I_p^{A2}) particularly during the repetitive recycling of potential is near unity; this can be considered as a criterion for the stability of 4-amino-*o*-benzoquinone (**4g**) produced at the surface of the electrode under the experimental conditions. In other words, hydroxylation or dimerization reaction is too slow to be observed on the time scale of cyclic voltammetry [32–36]. Controlled-potential coulometry was performed in a solution containing 1.0 mmol of 4-nitrocatechol (**1g**) at the potential of C_1 peak. Monitoring of the progress of electrolysis was carried out by cyclic voltammetry (Fig. 4). It is shown that, proportional to the advancement of coulometry,



Scheme 3 The total reactions in electrolytic cell for the formation of **5g** in the presence of ferrocyanide

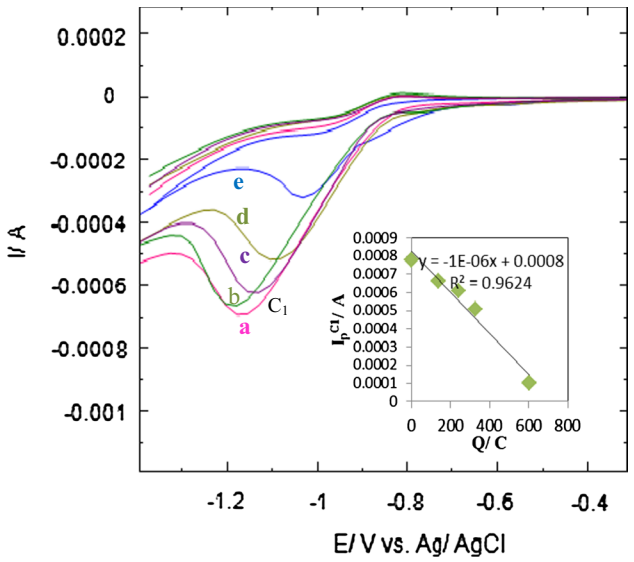


Fig. 4 Cyclic voltammograms of 1.0 mmol of **1g**, at a glassy carbon electrode during controlled potential coulometry at −0.89 V versus Ag/AgCl after consumption of *a* 0, *b* 140, *c* 240, *d* 330, and *e*, 605 C. Scan rate 100 mV s^{-1}; $T = 25 \pm 1$ °C; *inset* variation of peak current (Ip^{C1}) versus charge consumed

the height of C_1 decreases. The cathodic C_1 peak disappears when the charge consumption becomes about $6e^-$ per molecule of 1p (Fig. 4, inset). This number of electrons confirms the reduction of 4-nitrocatechol (**1g**) to 4-aminocatechol

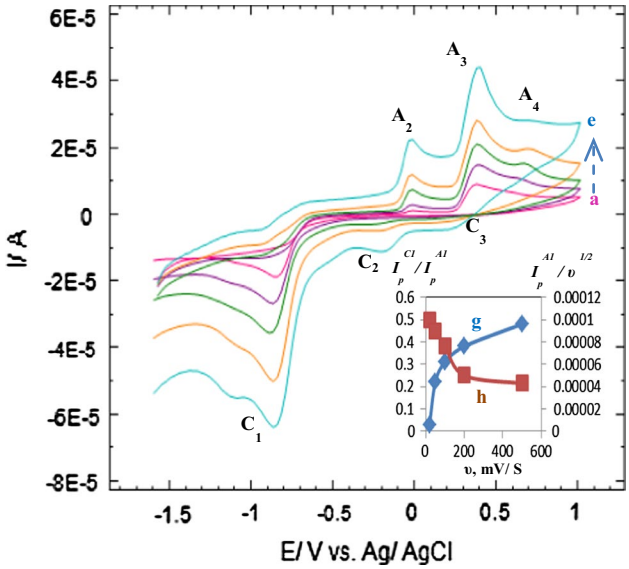


Fig. 5 Typical voltammograms of 1.0 mM of **1g** in the presence of 1.0 mM of **I** at various scan rates. Scan rates from *a* to *e* are 20, 50, 100, 200, 500 mV/s, respectively; *inset* (g) variation of peak current ratio (I_p^{C2}/I_p^{A2}) of 1 mM of **1g** in the presence of 1 mM of **I**; (h) Variation of peak current function ($I_p^{A2}/v^{1/2}$) of 1 mM of **1g** in the presence of 1 mM of **I** at a glassy carbon electrode in sodium phosphate solution (0.2 M, pH 6); scan rate: 100 mV s^{-1}; $T = 25 \pm 1$ °C

(**2g′**). The electrochemical behavior of 4-nitrocatechol (**1g**) in the presence of edaravone (**I**) was studied to some extent. Figure 5 shows the cyclic voltammograms obtained for a 1 mM solution of **1g** in the presence of 1 mM of **I**. The voltammograms exhibit three anodic peaks (A_2, A_3, and A_4) and three cathodic peaks (C_1, C_2 and C_3).

The new peaks (A_4) correspond to the oxidation of **5g** to its related *ortho*-benzoquinone. Furthermore, it is seen that, proportional to the increase of the potential sweep rate and in parallel with the decrease in height of C_3, the height of C_2 increases. In other words, the increase in the peak current ratio (I_p^{C2}/I_p^{A2}) versus scan rate (Fig. 5, inset, curve g) for a mixture of 4-nitrocatechol (**1g**) and edaravone (**I**) and the decrease in ($I_p^{A2}/v^{1/2}$) (Fig. 5, inset, curve h) confirms the reactivity of **2g′** towards **I**.

Preparative electrolyses to form **5g** performed in an aqueous solution of phosphate buffer (pH 6.0, *c* 0.2 M) containing 4-nitrocatechol (**1g**) and edaravone (**I**), at the potential of the cathodic peak C_1 (−0.89 V versus Ag/AgCl)) in an undivided cell led to the formation of **5g** in low yield. Attempts to increase the yield of **5g** directly have failed. The yield does not exceed 21 %, due to electrochemical oxidation of 4-nitrocatechol at the surface of the anode, and subsequent fast irreversible side reactions such as polymerization and/or oxidative ring cleavage [37–39].

In order to prevent oxidation of 4-nitrocatechol (**1g**) during electrolysis, we used an indirect method, mediated

by ferrocyanide ions ($Fe(CN)_6^{4-}$). A suitable mediator is a compound that oxidizes more convenient than 4-nitrocatechol (**1g**) without any side effect on **I**. Potassium ferrocyanide, K_4 $Fe(CN)_6$, is a stable, easily handled, and commercially available agent. The ferricyanide/ferrocyanide couple is used routinely by electrochemists as a stable (see supporting information) and simple model reaction and it is therefore important that its physical chemistry is well understood [40]. Scheme 3 shows the total reactions in electrolytic cell, in the presence of ferrocyanide. The indirect synthesis of **5g** mediated by ferrocyanide ions has also been successfully performed with good yield (Table 1).

In addition, the passivation that could be due to the amino-derivative during exhaustive electrolysis was not observed in this indirect method. According to our results, the oxidation of ferrocyanide ($Fe\ (CN)_6{}^{4-}$) in anode (counter electrode) prevents the oxidation of 4-nitrocatechol. Also, as shown in Scheme 3, the direct oxidation of 4-aminocatechol to its related *ortho*-quinone is possible.

Furthermore, it was seen that when the oxidation of 4-nitro catechol (**1g**) occurs at the first stage and reduction of 4-nitro catechol (**1g**) occurs at the second stage, that is, obtained when the starting potential was maintained at +0.20 V, the **3g** product was formed. In contrast, when the reduction of 4-nitro catechol (**1g**) occurs at the first stage and oxidation of 4-nitro catechol (**1g**) occurs at the second stage, that is, obtained when the starting potential was maintained at −0.89 V, the **5g** product was formed (see supporting information).

Conclusions

In conclusion, we have discovered an easy and one-pot electrochemical method for the synthesis of new edaravones in high yield and purity, using this environmentally friendly method with high atom economy. In addition, to improve synthetic procedures of these compounds, this present work has led to the development of a facile paired electrochemical method for synthesis of new edaravone derivatives in high EE and good yields.

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