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, ECECi, and ECECiC 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, ¹H NMR, ¹³C NMR, and MS.

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

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 O₂ 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, ECECl, and ECECiCi 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 was used in controlled-potential coulometry and bulk electrolysis (using an electronic potentiostat) an assembly of four rods of graphite electrodes, 6 mm in diameter, and ~10 cm in length, and a reticulated vitreous carbon (RVC electrode) constituted the counter electrode. The working electrode potentials were measured versus Ag/AgCl. 1H and 13C 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). 1H 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 (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, 1H NMR, 13C NMR, and MS. The final products

| Catechols | Peak potentials (V)ᵇ | Peak potentials (V)ᶜ | Applied potential at carbon rodsᵈ | Product | EE/Yield⁽⁶⁾ (%) | Solvent (CH₃CN/H₂O) |
|-----------|----------------------|----------------------|----------------------------------|--------|----------------|-------------------|
| 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             |
| 1h        | −0.89 −0.89          | −1.1 −1.1            | −0.89                            | 5g     | 78/89          | 20/80             |
| 1i        | 0.3323 0.2346        | 0.4544 −0.2291       | +0.13                            | 5a     | 86/84          | 10/90             |

ᵃ Cyclic voltammetry measurements were performed in phosphate buffer solution (0.2 M, pH 6) and CH₃CN, with glassy carbon (GC) as working electrode; scan rate 100 mVs. 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 CH₃CN, at carbon rods; reference electrode: Ag/AgCl
⁵ Calculated using the Faraday’s law
⁶ Isolated yields
were obtained in a purified form and no extra purification was needed.

**Compound (5a)**

Light tan solid; m.p = 233 °C; 1H NMR (400 MHz, DMSO-d6) δ (ppm): 2.89 (s, 3H, CH3), 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); 13C NMR (100 MHz, DMSO-d6) 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, 1157, 725, 689; MS (EI): m/z calcd for C16H12N2O3: 280.0848; found: 280.

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

Light tan solid; m.p = 233 °C; 1H NMR (400 MHz, DMSO-d6) δ (ppm): 2.89 (s, 3H, CH3), 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); 13C NMR (100 MHz, DMSO-d6) 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 C16H12N2O3: 280.0848; found: 280.

**Compound (5b)**

Light brown solid; m.p = 242 °C (decomposed); 1H NMR (400 MHz, DMSO-d6) δ (ppm): 1.96 (s, 3H, CH3), 2.26 (s, 3H, CH3), 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); 13C NMR (100 MHz, DMSO-d6) 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 C16H12N2O3: 294.10052; found: 294.

**Compound (5c)**

Amorphous brown solid; m.p = 210 °C (decomposed); 1H NMR (400 MHz, DMSO-d6) δ (ppm): 2.13 (s, 3H, CH3), 3.73 (s, 3H, CH3), 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); 13C NMR (100 MHz, DMSO-d6) 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 C17H14N2O4: 310.09542; found: 310.

**Compound (5d)**

Light gray solid; m.p = 266 °C (decomposed); 1H NMR (400 MHz, DMSO-d6) δ (ppm): 1.97 (s, 3H, CH3), 2.09 (s, 3H, CH3), 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); 13C NMR (100 MHz, DMSO-d6) 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 C17H14N2O4: 296.11618; found: 296.

**Compound (5e)**

Light tan solid; m.p = 235 °C (decomposed); 1H NMR (400 MHz, DMSO-d6) δ (ppm): 1.26 (s, 9H, 3CH3), 1.91 (s, 3H, CH3), 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); \(^{13}\text{C}\) NMR (100 MHz, DMSO-d\(_6\)) \(\delta\) (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) \(\nu\) (cm\(^{-1}\)): 692, 784, 1094, 1498, 1556, 1866, 2960; MS (EI): \(m/z\) calcd for C\(_{17}\)H\(_{16}\)N\(_2\)O\(_3\): 338.16316; found: 329.11145; found: 327.

**Compound (3g)**

Dark brown solid; m.p = 279 °C (decomposed); \(^1\text{H}\) NMR (400 MHz, DMSO-d\(_6\)) \(\delta\) (ppm): 1.90 (s, 3H, CH\(_3\)), 5.37 (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); \(^{13}\text{C}\) NMR (100 MHz, DMSO-d\(_6\)) \(\delta\) (ppm): 12.79, 117.78, 118.97, 120.50, 122.23, 126.78, 128.26, 129.06, 129.51, 137.28, 141.44, 145.47, 146.91, 154.96, 157.53; IR (neat) \(\nu\) (cm\(^{-1}\)): 692, 756, 1077, 1364, 1458, 1564, 1594, 2855, 2926, 3065; HRMS (EI): \(m/z\) calcd for C\(_{16}\)H\(_{15}\)N\(_3\)O\(_5\): 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. An aqueous solution of phosphate buffer (50 mL, pH \(\approx\) 6) in the absence of sodium phosphate, \(\text{pH} = 6\), 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 \((I_{\text{C}}^\text{a}/I_{\text{A}}^\text{a})\) 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.

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 ortho-benzoquinone 2a toward I and the formation of Michael adduct through an interfacial reaction at the electrode interface.
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 (A2 peak) at 0.429 V versus Ag/AgCl.

Edaravone (I) is an 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 (C1). As a result, the reactivity of 2a towards I can be monitored as an increase in the height of the cathodic peak C1 at higher scan rates. The cyclic voltammograms 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_{pC1}/I_{pA1}) versus scan rate for a mixture of 1a and I, which is an increase in the height of the cathodic peak C1 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 A1 peak, (I_{pA1}/v^{1/2}), decreased and such behavior is adopted as indicative of an ECEC_{1} 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_{pC1}/I_{pA1})
versus scan rate for a mixture of 1a and I and the current function for the anodic A1 peak (I_a/(I_p^1/2)) are different from a plot of peak current ratio (I_p^1/2/I_p^1) versus scan rate and the current function for the anodic A1 peak, (I_p^1/2/I_p^1) 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, A1 decreased and its related cathodic peak (C1) 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/intramolecular Michael-type addition/oxidative/intramolecular Michael-type addition (ECEC).

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, 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 ECECi 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 C1 of 1d increases (see supporting information). On the other hand, a plot of peak current ratio (I\text{C1}/I\text{A1}) versus scan rate and the current function for peak A1, (I\text{A1}/v\text{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. 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 A1 decreases (see supporting information). 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 intramolecular 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 can lead to the final product 5a (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-benzoquinones and would probably cause these Michael-type acceptors (2b, 2c, 2d, 2e, and 2g) 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 1H NMR, 13C NMR, and MS spectroscopic techniques (see supporting information). There are some noticeable differences in the 1H NMR, 13C 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 can lead to the final product 5a (Table 1).

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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 (C1, C3) and two anodic peaks (A2, A3) at −0.89, 0.33, 0.03, and 0.40 V versus Ag/AgCl. C1 and A2 peaks correspond to the reduction of
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]. A3 and C3 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 C1, a new cathodic peak (C2) 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 ($I_{pC2}/I_{pA2}$) 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 C1 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,
the height of $C_1$ decreases. The cathodic $C_1$ peak disappears when the charge consumption becomes about 6 e$^{-}$ per mole-
cule of $1p$ (Fig. 4, inset). This number of electrons confirms
the reduction of 4-nitrocatechol ($1g$) to 4-aminocatechol
($2g'$). 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 cur-
rent ratio ($I_{pC2}/I_{pA2}$) versus scan rate (Fig. 5, inset, curve g)
for a mixture of 4-nitrocatechol ($1g$) and edaravone ($I$) and
the decrease in ($I_{pA2}/\sqrt{v}$) (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 electro-
chemical 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)$_6^{3-}$). 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 ferrocyanide/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 reaction 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-amino-nocatechol 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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