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Electrochemical characterization of bioactive hydroxyxanthones by cyclic voltammetry

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ABSTRACT

The present study reports the electrochemical behavior of several phenolic and catecholic-substituted 2,3-diarylxanthones on a glassy carbon electrode, challenged by cyclic voltammetry at different pH values (4.0, 7.4, and 11.0). Higher pH values required lower anodic and cathodic peak voltages. The oxidation of catecholic groups occurred at lower peak potentials in a reversible and pH dependent manner. Anodic peak potentials appeared at higher pH values and were attributed to the electrochemically irreversible oxidation of the phenolic groups. The number and position of hydroxyl substituents were the determinants for the electrochemical behavior and found to correlate with the scavenging activity for reactive oxygen (ROS) and nitrogen species (RNS). A xanthone with two catechol units presented the lowest anodic potential voltage (E_{pa} = 0.15 V) and proved to be the most effective ROS and RNS scavenger.

Xanthones are redox-active compounds with a tricyclic scaffold, identified in some higher plants, with most of the derivatives restricted to the *Guttiferae* and *Gentianaceae* families. Several derivatives can also be isolated from a variety of fungi and lichens.[1] These compounds are highly diverse in their chemical structure, including simple oxygenated and prenylated substituents, or appearing as more complex frameworks as xanthonolignoids or bis-xanthones.[1,2] Naturally occurring analogues exhibit several biological and pharmacological properties such as anti-allergic, anti-inflammatory, antimalarial, antimicrobial, and antitumour activities and also play an important role in the inhibition of several enzymes.[3]

Studies on the antioxidant activity of both natural and synthetic xanthones have provided interesting results, including: (i) scavenging activity against reactive oxygen species (ROS) and reactive nitrogen species (RNS), (ii) inhibition of pro-oxidant enzymes, and (iii) metal chelating capacity.[3–5] Structure/activity studies of phenolic compounds revealed that the number and position of hydroxyl substituents in their skeleton are features of great importance for a high antioxidant activity.[6]

In a previous work, concerning the putative scavenging effects of several hydroxylated xanthones against ROS and RNS, it was demonstrated that compounds with a catechol motif were the most effective scavengers, in some cases being more active than natural xanthones.[7,8] In other chemical assays, involving human blood LDL and human skin keratinocytes, we could also establish structure–activity relationships.[9] From these studies, it may be predicted that the investigation of the redox potential of hydroxylated xanthones can provide valuable insights into the pharmacological properties of these molecules.

Electrochemical methodologies have been successfully used to establish correlations between structure, oxidation potential, and biological activity of electroactive species. Their operating simplicity, higher sensitivity, short time of analysis, and lower reagent consuming as well as lower costs are some advantages presented by these techniques compared with chromatographic or spectroscopic methods.[10,11] Thus cyclic voltammetry (CV) has become an important and widely used electroanalytical technique in many relevant studies of redox processes, in organic and inorganic chemistry, to clarify the electrochemical behavior of complex chemical and biochemical systems, and to obtain information about all types of interfacial processes depending on electrochemical currents.[12] The aim of the present study is to study the electrochemical

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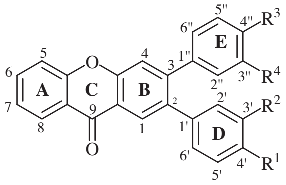


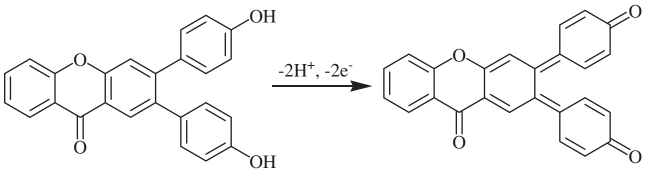
Compound	R^1	R^2	R^3	R^4	E_p (V) *versus* Ag/AgCl pH 4.0			pH 7.4			pH 11.0		
					E_{p1a}	E_{p2a}	E_{pc}	E_{p1a}	E_{p2a}	E_{pc}	E_{p1a}	E_{p2a}	E_{pc}
XH1	H	H	H	H	-	-	-	-	-	-	-	-	-
XH2	OH	H	H	H	-	0.84	-	-	0.58	-	-	0.38	-
XH3	OH	OH	H	H	0.42	-	0.27	0.16	-	0.12	-0.04	-	-0.07
XH4	H	H	OH	H	-	0.87	-	-	0.64	-	-	0.40	-
XH5	OH	H	OH	H	-	0.84	-	-	0.56	-	-	0.37	-
XH6	OH	OH	OH	H	0.42	0.96	-0.18	0.16	0.69	-0.12	0.00	0.51	-0.08
XH7	H	H	OH	OH	0.41	-	0.34	0.18	-	0.14	-0.01	-	-0.05
XH8	OH	H	OH	OH	0.44	0.93	-0.07	0.18	0.65	-0.11	0.04	0.37	-0.03
XH9	OH	OH	OH	OH	0.48	-	0.19	0.15	0.37	-0.06	-0.08	0.12	-0.12

Scheme 1. Chemical structures and anodic and cathodic potentials of 2,3-diarylxanthones **XH1**–**XH9**.

behavior of a group of phenolic and catecholic-substituted 2,3-diarylxanthones[13] (Scheme 1), in aqueous solution, by cyclic voltammetry,[14] and compare the obtained results with their scavenging activities for ROS and RNS.

In order to simulate the physiological conditions, the cyclic voltammograms were performed at pH 7.4 (sodium phosphate). Assays were also performed under acidic and basic conditions, using acetate (pH 4.0) and carbonate–bicarbonate (pH 11.0) buffers, respectively. The study on the electrochemical behavior of xanthone **XH1** was limited by its solubility, which only permitted a final concentration of 0.05 mM, and no detectable peaks were found in the cyclic voltammograms, for all tested pH values (Scheme 1). This limitation did not allow to investigate the influence of the 2,3-diphenylxanthone motif in the electrochemical behavior of the studied xanthones **XH2**–**XH9**. Masek et al.[15] performed the cyclic voltammogram of the parent xanthone at 1 mM and detected three oxidation peaks. In that study, the cyclic voltammogram of the parent flavone at 1 mM showed two oxidation peaks with higher potential values. These results indicate that the xanthone oxidation occurs at lower oxidation potentials, compared to the flavone, an important feature to enhance the well-documented antioxidant ability of xanthone-type compounds.[4,5]

By increasing pH values, the anodic and cathodic peak voltages of hydroxylated xanthones **XH2**–**XH9** decrease, similarly to that reported by other authors for several phenolic compounds.[16–19] At pH 7.4, compounds **XH2** and **XH4** (final concentration of 0.05 mM) presented voltammograms with a single irreversible oxidation peak at 0.58 V and 0.64 V, respectively (Scheme 1). The cyclic voltammetric profile of these compounds is similar to that observed in *para*-substituted flavonoids. In fact, genistein, a 4′-hydroxyisoflavone, has a comparable oxidation peak (0.51 V) with that of **XH2** and apigenin, the corresponding 4′-hydroxyflavone, presented the same oxidation peak (0.64 V) of **XH4** at pH 7.4 versus Ag/AgCl.[20] Cyclic voltammograms of several hydroxybenzoic and hydroxycinnamic acids also presented single anodic peaks at higher potentials and the absence of a cathodic peak in the reverse scan.[21] Moreover, the rapid decrease of the oxidation peak after multiple cyclic scans, without polishing the electrode between the cycles, clearly indicates that **XH2** and **XH4** products adsorb on the surface, blocking the diffusion process and their oxidation in the working surface electrode. Interestingly, derivative **XH5** (two *para*-phenolic groups) undergoes only one irreversible oxidation peak (0.56 V), with a lower potential compared to analogues **XH2** and **XH4**, indicating that the two phenolic groups were oxidized at the same potential. We can suggest that compound **XH5** can be oxidized to a quinoide structure and, due to their instable nature, it decomposes in the voltammetric cell, making it difficult to observe the reduction peak (Scheme 2).



Scheme 2. Proposed oxidation of xanthone **XH5** in phosphate buffer pH 7.4.

Cyclic voltammograms of the other derivatives **XH3** and **XH6**–**XH9** showed reversible oxidation peaks from 0.15 to 0.18 V, corresponding to the catechol unit (3,4-dihydroxyphenyl substituent) oxidation (Fig. 1). This lower electrochemical anodic peak (generally lower than 0.50 V) has already been reported in the flavonoid family on a glassy carbon electrode at neutral pH versus Ag/AgCl.[10,21–23] The results suggest that the D-catechol unit of the studied xanthones is more susceptible to oxidation than the E-catechol moiety. Thus, compound **XH3** (D-catechol, $E_{p1a} = 0.16$ V) presented a lower oxidation peak than compound **XH7** (E-catechol, $E_{p1a} = 0.18$ V) and the same is observed for compounds **XH6** and **XH8** ($E_{p1a} = 0.16$ V and 0.18 V, respectively). Of note, compound **XH9** (two catechol groups) showed the lowest potential oxidation peak at 0.15 V (Scheme 1). Such low oxidation potential and their effectiveness to donate hydrogen atoms, make **XH9** a highly potent antioxidant with the most powerful reducing ability.[24] In this regard, it is shown that, among all the xanthones under study, **XH9** is the only derivative which can repair the α-tocopheroxyl radical thereby restoring α-tocopherol.[8] Overall, these results are consistent with our previous studies on the electrochemical behavior of flavones and 2-styrylchromones, indicating that a higher number of hydroxyl groups correspond to a lower anodic potential peak of the catechol unit.[25]

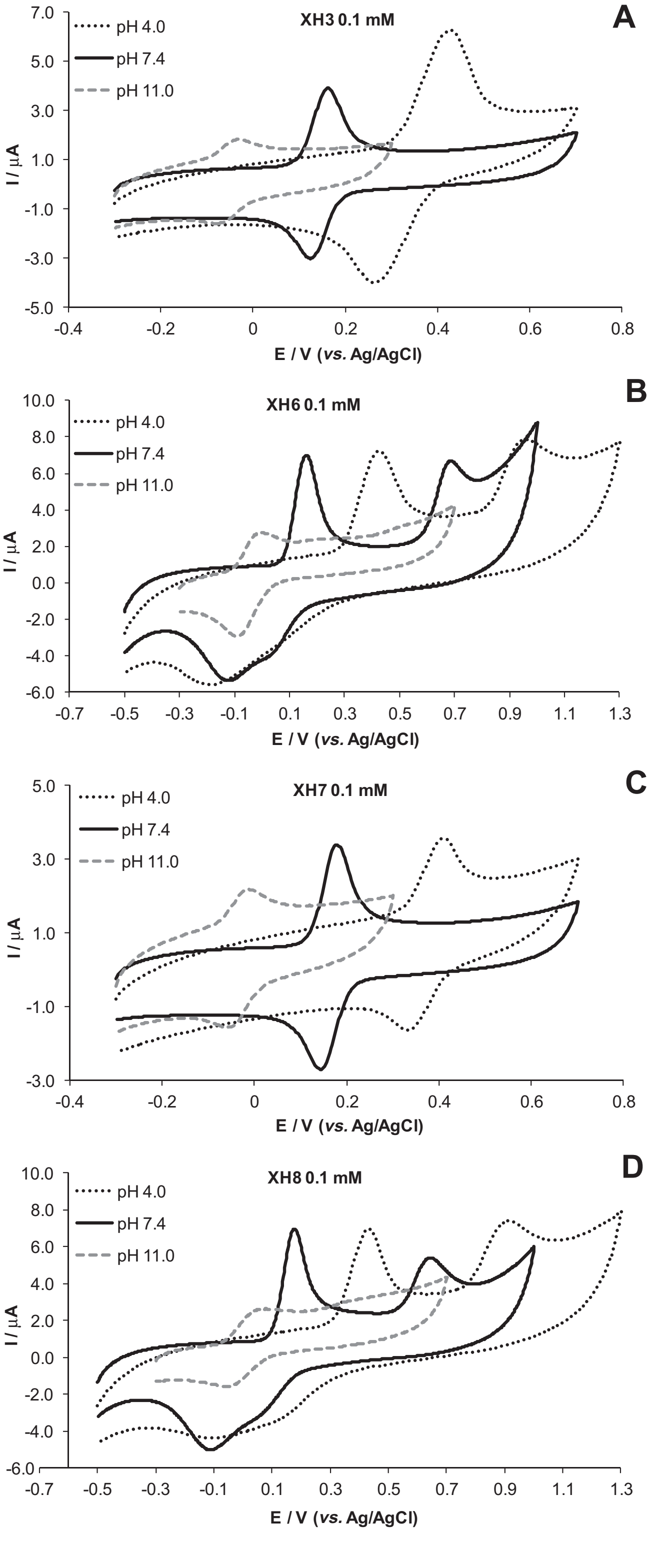


Figure 1. Cyclic voltammograms of compounds **XH3** (A), **XH6** (B), **XH7** (C), and **XH8** (D) 0.1 mM at pH 4.0, 7.4 and 11.0. Scan rate 100 mV s^{-1}.

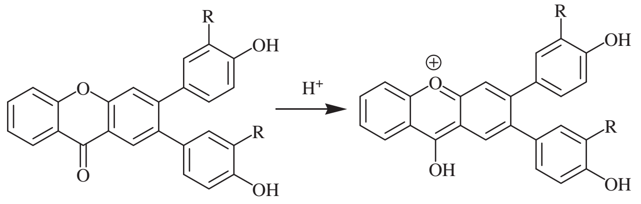
A second peak has been identified for derivatives **XH6** (E_{p2a} = 0.69 V) and **XH8** (E_{p2a} = 0.65 V), corresponding to oxidation of the *para*-phenol unit. Taking into account the results already discussed for **XH2** and **XH4** and the lower potential value of **XH8** comparing with the analogue **XH6**, it may be postulated that the oxidation of the D-phenol is more favorable than the E-phenol. The second oxidation peak of **XH9** presented the lowest potential at 0.37 V (Scheme 1). In fact, the two peaks of this molecule can be associated with the two oxidation centers and can be correlated with the analogues **XH3** and **XH7**. The lower anodic peak of **XH3** (E_{p1a} = 0.16 V) compared with that of **XH7** (E_{p1a} = 0.18 V) supports our postulate that the first peak of xanthone **XH9** corresponds to the D-catechol unit oxidation (E_{p1a} = 0.15 V) and the second peak corresponds to the E-catechol oxidation. However, Born et al.[26] in their voltammetric studies of verbascoside, a compound also bearing two catechol moieties, concluded that these units oxidize at the same anodic potential (E_{pa} = 0.19 V), at pH 7.4 versus Ag/AgCl. They could not establish a correspondence between the catechol oxidation and the oxidation products. In the same work, the catechol oxidation potential of two natural *ortho*-dihydroxyxanthones, mangiferin (E_{pa} = 0.32 V) and 1,3,6,7-tetrahydroxyxanthone (E_{pa} = 0.28 V) presented higher values than the *ortho*-dihydroxyxanthones **XH3** and **XH6**–**XH9**, leading us to consider that our studied synthetic xanthones have structural features for promising antioxidant applications.[26]

A defined cathodic peak can be observed in the cyclic voltammograms of compounds **XH3** and **XH6**–**XH9**, pointing to the reversibility of the oxidation of these catecholic compounds. Electrochemical reduction of compounds **XH3** and **XH6** is measured at lower potential values than their analogues **XH7** and **XH8**, respectively, suggesting once more that the redox reaction occurs easier in the presence of a D-catechol unit compared to a E-catechol unit.

Analysis of the electrochemical parameters of the tested xanthones showed a similar behavior at pH 11.0, in comparison to those discussed at pH 7.4 (Scheme 1). The defined oxidation peak of compound **XH2** presented a similar (although lower) potential value (E_{p2a} = 0.38 V) than the analogue **XH4** (E_{p2a} = 0.40 V), and derivative **XH5** presented a lower anodic peak at 0.37 V. The low intensity current peaks (from −0.08 to 0.04 V) presented in the cyclic voltammograms of compounds **XH3**, **XH6**–**XH9** may be ascribed to the catechol unit oxidation, at pH 11.0 versus Ag/AgCl (Fig. 1). Indeed, the electrochemical studies of quercetin and catechin referred anodic potentials at 0.07 and 0.23 V, respectively, at pH 8.0.[17] At the same pH, other authors observed a lower anodic potential of catechin at 0.16 V.[23] On the other hand and as expected, the oxidation peak of quercetin is shifted toward a less positive potential at 0.10 V, raising the pH at 9.0.[27] The second anodic peak is less pronounced and attributed to the oxidation of the *para*-phenol group of compounds **XH6** and **XH8** (Fig. 1). At pH 11.0, the highest catechol group oxidation peak was observed for compound **XH9** at 0.12 V.[8] Curiously, this compound exhibited two oxidation peaks, while hematoxylin, an important bioactive flavonoid having also two catechol units, presented only one anodic peak, both in acidic and basic pH values.[18]

No detectable reduction peaks were observed in the cyclic voltammograms of compounds **XH2**, **XH4**, and **XH5**, at pH 11.0 suggesting that the oxidation products undergo further irreversible chemical reactions. The cathodic signals of compounds **XH3**, **XH6**–**XH9** are probably due to the catechol moiety and displayed reduction potential values of −0.12 to −0.03 V (Scheme 1). Interestingly, it may be noted that a similar value of the reduction potential of **XH9** at pH 11 was estimated by a fast kinetic spectroscopy from the equilibrium observed during the electron transfer reaction between the Trolox® radical and the ionized **XH9** species.[8]

Further electrochemical studies were performed in the acidic medium at pH 4.0 and a decrease in the pH value led to an increase of both oxidation and reduction peak voltages (Scheme 1). A distinct lower anodic peak observed at 0.41–0.48 V may be attributed to the catechol group oxidation of compounds **XH3**, **XH6**–**XH9**. These results are in agreement with the work developed by Kilmartin et al.[28] where cyclic voltammetry was used to characterize the antioxidant properties of phenolic compounds commonly



Scheme 3. Protonation of xanthones under acidic conditions.

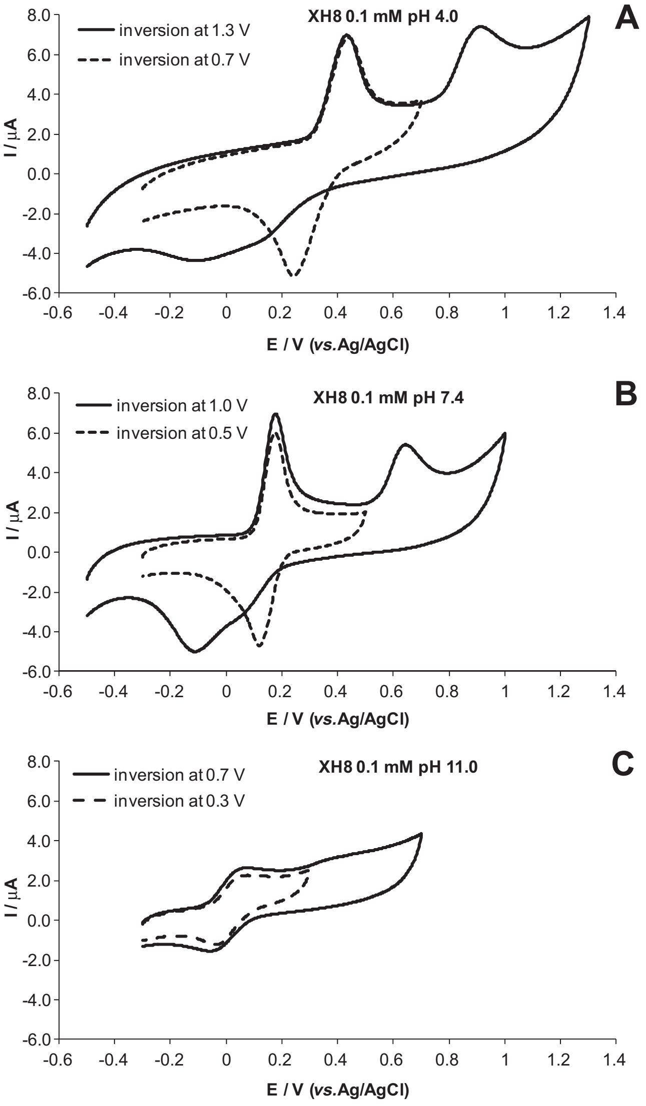


Figure 2. Cyclic voltammograms of compound **XH8** 0.1 mM: A (–) scan inversion at 1.3 V; (–) scan inversion at 0.7 V, pH 4.0. B (–) scan inversion at 1.0 V; (–) scan inversion at 0.6 V, pH 7.4. C (–) scan inversion at 0.7 V; (–) scan inversion at 0.3 V, pH 11.0. Scan rate 100 mV s^{-1}.

found in wines, in model wine solutions at pH 3.6. Phenolic antioxidants with a catechol moiety in their structure exhibited oxidation peaks in the 0.36–0.47 V range. This study involved phenolic acids and flavonoids as caffeic and gallic acids, catechin and quercetin, with rutin presenting the higher potential value at about 0.47 V. Similar potential values were obtained by other authors in the electrochemical oxidation of rutin, in acidic medium.[29–31] Contrary to the results discussed before, at pH 4.0 the anodic potential of compound **XH3** (E_{p1a} = 0.42 V) was higher than the analogue **XH7** (E_{p1a} = 0.41 V). This result can be explained by the xanthone carbonyl group protonation, under acid conditions, and the disappearance of the mesomeric stabilization effect of the heterocyclic oxygen atom on the D-ring phenoxyl radicals (Scheme 3).

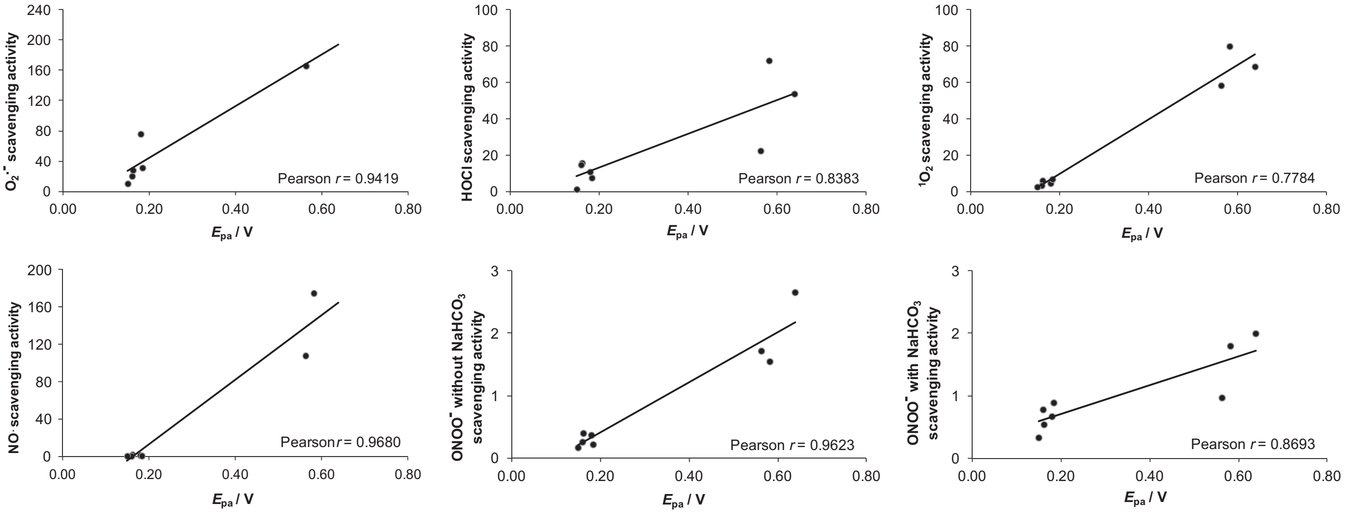
The anodic peak detected at higher potentials (from 0.84 to 0.96 V) may be ascribed to the *para*-phenol group oxidation (**XH2**, **XH4**–**XH6**, and **XH8**). *p*-Coumaric acid, a *para*-substituted cinnamic acid, presented a barely defined oxidation peak at 0.86 V[28,32] whereas 4′-hydroxyflavone and 4′-hydroxyisoflavone derivatives presented the same cyclic voltammogram profile.[21] In addition, the isoflavonoid genistein presented a lower potential value (E_{pa} = 0.80 V) than the flavonoid apigenin (E_{pa} = 0.87 V) [20] and a similar relationship is found in the anodic potentials of xanthones **XH2** and **XH4** (E_{pa} = 0.84 and 0.87 V, respectively), indicating that the D-phenol oxidation is more favorable than the E-phenol, at pH 4.0 versus Ag/AgCl. The presence of two phenolic groups in the xanthone core (**XH5**) provides a single anodic peak, at 0.84 V (Scheme 1).

The absence of a cathodic peak in the cyclic voltammogram of *para*-phenolic derivatives **XH2**, **XH4**, and **XH5** points to the irreversibility of the oxidation process (Scheme 1). This fact can be explained by subsequent oxidation chemical reactions or by the impossibility of these molecules to be reduced at the glassy carbon electrode.[28] The well-defined cathodic peak of xanthones **XH3** and **XH6**–**XH9** varies depending on the position of the catechol moiety in the xanthone core. The D-catechol derivatives were found to present lower reduction peak values (**XH3**, E_{pc} = 0.27 V; **XH6**, E_{pc} = −0.18 V) than the E-catechol analogues (**XH7**, E_{pc} = 0.34 V; **XH6**, E_{pc} = −0.07 V).

The electrochemical reactions of xanthones **XH1**–**XH9** were further studied for various scan rates from 0.01 to 0.2 V s^{-1}, recording the change of the peak current (I_p) and the potential peak values (E_{pa}), at pH 4.0, 7.4, and 11.0. Generally, by increasing the scan rate value, there was an increase in the oxidation peak current and a decrease in the reduction peak current. The absence of a cathodic peak already mentioned and the referred I_{pa} dependence with scan rate, indicates that compounds **XH2**, **XH4**, and **XH5** undergo an irreversible electron transfer mechanism in the glassy carbon electrode surface.[33]

The mechanism of the redox process can also be estimated by the ratio between the cathodic and anodic peak currents (I_{pa}/I_{pc}) as well as by the peak potential separation (ΔE_p).[33–35] After a detailed observation of figure 1A and 1C we can conclude that the peak current ratio (I_{pa}/I_{pc}) tends to be closer to the unit for compounds **XH3** and **XH7** showing a complete electrochemical reversible process, for all studied pH values.[35] For compounds **XH6** and **XH8**, it was not possible to determine the I_{pa}/I_{pc} ratio along with the scan rate interval probably due to the existence of a poorly defined reduction peak which stands in the same voltage of the lower cathodic peak. Meanwhile, when the potential scan of derivatives **XH6** and **XH8** was inverted before the second oxidation peak the voltammograms showed clear electroreduction peaks ($I_{pa}/I_{pc} \approx 1$) (example in Fig. 2).

Considering the electrochemical behavior of xanthones **XH3** and **XH7** regarding the peak potential separation (ΔE_p), one could observe that for pH 7.4 and 11.0, the E_{pc}–E_{pa} values ~30–35 mV point to the involvement of two-electrons in the oxidation reaction on the glassy carbon electrode. The results suggest that the catechol moiety of the xanthone core is implied in a two-electron two-proton redox process, leading to the formation of *ortho*-quinone-type intermediates.[36] In acidic medium, the separation of the redox peak potentials ΔE_p was 66 mV and 159 mV for **XH7** and **XH3**, respectively. We can postulate that the mechanism behind the oxidation of **XH7** involves the formation of a semiquinone intermediate which suffers disproportionation with formation of the *ortho*-quinone derivative and simultaneous regeneration of



Scheme 4. Correlations between the E_{pa} at pH 7.4 and the scavenging activity against ROS and RNS of hydroxy-2,3-diarylxanthones **XH2**–**XH9**.

XH7. These results are consistent with our previous report on the oxidation mechanism of 2-styrylchromones possessing a catechol moiety.[25]

When the potential scan was inverted before the second oxidation peak, the ΔE_p value of xanthones **XH6** and **XH8** at pH 7.4 and 11.0 decreased to approximately ~52–54 mV, corresponding to one-electron oxidation. Slightly changes occurred at pH 4.0 showing high ΔE_p values.

Based on the postulate that the electrochemical behavior of phenolic compounds is related to their antioxidant capacity,[25–27,37] the comparison between the oxidation potentials under physiological conditions (pH 7.4) and the scavenging activity against ROS and RNS of the hydroxy-2,3-diarylxanthones **XH2**–**XH9** is of great importance. In a previous work, we evaluated the scavenging activity of the hydroxy-2,3-diarylxanthones **XH2**–**XH9** against several ROS, including superoxide radical ($O_2^{\cdot-}$), hypochlorous acid (HOCl), and singlet oxygen ($^1O_2$) and RNS, including nitric oxide (·NO) and peroxynitrite anion ($ONOO^-$).[7]

Generally, the scavenging effect was related to the number and position of the hydroxyl substituents on the D- and E-rings of the xanthone core. In addition, compounds with a catechol motif presented a considerably higher effect than those lacking this structural feature as it can be confirmed by the IC_{50} values. In the present work, the correlations between the E_{pa} of the first peak at pH 7.4 and the scavenging activity against ROS and RNS by hydroxy-2,3-diarylxanthones **XH2**–**XH9** were studied by the Pearson correlation test (Scheme 4). Xanthones with lower oxidation potential values possess higher scavenging effects and the presence of a catechol group is an important structural feature for the antioxidant activity. Indeed, **XH9**, a xanthone with two catechol units, presented the lowest anodic potential voltage (E_{pa} = 0.15 V) and proved to be the most effective scavenger for all the ROS and RNS tested (Scheme 4). Excellent correlations are observed for $O_2^{\cdot-}$, ·NO, and $ONOO^-$, as expected for scavenging reactions involving electron transfer mechanisms. Significant correlations are also found for HOCl and $^1O_2$, the highly reactive oxygen species which are known for scavenging mechanisms involving structural features.[38]

In conclusion, the cyclic voltammetric study allowed the electrochemical characterization of a group of hydroxy-2,3-diarylxanthones, in aqueous solution. Increases in the pH value led to a decrease in the anodic and cathodic peak voltages. Furthermore, the increase of the scan rate value promoted an increase in the anodic peak currents and a decrease in the cathodic peak currents. Cyclic voltammograms of compounds **XH3**, **XH6**–**XH9** showed the permanent presence of a low oxidation peak attributed to the oxidation of the catechol group. The oxidation peak at higher potential values can be attributed to the phenolic groups. The electrochemical oxidation of **XH3** and **XH7** occurred in a complete reversible process, the number of electrons involved in the reaction being dependent on the structure and the pH. The lower oxidation potentials of the hydroxy-2,3-diarylxanthones, when compared with structurally related phenolic compounds, the correlations obtained between these potentials and the scavenging ability, are good and direct indicators for the promising antioxidant properties claimed by these molecules.

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13. Xanthones **XH1**–**XH9** were synthesized according to previously reported procedures. See: Santos, C. M. M.; Silva, A. M. S.; Cavaleiro, J. A. S. *Eur. J. Org. Chem.* **2009**, 2642–2660.
14. *Experimental procedure*: chemical reagents used for buffer solution preparation were of analytical grade, supplied by Sigma Chemical Co. (St. Louis, MO., USA). Stock solutions of **XH1**–**XH9** 5 mM were prepared in DMSO and further diluted

in the supporting electrolytes (ionic strength of 0.2) at the final concentration of 0.1 mM, unless otherwise mentioned. Voltammetric experiments were carried out using an Autolab electrochemical system (Eco Chemie model PGSAT 10). Before running the cyclic voltammetry experiments of our compounds control experiments were carried out to show that the solvent and supporting electrolytes have no influence on the potential region of interest. Data were acquired using the GPES (General Purpose Electrochemical System) software, version 4.9. The working electrode was a glassy carbon electrode (GCE) (3.0 mm). An Ag/AgCl (KCl 3 M) electrode and a carbon electrode were used as reference and auxiliary electrodes, respectively. Before use in electrochemical experiments and in order to obtain a clean renewed electrode surface, the glassy carbon working electrode was hand-polished with 0.075 μm alumina aqueous slurry using a polishing cloth and washed with purified water. Cyclic voltammograms were obtained by a single cycle performed at a scan rate of $100\ \mathrm{mV\ s^{-1}}$, at room temperature. For the scan rate studies, the scanning speed varied from 10 to $200\ \mathrm{m\ V\ s^{-1}}$. Voltammetric scans were recorded in the voltage range between -0.50 V and 1.20 V versus Ag/AgCl.

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