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View Article Online DOI: 10.1039/C5RA10140A

1	Correlating Experimental Electrochemistry and Theoretical Calculations
2	in 2'-Hydroxy Chalcones: The Role of Intramolecular Hydrogen Bond
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20 Abstract: In this work we present a study about the molecular structure and 21 electrochemical behavior of a series of methoxylated 2'-hydroxychalcones, whose 22 antitumor activity has been previously described. Cyclic voltammetry was used to 23 *quantitatively characterize the formation and stability of the anion radicals. The molecular* 24 structure of the neutral compounds and their anion radicals, particularly the 25 intramolecular hydrogen bonds (IHB), were investigated through density functional theory 26 (DFT) calculations. Geometrical and frontier orbitals changes in the anion, relative to the 27 neutral species, were examined and the adiabatic and vertical electron affinities (AEA, 28 VEA) as well as vertical detachment energy (VDE) were calculated. Natural bond orbital 29 (NBO) analysis was used to get insights about the electronic characteristics of the IHB and the results were correlated with <sup>1</sup>H-NMR chemical shifts. A direct relation among the 30 31 substitution pattern on rings A and B, the strength of the IHBs and the reduction potentials was found. NBO energies ( $\Delta E_{ii}^{(2)}$ ) show that the main contributions to the stabilization of 32 the IHBs arises from LP  $\rightarrow \sigma^*$  interactions. The strength of IHBs, given by  $\Delta E_{ii}^{(2)}$ , exhibit a 33 notable quantitative correlation with the experimental reduction potential, which, at least 34 35 to the best of our knowledge, has not been described before for any type of molecules. The 36 results show the importance of the methoxy substitution pattern on the IHB and redox 37 properties of these compounds. Our findings have potential implications in the design of 38 antitumor chalcones

39 Keywords

<sup>40</sup> Chalcone; Hydrogen Bonding; Electrochemistry; DFT; NBO

Studies concerning the chemistry of molecular radical ions has been an issue of great interest in physical organic chemistry for many years.<sup>1,2,3</sup> It is of fundamental importance to understand their formation, properties and behavior, because radical species participate in several important biochemical process, such as redox enzymatic reactions<sup>4,5</sup> and DNA strand break <sup>4, 6-8</sup>, among others. At the same time, chemical reactions mediated by radical species have received great attention for decades and remains as a very active field of research.<sup>9-11</sup>

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In this work the center of attention is a series of chalcone derivatives. These molecules are 51 52 known to have beneficial effects, such as antioxidant and tumor cell growth inhibitory activities, as well as apoptosis inductors in several cancer cell lines. These activities explain 53 the great attention received by chalcones as chemo-preventive agents.<sup>12</sup> Particularly 54 55 interesting is their ability to modify the mitochondrial membrane potential. On the above, it was found that chalcones with fewer hydroxyl groups on the aromatic rings were more 56 effective as mitochondrial uncouplers.<sup>13</sup> More recently, the role of the methoxylation in the 57 inhibition potency and cytotoxicity of chalcones towards breast cancer cells has been 58 critically studied.<sup>14</sup> Furthermore, it has been demonstrated that 2'-hydroxychalcones induce 59 apoptosis and inhibit invasion of human breast cancer cells.<sup>15</sup> 60

It has been suggested that the radical anion of 2'-hydroxychalcones play a central role in the catalyzed and uncatalyzed reactions with prenylflavonoid dienes,<sup>16, 17</sup> to give biologically active prenylflavonoid derivatives.<sup>18, 19</sup> The above has prompted the

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development of biomimetic total synthesis, mostly via catalysis, of these natural
 products.<sup>17,20, 21</sup>

Few studies that directly relate electrochemical properties with theoretical calculations have 66 been carried out in chalcone type structures. We found a computational study about the 67 68 electron affinities of substituted chalcones and their comparison with experimental reduction potentials that showed a highly linear correlation, however none of these 69 molecules presented IHB.<sup>22</sup> On the other hand, oxidation potential of hydroxychalcones 70 71 were studied by cyclic voltammetry and some thermodynamic and kinetic parameters compared with theoretical calculations.<sup>23</sup> Among their results, the authors claim that the 72 IHB, present in some of the studied structures, does not modify the redox properties, but it 73 74 does affect the molecular conformation, maintaining planar both, the neutral and the radical species.<sup>23</sup> 75

In this work, we study the influence of molecular structure, particularly the role of IHB, on the reduction potential, formation and stability of the radical anion of 2`-hydroxychalcones of pharmacological interest. In a previous study, cyclic voltammetry was employed to quantitatively characterize the formation and stability of the anion radical from three 2'hydroxychalcones.<sup>24</sup>

In this work, the molecular structure and electrochemical behaviour of six methoxylated 2'hydroxychalcones (**Figure 1**), which have been previously reported as antitumoral agents, were examined in detail.<sup>25,14</sup> First, cyclic voltammetry is used to quantitatively characterize the formation and stability of the anion radical of the series **Ch4**, **Ch5 and Ch6** and the results compared with three previously studied molecules (**Ch1-Ch3**).<sup>24</sup> Then, the Published on 03 June 2015. Downloaded by University of Georgia on 03/06/2015 20:33:22.

molecular structures of all six compounds, particularly their intramolecular hydrogen bond 86 87 (IHB) O2'-H2'...O7' in the neutral species and in their radical anions, were investigated 88 through DFT calculations. The strength of IHB  $O_{2'}-H_{2'}$  was experimentally assessed through <sup>1</sup>H-NMR chemical shift of H<sub>2</sub>. A comparison of geometrical parameters and 89 90 frontier orbitals between the neutral and the anion radical is presented, in particular, 91 adiabatic and vertical electron affinities (AEA, VEA) as well as vertical detachment 92 energies (VDE) were calculated. Finally, natural bond orbital (NBO) analysis was used to 93 get insight about the electronic characteristics of the IHB present in these molecules.

# 94 2. Experimental Section

### 95 **2.1. Synthesis**

Chalcones were prepared following a previously described methodology,<sup>24</sup> by adding, in a 96 97 dropwise manner, a solution of the corresponding substituted benzaldehyde, (7.34 mmol in 98 ethanol, 20 mL) to a stirred mixture of 4-methoxy-2-hydroxyacetophenone solution (7.34 99 mmol, in ethanol, 20 mL) and potassium hydroxide solution (2g in 10 mL distilled water). 100 The mixture was allowed to react overnight at room temperature. Then, it was diluted with 101 distilled water (200 mL), neutralized with hydrochloric acid, and extracted four times with 102 ethyl acetate (50 mL). The compounds were crystallized from ethanol. All these compounds have been described before.<sup>24,26</sup> <sup>1</sup>H-NMR spectra were obtained for all 103 104 compounds in DMSO and along with melting points were used to ensure the identity of the products. In addition, <sup>1</sup>H-NMR spectra from Ch3 and Ch4 in CDCl<sub>3</sub> were also obtained. 105 106 <sup>1</sup>H-NMR chemical shifts of  $H_2$  were used to experimentally assess the strength of IHB  $O_{2'}$ -107  $H_{2'}$ ... $O_{7'}$ .

# 108 **2.2 Electrochemical experiments.**

109 Cvclic Voltammetrv (CV) experiments carried in DMSO with were out tetrabutylammonium hexafluorophosphate (TBFP) as supporting electrolyte using a totally 110 111 automated BAS-100 voltammetric analyzer attached to a PC computer with the BAS 100-112 W software (v. 2.3), for total control of the experiments, data acquisition and treatment. All 113 CV experiments were carried out with 1.0 mM solution of each chalcone. A hanging 114 mercury drop electrode (HMDE) was used as working electrode (area 2.27 mm<sup>2</sup>). Platinum 115 wire was used as auxiliary electrode and all potentials were measured against a non aqueous Ag/Ag<sup>+</sup> CH Instrument 112 reference electrode. All the electrochemical 116 experiments were obtained after purging the cell with N<sub>2</sub> for ten minutes before each run, 117 118 and the temperature was maintained at  $25 \pm 1$  °C. Resistance was compensated before each 119 experiment. To obtain comparable results within the complete series we choose this methodology, because it is the same previously used with Ch1-Ch3.<sup>23</sup> 120

# 121 **2.3 Computational details**

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The calculations were carried out using the Gaussian  $09^{27}$  program package, running in a 122 123 Microsystem cluster of blades. Geometries were optimized at DFT B3P86/6-31+G(d,p) 124 level, using the conductor-like polarizable continuum model (C-PCM) approach to model 125 the role of the solvent, DMSO. This methodology has been proved to be reliable in the study of redox properties of chalcones.<sup>28-30</sup> No imaginary vibrational frequencies were 126 127 found at the optimized geometries, which indicate that they are true minima of the potential 128 energy surface. In solution, DMSO molecules can also act as hydrogen bond acceptors<sup>31, 32</sup> and thus they compete with the intramolecular hydrogen bond discussed here. It has been 129

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shown in previous works that even in this type of proton acceptor solvent, the
 intramolecular hydrogen bond remains. <sup>33,23</sup>

From frequency calculations, zero-point vibrational energies (ZPVE) were obtained and 132 133 used to correct the calculated enthalpies. The IHB analysis were obtained using hyperconjugation stabilization energies within the framework of NBO analysis.<sup>34</sup> The NBO 134 method involves a population analysis, which distributes computed electron density into 135 orbitals in the way chemist think, in terms of physical organic chemistry. The interaction 136 137 between filled orbitals and empty antibonding orbitals represents the deviation of the 138 molecule from the Lewis structure and can be used as a measurement of delocalization due 139 to the presence of hydrogen bond interaction. These hyperconjugative interactions play an 140 important role in hydrogen bonding. Donor-acceptor interaction energies (stabilization energy,  $\Delta E_{ii}^{(2)}$ ) can be calculated using second-order perturbation theory analysis.<sup>34</sup> Natural 141 resonance theory (NRT) calculations<sup>35,36,37</sup>, available from the NBOPro6 software,<sup>38</sup> have 142 been used to determine the bond order and the fraction of covalency and ionicity of the O-143 144 H<sup>...</sup>O IHB.

145 Electron affinities and bond dissociation energies were calculated as follow (where H
 146 corresponds to enthalpies):<sup>39</sup>

147 Adiabatic electron affinity (AEA) = H(optimized neutral) – H(optimized anion)

148 Vertical electron affinity (VEA) = H(optimized neutral) – H(anion at optimized neutral
149 geometry)

# 152 **3. Results and Discussion**

# 153 **3.1. Electrochemistry**

154 Chalcones **4-6** were electrochemically reduced on Hg electrode in a non-aqueous medium 155 containing DMSO as solvent and tetrabutylammonium hexafluorophosphate (TBFP) as 156 supporting electrolyte, in the same way as it was previously reported for **Ch1-Ch3**.<sup>24</sup> The 157 cyclic voltammograms were obtained for all three compounds, showing a behavior for the 158 redox process similar to that observed in **Ch1-Ch3**.<sup>24</sup> (**Figure 2**).

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When the reduction potentials are compared (**Table 1**), it can be noticed that **Ch5** needs more energy for reducing than **Ch4** and **Ch6**. Similar behavior was reported<sup>24</sup> for **Ch1**-**Ch3**, <sup>24</sup> where **Ch2** needs more energy than **Ch1** and **Ch3** to be reduced. A systematic decrease in the reduction potential is observed for **Ch4-Ch6** when compared with their respective analogues **Ch1-Ch3**, indicating that the presence of the -OCH<sub>3</sub> substituent, in *para* position with respect to the carbonyl on ring A, increases the energy of the molecular electronic state hindering the electron capture.

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Under the mentioned experimental conditions, the one electron reduction process produces very well resolved cyclic voltammograms due to the formation of the anion radicals. When the concentration of the species in solution increased, an increase in the magnitude of the current for the couple was observed (**Figure 3A**). The stability of the anion radical depends

mainly on the reaction media, and can be monitored by following the decay of the corresponding oxidation current,  $I_{p,a}$ , subsequent to the electrochemical generation (return sweep). In effect, a suitable measurement of the stability of the radical anion is expressed by the current ratio parameter,  $I_{pa} / I_{pc}$ , which reveals the tendency of an electrochemically generated species, *i.e.* the anion radical, to undergo subsequent chemical reactions.<sup>40</sup> The current ratio equals to one in the absence of further reactions but decreases if the radical subsequently reacts.

The calculation of the ratios  $I_{pa} / I_{pc}$  for the three species show that when the scan rate increases, it takes values close to 1 (**Figure 3B**), but when the concentration increases, the ratio of currents decreases (**Figure 3C**), indicative of a non-reversible process.

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## 183 **3.2. DFT calculations**

## 184 **3.2.1.** Geometries, electro affinities and molecular orbital analysis

185 Some key selected geometrical parameters and calculated AEAs, VEAs and VDEs for Ch1-Ch6 and their respective anon radicals are presented in Figure 4 and Table 2 186 187 respectively. It has been previously reported that for the most stable trans configuration of 188 chalcones, two conformers can exist, namely s-cis and s-trans. It has been found that the 189 difference in energy between the two conformers is in favor of the s-cis isomer by 5.6 190 kcal/mol, with a barrier of 8.3 kcal. In addition, it has been demonstrated that properties 191 such as bond dissociation energy and many energetic properties will not be modified from the s-cis to the s-trans conformers.<sup>28</sup> Thus, to carry out our calculations only the s-cis 192 193 conformers were taken into account.

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195 As can be observed from the table attached to Figure 4, most geometrical parameters do 196 not show significant differences between the neutral and the anion radical species, for all chalcones. Nevertheless, the  $C_{\alpha}=C_{\beta}$  - bond increases its length by 0.03-0.04 Å, while the 197  $C_{\alpha}$ - $C_{7'}$  bond shortens by 0.04-0.07 Å in the anion radicals. Carbonyl  $C_{7'}$ = $O_{7'}$  also present a 198 199 bond lengthening of 0.06-0.09 Å. The only notable geometrical differences between the 200 neutral species and the anion radicals was found for parameters corresponding to the IHB, 201 for instance, the distance  $O_{2'}$ -H<sub>2'</sub> lengthens by 0.06-0.08 Å for **Ch1-Ch4** and notably by 202 0.37-0.36 Å for Ch5 and Ch6, while oppositely, the distance  $H_{2'} = O_{7'}$ , shortens by 0.20-203 0.21 Å for Ch1-Ch4 and 0.47 Å for both Ch5 and Ch6. In addition, the angle  $O_{2'}-H_{2'}-O_{7'}$ 204 increased from 150-152° to 159-160° for all chalcones. These results indicate that the IHB 205 and the double bond are mostly affected upon the electron attachment.

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Particularly interesting is that the presence of a para-methoxy substituent on position 4' of 207 ring A, along with the presence of a methoxy substituent on ring B at C4 or C5 in the anion 208 radical, shortens the  $H_{2'}$  O<sub>7</sub> distance (lengthening the  $O_{2'}$ -H<sub>2'</sub> distance) to a point in which 209 210  $H_1^{\prime \prime \prime \prime \prime}O_7$  could be consider a covalent bond, in particular for Ch5 and Ch6. However, the 211 latter do not occur for Ch4, which exhibit the methoxy group in C3. Even though both, 212 **Ch4** and **Ch6** present a methoxy substituent in *ortho*- and *meta*- position with regard to the 213 double bond, only the *ortho*-methoxy group can deliver electron density to the  $C_{7'}=O_{7'}$ 214 bond through conjugation with the  $C_{\alpha}$ - $C_{\beta}$  double bond. In the case of **Ch4**, both methoxy groups are neighbors, which can affect the ability of the methoxy in C2 to remain in the 215 216 ring plane and deliver electron density to the  $C_{7'}=O_{7'}$  bond, reducing the effect exhibited in 217 **Ch5** and **Ch6**. Further bond order analysis (*vide infra*) helps to rationalizes these results.

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219 Table 2 shows the values of AEA, VEA and VDE calculated for Ch1-Ch6. If the VEA is 220 positive, the attachment of the electron to the molecule is energetically favorable, even 221 before geometrical rearrangements occur, *i.e.* the molecule can attract the excess of charge 222 density. On the other hand, a positive AEA indicates that the formed anion is stable in its 223 final geometry, *i.e.* that once the electron is trapped by the molecule, it stays there long 224 enough to rearrange and possibly to play a role in chemical reactions. When VDE is 225 positive the energy of the neutral molecule is higher than their anion, and it is stable with 226 respect to the vertical electron auto-detachment. VDE can be interpreted as the vertical 227 ionization potential of the anion. If the nuclear configuration of the anion and the neutral 228 molecule are similar, the values of VEA and VDE can be understood as lower and upper 229 bounds of the AEA, as can be seen in Table 2. Only in the case that electron attachment generates a significant change in geometry, VDE could be lower than AEA.<sup>41</sup> 230 231 We found that all AEAs are positive, indicating a favorable tendency to form stable anion 232 radicals in this series. For Ch1-Ch3 calculated AEAs correlate well with observed

233 reduction potentials, with Ch2 showing the lowest potential and the lower AEA. The same 234 tendency is observed for Ch4-Ch6, where Ch5 also possesses the lowest potential and the 235 lowest AEA. These results indicate that the presence of a methoxy substituent in C4 of ring 236 B (Ch2 and Ch5) decreases the ability of chalcones to form a stable anion radical. When 237 Ch1-Ch3 are compared with Ch4-Ch5, they present higher AEA and higher reduction 238 potential. These results indicate that the presence of a methoxy group at C4' of ring A 239 decreases the ability of the molecule to form a stable anion radical. On the other hand, all 240 VEAs are positive, which indicate that all molecules have favorable tendency to take an 241 electron. The effects of substituents have a similar impact for VEAs than for AEAs, which

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242 indicate that the presence of a methoxy groups at C4' of ring A and C4 of ring B decrease 243 the ability of the molecule to take an electron and form a stable anion radical. Besides, all 244 VDEs are positive, which indicates that electron auto-detachment from the anion radical is unlikely. In this case it is observed that the presence of a methoxy substituent at C4 of ring 245 246 B (Ch2 and Ch5) increases the possibility of an electron auto-detachment from the anion 247 radical, but does not affect in the same way to Ch4 and Ch6. Ch4 present a lower VDE than their analog Ch1, but Ch5 and Ch6 present a higher VDE than Ch2 and Ch3, which 248 249 indicates that a methoxy substituent at C4 of ring B decreases the capability of suffering an 250 electron auto-detachment in Ch4, but increases in Ch5 and Ch6.

252 The attachment of an extra electron to a neutral molecule leads to one of two different types of anions, valence-bound or dipole-bound anion.<sup>42</sup> In the first case, the attached electron is 253 254 strongly bound occupying a valence molecular orbital. In the second case, the attached electron is weakly bound, mainly by electrostatic charge-dipole interactions.<sup>43</sup> Therefore, a 255 valence-bound anion suffer a much notable effect on their structural parameters than a 256 dipole-bound anion.<sup>44,45</sup> In our cases, we found that the differences between AEAs and 257 258 VEAs is in all cases 0.2-0.3 eV. These differences indicate that the radical anions formed in all molecules should be valence-bound anions, since a difference energy of ~0.3 eV is close 259 to the expected amount for relaxation energy of a valence-bound anion.<sup>39, 46</sup> With the 260 261 purpose to study the distribution of the excess electron density of the anion radicals, the 262 singly occupied molecular orbitals (SOMOs) of the stable and vertically attached electron were obtained (see Figure 1 and Figure 2 of electronic supplementary information, ESI). 263 264 This approach also helps to distinguish between valence-bound and dipole-bound anions, 265 given that SOMO of a dipolo-bound anion is centered in a limited part of the molecules,

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Correlations between the experimental reduction potentials (-E<sub>p,c</sub>) and calculated AEAs and 270 VEAs are presented in Figure 5A and Figure 5B respectively. This kind of correlations 271 have been made for different kind of compounds <sup>47,48,49</sup> and an interpretation of the results 272 can be carried out from the work of Parker.<sup>50</sup> We found that the correlation between VEAs 273 and experimental reduction potentials ( $R^2 = 0.98$ ) was better than the correlation with 274 AEAs ( $R^2=0.88$ ). The above result suggests that the reduction potential depends more on 275 276 the ability of taking an extra electron than on the ability to form a stable anion radical. The 277 slopes in both cases are close to one, which indicate the absence of secondary effects such 278 as differential solvation and relaxation of the resulting anions. The results suggest that the different methoxy substitution patterns of these chalcones do not modify such secondary 279 effects which remain fairly constant, regardless the electron affinities. 280

These results support the reliability of our calculations and are in agreement with previously reported works, which states that the energetics of the reduction process should be controlled by the first single-electron uptake.<sup>48-51</sup>

# 284 **3.2.2. NBO analysis**

With the aim of studying the electronic characteristics and quantifying the strength of the  $O_{7'} H_{2'} O_{2'}$  IHB present in these chalcones, we carried out a detailed NBO analysis.  $\Delta E_{ij}^{(2)}$ is an appropriate tool to analyze hydrogen bonding, and allow us to quantify the strength of

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the donor-acceptor orbital interaction. <sup>1</sup>H-NMR chemical shifts of H<sub>2</sub> were used as an 288 experimental measurement of the strength of the IHB. Variation of solvent (DMSO and 289 290 CDCl<sub>3</sub>) do not affect this parameter, showing that the IHBs are strong enough to be 291 independent of the medium. Previously, we have reported a direct correlation between NBO stabilization energy  $\Delta E_{ii}^{(2)}$  and <sup>1</sup>H-NMR chemical shift of the hydrogen engaged in 292 the IHB in a series of hydroquinones.<sup>52</sup> We found a similar behaviour for these chalcone 293 derivatives. The second order stabilization energy  $\Delta E_{ij}^{(2)}$  for the IHB and the <sup>1</sup>H-NMR 294 chemical shift of H<sub>2</sub> are presented in **Table 3**. For all molecules, we found that the  $\sigma^*_{02'-H2'}$ 295 296 antibonding orbitals act as electron acceptors and oxygen 7' lone pair (LP<sub>07'</sub>) act as an electron donor in the IHBs. The total stabilization energy for the IHB (LP<sub>1+2</sub>O7'  $\rightarrow \sigma^*O_{2'}$ -297  $H_{2'}$ ) in Ch1, Ch2 and Ch3 are 43.9, 47.7 and 45.0 kcal/mol, respectively. A similar 298 299 behavior is observed for the analogue series Ch4, Ch5 and Ch6, with stabilization energies 300 of 49.6, 53.0 and 50.4 kcal/mol respectively. The series Ch1-Ch3 has lower reduction 301 potentials when compared with their analogs in the series Ch4-Ch6. The stabilization 302 energies for the IHBs are pointing in the same direction that the reduction potential, which 303 indicates that the strength of IHB has a strong influence in the capability of these chalcones 304 to capture an extra electron. Hyperconjugation is favored by a lower difference between orbital energies  $\varepsilon_i - \varepsilon_I$  and a higher overlap between them (F<sub>ii</sub>). For all LP  $O_{7'} \rightarrow \sigma^* O_{2'} - H_{2'}$ 305 interactions, we found that the difference among  $\Delta E_{ii}^{(2)}$  can be attributed to the difference in 306 the overlap ability between orbitals, instead of their energy differences. 307

308 Few quantitative relationships of NBO second-order stabilization energy with other 309 characteristic parameters of the hydrogen bond have been reported. Senthilkumar et al.<sup>53</sup> 310 showed a quantitative correlation between NBO energies and calculated hydrogen bond

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distances at B3LYP and MP2 level, in formic acid dimers. Also, recently we found good 311 correlations among the experimental <sup>1</sup>H-NMR chemical shift of O-H.<sup>52</sup> electrochemical 312 oxidation potentials<sup>54</sup> and NBO stabilization energy for the interaction O-H<sup>...</sup>O-C, in a 313 314 series of hydroquinones possessing IHB. As far as we know, there are no other reports in 315 the literature about a quantitative correlation between experimental IHB parameters and 316 calculated NBO energies. Figure 6a shows a good correlation between the <sup>1</sup>H-NMR chemical shift of  $H_{2'}$  and the  $\Delta E_{ij}^{(2)}$  for IHB. Having shown that this stabilization energy is 317 a good parameter for the IHB strength in these chalcones, we study their correlation with 318 the experimental reduction potentials  $(-E_{p,c})$  and the results are displayed in Figure 6b. As 319 observed from this figure, there exist a good correlation between the strength of the IHB 320 and the experimental reduction potentials ( $R^2 = 0.90$ ). This correlation allow us to establish 321 that, in this series of chalcone derivatives, the IHB strength is a very important factor to 322 323 determine their capability to attach an extra electron, a remarkable observation.

324 NBO method, besides determining the second-order stabilization energies, also allow us to 325 carry out a bond order analysis and to establish the covalency and ionicity of the bonds, based in the natural resonance theory (NRT, for details see references).<sup>35,36,37,55</sup> We focused 326 on calculating the bond order and the degree of covalency and ionicity for the bonds 327 328 involved in the  $O_{2'}$ -H<sub>2'</sub>...O<sub>7'</sub> IHB, both, in the neutral and the anion radical species. There 329 were three resonance structures considered by the NBO programme, third resonance 330 structures were neglected from all the analysis, since they represented less than 2% in all 331 cases. Figure 7 presents the resonance structures 1 and 2, along with the main data from 332 NRT calculations. Resonance structure 1 was always the major contributor to the neutral species (~95%) and has been consistently major for Ch1 to Ch3 than Ch4 to Ch6. The 333

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latter observation is supported by the small but consistent bond order differences for O-H in Ch1 to Ch3 when compared with Ch4 to Ch6 (see table attached to Figure 7). The O-H bond for all chalcones has a low covalent character, around 40%. On the other hand, as can be expected, the bond orders for  $H_2^{...}O_{7'}$  is lower than for  $O_2^{..}H_2^{..}$ , being higher for Ch4 to Ch6 than for Ch1 to Ch3. The ionic character dominates this bond in all cases (96-97%).

339 When the results for the anion radicals are examined, a very different behaviour is observed 340 between Ch1-Ch3 and Ch4-Ch6. Weights of resonance structures for Ch1 to Ch3 are 341 very similar to those that have the neutral species,  $\sim 92\%$  for resonance structure 1 and  $\sim 6\%$ 342 for resonance structure 2. Natural bond orders for  $O_{2'}-H_{2'}$  of Ch1-Ch3 are ~0.46, with a 343 30% of covalency and 70% of ionicity, while  $H_{2'}$  or  $O_{7'}$  present a natural bond order around 344 0.03 with  $\sim 91\%$  of ionicity for all three cases. On the other hand, for Ch4 the resonance 345 structure 2 takes a much greater weight than for Ch1 to Ch3, reaching  $\sim 34\%$ , while for 346 **Ch4** and **Ch5** the resonance structure 2 becomes the dominant one, with a 93% for both. Natural bond order and covalency of  $O_{2'}$ -H<sub>2'</sub> for **Ch4** decreases slightly, compared with 347 348 **Ch1** to **Ch3**, to values of 0.3214 and 28% respectively. However, both natural bond order 349 and covalency notably decrease to  $\sim 0.028$  and 8% respectively for Ch5 and Ch6. 350 Moreover,  $H_2$ ,  $O_2$  bond in **Ch4** presents a notable increases in their natural bond order and 351 even more for Ch5 and Ch6. The above was accompanied by a decrease in ionic character 352 and an increase in covalent character, being more important for Ch5 and Ch6. Taking 353 together, these results evidence that the presence of the methoxy substituents on ring B do 354 not significantly affect the IHB in the radical anion when compared with the neutral 355 molecule. Besides, the presence of methoxy substituent in C4' of ring A has a high impact, 356 modifying the IHB of the anion radical compared with the neutral molecule, being more Published on 03 June 2015. Downloaded by University of Georgia on 03/06/2015 20:33:22.

different for **Ch4** than for **Ch5** and **Ch6**. The later suggests that the difference described above in the values of VDEs between **Ch4** and **Ch5-Ch6** is closely related to their difference in the radical anion IHB structure. There is a switching of the minimum in the potential energy surface along the IHB coordinate.

# 361 **3.3 Implications with the biological activities of 2'-hydroxichalones**

362 The results of this work provide insights about the effect of methoxy substituents on the 363 IHB properties of Ch1-Ch6 and their ability to take an electron and generate a stable anion 364 radical. As we mentioned in the introduction, previous works have shown that this chalcones can inhibit the proliferation of different cancer cells lines.<sup>25, 14,26</sup> where the 365 366 presence of methoxy substituents seems to play a critical role. It has been proposed that 367 some of the anti-proliferative activities of these compounds is related to their capability of inducing mitochondrial mediated apoptosis.<sup>25</sup> The ability of chalcones to generate radical 368 369 species could impact, for example, in their capability to modify the mitochondrial 370 membrane potential, inhibit the electron chain or affect their ability to act as uncoupler of the oxidative phosphorylation.<sup>13,15</sup> 371

Our results suggest that if it is necessary to increase the ability of the chalcone to form an anion radical and their persistency in time, the presence of the methoxy substituent in C4 of ring B should be avoided; their presence do not significantly affect the IHB in the radical anion. On the other hand, the presence of a methoxy substituent in C4' has opposite impact in neutral and radical anion species. For the neutral specie, it decreases the ability to form a radical anion, but once it is formed , it presents lower possibility to return back to the

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neutral form. The above can have a high impact on the IHB, making it weaker for theanion radical than for the neutral species.

Our results also suggest that in addition to the predictability of the AEAs and VEAs to determine the reduction potential of these 2'-hydroxichalcone derivatives, the strength of the IHB is also an acceptable parameter to predict this important experimental data, which has been widely related to different biological activities. Nevertheless, this relationships needs to be tested for a more extensive series of chalcones to establish their actual reliability.

# 386 4. Conclusions

387 Cyclic Voltammetry is a very useful technique to investigate the formation and stability of 388 anion radicals from chalcone derivatives. We found that the presence of a -OCH3 389 substituent in para position with respect to the carbonyl on ring A, decreases the energy of 390 the electronic state of the anion radical when compared with derivatives without this 391 substituent. This is closely related with the energy of the molecular orbital where the extra 392 electron is going to be placed. The calculation of the ratios  $I_{pa} / I_{pc}$  for Ch4-Ch6 shows that, 393 as expected, the formed radicals appears to be stable at low concentration, but when the 394 concentration increases they experience subsequent reactions.

395 DFT results show that the IHB  $O_2 - H_2 - O_7$  and the double bond  $C_{\alpha} = C_{\beta}$  are the most 396 affected regions upon the electron attachment process. From the analysis of the AEAs, 397 VEAs and VDEs, we found that all chalcones can take an electron and form a stable 398 radical anion. Besides the auto-detachment process is very unlikely for all. The presence of 399 methoxy groups in C4 of ring B and in C4' of ring A decreases the ability to take an Published on 03 June 2015. Downloaded by University of Georgia on 03/06/2015 20:33:22.

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400 electron and form a stable radical anion. On the other hand, the presence of a methoxy 401 group in C4 of ring B, increases the ability to experience an electron auto-detachment by 402 the radical anion, in all cases. However, the presence of a methoxy group at C4' of ring A 403 has a different affect on Ch4 that on Ch5 and Ch6. For Ch4 the presence of a methoxy 404 decreases the trend to experience an electron auto-detachment once the anion radical is 405 formed, but for Ch5 and Ch6 this trend increases.

VEAs exhibit a better correlation than AEAs, with experimental reduction potentials which suggests that it is more influenced by the capability of taking the extra electron than by forming a stable anion radical. The slopes of the correlations, close to one, strongly suggests the absence of secondary effects, such as differential solvation and relaxation of the resulting anions. These indicate that the different methoxy substituents patterns of these chalcones does not modify such secondary effects, which remain fairly constant, regardless the electro affinity values.

Analyses of the second order stabilization NBO energies ( $\Delta E_{ij}^{(2)}$ ) for the IHBs, allows us to quantify the strength of the donor-acceptor orbital interaction. A comparison with <sup>1</sup>H-NMR data shows that NBO energy is a good parameter to measure the strength of the IHB. Stabilization energies for the IHBs are pointing in the same direction that reduction potentials, and they present a good semi-quantitative correlation (R<sup>2</sup> =0.90), which indicates that the strength of IHB has a significant influence in the reduction potential of these chalcones.

420 Natural bond order analysis shows that the presence of a methoxy substituent on ring B421 does not significantly affect the IHB in the radical anion, when compared with the neutral

422 species. On the other hand, the presence of a methoxy substituent at C4' of ring A has a 423 significant impact weakening the IHB of the radical anion when compared with the 424 neutral species.

425 Our results highlight the possibility of establishing direct links between molecular structure 426 details, such as the position of substituents on the aromatic rings and the presence of 427 intramolecular hydrogen bonds, with the electrochemical behavior of methoxylated 2-428 hydroxychalcones. We hope this work drives the search for similar correlations in a broader 429 spectrum of molecules engaged in IHB, and can be useful in the design of new chalcones 430 with potential pharmacological activity.

#### 431 5. Acknowledgements

We are grateful to FONDECYT grants 1140753, FONDECYT/POSTDOCTORADO 432 433 3140286 (M.M-C) and ACT grant 1107.

434

435 Electronic Supporting Information available: Optimized geometries, SOMO's and energies 436 for all molecules.

437

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# Figure 1. Compounds studied in this work



Ch1	Н	3
Ch2	Н	4
Ch3	Н	5
Ch4	OCH <sub>3</sub>	3
Ch5	OCH <sub>3</sub>	4
Ch6	OCH <sub>3</sub>	5

537 Figure 2. Cyclic voltammogram of 1 mM 2'-hydroxy chalcone derivatives in DMSO + 0.1

538 M TBPF at 1.0 Vs<sup>-1</sup>.



540

Figure 3. A: Cyclic voltagramm for chalcone 4 at different concentrations, with a scan rate
of 5 Vs<sup>-1</sup>. B: Dependence of the current ratio with the sweep rate for the one-electron redox
couple of chalcone 4. C: Current ratio dependence of chalcone 4 at different concentrations
and different sweep rates. All experiments were performed in DMSO and 0.1 M TBPF.







559							
007		Ch1	Ch2	Ch3	Ch4	Ch5	Ch6
	$C_{\alpha}$ - $C_{\beta}$	1.35 (1.39)	1.36 (1.39)	1.35 (1.39)	1.35 (1.39)	1.36 (1.39)	1.35 (1.39)
	$C_{\alpha}$ - $C_{7}$	1.46 (1.41)	1.45 (1.41)	1.46 (1.41)	1.46 (1.41)	1.47 (1.40)	1.46 (1.40)
	$C_{7'} = O_{7'}$	1.26 (1.32)	1.26 (1.32)	1.26 (1.32)	1.26 (1.32)	1.26 (1.35)	1.26 (1.35)
	$O_2 \cdot \text{-} H_2 \cdot$	1.00 (1.07)	1.01 (1.08)	1.01 (1.07)	1.01 (1.09)	1.02 (1.39)	1.01 (1.37)
	$H_{2'}{}^{\prime\prime}O_{7'}$	1.57 (1.37)	1.55 (1.35)	1.56 (1.37)	1.54 (1.33)	1.53 (1.06)	1.54 (1.07)
	$O_{2'}-H_{2'}-O_{7'}$	150 (159)	151 (160)	151 (160)	152 (160)	152 (160)	152 (160)

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562 Figure 5. Correlation graphics of experimental reduction potentials vs. theoretical AEAs

563 (5A) and VEAs (5B).

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571 **Figure 6**. Correlations between experimental chemical shift for  $\delta H_{2'}$  in DMSO-d6 (A) and

572 reduction potentials (B) vs. NBO stabilization energies for LP  $\rightarrow \sigma^*$  interactions in IHB

573

 $O_{7'}{}^{...}H_2-O_{2'}.$ 



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N		Weight		$O_2$ '- $H_2$ '	$H_{2'}{}^{\cdots}O_{7'}$	
	Neutral	Resonance structrure 1	Resonance structure 2	Bond order (C, I)	Bond order (C, I)	
_	Ch1	95.24	2.94	0.9524 (37, 63)	0.0294 (3, 97)	
	Ch2	95.07	3.09	0.9507 (37, 63)	0.0309 (4, 96)	
	Ch3	95.28	2.89	0.9528 (42, 58)	0.0289 (3, 97)	
	Ch4	94.94	3.21	0.9493 (36, 64)	0.0320 (3, 97)	
	Ch5	94.79	3.34	0.9478 (36, 64)	0.0335 (4, 96)	
	Ch6	94.89	3.24	0.9489 (36, 64)	0.0325 (4, 96)	
_						

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Radical	Weight		$O_{2}{}^{\prime}\text{-}H_{2}{}^{\prime}$	$H_{2'}{}^{\cdots}O_{7'}$	
anion	Resonance structrure 1	Resonance structure 2	Bond order (C, I)	Bond order (C, I)	
Ch1	92.52	5.89	0.4627 (37, 63)	0.0294 (8, 92)	
Ch2	92.18	6.23	0.4609 (37, 63)	0.0311 (9, 91)	
Ch3	92.49	5.93	0.4625 (42, 58)	0.0297 (9, 91)	
Ch4	64.28	34.70	0.3215 (36, 64)	0.1735 (16, 84)	
Ch5	5.48	92.95	0.0274 (36, 64	0.4647 (31, 69)	
Ch6	5.74	92.68	0.0288 (36, 64)	0.4634 (30, 70)	

582

Table 1. Characteristic electrochemical parameters of chalcones 1-6

Compound	$-E_{p,c}(mV)$	$k_2 \ge 10^{-3} (M^{-1} s^{-1})$	t <sub>1/2</sub> (s)
Ch1	1096	5.6 <u>+</u> 0.30	0.18
Ch2	1187	30.5 <u>+</u> 0.30	0.03
Ch3	1110	40.5 <u>+</u> 0.27	0.03
Ch4	1180	$4.4\pm0.30$	0.21
Ch5	1282	$18.5\pm0.26$	0.05
Ch6	1184	$20.8\pm0.14$	0.04

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584

# 586 **Table 2**. Calculated Adiabatic Electron Affinities (AEAs), Vertical Electron Affinities

587 (VEAs) and Vertical Detachment Energies (VDEs) for chalcones 1-6 in DMSO.

\_

	AEA	VEA	VDE
Ch1	3.78	3.59	4.03
Ch2	3.67	3.49	3.88
Ch3	3.78	3.60	4.01
Ch4	3.74	3.48	3.95
Ch5	3.61	3.38	3.92
Ch6	3.73	3.49	4.07

AEAs, VEAs and VDEs Values in eV

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597	Table 3. <sup>1</sup> H-NMR chemical shifts for $\delta H_{2'}$ (DMSO-d6 for all and CDCl <sub>3</sub> for CH4-5) and
598	stabilization energies (kcal/mol) for selected NBO pairs (donor-acceptor) given by second
599	order perturbation energies of the Fock matrix in the NBO basis for the chalcones 1-6
600	(HF/6-311G**//B3P86/6-31+G**).

Molecule	δH <sub>2</sub> · DMSO-d6 (CDCl <sub>3</sub> )	$\Phi_{i}$	$\Phi_{j}$	$\Delta E_{ij}^{(2)}$	ε <sub>j</sub> - ε <sub>i</sub> /au	F <sub>ij</sub> /au
Ch1	12.40	$LP_1 \ O_{7'}$	$\sigma^*O_{2'}\text{-}H_{2'}$	4.82	1.54	0.078
0.11		$LP_2 \: O_{7'}$	$\sigma^{*} \operatorname{O}_{2'}\text{-} \operatorname{H}_{2'}$	39.12	1.18	0.194
Ch2	12.82	$LP_1  O_{7'}$	$\sigma^{*}\operatorname{O}_{2'}\text{-}\operatorname{H}_{2'}$	4.90	1.53	0.078
CIIZ	12.02	$LP_2  O_{7'}$	$\sigma^{*} \operatorname{O}_{2'}\text{-} \operatorname{H}_{2'}$	42.82	1.18	0.203
Ch2	10 (0	$LP_1  O_{7'}$	$\sigma^{*} \operatorname{O}_{2'}\text{-} \operatorname{H}_{2'}$	4.87	1.54	0.078
Ch3	12.02	$LP_2 \: O_{7'}$	$\sigma^{*} \operatorname{O}_{2'}\text{-} \operatorname{H}_{2'}$	40.13	1.18	0.197
	13.42	$LP_1  O_{7'}$	$\sigma^{*} \operatorname{O}_{2'}\text{-} \operatorname{H}_{2'}$	4.88	1.52	0.078
Ch4	(13.43)	$LP_2 \ O_{7'}$	$\sigma^{*} \operatorname{O}_{2'}\text{-} \operatorname{H}_{2'}$	44.75	1.17	0.207
	13.67	$LP_1  O_{7'}$	$\sigma^{*} \operatorname{O}_{2'}\text{-} \operatorname{H}_{2'}$	4.93	1.51	0.078
Ch5	(13.68)	$LP_2 \: O_{7'}$	$\sigma^{*} \operatorname{O}_{2'}\text{-} \operatorname{H}_{2'}$	48.06	1.17	0.214
	10.51	$LP_1  O_{7'}$	$\sigma^*O_{2'}\text{-}H_{2'}$	4.89	1.52	0.078
Ch6	13.51	LP <sub>2</sub> O <sub>7'</sub>	$\sigma^* \operatorname{O}_{2'}\text{-}\operatorname{H}_{2'}$	45.52	1.17	0.209