# Supplementary

# Investigating the Antiparasitic Potential of the Marine Sesquiterpene Avarone, its reduced form Avarol, and the Novel Semisynthetic Thiazinoquinone analogue Thiazoavarone

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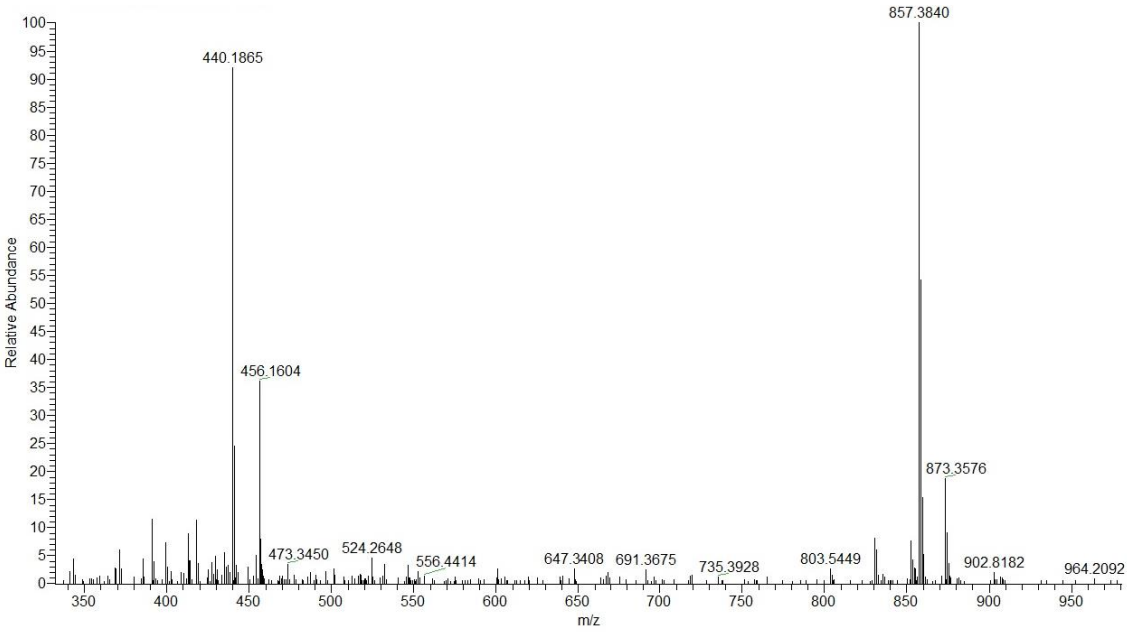



**Figure S1.** HRESIMS spectrum of thiazoavarone (**2**)

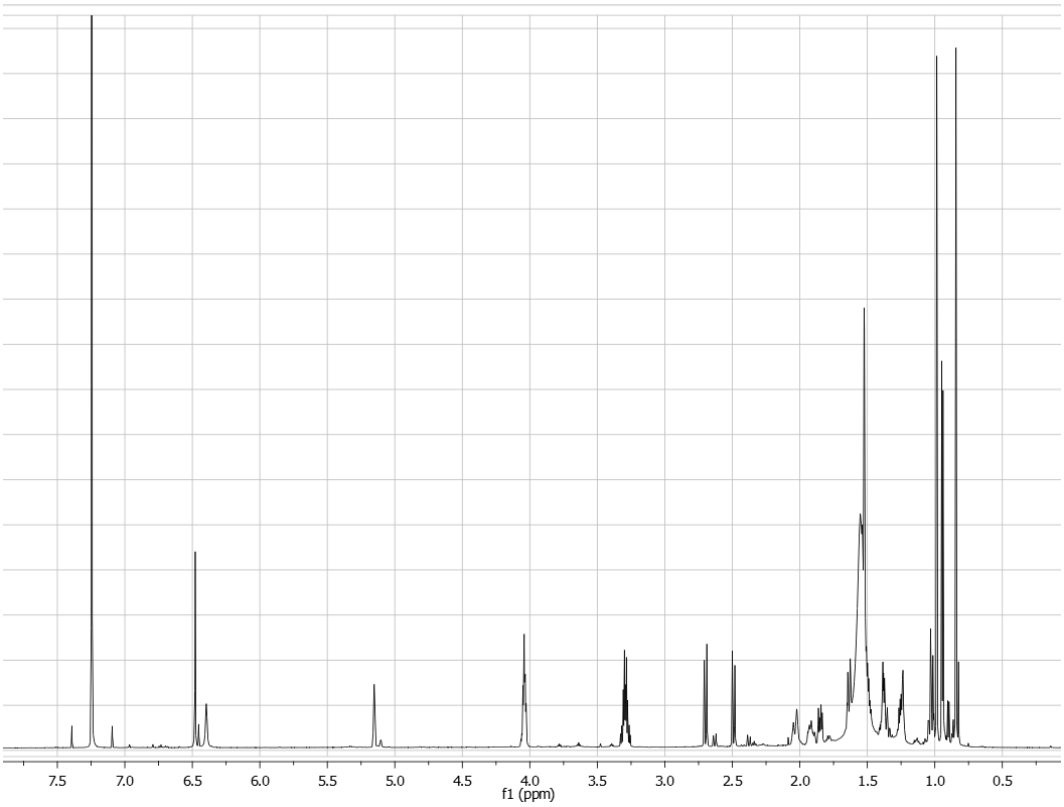



**Figure S2.** $^{1}$H NMR spectrum of thiazoavarone (**2**) in $CDCl_3$

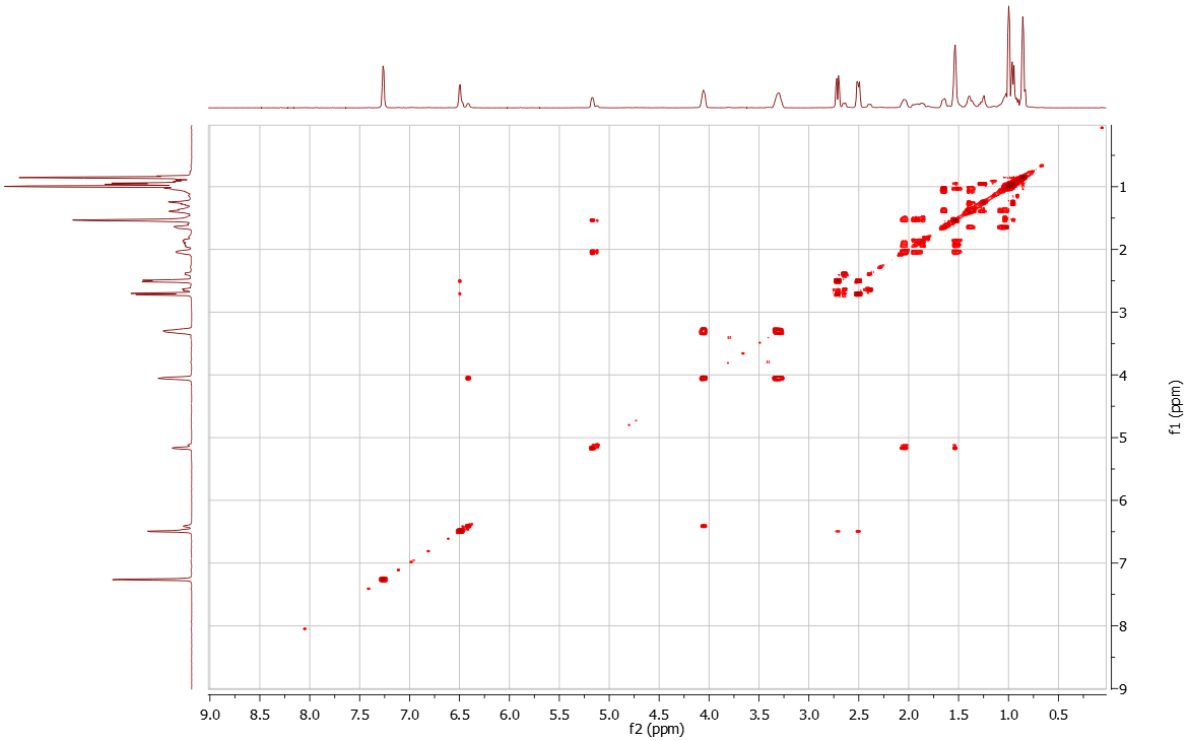



**Figure S3.** $^{1}$H-$^{1}$H COSY spectrum of thiazoavarone (**2**) in $CDCl_3$

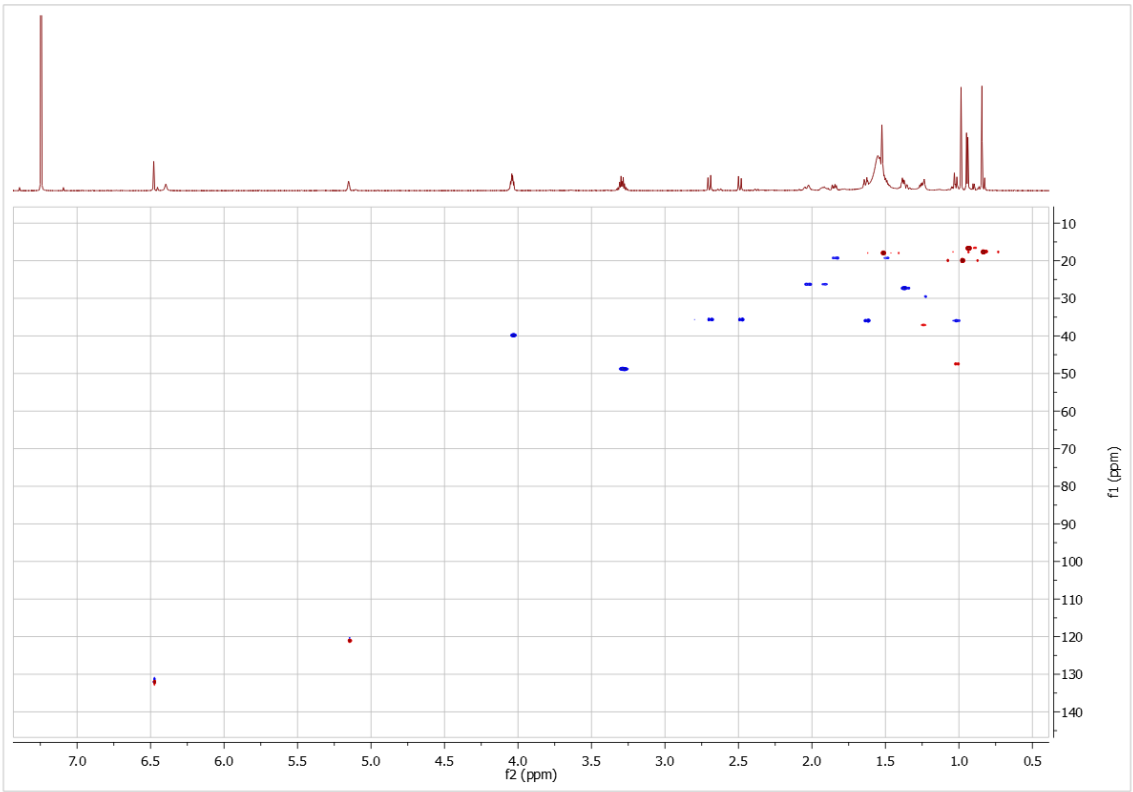



**Figure S4.** HSQC spectrum of thiazoavarone (**2**) in $CDCl_3$

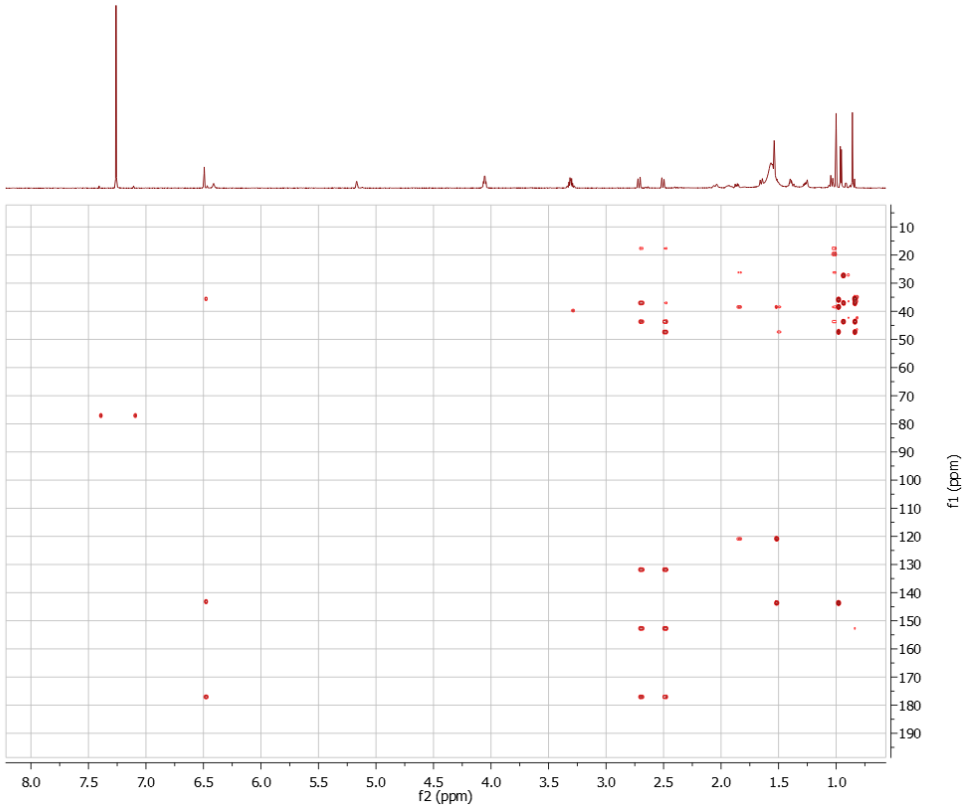



**Figure S5.** HMBC spectrum of thiazoavarone (**2**) in $CDCl_3$

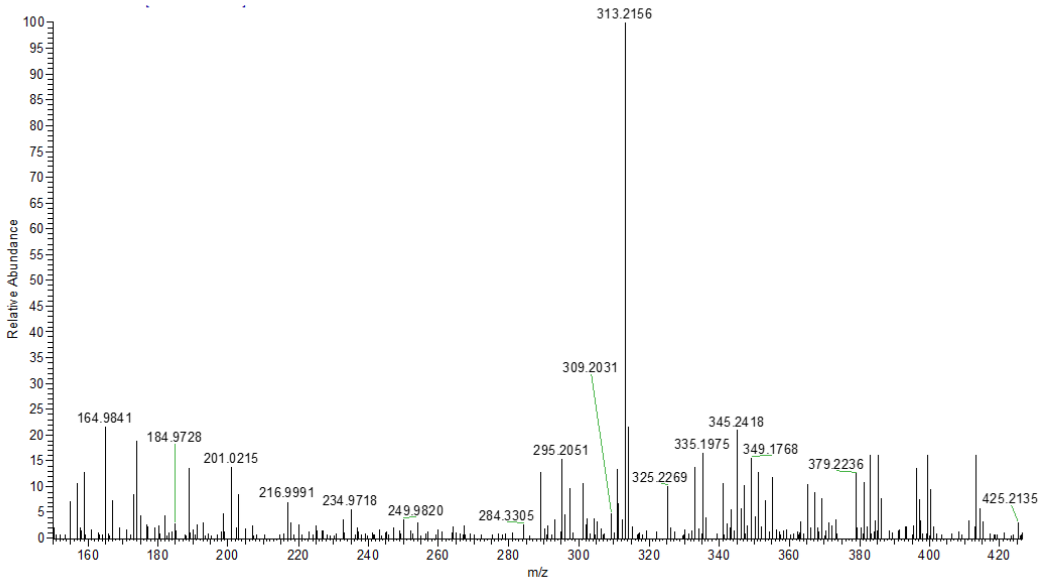



**Figure S6.** HRESIMS spectrum of avarone (**1**)

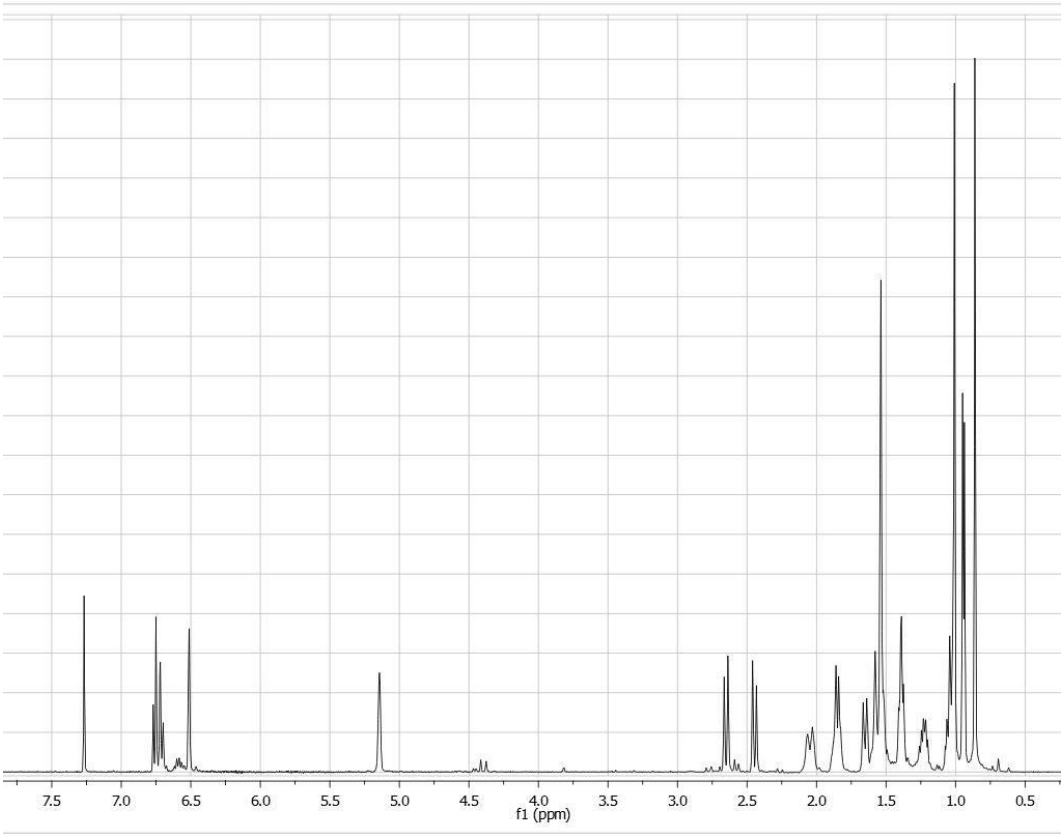



**Figure S7.** $^{1}$H-NMR spectrum of avarone (**1**) in $CDCl_3$

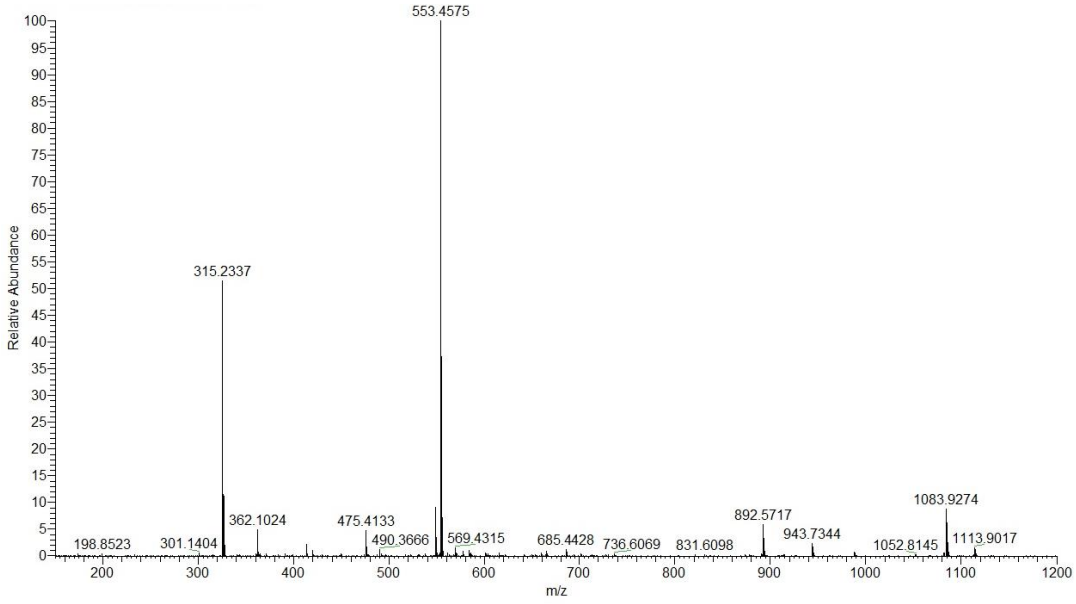



**Figure S8.** HRESIMS spectrum of avarol (**3**)

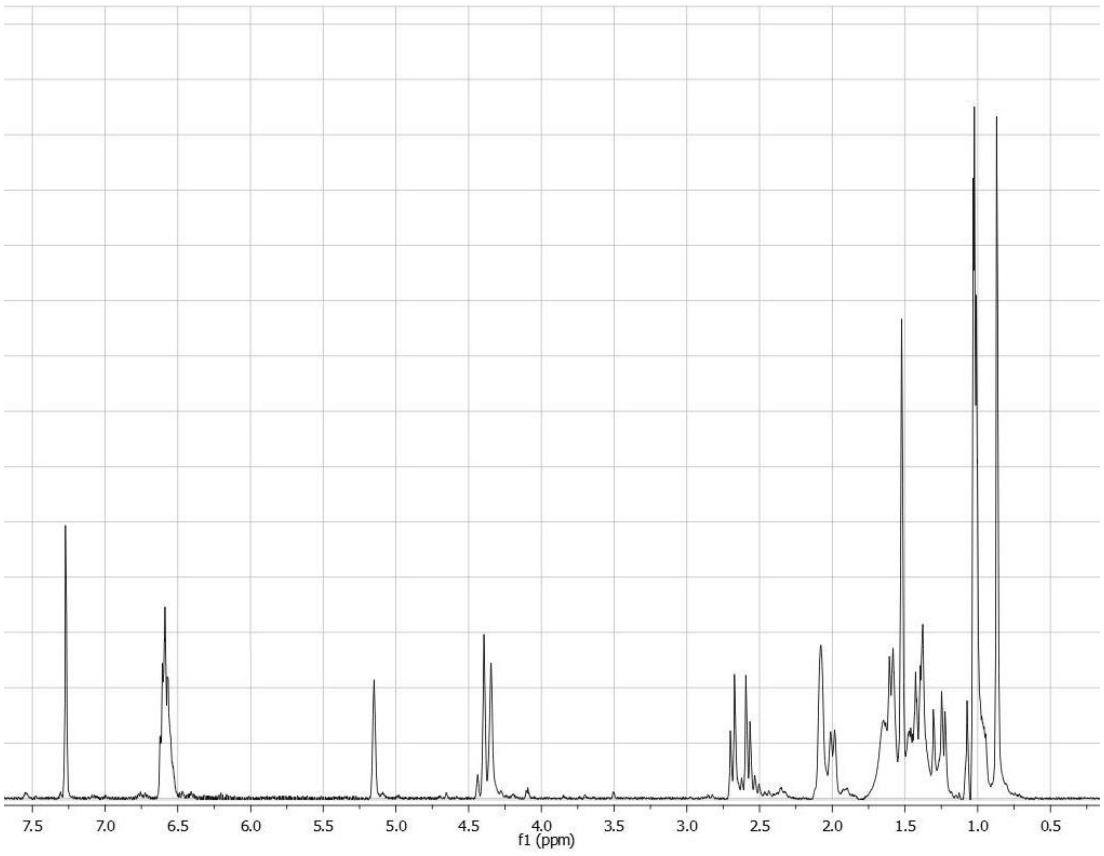



**Figure S9.** $^{1}$H-NMR spectrum of avarol (**3**) in $CDCl_3$

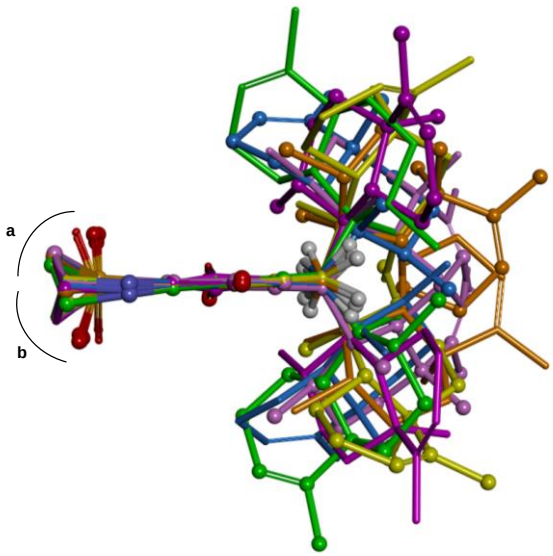



**Figure S10.** DFT conformers of compound **2** superimposed by the carbon atoms of quinone ring. The conformers characterized by flip a are showed in ball and stick while those characterized by the flip b are showed in stick. Carbon atoms are coloured according to family classification (I=green, II=magenta, III=pink, IV= loght blue, V= orange, and VI=Yellow); heteroatoms are colored by atom type (O= red, N= blue, S= yellow). Hydrogens are omitted for sake of clarity, with the exception of those of the first R' methylene group.

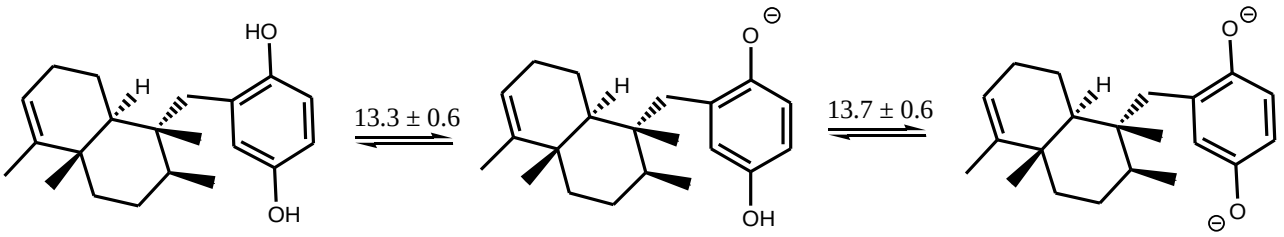



**Figure S11.** Structures of ionic forms and microcostant pka values calculated for **3** using the algorithm ACD/pKa Classic (ACD/Percepta software).

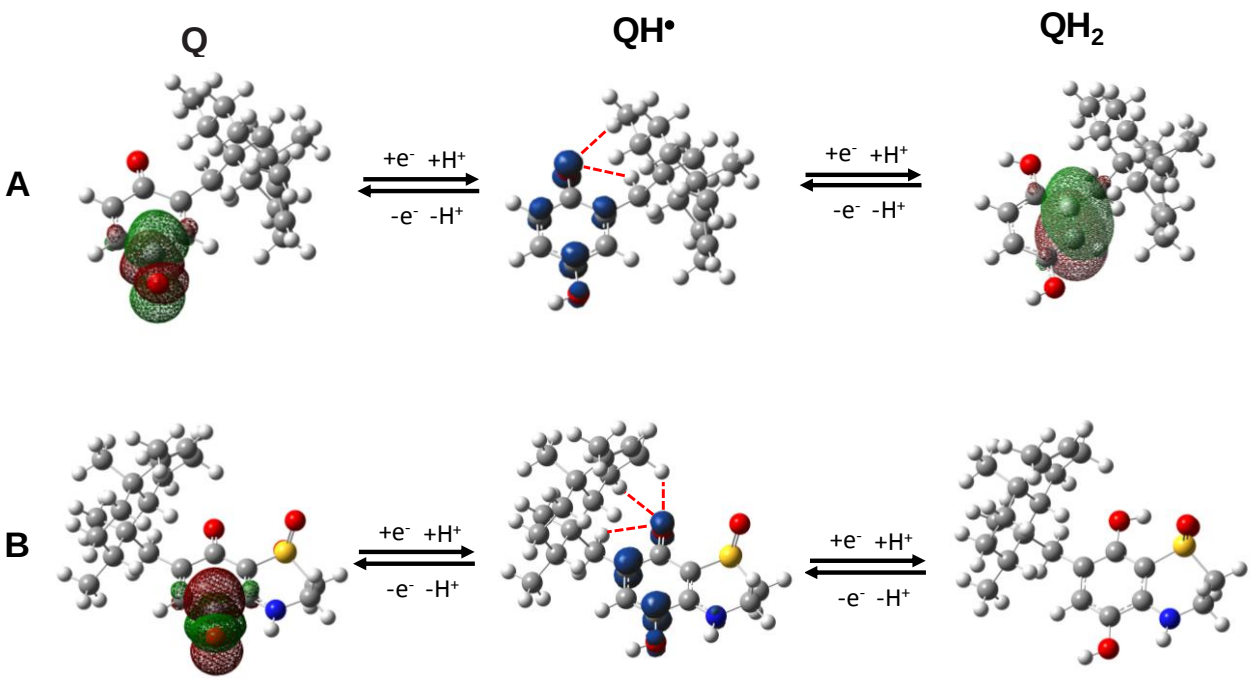
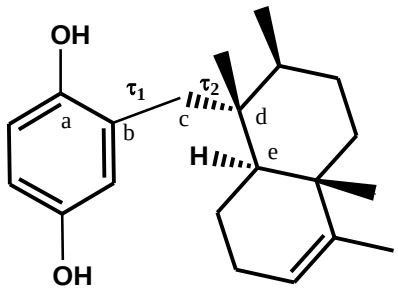



**Figure S12.** DFT conformer II of **1** (Q,), **3** ($QH_2$) and their semiquinone radical ($QH^{\bullet}$). (B) DFT conformer I of **2** (Q,) together with its one- and two-electron reduced species $QH^{\bullet}$ and $QH_2$. Atoms possibly involved in an intramolecular radical shift are evidenced with red dashed lines. The LUMO of **1** and **2**, and the HOMO of **3** are visualized using GaussView with an isosurface value of 0.02 $e^-$/a.u.$^3$ The NBO spin density isosurface of the $QH^{\bullet}$ species is displayed using GaussView with an isosurface value of 0.01 $e^-$/a.u.$^3$. The blue surface (positive spin density) corresponds to an excess of $\alpha$-electron density.

**Table S1.** $\Delta E_{GM}$ values (kcal/mol) and torsion angle values (degrees) of the DFT conformers of **3**.

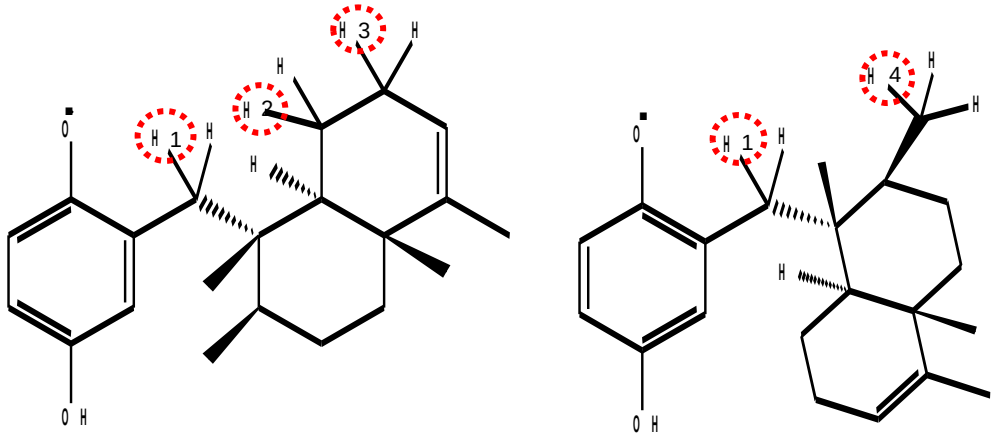



| Conf. | $\Delta E_{GM}$ (kcal/mol) | Torsion Angles (°) | |
|---|---|---|---|
| | | τ1[a] | τ2[b] |
| **II** | 0.00 | 96.77 | 56.16 |
| **I** | 0.23 | -104.40 | 59.80 |
| **III** | 1.45 | -102.26 | -179.87 |
| **IV** | 1.71 | 108.27 | -69.84 |
| **V** | 2.12 | 89.20 | 179.85 |
| **VI** | 2.68 | -86.45 | -76.24 |

[a]τ1 torsion angle is defined by a, b, c, and d atoms. [b]τ2 torsion angle is calculated considering b, c, d, and e atoms.

**Table S2.** List of the hydrogen atoms at a distance suitable for an intramolecular H-radical shift from a carbon atom of the R′ substituent to the reduced/oxidized oxygen atom of the semiquinone radical. Corresponding distances in the Q, QH• and $QH_2$ forms are also reported. Values are expressed in Å.

**Conf I** **Conf II**

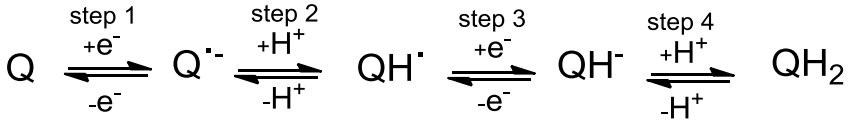



| Cmp | Conf | Distance | Q species | QH• species | $QH_2$ species |
|---|---|---|---|---|---|
| **Avarone/Avarol** | I | O-H1 | 2.43 | 2.41 | 2.43 |
| | I | O-H2 | 2.45 | 2.40 | 2.45 |
| | I | O-H3 | 2.92 | 3.02 | 2.77 |
| | II | O-H1 | 2.43 | 2.42 | 2.46 |
| | II | O-H4 | 2.49 | 2.45 | 2.54 |
| **Thiazoavarone** | I | O-H1 | 2.35 | 2.39 | 2.41 |
| | I | O-H2 | 2.39 | 2.39 | 2.44 |
| | I | O-H3 | 3.04 | 3.02 | 2.82 |
| | II | O-H1 | 2.38 | 2.40 | 2.45 |
| | II | O-H4 | 2.47 | 2.47 | 2.56 |

**Table S3.** ClogD of compounds **1-3**.

| Cmp | cLogD[a] |
|---|---|
| **1** | 6.13 |
| **2** | 3.83 |
| **3** | 5.22 |

[a]logD calculated considering pH values: 7.4, 7.2 and 5.5.




**Scheme S1.** Reduction pathway of quinone to hydroquinone in aqueous environment.