Supporting Information
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Supporting Information

Synthesis of new o-quinone methides from β-lapachone analogues

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Materials and methods

Reagents were purchased from Aldrich or Acros Chemical Co. and were used without further purification. Column chromatography was performed with silica gel 60 (Merck 70-230 mesh). Analytical thin-layer chromatography was performed with silica gel plates (Merck, TLC silica gel 60 F254), and the plots were visualized using UV light or aqueous solutions of sodium sulfate. Yields refer to chromatographically and spectroscopically homogeneous materials. Melting points were obtained on a Fischer-Johns apparatus and were uncorrected. Infrared spectra were measured using KBr pellets on a Perkin-Elmer model 1420 FT-IR Spectrophotometer, calibrated relative to the 1601.8 cm\textsuperscript{-1} absorbance of polystyrene. NMR spectra were recorded on a Varian Unity Plus VXR (300 and 500 MHz) instrument in DMSO-d$_6$ and CDCl$_3$ solutions. The
chemical shift data were reported in units of δ (ppm) downfield from tetramethylsilane, which was used as an internal standard; coupling constants (J) are reported in Hertz and refer to apparent peak multiplicities. The CHN elemental analyses were performed on a Perkin–Elmer 2400 CHN elemental analyzer (São Paulo University, USP/Brazil). Microwave irradiation experiments were performed using a model monowave 300 from Anton Paar.

**General Procedure for the reaction under conventional heating (9a-g).** To a round-bottom flask equipped with a magnetic stirring bar was added a solution of 1 mmol 4a-g and iodine (50 mg) in acetone (50 mL). The reaction mixture was stirred under reflux until the starting material (12 h) was consumed. The mixture was subsequently quenched with a saturated solution of sodium thiosulfate solution at room temperature and stirred for 30 minutes. The solution was filtered, evaporated under reduced pressure and dissolved with dichloromethane (50 mL). The organic phase was washed with water then brine, dried over anhydrous sodium sulfate and then filtered and concentrated under vacuum. The residual crude mixture was separated by flash chromatography using a silica gel column with hexanes and ethyl acetate as the mobile phase.

**General Procedure for the reaction under Microwave Irradiation (9a-g).** A solution of 4a-g (1 mmol) and iodine (25 mg) in acetone (10 mL) was inserted into a microwave oven capped tube (monowave 300 model, Anton Paar) and irradiated at 300 W for 10 minutes. The reaction was cooled to room temperature and subsequently quenched with a saturated sodium thiosulfate solution at room temperature for 30 minutes. The solution was filtered, evaporated under reduced pressure and dissolved with dichloromethane (50 mL). The organic phase was washed with water followed by brine, dried over anhydrous sodium sulfate and then filtered and concentrated under vacuum. The residual crude mixture was separated by flash chromatography on a silica gel column using a gradient mixture of hexanes and ethyl acetate.

**(E)-2-fenil-6-(2-oxopropilideno)-3,4-di-hidro-2H-benzo[h]cromen-5(6H)-ona (9a).** It was isolated as a yellowish oil 70% (thermal) and 80% (MW). IR (KBr, cm⁻¹): ν 3055-2985 (CH₃ and CH₂), 1584 (C=O); ¹H NMR (CDCl₃, 300 MHz): δ 2.2- 2.31 (1H,m, H-3), 2.34- 2.45 (1H, m, H-3), 2.56 (3H, d, J= 1.0 Hz, H-13) , 2.95 (1H ddd, J= 9.0; 6.3 and
(E)-2-(4-fluorfenil)-6-(2-oxopropilideno)-3,4-di-hidro-2H-benzo[h]cromen-5(6H)-ona (9b). It was isolated as a yellowish oil in 60% (thermal) and 65% (MW). IR (KBr, \text{cm}^{-1}): \nu 2921-2851 (\text{CH}_3 e \text{CH}_2), 1641 (C=O); \text{^1H NMR (CDCl}_3, 300 MHz): \delta 2,13-2,26 (1H, m, H-3), 2,32-2,43 (1H, m, H-3), 2,55 (3H, d, J=1,1, H-13), 2,92 (1H, ddd, J= 8,8; 10,2; 6,6 H-4), 5,21 (1H, dd, J= 10,2; 2,2, H-2), 6,43 (1H, q, J = 1,1 Hz; H-11), 7,07-7,13 (2H, m, H-1", H-2", H-3", H-5" and H-6"), 7,41 (1H, ddd, J= 10,2; 2,2 H-2, H-3", H-5" and H-6"), 7,40 (1H, ddd, J= 10,2; 2,2, H-2, H-3", H-5" and H-6"), 8,16 (dd, J= 8,8 and 1,3 Hz, H-10) 8,25 (dd, J= 8,4 and 2,0 Hz, H-7); \text{^13C NMR (CDCl}_3, 75 MHz): \delta 14.1 (C-13); 22.5 (C-4); 29.6 (C-3); 77.4 (C-2); 101.8 (C-11); 108.4 (C-4a); 115.0 and 115.3 (d, J= 21.4 Hz, C-3" and C-5"), 120.3 (C-10a); 122.8 (C-6a); 124.2 (C-1"); 160.5(C-4"); 137.7 (C-6); 145.3 (C-10b); 145.3 (C-5); 163.8 (C-12); 119.2; 122.2; 123.8; 125.8; 127.2 and 128.5 (C-2", C-3", C-4", C-5", C-6", C-7, C-8, C-9, C-10). Anal. Calcd for C_{22}H_{19}O_3: C, 79.98; H, 5.49. Found: C, 79.83; H, 5.23.

(E)-2-(4-clorofenil)-6-(2-oxopropilideno)-3,4-di-hidro-2H-benzo[h]cromen-5(6H)-ona (9c). It was isolated as a yellowish oil in 45% (thermal) and 58% (MW). IR (KBr, \text{cm}^{-1}): \nu 2921-2854 (\text{CH}_3 e \text{CH}_2), 1640 (C=O); \text{^1H NMR (CDCl}_3, 300 MHz): \delta 2,12-2,26 (1H, m, H-3), 2,32-2,43 (1H, m, H-3), 2,55 (3H, d, J=1,2, H-13), 2,92 (1H, ddd, J= 8,8; 10,2; 6,6 H-4), 5,21 (1H, dd, J= 10,2; 2,2, H-2), 6,43 (1H, q, J = 1,2 Hz; H-11), 7,37-7,48 (5H, m, H-2", H-3", H-5" and H-6", H-8), 7,52 (1H, ddd, J= 8,1; 6,8 and 1,2 Hz, H-9), 8,16 (dd, J= 8,3 and 1,2 Hz, H-10), 8,46 (dd, J= 8,3 and 1,2 Hz, H-7); \text{^13C NMR (CDCl}_3, 75 MHz): \delta 14.1 (C-13); 22.5 (C-4); 29.6 (C-3); 76.6 (C-2); 101.7 (C-11); 108.4 (C-4a); 120.3 (C-10a); 122.8 (C-6a); 124.1 (C-1"); 133.2 (C-4"); 140.4 (C-6); 144.0 (C-10b); 145.1 (C-5); 154.4 (C-12); 119.2; 122.2; 123.8; 125.8; 127.2 and 128.5 (C-2", C-3", C-4", C-5", C-6", C-7, C-8, C-9, C-10). Anal. Calcd for C_{22}H_{17}ClO_3: C, 72.43; H, 4.70. Found: C, 72.33; H, 4.68.
(E)-2-(4-bromofenil)-6-(2-oxopropilideno)-3,4-di-hidro-2H-benzo[h]cromen-5(6H)-ona (9d). It was isolated as a yellowish oil in 45% (thermal) and 52% (MW). IR (KBr, cm\(^{-1}\)): v 2919-2875 (CH\(_3\) and CH\(_2\)), 1639 (C=O); \(^1\)H NMR (CDCl\(_3\), 300 MHz): \(\delta\) 2,15-2,24 (1H, m, H-3), 2,33-2,42 (1H, m, H-3) 2,56 (3H, d, J=0,9, H-13), 2,93 (1H, ddd, J= 9,3; 6,3; 3,6 H-4), 3,12 (1H, ddd, J= 16,8; 10,5; 6,3 H-4), 5,20 (1H, dd, J= 9,9; 2,4 Hz H-2), 6,43 (1H, q, J = 0,9 Hz; H-11), 7,39-7,45 (3H,m, H-2", H-3", H-5" and H-6", H-8), 7,51-7,56 (4H, m, H-2", H-3", H-5" and H-6", H-8, H-9, H-10), 8,17 (dd, J=8,1 and 2,1 Hz, H-10) 8,25 (dd, J= 8,4 and 1,8 Hz, H-7); \(^13\)C NMR (CDCl\(_3\), 75 MHz): \(\delta\) 14.1 (C-13); 22.3 (C-4); 29.5 (C-3); 76.7 (C-2); 101.8 (C-11); 108.4 (C-4a) 120.3 (C-10a); 121.3 (C-6a); 122.1 (C-1") 124.1 (C-4") 140.9 (C-6); 144.0 (C-10b); 145.2 (C-5); 154.5 (C-12); 119.3; 122.2; 123.8; 125.8; 127.5 and 131.4 (C-2", C-3", C-5", C-6", C-7, C-8, C-9, C-10). Anal. Calcd for C\(_{22}\)H\(_{17}\)BrO\(_3\): C, 64.56; H, 4.19. Found: C, 64.50; H, 4.10.

(E)-6-(2-oxopropilideno)-2-p-toluil-3,4-di-hidro-2H-benzo[h]cromen-5(6H)-ona (9e). It was isolated as a yellowish oil in 20% (thermal) and 40% (MW). IR (KBr, cm\(^{-1}\)): v 2921-2854 (CH\(_3\) e CH\(_2\)), 1639 (C=O); \(^1\)H NMR (CDCl\(_3\), 300 MHz): \(\delta\) 2,19-2,30 (1H,m, H-3), 2,32-2,37 (1H, m, H-3), 2,39 (1H,s,CH\(_3\)) 2,55 (3H, d, J= 0,9, H-13), 2,95 (1H, ddd, J= 8,9; 6,3; 3,2 Hz H-4), 3,13 (1H, ddd, J= 17,3; 10,9; 6,3 Hz H-4), 5,21 (1H, dd, J= 9,8; 2,3, H-2), 6,44 (1H, q, J = 0,9 Hz; H-11), 7,22-7,24 (2H, m, H-1", H-2", H-3", H-5" and H-6") 7,37-7,44 (3H,m, H-1", H-2", H-3", H-5" and H-6", and H-9), 7,52 (1H, ddd, J= 8,2; 6,8 and 1,3 Hz, H-8), 8,16 (dd, J= 7,6 and 1,3 Hz, H-10) 8,28 (dd, J= 8,2 and 1,3 Hz, H-7); \(^13\)C NMR (CDCl\(_3\), 75 MHz): \(\delta\) 14.1 (C-13); 22.1 (C-4); 29.2(C-3); 76.3 (C-2); 101.5 (C-11); 108.1 (C-4a) 120.0 (C-10a); 122.4(C-6a); 123.8 (C-4") 132.9 (C-6); 140.1 (C-1") 144.9 (C-10b); 118.9; 121.9; 123.5; 125.5; 126.9; 128.2 (C-2", C-3", C-5", C-6", C-7, C-8, C-9, C-10). Anal. Calcd for C\(_{23}\)H\(_{20}\)O\(_3\): C, 80.21; H, 5.85. Found: C, 80.20; H, 5.80.

(E)-2-Metil-6-(2-oxopropilideno)-2-fenil-3,4-di-hidro-2H-benzo[h]cromen-5(6H)-ona (9f). It was isolated as a yellowish oil in 40% (thermal) and 48% (MW). IR (KBr, cm\(^{-1}\)): v 2924-2857 (CH\(_3\) and CH\(_2\)), 1640 (C=O); \(^1\)H NMR (CDCl\(_3\), 300 MHz): \(\delta\) 1.75 (3H, s, CH\(_3\)), 2.19-2.31 (1H,m, H-3), 2.49 (3H,d, J=0.9, H-13), 2.52-2.64 (2H, m, H-3 and H-4), 2.79-2.88 (1H, m, H-4), 6.31 (1H, q, J = 0.9 Hz; C-11), 7,14-7,43 (5H,m, H-1", H-2", H-3", H-4", H-5" and H-6"), 7,48 (1H,ddd, 9,9; 8,4 and 1,8 Hz, H-8), 7,54 (1H, ...
ddd, J= 8.4; 7.2 and 1.5 Hz, H-9), 8.16 (dd, J=7.8 and 1.5 Hz, H-10) 8.46 (dd, J= 8.4 and 1.2 Hz, H-7); 13C NMR (CDCl₃, 75 MHz): δ 14.5 (C-13); 20.7 (C-4); 30.5 (CH₃); 32.7 (C-3); 78.7 (C-2); 102.1 (C-11); 108.6 (C-4a); 120.9 (C-10a); 123.3 (C-6a); 124.5 (C-1") ; 144.2 (C-6); 144.4 (C-10b); 146.0 (C-5); 154.6 (C-12); 119.7; 122.6; 124.2; 125.0; 126.1. 127.0 and 128.6 (C-2", C-3", C-4", C-5", C-6", C-7, C-8, C-9, C-10). Anal. Calcd for C₂₃H₂₀O₃: C, 80.21; H, 5.85. Found: C, 80.19; H, 5.83