Supplementary Information

Convenient approach to an advanced intermediate toward the naturally occurring, bioactive 6-substituted 5-hydroxy-4-aryl-1H-quinolin-2-ones

Sebastian O. Simonetti, Enrique L. Larghi and Teodoro S. Kaufman*

Instituto de Química Rosario (IQUIR, CONICET-UNR) and Facultad de Ciencias Bioquímicas y Farmacéuticas, Universidad Nacional de Rosario, Suipacha 531, S2002LRK Rosario, Argentina.
# TABLE OF CONTENTS

Experimental Procedures and Spectral Data (Compounds 13, 14, 14a, 16, 17, 18 and 20) S3
Figures S1 and S2. $^1$H NMR (300 MHz) and $^{13}$C NMR (75 MHz) spectra of compound 13 S9
Figures S3 and S4. $^1$H NMR (300 MHz) and $^{13}$C NMR (75 MHz) spectra of compound 14a S10
Figures S5 and S6. $^1$H NMR (300 MHz) and $^{13}$C NMR (75 MHz) spectra of compound 16 S11
Figures S7 and S8. COSY and HSQC spectra of compound 16 S12
Figures S9 and S10. HMBC and NOE spectra of compound 16 S13
Figures S11 and S12. $^1$H NMR (300 MHz) and $^{13}$C NMR (75 MHz) spectra of compound 17 S14
Figures S13 and S14. COSY and HSQC spectra of compound 17 S15
Figures S15 and S16. $^1$H NMR (300 MHz) and $^{13}$C NMR (75 MHz) spectra of compound 18 S16
Figures S17 and S18. COSY and HSQC spectra of compound 18 S17
Figures S19 and S20. $^1$H NMR (300 MHz) and $^{13}$C NMR (75 MHz) spectra of compound 20 S18
Figures S21 and S22. COSY and HSQC spectra of compound 20 S19
Figures S23 and S24. $^1$H NMR (300 MHz) and $^{13}$C NMR (75 MHz) spectra of compound 22 S20
Figures S25 and S26. $^1$H NMR (300 MHz) and $^{13}$C NMR (75 MHz) spectra of compound 23 S21
Figures S27 and S28. $^1$H NMR (300 MHz) and $^{13}$C NMR (75 MHz) spectra of compound 24 S22
Figures S29 and S30. $^1$H NMR (300 MHz) and $^{13}$C NMR (75 MHz) spectra of compound 26 S23
Figures S31 and S32. $^1$H NMR (300 MHz) spectra of compound 19 S24
Figures S33 and S34. TOCSY and $^{13}$C NMR (75 MHz) spectra of compound 19 S25
Figures S35 and S36. $^1$H NMR (300 MHz) and $^{13}$C NMR (75 MHz) spectra of compound 27 S26
Figures S37 and S38. $^1$H NMR (300 MHz) and $^{13}$C NMR (75 MHz) spectra of compound 31 S27
Figures S39 and S40. $^1$H NMR (300 MHz) and $^{13}$C NMR (75 MHz) spectra of compound 32 S28
Figures S41 and S42. $^1$H NMR (300 MHz) and $^{13}$C NMR (75 MHz) spectra of compound 33 S29
Figures S43 and S44. $^1$H NMR (300 MHz) and $^{13}$C NMR (75 MHz) spectra of compound 35 S30
Figures S45 and S46. $^1$H NMR (300 MHz) and zoom of $^1$H spectra of compound 36 S31
Figure S47. $^{13}$C NMR (75 MHz) spectrum of compound 36 S32
References S33
2-Benzylbenzaldehyde (13): K$_2$CO$_3$ (679 mg, 4.91 mmol) was added to a stirred solution of commercial salicylaldehyde (12, 200 mg, 1.638 mmol) in absolute EtOH (3 mL); the mixture was stirred for 10 minutes at room temperature and then treated with benzyl chloride (415 mg, 3.28 mmol). The reaction mixture was stirred overnight at 70 °C, the EtOH was evaporated under reduced pressure and the resulting mixture was diluted with brine (10 mL) and 1M NaOH (10 mL). The reaction products were extracted with EtOAc (3 × 20 mL), and the combined extracts were washed with water (10 mL), dried (Na$_2$SO$_4$) and concentrated under reduced pressure to afford 13 (347 mg, 99%), as a pale yellow oil. IR (film, ν): 3734, 3250, 1646, 1626, 1578, 1368, 1340, 1283, 1153, 1081, 1010, 842 and 669 cm$^{-1}$. $^1$H NMR δ 5.20 (s, 2H, OCH$_2$Ar), 7.04 (t, J = 7.9, 1H, H-5), 7.05 (d, J = 7.9, 1H, H-3), 7.35-7.46 (m, 5H, ArH of Benzyl), 7.53 (dt, J = 1.9 and 7.9, 1H, H-4), 7.86 (dd, J = 1.9 and 7.9, 1H, H-6) and 10.57 (s, 1H, CHO). $^{13}$C NMR δ 70.5 (OCH$_2$Ar), 113.1 (C-3), 121.0 (C-5), 125.2 (C-1), 127.3 (C-1’ and C-6’), 128.3 (C-4’), 128.5 (C-6), 128.7 (C-3’ and C-5’), 135.9 (C-4), 136.1 (C-1’), 161.1 (C-2) and 189.8 (CHO). HRMS m/z calcd. for C$_{14}$H$_{11}$NNaO$_4$: 280.0578 [M +Na]$^+$; found: 280.0580.

Methyl 3-(2-benzylbenzyl)acrylate (14): $^1$ Trimethylphosphonoacetate (1236 mg, 6.798 mmol) was added to a stirred mixture of 13 (500 mg, 2.358 mmol), K$_2$CO$_3$ (875 mg, 6.249 mmol) and H$_2$O (0.5 mL) and the system was heated under reflux during 30 minutes, when it was assessed (TLC) the absence of the starting material. Then, the reaction products were extracted with EtOAc (3 × 20 mL), and the combined extracts were washed with brine (10 mL), dried over Na$_2$SO$_4$ and concentrated under reduce pressure. Column
chromatography of the residue afforded 14 (859 mg, 55%), as a pale yellow oil. IR (film, ν): 3032, 2947, 1714, 1597, 1452, 1321, 1242, 1170, 1014, 752 and 696 cm⁻¹. ¹H NMR δ 3.79 (s, 3H, OCH₃), 5.17 (s, 2H, OCH₂Ar), 6.55 (d, J = 16.2, 1H, Ar-CH=CH-CO₂CH₃), 6.96 (d, J = 8.0, 1H, H-3), 6.97 (t, J = 8.0, 1H, H-5), 7.30 (dt, J = 1.2 and 8.0, 1H, H-4), 7.34-7.46 (m, 5H, ArH of Benzyl), 7.54 (dd, J = 1.2 and 8.0, 1H, H-6) and 8.09 (d, J = 16.2, 1H, Ar-CH=CH-CO₂CH₃). ¹³C NMR δ 51.6 (OCH₃), 70.4 (OCH₂Ar), 112.8 (C-3), 118.4 (Ar-CH=CH-CO₂CH₃), 121.0 (C-5), 123.8 (C-1), 127.2 (C-2’ and C-6’), 128.0 (C-4’), 128.7 (C-3’ and C-5’), 128.9 (C-6), 131.4 (C-4), 136.6 (C-1’), 140.2 (Ar-CH=CH-CO₂CH₃), 157.4 (C-2) and 167.9 (Ar-CH=CH-CO₂CH₃).

**Ethyl 3-(2-benzyloxyphenyl)acrylate (14a):** A mixture of aldehyde 13 (265 mg, 1.03 mmol) and ethyl (triphenyl-λ₅-phosphanylidene)-acetate (1180 mg, 2.06 mmol) in dichloromethane (5 mL) was stirred at room temperature for 5 h. Once demonstrated the complete consumption of the starting material by TLC, the solvent was removed under reduced pressure and the residue was chromatographed, rendering 14a (297 mg, 88%), as a colorless oil. The major isomer (**E-14a**) is described. IR (film, ν): 2936, 1712, 1632, 1597, 1485, 1315, 1269, 1165, 1026, 991, 752 and 698 cm⁻¹. ¹H NMR δ 1.34 (t, J = 7.1, 3H, OCH₂CH₃), 4.26 (q, J = 7.1, 2H, OCH₂CH₃), 5.17 (s, 2H, OCH₂Ar), 6.55 (d, J = 16.2, 1H, Ar-CH=CH-CO₂CH₂CH₃), 6.94 (d, J = 7.5, 1H, H-3), 6.97 (t, J = 7.5, 1H, H-5), 7.30 (dt, J = 1.4 and 7.5, 1H, H-4), 7.34-7.46 (m, 5H), 7.55 (dd, J = 1.4 and 7.5, 1H, H-6) and 8.10 (d, J = 16.2, 1H, Ar-CH=CH-CO₂CH₂CH₃). ¹³C NMR δ 14.3 (OCH₂CH₃), 60.3 (OCH₂CH₃), 70.4 (OCH₂Ar), 112.8 (C-3), 118.9 (Ar-CH=CH-CO₂CH₂CH₃), 121.0 (C-5), 123.9 (C-1), 127.1 (C-2’ and C-6’).
128.4 (C-4'), 128.6 (C-3' and C-5'), 131.3 (C-4), 136.6 (C-1'), 139.9 (Ar-CH=CH-CO₂CH₂CH₃), 157.3 (C-2) and 167.5 (Ar-CH=CH-CO₂CH₂CH₃).

**Ethyl 3-(2-benzyloxyphenyl)-3-(4'-methoxyphenyl)acrylate (16):** The cinnamate 14 (118 mg, 0.440 mmol) was added to a stirred mixture of 4-iodoanisole (154 mg, 0.66 mmol) and Pd(OAc)₂ (5 mg, 0.022 mmol) in Et₃N (3 mL), under an Ar atmosphere. The mixture was stirred at 100 °C during 17 h, when the reaction was diluted in EtOAc (15 mL) and the organic phase was successively washed with 2N HCl solution (10 mL), saturated NaHCO₃ (10 mL) and brine (10 mL). The organic layer was dried with Na₂SO₄ and concentrated under reduced pressure. The residue was chromatographed, affording 16 (120 mg, 73%), as a yellow oil. IR (film, ν): 2934, 1717, 1603, 1508, 1448, 1362, 1252, 1173, 1028, 833 and 741 cm⁻¹. ¹H NMR δ 1.06 (t, J = 7.1, 3H, OCH₂CH₃), 3.82 (s, 3H, OCH₃), 3.99 (q, J = 7.1, 2H, OCH₂CH₃), 4.98 (s, 2H, OCH₂Ar), 6.40 (s, 1H, Ar₂-C=CH-CO₂CH₂CH₃), 6.83 (d, J = 9.0, 2H, H-3’ and H-5’), 6.98 (d, J = 7.3, 1H, H-3), 7.00 (t, J = 7.3, 1H, H-5), 7.11 (dd, J = 1.7 and 7.3, 1H, H-6), 7.18-7.34 (m, 5H, ArH of Benzyl), 7.29 (d, J = 9.0, 2H, H-2’ and H-6’) and 7.32 (t, J = 7.3, 1H, H-4). ¹³C NMR δ 14.0 (OCH₂CH₃), 55.3 (O-CH₃), 59.7 (OCH₂CH₃), 70.0 (OCH₂Ar), 112.5 (C-3), 113.7 (C-3’ and C-5’), 116.3 (Ar₂-C=CH-CO₂CH₂CH₃), 120.6 (C-5), 126.9 (Benzyl), 127.4 (Benzyl), 128.2 (Benzyl), 128.9 (C-1), 129.0 (C-2’ and C-6’), 129.2 (C-4), 130.3 (C-6), 133.1 (C-1’), 137.2 (Benzyl), 153.1 (Ar₂-C=CH-CO₂CH₂CH₃), 155.6 (C-2), 160.6 (C-4’) and 166.1 (CO₂Et). HRMS m/z calcd. for C₂₄H₂₂NO₆: 447.1567 [M + Na]⁺; found: 447.1555.
3-(2-Benzyl氧xyphenyl)-3-(4'-methoxyphenyl)-acrylic acid (17): A stirred solution of ester 16 (107 mg, 0.297 mmol) in EtOH:H₂O (1:1, v/v, 7 mL), was treated with KOH (40.1 mg, 0.714 mmol) during 18 h at room temperature. After assessing the absence of the starting material (TLC), the reaction was diluted with Et₂O (10 mL) and 2M NaOH (10 mL). The aqueous phase was separated, acidified with 2M HCl (15 mL), and extracted with Et₂O (3 x 15 mL). The organic layer was dried with Na₂SO₄ and concentrated under reduced pressure, affording 17 (89 mg, 90%), as a colorless solid, m.p.: 164-165 ºC (EtOAc). IR (KBr, ν): 3977, 2927, 1674, 1585, 1450, 1258, 1153, 1034, 748 and 605 cm⁻¹. ¹H NMR (Acetone-d₆) δ 3.81 (s, 3H, OCH₃), 5.00 (s, 2H, OCH₂Ar), 6.41 (s, 1H, Ar₂-C=CH-CO₂H), 6.91 (d, J = 8.8, 2H, H-3' and H-5'), 6.97 (dt, J = 0.9 and 7.9, 1H, H-5), 7.08 (d, J = 7.9, 1H, H-3), 7.11 (d, J = 7.9, 1H, H-6), 7.12 (d, J = 9.0, 2H, ArH of Benzyl), 7.20-7.23 (m, 3H, ArH of Benzyl), 7.31 (dt, J = 1.4 and 7.9, 1H, H-4) and 7.80 (d, J = 8.8, 2H, H-2' and H-6'). ¹³C NMR (Acetone-d₆) δ 54.8 (OCH₃), 70.0 (OCH₂Ar), 112.5 (C-3), 113.7 (C-3' and C-5'), 116.2 (Ar₂-C=CH-CO₂H), 120.3 (C-5), 127.0 (Benzyl), 127.3 (Benzyl), 128.1 (Benzyl), 128.8 (C-2' and C-6'), 129.0 (C-4), 129.0 (Ar₂-C=CH-CO₂H), 130.3 (C-6), 132.9 (C-1'), 137.5 (Benzyl), 153.1 (Ar₂-C=CH-CO₂H), 155.8 (C-2'), 160.8 (C-4') and 165.9 (Ar₂-C=CH-CO₂H). HRMS m/z calcd. for C₂₃H₂₀NaNO₆: 383.1254 [M + Na]⁺; found: 383.1254.

N-[3-(2-Benzyl氧xyphenyl)-3-(4'-methoxyphenyl)-acyloyloxy]-4-methyl benzenesulfonamide (18): A stirred solution of acid 17 (50 mg, 0.166 mmol) in anhydrous THF (1 mL) was treated with TsNCO (39.2 mg, 0.199 mmol). The mixture was stirred during 10 minutes at room temperature, when Et₃N (26.1
mg, 0.258 mmol) was added dropwise and the solution was further stirred overnight. The reaction was quenched with 2N HCl (5 mL) and the organic products were extracted with Et₂O (3 × 15 mL). The combined organic layers were dried over Na₂SO₄ and concentrated under reduce pressure, affording the sulfonimide 18 (68 mg, 95%), as a white solid, mp. 150-152 °C (EtOAc). IR (ATR, ν): 3167, 2928, 2862, 1663, 1585, 1443, 1339, 1258, 1130, 1084, 868, 602 cm⁻¹. ¹H NMR δ 2.43 (s, 3H, ArCH₃), 3.81 (s, 3H, OCH₃), 4.82 (s, 1H, NH), 4.95 (s, 2H, OCH₂Ar), 6.37 (s, 1H, Ar₂-C=CH-CONHTs), 7.03-7.06 (m, 5H, ArH of Benzyl), 7.09 (dd, J = 1.2 and 7.5, 1H, H-6), 7.26 (d, J = 8.6, 2H, H-2’ and H-6’), 7.31 (d, J = 8.1, 2H, ArH of Arenesulfonimide), 7.32 (dt, J = 1.2 and 7.5, 1H, H-4) and 7.81 (d, J = 8.1, 2H, ArH of Arenesulfonimide). ¹³C NMR δ 21.5 (ArCH₃), 55.4 (OCH₃), 70.1 (OCH₂Ar), 112.6 (C-3), 113.8 (C-3’ and C-5’), 115.3 (Ar₂-C=CH-CONHTs), 120.6 (C-5), 126.5 (Benzyl), 127.0 (Benzyl), 127.5 (Benzyl), 128.2 (Arenesulfonimide), 128.3 (Benzyl), 129.2 (C-2’ and C-6’), 129.5 (C-4), 129.7 (Arenesulfonimide), 130.4 (C-6), 132.7 (C-1), 137.0 (C-1’), 139.1 (Arenesulfonimide), 143.6 (Arenesulfonimide), 155.1 (Ar₂-C=CH-CONHTs), 155.6 (C-2), 160.9 (C-4’) and 169.5 (Ar₂-C=CH-CONHTs). HRMS m/z calcd. for C₃₀H₂₇NNaO₅S: 536.1500 [M + Na]⁺; found: 536.1502.

3-(2-Benzylxyloxyphenyl)-3-(4'-methoxyphenyl)acrylamide (20): Et₃N (0.5 mL) was added to a well ground and magnetically stirred mixture of carboxylic acid 17 (145 mg, 0.402 mmol), silica-supported ammonium salt (NH₄Cl, 43.8 mg, 0.809 mmol) prepared under literature conditions and TsCl (76.6 mg, 0.402 mmol). After 1 min, the reaction mixture was diluted with EtOAc (25 mL) and
filtered. The filtrate was washed with 0.02 N HCl (2 × 25 mL) and the aqueous layer was re-extracted with EtOAc (15 mL). The combined organic layers were dried over anhydrous MgSO₄ and concentrated under reduced pressure. The residue was purified by column chromatography, affording 20 (116 mg, 80%), as a pale yellow solid, m.p.: 168-170 °C (EtOAc). IR (KBr, v): 3348, 2932, 1674, 1585, 1450, 1258, 1123, 1034, 748, 683 cm⁻¹. ¹H NMR δ 3.81 (s, 3H, OCH₃), 4.95 (s, 2H, OCH₂Ar), 4.99 (s, 2H, -NH₂), 6.38 (s, 1H, Ar₂-C=CHCONH₂), 6.83 (d, J = 8.9, 2H, H-3’ and H-5’), 6.95 (d, J = 7.5, 1H, H-3), 6.98 (t, J = 7.5, 1H, H-5), 7.09 (dd, J = 1.6 and 7.5, 1H, H-6), 7.20-7.25 (m, 5H, ArH of Benzyl), 7.29 (d, J = 8.9, 2H, H-2’ and H-6’) and 7.30 (t, J = 7.5, 1H, H-4). ¹³C NMR δ 55.4 (OCH₃), 70.1 (OCH₂Ar), 112.6 (Ar₂-C=CHCONH₂), 113.8 (C-3’ and C-5’), 115.4 (C-3), 120.6 (C-5), 127.5 (Benzyl), 128.2 (Benzyl), 128.4 (C-1), 129.2 (Benzyl), 129.5 (C-4), 129.7 (C-2’ and C-6’), 130.4 (C-6), 132.8 (C-1’), 137.0 (Ar₂-C=CHCONH₂), 139.2 (Benzyl), 155.6 (C-2), 160.9 (C-4’) and 170.1 (Ar₂-C=CHCONH₂). HRMS m/z calcd. for C₂₃H₂₂NO₃: 360.1600 [M + H]⁺; found: 360.1594.
Figure S1. $^1$H NMR (300 MHz) spectrum of compound 13.

Figure S2. $^{13}$C NMR (75 MHz) spectrum of compound 13.
Figure S3. $^1$H NMR (300 MHz) spectrum of compound 14a.

Figure S4. $^{13}$C NMR (75 MHz) spectrum of compound 14a.
Figure S5. $^1$H NMR (300 MHz) spectrum of compound 16.

Figure S6. $^{13}$C NMR (75 MHz) spectrum of compound 16.
Figure S7. COSY spectrum of compound 16.

Figure S8. HSQC spectrum of compound 16.
Figure S9. HMBC spectrum of compound 16.

Figure S10. nOe spectrum. Irradiation at 6.40 ppm in compound 16.
Figure S11. $^1$H NMR (300 MHz) spectrum of compound 17 in acetone-$d_6$.

Figure S12. $^{13}$C NMR (75 MHz) spectrum of compound 17 in acetone-$d_6$. 
**Figure S13.** COSY spectrum of compound 17 in acetone-\(d_6\).

**Figure S14.** HSQC spectrum of compound 17 in acetone-\(d_6\).
Figure S15. $^1$H NMR (300 MHz) spectrum of compound 18.

Figure S16. $^{13}$C NMR (75 MHz) spectrum of compound 18.
Figure S17. COSY spectrum of compound 18.

Figure S18. HSQC spectrum of compound 18.
Figure S19. $^1$H NMR (300 MHz) spectrum of compound 20.

Figure S20. $^{13}$C NMR (75 MHz) spectrum of compound 20.
Figure S21. COSY spectrum of compound 20.

Figure S22. HSQC spectrum of compound 20.
Figure S23. $^1$H NMR (300 MHz) spectrum of compound 22.

Figure S24. $^{13}$C NMR (75 MHz) spectrum of compound 22.
Figure S25. $^1$H NMR (300 MHz) spectrum of compound 23.

Figure S26. $^{13}$C NMR (75 MHz) spectrum of compound 23.
Figure S27. $^1$H NMR (300 MHz) spectrum of compound 24.

Figure S28. $^{13}$C NMR (75 MHz) spectrum of compound 24.
Figure S29. $^1$H NMR (300 MHz) spectrum of compound 26.

Figure S30. $^{13}$C NMR (75 MHz) spectrum of compound 26.
**Figure S31.** $^1$H NMR (300 MHz) spectrum of compound 19 in DMSO-$d_6$.

**Figure S32.** $^1$H NMR (300 MHz) spectrum with water suppression of compound 19 in DMSO-$d_6$. 
Figure S33. TOCSY 1D NMR (300 MHz) spectrum of compound 19 in DMSO-\textit{d}_6.

Figure S34. $^{13}$C NMR (75 MHz) spectrum of compound 19 in DMSO-\textit{d}_6.
Figure S35. $^1$H NMR (300 MHz) spectrum of compound 27.

Figure S36. $^1$H NMR (300 MHz) spectrum of compound 27.
Figure S37. $^1$H NMR (300 MHz) spectrum of compound 31 in DMSO-$d_6$.

Figure S38. $^{13}$C NMR (75 MHz) spectrum of compound 31 in DMSO-$d_6$. 
Figure S39. $^1$H NMR (300 MHz) spectrum of compound $32$.

Figure S40. $^{13}$C NMR (75 MHz) spectrum of compound $32$. 
Figure S41. $^1$H NMR (300 MHz) spectrum of compound 33.

Figure S42. $^{13}$C NMR (75 MHz) spectrum of compound 33.
Figure S43. $^1$H NMR (300 MHz) spectrum of compound 35.

Figure S44. $^{13}$C NMR (75 MHz) spectrum of compound 35.
Figure S45. $^1$H NMR (300 MHz) spectrum of compound 36.

Figure S46. $^1$H NMR (300 MHz) zoom from 6.0 to 6.8 ppm of the spectrum of compound 36.
Figure S47. $^{13}$C NMR (75 MHz) spectrum of compound 36.
References

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