Supplementary Materials

Functionality study of chalcone-hydroxypyridinone hybrids as tyrosinase inhibitors and influence on anti-tyrosinase activity

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General procedure for the synthesis of compounds 1a-1o

Potassium tert-butoxide (0.79 mmol) was added to a stirred solution of the requisite phosphonate (7a-7d, 0.79 mmol) in THF (10 mL) at room temperature and stirred for 15 min. Aldehyde (4a-4e, 0.87 mmol) dissolved in THF (5 mL) was added dropwise via a syringe at 0-5 °C and the reaction mixture stirred for 2 h. The reaction was quenched with methanol (4 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were then washed with brine (15 mL), dried and concentrated in vacuo to give a solid residue, which was dissolved in CH₂Cl₂ (5 mL).
The resulting solution was cooled in an ice-bath to 0-5 °C, BBr₃ (1.0 M in CH₂Cl₂, 5 mL) was added dropwise. After stirring at 0-5 °C for 50 min, the mixture was quenched with MeOH, diluted with water and extracted with CH₂Cl₂. The combined organic extracts were dried over anhydrous Na₂SO₄ and evaporated. Column chromatography of the residue over silica gel, using 1:30 MeOH-CH₂Cl₂, gave final compounds (1a-1o) as a yellow solid.

(E)-2-(3-(4-fluorophenyl)-3-oxoprop-1-en-1-yl)-5-hydroxy-1-methylpyridin-4(1H)-one (1a). Yield: 71 %. ¹H NMR (400 MHz, DMSO-d₆) δ 8.30 (d, J = 5.5 Hz, 1H), 8.28 (d, J = 5.5 Hz, 1H), 8.08 (d, J = 15.4 Hz, 1H), 7.75 (d, J = 15.4 Hz, 2H), 7.45 (t, J = 8.9 Hz, 2H), 4.13 (s, 3H); ¹³C NMR (101 MHz, DMSO-d₆) δ 187.15, 166.91, 164.39, 159.58, 145.66, 143.22, 133.43, 132.22, 130.98, 116.38, 116.16, 112.54, 44.37; HRMS (ESI): calcd for C₁₅H₁₃FNO₃ [M + H]⁺ 274.0874, found 274.0880.

(E)-5-hydroxy-2-(3-(2-hydroxy-4-methoxyphenyl)-3-oxoprop-1-en-1-yl)-1-methylpyridin-4(1H)-one (1b). Yield: 69 %. ¹H NMR (400 MHz, DMSO) δ 8.48 (s, 1H), 8.31 (s, 1H), 8.15 (d, J = 15.2 Hz, 1H), 7.80 (m, 2H), 6.76 (s, 1H), 4.15 (s, 3H), 3.95 (s, 3H); ¹³C NMR (101 MHz, DMSO) δ 189.41, 164.35, 161.90, 159.49, 145.61, 142.87, 134.65, 133.30, 131.93, 130.94, 115.14, 112.62, 101.39, 101.24, 57.10, 44.22; HRMS (ESI): calcd for C₁₆H₁₅NO₅ [M + H]⁺ 302.1023, found 302.1026.

(E)-2-(3-(2,4-dimethoxyphenyl)-3-oxoprop-1-en-1-yl)-5-hydroxy-4H-pyran-4-one (1c). Yield: 65 %. ¹H NMR (400 MHz, DMSO) δ 8.13 (s, 1H), 8.07 (d, J = 9.0 Hz, 1H), 7.95 (d, J = 13.4 Hz, 1H), 7.45 (d, J = 15.4 Hz, 1H), 6.97 (s, 1H), 6.58 (d, J = 9.3 Hz, 1H), 6.40 (d, J = 8.5 Hz, 1H), 3.85 (s, 3H), 3.75 (s, 3H). HRMS (ESI): calcd for C₁₆H₁₄O₆ [M + H]⁺ 303.0863, found 303.0859.

(E)-2-(3-(4-fluorophenyl)-3-oxoprop-1-en-1-yl)-5-hydroxypyridin-4(1H)-one (1d). Yield: 66 %. ¹H NMR (400 MHz, DMSO) δ 8.26 (td, J = 8.8, 3.9 Hz, 3H), 8.18 (s,
\[ \text{1H, 7.80 (s, 1H), 7.67 (d, } J = 15.7 \text{ Hz, 1H), 7.47 (t, } J = 8.8 \text{ Hz, 2H); } ^{13}\text{C NMR (101 MHz, DMSO)} \delta 186.98, 166.86, 164.34, 160.77, 145.95, 140.62, 133.45, 131.97, 127.84, 116.36, 116.15, 112.48; \text{ HRMS (ESI) calcd for } \text{C}_{14}\text{H}_{10}\text{FNO}_{3} [M + H]^+ 260.0717, \text{ found } 260.0721. \]

\((E)-1\text{-ethyl-5-hydroxy-2-(3-oxo-3-phenylprop-1-en-1-yl)pyridin-4(1H)-one (1e).}\)

Yield: 61\%, \text{ } ^{1}\text{H NMR (600 MHz, DMSO)} \delta 8.32 (s, 1H), 8.20 – 8.18 (m, 3H), 8.11 (d, } J = 15.2 \text{ Hz, 1H), 7.77 (m, 2H), 7.62 (m, 2H), 4.53 (q, } J = 7.2 \text{ Hz, 2H), 1.38 (t, } J = 7.2 \text{ Hz, 3H); } ^{13}\text{C NMR (101 MHz, DMSO)} \delta 188.38, 159.85, 145.91, 142.40, 136.43, 134.07, 131.99, 131.68, 131.56, 129.03, 128.93, 113.04, 51.73, 15.81; \text{ HRMS (ESI): calcd for } \text{C}_{16}\text{H}_{15}\text{NO}_{3} [M + H]^+ 270.1125, \text{ found } 270.1129. \]

\((E)-2-(3-(3,4-dihydroxyphenyl)-3-oxoprop-1-en-1-yl)-1-ethyl-5-hydroxypyridin-4(1H)-one (1f).\)

Yield: 62\%, \text{ } ^{1}\text{H NMR (400 MHz, DMSO)} \delta 8.32 (s, 1H), 8.00 (d, } J = 15.3 \text{ Hz, 1H), 7.73 (s, 1H), 7.70 – 7.64 (m, 2H), 7.53 (d, } J = 2.9 \text{ Hz, 1H), 6.89 (d, } J = 8.2 \text{ Hz, 1H), 4.51 (q, } J = 7.2 \text{ Hz, 2H), 1.37 (t, } J = 7.2 \text{ Hz, 3H); } ^{13}\text{C NMR (101 MHz, DMSO)} \delta 186.15, 160.07, 152.01, 145.86, 142.77, 131.99, 131.76, 130.34, 128.61, 123.14, 115.50, 115.27, 112.79, 51.68, 15.81. \text{ HRMS (ESI): calcd for } \text{C}_{16}\text{H}_{15}\text{NO}_{5} [M + H]^+ 302.1023, \text{ found } 302.1028. \]

\((E)-1\text{-ethyl-5-hydroxy-2-(3-(2-hydroxy-4-methoxyphenyl)-3-oxoprop-1-en-1-yl)pyridin-4(1H)-one (1g).}\)

Yield: 58\%, \text{ } ^{1}\text{H NMR (400 MHz, DMSO)} \delta 8.46 (s, 1H), 8.36 (s, 1H), 8.16 (d, } J = 15.1 \text{ Hz, 1H), 7.82-7.79 (m, 3H), 6.76 (s, 1H), 4.54 (q, } J = 7.2 \text{ Hz, 2H), 3.95 (s, 3H), 1.38 (t, } J = 7.2 \text{ Hz, 3H); } ^{13}\text{C NMR (101 MHz, DMSO)} \delta 189.48, 164.35, 161.98, 159.68, 146.02, 142.22, 134.75, 132.23, 131.81, 131.47, 115.26, 113.20, 101.46, 101.31, 57.19, 51.90, 15.91. \text{ HRMS (ESI): calcd for } \text{C}_{17}\text{H}_{17}\text{NO}_{5} [M + H]^+ 316.1179, \text{ found } 316.1334. \]

\((E)-1\text{-ethyl-2-(3-(4-fluorophenyl)-3-oxoprop-1-en-1-yl)-5-hydroxypyridin-4(1H)-one (1h).}\)

Yield: 65\%, \text{ } ^{1}\text{H NMR (400 MHz, DMSO)} \delta 8.29 (m, 3H), 8.10 (d, } J = 15.3 \text{ Hz,
1H), 7.78 (d, J = 15.3 Hz, 1H), 7.73 (s, 1H), 7.45 (t, J = 8.8 Hz, 2H), 4.51 (q, J = 7.3 Hz, 2H), 1.37 (t, J = 7.2 Hz, 3H); \(^{13}\)C NMR (101 MHz, DMSO) \(\delta\) 187.09, 166.91, 164.39, 159.87, 146.05, 142.42, 133.28, 132.25, 132.15, 131.75, 116.14, 113.08, 51.90, 15.92; HRMS (ESI): calcd for C\(_{16}\)H\(_{14}\)FNO\(_3\) [M + H]\(^+\) 288.1030, found 288.1037.

\((E)-5\)-hydroxy-1-methyl-2-(3-oxo-3-phenylprop-1-en-1-yl)pyridin-4(1H)-one  \((II)\). Yield: 68 %, \(^1\)H NMR (400 MHz, DMSO) \(\delta\) 8.31 (s, 1H), 8.21 – 8.17 (m, 2H), 8.08 (d, J = 15.4 Hz, 1H), 7.81 (s, 1H), 7.78 – 7.71 (m, 2H), 7.62 (t, J = 7.8 Hz, 2H), 4.15 (s, 3H); \(^{13}\)C NMR (101 MHz, DMSO) \(\delta\) 196.45, 160.12, 147.59, 145.57, 143.76, 136.50, 134.59, 134.09, 129.07, 128.93, 128.04, 112.77, 43.96. HRMS (ESI): calcd for C\(_{15}\)H\(_{13}\)NO\(_3\) [M + H]\(^+\) 256.0968, found 256.0964.

\((E)-1\)-butyl-2-(3-(3,4-dihydroxyphenyl)-3-oxoprop-1-en-1-yl)-5-hydroxypyridin-4(1H)-one  \((Ij)\). Yield: 56 %, \(^1\)H NMR (400 MHz, DMSO) \(\delta\) 8.35 (s, 1H), 8.00 (d, J = 15.2 Hz, 1H), 7.77 (s, 1H), 7.69 (d, J = 15.2 Hz, 1H), 7.66 (dd, J = 8.4, 2.1 Hz, 1H), 7.53 (d, J = 2.1 Hz, 1H), 6.90 (d, J = 8.3 Hz, 1H), 4.50 (t, J = 7.4 Hz, 2H), 1.74 – 1.67 (m, 2H), 1.33 – 1.26 (m, 2H), 0.89 (t, J = 7.4 Hz, 3H). HRMS (ESI) calcd for C\(_{18}\)H\(_{19}\)NO\(_5\) [M + H]\(^+\) 330.1336, found 330.1335.

\((E)-1\)-butyl-5-hydroxy-2-(3-(2-hydroxy-4-methoxyphenyl)-3-oxoprop-1-en-1-yl)pyridin-4(1H)-one  \((Ik)\). Yield: 63 %, \(^1\)H NMR (400 MHz, DMSO) \(\delta\) 8.47 (s, 1H), 8.31 (s, 1H), 8.15 (d, J = 15.1 Hz, 1H), 7.86 – 7.74 (m, 3H), 6.76 (s, 1H), 4.52 – 4.49 (m, 2H), 3.95 (s, 3H), 1.76 – 1.67 (m, 2H), 1.30 (dq, J = 14.5, 7.2 Hz, 2H), 0.90 (t, J = 7.3 Hz, 3H). HRMS (ESI): calcd for C\(_{19}\)H\(_{21}\)NO\(_5\) [M + H]\(^+\) 344.1492, found 344.1500.

\((E)-1\)-butyl-2-(3-(4-fluorophenyl)-3-oxoprop-1-en-1-yl)-5-hydroxypyridin-4(1H)-one  \((Il)\). Yield: 55 %, \(^1\)H NMR (400 MHz, DMSO) \(\delta\) 8.29 (dd, J = 9.5, 6.2 Hz, 3H), 8.10 (d, J = 15.2 Hz, 1H), 7.79 (d, J = 15.3 Hz, 1H), 7.76 (s, 1H), 7.45 (t, J = 8.8 Hz, 2H), 4.49 (t, J = 7.5 Hz, 2H), 1.74 – 1.68 (m, 2H), 1.34 – 1.26 (m, 2H), 0.89 (t, J = 7.4 Hz,
(E)-5-hydroxy-2-(3-oxo-3-phenylprop-1-en-1-yl)pyridin-4(1H)-one (1m). Yield: 72 %, \(^1\)H NMR (400 MHz, DMSO) δ 8.27 (d, \(J = 15.8\) Hz, 1H), 8.20 (s, 1H), 8.18 – 8.16 (m, 2H), 7.84 (s, 1H), 7.74 (t, \(J = 7.4\) Hz, 1H), 7.68 (d, \(J = 15.8\) Hz, 1H), 7.62 (t, \(J = 7.7\) Hz, 2H); \(^{13}\)C NMR (101 MHz, DMSO) δ 188.40, 160.76, 145.87, 140.55, 136.65, 134.10, 133.24, 131.60, 129.13, 128.91, 128.34, 112.67. HRMS (ESI): calcd for C\(_{14}\)H\(_{11}\)NO\(_3\) [M + H]\(^+\) 242.0812, found 242.0823.

(E)-2-(3-(3,4-dimethoxyphenyl)-3-oxoprop-1-en-1-yl)-5-hydroxypyridin-4(1H)-one (1n). Yield: 63 %, \(^1\)H NMR (400 MHz, DMSO) δ 8.28 (d, \(J = 15.7\) Hz, 1H), 8.16 (s, 1H), 7.93 (dd, \(J = 8.5, 1.9\) Hz, 1H), 7.80 (s, 1H), 7.64 (d, \(J = 15.7\) Hz, 1H), 7.61 (d, \(J = 1.9\) Hz, 1H), 7.17 (d, \(J = 8.5\) Hz, 1H), 3.89 (s, 3H), 3.87 (s, 3H); \(^{13}\)C NMR (101 MHz, DMSO) δ 186.29, 160.82, 154.00, 149.03, 145.73, 140.77, 132.61, 129.65, 128.64, 128.26, 127.54, 124.16, 112.62, 111.12, 56.00, 55.80. HRMS (ESI): calcd for C\(_{16}\)H\(_{13}\)NO\(_5\) [M + H]\(^+\) 302.1023, found 302.1046.

(E)-5-hydroxy-2-(3-(2-hydroxy-4-methoxyphenyl)-3-oxoprop-1-en-1-yl)pyridin-4(1H) -one (1o). Yield: 60 %, \(^1\)H NMR (400 MHz, DMSO) δ 8.45 (s, 1H), 8.26 (d, \(J = 15.6\) Hz, 1H), 8.22 – 8.17 (m, 2H), 7.86 (s, 1H), 7.72 (d, \(J = 15.7\) Hz, 1H), 6.76 (s, 1H), 3.95 (s, 3H); \(^{13}\)C NMR (101 MHz, DMSO) δ 189.66, 164.71, 162.04, 160.72, 145.99, 140.44, 134.48, 133.49, 128.09, 127.78, 115.03, 112.60, 101.42, 101.32, 57.19. HRMS (ESI): calcd for C\(_{15}\)H\(_{13}\)NO\(_5\) [M + H]\(^+\) 288.0866, found 288.1258.