

## 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 CH<sub>2</sub>Cl<sub>2</sub> (5 mL).

The resulting solution was cooled in an ice-bath to 0-5 °C, BBr<sub>3</sub> (1.0 M in CH<sub>2</sub>Cl<sub>2</sub>, 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 CH<sub>2</sub>Cl<sub>2</sub>. The combined organic extracts were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and evaporated. Column chromatography of the residue over silica gel, using 1:30 MeOH-CH<sub>2</sub>Cl<sub>2</sub>, 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 %, <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 8.30 (d, *J* = 5.5 Hz, 1H), 8.28 (d, *J* = 5.5 Hz, 1H), 8.27 (s, 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); <sup>13</sup>C NMR (101 MHz, DMSO-d<sub>6</sub>) 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 C<sub>15</sub>H<sub>13</sub>FNO<sub>3</sub> [M + H]<sup>+</sup> 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 %, <sup>1</sup>H 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); <sup>13</sup>C 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 C<sub>16</sub>H<sub>15</sub>NO<sub>5</sub> [M + H]<sup>+</sup> 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 %, <sup>1</sup>H 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 C<sub>16</sub>H<sub>14</sub>O<sub>6</sub> [M + H]<sup>+</sup> 303.0863, found 303.0859.

(E)-2-(3-(4-fluorophenyl)-3-oxoprop-1-en-1-yl)-5-hydroxypyridin-4(1H)-one (**1d**). Yield: 66 %, <sup>1</sup>H NMR (400 MHz, DMSO) δ 8.26 (td, *J* = 8.8, 3.9 Hz, 3H), 8.18 (s,

1H), 7.80 (s, 1H), 7.67 (d,  $J$  = 15.7 Hz, 1H), 7.47 (t,  $J$  = 8.8 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; HRMS (ESI) calcd for  $\text{C}_{14}\text{H}_{10}\text{FNO}_3$  [M + H]<sup>+</sup> 260.0717, found 260.0721.

(E)-1-ethyl-5-hydroxy-2-(3-oxo-3-phenylprop-1-en-1-yl)pyridin-4(1H)-one (**1e**). Yield: 61 %,  $^1\text{H}$  NMR (600 MHz, DMSO)  $\delta$  8.32 (s, 1H), 8.20 – 8.18 (m, 3H), 8.11 (d,  $J$  = 15.2 Hz, 1H), 7.77 (m, 2H), 7.62 (m, 2H), 4.53 (q, 7.2 Hz, 2H), 1.38 (t,  $J$  = 7.2 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; HRMS (ESI): calcd for  $\text{C}_{16}\text{H}_{15}\text{NO}_3$  [M + H]<sup>+</sup> 270.1125, 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 %,  $^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  8.32 (s, 1H), 8.00 (d,  $J$  = 15.3 Hz, 1H), 7.73 (s, 1H), 7.70 – 7.64 (m, 2H), 7.53 (d,  $J$  = 2.9 Hz, 1H), 6.89 (d,  $J$  = 8.2 Hz, 1H), 4.51 (q,  $J$  = 7.2 Hz, 2H), 1.37 (t,  $J$  = 7.2 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. HRMS (ESI): calcd for  $\text{C}_{16}\text{H}_{15}\text{NO}_5$  [M + H]<sup>+</sup> 302.1023, found 302.1028.

(E)-1-ethyl-5-hydroxy-2-(3-(2-hydroxy-4-methoxyphenyl)-3-oxoprop-1-en-1-yl)pyridin-4(1H)-one (**1g**). Yield: 58 %,  $^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  8.46 (s, 1H), 8.36 (s, 1H), 8.16 (d,  $J$  = 15.1 Hz, 1H), 7.82–7.79 (m, 3H), 6.76 (s, 1H), 4.54 (q,  $J$  = 7.2 Hz, 2H), 3.95 (s, 3H), 1.38 (t,  $J$  = 7.2 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. HRMS (ESI): calcd for  $\text{C}_{17}\text{H}_{17}\text{NO}_5$  [M + H]<sup>+</sup> 316.1179, found 316.1334.

(E)-1-ethyl-2-(3-(4-fluorophenyl)-3-oxoprop-1-en-1-yl)-5-hydroxypyridin-4(1H)-one (**1h**). Yield: 65 %,  $^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  8.29 (m, 3H), 8.10 (d,  $J$  = 15.3 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);  $^{13}\text{C}$  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  $\text{C}_{16}\text{H}_{14}\text{FNO}_3$  [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 %,  $^1\text{H}$  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);  $^{13}\text{C}$  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  $\text{C}_{15}\text{H}_{13}\text{NO}_3$  [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 %,  $^1\text{H}$  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  $\text{C}_{18}\text{H}_{19}\text{NO}_5$  [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 %,  $^1\text{H}$  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  $\text{C}_{19}\text{H}_{21}\text{NO}_5$  [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 %,  $^1\text{H}$  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,

3H);  $^{13}\text{C}$  NMR (101 MHz, DMSO-d6)  $\delta$  187.12, 166.92, 164.40, 159.86, 145.87, 142.58, 133.27, 132.26, 131.87, 116.37, 116.15, 113.09, 56.02, 32.23, 18.93, 13.46; HRMS (ESI): calcd for  $\text{C}_{18}\text{H}_{18}\text{FNO}_3$  [M + H] $^+$  316.1343, found 316.1343.

(E)-5-hydroxy-2-(3-oxo-3-phenylprop-1-en-1-yl)pyridin-4(1H)-one (**1m**). Yield: 72 %,  $^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  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);  $^{13}\text{C}$  NMR (101 MHz, DMSO)  $\delta$  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  $\text{C}_{14}\text{H}_{11}\text{NO}_3$  [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 %,  $^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  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);  $^{13}\text{C}$  NMR (101 MHz, DMSO)  $\delta$  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  $\text{C}_{16}\text{H}_{15}\text{NO}_5$  [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 %,  $^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  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);  $^{13}\text{C}$  NMR (101 MHz, DMSO)  $\delta$  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  $\text{C}_{15}\text{H}_{13}\text{NO}_5$  [M + H] $^+$  288.0866, found 288.1258.