

3-Arylcoumarin derivatives manifest anti-proliferative activity through Hsp90 inhibition

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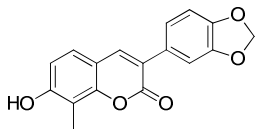
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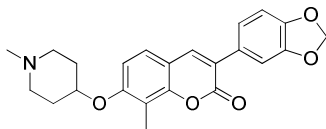
Supplementary Information

3-(benzo[d][1,3]dioxol-5-yl)-7-hydroxy-8-methyl-2H-chromen-2-one (6)



A solution of formyl-resorcinol **3** (500 mg, 3.29 mmol) and 3,4-methylenedioxyphenylacetic acid (590 mg, 3.29 mmol) in acetic anhydride (2 mL) was treated with pyridine (2 mL) under reflux for 12 hours. The excess acetic anhydride was evaporated under vacuum and the resulting brown oil was dissolved in a mixture of triethylamine and methanol (v/v: 1:10, 10 mL). After stirring for 8 hours, the solution was concentrated. The residue was dissolved in water, neutralized with hydrochloride and extracted with ethyl acetate (2x50 mL). The combined organic layer was dried over magnesium sulfate and the solvent was removed. The residue was purified via column chromatography (SiO₂, dichloromethane:acetone 40:1) to afford **6** as a yellow amorphous solid (520 mg, 2 steps, 53%). ¹HNMR (500 MHz, CDCl₃) δ 7.98 (s, 1H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.30 (s, 1H), 7.27 (d, *J* = 8.0, 1H), 6.90 (m, 2H), 6.05 (s, 2H), 2.29 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 161.05, 159.15, 152.94 147.41 (2C), 141.14, 129.23, 126.98, 122.52, 121.62, 112.71, 112.39, 110.80, 108.99, 108.52, 101.57, 8.2. HRMS (ESI) *m/z* [M+H]⁺ calcd for C₁₇H₁₁O₅ 295.0606, found 295.0602.

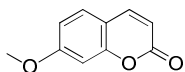
3-(benzo[d][1,3]dioxol-5-yl)-8-methyl-7-((1-methylpiperidin-4-yl)oxy)-2H-chromen-2-one: general procedure for the synthesis of **1** and **20a–e**.



Diisopropylazodicarboxylate (60.6 mg, 0.30 mmol) was added to a solution of *N*-methyl-4-hydroxypiperidine **7** (17.1 mg, 0.15 mmol), phenol **6** (44.0 mg, 0.15 mmol) and triphenylphosphine (78.7 mg, 0.30 mmol) in anhydrous THF (3 mL). After 2 h, the solvent was removed and the residue was purified via column chromatography (SiO₂, 10:1, CH₂Cl₂:methanol) to afford compound **1** as a yellow amorphous solid (51 mg, 88%). ¹HNMR (400 MHz, CDCl₃) δ 7.66 (s, 1H), 7.29 (d, *J* = 8.0 Hz, 1H), 7.21 (s, 1H),

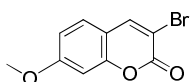
7.15 (d, $J = 8.0$ Hz, 1H), 6.85 (d, $J = 8.0$ Hz, 1H), 6.82 (d, $J = 8.0$ Hz, 1H), 5.99 (s, 2H), 4.51 (m, 1H), 2.70 (m, 2H), 2.67 (m, 2H), 2.47 (s, 3H), 2.37 (s, 3H), 2.06 (m, 2H), 1.94 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 161.3, 158.1, 153.0, 148.0, 147.8, 139.8, 129.3, 125.8, 124.3, 122.4, 115.1, 113.7, 109.8, 109.2, 108.4, 101.4, 71.9, 52.2, 46.2, 30.6, 8.6. HRMS (ESI⁺) m/z [$\text{M}+\text{H}^+$] calcd for $\text{C}_{22}\text{H}_{24}\text{NO}_5$ 382.1654, found 382.1655.

7-methoxy-2H-chromen-2-one (9)



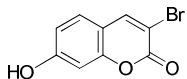
Sodium hydride (553 mg, 15 mmol) was added to a solution of umbelliferone (**8**, 1.62 g, 10 mmol) in DMF, followed by iodomethane (2.84 g, 20 mmol). The solution was stirred at room temperature for 4 hour and quenched by ice/water. The solid was filtered and dried under vacuum to give compound **9** as colorless amorphous solid (1.65 g, 94%). ^1H NMR (500 MHz, CDCl_3) δ 7.75 (d, $J = 8.0$ Hz, 1H), 7.68 (d, $J = 8.0$ Hz, 1H), 7.05 (s, 1H), 7.01 (d, $J = 8.0$ Hz, 1H), 6.12 (d, $J = 8.0$ Hz, 1H) 3.81 (s, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 159.21, 158.13, 153.90, 142.10, 129.77, 114.40, 113.03, 100.92, 101.53, 56.76. HRMS (ESI⁺) m/z [$\text{M}+\text{H}^+$] calcd for $\text{C}_{10}\text{H}_9\text{O}_3$ 177.0552, found 177.0554.

3-bromo-7-methoxy-2H-chromen-2-one (10)



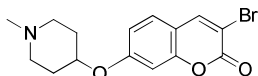
N-bromosuccinimide (1.78 g, 10 mmol) was added to a solution of compound **9** (880 mg, 5 mmol) and sodium acetate (41 mg, 0.5 mmol) in acetonitrile (100 mL). The resulting solution was stirred at room temperature until the starting material disappeared, and then quenched with water and extracted with ethyl acetate. The combined organic layers was washed with water and saturated sodium chloride solution, dried over anhydrous magnesium sulfate and concentrated to dryness. The residue was purified via column chromatography (SiO_2 , 100:1, CH_2Cl_2 :acetone) to give compound **10** as a brown amorphous solid (1.16 g, 91%). ^1H NMR (400 MHz, CDCl_3) δ 8.05 (s, 1H), 7.35 (d, $J = 8.0$ Hz, 1H), 6.85 (d, $J = 8.0$ Hz, 1H), 6.80 (s, 1H), 3.84 (s, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 160.12, 158.17, 154.90, 145.13, 128.32, 113.40, 113.38, 113.07, 100.63, 55.82. HRMS (ESI⁺) m/z [$\text{M}+\text{H}^+$] calcd for $\text{C}_{10}\text{H}_8\text{BrO}_3$ 254.9657, found 254.9659.

3-bromo-7-hydroxy-2H-chromen-2-one (11)



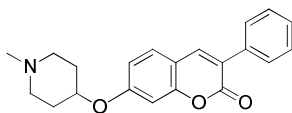
Tribromoborane (2.36 g, 9.46 mmol) was added to a solution of compound **10** (1.2 g, 4.73 mmol) in dichloromethane (50 mL) at 0 °C. The resulting mixture was refluxed for 12 hours and poured to an ice/water mixture after it was cooled to room temperature. The solid was filtered and vacuum-dried to give compound **11** as a grey amorphous solid (930 mg, 82%). ¹H NMR (400 MHz, CDCl₃) δ 8.05 (s, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 6.86 (d, *J* = 8.0 Hz, 1H), 6.81 (s, 1H). ¹³C NMR (126 MHz, CDCl₃) δ 161.68, 156.94, 154.77, 145.53, 129.30, 113.72, 111.94, 105.30, 102.10. HRMS (ESI) *m/z* [M+H]⁺ calcd for C₉H₄BrO₃ 238.9344, found 238.9345.

3-bromo-7-((1-methylpiperidin-4-yl)oxy)-2H-chromen-2-one (12)



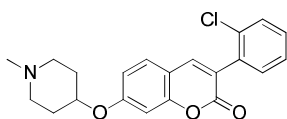
Diisopropylazodicarboxylate (885 mg, 3.74 mmol) was added to a solution of *N*-methyl-4-hydroxypiperidine (215 mg, 1.87 mmol) and phenol **11** (450 mg, 1.87 mmol), and triphenylphosphine (981 mg, 3.74 mmol) in anhydrous THF (20 mL). After 2 h, the solvent was removed and the residue purified via column chromatography (SiO₂, 10:1, CH₂Cl₂:methanol) to afford compound **12** as a brown amorphous solid (510 mg, 81%). ¹H NMR (500 MHz, CDCl₃) δ 8.01 (s, 1H), 7.34 (d, *J* = 8.0 Hz, 1H), 6.86 (d, *J* = 8.0 Hz, 1H), 6.82 (s, 1H), 4.40 (m, 1H), 2.72 (m, 2H), 2.34 (m, 2H), 2.32 (s, 3H), 2.05 (m, 2H), 1.89 (m, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 161.17, 157.75, 155.26, 144.65, 128.39, 114.60, 113.13, 107.82, 102.38, 73.08, 52.62, 46.30, 30.66. HRMS (ESI⁺) *m/z* [M+H]⁺ calcd for C₁₅H₁₇BrNO₃ 338.0392, found 338.0388.

7-((1-methylpiperidin-4-yl)oxy)-3-phenyl-2H-chromen-2-one (14a): General procedure for Suzuki coupling reaction.



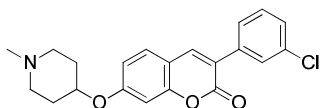
1,1'-Bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane (8.2 mg, 0.01 mmol) was added to a solution of compound **12** (34 mg, 0.1 mmol), phenylbromic acid (37 mg, 0.3 mmol) and potassium carbonate (1M, 0.05 mL) in 1,4-dioxane (5 mL). The mixture was stirred at 80 °C for 12 hours, quenched with water and extracted with ethyl acetate. The combined organic layer was washed with water and saturated sodium chloride solution, dried over anhydrous magnesium sulfate and concentrated to dryness. The residue was purified via column chromatography (SiO₂, 100:1, CH₂Cl₂: methanol) to give compound **14a** as a brown amorphous solid (26 mg, 78%). ¹HNMR (500 MHz, CDCl₃) δ 7.76 (s, 1H), 7.48 (d, *J* = 8.1 Hz, 2H), 7.44~7.39 (m, 5H), 6.88~7.85 (m, 2H), 4.41~4.39 (m, 1H), 2.74 (m, 2H), 2.35 (m, 2H), 2.34 (s, 3H), 2.07 (m, 2H), 1.91 (m, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 161.11, 160.69, 155.46, 140.21, 135.19, 129.14, 128.63, 128.61, 128.58, 124.92, 114.24, 113.47, 102.14, 72.95, 52.56, 46.15, 30.58. HRMS (ESI+) *m/z* [M+H⁺] calcd for C₂₁H₂₂NO₃ 336.1600, found 336.1604.

3-(2-chlorophenyl)-7-((1-methylpiperidin-4-yl)oxy)-2H-chromen-2-one (14b)



Compound **14b** was obtained as a white amorphous solid (28 mg, 76%). ¹HNMR (400 MHz, CDCl₃) δ 7.68 (s, 1H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.43~7.39 (m, 2H), 7.35~7.32 (m, 2H), 6.89~6.86 (m, 2H), 4.42 (m, 1H), 2.73 (m, 2H), 2.35 (m, 2H), 2.34 (s, 3H), 2.05 (m, 2H), 1.91 (m, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 161.11, 160.36, 156.02, 143.01, 134.26, 133.97, 131.75, 130.15, 129.97, 129.37, 127.07, 123.57, 114.25, 112.77, 102.44, 72.85, 52.56, 46.36, 30.69. HRMS (ESI+) *m/z* [M+H⁺] calcd for C₂₁H₂₁ClNO₃ 370.1210, found 370.1212.

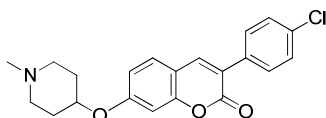
3-(3-chlorophenyl)-7-((1-methylpiperidin-4-yl)oxy)-2H-chromen-2-one (14c)



Compound **14c** was obtained as a colorless amorphous solid (34 mg, 75%). ¹HNMR (500 MHz, CDCl₃) δ 7.77 (s, 1H), 7.68 (s, 1H), 7.60~7.58 (m, 1H), 7.44 (d, *J* = 8.2 Hz,

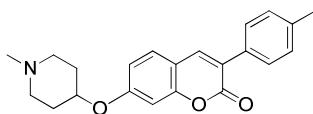
1H), 7.38~7.34 (m, 2H), 6.88~6.85 (m, 2H), 4.43 (m, 1H), 2.76 (m, 2H), 2.40 (m, 2H), 2.36 (s, 3H), 2.09 (m, 2H), 1.90 (m, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 161.01, 160.69, 155.61, 140.75, 136.89, 134.50, 129.84, 129.36, 128.67, 128.58, 126.78, 123.48, 114.36, 113.22, 102.17, 72.80, 52.49, 46.14, 30.48. HRMS (ESI⁺) m/z [M+H⁺] calcd for C₂₁H₂₁ClNO₃ 370.1210, found 370.1209.

3-(4-chlorophenyl)-7-((1-methylpiperidin-4-yl)oxy)-2H-chromen-2-one (14d)



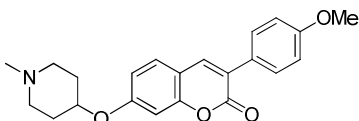
Compound **14d** was obtained as a brown amorphous solid (14 mg, 64%). ¹H NMR (500 MHz, CDCl₃) δ 7.77 (s, 1H), 7.65 (d, *J* = 8.5 Hz, 2H), 7.46~7.41 (m, 3H), 6.89~6.86 (m, 2H), 4.44 (m, 1H), 2.77 (m, 2H), 2.42 (m, 2H), 2.38 (s, 3H), 2.11 (m, 2H), 1.94 (m, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 160.88 (2C), 155.55, 140.26, 134.62, 133.60, 129.89, 129.26, 128.84, 123.74, 114.41, 113.34, 102.20, 72.80, 52.53, 46.17, 30.51. HRMS (ESI⁺) m/z [M+H⁺] calcd for C₂₁H₂₁ClNO₃ 370.1210, found 370.1214.

7-((1-methylpiperidin-4-yl)oxy)-3-(*p*-tolyl)-2H-chromen-2-one (14e)



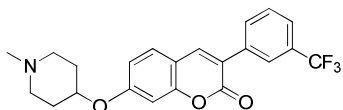
Compound **14e** was obtained as a white amorphous solid (13 mg, 63%). ¹H NMR (400 MHz, CDCl₃) δ 7.72 (s, 1H), 7.58 (d, *J* = 8.0 Hz, 2H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 2H), 6.85 (m, 2H), 4.41 (m, 1H), 2.74 (m, 2H), 2.50 (m, 2H), 2.38 (s, 3H), 3.37 (m, 2H), 2.35 (s, 3H), 1.92 (m, 2H), 1.89 (m, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 161.21, 160.40, 155.28, 139.59, 138.61, 132.21, 129.29, 129.03, 128.40, 124.87, 114.09, 113.54, 102.09, 72.55, 52.49, 46.15, 30.45, 21.46. HRMS (ESI⁺) m/z [M+H⁺] calcd for C₂₂H₂₄NO₃ 350.1756, found 350.1751.

3-(4-methoxyphenyl)-7-((1-methylpiperidin-4-yl)oxy)-2H-chromen-2-one (14f)



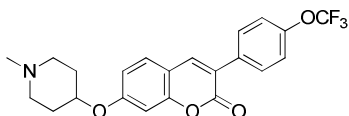
Compound **14f** was obtained as a brown amorphorous solid (28 mg, 65%). ¹H NMR (500 MHz, CDCl₃+CH₃OH) δ 7.69 (s, 1H), 7.64 (d, *J* = 8.0 Hz, 2H), 7.41 (d, *J* = 8.0 Hz, 1H), 6.95 (d, *J* = 8.0 Hz, 2H), 6.84 (m, 2H), 4.42 (m, 1H), 3.84 (s, 3H), 2.76 (m, 2H), 2.41 (m, 2H), 2.37 (s, 3H), 2.09 (m, 2H), 1.92 (m, 2H). ¹³C NMR (126 MHz, CDCl₃+CH₃OH) δ 161.30, 160.30, 160.03, 155.22, 138.90, 129.85, 128.95, 127.57, 124.64, 114.10, 114.07, 113.71, 102.22, 72.44, 55.58, 52.50, 46.13, 30.47. HRMS (ESI⁺) *m/z* [M+H⁺] calcd for C₂₂H₂₄NO₄ 366.1705, found 366.1709.

7-((1-methylpiperidin-4-yl)oxy)-3-(3-(trifluoromethyl)phenyl)-2H-chromen-2-one (14g)



Compound **14h** was obtained as a yellow amorphorous solid (11 mg, 46%). ¹H NMR (500 MHz, CDCl₃) δ 7.91 (s, 1H), 7.89 (d, *J* = 8.1 Hz, 1H), 7.80 (s, 1H), 7.62 (d, *J* = 8.8 Hz, 1H), 7.54 (t, *J* = 8.0 Hz, 1H), 7.45 (d, *J* = 8.5 Hz, 1H), 6.88~6.84 (m, 2H), 4.43 (m, 1H), 2.75 (m, 2H), 2.42 (m, 2H), 2.36 (s, 3H), 2.09 (m, 2H), 1.91 (m, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 161.08, 160.72, 155.69, 141.01, 135.93, 131.99, 131.19, 130.93, 129.45, 129.08, 125.29, 123.43, 114.40, 113.19, 102.20, 81.04, 72.58, 52.38, 46.05, 30.34. HRMS (ESI⁺) *m/z* [M+H⁺] calcd for C₂₂H₂₁F₃NO₃ 404.1474, found 404.1478.

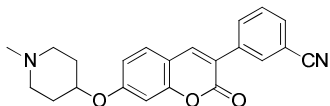
7-((1-methylpiperidin-4-yl)oxy)-3-(4-(trifluoromethoxy)phenyl)-2H-chromen-2-one (14h)



Compound **14h** was obtained as a yellow amorphorous solid (28 mg, 67%). ¹H NMR (500 MHz, CDCl₃) δ 7.76 (s, 1H), 7.73 (d, *J* = 8.0 Hz, 2H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.28 (m, 2H), 6.87 (m, 2H), 4.40 (m, 1H), 2.72 (m, 2H), 2.34 (m, 2H), 2.32 (s, 3H), 2.05 (m, 2H), 1.89 (m, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 161.06, 160.94, 155.59, 149.37, 149.35, 140.59, 133.83, 130.09, 129.27, 123.45, 121.03, 114.45, 113.20, 102.14, 73.12, 52.67,

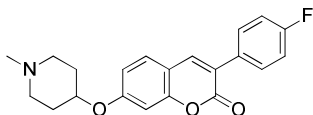
46.30, 30.73. HRMS (ESI⁺) m/z [M+H⁺] calcd for C₂₂H₂₁F₃NO₄ 420.1423 found 420.1419.

3-(7-((1-methylpiperidin-4-yl)oxy)-2-oxo-2H-chromen-3-yl)benzonitrile (14i)



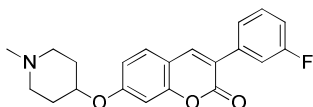
Compound **14i** was obtained as a brown amorphous solid (21 mg, 58%). ¹HNMR (500 MHz, CDCl₃) δ 7.97 (s, 1H), 7.98 (d, *J* = 7.9 Hz, 1H), 7.83 (s, 1H), 7.68 (d, *J* = 8.7 Hz, 1H), 7.56 (t, *J* = 7.9 Hz, 1H), 7.48 (d, *J* = 8.6 Hz, 1H), 6.90 (d, *J* = 8.5 Hz, 1H), 6.88 (s, 1H), 4.46 (m, 1H), 2.77 (m, 2H), 2.42 (m, 2H), 2.38 (s, 3H), 2.10 (m, 2H), 1.94 (m, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 161.39, 160.58, 155.81, 141.29, 136.44, 132.94, 132.09, 131.96, 129.56, 129.48, 122.51, 118.75, 114.59, 113.03, 112.94, 102.21, 72.76, 52.47, 46.16, 30.47. HRMS (ESI⁺) m/z [M+H⁺] calcd for C₂₂H₂₁N₂O₃ 361.1552, found 361.1555.

3-(4-fluorophenyl)-7-((1-methylpiperidin-4-yl)oxy)-2H-chromen-2-one (14j)



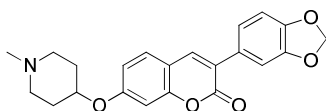
Compound **14j** was obtained as a brown amorphous solid (23 mg, 51%). ¹HNMR (400 MHz, CDCl₃) δ 7.72 (s, 1H), 7.68~7.64 (m, 2H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.13~7.09 (m, 2H), 6.88~6.85 (m, 2H), 4.43 (m, 1H), 2.75 (m, 2H), 2.40 (m, 2H), 2.36 (s, 3H), 2.09 (m, 2H), 1.90 (m, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 162.01, 161.07, 160.73, 155.46, 140.03, 130.45, 130.37, 129.16, 123.94, 115.71, 115.61, 113.39, 102.19, 72.95, 52.51, 46.14, 30.50. HRMS (ESI⁺) m/z [M+H⁺] calcd for C₂₁H₂₁FNO₃ 354.1505, found 354.1507.

3-(3-fluorophenyl)-7-((1-methylpiperidin-4-yl)oxy)-2H-chromen-2-one (14k)



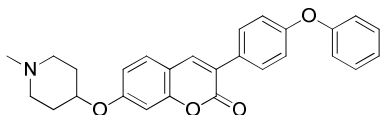
Compound **14k** was obtained as a colorless amorphous solid (25 mg, 72%). ¹H NMR (400 MHz, CDCl₃) δ 7.78 (s, 1H), 7.48~7.36 (m, 4H), 7.08 (t, *J* = 8.6 Hz, 1H), 6.87~6.85 (m, 2H), 4.40 (m, 1H), 2.72 (m, 2H), 2.34 (m, 2H), 2.33 (s, 3H), 2.05 (m, 2H), 1.90 (m, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 164.07, 161.63, 161.10, 160.75, 155.61, 140.63, 137.20, 130.15, 129.34, 124.13, 123.50, 115.61, 114.39, 113.14, 102.10, 73.17, 52.76, 46.38, 30.64. HRMS (ESI+) *m/z* [M+H⁺] calcd for C₂₁H₂₁FNO₃ 354.1505, found 354.1502.

3-(benzo[d][1,3]dioxol-5-yl)-7-((1-methylpiperidin-4-yl)oxy)-2H-chromen-2-one (14l)



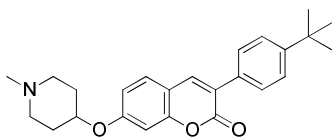
Compound **14l** was obtained as a brown amorphous solid (14.7 mg, 39%). 7.69 (s, 1H), 7.41 (d, *J* = 8.3 Hz, 1H), 7.22 (s, 1H), 7.16 (d, *J* = 8.1 Hz, 1H), 6.87 (d, *J* = 8.1 Hz, 2H), 6.84 (s, 1H), 6.00 (s, 2H), 4.39 (m, 1H), 2.72 (m, 2H), 2.34 (m, 2H), 2.33 (s, 3H), 2.05 (m, 2H), 1.89 (m, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 161.15, 160.58, 155.24, 148.04, 147.83, 139.36, 129.12, 128.97, 124.49, 122.46, 114.23, 113.44, 109.18, 108.47, 102.11, 101.46, 72.83, 52.74, 46.33, 30.81. HRMS (ESI+) *m/z* [M+H⁺] calcd for C₂₂H₂₂NO₅ 380.1498, found 380.1501.

7-((1-methylpiperidin-4-yl)oxy)-3-(4-phenoxyphenyl)-2H-chromen-2-one (14m)



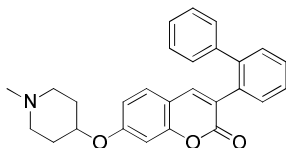
Compound **14m** was obtained as a white amorphous solid (29 mg, 68%). ¹H NMR δ 7.73 (s, 1H), 7.67 (d, *J* = 8.7 Hz, 2H), 7.42 (d, *J* = 8.7 Hz, 1H), 7.36 (t, *J* = 8.2 Hz, 2H), 7.14 (t, *J* = 7.4 Hz, 1H), 7.07~7.04 (m, 4H), 6.88~6.85 (m, 2H), 4.40 (m, 1H), 2.72 (m, 2H), 2.34 (m, 2H), 2.33 (s, 3H), 2.05 (m, 2H), 1.89 (m, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 161.18, 160.64, 157.83, 156.89, 155.33, 139.56, 130.05, 130.00, 129.97, 129.02, 124.21, 123.81, 119.44, 118.60, 114.26, 113.46, 102.13, 73.04, 52.68, 46.31, 30.77. HRMS (ESI+) *m/z* [M+H⁺] calcd for C₂₇H₂₆NO₄ 428.1862, found 428.1856.

3-(4-(tert-butyl)phenyl)-7-((1-methylpiperidin-4-yl)oxy)-2H-chromen-2-one (14n)



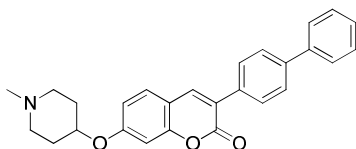
Compound **14n** was obtained as a brown amorphous solid (15 mg, 62%). ^1H NMR δ 7.74 (s, 1H), 7.63 (d, $J = 8.0$ Hz, 2H), 7.44 (d, $J = 8.0$ Hz, 2H), 7.42 (d, $J = 8.0$ Hz, 1H), 6.86 (m, 2H), 4.43 (m, 1H), 2.76 (m, 2H), 2.41 (m, 2H), 2.37 (s, 3H), 2.10 (m, 2H), 1.92 (m, 2H), 1.35 (s, 9H). ^{13}C NMR (126 MHz, CDCl_3) δ 161.20, 160.52, 155.42, 151.84, 139.59, 132.30, 129.07, 128.28, 125.63, 125.03, 114.14, 113.71, 102.33, 72.14, 52.54, 46.15, 34.88, 31.49, 30.52. HRMS (ESI $^+$) m/z $[\text{M}+\text{H}^+]$ calcd for $\text{C}_{25}\text{H}_{30}\text{NO}_3$ 392.2226, found 392.2230.

3-([1,1'-biphenyl]-2-yl)-7-((1-methylpiperidin-4-yl)oxy)-2H-chromen-2-one (14o)



Compound **14o** was obtained as a brown amorphous solid (18 mg, 64%). ^1H NMR (500 MHz, CDCl_3) δ 7.50~7.43 (m, 4H), 7.39 (s, 1H), 7.32~7.27 (m, 4H), 7.25~7.23 (m, 2H), 6.81~6.79 (m, 2H), 4.44 (m, 1H), 2.81 (m, 2H), 2.51 (m, 2H), 2.43 (s, 3H), 2.16 (m, 2H), 1.95 (m, 2H). ^{13}C NMR (126 MHz, CDCl_3) δ 160.83, 160.30, 155.51, 142.58, 141.96, 141.39, 133.83, 130.74, 130.61, 129.28, 129.00, 128.92, 128.41, 127.54, 127.10, 126.01, 113.79, 113.20, 102.33, 72.05, 52.26, 45.90, 30.10. HRMS (ESI $^+$) m/z $[\text{M}+\text{H}^+]$ calcd for $\text{C}_{27}\text{H}_{26}\text{NO}_3$ 412.1913, found 412.1910.

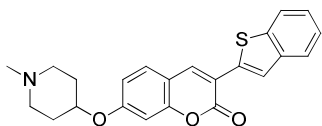
3-([1,1'-biphenyl]-4-yl)-7-((1-methylpiperidin-4-yl)oxy)-2H-chromen-2-one (14p)



Compound **14p** was obtained as a brown amorphous solid (28 mg, 68%). ^1H NMR (500 MHz, CDCl_3) δ 7.69 (s, 1H), 7.66 (m, 2H), 7.50 (m, 2H), 7.47 (m, 2H), 7.39 (m, 3H), 6.90 (m, 2H), 4.44 (m, 1H), 2.78 (m, 2H), 2.42 (m, 2H), 2.39 (s, 3H), 1.97 (m, 2H), 1.92 (m,

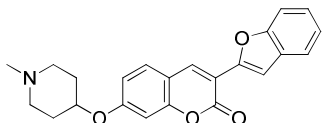
2H). ^{13}C NMR (126 MHz, CDCl_3) δ 161.13, 160.70, 155.49, 141.48, 140.73, 139.96, 134.13, 129.19, 129.05, 128.98, 127.74, 127.36, 127.30, 124.54, 114.26, 113.56, 102.22, 72.75, 52.54, 46.16, 30.54. HRMS (ESI^+) m/z $[\text{M}+\text{H}^+]$ calcd for $\text{C}_{27}\text{H}_{26}\text{NO}_3$ 412.1913, found 412.1914.

3-(benzo[b]thiophen-2-yl)-7-((1-methylpiperidin-4-yl)oxy)-2H-chromen-2-one (16a)



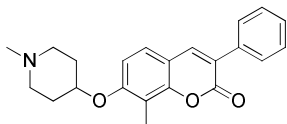
Compound **16a** was obtained as a yellow amorphous solid (12 mg, 52%). ^1H NMR (500 MHz, CDCl_3) δ 8.19 (s, 1H), 8.02 (s, 1H), 7.84 (t, $J = 12$ Hz, 2H), 7.49 (d, $J = 8.0$ Hz, 1H), 7.38 (m, 2H), 6.90 (m, 2H), 4.43 (m, 1H), 2.75 (m, 2H), 2.36 (m, 2H), 2.35 (s, 3H), 2.09 (m, 2H), 1.92 (m, 2H). ^{13}C NMR (126 MHz, CDCl_3) δ 161.11, 159.52, 155.03, 140.57, 139.42, 138.26, 136.94, 129.32, 125.32, 124.86, 124.65, 124.41, 122.14, 118.49, 114.67, 113.04, 102.10, 72.94, 52.71, 46.21, 30.70. HRMS (ESI^+) m/z $[\text{M}+\text{H}^+]$ calcd for $\text{C}_{23}\text{H}_{22}\text{NO}_3\text{S}$ 392.1320, found 392.1323.

3-(benzofuran-2-yl)-7-((1-methylpiperidin-4-yl)oxy)-2H-chromen-2-one (16b)



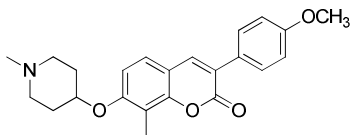
Compound **16b** was obtained as a colorless amorphous solid (16 mg, 46%). ^1H NMR (500 MHz, CDCl_3) δ 8.34 (s, 1H), 7.70 (s, 1H), 7.65 (m, 1H), 7.50 (m, 2H), 7.35 (m, 1H), 7.26 (m, 1H), 6.89 (d, $J = 8.0$ Hz, 1H), 6.86 (s, 1H), 4.47 (m, 1H), 2.82 (m, 2H), 2.56 (m, 2H), 2.43 (s, 3H), 2.13 (m, 2H), 1.96 (m, 2H). ^{13}C NMR (126 MHz, CDCl_3) δ 160.81, 158.64, 155.04, 154.73, 149.75, 136.69, 129.70, 129.52, 125.45, 123.39, 122.07, 114.94, 114.44, 113.19, 110.95, 108.30, 102.34, 71.72, 51.89, 45.70, 29.88. HRMS (ESI^+) m/z $[\text{M}+\text{H}^+]$ calcd for $\text{C}_{23}\text{H}_{22}\text{NO}_4$ 376.1549, found 376.1552.

8-methyl-7-((1-methylpiperidin-4-yl)oxy)-3-phenyl-2H-chromen-2-one (20a)



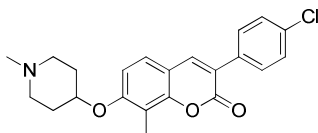
Compound **20a** was obtained as a brown solid (mg, %). ^1H NMR (500 MHz, DMSO) δ 8.21 (s, 1H), 7.71 (d, J = 8.0 Hz, 2H), 7.62 (d, J = 8.6 Hz, 1H), 7.46 (d, J = 8.0 Hz, 2H), 7.17 (d, J = 8.6, 1H), 4.81 (m, 1H), 3.13~3.01 (m, 4H), 2.69 (s, 3H), 2.28 (s, 3H), 2.19 (m, 2H), 2.00 (m, 2H). ^{13}C NMR (126 MHz, DMSO) δ 159.84, 157.28, 152.17, 140.96, 134.78, 128.19, 128.10, 127.27, 126.82, 123.07, 113.36, 113.15, 110.02, 72.62, 50.17, 42.63, 27.92, 8.00. HRMS (ESI⁺) m/z [M+H⁺] calcd for C₂₂H₂₄NO₃ 350.1756, found 350.1754.

3-(4-methoxyphenyl)-8-methyl-7-((1-methylpiperidin-4-yl)oxy)-2H-chromen-2-one
(**20b**)



Compound **20b** was obtained as a brown solid (67 mg, 63%). ^1H NMR (400 MHz, Acetone) δ 7.98 (s, 1H), 7.73 (d, J = 8.8 Hz, 2H), 7.52 (d, J = 8.6 Hz, 1H), 7.07 (d, J = 8.6 Hz, 1H), 6.99 (d, J = 8.6, 2H), 4.66 (m, 1H), 2.78 (m, 2H), 2.51 (m, 2H), 2.35 (s, 3H), 2.29 (s, 3H), 2.06 (m, 2H), 1.92 (m, 2H). ^{13}C NMR (101 MHz, Acetone) δ 161.05, 160.71, 154.79, 153.62, 147.09, 140.11, 130.56, 128.66, 127.25, 124.42, 114.62, 114.44, 110.64, 73.37, 55.67, 52.64, 45.84, 30.92, 8.49. HRMS (ESI⁺) m/z [M+H⁺] calcd for C₂₃H₂₆NO₄ 380.1862, found 380.1861.

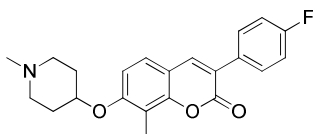
3-(4-chlorophenyl)-8-methyl-7-((1-methylpiperidin-4-yl)oxy)-2H-chromen-2-one
(**20c**)



Compound **20c** was obtained as a yellow solid (57 mg, 82%). ^1H NMR (400 MHz, DMSO) δ 8.18 (s, 1H), 7.95 (d, J = 8.8 Hz, 2H), 7.57 (d, J = 8.6 Hz, 1H), 7.50 (d, J = 8.6 Hz, 2H), 7.10 (d, J = 8.6, 1H), 4.63 (m, 1H), 2.72 (m, 2H), 2.49 (m, 2H), 2.34 (s, 3H),

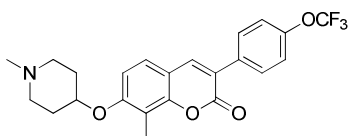
2.22 (s, 3H), 2.01 (m, 2H), 1.81 (m, 2H). ^{13}C NMR (100 MHz, DMSO) δ 160.01, 157.58, 156.30, 152.43, 141.53, 133.84, 132.95, 130.18, 128.34, 127.19, 121.83, 113.33, 110.31, 70.18, 50.76, 43.77, 28.56, 8.19. HRMS (ESI+) m/z [M+H+] calcd for $\text{C}_{22}\text{H}_{23}\text{ClNO}_3$ 384.1366, found 384.1370.

3-(4-fluorophenyl)-8-methyl-7-((1-methylpiperidin-4-yl)oxy)-2H-chromen-2-one (20d)



Compound **20d** was obtained as a brown solid (35 mg, 69%). ^1H NMR (500 MHz, Acetone) δ 8.04 (s, 1H), 7.80 (d, $J = 8.9$ Hz, 2H), 7.53 (d, $J = 8.6$ Hz, 1H), 7.22 (d, $J = 8.9$ Hz, 2H), 7.08 (d, $J = 8.6$, 1H), 4.64 (m, 1H), 2.71 (m, 2H), 2.43 (m, 2H), 2.30 (s, 3H), 2.28 (s, 3H), 2.06 (m, 2H), 1.88 (m, 2H). ^{13}C NMR (101 MHz, Acetone) δ 159.99, 158.33, 152.91, 140.50, 130.59, 130.36, 126.61, 122.68, 114.97, 114.75, 113.72, 113.39, 109.84, 72.56, 51.94, 45.24, 30.38, 7.53. HRMS (ESI+) m/z [M+H+] calcd for $\text{C}_{22}\text{H}_{23}\text{FNO}_3$ 368.1662, found 368.1658.

8-methyl-7-((1-methylpiperidin-4-yl)oxy)-3-(4-(trifluoromethoxy)phenyl)-2H-chromen-2-one (20e)



Compound **20e** was obtained as a brown solid (31 mg, 58%). ^1H NMR (500 MHz, Acetone) δ 8.16 (s, 1H), 7.92 (d, $J = 8.8$ Hz, 2H), 7.61 (d, $J = 8.6$ Hz, 1H), 7.42 (d, $J = 8.6$ Hz, 2H), 7.18 (d, $J = 8.6$, 1H), 4.99 (m, 1H), 2.81 (m, 2H), 2.50 (m, 2H), 2.35 (s, 3H), 2.30 (s, 3H), 2.26 (m, 2H), 2.10 (m, 2H). ^{13}C NMR (126 MHz, Acetone) δ 160.69, 158.83, 153.92, 149.65, 142.07, 135.57, 131.18, 127.84, 123.56, 122.41, 121.50, 114.96, 114.59, 110.64, 72.06, 49.83, 43.40, 27.90 8.42. HRMS (ESI+) m/z [M+H+] calcd for $\text{C}_{23}\text{H}_{23}\text{F}_3\text{NO}_4$ 434.1579, found 434.1581.

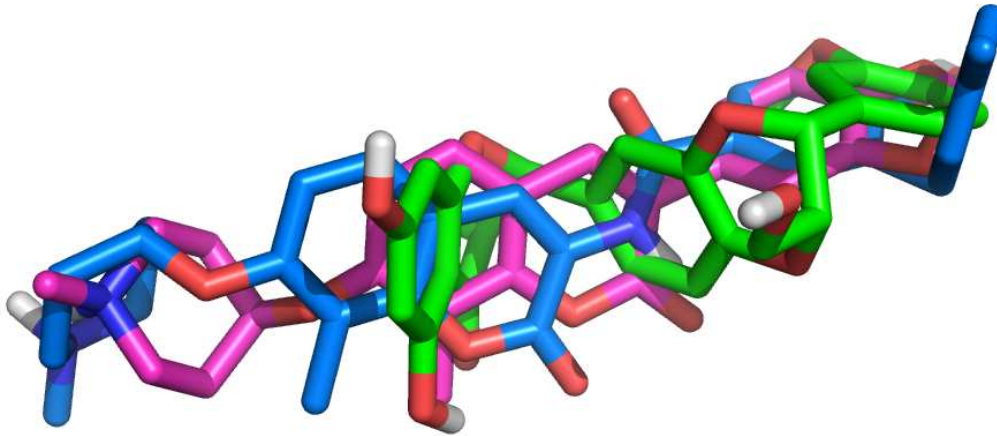


Figure 1s. Overlay of KU-398, silybin and arylcoumarin 1