

## Chromone-deferiprone hybrids as novel MAO-B inhibitors and iron chelators for the treatment of Alzheimer's disease

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#### 1. General procedure for the preparation of intermediate 14a-g

Intermediate **13** (0.950 g, 5 mmol), anhydrous K<sub>2</sub>CO<sub>3</sub> (1.382 g, 10 mmol), acetonitrile (40 mL), and corresponding substituted benzyl bromide (7.5 mmol) were added to the round-bottom flask. The reaction solution was refluxed for 1 h, and the crude product was purified by silica gel column chromatography with petroleum ether/ethyl acetate (5/1-3/1) to obtain intermediates **14a-g** as a yellow solid.

##### 7-((3-fluorobenzyl)oxy)-4-oxo-4*H*-chromene-3-carbaldehyde (**14a**)

Yellow solid, yield: 62.9%, m.p. 131.9-132.8 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 10.39 (s, 1H), 8.49 (s, 1H), 8.24 (d, *J* = 8.9 Hz, 1H), 7.44-7.38 (m, 1H), 7.23 (d, *J* = 8.3 Hz, 1H), 7.20-7.16 (m, 1H), 7.14 (dd, *J* = 8.9, 2.4 Hz, 1H), 7.10-7.06 (m, 1H), 6.99 (d, *J* = 2.3 Hz, 1H), 5.20 (s, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 188.81, 175.24, 163.58, 163.05 (d, <sup>1</sup>*J*<sub>C-F</sub> = 245.7 Hz), 160.26, 157.84, 137.84 (d, <sup>3</sup>*J*<sub>C-F</sub> = 7.4 Hz), 130.48 (d, <sup>3</sup>*J*<sub>C-F</sub> = 8.2 Hz), 127.76,

122.79 (d,  $^4J_{C-F}$  = 2.9 Hz), 120.31, 119.25, 115.92, 115.50 (d,  $^2J_{C-F}$  = 21.2 Hz), 114.32 (d,  $^2J_{C-F}$  = 22.2 Hz), 102.30, 69.90 (d,  $^4J_{C-F}$  = 2.1 Hz).

7-((4-fluorobenzyl)oxy)-4-oxo-4*H*-chromene-3-carbaldehyde (**14b**)

Yellow solid, yield: 42.1%, m.p. 140.8-142.4 °C.  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  10.39 (s, 1H), 8.49 (s, 1H), 8.23 (d,  $J$  = 8.9 Hz, 1H), 7.51-7.39 (m, 2H), 7.15-7.10 (m, 3H), 7.00 (d,  $J$  = 2.4 Hz, 1H), 5.16 (s, 2H);  $^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  188.84, 175.27, 163.72, 162.81 (d,  $^1J_{C-F}$  = 245.7 Hz), 160.28, 157.86, 131.07 (d,  $^4J_{C-F}$  = 3.3 Hz), 129.53 (d,  $^3J_{C-F}$  = 8.3 Hz, 2C), 127.70, 120.28, 119.13, 115.97, 115.85 (d,  $^2J_{C-F}$  = 21.5 Hz, 2C), 102.21, 70.12.

7-((3-chlorobenzyl)oxy)-4-oxo-4*H*-chromene-3-carbaldehyde (**14c**)

Yellow solid, yield: 71.1%, m.p. 145.7-146.9 °C.  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  10.39 (s, 1H), 8.48 (s, 1H), 8.24 (d,  $J$  = 8.8 Hz, 1H), 7.46 (s, 1H), 7.41-7.31 (m, 3H), 7.14 (dd,  $J$  = 8.9, 2.4 Hz, 1H), 6.99 (d,  $J$  = 2.4 Hz, 1H), 5.17 (s, 2H);  $^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  188.78, 175.22, 163.55, 160.24, 157.84, 137.34, 134.83, 130.14, 128.73, 127.77, 127.48, 125.40, 120.32, 119.28, 115.99, 102.29, 69.87.

3-(((3-formyl-4-oxo-4*H*-chromen-7-yl)oxy)methyl)benzotrile (**14d**)

Yellow solid, yield: 50.6%, m.p. 172.6-174.1 °C.  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  10.39 (s, 1H), 8.49 (s, 1H), 8.25 (d,  $J$  = 8.8 Hz, 1H), 7.78 (s, 1H), 7.72-7.68 (m, 2H), 7.57 (t,  $J$  = 7.7 Hz, 1H), 7.15 (dd,  $J$  = 8.9, 2.4 Hz, 1H), 7.00 (d,  $J$  = 2.4 Hz, 1H), 5.23 (s, 2H);  $^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  188.71, 175.17, 163.22, 160.31, 157.81, 136.98, 132.16, 131.54, 130.78, 129.72, 127.92, 120.34, 119.49, 118.36, 115.75, 113.13, 102.33, 69.36.

4-oxo-7-((3-(trifluoromethyl)benzyl)oxy)-4*H*-chromene-3-carbaldehyde (**14e**)

Yellow solid, yield: 27.5%, m.p. 111.6-113.4 °C.  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  10.39 (s, 1H), 8.50 (s, 1H), 8.25 (d,  $J$  = 9.0 Hz, 1H), 7.74 (s, 1H), 7.78-7.65 (m, 2H), 7.60-7.55 (m, 1H), 7.16 (dd,  $J$  = 8.9, 2.4 Hz, 1H), 7.02 (d,  $J$  = 2.4 Hz, 1H), 5.25 (s, 2H);  $^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  188.79, 175.25, 163.48, 160.33, 157.84, 136.34, 131.13 (q,  $^2J_{C-F}$  = 32.1 Hz), 130.69, 129.39, 127.82, 125.43 (q,  $^3J_{C-F}$  = 7.2 Hz), 124.21 (q,  $^3J_{C-F}$  = 7.2 Hz), 123.91 (q,  $^1J_{C-F}$  = 270.9 Hz), 120.30, 119.33, 115.86, 102.26, 69.89.

7-((3,4-difluorobenzyl)oxy)-4-oxo-4*H*-chromene-3-carbaldehyde (**14f**)

Yellow solid, yield: 56.8%, m.p. 174.9-175.9 °C.  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  10.38 (s, 1H), 8.49 (s, 1H), 8.23 (d,  $J$  = 8.8 Hz, 1H), 7.33-7.26 (m, 1H), 7.24-7.17 (m, 2H), 7.12 (dd,  $J$  = 8.9, 2.3 Hz, 1H), 6.98 (d,  $J$  = 2.4 Hz, 1H), 5.14 (s, 2H);  $^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  188.79, 175.22, 163.39, 160.32, 157.82, 151.69 (dd,  $^1J_{C-F}$  = 247.8,  $^2J_{C-F}$  = 19.7 Hz), 149.21 (dd,  $^1J_{C-F}$  = 247.9,  $^2J_{C-F}$  = 20.2 Hz), 132.30 (dd,  $^3J_{C-F}$  = 5.6,  $^4J_{C-F}$  = 3.8 Hz), 127.81, 123.53 (dd,  $^3J_{C-F}$  = 6.5,  $^4J_{C-F}$  = 3.7 Hz), 120.30, 119.31, 117.74 (d,  $^2J_{C-F}$  = 17.6 Hz), 116.64 (d,  $^2J_{C-F}$  = 18.0 Hz), 115.86, 102.27, 69.44 (d,  $^4J_{C-F}$  = 1.5 Hz).

7-((3,4-dichlorobenzyl)oxy)-4-oxo-4*H*-chromene-3-carbaldehyde (**14g**)

Yellow solid, yield: 51.6%, m.p. 173.2-174.3 °C.  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  10.39 (s, 1H), 8.49 (s, 1H), 8.25 (d,  $J$  = 8.9 Hz, 1H), 7.57 (d,  $J$  = 2.0 Hz, 1H), 7.51 (d,  $J$  = 8.3 Hz, 1H), 7.31 (d,  $J$  = 2.1 Hz, 1H), 7.13 (dd,  $J$  = 8.9, 2.4 Hz, 1H), 6.98 (d,  $J$  = 2.4 Hz, 1H), 5.15 (s, 2H);  $^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  188.73, 175.18, 163.32, 160.25, 157.82, 135.51, 133.12, 132.73, 130.86, 129.32, 127.86, 126.56, 120.35, 119.41, 115.80, 102.31, 69.24.

## 2. General procedure for the preparation of intermediate 8a-e and 15a-g

Intermediate **7a-e** or **14a-g** (3 mmol) was dissolved in MeOH or THF (30 ml) at 0 °C.  $\text{NaBH}_4$  (1 mmol) was then added in batches to the reaction flask. Upon completion, the reaction was quenched with a saturated ammonium chloride solution (30 ml) and extracted with DCM (20 ml  $\times$  3). The combined organic phase was washed with brine and dried over anhydrous  $\text{Na}_2\text{SO}_4$ . The crude product was purified by silica gel column chromatography using petroleum ether/ethyl acetate (2/1) to obtain intermediate **8a-e** or **15a-g** as a yellow solid.

3-(hydroxymethyl)-4*H*-chromen-4-one (**8a**)

Yellow solid, yield: 26.3%, m.p. 99.7-100.8 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.23 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.98 (s, 1H), 7.72-7.68 (m, 1H), 7.48 (dd, *J* = 8.5, 1.0 Hz, 1H), 7.45-7.41 (m, 1H), 4.61 (s, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 178.46, 156.62, 152.86, 133.93, 125.62, 125.29, 123.84, 123.33, 118.24, 58.58.

3-(hydroxymethyl)-6-methyl-4*H*-chromen-4-one (**8b**)

Yellow solid, yield: 36.6%, m.p. 145.0-146.3 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.02 (s, 1H), 7.94 (s, 1H), 7.51 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.39 (d, *J* = 8.6 Hz, 1H), 4.60 (s, 2H), 2.48 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 178.62, 154.94, 152.69, 135.34, 135.26, 124.85, 123.53, 123.04, 118.00, 58.81, 20.96.

3-(hydroxymethyl)-6-methoxy-4*H*-chromen-4-one (**8c**)

Yellow solid, yield: 40.9%, m.p. 151.1-152.3 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.96 (s, 1H), 7.57 (d, *J* = 3.1 Hz, 1H), 7.42 (d, *J* = 9.1 Hz, 1H), 7.32-7.26 (m, 1H), 4.61 (s, 2H), 3.91 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 178.35, 157.02, 152.61, 151.54, 124.41, 124.21, 122.44, 119.69, 104.44, 58.77, 55.95.

6-fluoro-3-(hydroxymethyl)-4*H*-chromen-4-one (**8d**)

Light yellow solid, yield: 19.3%, m.p. 153.7-155.3 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.99 (s, 1H), 7.86 (dd, *J* = 8.2, 3.1 Hz, 1H), 7.51 (dd, *J* = 9.2, 4.2 Hz, 1H), 7.44-7.41 (m, 1H), 4.61 (s, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 177.70 (d, <sup>4</sup>*J*<sub>C-F</sub> = 2.3 Hz), 159.56 (d, <sup>1</sup>*J*<sub>C-F</sub> = 247.3 Hz), 153.10, 152.87 (d, <sup>4</sup>*J*<sub>C-F</sub> = 1.8 Hz), 124.94 (d, <sup>3</sup>*J*<sub>C-F</sub> = 7.4 Hz), 122.72, 122.33 (d, <sup>2</sup>*J*<sub>C-F</sub> = 25.6 Hz), 120.44 (d, <sup>3</sup>*J*<sub>C-F</sub> = 8.1 Hz), 110.41 (d, <sup>2</sup>*J*<sub>C-F</sub> = 23.6 Hz), 58.42.

3-(hydroxymethyl)-7-methyl-4*H*-chromen-4-one (**8e**)

Light yellow solid, yield: 25.4%, m.p. 129.6-131.5 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.11 (d, *J* = 8.1 Hz, 1H), 7.92 (s, 1H), 7.27 (s, 1H), 7.25 (dd, *J* = 8.2, 1.5 Hz, 1H), 4.59 (s, 2H), 2.52 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 178.42, 156.79, 152.53, 145.40, 126.86, 125.34, 123.13, 121.63, 117.93, 58.73, 21.83.

7-((3-fluorobenzyl)oxy)-3-(hydroxymethyl)-4*H*-chromen-4-one (**15a**)

Yellow solid, yield: 38.6%, m.p. 124.6-125.9 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.16 (d, *J* = 8.9 Hz, 1H), 7.88 (s, 1H), 7.43-7.37 (m, 1H), 7.26-7.21 (m, 1H), 7.20-7.17 (m, 1H), 7.12-7.04 (m, 2H), 6.92 (d, *J* = 2.3 Hz, 1H), 5.17 (s, 2H), 4.58 (s, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 177.83, 163.03 (d, <sup>1</sup>*J*<sub>C-F</sub> = 245.4 Hz), 163.01, 158.31, 152.28, 138.14 (d, <sup>3</sup>*J*<sub>C-F</sub> = 7.4 Hz), 130.41 (d, <sup>3</sup>*J*<sub>C-F</sub> = 8.3 Hz), 127.20, 123.13, 122.79 (d, <sup>4</sup>*J*<sub>C-F</sub> = 3.0 Hz), 118.12, 115.36 (d, <sup>2</sup>*J*<sub>C-F</sub> = 21.1 Hz), 115.19, 114.31 (d, <sup>2</sup>*J*<sub>C-F</sub> = 22.3 Hz), 101.46, 69.72 (d, <sup>4</sup>*J*<sub>C-F</sub> = 2.1 Hz), 58.76.

7-((4-fluorobenzyl)oxy)-3-(hydroxymethyl)-4*H*-chromen-4-one (**15b**)

Yellow solid, yield: 28.9%, m.p. 137.2-139.1 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.16 (d, *J* = 8.9 Hz, 1H), 7.88 (s, 1H), 7.48-7.41 (m, 2H), 7.16-7.09 (m, 2H), 7.07 (dd, *J* = 8.9, 2.4 Hz, 1H), 6.93 (d, *J* = 2.4 Hz, 1H), 5.13 (s, 2H), 4.58 (s, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 177.87, 163.15, 162.76 (d, <sup>1</sup>*J*<sub>C-F</sub> = 246.1 Hz), 158.33, 152.27, 131.35 (d, <sup>4</sup>*J*<sub>C-F</sub> = 3.3 Hz), 129.51 (d, <sup>3</sup>*J*<sub>C-F</sub> = 8.2 Hz, 2C), 127.14, 123.09, 118.02, 115.78 (d, <sup>2</sup>*J*<sub>C-F</sub> = 21.6 Hz, 2C), 115.25, 101.37, 69.92, 58.79.

7-((3-chlorobenzyl)oxy)-3-(hydroxymethyl)-4*H*-chromen-4-one (**15c**)

Yellow solid, yield: 24.9%, m.p. 124.6-126.3 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.16 (d, *J* = 8.9 Hz, 1H), 7.88 (s, 1H), 7.47 (s, 1H), 7.41-7.30 (m, 3H), 7.08 (dd, *J* = 8.9, 2.4 Hz, 1H), 6.92 (d, *J* = 2.4 Hz, 1H), 5.15 (s, 2H), 4.58 (s, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 177.81, 162.98, 158.31, 152.29, 137.64, 134.77, 130.09, 128.61, 127.49, 127.22, 125.41, 123.14, 118.14, 115.17, 101.46, 69.69, 58.75.

3-(((3-(hydroxymethyl)-4-oxo-4*H*-chromen-7-yl)oxy)methyl)benzotrile (**15d**)

Yellow solid, yield: 19.7%, m.p. 128.5-130.2 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.18 (d, *J* = 8.9 Hz, 1H), 7.90 (s, 1H), 7.79 (s, 1H), 7.72-7.67 (m, 2H), 7.56 (t, *J* = 7.8 Hz, 1H), 7.09 (dd, *J* = 8.9, 2.4 Hz, 1H), 6.93 (d, *J* = 2.4 Hz, 1H), 5.21 (s, 2H), 4.59 (s, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 177.77, 162.65, 158.28, 152.32, 137.27, 132.06, 131.53, 130.78, 129.66, 127.40, 123.21, 118.41, 118.35, 115.01, 113.07, 101.50, 69.19, 58.74.

3-(hydroxymethyl)-7-((3-(trifluoromethyl)benzyl)oxy)-4*H*-chromen-4-one (**15e**)

Yellow solid, yield: 40.1%, m.p. 129.5-130.9 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.18 (d, *J* = 8.9 Hz, 1H), 7.90 (s, 1H), 7.74 (s, 1H), 7.66 (d, *J* = 7.8 Hz, 2H), 7.59-7.53 (m, 1H), 7.10 (dd, *J* = 8.9, 2.4 Hz, 1H), 6.95 (d, *J* = 2.4 Hz, 1H), 5.22 (s, 2H), 4.58 (s, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 177.84, 162.91, 158.31, 152.39, 136.61, 131.22 (q, <sup>2</sup>*J*<sub>C-F</sub> = 32.1 Hz), 130.68, 129.33, 127.28, 125.31 (q, <sup>3</sup>*J*<sub>C-F</sub> = 7.4 Hz), 124.21 (q, <sup>3</sup>*J*<sub>C-F</sub> = 7.4 Hz), 123.91 (q, <sup>1</sup>*J*<sub>C-F</sub> = 266.3 Hz), 123.15, 118.20, 115.14, 101.42, 69.71, 58.71.

7-((3,4-difluorobenzyl)oxy)-3-(hydroxymethyl)-4*H*-chromen-4-one (**15f**)

Yellow solid, yield: 36.4%, m.p. 154.9-155.8 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.17 (d, *J* = 8.9 Hz, 1H), 7.89 (s, 1H), 7.33-7.26 (m, 1H), 7.24-7.17 (m, 2H), 7.07 (dd, *J* = 8.9, 2.4 Hz, 1H), 6.91 (d, *J* = 2.4 Hz, 1H), 5.12 (s, 2H), 4.58 (s, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 177.84, 162.83, 158.29, 152.33, 151.72 (dd, <sup>1</sup>*J*<sub>C-F</sub> = 247.7, <sup>2</sup>*J*<sub>C-F</sub> = 19.7 Hz), 149.30 (dd, <sup>1</sup>*J*<sub>C-F</sub> = 248.3, <sup>2</sup>*J*<sub>C-F</sub> = 21.0 Hz), 132.59 (dd, <sup>3</sup>*J*<sub>C-F</sub> = 5.4, <sup>4</sup>*J*<sub>C-F</sub> = 4.1 Hz), 127.27, 123.48 (dd, <sup>3</sup>*J*<sub>C-F</sub> = 6.6, <sup>4</sup>*J*<sub>C-F</sub> = 3.6 Hz), 123.14, 118.19, 117.67 (d, <sup>2</sup>*J*<sub>C-F</sub> = 17.5 Hz), 116.56 (d, <sup>2</sup>*J*<sub>C-F</sub> = 17.9 Hz), 115.13, 101.43, 69.26 (d, <sup>4</sup>*J*<sub>C-F</sub> = 1.3 Hz), 58.76.

7-((3,4-dichlorobenzyl)oxy)-3-(hydroxymethyl)-4*H*-chromen-4-one (**15g**)

Yellow solid, yield: 47.1%, m.p. 164.6-166.4 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.17 (d, *J* = 8.9 Hz, 1H), 7.89 (s, 1H), 7.57 (d, *J* = 1.9 Hz, 1H), 7.51 (d, *J* = 8.2 Hz, 1H), 7.30 (s, 1H), 7.07 (dd, *J* = 8.9, 2.3 Hz, 1H), 6.91 (d, *J* = 2.2 Hz, 1H), 5.13 (s, 2H), 4.58 (s, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 177.78, 162.76, 158.28, 152.29, 135.82, 133.05, 132.58, 130.80, 129.31, 127.32, 126.56, 123.18, 118.26, 115.08, 101.48, 69.06, 58.75.

### 3. General procedure for the preparation of intermediate 21

Intermediate **20** (6.465g, 34mmol) and THF (160 ml) were added to the reaction flask. The mixture was stirred at 0 °C, and NaBH<sub>4</sub> (0.428g, 11.33mmol) was added to the reaction flask in portions. Subsequently, the reaction solution was stirred at room temperature for 24h. After the complete conversion of **20**, the reaction was quenched with a saturated solution of ammonium chloride (80 ml) and then extracted with DCM (50 ml × 3). The combined organic phase was washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The crude product was purified by silica gel column chromatography using DCM/MeOH (30/1) as the eluent to yield intermediate **21** as a yellow solid.

6-hydroxy-3-(hydroxymethyl)-4*H*-chromen-4-one (**21**)

Yellow solid, yield: 39.7%, m.p. 214.8-215.7 °C. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 10.02 (s, 1H), 8.16 (s, 1H), 7.51 (d, *J* = 9.0 Hz, 1H), 7.34 (d, *J* = 3.0 Hz, 1H), 7.23 (dd, *J* = 9.0, 3.0 Hz, 1H), 4.37 (s, 2H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ 176.32, 155.15, 153.81, 150.20, 124.52, 123.53, 123.33, 120.17, 107.79, 55.86.

### 4. General procedure for the preparation of intermediate 22a-m

Intermediate **21** (0.192 g, 1 mmol), anhydrous K<sub>2</sub>CO<sub>3</sub> (0.165 g, 1.2 mmol), acetonitrile (10 mL), and the corresponding substituted benzyl bromide (1.2 mmol) were added to the round-bottom flask. The reaction solution was refluxed for 3-6 h, and the crude product was purified by silica gel column chromatography with petroleum ether/ethyl acetate (1:1) to obtain intermediates **22a-m** as a yellow solid.

6-(benzyloxy)-3-(hydroxymethyl)-4*H*-chromen-4-one (**22a**)

Yellow solid, yield: 98.2%, m.p. 138.6-140.0 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.96 (s, 1H), 7.69 (d, *J* = 3.0 Hz, 1H), 7.50-7.47 (m, 2H), 7.46-7.35 (m, 5H), 5.17 (s, 2H), 4.61 (s, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 178.32,

156.13, 152.64, 151.63, 136.15, 128.71 (2C), 128.29, 127.71 (2C), 124.67, 124.42, 122.47, 119.79, 105.75, 70.67, 58.78.

6-((3-chlorobenzyl)oxy)-3-(hydroxymethyl)-4*H*-chromen-4-one (**22b**)

Yellow solid, yield: 87.5%, m.p. 138.1-139.9 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.96 (s, 1H), 7.69 (d, *J* = 3.0 Hz, 1H), 7.47 (d, *J* = 2.5 Hz, 1H), 7.44 (d, *J* = 9.2 Hz, 1H), 7.39-7.36 (m, 1H), 7.35-7.33 (m, 3H), 5.17 (s, 2H), 4.61 (s, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 178.17, 155.81, 152.95, 151.49, 138.19, 134.47, 130.02, 128.38, 127.60, 125.51, 124.62, 124.42, 122.08, 119.91, 105.71, 69.76, 58.75

6-((3-fluorobenzyl)oxy)-3-(hydroxymethyl)-4*H*-chromen-4-one (**22c**)

Yellow solid, yield: 89.3%, m.p. 124.9-126.5 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.96 (s, 1H), 7.65 (d, *J* = 3.0 Hz, 1H), 7.46 (d, *J* = 9.1 Hz, 1H), 7.42-7.38 (m, 1H), 7.37-7.35 (m, 1H), 7.26-7.22 (m, 1H), 7.22-7.18 (m, 1H), 7.08-7.03 (m, 1H), 5.16 (s, 2H), 4.61 (s, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 178.22, 163.01 (d, <sup>1</sup>*J*<sub>C-F</sub> = 246.5 Hz), 155.82, 152.68, 151.72, 138.73 (d, <sup>3</sup>*J*<sub>C-F</sub> = 7.4 Hz), 130.26 (d, <sup>3</sup>*J*<sub>C-F</sub> = 8.3 Hz), 124.58, 124.42, 122.92 (d, <sup>4</sup>*J*<sub>C-F</sub> = 2.9 Hz), 122.52, 119.91, 115.13 (d, <sup>2</sup>*J*<sub>C-F</sub> = 21.1 Hz), 114.37 (d, <sup>2</sup>*J*<sub>C-F</sub> = 22.2 Hz), 105.75, 69.76 (d, <sup>4</sup>*J*<sub>C-F</sub> = 1.9 Hz), 58.74.

6-((2-fluorobenzyl)oxy)-3-(hydroxymethyl)-4*H*-chromen-4-one (**22d**)

Light yellow solid, yield: 84.3%, m.p. 103.3-105.1 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.96 (s, 1H), 7.72 (d, *J* = 3.0 Hz, 1H), 7.56-7.51 (m, 1H), 7.46 (d, *J* = 9.2 Hz, 1H), 7.39 (d, *J* = 3.0 Hz, 1H), 7.37-7.35 (m, 1H), 7.22-7.16 (m, 1H), 7.14-7.09 (m, 1H), 5.24 (s, 2H), 4.61 (s, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 178.29, 160.69 (d, <sup>1</sup>*J*<sub>C-F</sub> = 247.6 Hz), 155.96, 152.63, 151.74, 130.14 (d, <sup>3</sup>*J*<sub>C-F</sub> = 8.1 Hz), 129.93 (d, <sup>3</sup>*J*<sub>C-F</sub> = 3.9 Hz), 124.52, 124.46, 124.31 (d, <sup>4</sup>*J*<sub>C-F</sub> = 3.6 Hz), 123.37 (d, <sup>2</sup>*J*<sub>C-F</sub> = 14.3 Hz), 122.50, 119.83, 115.55 (d, <sup>2</sup>*J*<sub>C-F</sub> = 21.3 Hz), 105.95, 64.55 (d, <sup>3</sup>*J*<sub>C-F</sub> = 4.5 Hz), 58.80.

6-((4-fluorobenzyl)oxy)-3-(hydroxymethyl)-4*H*-chromen-4-one (**22e**)

Yellow solid, yield: 85.7%, m.p. 108.6-110.1 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.96 (s, 1H), 7.67 (d, *J* = 3.0 Hz, 1H), 7.46 (dd, *J* = 5.3, 3.3 Hz, 2H), 7.44 (d, *J* = 1.5 Hz, 1H), 7.37 (dd, *J* = 9.2, 3.0 Hz, 1H), 7.15-7.07 (m, 2H), 5.13 (s, 2H), 4.61 (s, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 178.28, 162.68 (d, <sup>1</sup>*J*<sub>C-F</sub> = 246.6 Hz), 155.96, 152.66, 151.69, 131.94 (d, <sup>4</sup>*J*<sub>C-F</sub> = 3.3 Hz), 129.56 (d, <sup>3</sup>*J*<sub>C-F</sub> = 8.2 Hz, 2C), 124.65, 124.43, 122.50, 119.86, 115.64 (d, <sup>2</sup>*J*<sub>C-F</sub> = 21.2 Hz, 2C), 105.77, 69.99, 58.77.

6-((4-chlorobenzyl)oxy)-3-(hydroxymethyl)-4*H*-chromen-4-one (**22f**)

Yellow solid, yield: 80.4%, m.p. 141.3-142.5 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.96 (s, 1H), 7.65 (t, *J* = 2.4 Hz, 1H), 7.46-7.35 (m, 6H), 5.13 (s, 2H), 4.61 (s, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 178.26, 155.86, 152.69, 151.71, 134.65, 134.11, 128.98 (2C), 128.89 (2C), 124.61, 124.41, 122.50, 119.90, 105.75, 69.84, 58.75.

2-(((3-(hydroxymethyl)-4-oxo-4*H*-chromen-6-yl)oxy)methyl)benzotrile (**22g**)

Yellow solid, yield: 79.9%, m.p. 159.5-160.3 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.97 (s, 1H), 7.75 (d, *J* = 7.8 Hz, 1H), 7.72-7.61 (m, 3H), 7.51-7.43 (m, 2H), 7.40 (dd, *J* = 9.1, 3.0 Hz, 1H), 5.33 (s, 2H), 4.61 (s, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 178.12, 155.60, 152.70, 151.93, 139.63, 133.20, 133.09, 128.96, 128.85, 124.47, 124.33, 122.59, 120.05, 117.01, 111.83, 106.37, 68.47, 58.69.

3-(((3-(hydroxymethyl)-4-oxo-4*H*-chromen-6-yl)oxy)methyl)benzotrile (**22h**)

Yellow solid, yield: 83.4%, m.p. 133.9-135.1 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.98 (s, 1H), 7.80 (s, 1H), 7.73-7.66 (m, 2H), 7.65-7.63 (m, 1H), 7.54 (t, *J* = 7.8 Hz, 1H), 7.48 (d, *J* = 9.2 Hz, 1H), 7.39 (dd, *J* = 9.2, 3.1 Hz, 1H), 5.19 (s, 2H), 4.61 (s, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 178.15, 155.52, 152.87, 151.86, 137.84, 131.83, 131.62, 130.80, 129.52, 124.55, 124.41, 122.59, 120.12, 118.58, 112.88, 105.68, 69.21, 58.57.

3-(hydroxymethyl)-6-((3-(trifluoromethyl)benzyl)oxy)-4*H*-chromen-4-one (**22i**)

Yellow solid, yield: 83.6%, m.p. 112.9-114.6 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.97 (s, 1H), 7.76 (s, 1H),

7.72-7.65 (m, 2H), 7.61 (q,  $J = 7.8$  Hz, 1H), 7.57-7.49 (m, 1H), 7.46 (d,  $J = 9.2$  Hz, 1H), 7.39 (dd,  $J = 9.2, 3.0$  Hz, 1H), 5.21 (s, 2H), 4.61 (s, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  178.31, 155.79, 152.88, 151.81, 137.21, 130.98 (q,  $^2J_{\text{C-F}} = 32.0$  Hz), 129.16, 129.02, 125.05 (q,  $^3J_{\text{C-F}} = 3.9$  Hz), 124.89 (q,  $^1J_{\text{C-F}} = 272.5$  Hz), 124.72, 124.22 (q,  $^3J_{\text{C-F}} = 3.8$  Hz), 122.66, 122.50, 119.98, 105.68, 69.78, 58.59.

3-(hydroxymethyl)-6-((4-(trifluoromethyl)benzyl)oxy)-4H-chromen-4-one (**22j**)

Yellow solid, yield: 67.9%, m.p. 236.8-237.9 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.97 (s, 1H), 7.73-7.65 (m, 3H), 7.60 (d,  $J = 8.1$  Hz, 2H), 7.47 (d,  $J = 9.2$  Hz, 1H), 7.39 (dd, (d,  $J = 9.2, 3.0$  Hz, 1H), 5.23 (s, 2H), 4.61 (s, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  178.24, 155.74, 152.79, 152.66, 151.79, 140.20, 130.40 (q,  $^2J_{\text{C-F}} = 32.6$  Hz), 127.57 (2C), 125.66 (q,  $^3J_{\text{C-F}} = 3.8$  Hz, 2C), 124.91 (q,  $^1J_{\text{C-F}} = 270.5$  Hz), 124.67, 122.53, 120.00, 105.75, 69.69, 58.68.

6-((3,4-difluorobenzyl)oxy)-3-(hydroxymethyl)-4H-chromen-4-one (**22k**)

Light yellow solid, yield: 81.9%, m.p. 118.1-120.0 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.97(s, 1H), 7.64 (d,  $J = 3.1$  Hz, 1H), 7.47 (d,  $J = 9.2$  Hz, 1H), 7.37 (dd,  $J = 9.2, 3.1$  Hz, 1H), 7.35-7.30 (m, 1H), 7.25-7.17 (m, 2H), 5.12 (s, 2H), 4.61 (s, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  178.19, 155.68, 152.72, 151.79, 150.25 (dd,  $^1J_{\text{C-F}} = 246.8$ ,  $^2J_{\text{C-F}} = 20.3$  Hz), 150.12 (dd,  $^1J_{\text{C-F}} = 246.9$ ,  $^2J_{\text{C-F}} = 30.1$  Hz), 133.24 (dd,  $^3J_{\text{C-F}} = 5.6$ ,  $^4J_{\text{C-F}} = 3.9$  Hz), 124.56, 124.44, 123.50 (dd,  $^3J_{\text{C-F}} = 6.5$ ,  $^4J_{\text{C-F}} = 3.7$  Hz), 122.56, 119.96, 117.50 (d,  $^2J_{\text{C-F}} = 17.5$  Hz), 116.60 (d,  $^2J_{\text{C-F}} = 17.8$  Hz), 105.81, 69.34 ( $^4J_{\text{C-F}} = 1.1$  Hz), 58.69.

6-((3,5-difluorobenzyl)oxy)-3-(hydroxymethyl)-4H-chromen-4-one (**22l**)

Yellow solid, yield: 83.9%, m.p. 146.9-148.6 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.97 (s, 1H), 7.63 (d,  $J = 3.1$  Hz, 1H), 7.47 (d,  $J = 9.2$  Hz, 1H), 7.39 (dd,  $J = 9.2, 3.0$  Hz, 1H), 7.05-6.93 (m, 2H), 6.82-6.75 (m, 1H), 5.15 (s, 2H), 4.61 (s, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  178.15, 163.28 (d,  $^1J_{\text{C-F}} = 247.9$  Hz), 163.16 (d,  $^1J_{\text{C-F}} = 247.4$  Hz), 155.55, 152.74, 151.84, 140.19 (t,  $^3J_{\text{C-F}} = 9.2$  Hz), 124.49, 124.45, 122.59, 120.02, 109.92 (d,  $^2J_{\text{C-F}} = 25.9$  Hz), 109.91 (d,  $^3J_{\text{C-F}} = 11.7$  Hz), 105.85, 103.50 (t,  $^2J_{\text{C-F}} = 25.3$  Hz), 69.20 (t,  $^4J_{\text{C-F}} = 2.3$  Hz), 58.66.

6-((3,4-dichlorobenzyl)oxy)-3-(hydroxymethyl)-4H-chromen-4-one (**22m**)

Yellow solid, yield: 76.6%, m.p. 145.7-147.1 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.97 (s, 1H), 7.64 (d,  $J = 3.0$  Hz, 1H), 7.59 (d,  $J = 2.0$  Hz, 1H), 7.48 (dd,  $J = 9.6, 8.7$  Hz, 2H), 7.38 (dd,  $J = 9.2, 3.1$  Hz, 1H), 7.30 (dd,  $J = 8.2, 2.1$  Hz, 1H), 5.12 (s, 2H), 4.61 (s, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  178.22, 155.62, 152.72, 151.81, 136.40, 132.90, 132.29, 130.68, 129.38, 126.68, 124.57, 124.43, 122.54, 120.03, 105.72, 69.10, 58.76.

## 5. General procedure for the preparation of intermediate **9a-e**, **16a-g**, and **23a-m**

Intermediate **8a-e**, **15a-g**, or **22a-m** (1.2 mmol),  $\text{CBr}_4$  (1.44 mmol),  $\text{PPh}_3$  (1.44 mmol), and DCM (15 ml) were added to the reaction bottle. The mixture was then stirred at room temperature overnight under nitrogen. Subsequently, the mixture was purified by silica gel column chromatography using petroleum ether/ethyl acetate (5/1) to obtain intermediate **9a-e**, **16a-g**, or **23a-m** as a white or yellow solid or yellow oil.

3-(bromomethyl)-4H-chromen-4-one (**9a**)

White solid, yield: 69.7%, m.p. 145.3-146.2 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.28 (dd,  $J = 8.0, 1.7$  Hz, 1H), 8.14 (s, 1H), 7.73-7.69 (m, 1H), 7.51-7.43 (m, 2H), 4.43 (s, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  175.78, 156.49, 154.94, 134.02, 126.11, 125.59, 123.86, 121.93, 118.21, 23.62.

3-(bromomethyl)-6-methyl-4H-chromen-4-one (**9b**)

Yellow solid, yield: 76.5%, m.p. 155.8-157.2 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.11 (s, 1H), 8.05 (s, 1H), 7.51 (dd,  $J = 8.6, 2.2$  Hz, 1H), 7.37 (d,  $J = 8.6$  Hz, 1H), 4.42 (s, 2H), 2.47 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  175.86, 154.87, 154.77, 135.65, 135.26, 125.35, 123.52, 121.67, 117.95, 23.86, 20.97.

3-(bromomethyl)-6-methoxy-4*H*-chromen-4-one (**9c**)

White solid, yield: 91.3%, m.p. 152.4-153.8 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.13 (s, 1H), 7.63 (d, *J* = 3.1 Hz, 1H), 7.42 (d, *J* = 9.1 Hz, 1H), 7.32-7.27 (m, 1H), 4.44 (s, 2H), 3.92 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 175.69, 157.21, 154.70, 151.35, 124.48, 124.17, 121.08, 119.64, 105.03, 55.97, 23.91.

3-(bromomethyl)-6-fluoro-4*H*-chromen-4-one (**9d**)

White solid, yield: 62.4%, m.p. 162.5-163.3 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.15(s, 1H), 7.90 (dd, *J* = 8.1, 3.1 Hz, 1H), 7.51 (dd, *J* = 9.2, 4.2 Hz, 1H), 7.46-7.41 (m, 1H), 4.41 (s, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 175.11 (d, <sup>4</sup>*J*<sub>C-F</sub> = 2.6 Hz), 159.71 (d, <sup>1</sup>*J*<sub>C-F</sub> = 246.1 Hz), 155.10, 152.71 (d, <sup>4</sup>*J*<sub>C-F</sub> = 1.8 Hz), 124.99 (d, <sup>3</sup>*J*<sub>C-F</sub> = 7.7 Hz), 122.36 (d, <sup>2</sup>*J*<sub>C-F</sub> = 25.2 Hz), 121.34, 120.43 (d, <sup>3</sup>*J*<sub>C-F</sub> = 8.0 Hz), 110.94 (d, <sup>2</sup>*J*<sub>C-F</sub> = 23.7 Hz), 23.34.

3-(bromomethyl)-7-methyl-4*H*-chromen-4-one (**9e**)

Yellow solid, yield: 68.7%, m.p. 137.2-138.9 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.15 (d, *J* = 8.7 Hz, 1H), 8.10 (s, 1H), 7.28 (s, 1H), 7.26 (dd, *J* = 7.7, 1.2 Hz, 1H), 4.42 (s, 2H), 2.51 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 175.65, 156.64, 154.72, 145.49, 127.10, 125.83, 121.76, 121.63, 117.89, 23.78, 21.82.

3-(bromomethyl)-7-((3-fluorobenzyl)oxy)-4*H*-chromen-4-one (**16a**)

Yellow solid, yield: 60.4%, m.p. 147.7-149.5 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.19 (d, *J* = 8.9 Hz, 1H), 8.06 (s, 1H), 7.42-7.37 (m, 1H), 7.23-7.16 (m, 2H), 7.09-7.04 (m, 2H), 6.91 (d, *J* = 2.4 Hz, 1H), 5.17 (s, 2H), 4.39 (s, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 175.06, 163.02 (d, <sup>1</sup>*J*<sub>C-F</sub> = 245.4 Hz), 163.01, 158.12, 154.57, 138.11 (d, <sup>3</sup>*J*<sub>C-F</sub> = 7.3 Hz), 130.43 (d, <sup>3</sup>*J*<sub>C-F</sub> = 8.3 Hz), 127.65, 122.81 (d, <sup>4</sup>*J*<sub>C-F</sub> = 3.0 Hz), 121.79, 118.07, 115.46 (d, <sup>2</sup>*J*<sub>C-F</sub> = 21.2 Hz), 115.28, 114.31 (d, <sup>2</sup>*J*<sub>C-F</sub> = 22.3 Hz), 101.54, 69.72 (d, <sup>4</sup>*J*<sub>C-F</sub> = 1.9 Hz), 23.79.

3-(bromomethyl)-7-((4-fluorobenzyl)oxy)-4*H*-chromen-4-one (**16b**)

Yellow solid, yield: 85.8%, m.p. 133.4-135.2 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.20 (d, *J* = 8.9 Hz, 1H), 8.06 (s, 1H), 7.49-7.39 (m, 2H), 7.17-7.10 (m, 2H), 7.08 (dd, *J* = 8.9, 2.4 Hz, 1H), 6.92 (d, *J* = 2.3 Hz, 1H), 5.14 (s, 2H), 4.41 (s, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 175.34, 163.16, 162.76 (d, <sup>1</sup>*J*<sub>C-F</sub> = 245.7 Hz), 159.15, 154.52, 131.32 (d, <sup>4</sup>*J*<sub>C-F</sub> = 3.3 Hz), 129.50 (d, <sup>3</sup>*J*<sub>C-F</sub> = 8.4 Hz, 2C), 127.64, 121.84, 118.04, 115.79 (d, <sup>2</sup>*J*<sub>C-F</sub> = 21.6 Hz, 2C), 115.32, 101.47, 69.95, 23.77.

3-(bromomethyl)-7-((3-chlorobenzyl)oxy)-4*H*-chromen-4-one (**16c**)

Yellow solid, yield: 47.8%, m.p. 122.5-124.4 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.20 (d, *J* = 8.9 Hz, 1H), 8.06 (s, 1H), 7.47 (s, 1H), 7.39-7.31 (m, 3H), 7.08 (dd, *J* = 8.9, 2.4 Hz, 1H), 6.91 (d, *J* = 2.4 Hz, 1H), 5.15 (s, 2H), 4.40 (s, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 175.03, 162.99, 158.12, 154.53, 137.61, 134.77, 130.09, 128.62, 127.71, 127.47, 125.39, 121.84, 118.12, 115.24, 101.56, 69.71, 23.70.

3-(((3-(bromomethyl)-4-oxo-4*H*-chromen-7-yl)oxy)methyl)benzotrile (**16d**)

Yellow solid, yield: 61.2%, m.p. 144.8-146.3 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.22(d, *J* = 8.9 Hz, 1H), 8.07 (s, 1H), 7.78 (s, 1H), 7.72-7.67 (m, 2H), 7.56 (t, *J* = 7.8 Hz, 1H), 7.09 (dd, *J* = 8.8, 2.3 Hz, 1H), 6.92 (d, *J* = 2.4 Hz, 1H), 5.21 (s, 2H), 4.40 (s, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 175.02, 162.66, 158.09, 154.57, 137.24, 132.06, 131.53, 130.77, 129.67, 127.87, 121.93, 118.40, 118.34, 115.08, 113.07, 101.61, 69.21, 23.64.

3-(bromomethyl)-7-((3-(trifluoromethyl)benzyl)oxy)-4*H*-chromen-4-one (**16e**)

Yellow oil, yield: 32.6%. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.20 (d, *J* = 8.9 Hz, 1H), 8.07 (s, 1H), 7.74 (s, 1H), 7.68-7.62 (m, 2H), 7.56 (t, *J* = 7.7 Hz, 1H), 7.09 (dd, *J* = 8.9, 2.4 Hz, 1H), 6.93 (d, *J* = 2.4 Hz, 1H), 5.22 (s, 2H), 4.40 (s, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 175.02, 162.92, 158.12, 154.58, 136.62, 131.20 (q, <sup>2</sup>*J*<sub>C-F</sub> = 32.4 Hz), 130.68, 129.33, 127.72, 125.30 (q, <sup>3</sup>*J*<sub>C-F</sub> = 7.7 Hz), 124.18 (q, <sup>3</sup>*J*<sub>C-F</sub> = 7.7 Hz), 123.90 (q, <sup>1</sup>*J*<sub>C-F</sub> = 263.6 Hz), 121.84, 118.18, 115.19, 101.54, 69.73, 23.72.

3-(bromomethyl)-7-((3,4-difluorobenzyl)oxy)-4*H*-chromen-4-one (**16f**)

Yellow solid, yield: 50.6%, m.p. 123.9-125.7 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.20 (d, *J* = 8.9 Hz, 1H), 8.07 (s, 1H), 7.33-7.26 (m, 1H), 7.24-7.16 (m, 2H), 7.07 (dd, *J* = 8.9, 2.4 Hz, 1H), 6.90 (d, *J* = 2.4 Hz, 1H), 5.12 (s,

2H), 4.40 (s, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 175.05, 162.83, 158.10, 154.56, 151.65 (dd, <sup>1</sup>J<sub>C-F</sub> = 247.5, <sup>2</sup>J<sub>C-F</sub> = 23.7 Hz), 149.17 (dd, <sup>1</sup>J<sub>C-F</sub> = 247.9, <sup>2</sup>J<sub>C-F</sub> = 23.7 Hz), 132.56 (dd, <sup>3</sup>J<sub>C-F</sub> = 9.9, <sup>4</sup>J<sub>C-F</sub> = 5.5 Hz), 127.75, 123.49 (dd, <sup>3</sup>J<sub>C-F</sub> = 6.2, <sup>4</sup>J<sub>C-F</sub> = 3.7 Hz), 121.85, 118.16, 117.67 (d, <sup>2</sup>J<sub>C-F</sub> = 17.5 Hz), 116.61 (d, <sup>2</sup>J<sub>C-F</sub> = 17.9 Hz), 115.20, 101.53, 69.27 (d, <sup>4</sup>J<sub>C-F</sub> = 1.5 Hz), 23.72.

3-(bromomethyl)-7-((3,4-dichlorobenzyl)oxy)-4H-chromen-4-one (**16g**)

Yellow oil, yield: 42.8%. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.20 (d, *J* = 8.9 Hz, 1H), 8.07 (s, 1H), 7.57 (d, *J* = 2.0 Hz, 1H), 7.50 (d, *J* = 8.2 Hz, 1H), 7.30 (d, *J* = 2.1 Hz, 1H), 7.08 (dd, *J* = 8.9, 2.4 Hz, 1H), 6.90 (d, *J* = 2.4 Hz, 1H), 5.13 (s, 2H), 4.40 (s, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 175.00, 162.76, 158.09, 154.54, 135.78, 133.04, 132.58, 130.81, 129.31, 127.79, 126.57, 121.88, 118.23, 115.16, 101.56, 69.07, 23.67.

6-(benzyloxy)-3-(bromomethyl)-4H-chromen-4-one (**23a**)

Yellow solid, yield: 40.5%, m.p. 152.5-153.7 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.13 (s, 1H), 7.73 (d, *J* = 2.9 Hz, 1H), 7.50-7.47 (m, 2H), 7.45-7.35 (m, 5H), 5.17 (s, 2H), 4.43 (s, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 175.66, 156.32, 154.76, 151.44, 136.11, 128.72 (2C), 128.31, 127.72 (2C), 124.64, 124.47, 121.09, 119.75, 106.31, 70.68, 23.89.

3-(bromomethyl)-6-((3-chlorobenzyl)oxy)-4H-chromen-4-one (**23b**)

Yellow solid, yield: 38.8%, m.p. 159.8-161.5 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.13 (s, 1H), 7.70 (d, *J* = 3.0 Hz, 1H), 7.49 (d, *J* = 2.2 Hz, 1H), 7.46 (d, *J* = 9.2 Hz, 1H), 7.38 (dd, *J* = 9.1, 3.1 Hz, 1H), 7.35-7.34 (m, 3H), 5.14 (s, 2H), 4.43 (s, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 175.62, 156.00, 154.81, 151.56, 138.16, 134.84, 129.99, 128.41, 127.56, 125.55, 124.59, 124.46, 121.14, 119.89, 106.27, 69.75, 23.82.

3-(bromomethyl)-6-((3-fluorobenzyl)oxy)-4H-chromen-4-one (**23c**)

Yellow solid, yield: 84.1%, m.p. 174.3-175.4 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.13 (s, 1H), 7.70 (d, *J* = 3.0 Hz, 1H), 7.45 (d, *J* = 9.2 Hz, 1H), 7.43-7.34 (m, 2H), 7.26-7.23 (m, 1H), 7.22-7.18 (m, 1H), 7.08-7.03 (m, 1H), 5.17 (s, 2H), 4.43 (s, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 175.57, 163.02 (d, <sup>1</sup>J<sub>C-F</sub> = 246.4 Hz), 156.01, 154.76, 151.54, 138.69 (d, <sup>3</sup>J<sub>C-F</sub> = 7.4 Hz), 130.28 (d, <sup>3</sup>J<sub>C-F</sub> = 8.3 Hz), 124.56, 124.48, 122.92 (d, <sup>4</sup>J<sub>C-F</sub> = 2.9 Hz), 121.14, 119.87, 115.15 (d, <sup>2</sup>J<sub>C-F</sub> = 21.1 Hz), 114.36 (d, <sup>2</sup>J<sub>C-F</sub> = 22.3 Hz), 106.31, 69.78 (d, <sup>4</sup>J<sub>C-F</sub> = 1.9 Hz), 23.82.

3-(bromomethyl)-6-((2-fluorobenzyl)oxy)-4H-chromen-4-one (**23d**)

Yellow solid, yield: 48.1%, m.p. 163.1-164.5 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.13 (s, 1H), 7.76 (d, *J* = 3.0 Hz, 1H), 7.55-7.51 (m, 1H), 7.44 (d, *J* = 9.2 Hz, 1H), 7.41-7.32 (m, 2H), 7.22-7.18 (m, 1H), 7.16-7.11 (m, 1H), 5.24 (s, 2H), 4.44 (s, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 175.56, 160.69 (d, <sup>1</sup>J<sub>C-F</sub> = 247.9 Hz), 156.14, 154.74, 151.53, 130.15 (d, <sup>3</sup>J<sub>C-F</sub> = 8.2 Hz), 129.93 (d, <sup>3</sup>J<sub>C-F</sub> = 3.7 Hz), 124.51, 124.44, 124.31 (d, <sup>4</sup>J<sub>C-F</sub> = 3.6 Hz), 123.34 (d, <sup>2</sup>J<sub>C-F</sub> = 14.5 Hz), 121.14, 119.78, 115.57 (d, <sup>2</sup>J<sub>C-F</sub> = 21.1 Hz), 106.51, 64.58 (d, <sup>3</sup>J<sub>C-F</sub> = 4.4 Hz), 23.81.

3-(bromomethyl)-6-((4-fluorobenzyl)oxy)-4H-chromen-4-one (**23e**)

White solid, yield: 50.1%, m.p. 180.1-181.1 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.13 (s, 1H), 7.71 (d, *J* = 3.0 Hz, 1H), 7.50-7.41 (m, 3H), 7.36 (dd, *J* = 9.2, 3.0 Hz, 1H), 7.15-7.07 (m, 2H), 5.13 (s, 2H), 4.43 (s, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 175.60, 162.67 (d, <sup>1</sup>J<sub>C-F</sub> = 246.7 Hz), 156.13, 154.76, 151.49, 131.90 (d, <sup>4</sup>J<sub>C-F</sub> = 3.3 Hz), 129.59 (d, <sup>3</sup>J<sub>C-F</sub> = 8.3 Hz, 2C), 124.60, 124.48, 121.14, 119.81, 115.65 (d, <sup>2</sup>J<sub>C-F</sub> = 21.4 Hz, 2C), 106.29, 69.99, 23.82.

3-(bromomethyl)-6-((4-chlorobenzyl)oxy)-4H-chromen-4-one (**23f**)

White solid, yield: 49.1%, m.p. 166.7-168.4 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.13 (s, 1H), 7.69 (t, *J* = 2.4 Hz, 1H), 7.45-7.34 (m, 6H), 5.13 (s, 2H), 4.43 (s, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 175.61, 156.04, 154.78, 151.52, 134.61, 134.12, 128.99 (2C), 128.90 (2C), 124.58, 124.47, 121.14, 119.85, 106.31, 69.86, 23.83.

2-(((3-(bromomethyl)-4-oxo-4H-chromen-6-yl)oxy)methyl)benzotrile (**23g**)

Yellow solid, yield: 45.1%, m.p. 118.9-120.3 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.13 (s, 1H), 7.79-7.73 (m, 2H), 7.69-7.65 (m, 2H), 7.51-7.47 (m, 1H), 7.46 (s, 1H), 7.41 (dd, *J* = 9.2, 3.0 Hz, 1H), 5.34 (s, 2H), 4.43 (s, 2H);



$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  175.52, 155.79, 154.83, 151.74, 139.55, 133.24, 133.12, 128.98, 128.88, 124.50, 124.33, 121.18, 120.02, 117.02, 111.84, 106.85, 68.49, 23.80.

3-(((3-(bromomethyl)-4-oxo-4*H*-chromen-6-yl)oxy)methyl)benzonitrile (**23h**)

Yellow solid, yield: 21.7%, m.p. 169.5-171.1 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.14 (s, 1H), 7.80 (s, 1H), 7.75-7.69 (m, 2H), 7.68-7.64 (m, 1H), 7.55 (d,  $J = 7.7$  Hz, 1H), 7.48 (d,  $J = 9.2$  Hz, 1H), 7.39 (dd,  $J = 9.2, 3.1$  Hz, 1H), 5.20 (s, 2H), 4.43 (s, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  175.57, 155.71, 154.86, 151.69, 137.80, 131.85, 131.62, 130.79, 129.53, 124.57, 124.47, 121.20, 120.08, 118.57, 112.91, 106.20, 69.23, 23.74.

3-(bromomethyl)-6-((3-(trifluoromethyl)benzyl)oxy)-4*H*-chromen-4-one (**23i**)

White solid, yield: 31.5%, m.p. 145.5-147.2 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.14 (s, 1H), 7.76 (s, 1H), 7.72 (d,  $J = 3.0$  Hz, 1H), 7.69-7.61 (m, 2H), 7.56 (t,  $J = 7.7$  Hz, 1H), 7.47 (d,  $J = 9.1$  Hz, 1H), 7.40 (dd,  $J = 9.2, 3.1$  Hz, 1H), 5.25 (s, 2H), 4.44 (s, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  175.59, 155.96, 154.80, 151.62, 137.16, 131.02 (q,  $^2J_{\text{C-F}} = 32.1$  Hz), 129.19, 129.07, 125.09 (q,  $^3J_{\text{C-F}} = 3.9$  Hz), 124.93 (q,  $^1J_{\text{C-F}} = 270.9$  Hz), 124.78, 124.23 (q,  $^3J_{\text{C-F}} = 3.8$  Hz), 122.65, 121.19, 119.95, 106.23, 69.79, 23.78.

3-(bromomethyl)-6-((4-(trifluoromethyl)benzyl)oxy)-4*H*-chromen-4-one (**23j**)

Yellow solid, yield: 26.7%, m.p. 158.7-160.1 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.14 (s, 1H), 7.73-7.69 (m, 2H), 7.68 (s, 1H), 7.60 (d,  $J = 8.1$  Hz, 2H), 7.47 (d,  $J = 9.2$  Hz, 1H), 7.39 (dd,  $J = 9.2, 3.1$  Hz, 1H), 5.24 (s, 2H), 4.43 (s, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  175.56, 155.91, 154.79, 151.60, 140.16, 130.43 (q,  $^2J_{\text{C-F}} = 32.5$  Hz), 127.58 (2C), 125.69 (q,  $^3J_{\text{C-F}} = 7.6$  Hz, 2C), 124.53, 124.49, 124.04 (q,  $^1J_{\text{C-F}} = 270.3$  Hz), 121.18, 119.95, 106.31, 69.71, 23.76.

3-(bromomethyl)-6-((3,4-difluorobenzyl)oxy)-4*H*-chromen-4-one (**23k**)

Yellow solid, yield: 23.3%, m.p. 139.8-141.4 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.13 (s, 1H), 7.68 (d,  $J = 3.2$  Hz, 1H), 7.46 (d,  $J = 9.1$  Hz, 1H), 7.37 (dd,  $J = 9.2, 3.0$  Hz, 1H), 7.34-7.30 (m, 1H), 7.25-7.17 (m, 2H), 5.12 (s, 2H), 4.43 (s, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  175.53, 155.86, 154.79, 151.60, 150.45 (dd,  $^1J_{\text{C-F}} = 247.1$ ,  $^2J_{\text{C-F}} = 22.1$  Hz), 150.13, (dd,  $^1J_{\text{C-F}} = 247.5$ ,  $^2J_{\text{C-F}} = 30.4$  Hz), 133.18 (dd,  $^3J_{\text{C-F}} = 8.1$ ,  $^4J_{\text{C-F}} = 5.2$  Hz), 124.53, 124.48, 123.53 (dd,  $^3J_{\text{C-F}} = 6.3$ ,  $^4J_{\text{C-F}} = 3.9$  Hz), 121.20, 119.92, 117.51 (d,  $^2J_{\text{C-F}} = 17.7$  Hz), 116.60 (d,  $^2J_{\text{C-F}} = 17.9$  Hz), 106.35, 69.35 (d,  $^4J_{\text{C-F}} = 1.0$  Hz), 23.68.

3-(bromomethyl)-6-((3,5-difluorobenzyl)oxy)-4*H*-chromen-4-one (**23l**)

Yellow solid, yield: 54.6%, m.p. 198.6-200.3 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.14 (s, 1H), 7.67 (d,  $J = 3.1$  Hz, 1H), 7.47 (d,  $J = 9.1$  Hz, 1H), 7.39 (dd,  $J = 9.2, 3.1$  Hz, 1H), 7.03-6.98 (m, 2H), 6.83-6.77 (m, 1H), 5.16 (s, 2H), 4.43 (s, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  175.49, 163.29 (d,  $^1J_{\text{C-F}} = 247.6$  Hz), 163.17 (d,  $^1J_{\text{C-F}} = 248.5$  Hz), 155.73, 154.79, 151.66, 140.15 (t,  $^3J_{\text{C-F}} = 9.7$  Hz), 124.51, 124.46, 121.22, 119.98, 109.92 (d,  $^2J_{\text{C-F}} = 25.9$  Hz), 109.91 (d,  $^2J_{\text{C-F}} = 11.7$  Hz), 106.39, 103.52 (t,  $^2J_{\text{C-F}} = 25.2$  Hz), 69.23 (t,  $^4J_{\text{C-F}} = 4.1$  Hz), 23.66.

3-(bromomethyl)-6-((3,4-dichlorobenzyl)oxy)-4*H*-chromen-4-one (**23m**)

Yellow solid, yield: 34.7%, m.p. 158.7-160.3 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.14 (s, 1H), 7.68 (d,  $J = 3.1$  Hz, 1H), 7.58 (d,  $J = 2.0$  Hz, 1H), 7.51-7.43 (m, 2H), 7.37 (dd,  $J = 9.2, 3.0$  Hz, 1H), 7.30 (dd,  $J = 8.3, 2.1$  Hz, 1H), 5.12 (s, 2H), 4.43 (s, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  175.57, 155.80, 154.81, 151.62, 136.37, 132.91, 132.31, 130.69, 129.37, 126.69, 124.55, 124.47, 121.18, 119.98, 106.26, 69.12, 23.75.

## 6. General procedure for the preparation of intermediate 10a-e, 17a-g, and 24a-m

Intermediate **3** or **5** (0.292 g, 1.1 mmol), anhydrous  $\text{K}_2\text{CO}_3$  (0.152 g, 1.1 mmol), acetonitrile (10 mL), and the corresponding intermediates **9a-e**, **16a-g**, or **23a-m** (1 mmol) were added to the reaction vessel. The mixture was

refluxed for 3-12 h. After the reaction was completed, the solution was cooled to room temperature and purified by silica gel column chromatography using DCM/MeOH (30/1) to obtain intermediates **10a-e**, **17a-g**, or **24a-m** as a white, yellow, or red solids.

3-(benzyloxy)-2-methyl-1-((4-oxo-4*H*-chromen-3-yl)methyl)pyridin-4(1*H*)-one (**10a**)

White solid, yield: 77.3%, m.p. 129.9-131.1 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.22 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.77-7.73 (m, 1H), 7.53-7.44 (m, 2H), 7.43-7.35 (m, 3H), 7.34-7.23 (m, 4H), 6.47 (d, *J* = 7.5 Hz, 1H), 5.27 (s, 2H), 4.86 (s, 2H), 2.10 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 176.23, 173.55, 156.40, 152.84, 146.08, 141.03, 138.73, 137.34, 134.48, 129.32 (2C), 128.22 (2C), 128.08, 125.87, 125.74, 123.32, 119.79, 118.28, 117.64, 72.93, 49.08, 12.56.

3-(benzyloxy)-2-methyl-1-((6-methyl-4-oxo-4*H*-chromen-3-yl)methyl)pyridin-4(1*H*)-one (**10b**)

White solid, yield: 73.5%, m.p. 130.6-132.4 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.98 (s, 1H), 7.55 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.40 (d, *J* = 7.6 Hz, 4H), 7.34-7.22 (m, 4H), 6.47 (d, *J* = 7.5 Hz, 1H), 5.26 (s, 2H), 4.86 (s, 2H), 2.48 (s, 3H), 2.11 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 176.30, 173.23, 154.71, 152.92, 152.86, 146.02, 141.25, 138.80, 137.32, 136.02, 135.75, 129.32 (2C), 128.23 (2C), 128.09, 124.96, 123.00, 119.49, 118.03, 72.98, 49.15, 20.98, 12.59.

3-(benzyloxy)-1-((6-methoxy-4-oxo-4*H*-chromen-3-yl)methyl)-2-methylpyridin-4(1*H*)-one (**10c**)

Yellow solid, yield: 60.7%, m.p. 209.5-211.2 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.55 (d, *J* = 3.1 Hz, 1H), 7.45 (dd, *J* = 9.2, 4.1 Hz, 2H), 7.43-7.38 (m, 2H), 7.36-7.29 (m, 5H), 6.53 (*J* = 7.5 Hz, 1H), 5.27 (s, 2H), 4.90 (s, 2H), 3.88 (s, 3H), 2.14 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 176.11, 173.23, 157.44, 152.77, 151.31, 145.94, 141.51, 138.87, 137.25, 129.34 (2C), 128.26 (2C), 128.13, 124.71, 123.96, 119.75, 118.80, 117.43, 104.56, 73.05, 56.01, 49.32, 12.64.

3-(benzyloxy)-1-((6-fluoro-4-oxo-4*H*-chromen-3-yl)methyl)-2-methylpyridin-4(1*H*)-one (**10d**)

White solid, yield: 83.6%, m.p. 194.6-196.3 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.84 (dd, *J* = 8.0, 3.0 Hz, 1H), 7.53 (dd, *J* = 9.2, 4.2 Hz, 1H), 7.50-7.45 (m, 1H), 7.41-7.38 (m, 2H), 7.33-7.28 (m, 5H), 6.48 (d, *J* = 7.5 Hz, 1H), 5.26 (s, 2H), 4.87 (s, 2H), 2.11 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 175.57 (d, <sup>4</sup>*J*<sub>C-F</sub> = 2.6 Hz), 173.41, 159.81 (d, <sup>1</sup>*J*<sub>C-F</sub> = 247.2 Hz), 153.23, 152.64 (d, <sup>4</sup>*J*<sub>C-F</sub> = 1.8 Hz), 145.99, 141.32, 138.82, 137.23, 129.31 (2C), 128.26 (2C), 128.13, 124.45 (d, <sup>3</sup>*J*<sub>C-F</sub> = 7.3 Hz), 122.87 (d, <sup>2</sup>*J*<sub>C-F</sub> = 25.5 Hz), 120.56 (d, <sup>3</sup>*J*<sub>C-F</sub> = 8.0 Hz), 119.15, 117.55, 110.58 (d, <sup>2</sup>*J*<sub>C-F</sub> = 23.7 Hz), 72.98, 49.01, 12.61.

3-(benzyloxy)-2-methyl-1-((7-methyl-4-oxo-4*H*-chromen-3-yl)methyl)pyridin-4(1*H*)-one (**10e**)

White solid, yield: 77.2%, m.p. 156.7-158.5 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.09 (dd, *J* = 7.1, 1.7 Hz, 1H), 7.44-7.38 (m, 2H), 7.37 (d, *J* = 7.6 Hz, 1H), 7.34-7.24 (m, 5H), 7.20 (s, 1H), 6.46 (d, *J* = 7.5 Hz, 1H), 5.27 (s, 2H), 4.84 (s, 2H), 2.52 (s, 3H), 2.10 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 176.09, 173.55, 156.56, 152.55, 146.08, 146.07, 141.04, 138.73, 137.36, 129.32 (2C), 129.30, 128.22 (2C), 128.20, 128.07, 127.40, 125.44, 121.08, 119.63, 117.92, 117.62, 72.92, 49.10, 21.88, 12.54.

1-((7-((3-fluorobenzyl)oxy)-4-oxo-4*H*-chromen-3-yl)methyl)-3-((4-methoxybenzyl)oxy)-2-methylpyridin-4(1*H*)-one (**17a**)

Yellow solid, yield: 75.1%, m.p. 179.0-180.1 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.10 (d, *J* = 8.9 Hz, 1H), 7.43-7.36 (m, 1H), 7.35 (d, *J* = 7.4 Hz, 1H), 7.32-7.26 (m, 2H), 7.21 (d, *J* = 7.7 Hz, 1H), 7.18-7.11 (m, 2H), 7.08 (dd, *J* = 8.9, 2.3 Hz, 1H), 7.04 (dd, *J* = 8.5, 2.6 Hz, 1H), 6.89 (d, *J* = 2.4 Hz, 1H), 6.85-6.77 (m, 2H), 6.43 (d, *J* = 7.5 Hz, 1H), 5.19 (s, 2H), 5.16 (s, 2H), 4.81 (s, 2H), 3.76 (s, 3H), 2.06 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 175.42, 173.60, 163.28, 163.00 (d, <sup>1</sup>*J*<sub>C-F</sub> = 245.4 Hz), 159.55, 158.09, 152.45, 152.40, 145.86, 141.23, 138.74, 137.98 (d, <sup>3</sup>*J*<sub>C-F</sub> = 7.3 Hz), 130.95 (2C), 130.45 (d, <sup>3</sup>*J*<sub>C-F</sub> = 8.2 Hz), 129.50, 127.25, 122.77 (d, <sup>4</sup>*J*<sub>C-F</sub> = 3.0 Hz), 119.72, 117.49, 115.61, 115.39 (d, <sup>2</sup>*J*<sub>C-F</sub> = 21.2 Hz), 114.25 (d, <sup>2</sup>*J*<sub>C-F</sub> = 22.2 Hz), 113.55 (2C), 101.51, 72.40, 69.77 (d, <sup>4</sup>*J*<sub>C-F</sub> = 1.9 Hz), 55.17, 49.05, 12.56.

1-((7-((4-fluorobenzyl)oxy)-4-oxo-4*H*-chromen-3-yl)methyl)-3-((4-methoxybenzyl)oxy)-2-methylpyridin-4(1*H*)-one (**17b**)

Yellow solid, yield: 72.7%, m.p. 162.1-163.7 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.64 (d, *J* = 3.0 Hz, 1H), 7.51-7.47 (m, 1H), 7.45-7.23 (m, 7H), 7.19-7.15 (m, *J* = 7.6, 1.2 Hz, 1H), 7.13-7.05 (m, 1H), 6.86-6.73 (m, 2H), 6.43 (d, *J* = 7.5 Hz, 1H), 5.18 (s, 2H), 5.17 (s, 2H), 4.84 (s, 2H), 3.75 (s, 3H), 2.07 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 175.44, 173.58, 163.42, 162.74 (d, <sup>1</sup>*J*<sub>C-F</sub> = 245.7 Hz), 159.54, 158.10, 152.49, 152.46, 145.84, 141.29, 138.77, 131.20 (d, <sup>4</sup>*J*<sub>C-F</sub> = 3.2 Hz), 130.96 (2C), 129.50 (d, <sup>3</sup>*J*<sub>C-F</sub> = 8.4 Hz, 2C), 129.48, 127.18, 119.68, 117.49, 117.39, 115.78 (d, <sup>2</sup>*J*<sub>C-F</sub> = 21.9 Hz, 2C), 113.54 (2C), 101.41, 72.40, 69.99, 55.18, 49.06, 12.57.

1-((7-((3-chlorobenzyl)oxy)-4-oxo-4*H*-chromen-3-yl)methyl)-3-((4-methoxybenzyl)oxy)-2-methylpyridin-4(1*H*)-one (**17c**)

Yellow solid, yield: 67.9%, m.p. 178.9-180.8 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.12 (d, *J* = 8.9 Hz, 1H), 7.45 (d, *J* = 2.0 Hz, 1H), 7.36-7.28 (m, 6H), 7.12 (s, 1H), 7.09 (dd, *J* = 8.9, 2.4 Hz, 1H), 6.90 (d, *J* = 2.4 Hz, 1H), 6.86-6.79 (m, 2H), 6.44 (d, *J* = 7.5 Hz, 1H), 5.20 (s, 2H), 5.15 (s, 2H), 4.82 (s, 2H), 3.77 (s, 3H), 2.07 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 175.40, 173.59, 163.27, 159.57, 158.09, 152.34, 145.89, 141.19, 138.70, 137.47, 134.77, 130.97 (2C), 130.12, 129.52, 128.65, 127.42, 127.29, 125.38, 119.77, 117.55, 117.51, 115.61, 113.56 (2C), 101.50, 72.40, 69.76, 55.19, 49.07, 12.57.

3-(((3-((4-methoxybenzyl)oxy)-2-methyl-4-oxopyridin-1(4*H*)-yl)methyl)-4-oxo-4*H*-chromen-7-yl)oxy)methyl)benzotrile (**17d**)

Yellow solid, yield: 78.6%, m.p. 169.3-171.1 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.12 (d, *J* = 8.9 Hz, 1H), 7.75 (s, 1H), 7.72-7.62 (m, 2H), 7.54 (t, *J* = 7.8 Hz, 1H), 7.36 (d, *J* = 7.6 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.17 (s, 1H), 7.08 (dd, *J* = 9.0, 2.3 Hz, 1H), 6.91 (d, *J* = 2.4 Hz, 1H), 6.86-6.76 (m, 2H), 6.43 (d, *J* = 7.5 Hz, 1H), 5.19 (s, 2H), 5.18 (s, 2H), 4.82 (s, 2H), 3.76 (s, 3H), 2.08 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 175.40, 173.58, 162.95, 159.54, 158.06, 152.50, 145.88, 141.27, 138.76, 137.10, 132.07, 131.57, 130.94 (2C), 130.74, 129.70, 129.48, 127.43, 119.78, 118.41, 117.70, 117.52, 115.45, 113.55 (2C), 113.00, 101.55, 72.42, 69.24, 55.21, 48.05, 12.59.

3-((4-methoxybenzyl)oxy)-2-methyl-1-((4-oxo-7-((3-(trifluoromethyl)benzyl)oxy)-4*H*-chromen-3-yl)methyl)pyridin-4(1*H*)-one (**17e**)

Yellow solid, yield: 98.1%, m.p. 176.4-177.8 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.14 (d, *J* = 8.9 Hz, 1H), 7.73 (s, 1H), 7.68-7.62 (m, 2H), 7.57 (t, *J* = 7.8 Hz, 1H), 7.39 (d, *J* = 7.5 Hz, 1H), 7.34-7.31 (m, 2H), 7.17 (s, 1H), 7.12 (dd, *J* = 9.0, 2.4 Hz, 1H), 6.94 (d, *J* = 2.3 Hz, 1H), 6.86-6.82 (m, 2H), 6.51 (d, *J* = 7.4 Hz, 1H), 5.23 (s, 2H), 5.21 (s, 2H), 4.87 (s, 2H), 3.78 (s, 3H), 2.10 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 175.45, 173.40, 163.22, 159.59, 158.11, 152.47, 145.80, 141.58, 138.82, 136.44, 131.26 (q, <sup>2</sup>*J*<sub>C-F</sub> = 32.1 Hz), 131.01 (2C), 130.66, 129.41, 129.37, 127.37, 125.38 (q, <sup>3</sup>*J*<sub>C-F</sub> = 7.7 Hz), 124.16 (q, <sup>3</sup>*J*<sub>C-F</sub> = 7.5 Hz), 123.90 (q, <sup>1</sup>*J*<sub>C-F</sub> = 270.8 Hz), 119.73, 117.59, 117.44, 115.60, 113.57 (2C), 101.47, 72.51, 69.79, 55.19, 49.20, 12.64.

1-((7-((3,4-difluorobenzyl)oxy)-4-oxo-4*H*-chromen-3-yl)methyl)-3-((4-methoxybenzyl)oxy)-2-methylpyridin-4(1*H*)-one (**17f**)

Yellow solid, yield: 80.1%, m.p. 173.3-175.0 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.12 (d, *J* = 8.9 Hz, 1H), 7.37 (d, *J* = 7.5 Hz, 1H), 7.32-7.29 (m, 3H), 7.27-7.18 (m, 2H), 7.15 (s, 1H), 7.08 (dd, *J* = 9.0, 2.4 Hz, 1H), 6.90 (d, *J* = 2.4 Hz, 1H), 6.85-6.81 (m, 2H), 6.47 (d, *J* = 7.4 Hz, 1H), 5.20 (s, 2H), 5.12 (s, 2H), 4.84 (s, 2H), 3.78 (s, 3H), 2.09 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 175.43, 173.50, 163.13, 159.57, 158.09, 152.47, 151.65 (dd, <sup>1</sup>*J*<sub>C-F</sub> = 247.5, <sup>2</sup>*J*<sub>C-F</sub> = 21.9 Hz), 149.17 (dd, <sup>1</sup>*J*<sub>C-F</sub> = 247.9, <sup>2</sup>*J*<sub>C-F</sub> = 22.3 Hz), 145.83, 141.49, 138.80, 132.42 (dd, <sup>3</sup>*J*<sub>C-F</sub> = 5.7, <sup>4</sup>*J*<sub>C-F</sub> = 3.9 Hz), 130.98 (2C), 129.43, 127.34, 123.51 (dd, <sup>3</sup>*J*<sub>C-F</sub> = 6.6, <sup>4</sup>*J*<sub>C-F</sub> = 3.7 Hz), 119.72, 117.70 (d, <sup>2</sup>*J*<sub>C-F</sub> = 17.5 Hz), 117.56, 117.46, 116.59 (d, <sup>2</sup>*J*<sub>C-F</sub> = 17.9 Hz), 115.58, 113.57 (2C), 101.48, 72.49, 69.33 (d, <sup>4</sup>*J*<sub>C-F</sub> = 1.4 Hz), 55.20, 49.15, 12.62.

1-((7-((3,4-dichlorobenzyl)oxy)-4-oxo-4*H*-chromen-3-yl)methyl)-3-((4-methoxybenzyl)oxy)-2-

methylpyridin-4(1H)-one (**17g**)

Yellow solid, yield: 72.3%, m.p. 182.9-184.3 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.13 (d, *J* = 8.9 Hz, 1H), 7.56 (d, *J* = 2.0 Hz, 1H), 7.50 (d, *J* = 8.2 Hz, 1H), 7.38 (d, *J* = 7.5 Hz, 1H), 7.34-7.26 (m, 3H), 7.16 (s, 1H), 7.09 (dd, *J* = 8.9, 2.4 Hz, 1H), 6.90 (d, *J* = 2.4 Hz, 1H), 6.87-6.80 (m, 2H), 6.48 (d, *J* = 7.5 Hz, 1H), 5.21 (s, 2H), 5.13 (s, 2H), 4.85 (s, 2H), 3.79 (s, 3H), 2.10 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 175.39, 173.42, 163.07, 159.59, 158.08, 152.40, 145.88, 141.35, 138.72, 135.63, 133.08, 132.65, 130.97 (2C), 130.83, 129.50, 129.29, 127.40, 126.55, 119.81, 117.64, 117.50, 115.54, 113.58 (2C), 101.53, 72.48, 69.14, 55.20, 49.13, 12.61.

1-((6-(benzyloxy)-4-oxo-4H-chromen-3-yl)methyl)-3-((4-methoxybenzyl)oxy)-2-methylpyridin-4(1H)-one (**24a**)

Yellow solid, yield: 42.6%, m.p. 191.9-193.8 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.64 (d, *J* = 2.9 Hz, 1H), 7.48 (d, *J* = 1.9 Hz, 1H), 7.45 (d, *J* = 9.0 Hz, 3H), 7.42-7.41 (m, 3H), 7.40-7.35 (m, 1H), 7.33-7.30 (m, 2H), 7.24 (s, 1H), 6.86-6.82 (m, 2H), 6.53 (d, *J* = 7.5 Hz, 1H), 5.23 (s, 2H), 5.17 (s, 2H), 4.89 (s, 2H), 3.79 (s, 3H), 2.11 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 176.03, 173.33, 159.62, 156.49, 152.67, 151.39, 145.72, 141.73, 138.86, 135.94, 131.06 (2C), 129.36, 128.74 (2C), 128.37, 127.67 (2C), 125.12, 123.91, 119.82, 118.87, 117.38, 113.57 (2C), 105.85, 72.53, 70.70, 55.21, 49.37, 12.68.

1-(((6-(3-chlorobenzyl)oxy)-4-oxo-4H-chromen-3-yl)methyl)-3-((4-methoxybenzyl)oxy)-2-methylpyridin-4(1H)-one (**24b**)

White solid, yield: 39.9%, m.p. 178.9-180.5 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.61 (d, *J* = 3.0 Hz, 1H), 7.47 (t, *J* = 9.2 Hz, 2H), 7.41 (dd, *J* = 8.8, 3.1 Hz, 2H), 7.35-7.31 (m, 5H), 7.23 (s, 1H), 6.86-6.83 (m, 2H), 6.52 (d, *J* = 7.5 Hz, 1H), 5.23 (s, 2H), 5.14 (s, 2H), 4.89 (s, 2H), 3.80 (s, 3H), 2.11 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 175.99, 173.16, 159.63, 156.17, 152.82, 151.51, 145.88, 141.84, 138.89, 137.99, 134.68, 131.05 (2C), 130.01, 129.33, 128.47, 127.53, 125.51, 125.04, 123.93, 119.97, 118.90, 117.31, 113.58 (2C), 105.83, 72.56, 69.77, 55.21, 49.38, 12.71.

1-(((6-(3-fluorobenzyl)oxy)-4-oxo-4H-chromen-3-yl)methyl)-3-((4-methoxybenzyl)oxy)-2-methylpyridin-4(1H)-one (**24c**)

Yellow solid, yield: 50.6%, m.p. 204.3-206.0 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.61 (d, *J* = 2.9 Hz, 1H), 7.46 (d, *J* = 9.2 Hz, 1H), 7.42 (d, *J* = 3.0 Hz, 1H), 7.41-7.34 (m, 2H), 7.33-7.29 (m, 2H), 7.26-7.15 (m, 3H), 7.08-7.02 (m, 1H), 6.87-6.80 (m, 2H), 6.49 (d, *J* = 7.5 Hz, 1H), 5.22 (s, 2H), 5.16 (s, 2H), 4.87 (s, 2H), 3.79 (s, 3H), 2.09 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 175.96, 173.46, 163.00 (d, <sup>1</sup>*J*<sub>C-F</sub> = 246.7 Hz), 159.60, 156.17, 152.63, 151.48, 145.78, 141.42, 138.77, 138.52 (d, <sup>3</sup>*J*<sub>C-F</sub> = 7.3 Hz), 131.04 (2C), 130.31 (d, <sup>3</sup>*J*<sub>C-F</sub> = 8.3 Hz), 129.42, 125.01, 123.92, 122.88 (d, <sup>4</sup>*J*<sub>C-F</sub> = 3.0 Hz), 119.94, 118.99, 117.50, 115.20 (d, <sup>2</sup>*J*<sub>C-F</sub> = 21.0 Hz), 114.33 (d, <sup>2</sup>*J*<sub>C-F</sub> = 22.1 Hz), 113.55 (2C), 105.87, 72.43, 69.79 (d, <sup>4</sup>*J*<sub>C-F</sub> = 2.0 Hz), 55.20, 49.27, 12.64.

1-(((6-(2-fluorobenzyl)oxy)-4-oxo-4H-chromen-3-yl)methyl)-3-((4-methoxybenzyl)oxy)-2-methylpyridin-4(1H)-one (**24d**)

White solid, yield: 72.6%, m.p. 192.2-193.3 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.64 (d, *J* = 3.0 Hz, 1H), 7.51-7.47 (m, 1H), 7.44-7.23 (m, 7H), 7.19-7.15 (m, 1H), 7.13-7.05 (m, 1H), 6.86-6.74 (m, 2H), 6.43 (d, *J* = 7.5 Hz, 1H), 5.17 (s, 2H), 4.84 (s, 2H), 3.75 (s, 3H), 2.07 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 175.96, 173.51, 160.63 (d, <sup>1</sup>*J*<sub>C-F</sub> = 246.1 Hz), 159.56, 156.24, 152.87, 151.44, 145.78, 141.38, 138.84, 130.96 (2C), 130.23 (d, <sup>3</sup>*J*<sub>C-F</sub> = 8.1 Hz), 129.90 (d, <sup>3</sup>*J*<sub>C-F</sub> = 3.8 Hz), 129.44, 124.83, 124.34 (d, <sup>4</sup>*J*<sub>C-F</sub> = 3.7 Hz), 123.94, 123.16 (d, <sup>2</sup>*J*<sub>C-F</sub> = 14.3 Hz), 119.86, 118.92, 117.42, 115.54 (d, <sup>2</sup>*J*<sub>C-F</sub> = 21.1 Hz), 113.52 (2C), 105.97, 72.39, 64.54 (d, <sup>3</sup>*J*<sub>C-F</sub> = 4.3 Hz), 55.17, 49.15, 12.60.

1-(((6-(4-fluorobenzyl)oxy)-4-oxo-4H-chromen-3-yl)methyl)-3-((4-methoxybenzyl)oxy)-2-methylpyridin-4(1H)-one (**24e**)

White solid, yield: 49.4%, m.p. 145.9-147.5 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.59 (d, *J* = 3.0 Hz, 1H), 7.41

(dd,  $J = 8.9, 5.8$  Hz, 3H), 7.39-7.33 (m, 2H), 7.28 (dd,  $J = 8.7, 3.1$  Hz, 3H), 7.07 (t,  $J = 8.5$  Hz, 2H), 6.80 (d,  $J = 8.3$  Hz, 2H), 6.43 (d,  $J = 7.5$  Hz, 1H), 5.17 (s, 2H), 5.09 (s, 2H), 4.84 (s, 2H), 3.76 (s, 3H), 2.07 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  175.97, 173.48, 162.63 (d,  $^1J_{\text{C-F}} = 246.8$  Hz), 159.56, 156.23, 152.94, 151.39, 145.77, 141.42, 138.85, 131.78 (d,  $^4J_{\text{C-F}} = 3.3$  Hz), 130.95 (2C), 129.54 (d,  $^3J_{\text{C-F}} = 8.3$  Hz, 2C), 129.43, 124.94, 123.92, 119.87, 118.89, 117.38, 115.63 (d,  $^2J_{\text{C-F}} = 21.6$  Hz, 2C), 113.53 (2C), 105.86, 72.39, 69.96, 55.17, 49.14, 12.60.

1-(((6-((4-chlorobenzyl)oxy)-4-oxo-4*H*-chromen-3-yl)methyl)-3-((4-methoxybenzyl)oxy)-2-methylpyridin-4(1*H*)-one (**24f**)

White solid, yield: 48.3%, m.p. 192.9-194.4 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.60 (s, 1H), 7.45 (dd,  $J = 9.2, 2.3$  Hz, 1H), 7.39 (s, 5H), 7.29 (dd,  $J = 7.7, 4.9$  Hz, 3H), 7.24 (s, 1H), 6.82 (dd,  $J = 8.4, 2.6$  Hz, 2H), 6.48 (d,  $J = 6.6$  Hz, 1H), 5.20 (s, 2H), 5.12 (s, 2H), 4.87 (s, 2H), 3.78 (s, 3H), 2.09 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  175.98, 173.43, 159.60, 156.20, 152.73, 151.45, 145.76, 141.58, 138.84, 134.46, 134.17, 131.04 (2C), 129.38, 128.95 (2C), 128.91 (2C), 125.04, 123.90, 119.92, 118.93, 117.43, 113.56 (2C), 105.86, 72.48, 69.86, 55.20, 49.30, 12.66.

2-(((3-(((3-((4-methoxybenzyl)oxy)-2-methyl-4-oxopyridin-1(4*H*)-yl)methyl)-4-oxo-4*H*-chromen-6-yl)oxy)methyl)benzotrile (**24g**)

Red solid, yield: 48.3%, m.p. 160.0-161.5 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.75 (d,  $J = 7.7$  Hz, 1H), 7.70-7.65 (m, 3H), 7.52-7.41 (m, 3H), 7.39 (d,  $J = 7.7$  Hz, 1H), 7.34-7.29 (m, 2H), 7.23 (d,  $J = 3.2$  Hz, 1H), 6.86-6.80 (m, 2H), 6.49 (d,  $J = 7.5$  Hz, 1H), 5.33 (s, 2H), 5.22 (s, 2H), 4.88 (s, 2H), 3.79 (s, 3H), 2.10 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  175.89, 173.48, 159.61, 155.97, 152.69, 151.68, 145.77, 141.54, 139.37, 138.84, 133.23, 133.15, 131.04 (2C), 129.38, 129.00, 128.98, 124.81, 123.94, 120.08, 119.03, 117.46, 117.02, 113.55 (2C), 111.85, 106.30, 72.46, 68.51, 55.21, 49.27, 12.65.

3-(((3-(((3-((4-methoxybenzyl)oxy)-2-methyl-4-oxopyridin-1(4*H*)-yl)methyl)-4-oxo-4*H*-chromen-6-yl)oxy)methyl)benzotrile (**24h**)

Yellow solid, yield: 73.2%, m.p. 189.1-190.2 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.77 (s, 1H), 7.70-7.67 (m, 1H), 7.66-7.63 (m, 1H), 7.59 (d,  $J = 3.0$  Hz, 1H), 7.53 (t,  $J = 7.8$  Hz, 1H), 7.47 (d,  $J = 9.1$  Hz, 1H), 7.41 (dd,  $J = 9.2, 3.0$  Hz, 1H), 7.37 (d,  $J = 7.6$  Hz, 1H), 7.32-7.29 (m, 2H), 7.22 (s, 1H), 6.84-6.80 (m, 2H), 6.45 (d,  $J = 7.5$  Hz, 1H), 5.20 (s, 2H), 5.18 (s, 2H), 4.85 (s, 2H), 3.78 (s, 3H), 2.08 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  175.89, 173.59, 159.58, 155.86, 152.73, 151.61, 145.83, 141.26, 138.75, 137.66, 131.87, 131.57, 131.00 (2C), 130.74, 129.56, 129.45, 124.92, 123.94, 120.12, 119.05, 118.52, 117.52, 113.54 (2C), 112.91, 105.84, 72.39, 69.25, 55.20, 49.17, 12.61.

3-((4-methoxybenzyl)oxy)-2-methyl-1-((4-oxo-6-((3-(trifluoromethyl)benzyl)oxy)-4*H*-chromen-3-yl)methyl)pyridin-4(1*H*)-one (**24i**)

Yellow solid, yield: 53.3%, m.p. 179.1-180.5 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.73 (s, 1H), 7.68-7.58 (m, 3H), 7.54 (t,  $J = 7.7$  Hz, 1H), 7.46 (d,  $J = 9.2$  Hz, 1H), 7.44-7.36 (m, 3H), 7.29 (dd,  $J = 9.9, 7.9$  Hz, 2H), 6.88-6.76 (m, 2H), 6.47 (d,  $J = 7.5$  Hz, 1H), 5.20 (s, 2H), 5.19 (s, 2H), 4.87 (s, 2H), 3.77 (s, 3H), 2.09 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  175.94, 173.44, 159.59, 156.10, 152.81, 151.54, 145.78, 141.44, 138.81, 137.03, 131.27 (q,  $^2J_{\text{C-F}} = 32.1$  Hz), 131.10 (2C), 130.73, 130.72, 129.43, 129.21, 125.11 (q,  $^3J_{\text{C-F}} = 3.8$  Hz), 124.64 (q,  $^1J_{\text{C-F}} = 270.9$  Hz), 124.17 (q,  $^3J_{\text{C-F}} = 3.9$  Hz), 120.01, 119.91, 118.99, 117.44, 113.54 (2C), 105.83, 72.43, 69.79, 55.18, 49.21, 12.63.

3-((4-methoxybenzyl)oxy)-2-methyl-1-((4-oxo-6-((4-(trifluoromethyl)benzyl)oxy)-4*H*-chromen-3-yl)methyl)pyridin-4(1*H*)-one (**24j**)

Yellow solid, yield: 76.2%, m.p. 174.5-176.2 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.67 (d,  $J = 8.1$  Hz, 2H), 7.61 (d,  $J = 3.0$  Hz, 1H), 7.58 (d,  $J = 8.0$  Hz, 2H), 7.46 (d,  $J = 9.2$  Hz, 1H), 7.43-7.36 (m, 2H), 7.33-7.27 (m, 3H), 6.86-6.77 (m, 2H), 6.47 (d,  $J = 7.5$  Hz, 1H), 5.21 (s, 2H), 5.20 (s, 2H), 4.86 (s, 2H), 3.78 (s, 3H), 2.09 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  175.94, 173.45, 159.59, 156.06, 152.80, 151.53, 145.79, 141.41, 140.03, 138.79,

131.00 (2C), 130.27 (q,  $^2J_{C-F} = 32.4$  Hz), 129.43, 127.54 (2C), 125.67 (q,  $^3J_{C-F} = 3.7$  Hz, 2C), 124.93, 124.64 (q,  $^1J_{C-F} = 270.5$  Hz), 123.94, 120.01, 118.99, 117.45, 113.54 (2C), 105.89, 72.43, 69.71, 55.19, 49.21, 12.63.

1-((6-((3,4-difluorobenzyl)oxy)-4-oxo-4H-chromen-3-yl)methyl)-3-((4-methoxybenzyl)oxy)-2-methylpyridin-4(1H)-one (**24k**)

White solid, yield: 44.1%, m.p. 163.9-165.0 °C.  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  8.11 (s, 1H), 7.73 (d,  $J = 7.6$  Hz, 1H), 7.67 (d,  $J = 9.0$  Hz, 1H), 7.62-7.41 (m, 4H), 7.34 (d,  $J = 8.2$  Hz, 1H), 7.29 (d,  $J = 8.1$  Hz, 2H), 6.86 (d,  $J = 8.2$  Hz, 2H), 6.16 (d,  $J = 7.6$  Hz, 1H), 5.22 (s, 2H), 4.96 (s, 2H), 4.91 (s, 2H), 3.71 (s, 3H), 2.19 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$  175.94, 172.53, 159.47, 155.94, 155.76, 151.32, 149.91 (dd,  $^1J_{C-F} = 244.7$ ,  $^2J_{C-F} = 22.1$  Hz), 149.77 (dd,  $^1J_{C-F} = 244.1$ ,  $^2J_{C-F} = 22.1$  Hz), 145.37, 141.89, 140.28, 134.82 (dd,  $^3J_{C-F} = 9.2$ ,  $^4J_{C-F} = 3.9$  Hz), 130.79 (2C), 130.04, 125.07 (dd,  $^3J_{C-F} = 7.8$ ,  $^4J_{C-F} = 4.3$  Hz), 124.81, 124.22, 120.72, 118.96, 118.07 (d,  $^2J_{C-F} = 17.1$  Hz), 117.26 (d,  $^2J_{C-F} = 17.3$  Hz), 116.23, 113.91 (2C), 106.48, 71.84, 68.96, 55.46, 48.77, 12.64.

1-((6-((3,5-difluorobenzyl)oxy)-4-oxo-4H-chromen-3-yl)methyl)-3-((4-methoxybenzyl)oxy)-2-methylpyridin-4(1H)-one (**24l**)

Yellow solid, yield: 42.9%, m.p. 219.3-221.2 °C.  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  8.10 (s, 1H), 7.73 (d,  $J = 7.6$  Hz, 1H), 7.68 (d,  $J = 9.1$  Hz, 1H), 7.60-7.47 (m, 2H), 7.29 (d,  $J = 8.2$  Hz, 2H), 7.21 (t,  $J = 9.2$  Hz, 3H), 6.86 (d,  $J = 8.2$  Hz, 2H), 6.16 (d,  $J = 7.6$  Hz, 1H), 5.27 (s, 2H), 4.96 (s, 2H), 4.91 (s, 2H), 3.71 (s, 3H), 2.19 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$  175.93, 172.49, 162.97 (d,  $^1J_{C-F} = 245.6$  Hz), 162.84 (d,  $^1J_{C-F} = 245.0$  Hz), 159.47, 155.79, 155.76, 151.38, 145.36, 141.91, 141.75, 140.29, 140.21 (t,  $^3J_{C-F} = 7.9$  Hz), 130.79 (2C), 130.04, 124.81, 124.22, 120.78, 118.97, 113.91 (2C), 110.85 (d,  $^2J_{C-F} = 25.5$  Hz), 110.84 (d,  $^2J_{C-F} = 11.5$  Hz), 106.51, 103.63 (t,  $^2J_{C-F} = 25.5$  Hz), 71.84, 68.84, 55.46, 48.78, 12.64.

1-((6-((3,4-dichlorobenzyl)oxy)-4-oxo-4H-chromen-3-yl)methyl)-3-((4-methoxybenzyl)oxy)-2-methylpyridin-4(1H)-one (**24m**)

Yellow solid, yield: 73.3%, m.p. 177.1-178.9 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.58 (d,  $J = 3.0$  Hz, 1H), 7.56 (d,  $J = 2.0$  Hz, 1H), 7.47 (dd,  $J = 8.7$ , 6.5 Hz, 2H), 7.40 (d,  $J = 3.0$  Hz, 1H), 7.39-7.34 (m, 1H), 7.32-7.27 (m, 4H), 6.87-6.76 (m, 2H), 6.46 (d,  $J = 7.5$  Hz, 1H), 5.20 (s, 2H), 5.10 (s, 2H), 4.85 (s, 2H), 3.78 (s, 3H), 2.08 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  175.91, 173.53, 159.59, 155.93, 152.73, 151.43, 145.82, 141.34, 138.77, 136.24, 132.89, 132.32, 131.00 (2C), 130.69, 129.43, 129.31, 126.65, 124.92, 123.92, 120.03, 119.01, 117.49, 113.54 (2C), 105.88, 72.41, 69.11, 55.20, 49.19, 12.62.

## 7. General procedure for the preparation of compounds **11a-e**, **18a-g**, and **25a-m**

The key intermediate **10a-e** (0.5 mmol) was dissolved in anhydrous DCM (15 ml) and cooled to -30 °C. Subsequently,  $\text{BCl}_3$  (1.0 mol/L in DCM, 1.5 mmol) was slowly added dropwise to the reaction flask under nitrogen protection. Once the dropwise addition was complete, the mixture was stirred overnight at room temperature. The reaction was then quenched with methanol (15 mL), and the solvent was evaporated under reduced pressure. The residue was purified through methanol/ether recrystallization to yield the final compounds **11a-e** as white solids.

The intermediate **17a-g** or **24a-m** (0.5 mmol), 6M HCl (1 mL) and methanol (10 mL) were added to the flask. Subsequently, the solution was stirred for 2-3h at 60°C, and the solvent was removed under reduced pressure. The residue was purified through methanol/ether recrystallization to obtain the final compounds **18a-g** and **25a-m** as white solids.

3-hydroxy-2-methyl-1-((4-oxo-4H-chromen-3-yl)methyl)pyridin-4(1H)-one (**11a**)

White solid, yield: 75.6%, m.p. 245.6-247.5 °C.  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  8.65 (s, 1H), 8.37 (d,  $J = 7.1$  Hz, 1H), 8.04 (dd,  $J = 8.0$ , 1.7 Hz, 1H), 7.88-7.84 (m, 1H), 7.72 (dd,  $J = 8.5$ , 1.0 Hz, 1H), 7.55-7.51 (m, 1H),

7.34 (d,  $J = 7.1$  Hz, 1H), 5.39 (s, 2H), 2.67 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$  176.36, 159.57, 157.99, 156.43, 143.23, 142.61, 139.14, 135.25, 126.42, 125.42, 123.68, 119.06, 117.90, 110.87, 51.86, 13.34; HRMS  $m/z$ : calc. for  $\text{C}_{16}\text{H}_{14}\text{NO}_4$   $[\text{M}+\text{H}]^+$ , 284.0917, found, 284.0922; HPLC purity: 100%.

3-hydroxy-2-methyl-1-((6-methyl-4-oxo-4*H*-chromen-3-yl)methyl)pyridin-4(*1H*)-one (**11b**)

White solid, yield: 91.6%, m.p. 254.9-256.1 °C.  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  8.61 (s, 1H), 8.36 (d,  $J = 7.1$  Hz, 1H), 7.82 (d,  $J = 2.1$  Hz, 1H), 7.67 (dd,  $J = 8.7, 2.2$  Hz, 1H), 7.61 (d,  $J = 8.6$  Hz, 1H), 7.33 (d,  $J = 7.1$  Hz, 1H), 5.38 (s, 2H), 2.66 (s, 3H), 2.42 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$  176.26, 159.55, 157.82, 154.73, 143.23, 142.58, 139.08, 136.28, 136.07, 124.62, 123.37, 118.85, 117.72, 110.86, 51.85, 20.91, 13.33; HRMS  $m/z$ : calc. for  $\text{C}_{17}\text{H}_{16}\text{NO}_4$   $[\text{M}+\text{H}]^+$ , 298.1074, found, 298.1083; HPLC purity: 100%.

3-hydroxy-1-((6-methoxy-4-oxo-4*H*-chromen-3-yl)methyl)-2-methylpyridin-4(*1H*)-one (**11c**)

White solid, yield: 81.9%, m.p. 255.3-257.2 °C.  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  8.65 (s, 1H), 8.36 (d,  $J = 7.1$  Hz, 1H), 7.68 (d,  $J = 9.1$  Hz, 1H), 7.44 (dd,  $J = 9.2, 3.2$  Hz, 1H), 7.39 (d,  $J = 3.1$  Hz, 1H), 7.34 (d,  $J = 7.1$  Hz, 1H), 5.39 (s, 2H), 3.84 (s, 3H), 2.67 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$  176.05, 159.65, 157.71, 157.32, 151.20, 143.23, 142.50, 139.12, 124.38, 124.32, 120.68, 117.14, 110.86, 105.20, 56.28, 51.85, 13.34; HRMS  $m/z$ : calc. for  $\text{C}_{17}\text{H}_{16}\text{NO}_5$   $[\text{M}+\text{H}]^+$ , 314.1023, found, 314.1027; HPLC purity: 100%.

1-((6-fluoro-4-oxo-4*H*-chromen-3-yl)methyl)-3-hydroxy-2-methylpyridin-4(*1H*)-one (**11d**)

White solid, yield: 43.9%, m.p. 255.4-256.2 °C.  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  8.69 (s, 1H), 8.37 (d,  $J = 7.1$  Hz, 1H), 7.84 (dd,  $J = 9.2, 4.3$  Hz, 1H), 7.80-7.76 (m, 1H), 7.75-7.69 (m, 1H), 7.35 (d,  $J = 7.0$  Hz, 1H), 5.40 (s, 2H), 2.66 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$  175.80 (d,  $^4J_{\text{C-F}} = 2.2$  Hz), 159.60 (d,  $^1J_{\text{C-F}} = 243.9$  Hz), 159.59, 158.22, 152.92 (d,  $^4J_{\text{C-F}} = 1.5$  Hz), 143.23, 142.65, 139.22, 124.87 (d,  $^3J_{\text{C-F}} = 7.4$  Hz), 123.37 (d,  $^2J_{\text{C-F}} = 25.3$  Hz), 121.96 (d,  $^3J_{\text{C-F}} = 8.4$  Hz), 117.30, 110.84, 110.04 (d,  $^2J_{\text{C-F}} = 23.8$  Hz), 51.78, 13.34; HRMS  $m/z$ : calc. for  $\text{C}_{16}\text{H}_{13}\text{FNO}_4$   $[\text{M}+\text{H}]^+$ , 302.0823, found, 302.0829; HPLC purity: 100%.

3-hydroxy-2-methyl-1-((7-methyl-4-oxo-4*H*-chromen-3-yl)methyl)pyridin-4(*1H*)-one (**11e**)

White solid, yield: 87.5%, m.p. 278.2-279.5 °C.  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  8.59 (s, 1H), 8.35 (d,  $J = 7.1$  Hz, 1H), 7.92 (d,  $J = 8.1$  Hz, 1H), 7.53 (s, 1H), 7.38-7.31 (m, 2H), 5.37 (s, 2H), 2.67 (s, 3H), 2.47 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$  176.11, 159.60, 157.69, 156.55, 146.37, 143.24, 142.57, 139.11, 127.78, 125.20, 121.46, 118.53, 117.81, 110.90, 51.84, 21.71, 13.33; HRMS  $m/z$ : calc. for  $\text{C}_{17}\text{H}_{16}\text{NO}_4$   $[\text{M}+\text{H}]^+$ , 298.1074, found, 298.1084; HPLC purity: 100%.

1-((7-((3-fluorobenzyl)oxy)-4-oxo-4*H*-chromen-3-yl)methyl)-3-hydroxy-2-methylpyridin-4(*1H*)-one (**18a**)

White solid, yield: 47.5%, m.p. 253.8-255.5 °C.  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  8.58 (s, 1H), 8.36 (d,  $J = 7.0$  Hz, 1H), 7.95 (dd,  $J = 8.8, 2.1$  Hz, 1H), 7.46 (q,  $J = 7.4$  Hz, 1H), 7.39-7.27 (m, 4H), 7.24-7.13 (m, 2H), 5.36 (s, 2H), 5.31 (s, 2H), 2.66 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$  175.51, 163.36, 162.65 (d,  $^1J_{\text{C-F}} = 242.4$  Hz), 159.42, 158.18, 157.55, 143.18, 142.65, 139.36 (d,  $^3J_{\text{C-F}} = 7.3$  Hz), 139.10, 131.11 (d,  $^3J_{\text{C-F}} = 8.4$  Hz), 126.98, 124.24 (d,  $^4J_{\text{C-F}} = 2.7$  Hz), 117.75, 117.68, 116.16, 115.42 (d,  $^2J_{\text{C-F}} = 20.9$  Hz), 114.95 (d,  $^2J_{\text{C-F}} = 22.0$  Hz), 110.81, 102.41, 69.87, 51.81, 13.33; HRMS  $m/z$ : calc. for  $\text{C}_{23}\text{H}_{19}\text{FNO}_5$   $[\text{M}+\text{H}]^+$ , 408.1242, found, 408.1254; HPLC purity: 100%.

1-((7-((4-fluorobenzyl)oxy)-4-oxo-4*H*-chromen-3-yl)methyl)-3-hydroxy-2-methylpyridin-4(*1H*)-one (**18b**)

White solid, yield: 57.4%, m.p. 256.8-258.0 °C.  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  8.57 (s, 1H), 8.35 (d,  $J = 7.2$  Hz, 1H), 7.94 (d,  $J = 8.9$  Hz, 1H), 7.57-7.53 (m, 2H), 7.34-7.30 (m, 2H), 7.27-7.22 (m, 2H), 7.17 (d,  $J = 8.9$  Hz, 1H), 5.36 (s, 2H), 5.26 (s, 2H), 2.66 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$  175.50, 163.51, 162.42 (d,  $^1J_{\text{C-F}} = 242.4$  Hz), 159.47, 158.20, 157.51, 143.19, 142.58, 139.11, 132.70 (d,  $^4J_{\text{C-F}} = 3.0$  Hz), 130.79 (d,  $^3J_{\text{C-F}} = 8.4$  Hz, 2C), 126.94, 117.76, 117.59, 116.18, 115.88 (d,  $^2J_{\text{C-F}} = 21.5$  Hz, 2C), 110.82, 102.35, 69.88, 51.80, 13.32; HRMS  $m/z$ : calc. for  $\text{C}_{23}\text{H}_{19}\text{FNO}_5$   $[\text{M}+\text{H}]^+$ , 408.1242, found, 408.1254; HPLC purity: 100%.

1-((7-((3-chlorobenzyl)oxy)-4-oxo-4*H*-chromen-3-yl)methyl)-3-hydroxy-2-methylpyridin-4(1*H*)-one (**18c**)

White solid, yield: 69.8%, m.p. 262.0-263.1 °C. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 8.55 (s, 1H), 8.34 (d, *J* = 7.1 Hz, 1H), 7.96 (d, *J* = 8.9 Hz, 1H), 7.56 (t, *J* = 1.6 Hz, 1H), 7.49-7.38 (m, 3H), 7.34-7.26 (m, 2H), 7.19 (dd, *J* = 8.9, 2.4 Hz, 1H), 5.35 (s, 2H), 5.31 (s, 2H), 2.66 (s, 3H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ 175.48, 163.38, 159.64, 158.19, 157.50, 143.26, 142.53, 139.10, 139.07, 133.69, 130.96, 128.56, 127.98, 127.03, 126.84, 117.80, 117.74, 116.12, 110.91, 102.49, 69.64, 51.77, 13.32; HRMS *m/z*: calc. for C<sub>23</sub>H<sub>19</sub>ClNO<sub>5</sub> [M+H]<sup>+</sup>, 424.0946, found, 424.0957; HPLC purity: 100%.

3-(((3-((3-hydroxy-2-methyl-4-oxopyridin-1(4*H*)-yl)methyl)-4-oxo-4*H*-chromen-7-yl)oxy)methyl)benzotrile (**18d**)

White solid, yield: 68.4%, m.p. 254.8-255.9 °C. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 8.57 (s, 1H), 8.35 (d, *J* = 7.0 Hz, 1H), 8.02-7.92 (m, 2H), 7.84 (d, *J* = 7.6 Hz, 2H), 7.64 (t, *J* = 7.7 Hz, 1H), 7.33 (t, *J* = 3.5 Hz, 2H), 7.20 (dd, *J* = 8.8, 2.7 Hz, 1H), 5.35 (s, 4H), 2.66 (s, 3H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ 175.51, 163.25, 159.49, 158.17, 157.54, 143.20, 142.57, 139.12, 138.22, 133.12, 132.46, 131.75, 130.75, 130.35, 127.03, 119.07, 117.78, 116.12, 112.01, 110.82, 102.47, 69.34, 51.80, 13.32; HRMS *m/z*: calc. for C<sub>24</sub>H<sub>19</sub>N<sub>2</sub>O<sub>5</sub> [M+H]<sup>+</sup>, 415.1288, found, 415.1300; HPLC purity: 98.9%.

3-hydroxy-2-methyl-1-((4-oxo-7-((3-(trifluoromethyl)benzyl)oxy)-4*H*-chromen-3-yl)methyl)pyridin-4(1*H*)-one (**18e**)

White solid, yield: 30.9%, m.p. 237.9-239.2 °C. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 8.55 (s, 1H), 8.34 (d, *J* = 7.1 Hz, 1H), 7.97 (d, *J* = 8.9 Hz, 1H), 7.86 (d, *J* = 1.9 Hz, 1H), 7.81 (d, *J* = 7.6 Hz, 1H), 7.74 (d, *J* = 7.8 Hz, 1H), 7.67 (t, *J* = 7.7 Hz, 1H), 7.33 (d, *J* = 2.4 Hz, 1H), 7.29 (d, *J* = 7.0 Hz, 1H), 7.21 (dd, *J* = 8.9, 2.4 Hz, 1H), 5.40 (s, 2H), 5.35 (s, 2H), 2.66 (s, 3H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ 175.49, 163.38, 159.69, 158.20, 157.49, 143.28, 142.48, 139.11, 138.04, 132.34, 130.19, 129.78 (q, <sup>2</sup>*J*<sub>C-F</sub> = 31.9 Hz), 127.05, 125.36 (q, <sup>3</sup>*J*<sub>C-F</sub> = 7.9 Hz), 124.75 (q, <sup>3</sup>*J*<sub>C-F</sub> = 7.7 Hz), 124.61 (q, <sup>1</sup>*J*<sub>C-F</sub> = 270.9 Hz), 117.83, 117.79, 116.10, 110.92, 102.49, 69.69, 51.76, 13.31; HRMS *m/z*: calc. for C<sub>24</sub>H<sub>19</sub>F<sub>3</sub>NO<sub>5</sub> [M+H]<sup>+</sup>, 458.1210, found, 458.1217; HPLC purity: 100%.

1-((7-((3,4-difluorobenzyl)oxy)-4-oxo-4*H*-chromen-3-yl)methyl)-3-hydroxy-2-methylpyridin-4(1*H*)-one (**18f**)

White solid, yield: 69.3%, m.p. 260.7-262.5 °C. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 8.58 (s, 1H), 8.36 (d, *J* = 7.2 Hz, 1H), 7.94 (d, *J* = 8.9 Hz, 1H), 7.59 (t, *J* = 9.8 Hz, 1H), 7.48 (q, *J* = 9.4 Hz, 1H), 7.40-7.33 (m, 2H), 7.31 (s, 1H), 7.18 (d, *J* = 8.9 Hz, 1H), 5.36 (s, 2H), 5.26 (s, 2H), 2.66 (s, 3H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ 175.51, 163.28, 159.42, 158.17, 157.56, 151.03 (dd, <sup>1</sup>*J*<sub>C-F</sub> = 243.9, <sup>2</sup>*J*<sub>C-F</sub> = 12.4 Hz), 148.59 (dd, <sup>1</sup>*J*<sub>C-F</sub> = 243.9, <sup>2</sup>*J*<sub>C-F</sub> = 12.4 Hz), 143.18, 142.66, 139.11, 134.26 (dd, <sup>3</sup>*J*<sub>C-F</sub> = 5.8, <sup>4</sup>*J*<sub>C-F</sub> = 3.9 Hz), 126.98, 125.43 (dd, <sup>3</sup>*J*<sub>C-F</sub> = 6.8, <sup>4</sup>*J*<sub>C-F</sub> = 3.4 Hz), 118.16 (d, <sup>2</sup>*J*<sub>C-F</sub> = 17.2 Hz), 117.77, 117.71, 117.60 (d, <sup>2</sup>*J*<sub>C-F</sub> = 17.1 Hz), 116.13, 110.82, 102.41, 69.24, 51.81, 13.33; HRMS *m/z*: calc. for C<sub>23</sub>H<sub>18</sub>F<sub>2</sub>NO<sub>5</sub> [M+H]<sup>+</sup>, 426.1148, found, 426.1159; HPLC purity: 100%.

1-((7-((3,4-dichlorobenzyl)oxy)-4-oxo-4*H*-chromen-3-yl)methyl)-3-hydroxy-2-methylpyridin-4(1*H*)-one (**18g**)

White solid, yield: 32.9%, m.p. 256.2-257.9 °C. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 8.56 (s, 1H), 8.35 (d, *J* = 7.0 Hz, 1H), 7.95 (d, *J* = 9.0 Hz, 1H), 7.78 (s, 1H), 7.69 (d, *J* = 8.3 Hz, 1H), 7.49 (d, *J* = 8.2 Hz, 1H), 7.31 (d, *J* = 6.9 Hz, 2H), 7.19 (d, *J* = 8.9 Hz, 1H), 5.35 (s, 2H), 5.30 (s, 2H), 2.66 (s, 3H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ 175.50, 166.28, 163.20, 159.46, 158.16, 157.54, 143.20, 142.60, 139.12, 137.71, 131.67, 131.29, 131.22, 130.21, 128.55, 127.03, 117.77, 116.12, 110.81, 102.46, 68.94, 51.81, 13.32; HRMS *m/z*: calc. for C<sub>23</sub>H<sub>18</sub>Cl<sub>2</sub>NO<sub>5</sub> [M+H]<sup>+</sup>, 458.0557, found, 458.0563; HPLC purity: 100%.

1-((6-(benzyloxy)-4-oxo-4*H*-chromen-3-yl)methyl)-3-hydroxy-2-methylpyridin-4(1*H*)-one (**25a**)

White solid, yield: 74.1%, m.p. 269.4-270.6 °C. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 8.64 (s, 1H), 8.37 (d, *J* = 7.0 Hz, 1H), 7.69 (d, *J* = 8.9 Hz, 1H), 7.54-7.34 (m, 8H), 5.39 (s, 2H), 5.22 (s, 2H), 2.67 (s, 3H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ 176.03, 159.43, 157.74, 156.31, 151.27, 143.17, 142.76, 139.15, 136.95, 128.96 (2C), 128.44, 128.10 (2C), 124.90, 124.36, 120.74, 117.09, 110.84, 106.55, 70.32, 51.94, 13.36; HRMS *m/z*: calc. for



C<sub>23</sub>H<sub>20</sub>NO<sub>5</sub> [M+H]<sup>+</sup>, 390.1336, found, 390.1346; HPLC purity: 100%.

1-((6-((3-chlorobenzyl)oxy)-4-oxo-4*H*-chromen-3-yl)methyl)-3-hydroxy-2-methylpyridin-4(1*H*)-one (**25b**)

White solid, yield: 89.5%, m.p. 248.6-250.5 °C. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 8.63 (s, 1H), 8.35 (d, *J* = 7.1 Hz, 1H), 7.70 (d, *J* = 9.1 Hz, 1H), 7.57-7.52 (m, 2H), 7.48 (d, *J* = 3.0 Hz, 1H), 7.43 (d, *J* = 5.1 Hz, 2H), 7.42-7.37 (m, 1H), 7.32 (d, *J* = 7.0 Hz, 1H), 5.38 (s, 2H), 5.24 (s, 2H), 2.66 (s, 3H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ 176.02, 159.59, 157.72, 156.08, 151.37, 143.23, 142.55, 139.57, 139.15, 133.64, 130.91, 128.35, 127.70, 126.59, 124.89, 124.36, 120.81, 117.15, 110.84, 106.60, 69.37, 51.89, 13.33; HRMS *m/z*: calc. for C<sub>23</sub>H<sub>19</sub>ClNO<sub>5</sub> [M+H]<sup>+</sup>, 424.0946, found, 424.0957; HPLC purity: 100%.

1-((6-((3-fluorobenzyl)oxy)-4-oxo-4*H*-chromen-3-yl)methyl)-3-hydroxy-2-methylpyridin-4(1*H*)-one (**25c**)

White solid, yield: 68.9%, m.p. 256.1-257.9 °C. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 8.63 (s, 1H), 8.35 (d, *J* = 7.1 Hz, 1H), 7.71 (d, *J* = 9.2 Hz, 1H), 7.55 (dd, *J* = 9.2, 3.1 Hz, 1H), 7.48 (d, *J* = 3.1 Hz, 1H), 7.46-7.40 (m, 1H), 7.35-7.27 (m, 3H), 7.20-7.12 (m, 1H), 5.38 (s, 2H), 5.25 (s, 2H), 2.66 (s, 3H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ 176.02, 162.68 (d, <sup>1</sup>*J*<sub>C-F</sub> = 243.7 Hz), 159.56, 157.72, 156.09, 151.36, 143.22, 142.59, 139.93 (d, <sup>3</sup>*J*<sub>C-F</sub> = 7.6 Hz), 139.16, 131.03 (d, <sup>3</sup>*J*<sub>C-F</sub> = 8.1 Hz), 124.89, 124.36, 123.91 (d, <sup>4</sup>*J*<sub>C-F</sub> = 2.9 Hz), 120.80, 117.14, 115.18 (d, <sup>2</sup>*J*<sub>C-F</sub> = 20.9 Hz), 114.62 (d, <sup>2</sup>*J*<sub>C-F</sub> = 22.0 Hz), 110.84, 106.62, 69.44, 51.90, 13.33; HRMS *m/z*: calc. for C<sub>23</sub>H<sub>19</sub>FNO<sub>5</sub> [M+H]<sup>+</sup>, 408.1242, found, 408.1253; HPLC purity: 100%.

1-((6-((2-fluorobenzyl)oxy)-4-oxo-4*H*-chromen-3-yl)methyl)-3-hydroxy-2-methylpyridin-4(1*H*)-one (**25d**)

White solid, yield: 26.7%, m.p. 267.3-268.8 °C. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 8.63 (s, 1H), 8.35 (d, *J* = 7.1 Hz, 1H), 7.73-7.67 (m, 1H), 7.57 (dd, *J* = 7.5, 1.8 Hz, 1H), 7.55-7.51 (m, 2H), 7.46-7.41 (m, 1H), 7.32-7.20 (m, 3H), 5.39 (s, 2H), 5.25 (s, 2H), 2.67 (s, 3H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ 176.02, 160.90 (d, <sup>1</sup>*J*<sub>C-F</sub> = 246.3 Hz), 159.58, 157.74, 156.17, 151.41, 143.23, 142.59, 139.16, 131.16 (d, <sup>3</sup>*J*<sub>C-F</sub> = 4.1 Hz), 131.07 (d, <sup>3</sup>*J*<sub>C-F</sub> = 8.3 Hz), 125.05 (d, <sup>4</sup>*J*<sub>C-F</sub> = 3.4 Hz), 124.84, 124.38, 123.75 (d, <sup>2</sup>*J*<sub>C-F</sub> = 14.4 Hz), 120.82, 117.15, 115.93 (d, <sup>3</sup>*J*<sub>C-F</sub> = 21.0 Hz), 110.86, 106.55, 64.77 (d, <sup>3</sup>*J*<sub>C-F</sub> = 3.2 Hz), 51.90, 13.34; HRMS *m/z*: calc. for C<sub>23</sub>H<sub>19</sub>FNO<sub>5</sub> [M+H]<sup>+</sup>, 408.1242, found, 408.1253; HPLC purity: 100%.

1-((6-((4-fluorobenzyl)oxy)-4-oxo-4*H*-chromen-3-yl)methyl)-3-hydroxy-2-methylpyridin-4(1*H*)-one (**25e**)

White solid, yield: 36.9%, m.p. 265.8-267.6 °C. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 8.62 (s, 1H), 8.35 (d, *J* = 7.1 Hz, 1H), 7.70 (d, *J* = 9.0 Hz, 1H), 7.54-7.49 (m, 4H), 7.31 (d, *J* = 7.1 Hz, 1H), 7.26-7.19 (m, 2H), 5.38 (s, 2H), 5.20 (s, 2H), 2.67 (s, 3H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ 176.02, 162.30 (d, <sup>1</sup>*J*<sub>C-F</sub> = 243.9 Hz), 159.67, 157.70, 156.24, 151.32, 143.26, 142.53, 139.15, 133.20 (d, <sup>4</sup>*J*<sub>C-F</sub> = 3.1 Hz), 130.38 (d, <sup>3</sup>*J*<sub>C-F</sub> = 8.3 Hz, 2C), 124.89, 124.37, 120.74, 117.15, 115.78 (d, <sup>2</sup>*J*<sub>C-F</sub> = 21.5 Hz, 2C), 110.88, 106.66, 69.66, 51.88, 13.34; HRMS *m/z*: calc. for C<sub>23</sub>H<sub>19</sub>FNO<sub>5</sub> [M+H]<sup>+</sup>, 408.1242, found, 408.1254; HPLC purity: 100%.

1-((6-((4-chlorobenzyl)oxy)-4-oxo-4*H*-chromen-3-yl)methyl)-3-hydroxy-2-methylpyridin-4(1*H*)-one (**25f**)

White solid, yield: 66.7%, m.p. 266.8-268.3 °C. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 8.63 (s, 1H), 8.36 (d, *J* = 7.1 Hz, 1H), 7.70 (d, *J* = 9.2 Hz, 1H), 7.54 (d, *J* = 3.1 Hz, 1H), 7.52-7.50 (m, 1H), 7.49-7.43 (m, 4H), 7.33 (d, *J* = 7.1 Hz, 1H), 5.38 (s, 2H), 5.22 (s, 2H), 2.67 (s, 3H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ 176.01, 159.54, 157.72, 156.14, 151.33, 143.21, 142.65, 139.16, 136.04, 133.01, 129.90 (2C), 128.97 (2C), 124.88, 124.37, 120.77, 117.14, 110.87, 106.68, 69.50, 51.90, 13.35; HRMS *m/z*: calc. for C<sub>23</sub>H<sub>19</sub>ClNO<sub>5</sub> [M+H]<sup>+</sup>, 424.0946, found, 424.0959; HPLC purity: 99.7%.

2-(((3-((3-hydroxy-2-methyl-4-oxopyridin-1(4*H*)-yl)methyl)-4-oxo-4*H*-chromen-6-yl)oxy)methyl)benzotrile (**25g**)

White solid, yield: 73.7%, m.p. 269.7-270.6 °C. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 8.64 (s, 1H), 8.36 (d, *J* = 7.1 Hz, 1H), 7.93-7.91 (m, 1H), 7.78-7.70 (m, 3H), 7.61-7.54 (m, 3H), 7.32 (d, *J* = 7.1 Hz, 1H), 5.40 (s, 2H), 5.37 (s, 2H), 2.68 (s, 3H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ 176.01, 159.61, 157.78, 156.07, 151.57, 143.25, 142.62, 139.95, 139.14, 133.94, 133.86, 130.15, 129.74, 124.80, 124.41, 120.91, 117.60, 117.18, 111.86, 110.89, 106.83,

68.82, 51.88, 13.35; HRMS  $m/z$ : calc. for  $C_{24}H_{19}N_2O_5$   $[M+H]^+$ , 415.1288, found, 415.1301; HPLC purity: 99.3%.

3-(((3-((3-hydroxy-2-methyl-4-oxopyridin-1(4*H*)-yl)methyl)-4-oxo-4*H*-chromen-6-yl)oxy)methyl)benzotrile (**25h**)

White solid, yield: 67.5%, m.p. 204.4-206.3 °C.  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  8.66 (s, 1H), 8.38 (d,  $J$  = 7.2 Hz, 1H), 7.94 (s, 1H), 7.82 (d,  $J$  = 7.8 Hz, 2H), 7.71 (d,  $J$  = 9.2 Hz, 1H), 7.63 (t,  $J$  = 7.8 Hz, 1H), 7.56 (d,  $J$  = 9.2 Hz, 1H), 7.49 (s, 1H), 7.36 (d,  $J$  = 7.1 Hz, 1H), 5.40 (s, 2H), 5.28 (s, 2H), 2.67 (s, 3H);  $^{13}C$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$  176.03, 159.34, 157.79, 155.96, 151.40, 143.16, 142.80, 139.17, 138.73, 132.83, 132.25, 131.43, 130.28, 124.91, 124.34, 120.86, 119.12, 117.11, 111.94, 110.79, 106.55, 69.07, 51.95, 13.36; HRMS  $m/z$ : calc. for  $C_{24}H_{19}N_2O_5$   $[M+H]^+$ , 415.1288, found, 415.1298; HPLC purity: 99.4%.

3-hydroxy-2-methyl-1-((4-oxo-6-((3-(trifluoromethyl)benzyl)oxy)-4*H*-chromen-3-yl)methyl)pyridin-4(1*H*)-one (**25i**)

White solid, yield: 63.6%, m.p. 220.1-221.2 °C.  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  8.66 (s, 1H), 8.39 (d,  $J$  = 6.9 Hz, 1H), 7.84 (s, 1H), 7.79 (d,  $J$  = 7.6 Hz, 1H), 7.71 (d,  $J$  = 9.3 Hz, 2H), 7.66 (d,  $J$  = 7.7 Hz, 1H), 7.57 (dd,  $J$  = 9.3, 3.0 Hz, 1H), 7.51 (d,  $J$  = 3.0 Hz, 1H), 7.38 (d,  $J$  = 6.7 Hz, 1H), 5.40 (s, 2H), 5.33 (s, 2H), 2.68 (s, 3H);  $^{13}C$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$  176.03, 159.24, 157.79, 156.07, 151.38, 143.13, 142.93, 139.17, 138.51, 132.13, 130.12, 129.67 (q,  $^2J_{C-F}$  = 31.6 Hz), 125.18 (q,  $^3J_{C-F}$  = 6.2 Hz), 124.90, 124.62 (q,  $^1J_{C-F}$  = 270.9 Hz), 124.52 (q,  $^3J_{C-F}$  = 7.6 Hz), 124.35, 120.84, 117.10, 110.79, 106.51, 69.39, 51.98, 13.36; HRMS  $m/z$ : calc. for  $C_{24}H_{19}F_3NO_5$   $[M+H]^+$ , 458.1210, found, 458.1224; HPLC purity: 99.3%.

3-hydroxy-2-methyl-1-((4-oxo-6-((4-(trifluoromethyl)benzyl)oxy)-4*H*-chromen-3-yl)methyl)pyridin-4(1*H*)-one (**25j**)

White solid, yield: 81.7%, m.p. 246.4-248.3 °C.  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  8.64 (s, 1H), 8.36 (d,  $J$  = 7.1 Hz, 1H), 7.77 (d,  $J$  = 8.1 Hz, 2H), 7.71 (t,  $J$  = 9.2 Hz, 3H), 7.56 (dd,  $J$  = 9.2, 3.1 Hz, 1H), 7.50 (d,  $J$  = 3.1 Hz, 1H), 7.34 (d,  $J$  = 7.1 Hz, 1H), 5.39 (s, 2H), 5.35 (s, 2H), 2.67 (s, 3H);  $^{13}C$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$  176.00, 159.45, 157.76, 156.05, 151.40, 143.19, 142.79, 141.89, 139.16, 128.91 (q,  $^2J_{C-F}$  = 32.0 Hz), 128.43 (2C), 125.85 (q,  $^3J_{C-F}$  = 3.8 Hz, 2C), 125.21 (q,  $^1J_{C-F}$  = 270.2 Hz), 124.84, 124.39, 120.84, 117.14, 110.87, 106.73, 69.44, 51.94, 13.35; HRMS  $m/z$ : calc. for  $C_{24}H_{19}F_3NO_5$   $[M+H]^+$ , 458.1210, found, 458.1221; HPLC purity: 100%.

1-((6-((3,4-difluorobenzyl)oxy)-4-oxo-4*H*-chromen-3-yl)methyl)-3-hydroxy-2-methylpyridin-4(1*H*)-one (**25k**)

White solid, yield: 24.7%, m.p. 247.5-248.7 °C.  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  8.64 (s, 1H), 8.36 (d,  $J$  = 7.0 Hz, 1H), 7.71 (d,  $J$  = 9.1 Hz, 1H), 7.61-7.51 (m, 2H), 7.50-7.41 (m, 2H), 7.32 (d,  $J$  = 7.1 Hz, 2H), 5.39 (s, 2H), 5.21 (s, 2H), 2.66 (s, 3H);  $^{13}C$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$  176.02, 159.53, 157.74, 156.00, 151.37, 150.95 (dd,  $^1J_{C-F}$  = 244.3,  $^2J_{C-F}$  = 19.5 Hz), 148.51 (dd,  $^1J_{C-F}$  = 244.1,  $^2J_{C-F}$  = 19.8 Hz), 143.21, 142.55, 139.16, 134.80 (dd,  $^3J_{C-F}$  = 9.1,  $^4J_{C-F}$  = 3.7 Hz), 125.05 (dd,  $^3J_{C-F}$  = 9.9,  $^4J_{C-F}$  = 3.1 Hz), 124.90, 124.34, 120.82, 118.09 (d,  $^2J_{C-F}$  = 17.0 Hz), 117.24 (d,  $^2J_{C-F}$  = 17.6 Hz), 117.15, 110.79, 106.53, 68.95, 51.89, 13.33; HRMS  $m/z$ : calc. for  $C_{23}H_{18}F_2NO_5$   $[M+H]^+$ , 426.1148, found, 426.1161; HPLC purity: 100%.

1-((6-((3,5-difluorobenzyl)oxy)-4-oxo-4*H*-chromen-3-yl)methyl)-3-hydroxy-2-methylpyridin-4(1*H*)-one (**25l**)

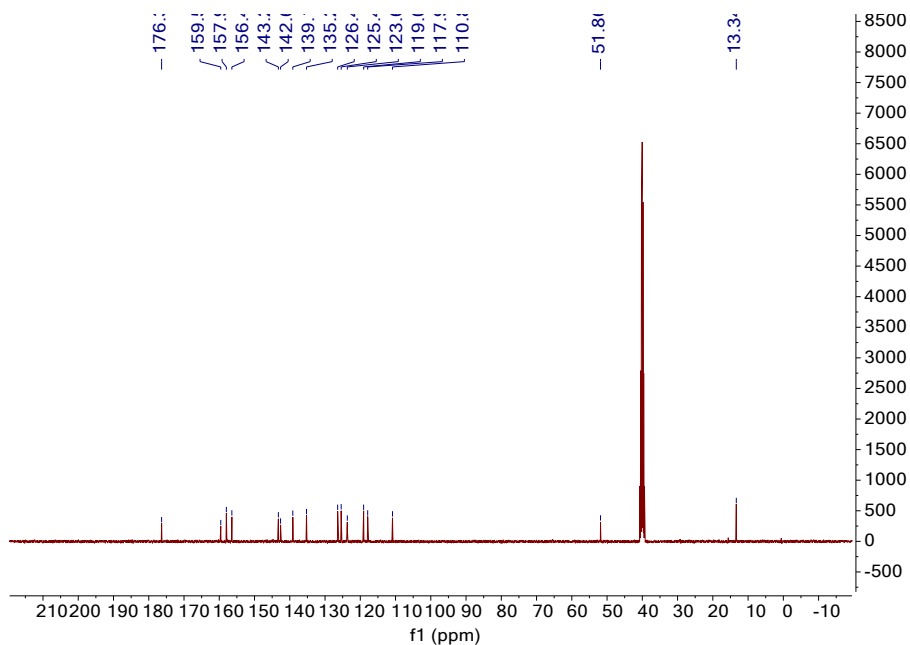
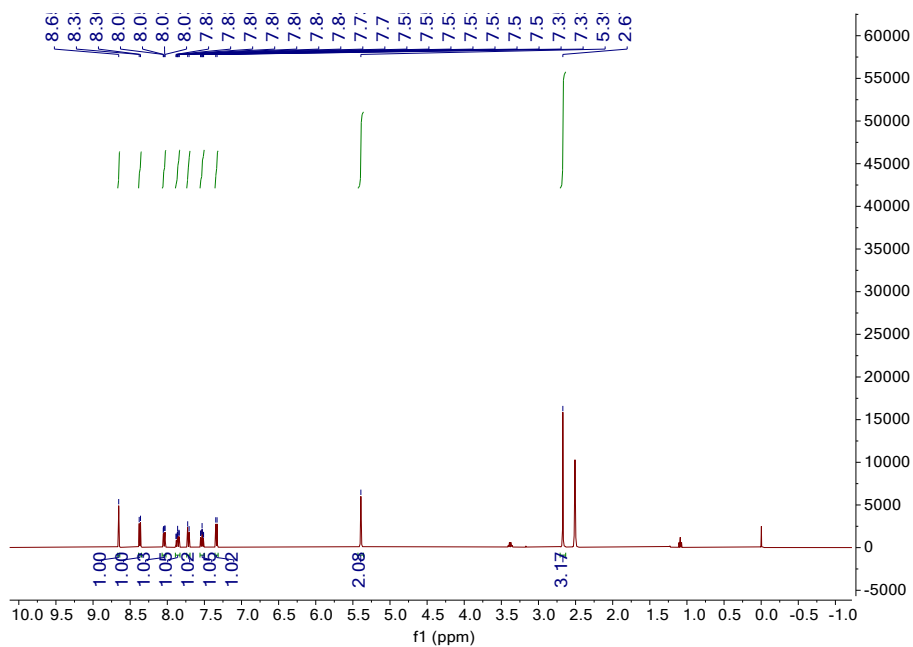
White solid, yield: 19.6%, m.p. 263.2-264.9 °C.  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  8.62 (s, 1H), 8.34 (d,  $J$  = 7.1 Hz, 1H), 7.72 (d,  $J$  = 9.2 Hz, 1H), 7.57 (dd,  $J$  = 9.2, 3.1 Hz, 1H), 7.49 (d,  $J$  = 3.1 Hz, 1H), 7.28 (d,  $J$  = 7.1 Hz, 1H), 7.25-7.15 (m, 3H), 5.38 (s, 2H), 5.27 (s, 2H), 2.66 (s, 3H);  $^{13}C$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$  176.00, 162.98 (d,  $^1J_{C-F}$  = 245.0 Hz), 162.85 (d,  $^1J_{C-F}$  = 245.0 Hz), 159.75, 157.70, 155.90, 151.45, 143.29, 142.23, 141.74 (t,  $^3J_{C-F}$  = 9.4 Hz), 139.15, 124.88, 124.38, 120.84, 117.20, 111.03, 110.84 (d,  $^2J_{C-F}$  = 18.6 Hz), 110.78 (d,  $^2J_{C-F}$  = 20.4 Hz), 106.74, 103.74 (t,  $^2J_{C-F}$  = 25.7 Hz), 68.93, 51.85, 13.31; HRMS  $m/z$ : calc. for  $C_{23}H_{18}F_2NO_5$   $[M+H]^+$ , 426.1148, found, 426.1161; HPLC purity: 100%.

1-((6-((3,4-dichlorobenzyl)oxy)-4-oxo-4*H*-chromen-3-yl)methyl)-3-hydroxy-2-methylpyridin-4(1*H*)-one  
**(25m)**

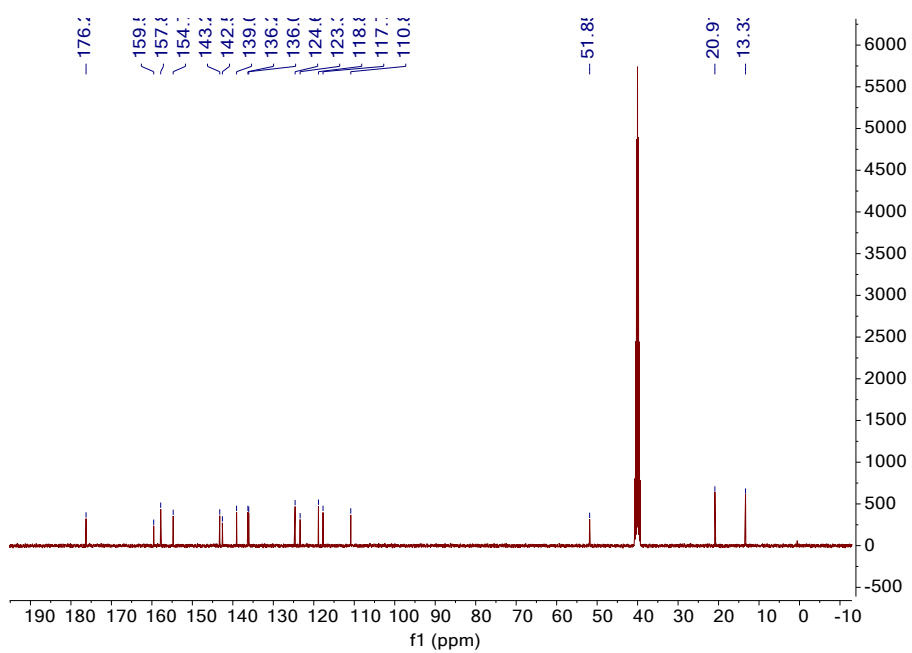
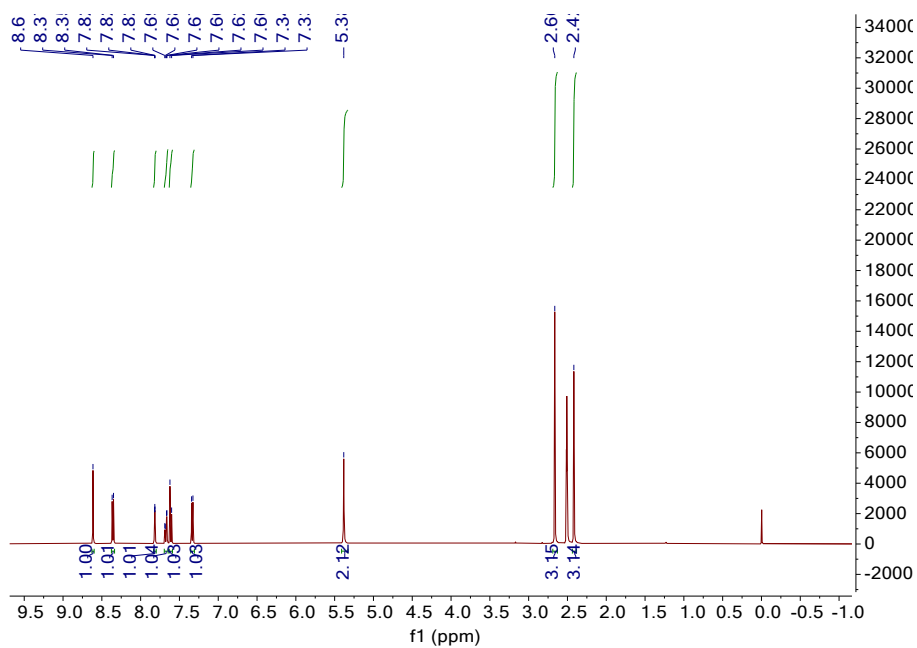
White solid, yield: 58.9%, m.p. 247.5-249.0 °C. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 8.64 (s, 1H), 8.36 (d, *J* = 7.0 Hz, 1H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.71-7.63 (m, 2H), 7.55 (d, *J* = 9.3 Hz, 1H), 7.47 (d, *J* = 9.3 Hz, 2H), 7.33 (d, *J* = 7.0 Hz, 1H), 5.39 (s, 2H), 5.24 (s, 2H), 2.67 (s, 3H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ 176.02, 159.48, 157.75, 155.92, 151.40, 143.20, 142.61, 139.17, 138.24, 131.62, 131.22, 130.95, 129.89, 128.25, 124.89, 124.34, 120.86, 117.15, 110.79, 106.56, 68.69, 51.90, 13.33; HRMS *m/z*: calc. for C<sub>23</sub>H<sub>18</sub>Cl<sub>2</sub>NO<sub>5</sub> [M+H]<sup>+</sup>, 458.0557, found, 458.0566; HPLC purity: 100%.

## 8. $^1\text{H}$ NMR, $^{13}\text{C}$ NMR of 11a-e, 18a-g, and 25a-m

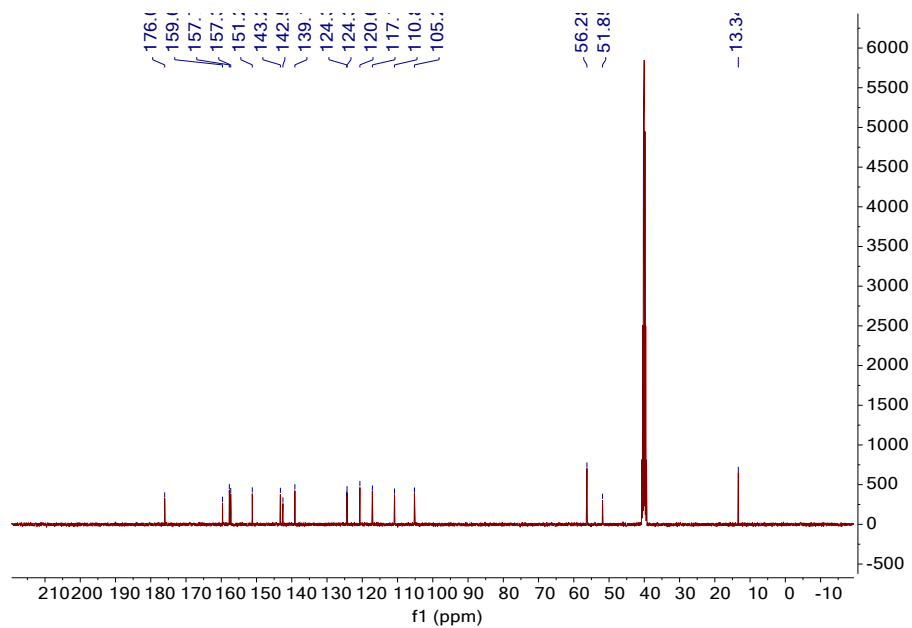
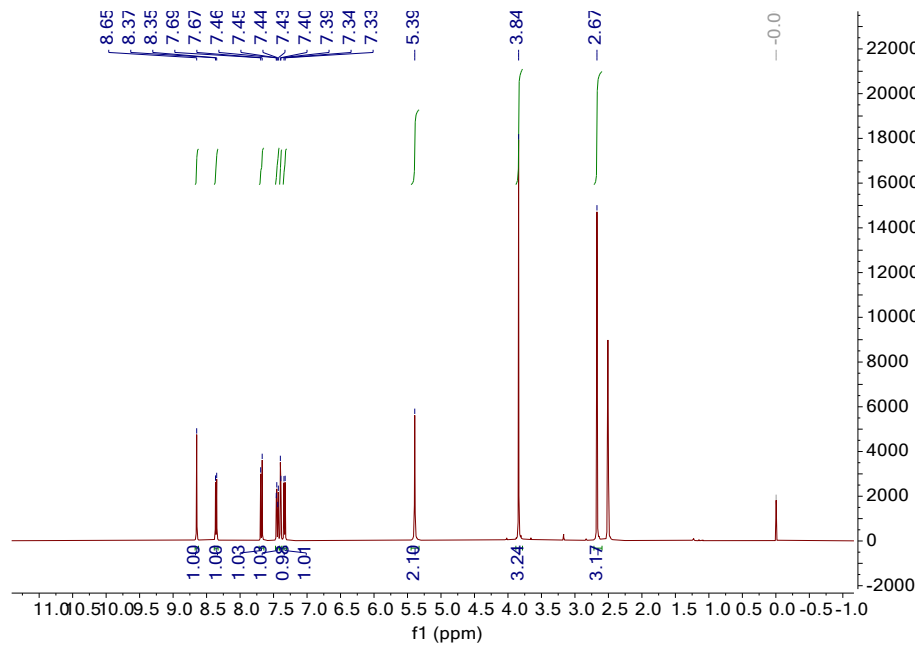
### 3-hydroxy-2-methyl-1-((4-oxo-4*H*-chromen-3-yl)methyl)pyridin-4(1*H*)-one (**11a**)



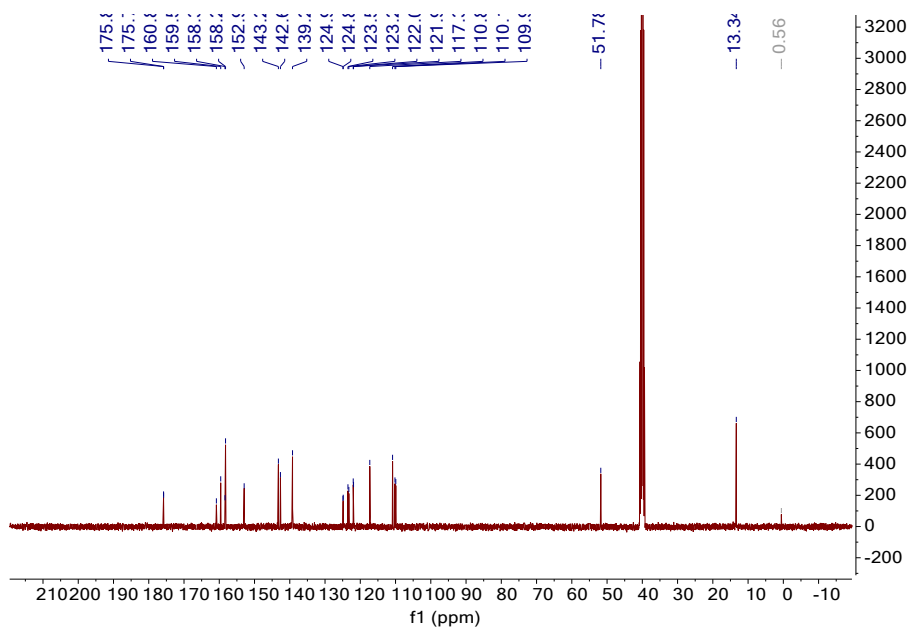
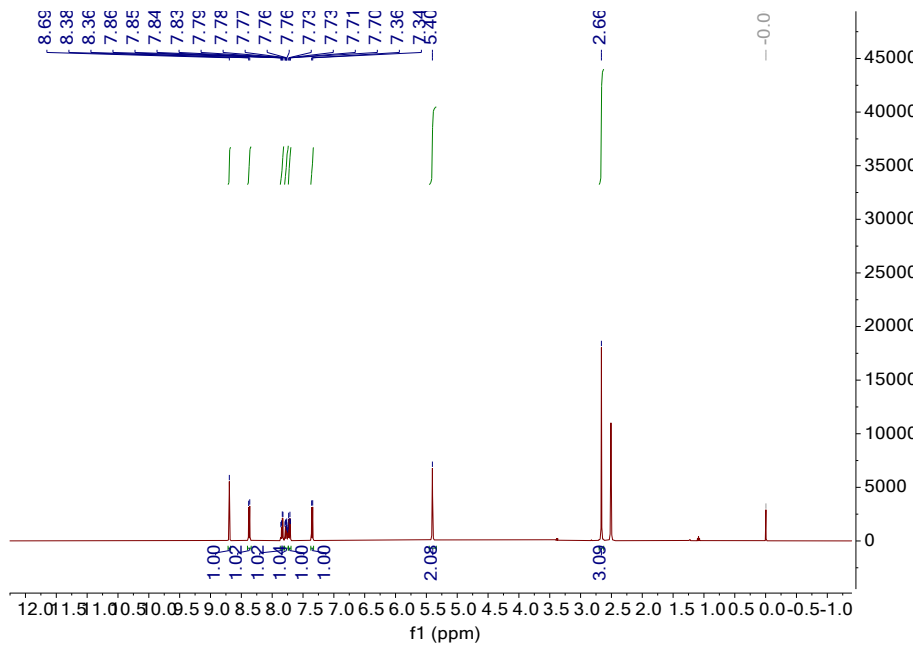
3-hydroxy-2-methyl-1-((6-methyl-4-oxo-4H-chromen-3-yl)methyl)pyridin-4(1H)-one (**11b**)



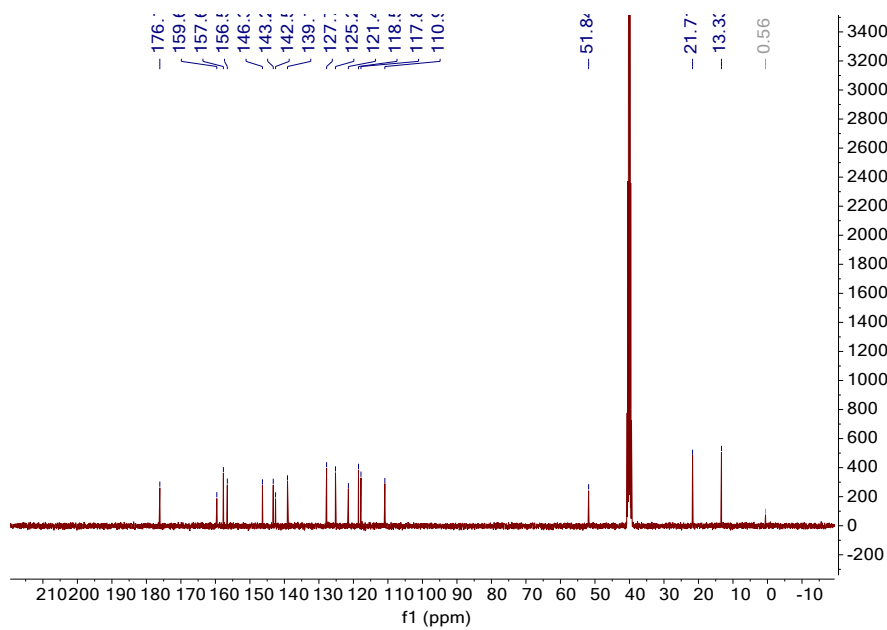
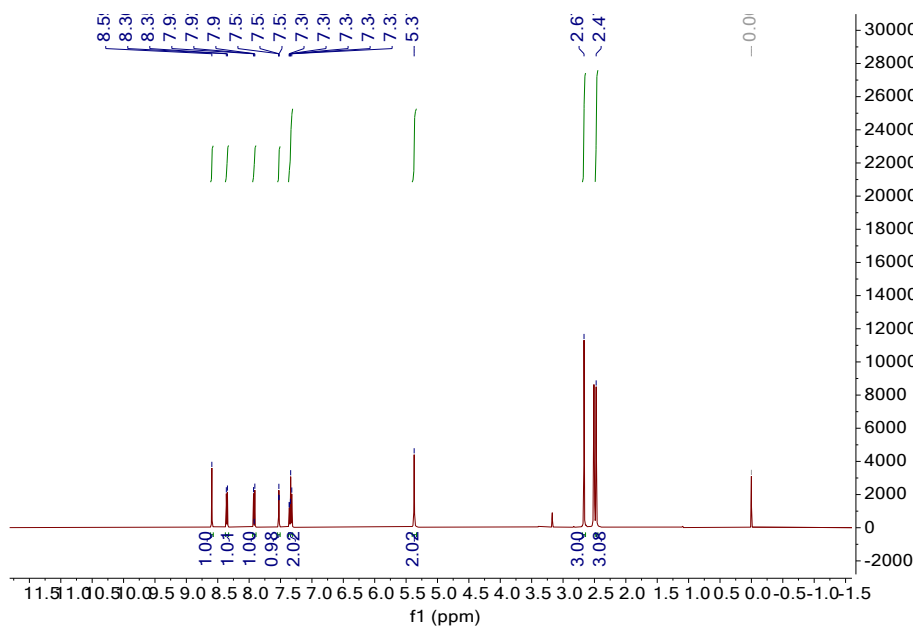
3-hydroxy-1-((6-methoxy-4-oxo-4*H*-chromen-3-yl)methyl)-2-methylpyridin-4(1*H*)-one (**11c**)



1-((6-fluoro-4-oxo-4*H*-chromen-3-yl)methyl)-3-hydroxy-2-methylpyridin-4(1*H*)-one (**11d**)

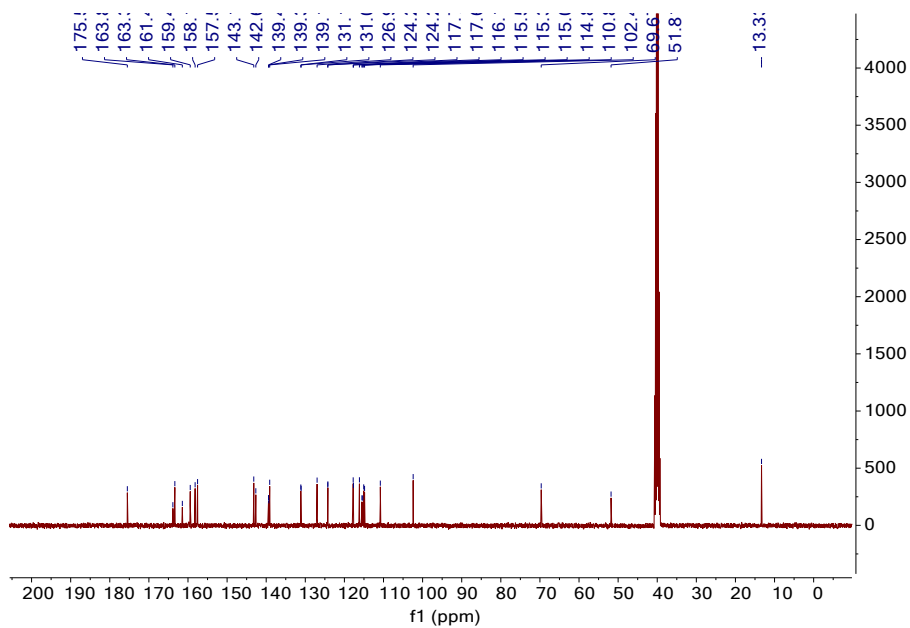
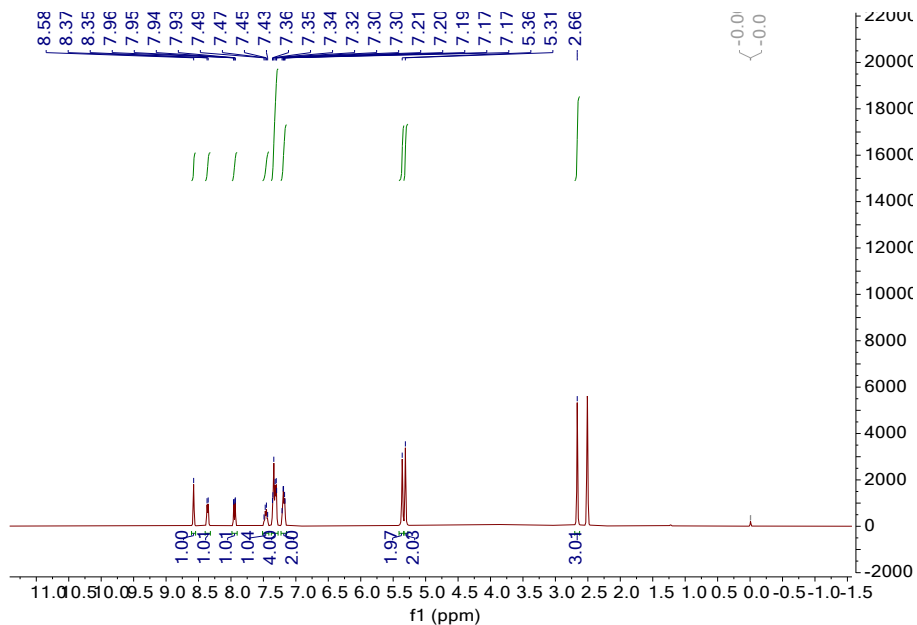


3-hydroxy-2-methyl-1-((7-methyl-4-oxo-4*H*-chromen-3-yl)methyl)pyridin-4(1*H*)-one (**11e**)

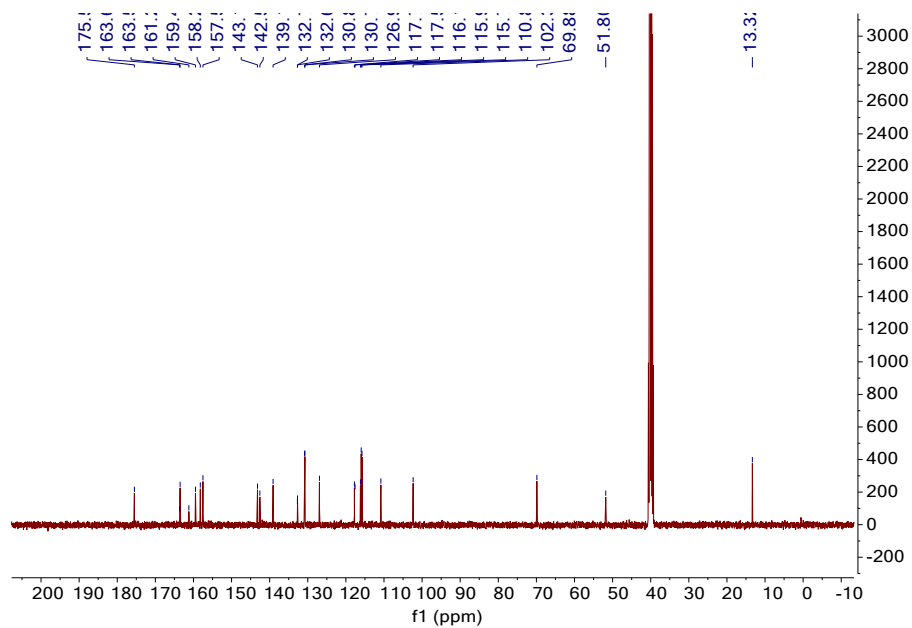
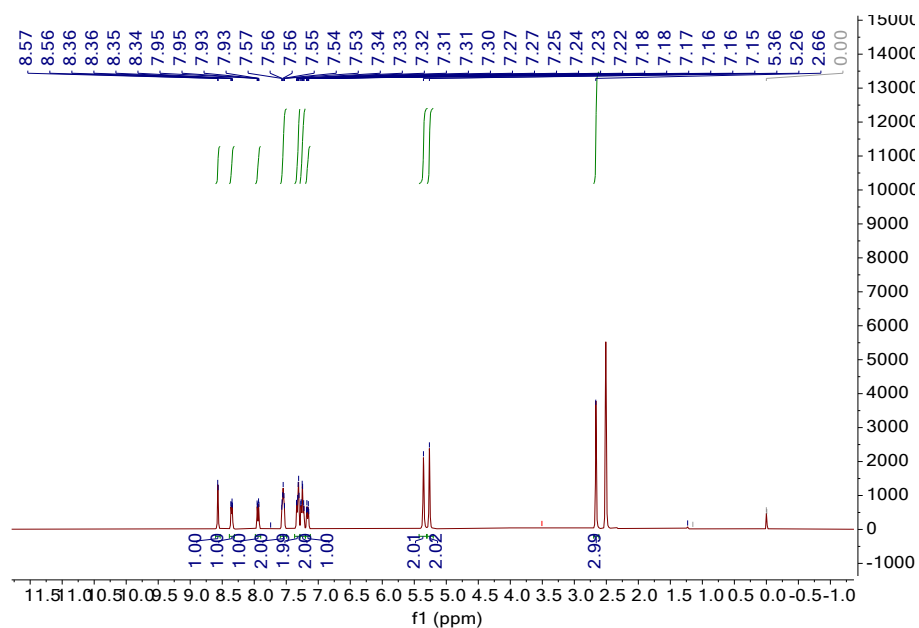




1-((7-((3-fluorobenzyl)oxy)-4-oxo-4H-chromen-3-yl)methyl)-3-hydroxy-2-methylpyridin-4(1H)-one (**18a**)

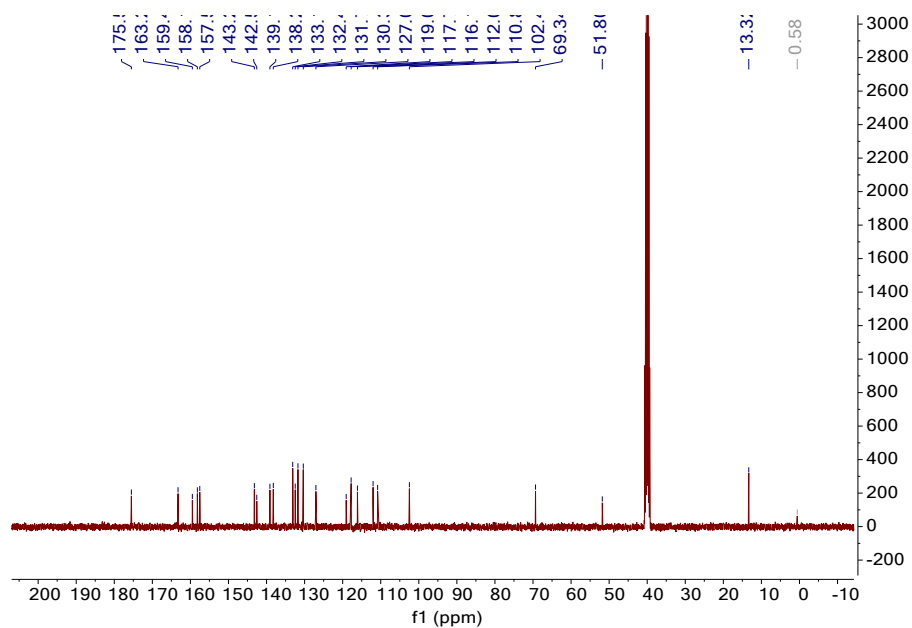
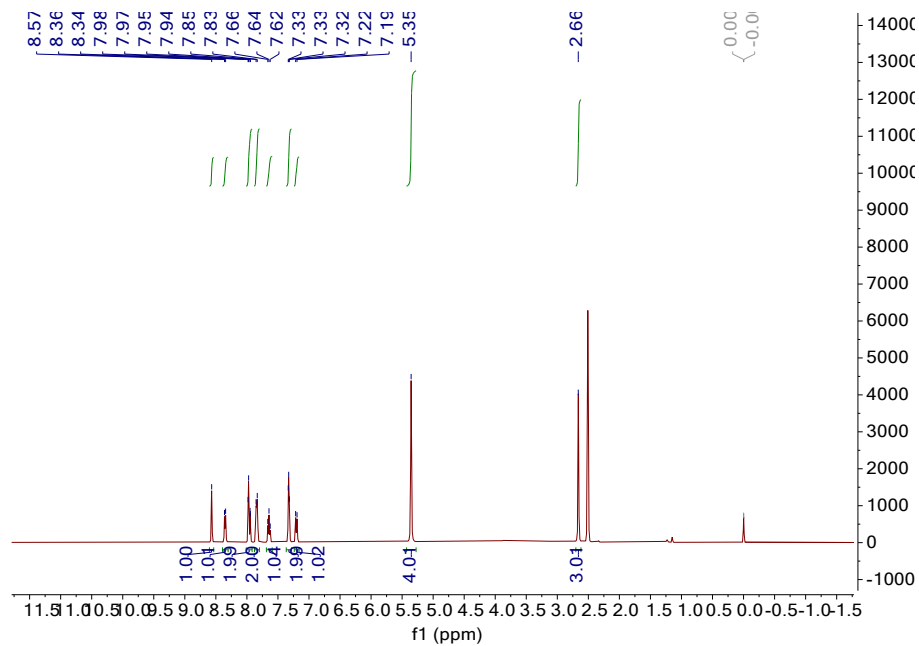


1-((7-((4-fluorobenzyl)oxy)-4-oxo-4H-chromen-3-yl)methyl)-3-hydroxy-2-methylpyridin-4(1H)-one (**18b**)

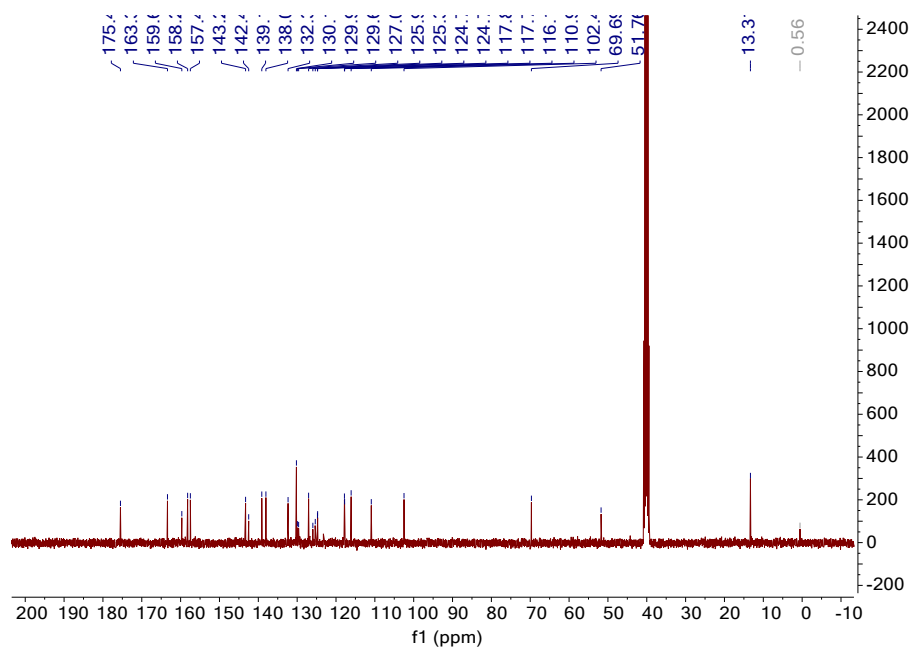
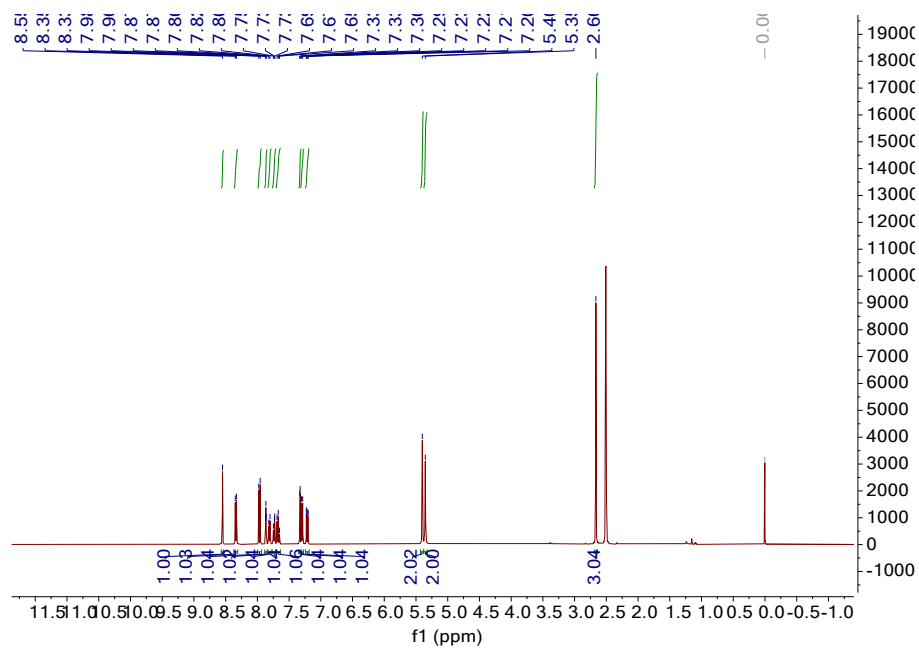




3-(((3-((3-hydroxy-2-methyl-4-oxopyridin-1(4H)-yl)methyl)-4-oxo-4H-chromen-7-yl)oxy)methyl)benzonitrile (**18d**)

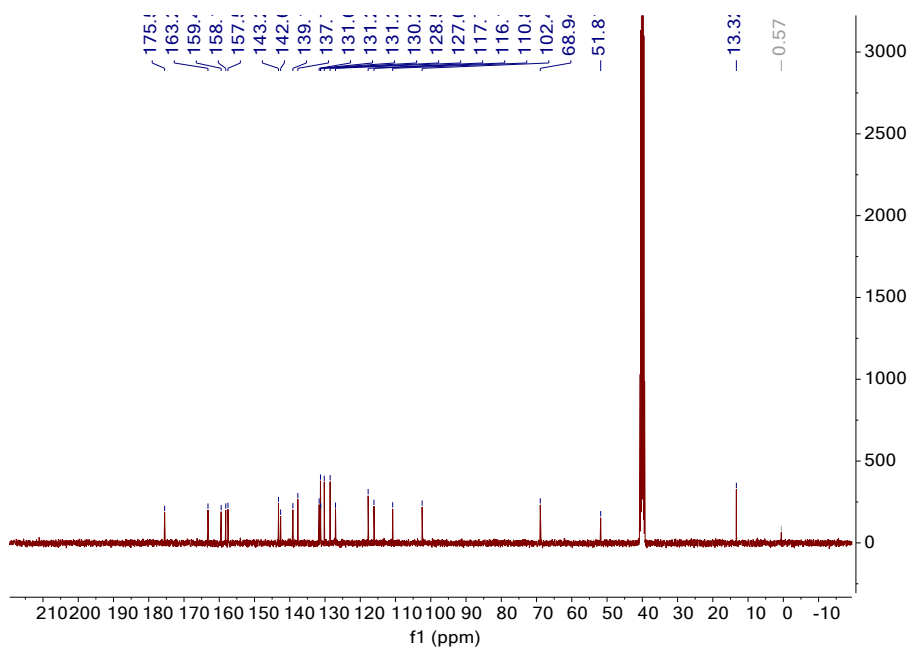
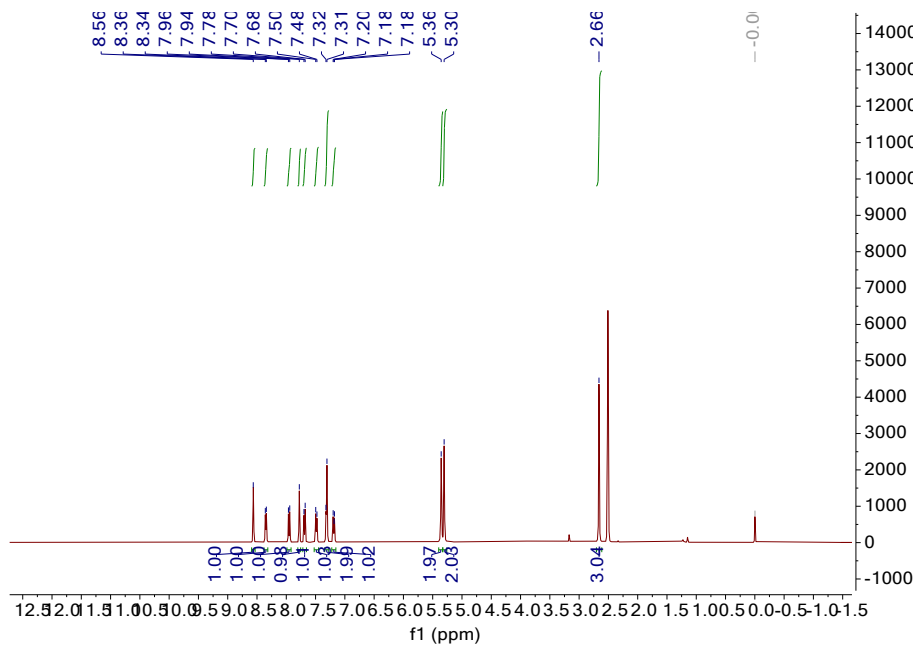


3-hydroxy-2-methyl-1-((4-oxo-7-((3-(trifluoromethyl)benzyl)oxy)-4H-chromen-3-yl)methyl)pyridin-4(1H)-one (**18e**)

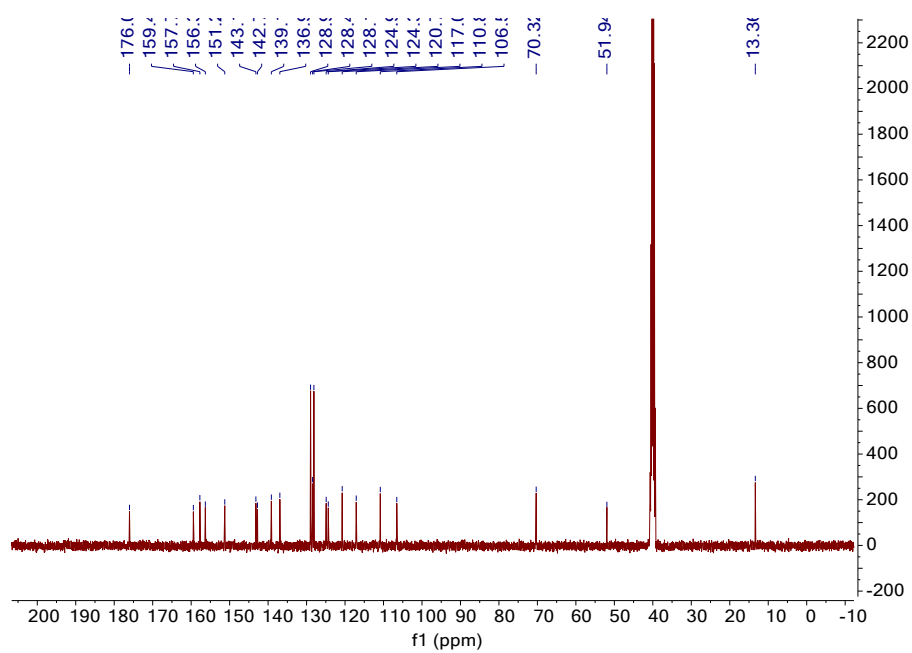
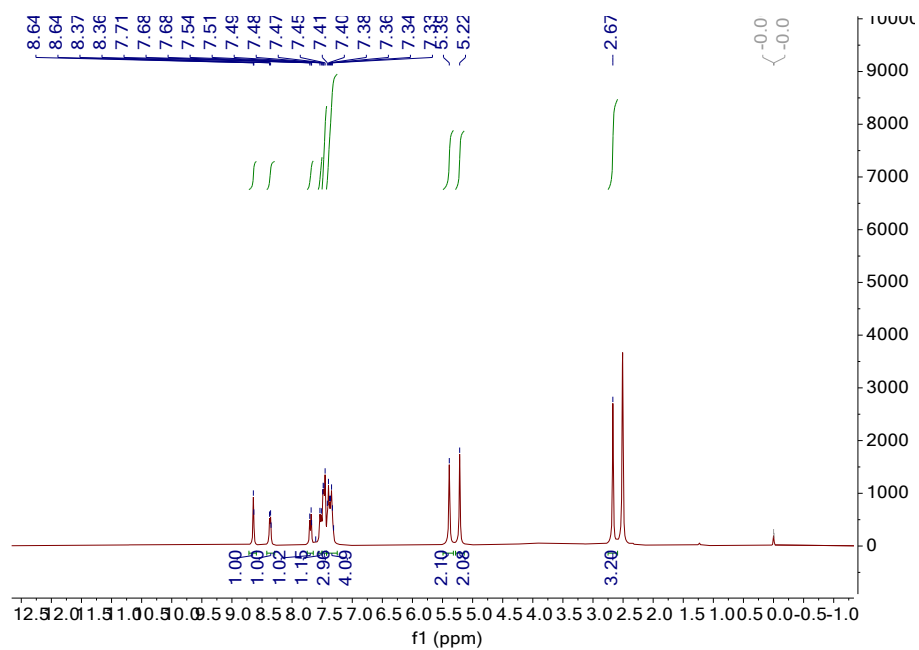




1-((7-((3,4-dichlorobenzyl)oxy)-4-oxo-4H-chromen-3-yl)methyl)-3-hydroxy-2-methylpyridin-4(1H)-one (**18g**)

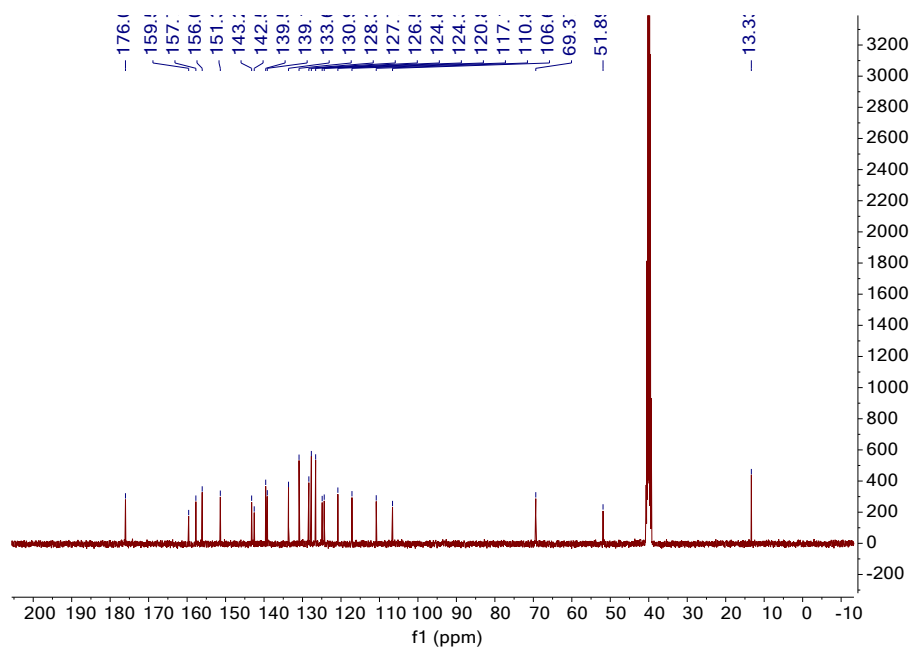
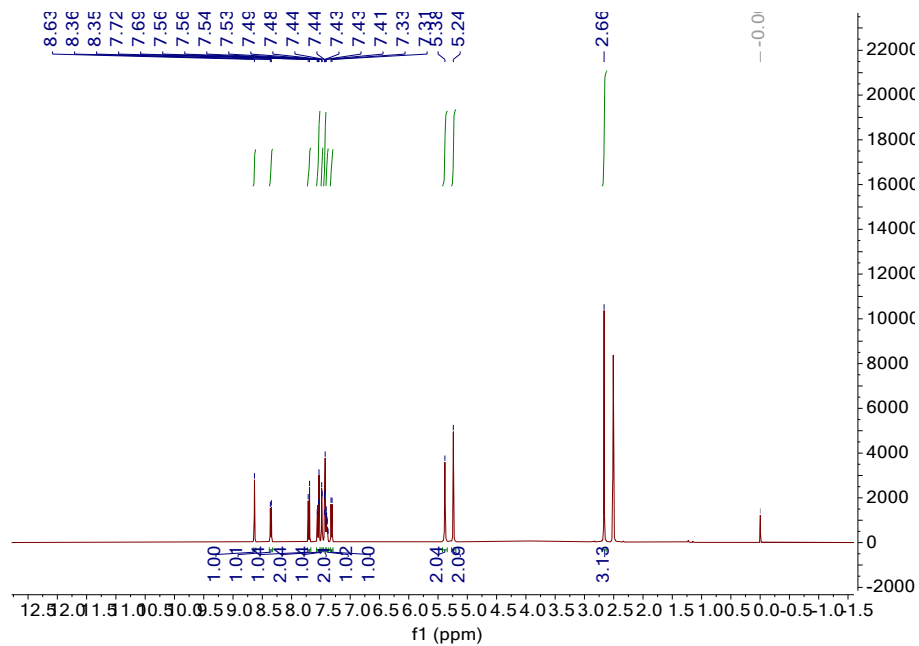


1-((6-(benzyloxy)-4-oxo-4H-chromen-3-yl)methyl)-3-hydroxy-2-methylpyridin-4(1H)-one (25a)

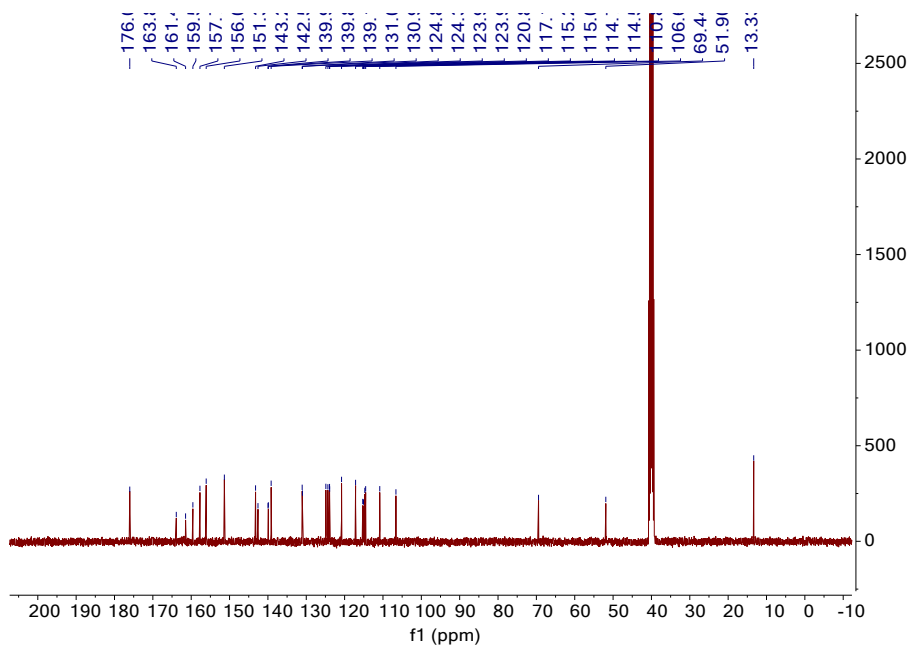
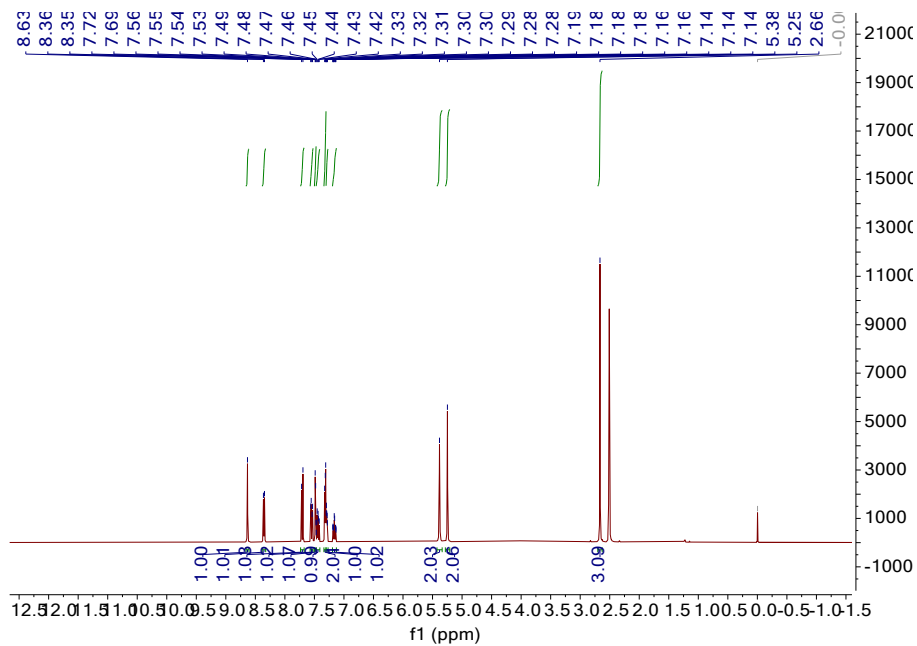




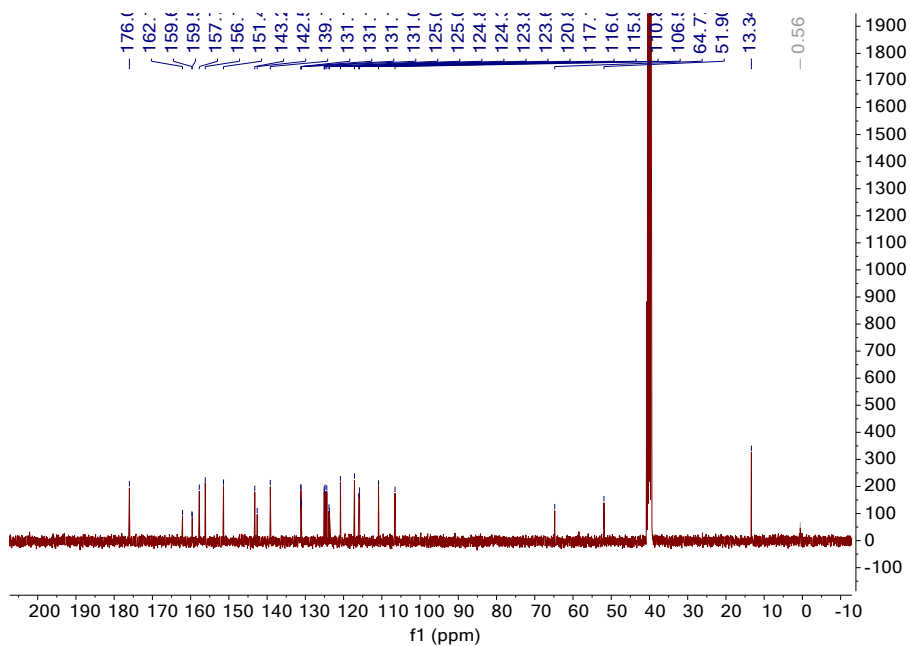
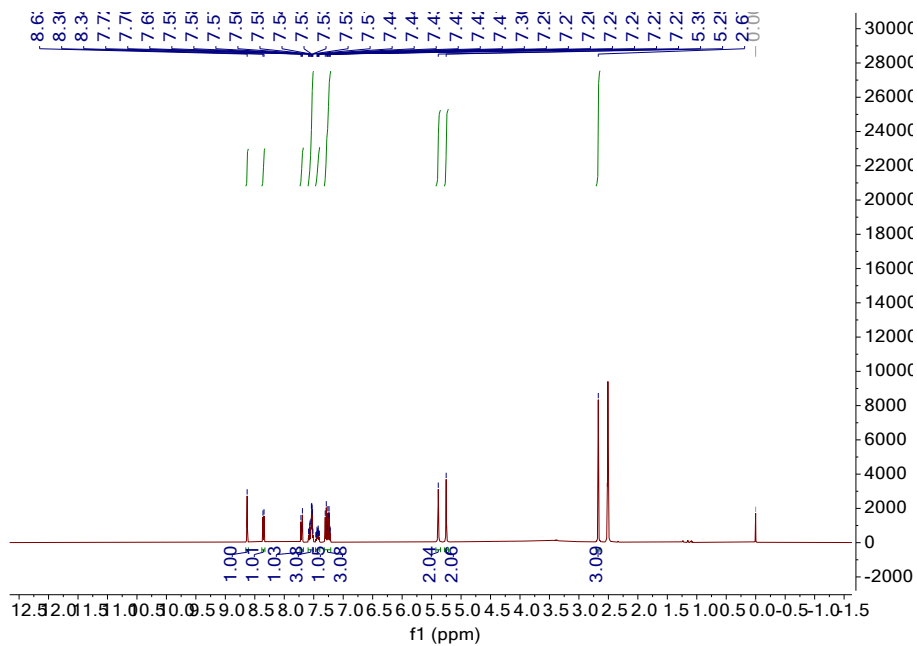
1-((6-((3-chlorobenzyl)oxy)-4-oxo-4H-chromen-3-yl)methyl)-3-hydroxy-2-methylpyridin-4(1H)-one (**25b**)



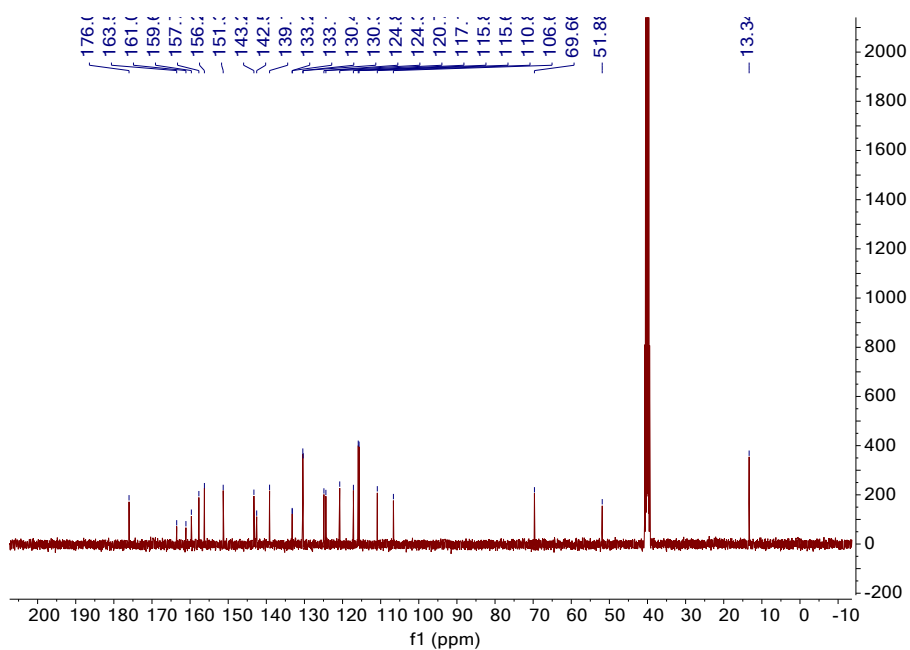
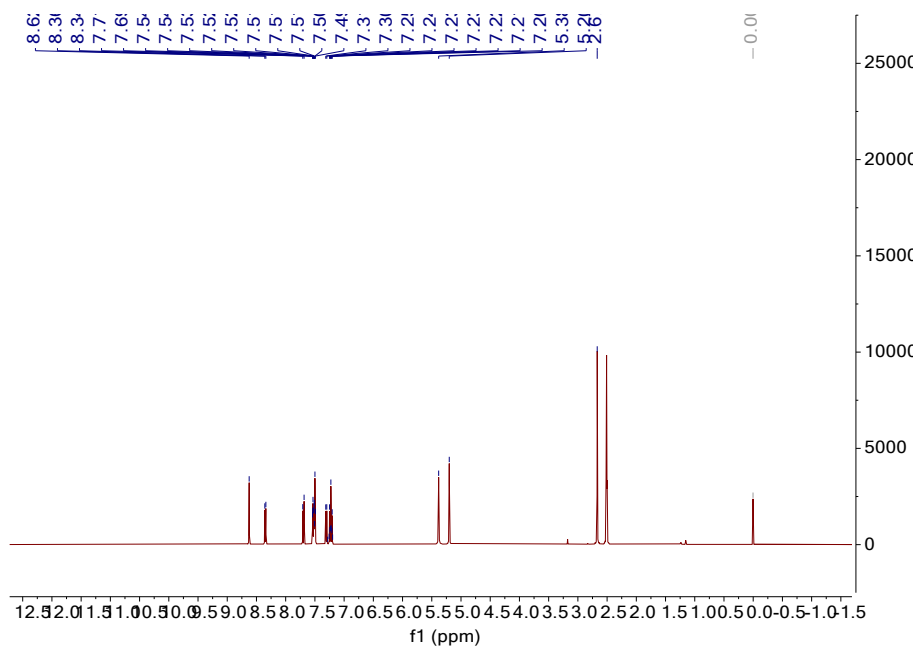
1-((6-((3-fluorobenzyl)oxy)-4-oxo-4H-chromen-3-yl)methyl)-3-hydroxy-2-methylpyridin-4(1H)-one (**25c**)



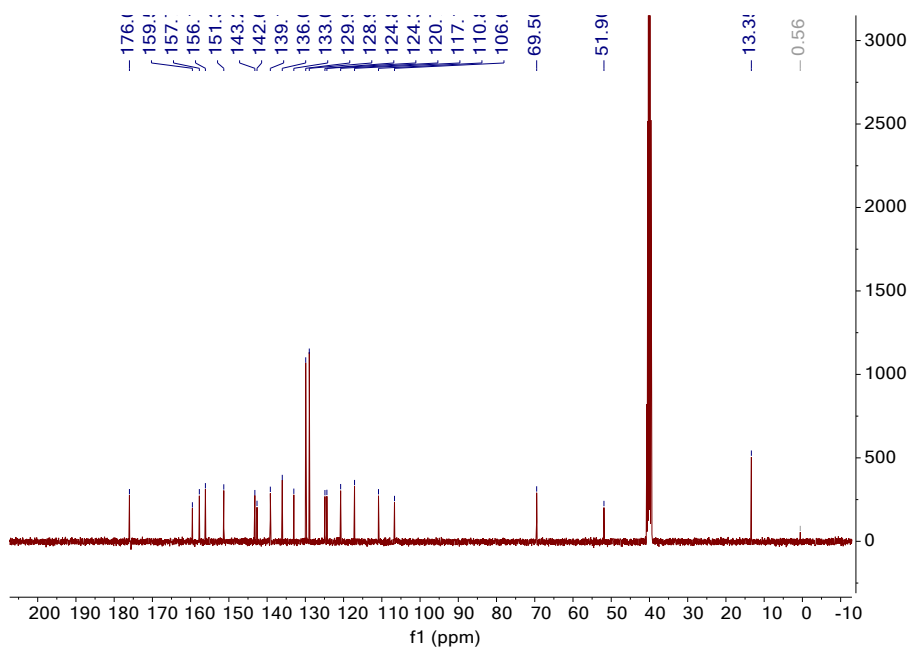
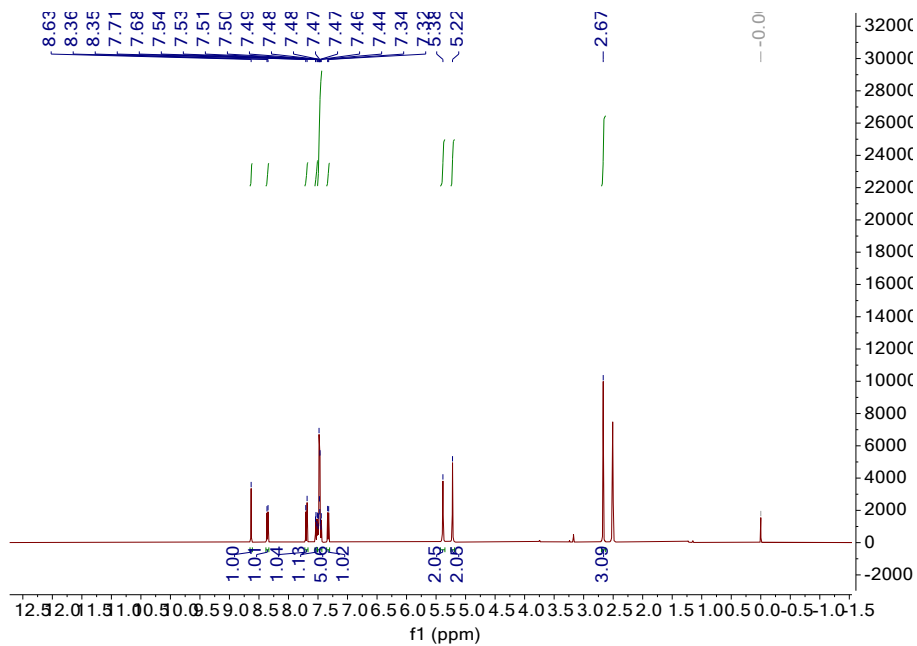
1-((6-((2-fluorobenzyl)oxy)-4-oxo-4H-chromen-3-yl)methyl)-3-hydroxy-2-methylpyridin-4(1H)-one (25d)



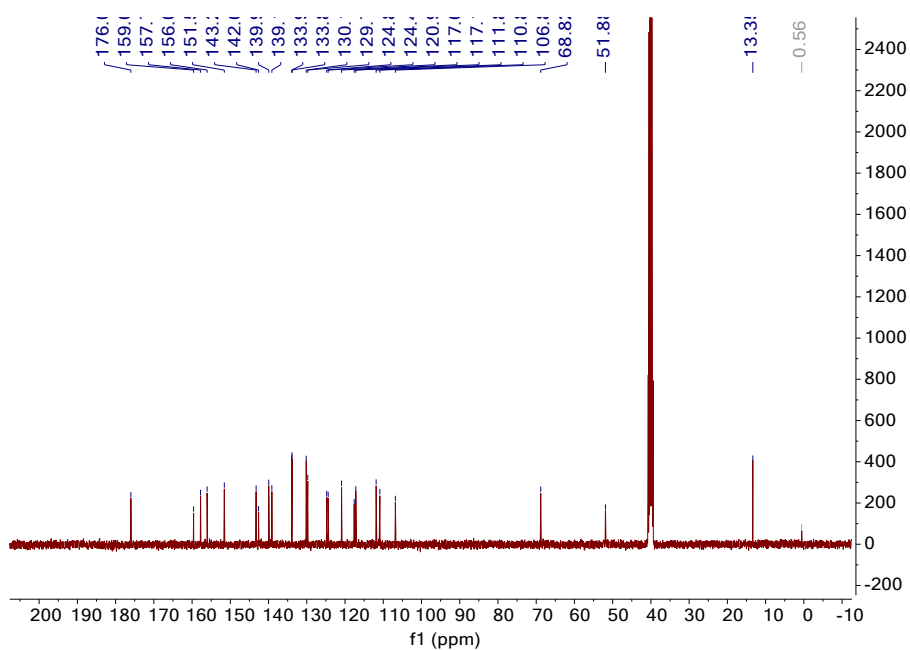
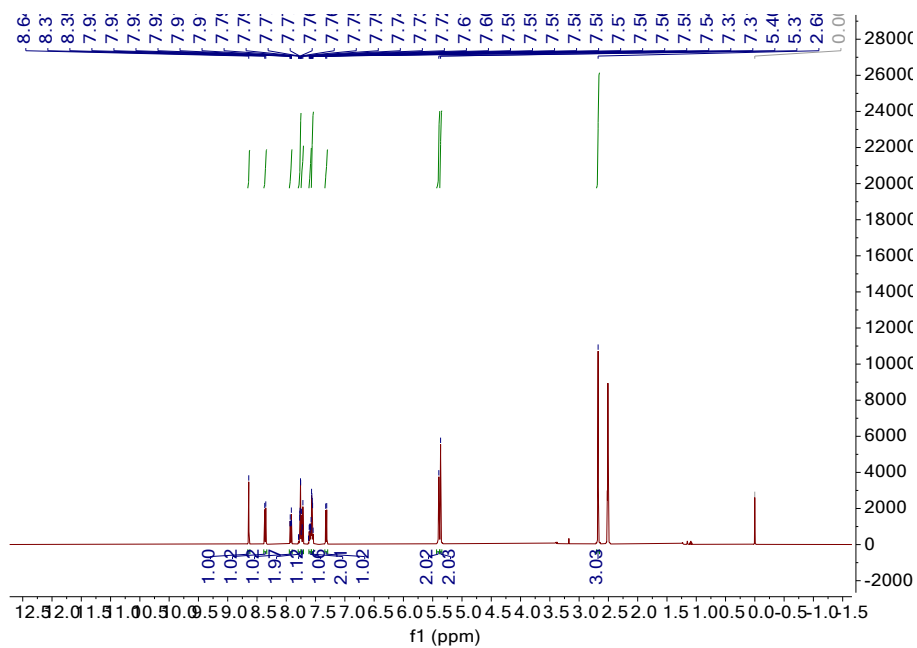
1-((6-((4-fluorobenzyl)oxy)-4-oxo-4H-chromen-3-yl)methyl)-3-hydroxy-2-methylpyridin-4(1H)-one (**25e**)



1-((6-((4-chlorobenzyl)oxy)-4-oxo-4H-chromen-3-yl)methyl)-3-hydroxy-2-methylpyridin-4(1H)-one (25f)

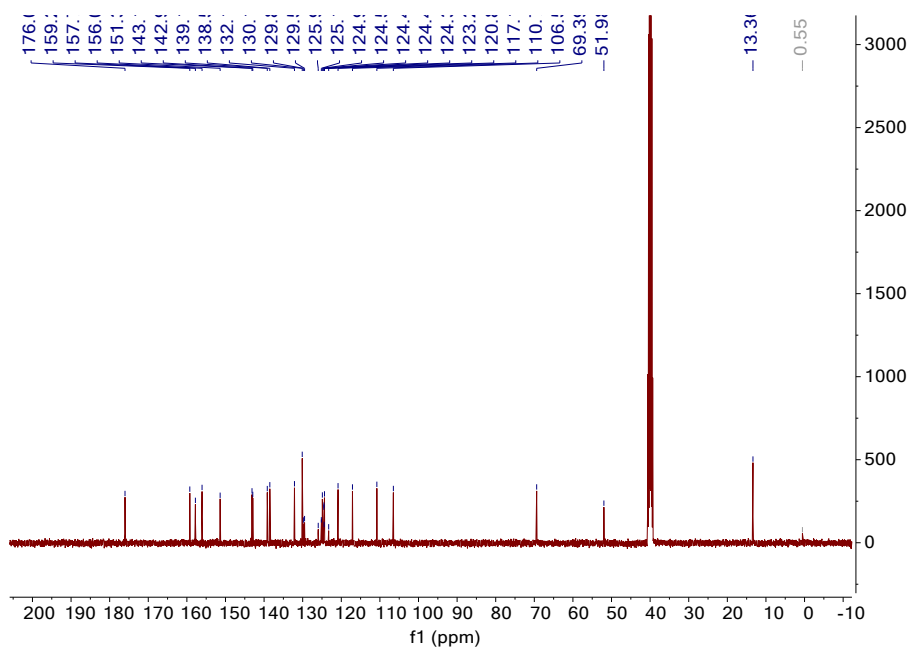
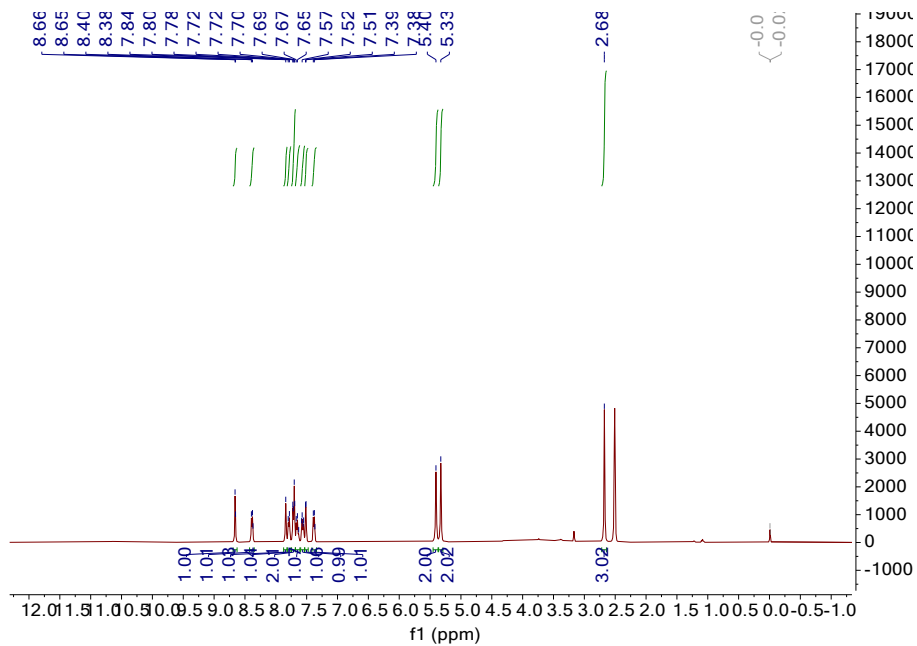


2-(((3-((3-hydroxy-2-methyl-4-oxopyridin-1(4H)-yl)methyl)-4-oxo-4H-chromen-6-yl)oxy)methyl)benzotrile (**25g**)



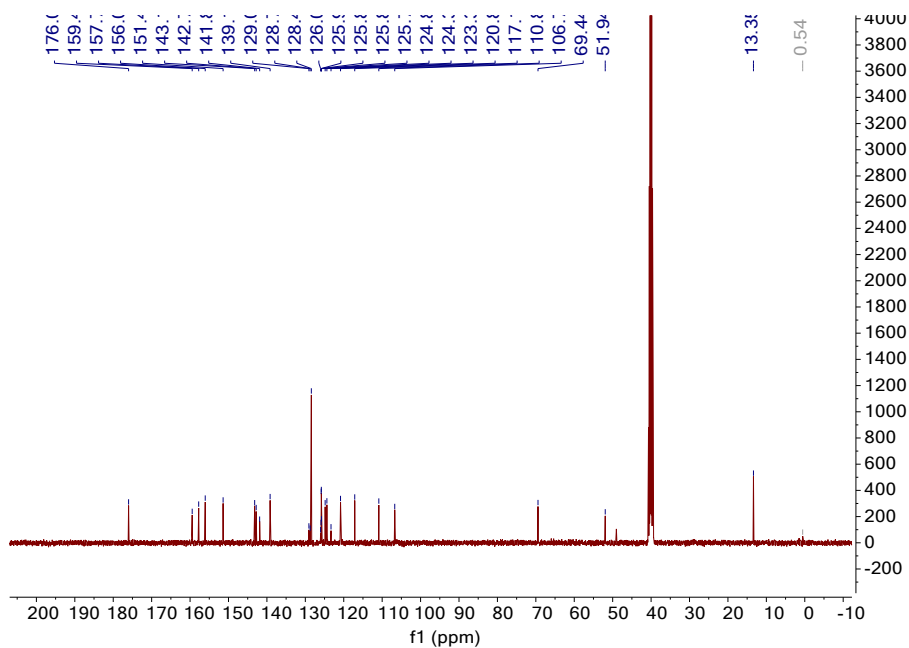
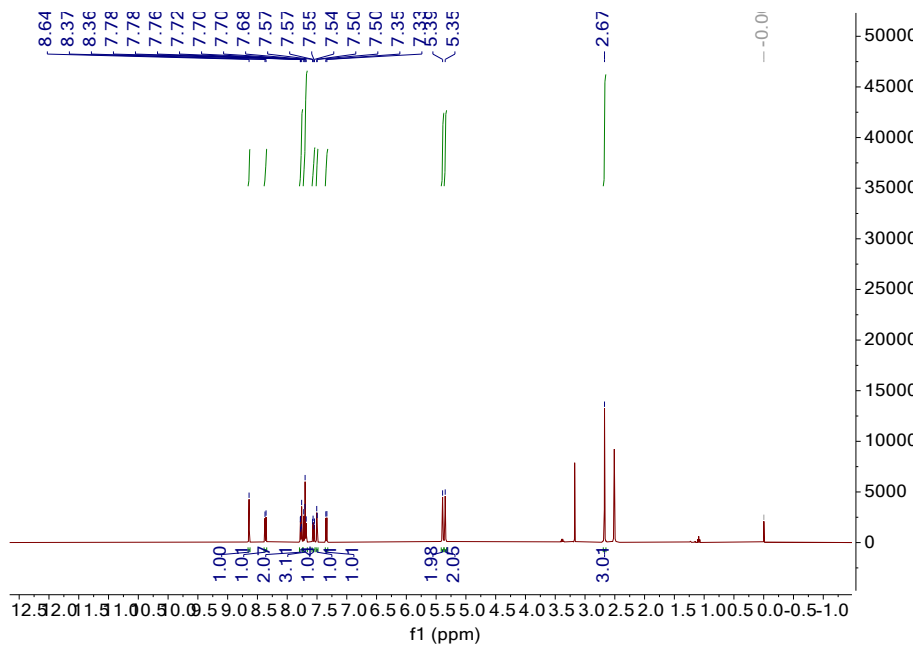


3-hydroxy-2-methyl-1-((4-oxo-6-((3-(trifluoromethyl)benzyl)oxy)-4H-chromen-3-yl)methyl)pyridin-4(1H)-one (25i)

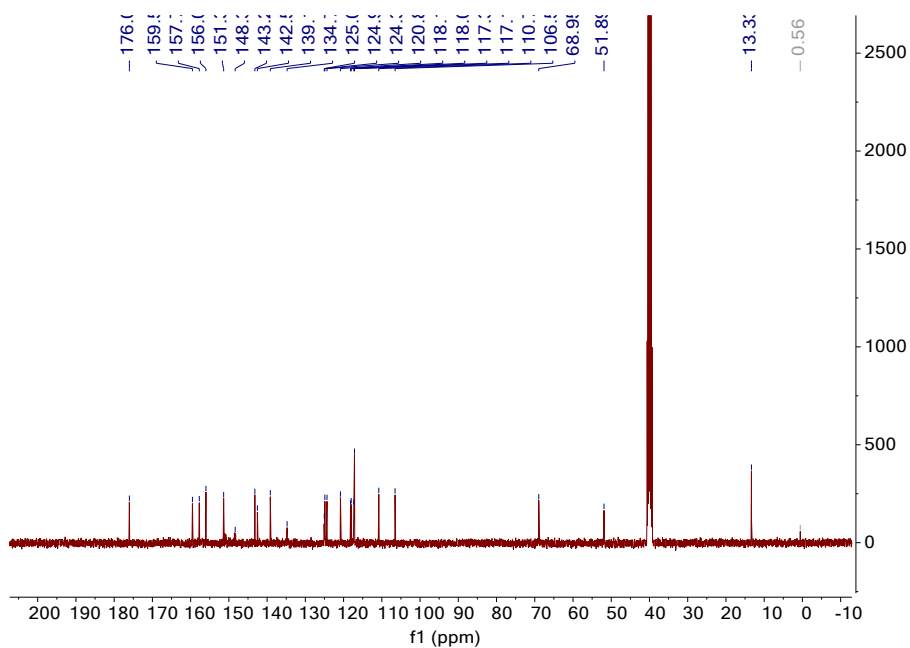
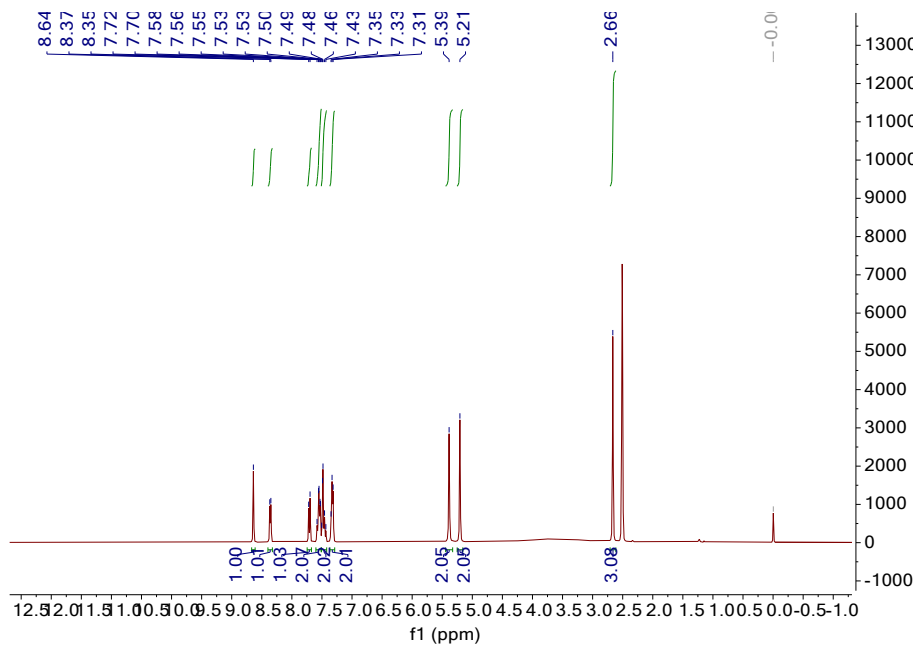




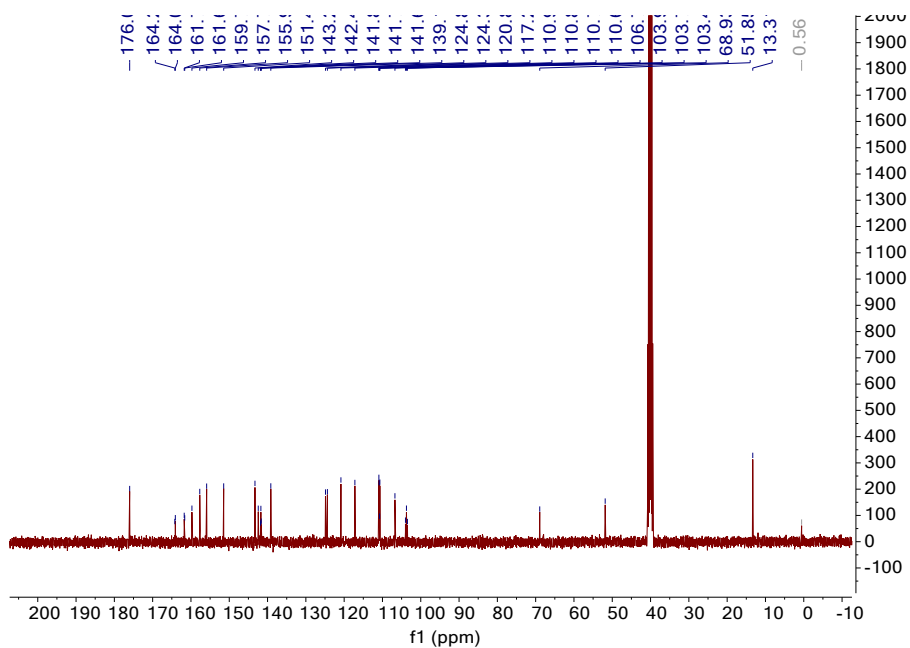
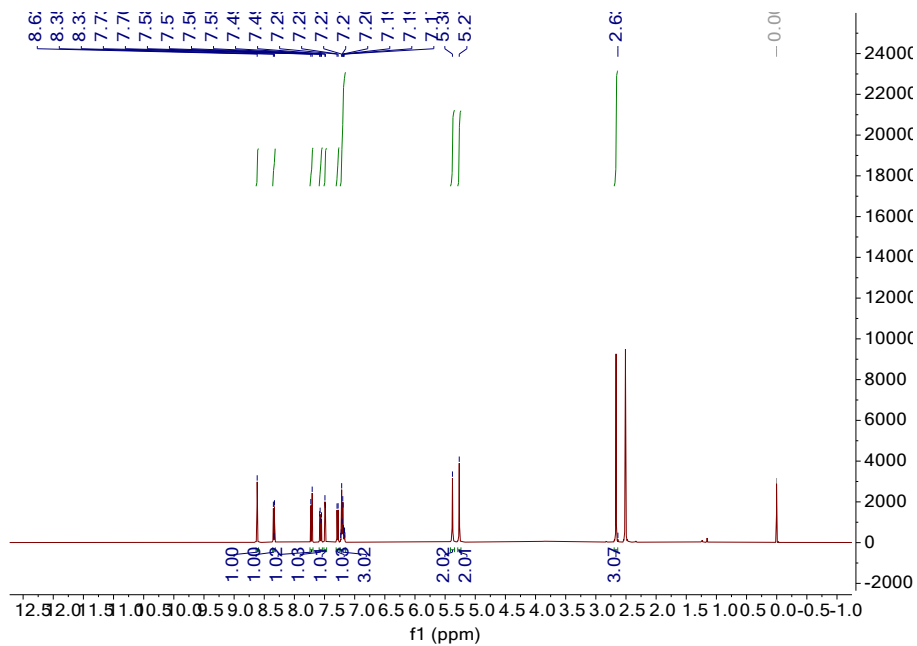
3-hydroxy-2-methyl-1-((4-oxo-6-((4-(trifluoromethyl)benzyl)oxy)-4H-chromen-3-yl)methyl)pyridin-4(1H)-one (25j)



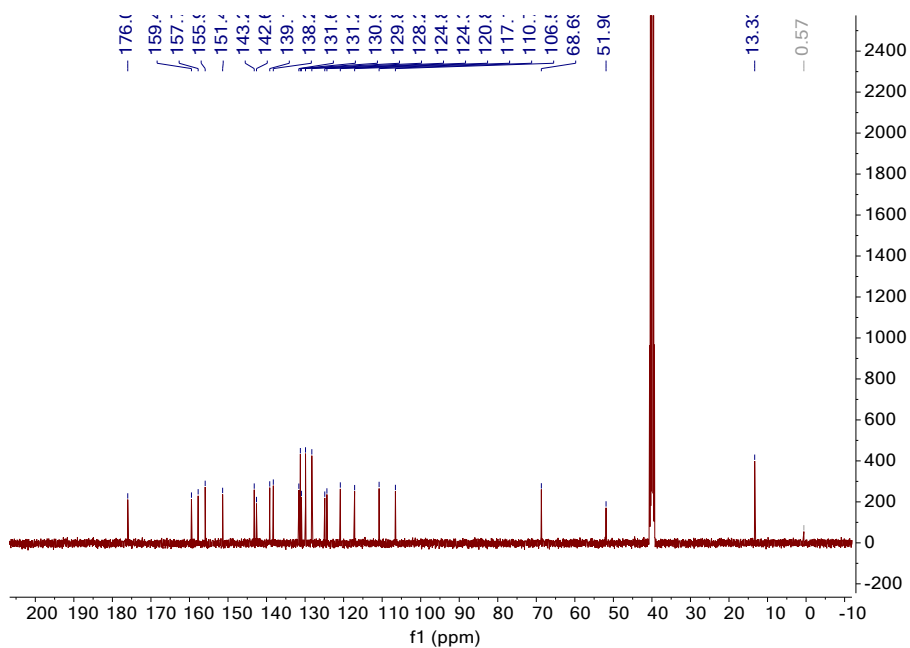
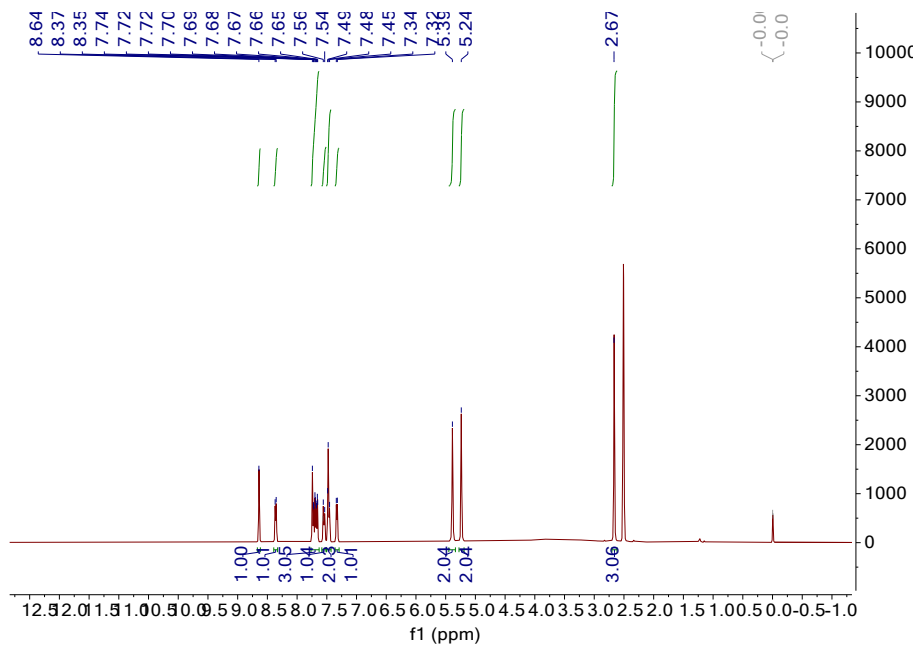
1-((6-((3,4-difluorobenzyl)oxy)-4-oxo-4H-chromen-3-yl)methyl)-3-hydroxy-2-methylpyridin-4(1H)-one (**25k**)



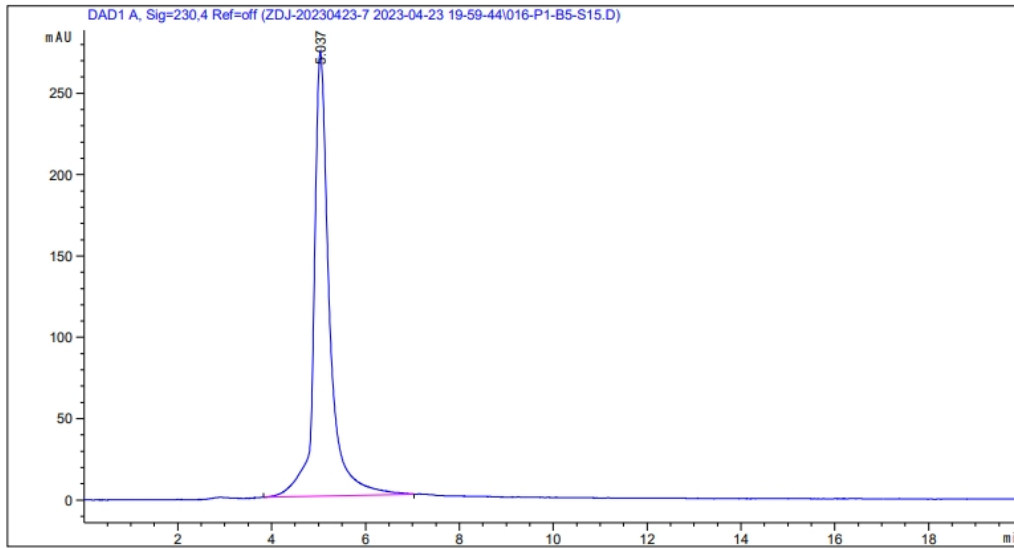
1-((6-((3,5-difluorobenzyl)oxy)-4-oxo-4H-chromen-3-yl)methyl)-3-hydroxy-2-methylpyridin-4(1H)-one (25I)



1-((6-((3,4-dichlorobenzyl)oxy)-4-oxo-4H-chromen-3-yl)methyl)-3-hydroxy-2-methylpyridin-4(1H)-one (**25m**)



## 9. HPLC Traces and HRMS of 25c

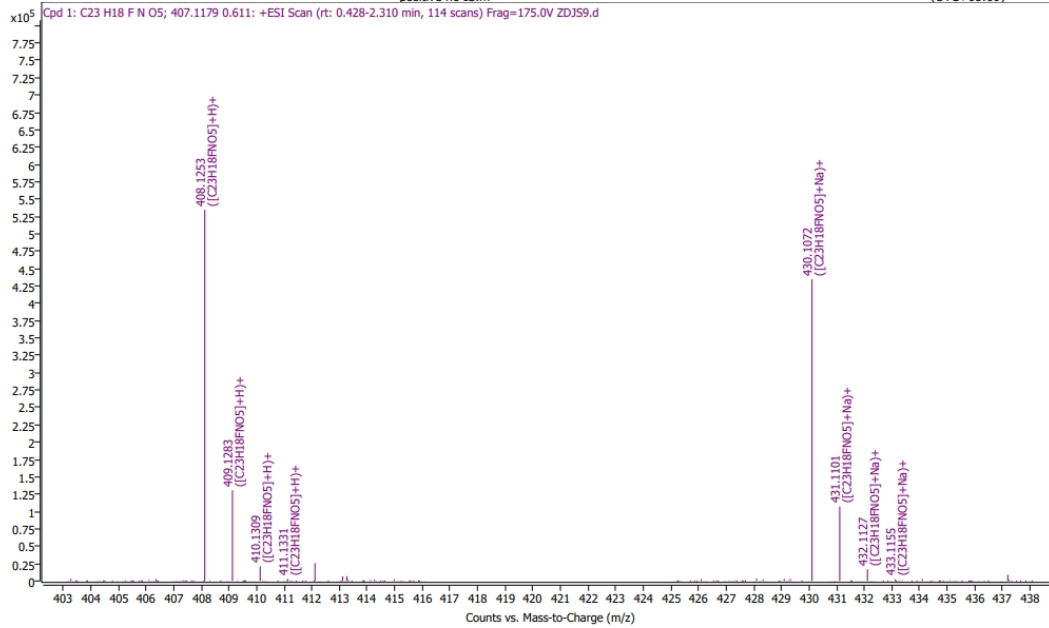


Peak	RT(min)	Area (mAU*s)	Height (mAU)	Area (%)
1	5.037	6294.24316	272.86835	100.000
Total		6294.24316	272.86835	100.000

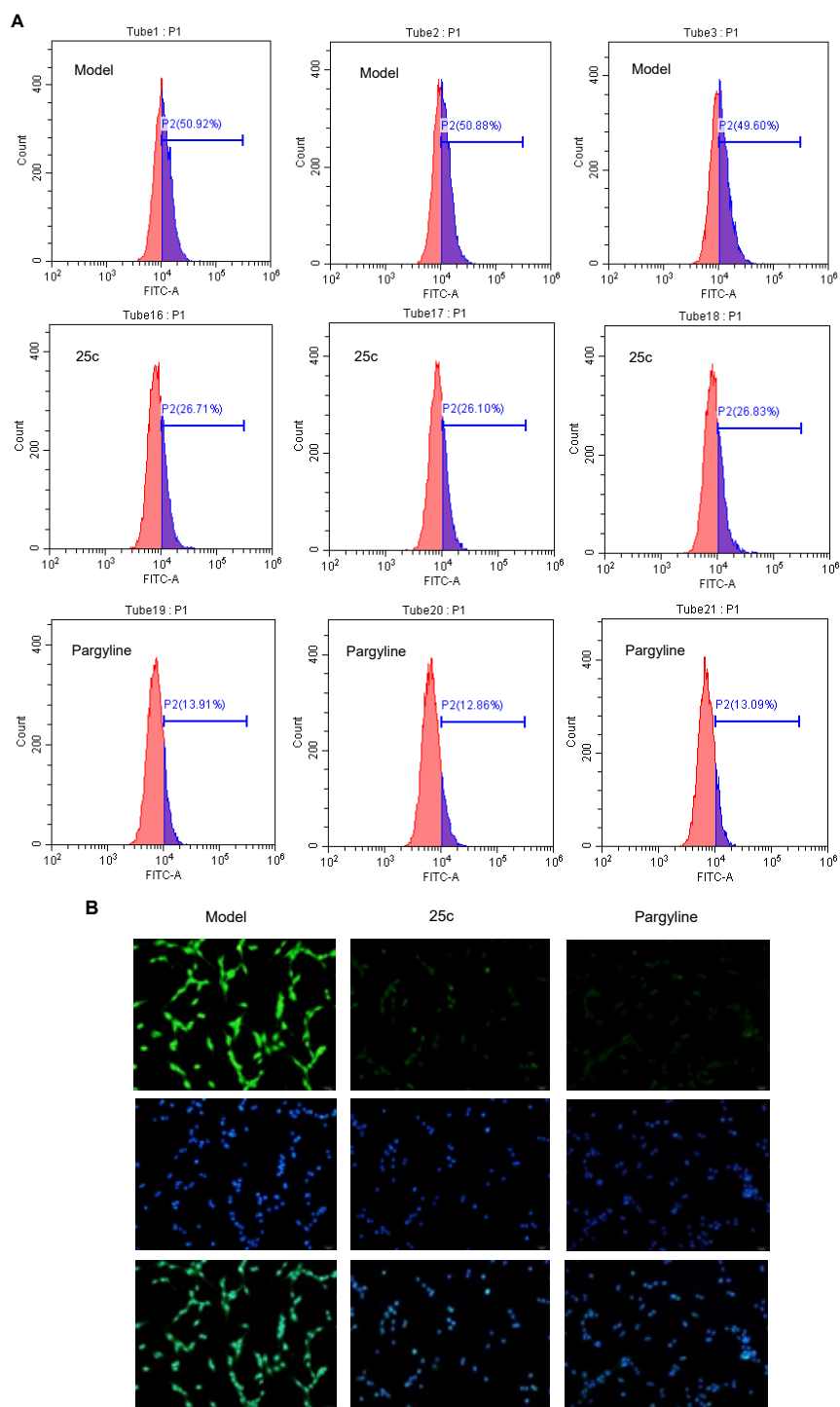
### Spectrum Plot Report



Name	ZDJS9	Rack Pos.	Instrument	Instrument 1	Operator
Inj. Vol. (ul)	2	Plate Pos.	IRM Status	Success	
Data File	ZDJS9.d	Method (Acq)	Comment		Acq. Time (Local)
		Direct injection 1D	positive no IS.m		2/22/2023 6:57:59 PM
					(UTC+08:00)

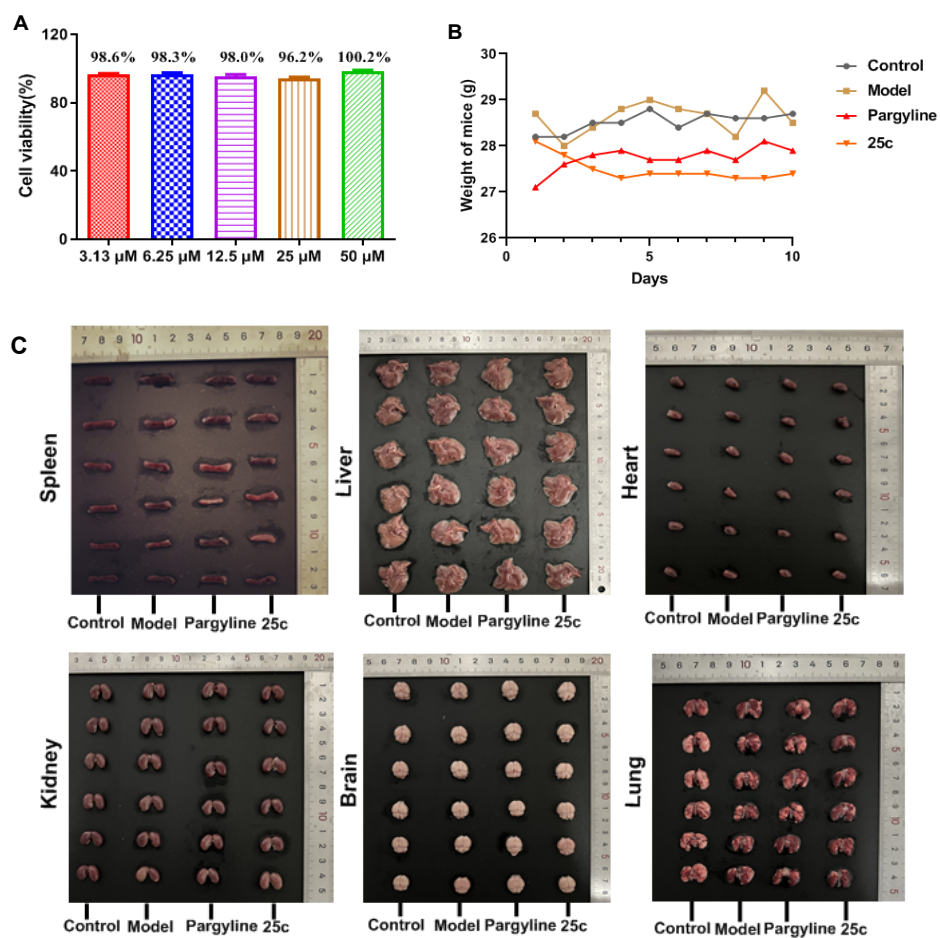


## 10. Antioxidant activity of compound 25c



**Fig. S1** The content of intracellular ROS using DCFH-DA fluorescent probe. (A) The intracellular ROS production (flow cytometry) at 50  $\mu$ M of **25c** with pargyline as the reference drugs. (B) The intracellular ROS production (fluorescence photography) of **25c** at 50  $\mu$ M.

## 11. Potential toxic effect of compound 25c



**Fig. S2** Toxicity assay of compound 25c. (A) The cytotoxic effect of 25c on PC-12 cells. (B) The weight changes of mice in the 25c group over 10 days. (C) The primary organs of mice in the 25c group.