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Design, synthesis and preliminary biological evaluation of 3′,4′,5′-trimethoxy flavonoid salicylate derivatives as potential anti-tumor agents

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1. Supplementary figure

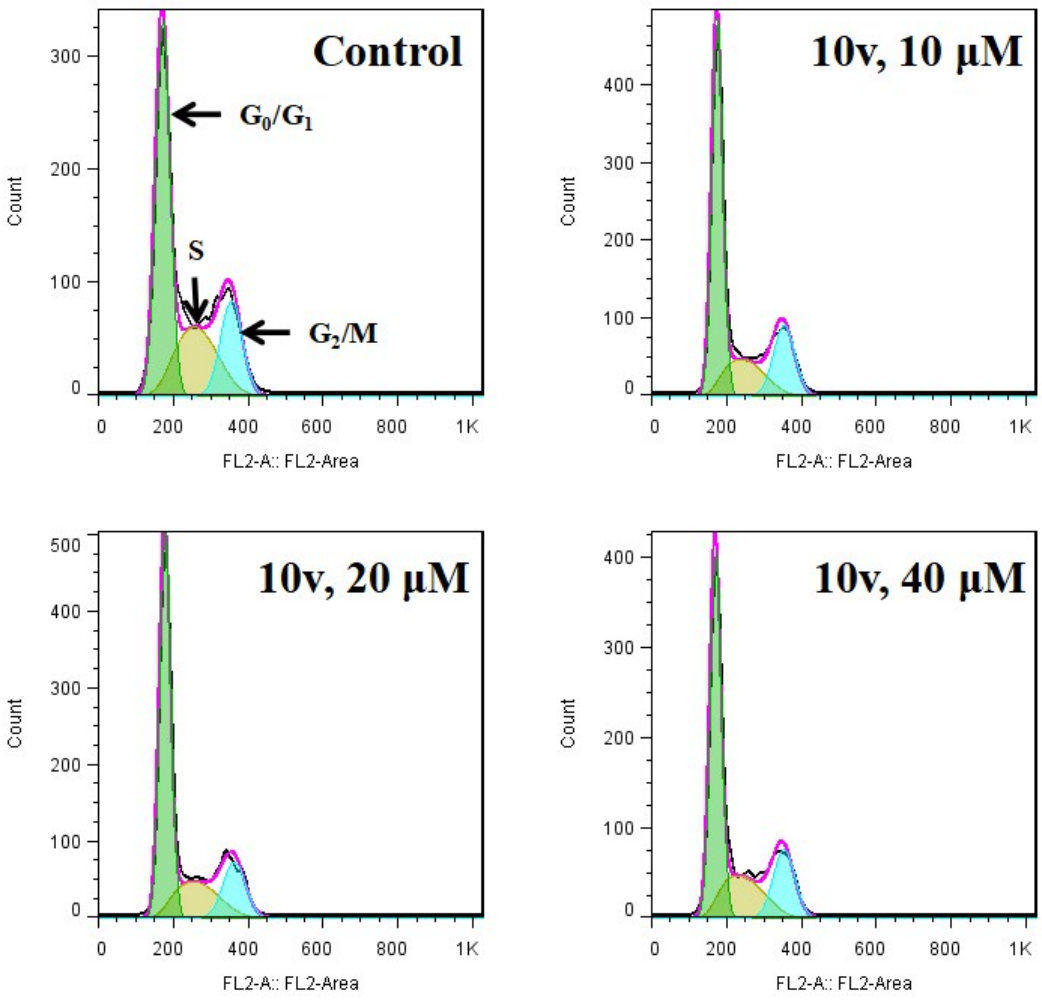


Fig. S1. Analysis of cell cycle distribution. The treatment with compound **10v** didn't effect the cell cycle of HCT-116 cells.

2. Experimental Section

2.1 Synthesis of compounds 7a-7h

4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-7-yl 2-methoxy-4-methylbenzoate (**7a**)

Yellow solid; yield: 77%; Mp: 166-167 °C; chemical formula: $C_{27}H_{24}O_8$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (t, J = 7.0 Hz, 1H), 7.87 (d, J = 8.3 Hz, 1H), 7.35 (d, J = 1.8 Hz, 1H), 7.20 (s, 2H), 7.10 (dd, J = 8.3, 1.9 Hz, 1H), 6.90 (d, J = 8.7 Hz, 2H), 6.85 (s, 1H), 3.98 (s, 3H), 3.96 (s, 6H), 3.95 (s, 3H), 2.47 (s, 3H); ESI-MS: m/z, 477.15 $[M]^+$. HPLC: (0.1% phosphoric acid and 80% acetonitrile in water), 234nm, t_R = 8.75 min, 95.55%.

4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-7-yl 2-methoxy-5-methylbenzoate (**7b**)

Orange solid; yield: 54%; Mp: 181-183 °C; chemical formula: $C_{27}H_{24}O_8$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 7.5 Hz, 2H), 7.41 (t, *J* = 10.0 Hz, 1H), 7.36 (s, 1H), 7.21 (s, 2H), 7.12 (d, *J* = 8.2 Hz, 1H), 7.00 (d, *J* = 8.4 Hz, 1H), 6.86 (s, 1H), 4.11 – 3.87 (m, 12H), 2.44 (d, *J* = 32.8 Hz, 3H); ESI-MS: m/z, 477.15 $[M]^+$. HPLC: (0.1% phosphoric acid and 80% acetonitrile in water), 234 nm, t_R = 8.840 min, 94.83%.

4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-7-yl 4-bromo-2-methoxybenzoate (**7c**)

Yellow solid; yield: 58%; Mp: 177-180 °C; chemical formula: $C_{26}H_{21}BrO_8$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 – 7.81 (m, 2H), 7.32 (s, 1H), 7.23 (d, *J* = 6.7 Hz, 2H), 7.16 (d, *J* = 9.9 Hz, 2H), 7.08 (d, *J* = 8.3 Hz, 1H), 6.84 (s, 1H), 3.97 (s, 3H), 3.93 (d, *J* = 5.6 Hz, 9H); ESI-MS: m/z, 441.05 $[M]^+$. HPLC: (0.1% phosphoric acid and 85% acetonitrile in water), 234 nm, t_R = 8.292 min, 91.68%.

4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-7-yl 5-bromo-2-methoxybenzoate (**7d**)

Yellow solid; yield: 68%; Mp: 176-177 °C; chemical formula: $C_{26}H_{21}BrO_8$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (dd, *J* = 6.4, 2.6 Hz, 1H), 7.89 (d, *J* = 8.3 Hz, 1H), 7.70 (ddd, *J* = 8.6, 6.4, 2.5 Hz, 1H), 7.34 (d, *J* = 1.8 Hz, 1H), 7.20 (s, 2H), 7.11 (dd, *J* = 8.3, 1.9 Hz, 1H), 7.01 – 6.96 (m, 1H), 6.86 (s, 1H), 3.98 (s, 3H), 3.97 – 3.95 (m, 6H), 3.95 (s, 3H); ESI-MS: m/z, 541.05 $[M]^+$. HPLC: (0.1% phosphoric acid and 80% acetonitrile in water), 234 nm, t_R = 10.532 min, 92.90%.

4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-7-yl 4-chloro-2-methoxybenzoate (**7e**)

Yellow solid; yield: 64%; Mp: 173-175 °C; chemical formula: $C_{26}H_{21}ClO_8$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 – 8.00 (m, 1H), 7.88 (d, *J* = 8.3 Hz, 1H), 7.34 (d, *J* = 1.8 Hz, 1H), 7.22 – 7.16 (m, 2H), 7.13 – 7.06 (m, 3H), 6.86 (s, 1H), 4.00 (d, *J* = 4.4 Hz, 3H), 3.96 (s, 6H), 3.95 (s, 3H); ESI-MS: m/z, 497.10 $[M]^+$. HPLC: (0.1% phosphoric acid and 80% acetonitrile in water), 234 nm, t_R = 9.759 min, 94.44%.

4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-7-yl 5-chloro-2-methoxybenzoate (**7f**)

Yellow solid; yield: 70%; Mp: 179-181 °C; chemical formula: $C_{26}H_{21}ClO_8$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (dd, *J* = 6.0, 2.8 Hz, 1H), 7.89 (d, *J* = 8.3 Hz, 1H), 7.57 (dd, *J* = 9.0, 2.7 Hz, 1H), 7.34 (d, *J* = 1.8 Hz, 1H), 7.19 (d, *J* = 9.3 Hz, 2H), 7.11 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.04 (dd, *J* = 9.0, 3.2 Hz, 1H), 6.86 (s, 1H), 3.98 (d, *J* = 2.9 Hz, 3H), 3.98 – 3.95 (m, 6H), 3.95 (s, 3H); ESI-MS: m/z, 497.10 $[M]^+$. HPLC: (0.1% phosphoric acid and 80% acetonitrile in water), 234 nm, t_R = 9.861 min, 96.07%.

4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-7-yl 2-methoxybenzoate (**7g**)

Yellow solid; yield: 75%; Mp: 186-188 °C; chemical formula: $C_{26}H_{22}O_8$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 – 8.00 (m, 1H), 7.86 (dd, *J* = 11.4, 6.5 Hz, 1H), 7.69 – 7.56 (m, 1H), 7.36 (d, *J* = 1.8 Hz, 1H), 7.18 (d, *J* = 12.2 Hz, 2H), 7.14 – 7.06 (m, 3H), 6.91 – 6.80 (m, 1H), 4.00 (d, *J* = 3.7 Hz, 3H), 3.96 (s, 6H), 3.95 (s, 3H); ESI-MS: m/z, 463.13 $[M]^+$. HPLC: (0.1% phosphoric acid and 80% acetonitrile in water), 234 nm, t_R = 7.195 min, 97.18%.

5-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-7-yl 2,3,5-trichloro-6-methoxybenzoate (**7h**)

Yellow solid; yield: 61%; Mp: 204-206 °C; chemical formula: $C_{26}H_{19}Cl_3O_8$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (t, *J* = 8.8 Hz, 1H), 7.70 (s, 1H), 7.35 (d, *J* = 1.6 Hz, 1H), 7.23 (s, 2H), 7.18 (dt, *J* = 11.0, 5.5 Hz, 1H), 6.91 (s, 1H), 4.06 (s, 3H), 4.01 (s, 6H), 3.98 (s, 3H); ESI-MS: m/z, 565.02 $[M]^+$. HPLC: (0.1% phosphoric acid and 80% acetonitrile in water), 234 nm, t_R = 15.402 min, 89.47%.

2.2 Synthesis of compounds 10a-10x

methyl 4-methyl-2-(2-((4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-7-yl)oxy)ethoxy)benzoate (**10a**)

Yellow solid; yield: 59%; Mp: 151-153 °C; chemical formula: $C_{29}H_{28}O_9$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (dd, *J* = 8.4, 2.3 Hz, 2H), 7.20 (s, 2H), 6.91 – 6.82 (m, 4H), 6.79 (s, 1H), 4.58 – 4.50 (m, 2H), 4.46 (t, *J* = 4.9 Hz, 2H), 3.98 (s, 6H), 3.94 (s, 3H), 3.84 (s, 3H), 2.42 (s, 3H); ESI-MS: m/z, 521.18 [M]+. HPLC: (0.1% phosphoric acid and 85% acetonitrile in water), 234 nm, t_R = 6.172 min, 94.34%.

methyl 5-methyl-2-(2-((4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-7-yl)oxy)ethoxy)benzoate (**10b**)

Yellow solid; yield: 48%; Mp: 247-249 °C; chemical formula: $C_{29}H_{28}O_9$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.4 Hz, 1H), 7.61 (s, 1H), 7.29 (s, 1H), 7.17 (s, 2H), 6.96 (d, *J* = 8.3 Hz, 1H), 6.82 (d, *J* = 13.7 Hz, 2H), 6.76 (s, 1H), 4.52 – 4.39 (m, 4H), 3.95 (s, 6H), 3.92 (s, 3H), 3.83 (s, 3H), 2.32 (s, 3H); ESI-MS: m/z, 521.18 $[M]^+$. HPLC: (0.1% phosphoric acid and 85% acetonitrile in water), 234 nm, t_R = 6.243 min, 87.04%.

methyl 4-bromo-2-(2-((4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-7-yl)oxy)ethoxy)benzoate (**10c**)

Yellow solid; yield: 50%; Mp: 149-151 °C; chemical formula: $C_{28}H_{25}BrO_9$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 – 7.73 (m, 1H), 7.70 (s, 1H), 7.26 – 7.18 (m, 4H), 6.88 – 6.78 (m, 3H), 4.51 (d, *J* = 24.1 Hz, 4H), 3.99 (d, *J* = 6.9 Hz,

6H), 3.95 (s, 3H), 3.85 (d, *J* = 8.0 Hz, 3H); ESI-MS: m/z, 585.07 $[M]^+$. HPLC: (0.1% phosphoric acid and 85% acetonitrile in water), 234 nm, t_R = 7.066 min, 92.30%.

methyl 5-bromo-2-(2-((4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-7-yl)oxy)ethoxy)benzoate (**10d**)

Yellow solid; yield: 61%; Mp: 166-168 °C; chemical formula: $C_{28}H_{25}BrO_9$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 2.6 Hz, 1H), 7.75 (d, *J* = 8.4 Hz, 1H), 7.61 (dd, *J* = 8.8, 2.6 Hz, 1H), 7.19 (s, 2H), 6.98 (d, *J* = 8.8 Hz, 1H), 6.87 – 6.81 (m, 2H), 6.79 (s, 1H), 4.53 (dd, *J* = 5.6, 3.7 Hz, 2H), 4.46 (dd, *J* = 5.6, 3.7 Hz, 2H), 3.98 (s, 6H), 3.94 (s, 3H), 3.86 (s, 3H); ESI-MS: m/z, 585.07 $[M]^+$. HPLC: (0.1% phosphoric acid and 85% acetonitrile in water), 234 nm, t_R = 7.132 min, 91.00%.

methyl 4-chloro-2-(2-((4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-7-yl)oxy)ethoxy)benzoate (**10e**)

Yellow solid; yield: 63%; Mp: 168-170 °C; chemical formula: $C_{28}H_{25}ClO_9$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (dd, *J* = 15.9, 8.4 Hz, 2H), 7.20 (s, 2H), 7.11 – 7.03 (m, 2H), 6.89 – 6.82 (m, 2H), 6.79 (s, 1H), 4.57 – 4.50 (m, 2H), 4.50 – 4.45 (m, 2H), 3.98 (s, 6H), 3.94 (s, 3H), 3.84 (s, 3H); ESI-MS: m/z, 541.12 $[M]^+$. HPLC: (0.1% phosphoric acid and 85% acetonitrile in water), 234 nm, t_R = 6.725 min, 97.84%.

methyl 5-chloro-2-(2-((4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-7-yl)oxy)ethoxy)benzoate (**10f**)

Yellow solid; yield: 69%; Mp: 167-169 °C; chemical formula: $C_{28}H_{25}ClO_9$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 2.7 Hz, 1H), 7.75 (d, *J* = 8.4 Hz, 1H), 7.47 (dd, *J* = 8.9, 2.7 Hz, 1H), 7.19 (s, 2H), 7.03 (d, *J* = 8.9 Hz, 1H), 6.87 – 6.81 (m, 2H), 6.79 (s, 1H), 4.55 – 4.50 (m, 2H), 4.46 (dd, *J* = 5.4, 3.6 Hz, 2H), 3.98 (s, 6H), 3.94 (s, 3H), 3.86 (s, 3H); ESI-MS: m/z, 541.12 $[M]^+$. HPLC: (0.1% phosphoric acid and 80% acetonitrile in water), 234 nm, t_R = 8.399 min, 89.39%.

methyl 2-(2-((4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-7-yl)oxy)ethoxy)benzoate (**10g**)

Yellow solid; yield: 61%; Mp: 164-165 °C; chemical formula: $C_{28}H_{26}O_9$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.75 (d, *J* = 8.5 Hz, 1H), 7.55 – 7.48 (m, 1H), 7.20 (s, 2H), 7.07 (dd, *J* = 7.9, 5.2 Hz, 2H), 6.89 – 6.82 (m, 2H), 6.79 (s, 1H), 4.56 – 4.51 (m, 2H), 4.51 – 4.46 (m, 2H), 3.98 (s, 6H), 3.94 (s, 3H), 3.86 (s, 3H); ESI-MS: m/z, 507.16 $[M]^+$. HPLC: (0.1% phosphoric acid and 85% acetonitrile in water), 234 nm, t_R = 5.215 min, 90.58%.

methyl 2,3,5-trichloro-6-(2-((4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-7-yl)oxy)ethoxy)benzoate (**10h**)

Yellow solid; yield: 40%; Mp: 157-160 °C; chemical formula: $C_{28}H_{23}Cl_3O_9$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.2 Hz, 1H), 7.61 (s, 1H), 7.18 (s, 2H), 6.88 – 6.76 (m, 3H), 4.46 (d, *J* = 28.7 Hz, 4H), 4.04 – 3.91 (m, 12H); ESI-MS: m/z, 609.04 $[M]^+$. HPLC: (0.1% phosphoric acid and 85% acetonitrile in water), 234 nm, t_R = 11.186 min, 92.57%.

methyl 4-methyl-2-(3-((4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-7-yl)oxy)propoxy)benzoate (**10i**)

Yellow solid; yield: 66%; Mp: 128-130 °C; chemical formula: $C_{30}H_{30}O_9$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 – 7.69 (m, 2H), 7.18 (s, 2H), 6.85 – 6.78 (m, 4H), 6.77 (s, 1H), 4.41 (t, *J* = 6.1 Hz, 2H), 4.26 (t, *J* = 5.7 Hz, 2H), 3.98 (d, *J* = 10.4 Hz, 6H), 3.94 (s, 3H), 3.87 (d, *J* = 7.1 Hz, 3H), 2.44 – 2.39 (m, 3H), 2.37 (d, *J* = 5.8 Hz, 2H); ESI-MS: m/z, 535.19 $[M]^+$. HPLC: (0.1% phosphoric acid and 80% acetonitrile in water), 234 nm, t_R = 7.533 min, 85.11%.

methyl 5-methyl-2-(3-((4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-7-yl)oxy)propoxy)benzoate (**10j**)

Orange solid; yield: 54%; Mp: 161-163 °C; chemical formula: $C_{30}H_{30}O_9$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.7 Hz, 1H), 7.62 (d, *J* = 12.9 Hz, 1H), 7.27 (s, 1H), 7.18 (s, 2H), 6.92 (d, *J* = 8.4 Hz, 1H), 6.85 – 6.74 (m, 3H), 4.40 (t, *J* = 5.4 Hz, 2H), 4.25 (s, 2H), 3.97 (s, 6H), 3.94 (s, 3H), 3.88 (s, 3H), 2.45 – 2.35 (m, 2H), 2.32 (s, 3H); ESI-MS: m/z, 535.19 $[M]^+$. HPLC: (0.1% phosphoric acid and 80% acetonitrile in water), 234 nm, t_R = 7.57 min, 87.46%.

methyl 4-bromo-2-(3-((4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-7-yl)oxy)propoxy)benzoate (**10k**)

Yellow solid; yield: 51%; Mp: 147-149 °C; chemical formula: $C_{29}H_{27}BrO_9$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (t, *J* = 7.6 Hz, 2H), 7.14 (d, *J* = 12.4 Hz, 4H), 6.78 (d, *J* = 5.8 Hz, 2H), 6.74 (s, 1H), 4.37 (t, *J* = 5.7 Hz, 2H), 4.25 (t, *J* = 5.4 Hz, 2H), 3.95 (d, *J* = 9.9 Hz, 6H), 3.92 (s, 3H), 3.85 (s, 3H), 2.43 – 2.31 (m, 2H); ESI-MS: m/z, 599.09 $[M]^+$. HPLC: (0.1% phosphoric acid and 85% acetonitrile in water), 234 nm, t_R = 6.929 min, 95.75%.

methyl 5-bromo-2-(3-((4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-7-yl)oxy)propoxy)benzoate (**10l**)

Yellow solid; yield: 60%; Mp: 154-156 °C; chemical formula: $C_{29}H_{27}BrO_9$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 2.6 Hz, 1H), 7.72 (d, *J* = 9.2 Hz, 1H), 7.57 (dt, *J* = 8.2, 4.1 Hz, 1H), 7.18 (s, 2H), 6.91 (d, *J* = 8.9 Hz, 1H), 6.85 – 6.73 (m, 3H), 4.39 (t, *J* = 6.0 Hz, 2H), 4.25 (t, *J* = 5.7 Hz, 2H), 4.04 – 3.95 (m, 6H), 3.94 (s, 3H), 3.88 (s, 3H), 2.45 – 2.33 (m, 2H); ESI-MS: m/z, 599.09 $[M]^+$. HPLC: (0.1% phosphoric acid and 85% acetonitrile in water), 234 nm, t_R = 9.168 min, 96.26%.

methyl 4-chloro-2-(3-((4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-7-yl)oxy)propoxy)benzoate (**10m**)

Yellow solid; yield: 63%; Mp: 118-120°C; chemical formula: $C_{29}H_{27}ClO_9$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.2 Hz, 1H), 7.75 – 7.70 (m, 1H), 7.17 (s, 2H), 7.05 – 6.96 (m, 2H), 6.84 – 6.74 (m, 3H), 4.40 (t, *J* = 6.0 Hz, 2H), 4.27 (t, *J* = 5.7 Hz, 2H), 3.98 (d, *J* = 9.8 Hz, 6H), 3.94 (s, 3H), 3.88 (d, *J* = 6.5 Hz, 3H), 2.46 – 2.35 (m, 2H); ESI-MS: m/z, 555.14 $[M]^+$. HPLC: (0.1% phosphoric acid and 80% acetonitrile in water), 234 nm, t_R = 8.353 min, 91.54%.

methyl 5-chloro-2-(3-((4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-7-yl)oxy)propoxy)benzoate (**10n**)

Yellow solid; yield: 65%; Mp: 149-151 °C; chemical formula: $C_{29}H_{27}ClO_9$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d,

J = 2.4 Hz, 1H), 7.77 – 7.68 (m, 1H), 7.45 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.20 (s, 2H), 6.98 (d, *J* = 8.9 Hz, 1H), 6.85 – 6.77 (m, 3H), 4.48 – 4.34 (m, 2H), 4.28 (t, *J* = 5.7 Hz, 2H), 3.99 (s, 6H), 3.96 (s, 3H), 3.91 (s, 3H), 2.41 (p, *J* = 5.6 Hz, 2H); ESI-MS: m/z, 555.14 $[M]^+$. HPLC: (0.1% phosphoric acid and 85% acetonitrile in water), 234 nm, t_R = 8.616 min, 98.41%.

methyl 2-(3-((4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-7-yl)oxy)propoxy)benzoate (**10o**)

Yellow solid; yield: 60%; Mp: 135-138 °C; chemical formula: $C_{29}H_{28}O_9$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.72 (d, *J* = 8.5 Hz, 1H), 7.52 – 7.45 (m, 1H), 7.18 (s, 2H), 7.05 – 6.99 (m, 2H), 6.84 – 6.75 (m, 3H), 4.41 (t, *J* = 6.1 Hz, 2H), 4.28 (t, *J* = 5.7 Hz, 2H), 3.98 (d, *J* = 10.4 Hz, 6H), 3.94 (s, 3H), 3.89 (s, 3H), 2.40 (p, *J* = 5.7 Hz, 2H); ESI-MS: m/z, 521.18 $[M]^+$. HPLC: (0.1% phosphoric acid and 80% acetonitrile in water), 234 nm, t_R = 6.353 min, 92.67%.

methyl 2,3,5-trichloro-6-(3-((4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-7-yl)oxy)propoxy)benzoate (**10p**)

Yellow solid; yield: 42%; Mp: 153-155 °C; chemical formula: $C_{29}H_{25}Cl_3O_9$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.4 Hz, 1H), 7.57 (s, 1H), 7.19 (s, 2H), 6.81 (t, *J* = 8.5 Hz, 3H), 4.32 (dd, *J* = 15.7, 9.9 Hz, 4H), 3.97 (s, 6H), 3.95 (s, 3H), 3.92 (s, 3H), 2.31 (d, *J* = 4.6 Hz, 2H); ESI-MS: m/z, 623.06 $[M]^+$. HPLC: (0.1% phosphoric acid and 90% acetonitrile in water), 234 nm, t_R = 10.615 min, 84.57%.

methyl 4-methyl-2-(4-((4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-7-yl)oxy)butoxy)benzoate (**10q**)

Yellow solid; yield: 68%; Mp: 124-127 °C; chemical formula: $C_{31}H_{32}O_9$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 – 7.70 (m, 2H), 7.18 (s, 2H), 6.82 (d, *J* = 5.2 Hz, 1H), 6.81 – 6.79 (m, 2H), 6.78 (dd, *J* = 3.7, 2.0 Hz, 2H), 4.24 (t, *J* = 6.0 Hz, 2H), 4.15 (t, *J* = 5.7 Hz, 2H), 3.97 (s, 6H), 3.94 (s, 3H), 3.87 (s, 3H), 2.39 (s, 3H), 2.11 (ddd, *J* = 12.8, 10.5, 6.3 Hz, 4H); ESI-MS: m/z, 549.21 $[M]^+$. HPLC: (0.1% phosphoric acid and 85% acetonitrile in water), 234 nm, t_R = 8.988 min, 90.45%.

methyl 5-methyl-2-(4-((4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-7-yl)oxy)butoxy)benzoate (**10r**)

Yellow solid; yield: 59%; Mp: 143-147 °C; chemical formula: $C_{31}H_{32}O_9$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 9.1 Hz, 1H), 7.60 (s, 1H), 7.24 (s, 1H), 7.16 (s, 2H), 6.87 (d, *J* = 8.4 Hz, 1H), 6.75 (s, 3H), 4.21 (t, *J* = 5.6 Hz, 2H), 4.11 (t, *J* = 5.0 Hz, 2H), 3.94 (s, 6H), 3.92 (s, 3H), 3.86 (d, *J* = 5.9 Hz, 3H), 2.30 (s, 3H), 2.14 – 2.02 (m, 4H); ESI-MS: m/z, 549.21 $[M]^+$. HPLC: (0.1% phosphoric acid and 85% acetonitrile in water), 234 nm, t_R = 9.198 min, 95.91%.

methyl 4-bromo-2-(4-((4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-7-yl)oxy)butoxy)benzoate (**10s**)

Yellow solid; yield: 53%; Mp: 133-136 °C; chemical formula: $C_{30}H_{29}BrO_9$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.3 Hz, 1H), 7.69 (s, 1H), 7.16 (d, *J* = 14.2 Hz, 4H), 6.77 (s, 3H), 4.19 (d, *J* = 33.3 Hz, 4H), 3.97 (t, *J* = 10.3

Hz, 9H), 3.88 (s, 3H), 2.12 (s, 4H); ESI-MS: m/z, 613.10 $[M]^+$. HPLC: (0.1% phosphoric acid and 80% acetonitrile in water), 234 nm, t_R = 14.109 min, 88.84%.

methyl 5-bromo-2-(4-((4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-7-yl)oxy)butoxy)benzoate (**10t**)

Yellow solid; yield: 64%; Mp: 163-166 °C; chemical formula: $C_{30}H_{29}BrO_9$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 2.6 Hz, 1H), 7.75 – 7.70 (m, 1H), 7.60 – 7.53 (m, 1H), 7.18 (s, 2H), 6.88 (d, *J* = 8.9 Hz, 1H), 6.78 (dd, *J* = 6.6, 2.2 Hz, 3H), 4.22 (t, *J* = 5.8 Hz, 2H), 4.14 (t, *J* = 5.5 Hz, 2H), 3.97 (s, 6H), 3.94 (s, 3H), 3.89 (s, 3H), 2.10 (dt, *J* = 17.9, 6.3 Hz, 4H); ESI-MS: m/z, 613.10 $[M]^+$. HPLC: (0.1% phosphoric acid and 85% acetonitrile in water), 234 nm, t_R = 10.801 min, 95.93%.

methyl 4-chloro-2-(4-((4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-7-yl)oxy)butoxy)benzoate (**10u**)

Yellow solid; yield: 70%; Mp: 130-133 °C; chemical formula: $C_{30}H_{29}ClO_9$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 – 7.76 (m, 1H), 7.72 (d, *J* = 9.1 Hz, 1H), 7.18 (s, 2H), 7.03 – 6.96 (m, 2H), 6.82 – 6.74 (m, 3H), 4.23 (t, *J* = 5.6 Hz, 2H), 4.15 (t, *J* = 5.4 Hz, 2H), 3.97 (s, 6H), 3.94 (s, 3H), 3.88 (s, 3H), 2.11 (dt, *J* = 12.0, 5.0 Hz, 4H); ESI-MS: m/z, 569.15 $[M]^+$. HPLC: (0.1% phosphoric acid and 85% acetonitrile in water), 234 nm, t_R = 10.160 min, 95.16%.

methyl 5-chloro-2-(4-((4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-7-yl)oxy)butoxy)benzoate (**10v**)

Yellow solid; yield: 63%; Mp: 146–149 °C; chemical formula: $C_{30}H_{29}ClO_9$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 2.7 Hz, 1H), 7.73 (d, *J* = 9.2 Hz, 1H), 7.43 (dd, *J* = 8.9, 2.7 Hz, 1H), 7.18 (s, 2H), 6.93 (d, *J* = 8.9 Hz, 1H), 6.78 (dd, *J* = 6.9, 2.0 Hz, 3H), 4.23 (t, *J* = 5.8 Hz, 2H), 4.14 (t, *J* = 5.6 Hz, 2H), 3.98 (d, *J* = 8.4 Hz, 6H), 3.94 (s, 3H), 3.89 (s, 3H), 2.10 (dt, *J* = 12.5, 7.0 Hz, 4H); ESI-MS: m/z, 569.15 $[M]^+$. HPLC: (0.1% phosphoric acid and 85% acetonitrile in water), 234 nm, t_R = 10.044 min, 98.18%.

methyl 2-(4-((4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-7-yl)oxy)butoxy)benzoate (**10w**)

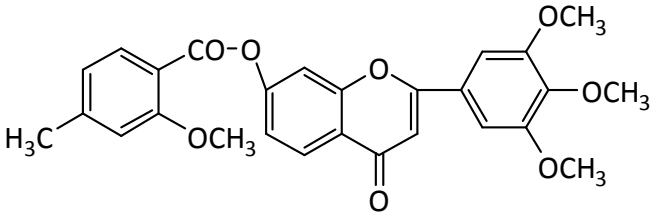
Yellow solid; yield: 68%; Mp: 127-130 °C; chemical formula: $C_{30}H_{30}O_9$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.74 – 7.70 (m, 1H), 7.51 – 7.44 (m, 1H), 7.18 (s, 2H), 7.01 (t, *J* = 7.8 Hz, 2H), 6.83 – 6.75 (m, 3H), 4.24 (t, *J* = 5.9 Hz, 2H), 4.16 (t, *J* = 5.6 Hz, 2H), 3.98 (d, *J* = 11.3 Hz, 6H), 3.94 (s, 3H), 3.89 (s, 3H), 2.11 (ddd, *J* = 12.7, 9.9, 4.6 Hz, 4H); ESI-MS: m/z, 535.19 $[M]^+$. HPLC: (0.1% phosphoric acid and 85% acetonitrile in water), 234 nm, t_R = 7.590 min, 95.39%.

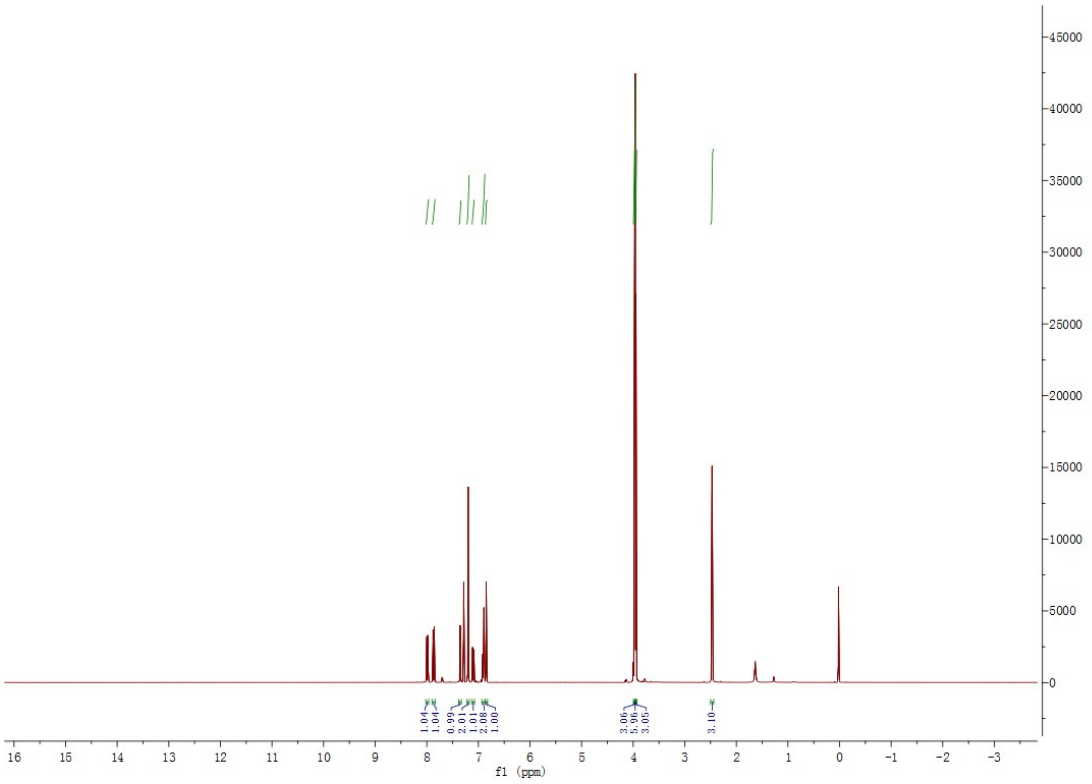
methyl 2,3,5-trichloro-6-(4-((4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-7-yl)oxy)butoxy)benzoate (**10x**)

Yellow solid; yield: 46%; Mp: 142-144 °C; chemical formula: $C_{30}H_{27}Cl_3O_9$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.5 Hz, 1H), 7.58 (s, 1H), 7.19 (s, 2H), 6.79 (d, *J* = 12.6 Hz, 3H), 4.17 (dd, *J* = 10.9, 5.2 Hz, 4H), 3.98 (d, *J* = 4.6 Hz, 9H), 3.95 (s, 3H), 2.03 (dd, *J* = 25.2, 6.1 Hz, 4H); ESI-MS: m/z, 637.08 $[M]^+$. HPLC: (0.1% phosphoric acid and 85% acetonitrile in water), 234 nm, t_R = 18.405 min, 86.75 %.

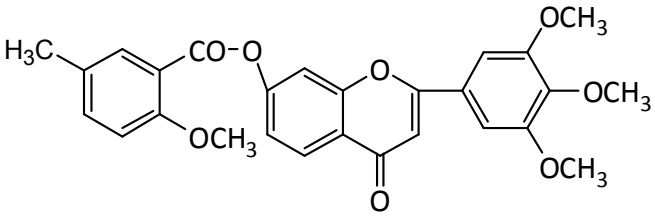
3. ^{1}H NMR spectra

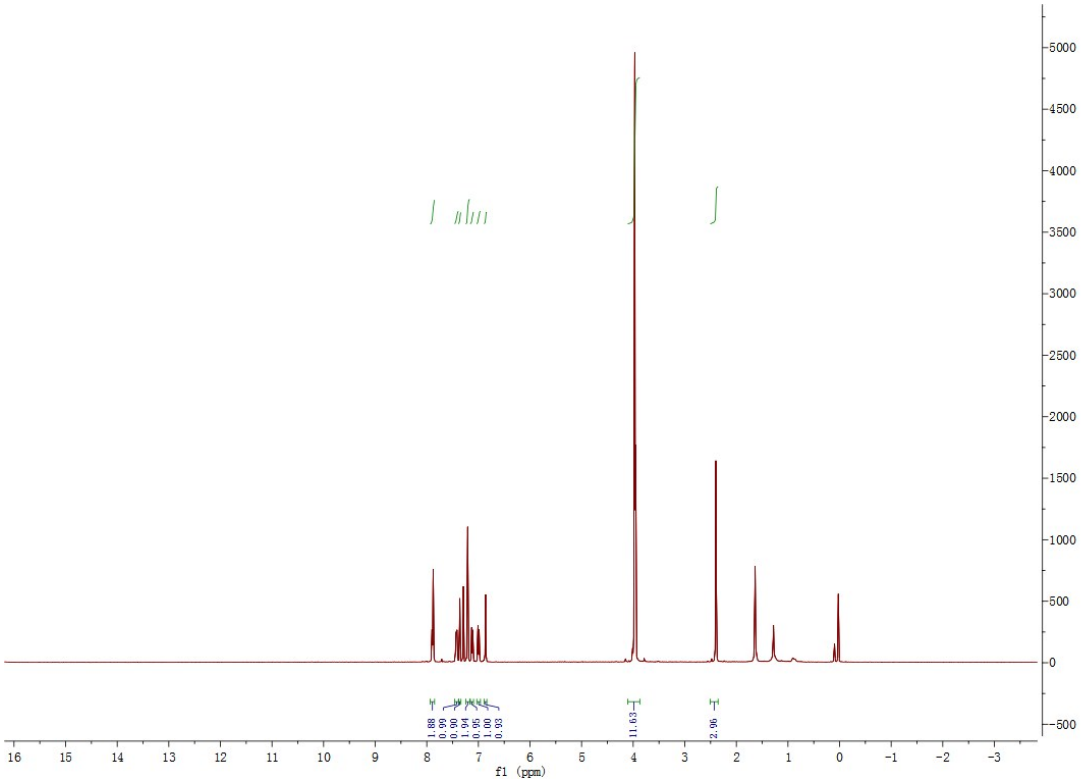
4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-7-yl 2-methoxy-4-methylbenzoate (**7a**)



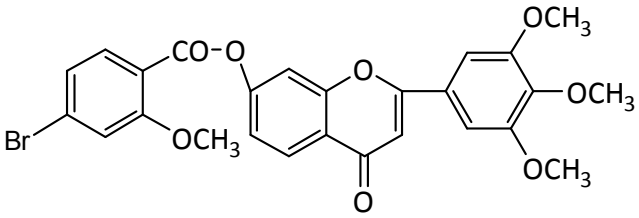


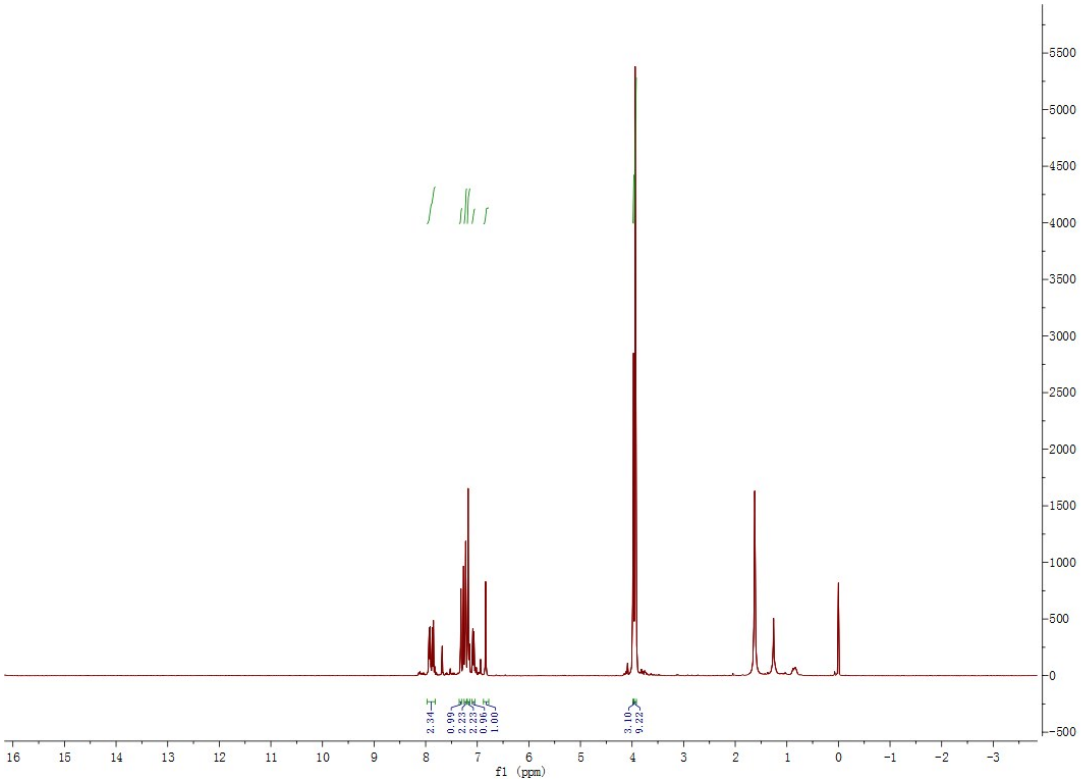
4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-7-yl 2-methoxy-5-methylbenzoate (**7b**)



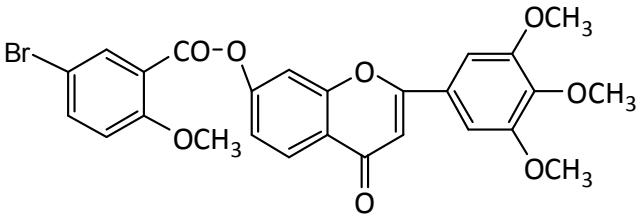


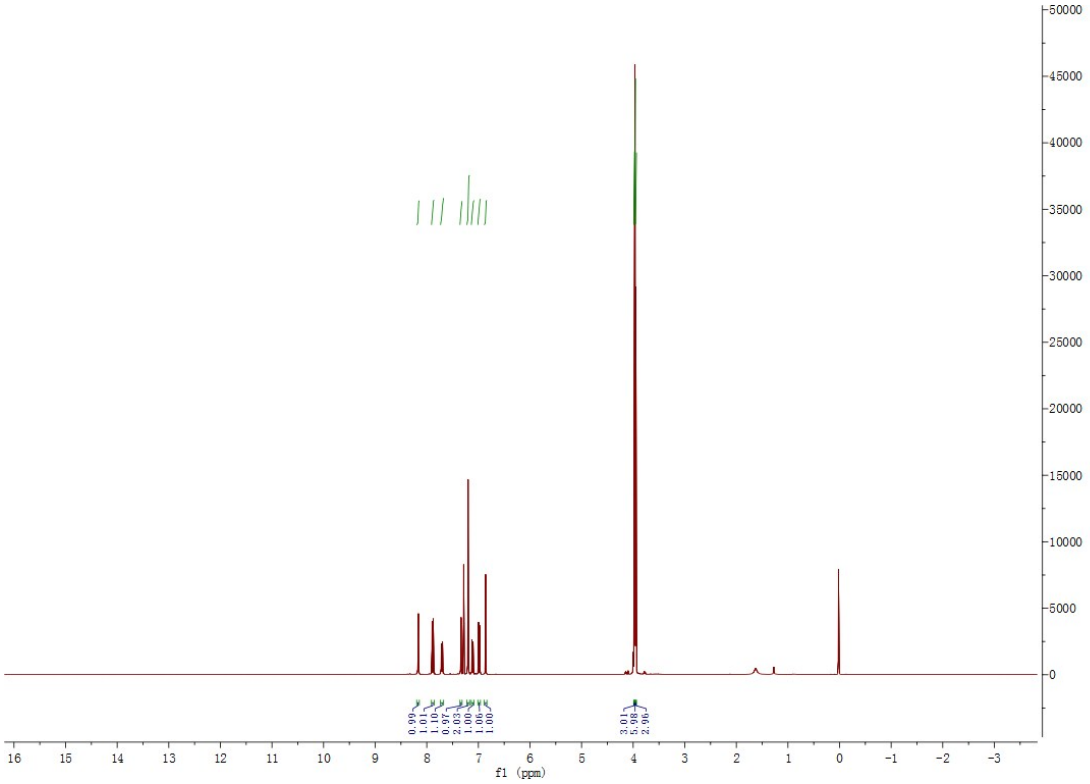
4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-7-yl 4-bromo-2-methoxybenzoate (**7c**)



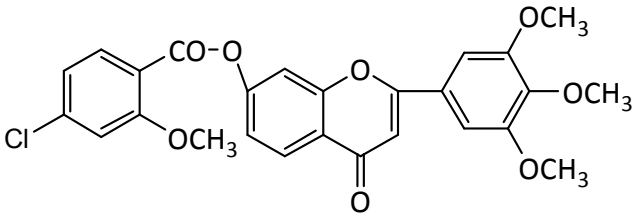


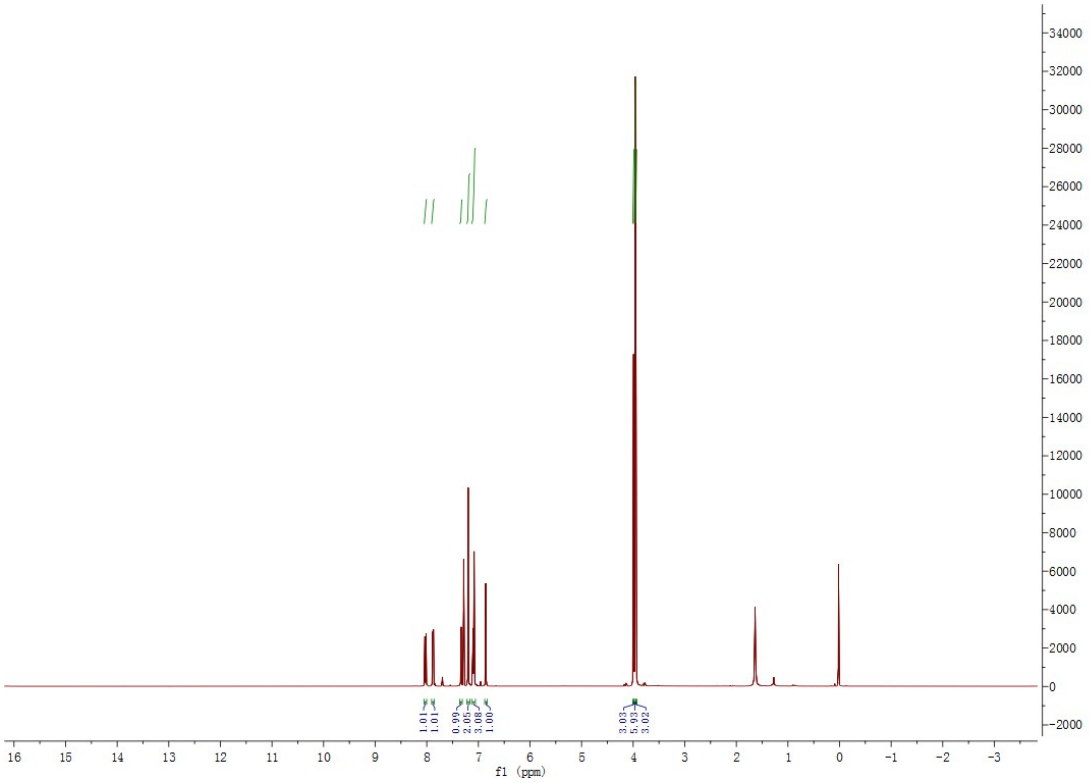
4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-7-yl 5-bromo-2-methoxybenzoate (**7d**)



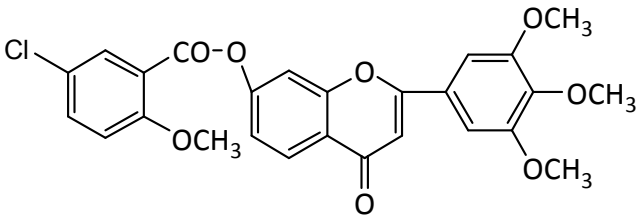


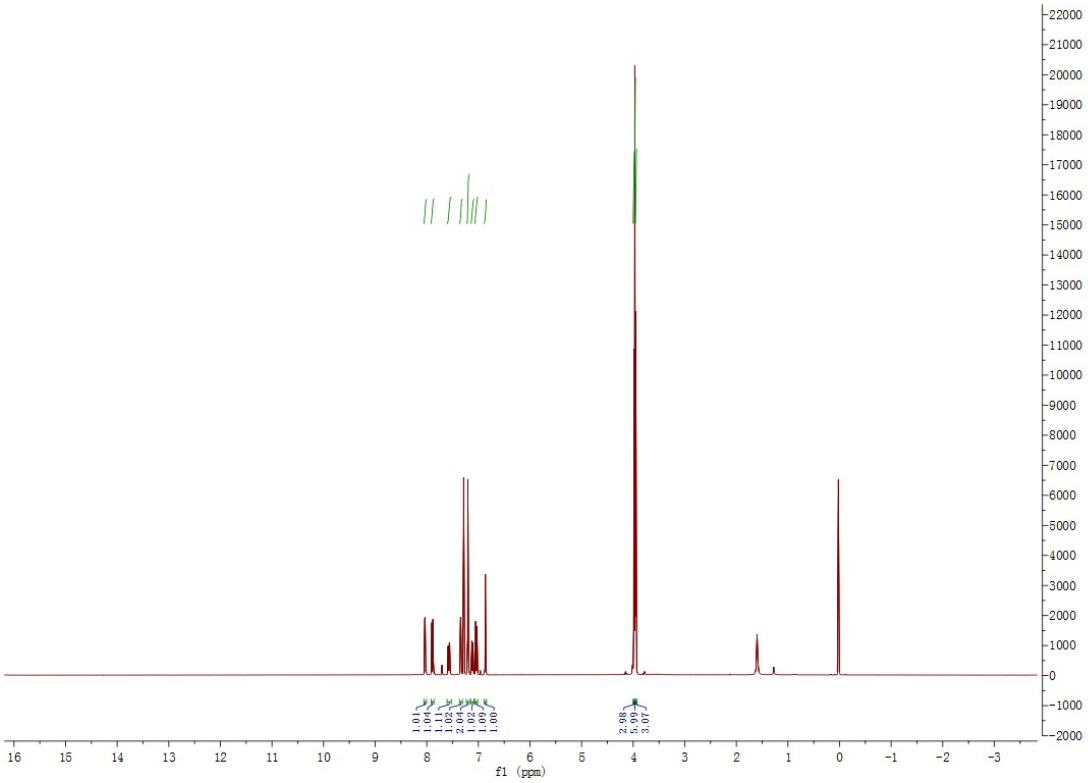
4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-7-yl 4-chloro-2-methoxybenzoate (**7e**)



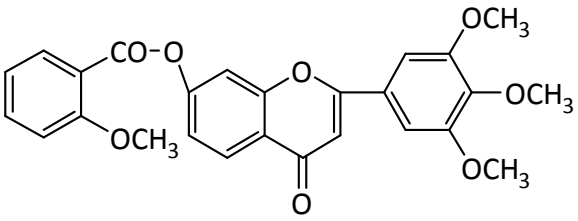


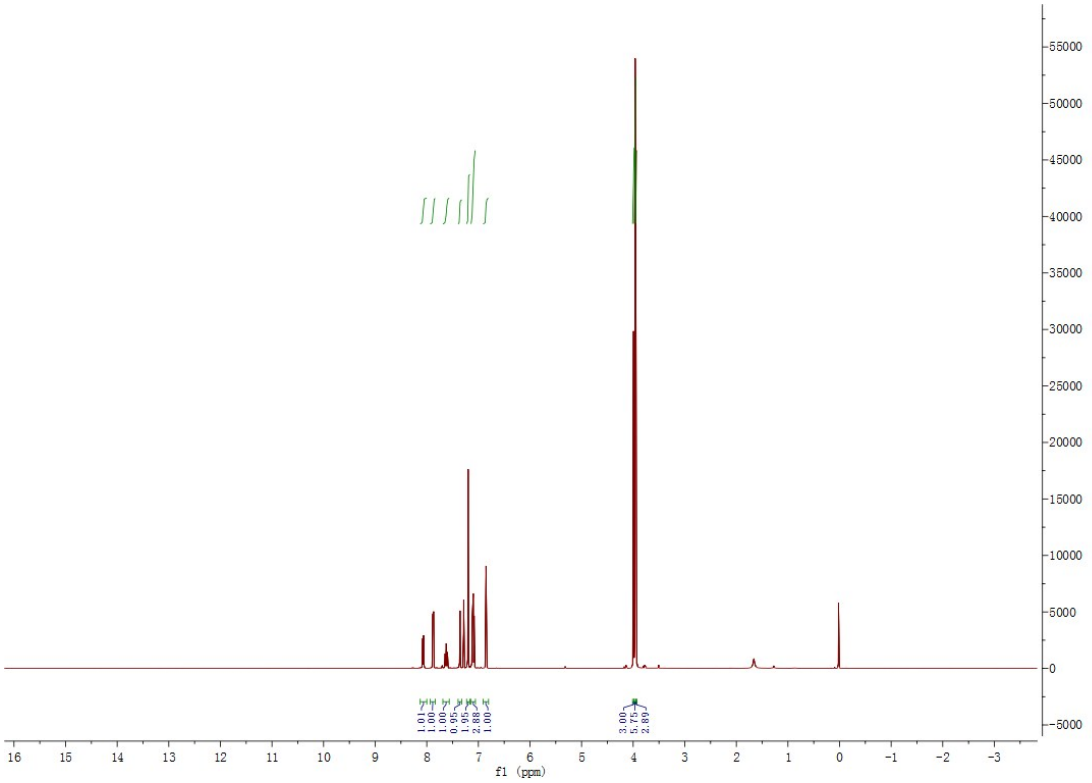
4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-7-yl 5-chloro-2-methoxybenzoate (**7f**)



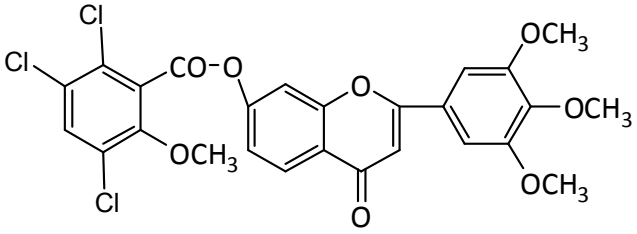


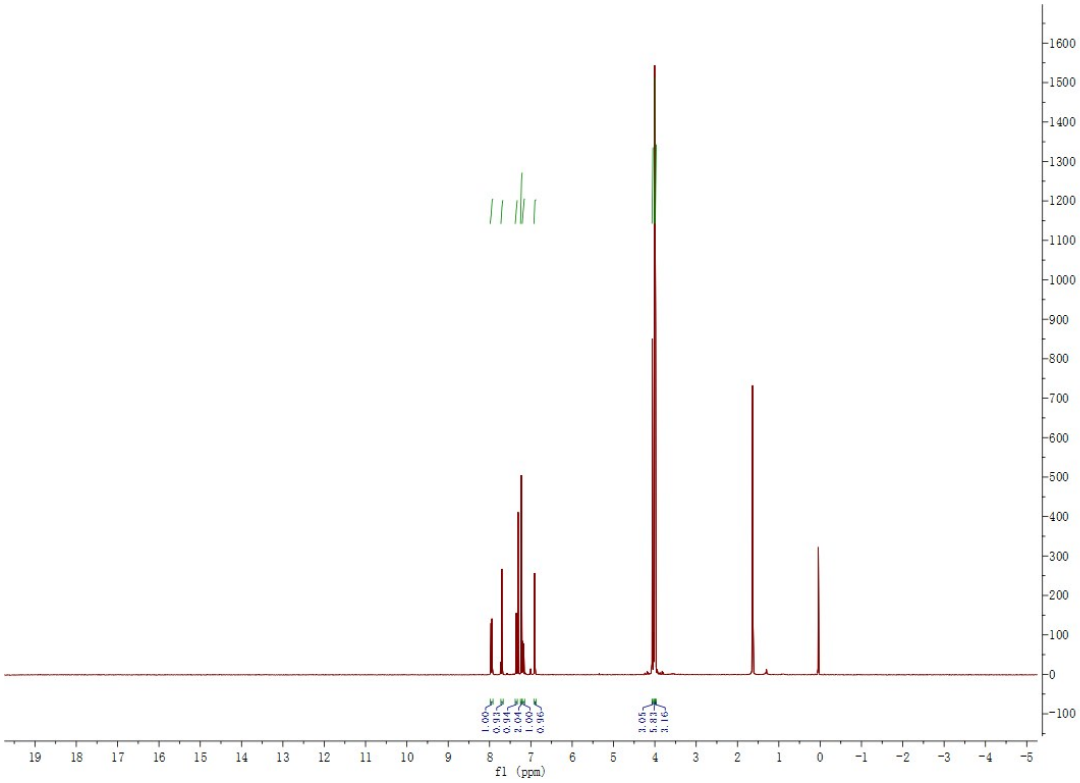
4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-7-yl 2-methoxybenzoate (**7g**)



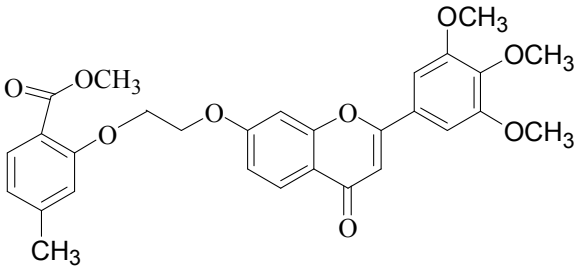


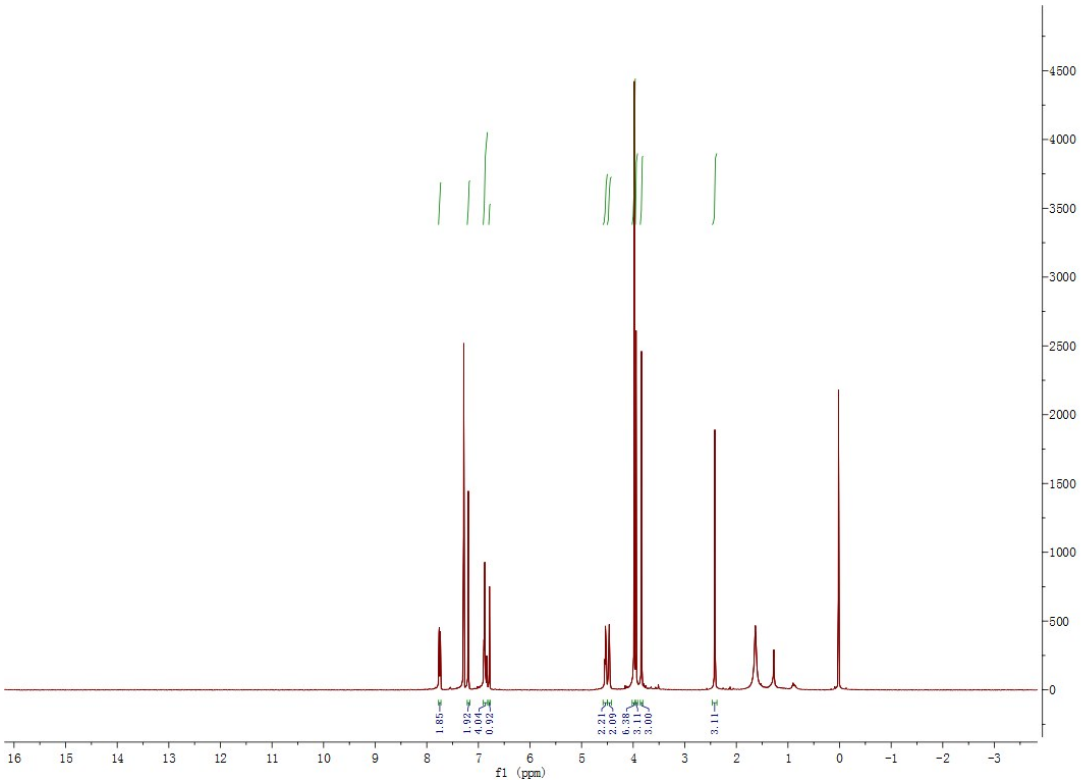
4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-7-yl 2,3,5-trichloro-6-methoxybenzoate (**7h**)



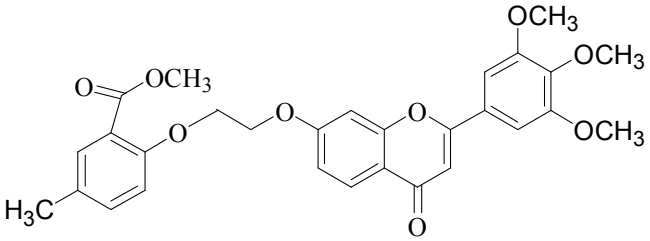


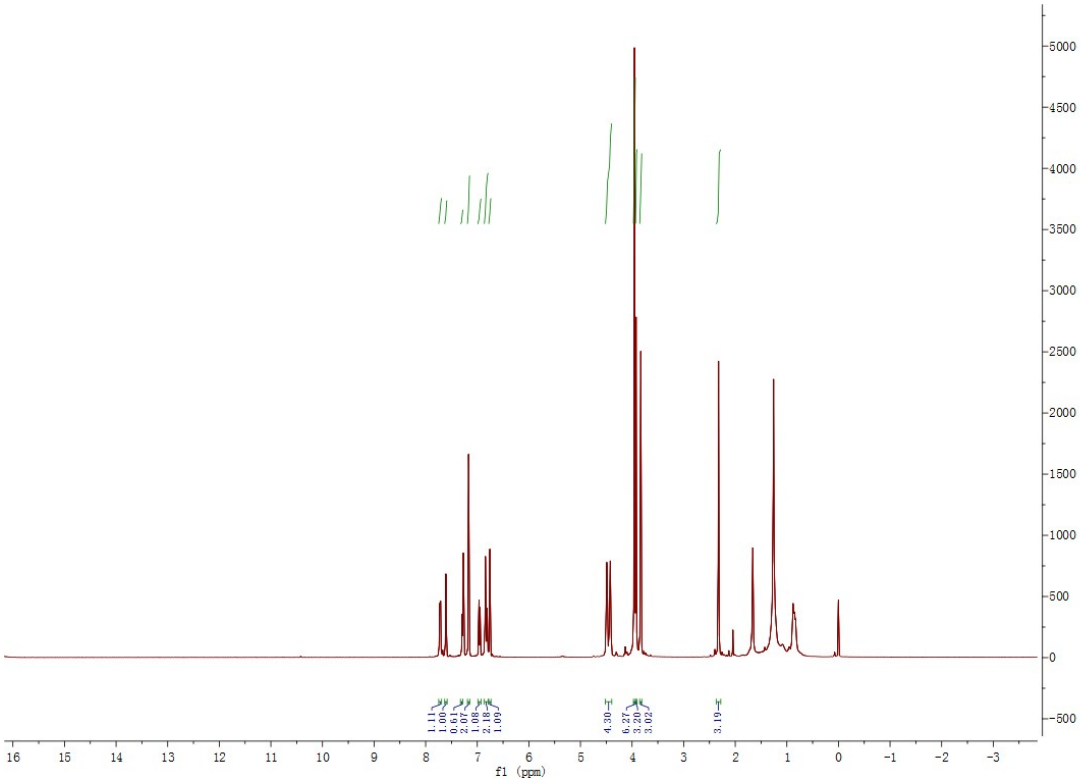
methyl 4-methyl-2-(2-((4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-7-yl)oxy)ethoxy)benzoate (**10a**)



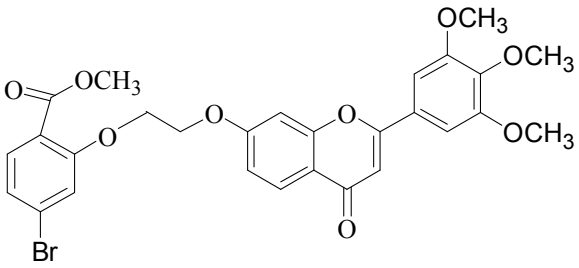


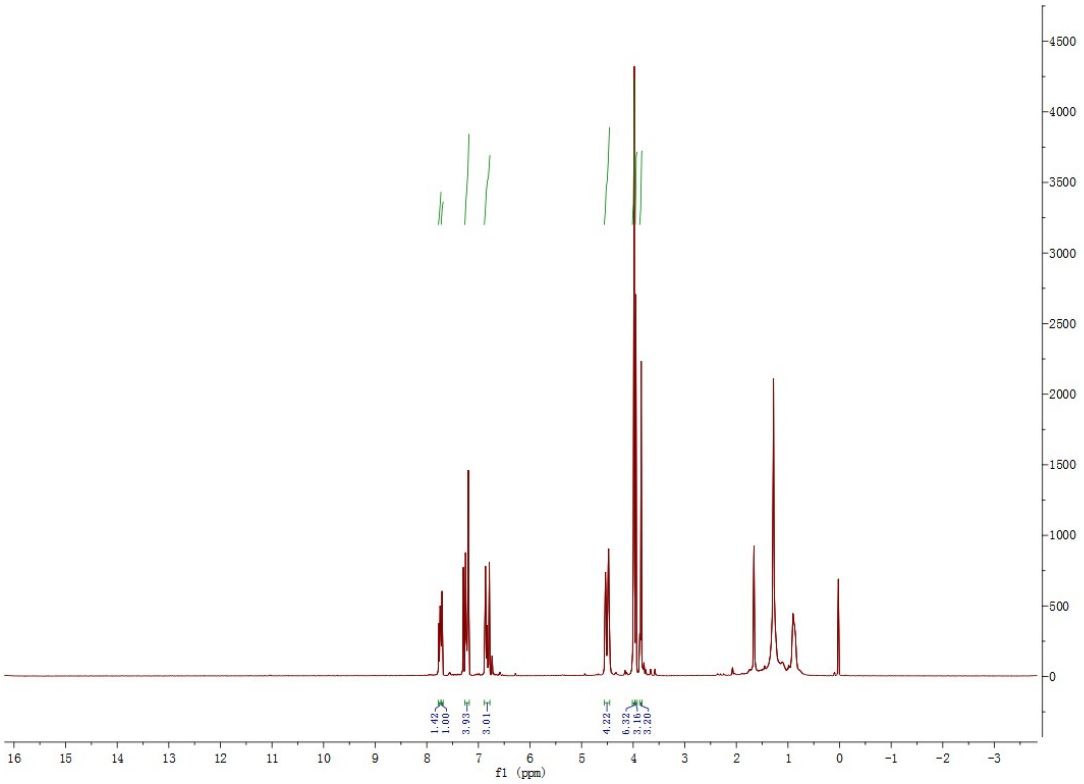
methyl 5-methyl-2-(2-((4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-7-yl)oxy)ethoxy)benzoate (**10b**)



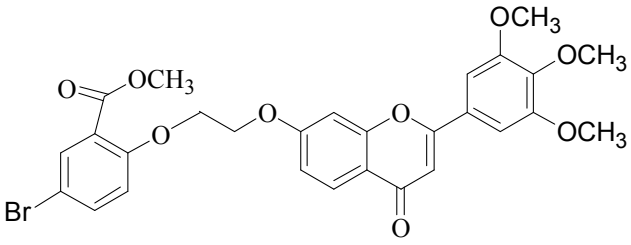


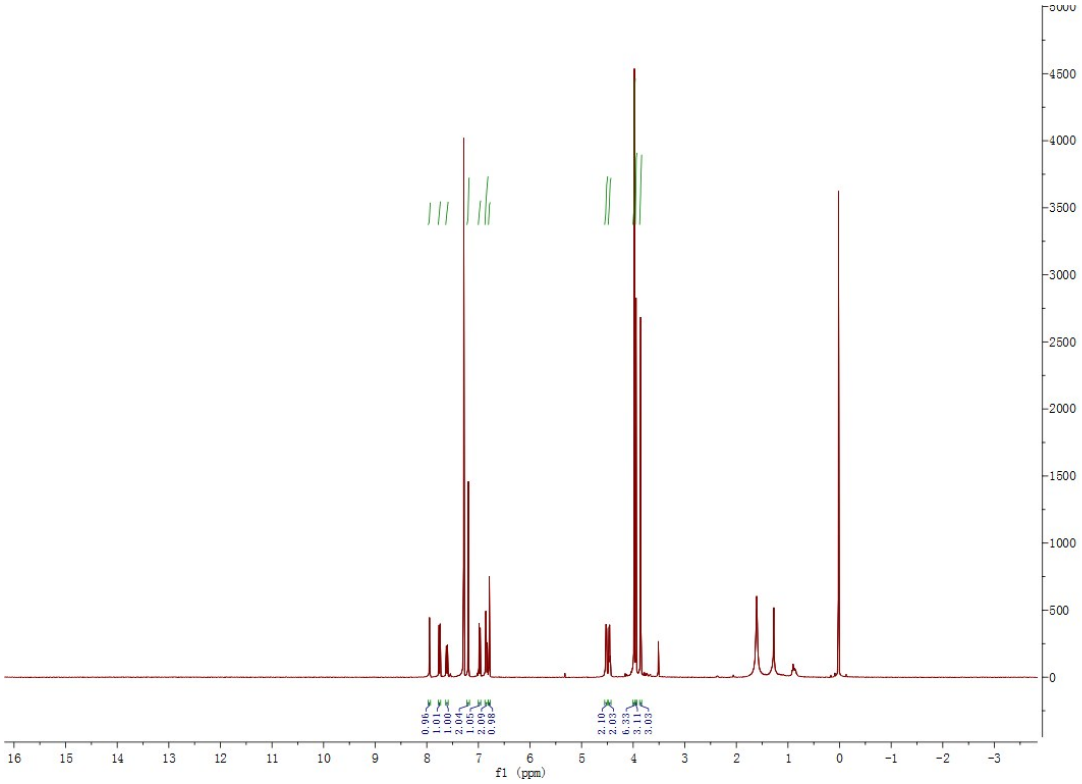
methyl 4-bromo-2-(2-((4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-7-yl)oxy)ethoxy)benzoate (**10c**)



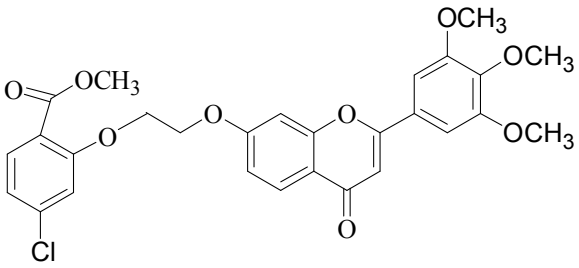


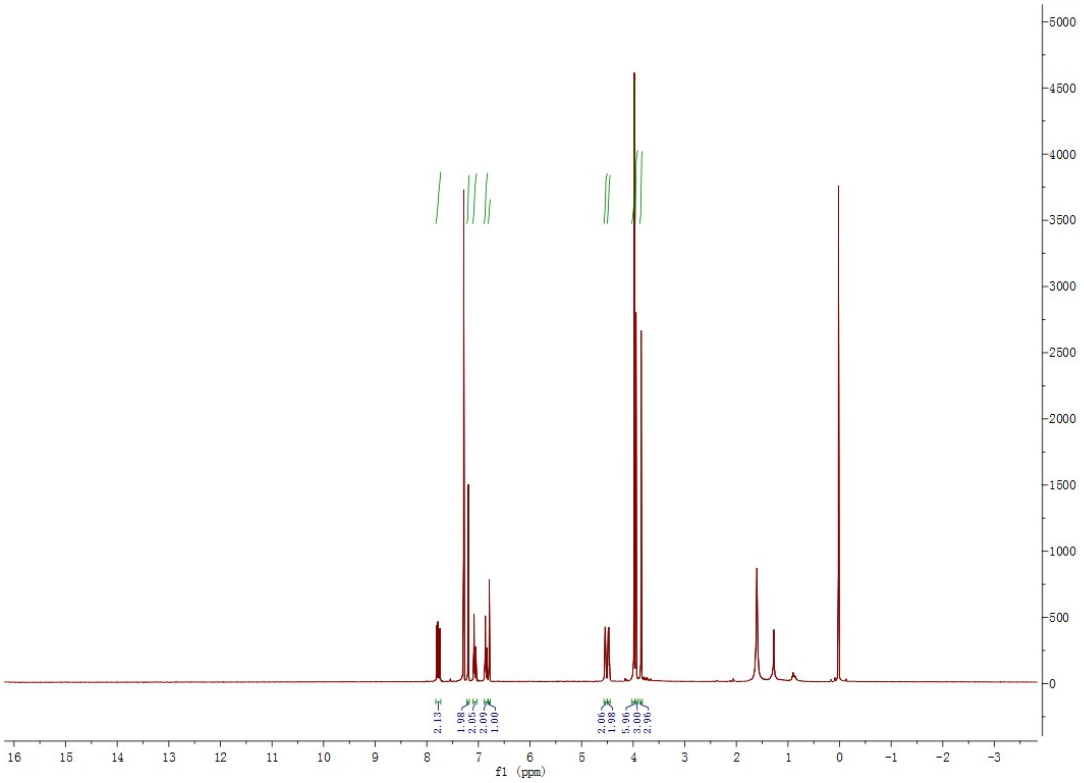
methyl 5-bromo-2-(2-((4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-7-yl)oxy)ethoxy)benzoate (**10d**)



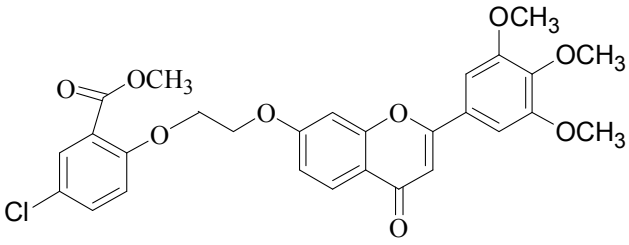


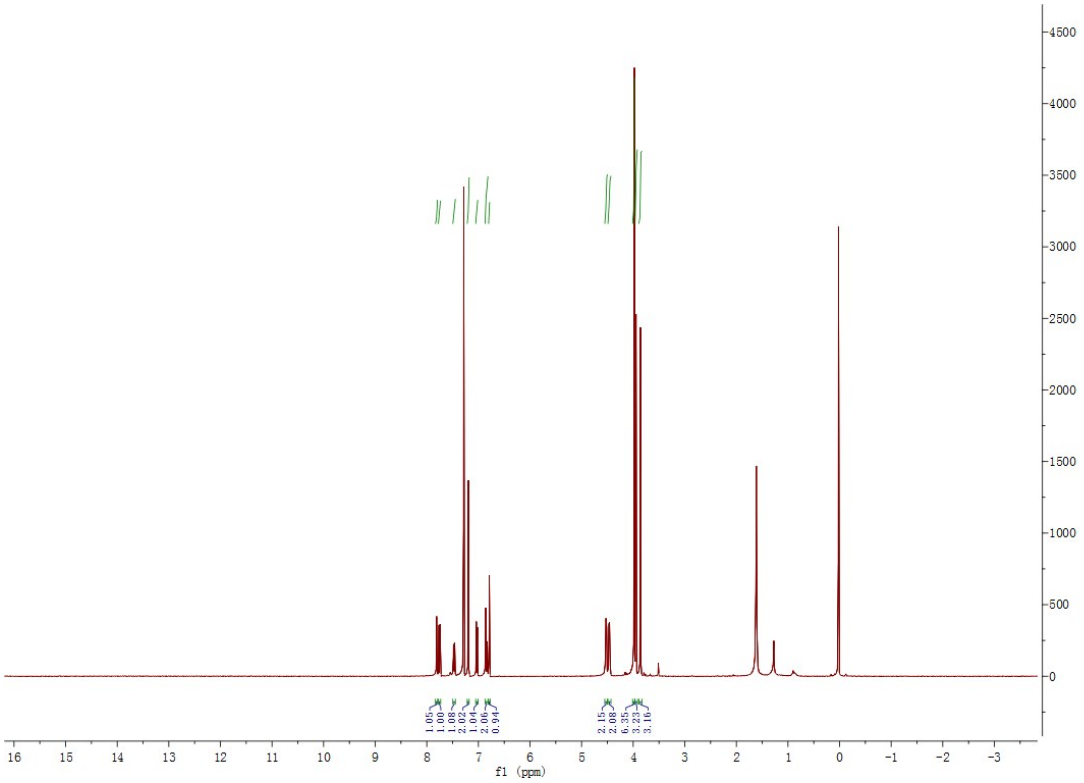
methyl 4-chloro-2-(2-((4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-7-yl)oxy)ethoxy)benzoate (**10e**)



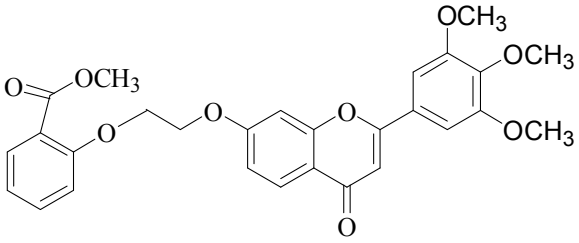


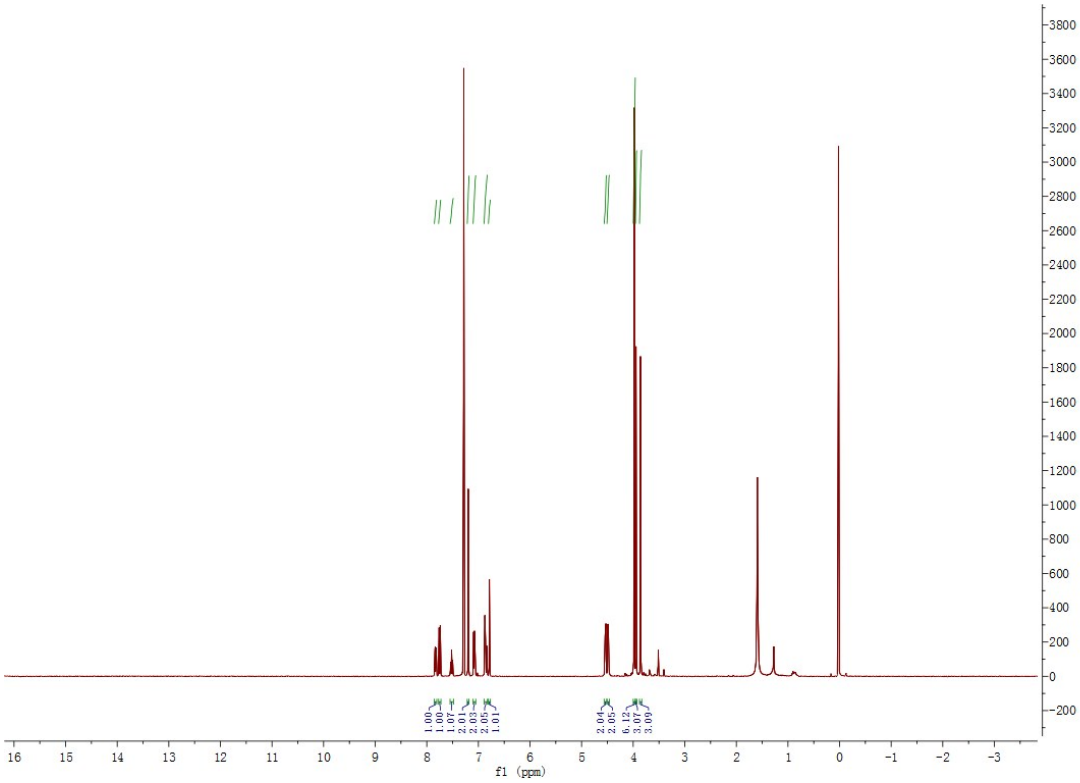
methyl 5-chloro-2-(2-((4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-7-yl)oxy)ethoxy)benzoate (**10f**)



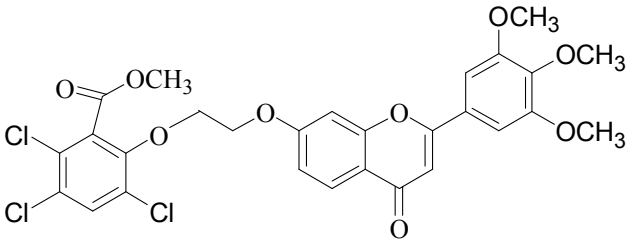


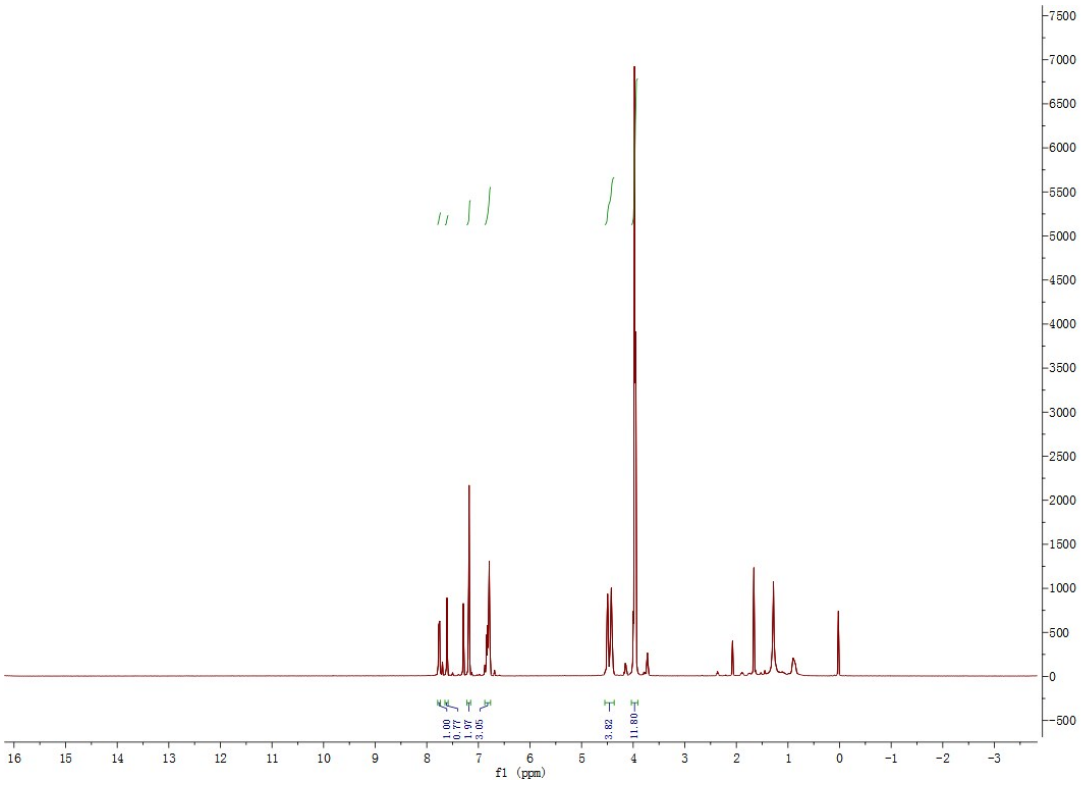
methyl 2-(2-((4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-7-yl)oxy)ethoxy)benzoate (**10g**)



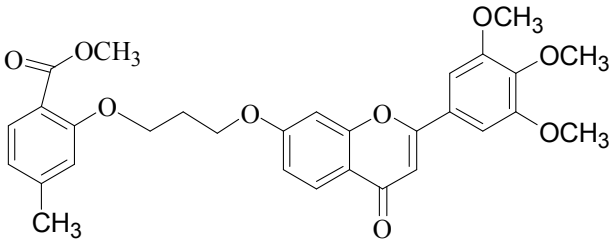


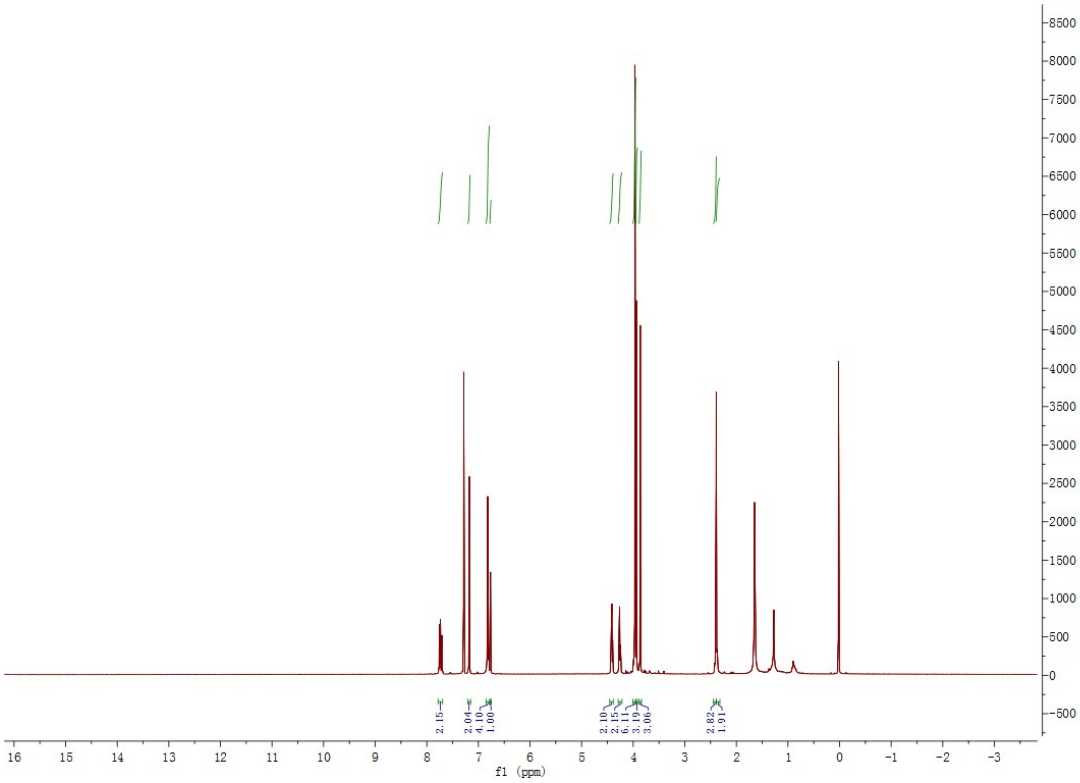
methyl 2,3,5-trichloro-6-(2-((4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-7-yl)oxy)ethoxy)benzoate (**10h**)



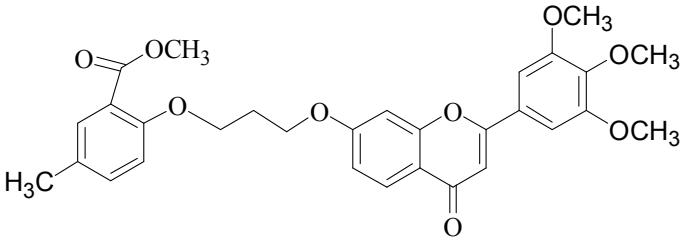


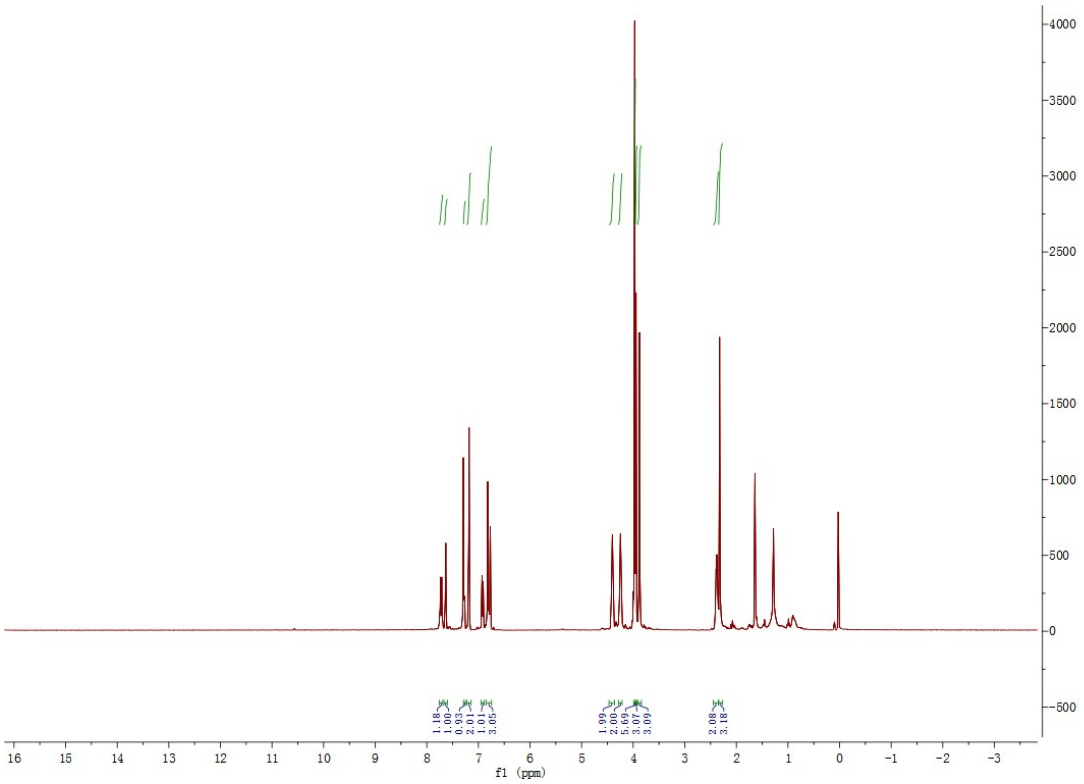
methyl 4-methyl-2-(3-((4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-7-yl)oxy)propoxy)benzoate (**10i**)



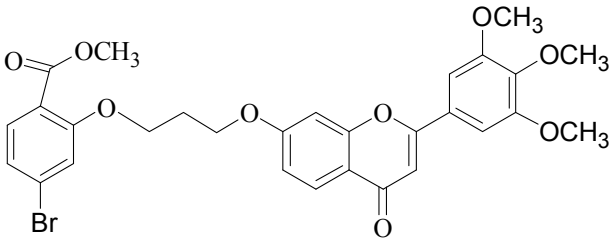


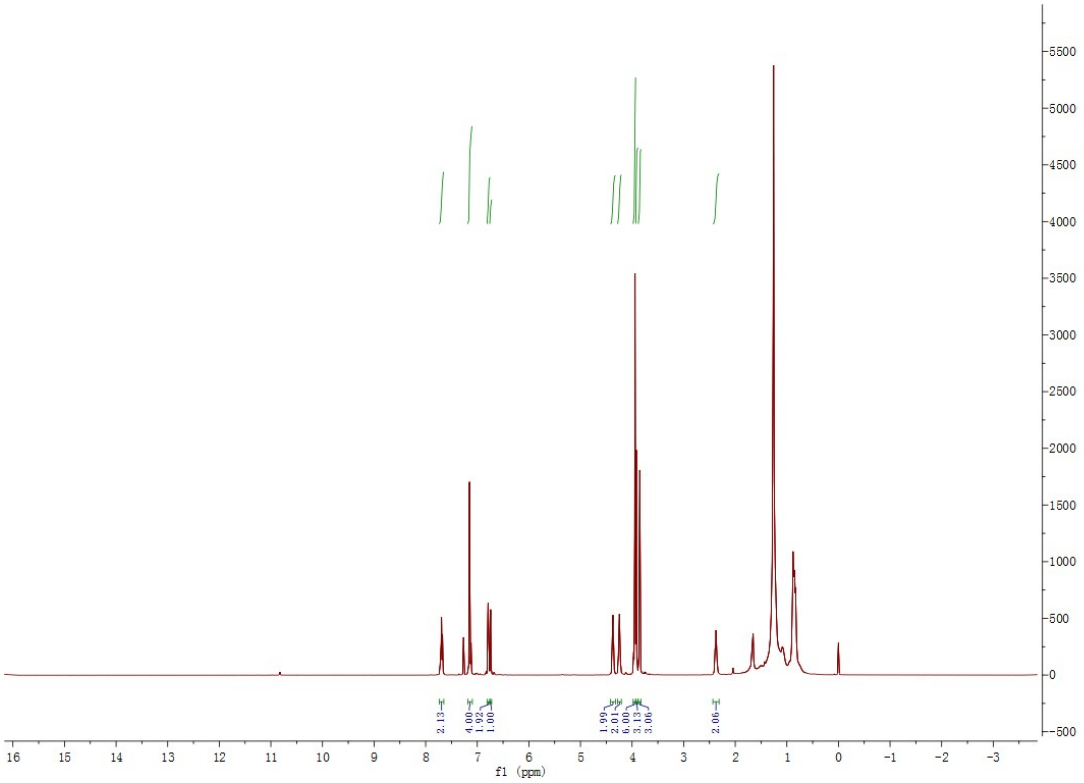
methyl 5-methyl-2-(3-((4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-7-yl)oxy)propoxy)benzoate (**10j**)



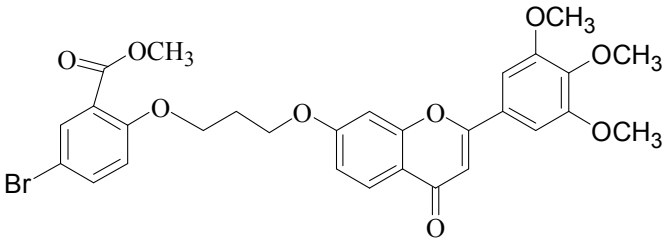


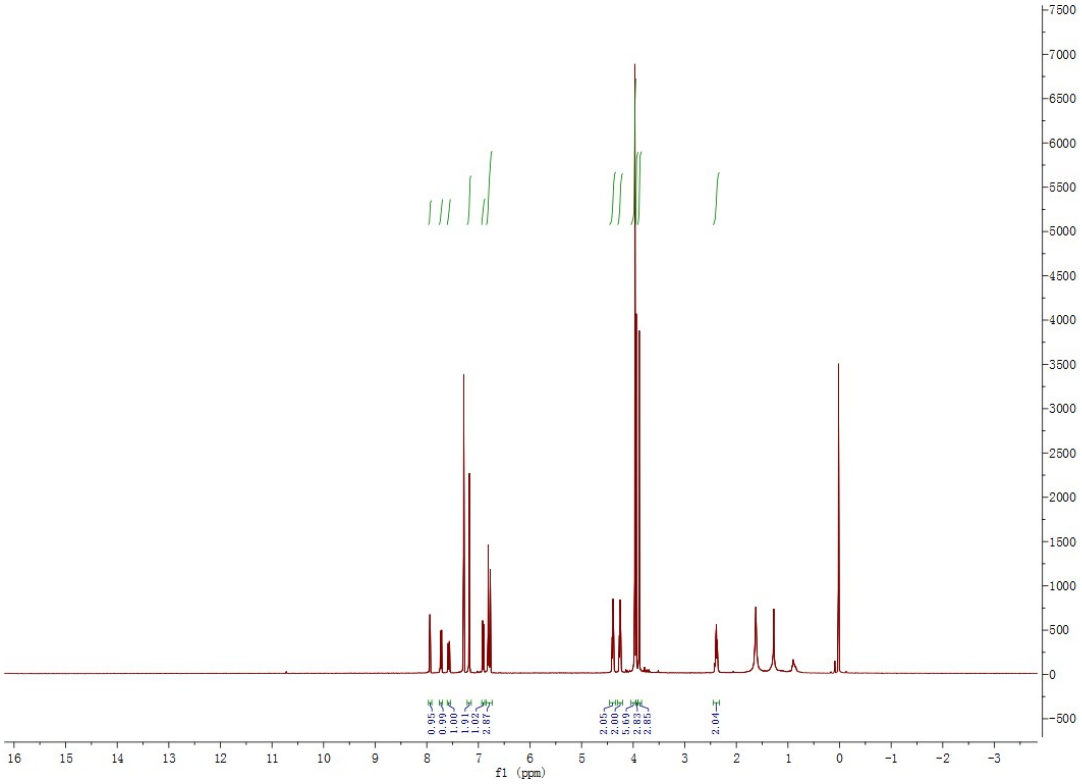
methyl 4-bromo-2-(3-((4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-7-yl)oxy)propoxy)benzoate (**10k**)



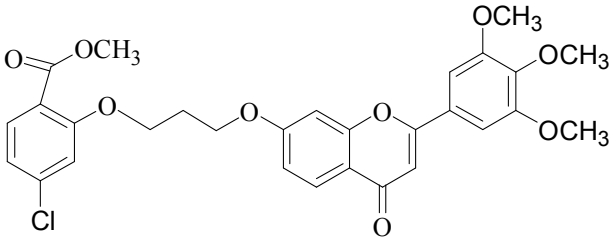


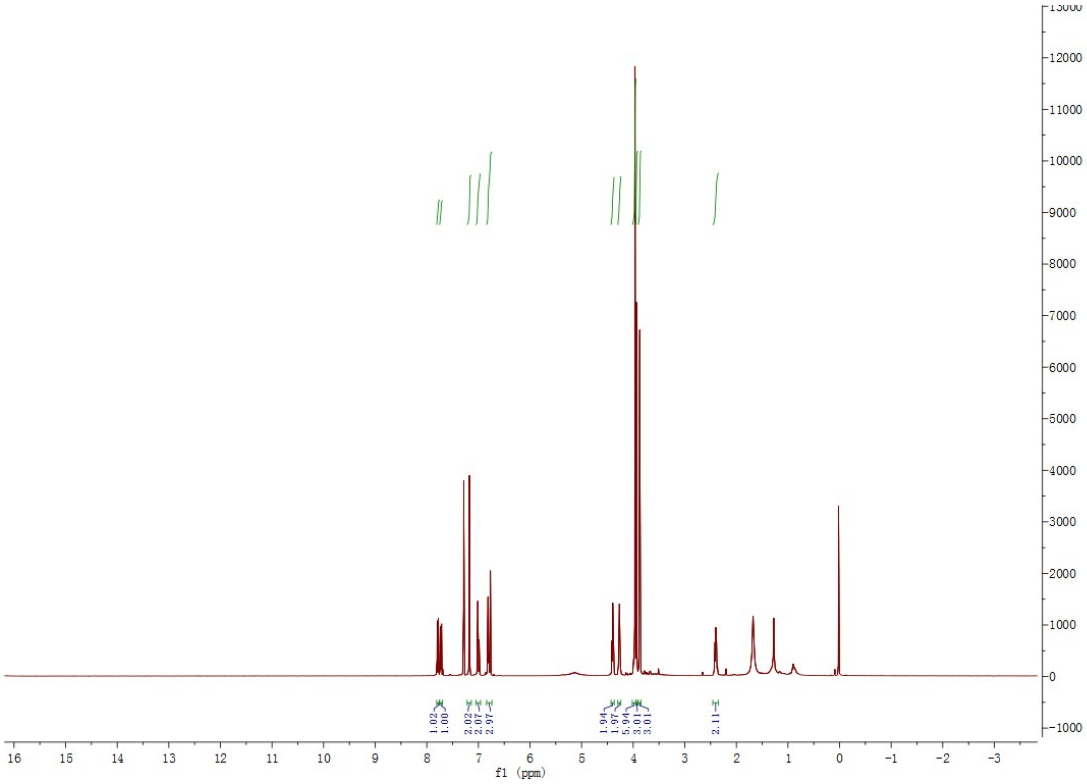
methyl 5-bromo-2-(3-((4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-7-yl)oxy)propoxy)benzoate (**10l**)



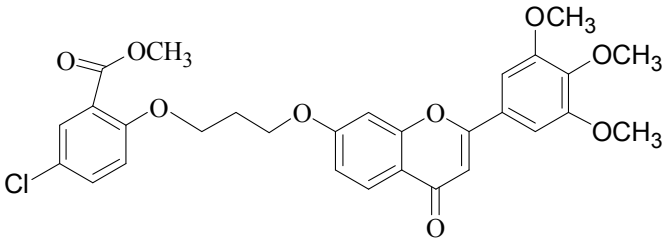


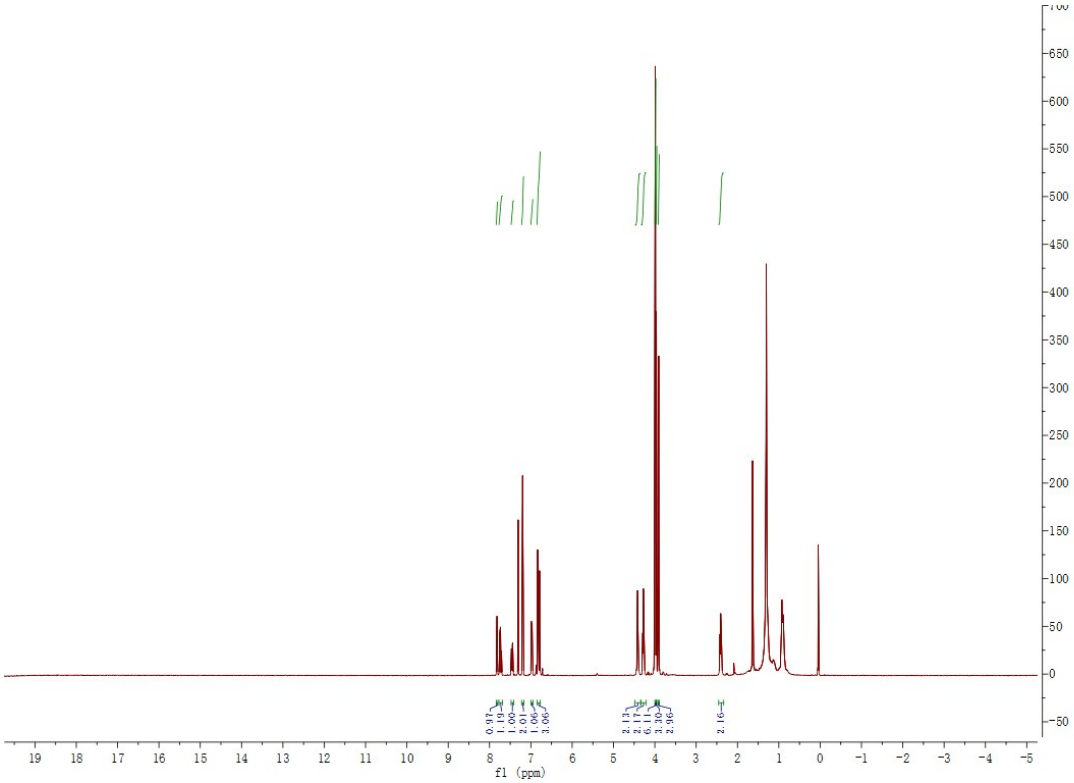
methyl 4-chloro-2-(3-((4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-7-yl)oxy)propoxy)benzoate (**10m**)



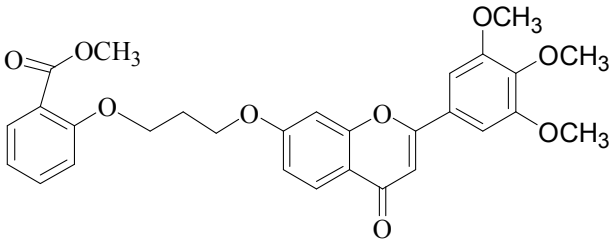


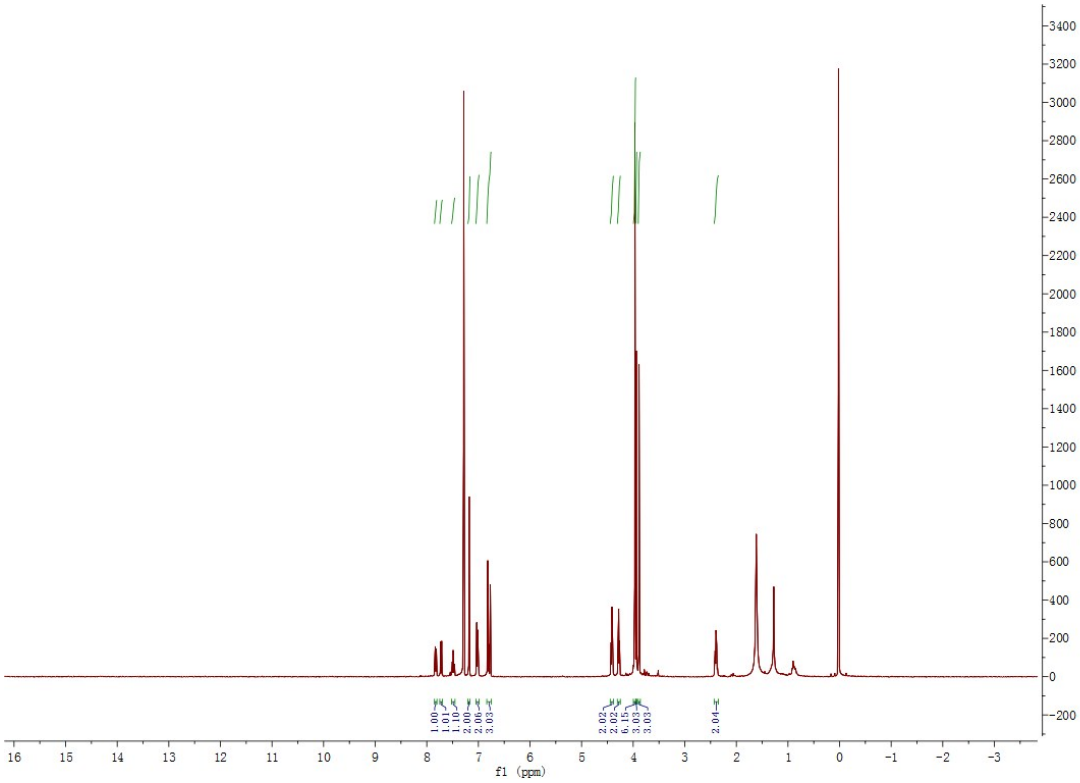
methyl 5-chloro-2-(3-((4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-7-yl)oxy)propoxy)benzoate (**10n**)



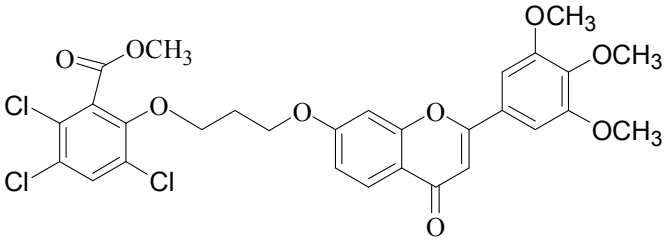


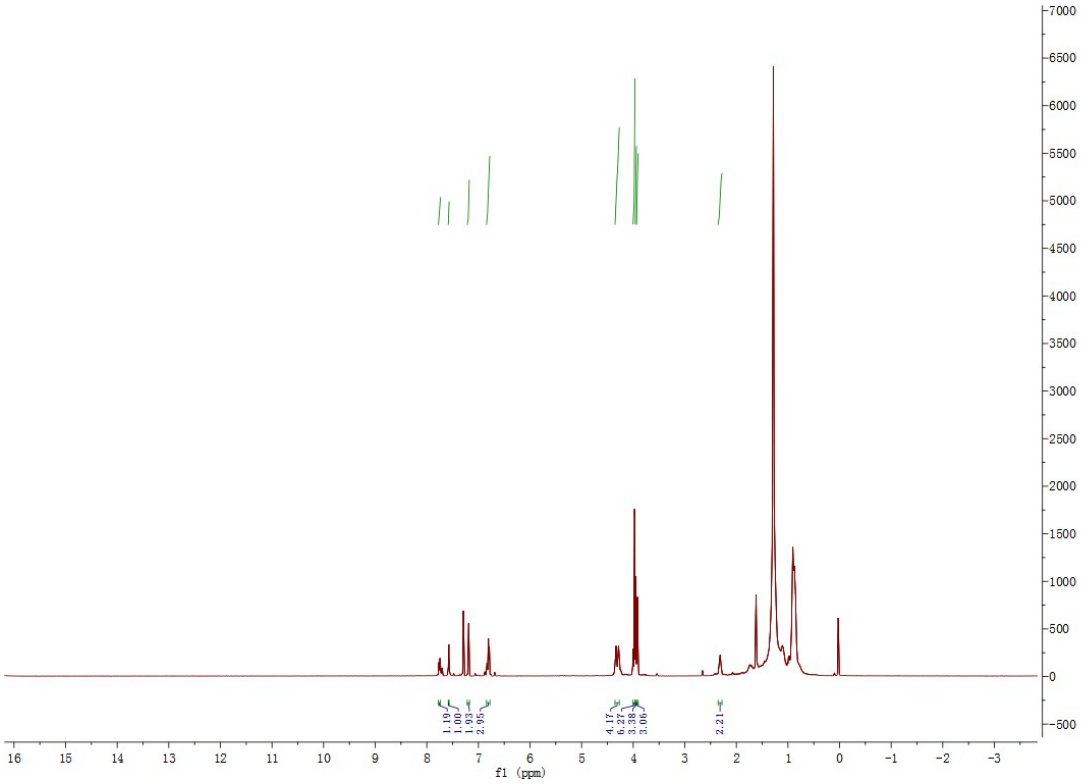
methyl 2-(3-((4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-7-yl)oxy)propoxy)benzoate (**10o**)



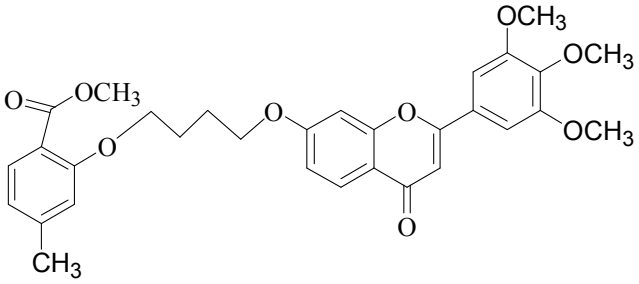


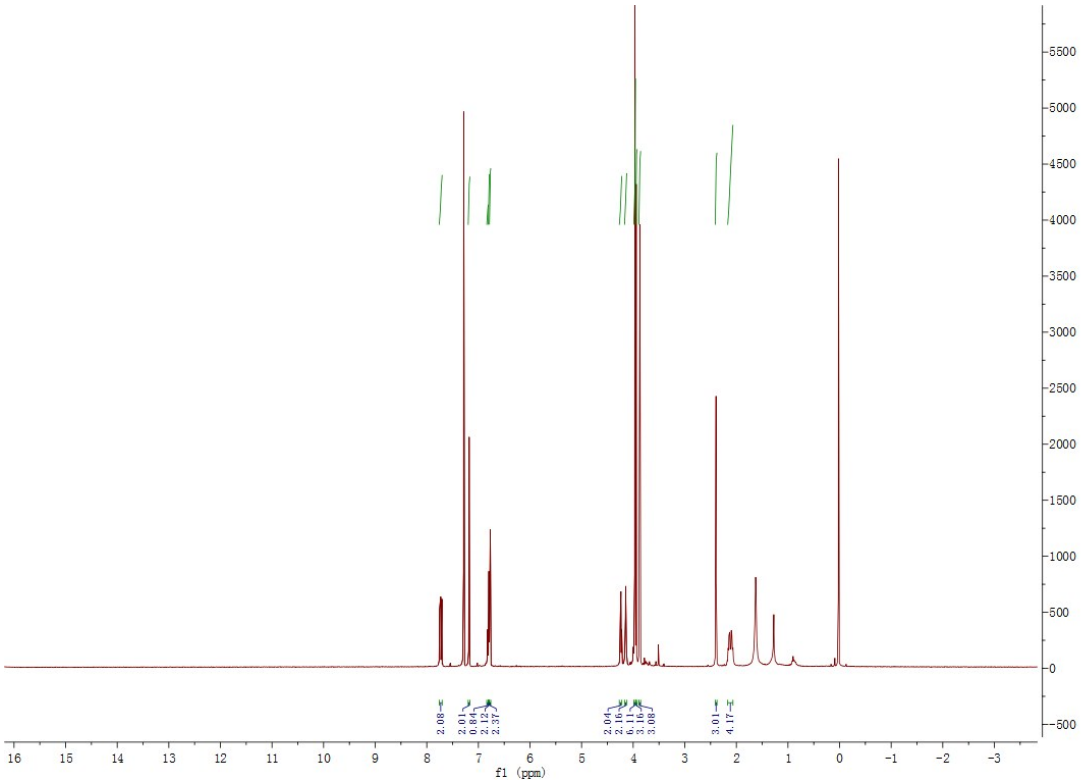
methyl 2,3,5-trichloro-6-(3-((4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-7-yl)oxy)propoxy)benzoate (**10p**)



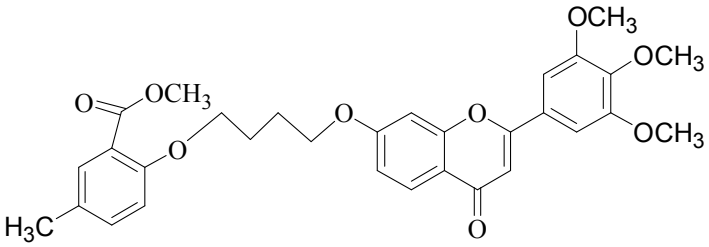


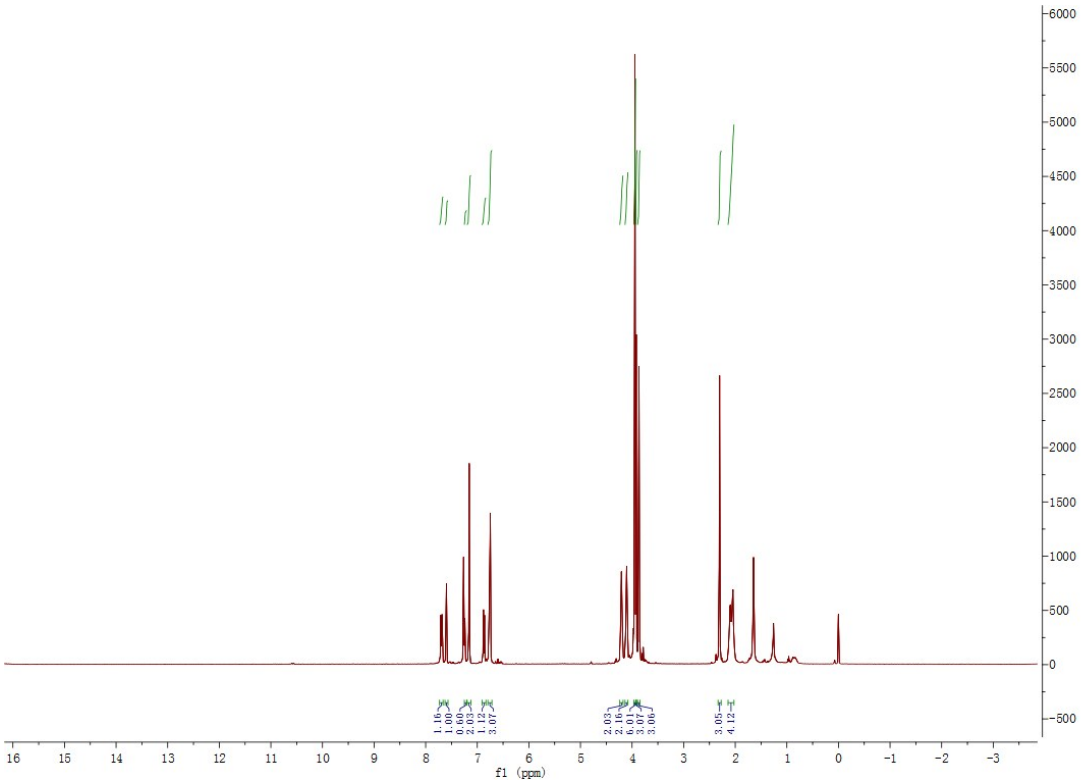
methyl 4-methyl-2-(4-((4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-7-yl)oxy)butoxy)benzoate (**10q**)



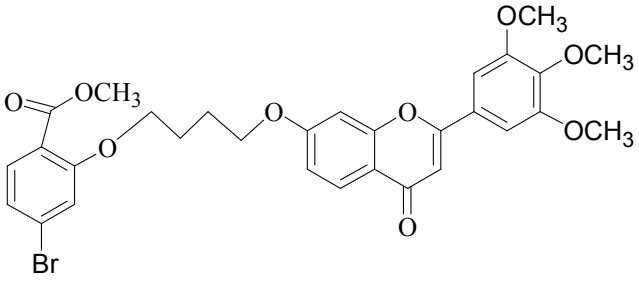


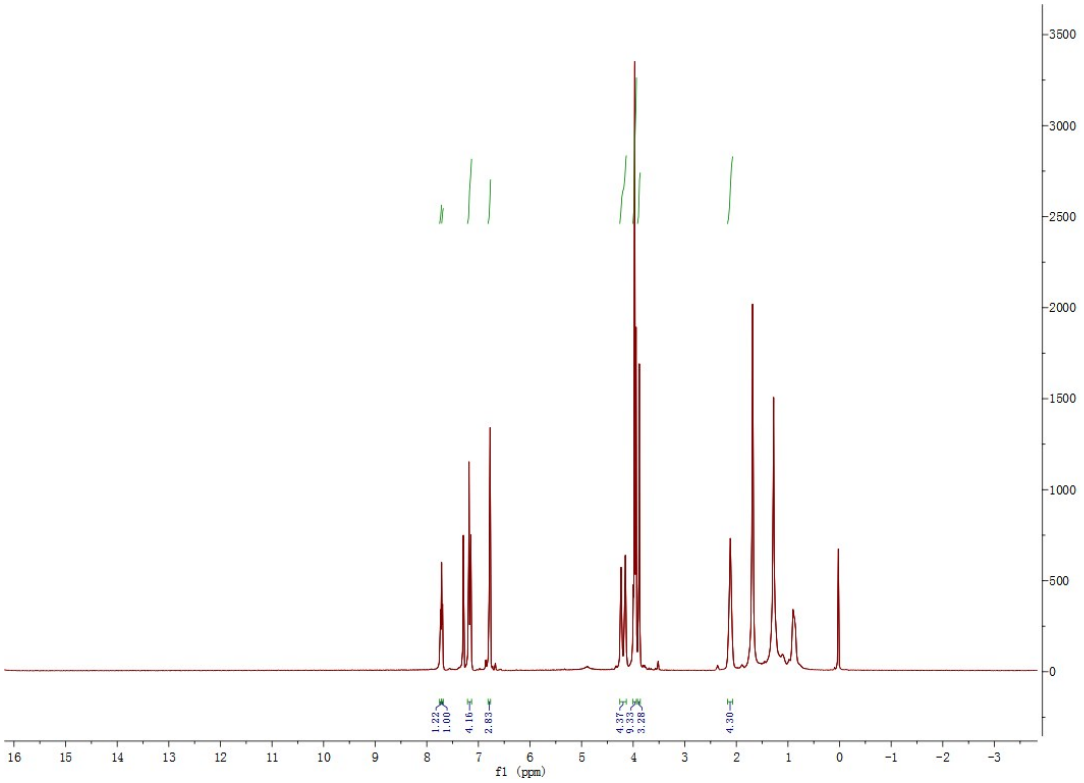
methyl 5-methyl-2-(4-((4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-7-yl)oxy)butoxy)benzoate (**10r**)



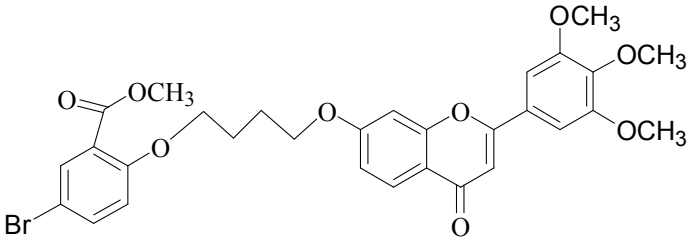


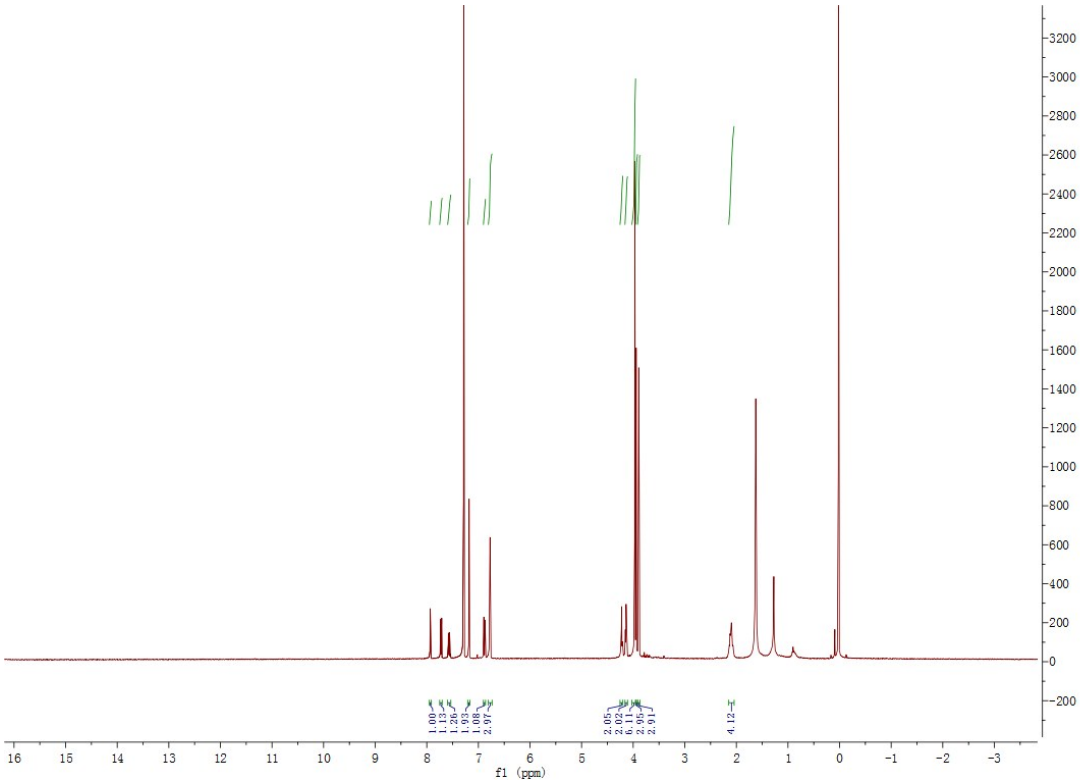
methyl 4-bromo-2-(4-((4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-7-yl)oxy)butoxy)benzoate (**10s**)



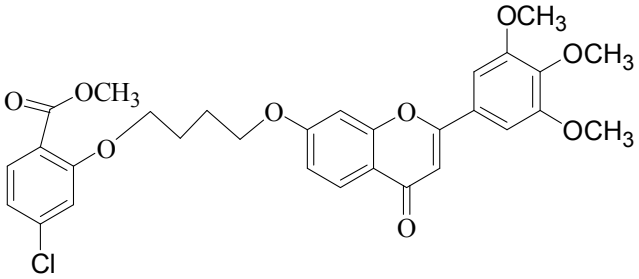


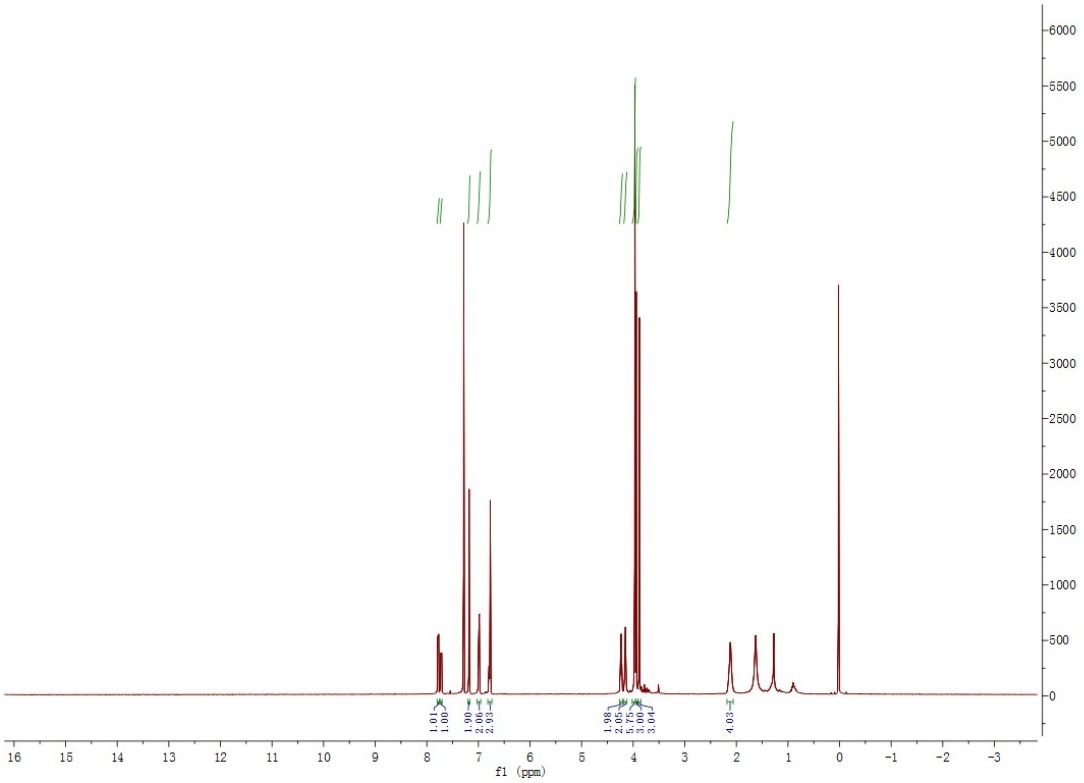
methyl 5-bromo-2-(4-((4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-7-yl)oxy)butoxy)benzoate (**10t**)



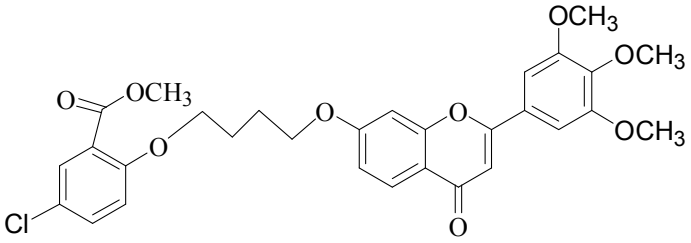


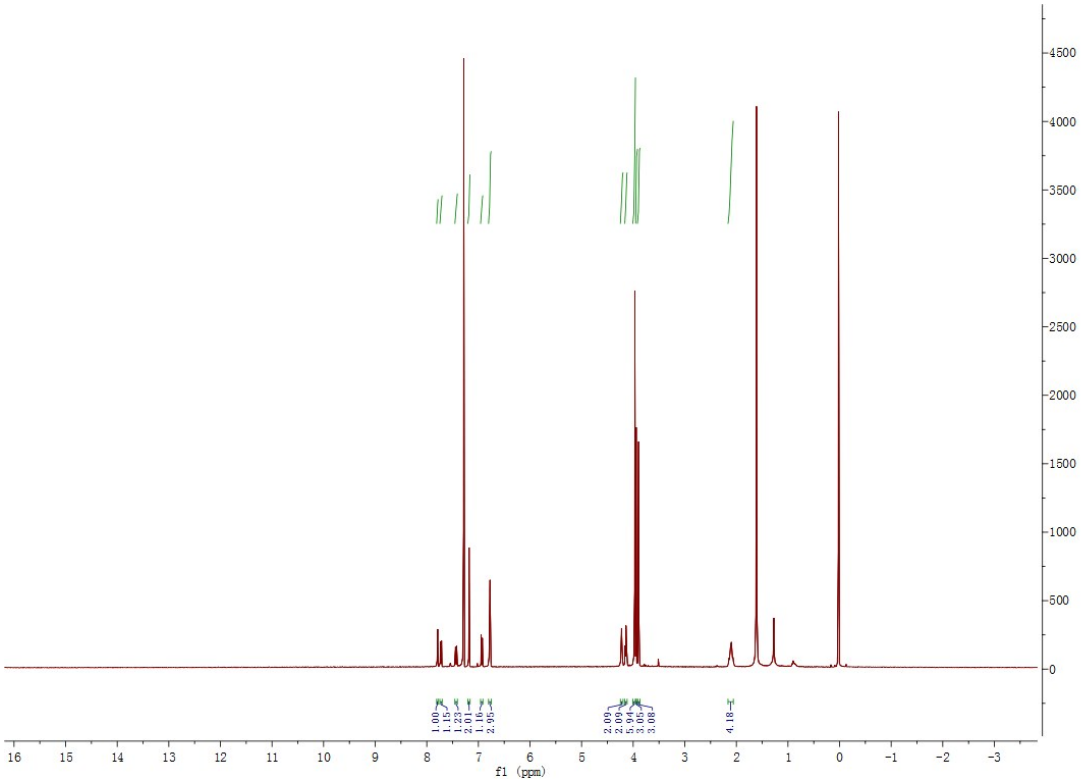
methyl 4-chloro-2-(4-((4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-7-yl)oxy)butoxy)benzoate (**10u**)



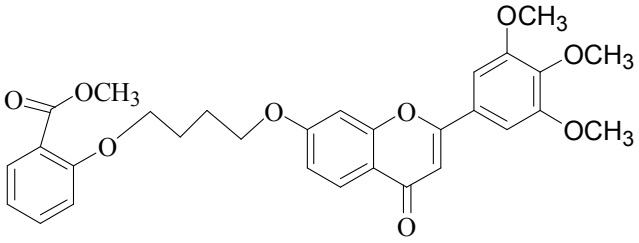


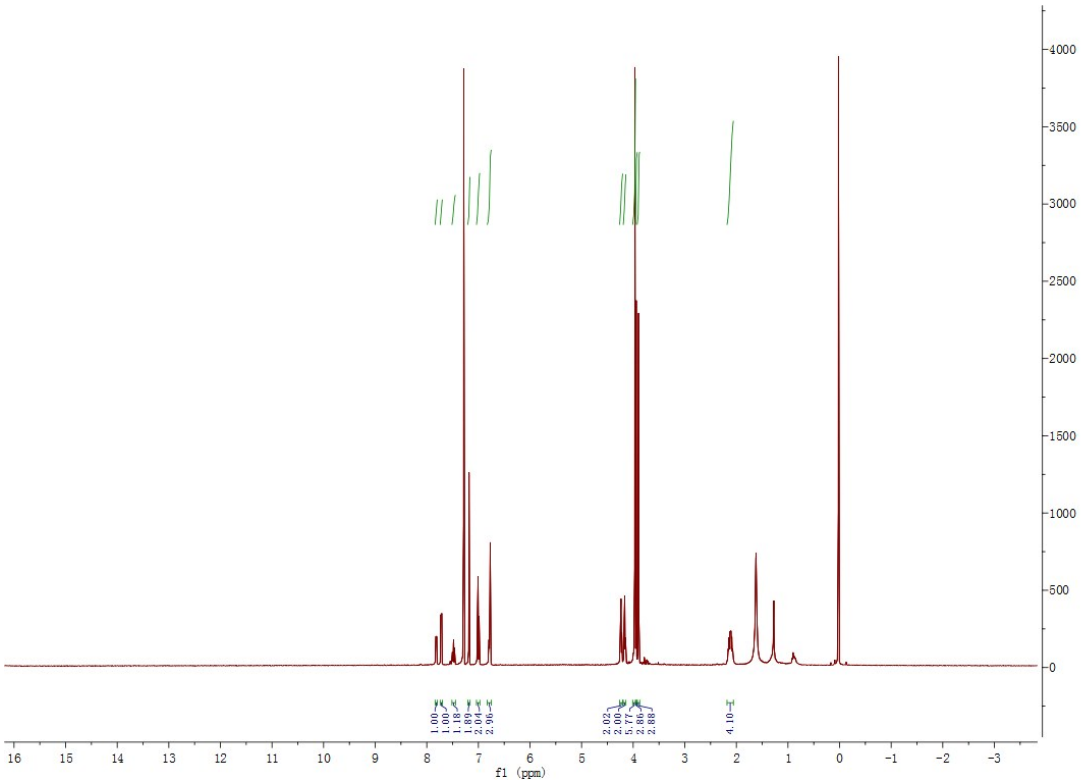
methyl 5-chloro-2-(4-((4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-7-yl)oxy)butoxy)benzoate (**10v**)



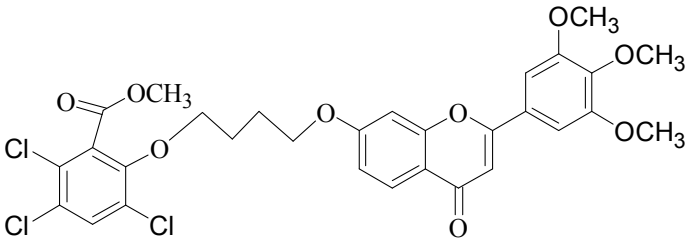


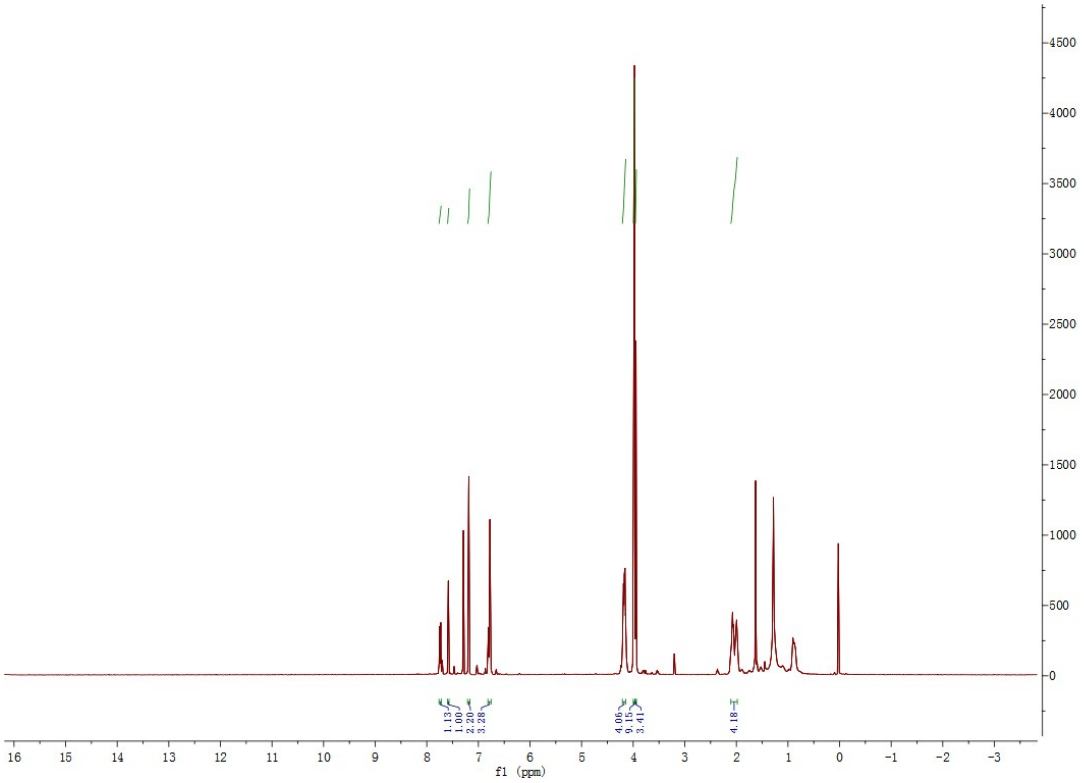
methyl 2-(4-((4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-7-yl)oxy)butoxy)benzoate (**10w**)





methyl 2,3,5-trichloro-6-(4-((4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-7-yl)oxy)butoxy)benzoate (**10x**)

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