

Design and synthesis of formononetin-dithiocarbamate hybrids that inhibit growth and migration of PC-3 cells via MAPK/Wnt signaling pathways

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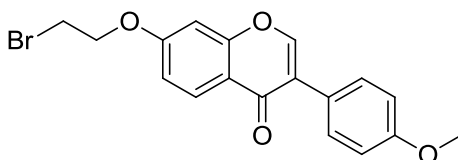
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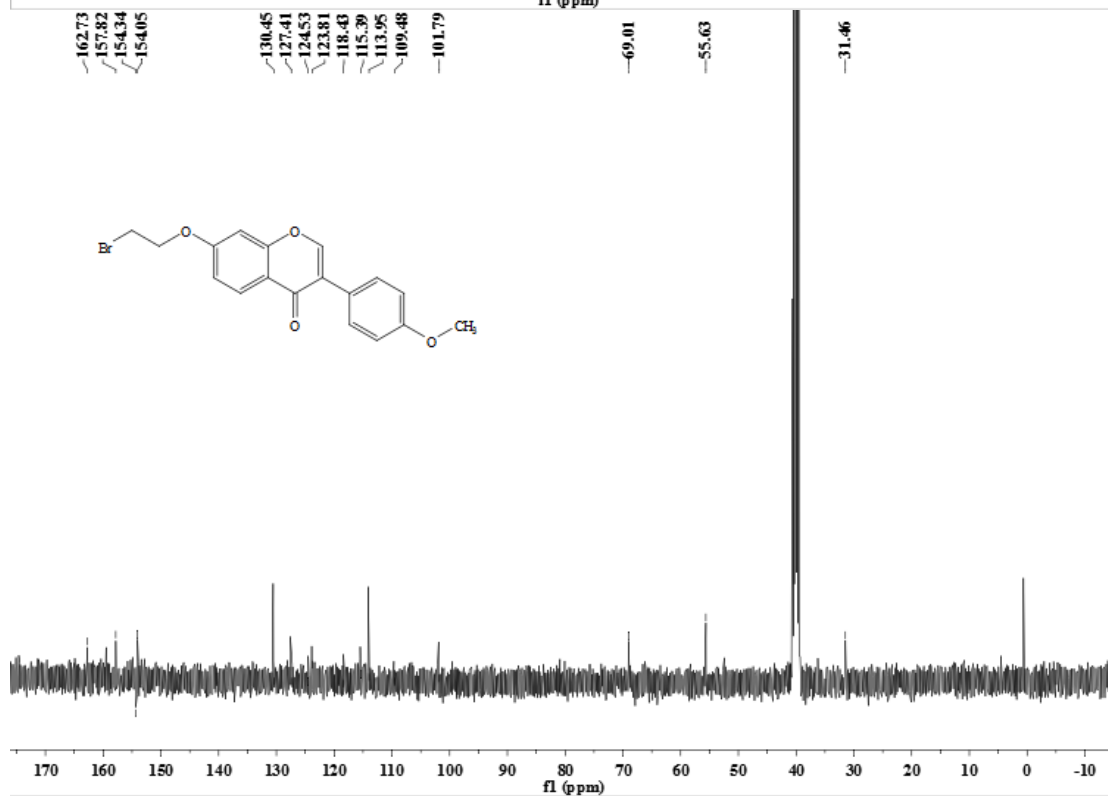
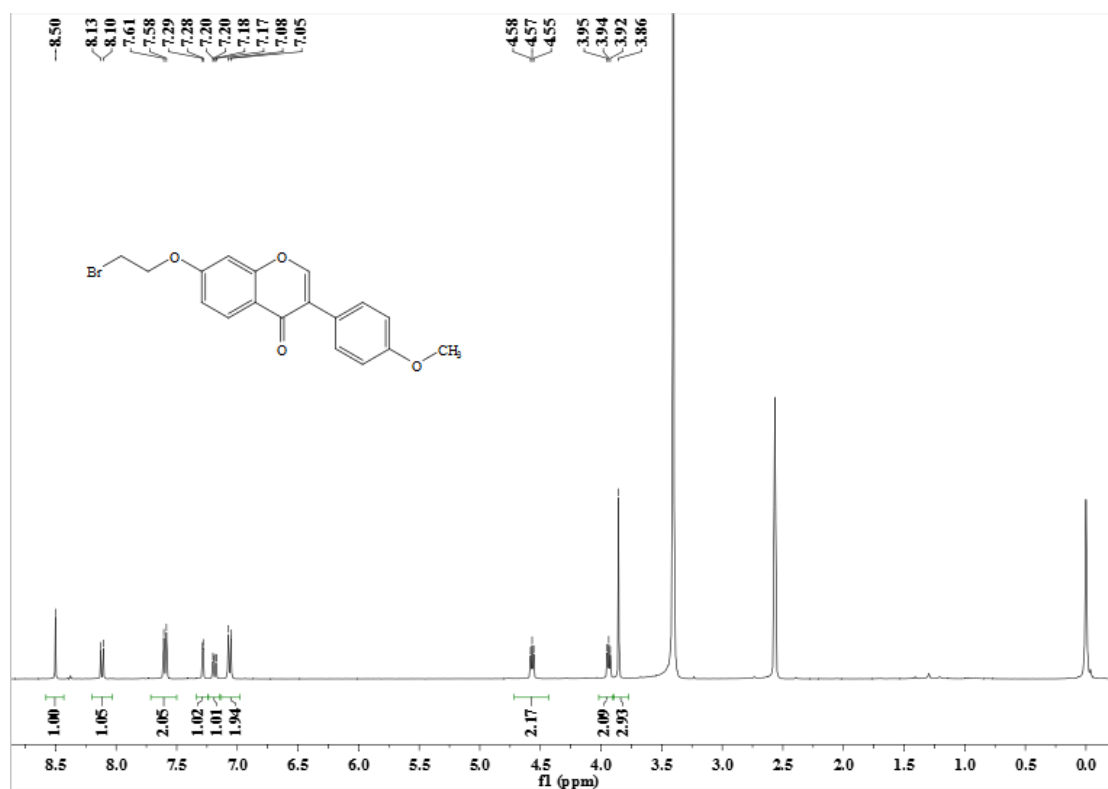
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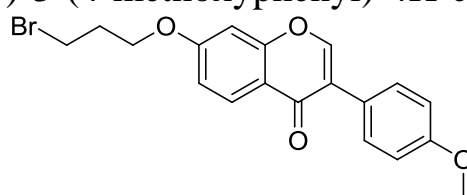
7-(2-bromoethoxy)-3-(4-methoxyphenyl)-4H-chromen-4-one (**7a**)



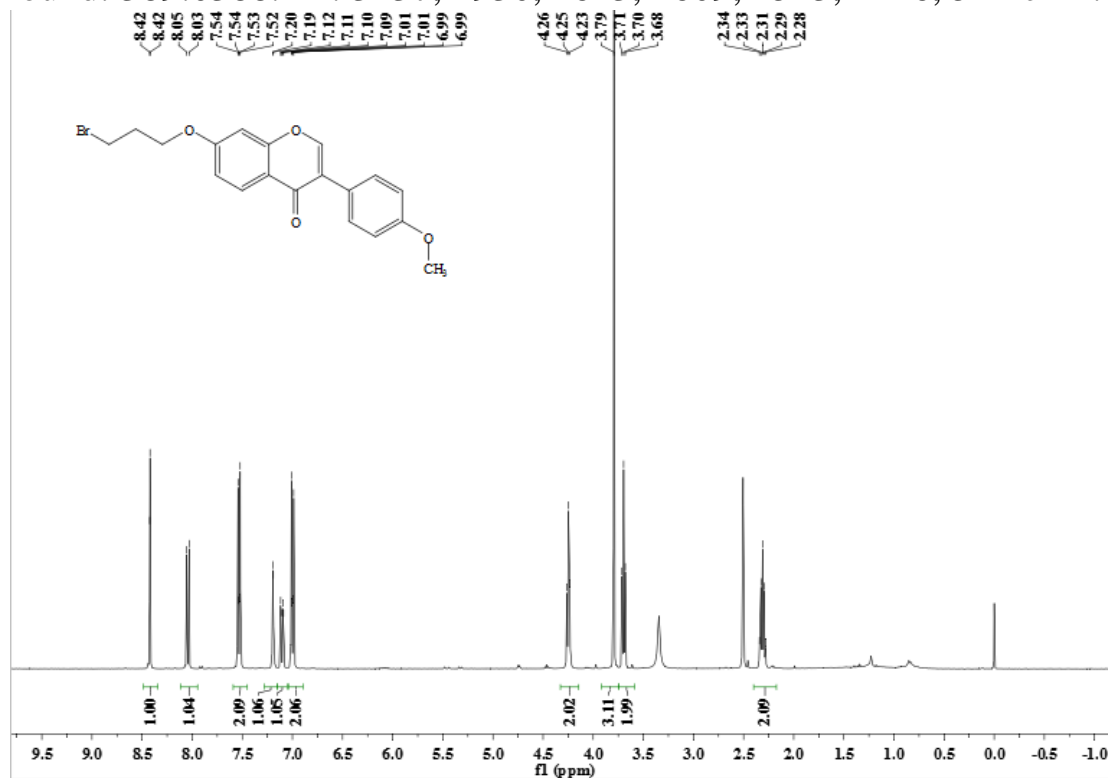
Yield 79%. White solid. Mp: 109~111°C. ¹H NMR (400 MHz, DMSO) δ 8.50 (s, 1H), 8.12 (d, *J* = 8.9 Hz, 1H), 7.60 (d, *J* = 8.7 Hz, 2H), 7.28 (d, *J* = 2.3 Hz, 1H), 7.19 (dd, *J* = 8.9, 2.3 Hz, 1H), 7.06 (d, *J* = 8.7 Hz, 2H), 4.72 – 4.43 (m, 2H), 4.02 – 3.89 (m, 2H), 3.86 (s, 3H). ¹³C NMR (100 MHz, DMSO) δ 162.73, 157.82, 154.34, 154.05, 130.45, 127.41, 124.53, 123.81, 118.43, 115.39, 113.95, 109.48, 101.79, 69.01, 55.63, 31.46. HR-MS (ESI): Calcd. C₁₈H₁₆BrO₄, [M+H]⁺*m/z*: 375.0239, found: 375.0232. IR: 3007, 2953, 1609, 1576, 1498, 1446, 544 cm⁻¹.

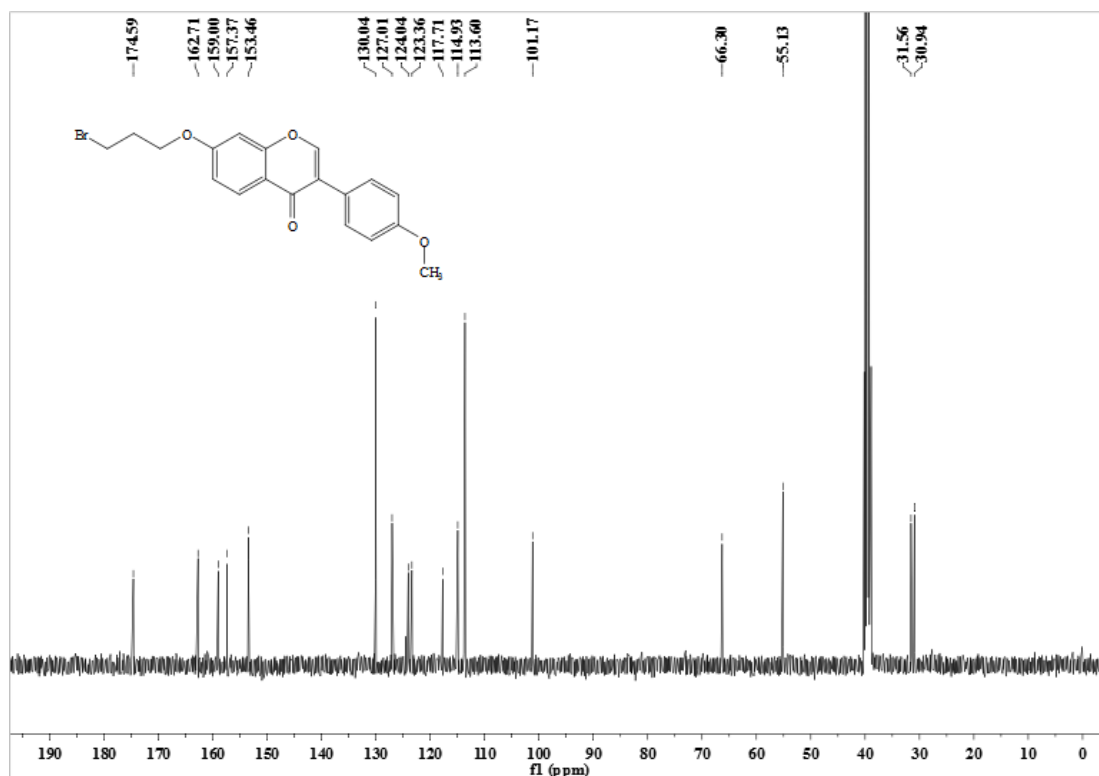


7-(3-bromopropoxy)-3-(4-methoxyphenyl)-4H-chromen-4-one (**7b**)

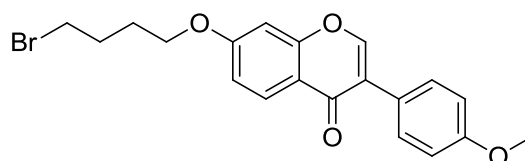


Yield 70%. White solid. Mp: 131~132°C. ^1H NMR (400 MHz, DMSO) δ 8.42 (d, $J = 1.2$ Hz, 1H), 8.04 (d, $J = 8.9$ Hz, 1H), 7.59 – 7.45 (m, 2H), 7.19 (d, $J = 2.0$ Hz, 1H), 7.10 (dd, $J = 8.9, 2.4$ Hz, 1H), 7.04 – 6.89 (m, 2H), 4.25 (t, $J = 6.0$ Hz, 2H), 3.79 (s, 3H), 3.70 (t, $J = 6.6$ Hz, 2H), 2.31 (p, $J = 6.2$ Hz, 2H). ^{13}C NMR (100 MHz, DMSO) δ 174.59, 162.71, 159.00, 157.37, 153.46, 130.04, 127.01, 124.04, 123.36, 117.71, 114.93, 113.60, 101.17, 66.30, 55.13, 31.56, 30.94. HR-MS (ESI): Calcd. $\text{C}_{19}\text{H}_{18}\text{BrO}_4$, $[\text{M}+\text{H}]^+m/z$: 389.0380, found: 389.0388. IR: 3437, 2930, 1623, 1609, 1513, 1446, 541 cm^{-1} .

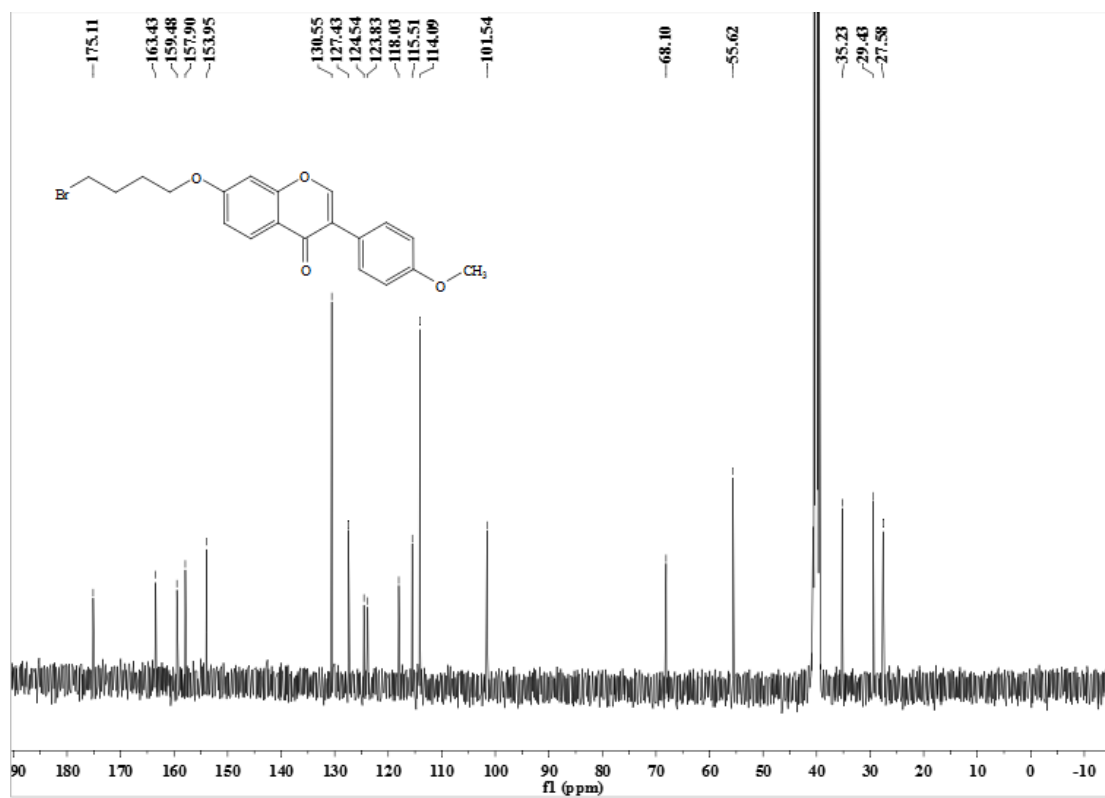
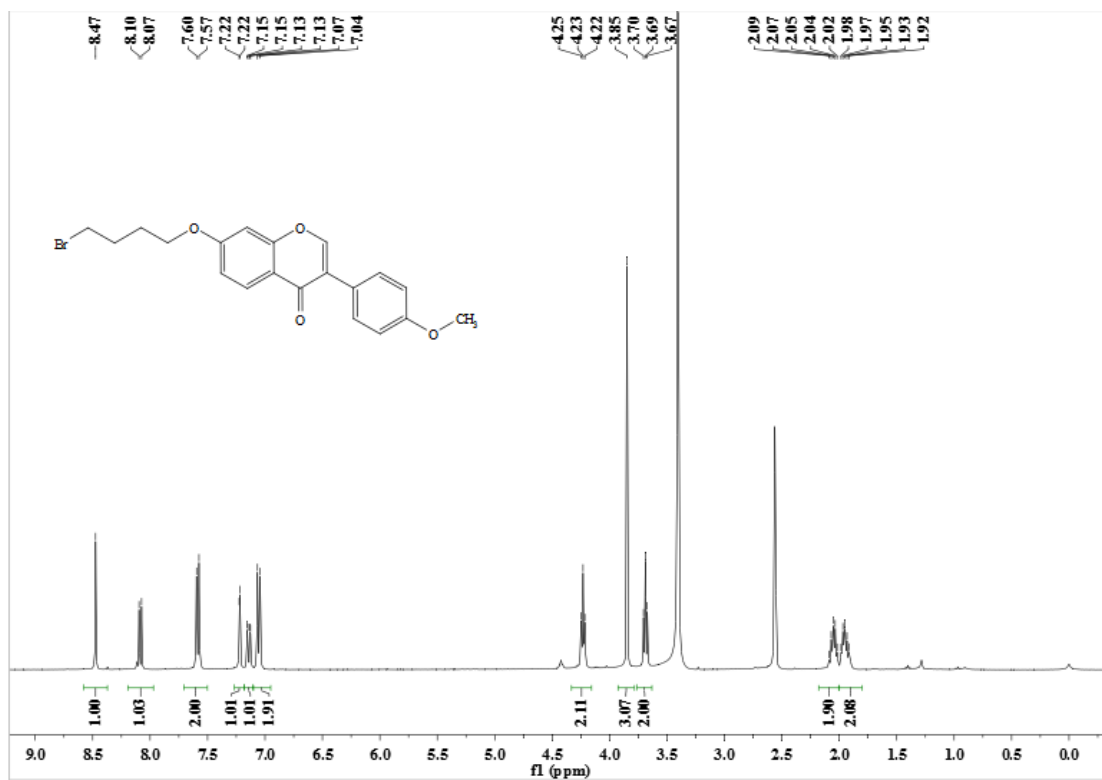




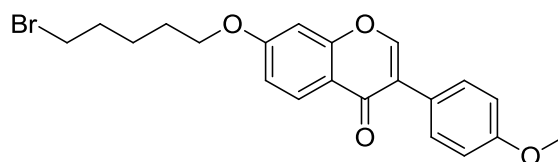
7-(4-bromobutoxy)-3-(4-methoxyphenyl)-4H-chromen-4-one (**7c**)



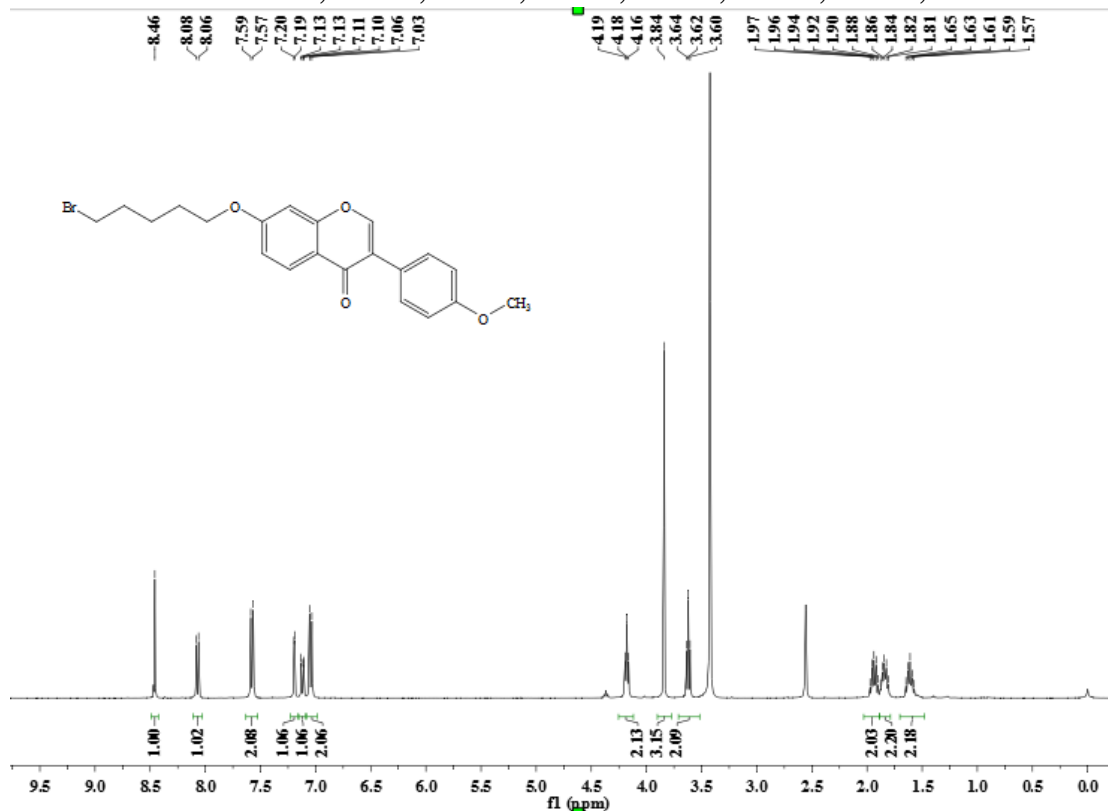
Yield 75%. White solid. Mp: 109~111°C. ¹H NMR (400 MHz, DMSO) δ 8.47 (s, 1H), 8.09 (d, *J* = 8.9 Hz, 1H), 7.59 (d, *J* = 8.7 Hz, 2H), 7.22 (d, *J* = 2.2 Hz, 1H), 7.14 (dd, *J* = 8.9, 2.2 Hz, 1H), 7.05 (d, *J* = 8.7 Hz, 2H), 4.23 (t, *J* = 6.2 Hz, 2H), 3.85 (s, 3H), 3.69 (t, *J* = 6.5 Hz, 2H), 2.18 – 2.00 (m, 2H), 2.01 – 1.80 (m, 2H). ¹³C NMR (100 MHz, DMSO) δ 175.11, 163.43, 159.48, 157.90, 153.95, 130.55, 127.43, 124.54, 123.83, 118.03, 115.51, 114.09, 101.54, 68.10, 55.62, 35.23, 29.43, 27.58. HR-MS (ESI): Calcd. C₂₀H₂₀BrO₄, [M+H]⁺ *m/z*: 403.0548, found: 403.0545. IR: 2963, 1633, 1608, 1515, 1446, 696 cm⁻¹.

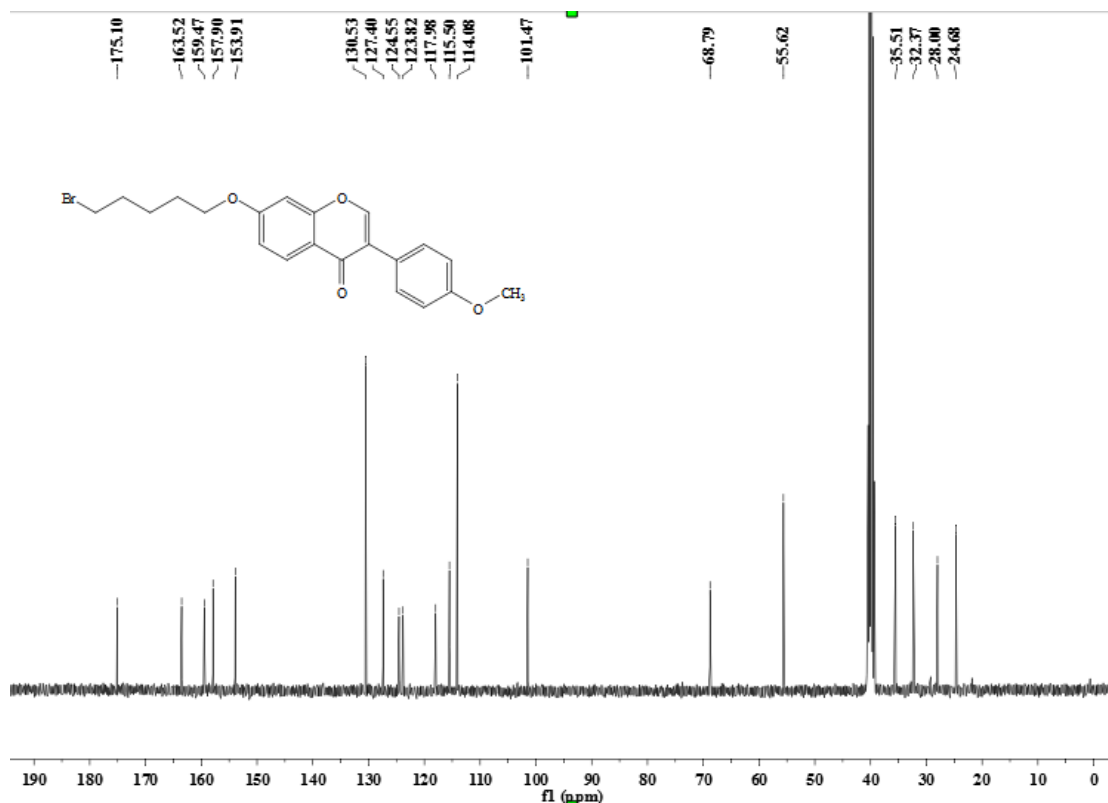


7-((5-bromopentyl)oxy)-3-(4-methoxyphenyl)-4H-chromen-4-one
(7d)

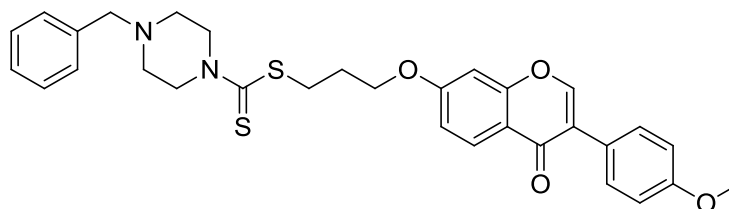


Yield 80%. White solid. Mp: 110~111°C. ^1H NMR (400 MHz, DMSO) δ 8.46 (s, 1H), 8.07 (d, $J = 8.9$ Hz, 1H), 7.58 (d, $J = 8.7$ Hz, 2H), 7.19 (d, $J = 2.2$ Hz, 1H), 7.12 (dd, $J = 8.9, 2.3$ Hz, 1H), 7.04 (d, $J = 8.8$ Hz, 2H), 4.18 (t, $J = 6.4$ Hz, 2H), 3.84 (s, 3H), 3.62 (t, $J = 6.7$ Hz, 2H), 2.03 – 1.89 (m, 2H), 1.89 – 1.79 (m, 2H), 1.61 (dt, $J = 15.1, 7.6$ Hz, 2H). ^{13}C NMR (100 MHz, DMSO) δ 175.10, 163.52, 159.47, 157.90, 153.91, 130.53, 127.40, 124.55, 123.82, 117.98, 115.50, 114.08, 101.47, 68.79, 55.62, 35.51, 32.37, 28.00, 24.68. HR-MS (ESI): Calcd. $\text{C}_{21}\text{H}_{22}\text{BrO}_4$, $[\text{M}+\text{H}]^+$ m/z : 417.0707, found: 417.0701. IR: 3450, 2962, 1632, 1610, 1576, 1515, 1446, 542 cm^{-1} .

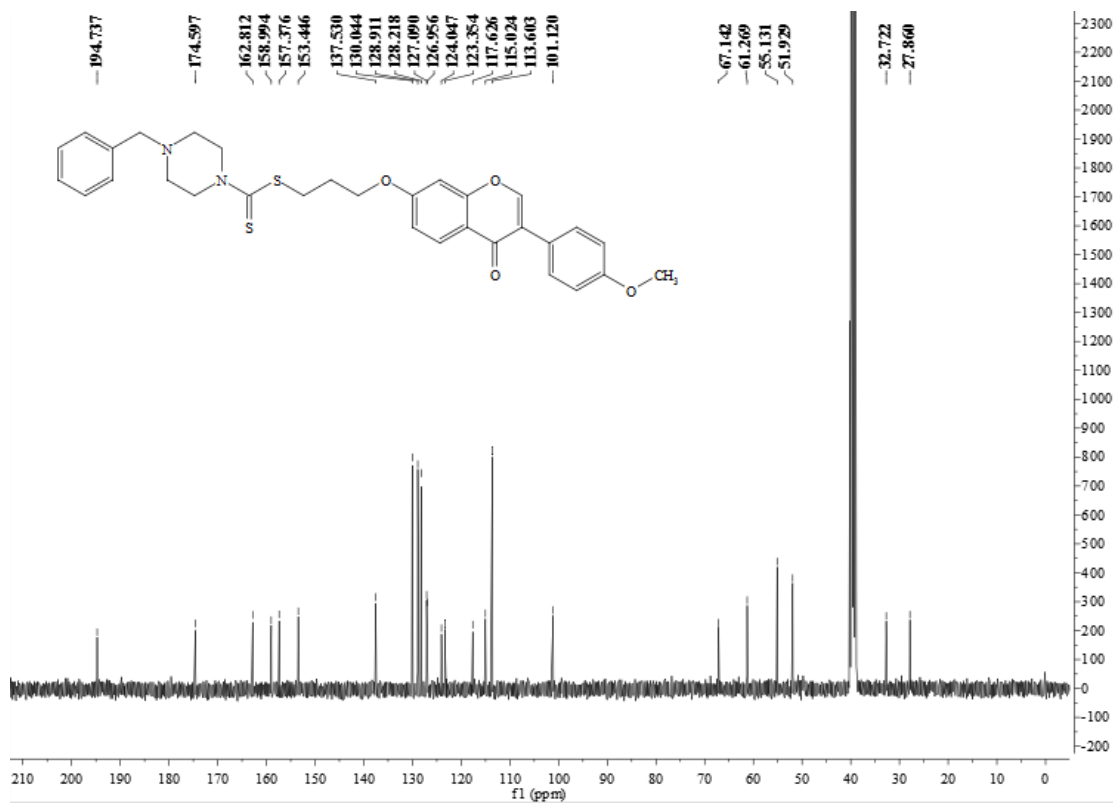
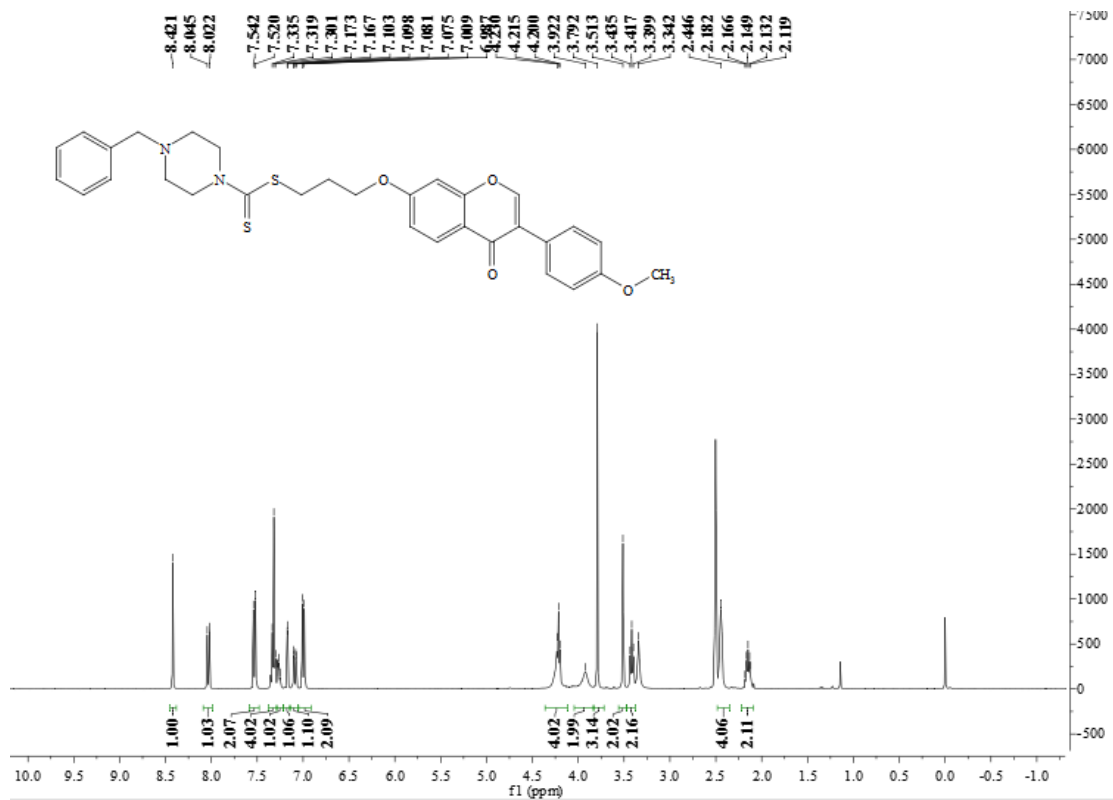




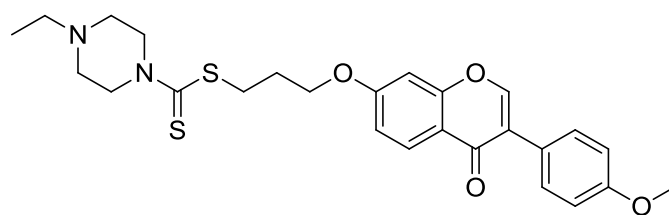
3-((3-(4-methoxyphenyl)-4-oxo-4H-chromen-7-yl)oxy)propyl 4-benzylpiperazine-1-carbodithioate (**8a**)



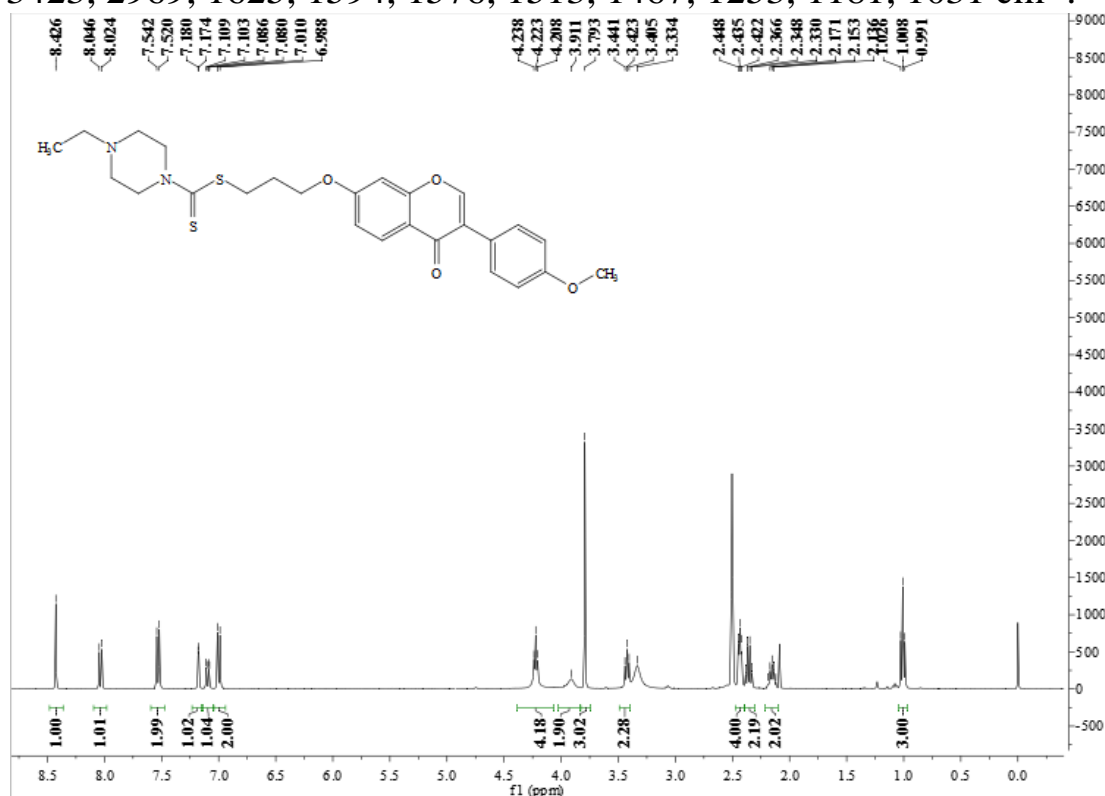
Yield 83%. White solid. Mp: 124~125°C. ^1H NMR (400 MHz, DMSO) δ 8.42 (s, 1H), 8.03 (d, $J = 8.9$ Hz, 1H), 7.53 (d, $J = 8.7$ Hz, 2H), 7.38 – 7.29 (m, 4H), 7.29 – 7.22 (m, 1H), 7.17 (d, $J = 2.2$ Hz, 1H), 7.09 (dd, $J = 8.9, 2.3$ Hz, 1H), 7.00 (d, $J = 8.8$ Hz, 2H), 4.22 (t, $J = 6.1$ Hz, 4H), 3.92 (s, 2H), 3.79 (s, 3H), 3.51 (s, 2H), 3.42 (t, $J = 7.2$ Hz, 2H), 2.45 (s, 4H), 2.22 – 2.09 (m, 2H). ^{13}C NMR (100 MHz, DMSO) δ 194.74, 174.60, 162.81, 158.99, 157.38, 153.45, 137.53, 130.04, 128.91, 128.22, 127.09, 126.96, 124.05, 123.35, 117.63, 115.02, 113.60, 101.12, 67.14, 61.27, 55.13, 51.93, 32.72, 27.86. HR-MS (ESI): Calcd. $\text{C}_{31}\text{H}_{33}\text{N}_2\text{O}_4\text{S}_2$, $[\text{M}+\text{H}]^+m/z$: 561.1885, found: 561.1882. IR: 3445, 2935, 1628, 1609, 1566, 1514, 1445, 1251 cm^{-1} .

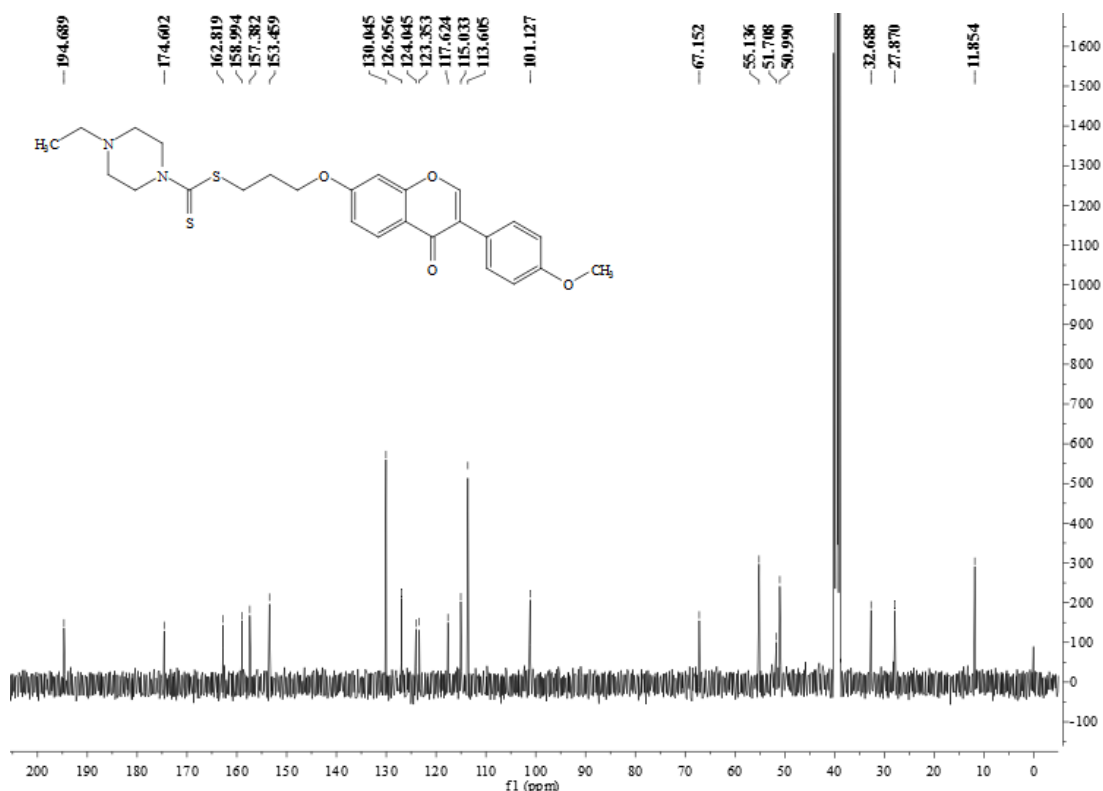


3-((3-(4-methoxyphenyl)-4-oxo-4H-chromen-7-yl)oxy)propyl 4-ethylpiperazine-1-carbodithioate (**8b**)

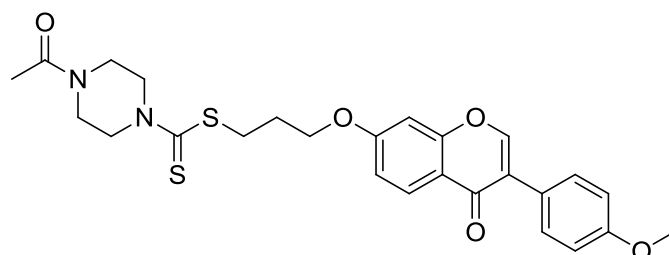


Yield 85%. Yellow solid. Mp: 167~168°C. ^1H NMR (400 MHz, DMSO) δ 8.43 (s, 1H), 8.03 (d, $J = 8.9$ Hz, 1H), 7.53 (d, $J = 8.8$ Hz, 2H), 7.18 (d, $J = 2.3$ Hz, 1H), 7.09 (dd, $J = 8.9, 2.3$ Hz, 1H), 7.00 (d, $J = 8.8$ Hz, 2H), 4.22 (t, $J = 6.1$ Hz, 4H), 3.91 (s, 2H), 3.79 (s, 3H), 3.42 (t, $J = 7.2$ Hz, 2H), 2.47 – 2.39 (m, 4H), 2.36 (q, $J = 7.2$ Hz, 2H), 2.21 – 2.10 (m, 2H), 1.01 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (100 MHz, DMSO) δ 194.69, 174.60, 162.82, 158.99, 157.38, 153.46, 130.05, 126.96, 124.05, 123.35, 117.62, 115.03, 113.61, 101.13, 67.15, 55.14, 51.71, 50.99, 32.69, 27.87, 11.85. HR-MS (ESI): Calcd. $\text{C}_{26}\text{H}_{31}\text{N}_2\text{O}_4\text{S}_2$, $[\text{M}+\text{H}]^+$ m/z : 499.1729, found: 499.1725. IR: 3423, 2969, 1625, 1594, 1576, 1513, 1467, 1253, 1181, 1031 cm^{-1} .

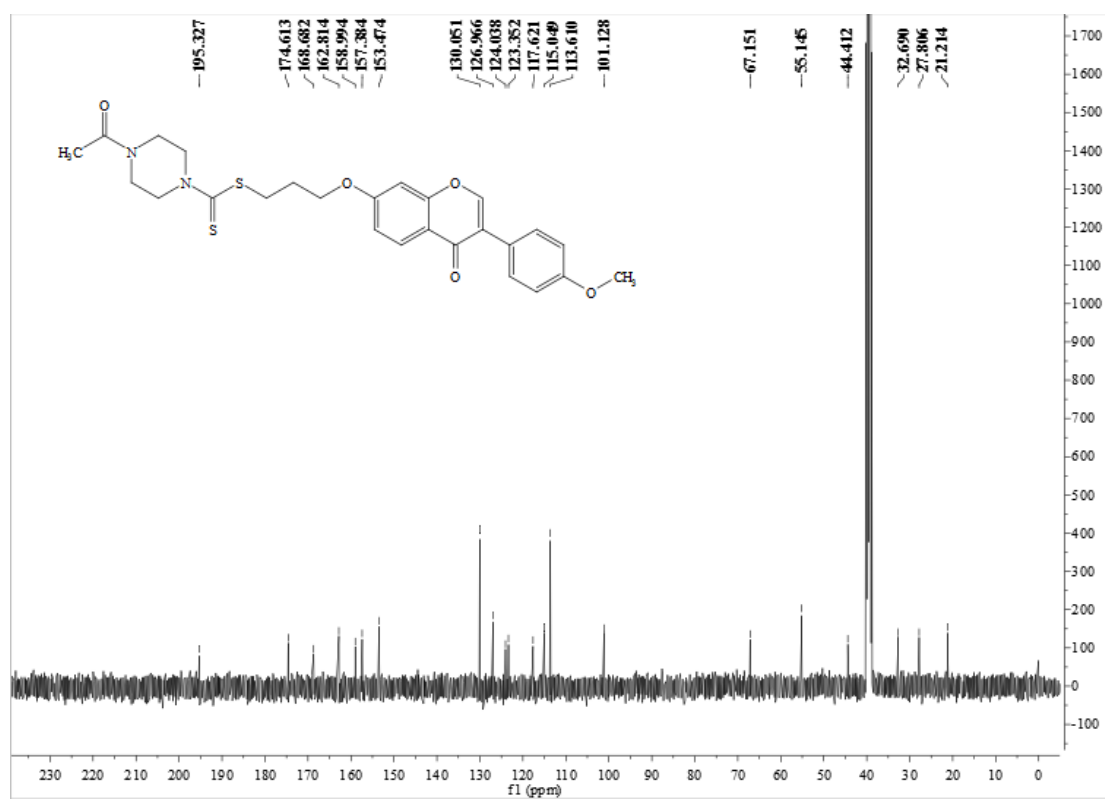
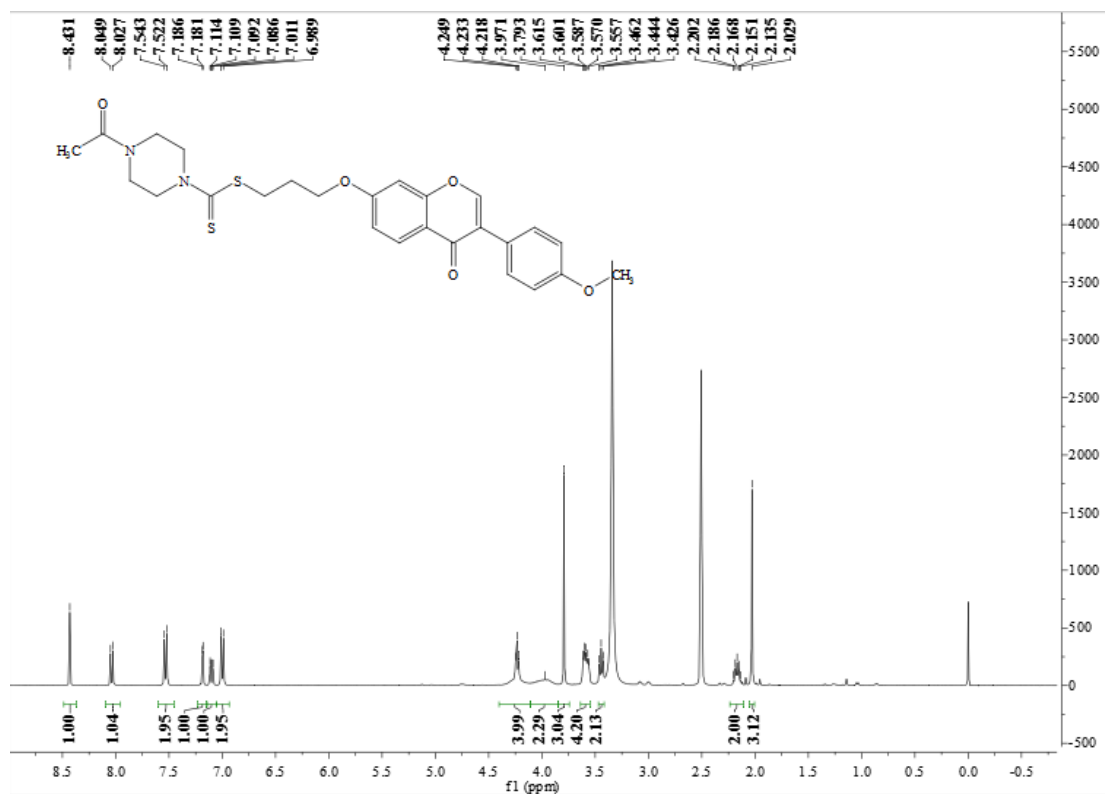




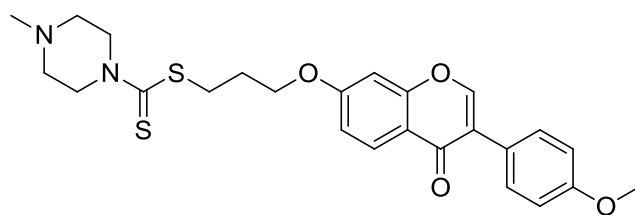
3-((3-(4-methoxyphenyl)-4-oxo-4H-chromen-7-yl)oxy)propyl 4-acetylpiperazine-1-carbodithioate (**8c**)



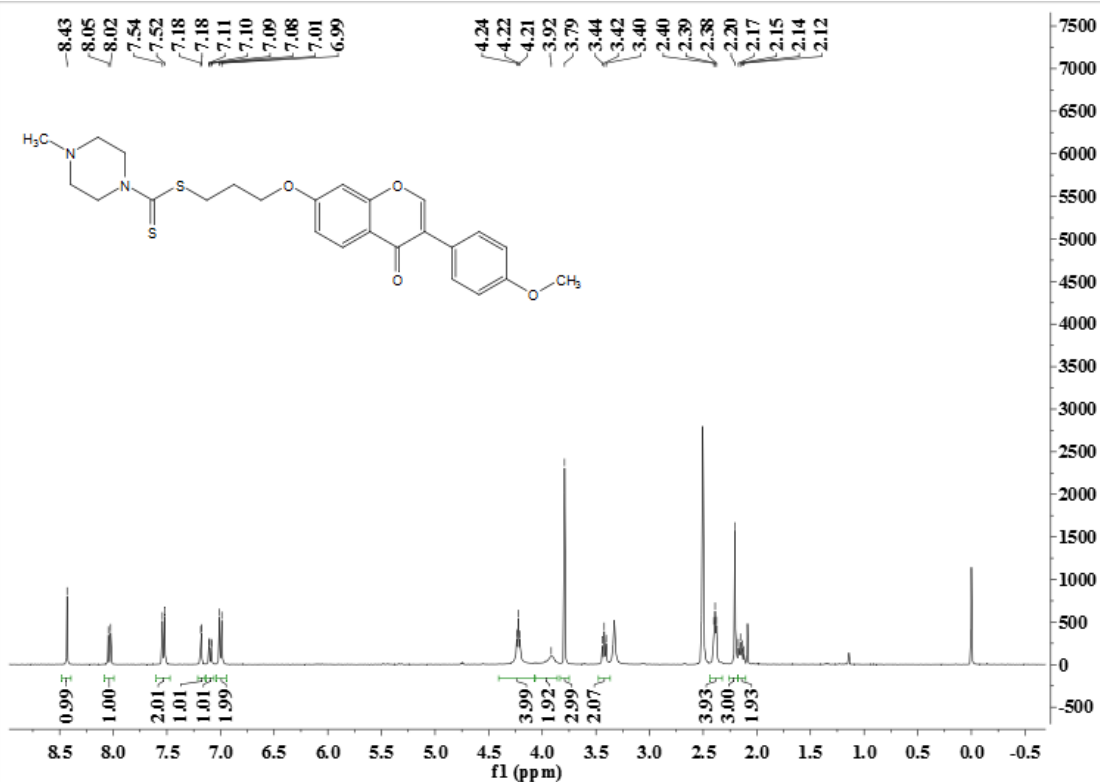
Yield 78%. White solid. Mp: 174~176°C. ^1H NMR (400 MHz, DMSO) δ 8.43 (s, 1H), 8.04 (d, $J = 8.9$ Hz, 1H), 7.53 (d, $J = 8.7$ Hz, 2H), 7.18 (d, $J = 2.2$ Hz, 1H), 7.10 (dd, $J = 8.9, 2.3$ Hz, 1H), 7.00 (d, $J = 8.8$ Hz, 2H), 4.23 (t, $J = 6.1$ Hz, 4H), 3.97 (s, 2H), 3.79 (s, 3H), 3.64 – 3.55 (m, 4H), 3.44 (t, $J = 7.2$ Hz, 2H), 2.24 – 2.11 (m, 2H), 2.03 (s, 3H). ^{13}C NMR (100 MHz, DMSO) δ 195.33, 174.61, 168.68, 162.81, 158.99, 157.38, 153.47, 130.05, 126.97, 124.04, 123.35, 117.62, 115.05, 113.61, 101.13, 67.15, 55.15, 44.41, 32.69, 27.81, 21.21. HR-MS (ESI): Calcd. $\text{C}_{26}\text{H}_{29}\text{N}_2\text{O}_5\text{S}_2$, $[\text{M}+\text{H}]^+$ m/z : 513.1510, found: 513.1518. IR: 3439, 2922, 1648, 1633, 1609, 1567, 1515, 1444, 1252, 1026 cm^{-1} .

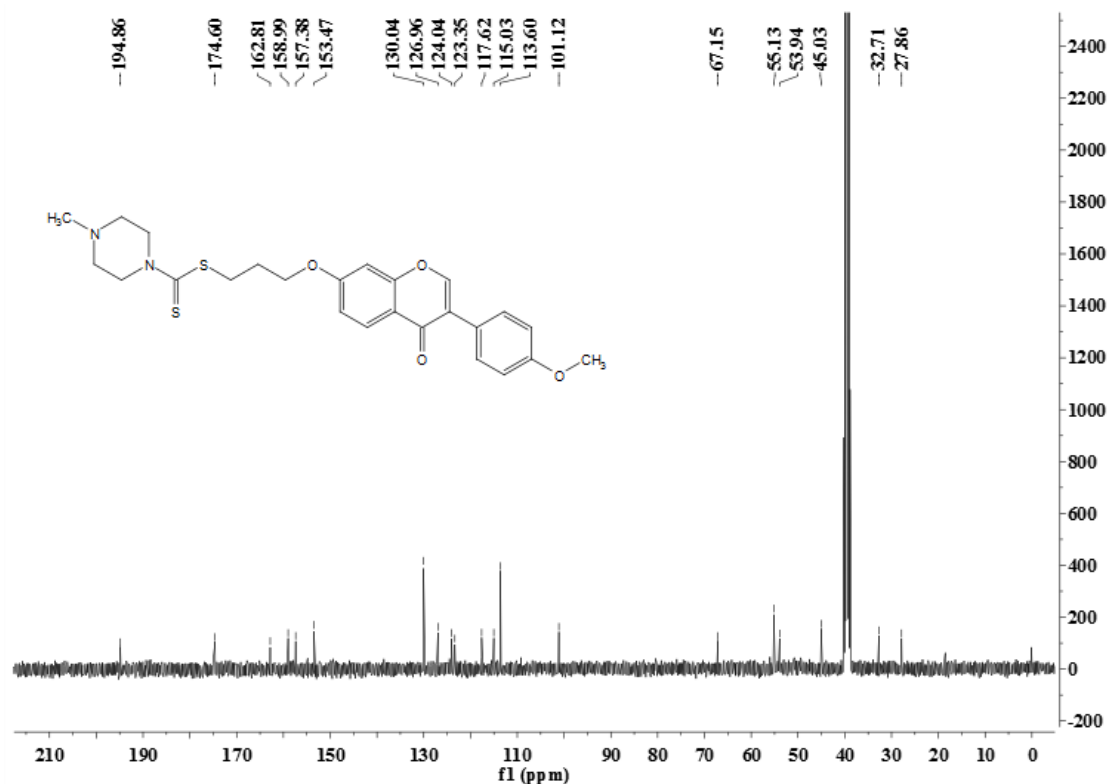


3-((3-(4-methoxyphenyl)-4-oxo-4H-chromen-7-yl)oxy)propyl 4-methylpiperazine-1-carbodithioate (**8d**)

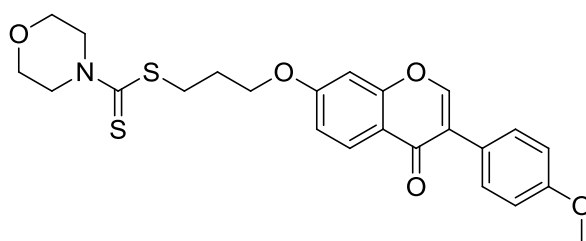


Yield 78%. Yellow solid. Mp: 167~169°C. ^1H NMR (400 MHz, DMSO) δ 8.43 (s, 1H), 8.04 (d, $J = 8.9$ Hz, 1H), 7.53 (d, $J = 8.7$ Hz, 2H), 7.18 (d, $J = 2.3$ Hz, 1H), 7.10 (dd, $J = 8.9, 2.3$ Hz, 1H), 7.00 (d, $J = 8.8$ Hz, 2H), 4.22 (t, $J = 6.1$ Hz, 4H), 3.92 (s, 2H), 3.79 (s, 3H), 3.42 (t, $J = 7.2$ Hz, 2H), 2.44 – 2.32 (m, 4H), 2.20 (s, 3H), 2.14 (dd, $J = 13.7, 7.0$ Hz, 2H). ^{13}C NMR (100 MHz, DMSO) δ 194.86, 174.60, 162.81, 158.99, 157.38, 153.47, 130.04, 126.96, 124.04, 123.35, 117.62, 115.03, 113.60, 101.12, 67.15, 55.13, 53.94, 45.03, 32.71, 27.86. HR-MS (ESI): Calcd. $\text{C}_{25}\text{H}_{29}\text{N}_2\text{O}_4\text{S}_2$, $[\text{M}+\text{H}]^+\text{m/z}$: 485.1574, found: 485.1569. IR: 3442, 2940, 1625, 1595, 1576, 1513, 1442, 1294, 1249, 1198, 1181, 1031 cm^{-1} .

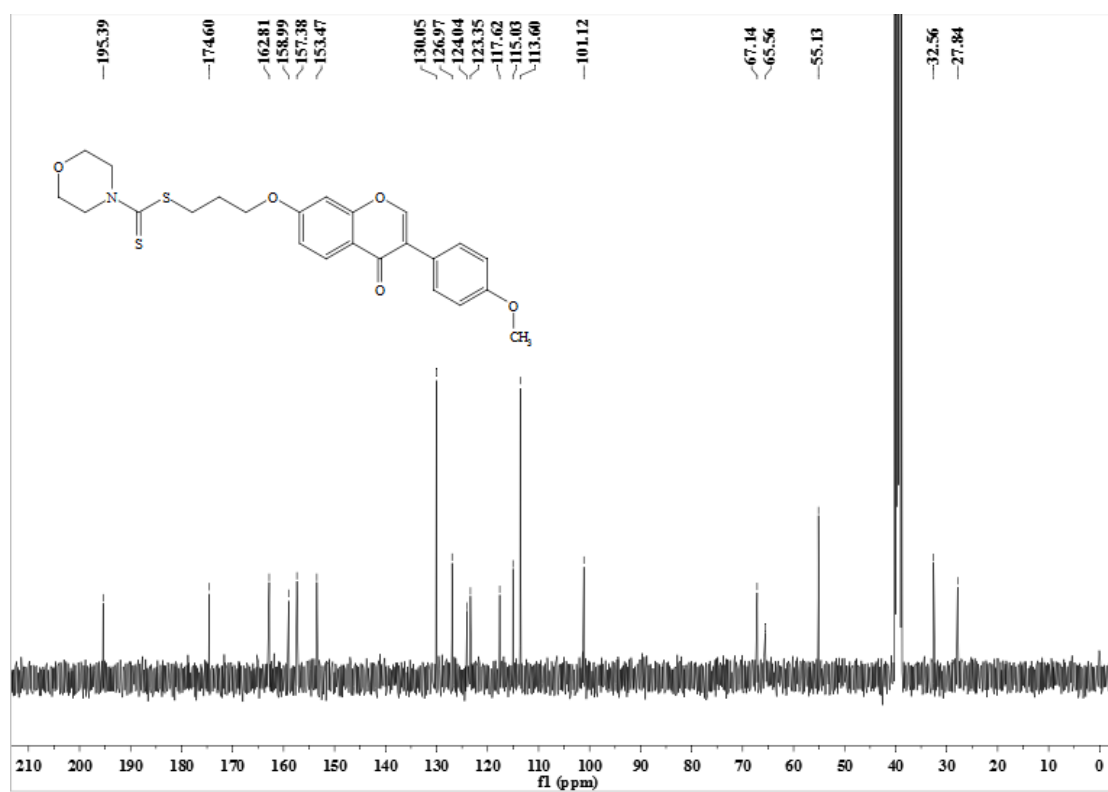
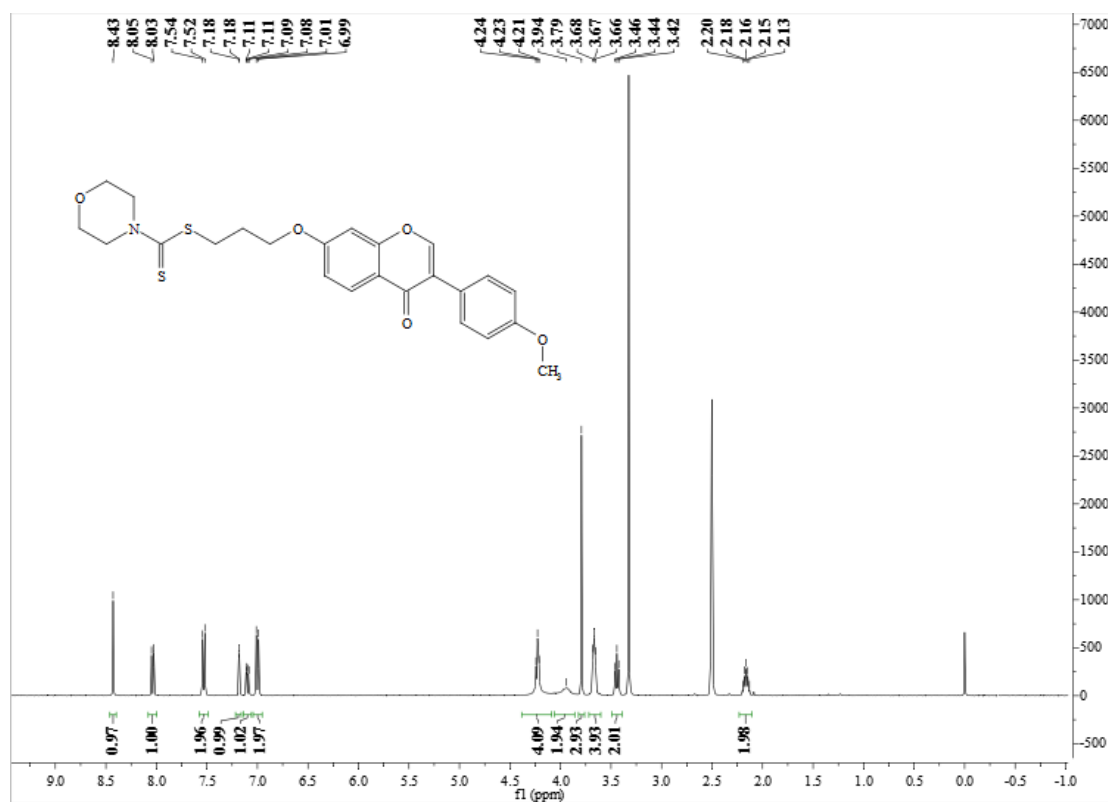




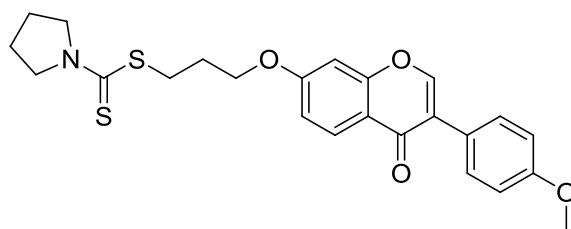
3-((3-(4-methoxyphenyl)-4-oxo-4H-chromen-7-yl)oxy)propyl morpholine-4-carbodithioate (**8e**)



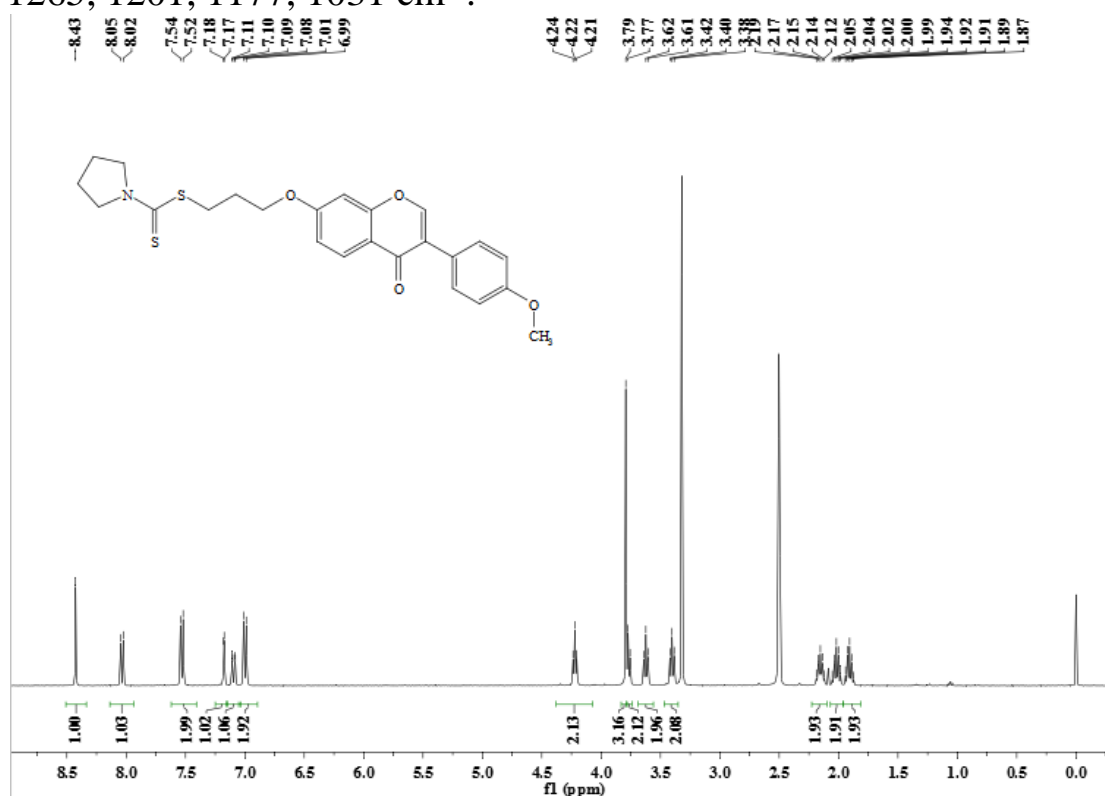
Yield 79%. White solid. Mp: 156~158°C. ^1H NMR (400 MHz, DMSO) δ 8.43 (s, 1H), 8.04 (d, $J = 8.9$ Hz, 1H), 7.53 (d, $J = 8.8$ Hz, 2H), 7.18 (d, $J = 2.3$ Hz, 1H), 7.10 (dd, $J = 8.9, 2.3$ Hz, 1H), 7.00 (d, $J = 8.8$ Hz, 2H), 4.23 (t, $J = 6.1$ Hz, 4H), 3.94 (s, 2H), 3.79 (s, 3H), 3.72 – 3.60 (m, 4H), 3.44 (t, $J = 7.2$ Hz, 2H), 2.23 – 2.11 (m, 2H). ^{13}C NMR (100 MHz, DMSO) δ 195.39, 174.60, 162.81, 158.99, 157.38, 153.47, 130.05, 126.97, 124.04, 123.35, 117.62, 115.03, 113.60, 101.12, 67.14, 65.56, 55.13, 32.56, 27.84. HR-MS (ESI): Calcd. $\text{C}_{24}\text{H}_{26}\text{NO}_5\text{S}_2$, $[\text{M}+\text{H}]^+m/z$: 472.1257, found: 472.1252. IR: 3442, 3077, 1638, 1624, 1609, 1575, 1514, 1441, 1250, 1199, 1177, 1138, 1116 cm^{-1} .

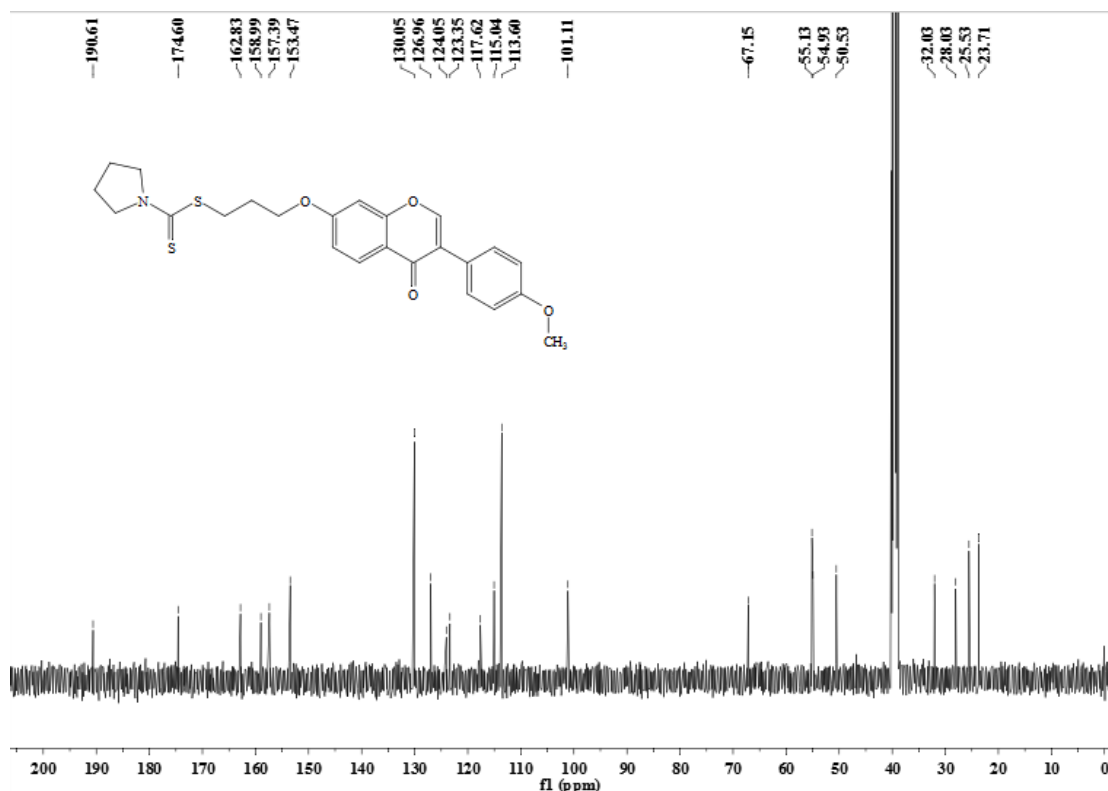


3-((3-(4-methoxyphenyl)-4-oxo-4H-chromen-7-yl)oxy)propyl pyrrolidine-1-carbodithioate (**8f**)

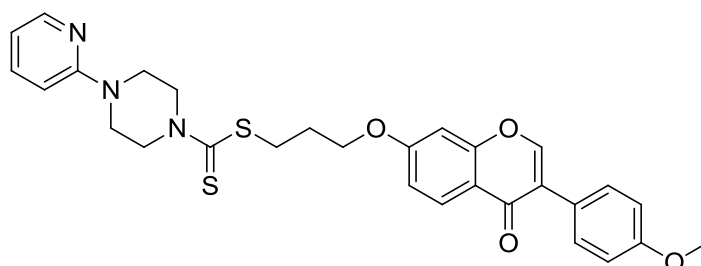


Yield 81%. White solid. Mp: 159~161°C. ^1H NMR (400 MHz, DMSO) δ 8.43 (s, 1H), 8.04 (d, $J = 8.9$ Hz, 1H), 7.53 (d, $J = 8.8$ Hz, 2H), 7.18 (d, $J = 2.3$ Hz, 1H), 7.09 (dd, $J = 8.9, 2.3$ Hz, 1H), 7.00 (d, $J = 8.8$ Hz, 2H), 4.22 (t, $J = 6.2$ Hz, 2H), 3.79 (s, 3H), 3.76 (d, $J = 6.9$ Hz, 2H), 3.62 (t, $J = 6.8$ Hz, 2H), 3.40 (t, $J = 7.2$ Hz, 2H), 2.23 – 2.10 (m, 2H), 2.07 – 1.96 (m, 2H), 1.91 (p, $J = 6.7$ Hz, 2H). ^{13}C NMR (100 MHz, DMSO) δ 190.61, 174.60, 162.83, 158.99, 157.39, 153.47, 130.05, 126.96, 124.05, 123.35, 117.62, 115.04, 113.60, 101.11, 67.15, 55.13, 54.93, 50.53, 32.03, 28.03, 25.53, 23.71. HR-MS (ESI): Calcd. $\text{C}_{24}\text{H}_{26}\text{NO}_4\text{S}_2$, $[\text{M}+\text{H}]^+$ m/z : 456.1306, found: 456.1303. IR: 3445, 2848, 1623, 1609, 1574, 1513, 1443, 1290, 1265, 1201, 1177, 1031 cm^{-1} .

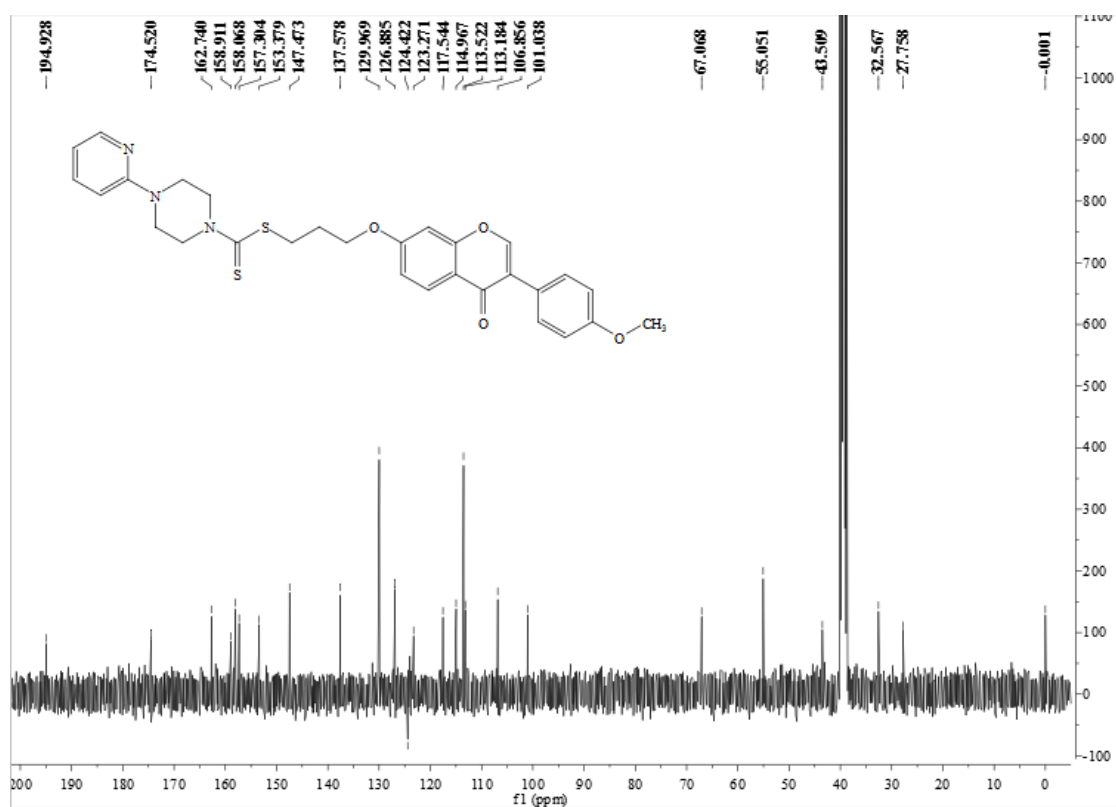
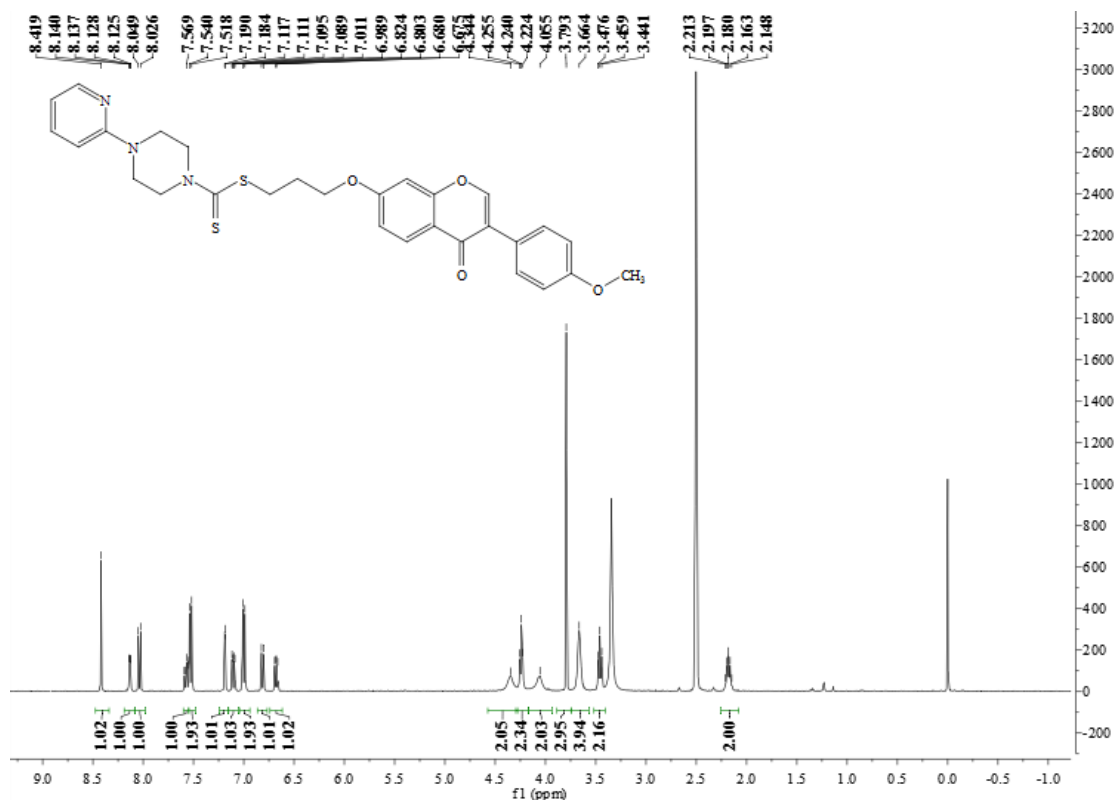




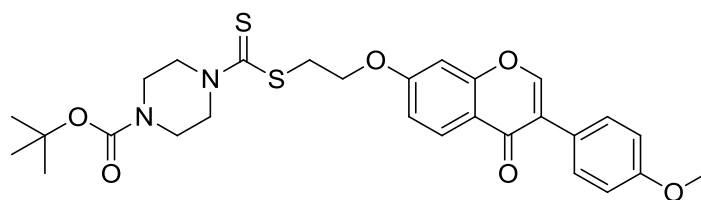
3-((3-(4-methoxyphenyl)-4-oxo-4H-chromen-7-yl)oxy)propyl 4-(pyridin-2-yl)piperazine-1-carbodithioate (**8g**)



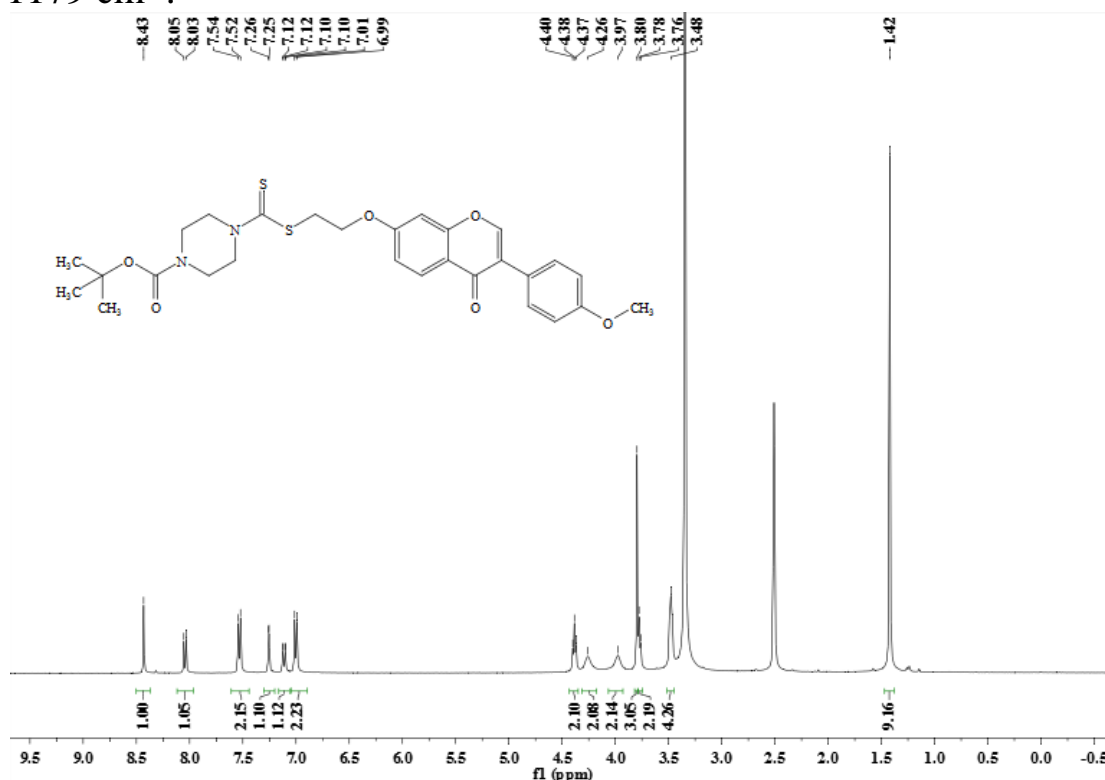
Yield 84%. White solid. Mp: 178~180°C. ^1H NMR (400 MHz, DMSO) δ 8.42 (s, 1H), 8.13 (dd, $J = 4.9, 1.3$ Hz, 1H), 8.04 (d, $J = 8.9$ Hz, 1H), 7.60 – 7.55 (m, 1H), 7.55 – 7.48 (m, 2H), 7.19 (d, $J = 2.3$ Hz, 1H), 7.10 (dd, $J = 8.9, 2.3$ Hz, 1H), 7.00 (d, $J = 8.8$ Hz, 2H), 6.81 (d, $J = 8.6$ Hz, 1H), 6.68 (dd, $J = 7.0, 5.0$ Hz, 1H), 4.34 (s, 2H), 4.24 (t, $J = 6.1$ Hz, 2H), 4.06 (s, 2H), 3.79 (s, 3H), 3.66 (s, 4H), 3.46 (t, $J = 7.1$ Hz, 2H), 2.26 – 2.08 (m, 2H). ^{13}C NMR (100 MHz, DMSO) δ 194.93, 174.52, 162.74, 158.91, 158.07, 157.30, 153.38, 147.47, 137.58, 129.97, 126.88, 124.42, 123.27, 117.54, 114.97, 113.52, 113.18, 106.86, 101.04, 67.07, 55.05, 43.51, 32.57, 27.76. HR-MS (ESI): Calcd. $\text{C}_{29}\text{H}_{30}\text{N}_3\text{O}_4\text{S}_2$, $[\text{M}+\text{H}]^+m/z$: 548.1684, found: 548.1678. IR: 3441, 2915, 1639, 1627, 1599, 1567, 1514, 1442, 1251, 1224, 1035 cm^{-1} .

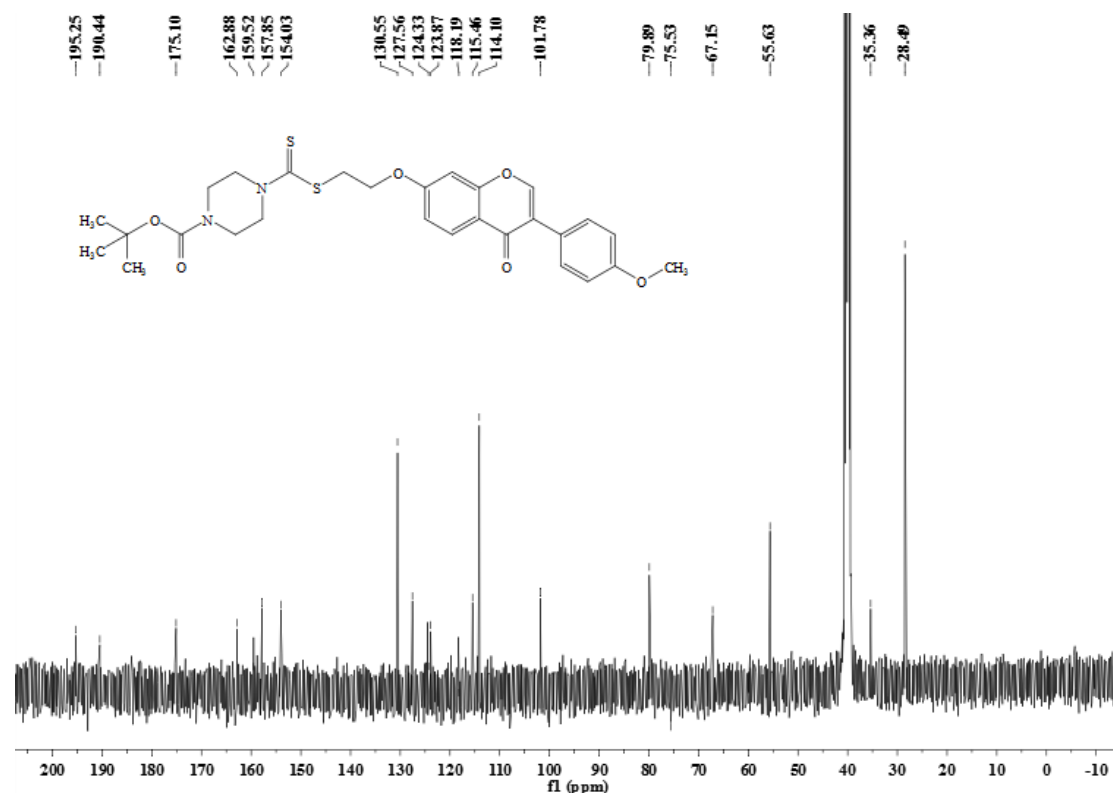


tert-butyl 4-(((2-((3-(4-methoxyphenyl)-4-oxo-4H-chromen-7-yl)oxy)ethyl)thio)carbonothioyl)piperazine-1-carboxylate (**8h**)

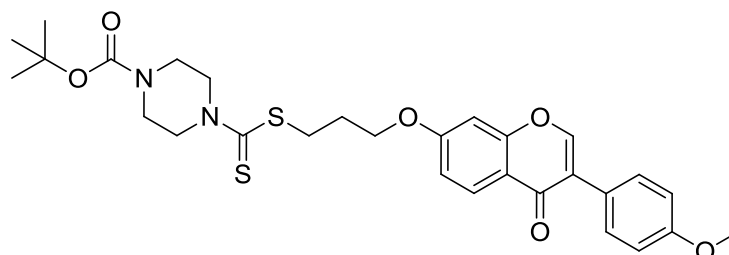


Yield 79%. White solid. Mp: 140~142°C. ^1H NMR (400 MHz, DMSO) δ 8.43 (s, 1H), 8.04 (d, $J = 8.9$ Hz, 1H), 7.53 (d, $J = 8.6$ Hz, 2H), 7.26 (d, $J = 1.8$ Hz, 1H), 7.11 (dd, $J = 9.0, 2.0$ Hz, 1H), 7.00 (d, $J = 8.6$ Hz, 2H), 4.38 (t, $J = 6.2$ Hz, 2H), 4.26 (s, 2H), 3.97 (s, 2H), 3.80 (s, 3H), 3.77 (t, $J = 6.2$ Hz, 2H), 3.48 (s, 4H), 1.42 (s, 9H). ^{13}C NMR (100 MHz, DMSO) δ 195.25, 190.44, 175.10, 162.88, 159.52, 157.85, 154.03, 130.55, 127.56, 124.33, 123.87, 118.19, 115.46, 114.10, 101.78, 79.89, 75.53, 67.15, 55.63, 35.36, 28.49. HR-MS (ESI): Calcd. $\text{C}_{28}\text{H}_{33}\text{N}_2\text{O}_6\text{S}_2$, $[\text{M}+\text{H}]^+m/z$: 557.1788, found: 557.1780. IR: 3440, 2972, 1701, 1627, 1513, 1443, 1289, 1251, 1179 cm^{-1} .

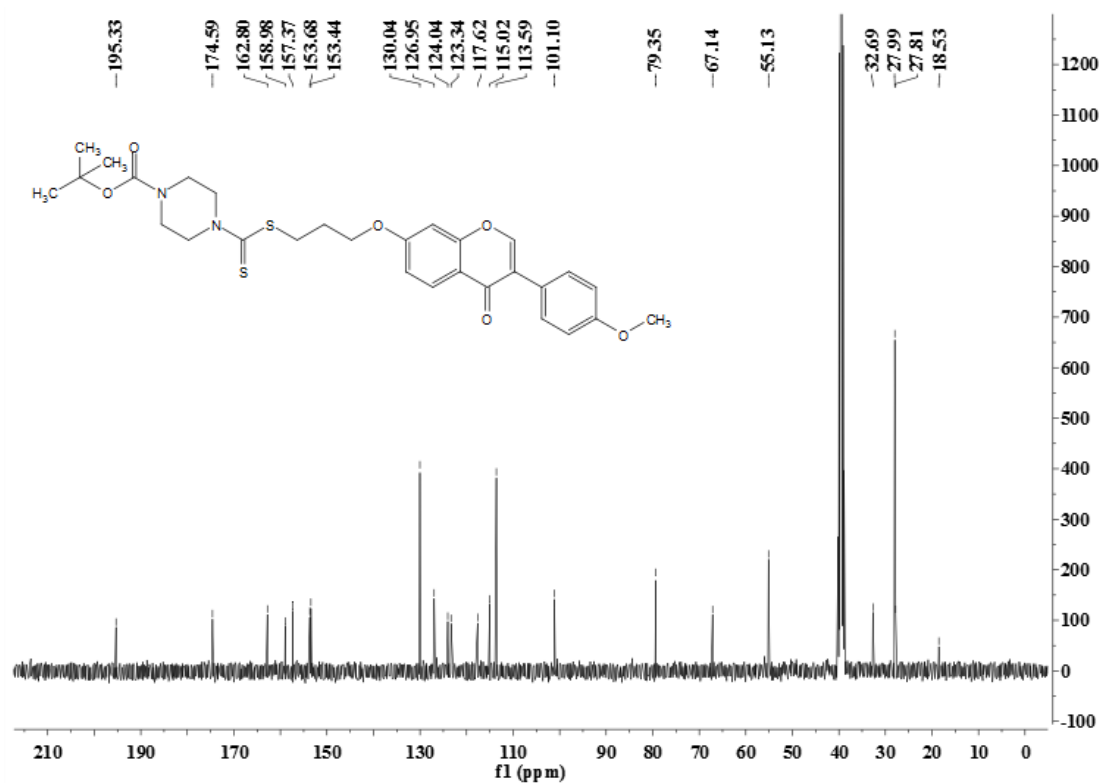
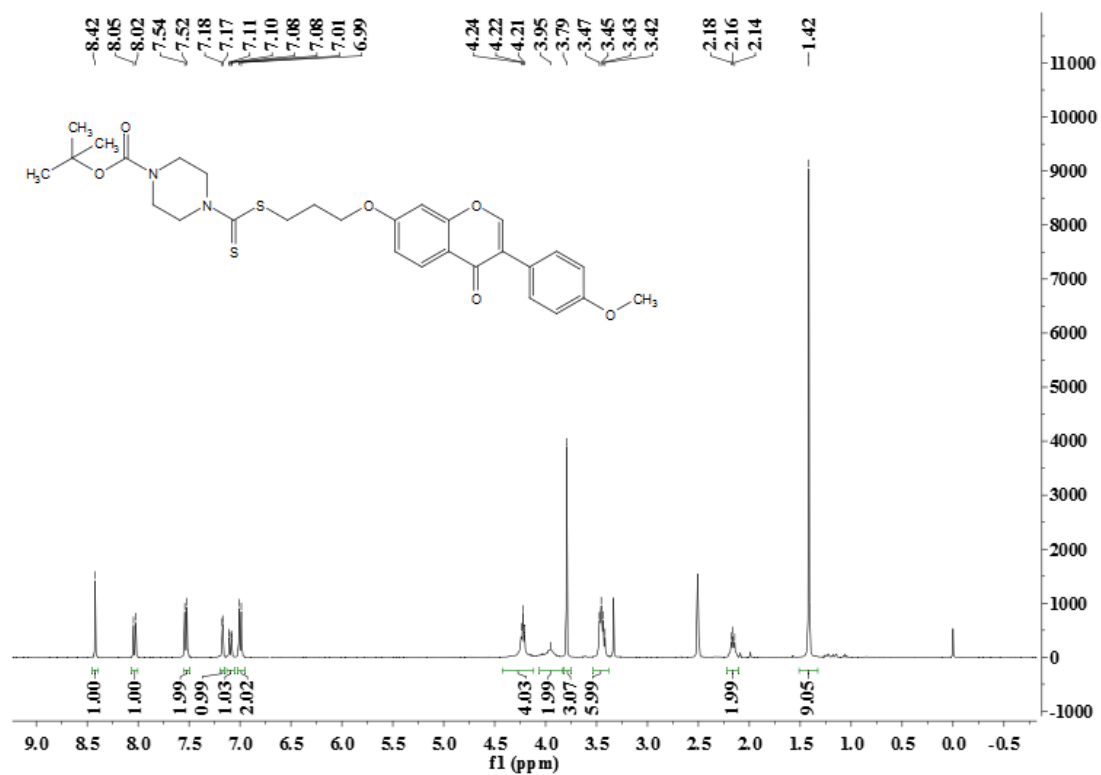




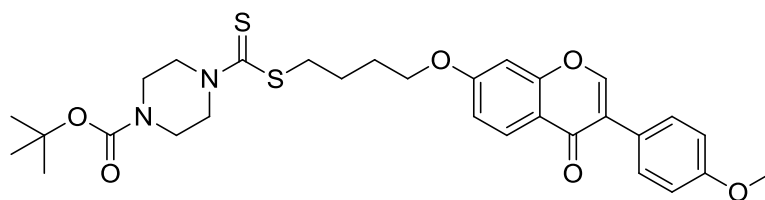
tert-butyl 4-(((3-((3-(4-methoxyphenyl)-4-oxo-4H-chromen-7-yl)oxy)propyl)thio)carbonothioyl)piperazine-1-carboxylate (**8i**)



Yield 83%. White solid. Mp: 165~167°C. ^1H NMR (400 MHz, DMSO) δ 8.42 (s, 1H), 8.03 (d, $J = 8.9$ Hz, 1H), 7.53 (d, $J = 8.8$ Hz, 2H), 7.17 (d, $J = 2.3$ Hz, 1H), 7.09 (dd, $J = 8.9, 2.3$ Hz, 1H), 7.00 (d, $J = 8.8$ Hz, 2H), 4.22 (t, $J = 6.1$ Hz, 4H), 3.95 (s, 2H), 3.79 (s, 3H), 3.44 (dd, $J = 15.1, 7.3$ Hz, 6H), 2.22 – 2.10 (m, 2H), 1.42 (s, 9H). ^{13}C NMR (100 MHz, DMSO) δ 195.33, 174.59, 162.80, 158.98, 157.37, 153.68, 153.44, 130.04, 126.95, 124.04, 123.34, 117.62, 115.02, 113.59, 101.10, 79.35, 67.14, 55.13, 32.69, 27.99, 27.81, 18.53. HR-MS (ESI): Calcd. $\text{C}_{29}\text{H}_{35}\text{N}_2\text{O}_6\text{S}_2$, $[\text{M}+\text{H}]^+$ m/z : 571.1940, found: 571.1937. IR: 3440, 2931, 1690, 1608, 1566, 1513, 1444, 1419, 1250, 1223, 1178 1031 cm^{-1} .



tert-butyl 4-(((4-((3-(4-methoxyphenyl)-4-oxo-4H-chromen-7-yl)oxy)butyl)thio)carbonothioyl)piperazine-1-carboxylate (**8j**)



Yield 85%. White solid. Mp: 143~144°C. ^1H NMR (400 MHz, DMSO) δ 8.41 (s, 1H), 8.02 (d, $J = 8.9$ Hz, 1H), 7.53 (d, $J = 8.7$ Hz, 2H), 7.15 (d, $J = 2.2$ Hz, 1H), 7.07 (dd, $J = 8.9, 2.2$ Hz, 1H), 7.00 (d, $J = 8.8$ Hz, 2H), 4.23 (s, 2H), 4.16 (t, $J = 5.8$ Hz, 2H), 3.94 (s, 2H), 3.51 – 3.42 (m, 4H), 1.95 – 1.76 (m, 4H), 1.42 (s, 9H). ^{13}C NMR (100 MHz, DMSO) δ 196.13, 175.10, 163.47, 159.48, 157.89, 154.18, 153.92, 130.54, 127.41, 124.55, 123.83, 118.01, 115.51, 114.09, 101.51, 79.86, 68.48, 55.62, 36.24, 28.49, 28.09, 25.55. HR-MS (ESI): Calcd. $\text{C}_{30}\text{H}_{37}\text{N}_2\text{O}_6\text{S}_2$, $[\text{M}+\text{H}]^+ m/z$: 585.2096, found: 585.2093. IR: 3435, 2931, 1707, 1630, 1514, 1445, 1406, 1252, 1264, 1168 1027 cm^{-1} .



