

Antiproliferative Phenothiazine Hybrids as Novel Apoptosis Inducers against MCF-7 Breast Cancer

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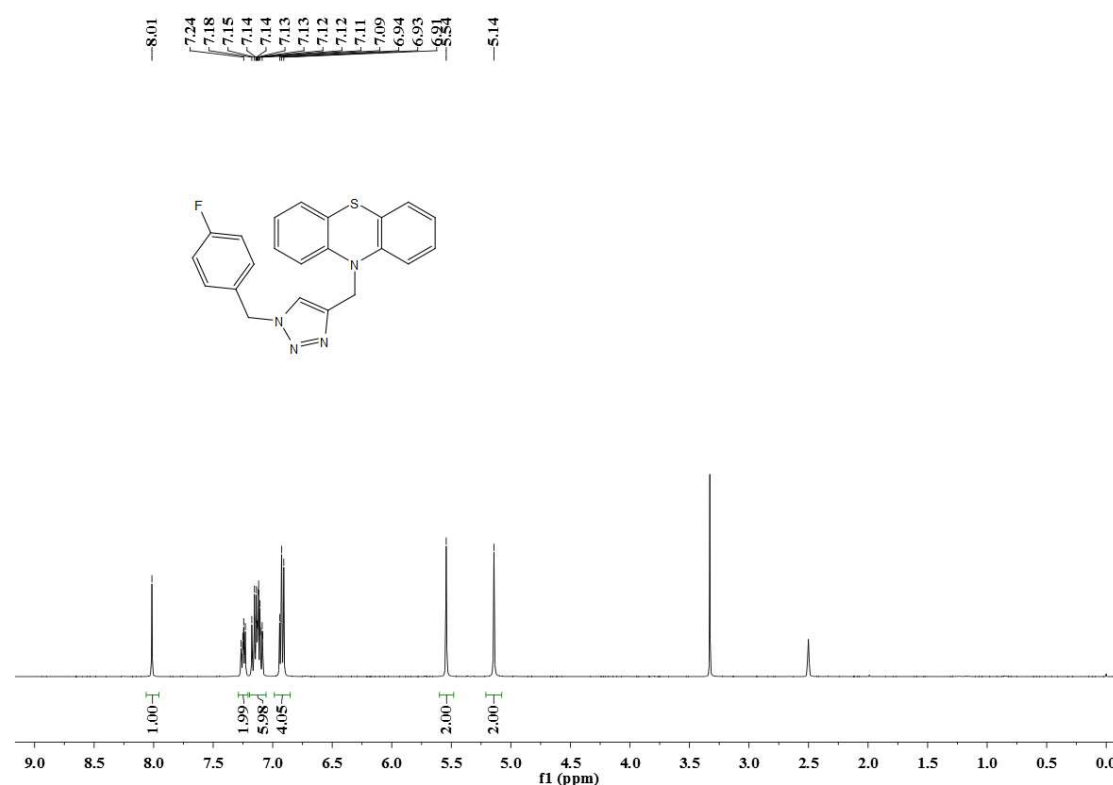
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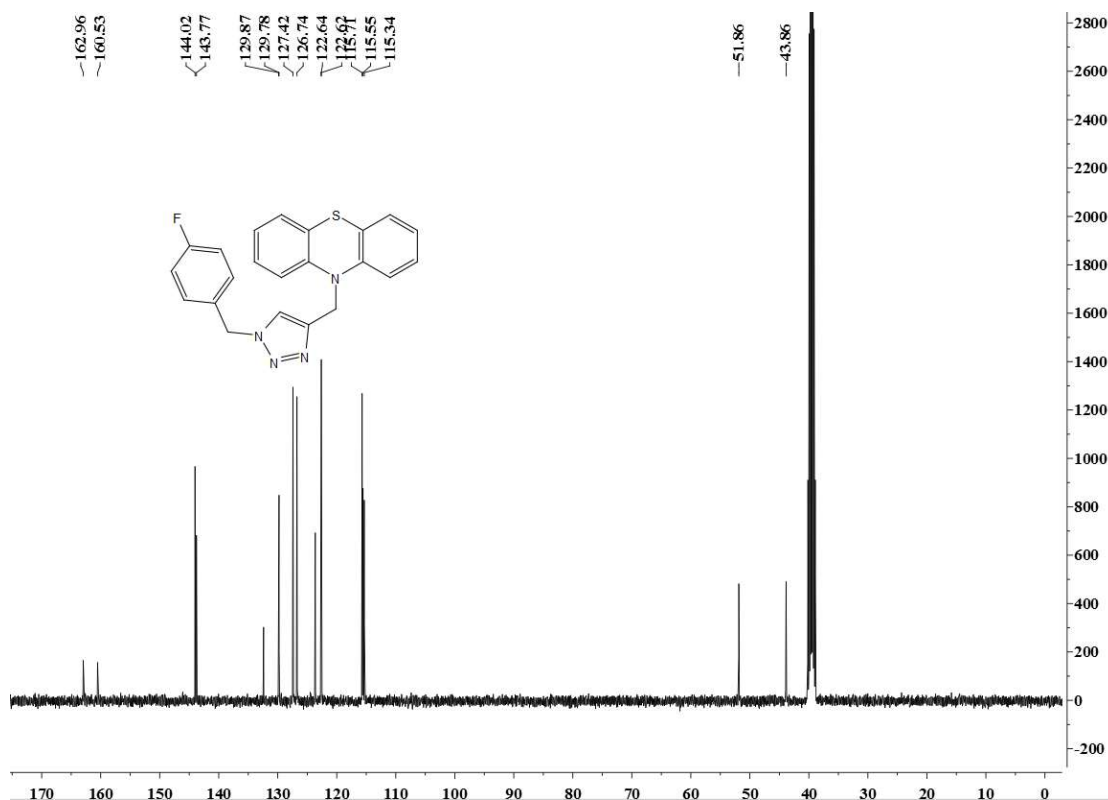
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10-((1-(4-Fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl)-10H-phenothiazine (9a)

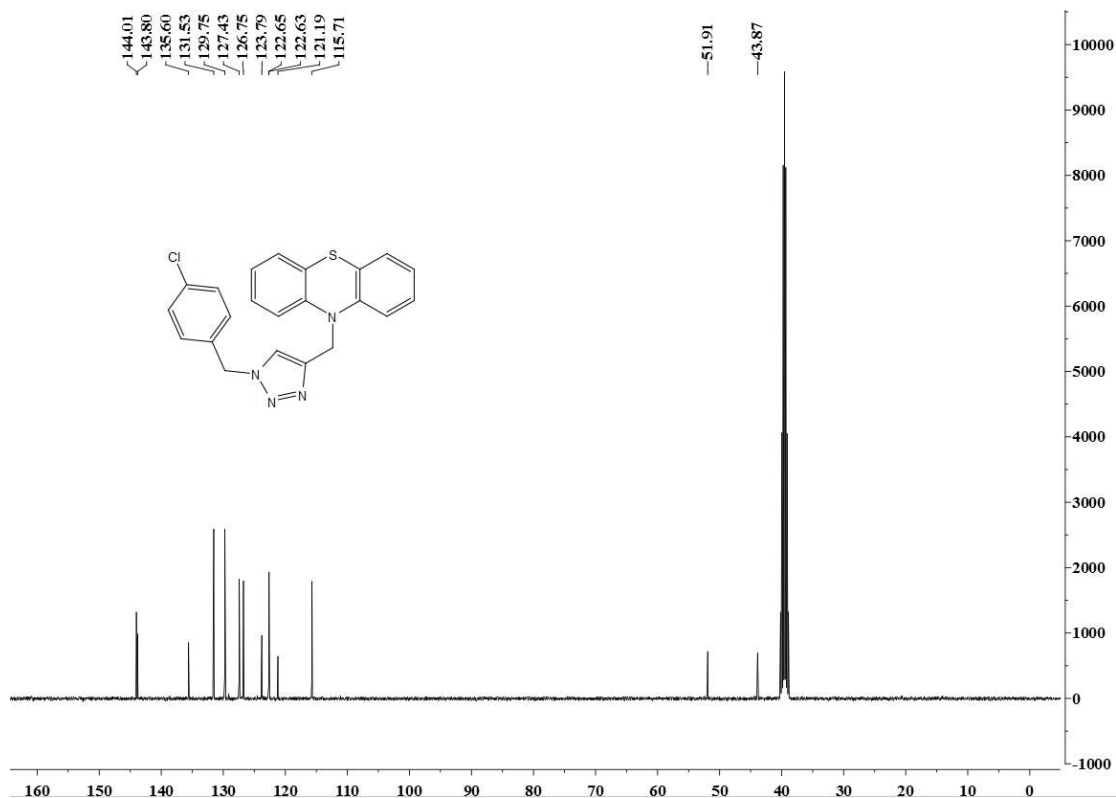
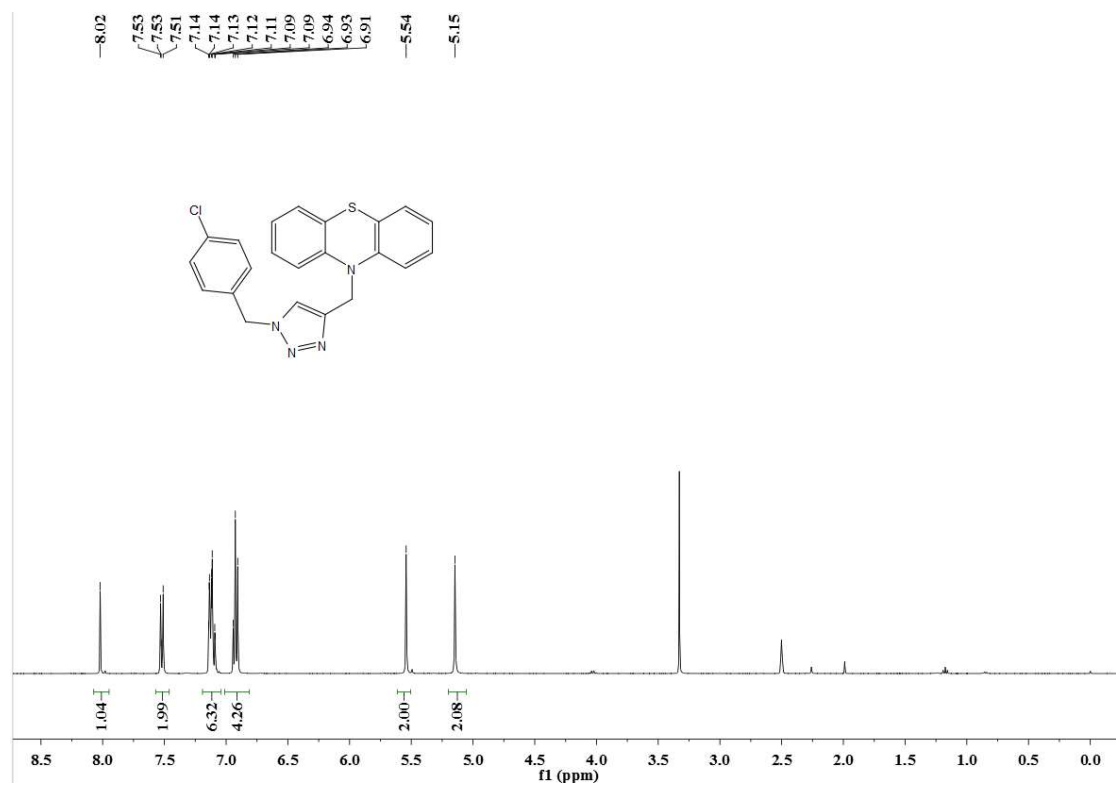
Yield: 87%. White solid. Mp: 166~167°C. ¹H NMR (400 MHz, DMSO) δ 8.01 (s, 1H), 7.29 – 7.21 (m, 2H), 7.19 – 7.06 (m, 6H), 6.99 – 6.85 (m, 4H), 5.54 (s, 2H), 5.14 (s, 2H). ¹³C NMR (100 MHz, DMSO) δ 162.96, 160.53, 144.02, 143.77, 132.42, 132.39, 129.87, 129.78, 127.42, 126.74, 123.64, 122.64, 122.62, 115.71, 115.55, 115.34, 51.86, 43.86. HR-MS (ESI): Calcd. C₂₂H₁₈FN₄S, [M+H]⁺m/z: 389.1236, found: 389.1239.





10-((1-(4-Chlorobenzyl)-1H-1,2,3-triazol-4-yl)methyl)-10H-phenothiazine (9b)

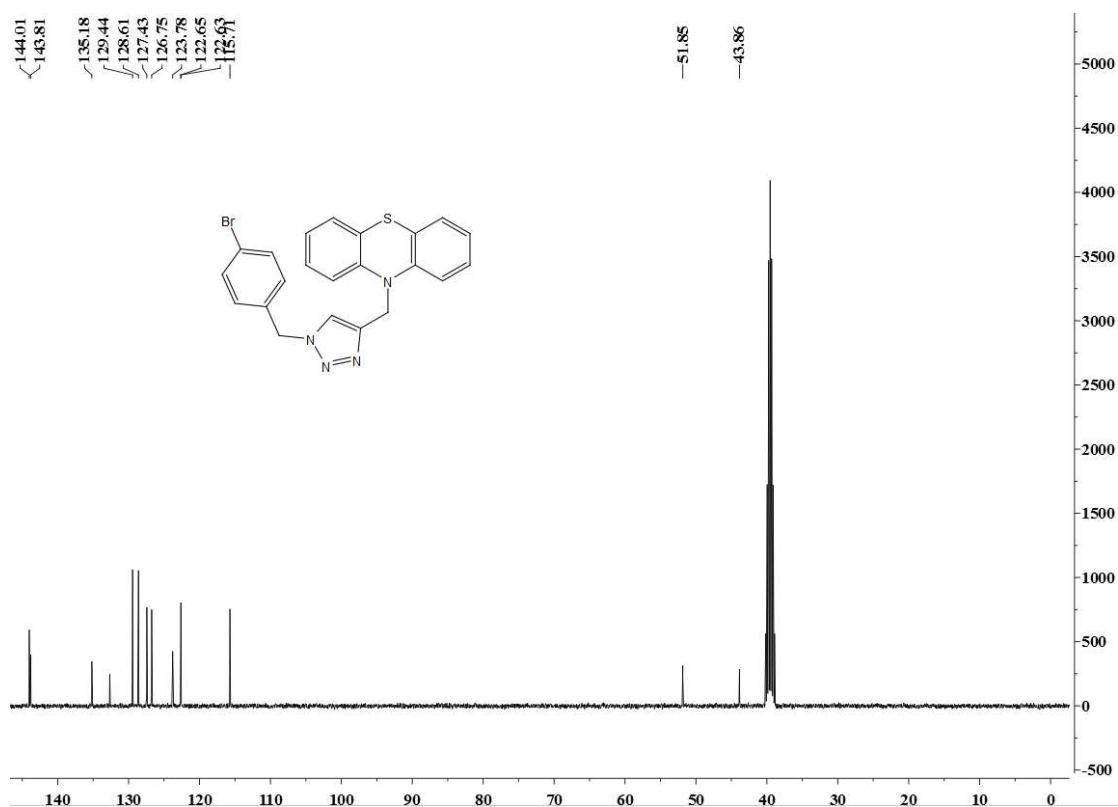
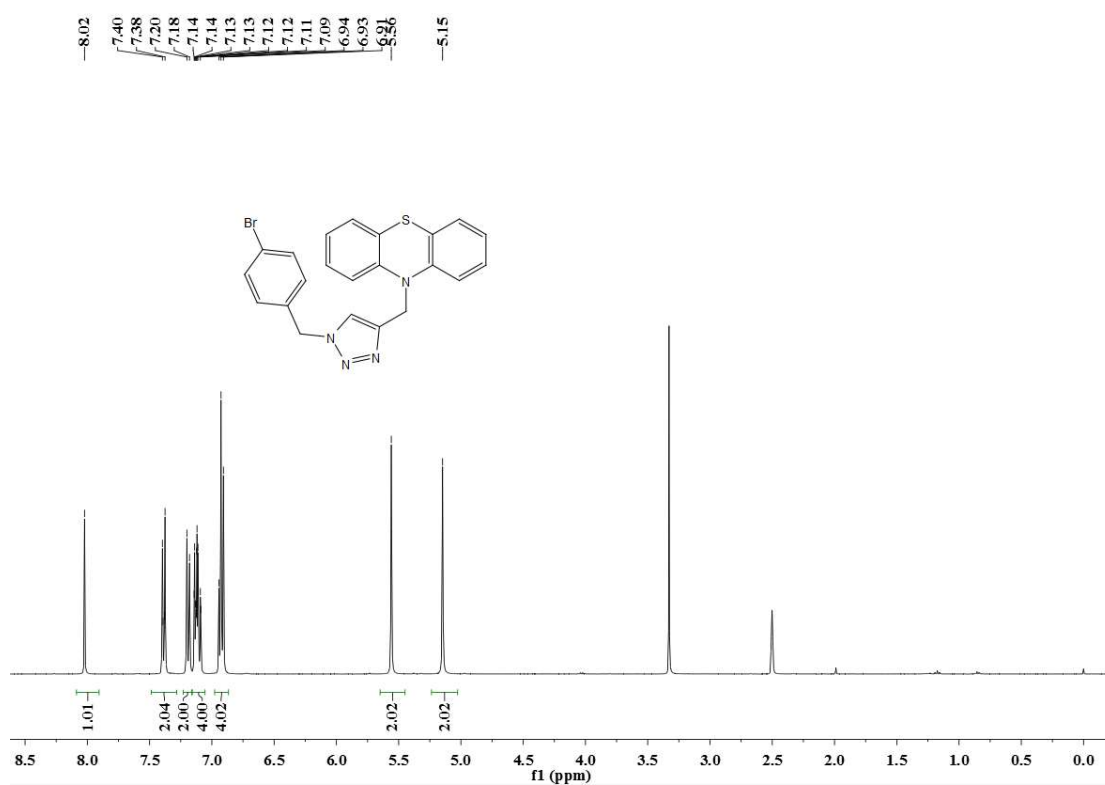
Yield: 69%. White solid. Mp: 150~151°C. ¹H NMR (400 MHz, DMSO) δ 8.02 (s, 1H), 7.57 – 7.46 (m, 2H), 7.19 – 7.04 (m, 6H), 6.92 (t, *J* = 7.3 Hz, 4H), 5.54 (s, 2H), 5.15 (s, 2H). ¹³C NMR (100 MHz, DMSO) δ 144.01, 143.80, 135.60, 131.53, 129.75, 127.43, 126.75, 123.79, 122.65, 122.63, 121.19, 115.71, 51.91, 43.87. HR-MS (ESI): Calcd. C₂₂H₁₈ClN₄S, [M+H]⁺*m/z*: 405.0941, found: 405.0948.



10-((1-(4-Bromobenzyl)-1H-1,2,3-triazol-4-yl)methyl)-10H-phenothiazine (9c)

Yield: 77%. White solid. Mp: 154~155°C. ^1H NMR (400 MHz, DMSO) δ 8.02 (s, 1H), 7.49 – 7.28 (m, 2H), 7.19 (d, J = 8.5 Hz, 2H), 7.16 – 7.05 (m, 4H), 6.93 (t, J = 7.2 Hz, 4H), 5.56 (s, 2H), 5.15 (s, 2H). ^{13}C NMR (100 MHz, DMSO) δ 144.01, 143.81, 135.18, 132.66, 129.44, 128.61, 127.43, 126.75, 123.78, 122.65, 122.63, 115.71, 51.85, 43.86. HR-MS (ESI): Calcd. $\text{C}_{22}\text{H}_{18}\text{BrN}_4\text{S}$, $[\text{M}+\text{H}]^+$ m/z : 449.0436,

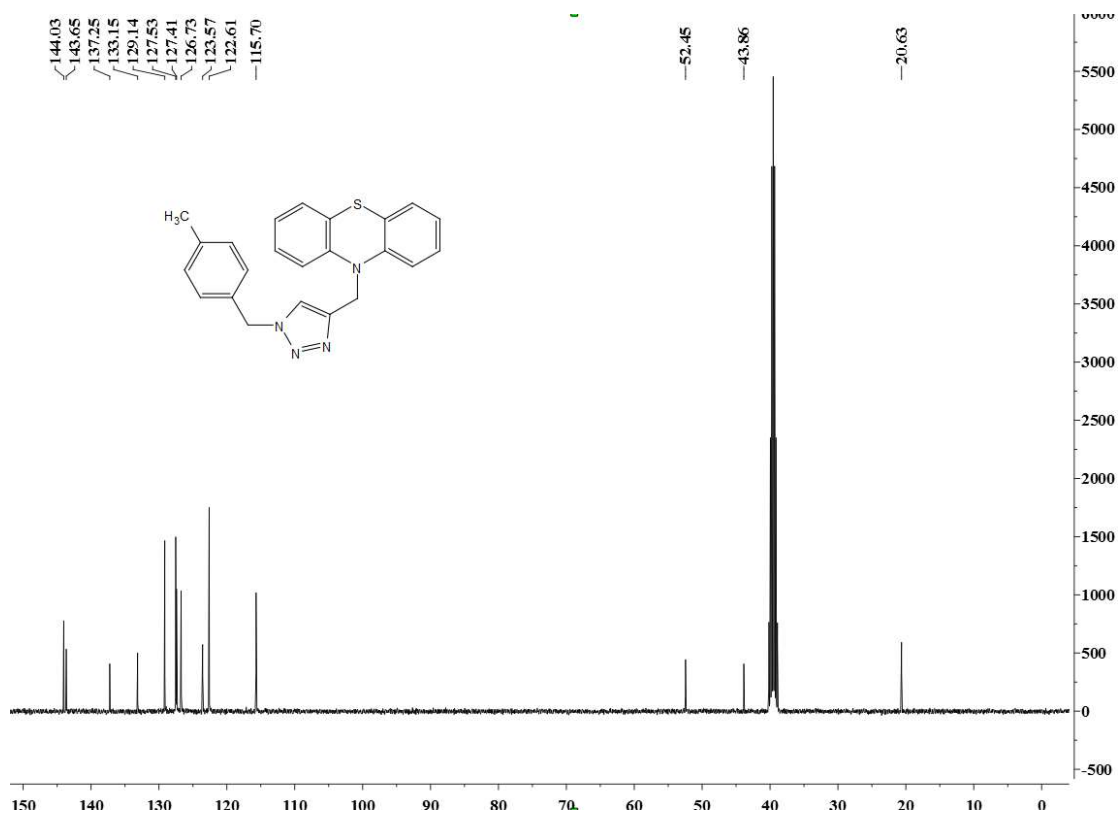
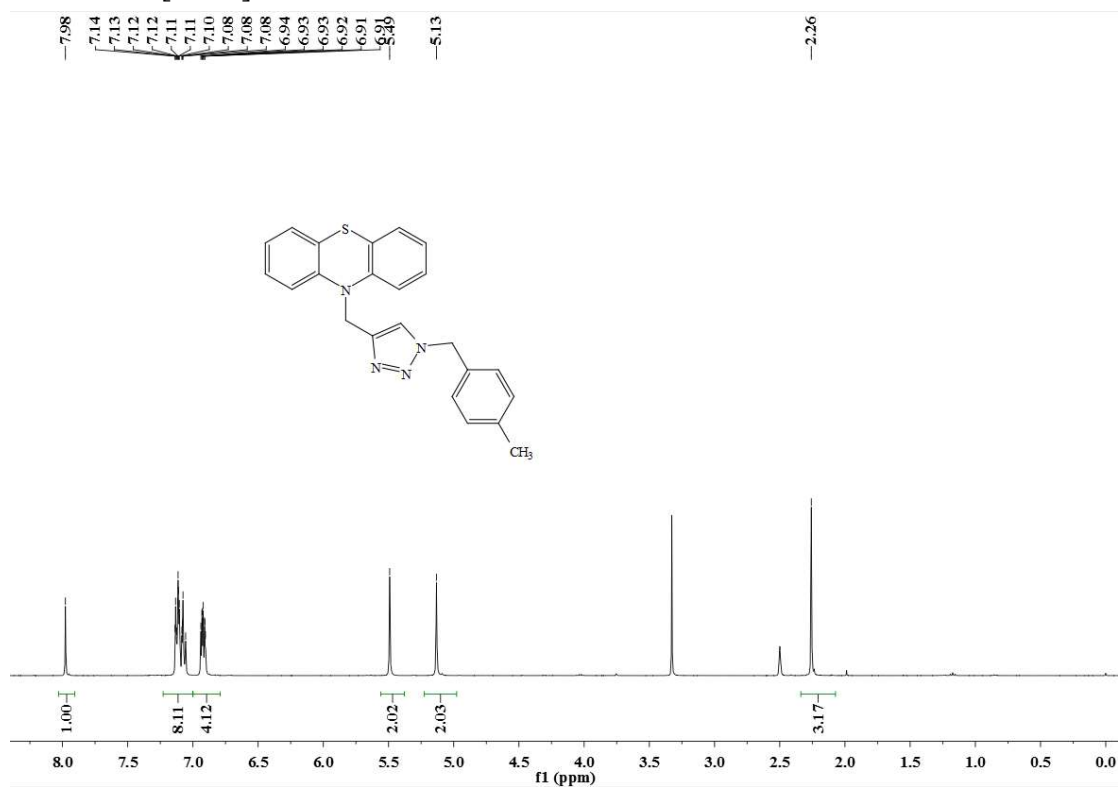
found: 449.0440.



10-((1-(4-Methylbenzyl)-1H-1,2,3-triazol-4-yl)methyl)-10H-phenothiazine (9d)

Yield: 90%. White solid. Mp: 151~152°C. ¹H NMR (400 MHz, DMSO) δ 7.98 (s, 1H), 7.23 – 7.00 (m, 8H), 7.00 – 6.79 (m, 4H), 5.49 (s, 2H), 5.13 (s, 2H), 2.26 (s, 3H). ¹³C NMR (100 MHz, DMSO) δ 144.03, 143.65, 137.25, 133.15, 129.14, 127.53,

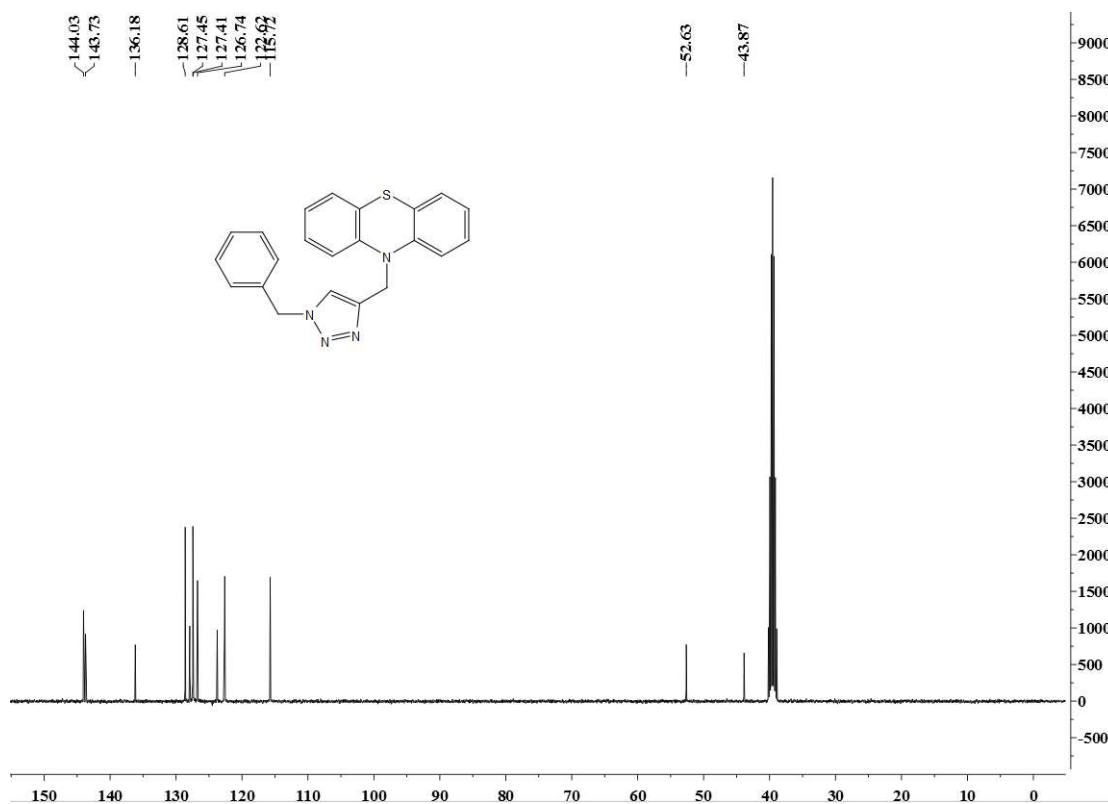
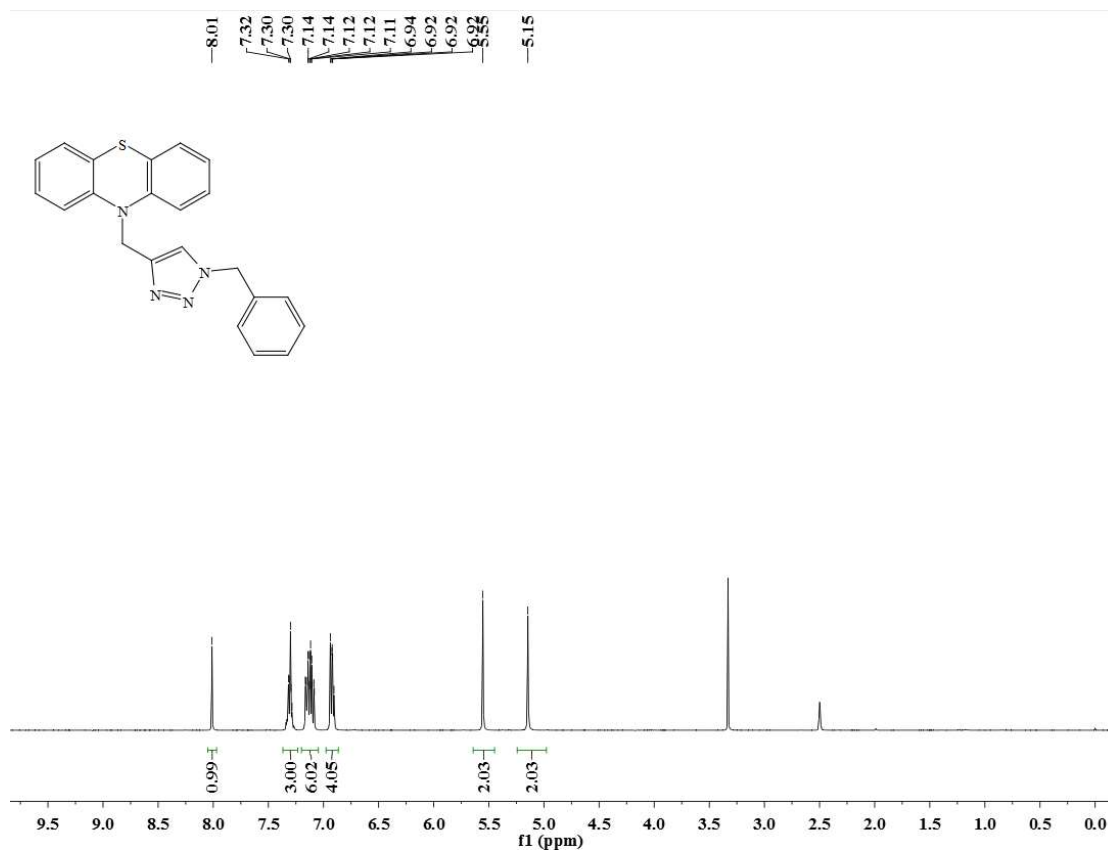
127.41, 126.73, 123.57, 122.61, 115.70, 52.45, 43.86, 20.63. HR-MS (ESI): Calcd. $C_{23}H_{21}N_4S$, $[M+H]^+$ m/z : 385.1487, found: 385.1489.



10-((1-Benzyl-1H-1,2,3-triazol-4-yl)methyl)-10H-phenothiazine (9e)

Yield: 82%. White solid. Mp: 150~152°C. ¹H NMR (400 MHz, DMSO) δ 8.01 (s, 1H), 7.37 – 7.23 (m, 3H), 7.20 – 7.05 (m, 6H), 6.98 – 6.87 (m, 4H), 5.55 (s, 2H), 5.15

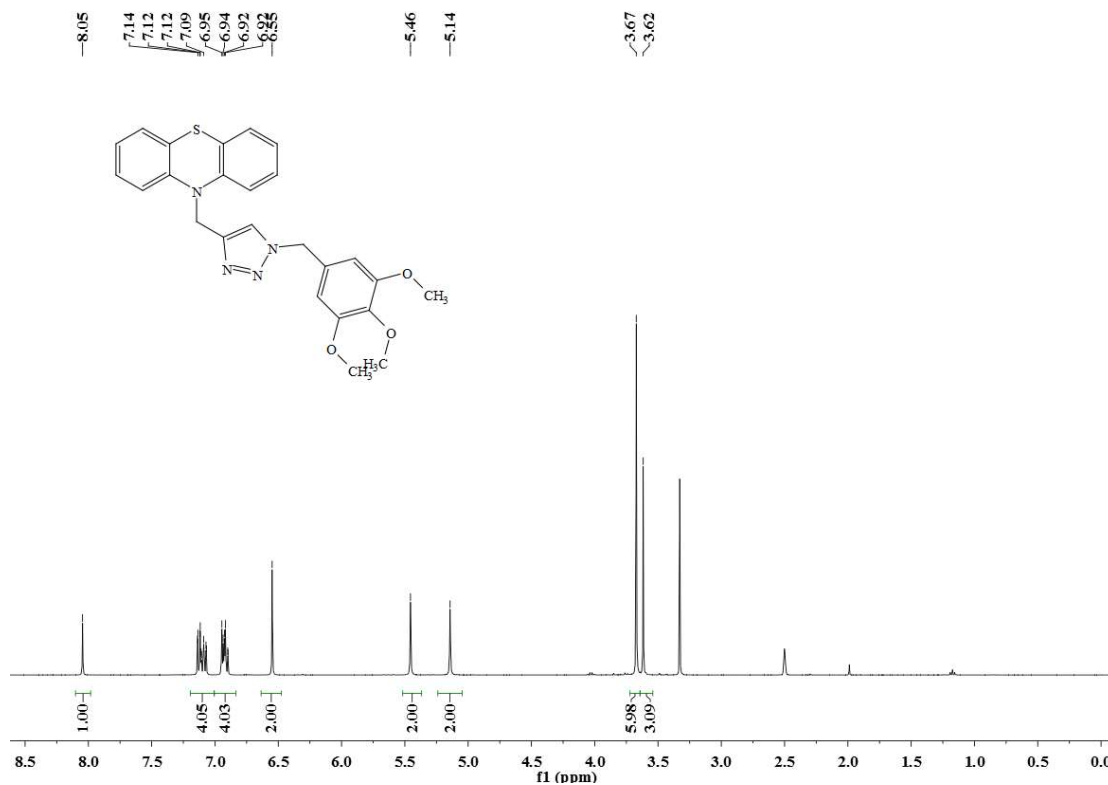
(s, 2H). ^{13}C NMR (100 MHz, DMSO) δ 144.03, 143.73, 136.18, 128.61, 127.92, 127.45, 127.41, 126.74, 123.75, 122.65, 122.62, 115.72, 52.63, 43.87. HR-MS (ESI): Calcd. $\text{C}_{22}\text{H}_{19}\text{N}_4\text{S}$, $[\text{M}+\text{H}]^+ m/z$: 371.1330, found: 371.1339.

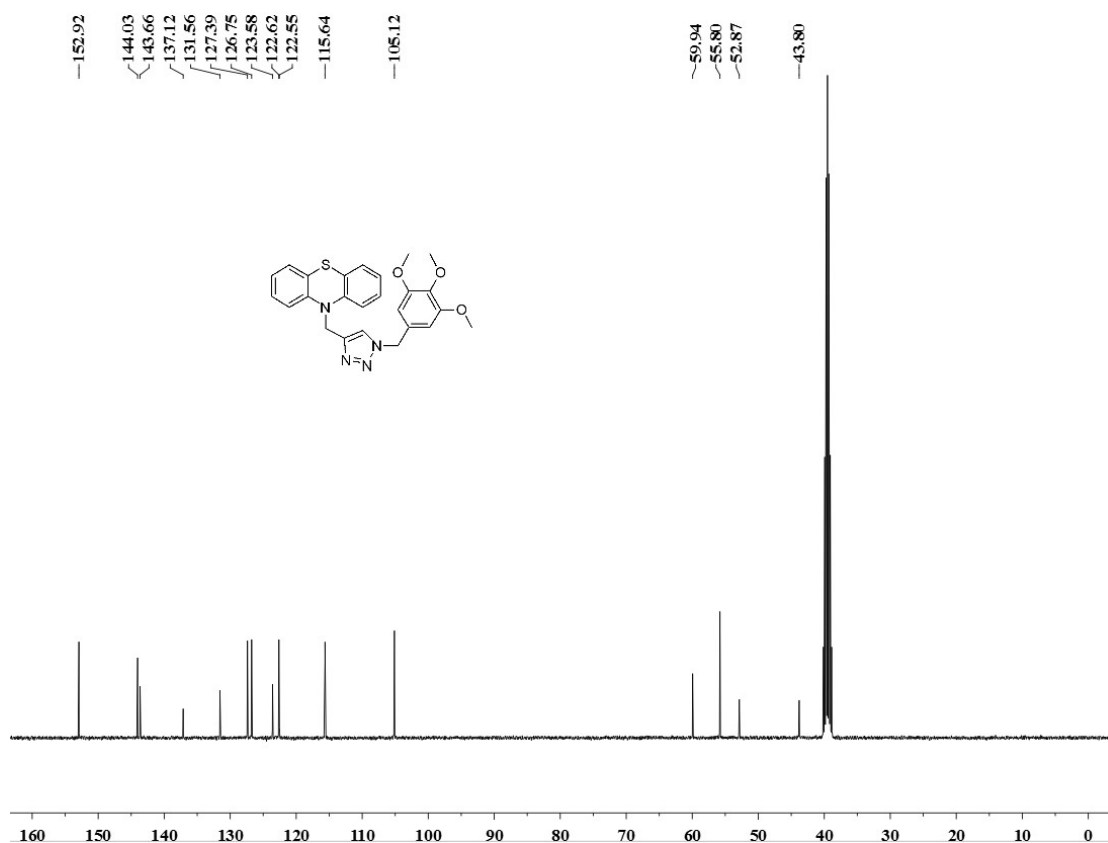


10-((1-(3,4,5-Trimethoxybenzyl)-1H-1,2,3-triazol-4-yl)methyl)-10H-phenothiazine

(9f)

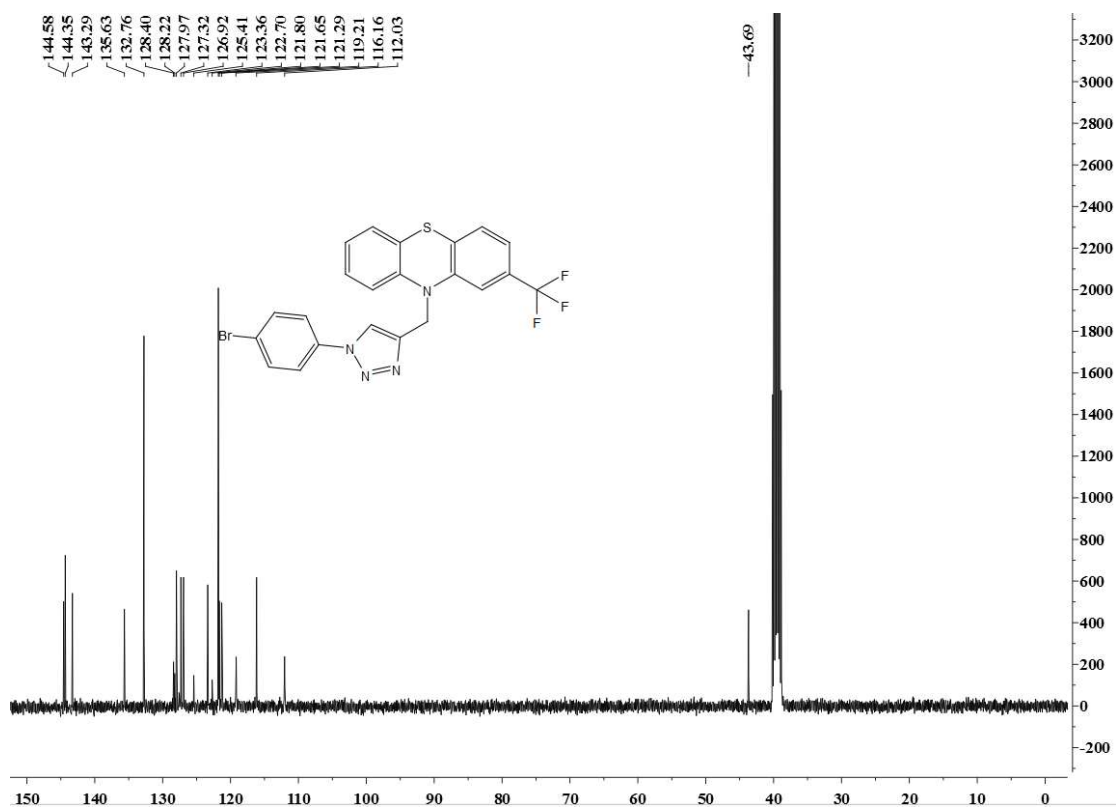
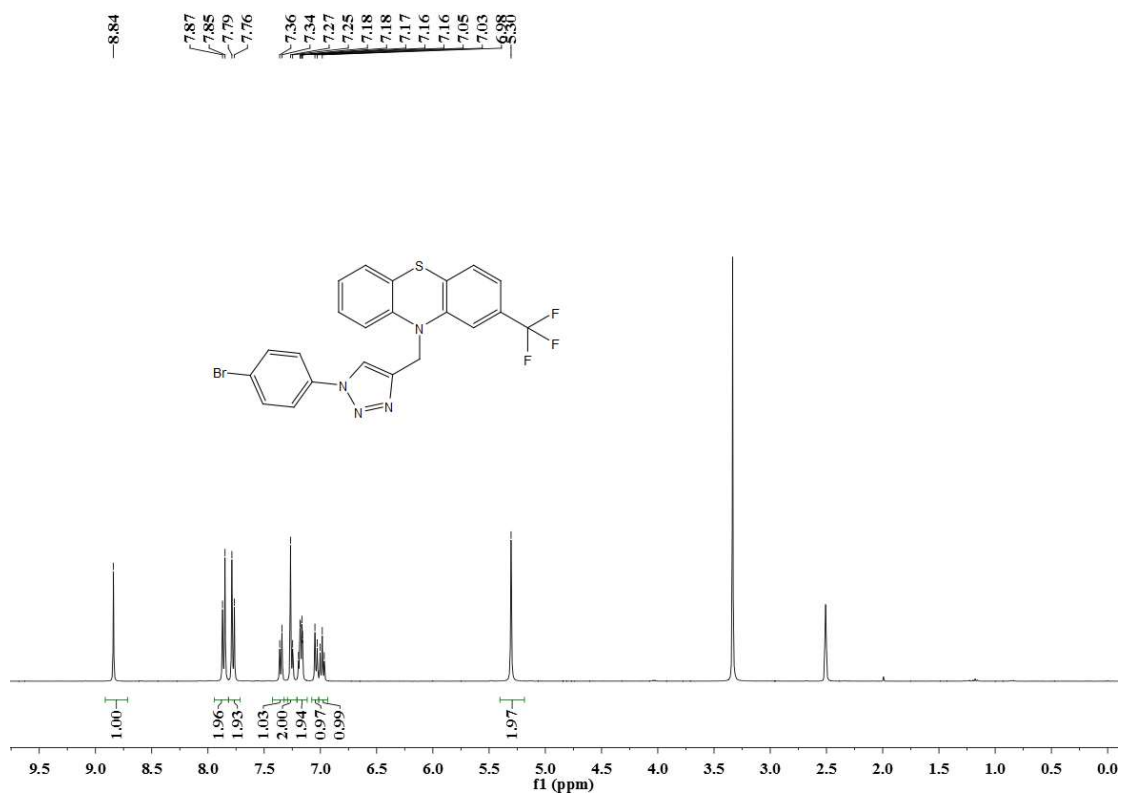
Yield: 88%. White solid. Mp: 146~147°C. ^1H NMR (400 MHz, DMSO) δ 8.05 (s, 1H), 7.19 – 7.01 (m, 4H), 7.01 – 6.83 (m, 4H), 6.55 (s, 2H), 5.46 (s, 2H), 5.14 (s, 2H), 3.67 (s, 6H), 3.62 (s, 3H). ^{13}C NMR (100 MHz, DMSO) δ 152.92, 144.03, 143.66, 137.12, 131.56, 127.39, 126.75, 123.58, 122.62, 122.52, 115.64, 105.12, 59.94, 55.80, 52.87, 43.80. HR-MS (ESI): Calcd. $\text{C}_{25}\text{H}_{25}\text{N}_4\text{O}_3\text{S}$, $[\text{M}+\text{H}]^+ m/z$: 461.1647, found: 461.1649.





10-((1-(4-Bromophenyl)-1H-1,2,3-triazol-4-yl)methyl)-2-(trifluoromethyl)-10H-phenothiazine (9g)

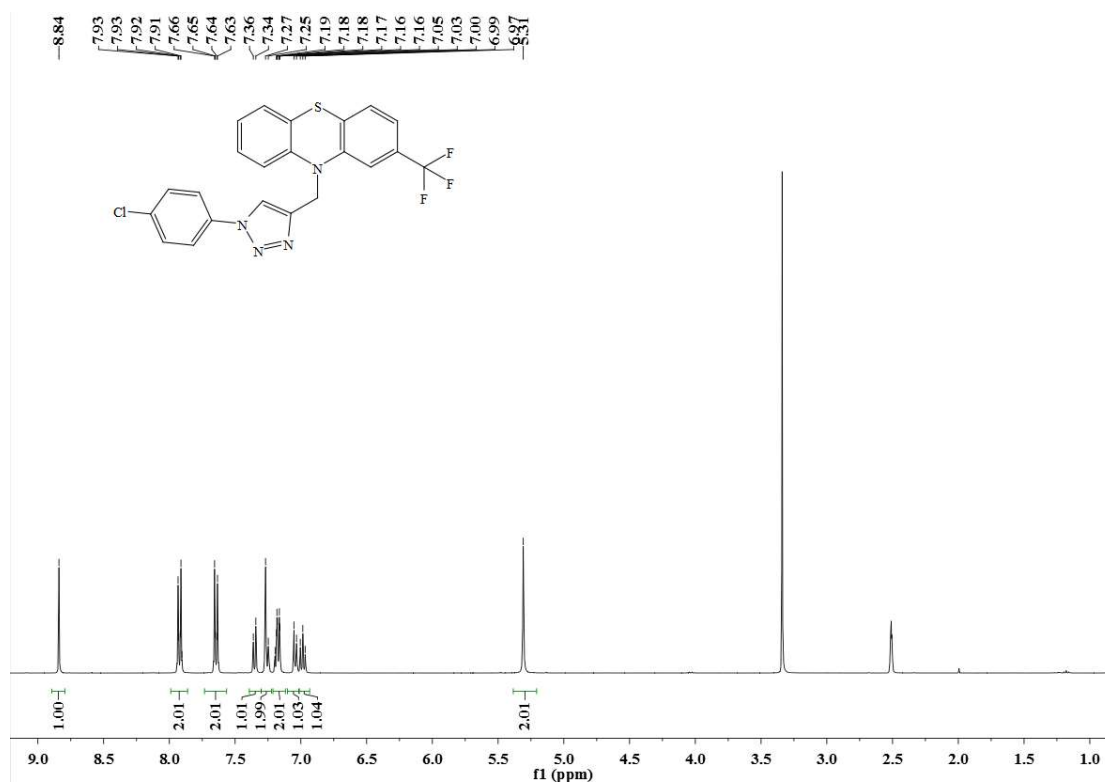
Yield: 93%. White solid. Mp: 161~162°C. ¹H NMR (400 MHz, DMSO) δ 8.84 (s, 1H), 7.86 (d, *J* = 8.9 Hz, 2H), 7.78 (d, *J* = 8.9 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.26 (d, *J* = 7.5 Hz, 2H), 7.21 – 7.12 (m, 2H), 7.04 (d, *J* = 8.0 Hz, 1H), 6.98 (t, *J* = 7.3 Hz, 1H), 5.30 (s, 2H). ¹³C NMR (100 MHz, DMSO) δ 144.58, 144.35, 143.29, 135.63, 132.76, 128.40, 128.22, 127.97, 127.32, 126.92, 125.41, 123.36, 122.70, 121.73 (d, *J* = 14.8 Hz), 121.29, 119.21, 116.16, 112.03, 43.69. HR-MS (ESI): Calcd. C₂₂H₁₅BrF₃N₄S, [M+H]⁺*m/z*: 503.0153, found: 503.0158.

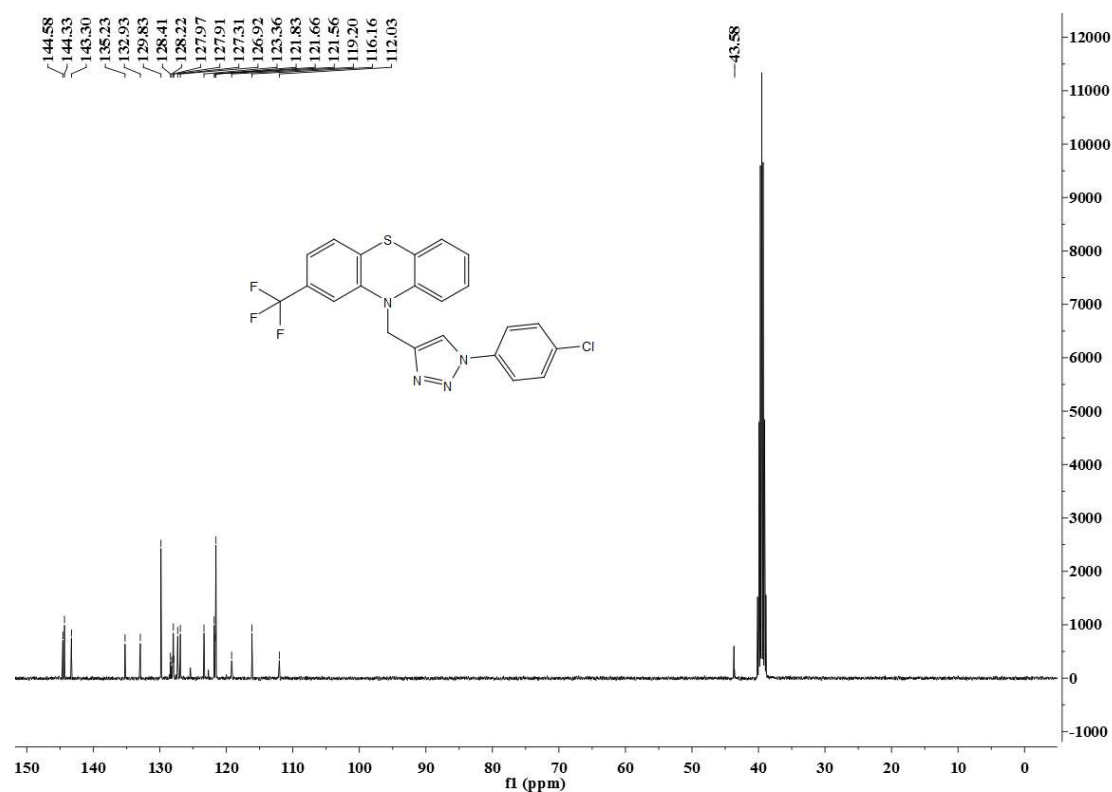


10-((1-(4-Chlorophenyl)-1H-1,2,3-triazol-4-yl)methyl)-2-(trifluoromethyl)-10H-phenothiazine (9h)

Yield: 90%. White solid. Mp: 153~155°C. ¹H NMR (400 MHz, DMSO) δ 8.84 (s,

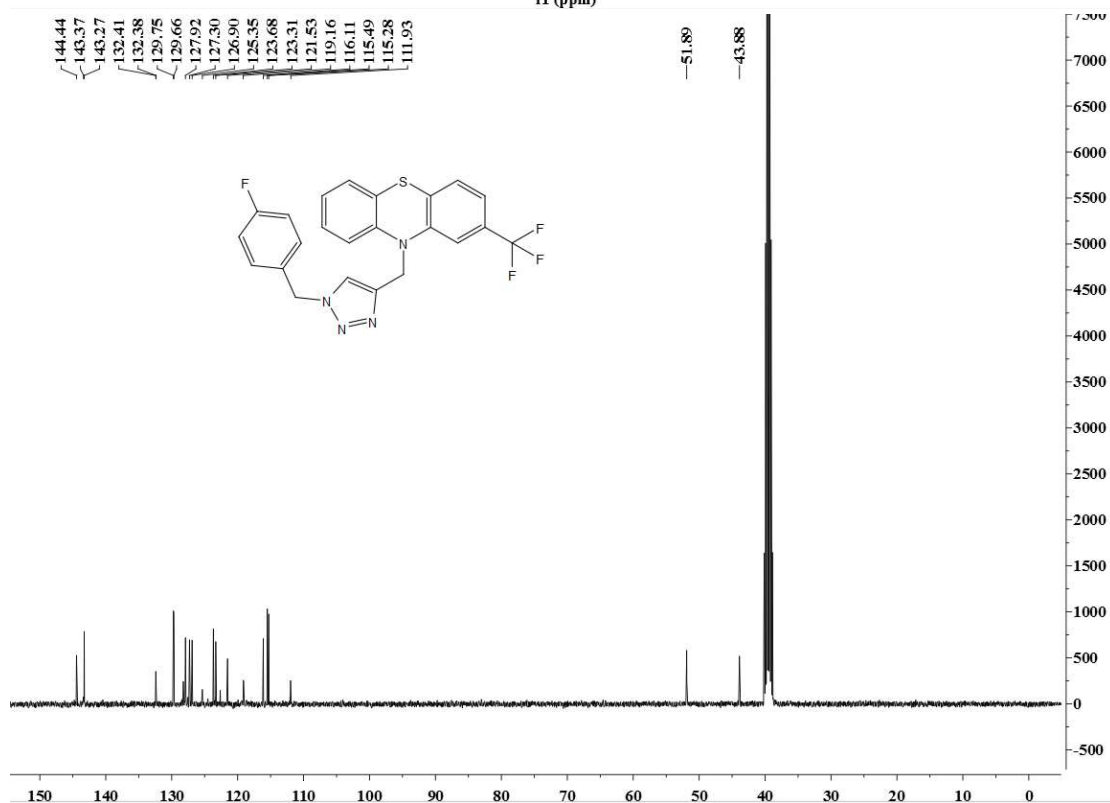
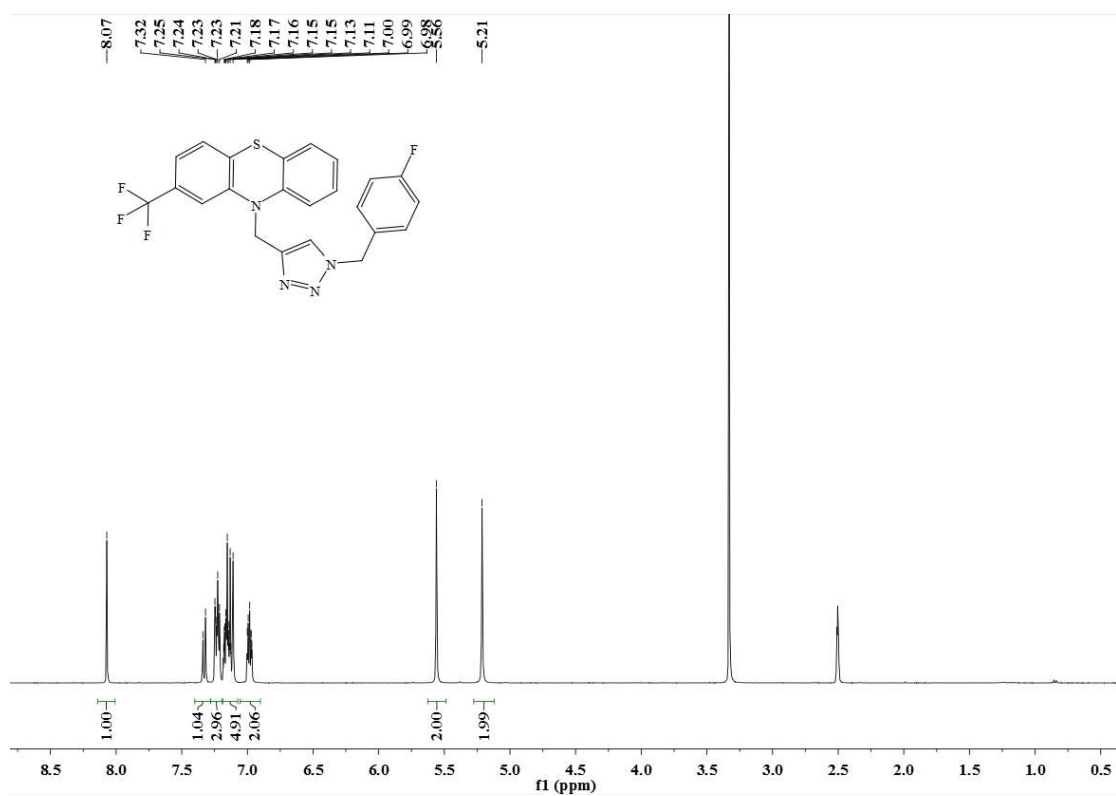
1H), 7.99 – 7.86 (m, 2H), 7.73 – 7.56 (m, 2H), 7.35 (d, $J = 7.7$ Hz, 1H), 7.26 (d, $J = 8.4$ Hz, 2H), 7.21 – 7.12 (m, 2H), 7.04 (d, $J = 7.9$ Hz, 1H), 6.99 (t, $J = 7.4$ Hz, 1H), 5.31 (s, 2H). ^{13}C NMR (100 MHz, DMSO) δ 144.58, 144.33, 143.30, 135.23, 132.93, 129.83, 128.41, 128.22, 127.97, 127.91, 127.31, 126.92, 123.36, 121.83, 121.66, 121.56, 119.20, 116.16, 112.03, 43.58. HR-MS (ESI): Calcd. $\text{C}_{22}\text{H}_{15}\text{ClF}_3\text{N}_4\text{S}$, $[\text{M}+\text{H}]^+ m/z$: 459.0658, found: 459.0662.





10-((1-(4-Fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl)-2-(trifluoromethyl)-10H-phenothiazine (9i)

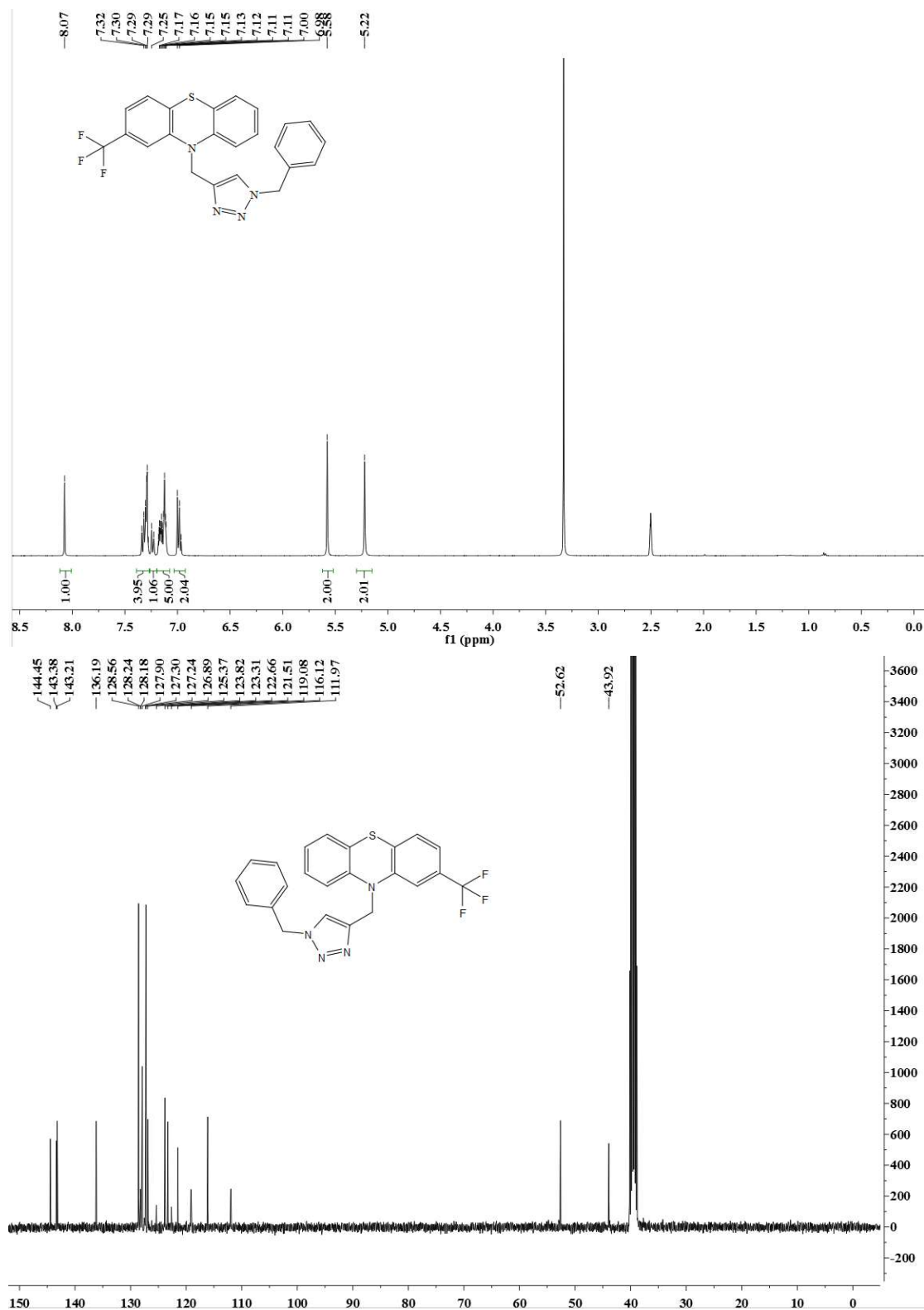
Yield: 81%. White solid. Mp: 134~136°C. ¹H NMR (400 MHz, DMSO) δ 8.07 (s, 1H), 7.33 (d, *J* = 7.9 Hz, 1H), 7.28 – 7.19 (m, 3H), 7.19 – 7.07 (m, 5H), 7.06 – 6.90 (m, 2H), 5.56 (s, 2H), 5.21 (s, 2H). ¹³C NMR (100 MHz, DMSO) δ 144.44, 143.37, 143.27, 132.41, 132.38, 129.75, 129.66, 127.92, 127.30, 126.90, 125.35, 123.68, 123.31, 121.53, 119.16, 116.11, 115.49, 115.28, 111.93, 51.89, 43.88. HR-MS (ESI): Calcd. C₂₃H₁₇F₄N₄S, [M+H]⁺*m/z*: 457.1110, found: 457.1118.



10-((1-Benzyl-1H-1,2,3-triazol-4-yl)methyl)-2-(trifluoromethyl)-10H-phenothiazine (9j)

Yield: 79%. White solid. Mp: 138~139°C. ¹H NMR (400 MHz, DMSO) δ 8.07 (s, 1H), 7.39 – 7.27 (m, 4H), 7.24 (d, *J* = 8.1 Hz, 1H), 7.20 – 7.07 (m, 5H), 7.03 – 6.93 (m, 2H), 5.58 (s, 2H), 5.22 (s, 2H). ¹³C NMR (100 MHz, DMSO) δ 144.45, 143.38, 143.21, 136.19, 128.56, 128.24, 128.18, 127.90, 127.30, 127.24, 126.89, 125.37,

123.82, 123.31, 122.66, 121.51, 119.08, 116.12, 111.97, 52.62, 43.92. HR-MS (ESI): Calcd. C₂₃H₁₈F₃N₄S, [M+H]⁺m/z: 439.1204, found: 439.1208.



10-((1-(4-Chlorobenzyl)-1H-1,2,3-triazol-4-yl)methyl)-2-(trifluoromethyl)-10H-phenothiazine (9k)

Yield: 86%. White solid. Mp: 140~142°C. ¹H NMR (400 MHz, DMSO) δ 8.08 (s, 1H), 7.43 – 7.28 (m, 3H), 7.24 (d, *J* = 8.0 Hz, 1H), 7.17 (ddd, *J* = 5.7, 3.8, 2.4 Hz, 4H),

7.12 (s, 1H), 7.05 – 6.85 (m, 2H), 5.58 (s, 2H), 5.22 (s, 2H). ^{13}C NMR (100 MHz, DMSO) δ 144.44, 143.31, 135.17, 132.66, 129.31, 128.54, 128.27, 128.17, 127.92, 127.85, 127.31, 126.90, 123.82, 123.31, 121.55, 119.13, 119.09, 116.12, 111.89, 51.88, 43.89. HR-MS (ESI): Calcd. $\text{C}_{23}\text{H}_{17}\text{ClF}_3\text{N}_4\text{S}$, $[\text{M}+\text{H}]^+ m/z$: 473.0815, found: 473.0819.

