

Discovery of Novel Thiosemicarbazides Containing 1,3,5-Triazines Derivatives as Potential Synergists against Fluconazole-Resistant *Candida albicans*

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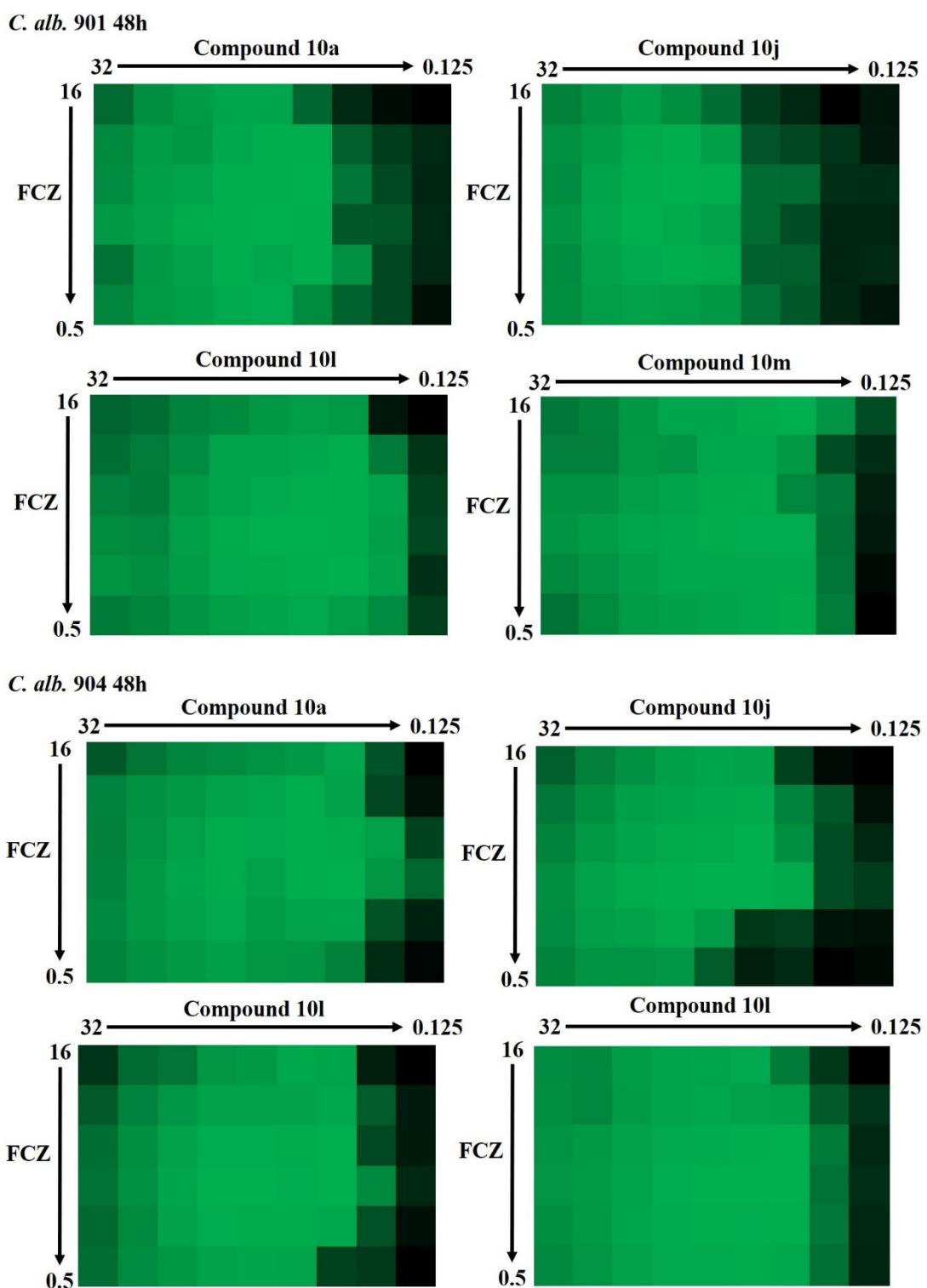


Figure S1. Checkerboard microdilution assay of FCZ with the target compounds **10a**, **10j**, **10l** and **10m**. The *in vitro* synergistic antifungal activity was shown in heat map. The color changes from green to black were used to express the relative growth of the fungi, if the color was greener, the inhibition was stronger. Abbreviations: *C. alb.*, *Candida albicans*; FCZ, fluconazole.

Table S1. Antifungal activity of compound **10l** against 8 Cryptococcus strains (MIC₈₀, µg/mL, 72h)

Species	Strains	FCZ	8	10l
<i>C. neoformans.</i>	HN-15	16.0	16.0	>64.0
<i>C. neoformans.</i>	HN-17	8.0	16.0	0.25
<i>C. neoformans.</i>	HN-19	16.0	16.0	0.5
<i>C. neoformans.</i>	HN-20	8.0	32.0	0.5
<i>C. neoformans.</i>	HN-68	4.0	16.0	≤0.125
<i>C. neoformans.</i>	BJ-3	8.0	32.0	≤0.125
<i>C. neoformans.</i>	BJ-72	16.0	16.0	0.25
<i>C. neoformans.</i>	BJ-95	4.0	16.0	≤0.125

Abbreviations: *C. neoformans.*, Cryptococcus neoformans; FCZ, fluconazole.

The characterization data of the compounds are given below:

1. **2-(4-((4-((cyclohexylmethyl)amino)-6-((4-fluorobenzyl)amino)-1,3,5-triazin-2-yl)amino)phenyl)-N-(2-fluorophenyl)acetamide (8b)**

White solid, yield: 65.2%; ^1H NMR (300 MHz, DMSO- d_6) δ 9.88 (s, 1H), 8.85 (dd, $J = 45.5, 18.0$ Hz, 1H), 7.85 (t, $J = 8.8$ Hz, 1H), 7.74 – 7.54 (m, 2H), 7.52 – 7.06 (m, 10H), 6.87 (t, $J = 33.9$ Hz, 1H), 4.44 (d, $J = 5.1$ Hz, 2H), 3.63 (s, 2H), 3.14 – 2.98 (m, 2H), 1.78 – 1.38 (m, 6H), 1.15 – 1.07 (m, 3H), 0.96 – 0.67 (m, 2H). ^{13}C NMR (75 MHz, DMSO- d_6) δ 170.34, 166.13, 165.99, 164.47, 163.06, 159.85, 155.74, 152.49, 139.66, 137.31, 129.40, 129.29, 128.94, 126.72, 126.57, 125.74, 125.64, 124.77, 124.72, 124.62, 120.24, 119.85, 116.03, 115.77, 115.40, 115.12, 46.98, 46.63, 43.18, 42.85, 42.49, 37.94, 31.07, 26.64, 25.92. MS (ESI) m/z : 558.0[M+H] $^+$, C₃₁H₃₃F₂N₇O. Purity: 97.4% (LC-MS).

2. **2-(4-((4-((cyclohexylmethyl)amino)-6-((4-fluorobenzyl)amino)-1,3,5-triazin-2-yl)amino)phenyl)-N-(3-fluorophenyl)acetamide (8c)**

White solid, yield: 60.1%; ^1H NMR (300 MHz, DMSO- d_6) δ 10.31 (s, 1H), 8.95 – 8.65 (m, 1H), 7.80 – 7.54 (m, 3H), 7.46 – 7.04 (m, 9H), 7.02 – 6.65 (m, 2H), 4.43 (s, 2H), 3.55 (s, 2H), 3.08 (s, 2H), 1.78 – 1.30 (m, 6H), 1.29 – 1.00 (d, $J = 24.4$ Hz, 3H), 0.97 – 0.66 (m, 2H). ^{13}C NMR (75 MHz, DMSO- d_6) δ 170.32, 166.46, 166.28, 166.17, 164.55, 164.19, 163.05, 161.00, 159.84, 141.54, 141.39, 139.81, 137.33, 130.85, 130.73, 129.41, 129.27, 128.65, 120.22, 119.86, 115.38, 115.27, 115.10, 110.18, 109.90, 106.46, 106.11, 46.93, 46.61, 43.22, 37.91, 31.07, 26.64, 25.92. MS (ESI) m/z : 558.0[M+H] $^+$, C₃₁H₃₃F₂N₇O. Purity: 98.8% (LC-MS).

3. **2-(4-((4-((cyclohexylmethyl)amino)-6-((4-fluorobenzyl)amino)-1,3,5-triazin-2-yl)amino)phenyl)-N-(4-fluorophenyl)acetamide (8d)**

White solid, yield: 64.3%; ^1H NMR (300 MHz, DMSO- d_6) δ 10.15 (s, 1H), 8.97 – 8.64 (m, 1H), 7.80 – 7.54 (m, 4H), 7.47 – 7.02 (m, 9H), 6.83 (t, $J = 34.5$ Hz, 1H), 4.43 (s, 2H), 3.53 (s, 2H), 3.17 – 2.96 (m, 2H), 1.78 – 1.30 (m, 6H), 1.22 – 1.01 (m, 3H), 0.98 – 0.67 (m, 2H). ^{13}C NMR (75 MHz, DMSO- d_6) δ 169.81, 166.41, 166.29, 166.12, 164.55, 163.03, 159.96, 159.85, 156.78, 156.51, 139.82, 137.35, 136.16, 129.41, 129.23, 128.90, 121.32, 121.21, 119.86, 115.84, 115.55, 115.39, 115.11, 47.07, 46.61, 43.12, 37.89, 31.06, 26.64, 25.92. MS (ESI) m/z : 558.0[M+H] $^+$, C₃₁H₃₃F₂N₇O. Purity: 99.1% (LC-MS).

4. **2-(4-((4-((cyclohexylmethyl)amino)-6-((4-fluorobenzyl)amino)-1,3,5-triazin-2-yl)amino)phenyl)-N-(4-methoxyphenyl)acetamide (8e)**

White solid, yield: 54.6%; ^1H NMR (300 MHz, DMSO- d_6) δ 9.95 (s, 1H), 8.91 – 8.71 (m, 1H), 7.79 – 7.56 (m, 2H), 7.49 (d, $J = 8.9$ Hz, 2H), 7.42 – 7.05 (m, 7H), 7.03 – 6.65 (m, 3H), 4.44 (d, $J = 5.4$ Hz, 2H), 3.70 (s, 3H), 3.50 (s, 2H), 3.10 – 3.02 (m, 2H), 1.78 – 1.34 (m, 6H), 1.38 – 1.06 (m, 3H), 0.96 – 0.68 (m, 2H). ^{13}C NMR (75 MHz, DMSO- d_6) δ 169.39, 166.38, 166.29, 166.20, 166.16, 164.58, 163.06, 159.86, 155.60, 139.65, 137.37, 132.93, 129.41, 129.30, 129.19, 121.10, 120.30, 120.23, 120.11, 119.92, 119.83, 115.39, 115.11, 114.28, 55.61, 46.67, 43.12, 37.88, 31.07, 26.64, 25.93. MS (ESI) m/z : 570.0[M+H] $^+$, C₃₂H₃₆FN₇O₂. Purity: 98.8% (LC-MS).

5. **2-(4-((4-((cyclohexylmethyl)amino)-6-((4-fluorobenzyl)amino)-1,3,5-triazin-2-yl)amino)phenyl)-N-(4-(2-methoxyethoxy)phenyl)acetamide (8f)**

White solid, yield: 48.7%; ^1H NMR (300 MHz, DMSO- d_6) δ 9.95 (s, 1H), 8.97 – 8.65 (m, 1H), 7.77 – 7.54 (m, 2H), 7.48 (d, $J = 8.9$ Hz, 2H), 7.22 (dt, $J = 17.1, 8.1$ Hz, 7H), 7.03 – 6.64 (m, 3H), 4.44 (d, $J = 6.2$ Hz, 2H), 4.12 – 3.92 (m, 2H), 3.70 – 3.56 (m, 2H), 3.49 (s, 2H), 3.29 (s,

3H), 3.10 – 3.02 (m, 2H), 1.73 – 1.59 (m, 6H), 1.19 – 1.07 (m, 3H), 0.93 – 0.75 (m, 2H). ^{13}C NMR (75 MHz, DMSO- d_6) δ 169.40, 166.30, 164.58, 163.06, 159.86, 154.79, 139.66, 137.37, 133.02, 129.41, 129.31, 129.18, 121.08, 119.84, 115.38, 115.10, 114.90, 70.90, 67.48, 58.61, 46.96, 46.64, 43.14, 37.92, 31.07, 26.65, 25.92. MS (ESI) m/z : 614.0[M+H] $^+$, C₃₄H₄₀FN₇O₃. Purity: 97.5% (LC-MS).

6. **2-((4-((cyclohexylmethyl)amino)-6-((4-fluorobenzyl)amino)-1,3,5-triazin-2-yl)amino)phenyl)-N-(4-fluorobenzyl)acetamide (**8g**)**

White solid, yield: 66.4%; ^1H NMR (300 MHz, DMSO- d_6) δ 8.96 – 8.65 (m, 1H), 8.47 (s, 1H), 7.78 – 7.52 (m, 2H), 7.46 – 7.21 (m, 5H), 7.20 – 7.02 (m, 6H), 6.84 (t, J = 35.7 Hz, 1H), 4.44 (s, 2H), 4.24 (d, J = 5.3 Hz, 2H), 3.38 (s, 2H), 3.13 – 2.96 (m, 2H), 1.80 – 1.33 (m, 6H), 1.26 – 1.00 (m, 3H), 0.98 – 0.67 (m, 2H). ^{13}C NMR (75 MHz, DMSO- d_6) δ 170.96, 166.42, 166.29, 166.18, 164.56, 163.21, 163.06, 160.00, 159.86, 139.55, 137.57, 137.38, 136.24, 136.20, 129.67, 129.56, 129.41, 129.35, 129.17, 120.16, 119.74, 115.55, 115.39, 115.27, 115.10, 46.95, 46.66, 43.27, 43.12, 42.96, 42.24, 41.95, 38.07, 37.91, 31.07, 26.65, 25.93. MS (ESI) m/z : 572.0[M+H] $^+$, C₃₂H₃₅F₂N₇O. Purity: 97.3% (LC-MS).

7. **2-((4-((cyclohexylmethyl)amino)-6-((4-fluorobenzyl)amino)-1,3,5-triazin-2-yl)amino)phenyl)-N-(4-methylbenzyl)acetamide (**8h**)**

White solid, yield: 62.8%; ^1H NMR (300 MHz, DMSO- d_6) δ 8.92 – 8.71 (m, 1H), 8.43 (t, J = 5.8 Hz, 1H), 7.78 – 7.53 (m, 2H), 7.45 – 7.03 (m, 11H), 6.86 (t, J = 35.4 Hz, 1H), 4.45 (d, J = 5.4 Hz, 2H), 4.21 (d, J = 5.8 Hz, 2H), 3.38 (s, 2H), 3.15 – 2.99 (m, 2H), 2.26 (s, 3H), 1.77 – 1.50 (m, 6H), 1.17 – 1.14 (m, 3H), 0.98 – 0.73 (m, 2H). ^{13}C NMR (75 MHz, DMSO- d_6) δ 170.85, 166.44, 166.31, 166.19, 164.57, 163.07, 159.87, 139.55, 137.37, 136.95, 136.22, 129.46, 129.24, 129.17, 127.66, 120.16, 120.03, 119.96, 119.71, 115.39, 115.11, 46.96, 46.63, 43.23, 42.97, 42.40, 42.27, 37.94, 31.08, 26.66, 25.93, 21.10. MS (ESI) m/z : 568.0[M+H] $^+$, C₃₃H₃₈FN₇O. Purity: 97.6% (LC-MS).

8. **2-((4-((cyclohexylmethyl)amino)-6-((4-fluorobenzyl)amino)-1,3,5-triazin-2-yl)amino)phenyl)-N-(furan-2-ylmethyl)acetamide (**8i**)**

White solid, yield: 70.1%; ^1H NMR (300 MHz, DMSO- d_6) δ 9.00 – 8.42 (m, 1H), 8.44 (t, J = 5.1 Hz, 1H), 7.69 – 7.56 (m, 3H), 7.40 – 7.09 (m, 7H), 6.84 (t, J = 34.6 Hz, 1H), 6.37 (s, 1H), 6.19 (d, J = 2.3 Hz, 1H), 4.44 (d, J = 4.3 Hz, 2H), 4.24 (d, J = 5.4 Hz, 2H), 3.35 (s, 2H), 3.18 – 2.94 (m, 2H), 1.74 – 1.59 (m, 6H), 1.19 – 1.07 (m, 3H), 0.94 – 0.76 (m, 2H). ^{13}C NMR (75 MHz, DMSO- d_6) δ 170.80, 166.28, 166.15, 164.54, 163.07, 159.86, 152.81, 142.51, 139.52, 137.35, 129.42, 129.30, 129.17, 120.15, 119.96, 119.71, 115.39, 115.11, 110.87, 107.16, 46.95, 46.65, 43.22, 42.97, 42.06, 37.92, 36.05, 31.07, 26.66, 25.93. MS (ESI) m/z : 544.0[M+H] $^+$, C₃₀H₃₄FN₇O₂. Purity: 97.2% (LC-MS).

9. **2-((4-((cyclohexylmethyl)amino)-6-((4-fluorobenzyl)amino)-1,3,5-triazin-2-yl)amino)phenyl)-N-((5-phenylfuran-2-yl)methyl)acetamide (**8g**)**

White solid, yield: 62.4%; ^1H NMR (300 MHz, DMSO- d_6) δ 8.98 – 8.66 (m, 1H), 8.52 (s, 1H), 7.80 – 7.53 (m, 4H), 7.49 – 7.02 (m, 10H), 7.00 – 6.65 (m, 2H), 6.30 (d, J = 2.6 Hz, 1H), 4.43 (s, 2H), 4.32 (d, J = 4.7 Hz, 2H), 3.39 (s, 2H), 3.14 – 2.97 (m, 2H), 1.81 – 1.34 (m, 6H), 1.29 – 1.01 (m, 3H), 0.98 – 0.68 (m, 2H). ^{13}C NMR (75 MHz, DMSO- d_6) δ 170.92, 166.42, 166.31, 166.18, 164.58, 163.06, 159.86, 152.75, 152.59, 139.59, 137.37, 130.78, 129.42, 129.28, 129.17, 127.71, 123.65, 120.13, 119.75, 115.38, 115.11, 109.37, 106.92, 46.95, 46.64, 43.21, 43.00, 42.12, 37.94, 36.28, 31.07, 26.65, 25.92. MS (ESI) m/z : 620.0[M+H] $^+$, C₃₆H₃₈FN₇O₂. Purity:

97.4% (LC-MS).

10. *2-(2-((4-((cyclohexylmethyl)amino)-6-((4-fluorobenzyl)amino)-1,3,5-triazin-2-yl)amino)phenyl)acetyl)-N-(2-chlorophenyl)hydrazine-1-carboxamide (**9a**)*

White solid, yield: 80.5%; ^1H NMR (300 MHz, DMSO- d_6) δ 10.04 (s, 1H), 8.96 – 8.69 (m, 2H), 8.19 (s, 1H), 8.09 (d, J = 8.1 Hz, 1H), 7.80 – 7.56 (m, 2H), 7.47 – 7.22 (m, 5H), 7.14 (s, 4H), 7.01 (t, J = 7.4 Hz, 1H), 6.79 (d, J = 35.0 Hz, 1H), 4.45 (s, 2H), 3.54 – 3.43 (m, 2H), 3.10 (s, 2H), 1.81 – 1.48 (m, 6H), 1.25 – 1.07 (s, 3H), 0.96 – 0.71 (m, 2H). ^{13}C NMR (75 MHz, DMSO- d_6) δ 170.81, 166.43, 166.29, 166.16, 164.56, 163.07, 162.77, 159.87, 155.24, 139.70, 137.34, 136.22, 129.64, 129.41, 129.24, 128.53, 128.05, 123.87, 122.43, 121.54, 120.06, 119.67, 115.40, 115.12, 46.92, 46.67, 43.18, 42.97, 37.96, 36.24, 31.08, 26.65, 25.93. MS (ESI) m/z : 632.0[M+H] $^+$, C₃₂H₃₃ClFN₉O₂. Purity: 97.5% (LC-MS).

11. *2-(2-((4-((cyclohexylmethyl)amino)-6-((4-fluorobenzyl)amino)-1,3,5-triazin-2-yl)amino)phenyl)acetyl)-N-(3-chlorophenyl)hydrazine-1-carboxamide (**9b**)*

White solid, yield: 86.2%; ^1H NMR (300 MHz, DMSO- d_6) δ 9.89 (s, 1H), 8.99 – 8.66 (m, 2H), 8.21 (s, 1H), 7.70 – 7.55 (m, 3H), 7.43 – 7.20 (m, 5H), 7.19 – 7.06 (m, 4H), 7.04 – 6.70 (m, 2H), 4.43 (s, 2H), 3.40 (s, 2H), 3.09 (s, 2H), 1.74 – 1.35 (m, 6H), 1.25 – 1.05 (m, 3H), 0.97 – 0.66 (m, 2H). ^{13}C NMR (75 MHz, DMSO- d_6) δ 170.91, 166.29, 164.56, 163.07, 159.86, 155.63, 141.71, 139.68, 137.40, 133.52, 130.72, 129.31, 128.61, 121.94, 120.07, 119.69, 118.23, 117.26, 115.40, 115.12, 56.50, 46.97, 46.64, 43.15, 37.94, 31.08, 26.66, 25.93, 19.02. MS (ESI) m/z : 631.9[M+H] $^+$, C₃₂H₃₃ClFN₉O₂. Purity: 95.9% (LC-MS).

12. *2-(2-((4-((cyclohexylmethyl)amino)-6-((4-fluorobenzyl)amino)-1,3,5-triazin-2-yl)amino)phenyl)acetyl)-N-(4-chlorophenyl)hydrazine-1-carboxamide (**9c**)*

White solid, yield: 80.4%; ^1H NMR (300 MHz, DMSO- d_6) δ 9.88 (s, 1H), 8.96 – 8.67 (m, 2H), 8.14 (s, 1H), 7.81 – 7.55 (m, 2H), 7.48 (d, J = 8.6 Hz, 3H), 7.32 (d, J = 10.2 Hz, 4H), 7.12 (s, 4H), 6.85 (t, J = 33.5 Hz, 1H), 4.44 (s, 2H), 3.40 (s, 2H), 3.17 – 2.95 (s, 2H), 1.79 – 1.40 (m, 6H), 1.23 – 1.06 (m, 3H), 0.97 – 0.67 (m, 2H). ^{13}C NMR (75 MHz, DMSO- d_6) δ 170.89, 166.30, 164.55, 163.07, 162.97, 155.68, 139.76, 139.13, 137.41, 129.30, 129.09, 128.94, 128.63, 125.99, 125.87, 120.40, 119.65, 115.40, 115.11, 56.50, 46.93, 46.66, 43.32, 42.87, 37.96, 31.08, 26.65, 25.93, 19.02. MS (ESI) m/z : 631.9[M+H] $^+$, C₃₂H₃₃ClFN₉O₂. Purity: 97.3% (LC-MS).

13. *2-(2-((4-((cyclohexylmethyl)amino)-6-((4-fluorobenzyl)amino)-1,3,5-triazin-2-yl)amino)phenyl)acetyl)-N-(2-fluorophenyl)hydrazine-1-carboxamide (**9d**)*

White solid, yield: 76.3%; ^1H NMR (300 MHz, DMSO- d_6) δ 9.99 (s, 1H), 8.98 – 8.67 (m, 1H), 8.57 (s, 1H), 8.39 (s, 1H), 8.00 (t, J = 7.5 Hz, 1H), 7.81 – 7.54 (m, 2H), 7.49 – 7.27 (m, 3H), 7.25 – 7.08 (m, 6H), 7.03 – 6.94 (m, 1H), 6.79 (d, J = 32.7 Hz, 1H), 4.44 (s, 2H), 3.40 (s, 2H), 3.18 – 2.97 (m, 2H), 1.84 – 1.39 (m, 6H), 1.29 – 0.99 (m, 3H), 0.98 – 0.65 (m, 2H). ^{13}C NMR (75 MHz, DMSO- d_6) δ 170.72, 166.43, 166.30, 166.17, 164.56, 163.07, 159.86, 155.37, 154.32, 154.28, 151.11, 139.66, 137.58, 137.37, 129.41, 129.24, 128.59, 127.81, 127.67, 124.92, 124.88, 123.32, 123.22, 121.51, 120.09, 119.99, 119.82, 119.69, 115.62, 115.38, 115.12, 46.97, 46.64, 43.23, 43.03, 37.96, 31.07, 26.65, 25.92. MS (ESI) m/z : 615.9[M+H] $^+$, C₃₂H₃₅F₂N₉O₂. Purity: 95.4% (LC-MS).

14. *2-(2-((4-((cyclohexylmethyl)amino)-6-((4-fluorobenzyl)amino)-1,3,5-triazin-2-yl)amino)phenyl)acetyl)-N-(3-fluorophenyl)hydrazine-1-carboxamide (**9e**)*

White solid, yield: 70.4%; ^1H NMR (300 MHz, DMSO- d_6) δ 9.90 (s, 1H), 9.13 – 8.68 (m, 2H), 8.21 (s, 1H), 7.81 – 7.55 (m, 2H), 7.53 – 7.06 (m, 10H), 7.04 – 6.69 (m, 2H), 4.44 (s, 2H), 3.48

–3.41 (m, 2H), 3.17 – 2.97 (m, 2H), 1.83 – 1.42 (m, 6H), 1.26 – 1.01 (m, 3H), 0.98 – 0.67 (m, 2H). ^{13}C NMR (75 MHz, DMSO- d_6) δ 170.86, 166.11, 164.37, 163.06, 161.19, 155.61, 152.81, 142.15, 142.00, 139.55, 137.28, 130.70, 130.56, 129.31, 128.71, 120.28, 119.70, 115.41, 115.13, 114.49, 108.71, 108.42, 105.58, 105.23, 46.95, 46.59, 43.18, 37.94, 31.07, 26.64, 25.92. MS (ESI) m/z : 616.0[M+H] $^+$, C₃₂H₃₅F₂N₉O₂. Purity: 98.0% (LC-MS).

15. 2-(2-((4-((cyclohexylmethyl)amino)-6-((4-fluorobenzyl)amino)-1,3,5-triazin-2-yl)amino)phenyl)acetyl)-N-(4-fluorophenyl)hydrazine-1-carboxamide (**9f**)

White solid, yield: 78.3%; ^1H NMR (300 MHz, DMSO- d_6) δ 9.87 (s, 1H), 8.96 – 8.65 (m, 2H), 8.08 (s, 1H), 7.78 – 7.55 (m, 2H), 7.44 (dd, J = 8.8, 4.9 Hz, 2H), 7.34 (t, J = 4.9 Hz, 2H), 7.25 – 7.01 (m, 6H), 6.85 (t, J = 31.3 Hz, 1H), 4.44 (s, 2H), 3.48 – 3.40 (m, 2H), 3.17 – 2.96 (m, 2H), 1.81 – 1.45 (m, 6H), 1.28 – 1.05 (m, 3H), 0.99 – 0.66 (m, 2H). ^{13}C NMR (75 MHz, DMSO- d_6) δ 170.89, 166.25, 166.12, 164.53, 163.07, 159.86, 159.39, 156.24, 155.89, 139.63, 137.36, 136.44, 129.40, 129.30, 128.68, 120.68, 120.58, 119.94, 119.68, 115.72, 115.42, 115.13, 46.90, 46.67, 43.20, 37.93, 31.07, 26.64, 25.92. MS (ESI) m/z : 615.9[M+H] $^+$, C₃₂H₃₅F₂N₉O₂. Purity: 96.5% (LC-MS).

16. 2-(2-((4-((cyclohexylmethyl)amino)-6-((4-fluorobenzyl)amino)-1,3,5-triazin-2-yl)amino)phenyl)acetyl)-N-(o-tolyl)hydrazine-1-carboxamide (**9g**)

White solid, yield: 74.5%; ^1H NMR (300 MHz, DMSO- d_6) δ 9.94 (s, 1H), 8.96 – 8.65 (m, 1H), 8.35 (s, 1H), 7.91 (s, 1H), 7.78 – 7.54 (m, 3H), 7.34 (s, 3H), 7.25 – 7.02 (m, 6H), 7.02 – 6.69 (m, 2H), 4.44 (s, 2H), 3.51 – 3.41 (m, 2H), 3.17 – 2.93 (m, 2H), 2.16 (s, 3H), 1.81 – 1.41 (m, 6H), 1.21 – 1.05 (m, 3H), 0.91 – 0.70 (m, 2H). ^{13}C NMR (75 MHz, DMSO- d_6) δ 170.71, 166.29, 164.55, 159.93, 155.95, 139.68, 137.62, 137.38, 130.62, 129.41, 129.27, 128.98, 128.68, 126.55, 123.59, 122.30, 120.06, 119.67, 115.41, 115.12, 56.51, 46.93, 46.65, 43.19, 37.92, 31.07, 26.65, 25.93, 19.02, 18.15. MS (ESI) m/z : 612.0[M+H] $^+$, C₃₃H₃₈FN₉O₂. Purity: 96.3% (LC-MS).

17. 2-(2-((4-((cyclohexylmethyl)amino)-6-((4-fluorobenzyl)amino)-1,3,5-triazin-2-yl)amino)phenyl)acetyl)-N-(m-tolyl)hydrazine-1-carboxamide (**9h**)

White solid, yield: 72.6%; ^1H NMR (300 MHz, DMSO- d_6) δ 10.12 (s, 1H), 9.22 – 8.85 (m, 1H), 8.85 (s, 1H), 8.28 (s, 1H), 8.04 – 7.80 (m, 2H), 7.71 – 7.45 (m, 5H), 7.41 – 7.31 (m, 5H), 7.28 – 6.96 (m, 2H), 4.69 (s, 2H), 3.73 – 3.65 (m, 2H), 3.41 – 3.23 (m, 2H), 2.76 (s, 3H), 2.01 – 1.62 (m, 6H), 1.51 – 1.29 (m, 3H), 1.24 – 0.92 (m, 2H). ^{13}C NMR (75 MHz, DMSO- d_6) δ 170.85, 166.35, 166.13, 164.54, 155.74, 139.97, 139.66, 138.26, 137.35, 129.41, 129.29, 128.96, 128.69, 123.06, 119.68, 119.34, 116.02, 115.41, 115.12, 101.03, 46.74, 46.63, 43.36, 37.97, 31.07, 26.66, 25.93, 21.64. MS (ESI) m/z : 612.0[M+H] $^+$, C₃₃H₃₈FN₉O₂. Purity: 97.2% (LC-MS).

18. 2-(2-((4-((cyclohexylmethyl)amino)-6-((4-fluorobenzyl)amino)-1,3,5-triazin-2-yl)amino)phenyl)acetyl)-N-(p-tolyl)hydrazine-1-carboxamide (**9i**)

White solid, yield: 78.6%; ^1H NMR (300 MHz, DMSO- d_6) δ 9.86 (s, 1H), 9.03 – 8.67 (m, 1H), 8.58 (s, 1H), 8.00 (s, 1H), 7.78 – 7.51 (m, 2H), 7.43 – 7.00 (m, 11H), 6.85 (t, J = 27.3 Hz, 1H), 4.44 (s, 2H), 3.48 – 3.40 (m, 2H), 3.19 – 2.95 (m, 2H), 2.22 (s, 3H), 1.82 – 1.38 (m, 6H), 1.27 – 1.02 (m, 3H), 0.98 – 0.66 (m, 2H). ^{13}C NMR (75 MHz, DMSO- d_6) δ 170.85, 166.40, 166.29, 166.17, 164.56, 163.07, 159.87, 155.82, 139.65, 137.50, 131.12, 129.50, 129.29, 128.70, 120.02, 119.68, 118.94, 115.40, 115.12, 46.89, 46.67, 43.20, 42.91, 37.95, 31.07, 26.65, 25.93, 20.78. MS (ESI) m/z : 612.0[M+H] $^+$, C₃₃H₃₈FN₉O₂. Purity: 97.1% (LC-MS).

19. 2-(2-((4-((cyclohexylmethyl)amino)-6-((4-fluorobenzyl)amino)-1,3,5-triazin-2-yl)amino)phenyl)acetyl)-N-(4-(trifluoromethyl)phenyl)hydrazine-1-carboxamide (**9j**)

White solid, yield: 79.8%; ^1H NMR (300 MHz, DMSO- d_6) δ 9.93 (s, 1H), 9.16 (s, 1H), 8.97 – 8.66 (m, 1H), 8.28 (s, 1H), 7.78 – 7.53 (m, 6H), 7.42 – 7.06 (m, 7H), 6.85 (t, J = 30.7 Hz, 1H), 4.40 (s, 2H), 3.55 – 3.41 (m, 2H), 3.19 – 2.95 (m, 2H), 1.78 – 1.41 (m, 6H), 1.27 – 1.03 (m, 3H), 0.98 – 0.68 (m, 2H). ^{13}C NMR (75 MHz, DMSO- d_6) δ 170.89, 166.43, 166.30, 166.17, 164.57, 163.06, 159.87, 155.51, 143.91, 139.68, 137.35, 129.41, 129.30, 128.60, 126.81, 126.37, 123.22, 122.51, 122.09, 120.05, 119.69, 118.51, 115.40, 115.11, 46.94, 46.62, 43.24, 42.98, 37.96, 31.07, 26.64, 25.93. MS (ESI) m/z : 665.9[M+H] $^+$, C₃₃H₃₅F₄N₉O₂. Purity: 97.2% (LC-MS).

20. 2-(2-((4-((cyclohexylmethyl)amino)-6-((4-fluorobenzyl)amino)-1,3,5-triazin-2-yl)amino)phenyl)acetyl)-N-(4-(trifluoromethoxy)phenyl)hydrazine-1-carboxamide (**9k**)

White solid, yield: 82.6%; ^1H NMR (300 MHz, DMSO- d_6) δ 9.90 (s, 1H), 8.99 – 8.68 (m, 2H), 8.17 (s, 1H), 7.77 – 7.47 (m, 4H), 7.39 – 7.07 (m, 9H), 6.90 (d, J = 32.3 Hz, 1H), 4.44 (s, 2H), 3.48 – 3.41 (m, 2H), 3.15 – 2.97 (m, 2H), 1.74 – 1.36 (m, 6H), 1.25 – 1.03 (m, 3H), 0.97 – 0.67 (m, 2H). ^{13}C NMR (75 MHz, DMSO- d_6) δ 172.35, 166.43, 166.30, 166.18, 164.58, 163.08, 159.88, 139.98, 137.61, 137.33, 129.50, 129.42, 129.31, 127.25, 120.09, 119.97, 119.82, 115.38, 115.10, 52.02, 46.98, 46.66, 43.27, 43.15, 42.98, 38.08, 37.92, 31.07, 26.65, 25.93. MS (ESI) m/z : 681.9[M+H] $^+$, C₃₃H₃₅F₄N₉O₃. Purity: 97.6% (LC-MS).

21. 2-(2-((4-((cyclohexylmethyl)amino)-6-((4-fluorobenzyl)amino)-1,3,5-triazin-2-yl)amino)phenyl)acetyl)-N-(4-cyanophenyl)hydrazine-1-carboxamide (**9l**)

White solid, yield: 83.3%; ^1H NMR (300 MHz, DMSO- d_6) δ 9.95 (s, 1H), 9.44 (s, 1H), 8.97 – 8.66 (m, 1H), 8.40 (s, 1H), 7.67 (dd, J = 18.0, 8.7 Hz, 6H), 7.47 – 7.07 (m, 7H), 6.85 (t, J = 29.8 Hz, 1H), 4.44 (s, 2H), 3.50 – 3.41 (m, 2H), 3.18 – 2.96 (m, 2H), 1.67 (m, 6H), 1.28 – 0.99 (m, 3H), 0.99 – 0.66 (m, 2H). ^{13}C NMR (75 MHz, DMSO- d_6) δ 170.84, 166.29, 164.54, 163.06, 159.86, 155.31, 144.72, 139.64, 137.34, 133.62, 129.41, 129.30, 128.59, 119.76, 118.62, 115.40, 115.12, 103.73, 99.99, 46.93, 42.94, 37.96, 31.06, 26.65, 25.92. MS (ESI) m/z : 665.9[M+H] $^+$, C₃₃H₃₅FN₁₀O₂. Purity: 96.5% (LC-MS).

22. 2-(2-((4-((cyclohexylmethyl)amino)-6-((4-fluorobenzyl)amino)-1,3,5-triazin-2-yl)amino)phenyl)acetyl)-N-(4-nitrophenyl)hydrazine-1-carboxamide (**9m**)

Yellow solid, yield: 75.4%; ^1H NMR (300 MHz, DMSO- d_6) δ 9.98 (s, 1H), 9.59 (d, J = 45.7 Hz, 1H), 8.97 – 8.64 (m, 1H), 8.45 (s, 1H), 8.17 (d, J = 9.1 Hz, 2H), 7.81 – 7.55 (m, 4H), 7.45 – 7.08 (m, 7H), 6.84 (t, J = 35.3 Hz, 1H), 4.44 (s, 2H), 3.51 – 3.42 (m, 2H), 3.18 – 2.95 (m, 2H), 1.74 – 1.39 (m, 6H), 1.28 – 1.01 (m, 3H), 0.99 – 0.66 (m, 2H). ^{13}C NMR (75 MHz, DMSO- d_6) δ 170.87, 166.30, 166.16, 164.56, 163.07, 159.86, 155.18, 146.84, 141.57, 139.69, 137.37, 129.41, 129.31, 128.54, 126.84, 125.46, 119.71, 118.15, 115.40, 115.12, 112.84, 46.97, 46.63, 43.27, 37.95, 31.07, 26.65, 25.93. MS (ESI) m/z : 642.9[M+H] $^+$, C₃₂H₃₅FN₁₀O₄. Purity: 97.3% (LC-MS).

23. 2-(2-((4-((cyclohexylmethyl)amino)-6-((4-fluorobenzyl)amino)-1,3,5-triazin-2-yl)amino)phenyl)acetyl)-N-benzylhydrazine-1-carboxamide (**9n**)

White solid, yield: 69.5%; ^1H NMR (300 MHz, DMSO- d_6) δ 9.74 (s, 1H), 8.98 – 8.65 (m, 1H), 7.89 (s, 1H), 7.82 – 7.53 (m, 2H), 7.47 – 7.21 (m, 8H), 7.15 – 7.03 (m, 4H), 7.01 – 6.71 (m, 2H), 4.44 (s, 2H), 4.24 (d, J = 5.8 Hz, 2H), 3.36 (s, 2H), 3.17 – 2.97 (m, 2H), 1.76 – 1.35 (m, 6H), 1.28 – 1.03 (m, 3H), 0.94 – 0.74 (m, 2H). ^{13}C NMR (75 MHz, DMSO- d_6) δ 170.88, 166.40, 166.28, 166.20, 164.56, 163.06, 159.87, 158.68, 140.96, 139.61, 137.63, 137.35, 129.41, 129.33, 128.76, 128.58, 127.53, 127.39, 126.99, 120.06, 119.95, 119.85, 119.65, 115.40, 115.12, 46.93,

46.63, 43.29, 43.11, 37.94, 31.08, 26.65, 25.93. MS (ESI) m/z : 612.0[M+H]⁺, C₃₃H₃₈FN₉O₂.

Purity: 97.5% (LC-MS).

24. 2-(2-((4-((cyclohexylmethyl)amino)-6-((4-fluorobenzyl)amino)-1,3,5-triazin-2-yl)amino)phenyl)acetyl)-N-(2-chlorophenyl)hydrazine-1-carbothioamide (**10a**)

White solid, yield: 78.6%; ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.33 – 9.99 (m, 1H), 9.95 – 9.66 (m, 1H), 9.45 (s, 1H), 8.99 – 8.65 (m, 1H), 7.79 – 7.56 (m, 2H), 7.49 (d, *J* = 7.8 Hz, 2H), 7.38 – 7.02 (m, 9H), 6.84 (t, *J* = 37.2 Hz, 1H), 4.44 (d, *J* = 5.0 Hz, 2H), 3.43 (t, *J* = 37.5 Hz, 2H), 3.16 – 2.95 (m, 2H), 1.79 – 1.29 (m, 6H), 1.26 – 1.01 (m, 3H), 0.98 – 0.67 (m, 2H). ¹³C NMR (75 MHz, DMSO-*d*₆) δ 182.18, 170.90, 166.42, 166.35, 166.19, 164.55, 163.04, 159.88, 139.70, 137.33, 131.00, 129.76, 129.56, 129.42, 128.30, 127.53, 119.91, 119.62, 115.41, 115.13, 46.92, 46.64, 43.31, 43.00, 37.94, 31.07, 26.65, 25.93. MS (ESI) m/z : 647.9[M+H]⁺, C₃₂H₃₅ClFN₉OS.

Purity: 96.4% (LC-MS).

25. 2-(2-((4-((cyclohexylmethyl)amino)-6-((4-fluorobenzyl)amino)-1,3,5-triazin-2-yl)amino)phenyl)acetyl)-N-(3-chlorophenyl)hydrazine-1-carbothioamide (**10b**)

White solid, yield: 75.4%; ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.14 (s, 1H), 9.92 – 9.54 (m, 2H), 8.99 – 8.63 (m, 1H), 7.65 (s, 3H), 7.47 – 7.03 (m, 10H), 6.84 (t, *J* = 32.1 Hz, 1H), 4.44 (s, 2H), 3.45 (s, 2H), 3.15 – 2.97 (m, 2H), 1.80 – 1.31 (m, 6H), 1.24 – 1.03 (m, 3H), 0.99 – 0.67 (m, 2H). ¹³C NMR (75 MHz, DMSO-*d*₆) δ 181.43, 170.69, 166.41, 166.28, 166.16, 164.54, 163.07, 159.86, 141.18, 139.68, 137.44, 132.66, 130.17, 129.53, 129.41, 129.31, 128.35, 125.19, 119.93, 119.65, 115.40, 115.13, 46.94, 46.74, 43.21, 42.93, 37.97, 31.07, 26.66, 25.93. MS (ESI) m/z : 647.9[M+H]⁺, C₃₂H₃₅ClFN₉OS. Purity: 95.4% (LC-MS).

26. 2-(2-((4-((cyclohexylmethyl)amino)-6-((4-fluorobenzyl)amino)-1,3,5-triazin-2-yl)amino)phenyl)acetyl)-N-(4-chlorophenyl)hydrazine-1-carbothioamide (**10c**)

White solid, yield: 70.3%; ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.27 – 9.91 (m, 1H), 9.71 (s, 2H), 8.99 – 8.66 (m, 1H), 7.79 – 7.56 (m, 2H), 7.54 – 7.42 (m, 2H), 7.43 – 7.01 (m, 9H), 6.85 (t, *J* = 34.2 Hz, 1H), 4.44 (d, *J* = 5.6 Hz, 2H), 3.44 (s, 2H), 3.16 – 2.97 (m, 2H), 1.86 – 1.32 (m, 6H), 1.25 – 1.03 (m, 3H), 0.97 – 0.66 (m, 2H). ¹³C NMR (75 MHz, DMSO-*d*₆) δ 181.53, 170.71, 166.46, 166.28, 166.11, 164.52, 163.05, 159.84, 139.70, 138.62, 137.40, 129.53, 129.41, 129.33, 128.47, 127.68, 119.97, 119.65, 115.40, 115.12, 46.94, 46.65, 43.31, 43.08, 38.00, 31.07, 26.65, 25.93. MS (ESI) m/z : 647.9[M+H]⁺, C₃₂H₃₅ClFN₉OS. Purity: 96.5% (LC-MS).

27. 2-(2-((4-((cyclohexylmethyl)amino)-6-((4-fluorobenzyl)amino)-1,3,5-triazin-2-yl)amino)phenyl)acetyl)-N-(2-fluorophenyl)hydrazine-1-carbothioamide (**10d**)

White solid, yield: 78.9%; ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.17 (s, 1H), 9.77 (s, 1H), 9.48 (s, 1H), 8.93 – 8.64 (m, 1H), 7.76 – 7.54 (m, 2H), 7.53 – 6.99 (m, 11H), 6.85 (t, *J* = 32.4 Hz, 1H), 4.44 (d, *J* = 4.8 Hz, 2H), 3.42 (t, *J* = 22.8 Hz, 2H), 3.16 – 2.98 (m, 2H), 1.79 – 1.31 (m, 6H), 1.26 – 1.00 (m, 3H), 0.97 – 0.67 (m, 2H). ¹³C NMR (75 MHz, DMSO-*d*₆) δ 182.65, 170.67, 166.33, 164.53, 163.06, 159.86, 139.66, 137.38, 129.54, 129.42, 128.37, 127.61, 124.40, 119.85, 119.60, 116.29, 116.02, 115.40, 115.13, 46.92, 46.63, 43.24, 43.01, 37.95, 31.06, 26.64, 25.93. MS (ESI) m/z : 631.9[M+H]⁺, C₃₂H₃₅F₂N₉OS. Purity: 97.2% (LC-MS).

28. 2-(2-((4-((cyclohexylmethyl)amino)-6-((4-fluorobenzyl)amino)-1,3,5-triazin-2-yl)amino)phenyl)acetyl)-N-(3-fluorophenyl)hydrazine-1-carbothioamide (**10e**)

White solid, yield: 72.2%; ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.14 (s, 1H), 9.90 – 9.54 (m, 2H), 8.96 – 8.66 (m, 1H), 7.78 – 7.57 (m, 2H), 7.51 (d, *J* = 9.0 Hz, 1H), 7.45 – 7.06 (m, 9H), 6.98 (t, *J* = 8.5 Hz, 1H), 6.79 (t, *J* = 31.2 Hz, 1H), 4.43 (s, 2H), 3.44 (s, 2H), 3.15 – 2.95 (m, 2H), 1.80

– 1.36 (m, 6H), 1.80 – 1.37 (m, 3H), 0.98 – 0.67 (m, 2H). ^{13}C NMR (75 MHz, DMSO- d_6) δ 181.40, 170.70, 166.30, 164.54, 163.62, 163.07, 160.42, 159.87, 141.51, 141.36, 139.73, 137.39, 130.10, 129.54, 129.42, 128.38, 120.04, 119.65, 115.41, 115.13, 111.89, 46.96, 46.62, 43.21, 42.98, 37.98, 31.08, 26.64, 25.93. MS (ESI) m/z : 631.9[M+H] $^+$, C₃₂H₃₅F₂N₉OS. Purity: 97.0% (LC-MS).

29. 2-(2-((4-((cyclohexylmethyl)amino)-6-((4-fluorobenzyl)amino)-1,3,5-triazin-2-yl)amino)phenyl)acetyl)-N-(4-fluorophenyl)hydrazine-1-carbothioamide (**10f**)

White solid, yield: 65.7%; ^1H NMR (300 MHz, DMSO- d_6) δ 10.21 (s, 1H), 9.64 (s, 2H), 8.98 – 8.63 (m, 1H), 7.82 – 7.54 (m, 2H), 7.49 – 7.02 (m, 11H), 6.84 (t, J = 31.3 Hz, 1H), 4.44 (s, 2H), 3.55 – 3.39 (m, 2H), 3.19 – 2.96 (m, 2H), 1.83 – 1.36 (m, 6H), 1.25 – 0.99 (m, 3H), 0.98 – 0.66 (m, 2H). ^{13}C NMR (75 MHz, DMSO- d_6) δ 181.83, 170.73, 166.42, 166.30, 166.17, 164.55, 163.08, 161.53, 159.87, 158.31, 139.69, 137.39, 135.93, 129.54, 129.42, 129.31, 128.41, 120.01, 119.62, 115.38, 115.08, 46.93, 46.63, 43.24, 42.93, 37.95, 31.07, 26.66, 25.93. MS (ESI) m/z : 631.9[M+H] $^+$, C₃₂H₃₅F₂N₉OS. Purity: 97.5% (LC-MS).

30. 2-(2-((4-((cyclohexylmethyl)amino)-6-((4-fluorobenzyl)amino)-1,3,5-triazin-2-yl)amino)phenyl)acetyl)-N-(o-tolyl)hydrazine-1-carbothioamide (**10g**)

White solid, yield: 73.6%; ^1H NMR (300 MHz, DMSO- d_6) δ 10.09 (s, 1H), 9.51 (s, 1H), 9.40 (s, 1H), 8.98 – 8.65 (m, 1H), 7.81 – 7.56 (m, 2H), 7.34 (s, 3H), 7.22 – 7.09 (m, 8H), 6.85 (t, J = 29.7 Hz, 1H), 4.44 (s, 2H), 3.43 (s, 2H), 3.19 – 2.97 (s, 2H), 2.16 (s, 3H), 1.73 – 1.43 (m, 6H), 1.21 – 1.06 (m, 3H), 0.96 – 0.72 (m, 2H). ^{13}C NMR (75 MHz, DMSO- d_6) δ 182.14, 170.66, 166.41, 166.31, 166.14, 164.55, 163.07, 159.87, 139.67, 138.35, 137.37, 136.14, 135.27, 131.25, 130.54, 129.99, 129.57, 129.42, 129.32, 128.46, 127.71, 127.12, 126.34, 126.29, 119.96, 119.59, 115.40, 115.12, 46.96, 46.64, 43.26, 43.11, 42.95, 39.18, 37.97, 31.08, 26.66, 25.94, 25.60, 18.28, 18.10. MS (ESI) m/z : 628.0[M+H] $^+$, C₃₃H₃₈FN₉OS. Purity: 97.3% (LC-MS).

31. 2-(2-((4-((cyclohexylmethyl)amino)-6-((4-fluorobenzyl)amino)-1,3,5-triazin-2-yl)amino)phenyl)acetyl)-N-(m-tolyl)hydrazine-1-carbothioamide (**10h**)

White solid, yield: 68.2%; ^1H NMR (300 MHz, DMSO- d_6) δ 10.21 (s, 1H), 9.58 (s, 2H), 8.99 – 8.66 (m, 1H), 7.80 – 7.55 (m, 2H), 7.43 – 7.04 (m, 10H), 7.02 – 6.66 (m, 2H), 4.44 (s, 2H), 3.53 – 3.40 (m, 2H), 3.18 – 2.97 (m, 2H), 2.29 (s, 3H), 1.81 – 1.35 (m, 6H), 1.29 – 1.01 (m, 3H), 0.99 – 0.66 (m, 2H). ^{13}C NMR (75 MHz, DMSO- d_6) δ 181.44, 170.69, 166.27, 164.54, 163.08, 159.87, 139.71, 139.46, 137.83, 137.36, 129.53, 129.42, 129.32, 128.46, 126.11, 119.95, 119.66, 115.40, 115.12, 46.67, 43.26, 37.96, 31.08, 26.66, 25.94, 21.40. MS (ESI) m/z : 627.9[M+H] $^+$, C₃₃H₃₈FN₉OS. Purity: 98.1% (LC-MS).

32. 2-(2-((4-((cyclohexylmethyl)amino)-6-((4-fluorobenzyl)amino)-1,3,5-triazin-2-yl)amino)phenyl)acetyl)-N-(p-tolyl)hydrazine-1-carbothioamide (**10i**)

White solid, yield: 66.5%; ^1H NMR (300 MHz, DMSO- d_6) δ 10.16 (s, 1H), 9.53 (s, 2H), 8.97 – 8.63 (m, 1H), 7.80 – 7.53 (m, 2H), 7.50 – 7.01 (m, 11H), 6.84 (t, J = 35.8 Hz, 1H), 4.44 (d, J = 4.7 Hz, 2H), 3.52 – 3.38 (m, 2H), 3.15 – 2.96 (m, 2H), 2.28 (s, 3H), 1.80 – 1.32 (m, 6H), 1.27 – 1.02 (m, 3H), 0.94 – 0.68 (m, 2H). ^{13}C NMR (75 MHz, DMSO- d_6) δ 181.61, 170.63, 166.29, 164.55, 163.07, 159.87, 139.68, 137.34, 137.01, 134.65, 129.53, 129.41, 129.31, 129.04, 128.46, 126.00, 119.90, 119.64, 115.39, 115.12, 46.88, 46.64, 43.24, 43.01, 37.94, 31.06, 26.65, 25.93, 21.01. MS (ESI) m/z : 627.9[M+H] $^+$, C₃₃H₃₈FN₉OS. Purity: 98.0% (LC-MS).

33. 2-(2-((4-((cyclohexylmethyl)amino)-6-((4-fluorobenzyl)amino)-1,3,5-triazin-2-yl)amino)phenyl)acetyl)-N-(4-(trifluoromethyl)phenyl)hydrazine-1-carbothioamide (**10j**)

White solid, yield: 67.4%; ^1H NMR (300 MHz, DMSO- d_6) δ 10.17 (s, 1H), 9.86 (s, 2H), 8.95 – 8.67 (m, 1H), 7.90 – 7.51 (m, 6H), 7.49 – 7.03 (m, 7H), 6.85 (t, J = 31.3 Hz, 1H), 4.43 (s, 2H), 3.45 (s, 2H), 3.16 – 2.96 (m, 2H), 1.80 – 1.30 (m, 6H), 1.28 – 1.00 (m, 3H), 0.98 – 0.65 (m, 2H). ^{13}C NMR (75 MHz, DMSO- d_6) δ 181.43, 166.24, 164.53, 163.07, 159.80, 143.47, 139.72, 137.34, 129.52, 129.40, 129.31, 128.37, 126.60, 125.97, 125.69, 125.53, 123.00, 120.00, 119.62, 115.40, 115.13, 46.92, 46.66, 43.27, 43.04, 37.95, 31.06, 30.98, 26.64, 25.92. MS (ESI) m/z : 681.9[M+H] $^+$, C₃₃H₃₅F₄N₉OS. Purity: 97.6% (LC-MS).

34. 2-(2-((4-((cyclohexylmethyl)amino)-6-((4-fluorobenzyl)amino)-1,3,5-triazin-2-yl)amino)phenyl)acetyl)-N-(4-(trifluoromethoxy)phenyl)hydrazine-1-carbothioamide (**10k**)
White solid, yield: 74.3%; ^1H NMR (300 MHz, DMSO- d_6) δ 10.13 (s, 1H), 9.74 (s, 2H), 8.96 – 8.62 (m, 1H), 7.82 – 7.48 (m, 4H), 7.47 – 7.02 (m, 9H), 6.84 (t, J = 31.7 Hz, 1H), 4.43 (s, 2H), 3.43 (t, J = 14.4 Hz, 2H), 3.17 – 2.95 (m, 2H), 1.80 – 1.32 (m, 6H), 1.28 – 1.01 (m, 3H), 0.99 – 0.66 (m, 2H). ^{13}C NMR (75 MHz, DMSO- d_6) δ 181.58, 166.57, 166.39, 166.16, 164.54, 163.06, 159.86, 139.68, 138.84, 137.45, 129.52, 129.41, 129.31, 128.35, 121.24, 120.00, 119.62, 118.89, 115.40, 115.12, 46.88, 46.64, 43.08, 37.89, 31.07, 26.65, 25.92. MS (ESI) m/z : 697.9[M+H] $^+$, C₃₃H₃₅F₄N₉O₂S. Purity: 95.4% (LC-MS).
35. 2-(2-((4-((cyclohexylmethyl)amino)-6-((4-fluorobenzyl)amino)-1,3,5-triazin-2-yl)amino)phenyl)acetyl)-N-(4-cyanophenyl)hydrazine-1-carbothioamide (**10l**)
White solid, yield: 80.3%; ^1H NMR (300 MHz, DMSO- d_6) δ 10.54 – 9.70 (m, 3H), 8.99 – 8.66 (m, 1H), 7.90 – 7.55 (m, 6H), 7.53 – 7.02 (m, 7H), 6.85 (t, J = 30.8 Hz, 1H), 4.44 (s, 2H), 3.46 (s, 2H), 3.18 – 2.96 (m, 2H), 1.77 – 1.33 (m, 6H), 1.27 – 1.00 (m, 3H), 0.99 – 0.66 (m, 2H). ^{13}C NMR (75 MHz, DMSO- d_6) δ 181.13, 166.27, 166.12, 164.51, 163.07, 159.86, 144.21, 139.73, 137.37, 132.82, 129.51, 129.42, 129.31, 128.34, 125.72, 125.28, 120.17, 120.00, 119.66, 119.43, 115.41, 115.12, 46.91, 46.63, 43.27, 42.97, 37.97, 31.07, 26.65, 25.93. MS (ESI) m/z : 639.0[M+H] $^+$, C₃₃H₃₅FN₁₀OS. Purity: 96.8% (LC-MS).
36. 2-(2-((4-((cyclohexylmethyl)amino)-6-((4-fluorobenzyl)amino)-1,3,5-triazin-2-yl)amino)phenyl)acetyl)-N-(4-nitrophenyl)hydrazine-1-carbothioamide (**10m**)
Yellow solid (203 mg), yield: 77.2%; ^1H NMR (300 MHz, DMSO- d_6) δ 10.59 – 9.61 (m, 3H), 9.03 – 8.60 (m, 1H), 8.21 (d, J = 8.6 Hz, 2H), 7.90 (d, J = 8.8 Hz, 2H), 7.66 (s, 2H), 7.48 – 7.03 (m, 7H), 6.85 (t, J = 33.4 Hz, 1H), 4.44 (s, 2H), 3.47 (s, 2H), 3.09 (s, 2H), 1.81 – 1.31 (m, 6H), 1.27 – 1.06 (m, 3H), 0.99 – 0.66 (m, 2H). ^{13}C NMR (75 MHz, DMSO- d_6) δ 181.09, 170.78, 166.21, 166.04, 164.49, 163.07, 159.86, 146.25, 143.59, 139.71, 137.33, 129.51, 129.42, 129.32, 128.34, 125.03, 124.70, 124.40, 124.28, 120.03, 119.93, 119.67, 115.41, 115.13, 46.94, 46.65, 43.23, 42.98, 37.94, 31.07, 26.64, 25.93. MS (ESI) m/z : 658.9[M+H] $^+$, C₃₂H₃₅FN₁₀O₃S. Purity: 97.5% (LC-MS).
37. 2-(2-((4-((cyclohexylmethyl)amino)-6-((4-fluorobenzyl)amino)-1,3,5-triazin-2-yl)amino)phenyl)acetyl)-N-phenylhydrazine-1-carbothioamide (**10n**)
White solid, yield: 65.8%; ^1H NMR (300 MHz, DMSO- d_6) δ 10.11 (s, 1H), 9.61 (s, 2H), 8.98 – 8.63 (m, 1H), 7.80 – 7.56 (m, 2H), 7.44 (d, J = 7.5 Hz, 2H), 7.33 (t, J = 7.6 Hz, 4H), 7.15 (dd, J = 15.6, 7.2 Hz, 6H), 6.84 (t, J = 34.0 Hz, 1H), 4.44 (s, 2H), 3.52 – 3.40 (m, 2H), 3.16 – 2.95 (m, 2H), 1.74 – 1.41 (m, 6H), 1.23 – 1.02 (m, 3H), 0.96 – 0.73 (m, 2H). ^{13}C NMR (75 MHz, DMSO- d_6) δ 181.52, 170.70, 170.64, 166.44, 166.29, 166.16, 164.55, 163.07, 159.87, 139.70, 139.61, 137.38, 129.53, 129.42, 129.31, 128.57, 128.44, 125.93, 125.58, 125.44, 119.96, 119.63, 115.40, 115.12, 46.65, 43.24, 37.96, 31.08, 26.66, 25.93. MS (ESI) m/z : 614.0[M+H] $^+$,

$C_{32}H_{36}FN_9OS$. Purity: 97.0% (LC-MS).

38. *2-(2-((4-((cyclohexylmethyl)amino)-6-((4-fluorobenzyl)amino)-1,3,5-triazin-2-yl)amino)phenyl)acetyl-N-benzylhydrazine-1-carbothioamide (10o)*

White solid, yield: 60.3%; 1H NMR (300 MHz, DMSO- d_6) δ 10.08 (s, 1H), 9.42 (s, 1H), 8.97 – 8.64 (m, 1H), 8.50 (s, 1H), 7.86 – 7.52 (m, 2H), 7.49 – 7.05 (m, 11H), 7.03 – 6.64 (m, 1H), 4.74 (d, J = 5.7 Hz, 2H), 4.45 (d, J = 5.0 Hz, 2H), 3.41 (s, 2H), 3.17 – 2.98 (m, 2H), 1.87 – 1.29 (m, 6H), 1.25 – 1.05 (m, 3H), 0.99 – 0.66 (m, 2H). ^{13}C NMR (75 MHz, DMSO- d_6) δ 182.69, 170.73, 166.42, 166.29, 166.13, 164.55, 163.08, 159.87, 139.76, 139.68, 137.38, 129.50, 129.31, 128.52, 128.40, 127.48, 127.07, 119.99, 119.86, 119.58, 115.40, 115.13, 47.17, 46.91, 46.62, 43.22, 42.93, 37.97, 31.07, 30.95, 26.66, 25.93. MS (ESI) m/z : 627.9[M+H] $^+$, $C_{33}H_{38}FN_9OS$. Purity: 96.9% (LC-MS).

39. *N²-(cyclohexylmethyl)-N⁴-(4-fluorobenzyl)-N⁶-(4-((4-chlorophenyl)amino)-1,3,4-oxadiazol-2-yl)methylphenyl)-1,3,5-triazine-2,4,6-triamine (11c)*

White solid, yield: 55.2%; 1H NMR (300 MHz, DMSO- d_6) δ 10.55 (s, 1H), 9.06 – 8.72 (m, 1H), 7.81 – 7.62 (m, 2H), 7.55 (d, J = 8.9 Hz, 2H), 7.47 – 7.23 (m, 5H), 7.21 – 7.04 (t, J = 8.7 Hz, 4H), 6.85 (t, J = 34.5 Hz, 1H), 4.43 (s, 2H), 4.08 (s, 2H), 3.16 – 2.95 (m, 2H), 1.72 – 1.45 (m, 6H), 1.19 – 1.00 (m, 3H), 0.97 – 0.73 (m, 2H). ^{13}C NMR (75 MHz, DMSO- d_6) δ 166.39, 166.28, 166.13, 164.55, 164.51, 163.07, 162.77, 160.14, 159.86, 159.73, 140.25, 140.22, 140.20, 138.23, 137.36, 137.31, 129.34, 129.01, 127.57, 125.69, 120.34, 120.11, 118.84, 115.39, 115.11, 100.03, 46.97, 46.63, 43.27, 37.90, 31.05, 30.57, 26.63, 25.91. MS (ESI) m/z : 614.0[M+H] $^+$, $C_{32}H_{33}ClFN_9O$. Purity: 96.7% (LC-MS).

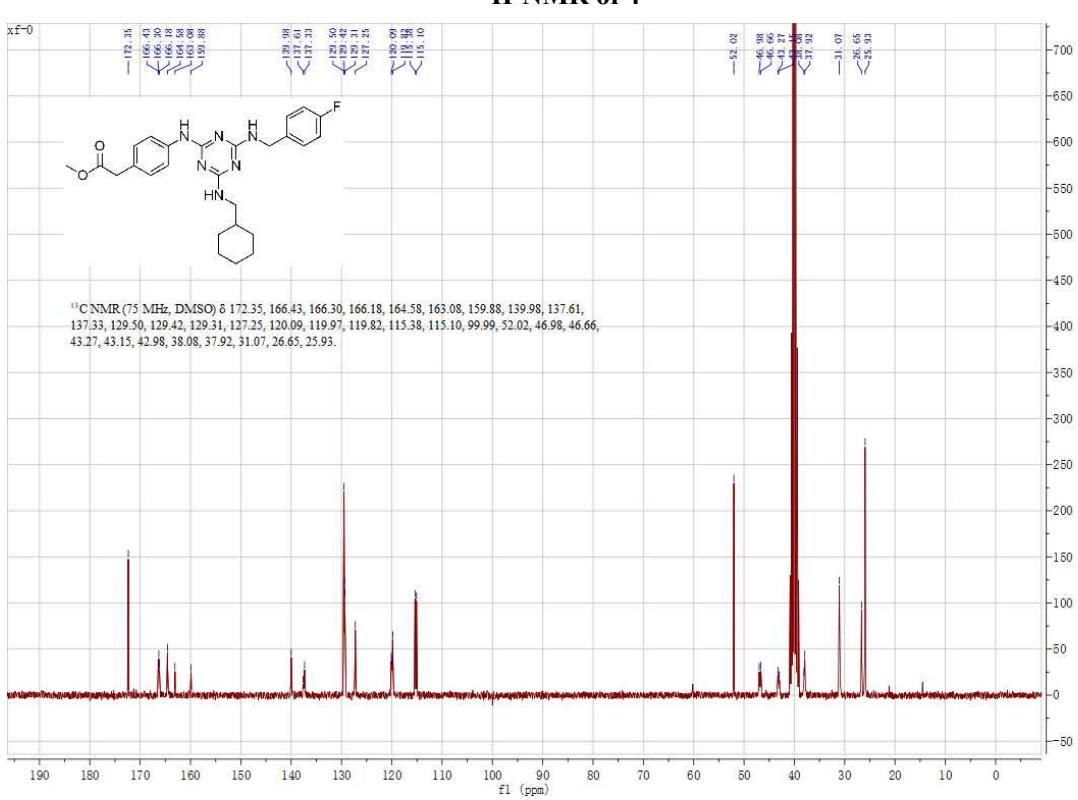
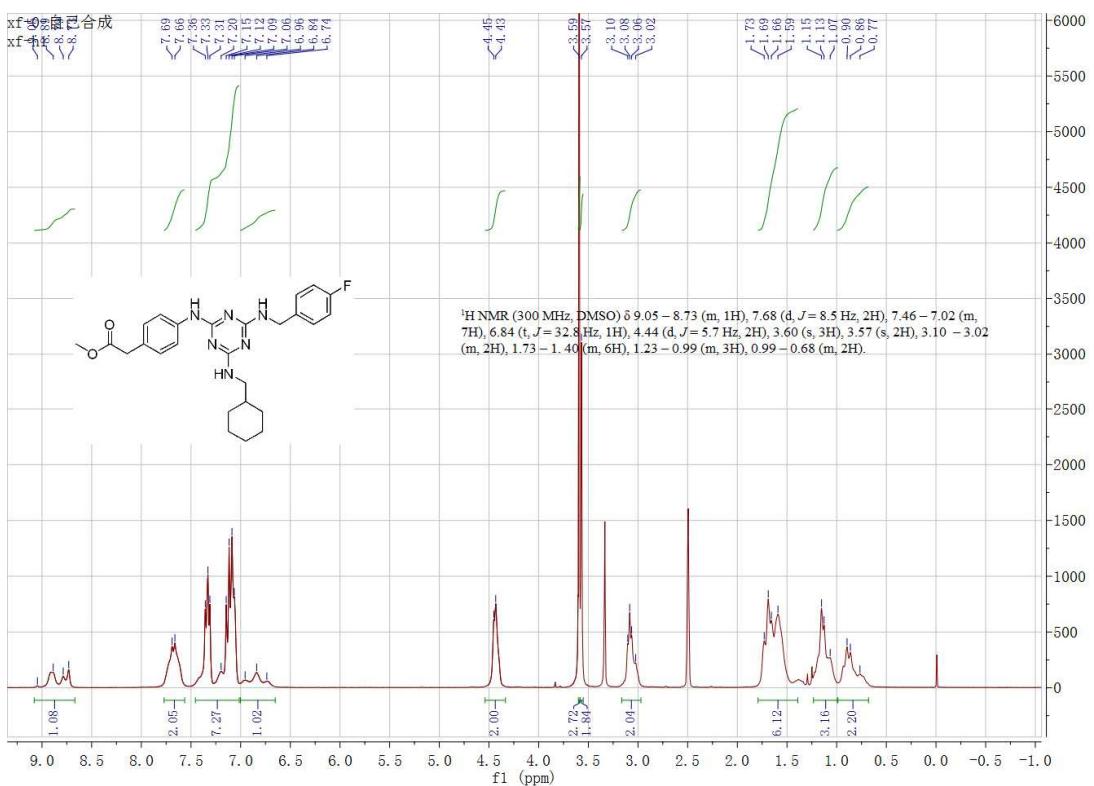
40. *N²-(cyclohexylmethyl)-N⁴-(4-fluorobenzyl)-N⁶-(4-((5-(p-tolylamino)-1,3,4-oxadiazol-2-yl)methyl)phenyl)-1,3,5-triazine-2,4,6-triamine (11i)*

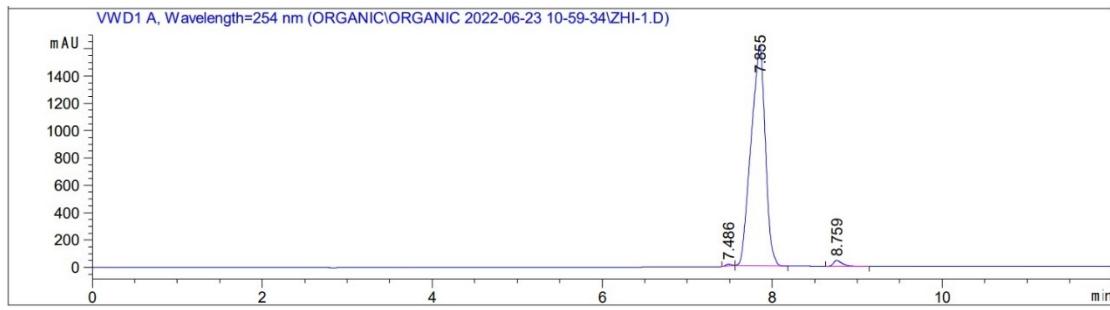
White solid, yield: 48.6%; 1H NMR (300 MHz, DMSO- d_6) δ 10.23 (s, 1H), 9.03 – 8.71 (m, 1H), 7.83 – 7.61 (m, 2H), 7.49 – 7.05 (m, 11H), 6.86 (t, J = 34.7 Hz, 1H), 4.43 (s, 2H), 4.06 (s, 2H), 3.15 – 2.97 (m, 2H), 2.23 (s, 3H), 1.77 – 1.46 (m, 6H), 1.19 – 1.01 (m, 3H), 0.97 – 0.68 (m, 2H). ^{13}C NMR (75 MHz, DMSO- d_6) δ 170.85, 166.40, 166.29, 166.17, 164.56, 163.07, 159.87, 155.82, 139.65, 137.50, 131.12, 129.50, 129.29, 128.70, 120.02, 119.68, 118.94, 115.40, 115.12, 46.89, 46.67, 43.20, 42.91, 37.95, 31.07, 26.65, 25.93, 20.78. MS (ESI) m/z : 594.0[M+H] $^+$, $C_{33}H_{36}FN_9O$. Purity: 96.4% (LC-MS).

41. *N²-(cyclohexylmethyl)-N⁴-(4-fluorobenzyl)-N⁶-(4-((5-((4-(trifluoromethyl)phenyl)amino)-1,3,4-oxadiazol-2-yl)methyl)phenyl)-1,3,5-triazine-2,4,6-triamine (11j)*

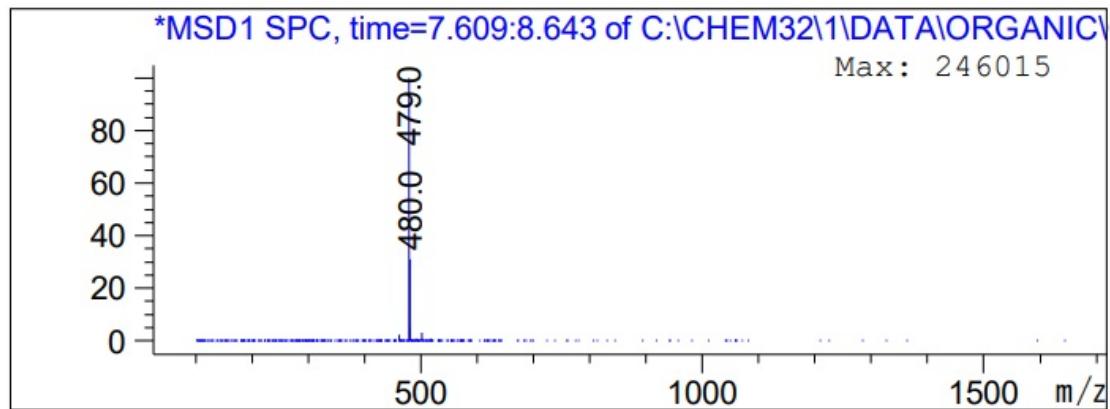
White solid, yield: 47.1%; 1H NMR (300 MHz, DMSO- d_6) δ 10.87 (s, 1H), 9.09 – 8.70 (m, 1H), 7.70 (s, 6H), 7.51 – 7.05 (m, 7H), 6.85 (t, J = 35.9 Hz, 1H), 4.43 (s, 2H), 4.11 (s, 2H), 3.12 – 2.97 (m, 2H), 1.81 – 1.38 (m, 6H), 1.25 – 1.08 (m, 3H), 0.96 – 0.69 (m, 2H). ^{13}C NMR (75 MHz, DMSO- d_6) δ 166.35, 166.26, 166.18, 164.54, 163.06, 160.08, 159.92, 142.73, 140.27, 137.33, 129.41, 129.31, 129.03, 127.49, 126.87, 126.82, 122.34, 121.91, 120.31, 120.13, 117.21, 115.39, 115.11, 46.92, 46.66, 43.27, 42.91, 37.90, 31.05, 30.57, 26.62, 25.90. MS (ESI) m/z : 647.9[M+H] $^+$, $C_{33}H_{33}F_4N_9O$. Purity: 96.2% (LC-MS).

¹H NMR, ¹³C NMR, HPLC purity and ESI-MS of All Compounds

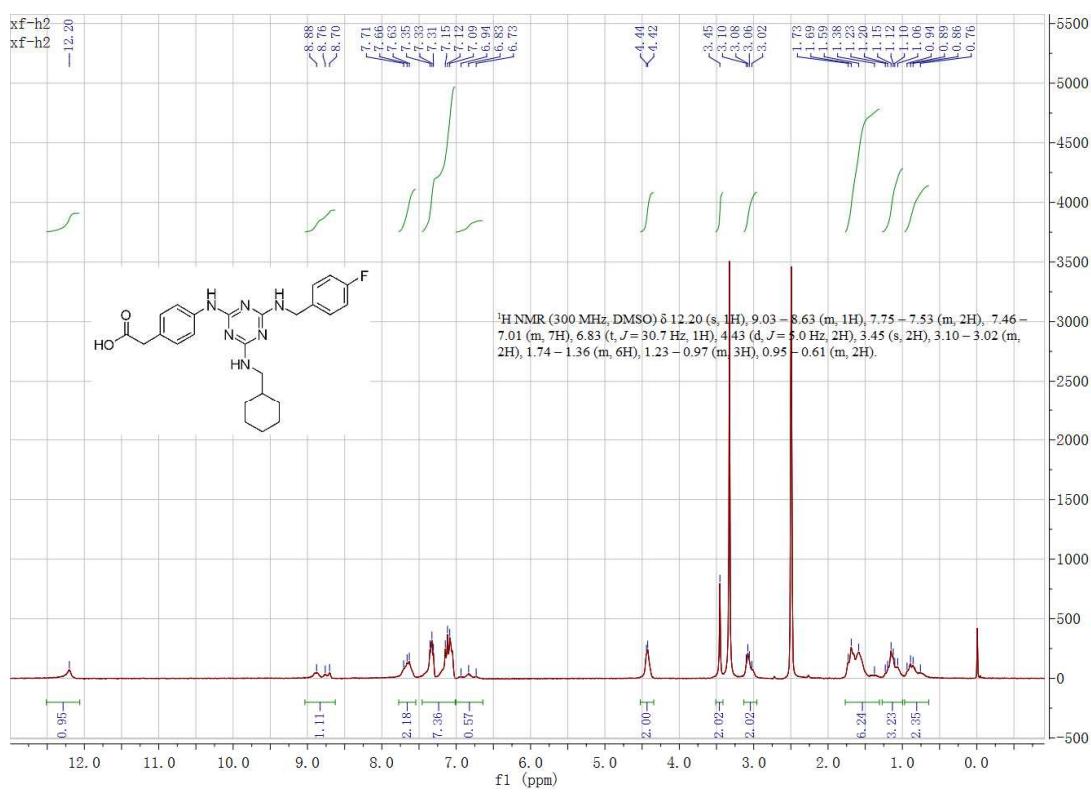




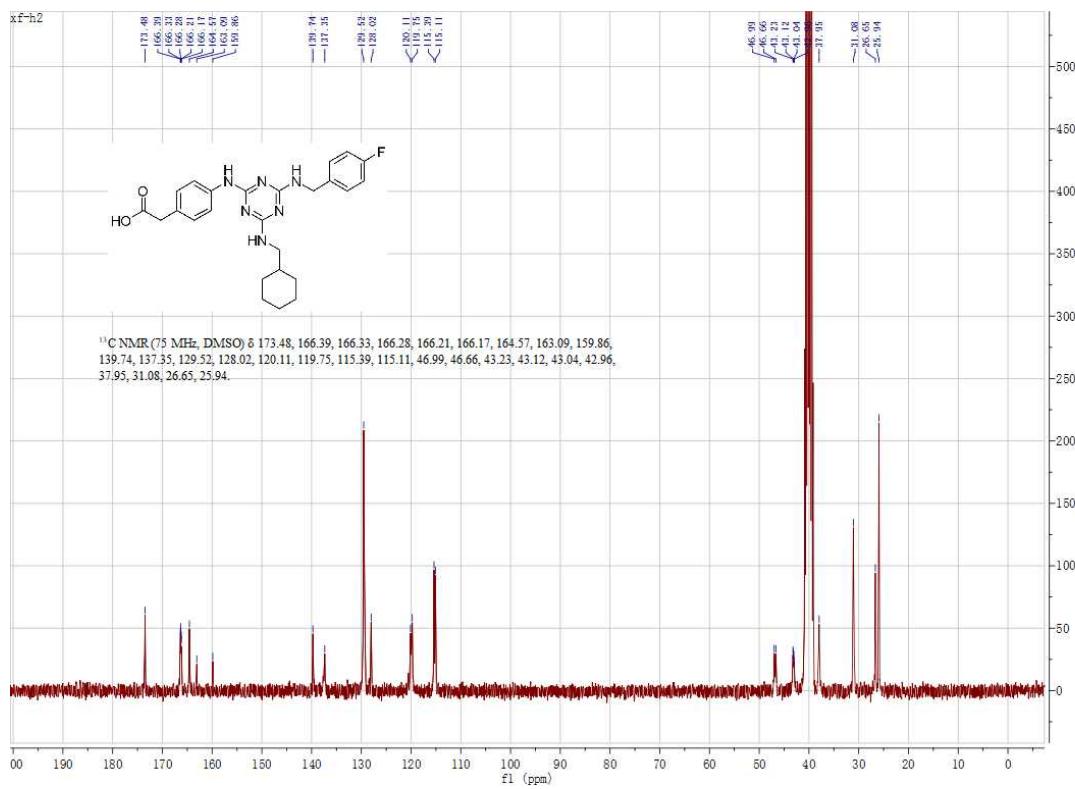
HPLC purity of 4



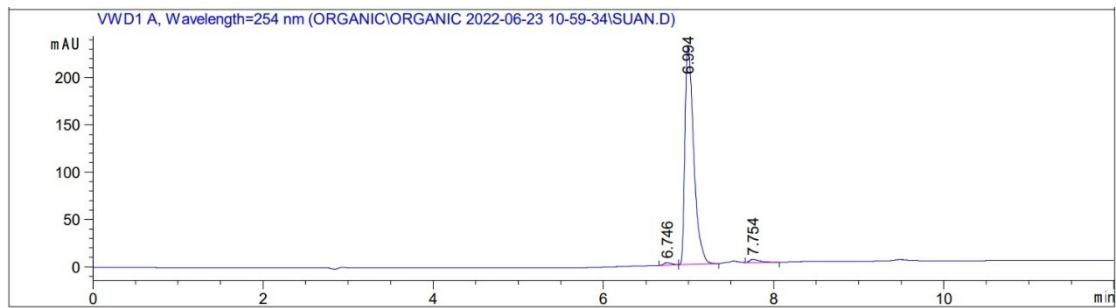
ESI-MS of 4



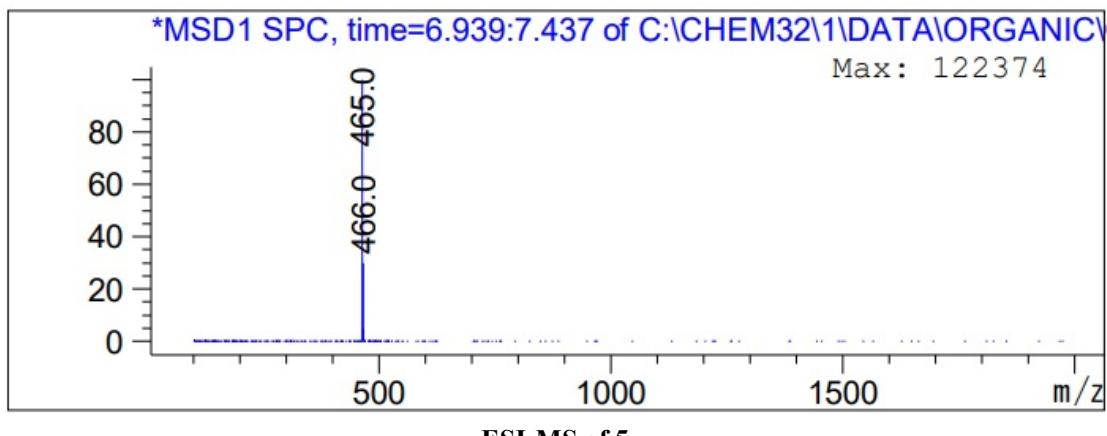
¹H-NMR of 5



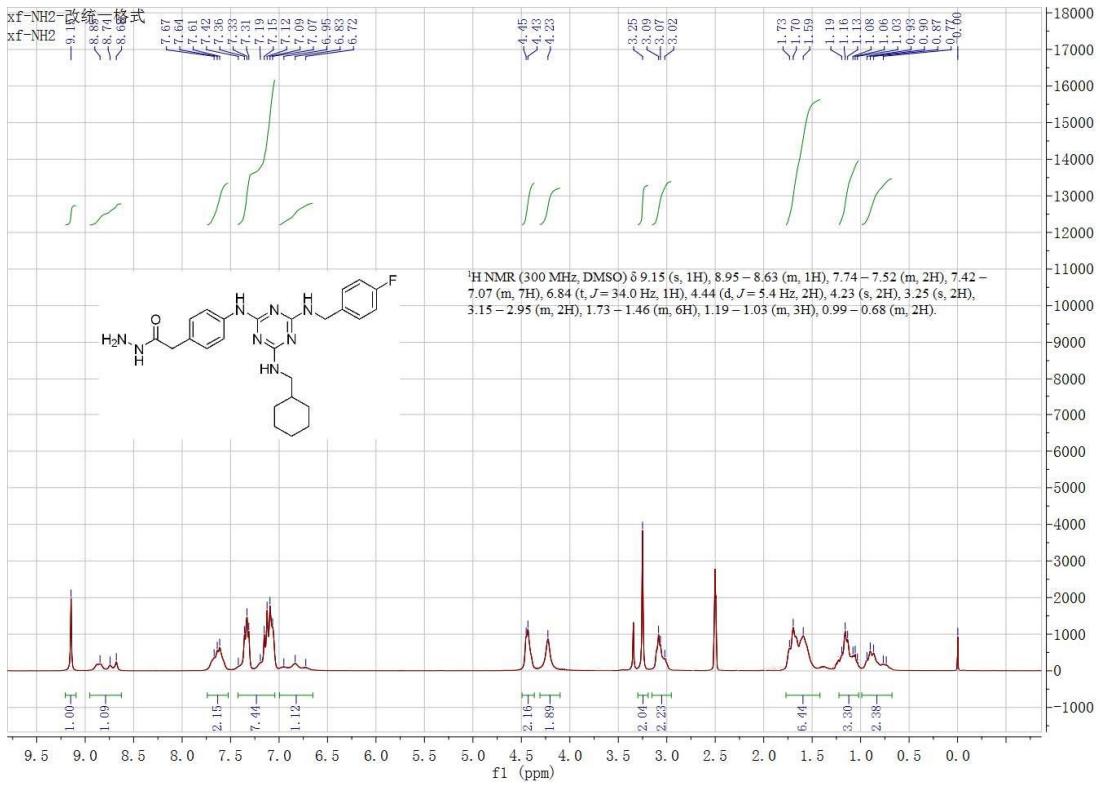
¹³C-NMR of 5



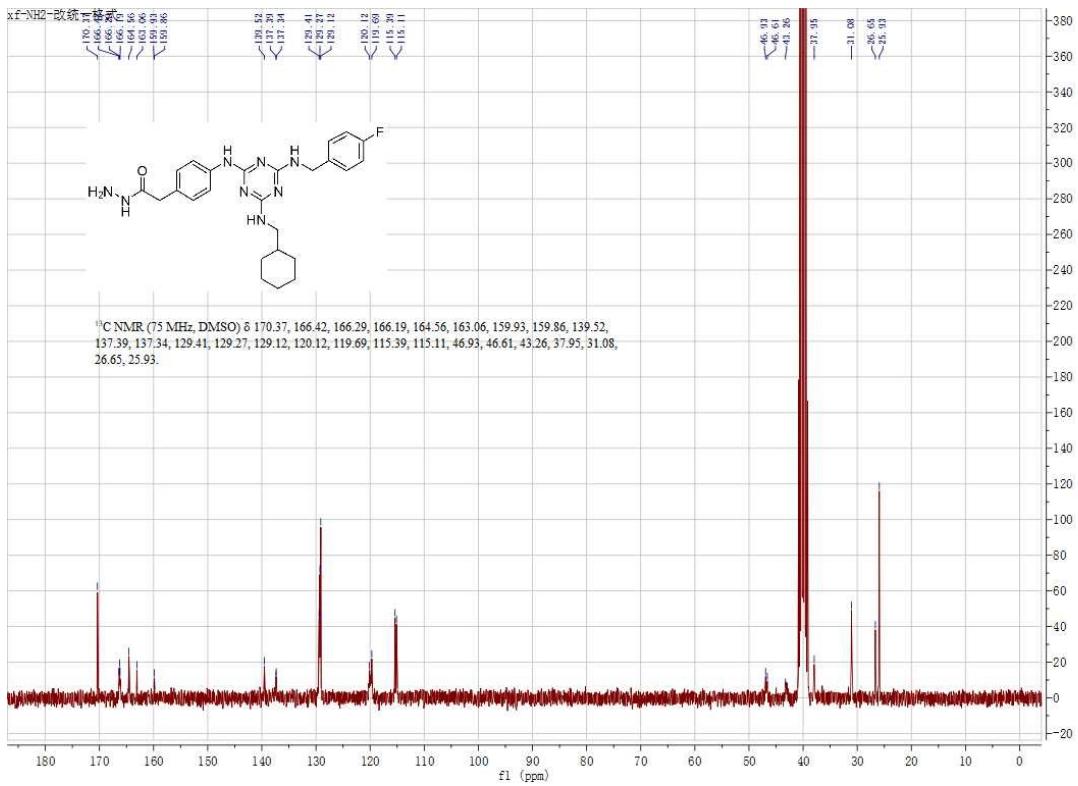
HPLC purity of 5



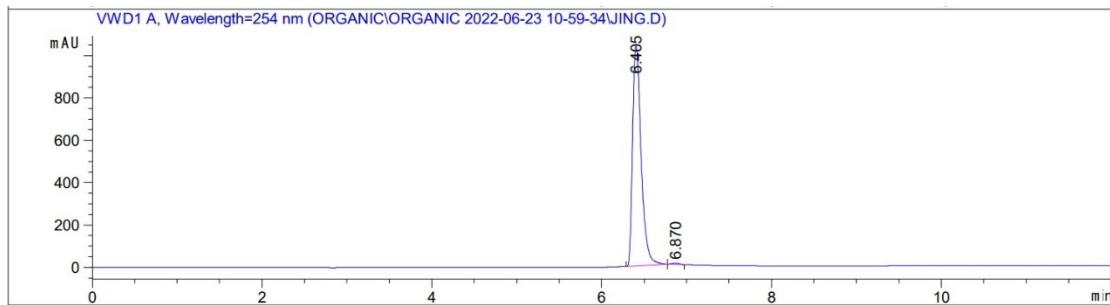
ESI-MS of 5



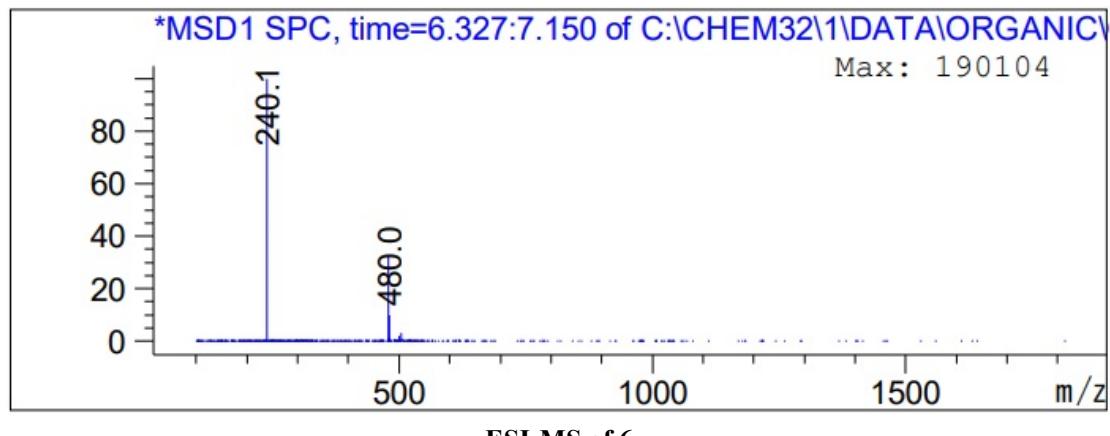
¹H-NMR of 6



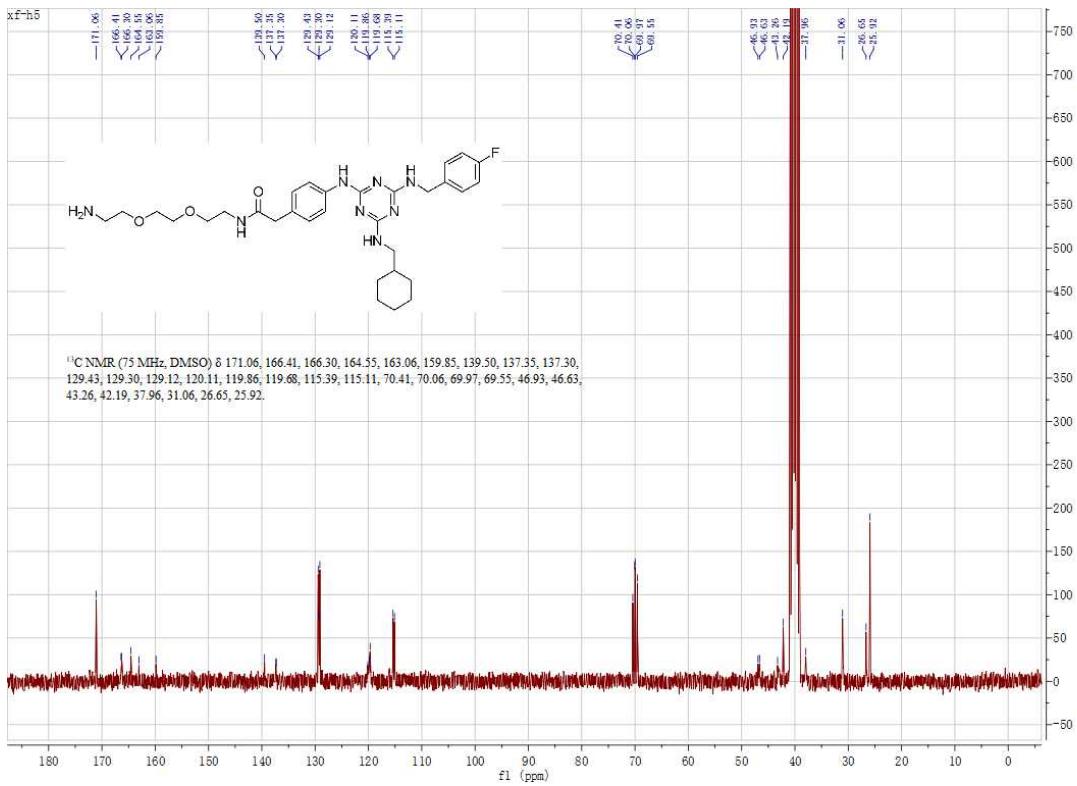
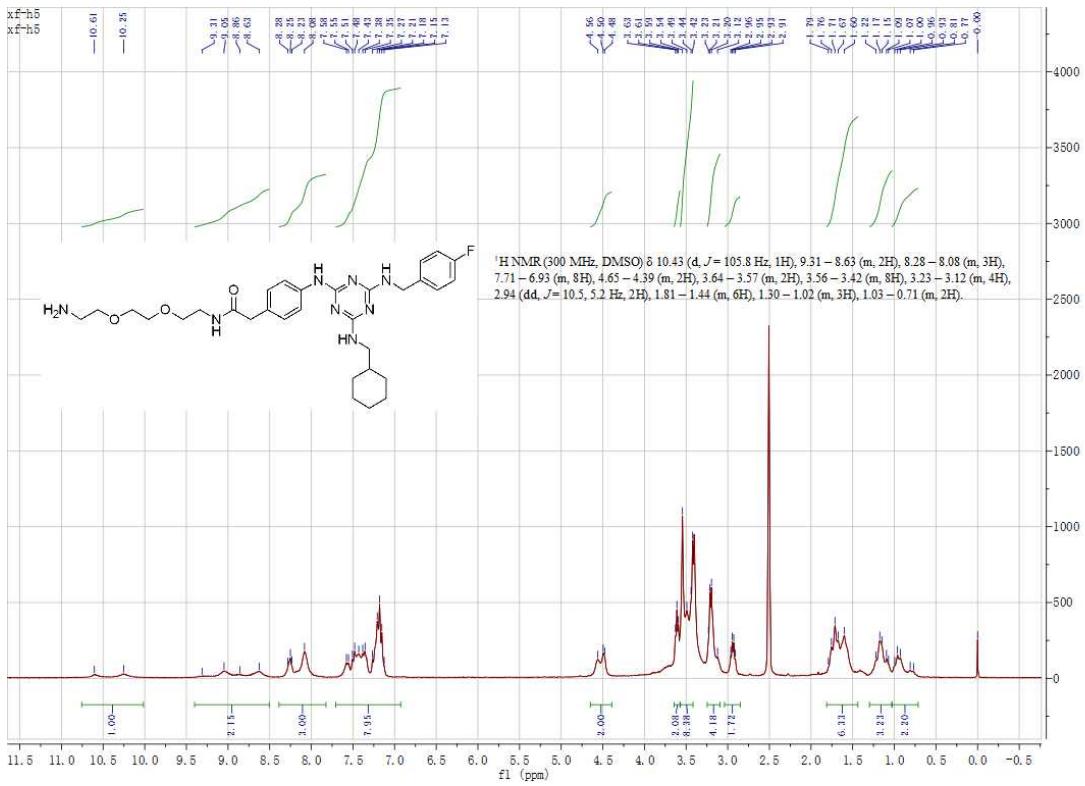
¹³C-NMR of 6



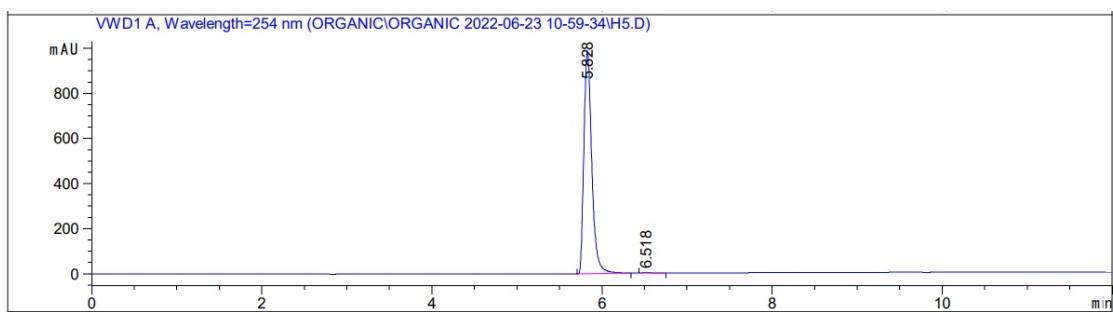
HPLC purity of 6



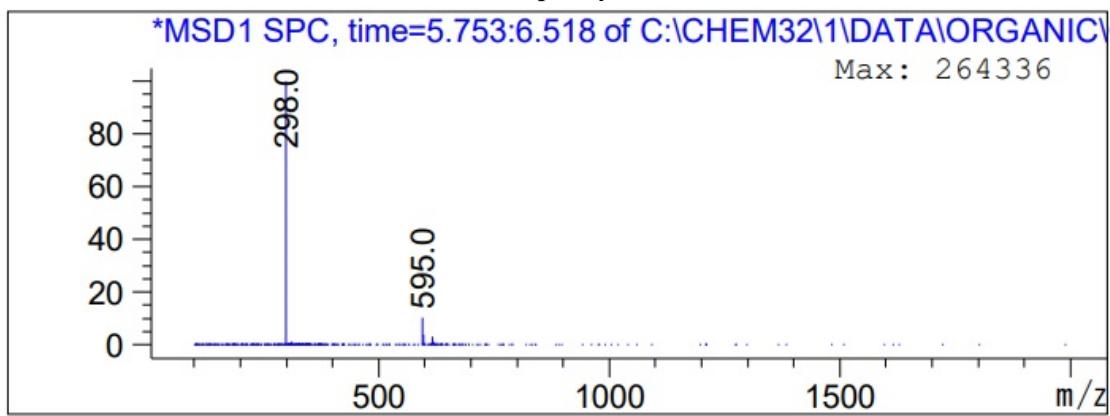
ESI-MS of 6



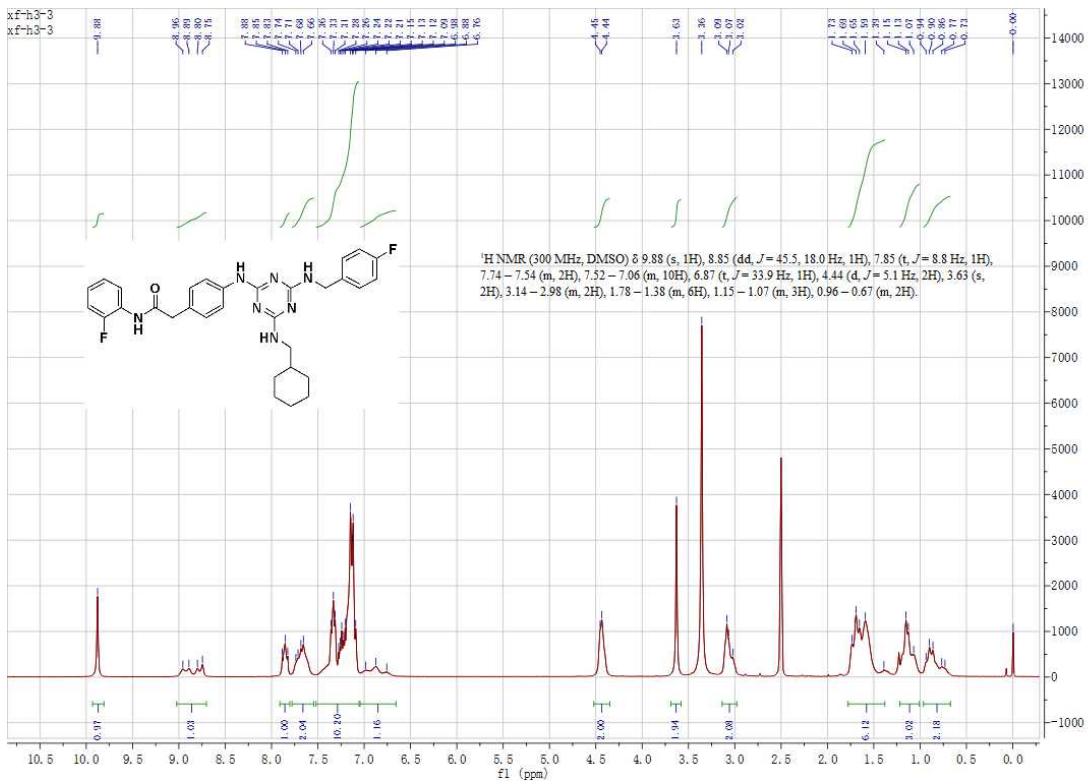
¹³C-NMR of 8



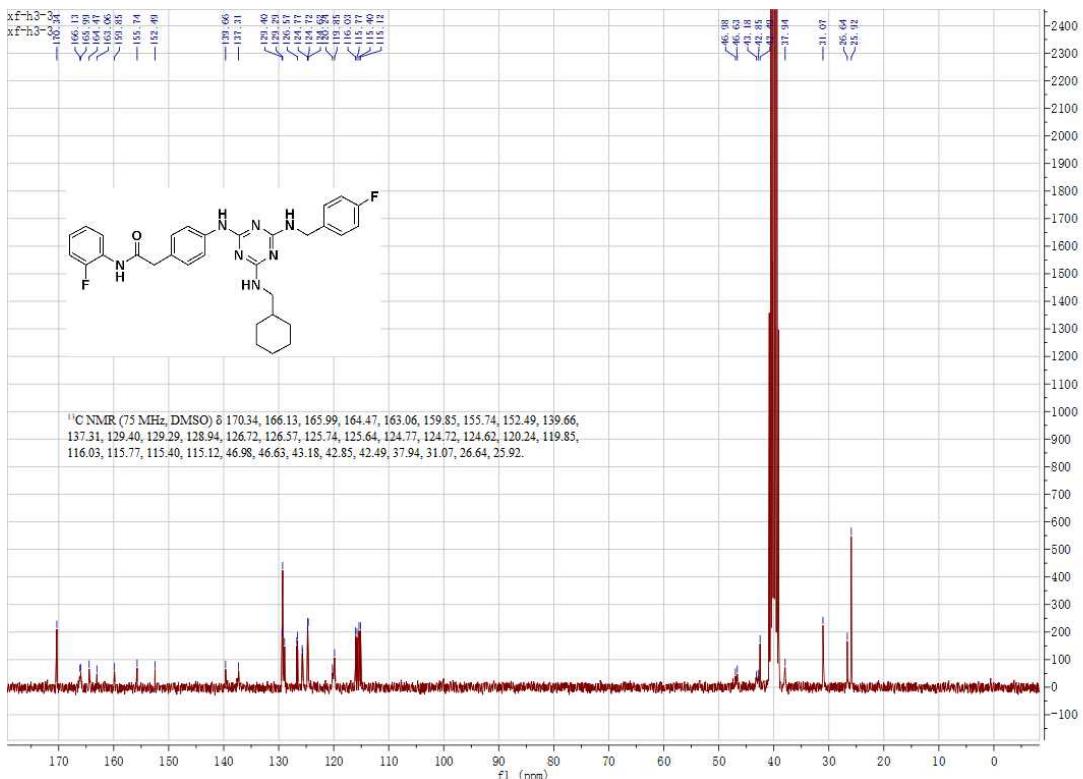
HPLC purity of 8



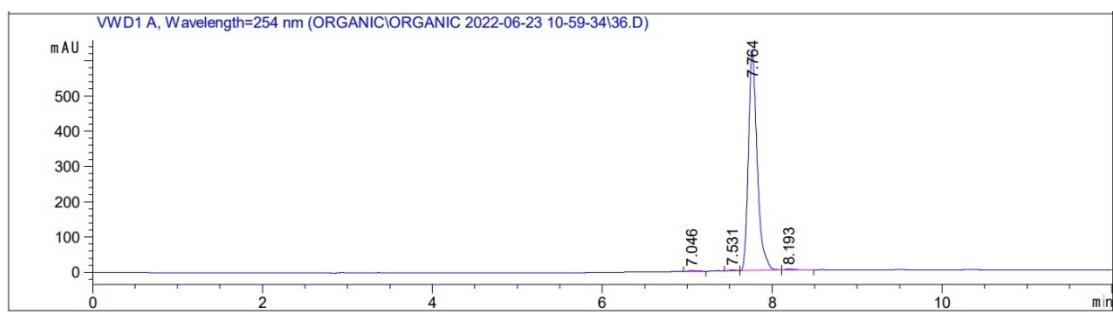
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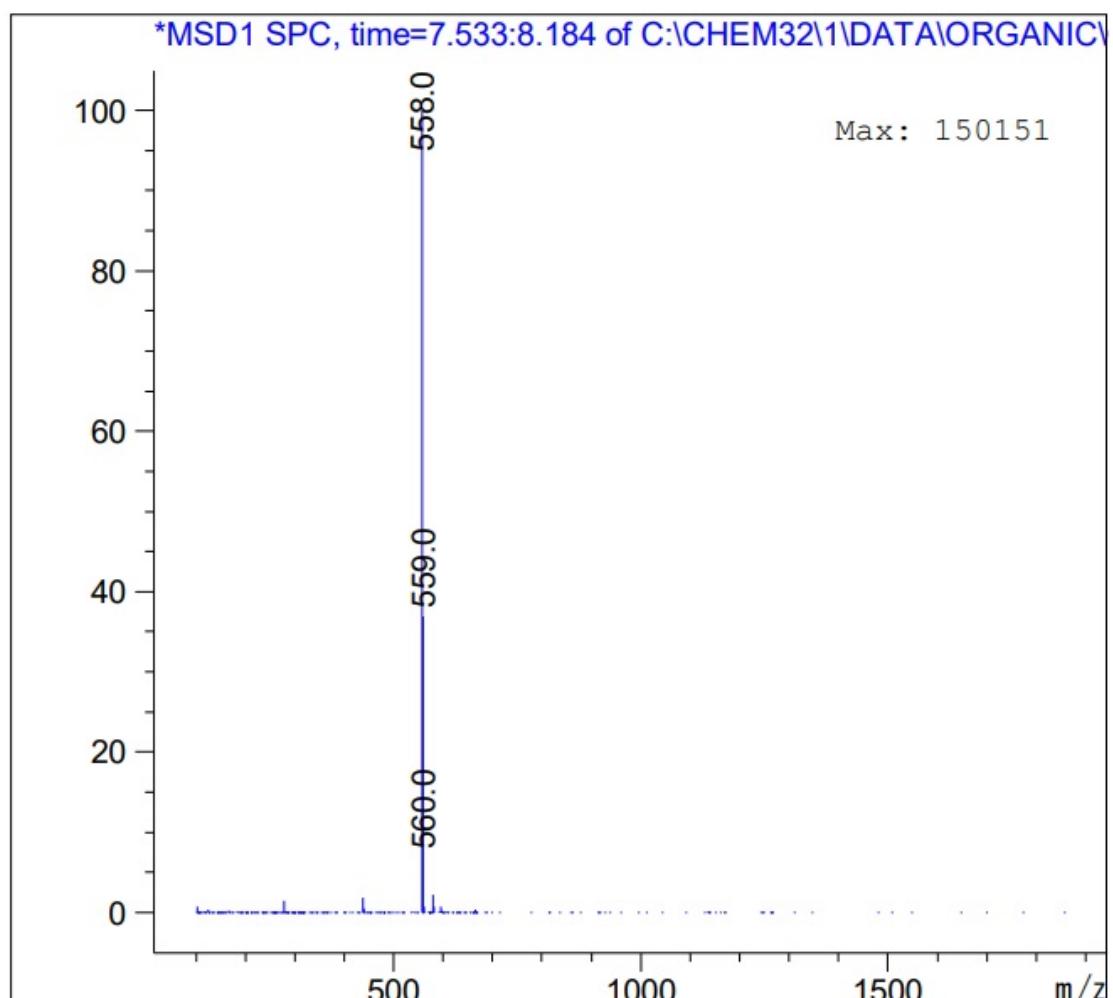
¹H-NMR of 8b



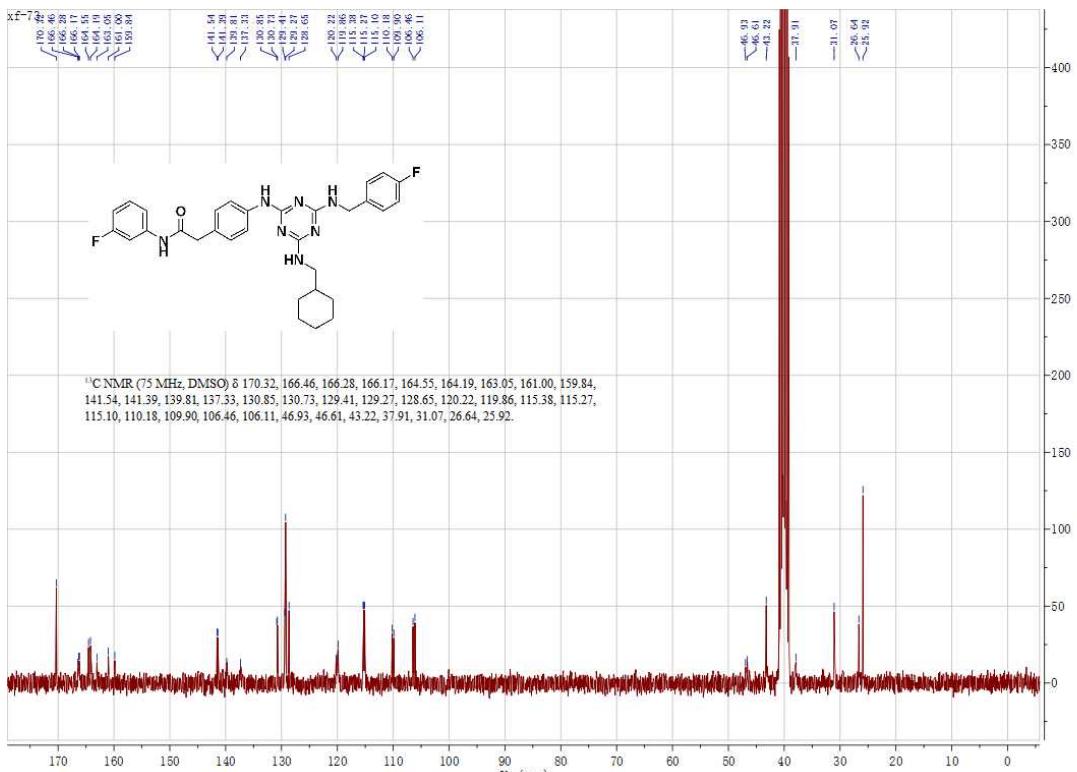
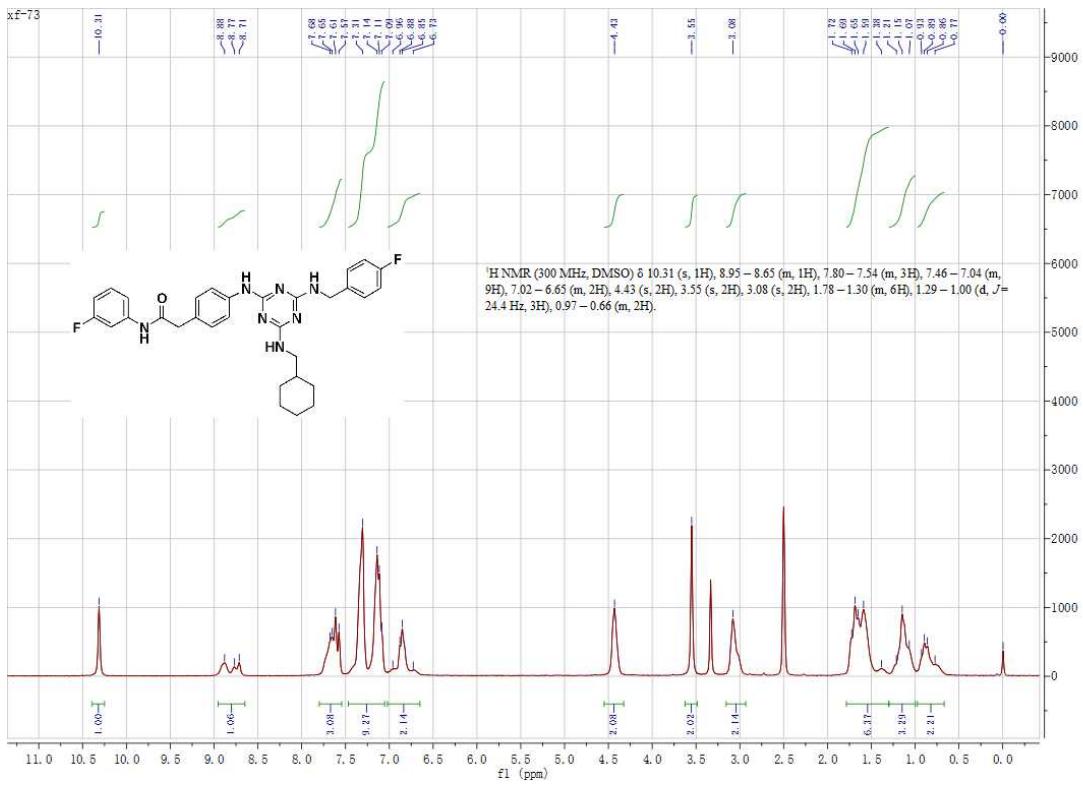
¹³C-NMR of 8b

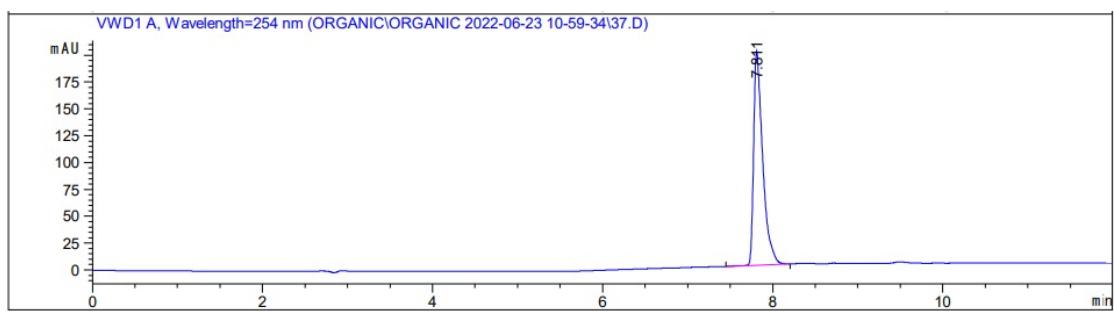


HPLC purity of 8b

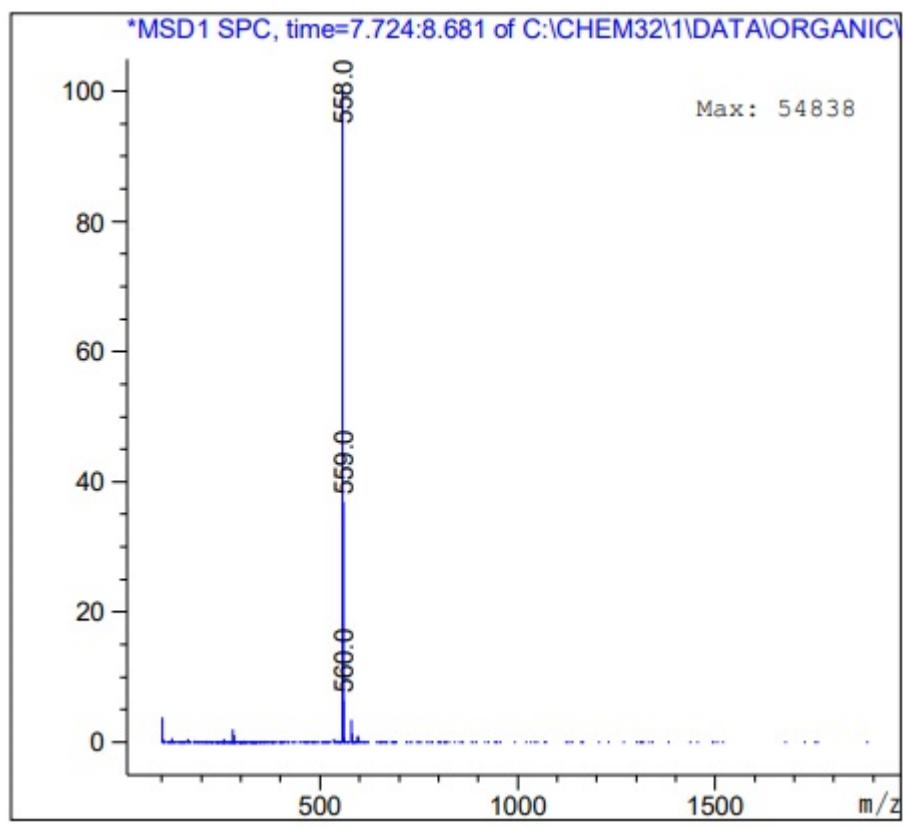


ESI-MS of 8b

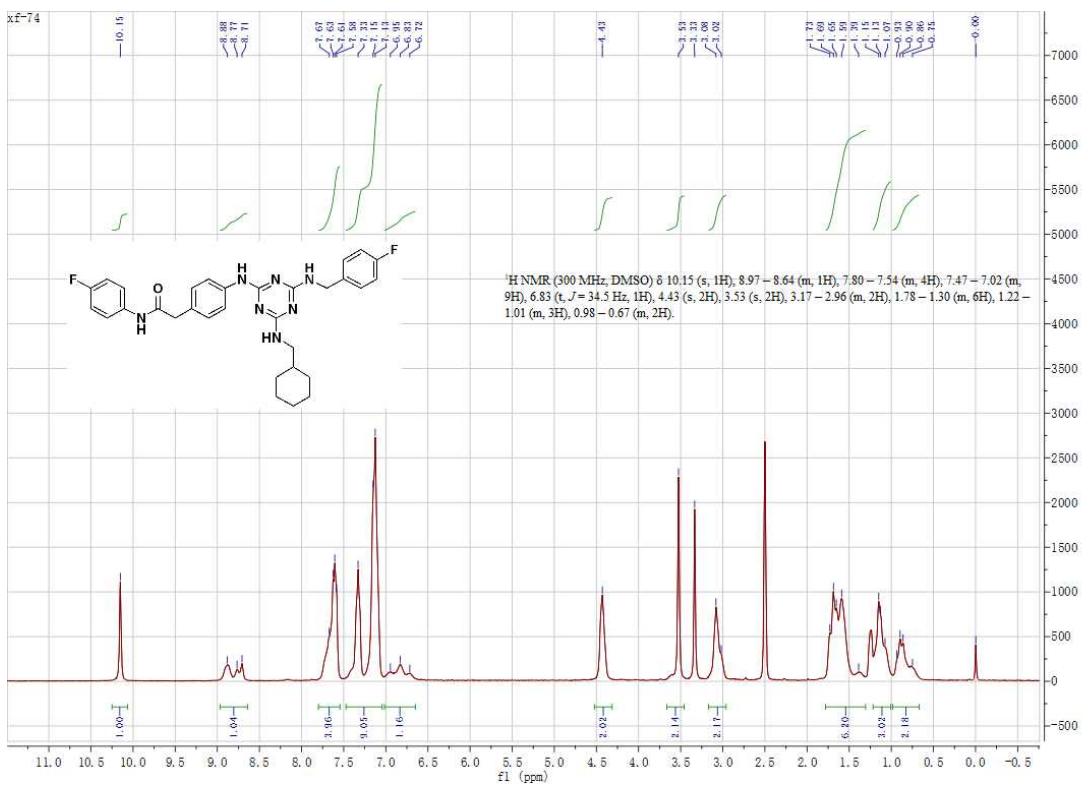




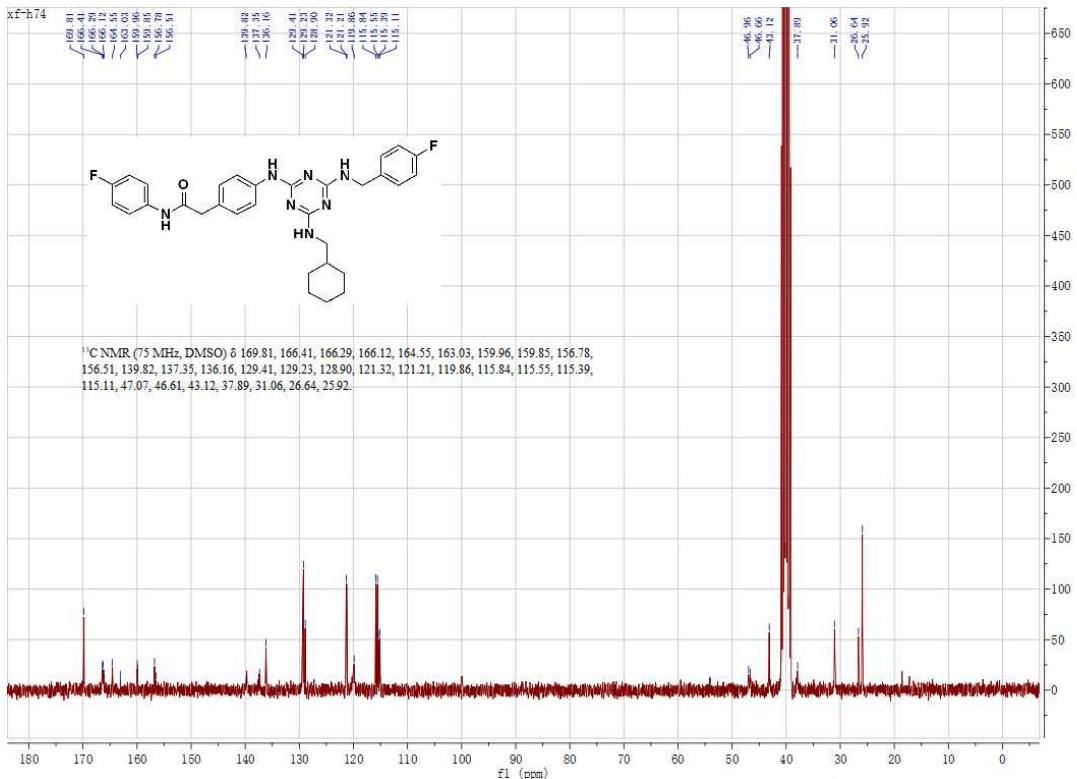
HPLC purity of 8c



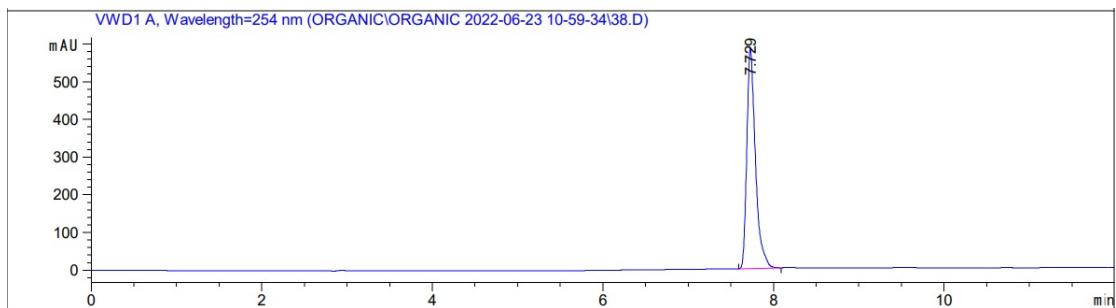
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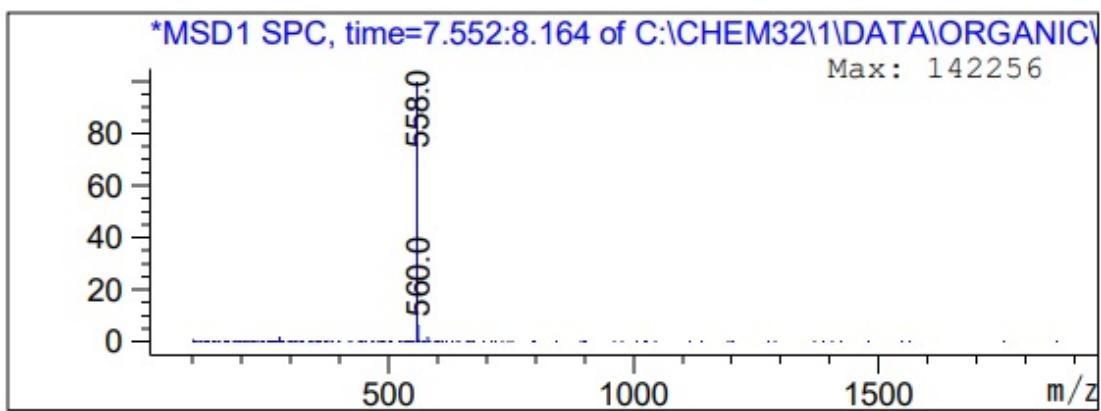
¹H-NMR of 8d



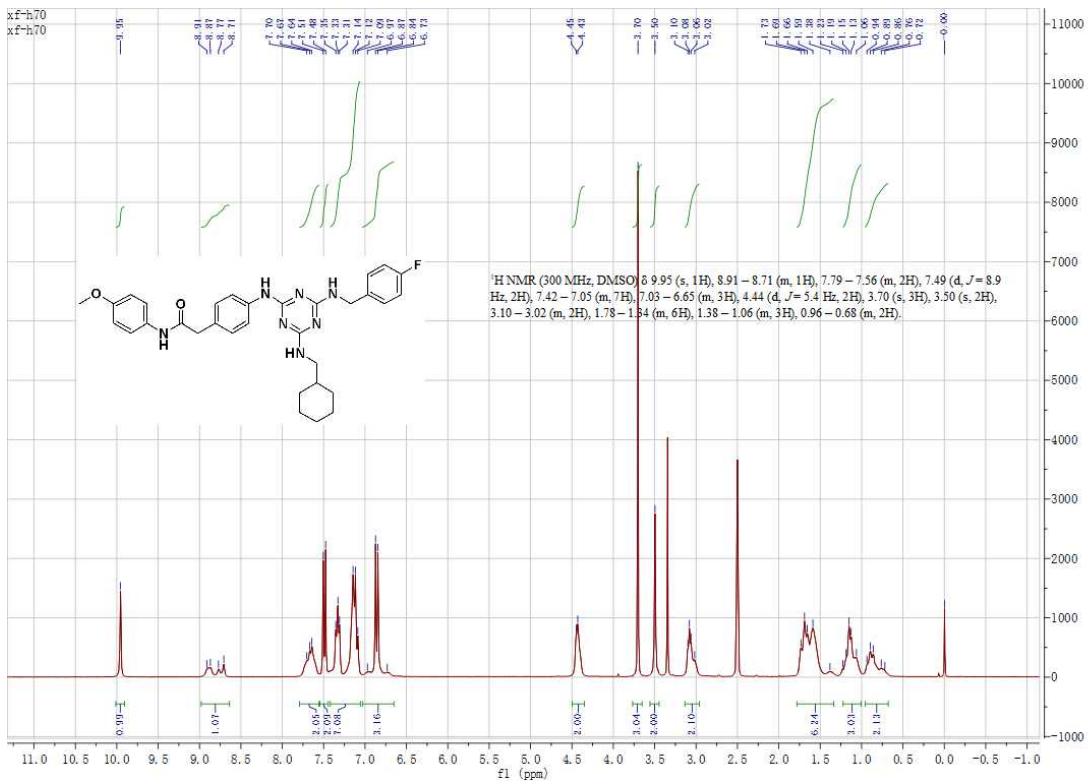
¹³C-NMR of 8d



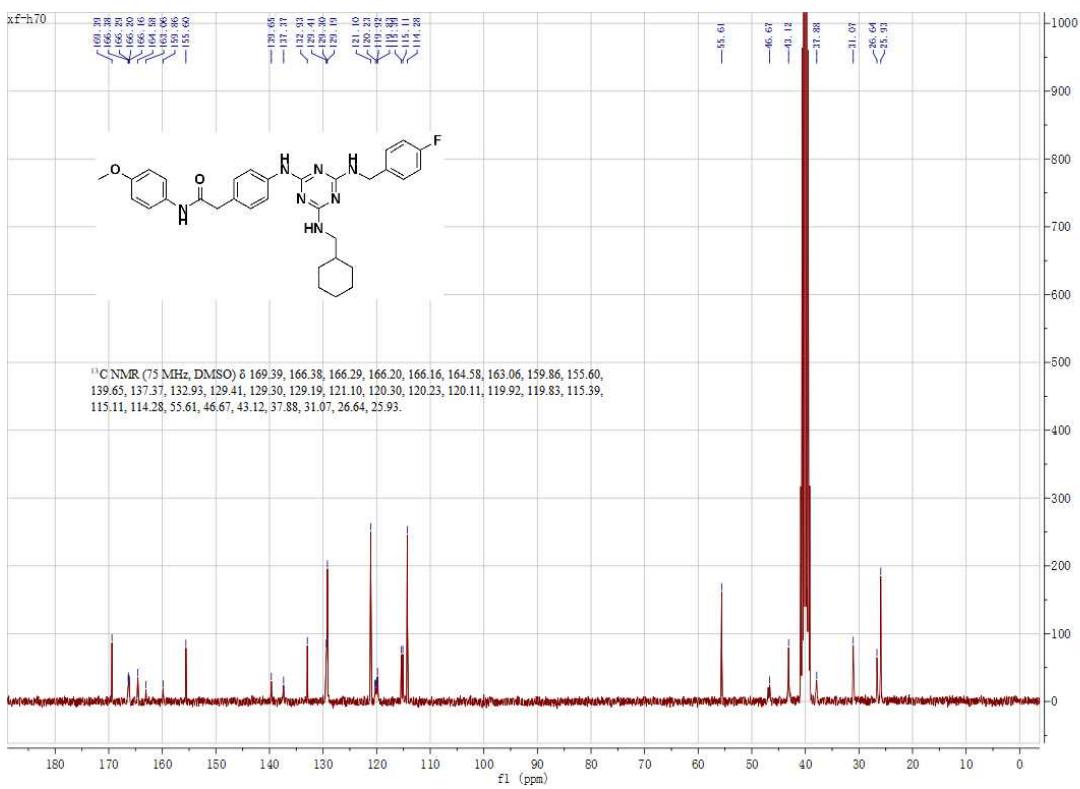
HPLC purity of 8d



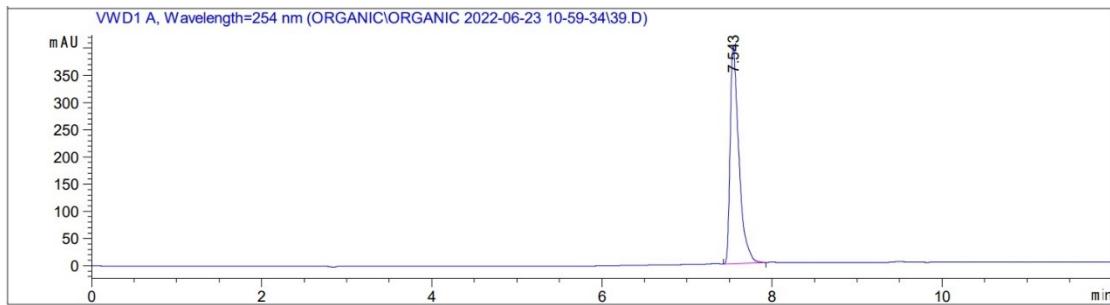
ESI-MS of 8d



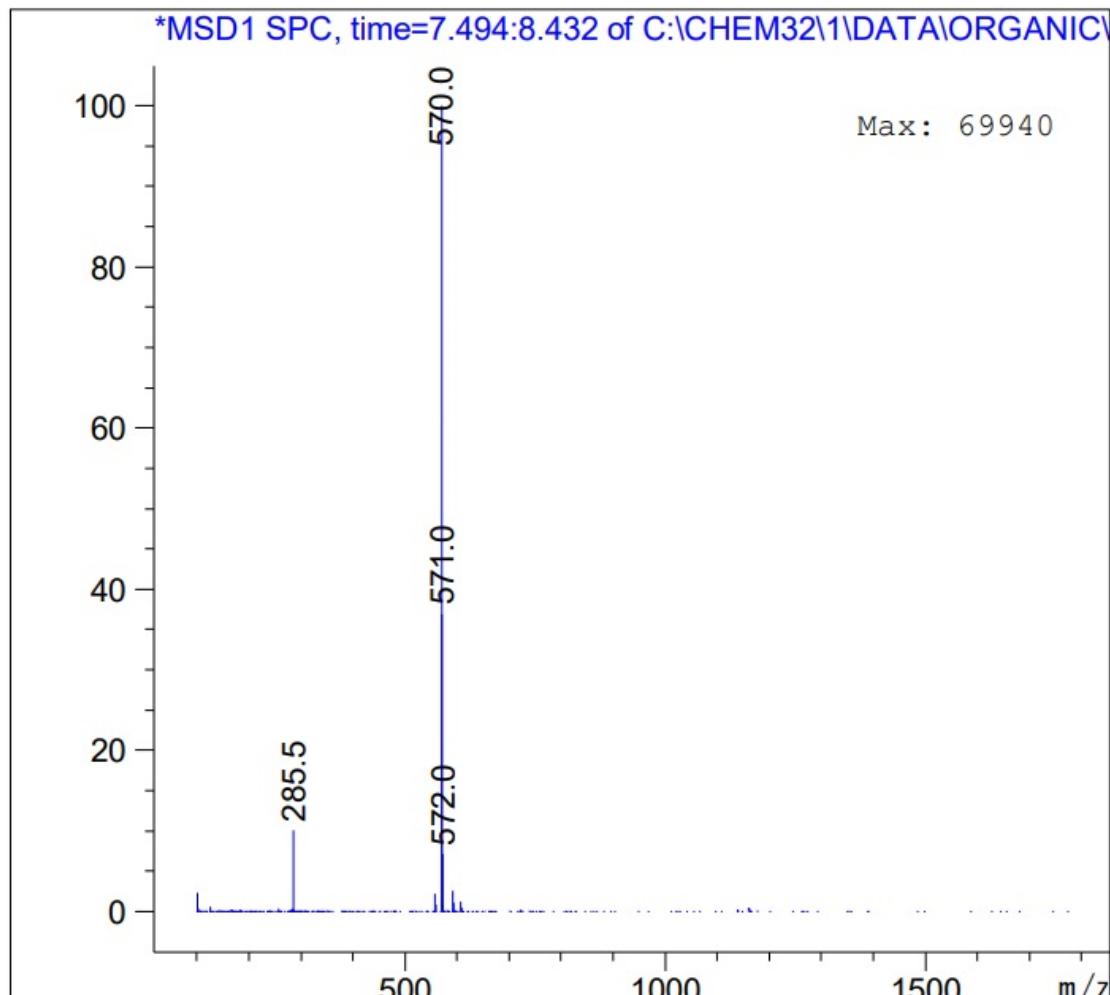
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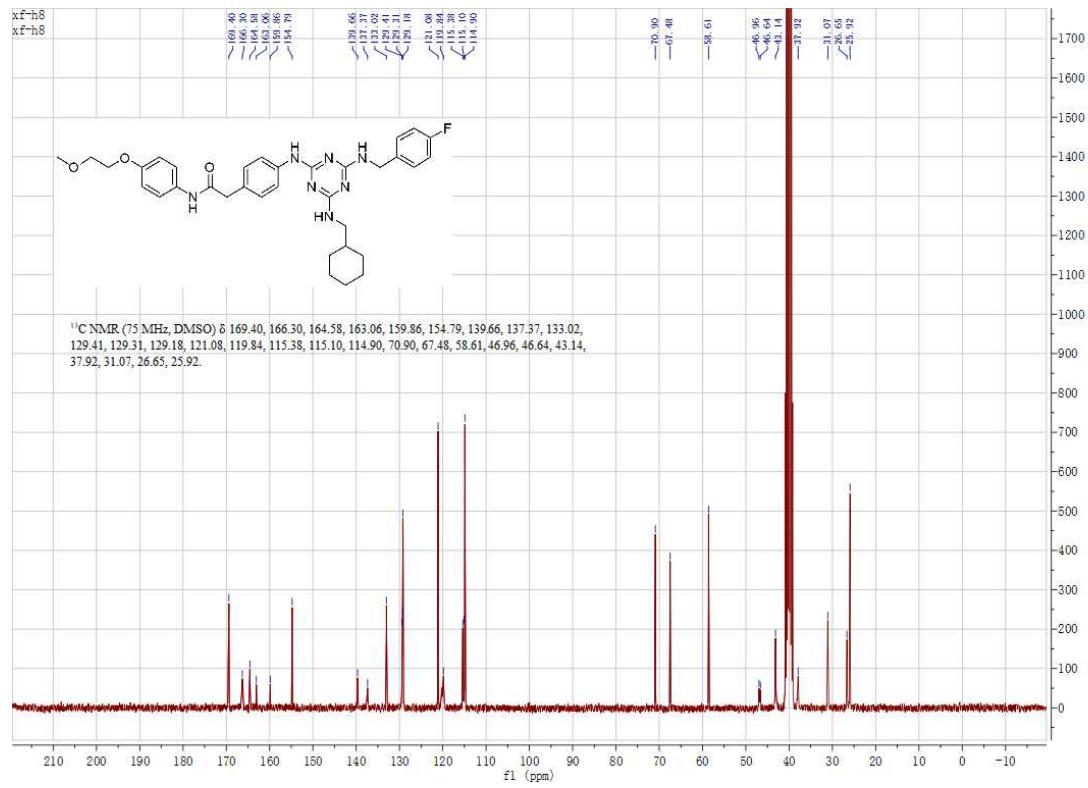
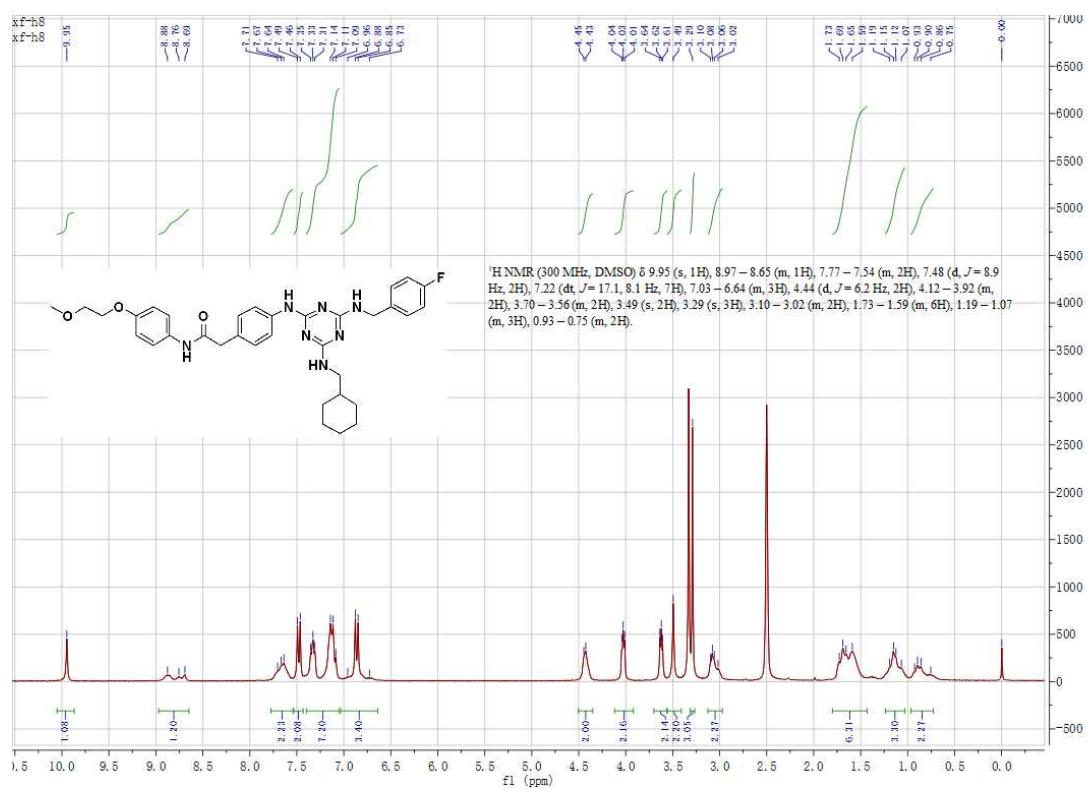
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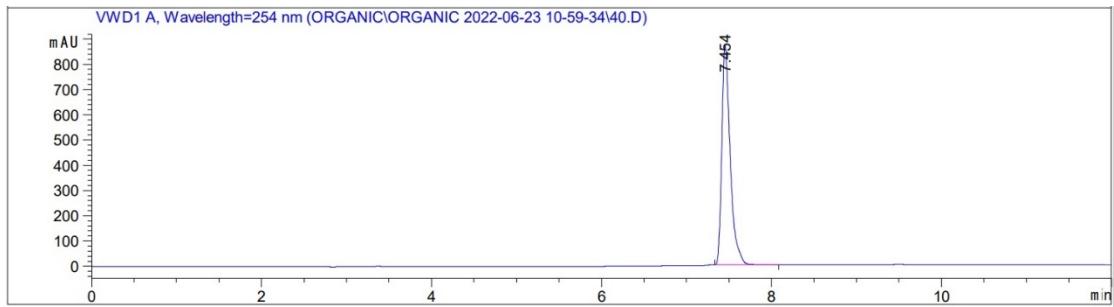


HPLC purity of 8e

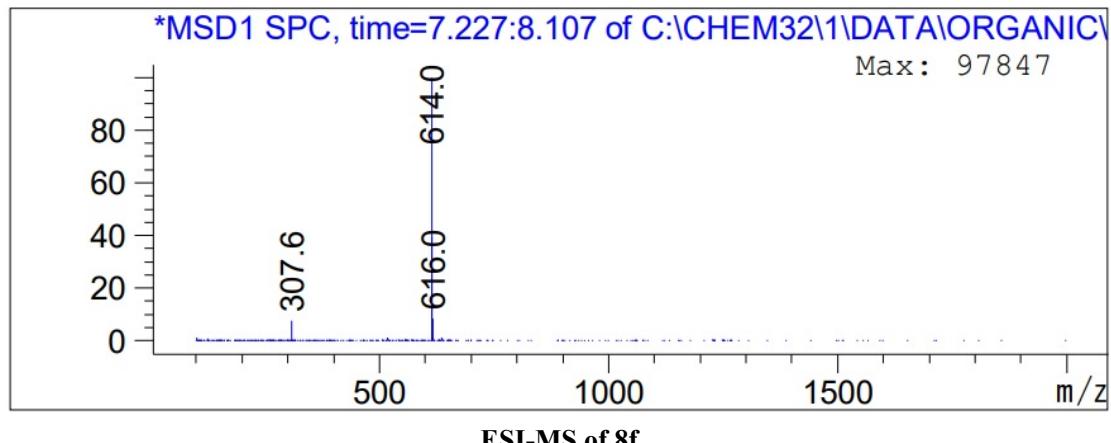


ESI-MS of 8e

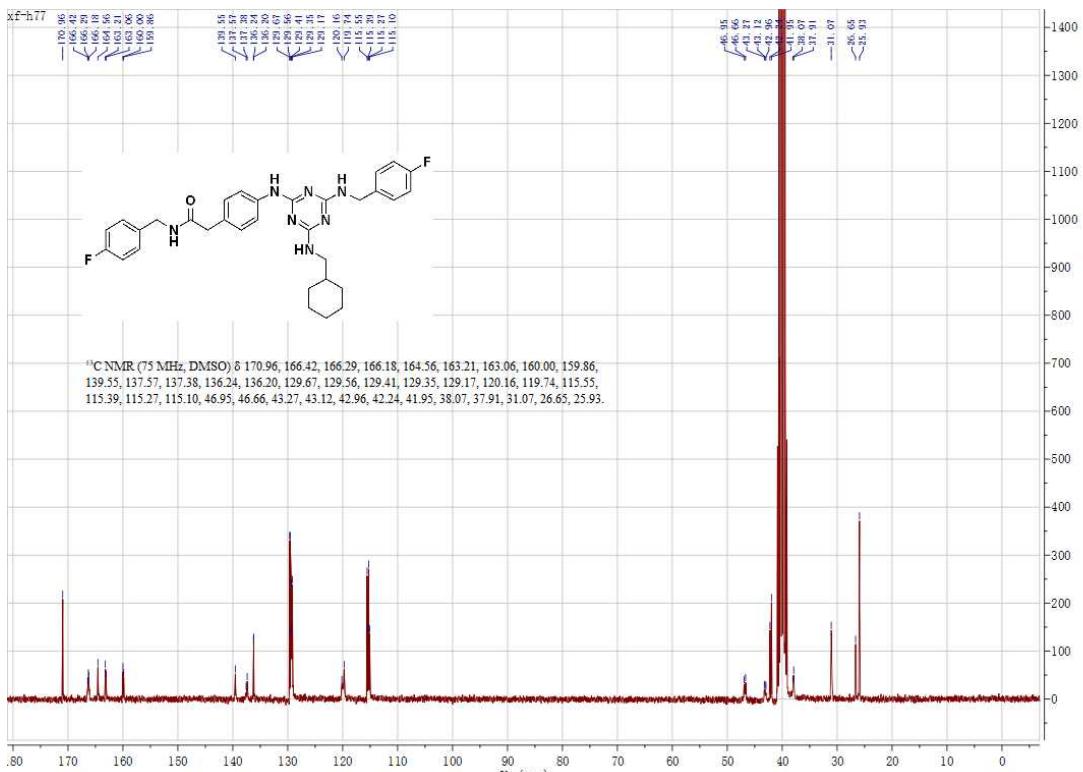
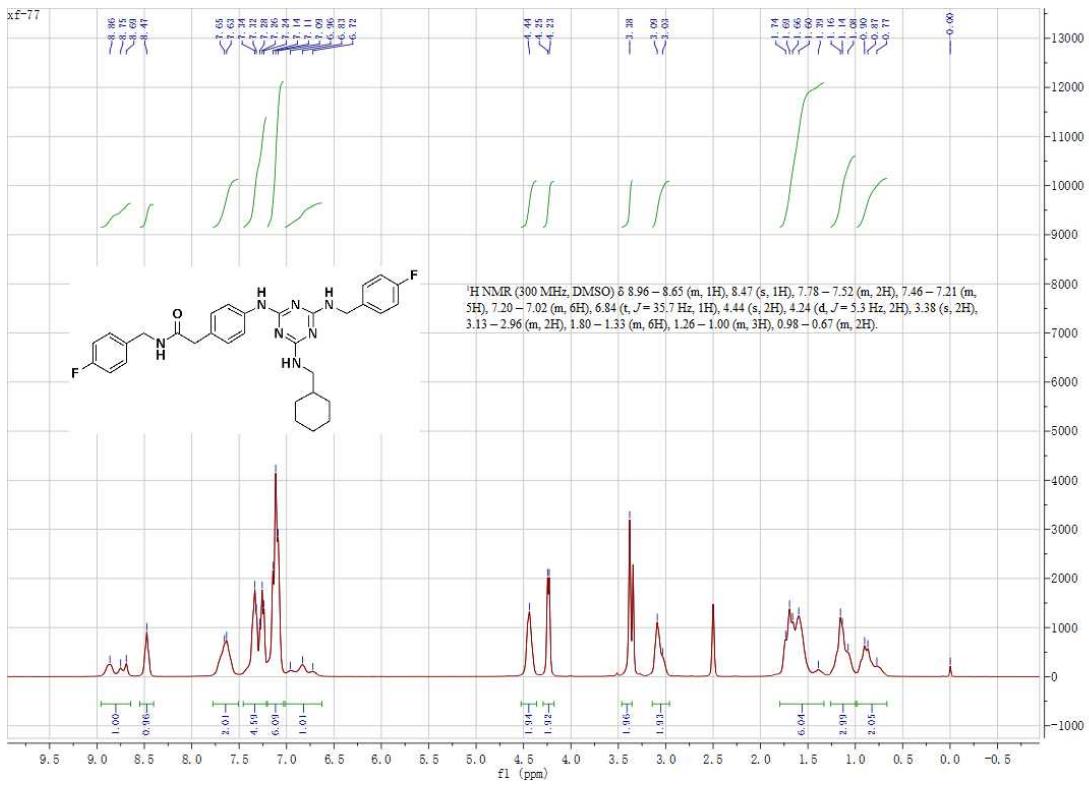


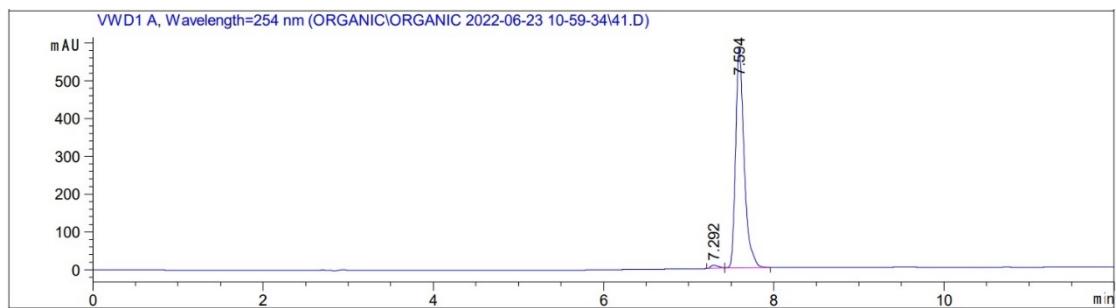


HPLC purity of 8f

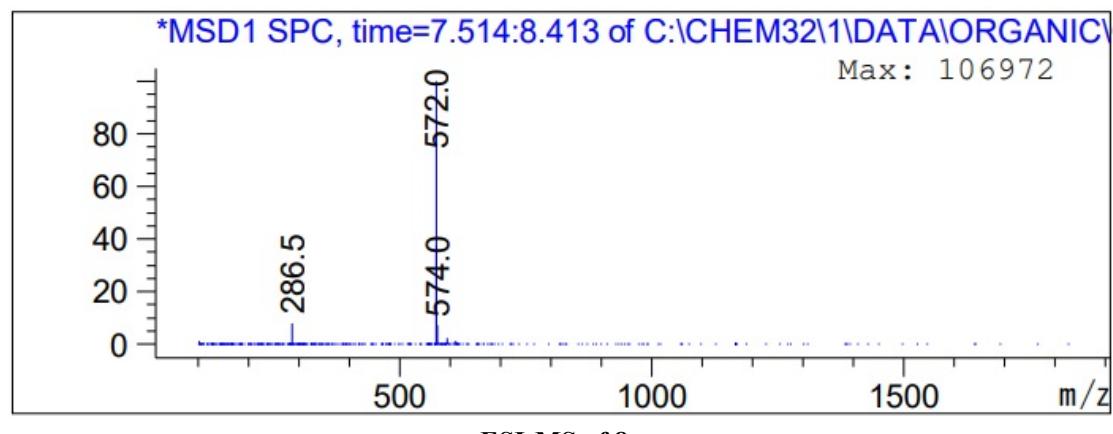


ESI-MS of 8f

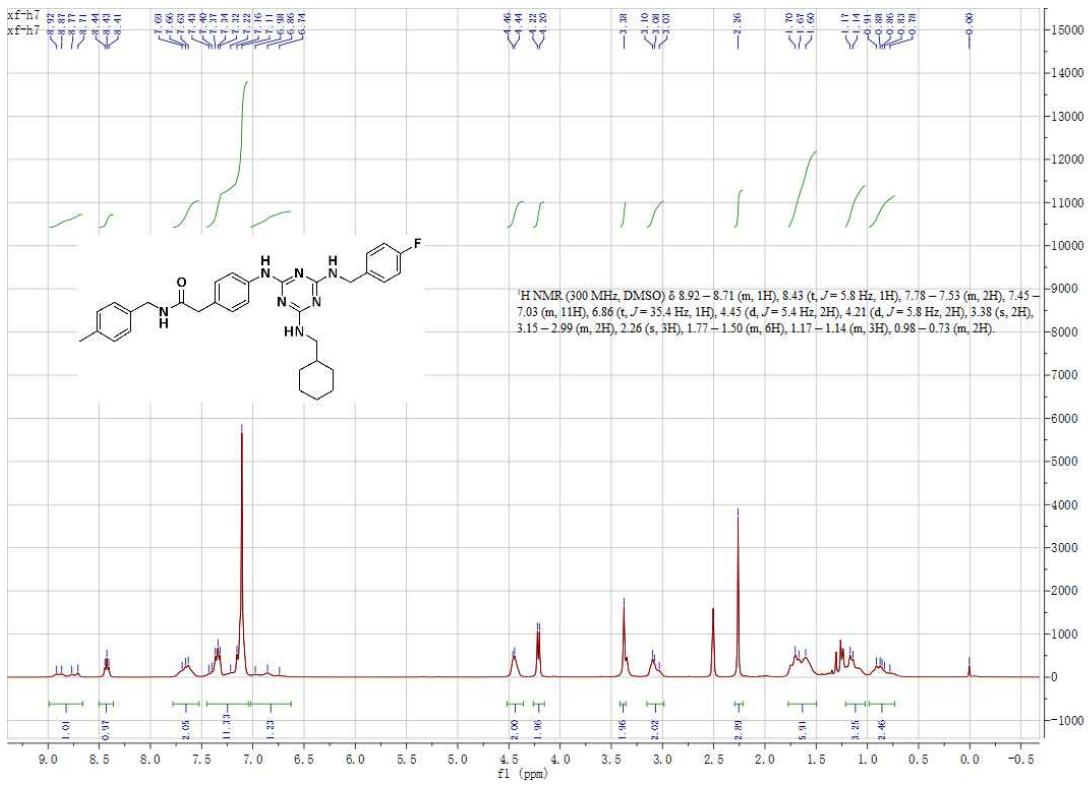




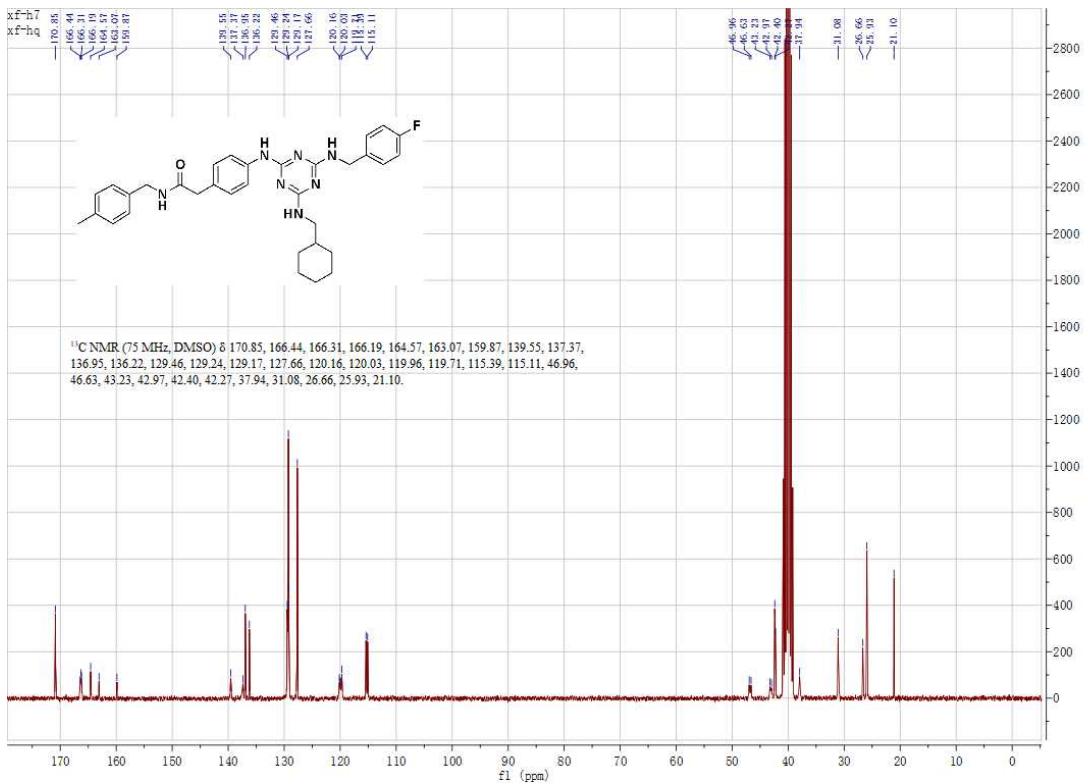
HPLC purity of 8g



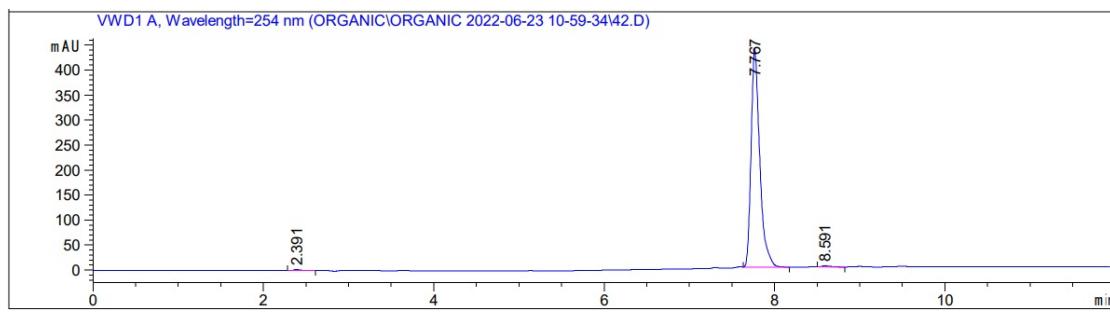
ESI-MS of 8g



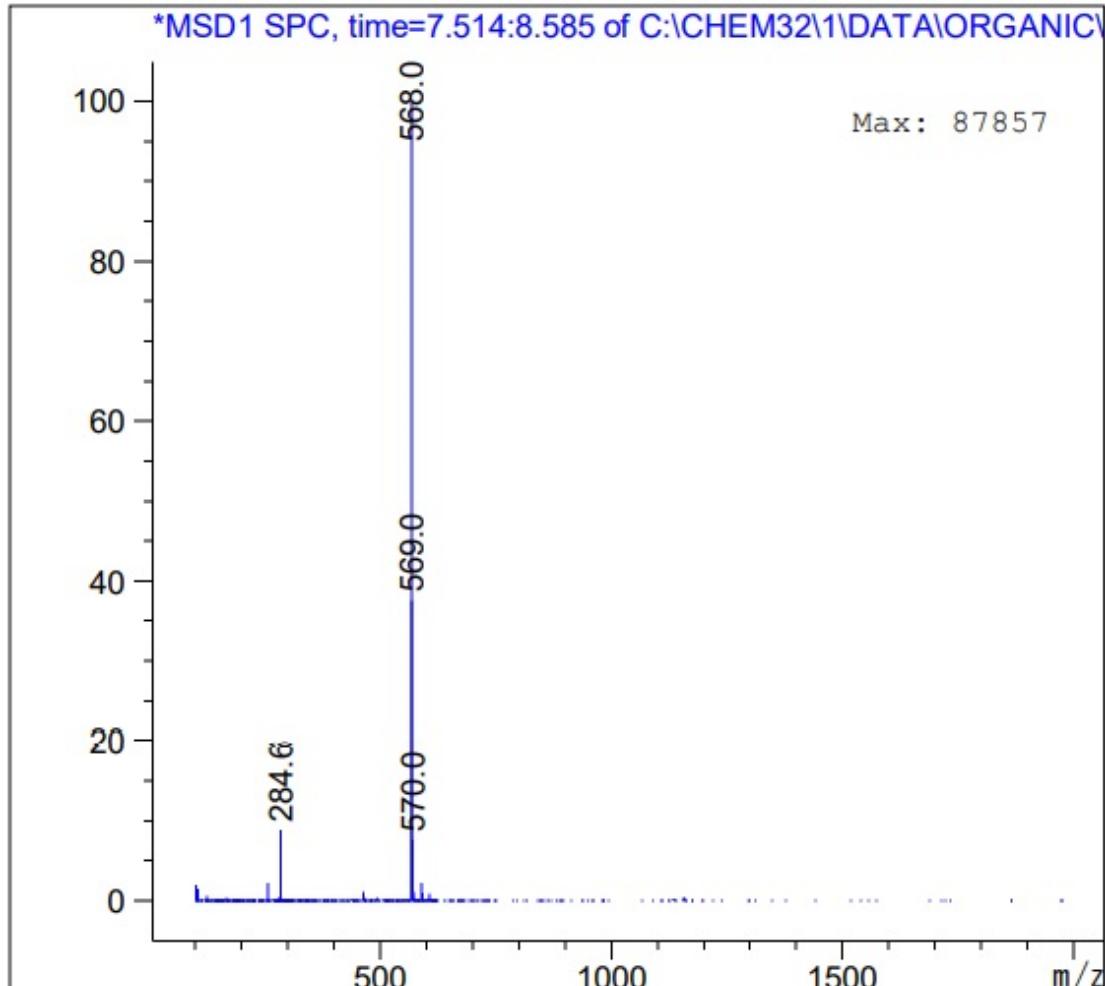
¹H-NMR of 8h



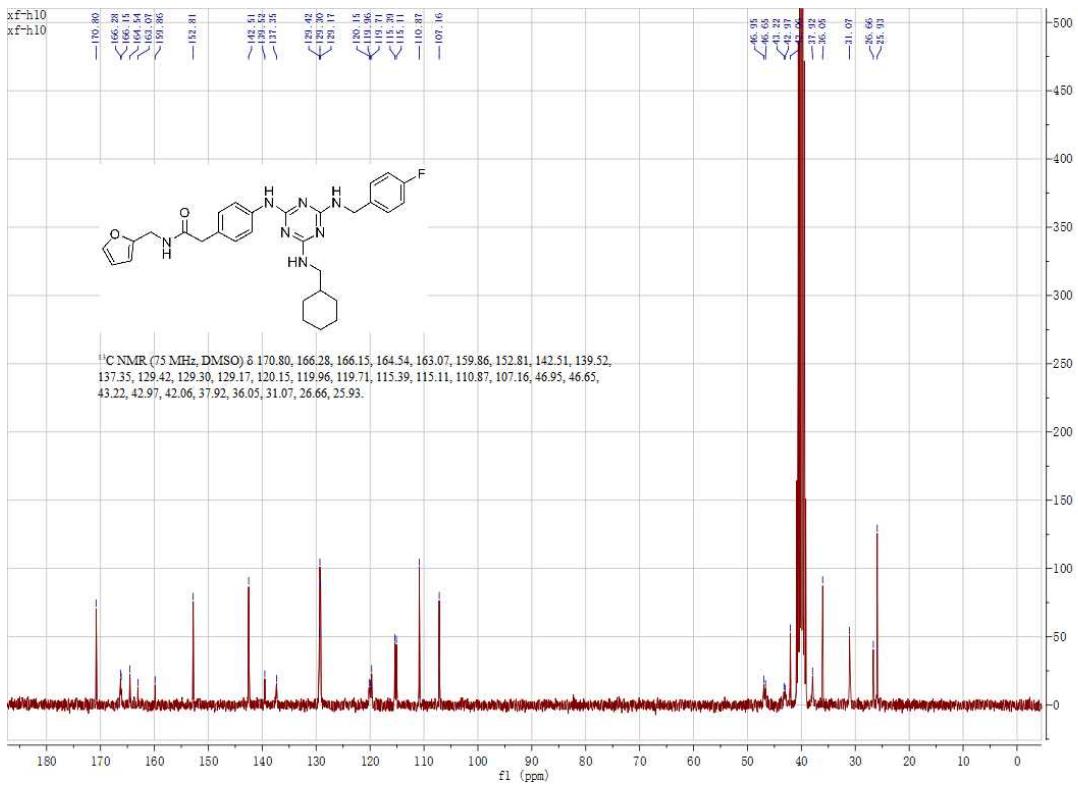
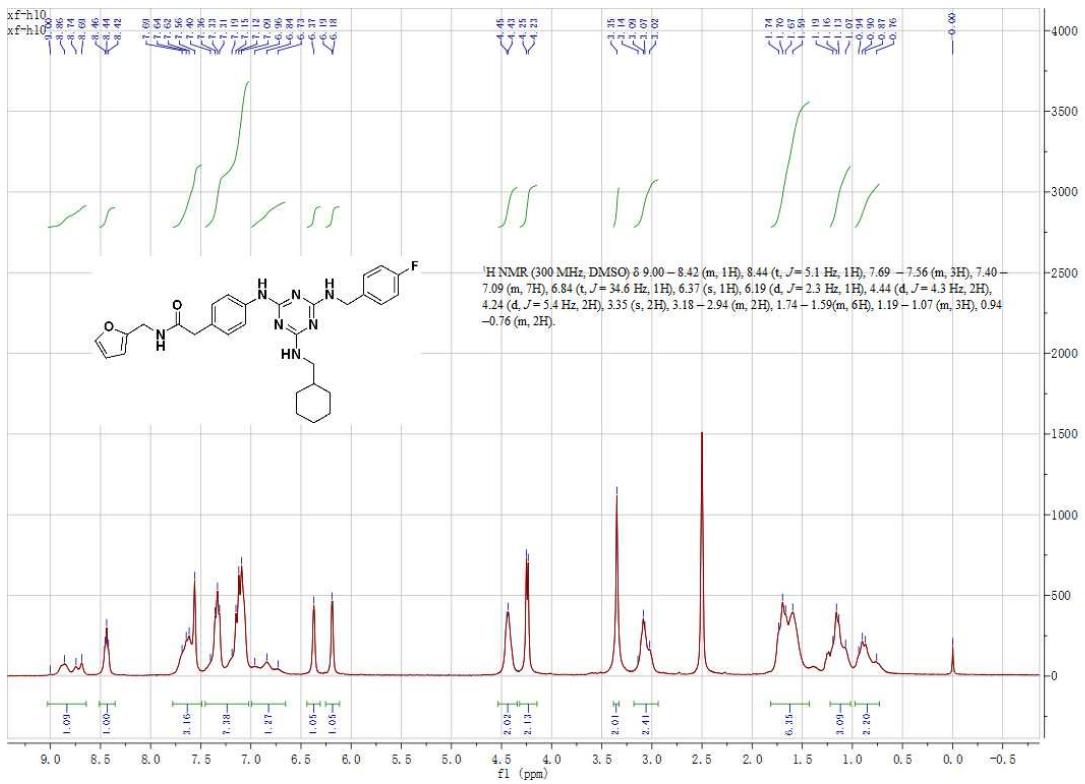
¹³C-NMR of 8h

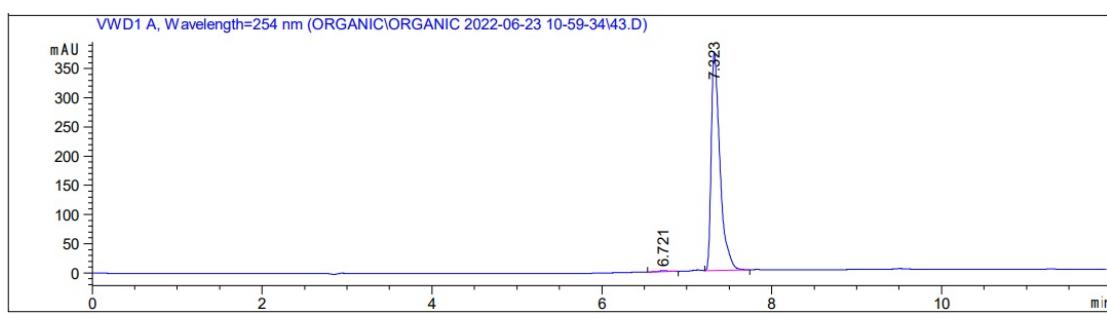


HPLC purity of 8h

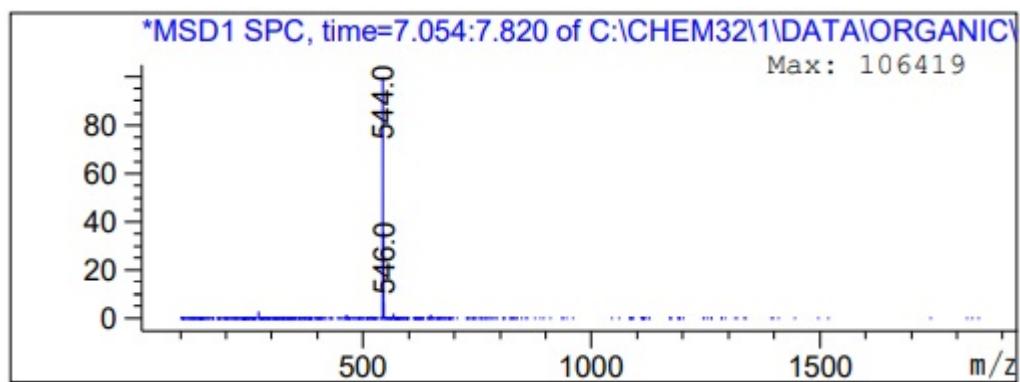


ESI-MS of 8h

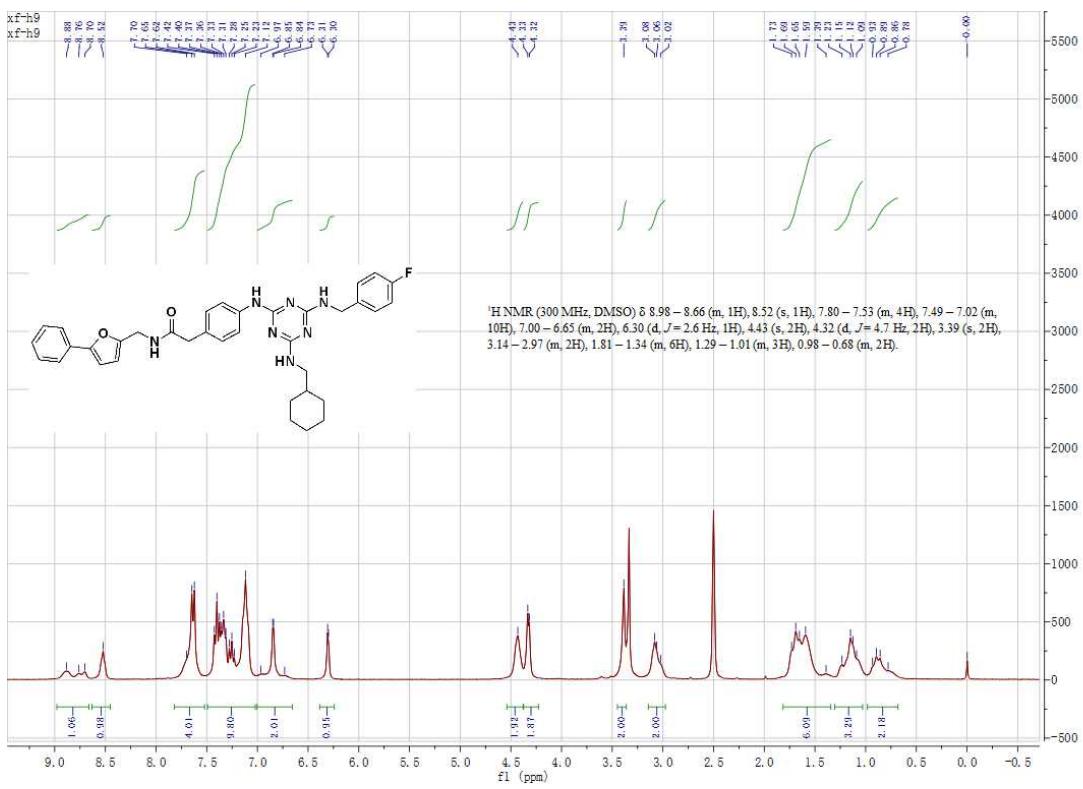




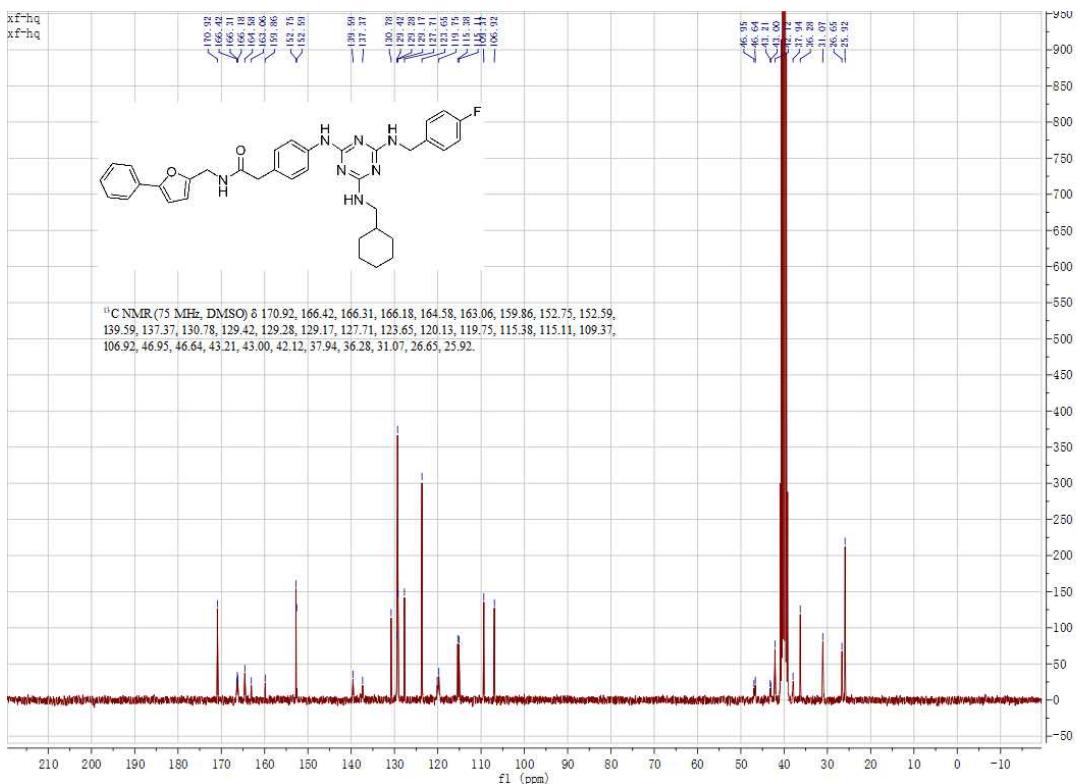
HPLC purity of 8i



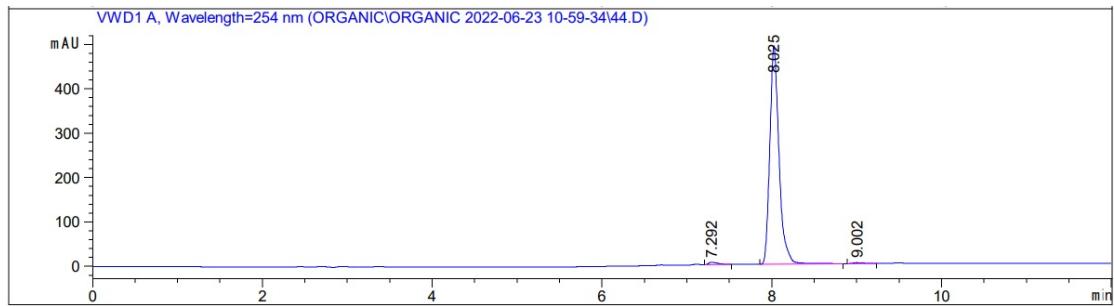
ESI-MS of 8i



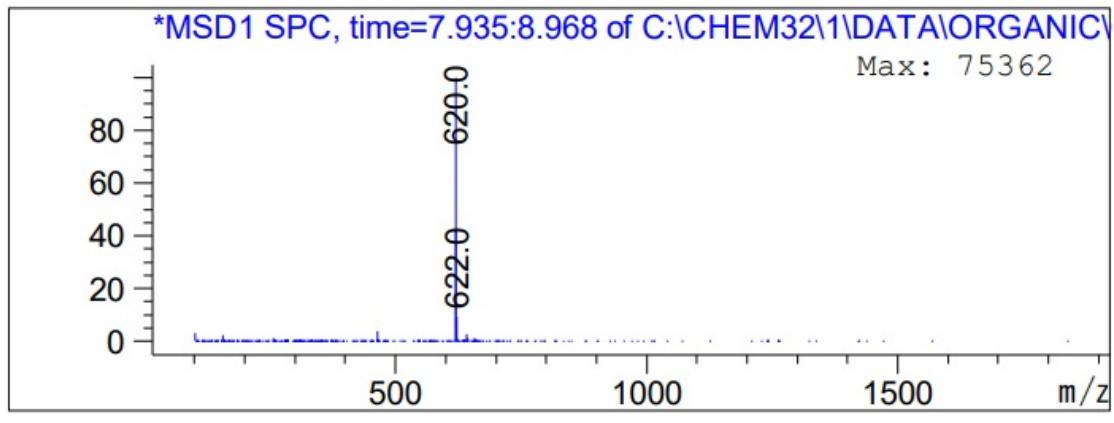
¹H-NMR of 8j



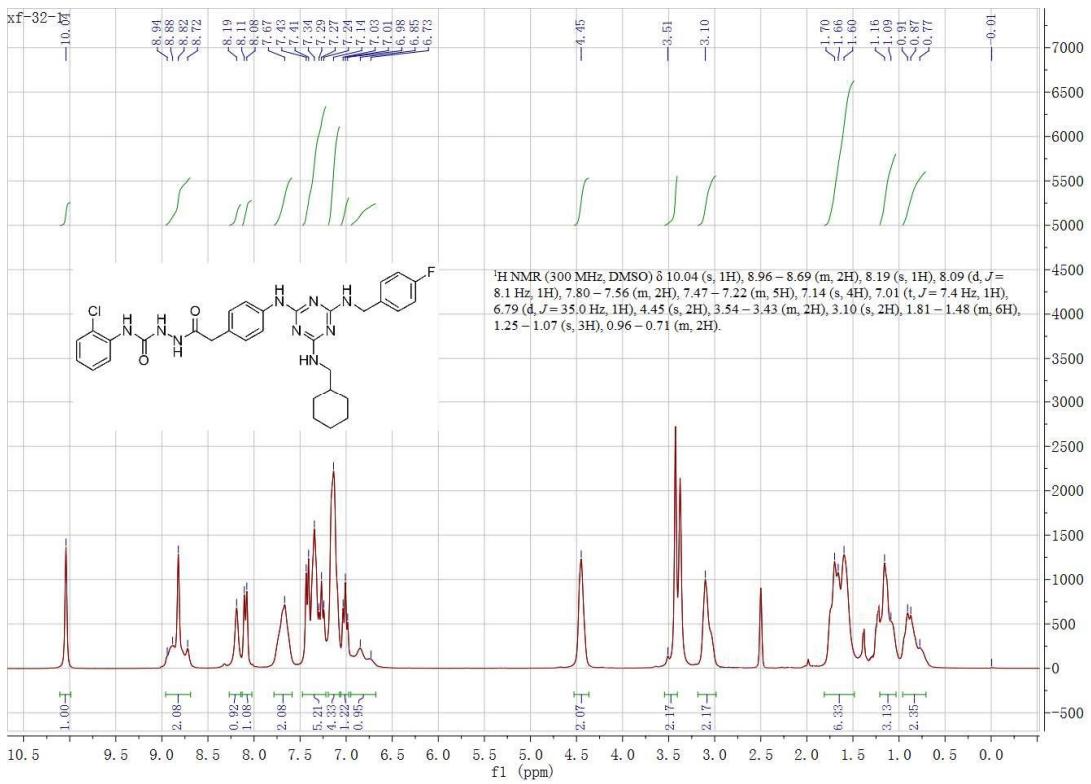
¹³C-NMR of 8j



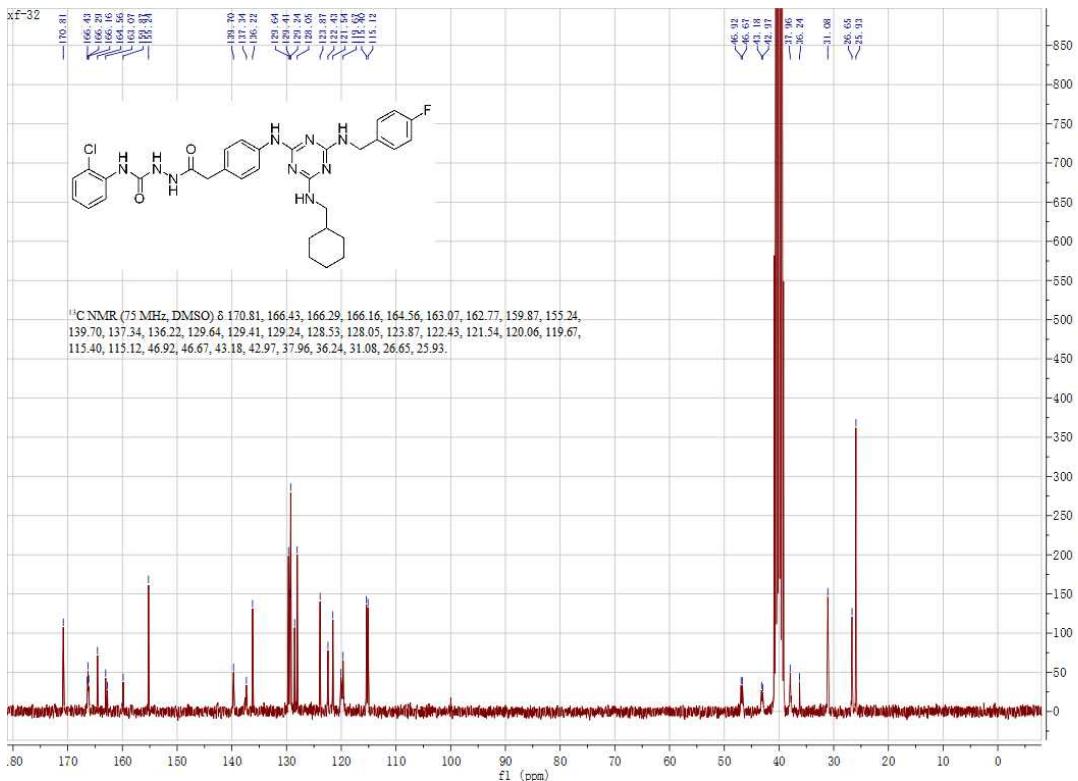
HPLC purity of 8j



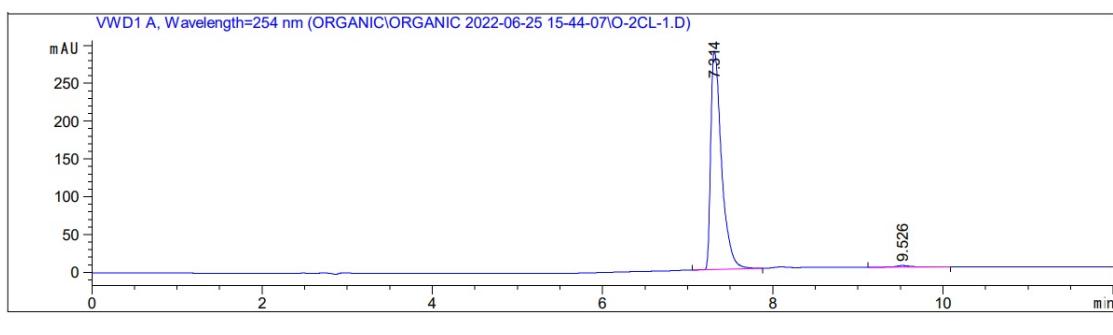
ESI-MS of 8j



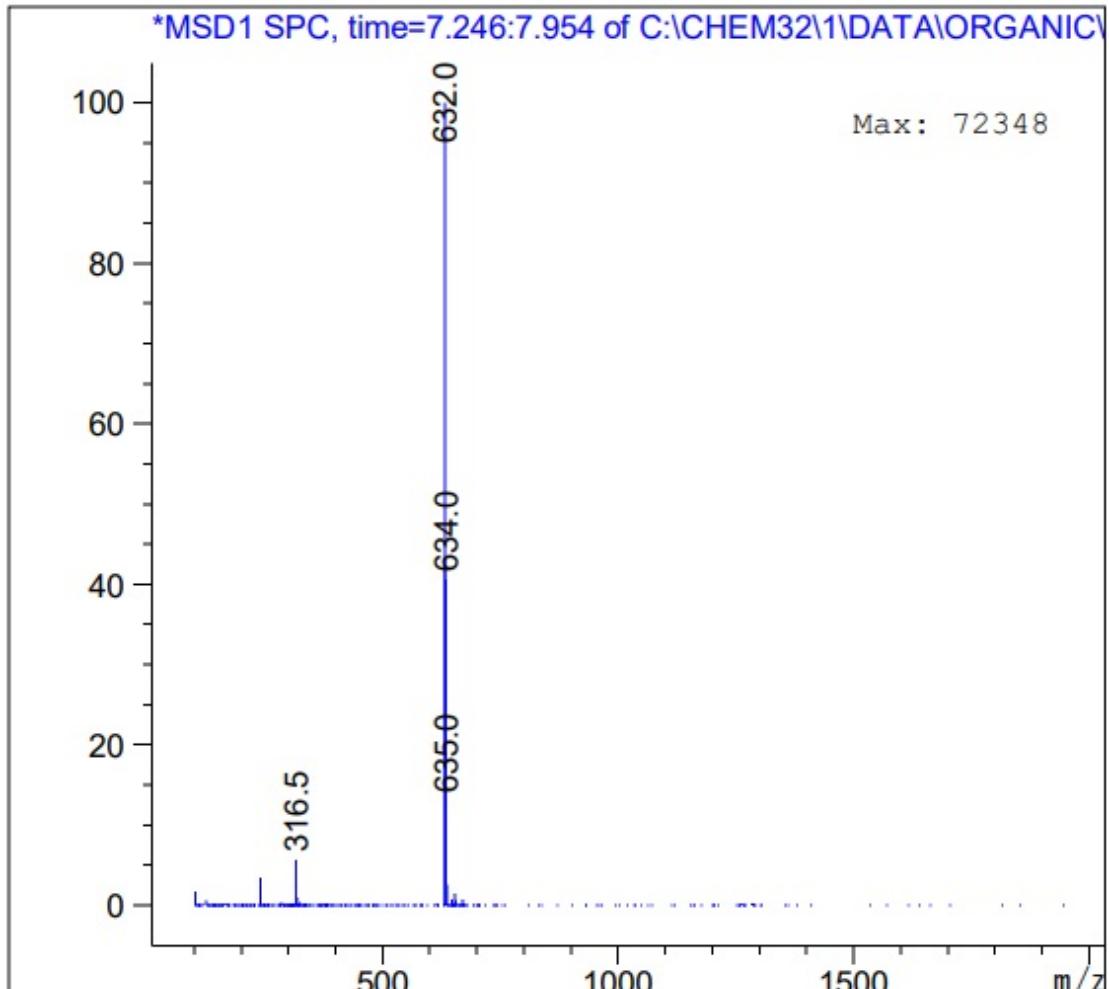
¹H-NMR of 9a



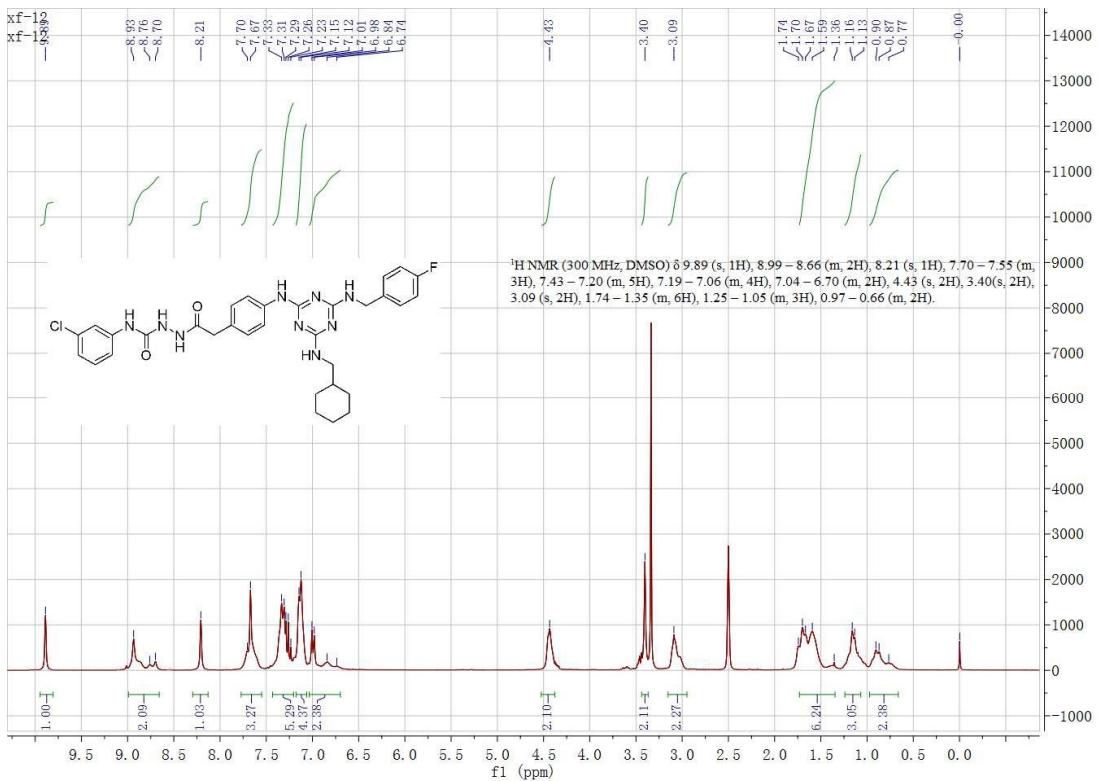
¹³C-NMR of 9a



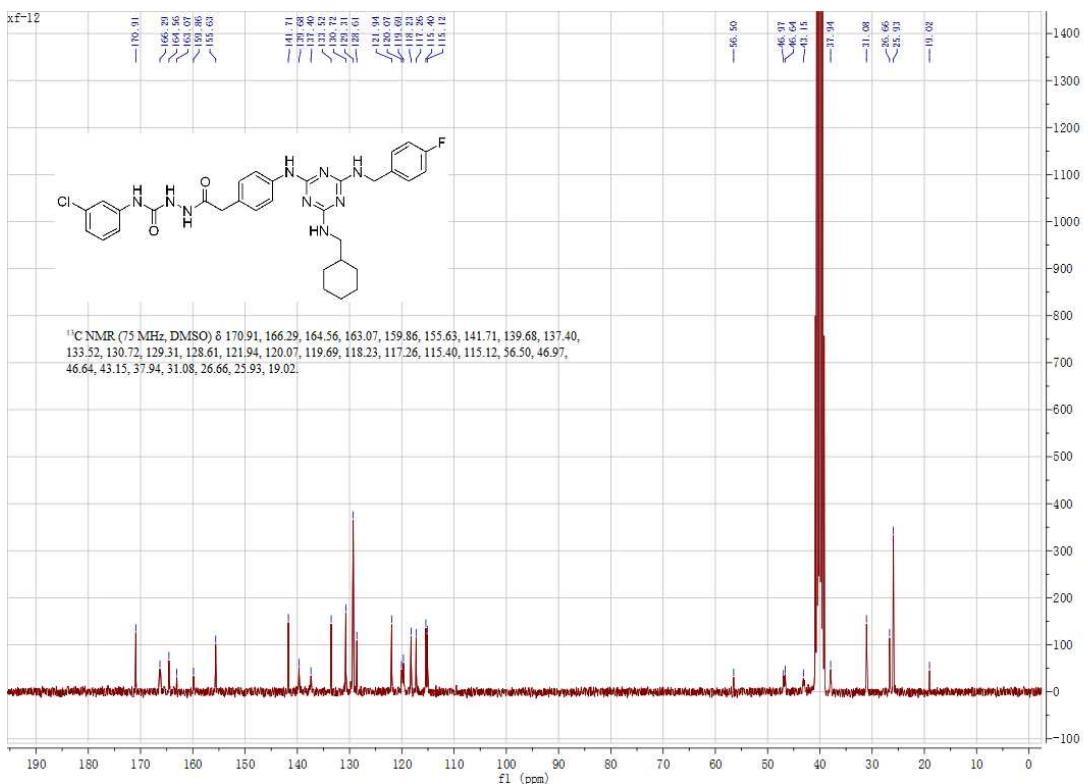
HPLC purity of 9a



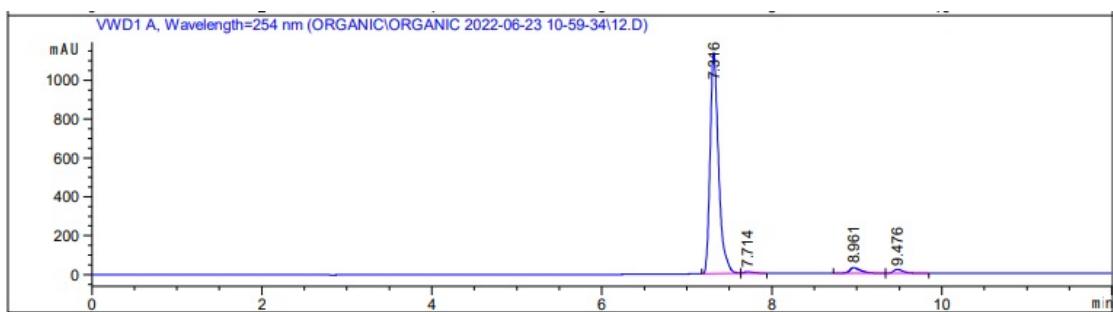
ESI-MS of 9a



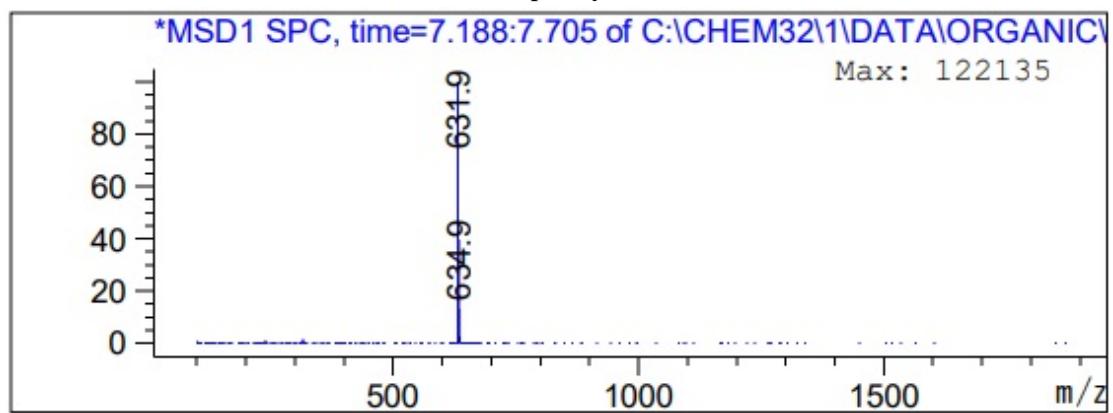
¹H-NMR of 9b



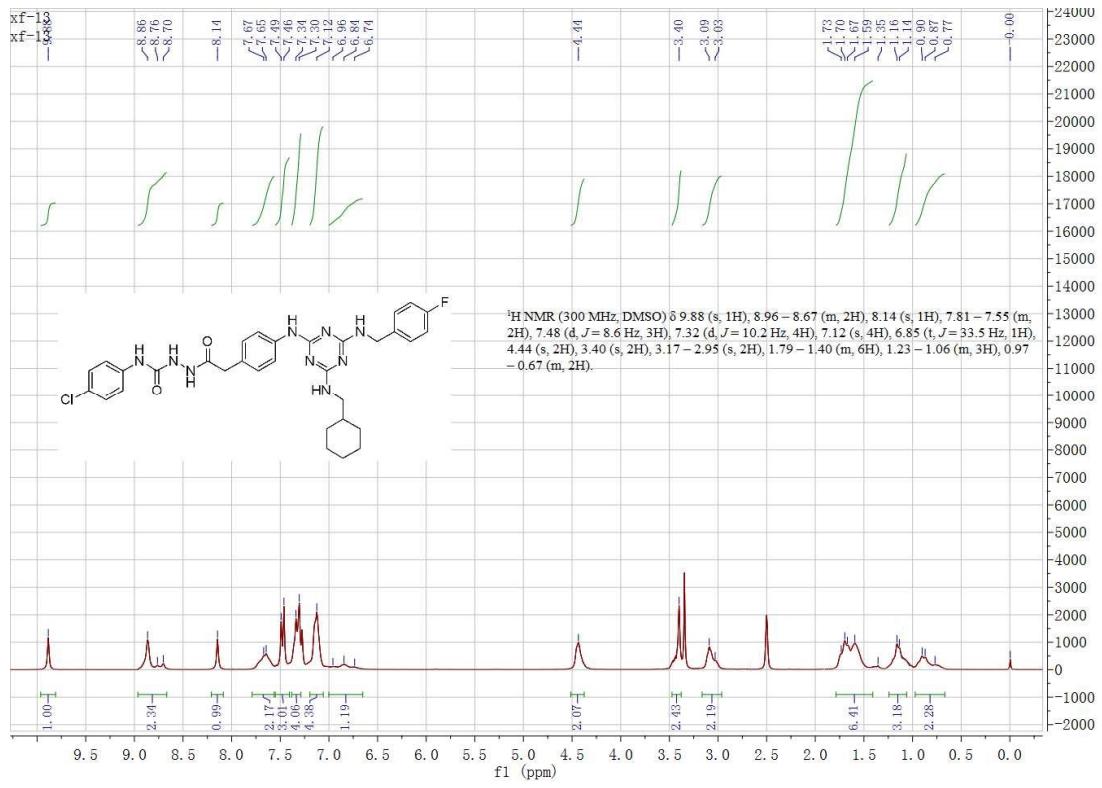
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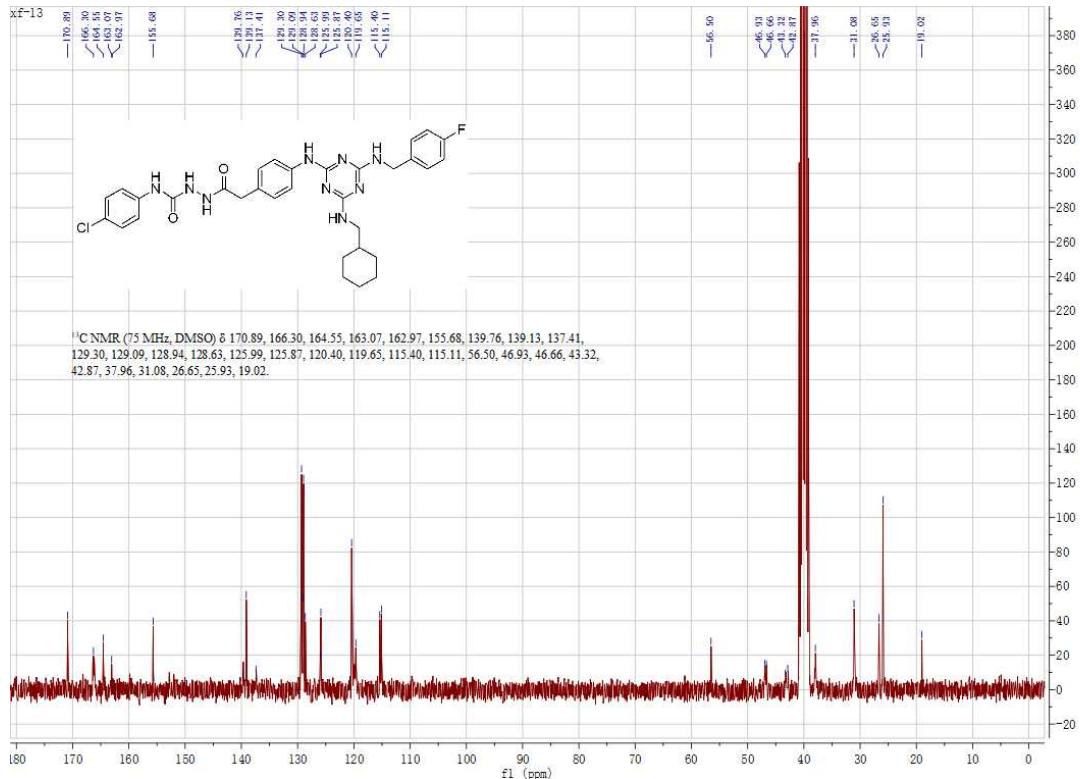
HPLC purity of 9b



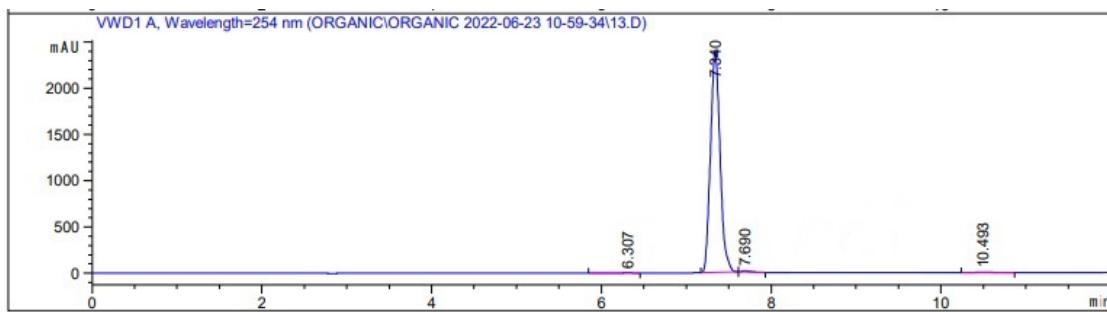
ESI-MS of 9b



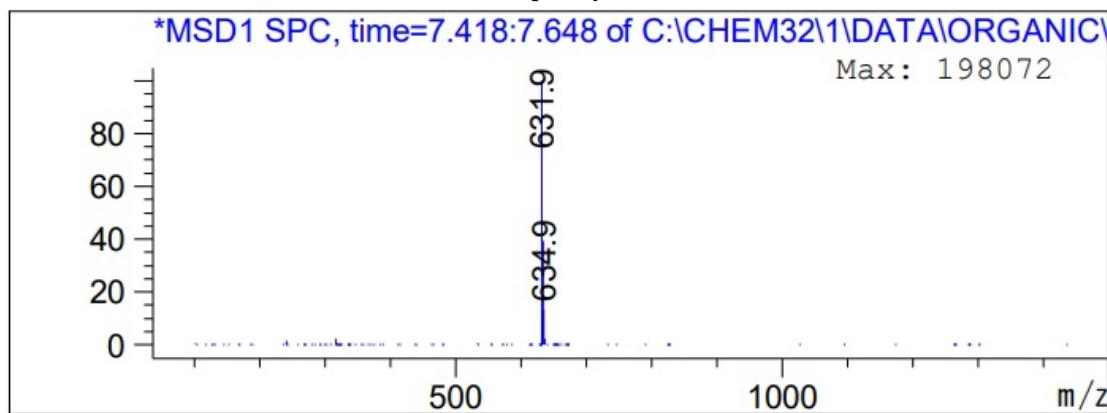
¹H-NMR of 9c



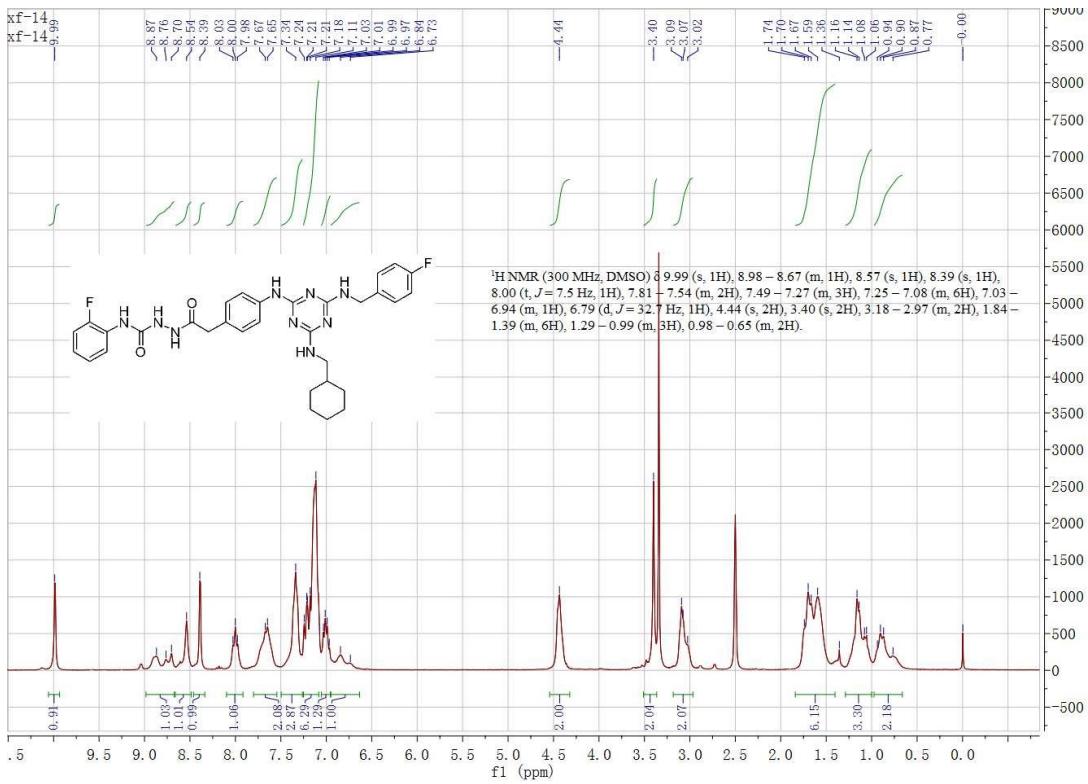
¹³C-NMR of 9c



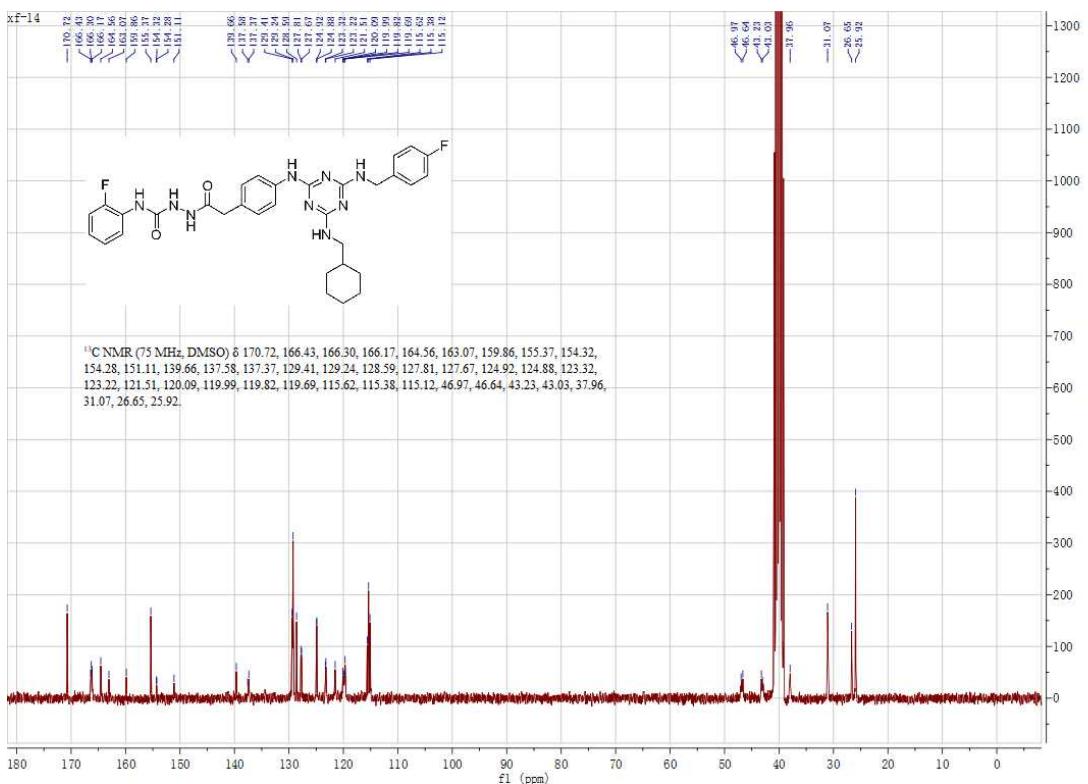
HPLC purity of 9c



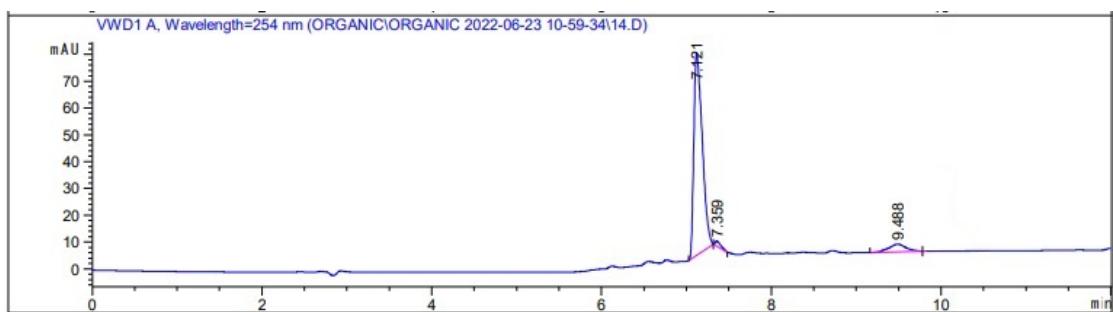
ESI-MS of 9c



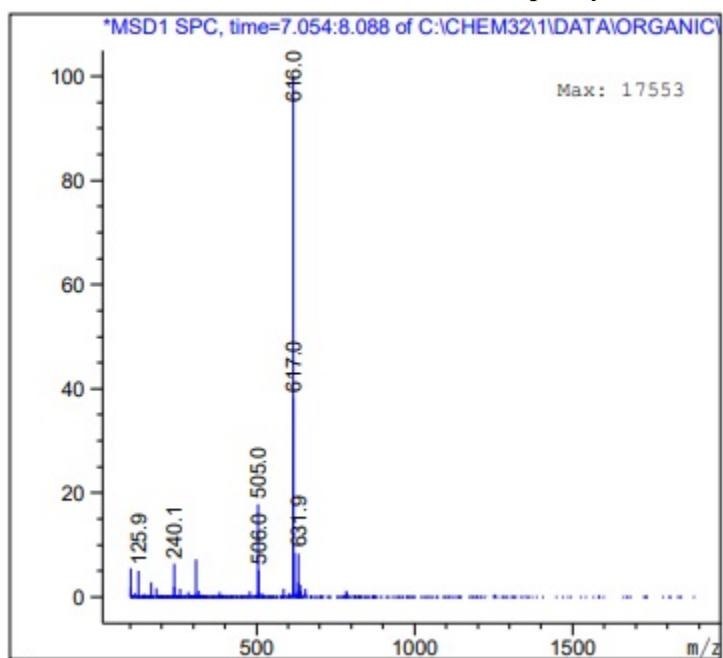
¹H-NMR of 9d



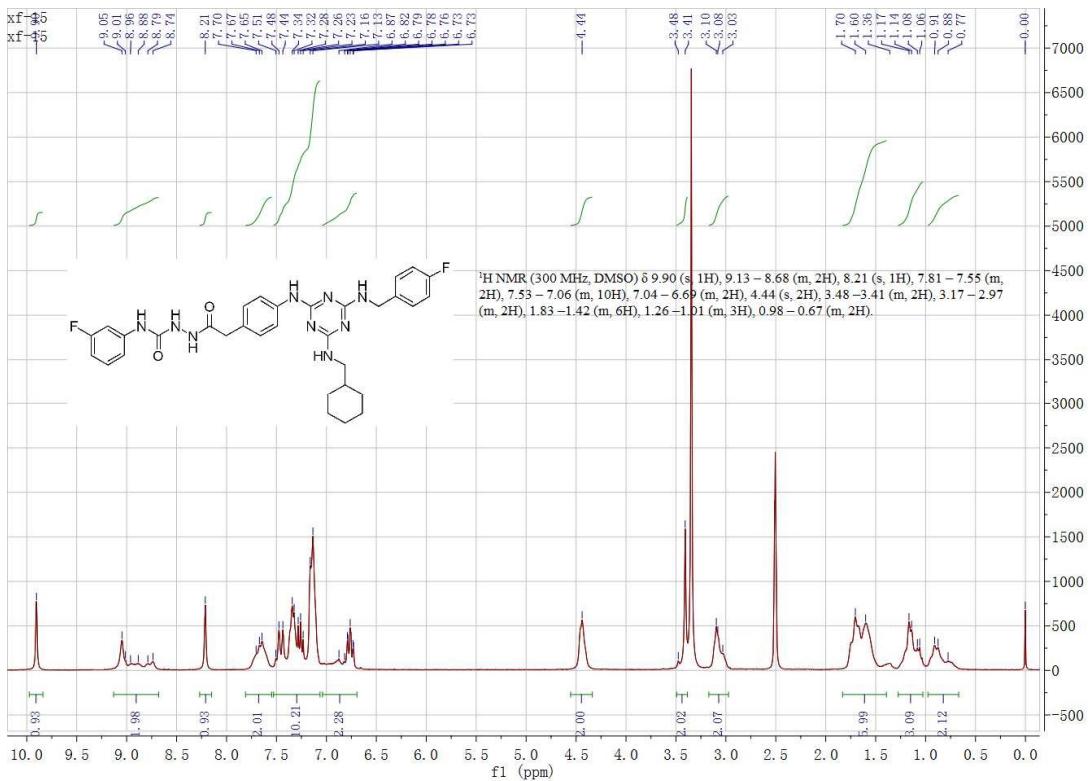
¹³C-NMR of 9d



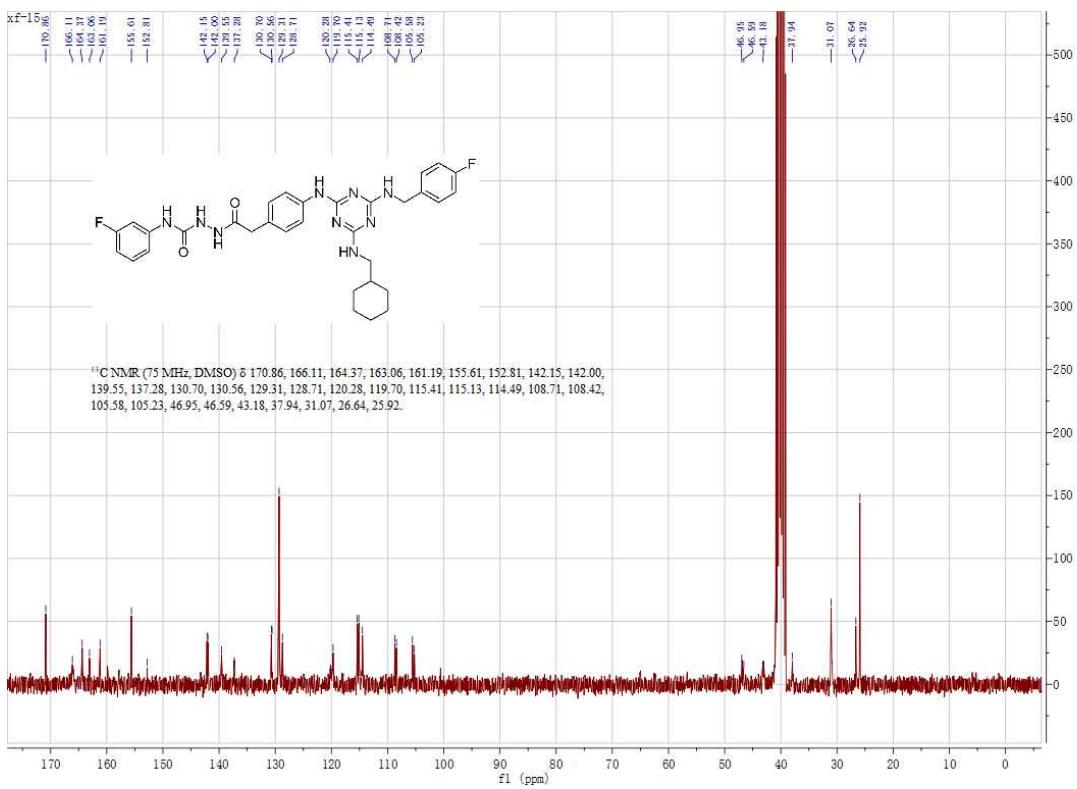
HPLC purity of 9d



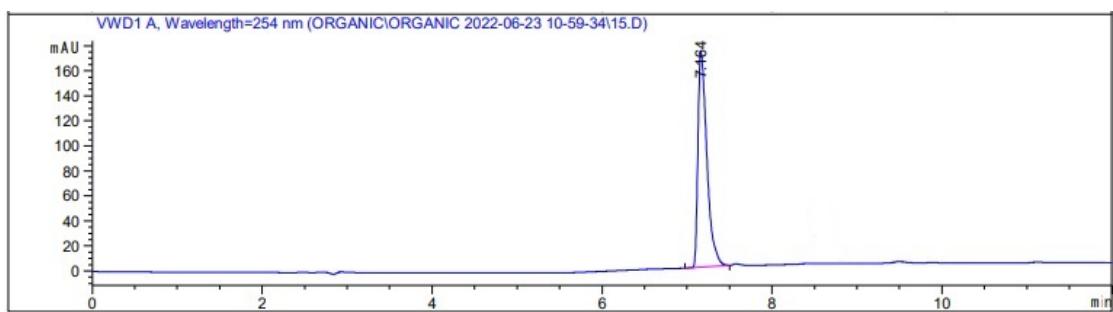
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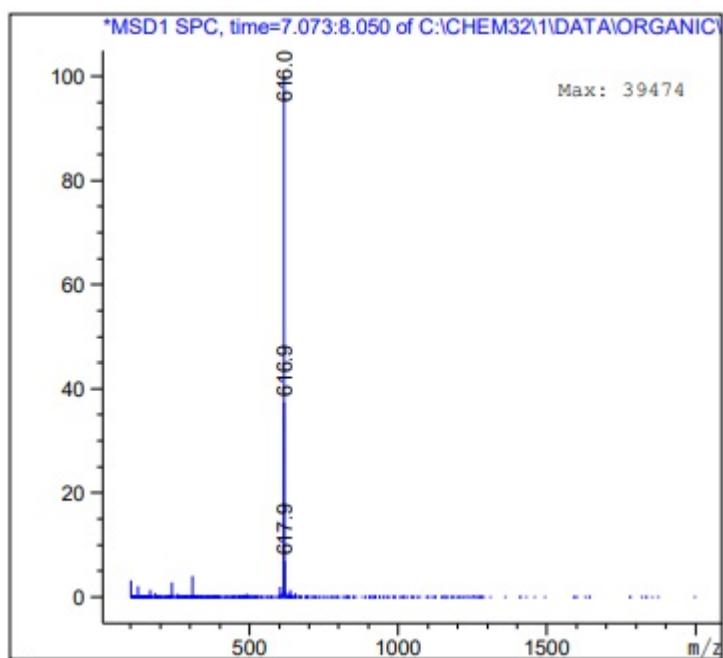
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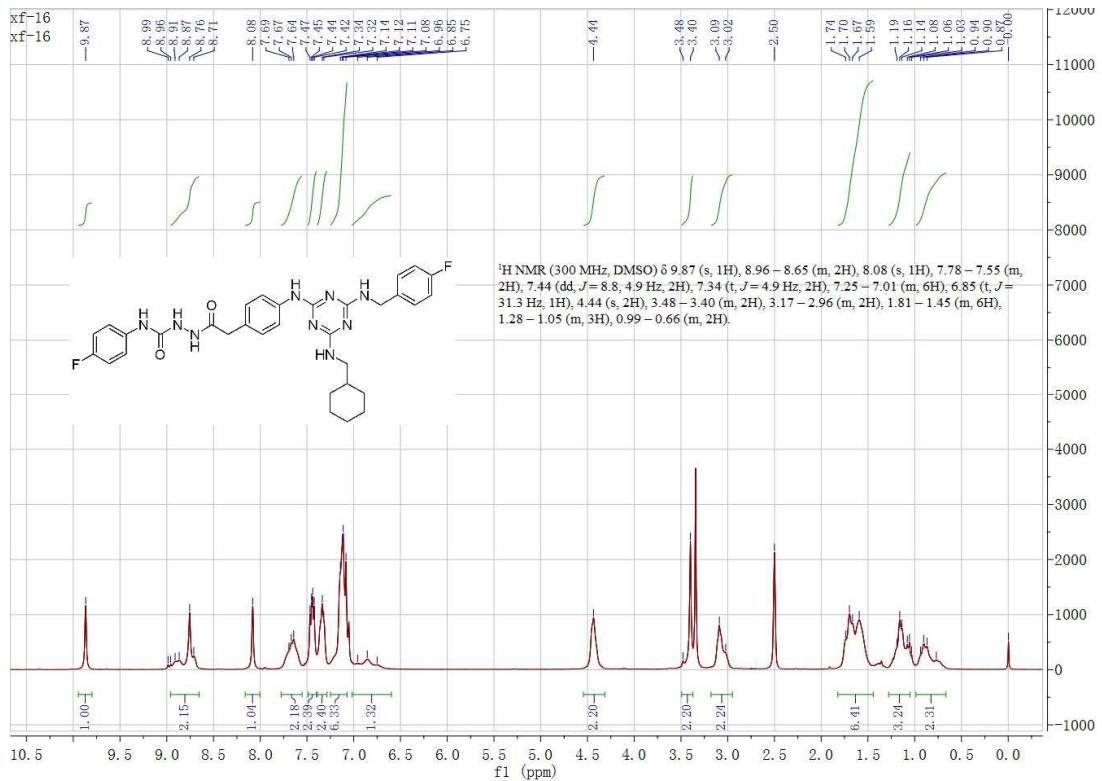
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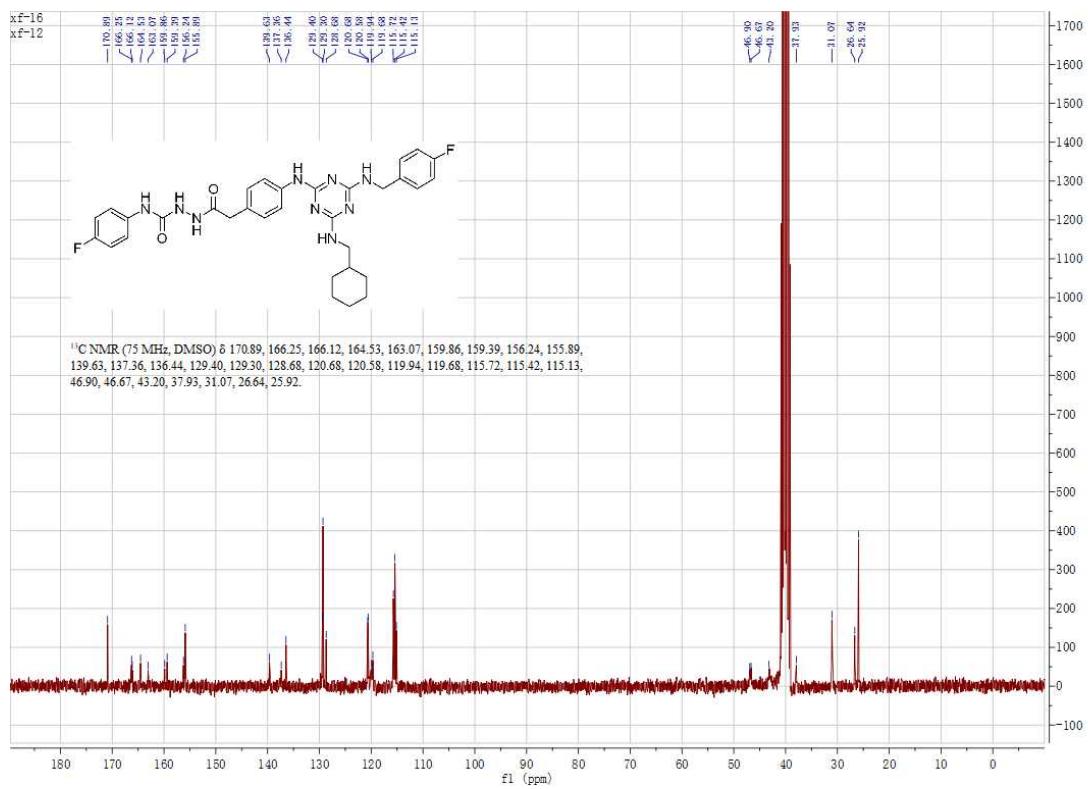
HPLC purity of 9e



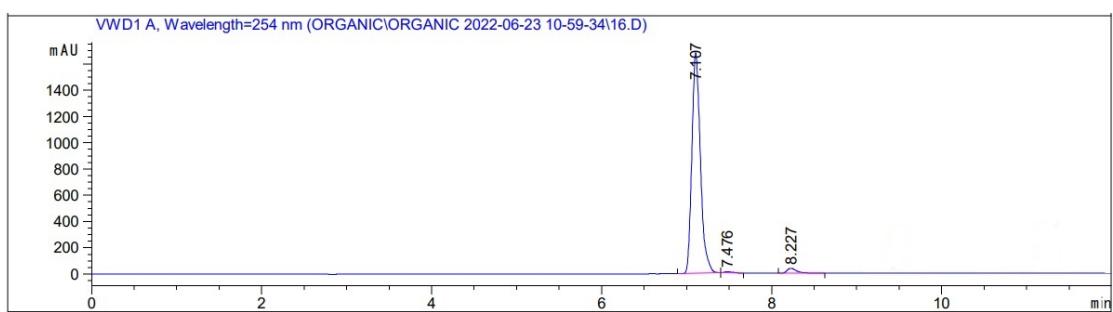
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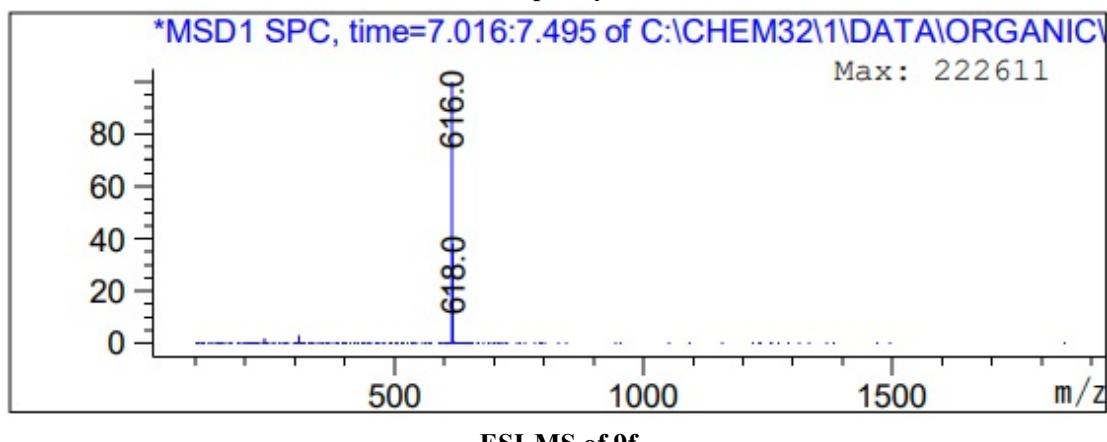
¹H-NMR of 9f



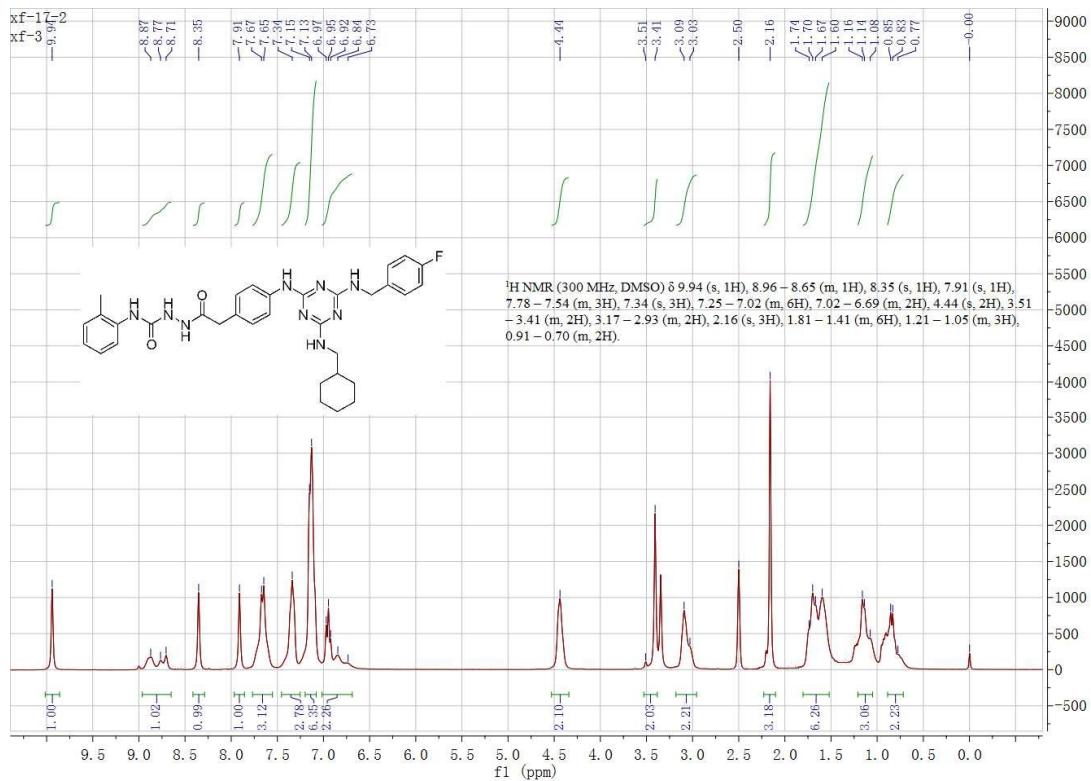
¹³C-NMR of 9f



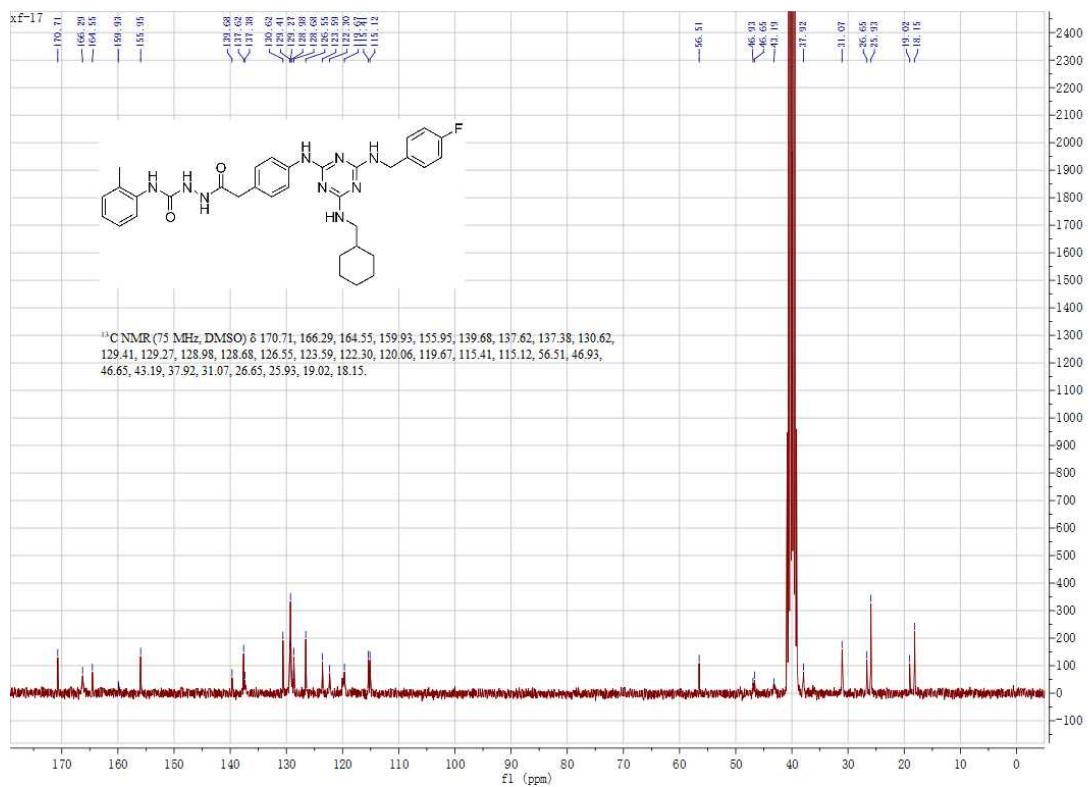
HPLC purity of 9f



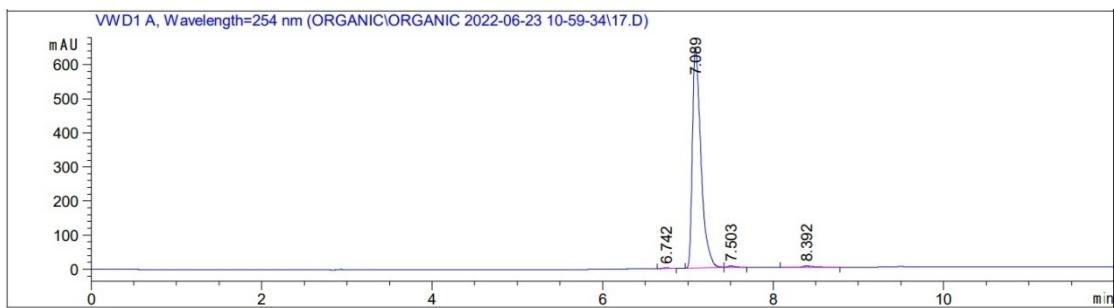
ESI-MS of 9f



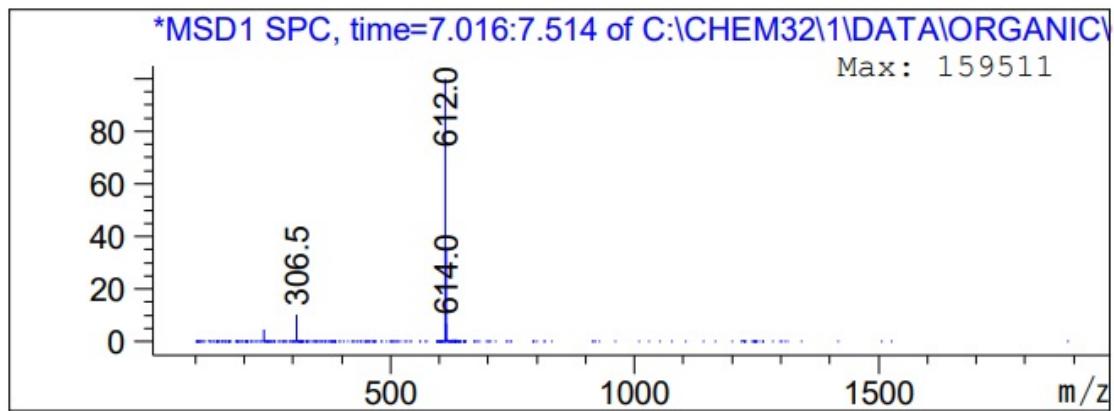
¹H-NMR of 9g



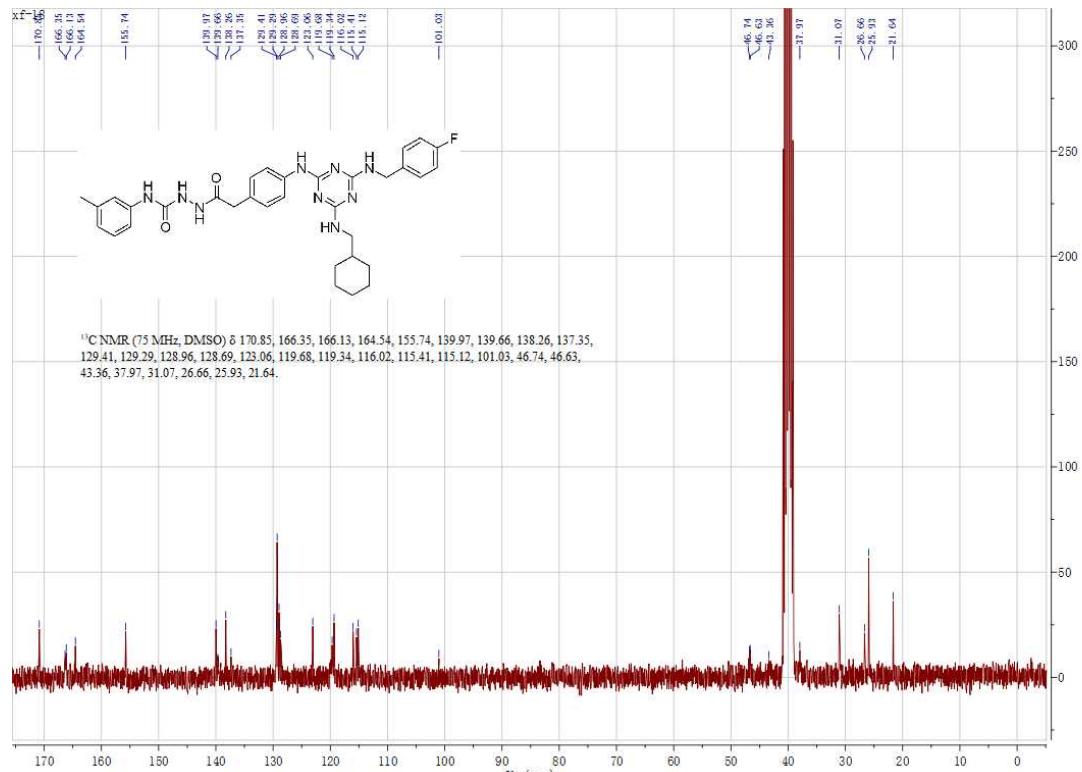
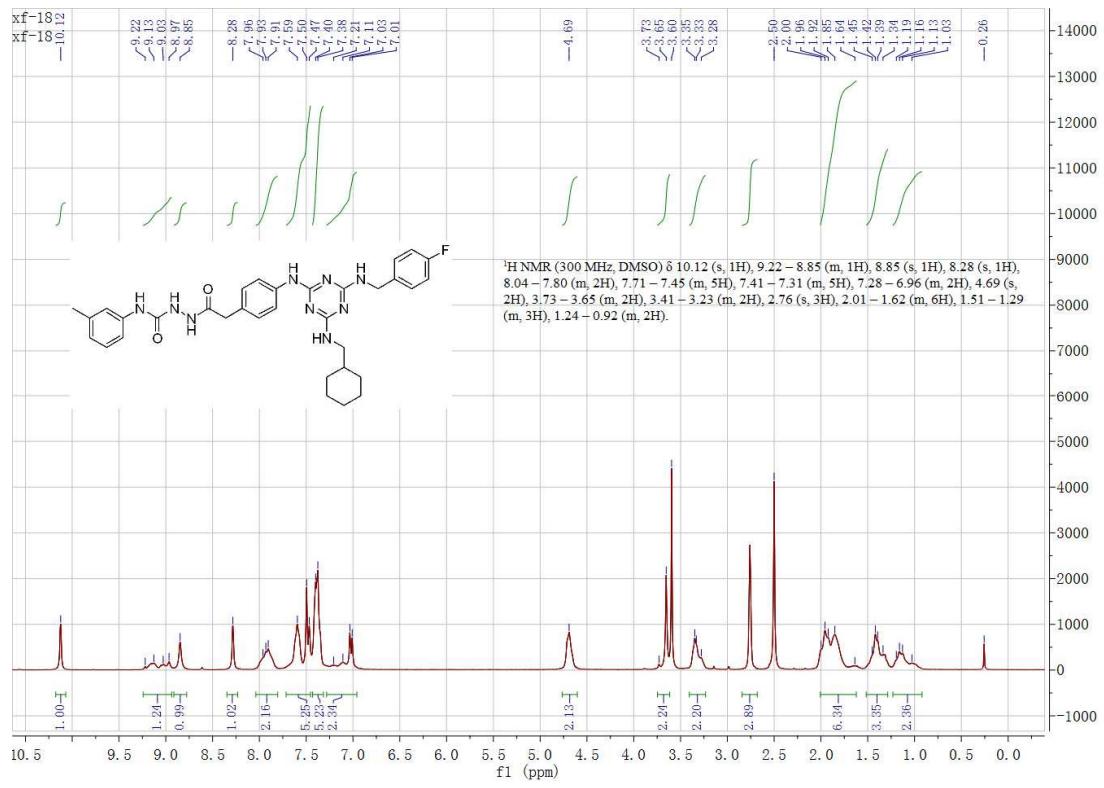
¹³C-NMR of 9g

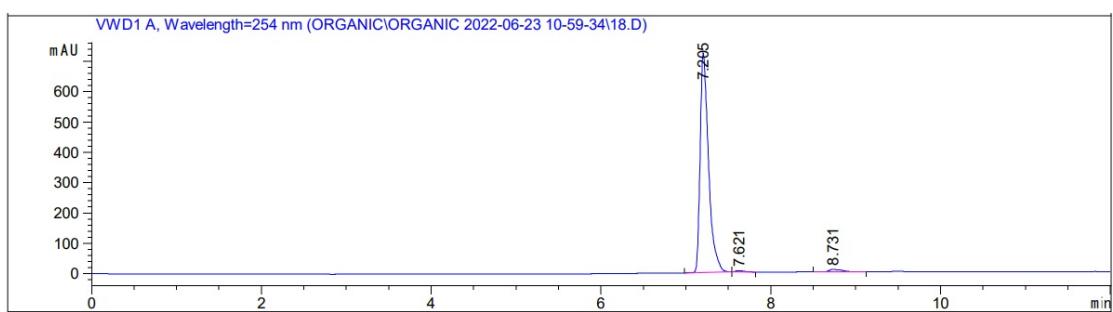


HPLC purity of 9g

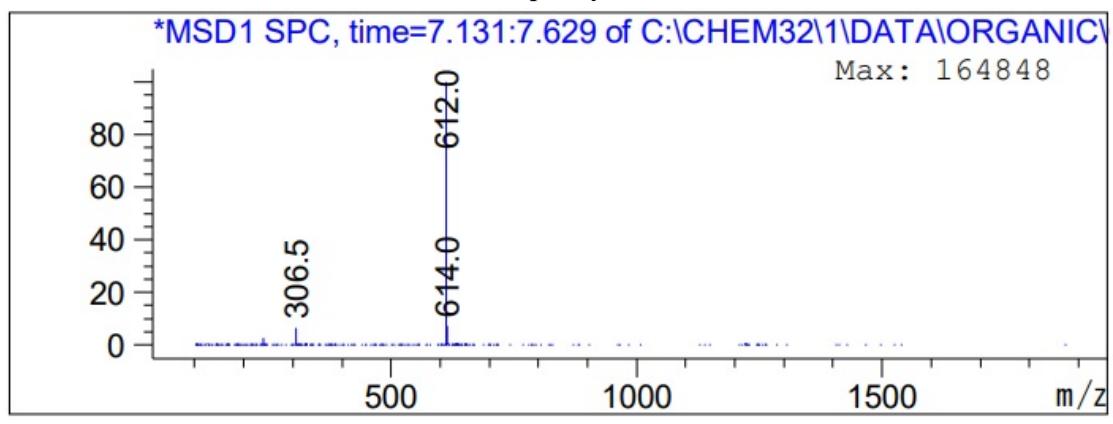


ESI-MS of 9g

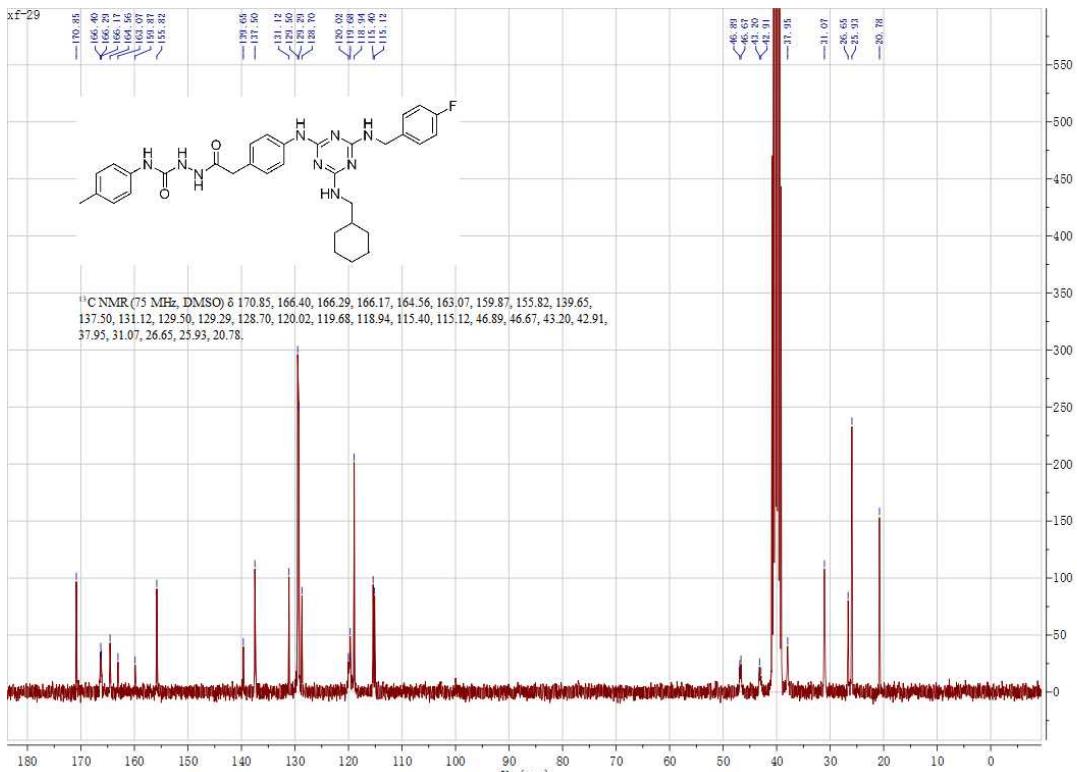
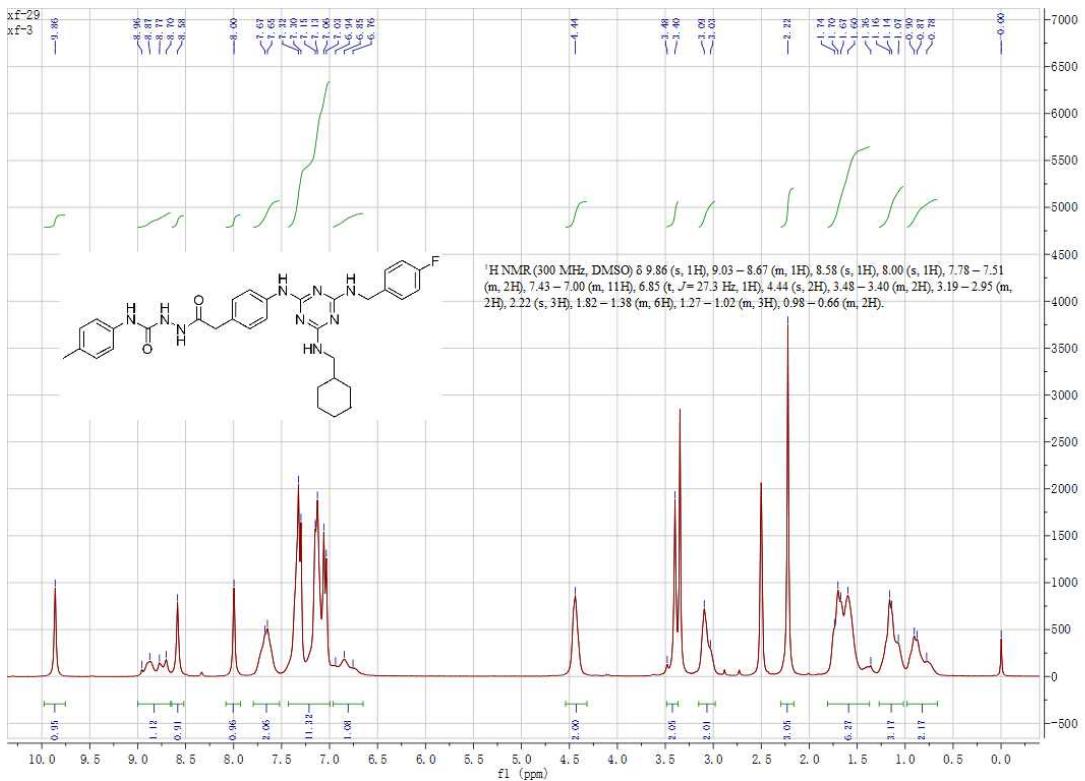


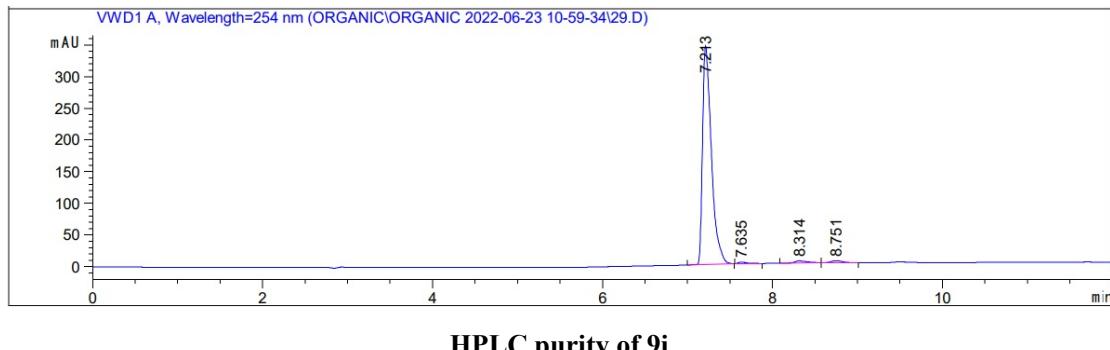


HPLC purity of 9h

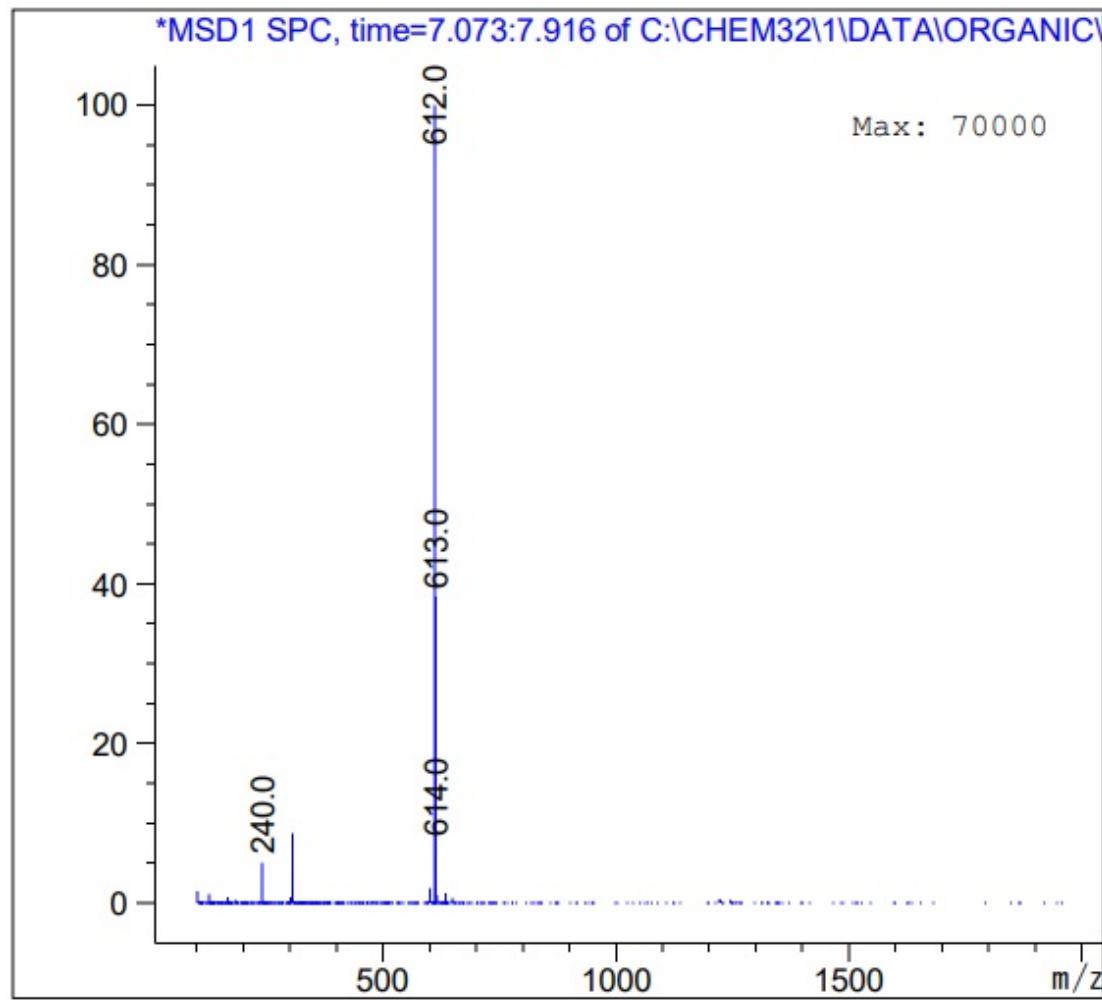


ESI-MS of 9h

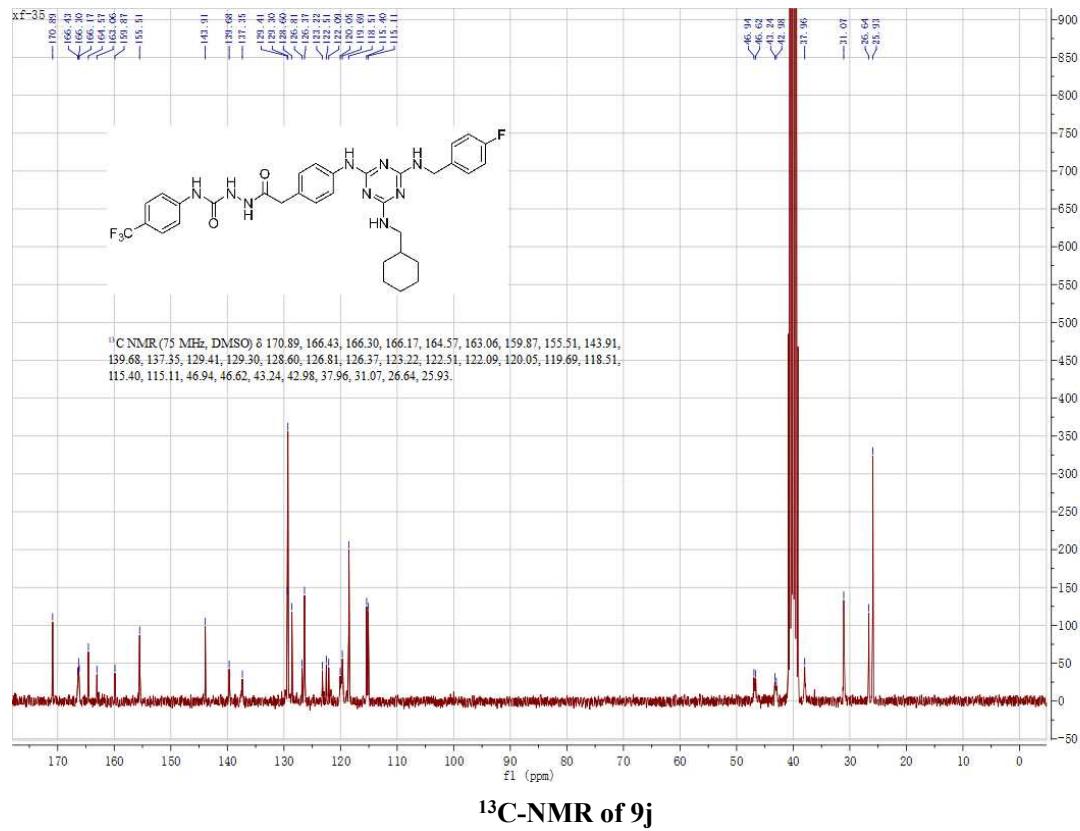
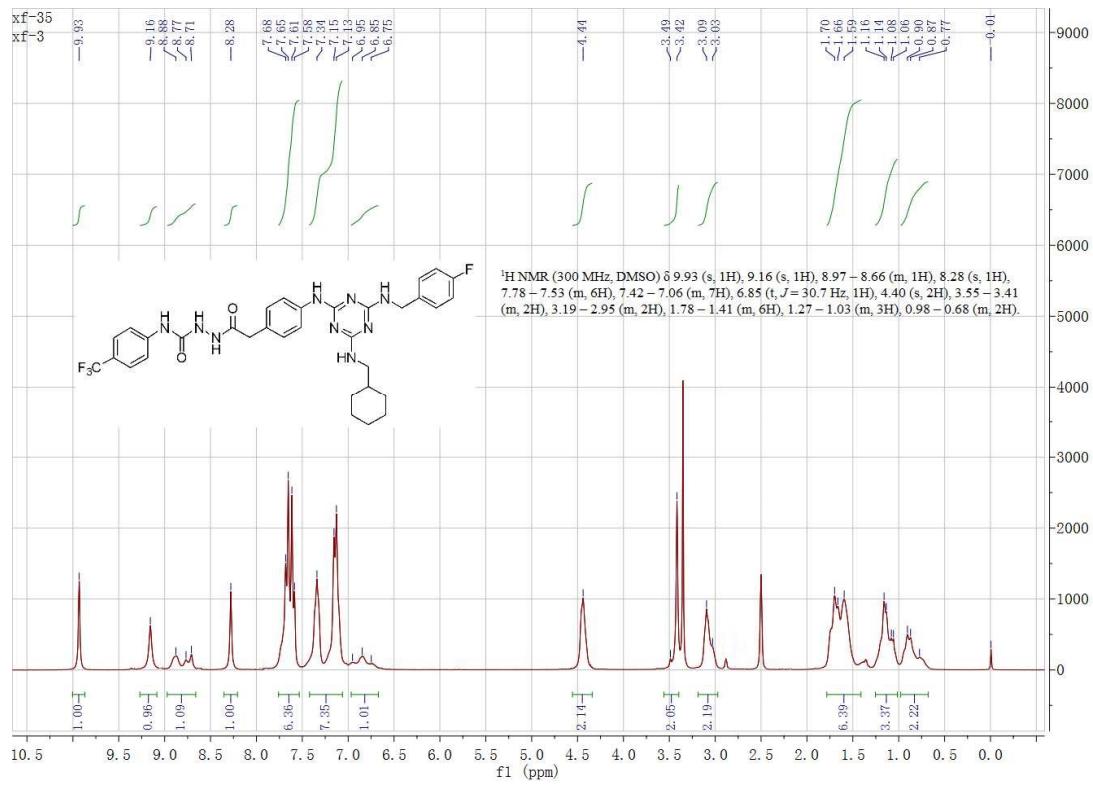


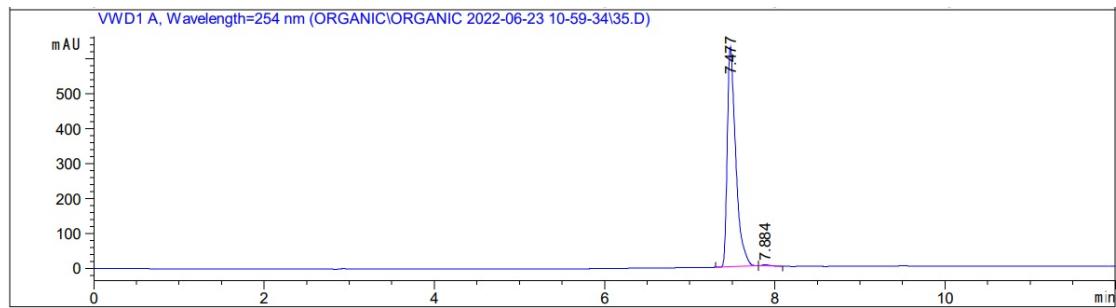


HPLC purity of 9i

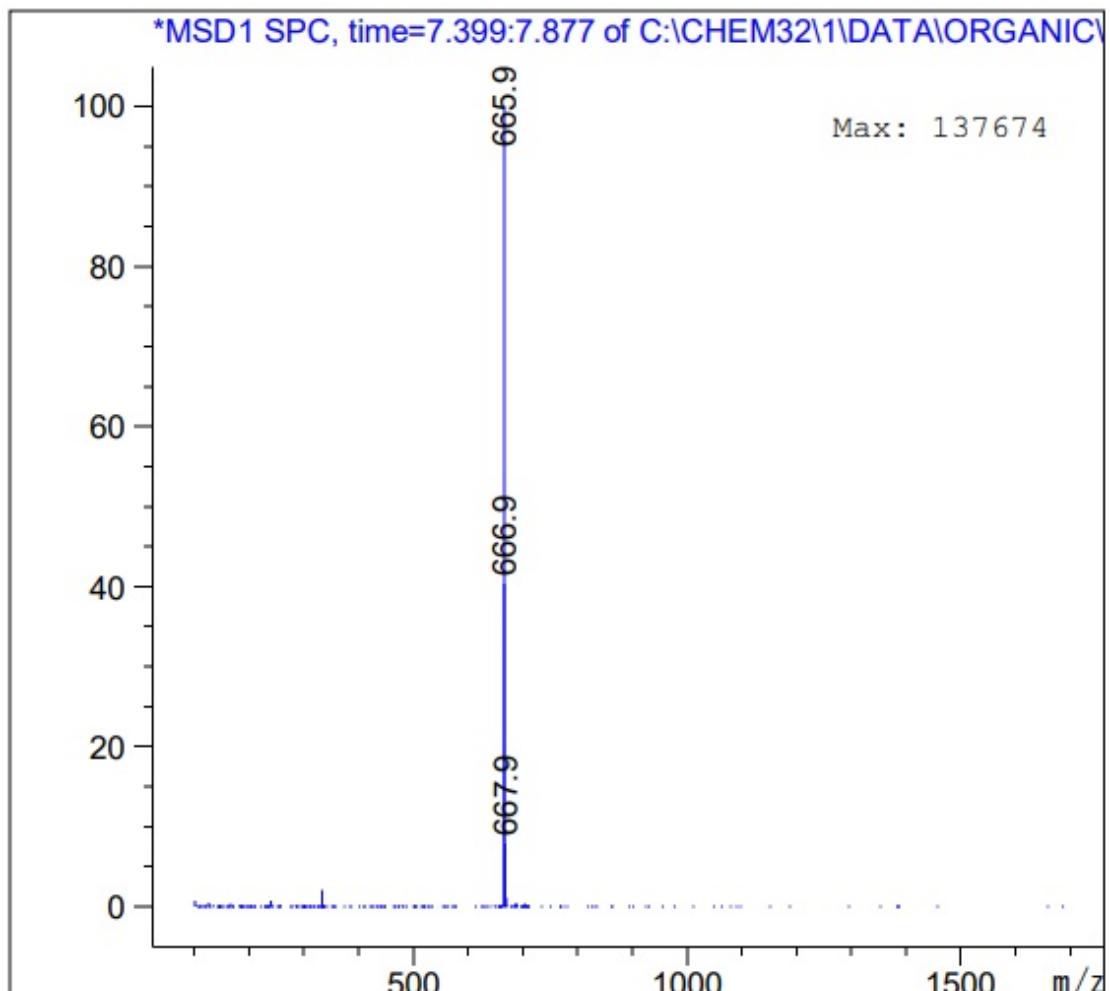


ESI-MS of 9i

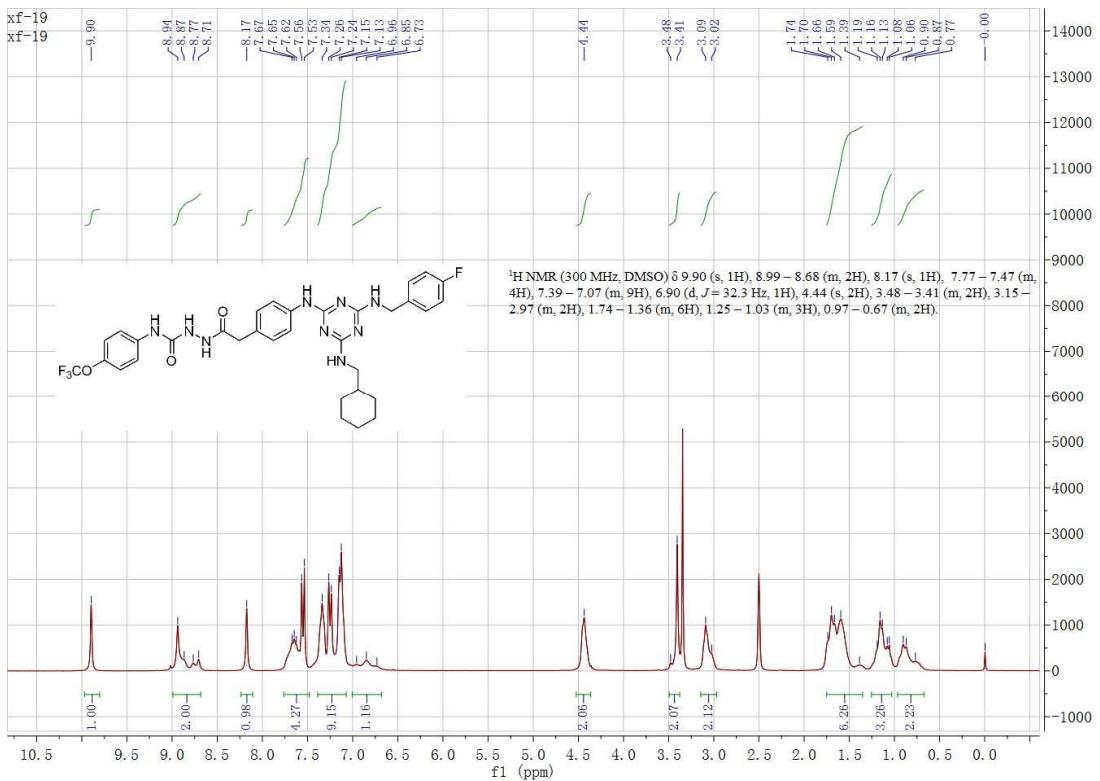




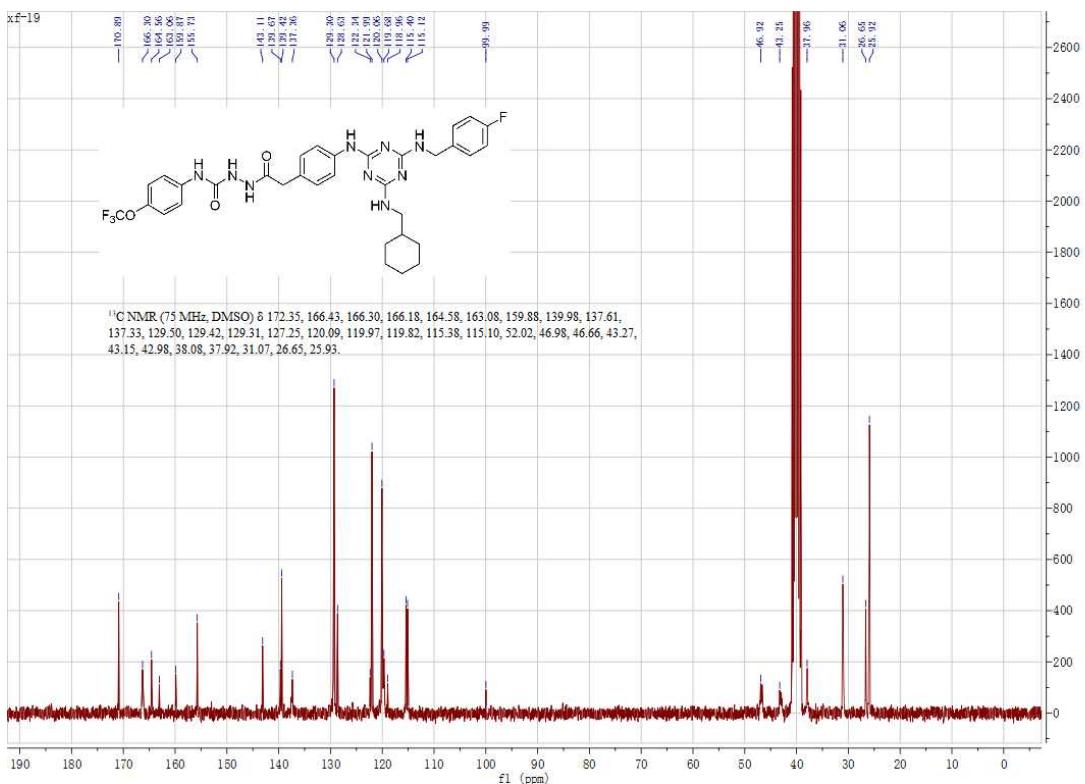
HPLC purity of 9j



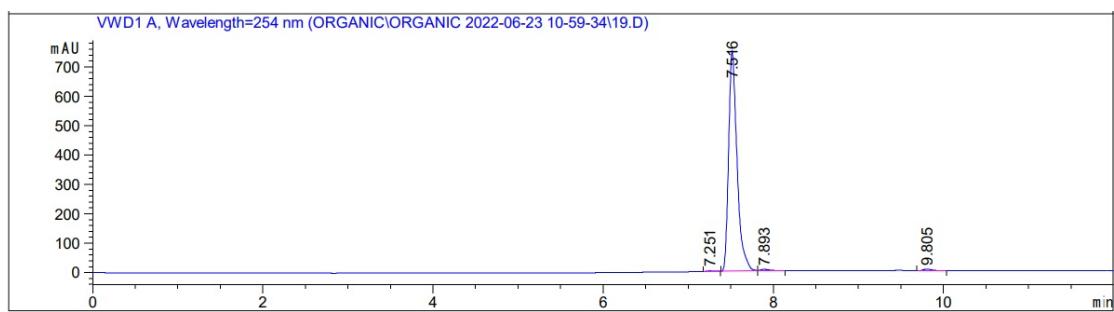
ESI-MS of 9j



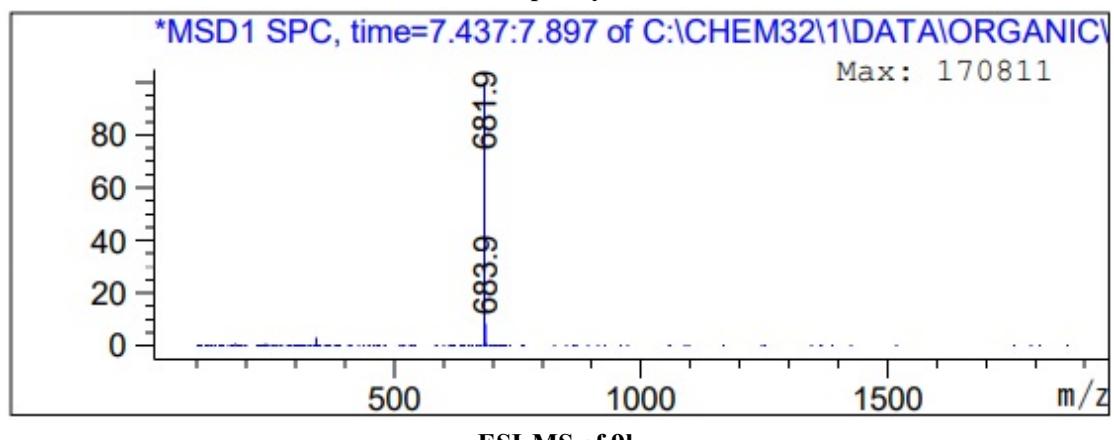
¹H-NMR of 9k



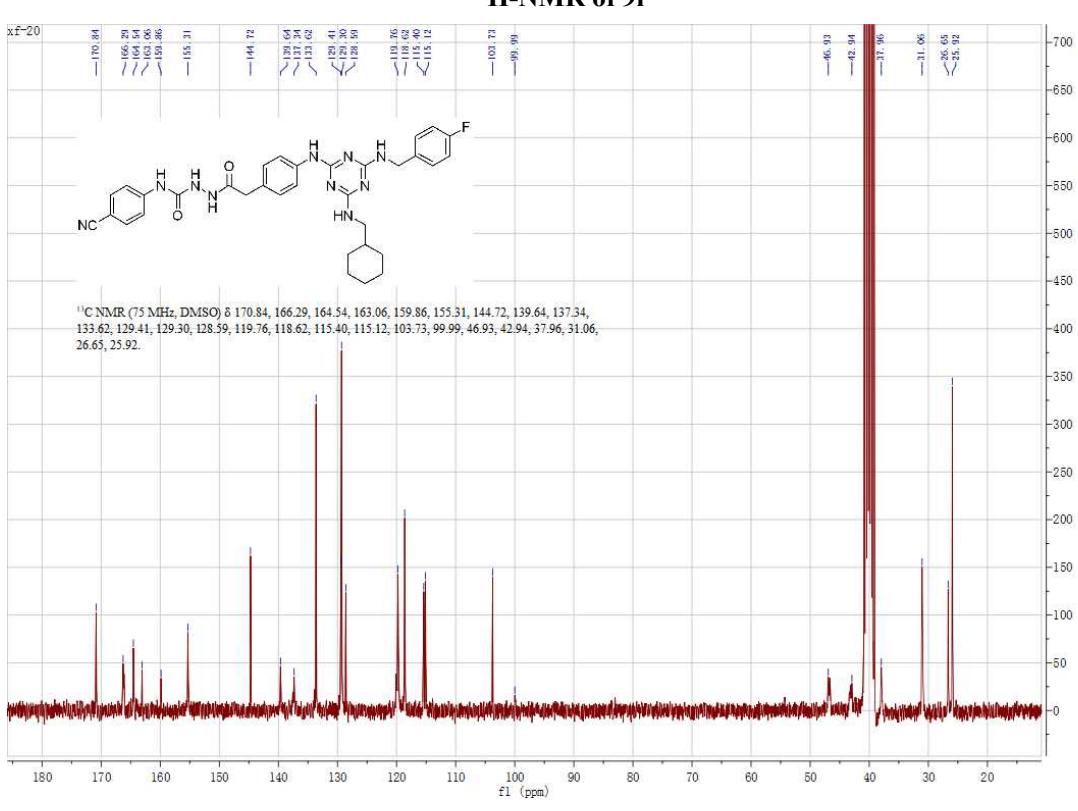
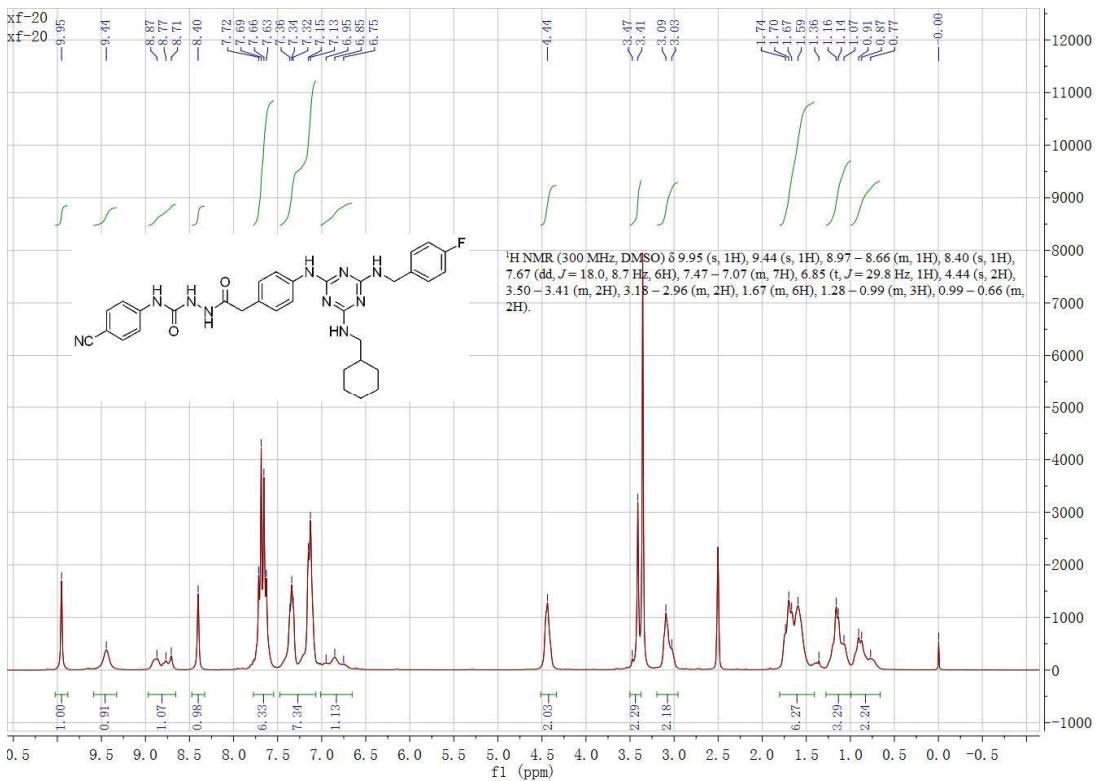
¹³C-NMR of 9k

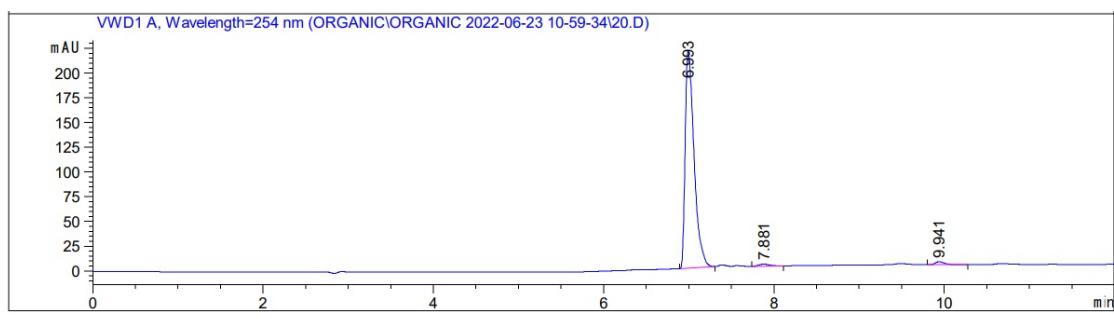


HPLC purity of 9k

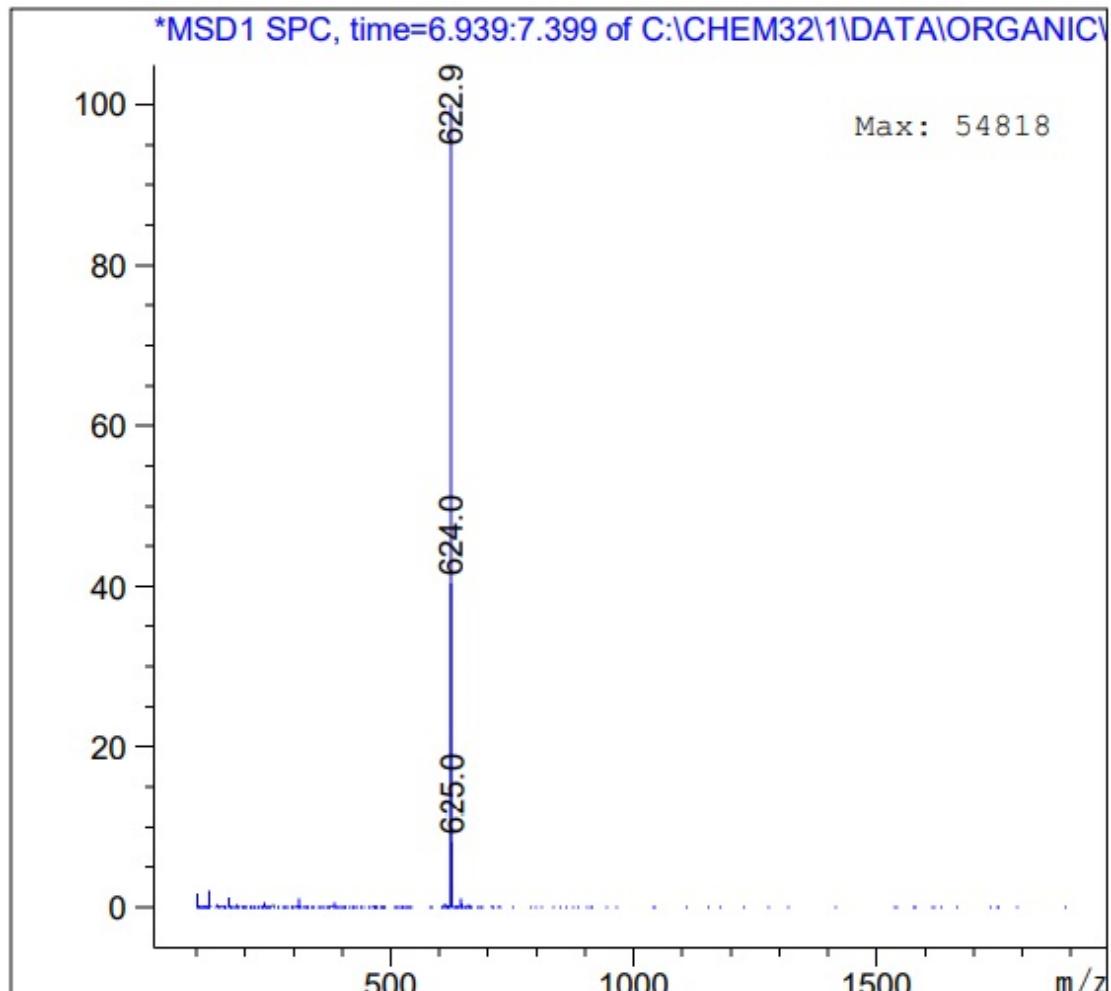


ESI-MS of 9k

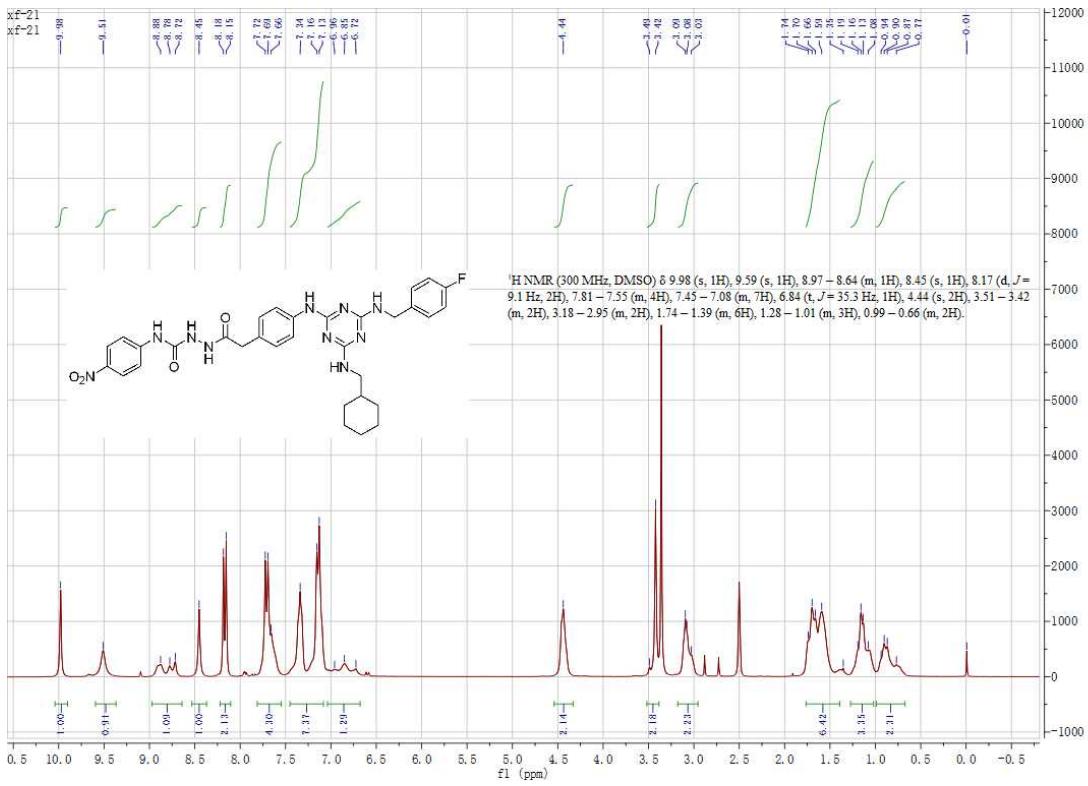




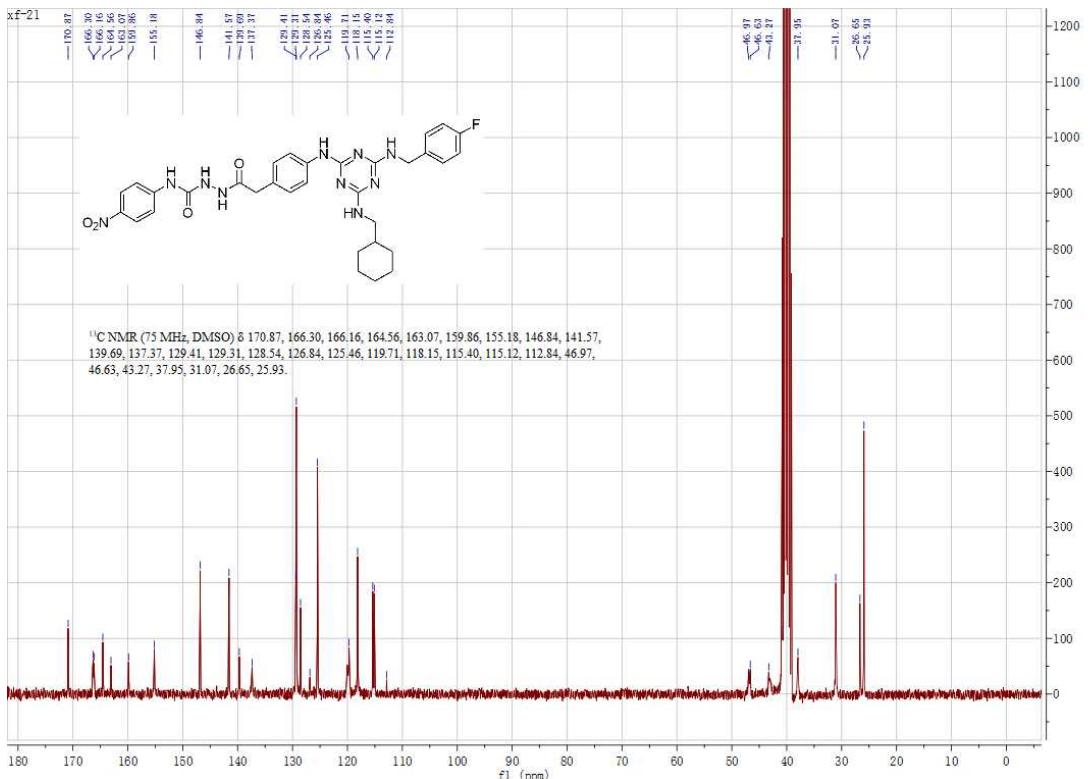
HPLC purity of 9l



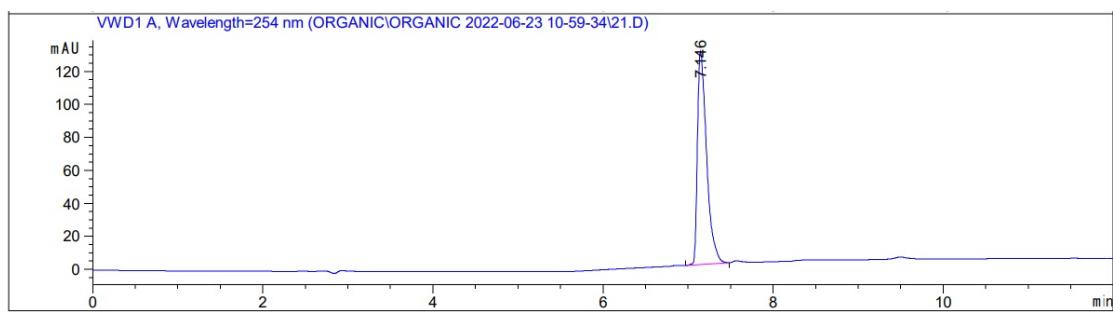
ESI-MS of 9l



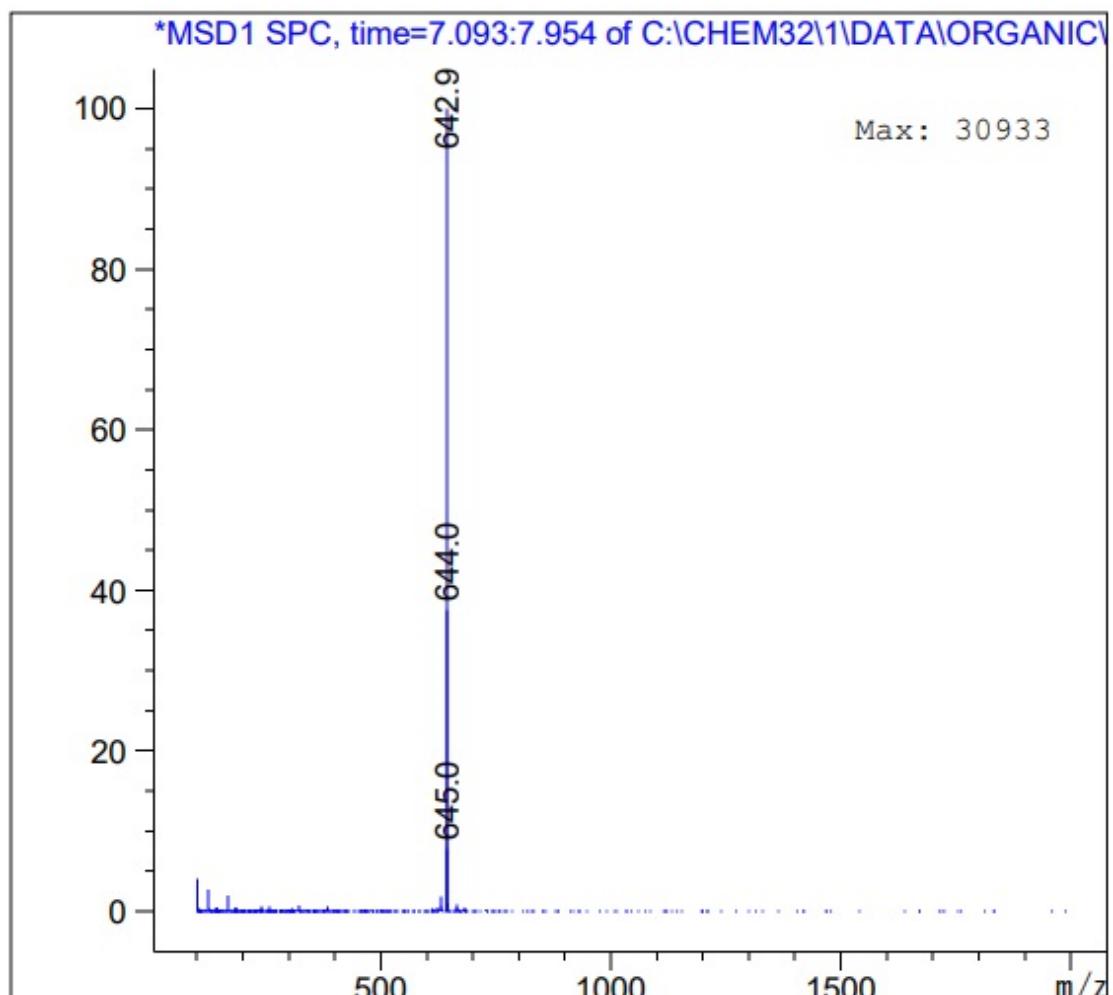
¹H-NMR of 9m



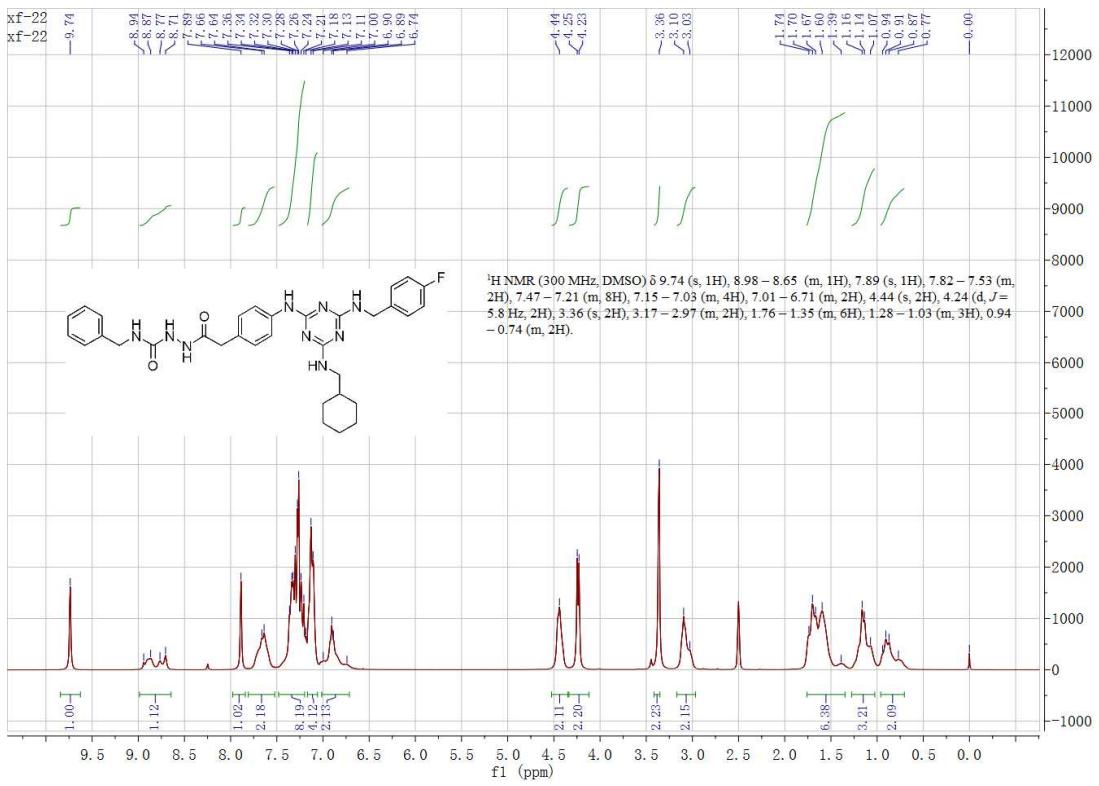
¹³C-NMR of 9m



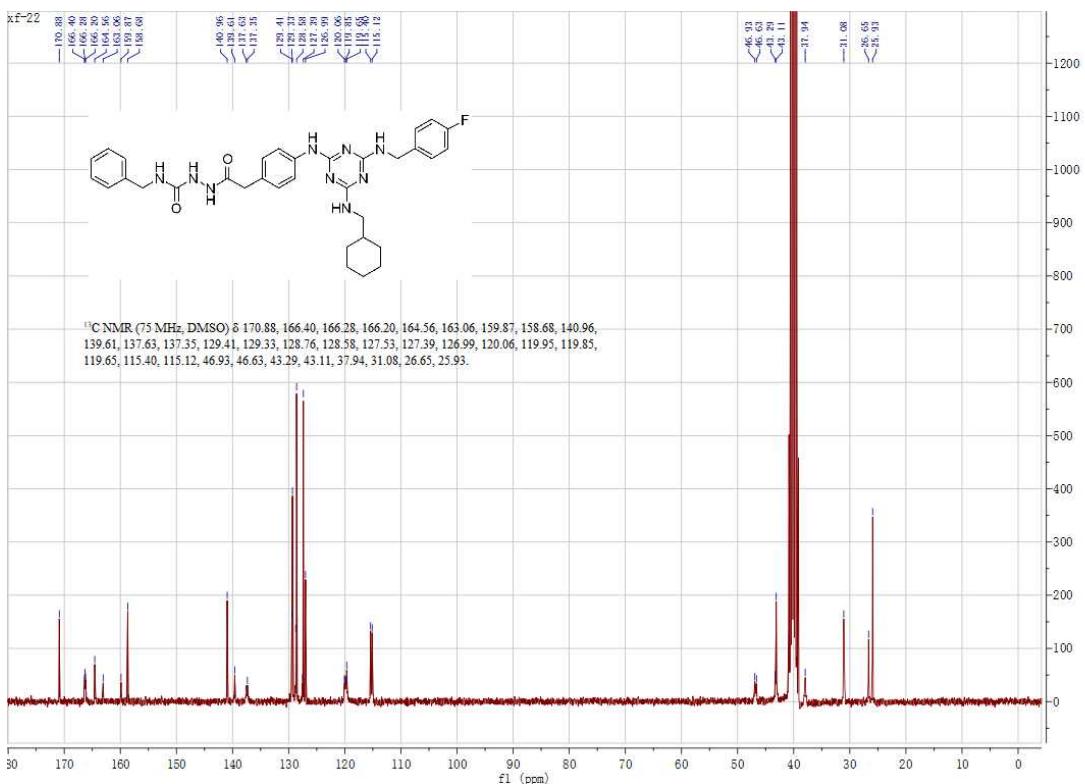
HPLC purity of 9m



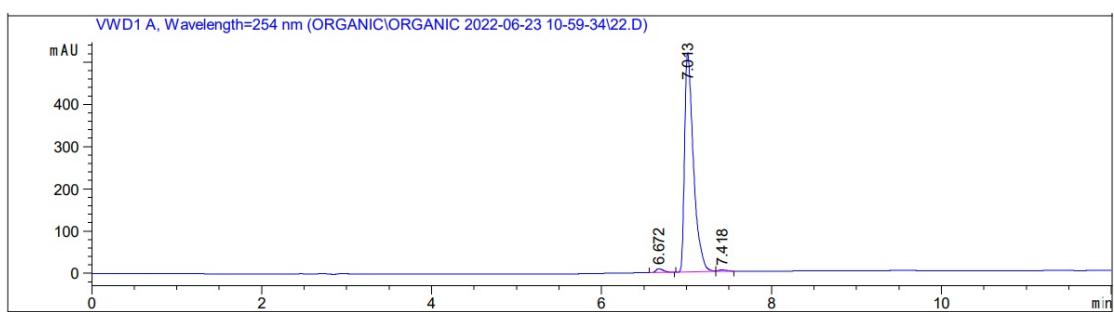
ESI-MS of 9m



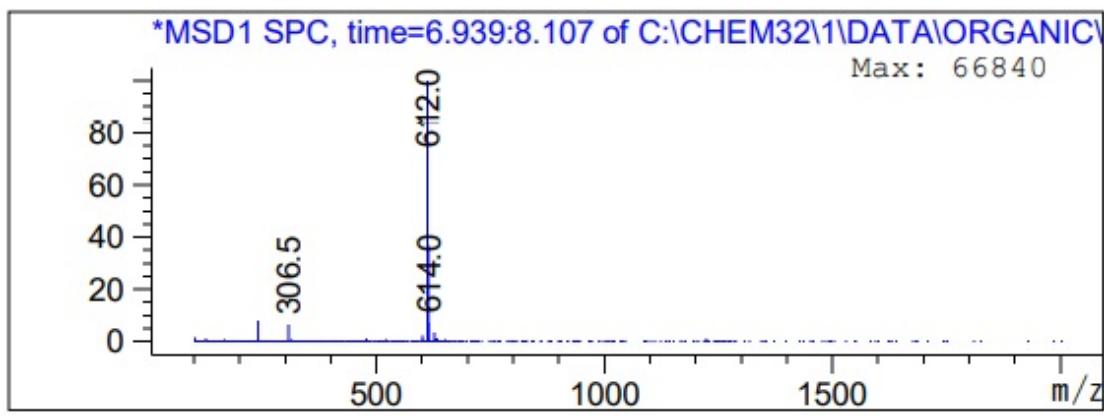
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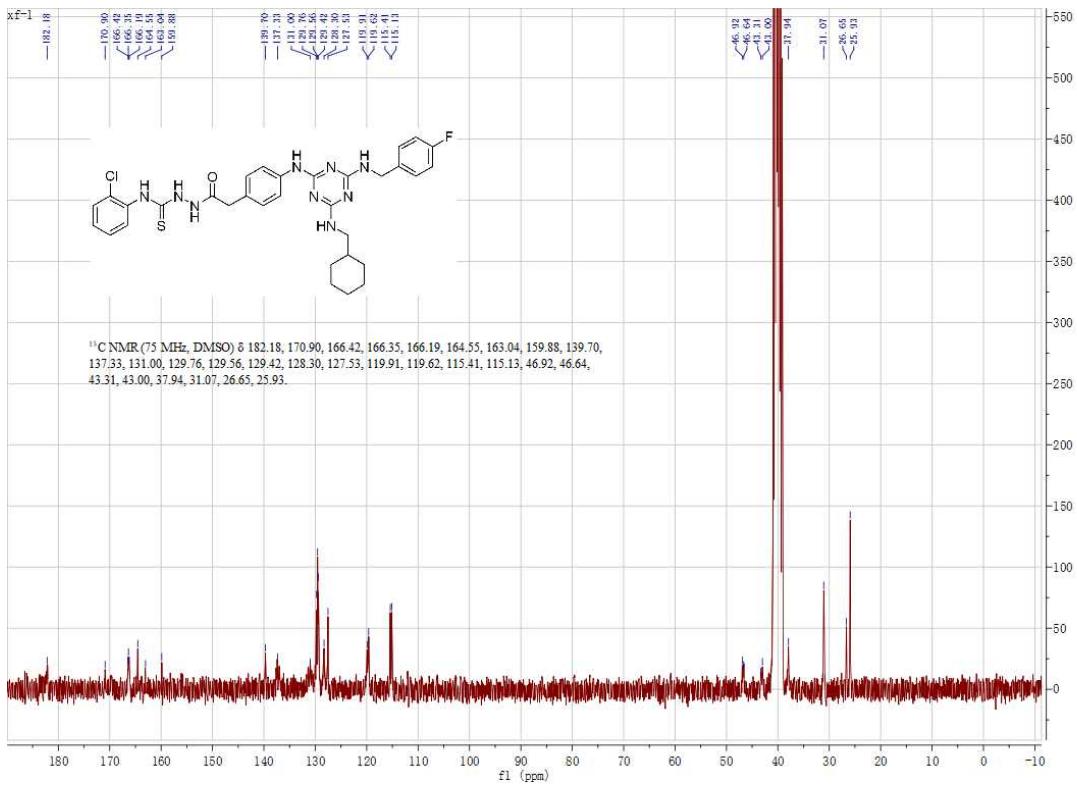
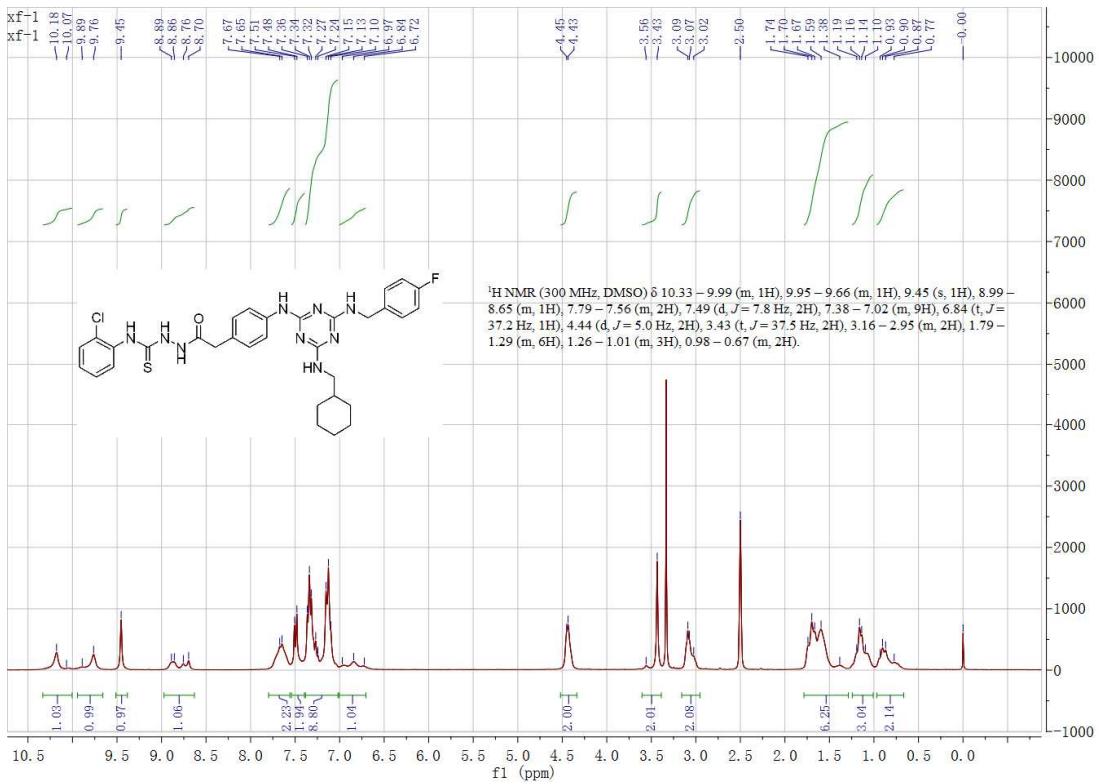
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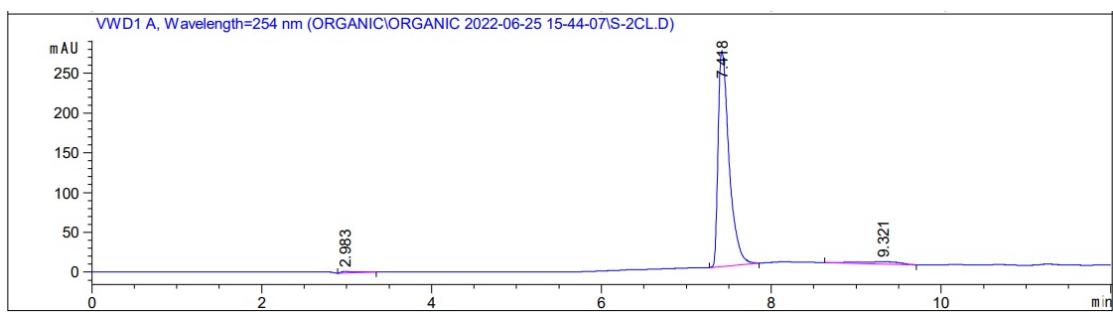


HPLC purity of 9n

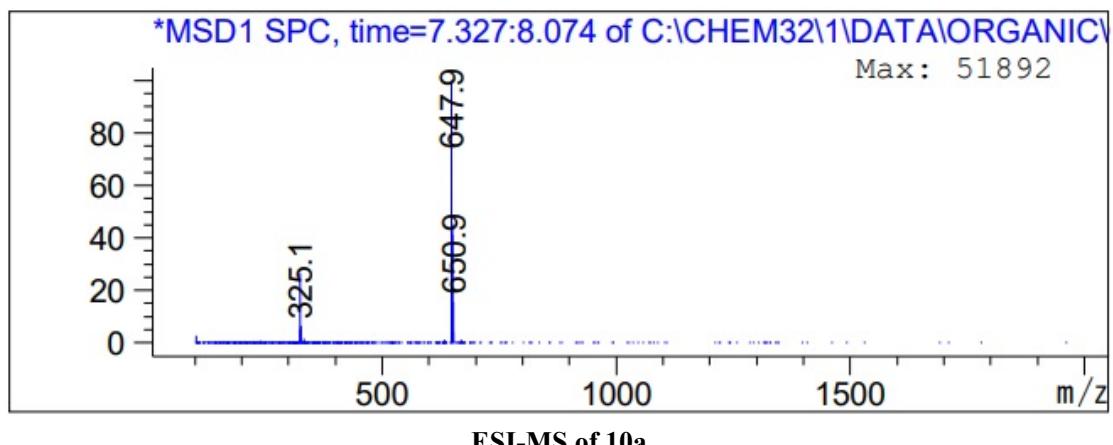


ESI-MS of 9n

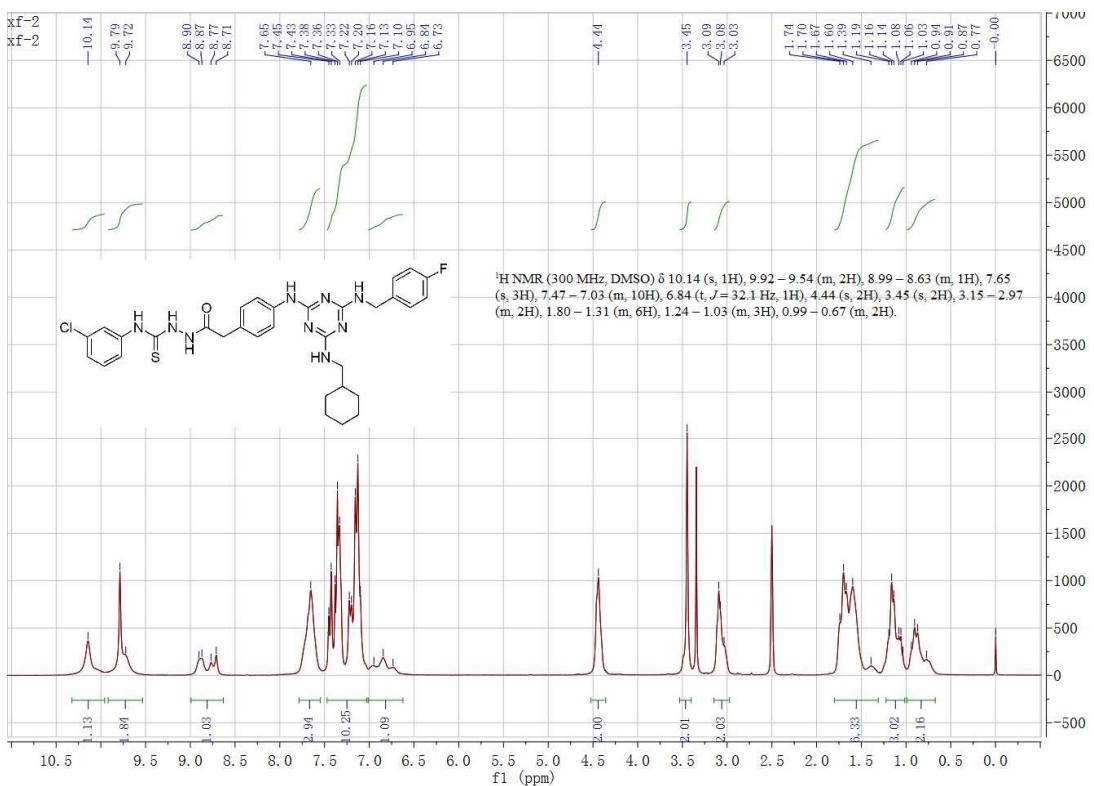




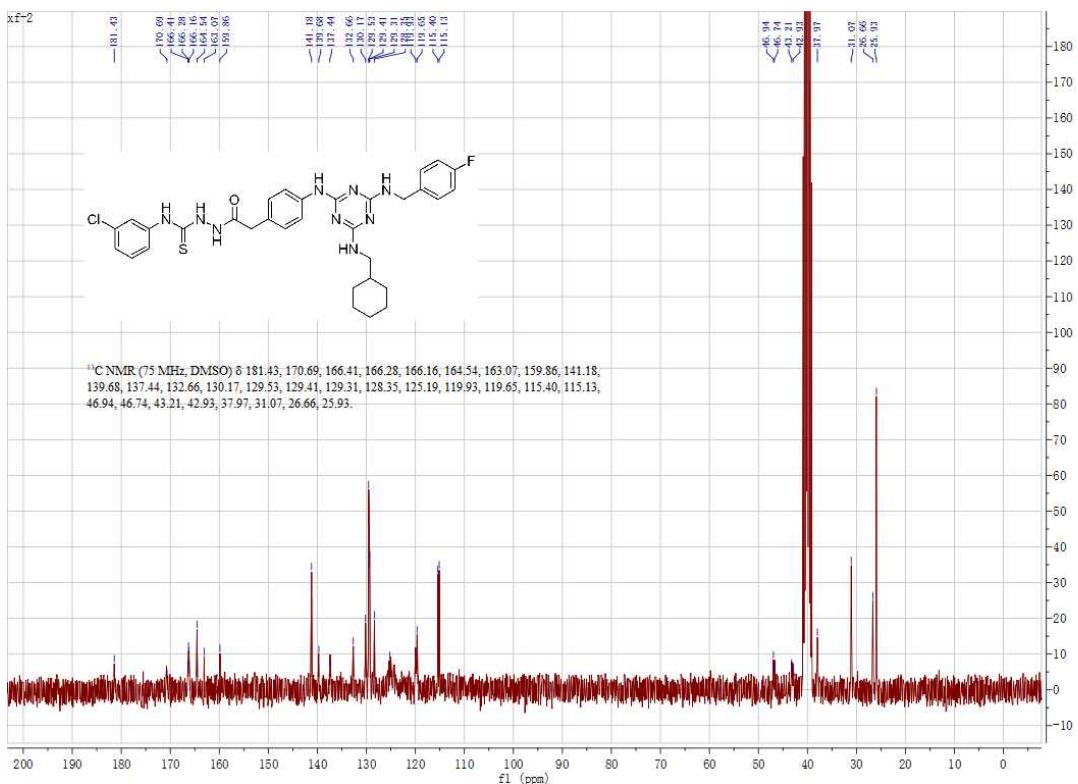
HPLC purity of 10a



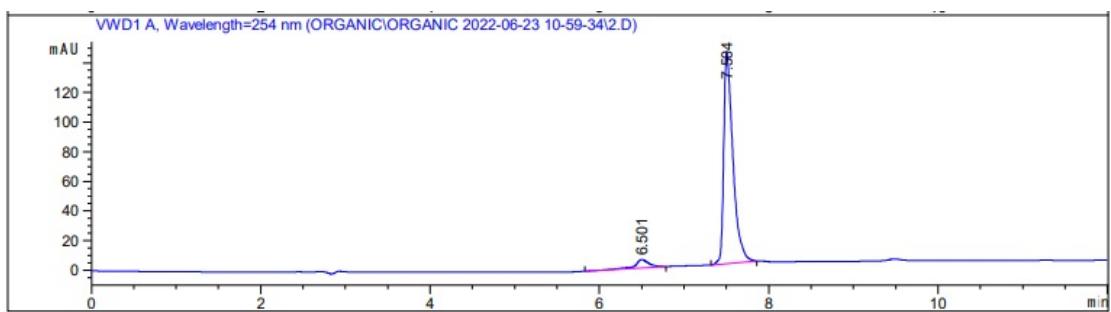
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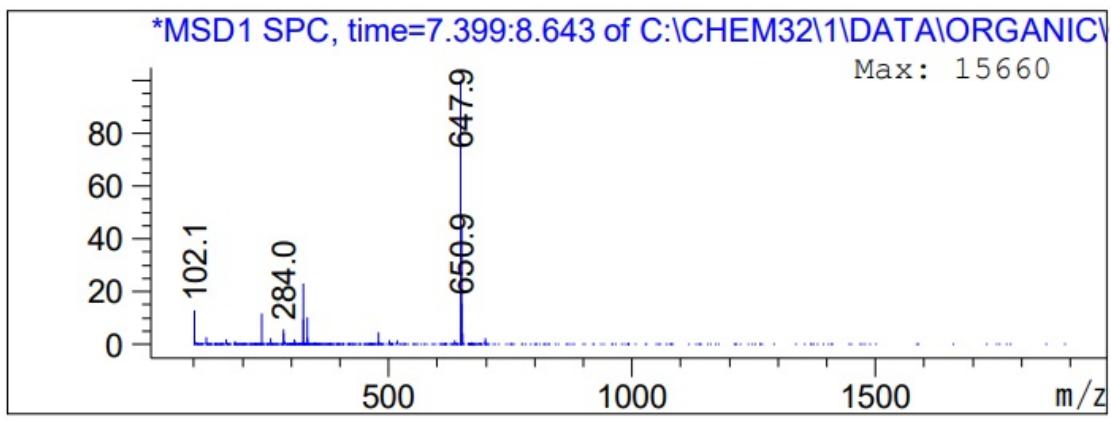
¹H-NMR of 10b



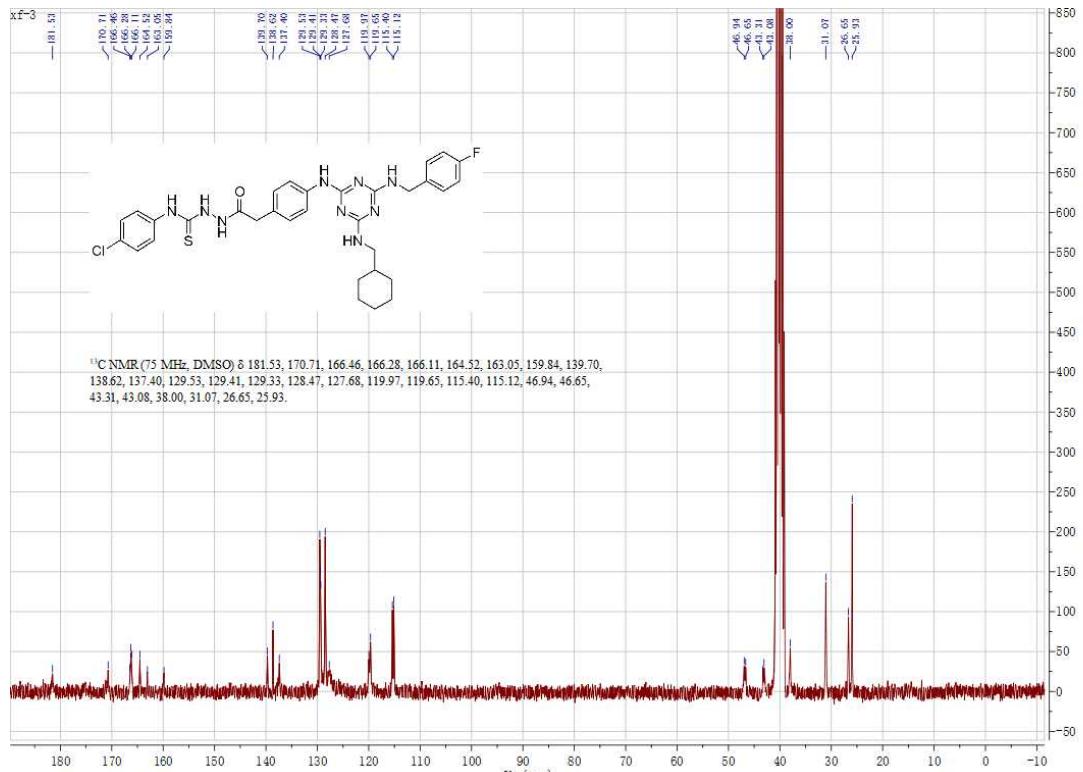
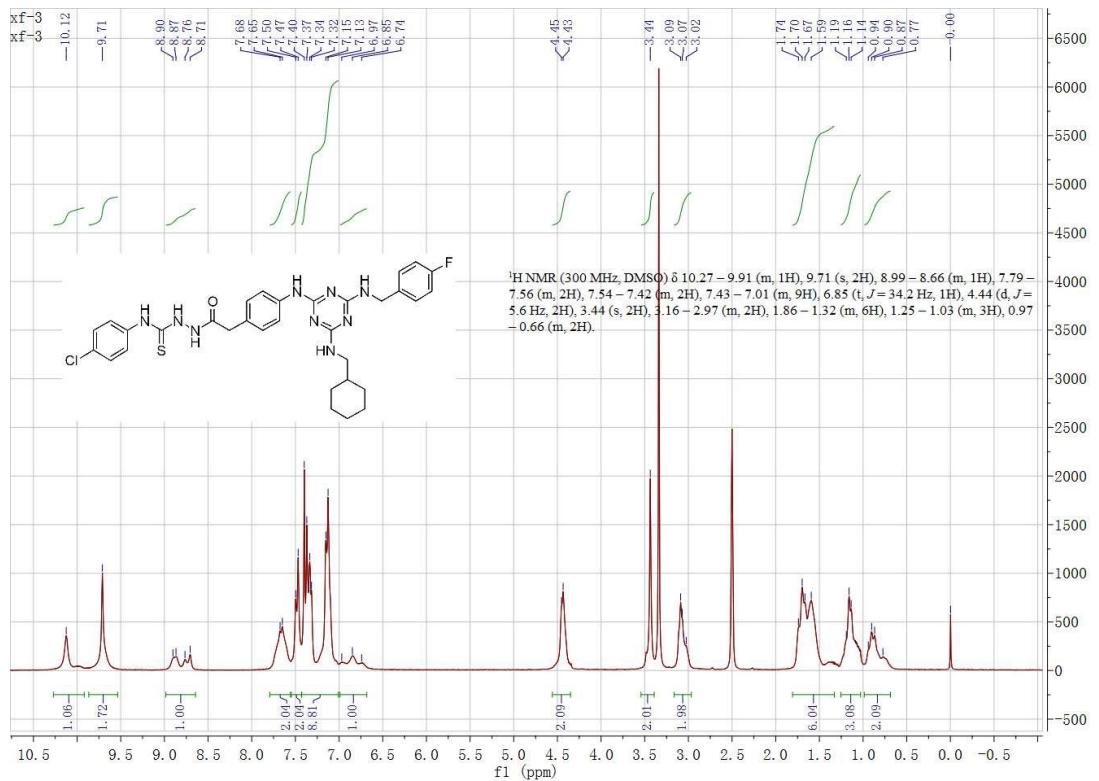
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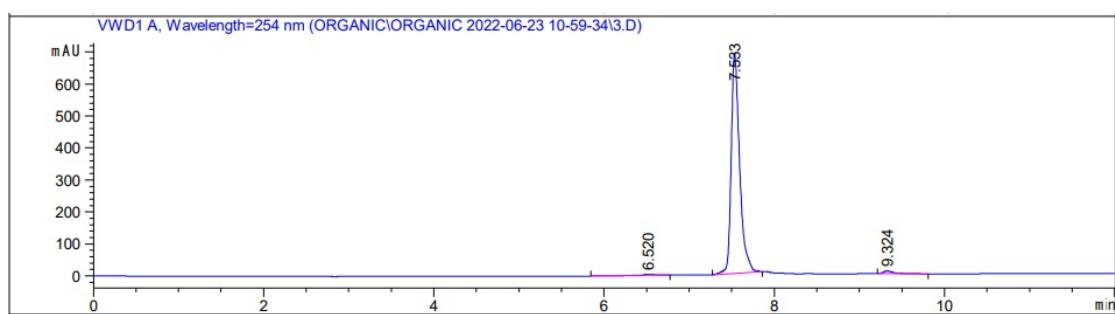


HPLC purity of 10b

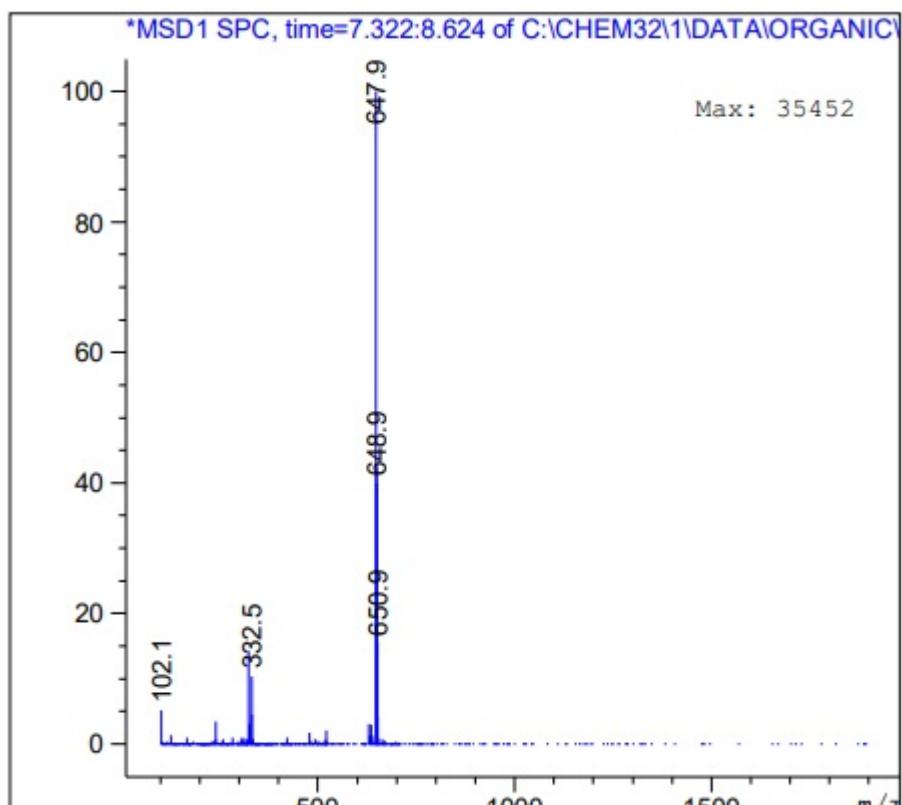


ESI-MS of 10b

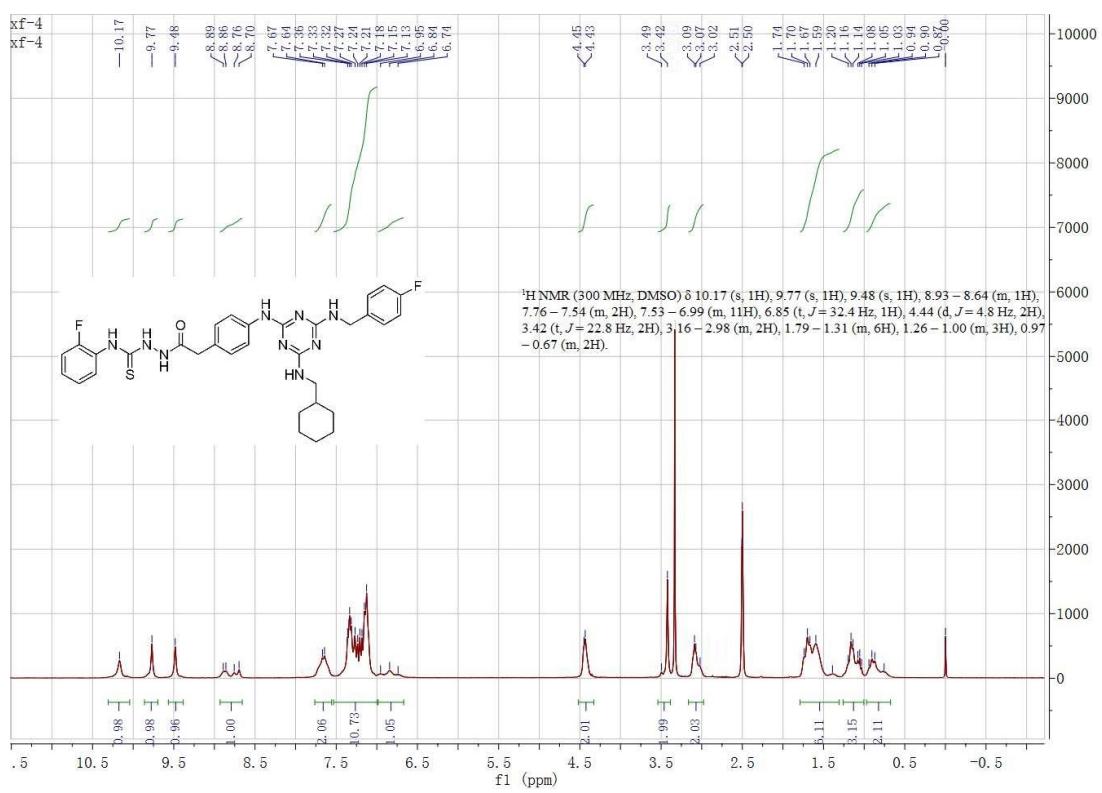




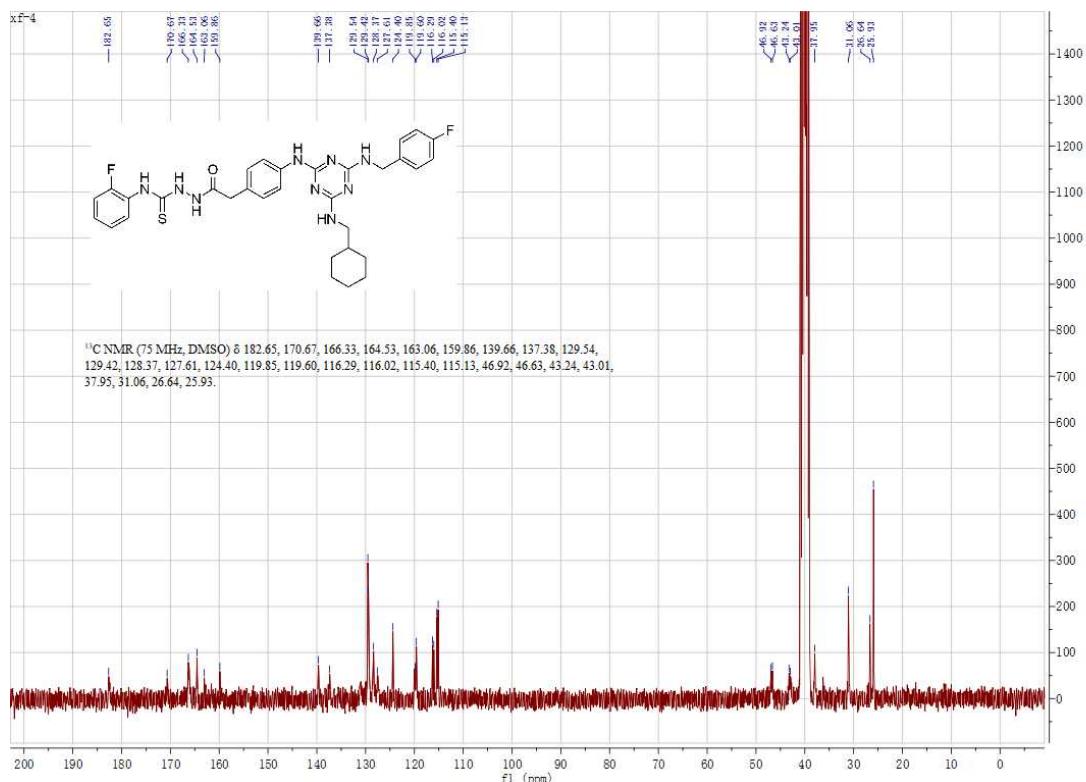
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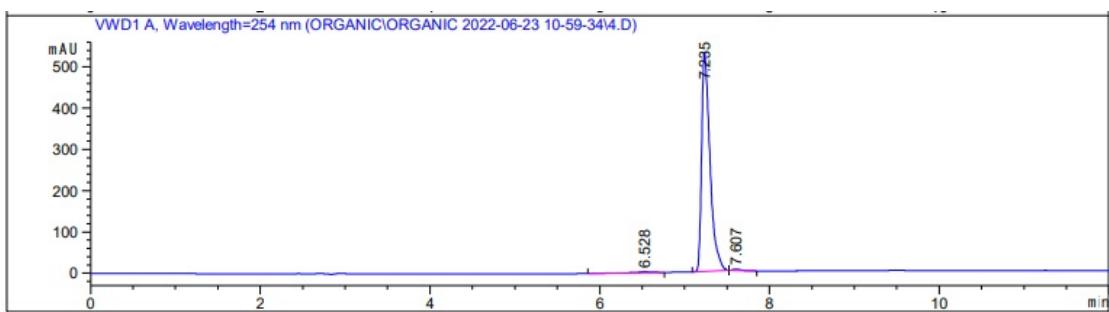
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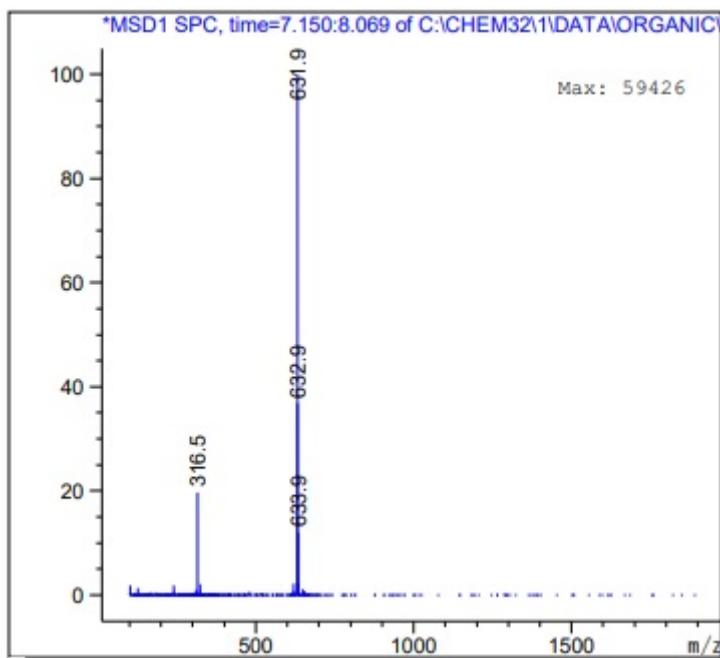
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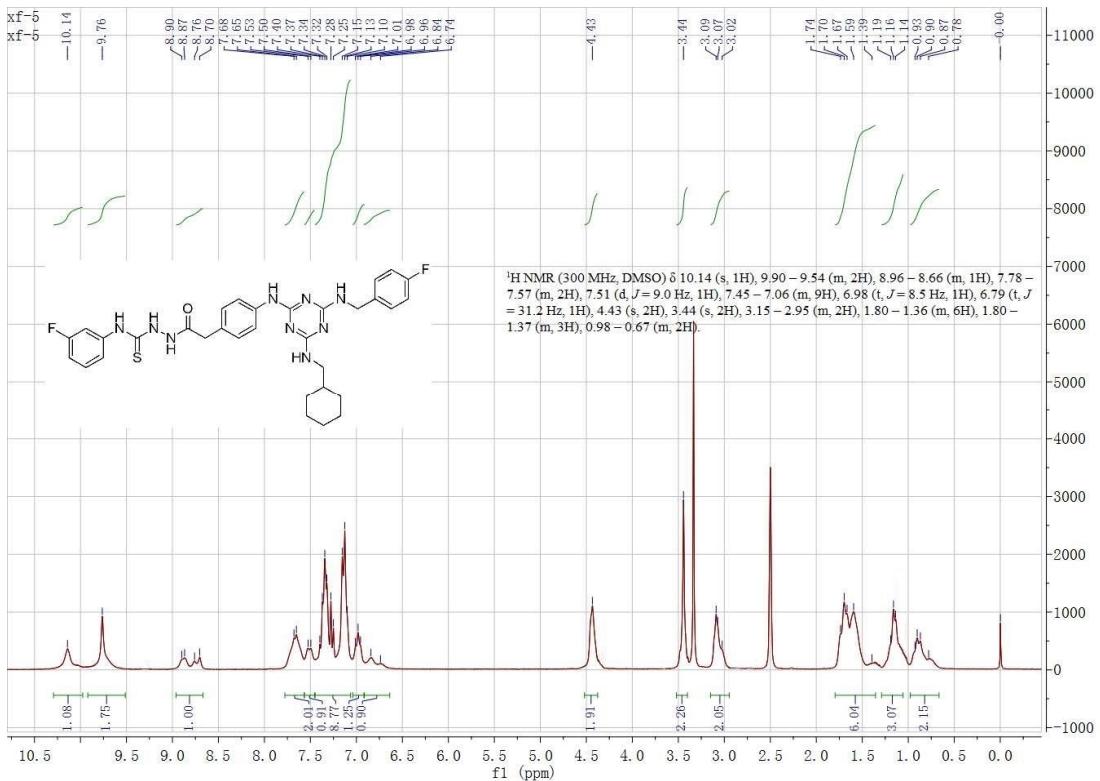
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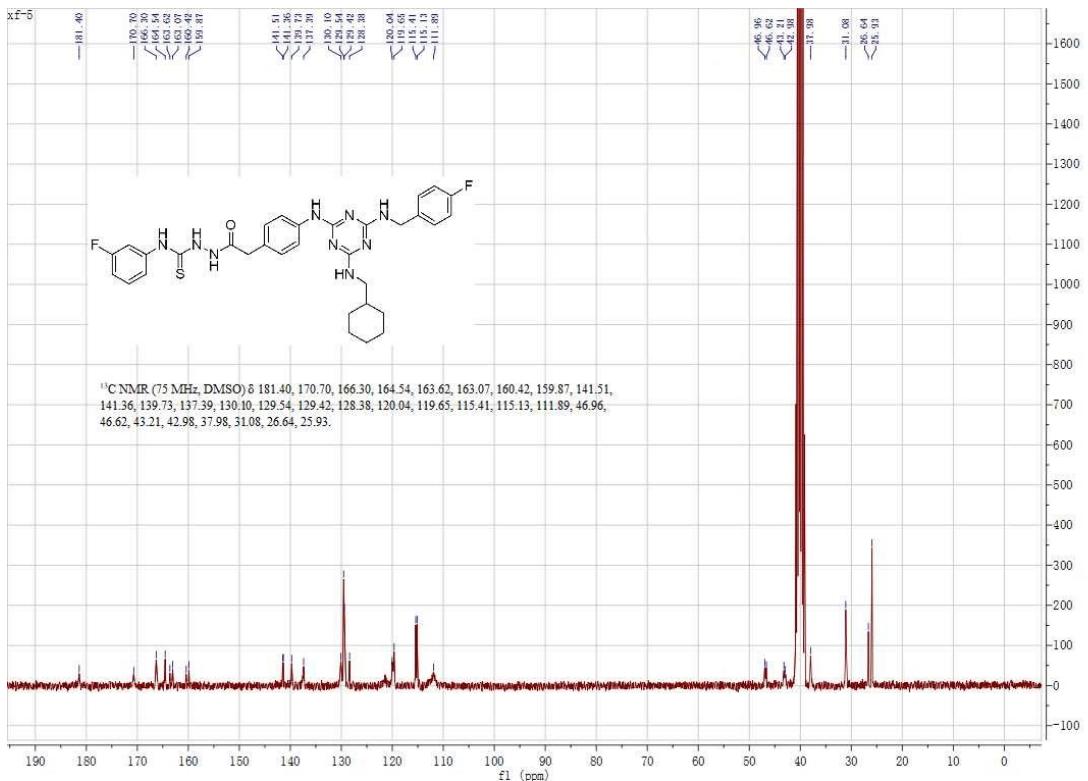
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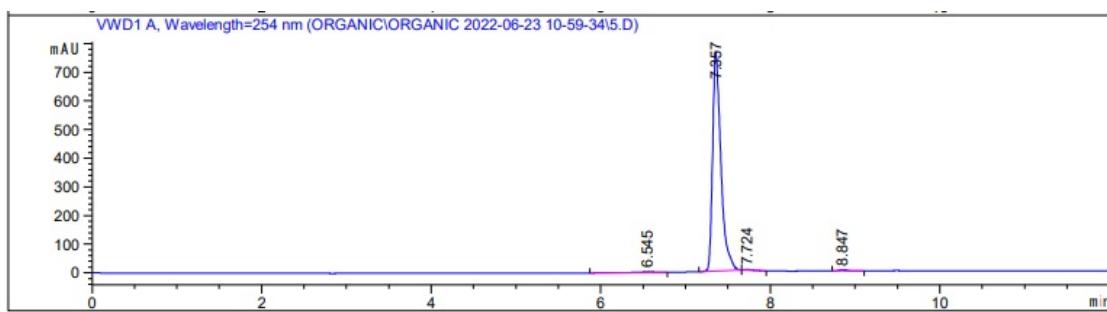
ESI-MS of 10d



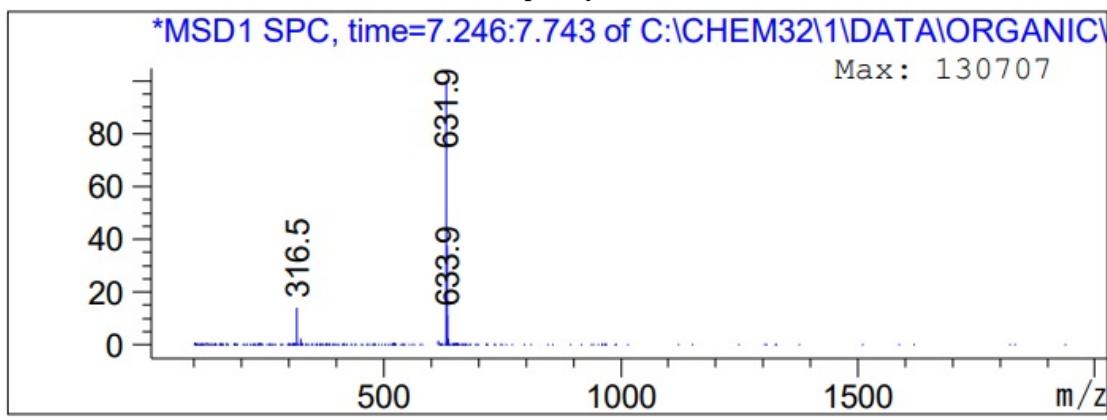
¹H-NMR of 10e



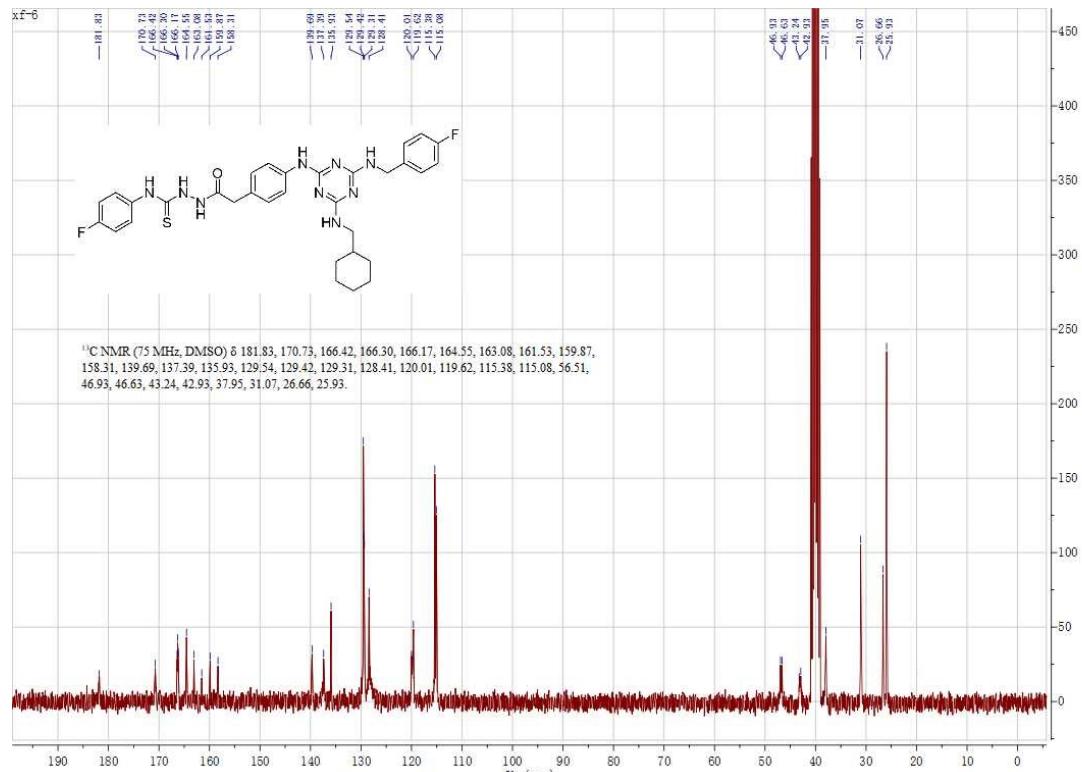
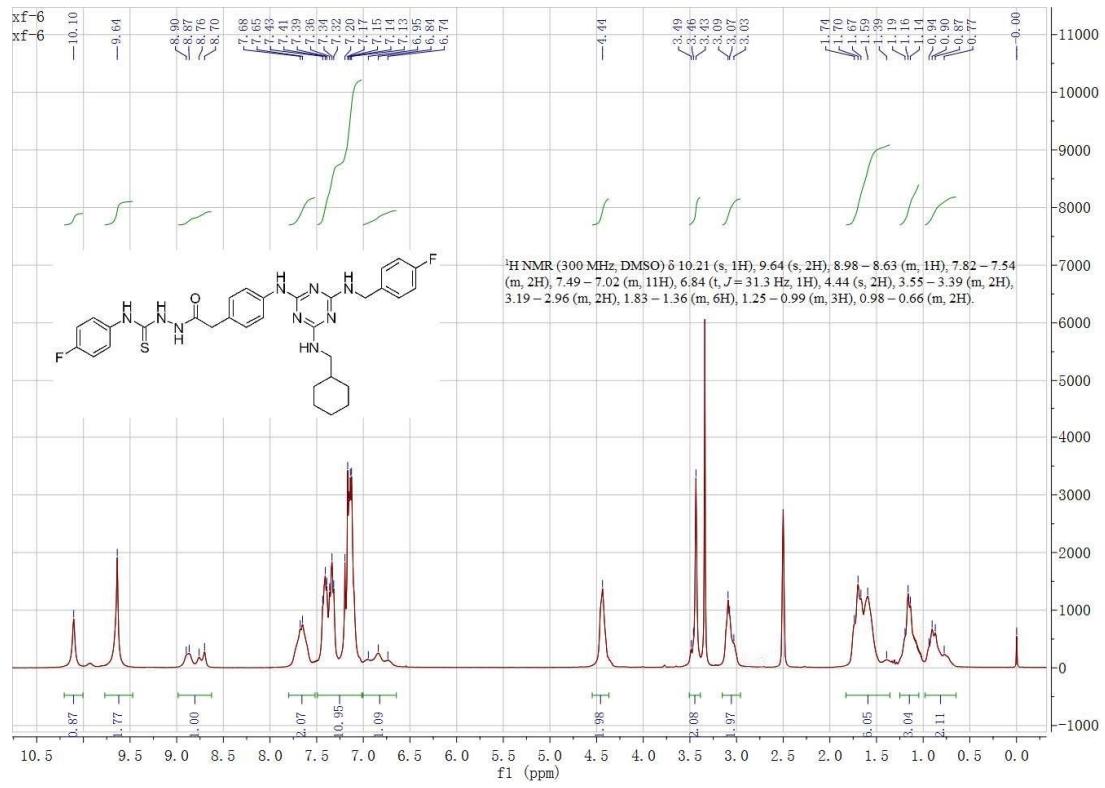
¹³C-NMR of 10e

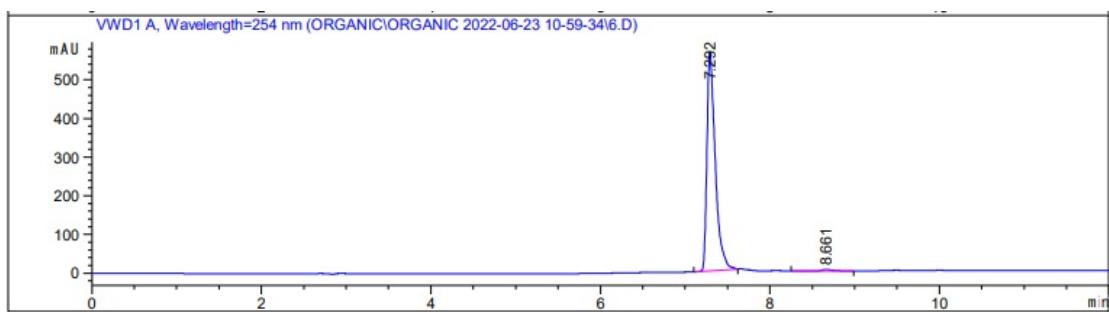


HPLC purity of 10e

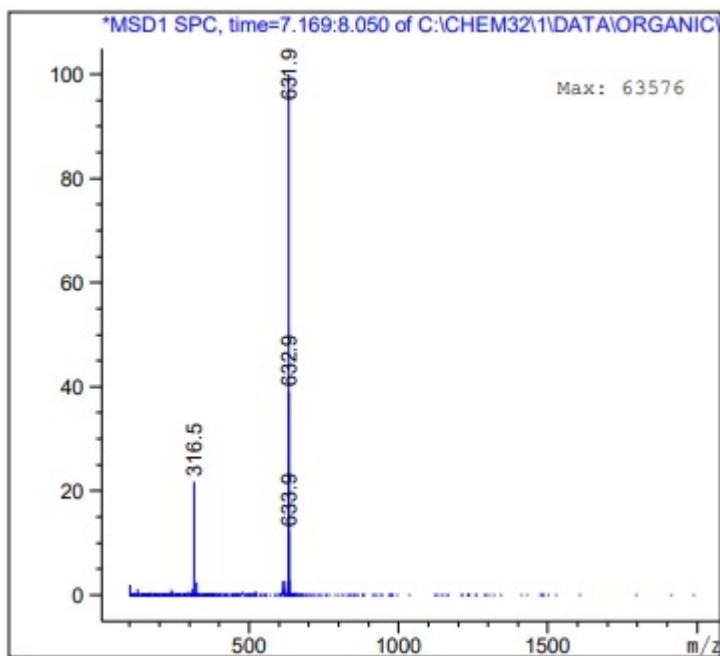


ESI-MS of 10e

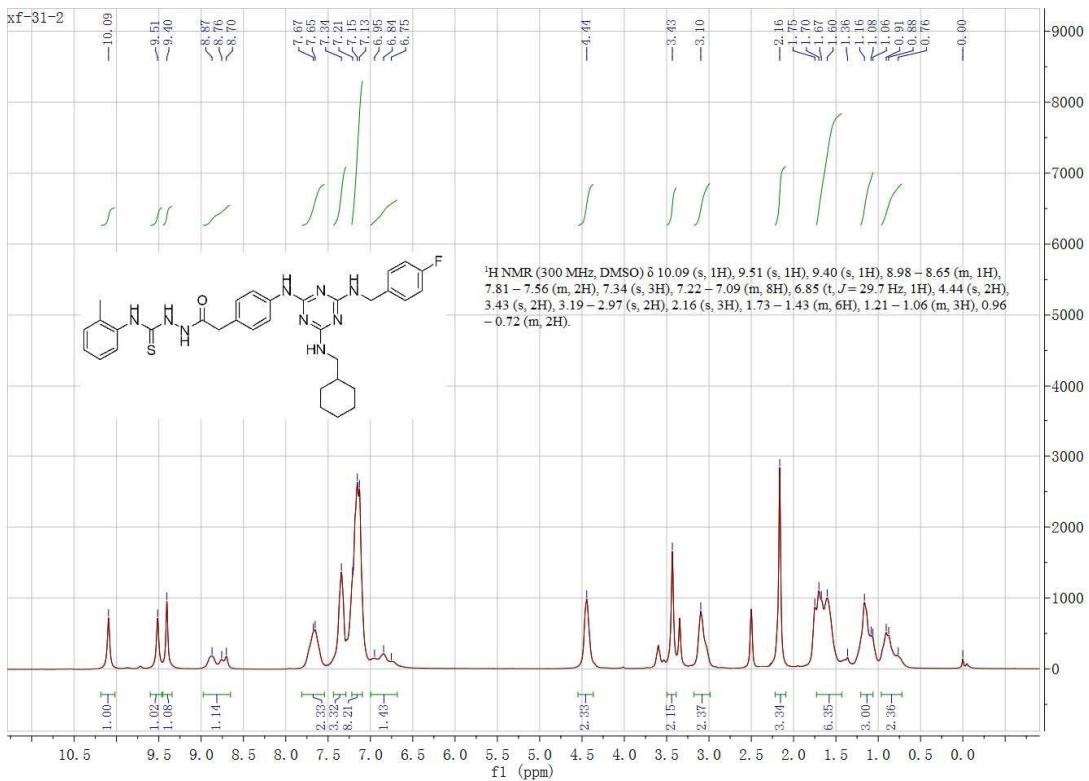




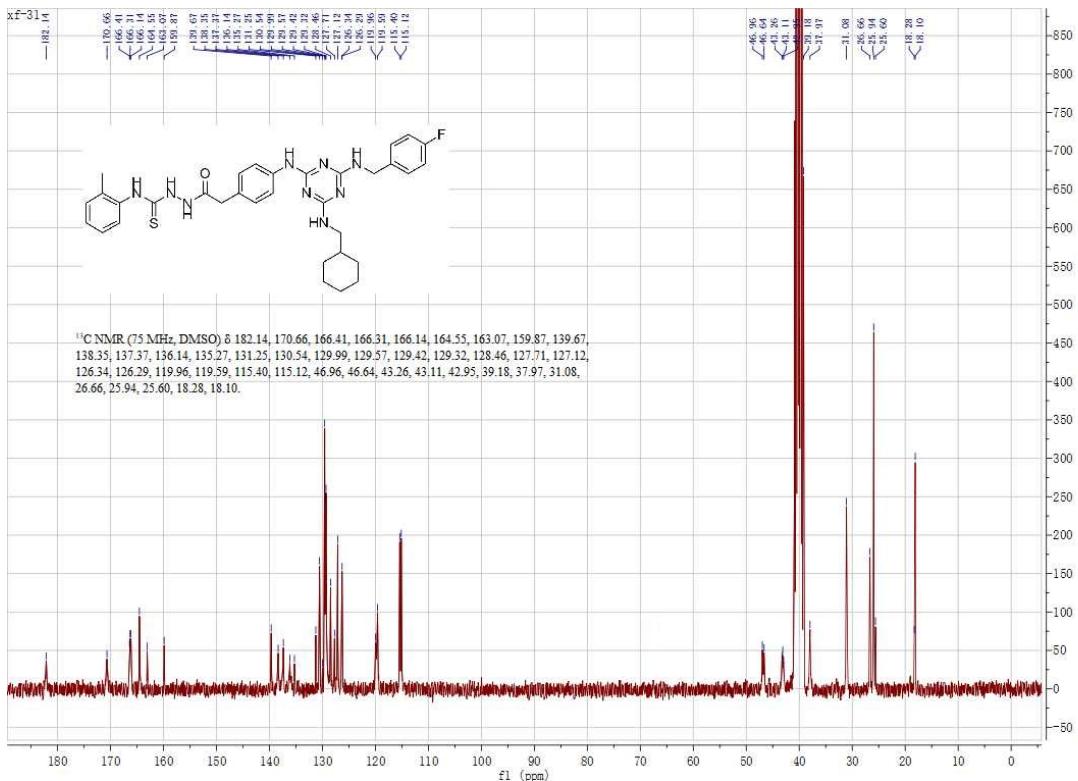
HPLC purity of 10f



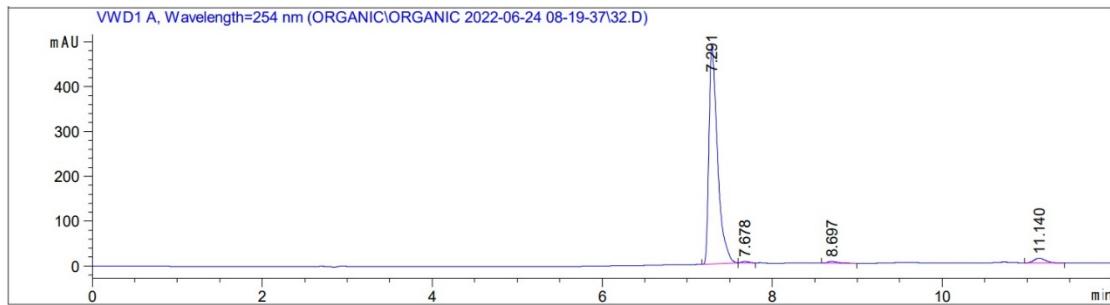
ESI-MS of 10f



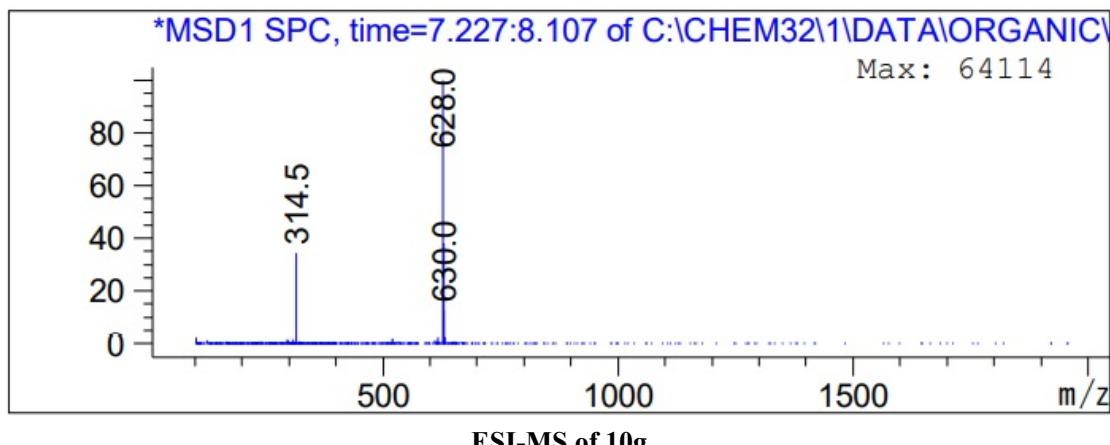
¹H-NMR of 10g



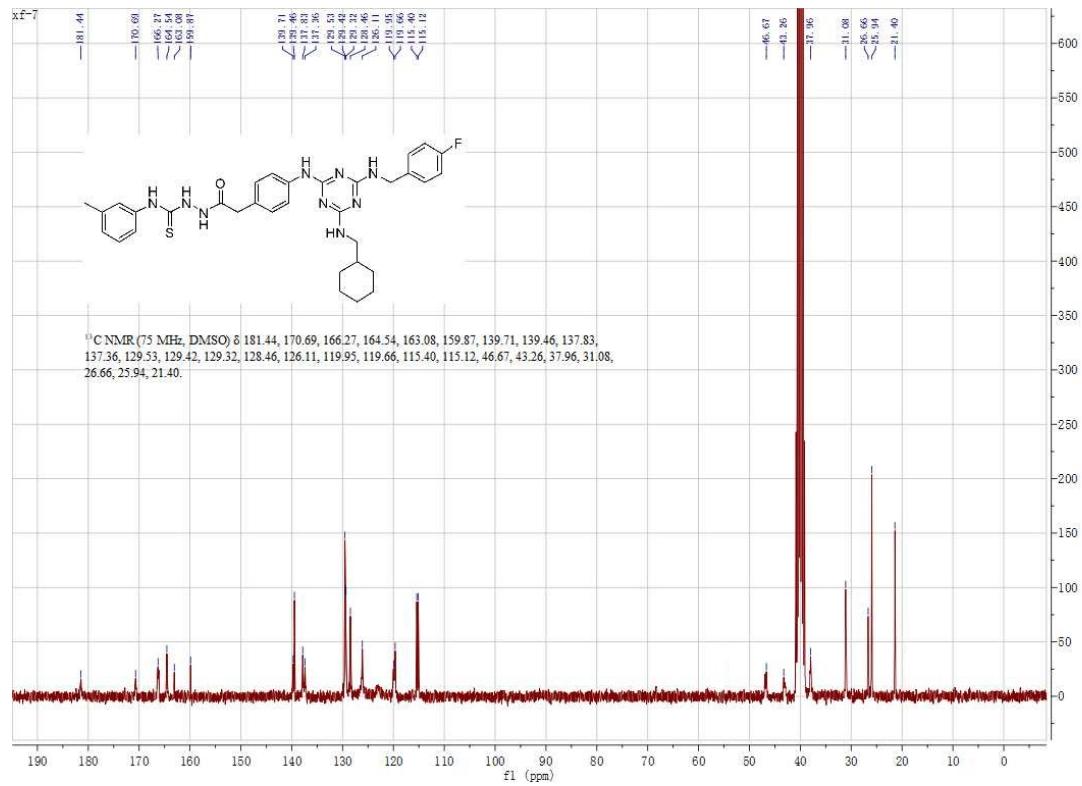
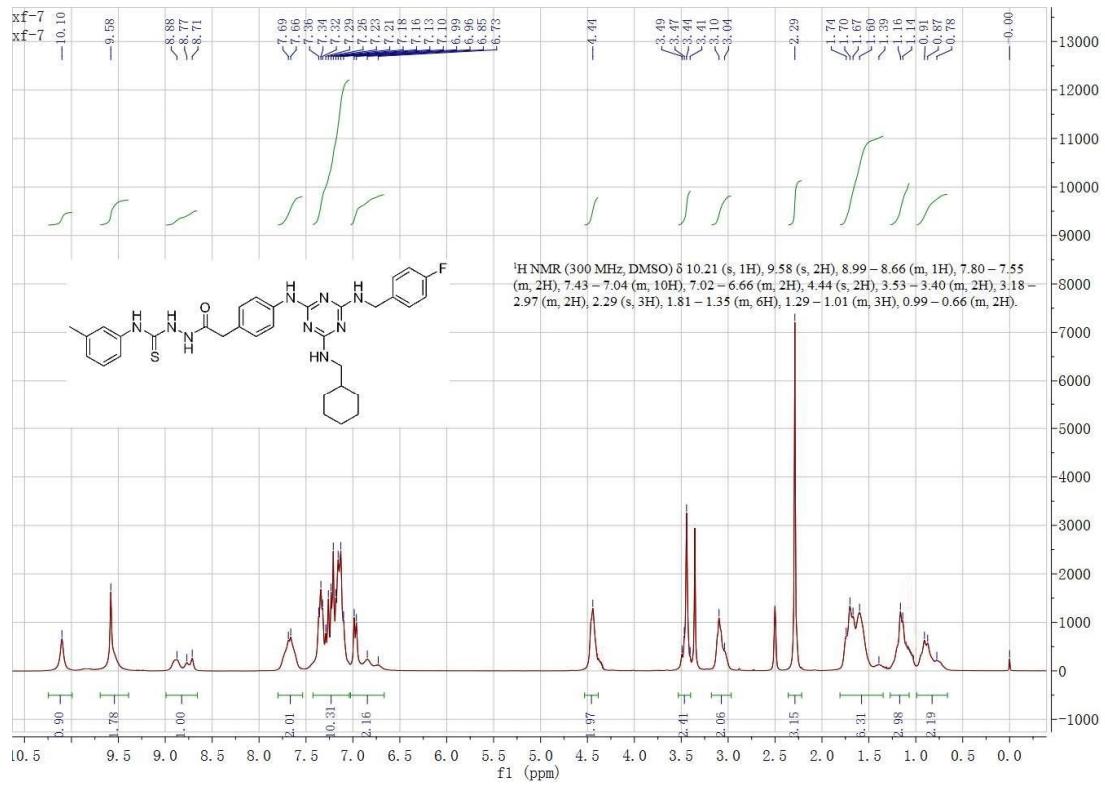
¹³C-NMR of 10g

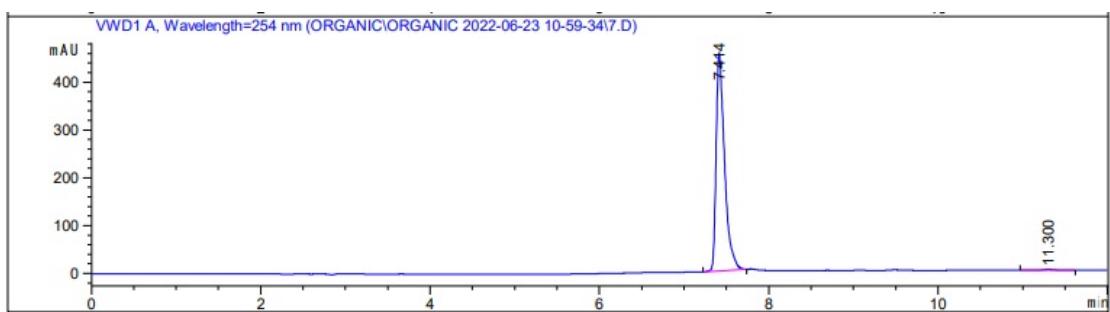


HPLC purity of 10g

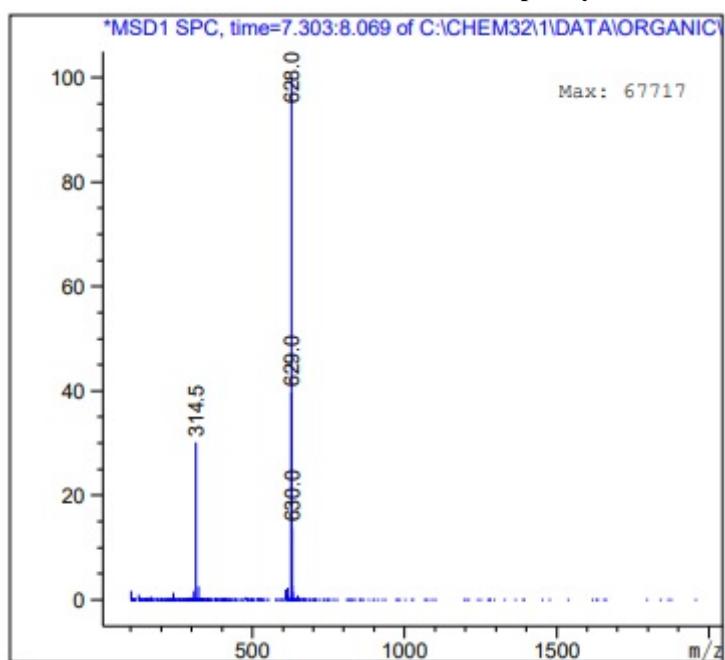


ESI-MS of 10g

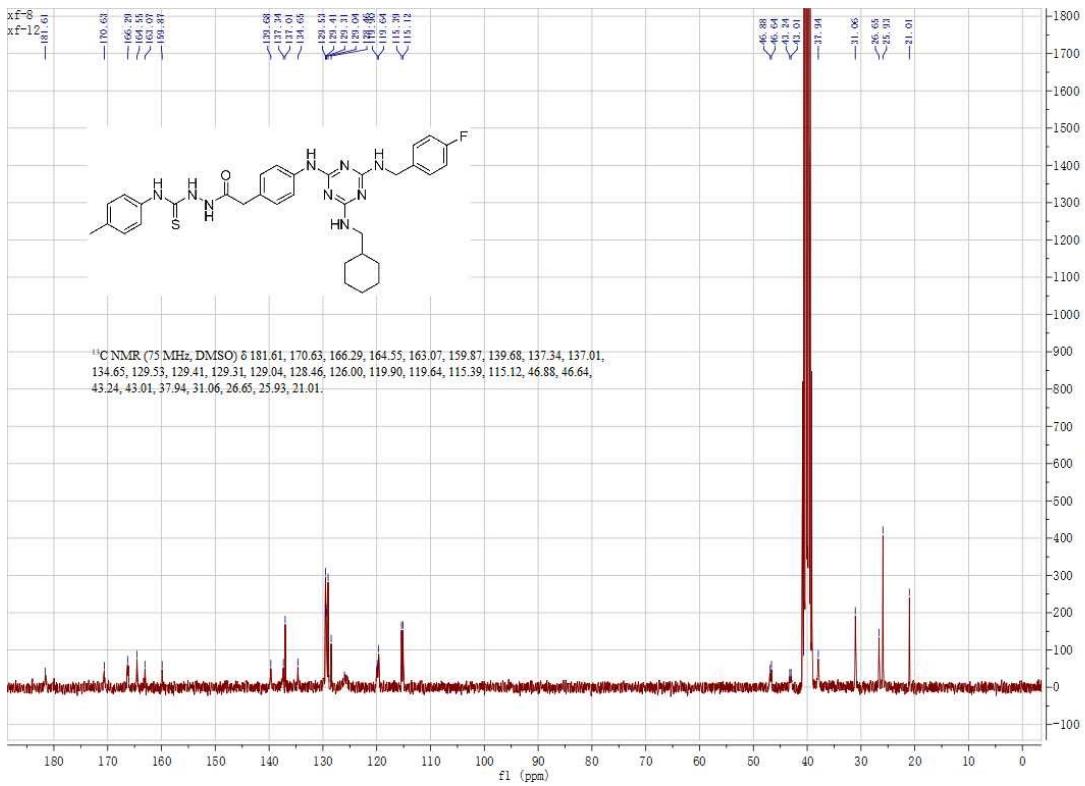
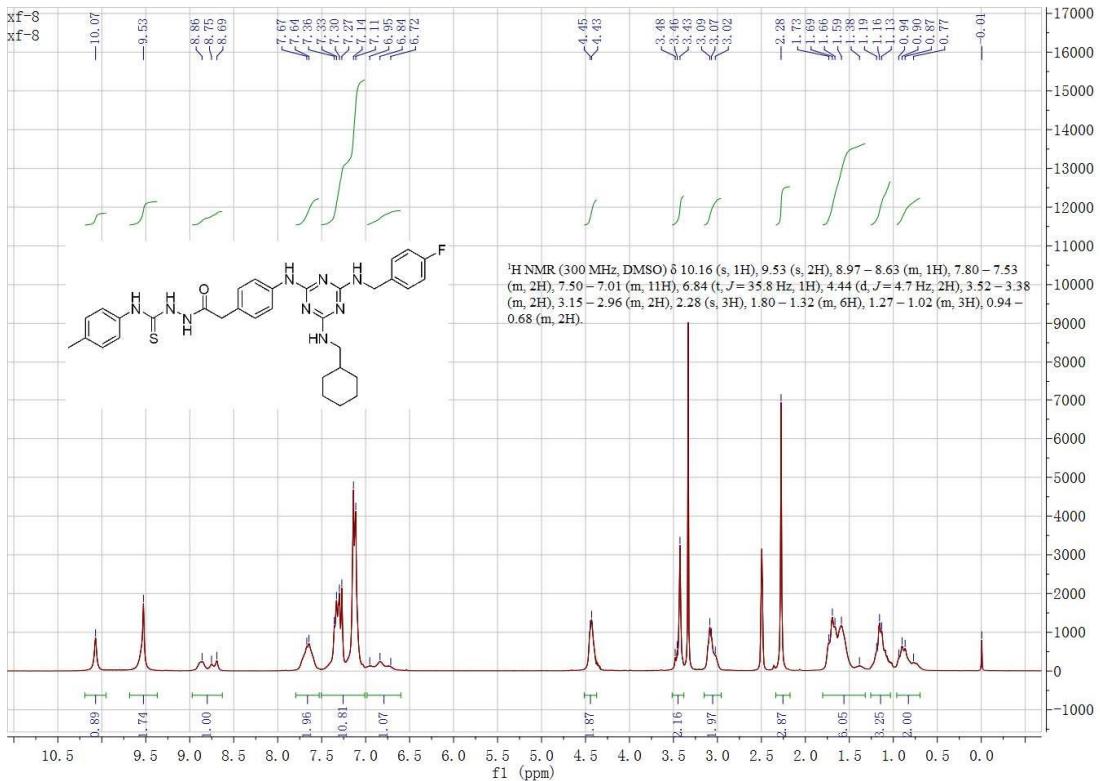


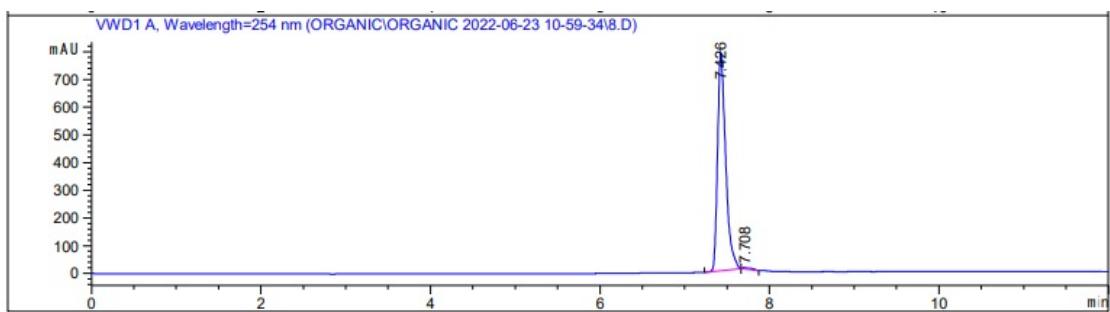


HPLC purity of 10h

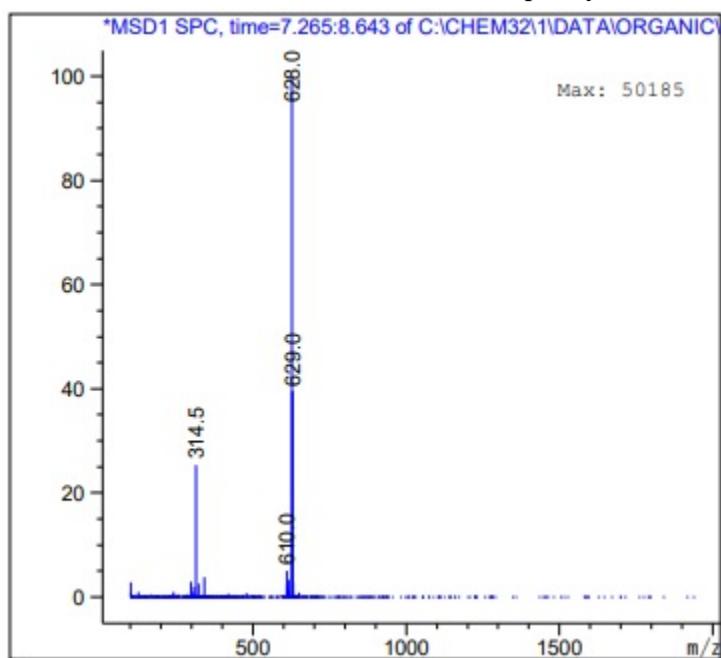


ESI-MS of 10h

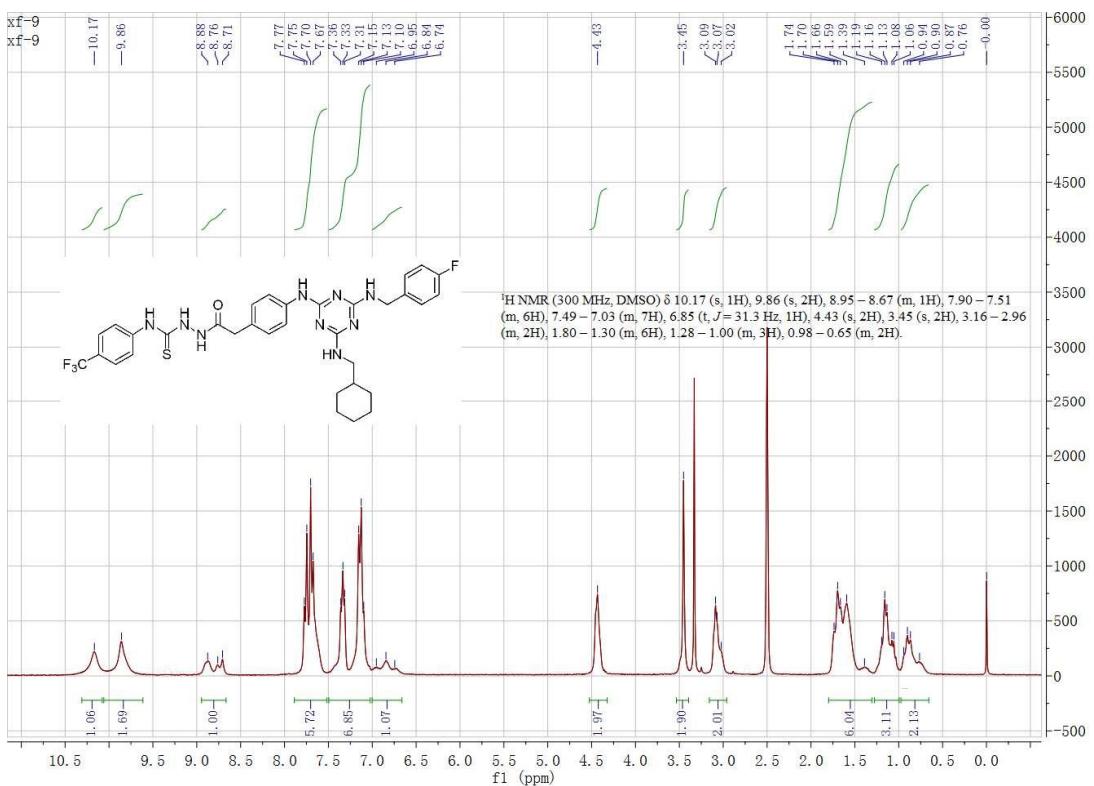




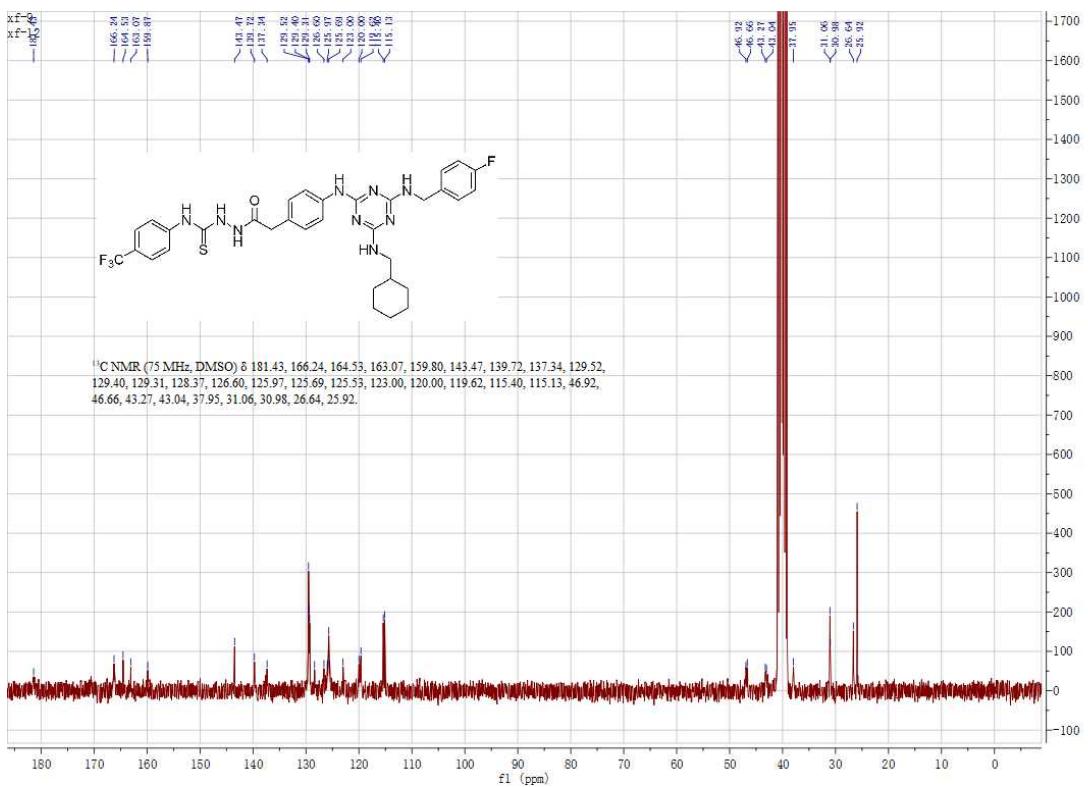
HPLC purity of 10i



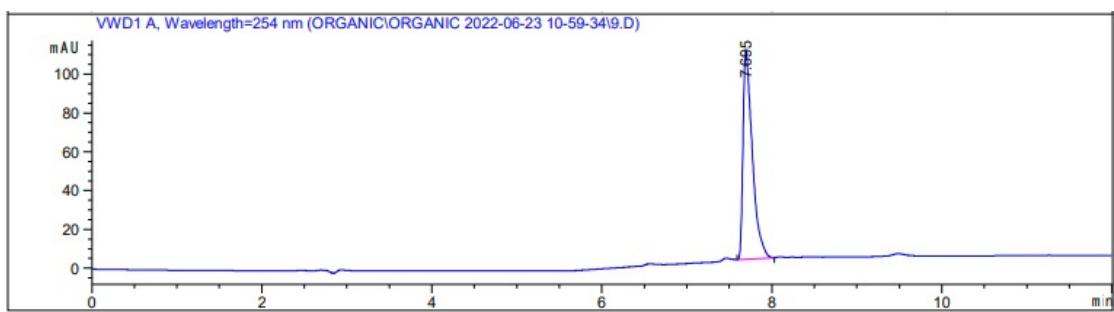
ESI-MS of 10i



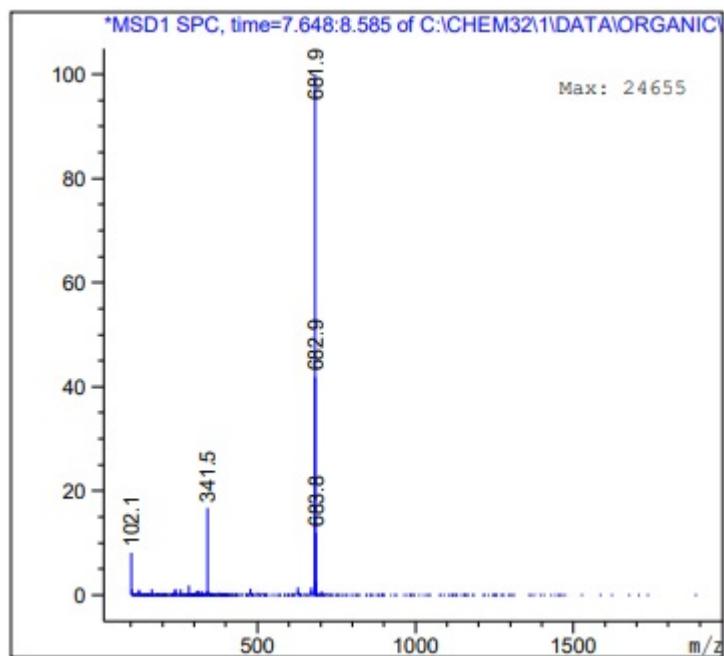
¹H-NMR of 10j



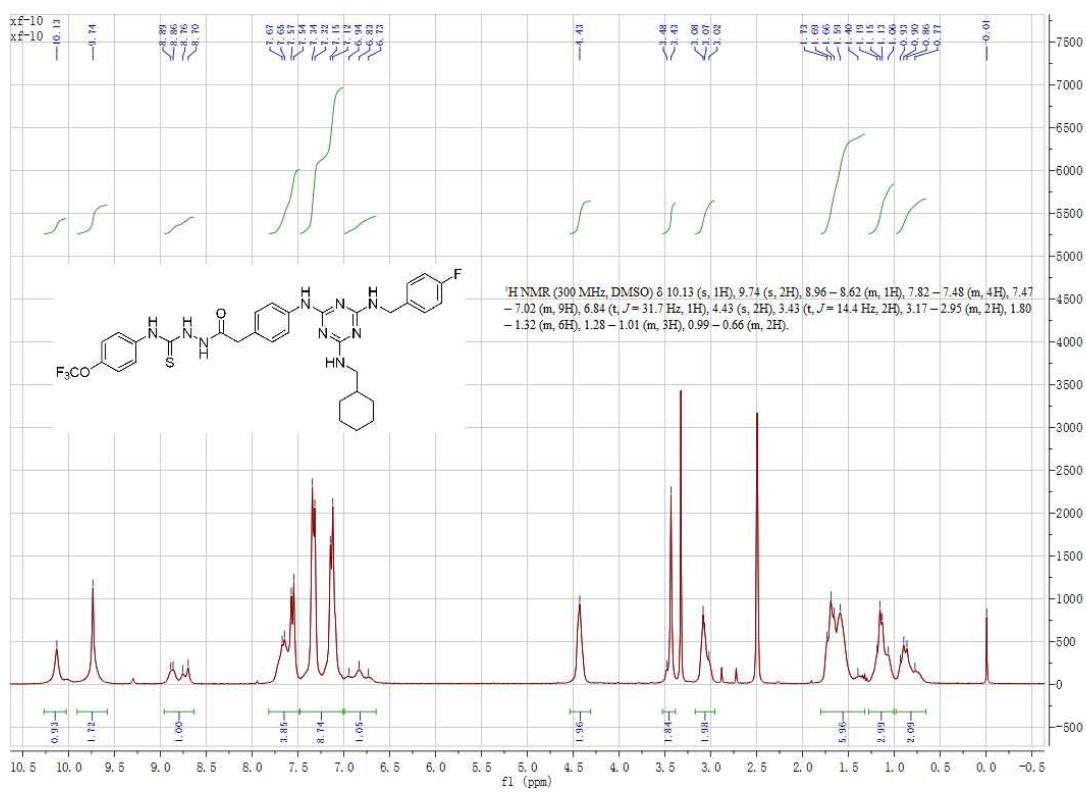
¹³C-NMR of 10j



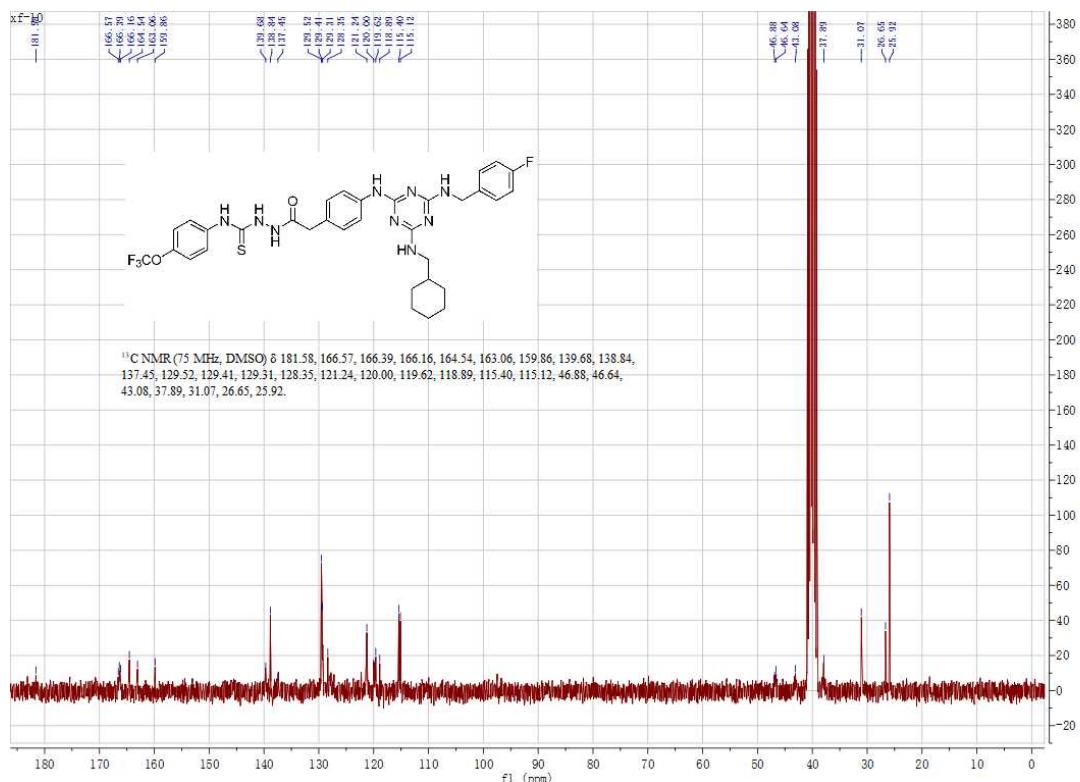
HPLC purity of 10j



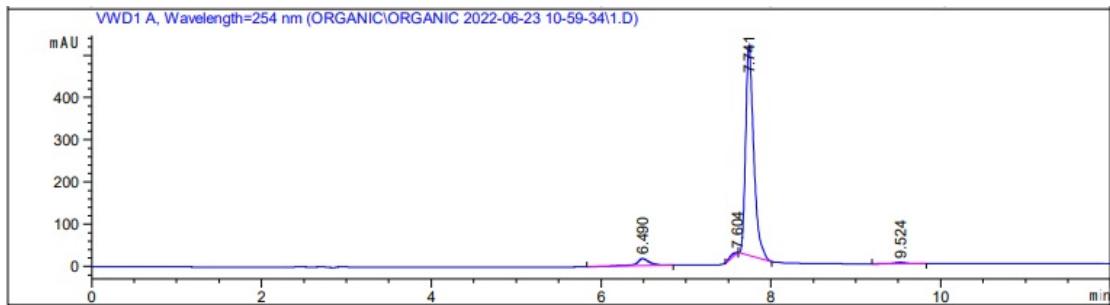
ESI-MS of 10j



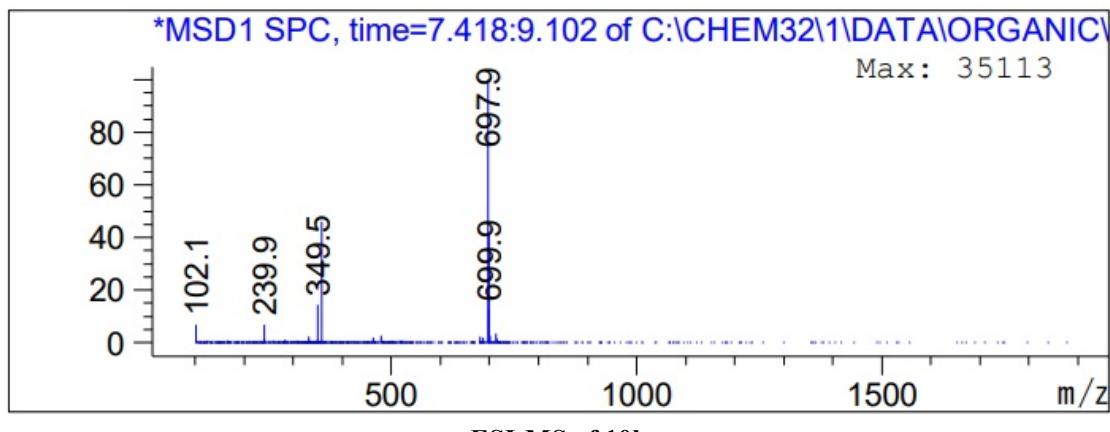
¹H-NMR of 10k



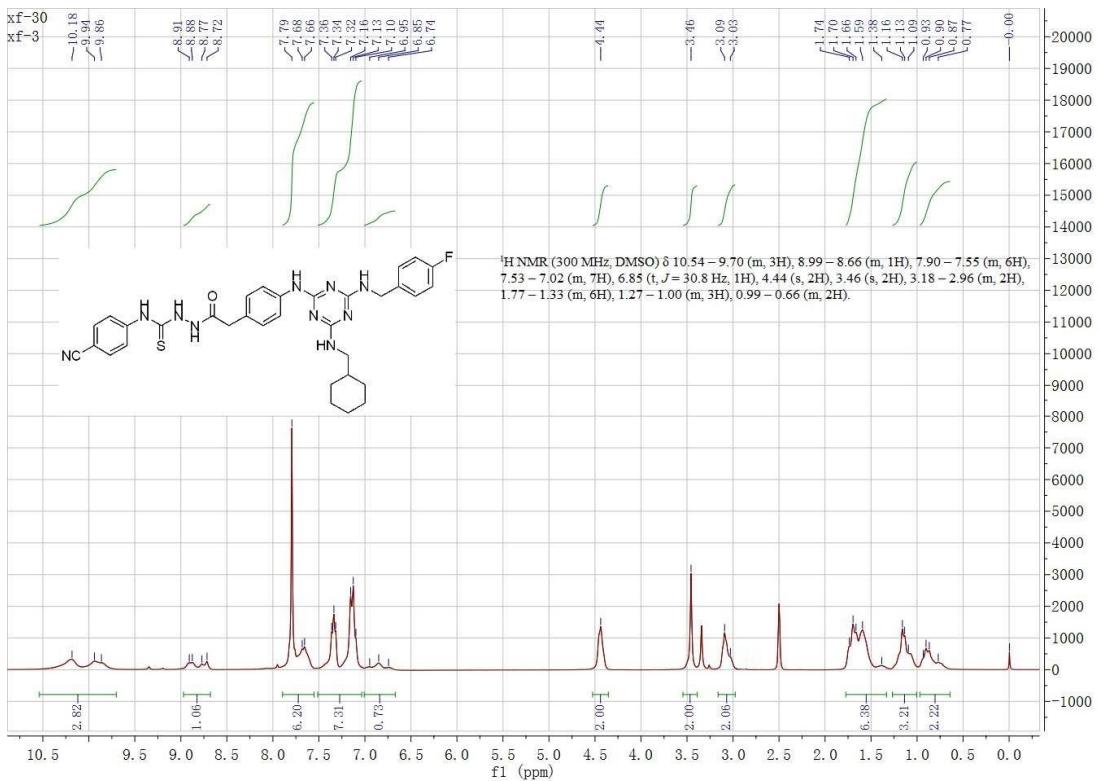
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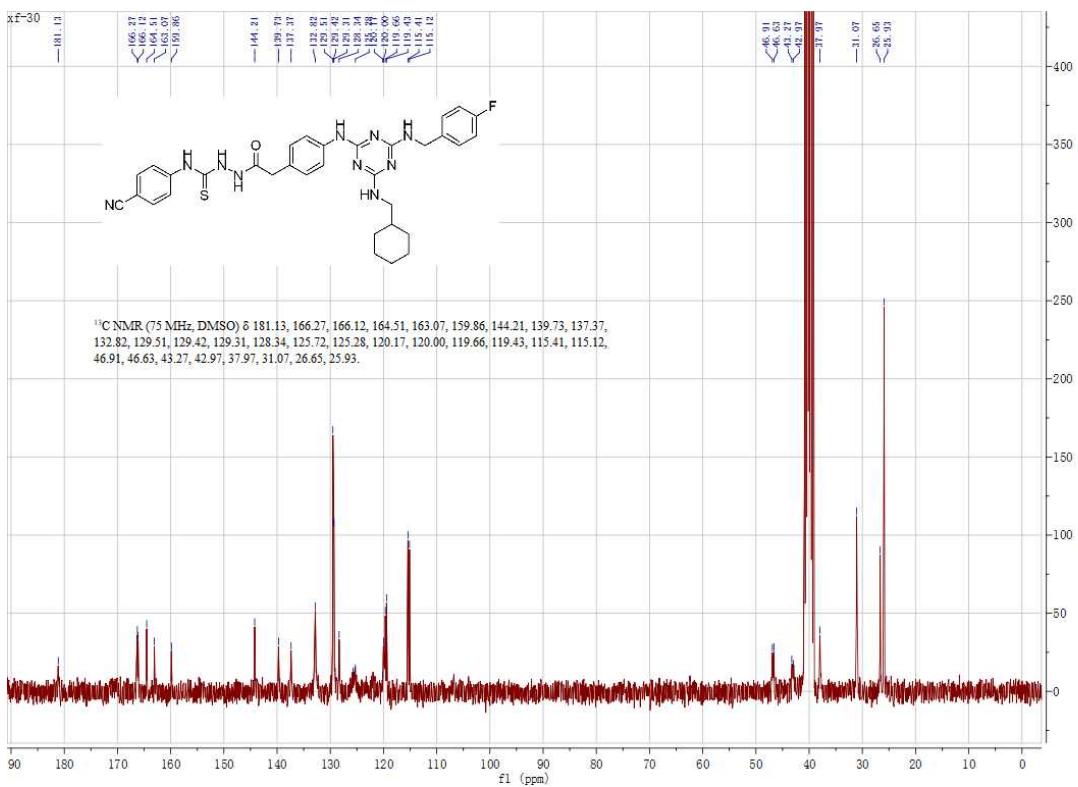
HPLC purity of 10k



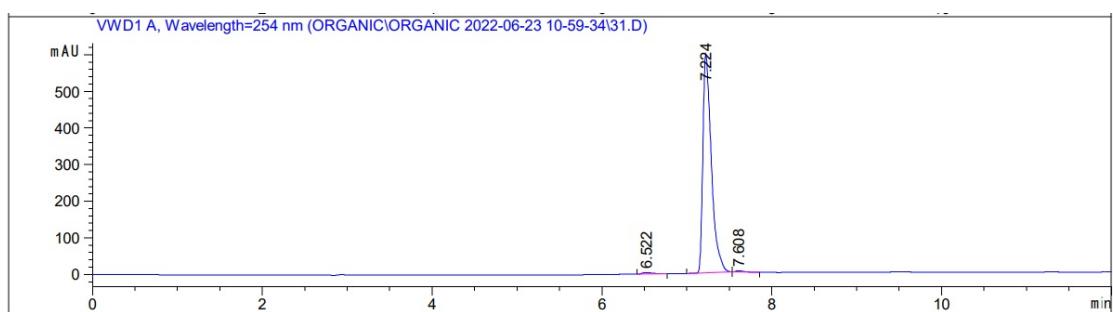
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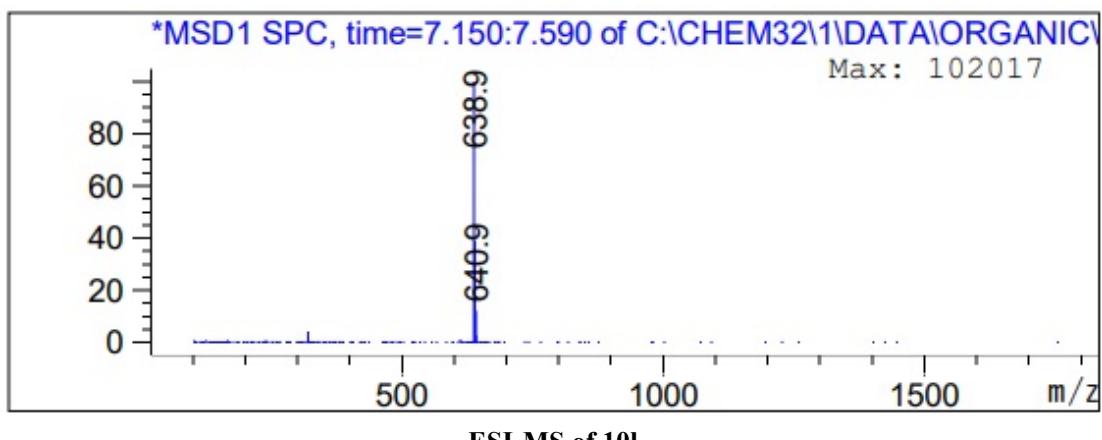
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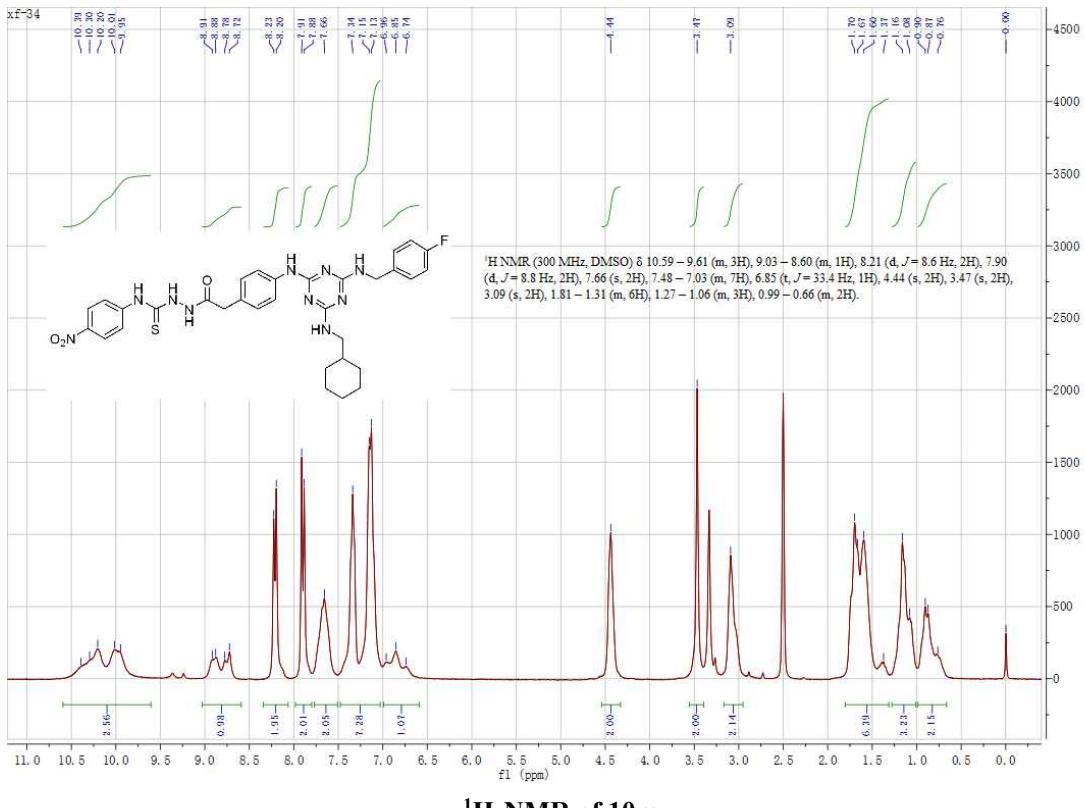
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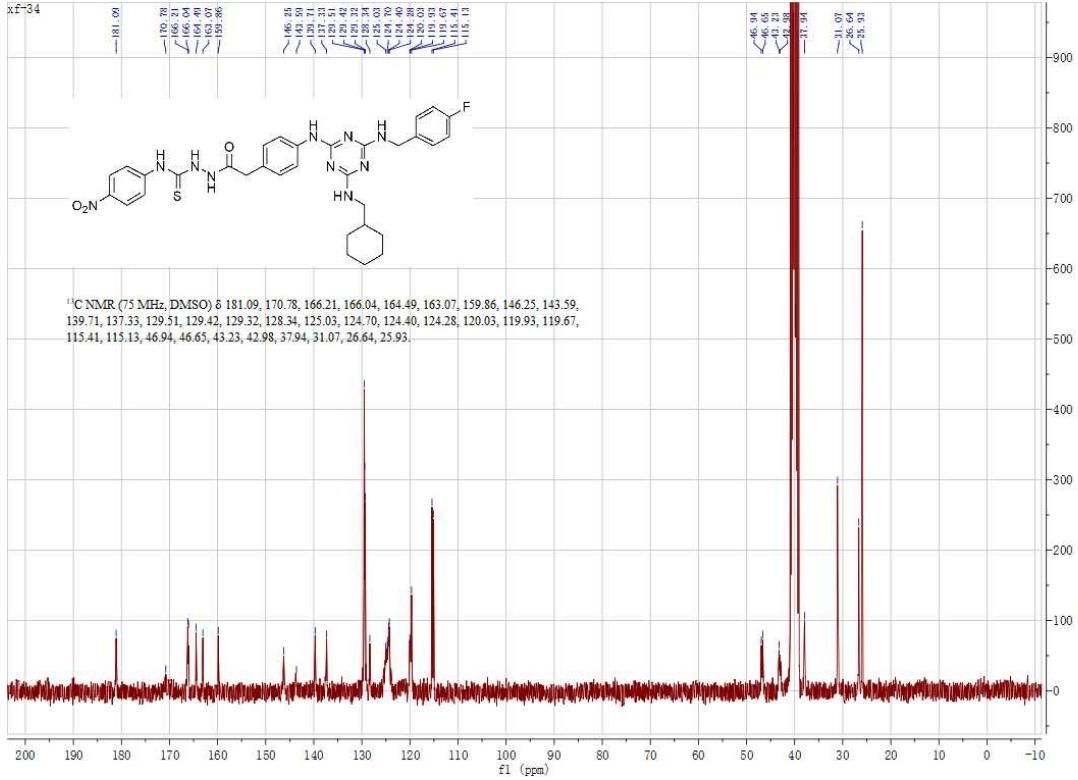
HPLC purity of 10l



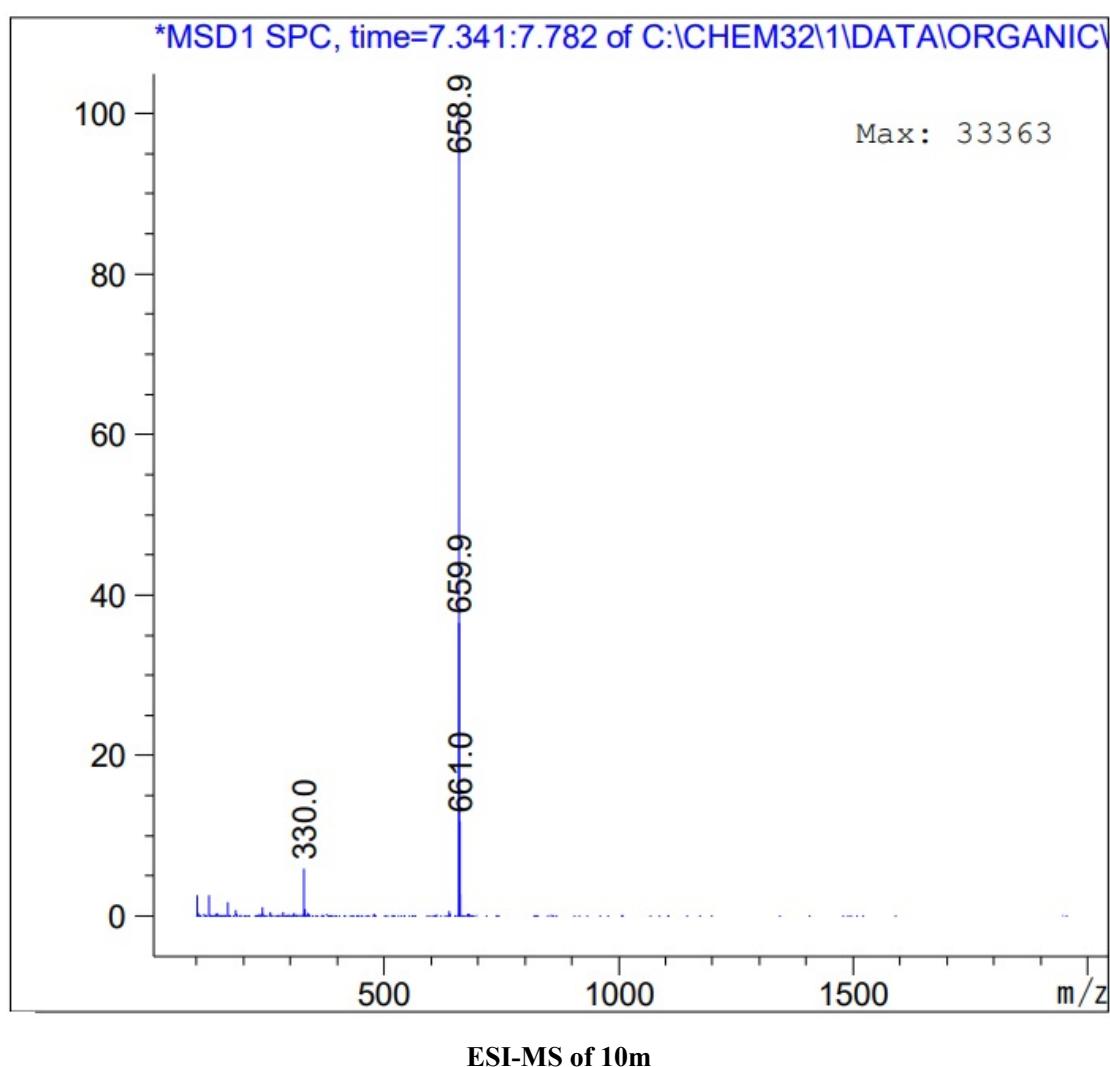
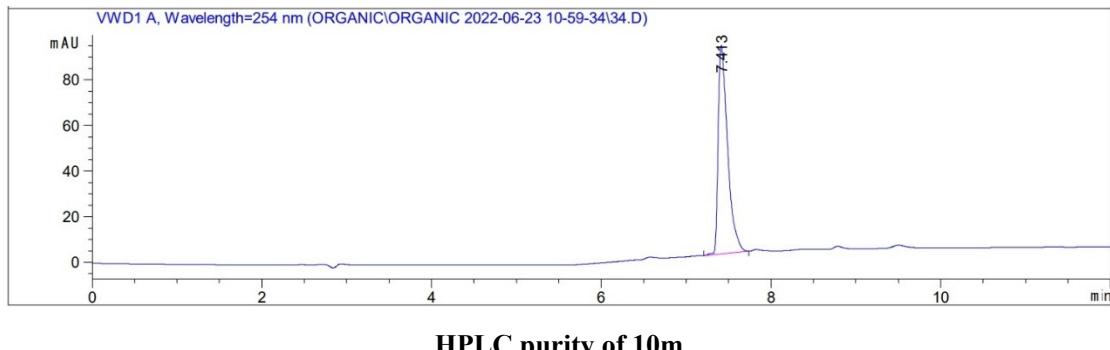
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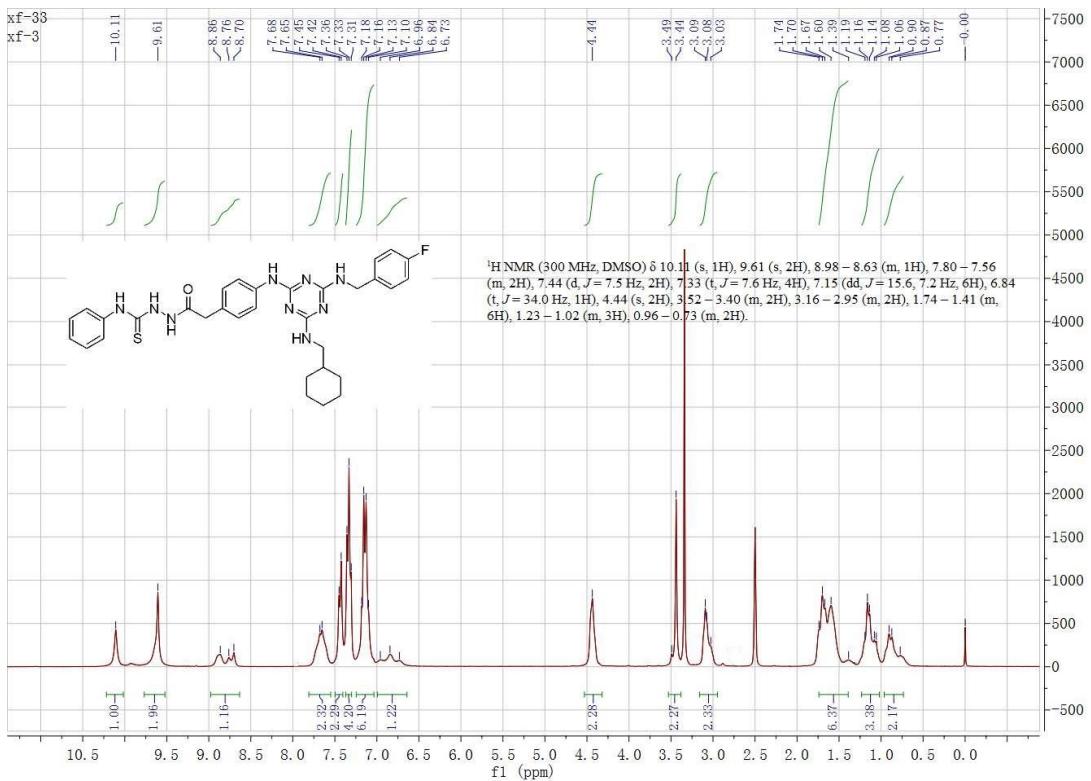


¹H-NMR of 10m

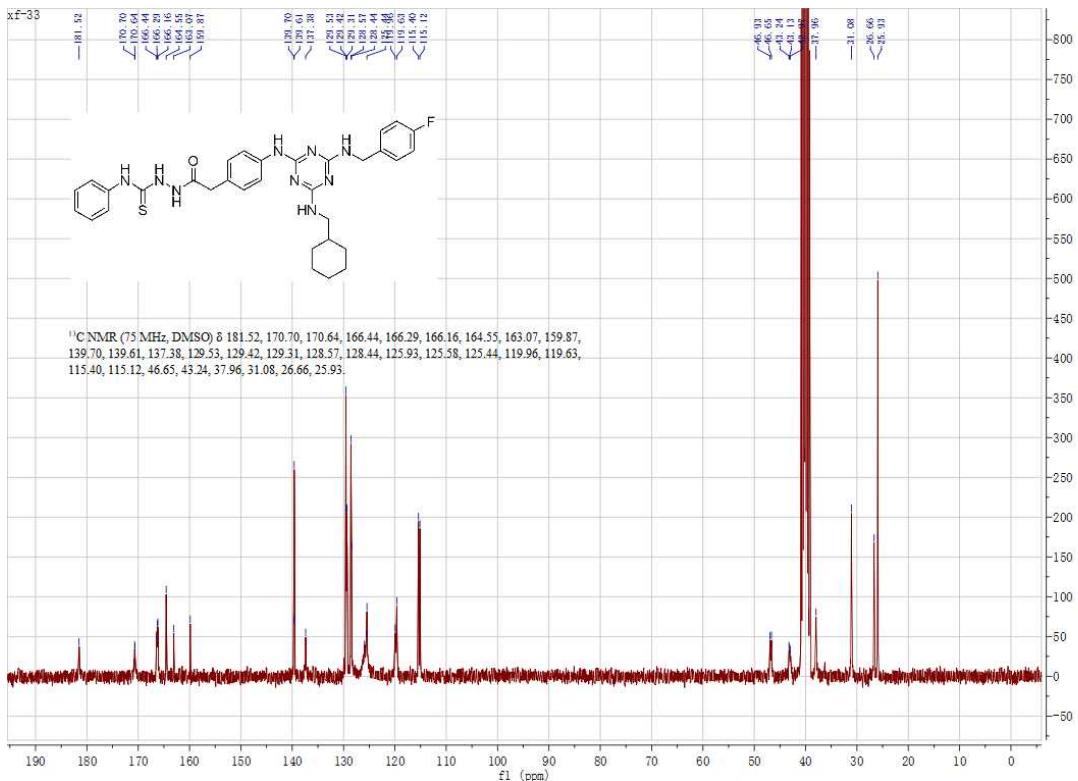


¹³C-NMR of 10m

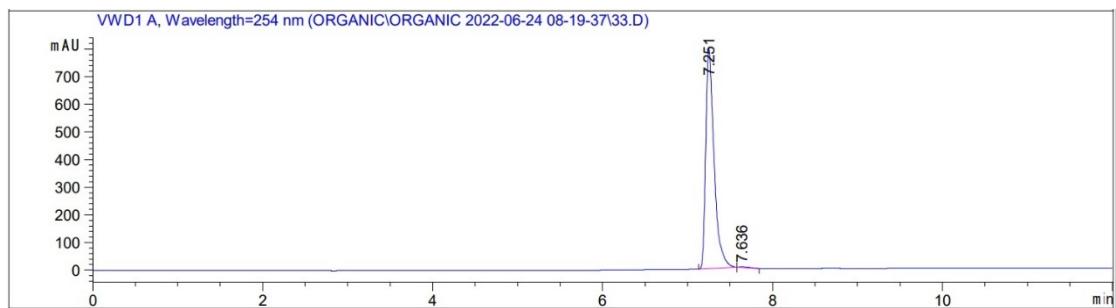




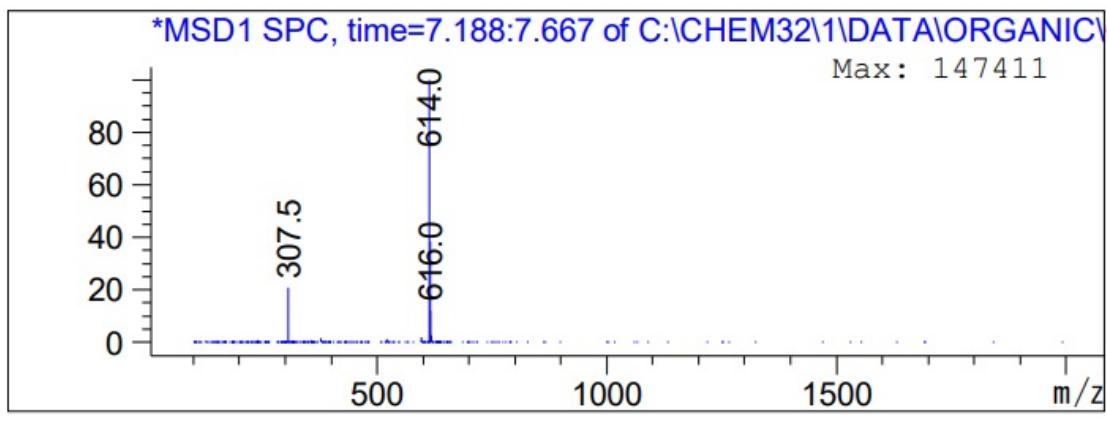
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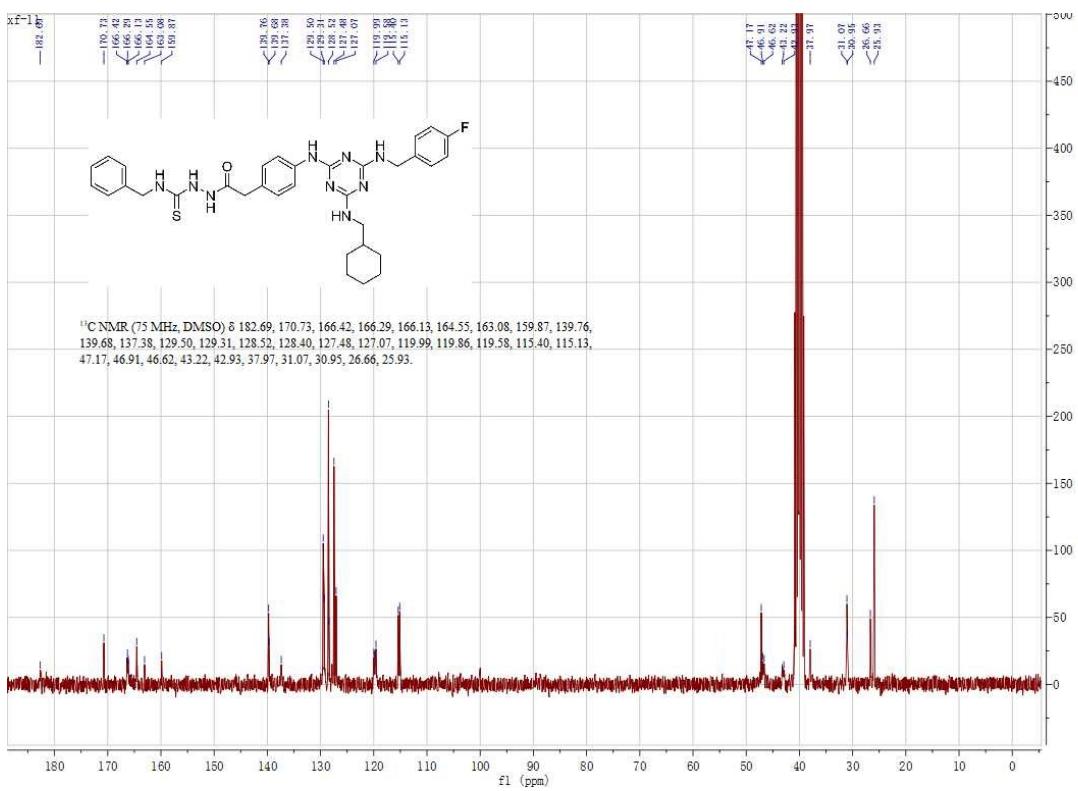
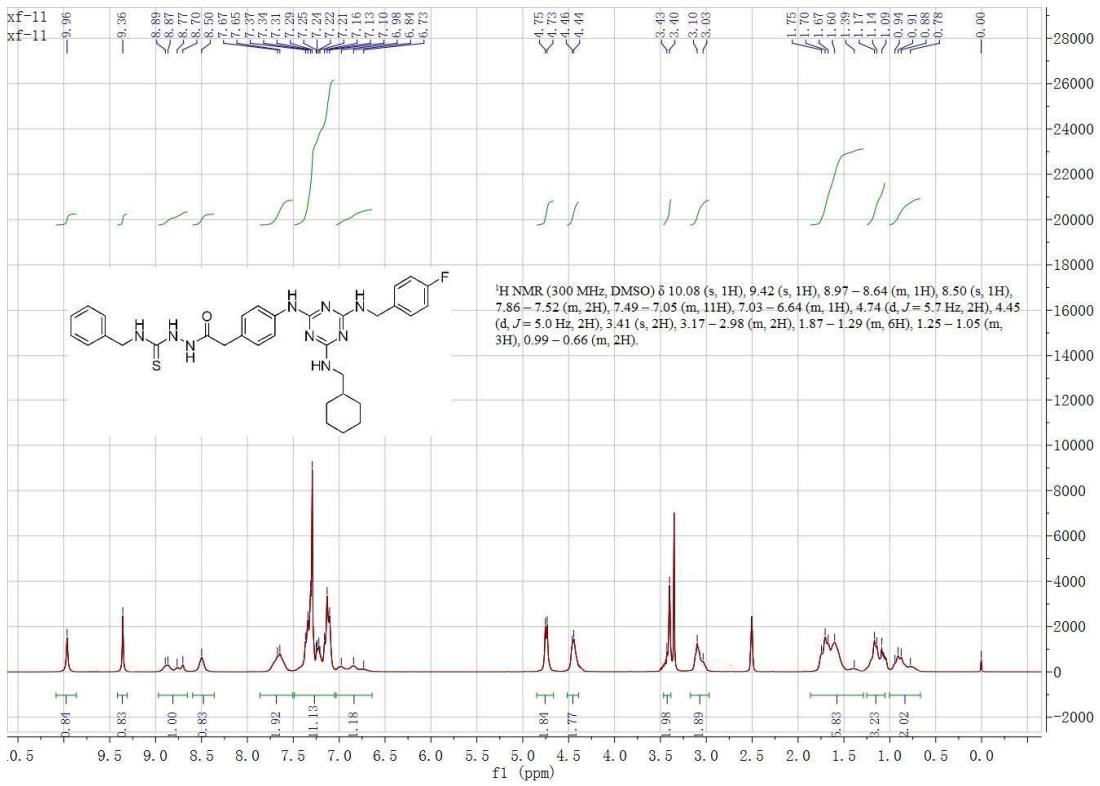
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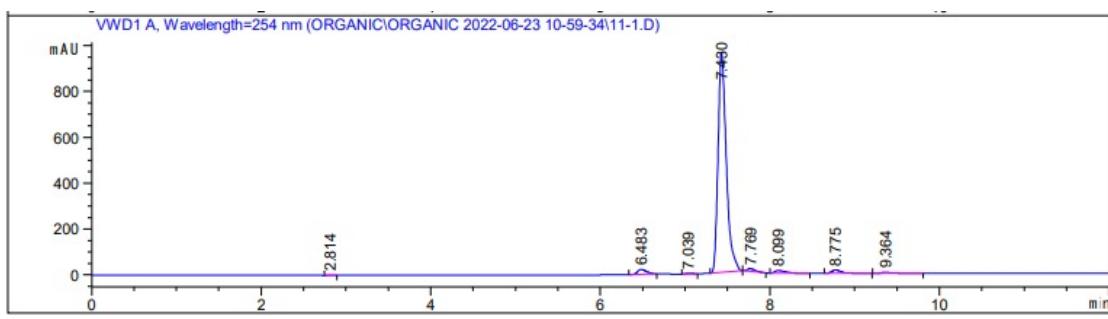


HPLC purity of 10n

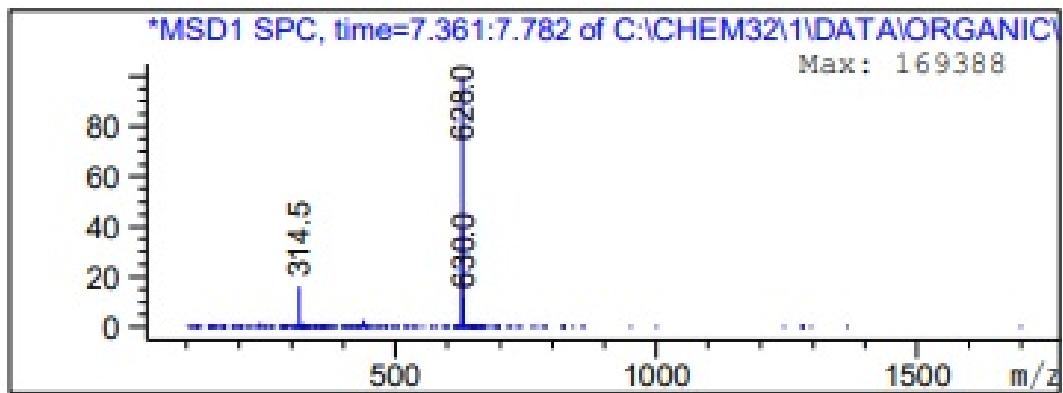


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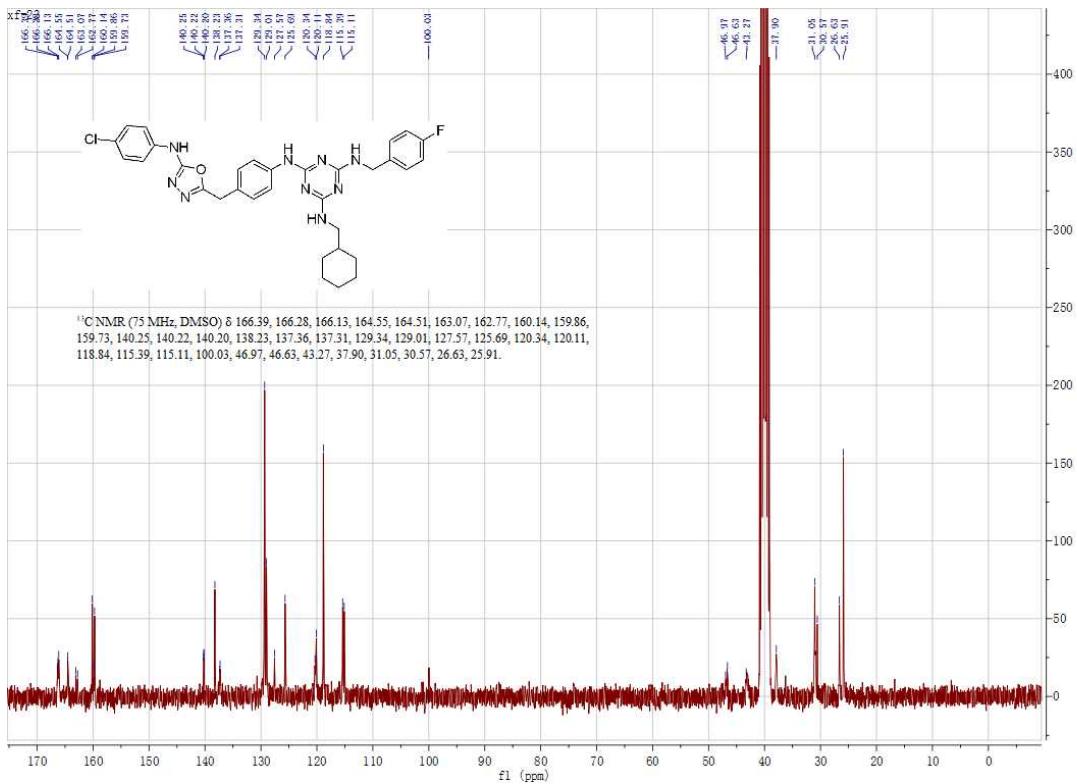
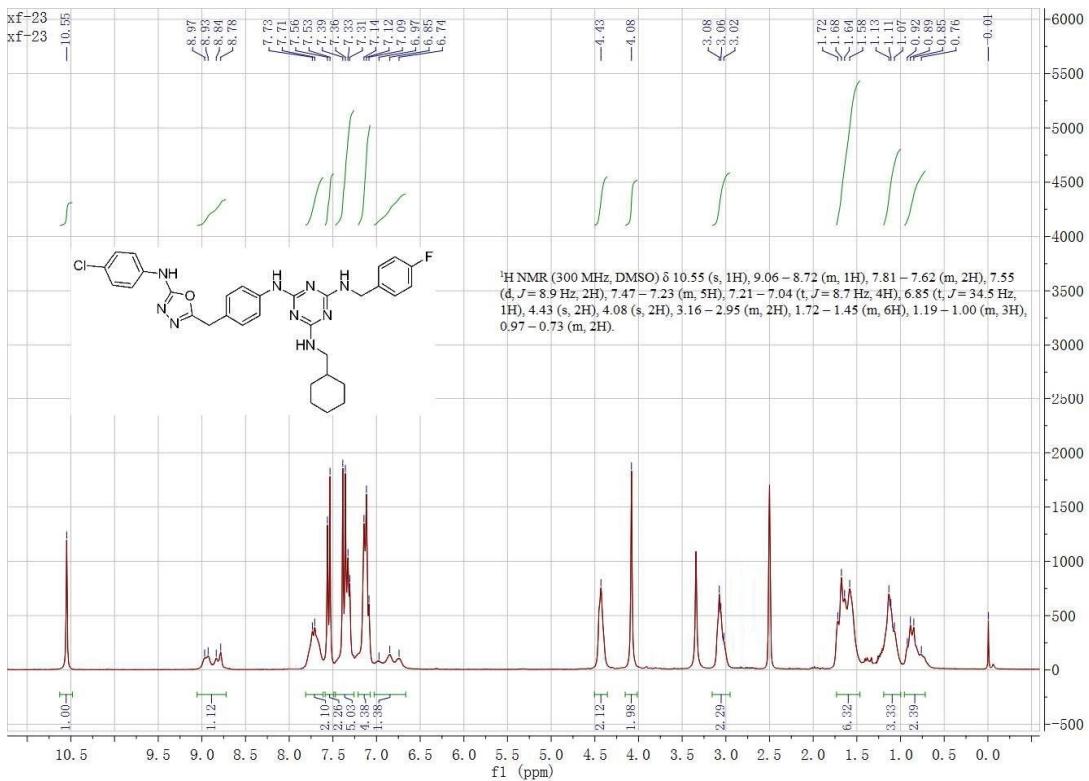


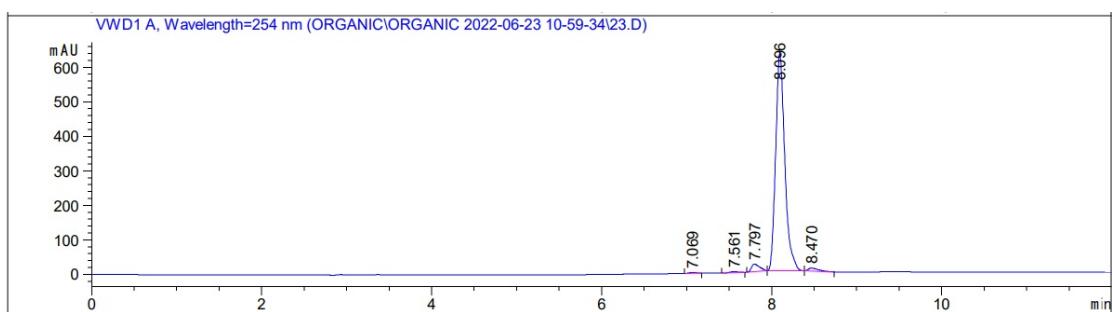


HPLC purity of 10o

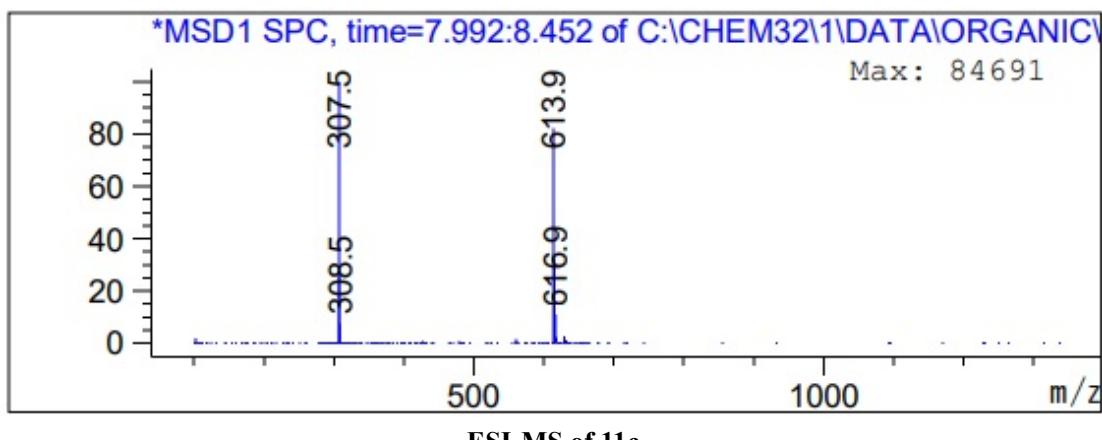


ESI-MS of 10o

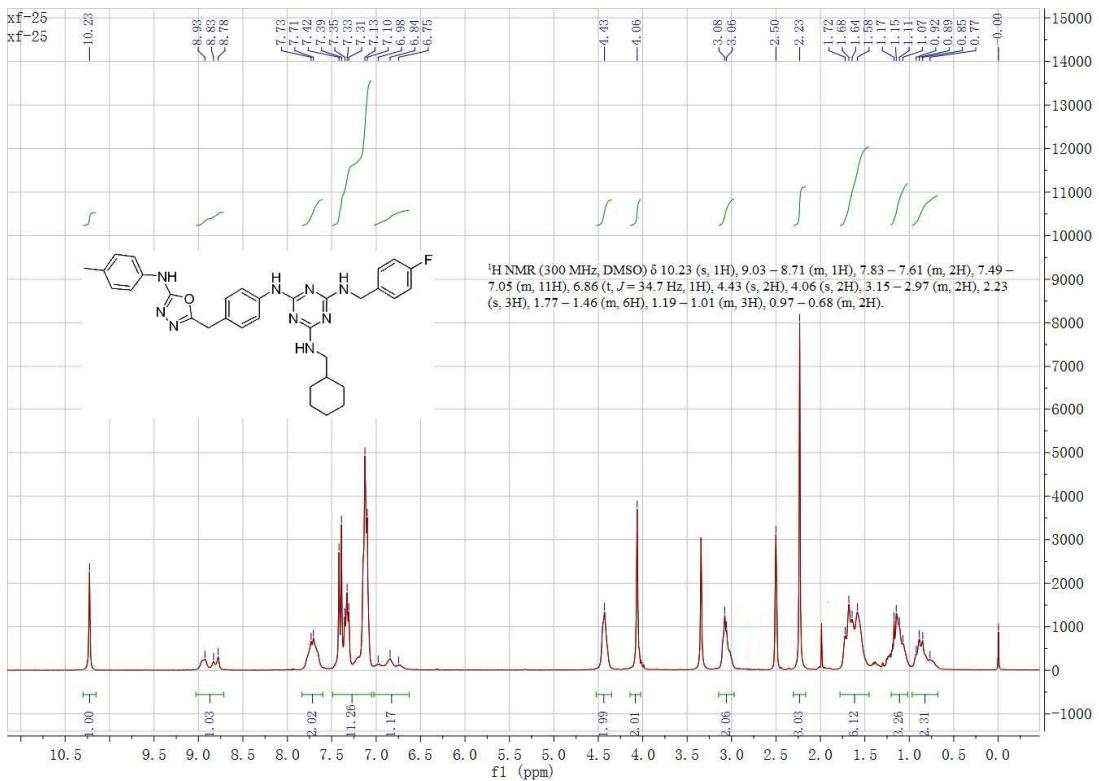




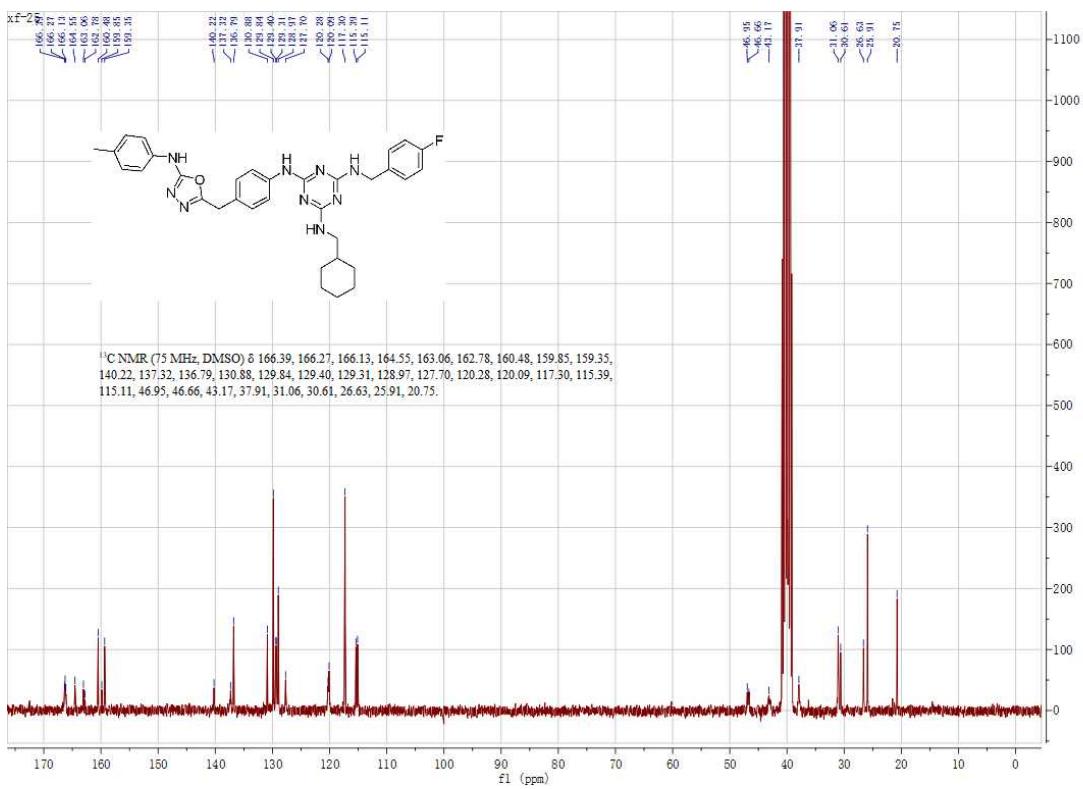
HPLC purity of 11c



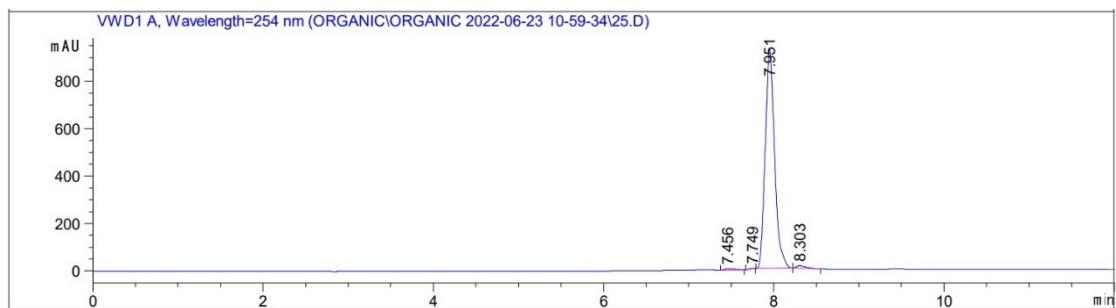
ESI-MS of 11c



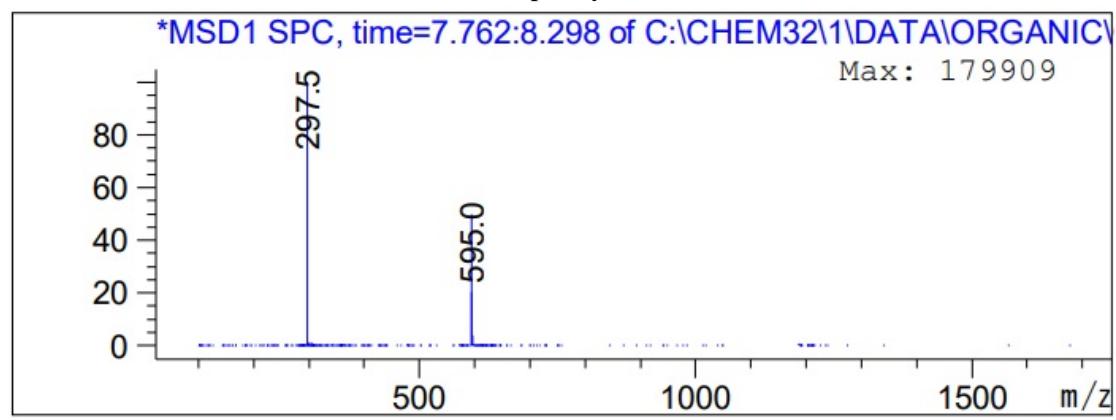
1H-NMR of 11i



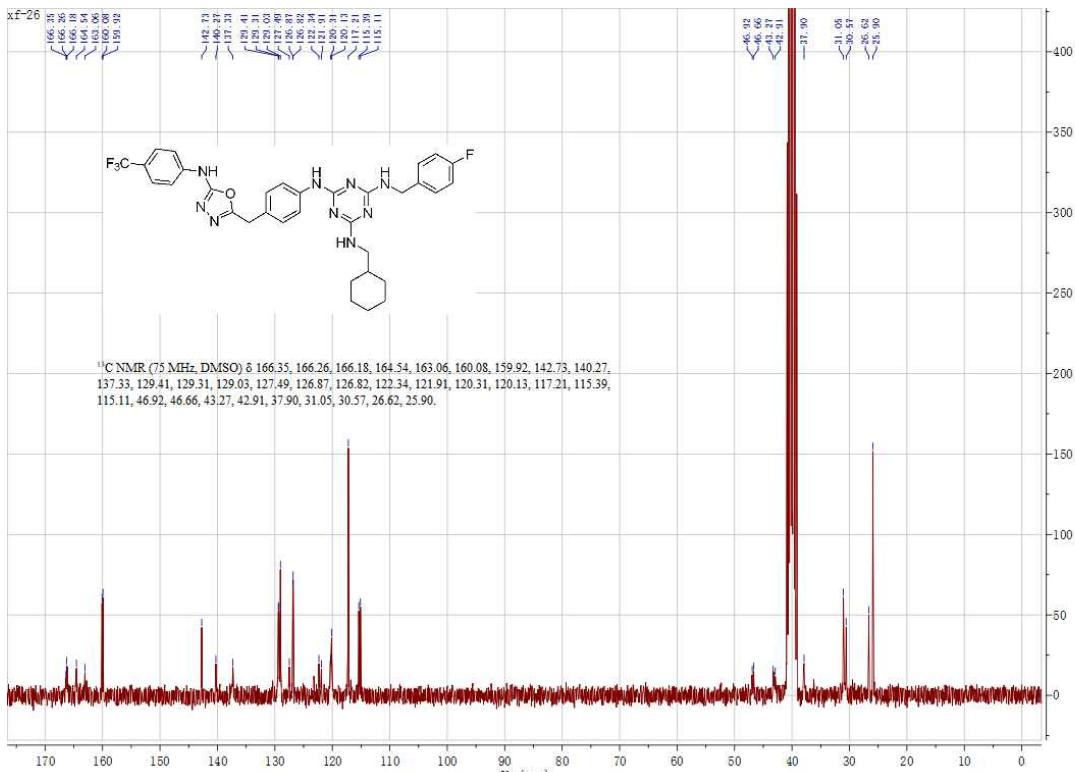
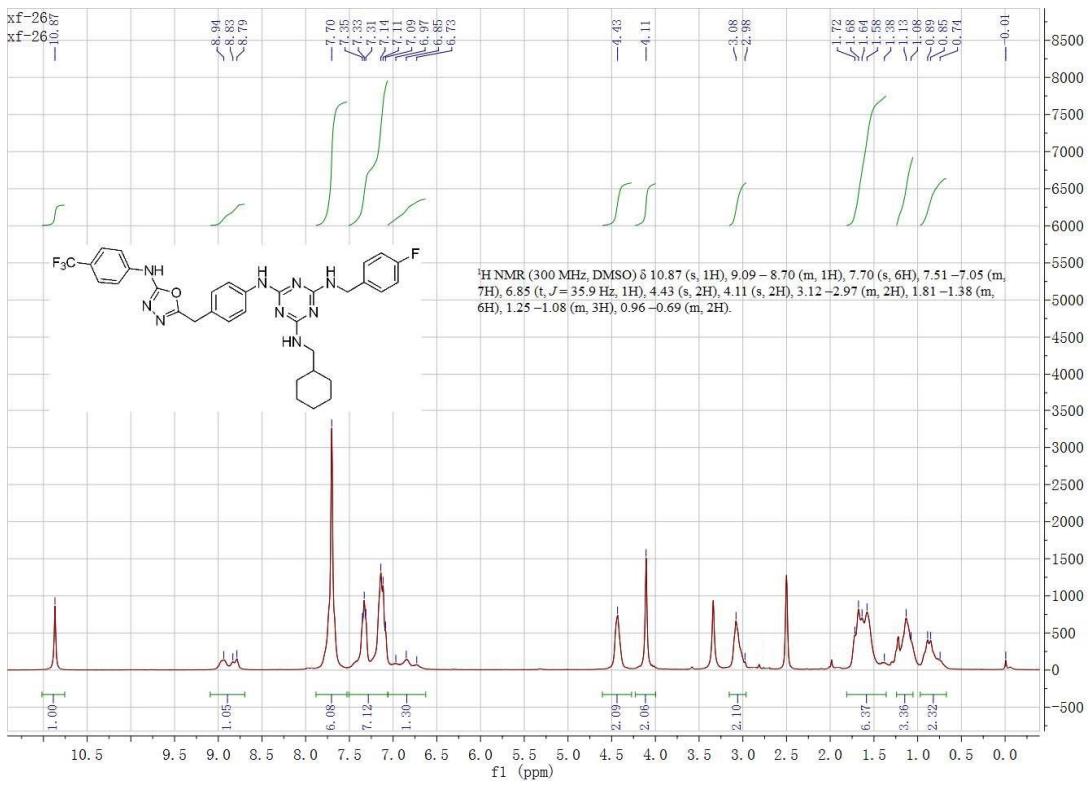
¹³C-NMR of 11i

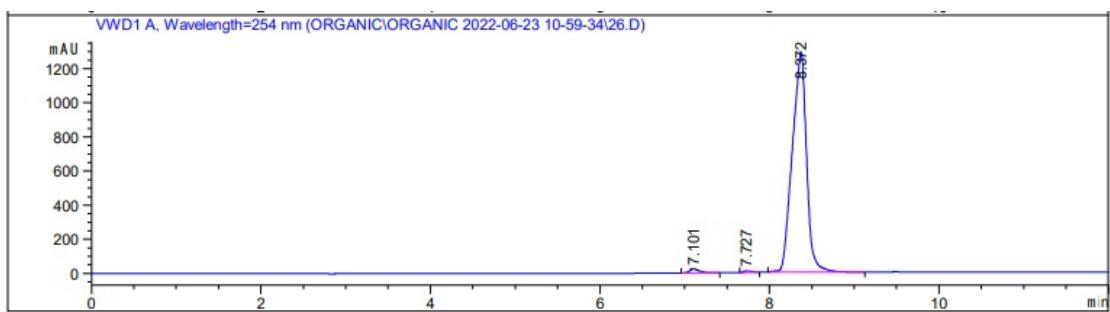


HPLC purity of 11i

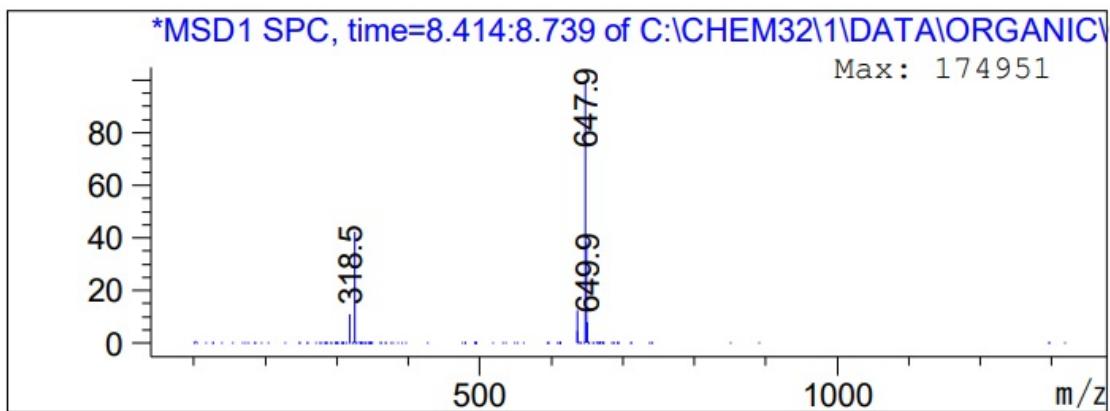


ESI-MS of 11i





HPLC purity of 11j



ESI-MS of 11j