

Supporting Information

Novel Approaches for the Solid-Phase Synthesis of Dihydroquinazoline-2(1H)-one Derivatives and Biological Evaluation as Potential Anticancer Agents

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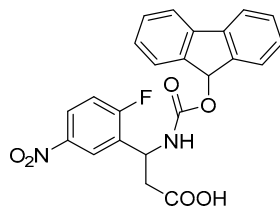
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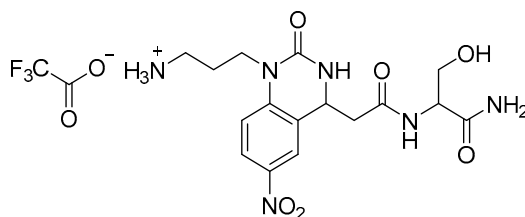
Analytical data of synthetic compounds

N-Fmoc-3-amino-3-(2-fluoro-5-nitrophenyl)propionic acid 3':



White solid; yield: 68.2%; mp 200.8-201.2°C; ^1H NMR (600 MHz, DMSO) δ 8.36 (dd, $J = 6.1, 2.8$ Hz, 1H), 8.22 (dd, $J = 8.7, 3.9$ Hz, 2H), 7.87 (t, $J = 7.2$ Hz, 2H), 7.65 (dd, $J = 15.3, 7.5$ Hz, 2H), 7.49 (t, $J = 9.1$ Hz, 1H), 7.39 (dt, $J = 11.9, 7.5$ Hz, 2H), 7.27 (dt, $J = 7.2, 3.6$ Hz, 2H), 5.27 (td, $J = 8.6, 6.1$ Hz, 1H), 4.34 – 4.28 (m, 2H), 4.20 (t, $J = 6.8$ Hz, 1H), 2.74 (ddd, $J = 22.1, 16.2, 7.5$ Hz, 2H); ^{13}C NMR (151 MHz, DMSO) δ 171.60, 164.11, 162.41(C-F, d, $^1J_{\text{C-F}} = 255.86$ Hz), 155.75, 144.63, 144.30, 143.98, 141.19, 141.16, 132.24, 132.13(C-F, d, $^2J_{\text{C-F}} = 16.5$ Hz), 128.12, 128.06 (C-F, d, $^3J_{\text{C-F}} = 8.68$ Hz), 127.48, 127.45, 125.71, 125.64 (C-F, d, $^3J_{\text{C-F}} = 10.61$ Hz), 125.54, 125.52, 124.36, 124.32, 120.63, 120.57, 117.61, 117.44(C-F, d, $^2J_{\text{C-F}} = 24.60$ Hz), 65.94, 47.09, 45.6; MS (ESI) (m/z): 450.12, $[\text{M}+\text{H}^+]$: 451.10.

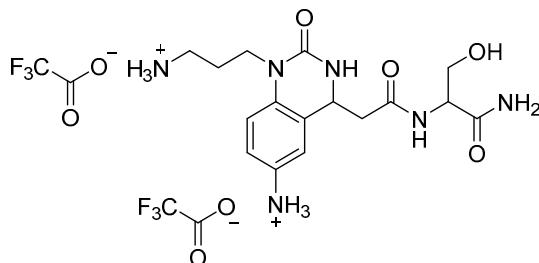
3-{4-{2-[(1-amino-3-hydroxy-1-oxopropan-2-yl)amino]-2-oxoethyl}-6-nitro-2-oxo-3,4-dihydroquinazolin-1(2H)-yl}propan-1-aminium 2,2,2-trifluoroacetate (CA1-6)·TFA:



Yellow solid; yield 93%; ^1H NMR (600 MHz, DMSO) δ 8.15 – 8.10 (m, 1H), 8.07 (dd, $J = 25.3, 2.5$ Hz, 1H), 7.96 (d, $J = 8.0$ Hz, 1H), 7.86 (s, 3H), 7.52 (dd, $J = 53.4, 2.7$ Hz, 1H), 7.34 – 7.19 (m, 2H), 7.08 (d, $J = 9.3$ Hz, 1H), 4.89 (dtd, $J = 25.9, 6.5, 2.8$ Hz, 1H), 4.19 (td, $J = 10.0, 5.1$ Hz, 1H), 3.97 – 3.90 (m, 2H), 3.56 – 3.39 (m, 2H), 2.90 (d, $J = 5.8$ Hz, 2H), 2.70 – 2.53 (m, 2H), 1.97 – 1.75 (m, 2H); ^{13}C NMR (151 MHz, DMSO) δ 172.39 (d, $J = 6.2$ Hz), 169.27, 158.74 (C-F, q, $^2J_{\text{C-F}} = 31.6$ Hz), 153.15, 143.77, 141.54, 124.69, 124.22, 122.70, 117.46 (C-F, q, $^1J_{\text{C-F}} = 299.3$ Hz), 114.01, 62.08, 55.25, 50.07, 44.45, 37.07, 25.46; MS (ESI) (m/z): 394. 16, $[\text{M}+\text{H}^+]$:

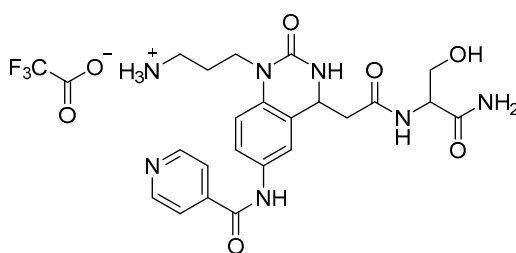
395.15.

4-{2-[(1-amino-3-hydroxy-1-oxopropan-2-yl)amino]-2-oxoethyl}-1-(3-ammoniopropyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-6-aminium 2,2,2-trifluoroacetate (CA1-7)·TFA:



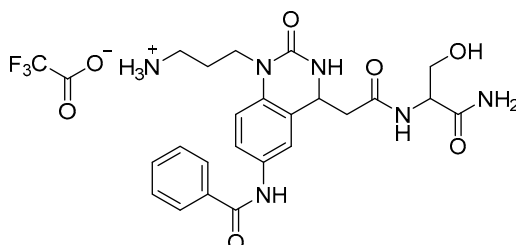
Brown solid; yield 76%; ^1H NMR (600 MHz, DMSO) δ 7.99 (dd, J = 20.8, 7.9 Hz, 1H), 7.88 (s, 1H), 7.33 (d, J = 14.9 Hz, 1H), 7.13 (ddd, J = 30.6, 18.0, 5.7 Hz, 2H), 7.05 (d, J = 1.8 Hz, 1H), 4.76 (dtd, J = 19.5, 6.6, 2.7 Hz, 1H), 4.23 (dd, J = 12.3, 5.5 Hz, 1H), 3.93 – 3.74 (m, 1H), 3.56 (dddd, J = 31.8, 26.5, 10.2, 5.4 Hz, 1H), 2.94 – 2.83 (m, 1H), 2.55 (td, J = 14.8, 7.5 Hz, 1H), 1.93 – 1.75 (m, 1H); ^{13}C NMR (151 MHz, DMSO) δ 172.52, 169.60, 159.08, 158.86 (C-F, q, $^2J_{\text{C-F}}$ = 32.4 Hz), 154.02, 135.78, 125.03, 121.84, 120.15, 119.92, 118.23, 116.25 (C-F, q, $^1J_{\text{C-F}}$ = 299.3 Hz), 114.55, 62.02, 55.46, 50.23, 44.42, 39.05, 37.13, 25.48; MS (ESI) (m/z): 364.19, $[\text{M}+\text{H}^+]$: 365.20.

3-{4-{2-[(1-amino-3-hydroxy-1-oxopropan-2-yl)amino]-2-oxoethyl}-6-(isonicotinamido)-2-oxo-3,4-dihydroquinazolin-1(2H)-yl}propan-1-aminium 2,2,2-trifluoroacetate (CA1-a)·TFA:

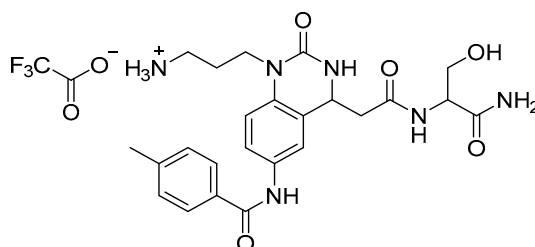


Orange solid; yield 86%; ^1H NMR (600 MHz, DMSO) δ 10.53 (d, J = 19.5 Hz, 1H), 8.85 (s, 2H), 8.06 – 7.93 (m, 3H), 7.79 (s, 3H), 7.68 (ddd, J = 18.6, 8.8, 2.3 Hz, 1H), 7.62 (s, 1H), 7.32 (d, J = 14.5 Hz, 1H), 7.18 – 7.11 (m, 1H), 7.11 – 7.00 (m, 2H), 4.80 (dd, J = 9.3, 3.8 Hz, 1H), 4.26 (dt, J = 7.8, 5.4 Hz, 1H), 3.94 – 3.84 (m, 2H), 3.54 (ddd, J = 15.9, 10.9, 5.5 Hz, 2H), 2.89 (dd, J = 12.5, 6.2 Hz, 2H), 2.73 – 2.52 (m, 2H), 1.88 (ddt, J = 19.1, 13.6, 6.7 Hz, 2H); ^{13}C NMR (151 MHz, DMSO) δ 172.58, 169.80, 163.55, 158.94 (C-F, q, $^2J_{\text{C-F}}$ = 32.4 Hz), 154.15, 149.58, 143.49,

3-{4-[2-[(1-amino-3-hydroxy-1-oxopropan-2-yl)amino]-2-oxoethyl]-6-benzamido-2-oxo-3,4-dihydroquinazolin-1(2H)-yl}propan-1-aminium 2,2,2-trifluoroacetate (CA1-b)·TFA:



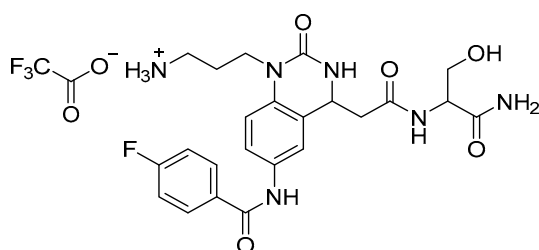
3-{4-[2-[(1-amino-3-hydroxy-1-oxopropan-2-yl)amino]-2-oxoethyl]-6-(4-methylbenzamide)-2-oxo-3,4-dihydroquinazolin-1(2H)-yl}propan-1-aminium 2,2,2-trifluoroacetate (CA1-c)·TFA:



5

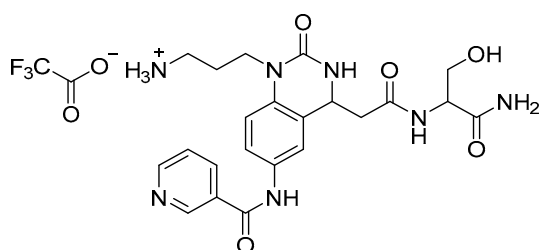
5.5 Hz, 2H), 2.88 (dd, $J = 12.6, 6.3$ Hz, 2H), 2.63 – 2.52 (m, 2H), 2.39 (s, 3H), 1.93 – 1.83 (m, 2H); ^{13}C NMR (151 MHz, DMSO) δ 172.56, 169.88, 169.73 (C-F, q, $^2J_{\text{C-F}} = 22.39$ Hz), 165.43, 154.17, 142.01, 133.98, 133.41, 132.40, 132.34, 129.40, 128.05, 120.81, 119.00 (C-F, q, $^1J_{\text{C-F}} = 279.55$ Hz), 118.32, 113.66, 62.09, 55.49, 50.67, 44.70, 38.82, 37.22, 25.67, 21.47; MS (ESI) (m/z): 482.23, $[\text{M}+\text{H}^+]$: 483.20.

3-{4-{2-[(1-amino-3-hydroxy-1-oxopropan-2-yl)amino]-2-oxoethyl}-6-(4-fluorobenzamido)-2-oxo-3,4-dihydroquinazolin-1(2H)-yl}propan-1-aminium 2,2,2-trifluoroacetate (CA1-d)·TFA:



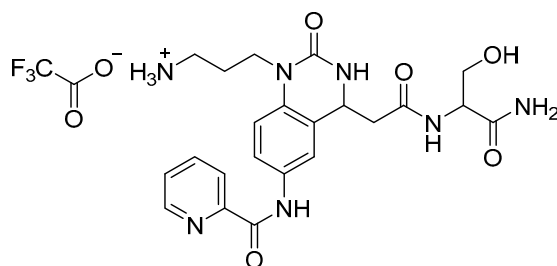
Yellow solid; yield 79%; ^1H NMR (600 MHz, DMSO) δ 10.20 (d, $J = 16.2$ Hz, 1H), 8.11 – 7.89 (m, 3H), 7.73 (s, 3H), 7.66 (ddd, $J = 17.0, 8.9, 2.2$ Hz, 1H), 7.61 (s, 1H), 7.43 – 7.35 (m, 2H), 7.32 (d, $J = 25.3$ Hz, 1H), 7.10 (d, $J = 13.3$ Hz, 1H), 7.08 – 6.96 (m, 2H), 4.83 – 4.71 (m, 1H), 4.29 – 4.22 (m, 1H), 3.95 – 3.83 (m, 2H), 2.89 (dd, $J = 12.5, 6.3$ Hz, 2H), 2.64 – 2.52 (m, 2H), 1.88 (ddd, $J = 21.5, 10.8, 5.5$ Hz, 2H); ^{13}C NMR (151 MHz, DMSO) δ 172.57, 169.77, 164.55, 163.69 (C-F, q, $^1J_{\text{C-F}} = 249.32$ Hz), 158.38 (C-F, q, $^2J_{\text{C-F}} = 31.83$ Hz), 154.15, 133.78, 133.56, 131.69, 130.75, 123.95, 120.83, 119.02 (C-F, q, $^1J_{\text{C-F}} = 274.60$ Hz), 115.88, 115.74, 113.70, 62.10, 55.49, 50.66, 44.65, 38.84, 37.19, 25.66; MS (ESI) (m/z): 486.20, $[\text{M}+\text{H}^+]$: 487.20.

3-{4-{2-[(1-amino-3-hydroxy-1-oxopropan-2-yl)amino]-2-oxoethyl}-6-(nicotinamido)-2-oxo-3,4-dihydroquinazolin-1(2H)-yl}propan-1-aminium 2,2,2-trifluoroacetate (CA1-e)·TFA:



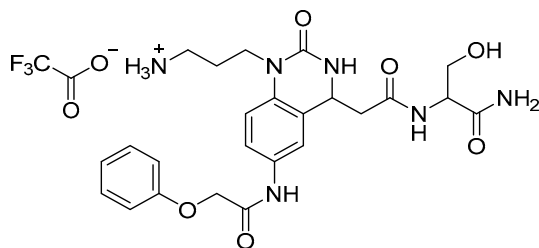
Yellow solid; yield 84%; ^1H NMR (600 MHz, DMSO) δ 10.45 (d, J = 15.6 Hz, 1H), 9.15 (d, J = 8.4 Hz, 1H), 8.80 (d, J = 4.6 Hz, 1H), 8.38 (ddd, J = 9.7, 8.0, 4.0 Hz, 1H), 7.99 (dd, J = 39.8, 7.9 Hz, 1H), 7.79 (s, 3H), 7.67 (dd, J = 11.7, 3.1 Hz, 1H), 7.65 – 7.63 (m, 1H), 7.62 (dd, J = 6.4, 2.2 Hz, 1H), 7.31 (s, 1H), 7.10 (dd, J = 12.0, 9.7 Hz, 2H), 7.07 – 6.99 (m, 1H), 4.80 – 4.74 (m, 1H), 4.27 – 4.25 (m, 1H), 3.93 – 3.82 (m, 2H), 3.62 – 3.48 (m, 2H), 2.89 (dd, J = 12.6, 6.3 Hz, 2H), 2.64 – 2.52 (m, 2H), 1.94 – 1.83 (m, 2H); ^{13}C NMR (151 MHz, DMSO) δ 172.58, 169.75, 163.82, 158.67 (C-F, q, $^2J_{\text{C-F}}$ = 35.9 Hz), 154.17, 151.69, 148.35, 136.83, 133.83, 133.47, 131.23, 124.40, 124.02, 120.84, 119.02, 117.32, 115.38 (C-F, q, $^1J_{\text{C-F}}$ = 283.7 Hz), 113.77, 62.06, 55.47, 50.65, 44.65, 38.88, 37.20, 25.66; MS (ESI) (m/z): 469.21, $[\text{M}+\text{H}^+]$: 470.20.

3-{4-{2-[(1-amino-3-hydroxy-1-oxopropan-2-yl)amino]-2-oxoethyl}-2-oxo-6-(picolinamido)-3,4-dihydroquinazolin-1(2H)-yl}propan-1-aminium 2,2,2-trifluoroacetate (CA1-f)·TFA:



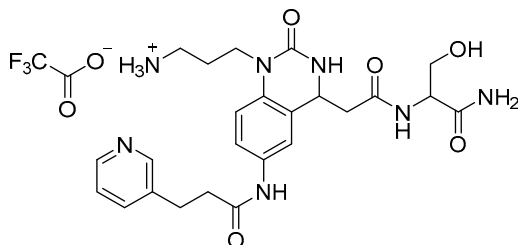
Orange solid; yield 76%; ^1H NMR (600 MHz, DMSO) δ 10.67 – 10.53 (m, 1H), 8.79 – 8.69 (m, 1H), 8.15 (d, J = 7.8 Hz, 1H), 8.07 (t, J = 7.7 Hz, 1H), 7.99 (dd, J = 17.4, 7.9 Hz, 1H), 7.78 (dd, J = 7.1, 4.4 Hz, 5H), 7.68 (dd, J = 6.6, 4.9 Hz, 1H), 7.29 (s, 1H), 7.08 (d, J = 7.3 Hz, 1H), 7.01 (dd, J = 52.7, 2.0 Hz, 2H), 4.84 – 4.74 (m, 1H), 4.33 – 4.20 (m, 1H), 3.97 – 3.80 (m, 2H), 3.65 – 3.49 (m, 2H), 2.89 (dt, J = 12.7, 6.3 Hz, 2H), 2.65 – 2.51 (m, 2H), 1.97 – 1.78 (m, 2H); ^{13}C NMR (151 MHz, DMSO) δ 172.54, 169.82, 162.62, 158.88 (C-F, q, $^2J_{\text{C-F}}$ = 34.93 Hz), 154.11, 150.32, 148.88, 138.61, 133.77, 133.07, 127.33, 123.94, 122.71, 120.74, 118.90, 117.17 (C-F, q, $^1J_{\text{C-F}}$ = 71.71 Hz), 113.78, 62.08, 55.48, 50.68 (d, J = 12.5 Hz), 44.58, 38.88, 37.20, 25.66; MS (ESI) (m/z): 469.21, $[\text{M}+\text{H}^+]$: 470.15.

3-{4-{2-[(1-amino-3-hydroxy-1-oxopropan-2-yl)amino]-2-oxoethyl}-2-oxo-6-(2-phenox yacetamido)-3,4-dihydroquinazolin-1(2H)-yl}propan-1-aminium 2,2,2-trifluoroacetate (CA1-g)·TFA:



White solid; yield 85%; ^1H NMR (600 MHz, DMSO) δ 10.03 (d, J = 14.1 Hz, 1H), 7.98 (dd, J = 37.5, 7.9 Hz, 1H), 7.77 (s, 3H), 7.58 – 7.51 (m, 1H), 7.4 (dd, J = 14.2, 2.0 Hz, 1H), 7.32 (t, J = 7.8 Hz, 2H), 7.30 (d, J = 3.8 Hz, 1H), 7.10 (s, 1H), 7.07 – 6.95 (m, 5H), 4.87 (d, J = 34.2 Hz, 1H), 4.78 – 4.69 (m, 1H), 4.60 (d, J = 4.2 Hz, 2H), 4.24 (dq, J = 10.4, 5.2 Hz, 1H), 3.93 – 3.79 (m, 2H), 3.55 (d, J = 42.7 Hz, 2H), 2.87 (d, J = 5.4 Hz, 2H), 2.62 – 2.51 (m, 2H), 1.86 (dq, J = 12.8, 6.9 Hz, 2H); ^{13}C NMR (151 MHz, DMSO) δ 172.63, 172.54, 169.73, 163.55, 158.83 (C-F, q, $^2J_{\text{C-F}}$ = 30.59 Hz), 154.12, 149.83, 149.58, 143.49, 134.05, 133.18, 124.04, 122.58, 120.97, 119.13, 115.48 (C-F, q, $^1J_{\text{C-F}}$ = 255.65 Hz), 113.79, 62.07, 55.48, 51.80, 50.63, 44.73, 38.92, 37.19, 25.65; MS (ESI) (m/z): 498.22, $[\text{M}+\text{H}^+]$: 499.20.

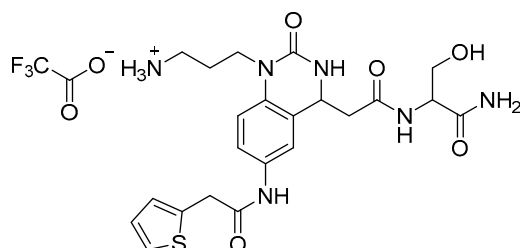
3-{4-{2-[(1-amino-3-hydroxy-1-oxopropan-2-yl)amino]-2-oxoethyl}-2-oxo-6-[3-(pyridin-3-yl)propanamido]-3,4-dihydroquinazolin-1(2H)-yl}propan-1-aminium 2,2,2-trifluoroacetate (CA1-h)·TFA:



Yellow solid; yield 92%; ^1H NMR (600 MHz, DMSO) δ 9.96 (d, J = 15.4 Hz, 1H), 8.78 (s, 1H), 8.70 (s, 1H), 8.27 (d, J = 7.6 Hz, 1H), 7.98 (dd, J = 38.9, 7.9 Hz, 1H), 7.85 (s, 3H), 7.83 – 7.80 (m, 1H), 7.42 (s, 1H), 7.40 (dd, J = 5.0, 2.6 Hz, 1H), 7.30 (d, J = 6.5 Hz, 1H), 7.11 (d, J = 7.3 Hz, 1H), 7.06 – 6.92 (m, 2H), 4.83 – 4.65 (m, 1H), 4.24 (dtd, J = 7.8, 5.3, 2.4 Hz, 1H), 3.89 – 3.79 (m, 2H), 3.64 – 3.44 (m, 2H), 3.06 (t, J = 7.1 Hz, 2H), 2.87 (dd, J = 12.3, 6.2 Hz, 2H), 2.74 (d, J = 7.2 Hz, 2H), 2.65 – 2.51 (m, 2H), 1.93 – 1.78 (m, 2H); ^{13}C NMR (151 MHz, DMSO) δ 172.55, 169.86, 169.68, 159.02, 158.80 (C-F, q, $^2J_{\text{C-F}}$ = 33.5 Hz), 154.18, 144.44, 143.33, 142.52, 140.36, 133.79, 133.09, 130.88, 126.24, 124.05, 119.56, 118.02, 117.71, 116.06 (C-F, q, $^1J_{\text{C-F}}$ =

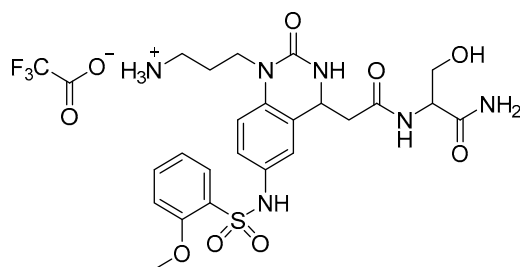
294.9 Hz), 113.78, 62.06, 55.47, 50.58, 44.56, 38.84, 37.14, 36.86, 28.04, 25.63; MS (ESI) (m/z): 497.24, [M+H⁺]: 498.25.

3-{4-{2-[(1-amino-3-hydroxy-1-oxopropan-2-yl)amino]-2-oxoethyl}-2-oxo-6-[2-(thiophen-2-yl)acetamido]-3,4-dihydroquinazolin-1(2H)-yl}propan-1-aminium 2,2,2-trifluoroacetate (CA1-i)·TFA:



Pale brown solid; yield 90%; ¹H NMR (600 MHz, DMSO) δ 10.18 (d, *J* = 15.2 Hz, 1H), 7.99 (dd, *J* = 38.4, 7.9 Hz, 1H), 7.8 (s, 3H), 7.45 (dd, *J* = 23.6, 5.1 Hz, 2H), 7.41 – 7.35 (m, 1H), 7.30 (d, *J* = 4.2 Hz, 1H), 7.10 (d, *J* = 9.6 Hz, 1H), 7.08 – 6.90 (m, 4H), 4.77 – 4.67 (m, 1H), 4.28 – 4.21 (m, 1H), 3.86 (t, *J* = 9.1 Hz, 4H), 3.61 – 3.48 (m, 2H), 2.93 – 2.82 (m, 2H), 2.62 – 2.51 (m, 2H), 1.86 (ddd, *J* = 22.5, 10.5, 4.8 Hz, 2H); ¹³C NMR (151 MHz, DMSO) δ 172.56, 169.79, 168.19, 158.70 (C-F, q, ²*J*_{C-F} = 32.3 Hz), 154.15, 137.64, 133.80, 133.27, 129.82, 127.11, 126.77, 125.49, 124.12, 119.62, 117.82, 115.69 (C-F, q, ¹*J*_{C-F} = 321.4 Hz), 113.82, 62.06, 55.46, 50.57, 44.53, 38.83, 37.86, 37.16, 25.63; MS (ESI) (m/z): 488.18, [M+H⁺]: 489.20.

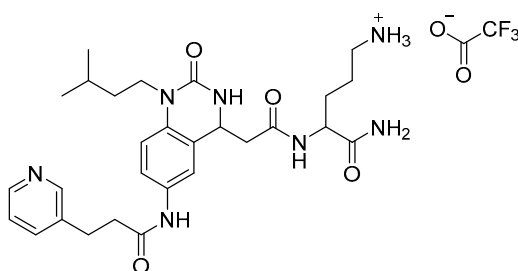
3-{4-{2-[(1-amino-3-hydroxy-1-oxopropan-2-yl)amino]-2-oxoethyl}-6-[(2-methoxyphenyl)sulfonamido]-2-oxo-3,4-dihydroquinazolin-1(2H)-yl}propan-1-aminium 2,2,2-trifluoroacetate (CA1-j)·TFA:



Yellow solid; yield 71%; ¹H NMR (600 MHz, DMSO) δ 9.73 (d, *J* = 35.7 Hz, 1H), 7.96 (dd, *J* = 10.1, 8.1 Hz, 1H), 7.75 (s, 3H), 7.72 – 7.68 (m, 1H), 7.59 – 7.54 (m, 1H), 7.33 (d, *J* = 24.0 Hz, 1H), 7.18 (d, *J* = 8.4 Hz, 1H), 7.12 (d, *J* = 22.3 Hz, 1H), 7.02 (td, *J* = 7.5, 2.7 Hz, 1H), 6.99 – 6.90 (m, 3H), 6.87 (d, *J* = 8.1 Hz, 1H), 4.67 – 4.59 (m, 1H), 4.24 (dt, *J* = 7.7, 5.3 Hz, 1H), 3.90 (s,

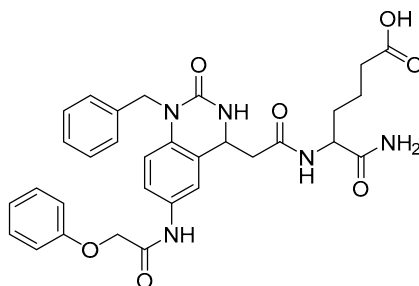
3H), 3.81 – 3.71 (m, 2H), 3.63 – 3.53 (m, 2H), 2.82 (d, $J = 6.0$ Hz, 2H), 2.41 (tt, $J = 14.6, 7.2$ Hz, 2H), 1.78 (ddd, $J = 19.9, 11.7, 4.8$ Hz, 2H); ^{13}C NMR (151 MHz, DMSO) δ 172.53, 169.57, 158.81 (C-F, q, $^2J_{\text{C-F}} = 33.8$ Hz), 154.15, 153.99, 135.47, 134.17, 132.17, 130.62, 126.85, 124.46, 120.98, 120.55, 119.43, 119.62, 116.85 (C-F, q, $^1J_{\text{C-F}} = 294.6$ Hz), 113.24, 62.11, 56.56, 55.45, 50.29, 44.42, 38.88, 37.14, 25.53; MS (ESI) (m/z): 534.19, $[\text{M}+\text{H}^+]$: 535.20.

5-amino-4-{2-[1-isopentyl-2-oxo-6-[3-(pyridin-3-yl)propanamido]-1,2,3,4-tetrahydroquinazolin-4-yl]acetamido}-5-oxopentan-1-aminium 2,2,2-trifluoroacetate (CA3)·TFA:



Light brown solid; yield 74%; ^1H NMR (600 MHz, DMSO) δ 9.95 (d, $J = 18.9$ Hz, 1H), 8.73 (d, $J = 45.9$ Hz, 1H), 8.25 (dd, $J = 12.5, 8.1$ Hz, 1H), 8.13 (dd, $J = 34.3, 8.2$ Hz, 1H), 7.80 (dd, $J = 13.1, 6.9$ Hz, 1H), 7.47 – 7.36 (m, 1H), 7.12 (d, $J = 4.7$ Hz, 1H), 6.92 – 6.85 (m, 1H), 4.70 – 4.59 (m, 1H), 4.30 – 4.18 (m, 1H), 3.91 – 3.67 (m, 1H), 3.10 – 3.02 (m, 1H), 2.82 – 2.69 (m, 2H), 2.45 (ddd, $J = 14.5, 7.7, 4.1$ Hz, 1H), 1.75 – 1.41 (m, 4H), 0.93 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (151 MHz, DMSO) δ 173.69, 169.78, 158.86 (C-F, q, $^2J_{\text{C-F}} = 31.9$ Hz), 153.95, 144.62, 143.24, 142.62, 133.65, 133.47, 133.29, 126.19, 124.50, 124.30, 119.64, 117.59, 116.05, (C-F, q, $^1J_{\text{C-F}} = 292.8$ Hz), 115.69, 113.79, 52.16, 51.82, 50.60, 44.28, 38.96, 36.87, 36.04, 29.27, 28.04, 26.16, 23.89, 23.04, 22.88; MS (ESI) (m/z): 537.31, $[\text{M}+\text{H}^+]$: 538.30.

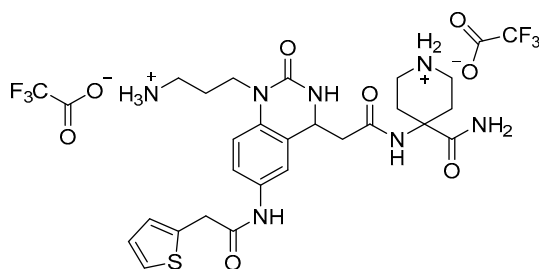
2-{2-[1-benzyl-2-oxo-6-(2-phenoxyacetamido)-1,2,3,4-tetrahydroquinazolin-4-yl]acetamido}-2-methylpropanamide (CA4):



White solid; yield 75%; ^1H NMR (600 MHz, DMSO) δ 10.07 (d, $J = 112.5$ Hz, 1H), 7.95 (d, $J = 13.3$ Hz, 1H), 7.48 (d, $J = 2.0$ Hz, 1H), 7.39 – 7.26 (m, 5H), 7.23 (dd, $J = 15.1, 7.5$ Hz, 2H),

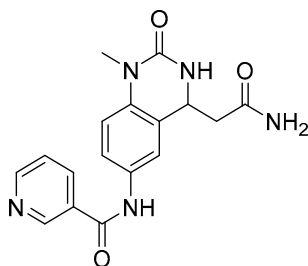
7.18 – 7.04 (m, 2H), 7.02 – 6.68 (m, 6H), 5.05 (d, $J = 11.9$ Hz, 1H), 4.80 – 4.62 (m, 3H), 4.52 – 4.45 (m, 1H), 2.53 (d, $J = 6.6$ Hz, 2H), 1.34 – 1.24 (m, 6H); ^{13}C NMR (151 MHz, DMSO) δ 176.74, 169.17, 166.70, 158.24, 154.24, 138.43, 133.85, 132.90, 129.96, 128.94, 127.15, 126.81, 124.02, 121.63, 120.05, 118.36, 115.08, 114.41, 67.45, 56.41, 50.70, 45.09, 25.92, 25.40; MS (ESI) (m/z): 529.23, $[\text{M}+\text{H}^+]$: 530.25.

4-{2-[1-(3-ammoniopropyl)-2-oxo-6-[2-(thiophen-2-yl)acetamido]-1,2,3,4-tetrahydroquinazolin-4-yl]acetamido}-4-carbamoylpiperidin-1-ium 2,2,2-trifluoroacetate (CA5)·TFA:



Yellowish white solid; yield 84%; ^1H NMR (600 MHz, DMSO) δ 10.18 (s, 1H), 8.57 (d, $J = 8.9$ Hz, 1H), 8.35 (d, $J = 9.0$ Hz, 1H), 8.14 (s, 1H), 7.79 (s, 3H), 7.49 – 7.42 (m, 2H), 7.39 (dd, $J = 4.4, 2.0$ Hz, 1H), 7.23 (s, 1H), 7.06 (d, $J = 2.6$ Hz, 1H), 7.02 – 6.97 (m, 4H), 4.69 (td, $J = 6.6, 2.7$ Hz, 1H), 3.94 – 3.88 (m, 2H), 3.85 (s, 2H), 3.13 – 2.84 (m, 6H), 2.64 – 2.54 (m, 2H), 2.13 – 2.06 (m, 2H), 1.97 (d, $J = 10.6$ Hz, 2H), 1.87 (ddd, $J = 23.3, 14.5, 7.2$ Hz, 2H); ^{13}C NMR (151 MHz, DMSO) δ 174.92, 169.92, 168.24, 158.58 (C-F, q, $^2J_{\text{C-F}} = 32.3$ Hz), 154.21, 137.63, 136.59, 133.79, 133.33, 127.15, 126.78, 125.54, 124.00, 119.58, 117.55 (C-F, q, $^1J_{\text{C-F}} = 305.48$ Hz), 113.91, 55.89, 50.19, 44.39, 39.11, 37.87, 37.17, 29.17, 28.02, 25.61; MS (ESI) (m/z): 527.23, $[\text{M}+\text{H}^+]$: 528.20.

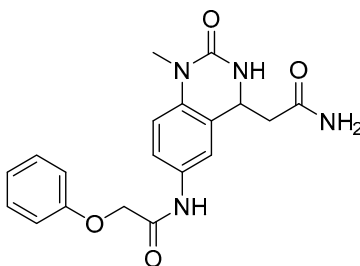
N-[4-(2-amino-2-oxoethyl)-1-methyl-2-oxo-1,2,3,4-tetrahydroquinazolin-6-yl]nicotinamide (CA6-a):



Yellow solid; yield 74%; ^1H NMR (600 MHz, DMSO) δ 10.48 (s, 1H), 9.17 (s, 1H), 8.82 (s, 1H), 8.42 (d, $J = 7.9$ Hz, 1H), 7.68 (dd, $J = 8.5, 1.8$ Hz, 2H), 7.59 (s, 1H), 7.35 (s, 1H), 7.03 (s,

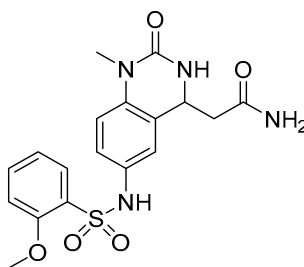
1H), 7.00 – 6.90 (m, 2H), 4.68 (t, $J = 5.4$ Hz, 1H), 3.19 (s, 3H), 2.44 (dd, $J = 6.8, 2.1$ Hz, 2H); ^{13}C NMR (151 MHz, DMSO) δ 171.53, 163.58, 154.49, 151.18, 148.20, 147.99, 137.31, 135.56, 133.25, 124.59, 124.42, 120.77, 118.68, 113.56, 50.20, 43.85, 29.64; MS (ESI) (m/z): 339.13, $[\text{M}+\text{H}^+]$: 340.15.

***N*-[4-(2-amino-2-oxoethyl)-1-methyl-2-oxo-1,2,3,4-tetrahydroquinazolin-6-yl]-2-phenoxyacetamide (CA6-b):**



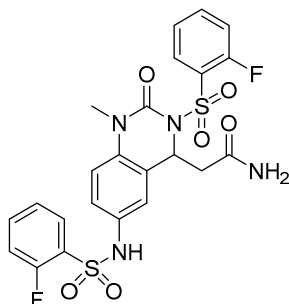
White solid; yield 78%; ^1H NMR (600 MHz, DMSO) δ 10.04 (s, 1H), 7.57 (dd, $J = 8.8, 2.2$ Hz, 1H), 7.43 (d, $J = 2.1$ Hz, 1H), 7.34 – 7.30 (m, 3H), 7.02 – 6.97 (m, 4H), 6.95 – 6.90 (m, 2H), 4.68 – 4.63 (m, 3H), 3.16 (s, 3H), 2.41 (dd, $J = 6.8, 3.8$ Hz, 2H); ^{13}C NMR (151 MHz, DMSO) δ 171.50, 166.66, 158.30, 154.47, 135.24, 132.93, 129.98, 124.43, 121.63, 120.10, 118.04, 115.14, 113.55, 67.54, 50.15, 43.77, 29.61; MS (ESI) (m/z): 368.15, $[\text{M}+\text{H}^+]$: 369.15.

2-{6-[(2-methoxyphenyl)sulfonamido]-1-methyl-2-oxo-1,2,3,4-tetrahydroquinazolin-4-yl}acetamide (CA7-a):



White solid; yield 84%; ^1H NMR (600 MHz, DMSO) δ 9.71 (s, 1H), 7.68 (dd, $J = 7.8, 1.6$ Hz, 1H), 7.56 – 7.52 (m, 1H), 7.27 (s, 1H), 7.17 (d, $J = 8.3$ Hz, 1H), 6.99 (t, $J = 7.6$ Hz, 1H), 6.95 (dd, $J = 8.7, 2.4$ Hz, 2H), 6.92 (d, $J = 2.3$ Hz, 1H), 6.84 (s, 1H), 6.78 (d, $J = 8.8$ Hz, 1H), 4.54 (td, $J = 6.8, 2.9$ Hz, 1H), 3.92 (s, 3H), 3.07 (s, 3H), 2.28 (ddd, $J = 50.0, 14.7, 6.9$ Hz, 2H); ^{13}C NMR (151 MHz, DMSO) δ 171.24, 156.76, 154.36, 135.83, 135.38, 131.95, 130.74, 126.64, 124.74, 121.05, 120.49, 119.14, 113.80, 113.17, 56.52, 49.87, 43.61, 29.55; MS (ESI) (m/z): 404.12, $[\text{M}+\text{H}^+]$: 405.10.

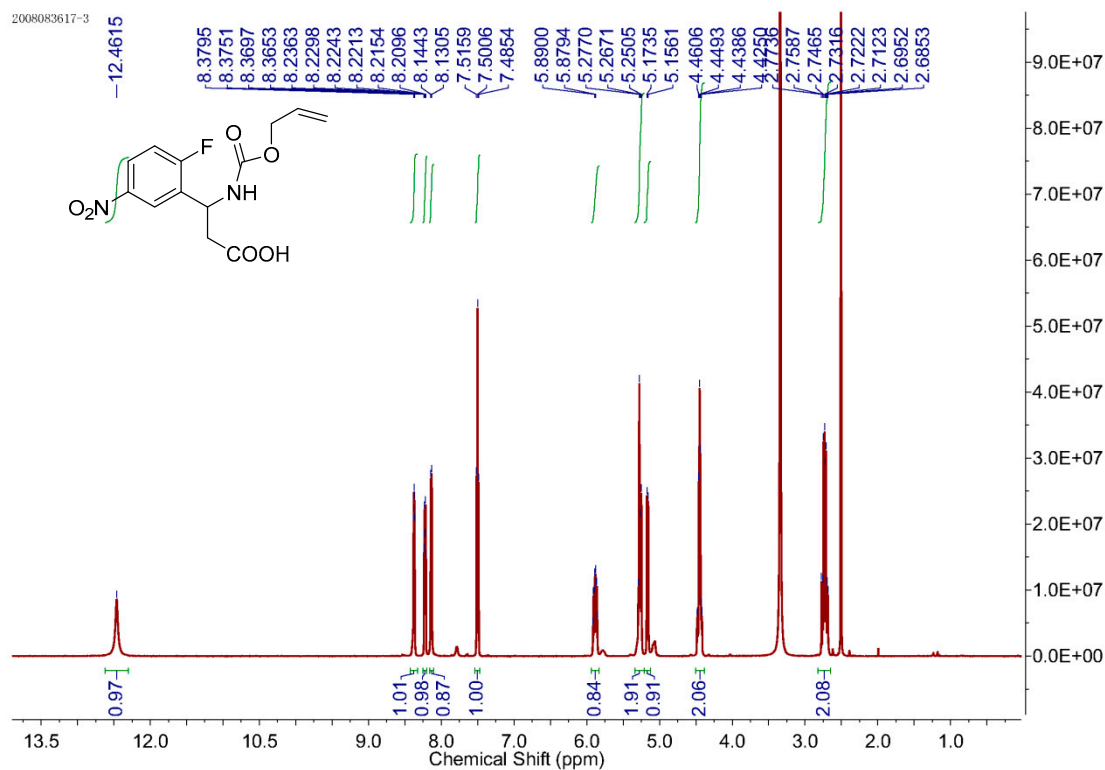
2-{6-[(2-fluorophenyl)sulfonamido]-3-[(2-fluorophenyl)sulfonyl]-1-methyl-2-oxo-1,2,3,4-tetrahydroquinazolin-4-yl}acetamide (CA7-b'):



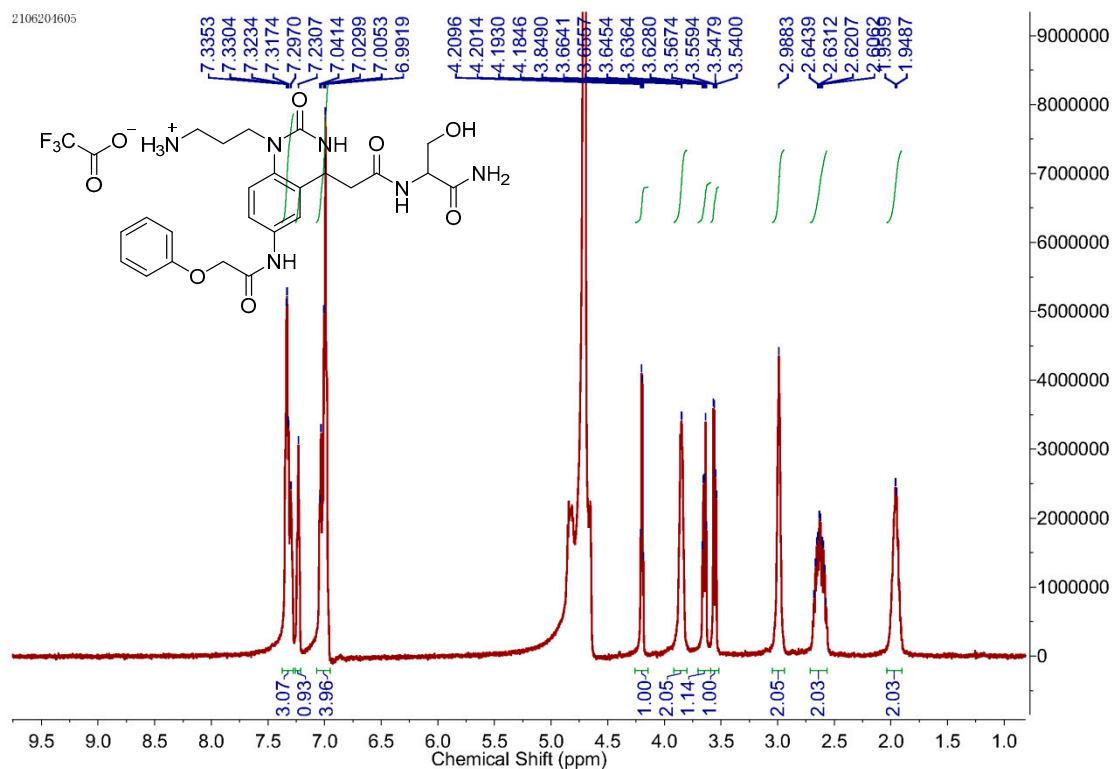
White solid; yield 76%; ^1H NMR (600 MHz, DMSO) δ 7.93 – 7.78 (m, 4H), 7.54 (t, J = 8.2 Hz, 2H), 7.47 (dt, J = 12.2, 7.7 Hz, 2H), 7.35 (s, 1H), 7.20 (d, J = 3.0 Hz, 1H), 7.10 (dd, J = 8.7, 2.1 Hz, 1H), 7.01 (dd, J = 7.6, 5.5 Hz, 2H), 6.94 (s, 1H), 4.65 (td, J = 6.8, 3.2 Hz, 1H), 3.18 (s, 3H), 2.32 (ddd, J = 21.4, 15.0, 6.9 Hz, 2H); ^{13}C NMR (151 MHz, DMSO) δ 171.11, 159.59, 157.89 (C-F, q, $^1J_{\text{C-F}}$ = 254.62 Hz), 153.93, 141.03, 138.46, 132.04, 131.89, 129.12, 125.74, 125.64, 124.99, 118.18, 114.20, 49.48, 43.65, 29.86; MS (ESI) (m/z): 550.08, $[\text{M}+\text{H}^+]$: 551.10.

^1H NMR and ^{13}C NMR Spectrometry

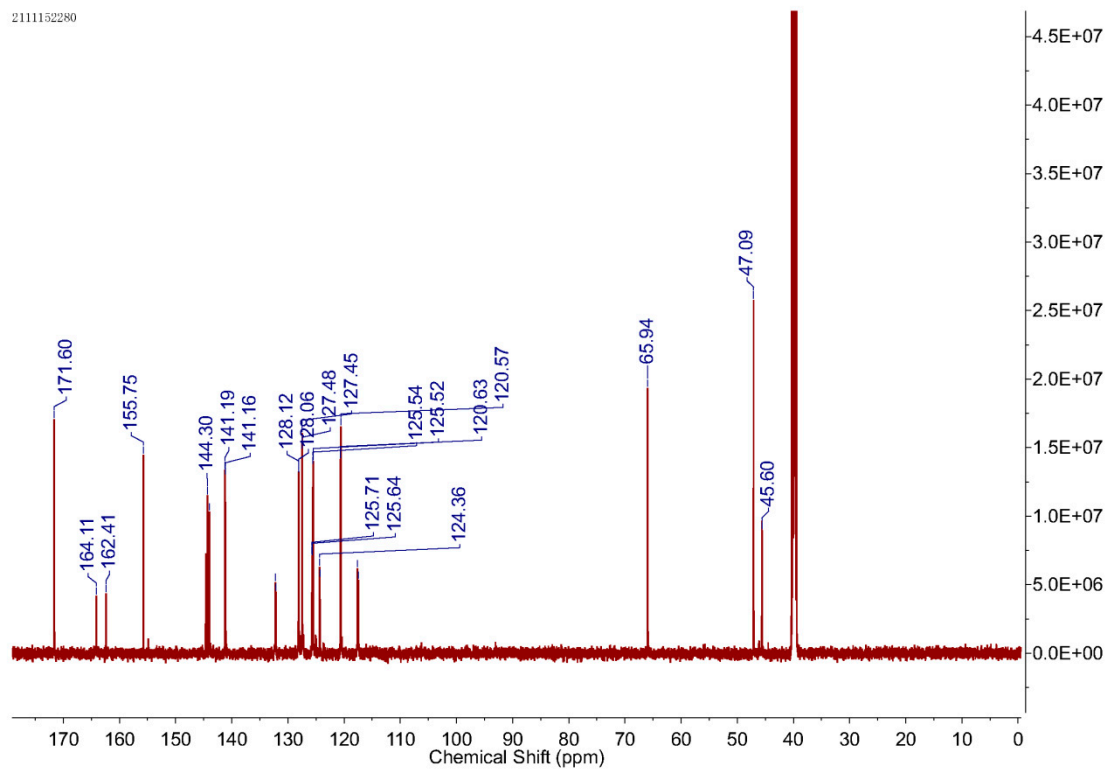
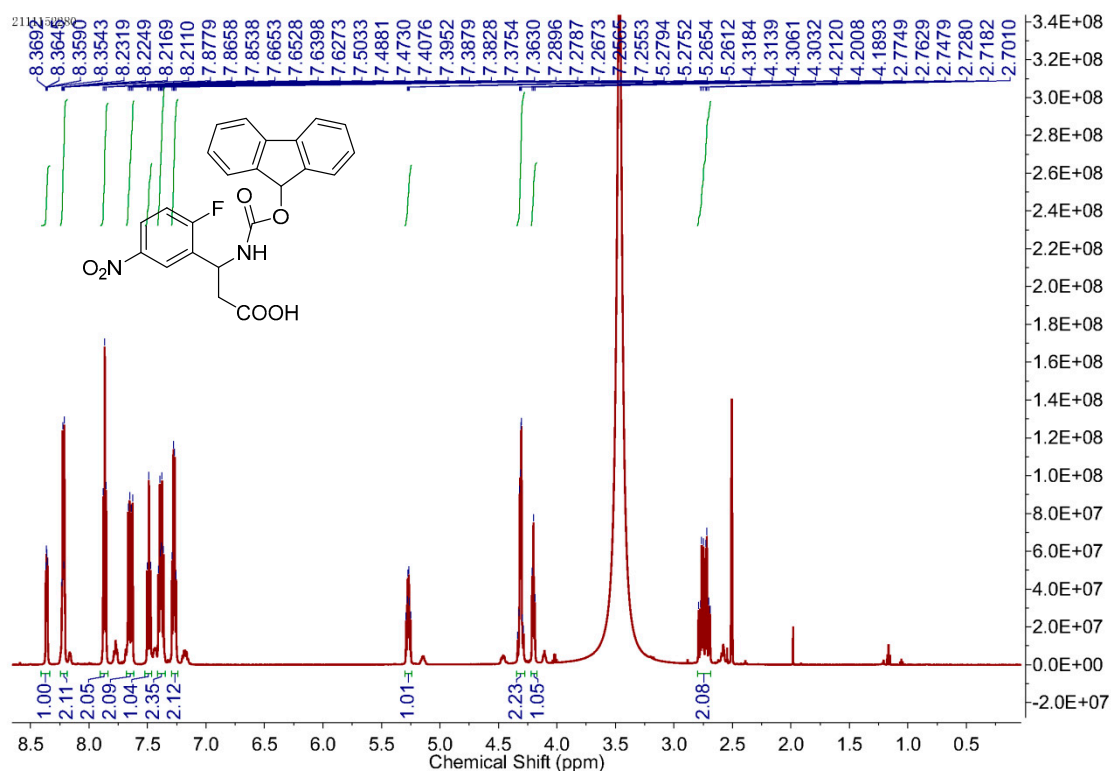
^1H NMR spectra (d_6 -DMSO) of *N*-Alloc-3-amino-3-(2-fluoro-5-nitrophenyl)propionic acid **3**



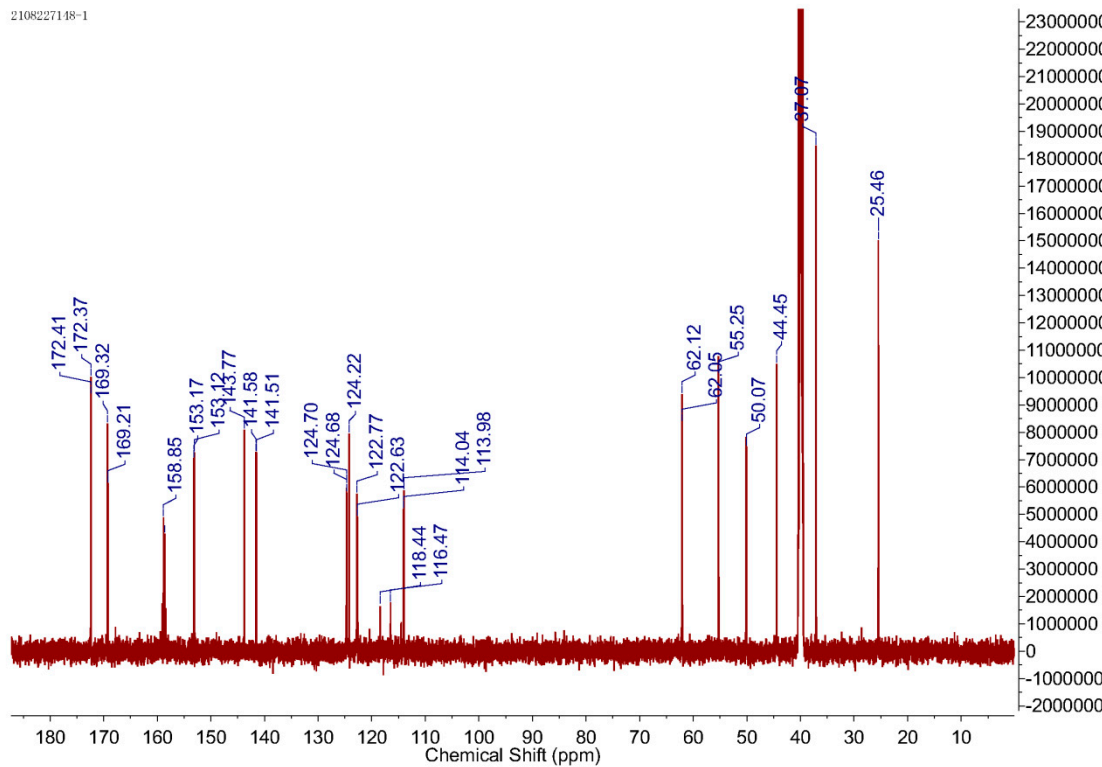
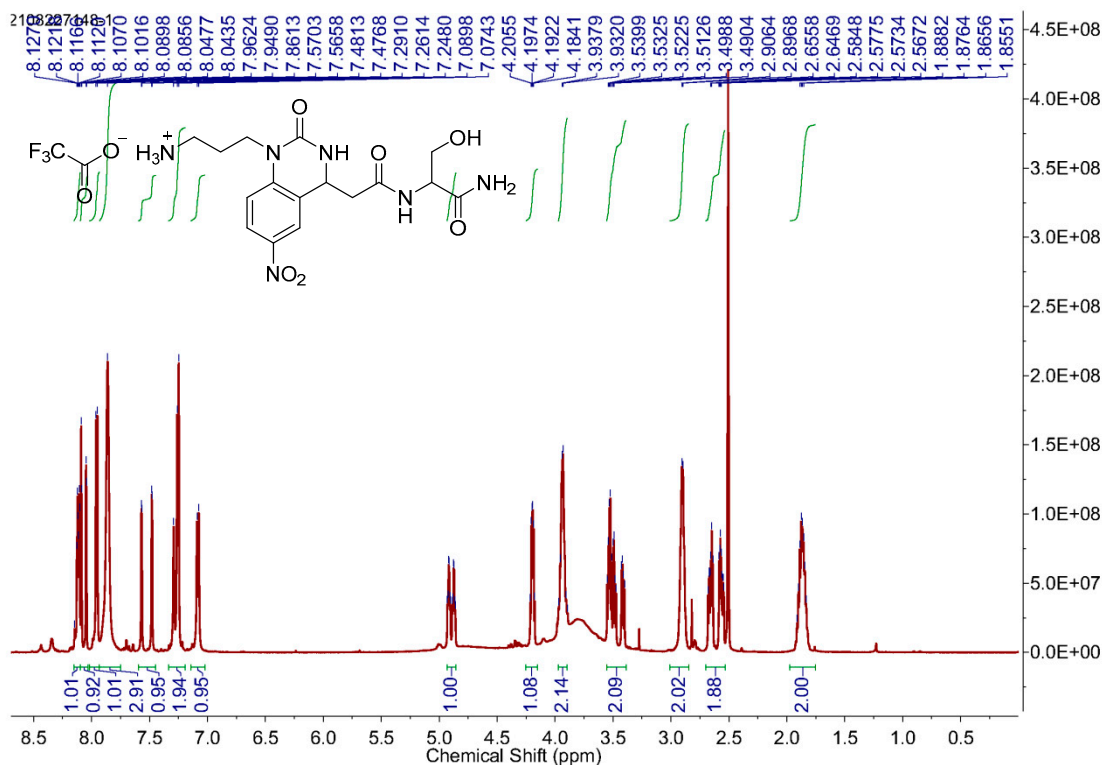
^1H NMR spectra (D_2O) of (CA1-g)·TFA



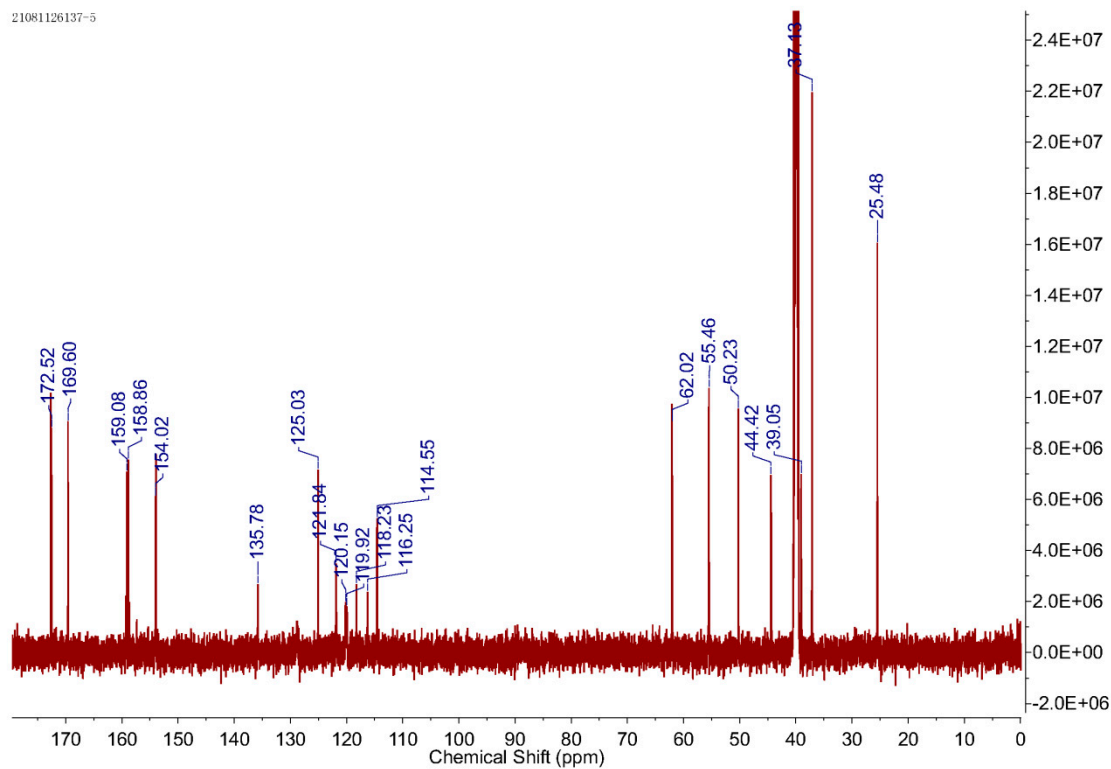
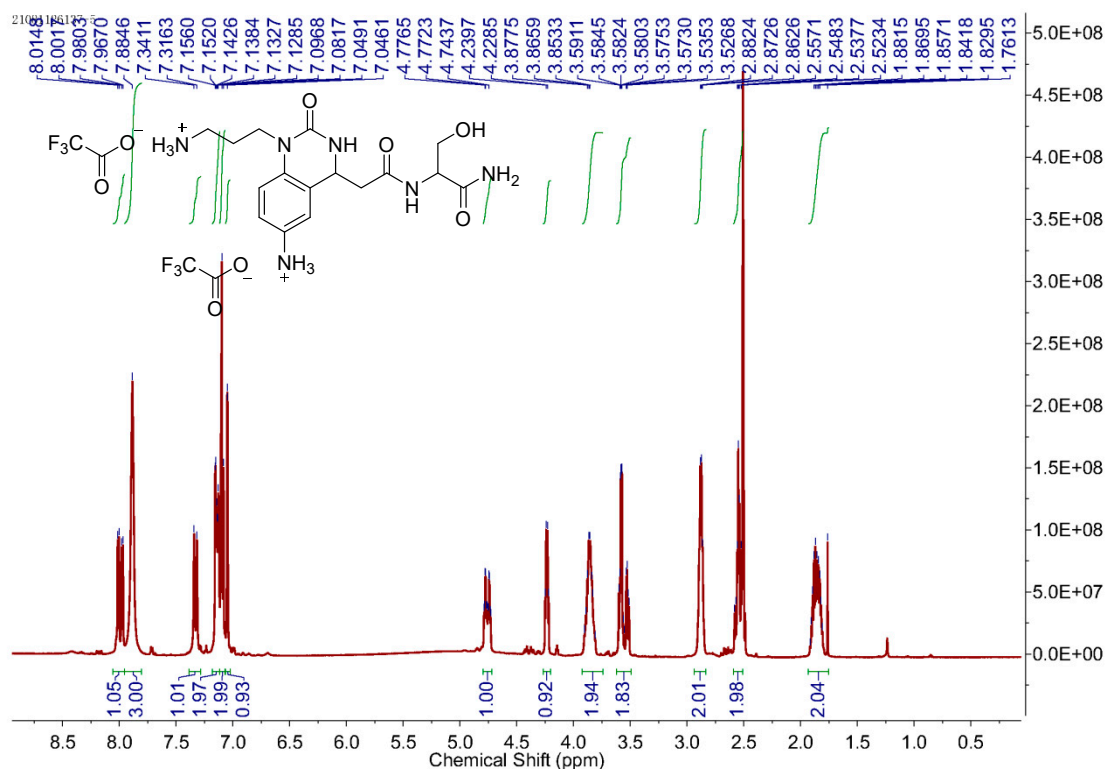
¹H NMR and ¹³C NMR spectra (d6-DMSO) of *N*-Alloc-3-amino-3-(2-fluoro-5-nitrophenyl) propionic acid 3'



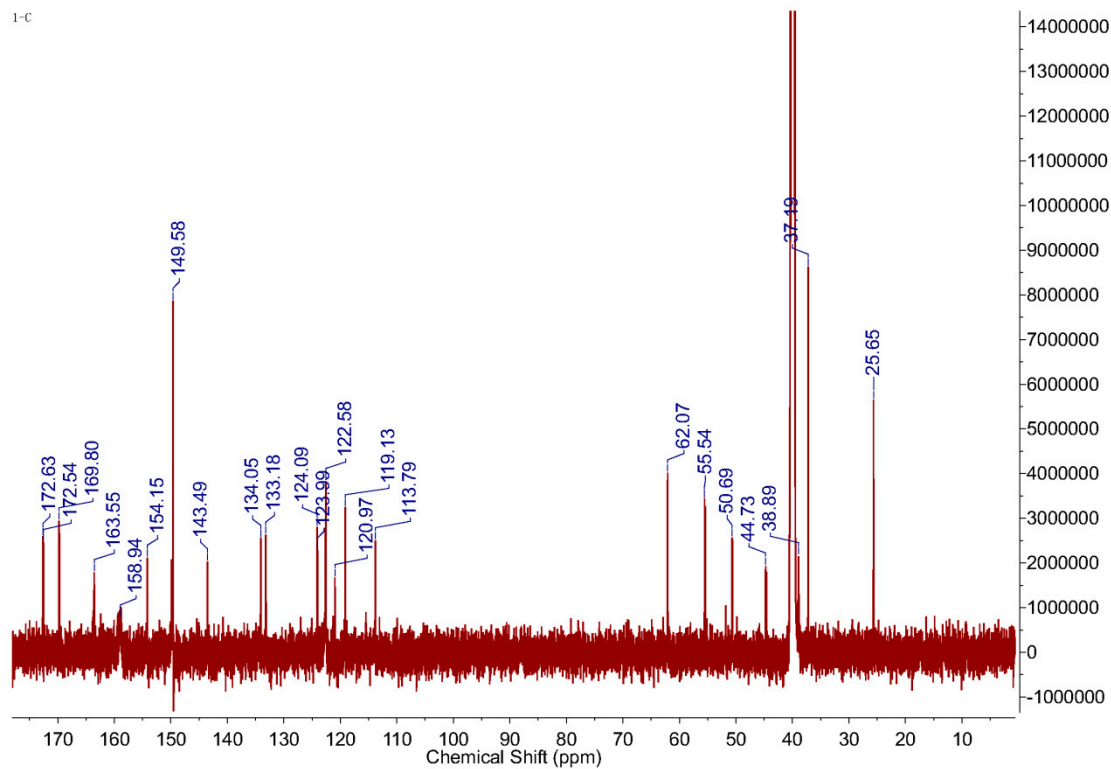
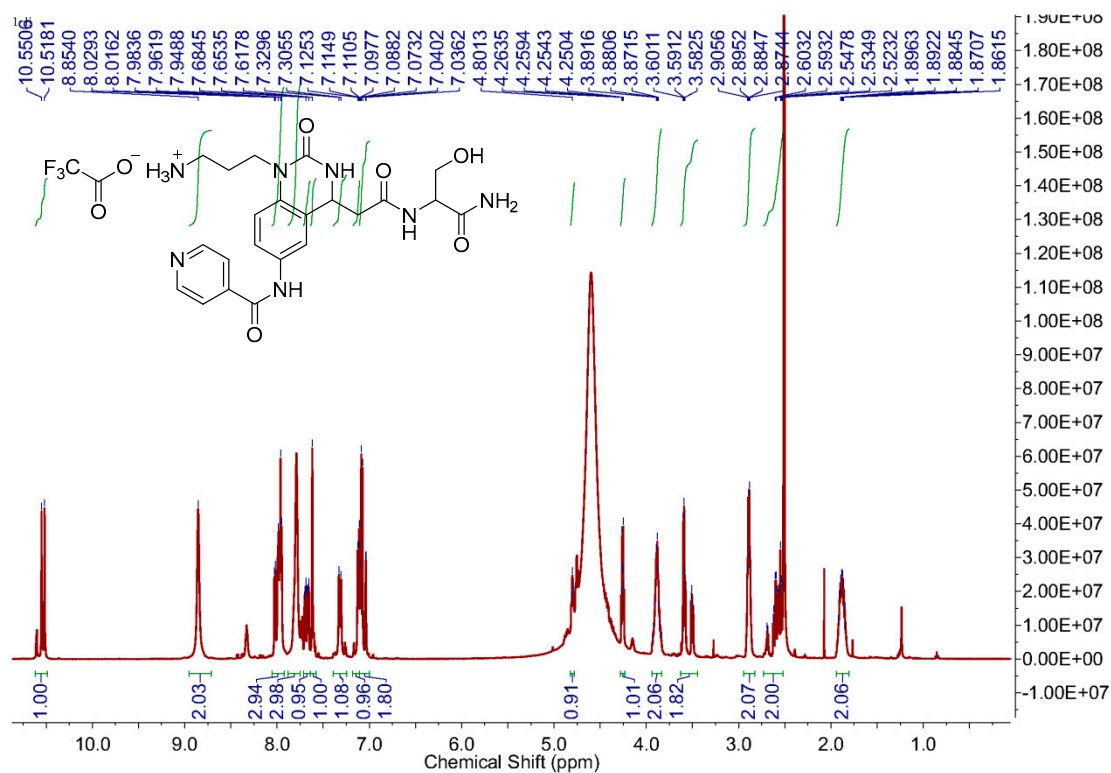
(CA1-6)·TFA



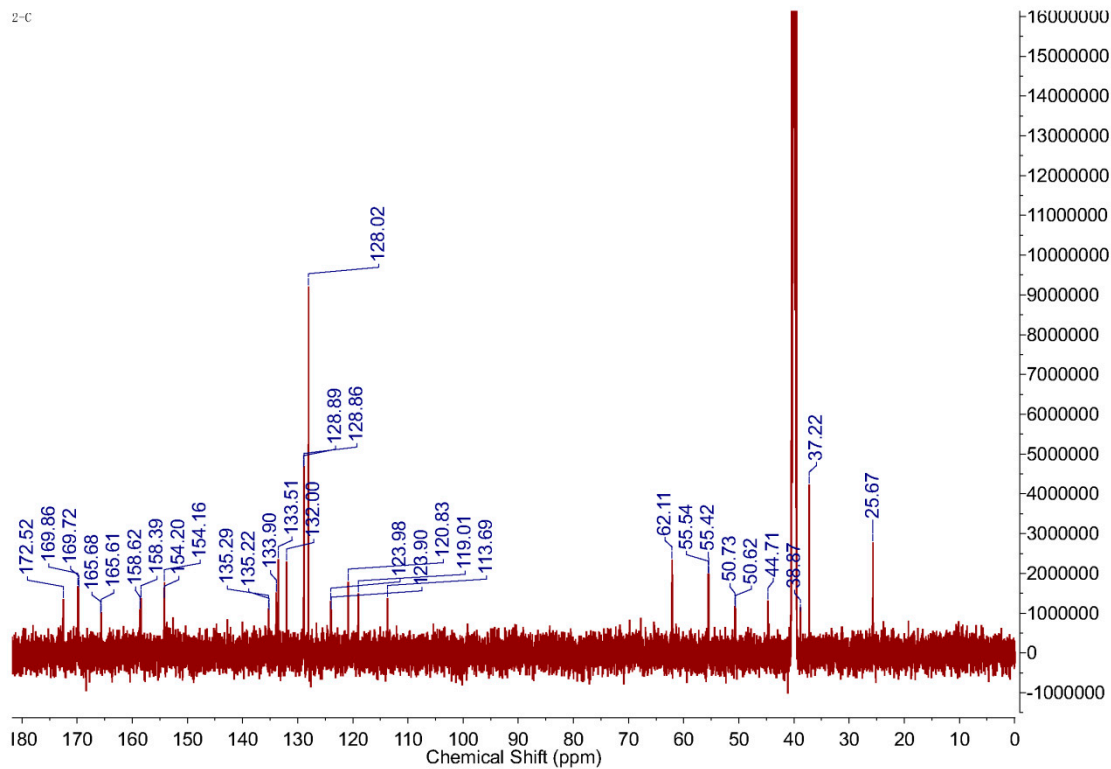
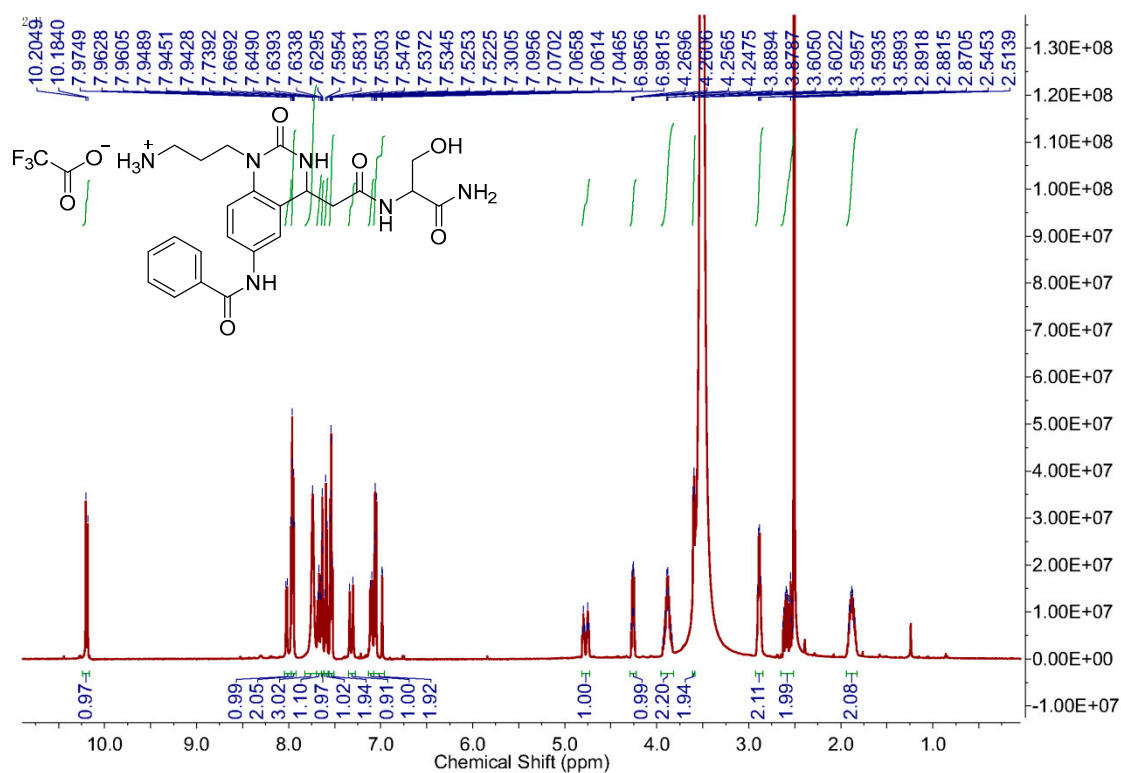
(CA1-7)·TFA



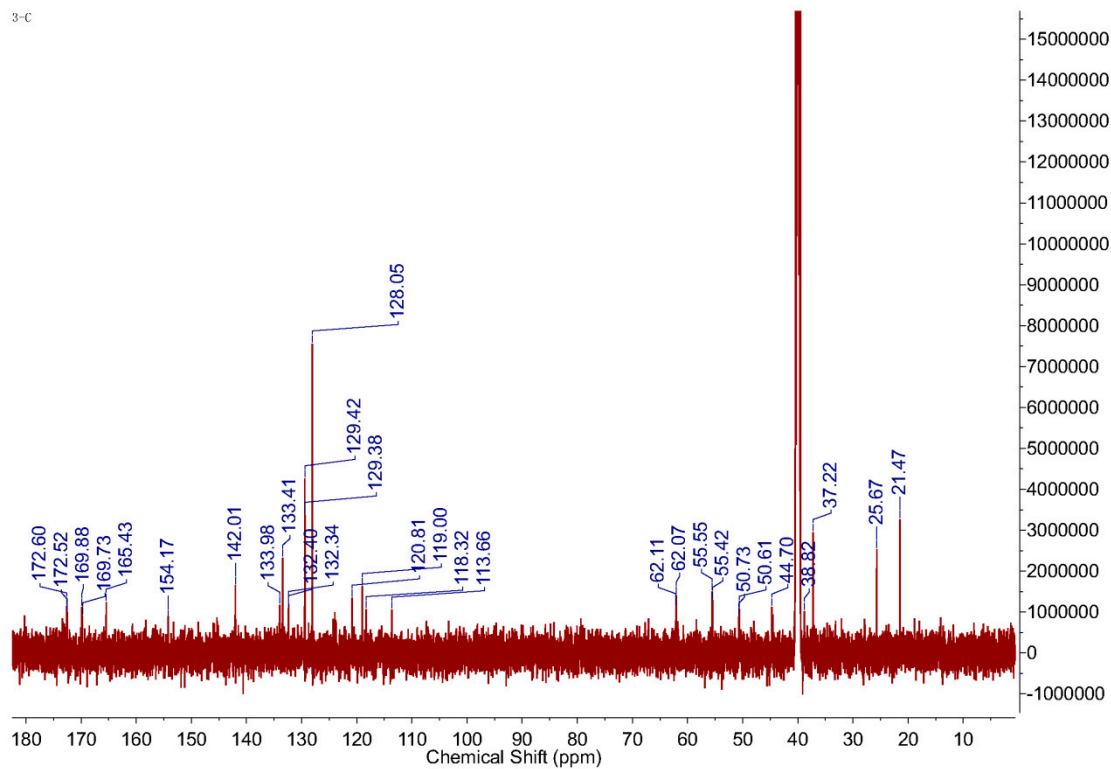
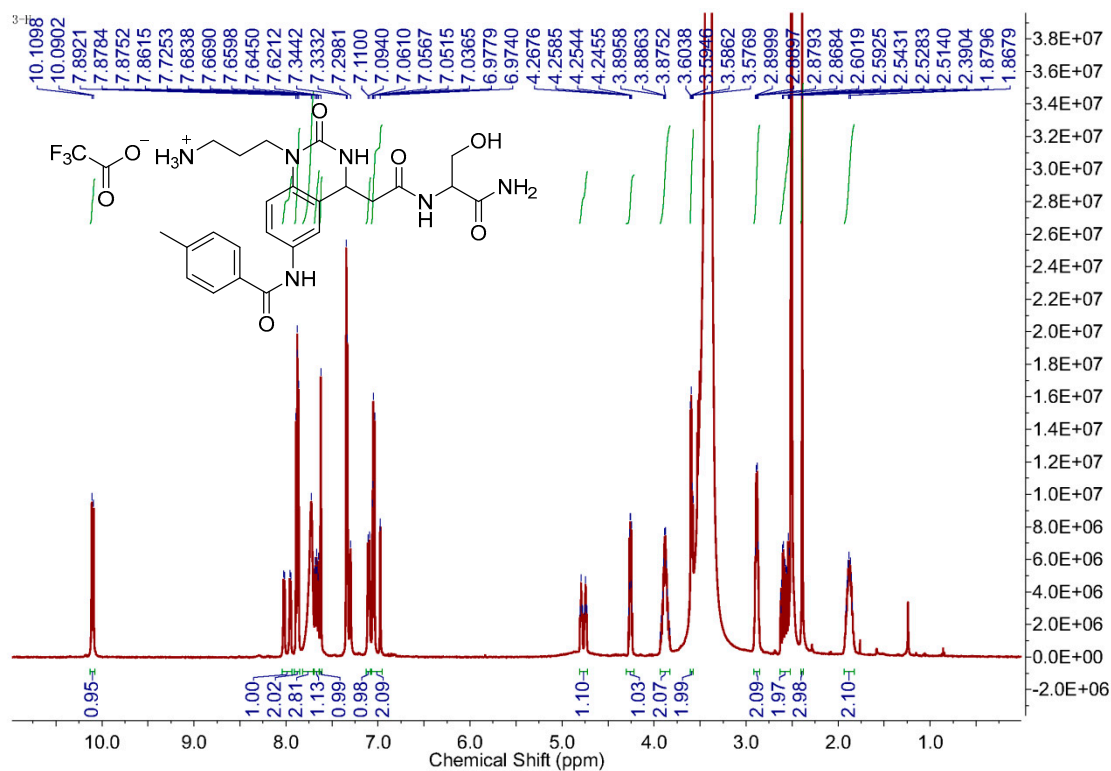
(CA1-a)·TFA



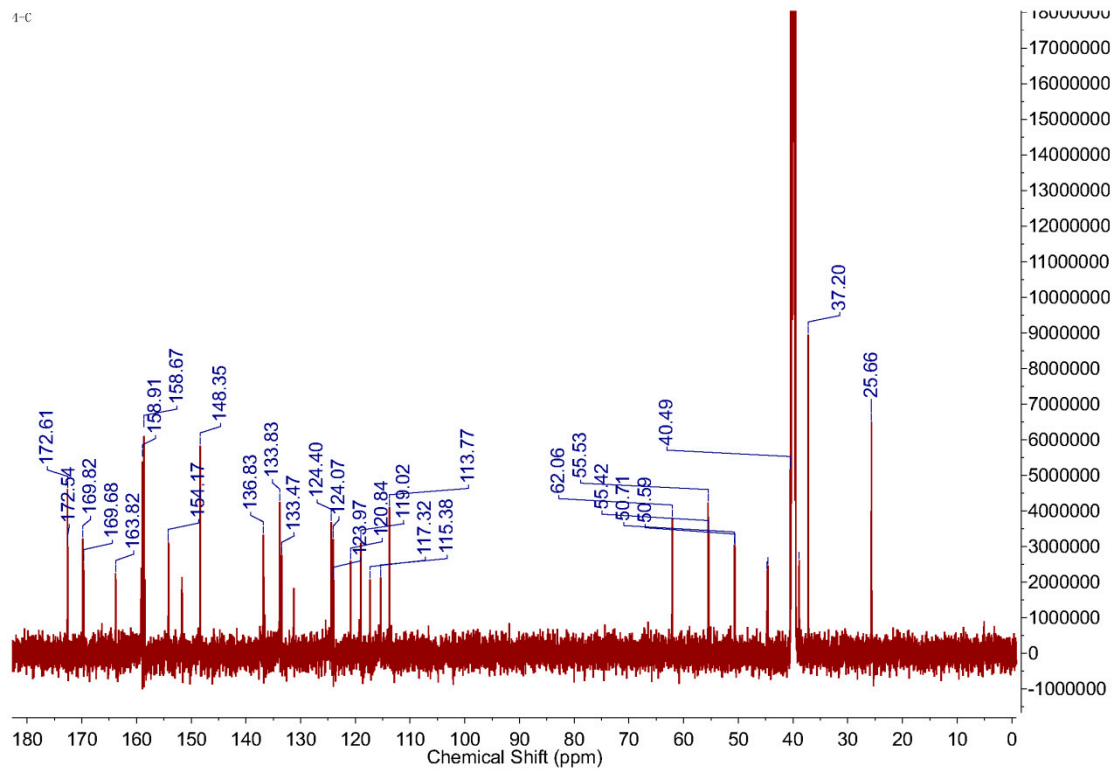
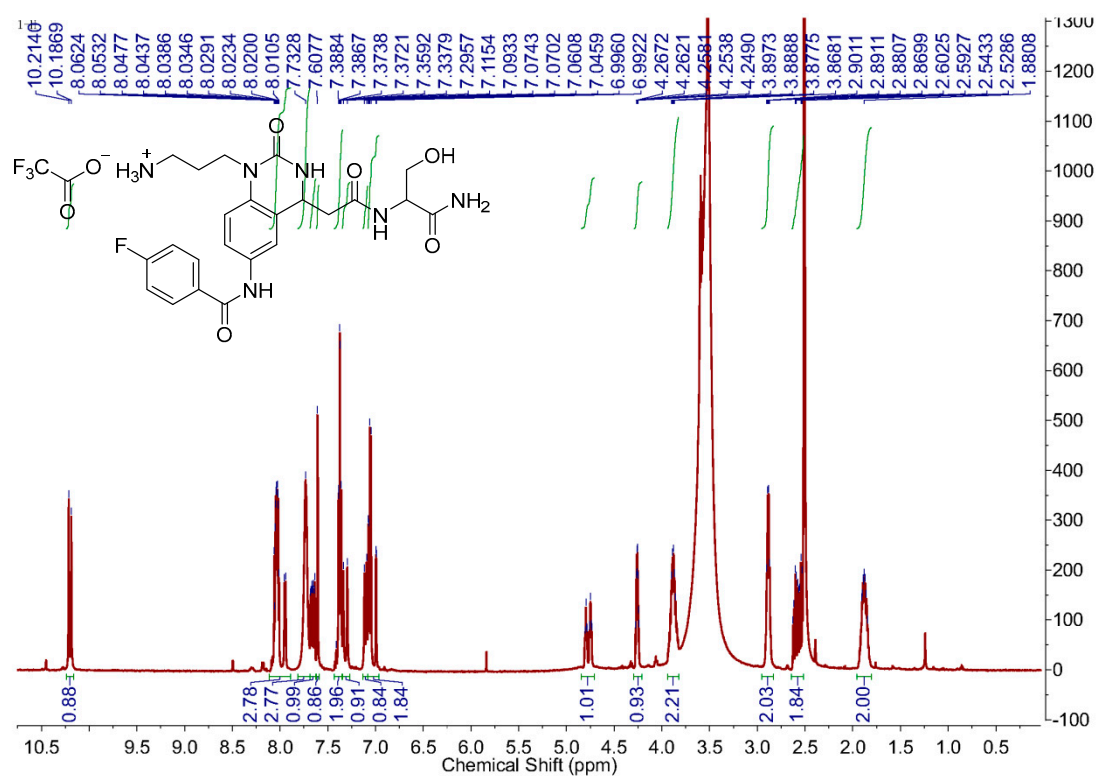
(CA1-b)·TFA



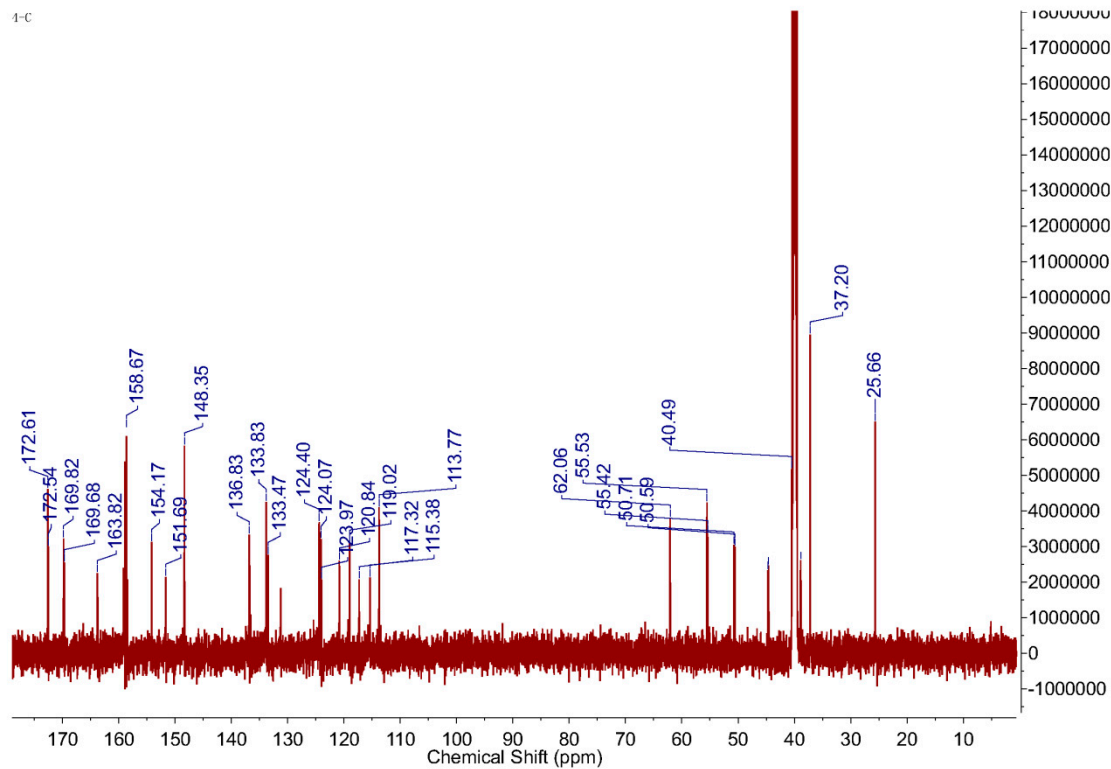
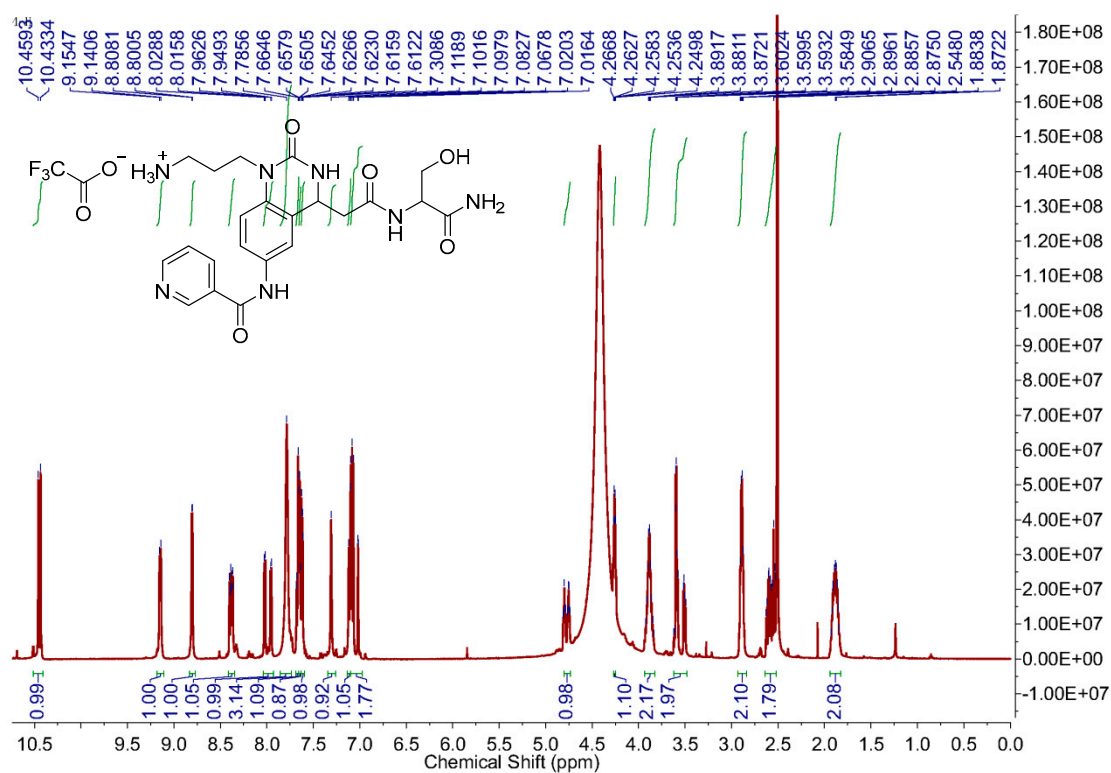
(CA1-c)·TFA



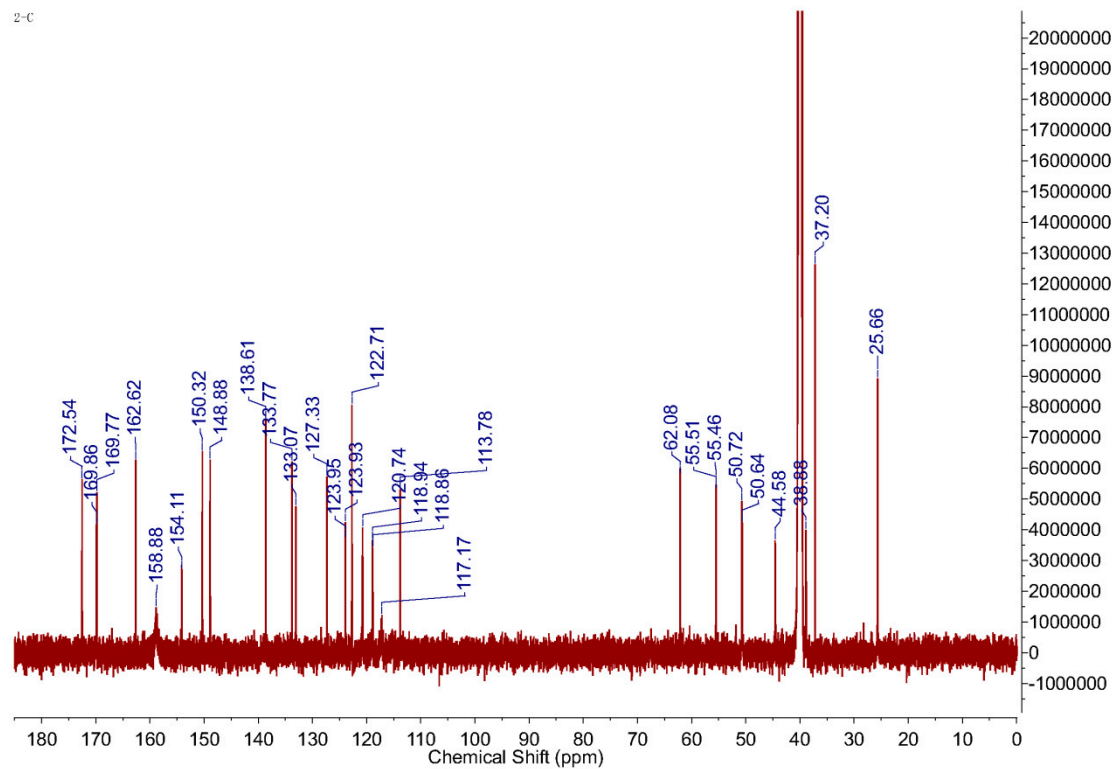
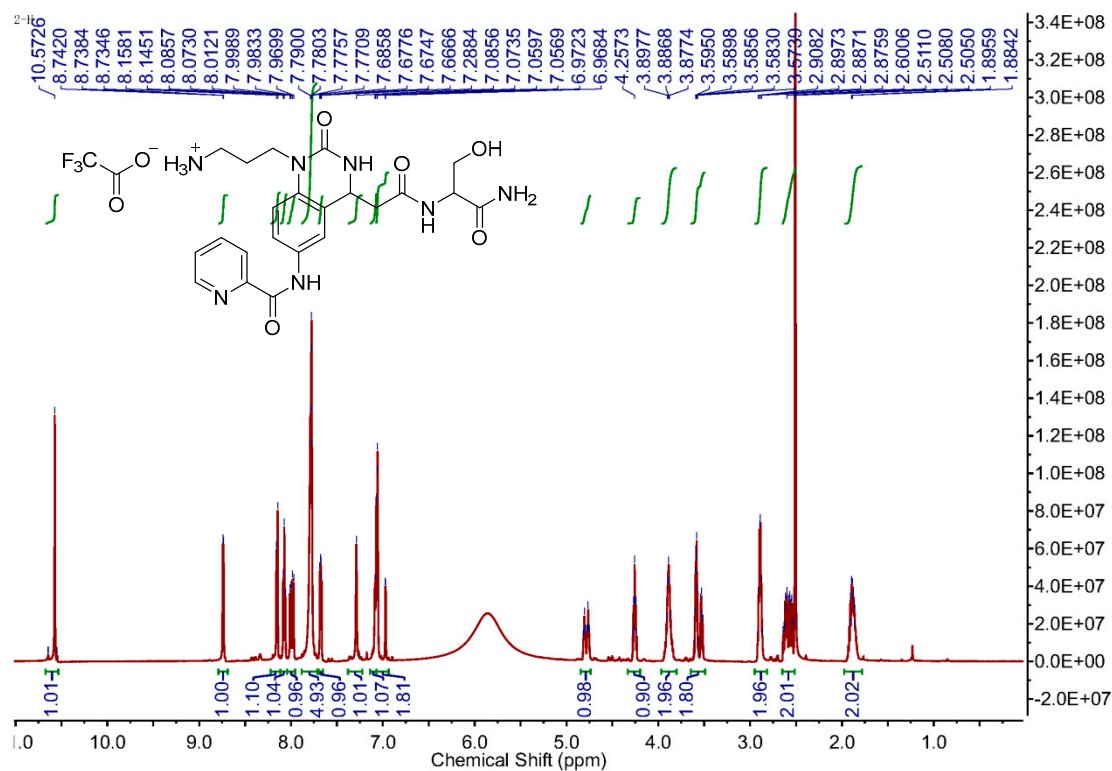
(CA1-d)·TFA



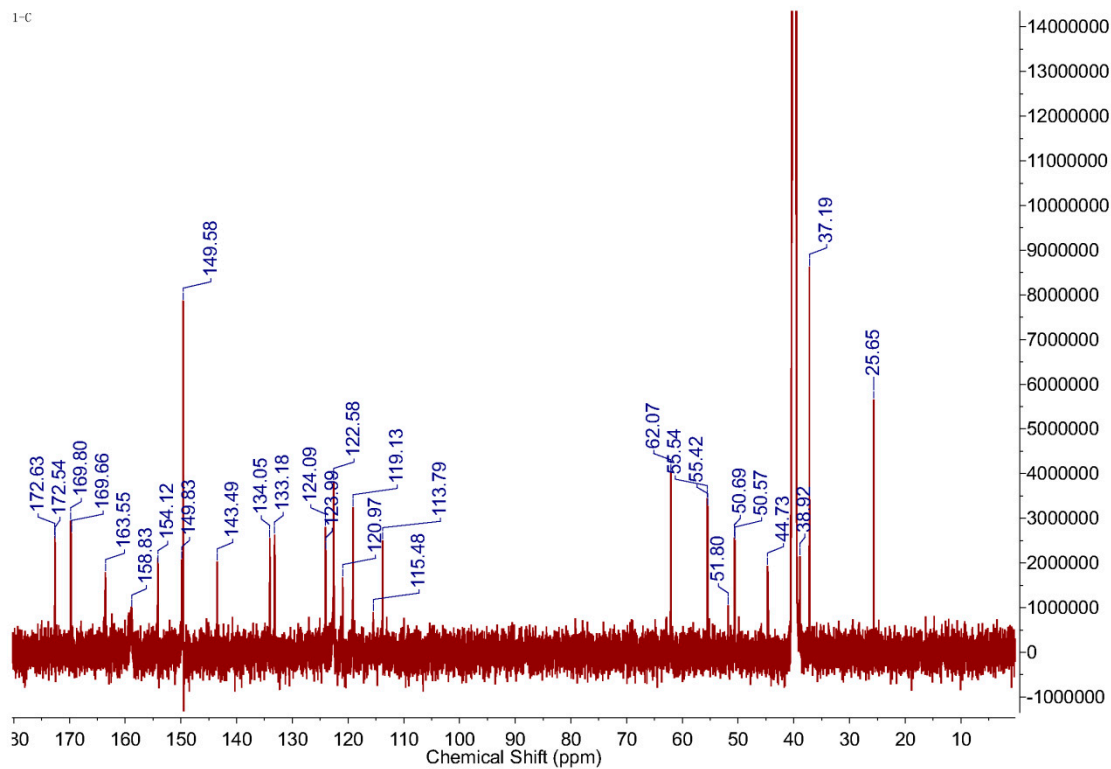
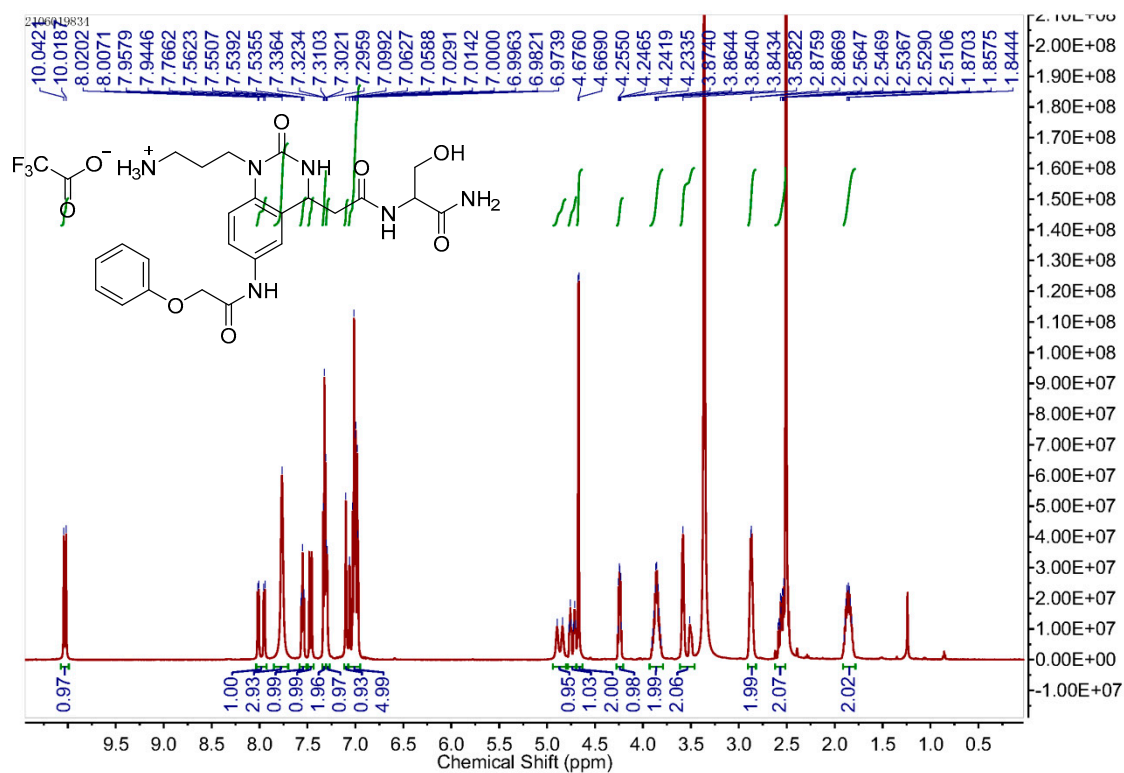
(CA1-e)·TFA



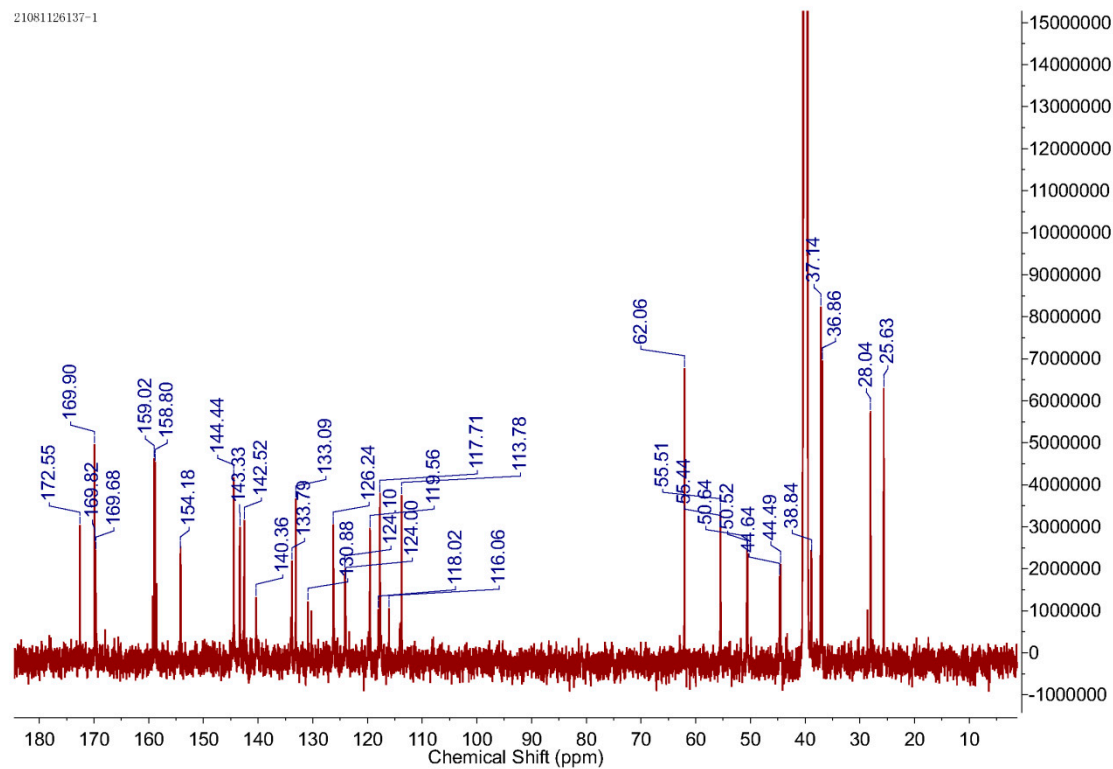
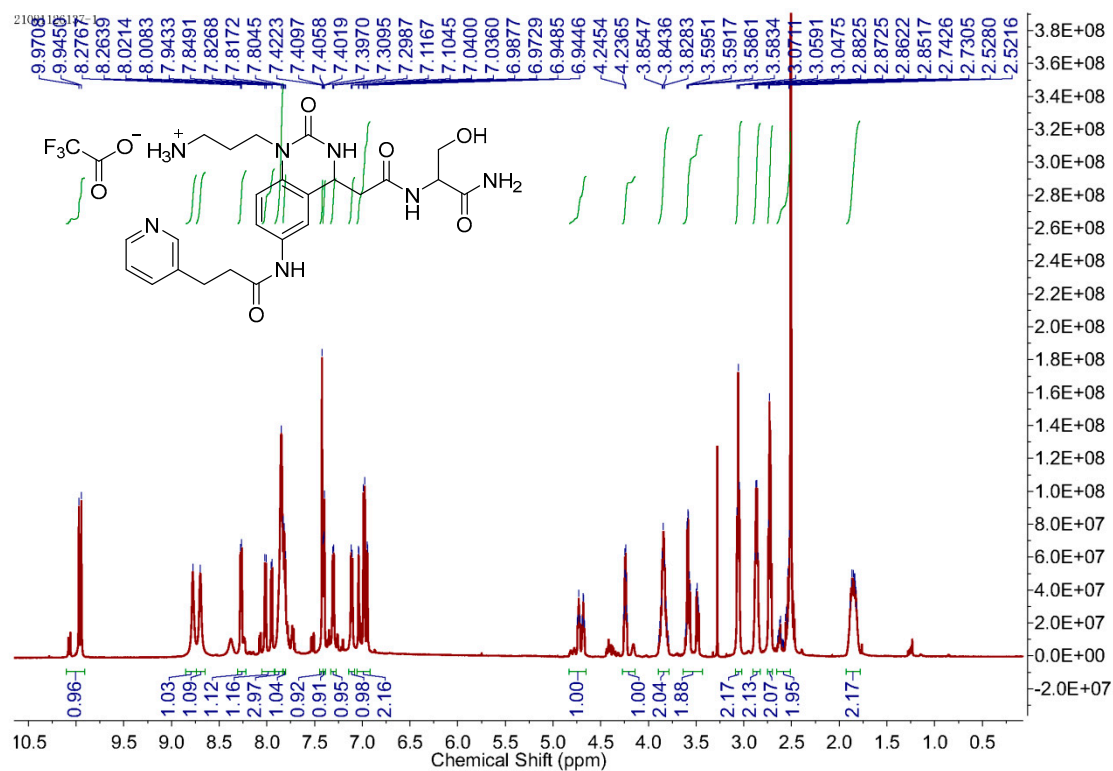
(CA1-f)·TFA



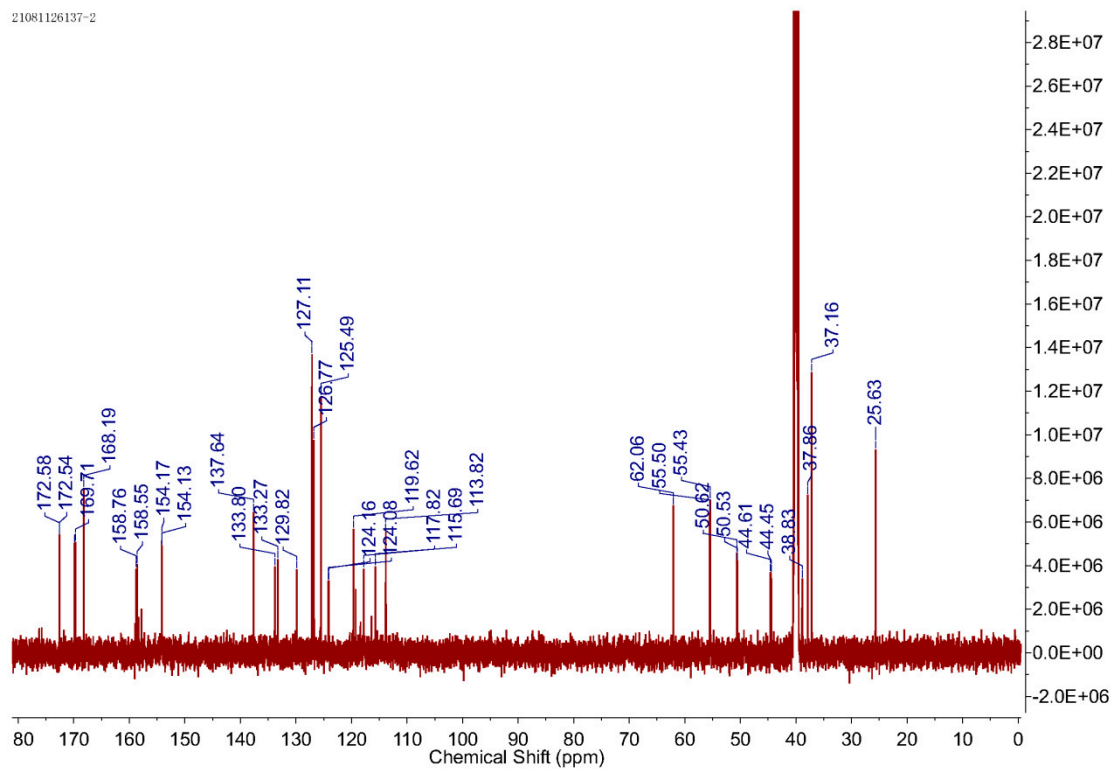
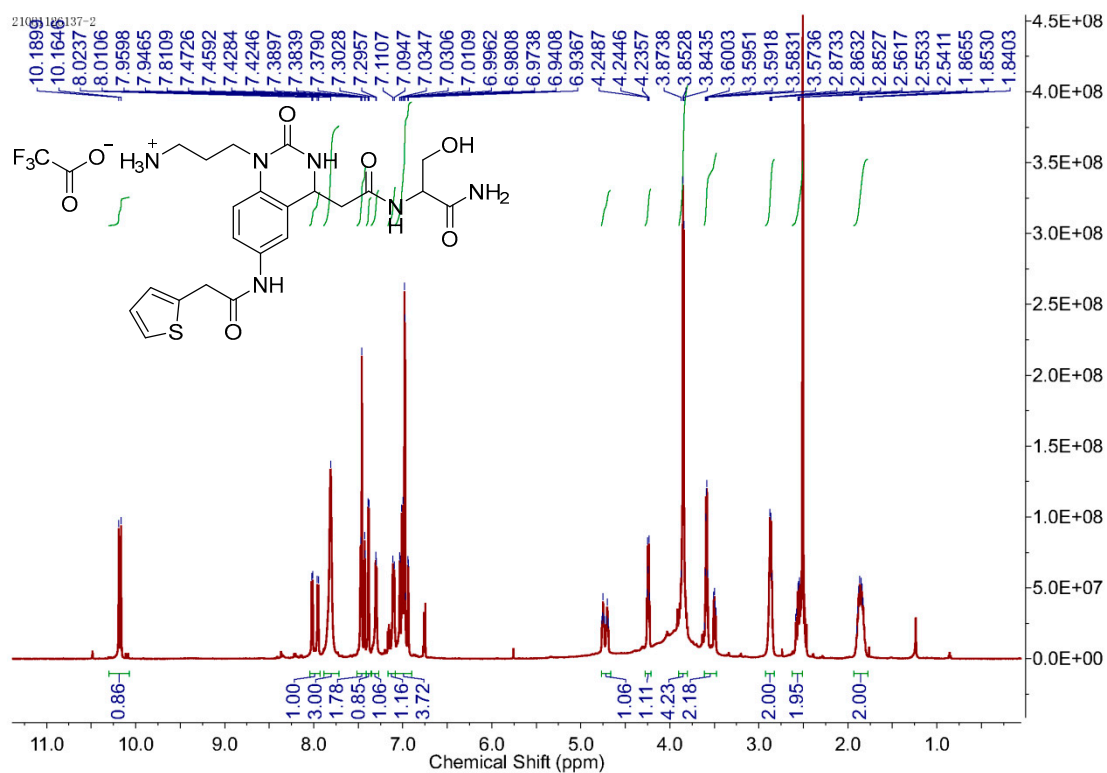
(CA1-g)·TFA



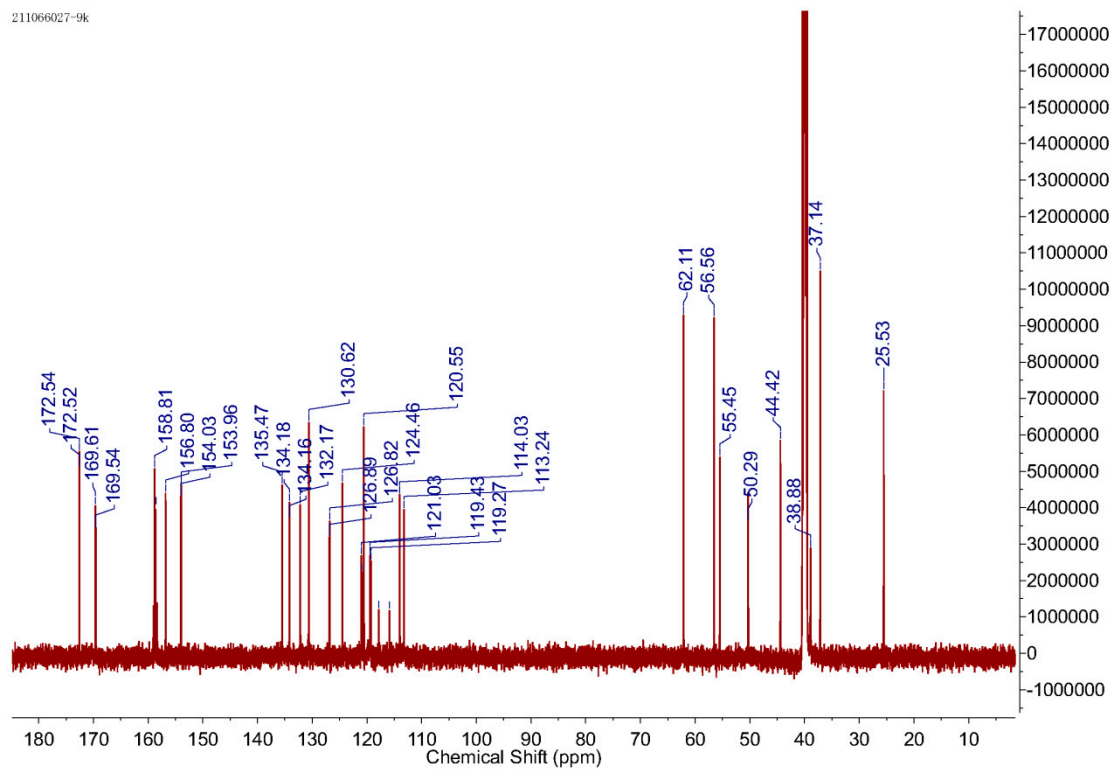
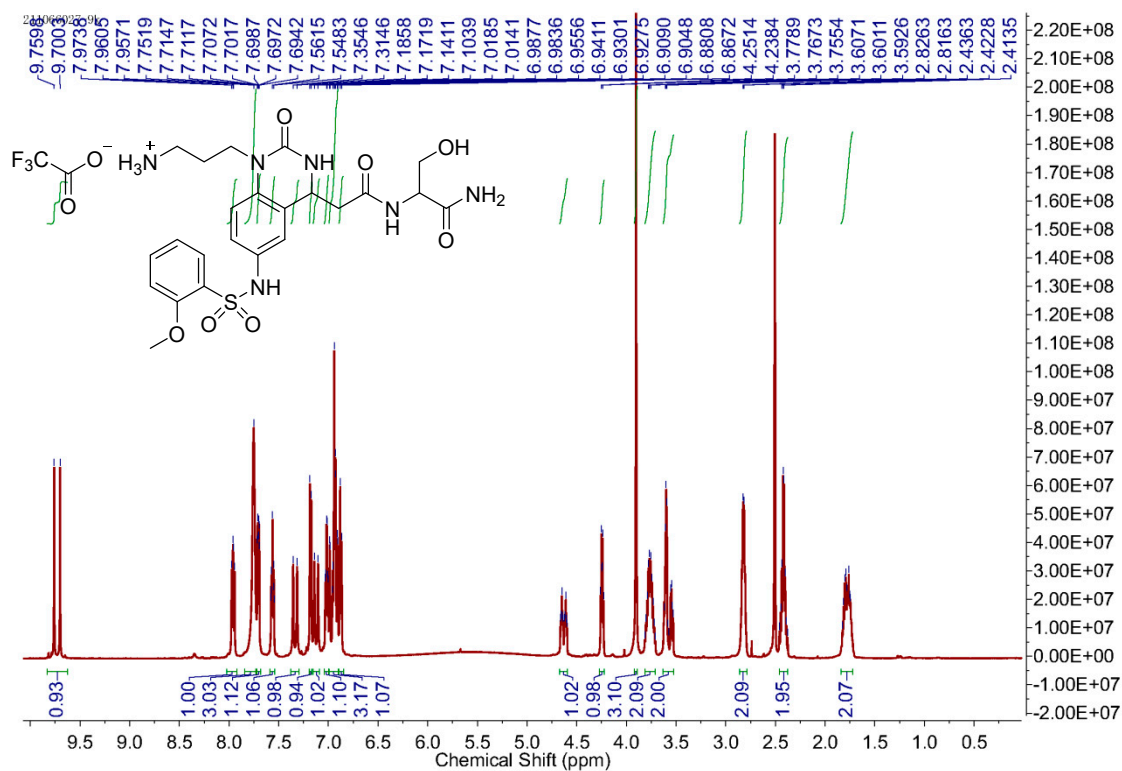
(CA1-h)·TFA



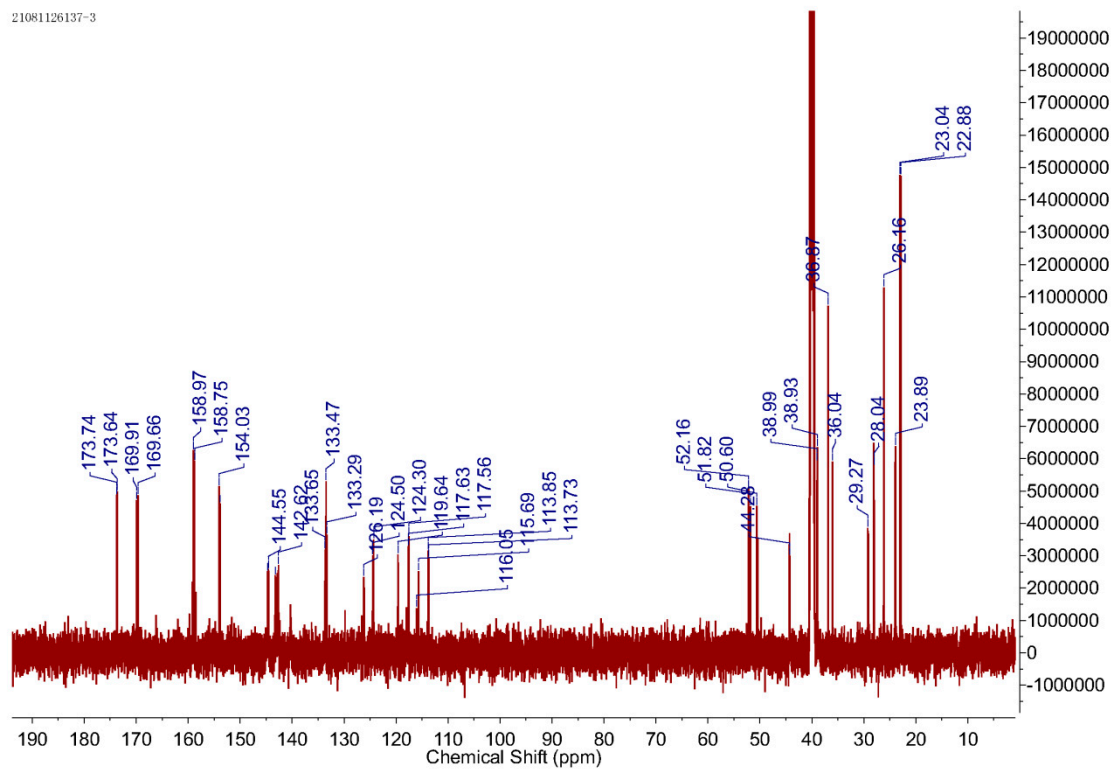
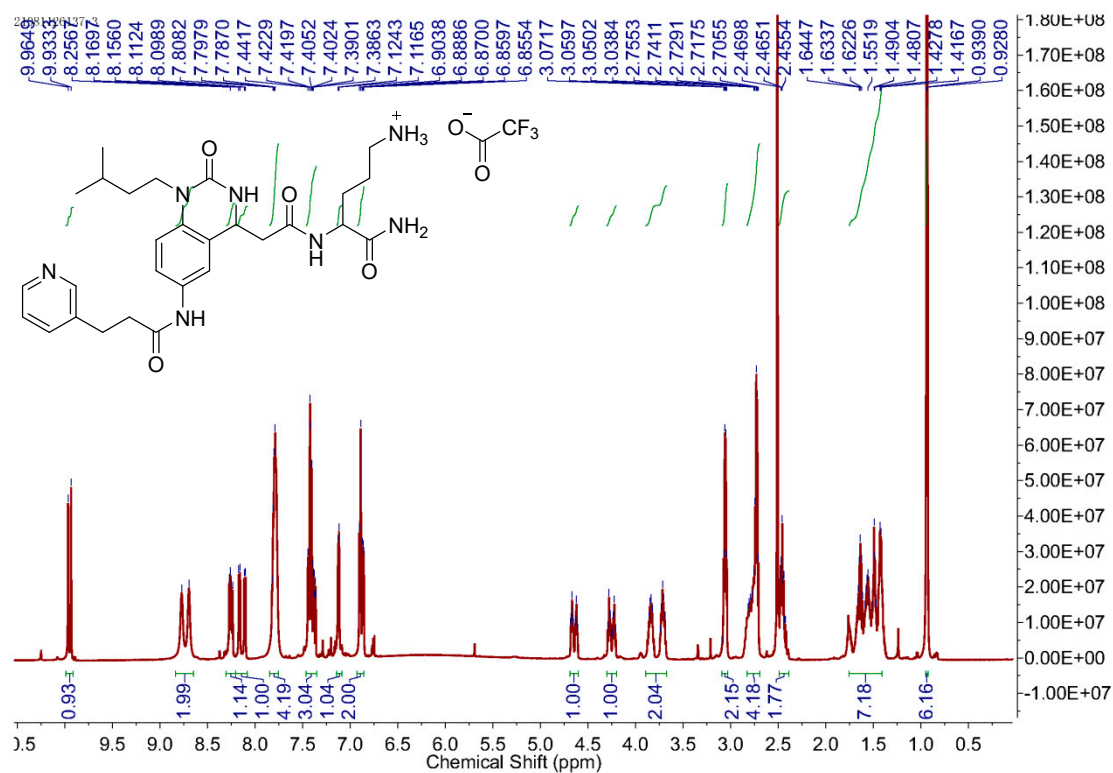
(CA1-i)·TFA



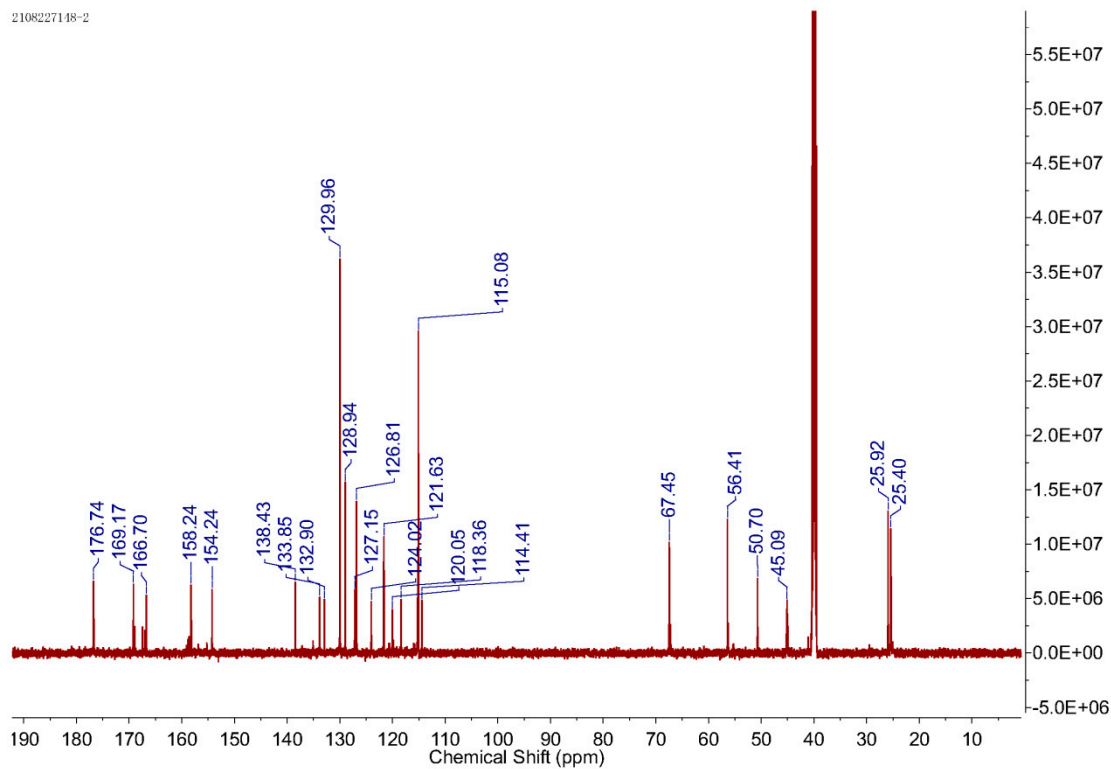
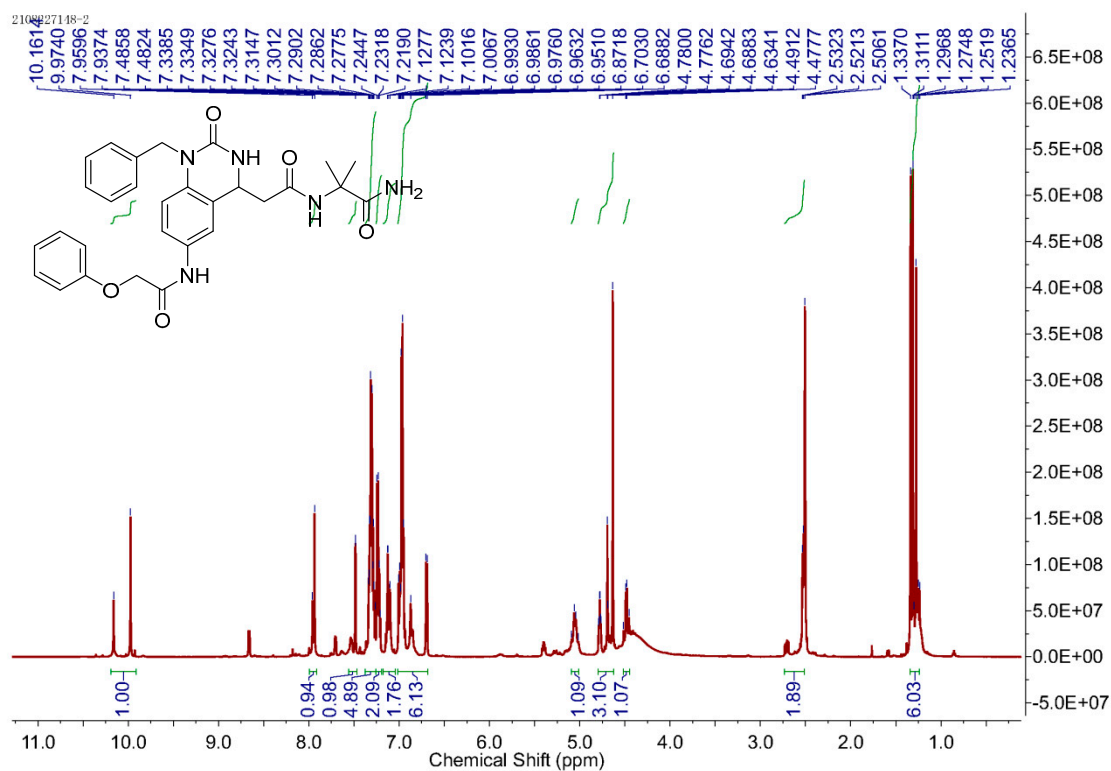
(CA1-j)·TFA



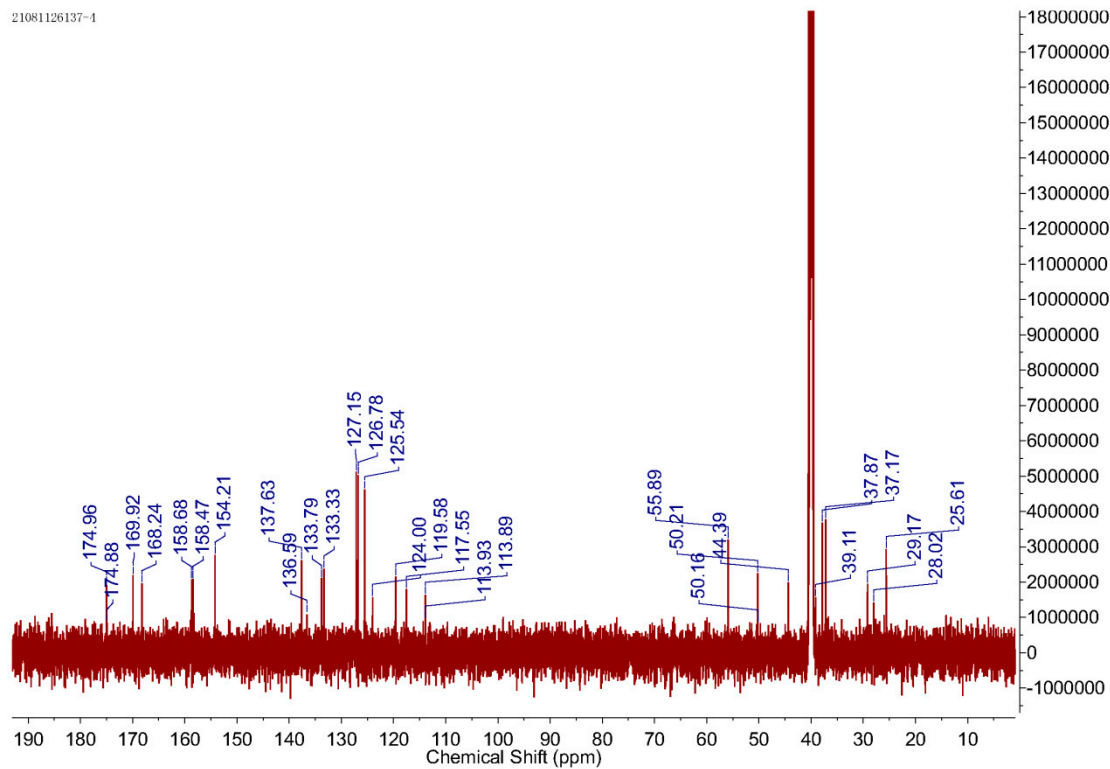
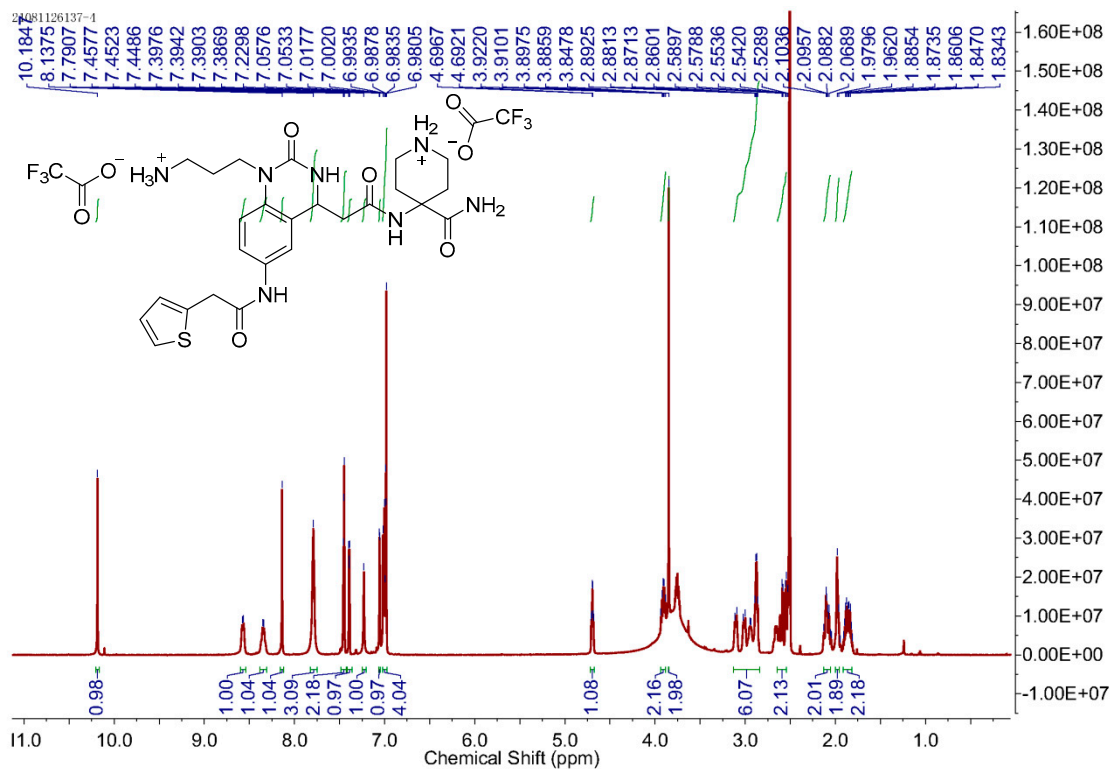
(CA3)·TFA



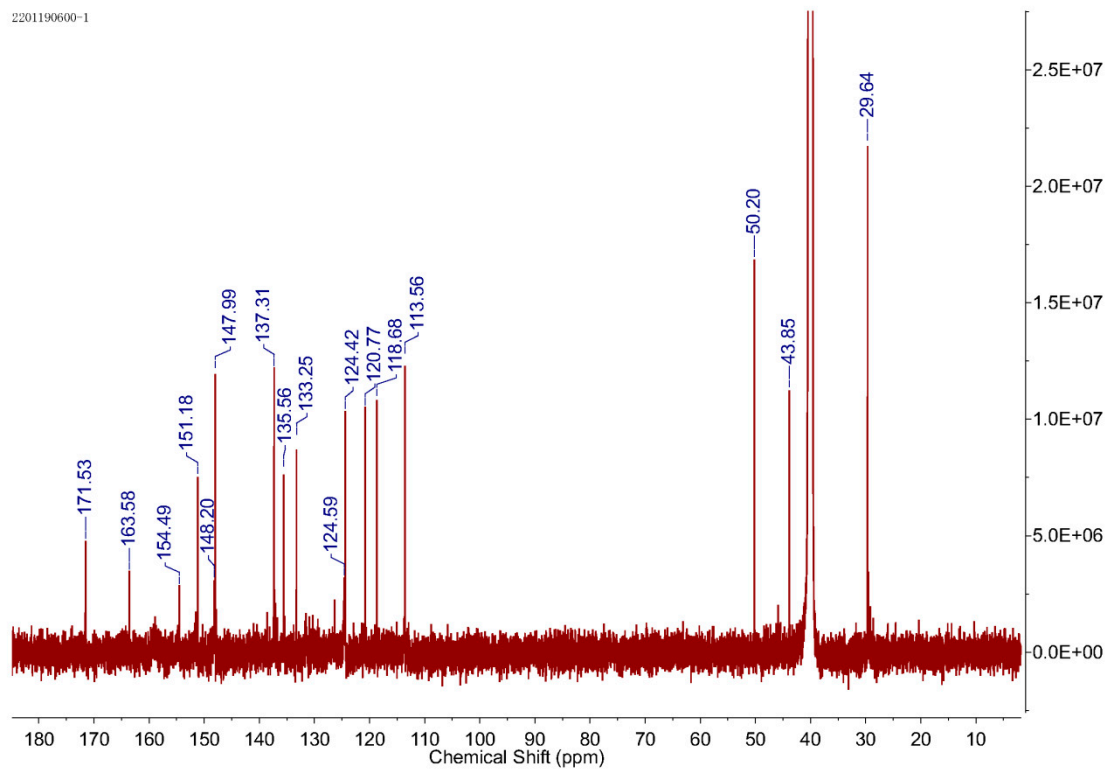
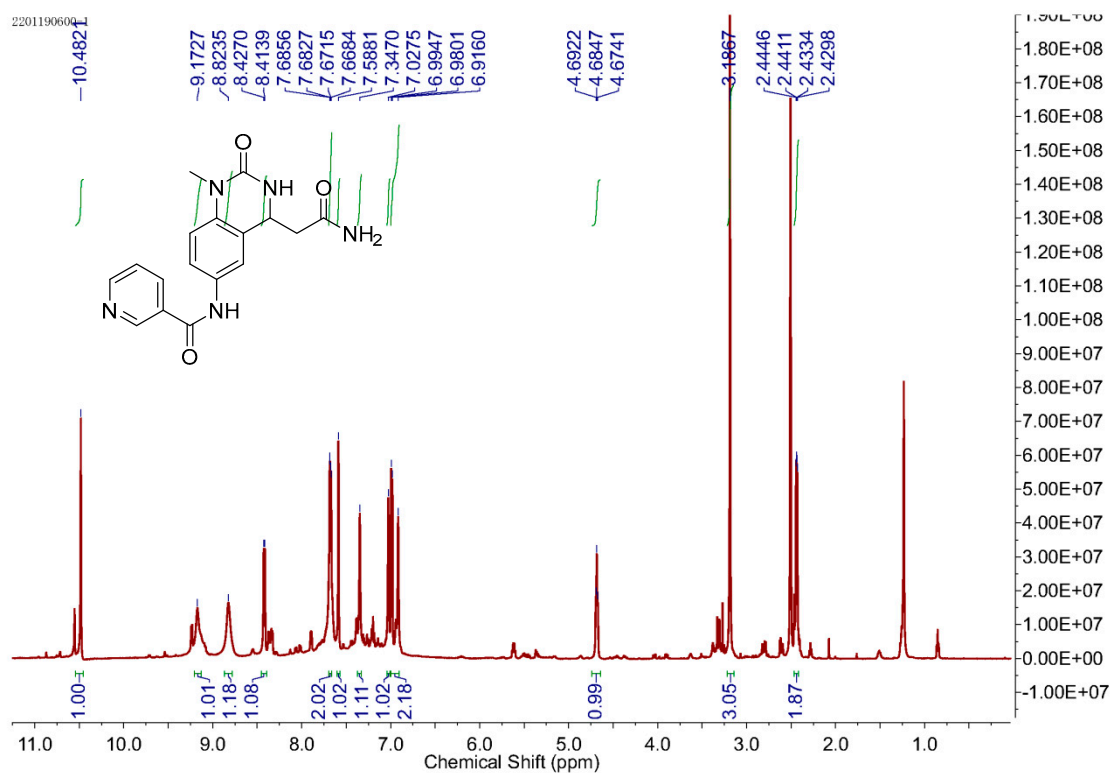
CA4



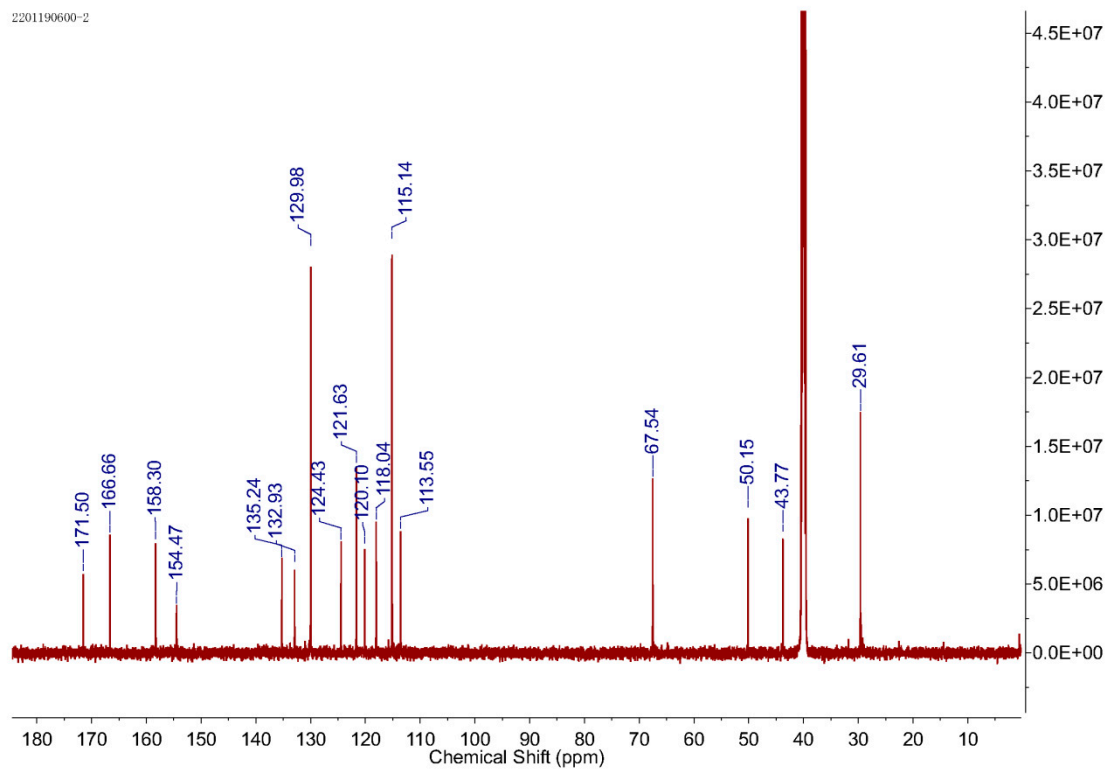
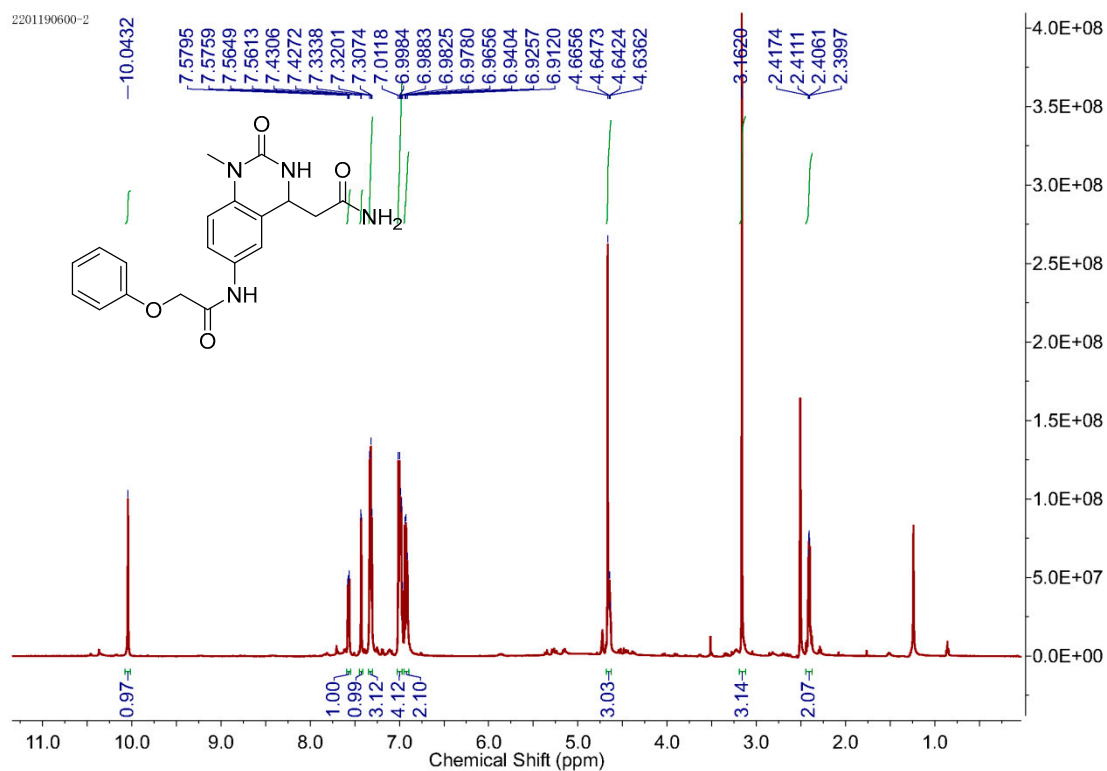
(CA5)·TFA



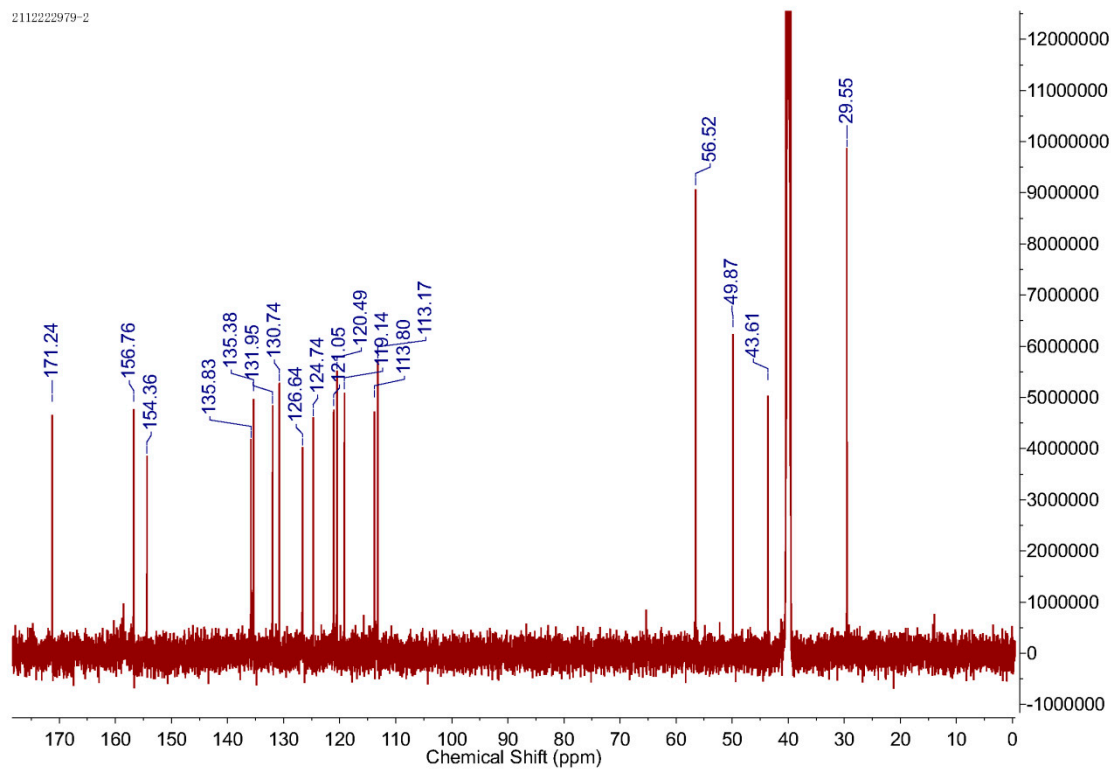
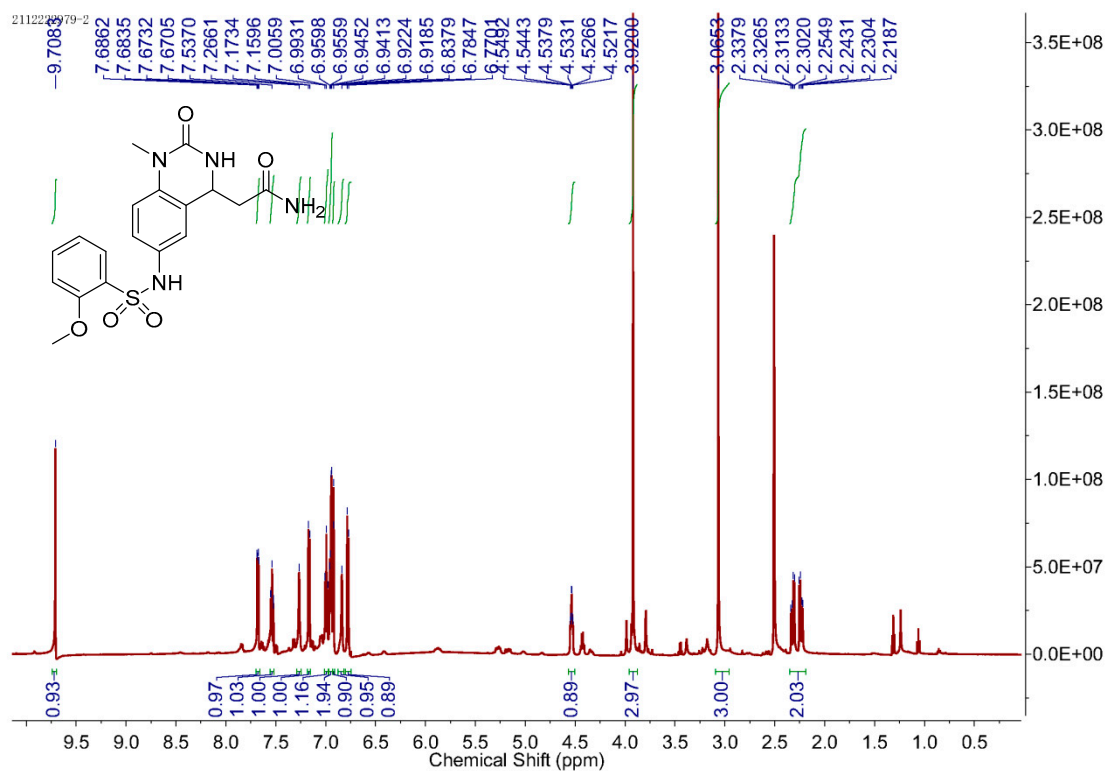
CA6-a



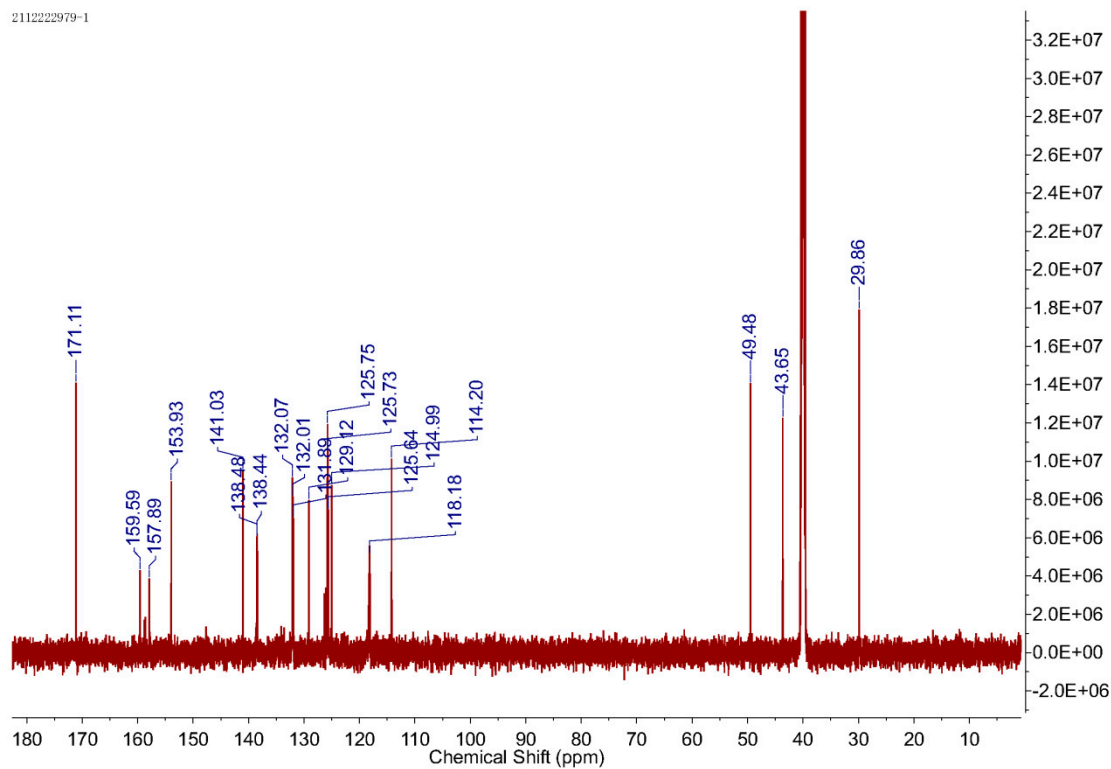
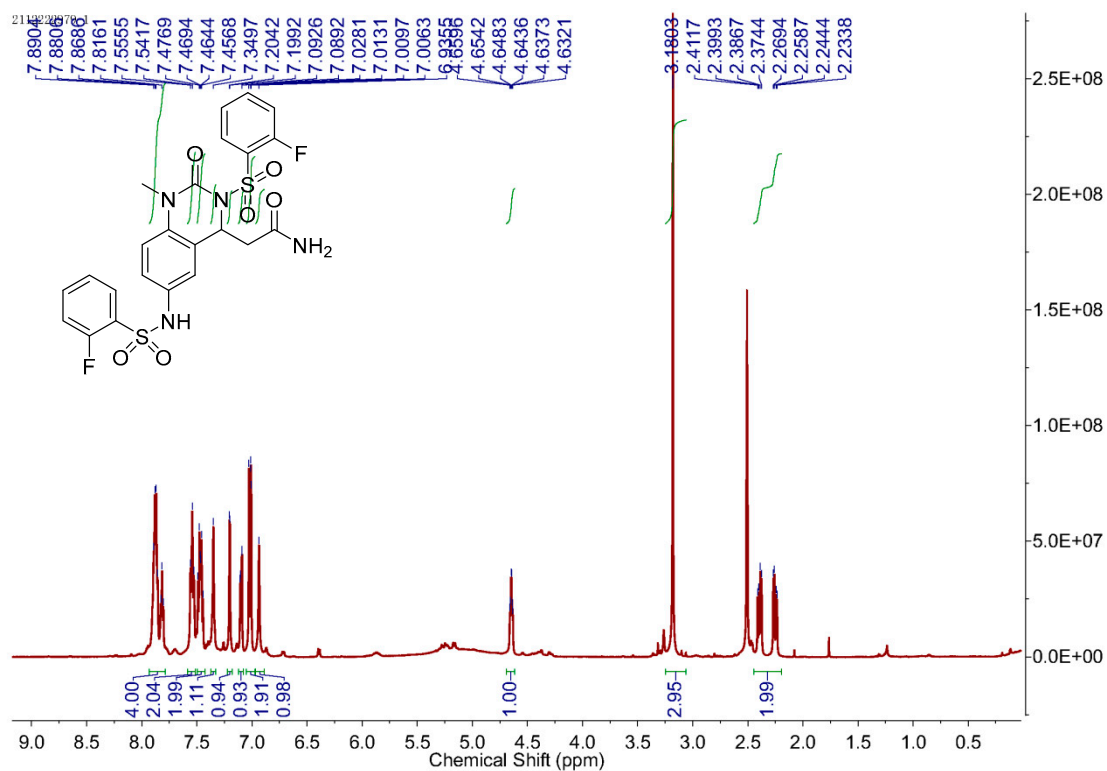
CA6-b



CA7-a

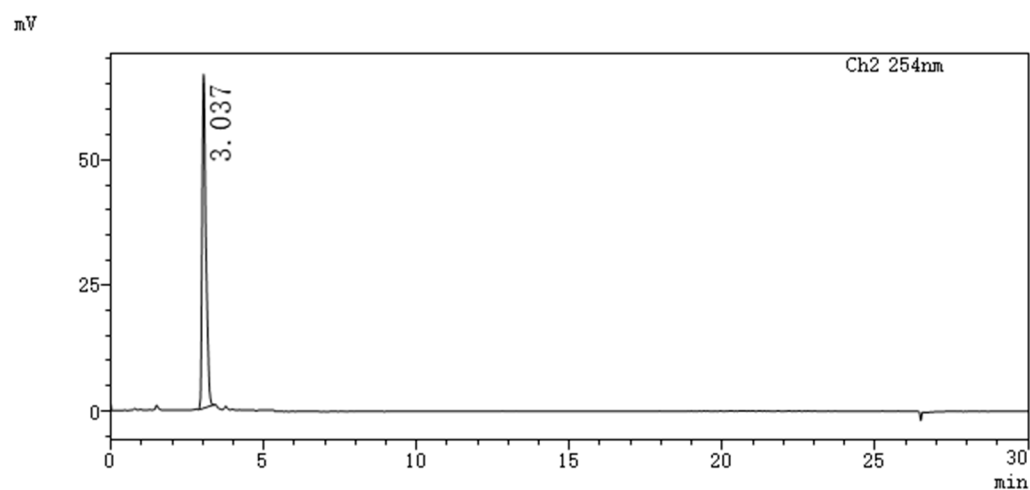


CA7-b'



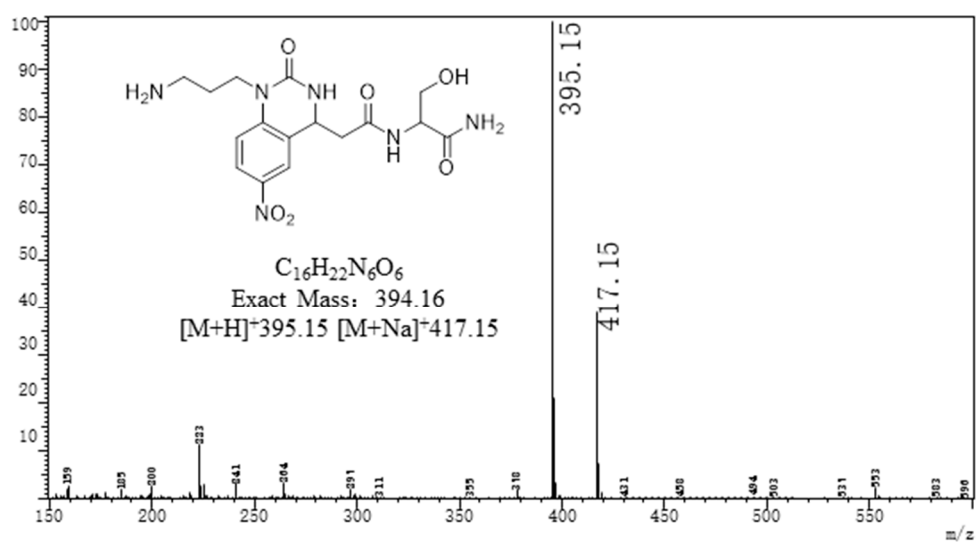
LC/MS Spectrometry

CA1-6



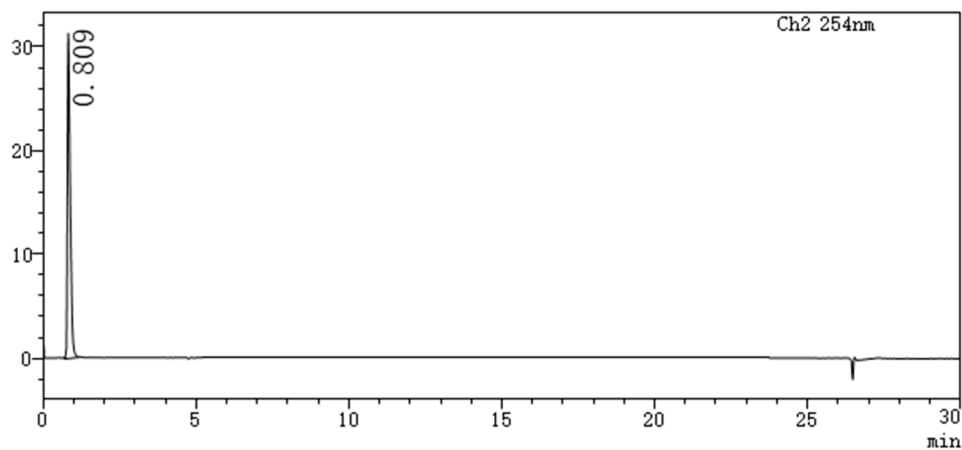
RT: 2.983 min (S#: 180)

Base peak: 395.15 (225870)



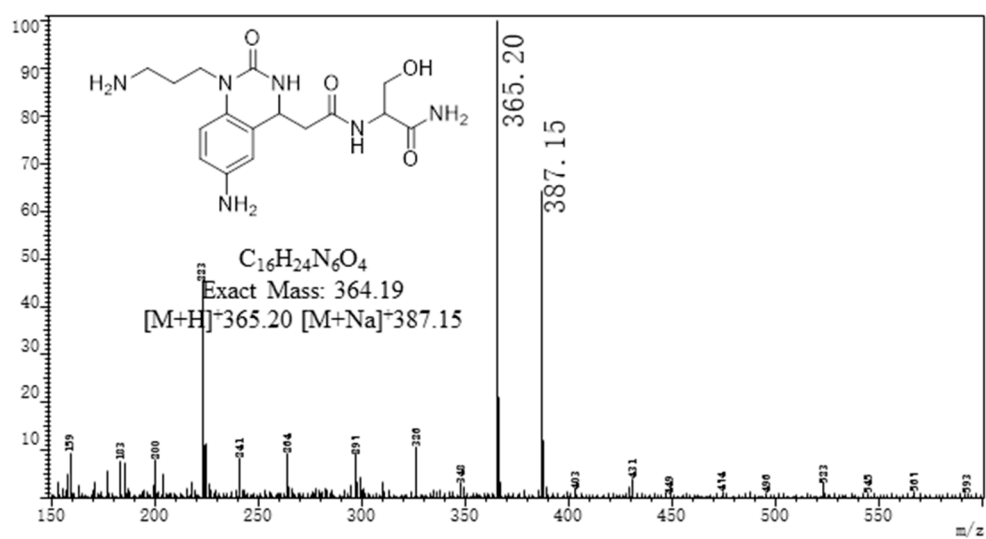
CA1-7

mV

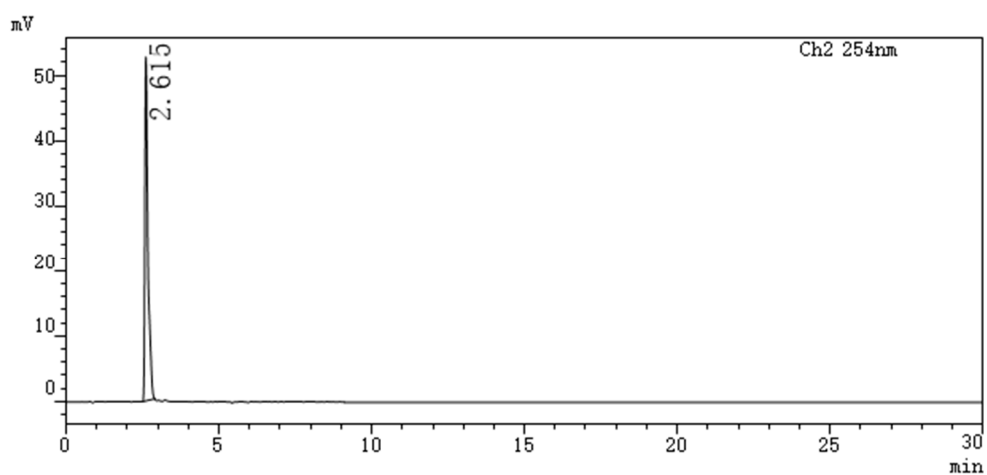


RT: 0.833 min (S#: 51)

Base peak: 365.20 (94449)

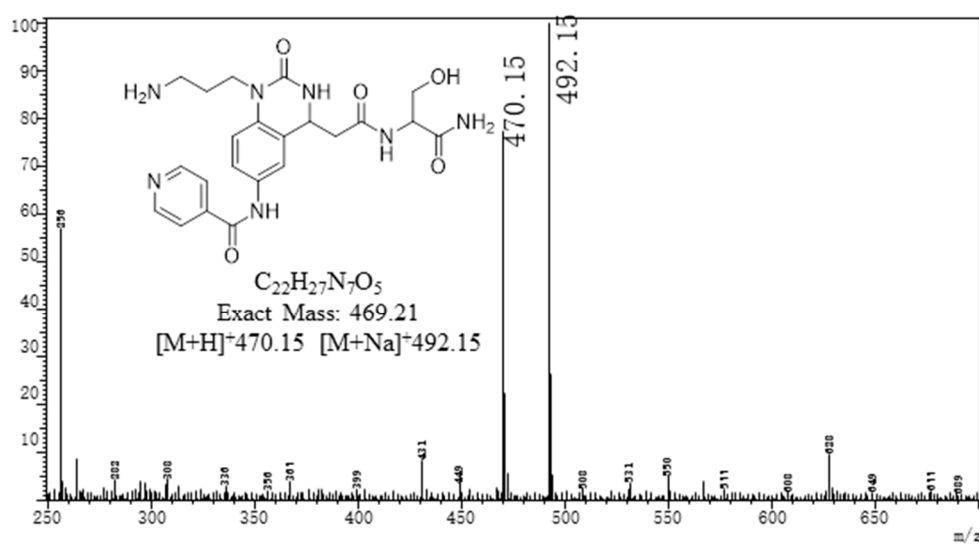


CA1-a

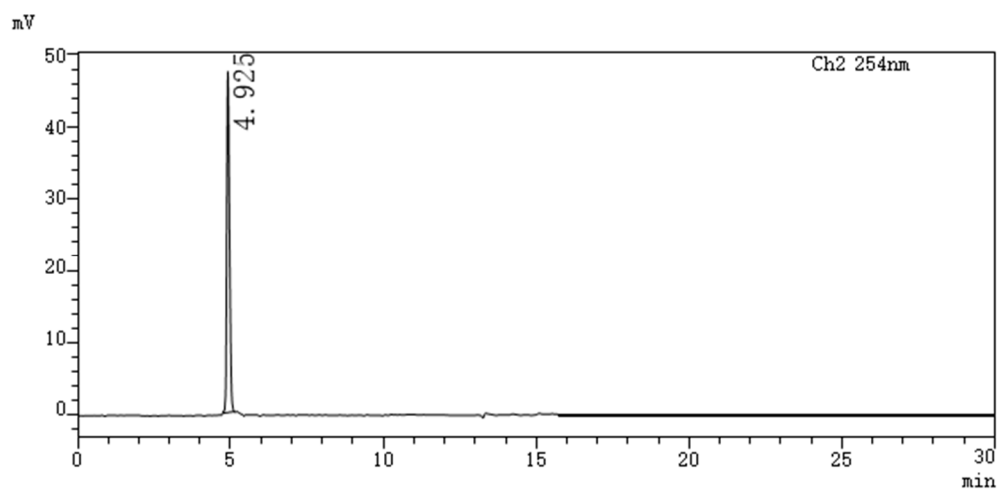


RT: 2.000 min (S#: 121)

Base peak: 492.15 (45287)

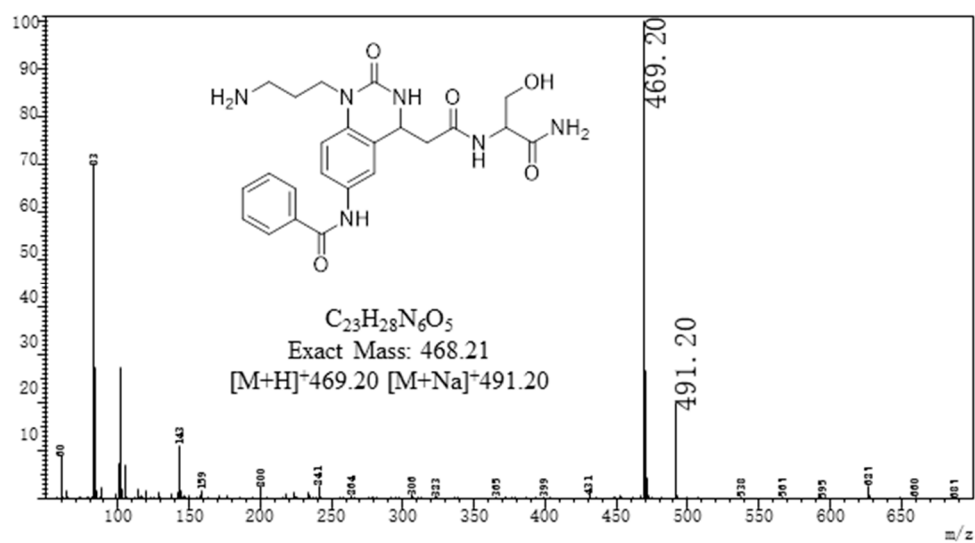


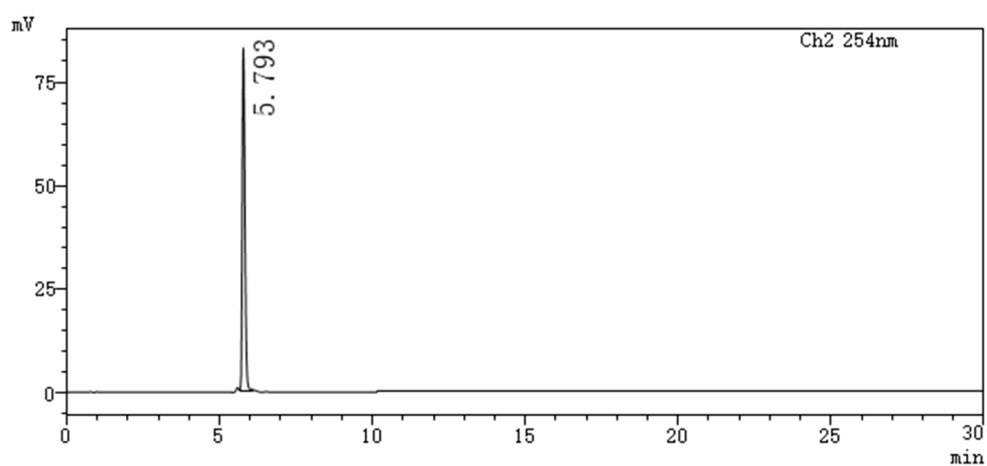
CA1-b



RT: 4.733 min (S#: 285)

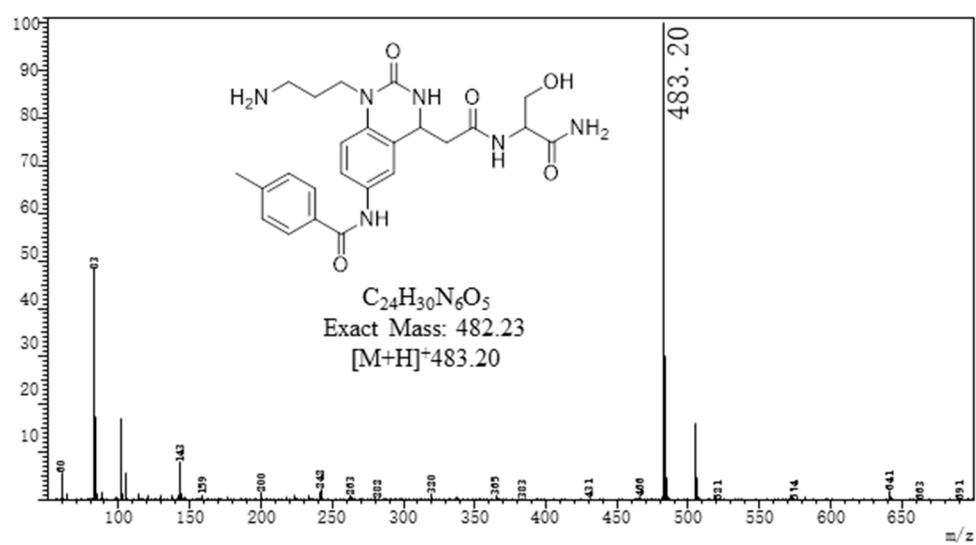
Base peak: 469.20 (350588)



CA1-c

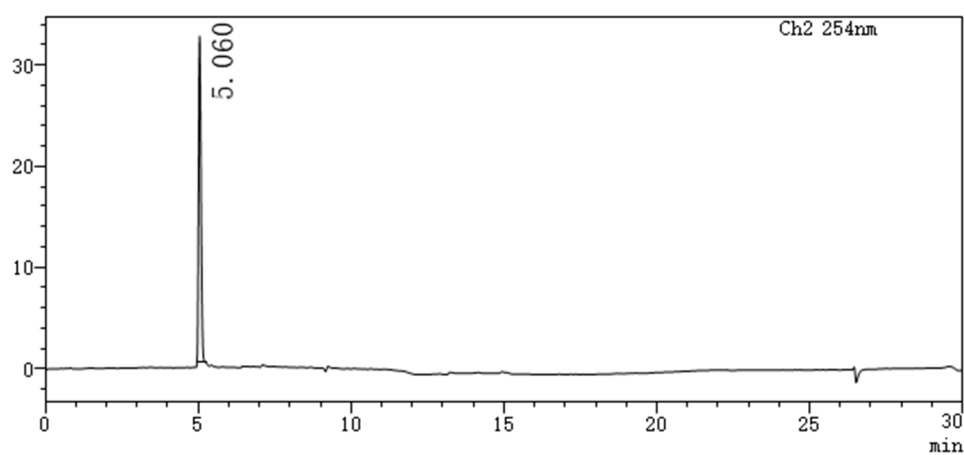
RT: 5.600 min (S#: 337)

Base peak: 483.20 (532953)



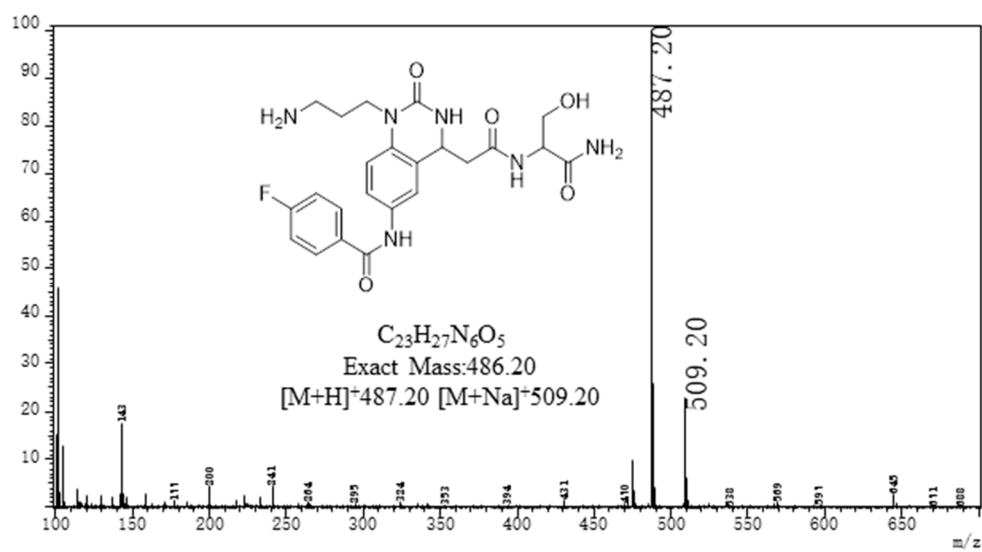
CA1-d

mV

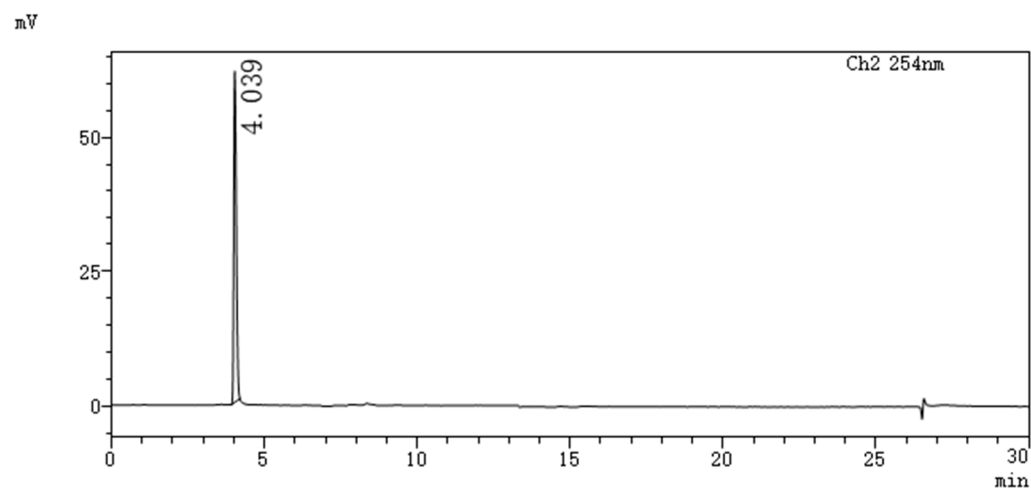


RT: 5.150 min (S#: 310)

Base peak: 487.20 (233021)

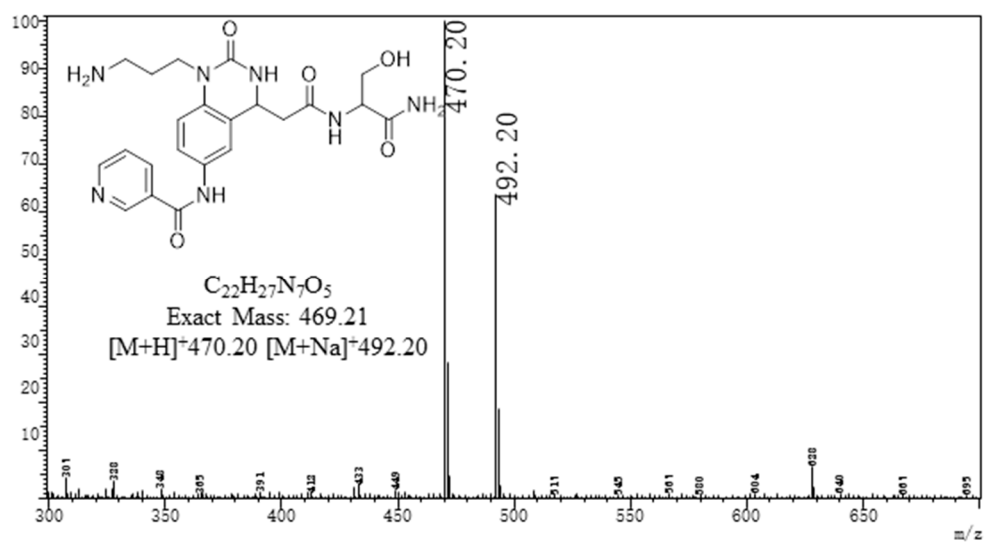


CA1-e

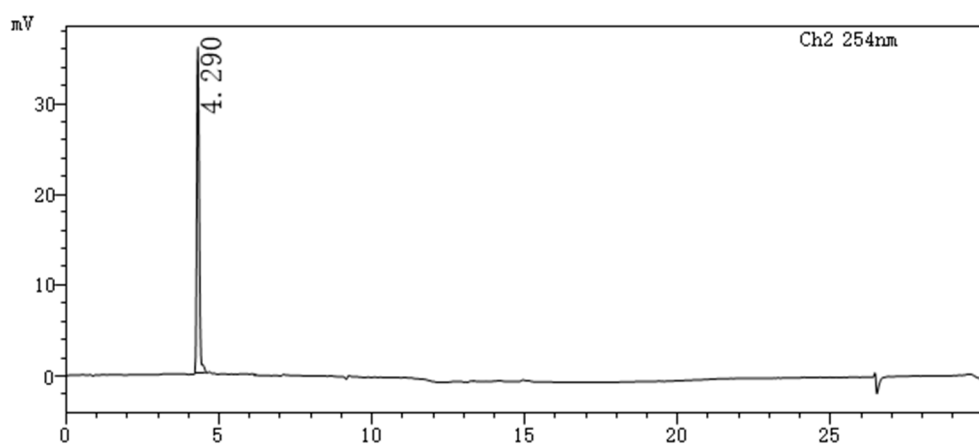


RT: 2.233 min (S#: 135)

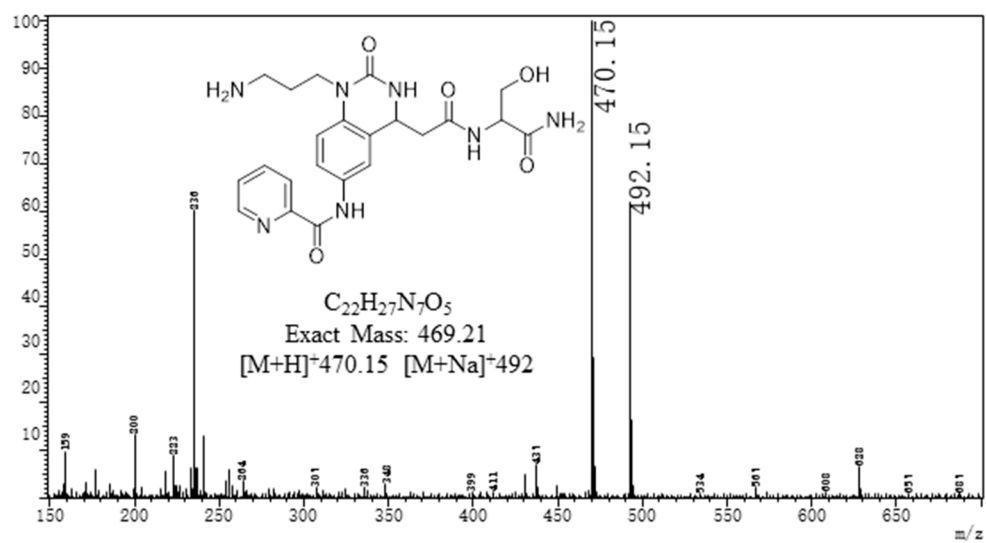
Base peak: 470.20 (87027)



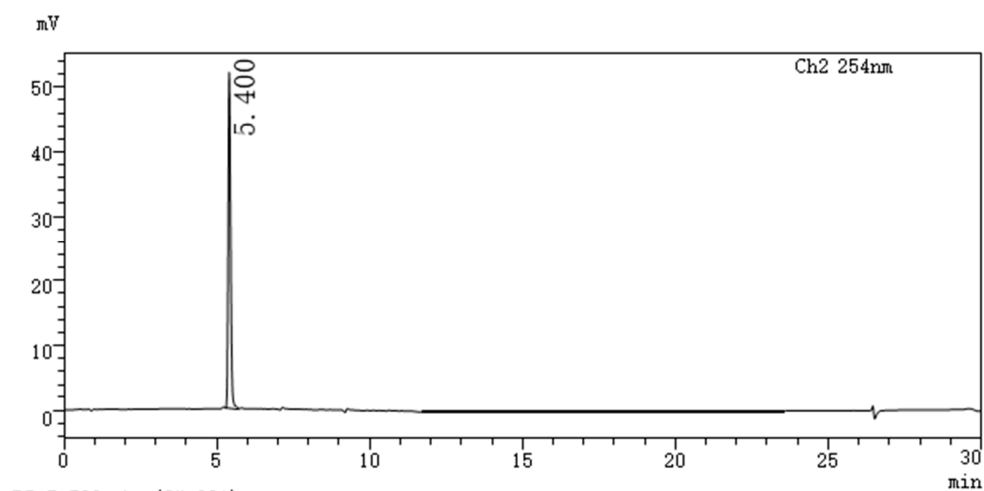
CA1-f



RT: 4.383 min (S#: 264)
Base peak: 470.15 (76198)

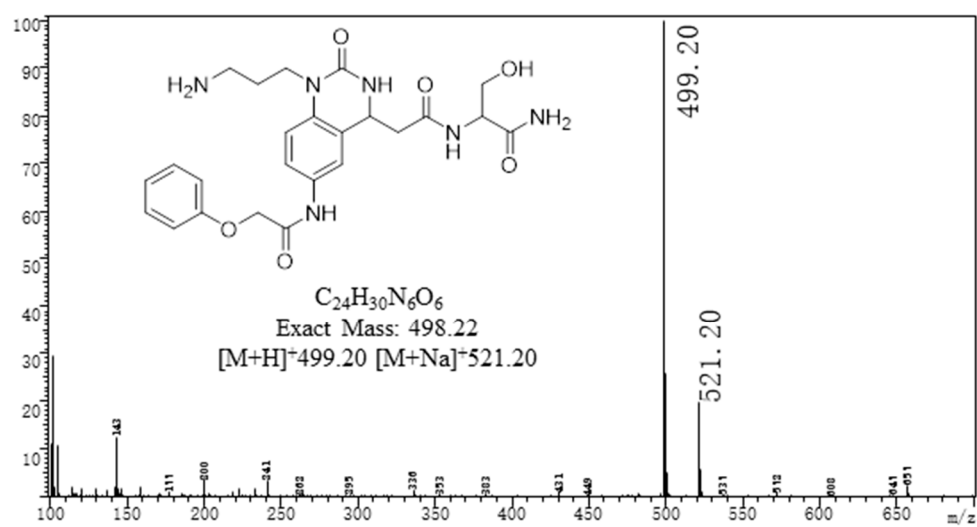


CA1-g

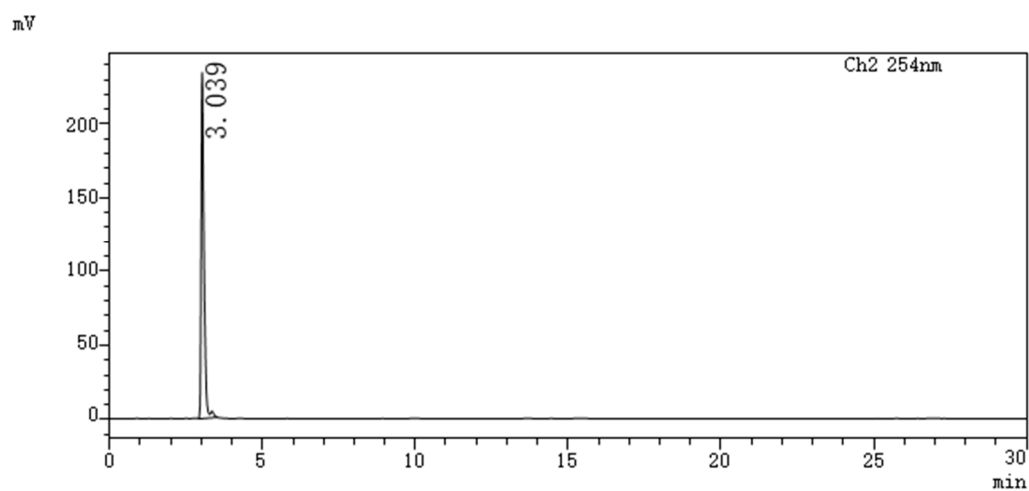


RT: 5.500 min (S#: 331)

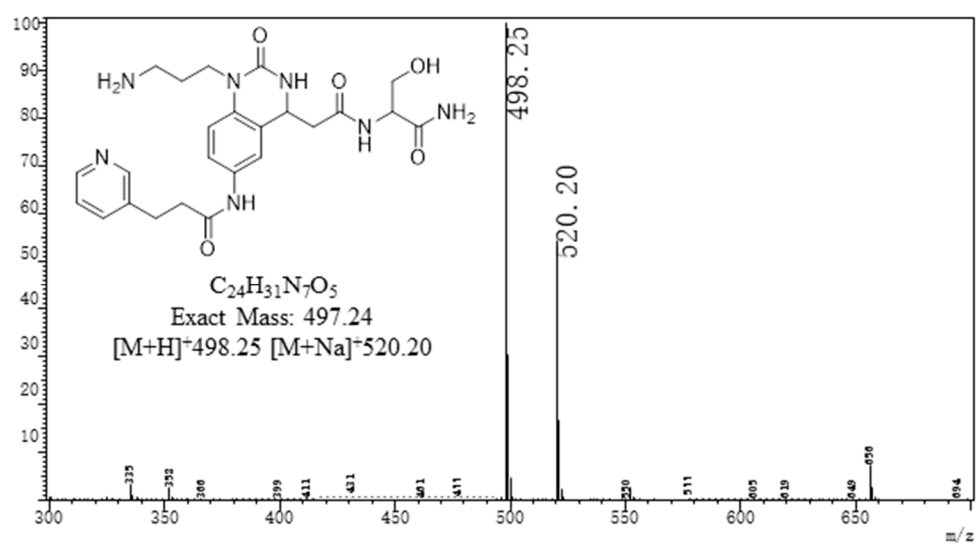
Base peak: 499.20 (322733)



CA1-h

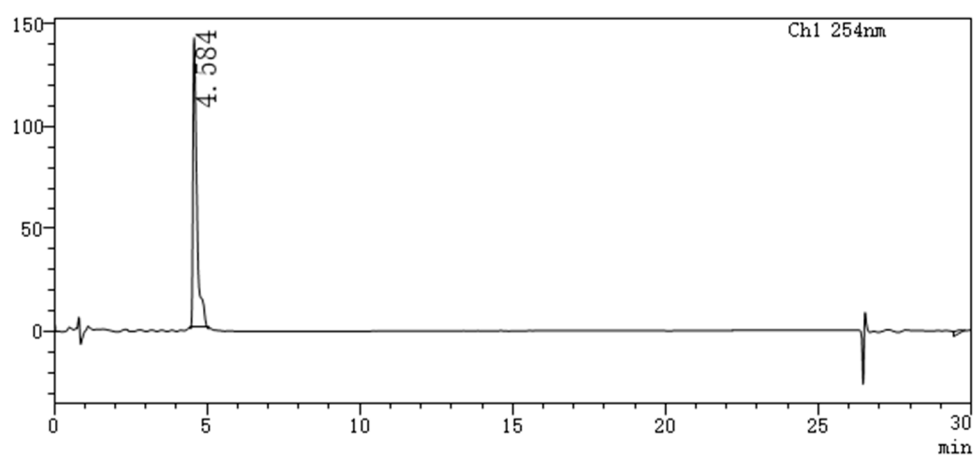


RT: 1.983 min (S#: 120)
Base peak: 498.25 (238352)



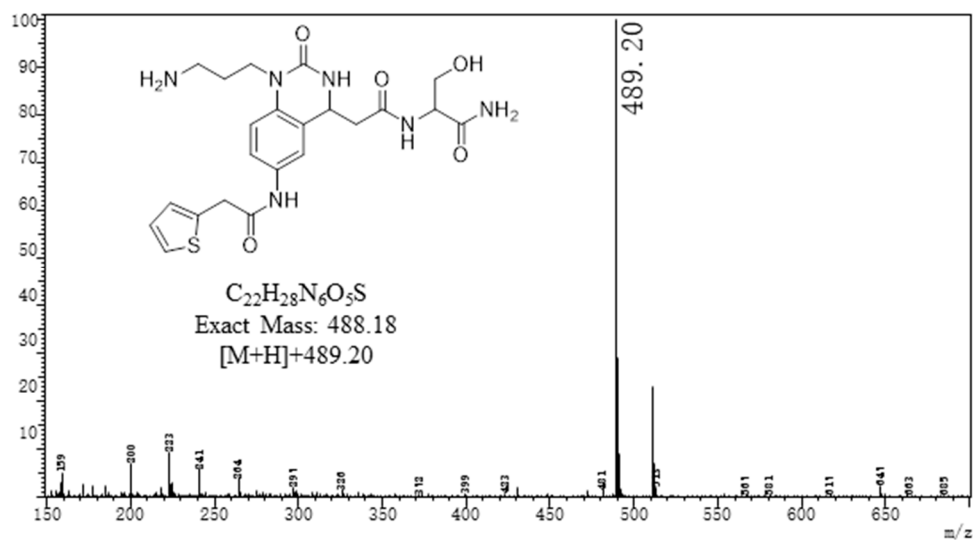
CA1-i

mV

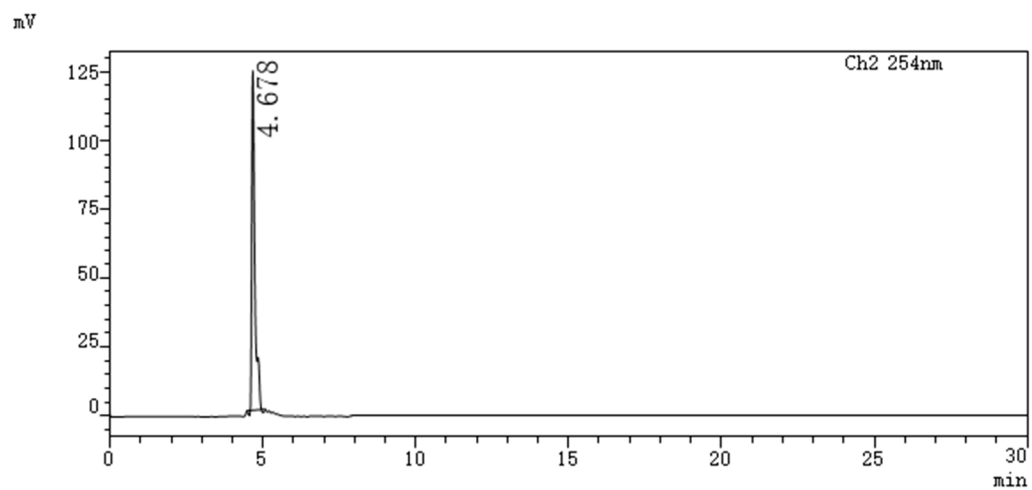


RT: 4.800 min (S#:289)

Base peak: 489.20 (161523)

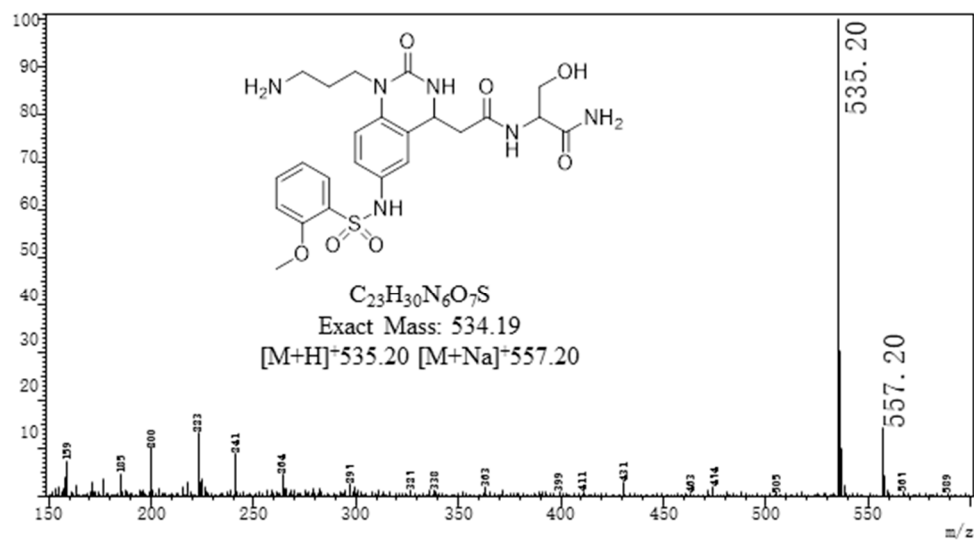


CA1-j

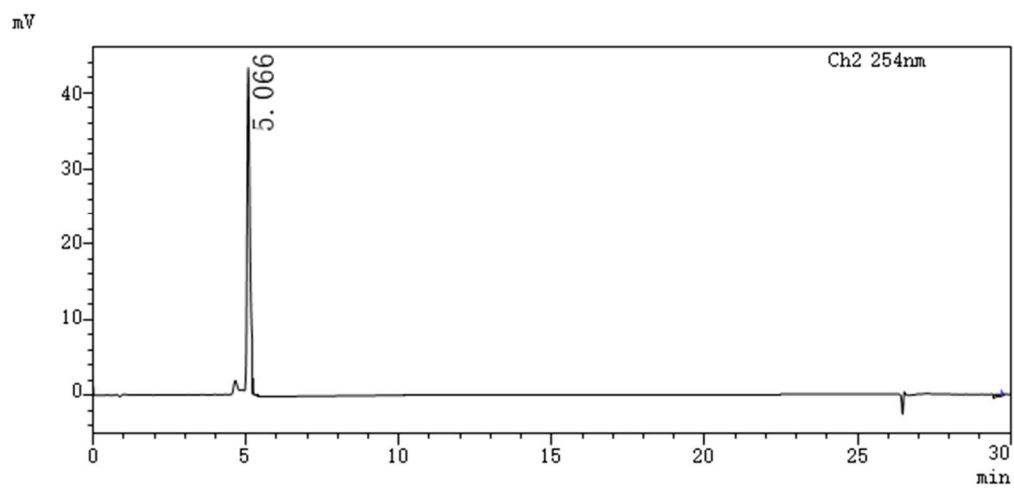


RT: 4.733 min (S#: 285)

Base peak: 535.20 (125733)

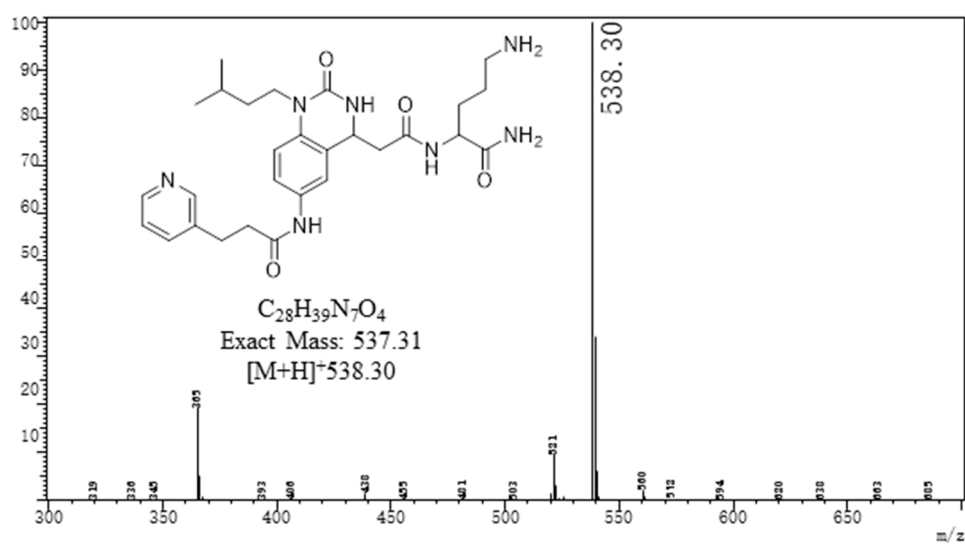


CA3



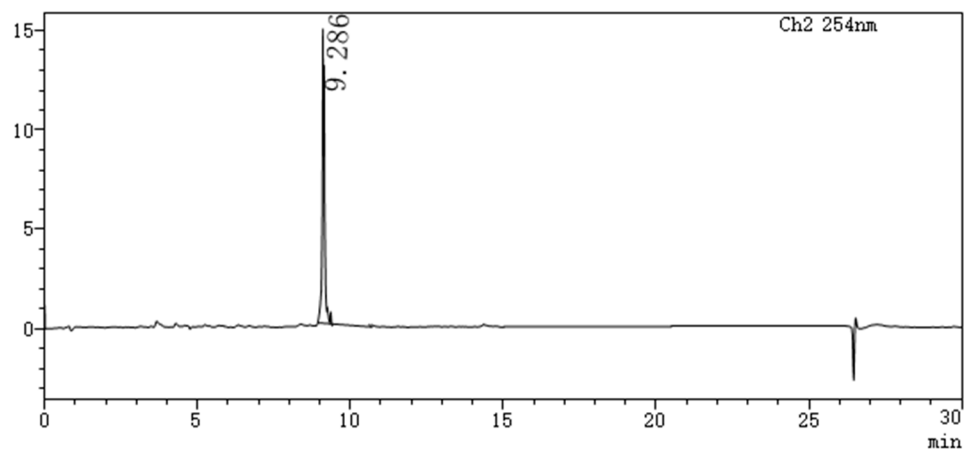
RT: 6.583 min (S#: 396)

Base peak: 538.30 (3551384)



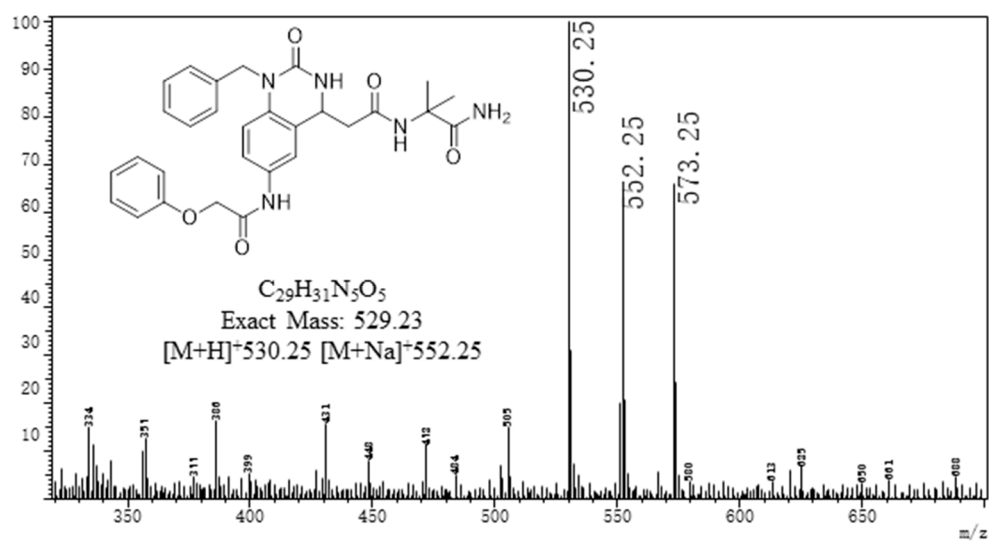
CA4

mV

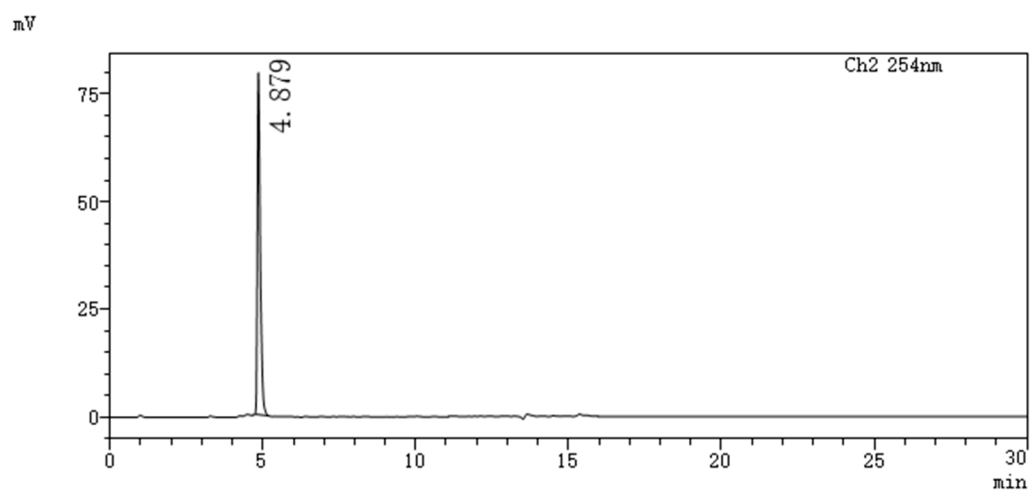


RT: 9.483 min (S#:570)

Base peak: 530.25 (28473)

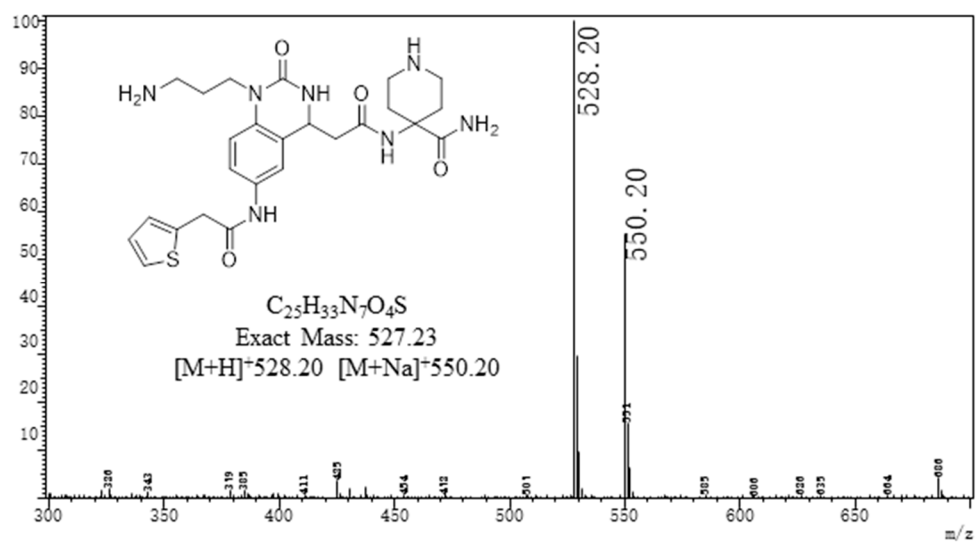


CA5



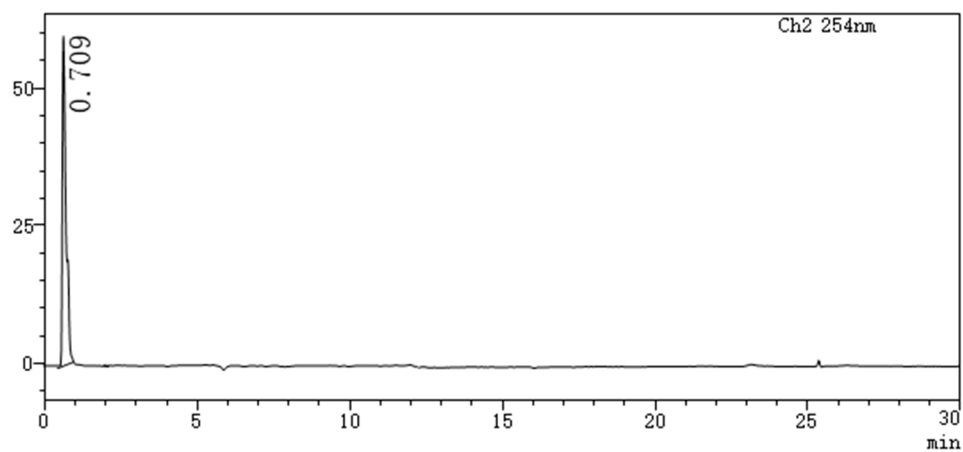
RT: 4.367 min (S#: 263)

Base peak: 528.20 (138703)



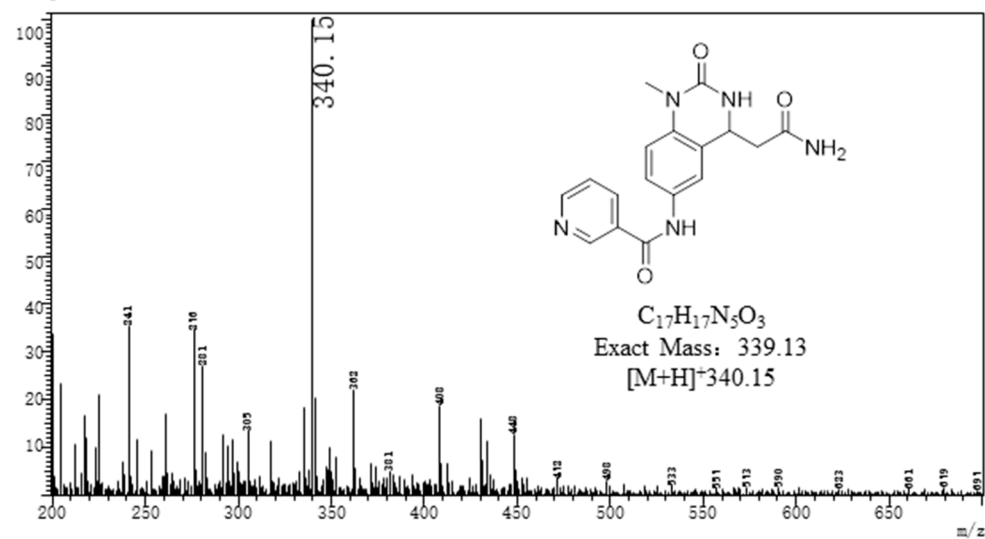
CA6-a

mV

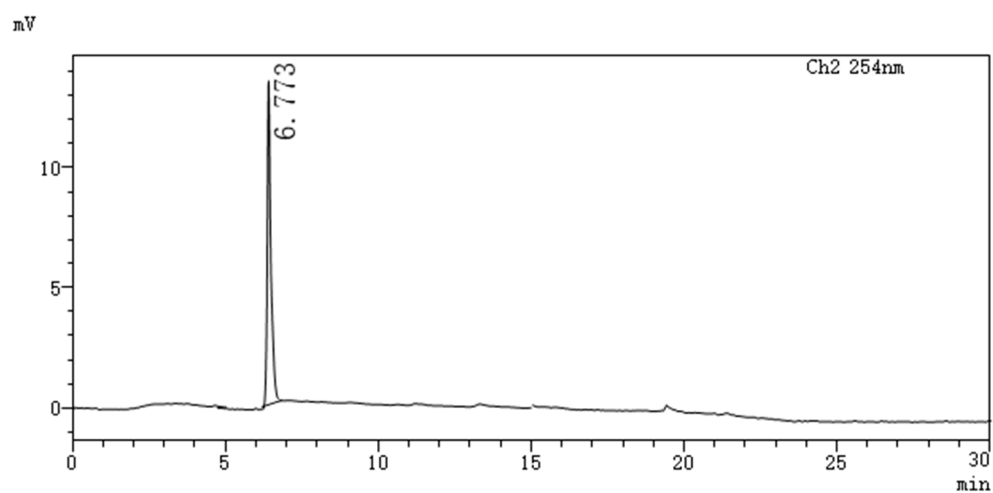


RT: 0.667 min (S#: 41)

Base peak: 340.15 (82566)

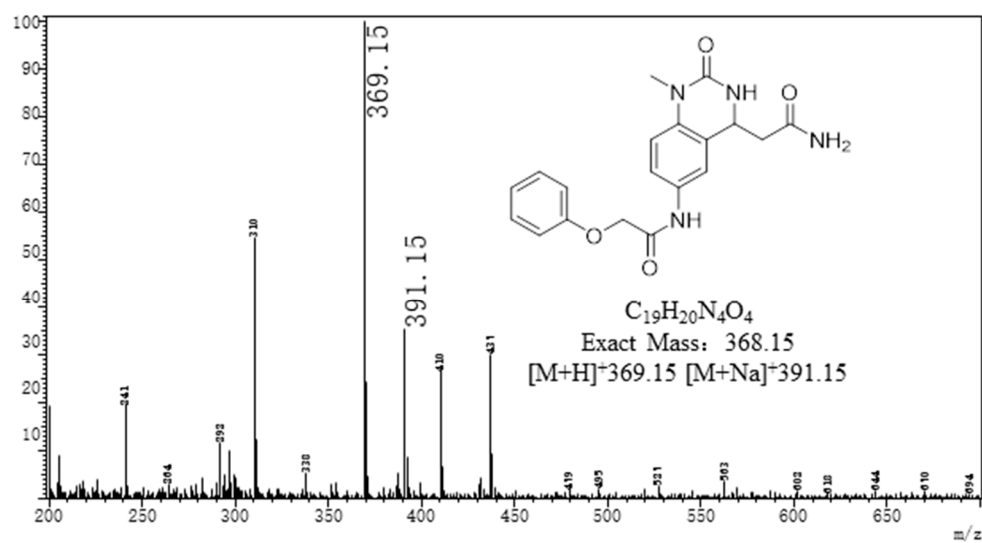


CA6-b

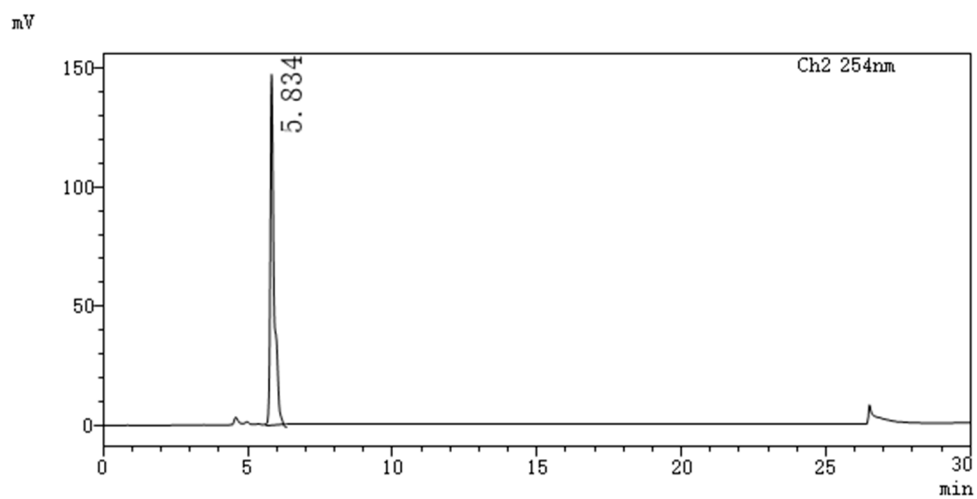


RT: 6.867 min (S#: 413)

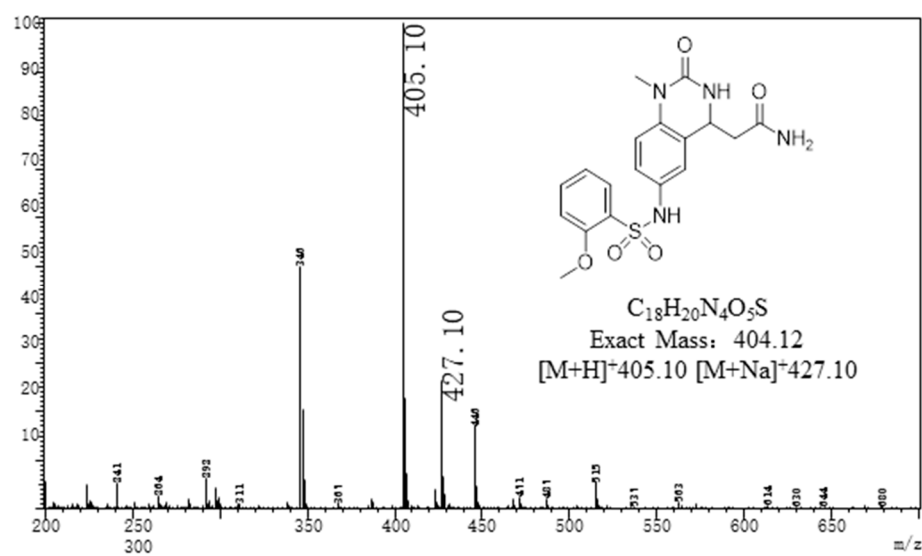
Base peak: 369.15 (71969)



CA7-a

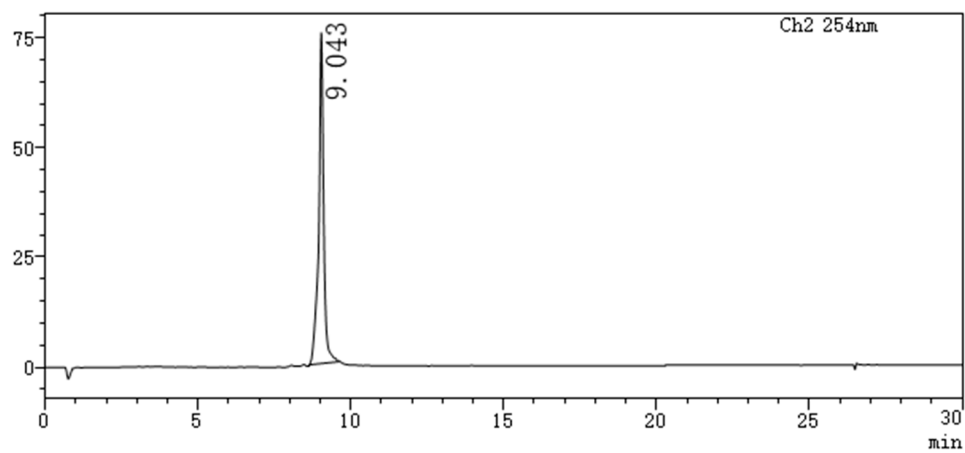


RT: 6.000 min (S#: 361)
Base peak: 405.10 (204349)



CA7-b'

mV



RT: 9.133 min (S#: 549)

Base peak: 551.10 (607196)

