Design, Synthesis, and Pharmacological Characterization of *N*-(4-(2 (6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)yl)ethyl)phenyl) quinazolin-4-amine Derivatives: Novel Inhibitors Reversing P-glycoprotein-Mediated Multidrug Resistance

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General Procedure for the Synthesis of 7a-s

Freshly prepared substituted aromatic acyl chloride (20 mmol) was slowly added to a solution of 15 ml pyridine with substituted anthranilic acids (30 mmol) in an ice-bath. After 30-min ice-bath stirring, the reaction mixture was stirred at room temperature for 12 h. After poured into water (200 ml), the solution was stirred vigorously until a large amount of solid precipitated, and then filtered. The filter cake was washed with water (20 ml × 5) for drying, to afford the intermediate **7a-s**.

2-phenyl-4H-benzo[d][1,3]oxazin-4-one (7a)

White solid; Yield 69.8%; m.p. 108-110 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.30 (d, J =8.07, 2H, ArH), 8.25 (d, J = 8.03 Hz, 1H, ArH), 7.85 (t, J = 7.4 Hz, 1H, ArH), 7.67 (d, J = 7.9 Hz, 1H, ArH), 7.50-7.45 (m, 1H, ArH), 7.52-7.40 (m, 3H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 159.72, 157.24, 154.20, 147.17, 136.73, 132.77, 130.38, 128.86, 128.71, 127.3, 122.25, 117.11; ESI-MS m/z: 224.12 ([M + H]+).

2-(2-methoxyphenyl)-4H-benzo[d][1,3]oxazin-4-one (7b)

White solid; Yield 72.7%; m.p. 153-155 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.26 (dd, J = 7.8, 1.5 Hz, 1H, ArH), 7.88 – 7.82 (m, 2H, ArH), 7.72 (d, J = 7.6 Hz, 1H, ArH), 7.56 – 7.50 (m, 2H, ArH), 7.09 – 7.03 (m, 2H, ArH), 3.94 (s, 3H, OCH3); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 159.81, 158.54, 157.77, 147.05, 136.42, 133.28, 131.33, 128.41, 128.30, 127.28, 120.53, 120.58, 116.92, 112.17, 56.09.; ESI-MS m/z: 254.05 ([M + H]+).

2-(3-methoxyphenyl)-4H-benzo[d][1,3]oxazin-4-one(7c)

Pale brown solid; Yield 81.2%; m.p. 98-100 °C; ^{1} H NMR (300 MHz, DMSO-d_6) δ: 8.22 (dd, J = 7.9, 1.2 Hz, 1H, ArH), 7.89 (d, J = 7.8 Hz, 1H, ArH), 7.83 – 7.78 (m, 2H, ArH), 7.67 (d, J

= 7.9 Hz, 1H, ArH), 7.53 – 7.47 (m, 1H, ArH), 7.39 (t, *J* = 8.0 Hz, 1H, ArH), 7.09 (dd, *J* = 8.2, 2.0 Hz, 1H, ArH), 3.89 (s, 3H, OCH3); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 159.88, 159.53, 156.97, 146.95, 136.55, 131.54, 129.77, 128.60, 128.28, 127.25, 120.88, 119.35, 117.04, 112.57, 55.55; ESI-MS m/z: 254.03 ([M + H]+).

2-(4-methoxyphenyl)-4H-benzo[d][1,3]oxazin-4-one (7d)

White solid; Yield 72.4%; m.p. 144-146 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.20 (d, *J* = 9.0 Hz, 1H, ArH), 7.72 (d, *J* = 7.7 Hz, 1H, ArH), 7.62 (d, *J* = 8.0 Hz, 1H, ArH), 7.40 (d, *J* = 7.5 Hz, 1H, ArH), 7.45-7.33 (m, 3 H, ArH), 7.31-7.25 (m, 1 H, ArH), 3.80 (s, 3H,OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 163.35, 159.80, 157.17, 147.44, 136.59, 130.32, 130.30, 128.68, 127.72, 122.55, 116.72, 114.47, 55.51; ESI-MS m/z: 254.10 ($[M + H]^+$).

2-(3,4-dimethoxyphenyl)-4H-benzo[d][1,3]oxazin-4-one (7e)

White solid; Yield 62.8%; m.p. 168-170℃; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.12 (dd, *J* = 7.7Hz, 1.2Hz, 1H, ArH), 7.84 (dd, *J* = 8.6Hz, 2.1Hz, 1H, ArH),7.68-7.76 (m, 2H, ArH), 7.54-7.61 (m, 1H, ArH), 7.35-7.44 (m, 1H, ArH), 7.32 (d, *J*=8.6Hz, 1H, ArH), 3.93 (s, 3H, OCH3), 3.88 (s, 3H, OCH3); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 159.72, 156.94, 152.91, 148.92, 147.25, 136.57, 128.53, 127.74, 126.83, 122.69, 122.31, 116.62, 110.67, 110.31, 56.17, 56.05; ESI-MS m/z: 284.18 ($[M + H]^+$).

2-(3,4,5-trimethoxyphenyl)-4H-benzo[d][1,3]oxazin-4-one (7f)

White solid; Yield 59.7%; m.p. 185-187 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.20 (d, *J* = 8.0 Hz, 1H, ArH), 7.80 (t, *J* = 8.0 Hz, 1H, ArH), 7.56 (d, *J* = 8.0 Hz, 1H, ArH), 7.52 (s, 2H, ArH), 7.48 (t, *J* = 8.0 Hz, 1 H, ArH), 3.92 (s, 3H,OCH_3), 3.96 (s, 6H,OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 160.97, 160.41, 154.16, 145.92, 139.76, 137.30, 129.07, 128.40, 127.31, 124.65, 115.13, 108.06, 60.70, 56.83.ESI-MS m/z: 314.06 ([M + H]+).

2-(benzo[d][1,3]dioxol-5-yl)-4H-benzo[d][1,3]oxazin-4-one (7g)

White solid; Yield 71.1%; m.p. 197-199 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.20 (d, J = 8.0 Hz, 1H, ArH), 7.73-7.95 (m, 3H, ArH), 7.62 (d, J = 8.0 Hz, 1H, ArH), 7.48 (t, J = 8.0 Hz, 1 H, ArH), 6.90 (d, J = 8.0 Hz, 1H, ArH), 6.06 (s, 2H,CH_2); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 160.41, 159.78, 152.85, 150.18, 145.92, 137.30, 129.07, 127.31, 124.65, 124.12, 122.57, 115.13, 109.85, 108.44, 101.95.ESI-MS m/z: 268.09 ($[M + H]^+$).

2-(m-tolyl)-4H-benzo[d][1,3]oxazin-4-one (7h)

White solid; Yield 69.1%; m.p.106-108 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.23 (d, J = 7.8 Hz, 1H, ArH), 8.10 (d, J = 7.5 Hz, 1H, ArH), 7.81 (t, J = 7.8 Hz, 1H, ArH), 7.68 (d, J = 7.8 Hz, 1H, ArH), 7.49 (t, J = 8.1 Hz, 2H, ArH), 7.39 (d, J = 7.3 Hz, 1H, ArH), 7.37 (s, 1H, ArH), 2.43 (s, 3H,CH_3); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 160.41, 159.78, 145.92, 139.88, 137.30, 133.72 , 131.64, 130.50, 129.07, 128.38, 127.31, 126.39, 124.65, 115.13, 21.23; ESI-MS m/z: 238.12 ($[M + H]^+$).

2-(p-tolyl)-4H-benzo[d][1,3]oxazin-4-one (7i)

White solid; Yield 62.6%; m.p. 174 -176 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.25-8.18 (m, 3H, ArH), 7.75 (t, J = 7.3 Hz, 1H, ArH), 7.60 (d, J = 8.0 Hz, 1H, ArH), 7.40, (t, J = 7.4 Hz, 1H, ArH), 7.30 (d, J = 7.5 Hz, 2H, ArH), 2.46(s, 3H,CH_3); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 159.83, 157.42, 147.27, 143.50, 136.68, 131.6,0 129.63, 128.74, 128.11, 127.56,122.24, 117.06, 21.84; ESI-MS m/z: 238.03 ($[M + H]^+$).

2-(4-(tert-butyl)phenyl)-4H-benzo[d][1,3]oxazin-4-one (7j)

Pale yellow solid; Yield 71.2%; m.p. 58-60 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.26−8.18 (m, 3H, ArH), 7.80 (d, J = 7.2 Hz, 1H, ArH), 7.68 (d, J = 7.2 Hz, 1H, ArH), 7.56−7.44 (m, 3H), 1.37 (s, 9H, $(CH3)_3$); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 159.71, 157.25, 156.48, 147.16, 136.42, 128.55, 128.17, 127.92, 127.41,127.16, 125.77, 116.90, 35.16, 31.12; ESI-MS m/z: 280.15 ($[M + H]^+$).

2-(pyridin-4-yl)-4H-benzo[d][1,3]oxazin-4-one (7k)

White solid; Yield 55.3%; m.p. 186-188 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 9.49 (s, 1H, ArH), 8.77 (d, J = 3.6 Hz, 1H, ArH), 8.56 – 8.49 (m, 1H, ArH), 8.23 (d, J = 7.9 Hz, 1H, ArH), 7.84 (t, J = 7.7 Hz, 1H, ArH, ArH), 7.69 (d, J = 8.1 Hz, 1H, ArH), 7.54 (t, J = 7.6 Hz, 1H, ArH), 7.47 – 7.40 (m, 1H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 158.92, 155.37, 152.97, 149.66, 146.45, 136.71, 135.42, 128.80, 128.74, 127.36, 126.32, 123.47, 117.11; ESI-MS m/z: 225.07 ([M + H]$^{+}$).

2-(pyridin-3-yl)-4H-benzo[d][1,3]oxazin-4-one (7l)

Pale yellow solid; Yield 80.3%; m.p. 139-140 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 9.37 (s, 1H, ArH), 8.83 (d, J = 8.0 Hz, 1H, ArH), 8.59 (d, J = 7.8 Hz, 1H, ArH), 8.22 (d, J = 8.0 Hz, 1H, ArH), 7.94 (t, J = 7.6 Hz, 1H, ArH), 7.73 (m, 3H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 163.01, 160.41, 150.78, 148.15, 145.92, 137.33, 133.94, 129.07, 127.31, 126.66, 124.65, 122.88, 115.13; ESI-MS m/z: 225.09 ([M + H]$^{+}$).

2-(quinolin-2-yl)-4H-benzo[d][1,3]oxazin-4-one (7m)

Pink solid; Yield 75.9%; m.p. 182-183°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.60 (d, J = 8.9 Hz, 1H, ArH), 8.46 (d, J = 8.4 Hz, 1H, ArH), 8.24 (d, J = 8.0 Hz, 1H, ArH), 8.23 (d, J = 7.6Hz, 1H, ArH), 8.11 (d, J = 8.4 Hz, 1H, ArH), 8.01 (d, J = 8.0 Hz, 1H, ArH), 7.90 (m, 1H, ArH), 7.84 (d, J = 8.0 Hz, 1H, ArH), 7.76(d, J= 8.0, 1H, ArH),7.71 (d, J = 7.6Hz, 1H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 159.07, 155.32, 148.06, 147.02, 145.91, 137.55, 136.91, 130.78, 129.71,129.54, 128.68, 128.61, 128.18,128.11, 127.34, 120.39,117.65; ESI-MS m/z: 275.03 ([M + H]$^{+}$).

2-(3-nitrophenyl)-4H-benzo[d][1,3]oxazin-4-one (7n)

White solid; Yield 68.2%; m.p. 142-144°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 9.13 (t, J = 2.0 Hz, 1H, ArH), 8.60 (d, J = 7.8 Hz, 1H, ArH), 8.40 (dd, J = 8.1, 2.4 Hz, 1H, ArH), 8.25 (dd, J = 7.9, 1.5 Hz, 1H, ArH), 7.86 (td, J = 7.8, 1.6 Hz, 1H, ArH), 7.75 – 7.70 (m, 2H, ArH), 7.57 (t, J = 7.6 Hz, 1H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 158.72, 154.85, 148.72, 146.35,

136.92, 133.65, 132.24, 129.99, 129.12, 128.89, 127.50, 126.83, 123.37, 117.18; ESI-MS m/z: 269.11 ($[M + H]^+$).

2-(4-nitrophenyl)-4H-benzo[d][1,3]oxazin-4-one (7o)

Yellow solid; Yield 53.3%; m.p. 197-198 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.50- 8.45 (m, 2H, ArH), 8.36 -8.31 (m, 2H, ArH), 8.25 (ddd, J = 7.9, 1.5, 0.5 Hz, 1H, ArH), 7.87 (ddd, J = 8.1, 7.4, 1.7 Hz, 1H, ArH), 7.72 (ddd, J = 8.1, 1.5, 0.7 Hz, 1H, ArH), 7.58 (ddd, J = 7.9, 7.2, 1.4 Hz, 1H, ArH). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 158.84, 155.07, 150.26, 146.38, 137.04, 135.99, 129.47, 129.37, 128.95, 127.78, 124.01, 117.23; ESI-MS m/z: 269.02 ($[M + H]^+$).

2-(4-chlorophenyl)-4H-benzo[d][1,3]oxazin-4-one (7p)

White solid; Yield 70.3%; m.p. 158-160 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.09-8.16 (m, 3H, ArH), 7.68-7.77 (m, 1H, ArH), 7.54-7.59 (m, 1H, ArH), 7.33-7.46 (m, 3H, ArH).; ^{13}C NMR (75 MHz, DMSO-d_6) δ: 159.18, 156.16, 146.62, 138.92, 136.63, 129.55, 129.02, 128.58, 128.56, 128.4, 127.16, 116.80; ESI-MS m/z: 258.05 ($[M + H]^+$).

2-(4-fluorophenyl)-4H-benzo[d][1,3]oxazin-4-one (7q)

White solid; Yield 57.2%; m.p. 175-177 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.30 (dd, J = 8.1, 5.7 Hz, 2H, ArH), 8.25 (d, J = 7.7 Hz, 1H, ArH), 7.80 (t, J = 7.5 Hz, 1H, ArH), 7.65 (d, J = 8.1 Hz, 1H, ArH), 7.45 (t, J = 7.5 Hz, 1H, ArH), 7.20 (t, J = 8.5 Hz, 2H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 167.34, 163.96, 159.42, 156.27, 146.98, 136.63, 130.80, 128.62, 127.25, 126.41, 116.87,115.93; ESI-MS m/z: 242.02 ($[M + H]^+$).

7-chloro-2-phenyl-4H-benzo[d][1,3]oxazin-4-one (7r)

white solid; Yield 60.2%; m.p. 180-182 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.30-8.25 (m, 2H, ArH), 8.05 (d, J = 8.3 Hz, 1H, ArH), 7.40 (s, 1H, ArH), 7.55-7.30 (m, 1H, ArH), 7.53-7.250 (m, 3H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 158.9, 158.4, 148.2, 143.1, 133.2, 130.0, 129.9, 129.2, 128.9, 128.6, 127.1, 115.5; ESI-MS m/z: 258.06 ($[M + H]^+$).

6,7-dimethoxy-2-phenyl-4H-benzo[d][1,3]oxazin-4-one (7s)

Pale yellow solid; Yield 76.7%; m.p. 196-198 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.15 (d, J = 7.3 Hz, 2H, ArH), 7.58-7.40 (m, 4H, ArH), 7.20 (s, 1H, ArH), 4.02 (s, 3H,OCH_3), 3.95 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 159.45, 156.66, 156.45, 149.61, 143.32, 132.35, 130.49, 129.32, 128.71, 116.82, 118.65, 108.11, 107.59, 56.43; ESI-MS m/z: 284.10 ($[M + H]^+$).

General Procedure for the Synthesis of 8a-s

The mixtures of 7a-s (15 mmol) and ammonia water (15ml) dissolved in ethanol (20ml) were sealed in the pressure bottle and heated to 80℃ for 12h-reflux. Then the reaction solutions were cooled to room temperature and filtered. Then the filter cake was washed and dried to afford solid product **8a-s**.

2-phenylquinazolin-4(3H)-one (8a)

Pale yellow solid; Yield 71.8%; m.p. 235-236 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.41 (s, 1H, NH), 8.19 - 8.17 (m, 2H, ArH), 8.15 (dd, J = 7.9, 1.6 Hz, 1H, ArH), 7.85 - 7.80 (m, 1H, ArH), 7.75 -7.71 (m, 1H, ArH), 7.58 - 7.56 (m, 1H, ArH), 7.56 -7.52 (m, 2H, ArH), 7.51 - 7.49 (m, 1H, ArH). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 162.55, 152.64, 148.85, 134.64, 133.00, 131.46, 128.70, 127.89, 127.52, 126.63, 125.98, 121.13; ESI-MS m/z: 223.11 ($[M + H]^+$).

2-(2-methoxyphenyl)quinazolin-4(3H)-one (8b)

White solid; Yield 72.1%; m.p. 208-210 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.00 (s, 1H, NH), 8.19 (d, J = 7.5 Hz, 1H, ArH),7.82 (t, J = 7.5 Hz, 1H, ArH),7.70 (d, J = 8.0 Hz, 1H, ArH),7.50-7.55 (m, 2H, ArH), 7.49 (d, J = 7.5 Hz, 1H, ArH),7.19 (d, J = 8.5 Hz, 1H, ArH),7.08 (t, J = 7.0 Hz, 1H, ArH), 3.88 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 161.12, 157.15, 152.22,148.96, 134.27, 132.16, 130.30,127.36, 126.41,125.77, 122.53, 120.93, 120.36, 111.82, 55.74; ESI-MS m/z: 253.14 ($[M + H]^+$).

2-(3-methoxyphenyl)quinazolin-4(3H)-one (8c)

White solid; Yield 73.9%; m.p. 206-208 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.45 (s, 1H, NH), 8.16 (t, *J* = 8.0 Hz, 1H, ArH), 7.73-7.85 (m, 4H, ArH), 7.52 (t, *J* = 7.5 Hz, 1H, ArH),7.45 (t, *J* = 7.5 Hz, 1H, ArH), 7.14 (d, *J* = 7.0 Hz, 1H, ArH), 3.87 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 162.17, 159.32, 151.99, 148.63, 134.42, 133.90, 129.65, 127.43, 126.41, 125.73, 120.92, 120.04, 117.43, 112.50, 55.37; ESI-MS m/z: 253.12 ([M + H]$^{+}$).

2-(4-methoxyphenyl)quinazolin-4(3H)-one (8d)

White solid; Yield 76.2%; m.p. 246-248 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.33 (s, 1H, NH), 8.20 (d, *J* = 8.5 Hz, 2H, ArH), 8.14 (d, *J* = 7.5 Hz, 1H, ArH), 7.80 (t, *J* = 7.5 Hz, 1H, ArH), 7.70 (d, *J* = 7.5 Hz, 1H, ArH), 7.48 (t, *J* = 7.5 Hz, 1H, ArH), 7.08 (d, *J* = 8.5 Hz, 2H, ArH), 3.85 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 162.27, 161.82, 151.85, 148.81, 134.38, 129.33, 127.10, 125.92, 125.75, 124.71, 120.69, 113.91, 55.34; ESI-MS m/z: 253.07 ([M + H]$^{+}$).

2-(3,4-dimethoxyphenyl)quinazolin-4(3H)-one (8e)

Pale brown solid; Yield 71.8%; m.p. 250-252℃ ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.32 (s, 1H, NH), 8.12 (dd, *J* = 8.2, 1.3 Hz, 1H, ArH), 7.87 (dd, *J* = 8.2, 2.2 Hz, 1H, ArH), 7.81 (d, *J* = 2.2 Hz, 1H, ArH), 7.80 -7.77 (m, 1H, ArH), 7.70 (d, J = 8.1, 1H, ArH), 7.49 - 7.44 (m, 1H, ArH), 7.10 (dd, J = 8.2, 4.0 Hz, 1H, ArH), 3.88 (s, 3H, OCH3), 3.84 (s, 3H, OCH3); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 162.67, 152.17, 151.72, 149.01, 148.70, 134.58, 127.32, 126.17, 125.96, 125.05, 121.29, 120.83, 111.55, 110.92, 55.84, 55.83; ESI-MS m/z: 283.16 ([M + H]$^{+}$).

2-(3,4,5-trimethoxyphenyl)quinazolin-4(3H)-one (8f)

White solid; Yield 79.3%; m.p. 258-260 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.92 (s, 1H, NH), 8.27 (d, *J* = 8.0 Hz, 1H, ArH), 7.81-7.85 (m, 2H, ArH), 7.50 (t, *J* = 6.8 Hz, 1H, ArH), 7.41 (s, 2H, ArH), 4.03 (s, 6H, 2OCH3), 3.95 (s, 3H, OCH3); ^{13}C NMR (75 MHz, DMSO-d_6)

δ: 164.45, 153.67, 153.51, 151.76, 149.52, 141.05, 134.90, 127.92,126.61, 126.07, 125.54, 105.27, 104.91, 60.92, 56.43; ESI-MS m/z: 313.12 ($[M + H]^+$).

2-(benzo[d][1,3]dioxol-5-yl)quinazolin-4(3H)-one (8g)

White solid; Yield 70.3% ; m.p. 276-278 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.38 (s, 1H, NH), 8.13 (d, *J* = 7.6 Hz, 1H, ArH), 7.81 (d, *J* = 7.7 Hz, 2H, ArH), 7.75 (s, 1H, ArH), 7.70 (d, J = 8.0 Hz, 1H, ArH), 7.50 (t, *J* = 7.3 Hz, 1H, ArH), 7.08 (d, *J* = 8.1 Hz, 1H, ArH), 6.15 (s, 2H, OCH2O, ArH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 162.41, 151.85, 150.20, 148.93, 147.96, 134.72, 127.59, 126.72, 126.45, 126.06, 123.01, 120.94, 108.45, 107.72, 102.17; ESI-MS m/z: 267.09 ($[M + H]^+$).

2-(m-tolyl)quinazolin-4(3H)-one (8h)

Yellow solid; Yield 85.4%; m.p. 210-212 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.47 (s, 1H, NH), 8.15 (dd, *J* = 8.0, 1.2 Hz, 1H, ArH), 7.96-8.03 (m, 2H, ArH), 7.82-7.86 (m, 1H, ArH), 7.73 (d, *J* = 7.6 Hz, 1H, ArH), 7.41-7.54 (m, 3H, ArH), 2.49 (s, 3H, CH3); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 162.29, 152.47, 148.63, 137.84, 134.58, 132.64, 131.90, 128.45, 128.22, 127.38, 126.51, 125.88, 124.82, 120.94, 20.91; ESI-MS m/z: 237.11 ($[M + H]^+$).

2-(p-tolyl)quinazolin-4(3H)-one (8i)

White solid; Yield 74.5%; m.p. 260-262℃; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.39 (s, 1H, NH), 8.14 (d, *J* = 8.0 Hz,1H), 8.10 (d, *J* = 8.5 Hz, 2H), 7.82 (t, *J* = 8.0 Hz, 1H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.50 (t, *J* = 8.0 Hz, 1H), 7.35 (d, *J* = 8.5 Hz, 2H), 2.39 (s, 3H, CH3); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 162.24, 152.29, 148.10, 141.32, 134.43, 129.82, 129.07, 127.66, 127.21, 126.25, 125.72, 120.80, 20.93; ESI-MS m/z: 237.18 ($[M + H]^+$).

2-(4-(tert-butyl)phenyl)quinazolin-4(3H)-one (8j)

White solid; Yield 84.1%; m.p. 160-162 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.47 (s, 1H, NH), 8.14 (d, *J* = 8.0 Hz, 3H, ArH), 7.81-7.85 (m, 1H, ArH), 7.72 (d, *J* = 7.0 Hz, 1H, ArH), 7.56 (d, *J* = 7.2 Hz, 2H, ArH), 7.49-7.52 (m, 1H, ArH), 1.33 (s, 9H, 3CH3); ^{13}C NMR (75

MHz, DMSO-d_6) δ: 162.29, 154.22, 152.17, 148.82, 134.55, 129.91, 127.52, 127.49, 126.45, 125.80, 125.48, 120.96, 34.67, 30.82; ESI-MS m/z: 279.17 ($[M + H]^+$).

2-(pyridin-4-yl)quinazolin-4(3H)-one (8k)

Yellow solid; Yield 78.3%; m.p. 270-272°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.76 (s, 1H, NH), 8.77 (d, J = 4.2 Hz, 2H, ArH), 8.16 (d, J = 7.8 Hz, 1H, ArH), 8.10 (d, J = 5.4 Hz, 2H, ArH), 7.85 (t, J =7.2 Hz, 1H, ArH), 7.77 (d, J = 8.4 Hz, 1H, ArH), 7.56 (t, J = 7.8 Hz, 1H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 161.62, 150.17, 149.91, 147.93, 139.68, 134.42, 127.46, 127.17, 125.60, 121.32, 121.27; ESI-MS m/z: 224.06 ($[M + H]^+$).

2-(pyridin-3-yl)quinazolin-4(3H)-one (8l)

White solid; Yield 55.9%; m.p. 272-275 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.26 (s, 1H, NH), 8.74 (d, J = 3.8 Hz, 1H, ArH), 8.49 (t, J = 8.2 Hz, 1H, ArH), 8.30 (d, J = 8.1 Hz, 1H, ArH), 7.84 (d, J = 4.2 Hz, 2H, ArH), 7.57 (t, J = 7.8 Hz, 2H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 161.19, 160.20, 152.63, 151.01, 144.92, 136.14, 135.62, 132.71, 126.96, 126.34, 125.05, 124.22, 121.18; ESI-MS m/z: 224.05 ($[M + H]^+$).

2-(quinolin-2-yl)quinazolin-4(3H)-one (8m)

White solid; Yield 74.5%; m.p. 186-187 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.23 (s, 1H, NH), 8.66 (d, J = 8.4 Hz, 1H, ArH), 8.38 (t, J = 7.8 Hz, 2H, ArH), 8.17 (d, J = 8.2 Hz, 1H, ArH), 7.90 (d, J = 8.4 Hz, 2H, ArH), 7.80-7.85 (m, 2H, ArH), 7.57-7.66 (m, 1H, ArH), 7.53-7.56 (t, J = 8.0 Hz, 1H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 118.41, 122.66, 126.72, 127.55, 127.72, 128.27, 129.20, 129.66, 130.41, 134.57, 137.59, 146.71, 148.05, 148.93, 149.17, 161.49; ESI-MS m/z: 274.08 ($[M + H]^+$).

2-(3-nitrophenyl)quinazolin-4(3H)-one (8n)

Yellow solid; Yield 70.7%; m.p. 349-351 ^{o}C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.82 (s, 1H, NH), 9.02 (s, 1H, ArH), 8.61 (d, J = 7.0 Hz, 1H, ArH), 8.41 (d, J = 7.0 Hz, 1H, ArH), 8.17 (d, J = 7.0 Hz, 1H, ArH), 7.79-7.86 (m, 3H, ArH), 7.57 (t, J = 7.5 Hz, 1H, ArH); ^{13}C NMR (75

MHz, DMSO-d_6) δ: 162.07,154.94, 149.29, 147.92, 134.67, 134.31, 133.98, 130.22, 127.51, 127.04, 125.85, 125.60, 122.62; ESI-MS m/z: 268.09 ($[M + H]^+$).

2-(4-nitrophenyl)quinazolin-4(3H)-one (8o)

Pale yellow solid; Yield 56.2%; m.p. 302-304°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.82 (s, 1 H, NH, ArH), 8.41 (d, *J* = 7.2 Hz, 2 H, ArH) 8.38 (d, *J* = 7.2 Hz, 2 H, ArH) , 8.18 (d, *J* = 6.0 Hz, 1 H, ArH), 7.88 (t, *J* = 6.0 Hz, 1 H, ArH), 7.79 (d, *J* = 6.4 Hz, 1 H, ArH), 7.58 (t, *J* = 6.0 Hz, 1 H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 161.99, 150.68, 148.95, 148.31, 138.51, 134.76, 129.27, 127.75, 127.33, 125.88, 123.60,121.22; ESI-MS m/z: 268.10 ($[M + H]^+$).

2-(4-chlorophenyl)quinazolin-4(3H)-one (8p)

White solid; Yield 65.5%; m.p. 297-299°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.59 (s, 1 H, NH), 8.20 (d, *J* = 8.7 Hz, 2 H, ArH), 8.15 (dd, *J* = 8.0, 1.5 Hz, 1 H, ArH), 7.84 (m, 1 H, ArH), 7.73 (d, *J* = 8.0 Hz, 1 H, ArH), 7.63 (d, *J* = 8.7 Hz, 2 H, ArH), 7.58 (m, 1 H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 162.18, 151.36, 148.49, 136.25, 134.62, 131.55, 129.59, 128.65, 127.43, 126.73, 125.84, 120.96; ESI-MS m/z: 257.07 ($[M + H]^+$).

2-(4-fluorophenyl)quinazolin-4(3H)-one (8q)

Yellow solid; Yield 66.5%; m.p. 290-292 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.53 (s, 1H, NH), 8.26 (dd, *J* = 9.0, 5.5 Hz, 2H, ArH), 8.15 (d, *J* = 7.5 Hz, 1H, ArH), 7.83 (t, *J* = 7.5 Hz, 1H, ArH), 7.73 (d, *J* = 7.5 Hz, 1H, ArH), 7.52 (t, *J* = 7.5 Hz, 1H, ArH), 7.38 (t, *J* = 9.0 Hz, 2H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 164.90, 162.57, 151.33, 148.59, 134.48, 130.22, 129.18, 127.25, 126.46, 125.75, 120.81, 115.43; ESI-MS m/z: 241.11 ($[M + H]^+$).

7-chloro-2-phenylquinazolin-4(3H)-one (8r)

White solid; Yield 84.4%; m.p. 284-286 °C ; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.60 (s, 1H, NH), 8.18 (d, *J* = 7.8 Hz, 2H, ArH), 8.14 (d, *J* = 8.4 Hz, 1H, ArH), 7.77 (s, 1H, ArH), 7.62 (t, *J* = 7.2 Hz, 1H, ArH),7.58-7.53 (m, 3H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 161.32,

153.49, 149.42, 138.83, 132.01,131.45, 128.32, 127.67, 126.44, 126.20, 119.53; ESI-MS m/z: 257.08 ($[M + H]^+$).

6,7-dimethoxy-2-phenylquinazolin-4(3H)-one (8s)

White solid; Yield 73.6%; m.p. 290 - 292 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.42 (s, 1H, NH), 8.21 (d, J = 8.0 Hz, 2H, ArH), 7.59 – 7.50 (m, 3H, ArH), 7.49 (d, J = 7.8 Hz, 1H, ArH), 7.22 (s, 1H, ArH), 3.94 (s, 3H, OCH3), 3.90 (s, 3H, OCH3); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 161.66, 154.82, 150.85, 148.63, 144.80, 132.81, 131.09, 128.64, 127.45, 114.07, 108.39, 104.92, 56.07, 55.78; ESI-MS m/z: 283.13 ($[M + H]^+$).

General Procedure for the Synthesis of 9a-s

The prepared compound **8a-s** (1 equiv) was added to thionyl chloride (10 equiv) in the presence of catalytic DMF for 6h-heating at 50℃. The solution was evaporated under reduced pressure to remove excess thionyl chloride to give solid remaining, which was added into the 1 N NaOH solution followed by strong stirring, and then extracted with DCM (20 ml × 3). Organic layers were washed with water (20 ml), brine (20 ml) respectively and dried over Na_2SO_4. The solvents were filtered and evaporated under reduced pressure to give white or yellow solid **9a-s**.

4-chloro-2-phenylquinazoline (9a)

Brown solid; Yield 68.5%; mp 260-262℃; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.19 (d, J = 8.3 Hz, 1H, ArH), 8.14 (dd, J = 8.2, 3.0 Hz, 2H, ArH), 7.90 - 7.85 (m, 2H, ArH), 7.64 (d, J = 7.8 Hz, 1H, ArH), 7.61 - 7.55 (m, 3H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 161.80, 153.93, 146.17, 135.15, 132.29, 131.09, 128.78, 128.50, 127.31, 126.21,125.70, 120.75; ESI-MS m/z: 241.09 ($[M + H]^+$).

4-chloro-2-(2-methoxyphenyl)quinazoline (9b)

White solid; Yield 76.7%; m.p. 148-150 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.15 (dd, J = 7.4, 3.5 Hz, 1H, ArH), 8.11 – 8.05 (m, 1H, ArH), 7.85 (dd, J = 7.5, 3.5 Hz, 2H, ArH), 7.61 (d, J = 7.8

Hz, 1H, ArH), 7.46 (d, *J* = 3.4 Hz, 1H, ArH), 7.18 (d, *J* = 7.6 Hz, 1H, ArH), 7.12 (dd, *J* = 7.4, 3.0 Hz, 1H, ArH), 3.84 (s, 3H, OCH3); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 161.75, 158.62, 154.90, 133.53, 130.83, 129.88, 129.66, 128.81, 126.95, 122.32, 120.70, 119.49, 111.74, 56.83; ESI-MS m/z: 271.08 ($[M + H]^+$).

4-chloro-2-(3-methoxyphenyl)quinazoline (9c)

White solid; Yield 80.2%; m.p.145-146 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.20 (d, *J* = 8.5, 2H, ArH), 7.92 (d, *J* = 8.2 Hz, 1H, ArH), 7.71 (d, *J* = 3.4 Hz, 1H, ArH), 7.51 (d, *J* = 3.2 Hz, 1H, ArH), 7.44 (t, *J* = 8.0 Hz, 1H, ArH), 7.25 (d, *J* = 2.9 Hz, 1H, ArH), 7.02- 6.97 (m, 1H, ArH), 3.81 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ:165.33, 163.62, 158.74, 151.23, 137.48, 133.53, 131.87, 129.95, 128.82, 126.74, 121.93, 119.95, 115.43, 110.24, 56.11; ESI-MS m/z: 271.09 ($[M + H]^+$).

4-chloro-2-(4-methoxyphenyl)quinazoline (9d)

White solid; Yield 83.9%; m.p. 126-128℃; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.28 (d, *J* = 8.2 Hz, 1H, ArH), 8.24 (d, *J* = 8.0 Hz, 1H, ArH), 8.12 (dd, *J* = 7.8, 3.2 Hz, 2H, ArH), 7.97 (dd, *J* =7.6, 3.0 Hz, 1H, ArH), 7.62 (d, *J* = 3.0 Hz, 1H, ArH), 7.07 – 6.98 (m, 2H, ArH), 3.78 (s, 3H, OCH3); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 163.98, 161.26, 158.67, 151.03, 133.53, 130.91, 130.08, 129.77, 129.41, 126.78, 121.82, 113.82, 56.08; ESI-MS m/z: 271.09 ($[M + H]^+$).

4-chloro-2-(3,4-dimethoxyphenyl)quinazoline (9e)

Brown solid; Yield 81.8%; m.p. 147-149℃; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.22 (d, *J* = 8.3 Hz, 1H, ArH), 8.09 (dd, *J* = 8.5, 3.0 Hz, 1H, ArH), 8.06 (d, *J* = 3.5 Hz, 2H, ArH), 8.00 (d, *J* = 3.0 Hz, 1H, ArH), 7.79 - 7.75 (m, 1H, ArH), 7.13 (d, *J* = 8.5 Hz, 1H, ArH), 3.89 (s, 3H, OCH3), 3.85 (s, 3H, OCH3); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 161.79, 158.95, 152.05,

151.43, 149.03, 135.91, 129.14, 128.60, 128.41, 125.74, 122.11, 121.55, 111.75, 110.97, 55.80, 55.71; ESI-MS m/z: 301.10 ($[M + H]^+$).

4-chloro-2-(3,4,5-trimethoxyphenyl)quinazoline (9f)

White solid; Yield 70.5%; m.p.178-180℃; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.22 (dd, J = 8.2, 3.1 Hz, 2H, ArH), 7.86 (d, J = 3.0 Hz, 1H, ArH), 7.58 (d, J = 8.0Hz, 1H, ArH), 6.97 (s, 2H, ArH), 3.83 (s, 6H, 2OCH3), 3.71 (s, 3H, OCH3); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 163.84, 160.05, 152.50, 151.01, 139.36, 133.53, 132.09, 130.83, 129.88, 127.01, 121.77, 111.53, 60.70, 56.83; ESI-MS m/z: 331.11 ($[M + H]^+$).

2-(benzo[d][1,3]dioxol-5-yl)-4-chloroquinazoline (9g)

White solid; Yield 63.7%; m.p. 191-193℃; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.15 (d, J = 7.8 Hz, 2H, ArH), 7.94 (dd, J = 8.0, 3.2 Hz, 1H, ArH), 7.85 (d, J = 7.6Hz, 1H, ArH), 7.60 (d, J = 3.0 Hz, 1H, ArH), 7.33 (s, 1H, ArH), 7.04 (d, J = 7.5 Hz, 1H, ArH), 6.07 (s, 2H, OCH2O); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 165.33, 158.74, 152.24, 151.23, 150.39, 133.62, 132.02, 130.76, 128.98, 126.89, 121.91, 112.59 , 107.65, 101.95; ESI-MS m/z: 285.06 ($[M + H]^+$).

4-chloro-2-(m-tolyl)quinazoline (9h)

Pale yellow solid; Yield 79.8%; m.p. 139- 141℃; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.18 (d, J = 7.8 Hz, 1H, ArH), 8.10 (dd, J = 7.9, 3.1 Hz, 2H, ArH), 7.84 – 7.73 (m, 2H, ArH), 7.52 (t, J = 3.0 Hz, 1H, ArH), 7.46 (d, J = 8.2 Hz, 1H, ArH), 7.16 (d, J = 3.0 Hz, 1H, ArH), 2.47 (s, 3H, CH3); ^{13}C NMR (75 MHz, DMSO-d_6) δ:165.33, 158.74, 151.23, 140.24, 137.96, 133.53, 130.83, 130.18, 129.77, 129.25, 126.86, 125.79, 121.86, 21.23; ESI-MS m/z: 255.09 ($[M + H]^+$).

4-chloro-2-(p-tolyl)quinazoline (9i)

White solid; Yield 69.2%; m.p. 170 - 171℃; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.59 (d, J = 8.0 Hz, 2H, ArH), 8.23 (t, J = 7.8 Hz, 2H, ArH), 7.85 (t, J = 3.2 Hz, 1H, ArH), 7.67 (t, J = 3.2Hz , 1H, ArH), 7.60-7.55 (m, 2H, ArH), 2.34 (s, 3H, CH3); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 163.98, 158.67, 151.03, 140.69, 134.02, 133.53, 130.87, 129.88, 129.49, 128.97, 126.95, 121.80, 21.15; ESI-MS m/z: 255.08 ([M + H]$^{+}$).

2-(4-(tert-butyl)phenyl)-4-chloroquinazoline (9j)

White solid; Yield 68.5%; m.p. 145 - 147℃; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.48 (d, J = 8.2 Hz, 2H, ArH), 8.16 (d, J = 8.0 Hz, 2H, ArH), 7.83 (t, J = 3.2 Hz, 1H, ArH), 7.59 (t, J = 3.0 Hz, 1H, ArH), 7.42 – 7.32 (m, 2H, ArH), 1.31 (s, 9H, 3CH3); ^{13}C NMR (75 MHz, DMSO-d_6) δ:163.98, 158.79, 152.79, 151.62, 133.59, 130.83, 130.46, 129.72, 126.83, 122.28, 121.91, 34.58 , 31.36; ESI-MS m/z: 297.13 ([M + H]$^{+}$).

4-chloro-2-(pyridin-4-yl)quinazoline (9k)

Pale yellow solid; Yield 75.1%; m.p. 167-169 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.83 (d, J = 6.1 Hz, 2H, ArH), 8.35 (d, J = 6.1 Hz, 2H, ArH), 8.32 (d, J = 8.4 Hz, 1H, ArH), 8.25-8.13 (m, 2H, ArH), 7.95 (m 1H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 163.02, 158.05, 151.68, 150.63, 143.97, 135.22, 129.37, 129.25, 125.91, 123.17,122.34; ESI-MS m/z: 242.06 ([M + H]$^{+}$).

4-chloro-2-(pyridin-3-yl)quinazoline (9l)

Pale yellow solid; Yield 75.1%; m.p. 176-178 °C ; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 9.07 (d, J = 3.2 Hz, 1H, ArH), 8.75 (dd, J =8.8, 3.0 Hz, 1H, ArH), 8.51-8.46 (m, 1H, ArH), 8.28 (d, J = 8.4 Hz, 1H, ArH), 8.22 (d, J = 8.4 Hz, 1H, ArH), 8.01 (s, 1H, ArH), 7.82-7.76 (m, 1H, ArH), 7.69 (m, 1H, ArH), 7.50 (dd, J = 8.0, 3.2 Hz, 1H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 154.62, 150.75, 149.27, 148.82, 143.61, 134.85, 134.17, 130.96, 130.13, 127.77, 125.54, 124.08, 123.79, 118.63; ESI-MS m/z: 242.07 ([M + H]$^{+}$).

4-chloro-2-(quinolin-2-yl)quinazoline (9m)

White solid; Yield 84.8%; m.p.170-172 °C ; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.33 (d, J = 7.5, 1H, ArH), 8.18 – 8.04 (m, 3H, ArH), 7.85 (d, J = 7.8, 1H, ArH), 7.79 (t, J = 7.6Hz, 1H, ArH), 7.72 (t, J = 7.8Hz, 1H, ArH), 7.68 (d, J = 7.8 Hz, 1H, ArH), 7.56-7.52 (m, 2H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 159.18, 157.53, 144.74, 140.56, 137.33, 133.69, 130.91, 130.61, 129.75, 128.83, 127.87, 127.61, 127.40, 126.92, 124.07, 122.64; ESI-MS m/z: 292.09 ($[M + H]^+$).

4-chloro-2-(3-nitrophenyl)quinazoline (9n)

Yellow solid; Yield 85.2 %; m.p.185-187 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.69 -8.64 (m, 2H, ArH), 8.31 (dd, J = 8.2, 3.2 Hz, 1H, ArH), 8.14 (dd, J = 8.4, 3.0 Hz, 2H, ArH), 7.93 – 7.72 (m, 2H, ArH), 7.54 (d, J = 3.0 Hz, 2H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 165.33, 158.74, 151.23, 145.68, 137.82, 135.43, 133.77, 130.83, 129.63, 128.62, 126.93, 124.67, 121.87; ESI-MS m/z: 286.07 ($[M + H]^+$).

4-chloro-2-(4-nitrophenyl)quinazoline (9o)

Yellow solid; Yield 63.5%; m.p.192-194 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.30 (d, J = 3.0, 1H, ArH), 8.25 (d, J = 3.2 Hz, 1H, ArH), 8.16 (dd, J = 8.3, 3.0 Hz, 2H, ArH), 8.05 (d, J = 3.2 Hz, 1H, ArH), 8.03 – 7.98 (m, 1H, ArH), 7.78 (t, J = 3.0 Hz, 1H, ArH), 7.60 (t, J = 3.2 Hz, 1H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 163.98, 158.67, 151.03, 144.66, 135.81, 133.72, 130.90, 130.21, 129.88, 127.02, 123.01, 121.91; ESI-MS m/z: 286.05 ($[M + H]^+$).

4-chloro-2-(4-chlorophenyl)quinazoline (9p)

White solid; Yield 78.2%; m.p.179-181 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.22 (d, J = 3.0, 1H, ArH), 8.18 (d, J = 3.2, 1H, ArH), 8.14 (dd, J = 7.8, 3.0 Hz, 2H, ArH), 7.81 (t, J = 8.0 Hz, 1H,

ArH), 7.59 – 7.47 (m, 3H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 163.98, 158.79, 151.03, 136.88, 135.11, 133.61, 130.77, 129.92, 129.41, 129.21, 126.90, 121.79; ESI-MS m/z: 275.02 ([M + H]$^+$).

4-chloro-2-(4-fluorophenyl)quinazoline (9q)

Pale yellow solid; Yield 80.3%; m.p.168-169 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.28 (dd, *J* = 7.8, 3.0 Hz, 2H, ArH), 7.84 – 7.69 (m, 3H, ArH), 7.54 (dd, *J* = 8.0, 3.2 Hz, 1H, ArH), 7.37 – 7.24 (m, 2H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 158.96, 151.37, 151.09, 133.64, 131.43, 130.97, 129.73, 129.46, 126.83, 121.82, 115.46; ESI-MS m/z: 259.07 ([M + H]$^+$).

4,7-dichloro-2-phenylquinazoline (9r)

White solid; Yield 81.6%; m.p.173-174 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.31 (d, *J* = 8.0 Hz, 2H, ArH), 8.10 (d, *J* = 3.6 Hz, 1H, ArH), 8.02 (d, *J* = 3.8 Hz, 1H, ArH), 7.90 (d, *J* = 8.2 Hz, 1H, ArH), 7.52-7.47 (m, 3H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 162.10, 159.15, 152.99, 136.08, 135.56, 129.77, 128.57, 128.36 , 126.96, 125.68, 124.11; ESI-MS m/z: 275.02 ([M + H]$^+$).

4-chloro-6,7-dimethoxy-2-phenylquinazoline (9s)

White solid; Yield 72.4%; m.p. 182-184 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.35 (d, *J* = 7.8 Hz, 2H, ArH), 7.66 (d, *J* = 5.9 Hz, 2H, ArH), 7.53 (m, 3H, ArH), 3.92 (s, 3H, OCH3), 3.89 (s, 3H, OCH3); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 158.64, 158.44, 153.87, 152.60, 145.36, 136.08, 129.72, 128.82, 128.60, 124.28, 112.89, 110.29, 56.83, 56.25; ESI-MS m/z: 301.09 ([M + H]$^+$).

General Procedure for the Synthesis of 10

The mixture of 1-(2-bromoethyl)-4-nitrobenzene (2.42g, 10mmol), 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (2.41g, 10.5mmo) and K_2CO_3 (3.48g,

25.2mmol) was heated and refluxed in 50ml acetonitrile for 18h. After cooling down, the solution was filtrated and the filter cake was washed by DCM. The filtrate was evaporated to give a yellow solid residue for recrystallization in alcohol to obtain 2.76 g yellow needle-shaped crystalline solid.

6,7-dimethoxy-2-(4-nitrophenethyl)-1,2,3,4-tetrahydroisoquinoline (10)

Yellow solid; Yield 81.2%; m.p. 88-90°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.15 (d, J = 8.7Hz, 2H, ArH), 7.55 (d, J =8.7Hz, 2H, ArH), 6.65 (s, 1H, ArH), 6.62 (s, 1H, ArH), 3.69 (s, 6H, 2×OCH3), 3.53(s, 2H, NCH2Ar), 3.00-2.94 (t, J = 6.9Hz, 2H, NCH2CH2Ar), 2.75-2.68 (m, 6H, -CH2CH2NCH2CH2-); ^{13}C NMR (75 MH_Z, DMSO-d_6) δ: 149.41, 148.19, 147.11, 145.07, 129.90, 128.14, 126.93, 124.70, 112.58, 111.35, 56.83, 56.64, 54.70, 51.36, 33.42, 28.76.; ESI-MS m/z: 343.21 ($[M + H]^+$)

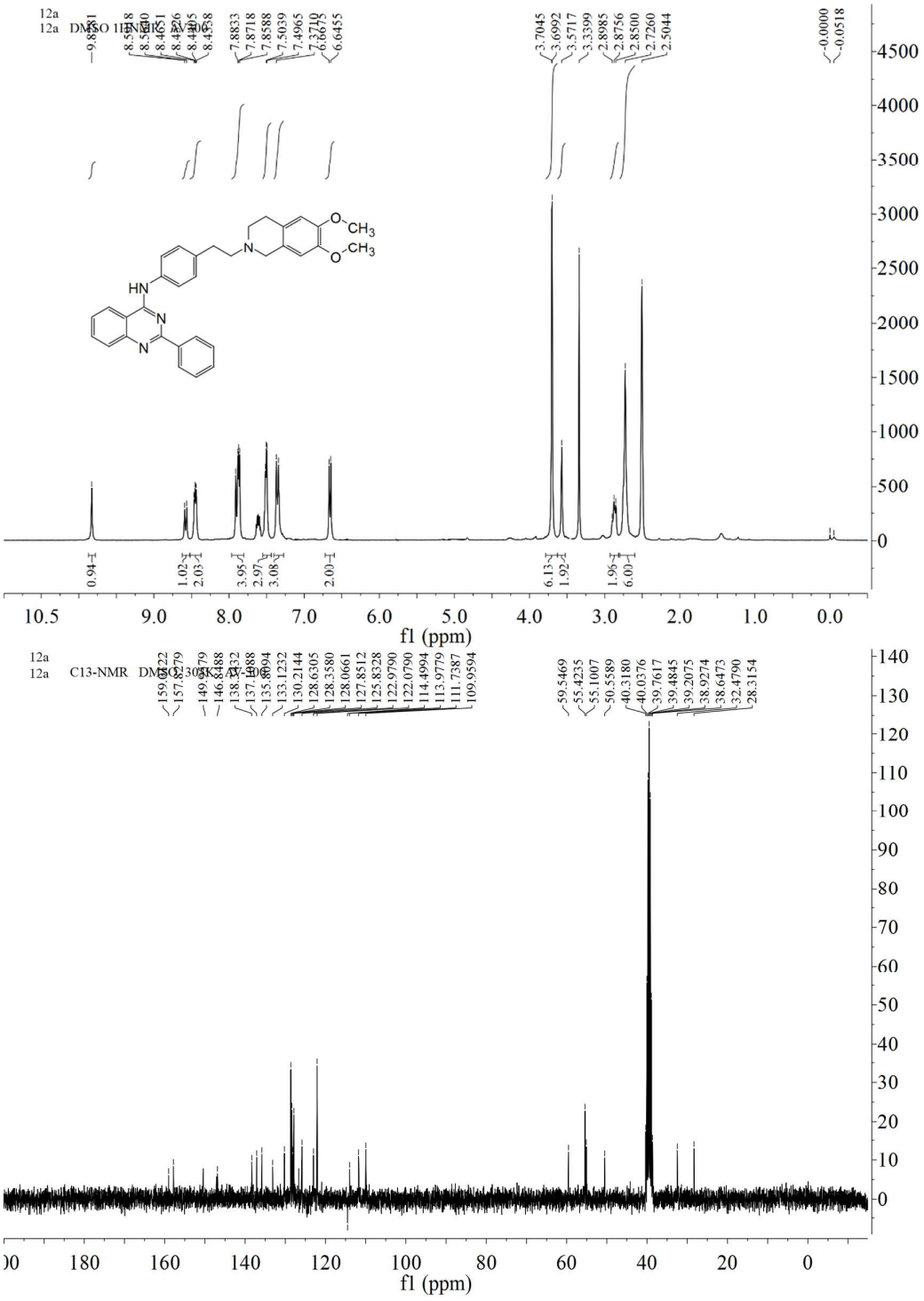
General Procedure for the Synthesis of 11

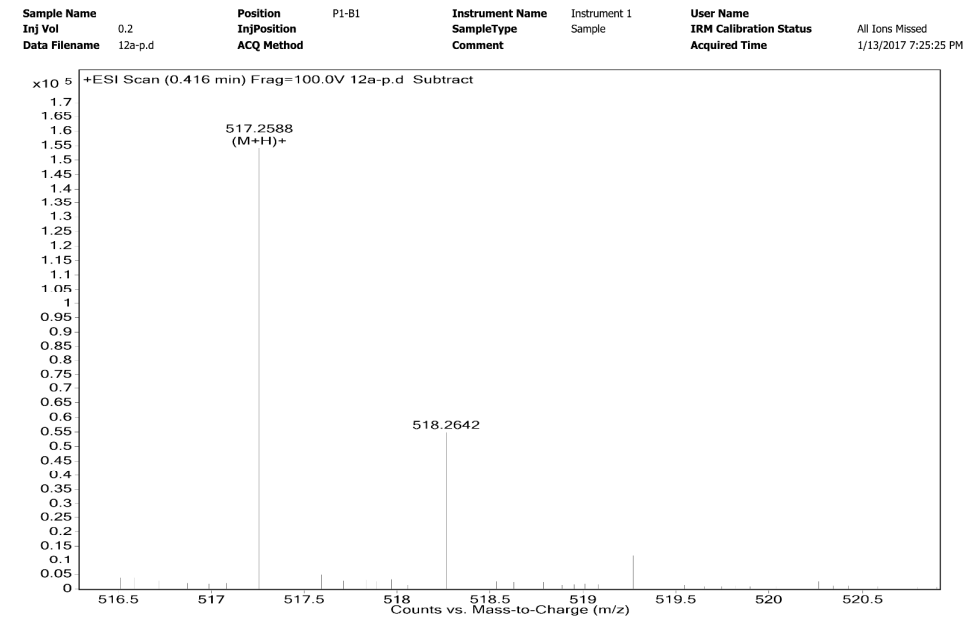
Compound **10** (5.62 g, 18 mmol) was dissolved in 50% acetic acid (40 ml). To this solution, sodium nitrite (1.74 g, 25.2 mmol) was slowly added at -5-0 ℃ within 30 min. The solution was vigorous stirred at 0-5 °C for 50 min. Sodium azide (1.76 g, 27.0 mmol) was batch added into the reaction mixture at 0-5 °C. The resulting solution was stirred at 0-5 °C for 1 h followed by diluting with ice water (200 ml) and extracting with EtOAc (3 × 100 ml). The combined organic layer was washed with water (3 × 150 ml), saturated aqueous $NaHCO_3$ (150 ml × 3) and brine (100 ml), dried over anhydrous Na_2SO_4, filtered and concentrated to afford 5.28 g white solid.

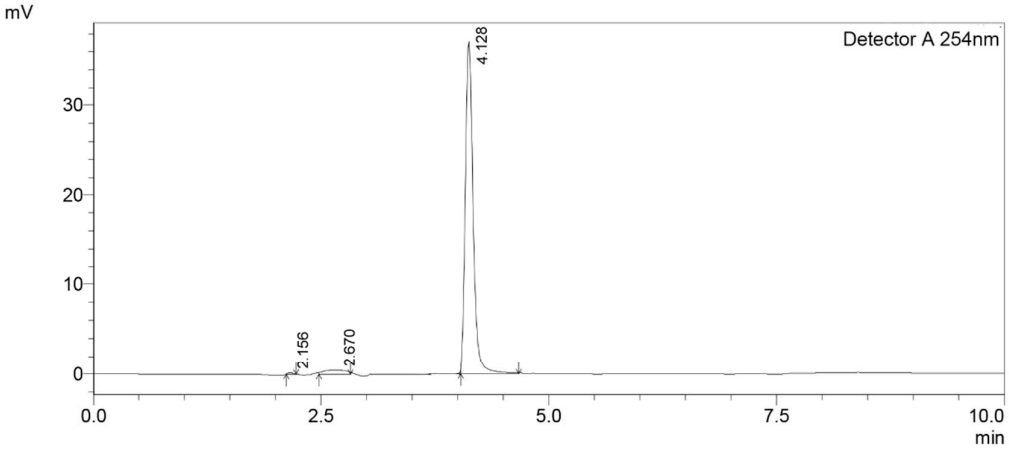
4-(2-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)ethyl)aniline (11)

White solid; Yield 86.7%, m.p.: 68−70 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.29 (d, J = 8.3 Hz, 2H, ArH), 7.02 (d, J = 8.3 Hz, 2H, ArH), 3.70, 3.69 (2s, 6H, $2OCH_3$), 3.52 (s, 2H, $ArCH_2N$), 2.83-2.78 (m, 2H, CH_2), 2.67-2.50 (m, 6H, $3CH_2$); ^{13}C NMR (75 MH_Z, DMSO-d_6) δ: 147.15, 146.83, 137.52, 136.86, 130.10, 126.52, 125.89, 118.84, 111.72, 109.91, 59.27, 55.44, 55.02, 50.47, 32.15, 28.22; ESI-MS m/z: 313.16 ($[M + H]^+$).

^{1}H and ^{13}C NMR spectra, ESI-HRMS spectra and HPLC chromatograms of compounds 12a-s







Peak	RT	Area	% Area
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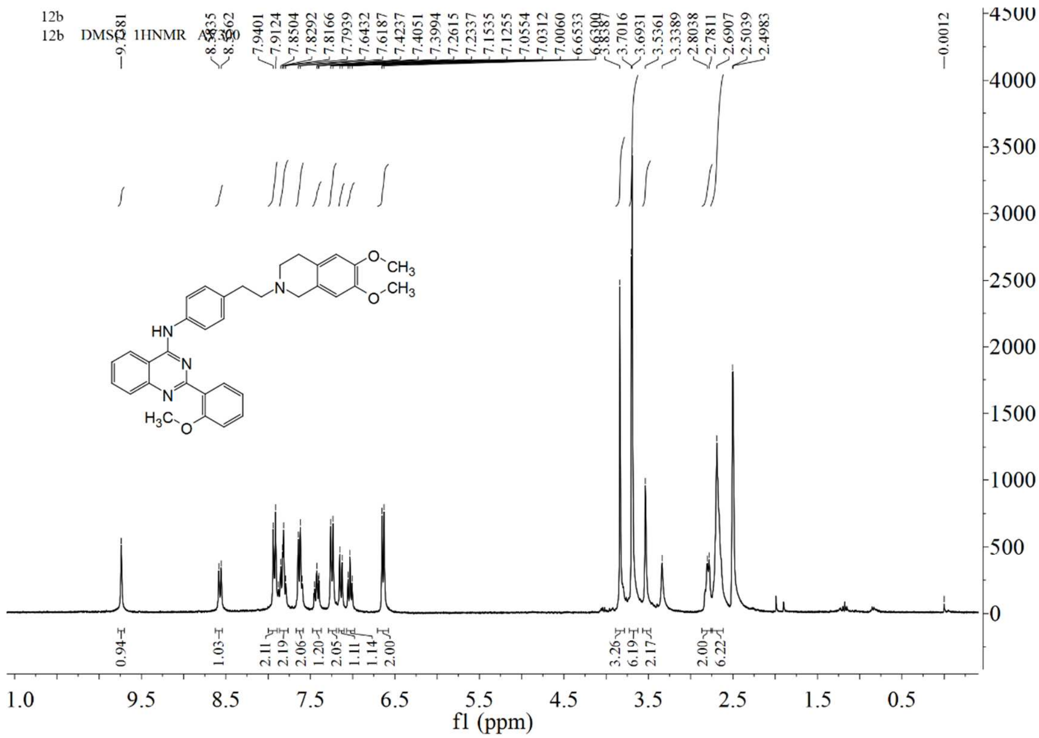
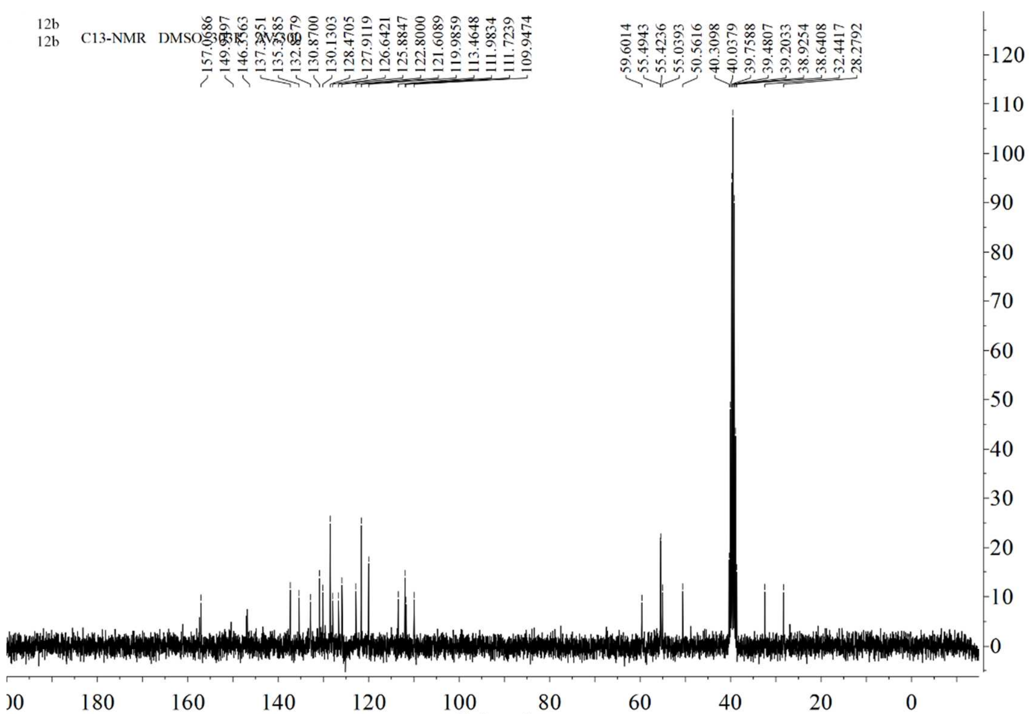
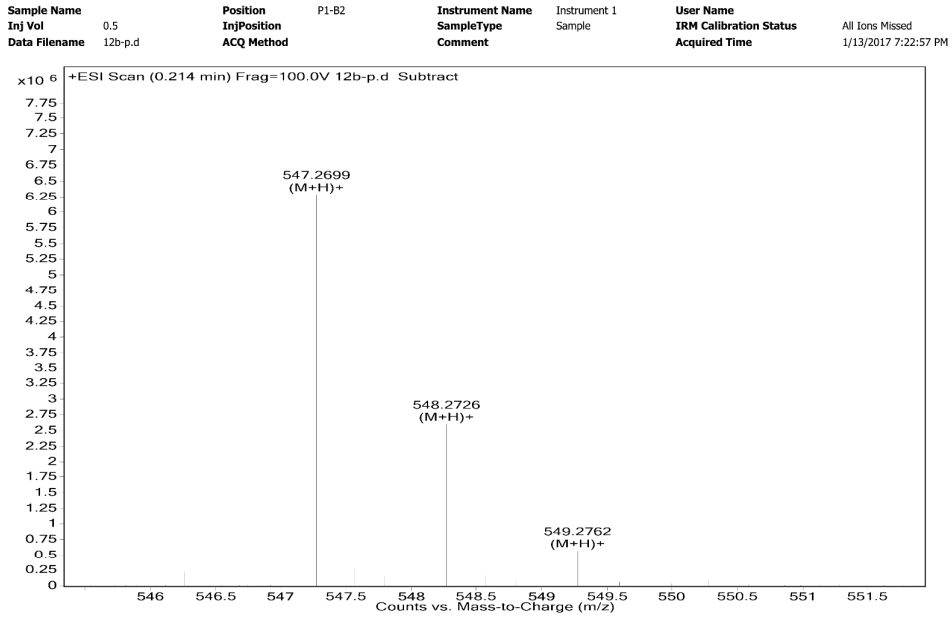
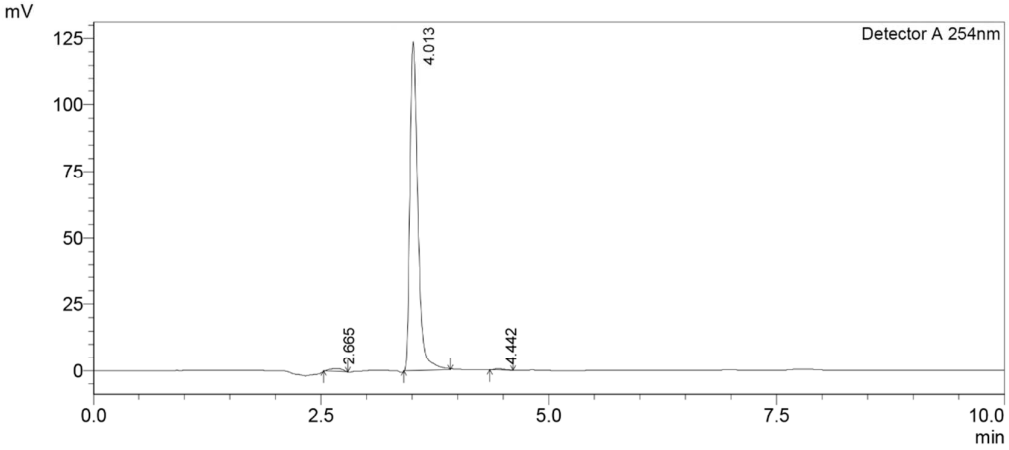
2	2.670	8190	3.565
3	4.128	220842	96.106
Total		229789	100.000

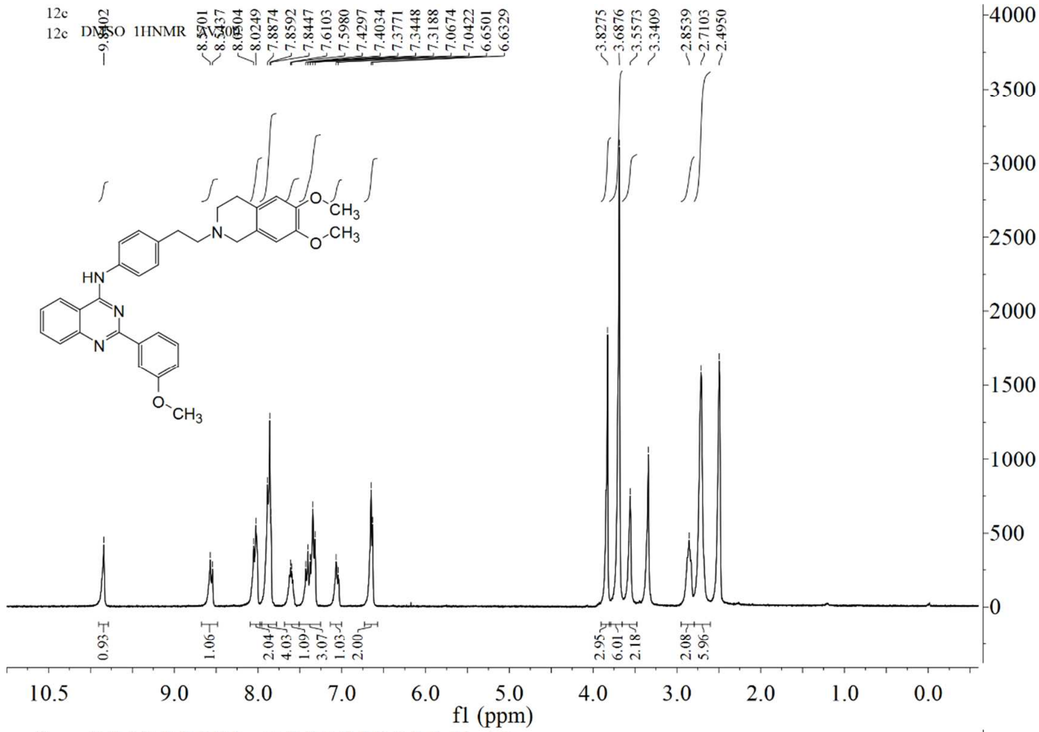








Peak	RT	Area	% Area
1	2.665	10131	1.324
2	4.013	751376	98.180
3	4.442	3801	0.496
Total		765308	100.000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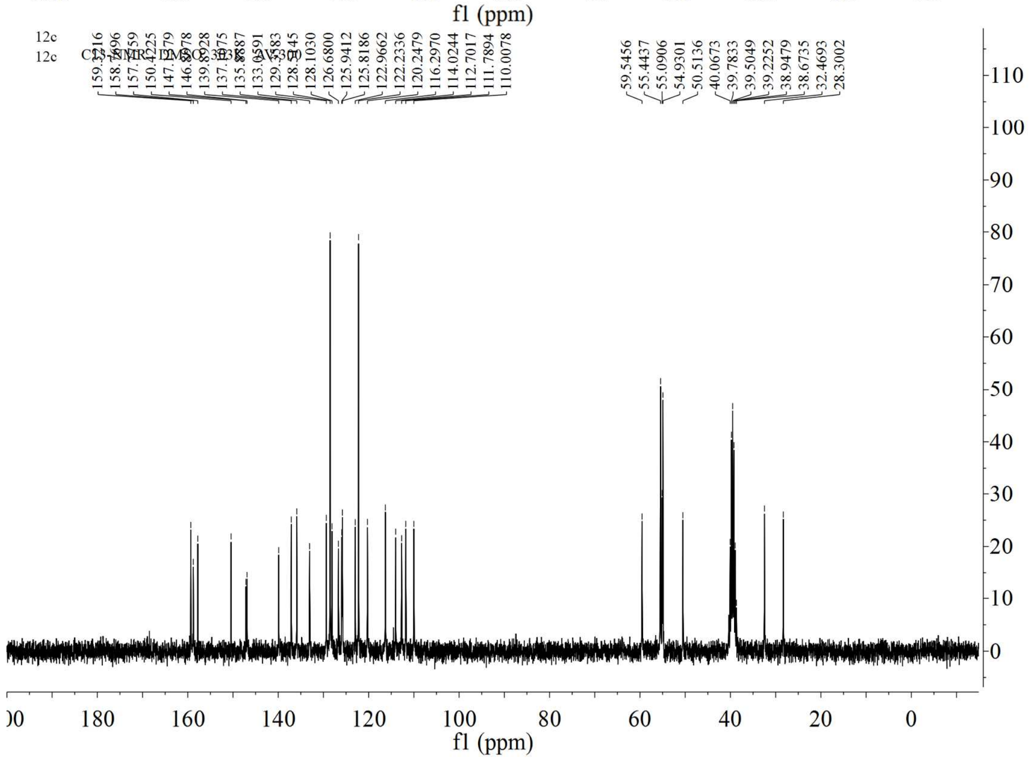
8.5437
8.0249
7.8874
7.8592
7.8447
7.6103
7.5980
7.4297
7.4034
7.3771
7.3448
7.3188
7.0674
7.0422
6.6501
6.6329
3.8275
3.6876
3.5573
3.3409
2.8539
2.7103
2.4950
HN
N
N
N
O
CH3
O
CH3
O
CH3
0.93
1.06
2.04
4.03
1.09
3.07
1.03
2.00
2.95
6.01
2.18
2.08
5.96
fl (ppm)


12c
12c
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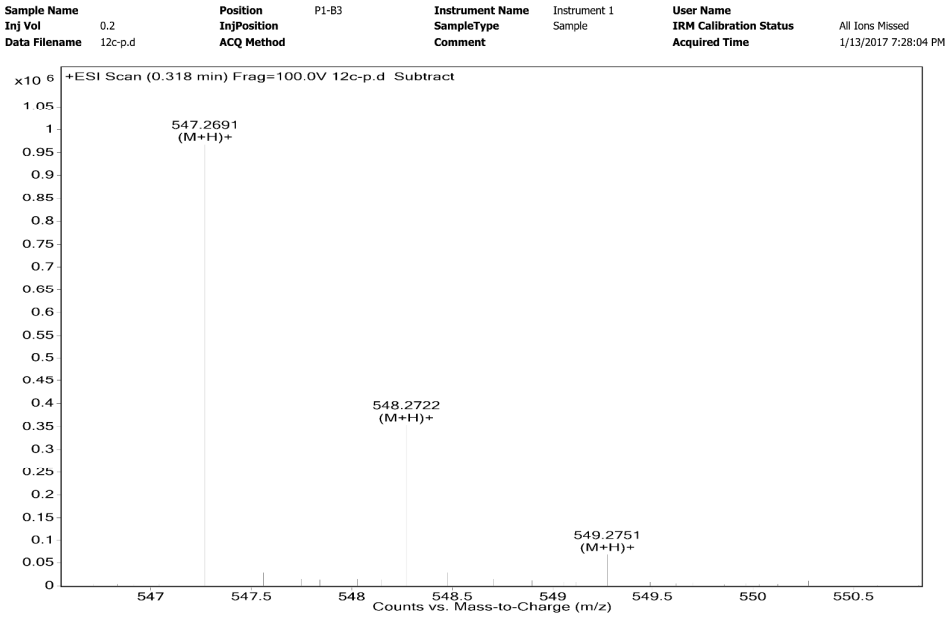
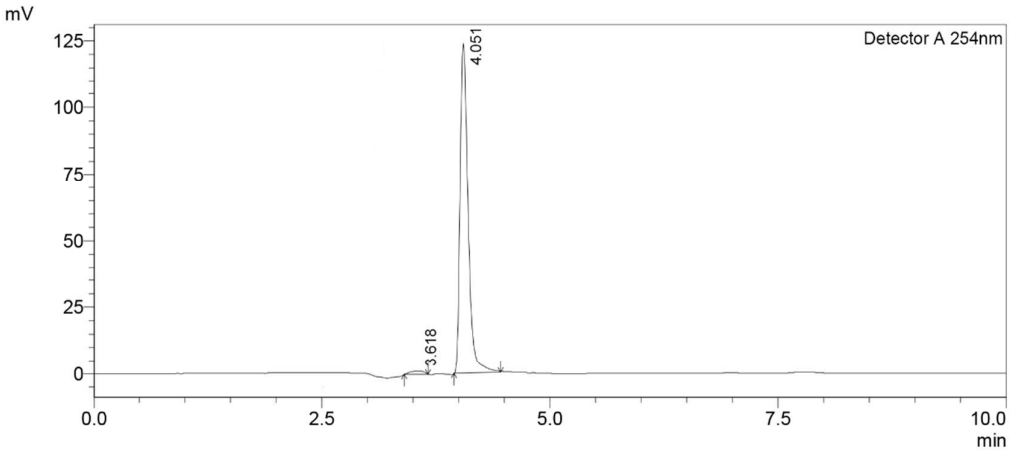
126.6800
125.9412
125.8186
122.9662
122.2336
120.2479
116.2970
114.0244
112.7017
111.7894
110.0078
59.5456
55.4437
55.0906
54.9301
50.5136
40.0673
39.7833
39.5049
39.2252
38.9479
38.6735
32.4693
28.3002
fl (ppm)





Peak	RT	Area	% Area
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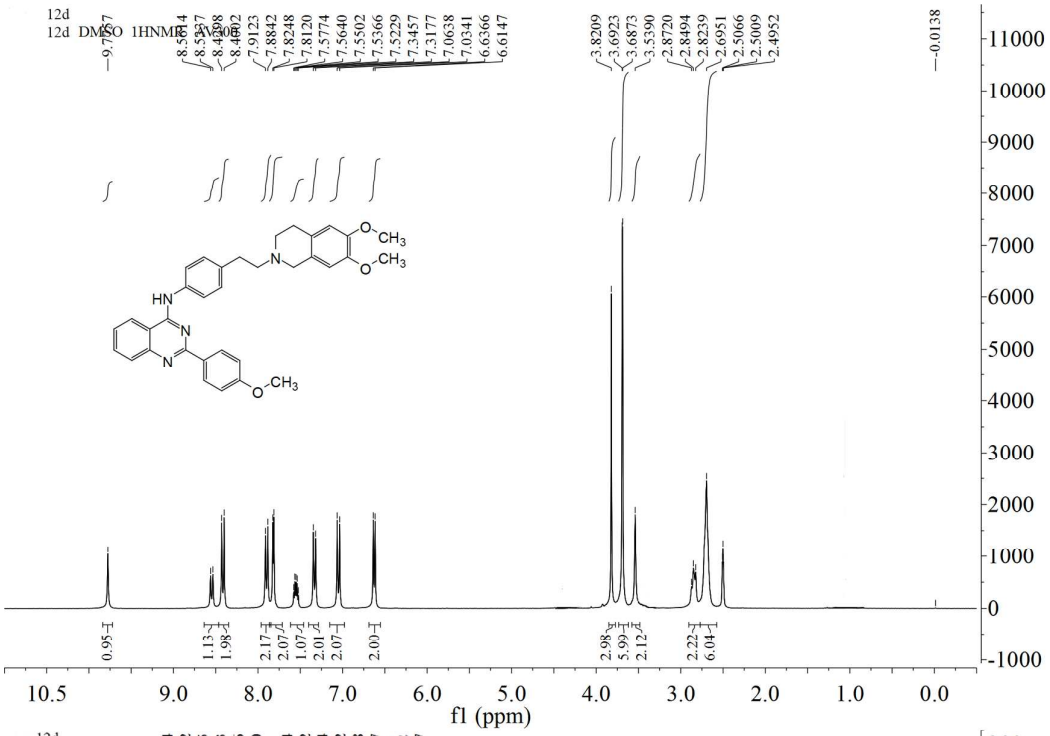
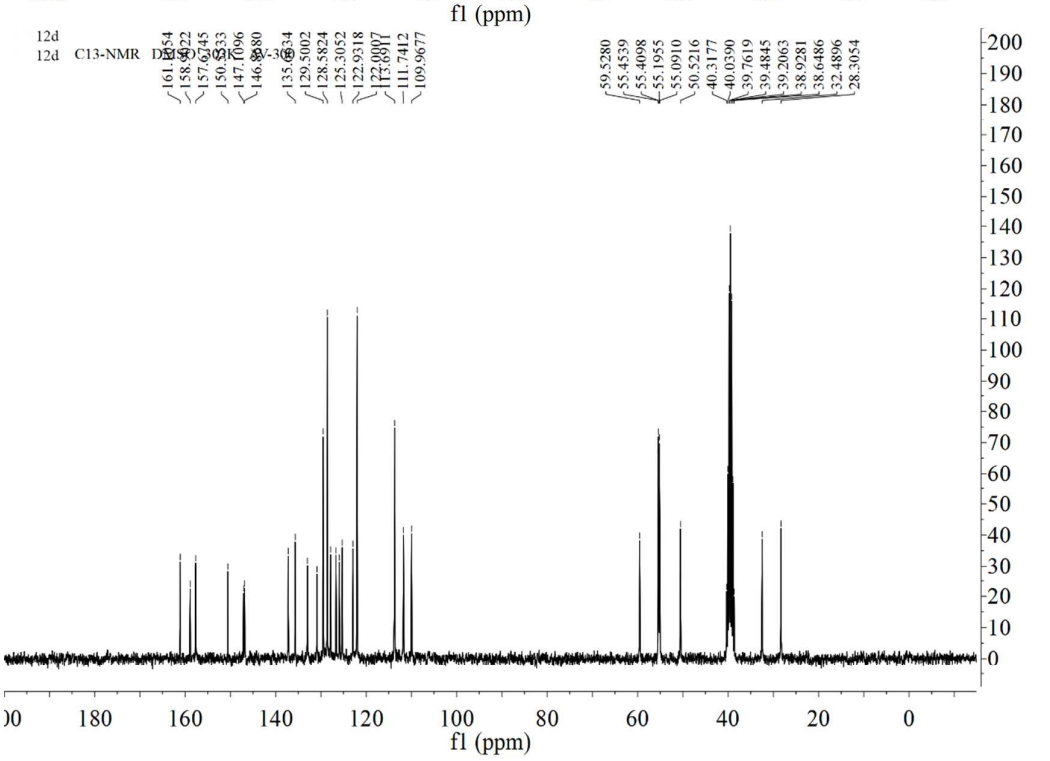
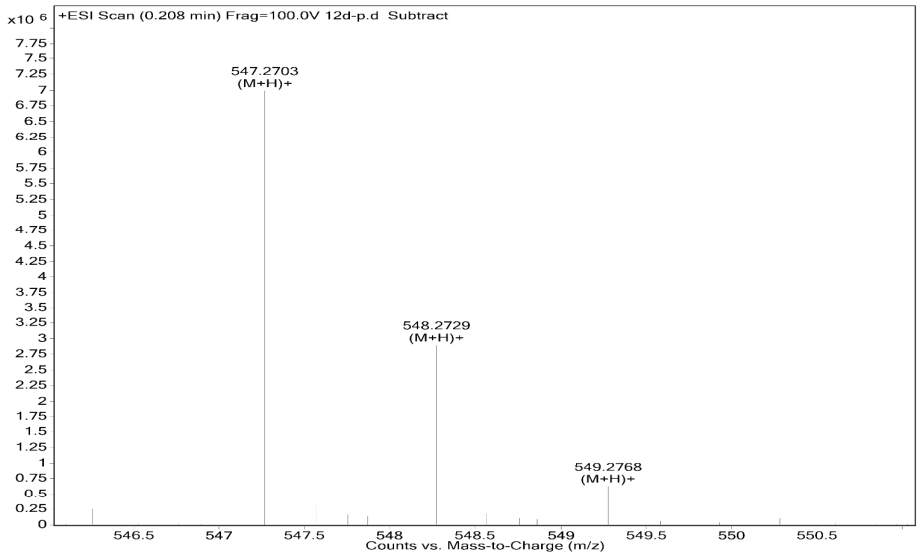
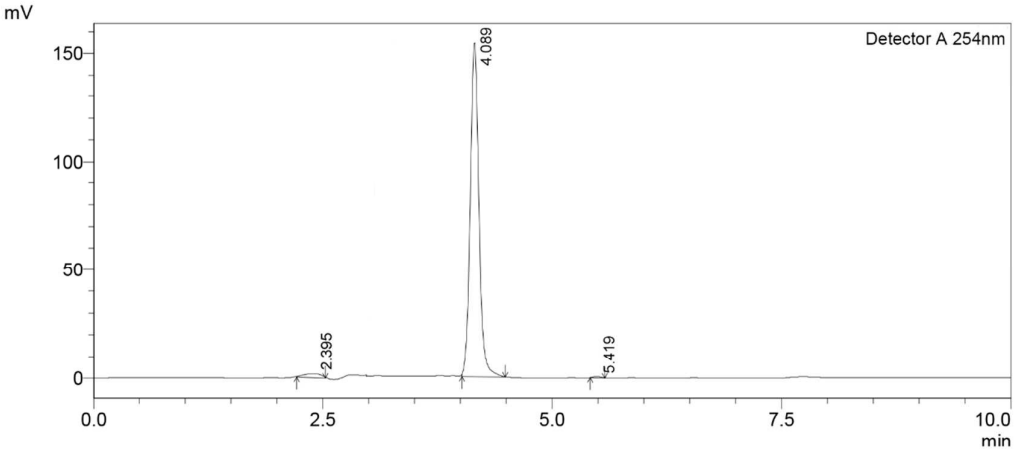
Total		762975	100.000


12d
12d DMSO 1HNMR
fl (ppm)


12d
12d C13-NMR DMSO-300
fl (ppm)

Sample Name		**Position**	P1-B4	**Instrument Name**	Instrument 1	**User Name**	
Inj Vol	0.2	**InjPosition**		**SampleType**	Sample	**IRM Calibration Status**	All Ions Missed
Data Filename	12d-p.d	**ACQ Method**		**Comment**		**Acquired Time**	1/13/2017 7:30:22 PM





Peak	RT	Area	% Area
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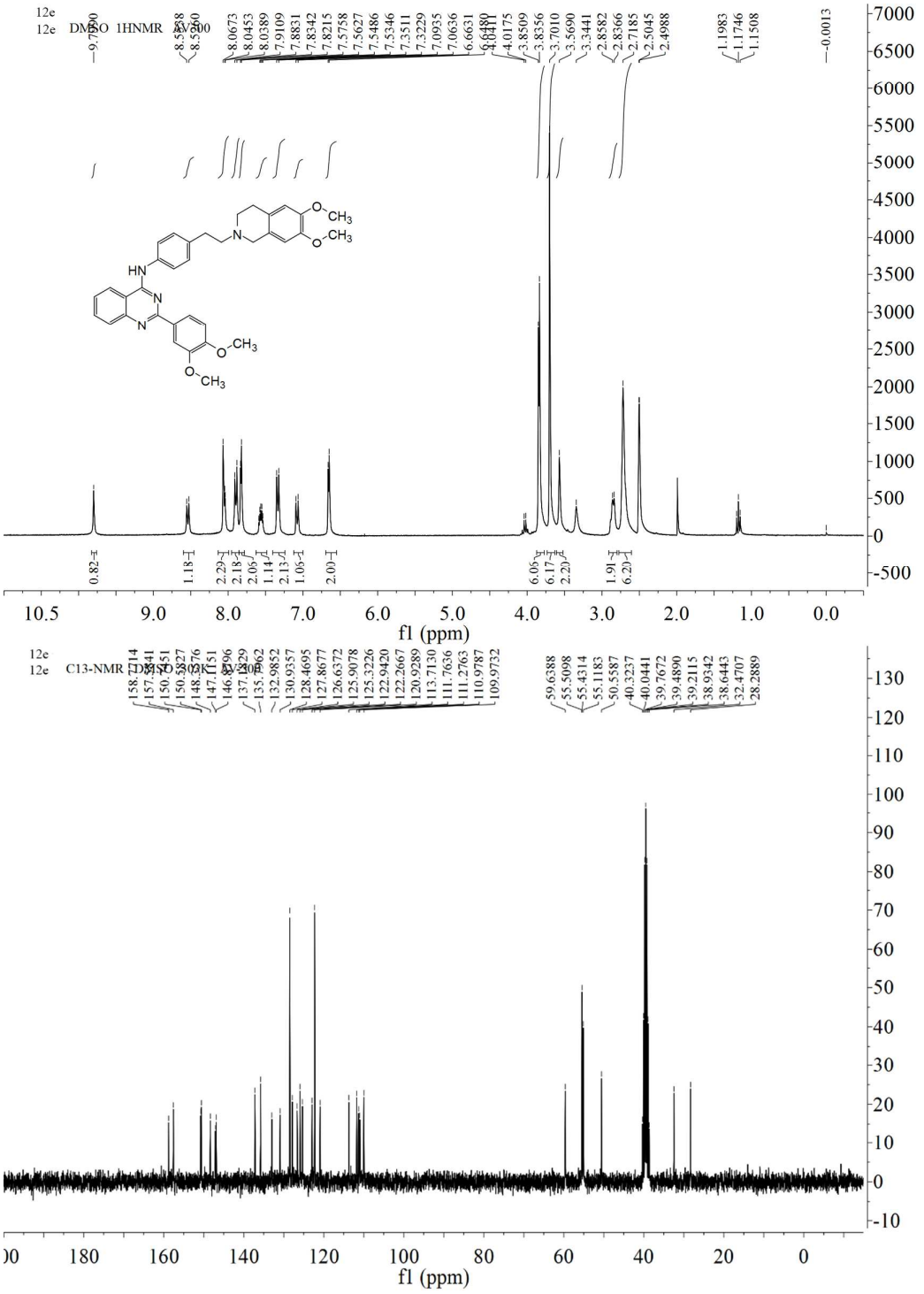
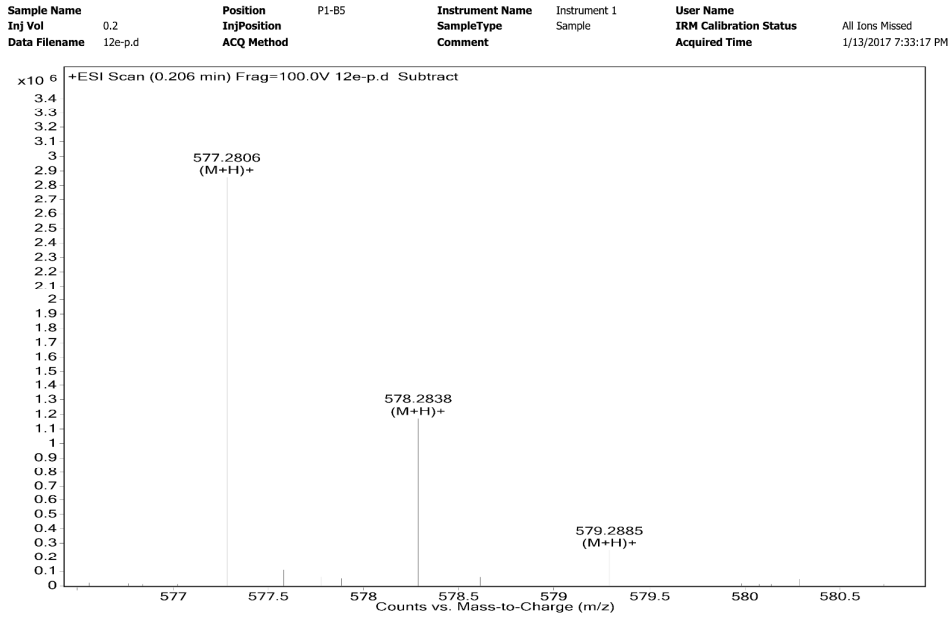
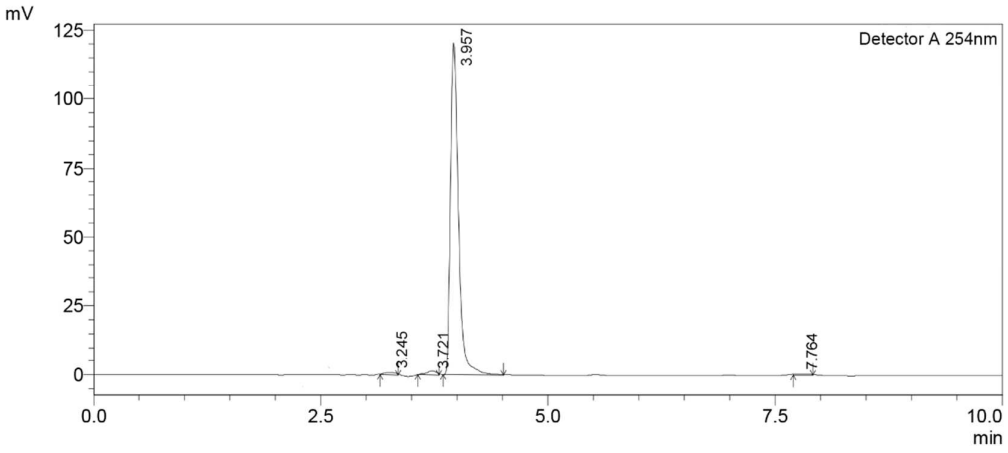
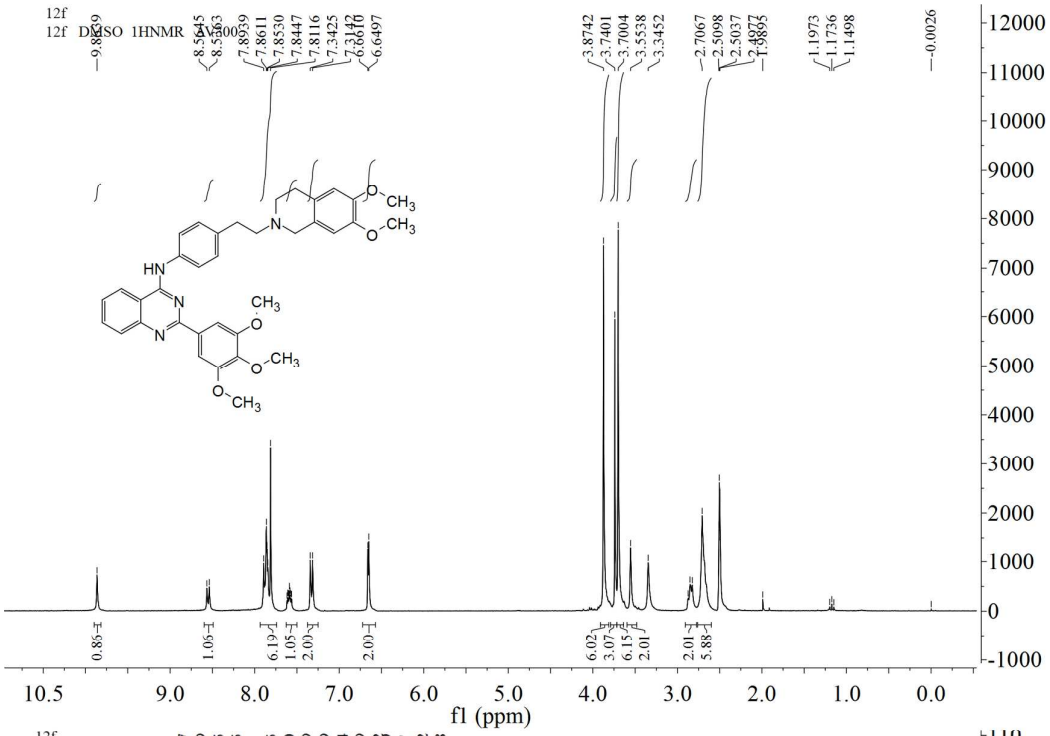
3	5.419	3764	0.409
Total		1039172	100.000

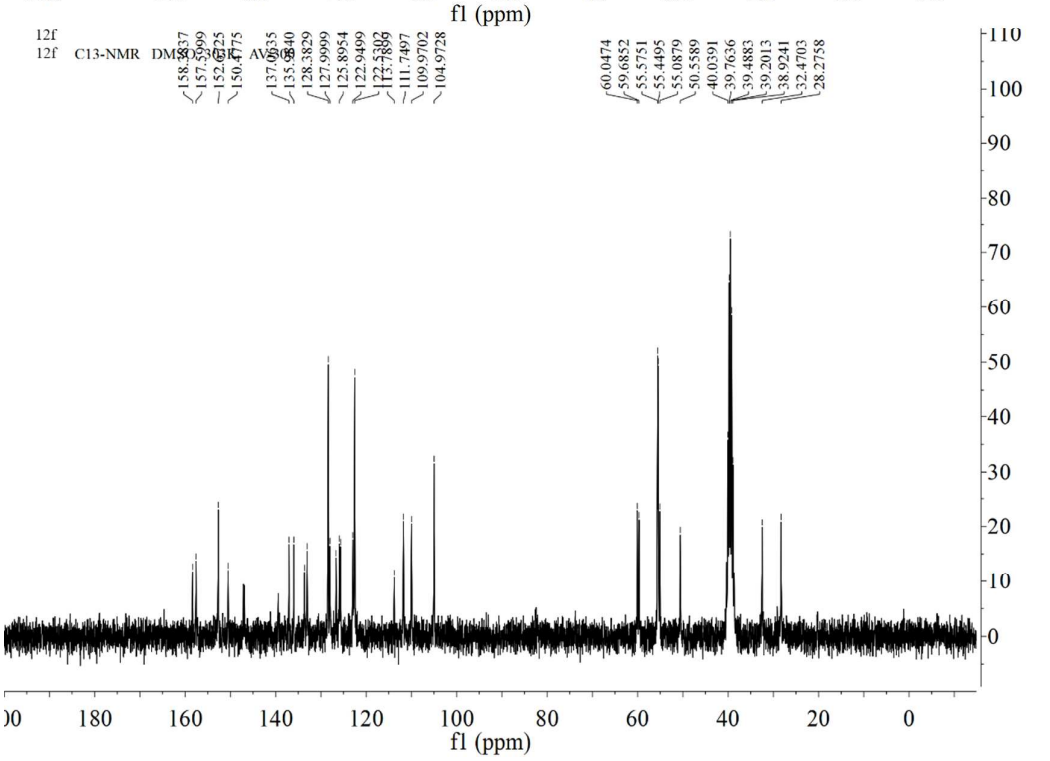

12e
12e DMSO 1HNMR AV500
fl (ppm)
12e
12e C13-NMR DMSO
fl (ppm)

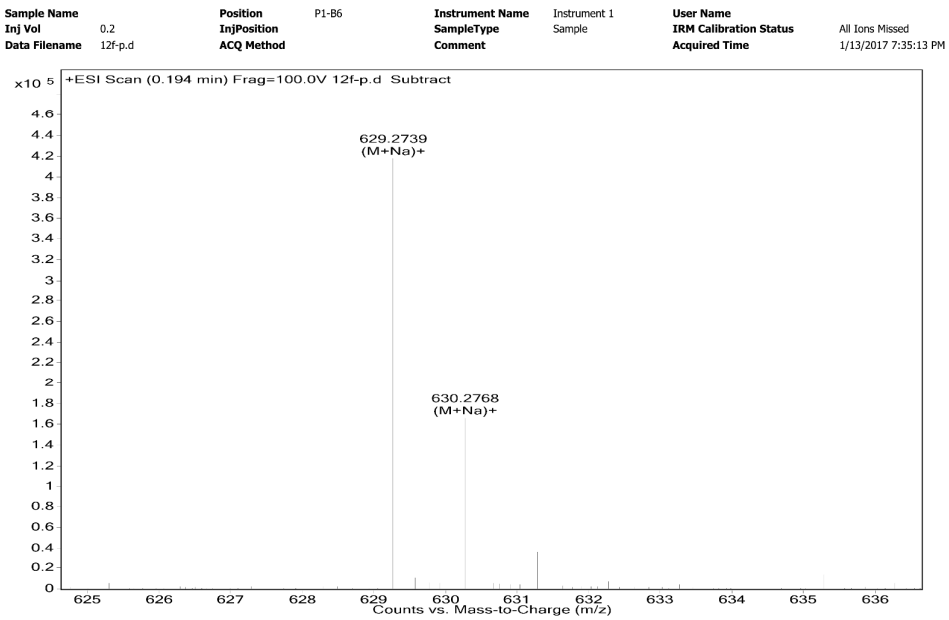


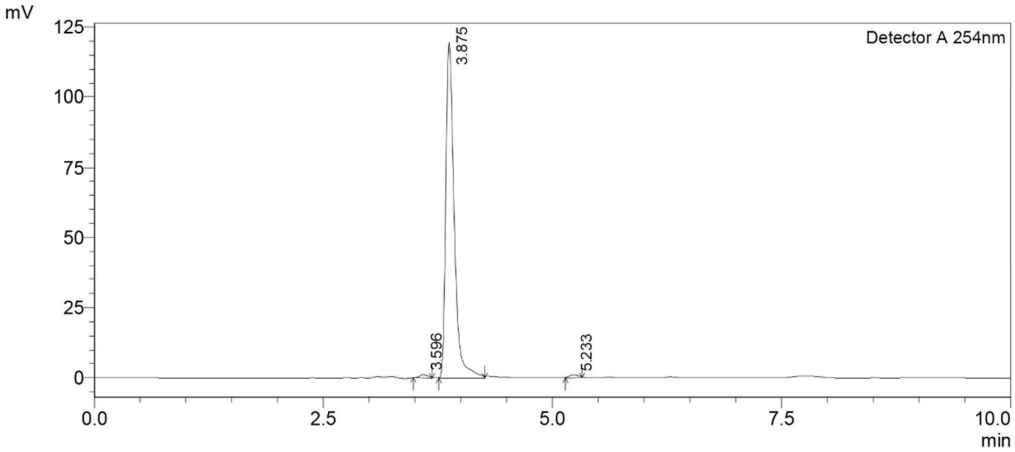


Peak	RT	Area	% Area
1	3.245	8113	1.071
2	3.721	11594	1.531
3	3.957	732322	96.705
4	7.764	5249	0.693
Total		757277	100.000

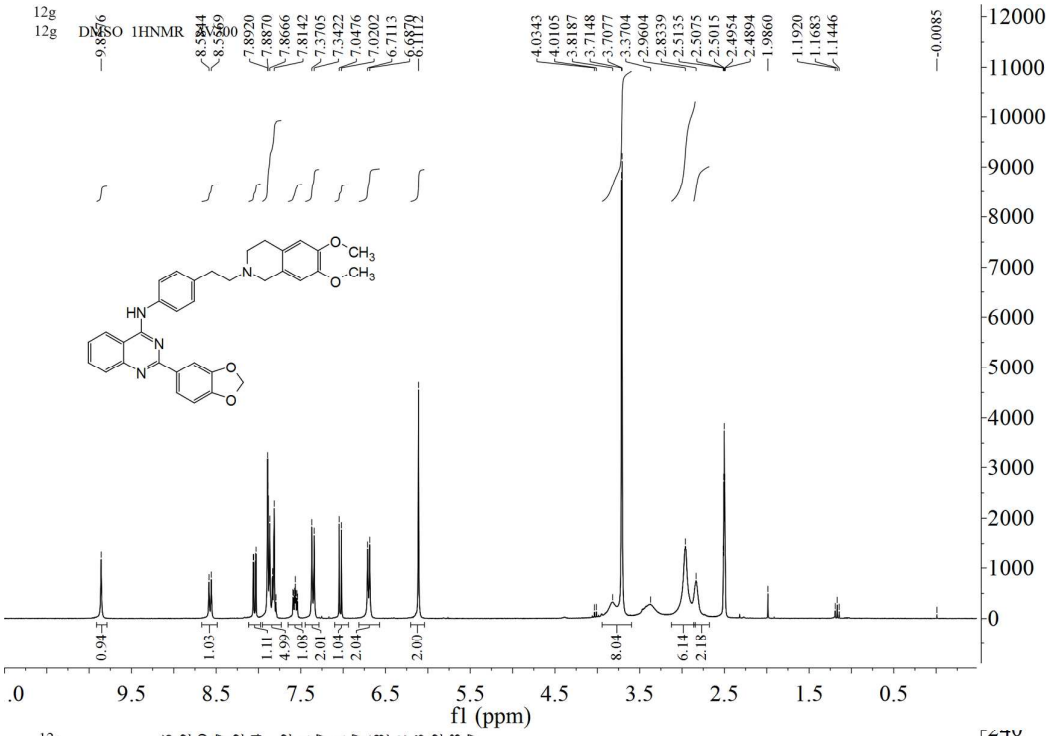

12f
12f DMSO 1HNMR AV500
fl (ppm)

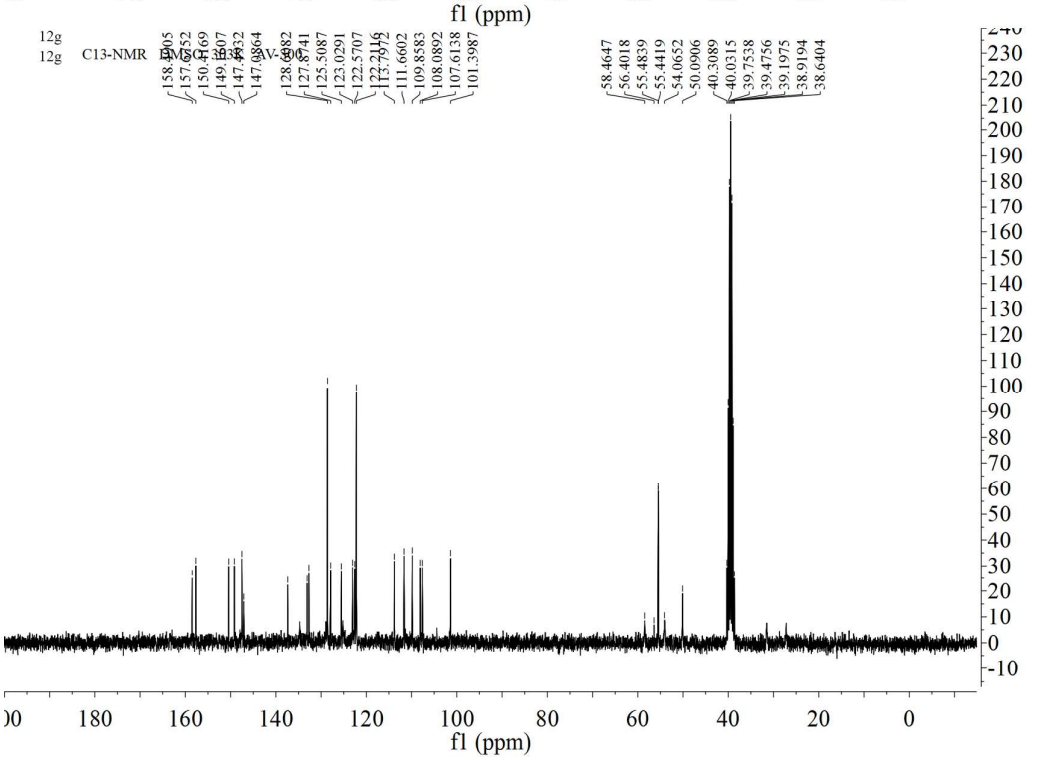

12f
12f C13-NMR DMSO AV500
fl (ppm)



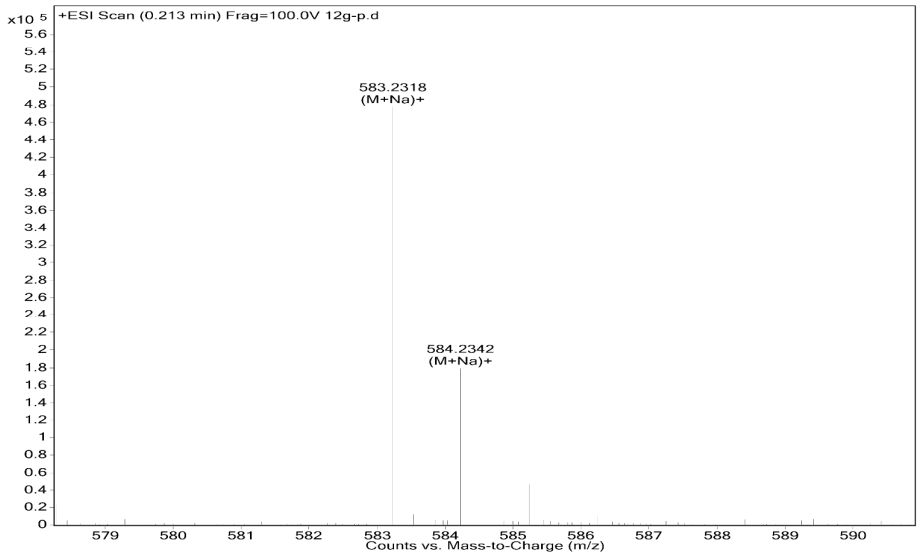


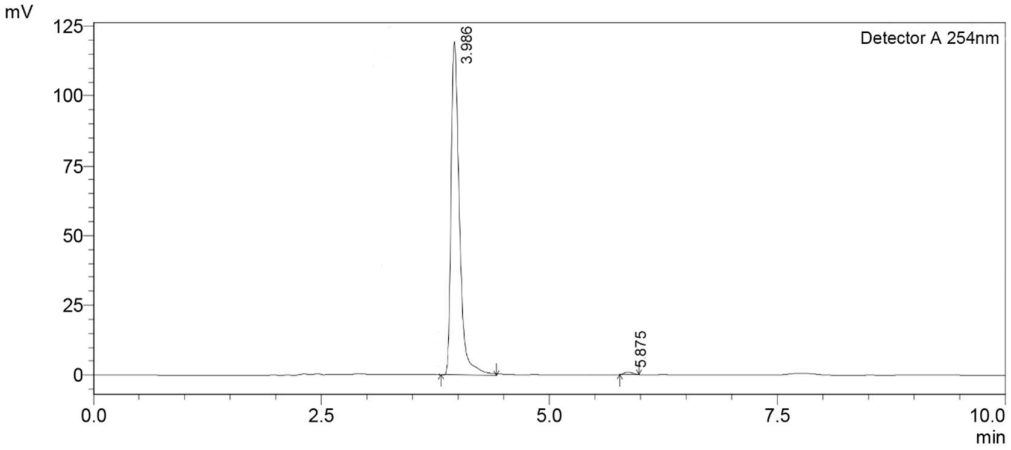
Peak	RT	Area	% Area
1	3.596	7120	0.915
2	3.875	763363	98.106
3	5.233	7622	0.979
Total		778104	100.000


12g
12g DMSO 1HNMR AV-500
fl (ppm)


12g
12g C13-NMR DMSO AV-500
fl (ppm)

Sample Name		**Position**	P1-B7	**Instrument Name**	Instrument 1	**User Name**	
Inj Vol	0.2	**InjPosition**		**SampleType**	Sample	**IRM Calibration Status**	All Ions Missed
Data Filename	12g-p.d	**ACQ Method**		**Comment**		**Acquired Time**	1/13/2017 7:37:22 PM





Peak	RT	Area	% Area
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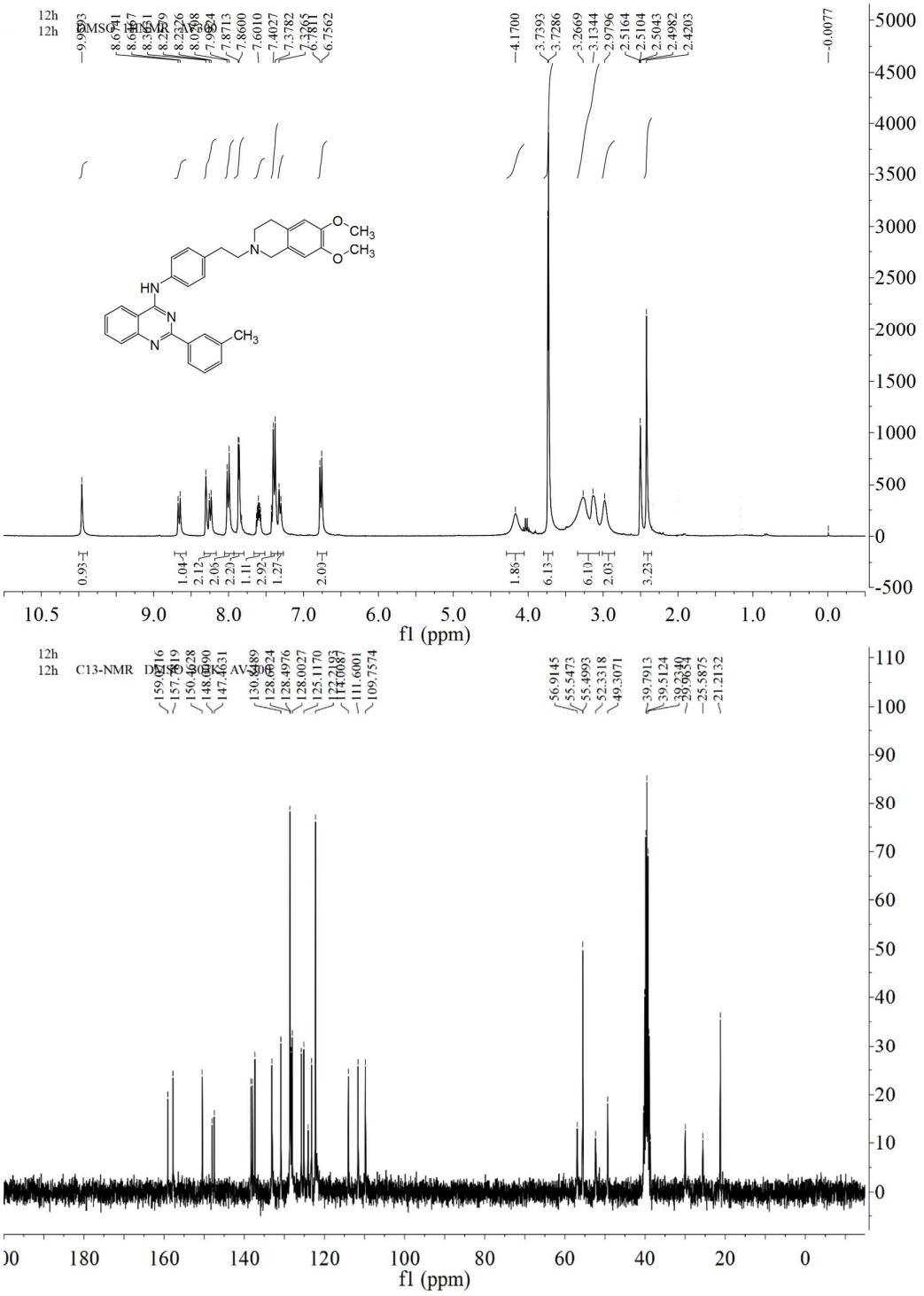
2	5.875	892	0.117
Total		759752	100.000


12h
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8.3851
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8.2216
8.0258
7.9864
7.8713
7.8600
7.6010
7.4027
7.3782
7.3805
7.3811
6.7562
4.1700
3.7393
3.7286
3.2669
3.1344
2.9796
2.5164
2.5104
2.5043
2.4982
2.4203
-0.0077
0.93
1.04
2.12
2.05
2.22
1.11
2.92
1.27
2.03
1.85
6.13
6.10
2.03
3.23
fl (ppm)
12h
12h C13-NMR DMSO AV-400
159.0116
157.3419
150.4628
148.0190
147.4631
130.3889
128.6624
128.4976
128.0027
125.1170
122.2183
114.0087
111.6001
109.7574
56.9145
55.5473
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49.3071
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39.5124
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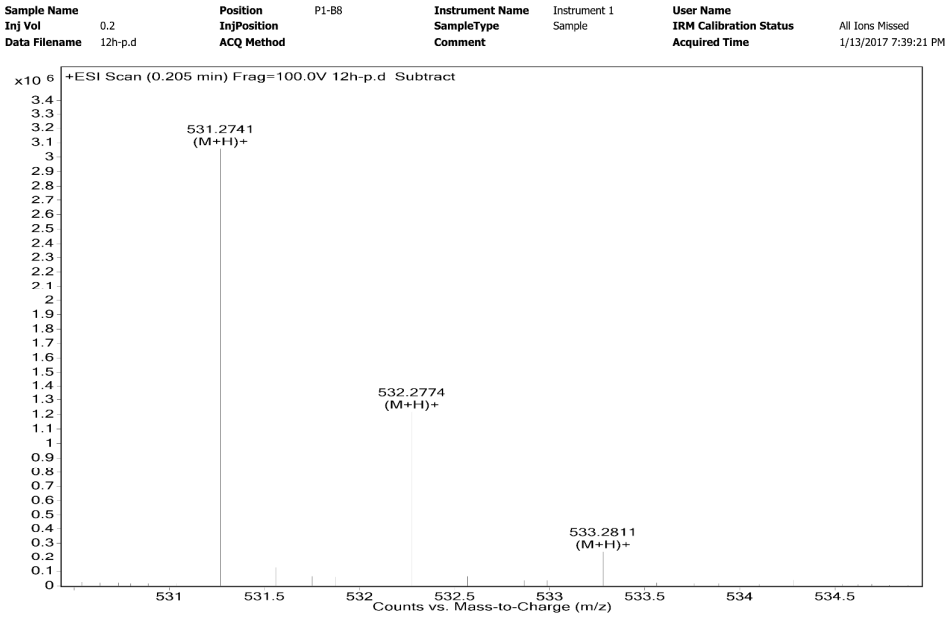
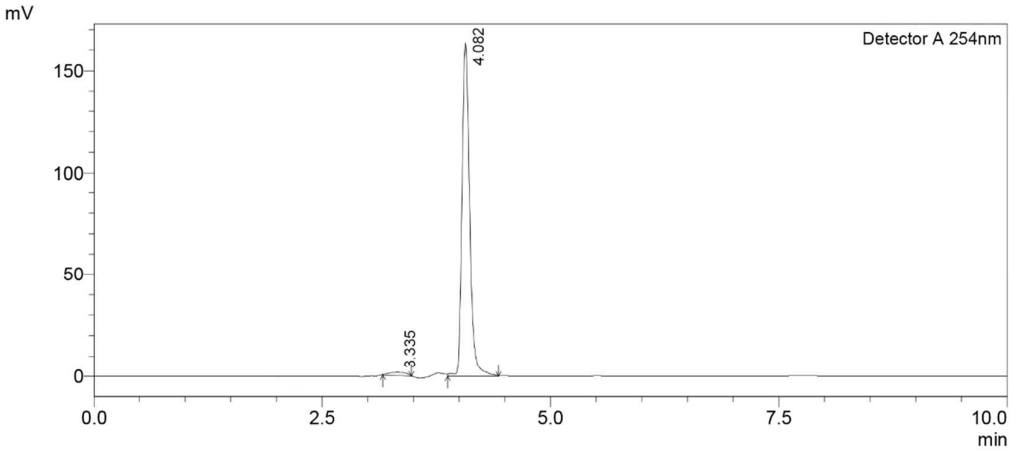
29.9634
25.5875
21.2132
fl (ppm)





Peak	RT	Area	% Area
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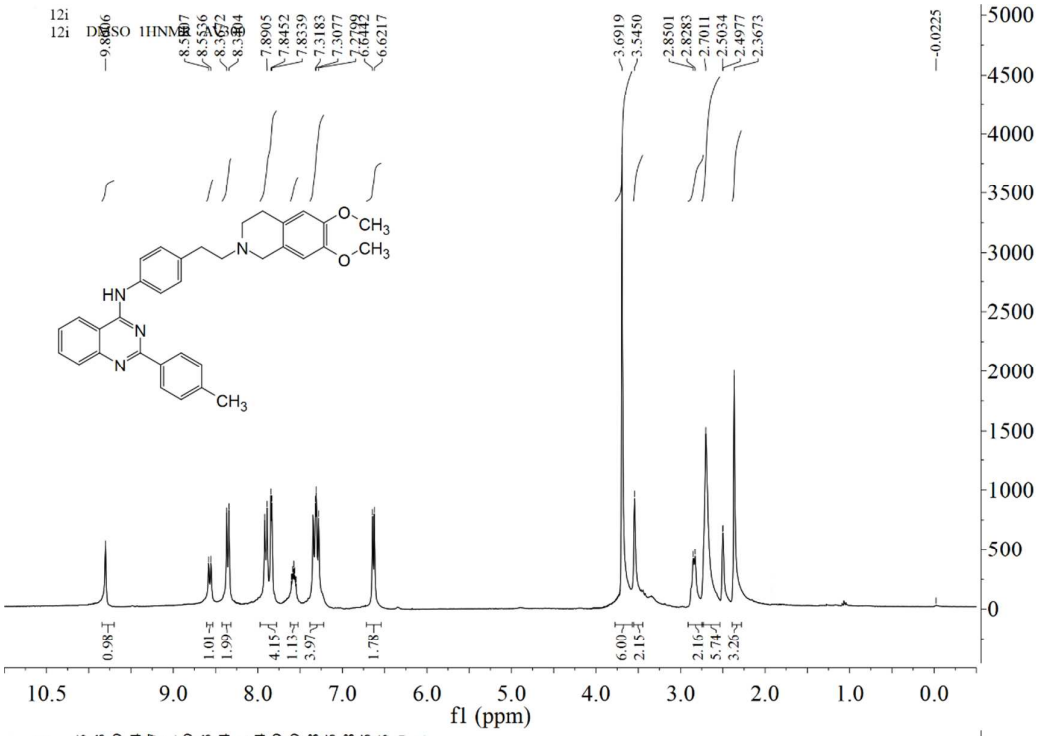
2	4.082	951271	97.801
Total		972659	100.000


12i
12i DMSO 1HNMR 25C 300
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8.3384
7.8905
7.8452
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7.3183
7.3077
7.2792
6.6442
6.6217
3.6919
3.5450
2.8501
2.8283
2.7011
2.5034
2.4977
2.3673
-0.0225
0.98
1.01
1.99
4.15
1.13
3.97
1.78
6.01
2.15
2.15
5.74
3.26
HN
N
N
O
CH3
O
CH3
CH3
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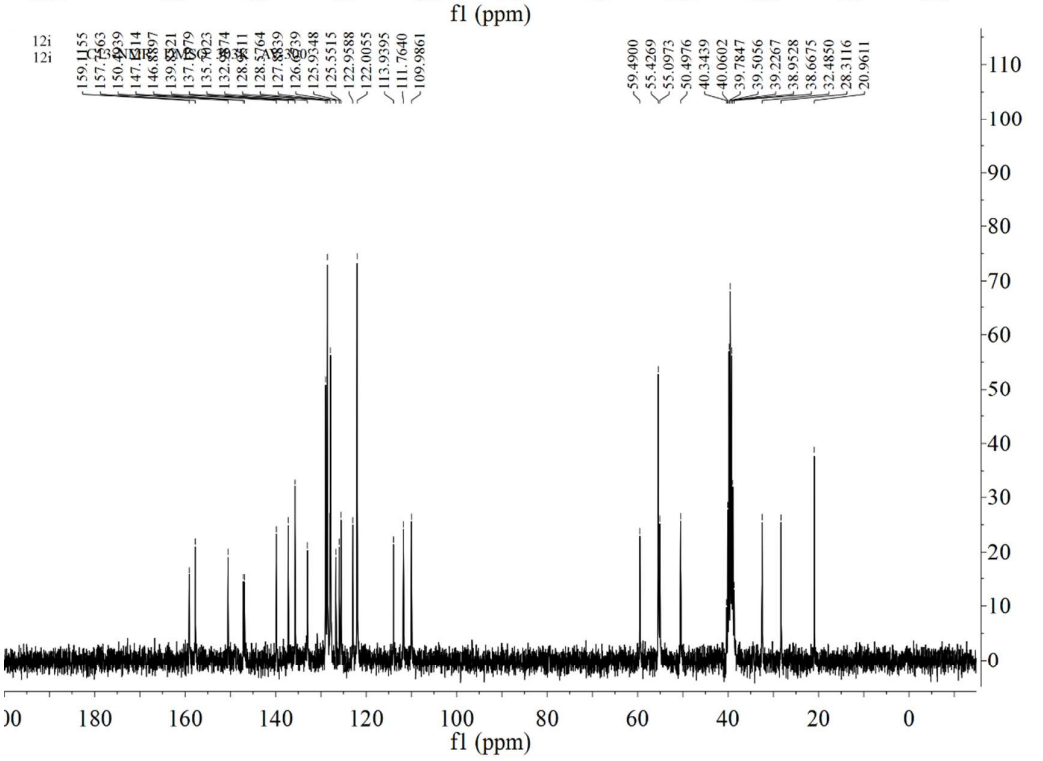
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)


12i
12i
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146.8597
139.8321
137.7879
135.7423
132.3874
128.7764
127.8839
126.8039
125.9348
125.5515
122.9588
122.0055
113.9395
111.7640
109.9861
59.4900
55.4269
55.0973
50.4976
40.3439
40.0602
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39.5056
39.2267
38.9528
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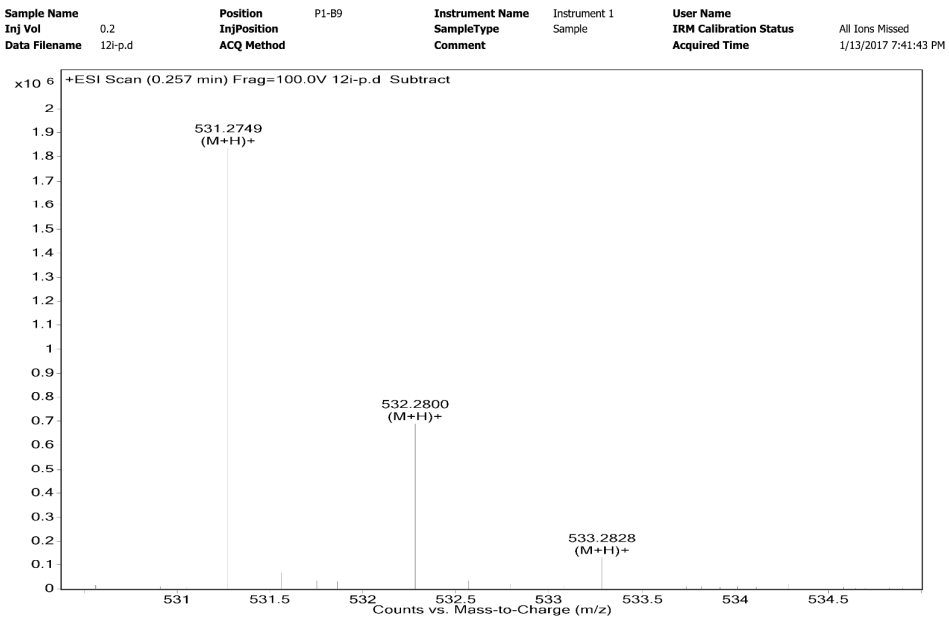
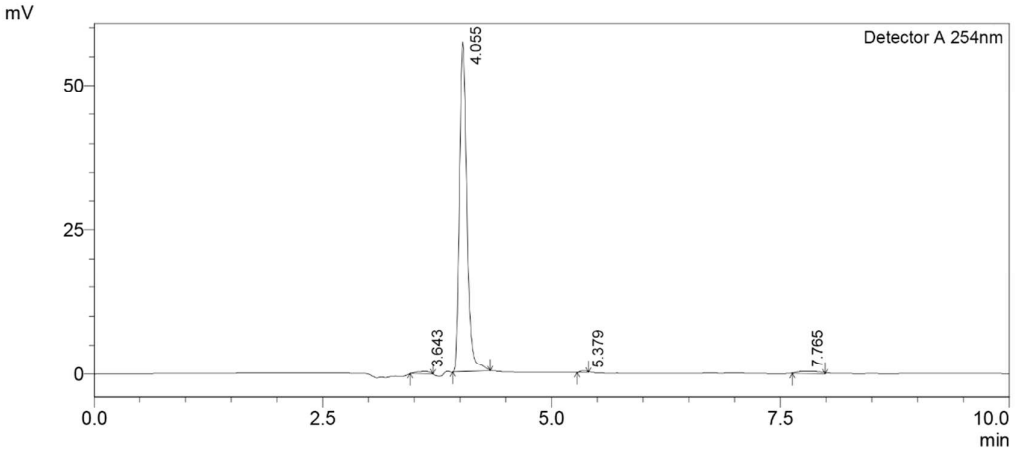
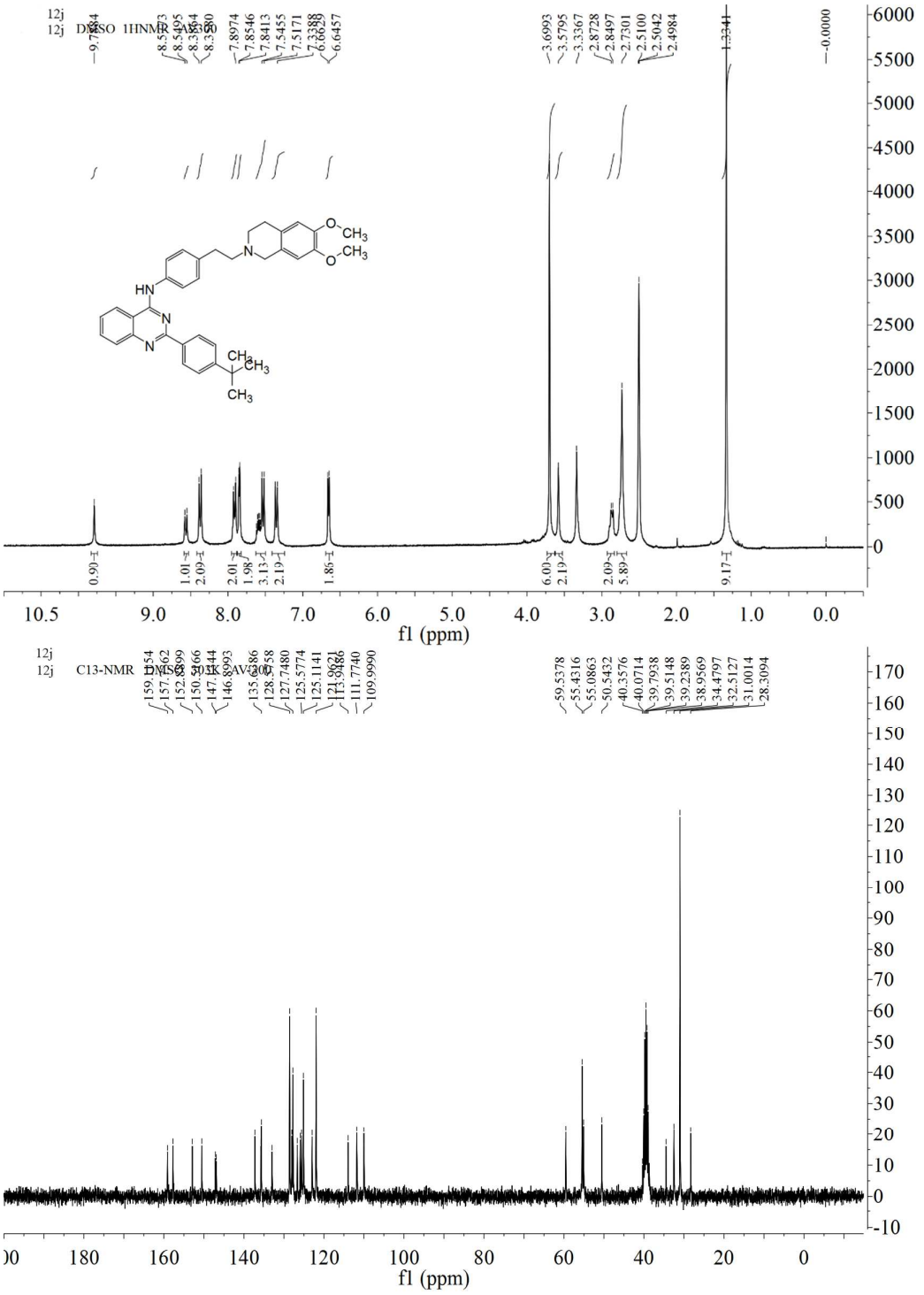
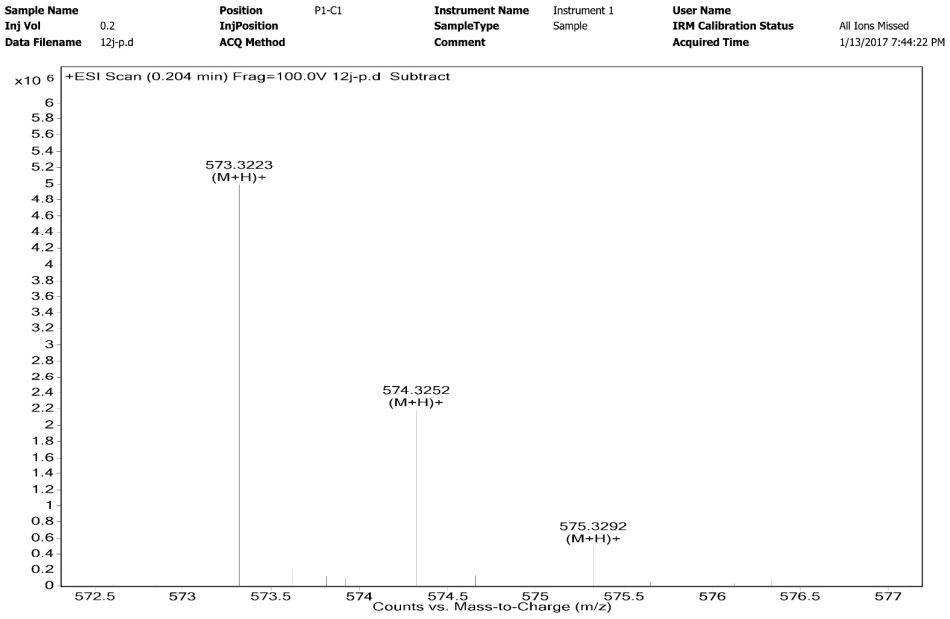
28.3116
20.9611
180
160
140
120
100
80
60
40
20
0
f1 (ppm)

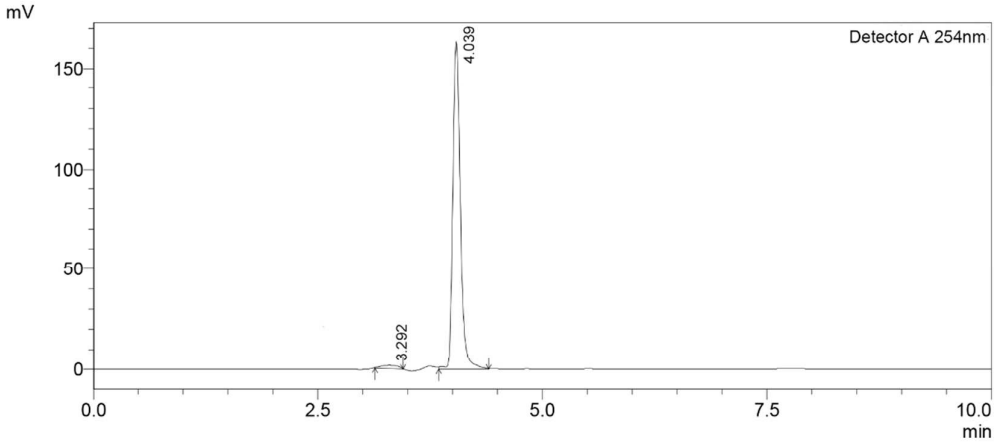




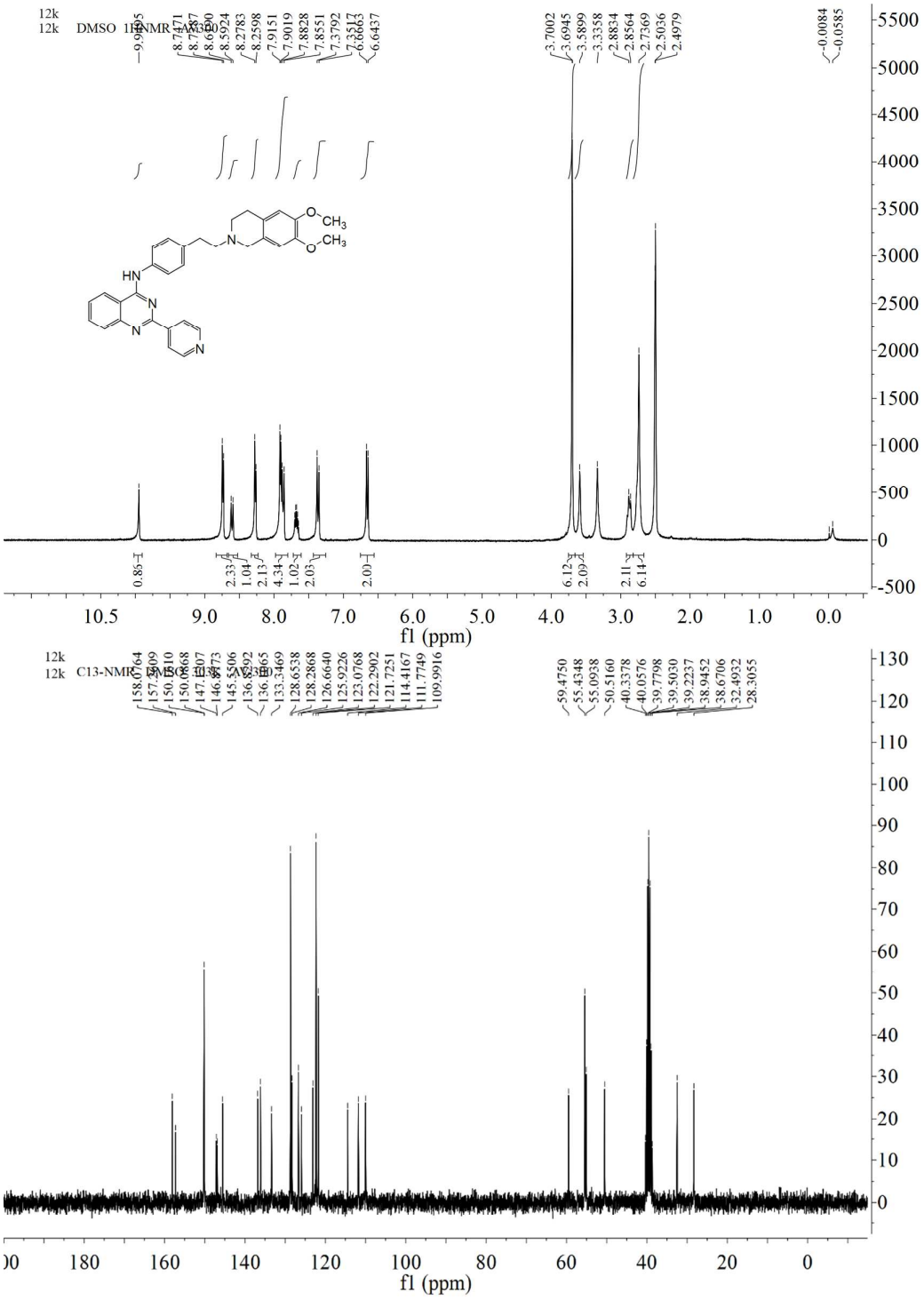
Peak	RT	Area	% Area
1	3.643	3754	1.127
2	4.055	321446	96.471
3	5.379	1226	0.368
4	7.765	6779	2.034
Total		333205	100.000

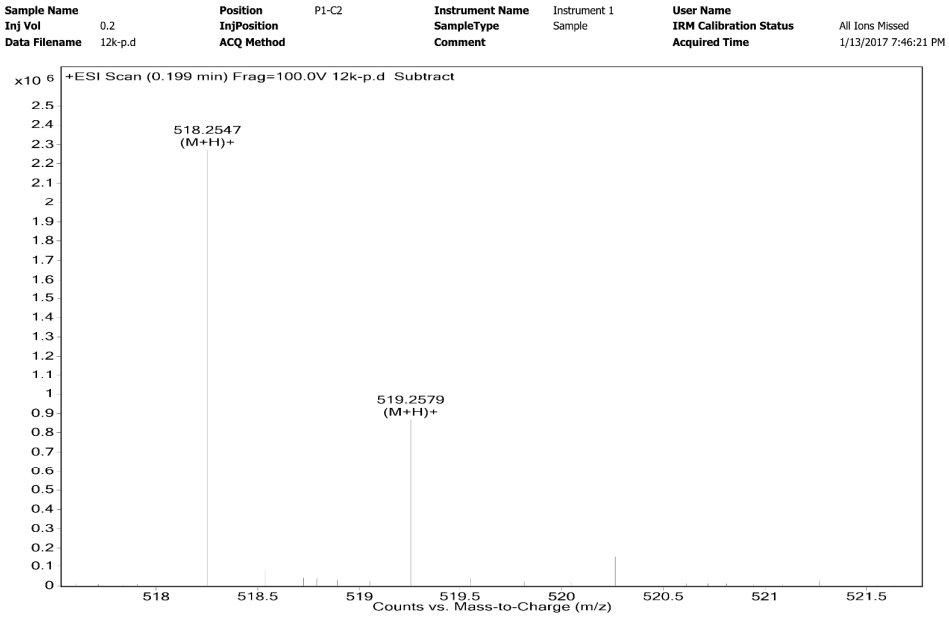

12j
12j DMSO 1HNMR 2-13-30
9.7884
8.5473
8.5455
8.3824
8.3580
7.8974
7.8546
7.8413
7.5455
7.5171
7.3388
6.6628
6.6457
3.6993
3.5795
3.3367
2.8728
2.8497
2.7301
2.5100
2.5042
2.4984
1.3341
-0.0000
0.93
1.01
2.09
2.01
1.98
3.13
2.19
1.85
6.00
2.19
2.09
5.89
9.17
fl (ppm)
12j
12j C13-NMR DMSO 213K 8AV 20Q
159.154
157.162
152.8599
150.3166
147.3144
146.8993
135.6286
128.3158
127.7480
125.5774
125.1141
121.9621
113.9486
111.7740
109.9990
59.5378
55.4316
55.0863
50.5432
40.3576
40.0714
39.7938
39.5148
39.2389
38.9569
34.4797
32.5127
31.0014
28.3094
fl (ppm)

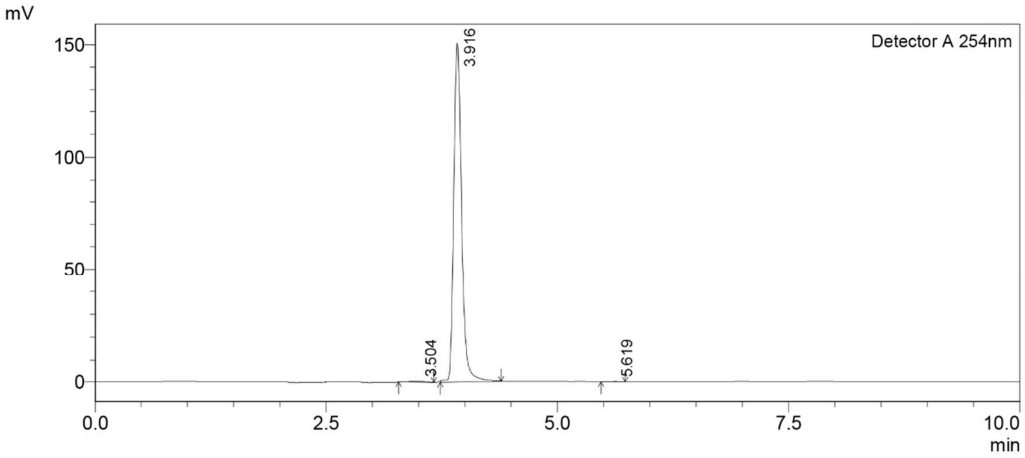




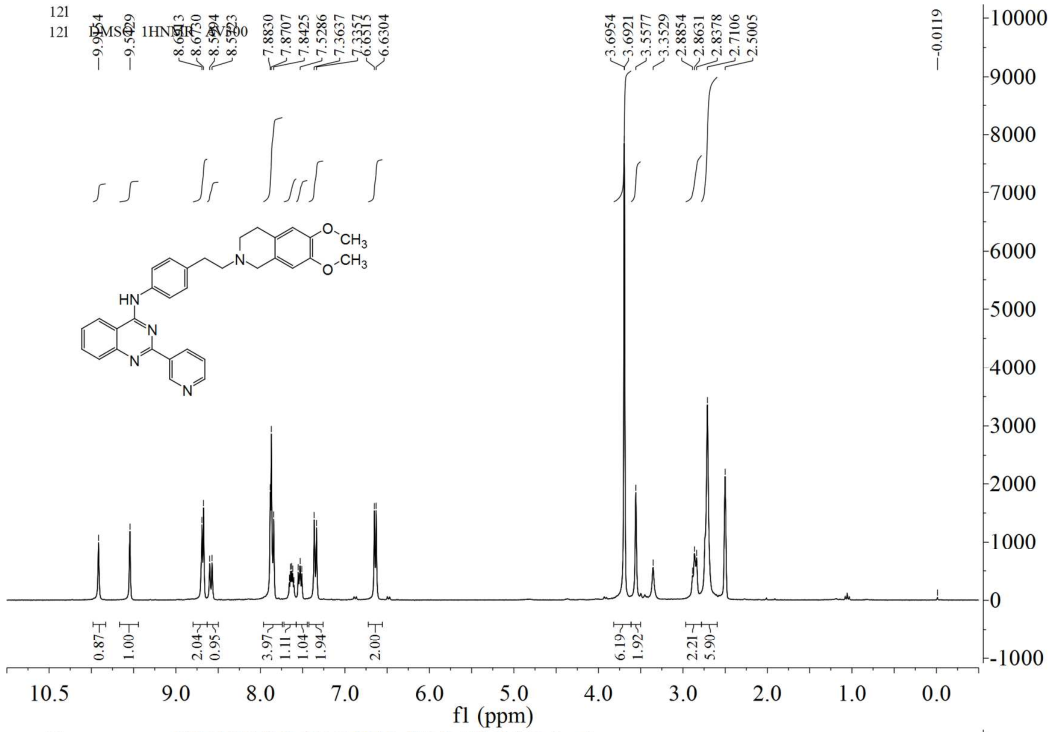
Peak	RT	Area	% Area
1	3.292	23469	2.709
2	4.039	842768	97.291
Total		866237	100.000

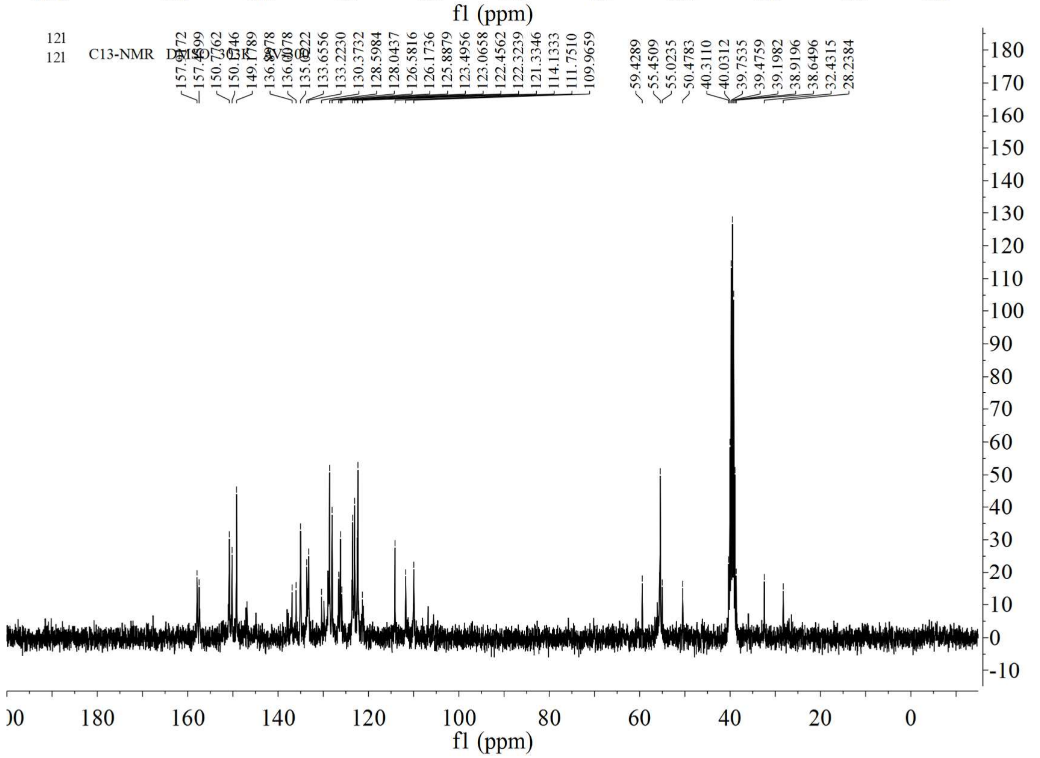

12k
12k DMSO 1HNMR 1A330
9.9935
8.7511
8.7387
8.6300
8.5924
8.2783
8.2598
7.9151
7.9019
7.8828
7.8551
7.3792
7.3517
6.6663
6.6437
3.7002
3.6945
3.5899
3.3358
2.8834
2.8564
2.7369
2.5036
2.4979
-0.0084
-0.0585
0.85
2.33
1.04
2.13
4.34
1.02
2.03
2.01
6.12
2.09
2.11
6.14
O
CH3
O
CH3
N
HN
N
N
N
fl (ppm)
12k
12k C13-NMR 1A330 DMSO
158.0764
157.4109
150.4110
150.0668
147.4107
146.8773
145.5106
136.5292
136.3665
133.3469
128.6538
128.2868
126.6640
125.9226
123.0768
122.2902
121.7251
114.4167
111.7749
109.9916
59.4750
55.4348
55.0938
50.5160
40.3378
40.0576
39.7798
39.5030
39.2237
38.9452
38.6706
32.4932
28.3055
fl (ppm)

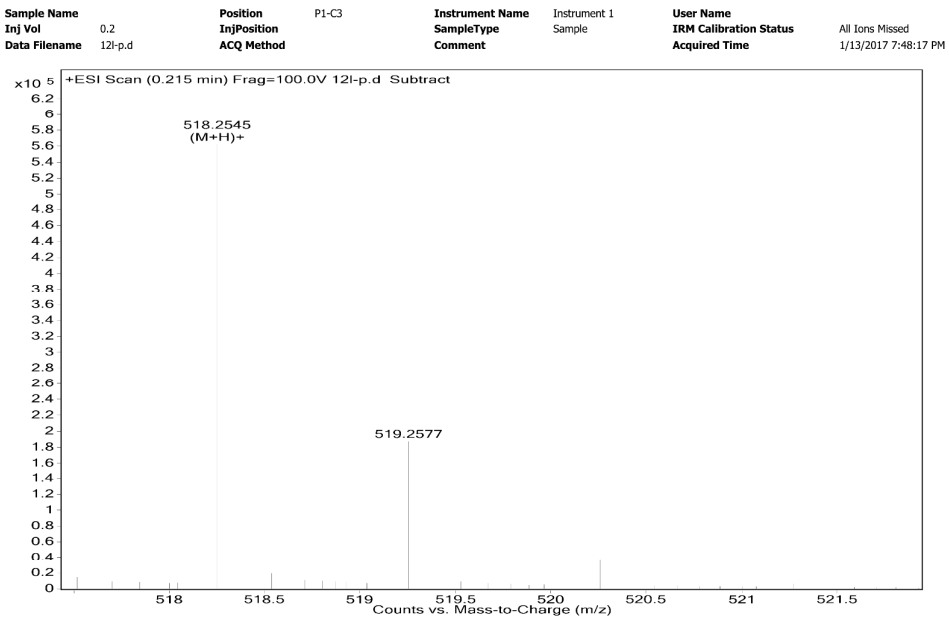


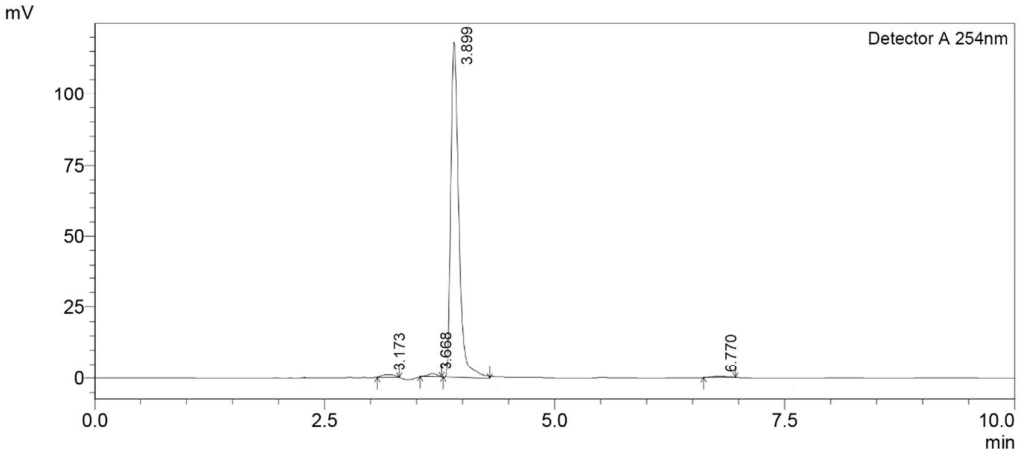


Peak	RT	Area	% Area
1	3.504	3205	0.359
2	3.916	888034	99.507
3	5.619	1193	0.134
Total		892431	100.000

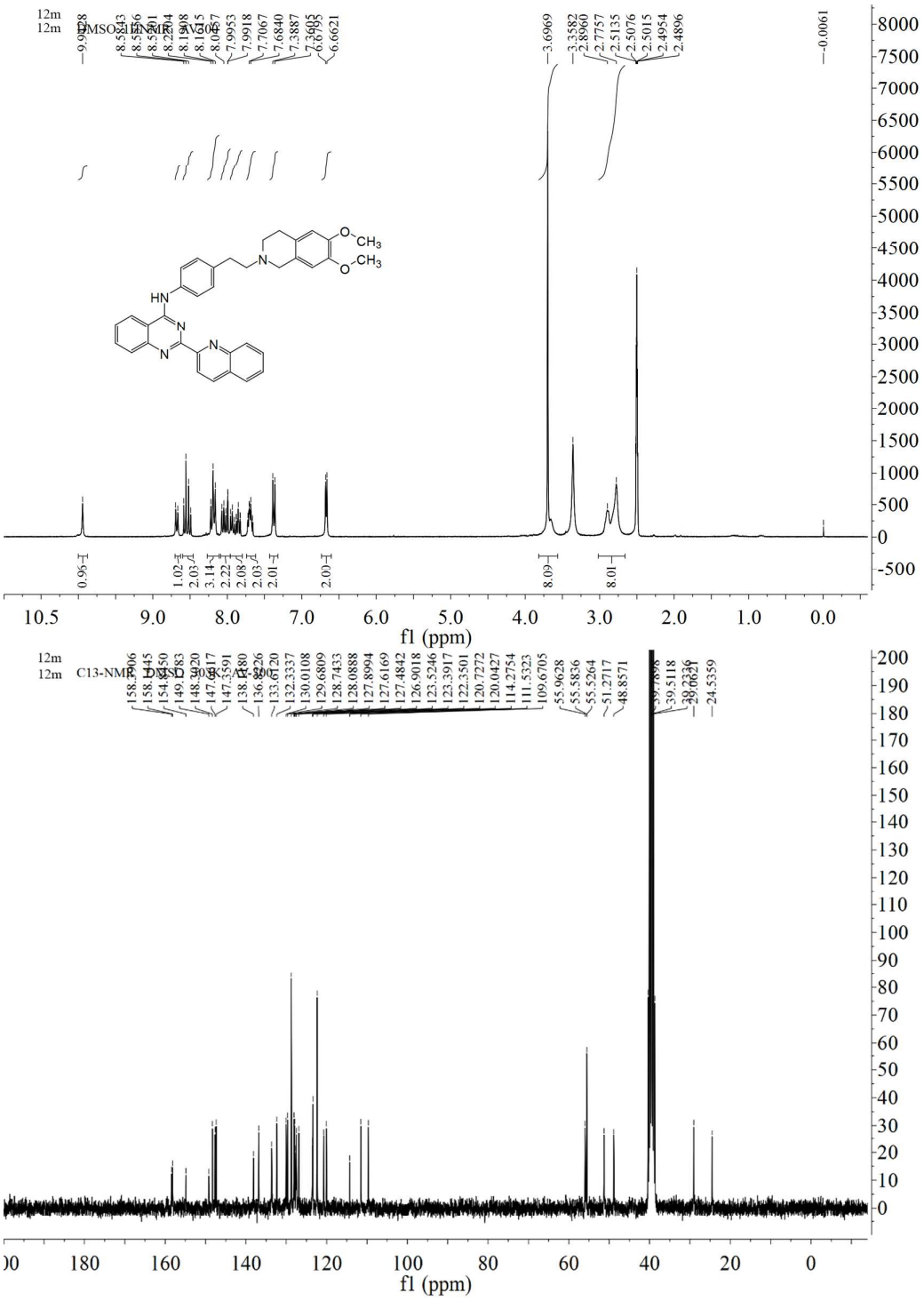

121
121 DMSO 1HNMR AV500
9.5529
8.6730
8.5723
7.8830
7.8707
7.8425
7.5286
7.3637
7.3357
6.6515
6.6304
3.6954
3.6921
3.5577
3.3529
2.8854
2.8631
2.8378
2.7106
2.5005
-0.0119
0.87
1.00
2.04
0.95
3.97
1.11
1.04
1.94
2.00
6.19
1.92
2.21
5.90
HN
N
N
N
N
O
O
CH_3
CH_3
f1 (ppm)

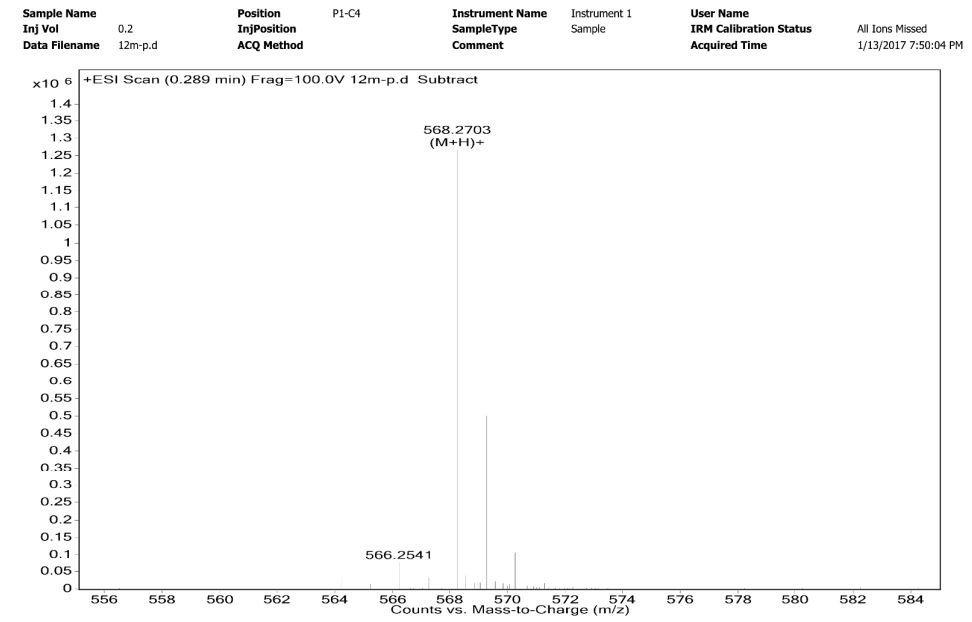

121
121 C13-NMR
150.7162
133.6556
133.2230
130.3732
128.5984
128.0437
126.5816
126.1736
125.8879
123.4956
123.0658
122.4562
122.3239
121.3346
114.1333
111.7510
109.9659
59.4289
55.4509
55.0235
50.4783
40.3110
40.0312
39.7535
39.4759
39.1982
38.9196
38.6496
32.4315
28.2384
f1 (ppm)

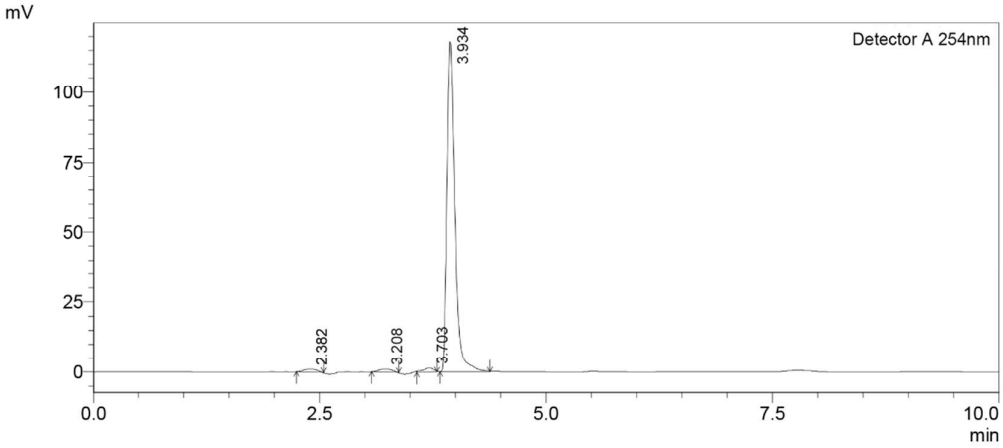




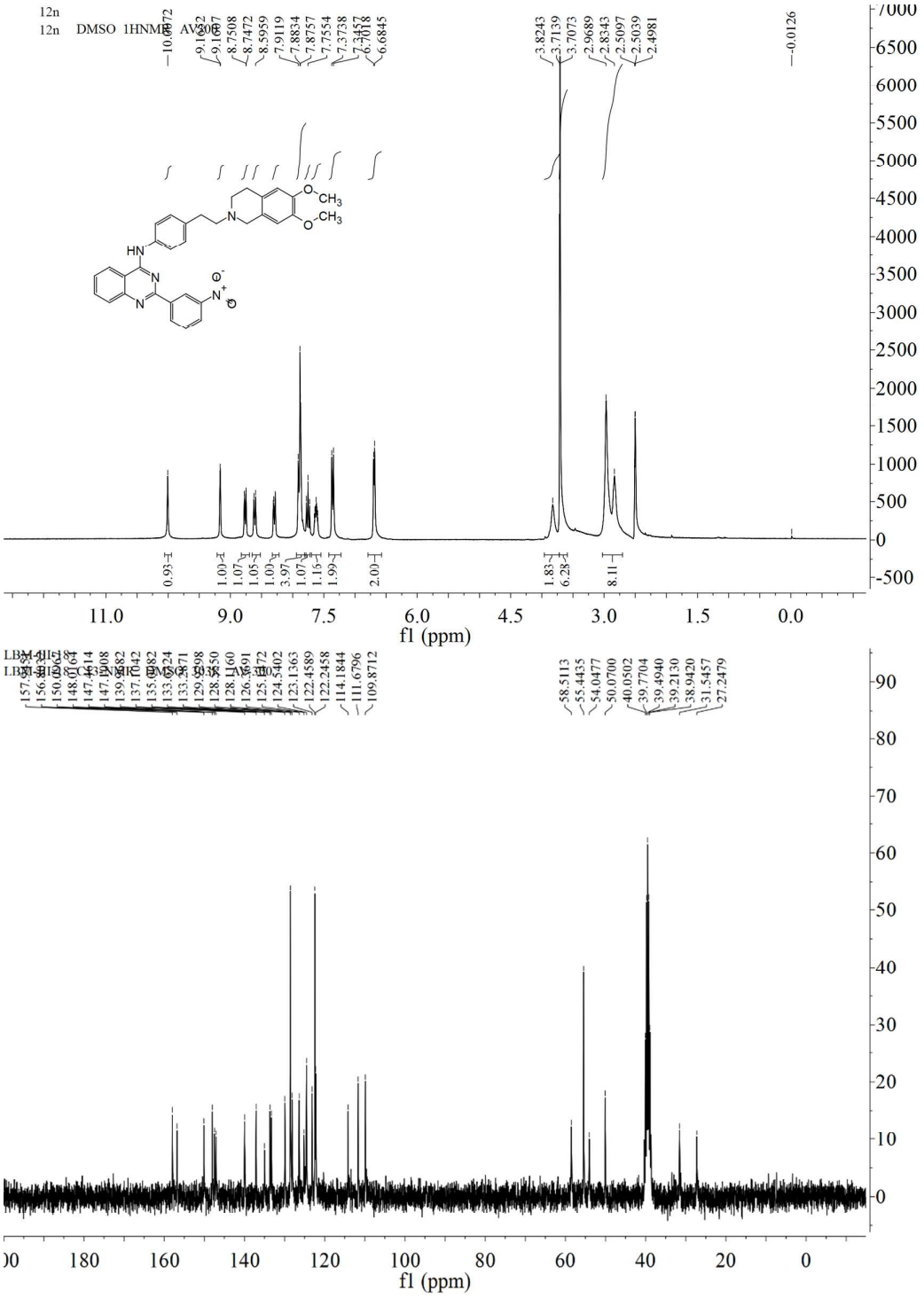
Peak	RT	Area	% Area
1	3.173	8772	1.198
2	3.668	6966	0.951
3	3.899	712052	97.221
4	6.770	4613	0.630
Total		732403	100.000

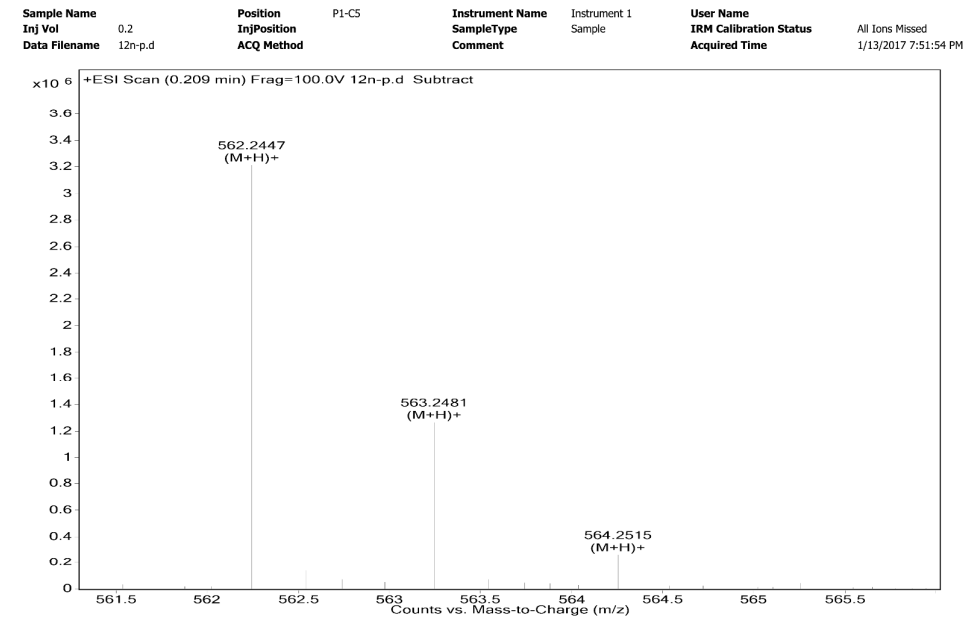

12m
DMSO-d6-NMR-JW-305
fl (ppm)
12m
C13-NMR-DMSO-JW-305
fl (ppm)

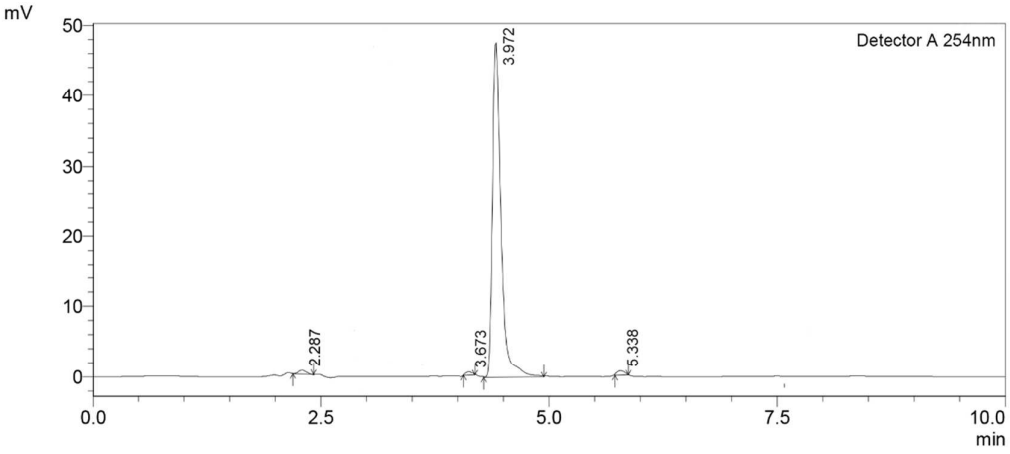




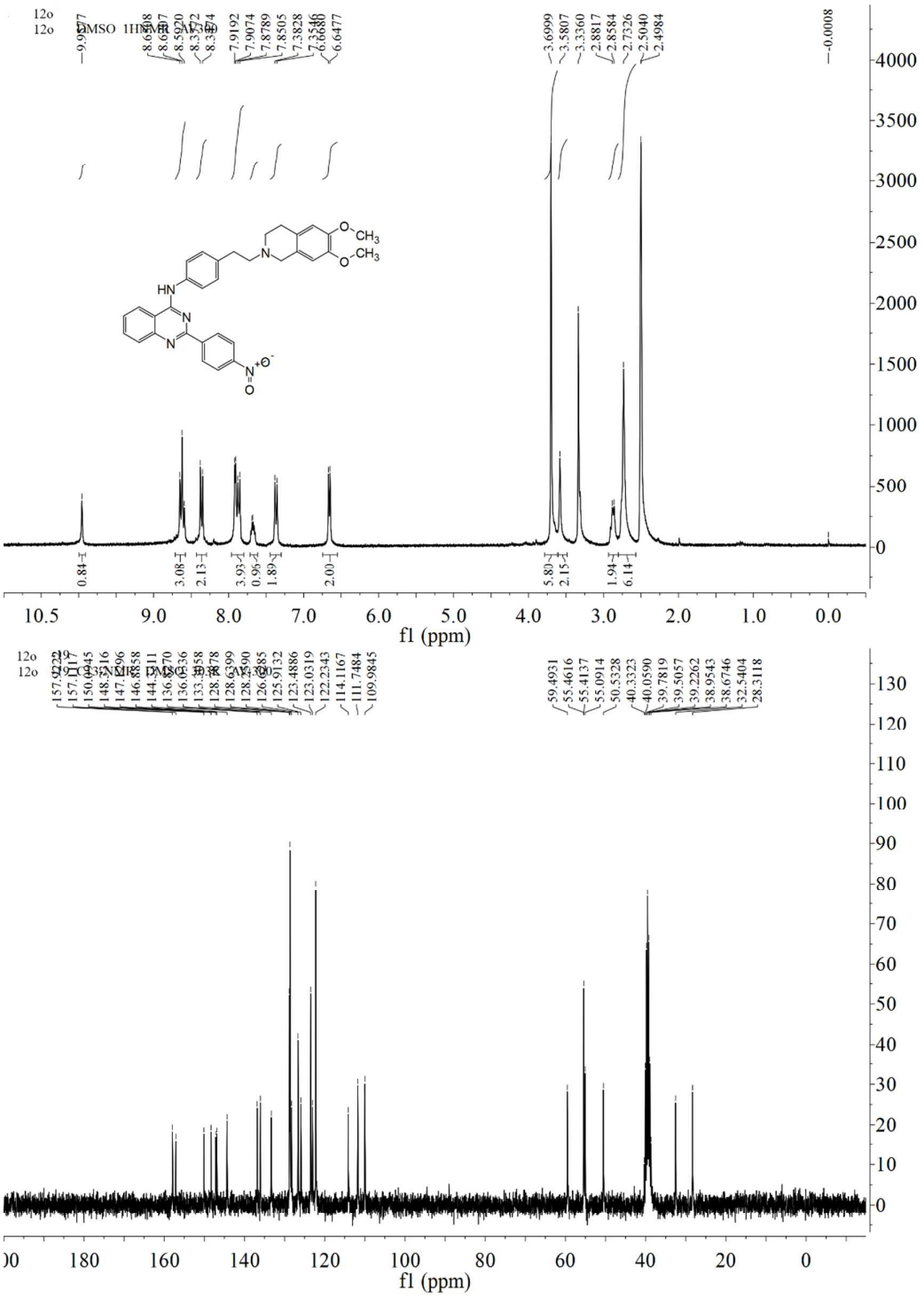
Peak	RT	Area	% Area
1	2.382	10499	1.377
2	3.208	10176	1.335
3	3.703	10951	1.437
4	3.934	730647	95.851
Total		762273	100.000


12n
12n DMSO 1HNMR AV300
10.0772
9.1622
9.1687
8.7508
8.7472
8.5959
7.9119
7.8834
7.8757
7.7554
7.3738
7.3457
7.1018
6.6845
3.8243
3.7139
3.7073
2.9689
2.8343
2.5097
2.5039
2.4981
-0.0126
HN
N
N
O
O
N+
O-
CH3
CH3
0.93
1.00
1.07
1.05
1.01
3.97
1.07
1.15
1.93
2.00
1.83
6.28
8.11
11.0
9.0
7.5
6.0
4.5
3.0
1.5
0.0
f1 (ppm)
157.9482
156.8165
150.0164
148.0164
147.4414
147.2008
139.9482
137.6142
135.6382
133.6524
133.3871
129.9598
128.8550
128.1160
126.3691
125.1672
124.5402
123.1363
122.4589
122.2458
114.1844
111.6796
109.8712
58.5113
55.4435
54.0477
50.0700
40.0502
39.7704
39.4940
39.2130
38.9420
31.5457
27.2479
180
160
140
120
100
80
60
40
20
0
f1 (ppm)

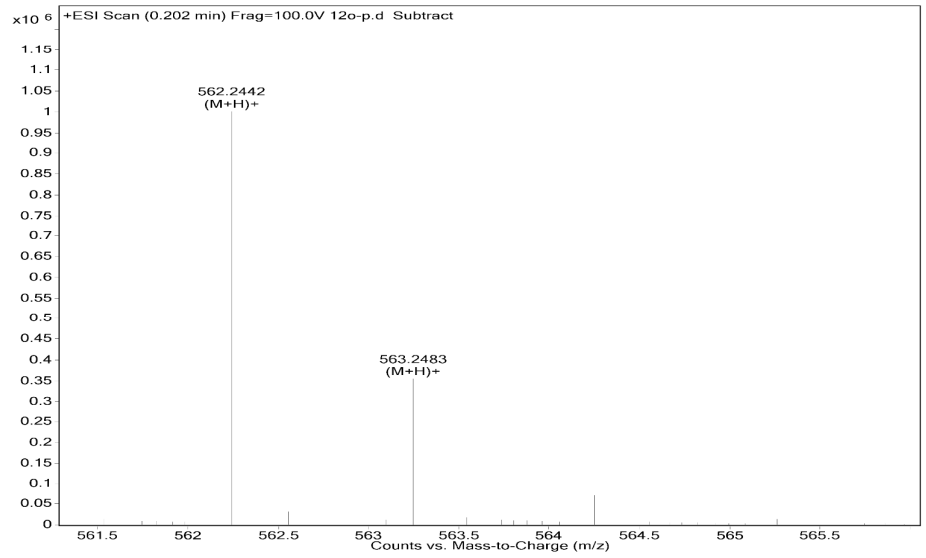


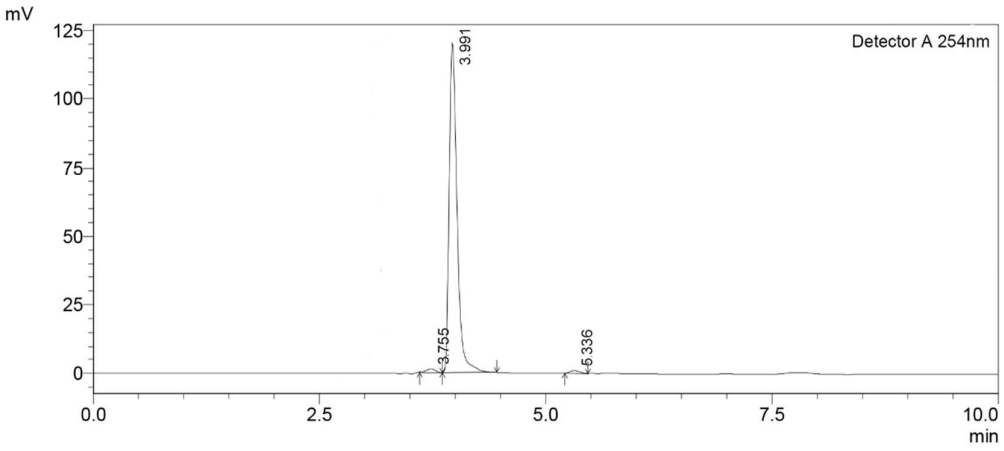


Peak	RT	Area	% Area
1	2.287	3407	1.056
2	3.673	2562	0.794
3	3.972	313494	97.189
4	5.338	3098	0.961
Total		322562	100.000

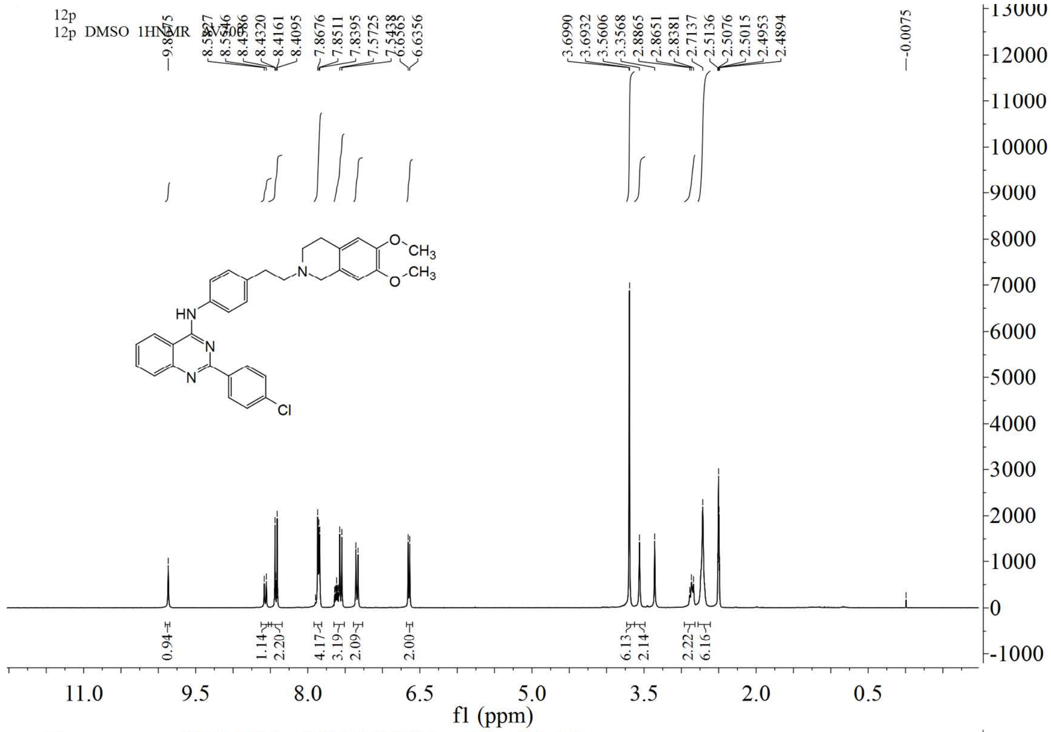

12o
12o DMSO 1HNMR 5AT 350
9.9577
8.6598
8.6287
8.5920
8.3522
8.3354
7.9192
7.9074
7.8789
7.8505
7.3828
7.3546
6.6680
6.6477
3.6999
3.5807
3.3360
2.8817
2.8584
2.7326
2.5040
2.4984
-0.0008
0.84
3.08
2.13
3.93
0.95
1.89
2.01
5.83
2.15
1.94
6.14
fl (ppm)
12o
12o
59.4931
55.4616
55.4137
55.0914
50.5328
40.3323
40.0590
39.7819
39.5057
39.2262
38.9543
38.6746
32.5404
28.3118
fl (ppm)

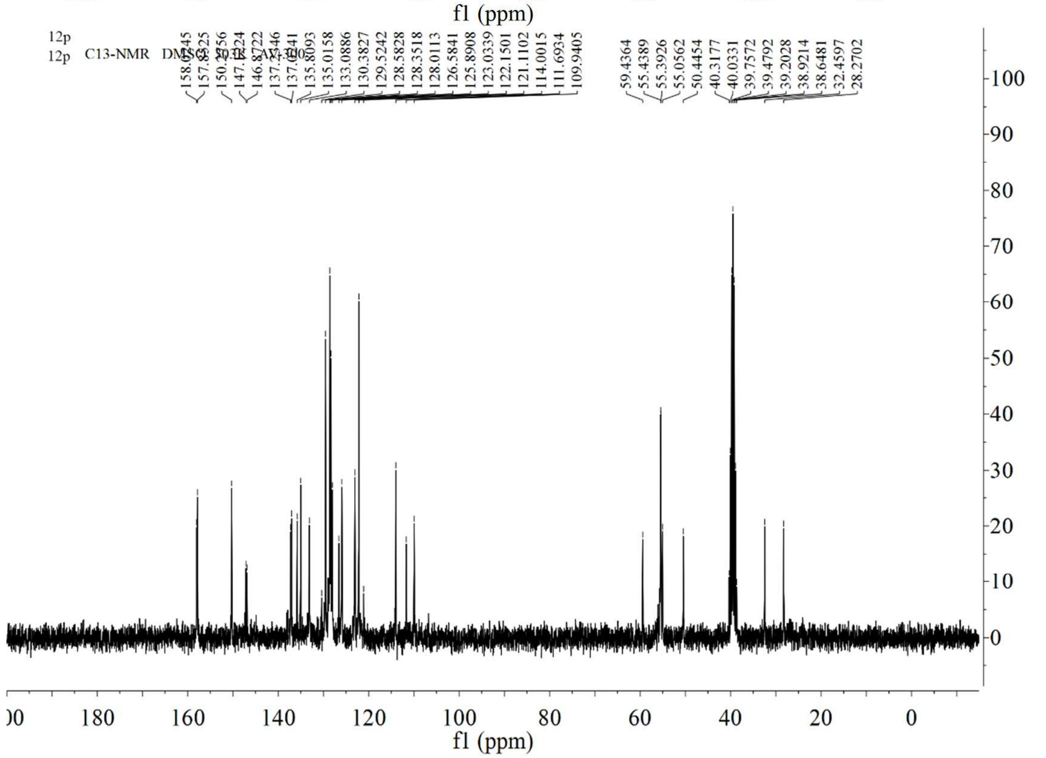
Sample Name		**Position**	P1-C6	**Instrument Name**	Instrument 1	**User Name**	
Inj Vol	0.2	**InjPosition**		**SampleType**	Sample	**IRM Calibration Status**	All Ions Missed
Data Filename	12o-p.d	**ACQ Method**		**Comment**		**Acquired Time**	1/13/2017 7:53:58 PM

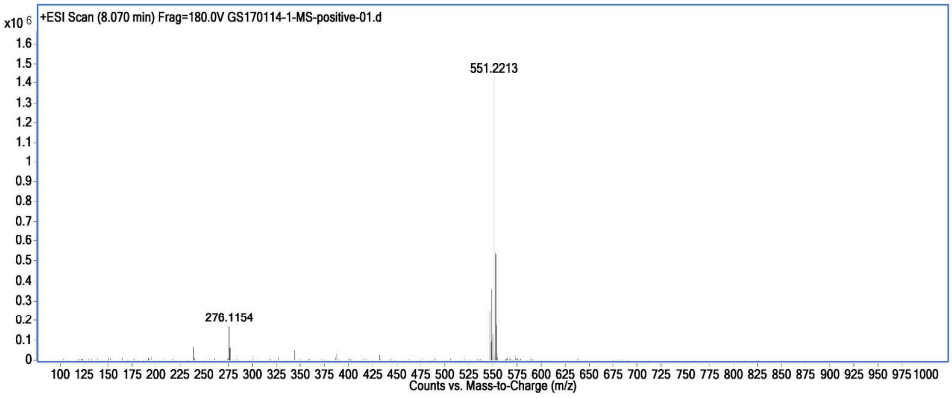


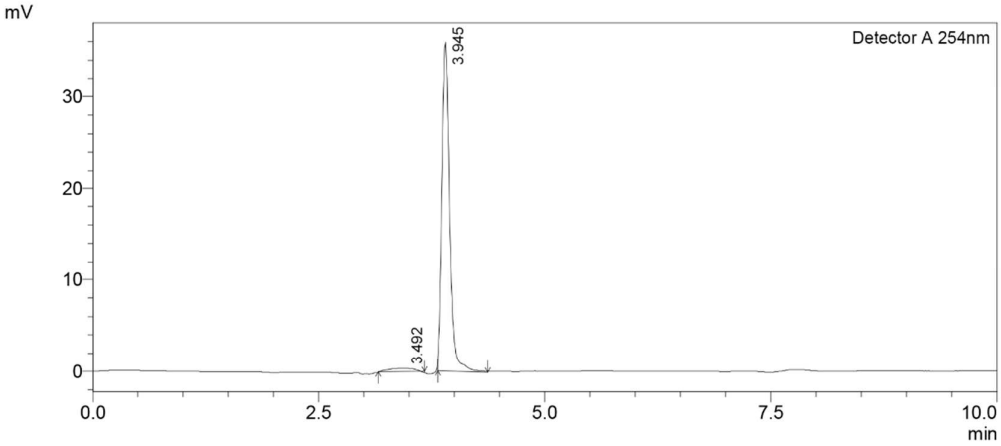


Peak	RT	Area	% Area
1	3.755	9509	1.285
2	3.991	722930	97.685
3	5.336	7625	1.030
Total		740064	100.000

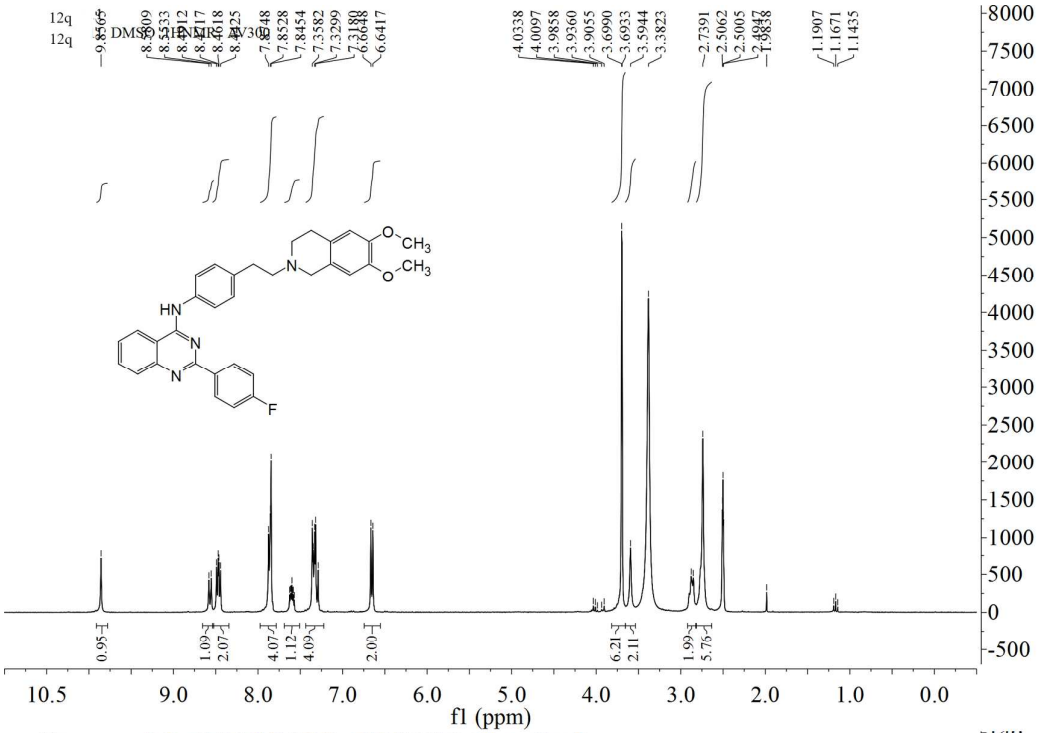

12p
12p DMSO 1HNMR
-9.8675
8.4586
8.4320
8.4161
8.4095
7.8676
7.8511
7.8395
7.5725
6.6356
3.6990
3.6932
3.5606
3.5568
2.8865
2.8651
2.8381
2.7137
2.5136
2.5076
2.5015
2.4953
2.4894
-0.0075
HN
N
N
Cl
O
CH3
0.94
1.14
2.20
4.17
3.19
2.09
2.00
6.13
2.14
2.22
6.16
f1 (ppm)

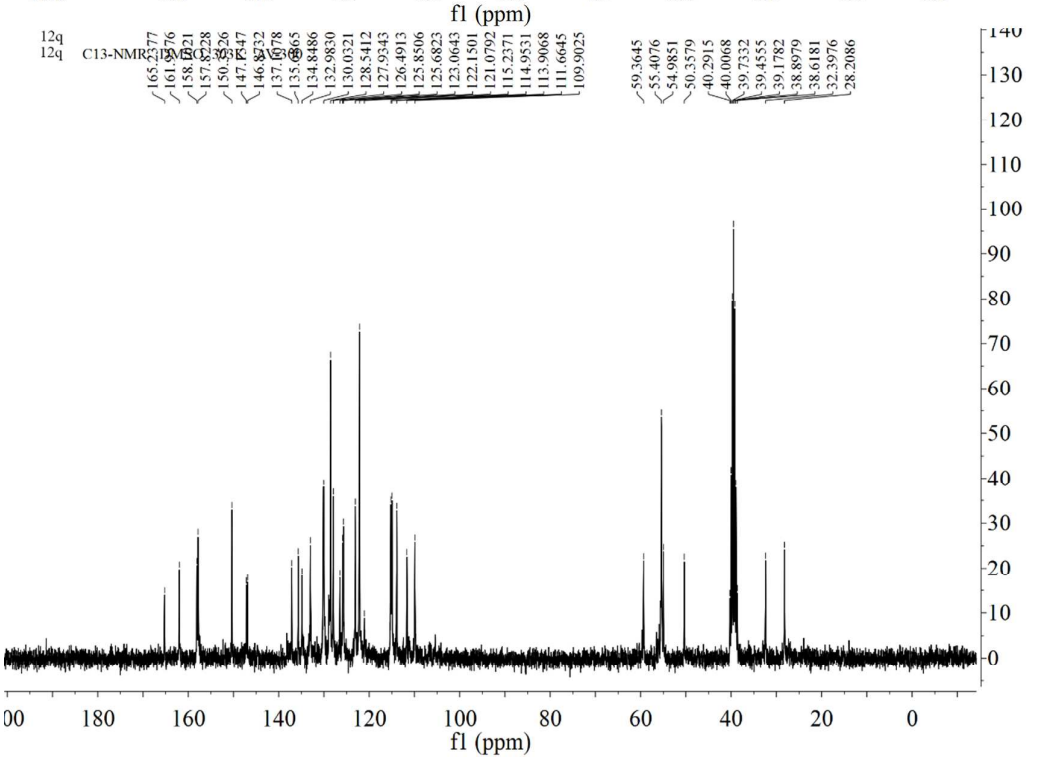

12p
12p C13-NMR
146.8722
135.8093
135.0158
133.0886
130.3827
129.5242
128.5828
128.3518
128.0113
126.5841
125.8908
123.0339
122.1501
121.1102
114.0015
111.6934
109.9405
59.4364
55.4389
55.3926
55.0562
50.4454
40.3177
40.0331
39.7572
39.4792
39.2028
38.9214
38.6481
32.4597
28.2702
f1 (ppm)

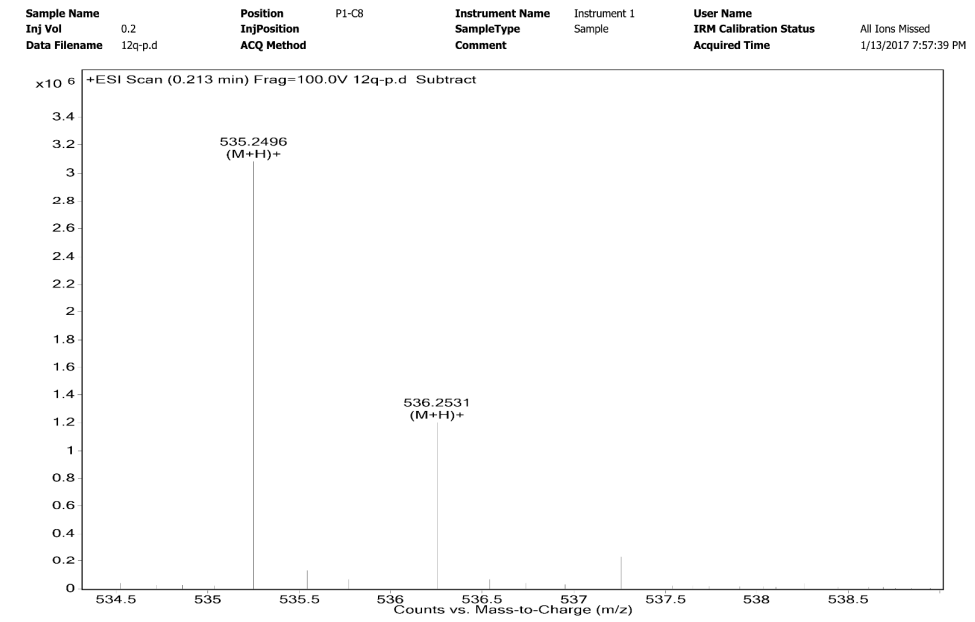


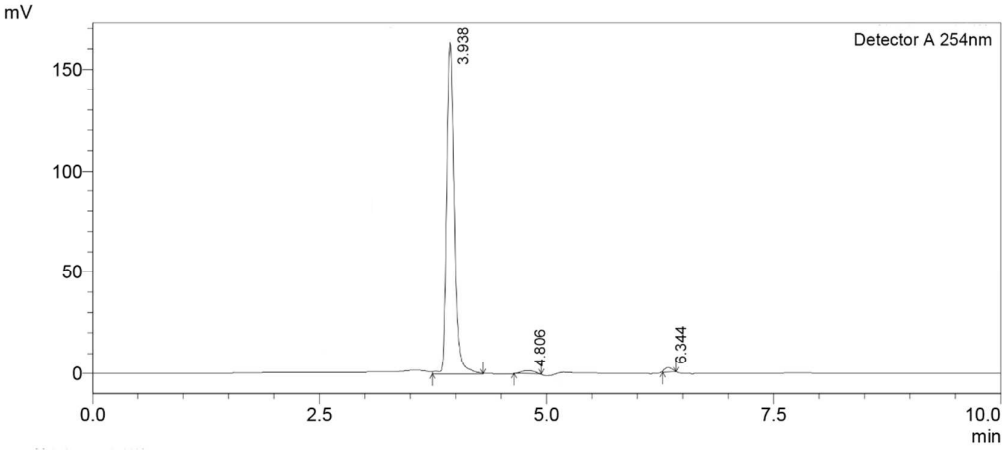


Peak	RT	Area	% Area
1	3.492	6500	2.963
2	3.945	212839	97.037
Total		219340	100.000

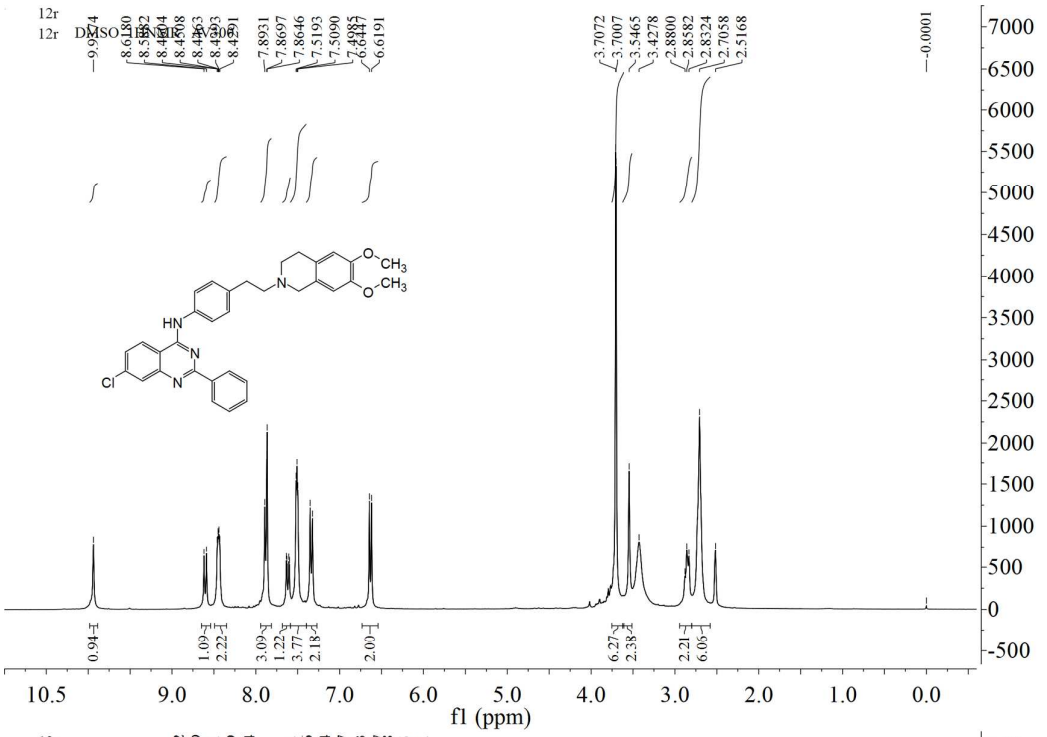

12q
12q
f1 (ppm)

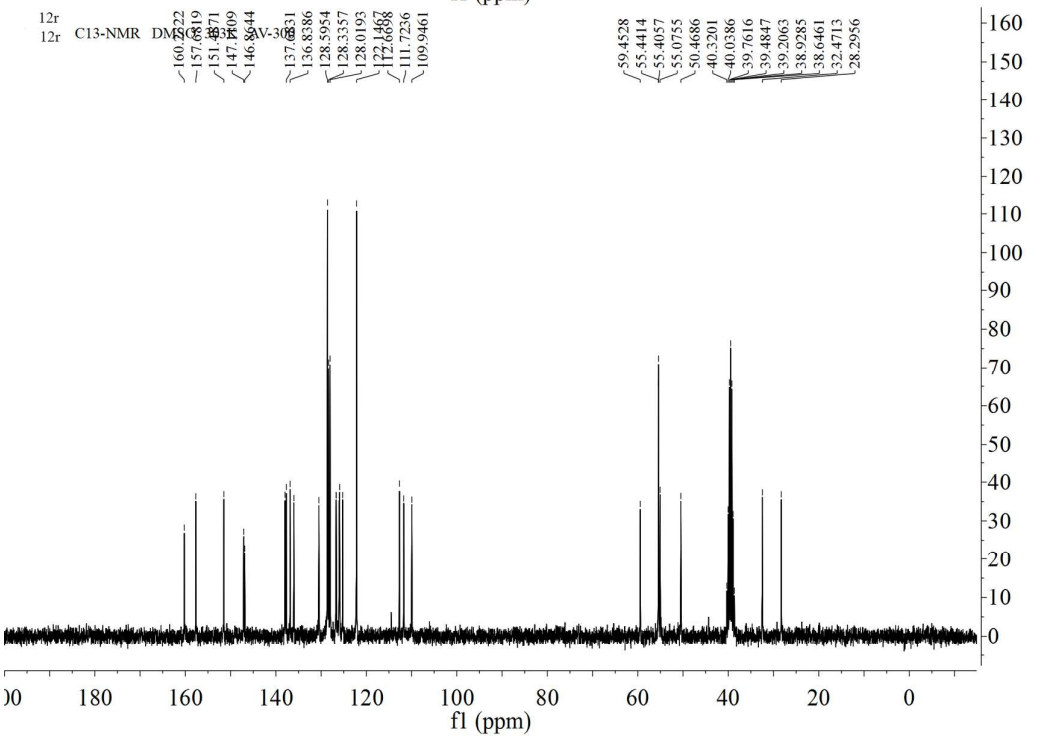

12q
12q
f1 (ppm)

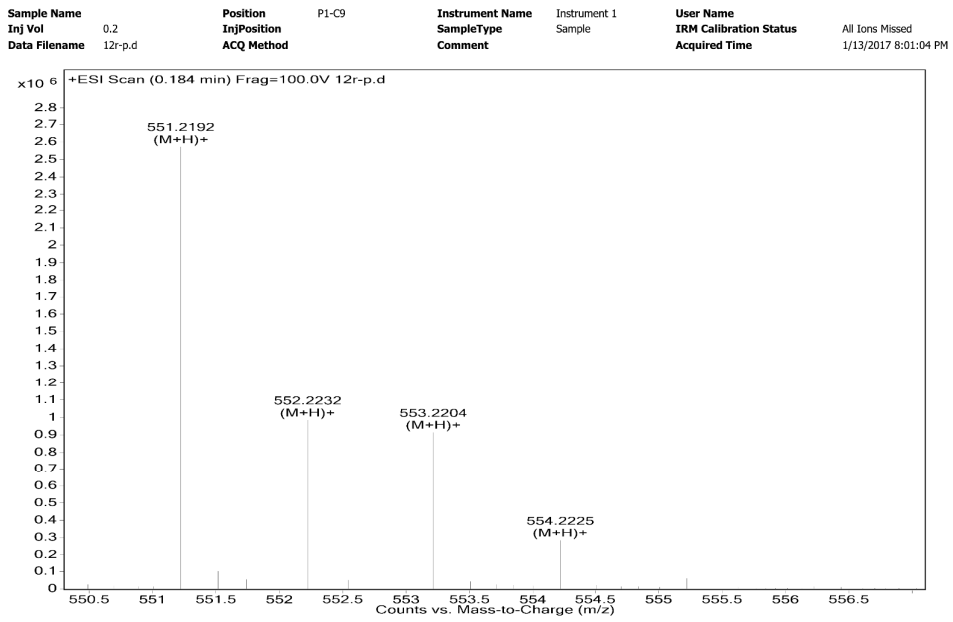


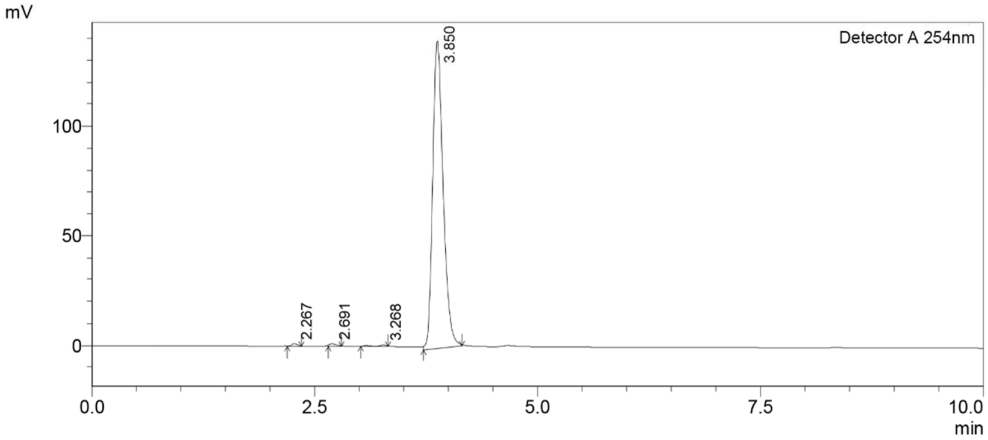


Peak	RT	Area	% Area
1	3.938	729653	97.018
2	4.806	13206	1.756
3	6.344	9220	1.226
Total		752079	100.000

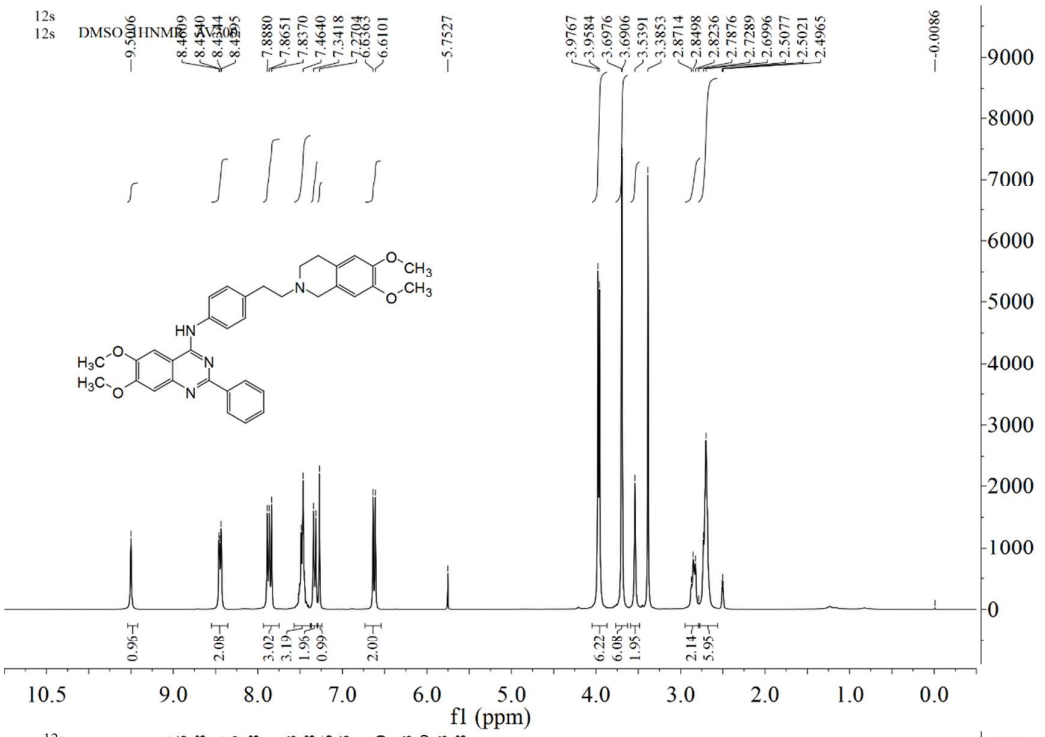

12r
12r DMSO-H-NMR DMS-16-AV-300
9.9474
8.6180
8.5922
8.4614
8.4478
8.4363
8.4253
8.4091
7.8931
7.8697
7.8646
7.5193
7.5090
7.4985
6.6447
6.6191
3.7072
3.7007
3.5465
3.4278
2.8800
2.8582
2.8324
2.7058
2.5168
0.0001
0.94
1.09
2.22
3.09
1.22
3.77
2.18
2.01
6.27
2.38
2.21
6.05
fl (ppm)

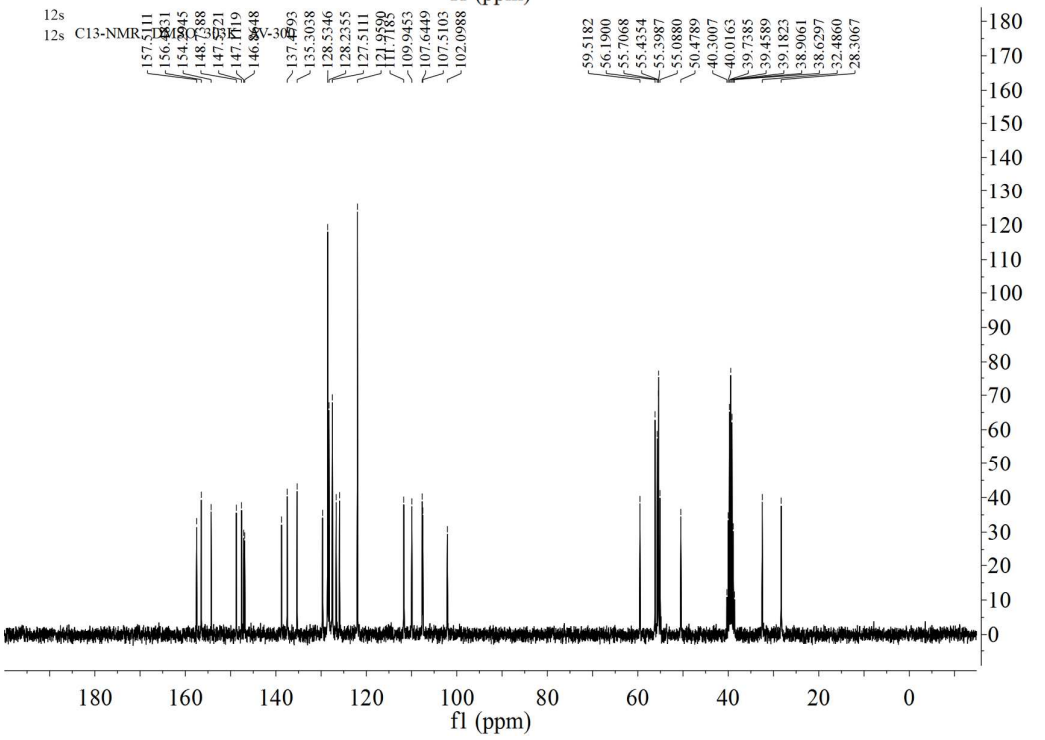

12r
12r C13-NMR DMS-16-AV-300
160.7222
157.6319
151.4371
147.3409
146.8544
137.8831
136.8386
128.5954
128.3357
128.0193
122.1467
112.6698
111.7236
109.9461
59.4528
55.4414
55.4057
55.0755
50.4686
40.3201
40.0386
39.7616
39.4847
39.2063
38.9285
38.6461
32.4713
28.2956
fl (ppm)

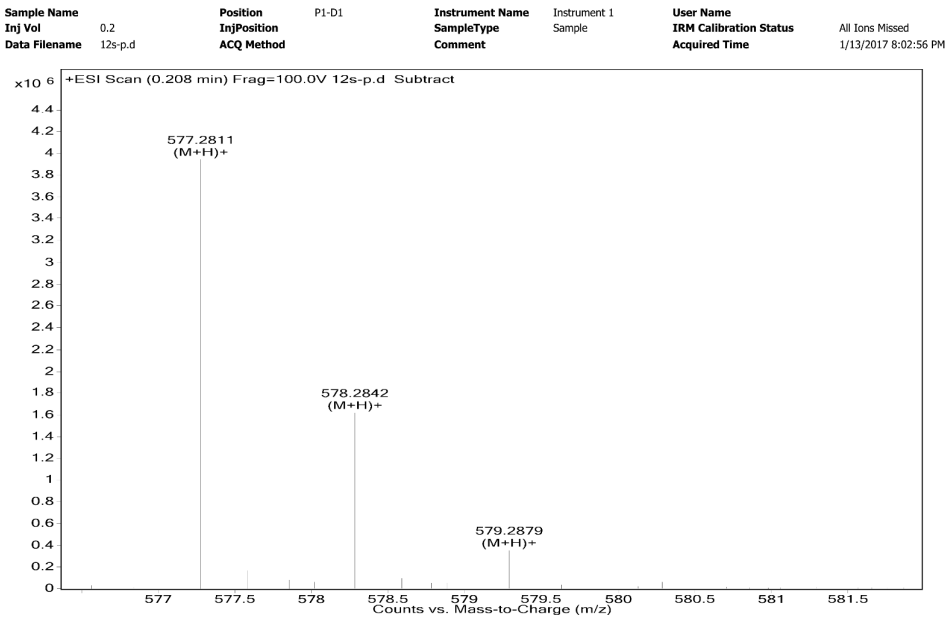


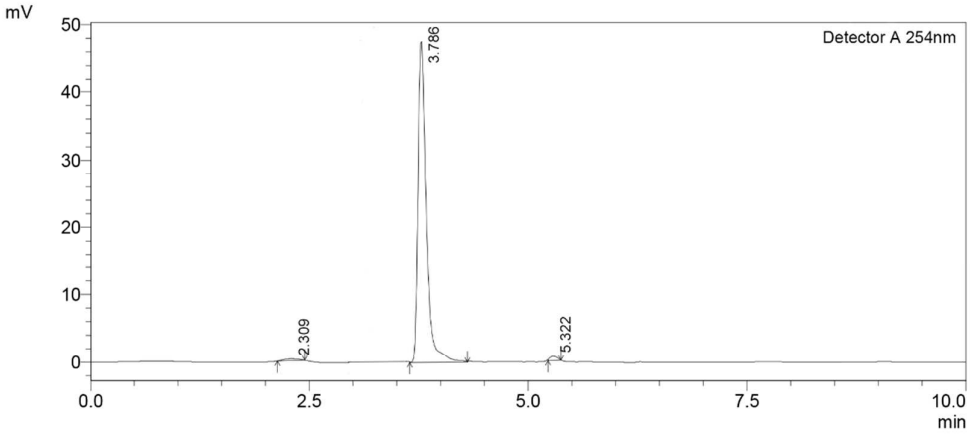


Peak	RT	Area	% Area
1	2.267	4805	0.417
2	2.691	6013	0.522
3	3.268	4510	0.391
4	3.850	1137606	98.670
Total		1152934	100.000


12s
12s DMSO-d6 1HNMR AV500
9.5006
8.4609
8.4540
8.4344
8.4295
7.8880
7.8651
7.8370
7.4640
7.3418
7.2704
6.6303
6.6101
5.7527
3.9767
3.9584
3.6976
3.6906
3.5391
3.3853
2.8714
2.8498
2.8236
2.7876
2.7289
2.6996
2.5077
2.5021
2.4965
0.0086
0.96
2.08
3.02
3.19
1.95
0.99
2.01
6.22
6.08
1.95
2.14
5.95
fl (ppm)


12s
12s C13-NMR-DMSO-303K AV-300
157.5111
156.8531
154.9945
148.5888
147.4221
147.2119
146.8448
137.3093
135.3038
128.5346
128.2355
127.5111
121.9599
111.7185
109.9453
107.6449
107.5103
102.0988
59.5182
56.1900
55.7068
55.4354
55.3987
55.0880
50.4789
40.3007
40.0163
39.7385
39.4589
39.1823
38.9061
38.6297
32.4860
28.3067
fl (ppm)





Peak	RT	Area	% Area
1	2.309	2709	0.765
2	3.786	347621	98.227
3	5.322	3568	1.008
Total		353898	100.000