Supplementary Information

Design, synthesis and biological activity of thioguanine modified pleuromutilin derivatives

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1. Synthetic experimental procedures

Analytical grade reagents were employed and provided by Energy Chemical (Shanghai, China) and Kelong Chemical (Chengdu, China). WRS-1B microscopic melting point meter (Shanghai Precision Scientific Instruments Co., Ltd.), Varian Unity INOVA-400MHz NMR (Varian Corporation, USA) and Agilent 6210 Time of Flight (TOF) liquid chromatograph (Agilent Technologies, USA) were used to analyze the structures. TLC was performed using silica gel plates (Yantai Silicone Development Co., Ltd.), and the analysis was conducted through absorption with a UV analyzer (Shanghai Anting Electronic Instrument Factory, Model ZF-2). The compounds were purified through column chromatography on silica gel (Grade H, Qingdao Ocean Chemical). Analytical HPLC analyses were performed on a Essentia LC-16 (Shimadzu,, Japan). The columns were NanoChrom ChromCore C18 (5 μm, 4.6 × 250 mm), with a flowrate of 1 mL·min^{-1}. For compounds **3**, **4a-4b**, **5a-5d** and **6a-6p** the eluent was a mixture of water and acetonitrile (water: acetonitrile= 3:7). For compounds **7** and **8a-8g** the eluent was a mixture of 0.1% TEA in water and acetonitrile (water: acetonitrile= 3:7). The columns were thermostated at 30 °C. All compounds are >95% pure by HPLC analysis.

1.1 Synthesis of compounds 3

Triethylamine (151 mg, 1.50 mmol) was added to a solution of 6-thioguanine (284 mg, 1.86 mmol) in dried DMF (5 mL), which was stirred at 80 °C for 30 min. Subsequently, compounds **2**[1] (1.0 g, 1.86 mmol) were added to the reaction solution.

The mixture was refluxed for 2 h, diluted by water, and then extracted with EtOAc (20 mL×3). The combined organic layer was washed with brine and then dried over anhydrous Na_2SO_4. Solvent evaporation was completed before the crude product was purified through silica gel column chromatography to prepare compound **3**.

White powder; yield: 85.5%; mp: 168.4-170.0 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 10.35 (s, 1H), 7.78 (s, 1H), 6.52 (dd, *J* = 17.2, 11.2 Hz, 1H), 5.76 (d, *J* = 8.4 Hz, 1H), 5.33 (d, *J* = 11.2 Hz, 1H), 5.19 (d, *J* = 17.2 Hz, 1H), 4.88 (s, 2H), 3.98 (ABq, *J* = 16.4 Hz, 2H), 3.33 (dd, *J* = 9.6, 6.8 Hz, 1H), 2.37 - 2.04 (m, 4H), 1.99 (dd, *J* = 16.0, 8.4 Hz, 1H), 1.77 (s, 1H), 1.66 - 1.57 (m, 2H), 1.53 - 1.45 (m, 2H), 1.45 - 1.40 (m, 4H), 1.36 - 1.27 (m, 2H), 1.14 (s, 3H), 1.08 (s, 1H), 0.85 (d, *J* = 6.8 Hz, 3H), 0.76 (d, *J* = 6.8 Hz, 3H). ; ^{13}C NMR (101 MHz, DMSO-d_6): δ (ppm) 217.6, 167.8, 159.8, 157.5 , 152.5, 141.2, 139.6, 124.3, 115.8, 73.1, 70.4, 57.7, 45.4, 44.6, 43.9, 42.0, 36.9, 36.8, 34.5 , 31.2, 30.6, 29.1, 27.1, 24.9, 16.6, 14.9, 12.0; HRMS: calculated for $C_{27}H_{37}N_5O_4S$ ($[M + H]^+$): 528.2639; found: 528.2638.

1.2 Synthesis of compounds 4a-4b

Methyl chloroformate or ethyl chloroformate (0.21 mmol) was added to the solution of compound **3** (100 mg, 0.19 mmol) and pyridine (15 mg, 0.19 mmol) in dry DCM, the mixture was stirred at ambient temperature for 6 h. The reaction was monitored using TLC. After the reaction completed, the solvent was evaporated, and the residue was purified through silica gel column chromatography to produce the compounds **4a**-**4b**.

4a: White powder; yield: 51.4%; mp: 151.8-153.1 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.30 (s, 1H), 6.77 (s, 2H), 6.09 (dd, J = 17.6, 11.2 Hz, 1H, H19), 5.53 (d, J = 8.4 Hz, 1H, H14), 5.05 (dd, J = 17.6, 1.6 Hz, 1H, H20), 4.98 (dd, J = 11.2, 1.6 Hz, 1H, H20), 4.49 (d, J = 6.0 Hz, 1H), 4.17 (ABq, J = 16.4 Hz, 2H, H22), 3.98 (s, 3H), 3.40 (t, J = 6.0 Hz, 1H, H11), 2.37 (s, 1H, H4), 2.23 – 1.96 (m, 4H, H10, H2, H13), 1.69 – 1.34 (m, 4H, H7, H1), 1.34 – 1.28 (m, 4H, H18, H8), 1.27 – 1.19 (m, 2H, H13, H6), 1.04 (s, 3H, H15), 1.00 – 0.94 (m, 1H, H8), 0.80 (d, J = 6.8 Hz, 3H, H17), 0.60 (d, J = 6.8 Hz, 3H, H16); ^{13}C NMR (101 MHz, DMSO-d_6): δ (ppm) 217.6(C3), 167.5(C21), 160.9, 159.3, 150.9, 148.8, 141.2, 139.3(C19), 124.4, 115.8(C20), 73.1(C11), 70.6(C14), 57.7(C4), 55.2, 45.4(C22), 44.6(C9), 43.9(C13), 41.9(C12), 36.9(C5), 36.8(C6), 34.5(C10), 31.1(C2), 30.6(C8), 29.1(C7), 27.1(C18), 24.9(C1), 16.6(C16), 14.9(C15), 11.9(C17); IR (KBr, cm^{-1}): 3428, 2928, 1761, 1730， 1618, 1560, 1465, 1385, 1296, 1191, 1118, 1025, 995, 768; HRMS: calculated for $C_{29}H_{39}N_5O_6S$ ([M + H]$^{+}$): 586.2694; found: 586.2681.

4b: White powder; yield: 52.3%; mp: 156.8-159.1 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.31 (s, 1H), 6.77 (s, 2H), 6.10 (dd, J = 17.6, 11.2 Hz, 1H, H19), 5.54 (d, J = 8.4 Hz, 1H, H14), 5.06 (dd, J = 17.6, 1.6 Hz, 1H, H20), 4.99 (dd, J = 11.2, 1.6 Hz, 1H, H20), 4.52 (d, J = 6.0 Hz, 1H), 4.44 (q, J = 7.2 Hz, 2H), 4.18 (ABq, J = 16.4 Hz, 2H, H22), 3.41 (dd, J = 7.2, 4.0 Hz, 1H, H11), 2.39 (s, 1H, H4), 2.24 – 2.00 (m, 4H, H10, H2, H13), 1.69 – 1.41 (m, 4H, H7, H1), 1.38 (t, J = 7.2 Hz, 3H), 1.34 – 1.29 (m, 4H, H18, H8), 1.28 – 1.22 (m, 2H, H13, H6), 1.05 (s, 3H, H15), 1.01 – 0.94 (m, 1H, H8), 0.81 (d, J = 6.8 Hz, 3H, H17), 0.61 (d, J = 6.8 Hz, 3H, H16); ^{13}C NMR

(101 MHz, DMSO-d_6): δ (ppm) 217.6(C3), 167.5(C21), 160.9, 159.3, 150.9, 147.9, 141.2, 139.3(C19), 124.4, 115.8(C20), 73.1(C11), 70.6(C14), 64.5, 60.2, 57.7(C4), 45.4(C22), 44.6(C9), 43.9(C13), 41.9(C12), 36.9(C5), 36.8(C6), 34.5(C10), 31.1(C2), 30.6(C8), 29.1(C7), 27.1(C18), 24.9(C1), 16.6(C16), 14.9(C15), 12.0(C17); IR (KBr, cm^{-1}): 3444, 2931, 1731, 1621, 1567, 1506, 1470, 1376, 1324, 1295, 1117, 1015, 915,768; HRMS: calculated for $C_{30}H_{41}N_5O_6S$ ($[M + H]^+$): 600.2850; found: 600.2848.

1.3 Synthesis of compounds 5a-5d

Substituted benzoic acid (0.82 mmol) was dissolved in 2 mL of $SOCl_2$ and then stirred at 60 ^oC for 2 h. The reaction was evaporated to prepare the crude product. The crude product, compound **3** (217 mg, 0.41 mmol) and pyridine (64 mg, 0.82 mmol) were added in dry DCM. The solution was stirred at ambient temperature for 2 h. Afterward, the reaction mixture was concentrated to obtain the crude intermediate, which was purified through silica gel column chromatography to compounds **5a-5d**.

5a: White powder; yield: 49.1%; mp: 121.6-122.3 ^oC; ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.25 (s, 1H), 7.85 (d, J = 8.8 Hz, 2H), 7.11 (d, J = 8.8 Hz, 2H), 6.60 (s, 2H), 6.10 (dd, J = 17.6, 11.2 Hz, 1H, H19), 5.54 (d, J = 8.4 Hz, 1H, H14), 5.06 (dd, J = 17.6, 1.6 Hz, 1H, H20), 4.99 (dd, J = 11.2, 1.6 Hz, 1H, H20), 4.50 (d, J = 6.0 Hz, 1H), 4.20 (ABq, J = 16.4 Hz, 2H, H22), 3.89 (s, 3H), 3.41 (t, J = 5.6 Hz, 1H, H11), 2.39 (s, 1H, H4), 2.23 – 1.98 (m, 4H, H10, H2, H13), 1.69 – 1.35 (m, 4H, H7, H1), 1.33 (d, J = 4.4 Hz, 3H, H18), 1.31 – 1.21 (m, 3H, H8, H13, H6), 1.04 (s, 3H, H15), 1.00 (d, J = 3.6 Hz, 1H, H8), 0.81 (d, J = 6.8 Hz, 3H, H17), 0.62 (d, J = 6.8 Hz, 3H, H16); ^{13}C

NMR (101 MHz, DMSO-d_6): δ (ppm) 217.6(C3), 167.6(C21), 165.5, 164.7, 160.5, 159.3, 151.6, 141.2(C19), 140.4, 133.9, 124.4, 124.0, 115.8(C20), 114.6, 73.1(C11), 70.6(C14), 57.7(C4), 56.3, 45.4(C22), 44.6(C9), 43.9(C13), 42.0(C12), 36.9(C5), 36.8(C6), 34.5(C10), 31.2(C2), 30.6(C8), 29.1(C7), 27.1(C18), 24.9(C1), 16.6(C16), 14.9(C15), 12.0(C17); IR (KBr, cm^{-1}): 3431, 2931, 1724, 1606, 1560, 1459, 1355, 1292, 1261, 1171, 1021, 899, 763; HRMS: calculated for $C_{35}H_{43}N_5O_6S$ ($[M + H]^+$): 662.3007; found: 662.2997.

5b: White powder; yield: 45.3%; mp: 147.5-148.4°C; ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.35 (s, 1H), 8.08 (d, J = 8.4 Hz, 2H), 7.47 (d, J = 8.4 Hz, 2H), 6.90 (s, 2H), 6.05 (dd, J = 17.6, 11.2 Hz, 1H, H19), 5.48 (d, J = 8.4 Hz, 1H, H14), 5.00 (dd, J = 17.6, 1.6 Hz, 1H, H20), 4.91 (dd, J = 11.2, 1.6 Hz, 1H, H20), 4.49 (d, J = 6.0 Hz, 1H), 4.14 (ABq, J = 16.4 Hz, 2H, H22), 3.37 (t, J = 6.0 Hz, 1H, H11), 2.38 (s, 3H), 2.32 (s, 1H, H4), 2.23 – 1.99 (m, 3H, H10, H2), 1.93 (dd, J = 15.6, 8.4 Hz, 1H, H13), 1.61 (t, J = 12.0 Hz, 2H, H7), 1.45 – 1.24 (m, 4H, H1, H13, H8), 1.23 – 1.19 (m, 4H, H18, H6), 1.01 (s, 3H, H15), 0.97 (d, J = 4.0 Hz, 1H, H6), 0.79 (d, J = 6.8 Hz, 3H, H17), 0.51 (d, J = 6.8 Hz, 3H, H16); ^{13}C NMR (101 MHz, DMSO-d_6): δ (ppm) 217.5(C3), 167.3(C21), 160.6, 160.1, 150.4, 147.1, 141.1(C19), 137.7, 134.0, 130.7, 128.5, 123.9, 115.7(C20), 73.1(C11), 70.6(C14), 57.7(C4), 45.4(C22), 44.5(C9), 43.9(C13), 41.9(C12), 36.8(C5), 36.7(C6), 34.5(C10), 31.3(C2), 30.5(C8), 29.0(C7), 27.0(C18), 24.9(C1), 21.7, 16.5(C16), 14.8(C15), 11.9(C17); IR (KBr, cm^{-1}): 3440, 2926, 1729, 1595, 1557, 1462, 1383, 1262, 1174, 1092, 912, 587; HRMS: calculated for $C_{35}H_{43}N_5O_5S$ ($[M + H]^+$): 646.3058; found: 646.3054.

5c: Light yellow foam; yield: 55.8%; mp: 155.1-156.3 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.54 (s, 1H), 8.35 (d, J = 8.0 Hz, 1H), 7.98 (t, J = 7.2 Hz, 1H), 7.88 (dd, J = 18.8, 7.6 Hz, 2H), 6.40 (s, 2H), 6.08 (dd, J = 17.6, 11.2 Hz, 1H, H19), 5.52 (d, J = 8.0 Hz, 1H, H14), 5.04 (d, J = 17.6 Hz, 1H, H20), 4.96 (d, J = 11.2 Hz, 1H, H20), 4.50 (d, J = 5.6 Hz, 1H), 4.15 (ABq, J = 16.4 Hz, 2H, H22), 3.43 – 3.37 (m, 1H, H11), 2.36 (s, 1H, H4), 2.24 – 2.00 (m, 4H, H10, H2, H13), 1.68 – 1.56 (m, 2H, H7), 1.52 – 1.33 (m, 3H, H1, H8), 1.31 – 1.20 (s, 5H, H18, H13, H6), 1.03 (s, 3H, H15), 0.97 (d, J = 14.0 Hz, 1H, H8), 0.80 (d, J = 6.4 Hz, 3H, H17), 0.58 (d, J = 6.4 Hz, 3H, H16); ^{13}C NMR (101 MHz, DMSO-d_6): δ (ppm) 217.6(C3), 167.4(C21), 163.8, 160.2, 159.7, 150.4, 145.9, 141.2(C19), 138.4, 135.7, 132.8, 130.1, 129.7, 125.0, 124.5, 115.8(C20), 73.1(C11), 70.6(C14), 57.7(C4), 45.4(C22), 44.6(C9), 43.9(C13), 42.0(C12), 36.9(C5), 36.8(C6), 34.5(C10), 31.2(C2), 30.6(C8), 29.1(C7), 27.0(C18), 24.9(C1), 21.2, 16.6(C16), 14.9(C15), 12.0(C17); IR (KBr, cm^{-1}): 3416, 2929, 1729, 1602, 1560, 1532, 1463, 1287, 1244, 1138, 1018, 896, 711; HRMS: calculated for $C_{34}H_{40}N_6O_7S$ ([M + H]$^+$): 677.2752; found: 677.2756.

5d: Light pink powder; yield: 60.5%; mp: 165.5-166.7 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.42 (s, 1H), 7.32 – 7.25 (m, 4H), 7.22 (d, J = 8.0 Hz, 1H), 6.74 (s, 2H), 6.09 (dd, J = 17.6, 11.2 Hz, 1H, H19), 5.53 (d, J = 8.4 Hz, 1H, H14), 5.06 (d, J = 18.0 Hz, 1H, H20), 4.98 (d, J = 11.2 Hz, 1H, H20), 4.47 (s, 1H), 4.15 (ABq, J = 16.4 Hz, 2H, H22), 3.63 (t, J = 7.6 Hz, 2H), 3.39 (t, J = 5.2 Hz, 1H, H11), 3.01 (t, J = 7.6 Hz, 2H), 2.37 (s, 1H, H4), 2.24 – 1.99 (m, 4H, H10, H2, H13), 1.70 – 1.55 (m, 2H, H7), 1.54 – 1.34 (m, 3H, H1, H8), 1.32 (s, 3H, H18), 1.26 – 1.22 (m, 2H, H13, H6) 1.04

(s, 3H, H15), 1.00 (d, *J*=14.0 Hz, 1H, H8), 0.81 (d, *J* = 6.8 Hz, 3H, H17), 0.61 (d, *J* = 6.8 Hz, 3H, H16); ^{13}C NMR (101 MHz, DMSO-d_6): δ (ppm) 217.6(C3), 170.9, 167.5(C21), 160.4, 159.5, 150.7, 141.2(C19), 140.8, 138.3, 129.0, 128.9, 128.7, 126.6, 125.0, 115.8(C20), 73.1(C11), 70.6(C14), 57.7(C4), 45.4(C22), 44.6(C9), 44.0(C13), 42.0(C12), 38.2, 36.9(C5), 36.8(C6), 34.5(C10), 31.2(C2), 30.6(C8), 29.7, 29.1(C7), 27.1(C18), 24.9(C1), 16.6(C16), 14.9(C15), 11.9(C17); IR (KBr, cm^{-1}): 3430, 2924, 2863, 1731, 1595, 1558, 1469, 1382, 1353, 1272, 1191, 1142, 1115, 1019, 912, 700; HRMS: calculated for $C_{36}H_{45}N_5O_5S$ ([M + H]$^+$): 660.3214; found: 660.3224.

1.4 Synthesis of compounds 6a-6p

BTC (49 mg, 0.16 mmol) was slowly added to the solution of substituted amines (0.16 mmol) and triethylamine (32 mg, 0.32 mmol) in dry DCM (4 mL) at 0 °C. The mixture was stirred at 0 °C for 0.5 h and then evaporated to afford the isocyanate intermediate. The compound **3** (84 mg, 0.16 mmol) and triethylamine (32 mg, 0.32 mmol) were added to a mixture of isocyanate intermediate in dry DCM. After stirring for 3 h at ambient temperature, the reaction mixture was concentrated to prepare the crude intermediate, which was purified through silica gel column chromatography to prepare **6a-6p**.

6a: White powder; yield: 55.9%; mp: 161.9-162.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 10.56 (s, 1H), 8.44 (s, 1H), 7.62 (d, *J* = 8.4 Hz, 2H), 7.40 (t, *J* = 7.6 Hz, 2H), 7.20 (t, *J* = 7.2 Hz, 1H), 6.52 (dd, *J* = 17.2, 11.2 Hz, 1H, H19), 5.77 (d, *J* = 8.4 Hz, 1H, H14), 5.34 (d, *J* = 11.2 Hz, 1H, H20), 5.20 (d, *J* = 17.2 Hz, 1H, H20), 5.12 (s, 2H), 3.98

(ABq, J = 16.4 Hz, 2H, H22), 3.34 (dd, J = 10.4, 6.4 Hz, 1H, H11), 2.36 – 2.06 (m, 4H, H10, H2, H4), 2.03 – 1.96 (m, 1H, H13), 1.75 (d, J = 14.4 Hz, 1H), 1.63 – 1.44 (m, 4H, H7, H1), 1.42 (s, 3H, H18), 1.40 – 1.30 (m, 3H, H8, H13, H6), 1.15 (s, 3H, H15), 1.12 (d, J = 4.4 Hz, 1H, H8), 0.86 (d, J = 7.2 Hz, 3H, H17), 0.76 (d, J = 7.2 Hz, 3H, H16); ^{13}C NMR (101 MHz, CD_3OD): δ (ppm) 219.6(C3), 169.6(C21), 161.2, 141.0(C19), 140.2, 130.2, 129.8, 124.0, 119.8, 116.7(C20), 75.5(C11), 71.8(C14), 61.5(C4), 59.2(C22), 46.8(C9), 45.6(C13), 45.3(C12), 43.2(C5), 38.1(C6), 37.6(C10), 35.3(C2), 31.5(C8), 28.2(C7), 28.0(C18), 25.8(C1), 17.1(C16), 14.5(C15), 11.7(C17); IR (KBr, cm^{-1}): 3383, 3197, 3132, 2926, 1733, 1605, 1548, 1500, 1388, 1266, 1228, 1118, 913, 756; HRMS: calculated for $C_{34}H_{42}N_6O_5S$ ($[M + Na]^+$): 669.2830; found: 669.2836.

6b: White powder; yield: 62.5%; mp: 194.2-195.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 10.98 (s, 1H), 8.45 (s, 1H), 8.28 (dd, J = 8.0, 1.6 Hz, 1H), 7.15 (td, J = 8.0, 1.6 Hz, 1H), 7.04 (t, J = 7.2 Hz, 1H), 6.97 (d, J = 8.0 Hz, 1H, H19), 6.52 (dd, J = 17.2, 11.2 Hz, 1H, H14), 5.78 (d, J = 8.4 Hz, 1H, H20), 5.34 (dd, J = 11.2, 1.6 Hz, 1H, H20), 5.20 (dd, J = 17.2, 1.6 Hz, 1H), 5.03 (s, 2H), 4.1-3.91 (m, 5H, H22), 3.34 (d, J = 4.8 Hz, 1H, H11), 2.39 – 2.06 (m, 4H, H10, H2, H4), 2.01 (dd, J = 15.6, 8.4 Hz, 1H, H13), 1.76 (d, J = 14.4 Hz, 1H), 1.72 – 1.51 (m, 4H, H7, H1), 1.51 – 1.44 (m, 2H, H8, H13), 1.42 (s, 3H, H18), 1.40 – 1.34 (m, 1H, H6), 1.16 (s, 3H, H15), 1.11 (dd, J = 14.0, 4.4 Hz, 1H, H8), 0.86 (d, J = 7.2 Hz, 3H, H17), 0.78 (d, J = 7.2 Hz, 3H, H16); ^{13}C NMR (101 MHz, DMSO-d_6): δ (ppm) 217.6(C3), 167.4(C21), 160.5, 159.4, 149.8, 149.5, 146.6, 141.2(C19), 138.4, 126.4, 125.5, 124.7, 121.0, 120.8, 115.8(C20), 111.7, 73.1(C11), 70.7(C14), 57.7(C4), 56.8, 45.4(C22), 44.6(C9), 43.9(C13), 42.0(C12), 36.9(C5),

36.8(C6), 34.5(C10), 31.4(C2), 30.6(C8), 29.0(C7), 27.1(C18), 24.9(C1), 16.6(C16), 14.9(C15), 11.2(C17); IR (KBr, cm^{-1}): 3506, 3370, 3132, 2935, 2883, 1731, 1604, 1548, 1495, 1462, 1388, 1262, 1231, 1108, 1026, 919, 747; HRMS: calculated for $C_{35}H_{44}N_6O_6S$ ($[M+Na]^+$): 699.2935; found: 699.2935.

6c: White powder; yield: 52.9%; mp: 188.2-189.4 °C; ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 10.86 (s, 1H), 9.45 (s, 1H), 8.44 (s, 1H), 8.14 (s, 1H), 7.42 – 6.96 (m, 5H), 6.10 (dd, *J* = 17.6, 11.2 Hz, 1H, H19), 5.54 (d, *J* = 8.0 Hz, 1H, H14), 5.07 (d, *J* = 17.6 Hz, 1H, H20), 4.99 (d, *J* = 11.2 Hz, 1H, H20), 4.50 (d, *J* = 6.0 Hz, 1H), 4.20 (ABq, *J* = 16.4 Hz, 2H, H22), 3.41 (d, *J* = 5.2 Hz, 1H, H11), 2.39 (s, 1H, H4), 2.26 – 2.00 (m, 4H, H10, H2, H13), 1.71 – 1.38 (m, 13H, H7, H1), 1.37 –1.30 (m, 4H, H18, H8), 1.30 – 1.21 (m, 2H, H13, H6), 1.05 (s, 3H, H15), 0.98 (d, *J* = 13.2 Hz, 1H, H8), 0.80 (d, *J* = 6.8 Hz, 3H, H17), 0.62 (d, *J* = 6.8 Hz, 3H, H16); ^{13}C NMR (101 MHz, DMSO-d_6): δ (ppm) 217.6(C3), 167.4(C21), 160.6, 159.4, 153.2, 149.5, 146.5, 141.2, 140.8(C19), 138.2, 137.6, 129.5, 124.5, 115.8(C20), 115.2, 114.7, 110.6, 79.6, 73.1(C11), 70.7(C14), 57.7(C4), 45.4(C22), 44.6(C9), 43.9(C13), 42.0(C12), 36.9(C5), 36.8(C6), 34.5(C10), 31.4(C2), 30.6(C8), 29.1(C7), 28.6, 27.1(C18), 24.9(C1), 16.6(C16), 14.9(C15), 12.0(C17); IR (KBr, cm^{-1}): 3428, 3348, 3223, 3139, 2929, 1741, 1712, 1605, 1548, 1384, 1275, 1228, 1157, 1014, 924, 787; HRMS: calculated for $C_{39}H_{51}N_7O_7S$ ($[M+Na]^+$): 784.3463; found: 784.3475.

6d: White powder; yield: 52.1%; mp: 142.4-144.0 °C; ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 10.92 (s, 1H), 10.08 (s, 1H), 8.44 (s, 1H), 8.16 (s, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.33 (t, *J* = 8.0 Hz, 1H), 7.27 – 6.97 (m, 3H), 6.09 (dd, *J* = 17.6, 11.2

Hz, 1H, H19), 5.54 (d, *J* = 8.0 Hz, 1H, H14), 5.06 (dd, *J* = 17.6, 1.6 Hz, 1H, H20), 4.99 (dd, *J* = 11.2 , 1.6 Hz, 1H, H20), 4.53 (d, *J* = 6.0 Hz, 1H), 4.19 (ABq, *J* = 16.4 Hz, 2H, H22), 3.40 (t, *J* = 6.0 Hz, 1H, H11), 2.39 (s, 1H, H4), 2.26 – 2.00 (m, 7H, H10, H2, H13), 1.70 – 1.37 (m, 4H, H7, H1), 1.37 – 1.31 (m, 4H, H18, H8), 1.30 – 1.19 (m, 2H, H13, H6), 1.05 (s, 3H, H15), 0.97 (d, *J* = 13.6 Hz, 1H, H8), 0.80 (d, *J* = 6.8 Hz, 3H, H17), 0.62 (d, *J* = 6.8 Hz, 3H, H16); ^{13}C NMR (101 MHz, DMSO-d_6): δ (ppm) 217.2(C3), 168.4(C21), 166.9, 160.1, 158.9, 149.0, 146.1, 140.8, 140.1(C19), 137.8, 137.2, 129.2, 124.0, 115.5(C20), 115.4, 115.1, 110.7, 72.6(C11), 70.2(C14), 57.2(C4), 45.0(C22), 44.1(C9), 43.4(C13), 41.6(C12), 36.4(C5), 36.3(C6), 34.0(C10), 30.9(C2), 30.1(C8), 28.6(C7), 26.6(C18), 24.5(C1), 24.0, 16.2(C16), 14.5(C15), 11.6(C17); IR (KBr, cm^{-1}): 3375, 2931, 1732, 1611, 1550, 1463, 1388, 1228, 1117, 921, 785; HRMS: calculated for $C_{36}H_{45}N_7O_6S$ ([M + Na]$^+$): 726.3044; found: 726.3038.

6e: White powder; yield: 55.1%; mp: 165.0-166.2 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 11.22 (s, 1H), 8.45 (s, 1H), 7.70 (d, *J* = 11.2 Hz, 1H), 7.63 (d, *J* = 8.4 Hz, 1H), 7.47 (q, *J* = 8.0 Hz, 1H), 7.24 (s, 2H), 7.02 (td, *J* = 8.4, 2.0 Hz 1H), 6.09 (dd, *J* = 17.6, 11.2 Hz, 1H, H19), 5.54 (d, *J* = 8.0 Hz, 1H, H14), 5.07 (d, *J* = 17.6 Hz, 1H, H20), 4.99 (d, *J* = 11.2 Hz, 1H, H20), 4.52 (d, *J* = 6.0 Hz, 1H), 4.19 (ABq, *J* = 16.4 Hz, 2H, H22), 3.40 (t, *J* = 5.6 Hz, 1H, H11), 2.39 (s, 1H, H4), 2.24 – 2.00 (m, 4H, H10, H2, H13), 1.74 – 1.37 (m, 4H, H7, H1), 1.36 – 1.29 (m, 4H, H18, H8), 1.29 – 1.18 (m, 2H, H13, H6) 1.05 (s, 3H, H15), 0.97 (d, *J* = 13.2 Hz, 1H, H8), 0.80 (d, *J* = 6.8 Hz, 3H, H17), 0.62 (d, *J* = 6.8 Hz, 3H, H16); ^{13}C NMR (101 MHz, DMSO-d_6): δ (ppm) 217.2(C3), 166.9(C21), 163.6, 161.2, 160.3, 158.9, 148.9, 146.2, 140.8, 138.9(C19),

138.8, 137.6, 131.0, 130.9, 123.9, 115.5(C20), 115.4, 111.2, 111.0, 106.7, 106.5, 72.6(C11), 70.2(C14), 57.2(C4), 45.0(C22), 44.2(C9), 43.4(C13), 41.6(C12), 36.4(C5), 36.3(C6), 34.0(C10), 30.9(C2), 30.1(C8), 28.7(C7), 26.6(C18), 24.5(C1), 16.2(C16), 14.5(C15), 11.6(C17); IR (KBr, cm^{-1}): 3446, 2925, 1733, 1624, 1555, 1457, 1391, 1228, 1117, 921, 786; HRMS: calculated for $C_{34}H_{41}FN_6O_5S$ ($[M + Na]^+$): 687.2735; found: 687.2741.

6f: White powder; yield: 53.1%; mp: 137.6-138.6 °C; ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 11.04 (s, 1H), 8.44 (s, 1H), 7.79 (dd, *J* = 9.2, 4.8 Hz, 2H), 7.40 – 6.94 (m, 4H), 6.09 (dd, *J* = 17.6, 11.2 Hz, 1H, H19), 5.54 (d, *J* = 8.4 Hz, 1H, H14), 5.06 (dd, *J* = 17.6, 1.6 Hz, 1H, H20), 4.98 (dd, *J* = 11.2, 1.6 Hz, 1H, H20), 4.52 (d, *J* = 6.0 Hz, 1H), 4.19 (ABq, *J* = 16.4 Hz, 2H, H22), 3.40 (s, 1H, H11), 2.38 (s, 1H, H4), 2.27 – 1.99 (m, 4H, H10, H2, H13), 1.72 – 1.37 (m, 4H, H7, H1), 1.37 – 1.29 (m, 4H, H18, H8), 1.29 – 1.19 (m, 2H, H13, H6), 1.04 (s, 3H, H15), 0.96 (dd, *J* = 13.2, 3.6 Hz, 1H, H8), 0.80 (d, *J* = 6.8 Hz, 3H, H17), 0.61 (d, *J* = 6.8 Hz, 3H, H16); ^{13}C NMR (101 MHz, DMSO-d_6): δ (ppm) 217.3(C3), 167.0(C21), 162.4, 160.2, 160.1, 158.9, 157.7, 149.0, 146.3, 140.8(C19), 137.7, 133.4, 124.0, 121.8, 121.7, 116.0, 115.8(C20), 115.4, 72.7(C11), 70.3(C14), 57.2(C4), 45.0(C22), 44.2(C9), 43.4(C13), 41.6(C12), 36.5(C5), 36.4(C6), 34.0(C10), 30.9(C2), 30.1(C8), 28.7(C7), 26.6(C18), 24.5(C1), 16.2(C16), 14.5(C15), 11.6(C17); IR (KBr, cm^{-1}): 3430, 2926, 1731, 1626, 1602, 1563, 1510, 1463, 1388, 1225, 1117, 1017, 922, 835; HRMS: calculated for $C_{34}H_{41}FN_6O_5S$ ($[M + Na]^+$): 687.2735; found: 687.2738.

6g: White powder; yield: 51.6%; mp: 192.9-193.7 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 11.01 (s, 1H), 8.48 (s, 1H), 8.25 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.60 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.42 (td, *J* = 8.0, 1.2 Hz, 1H), 7.23 (td, *J* = 8.0, 1.2 Hz, 1H), 6.93 (s, 2H), 6.09 (dd, *J* = 17.6, 11.2 Hz, 1H, H19), 5.54 (d, *J* = 8.0 Hz, 1H, H14), 5.07 (dd, *J* = 17.6, 1.6 Hz, 1H, H20), 4.99 (dd, *J* = 11.2, 1.6 Hz, 1H, H20), 4.51 (s, 1H), 4.19 (ABq, *J* = 16.4 Hz, 2H, H22), 3.40 (s, 1H, H11), 2.39 (s, 1H, H4), 2.27 – 2.00 (m, 4H, H10, H2, H13), 1.74 – 1.37 (m, 4H, H7, H1), 1.36 – 1.30(m, 4H, H18, H8), 1.30 – 1.19 (m, 2H, H13, H6), 1.04 (s, 3H, H15), 1.01 – 0.91 (m, 1H, H8), 0.80 (d, *J* = 6.8 Hz, 3H, H17), 0.62 (d, *J* = 6.8 Hz, 3H, H16); ^{13}C NMR (101 MHz, DMSO-d_6): δ (ppm) 217.2(C3), 166.9(C21), 160.2, 158.9, 149.0, 146.4, 140.8(C19), 137.9, 133.9, 129.6, 127.9, 126.0, 124.3, 124.0, 122.4, 115.4(C20), 72.6(C11), 70.2(C14), 57.2(C4), 45.0(C22), 44.1(C9), 43.4(C13), 41.6(C12), 36.4(C5), 36.3(C6), 34.0(C10), 30.9(C2), 30.1(C8), 28.6(C7), 26.6(C18), 24.5(C1), 16.2(C16), 14.4(C15), 11.6(C17); IR (KBr, cm^{-1}): 3545, 3433, 3231, 3109, 2926, 2868, 1742, 1608, 1542, 1455, 1388, 1226, 1116, 1015, 917, 761; HRMS: calculated for $C_{34}H_{41}ClN_6O_5S$ ([M + Na]$^+$): 703.2440; found: 703.2437.

6h: White powder; yield: 52.5%; mp:158.1-158.8 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 11.28 (s, 1H), 8.47 (s, 1H), 8.17 (s, 1H), 8.06 (d, *J* = 8.0 Hz, 1H), 7.69 (t, *J* = 8.0 Hz, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.25 (s, 2H), 6.09 (dd, *J* = 17.6, 11.2 Hz, 1H, H19), 5.54 (d, *J* = 8.0 Hz, 1H, H14), 5.07 (dd, *J* = 17.6, 1.6 Hz, 1H, H20), 4.99 (dd, *J* = 11.2, 1.6 Hz, 1H, H20), 4.51 (s, 1H), 4.20 (ABq, *J* = 16.4 Hz, 2H, H22), 3.41 (s, 1H, H11), 2.39 (s, 1H, H4), 2.25 – 2.00 (m, 4H, H10, H2, H13), 1.73 – 1.42 (m, 4H, H7,

H1), 1.41 – 1.23 (m, 6H, H18, H8, H13, H6), 1.05 (s, 3H, H15), 0.97 (dd, *J* = 13.2, 3.2 Hz, 1H, H8), 0.80 (d, *J* = 6.8 Hz, 3H, H17), 0.62 (d, *J* = 6.8 Hz, 3H, H16); ^{13}C NMR (101 MHz, DMSO-d_6): δ (ppm) 217.2(C3), 166.9(C21), 160.3, 158.9, 148.9, 146.5, 140.8(C19), 138.0, 137.6, 130.4,130.1, 128.8, 123.9, 121.04 123.6, 115.9, 115.4(C20), 72.6(C11), 70.3(C14), 57.2(C4), 45.0(C22), 44.2(C9),43.4(C13), 41.6(C12), 36.4(C5), 36.3(C6), 34.0(C10),30.8(C2), 30.1(C8), 28.7(C7), 26.6(C18), 24.5(C1), 16.2(C16), 14.5(C15), 11.6(C17); IR (KBr, cm^{-1}): 3415, 3130, 3079, 2931, 1740, 1614, 1552, 1461, 1388, 1323, 1229, 1114, 1066, 1016, 921, 844; HRMS: calculated for $C_{35}H_{41}F_3N_6O_5S$ ([M + H]$^+$): 715.2884; found: 715.2879.

6i: White powder; yield: 50.7%; mp: 186.6-187.6 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 9.20 (t, *J* = 6.4 Hz, 1H), 8.36 (s, 1H), 7.48 – 7.32 (m, 4H), 7.31 – 7.23 (m, 1H), 6.89 (s, 2H), 6.08 (dd, *J* = 17.6, 11.2 Hz, 1H, H19), 5.53 (d, *J* = 8.4 Hz, 1H, H14), 5.05 (dd, *J* = 17.6, 1.6 Hz, 1H, H20), 4.98 (dd, *J* = 11.2, 1.6 Hz, 1H, H20), 4.62 (d, *J* = 6.0 Hz, 2H), 4.47 (d, *J* = 6.0 Hz, 1H), 4.19 (ABq, *J* = 16.4 Hz, 2H, H22), 3.40 (t, *J* = 6.0 Hz, 1H, H11), 2.38 (s, 1H, H4), 2.27 – 1.94 (m, 4H, H10, H2, H13), 1.73 – 1.35 (m, 4H, H7, H1), 1.34 – 1.28 (m, 4H, H18, H8), 1.28 – 1.19 (m, 2H, H13, H6), 1.03 (s, 3H, H15), 0.98 (dd, *J* = 13.6, 4.0 Hz, 1H, H8), 0.81 (d, *J* = 6.8 Hz, 3H, H17), 0.61 (d, *J* = 6.8 Hz, 3H, H16); ^{13}C NMR (101 MHz, DMSO-d_6): δ (ppm) 217.2(C3), 166.9(C21), 159.9, 159.1, 149.2, 149.0, 140.7(C19), 138.2, 137.8, 128.6, 127.2, 127.0, 124.1, 115.3(C20), 72.6(C11), 70.2(C14), 57.2(C4), 45.0(C22), 44.1(C9), 43.4(C13), 43.1, 41.5(C12), 36.4(C5), 36.3(C6), 34.0(C10), 30.9(C2), 30.1(C8), 28.6(C7), 26.6(C18), 24.5(C1), 16.1(C16), 14.5(C15), 11.7(C17); IR (KBr, cm^{-1}): 3422, 2925, 2855, 1735,

1606, 1547, 1465, 1388, 1260, 1114, 1019, 917, 803; HRMS: calculated for $C_{35}H_{44}N_6O_5S$ ([M + Na]$^+$): 683.2986; found: 683.2997.

6j: White powder; yield: 59.5%; mp: 113.6-114.7 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.83 (t, J = 5.2 Hz, 1H), 8.32 (s, 1H), 7.30 (d, J = 4.4 Hz, 4H), 7.25 –7.15 (m, 1H), 6.88 (s, 2H), 6.08 (dd, J = 17.6, 11.2 Hz, 1H, H19), 5.53 (d, J = 8.4 Hz, 1H, H14), 5.05 (dd, J = 17.6, 1.2 Hz, 1H, H20), 4.97 (dd, J = 11.2, 1.2 Hz, 1H, H20), 4.53 (s, 1H), 4.18 (ABq, J = 16.4 Hz, 2H, H22), 3.59 (q, J = 6.8 Hz, 2H), 3.40 (s, 1H, H11), 2.93 (t, J = 7.2 Hz, 2H), 2.38 (s, 1H, H4), 2.24 – 1.98 (m, 4H, H10, H2, H13), 1.69 – 1.35 (m, 4H, H7, H1), 1.33 – 1.27 (m, 4H, H18, H8), 1.25 – 1.19 (m, 2H, H13, H6), 1.04 (s, 3H, H15), 0.97 (dd, J = 13.2, 3.6 Hz, 1H, H8), 0.80 (d, J = 6.8 Hz, 3H, H17), 0.60 (d, J = 6.8 Hz, 3H, H16); ^{13}C NMR (101 MHz, DMSO-d_6): δ (ppm) 217.2(C3), 167.0(C21), 159.9, 159.0, 149.1, 148.6, 140.7, 138.7(C19), 137.7, 128.8, 128.5, 126.4, 124.1, 115.3(C20), 72.6(C11), 70.2(C14), 57.2(C4), 45.0(C22), 44.1(C9), 43.4(C13), 41.5(C12), 41.4, 36.4(C5), 36.3(C6), 34.9, 34.0(C10), 30.9(C2), 30.1(C8), 28.6(C7), 26.6(C18), 24.5(C1), 16.1(C16), 14.4(C15), 11.6(C17); IR (KBr, cm^{-1}): 3437, 2925, 1730, 1604, 1547, 1456, 1389, 1230, 1139, 1116, 1018, 919, 700; HRMS: calculated for $C_{36}H_{46}N_6O_5S$ ([M + Na]$^+$): 697.3143; found: 697.3138.

6k: White powder; yield: 61.5%; mp: 134.8-135.9 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 9.15 (s, 1H), 8.36 (s, 1H), 7.26 (d, J = 7.2 Hz, 2H), 7.16 (d, J = 7.2 Hz, 2H), 6.91 (s, 2H), 6.09 (dd, J = 17.6, 11.2 Hz, 1H, H19), 5.53 (d, J = 7.6 Hz, 1H, H14), 5.05 (d, J = 17.6 Hz, 1H, H20), 4.98 (d, J = 11.2 Hz, 1H, H20), 4.56 (d, J = 5.2 Hz, 2H), 4.50 (d, J = 5.2 Hz, 1H), 4.18 (ABq, J = 16.4 Hz, 2H, H22), 3.40 (s, 1H, H11),

2.38 (s, 1H, H4), 2.28 (s, 3H), 2.22 – 1.97 (m, 4H, H10, H2, H13), 1.77 – 1.38 (m, 4H, H7, H1), 1.36 – 1.28 (m, 4H, H18, H8), 1.27 – 1.18 (m, 2H, H13, H6), 1.04 (s, 3H, H15), 0.97 (d, J = 13.2 Hz, 1H, H8), 0.80 (d, J = 6.0 Hz, 3H, H17), 0.61 (d, J = 6.0 Hz, 3H, H16); ^{13}C NMR (101 MHz, DMSO-d_6): δ (ppm) 217.6(C3), 167.4(C21), 160.3, 159.5, 149.7, 149.4, 141.2, 138.3(C19), 136.8, 135.6, 129.6, 129.2, 127.5, 127.5, 124.6, 115.8(C20), 73.1(C11), 70.6(C14), 57.7(C4), 45.4(C22), 44.6(C9), 43.9(C13), 43.4, 42.0(C12), 36.9(C5), 36.8(C6), 34.5(C10), 31.4(C2), 30.6(C8), 29.1(C7), 27.1(C18), 24.9(C1), 21.2, 16.6(C16), 14.9(C15), 12.0(C17); IR (KBr, cm^{-1}): 3435, 2925, 1729, 1613, 1548, 1461, 1388, 1228, 1116, 1047, 917; HRMS: calculated for $C_{36}H_{46}N_6O_5S$ ([M + Na]$^+$): 697.3143; found: 697.3152.

6l: White powder; yield: 60.5%; mp: 167.1-168.2 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 9.12 (s, 1H), 8.35 (s, 1H), 7.30 (d, J = 7.2 Hz, 2H), 6.91 (d, J = 6.8 Hz, 4H), 6.08 (dd, J = 17.2, 11.2 Hz, 1H, H19), 5.53 (d, J = 6.8 Hz, 1H, H14), 5.05 (d, J = 17.6 Hz, 1H, H20), 4.97 (d, J = 10.8 Hz, 1H, H20), 4.61 – 4.44 (m, 3H), 4.19 (ABq, J = 16.4 Hz, 2H, H22), 3.73 (s, 3H), 3.40 (s, 1H, H11), 2.38 (s, 1H, H4), 2.27 – 1.94 (m, 4H, H10, H2, H13), 1.70 – 1.39 (m, 4H, H7, H1), 1.36 – 1.28 (m, 4H, H18, H8), 1.27 – 1.19 (m, 2H, H13, H6), 1.03 (s, 3H, H15), 0.99 (d, J = 10.8 Hz 1H, H8), 0.80 (d, J = 6.4 Hz, 3H, H17), 0.60 (d, J = 6.4 Hz, 3H, H16); ^{13}C NMR (101 MHz, DMSO-d_6): δ (ppm) 217.6(C3), 167.4(C21), 160.3, 159.5, 159.0, 149.7, 149.3, 141.2, 138.3(C19), 130.5, 128.9, 124.6, 115.8(C20), 114.4, 73.1(C11), 70.6(C14), 57.7(C4), 55.6, 45.4(C22), 44.6(C9), 43.9(C13), 43.1, 42.0(C12), 36.9(C5), 36.8(C6), 34.5(C10), 31.3(C2), 30.6(C8), 29.1(C7), 27.1(C18), 24.9(C1), 16.6(C16), 14.9(C15), 12.0(C17);

IR (KBr, cm^{-1}): 3431, 2929, 1730, 1609, 1547, 1513, 1463, 1388, 1244, 1179, 1116, 1030, 915; HRMS: calculated for $C_{36}H_{46}N_6O_6S$ ($[M + H]^+$): 691.3272; found: 691.3271.

6m: White powder; yield: 45.1%; mp: 146.4-147.5 ^oC; ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 9.19 (t, J = 6.0 Hz, 1H), 8.36 (s, 1H), 7.27 (t, J = 8.0 Hz, 1H), 6.99 – 6.80 (m, 5H), 6.09 (dd, J = 17.6, 11.2 Hz, 1H, H19), 5.54 (d, J = 8.0 Hz, 1H, H14), 5.05 (dd, J = 17.6, 1.6 Hz, 1H, H20), 4.98 (dd, J = 11.2, 1.6 Hz, 1H, H20), 4.59 (d, J = 6.0 Hz, 2H), 4.50 (d, J = 6.0 Hz, 1H), 4.21 (ABq, J = 16.4 Hz, 2H, H22), 3.74 (s, 3H), 3.40 (t, J = 5.6 Hz, 1H, H11), 2.37 (s, 1H, H4), 2.28 – 1.98 (m, 4H, H10, H2, H13), 1.70 – 1.37 (m, 4H, H7, H1), 1.36 – 1.28 (m, 4H, H18, H8), 1.29 – 1.22 (m, 2H, H13, H6), 1.04 (s, 3H, H15), 0.97 (d, J = 13.2 Hz, 1H, H8), 0.80 (d, J = 6.8 Hz, 3H, H17), 0.61 (d, J = 6.8 Hz, 3H, H16); ^{13}C NMR (101 MHz, DMSO-d_6): δ (ppm) 217.6(C3), 167.4(C21), 160.3, 159.9, 159.5, 149.7, 149.5, 141.2, 140.2, 138.3(C19), 130.2, 124.6, 119.6, 115.8(C20), 113.2, 113.1, 73.1(C11), 70.6(C14), 57.7(C4), 55.5, 45.4(C22), 44.6(C9), 43.9(C13), 43.5, 42.0(C12), 36.9(C5), 36.8(C6), 34.5(C10), 31.4(C2), 30.6(C8), 29.0(C7), 27.1(C18), 24.9(C1), 16.6(C16), 14.9(C15), 12.0(C17); IR (KBr, cm^{-1}): 3421, 2931, 1729, 1602, 1547, 1463, 1388, 1265, 1229, 1152, 1026, 915, 786; HRMS: calculated for $C_{36}H_{46}N_6O_6S$ ($[M + H]^+$): 691.3272; found: 691.3268.

6n: White powder; yield: 48.5%; mp: 123.8-125.2 ^oC; ^1H NMR (400 MHz, DMSO-d_6): ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 9.15 (t, J = 6.4 Hz, 1H), 8.34 (s, 1H), 7.28 (t, J = 6.8 Hz, 2H), 7.06 – 6.99 (m, 1H), 6.95 – 6.82 (m, 3H), 6.08 (dd, J = 17.6, 11.2 Hz, 1H, H19), 5.53 (d, J = 8.4 Hz, 1H, H14), 5.04 (dd, J = 17.6, 1.6 Hz, 1H, H20), 4.97 (dd, J = 11.2, 1.6 Hz, 1H, H20), 4.54 (d, J = 6.4 Hz, 2H), 4.50 (d, J = 6.0

Hz, 1H), 4.21 (ABq, J = 16.4 Hz, 2H, H22), 3.87 (s, 3H), 3.39 (t, J = 6.0 Hz, 1H, H11), 2.38 (s, 1H, H4), 2.24 – 2.00 (m, 4H, H10, H2, H13), 1.72 – 1.34 (m, 4H, H7, H1), 1.33 – 1.28 (m, 4H, H18, H8), 1.27 – 1.22 (m, 2H, H13, H6), 1.03 (s, 3H, H15), 0.97 (dd, J = 13.6, 4.0 Hz, 1H, H8), 0.80 (d, J = 6.8 Hz, 3H, H17), 0.61 (d, J = 6.8 Hz, 3H, H16); ^{13}C NMR (101 MHz, DMSO-d_6): δ (ppm) 217.6(C3), 167.4(C21), 160.3, 159.6, 157.3, 149.7, 149.2, 141.2, 138.3(C19), 129.2, 128.5, 126.0, 124.6, 120.8, 115.8(C20), 111.2, 73.1(C11), 70.6(C14), 57.7(C4), 55.9, 45.4(C22), 44.6(C9), 43.9(C13), 42.0(C12), 36.9(C5), 36.8(C6), 34.5(C10), 31.3(C2), 30.6(C8), 29.0(C7), 27.1(C18), 24.9(C1), 16.6(C16), 14.9(C15), 12.0(C17); IR (KBr, cm^{-1}): 3430, 2926, 1729, 1603, 1543, 1496, 1463, 1387, 1246, 1118, 1026, 915; HRMS: calculated for $C_{36}H_{46}N_6O_6S$ ([M + H]$^+$): 691.3272; found: 691.3278.

6o: Light yellow powder; yield: 59.2%; mp: 128.1-129.4 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.80 (t, J = 5.6 Hz, 1H), 8.31 (s, 1H), 7.18 (d, J = 8.0 Hz, 2H), 7.10 (d, J = 8.0 Hz, 2H), 6.84 (s, 2H), 6.09 (dd, J = 17.6, 11.2 Hz, 1H, H19), 5.53 (d, J = 8.0 Hz, 1H, H14), 5.05 (dd, J = 17.6, 1.6 Hz, 1H, H20), 4.97 (dd, J = 11.2, 1.6 Hz, 1H, H20), 4.50 (d, J = 6.0 Hz, 1H), 4.20 (ABq, J = 16.4 Hz, 2H, H22), 3.56 (q, J = 6.8 Hz, 2H), 3.40 (t, J = 6.0 Hz, 1H, H11), 2.38 (s, 1H, H4), 2.22 – 1.97 (m, 4H, H10, H2, H13), 1.71 – 1.34 (m, 4H, H7, H1), 1.34 – 1.28 (m, 4H, H18, H8), 1.28 – 1.22 (m, 2H, H13, H6), 1.04 (s, 3H, H15), 0.98 (dd, J = 13.6, 4.0 Hz, 1H, H8), 0.81 (d, J = 6.8 Hz, 3H, H17), 0.60 (d, J = 6.8 Hz, 3H, H16); ^{13}C NMR (101 MHz, DMSO-d_6): δ (ppm) 217.6(C3), 167.4(C21), 160.4, 159.6, 149.7, 149.6, 147.2, 146.6, 141.2, 138.2(C19), 128.6, 124.6, 124.2, 115.8(C20), 73.1(C11), 70.6(C14), 57.7(C4), 45.4(C22), 44.6(C9),

43.9(C13), 42.0, 41.9(C12), 36.9(C5), 36.8(C6), 34.5(C10), 31.3(C2), 30.6(C8), 29.1(C7), 27.1(C18), 24.9(C1), 16.6(C16), 14.9(C15), 12.0(C17); IR (KBr, cm^{-1}): 3445, 2926, 1730, 1606, 1547, 1521, 1457, 1398, 1345, 1229, 1114, 916, 619; HRMS: calculated for $C_{35}H_{43}N_7O_7S$ ($[M + H]^+$): 706.3017; found: 706.3024.

6p: White powder; yield:42.9%; mp: 116.3-117.5 ^oC; ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 9.33 (t, *J* = 6.0 Hz, 1H), 8.36 (s, 1H), 8.25 (s, 1H), 8.15 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.86 (d, *J* = 7.6 Hz, 1H), 7.67 (t, *J* = 8.0 Hz, 1H), 6.87 (s, 2H), 6.08 (dd, *J* = 17.6, 11.2 Hz, 1H, H19), 5.53 (d, *J* = 8.4 Hz, 1H, H14), 5.05 (dd, *J* = 17.6, 1.6 Hz, 1H, H20), 4.98 (dd, *J* = 11.2, 1.6 Hz, 1H, H20), 4.74 (d, *J* = 6.0 Hz, 2H), 4.49 (d, *J* = 6.0 Hz, 1H), 4.18 (ABq, *J* = 16.4 Hz, 2H, H22), 3.40 (t, *J* = 6.0 Hz, 1H, H11), 2.38 (s, 1H, H4), 2.23 – 1.98 (m, 4H, H10, H2, H13), 1.69 – 1.34 (m, 4H, H7, H1), 1.33 – 1.28 (m, 4H, H18, H8), 1.28 – 1.21 (m, 2H, H13, H6), 1.03 (s, 3H, H15), 0.97 (dd, *J* = 14.0, 4.4 Hz, 1H, H8), 0.80 (d, *J* = 6.8 Hz, 3H, H17), 0.61 (d, *J* = 6.8 Hz, 3H, H16); ^{13}C NMR (101 MHz, DMSO-d_6): δ (ppm) 217.6(C3), 167.4(C21), 160.3, 159.5, 149.7, 149.6, 148.4, 141.2, 141.1, 138.3(C19), 134.4, 130.6, 124.6, 122.7, 122.4, 115.8(C20), 73.1(C11), 70.6(C14), 57.7(C4), 45.4(C22), 44.6(C9), 43.9(C13), 43.1, 42.0(C12), 36.9(C5), 36.8(C6), 34.5(C10), 31.3(C2), 30.6(C8), 29.1(C7), 27.1(C18), 24.9(C1), 16.6(C16), 14.9(C15), 11.9. (C17) IR (KBr, cm^{-1}): 3407, 2925, 1730, 1605, 1546, 1462, 1388, 1349, 1228, 1115, 916, 786; HRMS: calculated for $C_{35}H_{43}N_7O_7S$ ($[M + Na]^+$): 728.2837; found: 728.2853.

1.5 Synthesis of compound 7

To a solution of compound **3** (2.26 g, 4.3 mmol) and NMM (0.86 g, 8.6 mmol) in 20 mL of anhydrous THF, chloracetyl chloride (1.93 g, 17.2 mmol) was slowly added after the solution cooled to 0 ^{o}C. The mixture was stirred at ambient temperature for 12 h. Then, it was poured into water (40 mL) and extracted with DCM (20 mL×3), the organic phase was concentrated to obtain the crude intermediate, which was purified through silica gel column chromatography to prepare coumpound **7**.

7: Light yellow powder; yield: 71.5%; mp: 201.5-202.6 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 13.07 (s, 1H), 9.14 (s, 1H), 8.32 (s, 1H), 6.44 (dd, *J* = 17.6, 11.2 Hz, 1H, H19), 5.76 (d, *J* = 8.4 Hz, 1H, H14), 5.29 (d, *J* = 11.2 Hz, 1H, H20), 5.15 (d, *J* = 17.6 Hz, 1H, H20), 4.39 (s, 2H), 4.17 – 3.98 (m, 2H, H22), 3.33 (d, *J* = 6.4 Hz, 1H, H11), 2.33 – 2.11 (m, 4H, H10, H2, H4), 2.01 (dd, *J* = 16.0, 8.4 Hz 1H, H13), 1.79 – 1.71 (m, 1H), 1.71 – 1.52 (m, 4H, H7, H1), 1.44 (dd, *J* = 8.4, 5.2 Hz, 2H, H8, H13), 1.40 (s, 3H, H18), 1.36 (d, *J* = 14.4 Hz, 1H, H6), 1.17 – 1.06 (m, 4H, H15, H8), 0.84 (d, *J* = 6.8 Hz, 3H, H17), 0.75 (d, *J* = 6.8 Hz, 3H, H16); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 217.5(C3), 167.5(C21), 165.1, 151.8, 143.5, 141.2(C19), 115.6(C20), 73.1(C11), 70.7(C14), 57.7(C4), 45.4, 44.7(C22), 44.6(C9), 43.8(C13), 42.0(C12), 36.9(C5), 36.8(C6), 34.5(C10), 31.7(C2), 30.6(C8), 29.0(C7), 27.0(C18), 24.9(C1), 16.5(C16), 14.8(C15), 11.9(C17); IR (KBr, cm^{-1}): 3399, 3153, 2931, 1726, 1582, 1522, 1426, 1378, 1256, 1152, 1116, 1048, 912, 638; HRMS: calculated for $C_{29}H_{38}ClN_5O_5S$ ($[M + H]^+$): 604.2355; found: 604.2361.

1.6 Synthesis of compounds 8a-8g

K_2CO_3 (110 mg, 0.8 mmol) was added to a solution of compound **7** (242 mg, 0.4 mmol) in 5 mL of dry THF, and the solution was stirred at 60 °C with different secondary amines (0.5 mmol) for 10 h. The reaction was monitored using TLC. After the reaction completed, it was concentrated. The obtained residues were purified through column chromatography to give compounds **8a-8g**.

8a: White powder; yield: 50.8%; mp: 118.7-119.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 13.48 (s, 1H), 10.03 (s, 1H), 8.40 (s, 1H), 6.44 (dd, *J* = 17.2, 11.2 Hz, 1H, H19), 5.74 (d, *J* = 8.4 Hz, 1H, H14), 5.28 (dd, *J* = 11.2, 1.2 Hz, 1H, H20), 5.15 (dd, *J* = 17.2, 1.2 Hz, 1H, H20), 4.13 (ABq, *J* = 16.0 Hz, 2H, H22), 3.32 (dd, *J* = 10.4, 6.4 Hz, 1H, H11), 3.18 (ABq, *J* = 16.8 Hz, 2H), 2.60 (s, 4H), 2.37 – 2.09 (m, 4H, H10, H2, H4), 2.00 (dd, *J* = 16.0, 8.4 Hz, 1H, H13), 1.81 – 1.67 (m, 6H), 1.67 – 1.46 (m, 5H, H7, H1), 1.45 – 1.39 (m, 1H, H8), 1.38 (s, 3H, H18), 1.36 – 1.25 (m, 2H, H13, H6), 1.11 (s, 3H, H15), 1.10 – 1.04 (m, 1H, H8), 0.85 (d, *J* = 6.8 Hz, 3H, H17), 0.71 (d, *J* = 6.8 Hz, 3H, H16); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 217.0(C3), 169.2(C21), 167.6, 159.5, 150.7, 150.3, 144.5, 139.1(C19), 128.8, 117.3(C20), 74.7(C11), 70.1(C14), 63.2(C4), 58.2(C22), 55.1, 45.6(C9), 44.8(C13), 44.1(C12), 42.0(C5), 36.8(C6), 36.1(C10), 34.6(C2), 31.8(C8), 30.5 (C7), 27.0(C18), 26.5(C1), 26.3, 24.9, 23.8, 16.9(C16), 14.9(C15), 11.6(C17); IR (KBr, cm^{-1}): 3440, 2931, 1725, 1635, 1573, 1508, 1380, 1261, 1116, 913; HRMS: calculated for $C_{34}H_{48}N_6O_5S$ ([M + H]+): 653.3480; found: 653.3474.

8b: White powder; yield: 45.0 %; mp: 208.3-209.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 13.49 (s, 1H), 9.84 (s, 1H), 8.40 (s, 1H), 6.42 (dd, *J* = 17.6, 11.2 Hz, 1H, H19), 5.74 (d, *J* = 8.4 Hz, 1H, H14), 5.28 (dd, *J* = 11.2, 1.2 Hz, 1H, H20), 5.15 (dd, *J* = 17.6, 1.2 Hz, 1H, H20), 4.16 (s, 2H), 3.39 (ABq, *J* = 16.8 Hz 2H, H22), 3.32 (dd, *J* = 8.4, 4.0 Hz, 1H, H11), 2.75 (s, 4H), 2.37 – 2.04 (m, 4H, H10, H2, H4), 2.00 (dd, *J* = 16.0, 8.4 Hz, 1H, H13), 1.91 (s, 4H), 1.78 – 1.41 (m, 6H, H7, H1, H8), 1.38 (s, 3H, H18), 1.36 – 1.23 (m, 2H, H13, H6), 1.12 (s, 3H, H15), 1.09 (d, *J* = 12.0 Hz, 1H, H8), 0.85 (d, *J* = 6.8 Hz, 3H, H17), 0.74 (d, *J* = 6.8 Hz, 3H, H16); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 217.0(C3), 169.2(C21), 167.6, 159.5, 150.7, 150.2, 144.4, 139.0(C19), 128.7, 117.2(C20), 74.6(C11), 70.1(C14), 60.1(C4), 58.2(C22), 54.8, 45.5(C9), 44.7(C13), 44.0(C12), 42.0(C5), 36.8(C6), 36.0(C10), 34.5(C2), 31.8, 30.5(C8), 27.0(C7), 26.6(C18), 24.9(C1), 24.2, 16.8(C16), 14.9(C15), 11.5(C17);IR (KBr, cm^{-1}): 3435, 2926, 1727, 1572, 1506, 1379, 1261, 1115, 1019, 909, 801; HRMS: calculated for $C_{33}H_{46}N_6O_5S$ ([M + H]+): 639.3323; found: 639.3319.

8c: White powder; yield: 50.1%; mp: 192.4-193.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 13.40 (s, 1H), 9.84 (s, 1H), 8.40 (s, 1H), 6.42 (dd, *J* = 17.2, 11.2 Hz, 1H, H19), 5.73 (d, *J* = 8.4 Hz, 1H, H14), 5.27 (dd, *J* = 11.2, 1.2 Hz, 1H, H20), 5.15 (dd, *J* = 17.2, 1.2 Hz, 1H, H20), 4.13 (ABq, *J* = 16.8 Hz, 2H, H22), 3.85 (t, *J* = 4.4 Hz, 4H), 3.32 (dd, *J* = 10.4, 6.4 Hz, 1H, H11), 3.25 (ABq, *J* = 16.8 Hz, 2H), 2.69 (t, *J* = 4.4 Hz, 4H), 2.35 – 2.04 (m, 4H, H2, H10, H4), 1.99 (dd, *J* = 16.0, 8.4 Hz, 1H, H13), 1.77 (s, 1H), 1.76 – 1.40 (m, 5H, H7, H1, H8), 1.38 (s, 3H, H18), 1.36 – 1.23 (m, 2H, H13, H6), 1.11 (s, 3H, H15), 1.07 (dd, *J* = 14.0, 4.2 Hz, 1H, H8), 0.85 (d, *J* = 6.8 Hz, 3H, H17), 0.70 (d,

J = 6.8 Hz, 3H, H16); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 216.9, (C3) 168.1, 167.5(C21), 159.7, 150.5, 150.2, 144.6, 139.1(C19), 128.9, 117.3(C20), 74.7(C11), 70.1(C14), 67.1, 62.8(C4), 58.2(C22), 53.9, 45.5(C9), 44.8(C13), 44.1(C12), 42.0(C5), 36.8(C6), 36.1(C10), 34.5(C2), 31.9, 30.5(C8), 27.0(C7), 26.5(C18), 24.9(C1), 16.9(C16), 14.9(C15), 11.6(C17); IR (KBr, cm^{-1}): 3435, 2930, 2860, 1727, 1573, 1484, 1428, 1378, 1257, 1116, 1015, 914, 638; HRMS: calculated for $C_{33}H_{46}N_6O_6S$ ([M + H]$^+$): 655.3272; found: 655.3257.

8d: White powder; yield: 44.5%; mp: 144.6-145.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 13.43 (s, 1H), 10.12 (s, 1H), 8.38 (s, 1H), 6.45 (dd, *J* = 17.2, 11.2 Hz, 1H, H19), 5.73 (d, *J* = 8.4 Hz, 1H, H14), 5.28 (dd, *J* =10.8, 0.8 Hz, 1H, H20), 5.16 (dd, *J* = 17.2, 0.8 Hz, 1H, H20), 4.13 (s, 2H), 4.02 (d, *J* = 11.6 Hz, 2H, H22), 3.53 (s, 2H), 3.42 (t, *J* = 11.6 Hz, 2H), 3.32 (dd, *J* = 10.4, 6.4 Hz, 1H, H11), 2.83 – 2.70 (m, 1H), 2.35 – 2.03 (m, 4H, H10, H2, H4), 2.03 – 1.97 (m, 1H, H13), 1.94 (d, *J* = 15.2 Hz, 2H), 1.74 (d, *J* = 12.0 Hz, 2H), 1.64 (d, *J* = 13.2 Hz, 1H), 1.59 – 1.41 (m, 5H, H7, H1, H8), 1.38 (s, 3H, H18), 1.33 (d, *J* = 17.2 Hz, 1H, H13), 1.27 (d, *J* = 16.4 Hz, 1H, H6), 1.16 – 1.06 (m, 4H, H15, H8), 0.85 (d, *J* = 6.8 Hz, 3H, H17), 0.72 (d, *J* = 6.8 Hz, 3H, H16); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 217.1(C3), 167.6(C21), 159.6, 150.6, 150.2, 144.5, 139.2(C19), 128.8, 117.3(C20), 74.7(C11), 70.1(C14), 66.9, 58.2(C4), 55.1(C22), 50.5(C9), 45.5(C13), 44.7(C12), 44.0(C5), 42.0, 36.8(C6), 36.0(C10), 34.6, 34.0(C2), 31.8(C8), 30.5(C7), 27.0(C18), 26.5, 24.9(C1), 17.0(C16), 15.0(C15), 11.6(C17); IR (KBr, cm^{-1}): 3431, 2928, 1726, 1575, 1502, 1378, 1283, 1180, 1116, 1077, 914, 795; HRMS: calculated for $C_{34}H_{48}N_6O_6S$ ([M + Na]$^+$): 691.3248; found: 691.3214.

8e: White powder; yield: 45.9%; mp: 241.4-242.9 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 9.66 (s, 1H), 8.04 (s, 1H), 6.06 (dd, J = 17.6, 11.2 Hz, 1H, H19), 5.51 (d, J = 8.4 Hz, 1H, H14), 5.02 (dd, J = 17.6, 1.6 Hz, 1H, H20), 4.93 (dd, J = 11.2, 1.6 Hz, 1H, H20), 4.48 (s, 1H), 4.23 (ABq, J = 16.0 Hz, 2H, H22), 3.40(s, 1H, H11) 3.09 (s, 2H), 2.76 (t, J = 4.4 Hz, 4H), 2.45 (t, J = 4.4 Hz, 4H), 2.35 (s, 1H, H4), 2.26 – 1.88 (m, 5H, H10, H2, H13), 1.68 – 1.52 (m, 2H, H7), 1.50 – 1.30 (m, 3H, H1, H8), 1.28 (s, 3H, H18), 1.24 – 1.17 (m, 2H, H13, H6), 1.01 (s, 3H, H15), 0.99 – 0.93 (m, 1H, H8), 0.80 (d, J = 6.8 Hz, 3H, H17), 0.59 (d, J = 6.8 Hz, 3H, H16); ^{13}C NMR (101 MHz, DMSO-d_6): δ (ppm) 217.6(C3), 168.0(C21), 141.2(C19), 115.7(C20), 73.1(C11), 70.3(C14), 63.0, 57.7(C4), 54.6, 46.1, 45.4(C22), 44.6(C9), 43.9(C13), 42.0(C12), 36.9(C5), 36.8(C6), 34.5(C10), 31.4(C2), 30.6(C8), 29.2(C7), 27.2(C18), 27.1, 27.0, 24.9(C1), 24.8, 16.5(C16), 14.9(C15), 12.0(C17); IR (KBr, cm^{-1}): 3408, 2936, 2476, 1725, 1576, 1377, 1283, 1118, 1018, 914, 638; HRMS: calculated for $C_{33}H_{47}N_7O_5S$ ([M + H]$^{+}$): 654.3432; found: 654.3430.

8f: White powder; yield: 45.5%; mp: 175.9-176.3 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.95 (s, 1H), 8.33 (s, 1H), 6.06 (dd, J = 17.6, 11.2 Hz, 1H, H19), 5.52 (d, J = 8.4 Hz, 1H, H14), 5.00 (dd, J = 17.6, 1.6 Hz, 1H, H20), 4.92 (dd, J = 11.2, 1.6 Hz, 1H, H20), 4.52 (d, J = 6.0 Hz, 1H), 4.24 (ABq, J = 16.4 Hz, 2H, H22), 3.40 (s, 1H, H11), 3.18 (s, 2H), 2.56 (s, 4H), 2.43 (s, 4H), 2.37 (s, 1H, H4), 2.21 (s, 3H), 2.19 – 1.93 (m, 4H, H10, H2, H13), 1.68 – 1.31 (m, 5H, H7, H1, H8), 1.28 (s, 3H, H18), 1.26 – 1.22 (m, 2H, H13, H6), 1.01 (s, 3H, H15), 0.96 (dd, J = 15.2, 5.6 Hz, 1H, H8), 0.80 (d, J = 6.8 Hz, 3H, H17), 0.57 (d, J = 6.8 Hz, 3H, H16); ^{13}C NMR (101 MHz, DMSO-d_6): δ

(ppm) 217.6(C3), 167.5(C21), 151.6, 141.2(C19), 115.6(C20), 73.0(C11), 70.6(C14), 62.0, 57.7(C4), 55.1, 52.9, 45.4(C22), 44.6(C9), 43.9(C13), 42.0(C12), 36.9(C5), 36.8(C6), 34.5(C10), 31.6(C2), 30.7(C8),29.1(C7), 27.6(C18), 24.9(C1), 16.5(C16), 14.9(C15), 12.0(C17); IR (KBr, cm-1): 3434, 2935, 1726, 1574, 1485, 1376, 1284, 1261, 1148, 1117, 1014, 912, 793; HRMS: calculated for $C_{34}H_{49}N_7O_5S$ ($[M + Na]^+$): 690.3408; found: 690.3375.

8g: White powder; yield: 39.8%; mp: 164.9-165.9 ^oC; ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 9.51 (s, 1H), 7.89 (s, 1H), 7.07 (d, J = 2.4 Hz, 1H), 6.07 (dd, J = 17.6, 11.2 Hz, 1H, H19), 5.51 (d, J = 8.4 Hz, 1H, H14), 5.02 (dd, J = 17.6, 1.6 Hz, 1H, H20), 4.93 (dd, J = 11.2, 1.6 Hz, 1H, H20), 4.47 (s, 1H), 4.31 – 4.11 (m, 2H, H22), 3.40 (s, 1H, H11), 3.09 (s, 2H), 2.80 – 2.72 (m, 2H), 2.35 (s, 1H, H4), 2.32 – 1.91 (m, 7H, H10, H2, H13), 1.71 – 1.60 (m, 2H, H7), 1.59 –1.29 (m, 7H, H1, H8), 1.28 (s, 3H, H18), 1.25 (d, J = 8.8 Hz, 2H, H13, H6), 1.01 (s, 3H, H15), 0.97 (dd, J = 13.6, 4.0 Hz, 1H, H8), 0.80 (d, J = 6.8 Hz, 3H, H17), 0.60 (d, J = 6.8 Hz, 3H, H16); ^{13}C NMR (101 MHz, DMSO-d_6): δ (ppm) 217.5(C3), 167.9, 167.5(C21), 151.6, 141.2(C19), 115.6(C20), 73.1(C11), 70.6(C14), 62.3, 57.7(C4), 51.4, 45.4(C22), 44.6(C9), 43.8(C13), 42.0(C12), 36.9(C5), 36.8(C6), 34.7, 34.5(C10), 31.5(C2), 30.6(C8), 29.1(C7), 27.0(C18), 24.9(C1), 16.8(C16), 14.8(C15), 11.9(C17); IR (KBr, cm^{-1}): 3424, 2929, 1726, 1572, 1500, 1428, 1377, 1283, 1187, 1150, 1116, 912, 639; HRMS: calculated for $C_{34}H_{48}N_6O_6S$ ($[M + H]^+$): 669.3429; found: 669.3436.

Safety Statement

No unexpected or unusually high safety hazards were encountered.

2. Biology experimental methods

2. 1 MIC And MBC assays

MIC values were set *in vitro* using the agar dilution method[2] . *S. aureus* ATCC 25923, *MSSA* ATCC29213, *MRSA* ATCC 33591, *MRSA* ATCC 43300**,** *MSSR* ATCC 12228 and *MRSE* ATCC 51625 were employed for susceptibility evaluation on Mueller−Hinton (MH) broth. Testing was performed using a 96-well plate and microbroth serial dilution assay. The bacterial solution was regulated to 0.5 McFarland standard with saline and then diluted with MH broth to the approximate concentration of 10^6~10^7 CFU·mL^{-1}. All test compounds, reference drugs tiamulin fumarate and retapamulin, were dissolved in DMSO with a concentration of 12800 μg·mL^{-1}. 96 μL MH broth was mixed with 4 μL compounds solution in the first row of sterile 96-well plates, while 100 μL volume of MH broth was added to others wells. Subsequently, the solution was diluted using the double dilution method. A 100 μL volume of bacteria in MH broth was mixed in the sterile 96-well plates. The plates were incubated at 37 ^{o}C for 20−24 h. MIC was defined as the lowest concentration without apparent visible bacteria growth. To determine the MBC, aliquots of 5 μL were taken from the wells exhibiting no visible turbidity, spot plated onto the surface of a Mueller Hinton agar

(MHA) plate and further incubated for 24 h at 37 °C. The lowest test concentration of the antimicrobial that resulted in the absence of bacterial growth was reported as the MBC.

2.2 Time-kill kinetics assay

MRSA ATCC 33591 grown in MH broth was diluted to nearly 1×10^6 CFU·mL^{-1} and administrated with compound **6j** and tiamulin with the final concentrations of 1 × MIC, 2 × MIC, 4 × MIC. After the time intervals were specified (0, 2, 4, 6, 8, 12 and 24 h), 10 μL aliquots were serially diluted to 10^{-1} to 10^{-3} in 0.9% saline. Subsequently, 25 μL of the dilutions were plated on sterile MHA plates and incubated at 37 °C for 20 h. The time-kill curve is expressed as $\log_{10}$ (CFU·mL^{-1}) of bacteria counts versus time.

2.3 Cytotoxicity assay

Cell viability was examined through MTT assay. The cell line employed in the experiment comprised HepG2, Hela, RAW264.7 and A549. The exponentially growing cells were seeded in 96-well and 24 h later cells were administrated with **6j** at concentrations from 0 to 40 μM at 37 °C under 5% CO_2 for 24 h. Next, the cells were incubated with 150 μL per well of MTT (0.5 mg·mL^{-1} in PBS) at 37 ℃ under 5% CO_2 for 4h. After the incubation, the MTT was removed, and then the cells were dissolved in 150 μL DMSO for 10 min at 37 °C. The absorbance of the samples at 570 nm was examined using the microplate reader.

2.4 *In vivo* efficacy in the mouse model

2.4.1 Thigh infection models

All mice (ICR female mice weight of 22 to 25 g) were rendered neutropenic by intraperitoneally injection of cyclophosphamide (150 $mg \cdot kg^{-1}$ for 4 days and 100 $mg \cdot kg^{-1}$ for 1 day). Next, the mice received a 0.1 mL MH broth with the bacterial solution of *MRSA*-33591 at a concentration of 10^7 $CFU \cdot mL^{-1}$ via intraperitoneal injection. After 2 h, 0.9% saline, retapamulin (20, 40 $mg \cdot kg^{-1}$), tiamulin (20, 40 mg· kg-1), **6j** (20, 40 mg· kg-1) were injected respectively via the tail vein. The mice were euthanized after being treated for 24 h. The tissue of the thigh was separated, which was mixed with ice-cold saline and examined by plate counting method. The other part of the thigh was then embedded in paraffin, sectioned, and stained with hematoxylin and eosin (H&E), which was processed for light microscopy.

2.4.2 Murine skin wound model

Different amounts of **6j** (0.05, 0.10, and 0.15 g) and retapamulin (0.10 g) used in this study were made as ointments (1%, 2%, and 3% compound **6j** and 2% retapamulin, respectively) with matrix (i.e., albolene (3 g), liquid paraffin (1.5 mL), lanolin (0.1 g), and anhydrous alcohol (0.4 mL)). The mice were randomly assigned into six groups and anesthetized intraperitoneally with 10% chloral hydrate. The surgical area was exposed by shearing on the back of the mice, and the skin was disinfected with alcohol. A wound of a depth of nearly 1.5 cm was created using a

sterile scissors. The blood from the wound was cleaned with cotton ball, and an inoculum of 0.1 mL PBS (bacterial solution of *MRSA*-43300 at a concentration of 10^{12} CFU·mL^{-1}) was smeared evenly on the whole wound of mice except for the blank control group only administrated with a blank ointment matrix. After 4 h, the treatment groups were administrated with 1%, 2%, 3% compound **6j** ointment and 2% retapamulin ointment, the positive control group was administrated with a blank ointment matrix. 15 mg per mouse of ointment was applied for the respective treatment. The dosage for each group was continued for 5 days with 24 h intervals. After inoculation, the mice were caged separately and observed twice daily for their clinical signs and mortality. Wound camera records, from the day of modeling take a photo record once a day. The levels of TNF-α, IL-6, and MCP-1 were examined by ELISA.

3. Molecular docking

The binding mode of compounds **5c**, **6j** and **8a** was explored by docking using the PTC ribosome complex with Tiamulin (PDB ID: 1XBP) [3]. In particular, the PTC ribosome model was constructed using residues in 30 Å from the binding site after extraction of the original ligand tiamulin. Moreover, **5c**, **6j**, **8a** and the above ribosome model were prepared using AutoDockTools by removing water molecules, adding polar hydrogens, and assigning Gasteiger charges. Lastly, the box (52.791, 122.679, 114.289) was set using the original ligand as the grid center with box sizes (36.758, 44.448, 36.761). Docking was performed using DOCK 6[4].

4. References for supporting information

(1) Zhang, Y.; Xie, C.; Liu, Y.; Shang, F.; Shao, R.; Yu, J.; Wu, C.; Yao, X.; Liu, D.; Wang, Z. Synthesis, biological activities and docking studies of pleuromutilin derivatives with piperazinyl urea linkage. *J. Enzyme Inhib. Med. Chem.* **2021**, 36, 764-775.

(2) Reynolds, R.; Shackcloth, J.; Felmingham, D.; Macgowan, A.; Surveillance, B.E.W.P.O.R.R. Comparison of BSAC agar dilution and NCCLS broth microdilution MIC methods for in vitro susceptibility testing of Streptococcus pneumoniae, Haemophilus influenzae and Moraxella catarrhalis: the BSAC Respiratory Resistance Surveillance Programme. *J. Antimicrob. Chemother.* **2003**, 52, 925-930.

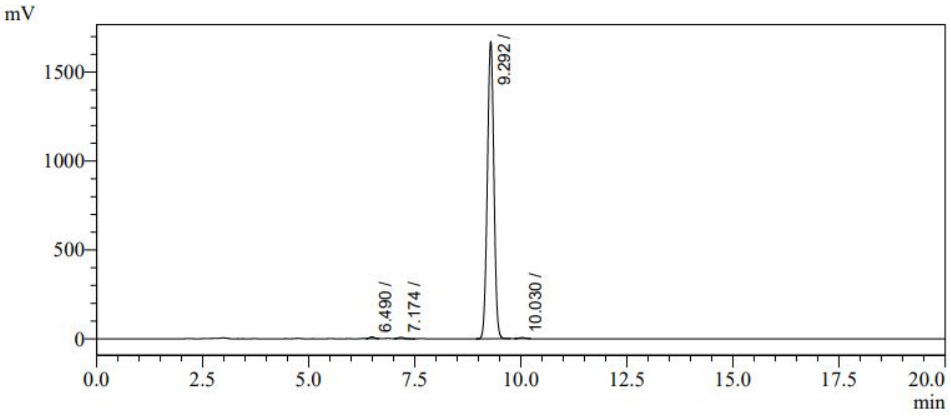
(3) Schlunzen, F.; Pyetan, E.; Fucini, P.; Yonath, A.; Harms, J.M. Inhibition of peptide bond formation by pleuromutilins: the structure of the 50S ribosomal subunit from Deinococcus radiodurans in complex with tiamulin. *Mol. Microbiol.* **2004**, 54, 1287-1294.

(4) Lang, P.T.; Brozell, S.R.; Mukherjee, S.; Pettersen, E.F.; Meng, E.C.; Thomas, V.; Rizzo, R.C.; Case, D.A.; James, T.L.; Kuntz, I.D. DOCK 6: combining techniques to model RNA-small molecule complexes. *RNA.* **2009**, 15, 1219-1230.

5. HPLC, ^{1}H NMR, ^{13}C NMR and HRMS of intermediate compound 3 and 7

Figure S1. HPLC, ^{1}H NMR, ^{13}C NMR and HRMS spectrum of intermediate compound **3**

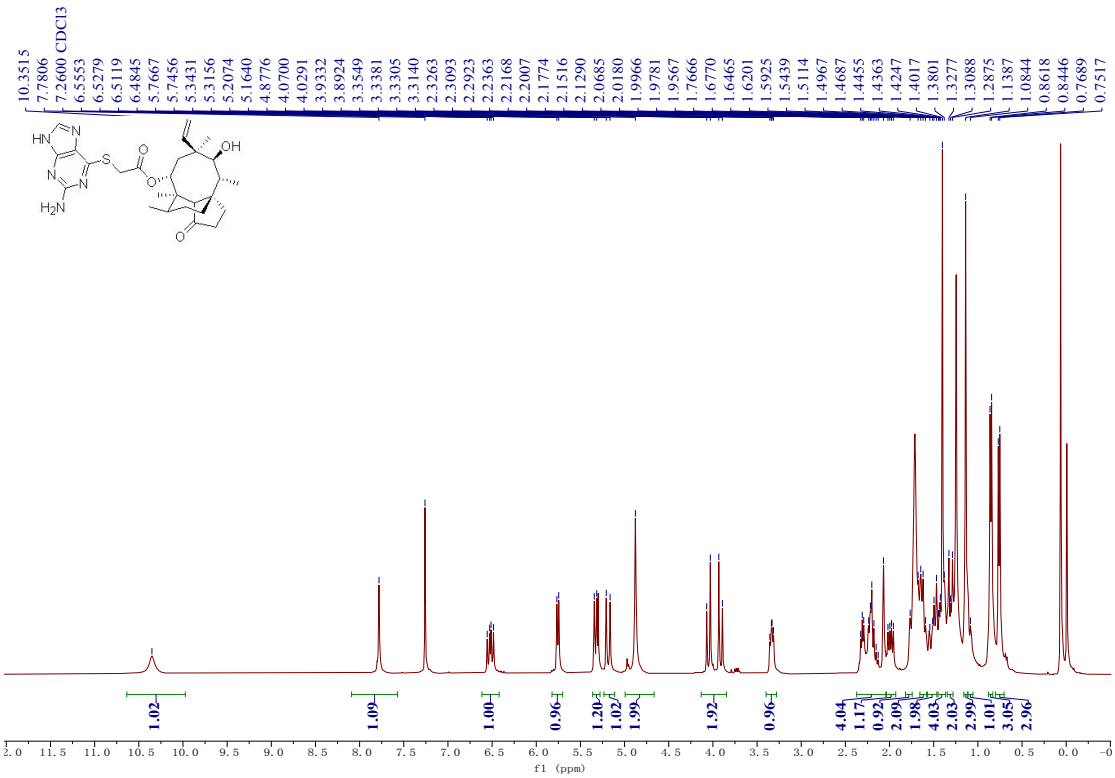
HPLC spectrum of **3**



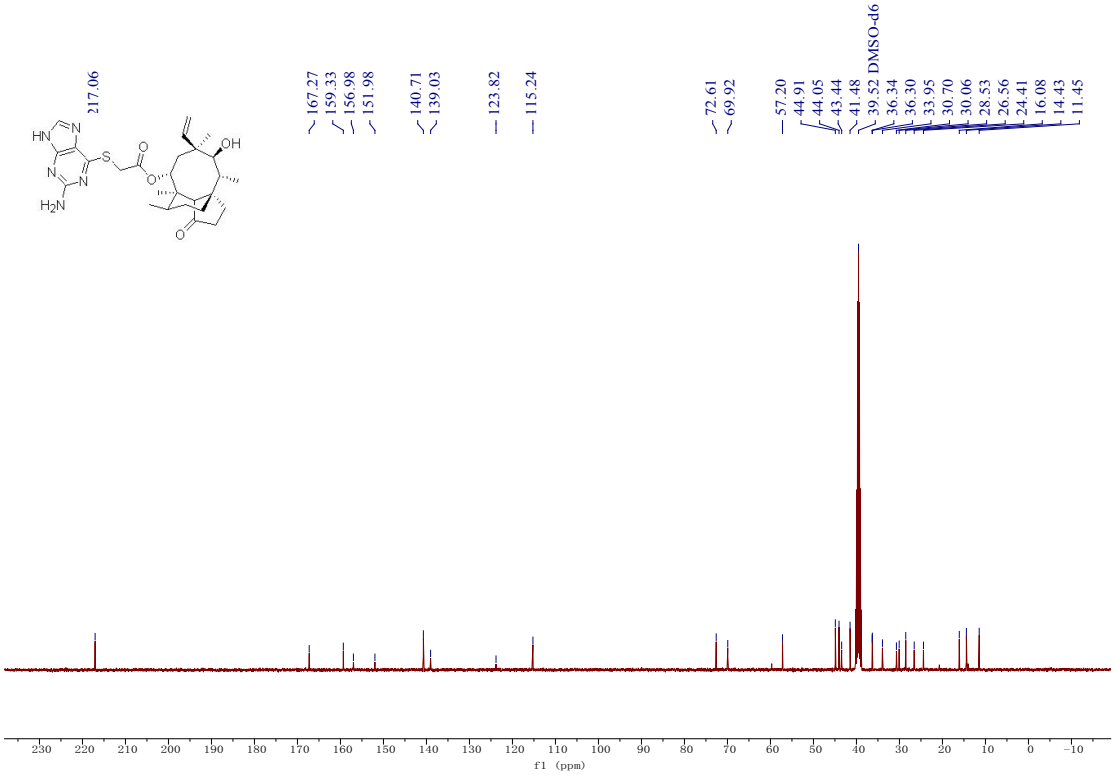
检测器A 254nm

Peak#	Ret. Time	Height	Area	Area%
1	6.490	9416	68120	0.377
2	7.174	7578	68457	0.379
3	9.292	1670730	17876586	98.906
4	10.030	6156	61101	0.338

^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **3**



^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **3**



HRMS spectrum of **3**

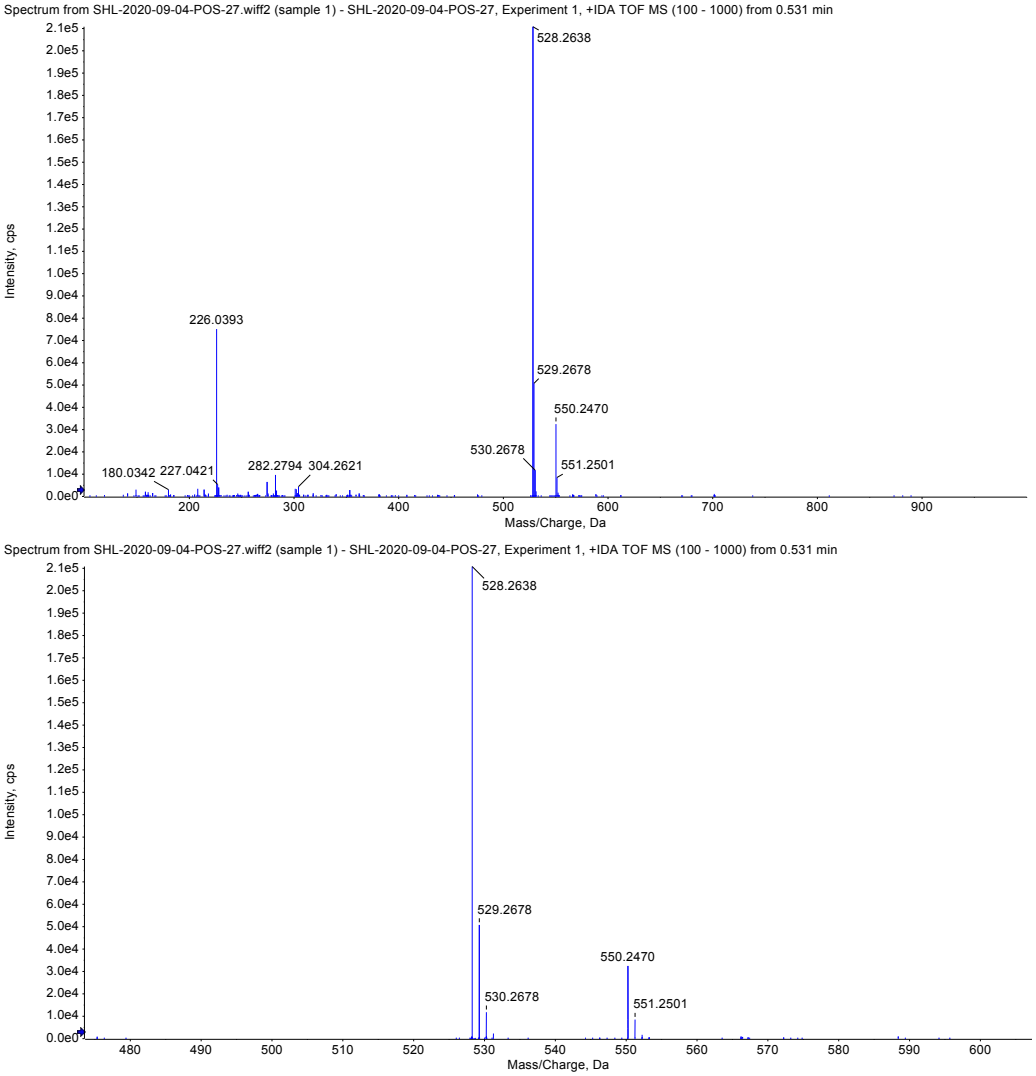
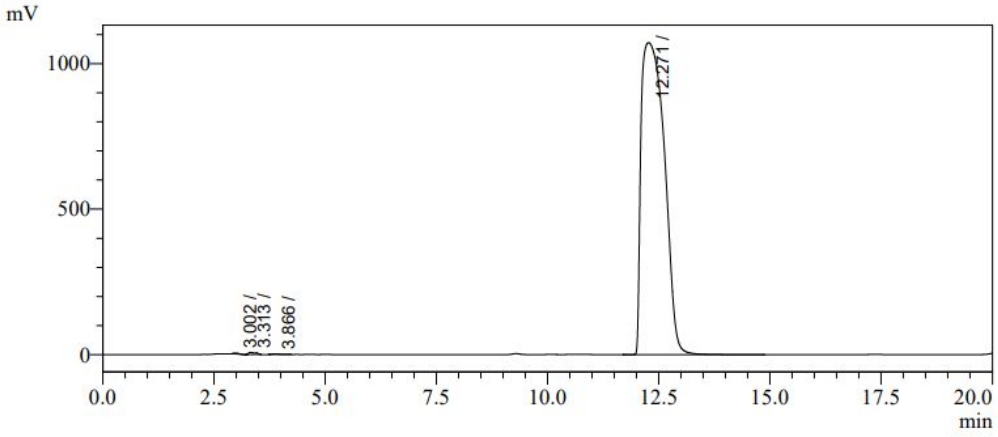


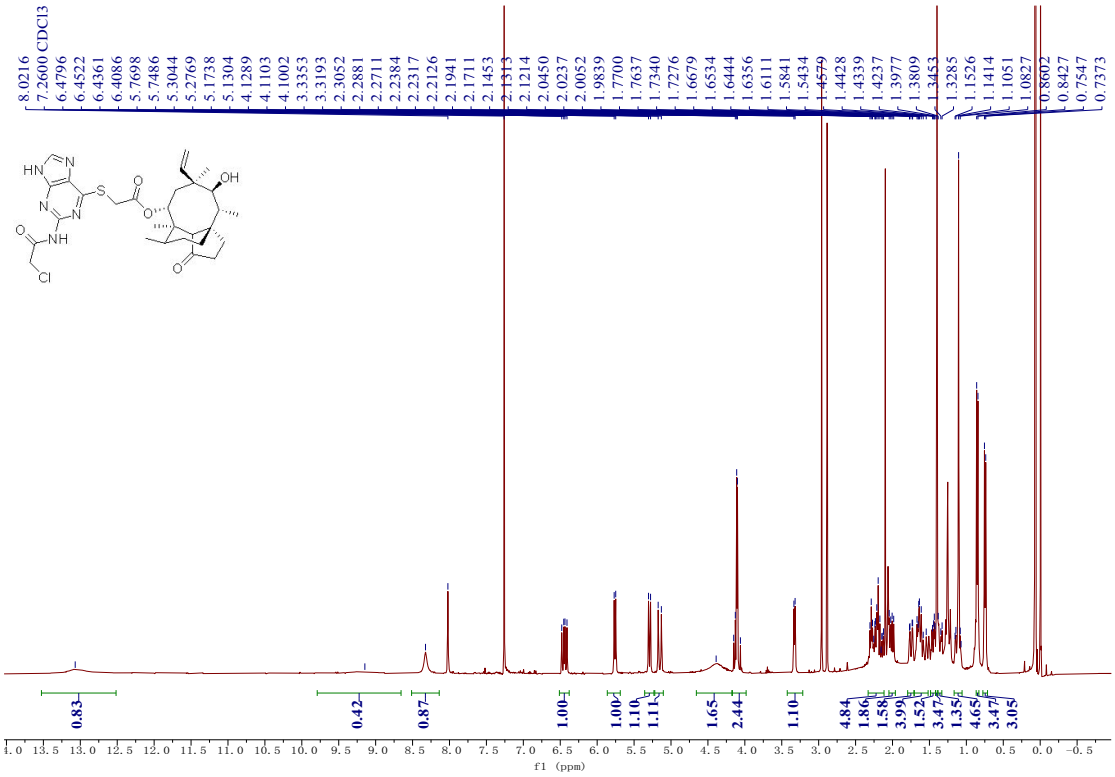
Figure S2. HPLC, ^{1}H NMR, ^{13}C NMR and HRMS spectrum of intermediate compound **7**
HPLC spectrum of **7**



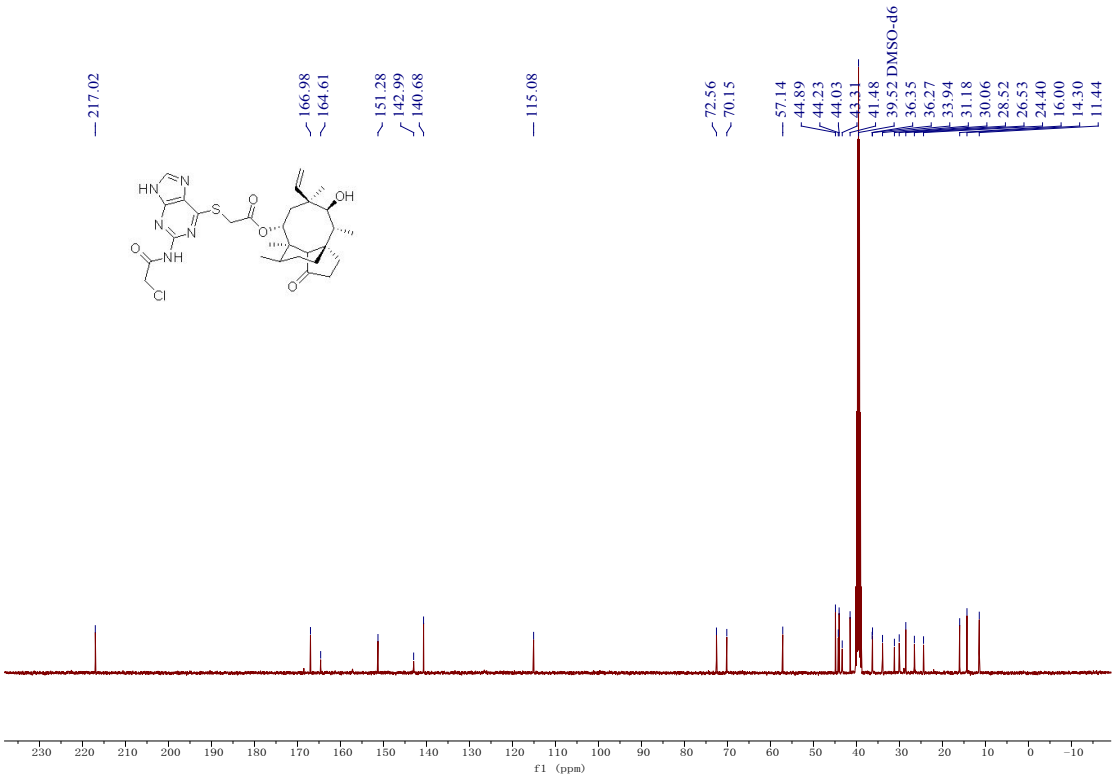
检测器A 254nm

Peak#	Ret. Time	Height	Area	Area%
1	3.002	3415	25711	0.066
2	3.313	7825	91346	0.234
3	3.866	1838	22227	0.057
4	12.271	1071688	38902486	99.643

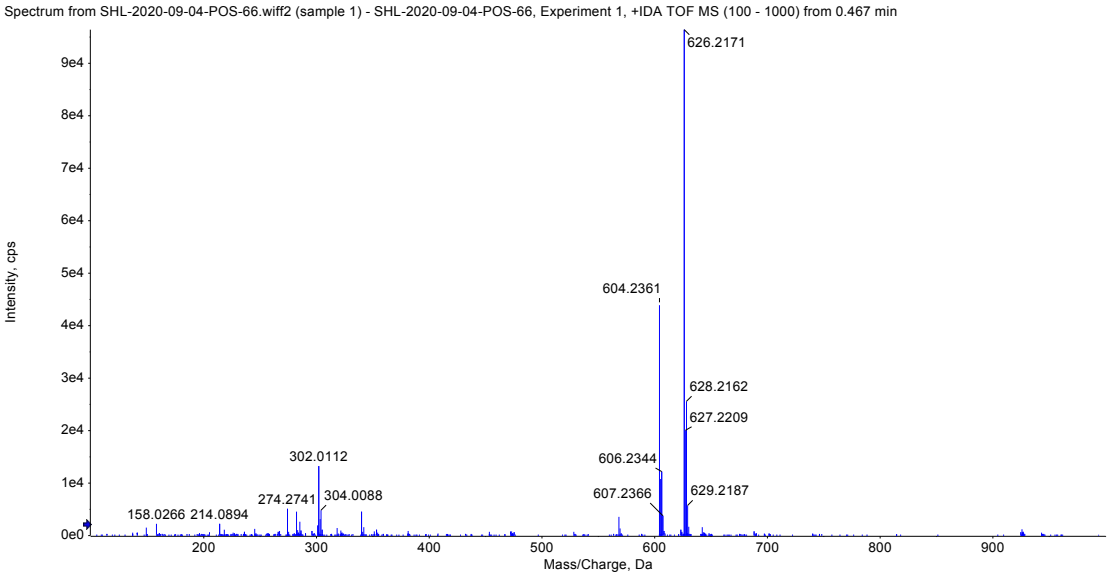
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **7**

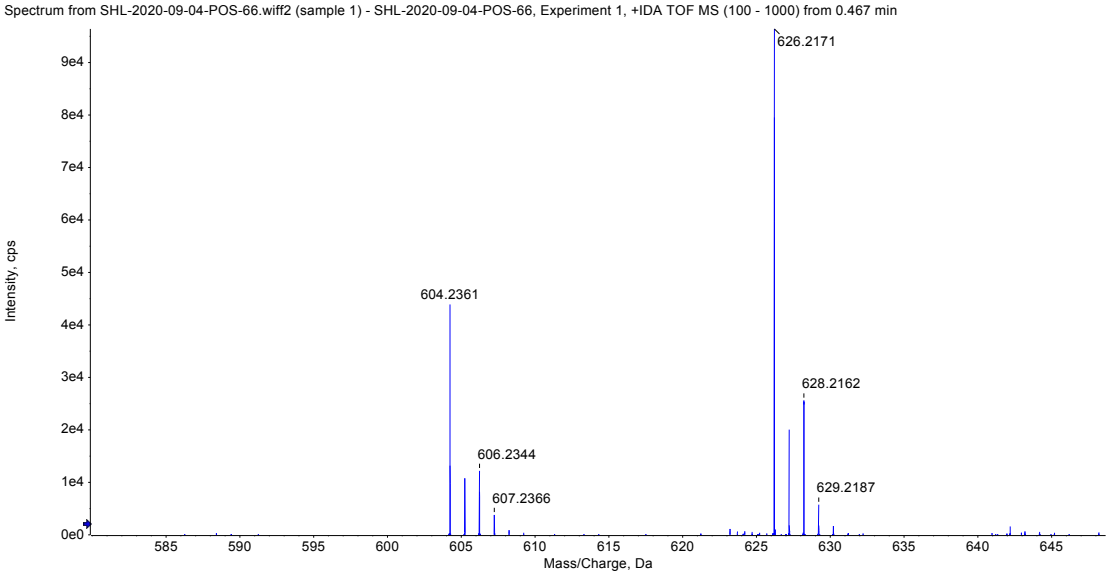


^{13}C NMR (101 MHz, DMSO-d_6) spectrum of 7



HRMS spectrum of **7**

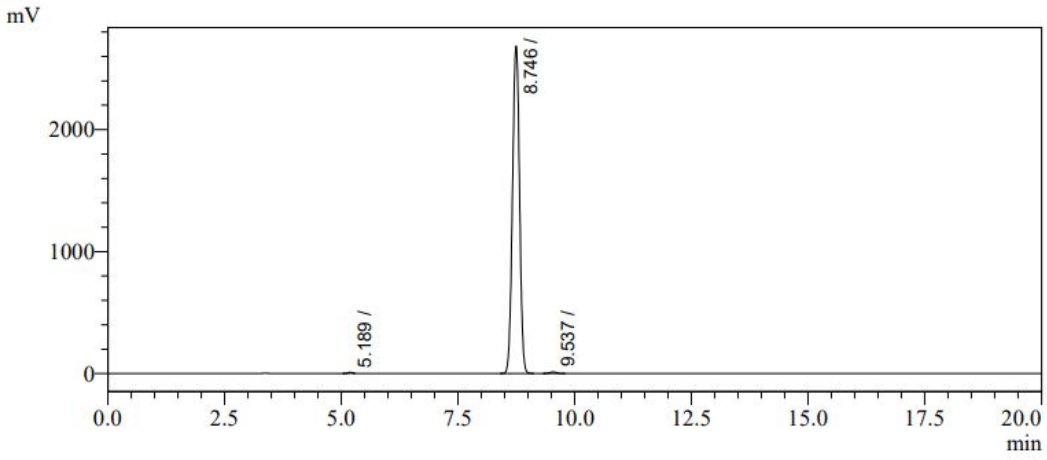




6. HPLC, ^{1}H NMR, ^{13}C NMR, HRMS, IR of all final compounds

Figure S3. HPLC, ^{1}H NMR, ^{13}C NMR, HRMS and IR spectrum of final compound **4a**

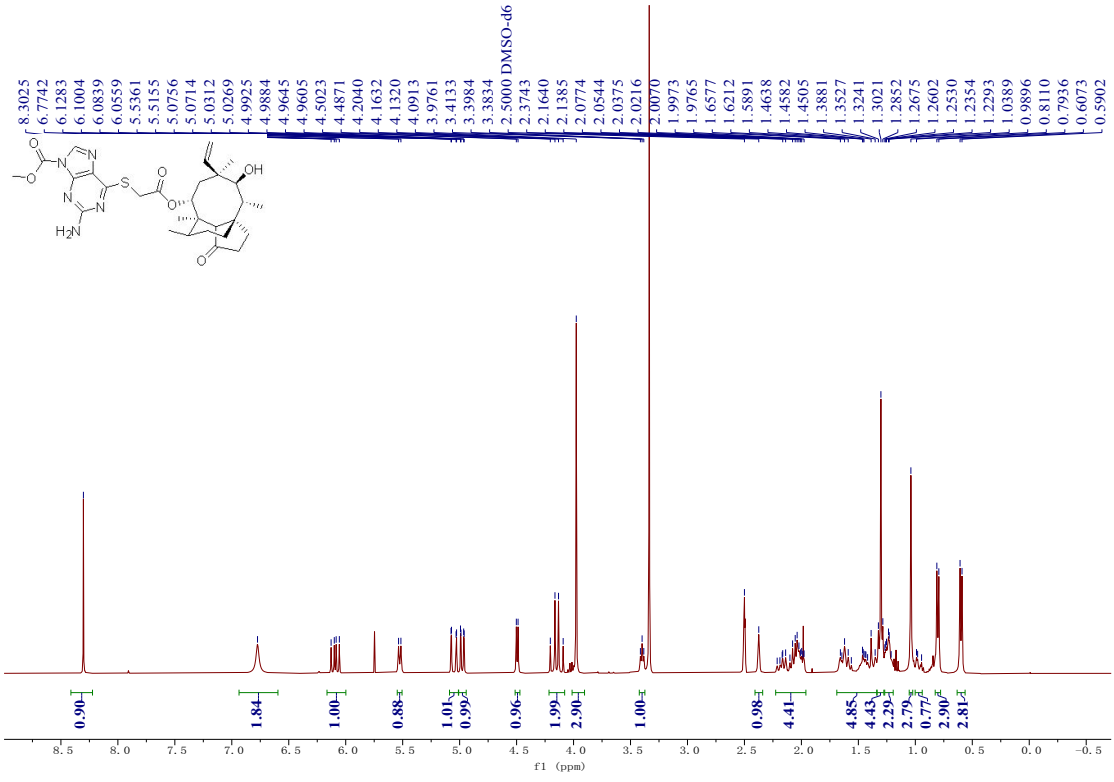
HPLC spectrum of **4a**



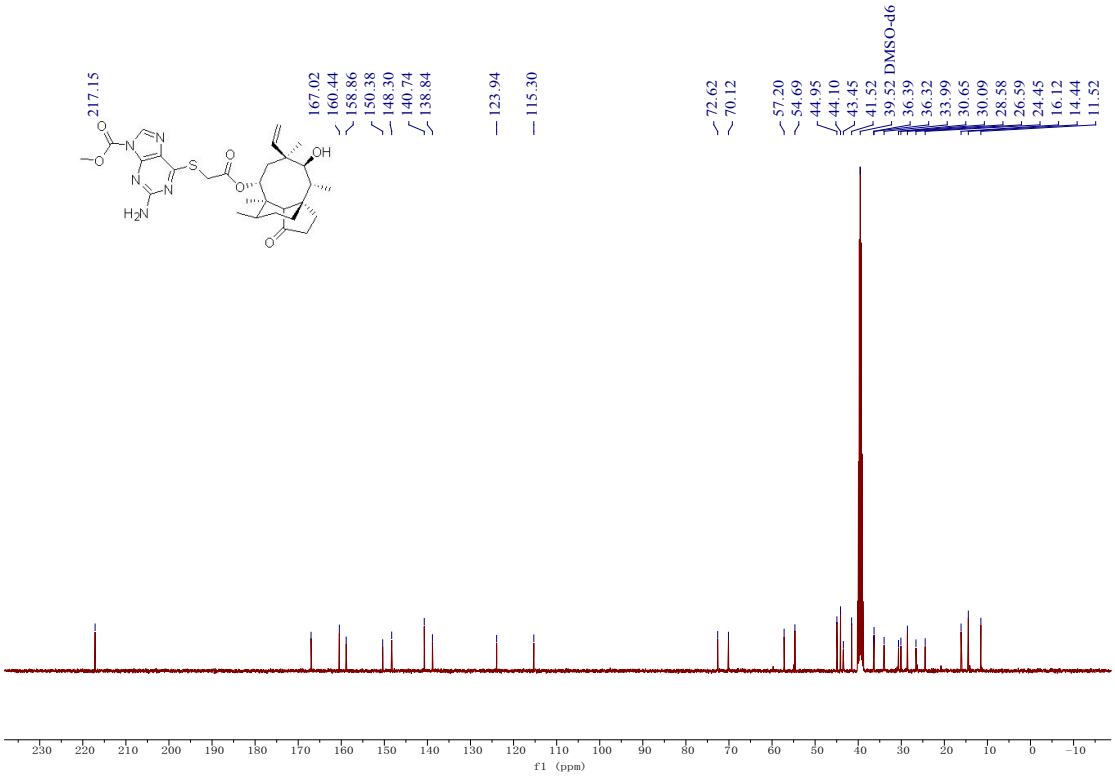
检测器A 254nm

Peak#	Ret. Time	Height	Area	Area%
1	5.189	8960	47476	0.167
2	8.746	2684074	28210906	99.365
3	9.537	12570	132744	0.468

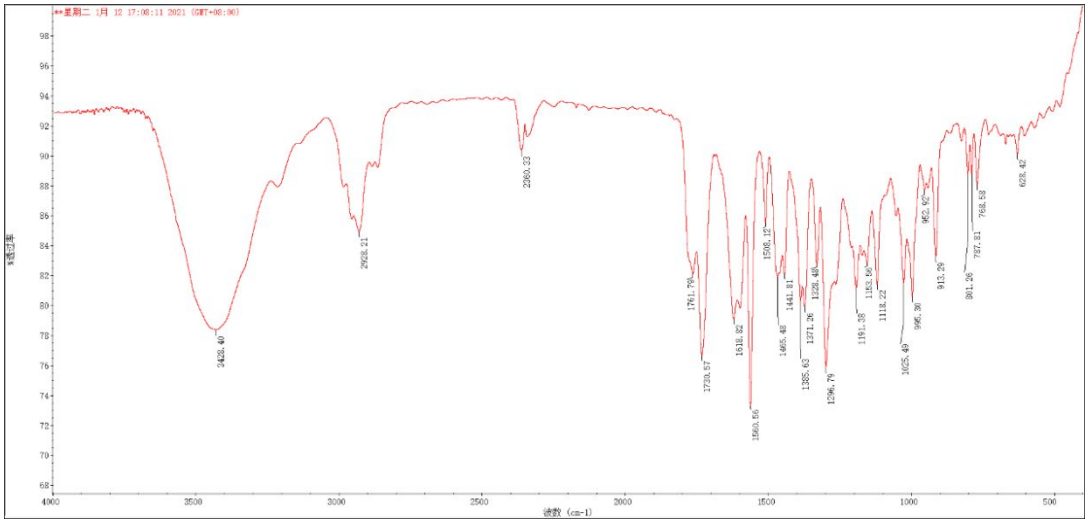
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **4a**



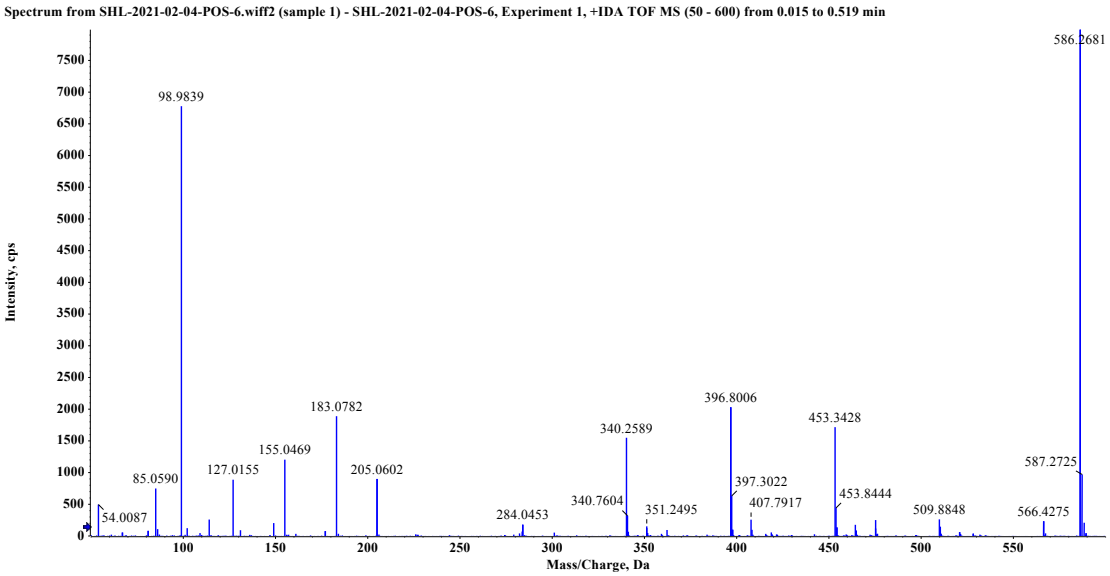
^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **4a**



IR (KBr, cm^{-1}) spectrum of **4a**



HRMS spectrum of **4a**



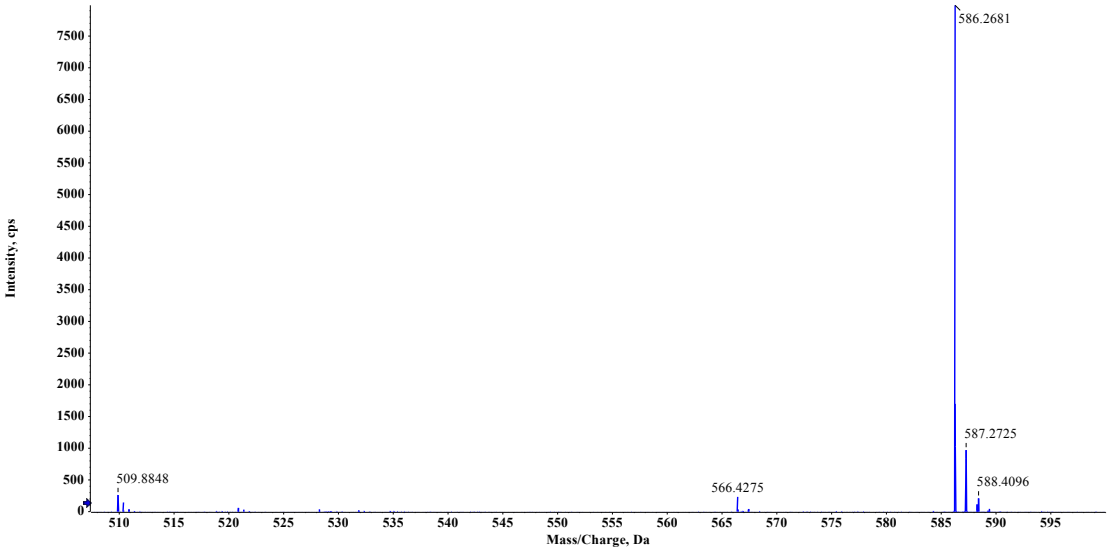
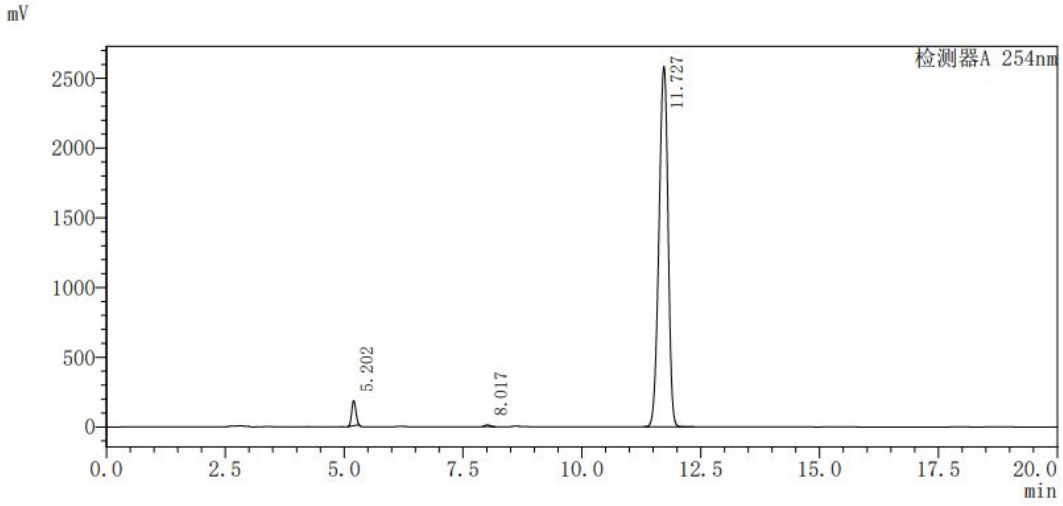


Figure S4. HPLC, ^{1}H NMR, ^{13}C NMR, HRMS and IR spectrum of final compound **4b**

HPLC spectrum of **4b**

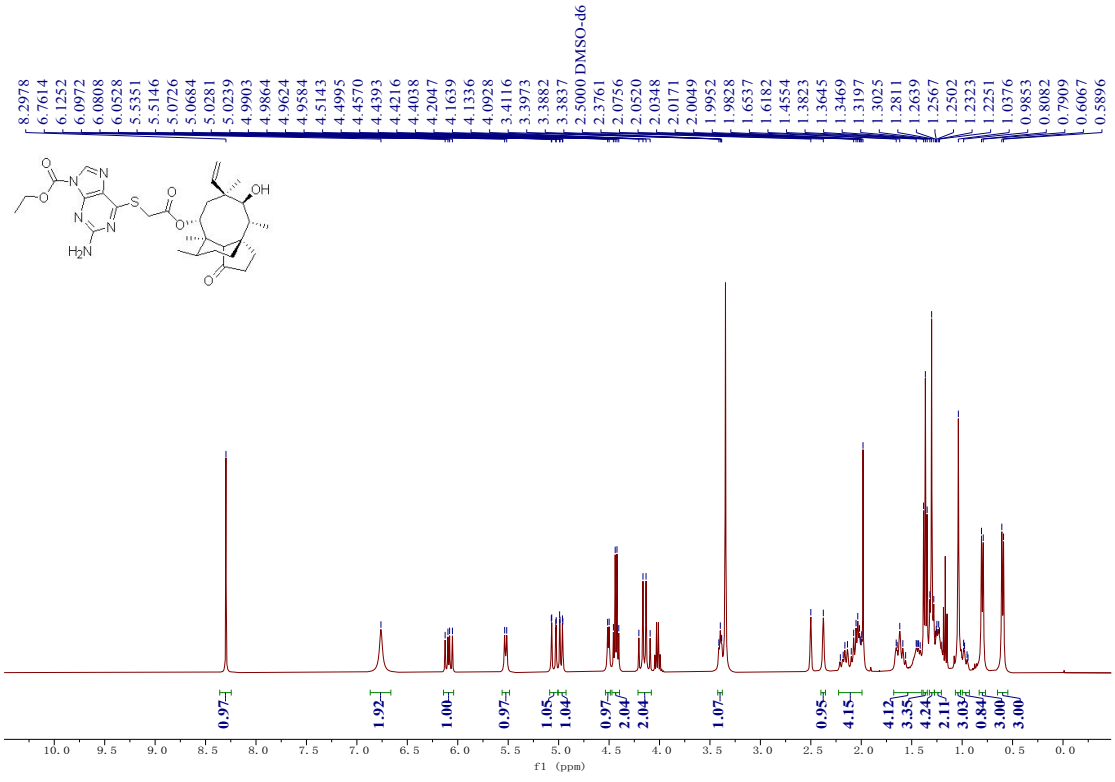


〈峰表〉

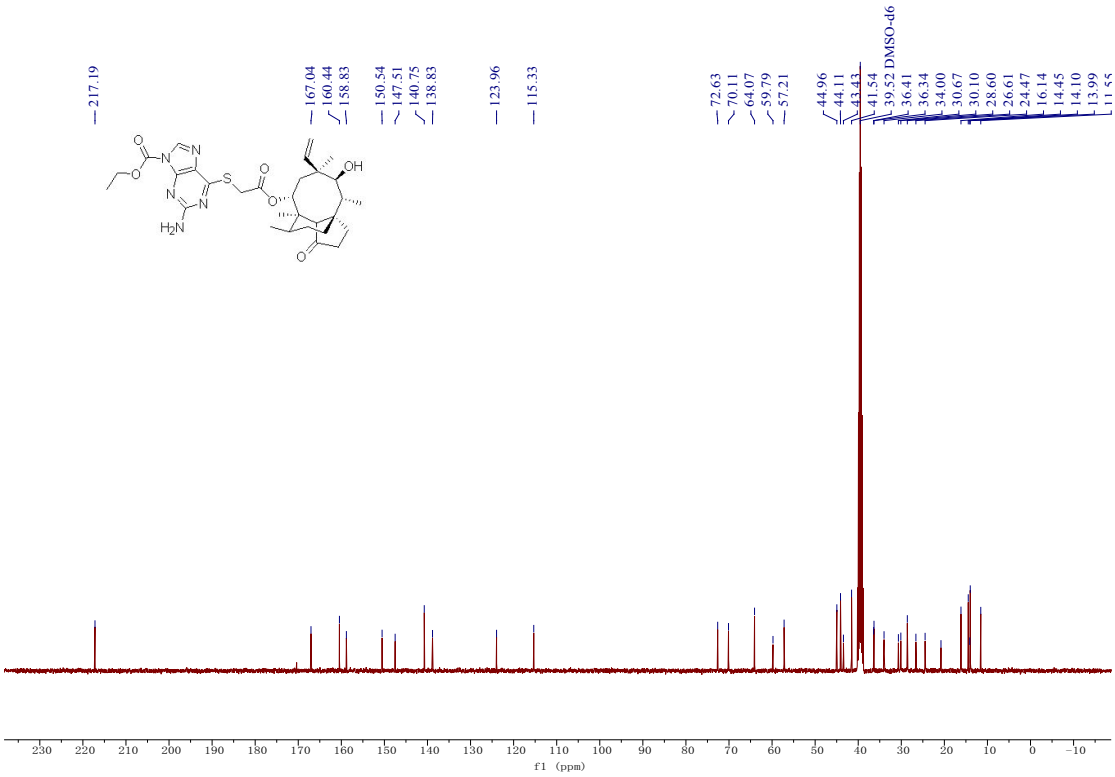
检测器A 254nm

峰号	保留时间	高度	面积	面积%
1	5.202	178402	1088453	3.068
2	8.017	10654	79449	0.224
3	11.727	2582646	34315418	96.709
总计		2771702	35483320	100.000

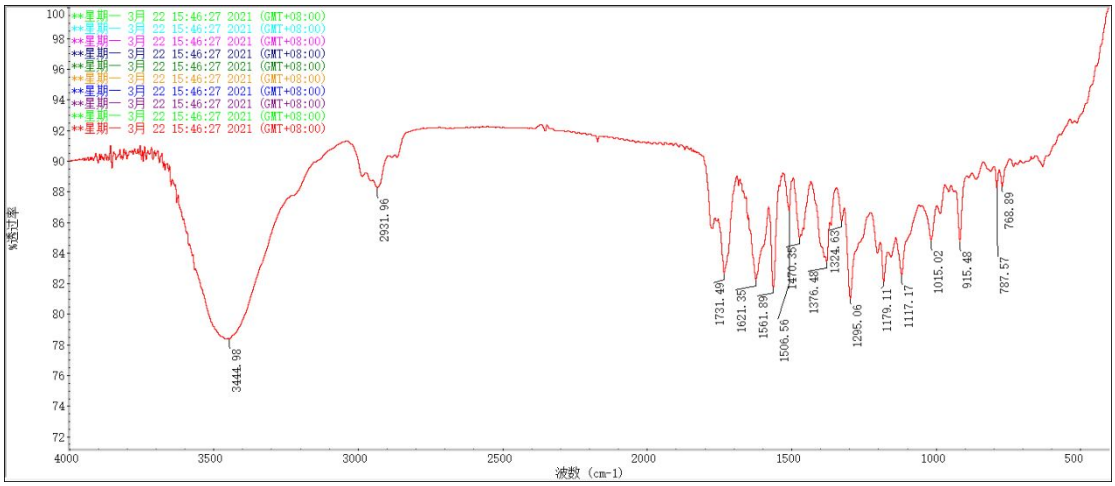
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **4b**



^{13}C NMR (101 MHz, DMSO-d_6) spectrum of spectrum 4b



IR (KBr, cm^{-1}) spectrum of **4b**



HRMS spectrum of **4b**

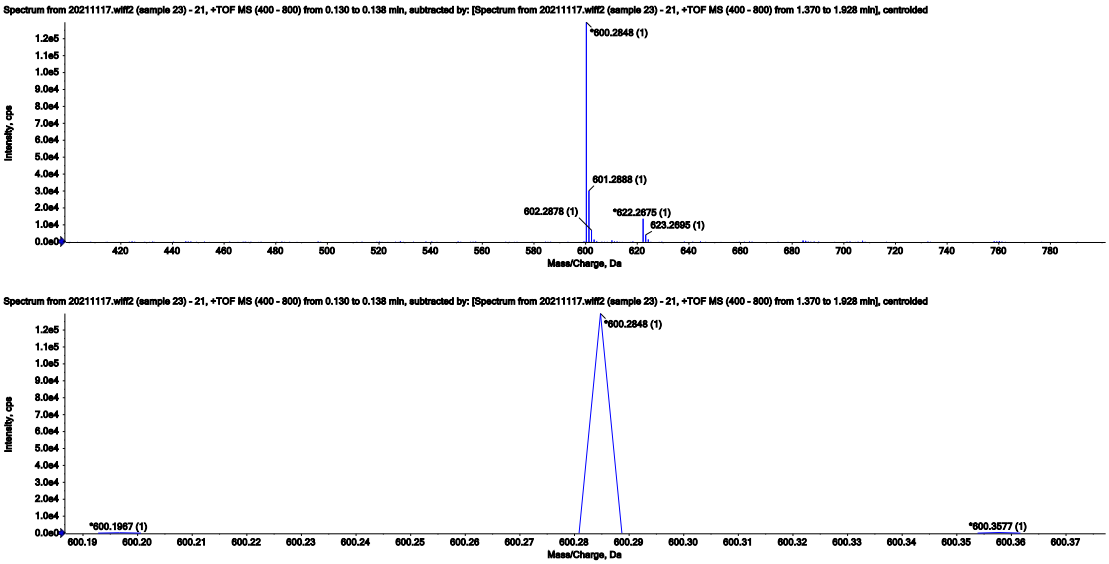
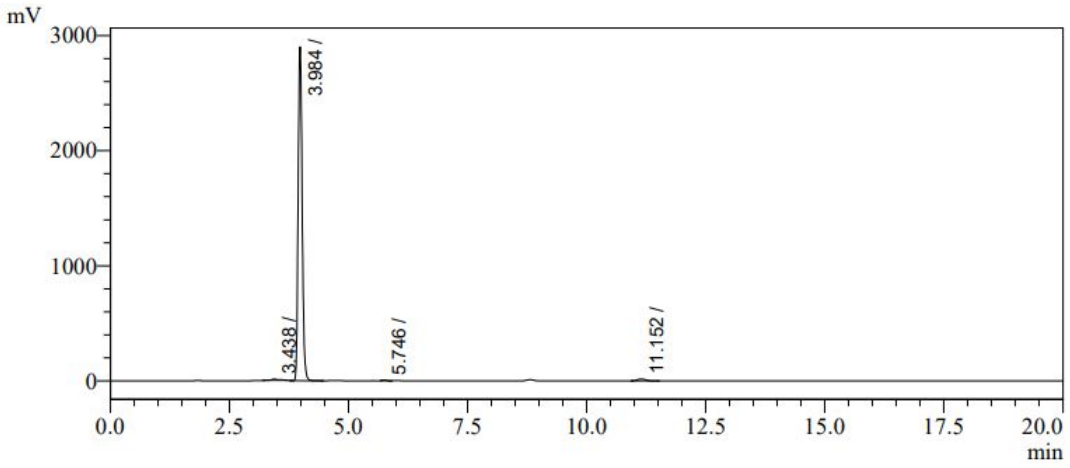


Figure S5. HPLC, ^{1}H NMR, ^{13}C NMR, HRMS and IR spectrum of final compound **5a**

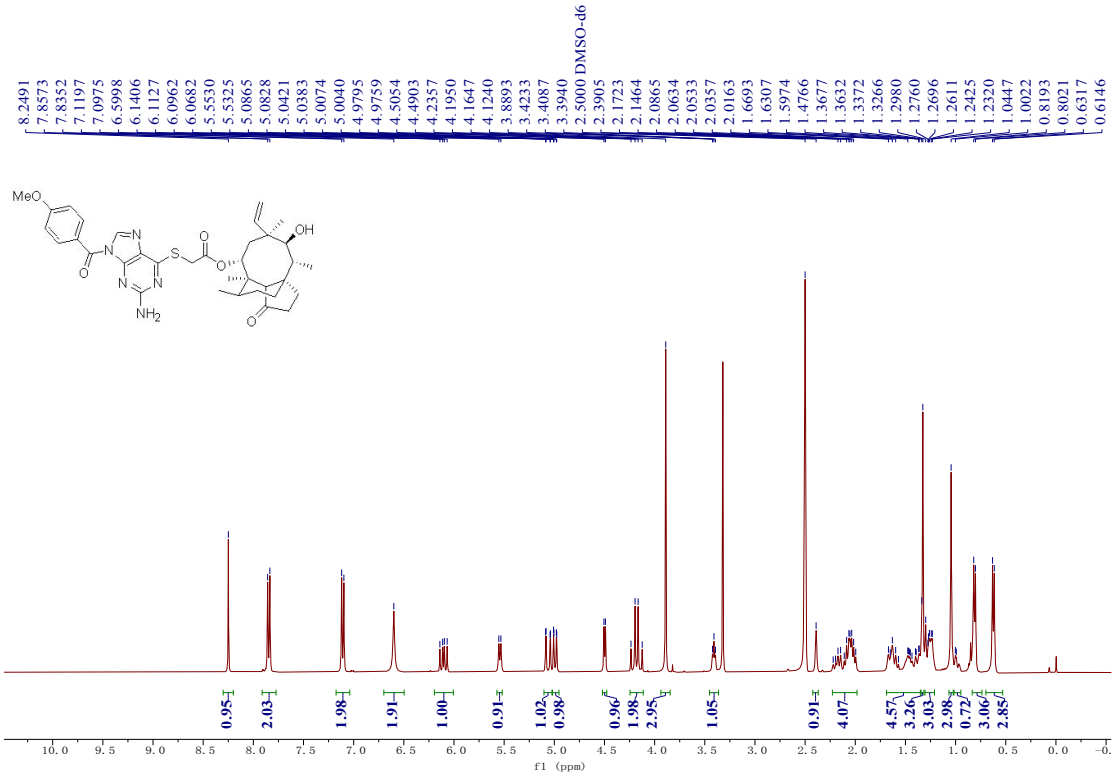
HPLC spectrum of **5a**



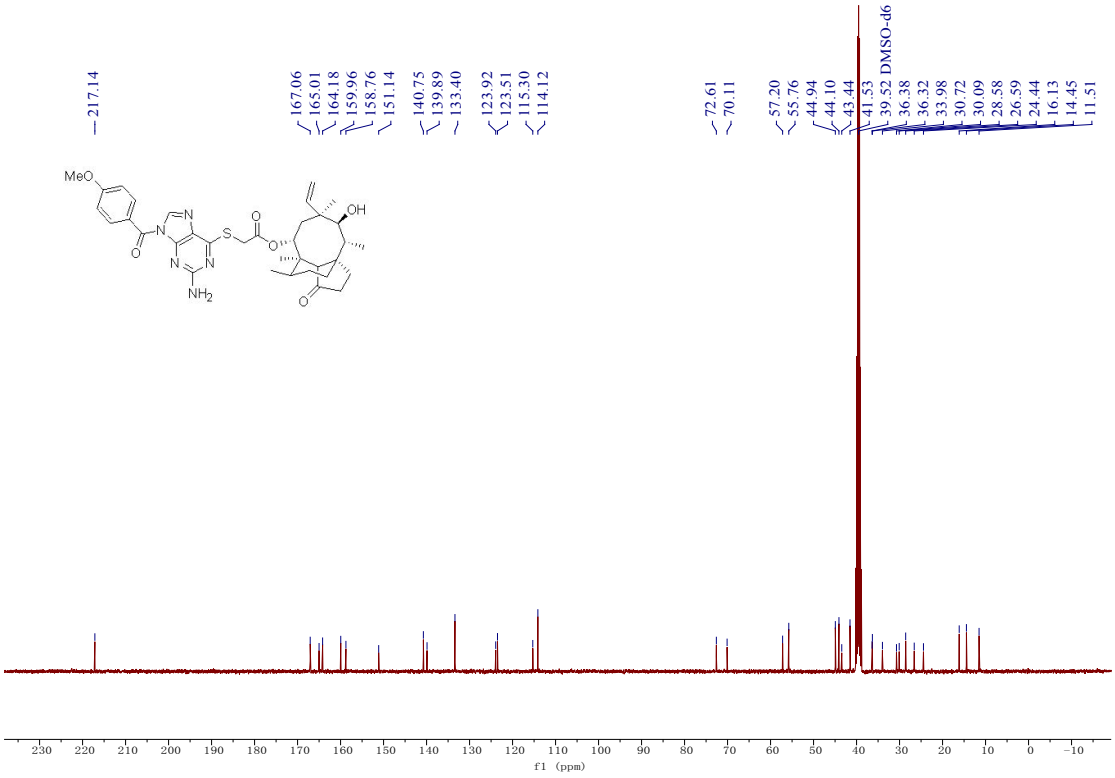
检测器A 254nm

Peak#	Ret. Time	Height	Area	Area%
1	3.438	10302	112504	0.652
2	3.984	2900213	16919123	98.054
3	5.746	4627	27199	0.158
4	11.152	15818	196161	1.137

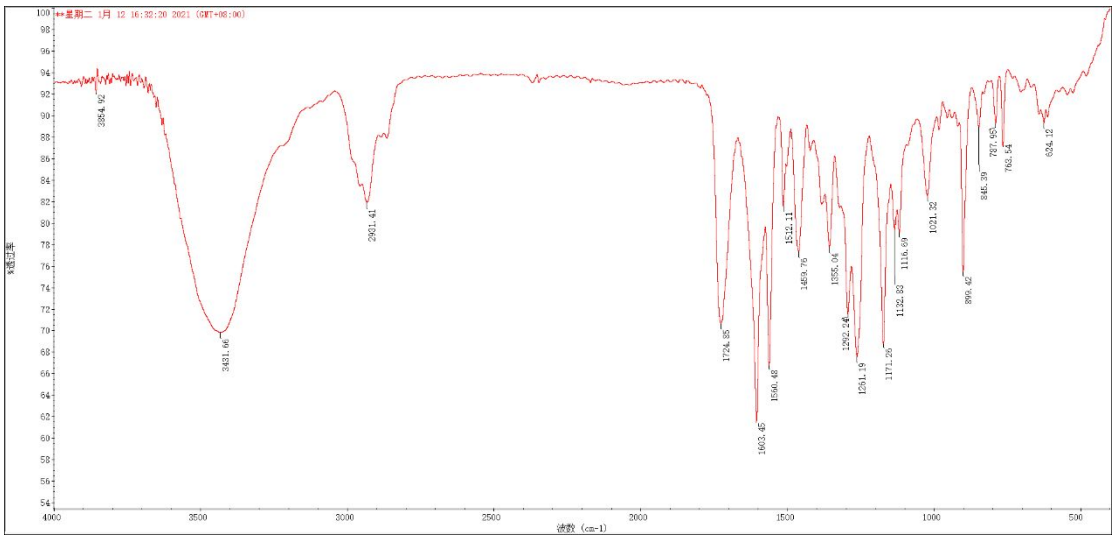
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **5a**



^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **5a**



IR (KBr, cm^{-1}) spectrum of **5a**



HRMS spectrum of **5a**

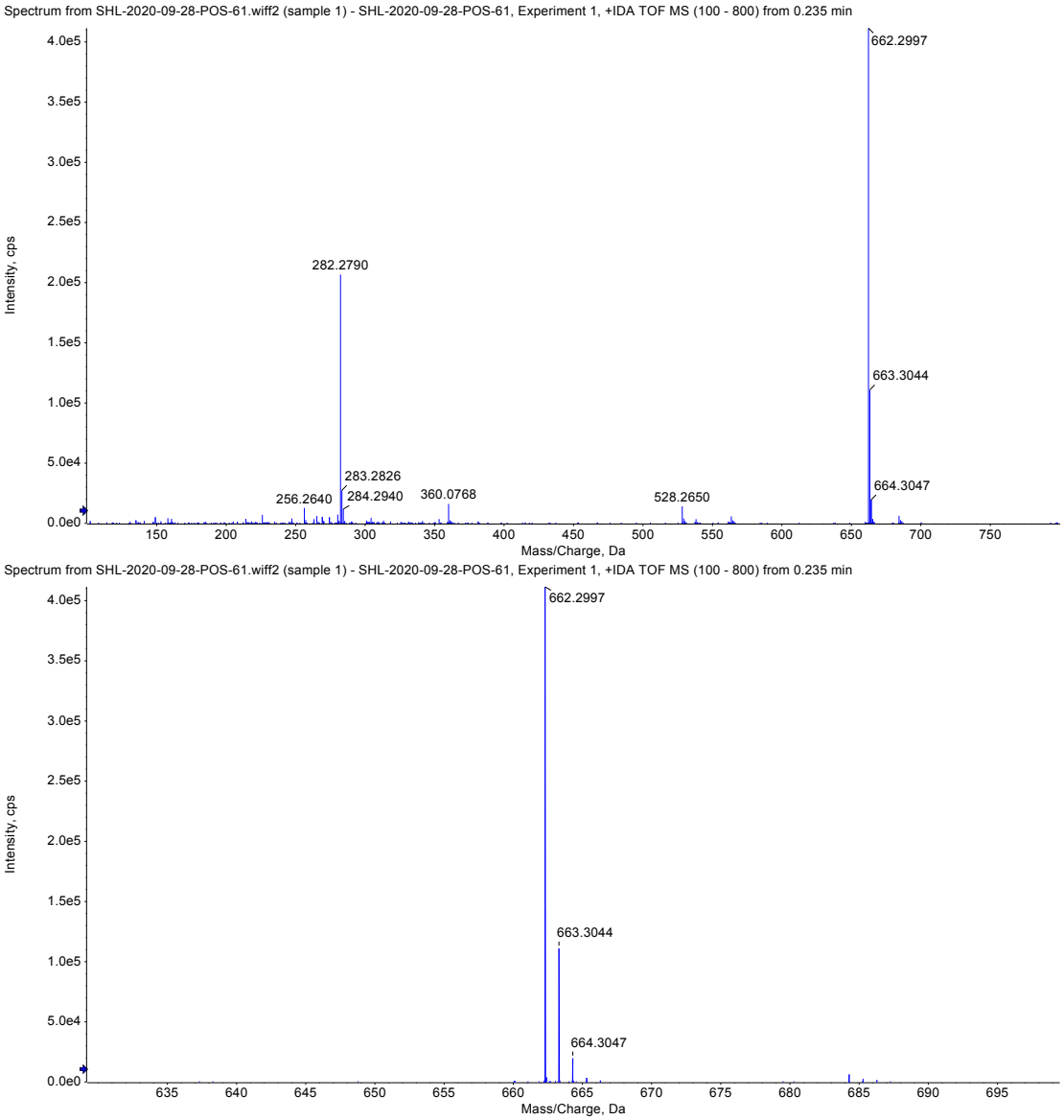
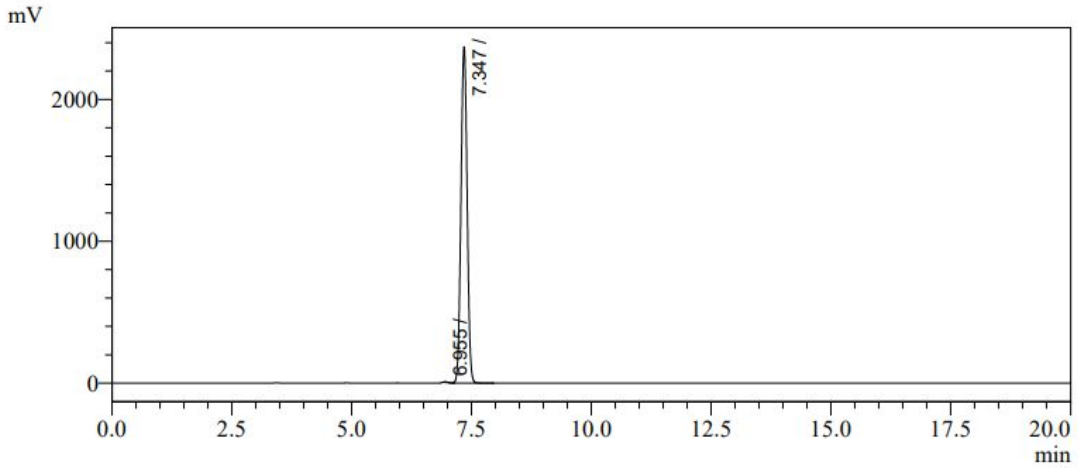


Figure S6. HPLC, ^{1}H NMR, ^{13}C NMR, HRMS and IR spectrum of final compound **5b**

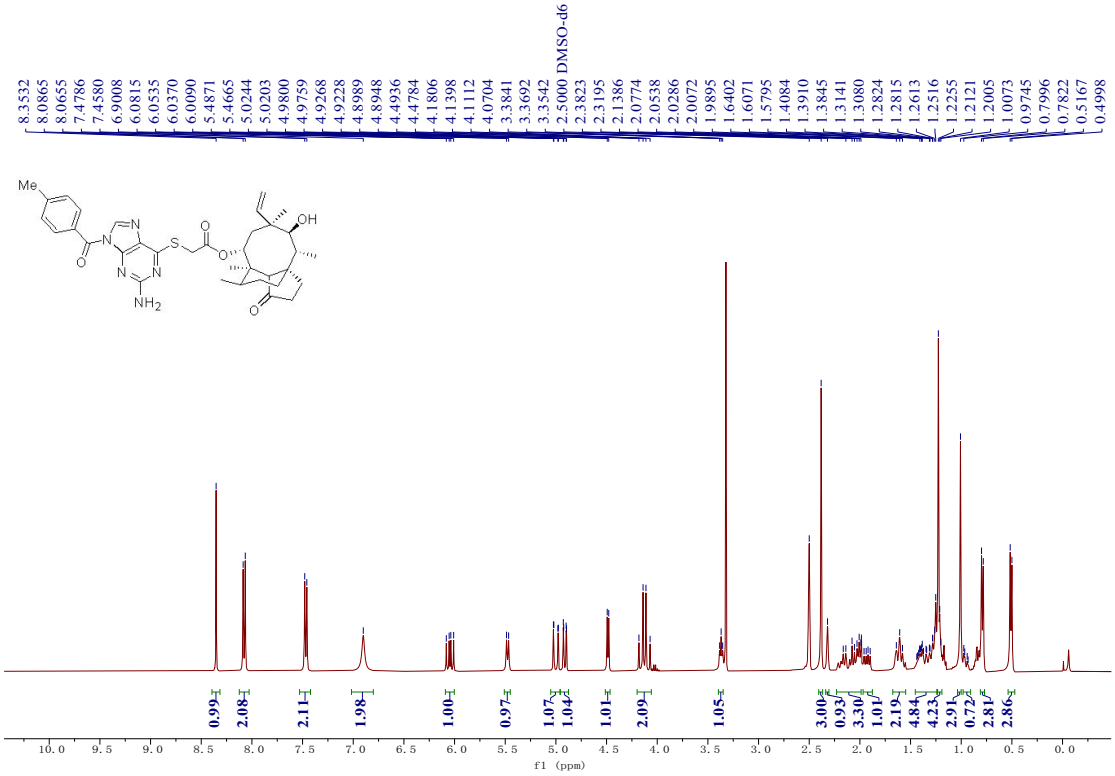
HPLC spectrum of **5b**



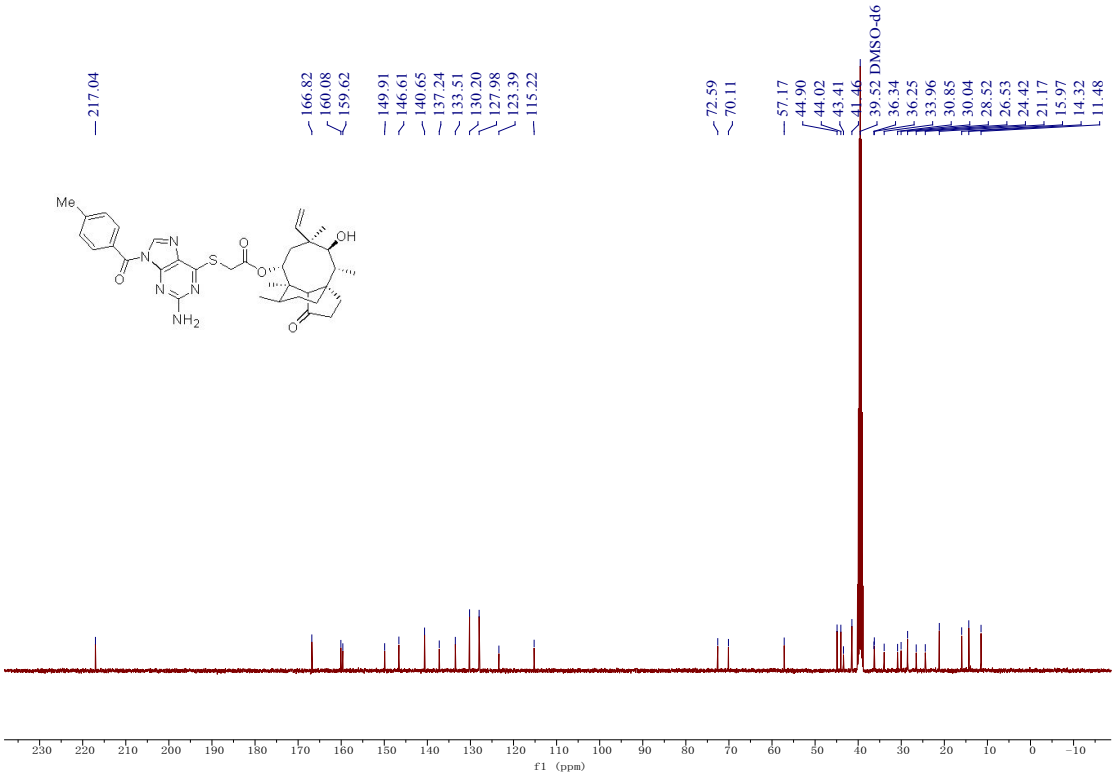
检测器A 254nm

Peak#	Ret. Time	Height	Area	Area%
1	6.955	5662	30803	0.145
2	7.347	2369803	21189052	99.855

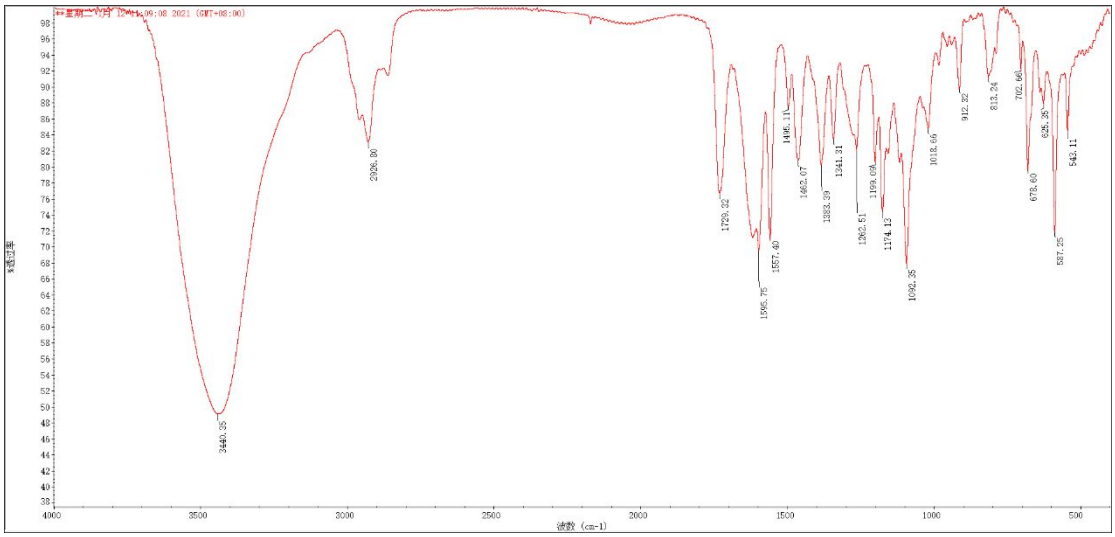
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **5b**



^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **5b**



IR (KBr, cm^{-1}) spectrum of **5b**



HRMS spectrum of **5b**

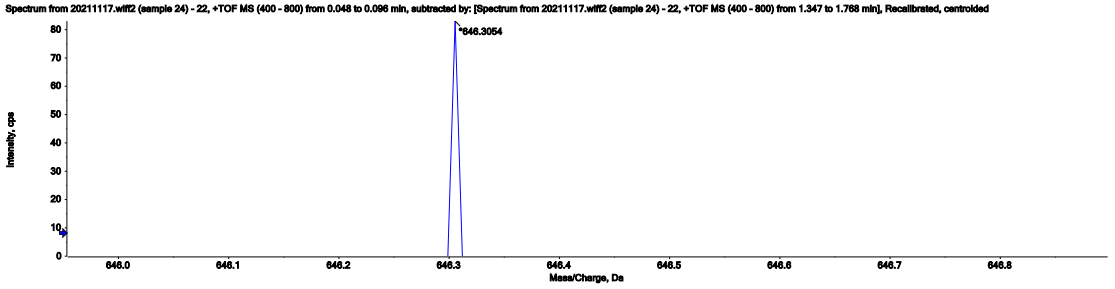
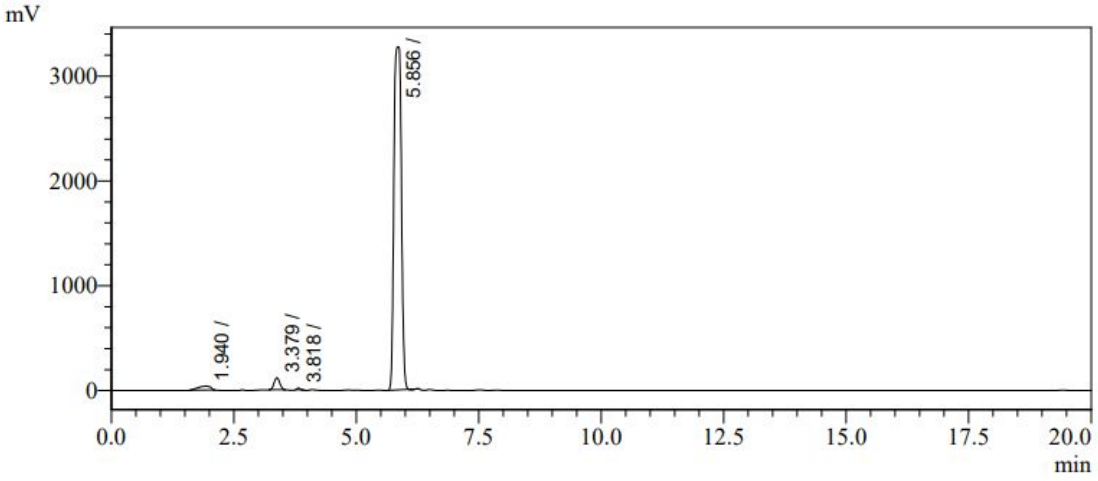


Figure S7. HPLC, ^{1}H NMR, ^{13}C NMR, HRMS and IR spectrum of final compound **5c**

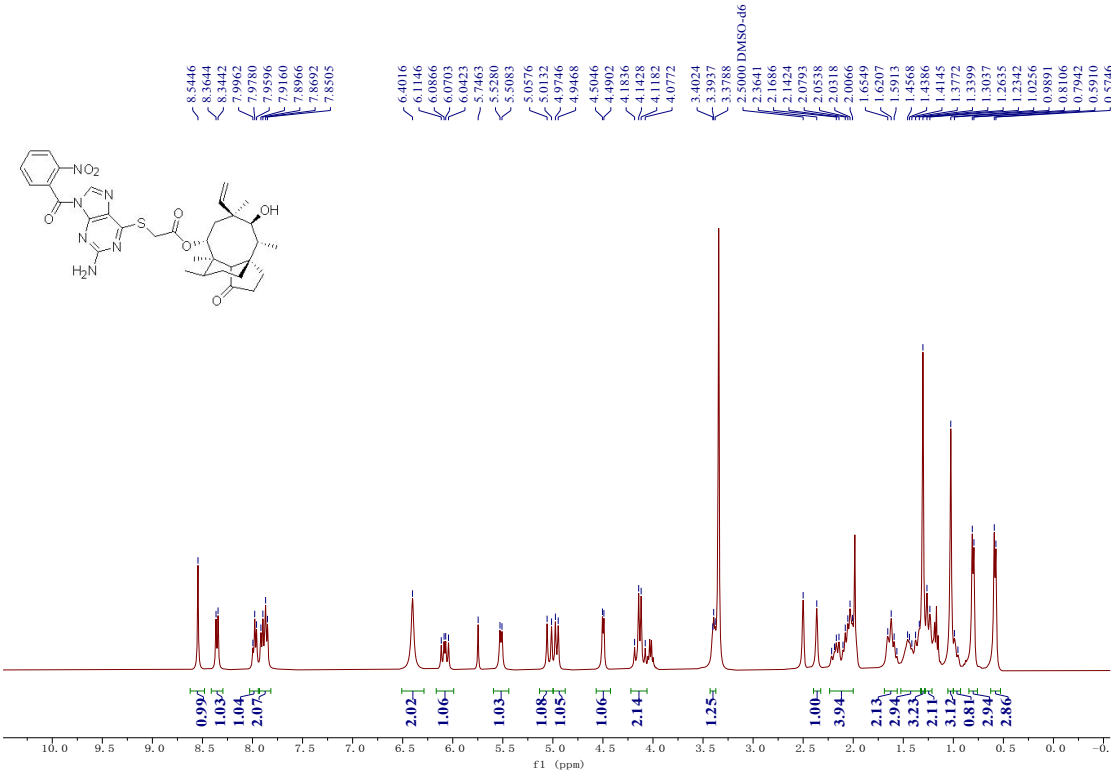
HPLC spectrum of **5c**



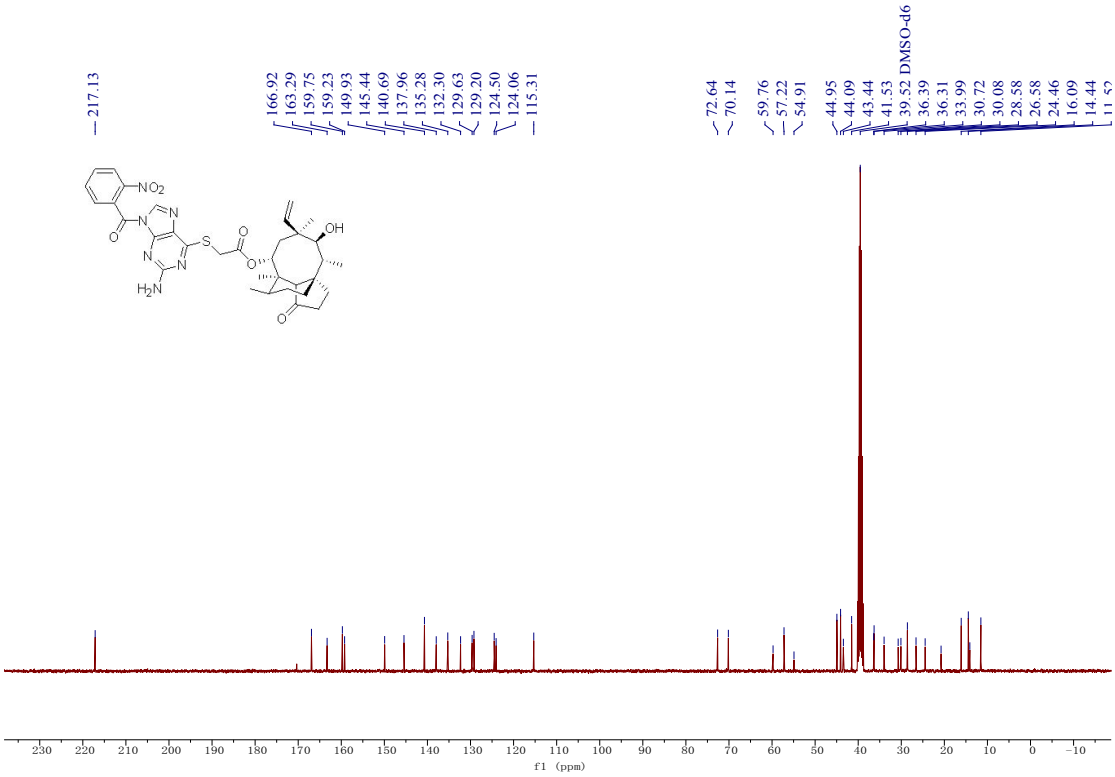
检测器A 254nm

Peak#	Ret. Time	Height	Area	Area%
1	1.940	37808	645656	1.796
2	3.379	111928	892018	2.481
3	3.818	14032	54636	0.152
4	5.856	3274281	34358946	95.571

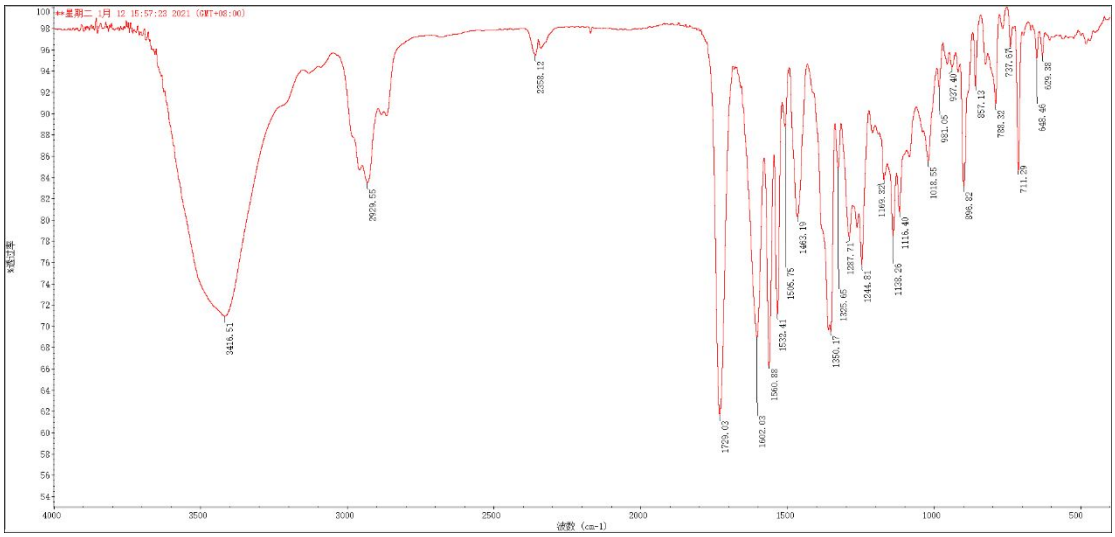
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **5c**



^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **5c**



IR (KBr, cm^{-1}) spectrum of **5c**



HRMS spectrum of **5c**

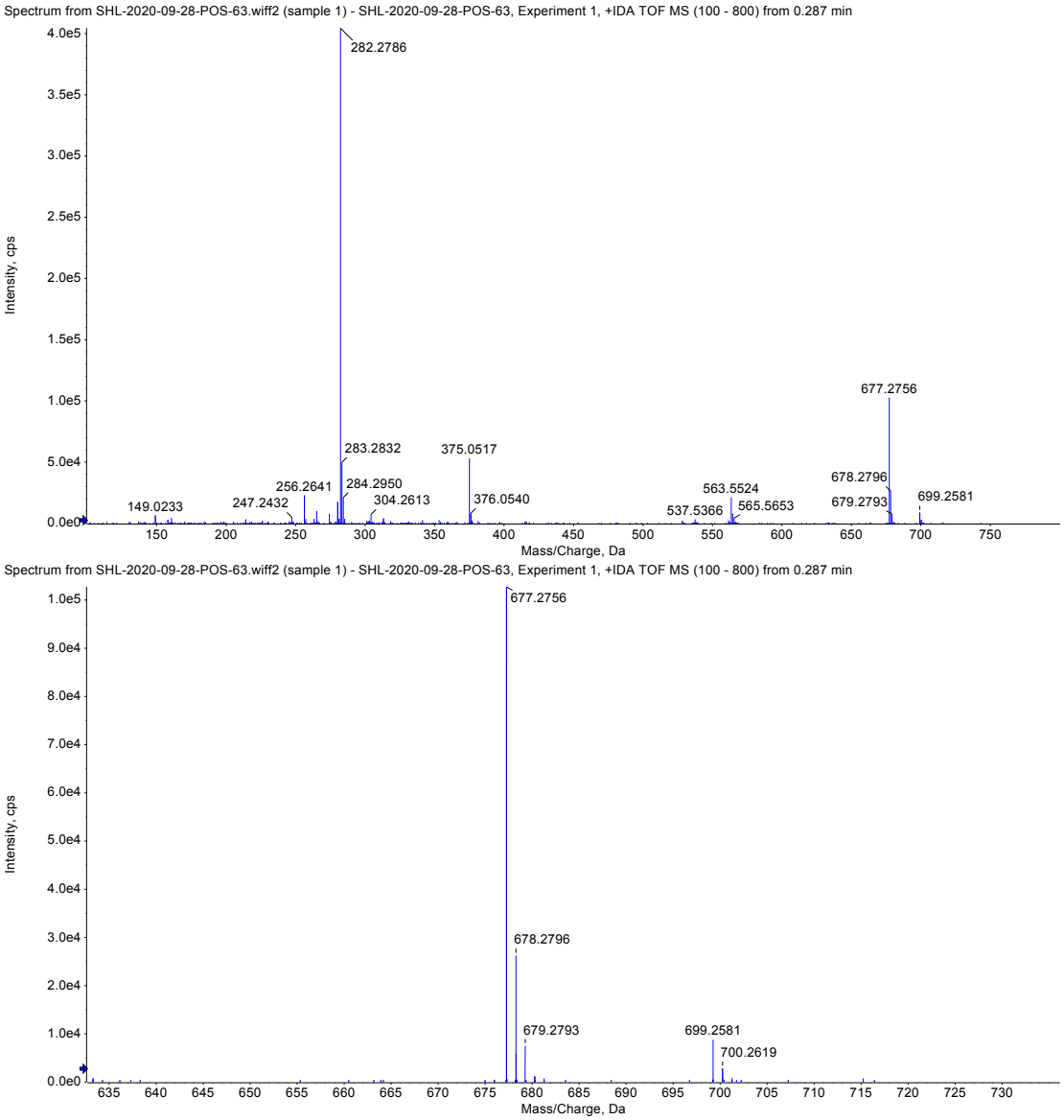
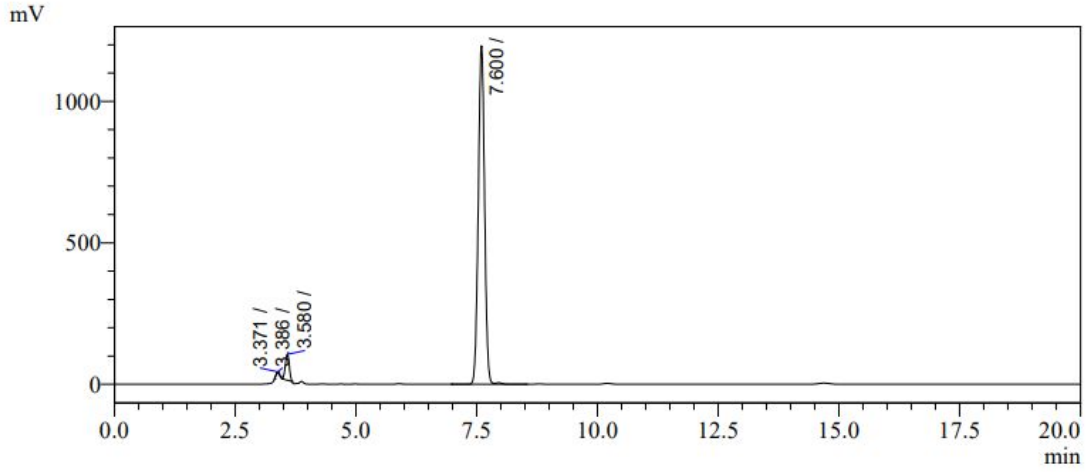


Figure S8. HPLC, ^{1}H NMR, ^{13}C NMR, HRMS and IR spectrum of final compound **5d**

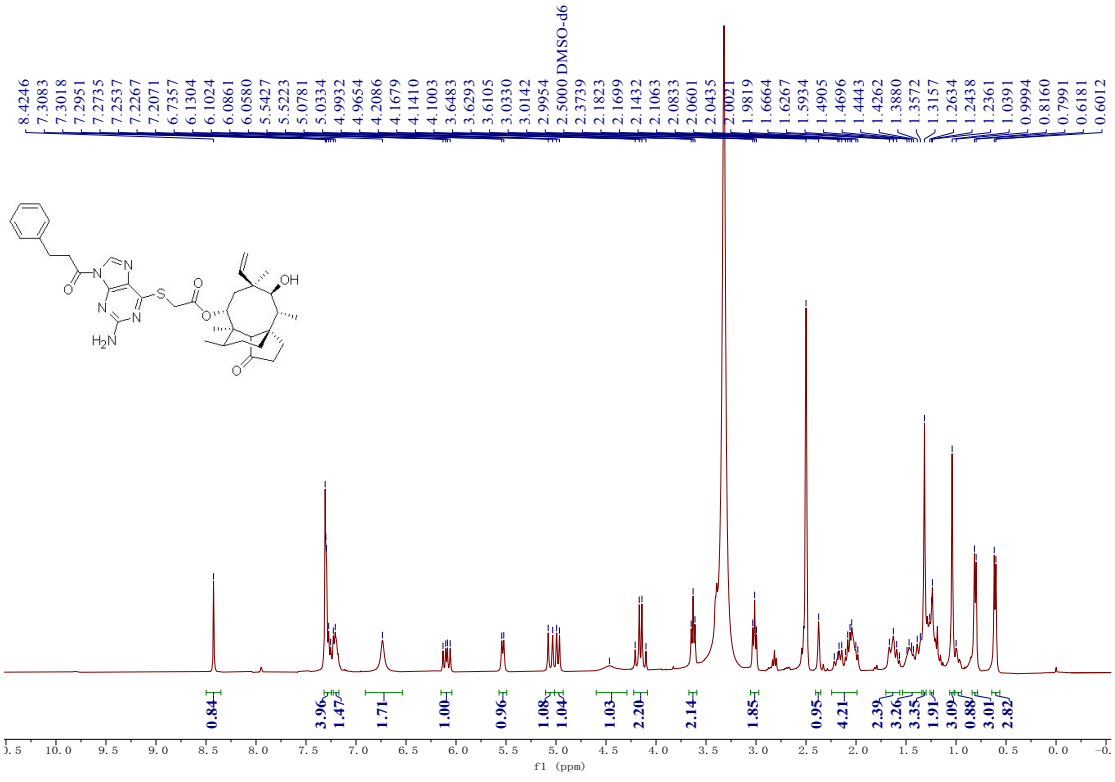
HPLC spectrum of **5d**



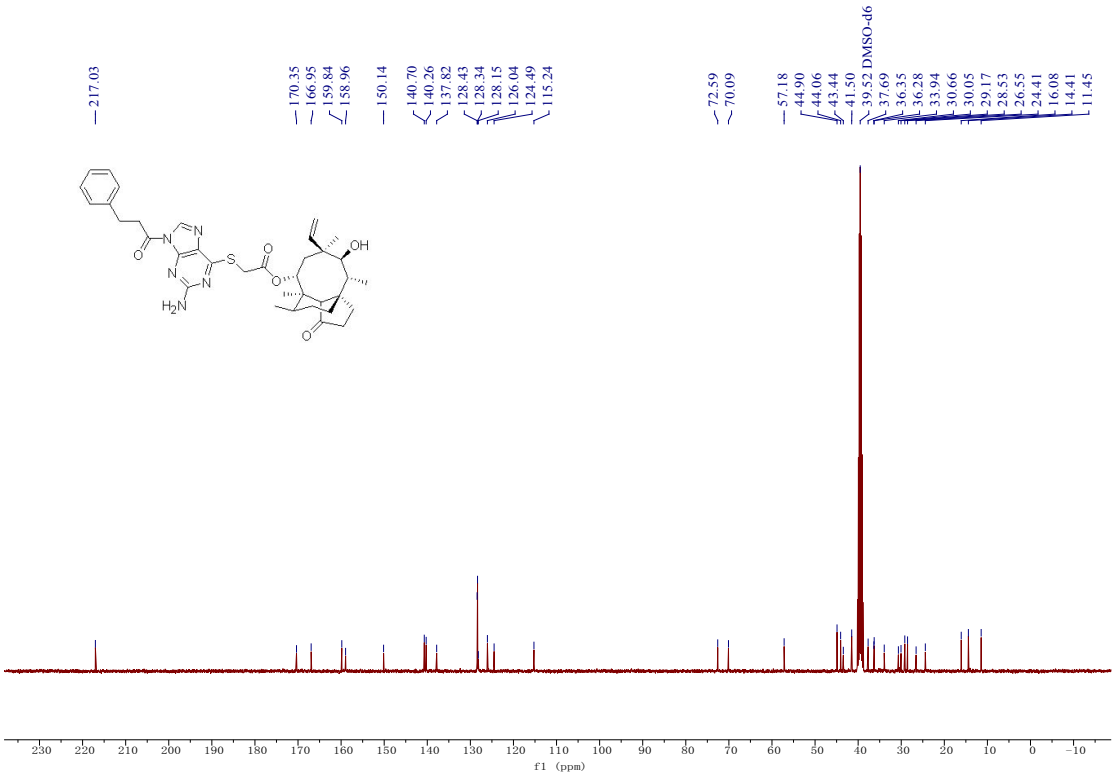
检测器A 254nm

Peak#	Ret. Time	Height	Area	Area%
1	3.371	-203	10839	0.095
2	3.386	3818	10120	0.089
3	3.580	91208	518421	4.555
4	7.600	1196853	10842553	95.261

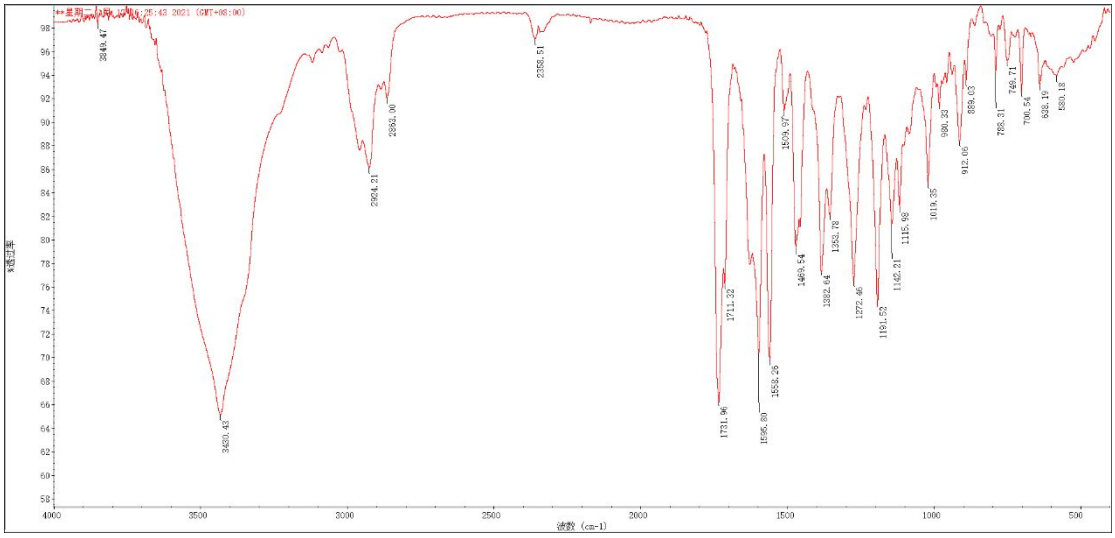
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **5d**



^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **5d**



IR (KBr, cm^{-1}) spectrum of **5d**



HRMS spectrum of **5d**

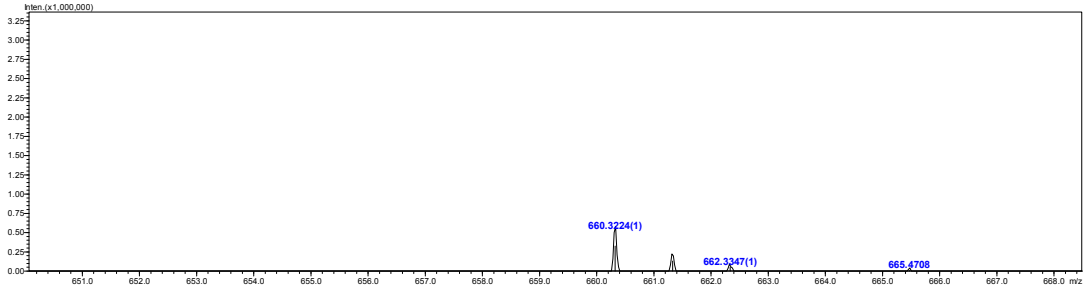
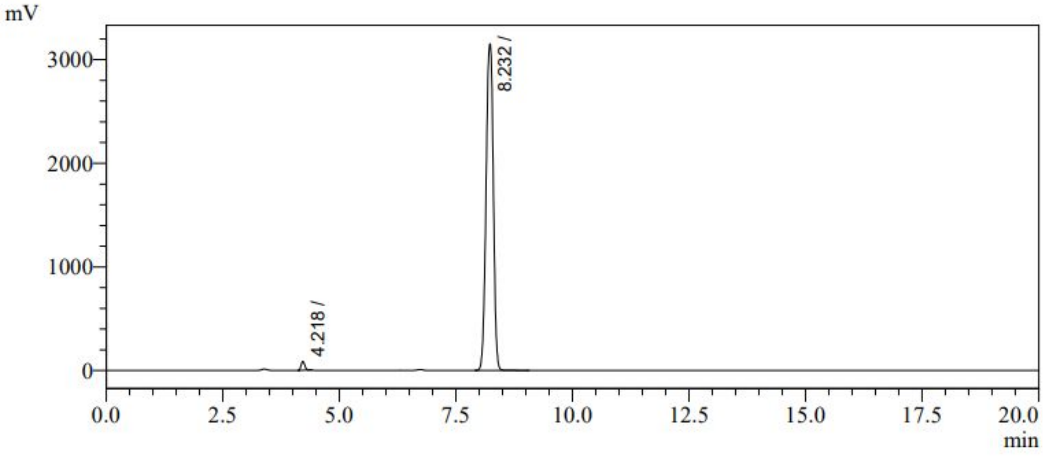


Figure S9. HPLC, ^{1}H NMR, ^{13}C NMR, HRMS and IR spectrum of final compound **6a**

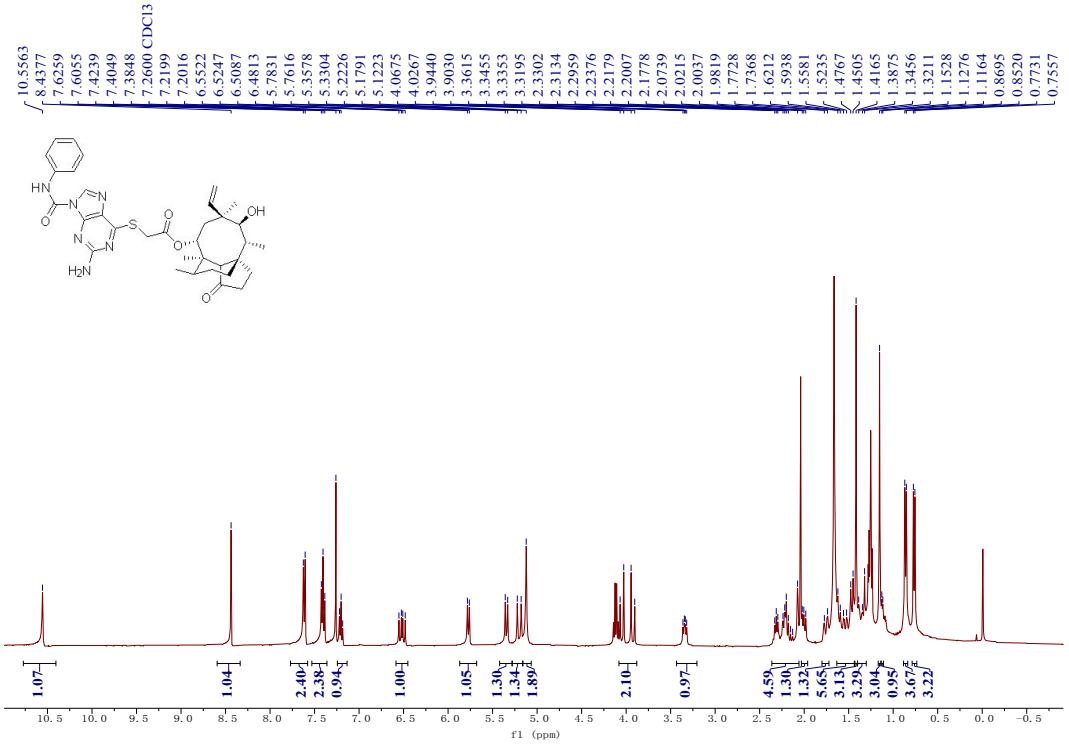
HPLC spectrum of **6a**



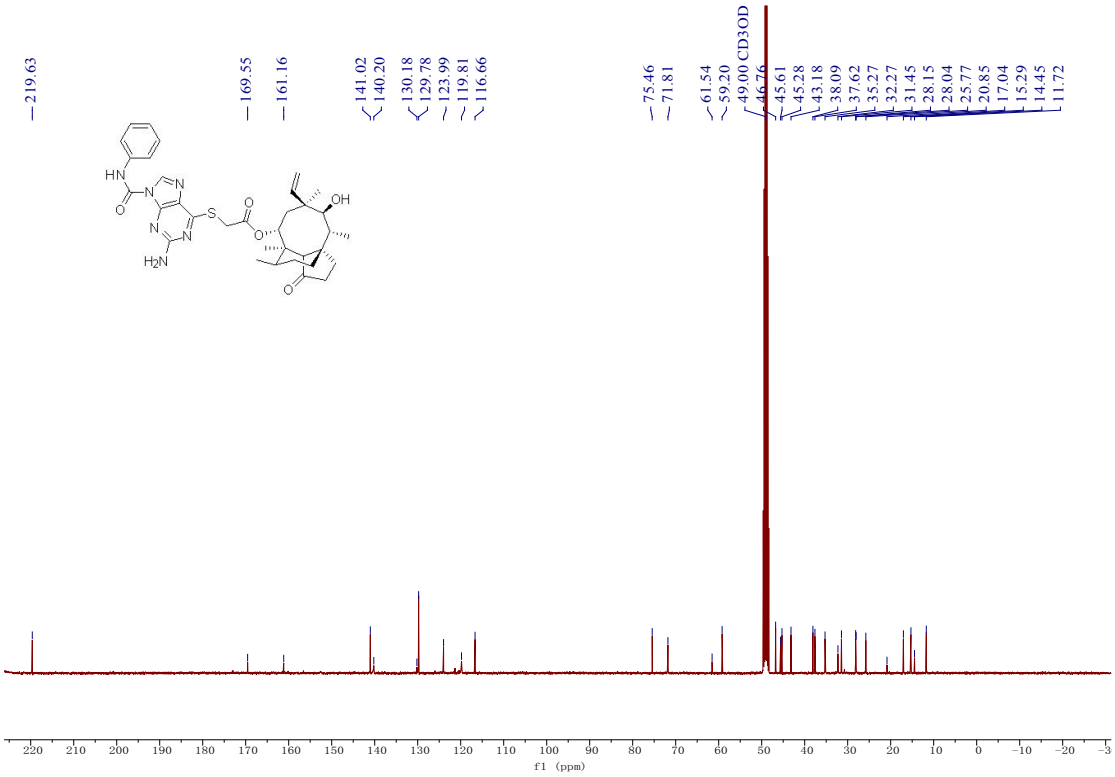
检测器A 254nm

Peak#	Ret. Time	Height	Area	Area%
1	4.218	85970	466259	1.357
2	8.232	3154092	33900460	98.643

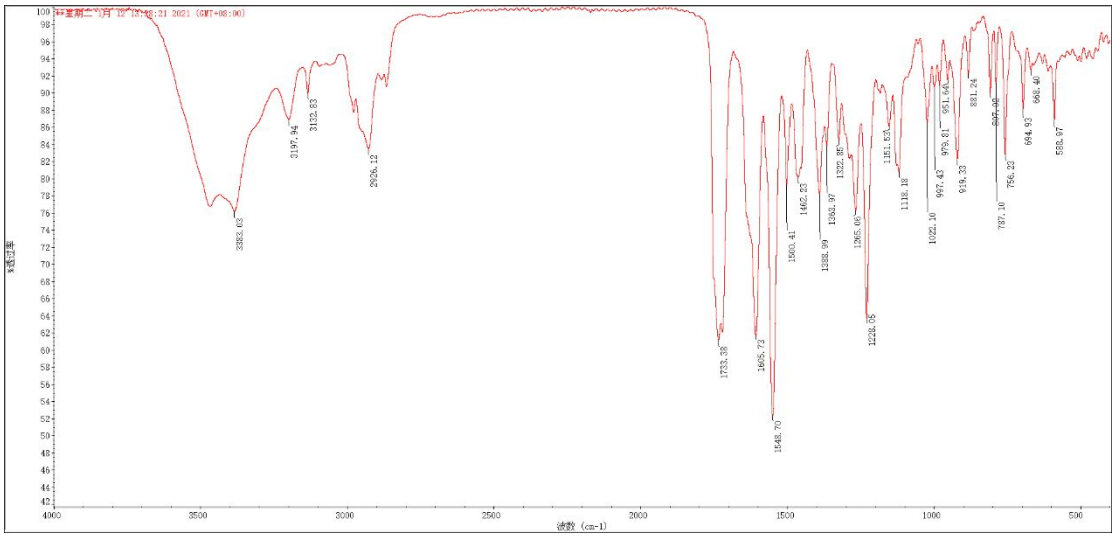
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **6a**



^{13}C NMR (101 MHz, $CDCl_3$) spectrum of **6a**



IR (KBr, cm^{-1}) spectrum of **6a**



HRMS spectrum of **6a**

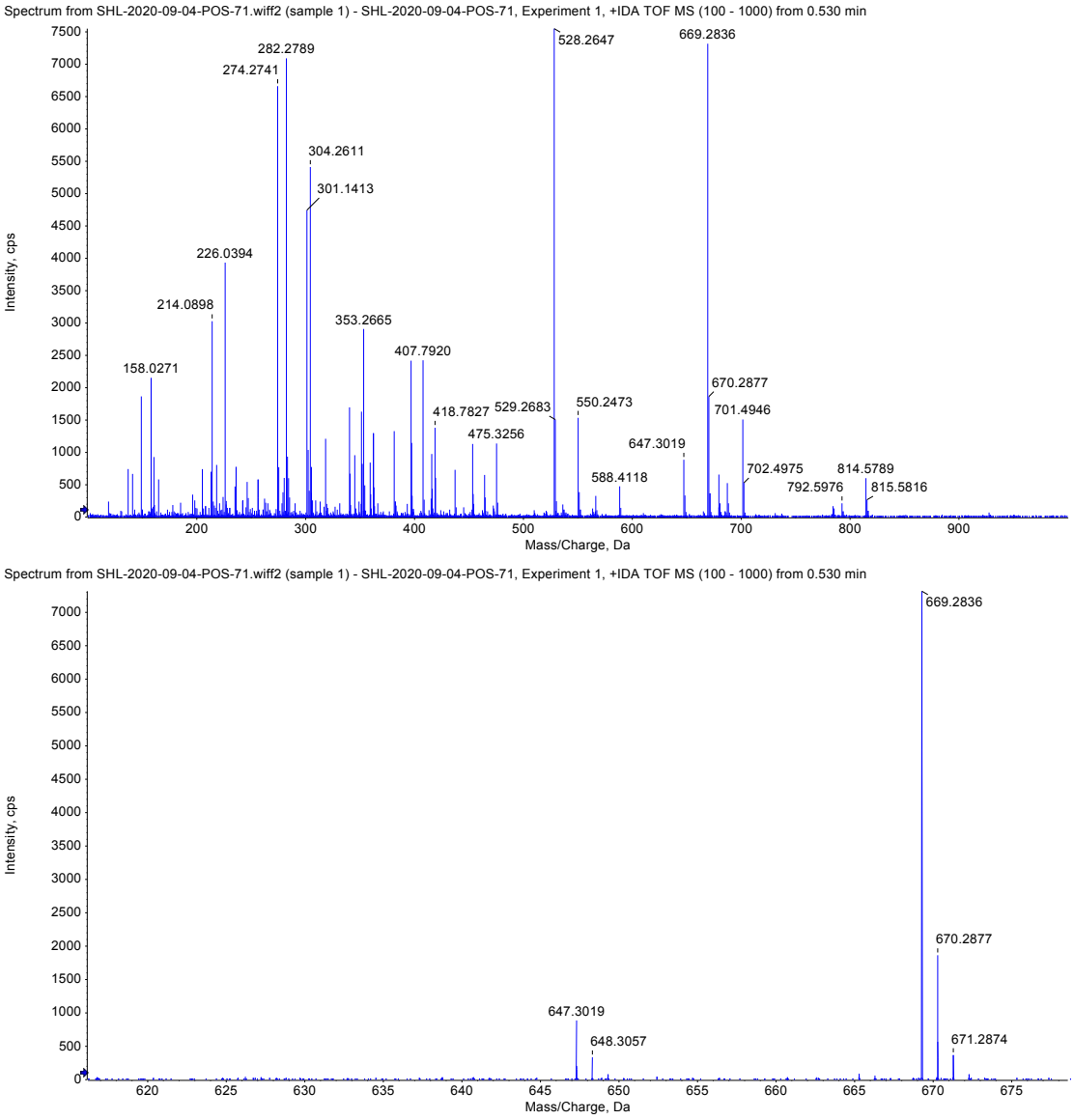
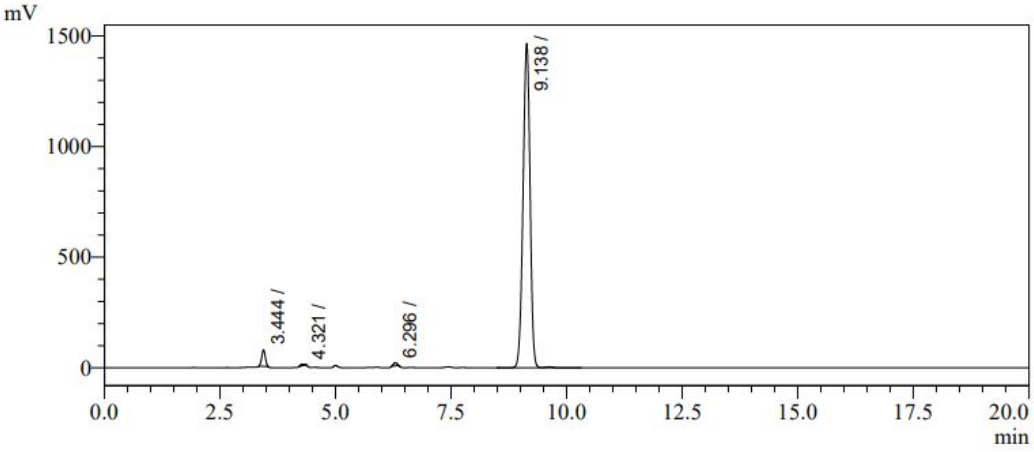


Figure S10. HPLC, ^{1}H NMR, ^{13}C NMR, HRMS and IR spectrum of final compound **6b**

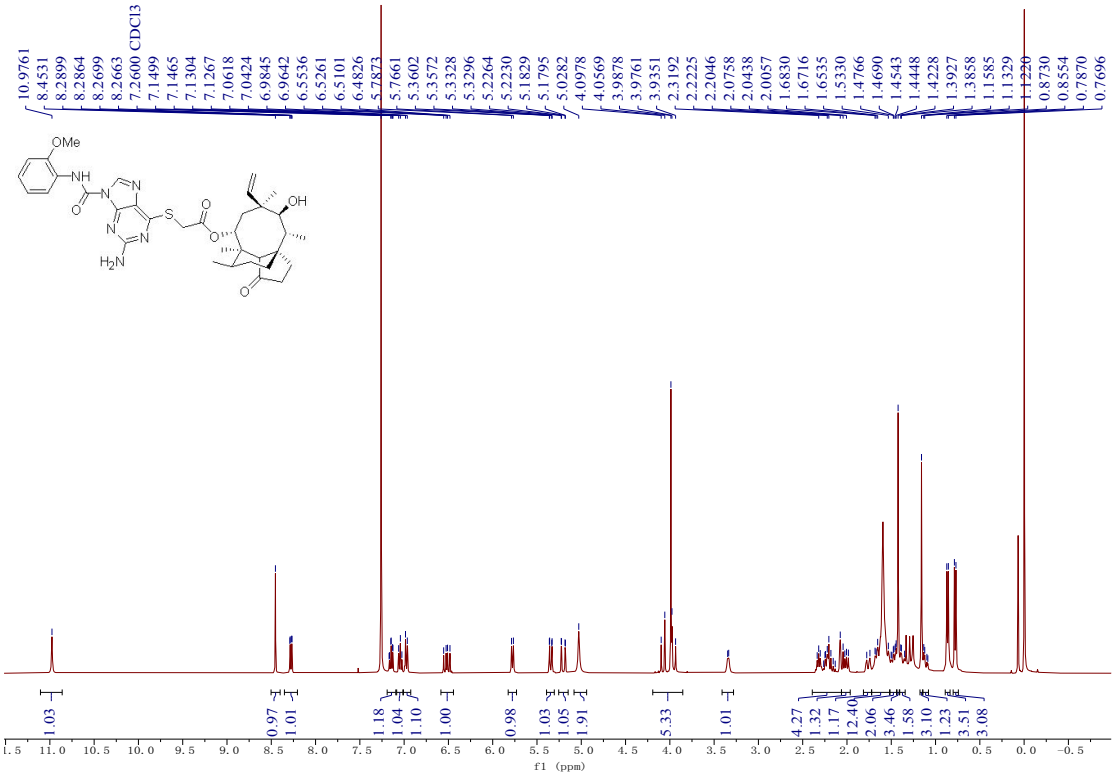
HPLC spectrum of **6b**



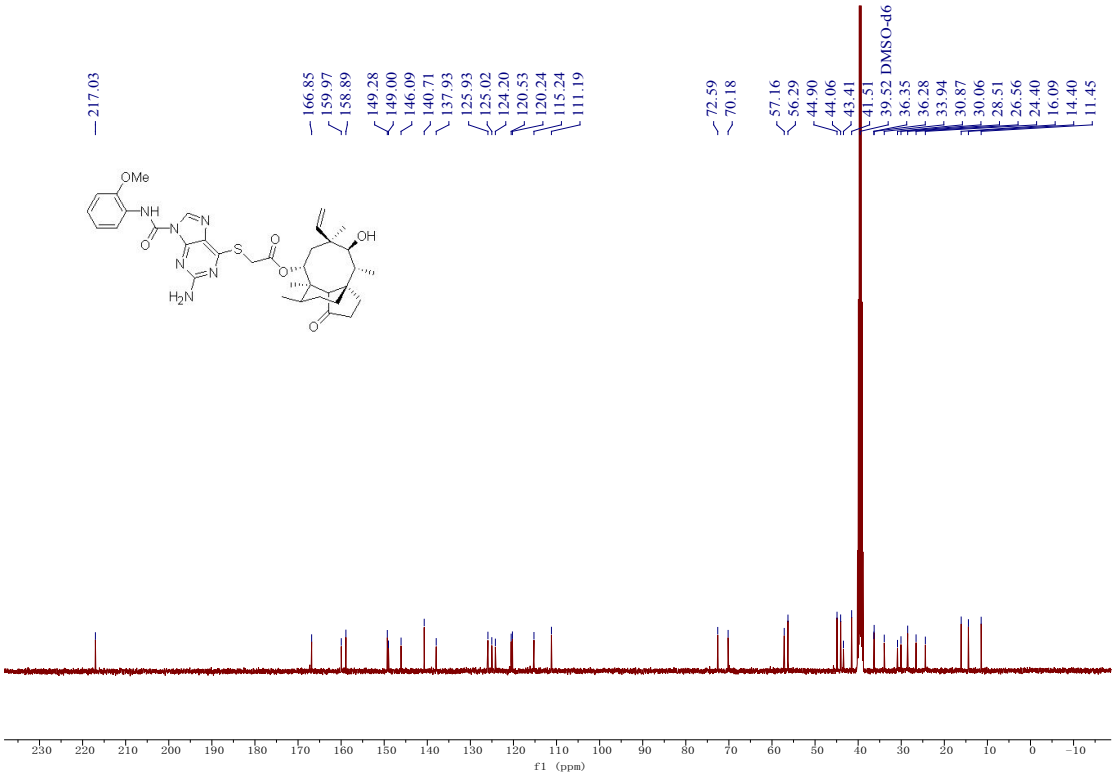
检测器A 254nm

Peak#	Ret. Time	Height	Area	Area%
1	3.444	74687	404513	2.545
2	4.321	5721	40406	0.254
3	6.296	14039	71848	0.452
4	9.138	1465946	15376410	96.748

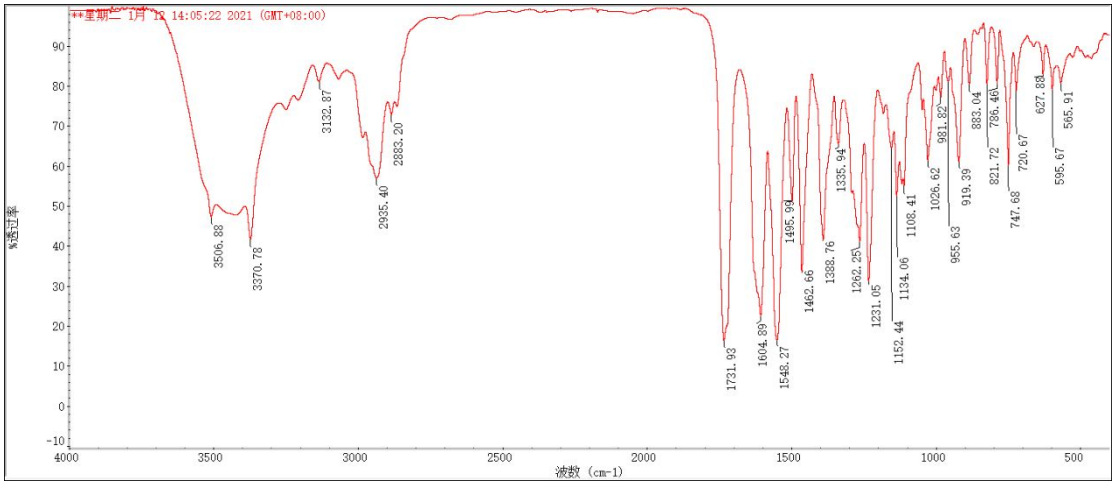
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **6b**



^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **6b**



IR (KBr, cm^{-1}) spectrum of **6b**



HRMS spectrum of **6b**

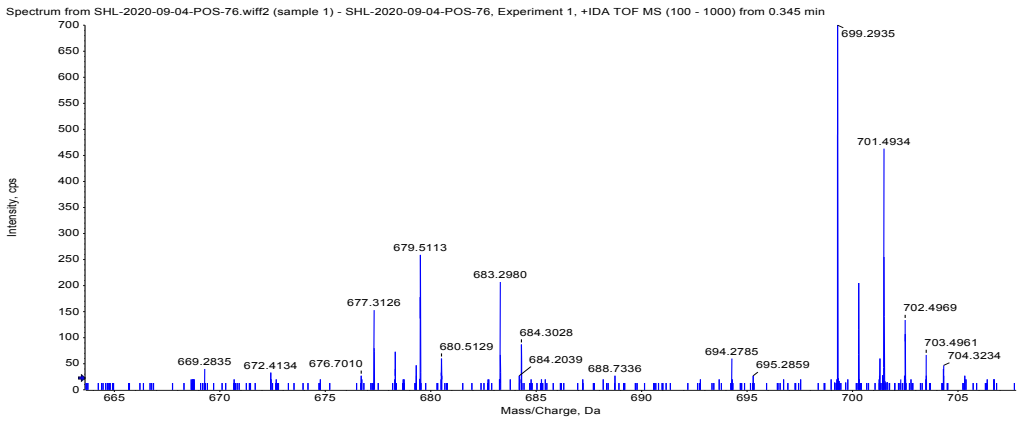
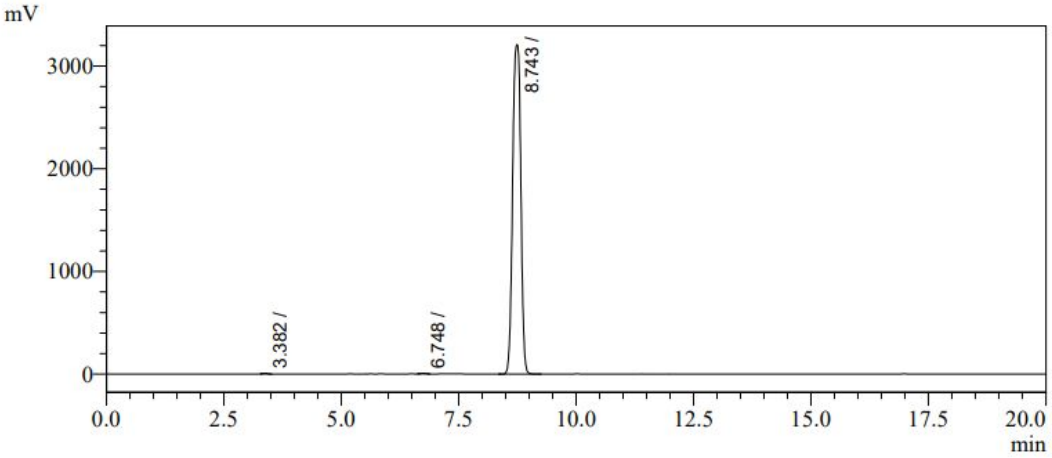


Figure S11. HPLC, ^{1}H NMR, ^{13}C NMR, HRMS and IR spectrum of final compound **6c**

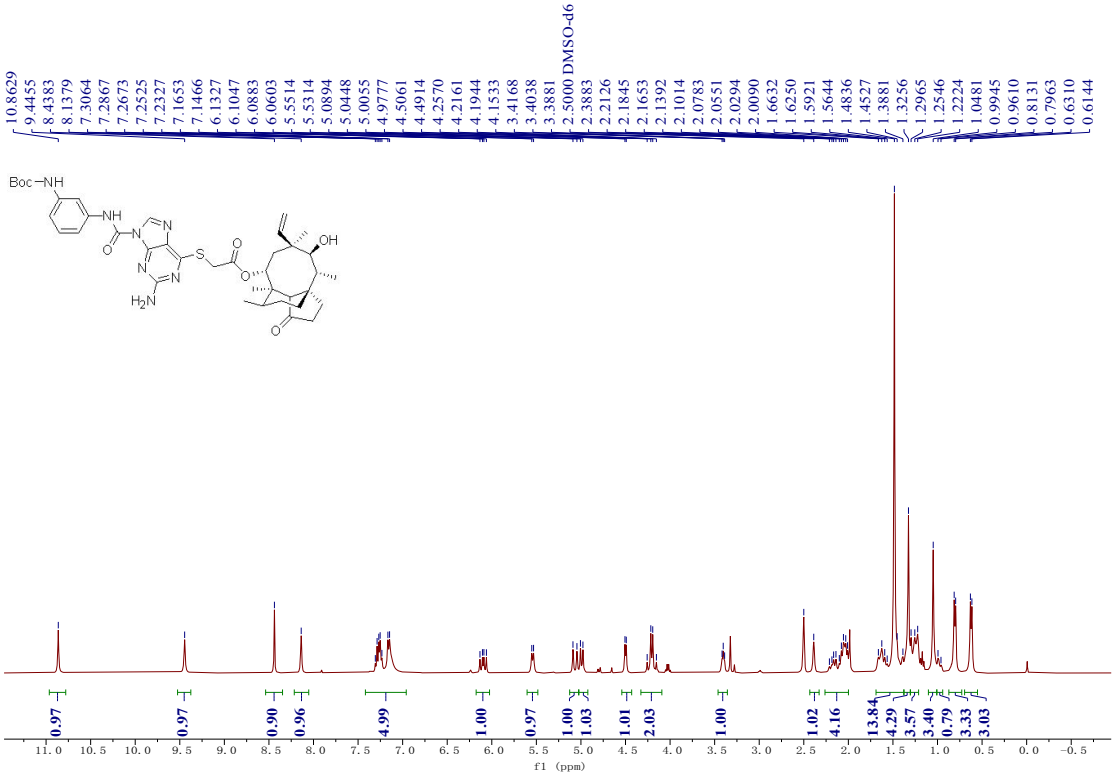
HPLC spectrum of **6c**



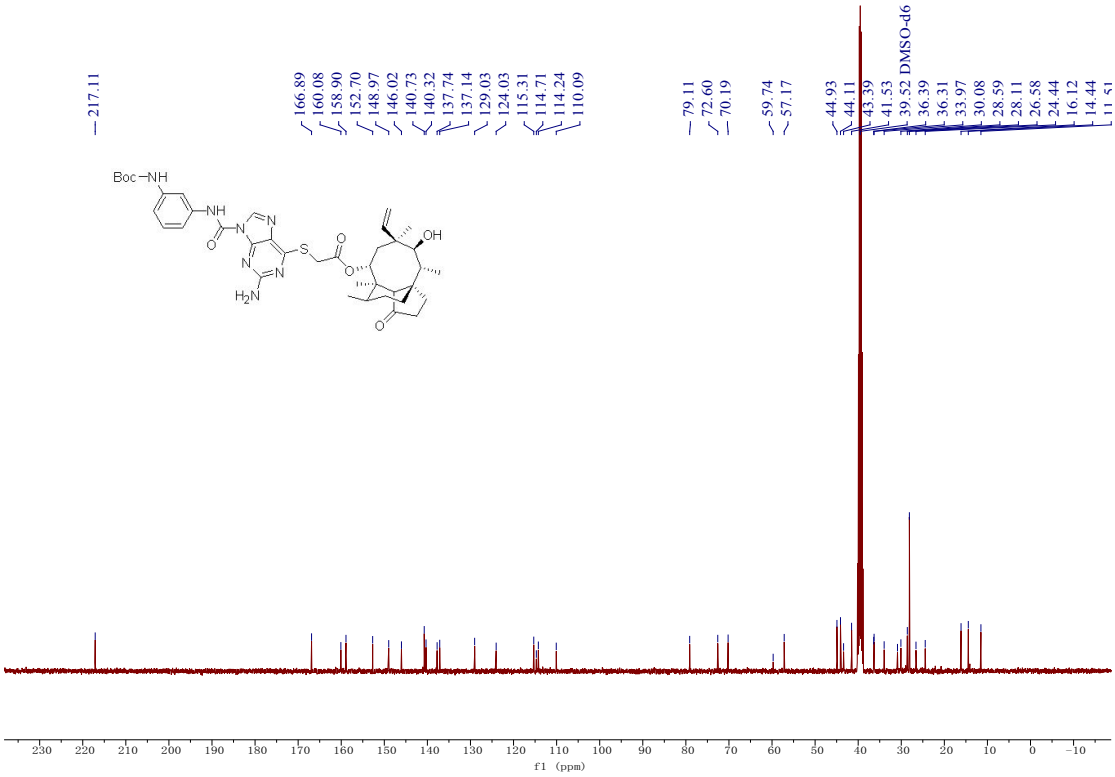
检测器A 254nm

Peak#	Ret. Time	Height	Area	Area%
1	3.382	6517	42647	0.110
2	6.748	5300	40652	0.105
3	8.743	3211358	38717198	99.785

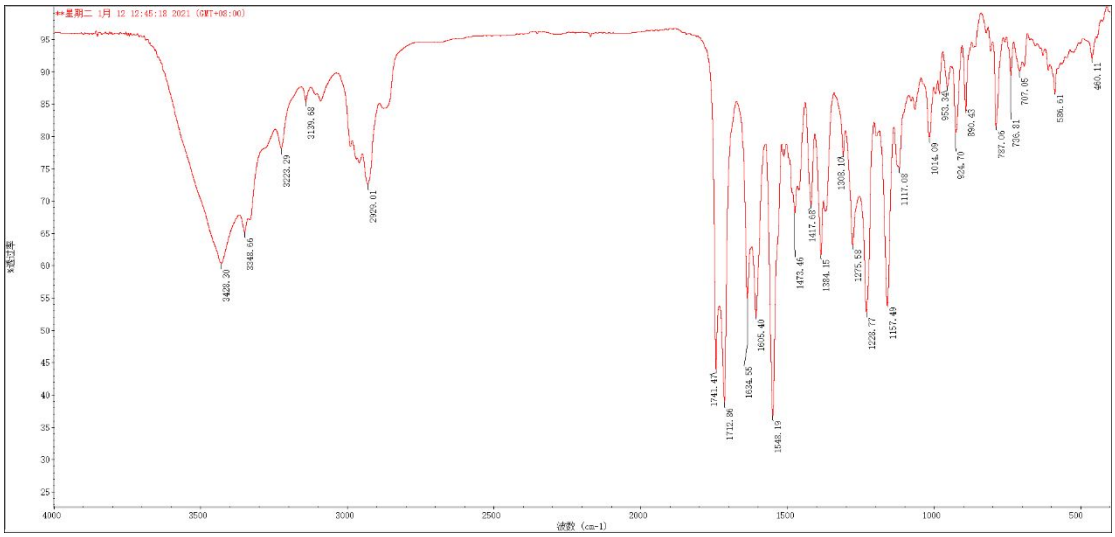
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **6c**



^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **6c**



IR (KBr, cm^{-1}) spectrum of **6c**



HRMS spectrum of **6c**

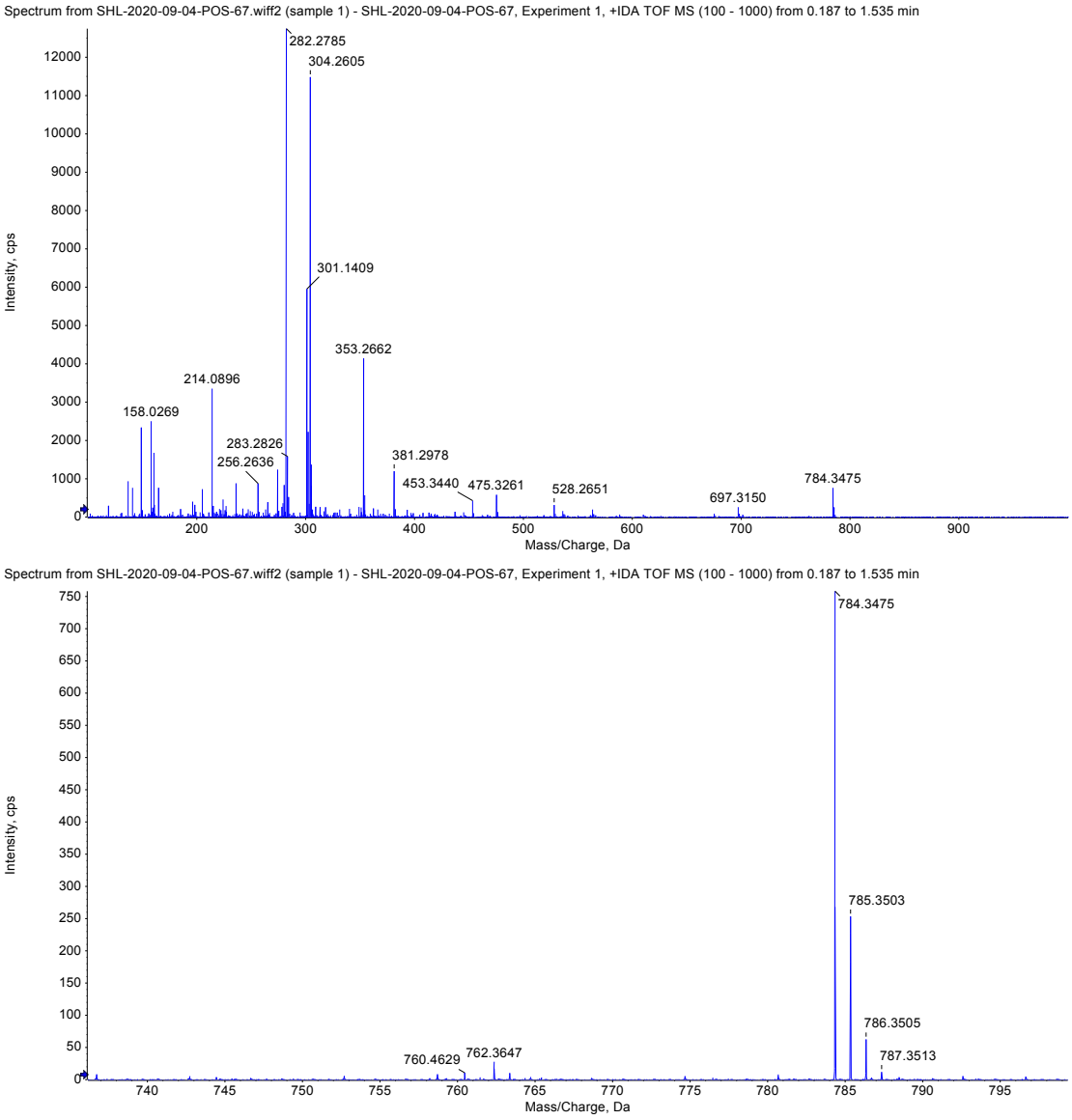
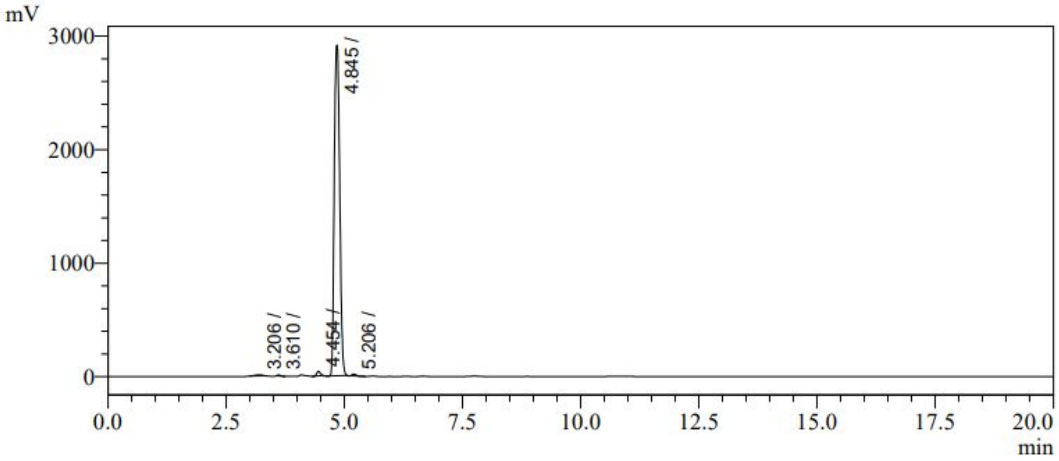


Figure S12. HPLC, ^{1}H NMR, ^{13}C NMR, HRMS and IR spectrum of final compound **6d**

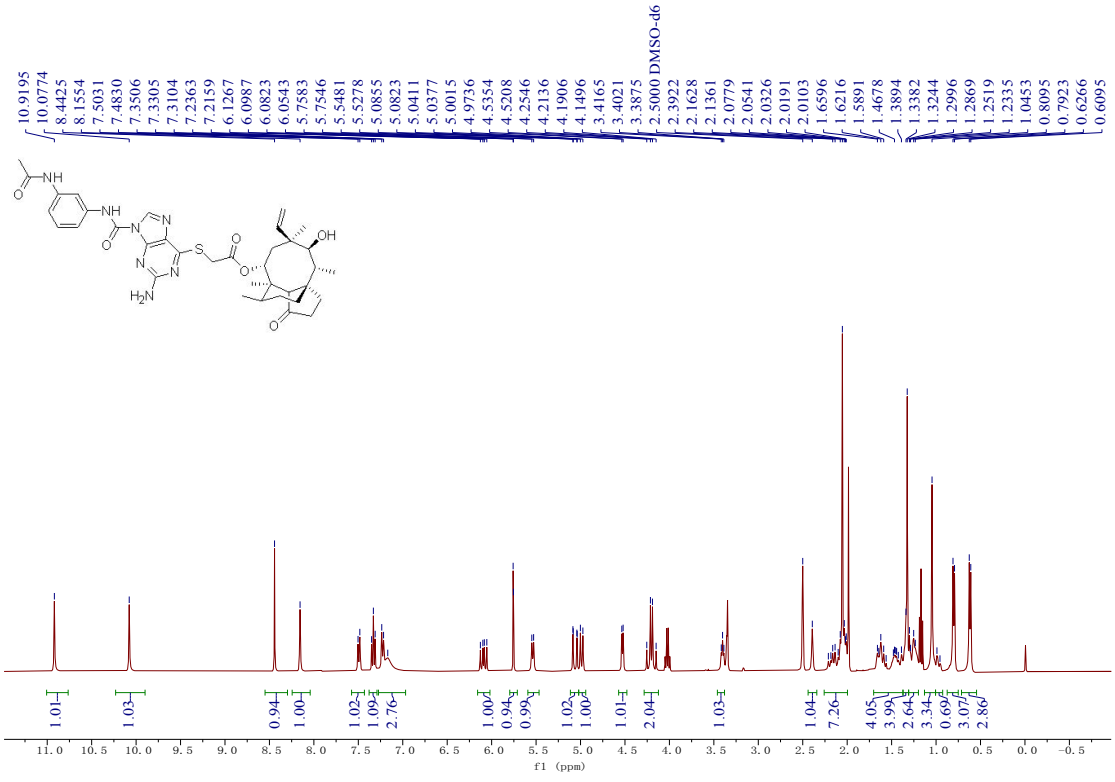
HPLC spectrum of **6d**



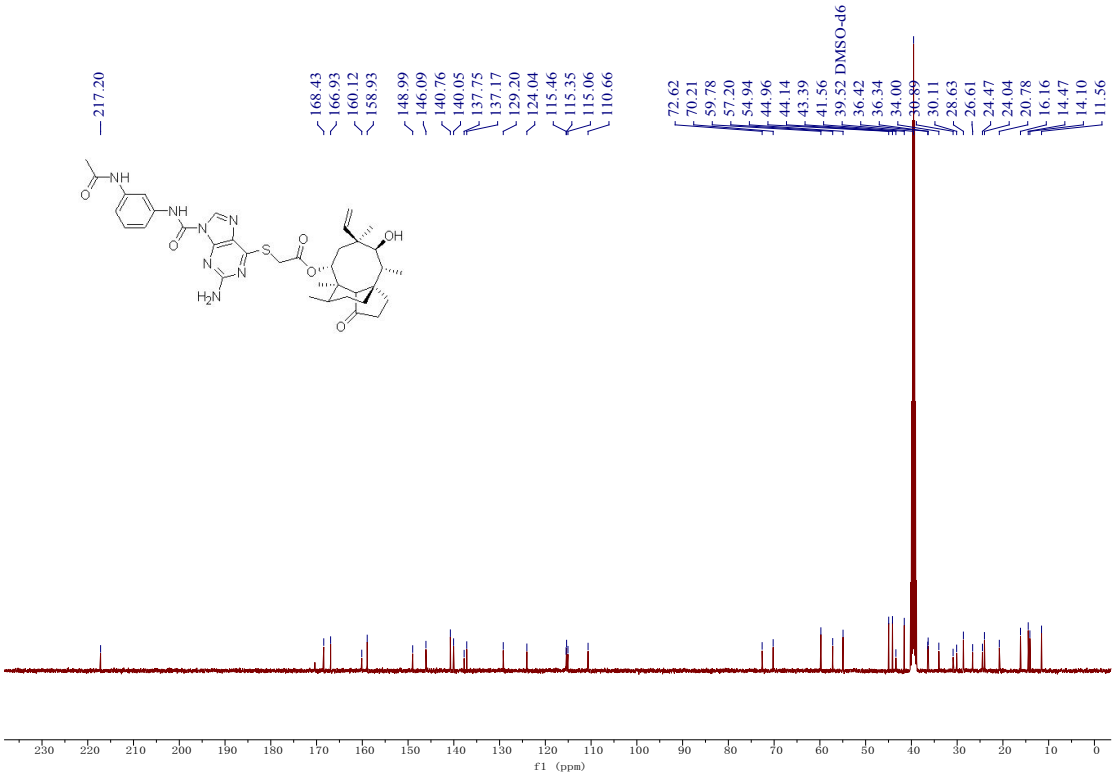
检测器A 254nm

Peak#	Ret. Time	Height	Area	Area%
1	3.206	8334	95704	0.403
2	3.610	9182	40996	0.173
3	4.454	39300	210718	0.888
4	4.845	2915580	23282334	98.130
5	5.206	17042	96198	0.405

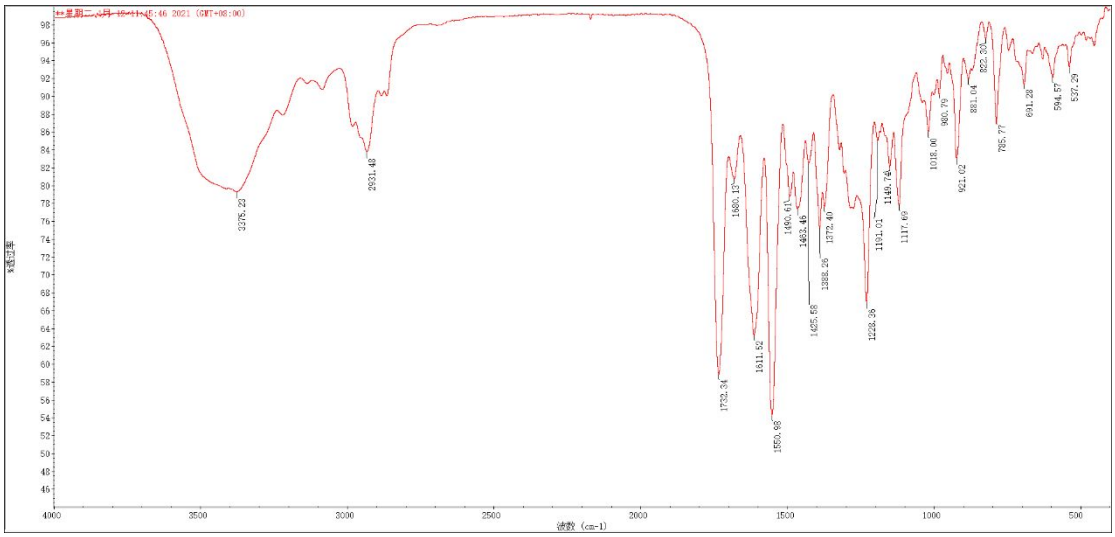
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **6d**



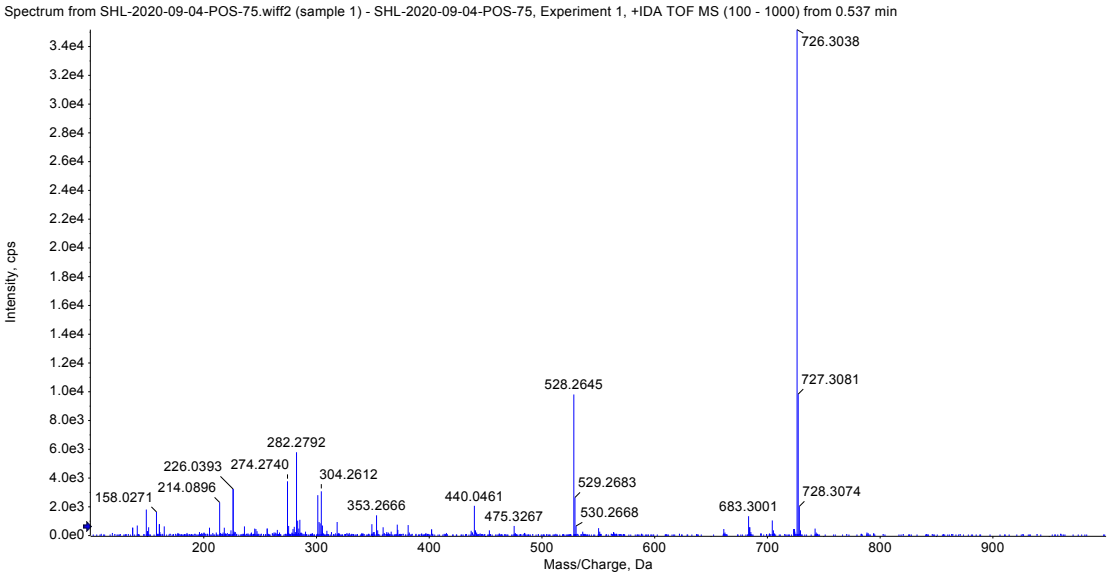
^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **6d**



IR (KBr, cm^{-1}) spectrum of **6d**



HRMS spectrum of **6d**



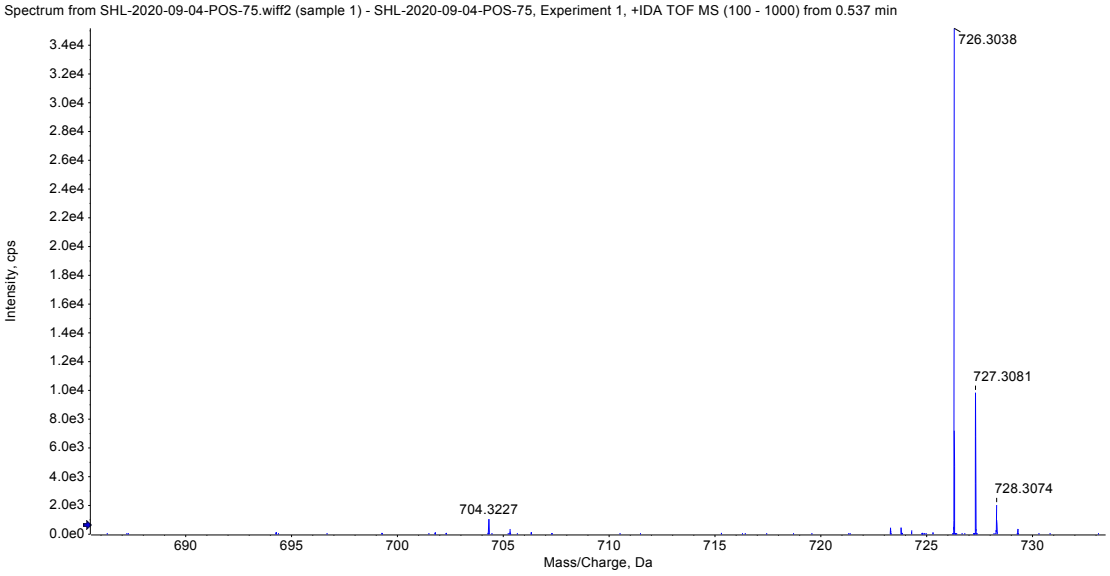
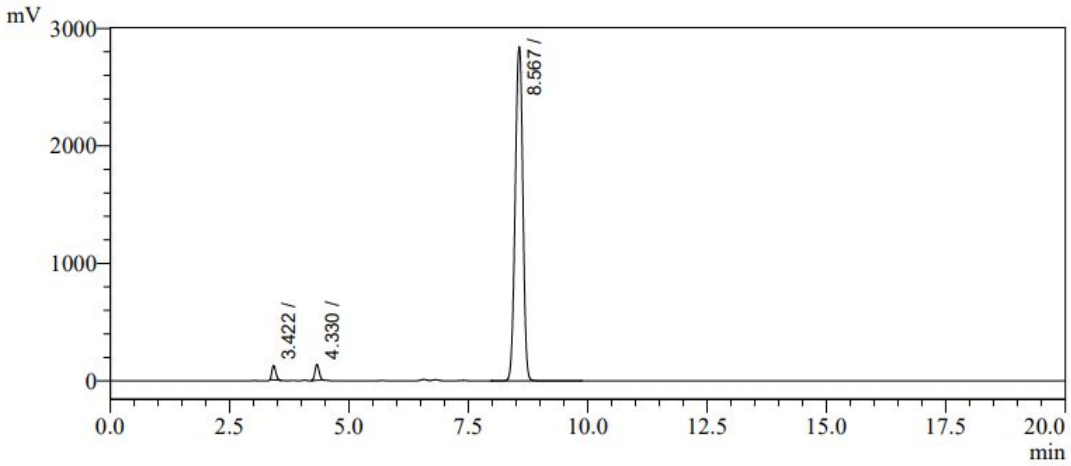


Figure S13. HPLC, ^{1}H NMR, ^{13}C NMR, HRMS and IR spectrum of final compound **6e**

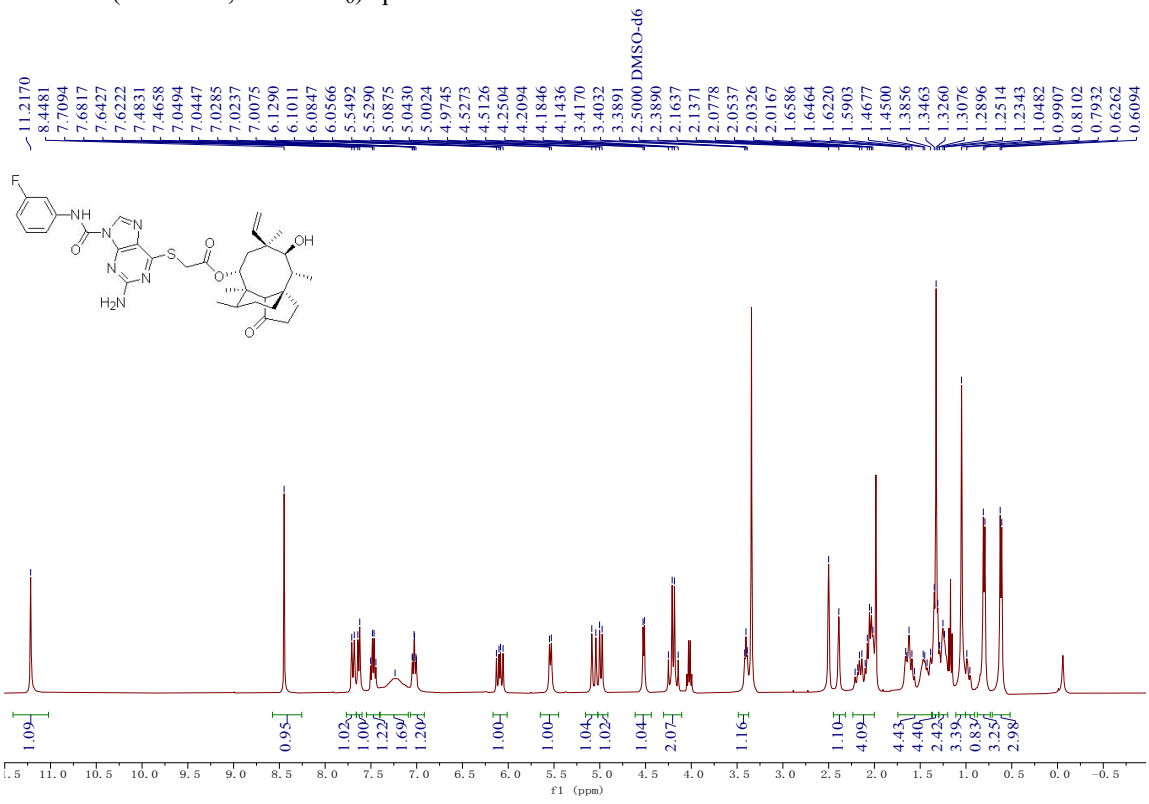
HPLC spectrum of **6e**



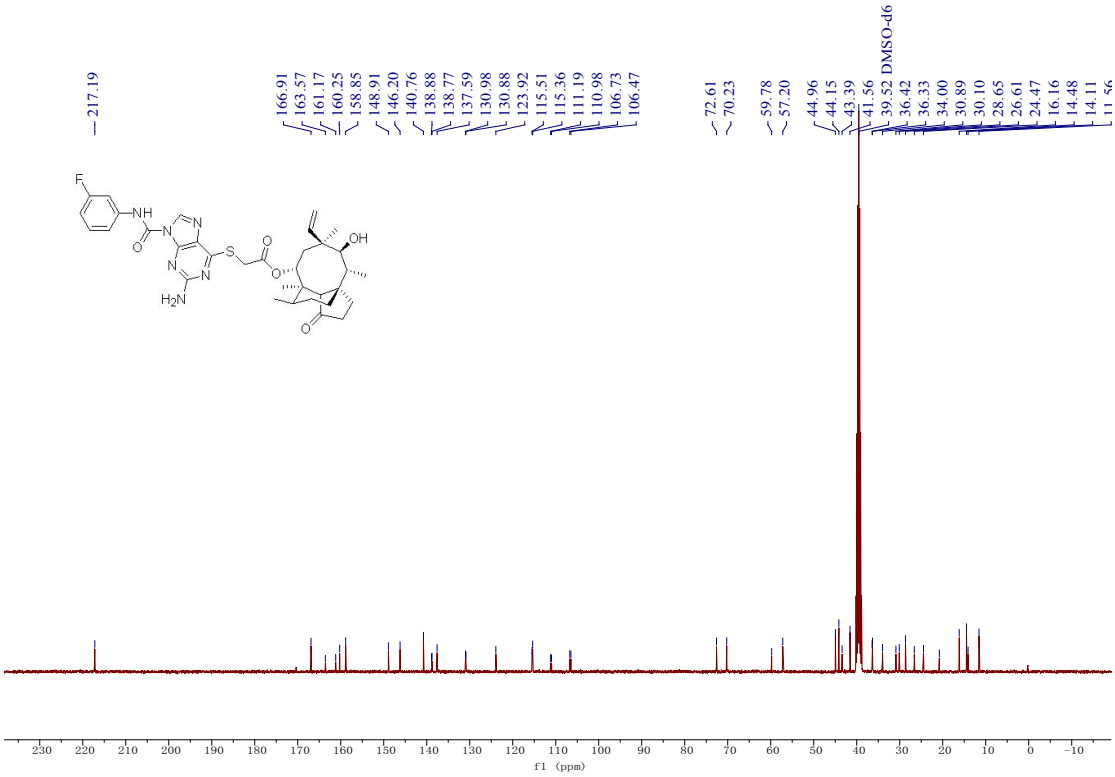
检测器A 254nm

Peak#	Ret. Time	Height	Area	Area%
1	3.422	122391	680641	2.056
2	4.330	135798	825672	2.495
3	8.567	2843352	31591029	95.449

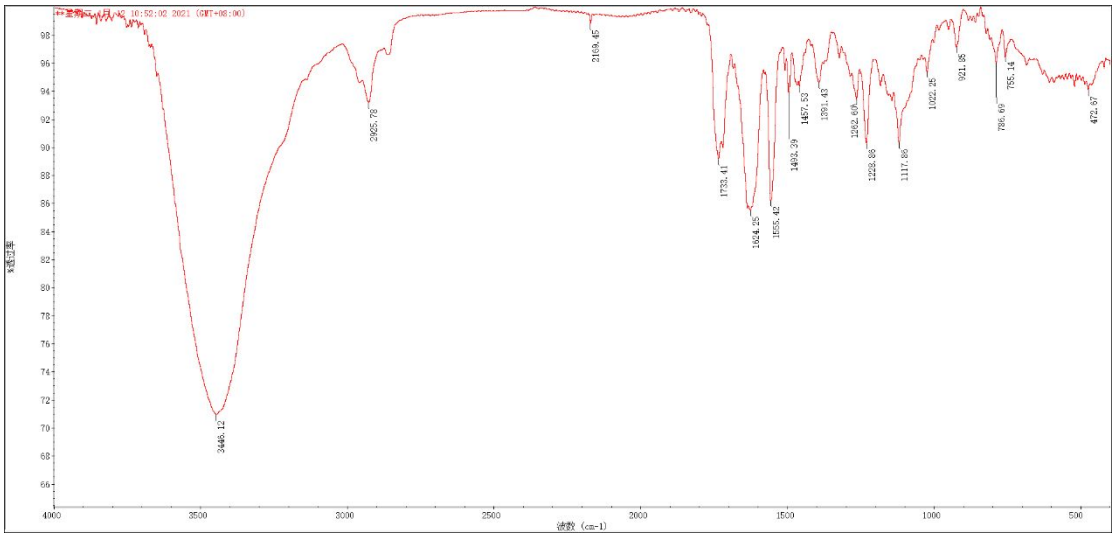
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **6e**



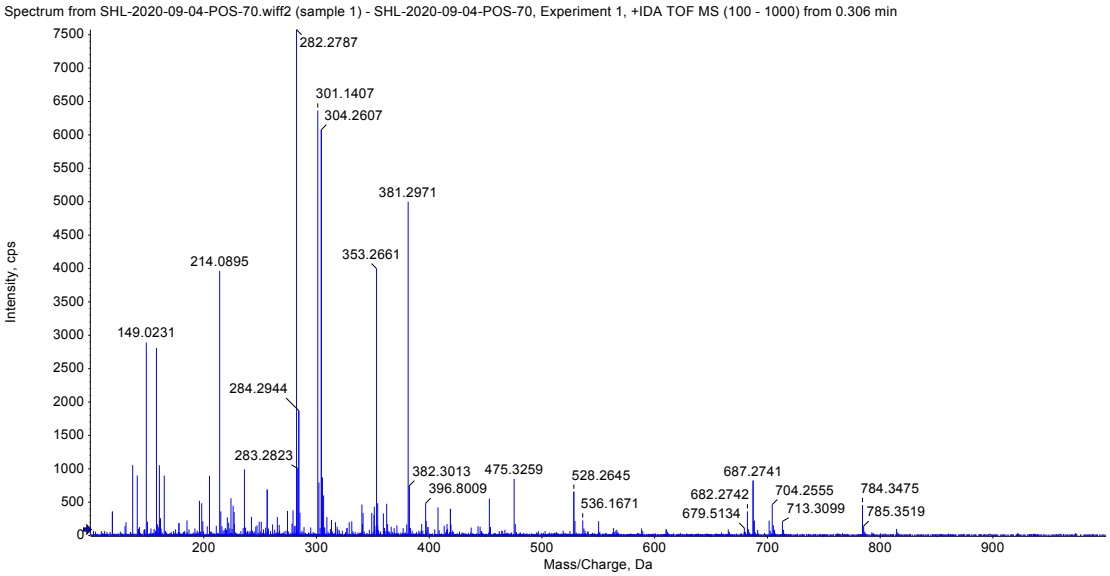
^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **6e**



IR (KBr, cm^{-1}) spectrum of **6e**



HRMS spectrum of **6e**



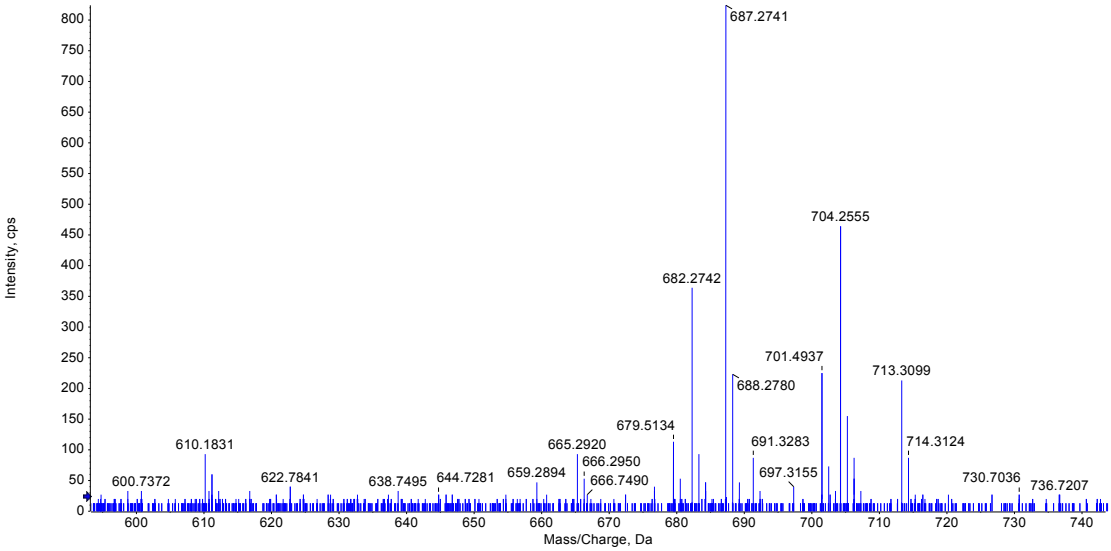
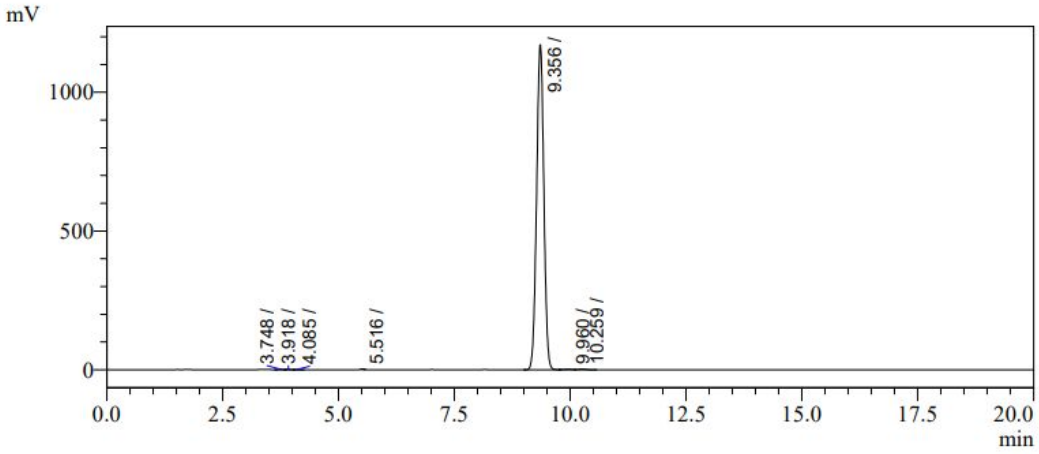


Figure S14. HPLC, ^{1}H NMR, ^{13}C NMR, HRMS and IR spectrum of final compound **6f**

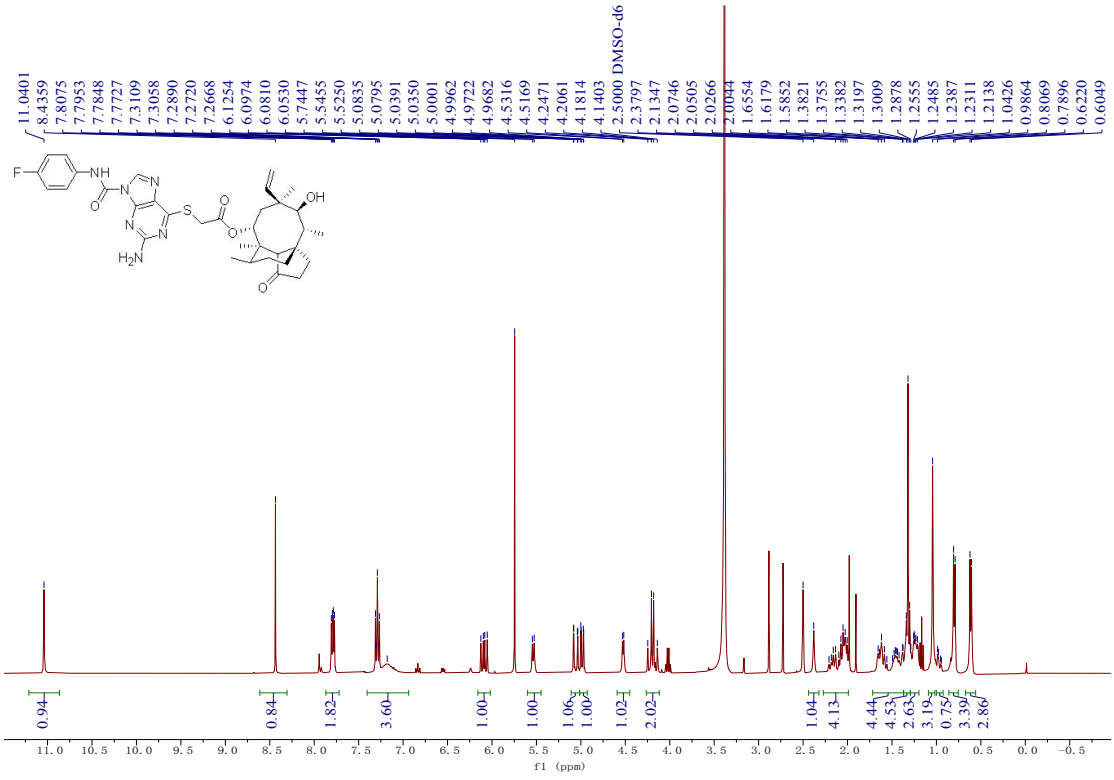
HPLC spectrum of **6f**



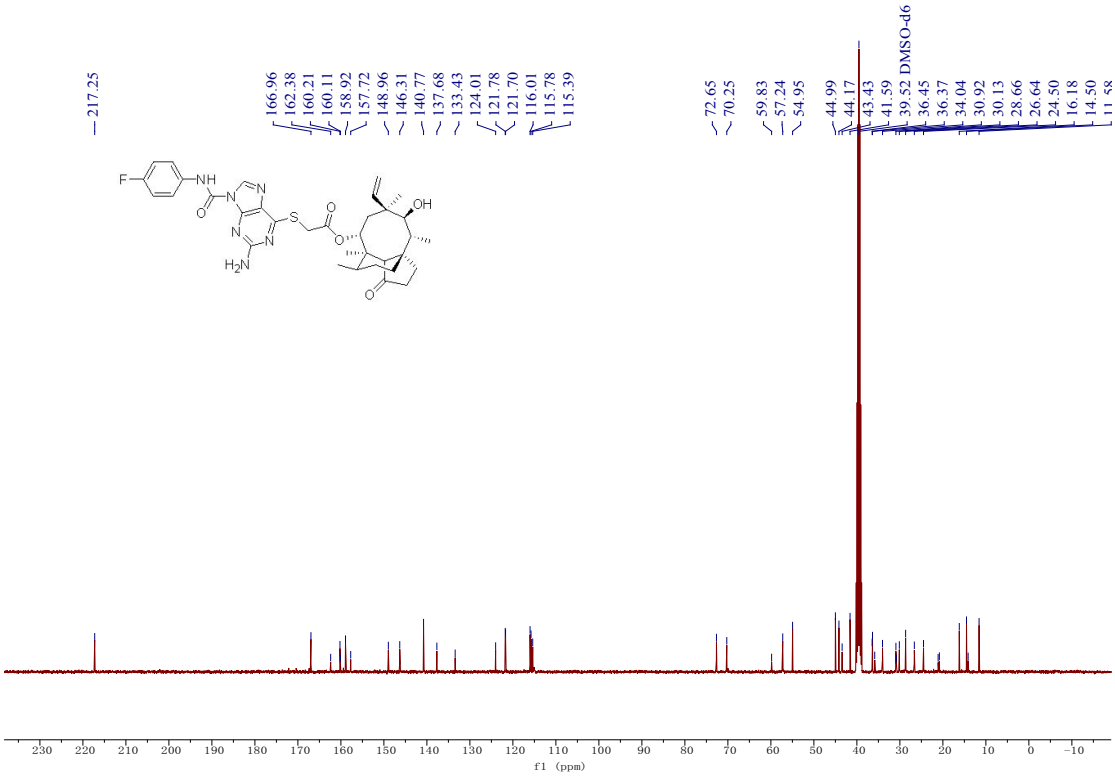
检测器A 254nm

Peak#	Ret. Time	Height	Area	Area%
1	3.748	2112	13113	0.102
2	3.918	1876	11544	0.090
3	4.085	499	3509	0.027
4	5.516	446	1075	0.008
5	9.356	1172068	12726677	99.341
6	9.960	2215	27579	0.215
7	10.259	2357	27592	0.215

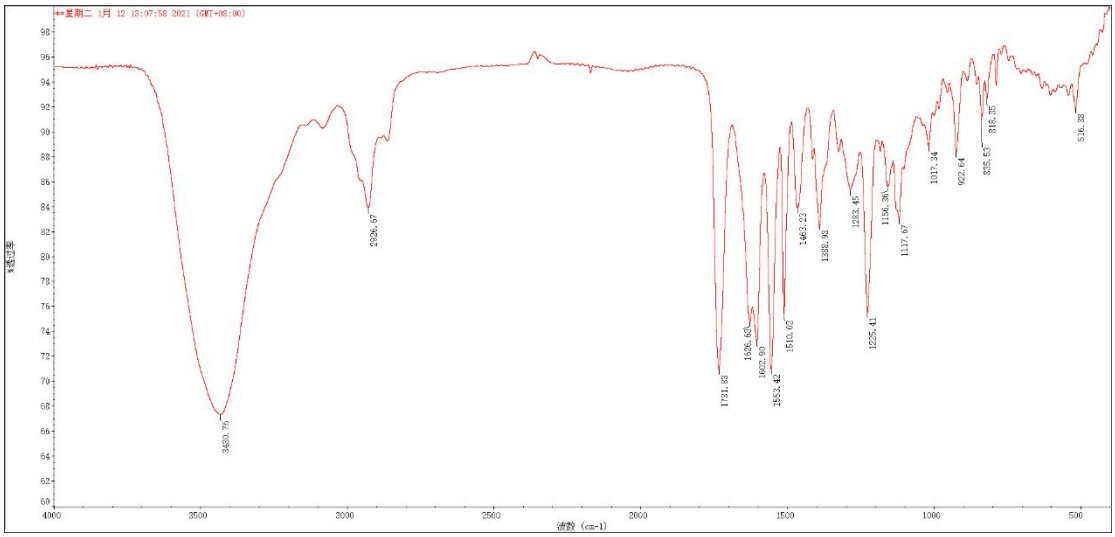
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **6f**



^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **6f**



IR (KBr, cm^{-1}) spectrum of **6f**



HRMS spectrum of **6f**

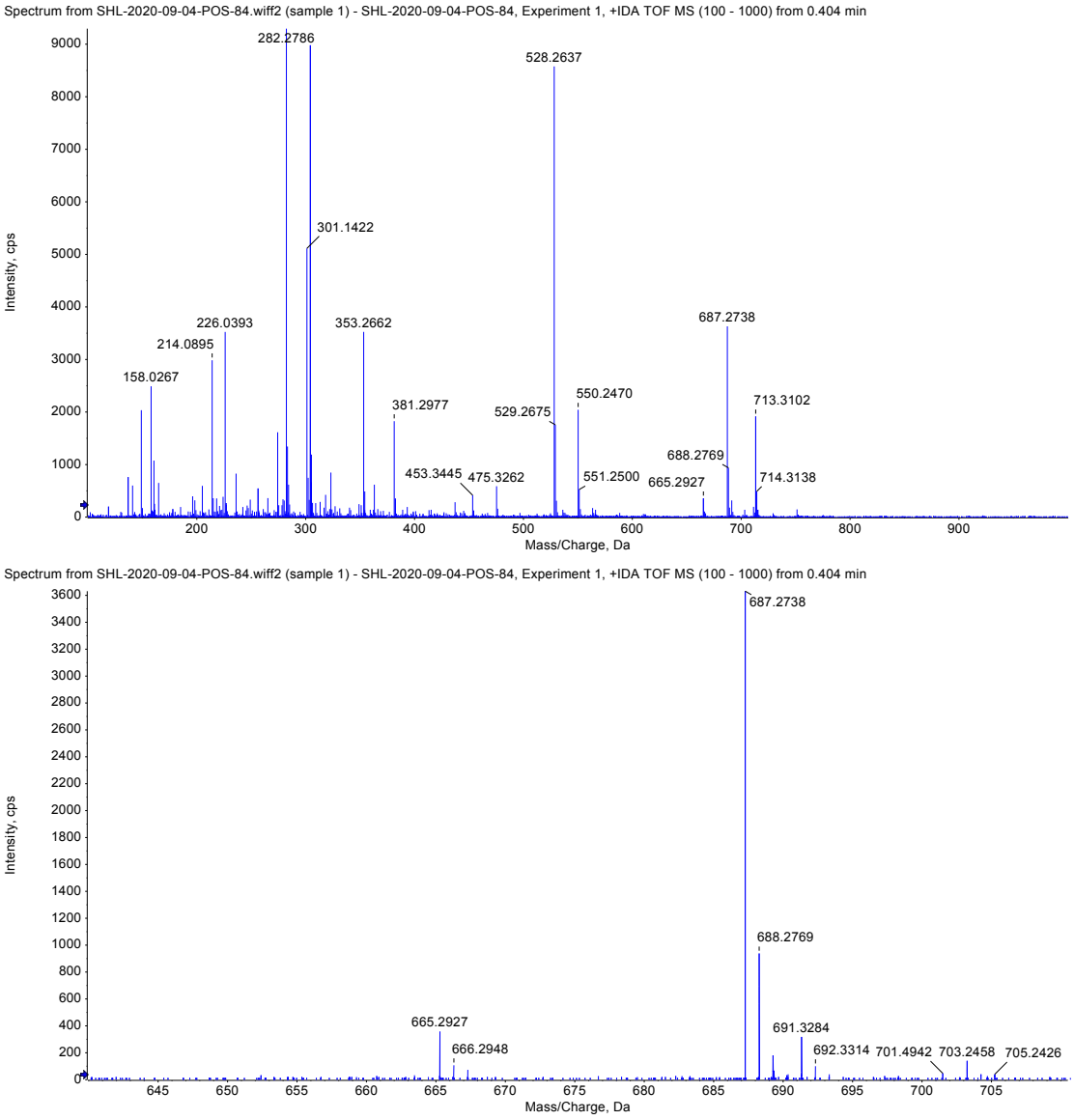
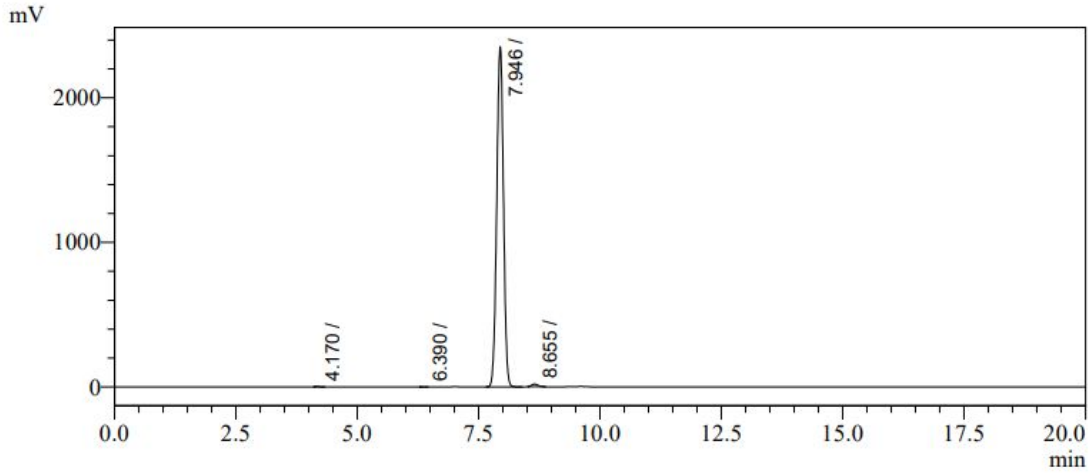


Figure S15. HPLC, ^{1}H NMR, ^{13}C NMR, HRMS and IR spectrum of final compound **6g**

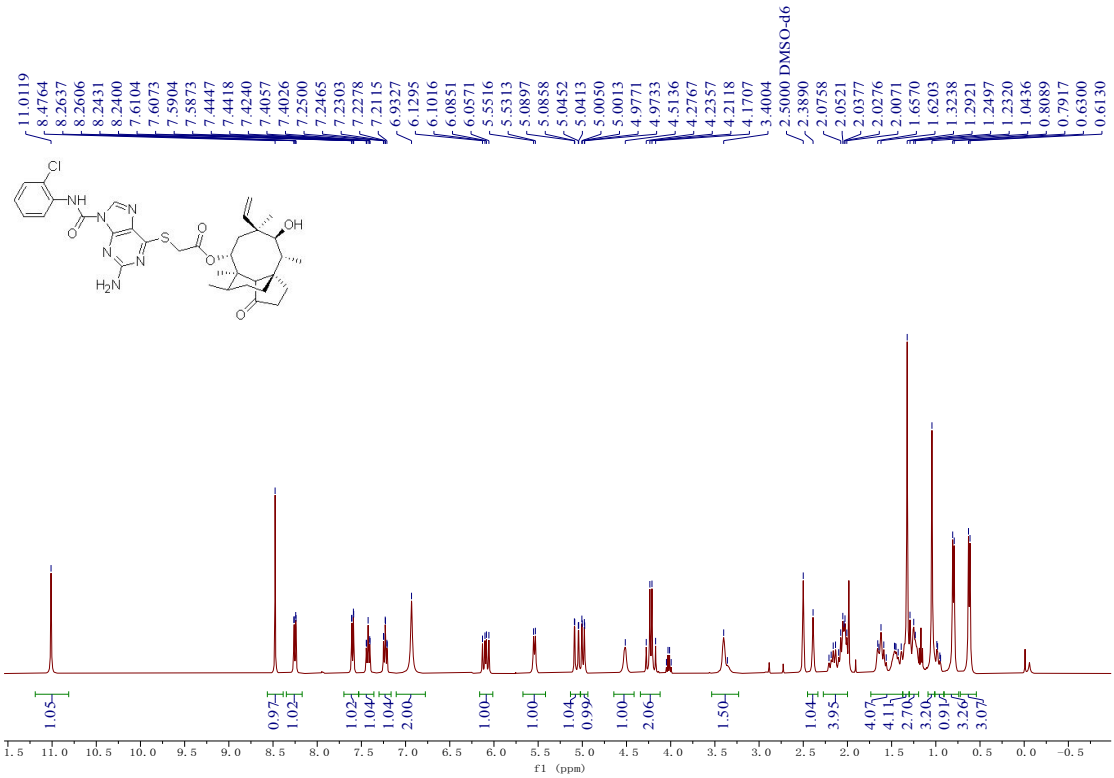
HPLC spectrum of **6g**



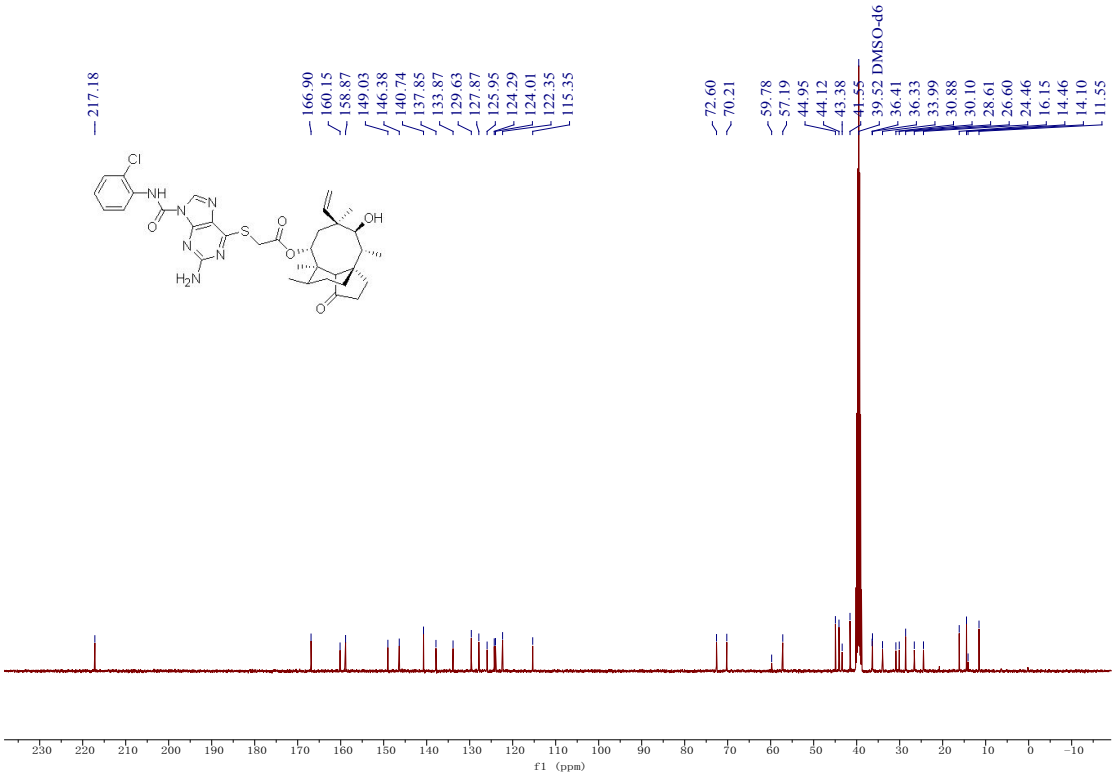
检测器A 254nm

Peak#	Ret. Time	Height	Area	Area%
1	4.170	4193	20457	0.090
2	6.390	293	1478	0.006
3	7.946	2354660	22655930	99.197
4	8.655	17507	161517	0.707

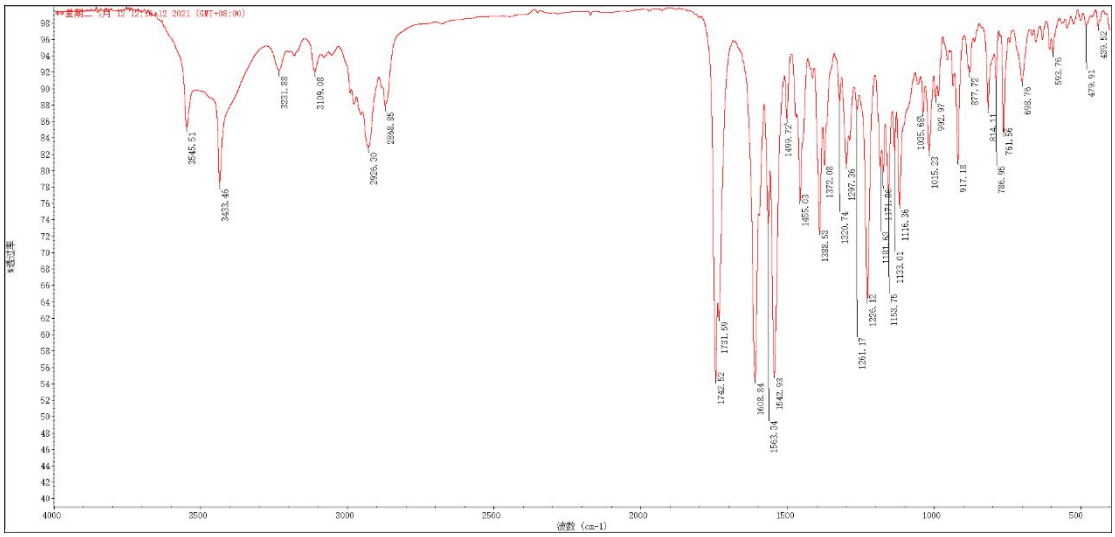
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **6g**



^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **6g**



IR (KBr, cm^{-1}) spectrum of **6g**



HRMS spectrum of **6g**

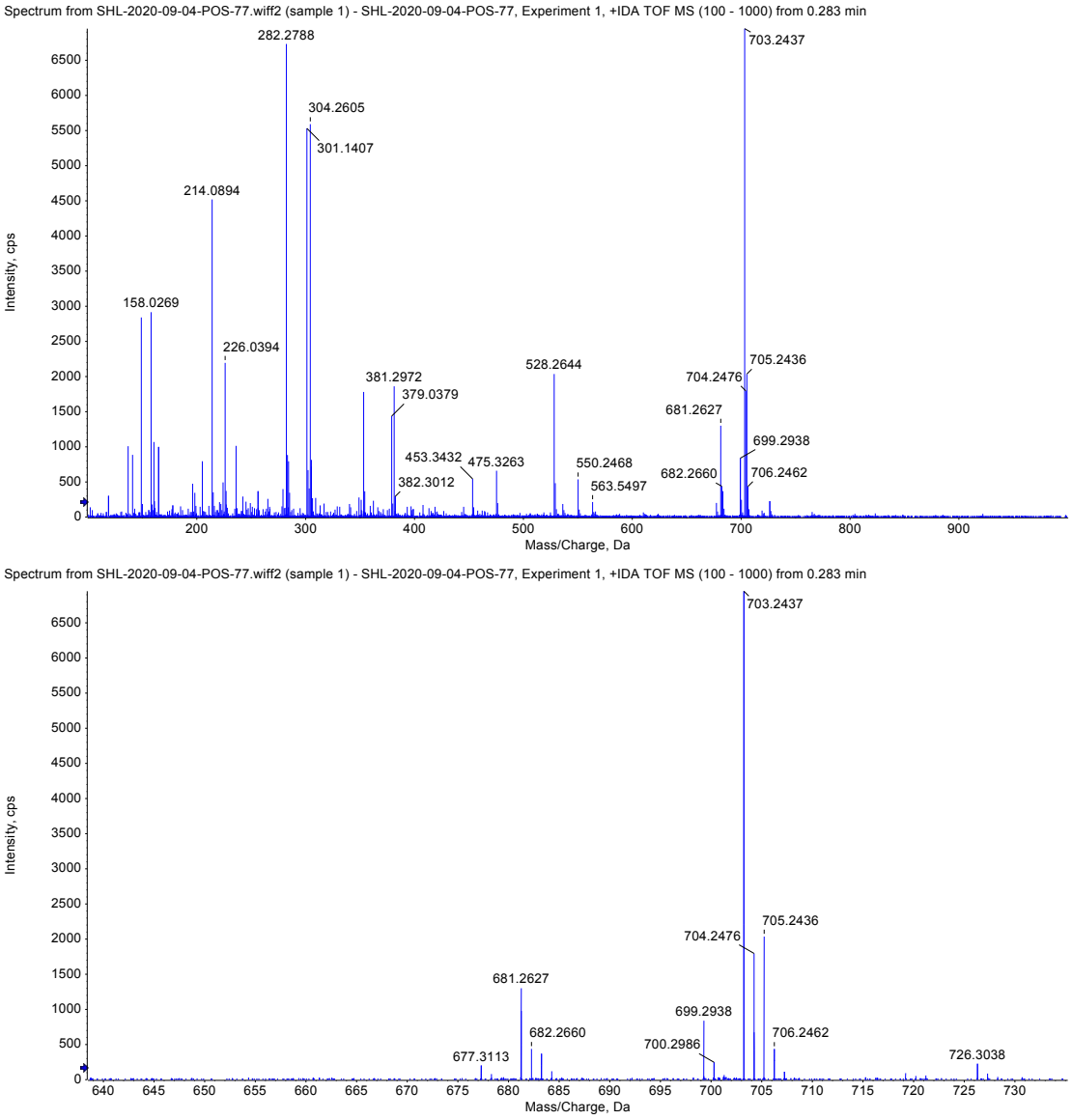
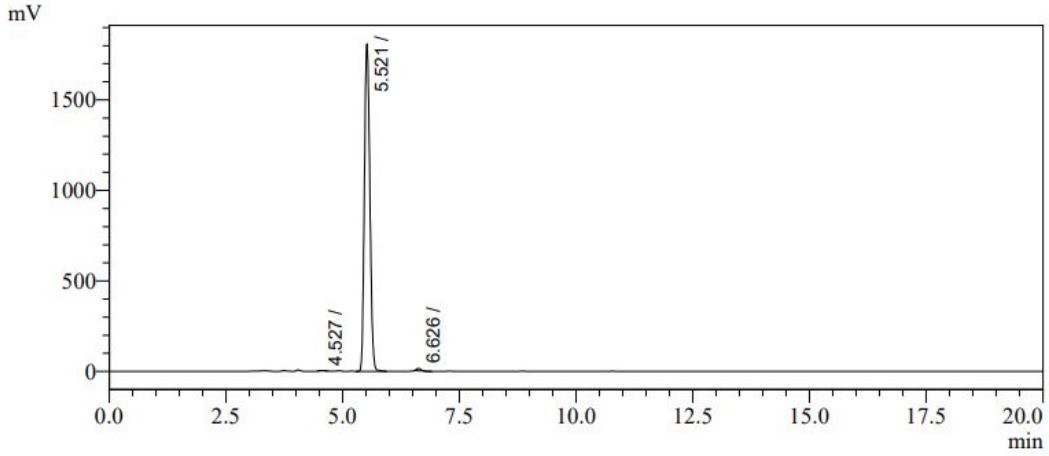


Figure S16. HPLC, ^{1}H NMR, ^{13}C NMR, HRMS and IR spectrum of final compound **6h**

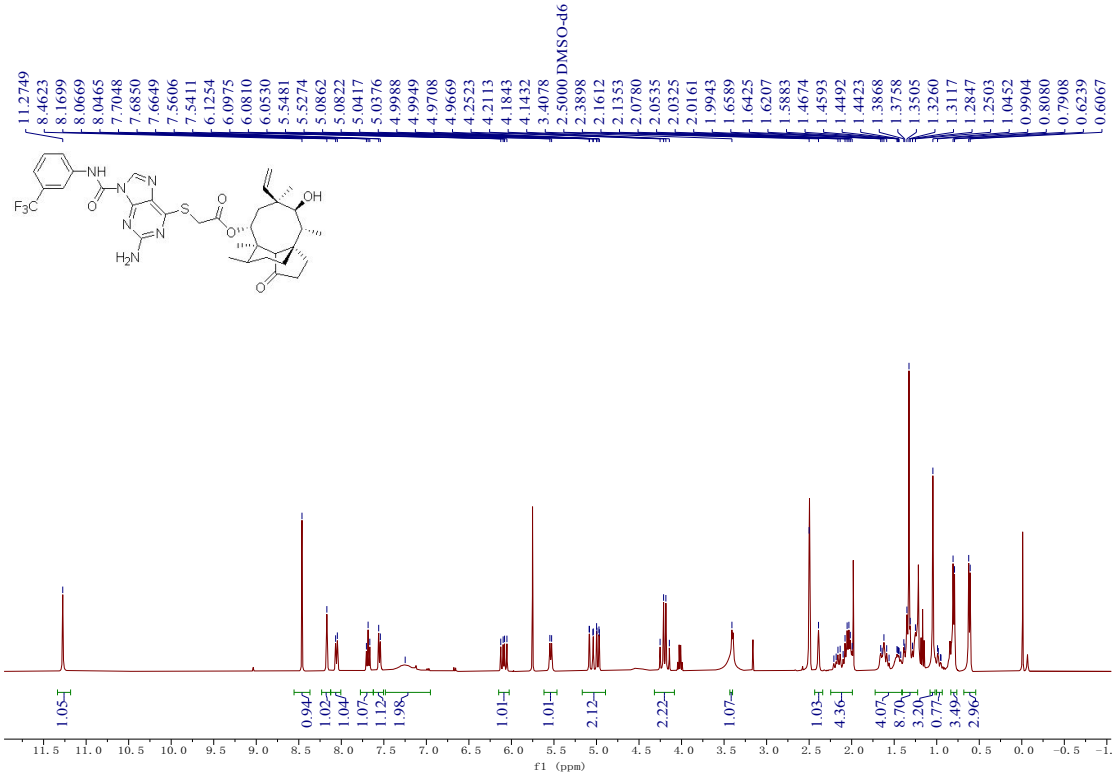
HPLC spectrum of **6h**



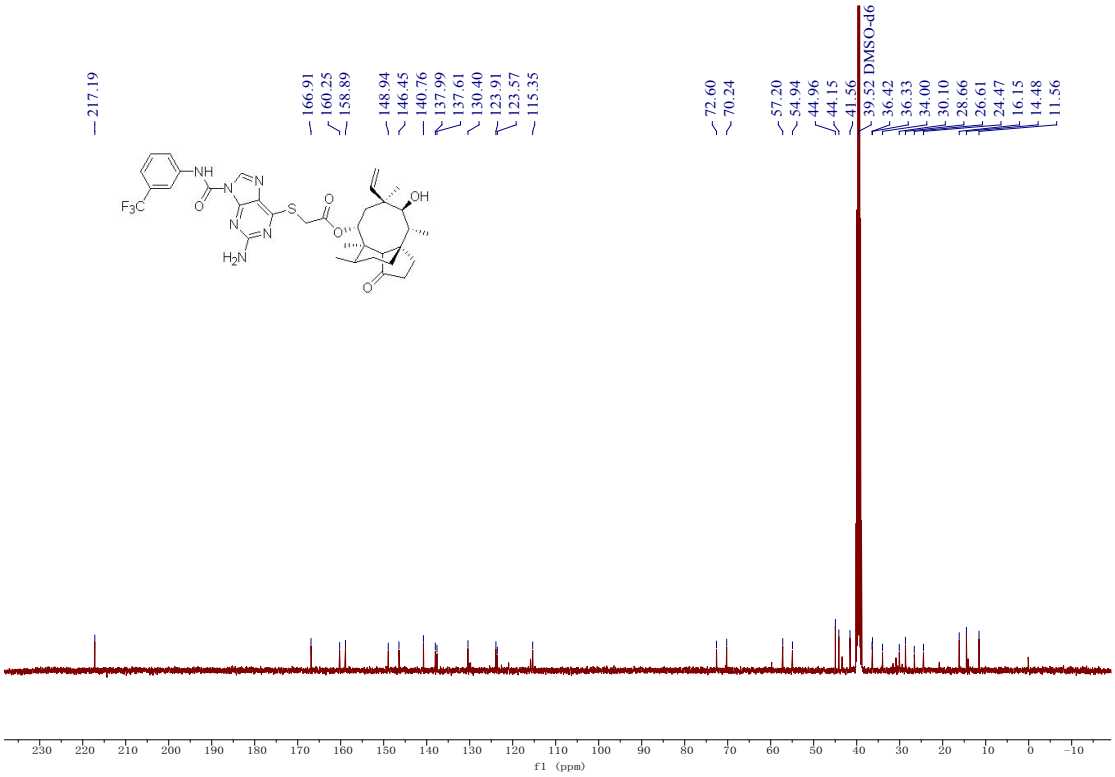
检测器A 254nm

Peak#	Ret. Time	Height	Area	Area%
1	4.527	2204	16611	0.112
2	5.521	1808897	14716176	99.359
3	6.626	12656	78263	0.528

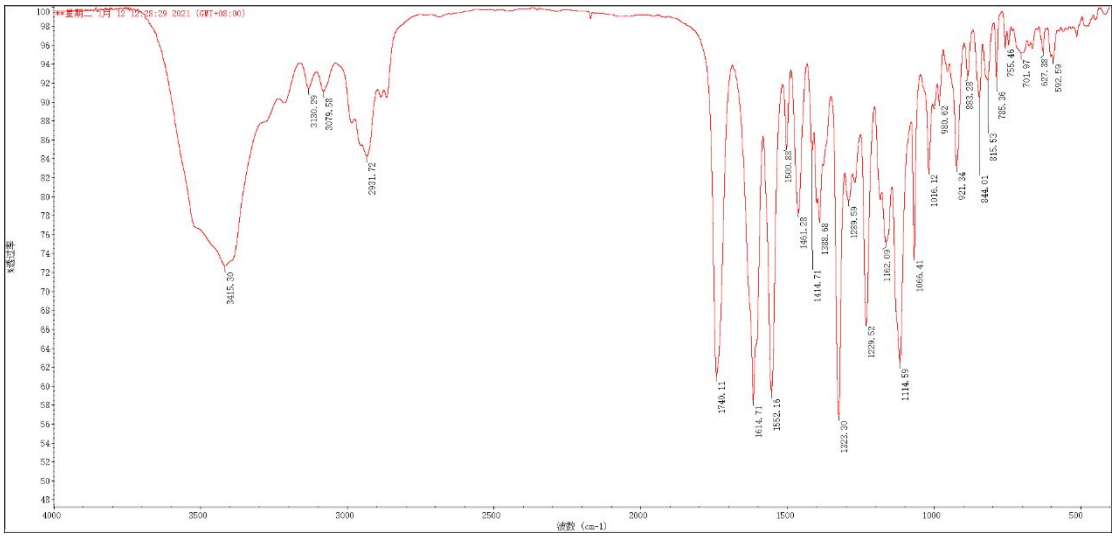
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **6h**



^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **6h**



IR (KBr, cm^{-1}) spectrum of **6h**



HRMS spectrum of **6h**

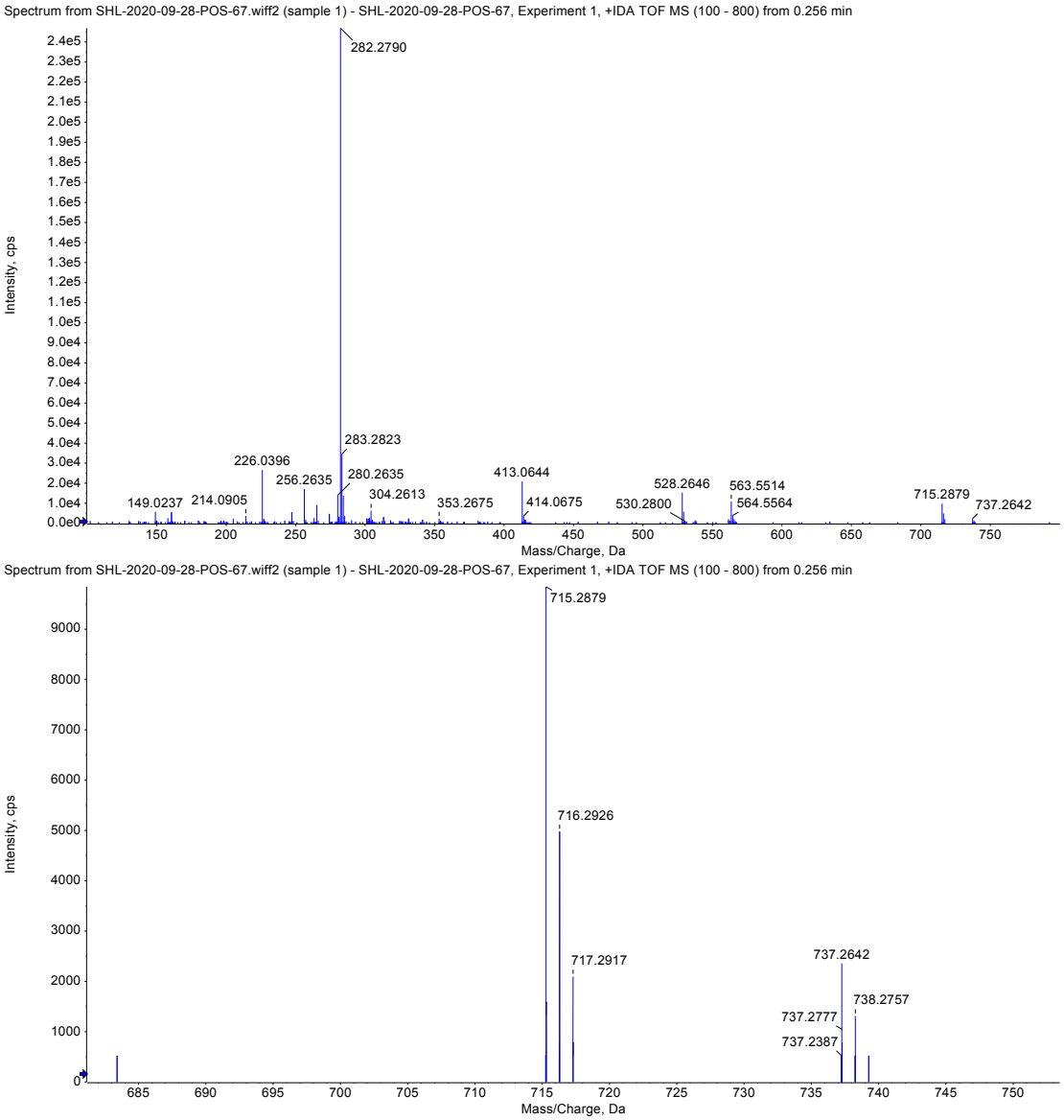
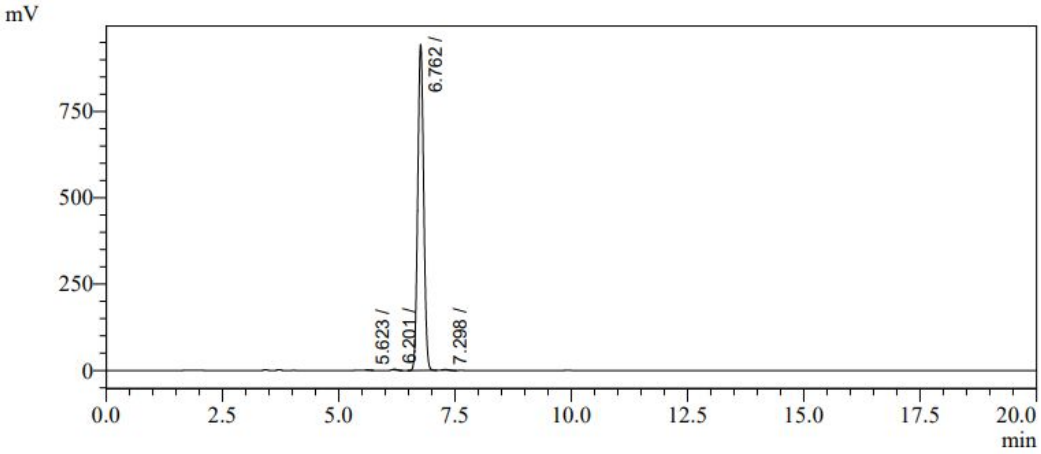


Figure S17. HPLC, ^{1}H NMR, ^{13}C NMR, HRMS and IR spectrum of final compound **6i**

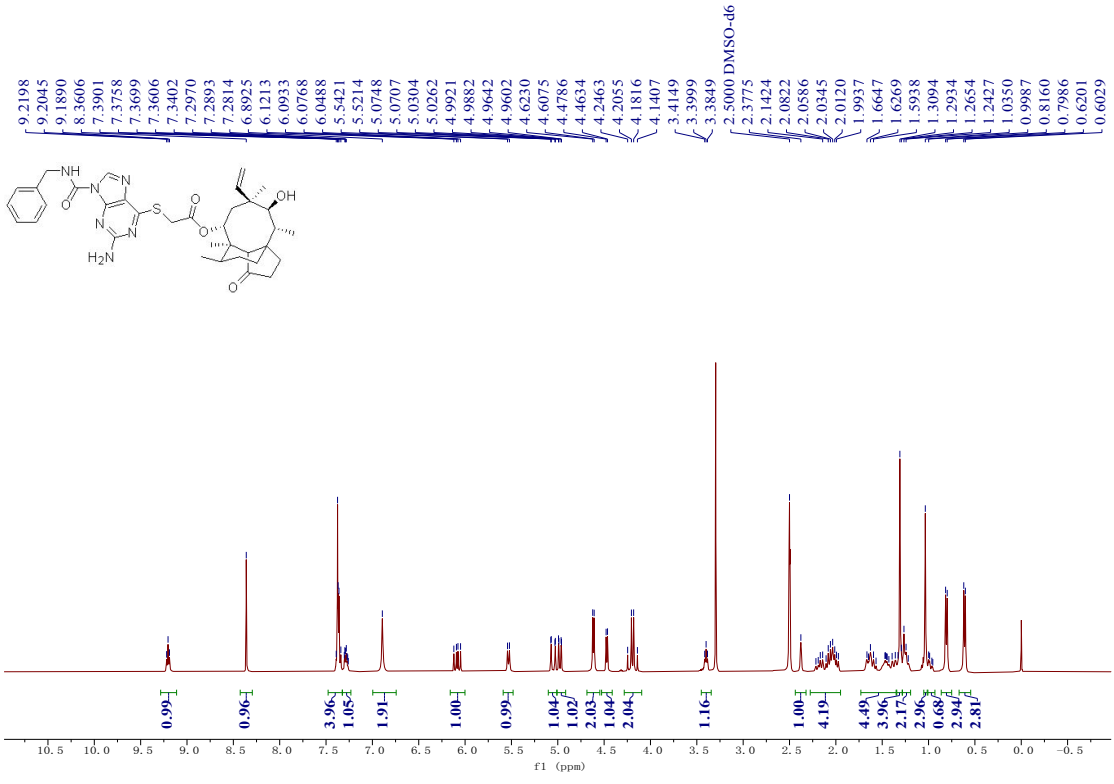
HPLC spectrum of **6i**



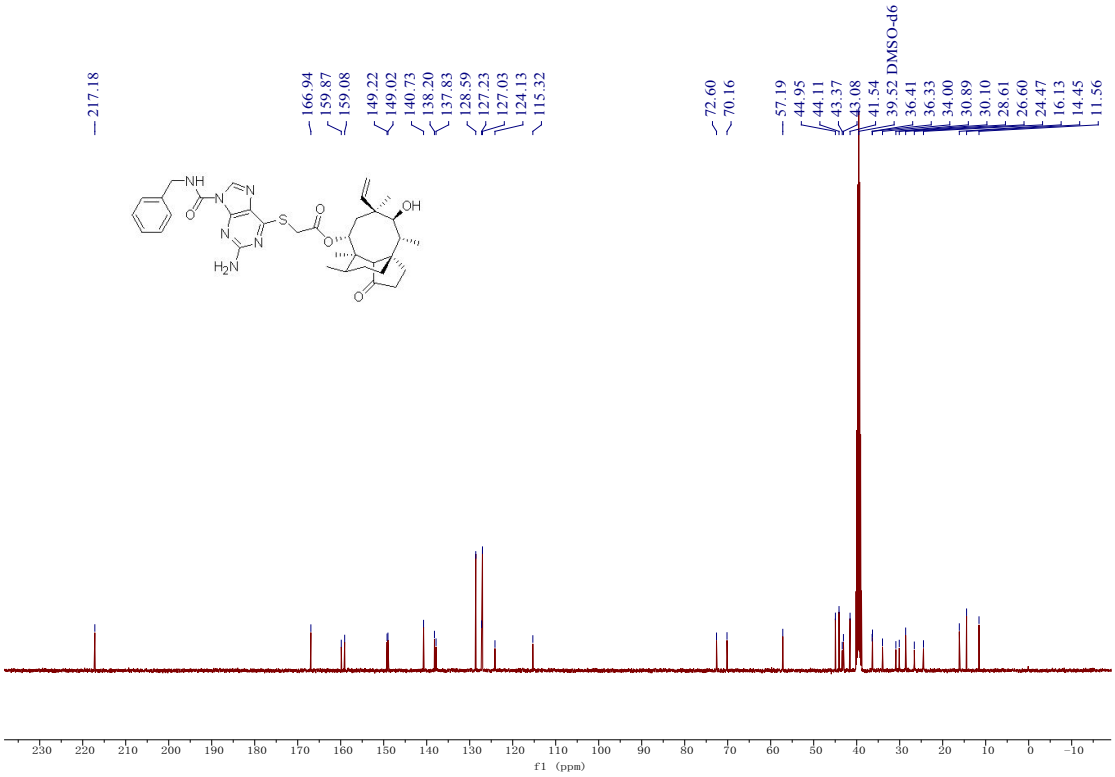
检测器A 254nm

Peak#	Ret. Time	Height	Area	Area%
1	5.623	425	1966	0.023
2	6.201	2084	12212	0.145
3	6.762	943392	8371542	99.629
4	7.298	2413	17031	0.203

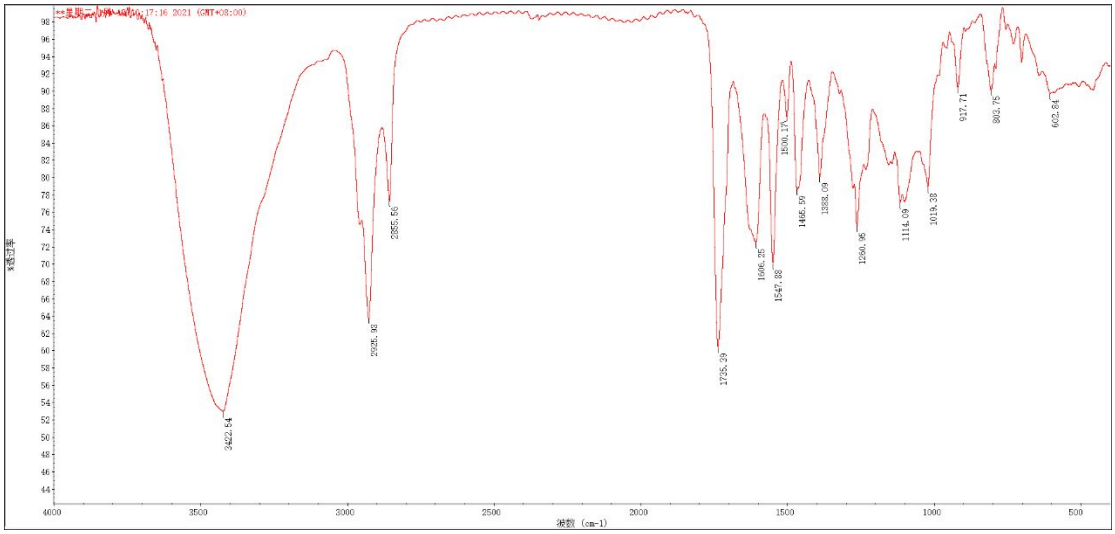
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **6i**



^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **6i**



IR (KBr, cm^{-1}) spectrum of **6i**



HRMS spectrum of **6i**

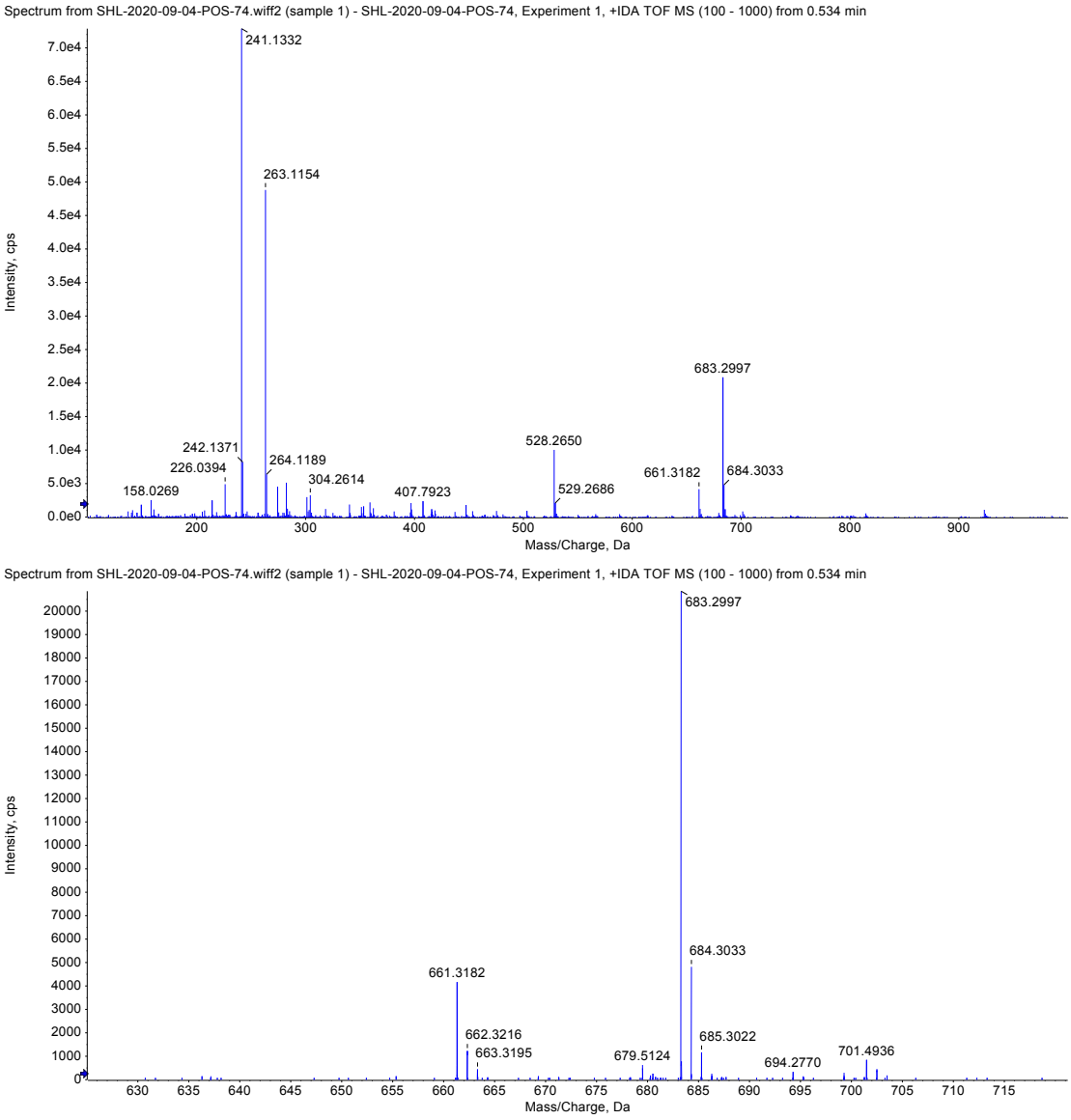
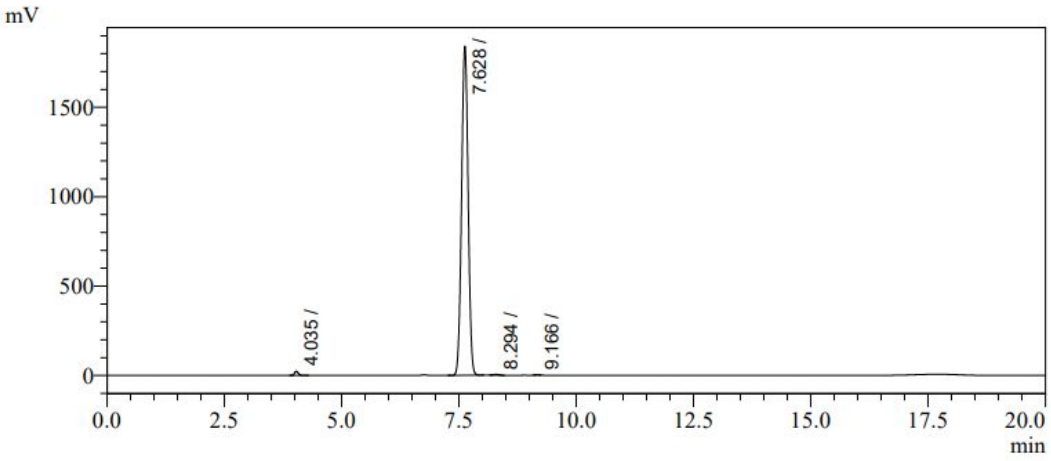


Figure S18. HPLC, ^{1}H NMR, ^{13}C NMR, HRMS and IR spectrum of final compound **6j**

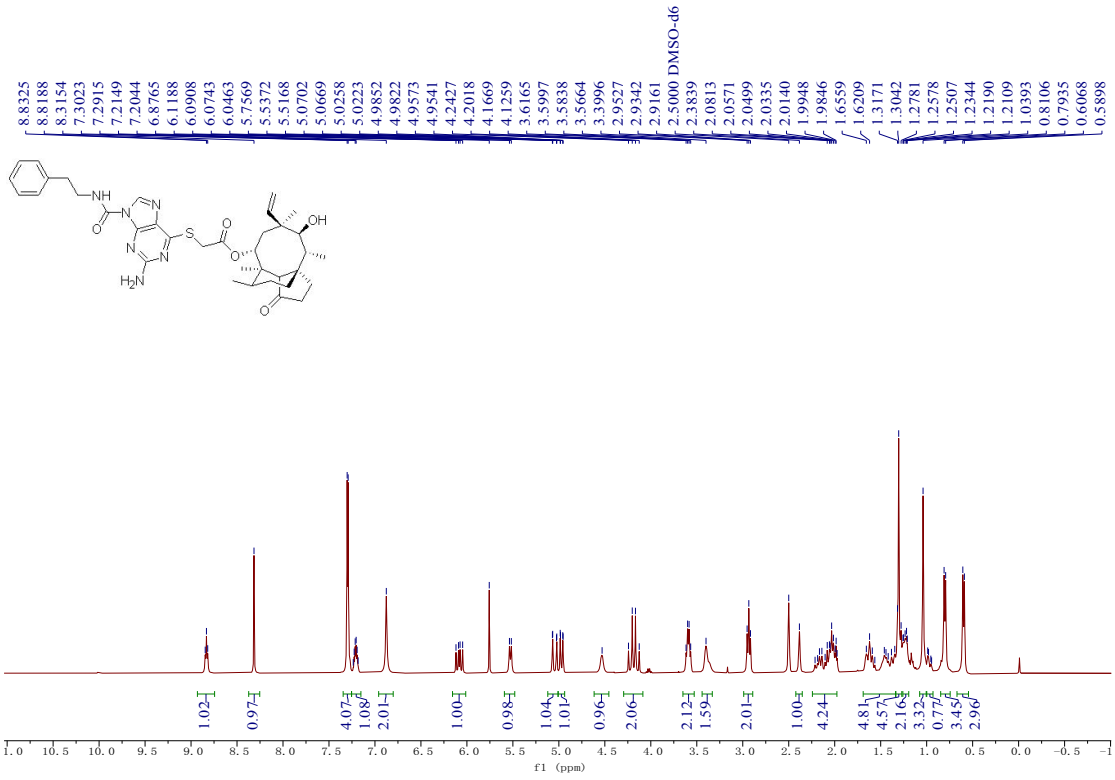
HPLC spectrum of **6j**



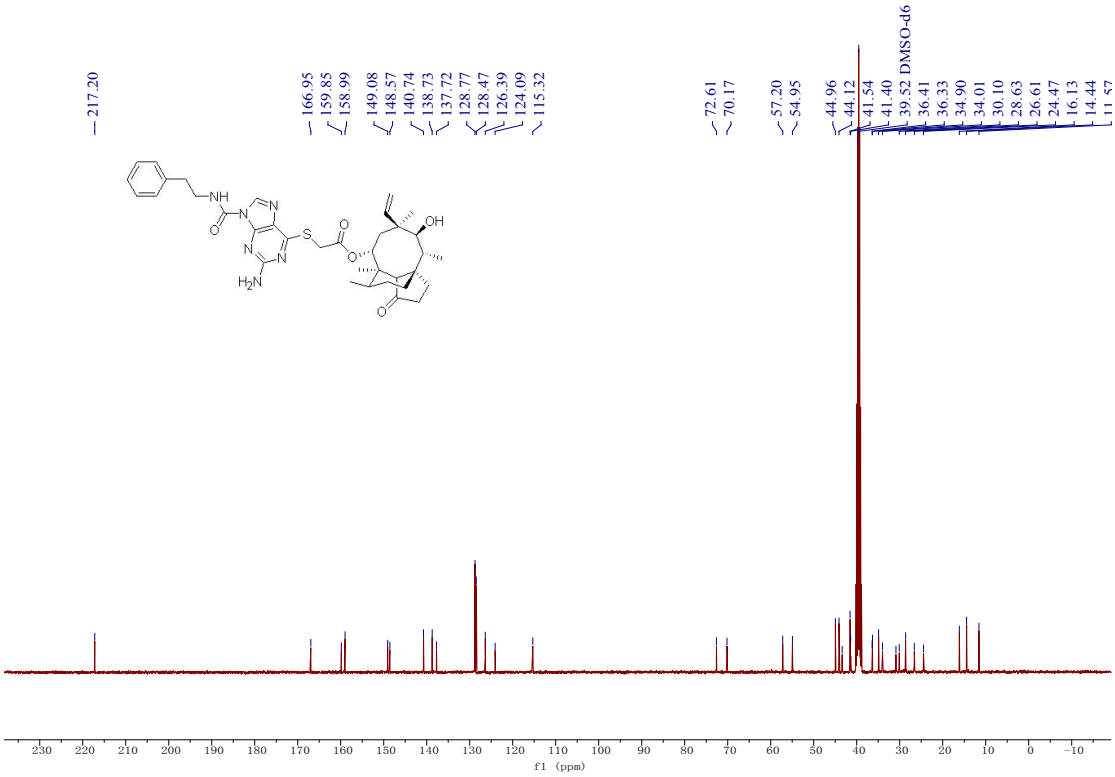
检测器A 254nm

Peak#	Ret. Time	Height	Area	Area%
1	4.035	23462	130175	0.721
2	7.628	1839597	17865849	99.011
3	8.294	5028	43146	0.239
4	9.166	1073	5185	0.029

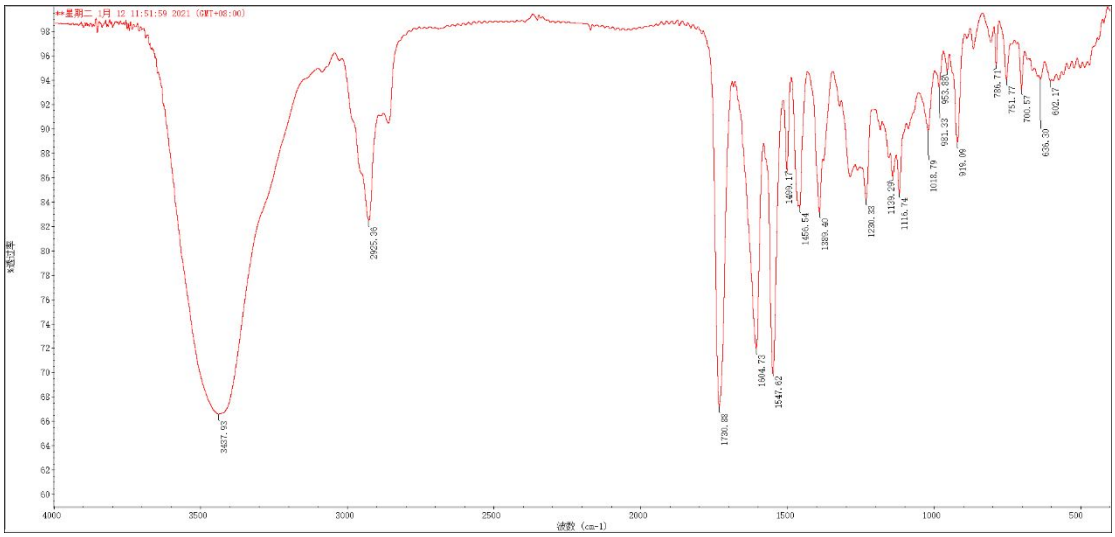
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **6j**



^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **6j**

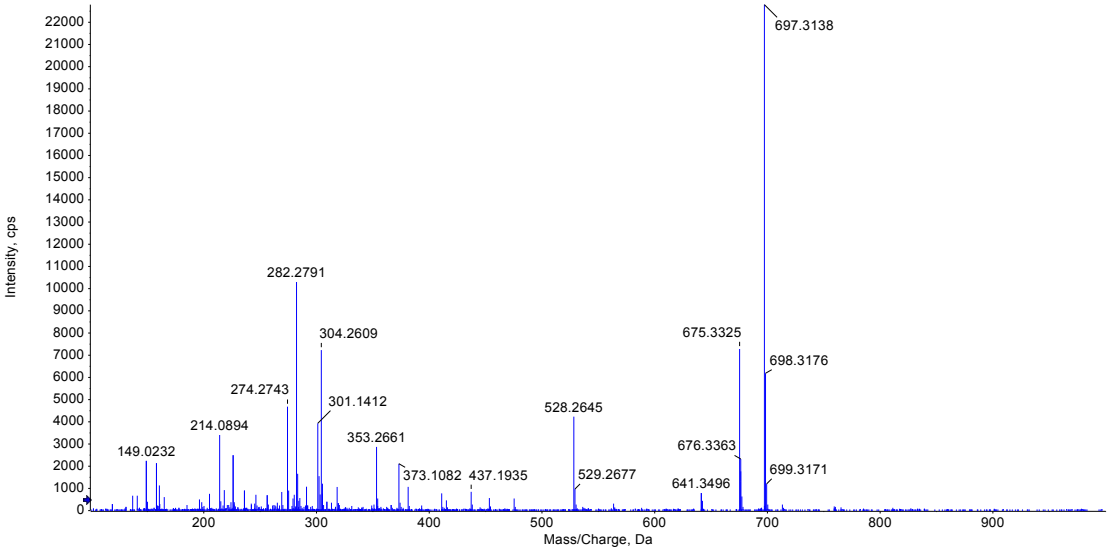


IR (KBr, cm^{-1}) spectrum of **6j**



HRMS spectrum of **6j**

Spectrum from SHL-2020-09-04-POS-65.wiff2 (sample 1) - SHL-2020-09-04-POS-65, Experiment 1, +IDA TOF MS (100 - 1000) from 0.496 min



Spectrum from SHL-2020-09-04-POS-65.wiff2 (sample 1) - SHL-2020-09-04-POS-65, Experiment 1, +IDA TOF MS (100 - 1000) from 0.496 min

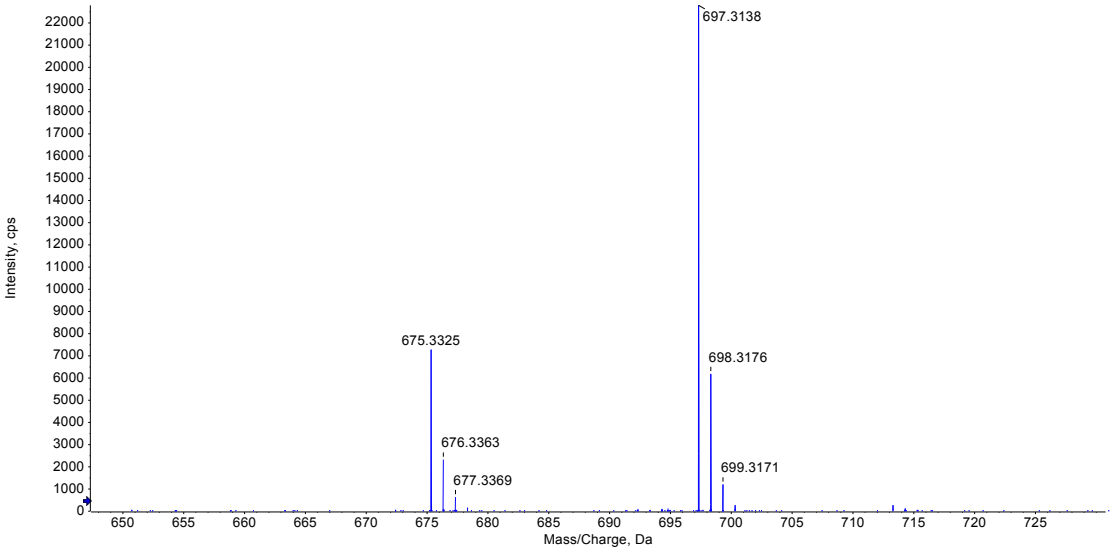
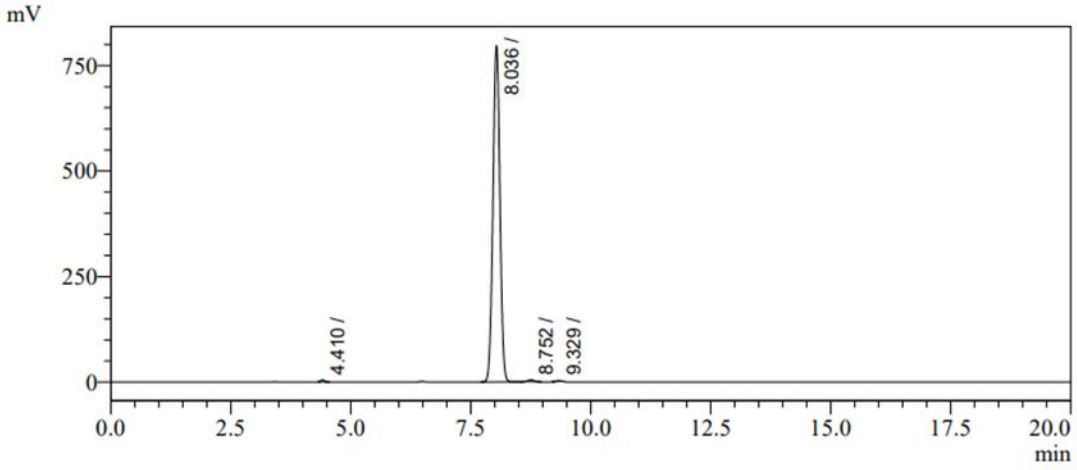


Figure S19. HPLC, ^{1}H NMR, ^{13}C NMR, HRMS and IR spectrum of final compound **6k**

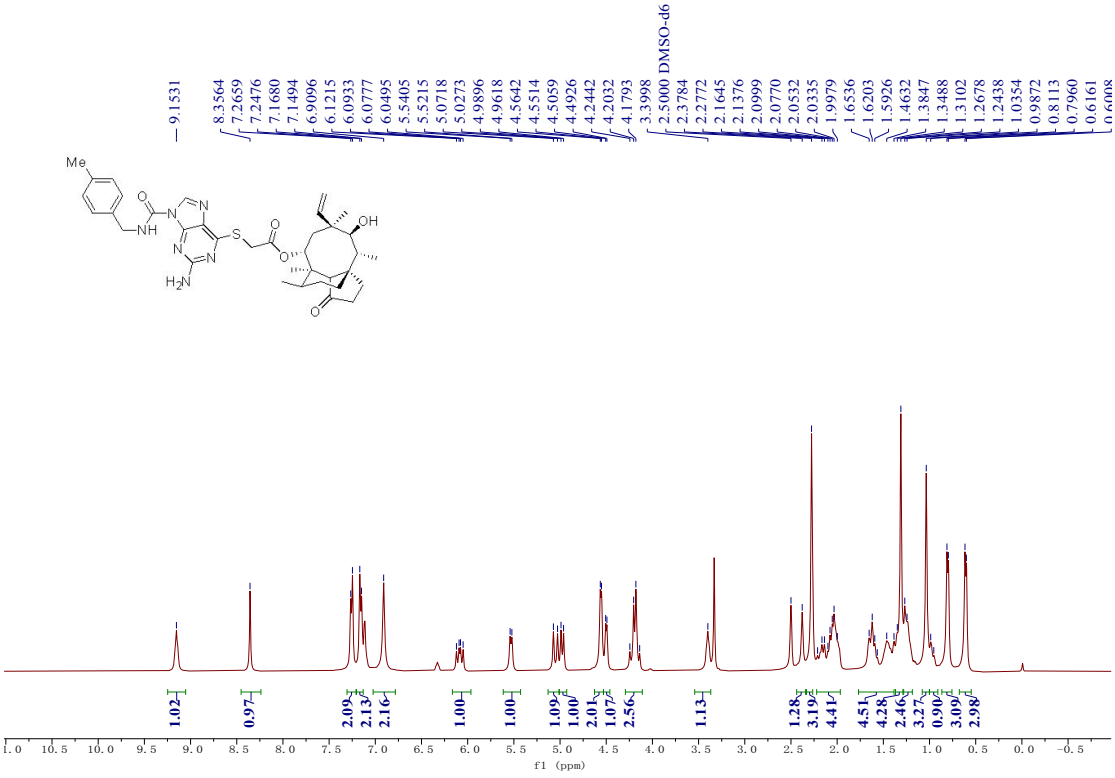
HPLC spectrum of **6k**



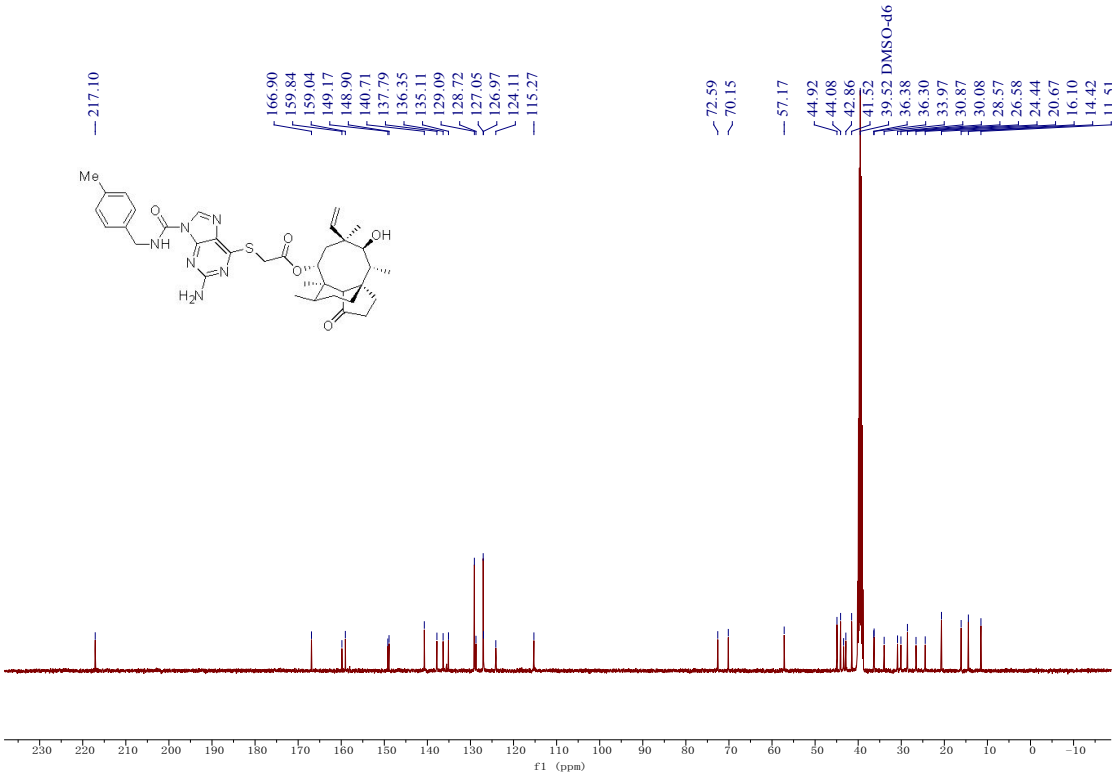
检测器A 254nm

Peak#	Ret. Time	Height	Area	Area%
1	4.410	4309	24994	0.309
2	8.036	796190	8010281	99.155
3	8.752	3666	31996	0.396
4	9.329	1588	11314	0.140

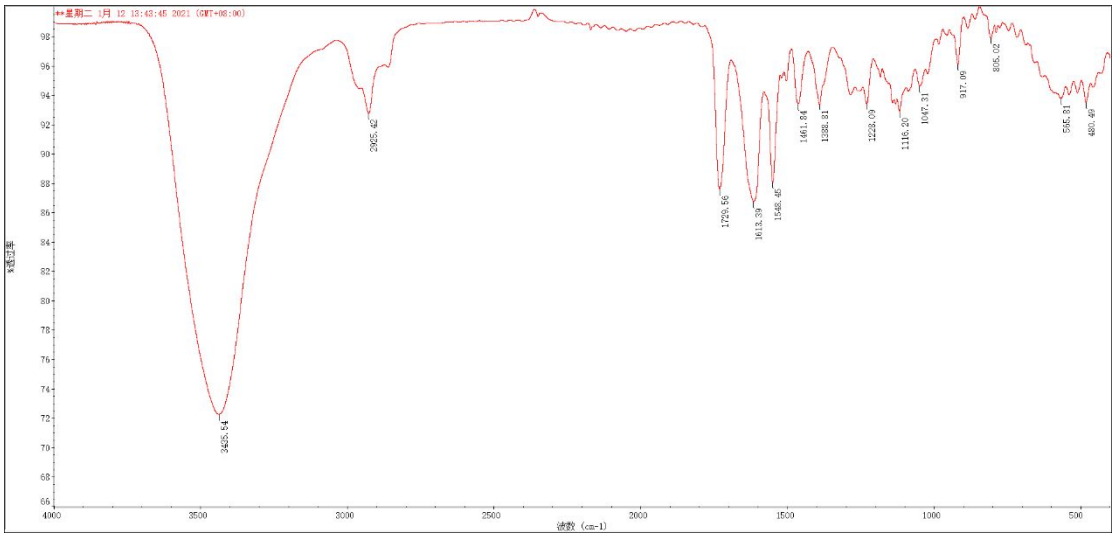
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **6k**



^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **6k**



IR (KBr, cm^{-1}) spectrum of **6k**



HRMS spectrum of **6k**

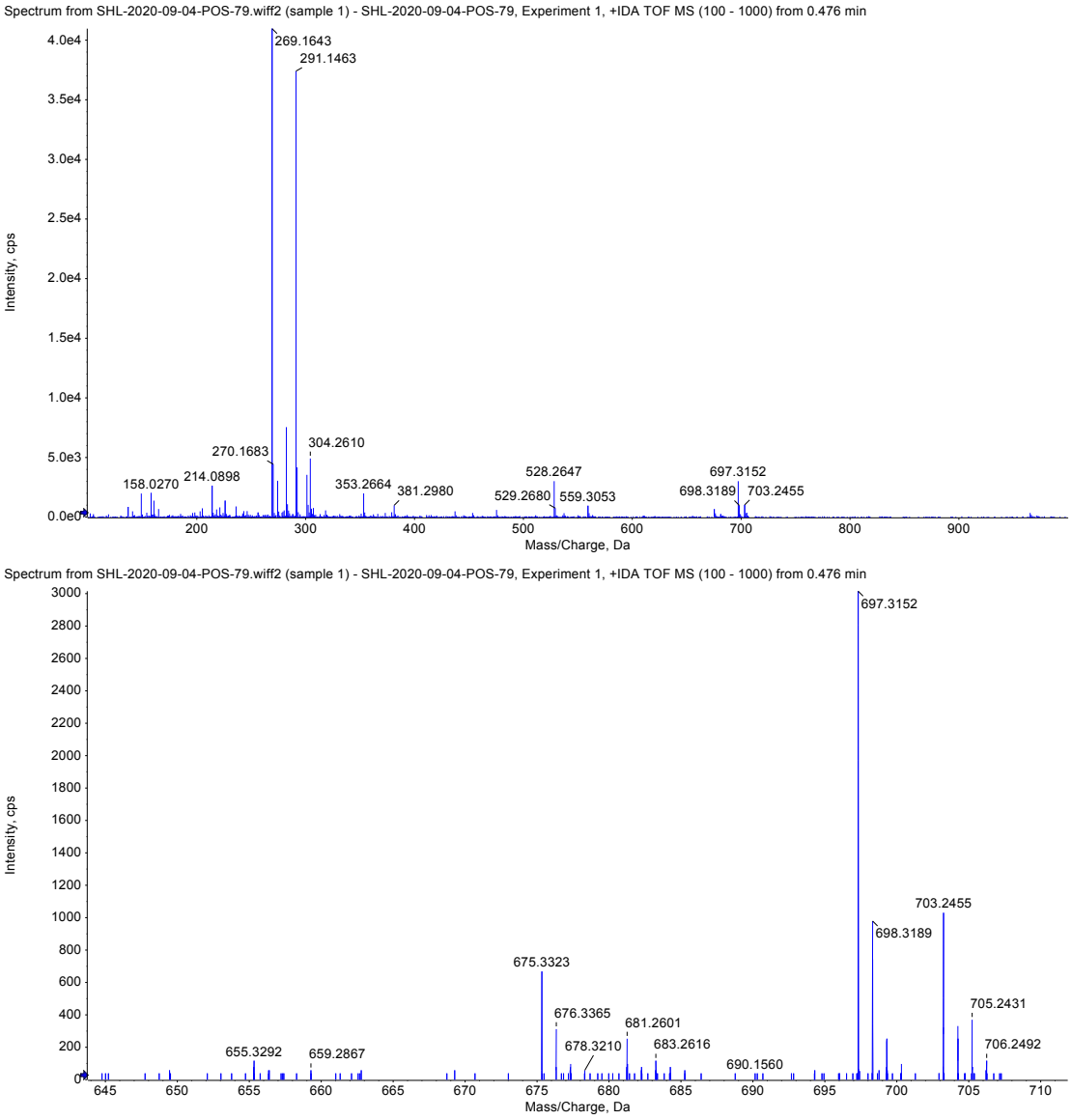
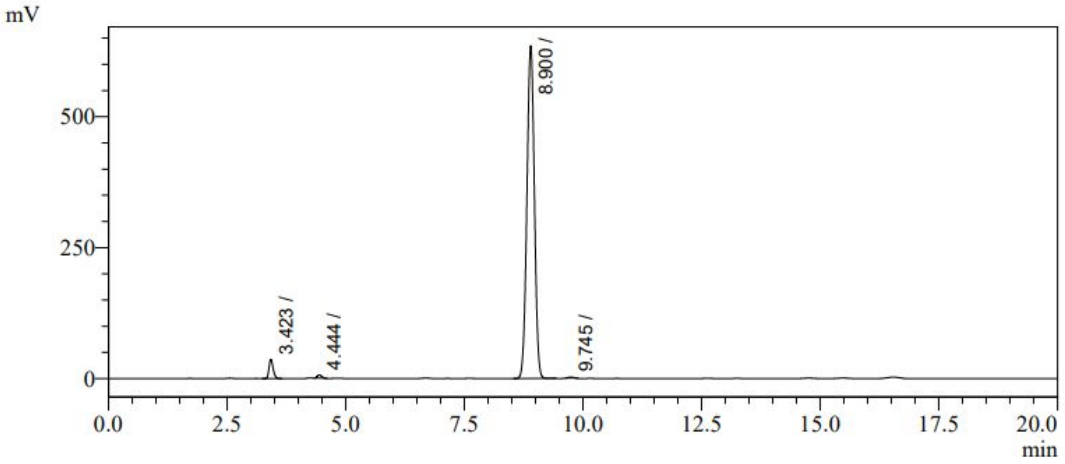


Figure S20. HPLC, ^{1}H NMR, ^{13}C NMR, HRMS and IR spectrum of final compound **6l**

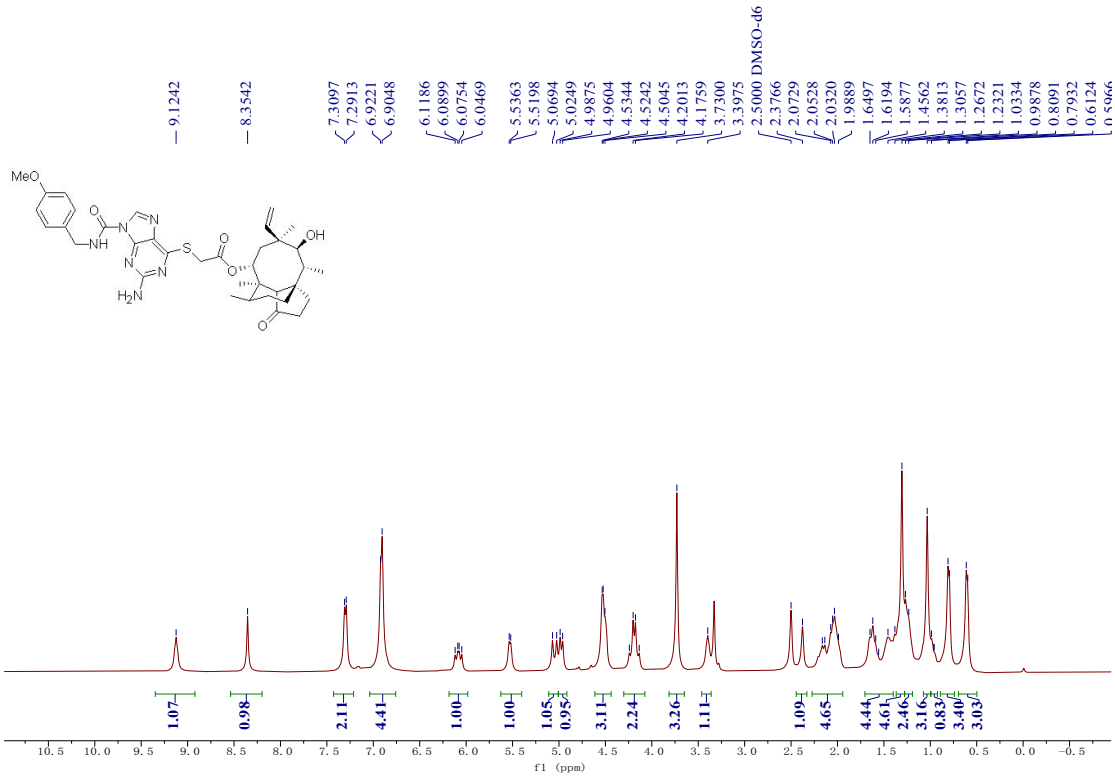
HPLC spectrum of **6l**



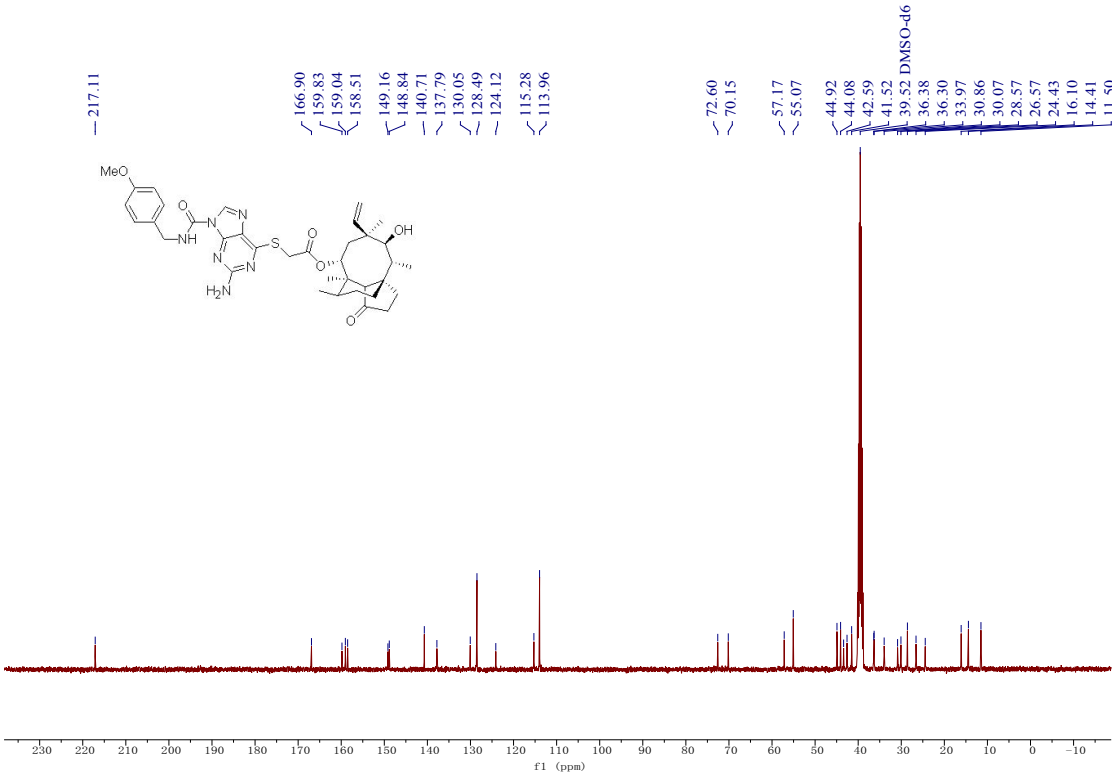
检测器A 254nm

Peak#	Ret. Time	Height	Area	Area%
1	3.423	36373	218109	3.027
2	4.444	6141	39877	0.553
3	8.900	634715	6936278	96.250
4	9.745	1630	12253	0.170

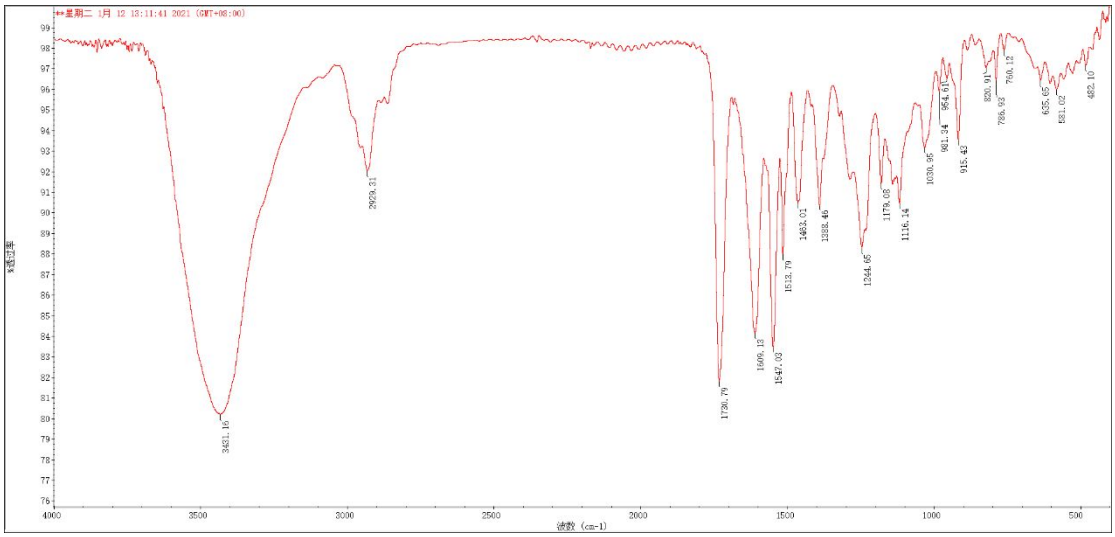
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **6l**



^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **6l**

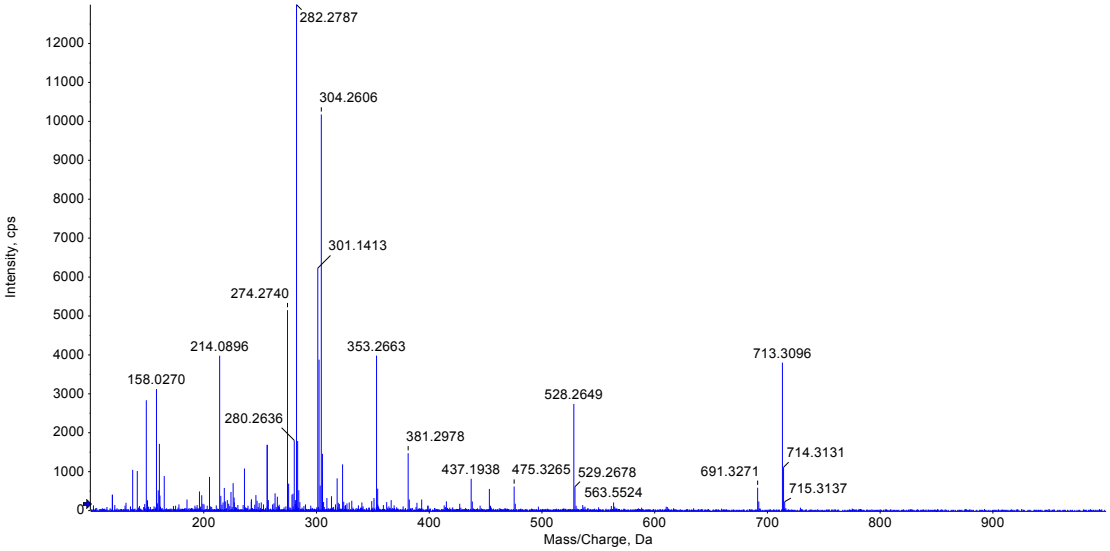


IR (KBr, cm^{-1}) spectrum of **6l**



HRMS spectrum of **6l**

Spectrum from SHL-2020-09-04-POS-63.wiff2 (sample 1) - SHL-2020-09-04-POS-63, Experiment 1, +IDA TOF MS (100 - 1000) from 0.581 min



Spectrum from SHL-2020-09-04-POS-63.wiff2 (sample 1) - SHL-2020-09-04-POS-63, Experiment 1, +IDA TOF MS (100 - 1000) from 0.581 min

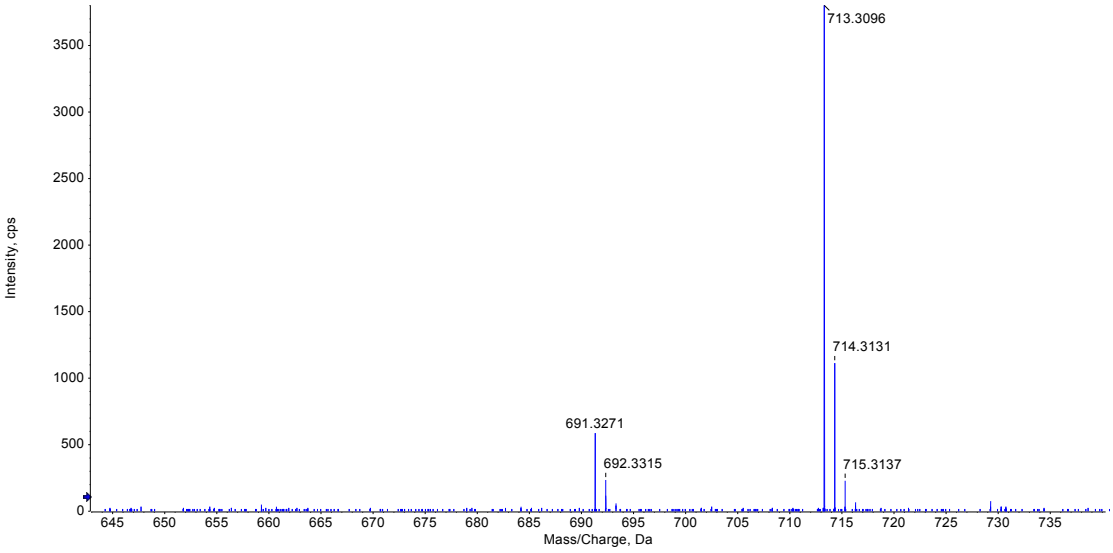
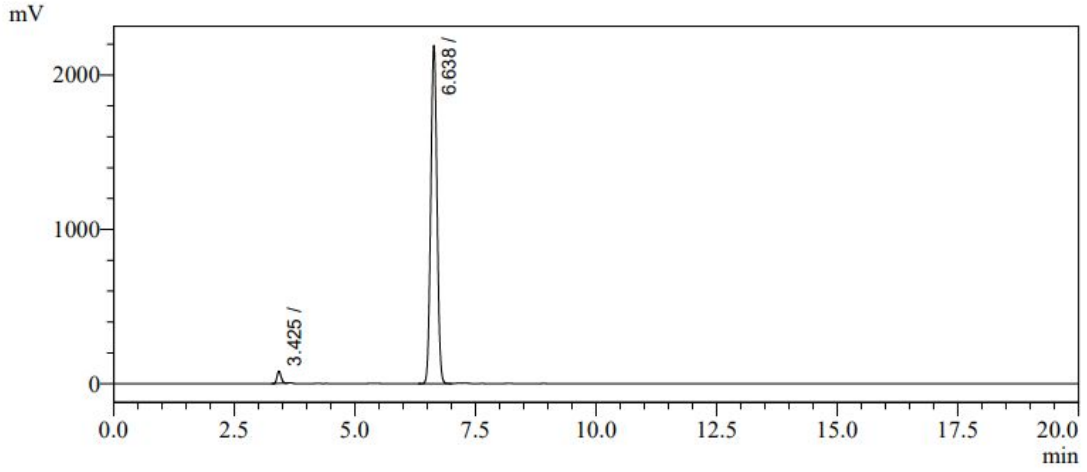


Figure S21. HPLC, ^{1}H NMR, ^{13}C NMR, HRMS and IR spectrum of final compound **6m**

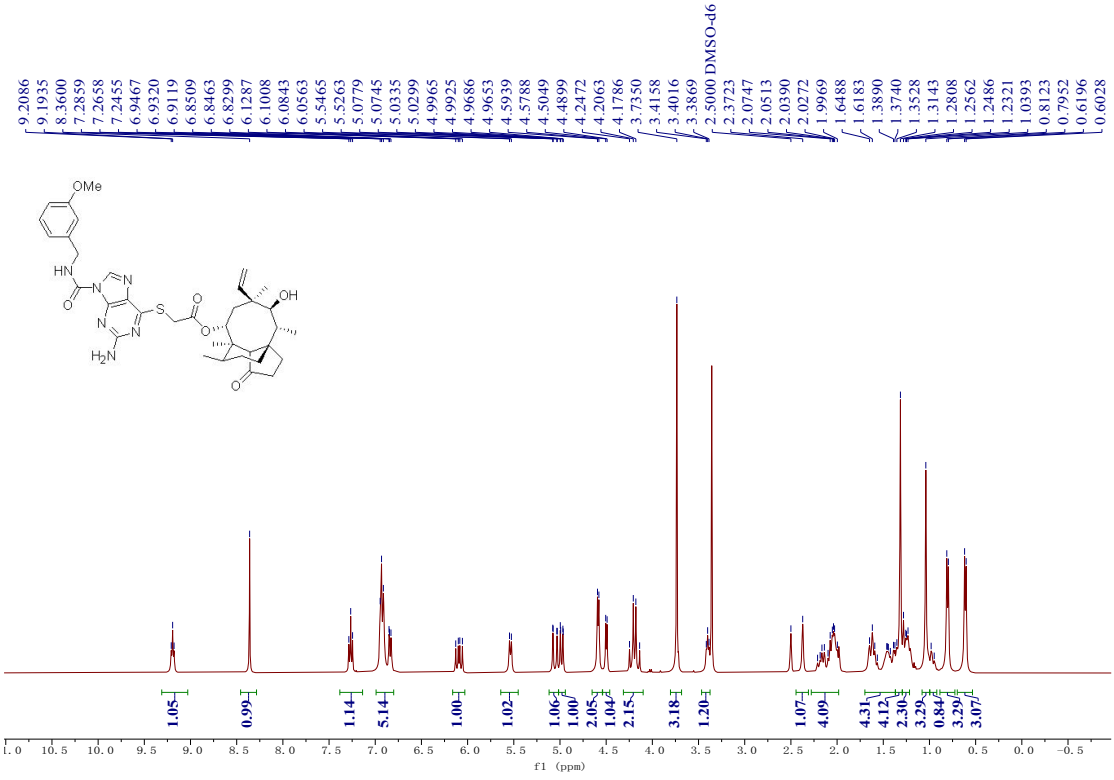
HPLC spectrum of **6m**



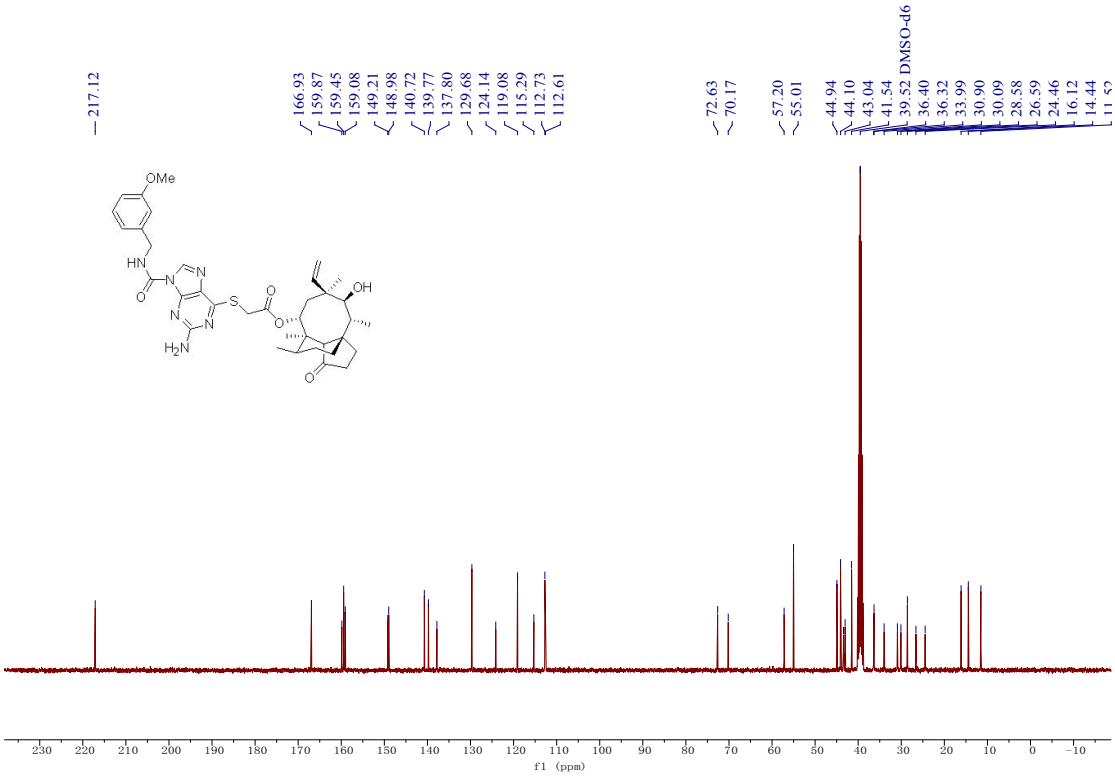
检测器A 254nm

Peak#	Ret. Time	Height	Area	Area%
1	3.425	77845	426453	2.128
2	6.638	2190551	19616998	97.872

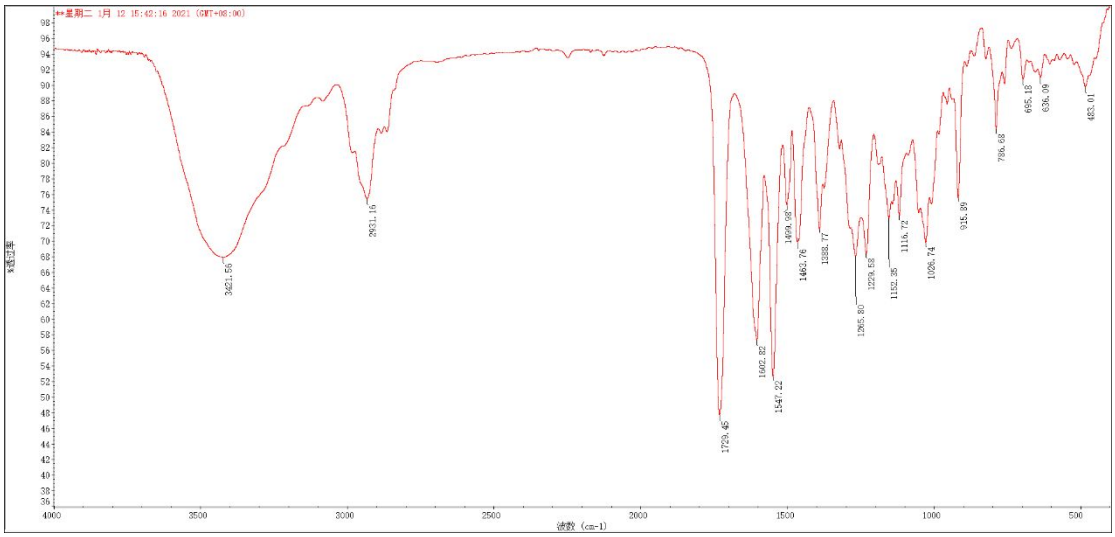
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **6m**



^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **6m**



IR (KBr, cm^{-1}) spectrum of **6m**



HRMS spectrum of **6m**

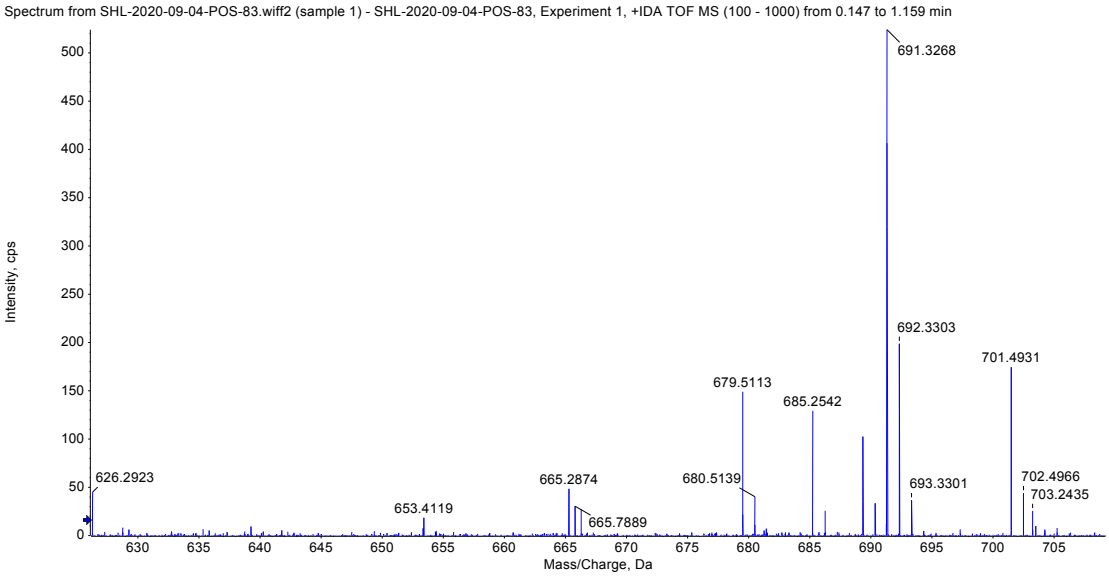
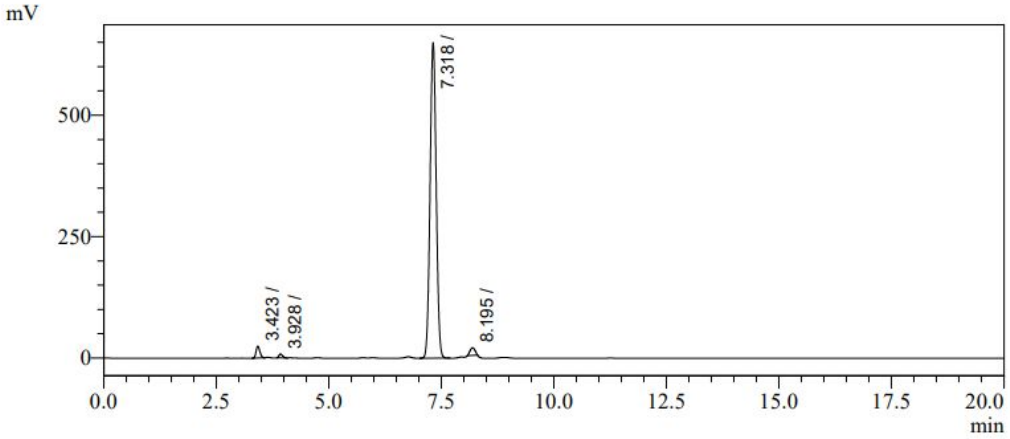


Figure S22. HPLC, ^{1}H NMR, ^{13}C NMR, HRMS and IR spectrum of final compound **6n**

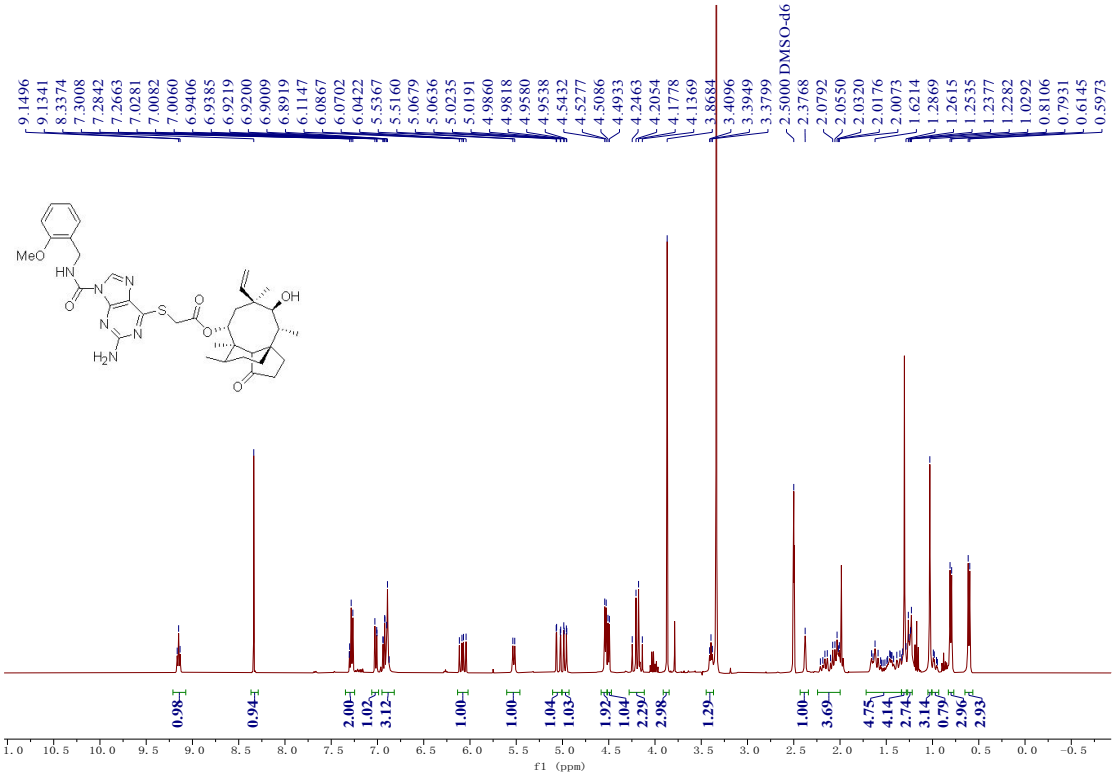
HPLC spectrum of **6n**



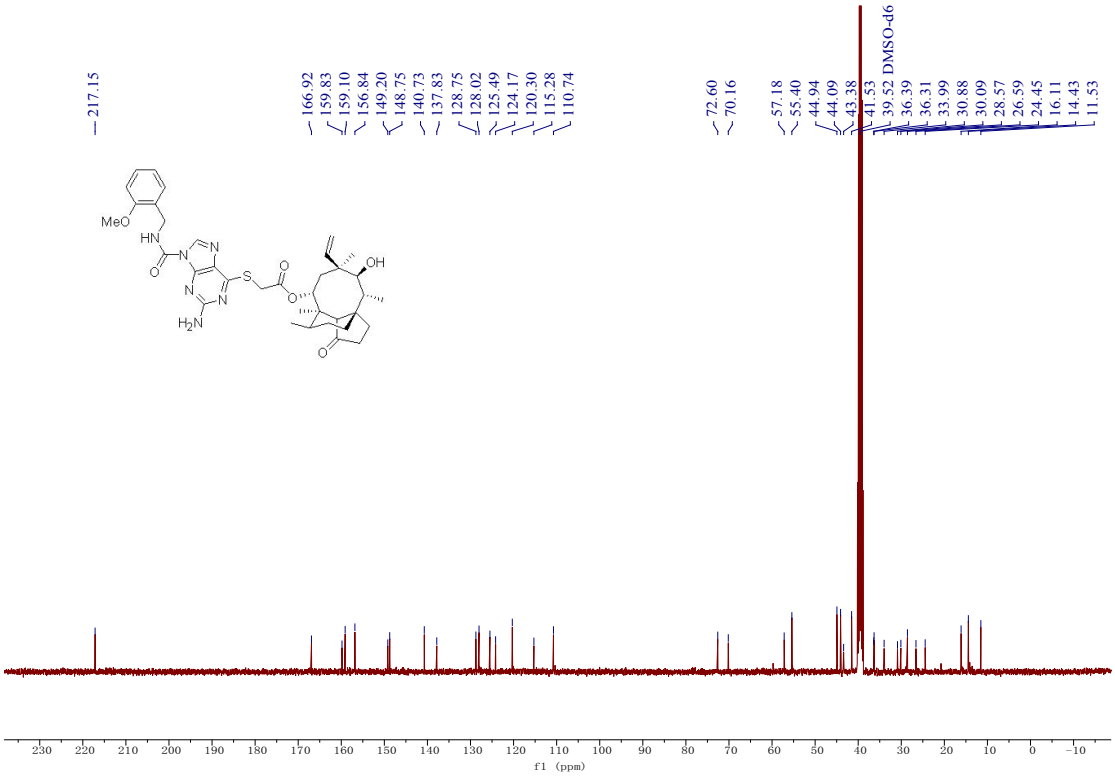
检测器A 254nm

Peak#	Ret. Time	Height	Area	Area%
1	3.423	24341	142112	2.203
2	3.928	7819	45004	0.698
3	7.318	648440	6144271	95.231
4	8.195	15540	120595	1.869

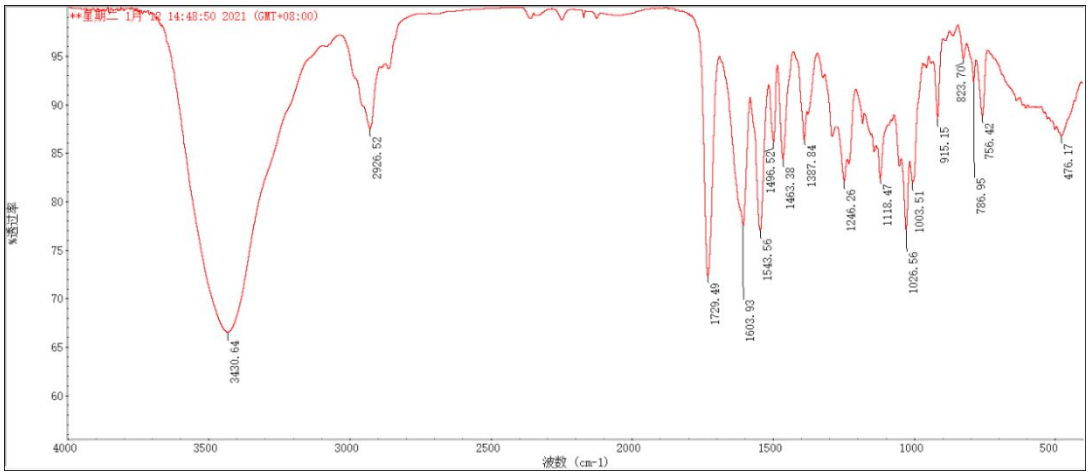
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **6n**



^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **6n**



IR (KBr, cm^{-1}) spectrum of **6n**



HRMS spectrum of **6n**

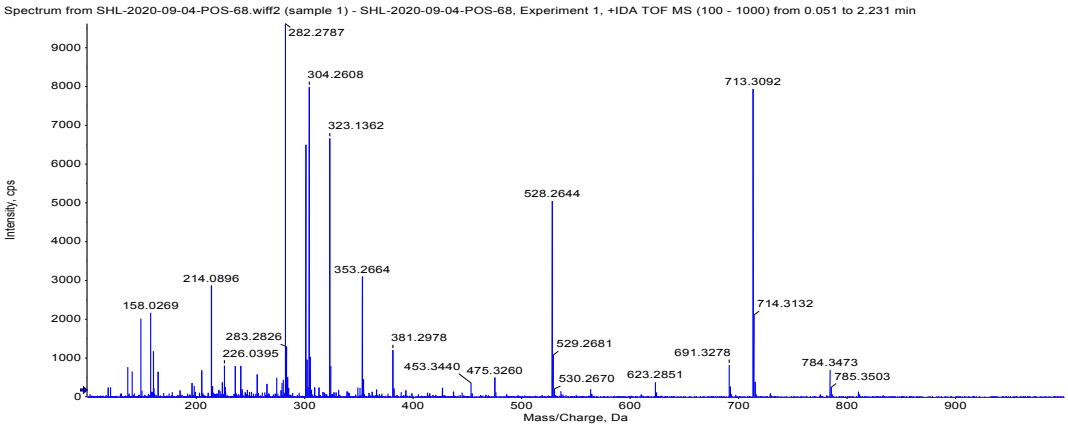
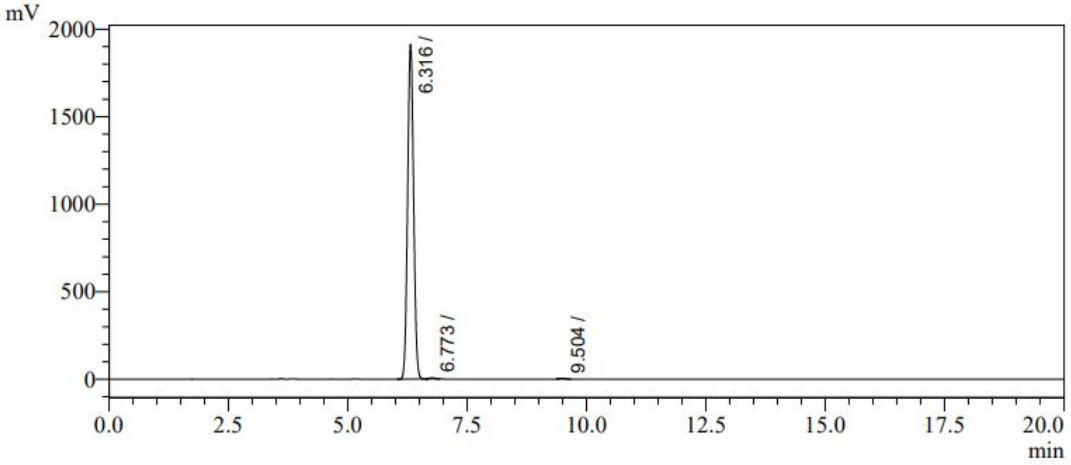

Spectrum from SHL-2020-09-04-POS-68.wiff2 (sample 1) - SHL-2020-09-04-POS-68, Experiment 1, +IDA TOF MS (100 - 1000) from 0.051 to 2.231 min
Intensity, cps
Mass/Charge, Da
282.2787
304.2608
323.1362
713.3092
528.2644
353.2664
214.0896
158.0269
714.3132
283.2826
381.2978
529.2681
226.0395
691.3278
453.3440
475.3260
784.3473
530.2670
623.2851
785.3503

Figure S23. HPLC, ^{1}H NMR, ^{13}C NMR, HRMS and IR spectrum of final compound **6o**

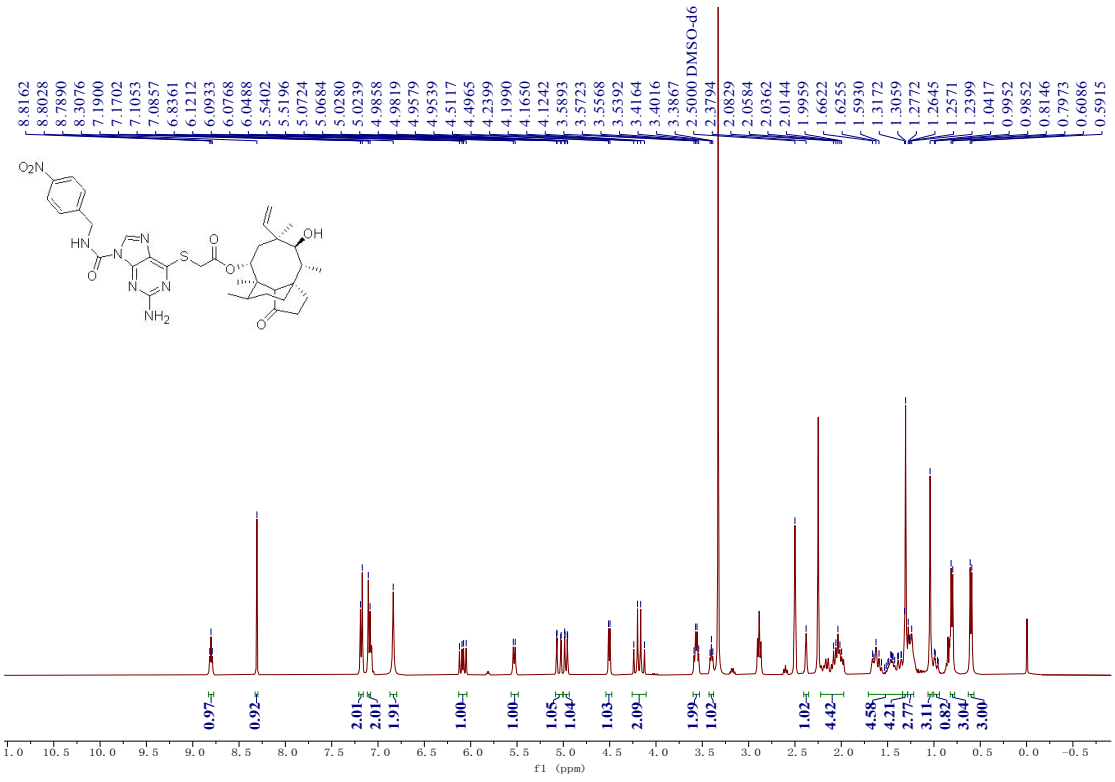
HPLC spectrum of **6o**



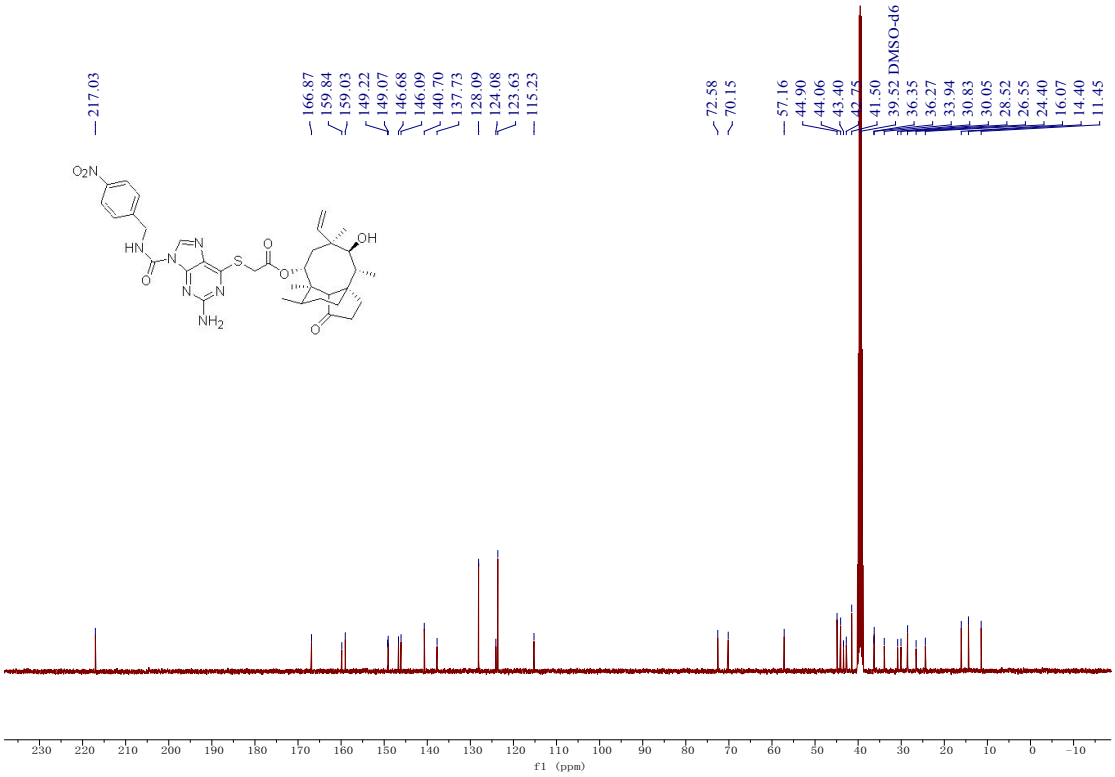
检测器A 254nm

Peak#	Ret. Time	Height	Area	Area%
1	6.316	1910086	16582216	99.458
2	6.773	6883	52767	0.316
3	9.504	4141	37520	0.225

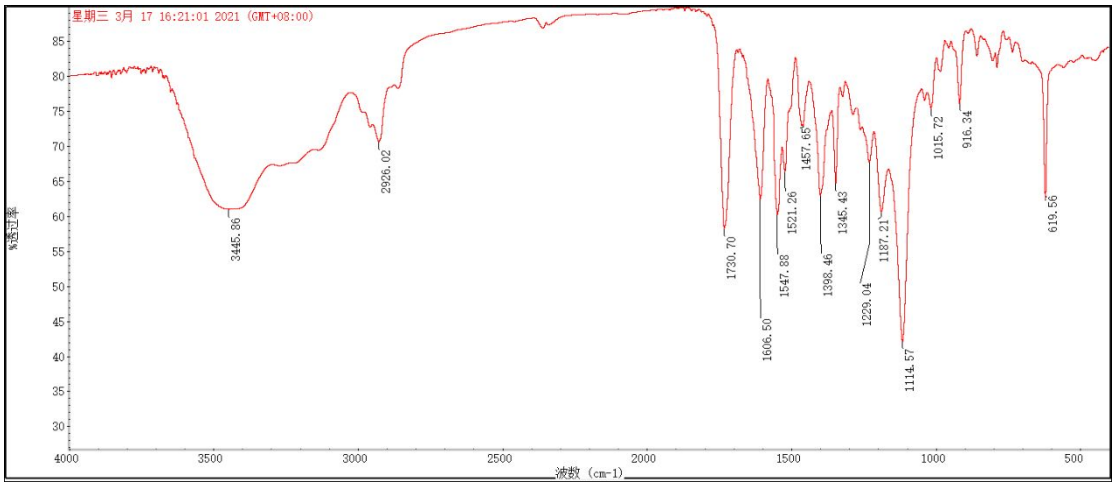
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **6o**



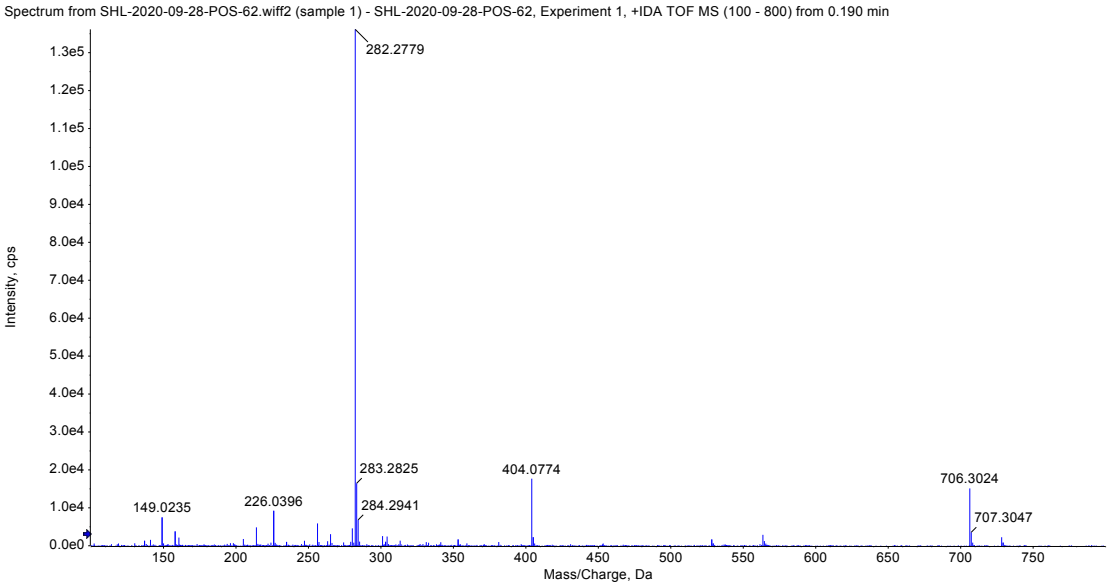
^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **6o**



IR (KBr, cm^{-1}) spectrum of **6o**



HRMS spectrum of **6o**



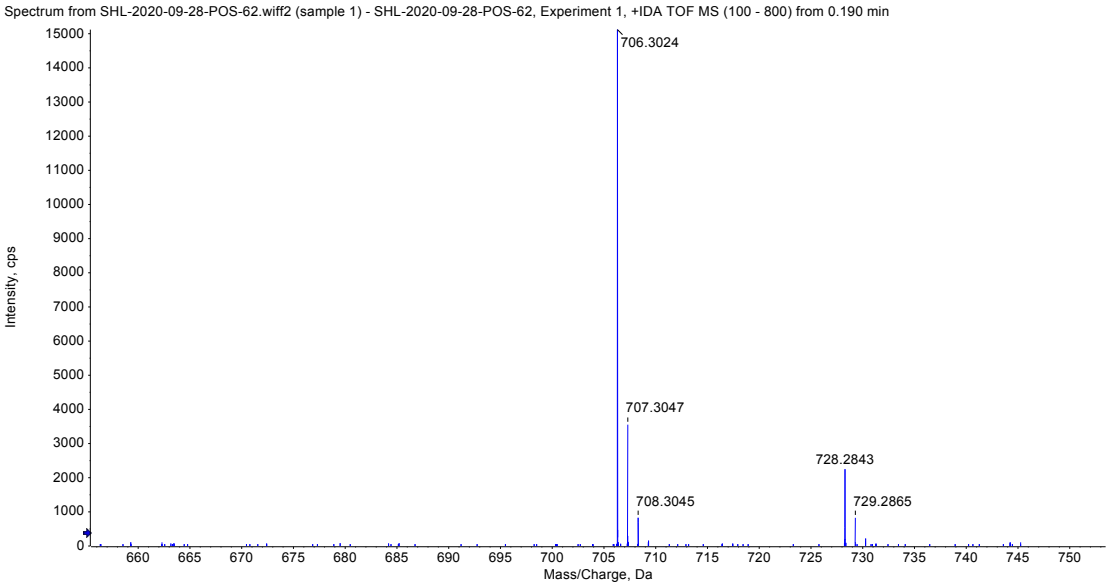
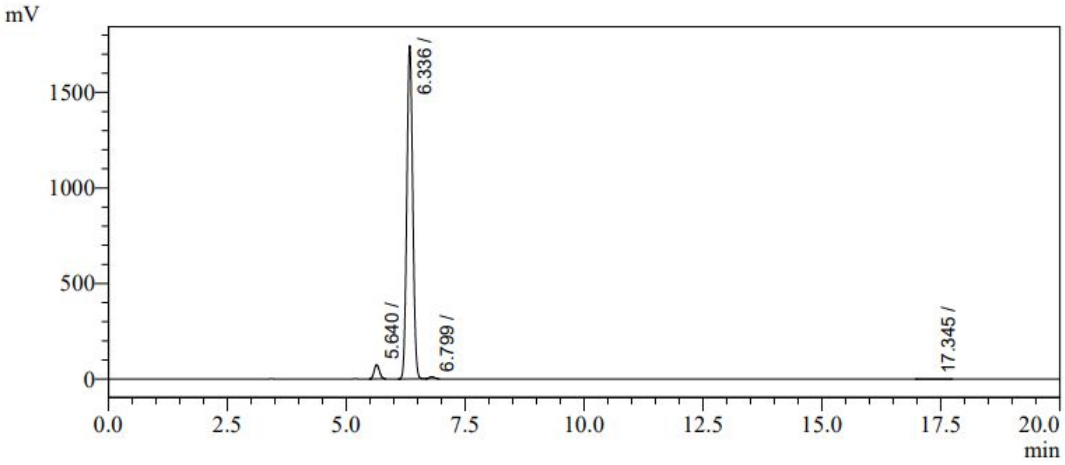


Figure S24. HPLC, ^{1}H NMR, ^{13}C NMR, HRMS and IR spectrum of final compound **6p**

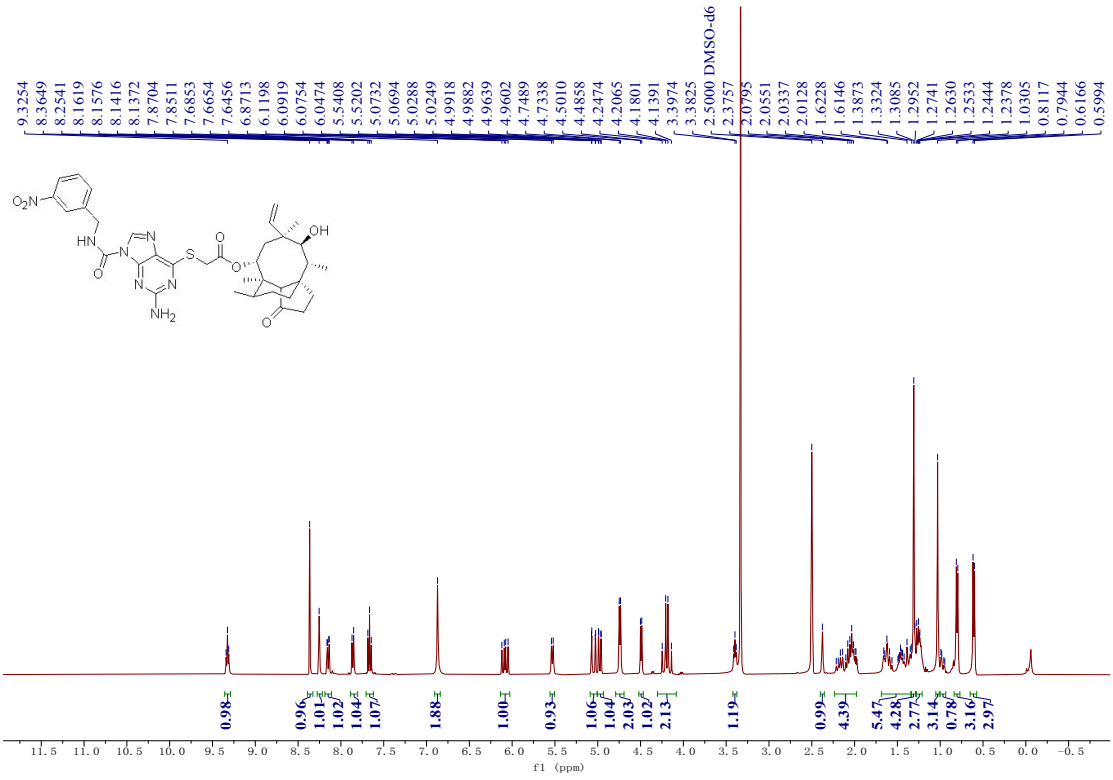
HPLC spectrum of **6p**



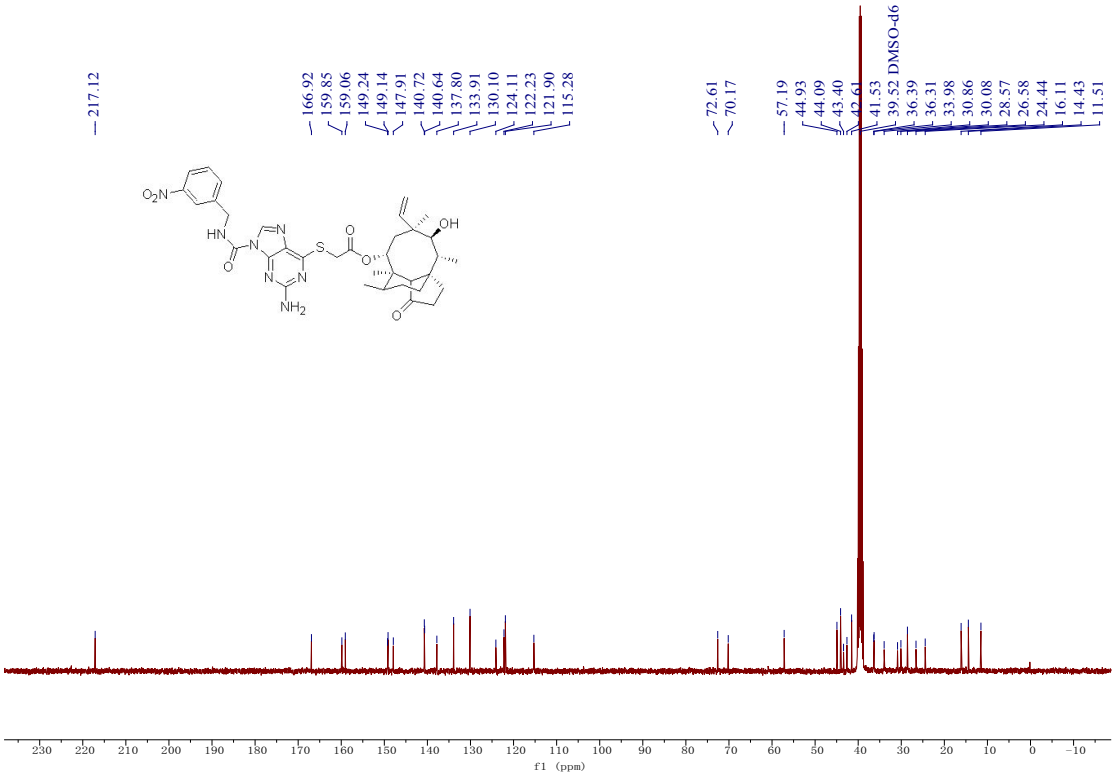
检测器A 254nm

Peak#	Ret. Time	Height	Area	Area%
1	5.640	73643	561668	3.582
2	6.336	1741326	15042409	95.920
3	6.799	9819	74926	0.478
4	17.345	170	3213	0.020

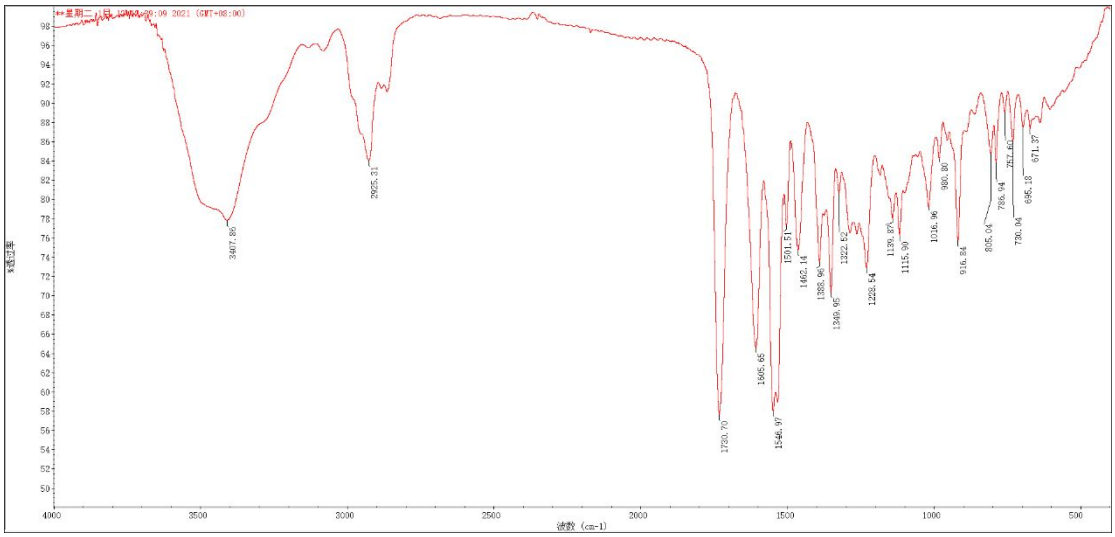
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **6p**



^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **6p**

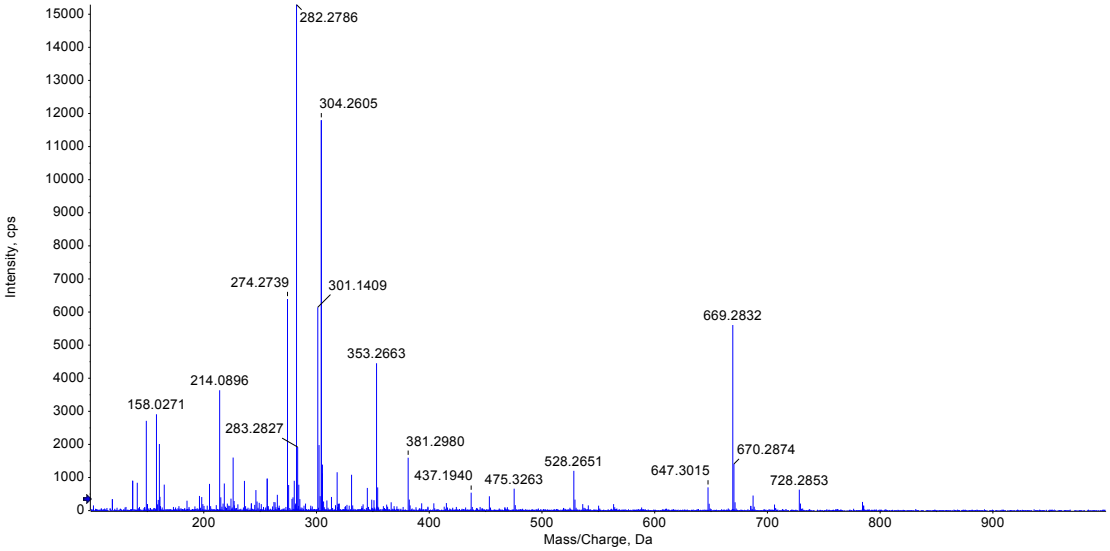


IR (KBr, cm^{-1}) spectrum of **6p**



HRMS spectrum of **6p**

Spectrum from SHL-2020-09-04-POS-72.wiff2 (sample 1) - SHL-2020-09-04-POS-72, Experiment 1, +IDA TOF MS (100 - 1000) from 0.514 min



Spectrum from SHL-2020-09-04-POS-72.wiff2 (sample 1) - SHL-2020-09-04-POS-72, Experiment 1, +IDA TOF MS (100 - 1000) from 0.514 min

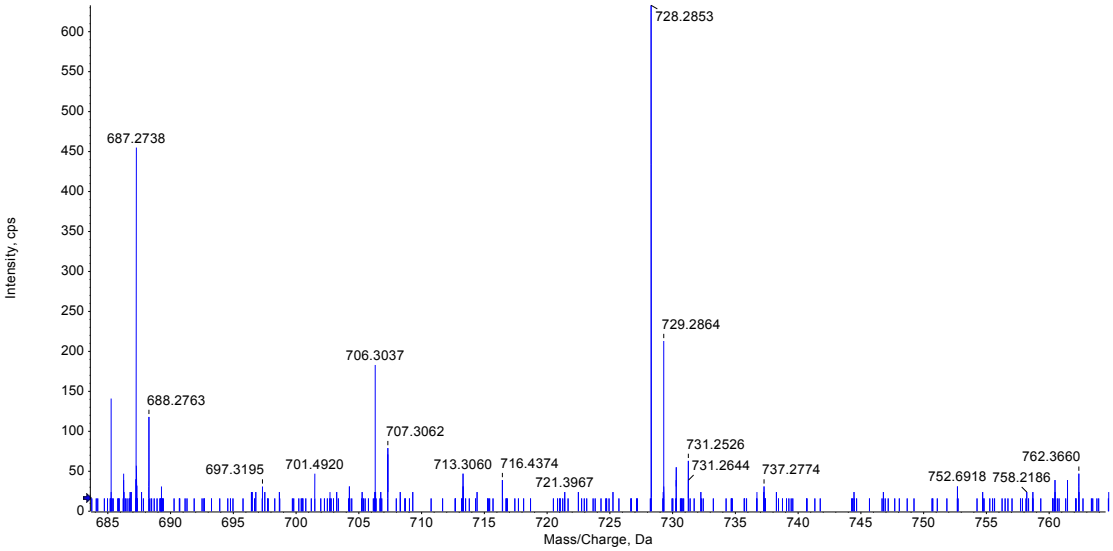
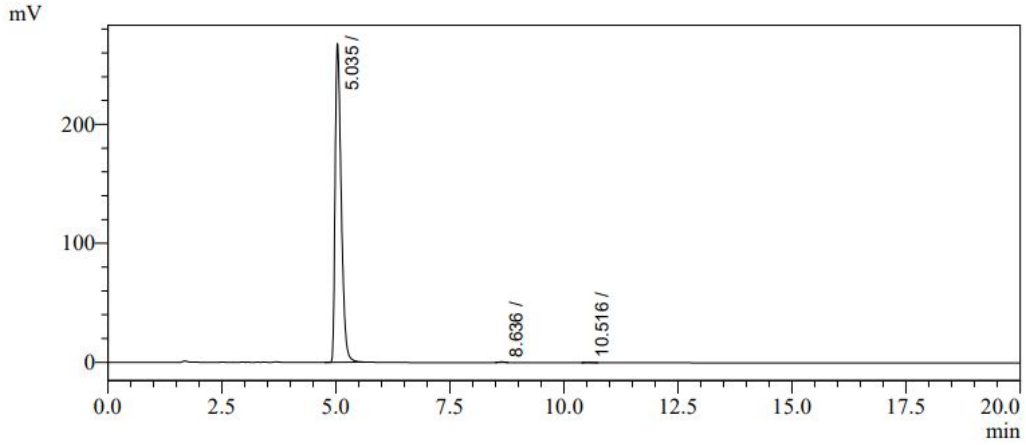


Figure S25. HPLC, ^{1}H NMR, ^{13}C NMR, HRMS and IR spectrum of final compound **8a**

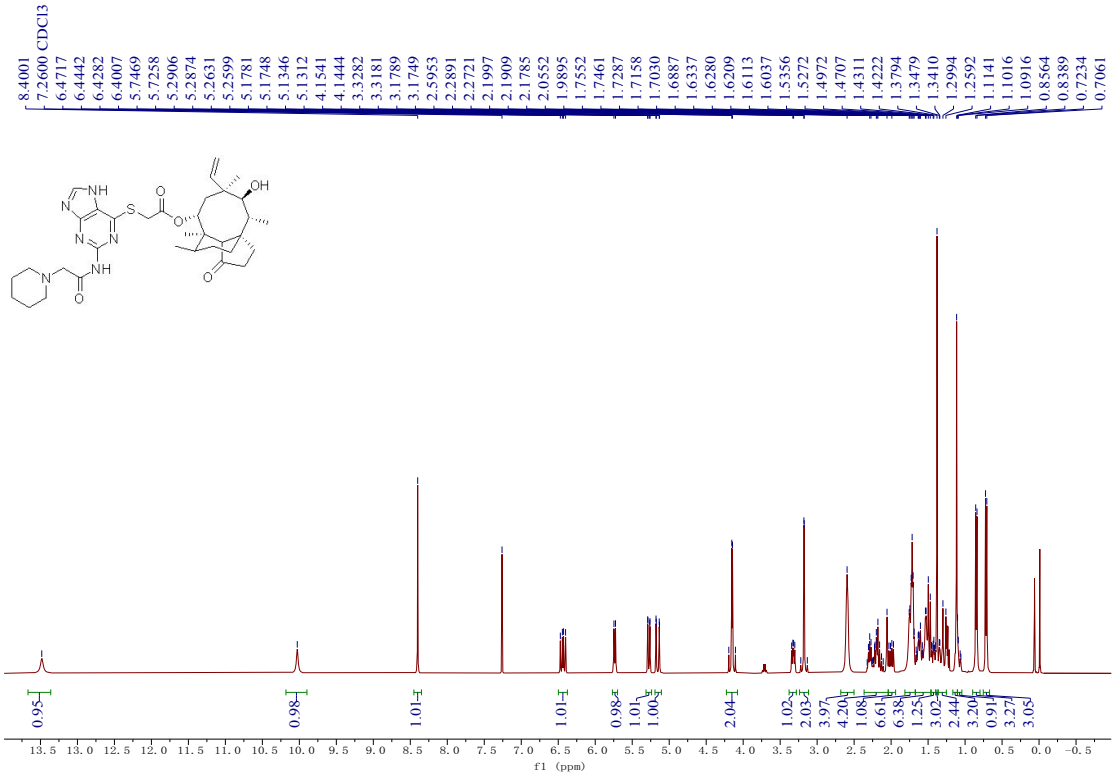
HPLC spectrum of **8a**



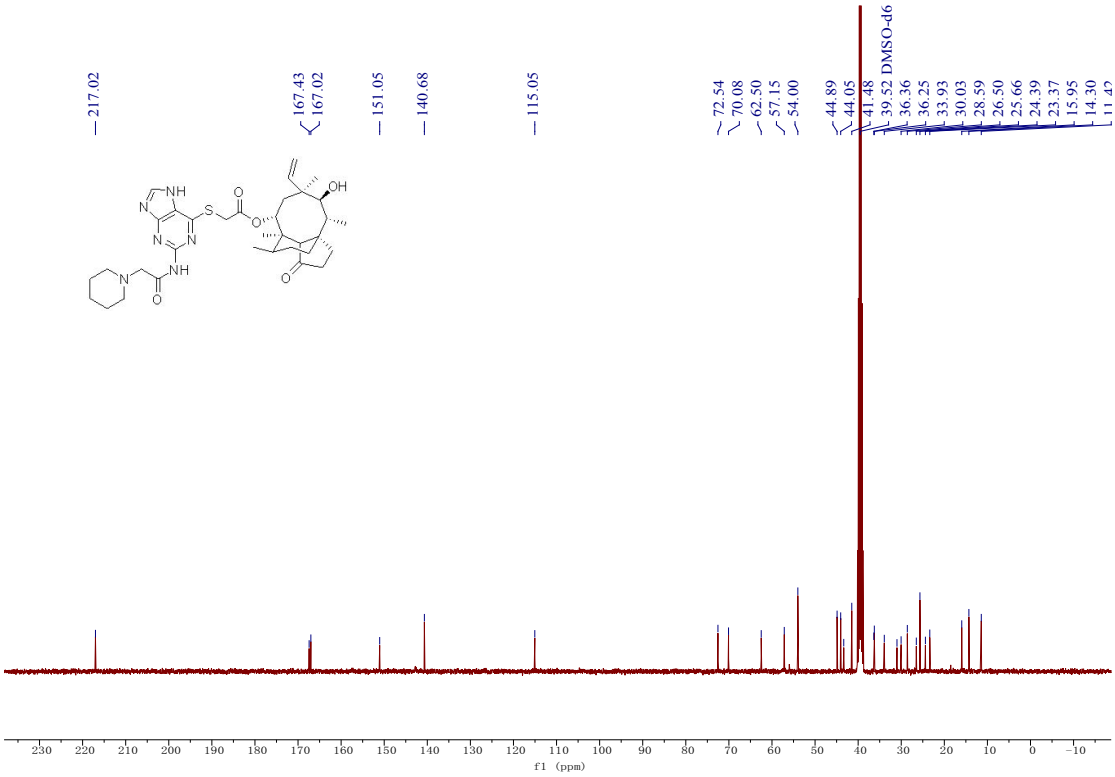
检测器A 254nm

Peak#	Ret. Time	Height	Area	Area%
1	5.035	268272	2474917	99.702
2	8.636	564	4599	0.185
3	10.516	309	2787	0.112

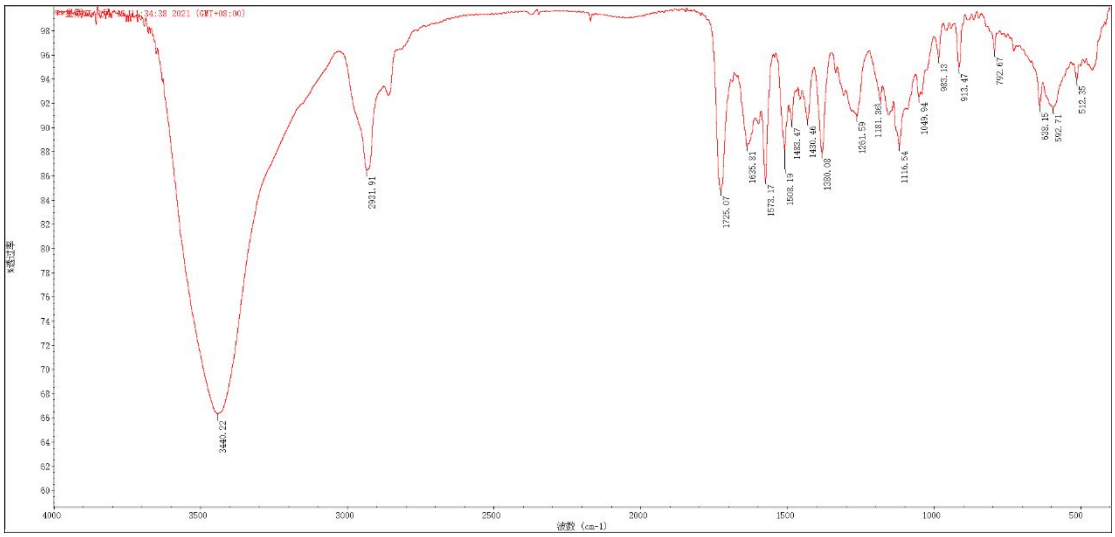
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **8a**



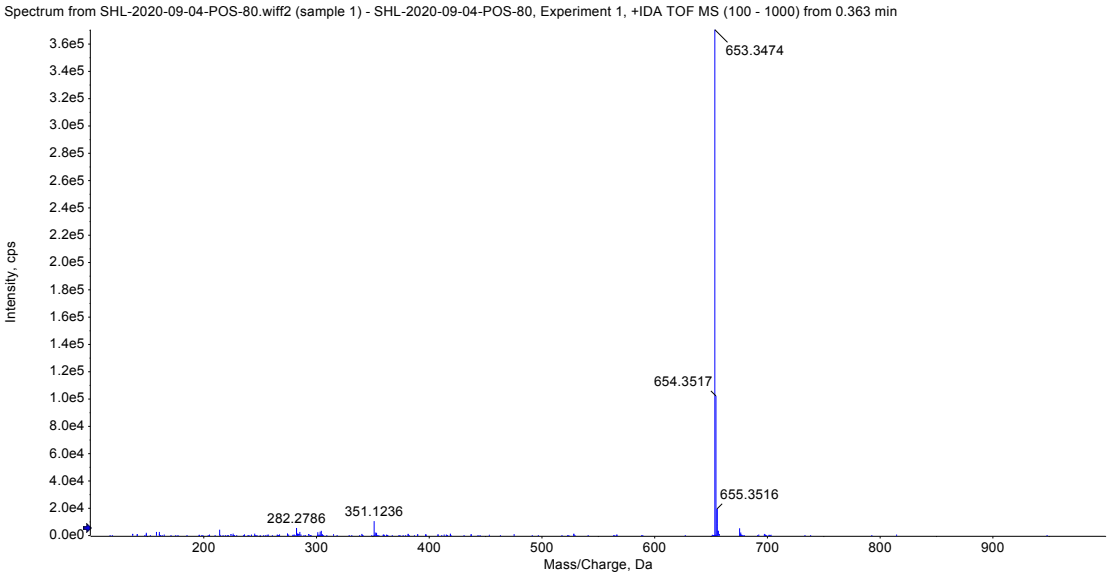
^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **8a**



IR (KBr, cm^{-1}) spectrum of **8a**



HRMS spectrum of **8a**



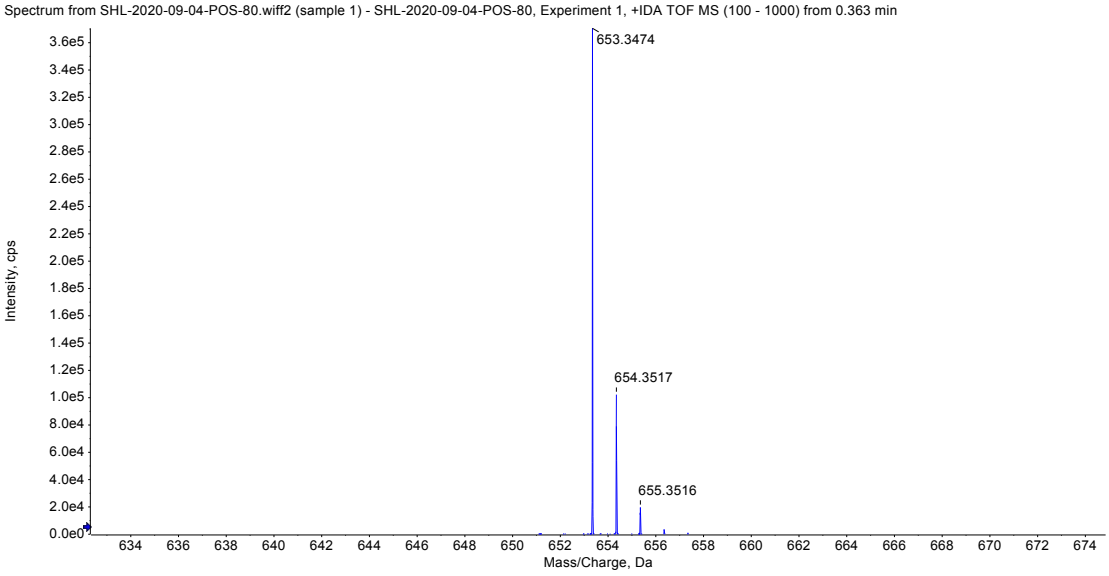
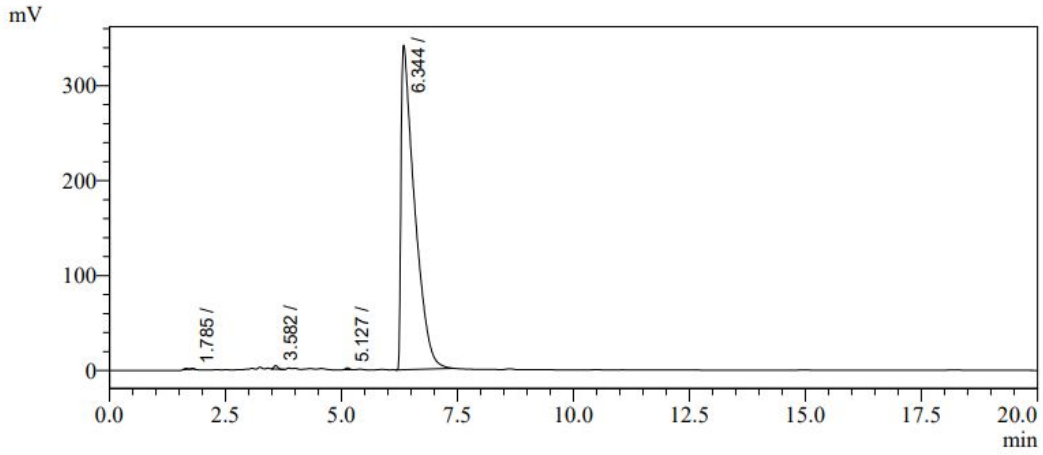


Figure S26. HPLC, ^{1}H NMR, ^{13}C NMR, HRMS and IR spectrum of final compound **8b**

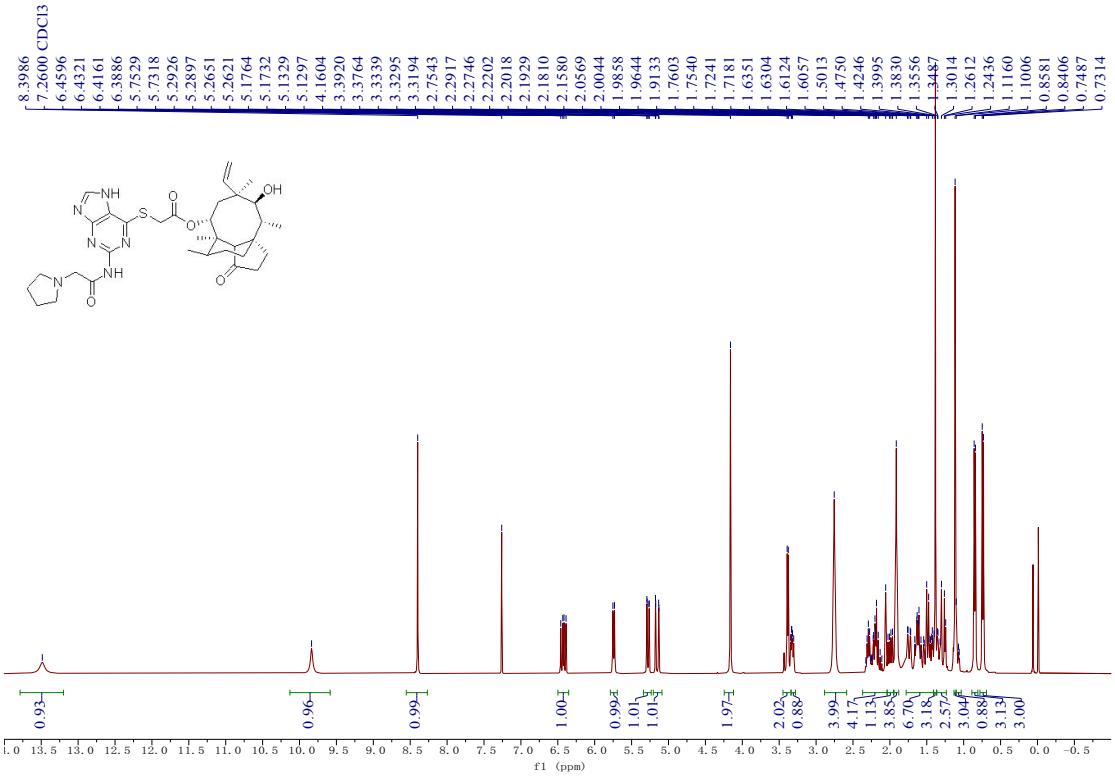
HPLC spectrum of **8b**



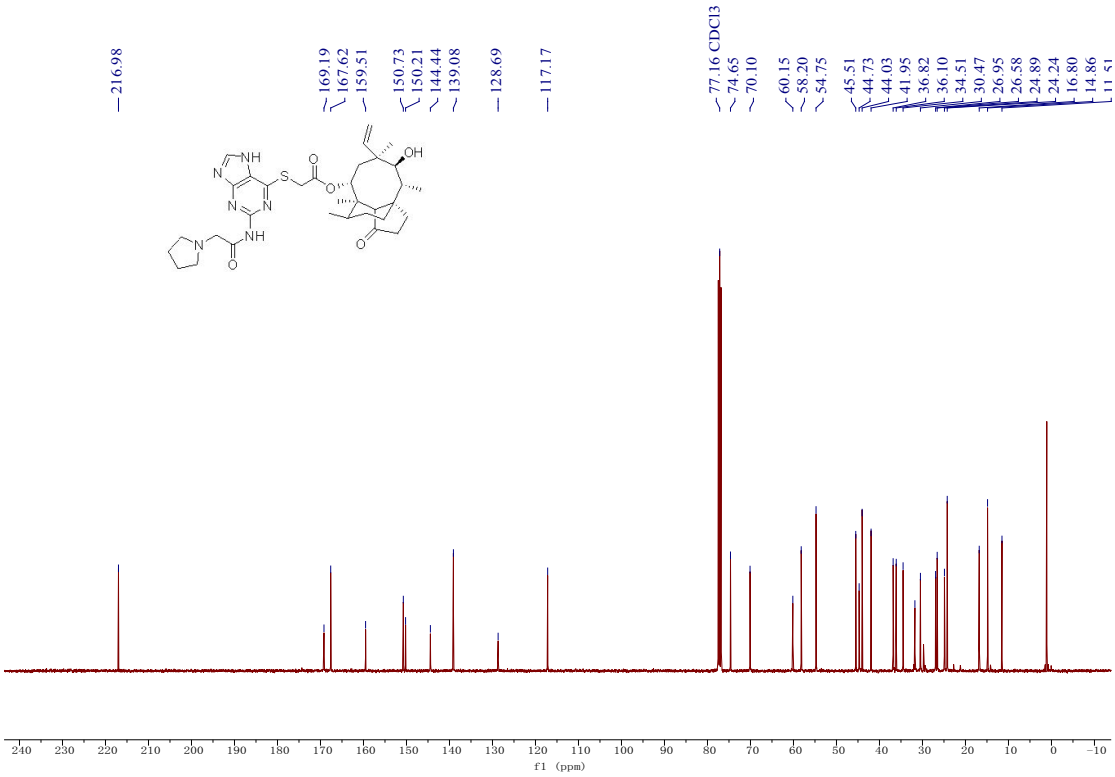
检测器A 254nm

Peak#	Ret. Time	Height	Area	Area%
1	1.785	568	6907	0.099
2	3.582	3622	20670	0.296
3	5.127	1897	10701	0.153
4	6.344	341961	6935126	99.451

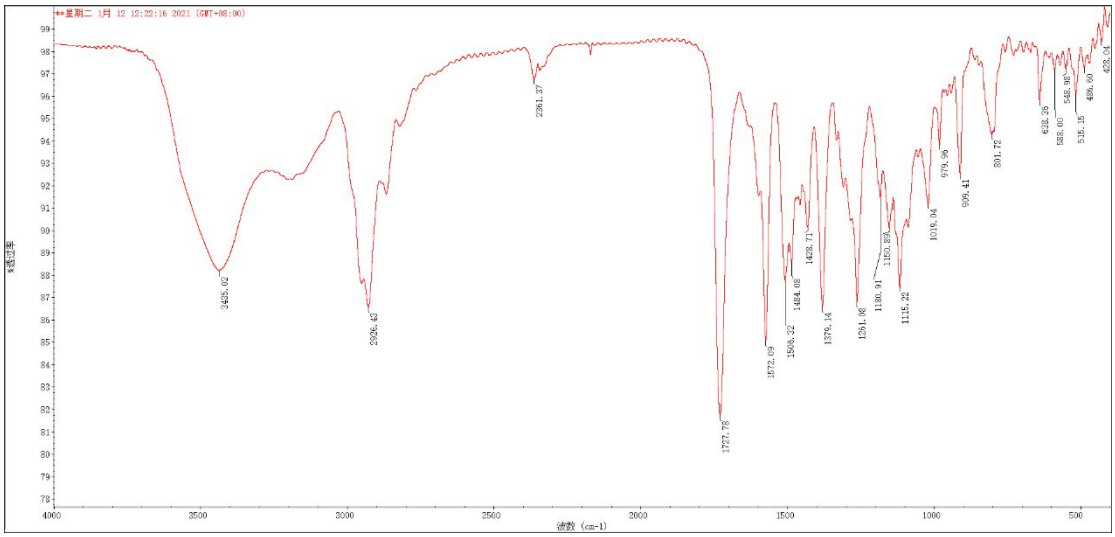
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **8b**



^{13}C NMR (101 MHz, $CDCl_3$) spectrum of **8b**



IR (KBr, cm^{-1}) spectrum of **8b**



HRMS spectrum of **8b**

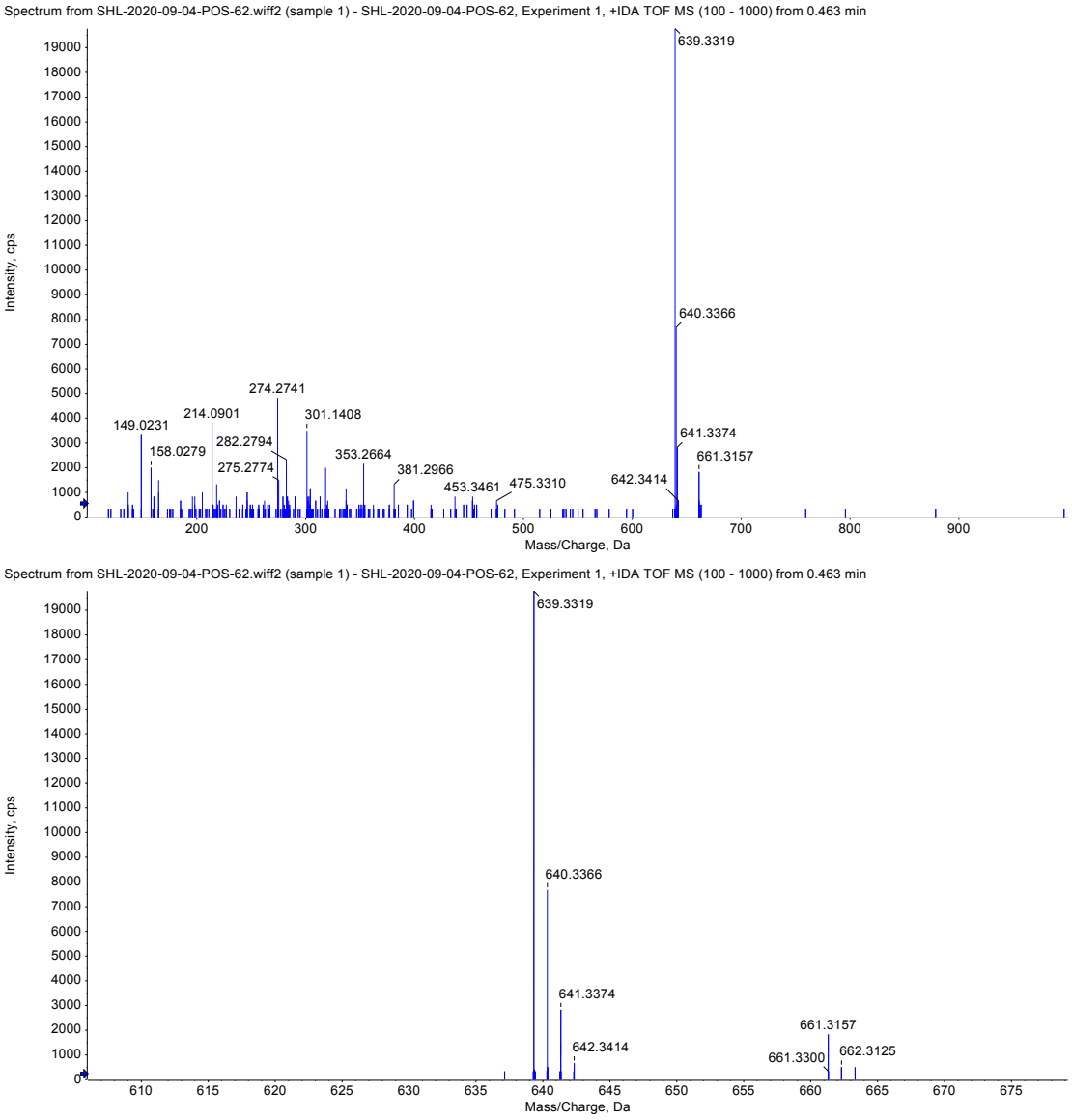
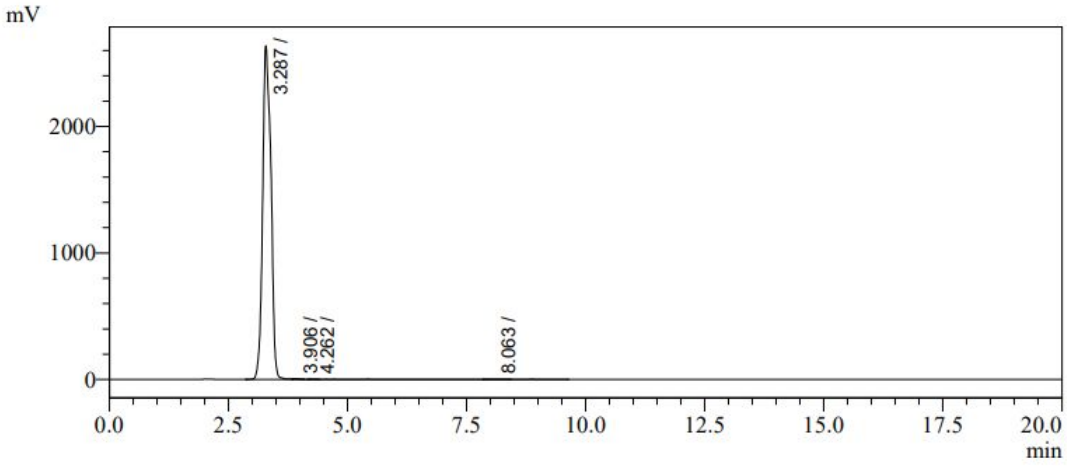


Figure S27. HPLC, ^{1}H NMR, ^{13}C NMR, HRMS and IR spectrum of final compound **8c**

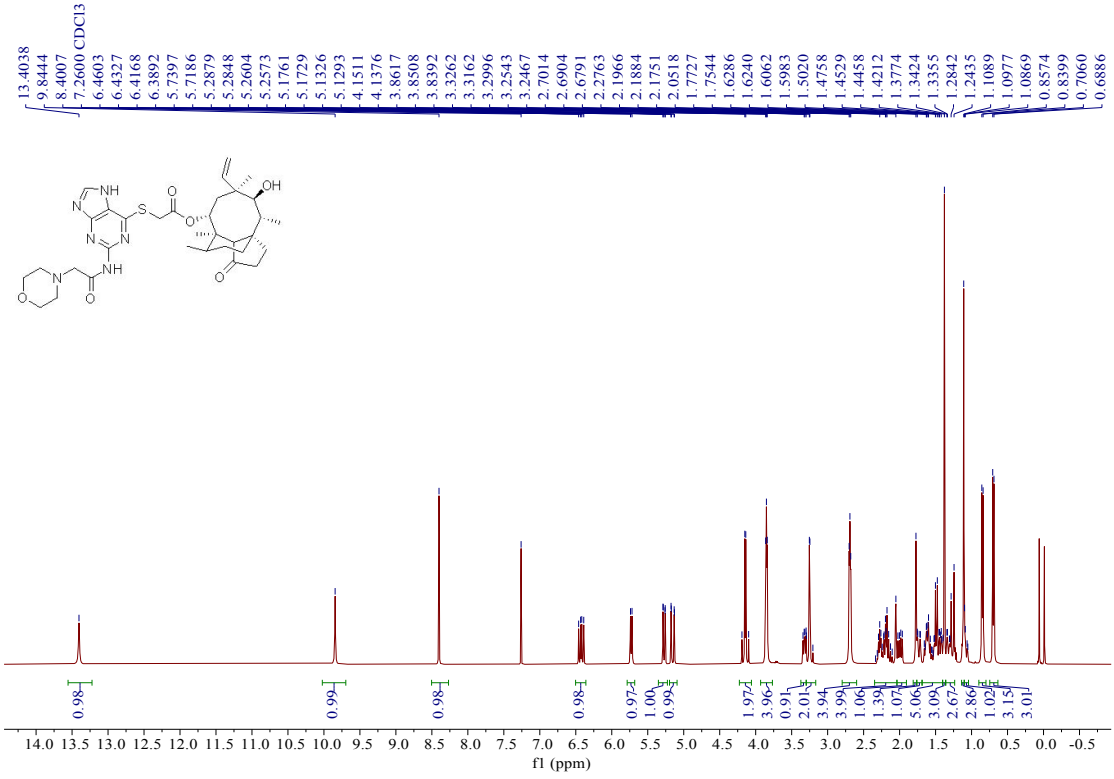
HPLC spectrum of **8c**



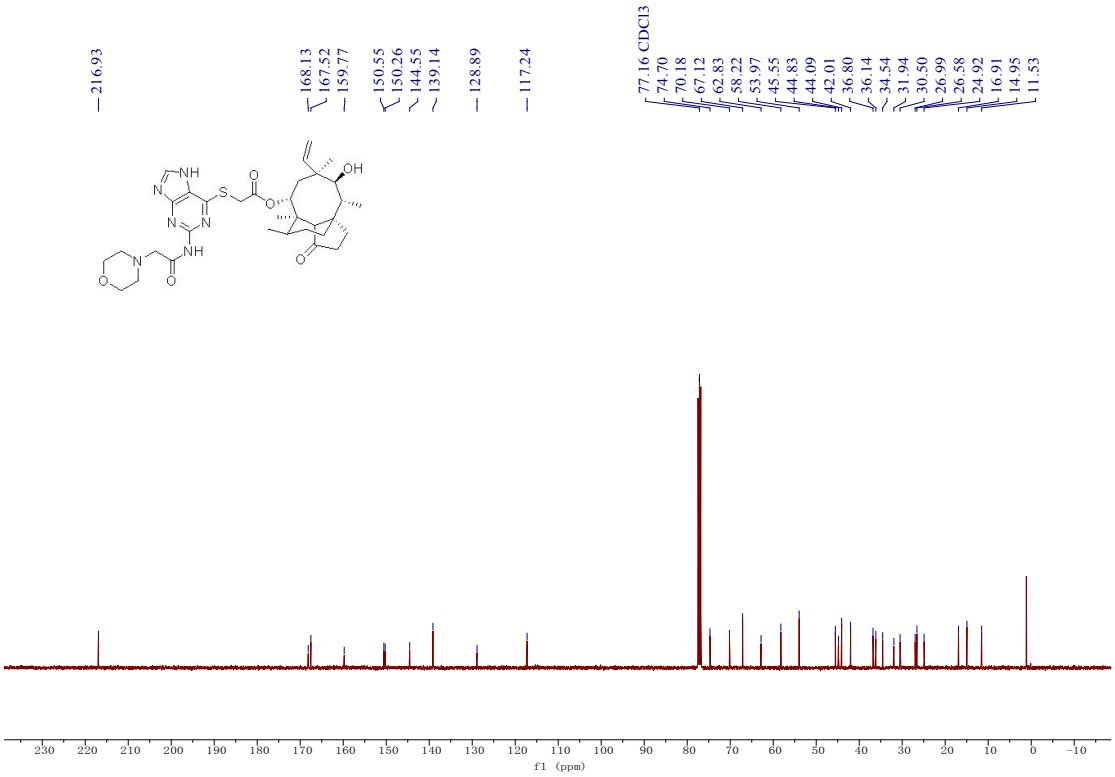
检测器A 254nm

Peak#	Ret. Time	Height	Area	Area%
1	3.287	2637923	32092708	99.898
2	3.906	3218	16920	0.053
3	4.262	2065	12513	0.039
4	8.063	315	3474	0.011

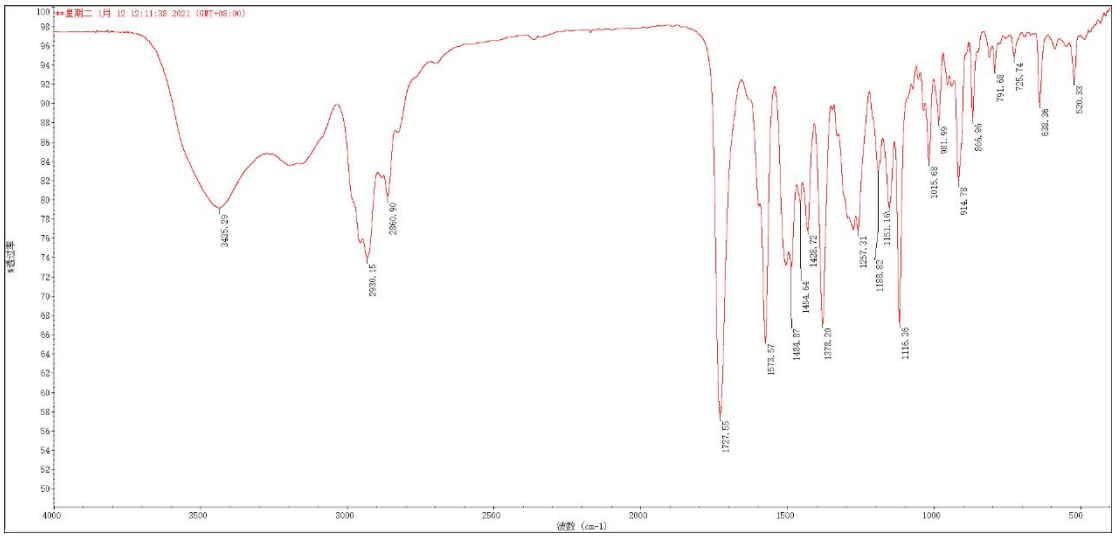
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **8c**



^{13}C NMR (101 MHz, $CDCl_3$) spectrum of **8c**



IR (KBr, cm^{-1}) spectrum of **8c**



HRMS spectrum of **8c**

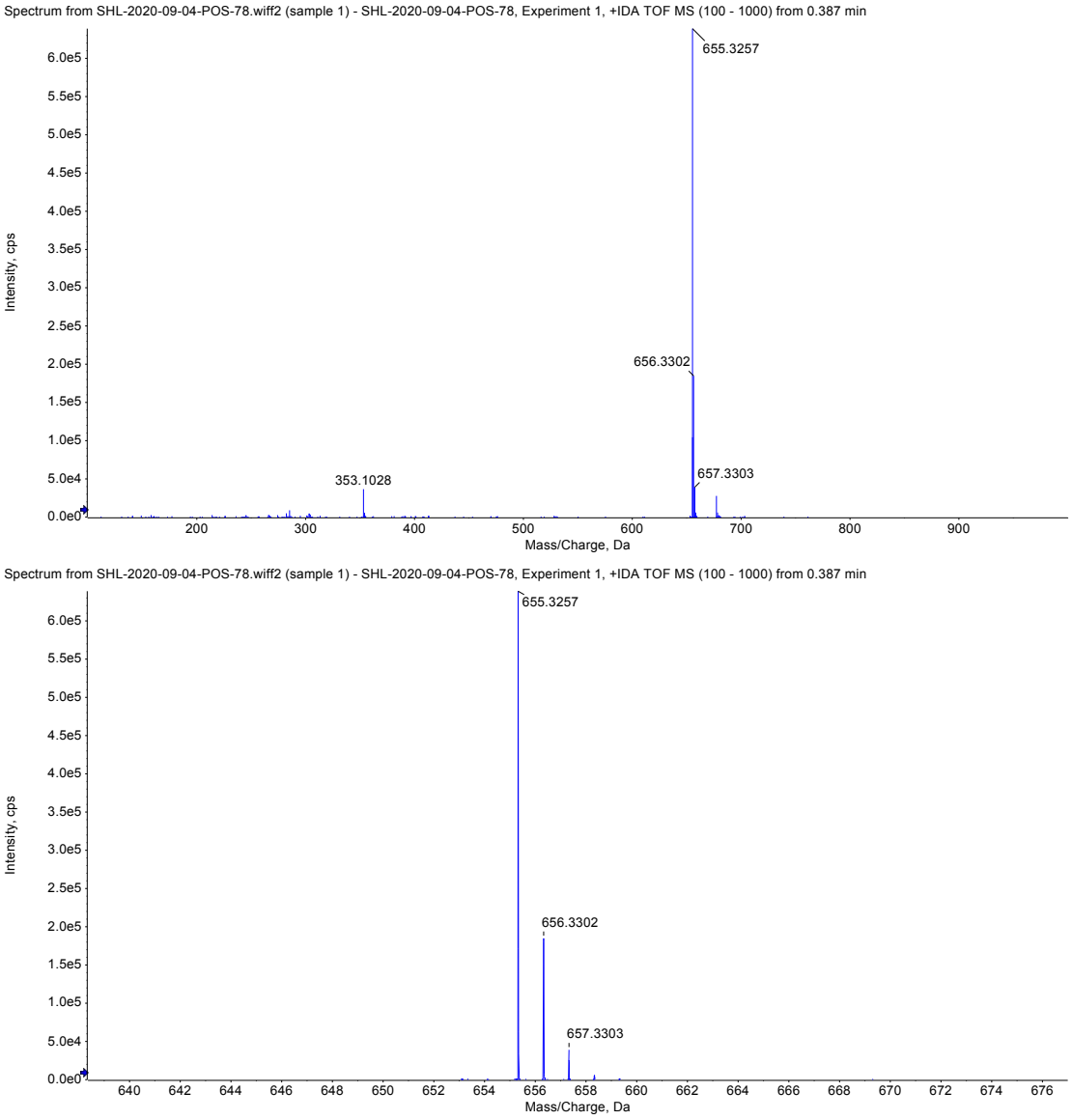
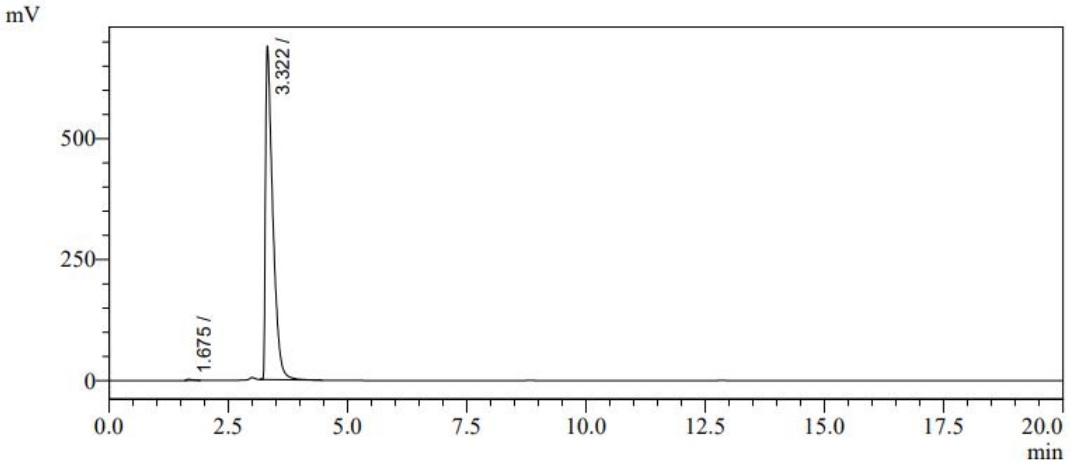


Figure S28. HPLC, ^{1}H NMR, ^{13}C NMR, HRMS and IR spectrum of final compound **8d**

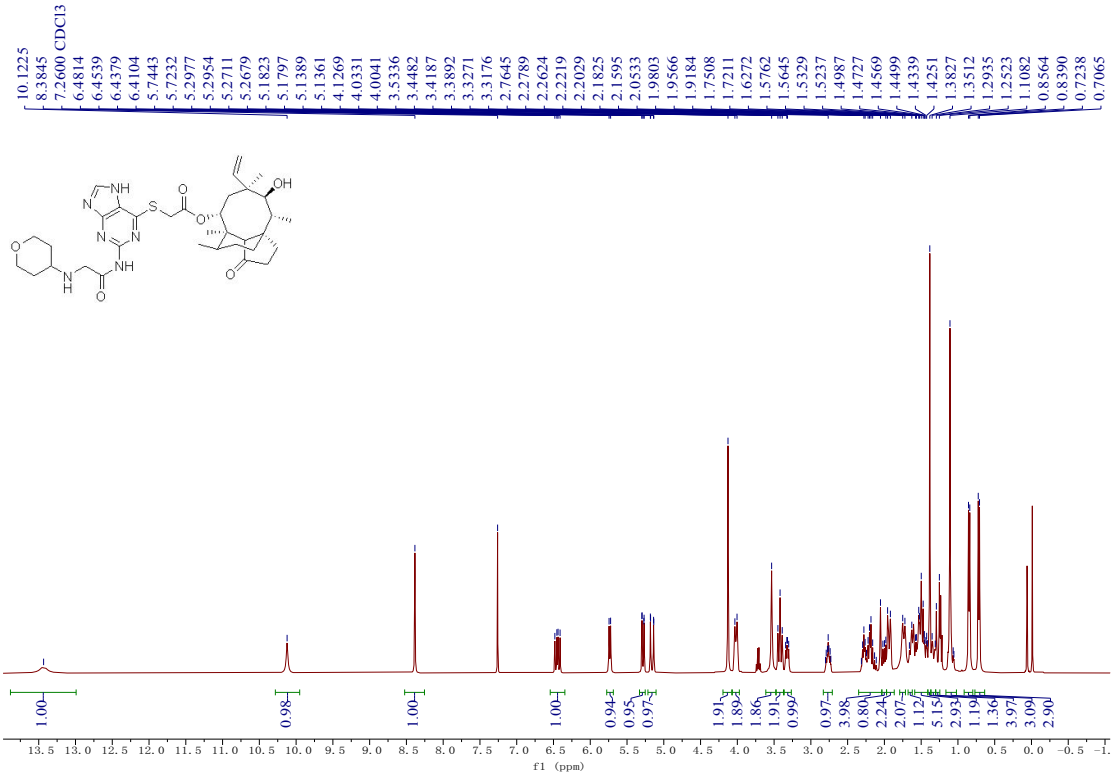
HPLC spectrum of **8d**



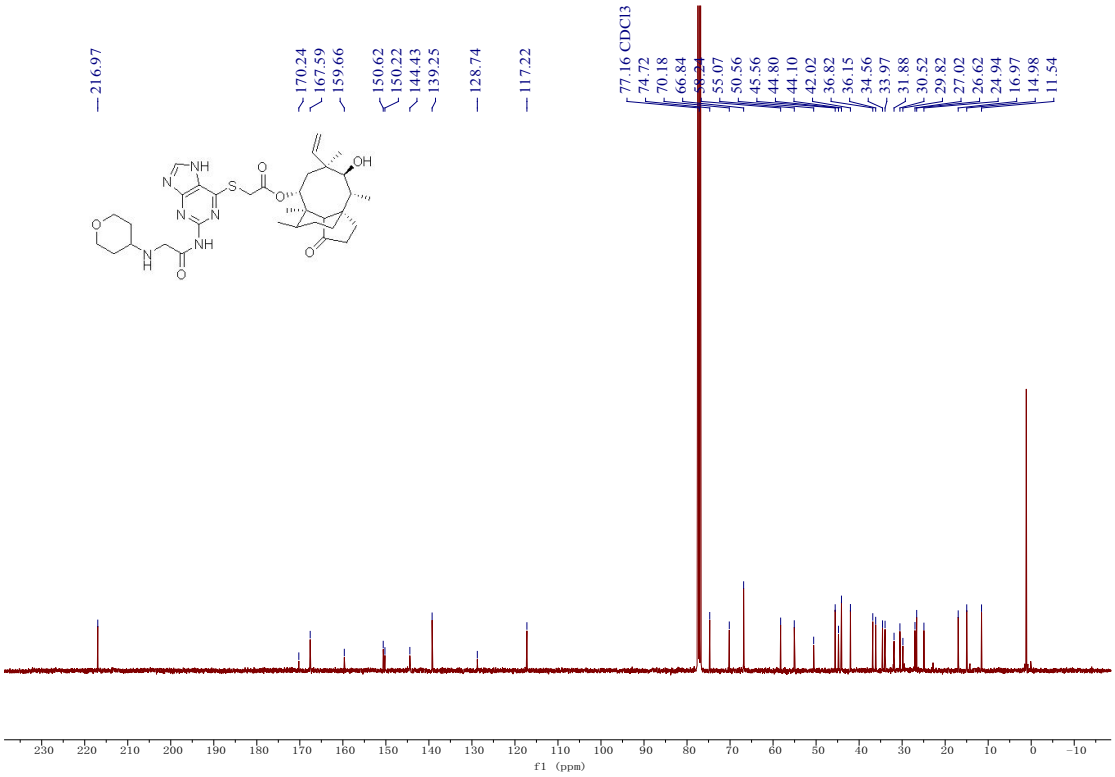
检测器A 254nm

Peak#	Ret. Time	Height	Area	Area%
1	1.675	2419	17612	0.239
2	3.322	689822	7340259	99.761

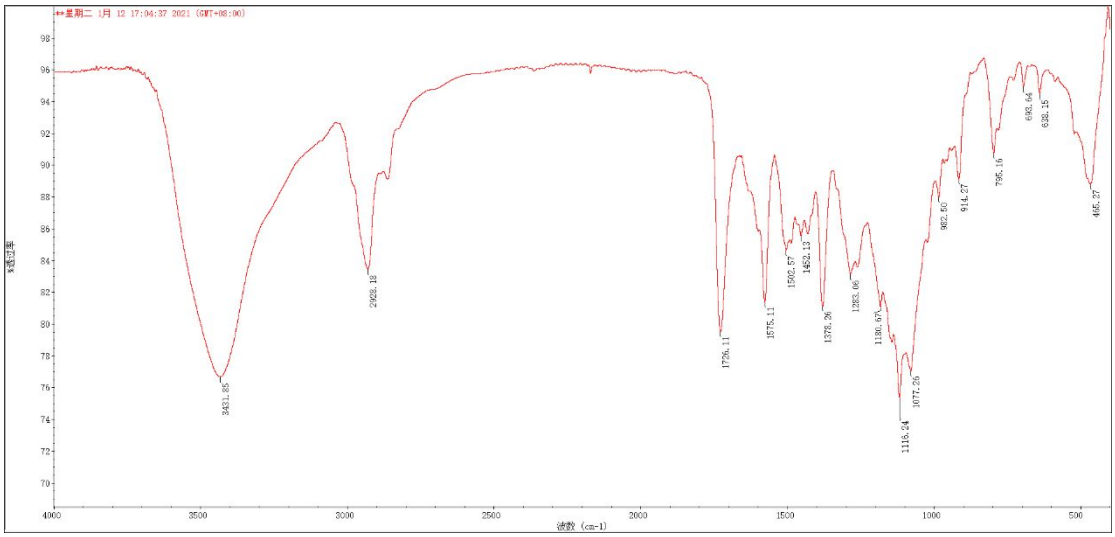
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **8d**



^{13}C NMR (101 MHz, $CDCl_3$) spectrum of **8d**



IR (KBr, cm^{-1}) spectrum of **8d**



HRMS spectrum of **8d**

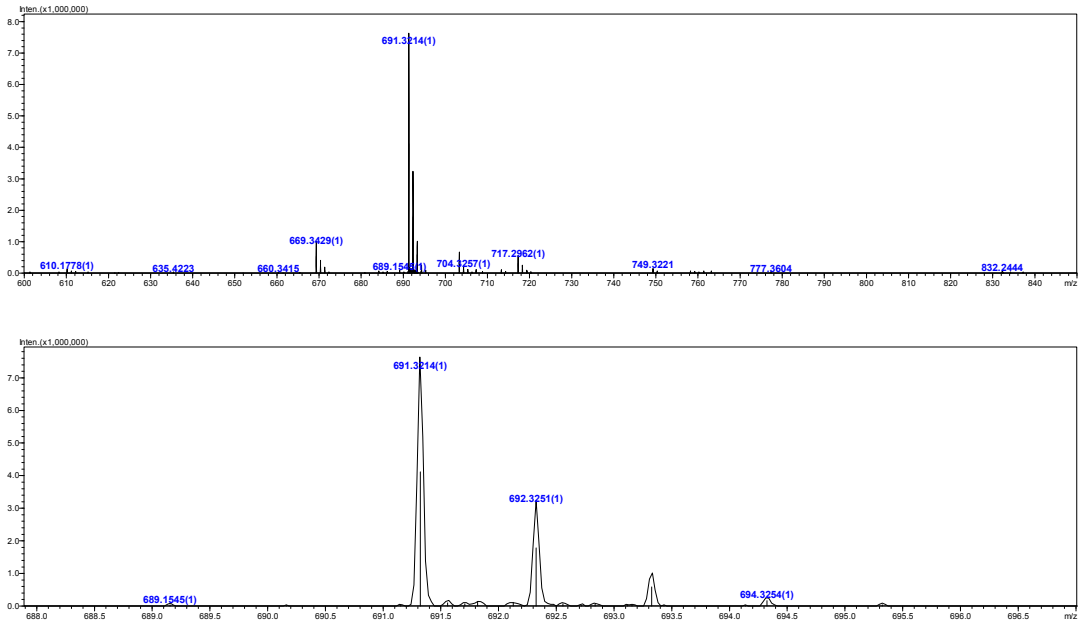
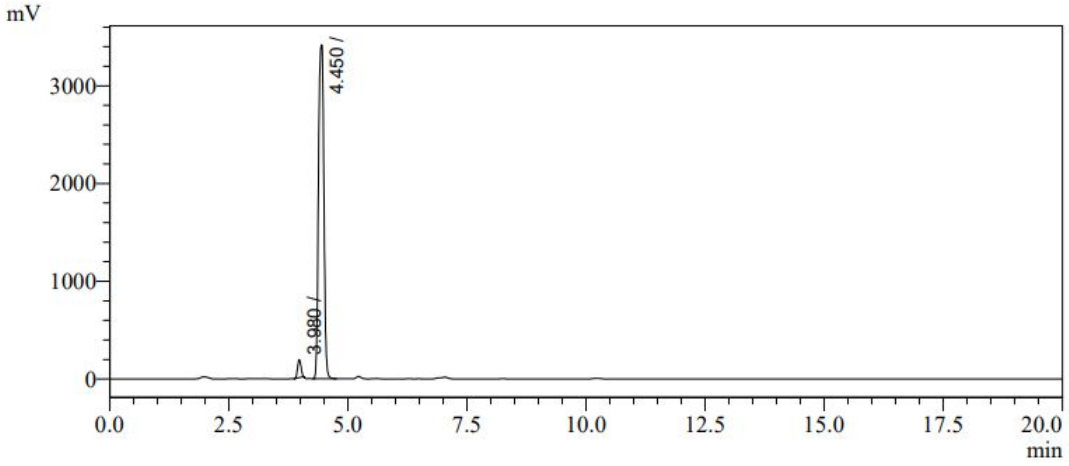


Figure S29. HPLC, ^{1}H NMR, ^{13}C NMR, HRMS and IR spectrum of final compound **8e**

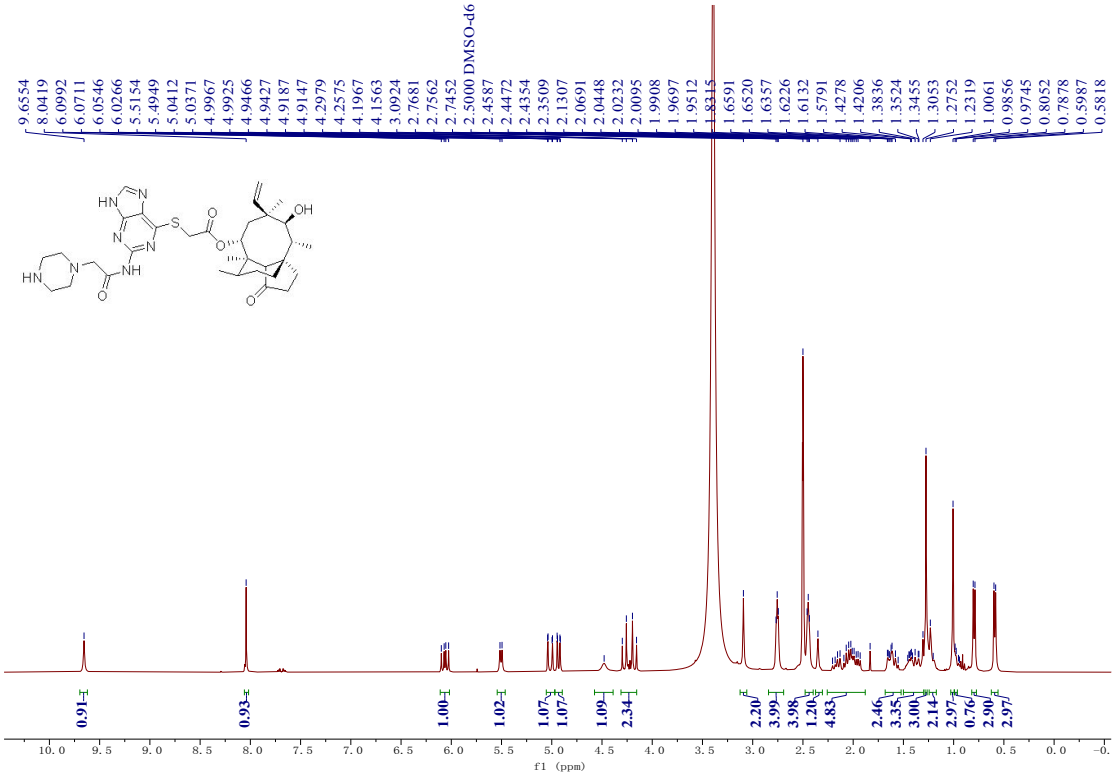
HPLC spectrum of **8e**



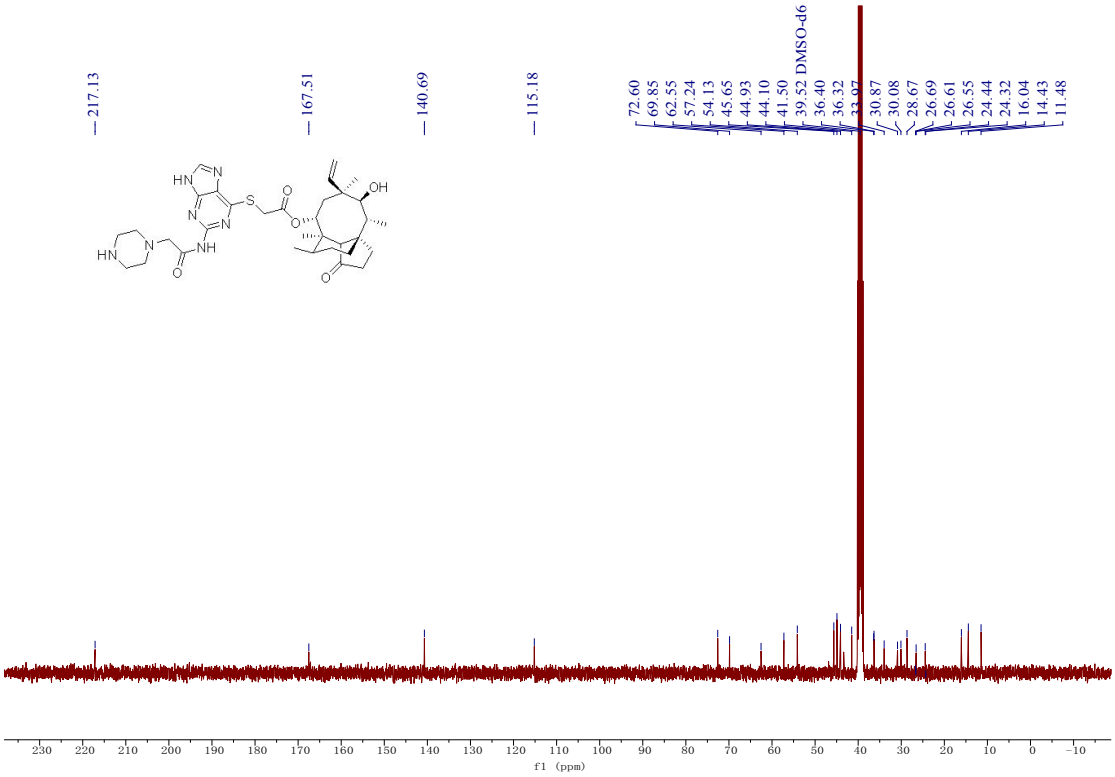
检测器A 254nm

Peak#	Ret. Time	Height	Area	Area%
1	3.980	183937	917976	3.332
2	4.450	3417578	26631308	96.668

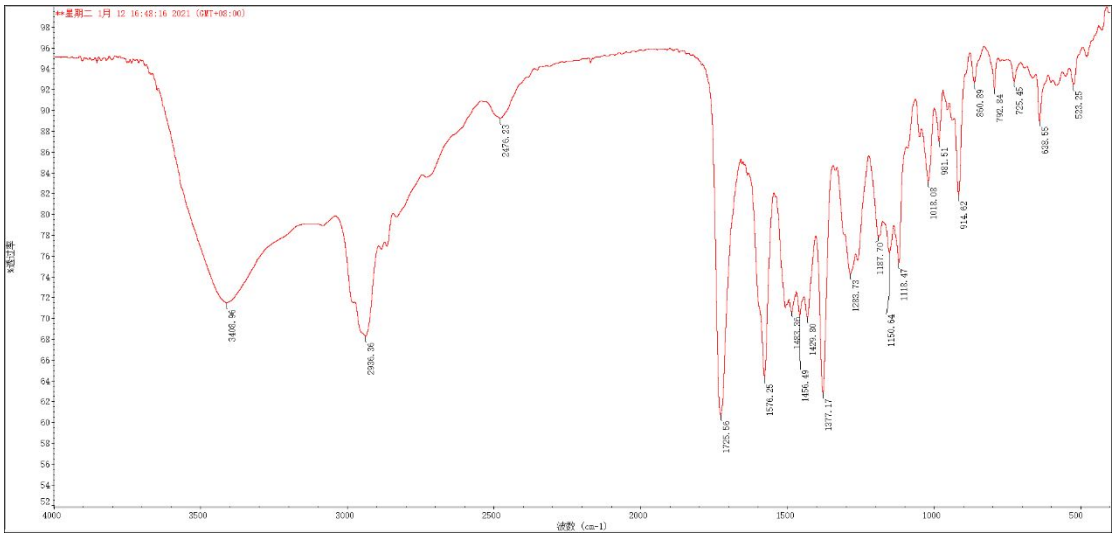
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **8e**



^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **8e**



IR (KBr, cm^{-1}) spectrum of **8e**



HRMS spectrum of **8e**

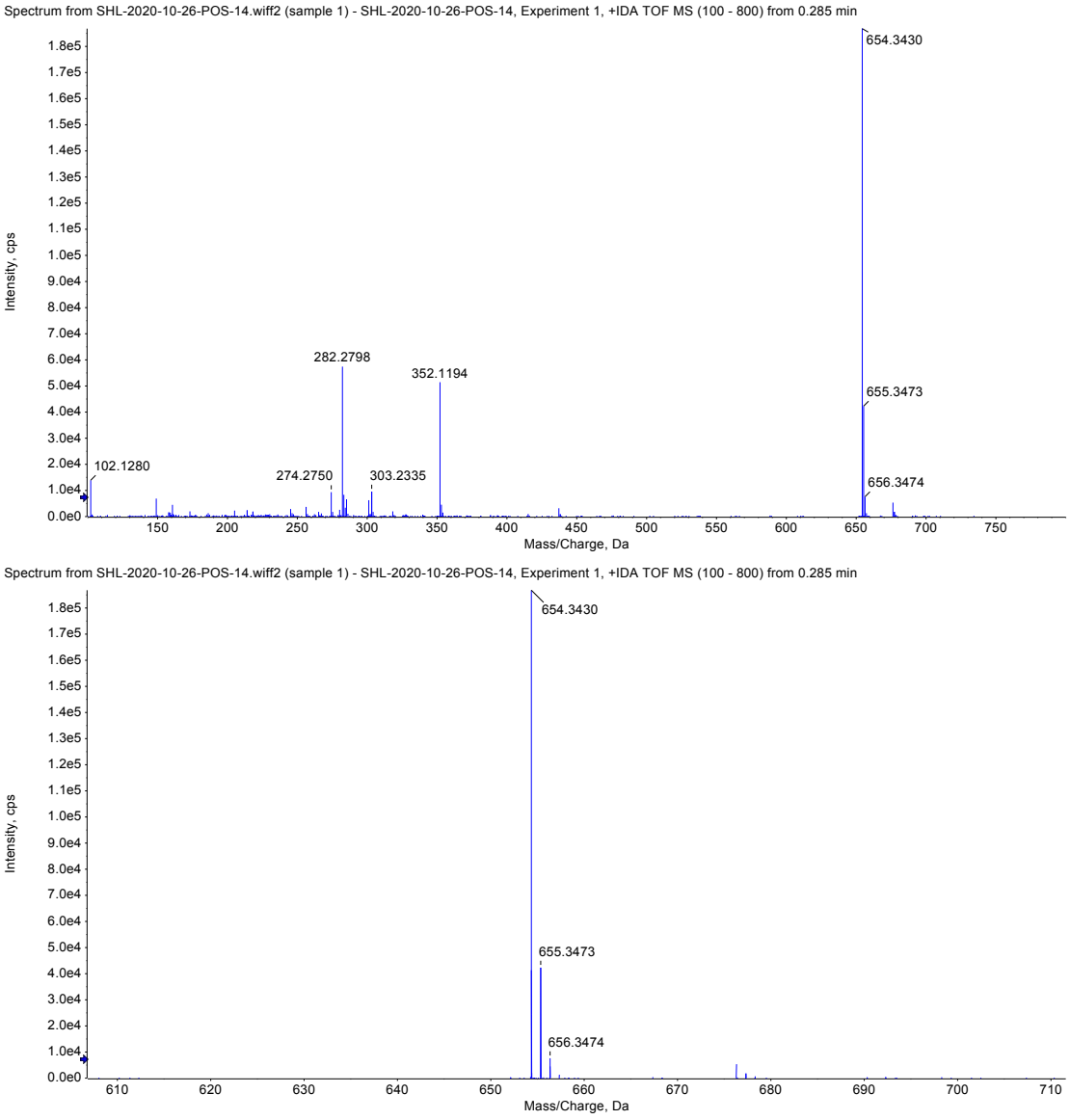
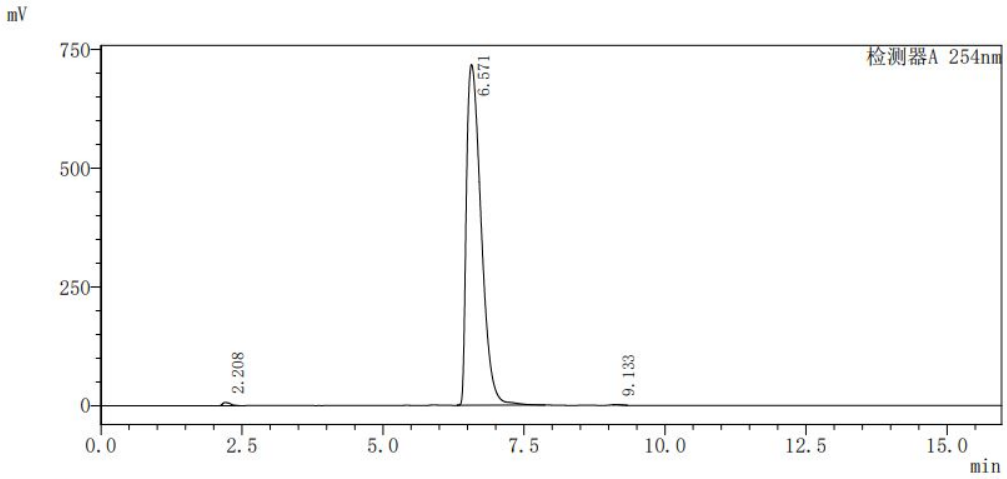


Figure S30. HPLC, ^{1}H NMR, ^{13}C NMR, HRMS and IR spectrum of final compound **8f**

HPLC spectrum of **8f**

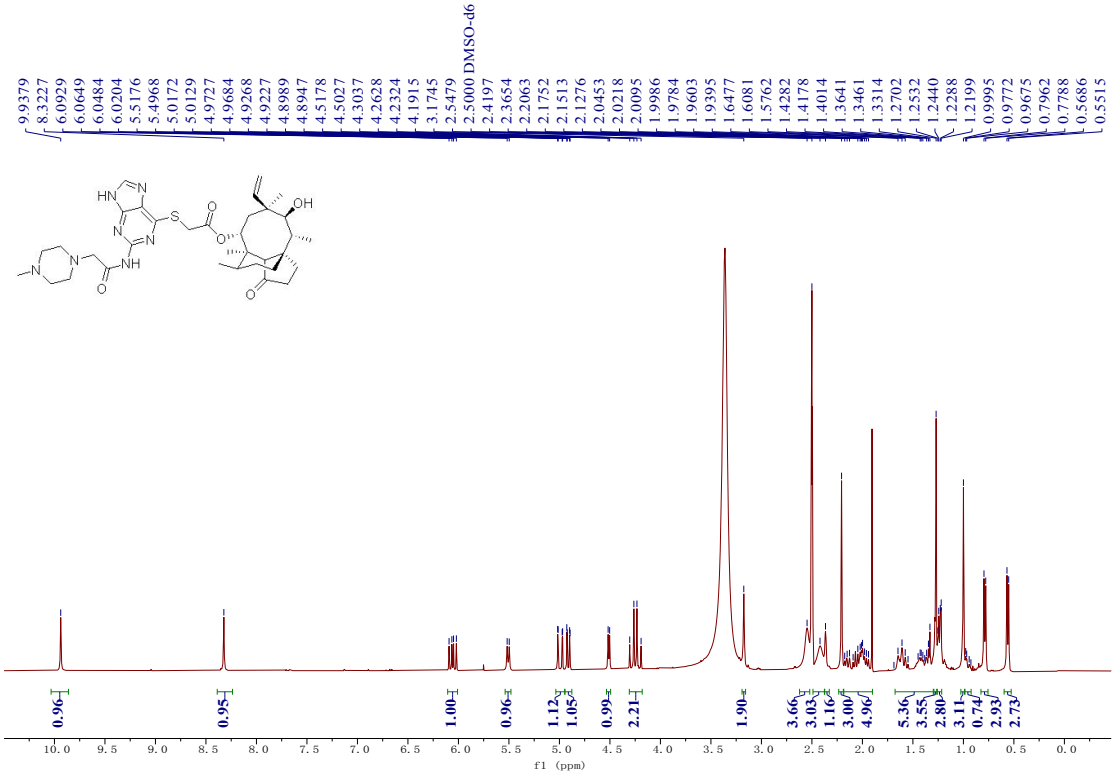


〈峰表〉

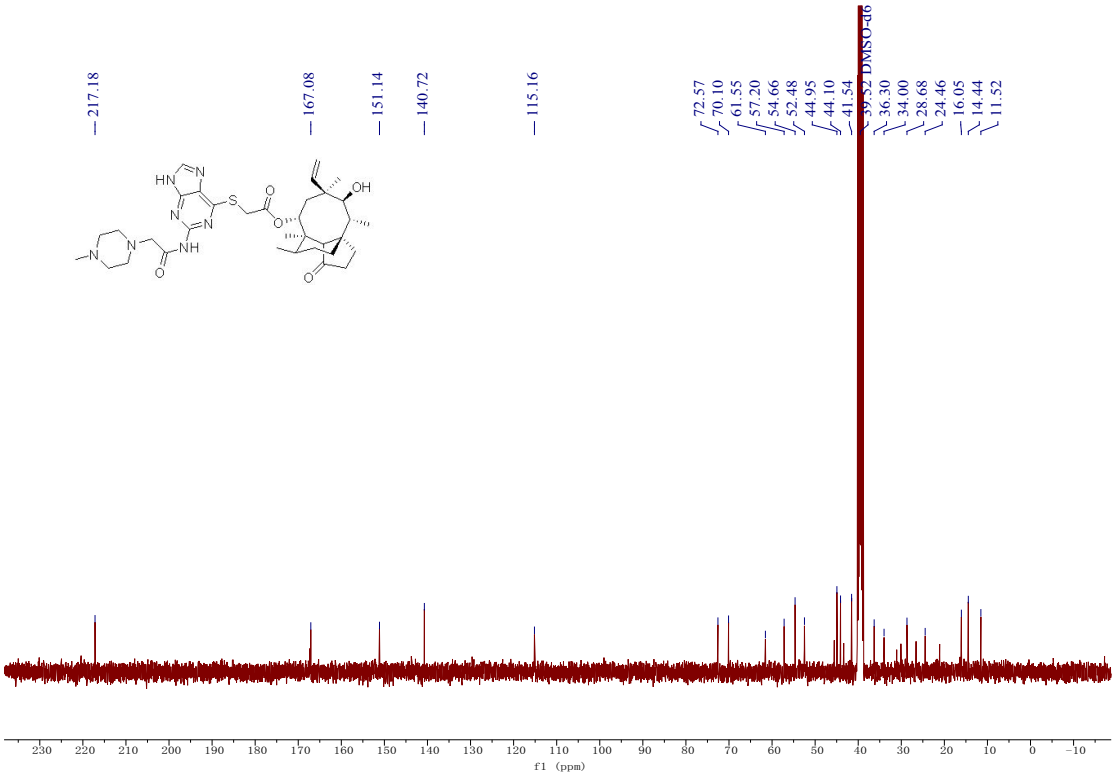
检测器A 254nm

峰号	保留时间	高度	面积	面积%
1	2.208	6521	61716	0.472
2	6.571	717558	13001028	99.486
3	9.133	618	5471	0.042

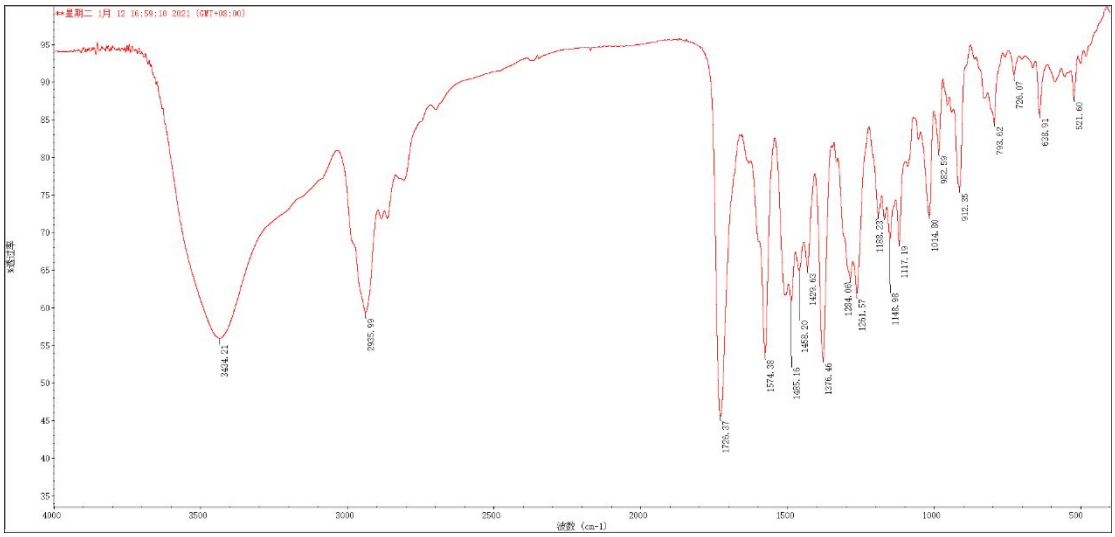
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **8f**



^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **8f**



IR (KBr, cm^{-1}) spectrum of **8f**



HRMS spectrum of **8f**

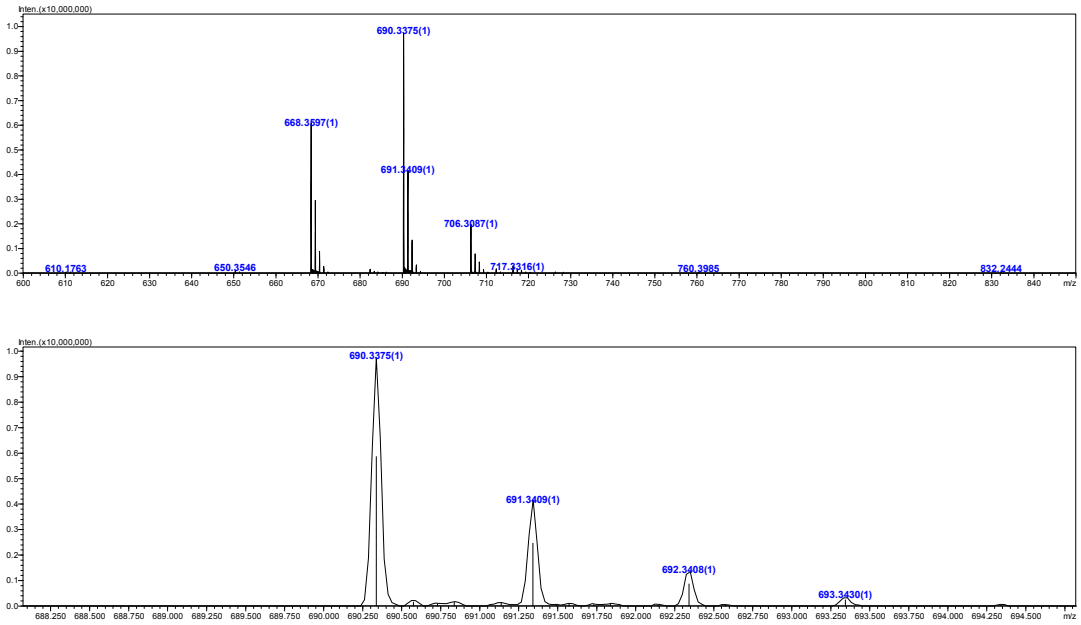
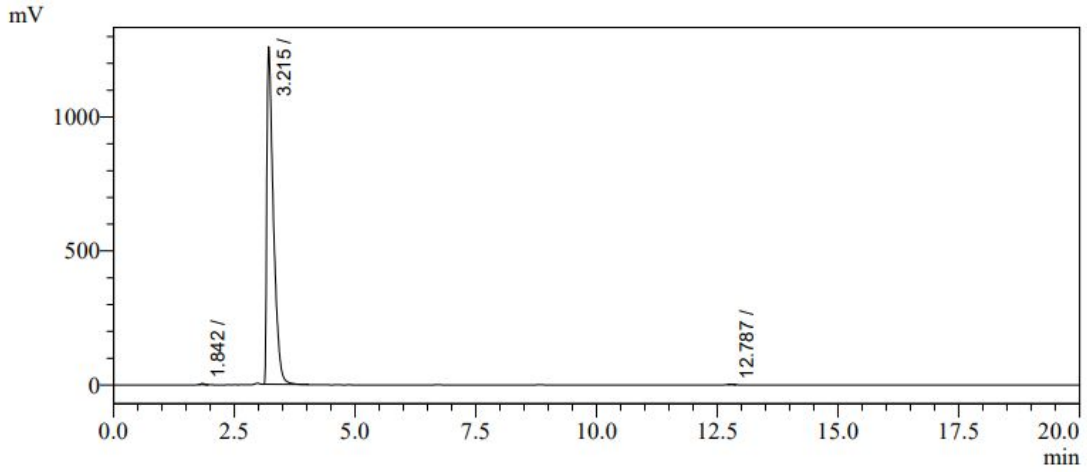


Figure S31. HPLC, ^{1}H NMR, ^{13}C NMR, HRMS and IR spectrum of final compound **8g**

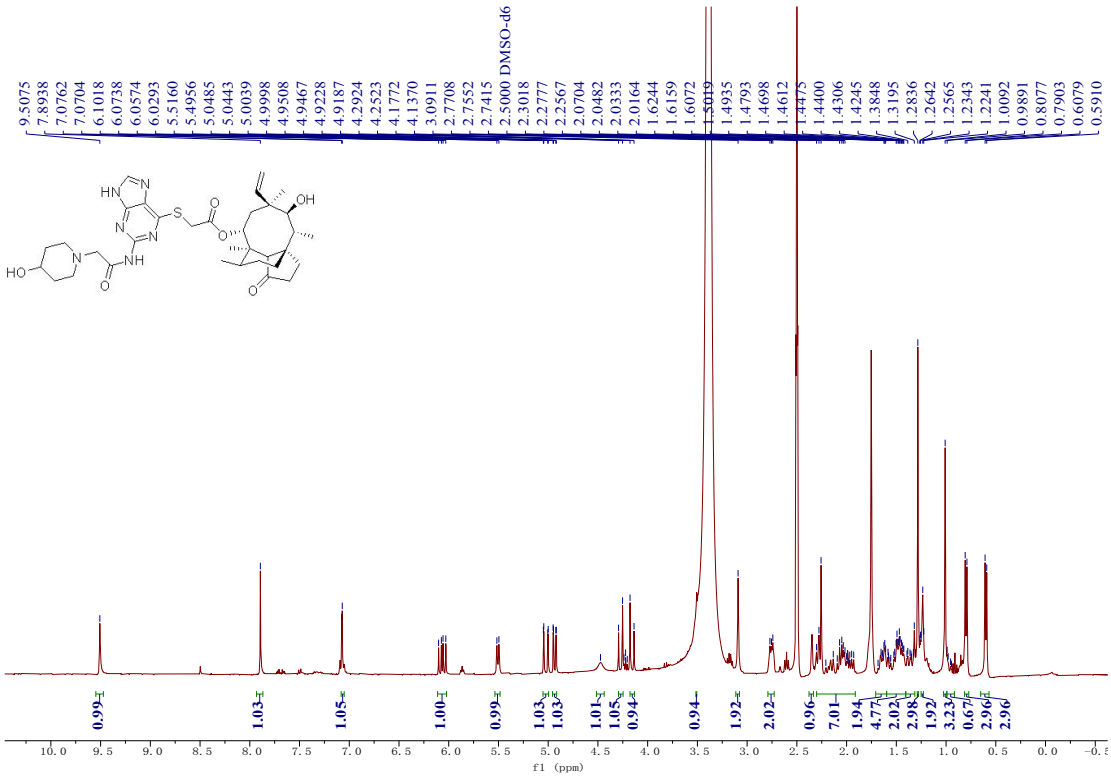
HPLC spectrum of **8g**



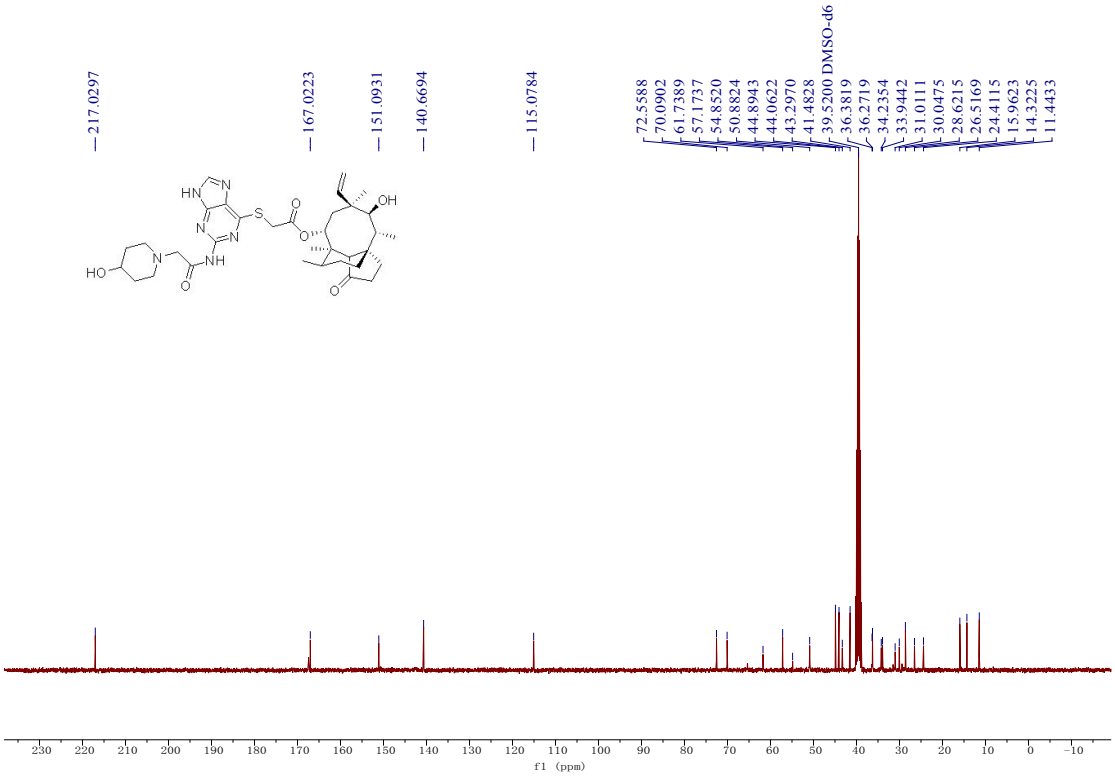
检测器A 254nm

Peak#	Ret. Time	Height	Area	Area%
1	1.842	4570	17453	0.146
2	3.215	1259891	11939052	99.827
3	12.787	587	3178	0.027

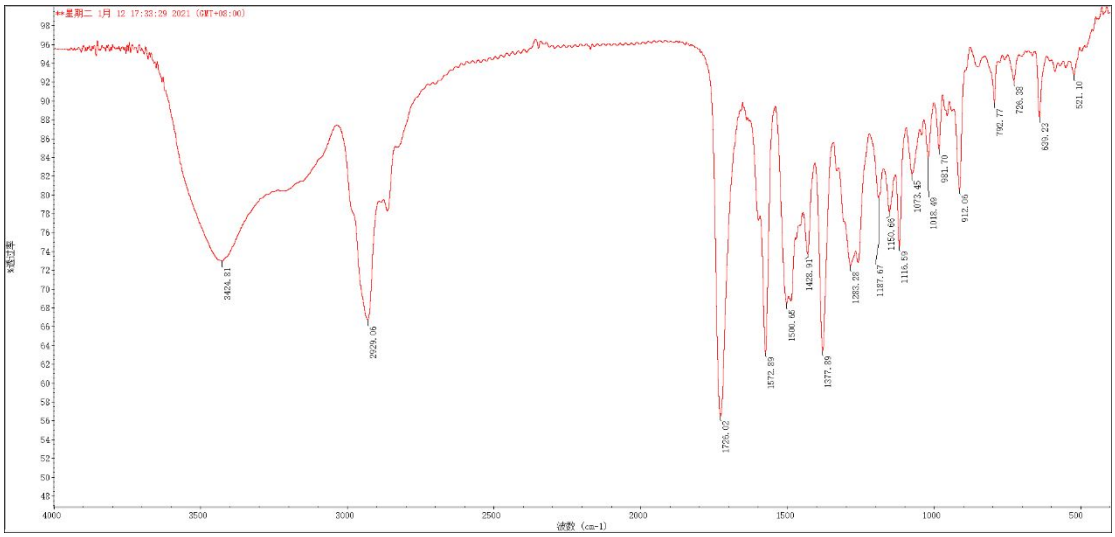
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **8g**



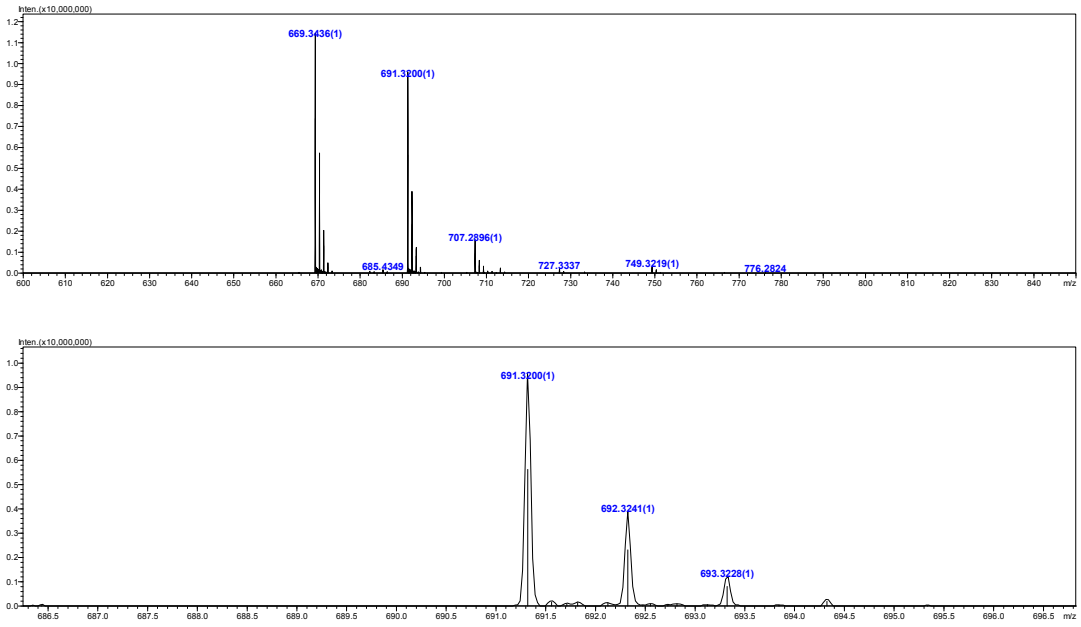
^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **8g**



IR (KBr, cm^{-1}) spectrum of **8g**



HRMS spectrum of **8g**



7. The crystal data of compound 6b and 6i

Figure. S32 Crystal structure of compound **6b**

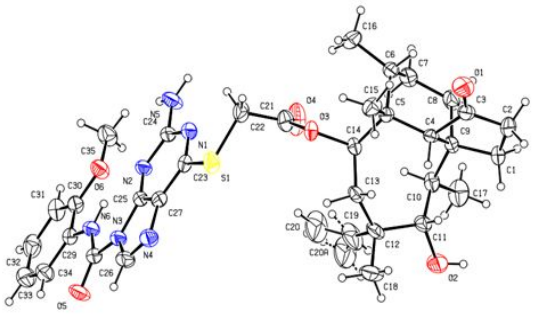


Table S1. the crystal data of compound **6b**

Identification code	Compound **6b**
Empirical formula	$C_{35}H_{45}N_6O_6S$
Formula weight	685.83
Temperature/K	293.15
Crystal system	monoclinic
Space group	$P2_1$
a/Å	8.3074(4)
b/Å	48.604(2)
c/Å	9.4369(6)
α/°	90
β/°	116.078(7)
γ/°	90
Volume/Å^3	3422.5(4)
Z	4
ρ_{calc}g/cm^3	1.331
μ/mm^{-1}	0.151
F(000)	1460.0
Crystal size/mm^3	0.35 × 0.3 × 0.25
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	5.712 to 52.74
Index ranges	$-10 \le h \le 10$, $-46 \le k \le 60$, $-10 \le l \le 11$
Reflections collected	14498
Independent reflections	10570 [R_{int} = 0.0189, R_{sigma} = 0.0369]
Data/restraints/parameters	10570/1/905
Goodness-of-fit on F^2	1.029
Final R indexes [I>=2σ (I)]	R_1 = 0.0411, wR_2 = 0.0930

Final R indexes [all data]	$R_1 = 0.0504$, $wR_2 = 0.1010$
Largest diff. peak/hole / e Å^{-3}	0.20/-0.18
Flack parameter	0.03(4)
CCDC	2210828

Figure. S33 Crystal structure of compound **6i**

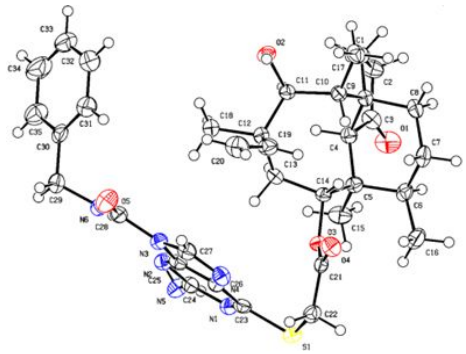


Table S2. the crystal data of compound **6i**

Identification code	Compound **6i**
Empirical formula	$C_{35}H_{44}N_6O_5S$
Formula weight	660.82
Temperature/K	150
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	9.9564(5)
b/Å	12.5757(8)
c/Å	26.1165(16)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	3270.0(3)
Z	4
D_x, g/cm^3	1.342
μ/mm^{-1}	0.152
F(000)	1408.0
Crystal size/mm^3	0.46 × 0.07 × 0.05
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.378 to 50
Index ranges	$-11 \le h \le 9$, $-14 \le k \le 14$, $-31 \le l \le 29$
Reflections collected	22481
Independent reflections	5740 [R_{int} = 0.1165, R_{sigma} = 0.0987]
Data/restraints/parameters	5740/0/430
Goodness-of-fit on F^2	1.023
Final R indexes [I>=2σ (I)]	R_1 = 0.0489, wR_2 = 0.1120
Final R indexes [all data]	R_1 = 0.0590, wR_2 = 0.1199
Largest diff. peak/hole / e Å^{-3}	0.26/-0.28
Flack parameter	0.02(8)