Design, synthesis and evaluation of PD176252 analogues for ameliorating cisplatin-induced nephrotoxicity

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Supplementary material

Experimental section

Figure captions

Experimental section

Chemistry

All reagents were purchased from commercial sources and were used without further purification. The reactions were monitored by thin layer chromatography on pre-coated silica GF254 plates. Melting points were determined by XT4MP apparatus and uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 600 MHz NMR spectrometer with DMSO-d_6 solvent. The chemical shift values are reported in δ units (parts per million) relative to TMS as an internal standard. The FT-IR spectra were recorded in solid-state KBr dispersion on a Perkins-Elmer FT-IR spectrophotometer. TOF-HRMS were obtained on a LCT Premier XE mass spectrometer. Elemental analyses were performed on a Vario EL C and were within ±0.4% of the theoretical values.

The synthesis of 5a-p

The procedure[40] for the synthesis of the target compounds 5a-p was illustrated in Scheme 1. Phenylacetic acid derivatives (3.0 mmol)， amino acid methyl ester hydrochloride (3.3 mmol) and Triethylamine (TEA) (7.9 mmol) was added into dry CH_2Cl_2 (50 mL) and stirred for 30 min at 0 °C. Subsequently the 3-(3-dimethylaminopropyl)-1-ethylcarbodiimide hydrochloride (EDCI) (3.3mmol) and 1-hydroxybenzotriazole (HoBt) (0.33mmol) was added, then mixture under N_2 was stirred at room temperature for 24 h. The reaction mixture was washed with water. The organic phase was concentrated under vacum. The crude product was purified by flash chromatograph to afford the compound 3a-h (in 90–98% yield). Then, the 3a-h were hydrolyzed in a mixed solvent of MeOH and water (1:1, V/V) in the presence of Na_2CO_3 at 60℃. After reacting, the reaction mixture was cooled to room temperature and acidified to pH 1-2 with dilute hydrochloric acid and a large amount of solid was gradually precipitated to afford the compound 4a-h (in 90- 95% yield). The compounds 4a-h (1.0 mmol), 2-morpholinoethan-1-amine (or 2-(1H-imidazol-1-yl)ethan-1-amine) (1.1 mmol) and TEA (1.5 mmol) was added into dry CH_2Cl_2 (30 mL) at 0 ℃. Then EDCI (1.2mmol) and HoBt (0.12mmol) was added and stirred at room temperature under N_2 for overnight. The mixture was washed with water, the bulk of CH_2Cl_2 was removed under vacum. The crude product was pruified by flash chromatograph or cyrstallization in ethyl acetate/ petroleum ether to afford target compound 5a-p.

5a: off white solid, yield: 89.2%, MP: 173.9-174.3℃; ^{1}H NMR(600 MHz, DMSO-d_6) δ 8.54 (d, J = 8.5 Hz, 1H, NH), 8.31 (t, J = 5.6 Hz, 1H, NH), 8.10 (d, J = 8.7 Hz, 2H, Ph-H), 7.57 (s, 1H, midazole-H), 7.35 (d, J = 8.7 Hz, 2H, Ph-H), 7.27-7.22 (m, 2H, Ph-H), 7.22-7.17 (m, 3H, Ph-H), 7.12 (s, 1H, midazole-H), 6.88 (s, 1H, midazole-H), 4.47 (td, J = 9.8, 4.7 Hz, 1H, CH), 4.13-3.91 (m, 2H, CH_2), 3.58 (dd, J = 33.2, 14.2 Hz, 2H, CH_2), 3.48-3.26 (m, 2H, CH_2), 2.92 (dd, J = 13.7, 4.6 Hz, 1H, CH_2),

2.72 (dd, J = 13.6, 10.2 Hz, 1H, CH_2). ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.46 (C=O), 168.82 (C=O), 146.12 (Ph-C), 144.45 (Ph-C), 137.77 (midazole-C), 137.40 (Ph-C), 130.22 (Ph-C), 129.14 (Ph-C), 128.31 (Ph-C), 128.07 (Ph-C), 126.27 (Ph-C), 123.16 (midazole-C), 119.58 (midazole-C), 54.13 (CH), 45.27 (CH_2), 41.74 (CH_2), 39.88 (CH_2), 37.77 (CH_2); TOF-HRMS [$C_{22}H_{23}N_5O_4$]: m/z 422.1634 $[M+H]^+$ (calcd. 422.1828); FT-IR ν /cm^{-1}: 3278(N-H), 1646(C=O), 1527(N-H); Anal. Calcd for: N, 16.62; C, 62.70; H, 5.50%. Found: N, 16.36; C, 62.50; H, 5.595%.

5b: off white solid, yield: 91.3%. MP: 113.5-115.2℃; ^1H NMR(600 MHz, DMSO-d_6) δ 10.81 (s, 1H, $NH_{indenoindoly}$), 8.44 (d, J = 8.1 Hz, 1H, NH), 8.27 (t, J = 5.4 Hz, 1H, NH), 8.06 (d, J = 8.7 Hz, 2H, Ph-H), 7.64-7.54 (m, 2H, midazole-H, Ph-H), 7.32 (dd, J = 8.2, 4.3 Hz, 3H, Ph-H), 7.09 (s, 1H, midazole-H), 7.07 (s, 1H, Ph-H), 7.05 (t, J =7.5 Hz, 1H, Ph-H), 6.96 (t, J = 7.4 Hz, 1H, midazole-H), 6.89 (s, 1H, midazole-H), 4.47 (td, J = 8.8, 5.3 Hz, 1H, CH), 4.08-3.89 (m, 2H, CH_2), 3.57(dd, J = 36.2, 14.2 Hz, 2H, CH_2), 3.46-3.16 (m, 2H, CH_2), 3.03 (dd, J = 14.5, 5.0 Hz, 1H, CH_2), 2.88 (dd, J = 14.5, 9.4Hz, 1H, CH_2). ^{13}C NMR(101 MHz, DMSO-d_6) δ 171.94 (C=O), 168.85 (C=O), 146.11 (Ph-C), 144.51(Ph-C), 137.27 (midazole-C), 136.09 (Ph-C), 130.19 (Ph-C), 127.72 (Ph-C), 127.22 (Ph-C), 123.72 (Ph-C), 123.17 (indenoindoly-C), 120.90 (indenoindoly-C), 119.78 (indenoindoly-C), 118.52 (indenoindoly-C), 118.24 (indenoindoly-C), 111.30 (indenoindoly-C), 109.99 (indenoindoly-C), 53.70 (CH), 45.44 (CH_2), 41.77 (CH_2), 39.10 (CH_2), 27.98 (CH_2); TOF-HRMS[$C_{24}H_{24}N_6O_4$]: m/z 461.1704 $[M+H]^+$ (calcd. 461.1937); FT-IR ν/cm^{-1}: 3282 (N-H), 1644(C=O), 1517(N-H); Anal. Calcd for: N, 18.25; C, 62.60; H, 5.25%. Found: N, 18.04; C, 62.80; H, 5.534%.

5c: off white solid, yield: 82.2%. MP: 215.3-217.0℃; ^1H NMR(600 MHz, DMSO-d_6) δ 9.18 (s, 1H, PhOH), 8.22-8.12 (m, 2H, NH), 7.53 (s, 1H, midazole-H), 7.08 (s, 1H, Ph-H), 7.03 (d,J =7.8 Hz, 2H, Ph-H), 6.96 (dd, J = 8.1, 3.9 Hz, 4H, Ph-H), 6.85 (s, 1H, Ph-H), 6.61 (d, J = 8.4 Hz, 2H, midazole-H), 4.38-4.29 (m, 1H, CH),4.06-3.89 (m, 2H, CH_2), 3.41-3.25 (m, 4H, CH_2), 2.76 (dd,J = 13.8, 4.8 Hz, 1H, CH_2), 2.60 (dd, J = 13.7, 9.7 Hz, 1H, CH_2), 2.24 (s, 3H, CH_2). ^{13}C NMR(101 MHz, DMSO-d_6) δ 171.45 (C=O), 168.82 (C=O), 146.12 (Ph-C), 144.45 (Ph-C), 137.76 (Ph-C), 137.40 (midazole-C), 130.22 (Ph-C), 129.14 (Ph-C), 129.31 (Ph-C), 128.31 (Ph-C), 128.07 (Ph-C), 123.16 (midazole-C), 119.58 (midazole-C), 54.13 (CH), 45.27 (CH_2), 41.74 (CH_2), 40.15 (CH_2), 37.77 (CH_2); TOF-HRMS[$C_{23}H_{26}N_4O_3$]: m/z 407.2092 $[M+H]^+$ (calcd. 407.2083); FT-IR ν/cm^{-1}: 3276(N-H), 1643(C=O), 1540(N-H); Anal. Calcd

for: N, 13.78; C, 67.96; H, 6.45%. Found: N, 13.74; C, 67.69; H, 6.518%.

5d: off white solid, yield 88.2%. MP: 137.4-138.4℃; ^{1}H NMR(600 MHz, DMSO-d_6) δ 8.29 (d, J = 8.4 Hz, 1H, NH), 8.23 (t, J = 5.6 Hz, 1H, NH), 7.54 (s, 1H, midazole-H), 7.27-7.21(m, 2H, Ph-H), 7.21-7.15 (m, 3H, Ph-H), 7.09 (s, 1H, Ph-H), 7.01 (d, J= 7.8 Hz, 2H, Ph-H), 6.95 (d, J= 7.9 Hz, 2H, midazole-H), 6.85 (s, 1H, Ph-H, 4.41 (d, J = 3.7 Hz, 1H, CH), 4.02-3.92 (m, 2H, CH_2), 3.41-3.27 (m, 4H, CH_2), 2.87 (dd, J= 13.7, 4.7 Hz, 1H, CH_2), 2.71(dd, J = 13.6, 9.9 Hz, 1H, CH_2), 2.24 (s, 3H, CH_2). ^{13}C NMR(101 MHz, DMSO-d_6) δ 171.61 (C=O), 170.13 (C=O), 137.87 (midazole-C), 137.40 (Ph-C), 135.13 (Ph-C), 133.18 (Ph-C), 129.17 (Ph-C), 128.83 (Ph-C), 128.63 (Ph-C), 128.32 (Ph-C), 128.06 (Ph-C), 126.26 (midazole-C), 119.58 (midazole-C), 54.14 (CH), 45.25 (CH_2), 41.66 (CH_2), 39.89 (CH_2), 37.68 (CH_2), 20.65 (CH_3), TOF-HRMS [$C_{23}H_{26}N_4O_2$]: m/z 391.1882 $[M+H]^+$ (calcd. 391.2134). FT-IR ν/cm^{-1}: 3305 (N-H), 1641(C=O), 1546(N-H); Anal. Calcd for: N, 14.35; C, 70.75; H, 6.71%. Found: N, 14.12; C, 70.79; H, 6.717%.

5e: off white solid, yield 88.9%. MP: 214.8-215.3℃; ^{1}H NMR(600 MHz, DMSO-d_6) δ 9.22 (s, 1H, PhOH), 8.30 (d, J = 8.4 Hz, 1H, NH), 8.22 (t, J = 5.5 Hz, 1H, NH), 7.57 (s,1H, midazole-H), 7.12-7.06 (m, 3H, Ph-H), 7.03 (t, J = 8.7 Hz, 2H, Ph-H), 6.97 (d, J = 8.2 Hz, 2H, Ph-H), 6.87 (s, 1H, Ph-H), 6.62 (d, J = 8.1Hz, 2H, midazole-H), 4.34 (td, J = 9.2, 4.9 Hz, 1H, CH), 4.04-3.92 (m, 2H, CH_2), 3.36 (ddd, J = 21.8, 14.2, 8.9 Hz, 4H, CH_2), 2.77(dd, J = 13.7, 4.7 Hz, 1H, CH_2), 2.59 (dd, J = 13.6, 10.0 Hz, 1H, CH_2). ^{13}C NMR(101 MHz, DMSO-d_6) δ 171.79 (C=O), 169.87 (C=O), 161.73 (indenoindoly-C), 160.12 (Ph-C), 155.87 (indenoindoly-C), 137.43 (midazole-C), 132.56 (Ph-C), 132.55 (Ph-C), 130.81 (indenoindoly-C), 130.76 (indenoindoly-C), 130.16 (indenoindoly-C), 128.26 (indenoindoly-C), 127.93 (Ph-C), 119.68 (midazole-C), 114.92 (midazole-C), 114.84 (indenoindoly-C), 114.70 (indenoindoly-C), 54.54 (CH), 45.34 (CH_2), 41.17 (CH_2), 39.94 (CH_2), 37.03 (CH_2).TOF-HRMS[$C_{22}H_{23}FN_4O_3$]: m/z 411.1833 $[M+H]^+$(calcd. 411.1832); FT-IR ν/cm^{-1}: 3282 (N-H), 1644(C=O), 1513(N-H); Anal. Calcd for: N, 16.62; C, 62.70; H, 5.50%. Found: N, 16.36; C, 62.50; H, 5.595%.

5f: off white solid, yield 88.9%. MP: 159.3-161.2℃; ^{1}H NMR(600 MHz, DMSO-d_6) δ 8.35 (d, J = 8.4 Hz, 1H, NH), 8.24 (t, J = 5.4 Hz, 1H, NH), 7.53 (s, 1H, midazole-H), 7.28-7.19(m, 2H, Ph-H), 7.17 (d, J = 6.2 Hz, 3H, Ph-H), 7.13-7.04 (m, 3H, Ph-H), 7.01 (t, J = 8.8 Hz, 2H, midazole-H, Ph-H), 6.84 (s, 1H, midazole-H), 4.41 (td, J =9.5, 4.8 Hz, 1H, CH), 4.07-3.87 (m, 2H, CH_2), 3.34 (tt, J = 11.6, 9.8 Hz, 4H,

CH_2), 2.87 (dd, J = 13.6, 4.6 Hz, 1H, CH_2), 2.69(dd, J = 13.5, 10.2 Hz, 1H, CH_2). ^{13}C NMR(101 MHz, DMSO-d_6) δ 171.59 (C=O), 169.89 (C=O), 162.12 (Ph-C), 159.72 (midazole-C), 137.85 (Ph-C), 137.42 (Ph-C), 132.46 (Ph-C), 130.78 (Ph-C), 130.70 (Ph-C), 129.17 (Ph-C), 128.34 (Ph-C), 128.08 (Ph-C), 126.30 (Ph-C), 119.60 (Ph-C), 114.85 (midazole-C), 114.64 (midazole-C), 54.14 (CH), 45.27 (CH_2), 41.11 (CH_2), 38.89 (CH_2), 37.73 (CH_2); TOF-HRMS [$C_{22}H_{23}FN_4O_2$]: m/z 395.1595 $[M+H]^+$(calcd. 395.1883); FT-IR ν/cm^{-1}: 3286 (N-H), 1644(C=O), 1537(N-H); Anal. Calcd for: N, 14.20; C, 66.99; H, 5.88%. Found: N, 14.12; C, 66.74; H, 6.023%.

5g: off white solid, yield 91.7%. MP: 131.1-132.2℃; ^1H NMR(600 MHz, DMSO-d_6) δ 10.84 (s, 1H, $NH_{indenoindoly}$), 8.34 (d,J = 5.7 Hz, 1H, NH), 8.28 (s, 1H, NH), 7.97 (s, 1H, Ph-H), 7.60 (d, J = 7.9 Hz, 1H, midazole-H), 7.35 (d, J = 8.0 Hz, 1H, Ph-H), 7.25 (s, 1H, Ph-H), 7.15-7.01 (m, 7H, Ph-H, midazole-H), 6.98 (t, J = 7.4 Hz, 1H, midazole-H), 4.50-4.38 (m, 1H, CH), 4.12-3.99 (m, 2H, CH_2), 3.53-3.25 (m, 4H, CH_2), 3.04 (dd, J = 14.5, 5.1 Hz, 1H, CH_2), 2.90 (dd, J =14.4, 9.3 Hz, 1H, CH_2). ^{13}C NMR(101 MHz, DMSO-d_6) δ 172.12 (C=O), 169.95 (C=O), 162.10 (Ph-C), 159.69 (midazole-C), 136.77 (Ph-C), 136.09 (Ph-C), 132.48 (Ph-C), 132.45 (Ph-C), 130.79 (Ph-C), 130.71 (Ph-C), 127.21 (indenoindoly-C), 125.49 (midazole-C), 123.73 (indenoindoly-C), 120.89, 120.48 (indenoindoly-C), 118.50 (midazole-C), 118.23 (indenoindoly-C), 114.85 (indenoindoly-C), 114.64 (indenoindoly-C), 111.32 (indenoindoly-C), 110.03 (indenoindoly-C), 53.80 (CH), 46.18 (CH_2), 40.15 (CH_2), 39.10 (CH_2), 27.87 (CH_2). TOF-HRMS[$C_{24}H_{24}FN_5O_2$]: m/z 434.1672 $[M+H]^+$ (calcd. 343.1992); FT-IR ν/cm^{-1}: 3411(N-$H_{indenoindoly}$), 3278 (N-H), 1643(C=O), 1554(N-H); Anal. Calcd for: N, 14.20; C, 66.50; H, 5.88%. Found: N, 14.27; C, 66.70; H, 5.785%.

5h: off white solid, yield 85.9%. MP: 191.2-192.5℃; ^1H NMR(600 MHz, DMSO-d_6) δ 10.83 (s, 1H, $NH_{indenoindoly}$), 8.42 (d, J = 8.1 Hz, 1H, NH), 8.26 (t, J = 5.5 Hz, 1H, NH), 7.59 (d, J= 7.9 Hz, 1H, Ph-H), 7.55 (d, J = 8.0 Hz, 2H, Ph-H), 7.51 (s, 1H, midazole-H), 7.33 (d, J = 8.1 Hz, 1H, Ph-H), 7.27 (d, J = 8.0 Hz, 2H, Ph-H), 7.11 (s, 1H, Ph-H), 7.05 (t, J = 7.2 Hz, 2H, Ph-H), 6.96 (t, J = 7.4 Hz, 1H, midazole-H), 6.84 (s, 1H, midazole-H), 4.47 (td, J = 8.7, 5.5 Hz, 1H, CH),4.03-3.87 (m, 2H, CH_2), 3.52 (dd, J = 31.9, 14.2 Hz, 2H, CH_2), 3.44-3.26 (m, 2H, CH_2), 3.03 (dd, J = 14.5, 5.1 Hz, 1H, CH_2), 2.88 (dd, J = 14.4, 9.3 Hz, 1H, CH_2). ^{13}C NMR(101 MHz, DMSO-d_6) δ 171.87 (C=O), 169.16 (C=O), 141.17 (midazole-C), 137.31 (Ph-C), 136.07 (indenoindoly-C), 129.70 (Ph-C), 128.25 (Ph-C), 127.21 (Ph-C), 126.79

(indenoindoly-C), 124.69 (indenoindoly-C), 124.60 (midazole-C), 123.66 (CF_3), 120.84 (midazole-C), 119.50 (indenoindoly-C), 118.48 (indenoindoly-C), 118.16 (indenoindoly-C), 111.23 (indenoindoly-C), 110.01 (indenoindoly-C), 53.65 (CH), 45.17 (CH_2), 41.67 (CH_2), 40.13 (CH_2), 27,95 (CH_2). TOF-HRMS [$C_{25}H_{24}F_3N_5O_2$]: m/z 484.1838 $[M+H]^+$(calcd. 484.1960); FT-IR ν/cm^{-1}: 3257(N-H), 1637(C=O), 1548(N-H); Anal. Calcd for: N, 16.16; C, 62.11; H, 5.00%. Found: N, 16.40; C, 61.94; H, 5.158%.

5i: off white solid, yield 85.5%. MP: 196.3-197.4℃; ^{1}H NMR(600 MHz, DMSO-d_6) δ 8.46 (d, J = 8.6 Hz, 1H, NH), 8.05 (d, J = 8.7 Hz, 2H, Ph-H), 7.96 (t, J = 5.5 Hz, 1H, NH), 7.30 (d, J = 8.7 Hz, 2H, Ph-H), 7.21-7.10 (m, 5H, Ph-H), 4.45 (td, J = 9.2, 5.1 Hz, 1H, CH), 3.60- 3.44 (m, 6H, CH_2), 3.15 (dd, J = 13.2, 6.6 Hz, 1H, CH_2), 3.09 (dd, J = 13.0, 6.4 Hz, 1H, CH_2), 2.93 (dd, J = 13.6, 5.0 Hz, 1H, CH_2), 2.72 (d, J = 9.7 Hz,1H, CH_2), 2.29 (m, 4H, CH_2), 2.23 (d, J = 4.1 Hz, 2H, CH_2). ^{13}C NMR(101 MHz, DMSO-d_6) δ 170.87 (C=O), 168.69 (C=O), 146.13 (Ph-C), 144.49 (Ph-C), 137.76 (Ph-C), 130.22 (Ph-C), 129.21 (Ph-C), 128.03 (Ph-C), 126.23 (Ph-C), 123.16 (Ph-C), 66.17 (CH_2), 57.20 (CH), 54.05 (CH_2), 53.23 (CH_2), 41.77 (CH_2), 38.06 (CH_2), 35.89(CH_2), TOF-HRMS[$C_{23}H_{28}N_4O_5$]: m/z 441.1856 $[M+H]^+$ (calcd. 441.2138); FT-IR ν/cm^{-1}: 3286(N-H), 1643(C=O), 1519(N-H); Anal. Calcd for: N, 12.72; C, 62.71; H, 6.41%. Found: N, 12.39; C, 62.60; H, 6.492%.

5j: off white solid, yield 88.8%. MP： 219.6-221.2℃; ^{1}H NMR(600 MHz, DMSO-d_6) δ 10.79 (s, 1H, $NH_{indenoindoly}$), 8.41 (d, J = 8.3 Hz, 1H, NH), 8.04 (d, J = 8.7 Hz, 2H, Ph-H), 7.90 (t, J= 5.5 Hz, 1H, NH), 7.55 (d, J = 7.9 Hz, 1H, Ph-H), 7.30 (d, J = 8.7 Hz, 3H, Ph-H), 7.07 (d, J = 1.8 Hz, 1H, Ph-H), 7.03 (t, J = 7.3Hz, 1H, Ph-H), 6.93 (t, J = 7.3 Hz, 1H, Ph-H), 4.53-4.45 (m, 1H, CH), 3.56 (dd, J = 32.8, 14.2 Hz, 2H, CH_2), 3.51-3.47 (m,4H, CH_2), 3.15 (td, J = 13.1, 6.6 Hz, 1H, CH_2), 3.12-3.05 (m, 2H, CH_2), 2.90 (dd,J = 14.4, 8.9 Hz, 1H, CH_2), 2.27 (s, 4H, CH_2), 2.21 (qt, J = 12.6, 6.3 Hz, 2H, CH_2). ^{13}C NMR(101 MHz, DMSO-d_6) δ 171.29 (C=O), 168.70 (C=O), 146.11 (Ph-C), 144.54 (indenoindoly-C), 136.07 (Ph-C), 130.19 (Ph-C), 127.31(indenoindoly-C), 123.67 (indenoindoly-C), 123.16 (Ph-C), 120.85 (indenoindoly-C), 118.51 (indenoindoly-C), 118.21 (indenoindoly-C), 111.24 (indenoindoly-C), 110.01 (indenoindoly-C), 66.17 (CH_2), 57.11 (CH), 53.65 (CH_2), 53.20 (CH_2), 41.79 (CH_2), 35.93(CH_2), 28.23 (CH_2); TOF-HRMS[$C_{25}H_{29}N_5O_5$]: m/z 480.2058 $[M+H]^+$ (calcd. 480.2247); FT-IR ν/cm^{-1}: 3407($N\text{-}H_{indenoindoly}$), 3274(N-H), 1643(C=O), 1521(N-H); Anal. Calcd for: N, 14.60; C, 62.62; H, 6.10%. Found: N, 14.53; C, 62.36; H, 6.304%.

5k: off white solid, yield 85.5%. MP: 188.3-189.5℃; ^{1}H NMR(600 MHz, CD_3OD) δ 7.01 (d, J = 7.7 Hz, 2H, Ph-H), 6.96 (d, J = 7.8 Hz, 2H, Ph-H), 6.91 (d, J = 8.3 Hz,

2H, Ph-H),6.59 (d, J = 8.3 Hz, 2H, Ph-H), 4.41 (t, J = 7.5 Hz, 1H, CH), 3.57 (s, 4H, CH_2), 3.38 (q, J = 14.4 Hz, 2H, CH_2), 3.25 (s, 2H, CH_2), 3.17 (ddt, J = 27.2, 13.5, 6.8 Hz, 2H, CH_2), 2.90 (dd, J = 13.7, 6.9 Hz, 1H, CH2), 2.74 (dd, J = 13.7, 8.2 Hz, 1H, CH_2),2.32 (d, J = 16.1 Hz, 4H, CH_2), 2.27 (dd, J = 14.1, 6.8 Hz, 2H, CH_2), 2.24 (s, 3H, CH_3). ^{13}C NMR(101 MHz, DMSO-d_6) δ 171.10 (C=O), 169.95 (C=O), 155.79 (Ph-C), 135.14 (Ph-C), 133.25 (Ph-C), 130.11 (Ph-C), 128.85 (Ph-C), 128.64 (Ph-C), 127.84 (Ph-C), 114.82 (Ph-C), 66.18 (CH_2), 57.16 (CH), 54.37 (CH_2), 53.22 (CH_2), 41.72 (CH_2), 37.19 (CH_2), 35.84 (CH_2), 20.67 (CH_3), TOF-HRMS[C24H31N3O4]: m/z 426.2353 [M+H]+(calcd. 426.2393); FT-IR ν/cm^{-1}: 3299(N-H), 1616(C=O), 1517(N-H); Anal. Calcd for: N, 9.88; C, 67.74; H, 7.34%. Found: N, 9.68; C, 67.77; H, 7.504%.

5l: off white solid, yield 86.1%. MP: 150.1-152.0℃; ^{1}H NMR(600 MHz, DMSO-d_6) δ 8.26 (d, J = 8.5 Hz, 1H, NH), 7.91 (t, J = 5.5 Hz, 1H, NH), 7.28-7.14 (m, 5H, Ph-H), 7.02(d, J = 7.8 Hz, 2H, Ph-H), 6.96 (d, J = 7.9 Hz, 2H, Ph-H), 4.45 (td, J = 9.0, 5.2 Hz, 1H, CH), 3.53 (t, J = 4.3 Hz, 4H, CH_2), 3.40– 3.26 (m, 2H, CH_2), 3.18 (td, J = 13.1, 6.6 Hz, 1H, CH_2), 3.11 (td, J = 12.8, 6.5 Hz, 1H, CH_2), 2.95 (dd, J = 13.6, 5.1 Hz, 1H, CH_2), 2.75 (dd, J = 13.6, 9.5 Hz, 1H, CH_2), 2.30 (d, J = 19.5 Hz, 4H, CH_2), 2.26 (dd, J = 6.8, 3.4 Hz, 2H, CH_2), 2.24 (s,3H, CH_3). ^{13}C NMR NMR(101 MHz, DMSO-d_6) δ 170.91 (C=O), 169.95 (C=O), 137.81 (Ph-C), 135.10 (Ph-C), 133.16 (Ph-C), 129.17 (Ph-C), 128.79 (Ph-C), 128.59 (Ph-C), 127.96 (Ph-C), 126.16 (Ph-C), 66.15 (CH_2), 57.12 (CH), 53.96 (CH_2), 53.18 (CH_2), 37.88 (CH_2), 35.84 (CH_3). TOF-HRMS [$C_{24}H_{31}N_3O_3$]: m/z 410.2439 [M+H]$^+$ (calcd. 410.2444); FT-IR ν/cm^{-1}: 3280(N-H), 1639(C=O), 1525(N-H); Anal. Calcd for: N, 10.26; C, 70.39; H, 7.63%. Found: N, 10.27; C, 70.25; H, 7.652%.

5m: off white solid, yield 88.2%. MP: 180.2-182.5℃; ^{1}H NMR(600 MHz, DMSO-d_6) δ 9.18 (s, 1H, PhOH), 8.26 (d, J = 8.5 Hz, 1H, NH), 7.88 (t, J = 5.4 Hz, 1H, NH), 7.10 (dd, J= 8.2, 5.9 Hz, 2H, Ph-H), 7.04 (t, J = 8.8 Hz, 2H, Ph-H), 6.98 (d, J = 8.3 Hz, 2H, Ph-H), 6.61 (d, J = 8.3 Hz, 2H, Ph-H), 4.37 (td, J= 8.8, 5.5 Hz, 1H, CH), 3.54 (d, J = 3.9 Hz, 4H, CH_2), 3.41 (d, J = 14.0 Hz, 1H, CH_2), 3.37 – 3.30 (m, 2H, CH_2), 3.17 (td, J =13.0, 6.5 Hz, 1H, CH_2), 3.10 (td, J = 12.7, 6.3 Hz, 1H, CH_2), 2.84 (dd, J = 13.6, 5.1 Hz, 1H, CH_2), 2.63 (dd, J = 13.6, 9.5Hz, 1H, CH_2), 2.31 (d, J = 17.7 Hz, 4H, CH_2), 2.25 (dt, J = 11.9, 6.0 Hz, 2H, CH_2) ,^{13}C NMR(101 MHz, DMSO-d_6) δ 171.03 (C=O), 169.62 (C=O), 162.07 (Ph-C), 159.67 (Ph-C), 155.76 (Ph-C), 132.48 (Ph-C), 132.45 (Ph-C), 130.72 (Ph-C), 130.64 (Ph-C), 130.07 (Ph-C), 127.80 (Ph-C), 114.80 (Ph-C), 114.77 (Ph-C), 114.55 (Ph-C), 66.14 (CH_2), 57.12 (CH), 54.32 (CH_2), 53.18 (CH_2), 41.11(CH_2) , 37.17 (CH_2), 35.82 (CH_2). TOF-HRMS [$C_{23}H_{28}N_3O_4$]: m/z 430.2150 [M+H]$^+$ (calcd. 430.2142); FT-IR ν/cm^{-1}: 3284(N-H), 1641(C=O), 1541(N-H); Anal.

Calcd for: N, 9.78; C, 64.32; H, 6.57%. Found: N, 9.86; C, 64.09; H, 6.734%.

5n: off white solid, yield 84.4%. MP: 172.2-174.4℃; ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.36 (d, J = 8.5 Hz, 1H, NH), 7.97 (t, J = 5.3 Hz, 1H, NH), 7.30 – 7.16 (m, 5H, Ph-H), 7.12 (dd, J = 8.2, 5.8 Hz, 2H, Ph-H), 7.05 (t, J = 8.8 Hz, 2H, Ph-H), 4.48 (td, J = 9.0, 5.2 Hz, 1H, CH), 3.65 – 3.49 (m, 4H, CH_2), 3.46 – 3.34 (m, 2H, CH_2), 3.21 (td, J = 13.1, 6.5 Hz, 1H, CH_2), 3.17 – 3.10 (m, 1H, CH_2), 2.98 (dd, J = 13.6, 5.0 Hz, 1H, CH_2), 2.77 (dd, J = 13.5, 9.6 Hz, 1H, CH_2), 2.33 (d, J = 24.7 Hz, 4H, CH_2), 2.28 (dt, J = 10.3, 5.3 Hz, 2H, CH_2),^{13}C NMR(101 MHz, DMSO-d_6) δ 170.75 (C=O), 169.52 (C=O), 161.91 (Ph-C), 159.50 (Ph-C), 137.61 (Ph-C), 132.27 (Ph-C), 132.24 (Ph-C), 130.55 (Ph-C), 130.47 (Ph-C), 129.00 (Ph-C), 127.80 (Ph-C), 126.02 (Ph-C), 114.62 (Ph-C), 114.41 (Ph-C), 65.97 (CH_2), 56.97 (CH), 53.80 (CH_2), 53.01 (CH_2), 40.91 (CH_2), 37.76 (CH_2), 35.67(CH_2); TOF-HRMS [$C_{23}H_{28}FN_3O_3$]: m/z 414.2188 $[M+H]^+$ (calcd. 414.2193); FT-IR ν/cm^{-1}: 3315(N-H), 1641(C=O), 1533(N-H); Anal. Calcd for: N, 10.16; C, 66.81; H, 6.83%. Found: N, 10.07; C, 66.55; H, 6.825%.

5o: off white solid, yield 87.7%. MP: 191.2-192.1℃; ^{1}H NMR(600 MHz, DMSO-d_6) δ 10.81 (s, 1H, $NH_{indenoindoly}$), 8.29 (d, J = 8.2 Hz, 1H, NH), 7.87 (t, J = 5.3 Hz, 1H, NH), 7.57 (d, J= 7.9 Hz, 1H, Ph-H), 7.32 (d, J = 8.1 Hz, 1H, Ph-H), 7.11 (dd, J = 8.4, 5.9 Hz, 3H, Ph-H), 7.08-6.99 (m, 3H, Ph-H), 6.96 (t, J =7.4 Hz, 1H, Ph-H), 4.48 (dd, J = 14.2, 8.3 Hz, 1H, CH), 3.51 (s, 4H, CH_2), 3.40 (q, J = 14.1 Hz, 2H, CH_2), 3.16 (td, J = 13.1, 6.6Hz, 1H), 3.13-3.04 (m, 2H), 2.91 (dd, J = 14.4, 8.6 Hz, 1H), 2.29 (m, 4H, CH_2), 2.22 (m, 2H, CH_2). ^{13}C NMR(101 MHz, DMSO-d_6) δ 171.37 (C=O), 169.75 (C=O), 162.11 (Ph-C), 159.71 (indenoindoly-C), 136.07 (Ph-C), 132.53 (Ph-C), 132.50 (indenoindoly-C), 130.78 (Ph-C), 130.70 (Ph-C), 127.33 (indenoindoly-C), 123.65(indenoindoly-C), 120.85 (Ph-C), 118.50 (Ph-C), 118.21 (Ph-C), 114.85 (Ph-C), 114.64 (Ph-C), 111.26 (indenoindoly-C), 110.06 (indenoindoly-C), 66.17 (CH_2), 57.07 (CH), 53.62 (CH_2), 53.19 (CH_2), 41.12 (CH_2), 35.90(CH_2), 28.16 (CH_2); TOF-HRMS [$C_{25}H_{29}FN_4O_3$]: m/z 453.2341 $[M+H]^+$(calcd. 453.2302); FT-IR ν/cm^{-1}: 3318(N-$H_{indenoindoly}$), 3270(N-H), 1631(C=O), 1533(N-H); Anal. Calcd for: N, 12.38; C, 66.35; H, 6.46%. Found: N, 12.35; C, 66.21; H, 6.580%.

5p: off white solid, yield 90.3%. MP: 187.1-188.4℃; ^{1}H NMR(600 MHz, DMSO-d_6) δ 10.84 (s, 1H, $NH_{indenoindoly}$), 8.43 (d, J = 8.3 Hz, 1H, NH), 7.92 (t, J = 5.5 Hz, 1H, NH), 7.57 (dd, J= 14.8, 8.0 Hz, 3H, Ph-H), 7.32 (d, J = 8.1 Hz, 1H, Ph-H), 7.28 (d, J = 8.0 Hz, 2H, Ph-H), 7.13 (d, J = 2.0 Hz, 1H, Ph-H), 7.05 (t, J= 7.5 Hz, 1H, Ph-H), 6.96 (t, J = 7.5 Hz, 1H, Ph-H), 4.50 (td, J = 8.5, 5.9 Hz, 1H, CH), 3.53 (q, J = 14.0 Hz, 6H, CH_2), 3.16 (dt, J = 13.0, 6.5 Hz, 1H, CH_2), 3.10 (dt, J = 14.2, 6.1 Hz, 2H, CH_2), 2.92 (dd, J = 14.4, 8.7 Hz, 1H, CH_2), 2.37-2.24 (m, 4H, CH_2),2.21 (ddd, J = 15.1, 9.6, 4.8 Hz, 2H, CH_2).^{13}C NMR(101 MHz, DMSO-d_6) δ 171.33 (C=O), 169.12 (C=O), 141.27

(Ph-C), 136.09 (indenoindoly-C), 129.75 (Ph-C), 127.33 (Ph-C), 127.15 (indenoindoly-C), 126.84 (Ph-C), 124.90 (indenoindoly-C), 124.86 (indenoindoly-C), 123.69 (CF_3), 120.85, 118.53 (indenoindoly-C), 118.22 (indenoindoly-C), 111.24 (indenoindoly-C), 110.07 (indenoindoly-C), 66.18 (CH_2), 57.10 (CH) , 53.68 (CH_2), 53.20(CH_2) , 41.74 (CH_2), 35.92 (CH_2), 28.22 (CH_2); TOF-HRMS [$C_{26}H_{29}F_3N_4O_3$]: m/z 503.2267 $[M+H]^+$ (calcd. 503.2270). FT-IR ν/cm^{-1}: 3407($N\text{-}H_{indenoindoly}$), 3284(N-H), 1643(C=O), 1544(N-H); Anal. Calcd for: N, 11.15; C, 62.14; H, 5.82%. Found: N, 11.10; C, 62.08; H, 5.872%.

Cell culture

Kidney tubular epithelial cells of human(HK2) were from American type culture collection(ATCC) and cultured in 5% FBS-containing HyClone™ DMEM/F12 medium at 37 ℃ in a 5% CO_2 humidified atmosphere. After overnight starving in DMEM/F12 medium containing 0.5% FBS, HK2 cells were pretreated with compounds for 6 h before being exposed to cisplatin(20 μM). The cells were harvested for cell viability and inflammatory response such as MCP-1, TNF-α and IL-6 used real-time PCR, Enzyme-Linked Immuno-Sorbent Assay, western blot analysis or other methods after 24 hours. In addition three to four in vitro experiments were performed independently.

Assay for cell viability

Cell viability was determined by MTT method, according to a purple formazan product produced by mitochondrial dehydrogenase of viable cells. Human HK2 cells (ATCC, USA) were seeded into 96-well microtiter plates at 120 cells per well by a series of the compounds (arranged from 0.25-0.8μM). The compounds were prepared as 5 mM DMSO stocks. Twelve hours later, the cells were stimulation with cisplatin (20 μM) for 24 h in incubator. After removing supernatant, DMSO (150μL) was applied to dissolve formazan crystals. The optical density (OD) was detected with mircoplate reader (Multiskan MK3, Thermo, USA) at 492 nm wave length.

Cell cytotoxicity

Cells cytotoxicity was evaluated by methyl thiazolyl tetrazolium (MTT) assay. The medium was changed before the assay. MTT dissolved in phosphate buffered saline (PBS) and was added to the cultured medium to reach a final concentration of 0.5 mg/mL. After incubation at 37℃ for 4 h, the culture media containing MTT were removed, and than DMSO was added into each well and absorbance at 492 nm was measured by microplate reader (Multiskan MK3, Thermo, USA).

RNA Extraction and Real-Time PCR[41]

Total RNA was extracted by the RNeasy Isolation Kit (Qiagen, Valencia, CA,

USA), and related operations were based on instruction. RNA, nuclease-freewater and Real Master Mix (Bio-Rad, Hercules, CA, USA) was involved Synthesis of cDNA. Real-time PCR was operated in mixed solution containing 2 ml cDNAsolution, 4 ml Bio-Rad iQ SYBR Green supermix with Opticon 2 (Bio-Rad, Hercules, CA, USA), 2.4 ml nuclease-freewater, and 0.6 ml eachprimer.

Enzyme-Linked Immuno-Sorbent Assay (ELISA)

Cytokine production was measured by Enzyme-Linked Immuno-Sorbent Assay (ELISA). The culture medium was used to assay the cytokine production with human ELISA kit (TNF-α: VAL105; IL-6: VAL102; MCP-1: CSB) according to manufacturer's instructions.

Western blot analysis

Protein was isolated from pulverized tissue or cells from 6-well plates in ice-cold RIPA-Buffer (Beyotime, Jiangsu, China). BCA protein quantitative kit (Beyotime, Jiangsu, China) was used to evaluate the protein concentration. For Western blots, total protein were loaded in 10% SDS-PAGE and transferred onto nitrocellulose membranes. After blocking, membranes were incubated with rabbit anti-Nox2, Nox4, anti-KIM-1, antiRIP1, anti-RIP3, anti-P-MLKL, anti-cleaved-caspase-3 antibody, anti-cleaved-caspase-8, anti-cleaved-caspase-12, and mouse antib-actin antibody for 18 h at 4◦C, then incubated with IRDye 800-conjugated secondary antibody for 1.5 h at room temperature(1:10000, Rockland immunochemicals, Gilbertsville, PA, USA). Images were detected by Li-Cor/Odyssey infrared image system (LI-COR Biosciences, Lincoln, NE, USA) and quantified using the Image J software (NIH, Bethesda, MD, USA).

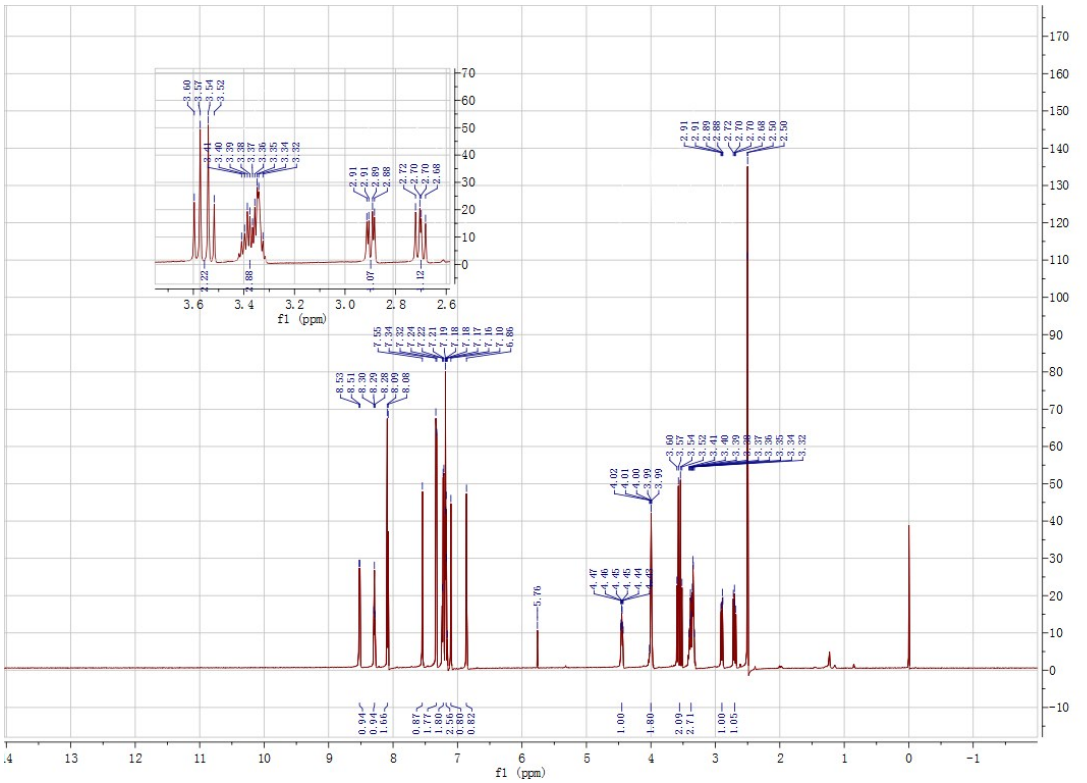

Fig. S1. ^{1}H-NMR spectrum of compound **5a** in DMSO-d_6.

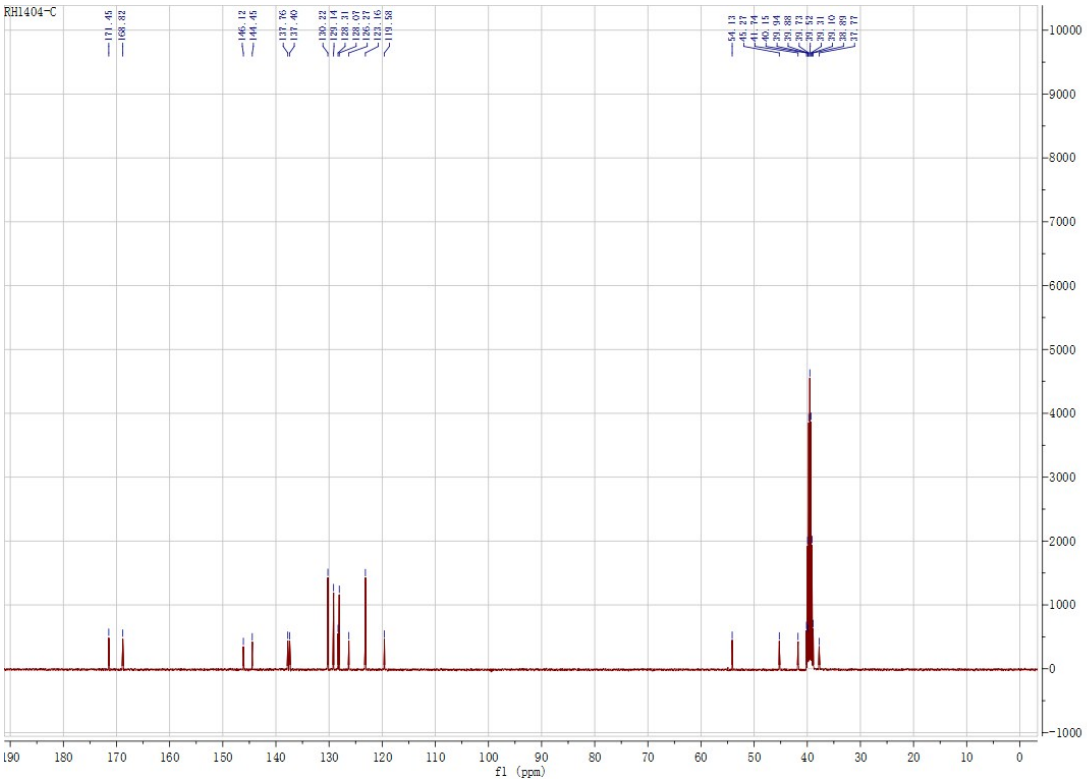

Fig. S2. ^{13}C-NMR spectrum of compound **5a** in DMSO-d_6.

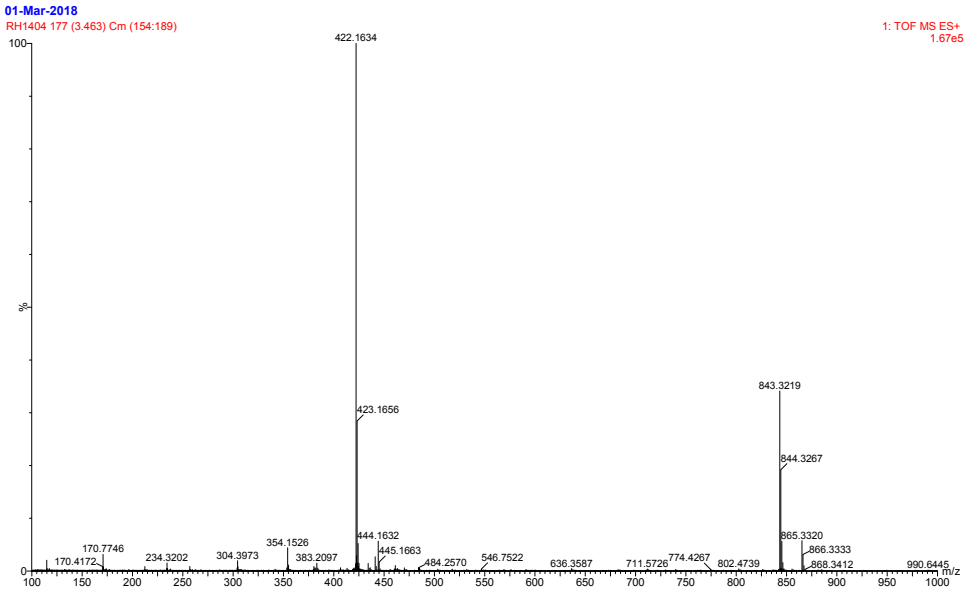

Fig. S3. TOF-HRMS spectrum of compound **5a.**

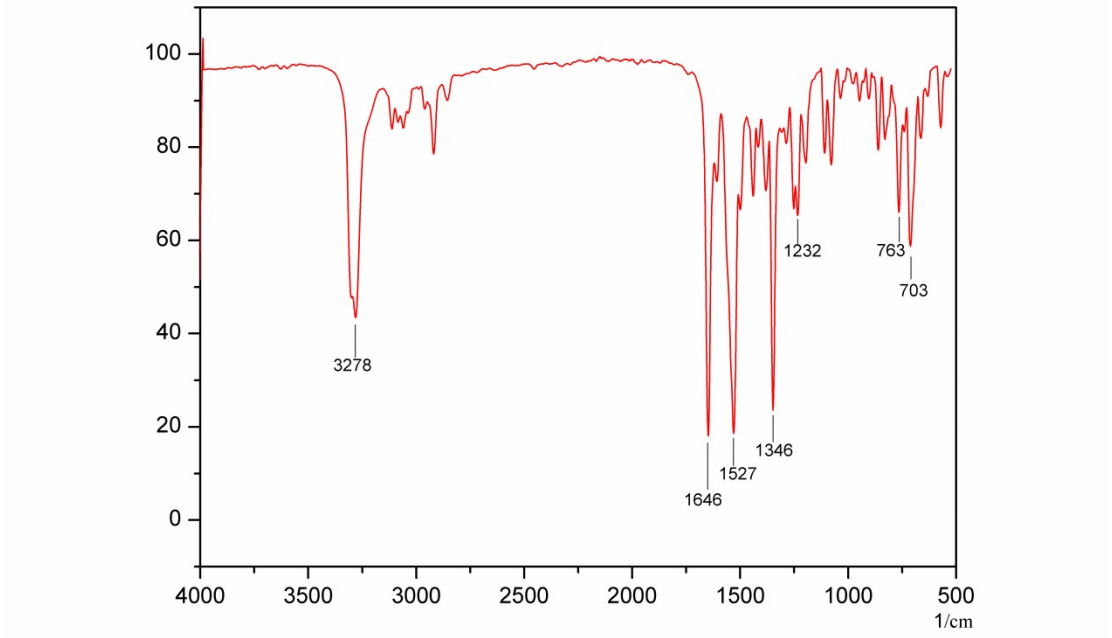

Fig. S4. FT-IR spectrum of compound **5a.**

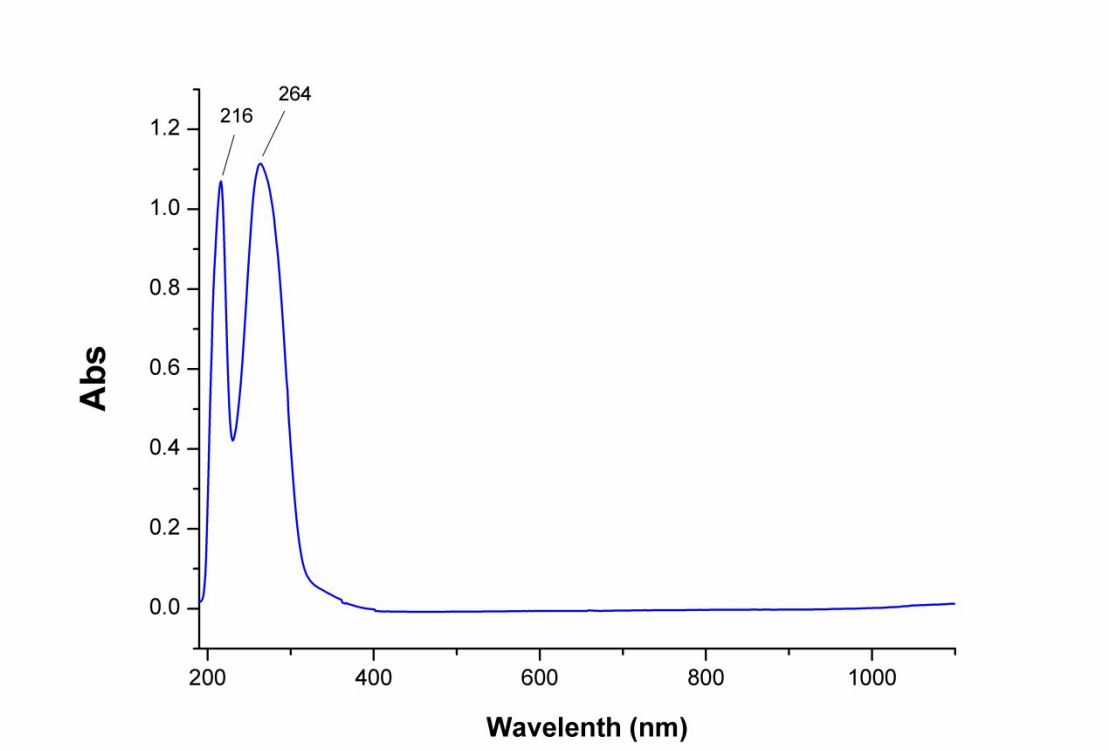

Fig. S5. UV-Vis spectrum of compound **5a.**

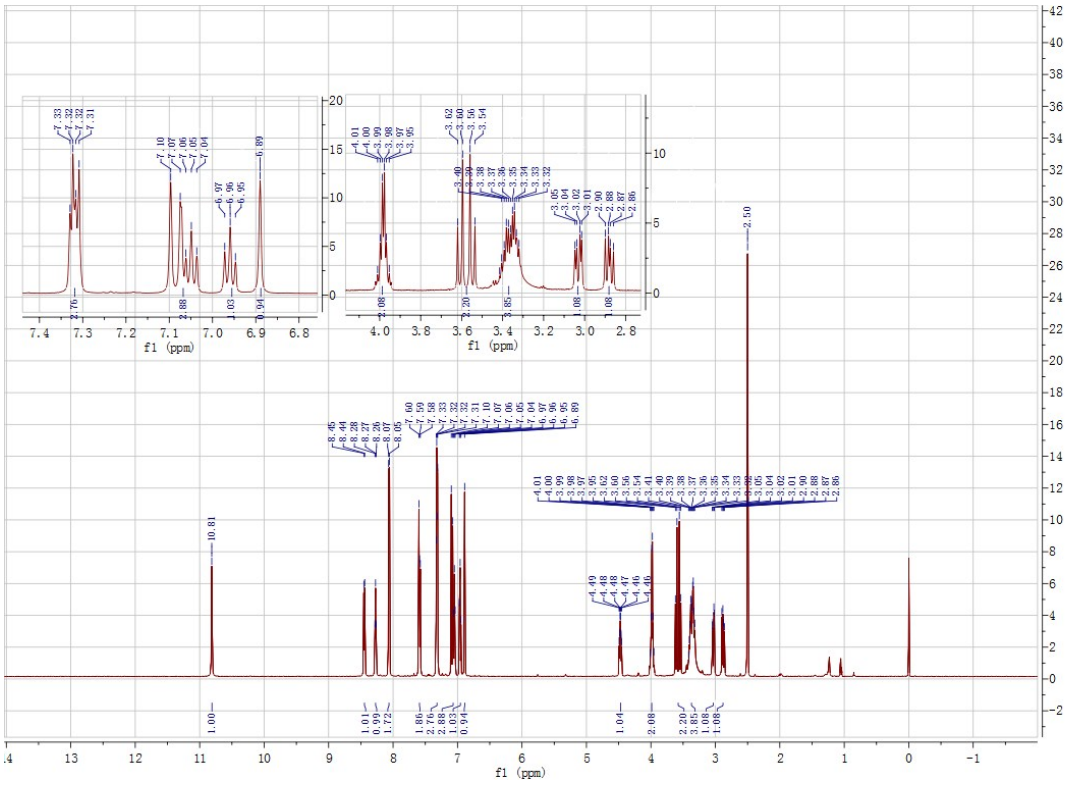

Fig. S6. [1]H-NMR spectrum of compound **5b** in DMSO-d_6.

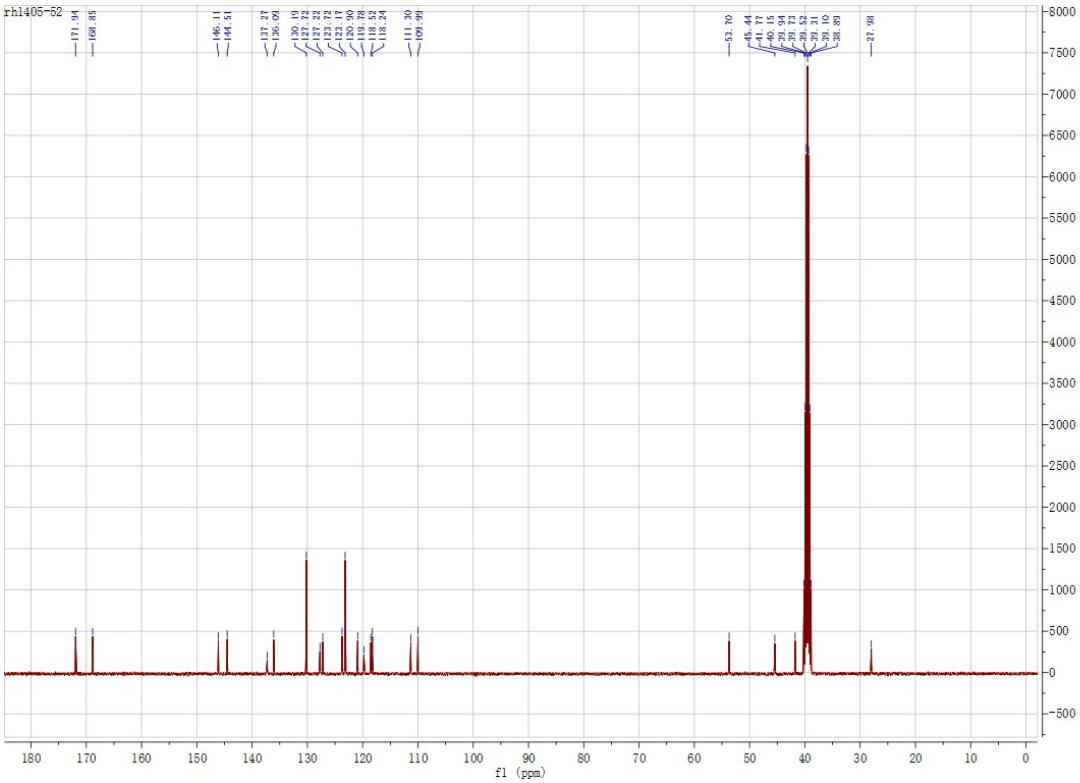

Fig. S7. ^{13}C-NMR spectrum of compound **5b** in DMSO-d_6.

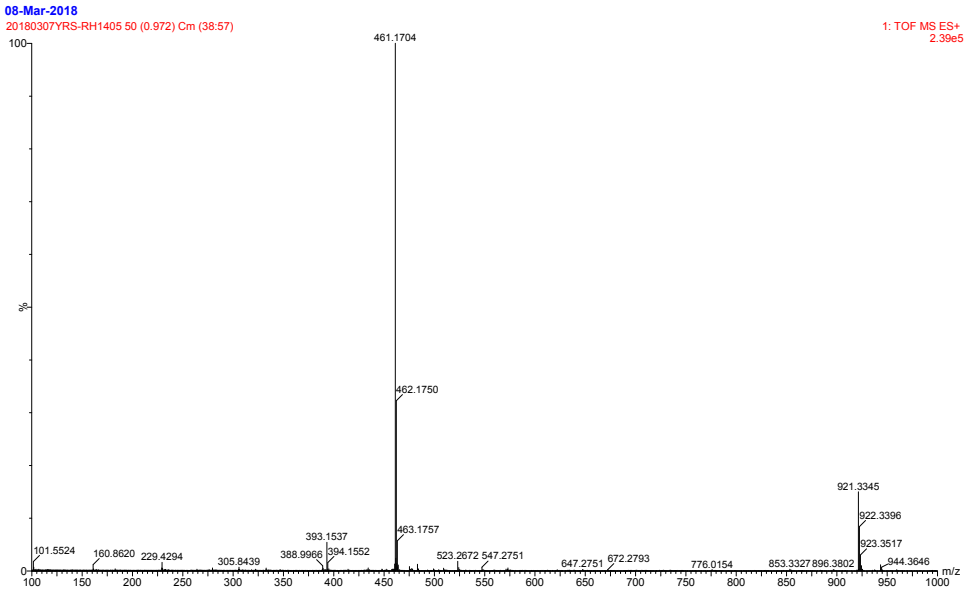

Fig. S8. TOF-HRMS spectrum of compound **5b.**

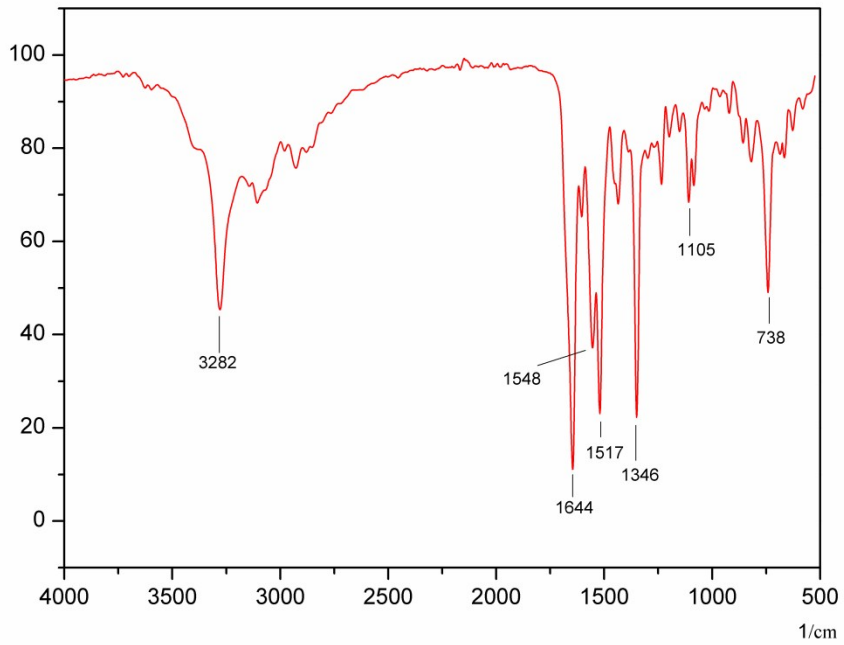

Fig. S9. FT-IR spectrum of compound **5b.**

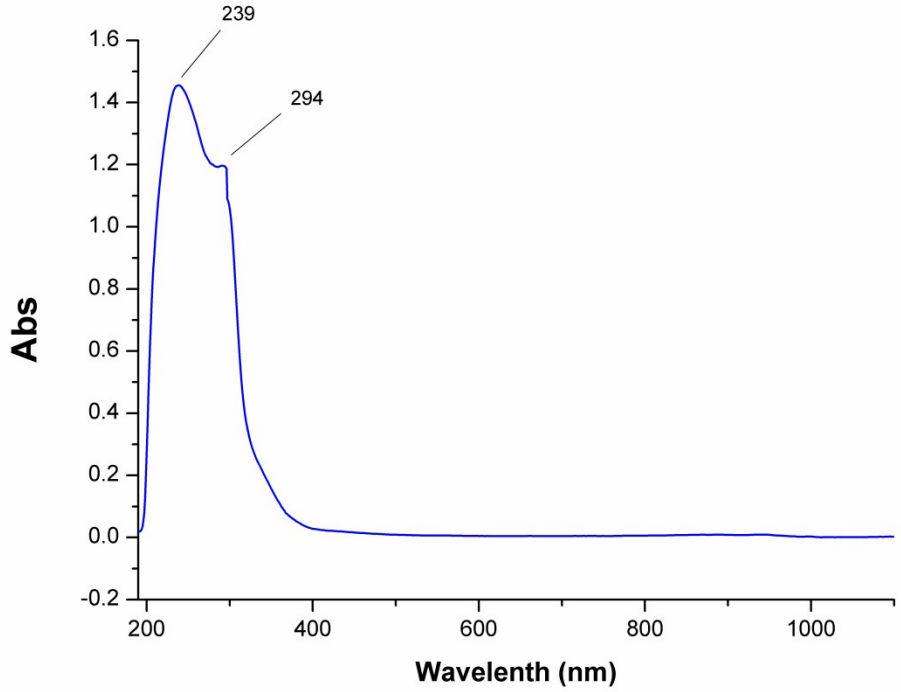

Fig. S10. UV-Vis spectrum of compound **5b.**

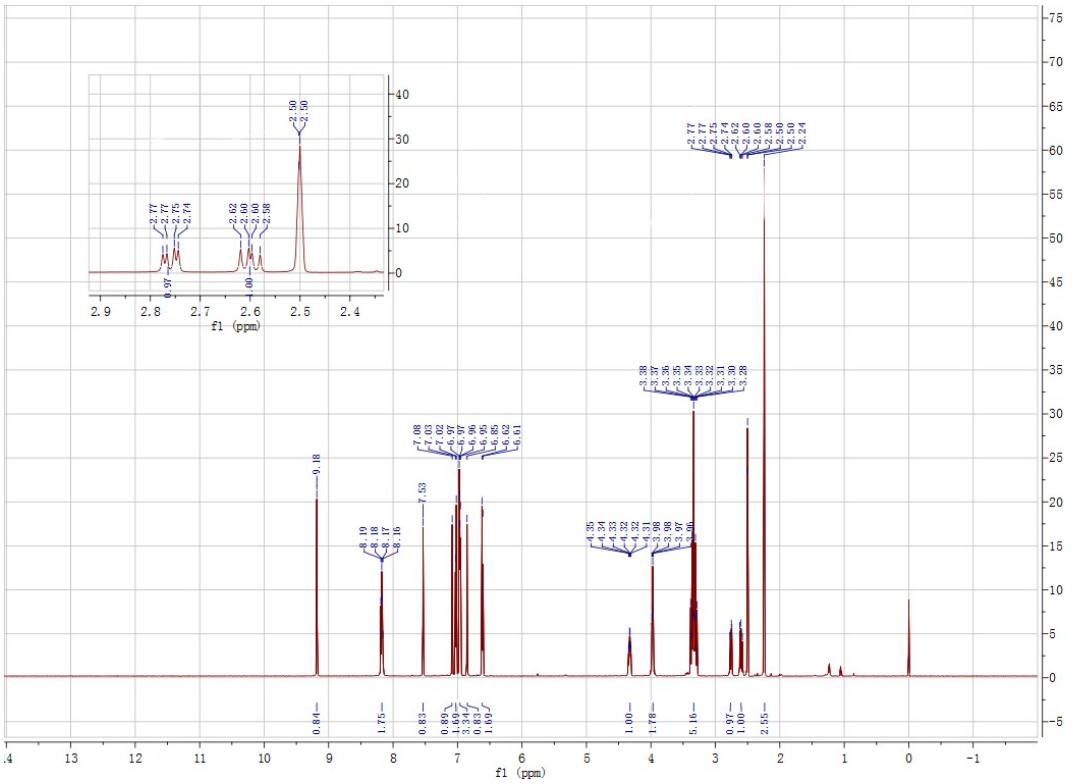

Fig. S11. [1]H-NMR spectrum of compound **5c** in DMSO-d_6.

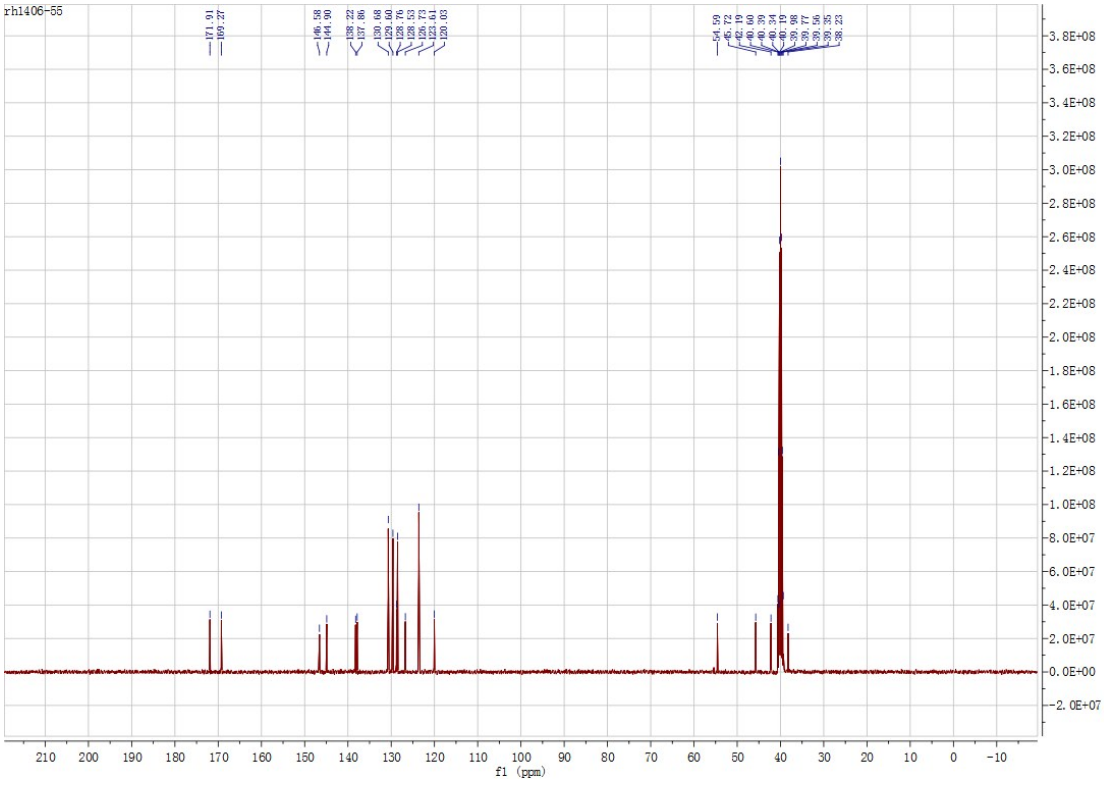

Fig. S12. [13]C-NMR spectrum of compound **5c** in DMSO-d_6.

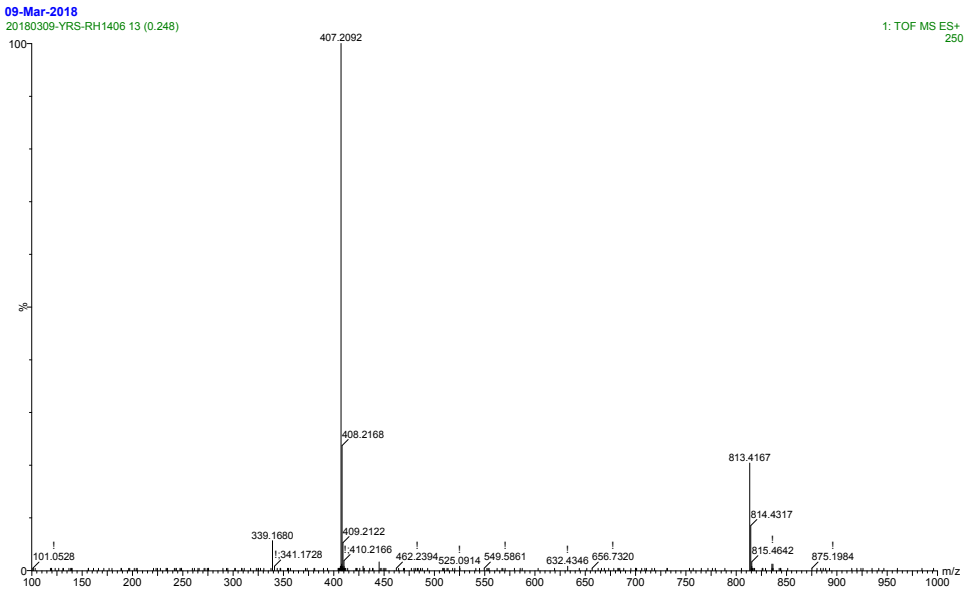

Fig. S13. TOF-HRMS spectrum of compound **5c.**

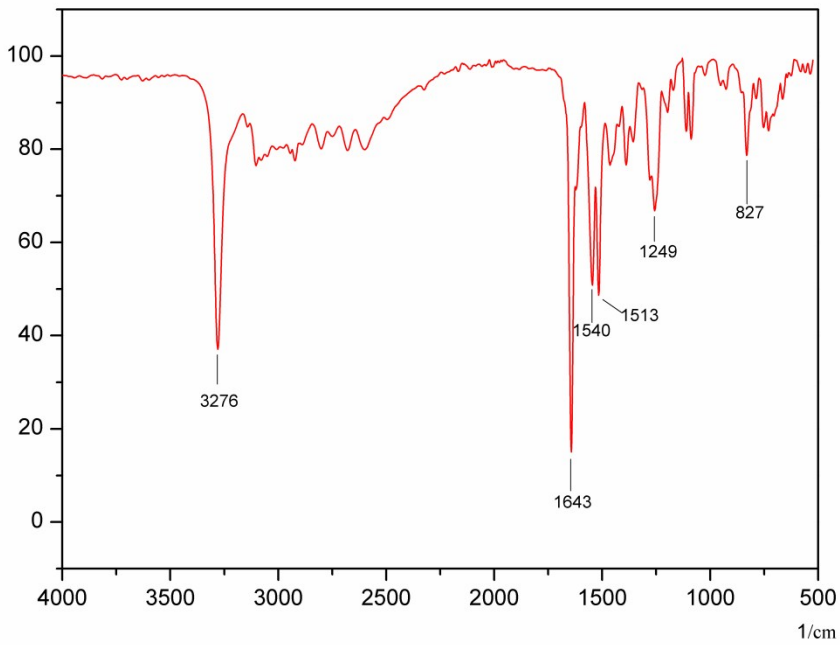

Fig. S14. FT-IR spectrum of compound **5c.**

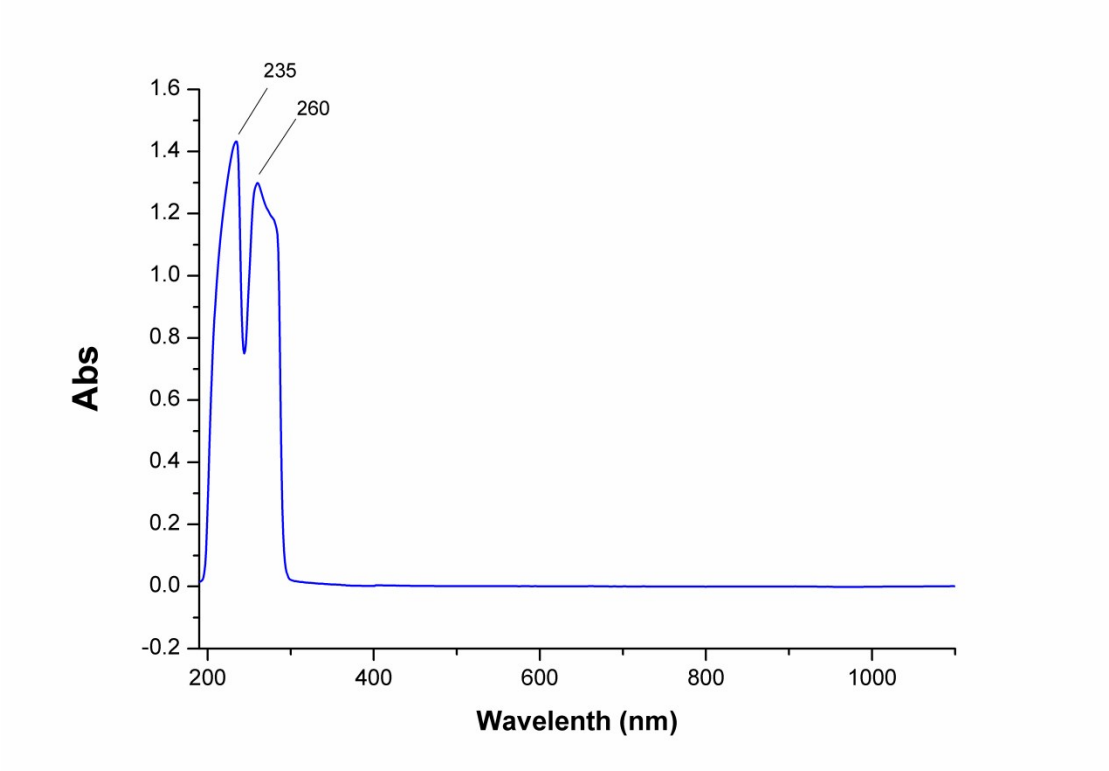

Fig. S15. UV-Vis spectrum of compound **5c.**

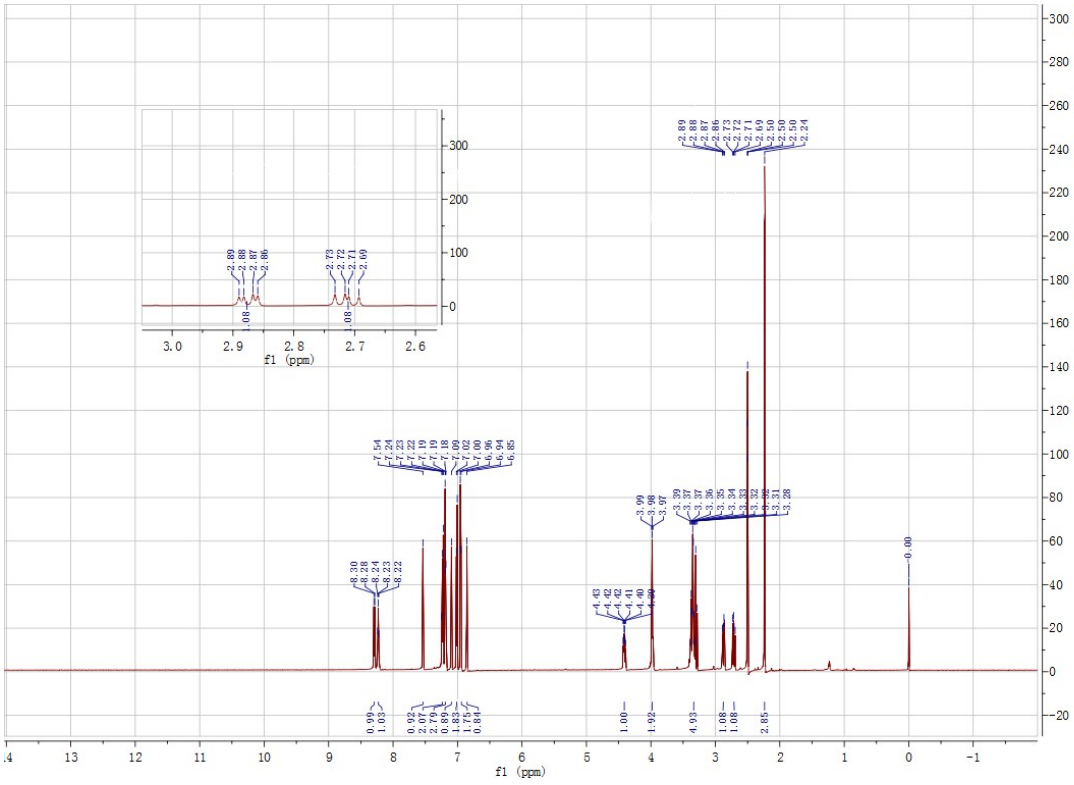

Fig. S16. ^{1}H-NMR spectrum of compound **5d** in DMSO-d_6.

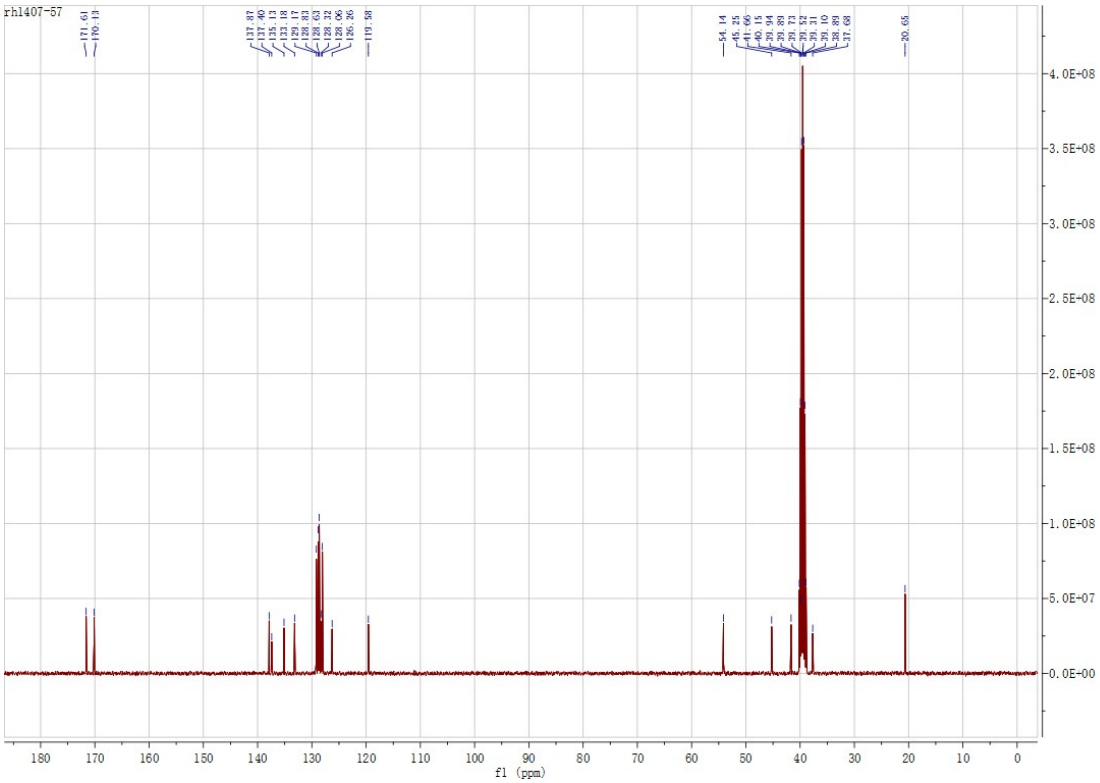

Fig. S17. ^{13}C-NMR spectrum of compound **5d** in DMSO-d_6.

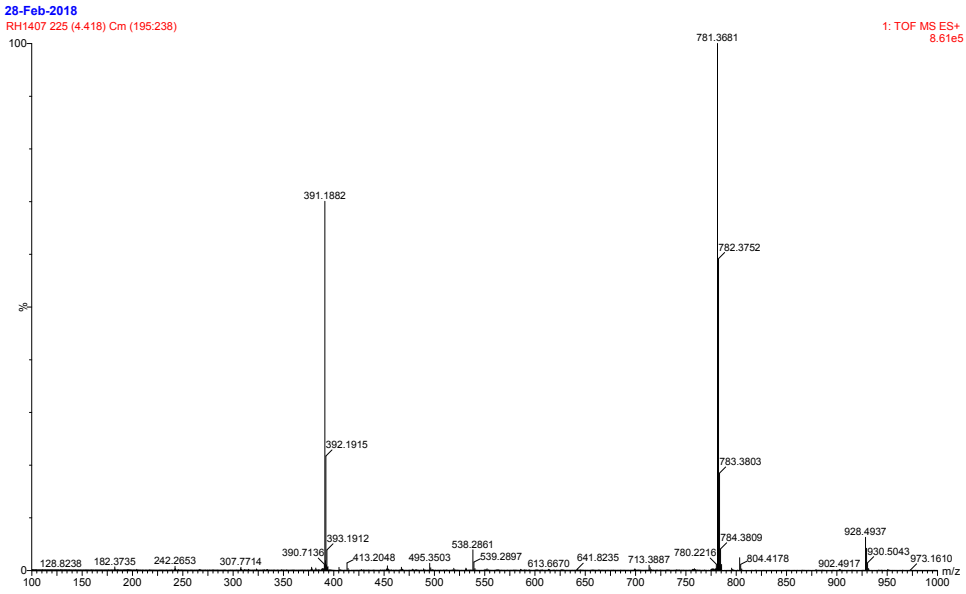

Fig. S18. TOF-HRMS spectrum of compound **5d.**

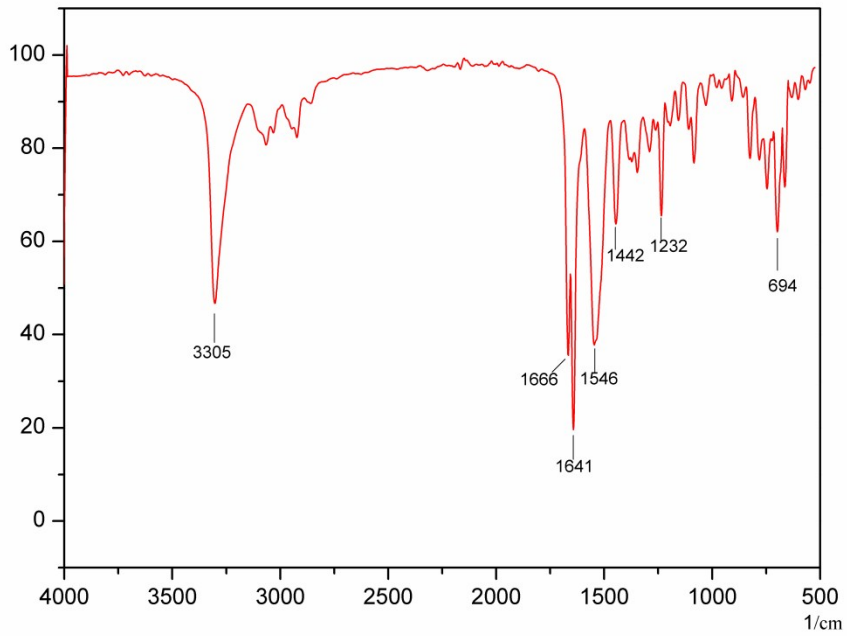

Fig. S19. FT-IR spectrum of compound **5d.**

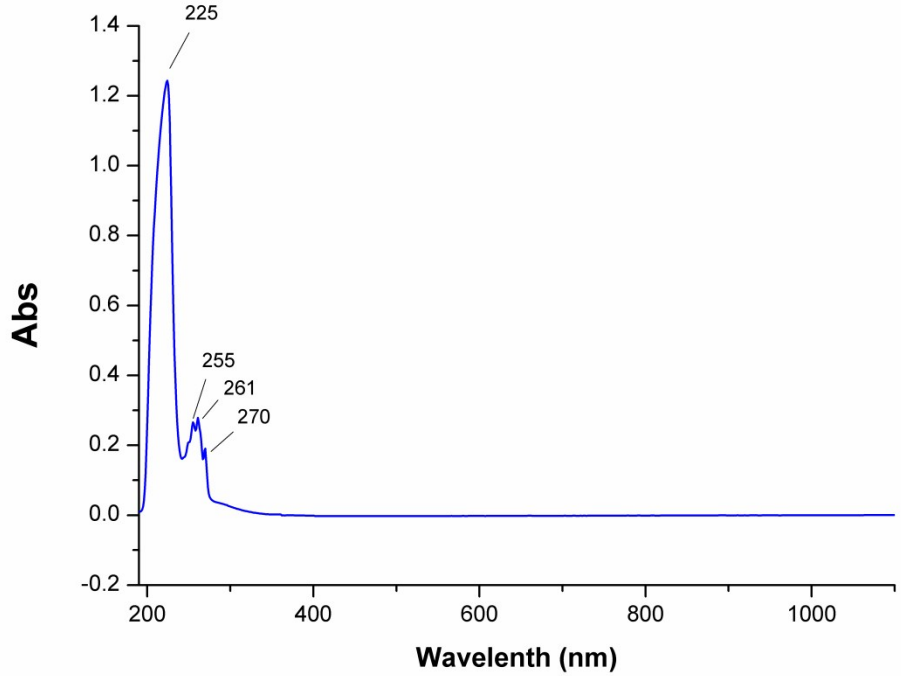

Fig. S20. UV-Vis spectrum of compound **5d.**

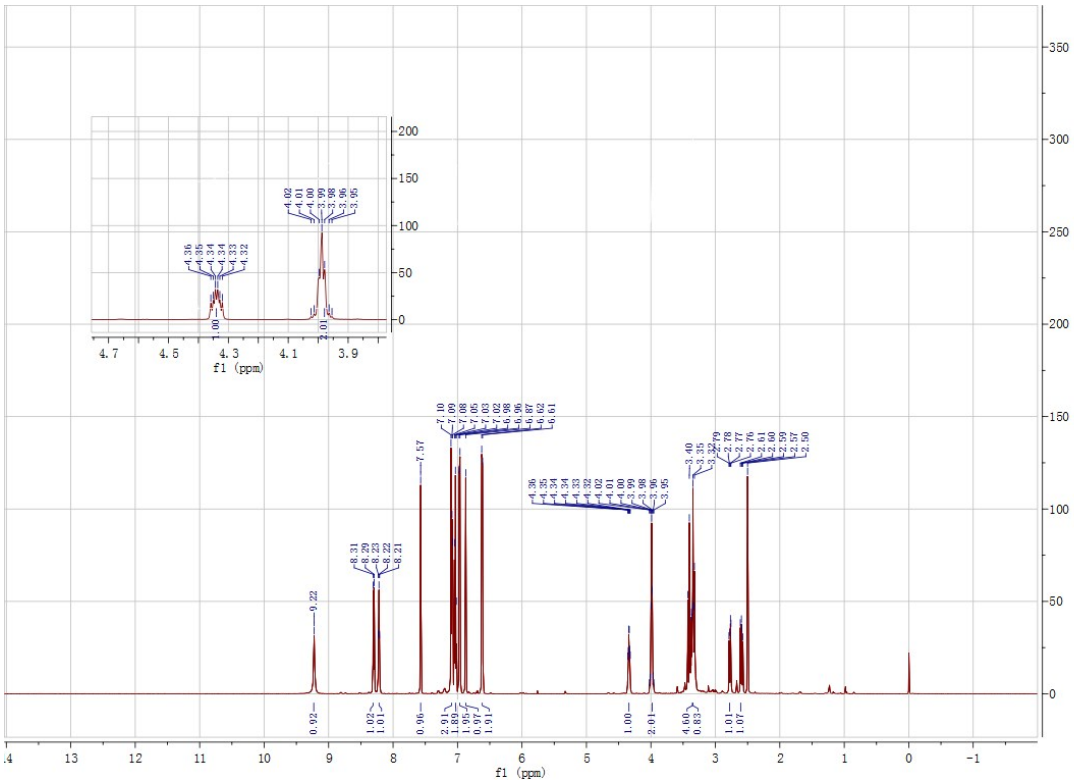

Fig. S21. [1]H-NMR spectrum of compound **5e** in DMSO-d_6.

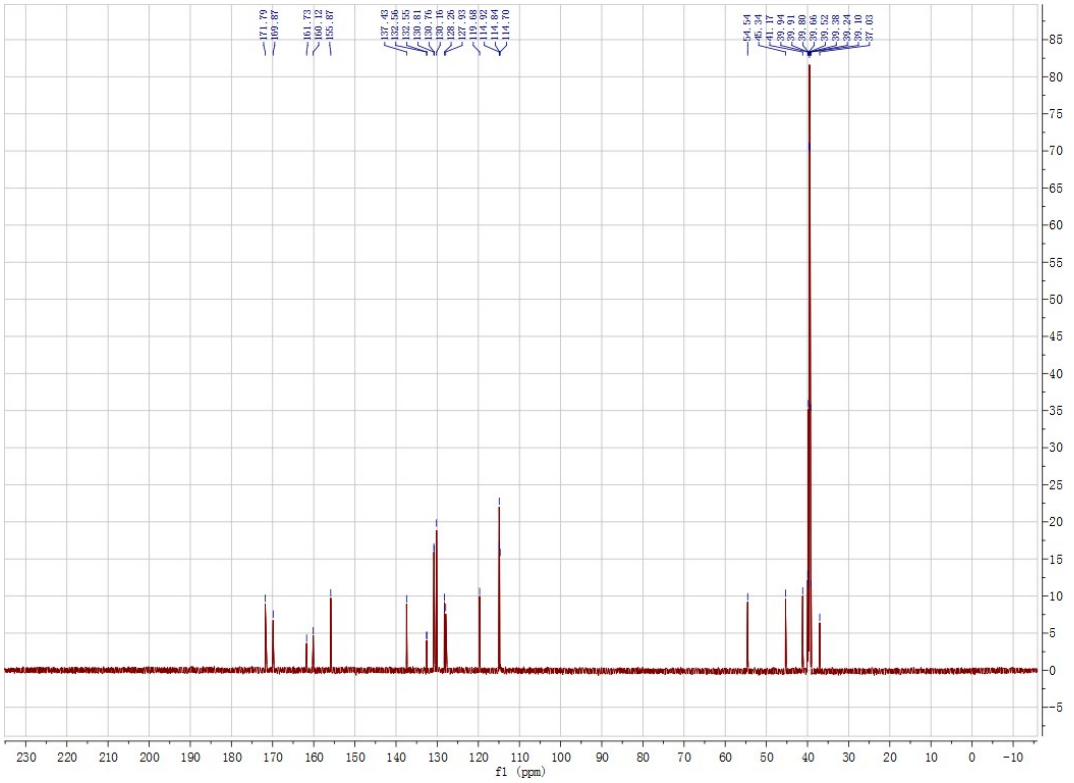

Fig. S22. [13]C-NMR spectrum of compound **5e** in DMSO-d_6.

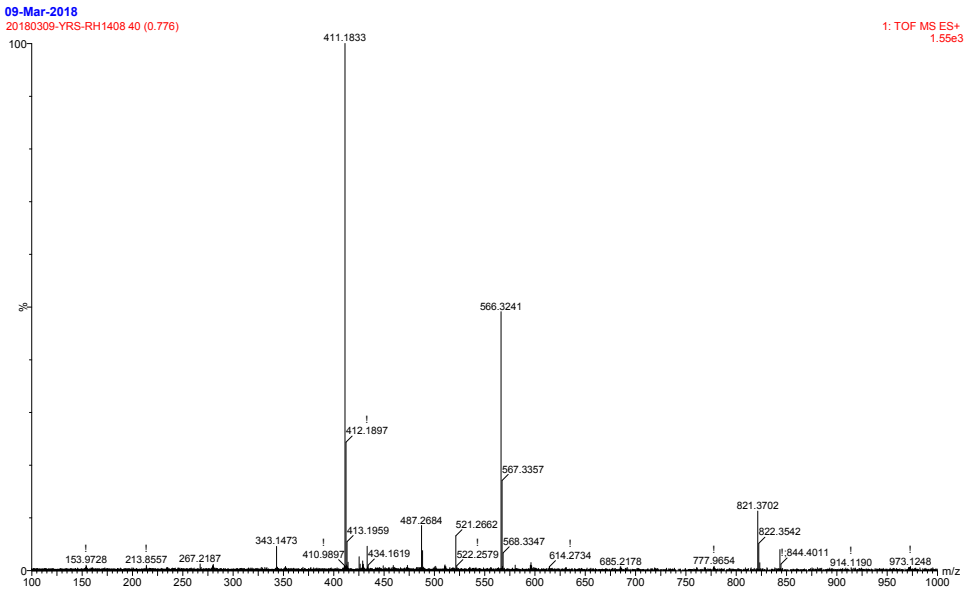

Fig. S23. TOF-HRMS spectrum of compound **5e.**

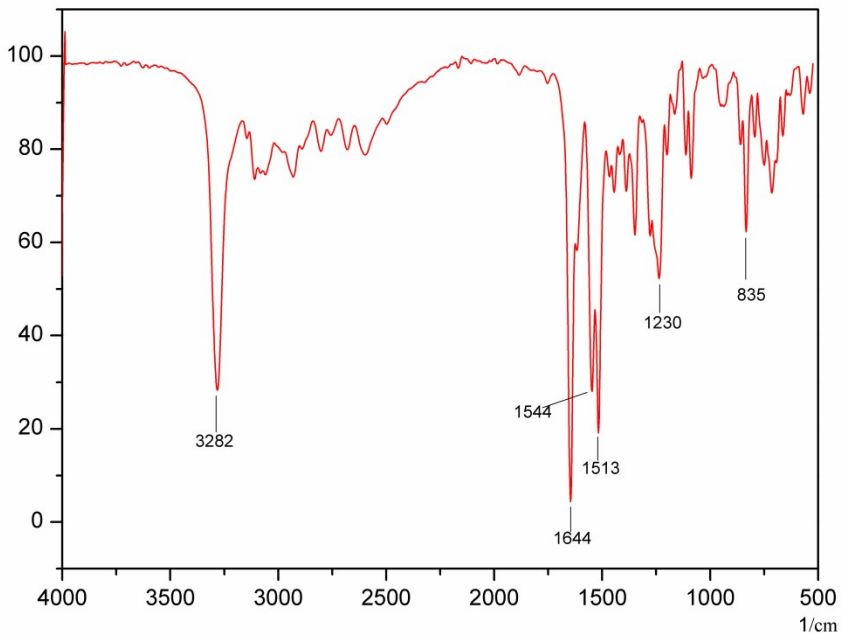

Fig. S24. FT-IR spectrum of compound **5e.**

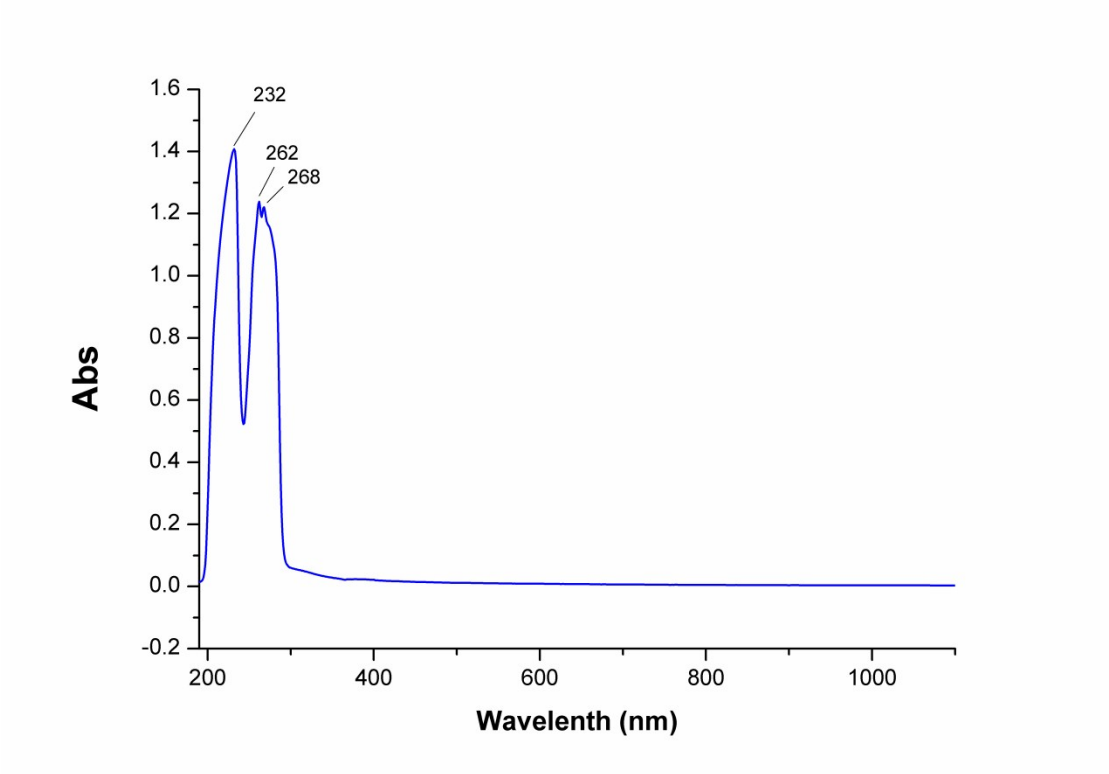

Fig. S25. UV-Vis spectrum of compound **5e.**

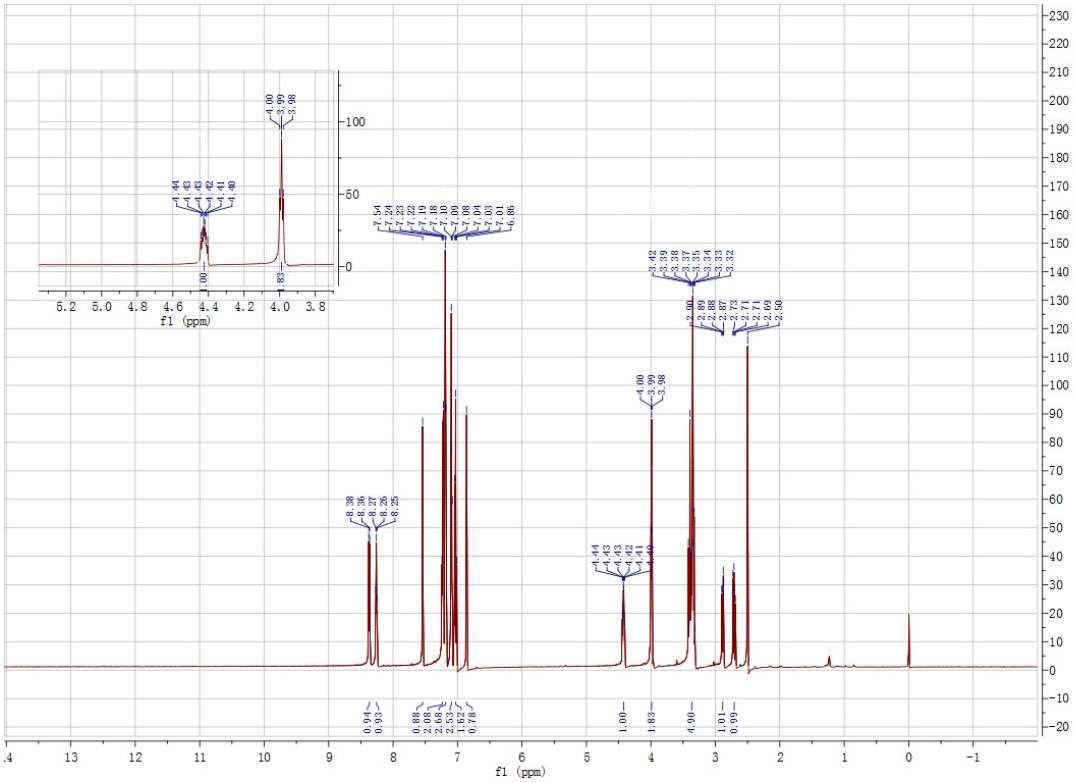

Fig. S26. ^{1}H-NMR spectrum of compound **5f** in DMSO-d_6.

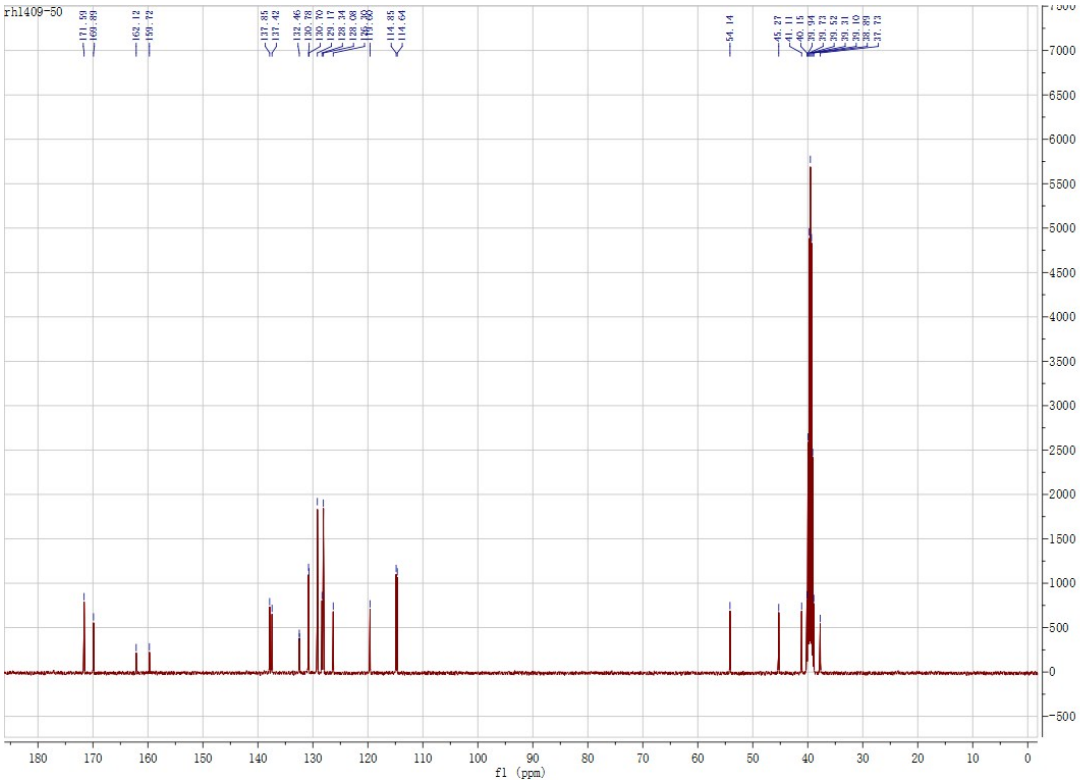

Fig. S27. ^{13}C-NMR spectrum of compound **5f** in DMSO-d_6.

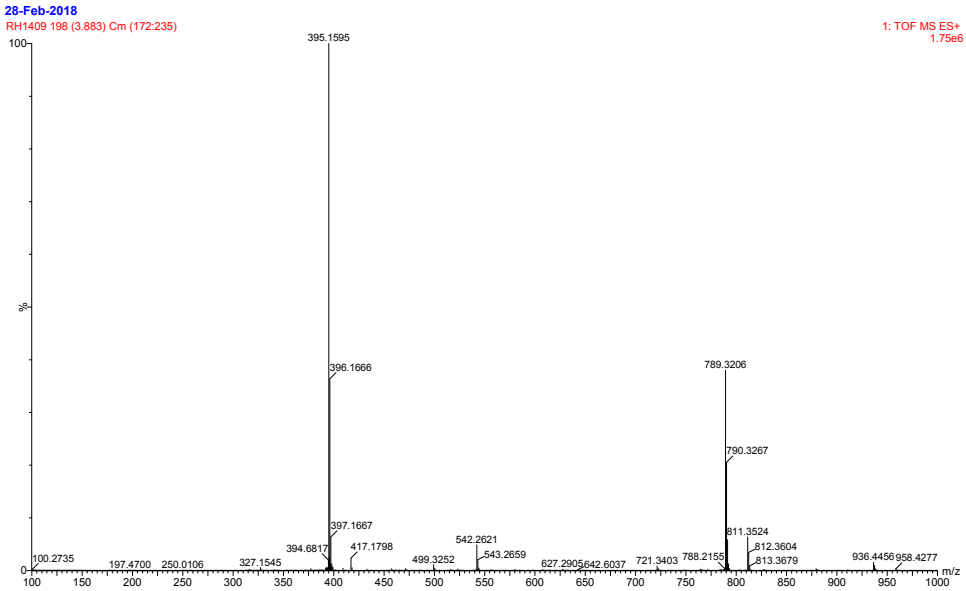

Fig. S28. TOF-HRMS spectrum of compound **5f.**

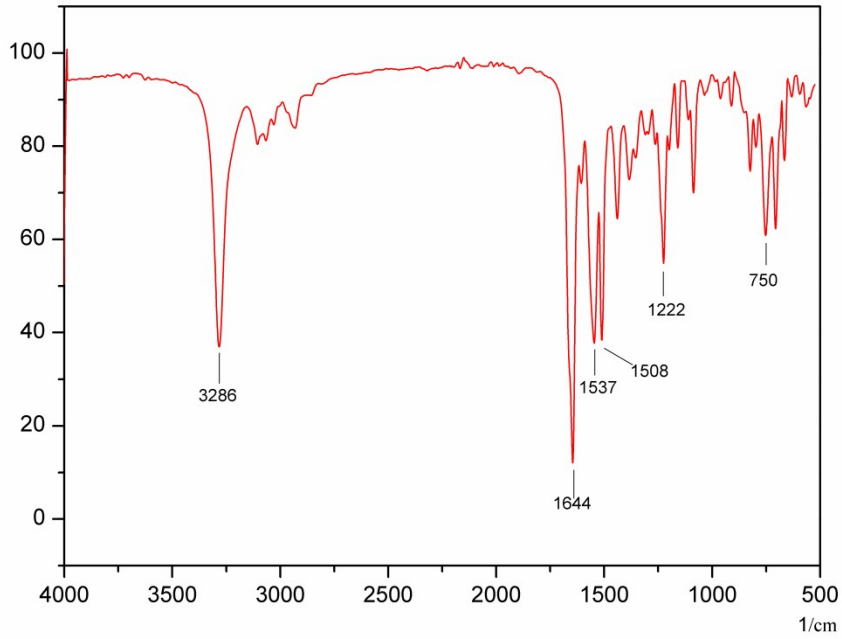

Fig. S29. FT-IR spectrum of compound **5f.**

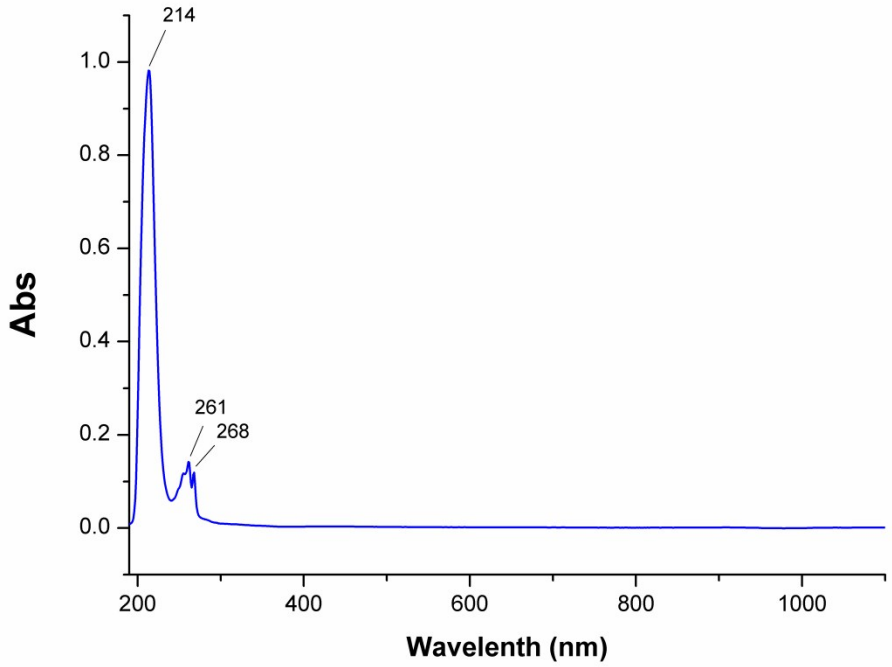

Fig. S30. UV-Vis spectrum of compound **5f.**

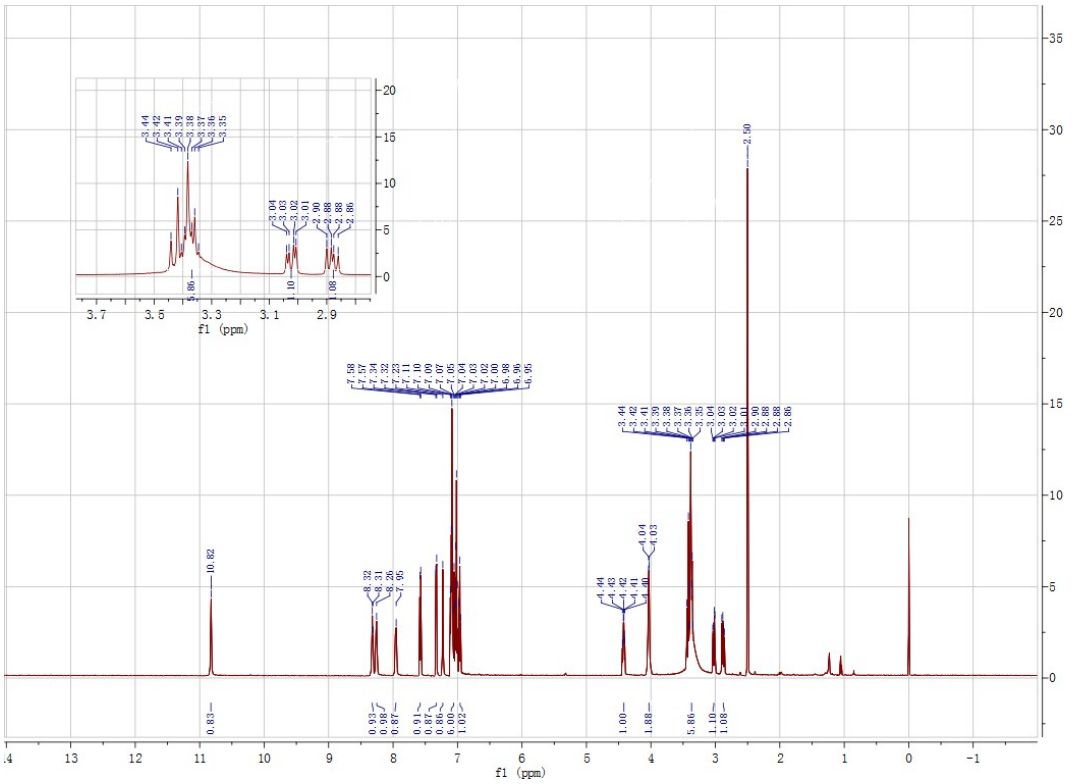

Fig. S31. ^{1}H-NMR spectrum of compound **5g** in DMSO-d_6.

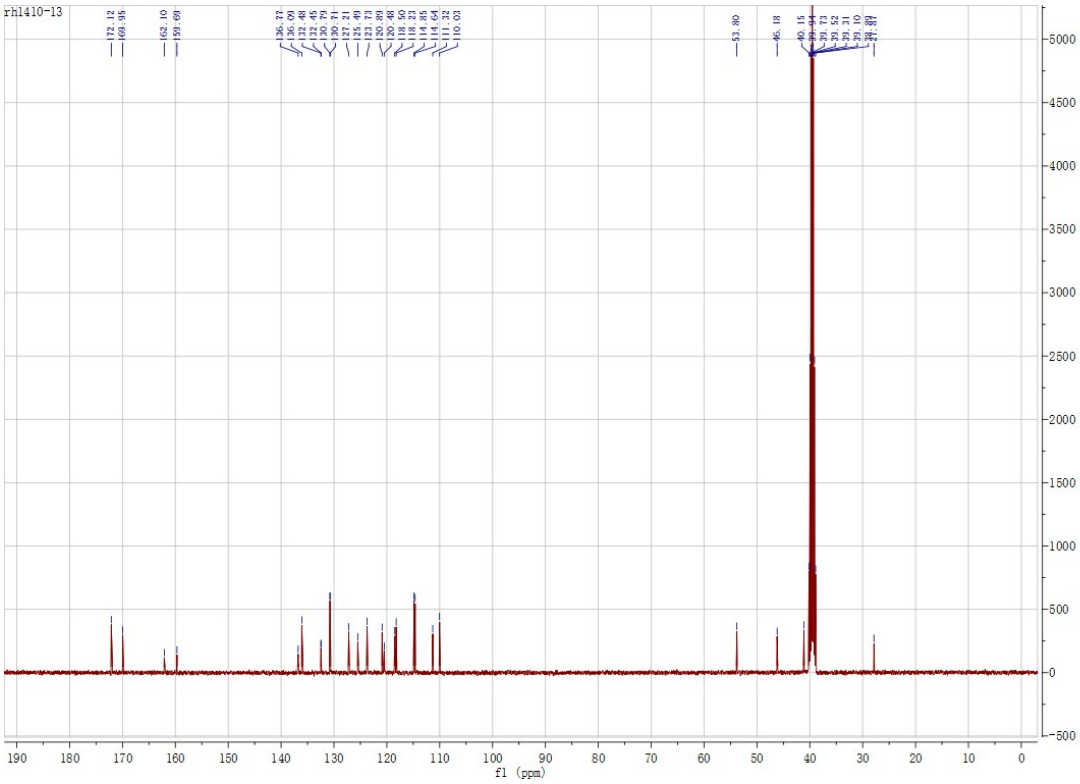

Fig. S32. ^{13}C-NMR spectrum of compound **5g** in DMSO-d_6.

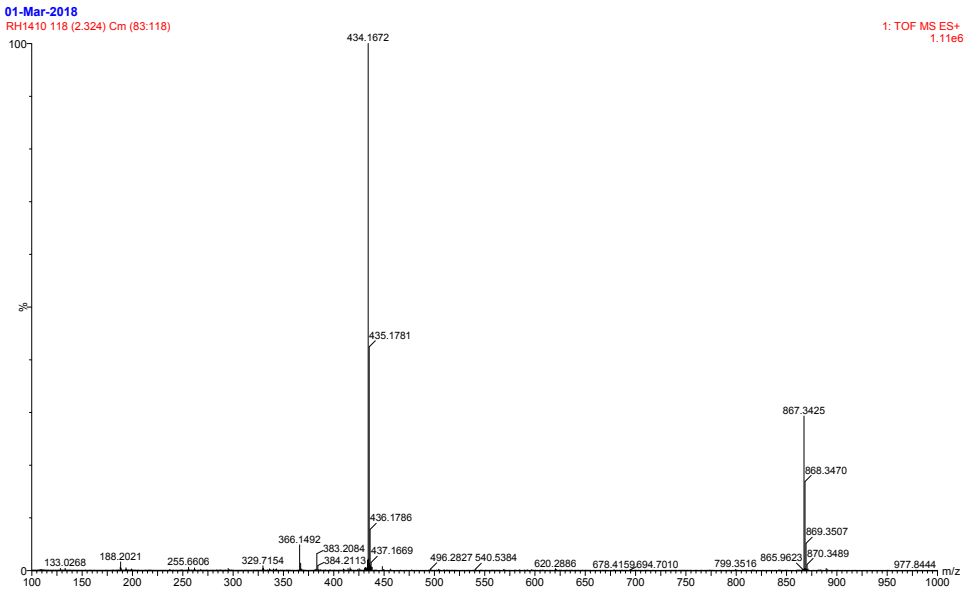

Fig. S33. TOF-HRMS spectrum of compound **5g.**

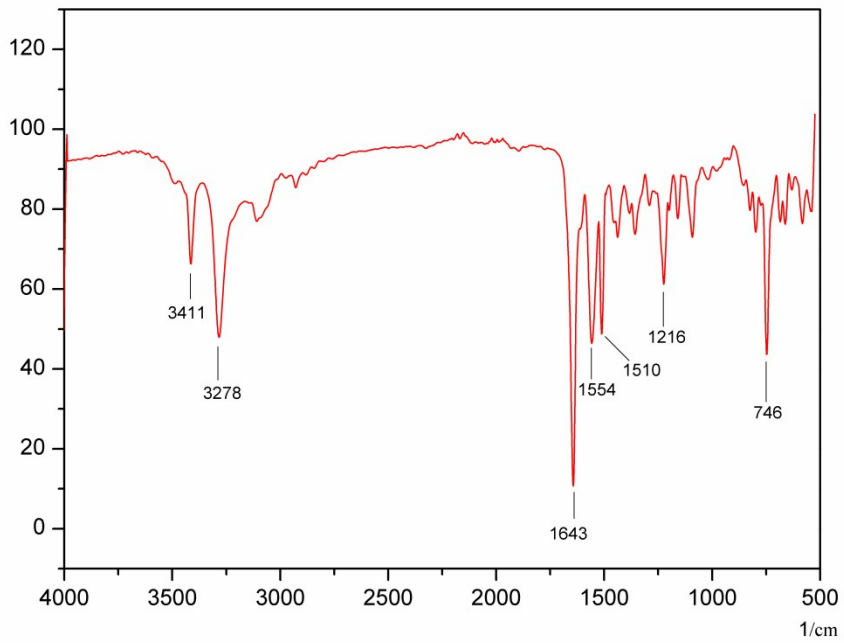

Fig. S34. FT-IR spectrum of compound **5g.**

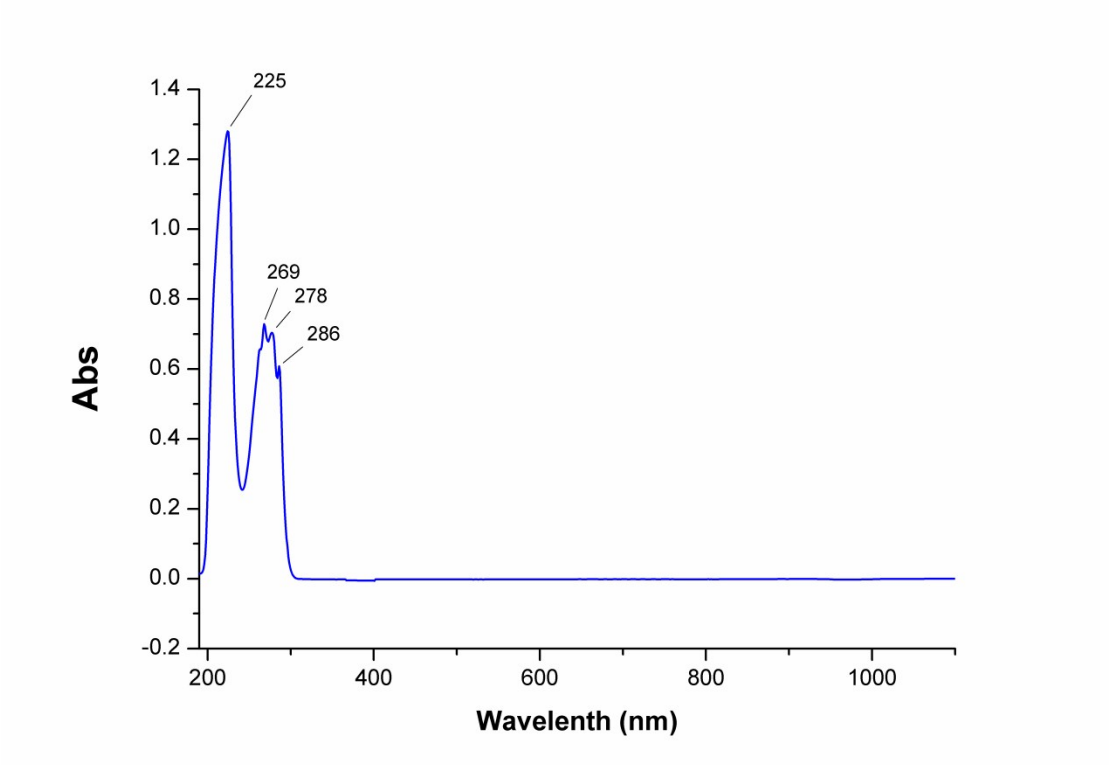

Fig. S35. UV-Vis spectrum of compound **5g.**

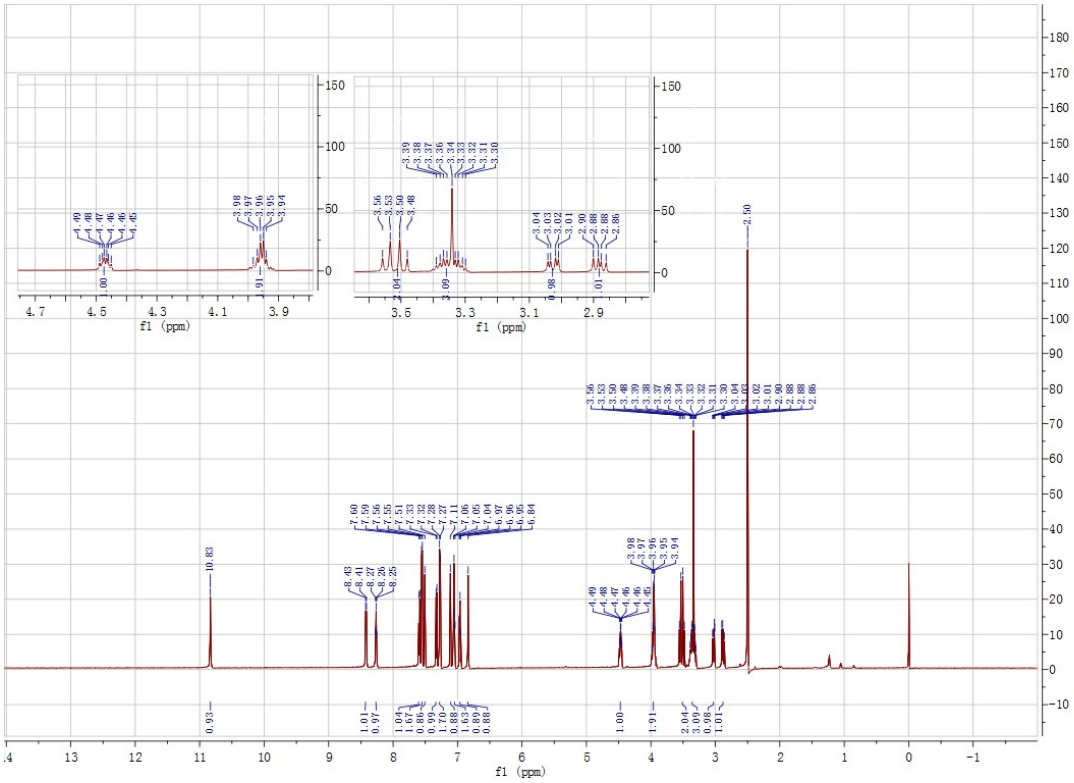

Fig. S36. ^{1}H-NMR spectrum of compound **5h** in DMSO-d_6.

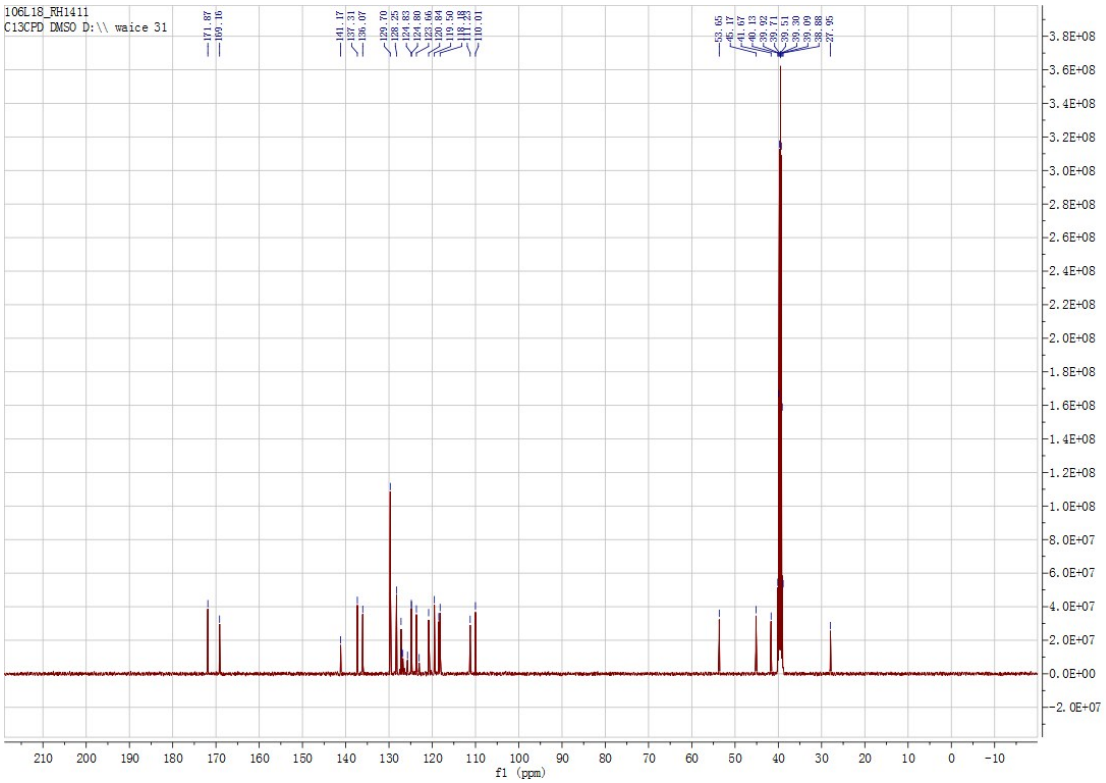

Fig. S37. ^{13}C-NMR spectrum of compound **5h** in DMSO-d_6.

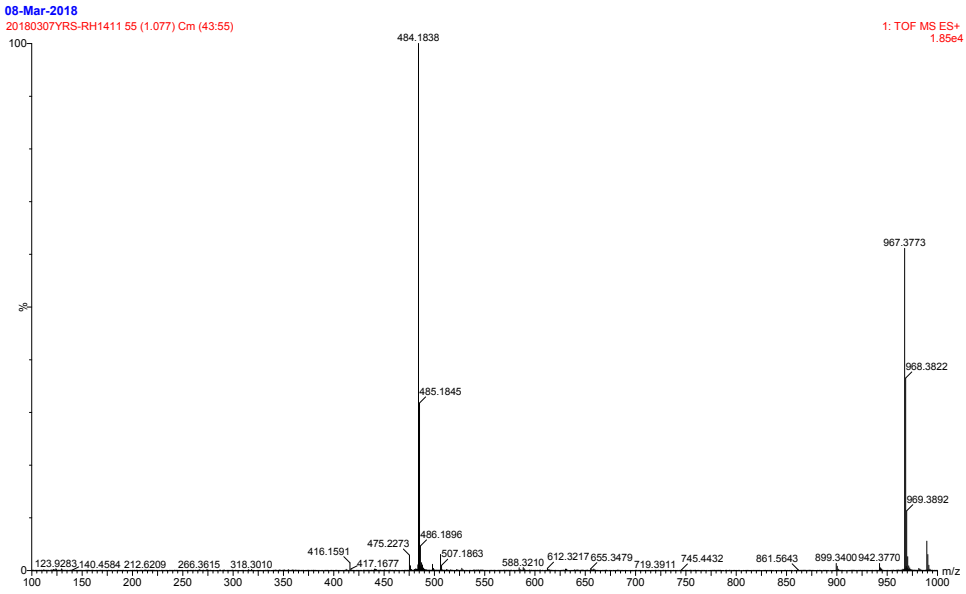

Fig. S38. TOF-HRMS spectrum of compound **5h.**

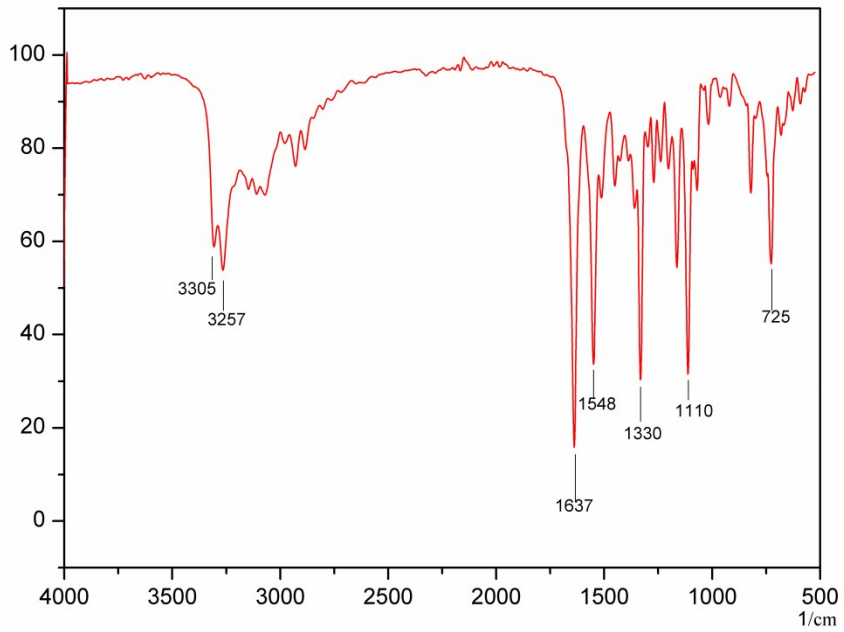

Fig. S39. FT-IR spectrum of compound **5h.**

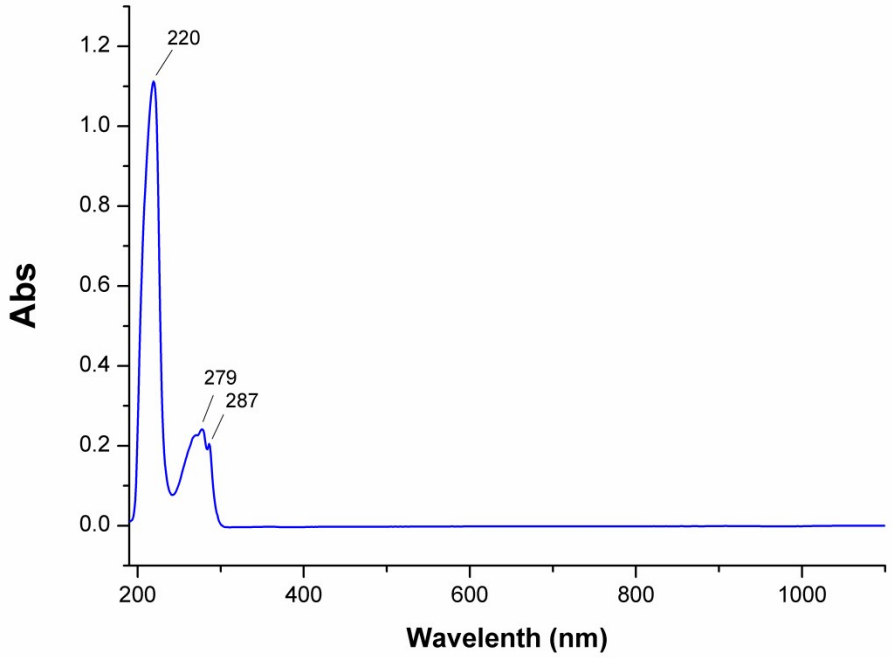

Fig. S40. UV-Vis spectrum of compound **5h.**

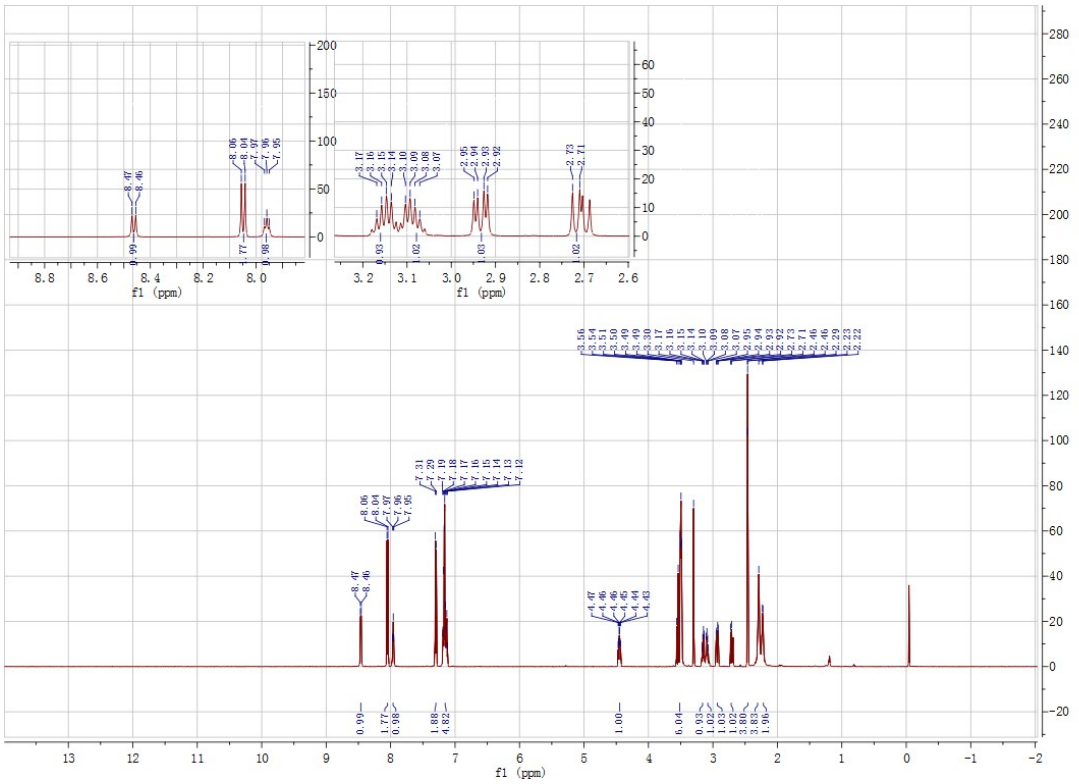

Fig. S41. [1]H-NMR spectrum of compound **5i** in DMSO-d_6.

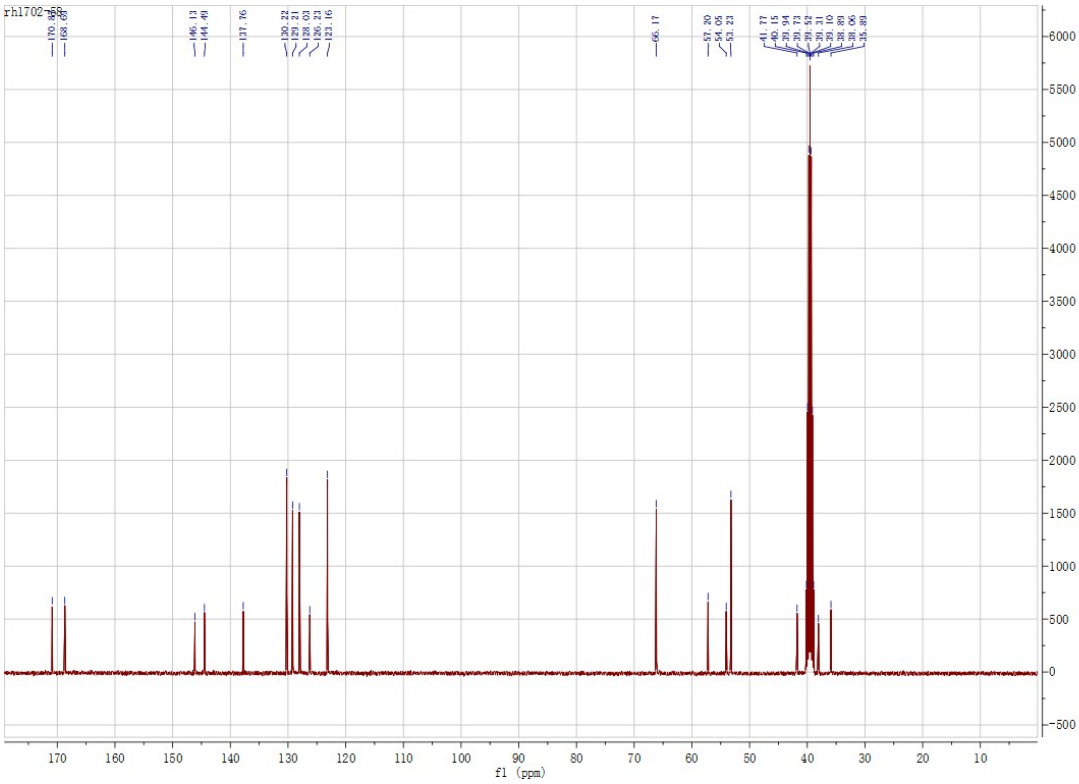

Fig. S42. [13]C-NMR spectrum of compound **5i** in DMSO-d_6.

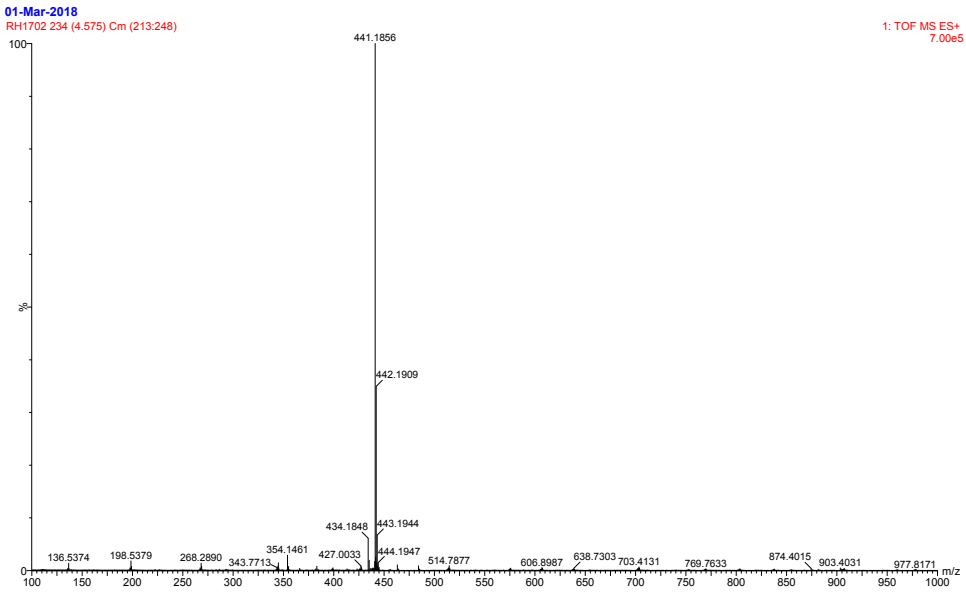

Fig. S43. TOF-HRMS spectrum of compound **5i.**

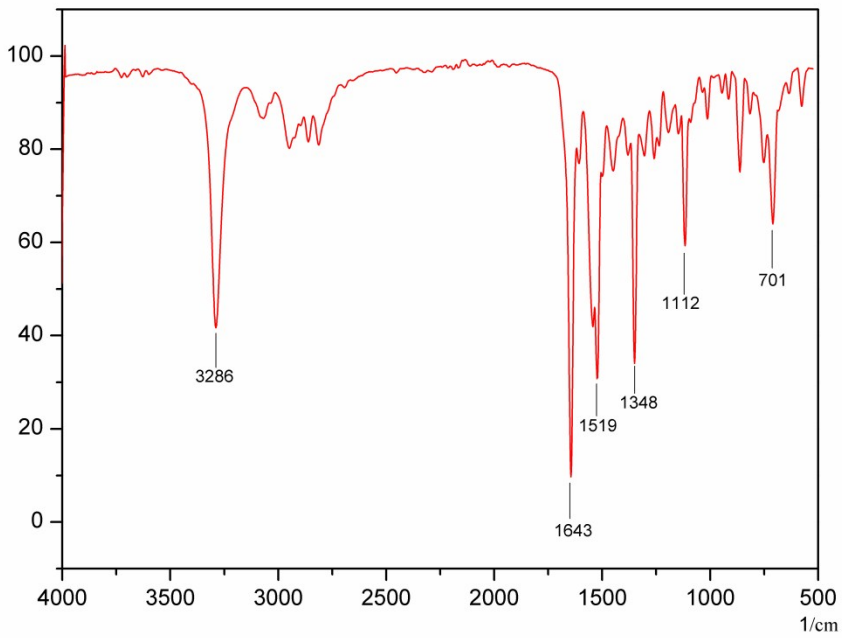

Fig. S44. FT-IR spectrum of compound **5i.**

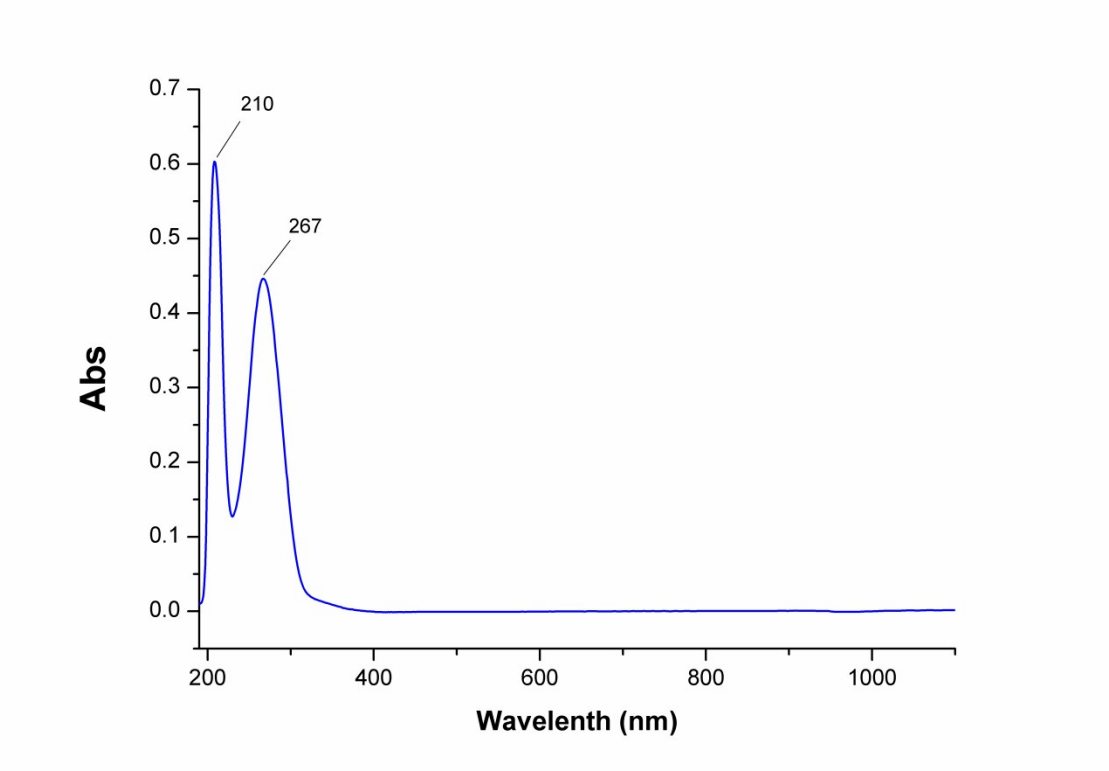

Fig. S45. UV-Vis spectrum of compound **5i.**

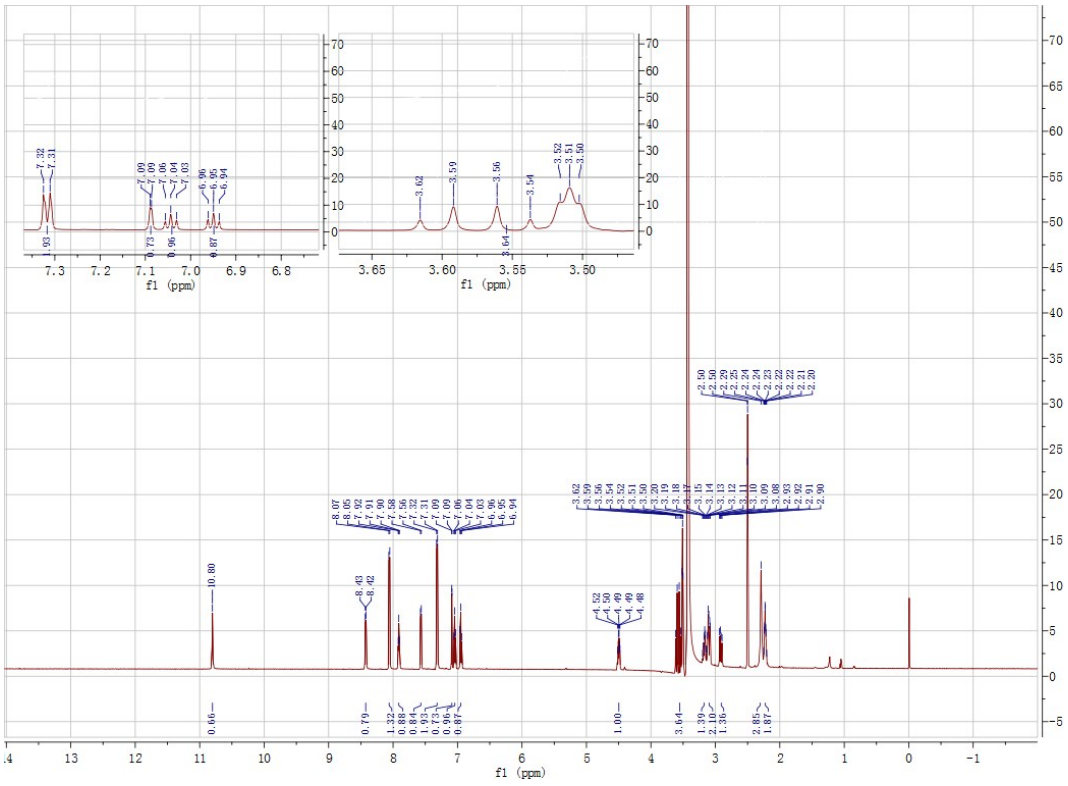

Fig. S46. ^{1}H-NMR spectrum of compound **5j** in DMSO-d_6.

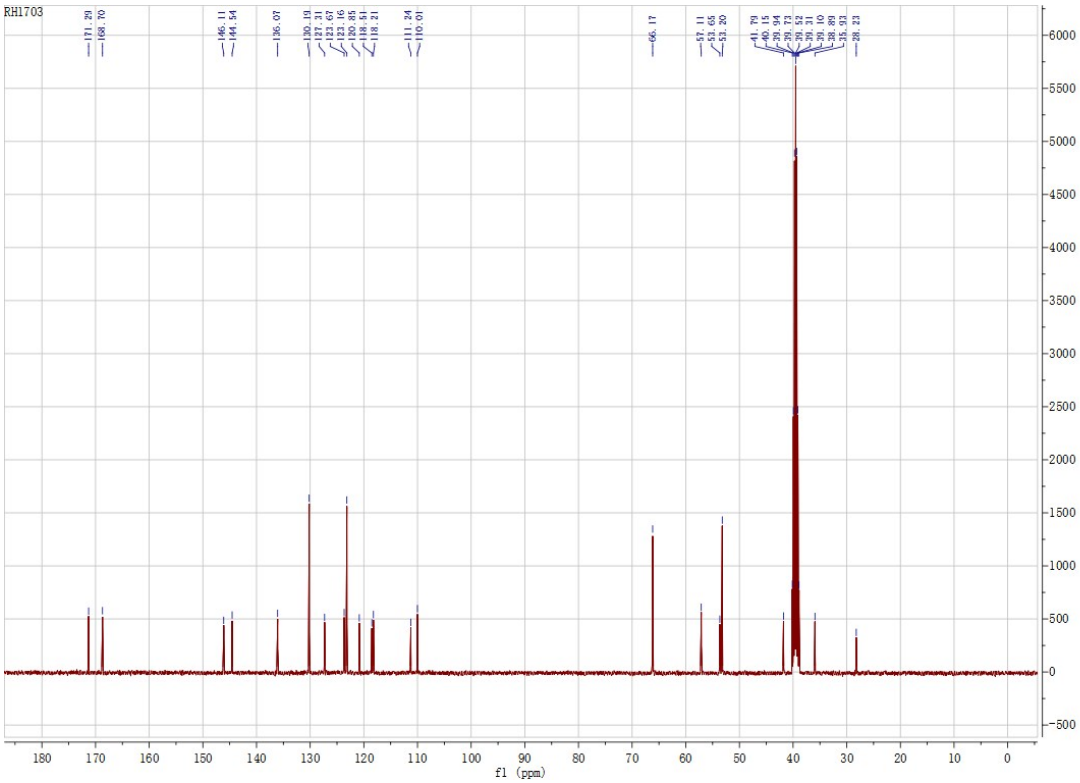

Fig. S47. ^{13}C-NMR spectrum of compound **5j** in DMSO-d_6.

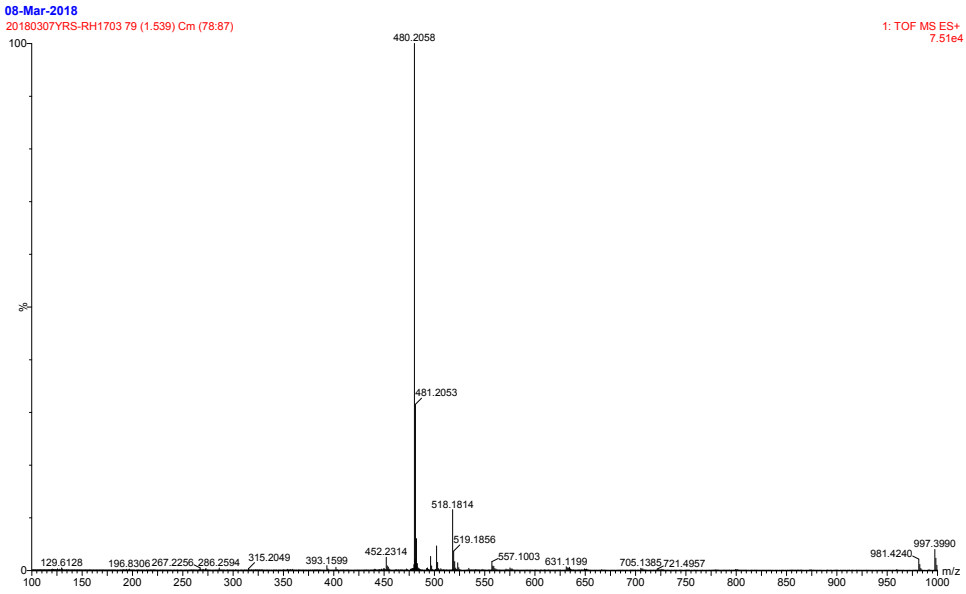

Fig. S48. TOF-HRMS spectrum of compound **5j.**

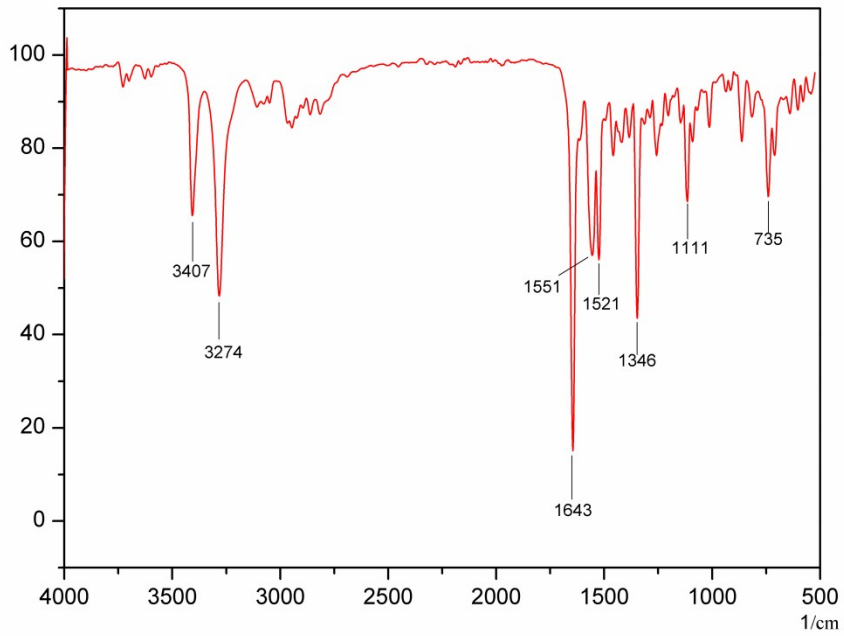

Fig. S49. FT-IR spectrum of compound **5j.**

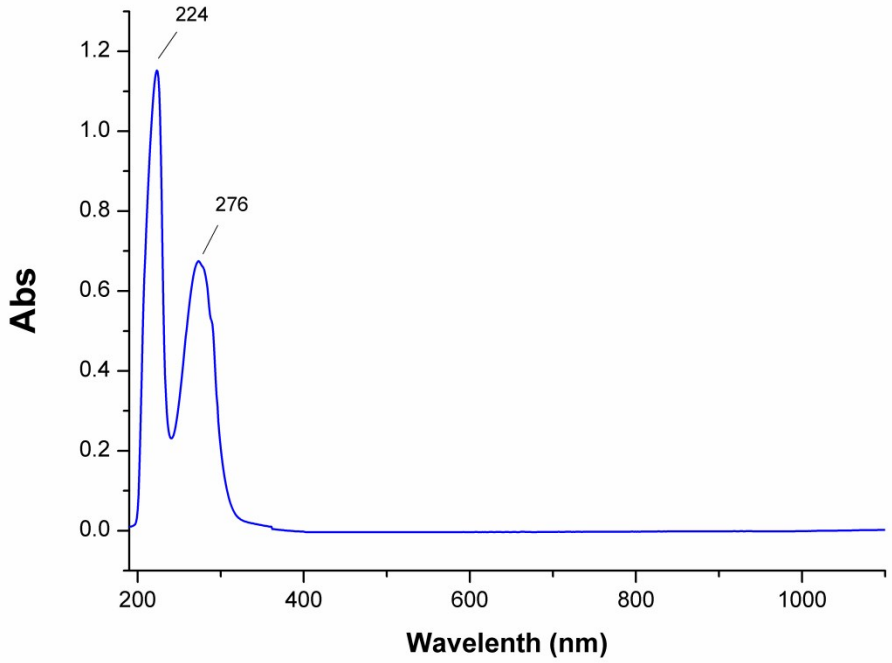

Fig. S50. UV-Vis spectrum of compound **5j.**

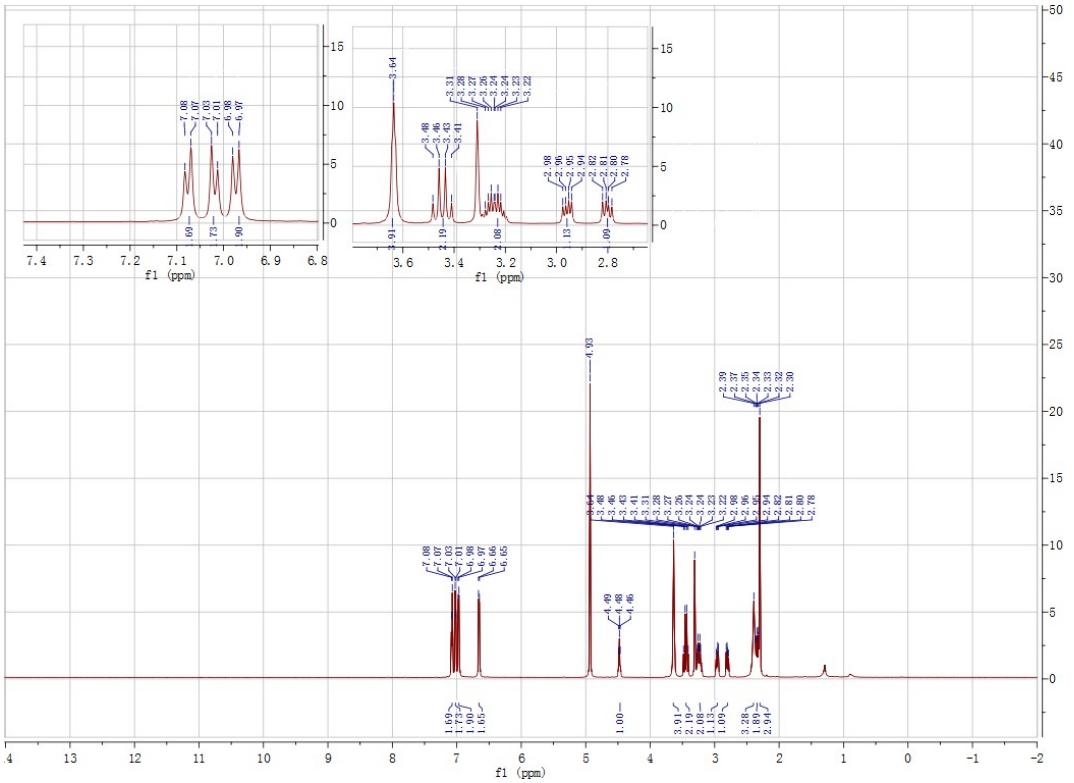

Fig. S51. [1]H-NMR spectrum of compound **5k** in DMSO-d_6.

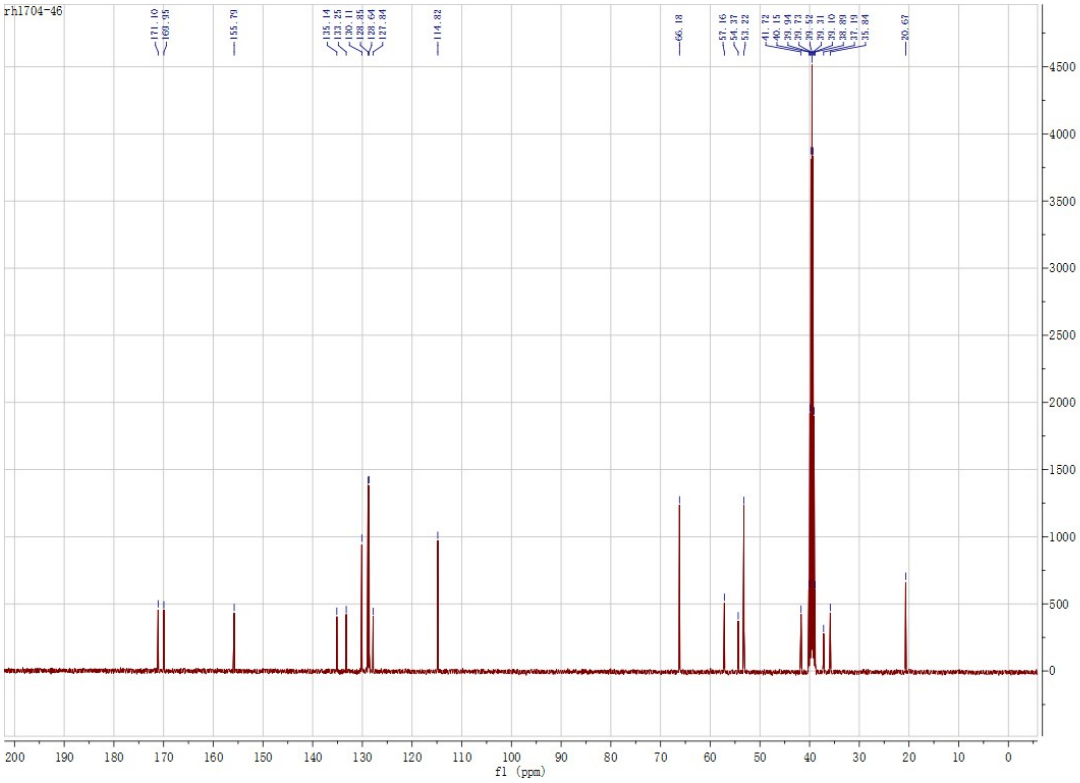

Fig. S52. [13]C-NMR spectrum of compound **5k** in DMSO-d_6.

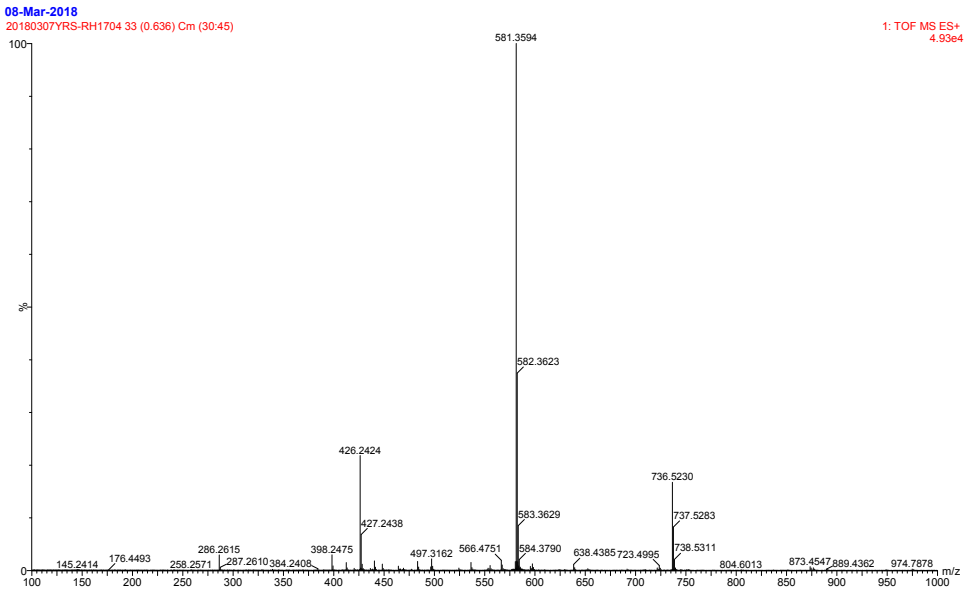

Fig. S53. TOF-HRMS spectrum of compound **5k.**

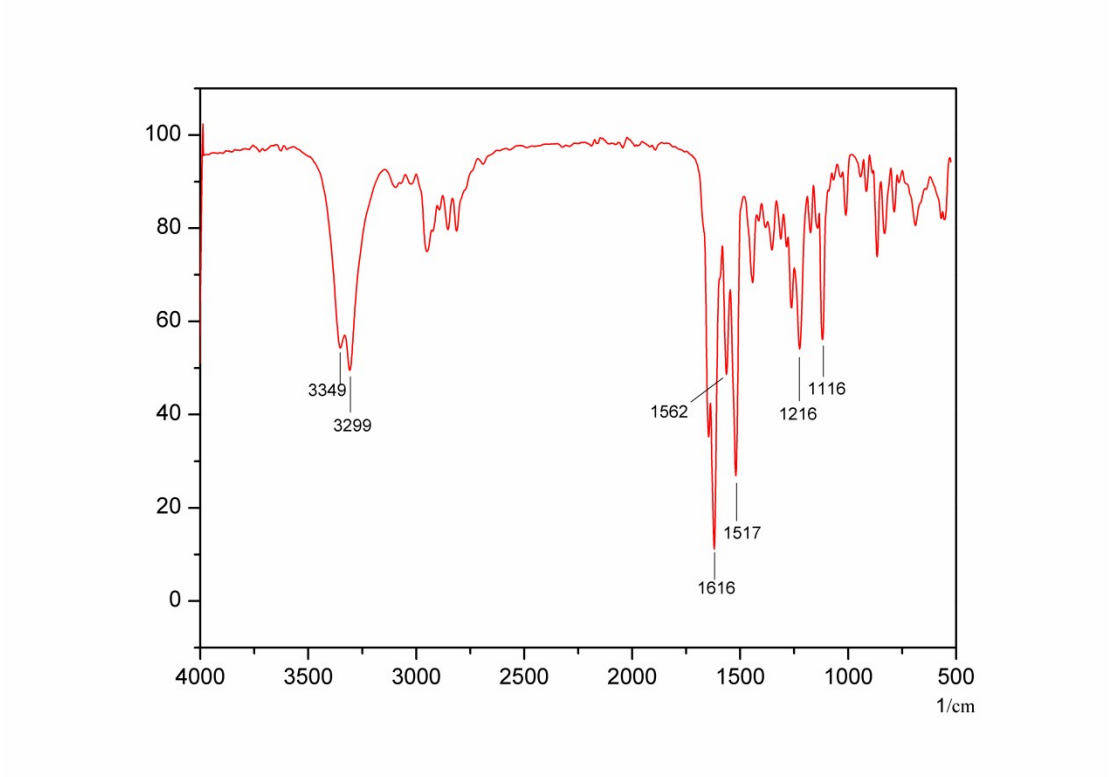

Fig. S54. FT-IR spectrum of compound **5k.**

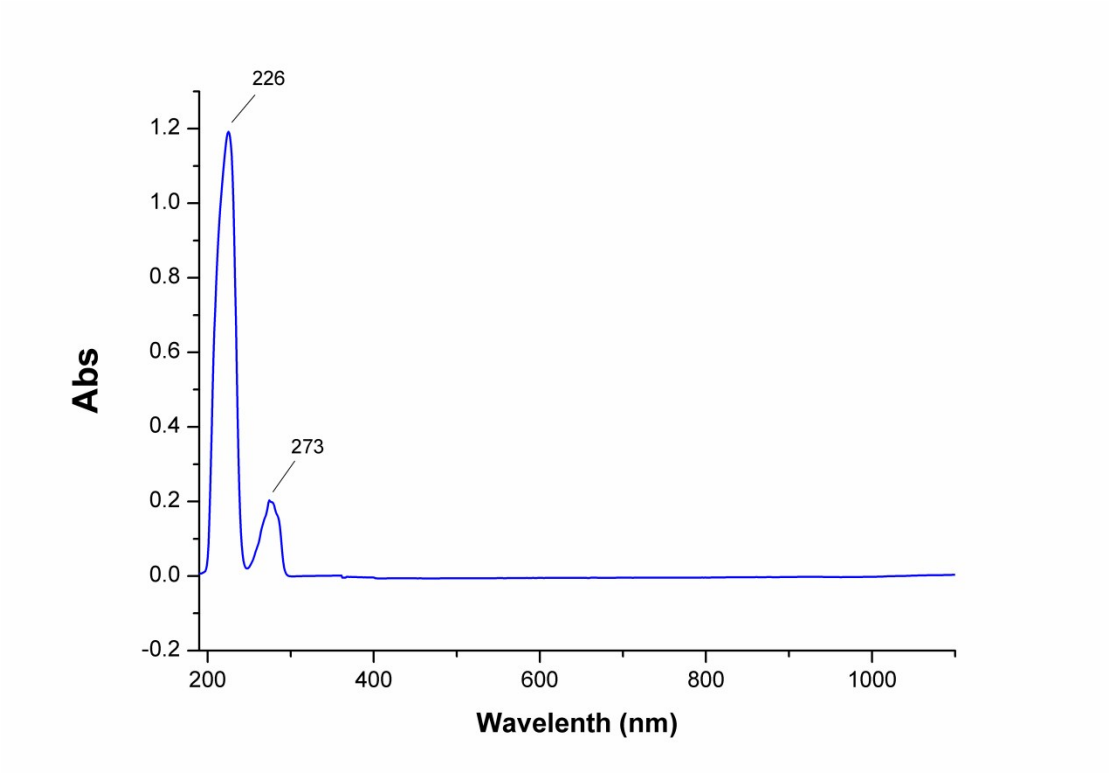

Fig. S55. UV-Vis spectrum of compound **5k.**

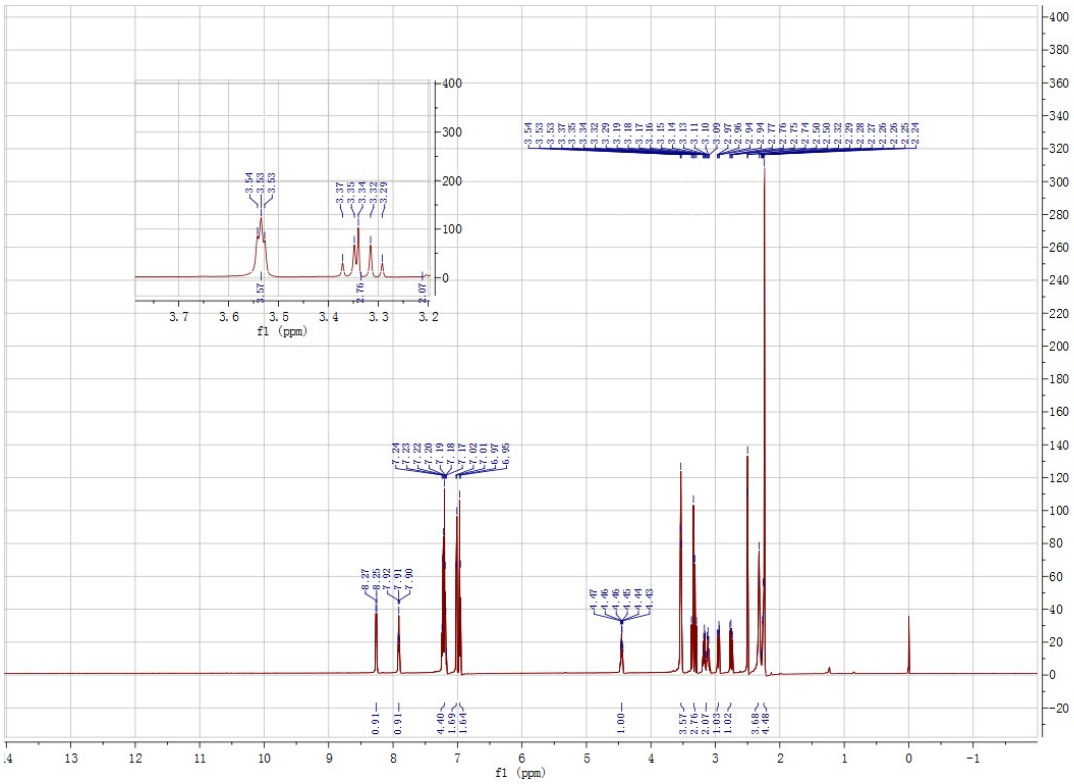

Fig. S56. [1]H-NMR spectrum of compound **5l** in DMSO-d_6.

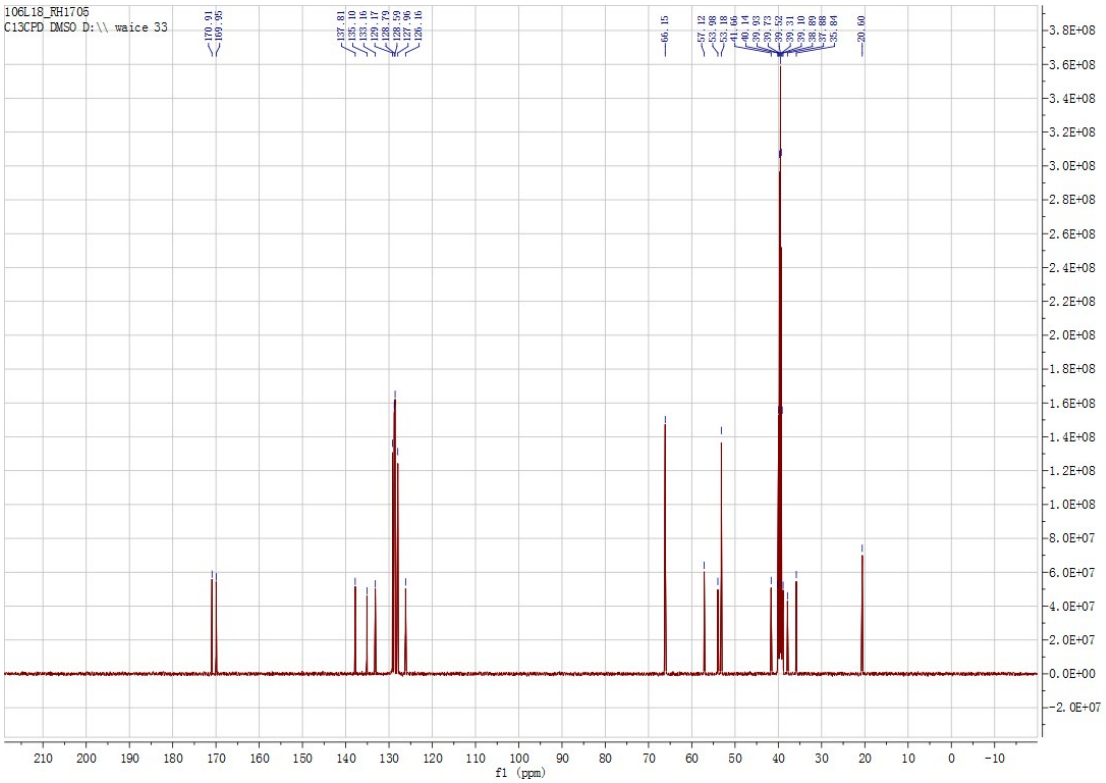

Fig. S57. ^{13}C-NMR spectrum of compound **5l** in DMSO-d_6.

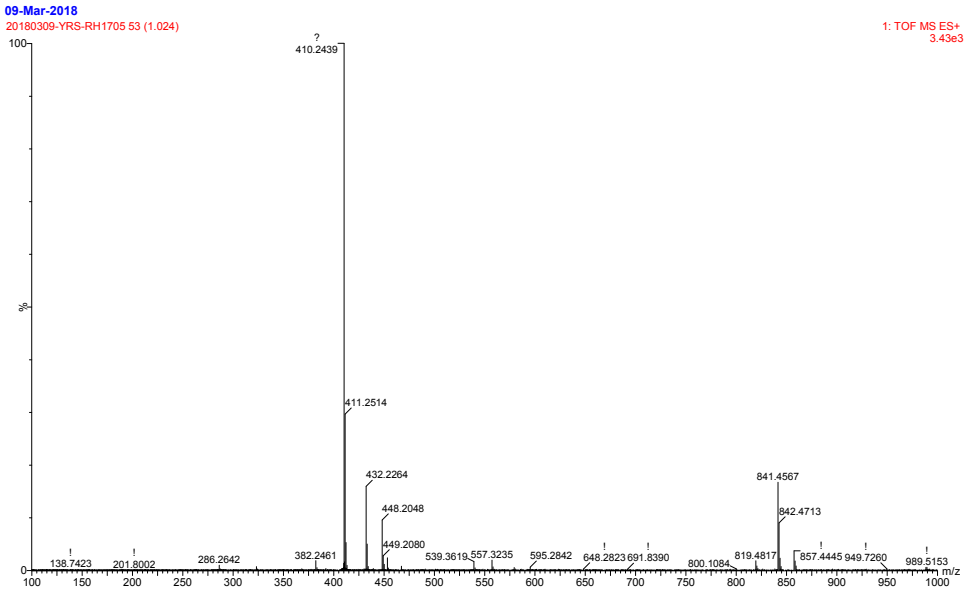

Fig. S58. TOF-HRMS spectrum of compound **5l.**

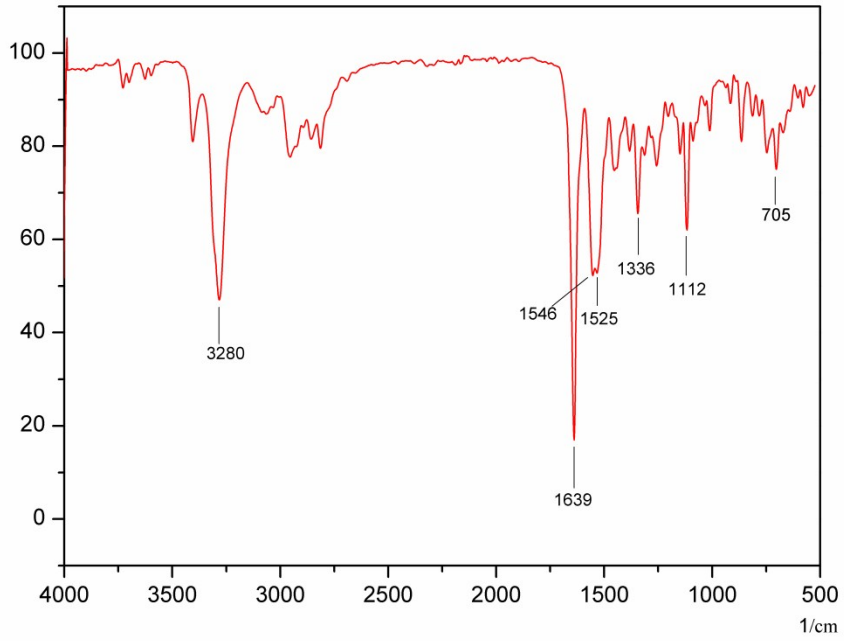

Fig. S59. FT-IR spectrum of compound **5l.**

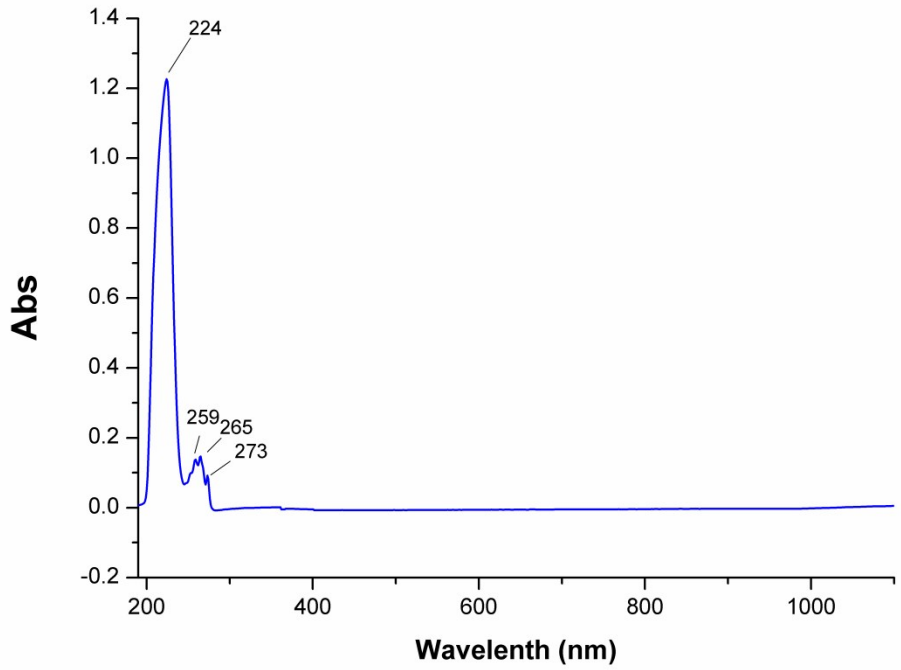

Fig. S60. UV-Vis spectrum of compound **5l.**

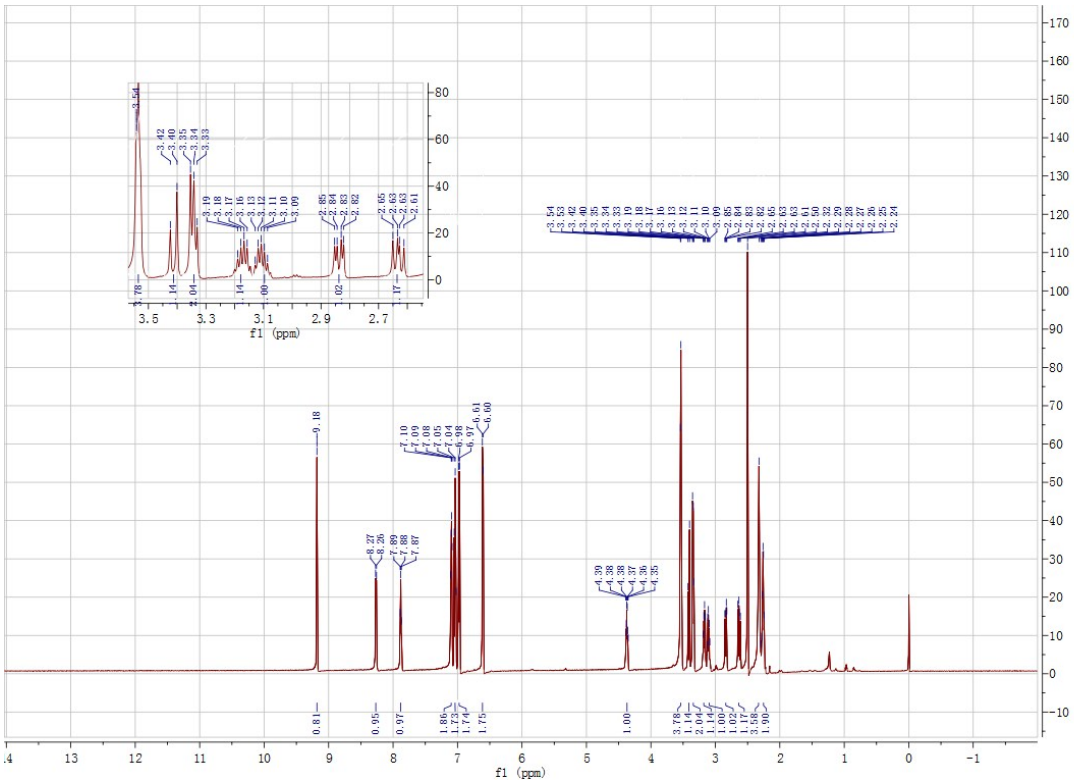

Fig. S61. [1]H-NMR spectrum of compound **5m** in DMSO-d_6.

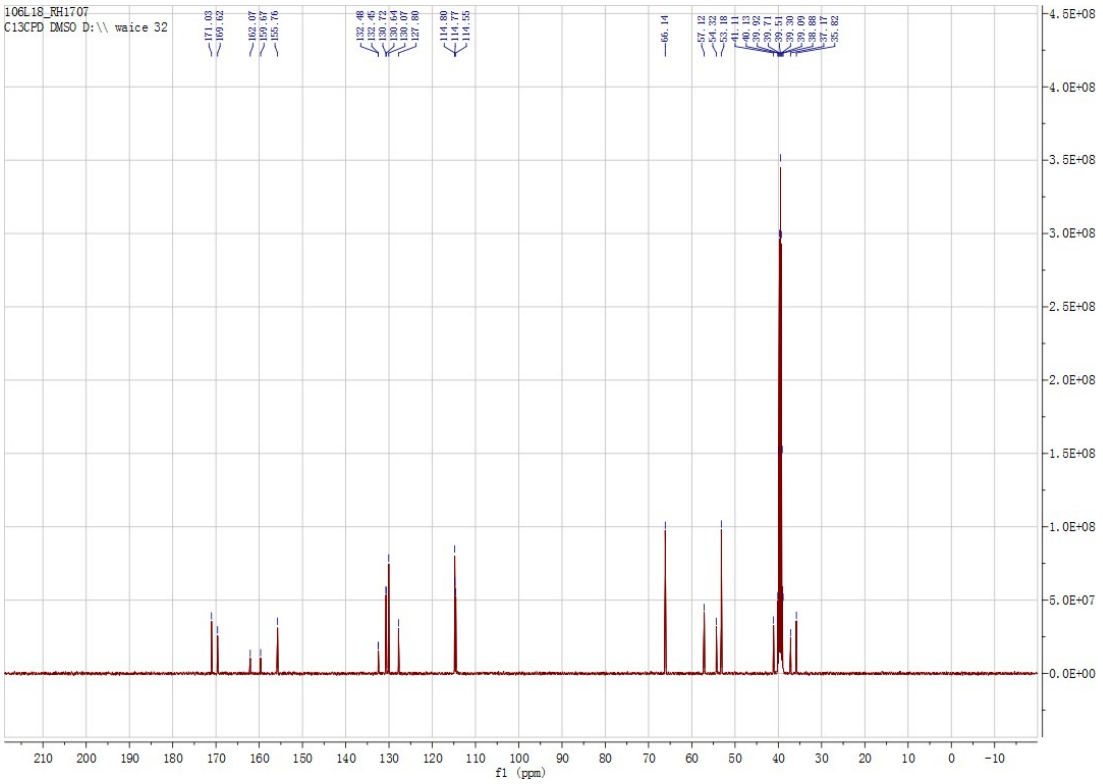

Fig. S62. [13]C-NMR spectrum of compound **5m** in DMSO-d_6.

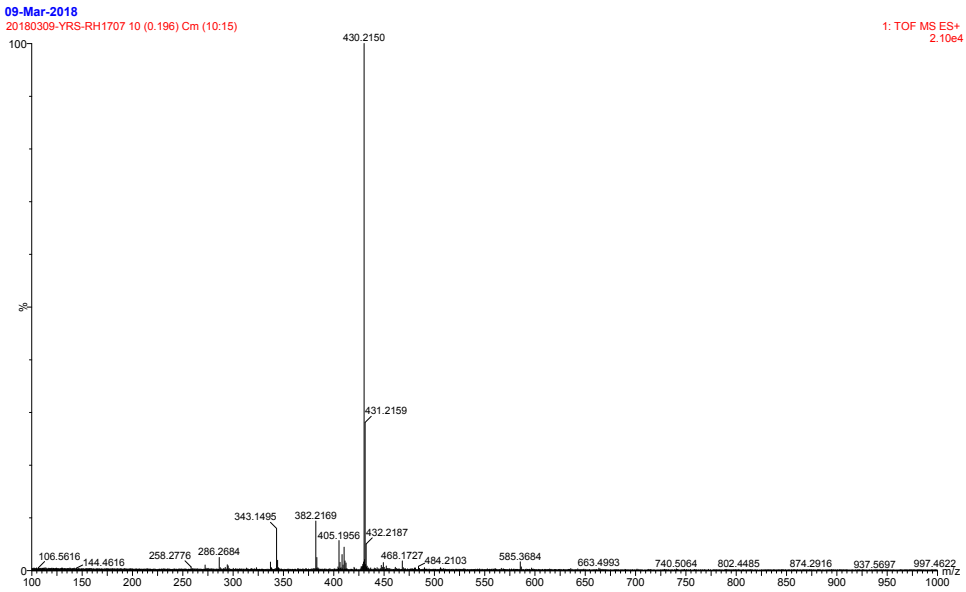

Fig. S63. TOF-HRMS spectrum of compound **5m.**

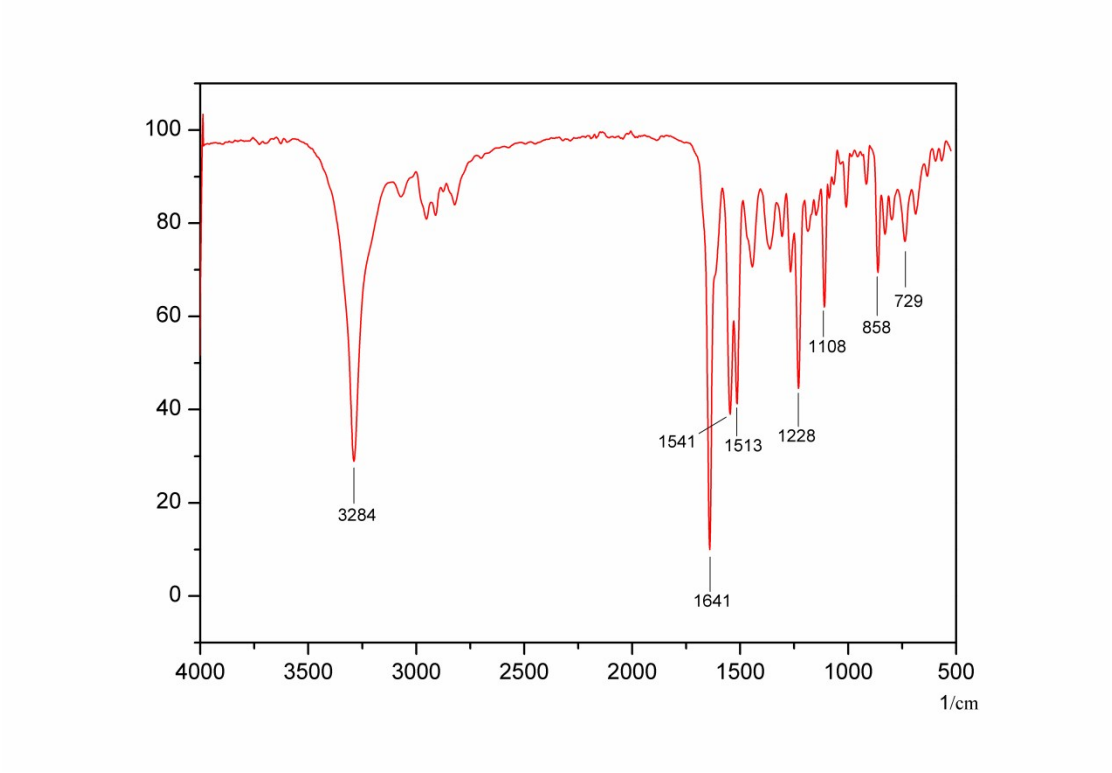

Fig. S64. FT-IR spectrum of compound **5m.**

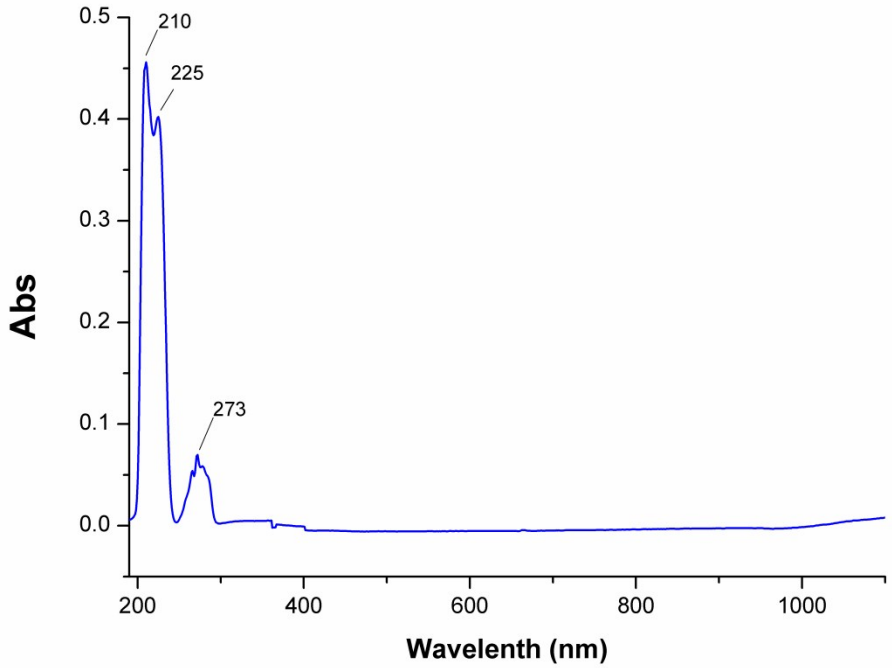

Fig. S65. UV-Vis spectrum of compound **5m.**

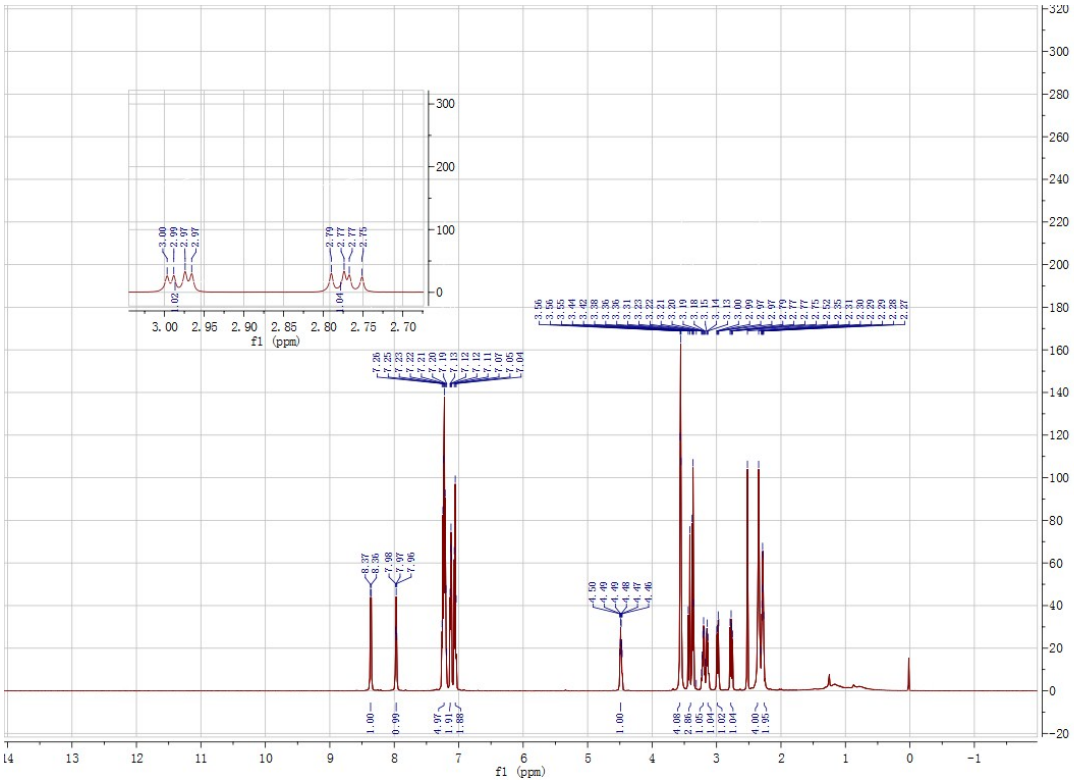

Fig. S66. ^{1}H-NMR spectrum of compound **5n** in DMSO-d_6.

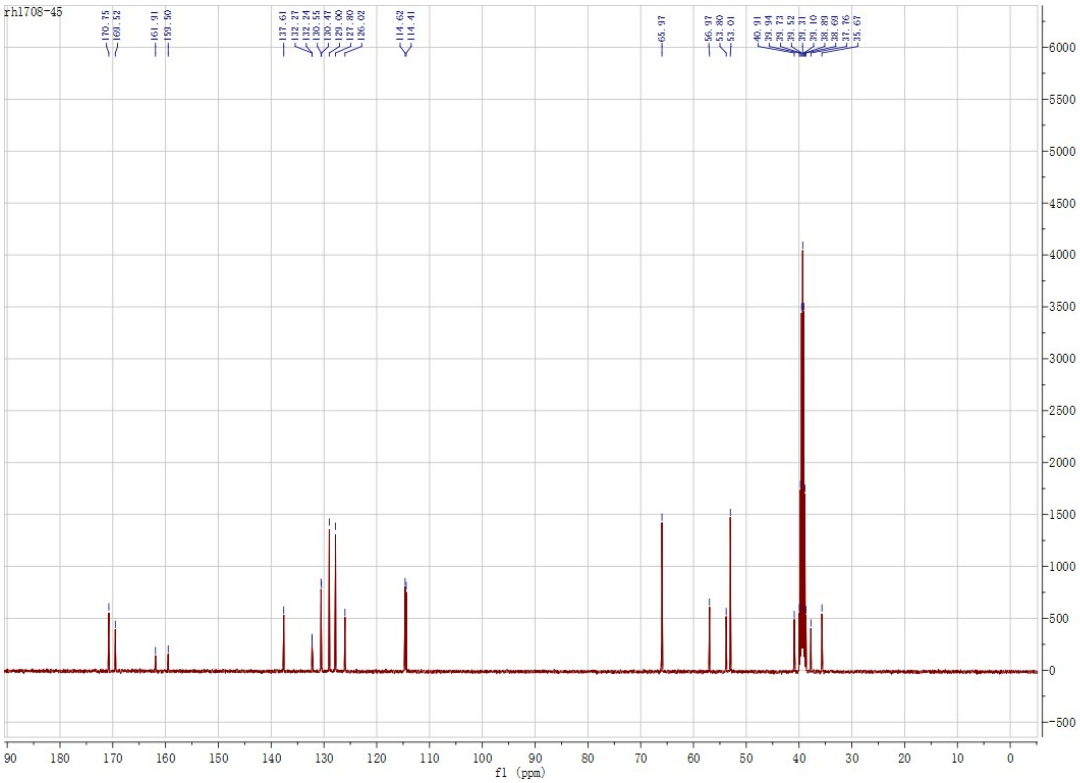

Fig. S67. ^{13}C-NMR spectrum of compound **5n** in DMSO-d_6.

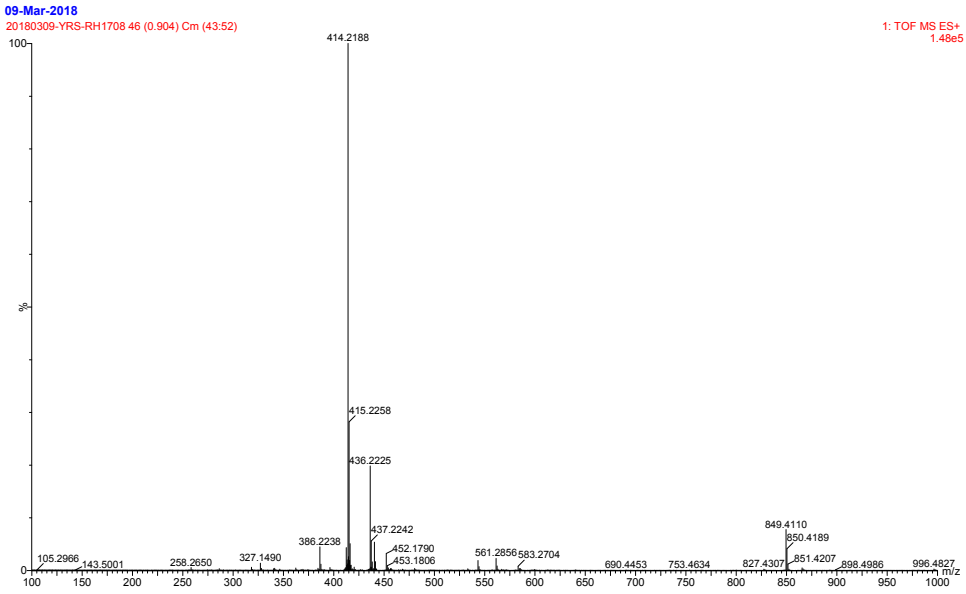

Fig. S68. TOF-HRMS spectrum of compound **5n**

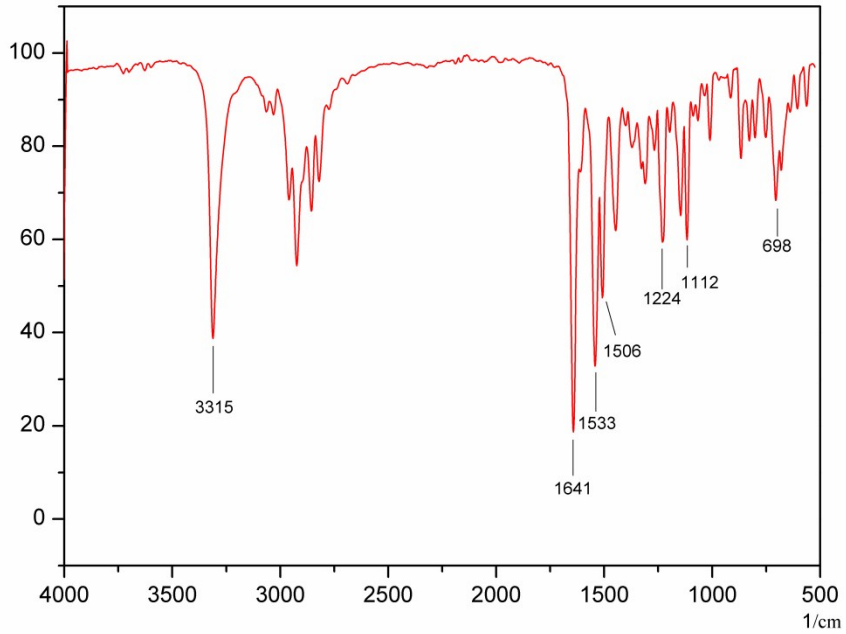

Fig. S69. FT-IR spectrum of compound **5n**

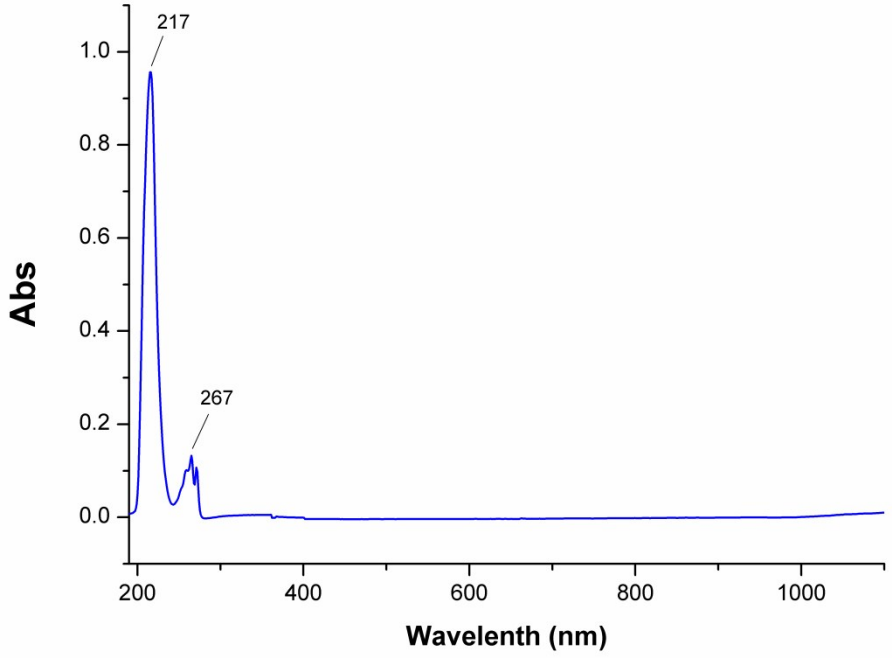

Fig. S70. UV-Vis spectrum of compound **5n**

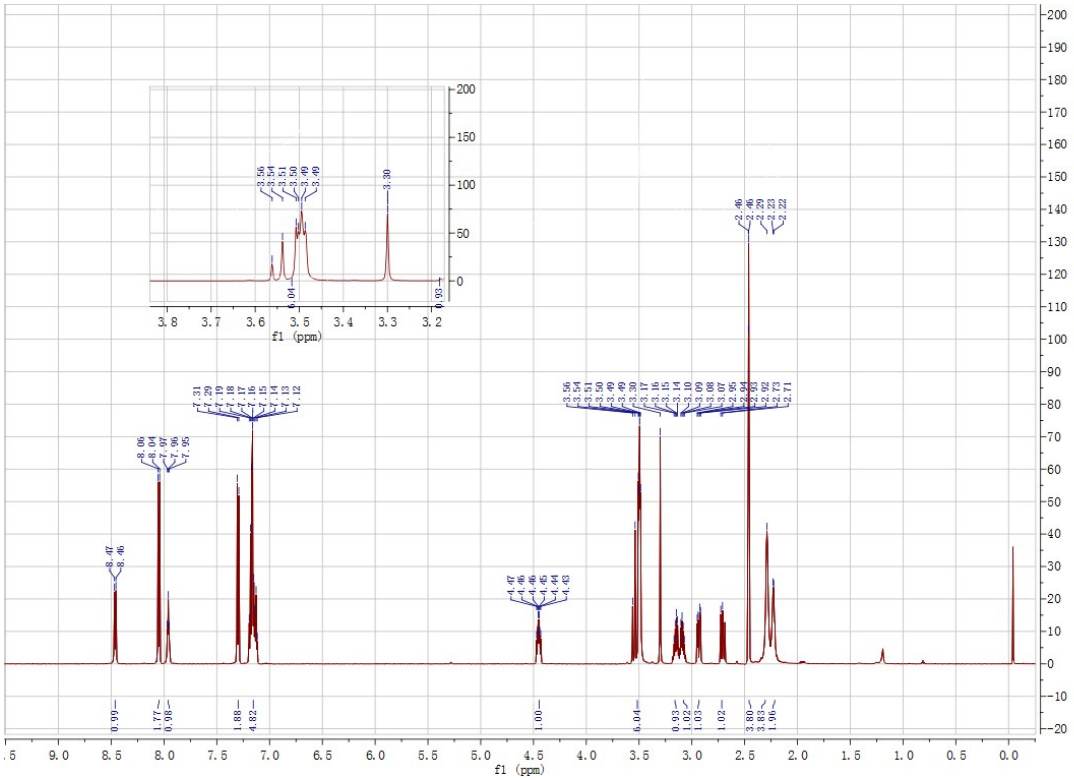

Fig. S71. [1]H-NMR spectrum of compound **5o** in DMSO-d_6.

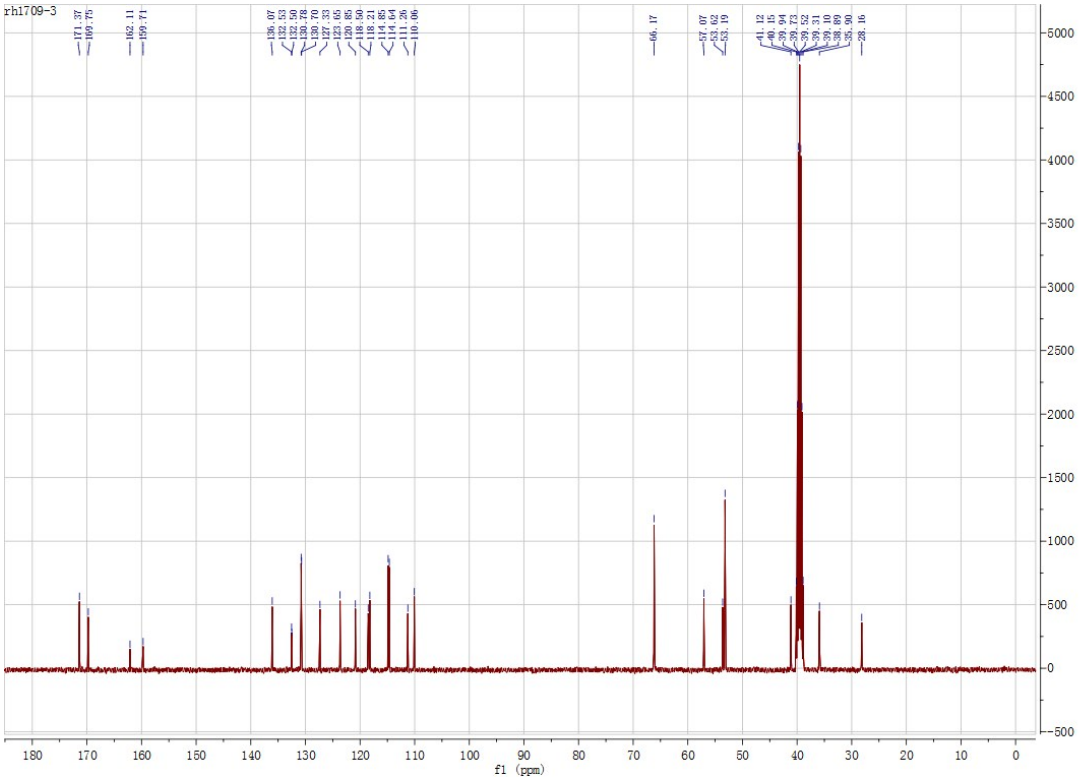

Fig. S72. [13]C-NMR spectrum of compound **5o** in DMSO-d_6.

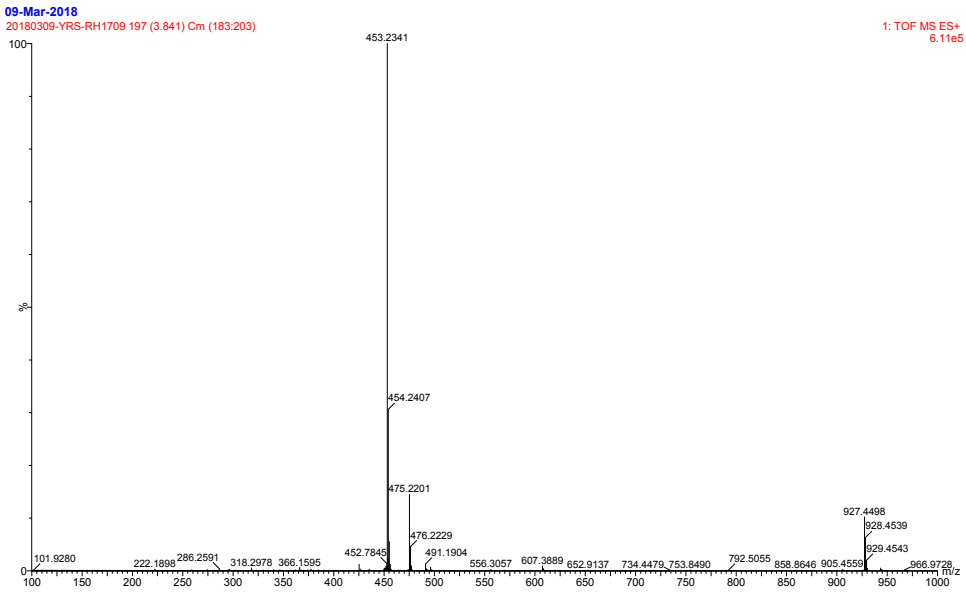

Fig. S73. TOF-HRMS spectrum of compound **5o.**

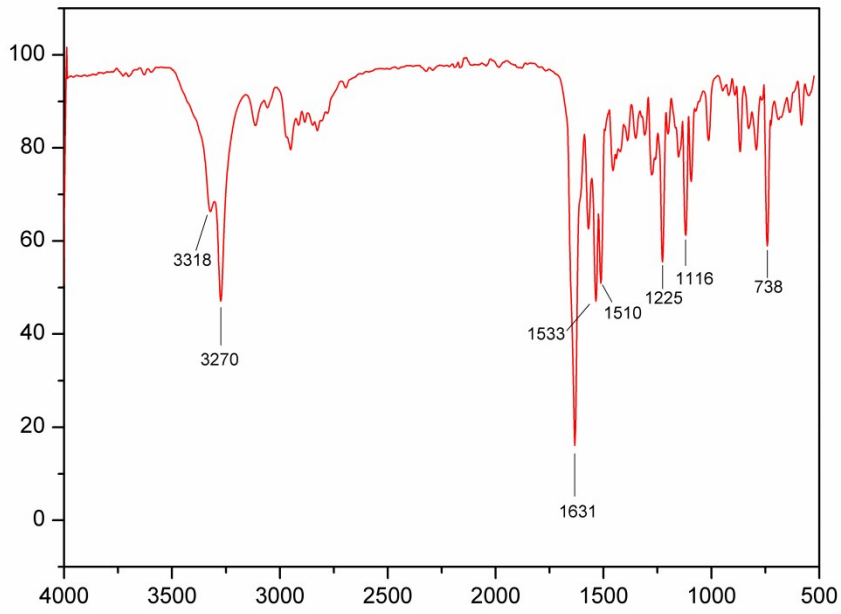

Fig. S74. FT-IR spectrum of compound **5o.**

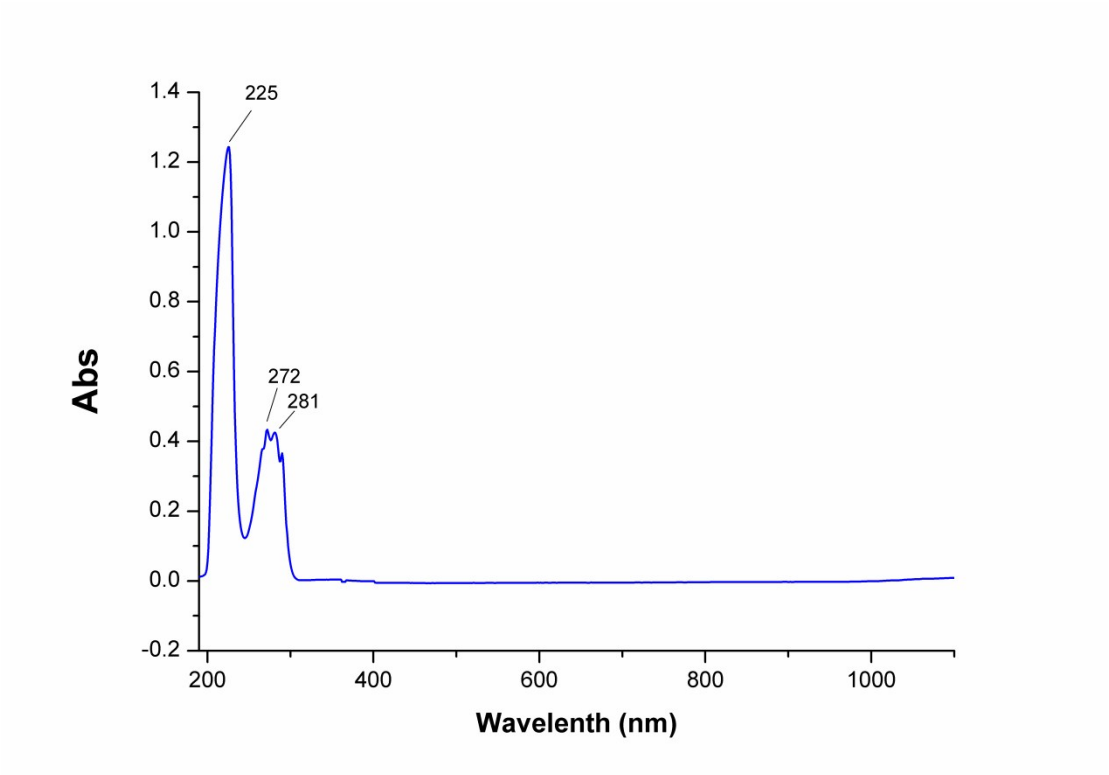

Fig. S75. UV-Vis spectrum of compound **5o.**

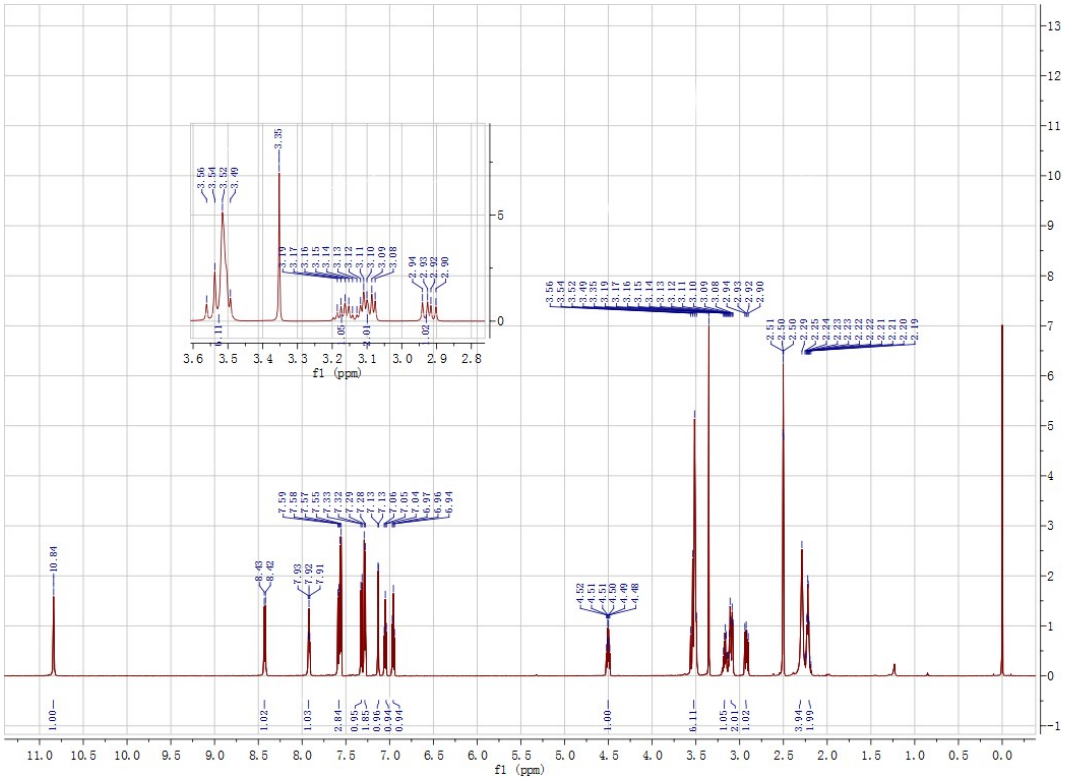

Fig. S76. ^{1}H-NMR spectrum of compound **5p** in DMSO-d_6.

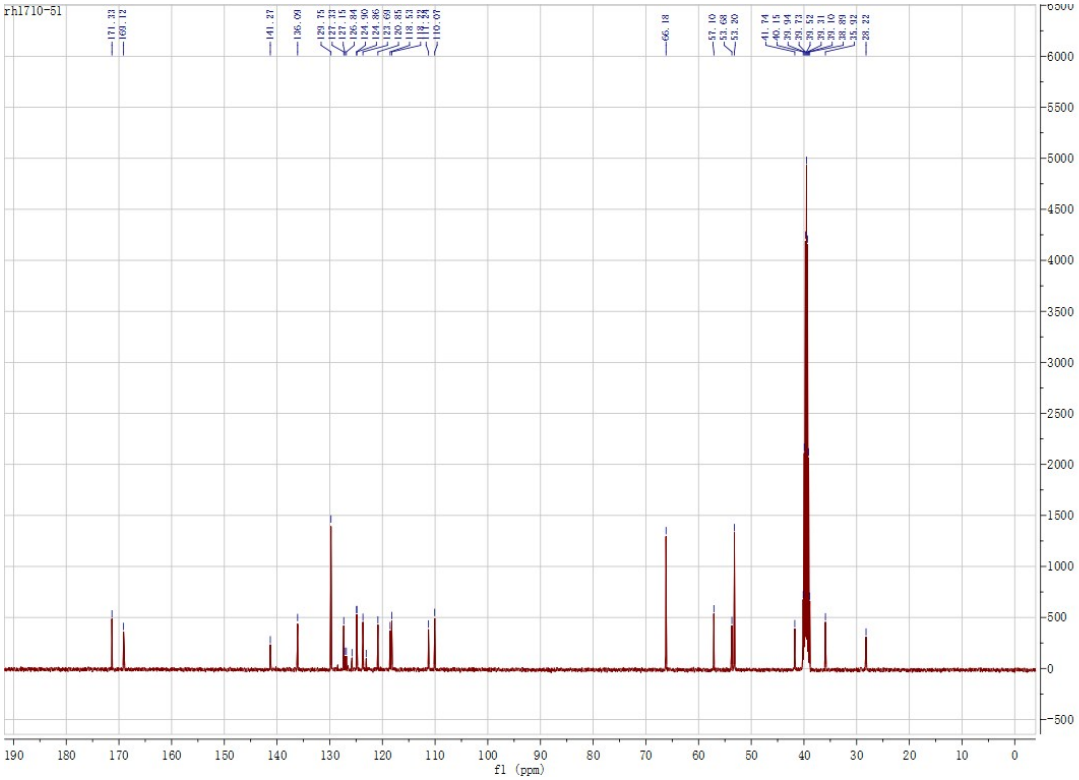

Fig. S77. ^{13}C-NMR spectrum of compound **5p** in DMSO-d_6.

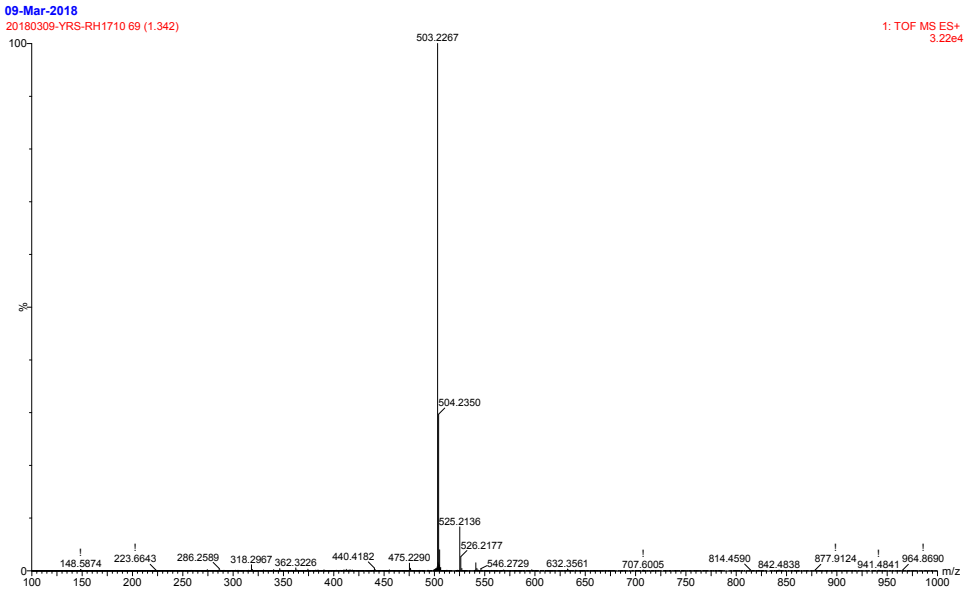

Fig. S78. TOF-HRMS spectrum of compound **5p.**

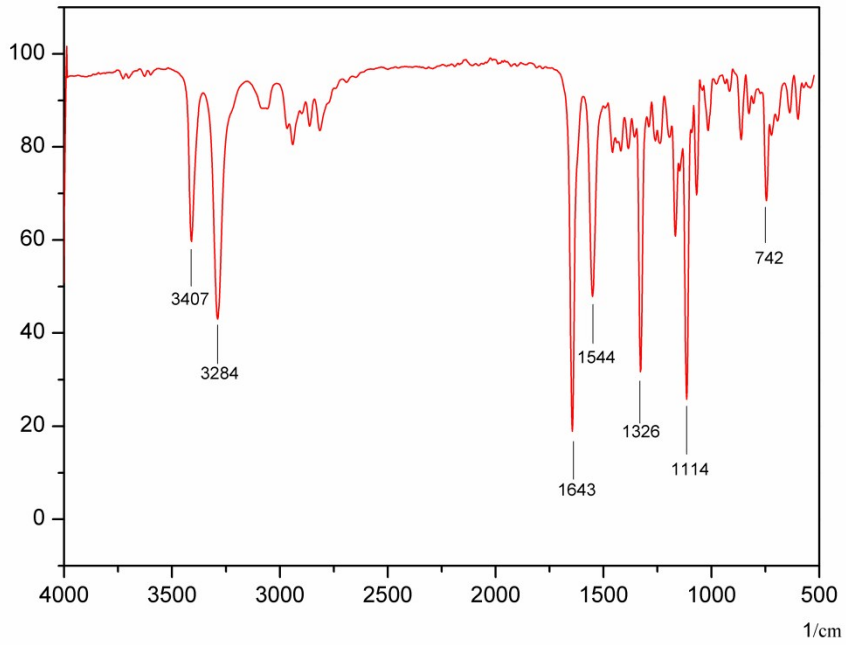

Fig. S79. FT-IR spectrum of compound **5p.**

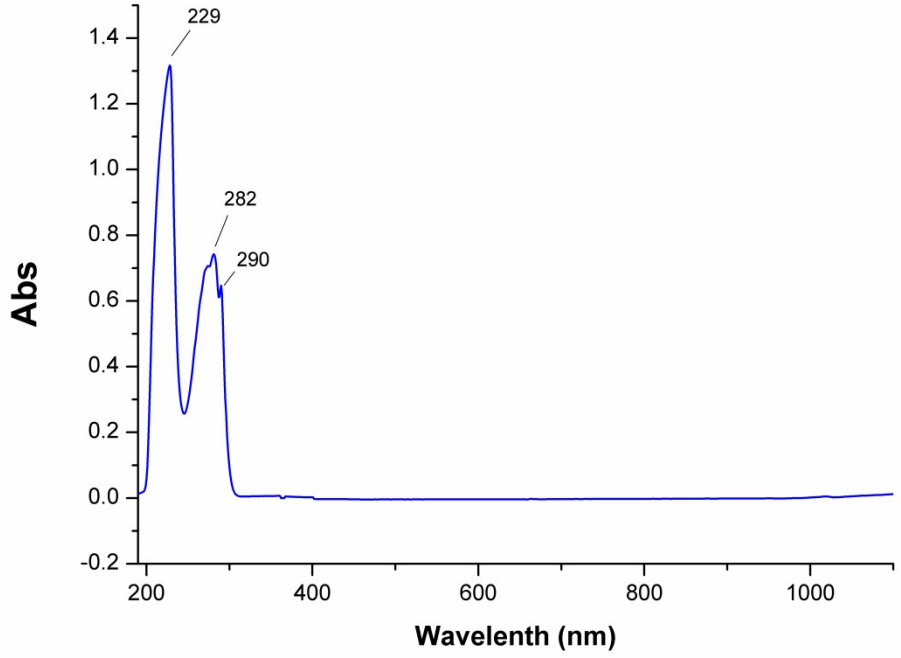

Fig. S80. UV-Vis spectrum of compound **5p.**