Synthesis and biological evaluation of a new class of multi-target heterocycle piperazine derivatives as potential antipsychotics

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Table of Contents:

1. Synthesis

All available chemicals and reagents are commercially available (e.g. Shanghai Aladdin Biochemical Technology Co., Ltd.). All reagents used were analytical grade and chemical purity, without further purification unless otherwise specified. TLC was conducted on silica gel GF254. ^{1}H NMR and ^{13}C NMR were recorded on Bruker Avance III 600 spectrometer at 600 MHz (600 MHz for ^{1}H NMR, 151 MHz for ^{13}C NMR) or Bruker Avance II 400 spectrometer at 400 MHz (400 MHz for ^{1}H NMR, 101 MHz for ^{13}C NMR), the use of $CDCl_3$ and DMSO-d_6 as solvent and TMS as internal standard. Chemical shifts were given in δ values (ppm), coupling constants (J) were given in Hz. Signal multiplicities were characterized as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad). Products were separated and purified with chromatographic methods. The WC-1 apparatus is used for measuring the melting point of new compounds. The purity of all the test compounds higher than 95% and by means conducted on high performance liquid chromatography (HPLC).HPLC methods: Shimadzu LC-20AD spectrometer; column, SHIMADZU VP-ODS (4.6 mm × 250 mm, 5 μm) C18-253; High resolution mass spectra (HRMS) spectrometer, Agilent 6530 Q-TOF LC/MS, Agilent 1290 Infinity (G4212A) spectrometer; The HPLC conditions as following: column, Waters X Bridge ^{R} Shield RP18 (4.6×150 mm, 3.5 μm), C18-330; Low resolution mass spectrometry (LRMS) and high performance liquid chromatography-mass spectrometry (HPLC-MS) were obtained using Agilent MS/1200 HPLC liquid chromatograph/mass spectrometer (JXZX-FXS-064).Agilent ZORBAX SB-C18 (4.6×150 mm, 5 μm).

1.1. The Procedure for the Preparation of Intermediates **1a** and **1b**

*1-(Benzo[b]thiophen-4-yl)-4-(2-chloroethyl)piperazine(**1a**)*.1-(Benzo[b]thiophen-4-yl) piperazine (6.58 g, 30.84 mmol) and 2-bromoethanol (5.78 g, 46.26 mmol) dispersed in 150 mL acetone, anhydrous potassium carbonate (10.61 g, 76.8 mmol) added, then stirred at reflux for 10 h. The mixture was filtered and filtrate concentrated in vacuo, and the residual was proceded to next step without separation. The obtained intermediate dissolved in 100 mL dichloromethane, and 20 mL thionyl chloride was gradually added at 0-5 ℃ and then reflux for 2 h. The mixture

concentrated by rotary evaporation, the residual dissolved in 100 mL dichloromethane, washed with 5% NaOH (wt%), water and brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo, The crude mixture was purified by column chromatography (SiO_2; eluent CH_2Cl_2 : MeOH = 95:5) give **1a**; yield 67% (5.3 g, 20.02 mmol); White solid; Mp 134-136 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.6 (d, *J* = 8.0 Hz, 1H,Ph-H), 7.43 (d,*J* = 3.4 Hz, 2H, thiophene-H), 7.31 (t, *J* = 7.8 Hz 1H, Ph-H), 6.93 (d, *J* = 7.6 Hz, 1H, Ph-H), 3.69 (t, *J* = 7.0 Hz, 2H, Cl-CH_2-), 3.23 (s, 4H, piperazinyl-H), 2.88 (t, *J* = 7.0 Hz, 2H, piperazine-CH_2-), 2.81 (s, 4H, piperazinyl-H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 148.33, 141.14, 134.10, 125.0, 125.04, 121.82, 117.14, 112.27, 59.88, 53.53, 51.99, 40.96. MS (ESI) m/z: 281.2 (calcd281.1 for $C_{14}H_{18}ClN_2S^+$ $[M + H]^+$).

*1-(Benzo[b]thiophen-4-yl)-4-(3-chloropropyl)piperazine(**1b**)*.The mixture of 1-(benzo[b] thiophen -4-yl)piperazine (10.0 g, 39.3mmol) and 1-bromo-3-chloropropane (9.27g, 58.9 mmol) in 200 mL acetone, and anhydrous K_2CO_3 (10.86 g, 78.6 mmol) added, then stirred at room temperature for 24 h, the reaction mixture was filtered and the filtrate was concentrated to dryness, and dissolved in80 mL dichloromethane added, washed with water and brine, dried over anhydrous Na_2SO_4. After concentration, the residue was purified by flash column chromatography (SiO_2; eluent CH_2Cl_2 : MeOH = 95:5 to 90:10) give **1b**; Yield 21% (2.35 g, 8.0 mmol); Pale yellow solid; Mp 128-129 °C;^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.1 Hz, 1H, Ph-H), 7.45 (d, *J* = 2.8 Hz, 2H, thiophene-H), 7.36 – 7.31 (t, J = 7.8 Hz, 1H, Ph-H), 6.95 (d, *J* = 7.8 Hz, 1H, Ph-H), 3.70 (t, *J* = 6.5 Hz, 2H, Cl-CH_2-), 3.25 (s, 4H, piperazinyl-H), 2.78 (s, 4H, piperazinyl-H), 2.67 (t, *J* = 7.1 Hz, 2H, piperazinyl-CH_2-), 2.12 – 2.05 (m, 2H, -CH_2-);^{13}C NMR (101 MHz, $CDCl_3$) δ 148.40, 141.15, 134.09, 125.04, 125.03, 121.87, 117.09, 112.23, 55.54, 53.63, 52.08, 43.24, 29.88; MS (ESI) m/z: 295.3 (calcd 295.1 for $C_{15}H_{20}ClN_2S^+$$[M + H]^+$).

1.2. General Procedure for the Preparation of Compounds **2a-2y**

*2-Methyl-4-(pyrrolidin-1-ylmethyl)phenol(**2a**)*.4-hydroxy-3-methylbenzaldehyde (3.6 g, 26.4 mmol) and pyrrolidine (2.3g, 31.7mmol) were added to 150 mL dichloromethane, the mixture was stirred at room temperature for 2 h, sodium

triacetyloxyborohydride (8.39 g, 39.6 mmol) was added by portions, continue stirring for 24 h in room temperature, 40 mL water added, stirred for 5 min, the organic layer was separated and washed with 5% NaOH, water and brine, dried over anhydrous Na_2SO_4, concentrated and the residue was purified via chromatography (SiO_2; eluent CH_2Cl_2 : MeOH = 95 : 5) to afford **2a**.

*2-Methyl-4-(pyrrolidin-1-ylmethyl)phenol (**2a**)*. Yellowish oil; Yield 42%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.07 (s, 1H, Ph-H), 6.99 – 6.91 (d, J = 8.0 Hz, 1H, Ph-H), 6.54 (d, J = 8.0 Hz, 1H, Ph-H), 3.57 (s, 2H, Ph-CH_2-), 2.60 (s, 4H, pyrrolidyl-H), 2.20 (s, 3H, Ph-CH_3), 1.82 (dd, J = 6.3, 3.1 Hz, 4H,pyrrolidyl-H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 153.95, 131.92, 129.29, 127.81, 124.25, 114.91, 60.10, 53.93, 23.22, 16.10; MS (ESI) m/z: 192.1 (calcd 192.1 for $C_{12}H_{18}NO^+[M + H]^+$).

*3-Methyl-4-(pyrrolidin-1-ylmethyl)phenol (**2b**)*.Yellowish oil; Yield 37.3%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.10 (dd, J = 8.2, 2.2 Hz, 1H, Ph-H), 6.56 – 6.48 (d, J = 8.2, 1H, Ph-H), 6.42 (s, 1H, Ph-H), 3.69 (s, 2H, Ph-CH_2-), 2.80 (s, 4H, pyrrolidyl-H), 2.26 (s, 3H, Ph-CH_3), 1.90 (s, 4H, pyrrolidyl-H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 156.47, 138.40, 131.44, 117.92, 117.57, 113.46, 56.65, 53.44, 23.15, 19.63; MS (ESI) m/z: 192.3 (calcd 192.1 for $C_{12}H_{18}NO^+[M + H]^+$).

*2-Fluoro-4-(pyrrolidin-1-ylmethyl)phenol (**2c**)*. Yellowish oil; Yield 41.3%; ^{1}H NMR (600 MHz, $CDCl_3$) δ7.00 (dd, *J* = 8.6 , 1.9 Hz, 1H,Ph-H), 6.93 – 6.88 (d, J = 8.2 Hz, 1H, Ph-H), 6.72 (t, *J* = 8.6 Hz, 1H, Ph-H), 3.63 (s, 2H, Ph-CH_2-), 2.72 (s, 4H, pyrrolidyl-H), 1.90 – 1.85 (m, 4H, pyrrolidyl-H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 152.52, 150.93, 145.02, 125.67, 118.25, 116.92, 59.41, 53.66, 23.23; MS (ESI) m/z: 196.1 (calcd 196.1 for $C_{11}H_{15}FNO^+[M + H]^+$).

*3-Fluoro-4-(pyrrolidin-1-ylmethyl)phenol (**2d**)*. Yellowish oil; Yield 45.2%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.06 (t, *J* = 8.4 Hz, 1H, Ph-H), 6.34 (dd, *J* = 8.5, 2.3 Hz, 1H, Ph-H), 6.29 (dd, *J* = 8.4, 2.3 Hz, 1H, Ph-H), 3.69 (s, 2H, Ph-CH_2-), 2.78 (s, 4H, pyrrolidyl-H), 1.88 (m, 4H, pyrrolidyl-H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 162.65, 161.09, 159.23, 132.44, 112.46, 103.72, 53.58, 52.05, 23.12; MS (ESI) m/z: 196.2 (calcd 196.1 for $C_{11}H_{15}FNO^+[M + H]^+$).

*2-Chloro-4-(pyrrolidin-1-ylmethyl)phenol (**2e**)*. Yellowish oil; Yield 35.6%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.02 (d, J = 9.1 Hz, 1H, Ph-H), 6.92 (d, J = 9.1 Hz, 1H, Ph-H), 6.85 (t, J = 8.5 Hz, 1H,Ph-H), 3.79 – 3.74 (m, 4H, pyrrolidyl-H), 3.47 (s, 2H, Ph-CH_2-), 2.52 (s, 4H, pyrrolidyl-H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 152.06, 143.58, 143.49, 125.85, 117.77, 116.80, 66.68, 66.54, 62.45, 53.24, 23.61; MS (ESI) m/z: 212.2 (calcd 212.1 for $C_{11}H_{15}ClNO^+$ $[M + H]^+$).

*3-Chloro-4-(pyrrolidin-1-ylmethyl)phenol (**2f**)*.Yellowish oil; Yield 33.5%;^{1}H NMR (600 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.5 Hz, 1H, Ph-H), 6.89 (d, *J* = 2.4 Hz, 1H, Ph-H), 6.77 (dd, *J* = 8.5, 2.4 Hz, 1H, Ph-H), 3.81 – 3.71 (m, 4H, pyrrolidyl-H), 3.47 (s, 2H, Ph-CH_2-), 2.52 (s, 4H, pyrrolidyl-H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.32, 134.92, 133.35, 117.25, 115.70, 112.96, 54.84, 53.36, 23.08; MS (ESI) m/z: 212.1 (calcd 212.1 for $C_{11}H_{15}ClNO^+$ $[M + H]^+$).

2-Methoxy-4-(pyrrolidin-1-ylmethyl)phenol(**2g**). Yellowish oil; Yield 48.2%; ^{1}H NMR (600 MHz, $CDCl_3$) δ7.07 (s, 1H, Ph-H), 6.99 – 6.94 (d, *J* = 6.4 Hz, 1H, Ph-H), 6.54 (d, *J* = 6.4 Hz, 1H, Ph-H), 3.57 (s, 2H, Ph-CH_2-), 2.60 (s, 4H, pyrrolidyl-H), 2.20 (s, 3H, -OCH_3), 1.82 (m, 4H, pyrrolidyl-H); ^{13}C NMR (151 MHz, $CDCl_3$) δ153.95, 131.92, 127.81, 124.25, 114.91, 60.10, 53.93, 23.22, 15.99; MS (ESI) m/z: 208.2 (calcd 208.1 for : $C_{12}H_{18}NO_2^+$ $[M + H]^+$).

*2-Methyl-4-(piperidin-1-ylmethyl)phenol (**2h**)*.Yellowish oil; Yield 45.7 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (s, 1H, Ph-H), 6.94 (dd, *J* = 8.1, 1.8 Hz, 1H, Ph-H), 6.58 (d, *J* = 8.1 Hz, 1H, Ph-H), 3.55 (s, 2H, Ph-CH_2-), 2.59 (s, 4H, piperidyl-H), 2.13 (d, *J* = 19.4 Hz, 3H, Ph-CH_3), 1.82 – 1.55 (m, 4H, piperidyl-H), 1.46 (s, 2H, piperidyl-H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.29, 155.16, 132.92, 128.77, 124.64, 115.09, 62.52, 53.60, 24.51, 23.60, 16.12; MS (ESI) m/z: 206.2 (calcd 206.2 for : $C_{13}H_{20}NO^+$ $[M +H]^+$).

*3-Methyl-4-(piperidin-1-ylmethyl)phenol(**2i**)*.Yellowish oil; Yield 38.2%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.04 (d, J = 8.2 Hz, 1H, Ph-H), 6.47 (dd, J = 8.2, 2.5 Hz, 1H, Ph-H), 6.35 (d, J = 2.4 Hz, 1H, Ph-H), 3.43 (s, 2H, Ph-CH_2-), 2.57 (s, 4H, piperidyl-H), 2.24 (s, 3H, Ph-CH_3), 1.66 (dd, J = 11.3, 5.7 Hz, 4H, piperidyl-H), 1.49 (s, 2H, piperidyl-H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 155.85, 138.89, 131.97, 129.91, 117.99,

113.24, 60.23, 54.48, 25.05, 23.99, 19.62; MS (ESI) m/z: 206.2 (calcd 206.2 for : $C_{13}H_{20}NO^+$ $[M + H]^+$).

*2-Fluoro-4-(piperidin-1-ylmethyl)phenol(**2j**)*.Yellowish oil; Yield 41.2%;^{1}H NMR (600 MHz, $CDCl_3$) δ 6.96 (dd, *J* = 8.6, 1.8 Hz, 1H, Ph-H), 6.86 (dd, *J* = 8.2, 1.1 Hz, 1H, Ph-H), 6.71 (t, *J* = 8.6 Hz, 1H, Ph-H), 3.48 (s, 2H, Ph-CH_2-), 2.57 (s, 4H, piperidyl-H), 1.76 – 1.63 (m, 4H, piperidyl-H), 1.48 (s, 2H, piperidyl-H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 152.52, 150.94, 144.91, 126.28, 118.09, 117.44, 62.60, 54.06, 24.69, 23.82; MS (ESI) m/z: 210.2 (calcd 210.1 for $C_{12}H_{17}FNO^+$ $[M + H]^+$).

*3-Fluoro-4-(piperidin-1-ylmethyl)phenol(**2k**)*.Yellowish oil; Yield 38.4%;^{1}H NMR (600 MHz, $CDCl_3$) δ 7.23 (d, 8.4 Hz, 1H, Ph-H), 6.64 (d, J = 2.4 Hz, 1H, Ph-H), 6.47 (dd, J = 8.4, 2.4 Hz, 1H, Ph-H), 3.77-3.74 (m, 2H, Ph-CH_2-), 3.68 (s, 2H, piperidyl-H), 2.73 (s, 4H, piperidyl-H), 1.78 – 1.70 (m, 4H, piperidyl-H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 135.21, 132.75, 132.03, 117.36, 115.16, 66.81, 59.20, 54.23, 53.36, 24.58, 23.61; MS (ESI) m/z: 210.1 (calcd 210.1 for $C_{12}H_{17}FNO^+$ $[M + H]^+$).

*2-Chloro-4-(piperidin-1-ylmethyl)phenol(**2l**)*. Yellowish oil; Yield 35.1%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.05 (d, J = 1.5 Hz, 1H, Ph-H), 6.95 (dd, J = 7.8, 1.8 Hz, 1H,Ph-H), 6.53 (d, J = 7.8 Hz, 1H, Ph-H), 3.57 (s, 2H, Ph-CH_2-), 2.61 (s, 4H, piperidyl-H), 2.19 (s, 2H, piperidyl-H), 1.87 – 1.78 (m, 4H,piperidyl-H); ^{13}C NMR (151 MHz, $CDCl_3$)δ 154.26, 131.98, 127.83, 124.45, 114.96, 60.04, 53.85, 23.19,16.06; MS (ESI) m/z: 226.1 (calcd 226.1 for $C_{12}H_{17}ClNO^+$$[M + H]^+$).

*3-Chloro-4-(piperidin-1-ylmethyl)phenol (**2m**)*. Yellowish oil; Yield 38.4%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.05 (t, *J* = 8.4 Hz, 1H, Ph-H), 6.36 (dd, *J* = 8.6, 2.4 Hz, 1H, Ph-H), 6.33 – 6.29 (d, *J* = 8.4 Hz, 1H, Ph-H), 3.59 (s, 2H, Ph-CH_2-), 2.69 (s, 4H, piperidyl-H), 1.75 – 1.67 (m, 4H, piperidyl-H), 1.51 (s, 2H, piperidyl-H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 163.01, 161.38, 159.35, 132.88, 112.53, 103.47, 55.25, 53.68, 24.42, 23.44; MS (ESI) m/z: 226.1 (calcd 226.1 for $C_{12}H_{17}ClNO^+$ $[M + H]^+$).

*2-Methoxy-4-(piperidin-1-ylmethyl)phenol(**2n**)*. White solid; Yield 57.3%; Mp 131-132 ℃; ^{1}H NMR (600 MHz, $CDCl_3$)δ6.99 (s, 1H, Ph-H), 6.80 (d, *J* = 8.0 Hz, 1H, Ph-H), 6.75 (dd, *J* = 8.0, 1.7 Hz, 1H, Ph-H), 3.81 (s, 3H, Ph-OCH_3), 3.54 (s, 2H, Ph-CH_2-), 2.52 (s, 4H, piperidyl-H), 1.72 – 1.60 (m, 4H, piperidyl-H), 1.47 (s, 2H, piperidyl-

H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 146.82, 145.39, 122.61, 114.50, 114.10, 112.48, 63.11, 55.83, 53.88, 24.99, 23.90; MS (ESI) m/z: 222.2 (calcd 222.1 for $C_{13}H_{20}NO_2^+$ $[M + H]^+$).

2-Methyl-4-(morpholinomethyl)phenol(**2o**). Yellowish oil; Yield 42.8%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.08 (s, 1H,Ph-H), 6.98 (d, *J* = 8.1 Hz, 1H, Ph-H), 6.61 (d, *J* = 8.1 Hz, 1H, Ph-H), 3.75 (s, 4H, morpholinyl-H), 3.44 (s, 2H, Ph-CH_2-), 2.50 (s, 4H, morpholinyl-H), 2.23 (s, 3H, Ph-CH_3); ^{13}C NMR (151 MHz, $CDCl_3$) δ 153.58, 132.40, 128.45, 128.16, 124.20, 114.70, 66.78, 63.01, 53.53, 15.92; MS (ESI) m/z: 208.1 (calcd 208.1 for $C_{12}H_{18}NO_2^+[M + H]^+$).

*3-Methyl-4-(morpholinomethyl)phenol (**2p**)*. Yellowish oil; Yield 37.6%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.08 (d, *J* = 8.1 Hz, 1H, Ph-H), 6.59 (s, 1H, Ph-H), 6.57 (d, *J* = 8.1 Hz, 1H, Ph-H), 3.73 (s, 4H, morpholinyl-H), 3.43 (s, 2H, Ph-CH_2-), 2.50 (s, 4H, morpholinyl-H), 2.32 (s, 3H, Ph-CH_3); ^{13}C NMR (151 MHz, $CDCl_3$) δ 155.11, 139.32, 131.59, 127.28, 117.49, 112.17, 66.92, 60.47, 53.49, 19.39; MS (ESI) m/z: 208.1 (calcd 208.1 for $C_{12}H_{18}NO_2^+$ $[M + H]^+$).

*2-Fluoro-4-(morpholinomethyl)phenol(**2q**)*. Yellowish oil; Yield 45.6%;^{1}H NMR (600 MHz, $CDCl_3$) δ 7.08 (dd, *J* = 8.5, 1.7 Hz, 1H, Ph-H), 6.97 (d, *J* = 8.3 Hz, 1H,Ph-H), 6.92 (t, *J* = 8.5 Hz, 1H, Ph-H), 3.79 – 3.72 (m, 4H, morpholinyl-H), 3.44 (s, 2H, Ph-CH_2-), 2.48 (s, 4H, morpholinyl-H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 151.83, 150.25, 142.89, 125.52, 117.05, 116.23, 66.86, 62.50, 53.43; MS (ESI) m/z: 212.2 (calcd 212.1 for $C_{11}H_{15}FNO_2^+$ $[M + H]^+$).

*3-Fluoro-4-(morpholinomethyl)phenol(**2r**)*. Yellowish solid; Yield 39.6%; Mp 127-129 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (t, *J* = 8.5 Hz, 1H, Ph-H), 6.46 (d, *J*= 2.9 Hz, 1H, Ph-H), 6.44 (s, 1H, Ph-H), 3.92 – 3.68 (m, 4H, morpholinyl-H), 3.53 (s, 2H, Ph-CH_2-), 2.57 (s, 4H, morpholinyl-H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.23, 160.78, 156.98, 132.69, 111.50, 103.38, 103.12, 66.54, 55.34, 53.04; MS (ESI) m/z: 212.2 (calcd 212.1 for $C_{11}H_{15}FNO_2^+$ $[M + H]^+$).

*2-Chloro-4-(morpholinomethyl)phenol(**2s**)*.Yellowish oil; Yield 36.3%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.29 (s, 1H, Ph-H), 6.81 (d, *J* = 2.5 Hz, 1H, Ph-H), 6.67 (dd, *J* = 8.3, 2.5 Hz, 1H, Ph-H), 3.78 – 3.73 (m, 4H, morpholinyl-H), 3.59 (s, 2H, Ph-CH_2-), 2.57

(s, 4H, morpholinyl-H);^{13}C NMR (151 MHz, $CDCl_3$) δ 155.68, 135.07, 132.11, 130.48, 116.65, 114.22, 66.79, 59.05, 53.42;MS (ESI) m/z: 228.2 (calcd 228.08 for $C_{11}H_{15}ClNO_2^+$ $[M + H]^+$).

*3-Chloro-4-(morpholinomethyl)phenol(**2t**).*Yellowish oil; Yield 42.7%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.32 – 7.28 (m, 1H, Ph-H), 6.80 (d, *J* = 2.5 Hz, 1H, Ph-H), 6.65 (dd, *J* = 8.3, 2.5 Hz, 1H, Ph-H), 3.76 (s, 4H, morpholinyl-H), 3.59 (s, 2H, Ph-CH_2-), 2.58 (s, 4H, morpholinyl-H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 155.68, 135.07, 132.11, 130.48, 116.65, 114.22, 66.79, 59.05, 53.42; MS (ESI) m/z: 228.1(calcd 228.1 for $C_{11}H_{15}ClNO_2^+$ $[M + H]^+$).

*2-Methoxy-4-(morpholinomethyl)phenol(**2u**).* White solid; Yield 54.7%; Mp121-123 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.99 (s, 1H, Ph-H), 6.83 (d, *J* = 8.0 Hz, 1H, Ph-H), 6.75 (dd, *J* = 8.0, 1.7 Hz, 1H, Ph-H), 3.82 (d, *J* = 14.3 Hz, 3H, -OCH_3), 3.54 (s, 2H, Ph-CH_2-), 2.52 (s, 4H, morpholinyl-H), 1.75–1.63 (m, 4H, morpholinyl-H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 146.82, 145.39, 122.74, 114.10, 112.48, 63.11, 53.92, 24.99, 23.90; MS (ESI) m/z: 224.2 (calcd 224.1 for $C_{12}H_{18}NO_3^+$$[M + H]^+$).

*4-(Pyrrolidin-1-ylmethyl)phenol (**2v**)*. Yellowish solid; Yield 51.3%; Mp 108-110 ℃;^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (d, *J* = 8.5 Hz, 2H,Ph-H), 6.63 (d, *J* = 8.5 Hz, 2H,Ph-H), 3.62 (s, 2H, Ph-CH_2-), 2.66 (s, 4H, pyrrolidyl-H), 1.84 (s, 4H, pyrrolidyl-H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.76, 130.78, 127.93, 115.83, 59.91, 53.73, 23.10; MS (ESI) m/z: 178.2 (calcd 178.1 for $C_{11}H_{16}NO^+$$[M + H]^+$).

*4-(Piperidin-1-ylmethyl)phenol(**2w**)*

^{1}H NMR (600 MHz, $CDCl_3$) δ7.07 (d, *J* = 8.4 Hz, 2H, Ph-H), 6.56 (d, *J* = 8.4 Hz, 2H, Ph-H), 3.43 (s, 2H, Ph-CH_2-), 2.51 (s, 4H, pyrrolidyl-H), 1.63 (s, 4H, pyrrolidyl-H), 1.47 (s, 2H, pyrrolidyl-H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 156.18, 131.31, 115.75, 63.29, 54.23, 25.12, 24.10. MS (ESI) m/z: 192.2 (calcd 228.08 for $C_{12}H_{18}NO^+$ $[M + H]^+$).

*4-(Morpholinomethyl)phenol(**2x**).*White crystals; Yield 65.3%; Mp173-175 °C;^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.16 (d, J = 8.4 Hz, 2H,Ph-H), 6.72 (d, J = 8.5 Hz, 2H, Ph-H), 3.78 (t, J = 4.6 Hz, 4H, morpholinyl-H), 3.59 (s, 2H, Ph-CH_2-), 2.63 (s, 4H, morpholine-H);^{13}C-NMR (^{151}MHz, $CDCl_3$) δ 156.53, 131.33, 115.59, 65.99, 62.39,

52.79, 23.12; MS (ESI) m/z: 194.2 (calcd 194.1 for $C_{11}H_{16}NO_2^+$[M+H]$^+$).

*4-((4-Methylpiperazin-1-yl)methyl)phenol(**2y**).*Yellow solid; Yield 67.4%; Mp 138-141 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.08 (d, *J* = 8.4 Hz, 2H,Ph-H), 6.62 (d, *J* = 8.4 Hz, 2H,Ph-H), 3.50 (s, 2H, Ph-CH_2-), 2.72 – 2.40 (m, 8H, piperazinyl-H), 2.32 (s, 3H, -CH_3); ^{13}C NMR (151 MHz, $CDCl_3$) δ 156.53, 131.33, 125.69, 115.59, 65.99, 62.39, 52.79, 23.12; MS (ESI) m/z: 207.2 (calcd 207.2 for $C_{12}H_{19}N_2O^+$ [M + H]$^+$).

1.3. General Procedure for the Preparation of Compounds **3a-3w**

*1-(Benzo[b]thiophen-4-yl)-4-(3-(2-methyl-4-(pyrrolidin-1-ylmethyl)phenoxy)propyl)piperazine (**3a**).*The intermediate compound **1a** (1.53g, 5.2 mmol) and **2a** (1.08 g, 5.2 mmol) were added to 50 mL of acetonitrile, then K_2CO_3 (1.93 g, 10.4 mmol) and a catalytic amount of KI were added, and then the suspension was stirred for 10 h at 80 ℃, filtered and the filtrate was concentrated, the residue dissolved in 50 mL dichloromethane, washed with water and brine, dried over anhydrous Na_2SO_4.The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (SiO_2; eluent CH_2Cl_2 : MeOH = 95:5~90:10) to yield of **3a**. Off-white solid; Yield 78.5% (1.83g, 4.08 mmol); Mp138-139℃;^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.0 Hz, 1H, Ph-H), 7.44 (d, *J* = 5.5 Hz, 1H, thiophene-H), 7.41 (d, *J* = 5.5 Hz, 1H, thiophene-H), 7.31 – 7.28 (m, 1H, Ph-H), 7.26 (d, *J* = 8.2 Hz, 1H, Ph-H),7.23 (s, 1H, Ph-H), 6.92 (d, *J* = 7.6 Hz, 1H, Ph-H), 6.83 (d, *J* = 8.3 Hz, 1H, Ph-H), 4.08 (t, *J* = 6.1 Hz, 2H, -CH_2-O-), 3.80 (s, 2H, pyrrolidyl-CH_2-), 3.22 (s, 4H, piperazinyl-H), 2.84 (s, 4H, piperazinyl-H), 2.76 (s, 4H, pyrrolidyl-H), 2.70 – 2.63 (m, 2H, piperazinyl-CH_2-), 2.26 (d, *J* = 4.3 Hz, 3H, -CH_3), 2.11 – 2.05 (m, 2H, -CH_2-), 1.94 (s, 4H,pyrrolidyl-H); ^{13}C-NMR (151 MHz, $CDCl_3$) δ 157.10, 148.48, 141.12, 134.09, 132.07, 128.32, 127.08, 125.03, 124.96, 121.92, 117.01, 112.20, 110.91, 66.26, 59.10, 55.40, 53.67, 53.33, 52.14, 26.91, 23.25, 16.27; HRMS (ESI) m/z: 450.2572 (calcd 450.2574 for $C_{27}H_{36}N_3OS^+$[M + H]$^+$).

*1-(Benzo[b]thiophen-4-yl)-4-(3-(3-methyl-4-(pyrrolidin-1-ylmethyl)phenoxy)propyl)piperazine (**3b**).*White solid; Yield 76.2%; Mp 149-150℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.58 (d, J = 8.0 Hz, 1H, Ph-H), 7.45 (d, *J* = 5.5 Hz, 1H, thienyl-H), 7.41 (d, *J* = 5.5 Hz, 1H, thienyl-H), 7.32 – 7.26 (m, 2H, Ph-H), 6.93 (d, *J*

= 7.6 Hz, 1H, Ph-H), 6.81 – 6.73 (m, 2H, Ph-H), 4.07 (t, *J* = 6.3 Hz, 2H, -O-CH_2-), 3.69 (s, 2H, Ph-CH_2-), 3.23 (s, 4H, piperazinyl-H), 2.76 (s, 4H, piperazinyl-H), 2.70 – 2.64 (m, 4H, pyrrolidyl-H; 2H, piperazinyl-CH_2-), 2.40 (s, 3H, -CH_3), 2.08 – 2.03 (m, 2H,-CH_2-), 1.88 – 1.85 (m, 4H, pyrrolidyl-H) ; ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.28, 148.51, 141.13, 138.45, 134.10, 131.09, 125.05, 124.96, 121.95, 117.00, 116.62, 112.20, 111.50, 66.16, 56.95, 55.30, 53.94, 53.65, 52.15, 26.89, 23.45, 19.75; HRMS (ESI) m/z: 450.25872(calcd 450.2574 for $C_{27}H_{36}N_3OS^+$[M + H]$^+$).

*1-(Benzo[b]thiophen-4-yl)-4-(3-(2-fluoro-4-(pyrrolidin-1-ylmethyl)phenoxy)propyl)piperazine (**3c**).* Yellowish oil; Yield 73.4%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.57 (d, J =8.4 Hz, 1H, Ph-H), 7.44 (d, J = 5.5 Hz, 1H, thienyl-H), 7.41 (d, J = 5.5 Hz, 1H, thienyl-H), 7.30 (t, J = 4.2 Hz, 1H,Ph-H), 7.14 (dd, J = 7.2, 1.8 Hz, 1H, Ph-H), 7.10 (d, J = 8.4 Hz, 1H, Ph-H), 6.97 (t, J = 8.4 Hz, 1H, Ph-H), 6.92 (d, J = 7.2 Hz, 1H, Ph-H), 4.15 (t, J = 6.4 Hz, 2H, -O-CH_2-), 3.64 (s, 2H, Ph-CH_2-), 3.21 (s, 4H, piperazinyl-H), 2.75 (s, 4H, piperazinyl-H), 2.68 (t, J = 7.3 Hz, 2H, piperazinyl-CH_2-), 2.62 (s, 4H, pyrrolidyl-H), 2.11 – 2.05 (m, 2H, -CH_2-), 1.85 m, 4H, pyrrolidyl-H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 153.34, 151.71, 148.50, 146.27, 141.13, 134.09, 125.03, 124.95, 121.94, 116.99, 114.86, 112.19, 67.83, 59.37, 55.03, 53.87, 53.61, 52.14, 29.72, 26.77, 23.40; HRMS (ESI) m/z: 454.2321 (calcd 454.2323 for $C_{26}H_{33}FN_3OS^+$[M + H]$^+$).

*1-(Benzo[b]thiophen-4-yl)-4-(3-(3-fluoro-4-(pyrrolidin-1-ylmethyl)phenoxy)propyl)piperazine(**3d**).*Yellowish oil; Yield 76%;^{1}H NMR (600 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.0 Hz, 1H, Ph-H), 7.47 – 7.41 (m, 2H, thienyl-H), 7.36 – 7.27 (m, 2H, Ph-H), 6.93 (d, J = 7.6 Hz, 1H, Ph-H), 6.83 (dd, *J* = 8.6, 3.6 Hz, 1H, Ph-H), 6.70 (dd, *J* = 8.5, 3.6 Hz, 1H, Ph-H), 4.21 (s, 2H, -O-CH_2-), 4.10 (t, J = 6.2 Hz, 2H, Ph-CH_2-), 3.25 (s, 8H, piperazinyl-H), 2.86 – 2.79 (m, 4H, pyrrolidyl-H), 2.70 (t, J = 7.3 Hz, 2H, piperazinyl-CH_2-), 2.09 (s, 4H, pyrrolidyl-H), 2.11 – 2.07 (m, 2H, -CH_2-); ^{13}C NMR (151 MHz, $CDCl_3$) δ 162.80, 161.91, 161.16, 148.26, 141.15, 134.68, 134.65, 134.08, 125.08, 121.81, 117.16, 112.29, 111.46, 102.47, 66.76, 54.94, 53.58, 52.62, 51.90, 50.27, 26.37, 23.08; HRMS (ESI) m/z: 454.2321 (calcd 454.2323 for $C_{26}H_{33}FN_3OS^+$ [M + H]$^+$).

*1-(Benzo[b]thiophen-4-yl)-4-(3-(2-chloro-4-(pyrrolidin-1-ylmethyl)phenoxy)propyl)piperazine (**3e**).*Yellowish oil; Yield 79.4 %;^{1}H NMR (600 MHz, $CDCl_3$) δ 7.57 (d, J = 7.2 Hz, 1H, Ph-H), 7.45 (d, J = 5.4 Hz, 1H, thienyl-H), 7.43 – 7.39 (m, 2H), 7.30 (t, J = 8.4 Hz, 1H, Ph-H), 6.97 (d, J = 3.0 Hz, 1H, Ph-H), 6.93 (d, J = 8.4 Hz, 1H, Ph-H), 6.84 (dd, J = 8.4, 2.4 Hz, 1H, Ph-H), 4.06 (t, J = 6.3 Hz, 2H,-O-CH_2-), 3.75 (s, 2H, Ph-CH_2-), 3.23 (s, 4H, piperazinyl-H), 2.75 (s, 4H, piperazinyl-H), 2.64 (m, 4H, pyrrolidyl-H; 2H, piperazinyl-CH_2-), 2.17 – 2.00 (m, 2H, -CH_2-), 1.83 (s, 4H,pyrrolidyl-H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.46, 148.50, 141.14, 134.40, 134.10, 131.53, 125.04, 124.95, 121.94, 117.01, 115.22, 113.44, 112.20, 66.53, 56.20, 55.12, 54.01, 53.65, 52.15, 26.75, 23.53; HRMS (ESI) m/z: 470.2026 (calcd 470.2027 for $C_{26}H_{33}ClN_3OS^+$ $[M + H]^+$).

*1-(Benzo[b]thiophen-4-yl)-4-(3-(3-chloro-4-(pyrrolidin-1-ylmethyl)phenoxy)propyl)piperazine (**3f**).* Yellowish oil; Yield 80.2 %;^{1}H NMR (600 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.4 Hz, 1H, Ph-H), 7.50 (d, *J* = 8.4 Hz, 1H, Ph-H), 7.44 (d, *J* = 5.5 Hz, 1H, thienyl-H), 7.41 (d, *J* = 5.5 Hz, 1H, thienyl-H), 7.30 (d, *J* = 7.8 Hz, 1H, Ph-H), 6.97 (d, *J* = 2.5 Hz, 1H, Ph-H), 6.92 (d, *J* = 6.5 Hz, 1H, Ph-H), 6.86 (dd, *J* = 6.5, 2.6 Hz, 1H, Ph-H), 4.06 (t, *J* = 6.2 Hz, 2H, -O-CH_2-), 3.83 (s, 2H, Ph-CH_2-), 3.22 (s, 4H, pyrrolidyl-H), 2.78 – 2.70 (m, 8H, piperazinyl-H), 2.64 (t, *J* = 7.2 Hz, 2H, piperazinyl-CH_2-), 2.07 – 2.01 (m, 2H, -CH_2-), 1.87 (dd, *J* = 6.1, 2.9 Hz, 4H, pyrrolidyl-H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.79, 148.49, 141.13, 134.53, 134.09, 132.02, 127.20, 125.05, 124.97, 121.94, 117.01, 115.35, 113.56, 112.21, 66.56, 55.85, 55.08, 53.84, 53.64, 52.14, 26.72, 23.47;HRMS (ESI) m/z: 470.2026 (calcd 470.2027 for $C_{26}H_{33}ClN_3OS^+$$[M + H]^+$).

*1-(Benzo[b]thiophen-4-yl)-4-(3-(2-methoxy-4-(pyrrolidin-1-ylmethyl)phenoxy)propyl)piperazine(**3g**).*Yellowish oil; Yield 82.6 %;^{1}H NMR (600 MHz, $CDCl_3$) δ 7.55 (d, J = 8.0 Hz, 1H, Ph-H), 7.42 (d, J = 5.5 Hz, 1H, thienyl-H), 7.38 (d, J = 5.5 Hz, 1H, thienyl-H), 7.28 (d, J = 8.1 Hz, 1H, Ph-H), 7.02 (s, 1H, Ph-H), 6.92 – 6.88 (m, 1H, Ph-H), 6.88 – 6.84 (m, 2H, Ph-H), 4.12 (t, J = 6.6 Hz, 2H, -O-CH_2-), 3.90 (s, 3H, -OCH_3), 3.64 (s, 2H, Ph-CH_2-), 3.19 (s, 4H, piperazinyl-H), 2.72 (s, 4H, piperazinyl-H), 2.65 (s, 2H, piperazinyl-CH_2-), 2.61 (s, 4H, pyrrolidyl-H), 2.12

– 2.06 (m, 2H, -CH_2-), 1.84 (s, 4H, pyrrolidyl-H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 149.45, 148.52, 147.73, 141.11, 134.07, 125.04, 124.93, 121.97, 121.28, 116.95, 112.91, 112.85, 112.17, 67.49, 60.27, 56.12, 55.16, 53.95, 53.58, 52.15, 26.74, 23.42; HRMS (ESI) m/z: 466.2521 (calcd 466.2523 for $C_{27}H_{36}N_3O_2S^+$ $[M + H]^+$).

*1-(Benzo[b]thiophen-4-yl)-4-(2-(2-methoxy-4-(pyrrolidin-1-ylmethyl)phenoxy)ethyl)piperazine (**3h**).*Yellowish oil; Yield 82.6 %;^{1}H NMR (600 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.4 Hz, 1H), 7.42 (d, *J* = 5.5 Hz, 1H), 7.38 (d, *J* = 5.4 Hz, 1H), 7.29 – 7.24 (m, 1H), 7.06 (s, 1H), 6.90 (d, *J* = 7.5 Hz, 1H), 6.88 – 6.80 (m, 2H), 4.25 – 4.18 (m, 2H, -O-CH_2-), 3.91 (dd, *J* = 5.7, 1.3 Hz, 3H, -OCH_3), 3.66 (d, *J* = 6.9 Hz, 2H, Ph-CH_2-), 3.21 (s, 4H, piperazinyl-H), 2.99 – 2.95 (m, 2H, piperazinyl-CH_2-), 2.85 (s, 4H, piperazinyl-H), 2.64 (s, 4H, pyrrolidyl-H), 1.85 (s, 4H, pyrrolidyl-H);^{13}C NMR (151 MHz, $CDCl_3$) δ 149.56, 148.46, 147.61, 141.10, 134.09, 125.03, 124.97, 121.92, 121.37, 117.01, 113.20, 112.92, 112.23, 66.93, 60.15, 57.19, 56.12, 54.05, 53.98, 53.90, 52.07, 23.40; HRMS (ESI) m/z: 452.2365 (calcd 452.2366 for $C_{26}H_{34}N_3O_2S^+$$[M + H]^+$).

*1-(Benzo[b]thiophen-4-yl)-4-(3-(4-(pyrrolidin-1-ylmethyl)phenoxy)propyl)piperazine(**3i**).*Yellowish oil; Yield 73.5 %;^{1}H NMR (600 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.0 Hz, 1H, Ph-H), 7.41 (d, *J* = 4.9 Hz, 1H, thienyl-H), 7.37 (d, *J* = 5.4 Hz, 1H, thienyl-H), 7.33 (d, *J* = 7.6 Hz, 2H, Ph-H), 7.26 (td, *J* = 7.8, 2.6 Hz, 1H, Ph-H), 6.90 – 6.86 (m, 3H, Ph-H), 4.04 (t, *J* = 4.5 Hz, 2H, -O-CH_2-), 3.72 (s, 2H, Ph-CH_2-), 3.18 (s, 4H, piperazinyl-H), 2.69 (s, 4H, piperazinyl-H; 4H pyrrolidyl-H), 2.62 (d, *J* = 7.2 Hz, 2H, piperazinyl-CH_2-), 2.01 (d, *J* = 6.6 Hz, 2H,-CH_2-), 1.86 (d, *J* = 2.5 Hz, 4H, pyrrolidyl-H);^{13}C NMR (151 MHz, $CDCl_3$) δ 158.65, 148.50, 141.10, 134.07, 130.70, 125.06, 124.96, 121.96, 116.96, 114.49, 112.19, 66.25, 59.30, 55.21, 53.61, 53.58, 52.13, 26.82, 23.32; HRMS (ESI) m/z: 436.2415 (calcd 436.2417 for $C_{26}H_{34}N_3OS^+$ $[M + H]^+$).

*1-(Benzo[b]thiophen-4-yl)-4-(3-(2-methyl-4-(piperidin-1-ylmethyl)phenoxy)propyl)piperazine(**3j**).* Yellowish oil; Yield 76.4 %; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.58 (d, J = 8.0 Hz, 1H,Ph-H), 7.45 (d, J = 5.5 Hz, 1H, thienyl-H), 7.41 (d, J = 5.5 Hz, 1H, thienyl-H), 7.31 (t, J = 7.8 Hz, 1H, Ph-H), 7.14 (d, J = 9.2 Hz,

2H, Ph-H), 6.93 (d, J = 7.5 Hz, 1H, Ph-H), 6.82 (d, J = 8.0 Hz, 1H, Ph-H), 4.08 (t, J = 6.2 Hz, 2H, -O-CH_2-), 3.49 (s, 2H, Ph-CH_2-), 3.23 (s, 4H, piperazinyl-H), 2.77 (s, 4H, piperazinyl-H), 2.72 – 2.67 (m, 2H, piperazinyl-CH_2-), 2.46 (s, 4H, piperidyl-H), 2.27 (s, 3H, Ph-CH_3), 2.16 – 2.06 (m, 2H, -CH_2-), 1.66 (m, 4H, piperidyl-H), 1.47 (s, 2H, piperidyl-H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 156.42, 148.52, 141.14, 134.11, 132.03, 128.02, 126.53, 125.05, 124.95, 121.95, 117.01, 112.20, 110.59, 66.22, 63.09, 55.47, 54.17, 53.68, 52.17, 27.01, 25.57, 24.18, 16.30; HRMS (ESI) m/z:464.2728 (calcd 464.2730 for $C_{28}H_{38}N_3OS^+$ $[M + H]^+$).

*1-(Benzo[b]thiophen-4-yl)-4-(3-(3-methyl-4-(piperidin-1-ylmethyl)phenoxy)propyl)piperazine (**3k**).*Yellowish oil; Yield 78.1 %; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.59 (d, *J* = 7.8 Hz, 1H, Ph-H), 7.47 (d, *J* = 5.5 Hz, 1H, thienyl-H), 7.42 (d, *J* = 5.5 Hz, 1H, thienyl-H), 7.31 (t, *J* = 7.8 Hz, 1H, Ph-H), 7.23 (d, *J* = 8.3 Hz, 1H, Ph-H), 6.94 (d, *J* = 7.8 Hz, 1H, Ph-H), 6.78 (d, *J* = 2.4 Hz, 1H, Ph-H), 6.74 (dd, *J* = 8.3, 2.4 Hz, 1H, Ph-H), 4.07 (t, *J* = 6.3 Hz, 2H, -O-CH_2-), 3.43 (d, *J* = 6.0 Hz, 2H, Ph-CH_2-), 3.25 (s, 4H, piperazinyl-H), 2.79 (s, 4H, piperazinyl-H), 2.69(m, 2H, piperazinyl-CH_2-), 2.74 – 2.67 (m, 2H, piperidyl-H), 2.39 (s, 3H, Ph-CH_3), 2.13 – 2.05 (m, 2H, -CH_2-), 1.62 (m, 6H, piperidyl-H), 1.48 (s, 2H, piperidyl-H); ^{13}C NMR (151 MHz, $CDCl_3$)δ 157.97, 148.49, 141.16, 138.97, 134.12, 131.27, 125.08, 121.97, 117.05, 116.55, 112.25, 111.07, 66.11, 60.80, 55.40, 54.52, 54.45, 53.66, 52.10, 26.88, 25.96, 24.53, 19.66, 19.61; HRMS (ESI) m/z:464.2729 (calcd 464.2730 for $C_{28}H_{38}N_3OS^+$ $[M + H]^+$).

*1-(Benzo[b]thiophen-4-yl)-4-(3-(2-fluoro-4-(piperidin-1-ylmethyl)phenoxy)propyl)piperazine (**3l**)*. Yellowish oil; Yield 74.5 %; ^{1}H NMR (600 MHz, $CDCl_3$)δ 7.57 (d, J = 8.4 Hz, 1H, Ph-H), 7.44 (d, J = 5.5 Hz, 1H, thienyl-H), 7.41 (d, J = 5.5 Hz, 1H, thienyl-H), 7.30 (d, J = 7.6 Hz, 1H, Ph-H), 7.12 (dd, J =8.5, 1.8 Hz, 1H, Ph-H), 7.03 (d, J = 8.4 Hz, 1H, Ph-H), 6.96 (t, J = 8.4 Hz, 1H, Ph-H), 6.92 (d, J = 7.6 Hz, 1H, Ph-H), 4.15 (t, J = 6.4 Hz, 2H, -O-CH_2-), 3.45 (d, J = 4.8 Hz, 2H, Ph-CH_2-), 3.22 (s, 4H, piperazinyl-H), 2.75 (s, 4H, piperazinyl-H), 2.71 – 2.65 (m, 2H, piperazinyl-CH_2-), 2.42 (s, 4H, piperidyl-H), 2.15 – 2.06 (m, 2H, -CH_2-), 1.70 – 1.59 (m, 4H, piperidyl-H), 1.46 (s, 2H, piperidyl-H); ^{13}C NMR (151 MHz, $CDCl_3$)

δ153.38, 151.75, 148.51, 146.01, 141.13, 134.10, 125.02, 124.94, 121.94, 117.08, 116.99, 114.68, 112.18, 67.84, 62.71, 55.06, 54.29, 53.62, 52.15, 26.81, 25.77, 24.24; HRMS (ESI) m/z: 468.2478 (calcd 468.2479 for $C_{27}H_{35}FN_3OS^+$ $[M + H]^+$).

*1-(Benzo[b]thiophen-4-yl)-4-(3-(3-fluoro-4-(piperidin-1-ylmethyl)phenoxy)propyl)piperazine (**3m**).*Yellowish oil; Yield 76.8 %;^{1}H NMR (600 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.4Hz, 1H, Ph-H), 7.44 (d, *J* = 5.4 Hz, 1H, thienyl-H), 7.41 (d, *J* = 5.4 Hz, 1H, thienyl-H), 7.31 (d, *J* = 7.8 Hz, 2H, Ph-H), 6.93 (d, *J* = 7.8 Hz, 1H, Ph-H), 6.71 (dd, *J* = 8.4, 2.4 Hz, 1H, Ph-H), 6.65 (dd, *J* = 8.5, 2.4 Hz, 1H, Ph-H), 4.06 (t, *J* = 6.3 Hz, 2H, -O-CH_2-), 3.55 (s, 2H, Ph-CH_2-), 3.22 (s, 4H,piperazinyl-H), 2.75 (d, *J* = 5.2 Hz, 4H, piperazinyl-H), 2.70 – 2.62 (m, 2H, piperazinyl-CH_2-), 2.46 (s, 4H, piperidyl-H), 2.11 – 2.02 (m, 2H,-CH_2-), 1.71-1.62 (m, 4H, piperidyl-H), 1.44 (s, 2H, piperidyl-H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.62, 148.50, 141.15, 134.99, 134.11, 131.67, 127.34, 125.08, 124.98, 121.97, 117.03, 115.33, 113.40, 112.22, 67.09, 66.53, 59.19, 55.10, 53.65, 53.52, 52.15, 26.74; HRMS (ESI) m/z: 468.2478 (calcd 468.2479 for $C_{27}H_{35}FN_3OS^+$[M + H]$^+$).

*1-(Benzo[b]thiophen-4-yl)-4-(3-(2-chloro-4-(piperidin-1-ylmethyl)phenoxy)propyl)piperazine(**3n**).*Pale yellow solid; Yield 74.2 %;Mp151-152 ℃;^{1}H NMR (600 MHz, $CDCl_3$) δ 7.57 (d, J = 8.0 Hz, 1H, Ph-H), 7.44 (d, J = 5.2 Hz, 1H, thienyl-H), 7.41 (d, *J* = 5.2, 1H, thienyl-H), 7.36 (d, *J* = 8.5 Hz, 1H, Ph-H), 7.33 – 7.27 (t, *J* = 7.8, Ph-H), 6.99 (s, 1H, Ph-H), 6.91 (d, J = 8.5 Hz, 1H, Ph-H), 6.84 (dd, J = 8.5, 2.2 Hz, 1H, Ph-H), 4.11 – 4.02 (m, 2H, -O-CH_2-), 3.76 – 3.70 (m, 4H,piperazinyl-H), 3.57 (d, *J* = 5.5 Hz, 2H, Ph-CH_2-), 3.22 (s, 4H,piperazinyl-H), 2.74 (s, 4H, piperidyl-H), 2.64 (d, J = 5.2 Hz, 2H, piperazinyl-CH_2-), 2.51 (s, 4H, piperidyl-H), 2.03 (d, *J* = 6.6 Hz, 2H, -CH_2-), 1.48 (s, 2H, piperidyl-H);^{13}C NMR (151 MHz, $CDCl_3$) δ158.62, 148.50, 141.15, 134.99, 134.11, 131.67, 127.34, 125.08,124.98, 121.97, 117.03, 115.33, 113.40, 112.22, 67.09, 66.53, 59.19, 55.50, 55.10, 53.65, 53.52, 52.15, 26.74; HRMS (ESI) m/z: 484.2182 (calcd 484.2184 for $C_{27}H_{35}ClN_3OS^+$ $[M + H]^+$).

*1-(Benzo[b]thiophen-4-yl)-4-(3-(3-chloro-4-(piperidin-1-ylmethyl)phenoxy)propyl)piperazine (**3o**).*Pale yellow solid; Yield 74.2 %;Mp 149-

151℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.58 (d, J = 8.4 Hz, 1H,Ph-H), 7.45 (d, J = 6.0 Hz, 1H, thienyl-H), 7.41 (m, 2H,Ph-H, thienyl-H), 7.30 (t, J = 7.8 Hz, 1H, Ph-H), 6.96 (d, J = 2.5 Hz, 1H, Ph-H), 6.93 (d, J = 7.8 Hz, 1H, Ph-H), 6.84 (dd, J = 8.4, 2.4 Hz, 1H, Ph-H), 4.06 (t, J = 12.0 Hz, 2H, -O-CH_2-), 3.55 (s, 2H, Ph-CH_2-), 3.23 (s, 4H, piperazinyl-H), 2.75 (s, 4H, piperazinyl-H), 2.69 – 2.62 (m, 2H, piperazinyl-CH_2-), 2.46 (s, 4H, piperidyl-H), 2.08 – 2.02 (m, 2H,-CH_2-), 1.60 (dd, J = 11.4, 5.4 Hz, 4H, piperidyl-H), 1.47 (s, 2H, piperidyl-H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.32, 148.51, 141.14, 134.74, 134.11, 131.55, 125.04, 124.95, 121.94, 117.01, 115.12, 113.34, 112.20, 66.51, 59.40, 55.14, 54.48, 53.66, 52.16, 26.77, 26.05, 24.39;HRMS (ESI) m/z: 484.2182 (calcd 484.2184 for $C_{27}H_{35}ClN_3OS^+$[M + H]$^+$).

*1-(Benzo[b]thiophen-4-yl)-4-(3-(2-methoxy-4-(piperidin-1-ylmethyl)phenoxy)propyl)piperazine (**3p**)*. Pale yellow solid; Yield 81.9 %;Mp 153-155℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.0 Hz, 1H, Ph-H), 7.42 (d, *J* = 5.5 Hz, 1H, thienyl-H), 7.39 (d, *J* = 5.5 Hz, 1H, thienyl-H), 7.28 (t, *J* = 7.8 Hz, 1H, Ph-H), 7.12 (s, 1H, Ph-H), 6.90 (d, *J* = 7.6 Hz, 1H, Ph-H), 6.87 (s, 2H, Ph-H), 4.12 (t, J = 7.2 Hz, 2H, -O-CH_2-), 3.90 (s, 4H, piperazinyl-H), 3.66 (s, 2H, Ph-CH_2-), 3.20 (s, 4H, piperazinyl-H), 2.77 – 2.71 (m, 4H, piperidyl-H), 2.68 – 2.64 (m, 3H, -OCH_3), 2.60 (s, 2H, piperazinyl-CH_2-), 2.12 – 2.05 (m, 2H, -CH_2-), 1.83 – 1.70 (m, 4H, piperidyl-H), 1.52 (s, 2H, piperidyl-H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 149.50, 148.48, 148.14, 141.11, 134.06, 124.96, 123.11, 122.28, 121.94, 116.98, 113.67, 112.18, 67.45, 62.74, 58.84, 56.31, 55.15, 53.85, 53.57, 52.10, 29.70, 26.66, 24.82, 23.65; HRMS (ESI) m/z: 480.2678 (calcd 480.2679 for $C_{28}H_{38}N_3O_2S^+$ [M + H]$^+$).

*1-(benzo[b]thiophen-4-yl)-4-(3-(4-(piperidin-1-ylmethyl)phenoxy)propyl)piperazine (**3q**)*. White solid; Yield 72.3%; Mp 154-156 ℃;^{1}H NMR (600 MHz, $CDCl_3$) δ 7.58 (d, J = 8.0 Hz, Ph-H), 7.45 (d, J = 5.5 Hz, 1H, thienyl-H), 7.41 (d, J = 5.5 Hz, 1H, thienyl-H), 7.33 – 7.25 (m, 3H, Ph-H), 6.93 (d, J = 7.6 Hz, 1H, Ph-H), 6.90 (d, J = 8.5 Hz, 2H, Ph-H), 4.08 (s, 2H, -O-CH_2-), 3.49 (s, 2H, Ph-CH_2-), 3.23 (s, 4H, piperazinyl-H), 2.76 (s, 4H, piperidyl-H), 2.67 (s, 2H, piperazinyl-CH_2-), 2.43 (s, 4H, piperidyl-H), 2.06 (s, 2H, -CH_2-), 1.63 (s, 4H, piperidyl-H), 1.46 (s, 2H, piperidyl-

H).^{13}C NMR (151 MHz, $CDCl_3$) δ 158.21, 148.52, 141.14, 134.10, 130.62, 125.04, 124.94, 121.94, 116.99, 114.18, 112.19, 66.24, 63.08, 55.30, 54.22, 53.65, 52.17, 26.90, 25.75, 24.28. HRMS (ESI) m/z: 480.2580 (calcd 452.2574 for $C_{27}H_{36}N_3O_2S^+$ $[M + H]^+$).

*4-(4-(3-(4-(Benzo[b]thiophen-4-yl)piperazin-1-yl)propoxy)-3-methylbenzyl)morpholine (**3r**).*Pale yellow solid; Yield 73.5 %;Mp 145-147℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.0 Hz, 1H, Ph-H), 7.45 (t, *J* = 5.3 Hz, 1H, thienyl-H), 7.41 (dd, *J* = 5.3, 2.7 Hz, 1H, thienyl-H), 7.30 (dd, 8.0, 5.0Hz, 1H, Ph-H), 7.14 (s, 1H, Ph-H), 7.13 – 7.09 (m, 1H, Ph-H), 6.93 (d, *J* = 7.2 Hz, 1H, Ph-H), 6.83 – 6.77 (m, 1H, Ph-H), 4.08 (t, *J* = 6.2 Hz, 2H, O-CH_2-), 3.74 (m, 4H, morpholinyl-H), 3.44 (d, *J* = 4.2 Hz, 2H, Ph-CH_2-), 3.23 (s, 4H, piperazinyl-H), 2.77 (s, 3H, -CH_3), 2.74 – 2.67 (m, 2H, piperazinyl-CH_2-), 2.46 (s, 4H, piperazinyl-H), 2.28 (s, 4H, morpholinyl-H), 2.15 – 2.05 (m, 2H, -CH_2-); ^{13}C NMR (151 MHz, $CDCl_3$) δ 156.38, 148.50, 141.15, 134.11, 131.75, 127.70, 126.60, 125.07, 124.98, 121.95, 117.04, 112.22, 110.64, 67.02, 66.23, 63.04, 55.46, 53.58, 52.14, 41.70, 32.49, 26.98, 16.35. HRMS (ESI) m/z: 466.2521 (calcd 466.2523 for $C_{27}H_{36}N_3O_2S^+$ $[M + H]^+$).

*4-(4-(3-(4-(Benzo[b]thiophen-4-yl)piperazin-1-yl)propoxy)-3-fluorobenzyl)morpholine(**3s**).*White solid; Yield 75.6%; Mp 161-162 ℃;^{1}H NMR (600 MHz, $CDCl_3$) δ 7.57 (d, J = 8.4 Hz, 1H, Ph-H), 7.44 (d, J = 5.5 Hz, 1H, thienyl-H), 7.41 (d, J = 5.5 Hz, 1H, thienyl-H), 7.31 (d, J = 7.8 Hz, 1H, Ph-H), 7.12 (dd, J = 7.8, 1.8 Hz, 1H, Ph-H), 7.01 (d, J = 8.4 Hz, 1H, Ph-H), 6.96 (t, J = 8.3 Hz, 1H, Ph-H), 6.92 (d, J = 7.6 Hz, 1H, Ph-H), 4.15 (t, J = 6.4 Hz, 2H, -O-CH_2-), 3.85 – 3.68 (m, 4H, morpholinyl-H), 3.44 (s, 2H, Ph-CH_2-), 3.22 (s, 4H, piperazinyl-H), 2.76 (s, 4H, piperazinyl-H), 2.68 (t, J = 7.3 Hz, 2H, piperazinyl-CH_2-), 2.45 (s, 4H, morpholinyl-H), 2.14 – 2.02 (m, 2H,-CH_2-); ^{13}C NMR (151 MHz, $CDCl_3$) δ 153.47, 151.84, 148.50, 146.13, 146.06, 141.14, 134.10, 131.18, 125.02, 124.95, 124.65, 121.93, 117.01, 116.89, 116.77, 114.72, 112.17, 67.85, 67.02, 62.48, 55.04, 53.62, 53.53, 52.16, 26.80; HRMS (ESI) m/z: 470.2270 (calcd470.2272 for $C_{26}H_{33}FN_3O_2S^+$ $[M + H]^+$).

*4-(4-(3-(4-(Benzo[b]thiophen-4-yl)piperazin-1-yl)propoxy)-2-fluorobenzyl)morpholine (**3t**)*.Yellowish oil; Yield 78.0%;Mp 151-152 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.57 (d, *J* =7.8 Hz, 1H,Ph-H), 7.44 (d, *J* = 6.3 Hz, 1H, thienyl-H), 7.40 (d, *J* = 6.3 Hz, 1H, thienyl-H), 7.32 – 7.22 (m, 2H, Ph-H), 6.91 (d, *J* = 7.8 Hz, 1H, Ph-H), 6.72 (dd, *J* = 8.4, 2.4 Hz, 1H, Ph-H), 6.68 (dd, *J* = 7.8, 2.4 Hz, 1H, Ph-H), 4.05 (t, *J* = 6.3 Hz, 2H, -O-CH_2-), 3.75 – 3.70 (m, 4H, morpholinyl-H), 3.53 (s, 2H, Ph-CH_2-), 3.21 (s, 4H, piperazinyl-H), 2.73 (s, 4H, piperazinyl-H), 2.63 (t, *J* = 7.3 Hz, 2H, piperazinyl-CH_2-), 2.48 (s, 4H, morpholinyl-H), 2.07 – 2.00 (m, 2H, -CH_2-);^{13}C NMR (151 MHz, $CDCl_3$) δ 162.83, 161.20, 159.66, 148.51, 141.15, 134.10, 132.21, 125.09, 124.98, 121.98, 117.03, 116.05, 112.21, 110.36, 102.00, 67.00, 66.56, 55.40, 55.10, 53.64, 53.24, 52.16, 26.73; HRMS (ESI) m/z:470.2270 (calcd470.2272 for $C_{26}H_{33}FN_3O_2S^+$ $[M + H]^+$).

*4-(4-(3-(4-(Benzo[b]thiophen-4-yl)piperazin-1-yl)propoxy)-2-chlorobenzyl)morpholine (**3u**)*.Pale yellow solid; Yield 78.7%; Mp 139-142 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.4 Hz, 1H, Ph-H), 7.44 (d, *J* = 5.5 Hz, 1H, thienyl-H), 7.39 (d, *J* = 5.5 Hz, 1H, thienyl-H), 7.36 (d, *J* = 8.4Hz, 1H, Ph-H), 7.29 (t, *J* = 7.8 Hz, 1H,Ph-H), 7.01 (d, *J* = 2.5 Hz, 1H, Ph-H), 6.90 (d, *J* = 7.8 Hz, 1H, Ph-H), 6.85 (dd, *J* = 8.5, 2.5 Hz, 1H, Ph-H), 4.04 (t, *J* = 6.3 Hz, 2H,-O-CH_2-), 3.79 – 3.68 (m, 4H, morpholinyl-H), 3.57 (s, 2H, Ph-CH_2-), 3.20 (s, 4H, piperazinyl-H), 2.71 (s, 4H, piperazinyl-H), 2.62 (t, *J* = 7.2 Hz, 2H, piperazinyl-CH_2-), 2.50 (s, 4H, morpholinyl-H), 2.09 – 1.96 (m, 2H, -CH_2-);^{13}C NMR (151 MHz, $CDCl_3$) δ158.65, 148.51, 141.16, 135.00, 134.11, 131.72, 127.33, 125.13, 125.01, 122.02, 117.04, 115.35, 113.43, 112.24, 67.08, 66.52, 59.21, 55.10, 53.64, 53.53, 52.15, 26.75; HRMS (ESI) m/z: 486.1952 (calcd 486.1977 for $C_{26}H_{33}ClN_3O_2S^+$ $[M + H]^+$).

*4-(4-(3-(4-(Benzo[b]thiophen-4-yl)piperazin-1-yl)propoxy)-3-methoxybenzyl)morpholine(**3v**)*.Pale yellow solid; Yield 72.6 %; Mp 153-155 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.56 (d, J = 8.0 Hz, 1H, Ph-H), 7.43 (d, J = 5.5 Hz, 1H, thienyl-H), 7.40 (d, J = 5.5 Hz, 1H, thienyl-H), 7.29 (t, J = 7.8 Hz, 1H, Ph-H), 6.92 (d, J = 8.5 Hz, 2H, Ph-H), 6.89 (d, J = 8.5, 2H, Ph-H), 6.85 (dd, J = 8.1, 1.7 Hz, 1H, Ph-H), 4.14 (t, *J* = 6.6 Hz, 2H, -O-CH_2-), 3.90 (s, 3H, -OCH_3), 3.73 (t, *J* = 4.6 Hz, 4H,

morpholinyl-H), 3.45 (s, 2H, Ph-CH_2-), 3.20 (s, 4H, piperazinyl-H), 2.74 (s, 4H, piperazinyl-H), 2.66 (t, *J* = 7.3 Hz, 2H, piperazinyl-CH_2-), 2.45 (s, 4H, morpholinyl-H), 2.14 – 2.08 (m, 2H,-CH_2-); ^{13}C NMR (151 MHz, $CDCl_3$) δ 149.42, 148.50, 147.65, 141.13, 134.08, 130.56, 125.05, 124.96, 121.96, 121.48, 117.00, 112.84, 112.19, 67.49, 67.03, 63.25, 56.06, 55.19, 53.61, 53.59, 52.14, 26.75; HRMS (ESI) m/z: 482.2470 (calcd 482.2474 for $C_{27}H_{36}N_3O_3S^+$[M + H]$^+$).

*4-(4-(3-(4-(Benzo[b]thiophen-4-yl)piperazin-1-yl)propoxy)benzyl)morpholine(**3w**).* White solid; Yield 76.2 %;Mp 143-145 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.4 Hz, 1H, Ph-H), 7.45 (d, *J* = 5.5 Hz, 1H, thienyl-H), 7.41 (d, *J* = 5.5 Hz, 1H, thienyl-H), 7.30 (t, 7.2 Hz, 1H, Ph-H), 7.26 (d, *J* = 8.4 Hz, 2H, Ph-H), 6.93 (d, *J* = 7.8 Hz, 1H, Ph-H), 6.90 (d, *J* = 7.8 Hz, 2H, Ph-H), 4.08 (t, *J* = 6.3 Hz, 2H, -O-CH_2-), 3.73 (t, *J* = 4.6 Hz, 4H, morpholinyl-H), 3.46 (s, 2H, Ph-CH_2-), 3.23 (s, 4H, piperazinyl-H), 2.76 (s, 4H, piperazinyl-H), 2.70 – 2.65 (m, 2H, piperazinyl-CH_2-), 2.45 (s, 4H, morpholinyl-H), 2.09 – 2.03 (m, 2H, -CH_2-); ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.26, 148.49, 141.14, 134.10, 130.41, 129.70, 125.03, 124.96, 121.92, 117.01, 114.27, 112.18, 67.04, 66.26, 62.88, 55.28, 53.65, 53.55, 52.15, 26.87; HRMS (ESI) m/z: 452.2364 (calcd 452.2366 for $C_{26}H_{34}N_3O_2S^+$ [M + H]$^+$).

*1-(Benzo[b]thiophen-4-yl)-4-(3-(4-((4-methylpiperazin-1-yl)methyl)phenoxy)propyl)piperazine (**3x**).*White solid; Yield 72.2 %; Mp 132-135℃;^{1}H NMR (600 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.4 Hz, 1H, Ph-H), 7.44 (d, *J* = 5.5 Hz, 1H，thienyl-H), 7.41 (d, *J* = 5.5 Hz, 1H，thienyl-H), 7.30 (d, *J* = 7.8 Hz, 1H, Ph-H), 7.25 (d, *J* = 8.4 Hz, 2H, Ph-H), 6.92 (d, *J* = 7.8 Hz, 1H, Ph-H), 6.89 (t, *J* = 5.7 Hz, 2H, Ph-H), 4.07 (s, 2H, -O-CH_2-), 3.48 (s, 2H, Ph-CH_2-), 3.22 (s, 4H, Ph-piperazinyl-H), 2.75 (s, 4H, Ph-piperazinyl-H), 2.66 (s, 3H, N-CH_3), 2.45-2.51 (m, 2H, piperazinyl-CH_2-; 4H, piperazinyl-H), 2.32 (s, 4H, piperazinyl-H), 2.06 (s, 2H,-CH_2-);^{13}C NMR (151 MHz, $CDCl_3$) δ 158.20, 148.48, 141.12, 134.08, 130.41, 129.96, 125.02, 124.94, 121.92, 116.99, 114.23, 112.17, 66.24, 62.38, 55.27, 55.05, 53.64, 52.80, 52.14, 45.93, 26.87; HRMS (ESI) m/z: 465.2681 (calcd 456.2683 for $C_{27}H_{37}N_4OS^+$ [M + H]$^+$).

*8-(4-(3-(4-(benzo[b]thiophen-4-yl)piperazin-1-yl)propyl)piperazin-1-yl)quinoline(**3y**).*

White solid; Yield 68.6%; Mp 151-153℃;^{1}H NMR (600 MHz, $CDCl_3$) δ 8.91 (dd, *J* = 4.1, 1.6 Hz, 1H, pyridyl-H), 8.12 (dd, *J* = 8.2, 1.5 Hz, 1H, pyridyl-H), 7.57 (d, *J* = 8.0 Hz, 1H, Ph-H), 7.45 (t, *J = 7.0 Hz*, 1H, pyridyl-H, 2H, Ph-H), 7.41 (d, *J* = 5.4 Hz, 1H, thienyl-H), 7.39 – 7.36 (m, 1H, thienyl-H), 7.30 – 7.27 (m, 1H, Ph-H), 7.18 (d, *J* = 6.8 Hz, 1H, Ph-H), 6.93 (d, *J* = 7.6 Hz, 1H, Ph-H), 3.50 (s, 4H, piperazinyl-H), 3.23 (s, 4H, piperazinyl-H), 2.88 (s, 4H, piperazinyl-H), 2.75 (s, 4H, piperazinyl-H), 2.61–2.54 (m, 4H, piperazinyl-CH_2-), 1.92–1.84 (m, 2H, -CH_2-).^{13}C NMR (151 MHz, $CDCl_3$) δ 149.48, 148.53, 148.19, 142.74, 141.12, 136.49, 134.10, 129.62, 126.73, 125.04, 121.96, 121.63, 120.83, 116.98, 115.96, 112.20, 56.86, 53.65, 53.47, 52.16, 52.06, 24.45. HRMS (ESI) m/z: 472.2520 (calcd 472.2529 for $C_{28}H_{34}N_5OS^+$ [M + H]$^+$).

2. **Receptor Binding Studies**

Reagents

^{3}H-spiperone, ^{3}H-lysergic acid diethylamide, ^{3}H-ketanserin,^{3}H-mesulergine, ^{3}H-prazosin, ^{3}H-8-OH-DPAT, ^{3}H-pyrilamine ^{3}H-N-α methylhistamine and ^{3}H-mepyramine, were bought from China Isotope Co., Ltd; butaclamol, methysergide, promethazine and ketanserin, Imetit, Ciproxifan, WAY-100635, ketanserin, SCH23390, Haloperidol, Risperidone, Apo morphine were bought from Sigma Co., Ltd; Tris, NaCl, KCl, $MgCl_2$, $CaCl_2$, potassium dihydrogen phosphate, sodium hydroxide, ascorbic acid, pargyline and other chemical reagents were of analytical grade, Sinopharm Chemical Reagent Co., Ltd. PEG400 from Sinopharm Reagent Co. Ltd. In the test, the drug given orally in a vehicle of 10:90 PEG400/H_2O at a volume of 0.1 mL/10 g, or given intravenously in a vehicle of saline solution (prepared as oxalate complexes) or a mixture of DMSO/PEG400/H_2O at a volume of 0.1 mL/10 g.

Preparation of solution

Solution (**A**): 50 mM Tris-HCl buffer solution (Used for prepare membrane receptor of 5-HT_{2A} and 5-HT_{2C}). 6.05 g Tris dissolved in1000 mL high purity water, the pH value adjust to 7.4 with diluted hydrochloric acid, finally diluted with deionized water to 4000 mL; Solution (**B**): 20 mM HEPES, 2 mM $MgCl_2$, pH=7.4. 0.0076 g $MgCl_2$ dissolved in 20 mM HEPES, diluted with deionized water to 100 mL. Solution (**C**): 50 mM Tris-HCl buffer solution contain 0.1% ascorbic acid, 1 mM EDTA, 20 uM pargyline and 10 mM $MgSO_4$, pH=7.4. Solution (**D**): 50 mM Tris-HCl buffer solution contain 0.5 mM EDTA, 0.0585 g EDTA dissolved and diluted with solution, pH=7.4. (**A**) to 400 mL. Solution (**E**): 1.36 g KH_2PO_4 and 0.1 mol/L sodium hydroxide solution 79 mL dissolved in Solution (A), finally diluted 200 mL. Solution (**F**): 50 mM Tris-HCl buffer solution, 5 nM EDTA, pH=7.4. Solution (**A**) diluted with Solution (**D**), the volume ratio of **A** to **D** is 100000. Solution (**G**): 50 mM Tris-HCl, 1 mM $MgCl_2$, pH=7.4. 0.0380 g $MgCl_2$ dissolved and diluted with solution (**A**) to 400 mL. Solution (**H**): 50 mM Tris-HCl, 10 mM $MgCl_2$, 0.5 mM EDTA, pH=7.4. 0.3808 g $MgCl_2$ and 0.0585 g EDTA, dissolved and diluted with solution (**A**) to 400 mL. Before testing, the new compounds were dissolved in dimethyl sulfoxide solution

(50%, v/v), and then diluted to 2×10^{-4} M, the prepared solution stored in the 4 ℃ fridge.

General Procedures for the binding assays

Total binding (TB) was determined under the condition with non-existence of nonspecific binding and compounds. Specific binding (SB) was recorded as the compounds existed. Nonspecific binding (NB) was recorded as the difference between total and specific binding. inhibition ratio obtained based on following equation:

Percentage of inhibition (%) = (TB - SB) / (TB - NB) × 100%.

The groups only contained 5% DMSO as blank experiments which have no binging on the receptors. Each compound was tested more than three times in gradient of concentration ($1\times10^{-5}\sim1\times10^{-10}$ M). The IC_{50} value was calculated through non-linearity regressive analysis via Hill equation curve fitting. K_i value was calculated using Cheng-Prus off equation: $K_i = IC_{50}/(1+C/K_d)$. In this equation, the concentration of the hot ligand expressed as C; Receptor's dissociation constant expressed as K_d; Both obtained by Scatchard analysis and calculated for each labeled ligand. Mean K_i values and SEM were calculated for three separate experiments.

Preparation of receptor D_2 membrane[1-3]

The rats were cut off the head in ice, take out the striatum and place in centrifuge tubes, and then solution **A** added, the mixture was homogenized in homogenizer for 3-4 seconds and repeated four times, following centrifuged at 48000 g for 15 min at 4 ℃, the resulting precipitate was preserved and supernatant discarded. This procedure was repeated two times again, finally the suspension stored in a -80 ℃ refrigerator.

Preparation of receptor 5-HT_{1A} membrane[1-3]

The rats were cut off the head in ice, take out the cerebral cortex and place in centrifuge tubes, and then solution **A** added, the mixture was homogenized in homogenizer for 3-4 seconds and repeated four times, following centrifuged at 32000 g for 10 min at 4 ℃, the resulting precipitate was preserved and supernatant discarded. This procedure was repeated two times again, finally the suspension stored in a -80 ℃ refrigerator.

Preparation of receptor 5-HT_{2A} and 5-HT_{2c} membrane[1-3]

The rats were cut off the head in ice, take out the cerebral cortex and place in centrifuge tubes, then the solution **A** added, the mixture was homogenized in homogenizer for 3-4 seconds and repeated four times, following centrifuged at 32000 g for 10 min at 4 ℃, the resulting precipitate was preserved and supernatant discarded. This procedure was repeated two times again, finally the suspension stored in a -80 ℃ refrigerator.

Preparation of receptor H_1 membrane[1-3]

Guinea pig cerebellum place in centrifuge tubes, the solution E added and the mixture was homogenized in homogenizer for 3-4 seconds and repeated four times, then centrifuged at 50000 g for 20 min at 4 ℃, the resulting precipitate was preserved and supernatant discarded. This procedure was repeated two times again, finally the suspension stored in a -80 ℃ refrigerator.

Preparation of receptor H_3 membrane[1-3]

The rats were cut off the head in ice, take out the cerebral cortex and place in centrifuge tubes, the solution **C** added and the mixture was homogenized in homogenizer for 3-4 seconds and repeated four times, following centrifuged at 40000 g for 30 min at 4 ℃, the resulting precipitate was preserved and supernatant discarded. This procedure was repeated two times again, finally the suspension stored in a -80 ℃ refrigerator.

Preparation of receptor α_1 membrane[1-3]

The rats were cut off the head in ice, take out the cerebral cortex and place in centrifuge tubes, the solution **A** added and the mixture was homogenized in homogenizer for 3-4 seconds and repeated four times, following centrifuged at 50000 g for 15 min at 4 ℃, the precipitate was preserved and supernatant discarded. This procedure was repeated two times again, finally the suspension stored in a -80 ℃ refrigerator.

Preparation of 5-HT_6 receptor[1-3]

The 5-HT_6 receptor cell used came from CHO-5-HT_6 cells that stably transfection with the human 5-HT_6 receptor. Solution **H** added to the harvested CHO cell

suspension, the mixture was homogenized in homogenizer, following centrifuged at 100000 g for 45 min at 4 ℃, the precipitate was preserved and supernatant discarded. Then the precipitate suspended in Tris-HCl (pH=7.4, cell concentration about 4×10^7 cells/mL), finally the suspension stored in a -80 ℃ refrigerator.

Dopamine D_2 receptor[1-3]

The prepared D_2 membrane added solution **B**, the mixture contain tissue suspension and solution **B** was homogenized, then appropriate amount of solution **A** added to the mixture adjusted the volume to 50 mL, and the membrane suspension prepared. Each reaction tube added the following substances: Total binding (TB) tube, first added to the tube 50 μL of solution **B** and 50 μL of 0.5 nM ^{3}H-spiperone added, then 50 μL Tris HCl buffer (containing 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, 1 mM $MgCl_2$, 0.1% ascorbic acid, 5 mM pargyline), then 900 μL of prepared D_2 membrane added into the mixture; Nonspecific binding tube (NB), 900 μL of prepared D_2 membrane added into the mixture of 50 μL of 0.5 nM ^{3}H-spiperone and 50 μL of 10 mM (t)-butaclamol; Specific binding (SB), first added to the tube then 900 μL of prepared D_2 membrane, then50 μL of 0.5 nM ^{3}H-spiperone and 50 μL of new compounds or positive control drugs (concentration from 10^{-10} to 10^{-5} nM) added. Following the tubes were transferred to electro-heating standing-temperature cultivator incubated for 30 min at 37 °C, the incubation filtered through Whatman GF/B glass filters, filtrates were washed twice with 4 mL cold buffer solution, then transferred to a 3 mL scintillation vials, 2 mL scintillation solution added and the mixture was detected by PE Microbeta 2450 liquid scintillation counter.

Serotonin 5-HT_{1A} receptor[1-3]

The prepared 5-HT_{1A} membrane added solution **C**, the mixture contain tissue suspension and solution **C** was homogenized, then appropriate amount of solution **A** added to the mixture adjusted the volume to 50 mL, and the membrane suspension prepared. Each reaction tube added the following substances: Total binding (TB) tube, first added to the tube 50 μL of solution **B**, then 50 μL of 0.5 nM ^{3}H-8-OH-DAPAT and 50 μL of Tris-HCl buffer (containing 10 mM pargyline, 4 mM $CaCl_2$, and 0.1% ascorbic acid) added, finally 900 μL of prepared 5-HT_{1A} membrane added into the

mixture; Nonspecific binding tube (NB), 900 μL of prepared5-HT_{1A} membrane added into the mixture of 50 μL of ^{3}H-8-OH-DPAT and 50 μL of 10 mM serotonin; Specific binding (SB), First added to the tube50 μL of ^{3}H-8-OH-DAPAT, then 900 μL of prepared 5-HT_{1A} membrane added, finally 50 μL of new compounds or positive control drugs (concentration from 10^{-10} to 10^{-5} nM) into the mixture. The subsequent testing operation as described for the bending of dopamine D_2 receptor.

Serotonin 5-HT_{2A} receptor[1-3]

The prepared 5-HT_{2A} membrane added solution **A**, the mixture contain tissue suspension and solution **A** was homogenized, then appropriate amount of solution **A** added to the mixture adjusted the volume to 50 mL, and the membrane suspension prepared. Each reaction tube added the following substances: Total binding (TB) tube, first added to the tube 50 μL of solution **A**, then 50 μL of 0.6 nM ^{3}H-ketanserin, finally 900 μL of prepared 5-HT_{2A} membrane added into the mixture; Nonspecific binding tube (NB), 900 μL of prepared5-HT_{2A} membrane added into the mixture of 50 μL of 0.6 mM methysregide and 50 μL of 0.6 mM ^{3}H-ketanserin; For specific binding (SB), first added to the tube 900 μL of prepared 5-HT_{2A} membrane, then 50 μL of 0.6 nM ^{3}H-ketanserin added, finally 50 μL of new compounds or positive control drugs (concentration from 10^{-10} to 10^{-5} nM) added into the mixture. The subsequent testing operation as described for the bending of dopamine D_2 receptor.

Serotonin 5-HT_{2c} receptor[1-3]

The prepared 5-HT_{2c} membrane added solution **A** and 40 nM spiperone, the mixture contain tissue suspension and solution **A** was homogenized, then appropriate amount of solution **A** added to the mixture adjusted the volume to 50 mL, and the membrane suspension prepared. Each reaction tube added the following substances: Total binding (TB) tube, first added to the tube 50 μL of solution **A**, then 50 μL of 1 nM ^{3}H-ketanserin, finally 900 μL of prepared 5-HT_{2c} membrane added into the mixture; Nonspecific binding tube (NB), 900 μL of prepared 5-HT_{2c} membrane added into the mixture of 50 μL of 1 nM ^{3}H-ketanserin and 50 μL of 10 μM mianserin; Specific binding (SB), first added to the tube 900 μL of prepared 5-HT_{2c} membrane, then 50 μL of 0.6 nM ^{3}H-ketanserin added, finally 50 μL of new compounds or

positive control drugs (concentration from 10^{-10} to 10^{-5} nM) added into the mixture. The subsequent testing operation as described for the bending of dopamine D_2 receptor.

Serotonin 5-HT_6 receptor[1-3]

The prepared CHO-5-HT_6 membrane added solution **H**, the mixture was homogenized, then appropriate amount of solution **A** added to the mixture adjusted the volume to 50 mL, and the membrane suspension prepared. Each reaction tube added the following substances: Total binding (TB) tube, first added to the tube50 μL of solution **H**, then 50 μL 2 nM ^{3}H-lysergic acid, finally 900 μL of prepared CHO-5-HT_6 membrane added into the mixture; Nonspecific binding tube (NB), 900 μL of prepared CHO-5-HT_6 membrane added into the mixture of 50 μL of 2 nM ^{3}H-lysergic acid and 50 μL of 10 μM serotonin; Specific binding (SB), first added to the tube 50 μL of 2 nM ^{3}H-lysergic acid, then 900 μL of prepared CHO-5-HT_6 membrane added, finally 50 μL of positive control drugs or new compounds (concentration from 10^{-10} to 10^{-5} nM) added into the mixture. The subsequent testing operation as described for the bending of dopamine D_2 receptor.

Histidine H_1 receptor[1-3]

The prepared H_1 membrane added solution **E**, the mixture was homogenized, then appropriate amount of solution **A** added to the mixture adjusted the volume to 50 mL, and the membrane suspension prepared. Each reaction tube added the following substances: Total binding (TB) tube, first added to the tube 50 μL of solution E added, then 1 nM ^{3}H-mepyramine 50 μL added, finally 900 μL of prepared H_1 membrane added into the mixture; Nonspecific binding tube(NB), 1 mM promethazine 50 μL, H_1 membrane 900 μL added in to the mixture of finally added 1 nM ^{3}H-mepyramine 50 μL; Specific binding (SB), first added to the tube 1 nM ^{3}H-mepyramine 50 μL, then H_1 membrane 900 μL added, finally 50 μL of new compounds or positive control drugs (concentration from 10^{-10} to 10^{-5} nM) added in to the mixture. Following the tubes were transferred to electro-heating standing-temperature cultivator incubated for 60 min at 37 °C, and the subsequent testing operation as described for the bending of dopamine D_2 receptor.

Histidine H_3 receptor [4, 5]

The prepared H_3 membrane added solution **G**, the mixture was homogenized, then appropriate amount of solution **A** added to the mixture adjusted the volume to 50 mL, and the membrane suspension prepared. Each reaction tube added the following substances: Total binding (TB) tube, first added to the tube 50 μL of solution C, then 50 μL of 1 nM ^{3}H-N-α-methylhistamine added, finally 900 μL of prepared H_3 membrane added into the mixture; Nonspecific binding tube (NB), 900 μL of prepared H_3 membrane added into the mixture of 50 μL of 10 μM thioperamide and 50 μL of 1 nM ^{3}H-N-α-methylhistamine; Specific binding (SB), first added to the tube 50 μL of 1 nM ^{3}H -N-α-methyl histamine, then 900 μL of prepared H_3 membrane added, finally 50 μL positive control drugs or new compounds (concentration from 10^{-10} to 10^{-5} nM) added into the mixture. Following the tubes were transferred to electro-heating standing-temperature cultivator incubated for 30 min at 25 °C, then the subsequent testing operation as described for the bending of dopamine D_2 receptor.

Adrenaline α_1 Receptor[1-23]

The prepared α_1 membrane added solution **F**, the mixture was homogenized, then appropriate amount of solution **A** added to the mixture adjusted the volume to 50 mL, and the membrane suspension prepared. Each reaction tube added the following substances: Total binding (TB) tube, first added to the tube50 μL of solution F, then 50 μL of 1 nM ^{3}H-prazosin added, finally 900 μL of prepared α_1 membrane added into the mixture; Nonspecific binding tube (NB), 900 μL of prepared α_1 membrane added into the mixture of 50 μL of 1 nM ^{3}H-prazosin and 50 μL of 10 μM prazosin; Specific binding (SB), first added to the tube 50 μL of 1 nM ^{3}H-prazosin, then 900 μL of prepared α_1 membrane added, finally 50 μL positive control drugs or new compounds (concentration from 10^{-10} to 10^{-5} nM) added into the mixture. Following the tubes were transferred to electro-heating standing-temperature cultivator incubated for 30 min under 25 °C, then the subsequent testing operation as described for the bending of dopamine D_2 receptor.

hERG Affinity[1-3]

The potential for block hERG potassium channels was recorded by whole-cell patch clamp technique, the HEK 293 cells were used stably transfected with human hERG potassium channels, trypsinized and stored in serum under room temperature. All the solutions used in this test were newly prepared before testing. The bath solution prepared according the literature. The **3w** dissolved in DMSO solution (10%, V: V) and diluted to the test concentration (contain 1% DMSO) with bath solution before usage. When the whole cell configuration prepared, the HEK 293 cells cell held between -80 to +50 mV and switched within 2 seconds, after an interval of 30 seconds, membrane potential adjusted to -50 mV for 3 seconds to reveal the hERG tail current. And this procedure conducted in control and in the presence of different concentration of **3w** (0.3, 1.0, 3.0, and 10 μM). Tail currents were detected at -50 mV in control and in the presence of **3w**, and the concentration control was a matter of experience. The hERG inhibition experiments carried out three parallel experiments. All of the test results were recorded and analysis by using SPSS software.

Intrinsic Activity of Compound 3w[1]

The D_2, D_3, 5-HT_{1A}, 5-HT_{2A} and 5-HT_6 receptors functional activity of compound **3w.**

The D_2 functional activity of compound **3w**.

Method: HEK cells expressing D_2 receptor (HEK293T/hD_2 cell line) were seeded in a 384-well black-walled, clear bottom plate at a density of 1.5×10^4 cells/well in cell seeding medium (90% DMEM and 10% dialyzed serum) and incubated in CO_2 incubator for 16-24 hours (at least 12 hours).

For the D_2 assay, all compounds were diluted with DMSO, 1/2 log dilution(3.17 fold) , 11 points and triplicate to get the compounds dose, then added the assay buffer to get the working concentration and did the test.

Agonist mode: 1: Diluted the reference compound Dopamine to 50 μM (11points, 5X); 2: Diluted the test compounds to working concentration (11 points, 5X);

Antagonist mode: 1: Diluted the reference compound SCH23390 to 600 μM (11 points, 6X); 2: Diluted the test compounds to working concentration (11 points, 6X).

Assay buffer: 1 x DPBS + 0.5 mM IBMX. cAMP-d2 detection buffer: 20 μL d2 stock

solution to 4 mL lysis buffer. Anti-cAMP antibody-cryptate detection buffer: 20 μL antibody to cAMP stock solution to 4 mL lysis buffer.

Agonist mode:

1. Cells were gently trypsinized and seeded 10 μL cells (500 cells/ well) into384-well assay plate with compounds dose (Corning 3824)
2. Incubate for 30 min at 37 °C incubator.
3. Add 5 μL cAMP–d2 detection buffer and 5 μL antibody for detection andincubate for 60 min at room temperature.
4. Read the assay plate on EnVision with HTRF program to get the data

Antagonist mode:

1. Cells were gently trypsinized and seeded 5 μL cells (500 cells/ well) into 384-well assay plate with compounds dose (Corning 3824) and stayed for 15 min
2. Add 5 μL Dopamine (EC_{80}) to stimulate the cell.
3. Incubate for 30 min at 37 °C incubator.
4. Add 5 μL cAMP–d2 detection buffer and 5 μL antibody for detection and incubate for 60 min at room temperature.
5. Read the assay plate on Envision with HTRF program to get the data analysis:

Read the plate with EnVision and got the fluorescence signal data using HTRF program. All results for test compounds were test three times. According to the positive control (HPE) and negative control (ZPE) results, calculated the Effect (%) or Inhibition (%) of reference and the test compounds, used GraphPad Prism 5 to analyze the data, and got the dose response curve and the value of EC_{50} and IC_{50}.Effcet (%) for agonist mode was calculated from the following equation:

$$\text{Effcet (\%)} = (\text{Average}_{(\text{HPE})} - \text{Value}_{(\text{Raw Data})}) / (\text{Average}_{(\text{HPE})} - \text{Average}_{(\text{ZPE})}) \times 100$$

The % activation was then plotted as a function of the log of the cumulative doses of compounds. Inhibition (%) for antagonist mode was calculated from the following equation:

$$\text{Inhibition (\%)} = (\text{Value}_{(\text{Raw Data})} - \text{Average}_{(\text{ZPE})}) / (\text{Average}_{(\text{HPE})} - \text{Average}_{(\text{ZPE})}) \times 100$$

The % inhibition was then plotted as a function of the log of the cumulative doses of compounds.

The assay for D_3, 5-HT_{1A}, 5-HT_{2A} and 5-HT_6 receptors functional activity of compound **3w** use the similar method described above (**Table 1)**.

The H_3 receptors functional activity of Compound 3w

Antagonist potency was determined according to literature[2,3], by measuring inhibition of RAMH-induced [^{35}S]GTPγS binding in recombinant hH_3R membranes as previously. The concentration of RAMH was 100 nM, which produces approximately 80% of maximum RAMH-induced signal. Inverse agonist potency was conducted by measuring inhibition of basal [^{35}S]GTPγS binding in recombinant hH_3 Rmembranes. Test compound or vehicle was added to the wells, followed by [^{35}S]GTPγS to a final concentration of 0.2 nM. Nonspecific binding was determined in the presence of 10 μM unlabeled GTPγS. The control agonist signal was determined in wells containing vehicle in place of the test compound, and the basal signal was determined in wells containing vehicle in place of both diluted compound and the RAMH challenge. Ciproxifan decreased basal [^{35}S]GTPγS binding in a concentration-dependent manner in the recombinant systems consistent with known inverse agonist activity of the compound **3w**

Acute Toxicity[1, 2]

Mice (10 mice in each group) were orally dosed with increasing doses of the compound **3w** (250.0, 500.0, 1000.0, 1500.0, and 2000.0 mg/kg). The number of surviving animals was recorded after 24 h of drug administration, and the percent mortality in each group was calculated. The LD_{50} values were calculated by using the program SPSS (Statistical Package for the Social Sciences)

Behavioral studies

Apomorphine-Induced Climbing[1-3]

Mice randomly divided into 10 mice each group; each group corresponds to a dose. Each group oral administration of equal volumes of vehicle (blank control group), haloperidol (0.01, 0.1, 0.3, and 1.0 mg/kg), risperidone (0.01, 0.1, 0.3, and 1.0 mg/kg) (model group), and compound **3w** (0.01, 0.1, 0.3, and 1.0 mg/kg). The mice were placed in a cylindrical wire cages (12 cm in diameter and 14 cm in height) to observe their climbing behavior. After 30 minutes, blank control group injected equal

volumes of saline, the model group and other groups mice were injected with 1.0 mg/kg of the APO (dissolved in 0.9% NaCl solution contain 0.1% ascorbic acid), then observed and recorded their climbing behavior during 10 to 11, 20 to 21 and 30 to 31 min. The score standard of climbing behavior as follows: 4 paws on the cage recorded as 2 scores; 3 and 2 paws on the cage recorded as 1 score; 4 or 3 paws on the cage floor recorded as 0 score. Data analyzing, processing were performed by using the nonparametric two-tailed Mann-Whitney U-test. $p < 0.05$ considered have statistically significant differences. Text: #, $p < 0.05$versus vehicle treated (Veh); **, $p < 0.01$ and *, $p < 0.05$ versus APO treatment.

MK-801-Induced Hyperactivity[1-3]

Mice randomly divided into 10 mice a group; each group corresponds to a dose. Each group oral administration of equal volumes of vehicle (blank control group), haloperidol (0.01, 0.03, 0.1 and 0.3 mg/kg) and risperidone (0.01, 0.03, 0.1 and 0.3 mg/kg) (model group), compound **3w** (0.1, 0.3, 1.0 and 3.0 mg/kg). The mice were put in a Plexiglas cages (60*60*50cm), and the Plexiglas cages equipped with an intelligent video analysis system (ZH-ZFT, Anhui Zhenghua Biological Instrument Equipment Co. Ltd) to observe their locomotors activity. At the 60 min, blank control group injected equal volumes of saline, the model group and other groups each injected 0.3 mg/kg of MK-801, then the observation last for another 90 min. The total distance of each mouse can be automatically collected by computer data acquisition system. Compared with the blank control group, if a group's average total distance increased, the test recorded as locomotor activity increased, if the average total distance decreased, it is considered to have inhibitory effect on spontaneous activity. Data analyzing, processing was performed by using the nonparametric two-tailed Mann-Whitney U-test. The alpha value was set at $P < 0.05$. #, $p < 0.05$ versus vehicle treated (Vehicle); **, $p < 0.01$, *, $p < 0.05$ versus MK-801treatment.

Catalepsy Test[1- 3]

Mice randomly divided into 10 mice each group; each group corresponds to a dose. Each group oral administration of vehicle, haloperidol (0.01, 0.03, 0.1, 0.3, and 1.0 mg/kg), risperidone (0.01, 0.03, 0.1, 0.3, and 1.0 mg/kg), and compound **3w** (1.0, 3.0,

10.0, 30.0 and 100.0 mg/kg). At the 30min, 60min and 90min after giving medicine, put the forepaws on a metal bar (diameter 0.3 cm; length 20 cm; height 5.5 cm) and back paws onto tabletop, observe and record the time of mice holding this position. Mice were considered cataleptic if time exceed 60 seconds, the test ended and recorded as 60 seconds, within 60 seconds recorded the time actually used. A mean immobility time 30 seconds as positive control. ED_{50} calculated by Hill (Probability unit regression) method.

Conditioned Avoidance Response (CAR)[1, 2]

The regularly training of rats were conducted in shuttle box, the box contains two identical compartments, an escape passage installed on the partition between the two parts. The box equipped with a tilting grid floor with microswitch detection and connected to a high resistant power supply (Ac 50Hz, 0.5 mA, voltage and current are adjustable), light source, dark avoidance recorder and shuttle experimental video analysis system(ZH-CSC Anhui Zhenghua Biological Instrument Equipment Co. Ltd). When rats given conditioned stimulus (CS) through light, it had 3 seconds to escape to another compartment. Otherwise, given unconditioned stimulus (UCS) with electric shock through the grid floor driven the rats to escape. If the rats have no response to light stimulus(CS) until given UCS, and still in the same compartment or all time used in this process exceeded 7 seconds, the trial ended and recorded as failure avoidance; If the rats escaped to another compartment within 3 seconds, recorded as active avoidance; If the rats escaped to another compartment within 7 seconds after the UCS, recorded as passive avoidance. Each training at an interval of 45 seconds. The training lasted for days until the rats have the ability to avoid 70-80% of conditioned stimulus. The selected rats divided into two groups, the control group treated with increasing doses of risperidone (0.06, 0.2, 0.6 mg/kg, p.o.), another treated with increasing doses of **3w** (1.0, 2.5, 5.0 and 10.0 mg/kg, p.o.), the test of CAR conducted at 60 min after treatment. In the training stage, 40 trials as a session and once a day. In the testing stage, 20 trials one session and the session corresponding to the time point of each does of the tested compounds. The percentage avoidance response is the ratio of total number of trials per session to the number of

active avoidances. The avoidance values of the **3w** and risperidone were analyzed by repeated measures analysis of variance. The results were compared by using the Bonferroni adjustment for multiple comparisons, $P < 0.05$ considered have the level of significance indicated versus vehicle treated and expressed (**, $P < 0.05$). Data processing and analysis were performed by using SPSS software.

Novel Object Recognition (NOR) Training and Testing [2]

The experiment consists of two stages, the first stage is training stage (acquisition trials), the rats were trained to familiarize two identical objects (two ball, diameter 3cm) and observed a acquire memory. The next stage is testing stage (retention trial), an identical object was replaced by a "novel" one (a cube with edges of 3 cm), the rats will give preference to explore the "novel" object if the memory of previously reserved. Given rats drugs with unction of memory enhancement and combine with proper training that can improve its performance in memory, and it has the same effect with the rats just given stronger training. Rats randomly divided into several groups (10 rats each group) and placed in cage, each cage two groups and kept in a light-controlled room, light and darkness simulated by switching lights every 12 hours. Rats access to food and drinking freely, acclimated for a week before experiment. Before training stage, in order to make rats get familiar with the test arena, they were placed in a plastic box (length 40 cm; width 50 cm; height 40 cm) for 3 times a day and each time 10 mins, continue for 3 days. In the training stage, rats given vehicle, positive medicine risperidone(0.02, 0.06, 0.2 mg/kg), rivastigmine(0.1, 0.3, 1.0 mg/kg), and **3w** (0.1, 0.3, 1.0 mg/kg) orally (dissolved in vehicle), 60 min latter, the rats transferred to the test arena of the box which contained two identical objects in center, each rat give 5 min to explore the objects. If the rat's sharp nose poke pint to object less than 2 cm or sniff, lick the object, it was considered as exploring. If standing or sitting on the object, and touch it with other parts of the body but sharp nose not poke pint to it, it was not considered as exploring. Objects and arenas were cleaned with diluted 75% alcohol solution between trials to remove rat feces and urine. To determine the trained rat's memory performance, the trained rats put into the test arena of box again after 24 hours, one of the "familiar" objects and a

"novel" object placed in the area previously familiar with, observe the rat's behavior and record the exploration time (for familiar objects recorded as T_f; for new objects recorded as T_n;. Rats were excluded from the analysis if total exploration time in the acquisition trial was less than 10 s. The novelty discrimination index (NDI) was calculated as: (T_n-T_f/ T_n＋T_f) ×100 (%)(**Figure 7. A-C**).

Weight Gain and Serum Prolactin[1-3]

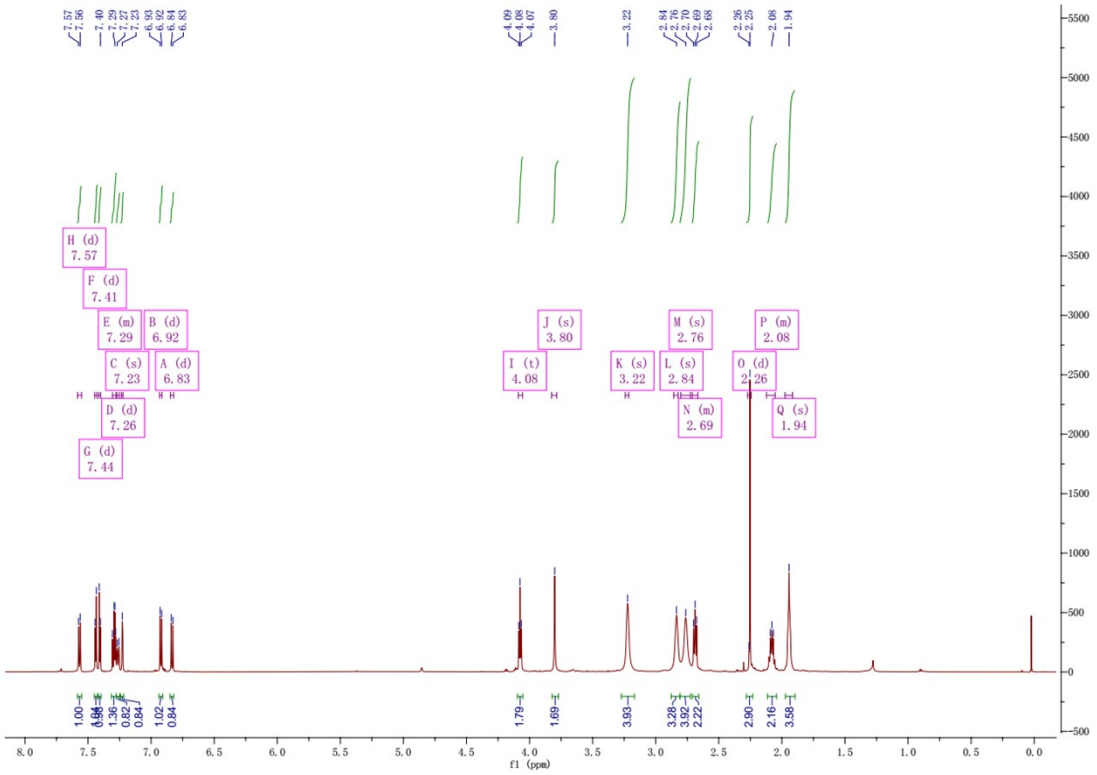
Mice randomly divided into 10 mice each group, each group given oral increasing dose of vehicle, risperidone (0.02, 0.06 and 0.2 mg/kg) and **3w** (0.02, 0.06, and 0.2 mg/kg), respectively. The body weight of mice was recorded during 28 days feeding. Subsequently, the mice were executed 3 hours after the last treatment, plasma was taken and centrifuged (3500 g for 15 min), serum was separated and stored at -20 ℃ for prolactin (PRL) detection. Serum PRL was determined by the Enzyme-linked immunosorbent assay. The EIA-kit from Amersham. The microplate reader from Pharmathea Co. Ltd. Data processing and analysis were performed by Student's t test (**, $p < 0.01$).

Table 1. Activities of Compound 3w and Reference Compounds to D_2, 5-HT_{1A}, 5-HT_{2A}, 5-HT_6 and H_3 Receptors

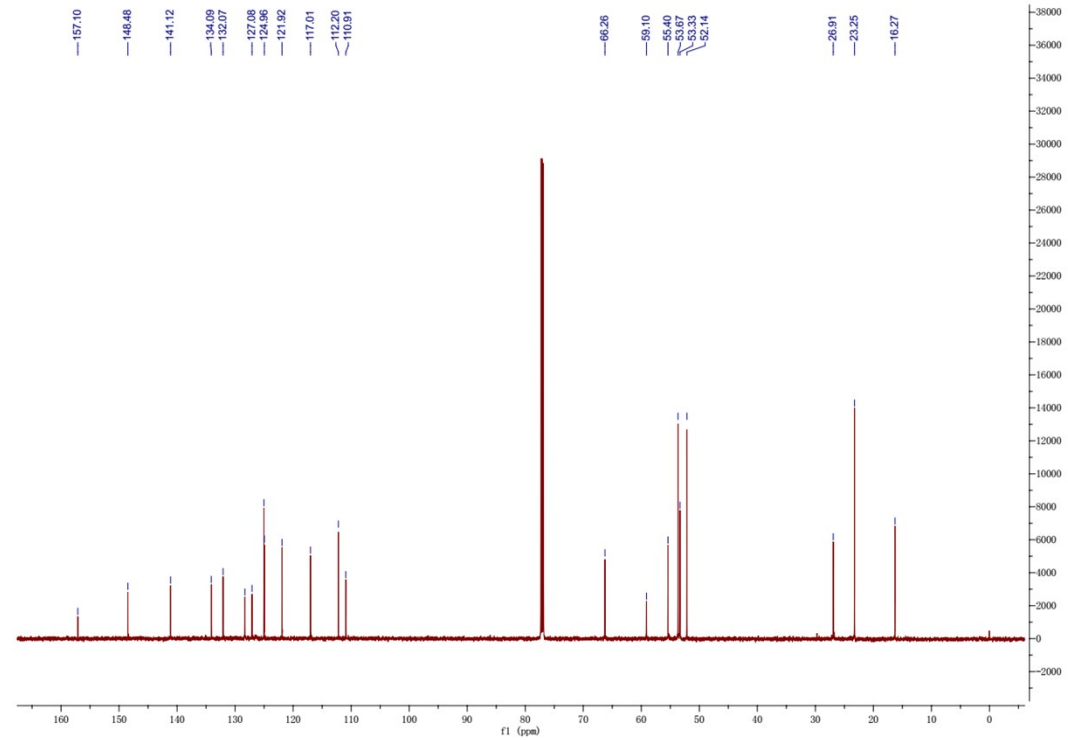
Receptor	Compd	Activation (10 μM, %) (n = 3)	EC_{50} (nM)	Inhibition (10 μM, %) (n = 3)	IC_{50} (nM)
D_2	Dopamine	99.4 ± 0.3	17.9		
	SCH23390			97.3 ± 1.6	33.1
	3w	9.7±1.2		96.3 ±2.6	11.6
5-HT_{1A}	5-HT	100.4 ±2.6	2.3		
	WAY-100635			98.5 ± 0.8	10.6
	3w	3.2±0.7		99.6 ± 1.8	218.5
5-HT_{2A}	5-HT	100.8 ±3.3	20.1		
	Ketanserin			99.6± 1.4	88.5
	3w	8.1±0.6		101.2 ± 2.6	141.8
H_3	Imetit	98.4 ± 4.1			
	Ciproxifan			99.6± 3.1	29.4
	3w	9.1±0.8		88.4 ±2.3	232.3
5-HT_6	5-HT	98.5 ± 1.8	47.9		
	Clozapine			100.8± 3.7	25.7
	3w	8.2±0.5		91.3 ±2.4	413.5

^{1}H-NMR and ^{13}C-NMR of target compounds 3a-3y

^{1}H-NMR of compound **3a**



^{13}C-NMR of compound **3a**



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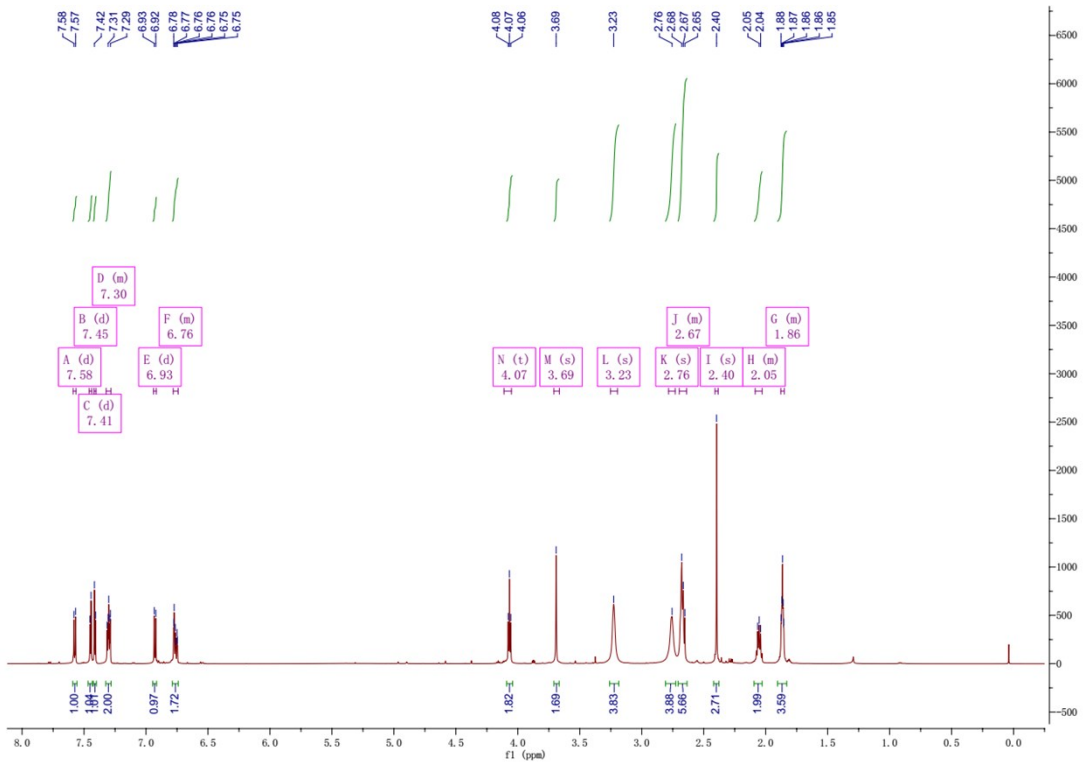
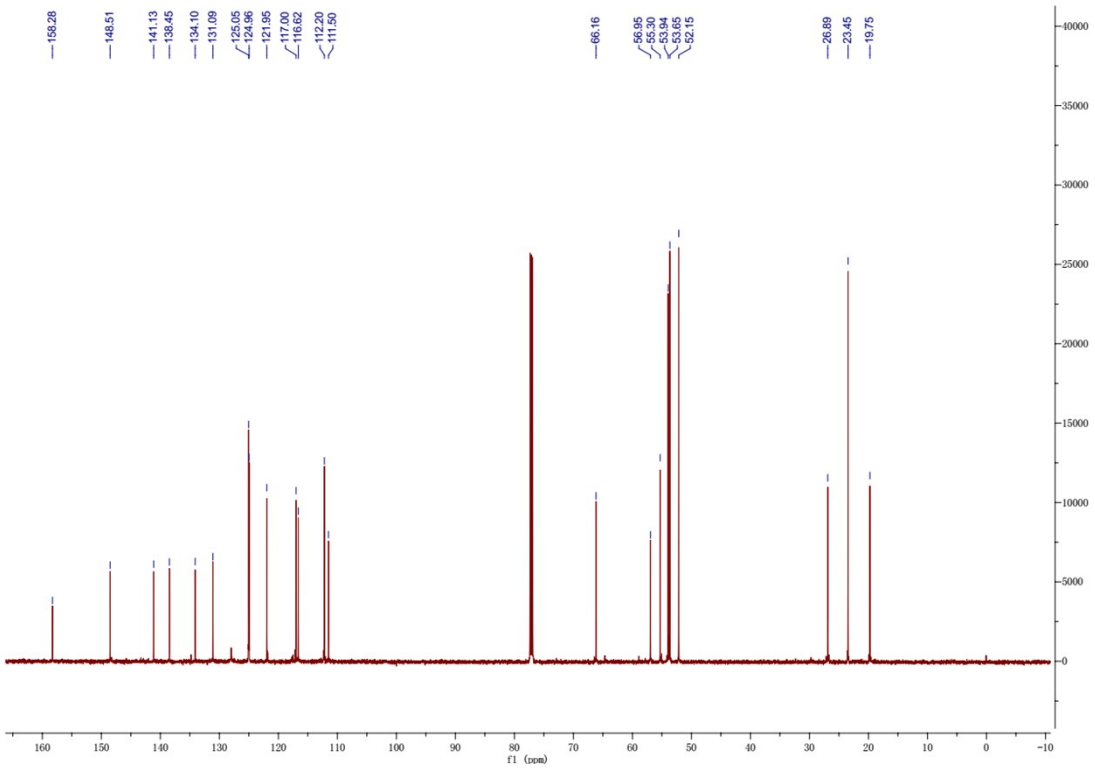
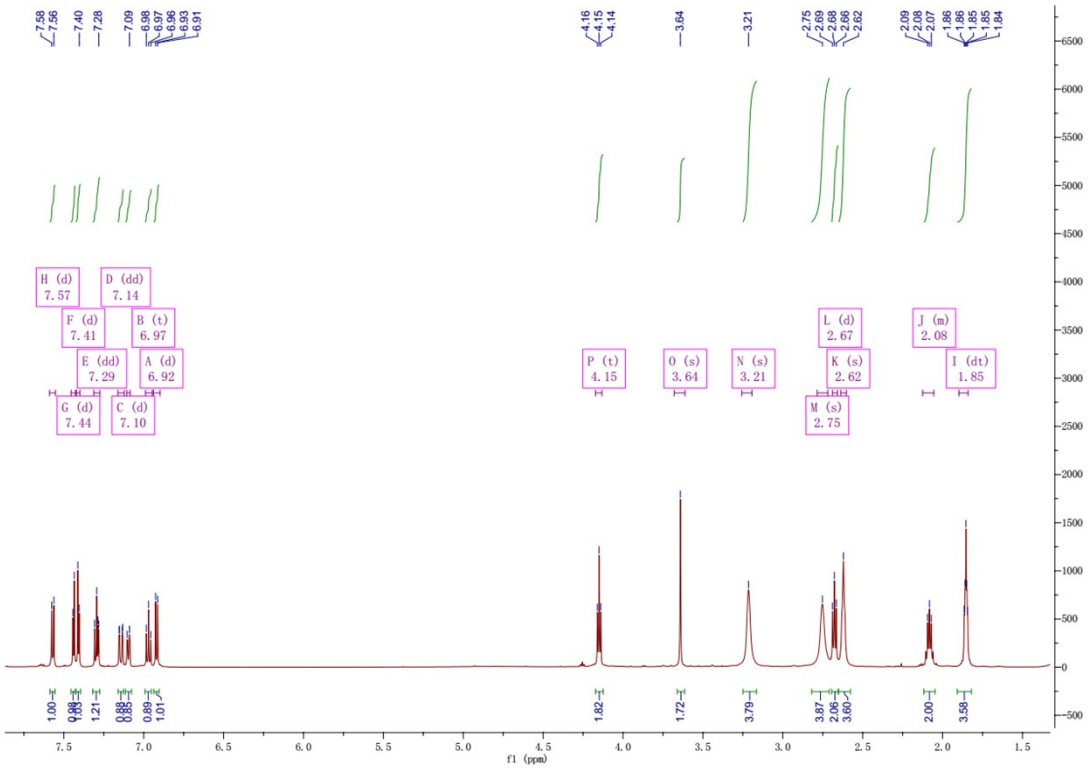


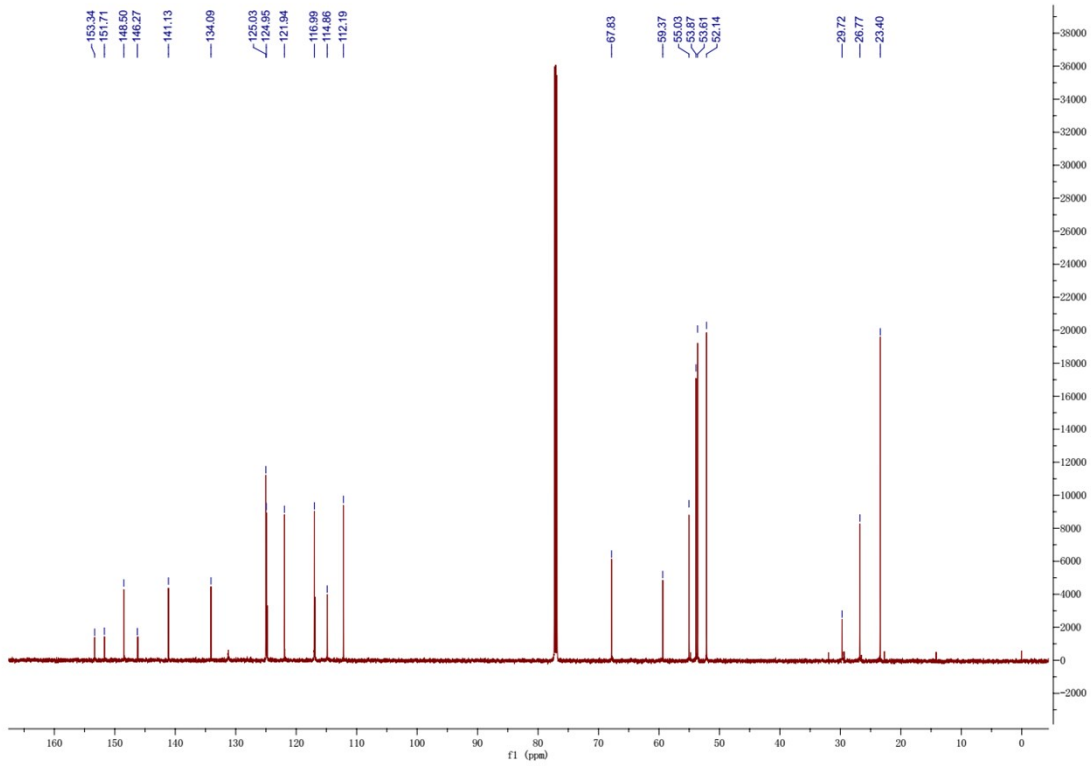
^{13}C-NMR of compound **3b**



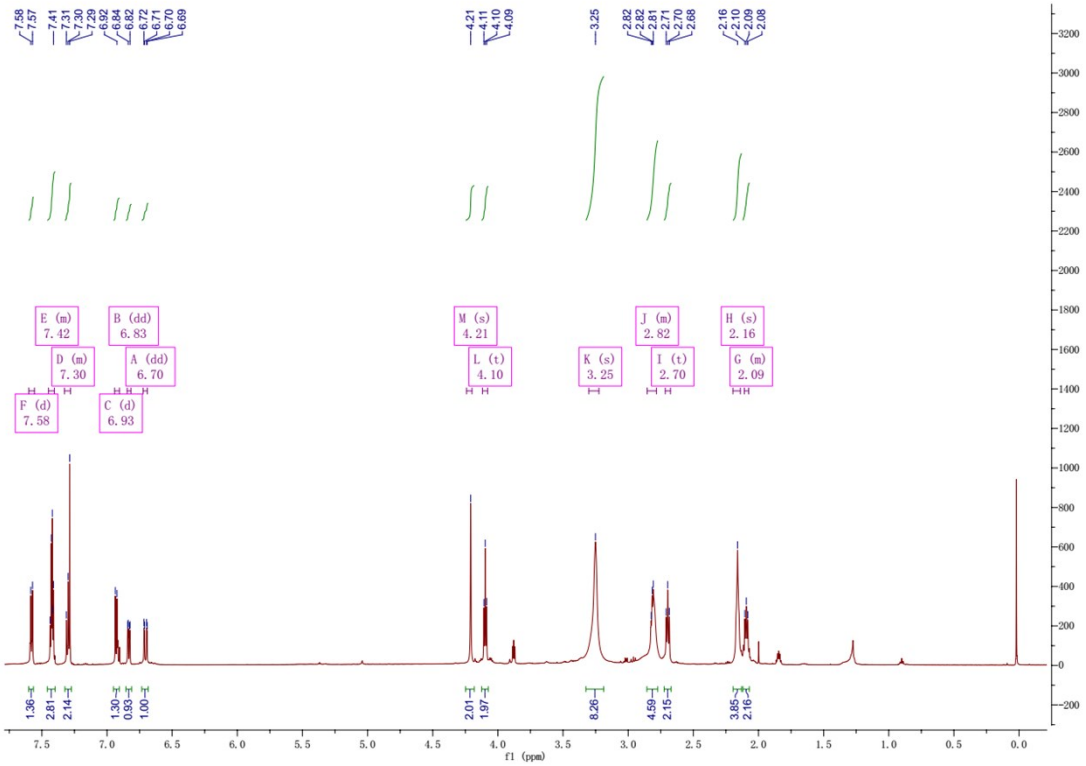
^{1}H-NMR of compound **3c**



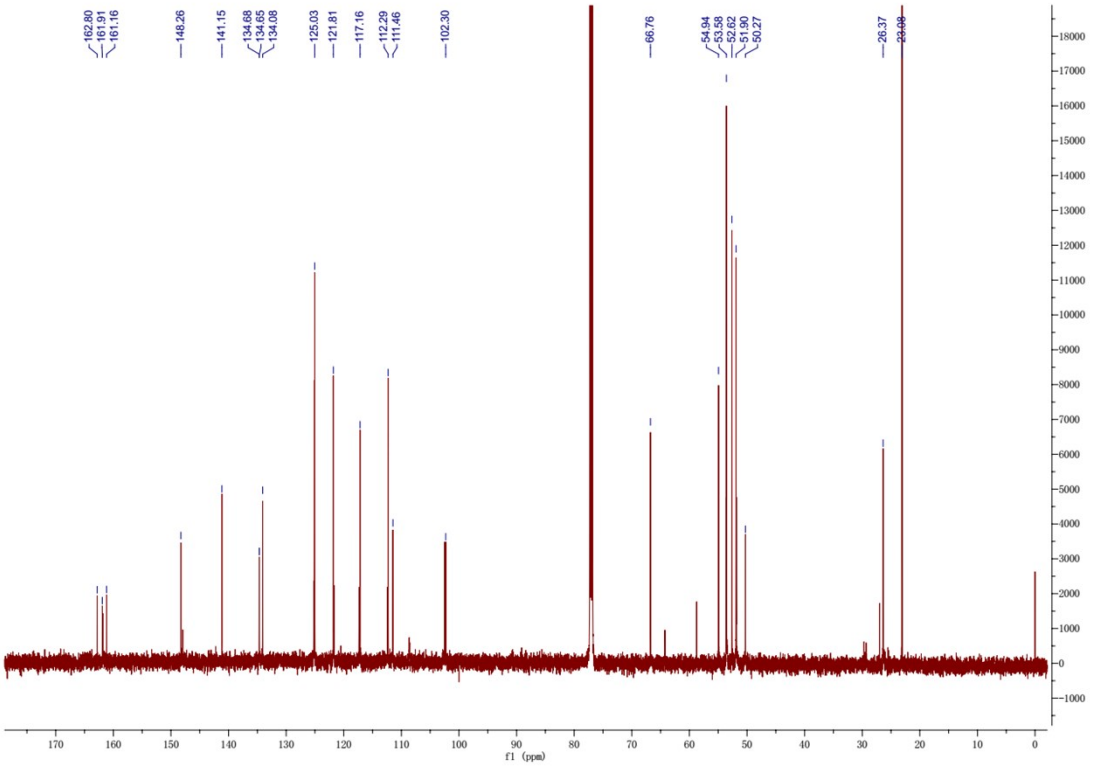
^{13}C-NMR of compound **3c**



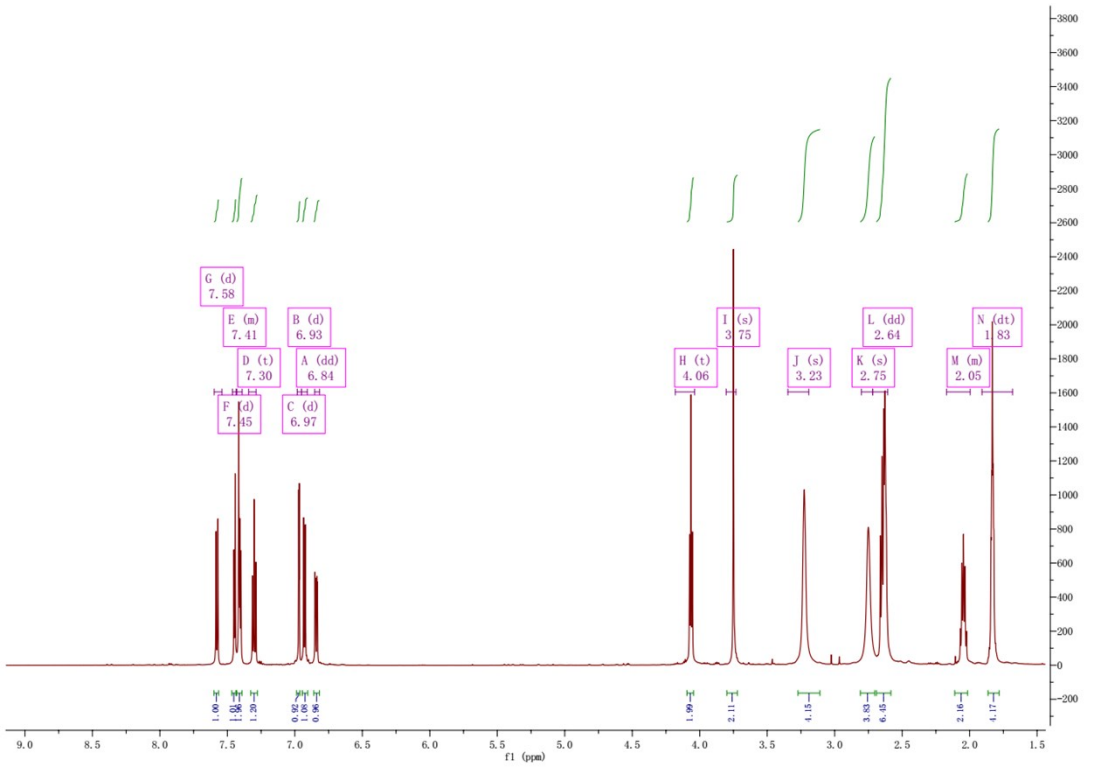
^{1}H-NMR of compound **3d**



^{13}C-NMR of compound **3d**



^{1}H-NMR of compound **3e**



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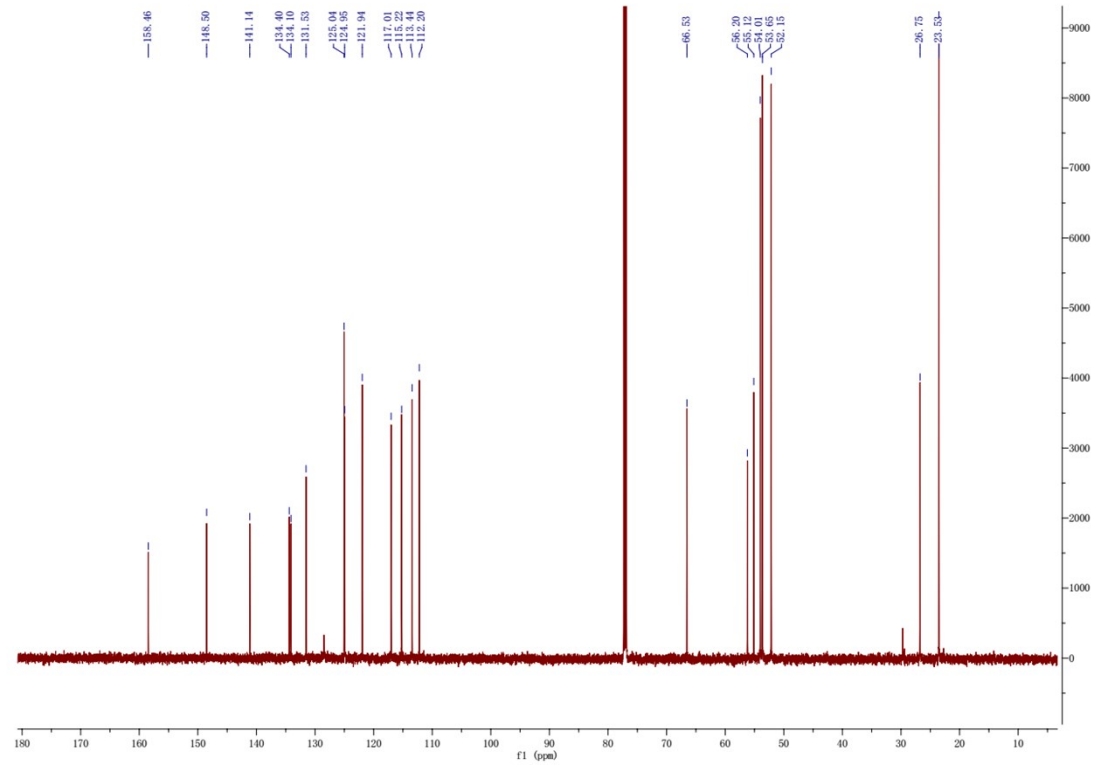

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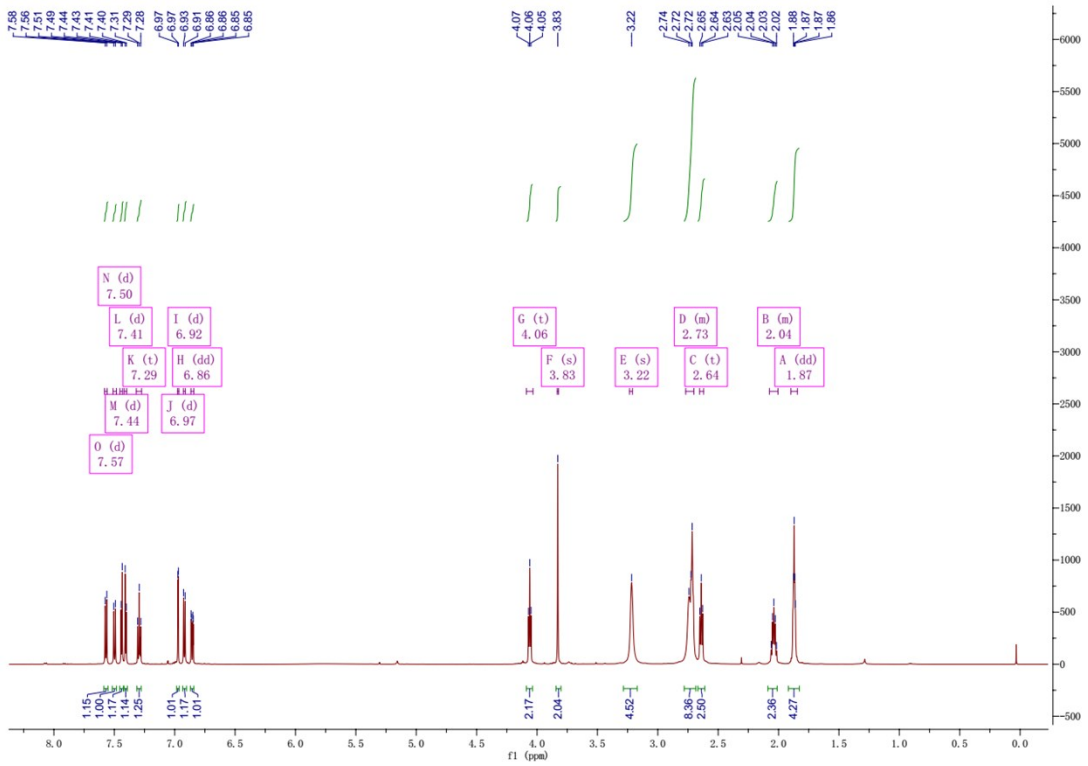
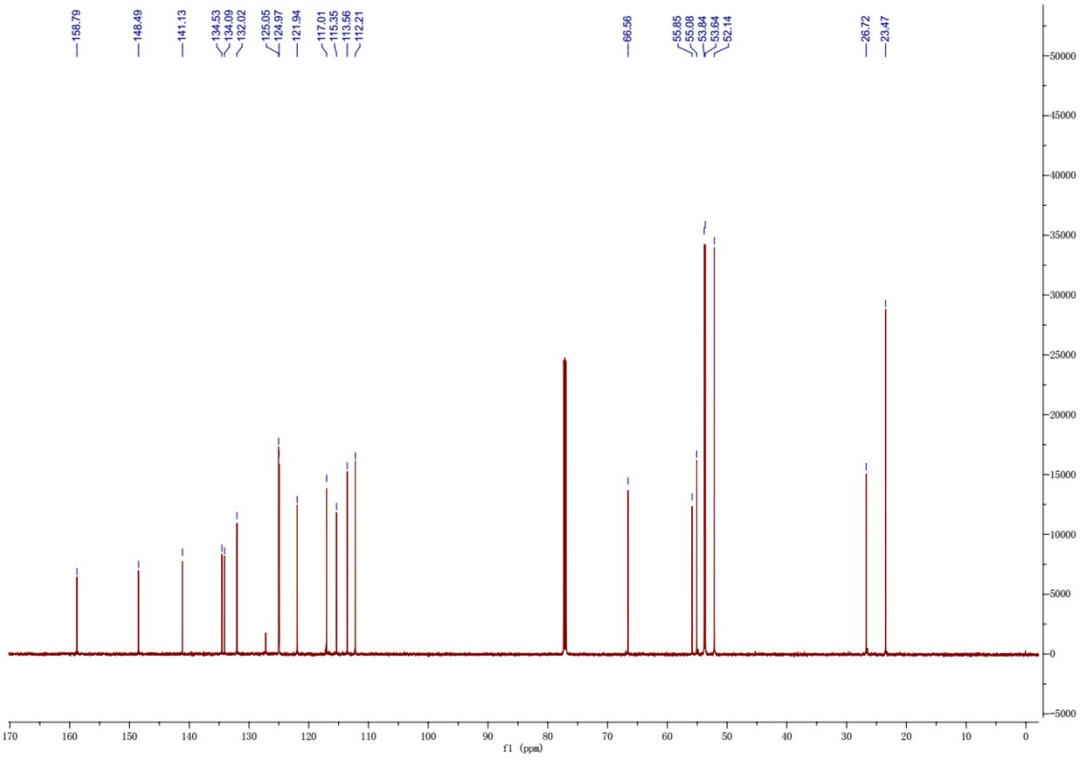
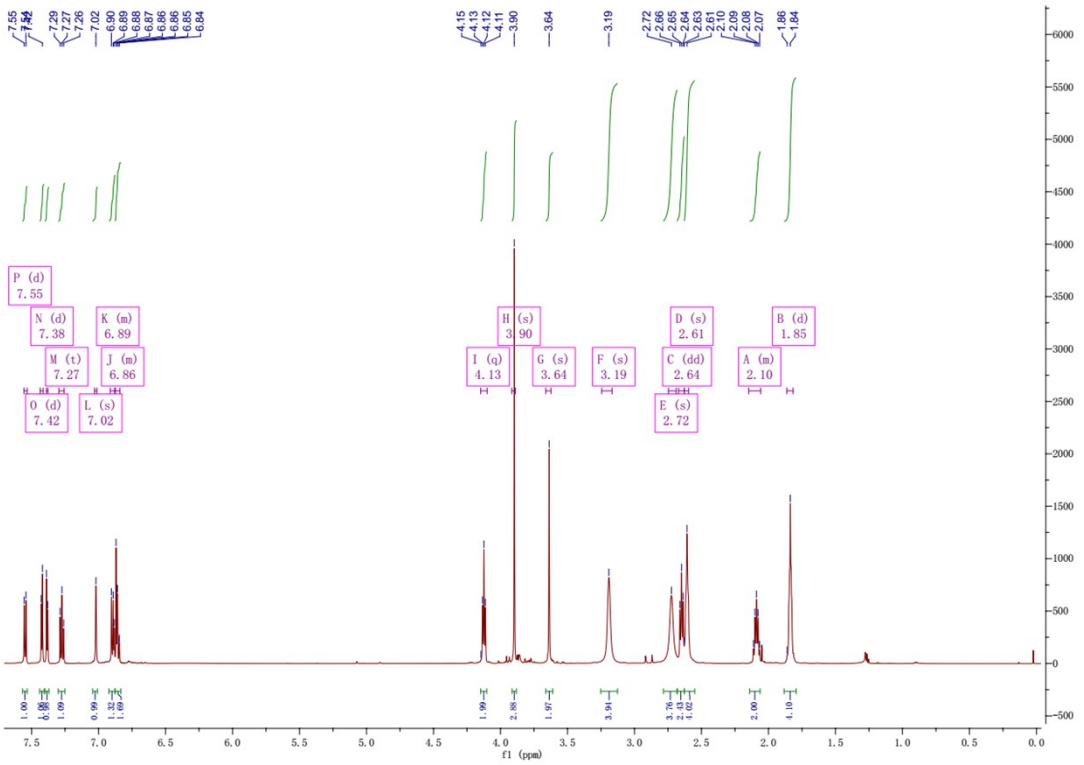


^{13}C-NMR of compound **3f**



^{1}H-NMR of compound **3g**



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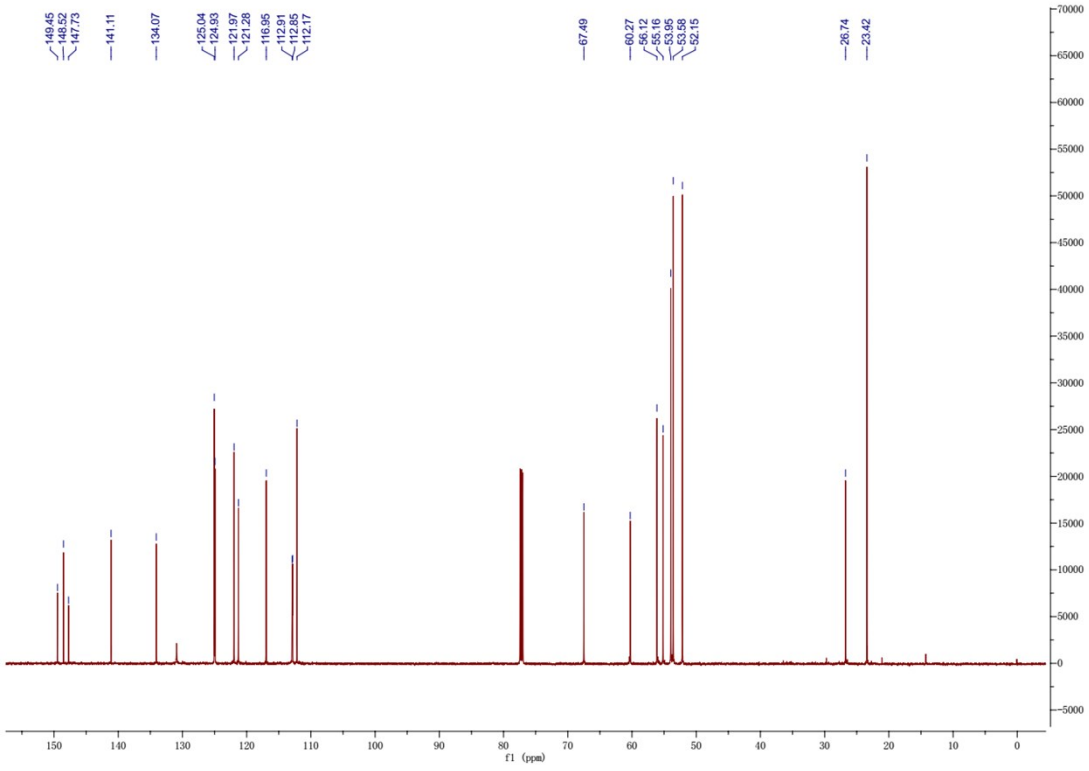
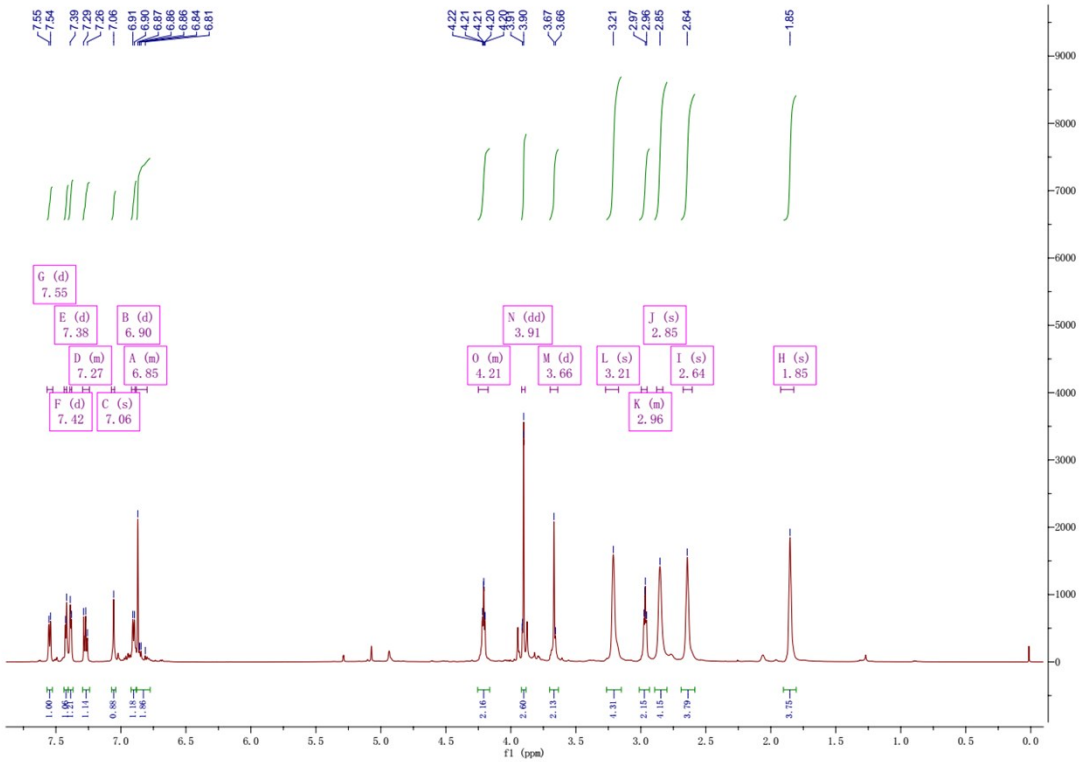


^{1}H-NMR of compound **3h**



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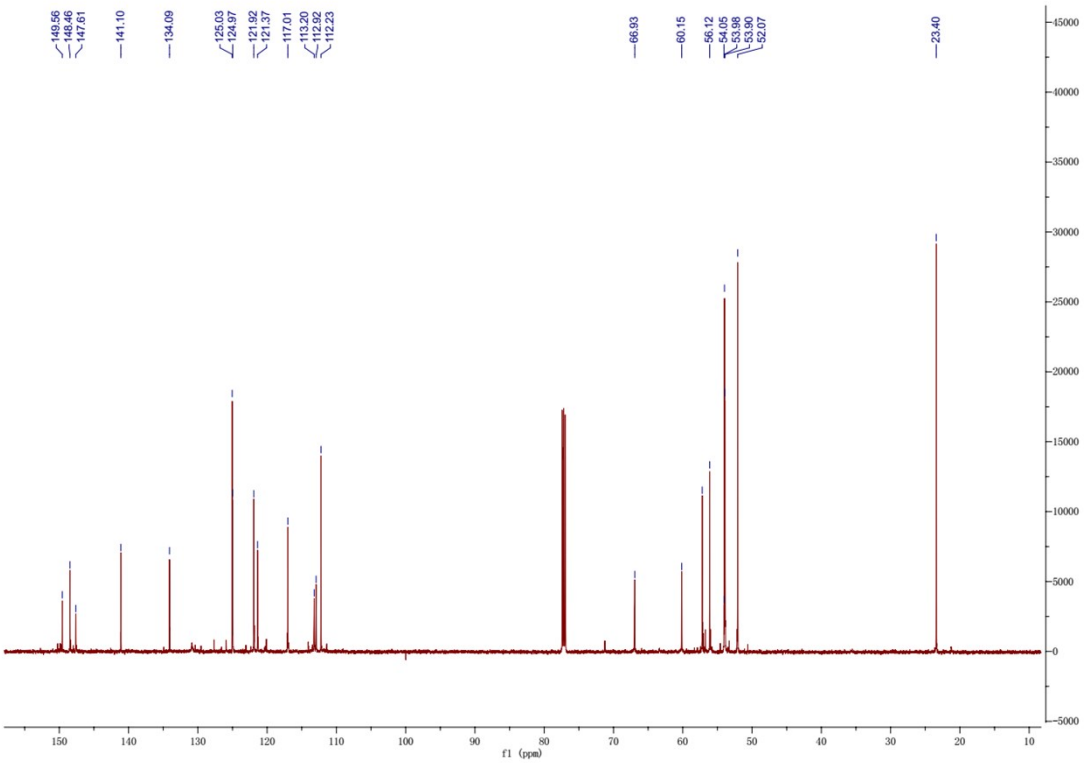
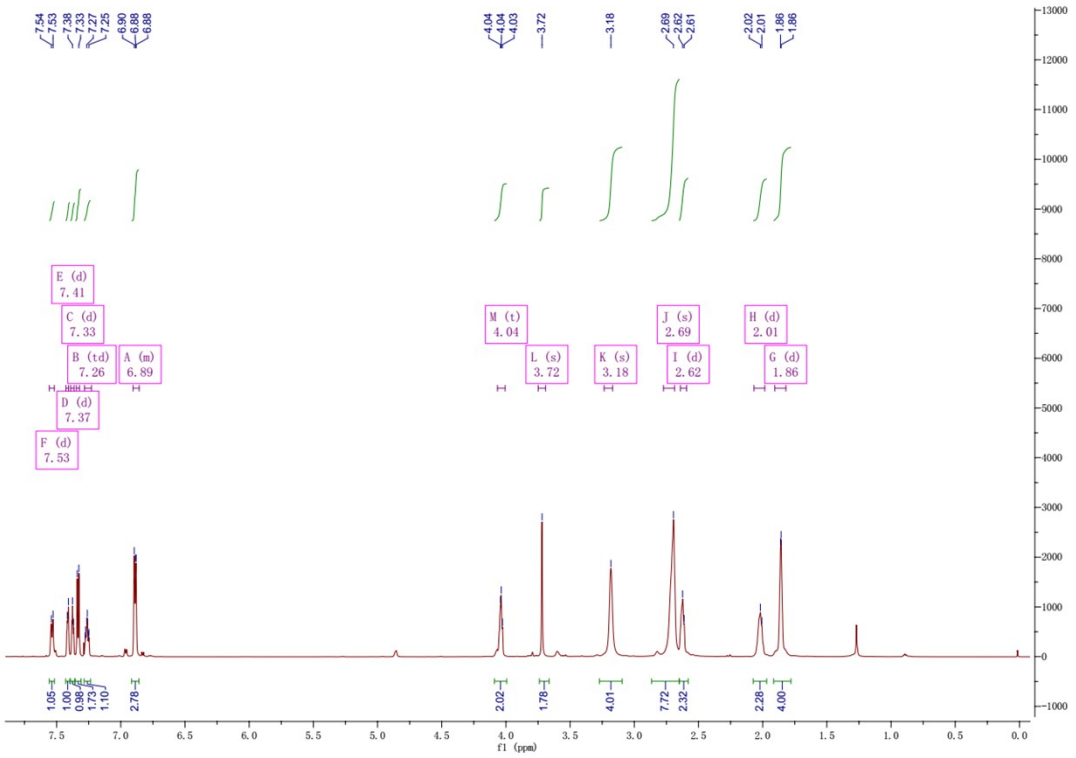


^{1}H-NMR of compound **3i**



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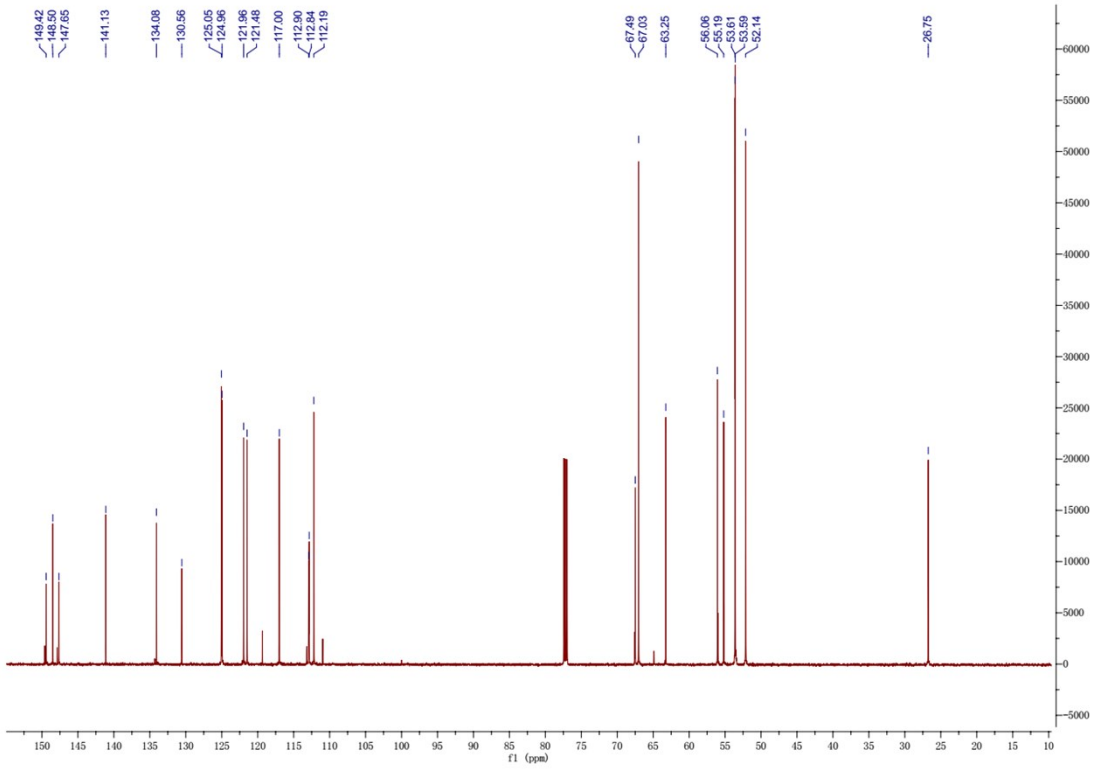

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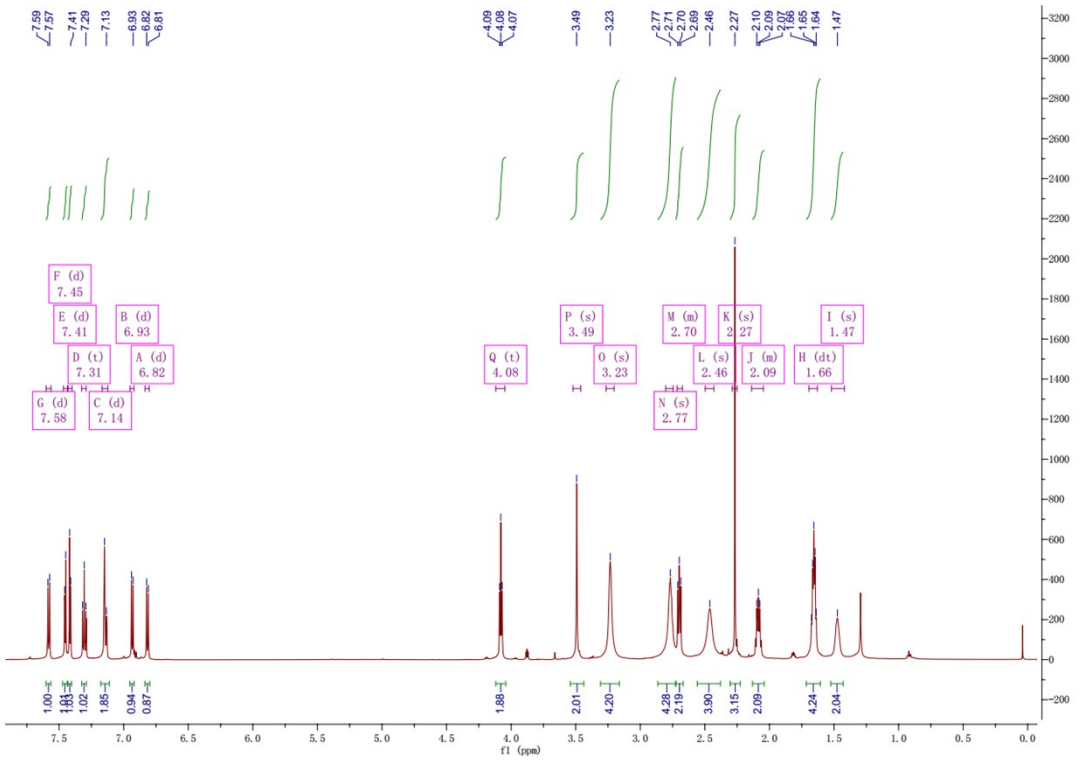
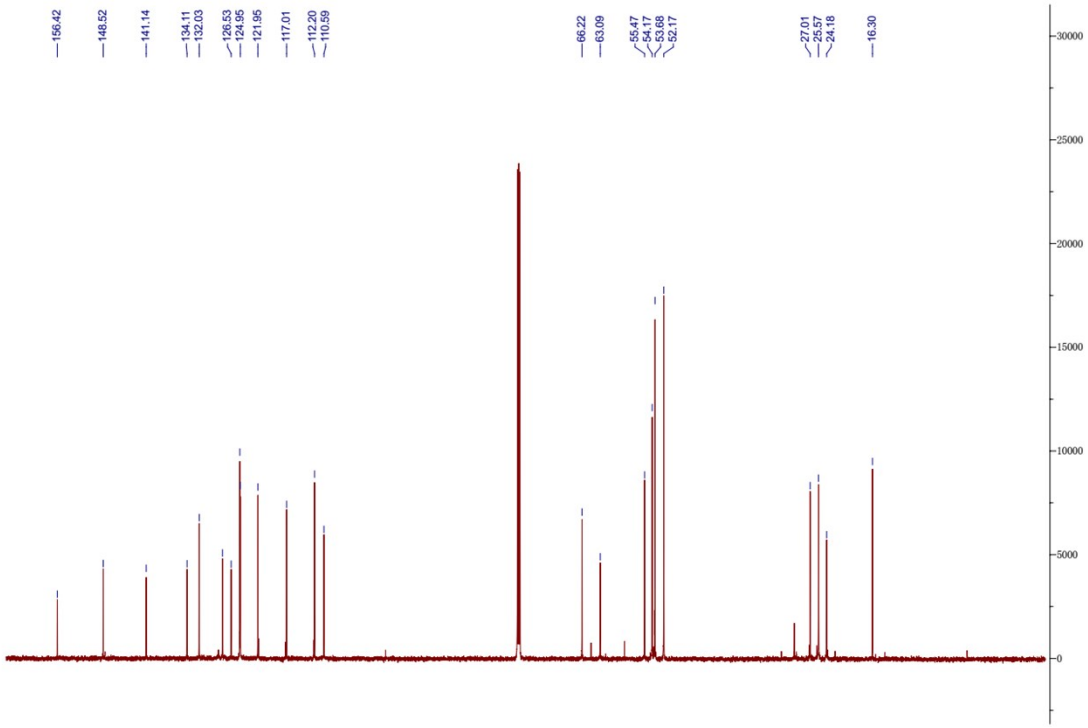
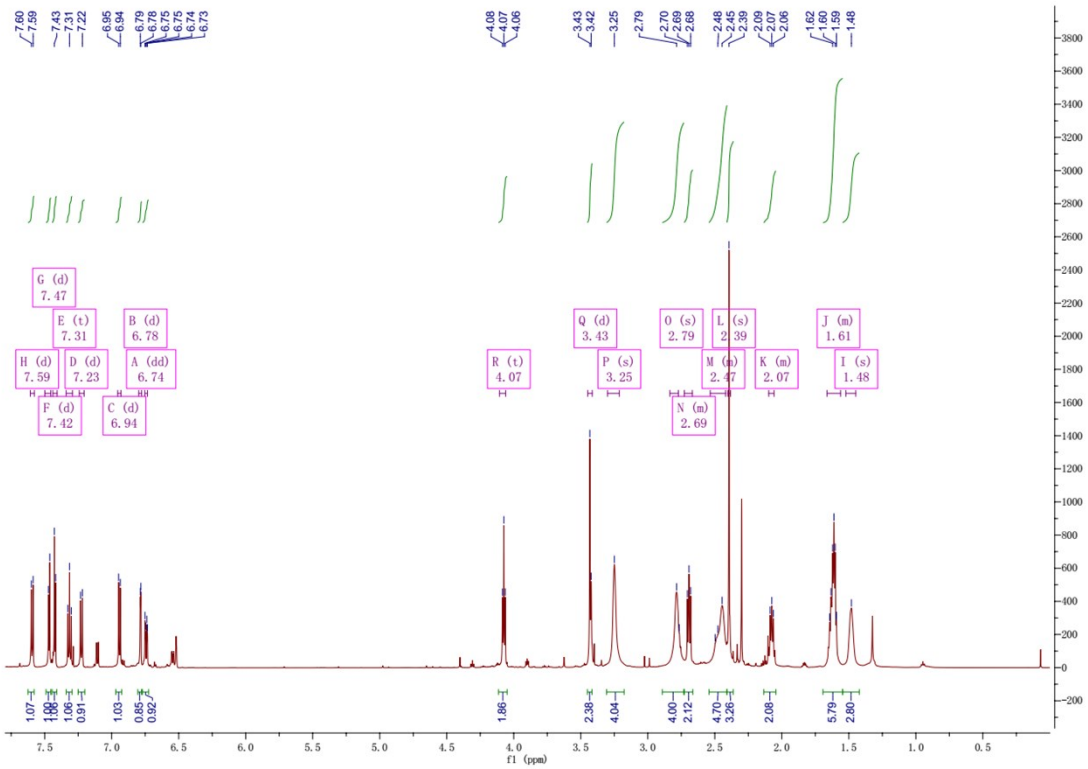


^{13}C-NMR of compound **3j**



^{1}H-NMR of compound **3k**



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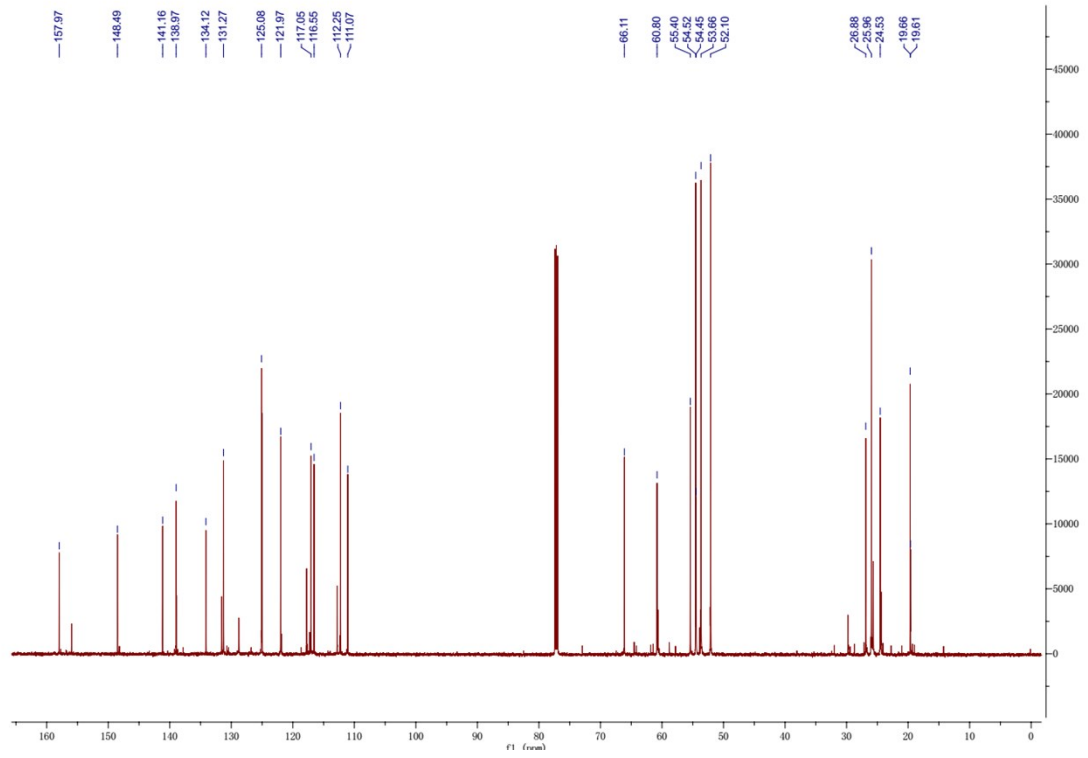
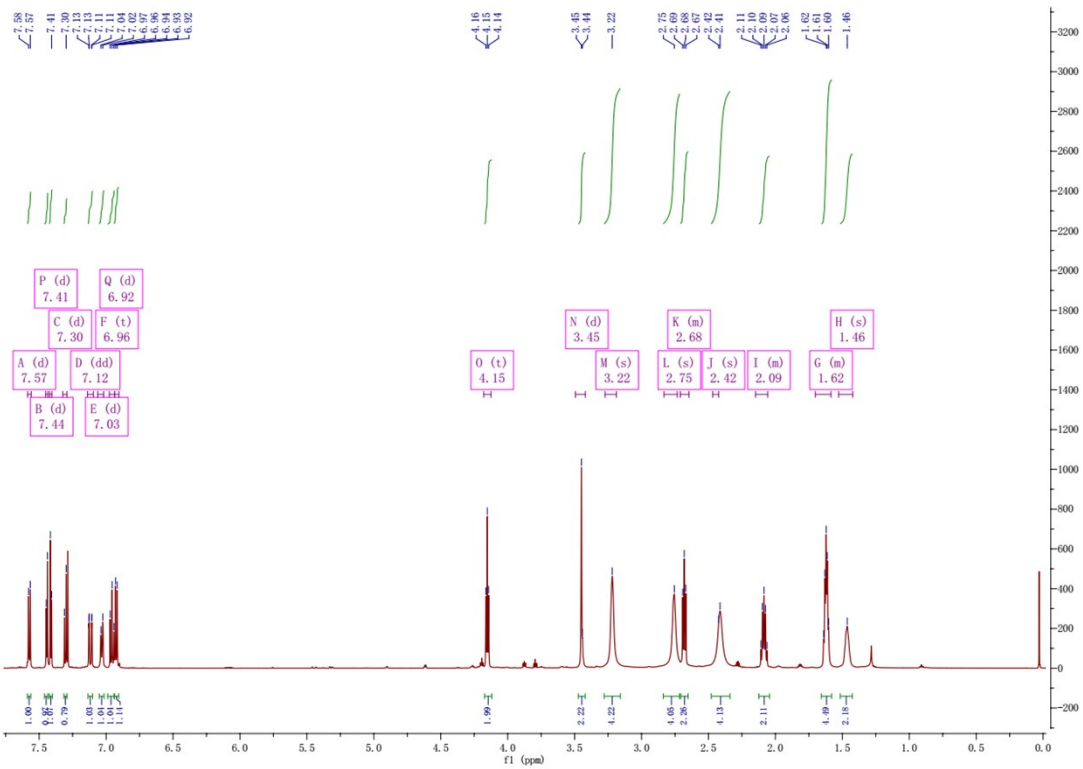
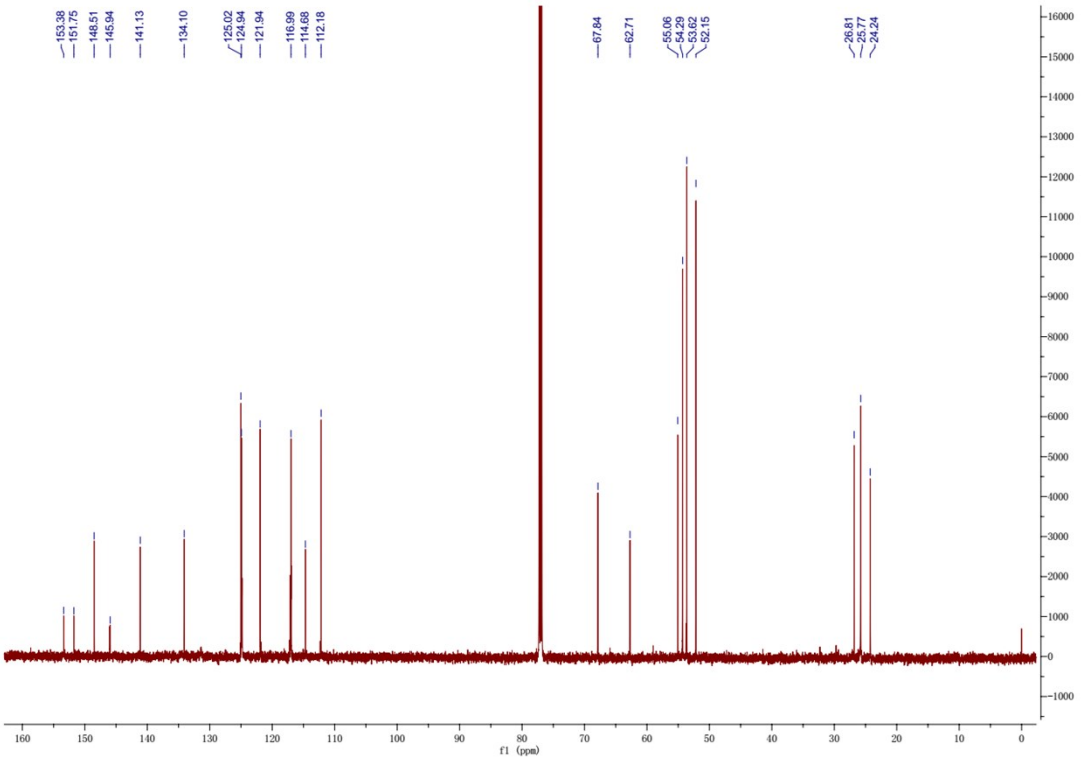


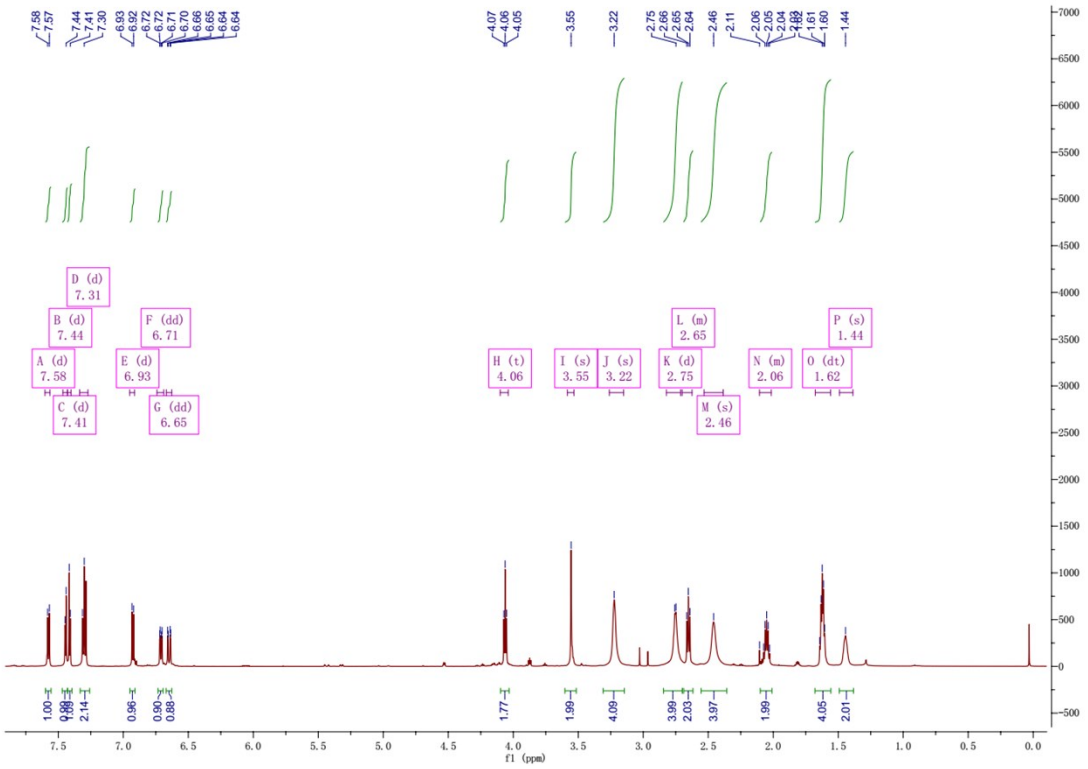
^{1}H-NMR of compound **3l**



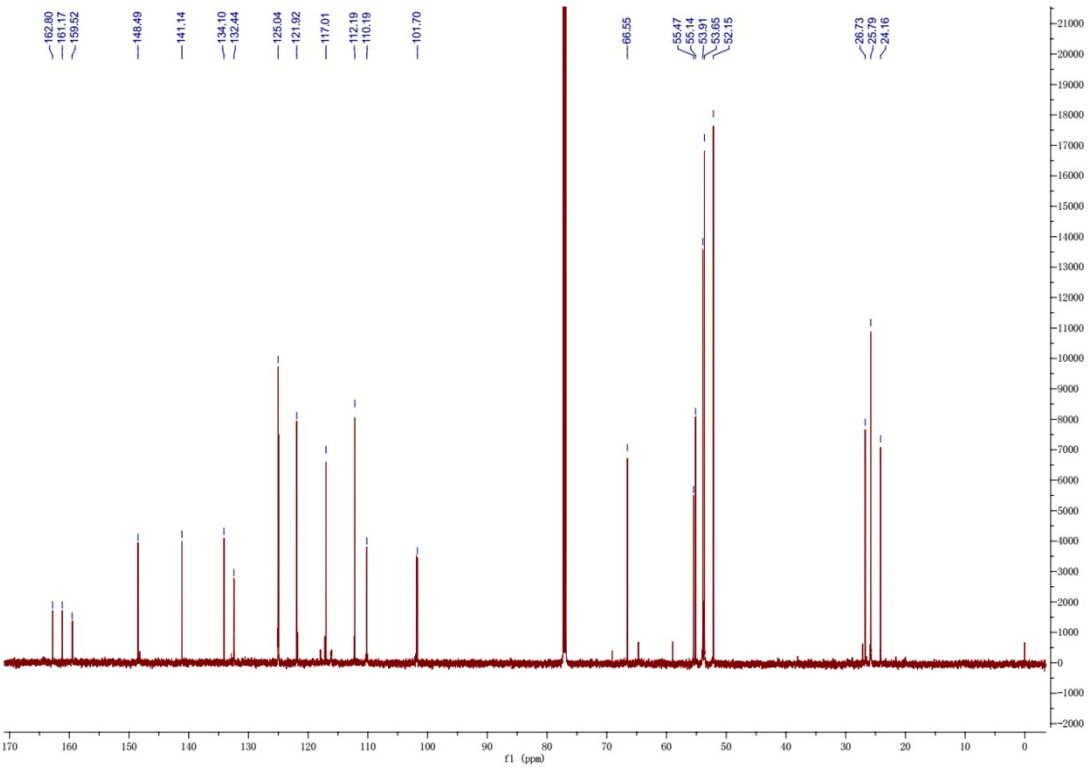
^{13}C-NMR of compound **3l**



^{1}H-NMR of compound **3m**



^{13}C-NMR of compound **3m**



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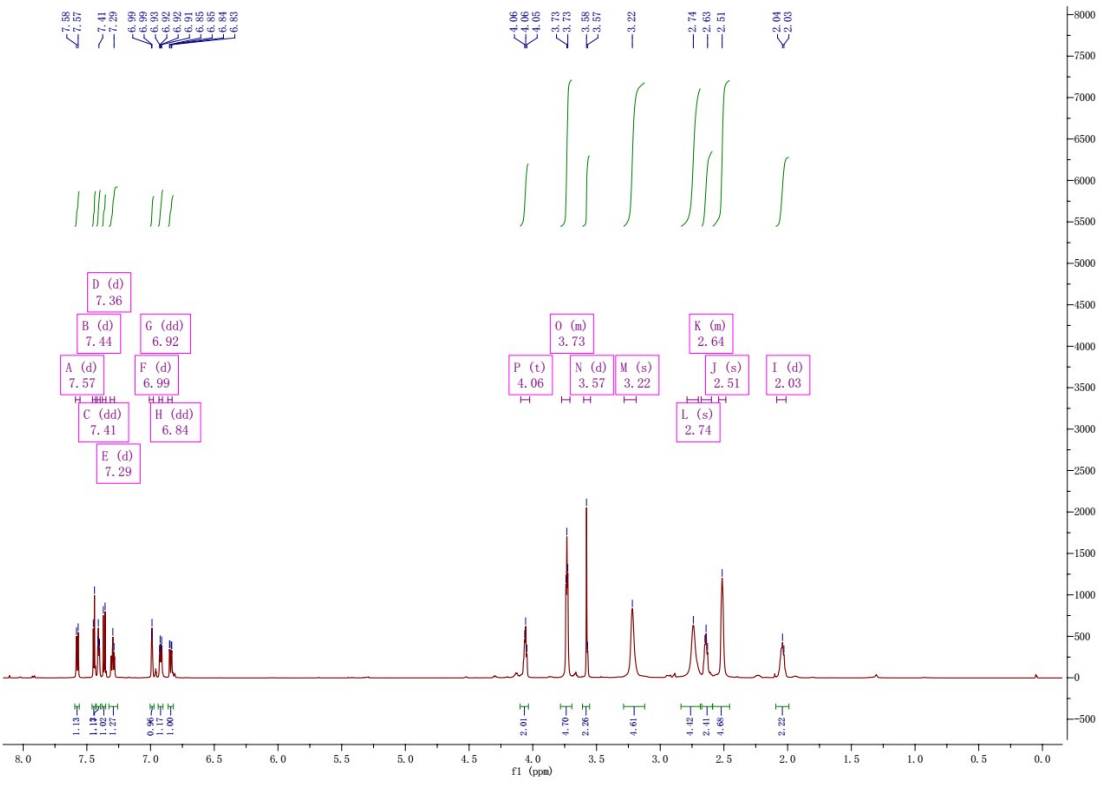

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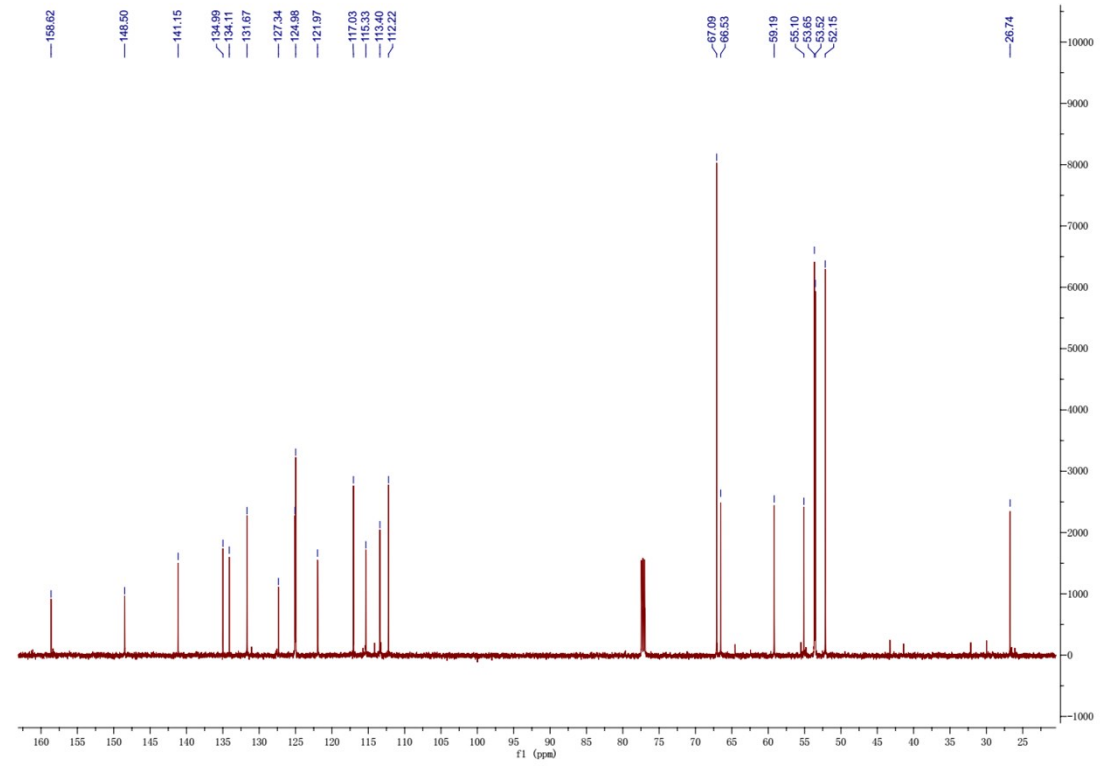
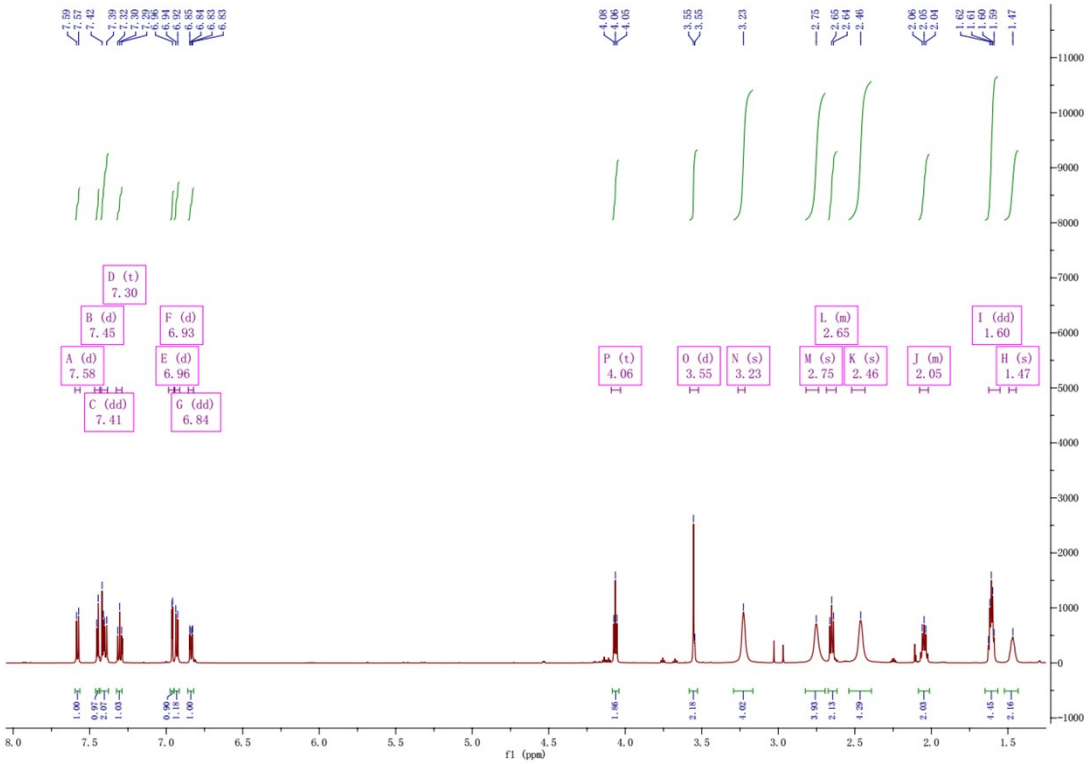
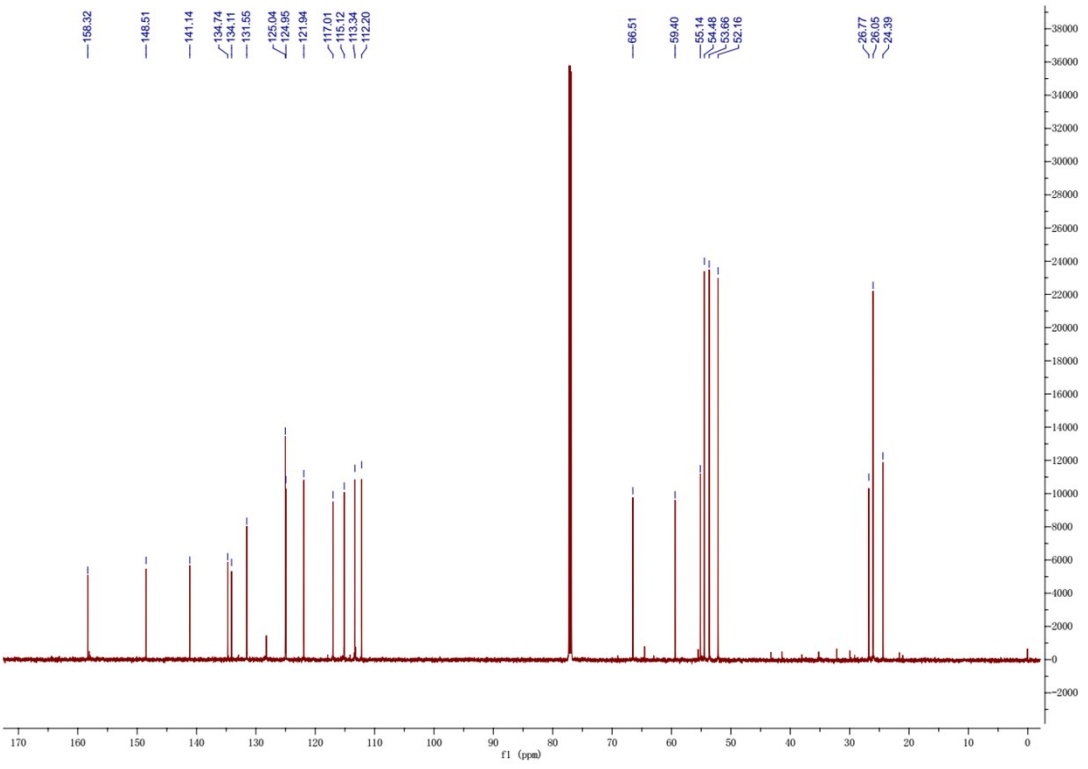


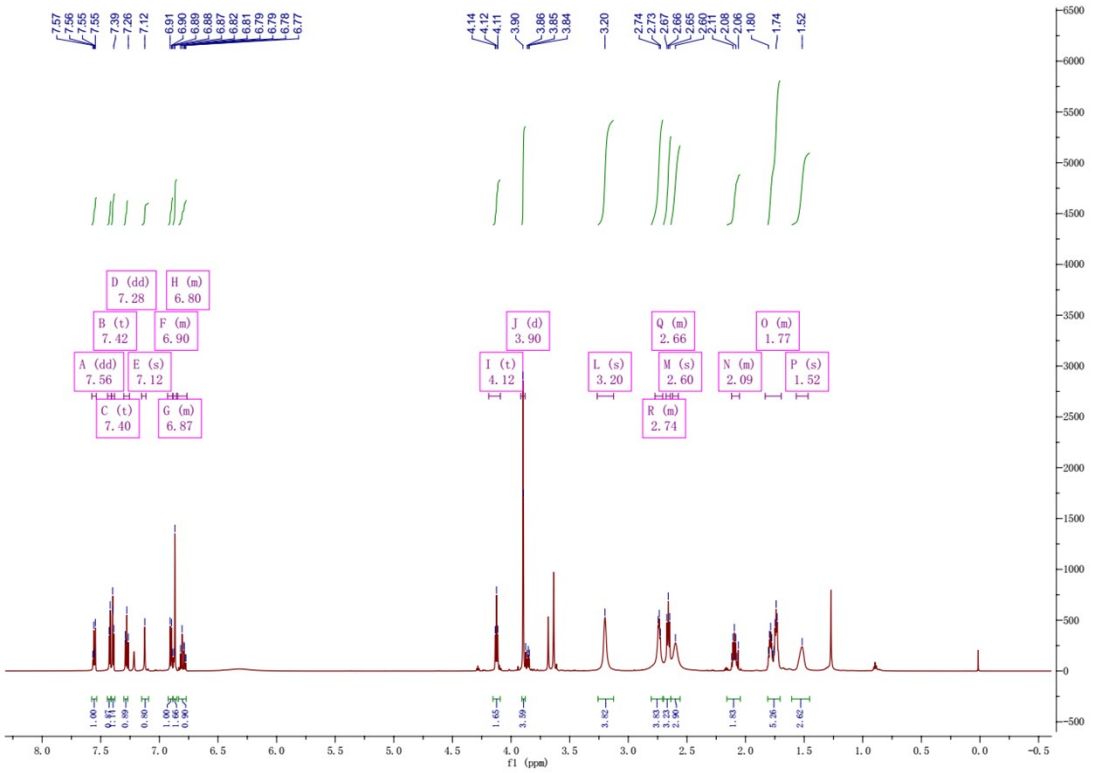
^{1}H-NMR of compound **3o**



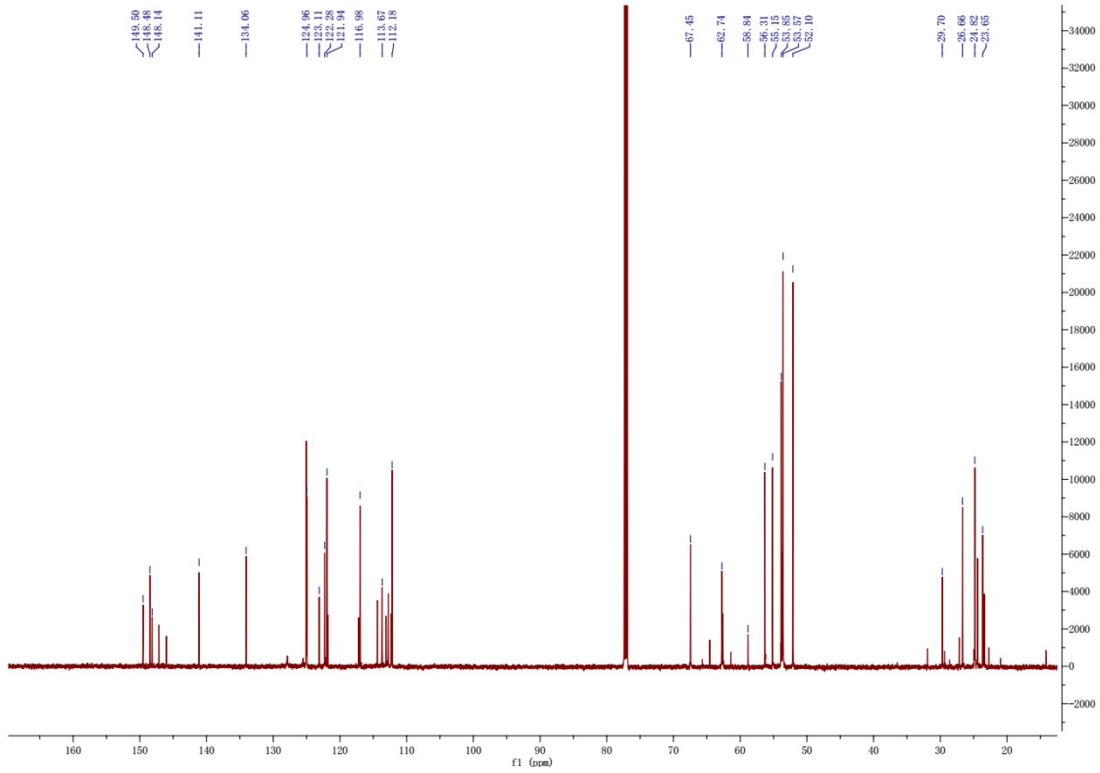
^{13}C-NMR of compound **3o**



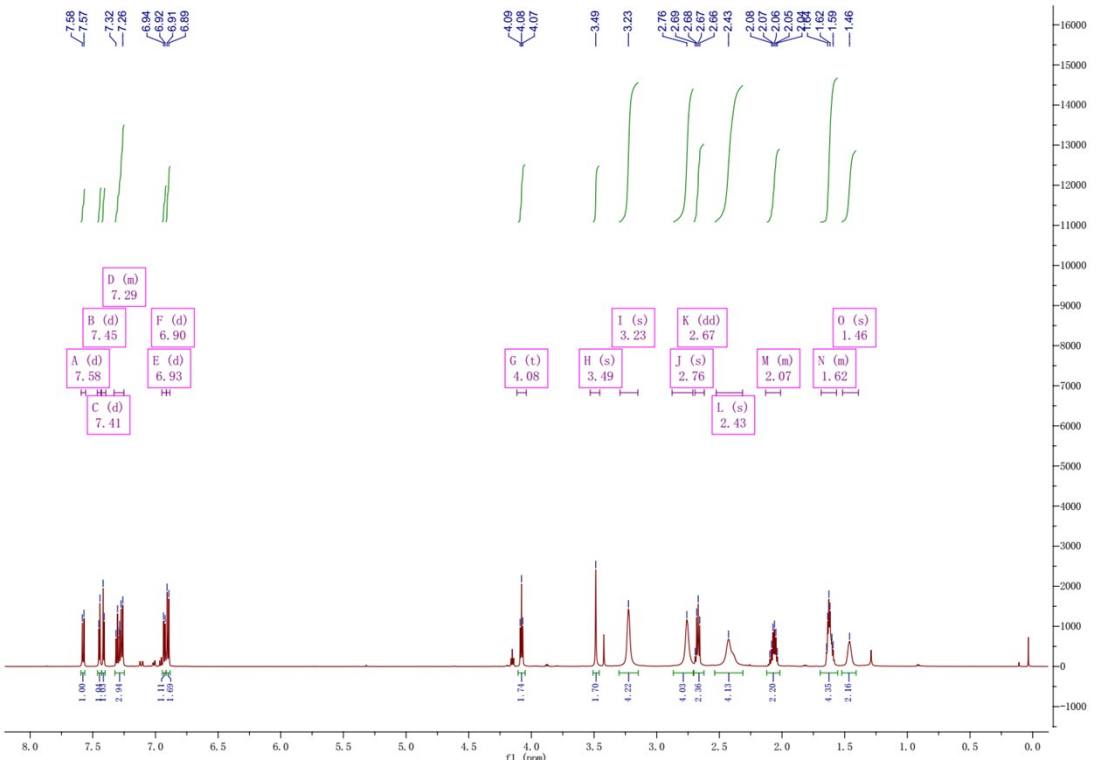
^{1}H-NMR of compound **3p**



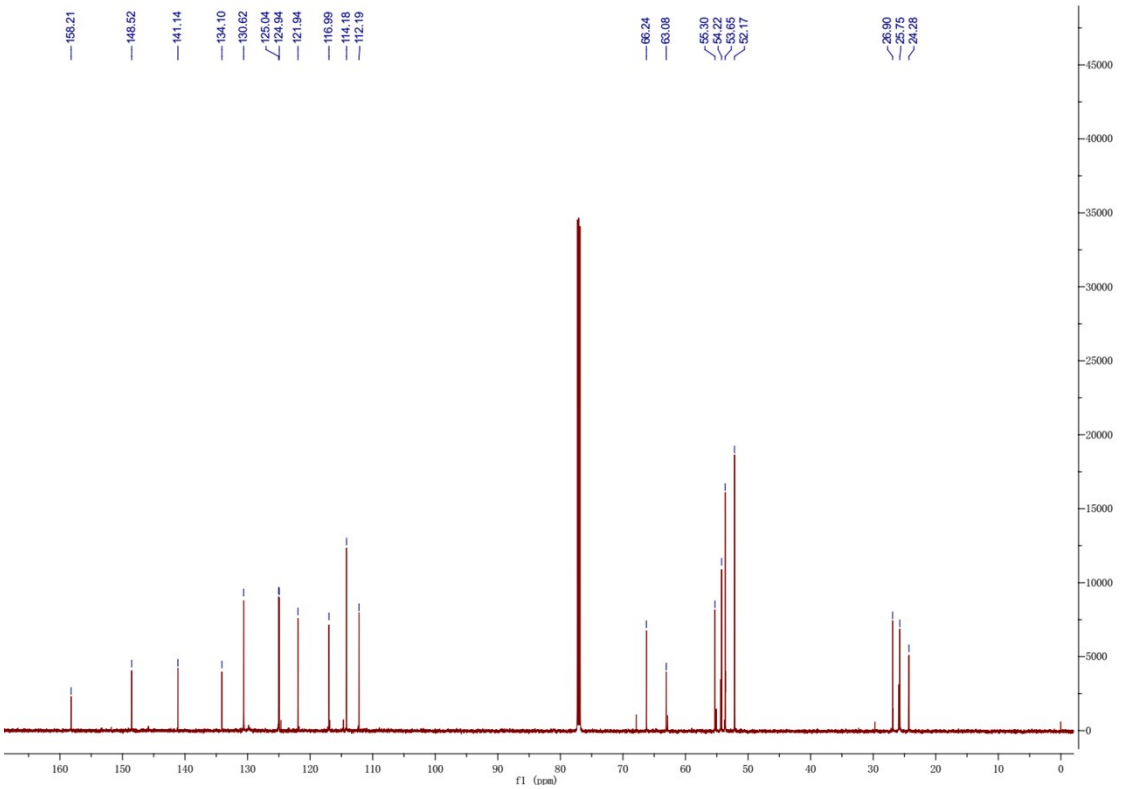
^{13}C-NMR of compound **3p**



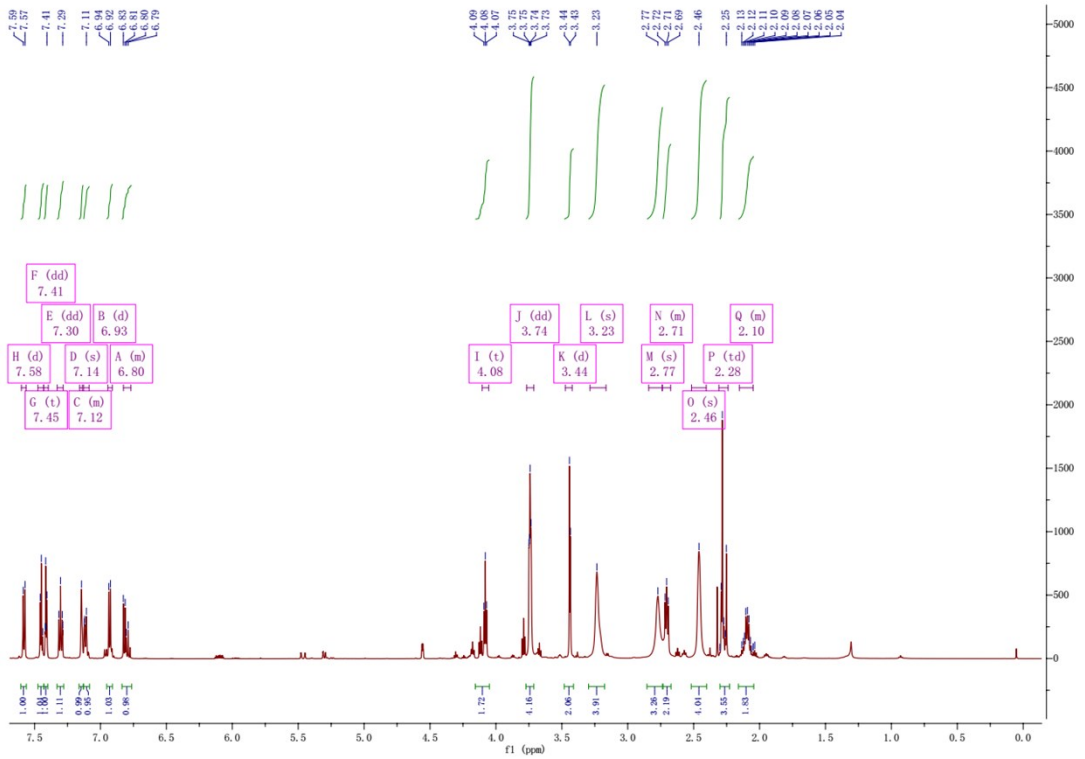
^{1}H-NMR of compound **3q**



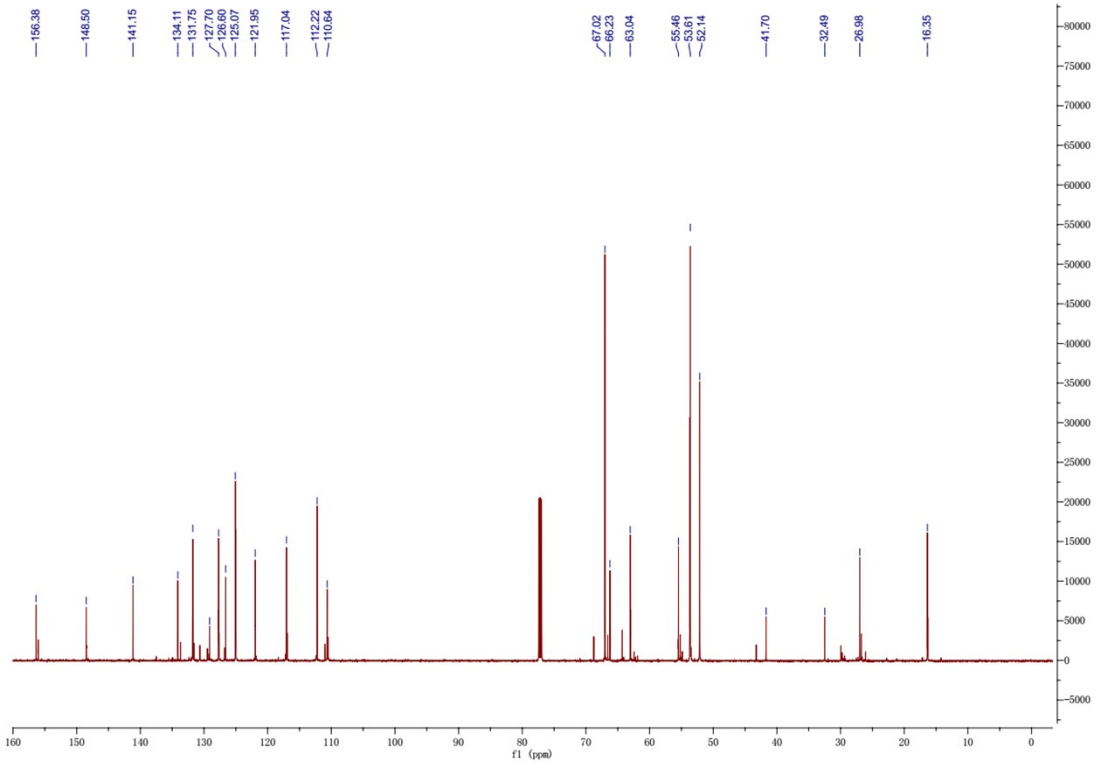
^{13}C-NMR of compound **3q**



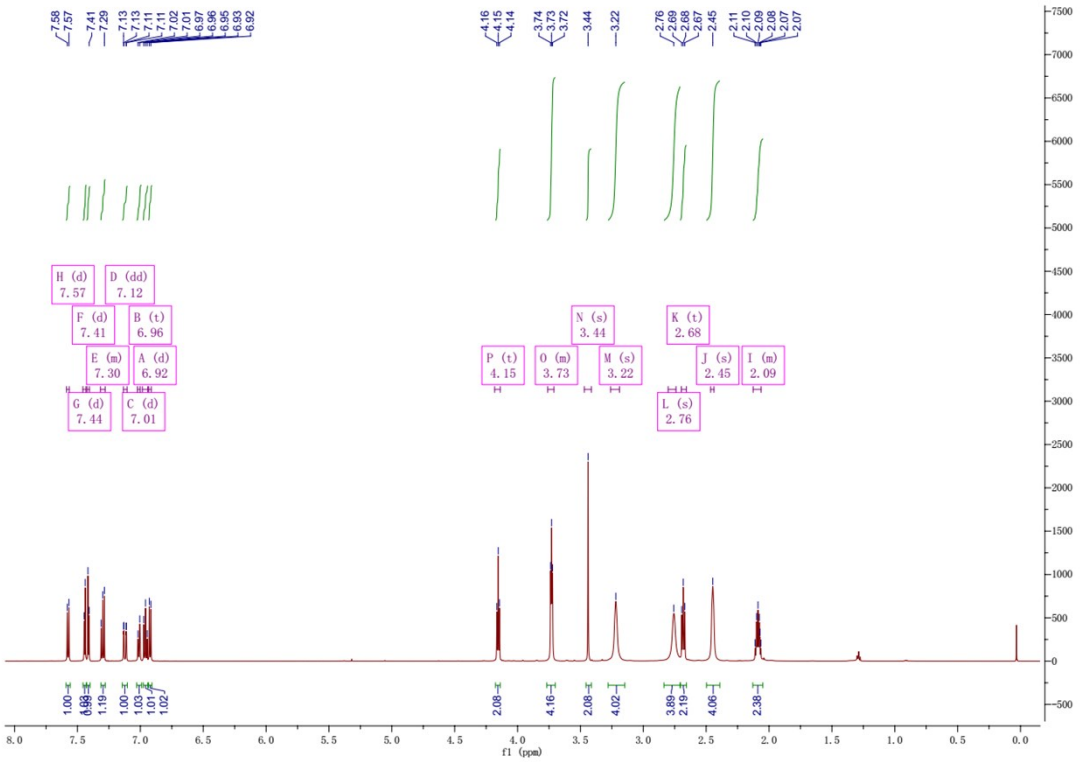
^{1}H-NMR of compound **3r**



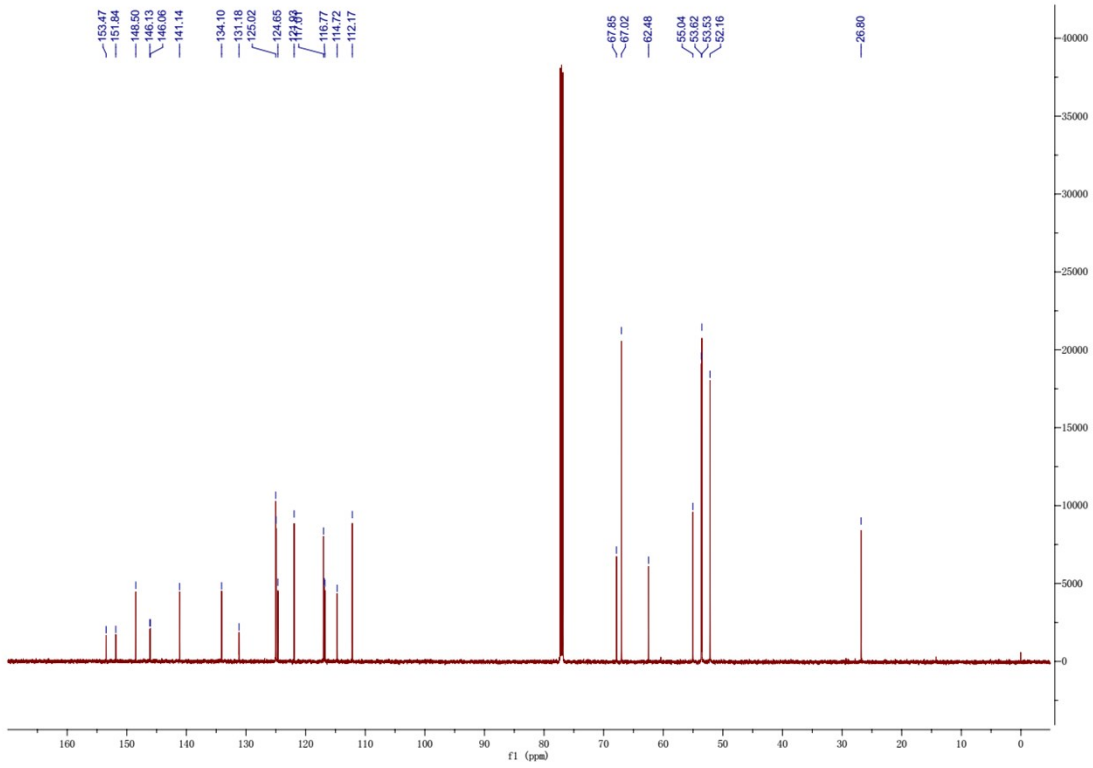
^{13}C-NMR of compound **3r**



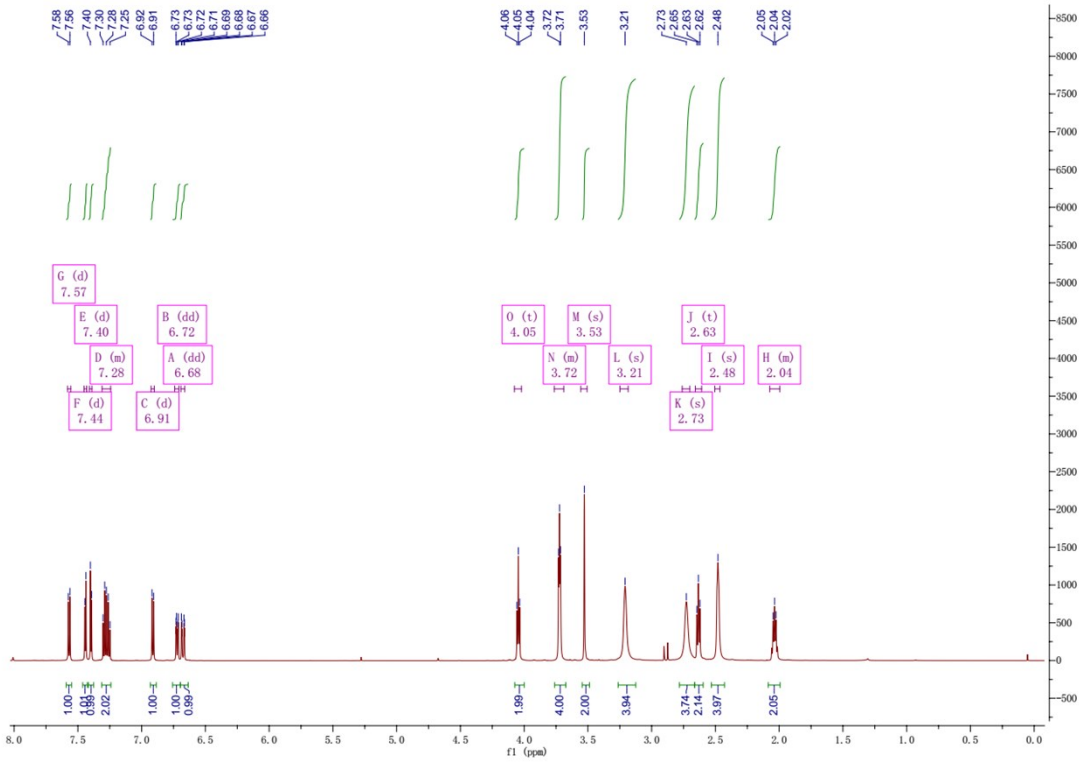
^{1}H-NMR of compound **3s**



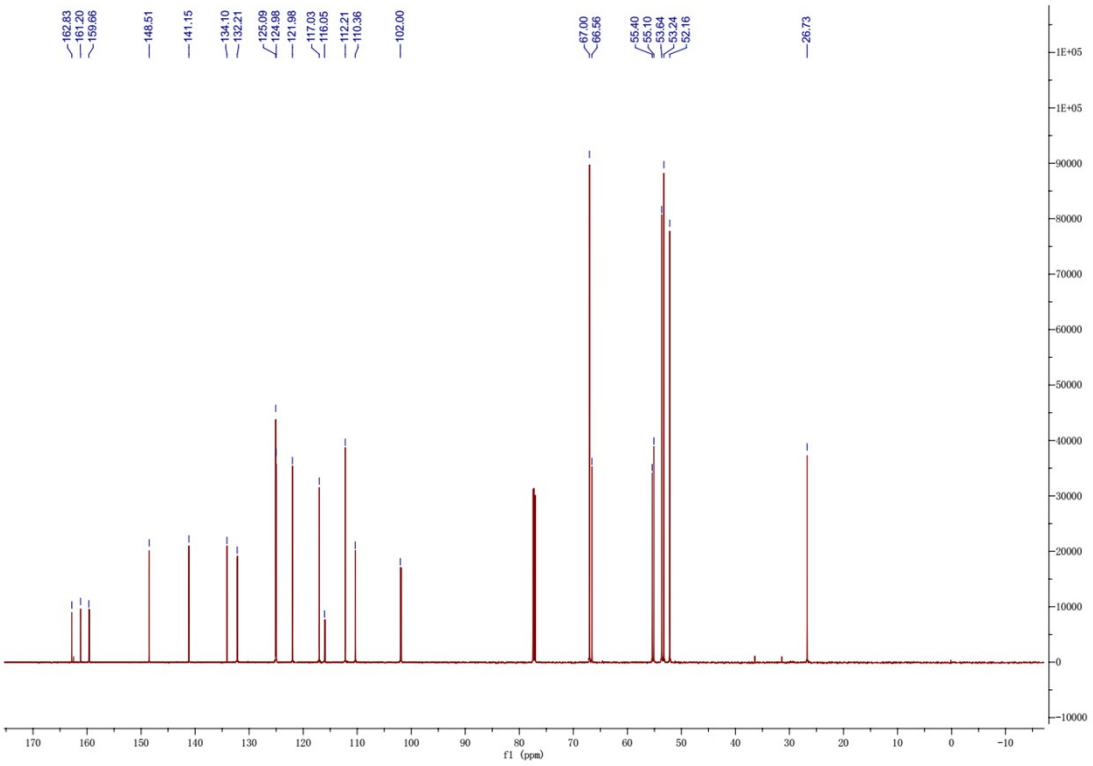
^{13}C-NMR of compound **3s**



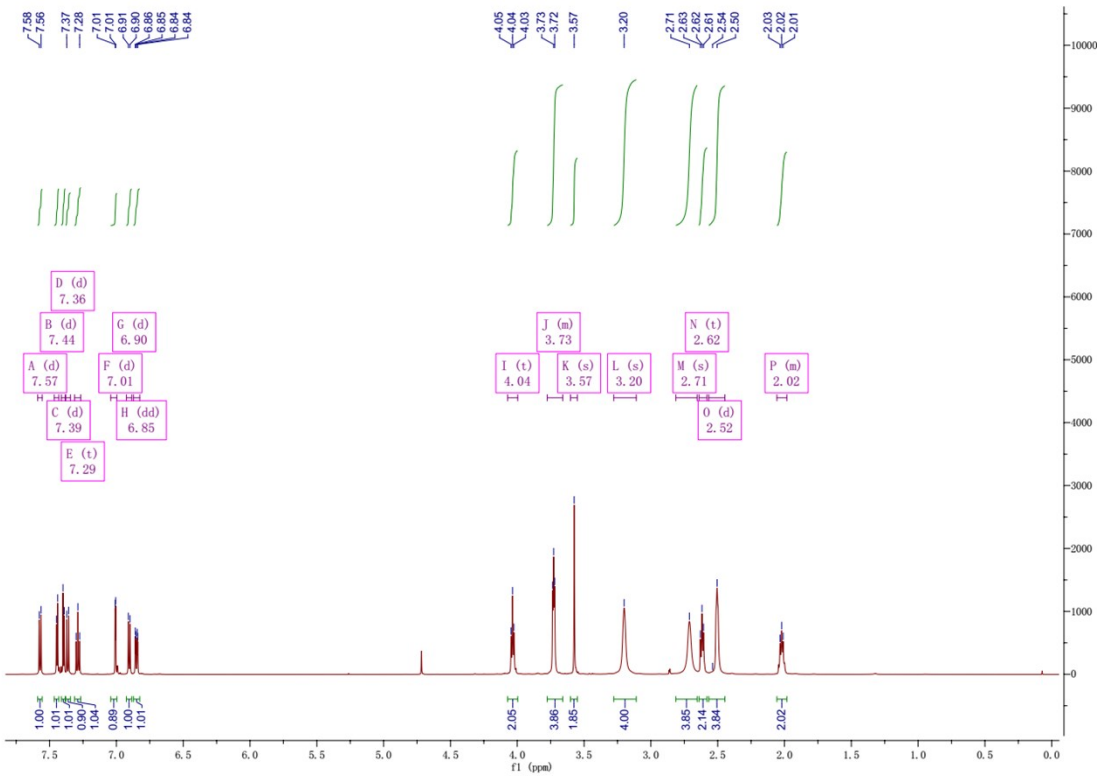
^{1}H-NMR of compound **3t**



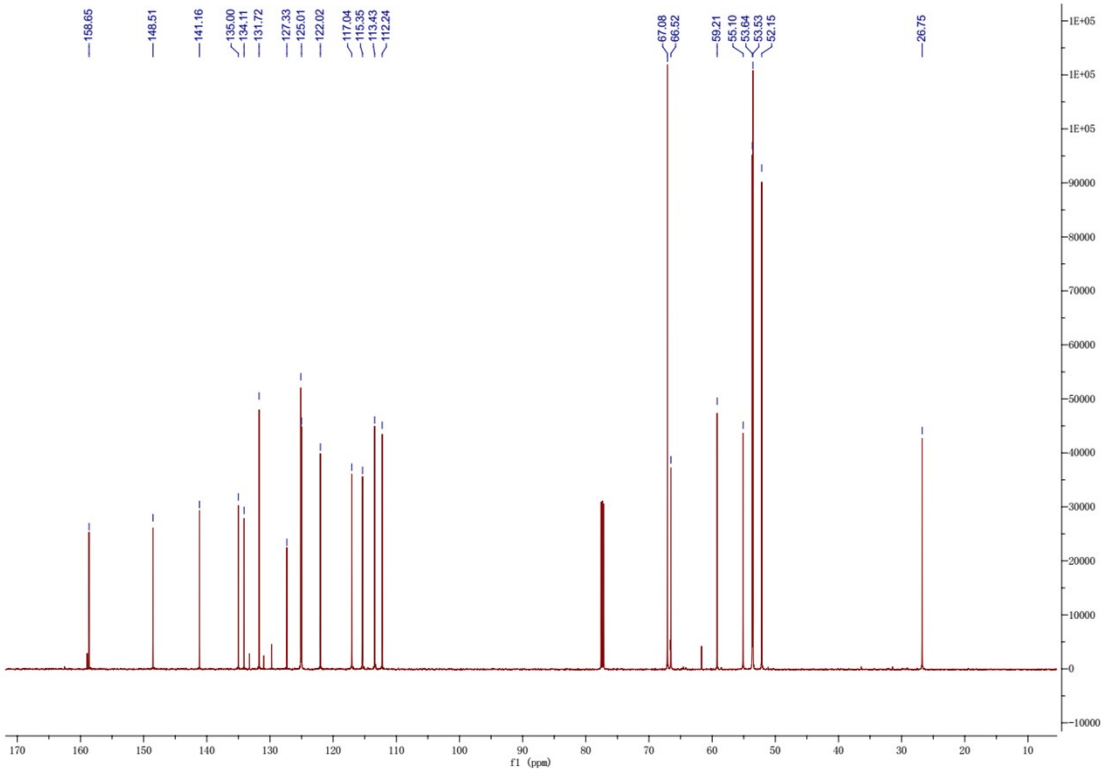
^{13}C-NMR of compound **3t**



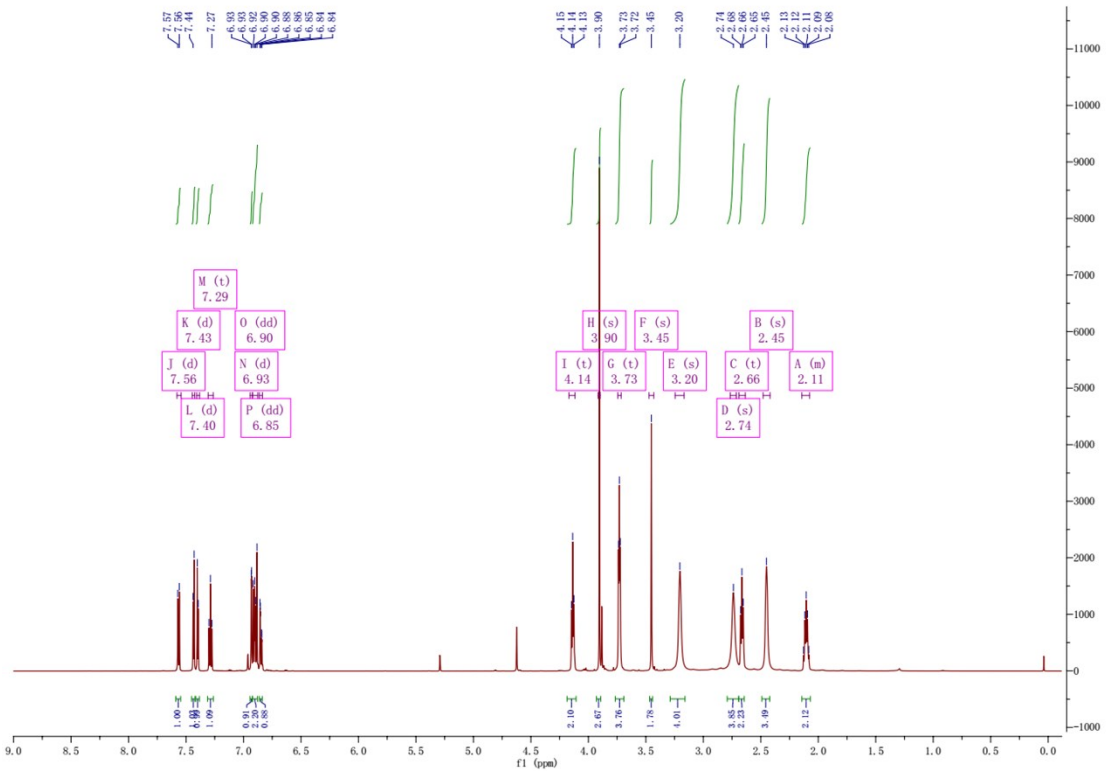
^{1}H-NMR of compound **3u**



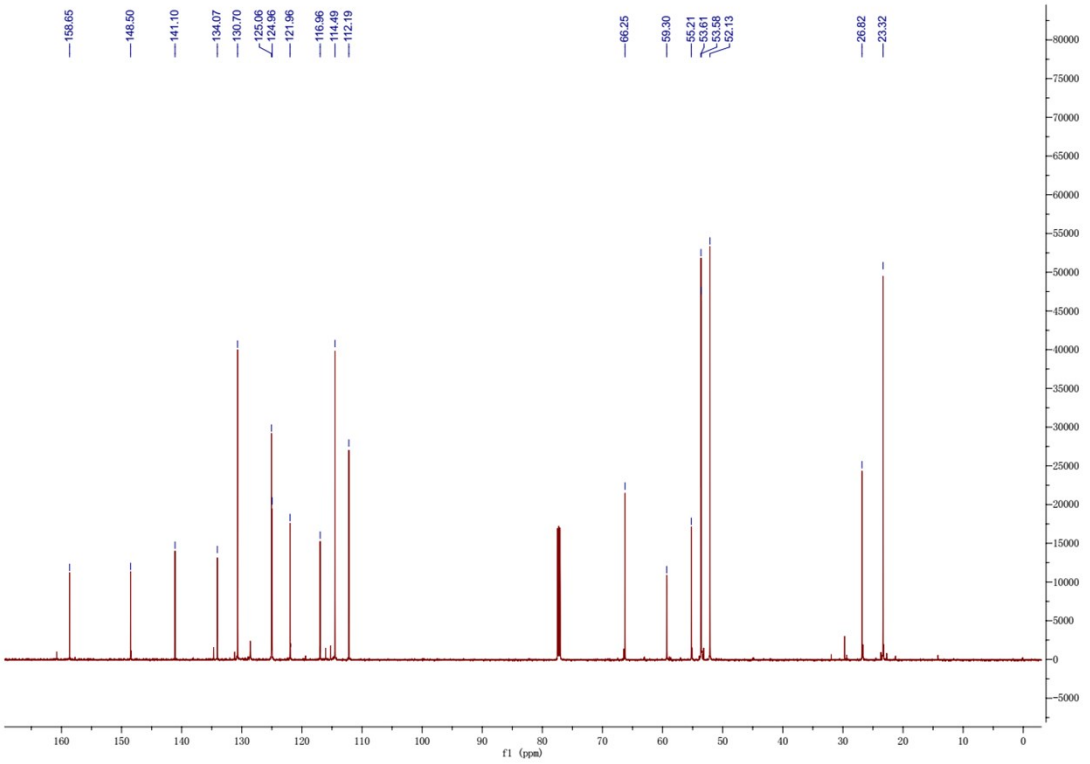
^{13}C-NMR of compound **3u**



^{1}H-NMR of compound **3v**

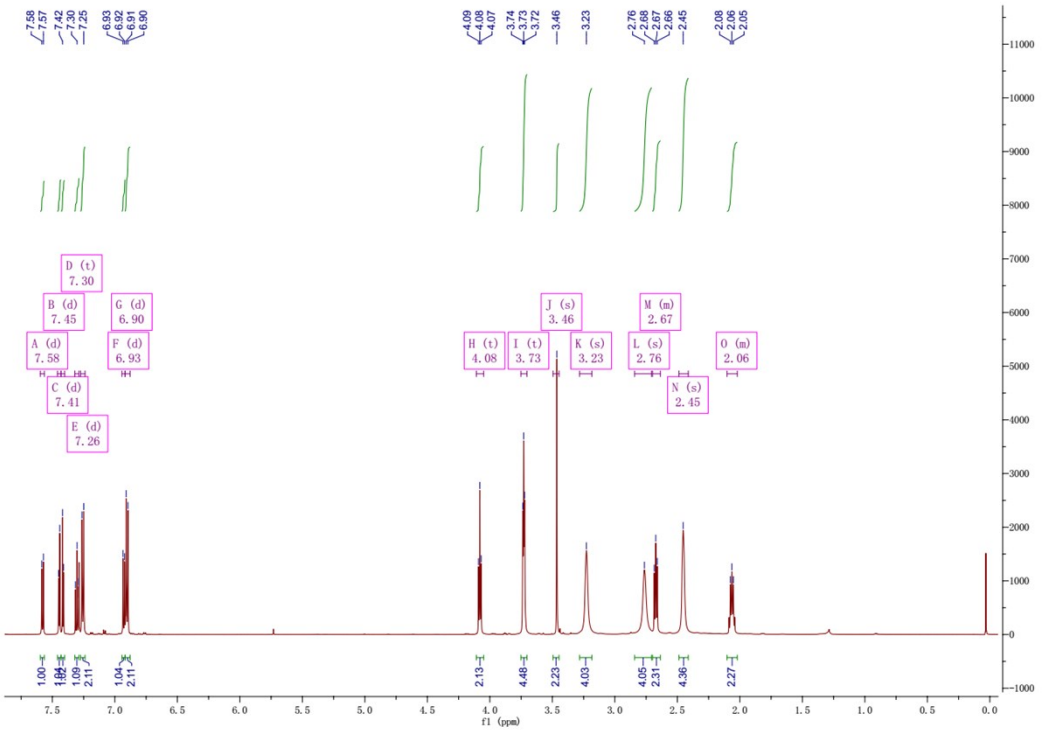


^{13}C-NMR of compound **3v**

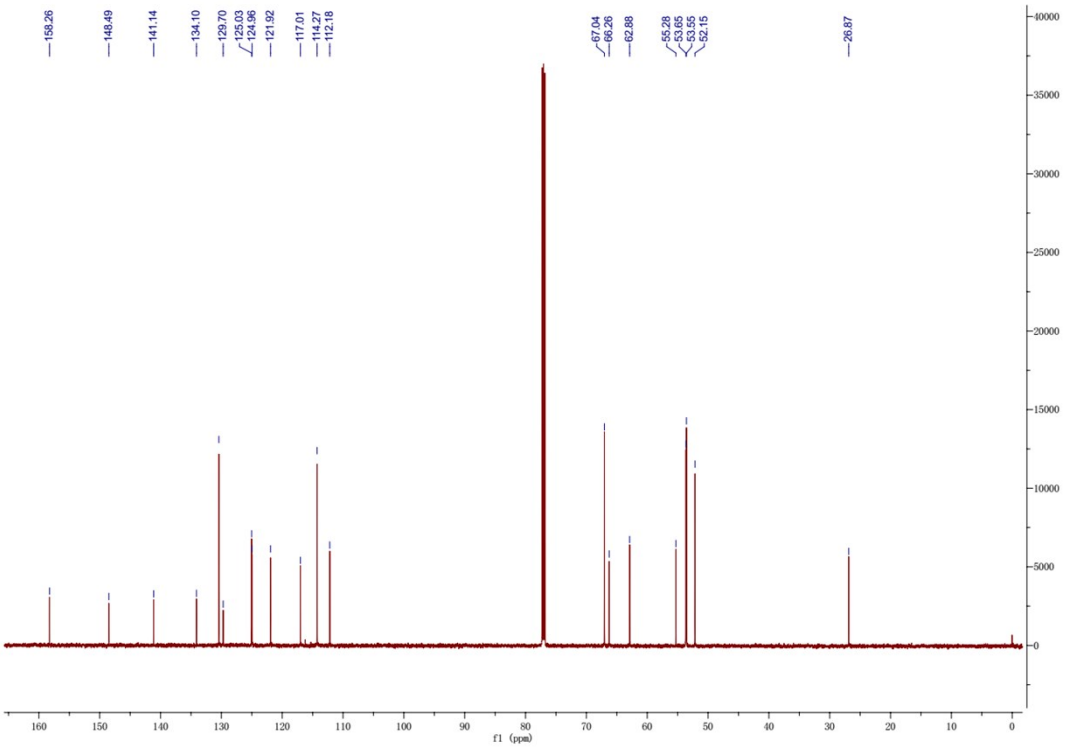


^{1}H-NMR, ^{13}C-NMR and HR-MS of 3w

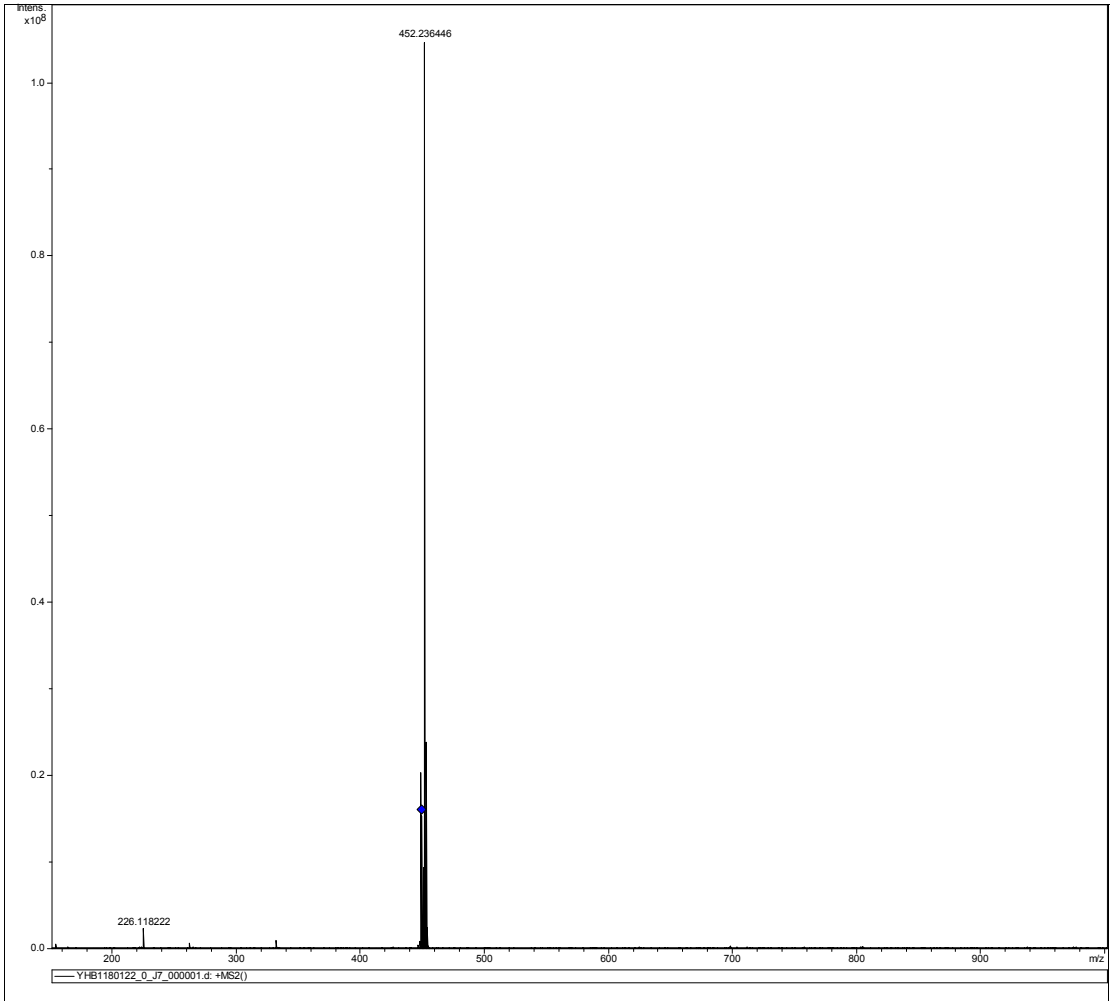
^{1}H-NMR of compound **3w**



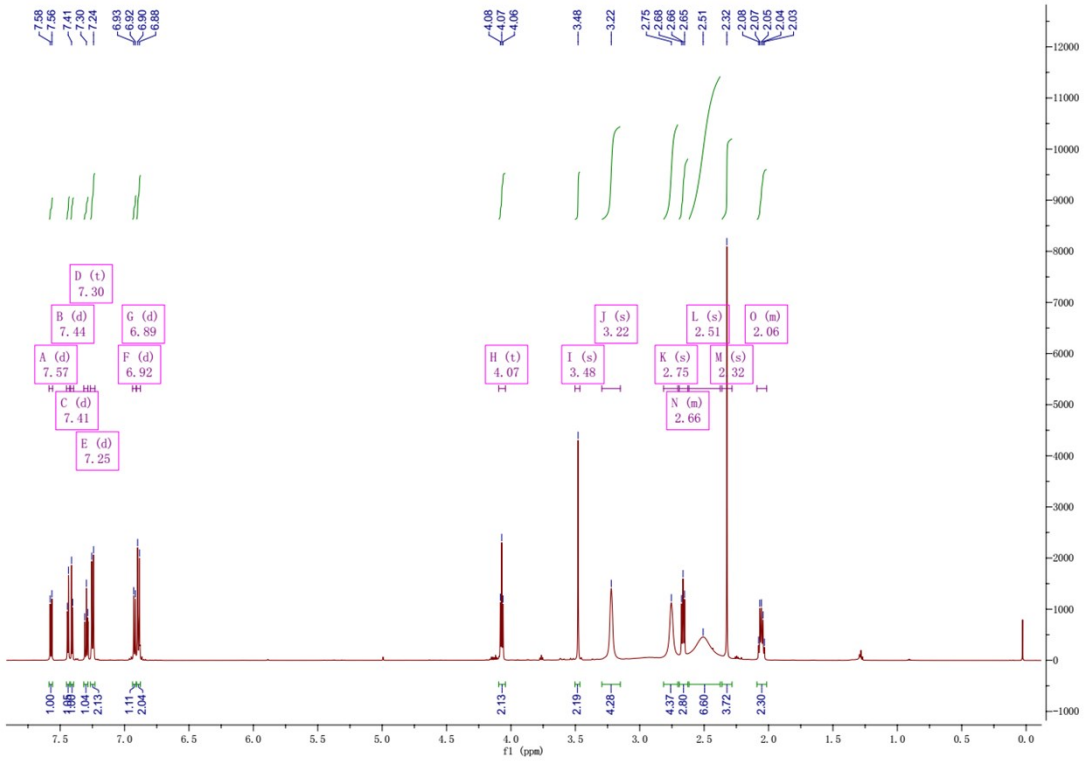
^{13}C-NMR of compound **3w**



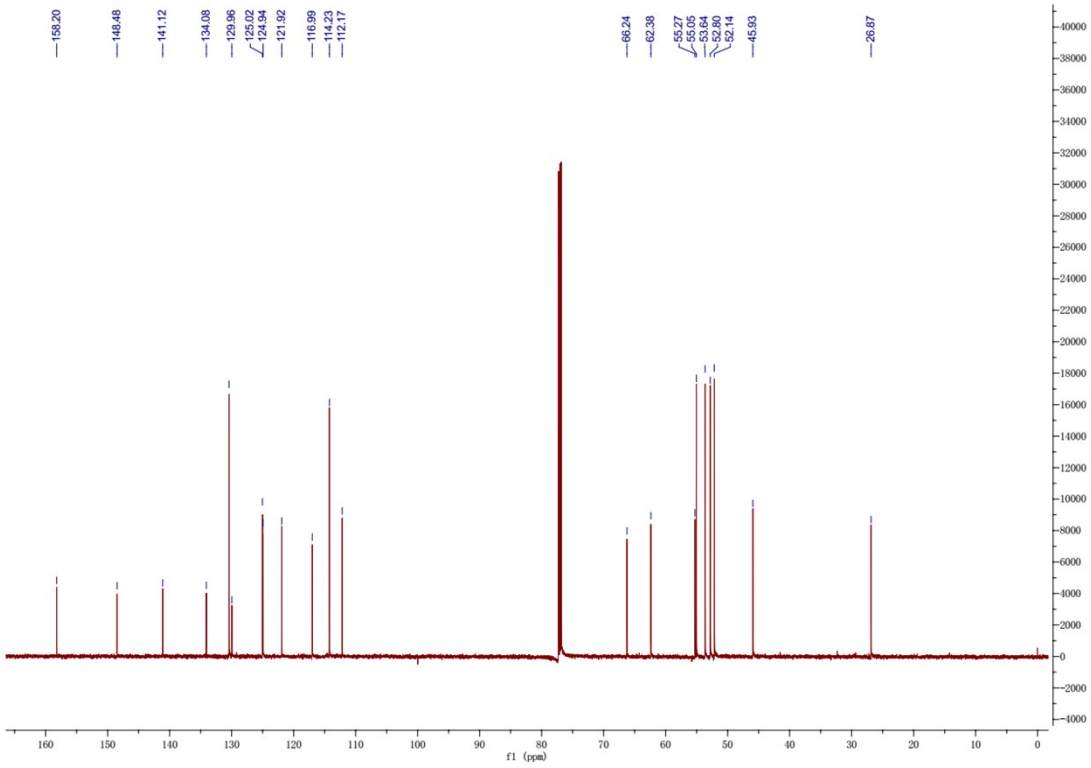
HR-MS of compound **3w**



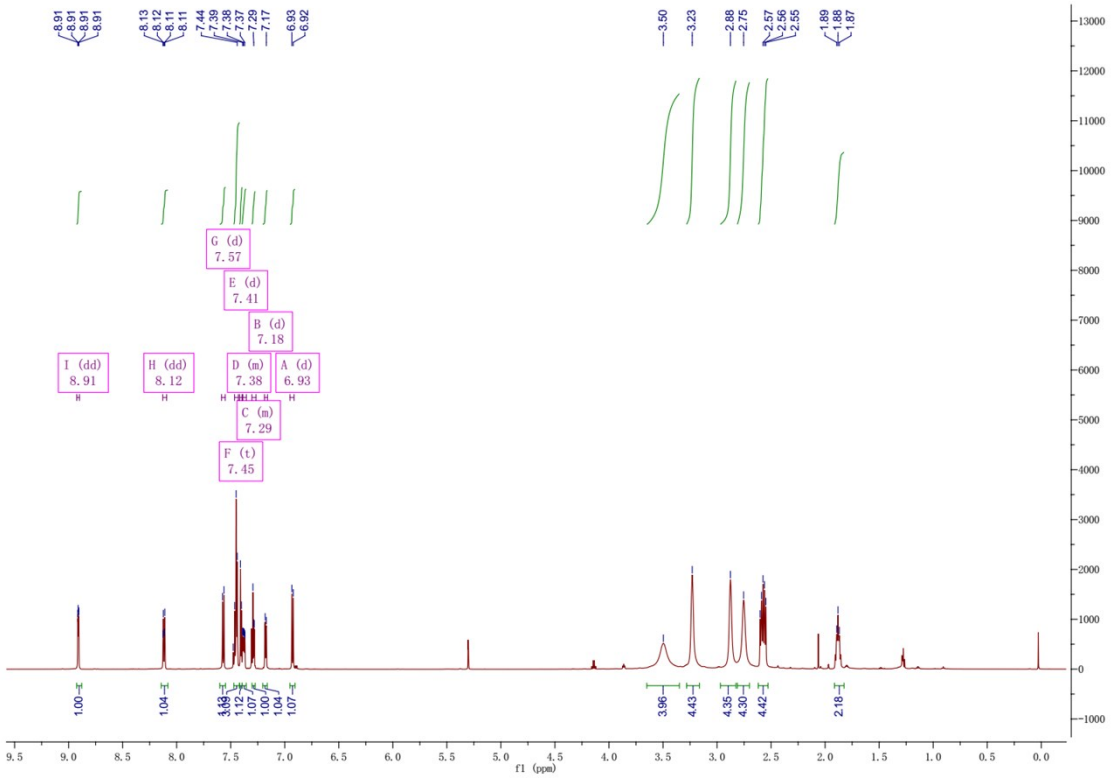
[1]H-NMR of compound **3x**



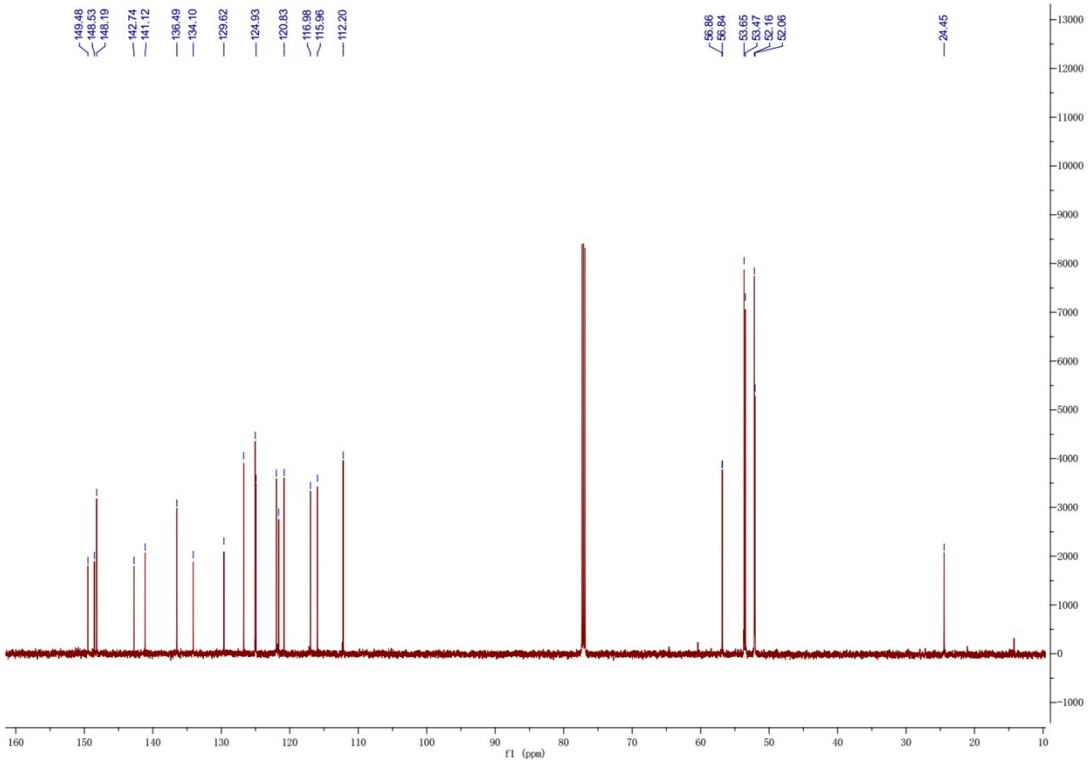
[13]C-NMR of compound **3x**



^{1}H-NMR of compound **3y**



^{13}C-NMR of compound **3y**



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