Supplementary Information

# Discovery of 4-benzoylpiperidine and 3-(piperidin-4-yl)benzo[*d*]isoxazole derivatives as potential and selective GlyT1 inhibitors

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**Part I: Experimental section:**

All reagents were purchased from commercial suppliers and used without further purification unless otherwise stated. Yields were not optimized. Microwave reactions were performed in a Biotage Initiator. Column chromatography was performed using pre-packed silica cartridges (from 4 to 40 g) from Bonna-Agela Technologies Inc. (Tianjin, China) and eluted with a CombiFlash® Rf 200 from Teledyne Isco. $^{1}$H NMR and $^{13}$C NMR spectra was recorded on a Bruker AC300 or a Bruker AC400 NMR spectrometer, using tetramethylsilane as an internal reference. Low-resolution mass spectra were determined on Agilent liquid-chromatography mass spectrometer system that consisted of an Agilent 1260 infinity LC coupled to Agilent 6120 Quadrupole mass spectrometer (electrospray positive ionization; ESI) using an Agilent ZORBAX 1.8 mm SB-C18 column (2.1×50 mm) with aqueous $CH_3CN$ (30–90%) containing 0.05% formic acid monitored at 240 nm. High-resolution mass spectra were recorded on a Q-Tof Ultima Globe mass spectrometer (Micromass, Manchester, UK). HPLC analysis for all compounds tested in biological systems was performed on an Agilent 1200 series LC system (Agilent ChemStation, Agilent Eclipse XDB-C18, 5 μm, 4.6×150 mm, 30 °C, UV240 nm, 1.0 ml/min) with aqueous $CH_3CN$ (35–90%) containing formic acid (0.05%) for 25 min. Experiments in pharmacokinetics study and behavioral tests with live animals were performed in compliance with the Guidelines for the Care and Use of Laboratory Animals (National Research Council, People's Republic of China, 1996). The animal protocols were approved by the Institutional Animal Care and Use Committees of Shanghai Institute of Materia Medica (SIMM) and Soochow University.

**General synthetic procedure for compounds 10a–c:**

Methyl 2-hydroxy-5-nitrobenzoate (0.5 g, 2.54 mmol) and $K_2CO_3$ (0.53 g, 3.83 mmol) were dissolved in dry DMF (10 ml), followed by adding corresponding alkyl halides (5.08 mmol). The reaction was heated in a 40–60 °C oil bath overnight. After completion, the reaction mixture was poured into $H_2O$ (40 ml) and extracted by EtOAc (3 × 30 mL). The organic layer was collected and washed three times with brine. Then the organic phase was dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography to afford **9a–c**. The compound obtained was dissolved in MeOH/$H_2O$/THF (10 ml, 1:1:1), and then NaOH (2 equiv) was added. The mixture was stirred at room temperature for 5 h and then the organic phase was removed in vacuo. The residue was put into an

ice bath and acidified with HCl (4N). The precipitate was filtered, washed with $H_2O$, and dried in vacuo to afford the desired compounds.

**2-Isopropoxy-5-nitrobenzoic acid (10a)**: White solid (0.45 g, 78%); $^1$H NMR (400 MHz, $CDCl_3$): δ 9.03 (d, *J* = 3.0 Hz, 1H), 8.41 (dd, *J* = 9.1, 3.0 Hz, 1H), 7.17 (d, *J* = 9.2 Hz, 1H), 4.99 (p, *J* = 6.1 Hz, 1H), 1.56 ppm (d, *J* = 6.1 Hz, 6H); MS (ESI): *m/z* 224.1 $[M-H]^+$.

**2-(Cyclopentyloxy)-5-nitrobenzoic acid (10b):** White solid (0.43 g, 67%); $^1$H NMR (400 MHz, $CDCl_3$): δ 9.04 (d, *J* = 2.9 Hz, 1H), 8.42 (dd, *J* = 9.2, 3.0 Hz, 1H), 7.18 (d, *J* = 9.2 Hz, 1H), 5.18 (tt, *J* = 5.6, 2.5 Hz, 1H), 2.18 – 2.06 (m, 2H), 2.06 – 1.96 (m, 2H), 1.94 – 1.71 ppm (m, 4H); MS (ESI): *m/z* 250.1 $[M-H]^+$.

**2-(Cyclopropylmethoxy)-5-nitrobenzoic acid (10c)**: White solid (0.49 g, 83%); $^1$H NMR (400 MHz, $CDCl_3$): δ 9.05 (d, *J* = 2.9 Hz, 1H), 8.42 (dd, *J* = 9.2, 2.9 Hz, 1H), 7.14 (d, *J* = 9.2 Hz, 1H), 4.21 (d, *J* = 7.4 Hz, 2H), 1.43 (pt, *J* = 7.6, 4.7 Hz, 1H), 0.86 – 0.79 (m, 2H), 0.53 – 0.47 ppm (m, 2H); MS (ESI): *m/z* 236.1 $[M-H]^+$.

**General synthetic procedure for compounds 10d–10h:**

This procedure was similar to previously described methods.[9] Methyl 2-hydroxy-5-(methylsulfonyl)benzoate or methyl 2-hydroxy-5-(N-methylsulfamoyl)benzoate (2.5 mmol, 1 equiv), triphenylphosphine (0.66 g, 2.5 mmol, 1 equiv), and alkyl alcohol (2.5 mmol, 1 equiv) were stirred in dry THF (5 ml). Then, diisopropyl azodicarboxylate (2.5 mmol, 1 equiv) was added dropwise. The reaction mixture was stirred for 24 h at room temperature and then diluted with EtOAc (20 mL) and washed with $H_2O$. The organic phase was dried over $MgSO_4$ and concentrated in vacuo. Purification was performed by flash column chromatography to give **9d–h**. Then, the compounds were dissolved in MeOH (5 mL), and NaOH (2N, 2 equiv) solution was added. The mixture was heated to 60 °C for 1.5 h and then cooled to room temperature. MeOH was removed and the residue was diluted with water (10 mL) and acidified with HCl (4N) to pH 2. The aqueous phase was extracted by EtOAc (3 × 30 mL). The organic phase was dried over $MgSO_4$ and concentrated in vacuo to afford the desired products.

**2-Isopropoxy-5-(methylsulfonyl)benzoic acid (10d)**: White solid (0.32 g, 50%). $^1$H NMR (300 MHz, DMSO): δ 8.06 (d, *J* = 2.5 Hz, 1H), 7.95 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.36 (d, *J* = 8.9 Hz, 1H), 4.81 (hept, *J* = 5.9 Hz, 1H), 3.19 (s, 3H), 1.29 ppm (d, *J* = 6.0 Hz, 6H); MS (ESI): *m/z* 257.1 $[M-H]^+$.

**2-Isobutoxy-5-(methylsulfonyl)benzoic acid (10e)**: White solid (0.45 g, 67%). $^1$H NMR (300 MHz, CDCl3): δ 8.73 (d, J = 2.4 Hz, 1H), 8.12 (dd, J = 8.7, 2.4 Hz, 1H), 7.20 (d, J = 8.7 Hz, 1H), 4.10 (d, J = 6.5 Hz, 2H), 3.08 (s, 3H), 2.25 (hept, J = 6.7 Hz, 1H), 1.12 ppm (d, J = 6.7 Hz, 6H); MS (ESI): *m/z* 271.1 $[M-H]^+$.

**2-Isobutoxy-5-(N-methylsulfamoyl)benzoic acid (10f)**: White solid (0.43 g, 60%); $^1$H NMR (400 MHz, DMSO): δ 13.05 (s, 1H), 8.02 (d, *J* = 2.5 Hz, 1H), 7.85 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.42 (q, *J* = 5.0 Hz, 1H), 7.31 (d, *J* = 8.8 Hz, 1H), 3.91 (d, *J* = 6.4 Hz, 2H), 2.39 (d, *J* = 5.0 Hz, 3H), 2.05 (m, 1H), 1.00 ppm (d, *J* = 6.7 Hz, 6H); MS (ESI): *m/z* 286.1 $[M-H]^+$.

**2-(Cyclopropylmethoxy)-5-(N-methylsulfamoyl)benzoic acid (10g)**: White solid (0.48 g, 67%); $^1$H NMR (400 MHz, DMSO): δ 13.04 (s, 1H), 8.00 (d, *J* = 2.5 Hz, 1H), 7.84 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.41 (q, *J* = 5.0 Hz, 1H), 7.30 (d, *J* = 8.9 Hz, 1H), 4.02 (d, *J* = 6.7 Hz, 2H), 2.39 (d, *J* = 5.0 Hz, 3H), 1.35 – 1.11 (m, 1H), 0.61 – 0.53 (m, 2H), 0.41 – 0.33 ppm (m, 2H); MS (ESI): *m/z* 284.1 $[M-H]^+$.

**2-Isopropoxy-5-(N-methylsulfamoyl)benzoic acid (10h)**: White solid (0.48 g, 71%); $^1$H NMR (400 MHz, DMSO) δ 12.99 (s, 1H), 7.98 (d, *J* = 2.5 Hz, 1H), 7.83 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.40 (q, *J* = 5.0 Hz, 1H), 7.35 (d, *J* = 8.9 Hz, 1H), 4.79 (h, *J* = 6.0 Hz, 1H), 2.39 (d, *J* = 5.1 Hz, 3H), 1.31 ppm (d, *J* = 6.0 Hz, 6H); MS (ESI): *m/z* 272.1 $[M-H]^+$.

**Methyl 5-nitro-2-(((trifluoromethyl)sulfonyl)oxy)benzoate (11a)**: To a solution of methyl 2-hydroxy-5-nitrobenzoate (1.5g, 1 equiv) and $Et_3N$ (3.16 mL, 3 equiv) in dry $CH_2Cl_2$ at 0 °C was slowly added triflic anhydride (1.93 mL, 1.5 equiv). The reaction mixture was stirred at room temperature for 20 min and then poured into 50 mL saturated aqueous $NH_4Cl$. The mixture was separated and the aqueous layer was extracted with $CH_2Cl_2$ (2 × 10 mL). The combined extracts were washed with brine, dried over $MgSO_4$ and concentrated. The crude was purified by flash column chromatography to give **11a** as a yellow oil. (2.0 g, 79%).

**2-(Isopropylamino)-5-nitrobenzoic acid (13a)**: To a solution of **11a** (0.5 g, 1 equiv) in 5 mL NMP in a microwave tube was added propan-2-amine (0.22 g, 2.5 equiv). The mixture was heated at 210 °C by microwave for 5 min and then cooled to room temperature. The solvent was diluted with water (10 mL) and then extracted with EtOAc (3 × 20 mL). The combined EtOAc layers were washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography to afford **12a** as a yellow solid. **12a** was dissolved in 5 mL mixed solvent (MeOH/THF/$H_2O$, 1:1:1) and then NaOH (2 equiv) was added. The mixture was heated at 60 °C for 2h and then cooled to room temperature. Organic solvent was evaporated in vacuo and the residue was diluted with 5 mL $H_2O$, acidified with 4N HCl and extracted with EtOAc. The EtOAc layer was dried over $MgSO_4$ and concentrated to give **13a** (0.18 g, 51%) as a yellow solid. $^1$H NMR (400 MHz, $CDCl_3$): δ 8.95 (d, *J* = 2.7 Hz, 1H), 8.36 (d, *J* = 7.4 Hz, 1H), 8.29 – 8.17 (m, 1H), 6.73 (d, *J* = 9.6 Hz, 1H), 3.85 (h, *J* = 6.5 Hz, 1H), 1.35 ppm (d, *J* = 6.4 Hz, 6H); MS (ESI): *m/z* 223.1 $[M-H]^+$

**5-Nitro-2-(piperidin-1-yl)benzoic acid (13b)**: **13b** was prepared from **11a** (0.5 g) and piperidine (0.32 g) by the same procedure of **13a**. Yellow solid (0.22 g, 56%). $^1$H NMR (400 MHz, $CDCl_3$): δ 9.12 (d, *J* = 2.5 Hz, 1H), 8.48 – 8.34 (m, 1H), 7.60 (d, *J* = 8.5 Hz, 1H), 3.04 (d, *J* = 5.4 Hz, 4H), 1.91 (brs, 4H), 1.74 ppm (s, 2H); MS (ESI): *m/z* 249.2 $[M-H]^+$.

**General procedure for compounds 16a-16e**:

To a solution of methyl 2-fluoro-5-(methylsulfonyl)benzoate (**14a**) or methyl 2-fluoro-5-(N-methylsulfamoyl)benzoate (**14b**) (3 mmol, 1 equiv) in THF (5 mL) in a microwave vial was added alkylamine (7.5 mmol, 2.5 equiv). The mixture was stirred at 100 °C by microwave irradiation for 40 min. Then 2N NaOH (6 mmol, 2equiv) was added and the mixture was heated at 60 °C in an oil bath for 2h. The mixture was concentrated and diluted with 10 mL water. Then the mixture was acidified with 4N HCl and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated to give desired compounds **16a-e**.

**2-(Isopropylamino)-5-(methylsulfonyl)benzoic acid (16a)**: **16a** was prepared from **14a** and propan-2-amine. White solid (0.66 g, 85%). $^1$H NMR (300 MHz, DMSO): δ 13.22 (s, 1H), 8.36 (d, *J* = 7.5 Hz, 1H), 8.23 (d, *J* = 2.3 Hz, 1H), 7.77 (dd, *J* = 9.1, 2.3 Hz, 1H), 6.93 (d, *J* = 9.1 Hz, 1H), 3.93 – 3.73 (m, 1H), 3.09 (s, 3H), 1.20 ppm (d, *J* = 6.3 Hz, 6H); MS (ESI): *m/z* 256.1 $[M-H]^+$.

**5-(Methylsulfonyl)-2-(piperidin-1-yl)benzoic acid (16b)**: **16b** was prepared from **14a** and piperidine. White solid (0.67 g, 79%). $^1$H NMR (300 MHz, $CDCl_3$): δ 8.85 (d, *J* = 2.2 Hz, 1H), 8.17 (dd, *J* = 8.3, 2.4 Hz, 1H), 7.64 (d, *J* = 8.5 Hz, 1H), 3.11 (s, 3H), 3.05 (t, *J* = 5.4 Hz, 4H), 2.00 – 1.85 (m, 4H), 1.79 – 1.63 ppm (m, 2H). MS (ESI): *m/z* 282.1 $[M-H]^+$.

**2-(Isopropylamino)-5-(N-methylsulfamoyl)benzoic acid (16c)**: **16c** was prepared from **14b** and propan-2-amine. Light yellow solid (0.47 g, 58%). $^1$H NMR (400 MHz, $CD_3OD$): δ 8.34 (d, *J* = 2.4 Hz, 1H), 7.71 (dd, *J* = 9.0, 2.4 Hz, 1H), 6.88 (d, *J* = 9.1 Hz, 1H), 3.83 (hept, *J* = 6.4 Hz, 1H), 2.49 (s, 3H), 1.28 ppm (d, *J* = 6.4 Hz, 6H); MS (ESI): *m/z* 271.1 $[M-H]^+$.

**5-(N-methylsulfamoyl)-2-(piperidin-1-yl)benzoic acid (16d)**: **16d** was prepared from **14b** and piperidine. Light yellow solid (0.46 g ,52%). $^1$H NMR (400 MHz, DMSO): δ 8.18 (d, *J* = 2.4 Hz, 1H), 7.91 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.66 (d, *J* = 8.6 Hz, 1H), 7.60 (s, 1H), 3.18 (t, *J* = 5.3 Hz, 4H), 2.40 (s, 3H), 1.77 – 1.66 (m, 4H), 1.61 ppm (q, *J* = 5.7 Hz, 2H); MS (ESI): *m/z* 297.1 $[M-H]^+$.

**5-(N-methylsulfamoyl)-2-morpholinobenzoic acid (16e)**: **16e** was prepared from **14b** and morpholine. White solid (0.50 g, 56%). $^1$H NMR (400 MHz, $CD_3OD$): δ 8.54 (d, *J* = 2.2 Hz, 1H), 8.19 (dd, *J* = 8.6, 2.3 Hz, 1H), 8.00 (d, *J* = 8.6 Hz, 1H), 4.08 – 4.01 (m, 4H), 3.64 – 3.60 (m, 4H), 2.56 ppm (s, 3H); MS (ESI): *m/z* 299.1 $[M-H]^+$.

**General procedure for compounds 18a–18c**:

A solution of 2-fluoro-5-(methylsulfonyl)benzoic acid (**17a**, 1 equiv) or 2-fluoro-5-(N-methylsulfamoyl)benzoic acid (**17b**, 1 equiv) in 20 mL dry THF was added alkyl alcohol (1.1 equiv) at room temperature. The mixture was slowly added *t*-BuOK (2.1 equiv) portionwise. The suspension was stirred at room temperature for 1h and then warmed to 60 °C. The reaction was held at 60°C for 1h and then added formic acid (3 equiv) within 5 min. The solvent was concentrated, diluted with 20 mL water and stirred at 0 °C for 20 min. The formed precipitate was filtered, washed with cold water, and dried under vacuum to afford **18a-c**.

**5-(Methylsulfonyl)-2-((1,1,1-trifluoropropan-2-yl)oxy)benzoic acid (18a)**: **18a** was prepared from **17a** (3.1 g) and 1,1,1-trifluoropropan-2-ol (1.42 mL). White solid (3.9 g, 88%). $^1$H NMR (400 MHz, DMSO) δ 13.33 (s, 1H), 8.16 (d, *J* = 2.5 Hz, 1H), 8.06 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.59 (d, *J* = 8.9 Hz, 1H), 5.52 (p, *J* = 6.4 Hz, 1H), 3.25 (s, 3H), 1.47 ppm (d, *J* = 6.3 Hz, 3H); MS (ESI): *m/z* 311.0 $[M-H]^+$.

**5-(Methylsulfonyl)-2-(2,2,3,3,3-pentafluoropropoxy)benzoic acid (18b)**: **18b** was prepared from **17a** (0.5 g) and 2,2,3,3,3-pentafluoropropan-1-ol (0.38 g). Light yellow solid (0.44 g, 55%). $^1$H NMR (400 MHz, DMSO): δ 13.32 (s, 1H), 8.17 (d, *J* = 2.5 Hz, 1H), 8.09 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.52 (d, *J* = 8.9 Hz, 1H), 5.06 (t, *J* = 13.1 Hz, 2H), 3.25 ppm (s, 3H); MS (ESI): *m/z* 347.0 $[M-H]^+$.

**5-(N-methylsulfamoyl)-2-(2,2,3,3,3-pentafluoropropoxy)benzoic acid (18c)**: **18c** was prepared from **17b** (0.5 g) and 2,2,3,3,3-pentafluoropropan-1-ol (0.35 g). White solid (0.40 g, 51%). $^1$H NMR (300 MHz, DMSO): δ = 8.03 (d, *J*=2.3 Hz, 1H), 7.90 (dd, *J*=8.8, 2.4 Hz, 1H), 7.55 (q, *J*=5.2 Hz, 1H), 7.46 (d, *J*=8.8 Hz, 1H), 5.01 (t, *J*=13.2 Hz, 2H), 2.40 ppm (d, *J*=5.0 Hz, 3H); MS (ESI): *m/z* 362.1 $[M-H]^+$.

**2-(Isopropylthio)-5-(N-methylsulfamoyl)benzoic acid (18d)**: A solution of **17b** (0.5 g, 1 equiv), $Cs_2CO_3$ (2.1 g, 3 equiv) and 2-propanethiol (0.33 g, 2 equiv) in 10 mL DMA was stirred at 100 °C for 4h. Then the mixture was cooled to room temperature and acidified with HCl (4N) to pH 1. The mixtute was diluted with 10 mL water and extracted with EtOAc (3 × 30 mL). The organic phase was dried over $MgSO_4$ and concentrated to give the desired compound as an off-white solid which was used in the next step without further purification. (Crude product 0.38 g, 62%). MS (ESI): *m/z* 288.1 $[M-H]^+$.

**(4-Fluorophenyl)(piperidin-4-yl)methanone (21a)**: Magnesium turnings (0.18 g, 7.5 mmol, 1.6 equiv) and iodide (0.03 g) were mixed in 5 mL dry THF at room temperature under nitrogen and then heated to 70 °C. A solution of 4-fluorobromobenzene (1.23 g, 7.0 mmol, 1.5 equiv) in 10 mL dry THF was added dropwise. After addition the mixture was heated to reflux for 40 min and then cooled to room temperature. The resulting mixture was added dropwise to a solution of 1-acetyl-N-methoxy-N-methylpiperidine-4-carboxamide (1.0 g, 4.67 mmol, 1 equiv) in dry THF (10 mL) at 0 °C. The mixture was warmed to room temperature and stirred overnight. Saturated aqueous $NH_4Cl$ (25 mL) was added and the mixture was extracted with EtOAc (3 × 20 mL). The organic layers were dried over $MgSO_4$ and concentrated. Purification was performed by flash column chromatography to give **20a** as a light yellow oil. **20a** was dissolved in 5 mL HCl (6N) and the suspension was heated to reflux for 4h. The mixture was cooled

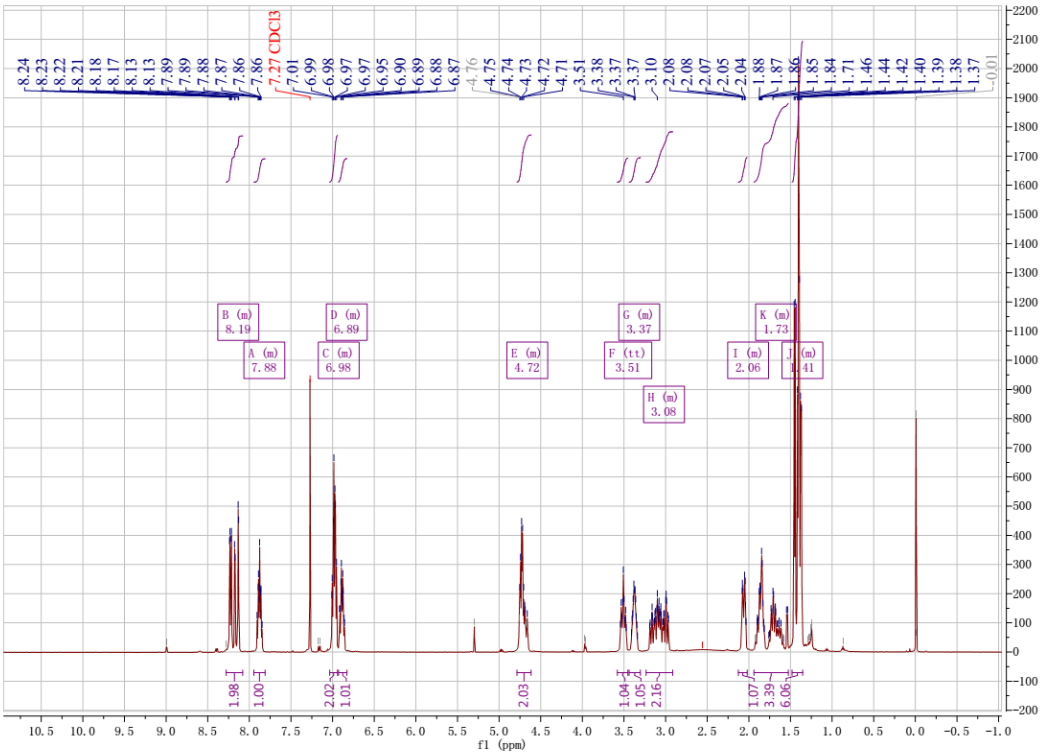
to room temperature and basified with NaOH (2N) to pH 8. Then the mixture was extracted with EtOAc (3 × 20 mL). The EtOAc layers were dried over $MgSO_4$ and concentrated in vacuo to afford **21a** as an off-white solid. (0.35 g, 36%). $^1$H NMR (300 MHz, $CDCl_3$): δ 8.03 – 7.91 (m, 2H), 7.14 (t, *J* = 8.6 Hz, 2H), 3.37 (tt, *J* = 11.1, 3.7 Hz, 1H), 3.27 – 3.16 (m, 2H), 2.79 (td, *J* = 12.2, 2.8 Hz, 2H), 2.25 (s, 1H), 1.92 – 1.79 (m, 2H), 1.79 – 1.60 ppm (m, 2H); MS (ESI): *m/z* 208.2 $[M+H]^+$.

**Piperidin-4-yl(4-(trifluoromethyl)phenyl)methanone (21b)**: **21b** was prepared from 1-bromo-4-(trifluoromethyl)benzene (1.13 g, 5.0 mmol, 1.5 equiv) and 1-acetyl-N-methoxy-N-methylpiperidine-4-carboxamide (0.71g, 3.3 mmol, 1 equiv) by the same procedure as **21a** to give a light yellow oil. (0.20 g, 23%). $^1$H NMR (400 MHz, $CDCl_3$): δ 8.03 (d, *J* = 8.1 Hz, 2H), 7.74 (d, *J* = 8.1 Hz, 2H), 3.42 (tt, *J* = 11.0, 3.7 Hz, 1H), 3.30 – 3.15 (m, 2H), 2.83 (td, *J* = 12.2, 2.7 Hz, 2H), 1.96 – 1.84 (m, 2H), 1.83 – 1.62 ppm (m, 2H). MS (ESI): *m/z* 258.2 $[M+H]^+$.

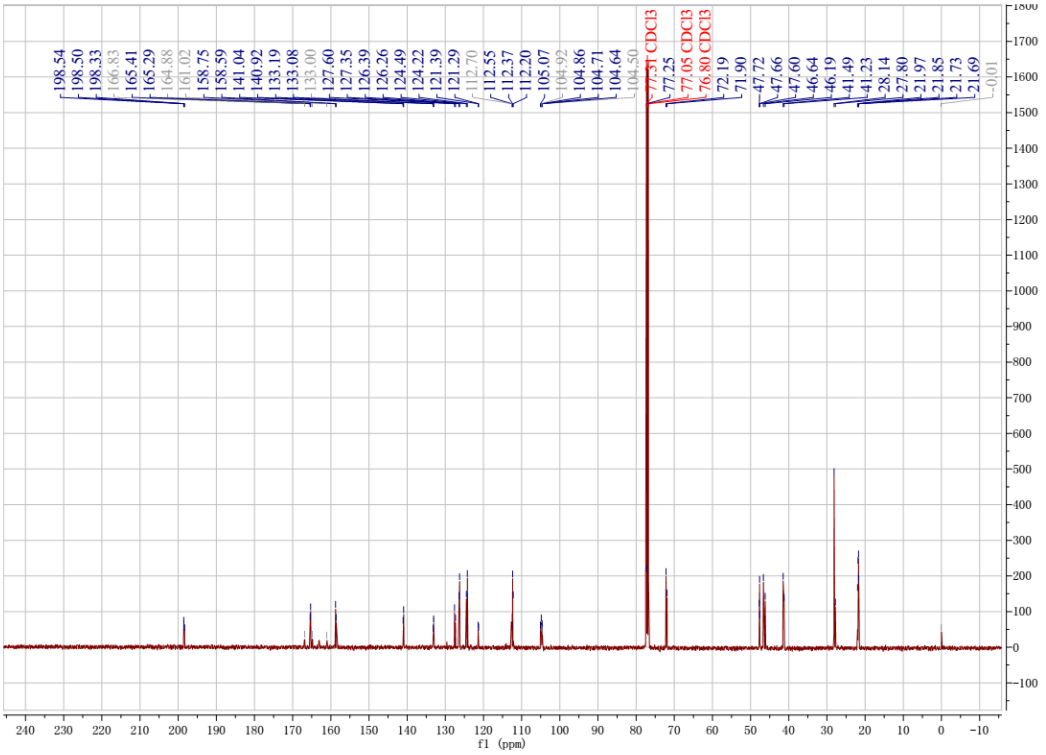
**Part II: $^1$H NMR and $^{13}$C NMR copies of final compounds:**

**Compound 23a:**

**$^{1}$H NMR:**

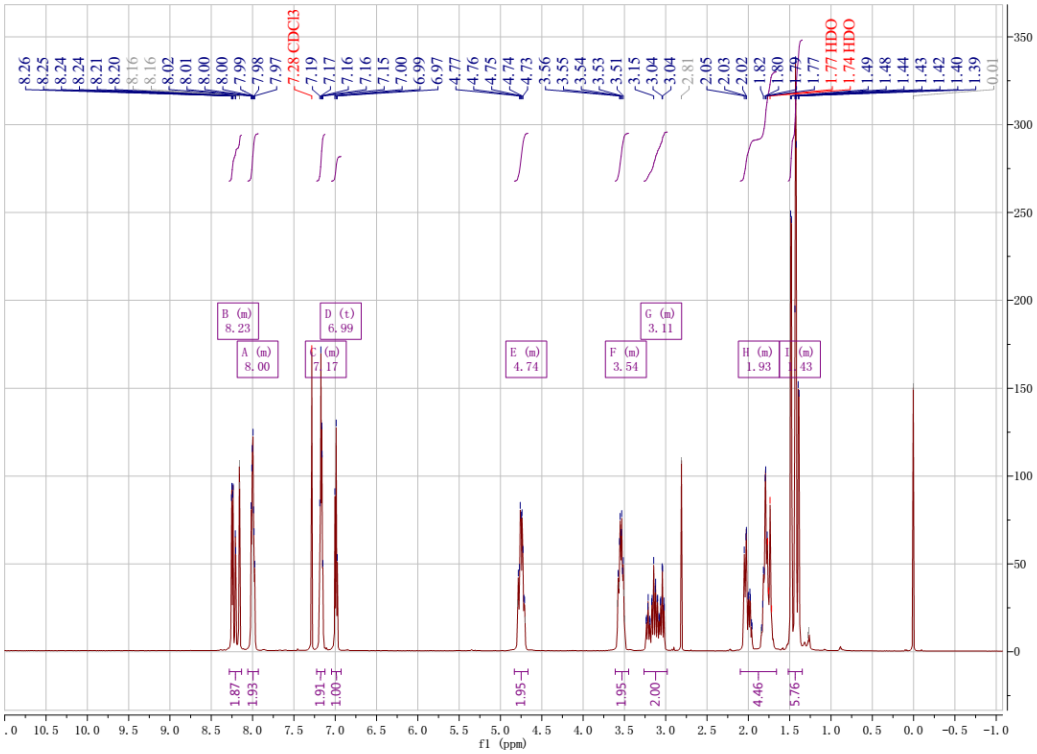



**$^{13}$C NMR:**

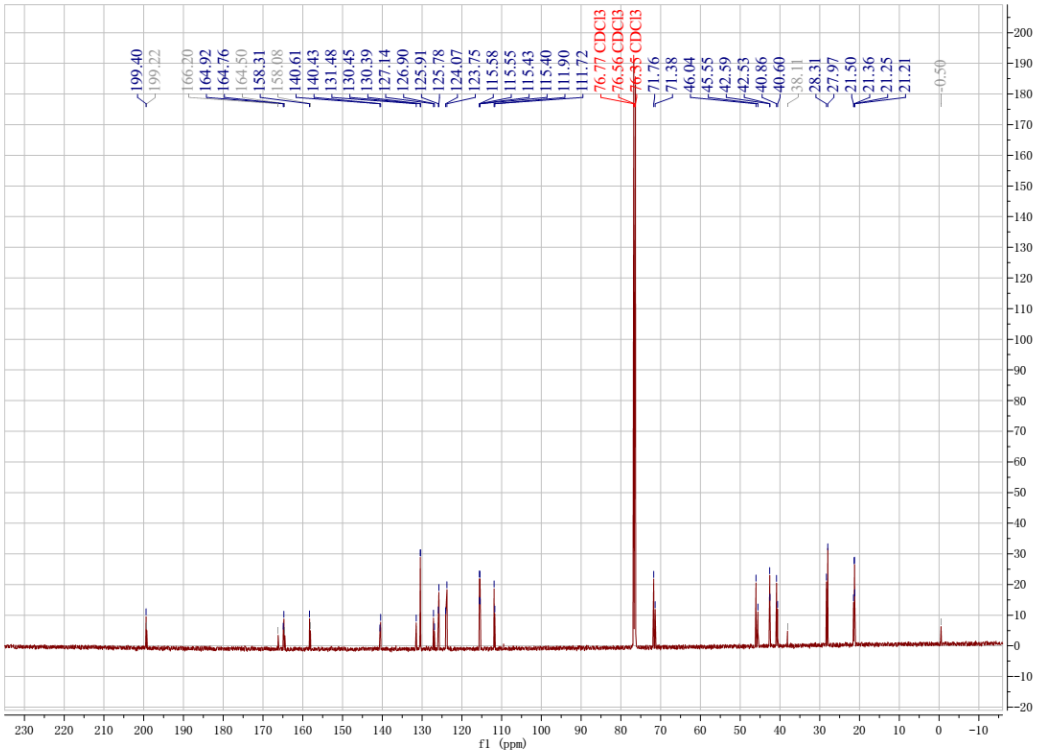


**Compound 23b:**

**$^{1}$H NMR:**

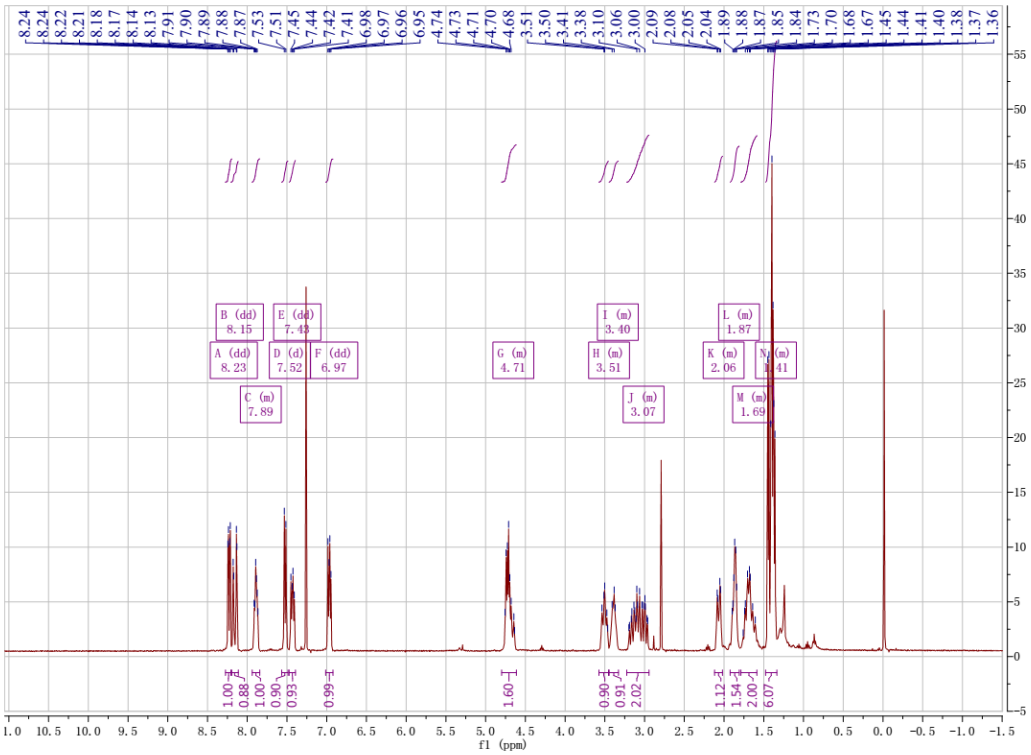



**$^{13}$C NMR:**

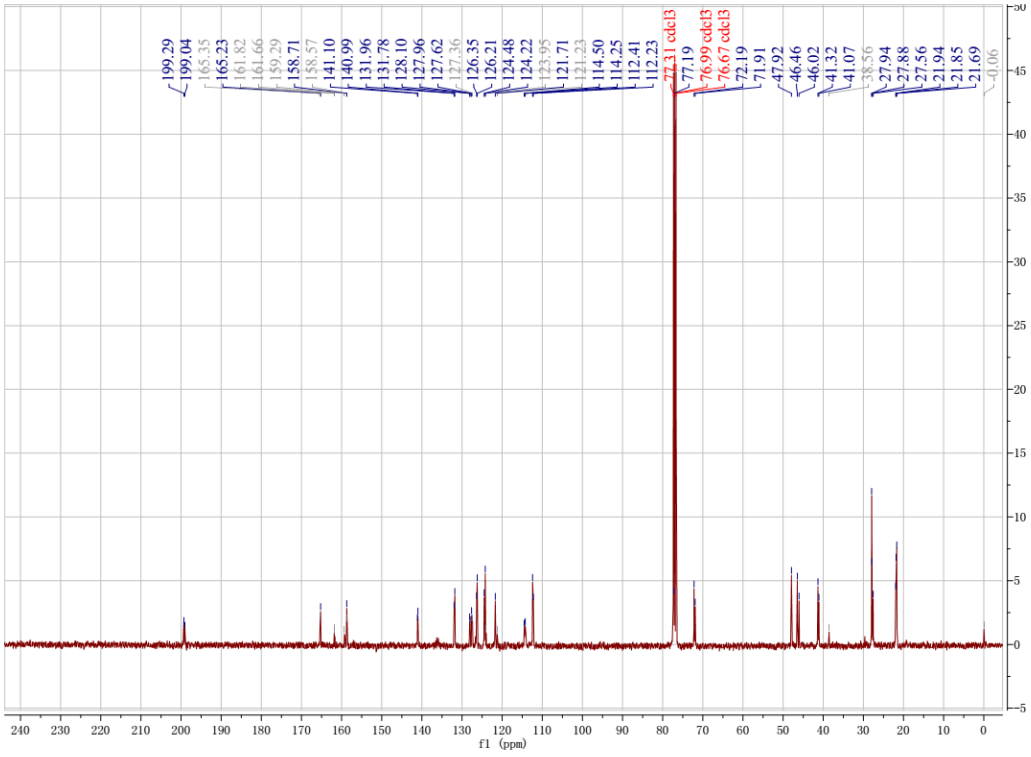


**Compound 23c:**

**$^{1}$H NMR:**

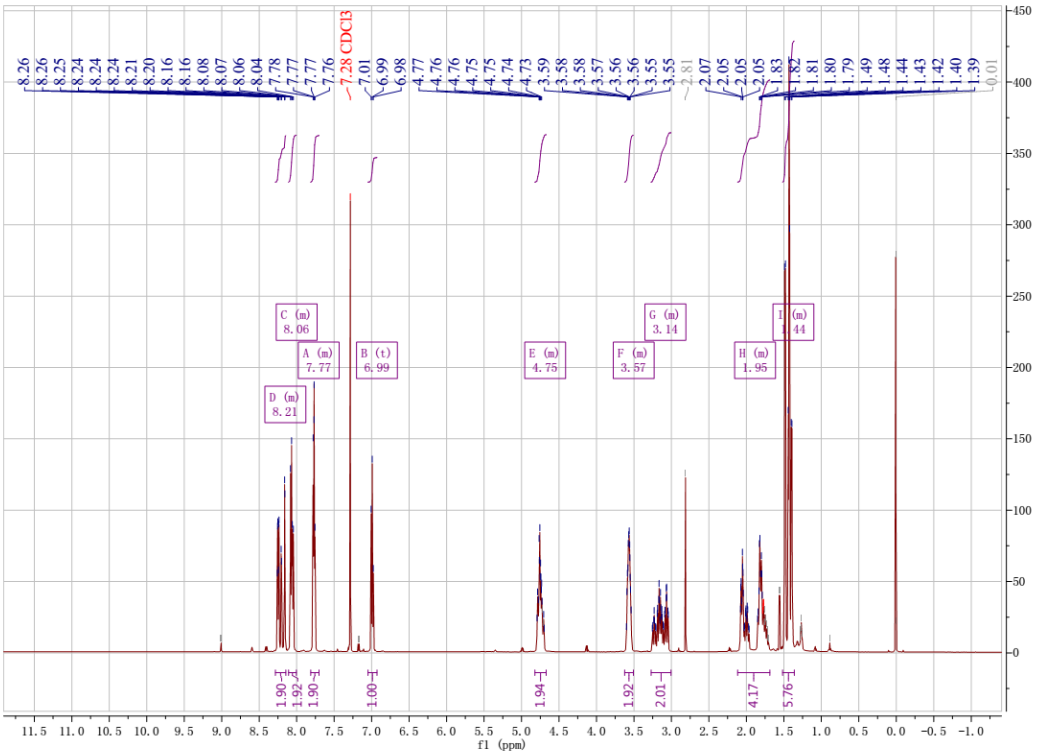



**$^{13}$C NMR:**

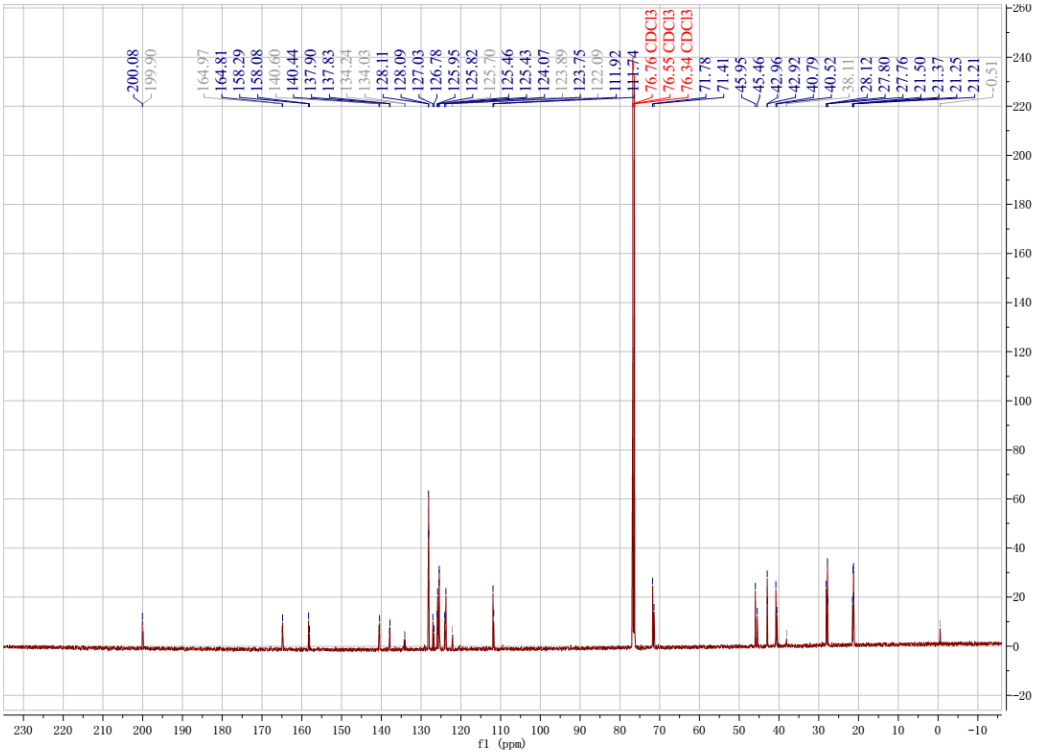


**Compound 23d:**

**$^{1}$H NMR:**

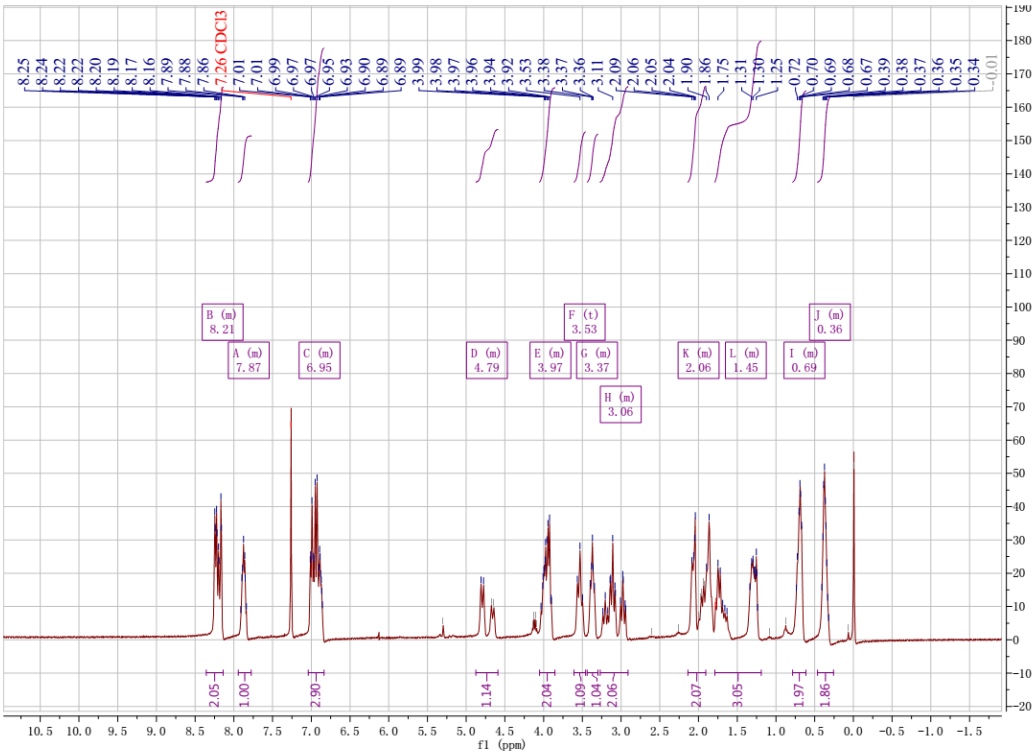



**$^{13}$C NMR:**

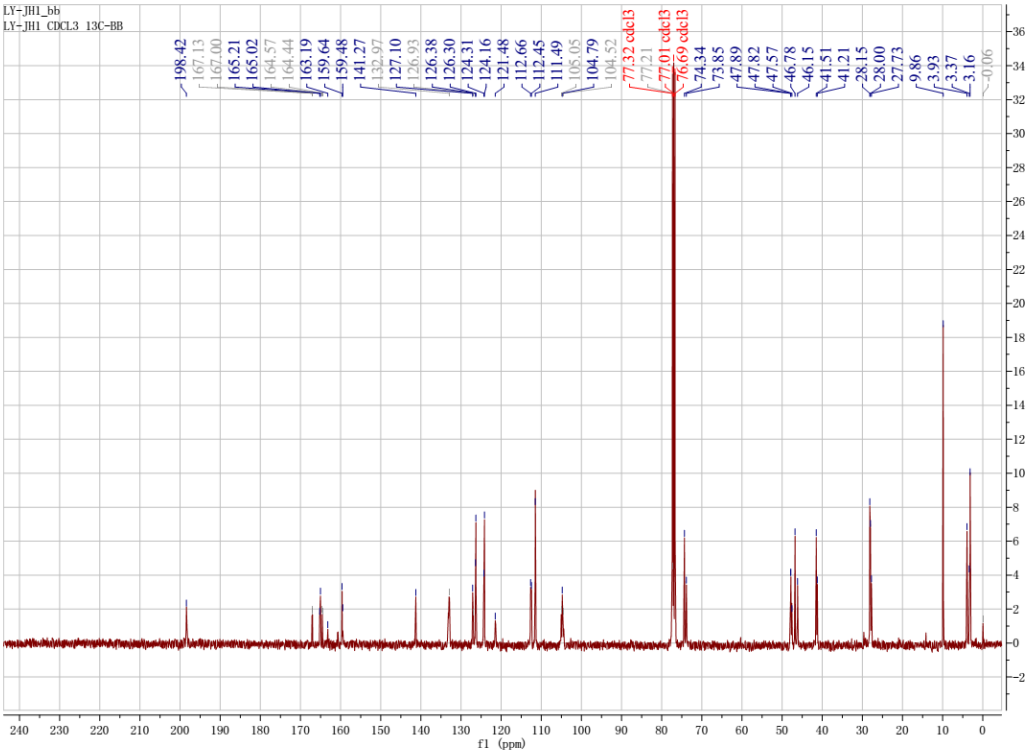


**Compound 23e:**

**$^{1}$H NMR:**

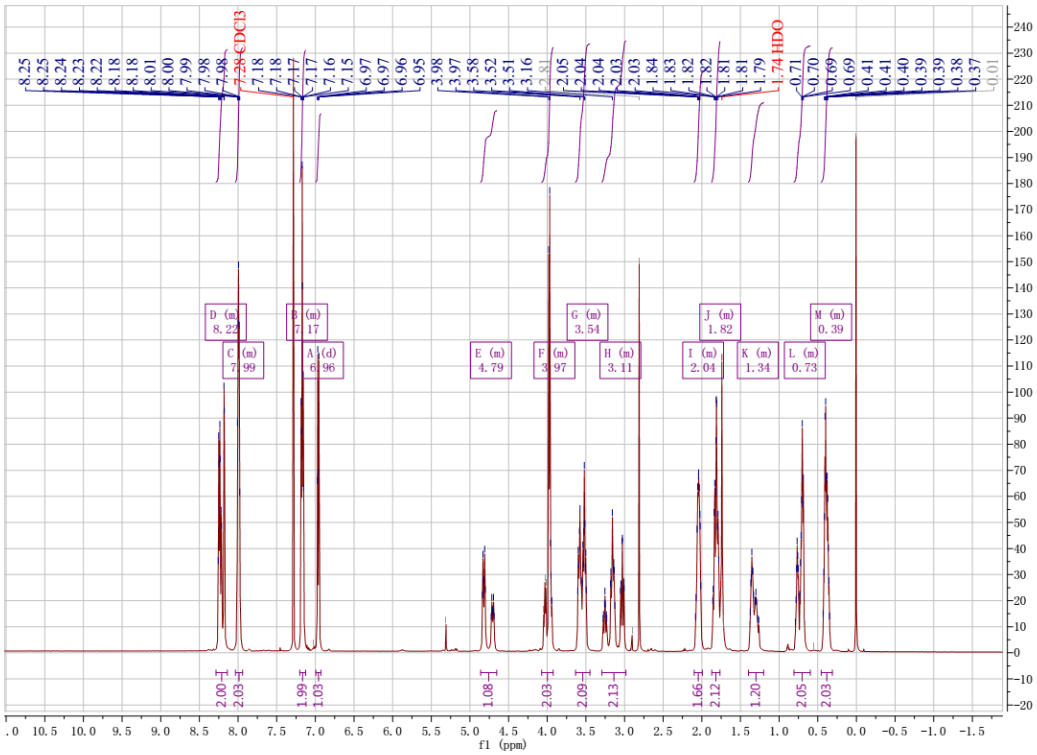



**$^{13}$C NMR:**

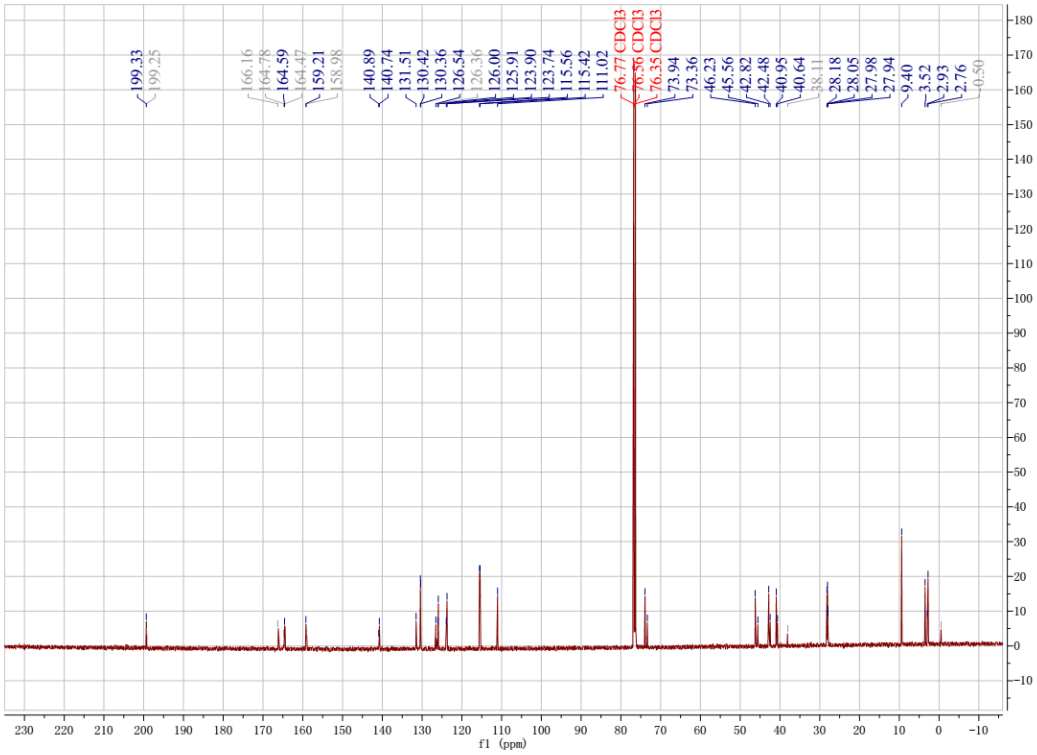


**Compound 23f:**

**$^{1}$H NMR:**

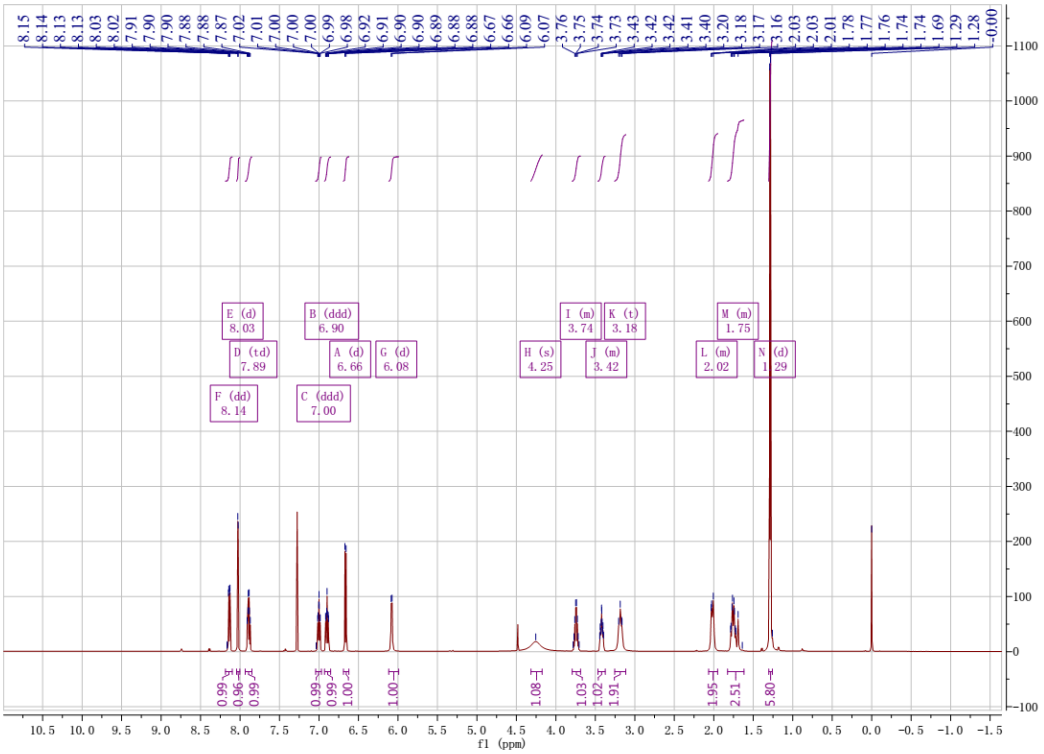


**$^{13}$C NMR:**

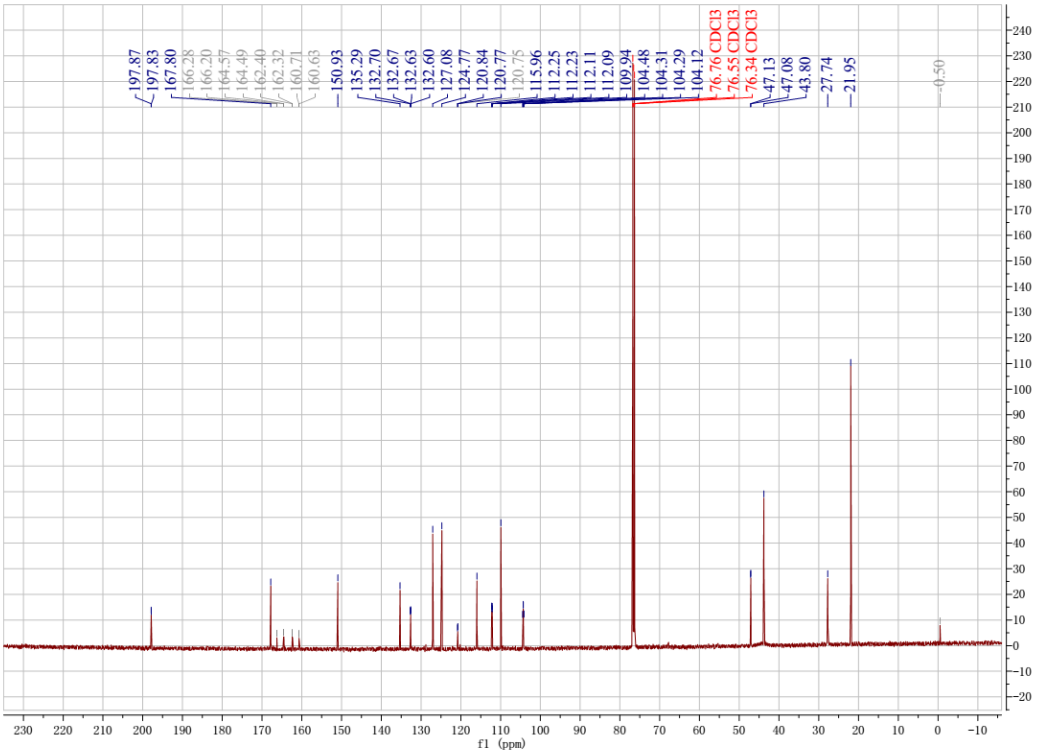


**Compound 23g:**

**$^{1}$H NMR:**

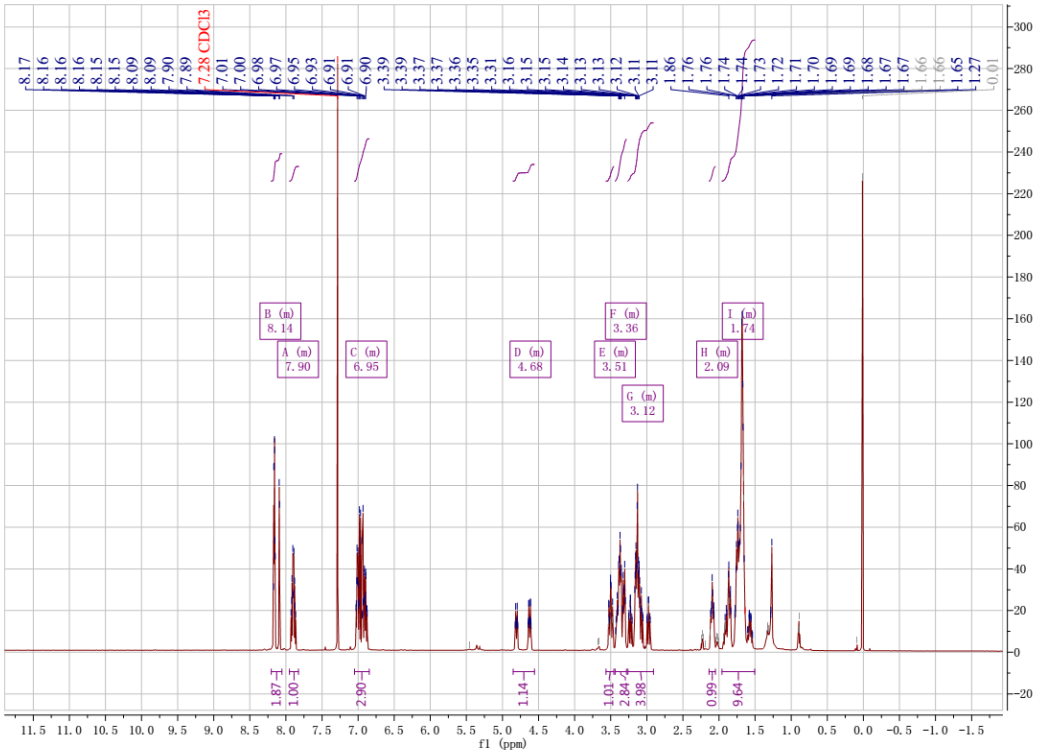



**$^{13}$C NMR:**

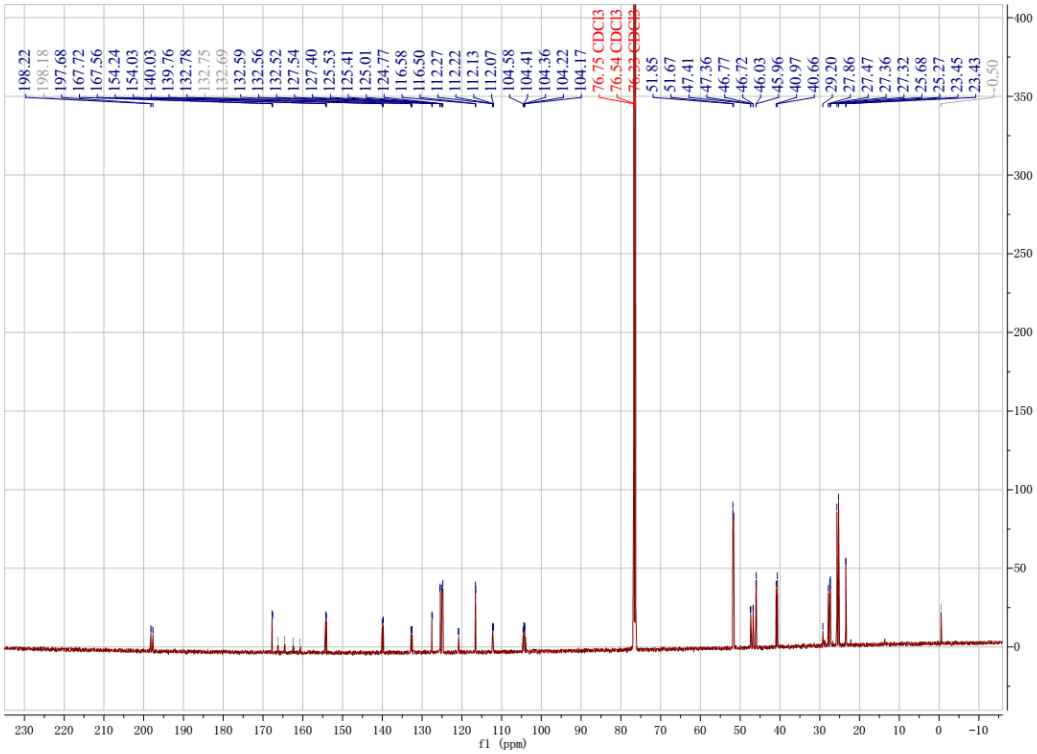


**Compound 23h:**

**$^{1}$H NMR:**

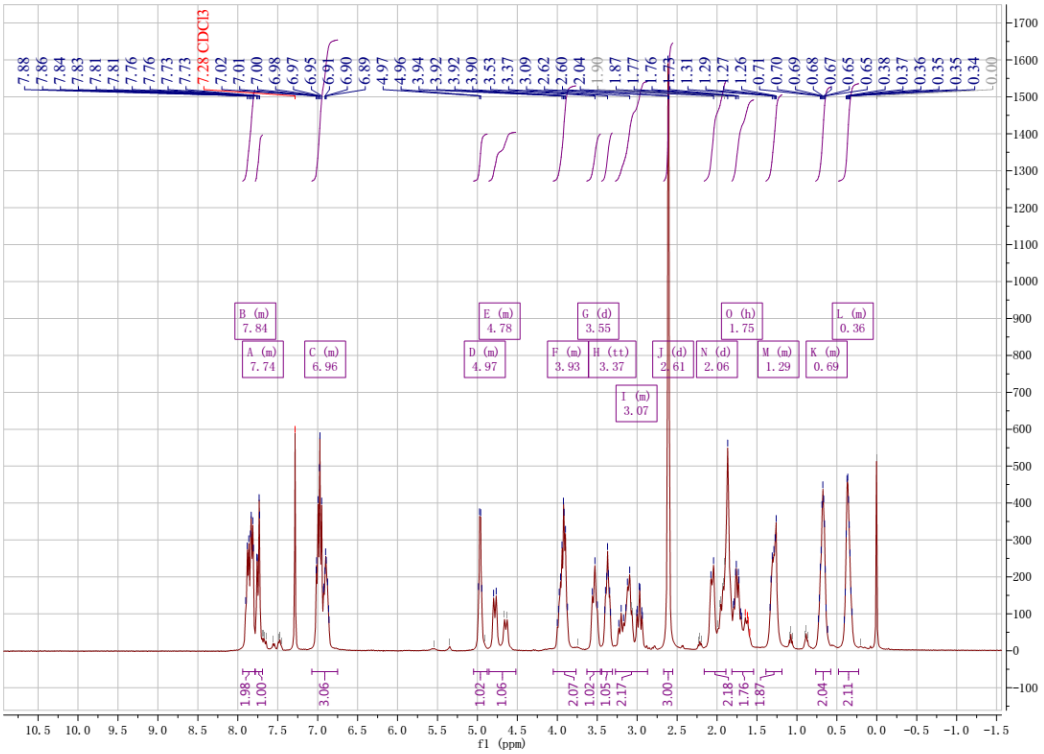



**$^{13}$C NMR:**

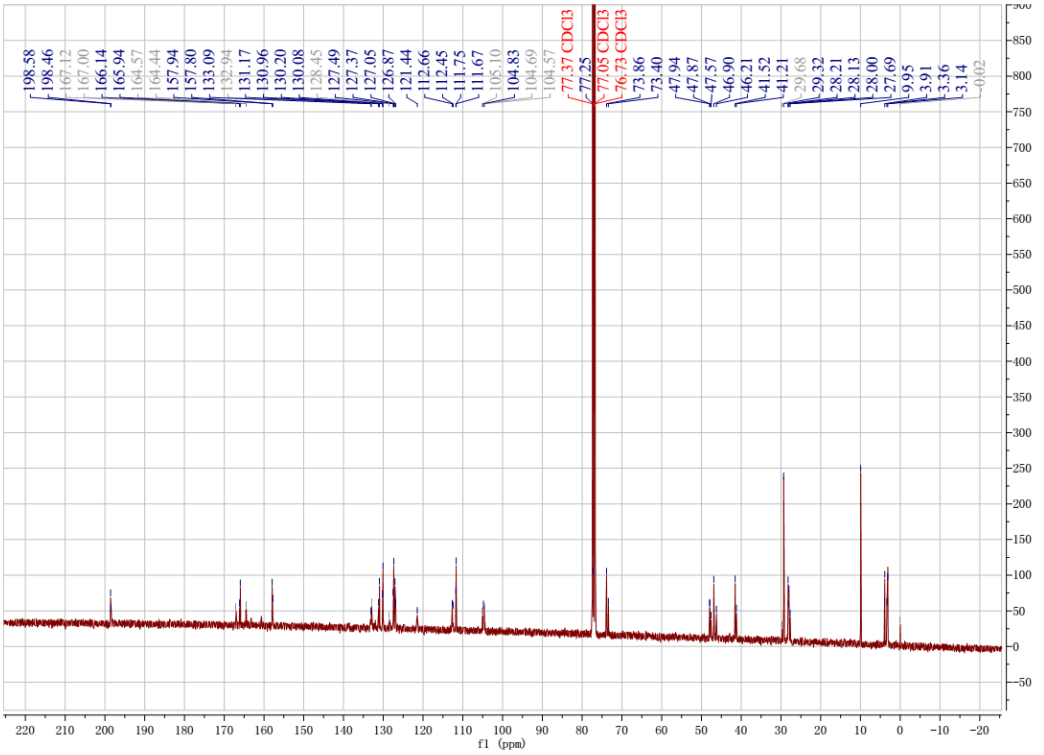


**Compound 23i:**

**$^{1}$H NMR:**

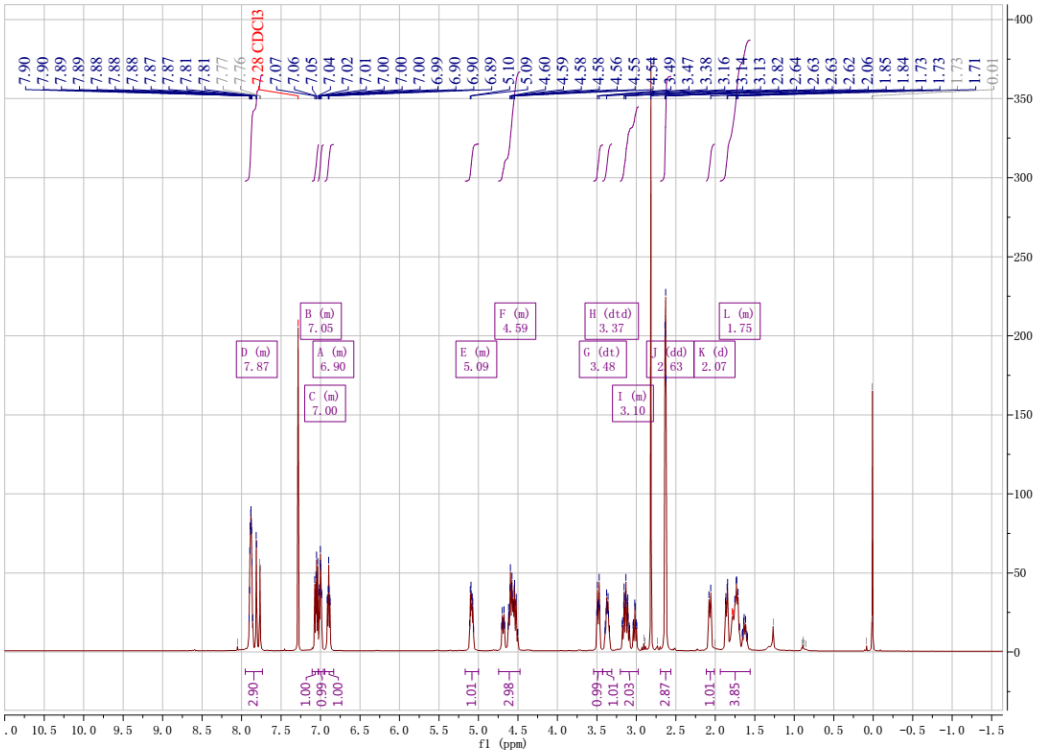


**$^{13}$C NMR:**

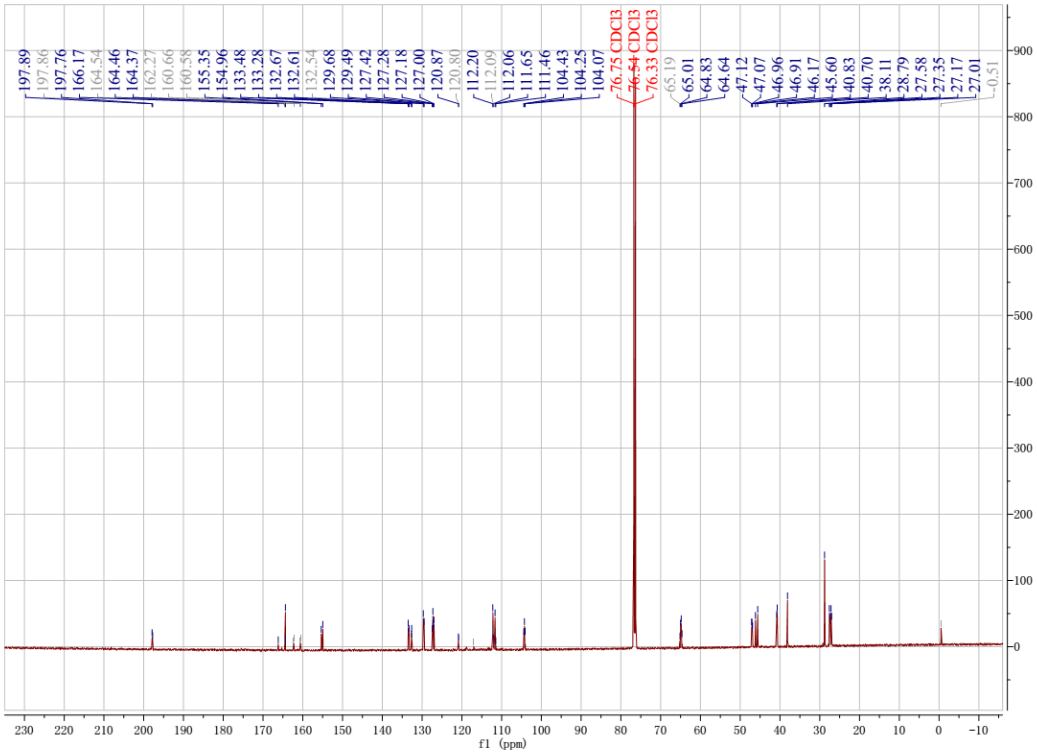


**Compound 23j:**

**$^{1}$H NMR:**

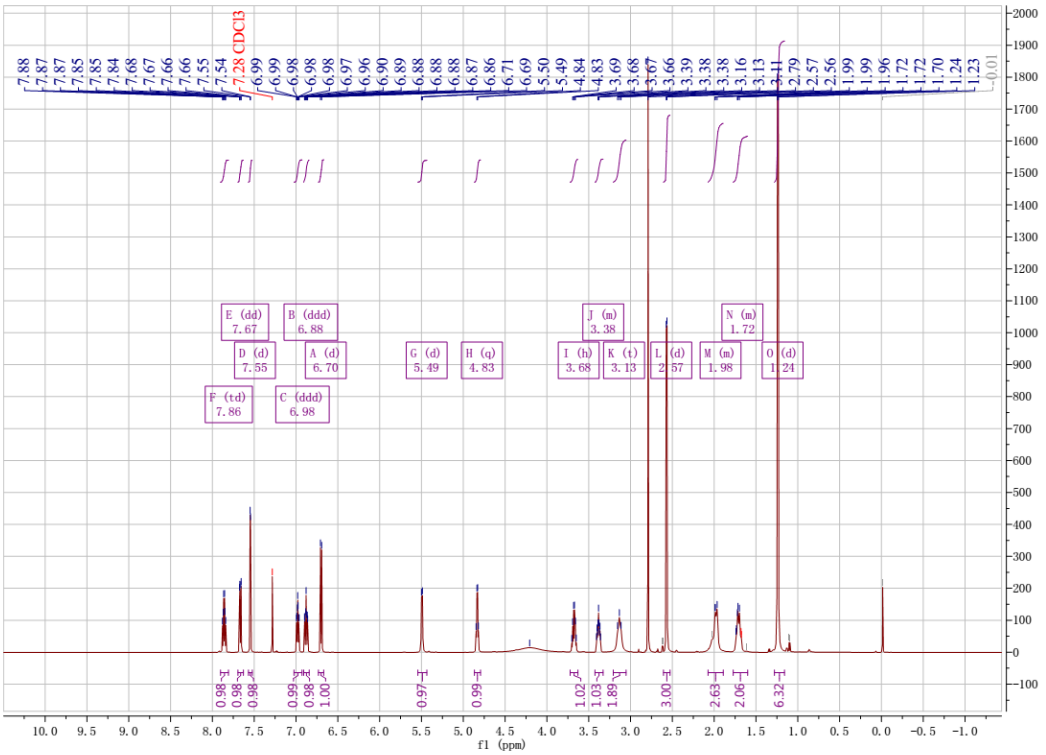



**$^{13}$C NMR:**

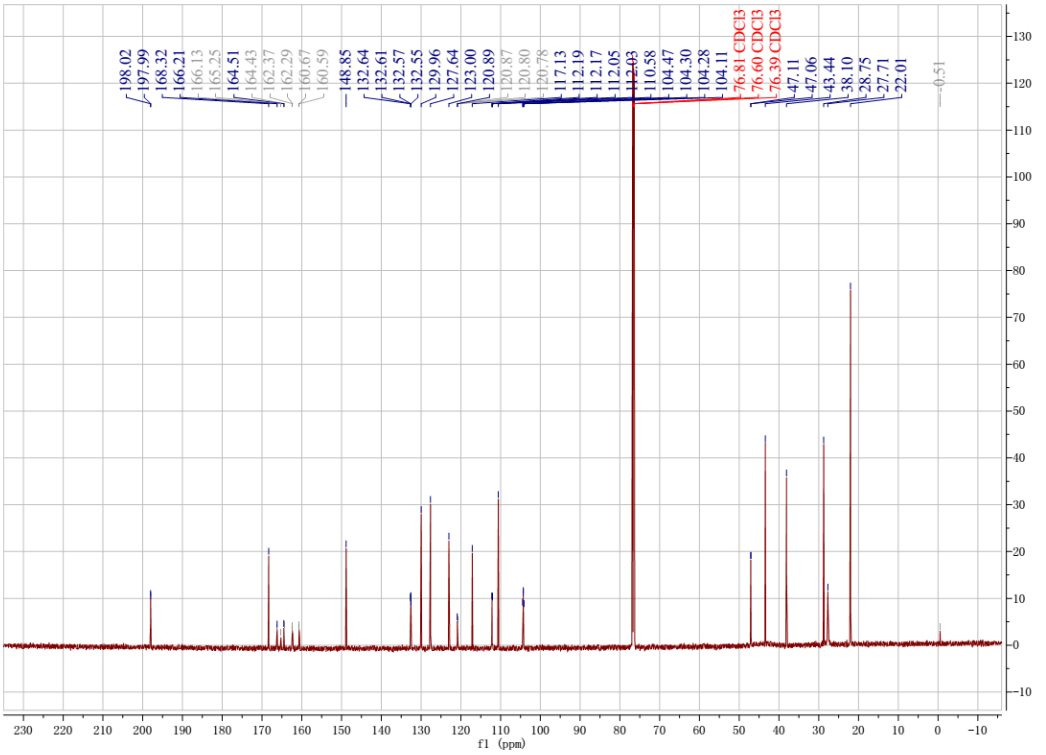


**Compound 23k:**

**$^{1}$H NMR:**

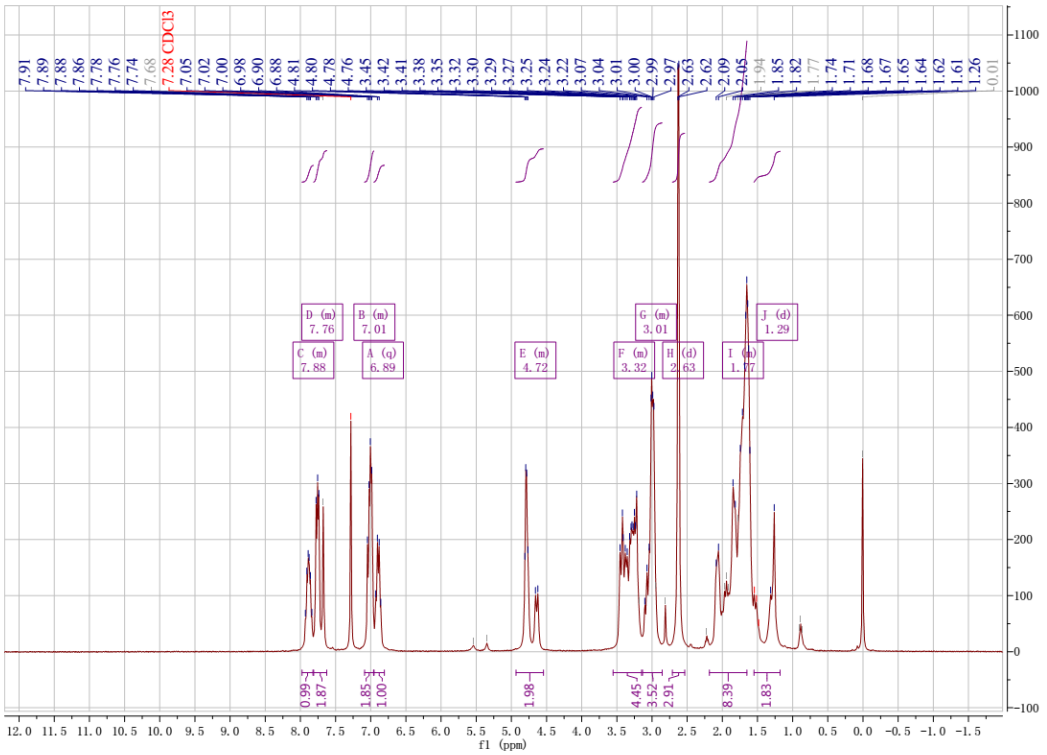



**$^{13}$C NMR:**

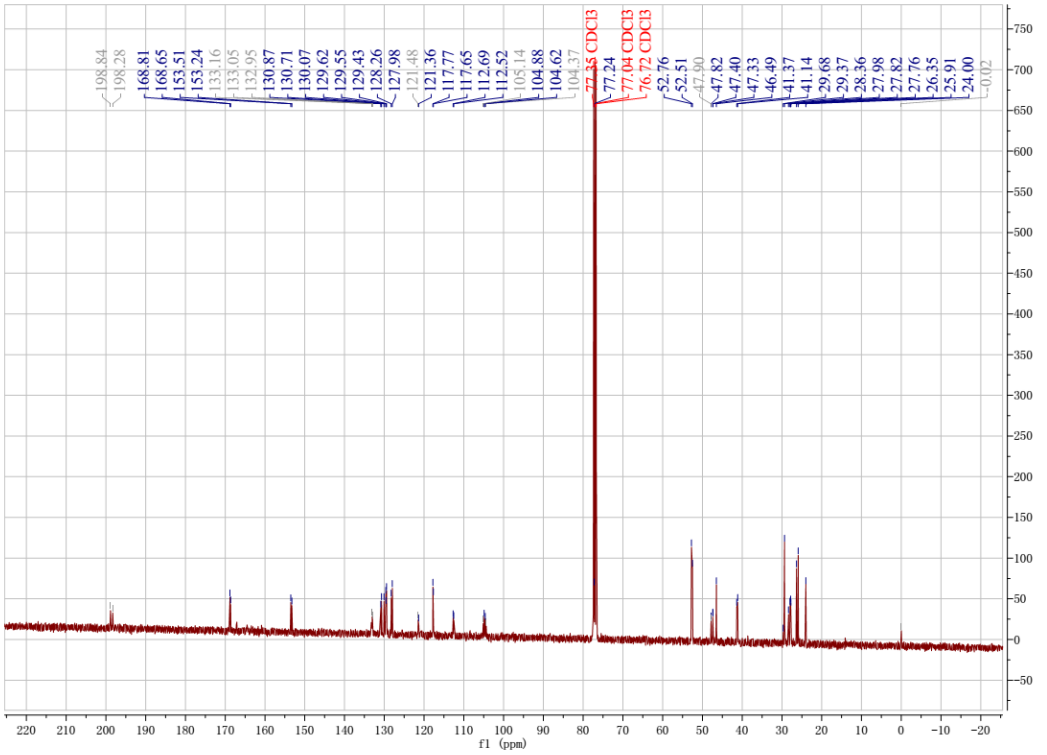


**Compound 23l:**

**$^{1}$H NMR:**

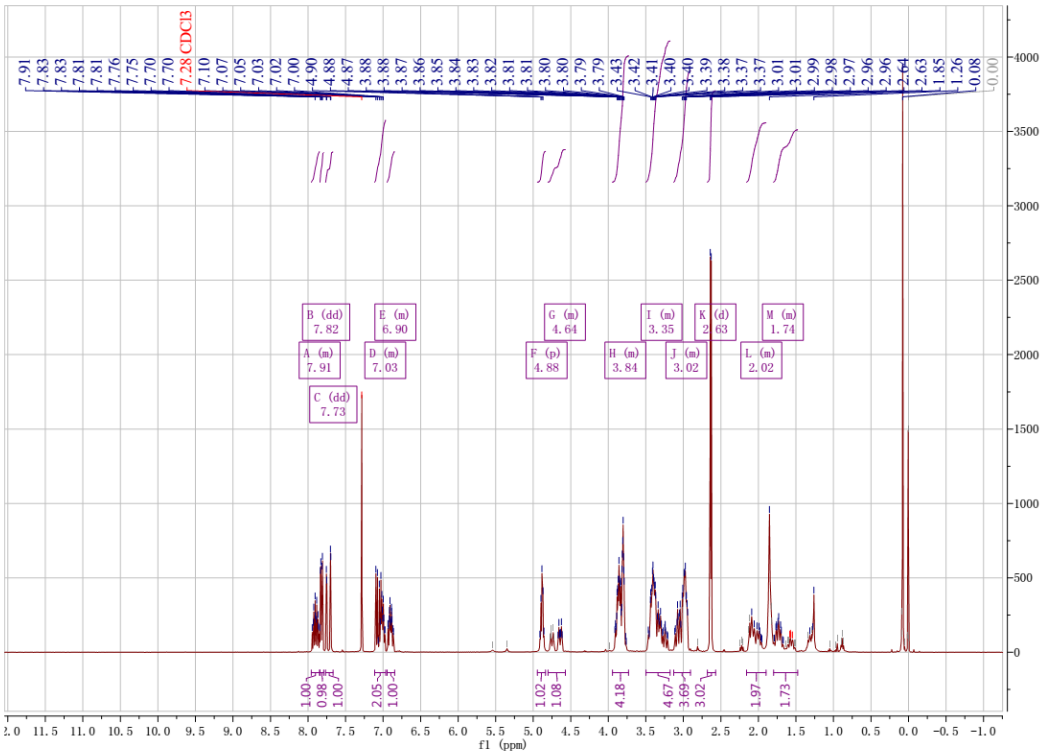


**$^{13}$C NMR:**

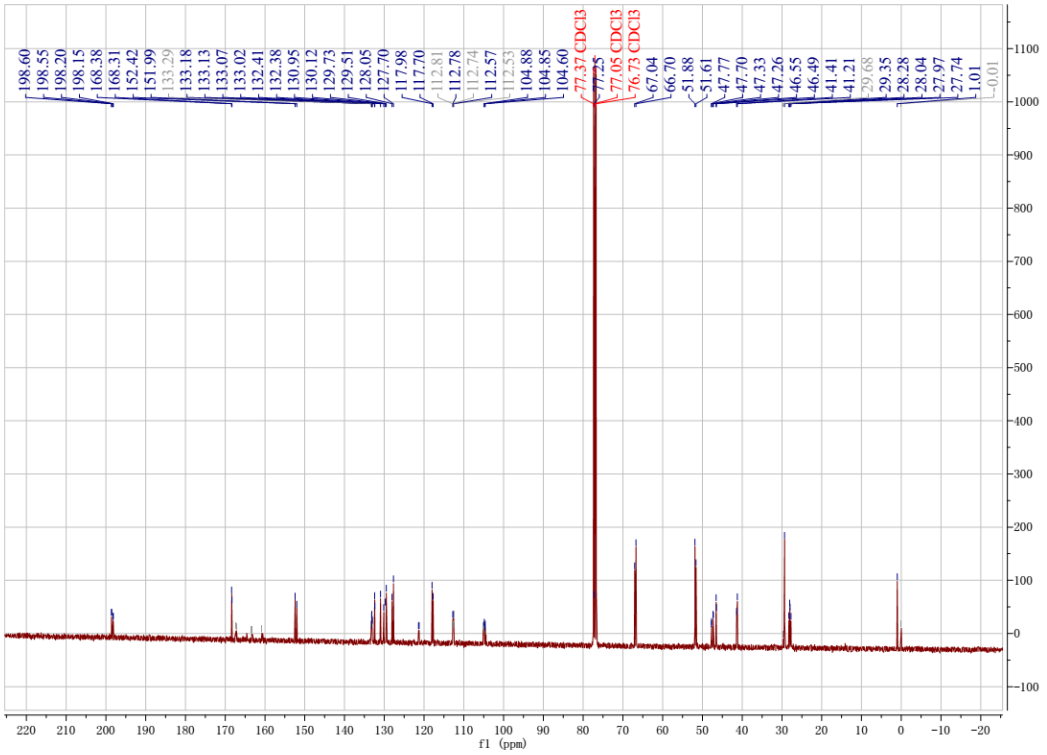


**Compound 23m:**

**$^{1}$H NMR:**

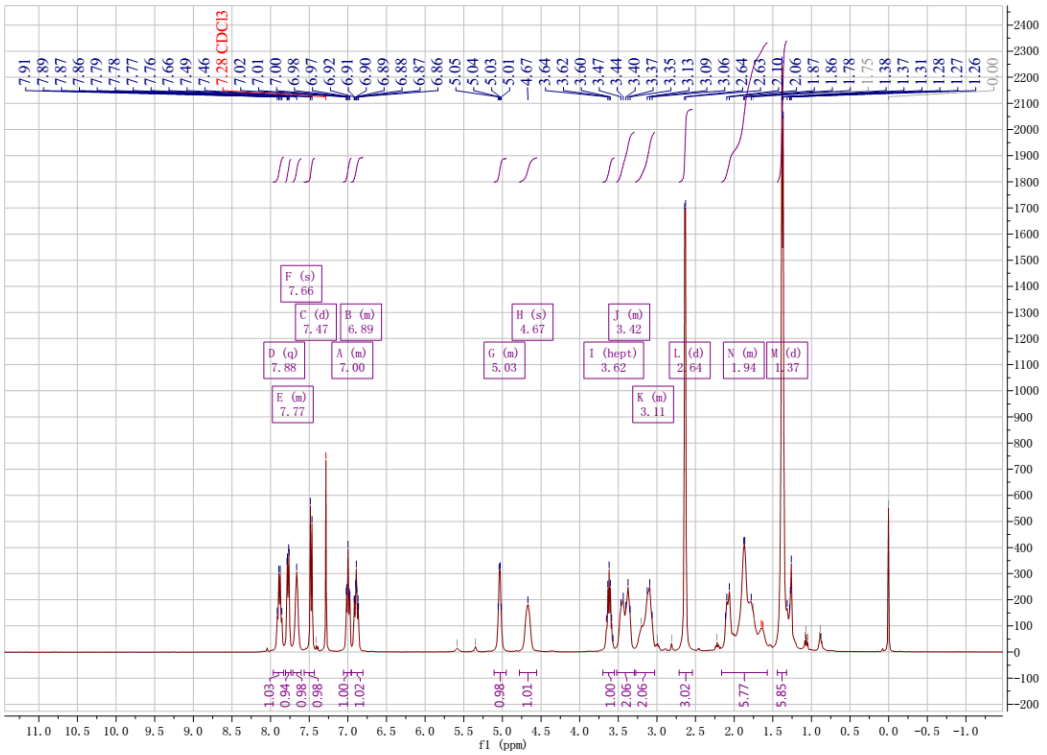



**$^{13}$C NMR:**

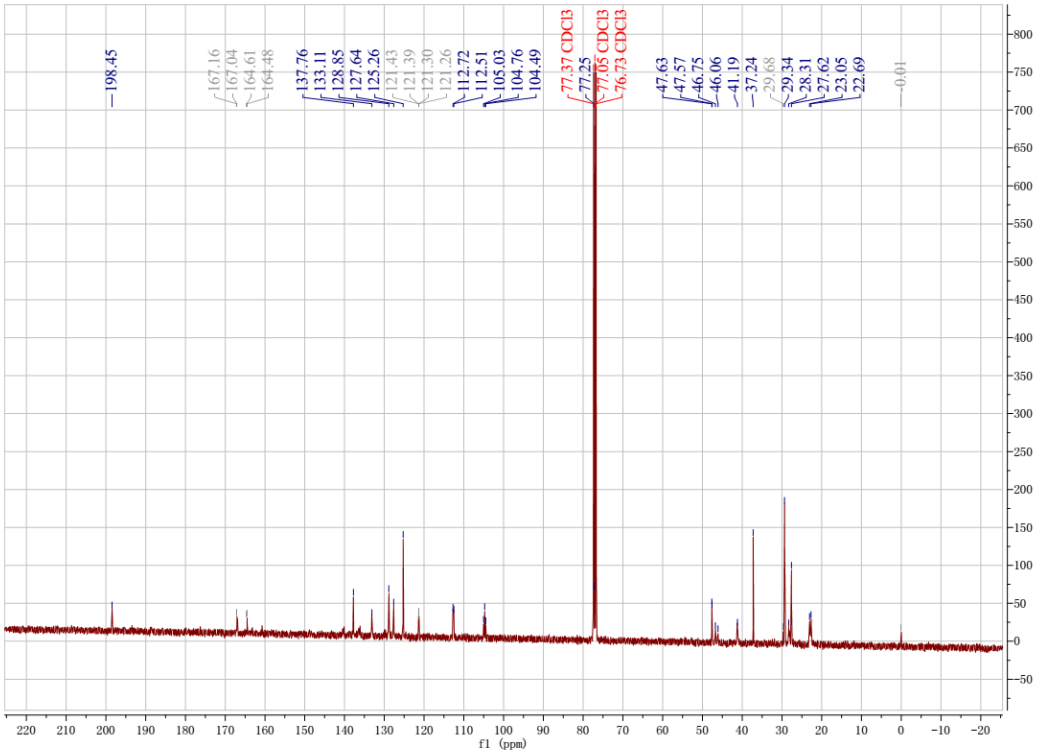


**Compound 23n:**

**$^{1}$H NMR:**

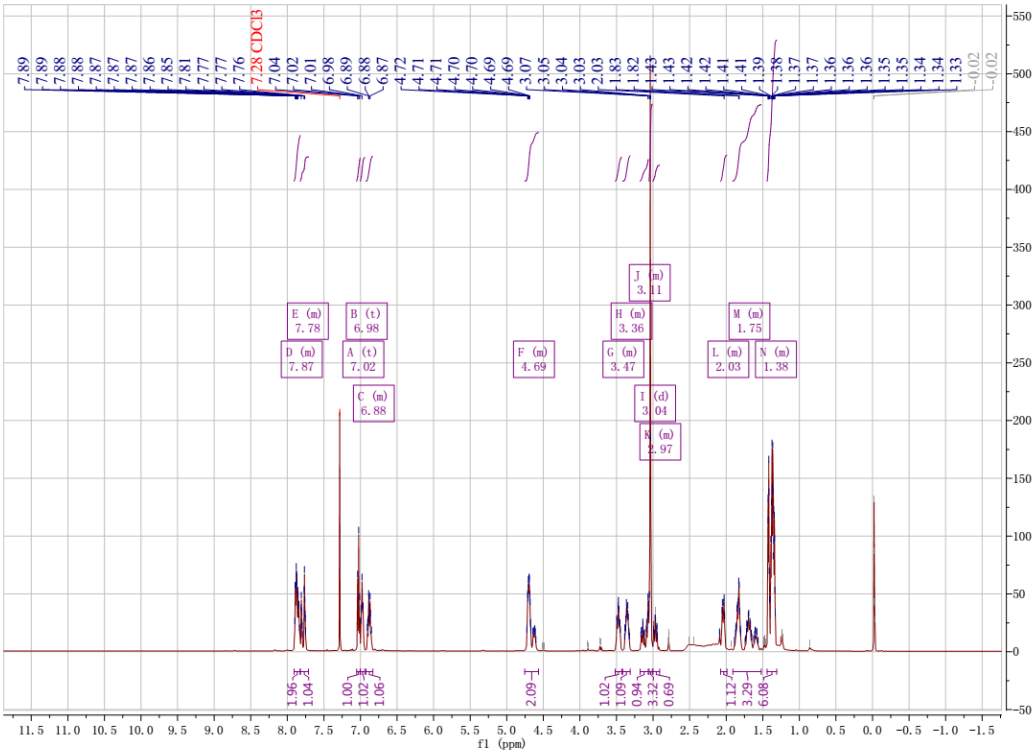



**$^{13}$C NMR:**

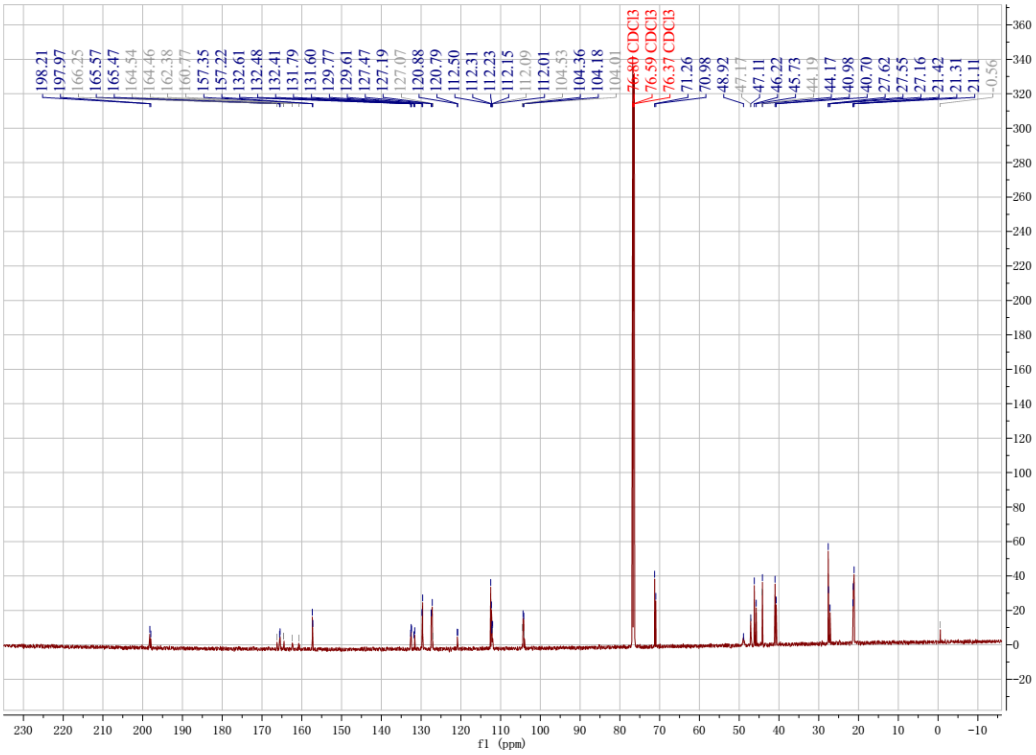


**Compound 23o:**

**$^{1}$H NMR:**

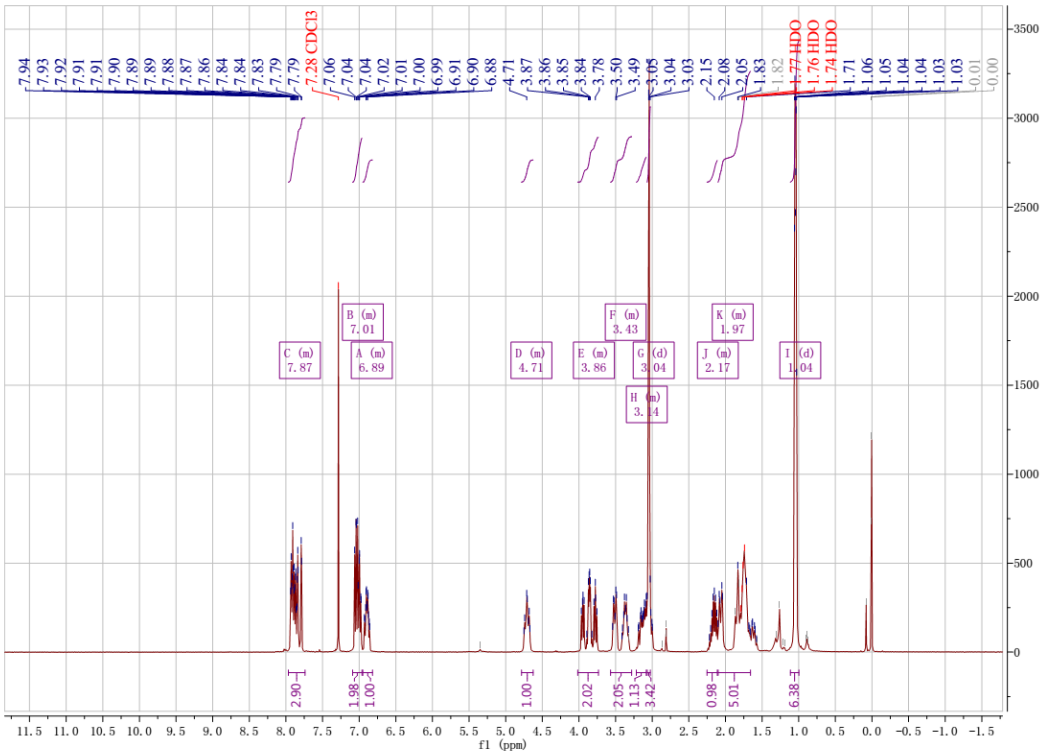


**$^{13}$C NMR:**

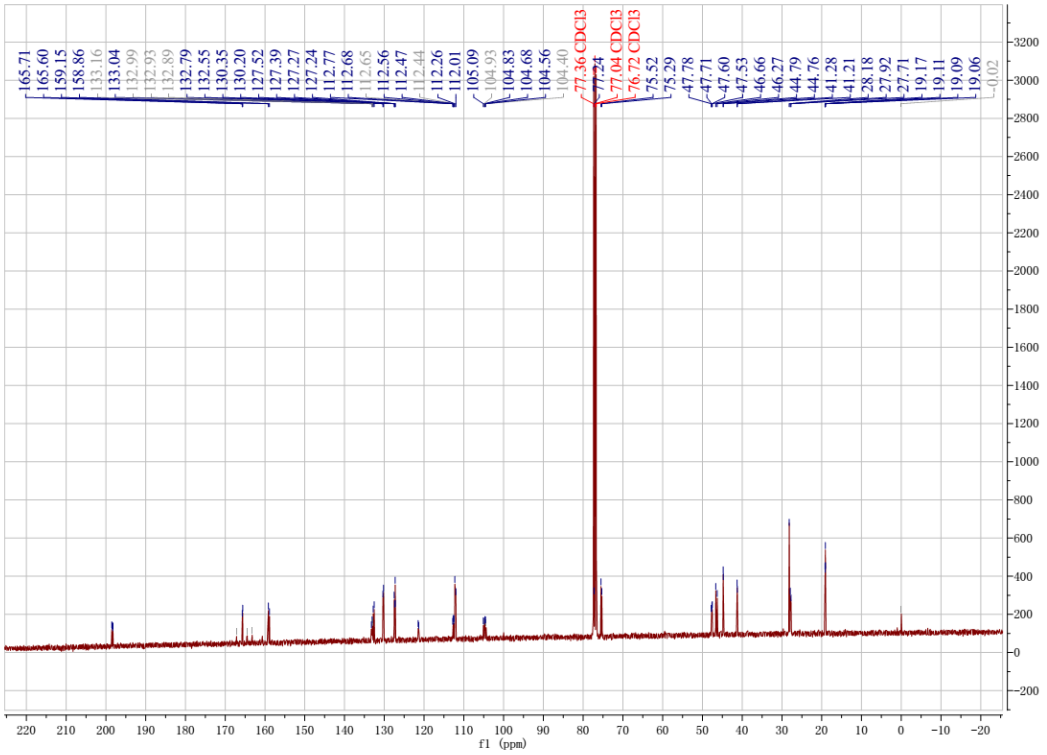


**Compound 23p:**

**$^{1}$H NMR:**

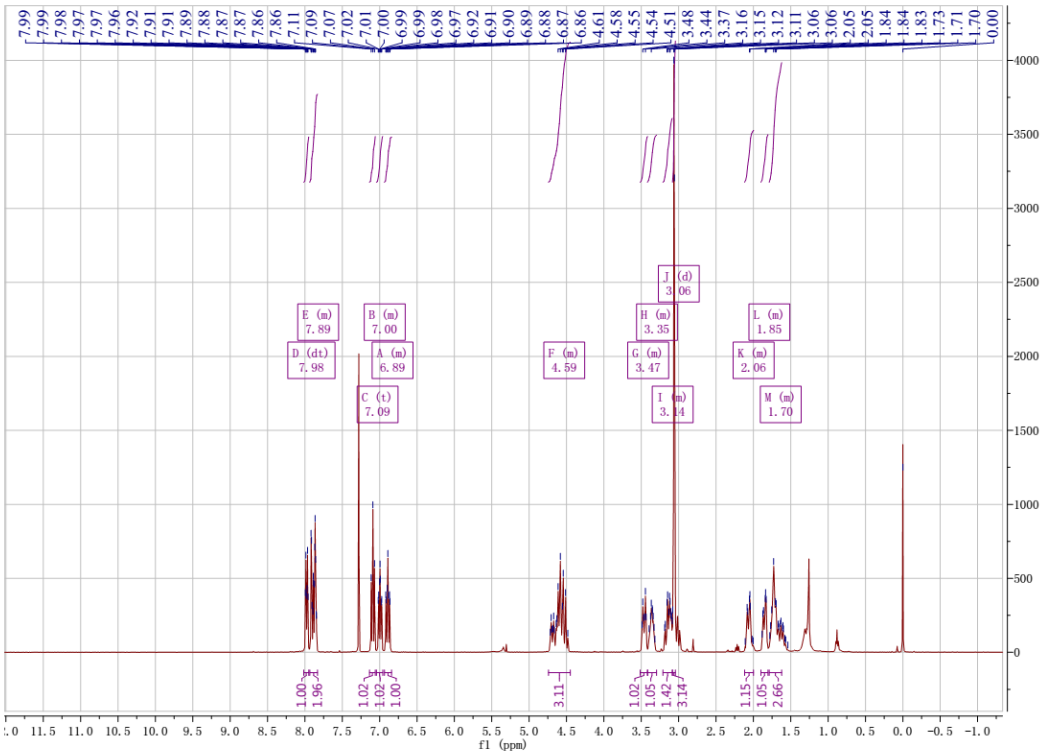


**$^{13}$C NMR:**

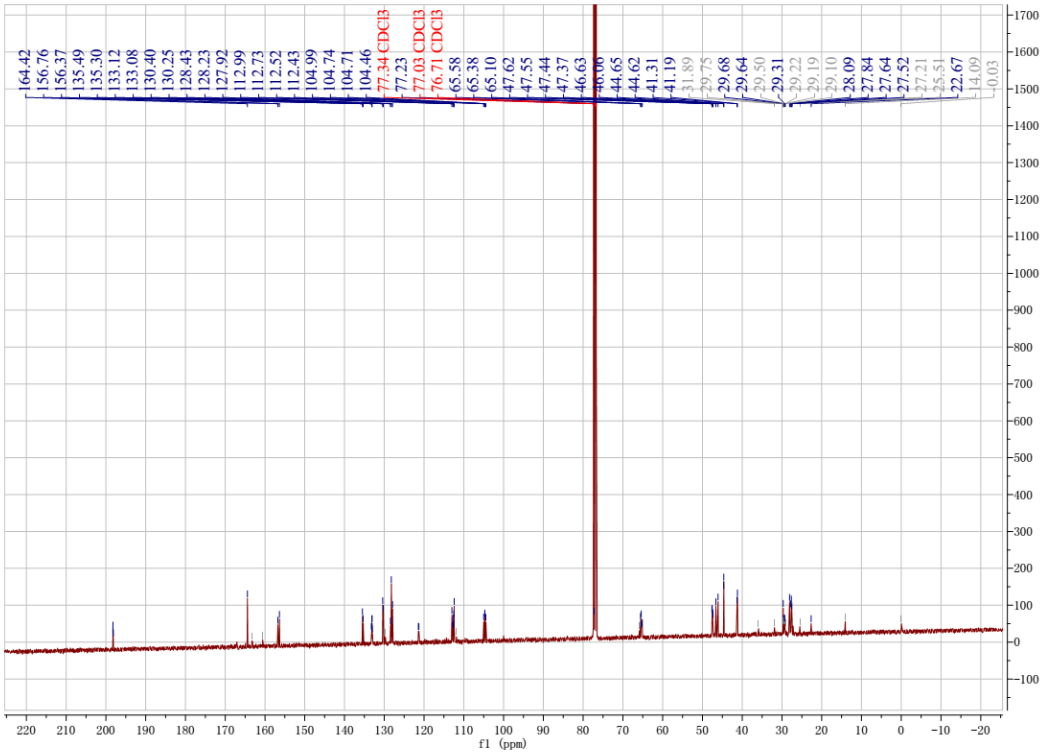


**Compound 23q:**

**$^{1}$H NMR:**

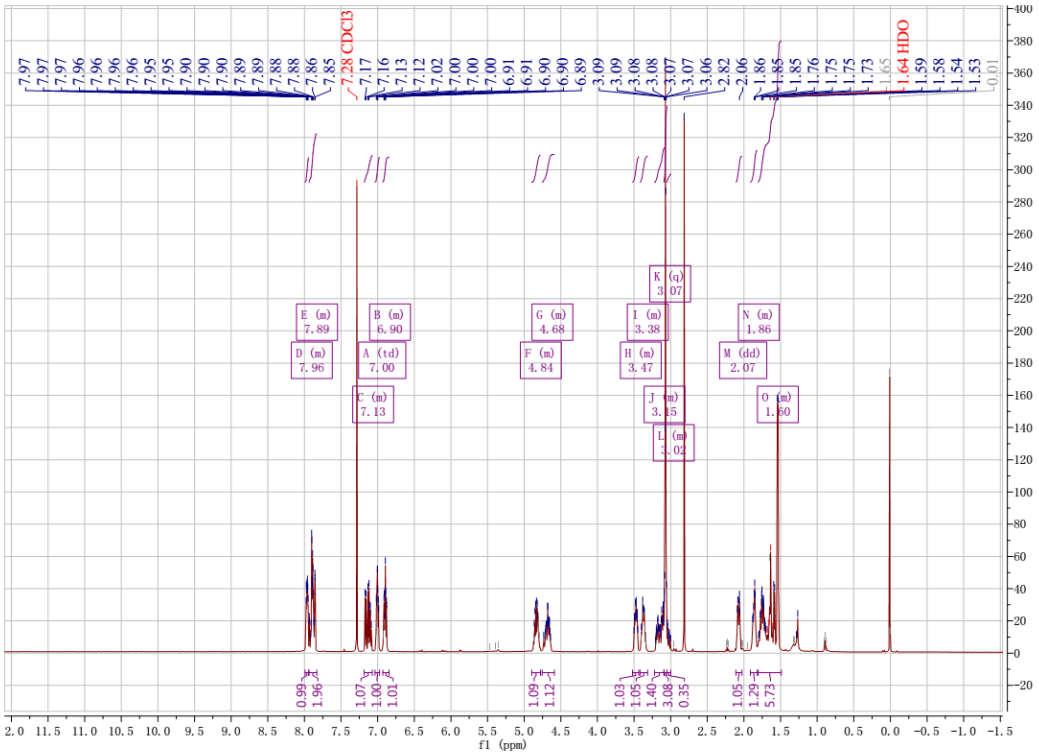



**$^{13}$C NMR:**

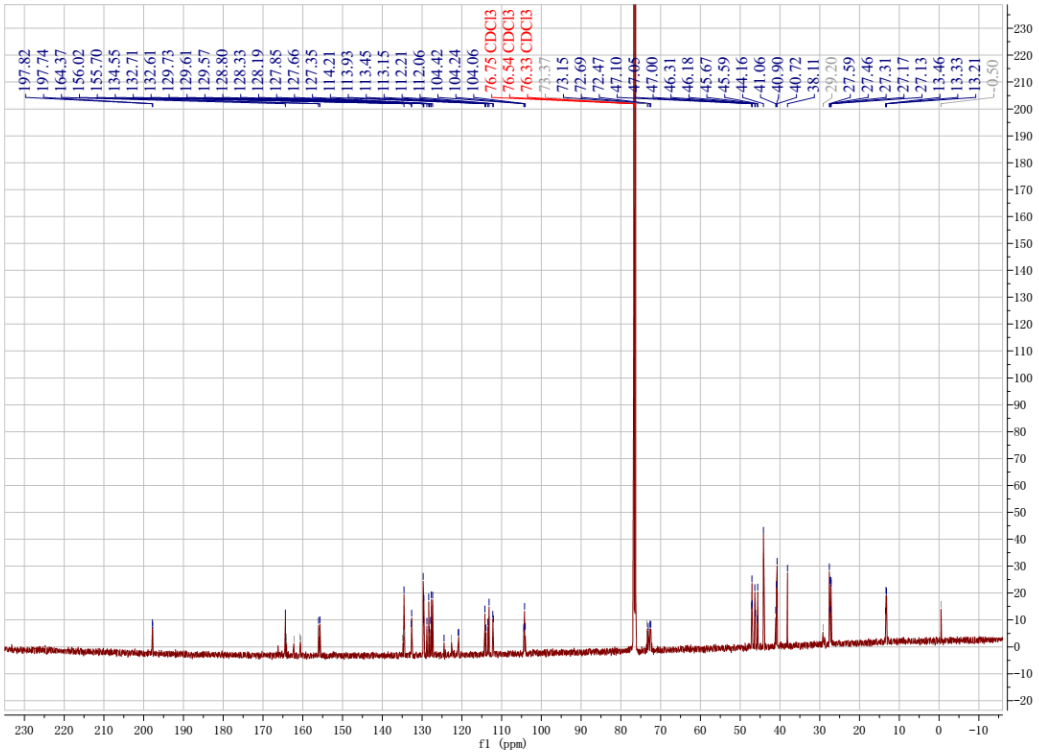


**Compound 23r:**

**$^{1}$H NMR:**

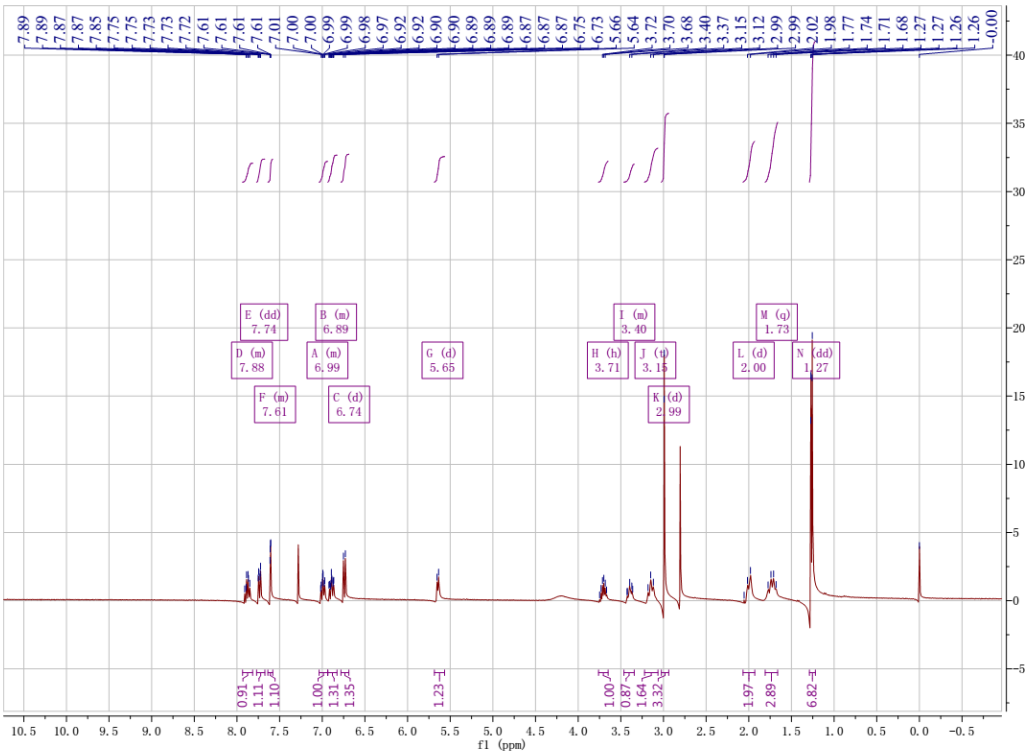



**$^{13}$C NMR:**

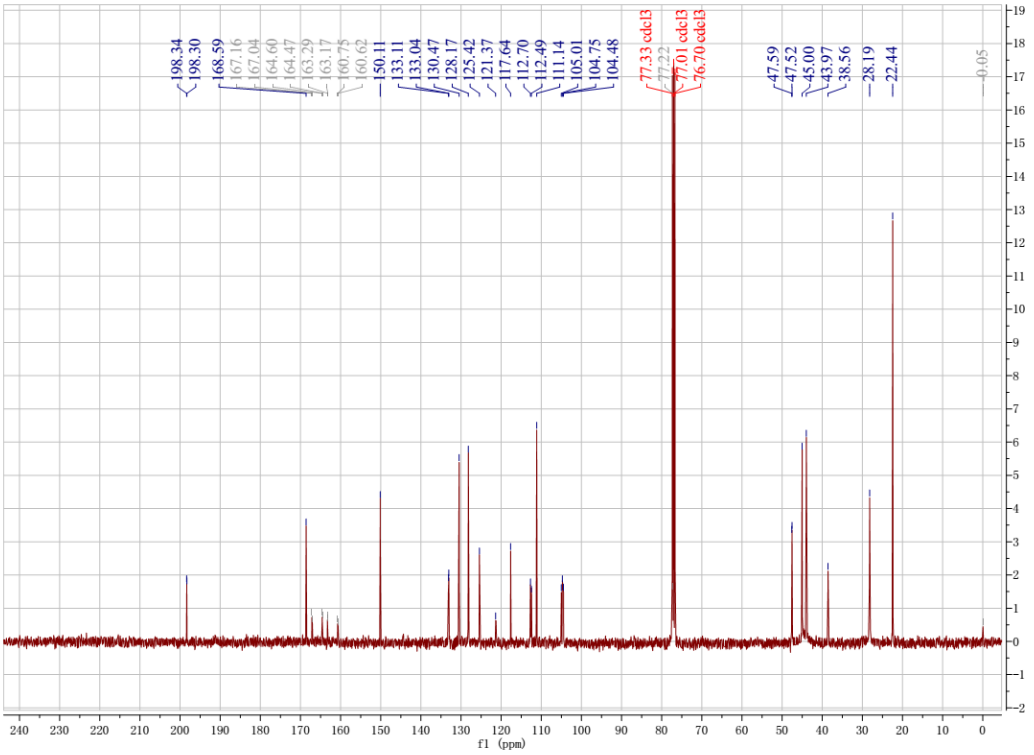


**Compound 23s:**

**$^{1}$H NMR:**



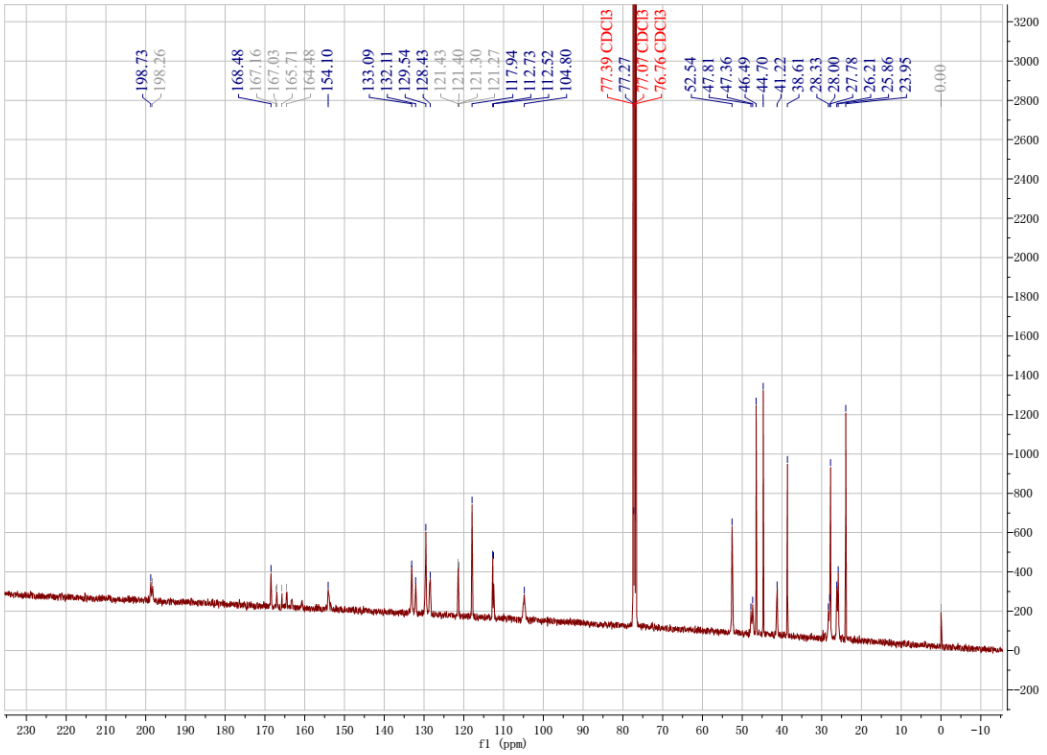

**$^{13}$C NMR:**



**Compound 23t:**

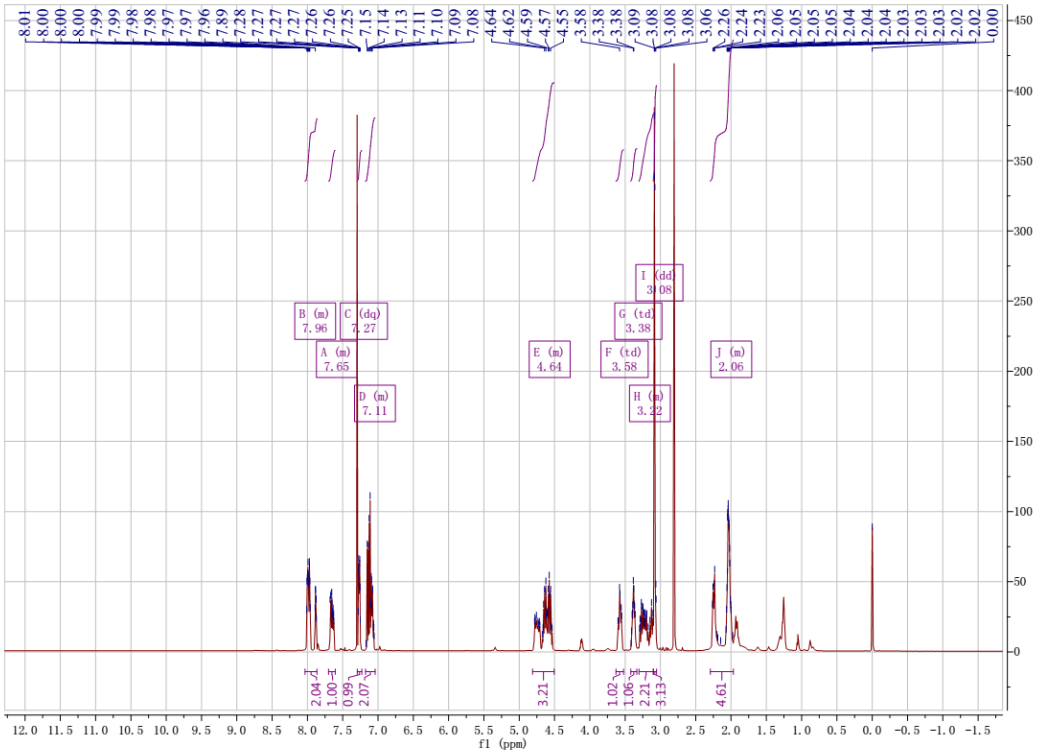
**$^{1}$H NMR:**


**$^{13}$C NMR:**

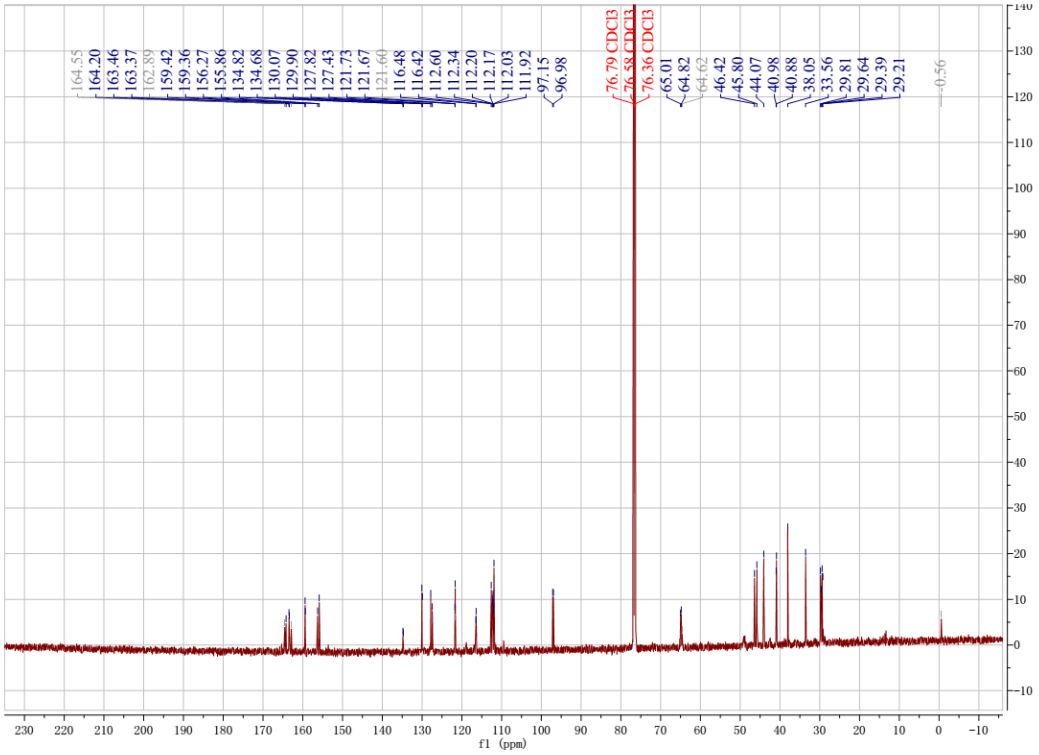


**Compound 24a:**

**$^{1}$H NMR:**

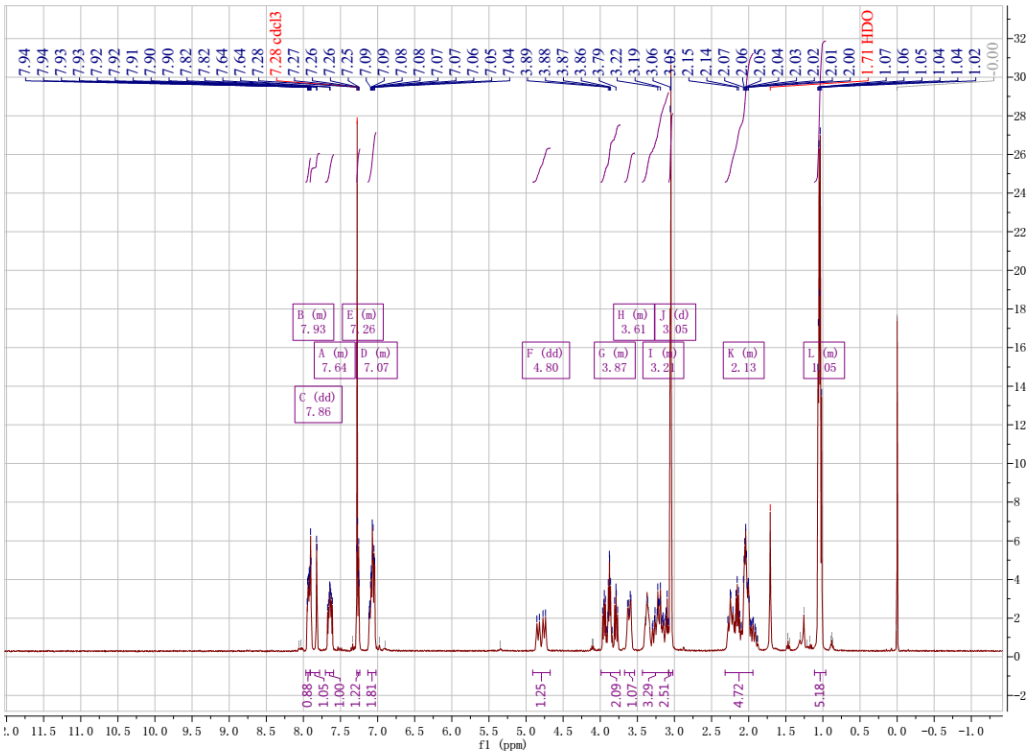



**$^{13}$C NMR:**

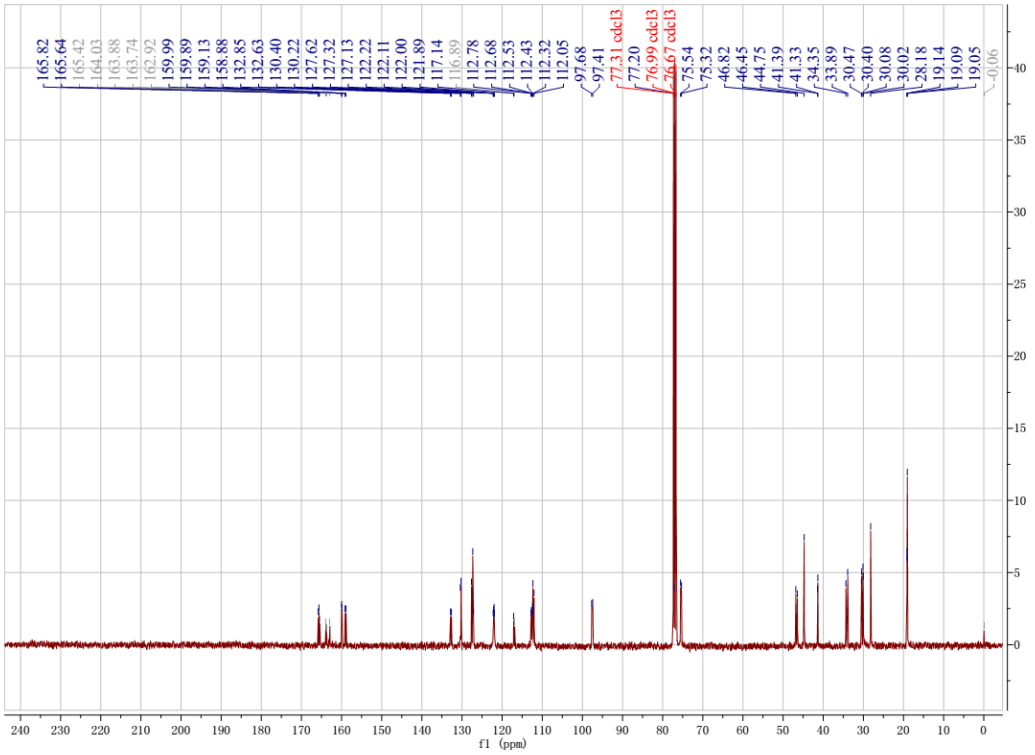


**Compound 24b:**

**$^{1}$H NMR:**

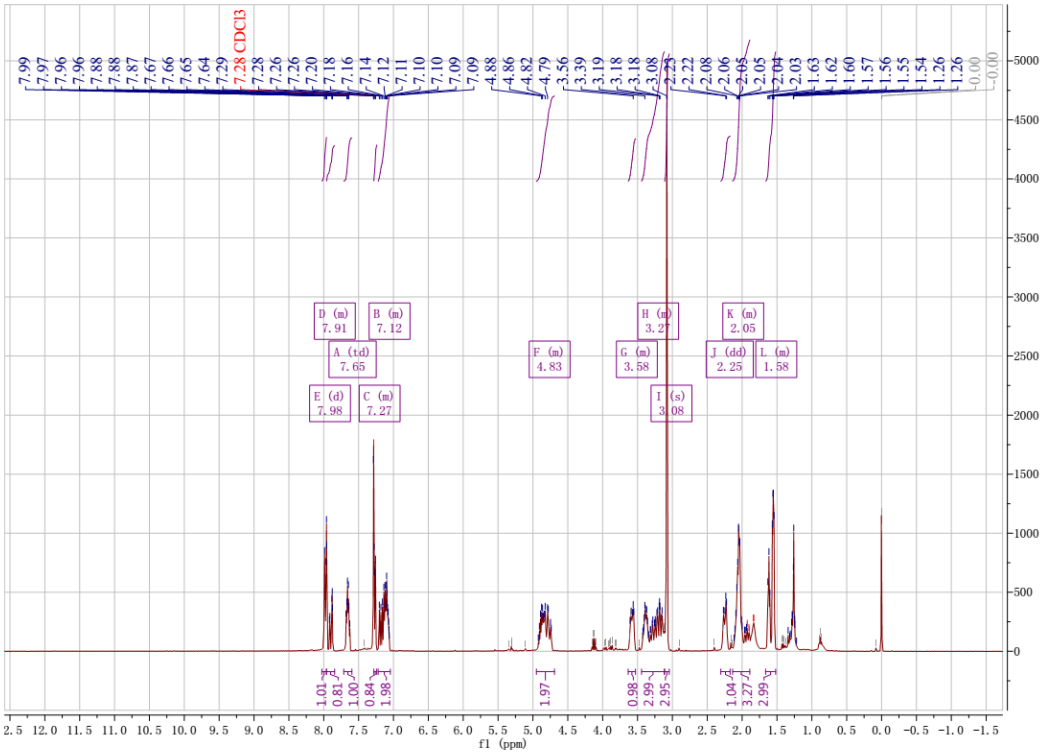


**$^{13}$C NMR:**

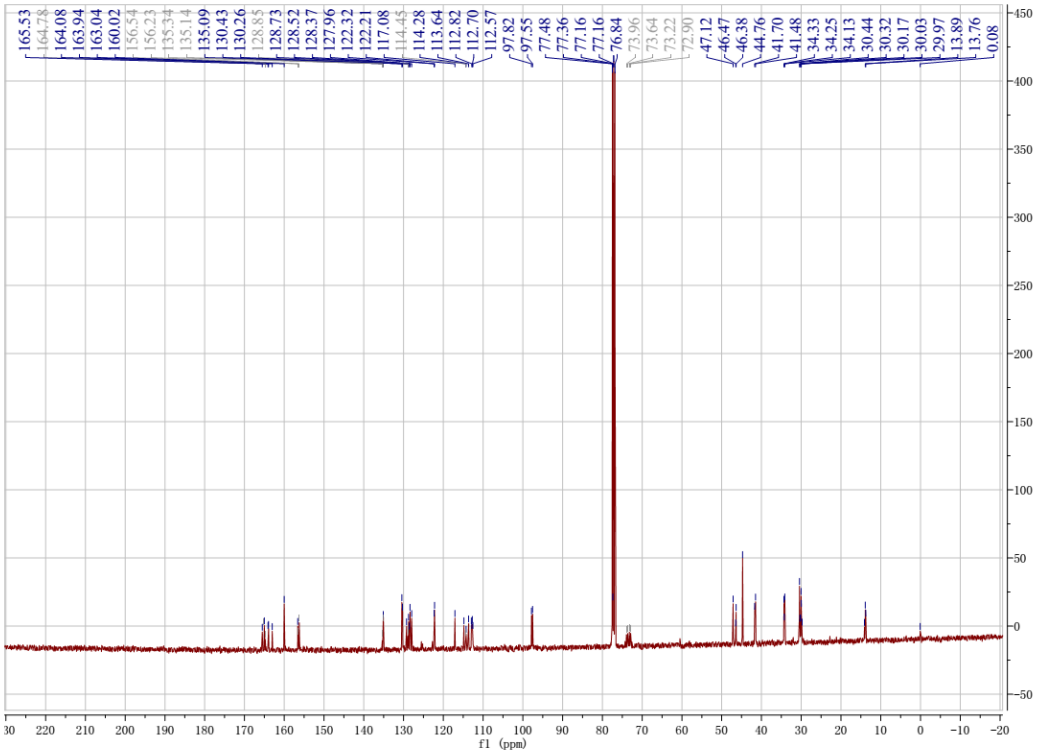


**Compound 24c:**

**$^{1}$H NMR:**

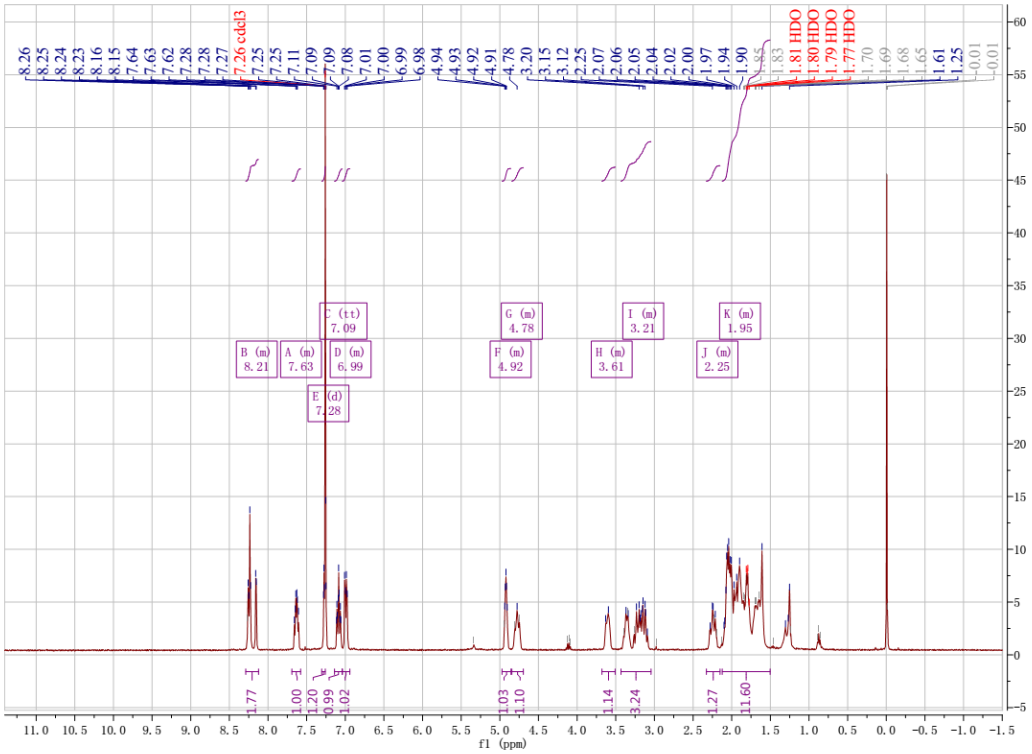



**$^{13}$C NMR:**

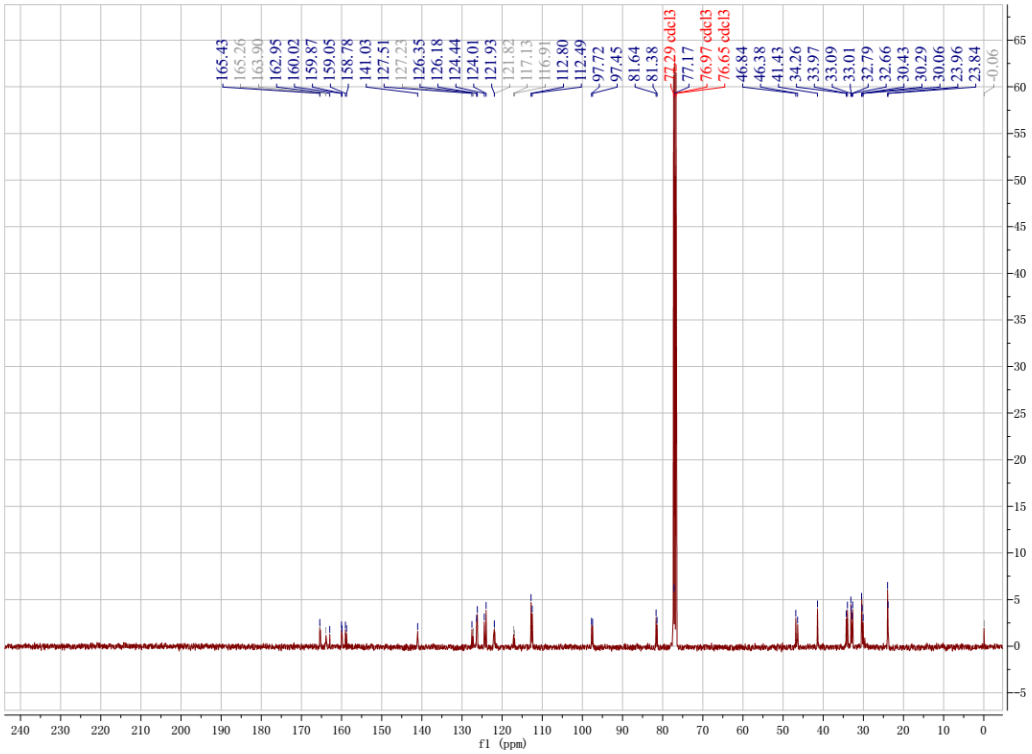


**Compound 24d:**

**$^{1}$H NMR:**

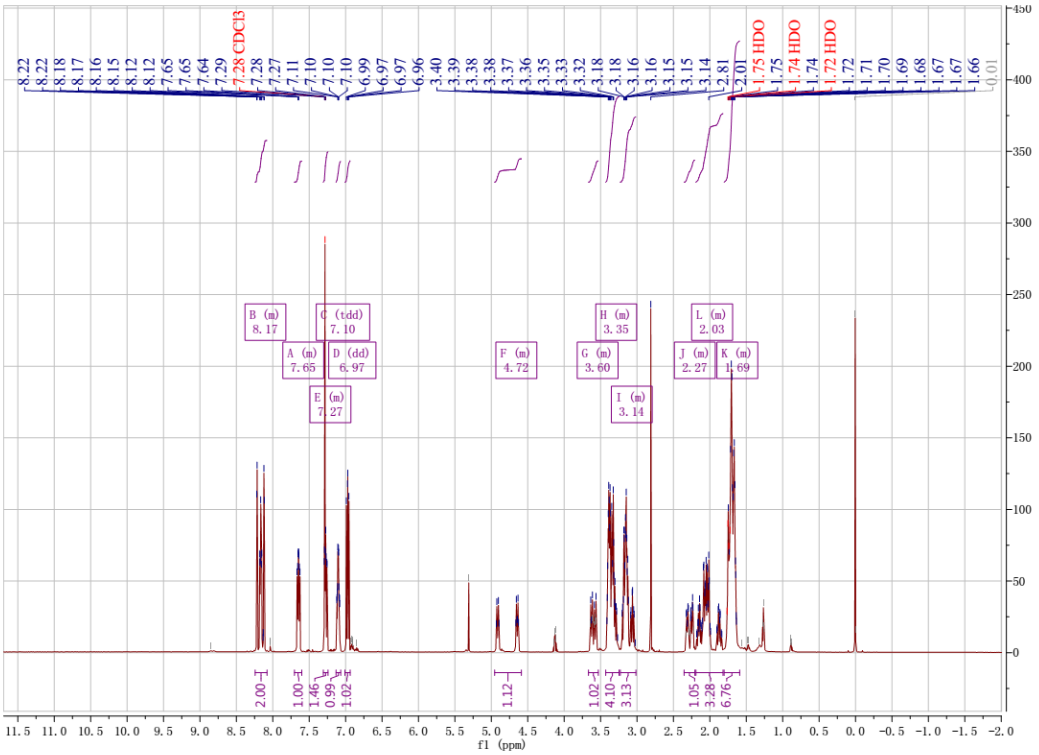



**$^{13}$C NMR:**

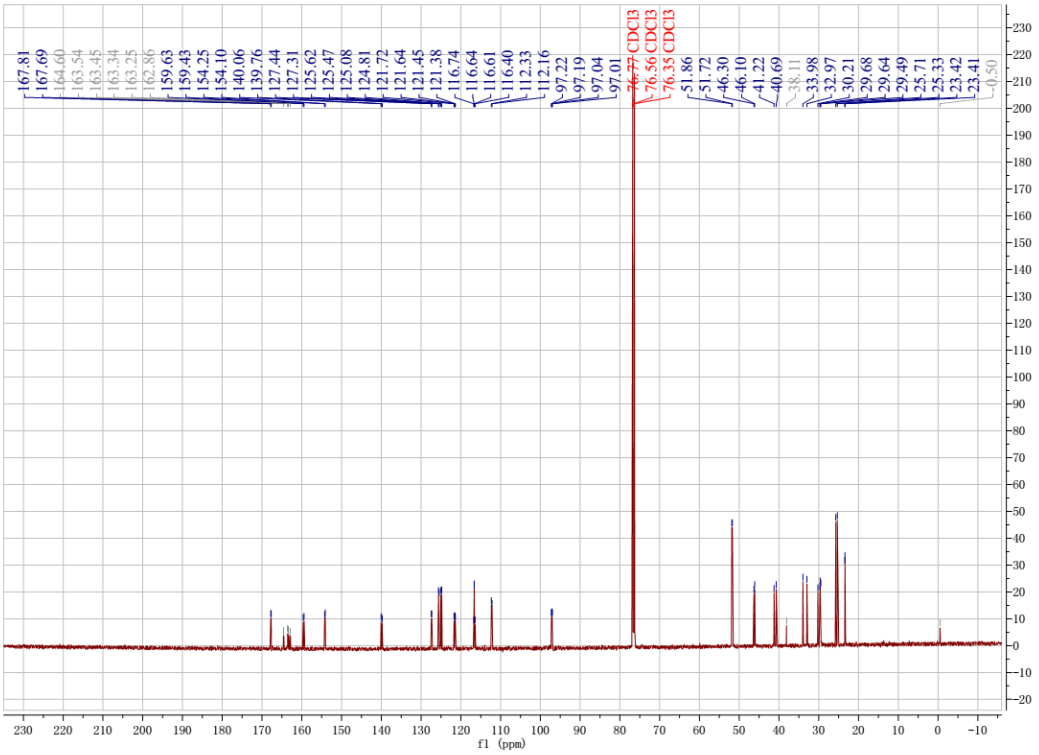


**Compound 24e:**

**$^{1}$H NMR:**

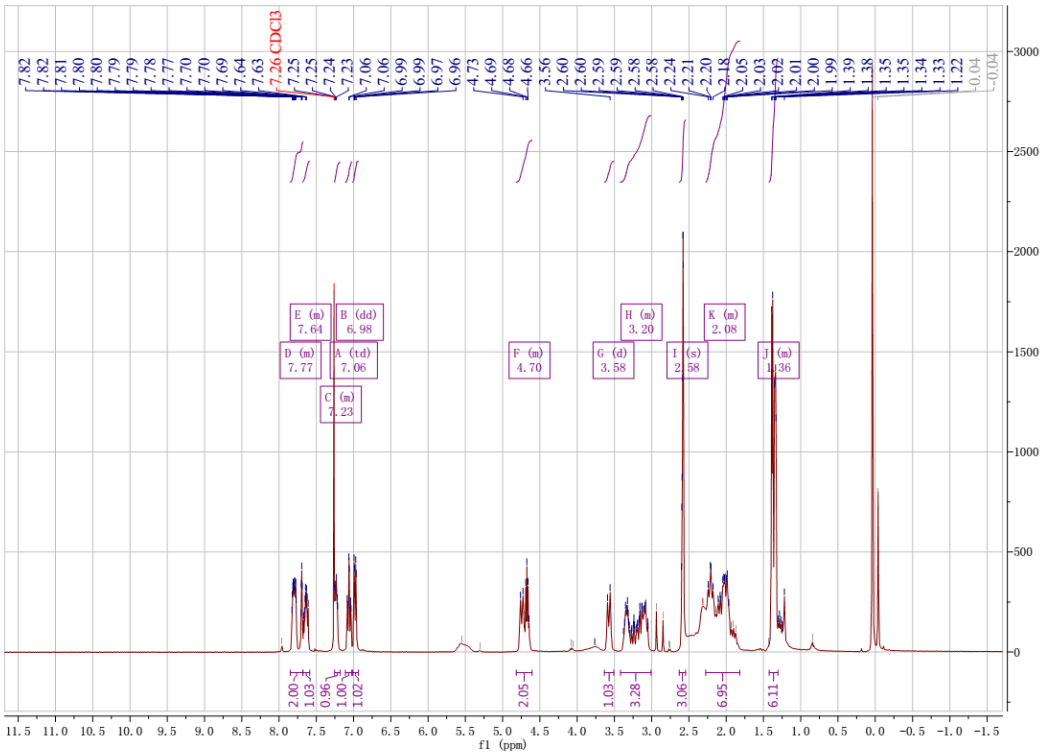


**$^{13}$C NMR:**

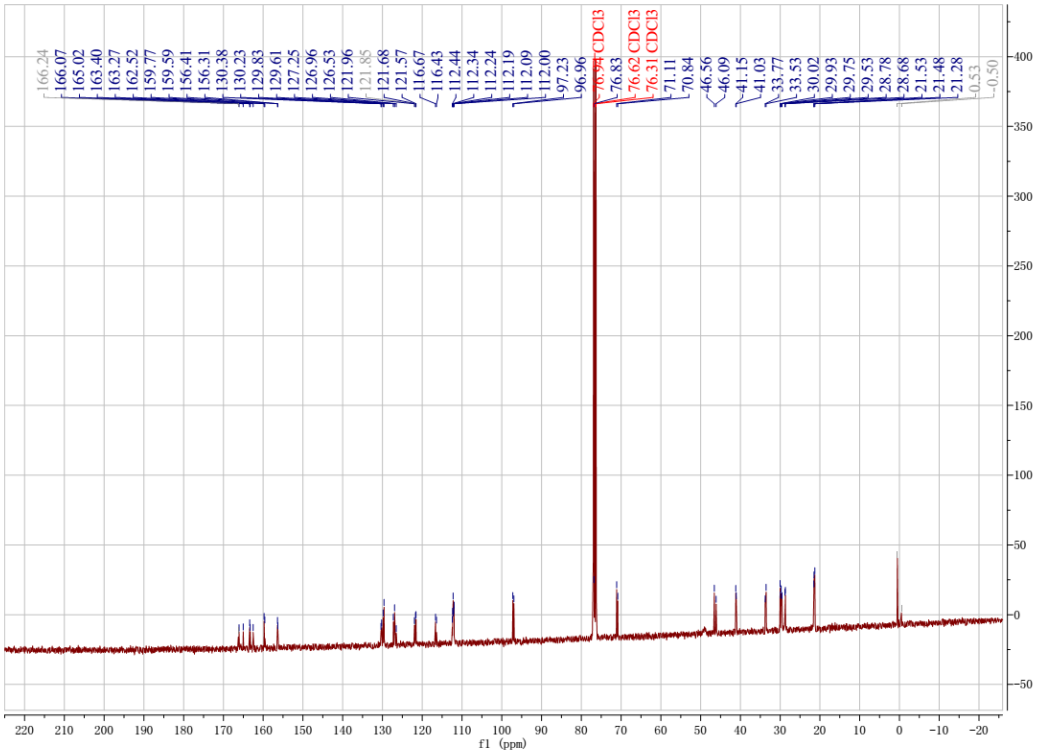


**Compound 24f:**

**$^{1}$H NMR:**

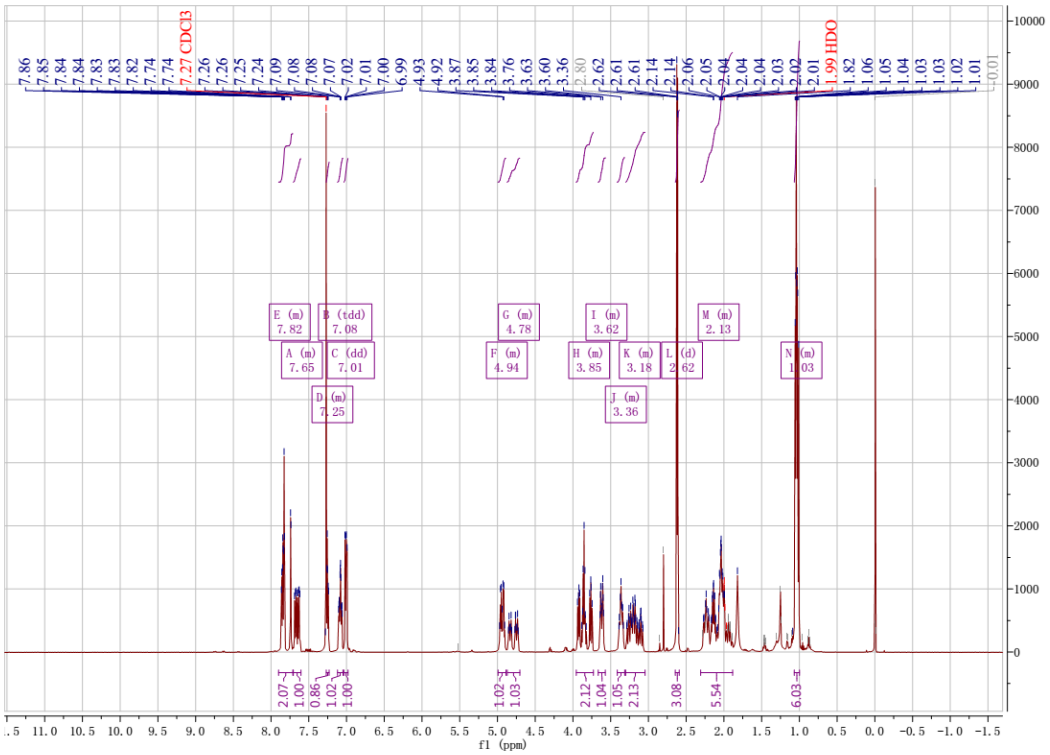


**$^{13}$C NMR:**



**Compound 24g:**

**$^{1}$H NMR:**



**$^{13}$C NMR:**