Supporting Information for

Synthesis and Biological Evaluation of Novel Gardenamide A Derivatives as Multifunctional Neuroprotective agents

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1. Chemistry

Commercially available reagents were used without further purification. Organic solvents were evaporated with reduced pressure using a rotary evaporator. Reactions were monitored by analytical thin-layer chromatography (TLC) using GF254 silica gel plates (Qingdao Haiyang Chemical Co. Ltd., China) and spots were visualized by irradiation with UV light (254 nm). Silica gel column chromatography was performed on silica gel (200-300 mesh) from Qingdao Haiyang Chemical Co. Ltd. (China). All melting points were determined on SGWX-4 micro melting point apparatus and uncorrected. The ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra was recorded on a Bruker Avance 300 MHz spectrometer (Bruker, Fallanden, Switzerland). Chemical shifts were expressed in δ(ppm) and coupling constants (J) in Hz using solvent signals as internal standards ($CDCl_3$, δ_H 7.26 ppm; δ_C 77.0 ppm; D_2O, δ_H 4.70 ppm). Mass Spectra (ESI-MS) was measured with a Hewlett-Packard 1100 LC/MSD spectrometer (Agilent, Waldbronn, Germany).

1.1. (1R, 4aS, 7aS)-methyl 7-((tert-butyldimethylsilyloxy)methyl)-1-hydroxy-1,4a,5,7a-tetrahydrocyclopenta[c]pyran-4-carboxylate (**4**)

To a solution of Genipin **2** (10.0 g, 44.2 mmol) and imidazole (6.02 g, 88.4 mmol) in DMF (60 mL) was added dimethyl tertbutylsilylchloride (TBDMSCl, 13.32 g, 88.4 mmol) in DMF (30 mL) dropwise at 0 ºC, then the reaction mixture was stirred for 2 h. After the addition of 100 mL CH_2Cl_2, the mixture was washed with water (3×100 mL) and saline (60 mL). The organic phase was dried over Na_2SO_4. After removal of solvent under reduced pressure, the residues were purified by column chromatography with petroleum ether/EtOAc (4:1) to afford **4** as a white solid (12.5 g, 83.06%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (s, 1H, =CH), 5.78 (s, 1H, =CH), 4.74 (d, J = 6.6 Hz, 1H, CH), 4.31 (s, 2H, CH_2), 3.68 (s, 3H, $COOCH_3$), 3.15 (q, J = 8.1 Hz, 1H, CH_2), 2.86-2.77 (m, 1H, CH), 2.42 (t, J = 7.5 Hz, 1H, OH), 2.06-1.95 (m, 1H, CH), 0.88 (s, 9H, $SiC(CH_3)_3$), 0.07 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.07, 152.80, 142.14, 129.19, 110.47, 96.40, 62.23, 51.24, 48.22, 38.89, 36.73, 25.83, 25.71, -5.45, -5.48.

1.2. (4aS, 7aS)-methyl 7-((tert-butyldimethylsilyloxy)methyl)-1-oxo-1,4a,5,7a-tetrahydrocyclopenta[c]pyran-4-carboxylate (**5**)

Dess-Martin periodinane (DMP; 25 g, 58.9 mmol) was added to a solution of compound **4** (12.5 g, 36.7 mmol) in CH_2Cl_2 (80 mL). The mixture was stirred at room temperature for 1 h. After the reaction mixture was treated with aqueous saturated $NaHCO_3$ (120 mL) and $Na_2S_2O_3$ (120 mL) for 10 min respectively, the mixture was extracted with CH_2Cl_2 (2×40 mL). The organic layer was combined and dried over anhydrous Na_2SO_4. After removal of solvent under reduced pressure, the residues were purified by column chromatography with petroleum ether/EtOAc (10:1) to afford **5** as a white solid (10.0 g, 80.52%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (s, 1H, =CH), 5.85 (s, 1H, =CH), 4.51-4.38 (m, 2H, CH_2), 3.77 (s, 3H, $COOCH_3$), 3.64 (d, J = 10.2 Hz, 1H, CH_2a), 3.56-3.43 (m, 1H, CH_2b), 2.94-2.86 (m, 1H, CH), 2.26-2.14 (m, 1H, CH), 0.89 (s, 9H, $SiC(CH_3)_3$), 0.07 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.48, 166.09, 148.42, 140.91, 127.55, 113.27, 61.44, 51.90, 45.86, 39.22, 36.14, 25.89, 25.63, -5.37, -5.42.

1.3. (4aS, 7aS)-methyl 7-(hydroxymethyl)-2-methyl-1-oxo-2,4a,5,7a-tetrahydro-1H-cyclopenta[c]pyridine-4-carboxylate (**6a**)

To a solution of compound **5** (10.0 g, 29.54 mmol), methylamine (30-33% solution in ethanol, 8 mL) and pyridine (20 mL) in a sealed tube and the mixture was stirred at 65 ºC for 2 h. After the reaction was finished, the excess solvent was removed under reduced pressure. The residues were transferred to a sealed tube with THF (20 mL) and TFA (20 mL). The mixture was stirred at 65 ºC for 2.5 h. After the complement of the reaction, the reaction mixture was diluted with CH_2Cl_2 (100 mL) and adjusted the pH to 7 with aqueous saturated $NaHCO_3$. The mixture was separated and the organic phase was washed with water (3×100 mL) and saline (60 mL). The CH_2Cl_2 extracts were dried over anhydrous Na_2SO_4. After removal of solvent under reduced pressure, the residues were purified by column chromatography with petroleum ether/EtOAc (1:1) to afford **6a** as a yellow solid (2.9 g, 41.43%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13 (s, 1H, =CH), 5.75 (s, 1H, =CH), 4.31-4.20 (m, 2H, CH_2), 3.69 (s, 3H, $COOCH_3$), 3.61 (d, J = 10.8 Hz, 1H, CH_2a), 3.52-3.43 (m, 1H, CH_2b), 3.11 (s, 3H, NCH_3), 2.88-2.78 (m, 1H, CH), 2.21-2.11 (m, 1H, CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.83, 166.79, 141.21, 138.31, 129.10, 111.11, 60.96, 51.65, 50.10, 40.19, 37.45, 35.53.

1.4. (4aS, 7aS)-methyl 7-(hydroxymethyl)-2-isopropyl-1-oxo-2,4a,5,7a-tetrahydro-1H-cyclopenta[c]pyridine-4-carboxylate (**6b**)

The compound **6b** was arrived by reaction of intermediates **5** (11.5 g, 33.98 mmol) with isopropamide (15 mL), following the same procedure of **6a**. Yellow oil (2.0 g, 22.19%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (s, 1H, =CH), 5.83 (s, 1H, =CH), 4.92-4.83 (m, 1H, $CHCH_3$), 4.39-4.27 (m, 2H, CH_2), 3.78 (s, 3H, $COOCH_3$), 3.68 (d, J = 10.8 Hz, 1H, CH_2a), 3.56-3.46 (m, 1H, CH_2b), 2.89 (dd, J = 16.5, 8.7 Hz, 1H, CH), 2.22 (dd, J = 16.5, 8.7 Hz, 1H, CH), 1.23 (t, J = 7.0 Hz, 6H, $CHCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.95, 166.92, 141.42, 132.61, 129.19, 111.57, 61.03, 51.63, 50.65, 45.26, 40.04, 36.84, 21.10, 20.58.

1.5. (4aS, 7aS)-methyl 7-(((methylsulfonyl)oxy)methyl)-2-methyl-1-oxo-2,4a,5,7a-tetrahydro-1H-cyclopenta[c]pyridine-4-carboxylate (**7a**)

To a solution of compound **6a** (0.5 g, 2.1 mmol), trimethylamine (1.2mL, 8.4 mmoL) in CH_2Cl_2 (20 mL) was added methanesulfonyl chloride (0.65 mL, 8.4 mmol) and the mixture was stirred at 0 ºC for 1 h. After the reaction was finished, the mixture was diluted with DCM (50 mL) and washed with water (3×50 mL) and saline (50 mL). The organic part was dried over anhydrous Na_2SO_4. After removal of solvent under reduced pressure, the residues were used directly to the next step.

1.6. (4aS, 7aS)-methyl 7-(((methylsulfonyl)oxy)methyl)-2-isopropyl-1-oxo-2,4a,5,7a-tetrahydro-1H-cyclopenta[c]pyridine-4-carboxylate (**7b**)

The compound **7b** was synthesized by reaction of compound **6b** with methanesulfonyl chloride, following the same procedure of **7a**.

1.7. General method for the synthesis of Gardenamide A derivatives (**10a-r**)

To a mixture of the intermediates **7a-b** (crud), compound **9a-i** (3.15 mmol) and anhydrous K_2CO_3 (4.2 mmol) in DMF (15 mL) and the mixture was stirred at room temperature for 18 h.

After the complement of the reaction, the reaction mixture were diluted with CH_2Cl_2 (60 mL) and washed with water (3×100 mL) and saline (60 mL). The organic phase was dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with CH_2Cl_2/MeOH (20:1) to afford as a yellow oil. The product was solved in acetone (5 mL) and 5 drops of con. HCl was added. The mixture was frozen and white solid were separated to afford the desired products **10a-r**.

1.7.1. (4aS, 7aS)-methyl 7-((4-benzylpiperazin-1-yl)methyl)-2-methyl-1-oxo-2,4a,5,7a-tetrahydro-1H-cyclopenta[c]pyridine-4-carboxylate (**10a**)

A white solid (0.5 g, 50.81%). m.p. 236.1-239.2 ºC; ^{1}H NMR (300 MHz, D_2O) δ 7.44 (s, 5H, Ar-H), 7.28 (s, 1H, =CH), 6.29 (s, 1H, =CH), 4.40 (s, 2H, CH_2), 4.05 (q, J = 13.2 Hz, 2H, CH_2), 3.72 (d, J = 11.1 Hz, 2H, CH_2), 3.67 (s, 3H, $COOCH_3$), 3.61-3.42 (m, 8H, piperazine-H), 3.07 (s, 3H, NCH_3), 2.85-2.75 (m, 1H, CH), 2.25-2.16 (m, 1H, CH); ^{13}C NMR (75 MHz, D_2O) δ 171.97, 169.02, 142.85, 139.74, 131.20, 130.60, 129.44, 128.51, 127.56, 110.80, 60.52, 56.18, 52.12, 50.06, 48.40, 48.29, 39.25, 37.42, 35.42; ESI-MS m/z: 396.26 $[M+H]^+$.

1.7.2. (4aS, 7aS)-methyl 7-((4-(4-methylbenzyl)piperazin-1-yl)methyl)-2-methyl-1-oxo-2,4a,5,7a-tetrahydro-1H-cyclopenta[c]pyridine-4-carboxylate (**10b**)

A white solid (0.49 g, 48.37%). m.p. 224.4-227.1 ºC; ^{1}H NMR (300 MHz, D_2O) δ 7.32 (d, J = 8.1 Hz, 2H, Ar-H), 7.28 (s, 1H, =CH), 7.26 (d, J = 7.8 Hz, 2H, Ar-H), 6.28 (s, 1H, =CH), 4.35 (s, 2H, CH_2), 4.04 (q, J = 13.4 Hz, 2H, CH_2), 3.71 (d, J = 11.1 Hz, 2H, CH_2), 3.66 (s, 3H, $COOCH_3$), 3.64-3.40 (m, 8H, piperazine-H), 3.07 (s, 3H, NCH_3), 2.87-2.73 (m, 1H, CH), 2.27 (s, 3H, $ArCH_3$), 2.25-2.14 (m, 1H, CH); ^{13}C NMR (75 MHz, D_2O) δ 171.98, 169.02, 142.85, 141.28, 139.73, 131.15, 129.98, 128.51, 124.44, 110.81, 60.29, 56.18, 52.11, 50.06, 48.27, 39.24, 37.42, 35.41, 20.34; ESI-MS m/z: 410.27 $[M+H]^+$.

1.7.3. (4aS, 7aS)-methyl 7-((4-(3-methylbenzyl)piperazin-1-yl)methyl)-2-methyl-1-oxo-2,4a,5,7a-tetrahydro-1H-cyclopenta[c]pyridine-4-carboxylate (**10c**)

A white solid (0.45 g, 44.42%). m.p. 236.2-239.8 ºC; ^{1}H NMR (300 MHz, D_2O) δ 7.32 (t, J = 7.5 Hz, 2H, Ar-H), 7.29 (s, 1H, =CH), 7.27-7.19 (m, 2H, Ar-H), 6.29 (s, 1H, =CH), 4.35 (s, 2H, CH_2), 4.04 (q, J = 13.2 Hz, 2H, CH_2), 3.72 (d, J = 11.1 Hz, 2H, CH_2), 3.67 (s, 3H, $COOCH_3$), 3.64-3.41 (m, 8H, piperazine-H), 3.07 (s, 3H, NCH_3), 2.88-2.73 (m, 1H, CH), 2.28 (s, 3H, $ArCH_3$), 2.25-2.15 (m, 1H, CH); ^{13}C NMR (75 MHz, D_2O) δ 171.99, 169.03, 142.81, 139.78, 139.73, 131.68, 131.16, 129.32, 128.53, 128.06, 127.55, 110.82, 60.52, 56.19, 52.11, 50.06, 48.38, 48.28, 39.24, 37.42, 35.41, 20.29; ESI-MS m/z: 410.23 $[M+H]^+$.

1.7.4. (4aS, 7aS)-methyl 7-((4-(3-methoxybenzyl)piperazin-1-yl)methyl)-2-methyl-1-oxo-2,4a,5,7a-tetrahydro-1H-cyclopenta[c]pyridine-4-carboxylate (**10d**)

A white solid (0.5 g, 47.76%). m.p. 223.6-226.8 ºC; ^{1}H NMR (300 MHz, D_2O) δ 7.38 (t, J = 7.8 Hz, 1H, Ar-H), 7.28 (s, 1H, =CH), 7.08-7.00 (m, 3H, Ar-H), 6.29 (s, 1H, =CH), 4.37 (s, 2H, CH_2), 4.05 (q, J = 13.2 Hz, 2H, CH_2), 3.76 (s, 3H, Ar-OCH_3), 3.72 (d, J = 11.1 Hz, 2H, CH_2), 3.67 (s, 3H, $COOCH_3$), 3.61-3.42 (m, 8H, piperazine-H), 3.07 (s, 3H, NCH_3), 2.85-2.75 (m, 1H, CH), 2.25-2.16 (m, 1H, CH); ^{13}C NMR (75 MHz, D_2O) δ 171.97, 169.01, 159.40, 142.88, 139.73, 130.77, 129.06, 128.49, 123.71, 116.65, 116.05, 110.80, 60.34, 56.19, 55.46, 52.11,

50.06, 48.45, 48.28, 39.25, 37.42, 35.42; ESI-MS m/z: 426.28 $[M+H]^+$.

1.7.5. (4aS, 7aS)-methyl 7-((4-(4-fluorobenzyl)piperazin-1-yl)methyl)-2-methyl-1-oxo-2,4a,5,7a-tetrahydro-1H-cyclopenta[c]pyridine-4-carboxylate (**10e**)

A white solid (0.53 g, 51.96%). m.p. 242.5-245.8 ºC; ^{1}H NMR (300 MHz, D_2O) δ 7.47-7.40 (m, 2H, Ar-H), 7.26 (s, 1H, =CH), 7.13 (t, J = 8.7 Hz, 2H, Ar-H), 6.27 (s, 1H, =CH), 4.37 (s, 2H, CH_2), 4.03 (q, J = 13.2 Hz, 2H, CH_2), 3.70 (d, J = 11.1 Hz, 2H, CH_2), 3.64 (s, 3H, $COOCH_3$), 3.60-3.39 (m, 8H, piperazine-H), 3.05 (s, 3H, NCH_3), 2.82-2.72 (m, 1H, CH), 2.25-2.11 (m, 1H, CH); ^{13}C NMR (75 MHz, D_2O) δ 171.95, 169.00, 163.70 ($J_{C\text{-}F}$ 246.6 Hz), 142.89, 139.73, 133.47 ($J_{C\text{-}F}$ 8.9 Hz), 128.47, 123.57 ($J_{C\text{-}F}$ 3.1 Hz), 116.34 ($J_{C\text{-}F}$ 22.0 Hz), 110.78, 59.66, 56.17, 52.10, 50.04, 48.30, 47.75, 39.24, 37.40, 35.42; ESI-MS m/z: 414.22 $[M+H]^+$.

1.7.6. (4aS, 7aS)-methyl 7-((4-(4-chlorobenzyl)piperazin-1-yl)methyl)-2-methyl-1-oxo-2,4a,5,7a-tetrahydro-1H-cyclopenta[c]pyridine-4-carboxylate (**10f**)

A white solid (0.51 g, 48.30%). m.p. 237.4-240.1 ºC; ^{1}H NMR (300 MHz, D_2O) δ 7.45 (d, J = 8.7 Hz, 2H, Ar-H), 7.40 (d, J = 8.7 Hz, 2H, Ar-H), 7.28 (s, 1H, =CH), 6.29 (s, 1H, =CH), 4.38 (s, 2H, CH_2), 4.05 (q, J = 13.3 Hz, 2H, CH_2), 3.72 (d, J = 11.1 Hz, 2H, CH_2), 3.66 (s, 3H, $COOCH_3$), 3.64-3.38 (m, 8H, piperazine-H), 3.07 (s, 3H, NCH_3), 2.87-2.72 (m, 1H, CH), 2.30-2.14 (m, 1H, CH); ^{13}C NMR (75 MHz, D_2O) δ 171.97, 169.01, 142.90, 139.73, 136.16, 132.74, 129.48, 128.48, 126.21, 110.81, 59.67, 56.19, 52.12, 50.06, 48.41, 48.28, 39.26, 37.42, 35.43; ESI-MS m/z: 430.32 $[M+H]^+$.

1.7.7. (4aS, 7aS)-methyl 7-((4-(4-nitrobenzyl)piperazin-1-yl)methyl)-2-methyl-1-oxo-2,4a,5,7a-tetrahydro-1H-cyclopenta[c]pyridine-4-carboxylate (**10g**)

A white solid (0.70 g, 64.94 %). m.p. 245.3-248.2 ºC; ^{1}H NMR (300 MHz, D_2O) δ 8.21 (d, J = 8.4 Hz, 2H, Ar-H), 7.68 (d, J = 8.4 Hz, 2H, Ar-H), 7.24 (s, 1H, =CH), 6.28 (s, 1H, =CH), 4.52 (s, 2H, CH_2), 4.06 (q, J = 13.3 Hz, 2H, CH_2), 3.71 (d, J = 11.1 Hz, 2H, CH_2), 3.65 (s, 3H, $COOCH_3$), 3.63-3.30 (m, 8H, piperazine-H), 3.05 (s, 3H, NCH_3), 2.85-2.70 (m, 1H, CH), 2.25-2.10 (m, 1H, CH); ^{13}C NMR (75 MHz, D_2O) δ 171.92, 168.94, 148.73, 142.93, 139.72, 134.84, 132.53, 128.45, 124.38, 110.74, 59.21, 56.18, 52.11, 50.03, 48.77, 48.32, 39.29, 37.38, 35.45; ESI-MS m/z: 441.20 $[M+H]^+$.

1.7.8. (4aS, 7aS)-methyl 7-((4-(4-trifluoromethylbenzyl)piperazin-1-yl)methyl)-2-methyl-1-oxo-2,4a,5,7a-tetrahydro-1H-cyclopenta[c]pyridine-4-carboxylate (**10h**)

A white solid (0.47 g, 41.74%). m.p. 240.5-243.6 ºC; ^{1}H-NMR (300 MHz, D_2O) δ 7.75 (d, J = 8.4 Hz, 2H, Ar-H), 7.62 (d, J = 8.4 Hz, 2H, Ar-H), 7.28 (s, 1H, =CH), 6.30 (s, 1H, =CH), 4.47 (s, 2H, CH_2), 4.06 (q, J = 13.3 Hz, 2H, CH_2), 3.72 (d, J = 11.1 Hz, 2H, CH_2), 3.67 (s, 3H, $COOCH_3$), 3.65-3.41 (m, 8H, piperazine-H), 3.08 (s, 3H, NCH_3), 2.89-2.72 (m, 1H, CH), 2.30-2.14 (m, 1H, CH); ^{13}C NMR (75 MHz, D_2O) δ 171.98, 169.01, 142.92, 139.73, 131.79, 131.75, 131.70 ($J_{C\text{-}F}$ 32.6 Hz), 128.46, 126.32 ($J_{C\text{-}F}$ 3.9 Hz), 123.75 ($J_{C\text{-}F}$ 271.7 Hz), 110.81, 59.71, 56.19, 52.11, 50.07, 48.62, 48.31, 39.24, 37.42, 35.42; ESI-MS m/z: 464.25 $[M+H]^+$.

1.7.9. (4aS, 7aS)-methyl 7-((4-(3-trifluoromethylbenzyl)piperazin-1-yl)methyl)-2-methyl-1-oxo-2,4a,5,7a-tetrahydro-1H-cyclopenta[c]pyridine-4-carboxylate (**10i**)

A white solid (0.68 g, 60.39%). m.p. 241.4-244.3 ºC; ^{1}H NMR (300 MHz, D_2O) δ 7.74 (d, J = 9.9 Hz, 2H, Ar-H), 7.67 (d, J = 7.8 Hz, 1H, Ar-H), 7.57 (t, J = 7.8 Hz, 1H, Ar-H), 7.25 (s, 1H, =CH), 6.27 (s, 1H, =CH), 4.43 (s, 2H, CH_2), 4.03 (q, J = 13.2 Hz, 2H, CH_2), 3.70 (d, J = 11.2 Hz, 2H, CH_2), 3.63 (s, 3H, $COOCH_3$), 3.61-3.37 (m, 8H, piperazine-H), 3.04 (s, 3H, NCH_3), 2.86-2.68 (m, 1H, CH), 2.27-2.08 (m, 1H, CH); ^{13}C NMR (75 MHz, D_2O) δ 171.94, 168.98, 142.83, 139.73, 134.88, 130.83 (J_{C-F} 32.4 Hz), 130.19, 128.83, 128.51, 127.92 (J_{C-F} 3.9 Hz), 127.31 (J_{C-F} 3.9 Hz), 123.68 (J_{C-F} 271.8 Hz), 110.76, 59.77, 56.18, 52.10, 50.03, 48.57, 48.38, 39.26, 37.39, 35.44; ESI-MS m/z: 464.31 $[M+H]^+$.

1.7.10. (4aS, 7aS)-methyl 7-((4-benzylpiperazin-1-yl)methyl)-2-isopropyl-1-oxo-2,4a,5,7a-tetrahydro-1H-cyclopenta[c]pyridine-4-carboxylate (**10j**)

A white solid (0.46 g, 46.56%). m.p. 223.5-225.8 ºC; ^{1}H NMR (300 MHz, D_2O) δ 7.45 (s, 5H, Ar-H), 7.37 (s, 1H, =CH), 6.29 (s, 1H, =CH), 4.63 (q, J = 6.8 Hz 1H, $CHCH_3$), 4.40 (s, 2H, CH_2), 4.06 (q, J = 13.4 Hz, 2H, CH_2), 3.72 (d, J = 11.1 Hz, 2H, CH_2), 3.68 (s, 3H, $COOCH_3$), 3.64-3.37 (m, 8H, piperazine-H), 2.79 (m, 1H, CH), 2.86-2.73 (m, 1H, CH), 1.27-2.14 (d, J = 6.8 Hz, 3H, $CHCH_3$), 1.11 (d, J = 6.8 Hz, 3H, $CHCH_3$); ^{13}C NMR (75 MHz, D_2O) δ 171.00, 169.01, 142.77, 133.83, 131.21, 130.60, 129.44, 128.80, 127.52, 111.62, 60.52, 56.19, 52.09, 50.47, 48.36, 46.28, 39.05, 36.80, 30.22, 19.91, 19.29; ESI-MS m/z: 424.28 $[M+H]^+$.

1.7.11. (4aS, 7aS)-methyl 7-((4-(4-methylbenzyl)piperazin-1-yl)methyl)-2- isopropyl-1-oxo-2,4a,5,7a-tetrahydro-1H-cyclopenta[c]pyridine-4-carboxylate (**10k**)

A white solid (0.48 g, 47.24%). m.p. 208.5-211.7 ºC; ^{1}H NMR (300 MHz, D_2O) δ 7.36 (s, 1H, =CH), 7.32 (d, J = 8.1 Hz, 2H, Ar-H), 7.25 (d, J = 8.1 Hz, 2H, Ar-H), 6.28 (s, 1H, =CH), 4.64 (q, J = 6.8 Hz, 1H, $CHCH_3$), 4.34 (s, 2H, CH_2), 4.05 (q, J = 13.4 Hz 2H, CH_2), 3.72 (d, J = 11.1 Hz, 2H, CH_2), 3.67 (s, 3H, $COOCH_3$), 3.62-3.36 (m, 8H, piperazine-H), 2.85-2.72 (m, 1H, CH), 2.26 (s, 3H, Ar-CH_3), 2.24-2.13 (m, 1H, CH), 1.14 (d, J = 6.8 Hz, 3H, $CHCH_3$), 1.10 (d, J = 6.8 Hz, 3H, $CHCH_3$); ^{13}C NMR (75 MHz, D_2O) δ 170.97, 168.98, 142.58, 141.19, 133.84, 131.17, 129.97, 128.95, 124.58, 111.59, 60.28, 52.11, 50.44, 48.29, 46.29, 39.08, 36.78, 30.24, 20.38, 19.95, 19.33; ESI-MS m/z: 438.29 $[M+H]^+$.

1.7.12. (4aS, 7aS)-methyl 7-((4-(3-methylbenzyl)piperazin-1-yl)methyl)-2-isopropyl-1-oxo-2,4a,5,7a-tetrahydro-1H-cyclopenta[c]pyridine-4-carboxylate (**10i**)

A white solid (0.53 g, 52.17%). m.p. 204.5-206.7 ºC; ^{1}H NMR (300 MHz, D_2O) δ 7.36 (s, 1H, =CH), 7.34-7.19 (m, 4H, Ar-H), 6.29 (s, 1H, =CH), 4.64 (q, J = 6.8 Hz, 1H, $CHCH_3$), 4.36 (s, 2H, CH_2), 4.06 (q, J = 13.3 Hz, 2H, CH_2), 3.72 (d, J = 11.1 Hz, 2H, CH_2), 3.67 (s, 3H, $COOCH_3$), 3.64-3.36 (m, 8H, piperazine-H), 2.88-2.71 (m, 1H, CH), 2.27 (s, 3H, Ar-CH_3), 2.25-2.13 (m, 1H, CH), 1.14 (d, J = 6.8 Hz, 3H, $CHCH_3$), 1.10 (d, J = 6.8 Hz, 3H, $CHCH_3$); ^{13}C NMR (75 MHz, D_2O) δ 170.99, 169.00, 142.80, 139.78, 133.83, 131.72, 131.21, 129.34, 128.79, 128.11, 127.42, 111.61, 60.50, 56.20, 52.10, 50.47, 48.32, 46.29, 39.06, 36.80, 20.32, 19.92, 19.30; ESI-MS m/z: 438.36 $[M+H]^+$.

1.7.13. (4aS, 7aS)-methyl 7-((4-(3-methoxybenzyl)piperazin-1-yl)methyl)-2-isopropyl-1-oxo-2,4a,5,7a-tetrahydro-1H-cyclopenta[c]pyridine-4-carboxylate (**10m**)

A white solid (0.51 g, 48.66%). m.p. 197.6-200.2 ºC; ^{1}H NMR (300 MHz, D_2O) δ 7.36 (s, 1H,

=CH), 7.05-6.99 (m, 4H, Ar-H), 6.29 (s, 1H, =CH), 4.64 (q, *J* = 6.9 Hz, 1H, $CHCH_3$), 4.37 (s, 2H, CH_2), 4.06 (q, *J* = 13.4 Hz, 2H, CH_2), 3.76 (s, 3H, Ar-OCH_3), 3.69 (d, *J* = 11.1 Hz, 2H, CH_2), 3.67 (s, 3H, $COOCH_3$), 3.61-3.39 (m, 8H, piperazine-H), 2.83-2.73 (m, 1H, CH), 2.24-2.15 (m, 1H, CH), 1.14 (d, *J* = 6.9 Hz, 3H, $CHCH_3$), 1.10 (d, *J* = 6.9 Hz, 3H, $CHCH_3$); ^{13}C NMR (75 MHz, D_2O) *δ* 171.00, 169.00, 159.39, 142.81, 133.83, 130.77, 129.00, 128.77, 123.73, 116.66, 116.08, 111.62, 60.33, 60.25, 56.20, 55.46, 52.09, 50.48, 48.41, 48.24, 48.11, 46.29, 39.04, 36.80, 19.91, 19.29; ESI-MS m/z: 454.35 $[M+H]^+$.

1.7.14. (4aS, 7aS)-methyl 7-((4-(4-fluorobenzyl)piperazin-1-yl)methyl)-2-isopropyl-1-oxo-2,4a,5,7a-tetrahydro-1H-cyclopenta[c]pyridine-4-carboxylate (**10n**)

A white solid (0.5 g, 48.83%). m.p. 241.5-244.3 ºC; ^{1}H NMR (300 MHz, D_2O) *δ* 7.50-7.42 (m, 2H, Ar-H), 7.36 (s, 1H, =CH), 7.15 (t, *J* = 8.7 Hz, 2H, Ar-H), 6.29 (s, 1H, =CH), 4.64 (q, *J* = 6.8 Hz, 1H, $CHCH_3$), 4.39 (s, 2H, CH_2), 4.06 (q, *J* = 13.3 Hz, 2H, CH_2), 3.72 (d, *J* = 11.1 Hz, 2H, CH_2), 3.67 (s, 3H, $COOCH_3$), 3.64-3.37 (m, 8H, piperazine-H), 2.87-2.71 (m, 1H, CH), 2.28-2.13 (m, 1H, CH), 1.14 (d, *J* = 6.8 Hz, 3H, $CHCH_3$), 1.10 (d, *J* = 6.8 Hz, 3H, $CHCH_3$); ^{13}C NMR (75 MHz, D_2O) *δ* 171.01, 169.02, 163.65 ($J_{C\text{-}F}$ 246.5 Hz), 142.59, 133.83, 133.37($J_{C\text{-}F}$ 8.7 Hz), 128.92, 123.97($J_{C\text{-}F}$ 3.2 Hz), 116.30 ($J_{C\text{-}F}$ 22.0 Hz), 111.62, 59.67, 56.19, 52.09, 50.46, 48.36, 48.18, 46.27, 39.04, 36.79, 19.90, 19.28; ESI-MS m/z: 442.31 $[M+H]^+$.

1.7.15. (4aS, 7aS)-methyl 7-((4-(4-chlorobenzyl)piperazin-1-yl)methyl)-2-isopropyl-1-oxo-2,4a,5,7a-tetrahydro-1H-cyclopenta[c]pyridine-4-carboxylate (**10o**)

A white solid (0.53 g, 50.14%). m.p. 229.1-232.4 ºC; ^{1}H NMR (300 MHz, D_2O) *δ* 7.44-7.35 (m, 4H, Ar-H), 7.33 (s, 1H, =CH), 6.27 (s, 1H, =CH), 4.62 (q, *J* = 6.8 Hz, 1H, $CHCH_3$), 4.37 (s, 2H, CH_2), 4.04 (q, *J* = 13.4 Hz, 2H, CH_2), 3.70 (d, *J* = 11.1 Hz, 2H, CH_2), 3.64 (s, 3H, $COOCH_3$), 3.62-3.30 (m, 8H, piperazine-H), 2.84-2.68 (m, 1H, CH), 2.24-2.10 (m, 1H, CH), 1.12 (d, *J* = 6.8 Hz, 3H, $CHCH_3$), 1.07 (d, *J* = 6.8 Hz, 3H, $CHCH_3$); ^{13}C NMR (75 MHz, D_2O) *δ* 170.94, 168.95, 142.81, 136.16, 133.83, 132.79, 129.48, 128.77, 126.12, 111.56, 59.62, 56.17, 52.10, 50.43, 48.35, 46.28, 39.07, 36.78, 30.24, 19.95, 19.33; ESI-MS m/z: 458.28 $[M+H]^+$.

1.7.16. (4aS, 7aS)-methyl 7-((4-(4-nitrobenzyl)piperazin-1-yl)methyl)-2-isopropyl-1-oxo-2,4a,5,7a-tetrahydro-1H-cyclopenta[c]pyridine-4-carboxylate (**10p**)

A white solid (0.5 g, 46.38%). m.p. 214.5-217.4 ºC; ^{1}H NMR (300 MHz, D_2O) *δ* 8.21 (d, *J* = 8.7 Hz, 2H, Ar-H), 7.68 (d, *J* = 8.7 Hz, 2H, Ar-H), 7.33 (s, 1H, =CH), 6.28 (s, 1H, =CH), 4.62 (q, *J* = 6.8 Hz 1H, $CHCH_3$), 4.52 (s, 2H, CH_2), 4.06 (q, *J* = 13.4 Hz, 2H, CH_2), 3.71 (d, *J* = 11.1 Hz, 2H, CH_2), 3.64 (s, 3H, $COOCH_3$), 3.63-3.57 (m, 8H, piperazine-H), 2.83-2.69 (m, 1H, CH), 2.25-2.10 (m, 1H, CH), 1.11 (d, *J* = 6.8 Hz, 3H, $CHCH_3$), 1.07 (d, *J* = 6.8 Hz, 3H, $CHCH_3$); ^{13}C NMR (75 MHz, D_2O) *δ* 170.96, 168.96, 148.75, 142.86, 134.79, 133.82, 132.54, 128.75, 124.38, 111.56, 59.21, 56.20, 52.09, 50.45, 48.74, 48.31, 48.24, 46.26, 40.65, 39.07, 36.79, 19.93, 19.31; ESI-MS m/z: 469.25 $[M+H]^+$.

1.7.17. (4aS, 7aS)-methyl 7-((4-(4-trifluoromethylbenzyl)piperazin-1-yl)methyl)-2-isopropyl-1-oxo-2,4a,5,7a-tetrahydro-1H-cyclopenta[c]pyridine-4-carboxylate (**10q**)

A white solid (0.54 g, 48.09%). m.p. 233.2-236.3 ºC; ^{1}H NMR (300 MHz, D_2O) *δ* 7.75 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.63 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.36 (s, 1H, =CH), 6.30 (s, 1H, =CH), 4.65

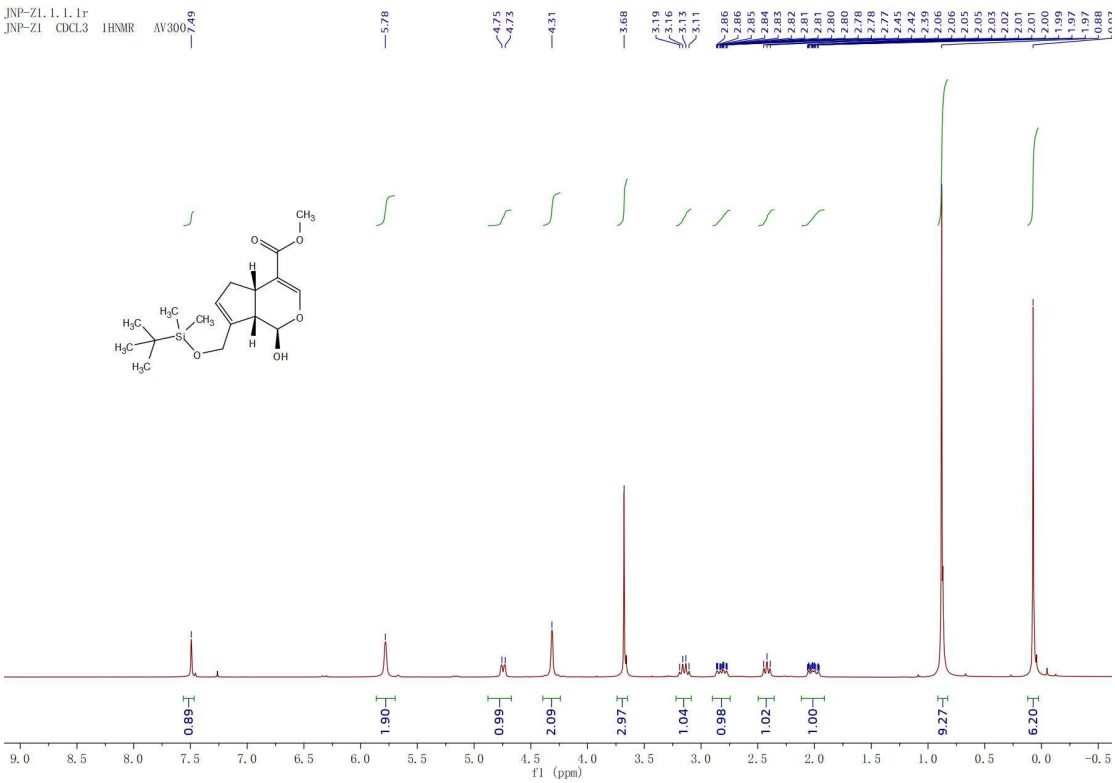
(d, J = 6.8 Hz, 1H, $CHCH_3$), 4.49 (s, 2H, CH_2), 4.07 (q, J = 13.3 Hz, 2H, CH_2), 3.73 (d, J = 11.1 Hz, 2H, CH_2), 3.67 (s, 3H, $COOCH_3$), 3.64-3.37 (m, 8H, piperazine-H), 2.87-2.72 (m, 1H, CH), 2.28-2.14 (m, 1H, CH), 1.14 (d, J = 6.8 Hz, 3H, $CHCH_3$), 1.10 (d, J = 6.8 Hz, 3H, $CHCH_3$); ^{13}C NMR (75 MHz, D_2O) δ 170.99, 168.99, 142.86, 133.84, 131.72 ($J_{C\text{-}F}$ 32.6 Hz), 131.62, 128.75, 126.34 ($J_{C\text{-}F}$ 3.9 Hz), 123.75 ($J_{C\text{-}F}$ 272.6 Hz), 111.60, 59.68, 56.20, 52.10, 50.47, 48.57, 48.27, 48.08, 46.30, 40.63, 39.06, 36.80, 19.93, 19.30; ESI-MS m/z: 492.29 $[M+H]^+$.

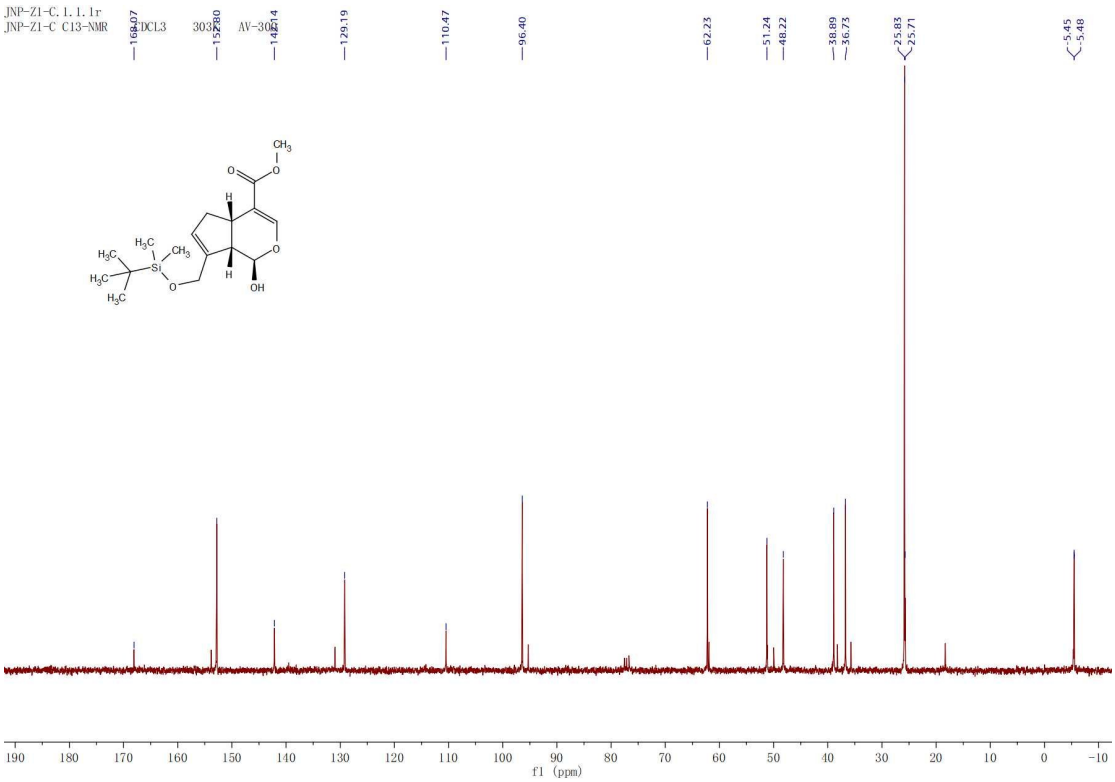
1.7.18. (4aS, 7aS)-methyl 7-((4-(3-trifluoromethylbenzyl)piperazin-1-yl)methyl)-2-isopropyl-1-oxo-2,4a,5,7a-tetrahydro-1H-cyclopenta[c]pyridine-4-carboxylate (**10r**)

A white solid (0.49 g, 43.63%). m.p. 218.8-220.3ºC; ^{1}H NMR (300 MHz, D_2O) δ 7.76 (d, J = 10.2 Hz, 2H, Ar-H), 7.68 (d, J = 7.8 Hz, 1H, Ar-H), 7.58 (t, J = 7.8 Hz, 1H, Ar-H), 7.34 (s, 1H, =CH), 6.27 (s, 1H, =CH), 4.63(q, J = 6.8 Hz, 1H, $CHCH_3$), 4.47 (s, 2H, CH_2), 4.05 (q, J = 13.4 Hz, 2H, CH_2), 3.70 (d, J = 11.1 Hz, 2H, CH_2), 3.65 (s, 3H, $COOCH_3$), 3.63-3.31 (m, 8H, piperazine-H), 2.81-2.71 (m, 1H, CH), 2.22-2.13 (m, 1H, CH), 1.12 (d, J = 6.8 Hz, 3H, $CHCH_3$), 1.07 (d, J = 6.8 Hz, 3H, $CHCH_3$); ^{13}C NMR (75 MHz, D_2O) δ 170.97, 168.98, 142.85, 134.94, 133.82, 130.87 ($J_{C\text{-}F}$ 32.4 Hz), 130.22, 128.74, 128.50, 127.98 ($J_{C\text{-}F}$ 3.7 Hz), 127.42 ($J_{C\text{-}F}$ 3.7 Hz), 123.66 ($J_{C\text{-}F}$ 271.8 Hz), 111.58, 59.74, 56.19, 52.09, 50.45, 48.50, 48.27, 46.26, 39.05, 36.78, 19.91, 19.29; ESI-MS m/z: 492.65 $[M+H]^+$.

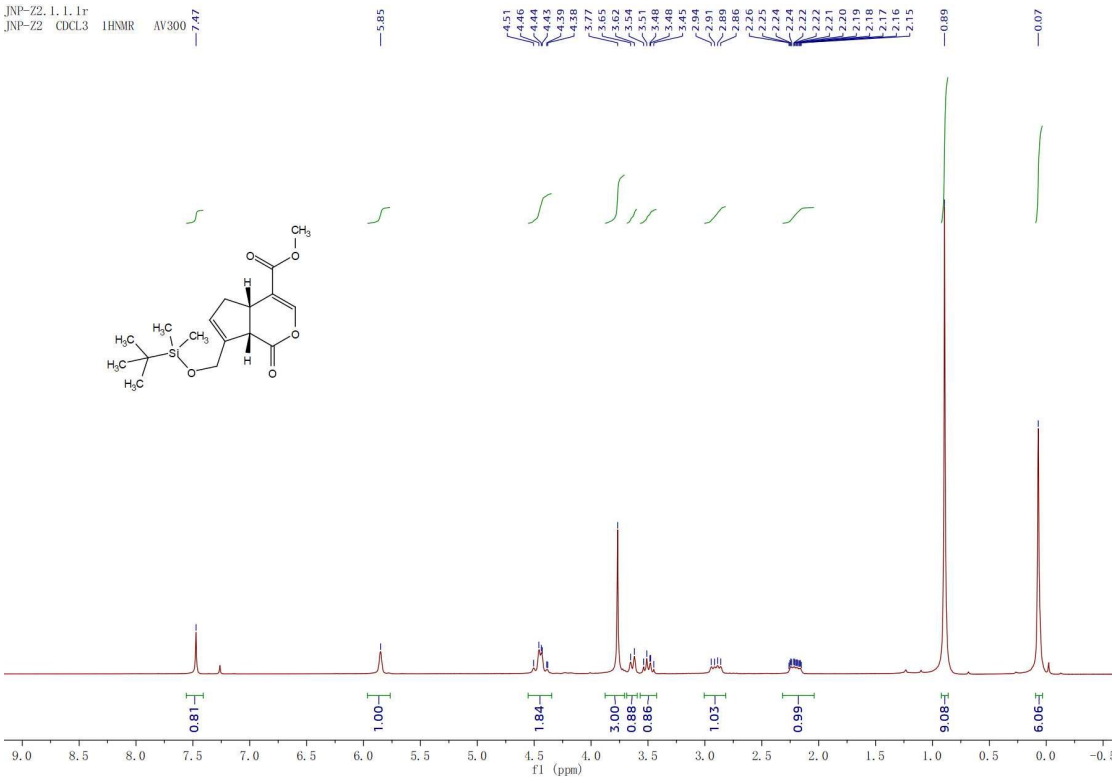
2. ^{1}H and ^{13}C NMR spectra

Compound **4**





Compound **5**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JNP-Z2 CDCL3 1HNMR AV300
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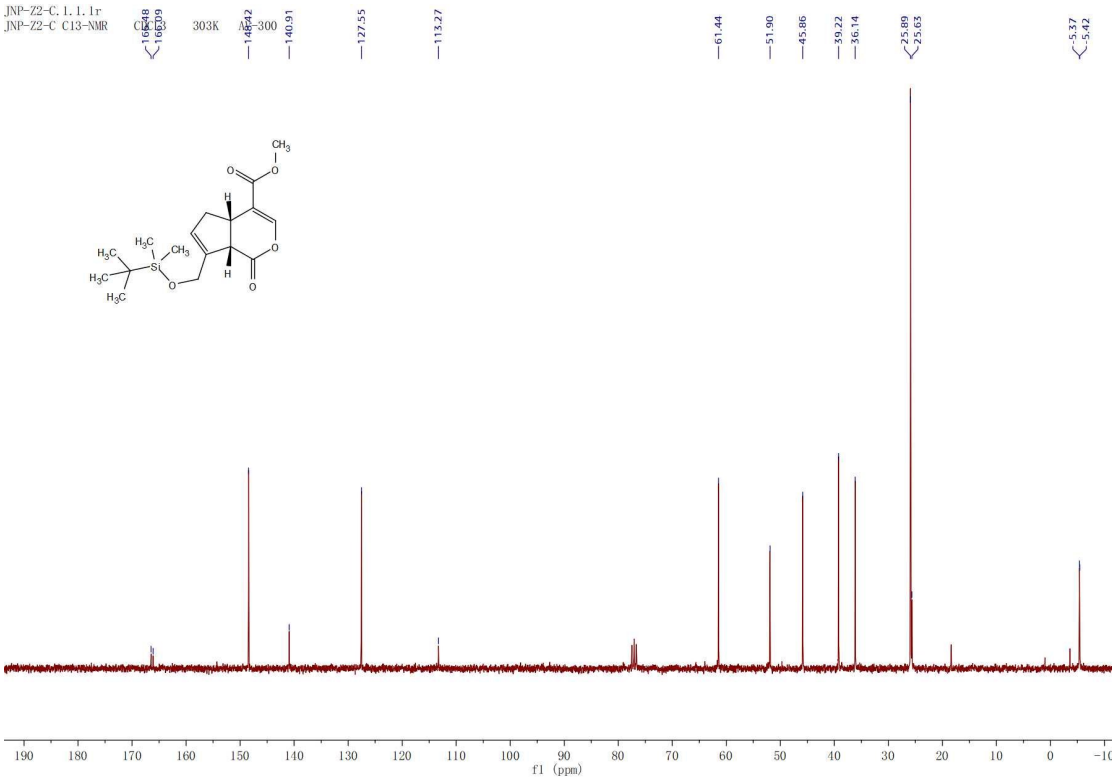
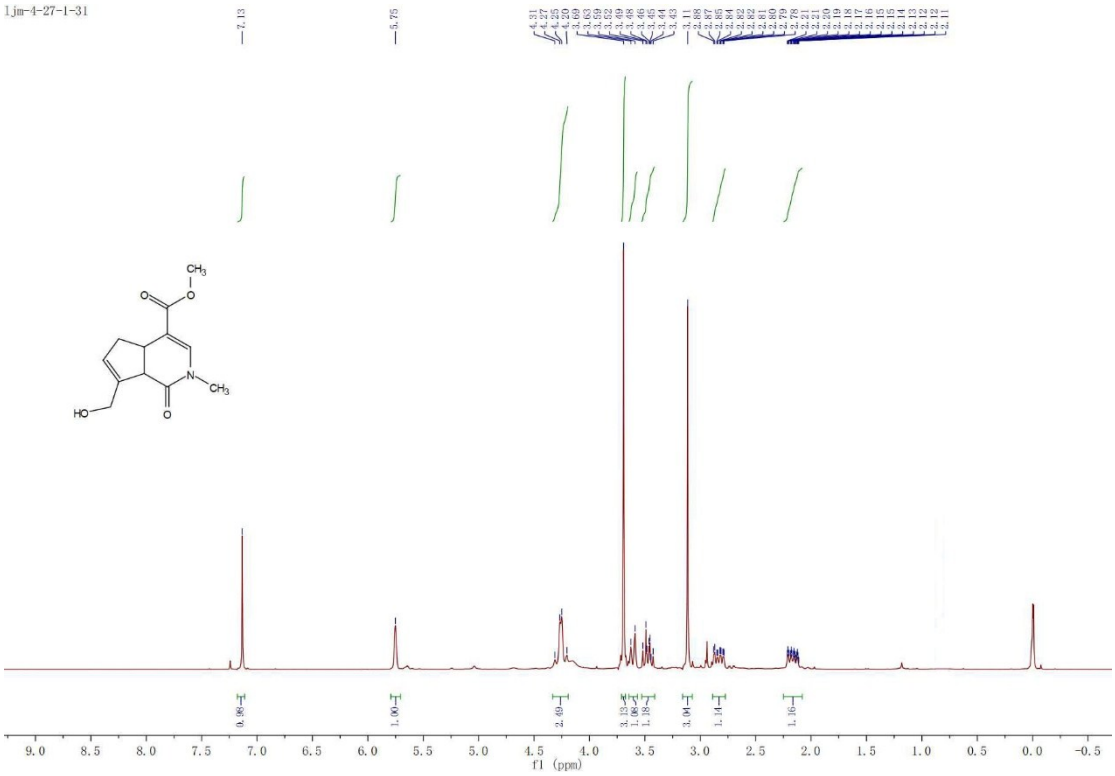
5.85
4.51
4.46
4.44
4.43
4.39
4.38
3.77
3.65
3.62
3.54
3.51
3.48
3.45
2.94
2.91
2.89
2.86
2.26
2.25
2.24
2.22
2.21
2.20
2.19
2.18
2.17
2.16
2.15
0.89
0.07
0.81
1.00
1.84
3.00
0.88
0.86
1.03
0.99
9.08
6.06
f1 (ppm)


JNP-Z2-C.1.1.1r
JNP-Z2-C C13-NMR CDCL3 303K AV300
165.48
165.09
148.42
140.91
127.55
113.27
61.44
51.90
45.86
39.22
36.14
25.89
25.63
5.37
5.42
f1 (ppm)

Compound **6a**


ljm-4-27-1-31
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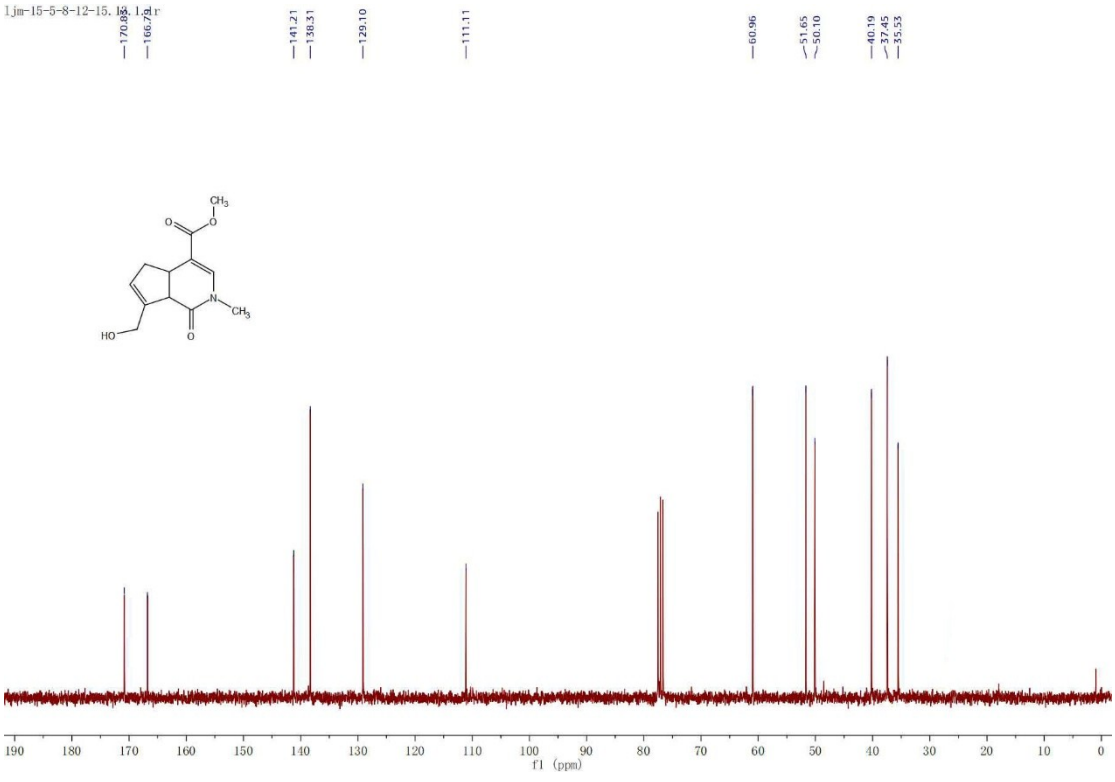
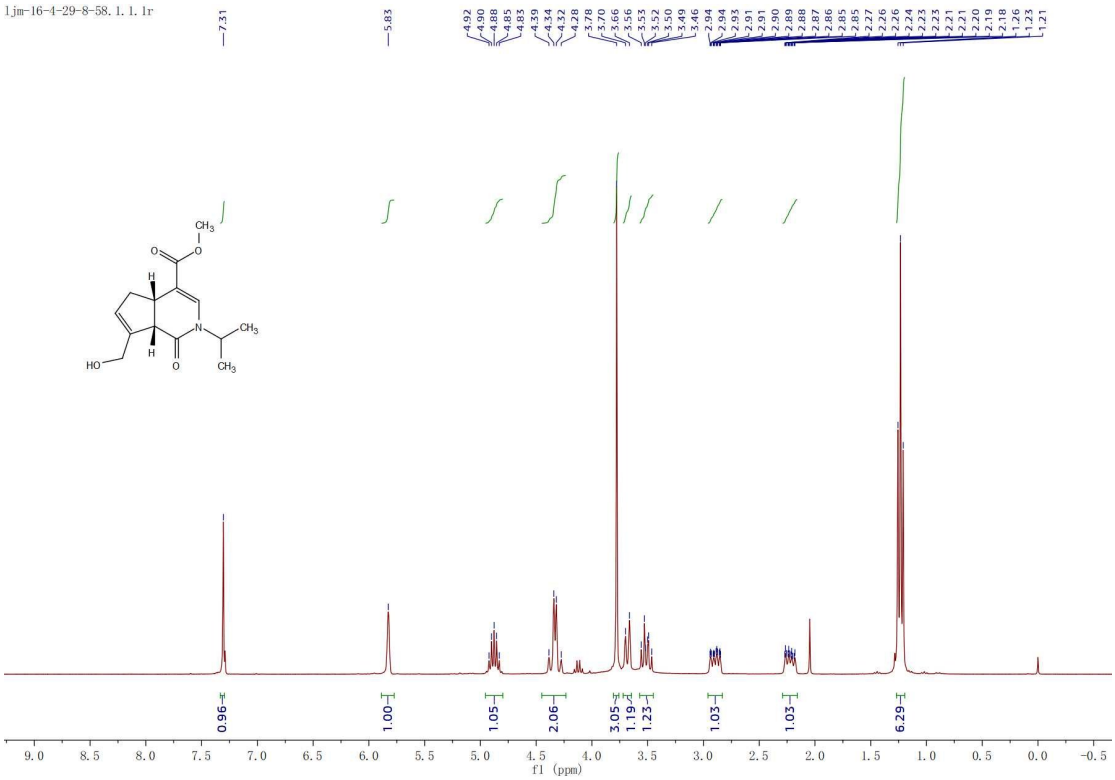
5.75
4.31
4.27
4.25
4.20
4.09
3.65
3.59
3.52
3.49
3.48
3.46
3.45
3.44
3.43
3.11
2.88
2.87
2.85
2.84
2.82
2.82
2.81
2.80
2.79
2.78
2.21
2.20
2.19
2.18
2.17
2.16
2.15
2.15
2.14
2.13
2.12
2.12
2.11
0.86
1.00
2.69
3.13
1.06
1.18
3.01
1.14
1.16
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


ljm-15-5-8-12-15.1.1.1r
170.85
166.79
141.21
138.31
129.10
111.11
60.96
51.65
50.10
40.19
37.45
35.53
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

Compound **6b**


ljm-16-4-29-8-58.1.1.1r
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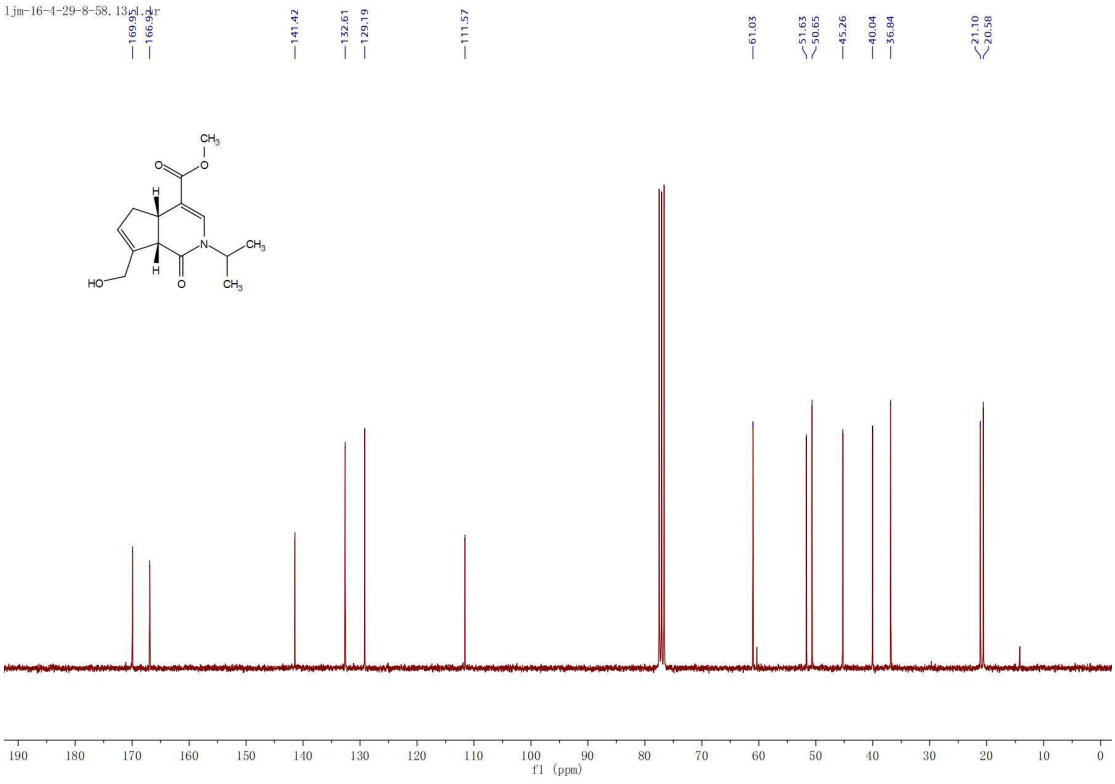
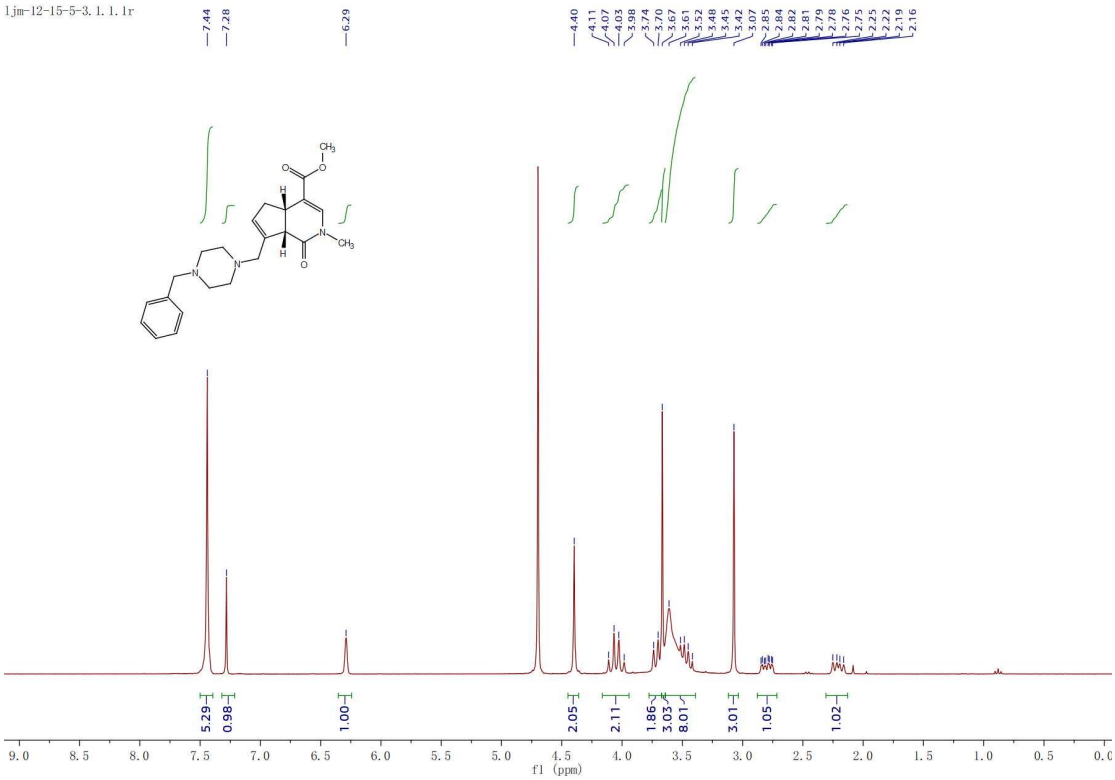
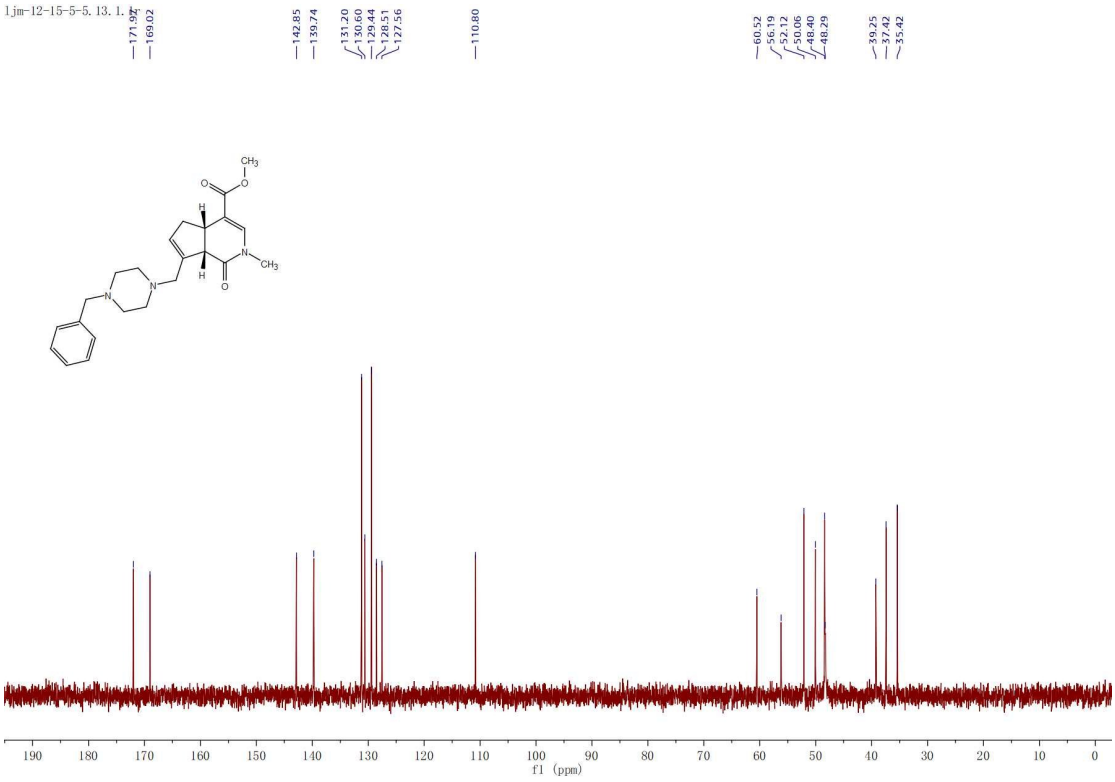
4.92
4.90
4.88
4.85
4.83
4.39
4.34
4.32
4.28
3.78
3.70
3.66
3.56
3.53
3.52
3.50
3.49
3.46
2.94
2.93
2.91
2.90
2.89
2.88
2.87
2.86
2.85
2.27
2.26
2.24
2.23
2.23
2.21
2.21
2.20
2.19
2.18
1.26
1.23
1.21
0.96
1.00
1.05
2.06
3.05
1.19
1.23
1.03
1.03
6.29
f1 (ppm)

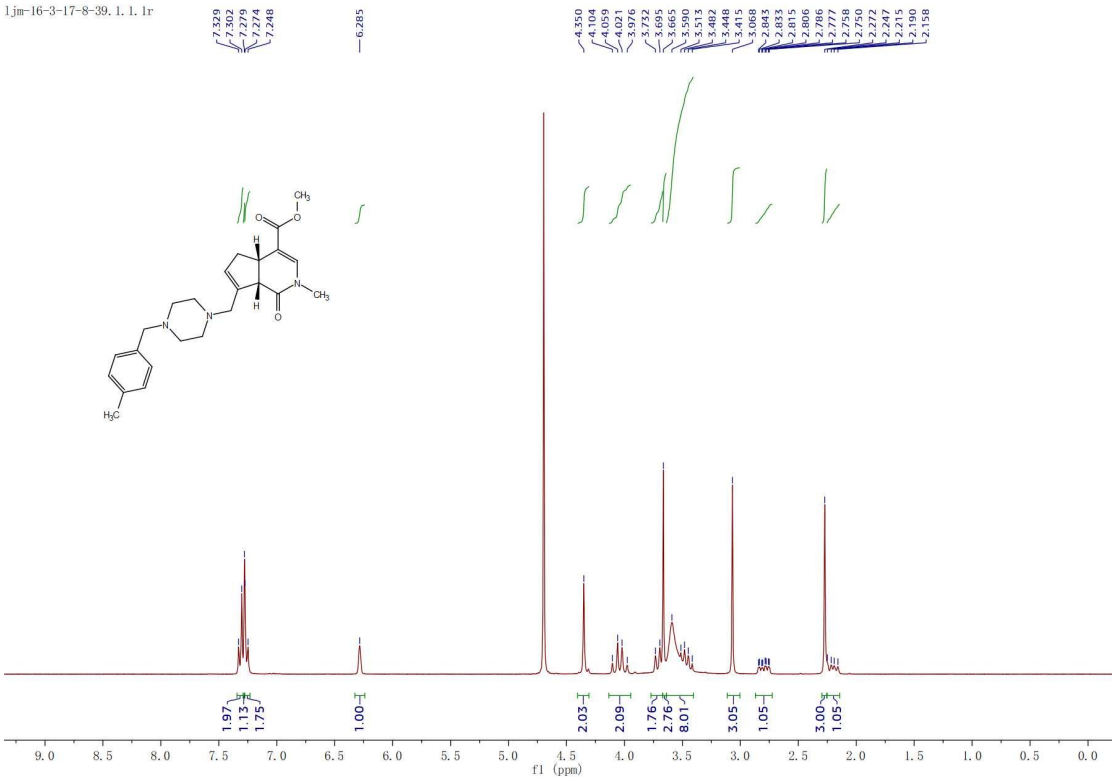

ljm-16-4-29-8-58.13c.1r
169.95
166.92
141.42
132.61
129.19
111.57
61.03
51.63
50.65
45.26
40.04
36.84
21.10
20.58
f1 (ppm)

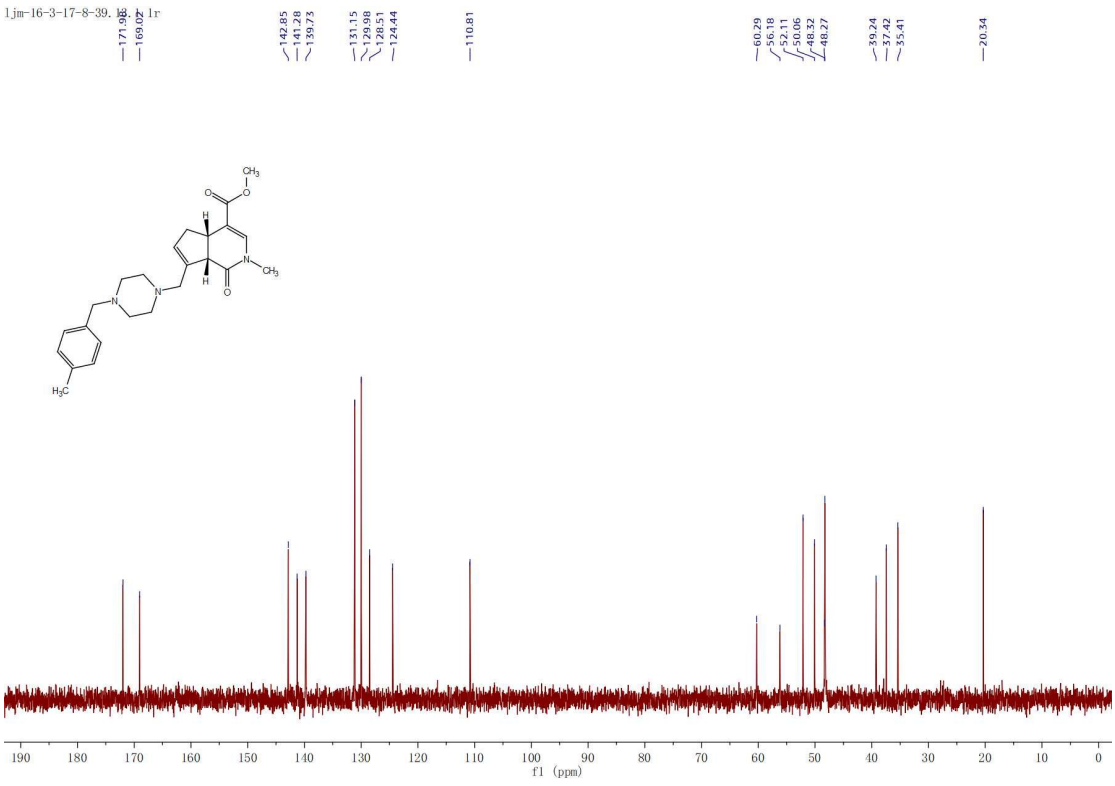
Compound **10a**



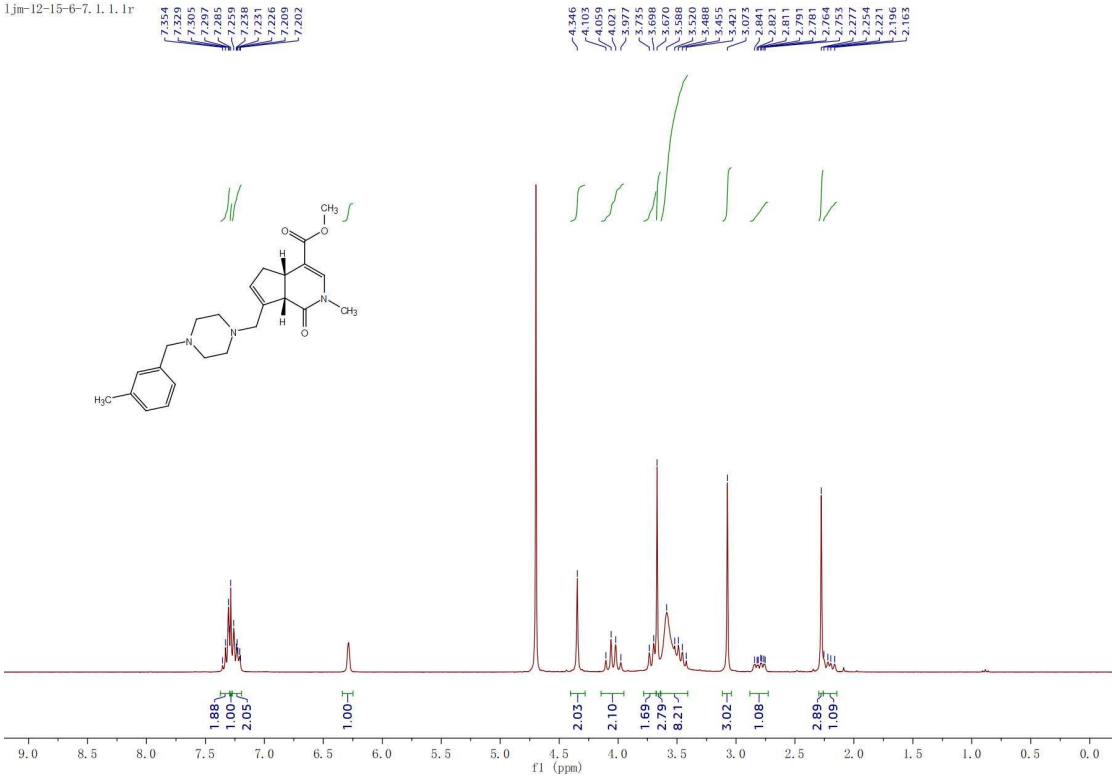


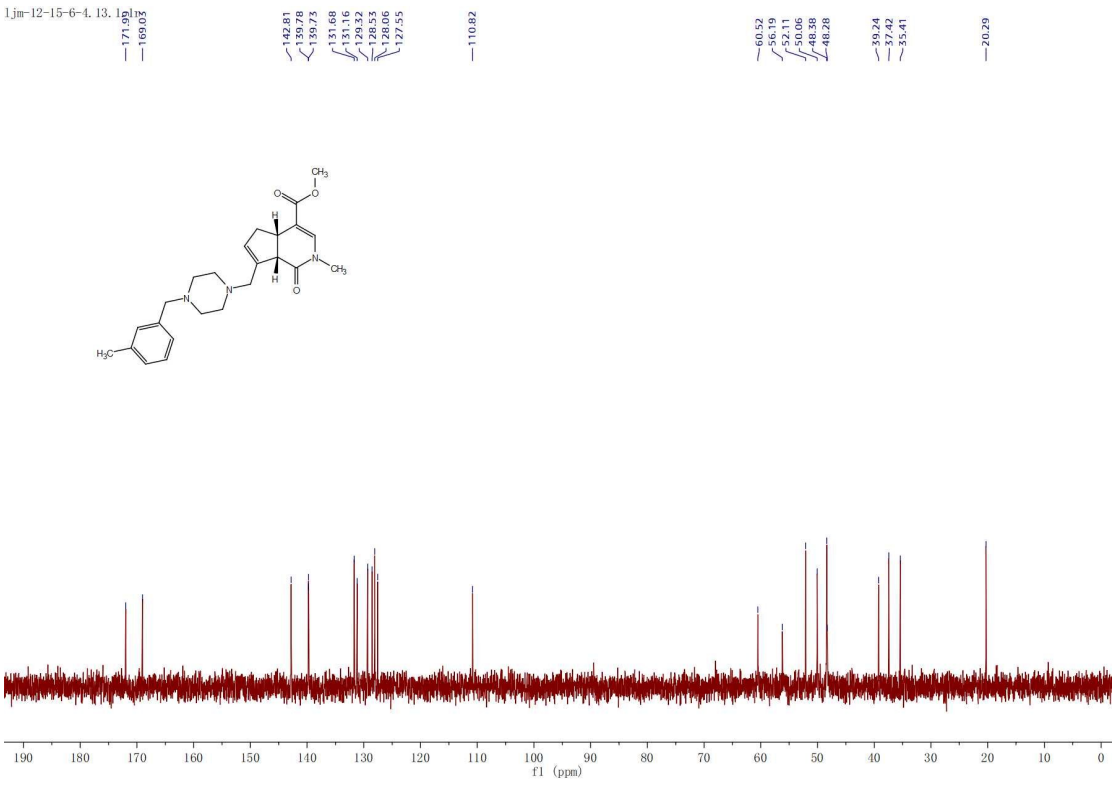
Compound **10b**



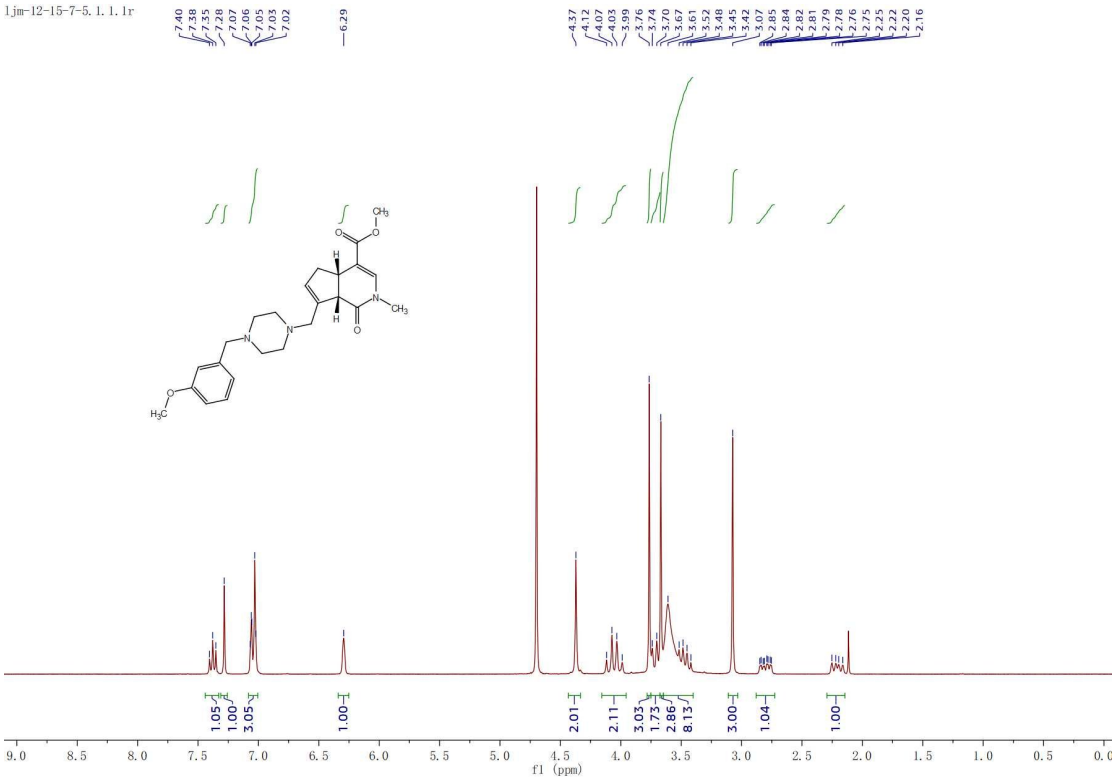


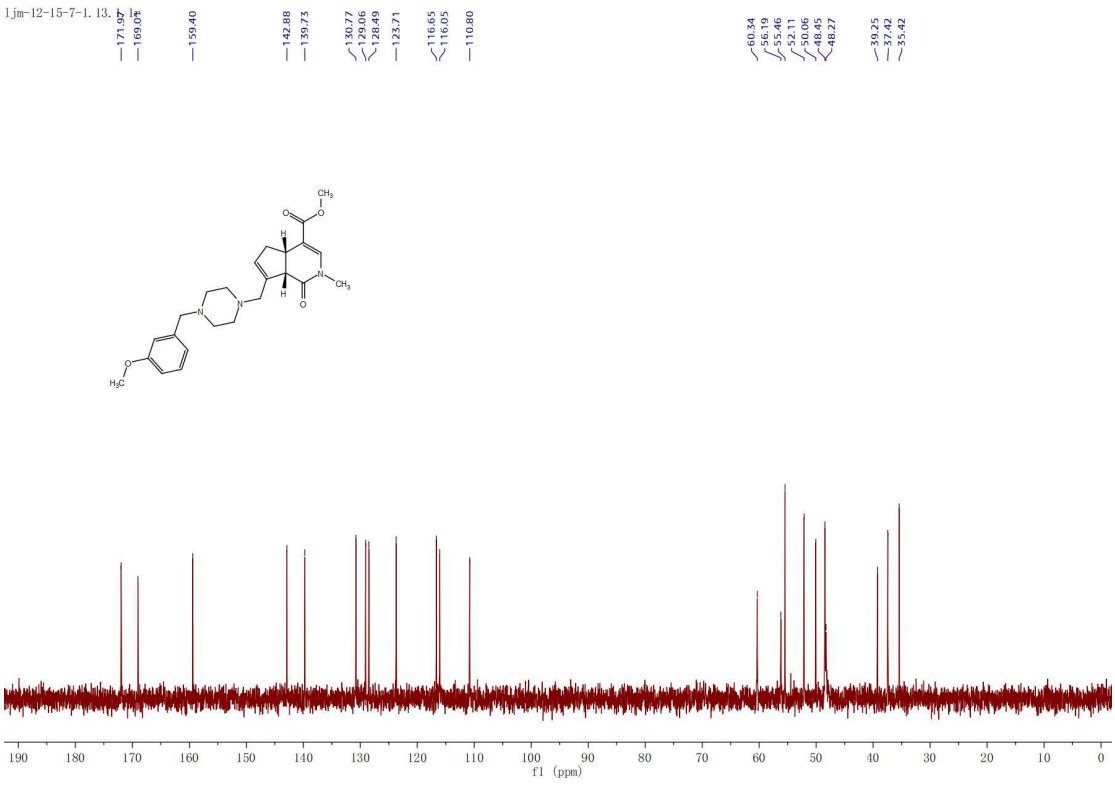
Compound **10c**



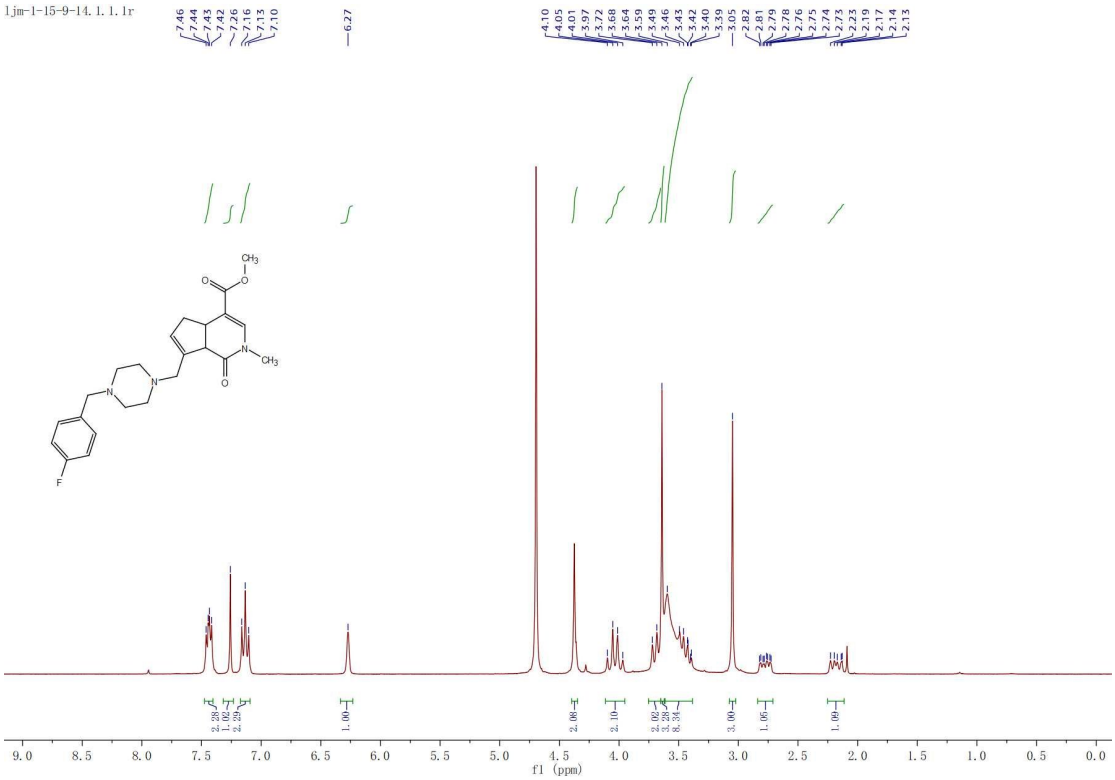


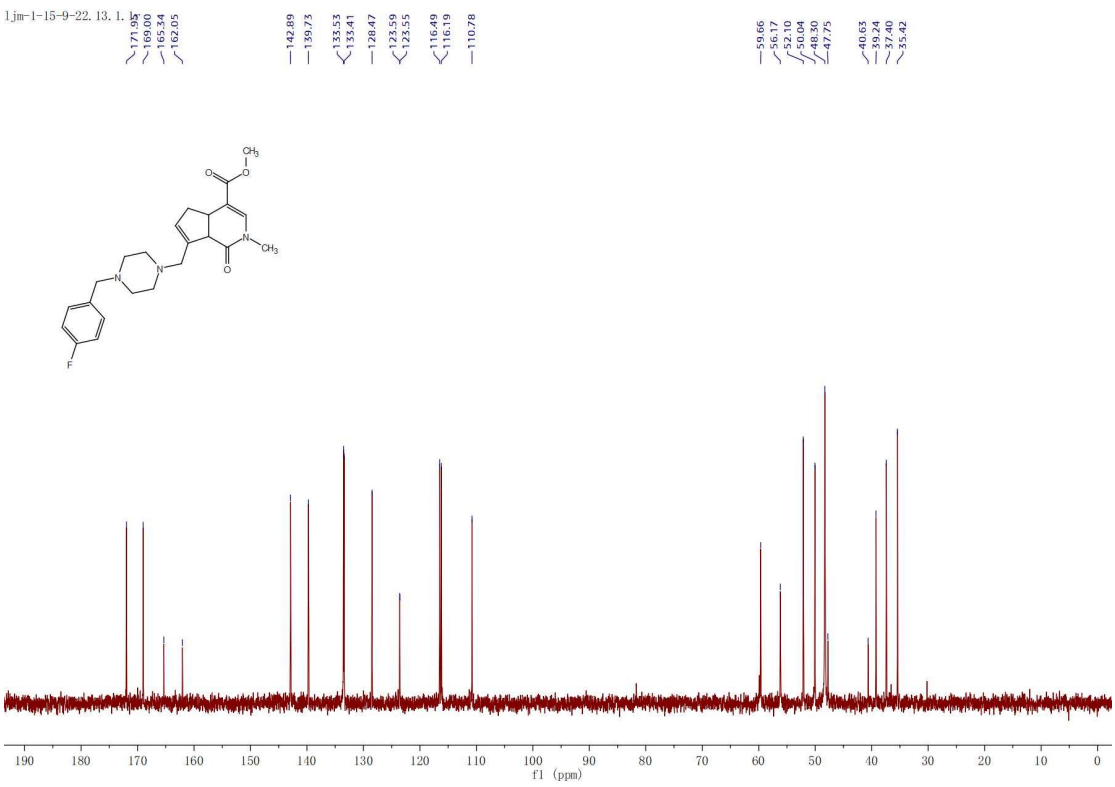
Compound **10d**



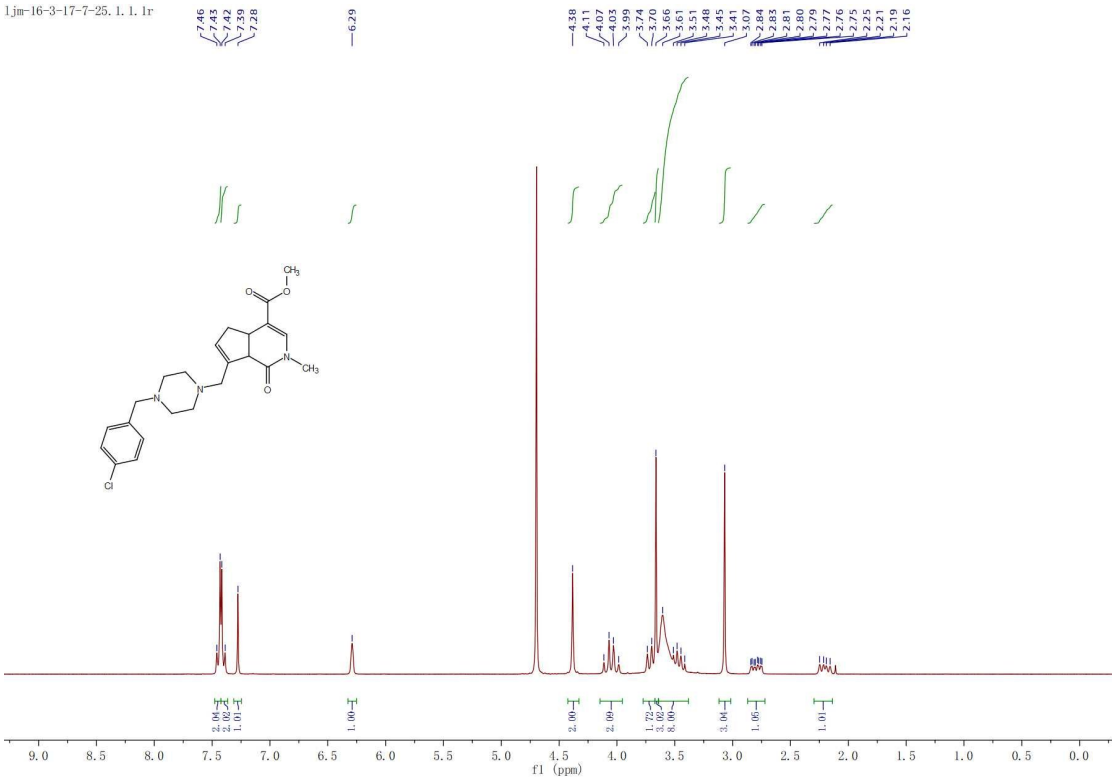


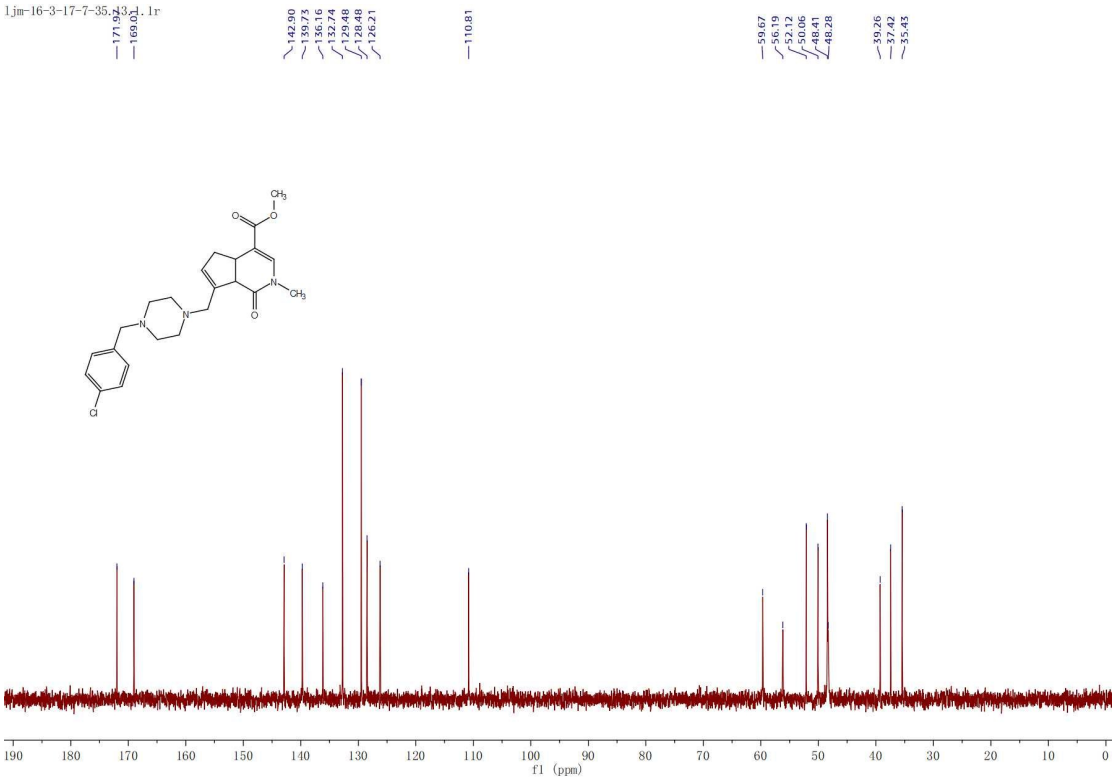
Compound **10e**



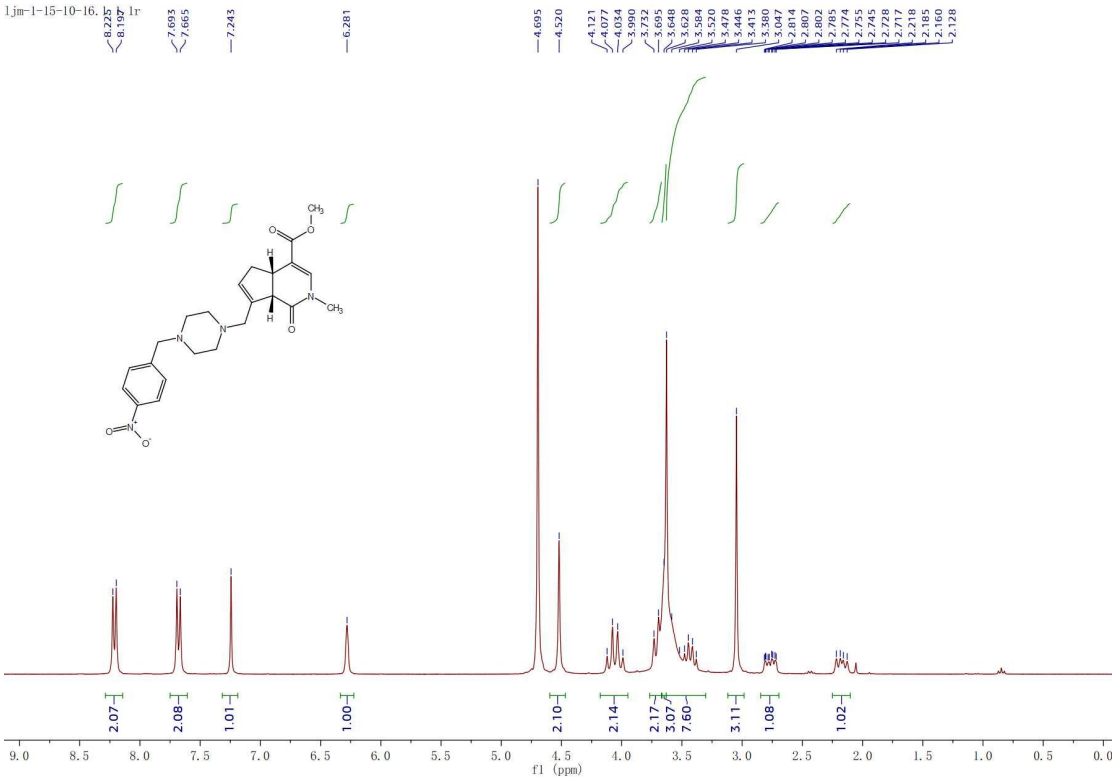


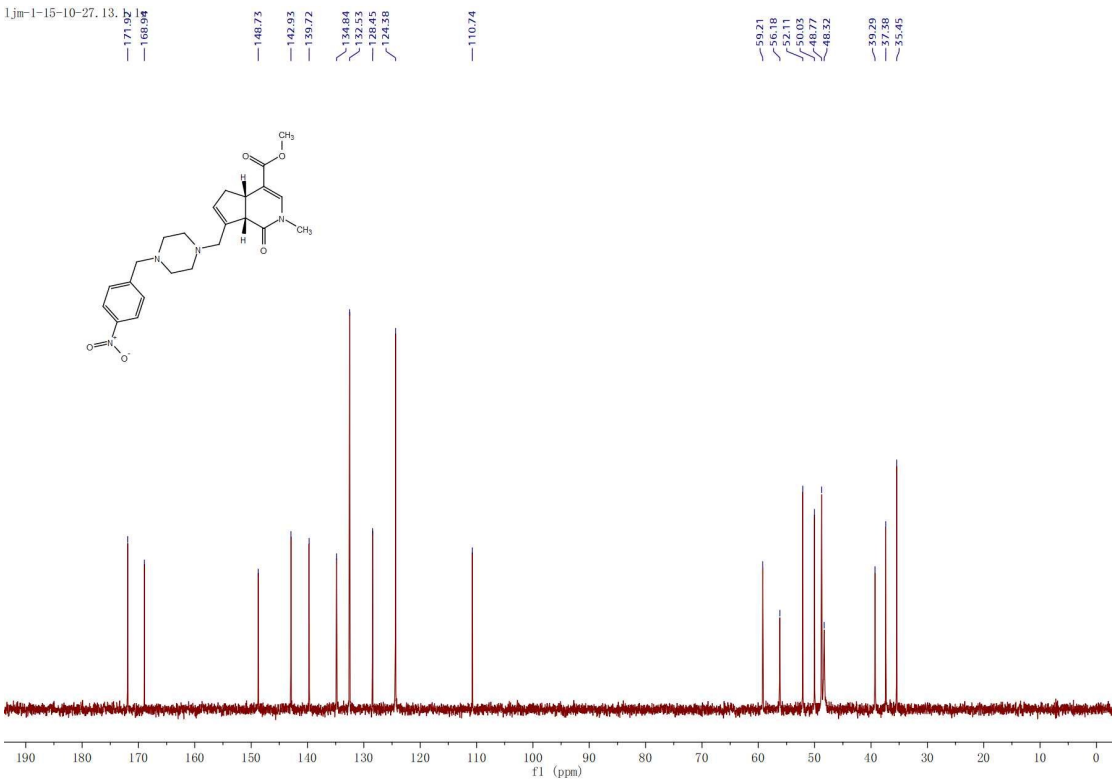
Compound **10f**



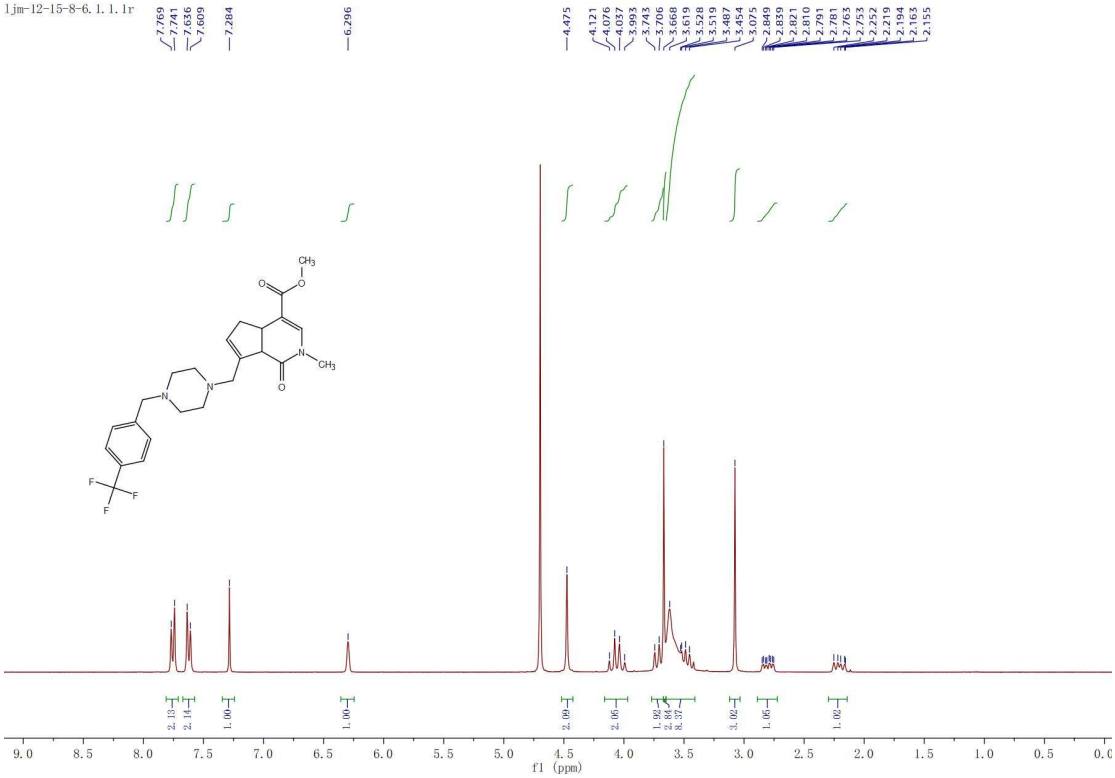


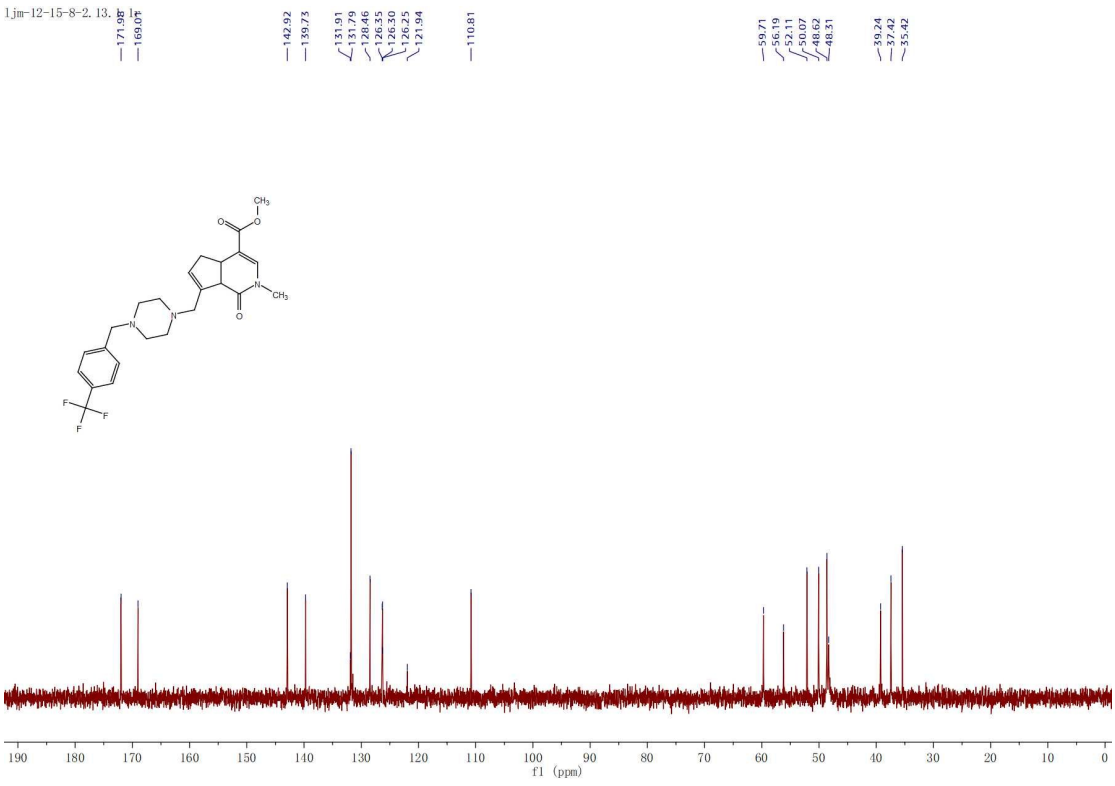
Compound **10g**



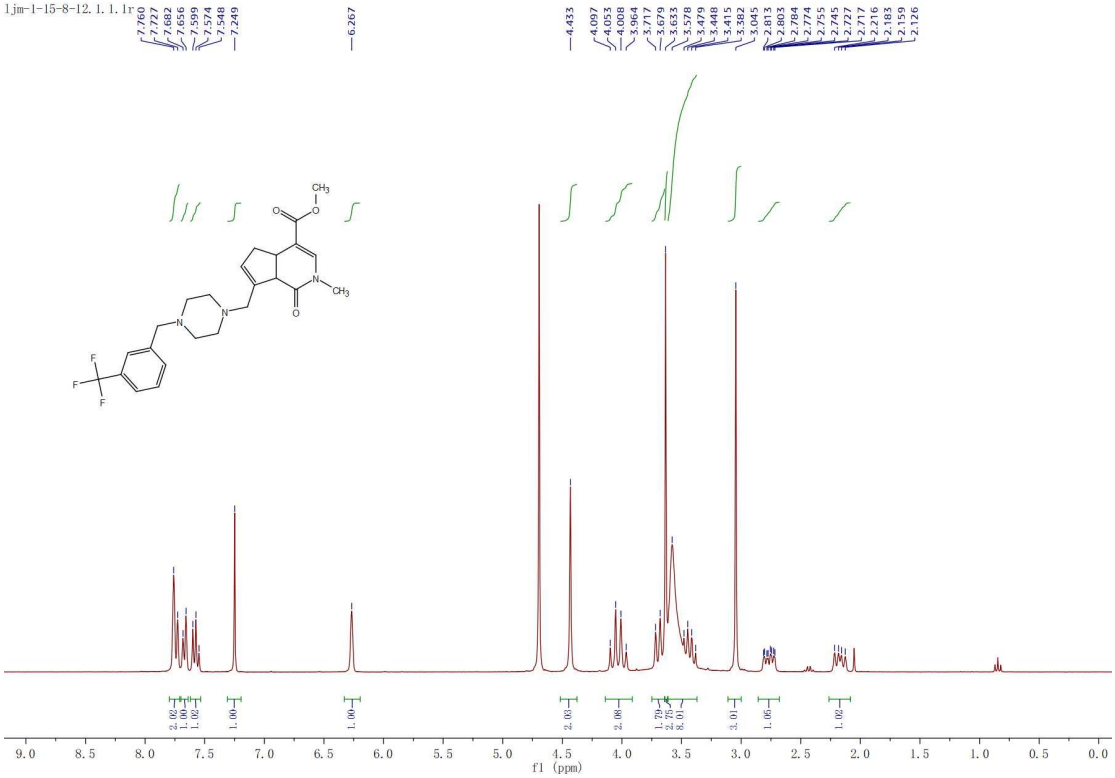


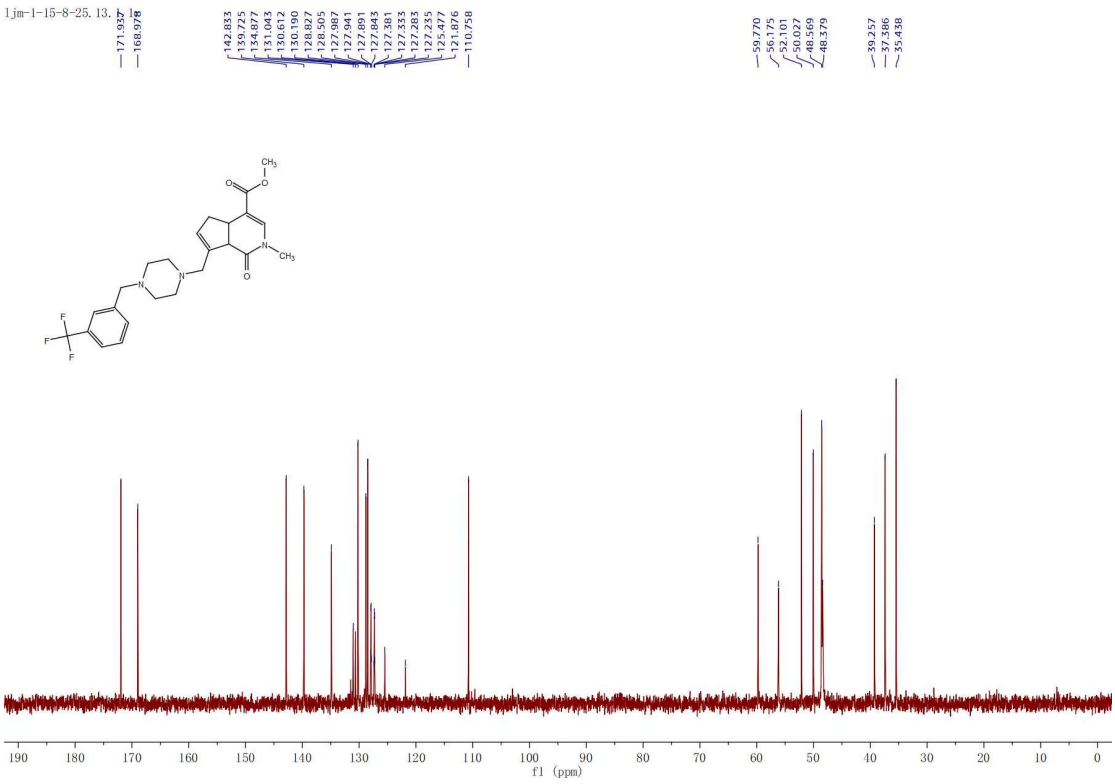
Compound **10h**





Compound **10i**





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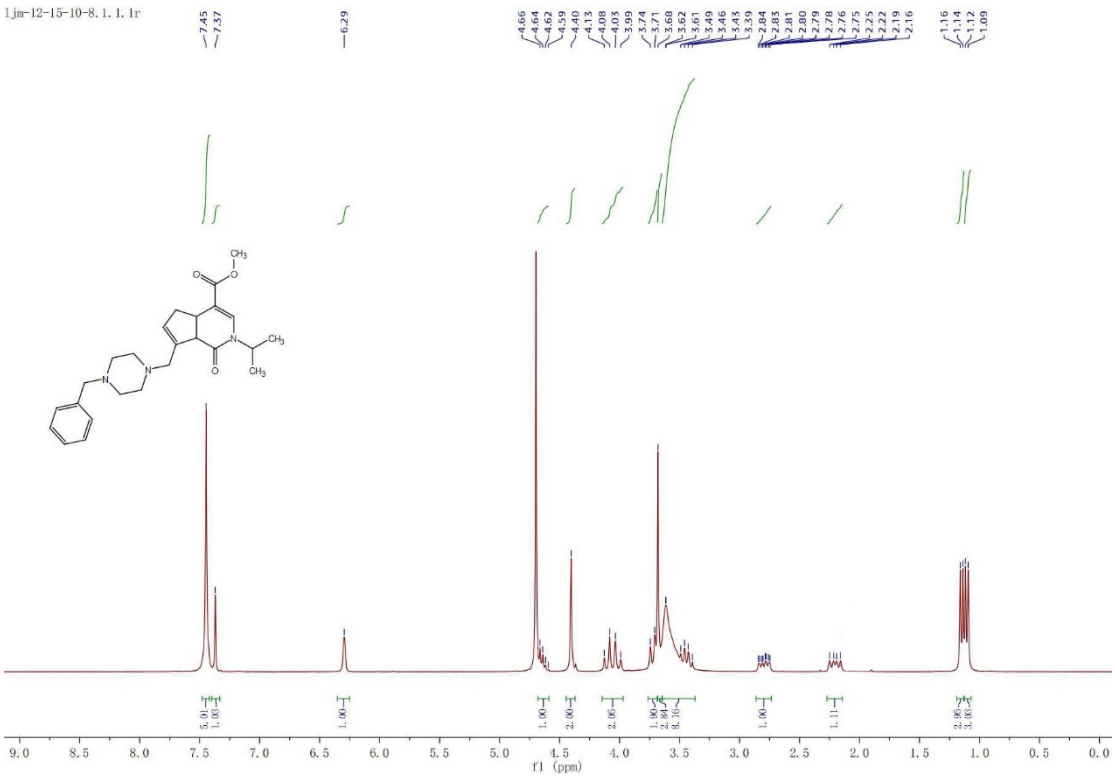
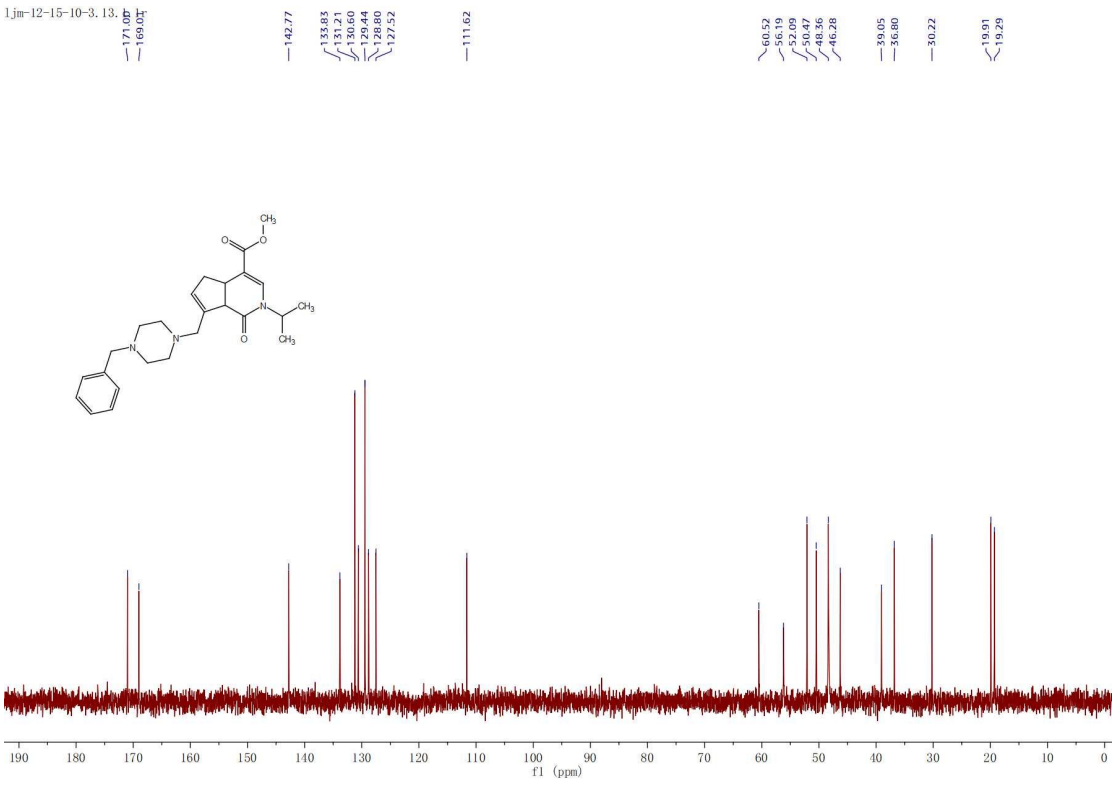
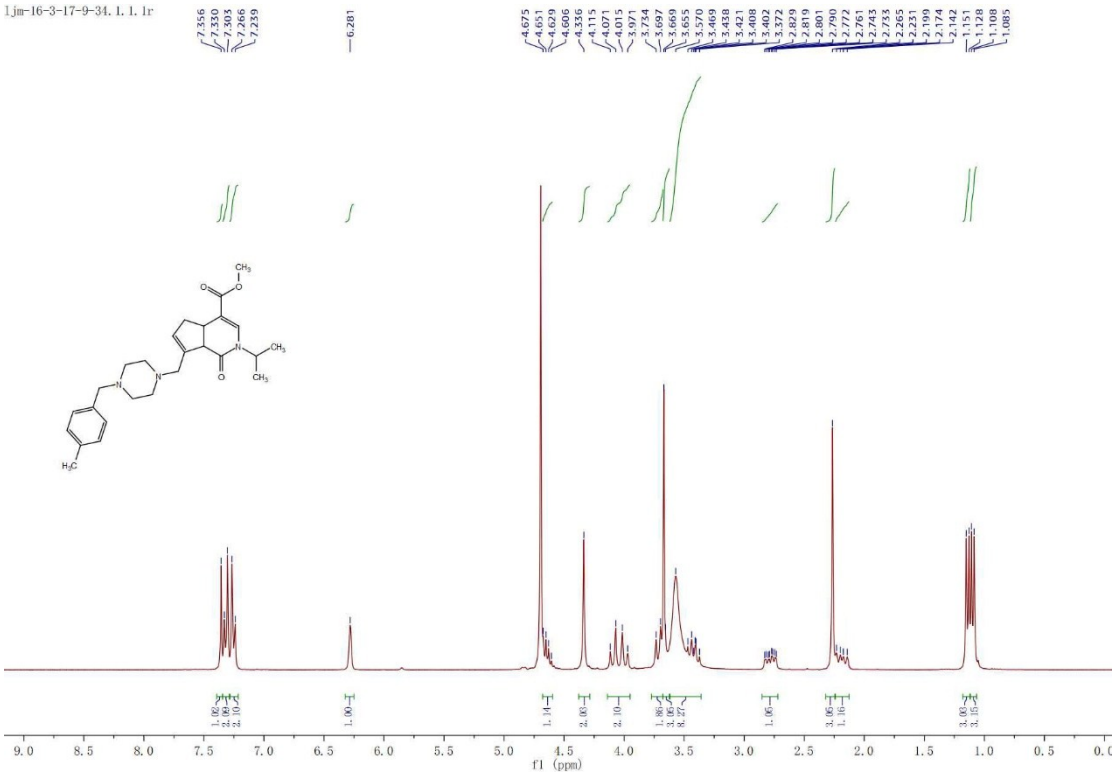
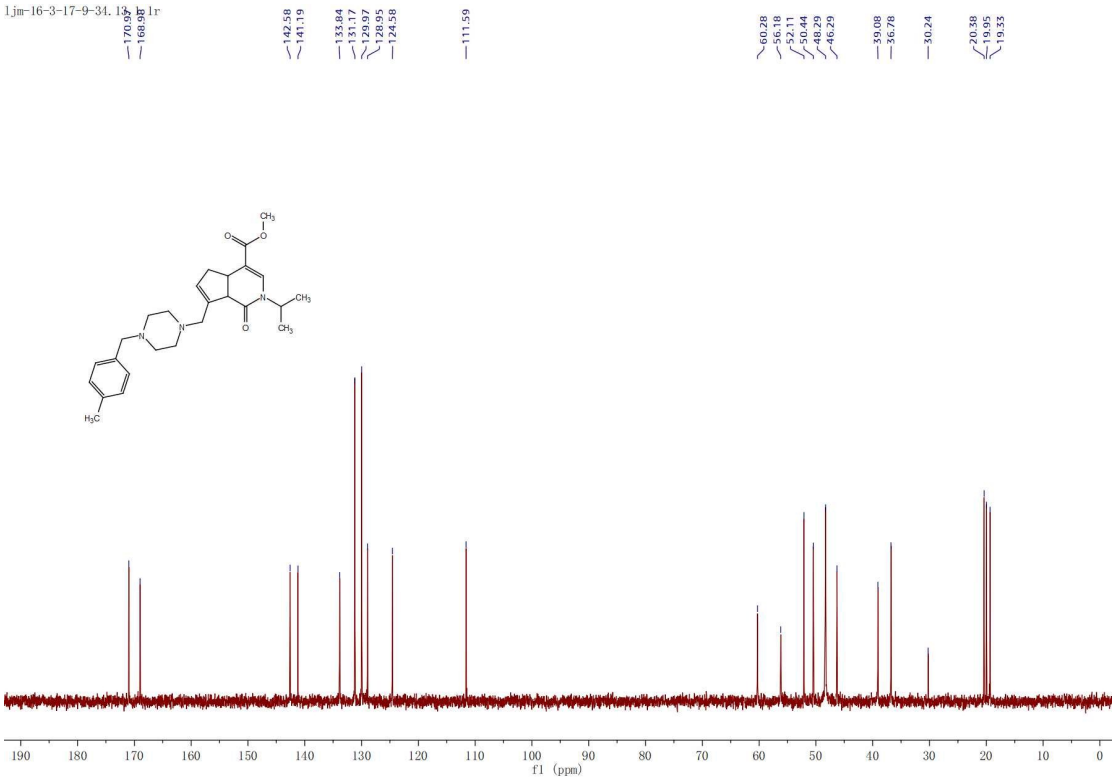


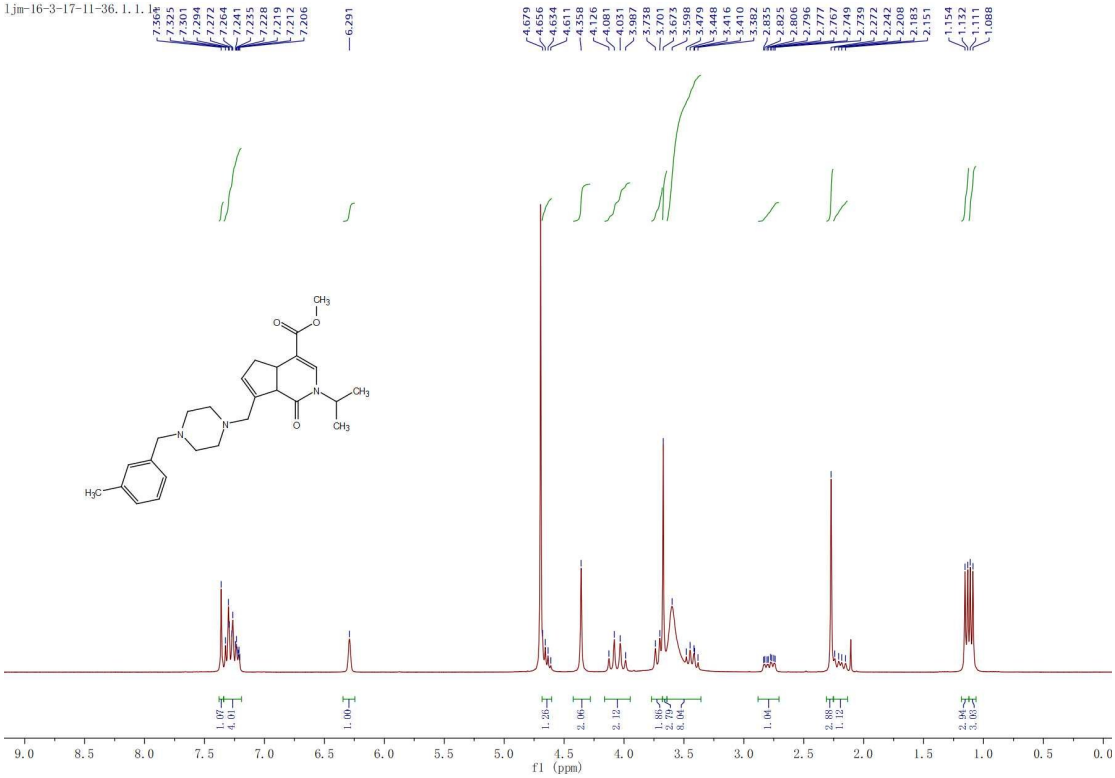


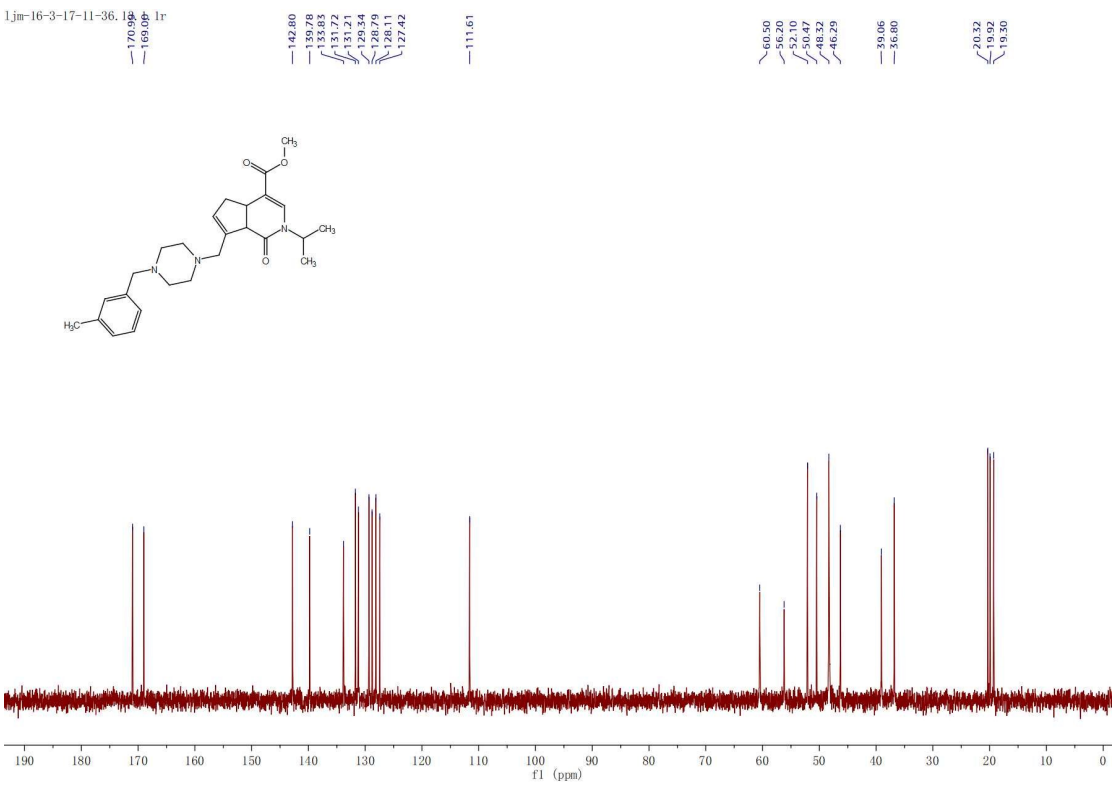
Compound **10k**



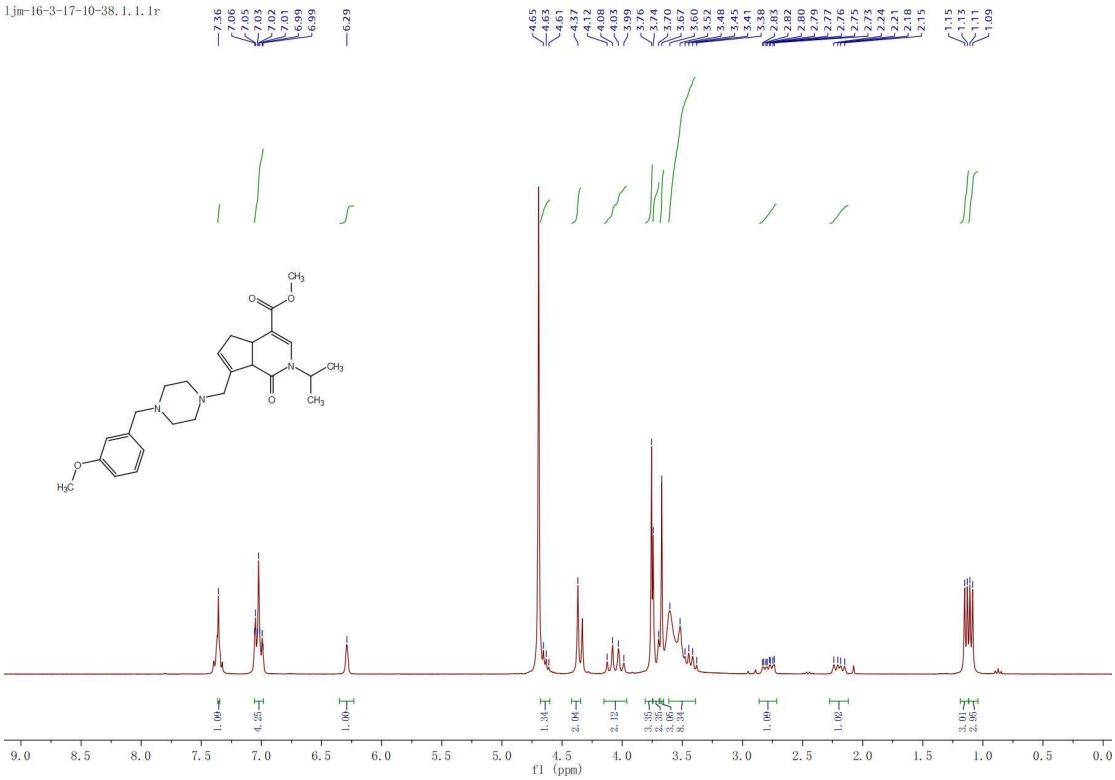


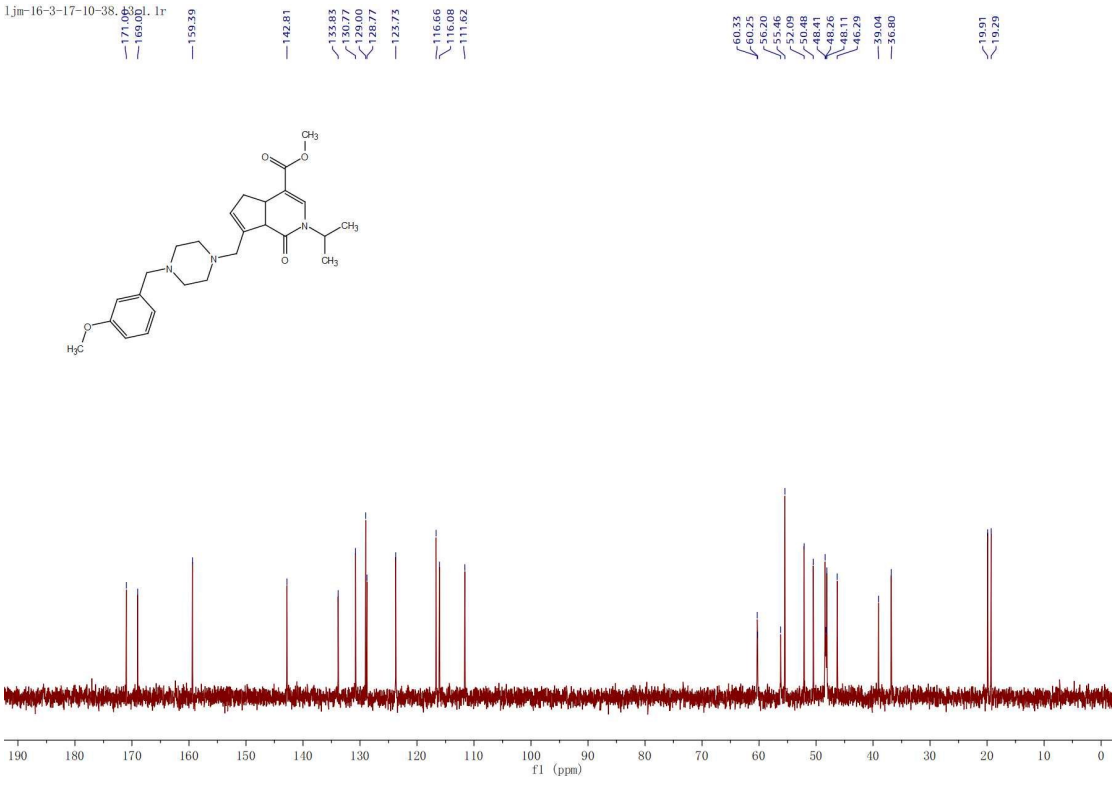
Compound **10l**



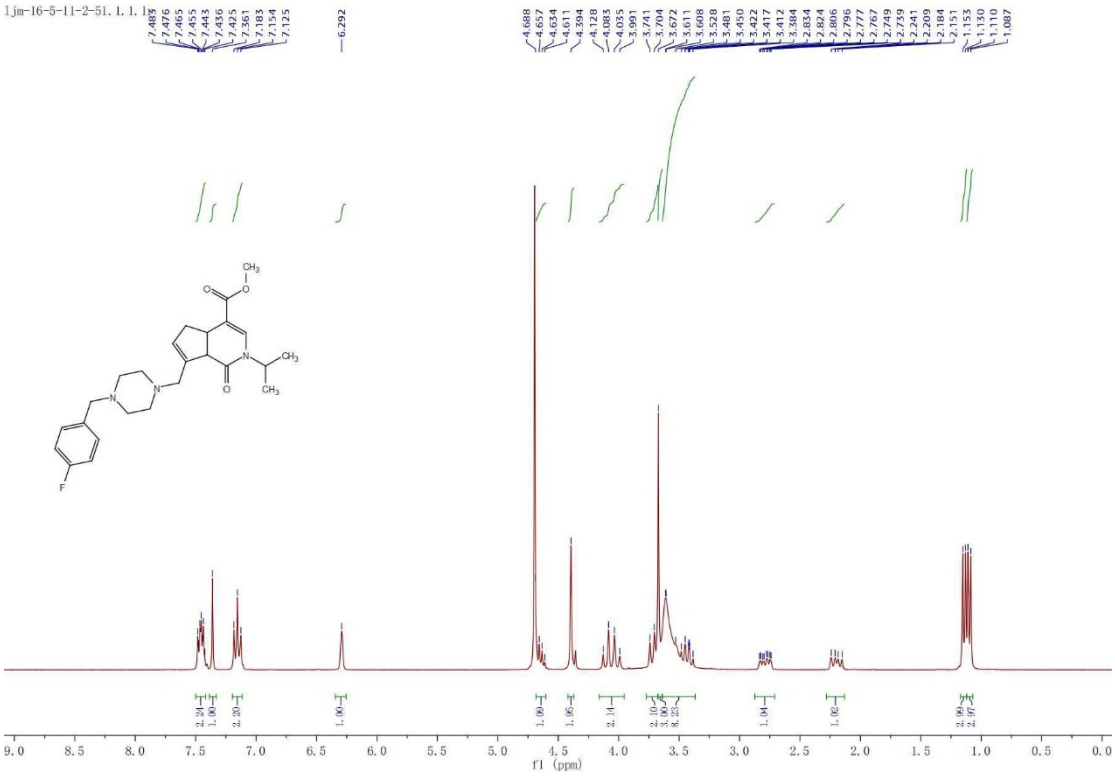


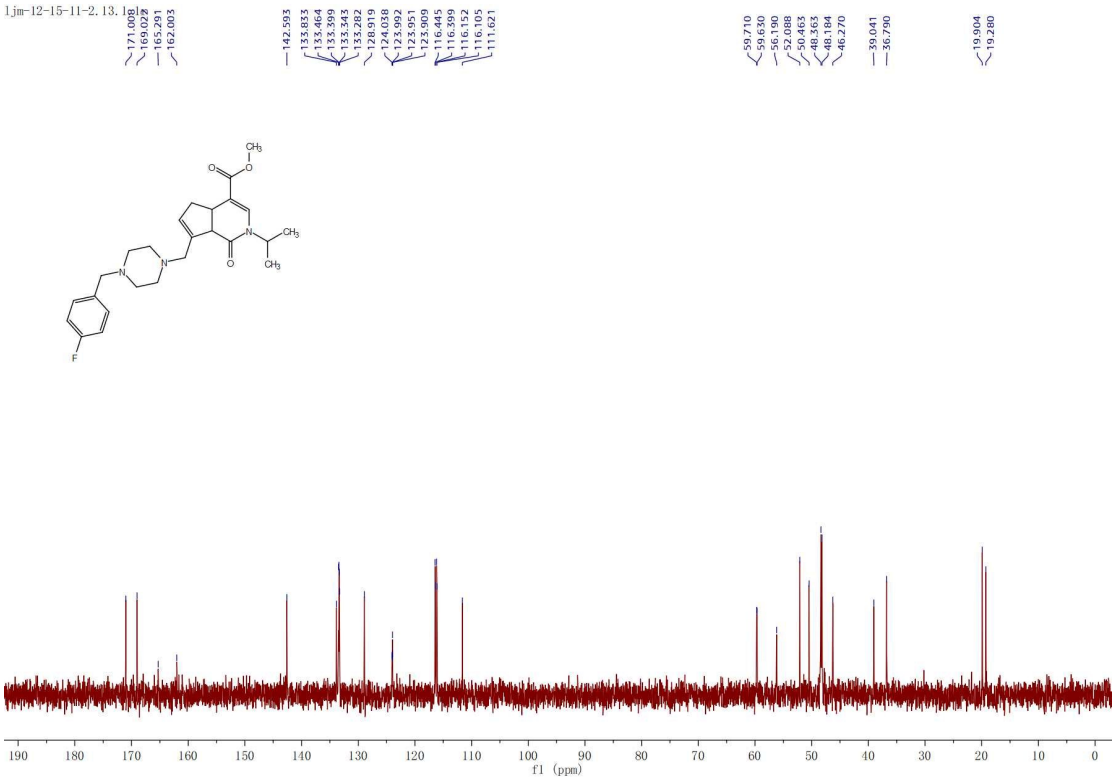
Compound **10m**



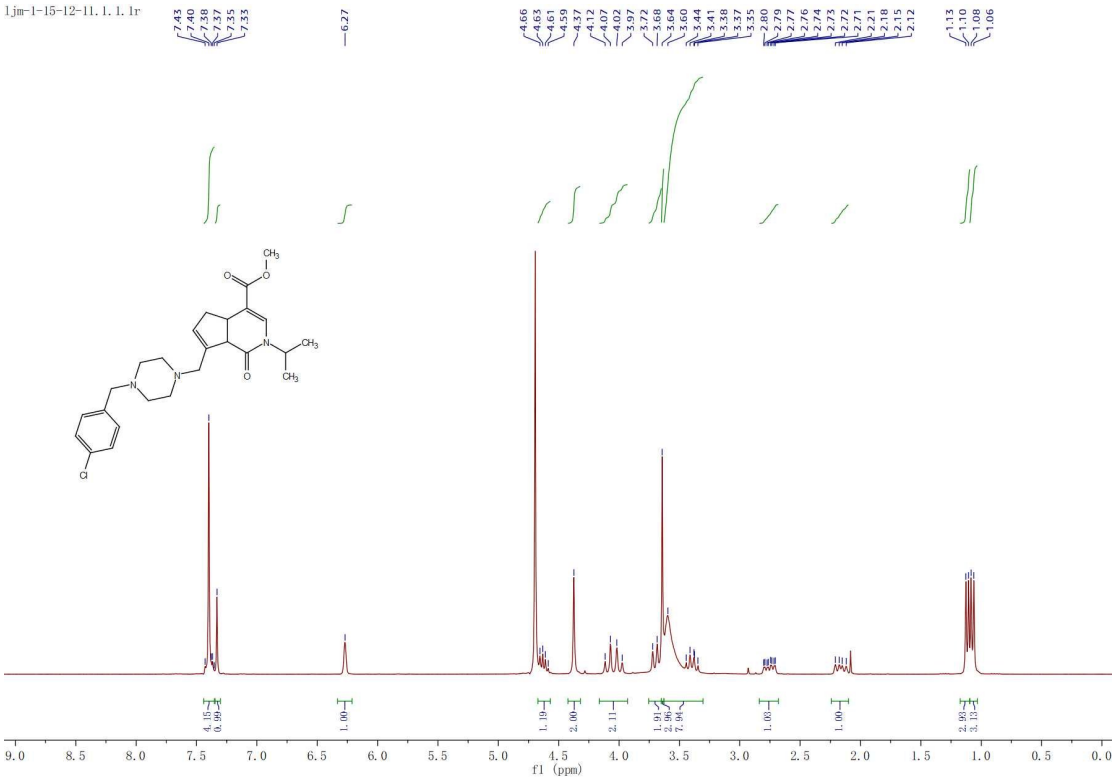


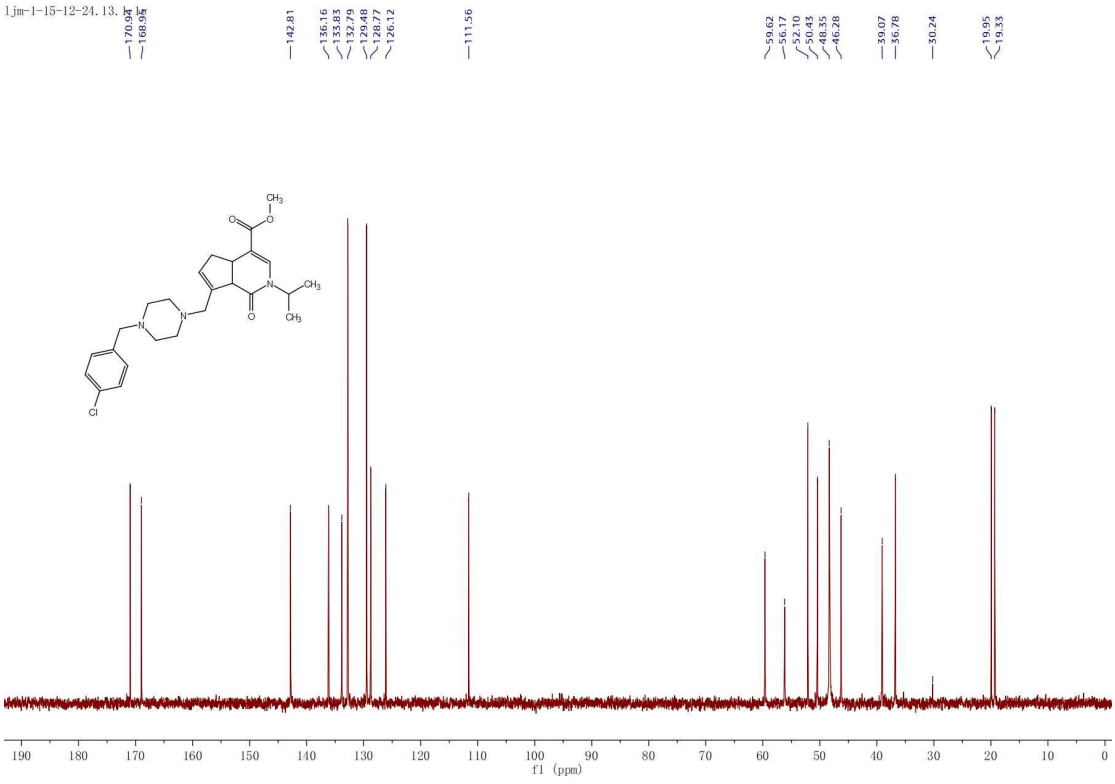
Compound **10n**



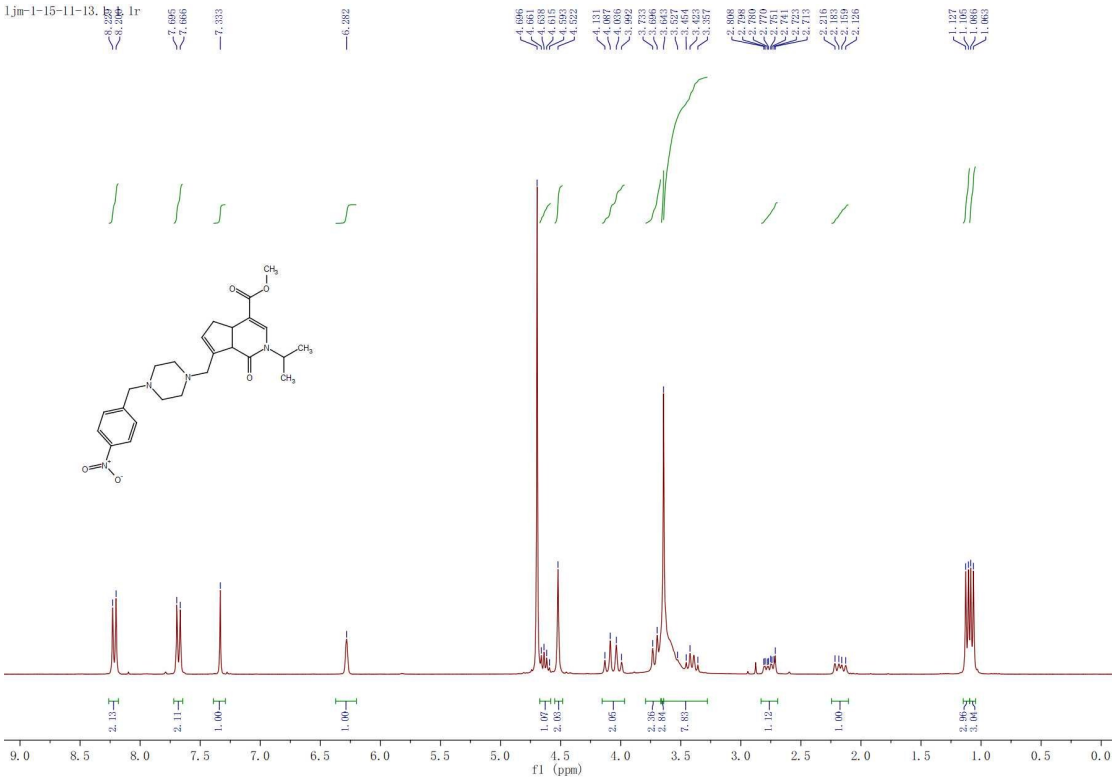


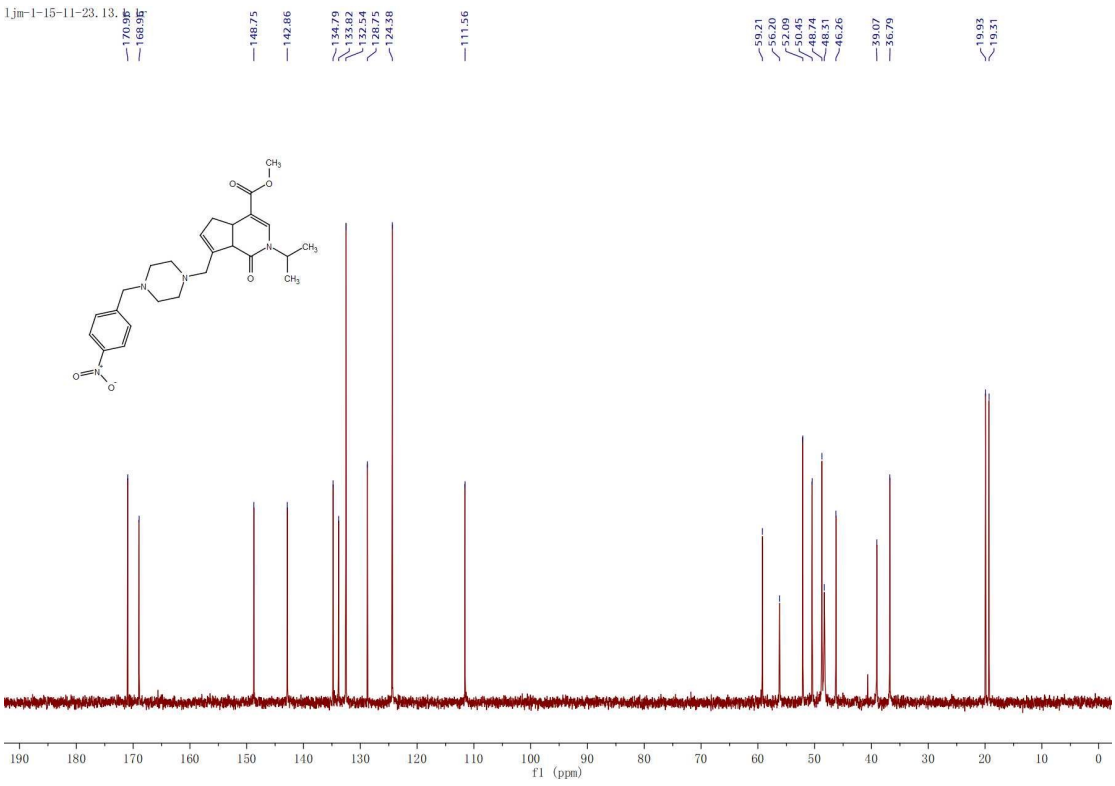
Compound **10o**



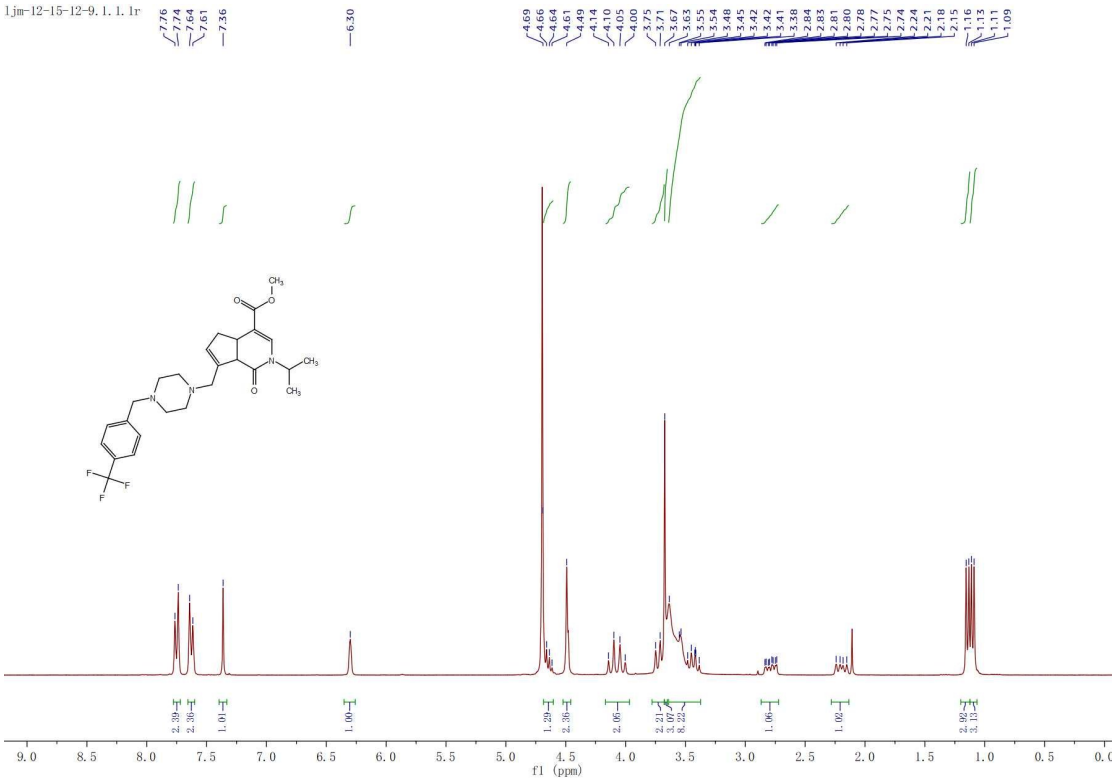


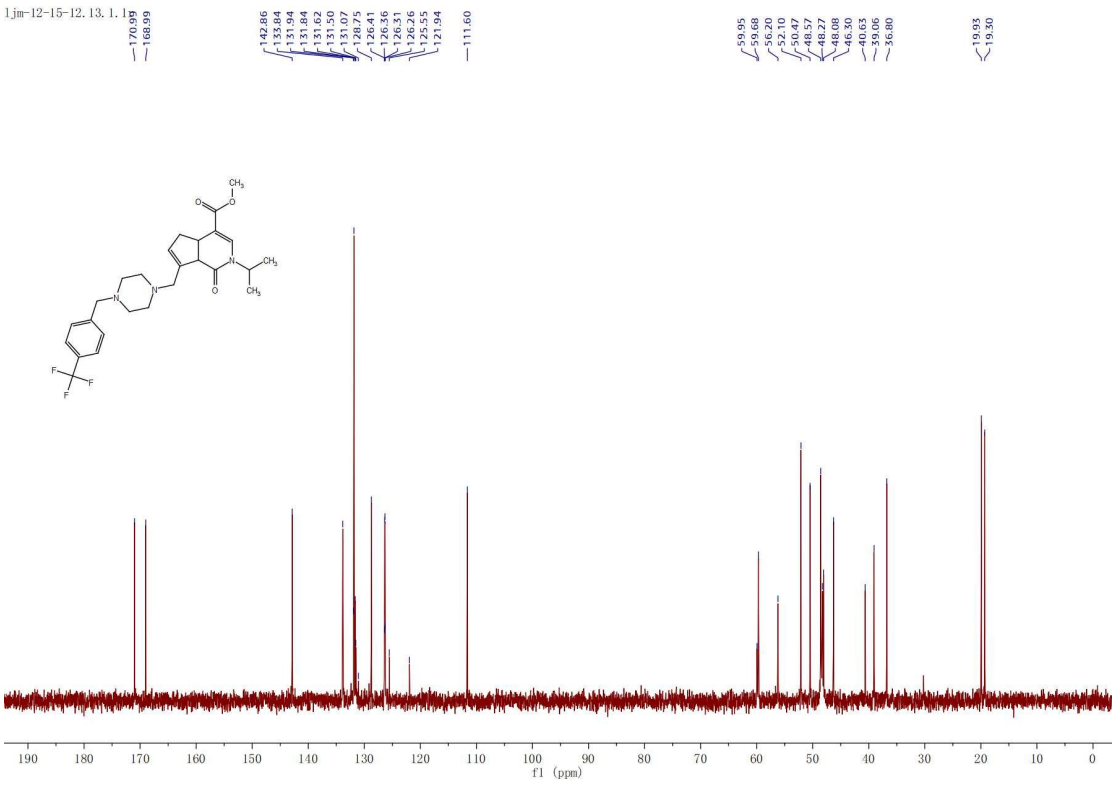
Compound **10p**





Compound **10q**





Compound **10r**