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Electronic Supplementary Information

Ynamides enabled 6-, 7-, and 8-*endo-dig* iodocyclization of ethoxyethyl ethers: rapid construction of medium-sized oxacycles at room temperature

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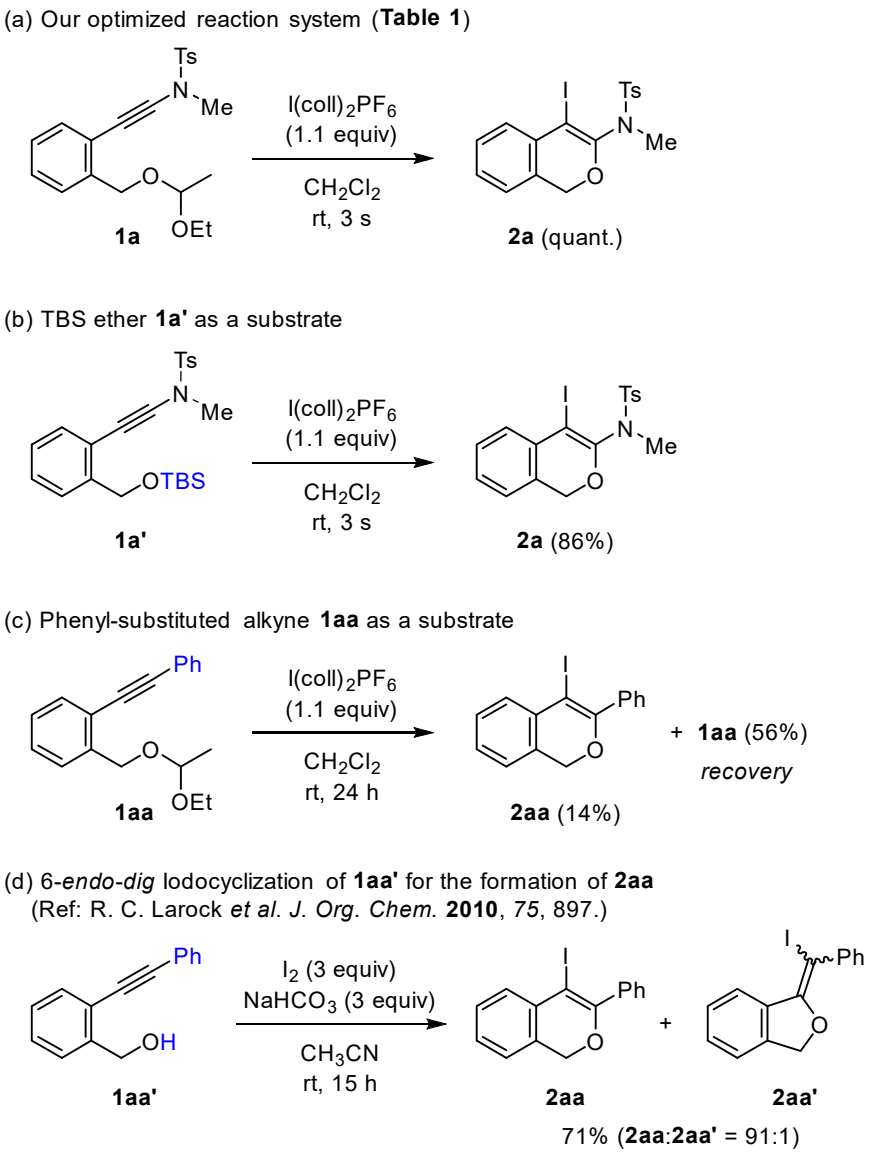
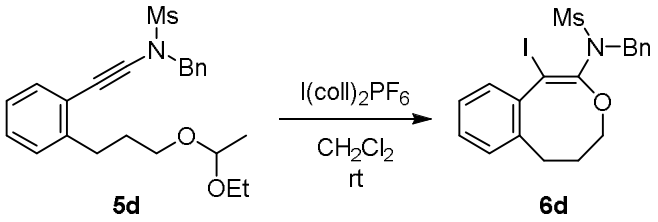
Scheme S1: Comparison of Reactivity between Ynamides and Other Alkynes



Our rapid and regioselective iodocyclization of ynamide **1** was characterized by comparing with other substrates (Scheme S1). Iodocyclization of ynamide **1a'**, having TBS ether as *O*-nucleophile, also afforded **2a** in high yield, albeit trace amount of unreacted **1a'** was observed when reaction was quenched 3 seconds later. Thus, ethoxyethyl group was better leaving group than TBS group in iodocyclization (optimization of protecting group for hydroxyl group, also see: T. Okitsu, D. Nakazawa, R. Taniguchi, A. Wada, *Org. Lett.* **2008**, *10*, 4967). Iodocyclization of phenyl-substituted alkyne **1aa** was slower than that of **1a**, and 6-*endo-dig* product **2aa** was obtained in low yield. Larock and co-workers reported the iodocyclization of phenyl-substituted alkynylbenzylalcohol **1aa'** leading to 6-*endo-dig* product **2aa** with a small amount of 5-*exo-dig* product **2aa'**.

Table S1: Optimization of 8-*endo-dig* Iodocyclization of 5d



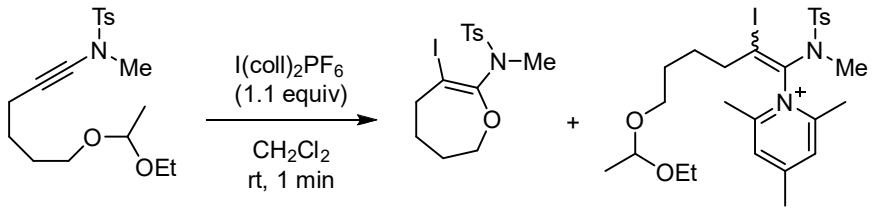
5d **6d**

Entry	$I(coll)_2PF_6$	Time	Yield of **6d**
1[a]	1.1 equiv	1 h	30%
2[a]	1.1 equiv	3 h	39%
3	2.0 equiv	3 h	49%

[a] Some of **5d** remained.

Reaction conditions of 8-*endo-dig* iodocyclization were optimized using **5d** as substrate (Table S1). 1.1 equiv of $I(coll)_2PF_6$ was inefficient for the complete consumption of **5d** (entries 1-2). Therefore, the use of $I(coll)_2PF_6$ was increased to 2.0 equiv, and as a result, **5d** was almost consumed and 8-*endo-dig* product **6d** was obtained in moderate yield (entry 3).

Scheme S2: Formation of Collidinium Salt C

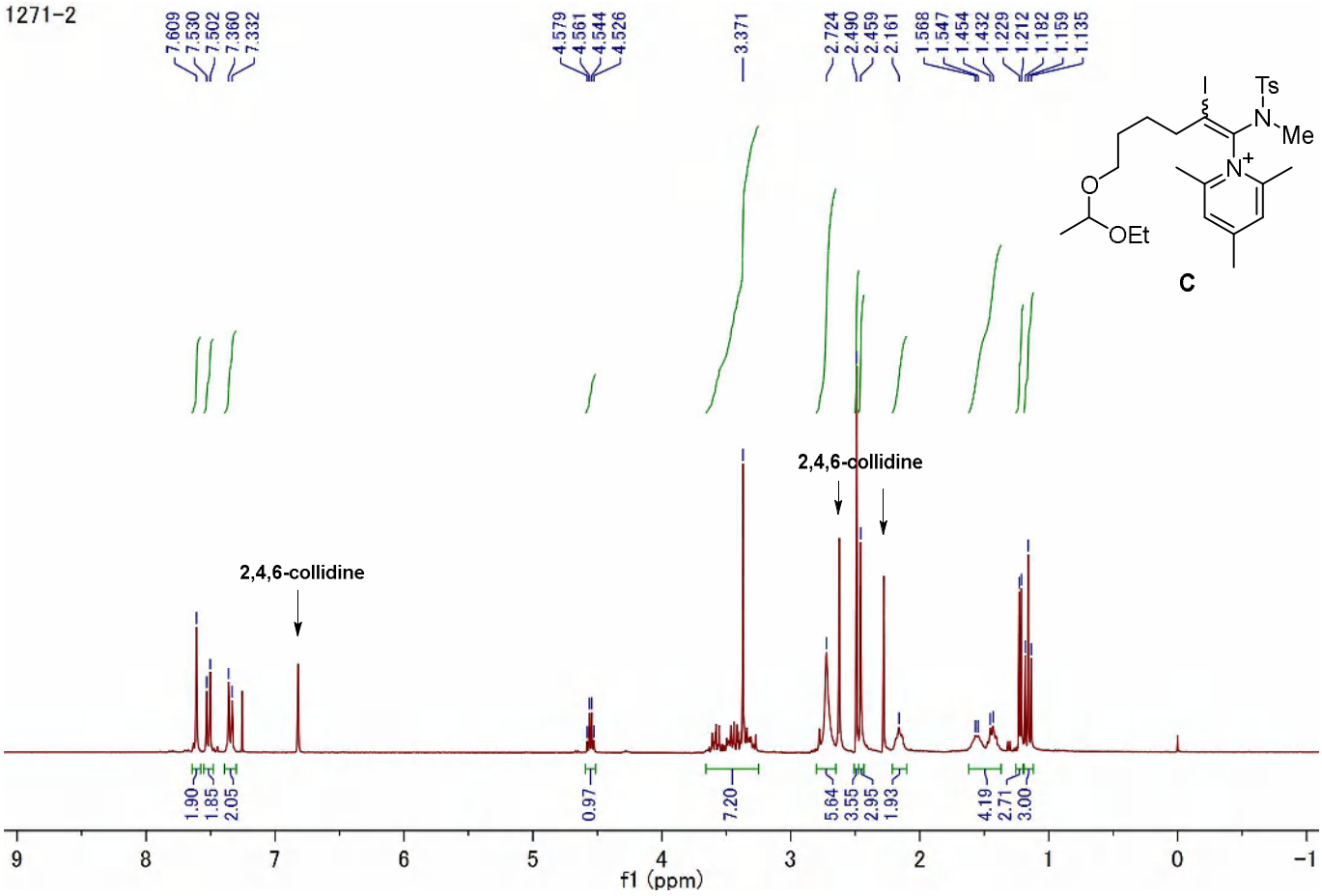


3p **4p** (34%) **C** (37%)

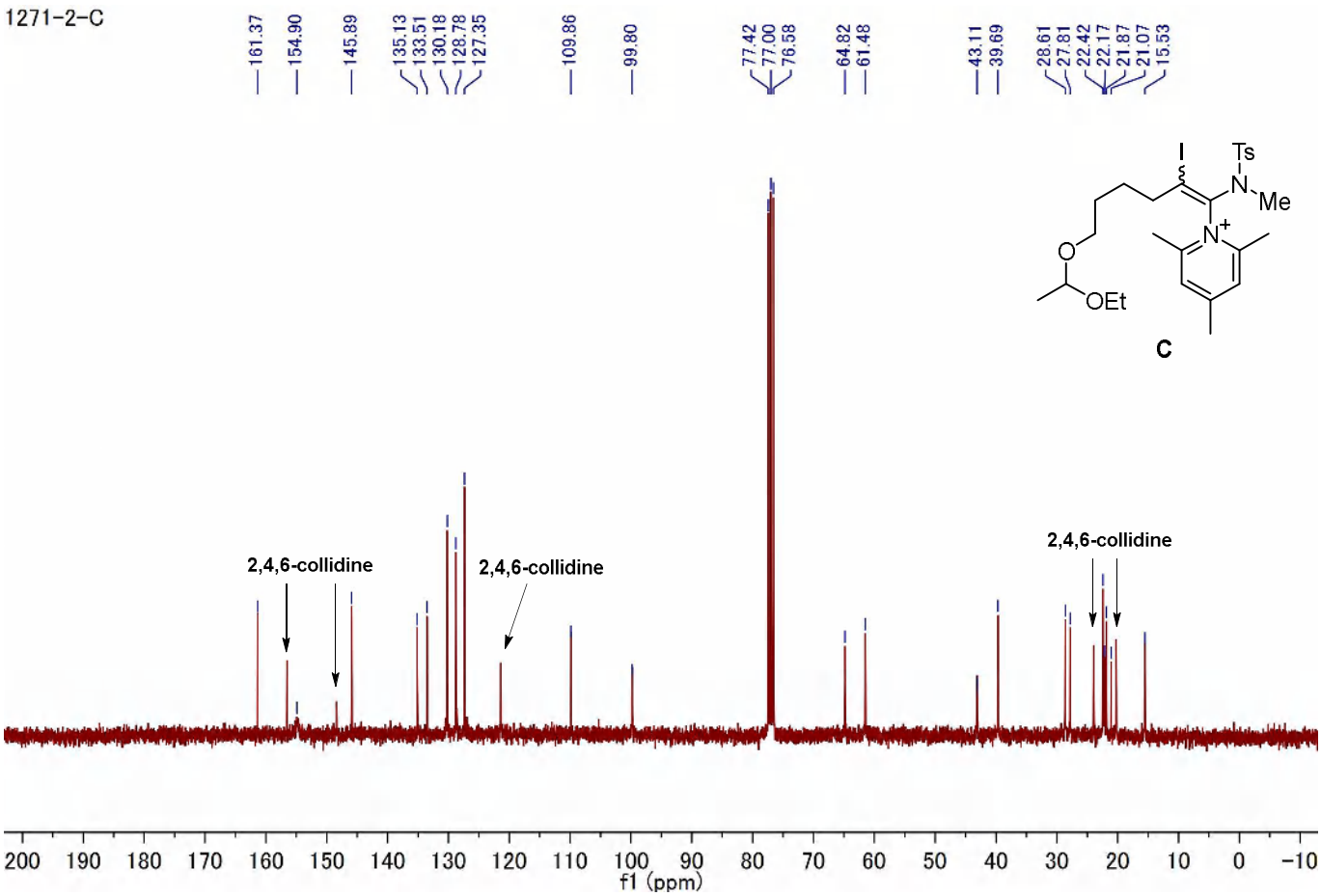
According to **GP-3** (see page S36), **4p** (27.8 mg, 34%) and **C** (54.9 mg, 37% as PF_6^- salt, 2,4,6-collidine was contaminated as a molar ratio of **C**/2,4,6-collidine = 3:2) were obtained from **3p** (70.7 mg, 0.200 mmol) and $I(coll)_2PF_6$ (113 mg, 0.220 mmol). Eluent: hexane/EtOAc = 5:1 to CH_2Cl_2/MeOH = 20:1.

C: brown oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (s, 2H), 7.52 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.4 Hz, 2H), 4.55 (q, *J* = 5.1 Hz, 1H), 3.68-3.26 (m, 7H), 2.72 (br s, 6H), 2.49 (s, 3H), 2.46 (s, 3H), 2.16 (br t, *J* = 6.9 Hz, 2H), 1.62-1.38 (m, 4H), 1.22 (d, *J* = 5.1 Hz, 3H), 1.16 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.4, 154.9, 145.9, 135.1, 133.5, 130.2, 128.8, 127.4, 109.9, 99.8, 64.8, 61.5, 43.1, 39.7, 28.6, 27.8, 22.4, 22.2, 21.9, 21.1, 15.5.

Compound **C** (^{1}H NMR, 300 MHz, $CDCl_3$)

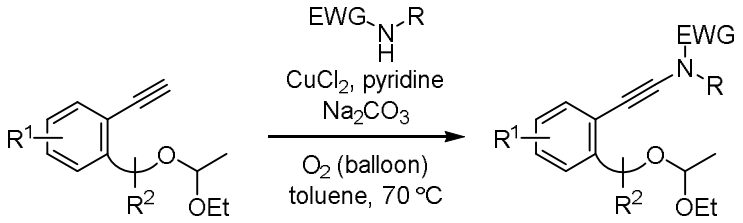


Compound **C** (^{13}C NMR, 75 MHz, $CDCl_3$)



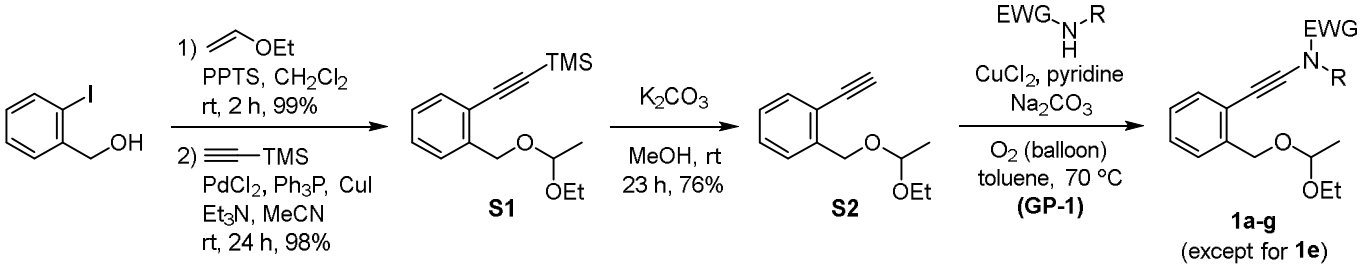
General. Melting point was measured by Yanagimoto micro melting point apparatus. Optical rotations were measured on a JASCO P-2200 polarimeter ($[\alpha]_D$ values are in units of 10^{-1} deg cm^2 g^{-1}). IR spectra were measured on a Perkin Elmer Spectrum 100 FT-IR spectrometer using $CHCl_3$. ^1H NMR and ^{13}C NMR spectra were determined on a Varian Mercury-300 or a Varian VXR-500 or a Brucker-600 superconducting FT-NMR spectrometer, respectively. Chemical shifts (δ) are reported in ppm relative to tetramethylsilane as internal reference ($CDCl_3$: δ = 0 ppm for ^1H) and residual solvent signal ($CDCl_3$: δ = 77.0 ppm for ^{13}C). *J*-Values are given in Hz. MS was performed on an Exactive Orbitrap mass spectrometer. Column chromatography was performed using Kanto Silica Gel 60 N (spherical, neutral). All reaction was carried out under argon atmosphere. All reagents were directly used as obtained commercially.

General Procedure for the Preparation of Ynamides (GP-1)



According to literature,[1] in a 1 L three-neck round-bottom flask equipped with a stir-bar, $CuCl_2$ (0.2 equiv), amide (5 equiv) and Na_2CO_3 (2 equiv) were combined. The reaction flask was purged with oxygen gas. A solution of pyridine (2 equiv) in 0.1 M dry toluene was added to the reaction flask via a syringe. A balloon filled with oxygen gas was connected to the reaction flask via a needle. The flask was placed in an oil-bath and heated to 70 °C. A solution of terminal alkyne (1 equiv) in 0.1 M dry toluene was added to the flask over 4 h by using a syringe pump. After the addition of terminal alkyne/toluene solution, the reaction mixture was allowed to stir at 70 °C for another 4 h and then cooled to rt. After the crude mixture was filtered through Celite, the filtrate was concentrated in vacuo. The residue was purified by flash chromatography on silica gel with hexane/EtOAc to yield the ynamide.

Preparation of Ynamides 1a-g



((2-((1-Ehoxyethoxy)methyl)phenyl)ethynyl)trimethylsilane (S1)

To a mixture of 2-iodobenzyl alcohol (10.0 g, 42.7 mmol) and PPTS (1.07 g, 4.27 mmol) in dry CH_2Cl_2 (200 mL) was added ethyl vinyl ether (7.37 mL, 76.9 mmol) and stirred at rt for 2 h. After reaction completed, the mixture was quenched with saturated aqueous solution of $NaHCO_3$, extracted with CH_2Cl_2, dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 20:1 to give 1-((1-ethoxyethoxy)methyl)-2-iodobenzene (13.0 g, 99%) as colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 8.1, 1.2 Hz, 1H),

7.47 (dd, J = 7.5, 1.2 Hz, 1H), 7.35 (td, J = 7.2, 1.2 Hz, 1H), 6.98 (td, J = 7.5, 1.5 Hz, 1H), 4.89 (q, J = 5.4 Hz, 1H), 4.63 (d, J = 12.6 Hz, 1H), 4.50 (d, J = 12.6 Hz, 1H), 3.76-3.66 (m, 1H), 3.61-3.50 (m, 1H), 1.42 (d, J = 5.4 Hz, 3H), 1.23 (t, J = 7.2 Hz, 3H).

A mixture of 1-((1-ethoxyethoxy)methyl)-2-iodobenzene (13.0 g, 42.4 mmol), $PdCl_2$ (188 mg, 1.06 mmol), Ph_3P (555 mg, 2.12 mmol), CuI (290 mg, 1.53 mmol), Et_3N (17.7 mL, 127 mmol), and ethynyltrimethylsilane (8.98 mL, 1.53 mmol) in dry MeCN (84.0 mL) was stirred at rt for 24 h. After reaction completed, the mixture was quenched with 5% aqueous solution of NH_3. The mixture was extracted with Et_2O, washed with brine, dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 20:1 to give **S1** (11.4 g, 98%) as brown oil.

IR ν_{max}: 3010, 2155, 1601 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45 (d, J = 7.5 Hz, 1H), 7.42 (d, J = 7.2 Hz, 1H), 7.29 (td, J = 7.5, 1.5 Hz, 1H), 7.17 (td, J = 7.5, 1.2 Hz, 1H), 4.84 (q, J = 5.4 Hz, 1H), 4.79 (d, J = 12.9 Hz, 1H), 4.68 (d, J = 12.9 Hz, 1H), 3.75-3.64 (m, 1H), 3.58-3.47 (m, 1H), 1.39 (d, J = 5.4 Hz, 3H), 1.22 (t, J = 7.2 Hz, 3H), 0.26 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.5, 132.1, 128.5, 127.2, 126.8, 121.4, 102.6, 99.6, 98.8, 65.2, 61.0, 19.9, 15.4, 0.0; HR-ESIMS calcd for $C_{16}H_{24}NaO_2Si$ $[M+Na]^+$ 299.1438. Found 299.1435.

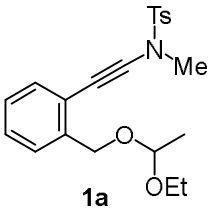
1-((1-Ethoxyethoxy)methyl)-2-ethynylbenzene (S2)

To a solution of **S1** (5.02 g, 23.2 mmol) in MeOH (11 mL) at rt was added K_2CO_3 (1.60 g, 11.6 mmol), and was stirred for 23 h. After reaction completed, the mixture was quenched with water, extracted with Et_2O, washed with brine, dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 20:1 to give **S2** (3.60 g, 76%) as colorless oil.

IR ν_{max}: 3305, 3012, 2106, 1602, 1134 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.47 (d, J = 8.1 Hz, 2H), 7.34 (td, J = 7.5, 1.2 Hz, 1H), 7.22 (td, J = 7.5, 1.2 Hz, 1H), 4.85 (q, J = 5.7 Hz, 1H), 4.80 (d, J = 12.6 Hz, 1H), 4.70 (d, J = 12.6 Hz, 1H), 3.76-3.64 (m, 1H), 3.58-3.47 (m, 1H), 3.28 (s, 1H), 1.40 (d, J = 5.7 Hz, 3H), 1.22 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.8, 132.5, 128.9, 127.5, 127.0, 120.4, 99.5, 81.6, 81.3, 65.0, 60.9, 19.9, 15.4; HR-ESIMS calcd for $C_{13}H_{16}NaO_2$ $[M+Na]^+$ 227.1043. Found 227.1040.

***N*-((2-((1-Ethoxyethoxy)methyl)phenyl)ethynyl)-*N*,4-dimethylbenzenesulfonamide (1a)**

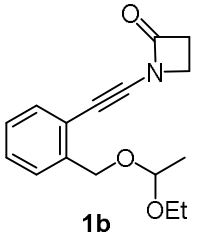
According to **GP-1**, **1a** (496 mg, 85%) was obtained from **S2** (306 mg, 1.50 mmol), *N*-methyl-*p*-toluenesulfonamide (1.39 g, 7.50 mmol), $CuCl_2$ (40.3 mg, 0.300 mmol), Na_2CO_3 (318 mg, 3.00 mmol), and pyridine (243 μL, 3.00 mmol). Eluent: hexane/EtOAc = 6:1.



1a

Colorless oil; IR ν_{max}: 3010, 2234, 1598, 1368, 1133 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, J = 8.7 Hz, 2H), 7.45 (d, J = 7.5 Hz, 1H), 7.37-7.24 (m, 4H), 7.18 (td, J = 7.5, 1.5 Hz, 1H), 4.83 (q, J = 5.1 Hz, 1H), 4.74 (d, J = 12.9 Hz, 1H), 4.64 (d, J = 12.9 Hz, 1H), 3.74-3.63 (m, 1H), 3.57-3.46 (m, 1H), 3.15 (s, 3H), 2.44 (s, 3H), 1.37 (d, J = 5.1 Hz, 3H), 1.19 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.5, 139.6, 133.0, 131.2, 129.6, 127.7, 127.6, 127.1, 126.8, 120.8, 99.5, 88.2, 66.9, 65.3, 61.1, 39.4, 21.8, 20.1, 15.5; HR-ESIMS calcd for $C_{21}H_{25}NNaO_4S$ $[M+Na]^+$ 410.1397. Found 410.1395.

1-((2-((1-Ethoxyethoxy)methyl)phenyl)ethynyl)azetidin-2-one (1b)

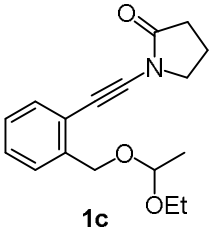


1b

According to **GP-1**, **3b** (332 mg, 81%) was obtained from **S2** (306 mg, 1.50 mmol), azetidin-2-one (533 mg, 7.50 mmol), $CuCl_2$ (40.3 mg, 0.300 mmol), Na_2CO_3 (318 mg, 3.00 mmol), and pyridine (243 μL, 3.00 mmol). Eluent: hexane/EtOAc = 2:1.

Colorless oil; IR ν_{max}: 3012, 2239, 1771, 1601 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.5 Hz, 1H), 7.38 (d, *J* = 7.5 Hz, 1H), 7.29 (t, *J* = 7.8 Hz, 1H), 7.19 (t, *J* = 7.5 Hz, 1H), 4.85 (q, *J* = 5.4 Hz, 1H), 4.75 (d, *J* = 12.6 Hz, 1H), 4.64 (d, *J* = 12.6 Hz, 1H), 3.78-3.65 (m, 3H), 3.59-3.48 (m, 1H), 3.10 (t, *J* = 4.8 Hz, 2H), 1.40 (d, *J* = 5.4 Hz, 3H), 1.21 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2, 139.8, 131.8, 128.2, 127.5, 127.0, 120.6, 99.6, 82.8, 67.6, 65.4, 61.0, 43.2, 38.1, 20.0, 15.4; HR-ESIMS calcd for $C_{16}H_{19}NNaO_3$ $[M+Na]^+$ 296.1257. Found 296.1257.

1-((2-((1-Ethoxyethoxy)methyl)phenyl)ethynyl)pyrrolidin-2-one (1c)

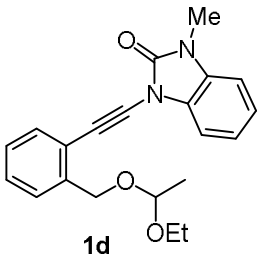


1c

According to **GP-1**, **1c** (108 mg, 25%) was obtained from **S2** (306 mg, 1.50 mmol), 2-pyrrolidone (0.575 mL, 7.50 mmol), $CuCl_2$ (40.3 mg, 0.300 mmol), Na_2CO_3 (318 mg, 3.00 mmol), and pyridine (242 μL, 3.00 mmol). Eluent: hexane/EtOAc = 1:1.

Colorless oil; IR ν_{max}: 3012, 2246, 1717, 1602 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.46 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.41 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.27 (td, *J* = 7.5, 1.5 Hz 1H), 7.19 (td, *J* = 7.5, 1.5 Hz, 1H), 4.86 (q, *J* = 5.1 Hz, 1H), 4.79 (d, *J* = 12.9 Hz, 1H), 4.70 (d, *J* = 12.9 Hz, 1H), 3.77 (t, *J* = 6.9 Hz, 2H), 3.77-3.65 (m, 1H), 3.58-3.47 (m, 1H), 2.48 (t, *J* = 8.1 Hz, 2H), 2.17 (quint, *J* = 7.5 Hz, 2H), 1.39 (d, *J* = 5.1 Hz, 3H), 1.21 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.3, 139.6, 131.5, 127.9, 127.3, 126.9, 120.9, 99.6, 84.7, 70.3, 65.5, 61.0, 50.0, 29.7, 20.0, 18.9, 15.4; HR-ESIMS calcd for $C_{17}H_{21}NNaO_3$ $[M+Na]^+$ 310.1414. Found 310.1409.

1-((2-((1-Ethoxyethoxy)methyl)phenyl)ethynyl)-3-methyl-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one (1d)

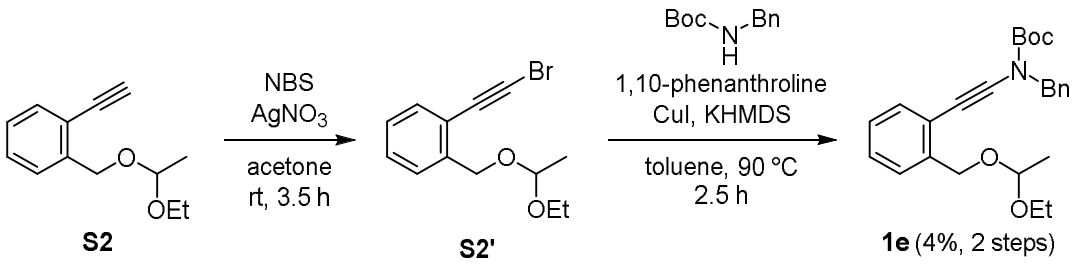


1d

According to **GP-1**, **1d** (193 mg, 36%) was obtained from **S2** (306 mg, 1.50 mmol), 1-methyl-2-benzimidazolinone (1.11 g, 7.50 mmol), $CuCl_2$ (40.3 mg, 0.300 mmol), Na_2CO_3 (318 mg, 3.00 mmol), and pyridine (242 μL, 3.00 mmol). Eluent: hexane/EtOAc = 3:1.

Colorless crystals; mp 67-69 ºC (hexane/EtOAc); IR ν_{max}: 3011, 2255, 1734, 1621 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.56 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.51 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.38-7.23 (m, 3H), 7.22-7.12 (m, 2H), 6.98 (dd, *J* = 6.9, 1.5 Hz, 1H), 4.89 (d, *J* = 12.9 Hz, 1H), 4.88 (q, *J* = 5.4 Hz, 1H), 4.80 (d, *J* = 12.9 Hz, 1H), 3.76-3.65 (m, 1H), 3.58-3.47 (m, 1H), 3.44 (s, 3H), 1.40 (d, *J* = 5.1 Hz, 3H), 1.18 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.9, 140.1, 132.1, 129.7, 128.5, 128.1, 127.5, 127.1, 123.5, 122.2, 120.5, 109.8, 107.9, 99.7, 79.7, 73.0, 65.5, 61.1, 27.7, 20.1, 15.4; HR-ESIMS calcd for $C_{21}H_{22}N_2NaO_3$ $[M+Na]^+$ 373.1523. Found 373.1524.

***tert*-Butyl benzyl((2-((1-ethoxyethoxy)methyl)phenyl)ethynyl)carbamate (1e)**

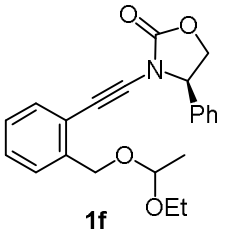


To a solution of **S2** (2.04 g, 10.0 mmol) in dry acetone (60 mL) at rt was added $AgNO_3$ (170 mg, 1.00 mmol) and NBS (1.96 g, 11.0 mmol) were added successively, each in a single portion. After the mixture was stirred at rt under dark for 3.5 h, the reaction mixture was diluted with hexane and vigorously stirred for 5 min. The mixture was filtered and concentrated in vacuo. The residue was purified by short silica gel pad (3 cm) eluting with hexane to give **S2'** (2.41 g) that was directly used in the next reaction.

According to literature,[2] to a mixture of **S2'** (2.41 g, 8.51 mmol), *tert*-butyl benzylcarbamate (1.04 g, 5.00 mmol), CuI (290 mg, 1.50 mmol), 1,10-phenanthroline (320 mg, 1.80 mmol) in dry toluene (8.5 mL) at 90 °C was added KHMDS (0.5 M in toluene, 15.0 mL, 7.50 mmol) over 1 h by using a syringe pump. After the addition of KHMDS solution, the reaction mixture was stirred at 90 °C for another 2.5 h. The reaction mixture was cooled to rt and quenched with water, extracted with EtOAc. The organic layer was washed with brine, and filtered through Celite, and the filtrate was concentrated in vacuo. The crude products were purified by silica gel column chromatography eluting with hexane/EtOAc = 7:1 to afford **1e** (143 mg, 4%, 2 steps) as yellow oil.

IR ν_{max}: 2983, 2243, 1715, 1601 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.46-7.29 (m, 7H), 7.24 (td, *J* = 7.5, 1.5 Hz, 1H), 7.17 (td, *J* = 7.5, 1.5 Hz, 1H), 4.77 (q, *J* = 5.5 Hz, 1H), 4.68 (s, 2H), 4.67 (d, *J* = 13.0 Hz, 1H), 4.58 (d, *J* = 13.0 Hz, 1H), 3.69-3.61 (m, 1H), 3.51-3.44 (m, 1H), 1.54 (s, 9H), 1.34 (d, *J* = 5.5 Hz, 3H), 1.17 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.8, 139.2, 136.4, 131.0, 128.6, 128.3, 127.9, 127.3, 127.0, 126.9, 121.7, 99.5, 88.4, 82.8, 68.8, 65.4, 60.8, 53.1, 28.1, 20.0, 15.3; HR-ESIMS calcd for $C_{25}H_{31}NNaO_4$ $[M+Na]^+$ 432.2145. Found 432.2146.

(4*R*)-3-((2-((1-Ethoxyethoxy)methyl)phenyl)ethynyl)-4-phenyloxazolidin-2-one (1f)

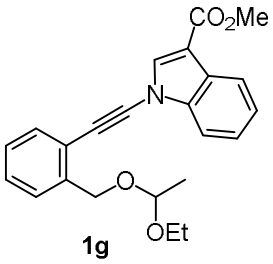


1f

According to **GP-1**, **1f** (198 mg, 36%) was obtained as 1:1 diastereomer mixture from **S2** (306 mg, 1.50 mmol), (*R*)-(-)-4-phenyl-2-oxazolidinone (1.22 g, 7.50 mmol), $CuCl_2$ (40.3 mg, 0.300 mmol), Na_2CO_3 (318 mg, 3.00 mmol), and pyridine (242 μL, 3.00 mmol). Eluent: hexane/EtOAc = 3:1.

Colorless oil; $[\alpha]_D^{26}$ -163 (*c* 1.01, $CHCl_3$); IR ν_{max}: 3011, 2254, 1777, 1603 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.48-7.35 (m, 6H), 7.22 (t, *J* = 7.8, Hz, 2H), 7.10 (td, *J* = 7.2, 1.5 Hz, 1H), 5.12 (dd, *J* = 8.7, 7.2 Hz, 1H), 4.76 (t, *J* = 8.7 Hz, 1H), 4.69 (q, *J* = 5.4 Hz, 0.5H), 4.66 (q, *J* = 5.4 Hz, 0.5H), 4.48 (dd, *J* = 12.9, 3.0 Hz, 0.5H), 4.38 (dd, *J* = 12.9, 4.8 Hz, 0.5H), 4.28 (dd, *J* = 9.3, 7.2 Hz, 1H), 3.68-3.57 (m, 1H), 3.49-3.39 (m, 1H), 1.30 (d, *J* = 5.4 Hz, 1.5H), 1.29 (d, *J* = 5.4 Hz, 1.5H), 1.18 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.1, 139.79, 139.75, 135.9, 131.5, 129.4, 129.2, 128.0, 126.90, 126.87, 126.69, 126.68, 120.13, 120.09, 99.66, 99.61, 82.4, 70.7, 70.4, 65.3, 65.2, 62.1, 61.0, 60.9, 20.0, 15.4; HR-ESIMS calcd for $C_{22}H_{23}NNaO_4$ $[M+Na]^+$ 388.1519. Found 388.1528.

Methyl 1-((2-(2-(1-ethoxyethoxy)ethyl)phenyl)ethynyl)-1*H*-indole-3-carboxylate (1g)

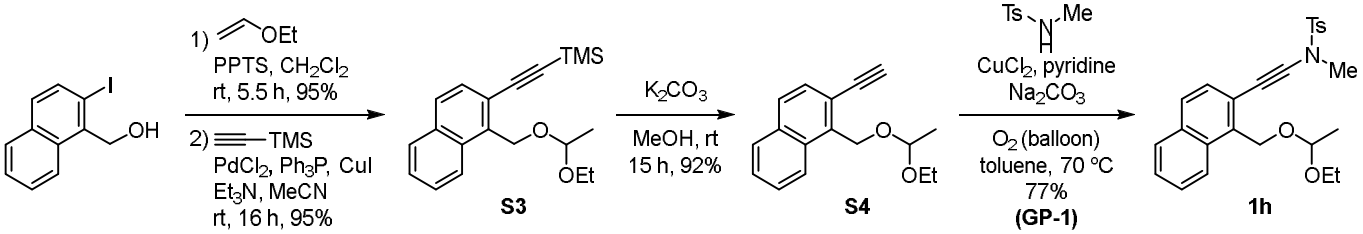


1g

According to **GP-1**, **1g** (490 mg, 83%) was obtained from **S2** (306 mg, 1.50 mmol), methyl 1*H*-indole-3-carboxylate (1.31 g, 7.50 mmol), $CuCl_2$ (40.3 mg, 0.300 mmol), Na_2CO_3 (318 mg, 3.00 mmol), and pyridine (242 μL, 3.00 mmol). Eluent: hexane/EtOAc = 7:1.

Red oil; IR ν_{max}: 3011, 2254, 1709, 1614 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.17 (dd, *J* = 6.9, 2.4 Hz, 1H), 7.96 (s, 1H), 7.57-7.51 (m, 2H), 7.42-7.26 (m, 4H), 4.89 (d, *J* = 12.6 Hz, 1H), 4.88 (q, *J* = 5.1 Hz, 1H), 4.78 (d, *J* = 12.6 Hz, 1H), 3.93 (s, 1H), 3.74-3.63 (m, 1H), 3.58-3.47 (m, 1H), 1.40 (d, *J* = 5.1 Hz, 3H), 1.17 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.1, 140.1, 138.3, 134.6, 132.1, 128.8, 127.9, 127.3, 125.3, 124.5, 123.7, 121.9, 120.1, 111.5, 111.1, 99.4, 83.3, 69.7, 65.3, 60.8, 51.4, 20.0, 15.4; HR-ESIMS calcd for $C_{23}H_{23}NNaO_4$ $[M+Na]^+$ 400.1519. Found 400.1520.

Preparation of Ynamide 1h



((1-((1-Ethoxyethoxy)methyl)naphthalen-2-yl)ethynyl)trimethylsilane (S3)

To a mixture of (2-iodonaphthalen-1-yl)methanol[3] (615 mg, 2.17 mmol) and PPTS (54.5 mg, 0.217 mmol) in dry CH_2Cl_2 (11 mL) was added ethyl vinyl ether (373 μL, 3.90 mmol) and stirred at rt for 5.5 h. After reaction completed, the mixture was quenched with saturated aqueous solution of $NaHCO_3$, extracted with CH_2Cl_2, dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 25:1 to give 1-((1-ethoxyethoxy)methyl)-2-iodonaphthalene (735 mg, 95%) as colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 8.18 (d, *J* = 5.1 Hz, 1H), 7.87 (d, *J* = 8.7 Hz, 1H), 7.79 (d, *J* = 7.5 Hz, 1H), 7.58-7.46 (m, 3H), 5.26 (d, *J* = 11.1 Hz, 1H), 5.15 (d, *J* = 10.8 Hz, 1H), 4.94 (q, *J* = 5.4 Hz, 1H), 3.83-3.71 (m, 1H), 3.63-3.51 (m, 1H), 1.44 (d, *J* = 5.4 Hz, 3H), 1.27 (t, *J* = 7.2 Hz, 3H).

A mixture of 1-((1-ethoxyethoxy)methyl)-2-iodonaphthalene (750 mg, 2.11 mmol), $PdCl_2$ (9.4 mg, 0.0530 mmol), Ph_3P (28.9 mg, 0.110 mmol), CuI (14.5 mg, 0.0761 mmol), Et_3N (0.882 mL, 6.33 mmol), and ethynyltrimethylsilane (0.880 mL, 6.23 mmol) in dry MeCN (5.0 mL) was stirred at rt for 16 h. After reaction completed, the mixture was quenched with 5% aqueous solution of NH_3. The mixture was extracted with Et_2O, washed with brine, dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 25:1 to give **S3** (655 mg, 95%) as brown oil.

IR ν_{max}: 3010, 2152, 1596 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.1 Hz, 1H), 7.77 (d, *J* = 5.1 Hz, 1H), 7.70 (d, *J* = 8.7 Hz, 1H), 7.56-7.43 (m, 1H), 5.29 (d, *J* = 11.1 Hz, 1H), 5.21 (d, *J* = 11.4 Hz, 1H), 4.87 (q, *J* = 5.1 Hz, 1H), 3.78-3.66 (m, 1H), 3.53-3.41 (m, 1H), 1.40 (d, *J* = 5.1 Hz, 3H), 1.21 (t, *J* = 7.2 Hz, 3H), 0.29 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.4, 133.4, 132.2, 128.7, 128.3, 128.2, 126.7, 126.4, 125.1, 121.3, 104.1, 99.7, 98.9, 63.3, 61.5, 20.2, 15.5, 0.1; HR-ESIMS calcd for $C_{20}H_{26}NaO_2Si$ $[M+Na]^+$ 349.1594. Found 349.1593.

1-((1-Ethoxyethoxy)methyl)-2-ethynylnaphthalene (S4)

To a solution of **S3** (656 mg, 2.01 mmol) in MeOH (1 mL) at rt was added K_2CO_3 (139 mg, 1.01 mmol), and was stirred for 15 h. After reaction completed, the mixture was quenched with water, extracted with Et_2O, washed with brine, dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 30:1 to give **S4** (468 mg, 92%) as colorless oil.

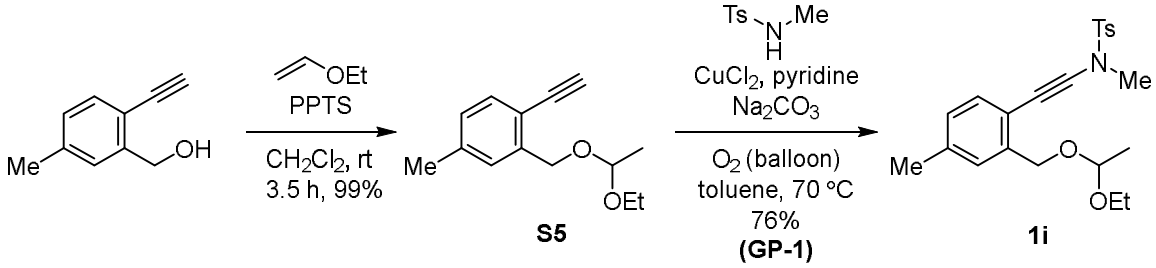
IR ν_{max}: 3303, 3011, 2104, 1597 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.20 (d, J = 8.7 Hz, 1H), 7.78 (d, J = 7.5 Hz, 1H), 7.73 (d, J = 8.4 Hz, 1H), 7.57-7.44 (m, 3H), 5.28 (d, J = 11.1 Hz, 1H), 5.23 (d, J = 10.8 Hz, 1H), 4.89 (q, J = 5.1 Hz, 1H), 3.79-3.66 (m, 1H), 3.56-3.54 (m, 1H), 3.36 (s, 1H), 1.41 (d, J = 5.1 Hz, 3H), 1.22 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.9, 133.5, 132.2, 128.7, 128.5, 128.2, 126.8, 126.6, 125.0, 120.2, 99.4, 82.7, 81.5, 62.7, 61.1, 20.0, 15.3; HR-ESIMS calcd for $C_{17}H_{18}NaO_2$ $[M+Na]^+$ 227.1199. Found 277.1203.

***N*-((1-((1-Ethoxyethoxy)methyl)naphthalen-2-yl)ethynyl)-*N*,4-dimethylbenzenesulfonamide (1h)**

According to **GP-1**, **1h** (484 mg, 77%) was obtained from **S4** (366 mg, 1.44 mmol), *N*-methyl-*p*-toluenesulfonamide (1.34 g, 7.20 mmol), $CuCl_2$ (39.0 mg, 0.288 mmol), Na_2CO_3 (305 mg, 2.88 mmol), and pyridine (233 μL, 2.88 mmol). Eluent: hexane/EtOAc = 5:1.

Yellow oil; IR ν_{max}: 3010, 2234, 1598, 1369, 1170 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.18 (d, J = 8.4 Hz, 1H), 7.85 (d, J = 8.4 Hz, 2H), 7.78 (dd, J = 7.8, 1.5 Hz, 1H), 7.70 (d, J = 8.4 Hz, 1H), 7.56-7.49 (m, 1H), 7.48-7.42 (m, 1H), 7.39-7.30 (m, 3H), 5.23 (d, J = 10.8 Hz, 1H), 5.15 (d, J = 10.8 Hz, 1H), 4.87 (q, J = 5.4 Hz, 1H), 3.74-3.63 (m, 1H), 3.53-3.42 (m, 1H), 3.20 (s, 3H), 2.44 (s, 3H), 1.35 (d, J = 5.4 Hz, 3H), 1.17 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.7, 134.9, 132.9, 129.8, 129.6, 128.4, 128.2, 128.1, 127.9, 127.7, 126.7, 126.1, 124.8, 121.0, 99.8, 88.2, 68.6, 63.5, 61.4, 39.3, 21.7, 20.3, 15.4; HR-ESIMS calcd for $C_{25}H_{27}NNaO_4S$ $[M+Na]^+$ 424.1553. Found 460.1549.

Preparation of Ynamide 1i



2-((1-Ethoxyethoxy)methyl)-1-ethynyl-4-methylbenzene (S5)

To a mixture of (2-ethynyl-5-methylphenyl)methanol[4] (770 mg, 5.27 mmol) and PPTS (132 mg, 0.527 mmol) in dry CH_2Cl_2 (26.3 mL) was added ethyl vinyl ether (0.757 mL, 7.90 mmol) and stirred at rt for 3.5 h. After reaction completed, the mixture was quenched with saturated aqueous solution of $NaHCO_3$, extracted with CH_2Cl_2, dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 25:1 to give **S5** (1.13 g, 99%) as pale yellow oil.

IR ν_{max}: 3300, 3011, 2103, 1611 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36 (d, J = 7.8 Hz, 1H), 7.28 (br s, 1H), 7.02 (br d, J = 7.8 Hz, 1H), 4.85 (q, J = 5.4 Hz, 1H), 4.76 (d, J = 12.6 Hz, 1H), 4.66 (d, J = 12.6 Hz,

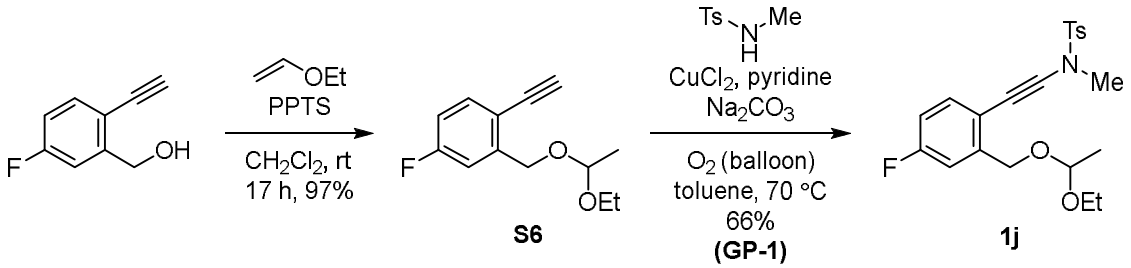
1H), 3.76-3.65 (m, 1H), 3.59-3.48 (m, 1H), 3.23 (s, 1H), 2.35 (s, 1H), 1.40 (d, J = 5.4 Hz, 3H), 1.22 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.3, 138.9, 132.4, 128.2, 127.7, 117.4, 99.5, 81.4, 80.8, 65.1, 60.9, 21.7, 20.0, 15.5; HR-ESIMS calcd for $C_{14}H_{18}NaO_2$ $[M+Na]^+$ 241.1199. Found 241.1198.

***N*-((2-((1-Ethoxyethoxy)methyl)-4-methylphenyl)ethynyl)-*N*,4-dimethylbenzenesulfonamide (1i)**

According to **GP-1**, **1i** (456 mg, 76%) was obtained from **S5** (327 mg, 1.50 mmol), *N*-methyl-*p*-toluenesulfonamide (1.39 g, 7.50 mmol), $CuCl_2$ (40.3 mg, 0.300 mmol), Na_2CO_3 (318 mg, 3.00 mmol), and pyridine (243 μL, 3.00 mmol). Eluent: hexane/acetone = 8:1.

Colorless oil; IR ν_{max}: 3010, 2235, 1598, 1368, 1169 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 8.4 Hz, 2H), 7.26 (br s, 1H), 7.21 (d, J = 7.5 Hz, 1H), 6.99 (br d, J = 7.8 Hz, 1H), 4.83 (q, J = 5.4 Hz, 1H), 4.70 (d, J = 12.6 Hz, 1H), 4.59 (d, J = 12.6 Hz, 1H), 3.75-3.63 (m, 1H), 3.57-3.46 (m, 1H), 3.14 (s, 3H), 2.44 (s, 3H), 2.34 (s, 3H), 1.37 (d, J = 5.4 Hz, 3H), 1.20 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.5, 139.5, 137.9, 133.0, 131.4, 129.6, 127.9, 127.62, 127.57, 117.8, 99.6, 87.3, 66.8, 65.3, 61.1, 39.5, 21.8, 21.7, 20.1, 15.5; HR-ESIMS calcd for $C_{22}H_{27}NNaO_4S$ $[M+Na]^+$ 424.1553. Found 420.1555.

Preparation of Ynamide 1j



2-((1-Ethoxyethoxy)methyl)-1-ethynyl-4-fluorobenzene (S6)

To a mixture of (2-ethynyl-5-fluorophenyl)methanol[5] (368 mg, 2.45 mmol) and PPTS (61.6 mg, 0.245 mmol) in dry CH_2Cl_2 (12.3 mL) was added ethyl vinyl ether (352 μL, 3.68 mmol) and stirred at rt for 17 h. After reaction completed, the mixture was quenched with saturated aqueous solution of $NaHCO_3$, extracted with CH_2Cl_2, dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 25:1 to give **S6** (530 mg, 97%) as pale yellow oil.

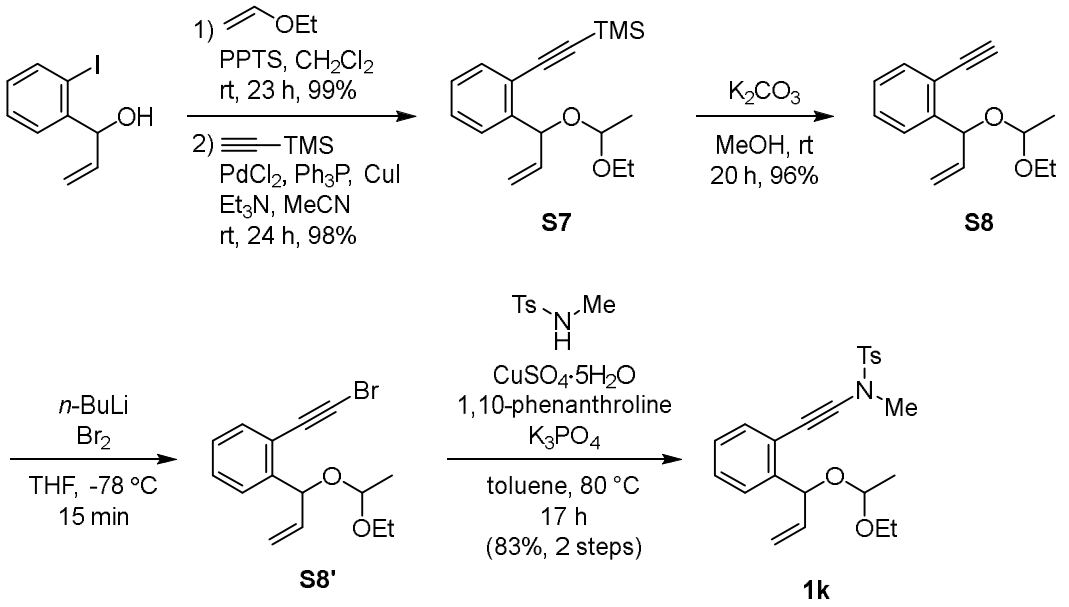
IR ν_{max}: 3306, 2981, 2107, 1609 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (dd, J = 8.4, 5.7 Hz, 1H), 7.22 (dd, J = 9.6, 3.0 Hz, 1H), 6.90 (td, J = 8.4, 3.0 Hz, 1H), 4.86 (q, J = 5.4 Hz, 1H), 4.78 (d, J = 13.5 Hz, 1H), 4.67 (d, J = 13.5 Hz, 1H), 3.74-3.63 (m, 1H), 3.58-3.47 (m, 1H), 3.27 (s, 1H), 1.40 (d, J = 5.4 Hz, 3H), 1.21 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.6 (d, J = 247.6 Hz), 143.9 (d, J = 8.0 Hz), 134.1 (d, J = 8.6 Hz), 115.7 (d, J = 3.4 Hz), 114.1 (d, J = 23.4 Hz), 114.0 (d, J = 22.2 Hz), 99.5, 81.5, 80.1, 64.3 (d, J = 1.1 Hz), 61.0, 19.9, 15.5; HR-ESIMS calcd for $C_{13}H_{15}FNaO_2$ $[M+Na]^+$ 245.0948. Found 245.0949.

***N*-((2-((1-Ethoxyethoxy)methyl)-4-fluorophenyl)ethynyl)-*N*,4-dimethylbenzenesulfonamide (1j)**

According to **GP-1**, **1j** (403 mg, 66%) was obtained from **S6** (333 mg, 1.50 mmol), *N*-methyl-*p*-toluenesulfonamide (1.39 g, 7.50 mmol), $CuCl_2$ (40.3 mg, 0.300 mmol), Na_2CO_3 (318 mg, 3.00 mmol), and pyridine (243 μL, 3.00 mmol). Eluent: hexane/acetone = 8:1.

Colorless oil; IR ν_{max}: 2983, 2237, 1607, 1369, 1168 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.1 Hz, 2H), 7.36 (d, *J* = 8.1 Hz, 2H), 7.27 (dd, *J* = 8.4, 5.7 Hz, 1H), 7.20 (dd, *J* = 9.6, 2.7 Hz, 1H), 6.87 (td, *J* = 8.4, 2.7 Hz, 1H), 4.84 (q, *J* = 5.4 Hz, 1H), 4.71 (d, *J* = 13.5 Hz, 1H), 4.60 (d, *J* = 13.5 Hz, 1H), 3.73-3.62 (m, 1H), 3.57-3.46 (m, 1H), 3.15 (s, 3H), 2.45 (s, 3H), 1.38 (d, *J* = 5.4 Hz, 3H), 1.20 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.1 (d, *J* = 246.5 Hz), 144.6, 143.0 (d, *J* = 7.4 Hz), 133.1 (d, *J* = 6.8 Hz), 133.0, 129.7, 127.5, 116.2 (d, *J* = 3.4 Hz), 114.0 (d, *J* = 23.4 Hz), 113.7 (d, *J* = 21.7 Hz), 99.6, 87.9, 65.7, 64.5 (d, *J* = 1.6 Hz), 61.2, 39.4, 21.9, 20.1, 15.5; HR-ESIMS calcd for $C_{21}H_{24}FNNaO_4S$ $[M+Na]^+$ 428.1302. Found 428.1303.

Preparation of Ynamide 1k



((2-(1-(1-Ethoxyethoxy)allyl)phenyl)ethynyl)trimethylsilane (S7)

To a mixture of 1-(2-iodophenyl)prop-2-en-1-ol[6] (5.20 g, 20.0 mmol) and PPTS (503 mg, 2.00 mmol) in dry CH_2Cl_2 (100 mL) was added ethyl vinyl ether (3.45 mL, 36.0 mmol) and stirred at rt for 23 h. After reaction completed, the mixture was quenched with saturated aqueous solution of $NaHCO_3$, extracted with CH_2Cl_2, dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 20:1 to give 1-(1-(1-ethoxyethoxy)allyl)-2-iodobenzene (6.38 g, 99%) as 1:1 diastereomer mixture.

Colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 7.78 (dd, *J* = 7.8, 1.2 Hz, 0.5H), 7.77 (dd, *J* = 7.8, 1.2 Hz, 0.5H), 7.47 (dd, *J* = 7.8, 1.8 Hz, 0.5H), 7.40 (dd, *J* = 7.8, 1.8 Hz, 0.5H), 7.37-7.29 (m, 1H), 6.98-6.90 (m, 1H), 5.98-5.74 (m, 1H), 5.45-5.13 (m, 3H), 4.85 (q, *J* = 5.4 Hz, 0.5H), 4.58 (q, *J* = 5.4 Hz, 0.5H), 3.64-3.44 (m, 1.5H), 3.41-3.30 (m, 0.5H), 1.31 (d, *J* = 5.4 Hz, 1.5H), 1.30 (d, *J* = 5.4 Hz, 1.5H), 1.21 (t, *J* = 7.2 Hz, 0.5H), 1.11 (t, *J* = 7.2 Hz, 0.5H).

A mixture of 1-(1-(1-ethoxyethoxy)allyl)-2-iodobenzene (6.38 g, 19.2 mmol), $PdCl_2$ (85.5 mg, 0.482 mmol), Ph_3P (253 mg, 0.964 mmol), CuI (132 mg, 0.694 mmol), Et_3N (8.07 mL, 57.9 mmol), and ethynyltrimethylsilane (4.09 mL, 28.9 mmol) in dry MeCN (5.0 mL) was stirred at rt for 24 h. After reaction completed, the mixture was quenched with 5% aqueous solution of NH_3. The mixture was extracted with Et_2O, washed with brine, dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 30:1 to give **S7** (5.68 g, 98%)

as 1:1 diastereomer mixture.

Brown oil; IR ν_{max}: 3010, 2156, 1640, 1599 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.52-7.48 (m, 0.5H), 7.45-7.38 (m, 1.5H), 7.31 (t, *J* = 7.5 Hz, 1H), 7.21-7.13 (m, 1H), 6.01-5.77 (m, 1H), 5.71 (d, *J* = 6.3 Hz, 0.5H), 5.61 (d, *J* = 6.6 Hz, 0.5H), 5.34 (ddd, *J* = 16.2, 1.8, 1.2 Hz, 0.5H), 5.28 (dt, *J* = 16.5, 1.5 Hz, 0.5H), 5.13 (ddd, *J* = 9.0, 1.5, 1.2 Hz, 0.5H), 5.10 (dt, *J* = 9.0, 1.5 Hz, 0.5H), 4.84 (q, *J* = 5.4 Hz, 0.5H), 4.60 (q, *J* = 5.4 Hz, 0.5H), 3.66-3.45 (m, 1.5H), 3.41-3.30 (m, 0.5H), 1.32 (d, *J* = 5.4 Hz, 1.5H), 1.29 (d, *J* = 5.4 Hz, 1.5H), 1.20 (t, *J* = 7.2 Hz, 1.5H), 1.12 (t, *J* = 7.2 Hz, 1.5H), 0.27 (s, 4.5H), 0.26 (s, 4.5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.8, 143.3, 138.03, 137.95, 132.1, 131.9, 128.75, 128.74, 126.9, 126.7, 126.3, 126.2, 121.6, 120.7, 115.4, 114.9, 102.9, 102.7, 99.2, 99.1, 98.2, 98.1, 75.8, 75.3, 61.0, 60.8, 20.9, 20.7, 15.6, 15.4, 0.21, 0.19; HR-ESIMS calcd for $C_{18}H_{26}NaO_2Si$ $[M+Na]^+$ 325.1594. Found 325.1602.

1-(1-(1-Ethoxyethoxy)allyl)-2-ethynylbenzene (S8)

To a solution of **S5** (5.53 g, 18.9 mmol) in MeOH (9.2 mL) at rt was added K_2CO_3 (1.26 g, 9.15 mmol), and was stirred for 20 h. After reaction completed, the mixture was quenched with water, extracted with Et_2O, washed with brine, dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 30:1 to give **S8** (4.03 g, 96%) as 1:1 diastereomer mixture.

Colorless oil; IR ν_{max}: 3304, 3011, 2105, 1640, 1601 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.54-7.50 (m, 0.5H), 7.48-7.42 (m, 1.5H), 7.34 (t, *J* = 7.5 Hz, 1H), 7.24-7.15 (m, 1H), 6.03-5.81 (m, 1H), 5.69 (d, *J* = 6.0 Hz, 0.5H), 5.61 (d, *J* = 6.6 Hz, 0.5H), 5.32 (dt, *J* = 17.1, 1.5 Hz, 0.5H), 5.26 (dt, *J* = 17.1, 1.5 Hz, 0.5H), 5.13 (dt, *J* = 10.5, 1.5 Hz, 0.5H), 5.11 (dt, *J* = 10.5, 1.5 Hz, 0.5H), 4.86 (q, *J* = 5.1 Hz, 0.5H), 4.62 (q, *J* = 5.4 Hz, 0.5H), 3.64-3.43 (m, 1.5H), 3.41-3.32 (m, 0.5H), 3.31 (s, 1H), 1.32 (d, *J* = 5.1 Hz, 1.5H), 1.29 (d, *J* = 5.1 Hz, 1.5H), 1.19 (t, *J* = 7.2 Hz, 1.5H), 1.10 (t, *J* = 7.2 Hz, 1.5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.9, 143.4, 137.99, 137.85, 132.5, 132.3, 128.99, 128.99, 127.0, 126.8, 126.50, 126.46, 120.5, 119.7, 115.4, 115.0, 98.3, 98.2, 81.83, 81.79, 81.5, 81.4, 75.5, 75.1, 60.9, 60.5, 20.8, 20.6, 15.5, 15.3; HR-ESIMS calcd for $C_{15}H_{18}NaO_2$ $[M+Na]^+$ 253.1199. Found 253.1200.

***N*-((2-(1-(1-Ethoxyethoxy)allyl)phenyl)ethynyl)-*N*,4-dimethylbenzenesulfonamide (1k)**

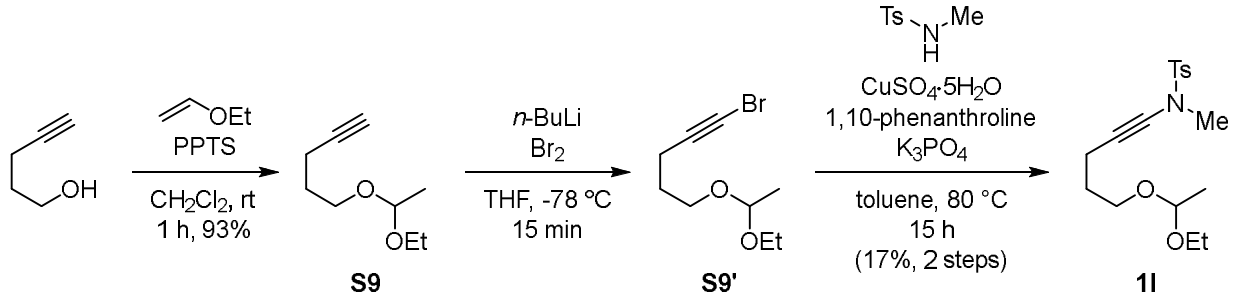
To a solution of **S8** (461 mg, 2.00 mmol) in dry THF (10 mL) at -78 °C was added *n*-BuLi (1.57 M in hexane, 1.53 mL, 2.40 mmol) dropwise, and the reaction mixture was stirred at -78 °C for 30 min. Then, Br_2 (133 μL, 2.60 mmol) was added dropwise, and the reaction mixture was stirred at -78 °C for 15 min. After reaction completed, the mixture was quenched with a saturated aqueous solution of $Na_2S_2O_3$, extracted with Et_2O, washed with brine, dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 30:1 to give **S8'** (520 mg) that was directly used in the next reaction.

According to literature,[6] a solution of **S8'** (520 mg, 1.68 mmol), *N*-methyl-*p*-toluenesulfonamide (374 mg, 2.02 mmol), $CuSO_4 \cdot 5H_2O$ (83.9 mg, 0.336 mmol), 1,10-phenanthroline (121 mg, 0.672 mmol), and K_3PO_4 (856 mg, 4.03 mmol) in dry toluene (5.1 mL) was stirred at 80 °C for 17 h. The mixture was cooled to rt, diluted with Et_2O, and filtered through Celite. The filtrate was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 5:1 to give **1k** (689 mg, 83% in 2 steps) as 1:1 diastereomer mixture.

Pale yellow oil; IR ν_{max}: 3010, 2234, 1598, 1370, 1168 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.5

Hz, 1H), 7.84 (d, J = 8.5 Hz, 1H), 7.52 (dd, J = 8.0, 1.5 Hz, 0.5H), 7.44 (dd, J = 8.0, 1.5 Hz, 0.5H), 7.36 (d, J = 8.5 Hz, 2H), 7.34-7.27 (m, 2H), 7.21-7.15 (m, 1H), 5.97 (ddd, J = 17.5, 10.0, 6.0 Hz, 0.5H), 5.87 (ddd, J = 17.5, 10.0, 6.0 Hz, 0.5H), 5.60 (dt, J = 6.0, 1.5 Hz, 0.5H), 5.53 (d, J = 6.5 Hz, 0.5H), 5.33 (dt, J = 17.0, 1.5 Hz, 0.5H), 5.27 (dt, J = 17.0, 1.5 Hz, 0.5H), 5.14-5.09 (m, 1H), 4.84 (q, J = 5.0 Hz, 0.5H), 4.64 (q, J = 5.0 Hz, 0.5H), 3.64-3.55 (m, 1H), 3.52-3.45 (m, 0.5H), 3.38-3.30 (m, 0.5H), 3.173 (s, 1.5H), 3.166 (s, 1.5H), 2.45 (s, 3H), 1.30 (d, J = 5.5 Hz, 1.5H), 1.28 (d, J = 5.5 Hz, 1.5H), 1.13 (t, J = 7.0 Hz, 1.5H), 1.06 (t, J = 7.0 Hz, 1.5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.8, 143.1, 142.5, 138.4, 138.3, 133.39, 133.38, 131.5, 131.4, 129.87, 129.86, 128.2, 128.1, 127.8, 127.1, 126.9, 126.7, 126.6, 121.3, 120.5, 115.6, 115.3, 98.5, 98.3, 88.33, 88.25, 75.8, 75.4, 67.1, 67.0, 61.0, 60.7, 39.27, 39.25, 21.6, 20.6, 15.3, 15.2; HR-ESIMS calcd for $C_{23}H_{27}NNaO_4S$ $[M+Na]^+$ 436.1558. Found 436.1553.

Preparation of Ynamide 1l



5-(1-Ethoxyethoxy)pent-1-yne (S9)

To a mixture of 4-pentyn-1-ol (1.68 g, 20.0 mmol) and PPTS (503 mg, 2.00 mmol) in dry CH_2Cl_2 (100 mL) was added ethyl vinyl ether (2.87 mL, 30.0 mmol) and stirred at rt for 1 h. After reaction completed, the mixture was quenched with saturated aqueous solution of $NaHCO_3$, extracted with CH_2Cl_2, dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 20:1 to give **S9** (2.89 g, 93%) as colorless oil.

IR ν_{max}: 3308, 3011, 2118 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.68 (q, J = 5.4 Hz, 1H), 3.71-3.59 (m, 2H), 3.55-3.42 (m, 2H), 2.30 (td, J = 7.2, 2.7 Hz, 2H), 1.94 (t, J = 2.7 Hz, 1H), 1.78 (quint, J = 7.2 Hz, 2H), 1.30 (d, J = 5.4 Hz, 3H), 1.20 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 99.4, 83.8, 68.5, 63.2, 60.8, 28.8, 19.9, 15.45, 15.43; HR-ESIMS calcd for $C_9H_{16}NaO_2$ $[M+Na]^+$ 179.1048. Found 179.1044.

***N*-(5-(1-Ethoxyethoxy)pent-1-yn-1-yl)-*N*,4-dimethylbenzenesulfonamide (1l)**

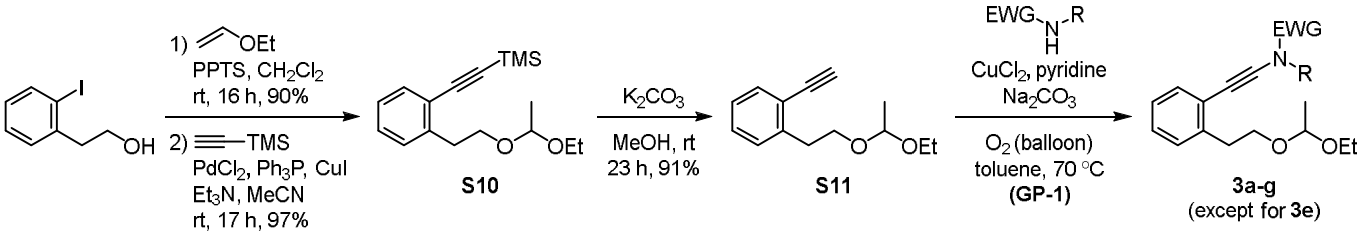
To a solution of **S9** (1.25 g, 8.00 mmol) in dry THF (40 mL) at -78 °C was added *n*-BuLi (1.57 M in hexane, 6.11 mL, 9.60 mmol) dropwise, and the reaction mixture was stirred at -78 °C for 30 min. Then, Br_2 (0.533 mL, 10.4 mmol) was added dropwise, and the reaction mixture was stirred at -78 °C for 15 min. After reaction completed, the mixture was quenched with a saturated aqueous solution of $Na_2S_2O_3$, extracted with Et_2O, washed with brine, dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 20:1 to give **S9'** (913 mg) that was directly used in the next reaction.

According to literature,[6] a solution of **S9'** (913 mg, 3.88 mmol), *N*-methyl-*p*-toluenesulfonamide (862 mg, 4.66 mmol), $CuSO_4 \cdot 5H_2O$ (194 mg, 0.777 mmol), 1,10-phenanthroline (280 mg, 1.55 mmol), and K_3PO_4 (1.98 g, 9.31 mmol) in dry toluene (11.8 mL) was stirred at 80 °C for 15 h. The mixture was cooled to rt,

diluted with Et_2O, and filtered through Celite. The filtrate was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 5:1 to give **1l** (468 mg, 17% in 2 steps) as pale yellow oil.

IR ν_{max}: 3009, 2254, 1598, 1365, 1172 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, J = 8.1 Hz, 2H), 7.33 (d, J = 8.1 Hz, 2H), 4.66 (q, J = 5.4 Hz, 1H), 3.69-3.57 (m, 2H), 3.52-3.40 (m, 2H), 3.00 (s, 3H), 2.45 (s, 3H), 2.35 (t, J = 6.9 Hz, 2H), 1.74 (quint, J = 6.9 Hz, 2H), 1.29 (d, J = 5.4 Hz, 3H), 1.19 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.2, 132.9, 129.4, 127.5, 99.6, 75.1, 67.9, 63.6, 60.9, 39.4, 29.3, 21.8, 20.1, 15.51, 15.47; HR-ESIMS calcd for $C_{17}H_{25}NNaO_4S$ $[M+Na]^+$ 362.1402. Found 362.1398.

Preparation of Ynamides 3a-g



((2-(2-(1-Ethoxyethoxy)ethyl)phenyl)ethynyl)trimethylsilane (S10)

To a mixture of 2-(2-iodophenyl)ethan-1-ol[7] (4.84 g, 19.5 mmol) and PPTS (490 mg, 1.95 mmol) in dry CH_2Cl_2 (100 mL) was added ethyl vinyl ether (3.47 mL, 35.1 mmol) and stirred at rt for 16 h. After reaction completed, the mixture was quenched with saturated aqueous solution of $NaHCO_3$, extracted with CH_2Cl_2, dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 30:1 to give 1-(2-(1-ethoxyethoxy)ethyl)-2-iodobenzene (5.63 g, 90%) as colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, J = 7.8 Hz, 1H), 7.27-7.20 (m, 2H), 6.92-6.83 (m, 1H), 4.68 (q, J = 5.1 Hz, 1H), 3.80-3.51 (m, 3H), 3.46-3.35 (m, 1H), 3.00 (t, J = 6.9 Hz, 2H), 1.29 (d, J = 5.1 Hz, 3H), 1.16 (t, J = 6.9 Hz, 3H).

A mixture of 1-(2-(1-ethoxyethoxy)ethyl)-2-iodobenzene (5.63 g, 17.6 mmol), $PdCl_2$ (78.0 mg, 0.440 mmol), Ph_3P (231 mg, 0.880 mmol), CuI (121 mg, 0.634 mmol), Et_3N (7.36 mL, 52.8 mmol), and ethynyltrimethylsilane (3.73 mL, 26.4 mmol) in dry MeCN (35 mL) was stirred at rt for 17 h. After reaction completed, the mixture was quenched with 5% aqueous solution of NH_3. The mixture was extracted with Et_2O, washed with brine, dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 20:1 to give **S10** (4.97 g, 97%) as brown oil.

IR ν_{max}: 3010, 2155, 1600 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.42 (d, J = 7.8 Hz, 1H), 7.24-7.17 (m, 2H), 7.16-7.08 (m, 1H), 4.66 (q, J = 5.1 Hz, 1H), 3.84-3.75 (m, 1H), 3.72-3.50 (m, 2H), 3.45-3.34 (m, 1H), 3.06 (t, J = 7.2 Hz, 2H), 1.28 (d, J = 5.1 Hz, 3H), 1.15 (t, J = 7.2 Hz, 3H), 0.25 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.1, 132.4, 129.5, 128.4, 126.0, 122.7, 103.6, 99.6, 97.9, 64.9, 60.9, 35.3, 20.0, 15.4, 0.1; HR-ESIMS calcd for $C_{17}H_{26}NaO_2Si$ $[M+Na]^+$ 313.1594. Found 313.1590.

1-((1-Ethoxyethoxy)methyl)-2-ethynylbenzene (S11)

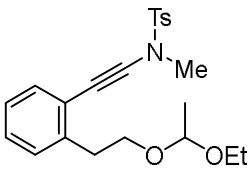
To a solution of **S10** (4.98 g, 17.2 mmol) in MeOH (8.5 mL) at rt was added K_2CO_3 (1.19 g, 8.58 mmol), and was stirred for 23 h. After reaction completed, the mixture was quenched with water, extracted with Et_2O, washed with brine, dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by

flash column chromatography on silica gel eluting with hexane/EtOAc = 20:1 to give **S11** (3.42 g, 91%) as colorless oil.

IR ν_{max}: 3304, 3011, 2105, 1600 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.5 Hz, 1H), 7.28-7.22 (m, 2H), 7.19-7.10 (m, 1H), 4.67 (q, *J* = 5.1 Hz, 1H), 3.85-3.65 (m, 2H), 3.59-3.48 (m, 1H), 3.44-3.33 (m, 1H), 3.24 (s, 1H), 3.07 (t, *J* = 7.2 Hz, 2H), 1.28 (d, *J* = 5.1 Hz, 3H), 1.15 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.3, 132.7, 129.5, 128.6, 126.1, 121.7, 99.4, 82.1, 80.7, 64.7, 60.8, 35.2, 19.9, 15.3; HR-ESIMS calcd for $C_{14}H_{18}NaO_2$ $[M+Na]^+$ 241.1199. Found 241.1200.

_N_-((2-(2-(1-Ethoxyethoxy)ethyl)phenyl)ethynyl)-_N_,4-dimethylbenzenesulfonamide (3a)

According to **GP-1**, **3a** (516 mg, 86%) was obtained from **S11** (327 mg, 1.50 mmol), *N*-methyl-*p*-toluenesulfonamide (1.39 g, 7.50 mmol), $CuCl_2$ (40.3 mg, 0.300 mmol), Na_2CO_3 (318 mg, 3.00 mmol), and pyridine (243 μL, 3.00 mmol). Eluent: hexane/EtOAc = 4:1.

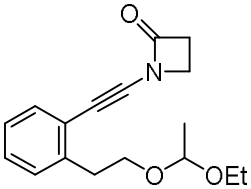


3a

Colorless oil; IR ν_{max}: 3009, 2235, 1598, 1369, 1168 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.4 Hz, 2H), 7.37-7.29 (m, 3H), 7.24-7.09 (m, 3H), 4.65 (q, *J* = 5.4 Hz, 1H), 3.83-3.74 (m, 1H), 3.71-3.63 (m, 1H), 3.57-3.46 (m, 1H), 3.42-3.31 (m, 1H), 3.16 (s, 3H), 2.99 (t, *J* = 7.2 Hz, 2H), 2.44 (s, 3H), 1.26 (d, *J* = 5.4 Hz, 3H), 1.12 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.6, 140.3, 133.3, 131.7, 129.7, 129.5, 127.7, 127.6, 126.0, 122.3, 99.5, 87.3, 67.6, 65.0, 60.9, 39.4, 35.3, 21.7, 20.0, 15.4; HR-ESIMS calcd for $C_{22}H_{27}NNaO_4S$ $[M+Na]^+$ 424.1553. Found 424.1548.

1-((2-(2-(1-Ethoxyethoxy)ethyl)phenyl)ethynyl)azetidin-2-one (3b)

According to **GP-1**, **3b** (170 mg, 39%) was obtained from **S11** (327 mg, 1.50 mmol), azetidin-2-one (533 mg, 7.50 mmol), $CuCl_2$ (40.3 mg, 0.300 mmol), Na_2CO_3 (318 mg, 3.00 mmol), and pyridine (243 μL, 3.00 mmol). Eluent: hexane/EtOAc = 2:1.

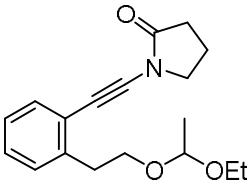


3b

Colorless oil; IR ν_{max}: 3011, 2241, 1770, 1600 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40-7.35 (m, 1H), 7.25-7.10 (m, 3H), 4.68 (q, *J* = 5.4 Hz, 1H), 3.85-3.75 (m, 1H), 3.73-3.64 (m, 3H), 3.60-3.49 (m, 1H), 3.45-3.34 (m, 1H), 3.09 (t, *J* = 4.8 Hz, 2H), 3.03 (t, *J* = 7.2 Hz, 2H), 1.28 (d, *J* = 5.4 Hz, 3H), 1.15 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2, 140.4, 132.0, 129.4, 128.0, 126.1, 121.8, 99.5, 82.1, 68.3, 64.8, 60.8, 43.2, 38.1, 35.2, 19.9, 15.3; HR-ESIMS calcd for $C_{17}H_{21}NNaO_3$ $[M+Na]^+$ 310.1414. Found 310.1412.

1-((2-(2-(1-Ethoxyethoxy)ethyl)phenyl)ethynyl)pyrrolidin-2-one (3c)

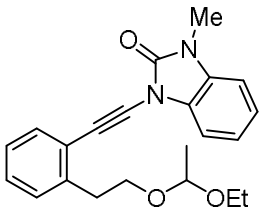
According to **GP-1**, **3e** (206 mg, 38%) was obtained from **S11** (327 mg, 1.50 mmol), 2-pyrrolidone (0.575 mL, 7.50 mmol), $CuCl_2$ (40.3 mg, 0.300 mmol), Na_2CO_3 (318 mg, 3.00 mmol), and pyridine (242 μL, 3.00 mmol). Eluent: hexane/EtOAc = 4:3.



3c

Colorless oil; IR ν_{max}: 3011, 2246, 1716, 1602 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40 (d, *J* = 6.6 Hz, 1H), 7.30-7.10 (m, 3H), 4.68 (q, *J* = 5.4 Hz, 1H), 3.87-3.66 (m, 4H), 3.60-3.48 (m, 1H), 3.45-3.33 (m, 1H), 3.06 (t, *J* = 7.2 Hz, 2H), 2.48 (t, *J* = 7.8 Hz, 2H), 2.18 (quint, *J* = 7.8 Hz, 2H), 1.28 (d, *J* = 5.4 Hz, 3H), 1.14 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.3, 140.3, 131.8, 129.4, 127.7, 126.0, 122.2, 99.5, 83.9, 71.1, 65.0, 60.8, 50.0, 35.3, 29.7, 20.0, 18.9, 15.3; HR-ESIMS calcd for $C_{18}H_{23}NNaO_3$ $[M+Na]^+$ 324.1570. Found 324.1561.

1-((2-(2-(1-Ethoxyethoxy)ethyl)phenyl)ethynyl)-3-methyl-1*H*-benzo[*d*]imidazol-2(3*H*)-one (3d)

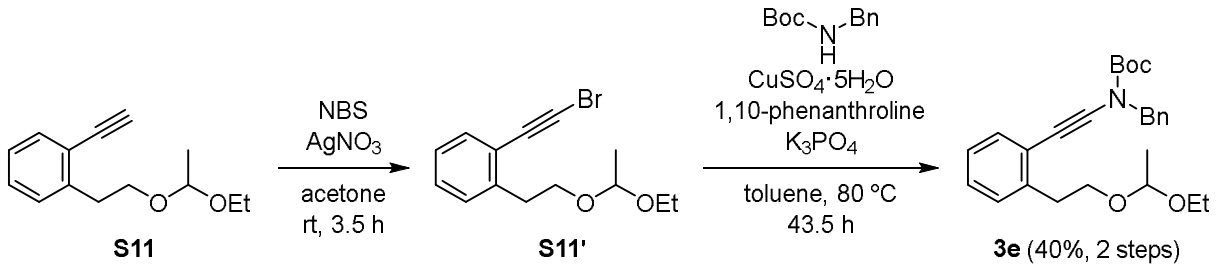


3d

According to **GP-1**, **3d** (174 mg, 32%) was obtained from **S11** (327 mg, 1.50 mmol), 1-methyl-2-benzimidazolinone (1.11 g, 7.50 mmol), $CuCl_2$ (40.3 mg, 0.300 mmol), Na_2CO_3 (318 mg, 3.00 mmol), and pyridine (242 μL, 3.00 mmol). Eluent: hexane/EtOAc = 3:1.

Colorless oil; IR ν_{max}: 3011, 2258, 1733, 1621 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.2 Hz, 1H), 7.33-7.12 (m, 6H), 6.97 (dd, *J* = 6.6, 2.1 Hz, 1H), 4.67 (q, *J* = 5.1 Hz, 1H), 3.94-3.73 (m, 2H), 3.58-3.44 (m, 1H), 3.44 (s, 3H), 3.43-3.29 (m, 1H), 3.17 (t, *J* = 7.2 Hz, 2H), 1.27 (d, *J* = 5.1 Hz, 3H), 1.09 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.9, 140.6, 132.2, 129.6, 129.5, 128.3, 128.0, 126.1, 123.4, 122.1, 121.7, 109.7, 107.9, 99.6, 78.9, 73.7, 65.0, 60.9, 35.4, 27.6, 20.0, 15.3; HR-ESIMS calcd for $C_{22}H_{24}N_2NaO_3$ $[M+Na]^+$ 387.1679. Found 387.1689.

***tert*-Butyl benzyl((2-(2-(1-ethoxyethoxy)ethyl)phenyl)ethynyl)carbamate (3e)**



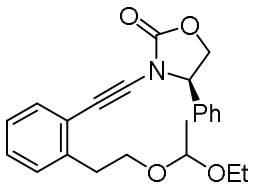
S11 **S11'** **3e** (40%, 2 steps)

To a solution of **S11** (202 mg, 0.925 mmol) in dry acetone (6 mL) at rt was added $AgNO_3$ (15.7 mg, 0.0925 mmol) and NBS (191 mg, 1.07 mmol) were added successively, each in a single portion. After the mixture was stirred at rt under dark for 3.5 h, the reaction mixture was diluted with hexane and vigorously stirred for 5 min. The mixture was filtered and concentrated in vacuo. The residue was purified by short silica gel pad (3 cm) eluting with hexane to give **S11'** (252 mg) that was directly used in the next reaction.

According to literature,[8] a solution of **S11'** (252 mg, 0.847 mmol), *tert*-butyl benzylcarbamate (211 mg, 1.02 mmol), $CuSO_4 \cdot 5H_2O$ (42.3 mg, 0.169 mmol), 1,10-phenanthroline (61.1 mg, 0.339 mmol), and K_3PO_4 (432 mg, 2.03 mmol) in dry toluene (2.6 mL) was stirred at 80 °C for 43.5 h. The mixture was cooled to rt, and diluted with EtOAc and filtered through Celite, and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/acetone = 20:1 to give **3e** (156 mg, 40% in 2 steps) as colorless oil.

IR ν_{max}: 2983, 2243, 1714, 1600 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41-7.05 (m, 9H), 4.67 (s, 2H), 4.60 (q, *J* = 5.4 Hz, 1H), 3.76-3.67 (m, 1H), 3.64-3.42 (m, 2H), 3.39-3.28 (m, 1H), 2.92 (t, *J* = 6.9 Hz, 2H), 1.53 (s, 9H), 1.24 (d, *J* = 5.4 Hz, 3H), 1.11 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.5, 139.3, 136.2, 130.9, 129.2, 128.3, 128.1, 127.7, 126.8, 125.8, 123.1, 99.4, 87.5, 82.7, 69.7, 64.8, 60.7, 53.2, 35.1, 28.3, 20.1, 15.5; HR-ESIMS calcd for $C_{26}H_{33}NNaO_4$ $[M+Na]^+$ 446.2302. Found 446.2299.

(4*R*)-3-((2-(2-(1-Ethoxyethoxy)ethyl)phenyl)ethynyl)-4-phenyloxazolidin-2-one (3f)

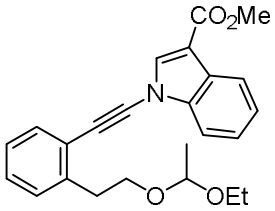


3f

According to **GP-1**, **3f** (141 mg, 25%) was obtained as 1:1 diastereomer mixture from **S11** (328 mg, 1.50 mmol), (*R*)-(-)-4-phenyl-2-oxazolidinone (1.22 g, 7.50 mmol), $CuCl_2$ (40.3 mg, 0.300 mmol), Na_2CO_3 (318 mg, 3.00 mmol), and pyridine (242 μL, 3.00 mmol). Eluent: hexane/EtOAc = 3:1.

Colorless oil; $[\alpha]_D^{26}$ -153 (*c* 1.09, $CHCl_3$); IR ν_{max}: 3008, 2255, 1776, 1602 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.48-7.36 (m, 5H), 7.25 (dd, *J* = 6.9, 1.5 Hz, 1H), 7.17-7.12 (m, 2H), 7.11-7.01 (m, 1H), 5.18-5.10 (m, 1H), 4.77 (t, *J* = 8.7 Hz, 1H), 4.55 (q, *J* = 5.4 Hz, 0.5H), 4.54 (q, *J* = 5.4 Hz, 0.5H), 4.30 (dd, *J* = 8.7, 7.2 Hz, 1H), 3.60-3.25 (m, 4H), 2.72 (t, *J* = 6.6 Hz, 2H), 1.221 (d, *J* = 5.4 Hz, 1.5H), 1.219 (d, *J* = 5.4 Hz, 1.5H), 1.12 (t, *J* = 7.2 Hz, 1.5H), 1.11 (t, *J* = 7.2 Hz, 1.5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.2, 140.64, 140.57, 136.0, 131.83, 131.79, 129.5, 129.4, 129.2, 127.84, 127.83, 126.8, 125.9, 121.6, 99.5, 99.4, 81.5, 71.4, 70.8, 64.6, 62.3, 60.8, 60.7, 35.0, 19.99, 19.97, 15.4; HR-ESIMS calcd for $C_{23}H_{25}NNaO_4$ $[M+Na]^+$ 402.1676. Found 402.1673.

Methyl 1-((2-(2-(1-ethoxyethoxy)ethyl)phenyl)ethynyl)-1*H*-indole-3-carboxylate (3g)

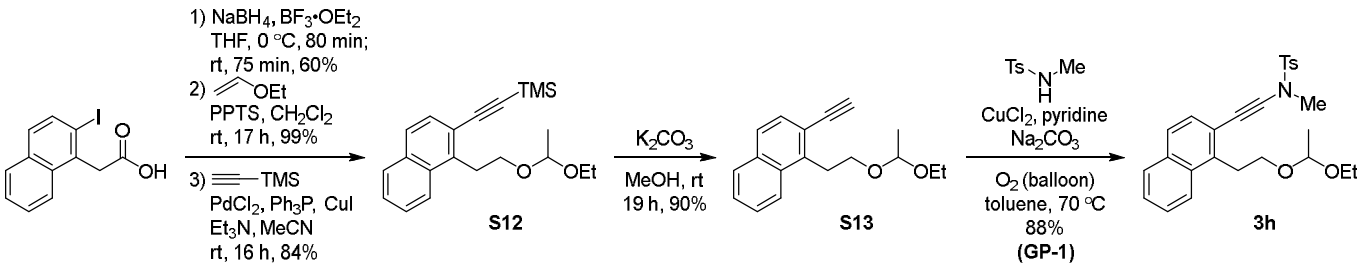


3g

According to **GP-1**, **3g** (449 mg, 77%) was obtained from **S11** (327 mg, 1.50 mmol), methyl 1*H*-indole-3-carboxylate (1.31 g, 7.50 mmol), $CuCl_2$ (40.3 mg, 0.300 mmol), Na_2CO_3 (318 mg, 3.00 mmol), and pyridine (242 μL, 3.00 mmol). Eluent: hexane/EtOAc = 7:1.

Red oil; IR ν_{max}: 3011, 2255, 1709, 1614 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.20-8.15 (m, 1H), 7.97 (s, 1H), 7.65 (dd, *J* = 6.9, 1.8 Hz, 1H), 7.53 (dd, *J* = 6.9, 1.5 Hz, 1H), 7.44-7.19 (m, 5H), 4.68 (q, *J* = 5.4 Hz, 1H), 3.93 (s, 3H), 3.92-3.82 (m, 1H), 3.81-3.70 (m, 1H), 3.58-3.43 (m, 1H), 3.42-3.31 (m, 1H), 3.17 (t, *J* = 7.2 Hz, 2H), 1.28 (d, *J* = 5.4 Hz, 3H), 1.08 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.1, 140.6, 138.2, 134.7, 132.1, 129.6, 128.6, 126.3, 125.3, 124.5, 123.6, 121.9, 121.3, 111.4, 111.0, 99.4, 82.5, 70.4, 64.8, 60.7, 51.4, 35.4, 19.9, 15.3; HR-ESIMS calcd for $C_{24}H_{25}NNaO_4$ $[M+Na]^+$ 414.1676. Found 414.1679.

Preparation of Ynamide 3h



1-(2-(1-Ethoxyethoxy)ethyl)-2-ethynylnaphthalene (S12)

To a mixture of 2-(2-iodonaphthalen-1-yl)acetic acid[9] (4.24 g, 13.6 mmol) in dry THF (35 mL) at 0 °C was added $NaBH_4$ (1.03 g, 27.2 mmol). Then, $BF_3 \cdot OEt_2$ (3.41 mL, 27.2 mmol) was added dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 80 min, followed by rt for 75 min. After reaction completed, the mixture was cooled to 0 °C, and was quenched with MeOH (23 mL) and 1 M HCl (23 mL), extracted with Et_2O, dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 20:1 to give 2-(2-iodonaphthalen-1-yl)ethan-1-

ol (2.43 g, 60%) as colorless solid.

To a mixture of 2-(2-iodonaphthalen-1-yl)ethan-1-ol (2.43 g, 8.17 mmol) and PPTS (205 mg, 0.817 mmol) in dry CH_2Cl_2 (42 mL) was added ethyl vinyl ether (1.41 mL, 14.7 mmol) and stirred at rt for 17 h. After reaction completed, the mixture was quenched with saturated aqueous solution of $NaHCO_3$, extracted with CH_2Cl_2, dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 25:1 to give 1-(2-(1-ethoxyethoxy)ethyl)-2-iodonaphthalene (2.98 g, 99%) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (d, *J* = 7.5 Hz, 1H), 7.83 (d, *J* = 8.7 Hz, 1H), 7.81-7.74 (m, 1H), 7.56-7.44 (m, 2H), 7.39 (d, *J* = 8.7 Hz, 1H), 4.73 (q, *J* = 5.1 Hz, 1H), 3.85-3.54 (m, 5H), 3.52-3.39 (m, 1H), 1.32 (d, *J* = 5.1 Hz, 3H), 1.17 (t, *J* = 6.9 Hz, 3H).

A mixture of 1-(2-(1-ethoxyethoxy)ethyl)-2-iodonaphthalene (2.98 g, 9.32 mmol), $PdCl_2$ (41.3 mg, 0.233 mmol), Ph_3P (122 mg, 0.466 mmol), CuI (64.0 mg, 0.336 mmol), Et_3N (3.90 mL, 28.0 mmol), and ethynyltrimethylsilane (1.98 mL, 14.0 mmol) in dry MeCN (19 mL) was stirred at rt for 16 h. After reaction completed, the mixture was quenched with 5% aqueous solution of NH_3. The mixture was extracted with Et_2O, washed with brine, dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 30:1 to give **S12** (2.65 g, 84%) as brown oil. IR ν_{max}: 3009, 2154, 1596 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.4 Hz, 1H), 7.76 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.62 (d, *J* = 8.4 Hz, 1H), 7.54-7.38 (m, 3H), 4.70 (q, *J* = 5.4 Hz, 1H), 3.90-3.78 (m, 1H), 3.77-3.54 (m, 4H), 3.48-3.37 (m, 1H), 1.30 (d, *J* = 5.4 Hz, 3H), 1.15 (t, *J* = 6.9 Hz, 3H), 0.29 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.3, 133.3, 131.9, 128.7, 128.5, 126.6, 126.4, 126.2, 124.3, 120.6, 104.6, 99.7, 98.7, 64.9, 60.9, 31.6, 20.1, 15.4, 0.2; HR-ESIMS calcd for $C_{21}H_{28}NaO_2Si$ $[M+Na]^+$ 363.1751. Found 363.1751.

1-((1-Ethoxyethoxy)methyl)-2-ethynylnaphthalene (S13)

To a solution of **S12** (1.35 g, 3.96 mmol) in MeOH (2 mL) at rt was added K_2CO_3 (274 mg, 1.98 mmol), and was stirred for 19 h. After reaction completed, the mixture was quenched with water, extracted with Et_2O, washed with brine, dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 30:1 to give **S13** (954 mg, 90%) as colorless oil.

IR ν_{max}: 3303, 3011, 2102, 1597 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.1 Hz, 1H), 7.77 (d, *J* = 7.5 Hz, 1H), 7.64 (d, *J* = 8.7 Hz, 1H), 7.55-7.42 (m, 3H), 4.71 (q, *J* = 5.1 Hz, 1H), 3.90-3.69 (m, 2H), 3.67-3.51 (m, 3H), 3.47-3.37 (m, 1H), 3.36 (s, 1H), 1.30 (d, *J* = 5.1 Hz, 3H), 1.14 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.6, 133.4, 131.9, 128.8, 128.5, 126.7, 126.5, 126.3, 124.3, 119.6, 99.5, 83.0, 81.3, 64.6, 60.8, 31.6, 20.0, 15.3; HR-ESIMS calcd for $C_{18}H_{20}NaO_2$ $[M+Na]^+$ 291.1356. Found 291.1353.

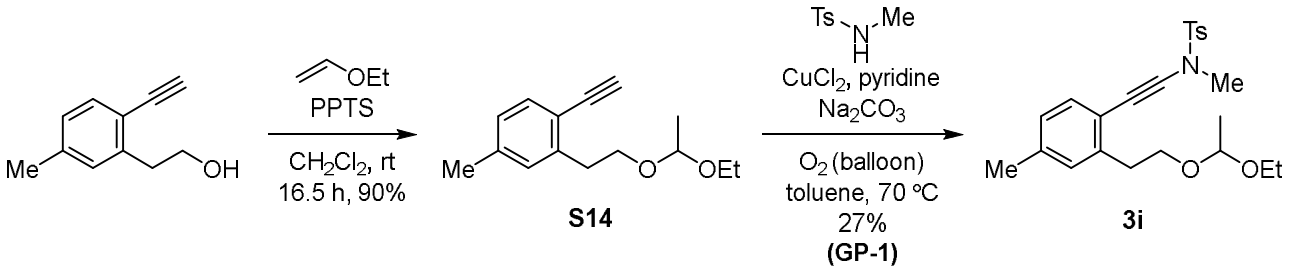
***N*-((1-(2-(1-Ethoxyethoxy)ethyl)naphthalen-2-yl)ethynyl)-*N*,4-dimethylbenzenesulfonamide (3h)**

According to **GP-1**, **3h** (597 mg, 88%) was obtained from **S13** (403 mg, 1.00 mmol), *N*-methyl-*p*-toluenesulfonamide (1.39 g, 7.50 mmol), $CuCl_2$ (40.3 mg, 0.300 mmol), Na_2CO_3 (318 mg, 3.00 mmol), and pyridine (243 μL, 3.00 mmol). Eluent: hexane/EtOAc = 5:1.

Colorless crystals; mp 99-101 ºC (hexane/EtOAc); IR ν_{max}: 3010, 2234, 1598, 1368, 1169 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.7 Hz, 1H), 7.90-7.82 (m, 2H), 7.76 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.62 (d, *J* = 8.4 Hz, 1H), 7.54-7.28 (m, 5H), 4.68 (q, *J* = 5.4 Hz, 1H), 3.90-3.66 (m, 2H), 3.60-3.46 (m, 3H), 3.46-3.32 (m, 1H), 3.20 (s, 3H), 2.44 (s, 3H), 1.27 (d, *J* = 5.4 Hz, 3H), 1.10 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75

MHz, $CDCl_3$) δ 144.6, 136.7, 133.4, 132.9, 132.0, 129.8, 128.4, 128.3, 127.7, 126.6, 126.4, 125.8, 124.1, 120.2, 99.7, 88.0, 68.8, 65.0, 60.9, 39.4, 31.7, 21.7, 20.1, 15.4; HR-ESIMS calcd for $C_{26}H_{29}NNaO_4S$ $[M+Na]^+$ 474.1710. Found 474.1710.

Preparation of Ynamide 3i



2-(2-(1-Ethoxyethoxy)ethyl)-1-ethynyl-4-methylbenzene (S14)

To a mixture of 2-(2-ethynyl-5-methylphenyl)ethan-1-ol[10] (234 mg, 1.46 mmol) and PPTS (36.7 mg, 0.146 mmol) in dry CH_2Cl_2 (7.3 mL) was added ethyl vinyl ether (210 μL, 2.19 mmol) and stirred at rt for 16.5 h. After reaction completed, the mixture was quenched with saturated aqueous solution of $NaHCO_3$, extracted with CH_2Cl_2, dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 20:1 to give **S14** (305 mg, 90%) as yellow oil.

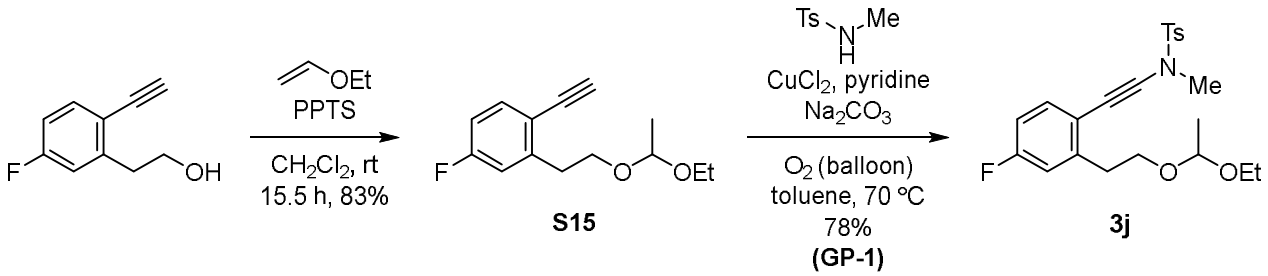
IR ν_{max}: 3301, 3010, 2103, 1611 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36 (d, J = 7.8 Hz, 1H), 7.07 (d, J = 1.2 Hz, 1H), 6.98 (dd, J = 7.8, 1.2 Hz, 1H), 4.69 (q, J = 5.4 Hz, 1H), 3.84-3.64 (m, 2H), 3.53-3.51 (m, 1H), 3.46-3.36 (m, 1H), 3.20 (s, 1H), 3.04 (t, J = 7.2 Hz, 2H), 2.32 (s, 3H), 1.30 (d, J = 5.4 Hz, 3H), 1.16 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.1, 138.9, 132.7, 130.4, 127.0, 118.8, 99.4, 82.2, 80.0, 64.7, 60.8, 35.0, 21.4, 19.8, 15.2; HR-ESIMS calcd for $C_{15}H_{20}NaO_2$ $[M+Na]^+$ 255.1356. Found 255.1358.

***N*-((2-(2-(1-Ethoxyethoxy)ethyl)-4-methylphenyl)ethynyl)-*N*,4-dimethylbenzenesulfonamide (3i)**

According to **GP-1**, **3i** (96.4 mg, 27%) was obtained from **S14** (204 mg, 0.877 mmol), *N*-methyl-*p*-toluenesulfonamide (813 mg, 4.39 mmol), $CuCl_2$ (23.5 mg, 0.175 mmol), Na_2CO_3 (185 mg, 1.75 mmol), and pyridine (142 μL, 1.75 mmol). Eluent: hexane/CH_2Cl_2/EtOAc = 15:15:1.

Colorless oil; IR ν_{max}: 3009, 2236, 1599, 1368, 1169 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 7.8 Hz, 2H), 7.21 (d, J = 7.8 Hz, 1H), 7.03 (d, J = 1.2 Hz, 1H), 6.94 (dd, J = 7.8, 1.2 Hz, 1H), 4.65 (q, J = 5.4 Hz, 1H), 3.81-3.48 (m, 3H), 3.44-3.32 (m, 1H), 3.14 (s, 3H), 2.95 (t, J = 7.2 Hz, 2H), 2.45 (s, 3H), 2.31 (s, 3H), 1.27 (d, J = 5.4 Hz, 3H), 1.13 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.4, 140.1, 137.7, 133.1, 131.7, 130.2, 129.6, 127.6, 126.8, 119.1, 99.5, 86.5, 67.5, 65.1, 61.0, 39.5, 35.3, 21.8, 21.6, 20.1, 15.5; HR-ESIMS calcd for $C_{23}H_{29}NNaO_4S$ $[M+Na]^+$ 438.1715. Found 438.1710.

Preparation of Ynamide 3j



2-(2-(1-Ethoxyethoxy)ethyl)-1-ethynyl-4-fluorobenzene (S15)

To a mixture of 2-(2-ethynyl-5-fluorophenyl)ethan-1-ol[10] (550 mg, 3.35 mmol) and PPTS (84.2 mg, 0.335 mmol) in dry CH_2Cl_2 (16.8 mL) was added ethyl vinyl ether (481 μL, 5.02 mmol) and stirred at rt for 15.5 h. After reaction completed, the mixture was quenched with saturated aqueous solution of $NaHCO_3$, extracted with CH_2Cl_2, dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 20:1 to give **S15** (655 mg, 83%) as orange oil.

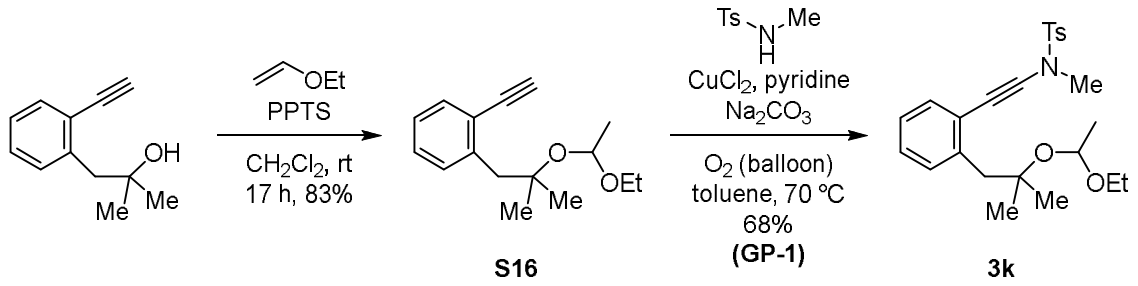
IR ν_{max}: 3305, 3011, 1608 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.43 (dd, *J* = 8.4, 5.7 Hz, 1H), 6.98 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.86 (td, *J* = 8.4, 2.7 Hz, 1H), 4.67 (q, *J* = 5.1 Hz, 1H), 3.85-3.76 (m, 1H), 3.73-3.64 (m, 1H), 3.59-3.48 (m, 1H), 3.44-3.33 (m, 1H), 3.59-3.33 (m, 2H), 3.21 (s, 1H), 3.05 (t, *J* = 7.2 Hz, 1H), 1.29 (d, *J* = 5.1 Hz, 3H), 1.15 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.2 (d, *J* = 247.6 Hz), 144.1 (d, *J* = 8.0 Hz), 134.1 (d, *J* = 8.6 Hz), 117.7 (d, *J* = 3.5 Hz), 116.5 (d, *J* = 21.8 Hz), 113.3 (d, *J* = 21.7 Hz), 99.3, 81.1, 80.5 (d, *J* = 1.7 Hz), 64.1, 60.8, 35.1 (d, *J* = 1.1 Hz), 19.9, 15.4; HR-ESIMS calcd for $C_{14}H_{17}FNaO_2$ $[M+Na]^+$ 259.1110. Found 259.1105.

***N*-((2-(2-(1-Ethoxyethoxy)ethyl)-4-fluorophenyl)ethynyl)-*N*,4-dimethylbenzenesulfonamide (3j)**

According to **GP-1**, **3j** (422 mg, 47%) was obtained from **S15** (503 mg, 2.13 mmol), *N*-methyl-*p*-toluenesulfonamide (1.97 g, 10.6 mmol), $CuCl_2$ (57.3 mg, 0.426 mmol), Na_2CO_3 (452 mg, 4.26 mmol), and pyridine (345 μL, 4.26 mmol). Eluent: hexane/EtOAc = 5:1.

Colorless oil; IR ν_{max}: 2987, 2238, 1599, 1369, 1168 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.4 Hz, 2H), 7.28 (dd, *J* = 8.7, 5.7 Hz, 1H), 6.96 (dd, *J* = 9.6, 2.4 Hz, 1H), 6.83 (td, *J* = 8.4, 2.7 Hz, 1H), 4.65 (q, *J* = 5.4 Hz, 1H), 3.83-3.74 (m, 1H), 3.70-3.62 (m, 1H), 3.57-3.46 (m, 1H), 3.43-3.32 (m, 1H), 3.15 (s, 3H), 2.97 (t, *J* = 6.9 Hz, 2H), 2.45 (s, 3H), 1.27 (d, *J* = 5.4 Hz, 3H), 1.13 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.7 (d, *J* = 246.5 Hz), 144.6, 143.3 (d, *J* = 8.0 Hz), 133.4 (d, *J* = 8.6 Hz), 133.1, 129.7, 127.6, 118.1 (d, *J* = 3.5 Hz), 116.4 (d, *J* = 21.7 Hz), 113.2 (d, *J* = 21.7 Hz), 99.5, 86.9, 66.6, 64.4, 60.9, 39.4, 35.2 (d, *J* = 1.5 Hz), 21.8, 20.0, 15.5; HR-ESIMS calcd for $C_{22}H_{26}FNNaO_4S$ $[M+Na]^+$ 442.1464. Found 442.1462.

Preparation of Ynamide 3k



1-(2-(1-Ethoxyethoxy)-2-methylpropyl)-2-ethynylbenzene (S16)

To a mixture of 1-(2-ethynylphenyl)-2-methylpropan-2-ol[10] (1.64 g, 9.43 mmol) and PPTS (237 mg, 0.943 mmol) in dry CH_2Cl_2 (47.2 mL) was added ethyl vinyl ether (1.35 mL, 14.1 mmol) and stirred at rt for 17 h. After reaction completed, the mixture was quenched with saturated aqueous solution of $NaHCO_3$, extracted with CH_2Cl_2, dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 40:1 to give **S16** (1.94 g, 83%) as pale yellow oil.

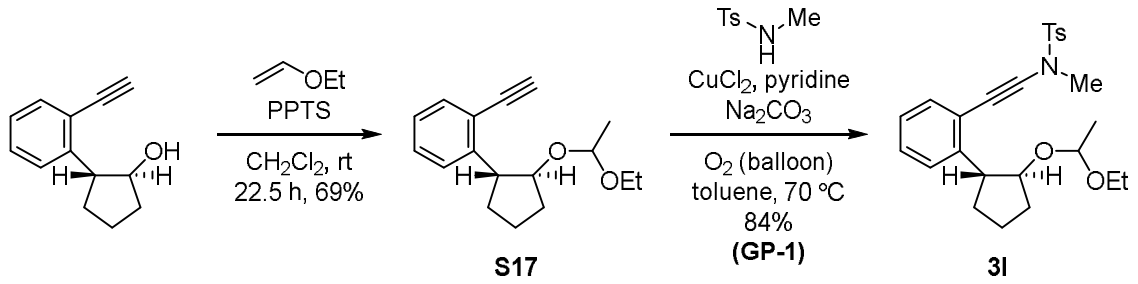
IR ν_{max}: 3305, 2981, 1600 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.37 (dd, *J* = 7.8, 1.5 Hz, 2H), 7.24 (td, *J* = 7.5, 1.5 Hz, 1H), 7.14 (td, *J* = 7.5, 1.5 Hz, 1H), 4.94 (q, *J* = 5.4 Hz, 1H), 3.57-3.38 (m, 2H), 3.21 (s, 1H), 3.10 (d, *J* = 16.2 Hz, 1H), 3.05 (d, *J* = 16.2 Hz, 1H), 1.29 (d, *J* = 5.4 Hz, 3H), 1.27 (s, 3H), 1.21 (s, 3H), 1.15 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.7, 132.5, 131.1, 127.9, 125.8, 122.7, 93.7, 83.4, 80.3, 76.9, 58.5, 46.0, 26.7, 25.7, 21.9, 15.6; HR-ESIMS calcd for $C_{16}H_{22}NaO_2$ $[M+Na]^+$ 269.1512. Found 269.1511.

***N*-((2-(2-(1-Ethoxyethoxy)-2-methylpropyl)phenyl)ethynyl)-*N*,4-dimethylbenzenesulfonamide (3k)**

According to **GP-1**, **3k** (845 mg, 68%) was obtained from **S16** (713 mg, 2.89 mmol), *N*-methyl-*p*-toluenesulfonamide (2.68 g, 14.5 mmol), $CuCl_2$ (77.8 mg, 0.579 mmol), Na_2CO_3 (614 mg, 5.79 mmol), and pyridine (468 μL, 5.79 mmol). Eluent: hexane/EtOAc = 6:1.

Pale yellow oil; IR ν_{max}: 2981, 2234, 1598, 1368, 1167 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.5 Hz, 2H), 7.38-7.34 (m, 3H), 7.31 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.19 (td, *J* = 7.5, 1.5 Hz, 1H), 7.13 (td, *J* = 7.5, 1.5 Hz, 1H), 4.94 (q, *J* = 5.0 Hz, 1H), 3.54-3.40 (m, 2H), 3.17 (s, 3H), 3.02 (d, *J* = 15.5 Hz, 1H), 2.99 (d, *J* = 15.5 Hz, 1H), 2.45 (s, 3H), 1.28 (d, *J* = 5.0 Hz, 3H), 1.25 (s, 3H), 1.19 (s, 3H), 1.13 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.7, 140.0, 133.4, 131.6, 131.4, 129.8, 127.7, 127.2, 125.9, 123.5, 93.8, 86.6, 76.9, 68.9, 58.6, 46.1, 39.3, 26.5, 25.3, 21.8, 21.6, 15.4; HR-ESIMS calcd for $C_{24}H_{31}NNaO_4S$ $[M+Na]^+$ 452.1866. Found 452.1862.

Preparation of Ynamide 3l



1-((1*R,2*S**)-2-(1-Ethoxyethoxy)cyclopentyl)-2-ethynylbenzene (S17)**

To a mixture of (1*R**,2*S**)-2-(2-ethynylphenyl)cyclopentan-1-ol[10] (1.44 g, 7.71 mmol) and PPTS (194 mg, 0.771 mmol) in dry CH_2Cl_2 (39 mL) was added ethyl vinyl ether (1.11 mL, 11.6 mmol) and stirred at rt for 22.5 h. After reaction completed, the mixture was quenched with saturated aqueous solution of $NaHCO_3$, extracted with CH_2Cl_2, dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 40:1 to give **S17** (1.37 g, 69%) as yellow oil as 1:1 diastereomer mixture.

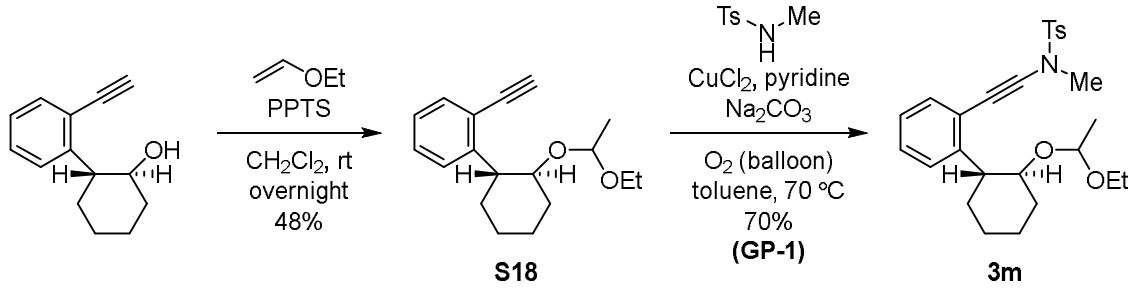
IR ν_{max}: 3305, 2976, 2104, 1598 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.8 Hz, 1H), 7.32-7.24 (m, 1H), 7.21 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.15-7.08 (m, 1H), 4.65 (q, *J* = 5.1 Hz, 0.5H), 4.55 (q, *J* = 5.1 Hz, 0.5H), 4.36-4.26 (m, 1H), 3.66-3.55 (m, 1H), 3.54-3.43 (m, 0.5H), 3.35-3.13 (m, 2.5H), 2.18-2.15 (m, 1H), 2.12-1.97 (m, 1H), 1.94-1.58 (m, 4H), 1.21 (d, *J* = 5.1 Hz, 1.5H), 1.18 (d, *J* = 5.1 Hz, 1.5H), 1.00 (t, *J* = 6.9 Hz, 1.5H), 0.99 (t, *J* = 6.9 Hz, 1.5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.7, 146.5, 132.95, 132.90, 128.9, 128.7, 126.42, 126.39, 125.58, 125.57, 121.5, 121.4, 99.0, 98.3, 83.1, 82.55, 82.49, 82.0, 81.13, 81.09, 60.6, 59.8, 50.6, 50.3, 33.7, 33.0, 32.7, 32.5, 23.6, 23.2, 21.0, 20.6, 15.3, 15.2; HR-ESIMS calcd for $C_{17}H_{22}NaO_2$ $[M+Na]^+$ 281.1512. Found 281.1509.

***N*-((2-((1*R**,2*S**)-2-(1-Ethoxyethoxy)cyclopentyl)phenyl)ethynyl)-*N*,4-dimethylbenzenesulfonamide (3l)**

According to **GP-1**, **3l** (940 mg, 84%) was obtained as 1:1 diastereomer mixture.from **S17** (644 mg, 2.49 mmol), *N*-methyl-*p*-toluenesulfonamide (2.31 g, 12.5 mmol), $CuCl_2$ (67.0 mg, 0.499 mmol), Na_2CO_3 (523 mg, 4.99 mmol), and pyridine (403 μL, 4.99 mmol). Eluent: hexane/EtOAc = 9:1.

Pale yellow oil; IR ν_{max}: 2977, 2234, 1598, 1369, 1168 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.88-7.82 (m, 2H), 7.38-7.29 (m, 3H), 7.26-7.17 (m, 2H), 7.13-7.06 (m, 1H), 4.63 (q, *J* = 5.4 Hz, 0.5H), 4.50 (q, *J* = 5.4 Hz, 0.5H), 4.37-4.27 (m, 1H), 3.52-3.36 (m, 1.5H), 3.34-3.08 (m, 4.5H), 2.45 (s, 3H), 2.22-1.98 (m, 2H), 1.89-1.51 (m, 4H), 1.17 (d, *J* = 5.4 Hz, 1.5H), 1.15 (d, *J* = 5.4 Hz, 1.5H), 1.00 (t, *J* = 6.9 Hz, 1.5H), 0.95 (t, *J* = 6.9 Hz, 1.5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.7, 145.5, 144.41, 144.38, 133.1, 132.1, 129.6, 129.5, 127.94, 127.85, 127.8, 127.7, 127.6, 126.4, 126.3, 125.6, 125.5, 122.1, 122.0, 99.1, 98.4, 87.4, 87.3, 82.7, 81.6, 68.0, 67.9, 60.7, 59.7, 50.8, 50.5, 39.5, 33.7, 33.2, 32.7, 32.6, 23.4, 23.1, 21.8, 21.0, 20.7, 15.3, 15.2; HR-ESIMS calcd for $C_{25}H_{31}NNaO_4S$ $[M+Na]^+$ 464.1866. Found 464.1864.

Preparation of Ynamide 3m



1-((1*R,2*S**)-2-(1-Ethoxyethoxy)cyclohexyl)-2-ethynylbenzene (S18)**

To a mixture of (1*R**,2*S**)-2-(2-ethynylphenyl)cyclohexan-1-ol[10] (1.79 g, 8.91 mmol) and PPTS (224 mg, 0.891 mmol) in dry CH_2Cl_2 (44.6 mL) was added ethyl vinyl ether (1.28 mL, 13.4 mmol) and stirred at rt overnight. After reaction completed, the mixture was quenched with saturated aqueous solution of $NaHCO_3$, extracted with CH_2Cl_2, dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 20:1 to give **S18** (1.15 g, 48%) as colorless oil as 4:3 diastereomer mixture.

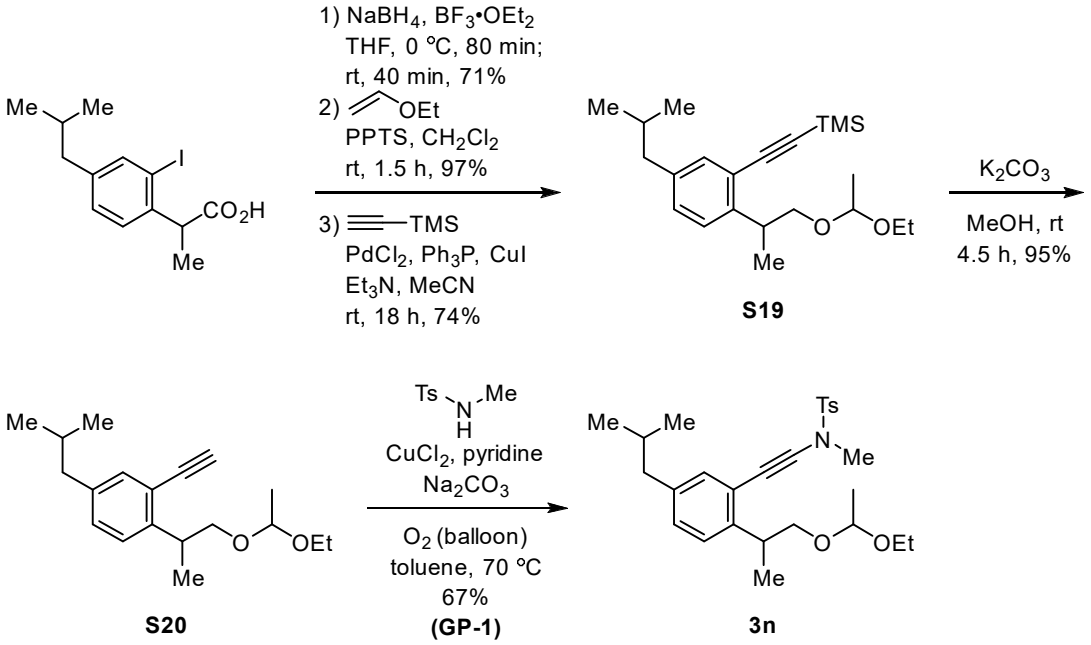
IR ν_{max}: 3305, 2936, 2104, 1599 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.47-7.42 (m, 1H), 7.31-7.23 (m, 2H), 7.15-7.07 (m, 1H), 4.57 (q, *J* = 5.1 Hz, 3/7H), 4.11 (q, *J* = 5.1 Hz, 4/7H), 3.76 (br s, 1H), 3.38 (q, *J* = 7.2 Hz, 1H), 3.25 (s, 4/7H), 3.2 (s, 3/7H), 3.24-3.05 (m, 10/7), 2.61-2.50 (m, 4/7H), 2.20-2.12 (m, 1H), 1.92-1.68 (m, 3H), 1.64-1.25 (m, 4H), 1.12 (d, *J* = 5.4 Hz, 9/7H), 1.11 (t, *J* = 7.2 Hz, 12/7H), 0.89 (t, *J* = 7.2 Hz, 12/7H), 0.84 (d, *J* = 5.4 Hz, 12/7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.9, 146.6, 132.9, 132.8, 128.43, 128.35, 126.6, 125.6, 125.4, 122.1, 100.3, 97.2, 82.6, 80.8, 80.5, 58.8, 58.5, 48.3, 34.6, 33.6, 33.2, 32.9, 26.1, 26.0, 25.4, 25.1, 20.9, 20.0, 15.6, 15.3; HR-ESIMS calcd for $C_{18}H_{20}NaO_2$ $[M+Na]^+$ 295.1669. Found 295.1667.

***N*-((2-((1*R**,2*S**)-2-(1-Ethoxyethoxy)cyclohexyl)phenyl)ethynyl)-*N*,4-dimethylbenzenesulfonamide (3m)**

According to **GP-1**, **3m** (639 mg, 70%) was obtained as 1:1 diastereomer mixture from **S18** (545 mg, 2.00 mmol), *N*-methyl-*p*-toluenesulfonamide (1.85 g, 10.0 mmol), $CuCl_2$ (53.8 mg, 0.400 mmol), Na_2CO_3 (434 mg, 4.00 mmol), and pyridine (324 μL, 4.00 mmol). Eluent: hexane/EtOAc = 9:1.

Colorless oil; IR ν_{max}: 2936, 2234, 1598, 1367, 1168 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.92-7.84 (m, 2H), 7.34 (d, *J* = 8.7 Hz, 2H), 7.29-7.17 (m, 3H), 7.12-7.03 (m, 1H), 4.56 (q, *J* = 5.4 Hz, 0.5H), 4.15 (q, *J* = 5.1 Hz, 0.5H), 3.71 (br s, 1H), 3.50-3.33 (m, 1H), 3.27-3.01 (m, 4.5H), 2.61-2.49 (m, 0.5H), 2.43 (s, 3H), 2.23-2.11 (m, 1H), 1.88-1.66 (m, 3H), 1.56-1.25 (m, 4H), 1.15 (d, *J* = 5.1 Hz, 1.5H), 1.12 (t, *J* = 5.1 Hz, 1.5H), 0.87 (t, *J* = 7.2 Hz, 1.5H), 0.79 (d, *J* = 5.4 Hz, 1.5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.8, 145.6, 144.3, 133.1, 133.0, 131.2, 129.6, 127.71, 127.67, 127.27, 127.25, 126.4, 125.5, 125.3, 122.7, 100.7, 97.5, 87.2, 80.9, 68.3, 59.3, 59.1, 48.2, 39.34, 39.32, 34.5, 33.4, 26.1, 26.0, 25.4, 25.2, 21.8, 21.2, 20.3, 15.6, 15.3; HR-ESIMS calcd for $C_{26}H_{33}NNaO_4S$ $[M+Na]^+$ 478.2023. Found 478.2027.

Preparation of Ynamide 3n



((2-(1-(1-Ethoxyethoxy)propan-2-yl)-5-isobutylphenyl)ethynyl)trimethylsilane (S19)

To a mixture of 2-(2-iodo-4-isobutylphenyl)propanoic acid[9] (5.36 g, 16.1 mmol) in dry THF (40 mL) at 0 °C was added $NaBH_4$ (1.22 g, 32.3 mmol). Then, $BF_3 \cdot OEt_2$ (4.05 mL, 32.3 mmol) was added dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 80 min, followed by rt for 40 min. After reaction completed, the mixture was cooled to 0 °C, and was quenched with MeOH (18 mL) and 1 M HCl (18 mL), extracted with Et_2O, dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 7:1 to give 2-(2-iodo-4-isobutylphenyl)propan-1-ol (3.63 g, 71%) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (s, 1H), 7.11-7.05 (m, 2H), 3.80-3.59 (m, 2H), 3.28 (sext, J = 6.6 Hz, 1H), 2.37 (d, J = 7.2 Hz, 2H), 1.92-1.73 (m, 1H), 1.50 (br s, 1H), 1.25 (d, J = 6.9 Hz, 3H), 0.90 (d, J = 6.6 Hz, 6H).

To a mixture of 2-(2-iodo-4-isobutylphenyl)propan-1-ol (3.62 g, 11.4 mmol) and PPTS (286 mg, 1.14 mmol) in dry CH_2Cl_2 (57 mL) was added ethyl vinyl ether (1.63 mL, 17.1 mmol) and stirred at rt for 1.5 h. After reaction completed, the mixture was quenched with saturated aqueous solution of $NaHCO_3$, extracted with CH_2Cl_2, dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 40:1 to give 1-(1-(1-ethoxyethoxy)propan-2-yl)-2-iodo-4-isobutylbenzene (4.31 g, 97%) as colorless oil as 1:1 diastereomer mixture. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (d, J = 1.5 Hz, 1H), 7.09 (d, J = 8.1 Hz, 1H), 7.05 (dd, J = 8.1, 1.5 Hz, 1H), 4.72-4.64 (m, 1H), 3.72-3.24 (m, 5H), 2.37 (d, J = 7.2 Hz, 2H), 1.90-1.74 (m, 1H), 1.30-1.25 (m, 6H), 1.16 (t, J = 6.9 Hz, 1.5H), 1.15 (t, J = 6.9 Hz, 1.5H), 0.89 (d, J = 6.6 Hz, 6H).

A mixture of 1-(1-(1-ethoxyethoxy)propan-2-yl)-2-iodo-4-isobutylbenzene (4.30 g, 11.0 mmol), $PdCl_2$ (48.8 mg, 0.275 mmol), Ph_3P (144 mg, 0.551 mmol), CuI (75.5 mg, 0.397 mmol), Et_3N (4.61 mL, 33.1 mmol), and ethynyltrimethylsilane (2.33 mL, 16.5 mmol) in dry MeCN (22 mL) was stirred at rt for 18 h. After reaction completed, the mixture was quenched with 5% aqueous solution of NH_3. The mixture was extracted with Et_2O, washed with brine, dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 60:1 to give **S19** (2.94 g, 74%) as yellow oil as 1:1 diastereomer mixture. IR ν_{max}: 2961, 2149, 1606 cm^{-1}; ^{1}H NMR (300

MHz, $CDCl_3$) δ 7.23 (d, *J* = 1.8 Hz, 1H), 7.12 (d, *J* = 8.1 Hz, 1H), 7.03 (dd, *J* = 8.1, 1.8 Hz, 1H), 4.70-4.64 (m, 1H), 3.74 (dd, *J* = 8.4, 4.8 Hz, 0.5H), 3.69-3.33 (m, 4.5H), 2.39 (d, *J* = 7.2 Hz, 2H), 1.92-1.74 (m, 1H), 1.32 (d, *J* = 6.6 Hz, 1.5H), 1.31 (d, *J* = 6.6 Hz, 1.5H), 1.29 (d, *J* = 5.4 Hz, 1.5H), 1.28 (d, *J* = 5.4 Hz, 1.5H), 1.162 (t, *J* = 7.2 Hz, 1.5H), 1.158 (t, *J* = 7.2 Hz, 1.5H), 0.88 (d, *J* = 6.6 Hz, 6H), 0.25 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.4, 143.3, 139.1, 139.0, 133.09, 133.08, 129.4, 125.7, 122.0, 104.1, 104.0, 99.6, 99.4, 97.55, 97.45, 70.3, 69.5, 61.0, 60.9, 44.8, 37.4, 37.2, 30.2, 22.5, 20.3, 20.0, 17.8, 17.7, 15.5, 0.3; HR-ESIMS calcd for $C_{22}H_{36}NaO_2Si$ $[M+Na]^+$ 383.2377. Found 383.2372.

1-(1-(1-Ethoxyethoxy)propan-2-yl)-2-ethynyl-4-isobutylbenzene (S20)

To a solution of **S19** (2.93 g, 8.13 mmol) in MeOH (4.1 mL) at rt was added K_2CO_3 (561 mg, 4.06 mmol), and was stirred for 4.5 h. After reaction completed, the mixture was quenched with water, extracted with Et_2O, washed with brine, dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 30:1 to give **S20** (2.23 g, 95%) as colorless oil as 1:1 diastereomer mixture.

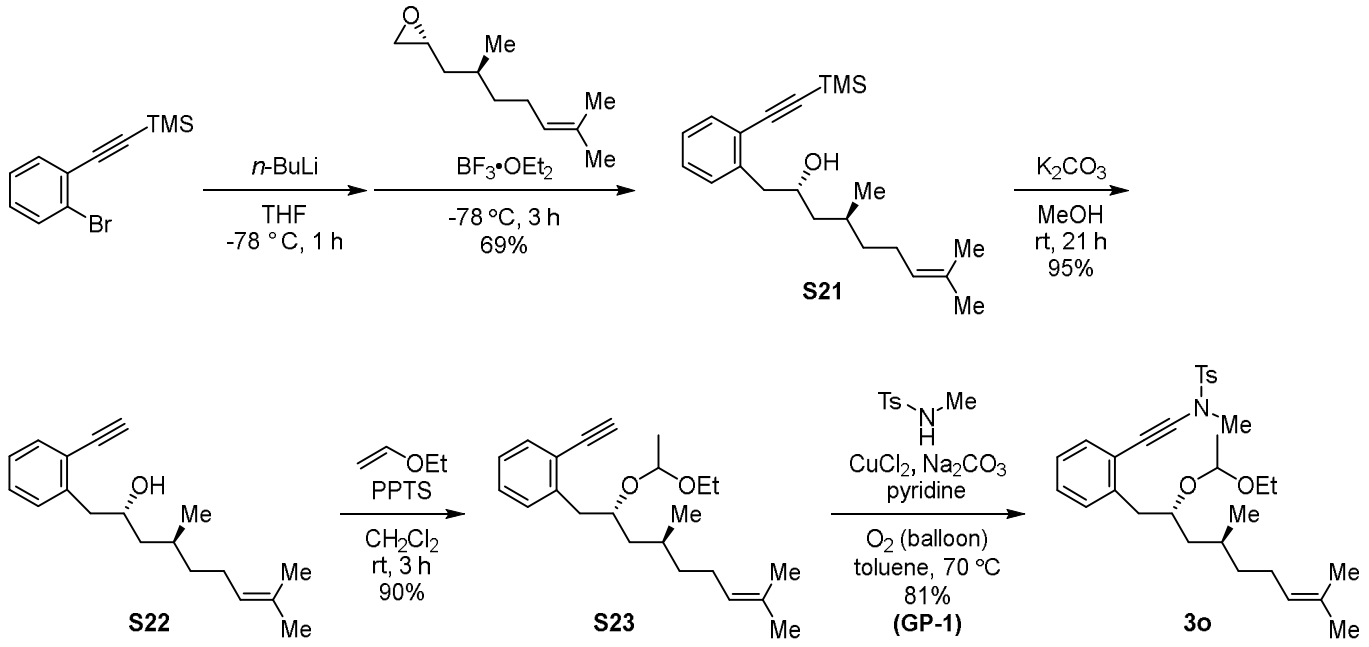
IR ν_{max}: 3305, 2961, 2102, 1607 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, *J* = 1.8 Hz, 1H), 7.15 (d, *J* = 8.1 Hz, 1H), 7.06 (dd, *J* = 8.1, 1.8 Hz, 1H), 4.71 (q, *J* = 5.4 Hz, 1H), 3.75 (dd, *J* = 9.0, 5.4 Hz, 0.5H), 3.70-3.31 (m, 4.5H), 3.220 (s, 0.5H), 3.216 (s, 0.5H), 2.40 (d, *J* = 7.2 Hz, 2H), 1.90-1.73 (m, 1H), 1.33-1.26 (m, 6H), 1.15 (t, *J* = 7.2 Hz, 1.5H), 1.14 (t, *J* = 7.2 Hz, 1.5H), 0.88 (d, *J* = 6.3 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.63, 143.60, 139.11, 139.09, 133.3, 129.7, 125.7, 121.0, 99.5, 99.3, 82.5, 80.5, 69.8, 69.6, 60.9, 60.7, 44.7, 37.1, 37.0, 30.2, 22.5, 20.0, 19.9, 18.0, 17.9, 15.4; HR-ESIMS calcd for $C_{19}H_{28}NaO_2$ $[M+Na]^+$ 311.1982. Found 311.1974.

***N*-((2-(1-(1-Ethoxyethoxy)propan-2-yl)-5-isobutylphenyl)ethynyl)-*N*,4-dimethylbenzenesulfonamide (3n)**

According to **GP-1**, **3n** (476 mg, 67%) was obtained as 1.1 diastereomer mixture from **S20** (433 mg, 1.50 mmol), *N*-methyl-*p*-toluenesulfonamide (1.39 g, 7.50 mmol), $CuCl_2$ (40.3 mg, 0.300 mmol), Na_2CO_3 (318 mg, 3.00 mmol), and pyridine (243 μL, 3.00 mmol). Eluent: hexane/EtOAc = 9:1.

Colorless oil; IR ν_{max}: 2960, 2236, 1598, 1368, 1168 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.8 Hz, 2H), 7.35 (d, *J* = 7.8 Hz, 2H), 7.14-7.10 (m, 2H), 7.00 (dd, *J* = 8.1, 2.1 Hz, 1H), 4.64 (q, *J* = 5.1 Hz, 1H), 3.74-3.67 (m, 0.5H), 3.63-3.29 (m, 4.5H), 3.16 (s, 3H), 2.45 (s, 3H), 2.39 (d, *J* = 7.2 Hz, 2H), 1.92-1.73 (m, 1H), 1.30-1.24 (m, 6H), 1.13 (t, *J* = 7.2 Hz, 1.5H), 1.12 (t, *J* = 7.2 Hz, 1.5H), 0.89 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.4, 142.6, 142.5, 139.1, 139.0, 133.1, 132.4, 129.6, 128.7, 127.64, 127.63, 125.63, 125.61, 121.54, 121.51, 99.54, 99.47, 86.9, 70.1, 69.7, 67.9, 67.8, 60.9, 60.8, 44.8, 39.5, 37.20, 37.15, 30.2, 22.52, 22.51, 21.8, 20.1, 19.9, 18.13, 18.05, 15.48, 15.46; HR-ESIMS calcd for $C_{27}H_{37}NNaO_4S$ $[M+Na]^+$ 494.2336. Found 494.2324.

Preparation of Ynamide 3o



(2*R*,4*S*)-4,8-Dimethyl-1-(2-((trimethylsilyl)ethynyl)phenyl)non-7-en-2-ol (S21)

According to literature,[11] to a solution of ((2-bromophenyl)ethynyl)trimethylsilane (1.53 g, 6.05 mmol) in dry THF (18 mL) at -78 ºC was added *n*-BuLi (8.36 mL, 1.57 M in hexane, 6.05 mmol). After stirring for 1 h at -78 ºC, (*R*)-2-((*S*)-2,6-dimethylhept-5-en-1-yl)oxirane[12] (764 mg, 4.54 mmol) in THF (3 mL) was added via cannula followed by adding $BF_3{\cdot}OEt_2$ (0.684 mL, 5.45 mmol). After stirring for 3 h at -78 ºC, the reaction mixture was quenched with saturated aqueous solution of $NaHCO_3$, extracted with EtOAc, washed with brine, dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 15:1 to give **S21** (1.07 g, 69%) as colorless oil.

$[\alpha]_D^{24}$ -40.0 (*c* 1.44, $CHCl_3$); IR ν_{max}: 3598, 2963, 2154, 1599 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45 (dd, *J* = 7.5, 0.6 Hz, 1H), 7.27-7.11 (m, 3H), 5.09 (tt, *J* = 6.9, 1.5 Hz, 1H), 4.10-3.98 (m, 1H), 3.05 (dd, *J* = 13.2, 3.9 Hz, 1H), 2.74 (dd, *J* = 13.2, 8.7 Hz, 1H), 2.07-1.92 (m, 2H), 1.81-1.53 (m, 8H), 1.46 (d, *J* = 3.6 Hz, 1H), 1.39-1.15 (m, 3H), 0.90 (d, *J* = 6.6 Hz, 3H), 0.25 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.0, 132.5, 130.9, 129.9, 128.4, 126.1, 124.6, 122.9, 103.9, 98.2, 69.7, 44.8, 43.8, 38.3, 29.1, 25.9, 25.7, 19.3, 17.9, 0.3; HR-ESIMS calcd for $C_{22}H_{34}NaOSi$ $[M+Na]^+$ 365.2271. Found 365.2276.

(2*R*,4*S*)-1-(2-Ethynylphenyl)-4,8-dimethylnon-7-en-2-ol (S22)

To a solution of **S21** (1.07 g, 3.12 mmol) in MeOH (9.4 mL) at rt was added K_2CO_3 (431 mg, 3.12 mmol), and was stirred for 21 h. After reaction completed, the mixture was quenched with water, extracted with Et_2O, washed with brine, dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 8:1 to give **S22** (798 mg, 95%) as colorless oil.

$[\alpha]_D^{24}$ -21.6 (*c* 1.40, $CHCl_3$); IR ν_{max}: 3599, 3304, 2926, 2104, 1600 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.48 (dd, *J* = 7.5, 1.2 Hz, 1H), 7.31-7.14 (m, 3H), 5.09 (tt, *J* = 7.2, 1.5 Hz, 1H), 4.10-3.98 (m, 1H), 3.25 (s, 1H), 3.05 (dd, *J* = 13.2, 3.9 Hz, 1H), 2.79 (dd, *J* = 13.2, 8.7 Hz, 1H), 2.09-1.87 (m, 2H), 1.77-1.53 (m, 8H), 1.47 (d, *J* = 3.3 Hz, 1H), 1.42-1.11 (m, 3H), 0.90 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.2,

132.9, 130.9, 129.9, 128.7, 126.2, 124.6, 121.9, 82.4, 81.0, 69.8, 44.7, 43.4, 37.9, 29.2, 25.9, 25.7, 19.3, 17.8; HR-ESIMS calcd for $C_{19}H_{26}NaO$ $[M+Na]^+$ 293.1876. Found 293.1872.

1-((2*R*,4*S*)-2-(1-Ethoxyethoxy)-4,8-dimethylnon-7-en-1-yl)-2-ethynylbenzene (S23)

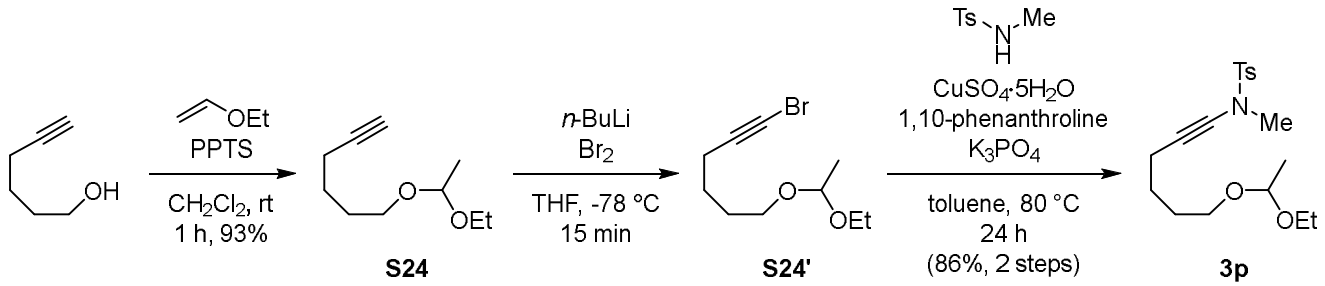
To a mixture of **S22** (707 mg, 2.61 mmol) and PPTS (65.7 mg, 0.261 mmol) in dry CH_2Cl_2 (13 mL) was added ethyl vinyl ether (376 μL, 3.92 mmol) and stirred at rt for 3 h. After reaction completed, the mixture was quenched with saturated aqueous solution of $NaHCO_3$, extracted with CH_2Cl_2, dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 50:1 to give **S23** (810 mg, 90%) as colorless oil as 1:1 diastereomer mixture. IR ν_{max}: 3304, 2930, 2104, 1600 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45 (br d, *J* = 6.9 Hz, 1H), 7.28-7.09 (m, 3H), 5.12-5.03 (m, 1H), 4.72 (q, *J* = 5.4 Hz, 0.5H), 4.41 (q, *J* = 5.4 Hz, 0.5H), 4.07-3.90 (m, 1H), 3.56-3.36 (m, 1.5H), 3.25 (s, 0.5H), 3.23 (s, 0.5H), 3.20-2.92 (m, 2.5H), 2.08-1.83 (m, 2H), 1.76-1.49 (m, 8H), 1.42-1.29 (m, 1H), 1.27-1.00 (m, 8H), 0.85 (d, *J* = 6.6 Hz, 1.5H), 0.82 (d, *J* = 6.6 Hz, 1.5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.5, 141.4, 132.69, 132.66, 130.8, 130.7, 130.5, 130.4, 128.4, 125.9, 125.8, 124.8, 124.6, 121.7, 99.0, 98.9, 82.65, 82.58, 80.9, 80.8, 74.7, 74.6, 60.1, 59.8, 43.4, 42.7, 41.1, 37.7, 37.6, 29.0, 28.9, 25.9, 25.7, 20.8, 20.6, 19.8, 19.5, 17.8, 15.5, 15.4; HR-ESIMS calcd for $C_{23}H_{34}NaO_2$ $[M+Na]^+$ 365.2451. Found 365.2448.

***N*-((2-((2*R*,4*S*)-2-(1-Ethoxyethoxy)-4,8-dimethylnon-7-en-1-yl)phenyl)ethynyl)-*N*,4-dimethylbenzenesulfonamide (3o)**

According to **GP-1**, **3o** (637 mg, 81%) was obtained as 1:1 diastereomer mixture from **S23** (514 mg, 1.50 mmol), *N*-methyl-*p*-toluenesulfonamide (1.39 g, 7.50 mmol), $CuCl_2$ (40.3 mg, 0.300 mmol), Na_2CO_3 (318 mg, 3.00 mmol), and pyridine (243 μL, 3.00 mmol). Eluent: hexane/EtOAc = 9:1.

Colorless oil; IR ν_{max}: 2930, 2234, 1598, 1369, 1168 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, *J* = 7.8 Hz, 2H), 7.38-7.29 (m, 3H), 7.24-7.08 (m, 3H), 5.10-5.00 (m, 1H), 4.71 (q, *J* = 5.1 Hz, 0.5H), 4.40 (q, *J* = 5.1 Hz, 0.5H), 4.01-3.83 (m, 1H), 3.54-3.38 (m, 1.5H), 3.27-3.18 (m, 0.5H), 3.154 (s, 1.5H), 3.149 (s, 1.5H), 3.09 (dd, *J* = 13.2, 6.0 Hz, 0.5H), 2.97-2.77 (m, 1.5H), 2.45 (s, 3H), 2.02-1.80 (m, 2H), 1.72-1.43 (m, 8H), 1.32-1.18 (m, 2.5H), 1.17-1.02 (m, 6.5H), 0.80 (d, *J* = 6.6 Hz, 1.5H), 0.78 (d, *J* = 6.6 Hz, 1.5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.4, 140.6, 140.5, 133.1, 132.2, 132.1, 130.8, 130.7, 130.1, 129.6, 127.63, 127.62, 125.9, 125.8, 124.7, 124.6, 122.4, 99.3, 98.7, 87.2, 87.1, 75.2, 74.5, 67.94, 67.87, 59.7, 43.1, 42.4, 41.08, 41.05, 39.42, 39.40, 38.1, 38.0, 28.8, 28.7, 25.9, 25.64, 25.60, 21.8, 20.7, 20.5, 19.6, 19.3, 17.8, 15.6, 15.5; HR-ESIMS calcd for $C_{31}H_{43}NNaO_4S$ $[M+Na]^+$ 548.2805. Found 548.2809.

Preparation of Ynamide 3p



6-(1-Ethoxyethoxy)hex-1-yne (S24)

To a mixture of 5-hexyn-1-ol (2.21 mL, 20.0 mmol) and PPTS (503 mg, 2.00 mmol) in dry CH_2Cl_2 (100 mL) was added ethyl vinyl ether (2.87 mL, 30.0 mmol) and stirred at rt for 1 h. After reaction completed, the mixture was quenched with saturated aqueous solution of $NaHCO_3$, extracted with CH_2Cl_2, dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 20:1 to give **S24** (3.17 g, 93%) as colorless oil.

IR ν_{max}: 3308, 3011, 2117 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.67 (q, J = 5.4 Hz, 1H), 3.70-3.54 (m, 2H), 3.53-3.39 (m, 2H), 2.22 (td, J = 6.9, 2.7 Hz, 2H), 1.95 (t, J = 2.7 Hz, 1H), 1.78-1.55 (m, 4H), 1.30 (d, J = 5.4 Hz, 3H), 1.20 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 99.4, 84.2, 68.4, 64.5, 60.7, 29.0, 25.4, 20.0, 18.4, 15.5; HR-ESIMS calcd for $C_{10}H_{18}NaO_2$ $[M+Na]^+$ 193.1199. Found 193.1200.

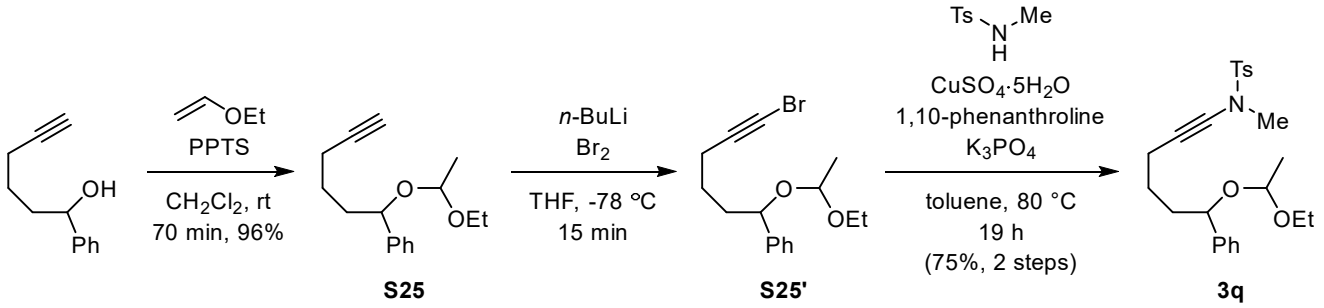
***N*-(6-(1-Ethoxyethoxy)hex-1-yn-1-yl)-*N*,4-dimethylbenzenesulfonamide (3p)**

To a solution of **S24** (1.36 g, 8.00 mmol) in dry THF (40 mL) at -78 °C was added *n*-BuLi (1.57 M in hexane, 6.11 mL, 9.60 mmol) dropwise, and the reaction mixture was stirred at -78 °C for 30 min. Then, Br_2 (0.533 mL, 10.4 mmol) was added dropwise, and the reaction mixture was stirred at -78 °C for 15 min. After reaction completed, the mixture was quenched with a saturated aqueous solution of $Na_2S_2O_3$, extracted with Et_2O, washed with brine, dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 20:1 to give **S24'** (1.85 g) that was directly used in the next reaction.

According to literature,[6] a solution of **S24'** (1.85 g, 7.43 mmol), *N*-methyl-*p*-toluenesulfonamide (1.65 g, 8.91 mmol), $CuSO_4 \cdot 5H_2O$ (371 mg, 1.49 mmol), 1,10-phenanthroline (535 mg, 2.97 mmol), and K_3PO_4 (3.78 g, 17.8 mmol) in dry toluene (22.3 mL) was stirred at 80 °C for 24 h. The mixture was cooled to rt, diluted with Et_2O, and filtered through Celite. The filtrate was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 6:1 to 5:1 to give **3p** (2.43 g, 86% in 2 steps) as colorless oil.

IR ν_{max}: 2939, 2254, 1598, 1364, 1172 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.4 Hz, 2H), 4.66 (q, J = 5.4 Hz, 1H), 3.69-3.36 (m, 4H), 3.00 (s, 3H), 2.45 (s, 3H), 2.27 (t, J = 6.6 Hz, 2H), 1.69-1.50 (m, 4H), 1.30 (d, J = 5.4 Hz, 3H), 1.20 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.2, 132.9, 129.4, 127.6, 99.5, 75.1, 68.3, 64.7, 60.8, 39.5, 29.1, 25.9, 21.8, 20.1, 18.4, 15.6; HR-ESIMS calcd for $C_{18}H_{27}NNaO_4S$ $[M+Na]^+$ 376.1553. Found 376.1556.

Preparation of Ynamide 3q



(1-(1-Ethoxyethoxy)hex-5-yn-1-yl)benzene (S25)

To a mixture of 1-phenylhex-5-yn-1-ol[13] (605 mg, 3.47 mmol) and PPTS (87.3 mg, 0.347 mmol) in dry CH_2Cl_2 (17.6 mL) was added ethyl vinyl ether (499 μL, 5.21 mmol) and stirred at rt for 70 min. After reaction completed, the mixture was quenched with saturated aqueous solution of $NaHCO_3$, extracted with CH_2Cl_2, dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 20:1 to give **S25** (825 mg, 96%) as colorless oil as 1:1 diastereomer mixture.

IR ν_{max}: 3308, 3010, 2117, 1603 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37-7.22 (m, 5H), 4.68 (q, J = 5.4 Hz, 0.5H), 4.62 (dd, J = 7.8, 6.0 Hz, 0.5H), 4.51 (q, J = 5.4 Hz, 0.5H), 4.42 (dd, J = 7.2, 5.7 Hz, 0.5H), 3.61-3.44 (m, 1.5H), 3.22-3.10 (m, 0.5H), 2.30-2.09 (m, 2H), 1.99-1.39 (m, 5H), 1.28 (d, J = 5.4 Hz, 1.5H), 1.24 (d, J = 5.4 Hz, 1.5H), 1.19 (t, J = 6.9 Hz, 1.5H), 0.97 (t, J = 6.9 Hz, 1.5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.2, 142.5, 128.3, 128.2, 127.5, 127.3, 126.8, 126.6, 99.0, 97.3, 84.2, 84.1, 77.6, 77.3, 68.5, 68.4, 61.2, 59.6, 37.3, 37.1, 24.8, 24.6, 20.33, 20.29, 18.3, 18.2, 15.4, 14.9; HR-ESIMS calcd for $C_{16}H_{22}NaO_2$ $[M+Na]^+$ 269.1512. Found 269.1509.

***N*-(6-(1-Ethoxyethoxy)-6-phenylhex-1-yn-1-yl)-*N*,4-dimethylbenzenesulfonamide (3q)**

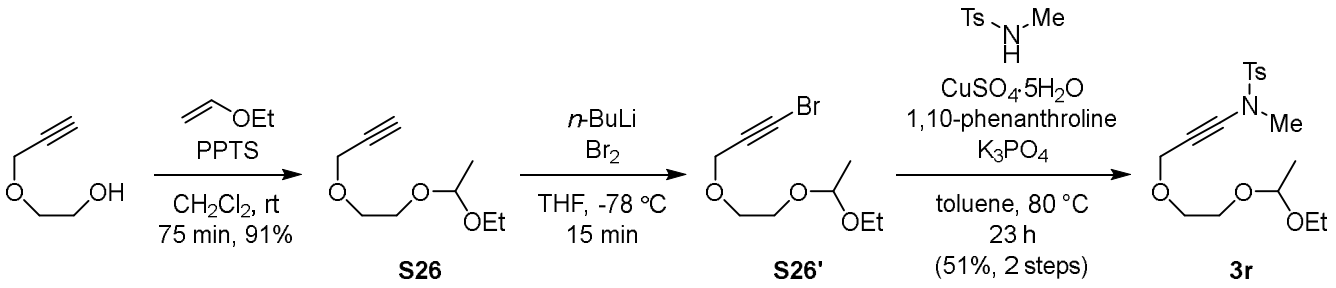
To a solution of **S25** (818 mg, 3.32 mmol) in dry THF (16.6 mL) at -78 °C was added *n*-BuLi (1.59 M in hexane, 2.51 mL, 3.98 mmol) dropwise, and the reaction mixture was stirred at -78 °C for 30 min. Then, Br_2 (221 μL, 4.32 mmol) was added dropwise, and the reaction mixture was stirred at -78 °C for 15 min. After reaction completed, the mixture was quenched with a saturated aqueous solution of $Na_2S_2O_3$, extracted with Et_2O, washed with brine, dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 20:1 to give **S25'** (840 mg) that was directly used in the next reaction.

According to literature,[6] a solution of **S25'** (840 mg, 2.58 mmol), *N*-methyl-*p*-toluenesulfonamide (574 mg, 3.10 mmol), $CuSO_4 \cdot 5H_2O$ (129 mg, 0.517 mmol), 1,10-phenanthroline (186 mg, 1.03 mmol), and K_3PO_4 (1.32 g, 6.20 mmol) in dry toluene (7.7 mL) was stirred at 80 °C for 19 h. The mixture was cooled to rt, diluted with Et_2O, and filtered through Celite. The filtrate was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 6:1 to give **3q** (1.07 g, 75% in 2 steps) as colorless oil as 1:1 diastereomer mixture.

IR ν_{max}: 3009, 2254, 1598, 1365, 1172 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, J = 8.5 Hz, 2H), 7.36-7.31 (m, 3H), 7.30-7.24 (m, 4H), 4.66 (q, J = 5.0 Hz, 0.5H), 4.60 (dd, J = 7.5, 5.5 Hz, 0.5H), 4.50 (q, J = 5.0 Hz, 0.5H), 4.39 (dd, J = 7.5, 5.5 Hz, 0.5H), 3.57-3.46 (m, 1.5H), 3.18-3.12 (m, 0.5H), 2.984 (s, 1.5H),

2.983 (s, 1.5H), 2.43 (s, 3H), 2.32-2.19 (m, 2H), 1.92-1.83 (m, 1H), 1.77-1.54 (m, 2H), 1.51-1.35 (m, 1H), 1.28 (d, J = 5.0 Hz, 1.5H), 1.23 (d, J = 5.0 Hz, 1.5H), 1.18 (t, J = 7.0 Hz, 1.5H), 0.97 (t, J = 7.0 Hz, 1.5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.37, 144.35, 143.3, 142.6, 133.1, 129.6, 128.4, 128.2, 127.8, 127.5, 127.3, 126.8, 126.6, 99.0, 97.4, 77.7, 77.4, 75.12, 75.08, 68.2, 68.1, 61.3, 59.8, 39.3, 37.3, 37.1, 25.2, 25.1, 21.6, 20.4, 18.3, 18.2, 15.5, 14.9; HR-ESIMS calcd for $C_{24}H_{31}NNaO_4S$ $[M+Na]^+$ 452.1866. Found 452.1862.

Preparation of Ynamide 3r



(1-(1-Ethoxyethoxy)hex-5-yn-1-yl)benzene (S26)

To a mixture of 2-(prop-2-yn-1-yloxy)ethan-1-ol[14] (1.03 g, 10.3 mmol) and PPTS (259 mg, 1.03 mmol) in dry CH_2Cl_2 (51 mL) was added ethyl vinyl ether (1.48 mL, 15.4 mmol) and stirred at rt for 75 min. After reaction completed, the mixture was quenched with saturated aqueous solution of $NaHCO_3$, extracted with CH_2Cl_2, dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 8:1 to give **S26** (1.62 g, 91%) as yellow oil.

IR ν_{max}: 3308, 3012, 2120 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.75 (q, J = 5.4 Hz, 1H), 4.20 (dd, J = 2.4, 1.2 Hz, 2H), 3.78-3.59 (m, 5H), 3.54-3.43 (m, 1H), 2.44 (t, J = 1.2 Hz, 1H), 1.95 (t, J = 2.7 Hz, 1H), 1.78-1.55 (m, 4H), 1.33 (d, J = 5.4 Hz, 3H), 1.20 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 99.4, 79.6, 74.4, 69.2, 63.5, 60.8, 58.4, 19.8, 15.4; HR-ESIMS calcd for $C_9H_{16}NaO_3$ $[M+Na]^+$ 195.0992. Found 195.0992.

***N*-(6-(1-Ethoxyethoxy)-6-phenylhex-1-yn-1-yl)-*N*,4-dimethylbenzenesulfonamide (3r)**

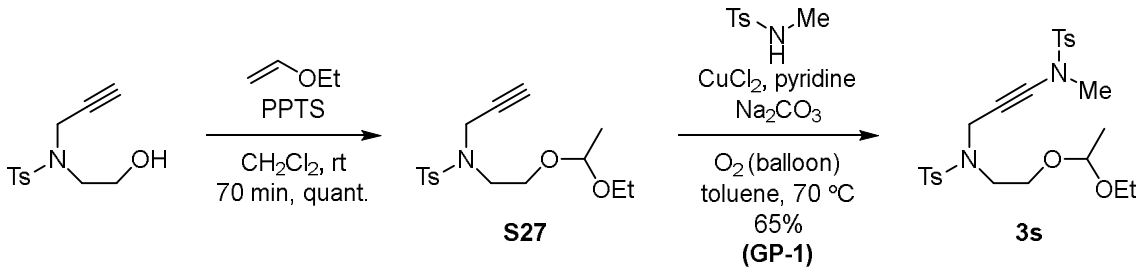
To a solution of **S26** (689 mg, 4.00 mmol) in dry THF (20 mL) at -78 °C was added *n*-BuLi (1.55 M in hexane, 3.10 mL, 4.80 mmol) dropwise, and the reaction mixture was stirred at -78 °C for 30 min. Then, Br_2 (266 μL, 5.20 mmol) was added dropwise, and the reaction mixture was stirred at -78 °C for 15 min. After reaction completed, the mixture was quenched with a saturated aqueous solution of $Na_2S_2O_3$, extracted with Et_2O, washed with brine, dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 10:1 to give **S26'** (852 mg) that was directly used in the next reaction.

According to literature,[6] a solution of **S26'** (852 mg, 3.39 mmol), *N*-methyl-*p*-toluenesulfonamide (754 mg, 4.07 mmol), $CuSO_4 \cdot 5H_2O$ (169 mg, 0.679 mmol), 1,10-phenanthroline (245 mg, 1.36 mmol), and K_3PO_4 (1.73 g, 8.14 mmol) in dry toluene (10.2 mL) was stirred at 80 °C for 23 h. The mixture was cooled to rt, diluted with Et_2O, and filtered through Celite. The filtrate was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/acetone = 5:1 to give **3r** (545 mg, 51% in 2 steps) as colorless oil.

IR ν_{max}: 3011, 2244, 1598, 1369, 1173 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, J = 8.1 Hz, 2H), 7.36

(d, J = 8.1 Hz, 2H), 4.76 (q, J = 5.4 Hz, 1H), 4.31 (s, 2H), 3.78-3.56 (m, 5H), 3.55-3.43 (m, 1H), 3.07 (s, 3H), 2.46 (s, 3H), 1.33 (d, J = 5.4 Hz, 3H), 1.20 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.8, 133.2, 129.7, 127.7, 99.5, 81.1, 68.7, 65.5, 63.5, 60.8, 58.6, 39.0, 21.6, 19.6, 15.2; HR-ESIMS calcd for $C_{17}H_{25}NNaO_5S$ $[M+Na]^+$ 378.1346. Found 378.1349.

Preparation of Ynamide 3s



***N*-(2-(1-Ethoxyethoxy)ethyl)-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (S27)**

To a mixture of *N*-(2-hydroxyethyl)-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide[15] (1.46 mg, 5.76 mmol) and PPTS (145 mg, 0.576 mmol) in dry CH_2Cl_2 (29 mL) was added ethyl vinyl ether (0.827 mL, 8.63 mmol) and stirred at rt for 70 min. After reaction completed, the mixture was quenched with saturated aqueous solution of $NaHCO_3$, extracted with CH_2Cl_2, dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 20:1 to give **S27** (1.87 g, quant.) as pale yellow oil.

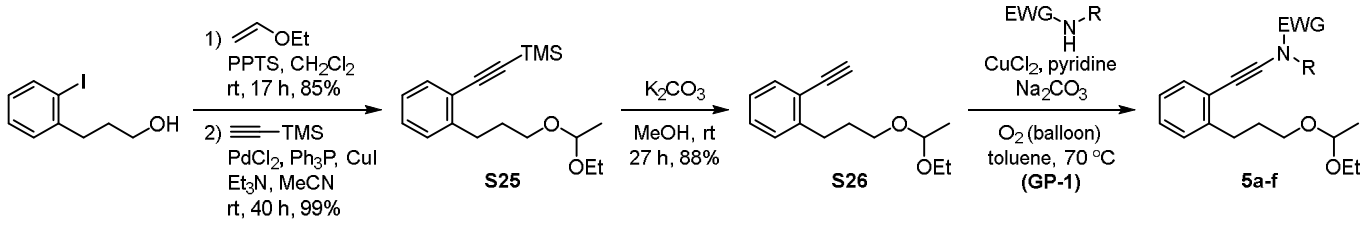
IR ν_{max}: 3308, 2982, 1599, 1349, 1161 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H), 4.68 (q, J = 5.4 Hz, 1H), 4.24 (d, J = 2.4 Hz, 2H), 3.80-3.71 (m, 1H), 3.68-3.56 (m, 2H), 3.51-3.42 (m, 1H), 3.38 (t, J = 5.7 Hz, 2H), 2.41 (s, 3H), 2.04 (t, J = 2.4 Hz, 1H), 1.28 (d, J = 5.4 Hz, 3H), 1.19 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.2, 135.9, 129.2, 127.5, 99.6, 77.2, 73.5, 63.9, 61.1, 46.3, 38.2, 21.7, 19.9, 15.5; HR-ESIMS calcd for $C_{16}H_{23}NNaO_4S$ $[M+Na]^+$ 348.1240. Found 348.1232.

***N*-(3-((*N*,4-Dimethylphenyl)sulfonamido)prop-2-yn-1-yl)-N-(2-(1-ethoxyethoxy)ethyl)-4-methylbenzenesulfonamide (3s)**

According to **GP-1**, **3s** (841 mg, 65%) was obtained as from **S27** (824 mg, 2.53 mmol), *N*-methyl-*p*-toluenesulfonamide (2.35 g, 12.7 mmol), $CuCl_2$ (68.1 mg, 0.506 mmol), Na_2CO_3 (537 mg, 5.06 mmol), and pyridine (410 μL, 5.06 mmol). Eluent: hexane/EtOAc = 3:1 to 7:3.

Colorless oil; IR ν_{max}: 3031, 2248, 1598, 1369, 1161 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, J = 8.1 Hz, 2H), 7.66 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 8.1 Hz, 2H), 7.24 (d, J = 8.1 Hz, 2H), 7.38-7.29 (m, 3H), 4.69 (q, J = 5.1 Hz, 1H), 4.35 (s, 2H), 3.79-3.71 (m, 1H), 3.69-3.58 (m, 2H), 3.43-3.41 (m, 1H), 3.32 (t, J = 5.7 Hz, 2H), 2.82 (s, 3H), 2.46 (s, 3H), 2.38 (s, 3H), 1.29 (d, J = 5.1 Hz, 3H), 1.20 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.8, 143.3, 136.2, 133.1, 129.8, 129.5, 127.6, 127.5, 99.7, 79.9, 64.0, 62.8, 61.2, 45.9, 38.7, 38.4, 21.6, 21.4, 19.8, 15.3; HR-ESIMS calcd for $C_{24}H_{32}N_2NaO_6S_2$ $[M+Na]^+$ 531.1594. Found 531.1594.

Preparation of Ynamides 5a-f



((2-(3-(1-Ethoxyethoxy)propyl)phenyl)ethynyl)trimethylsilane (S25)

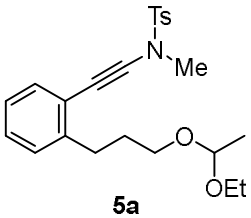
To a mixture of 3-(2-iodophenyl)propan-1-ol[16] (2.22 g, 8.48 mmol) and PPTS (213 mg, 0.848 mmol) in dry CH_2Cl_2 (43 mL) was added ethyl vinyl ether (1.46 mL, 15.3 mmol) and stirred at rt for 17 h. After reaction completed, the mixture was quenched with saturated aqueous solution of $NaHCO_3$, extracted with CH_2Cl_2, dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 20:1 to give 1-(3-(1-ethoxyethoxy)propyl)-2-iodobenzene (2.42 g, 85%) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (dd, J = 8.1, 0.9 Hz, 1H), 7.27-7.19 (m, 2H), 6.88-6.83 (m, 1H), 4.70 (q, J = 5.4 Hz, 1H), 3.72-3.58 (m, 2H), 3.55-3.42 (m, 2H), 2.79 (t, J = 7.5 Hz, 2H), 1.92-1.82 (m, 2H), 1.33 (d, J = 5.4 Hz, 3H), 1.21 (t, J = 7.2 Hz, 3H).

A mixture of 1-(3-(1-ethoxyethoxy)propyl)-2-iodobenzene (2.37 g, 7.09 mmol), $PdCl_2$ (31.4 mg, 0.177 mmol), Ph_3P (93.0 mg, 0.355 mmol), CuI (48.6 mg, 0.255 mmol), Et_3N (2.97 mL, 21.3 mmol), and ethynyltrimethylsilane (1.50 mL, 10.6 mmol) in dry MeCN (14 mL) was stirred at rt for 40 h. After reaction completed, the mixture was quenched with 5% aqueous solution of NH_3. The mixture was extracted with Et_2O, washed with brine, dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 20:1 to give **S25** (2.14 g, 99%) as brown oil. IR ν_{max}: 3009, 2154, 1599 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (dd, J = 7.5, 0.9 Hz, 1H), 7.24-7.17 (m, 2H), 7.13 (td, J = 7.5, 1.8 Hz, 1H), 4.70 (q, J = 5.4 Hz, 1H), 3.72-3.57 (m, 2H), 3.54-3.40 (m, 2H), 2.86 (t, J = 7.8 Hz, 2H), 1.98-1.88 (m, 2H), 1.32 (d, J = 5.4 Hz, 3H), 1.20 (t, J = 7.2 Hz, 3H), 0.25 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.4, 132.3, 128.7, 128.4, 125.6, 122.4, 103.8, 99.5, 97.8, 64.7, 60.7, 31.5, 30.5, 20.0, 15.4, 0.1; HR-ESIMS calcd for $C_{18}H_{28}NaO_2Si$ $[M+Na]^+$ 327.1751. Found 327.1753.

1-(3-(1-Ethoxyethoxy)propyl)-2-ethynylbenzene (S26)

To a solution of **S25** (2.13 g, 6.98 mmol) in MeOH (3.5 mL) at rt was added K_2CO_3 (482 mg, 3.49 mmol), and was stirred for 27 h. After reaction completed, the mixture was quenched with water, extracted with Et_2O, washed with brine, dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 10:1 to give **S26** (1.43 g, 88%) as colorless oil. IR ν_{max}: 3305, 3011, 2104, 1599 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (dd, J = 7.5, 1.8 Hz, 1H), 7.26 (td, J = 7.5, 1.8 Hz, 1H), 7.20 (dd, J = 7.5, 1.8 Hz, 1H), 7.13 (td, J = 7.5, 1.8 Hz, 1H), 4.68 (q, J = 5.4 Hz, 1H), 3.71-3.57 (m, 2H), 3.54-3.23 (m, 2H), 3.27 (s, 1H), 2.87 (t, J = 7.5 Hz, 2H), 1.93 (quint, J = 7.5 Hz, 2H), 1.32 (d, J = 5.4 Hz, 3H), 1.20 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.5, 132.8, 128.69, 128.66, 125.6, 121.5, 99.5, 82.2, 80.7, 64.6, 60.8, 31.2, 30.6, 20.0, 15.4; HR-ESIMS calcd for $C_{15}H_{20}NaO_2$ $[M+Na]^+$ 255.1356. Found 255.1355.

***N*-((2-(3-(1-Ethoxyethoxy)propyl)phenyl)ethynyl)-*N*,4-dimethylbenzenesulfonamide (5a)**

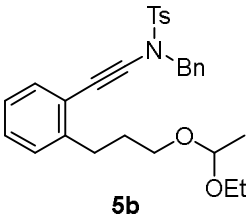


5a

According to **GP-1**, **5a** (470 mg, 75%) was obtained from **S26** (327 mg, 1.50 mmol), *N*-methyl-*p*-toluenesulfonamide (1.39 g, 7.50 mmol), $CuCl_2$ (40.3 mg, 0.300 mmol), Na_2CO_3 (318 mg, 3.00 mmol), and pyridine (242 μL, 3.00 mmol). Eluent: hexane/EtOAc = 4:1.

Colorless oil; IR ν_{max}: 3010, 2235, 1598, 1369, 1168 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.1 Hz, 2H), 7.38-7.27 (m, 3H), 7.21-7.15 (m, 2H), 7.14-7.06 (m, 1H), 4.66 (q, *J* = 5.4 Hz, 1H), 3.69-3.55 (m, 2H), 3.52-3.38 (m, 2H), 3.16 (s, 3H), 2.79 (t, *J* = 7.8 Hz, 2H), 2.44 (s, 3H), 1.88 (quint, *J* = 7.8 Hz, 2H), 1.29 (d, *J* = 5.4 Hz, 3H), 1.18 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.4, 143.2, 133.2, 131.5, 129.6, 128.6, 127.6 (2C), 125.5, 121.9, 99.6, 87.3, 67.8, 64.8, 60.9, 39.4, 31.5, 30.7, 21.8, 20.2, 15.5; HR-ESIMS calcd for $C_{23}H_{29}NNaO_4S$ $[M+Na]^+$ 438.1710. Found 438.1711.

***N*-Benzyl-*N*-((2-(3-(1-ethoxyethoxy)propyl)phenyl)ethynyl)-4-methylbenzenesulfonamide (5b)**

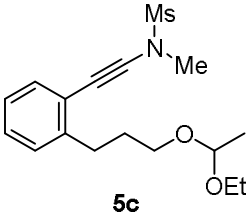


5b

According to **GP-1**, **5b** (422 mg, 57%) was obtained from **S26** (327 mg, 1.50 mmol), *N*-benzyl-*p*-toluenesulfonamide (1.96 g, 7.50 mmol), $CuCl_2$ (40.3 mg, 0.300 mmol), Na_2CO_3 (318 mg, 3.00 mmol), and pyridine (243 μL, 3.00 mmol). Eluent: hexane/EtOAc = 6:1.

Colorless oil; IR ν_{max}: 3008, 2235, 1599, 1367, 1169 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.4 Hz, 2H), 7.34-7.25 (m, 7H), 7.19-7.09 (m, 3H), 7.08-7.02 (m, 1H), 4.62 (q, *J* = 5.4 Hz, 1H), 4.58 (s, 2H), 3.68-3.56 (m, 1H), 3.52-3.39 (m, 2H), 3.35-3.25 (m, 1H), 2.62 (t, *J* = 7.5 Hz, 2H), 2.43 (s, 3H), 1.80-1.70 (m, 2H), 1.28 (d, *J* = 5.4 Hz, 3H), 1.17 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.3, 143.0, 134.5, 134.2, 131.5, 129.5, 128.51, 128.49, 128.3, 128.1, 127.4 (2C), 125.4, 121.9, 99.6, 85.8, 70.0, 64.7, 60.9, 55.7, 31.2, 30.5, 21.8, 20.2, 15.5; HR-ESIMS calcd for $C_{29}H_{33}NNaO_4S$ $[M+Na]^+$ 514.2023. Found 514.2027.

***N*-((2-(3-(1-Ethoxyethoxy)propyl)phenyl)ethynyl)-*N*-methylmethanesulfonamide (5c)**

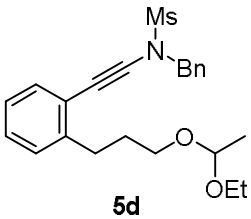


5c

According to **GP-1**, **5c** (383 mg, 75%) was obtained from **S26** (327 mg, 1.50 mmol), *N*-methylmethanesulfonamide (0.640 mL, 7.50 mmol), $CuCl_2$ (40.3 mg, 0.300 mmol), Na_2CO_3 (318 mg, 3.00 mmol), and pyridine (243 μL, 3.00 mmol). Eluent: hexane/EtOAc = 5:1.

Colorless oil; IR ν_{max}: 3008, 2237, 1599, 1363, 1163 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34 (d, *J* = 7.2 Hz, 1H), 7.21-7.15 (m, 2H), 7.15-7.07 (m, 1H), 4.66 (q, *J* = 5.4 Hz, 1H), 3.70-3.55 (m, 2H), 3.51-3.39 (m, 2H), 3.30 (s, 3H), 3.11 (s, 3H), 2.82 (t, *J* = 7.8 Hz, 2H), 1.90 (quint, *J* = 7.8 Hz, 2H), 1.30 (d, *J* = 5.4 Hz, 3H), 1.19 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.3, 131.5, 128.6, 127.8, 125.6, 121.5, 99.6, 86.3, 68.2, 64.8, 60.9, 39.3, 36.8, 31.6, 30.8, 20.2, 15.5; HR-ESIMS calcd for $C_{17}H_{25}NNaO_4S$ $[M+Na]^+$ 362.1397. Found 362.1398.

***N*-Benzyl-*N*-((2-(3-(1-ethoxyethoxy)propyl)phenyl)ethynyl)methanesulfonamide (5d)**

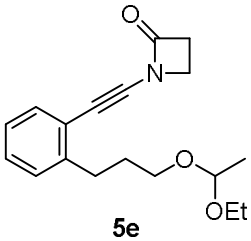


5d

According to **GP-1**, **5d** (418 mg, 67%) was obtained from **S26** (327 mg, 1.50 mmol), *N*-benzylmethanesulfonamide (1.39 g, 7.50 mmol), $CuCl_2$ (40.3 mg, 0.300 mmol), Na_2CO_3 (318 mg, 3.00 mmol), and pyridine (243 μL, 3.00 mmol). Eluent: hexane/EtOAc = 4:1.

Colorless oil; IR ν_{max}: 3010, 2235, 1600, 1362, 1163 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.52-7.46 (m, 2H), 7.44-7.34 (m, 3H), 7.32 (d, *J* = 7.2 Hz, 1H), 7.21 (td, *J* = 6.0, 1.5 Hz, 2H), 7.16-7.08 (m, 1H), 4.73 (s, 2H), 4.65 (q, *J* = 5.4 Hz, 1H), 3.69-3.33 (m, 4H), 2.95 (s, 3H), 2.74 (t, *J* = 7.5 Hz, 2H), 1.89-1.78 (m, 2H), 1.28 (d, *J* = 5.4 Hz, 3H), 1.18 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.5, 134.6, 131.8, 128.9, 128.82, 128.80, 128.7, 128.0, 125.7, 121.8, 99.6, 85.3, 70.2, 64.6, 60.9, 55.8, 38.9, 31.3, 30.5, 19.9, 15.3; HR-ESIMS calcd for $C_{23}H_{29}NNaO_4S$ $[M+Na]^+$ 438.1710. Found 438.1706.

1-((2-(3-(1-Ethoxyethoxy)propyl)phenyl)ethynyl)azetidin-2-one (5e)

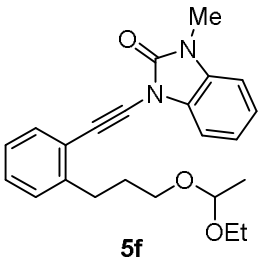


5e

According to **GP-1**, **5e** (809 mg, 80%) was obtained from **S26** (778 mg, 3.36 mmol), azetidin-2-one (1.19 g, 16.8 mmol), $CuCl_2$ (90.2 mg, 0.671 mmol), Na_2CO_3 (711 mg, 6.71 mmol), and pyridine (0.543 mL, 6.71 mmol). Eluent: hexane/EtOAc = 7:3.

Pale yellow oil; IR ν_{max}: 3009, 2241, 1769, 1601 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36 (d, *J* = 7.5 Hz, 1H), 7.21-7.15 (m, 2H), 7.14-7.08 (m, 1H), 4.68 (q, *J* = 5.4 Hz, 1H), 3.70 (t, *J* = 4.8 Hz, 2H), 3.67-3.58 (m, 2H), 3.53-3.41 (m, 2H), 3.09 (t, *J* = 4.8 Hz, 2H), 2.82 (t, *J* = 7.8 Hz, 2H), 1.92 (quint, *J* = 7.5 Hz, 2H), 1.31 (d, *J* = 5.4 Hz, 3H), 1.18 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.1, 143.4, 131.8, 128.5, 127.9, 125.6, 121.4, 99.6, 82.1, 68.5, 64.8, 60.9, 43.2, 38.1, 31.4, 30.6, 20.1, 15.5; HR-ESIMS calcd for $C_{18}H_{23}NNaO_3$ $[M+Na]^+$ 324.1570. Found 324.1567.

1-((2-(3-(1-Ethoxyethoxy)propyl)phenyl)ethynyl)-3-methyl-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one (5f)

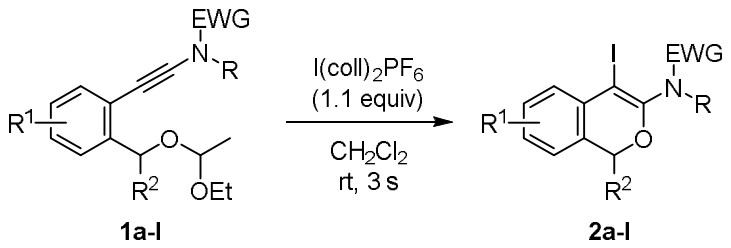


5f

According to **GP-1**, **5f** (178 mg, 31%) was obtained from **S26** (327 mg, 1.50 mmol), 1-methyl-2-benzimidazolinone (1.11 g, 7.50 mmol), $CuCl_2$ (40.3 mg, 0.300 mmol), Na_2CO_3 (318 mg, 3.00 mmol), and pyridine (242 μL, 3.00 mmol). Eluent: hexane/EtOAc = 7:3.

Colorless oil; IR ν_{max}: 3011, 2257, 1733, 1621, 1601 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.5 Hz, 1H), 7.29-7.22 (m, 3H), 7.21-7.14 (m, 3H), 6.97 (dd, *J* = 6.9, 2.1 Hz, 1H), 4.67 (q, *J* = 5.4 Hz, 1H), 3.68-3.57 (m, 2H), 3.52-3.40 (m, 5H), 2.97 (t, *J* = 7.8 Hz, 2H), 2.06-1.96 (m, 2H), 1.29 (d, *J* = 5.4 Hz, 3H), 1.16 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.8, 143.5, 132.2, 129.5, 128.6, 128.2, 127.9, 125.6, 123.3, 122.0, 121.3, 109.6, 107.8, 99.5, 78.8, 73.8, 64.7, 60.9, 31.6, 30.7, 27.7, 20.1, 15.5; HR-ESIMS calcd for $C_{23}H_{26}N_2NaO_3$ $[M+Na]^+$ 401.1836. Found 401.1828.

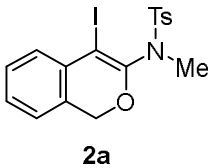
General Procedure for 6-*endo-dig* Iodocylization of 1 (Table 1, GP-2)



1a-l **2a-l**

Three seconds were precisely counted by stopwatch just after $I(coll)_2PF_6$ (1.1 equiv) added in one portion to a stirred solution of **1** (1 equiv) in CH_2Cl_2 (0.1 M) at rt, and after 3 seconds the reaction mixture was immediately quenched with a saturated aqueous solution of $Na_2S_2O_3$, and was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel to give **2**.

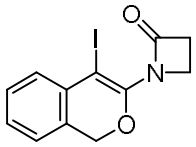
***N*-(4-Iodo-1*H*-isochromen-3-yl)-*N*,4-dimethylbenzenesulfonamide (2a)**



2a

According to **GP-2**, **2a** (88.0 mg, quant.) was obtained from **1a** (77.5 mg, 0.200 mmol) and $I(coll)_2PF_6$ (113 mg, 0.220 mmol). Eluent: hexane/EtOAc = 6:1.
Colorless crystals; mp 162-164 ºC (hexane/EtOAc); IR ν_{max}: 3030, 1611, 1355, 1157 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.4 Hz, 2H), 7.38-7.29 (m, 4H), 7.24 (td, *J* = 7.2, 1.8 Hz, 1H), 7.00 (d, *J* = 7.2 Hz, 1H), 5.16 (s, 2H), 3.05 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.1, 144.0, 135.6, 133.2, 129.5, 128.9, 128.6, 128.4, 128.3, 128.1, 123.4, 73.9, 70.1, 36.5, 21.6; HR-ESIMS calcd for $C_{17}H_{16}INNaO_3S$ $[M+Na]^+$ 463.9788. Found 463.9791.

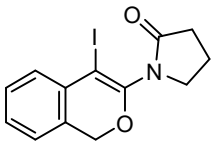
1-(4-Iodo-1*H*-isochromen-3-yl)azetidin-2-one (2b)



2b

According to **GP-2**, **2b** (65.1 mg, 98%) was obtained from **1b** (55.0 mg, 0.200 mmol) and $I(coll)_2PF_6$ (113 mg, 0.220 mmol). Eluent: hexane/EtOAc = 2:1.
Yellow oil; IR ν_{max}: 3013, 1769, 1607 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34-7.26 (m, 2H), 7.18 (td, *J* = 6.9, 2.4 Hz, 1H), 6.96 (d, *J* = 7.8 Hz, 1H), 5.10 (s, 2H), 3.80 (t, *J* = 4.8 Hz, 2H), 3.06 (t, *J* = 4.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.3, 133.4, 128.6, 128.3, 127.9, 127.3 (2C), 123.4, 69.8, 62.0, 41.3, 37.1; HR-ESIMS calcd for $C_{12}H_{10}INNaO_2$ $[M+Na]^+$ 349.9648. Found 349.9646.

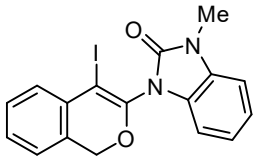
1-(4-Iodo-1*H*-isochromen-3-yl)pyrrolidin-2-one (2c)



2c

According to **GP-2**, **2c** (47.8 mg, 87%) was obtained from **1c** (46.0 mg, 0.200 mmol) and $I(coll)_2PF_6$ (90.3 mg, 0.220 mmol). Eluent: hexane/EtOAc = 3:2.
Colorless oil; IR ν_{max}: 3011, 1714, 1616, 1571 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34-7.25 (m, 2H), 7.19 (td, *J* = 6.9, 2.1 Hz, 1H), 6.96 (d, *J* = 7.2 Hz, 1H), 5.17 (s, 2H), 3.76 (t, *J* = 7.2 Hz, 2H), 2.49 (t, *J* = 8.1 Hz, 2H), 2.17 (quint, *J* = 7.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8, 132.9, 128.5 (2C), 128.4, 128.3, 127.8, 123.3, 71.4, 70.0, 47.9, 31.2, 19.2; HR-ESIMS calcd for $C_{13}H_{12}INNaO_2$ $[M+Na]^+$ 363.9805. Found 363.9801.

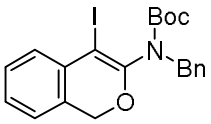
1-(4-Iodo-1*H*-isochromen-3-yl)-3-methyl-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one (2d)



2d

According to **GP-2**, **2d** (79.8 mg, 98%) was obtained from **1d** (70.1 mg, 0.200 mmol) and $I(coll)_2PF_6$ (113 mg, 0.220 mmol). Eluent: hexane/EtOAc = 3:1.
Colorless crystals; mp 180-183 ºC (hexane/EtOAc); IR ν_{max}: 3011, 1724, 1618 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.43-7.22 (m, 3H), 7.18-6.96 (m, 5H), 5.40 (d, *J* = 12.6 Hz, 1H), 5.28 (d, *J* = 12.6 Hz, 1H), 3.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.9, 144.6, 132.7, 130.1, 128.8, 128.62, 128.57, 128.5, 127.2, 123.6, 122.5, 121.5, 109.9, 107.8, 74.1, 70.4, 27.4; HR-ESIMS calcd for $C_{17}H_{13}IN_2NaO_2$ $[M+Na]^+$ 426.9914. Found 426.9906.

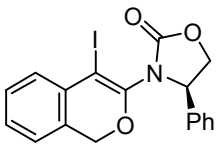
***tert*-Butyl benzyl(4-iodo-1*H*-isochromen-3-yl)carbamate (2e)**



2e

According to **GP-2**, **2e** (170 mg, 80%) was obtained from **1e** (188 mg, 0.458 mmol) and $I(coll)_2PF_6$ (259 mg, 0.504 mmol). Eluent: hexane/EtOAc = 9:1.
Pale yellow oil; IR ν_{max}: 3027, 1708, 1615, 1572 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.39 (d, *J* = 7.2 Hz, 2H), 7.31-7.21 (m, 5H), 7.19-7.15 (m, 1H), 6.93 (d, *J* = 7.2 Hz, 1H), 5.03 (br d, *J* = 8.4 Hz, 1H), 4.85-4.70 (br m, 2H), 4.63 (br d, *J* = 14.4 Hz, 1H), 1.47 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.1, 151.4, 136.8, 133.7, 128.8, 128.7, 128.4, 128.24, 128.19, 127.6, 127.4, 123.3, 81.6, 72.9, 69.7, 53.4, 51.8, 28.2; HR-ESIMS calcd for $C_{21}H_{22}INNaO_3$ $[M+Na]^+$ 486.0537. Found 486.0532.

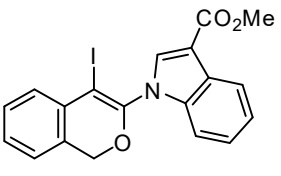
(*R*)-3-(4-Iodo-1*H*-isochromen-3-yl)-4-phenyloxazolidin-2-one (2f)



2f

According to **GP-2** except for reaction time (1 min), **2f** (50.0 mg, 85%) was obtained from **1f** (51.0 mg, 0.140 mmol) and $I(coll)_2PF_6$ (79.0 mg, 0.154 mmol). Eluent: hexane/EtOAc = 3:1.
Colorless amorphous solid; $[\alpha]_D^{26}$ -84.6 (*c* 1.03, $CHCl_3$); IR ν_{max}: 3027, 1774, 1621, 1572 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.2 Hz, 2H), 7.41 (t, *J* = 7.2 Hz, 2H), 7.36 (t, *J* = 7.2 Hz, 1H), 7.29 (d, *J* = 7.8 Hz, 1H), 7.25 (t, *J* = 7.8 Hz, 1H), 7.14 (t, *J* = 7.2 Hz, 1H), 6.85 (d, *J* = 7.8 Hz, 1H), 5.41 (t, *J* = 9.0 Hz, 1H), 4.89 (d, *J* = 12.6 Hz, 1H), 4.72 (t, *J* = 8.4 Hz, 1H), 4.39 (br s, 1H), 4.28 (t, *J* = 9.6 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 152.7, 145.7, 135.5, 133.0, 129.3, 129.0, 128.7, 128.60, 128.56, 127.81, 127.76, 123.3, 71.7, 70.4, 69.5, 61.2; HR-ESIMS calcd for $C_{18}H_{14}INNaO_3$ $[M+Na]^+$ 441.9911. Found 441.9904.

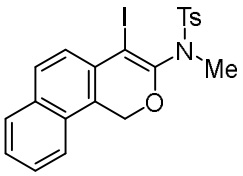
Methyl 1-(4-iodo-1*H*-isochromen-3-yl)-1*H*-indole-3-carboxylate (2g)



2g

According to **GP-2** except for reaction time (1 min), **2g** (80.8 mg, 94%) was obtained from **1g** (75.0 mg, 0.200 mmol) and $I(coll)_2PF_6$ (113 mg, 0.220 mmol). Eluent: hexane/EtOAc = 9:1.
Colorless amorphous solid; IR ν_{max}: 3012, 1708, 1618 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.23-8.16 (m, 1H), 8.01 (s, 1H), 7.46-7.26 (m, 6H), 7.06 (d, *J* = 7.5 Hz, 1H), 5.36 (s, 2H), 3.92 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.5, 147.0, 136.0, 134.6, 132.8, 128.9, 128.8, 128.3, 128.1, 126.1, 123.7, 123.6, 122.9, 121.7, 112.0, 110.1, 70.4, 68.6, 51.4; HR-ESIMS calcd for $C_{19}H_{14}INNaO_3$ $[M+Na]^+$ 453.9911. Found 453.9909.

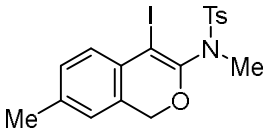
***N*-(4-Iodo-1*H*-benzo[*h*]isochromen-3-yl)-*N*,4-dimethylbenzenesulfonamide (2h)**



2h

According to **GP-2**, **2h** (98.0 mg, quant.) was obtained from **1h** (88.0 mg, 0.200 mmol) and $I(coll)_2PF_6$ (113 mg, 0.220 mmol). Eluent: hexane/EtOAc = 5:1.
Colorless amorphous solid; IR ν_{max}: 3031, 1610, 1355, 1157 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.90-7.75 (m, 5H), 7.57-7.42 (m, 3H), 7.32 (d, *J* = 7.8 Hz, 2H), 5.64 (s, 2H), 3.09 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.1, 143.9, 135.7, 133.3, 130.6, 129.4, 128.7, 128.4, 128.3, 127.9, 127.1, 127.0, 125.8, 122.9, 122.2, 73.7, 66.8, 36.7, 21.7; HR-ESIMS calcd for $C_{21}H_{18}INNaO_3S$ $[M+Na]^+$ 513.9944. Found 513.9947.

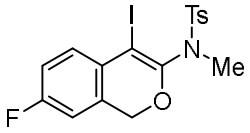
***N*-(4-Iodo-7-methyl-1*H*-isochromen-3-yl)-*N*,4-dimethylbenzenesulfonamide (2i)**



2i

According to **GP-2**, **2i** (82.2 mg, 90%) was obtained from **1i** (80.3 mg, 0.200 mmol) and $I(coll)_2PF_6$ (113 mg, 0.220 mmol). Eluent: hexane/EtOAc = 5:1.
Colorless crystals; mp 157-159 ºC (hexane/EtOAc); IR ν_{max}: 3030, 1613, 1354, 1159 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 8.1 Hz, 2H), 7.20 (d, *J* = 7.8 Hz, 1H), 7.08 (br d, *J* = 7.8 Hz, 1H), 6.78 (br s, 1H), 5.10 (s, 2H), 3.02 (s, 3H), 2.43 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.0, 143.7, 138.1, 135.4, 130.4, 129.3, 128.9, 128.7, 128.2, 128.1, 123.9, 74.2, 70.1, 36.6, 21.8, 21.3; HR-ESIMS calcd for $C_{18}H_{18}INNaO_3S$ $[M+Na]^+$ 477.9944. Found 477.9948

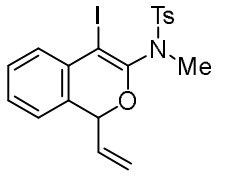
***N*-(7-Fluoro-4-iodo-1*H*-isochromen-3-yl)-*N*,4-dimethylbenzenesulfonamide (2j)**



2j

According to **GP-2**, **2j** (88.0 mg, 96%) was obtained from **1j** (81.1 mg, 0.200 mmol) and $I(coll)_2PF_6$ (113 mg, 0.220 mmol). Eluent: hexane/EtOAc = 6:1.
Colorless amorphous solid; IR ν_{max}: 3031, 1615, 1355, 1158 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.4 Hz, 2H), 7.35-7.29 (m, 3H), 6.97 (td, *J* = 8.7, 2.7 Hz, 1H), 6.73 (dd, *J* = 8.1, 2.7 Hz, 1H), 5.11 (s, 2H), 3.03 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.2 (d, *J* = 246.5 Hz), 150.4, 143.8, 135.3, 130.6 (d, *J* = 8.6 Hz), 130.0 (d, *J* = 7.4 Hz), 129.3, 128.1, 115.0 (d, *J* = 21.7 Hz), 110.6 (d, *J* = 22.8 Hz), 72.8, 69.52, 69.53, 36.6, 21.8; HR-ESIMS calcd for $C_{17}H_{15}FINNaO_3S$ $[M+Na]^+$ 481.9694. Found 481.9698.

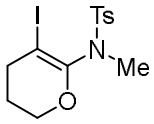
***N*-(4-Iodo-1-vinyl-1*H*-isochromen-3-yl)-*N*,4-dimethylbenzenesulfonamide (2k)**



2k

According to **GP-2**, **2k** (88.4 mg, 75%) was obtained from **1k** (104 mg, 0.251 mmol) and $I(coll)_2PF_6$ (141 mg, 0.276 mmol). Eluent: hexane/EtOAc = 6:1.
Colorless crystals; mp 63-65 °C (hexane/EtOAc); IR ν_{max}: 3031, 1616, 1600, 1356, 1157 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.1 Hz, 2H), 7.38 (d, *J* = 7.5 Hz, 1H), 7.34-7.19 (m, 4H), 6.94 (d, *J* = 7.5 Hz, 1H), 6.28-6.12 (m, 1H), 5.61 (d, *J* = 7.2 Hz, 1H), 5.43 (d, *J* = 10.2 Hz, 1H), 5.30 (d, *J* = 17.1 Hz, 1H), 3.02 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.3, 143.6, 135.4, 133.7, 132.5, 130.0, 129.2, 128.5, 128.2, 128.1, 123.7, 120.2, 80.9, 73.9, 70.6, 36.4, 21.8; HR-ESIMS calcd for $C_{19}H_{18}INNaO_3S$ $[M+Na]^+$ 489.9944. Found 489.9945.

***N*-(5-Iodo-3,4-dihydro-2*H*-pyran-6-yl)-*N*,4-dimethylbenzenesulfonamide (2l) (Scheme 2a)**

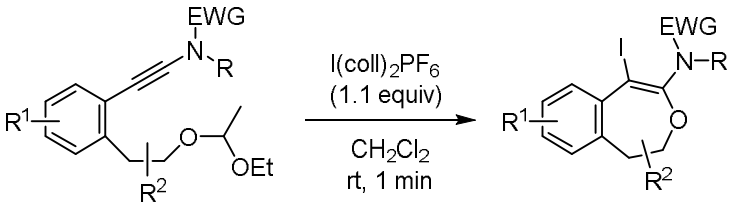


2l

According to **GP-2**, **2l** (80.8 mg, 95%) was obtained from **1l** (73.2 mg, 0.216 mmol) and $I(coll)_2PF_6$ (122 mg, 0.237 mmol). Eluent: hexane/EtOAc = 4:1.

Colorless amorphous solid; IR ν_{max}: 3029, 1654, 1599, 1352, 1157 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.1 Hz, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 4.13 (t, *J* = 5.1 Hz, 2H), 2.90 (s, 3H), 2.61 (t, *J* = 6.3 Hz, 2H), 2.42 (s, 3H), 1.88 (quint, *J* = 5.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.3, 143.6, 135.9, 129.3, 128.3, 70.3, 67.4, 35.4, 34.7, 24.8, 21.6; HR-ESIMS calcd for $C_{13}H_{16}INNaO_3S$ $[M+Na]^+$ 415.9788. Found 415.9787.

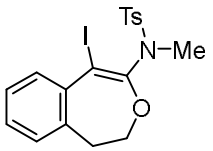
General Procedure for 7-*endo-dig* Iodocylization of 3 (Table 2, GP-3)



3a-o **4a-o**

One minute was precisely counted by stopwatch just after $I(coll)_2PF_6$ (1.1 equiv) added in one portion to a stirred solution of **3** (1 equiv) in CH_2Cl_2 (0.1 M) at rt, and after 1 min the reaction mixture was quenched with a saturated aqueous solution of $Na_2S_2O_3$, and was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel to give **4**.

***N*-(1-Iodo-4,5-dihydrobenzo[*d*]oxepin-2-yl)-*N*,4-dimethylbenzenesulfonamide (4a)**

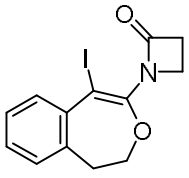


4a

According to **GP-3**, **4a** (85.8 mg, 94%) was obtained from **3a** (80.2 mg, 0.200 mmol) and $I(coll)_2PF_6$ (113 mg, 0.220 mmol). Eluent: hexane/EtOAc = 4:1.

Colorless crystals; mp 162-164 ºC (hexane/EtOAc); IR ν_{max}: 3030, 1599, 1348, 1153 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.4 Hz, 2H), 7.55 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.35-7.22 (m, 3H), 7.18 (td, *J* = 7.2, 1.2 Hz, 1H), 7.10 (dd, *J* = 7.5, 1.5 Hz, 1H), 4.62 (t, *J* = 5.7 Hz, 2H), 3.07 (t, *J* = 5.7 Hz, 2H), 3.01 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.5, 143.7, 139.1, 137.0, 135.7, 132.3, 129.3, 128.2, 128.1, 127.7, 126.7, 83.9, 81.1, 36.1, 33.9, 21.6; HR-ESIMS calcd for $C_{18}H_{18}INNaO_3S$ $[M+Na]^+$ 477.9944. Found 477.9934.

1-(1-Iodo-4,5-dihydrobenzo[*d*]oxepin-2-yl)azetidin-2-one (4b)

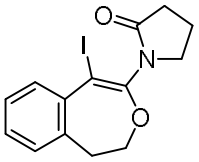


4b

According to **GP-3**, **4b** (61.6 mg, 90%) was obtained from **3b** (57.5 mg, 0.200 mmol) and $I(coll)_2PF_6$ (113 mg, 0.220 mmol). Eluent: hexane/EtOAc = 2:1.

Colorless oil; IR ν_{max}: 3013, 1760, 1614 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.0 Hz, 1H), 7.31 (t, *J* = 8.0 Hz, 1H), 7.19 (t, *J* = 7.5 Hz, 1H), 7.13 (d, *J* = 7.5 Hz, 1H), 4.62 (t, *J* = 6.0 Hz, 2H), 3.80-3.77 (m, 2H), 3.06-3.02 (m, 2H), 2.96 (t, *J* = 6.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.8, 144.0, 139.7, 136.7, 131.9, 128.0, 127.9, 127.0, 80.1, 72.8, 41.3, 36.8, 33.9; HR-ESIMS calcd for $C_{13}H_{12}INNaO_2$ $[M+Na]^+$ 363.9805. Found 363.9803.

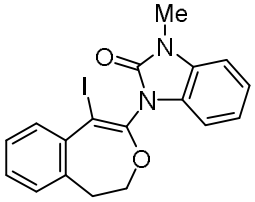
1-(1-Iodo-4,5-dihydrobenzo[*d*]oxepin-2-yl)pyrrolidin-2-one (4c)


4c

According to **GP-3**, **4c** (53.6 mg, 76%) was obtained from **3c** (72.9 mg, 0.200 mmol) and $I(coll)_2PF_6$ (113 mg, 0.220 mmol). Eluent: hexane/EtOAc = 3:1.

Pale yellow crystals; mp 110-112 ºC (hexane/EtOAc); IR ν_{max}: 3011, 1701, 1601 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.55 (dd, *J* = 7.5, 1.2 Hz, 1H), 7.28 (td, *J* = 7.5, 1.5 Hz, 1H), 7.21-7.09 (m, 2H), 4.58 (t, *J* = 6.0 Hz, 2H), 3.72 (t, *J* = 6.9 Hz, 2H), 3.07 (t, *J* = 6.0 Hz, 2H), 2.46 (t, *J* = 8.1 Hz, 2H), 2.16 (quint, *J* = 7.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2, 145.5, 139.1, 137.1, 131.9, 128.1, 127.9, 126.8, 82.7, 81.3, 47.1, 34.4, 31.0, 19.1; HR-ESIMS calcd for $C_{14}H_{14}INNaO_2$ $[M+Na]^+$ 377.9961. Found 377.9959.

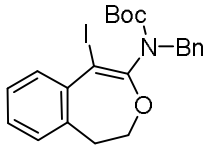
1-(1-Iodo-4,5-dihydrobenzo[*d*]oxepin-2-yl)-3-methyl-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one (4d)


4d

According to **GP-3**, **4d** (62.3 mg, 75%) was obtained from **3d** (72.9 mg, 0.200 mmol) and $I(coll)_2PF_6$ (113 mg, 0.220 mmol). Eluent: hexane/EtOAc = 4:1.

Colorless crystals; mp 203-204 ºC (hexane/EtOAc); IR ν_{max}: 3011, 1708, 1618 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.64 (d, *J* = 7.5 Hz, 1H), 7.34 (td, *J* = 7.2, 1.5 Hz, 1H), 7.29-6.94 (m, 6H), 4.95-4.83 (m, 1H), 4.62-4.48 (m, 1H), 3.60-3.40 (m, 1H), 3.45 (s, 3H), 2.95-2.80 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.4, 142.3, 139.1, 137.1, 132.1, 130.1, 128.6, 128.1, 127.3, 127.0, 122.2, 121.6, 109.7, 107.8, 85.7, 82.0, 34.4, 27.4; HR-ESIMS calcd for $C_{18}H_{15}IN_2NaO_2$ $[M+Na]^+$ 441.0070. Found 441.0062.

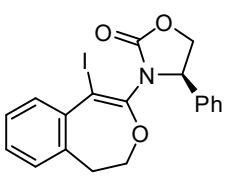
***tert*-Butyl benzyl(1-iodo-4,5-dihydrobenzo[*d*]oxepin-2-yl)carbamate (4e)**


4e

According to **GP-3**, **4e** (1.28 g, 97%) was obtained from **3e** (1.17 g, 2.75 mmol) and $I(coll)_2PF_6$ (1.56 g, 3.03 mmol). Eluent: hexane/EtOAc = 15:1.

Colorless amorphous solid; IR ν_{max}: 3011, 1702, 1618 cm^{-1}; The ^1H and ^{13}C NMR spectra of **4e** showed the presence of two rotamers (3:1); ^1H NMR (600 MHz, $CDCl_3$) δ 7.49 (br s, 1H), 7.40 (d, *J* = 7.2 Hz, 2H), 7.30 (t, *J* = 7.2 Hz, 2H), 7.29-7.23 (m, 2H), 7.16 (td, *J* = 7.2, 1.2 Hz, 1H), 7.08 (d, *J* = 7.2 Hz, 1H), 4.74 (d, *J* = 14.4 Hz, 1H), 4.65-4.43 (br m, 2H), 4.31 (br s, 1H), 3.34 (br s, 0.25H), 3.18 (br s, 0.75H), 2.62 (br d, *J* = 13.2 Hz, 1H), 1.56 (br s, 6.75H), 1.45 (br s, 2.25H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.3, 148.8, 139.9, 137.2, 136.6, 131.9, 129.0, 128.1, 128.0, 127.8, 127.3, 126.8, 83.4, 81.4, 80.5, 51.3, 33.7, 28.5; HR-ESIMS calcd for $C_{22}H_{24}INNaO_3$ $[M+Na]^+$ 500.0693. Found 500.0692.

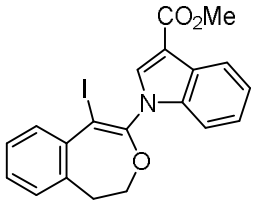
(*R*)-3-(1-Iodo-4,5-dihydrobenzo[*d*]oxepin-2-yl)-4-phenyloxazolidin-2-one (4f)


4f

According to **GP-3** except for the equivalents of $I(coll)_2PF_6$ (1.5 equiv), **4f** (40.6 mg, 63%) was obtained from **3f** (56.9 mg, 0.150 mmol) and $I(coll)_2PF_6$ (115 mg, 0.225 mmol). Eluent: hexane/EtOAc = 3:1.

Colorless amorphous solid; $[\alpha]_D^{27}$ -49.9 (*c* 0.700, $CHCl_3$); IR ν_{max}: 3029, 1765, 1602 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.0 Hz, 2H), 7.49 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.44-7.36 (m, 3H), 7.25 (td, *J* = 8.0, 1.5 Hz, 1H), 7.13 (td, *J* = 7.5, 1.0 Hz, 1H), 7.02 (dd, *J* = 7.5, 1.0 Hz, 1H), 5.36 (t, *J* = 9.0 Hz, 1H), 4.72 (t, *J* = 8.5 Hz, 1H), 4.43-4.30 (m, 2H), 4.27 (t, *J* = 8.5 Hz, 1H), 2.74-2.58 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.4, 143.5, 139.3, 136.5, 136.3, 132.2, 129.3, 129.1, 128.2, 127.8, 127.7, 126.9, 82.6, 81.2, 70.4, 60.6, 33.6; HR-ESIMS calcd for $C_{19}H_{16}INNaO_3$ $[M+Na]^+$ 456.0067. Found 456.0054.

Methyl 1-(1-iodo-4,5-dihydrobenzo[*d*]oxepin-2-yl)-1*H*-indole-3-carboxylate (4g)

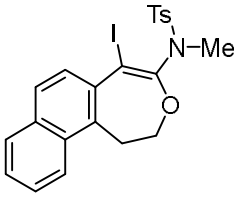


4g

According to **GP-3** except for the equivalents of $I(coll)_2PF_6$ (1.5 equiv) and reaction time (10 min), **4g** (78.2 mg, 88%) was obtained from **3g** (78.2 mg, 0.200 mmol) and $I(coll)_2PF_6$ (154 mg, 0.300 mmol). Eluent: hexane/EtOAc = 7:1.

Colorless crystals; mp 147-149 ºC (hexane/EtOAc); IR ν_{max}: 3012, 1705, 1620 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.24-8.16 (m, 1H), 8.03 (s, 1H), 7.70 (d, *J* = 7.8 Hz, 1H), 7.50-7.16 (m, 6H), 4.62 (t, *J* = 6.0 Hz, 2H), 3.93 (s, 3H), 3.16 (t, *J* = 6.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.9, 145.1, 138.6, 136.5, 135.6, 134.2, 132.7, 128.6, 128.2, 127.3, 126.1, 123.7, 122.7, 121.8, 111.9, 109.8, 81.4, 80.8, 51.3, 34.5; HR-ESIMS calcd for $C_{20}H_{16}INNaO_3$ $[M+Na]^+$ 468.0067. Found 468.0060.

***N*-(5-Iodo-1,2-dihydronaphtho[1,2-*d*]oxepin-4-yl)-*N*,4-dimethylbenzenesulfonamide (4h)**

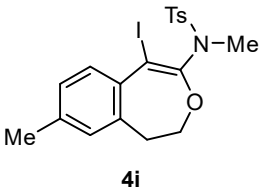


4h

According to **GP-3**, **4h** (100 mg, 99%) was obtained from **3h** (90.3 mg, 0.200 mmol) and $I(coll)_2PF_6$ (113 mg, 0.220 mmol). Eluent: hexane/EtOAc = 4:1.

Colorless amorphous solid; IR ν_{max}: 2929, 1599, 1349, 1154 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.1 Hz, 1H), 7.90 (d, *J* = 8.4 Hz, 2H), 7.86-7.78 (m, 1H), 7.76-7.70 (m, 1H), 7.61 (d, *J* = 8.7 Hz, 1H), 7.56-7.44 (m, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 4.81 (t, *J* = 5.7 Hz, 2H), 3.56 (t, *J* = 5.7 Hz, 2H), 3.04 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.1, 143.8, 136.7, 135.8, 133.5, 133.1, 130.1, 129.4, 128.9, 128.8, 128.2, 126.8, 126.7, 126.3, 123.1 84.1, 82.9, 36.3, 27.6, 21.7; HR-ESIMS calcd for $C_{22}H_{20}INNaO_3S$ $[M+Na]^+$ 528.0101. Found 528.0103.

***N*-(1-Iodo-7-methyl-4,5-dihydrobenzo[*d*]oxepin-2-yl)-*N*,4-dimethylbenzenesulfonamide (4i)**

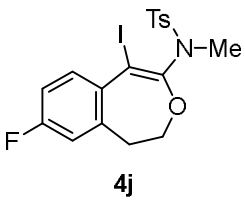


4i

According to **GP-3**, **4i** (90.3 mg, 86%) was obtained from **3i** (93.5 mg, 0.225 mmol) and $I(coll)_2PF_6$ (127 mg, 0.248 mmol). Eluent: hexane/EtOAc = 8:1.

Colorless crystals; mp 191-192 ºC (hexane/EtOAc); IR ν_{max}: 3030, 1610, 1349, 1154 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.4 Hz, 2H), 7.46 (d, *J* = 8.1 Hz, 1H), 7.32 (d, *J* = 8.4 Hz, 2H), 7.09 (dd, *J* = 8.1, 1.2 Hz, 1H), 6.93 (br s, 1H), 4.61 (t, *J* = 6.0 Hz, 2H), 3.03 (t, *J* = 6.0 Hz, 2H), 3.01 (s, 3H), 2.43 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.2, 143.8, 138.4, 137.0, 136.3, 135.8, 132.4, 129.5, 128.4, 128.2, 127.6, 84.3, 81.1, 36.0, 33.8, 21.6, 21.1; HR-ESIMS calcd for $C_{19}H_{20}INNaO_3S$ $[M+Na]^+$ 492.0101. Found 492.0104.

***N*-(7-Fluoro-1-iodo-4,5-dihydrobenzo[*d*]oxepin-2-yl)-*N*,4-dimethylbenzenesulfonamide (4j)**

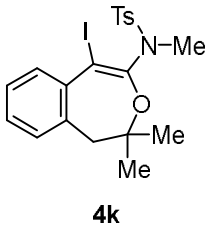


4j

According to **GP-3**, **4j** (124 mg, quant.) was obtained from **3j** (110 mg, 0.263 mmol) and $I(coll)_2PF_6$ (148 mg, 0.289 mmol). Eluent: hexane/EtOAc = 5:1.

Colorless crystals; mp 143-145 ºC (hexane/EtOAc); IR ν_{max}: 3030, 1601, 1349, 1152 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.1 Hz, 2H), 7.54 (dd, *J* = 8.7, 5.4 Hz, 1H), 7.31 (d, *J* = 8.1 Hz, 1H), 6.97 (td, *J* = 8.7, 2.4 Hz, 1H), 6.84 (dd, *J* = 8.7, 2.4 Hz, 1H), 4.62 (t, *J* = 5.7 Hz, 2H), 3.05 (t, *J* = 5.7 Hz, 2H), 3.00 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.6 (d, *J* = 247.0 Hz), 148.3, 143.8, 139.1 (d, *J* = 8.0 Hz), 135.5, 135.2 (d, *J* = 2.9 Hz), 134.2 (d, *J* = 8.6 Hz), 129.3, 128.1, 114.3 (d, *J* = 21.7 Hz), 113.7 (d, *J* = 21.7 Hz), 83.0, 80.8, 36.2, 34.0, 21.8; HR-ESIMS calcd for $C_{18}H_{17}FINNaO_3S$ $[M+Na]^+$ 495.9850. Found 495.9851.

***N*-(1-Iodo-4,4-dimethyl-4,5-dihydrobenzo[*d*]oxepin-2-yl)-*N*,4-dimethylbenzenesulfonamide (4k)**

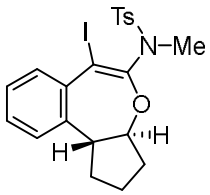


4k

According to **GP-3** except for reaction time (5 h), **4k** (110 mg, 87%) was obtained from **3k** (112 mg, 0.261 mmol) and $I(coll)_2PF_6$ (147 mg, 0.287 mmol). Eluent: hexane/acetone = 9:1.

Colorless needle crystals; mp 154-156 ºC (hexane/EtOAc); IR ν_{max}: 2981, 1599, 1353, 1153 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.0 Hz, 2H), 7.68 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.32-7.27 (m, 3H), 7.17 (td, *J* = 7.5, 1.5 Hz, 1H), 7.02 (dd, *J* = 7.5, 1.0 Hz, 1H), 3.08 (s, 3H), 2.78 (s, 2H), 2.43 (s, 3H), 1.12 (br s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.0, 143.5, 138.7, 136.1, 135.1, 133.1, 129.1, 129.0, 128.6, 127.7, 126.9, 94.8, 84.1, 45.1, 36.4, 28.1, 21.6; HR-ESIMS calcd for $C_{20}H_{22}INNaO_3S$ $[M+Na]^+$ 506.0257. Found 506.0260.

***N*-((3a*R**,10b*S**)-6-Iodo-2,3,3a,10b-tetrahydro-1*H*-benzo[*d*]cyclopenta[*b*]oxepin-5-yl)-*N*,4-dimethylbenzenesulfonamide (4l)**

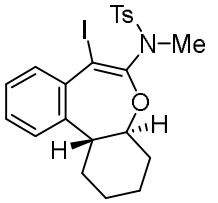


4l

According to **GP-3**, **4l** (101 mg, 82%) was obtained from **3l** (113 mg, 0.248 mmol) and $I(coll)_2PF_6$ (140 mg, 0.272 mmol). Eluent: hexane/EtOAc = 4:1.

Pale yellow crystals; mp 172-173 ºC (hexane/EtOAc); IR ν_{max}: 2966, 1598, 1350, 1158 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.00-7.65 (br m, 3H), 7.34-7.06 (m, 4H), 6.97 (d, *J* = 7.2 Hz, 1H), 4.20-4.10 (br m, 1H), 3.44 (br s, 1H), 3.01 (s, 3H), 2.42 (s, 3H), 2.21 (br s, 1H), 2.10-1.71 (br m, 3H), 1.70-1.40 (br m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.3, 143.3, 140.1, 137.0, 136.4, 135.9, 128.9, 128.1, 127.0, 126.0, 122.4, 90.4, 79.4, 50.1, 36.2, 32.7, 28.4, 24.4, 21.7; HR-ESIMS calcd for $C_{21}H_{22}INNaO_3S$ $[M+Na]^+$ 518.0257. Found 518.0260.

***N*-((4a*R**,11b*S**)-7-Iodo-1,2,3,4,4a,11b-hexahydrodibenzo[*b*,*d*]oxepin-6-yl)-*N*,4-dimethylbenzenesulfonamide (4m)**

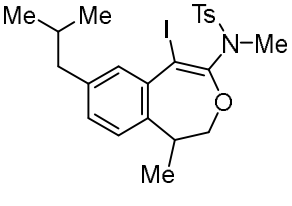


4m

According to **GP-3**, **4m** (86.7 mg, 88%) was obtained from **3m** (88.4 mg, 0.194 mmol) and $I(coll)_2PF_6$ (110 mg, 0.213 mmol). Eluent: hexane/EtOAc = 5:1.

Colorless crystals; mp 164-165 ºC (hexane/EtOAc); IR ν_{max}: 2941, 1600, 1352, 1153 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.82 (br d, *J* = 5.4 Hz, 2H), 7.63 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.32-7.20 (m, 4H), 7.12 (d, *J* = 7.2 Hz, 1H), 4.30-4.18 (br m, 1H), 3.04 (s, 3H), 2.71 (br s, 1H), 2.40 (s, 3H), 2.14-2.03 (br m, 1H), 1.87-1.54 (m, 5H), 1.37-1.13 (br m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.6, 143.3, 139.2, 139.0, 135.6, 131.9, 128.9, 128.2, 128.0, 126.3, 123.5, 97.2, 85.0, 43.7, 35.9, 35.1, 28.7, 25.4, 25.0, 21.7; HR-ESIMS calcd for $C_{22}H_{24}INNaO_3S$ $[M+Na]^+$ 532.0414. Found 532.0423.

***N*-(1-Iodo-8-isobutyl-5-methyl-4,5-dihydrobenzo[*d*]oxepin-2-yl)-*N*,4-dimethylbenzenesulfonamide (4n)**



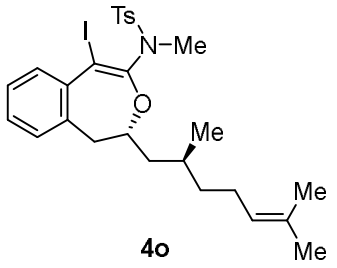
4n

According to **GP-3**, **4n** (104 mg, 99%) was obtained from **3n** (94.3 mg, 0.200 mmol) and $I(coll)_2PF_6$ (113 mg, 0.220 mmol). Eluent: hexane/EtOAc = 9:1.

Colorless needle crystals; mp 157-159 ºC (hexane/EtOAc); IR ν_{max}: 2958, 1617, 1600, 1349, 1154 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 1.5 Hz, 1H), 7.30 (d, *J* = 8.4 Hz, 2H), 7.07 (d, *J* = 7.8 Hz, 1H), 7.01 (dd, *J* = 7.8, 1.5 Hz, 1H), 4.65 (dd, *J* = 9.6, 5.4 Hz, 1H), 4.02 (dd, *J* = 11.4, 9.6 Hz, 1H), 3.58-3.45 (m, 1H), 3.01 (s, 3H), 2.46 (dd, *J* = 7.2, 1.5 Hz, 2H), 2.43 (s, 3H), 1.95-1.76 (m, 1H), 1.30 (d, *J* = 6.9 Hz, 3H), 0.92

(d, J = 6.6 Hz, 3H), 0.91 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.5, 143.6, 139.7, 138.6, 137.2, 135.6, 132.7, 129.3, 129.0, 128.0, 123.5, 86.3, 84.2, 45.0, 36.3, 34.6, 30.2, 22.7 (CH_3 of *i*Bu), 22.4 (CH_3 of *i*Bu), 21.8, 13.2; HR-ESIMS calcd for $C_{23}H_{28}INNaO_3S$ $[M+Na]^+$ 548.0727. Found 548.0711.

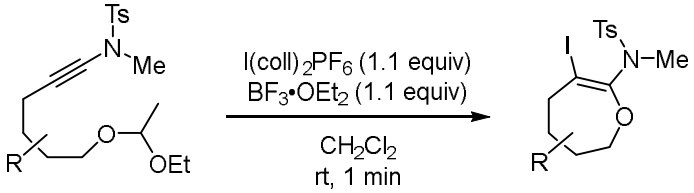
_N_-((_R_)-4-((_S_)-2,6-Dimethylhept-5-en-1-yl)-1-iodo-4,5-dihydrobenzo[_d_]oxepin-2-yl)-_N_,4-dimethylbenzenesulfonamide (4o)



4o

According to **GP-3**, **4o** (107 mg, 93%) was obtained from **3o** (105 mg, 0.200 mmol) and $I(coll)_2PF_6$ (113 mg, 0.220 mmol). Eluent: hexane/EtOAc = 10:1.
Colorless oil; $[\alpha]_D^{25}$ -32.0 (*c* 1.80, $CHCl_3$); IR ν_{max}: 2931, 1599, 1351, 1153 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, J = 8.4 Hz, 2H), 7.60 (dd, J = 7.8, 1.2 Hz, 1H), 7.31-7.23 (m, 3H), 7.16 (td, J = 7.5, 1.2 Hz, 1H), 7.04 (dd, J = 7.5, 1.2 Hz, 1H), 4.99 (tt, J = 7.2, 1.2 Hz, 1H), 4.94-4.83 (m, 1H), 3.27 (dd, J = 14.1, 5.1 Hz, 1H), 3.00 (s, 3H), 2.59 (dd, J = 14.1, 3.3 Hz, 1H), 2.42 (s, 3H), 1.96-1.71 (m, 2H), 1.65 (s, 3H), 1.59 (dt, J = 17.4, 4.2 Hz, 1H), 1.53 (s, 3H), 1.40-0.97 (m, 4H), 0.75 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.4, 143.4, 138.9, 135.6, 135.4, 132.4, 130.9, 129.2, 128.7, 128.1, 127.7, 126.6, 124.4, 89.5, 85.1, 42.0, 38.7, 37.7, 35.9, 28.5, 25.9, 25.5, 21.7, 18.8, 17.8; HR-ESIMS calcd for $C_{27}H_{34}INNaO_3S$ $[M+Na]^+$ 602.1196. Found 602.1195.

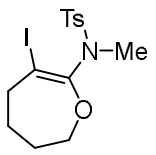
General Procedure for 7-*endo-dig* Iodocylization of 3p-s (Scheme 2b-c, GP-4)



3p-s **4p-s**

To a yellow solution of $I(coll)_2PF_6$ (113 mg, 0.220 mmol) in dry CH_2Cl_2 (0.8 mL) was added $BF_3{\cdot}OEt_2$ (27.6 μL, 0.220 mmol) at rt. The color of solution was immediately changed to purple, and the solution was stirred at rt for 5 min. The resulting solution was added to a stirred solution of **3** (0.200 mmol) in CH_2Cl_2 (2.0 mL) at rt via cannula, rinsed with dry CH_2Cl_2 (0.2 mL), and after 1 min the reaction mixture was quenched with a saturated aqueous solution of $Na_2S_2O_3$/$NaHCO_3$ = 1:1, and was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel to give **4**.

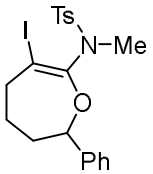
_N_-(3-Iodo-4,5,6,7-tetrahydrooxepin-2-yl)-_N_,4-dimethylbenzenesulfonamide (4p)



4p

According to **GP-4**, **4p** (54.0 mg, 66%) was obtained from **3p** (70.7 mg, 0.200 mmol). Eluent: hexane/EtOAc = 5:1.
Colorless oil; IR ν_{max}: 2938, 1636, 1599, 1351, 1155 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 8.4 Hz, 2H), 4.11 (t, J = 5.7 Hz, 2H), 2.93 (s, 3H), 2.82-2.76 (m, 2H), 2.42 (s, 3H), 1.83 (quint, J = 5.7 Hz, 2H), 1.66 (quint, J = 5.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.0, 143.3, 135.9, 129.2, 127.8, 79.9, 73.3, 41.2, 36.1, 29.9, 24.3, 21.8; HR-ESIMS calcd for $C_{14}H_{18}INNaO_3S$ $[M+Na]^+$ 429.9944. Found 429.9943.

***N*-(3-Iodo-7-phenyl-4,5,6,7-tetrahydrooxepin-2-yl)-*N*,4-dimethylbenzenesulfonamide (4q)**

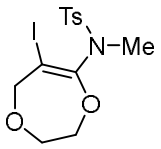


4q

According to **GP-4**, **4q** (22.5 mg, 23%) was obtained from **3q** (85.9 mg, 0.200 mmol). Eluent: hexane/EtOAc = 6:1.

Colorless amorphous solid; IR ν_{max}: 2937, 1635, 1599, 1350, 1154 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.80-6.80 (br m, 9H), 5.00 (br s, 1H), 2.91 (s, 2H), 2.88 (s, 3H), 2.33 (s, 3H), 2.08-1.91 (m, 3H), 1.74-1.66 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.2, 143.2, 141.4, 135.7, 129.1, 128.3, 128.0, 127.7, 126.0, 85.6, 81.4, 40.9, 37.7, 35.8, 24.6, 21.5; HR-ESIMS calcd for $C_{20}H_{22}INNaO_3S$ $[M+Na]^+$ 506.0257. Found 506.0260.

***N*-(6-Iodo-2,3-dihydro-5*H*-1,4-dioxepin-7-yl)-*N*,4-dimethylbenzenesulfonamide (4r)**

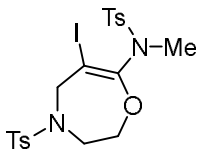


4r

According to **GP-4**, **4r** (29.7 mg, 36%) was obtained from **3r** (71.1 mg, 0.200 mmol). Eluent: hexane/EtOAc = 4:1.

Colorless oil; IR ν_{max}: 3029, 1629, 1599, 1359, 1157 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, J = 8.1 Hz, 2H), 7.32 (d, J = 8.1 Hz, 2H), 4.48 (s, 2H), 4.23-4.17 (m, 2H), 3.87-3.81 (m, 2H), 2.98 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.7, 143.9, 135.8, 129.5, 128.0, 74.5, 72.8, 70.8, 36.2, 21.6; HR-ESIMS calcd for $C_{13}H_{16}INNaO_4S$ $[M+Na]^+$ 431.9737. Found 431.9740.

***N*-(6-Iodo-4-tosyl-2,3,4,5-tetrahydro-1,4-oxazepin-7-yl)-*N*,4-dimethylbenzenesulfonamide (4s)**

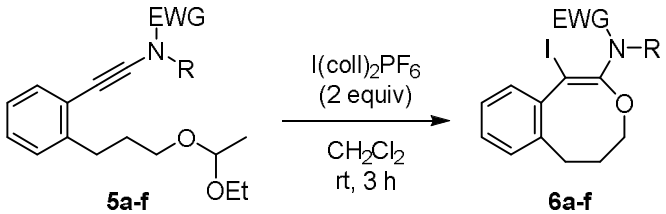


4s

According to **GP-4**, **4s** (93.1 mg, 83%) was obtained from **3s** (102 mg, 0.200 mmol). Eluent: hexane/acetone = 3:1.

Colorless amorphous solid; IR ν_{max}: 3031, 1642, 1599, 1356, 1160 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, J = 8.4 Hz, 4H), 7.34-7.27 (m, 4H), 4.28 (s, 2H), 4.16 (t, J = 5.1 Hz, 2H), 3.59 (t, J = 5.1 Hz, 2H), 2.74 (s, 3H), 2.43 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.2, 144.0, 143.7, 136.0, 135.6, 129.8, 129.4, 127.9, 127.3, 72.3, 70.4, 55.3, 48.9, 35.8, 21.54, 21.45; HR-ESIMS calcd for $C_{20}H_{23}IN_2NaO_5S_2$ $[M+Na]^+$ 584.9985. Found 584.9976.

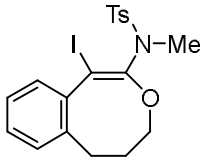
General Procedure for 8-*endo-dig* Iodocylization of 5 (Table 3, GP-5)



5a-f **6a-f**

To a solution of **5** (1 equiv) in dry CH_2Cl_2 (0.1 M) was added $I(coll)_2PF_6$ (2 equiv) at rt and the reaction mixture was stirred for 3 h. The reaction mixture was quenched with a saturated aqueous solution of $Na_2S_2O_3$, and was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel to give **6**.

(*E*)-*N*-(1-Iodo-5,6-dihydro-4*H*-benzo[*d*]oxocin-2-yl)-*N*,4-dimethylbenzenesulfonamide (6a)

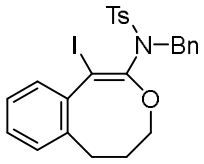


6a

According to **GP-5**, **6a** (52.8 mg, 56%) was obtained from **5a** (83.1 mg, 0.200 mmol) and $I(coll)_2PF_6$ (205 mg, 0.400 mmol). Eluent: hexane/EtOAc/acetone = 8:1:1.

Yellow amorphous solid; IR ν_{max}: 2930, 1618, 1599, 1353, 1156 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.8 Hz, 2H), 7.62 (d, *J* = 7.8 Hz, 1H), 7.31 (d, *J* = 7.8 Hz, 2H), 7.21 (t, *J* = 7.2 Hz, 1H), 7.18 (t, *J* = 7.2 Hz, 1H), 7.04 (d, *J* = 7.2 Hz, 1H), 3.84-3.62 (br m, 2H), 3.25-2.92 (br m, 4H), 2.83 (br d, *J* = 12.6 Hz, 1H), 2.44 (s, 3H), 2.04 (br s, 1H), 1.43 (br s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 149.1, 143.7, 139.3, 137.3, 136.1, 132.7, 129.3, 128.8, 128.6, 128.4, 126.3, 99.8, 66.0, 36.3, 30.5, 27.5, 21.6; HR-ESIMS calcd for $C_{19}H_{20}INNaO_3S$ $[M+Na]^+$ 492.0101. Found 492.0102.

(*E*)-*N*-Benzyl-*N*-(1-iodo-5,6-dihydro-4*H*-benzo[*d*]oxocin-2-yl)-4-methylbenzenesulfonamide (6b)

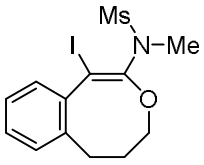


6b

According to **GP-5**, **6b** (75.5 mg, 69%) was obtained from **5b** (98.3 mg, 0.200 mmol) and $I(coll)_2PF_6$ (205 mg, 0.400 mmol). Eluent: hexane/EtOAc = 7:1.

Pale yellow amorphous solid; IR ν_{max}: 3018, 1610, 1599, 1352, 1163 cm^{-1}; The ^1H and ^{13}C NMR spectra of **6b** showed the presence of some rotamers; ^1H NMR (600 MHz, $CDCl_3$) δ 8.06-7.77 (br m, 1.6H), 7.73-7.58 (br m, 0.4H), 7.48-7.17 (br m, 8H), 7.11 (br s, 2H), 7.06-6.95 (br m, 0.6H), 6.90-6.76 (br m, 0.4H), 4.80 (br s, 0.3H), 4.59 (br s, 0.7H), 4.40 (br s, 0.5H), 4.25 (br s, 0.5H), 3.93 (br s, 0.5H), 3.74 (br s, 1H), 3.52 (br s, 0.5H), 3.32 (br s, 0.6H), 2.83 (br s, 0.6H), 2.46 (s, 3H), 2.28 (br s, 0.4H), 2.11 (br s, 0.6H), 1.80 (br s, 0.4H), 1.57 (br s, 0.4H), 1.43 (br s, 0.6H), 1.07 (br s, 0.4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 146.4, 145.6, 143.9, 139.9, 137.6, 136.3, 134.2, 133.7, 132.0, 130.2, 129.3, 128.8, 128.6, 128.4, 128.0 (2C), 126.1, 81.8, 65.7, 65.3, 52.6, 52.0, 30.3, 29.7, 27.6, 27.2, 21.6; HR-ESIMS calcd for $C_{25}H_{24}INNaO_3S$ $[M+Na]^+$ 568.0414. Found 568.0416.

(*E*)-*N*-(1-Iodo-5,6-dihydro-4*H*-benzo[*d*]oxocin-2-yl)-*N*-methylmethanesulfonamide (6c)

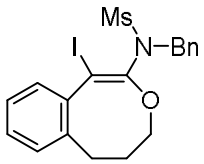


6c

According to **GP-5**, **6c** (46.4 mg, 59%) was obtained from **5c** (67.9 mg, 0.200 mmol) and $I(coll)_2PF_6$ (205 mg, 0.400 mmol). Eluent: hexane/EtOAc = 6:1.

Colorless amorphous solid; IR ν_{max}: 3030, 1624, 1601, 1346, 1147 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.60 (d, *J* = 7.8 Hz, 1H), 7.22 (td, *J* = 7.2, 1.8 Hz, 1H), 7.19 (td, *J* = 7.2, 1.2 Hz, 1H), 7.05 (dd, *J* = 7.2, 1.2 Hz, 1H), 3.92 (t, *J* = 5.4 Hz, 2H), 3.13 (br s, 4H), 3.12 (s, 3H), 2.84-2.79 (m, 1H), 2.16-2.05 (br m, 1H), 1.53-1.43 (br m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 148.1, 139.1, 137.7, 132.4, 128.9, 128.8, 126.3, 123.8, 66.0, 39.4, 30.3 (2C), 27.5; HR-ESIMS calcd for $C_{13}H_{16}INNaO_3S$ $[M+Na]^+$ 415.9788. Found 415.9788.

(*E*)-*N*-Benzyl-*N*-(1-iodo-5,6-dihydro-4*H*-benzo[*d*]oxocin-2-yl)methanesulfonamide (6d)



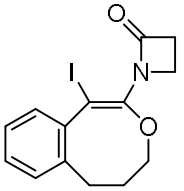
6d

According to **GP-5**, **6d** (45.9 mg, 49%) was obtained from **5d** (83.1 mg, 0.200 mmol) and $I(coll)_2PF_6$ (205 mg, 0.400 mmol). Eluent: hexane/EtOAc = 5:1.

Colorless amorphous solid; IR ν_{max}: 3032, 1621, 1600, 1341, 1152 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.50 (br s, 2H), 7.40-7.34 (m, 4H), 7.18-7.13 (m, 2H), 7.06 (br s, 1H), 4.75-4.48 (br m, 2H), 4.07-3.86 (br m, 2H), 3.19 (br s, 1H), 3.03 (s, 3H), 2.77 (br s, 1H), 2.03 (br s, 1H), 1.65-1.50 (br m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 146.6, 139.2, 138.8, 134.5, 131.4, 129.9, 129.0, 128.8, 128.5, 128.4, 126.1, 82.5, 65.8, 52.6, 41.6, 30.2, 27.5; HR-ESIMS calcd for

$C_{19}H_{20}INNaO_3S$ $[M+Na]^+$ 492.0101. Found 492.0103.

(*E*)-1-(1-Iodo-5,6-dihydro-4*H*-benzo[*d*]oxocin-2-yl)azetidin-2-one (6e)

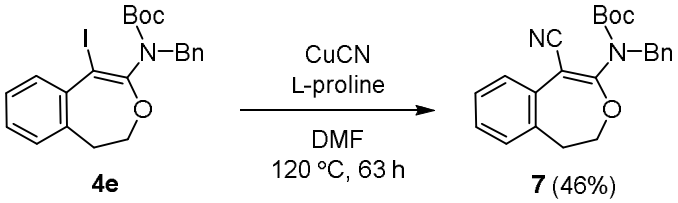


6e

According to **GP-5**, **6e** (9.5 mg, 13%) was obtained from **5e** (60.3 mg, 0.200 mmol) and $I(coll)_2PF_6$ (205 mg, 0.400 mmol). Eluent: hexane/acetone = 6:1.

Pale yellow amorphous solid; IR ν_{max}: 3012, 1761, 1628, 1601 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.54 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.22 (td, *J* = 7.8, 1.8 Hz, 1H), 7.19 (td, *J* = 7.8, 1.8 Hz, 1H), 7.14 (dd, *J* = 7.8, 1.8 Hz, 1H), 3.95 (dd, *J* = 11.4, 3.6 Hz, 1H), 3.75-3.69 (br m, 2H), 3.59-3.54 (m, 1H), 3.18-3.11 (m, 1H), 3.07-3.00 (m, 1H), 2.91 (dd, *J* = 13.2, 7.2 Hz, 1H), 2.80 (t, *J* = 13.2 Hz, 1H), 1.96-1.90 (br m, 1H), 1.80-1.70 (br m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.8, 144.1, 139.7, 137.9, 131.3, 129.3, 128.6, 126.2, 76.4, 68.1, 39.9, 36.8, 31.9, 27.8; HR-ESIMS calcd for $C_{14}H_{14}INNaO_2$ $[M+Na]^+$ 377.9961. Found 377.9964.

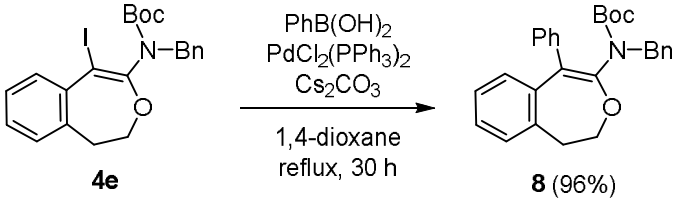
***tert*-Butyl benzyl(1-cyano-4,5-dihydrobenzo[*d*]oxepin-2-yl)carbamate (7) (Scheme 4)**



A mixture of **4e** (71.6 mg, 0.150 mmol), CuCN (26.9 mg, 0.300 mmol), L-proline (17.3 mg, 0.150 mmol) in dry DMF (0.45 mL) was heated at 120 °C for 63 h. After the reaction completed, the reaction mixture was cooled to rt, filtered through Celite, and the filtrate was diluted with water and brine. After the mixture was extracted with EtOAc, the organic layer was dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 8:1 to 6:1 to give **7** (26.0 mg, 46%).

Colorless oil; IR ν_{max}: 3014, 2221, 1714, 1602 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.8 Hz, 1H), 7.39 (d, *J* = 7.2 Hz, 2H), 7.31 (t, *J* = 7.2 Hz, 2H), 7.26 (d, *J* = 8.4 Hz, 1H), 7.25 (t, *J* = 7.2 Hz, 1H), 7.15 (td, *J* = 7.2, 1.2 Hz, 1H), 7.03 (d, *J* = 7.8 Hz, 1H), 4.77 (s, 2H), 4.30 (br s, 2H), 2.97 (br s, 2H), 1.50 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.4, 152.8, 137.7, 136.2, 129.2, 129.1, 128.8, 128.6, 128.3, 127.7, 127.2, 127.1, 118.5, 91.9, 82.4, 72.1, 51.5, 36.6, 28.1; HR-ESIMS calcd for $C_{23}H_{24}N_2NaO_3$ $[M+Na]^+$ 399.1679. Found 399.1682.

***tert*-Butyl benzyl(1-phenyl-4,5-dihydrobenzo[*d*]oxepin-2-yl)carbamate (8) (Scheme 4)**

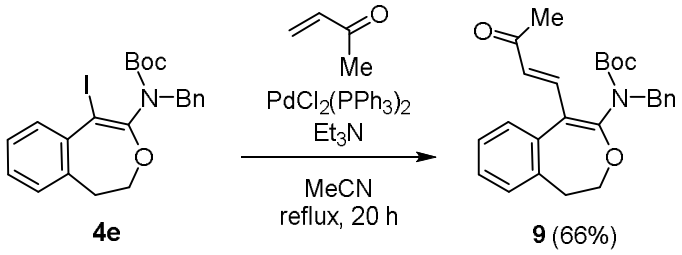


A solution of **4e** (71.6 mg, 0.150 mmol), phenylboronic acid (54.9 mg, 0.450 mmol), $PdCl_2(PPh_3)_2$ (10.5 mg, 0.0150 mmol) and Cs_2CO_3 (147 mg, 0.450 mmol) in dry 1,4-dioxane (3 mL) was heated under reflux

for 30 h. After the reaction completed, the reaction mixture was cooled to rt, and was quenched with water, extracted with EtOAc. The organic layer was dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 20:1 to give **8** (61.8 mg, 96%).

Colorless needle crystals; mp 136-137 ºC (hexane); IR ν_{max}: 3012, 1697, 1633 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36 (br s, 2H), 7.33-7.18 (m, 7H), 7.15 (t, *J* = 7.0 Hz, 1H), 7.11 (t, *J* = 7.5 Hz, 1H), 6.95 (br s, 2H), 6.83 (d, *J* = 7.5 Hz, 1H), 4.72 (br s, 1H), 4.47 (br s, 1H), 4.31 (br s, 2H), 3.23 (br s, 1H), 2.68 (br s, 1H), 1.22 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.7, 144.0, 140.0, 139.0 (2C), 138.1, 129.8, 129.6, 128.9, 128.24, 128.18, 128.0, 127.2, 126.9, 126.6, 126.4, 123.1, 80.6, 78.6, 50.8, 34.2, 28.0; HR-ESIMS calcd for $C_{28}H_{29}NNaO_3$ $[M+Na]^+$ 450.2040. Found 450.2026.

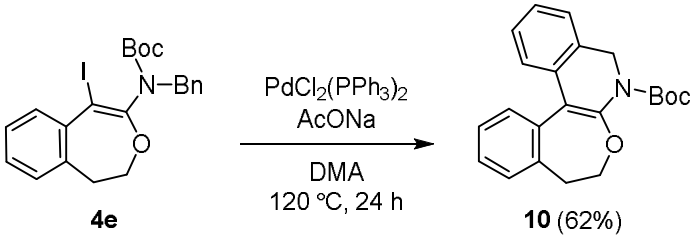
tert-Butyl (*E*)-benzyl(1-(3-oxobut-1-en-1-yl)-4,5-dihydrobenzo[*d*]oxepin-2-yl)carbamate (9) (Scheme 4)



A mixture of **4e** (57.2 mg, 0.120 mmol), methyl vinyl ketone (48.6 μL, 0.599 mmol), $PdCl_2(PPh_3)_2$ (5.0 mg, 7.19 μmol), and Et_3N (50.0 μL, 0.359 mmol) in dry MeCN (2.4 mL) was heated under reflux for 20 h. After the reaction completed, the reaction mixture was cooled to rt, and was quenched with water, extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NH_4Cl, dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 6:1 to 4:1 to give **9** (33.2 mg, 66%).

Colorless amorphous solid; IR ν_{max}: 3012, 1701, 1655, 1613, 1597 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.40 (d, *J* = 7.2 Hz, 2H), 7.32 (t, *J* = 7.2 Hz, 2H), 7.30-7.23 (m, 4H), 7.14 (br d, *J* = 7.2 Hz, 1H), 6.99 (br d, *J* = 16.2 Hz, 2H), 5.96 (d, *J* = 16.2 Hz, 1H), 4.95 (br s, 1H), 4.63 (br s, 1H), 4.49 (br s, 1H), 4.41 (br s, 1H), 3.13 (br s, 1H), 2.66 (br s, 1H), 2.04 (s, 3H), 1.47 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 198.5, 154.0, 149.0, 141.0, 138.2, 137.1, 134.5, 129.2, 128.9, 128.7, 128.5, 128.3, 127.9, 127.8, 126.6, 120.6, 81.7, 81.1, 50.8, 33.0, 28.3, 26.5; HR-ESIMS calcd for $C_{26}H_{29}NNaO_4$ $[M+Na]^+$ 442.1989. Found 442.1987.

tert-Butyl 8,9-dihydrobenzo[4,5]oxepino[2,3-*c*]isoquinoline-6(5*H*)-carboxylate (10) (Scheme 4)



A mixture of **4e** (50.0 mg, 0.105 mmol), $PdCl_2(PPh_3)_2$ (3.7 mg, 5.24 μmol), and AcONa (17.2 mg, 0.210 mmol) in dry DMA (2 mL) was stirred at 120 °C for 24 h. After the reaction completed, the reaction mixture

was cooled to rt, and was quenched with water, extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 20:1 to give **10** (22.7 mg, 62%).

Colorless amorphous solid; IR ν_{max}: 2928, 1702, 1617, 1601 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.33-7.22 (m, 4H), 7.21-7.12 (m, 3H), 7.06-6.99 (m, 1H), 4.77 (br s, 4H), 3.00 (br s, 2H), 1.52 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.4, 145.4, 139.5, 135.6, 134.5, 132.3, 129.5, 128.1, 127.0, 126.9, 126.4, 125.8, 124.9, 124.8, 109.7, 81.6, 81.4, 48.6, 33.9, 28.5; HR-ESIMS calcd for $C_{22}H_{23}NNaO_3$ $[M+Na]^+$ 372.1570. Found 372.1576.

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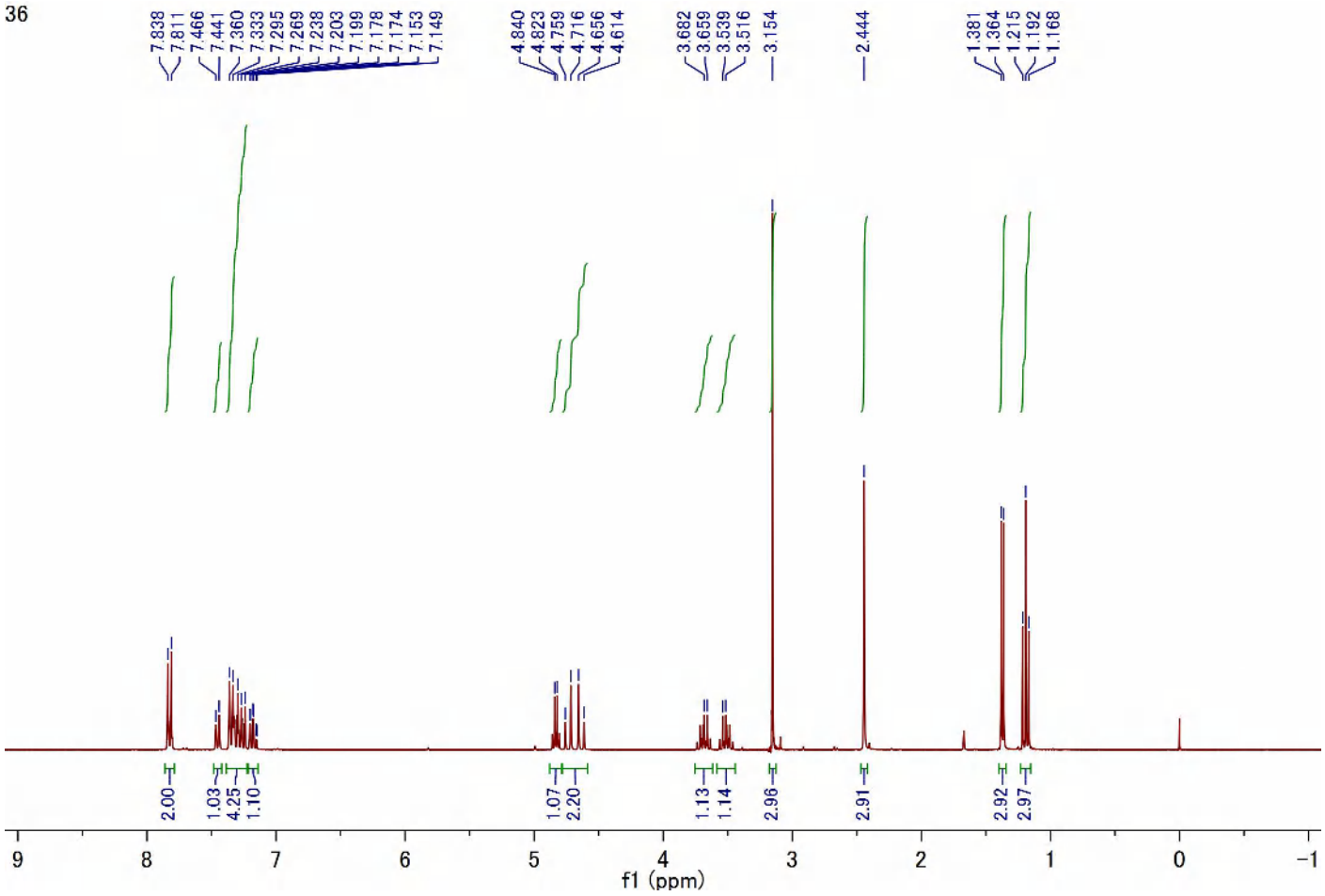
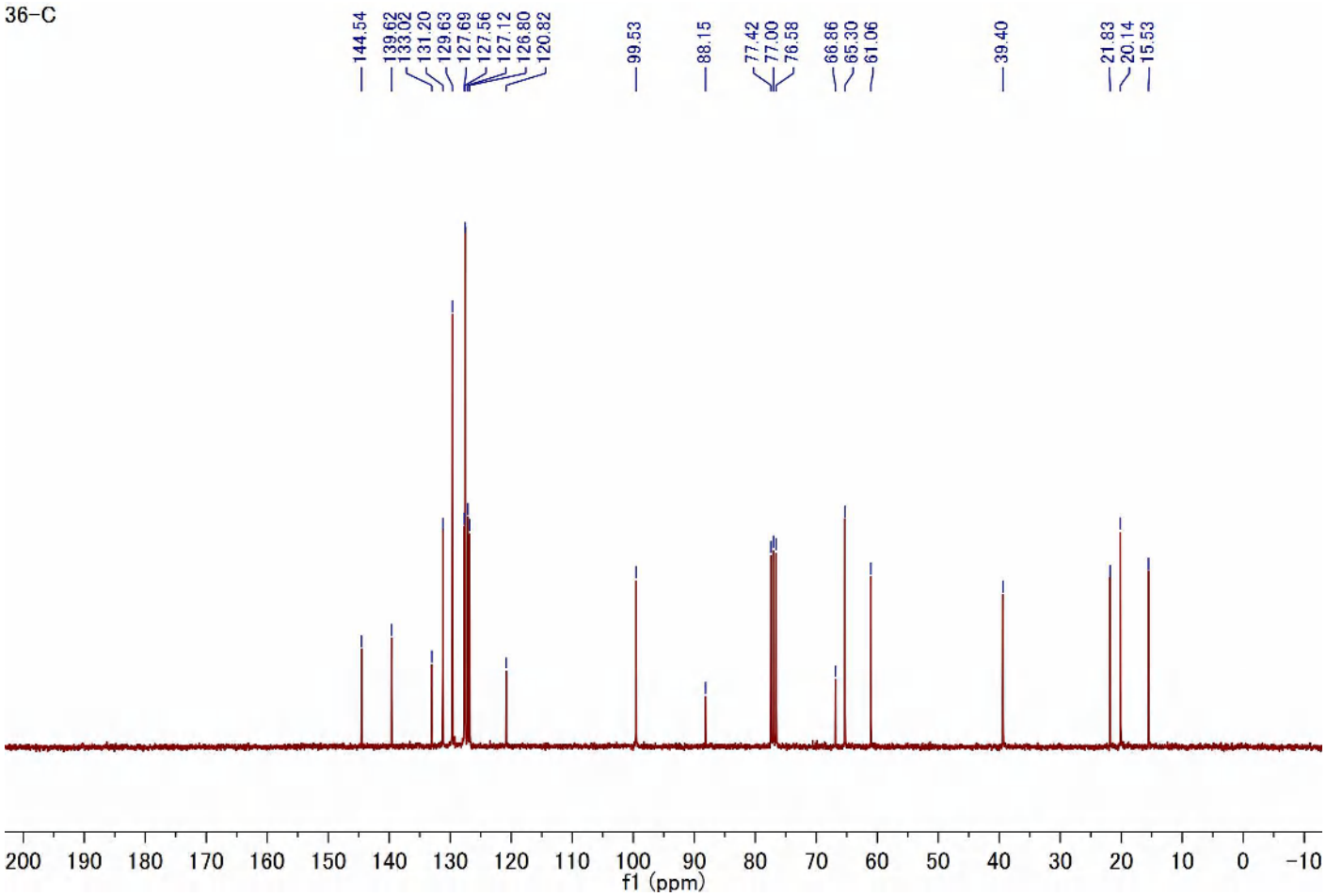
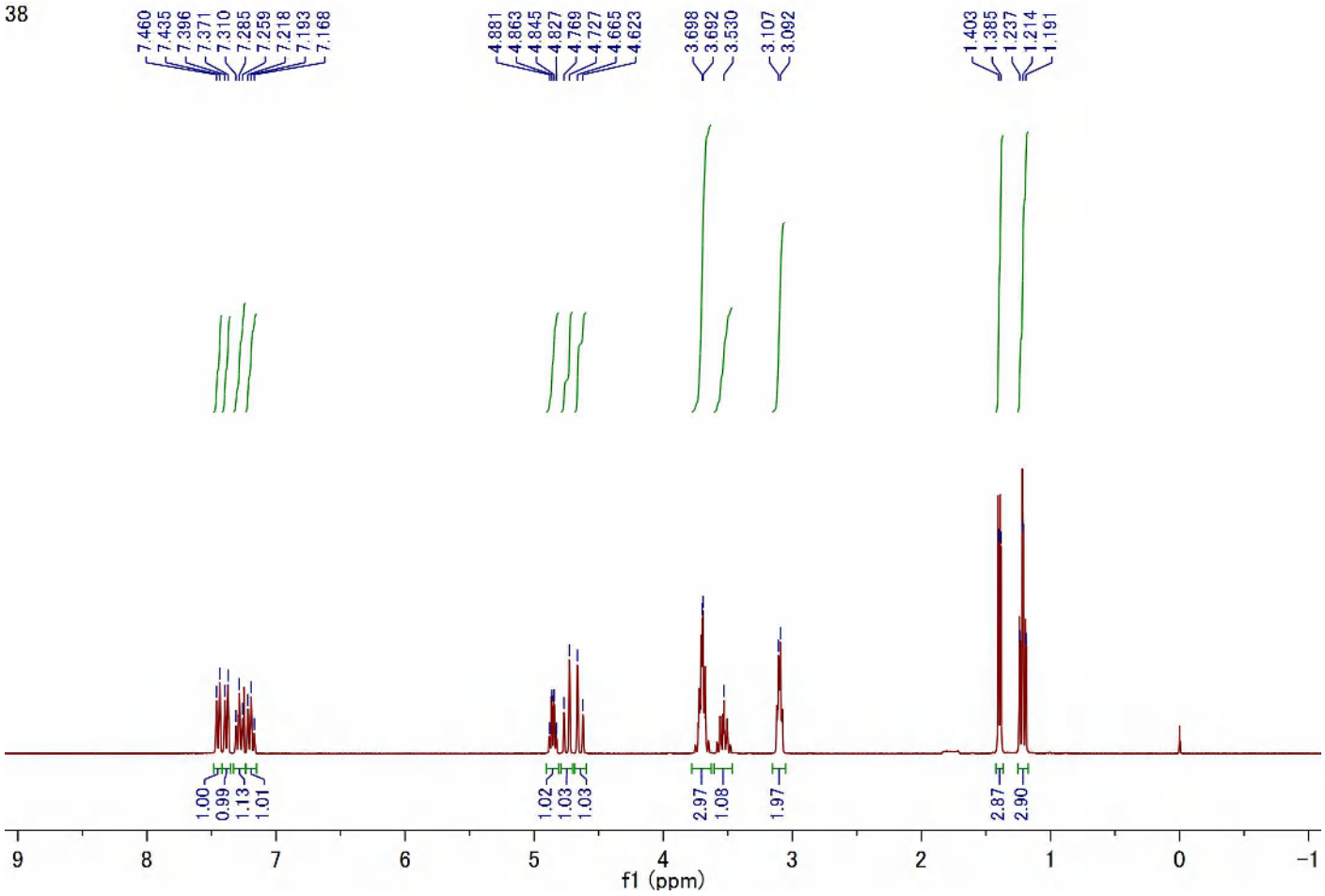
Compound **1a** (^{1}H NMR, 300 MHz, $CDCl_3$)



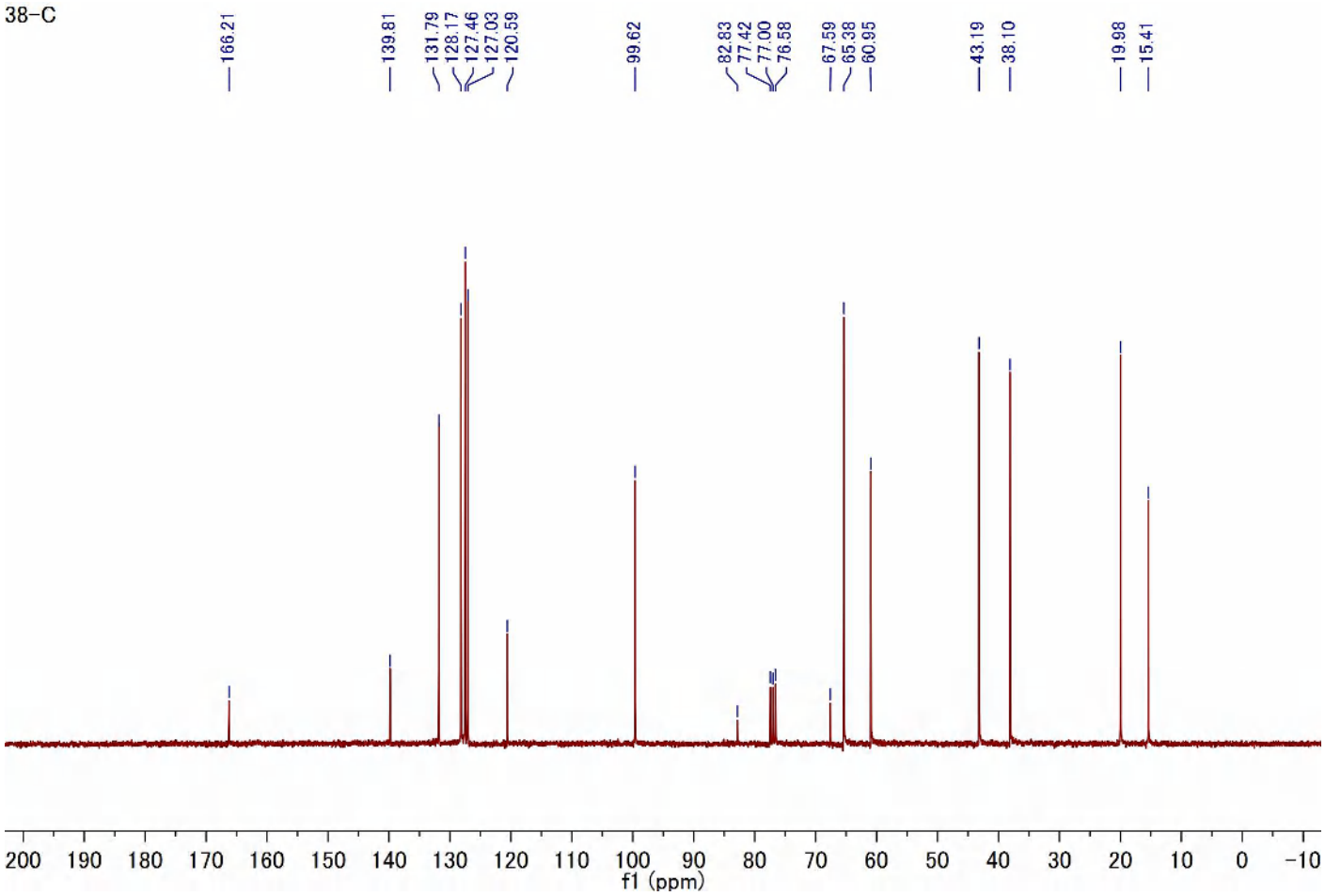
Compound **1a** (^{13}C NMR, 75 MHz, $CDCl_3$)



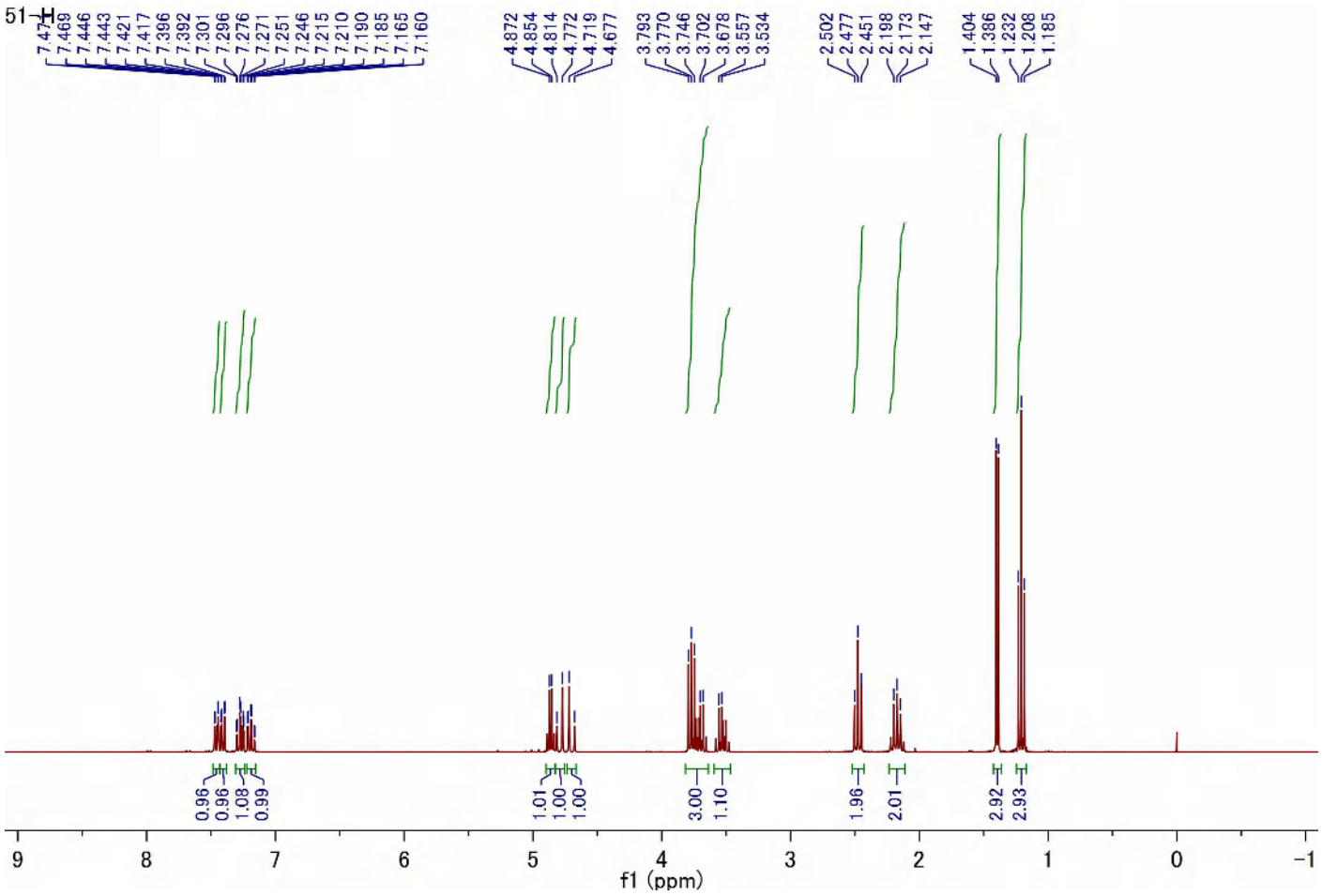
Compound **1b** (^{1}H NMR, 300 MHz, $CDCl_3$)



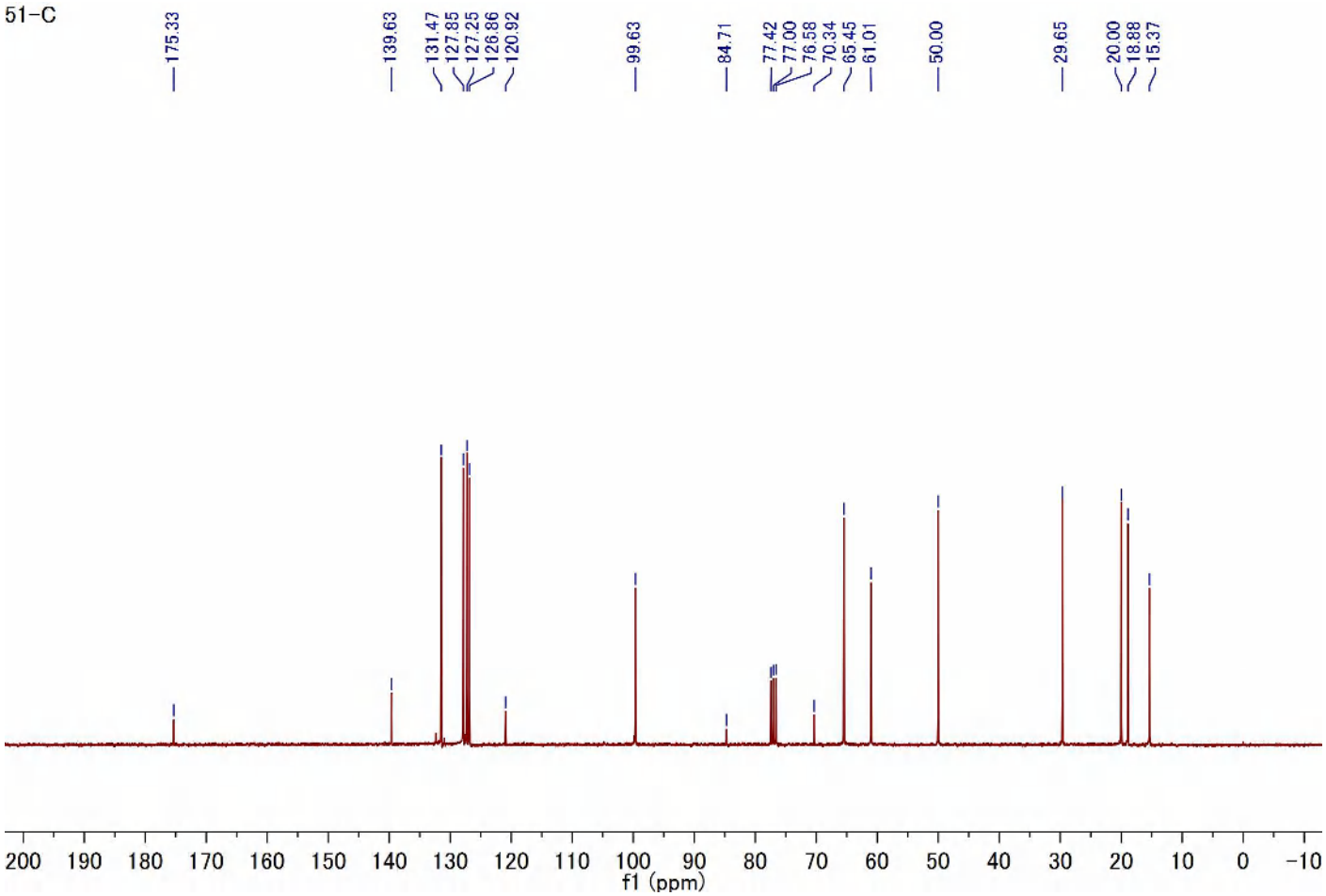
Compound **1b** (^{13}C NMR, 75 MHz, $CDCl_3$)



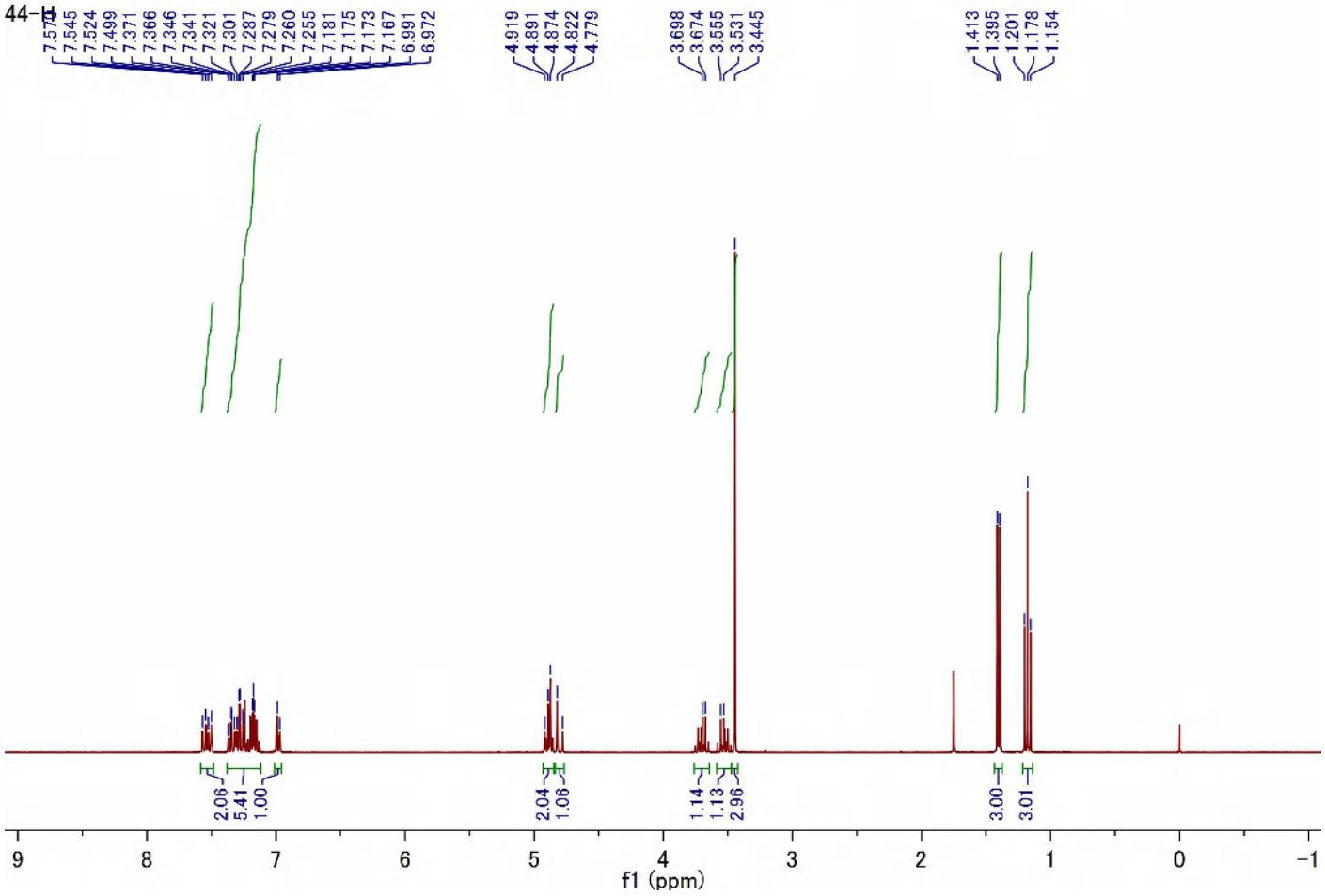
Compound **1c** (^{1}H NMR, 300 MHz, $CDCl_3$)



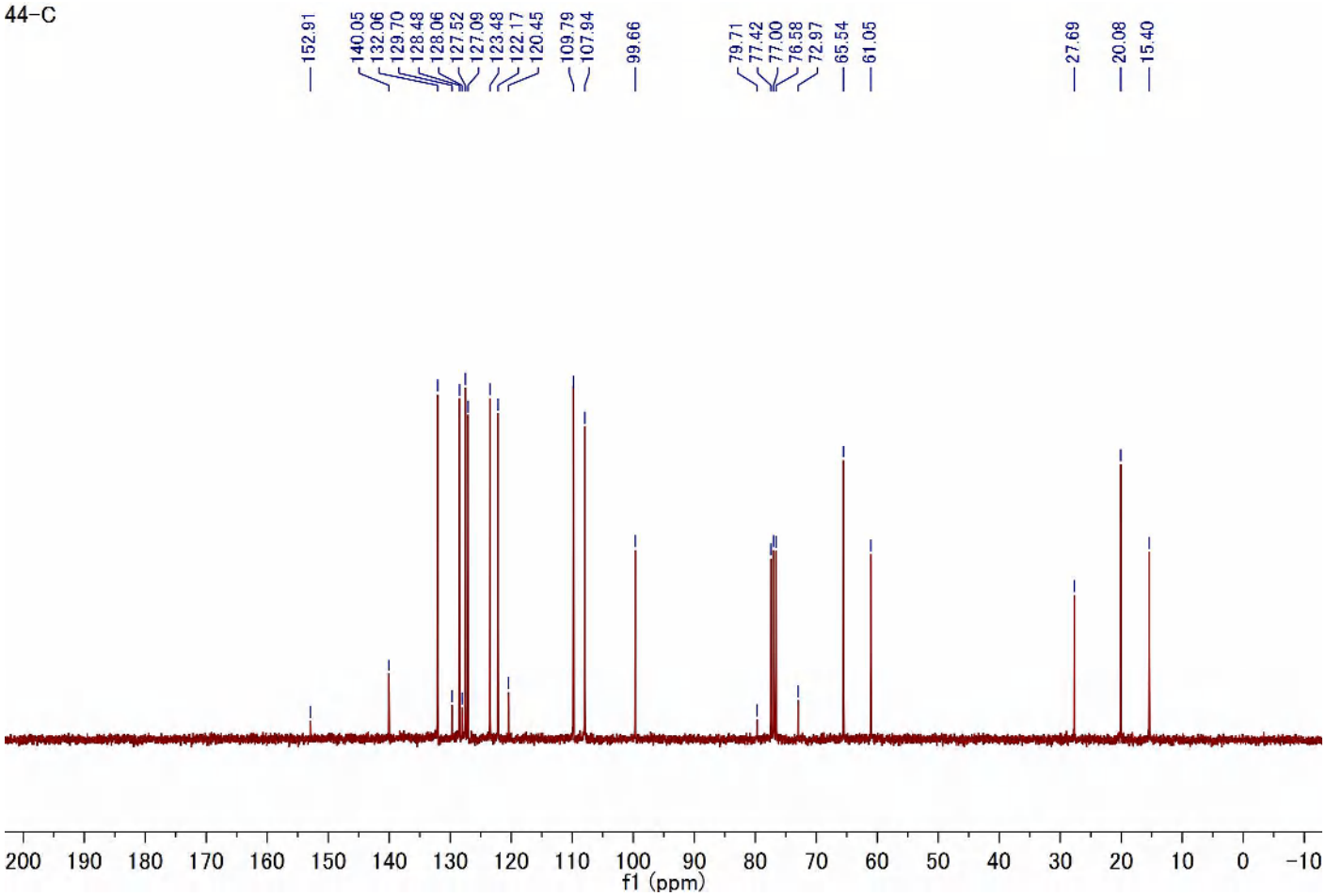
Compound **1c** (^{13}C NMR, 75 MHz, $CDCl_3$)



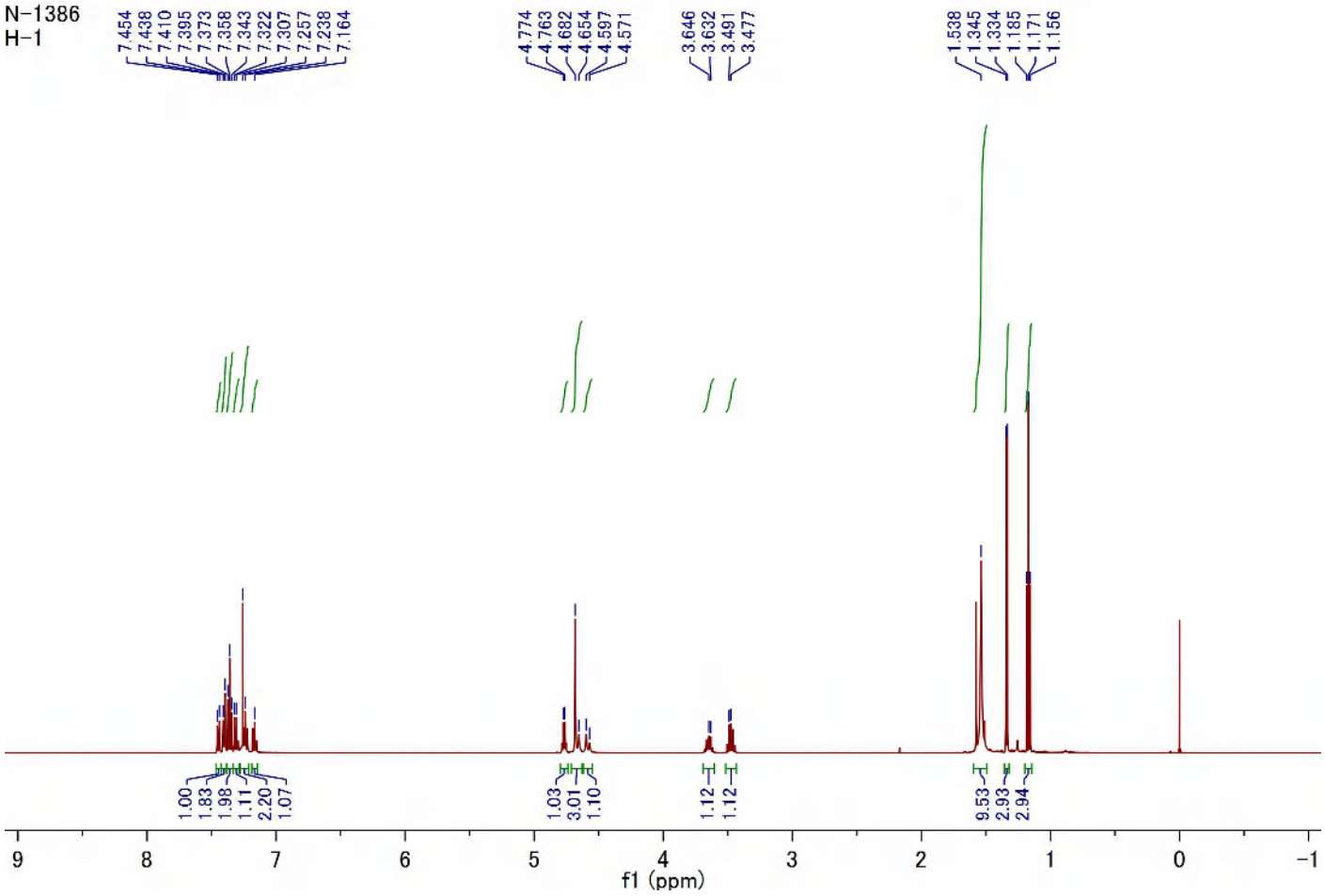
Compound **1d** (^{1}H NMR, 300 MHz, $CDCl_3$)



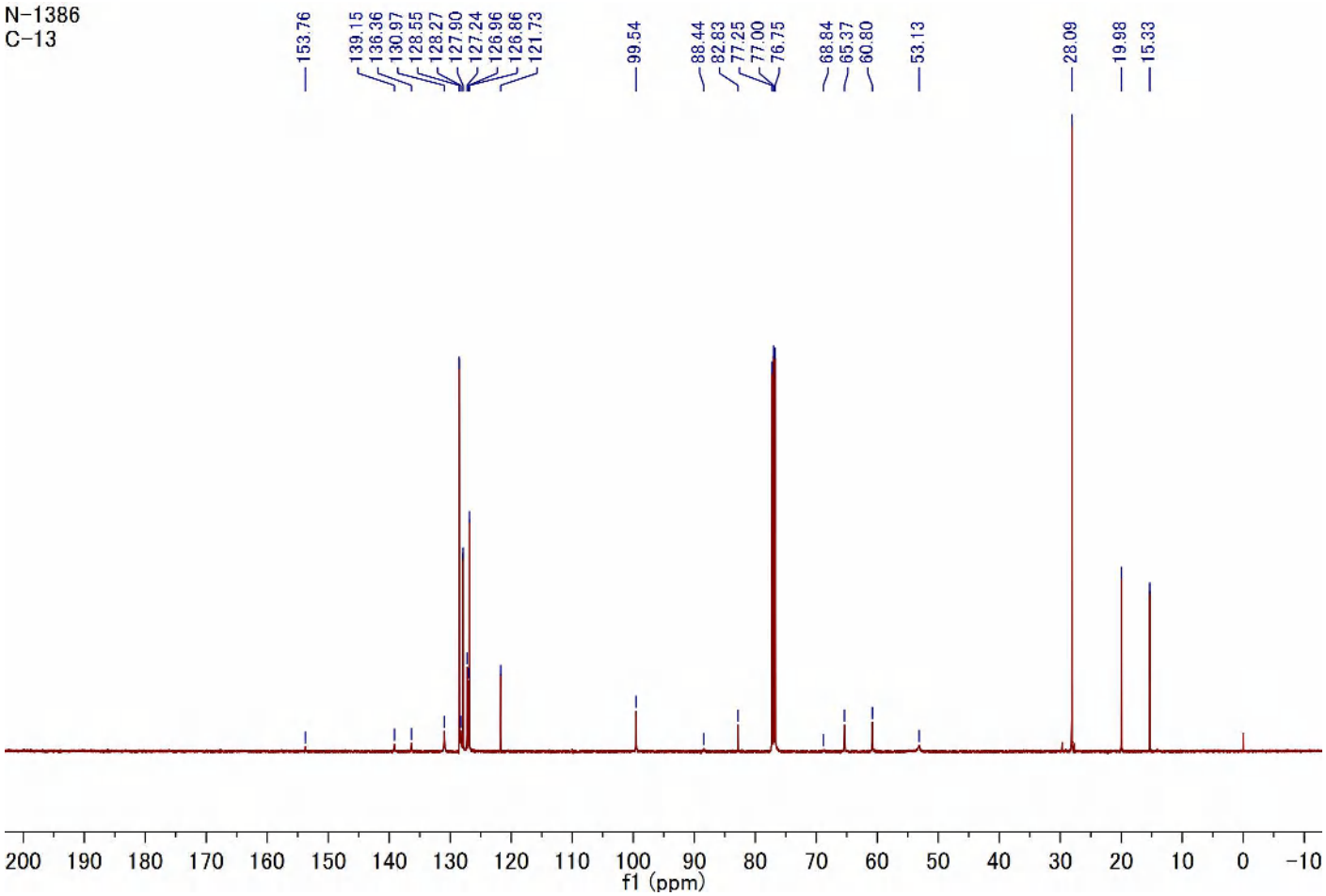
Compound **1d** (^{13}C NMR, 75 MHz, $CDCl_3$)



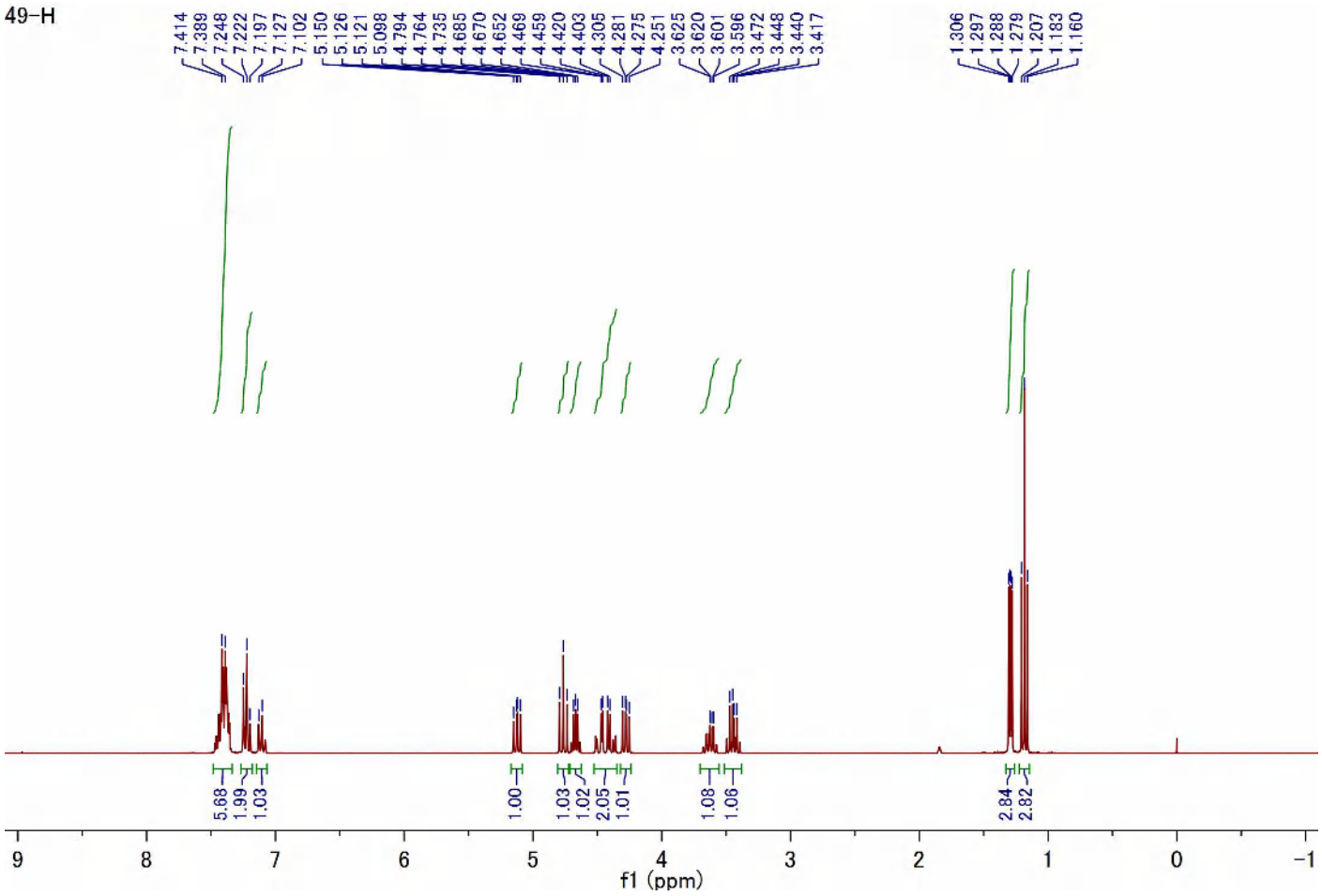
Compound **1e** (^{1}H NMR, 500 MHz, $CDCl_3$)



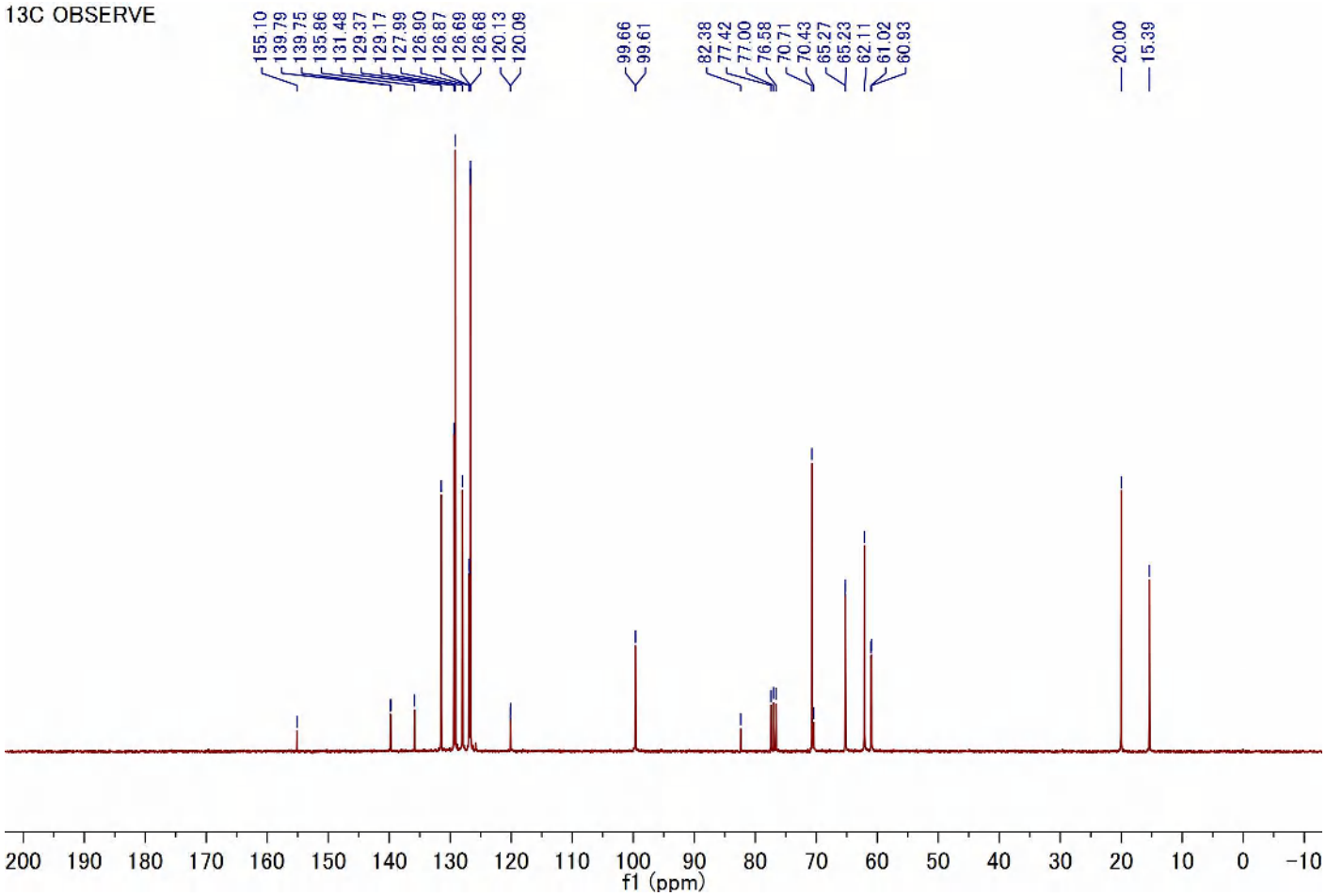
Compound **1e** (^{13}C NMR, 125 MHz, $CDCl_3$)



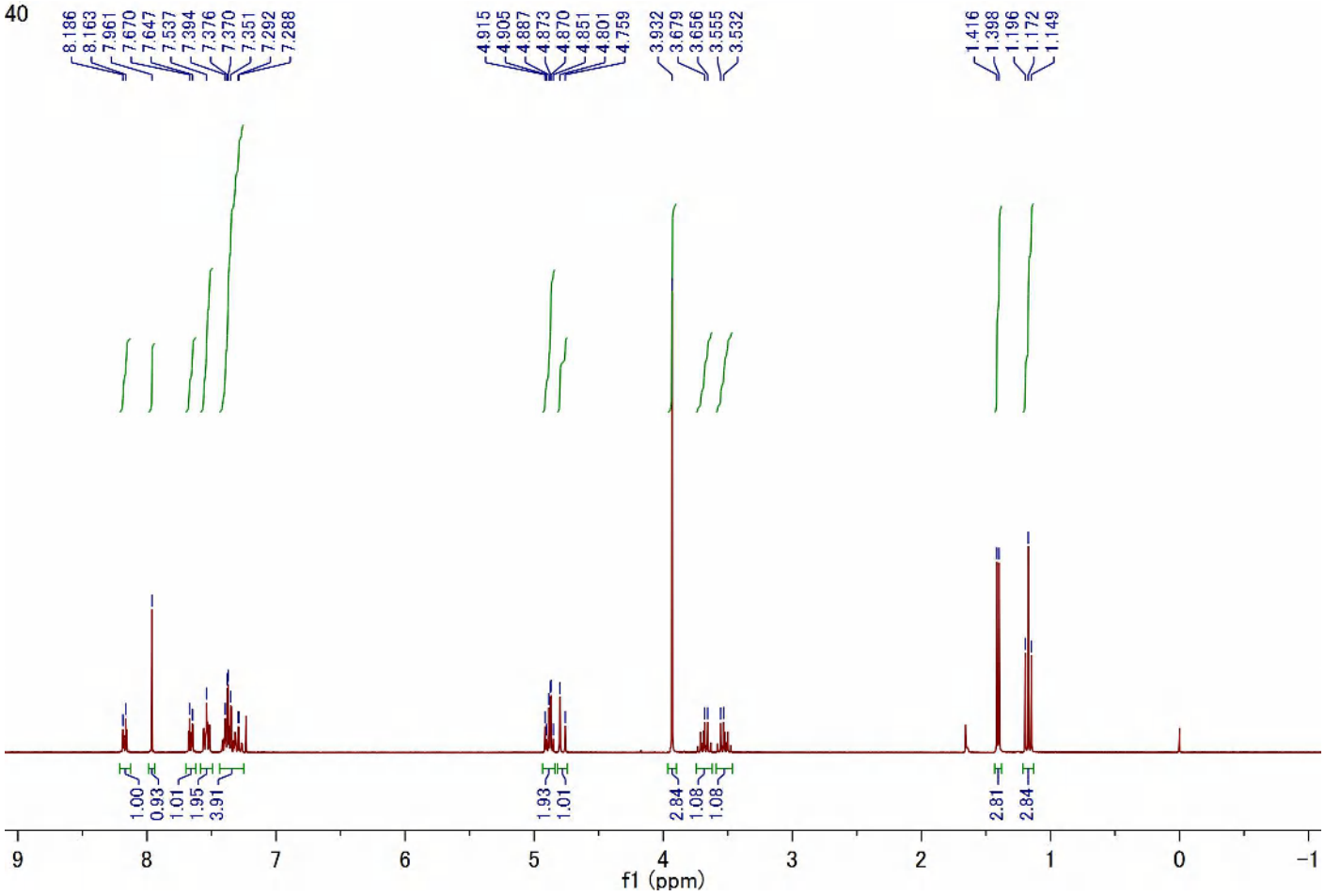
Compound **1f** (^{1}H NMR, 300 MHz, $CDCl_3$)



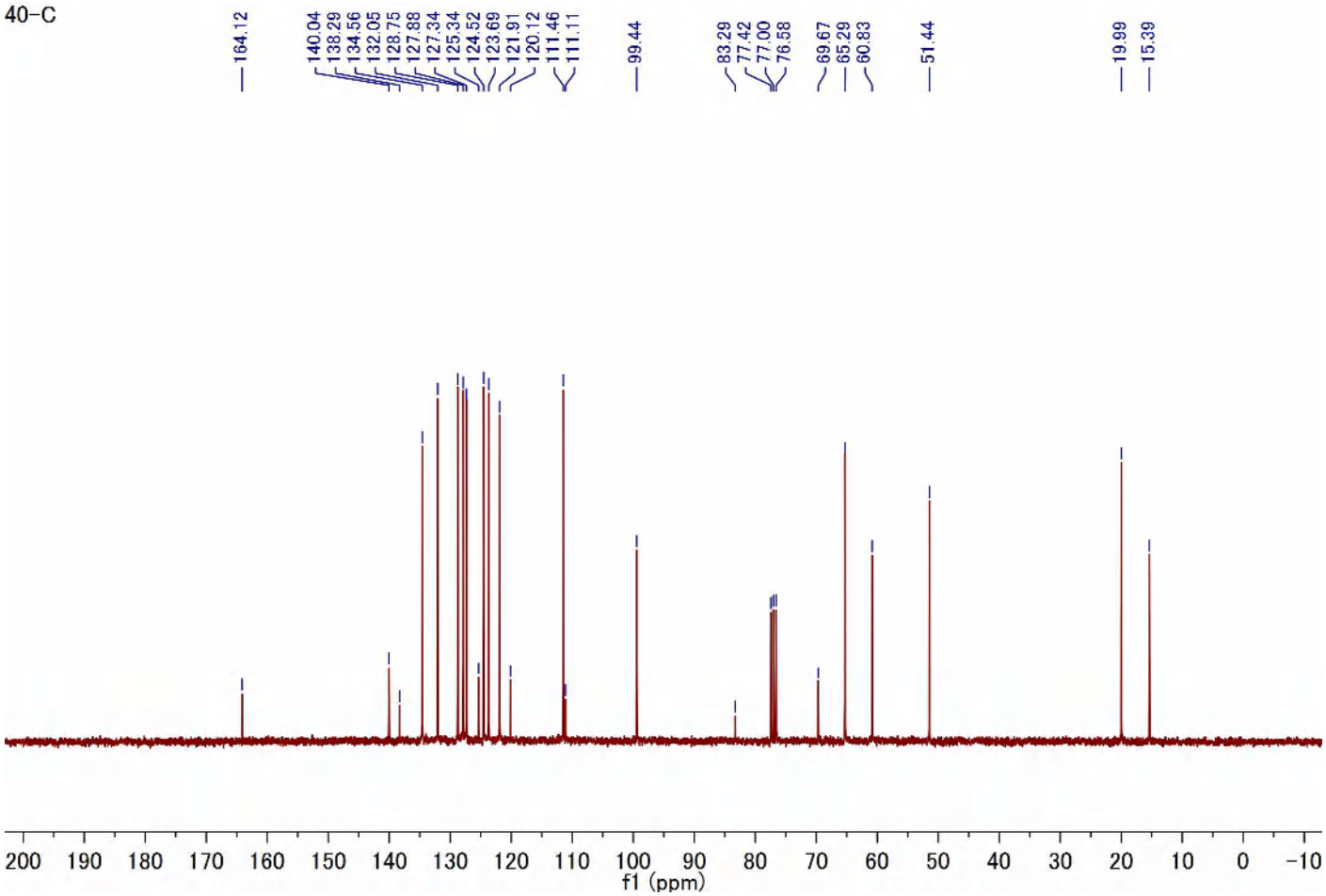
Compound **1f** (^{13}C NMR, 75 MHz, $CDCl_3$)



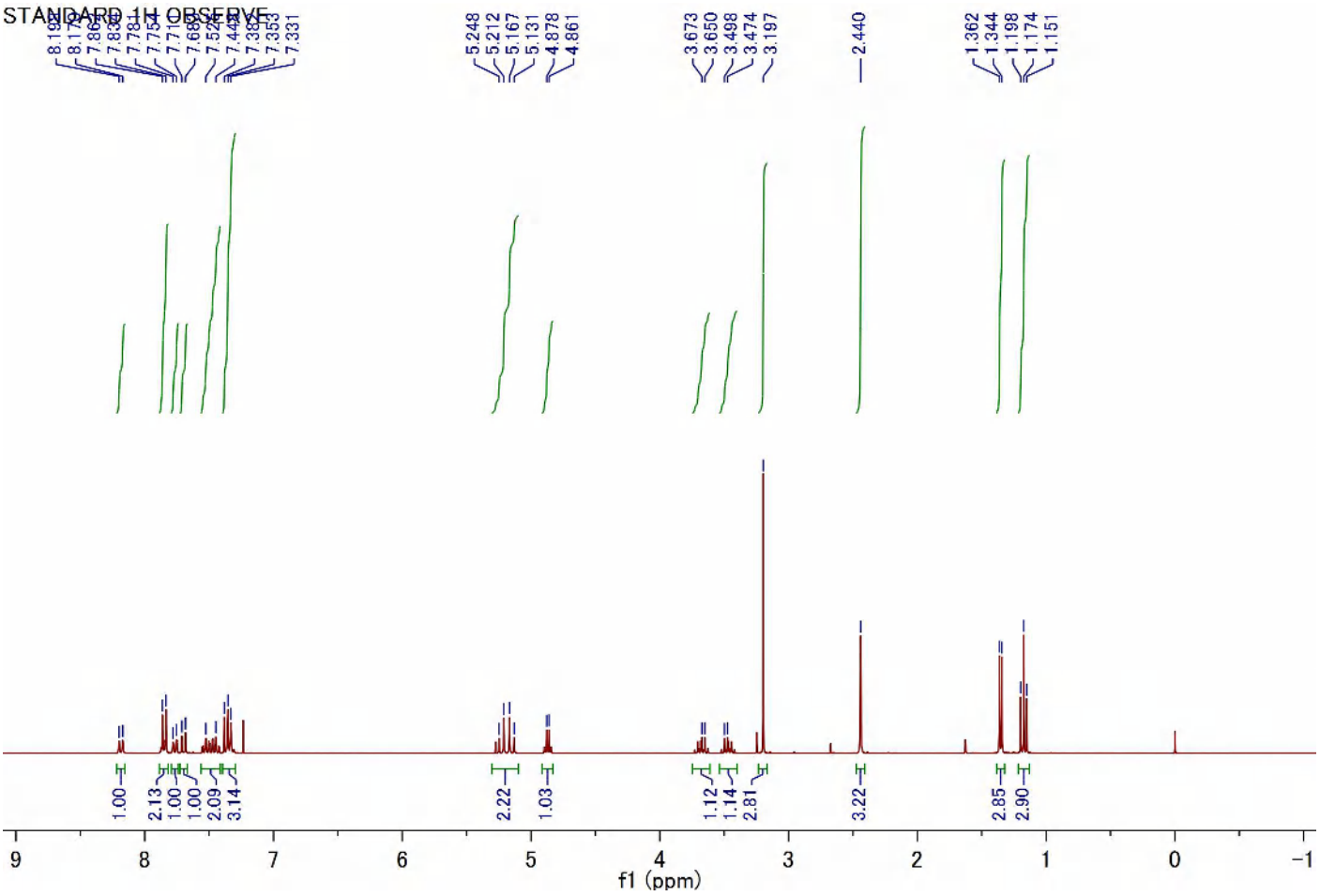
Compound **1g** (^{1}H NMR, 300 MHz, $CDCl_3$)



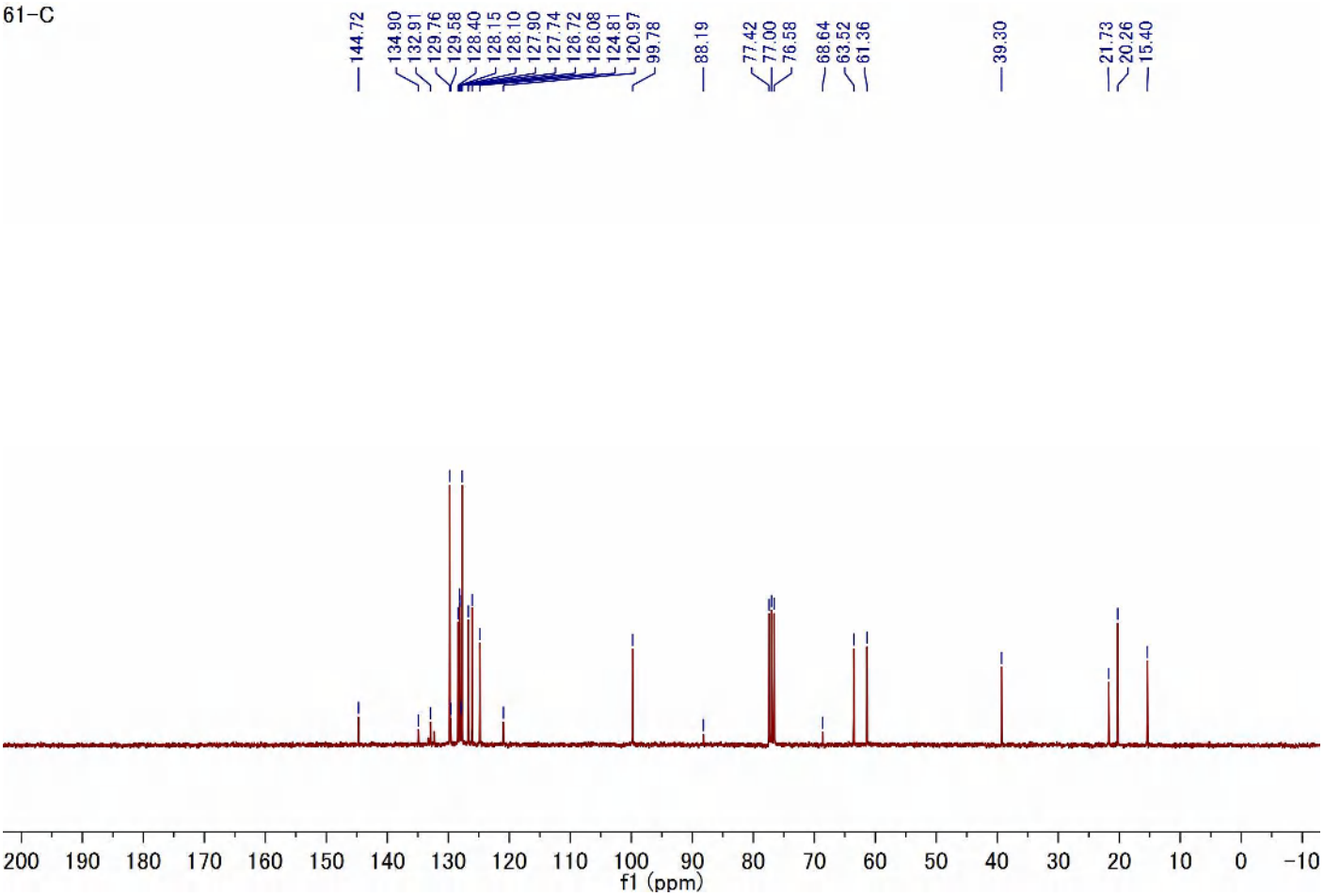
Compound **1g** (^{13}C NMR, 75 MHz, $CDCl_3$)



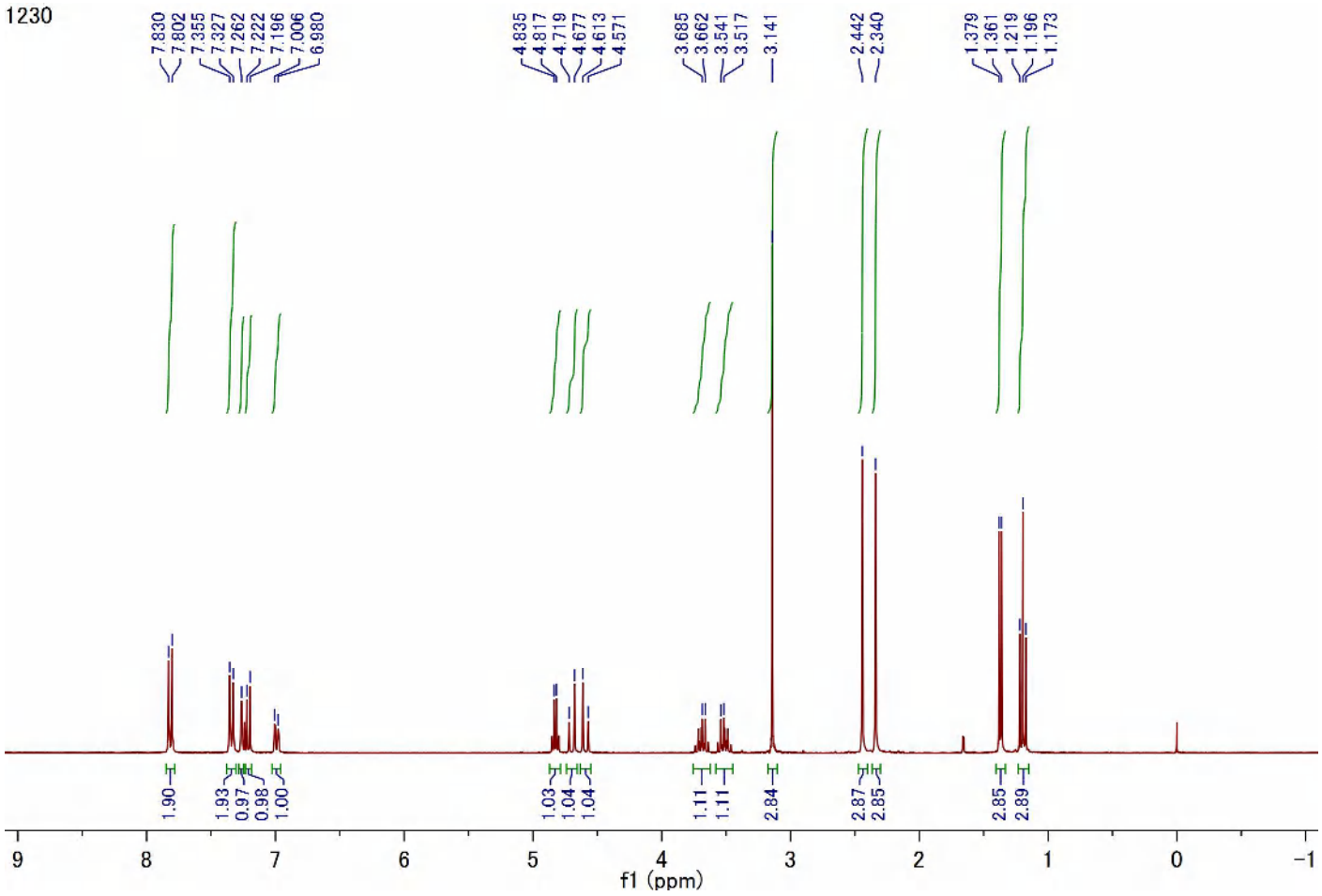
Compound **1h** (^{1}H NMR, 300 MHz, $CDCl_3$)



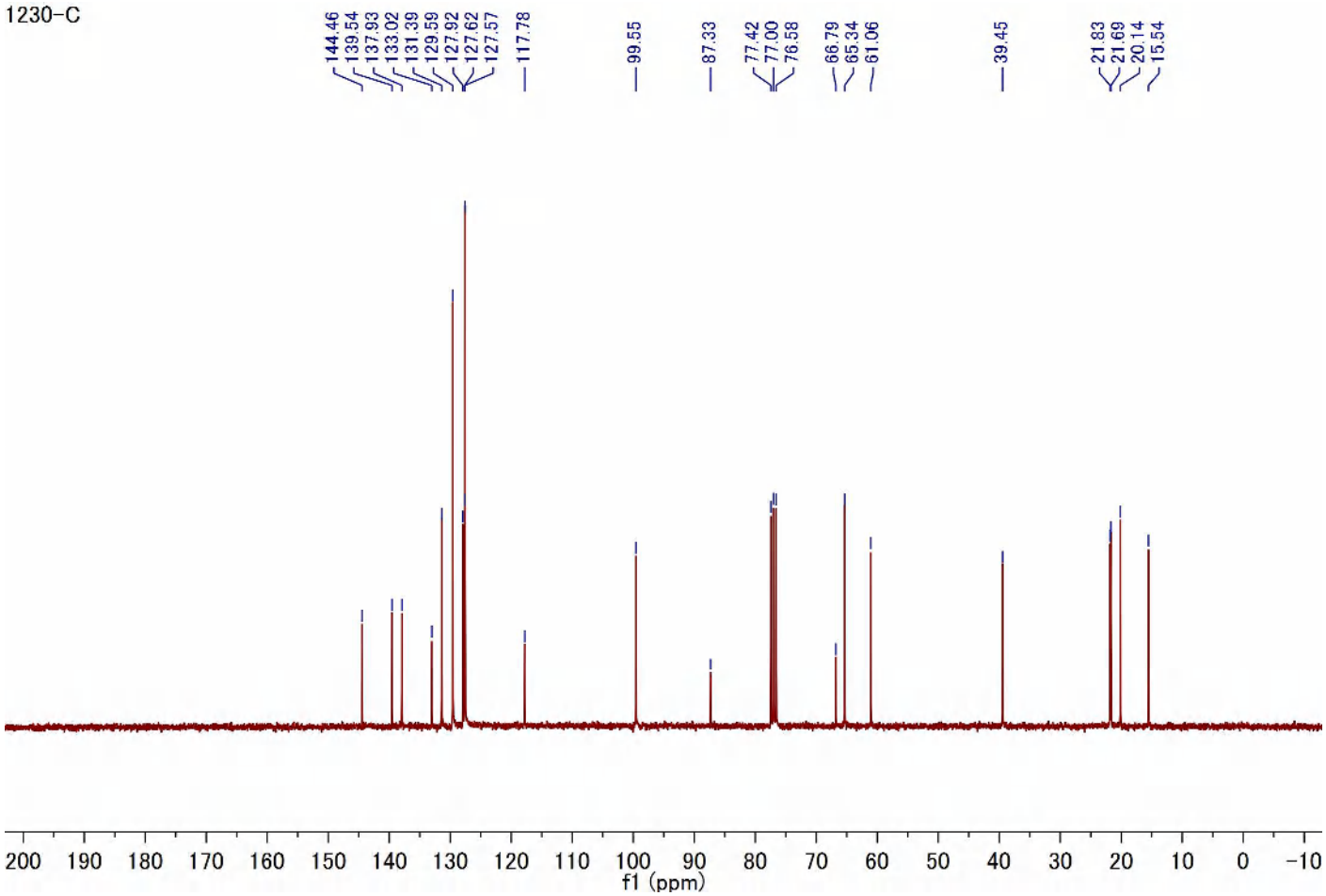
Compound **1h** (^{13}C NMR, 75 MHz, $CDCl_3$)



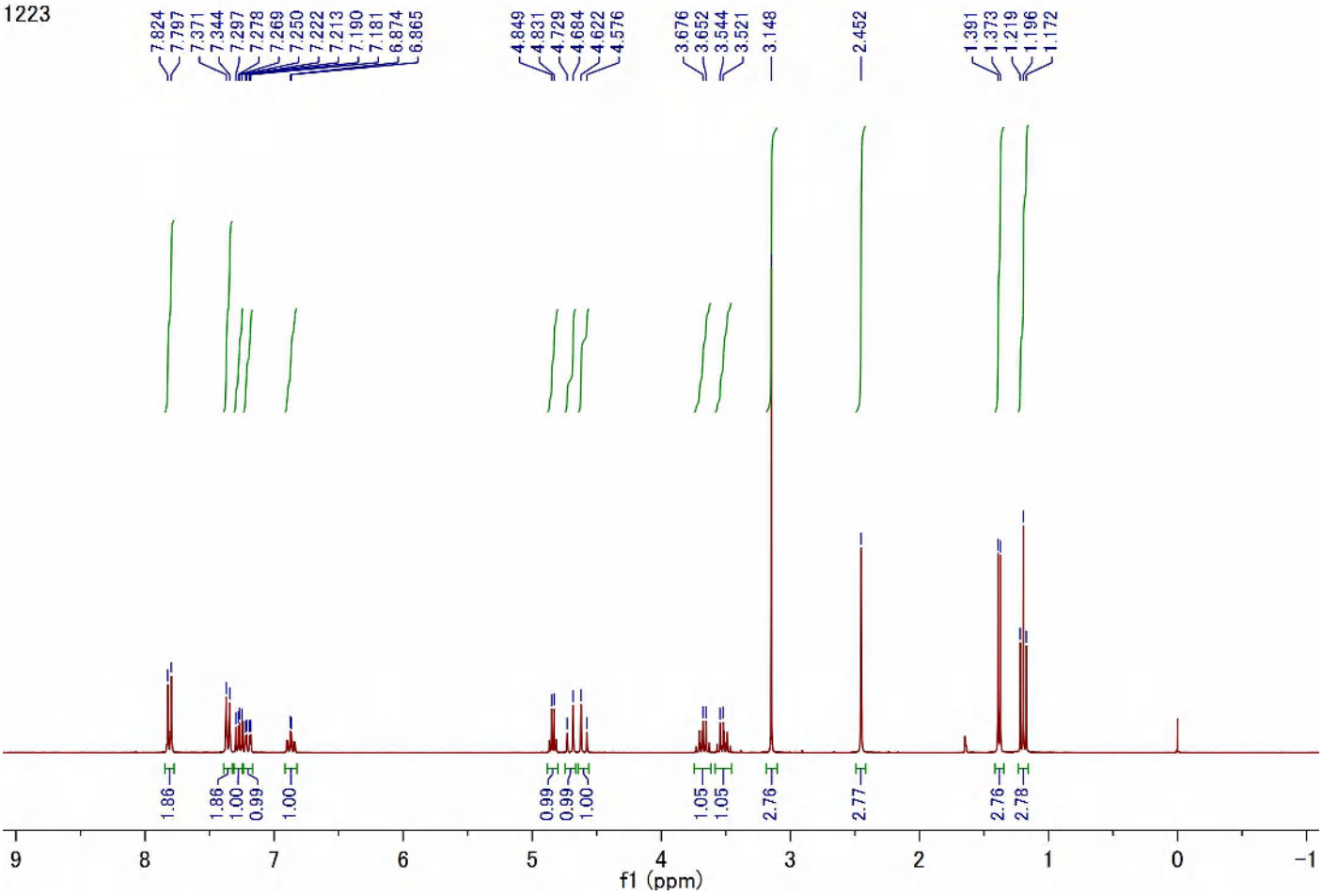
Compound **1i** (^{1}H NMR, 300 MHz, $CDCl_3$)



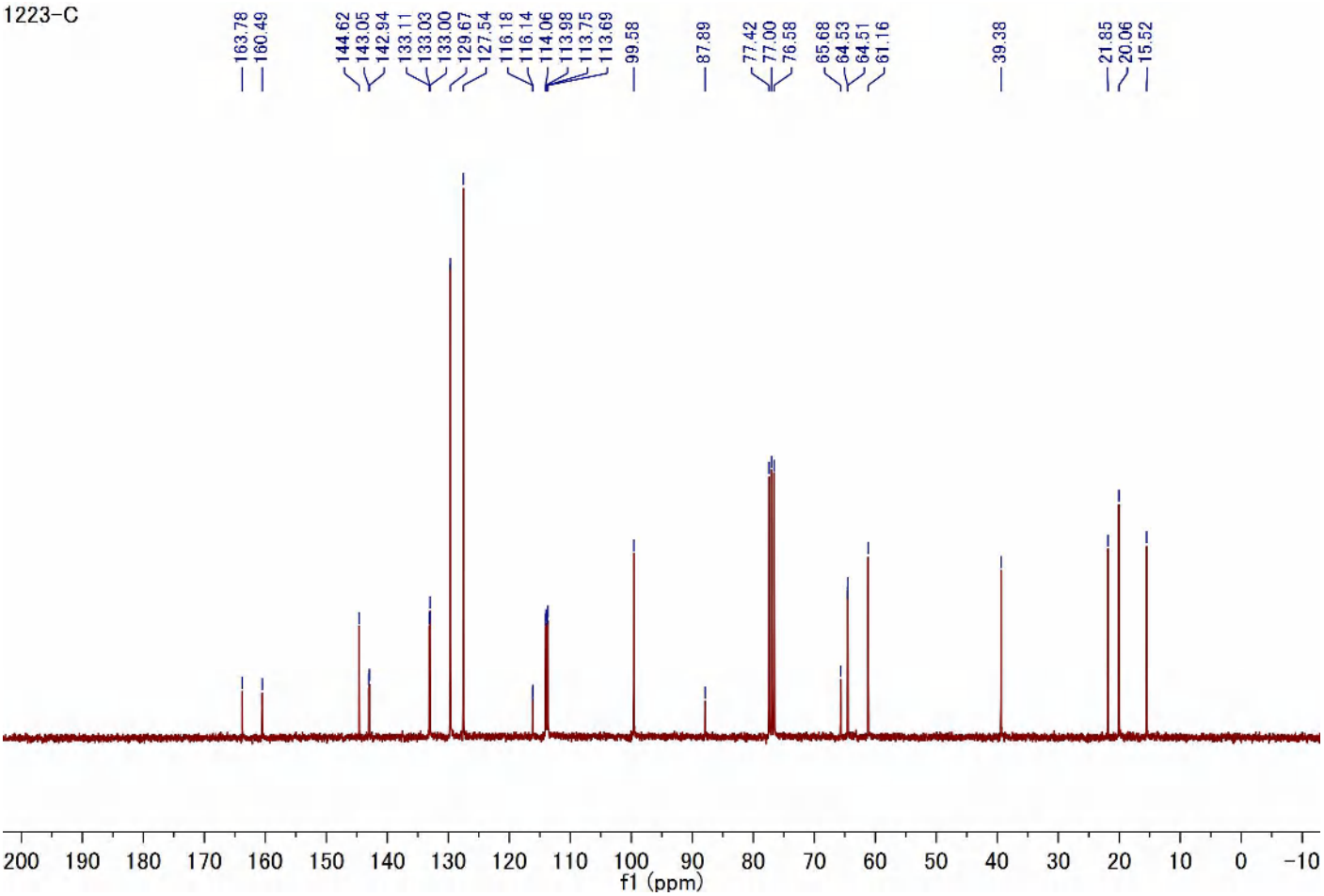
Compound **1i** (^{13}C NMR, 75 MHz, $CDCl_3$)



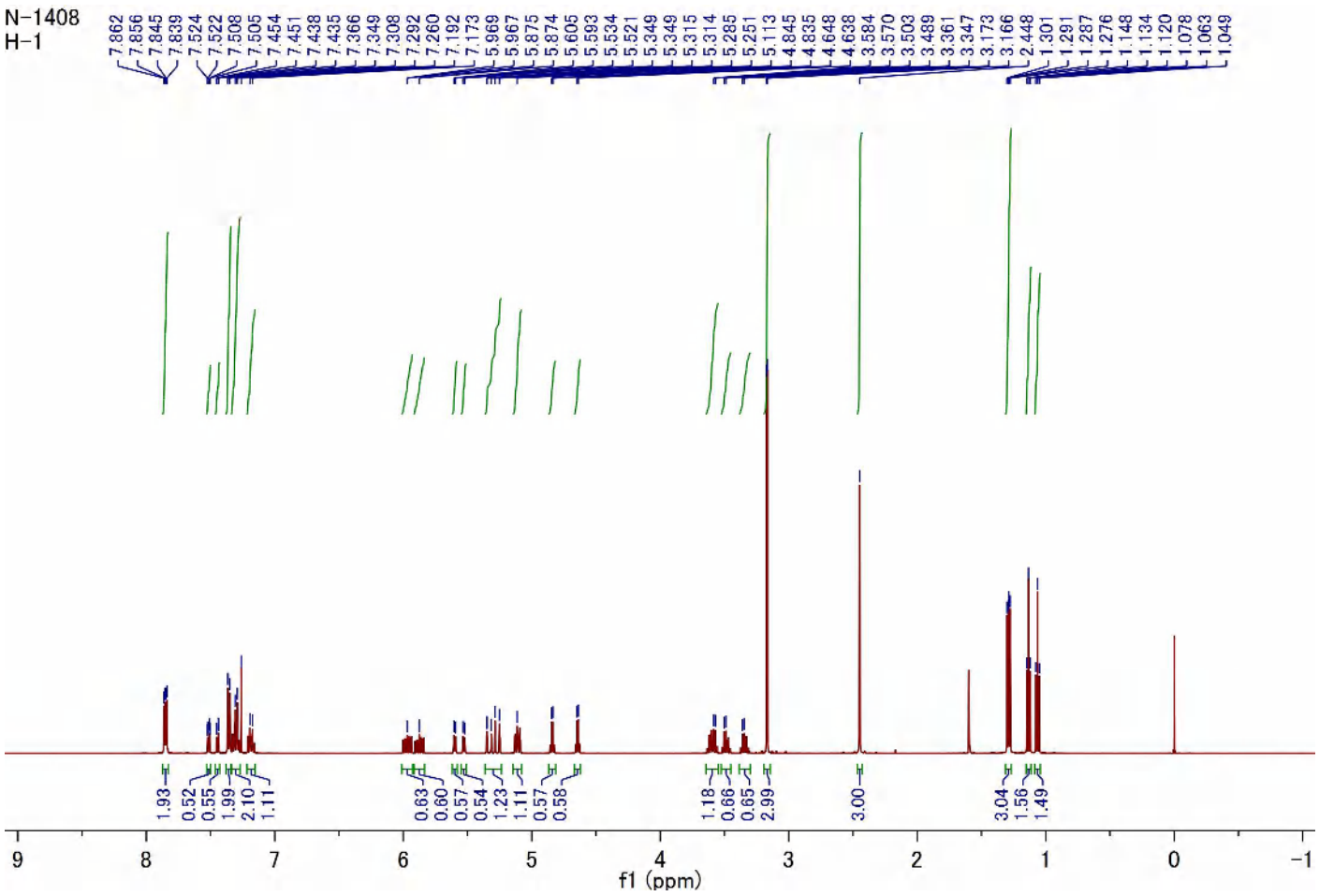
Compound **1j** (^{1}H NMR, 300 MHz, $CDCl_3$)



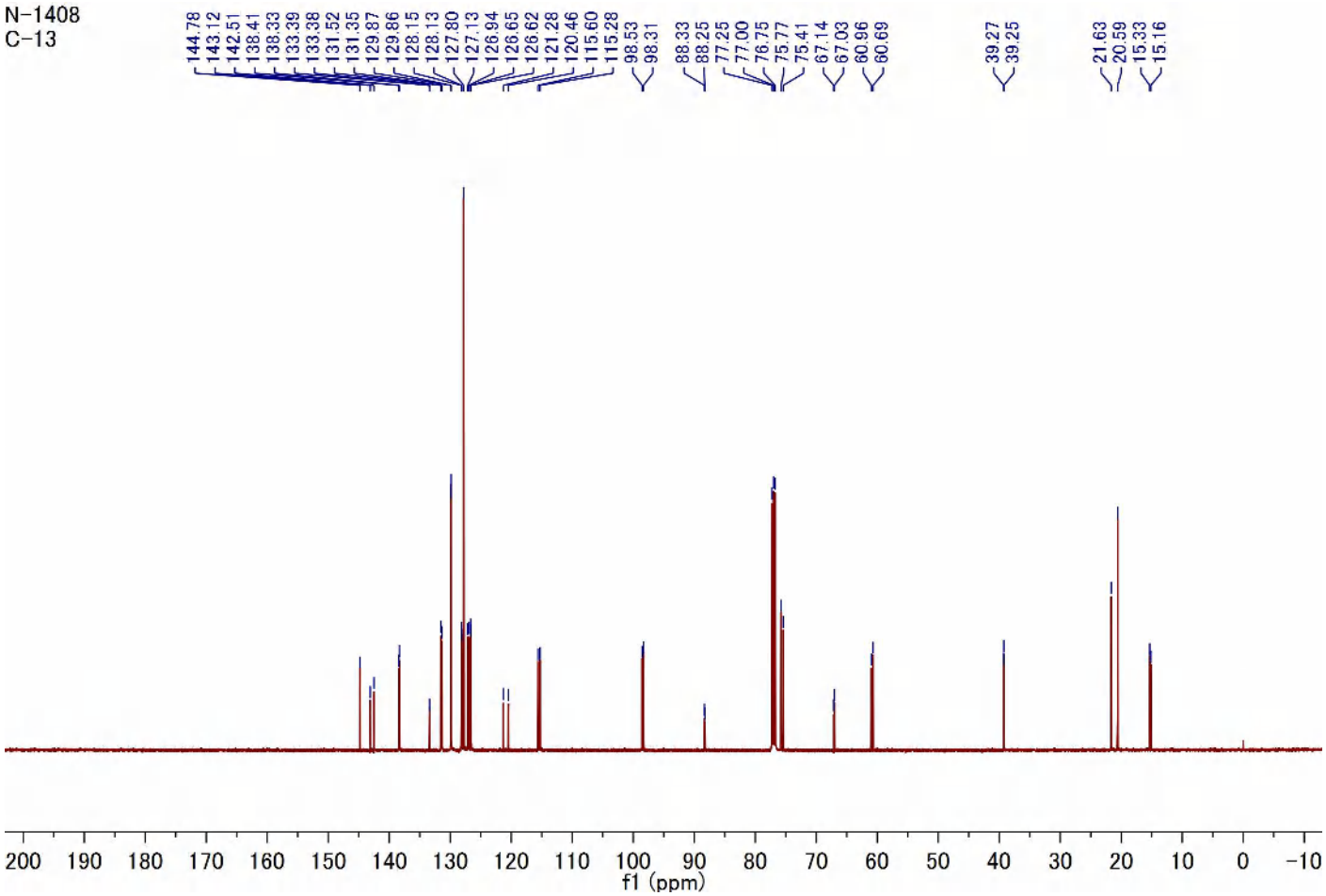
Compound **1j** (^{13}C NMR, 75 MHz, $CDCl_3$)



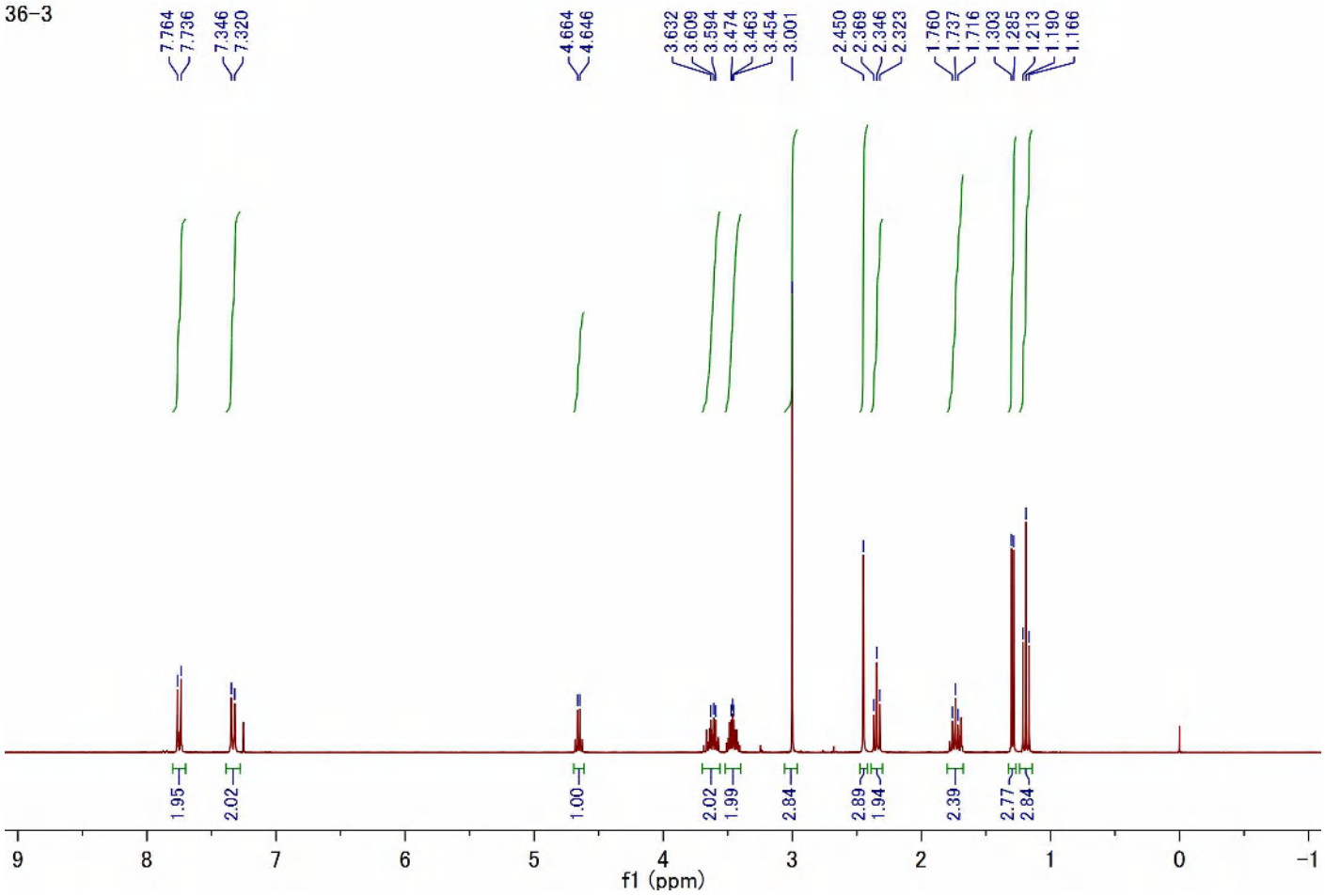
Compound **1k** (^{1}H NMR, 500 MHz, $CDCl_3$)



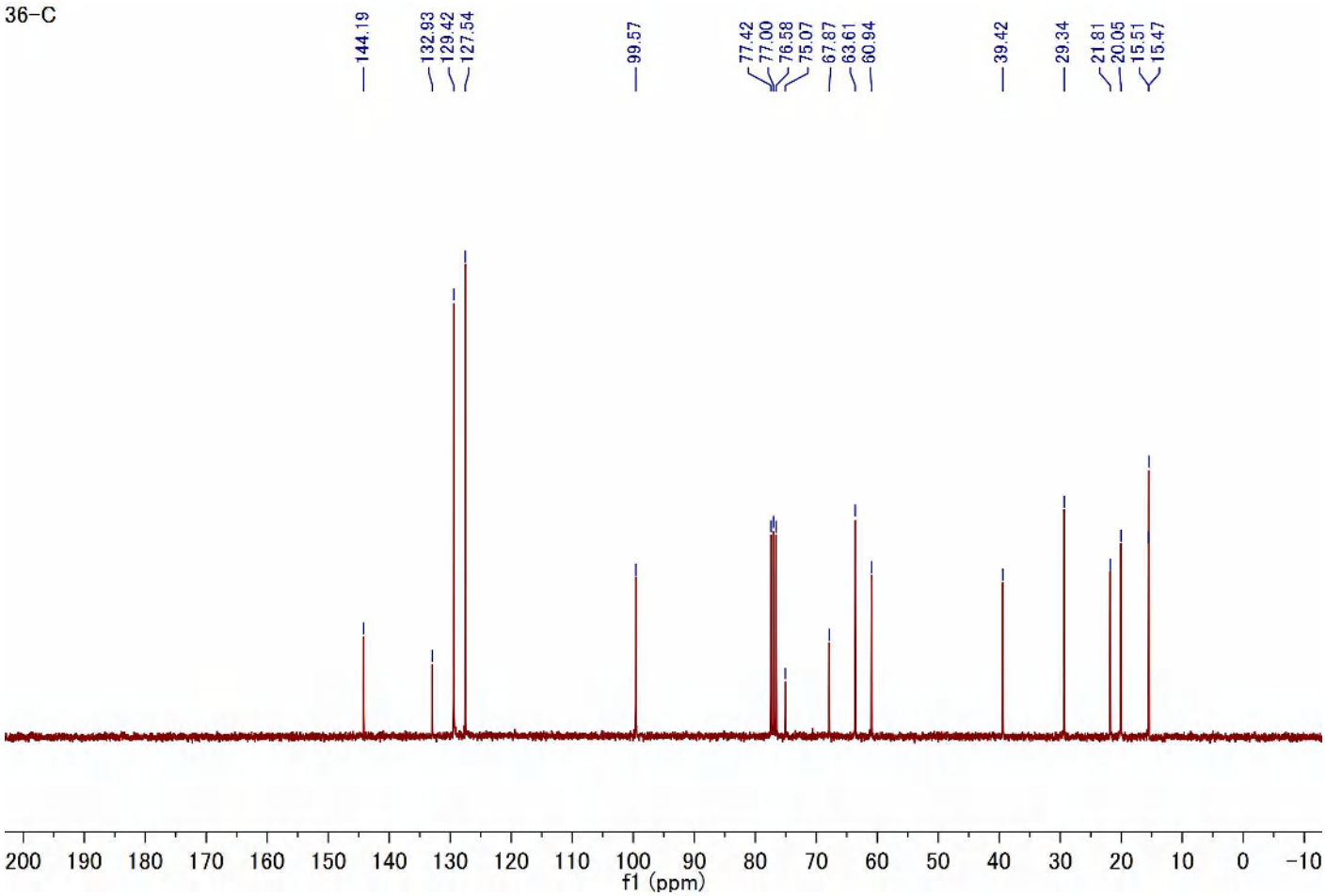
Compound **1k** (^{13}C NMR, 125 MHz, $CDCl_3$)



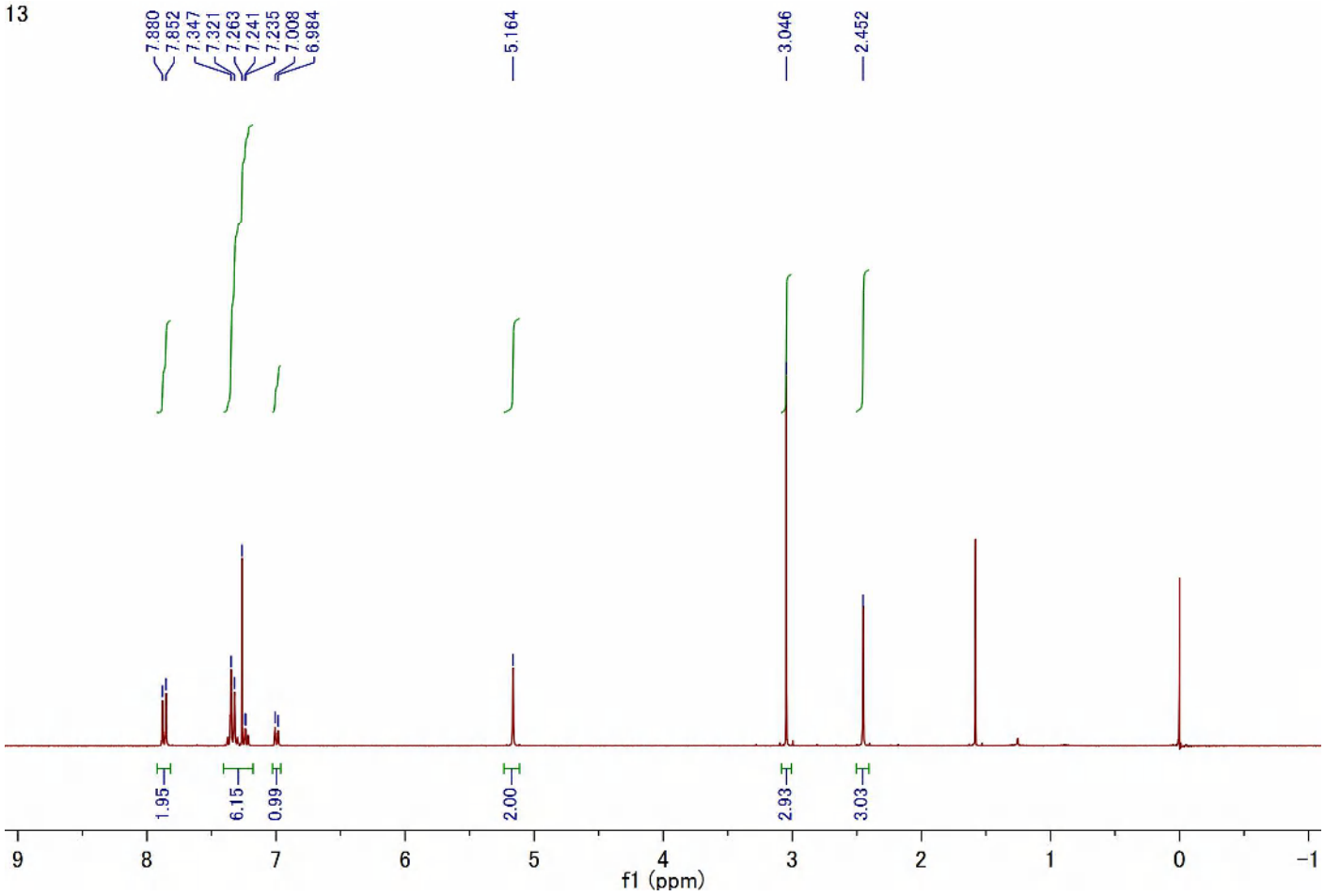
Compound **1l** (^{1}H NMR, 300 MHz, $CDCl_3$)



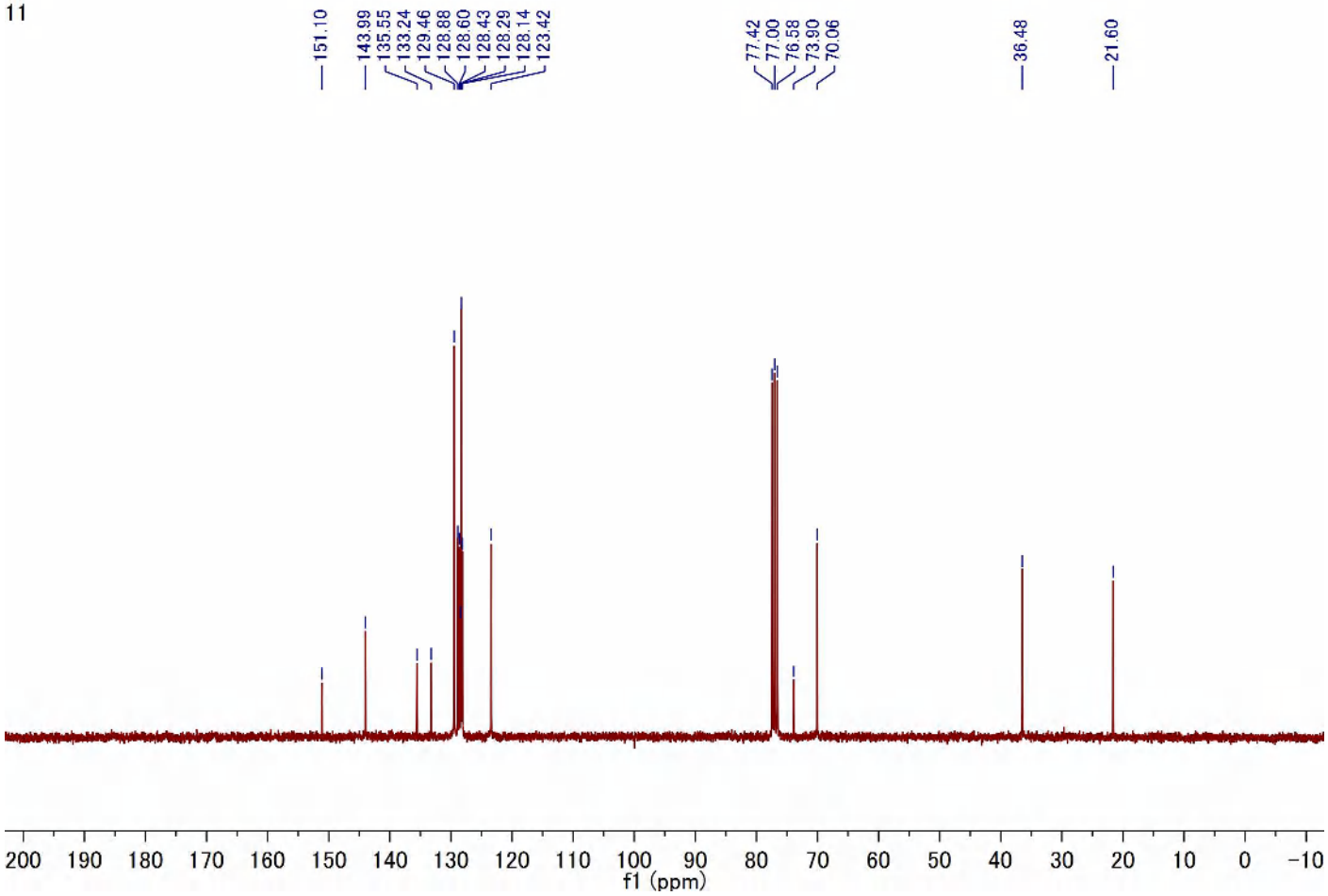
Compound **1l** (^{13}C NMR, 75 MHz, $CDCl_3$)



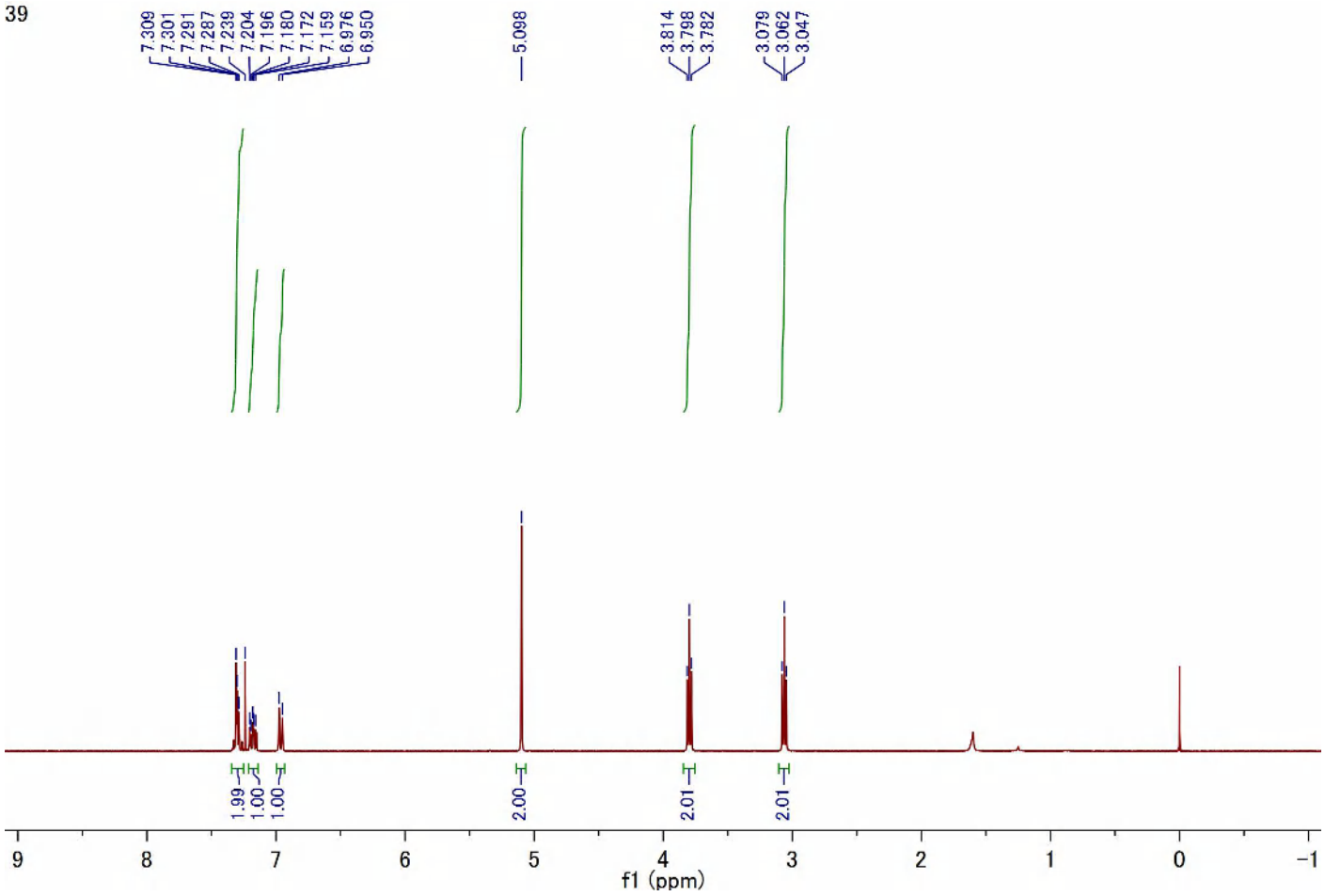
Compound **2a** (^{1}H NMR, 300 MHz, $CDCl_3$)



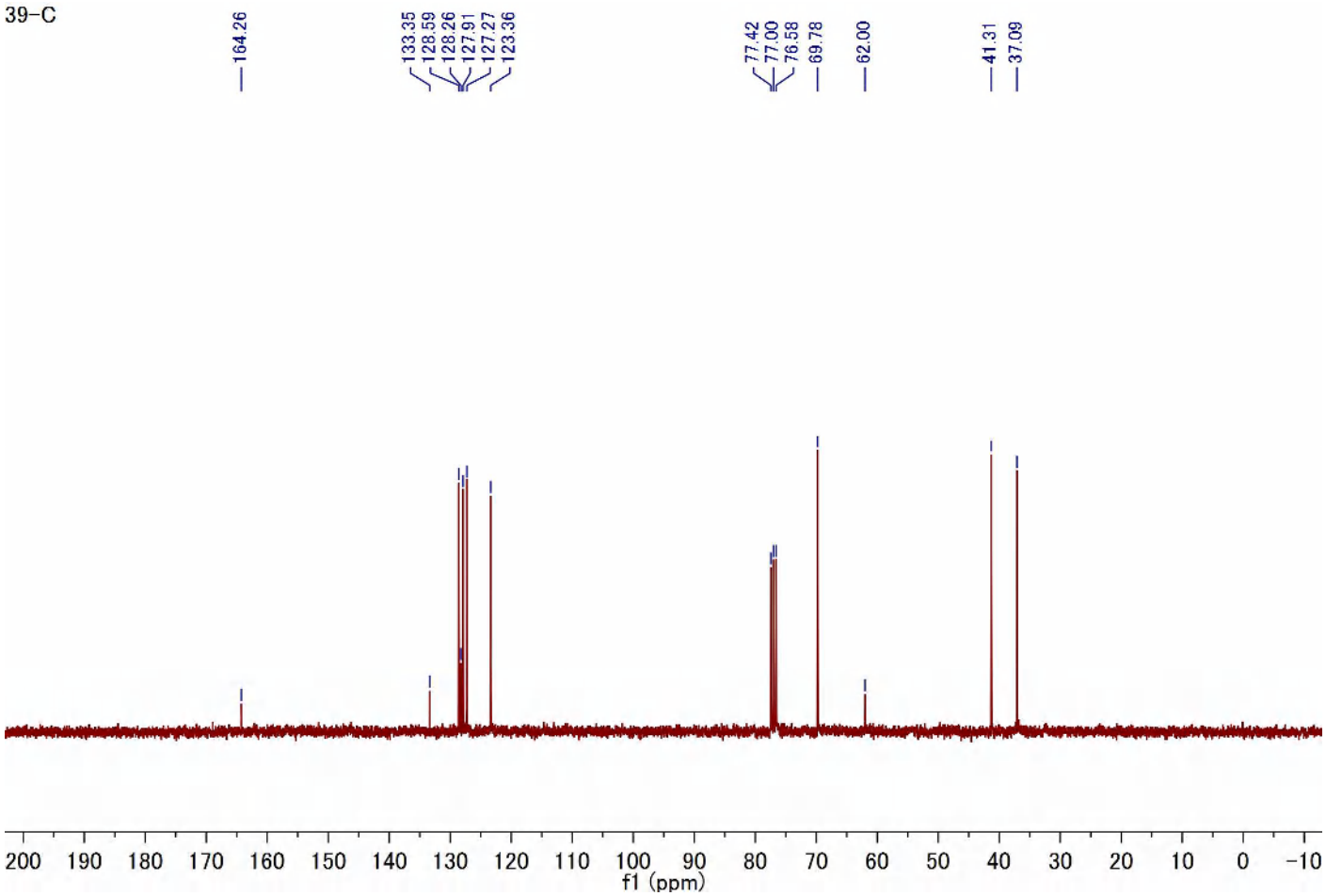
Compound **2a** (^{13}C NMR, 75 MHz, $CDCl_3$)



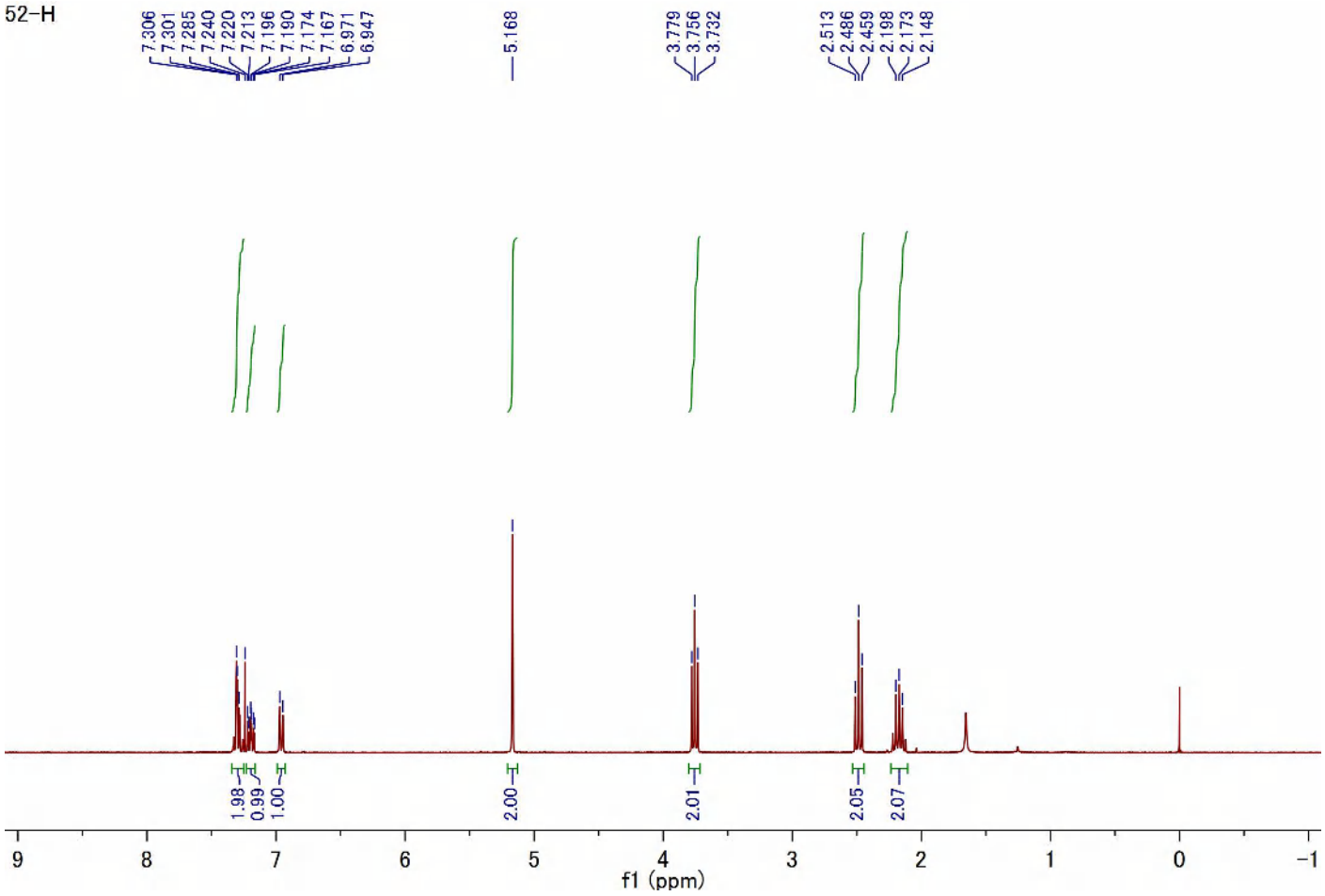
Compound **2b** (^{1}H NMR, 300 MHz, $CDCl_3$)



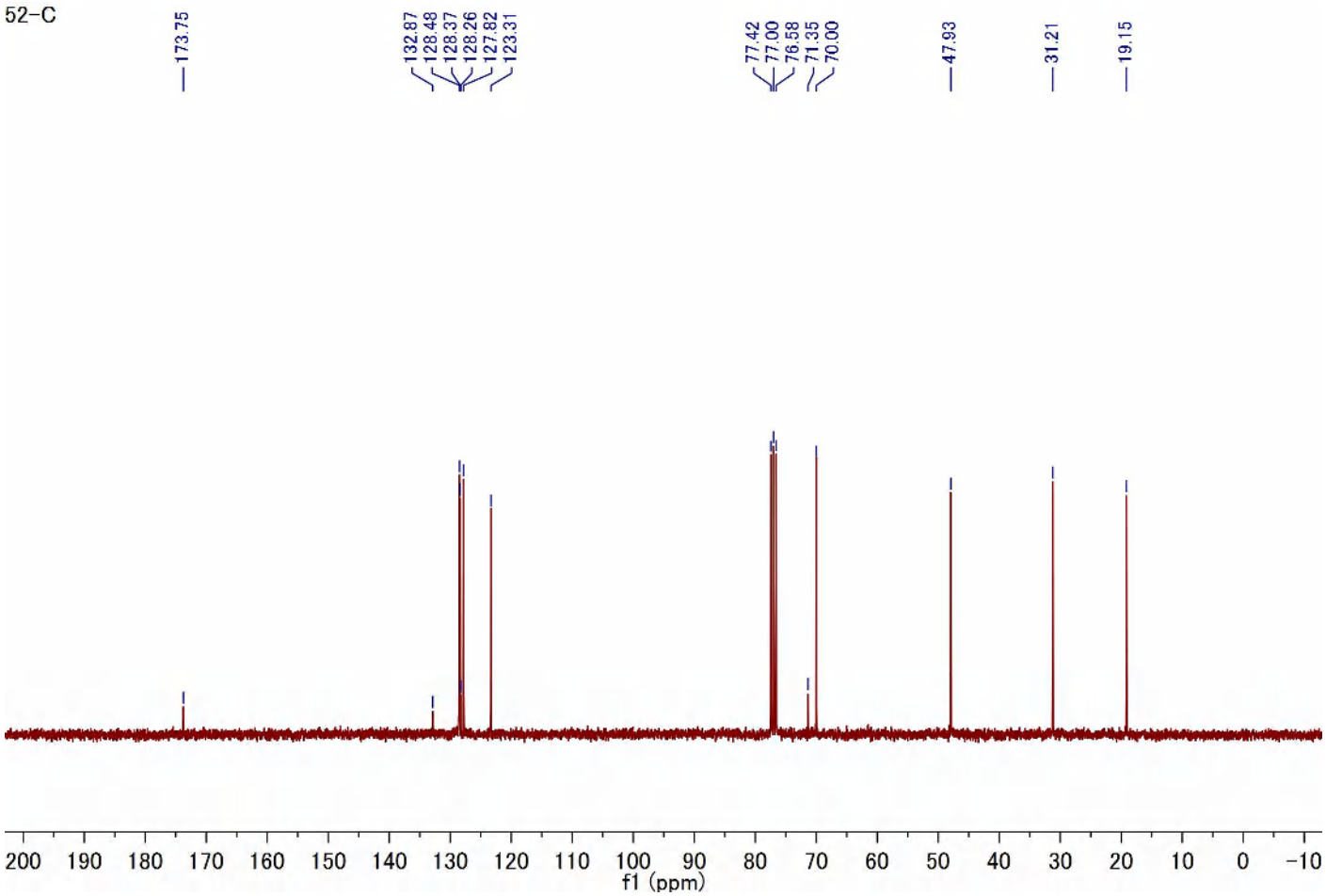
Compound **2b** (^{13}C NMR, 75 MHz, $CDCl_3$)



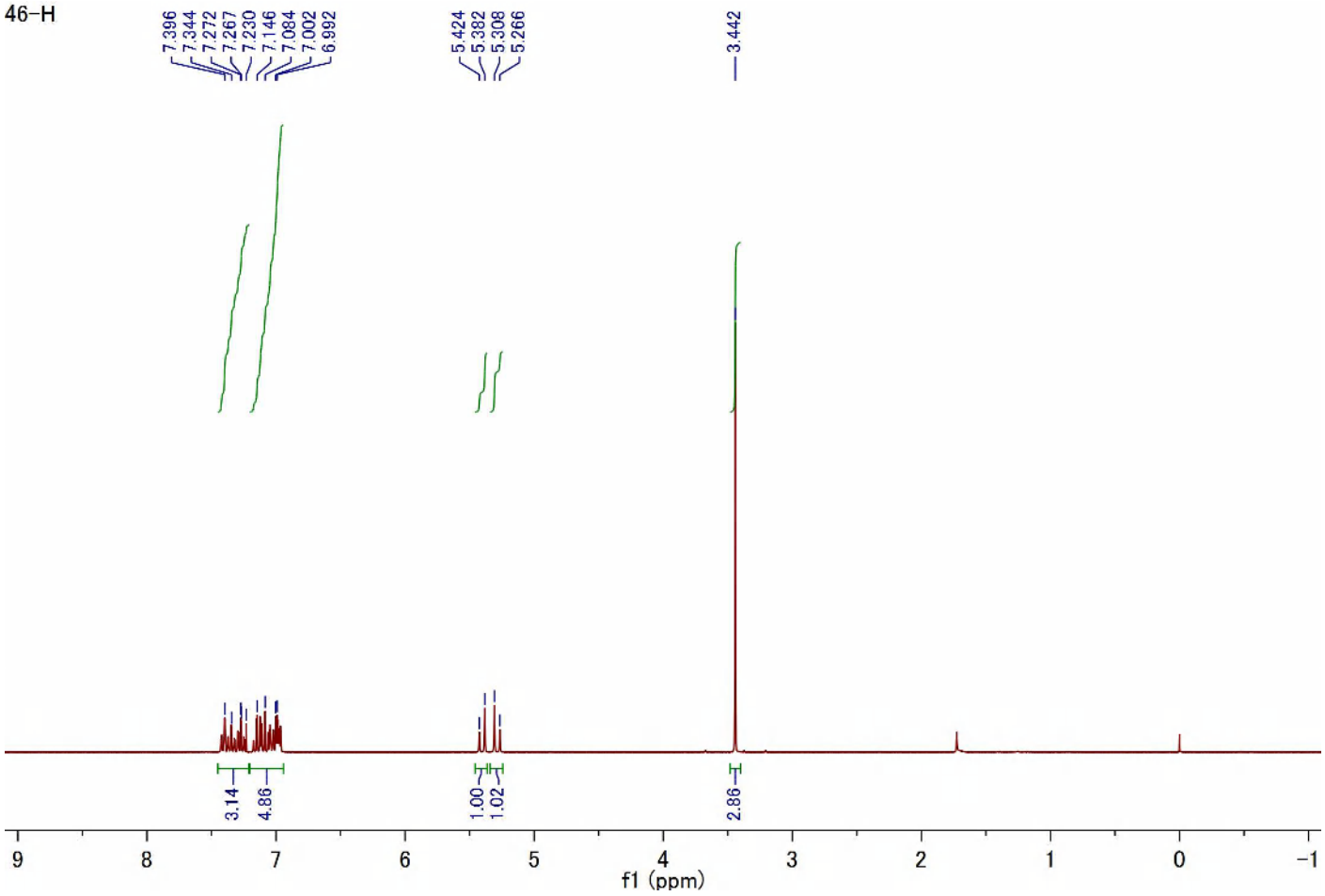
Compound **2c** (^{1}H NMR, 300 MHz, $CDCl_3$)



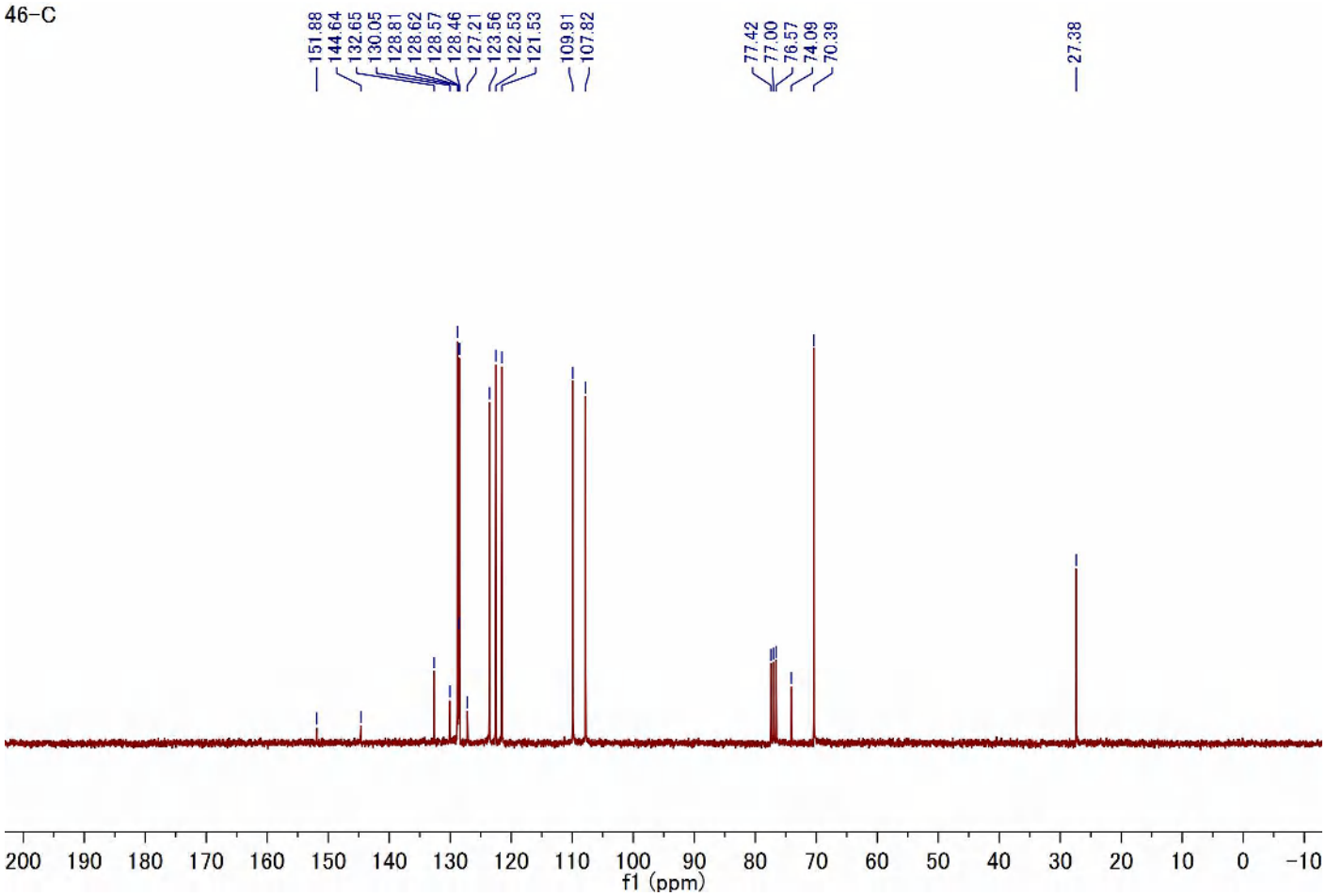
Compound **2c** (^{13}C NMR, 75 MHz, $CDCl_3$)



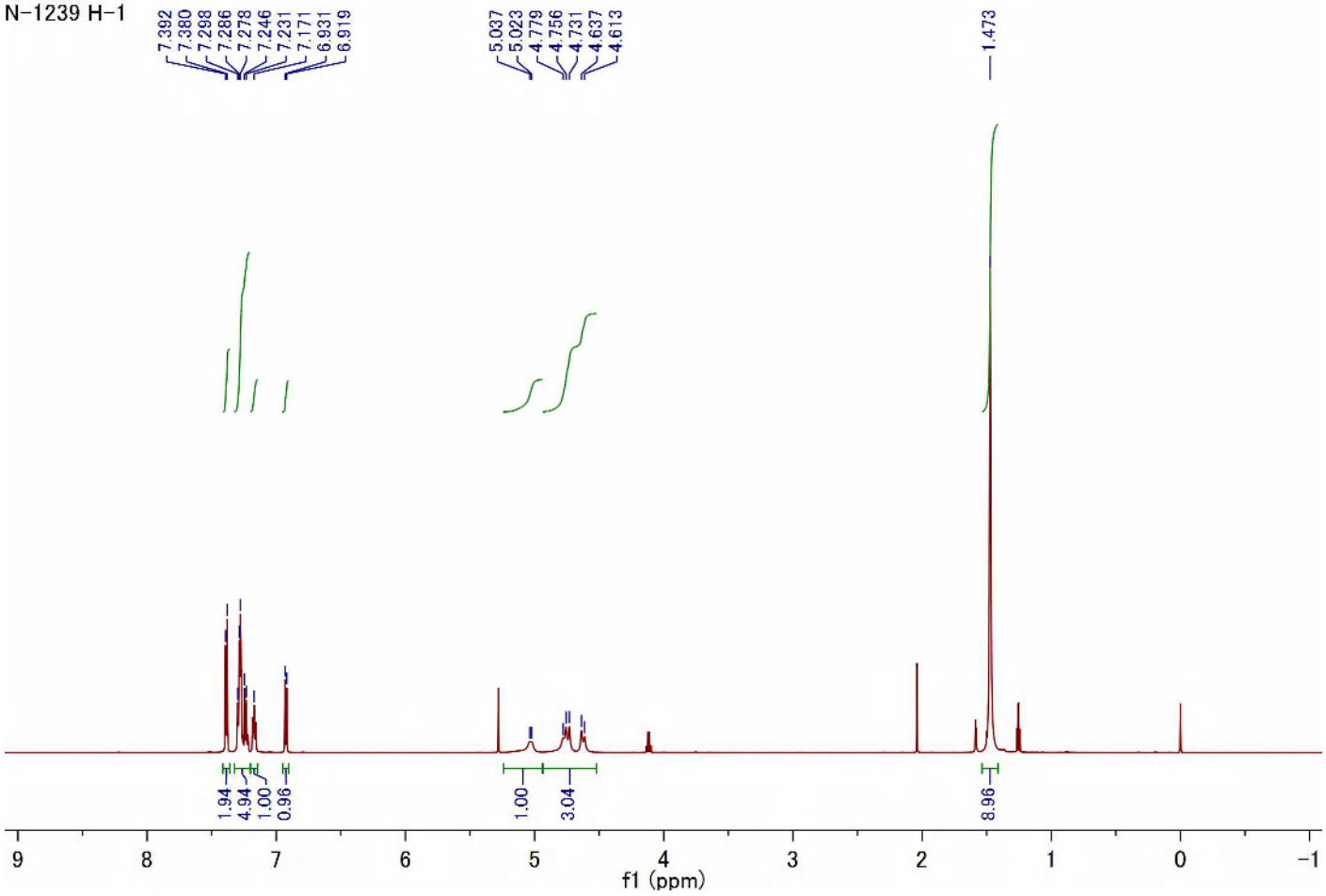
Compound **2d** (^{1}H NMR, 300 MHz, $CDCl_3$)



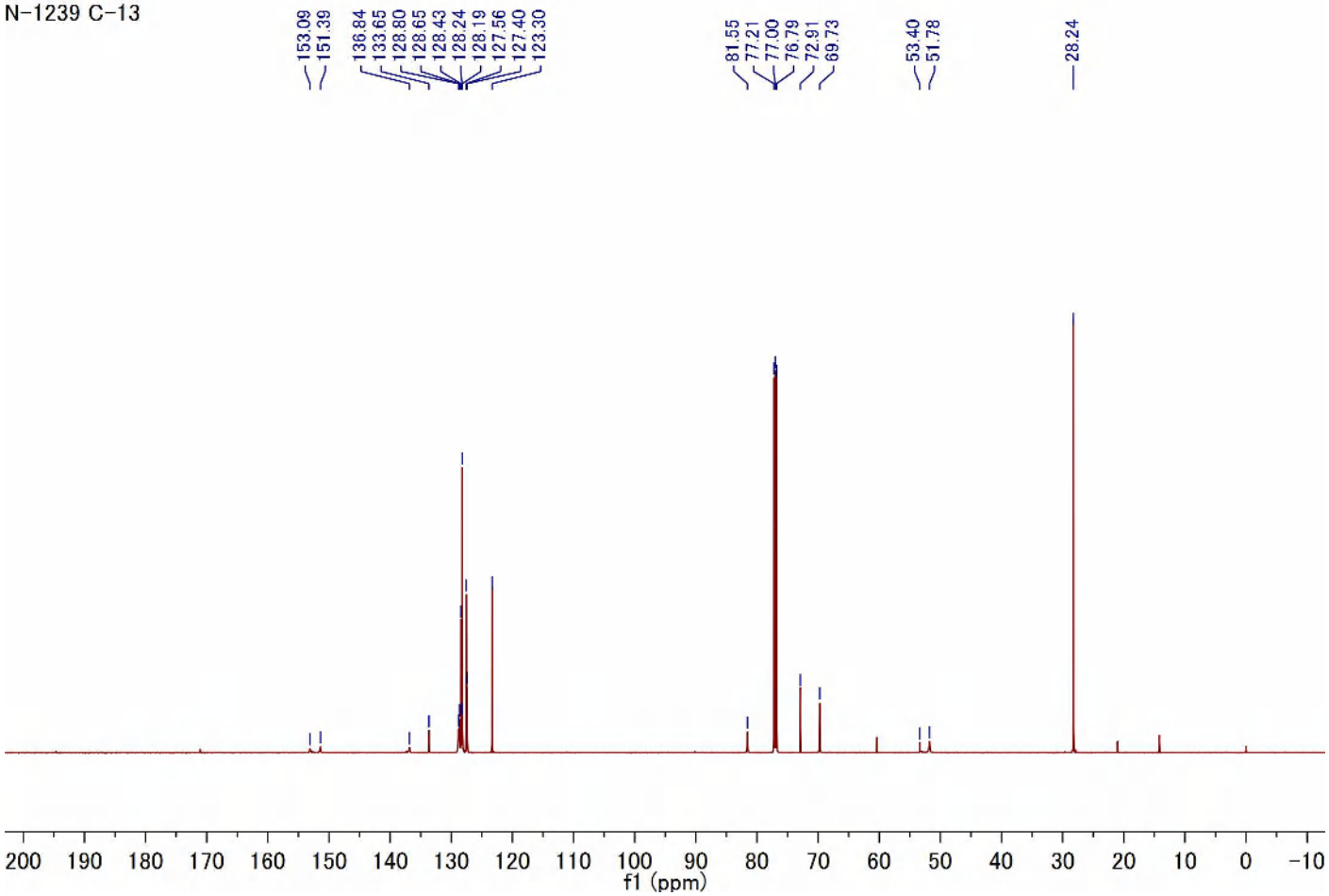
Compound **2d** (^{13}C NMR, 75 MHz, $CDCl_3$)



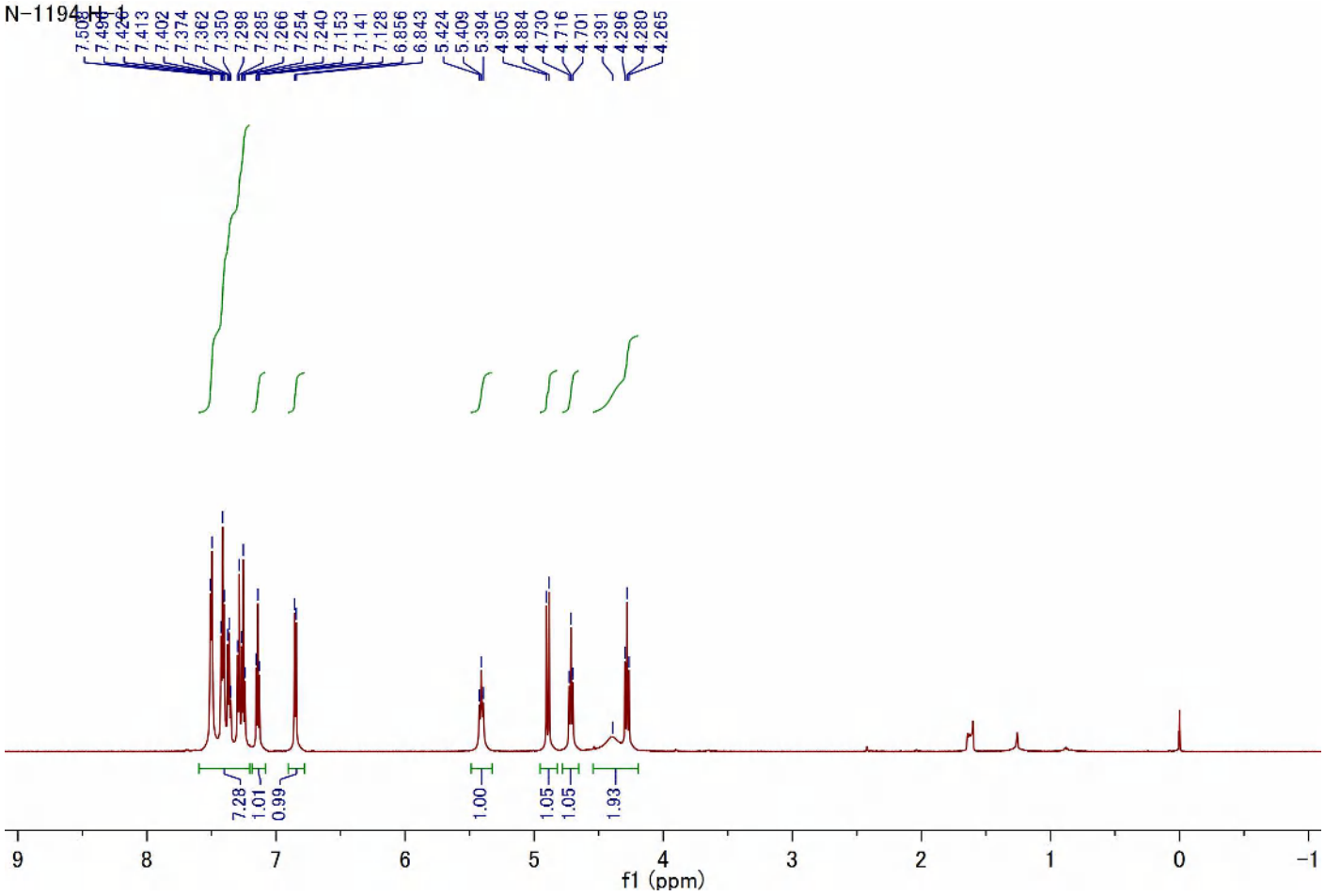
Compound **2e** (^{1}H NMR, 600 MHz, $CDCl_3$)



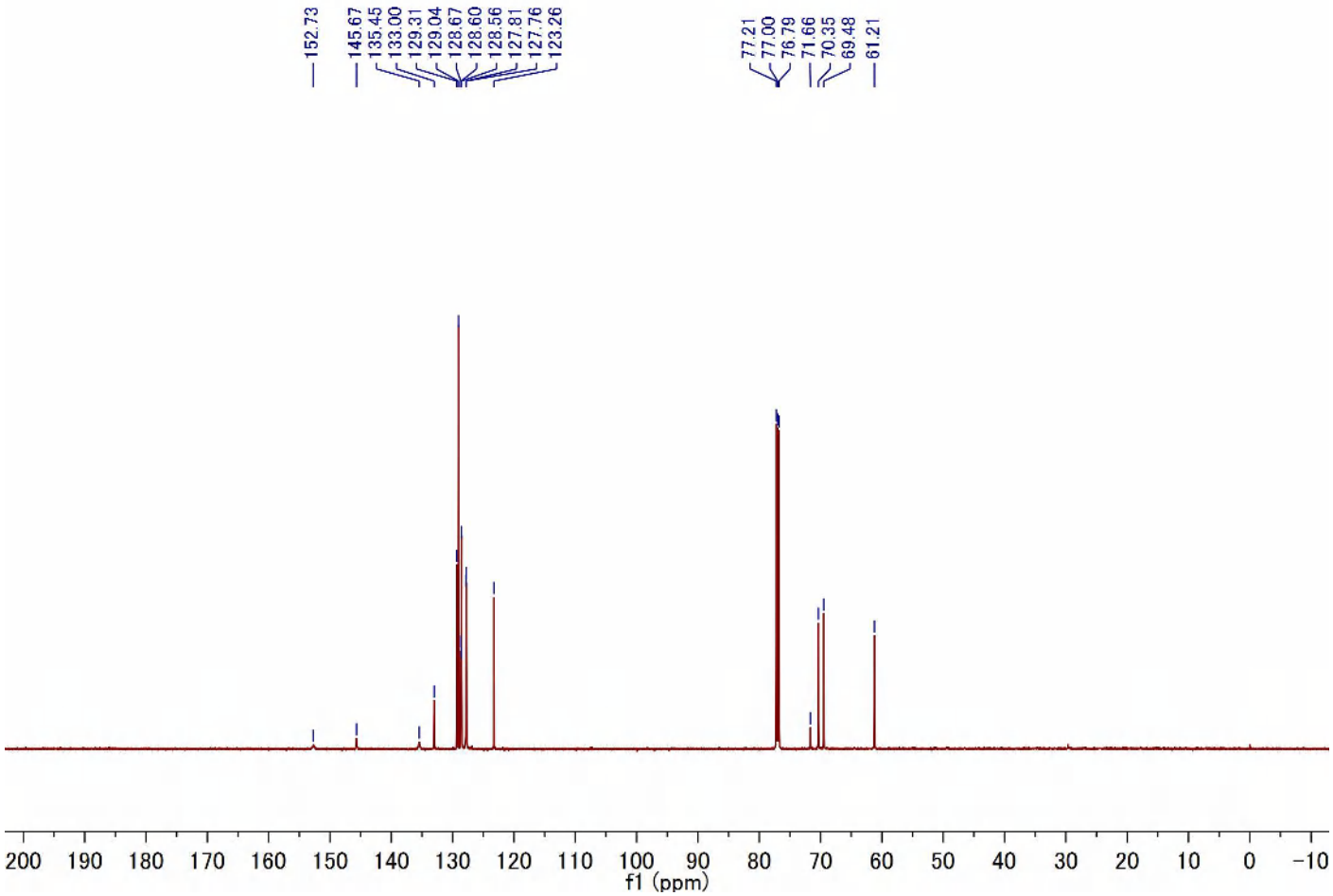
Compound **2e** (^{13}C NMR, 150 MHz, $CDCl_3$)



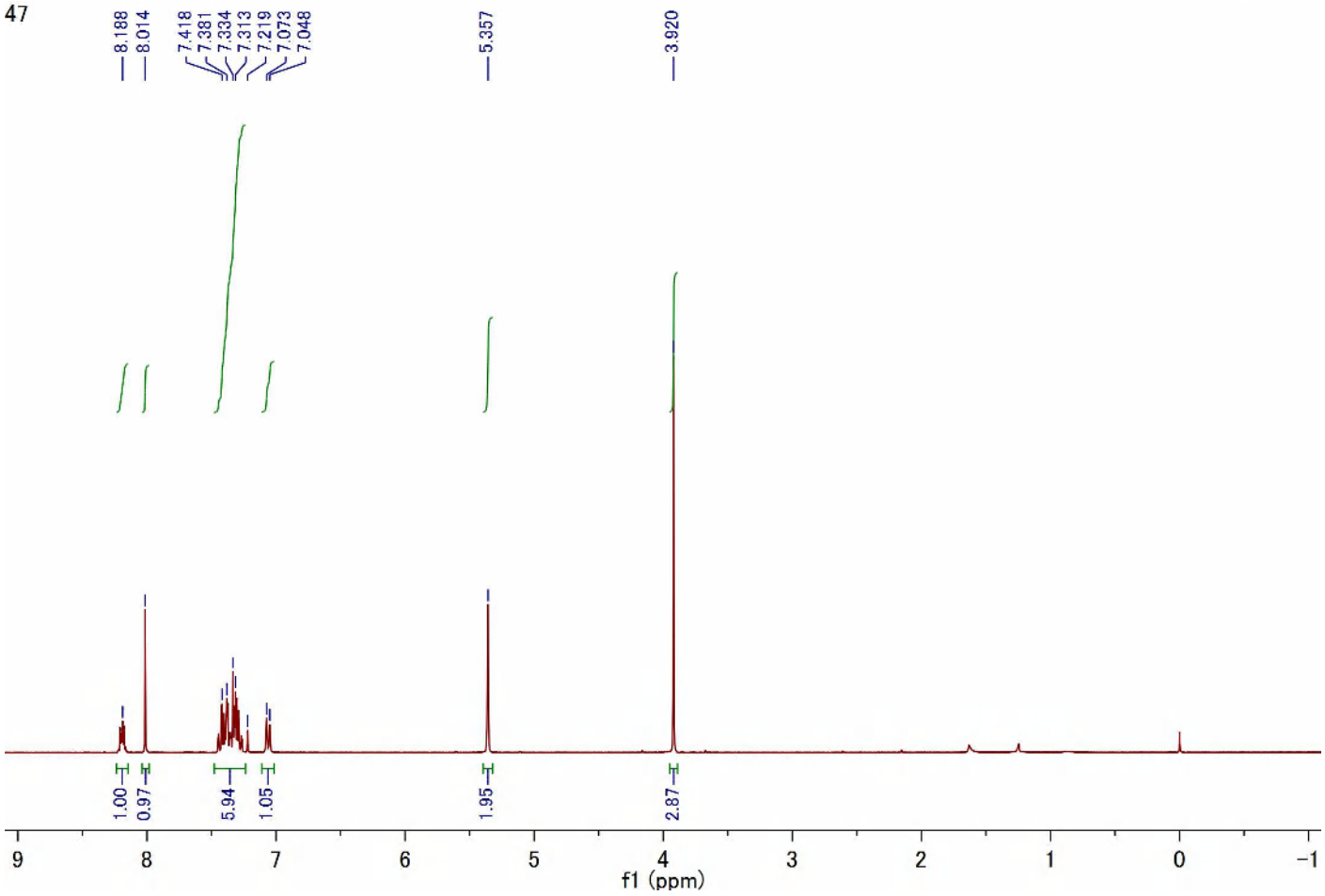
Compound **2f** (^{1}H NMR, 600 MHz, $CDCl_3$)



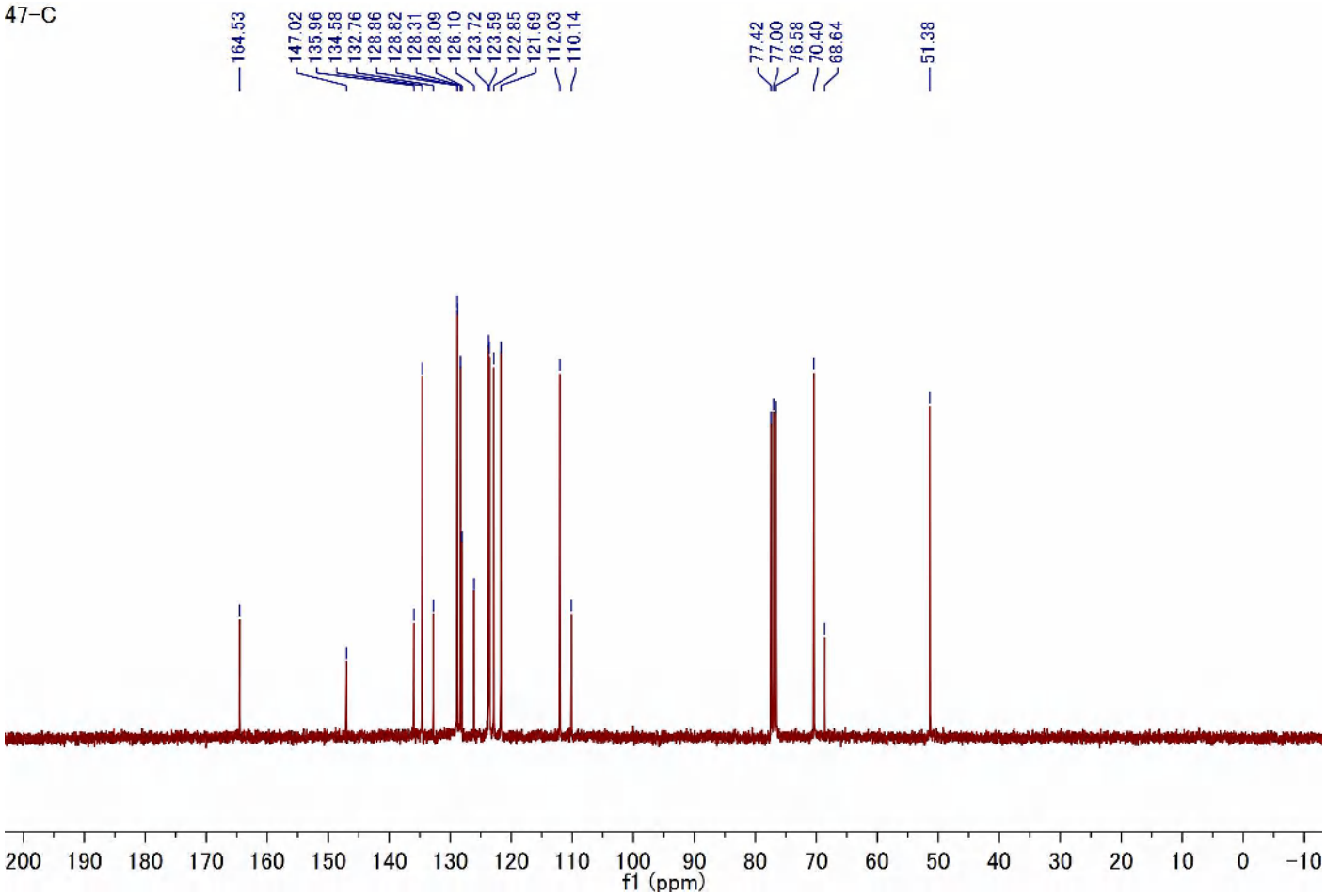
Compound **2f** (^{13}C NMR, 150 MHz, $CDCl_3$)



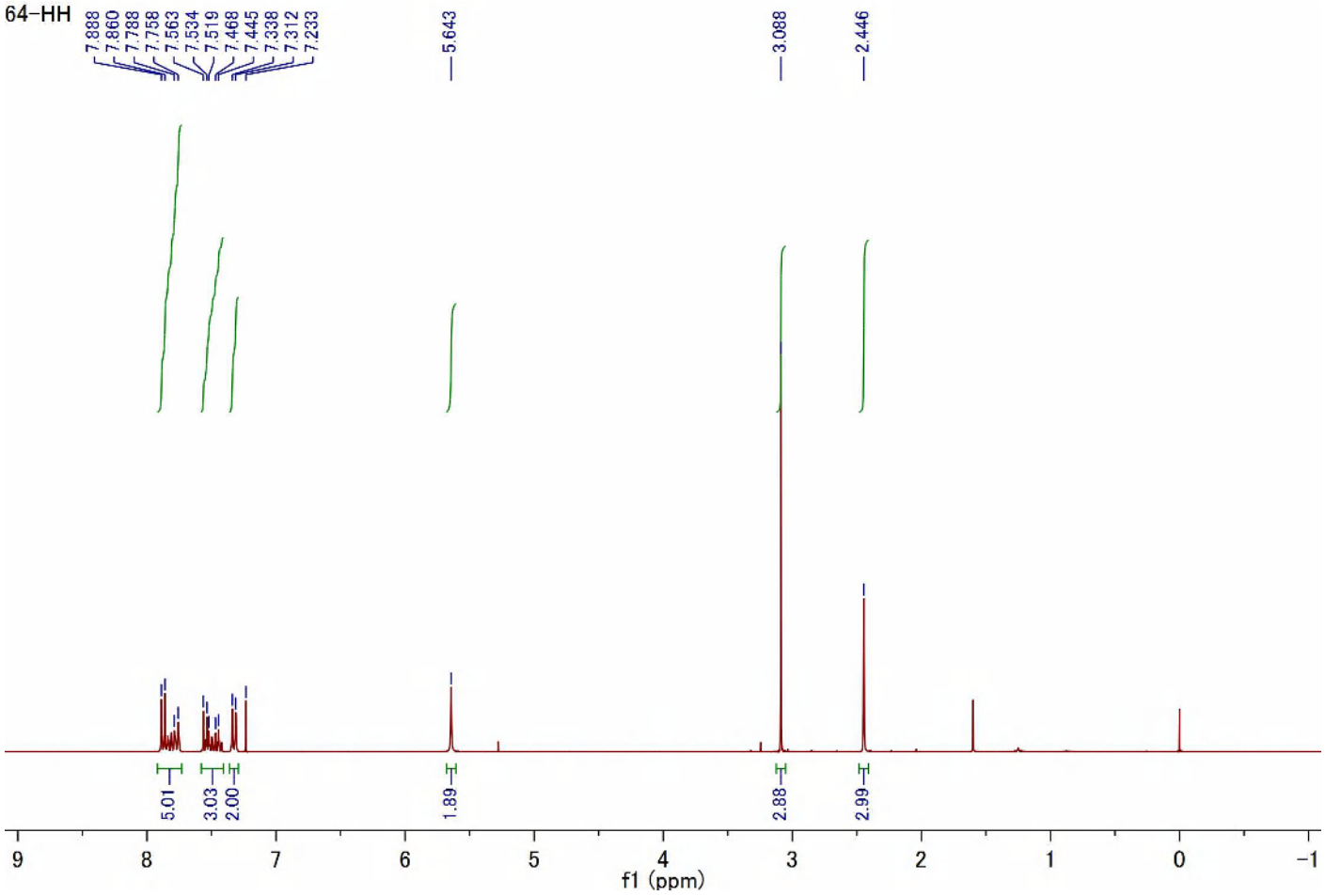
Compound **2g** (^{1}H NMR, 300 MHz, $CDCl_3$)



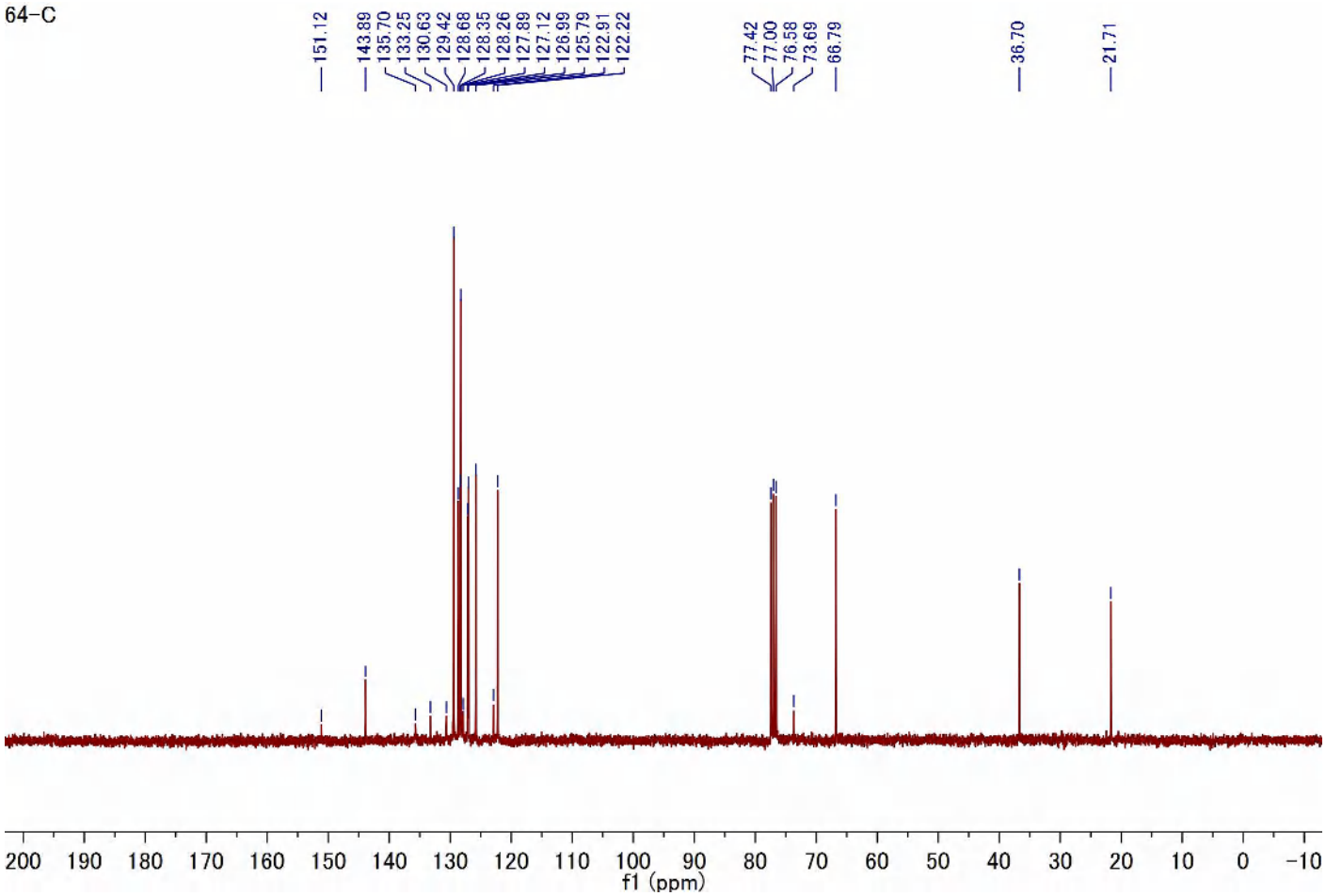
Compound **2g** (^{13}C NMR, 75 MHz, $CDCl_3$)



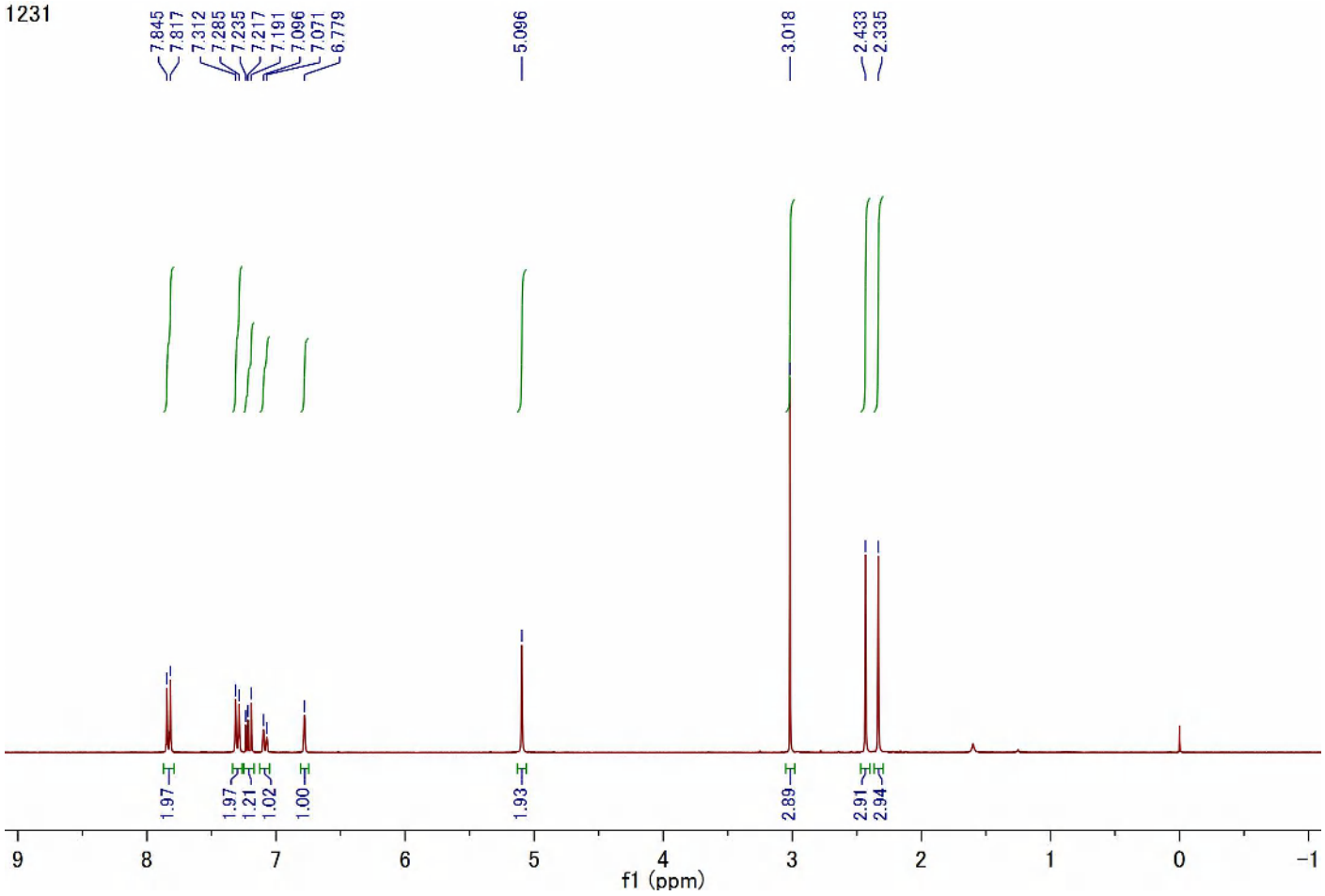
Compound **2h** (^{1}H NMR, 300 MHz, $CDCl_3$)



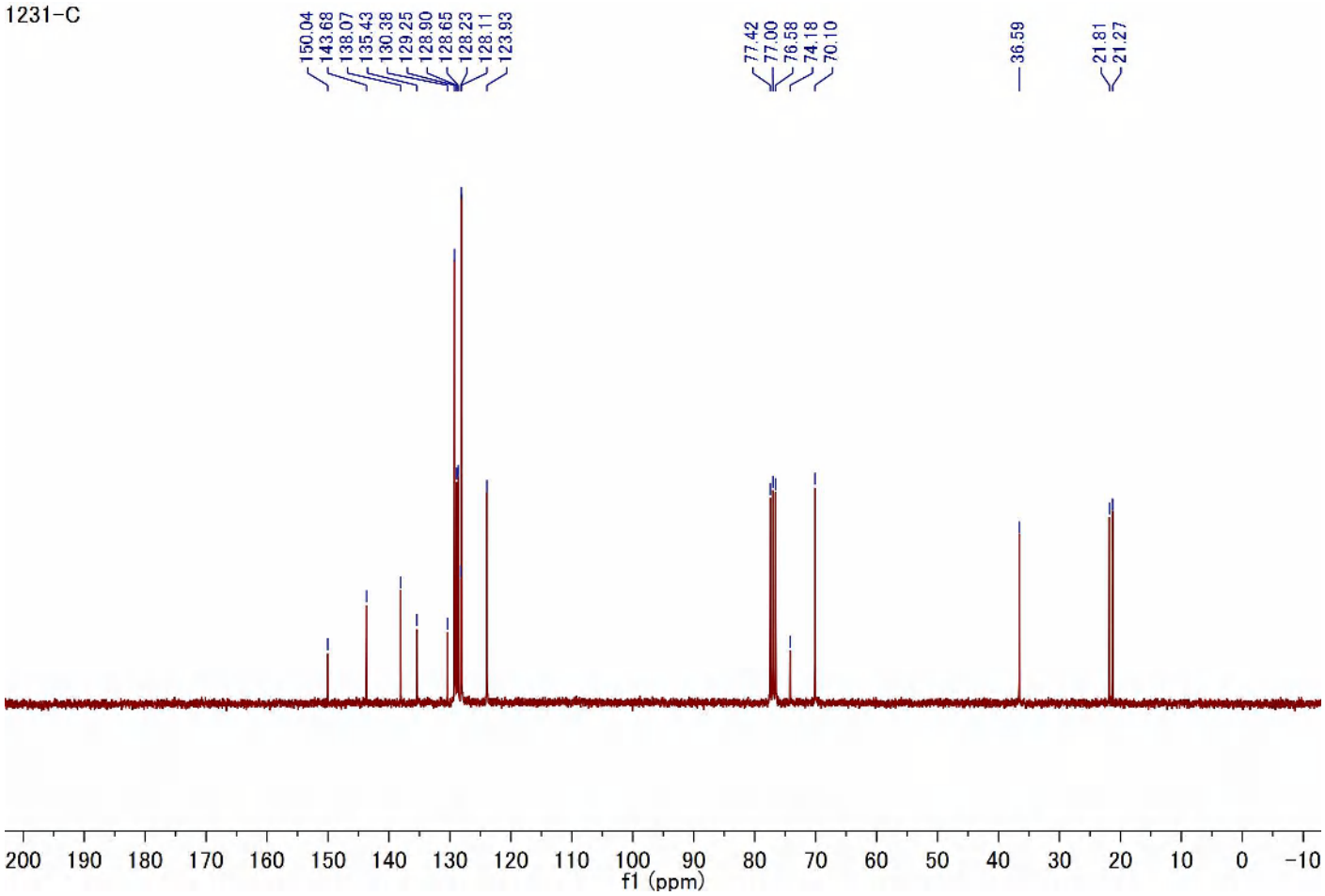
Compound **2h** (^{13}C NMR, 75 MHz, $CDCl_3$)



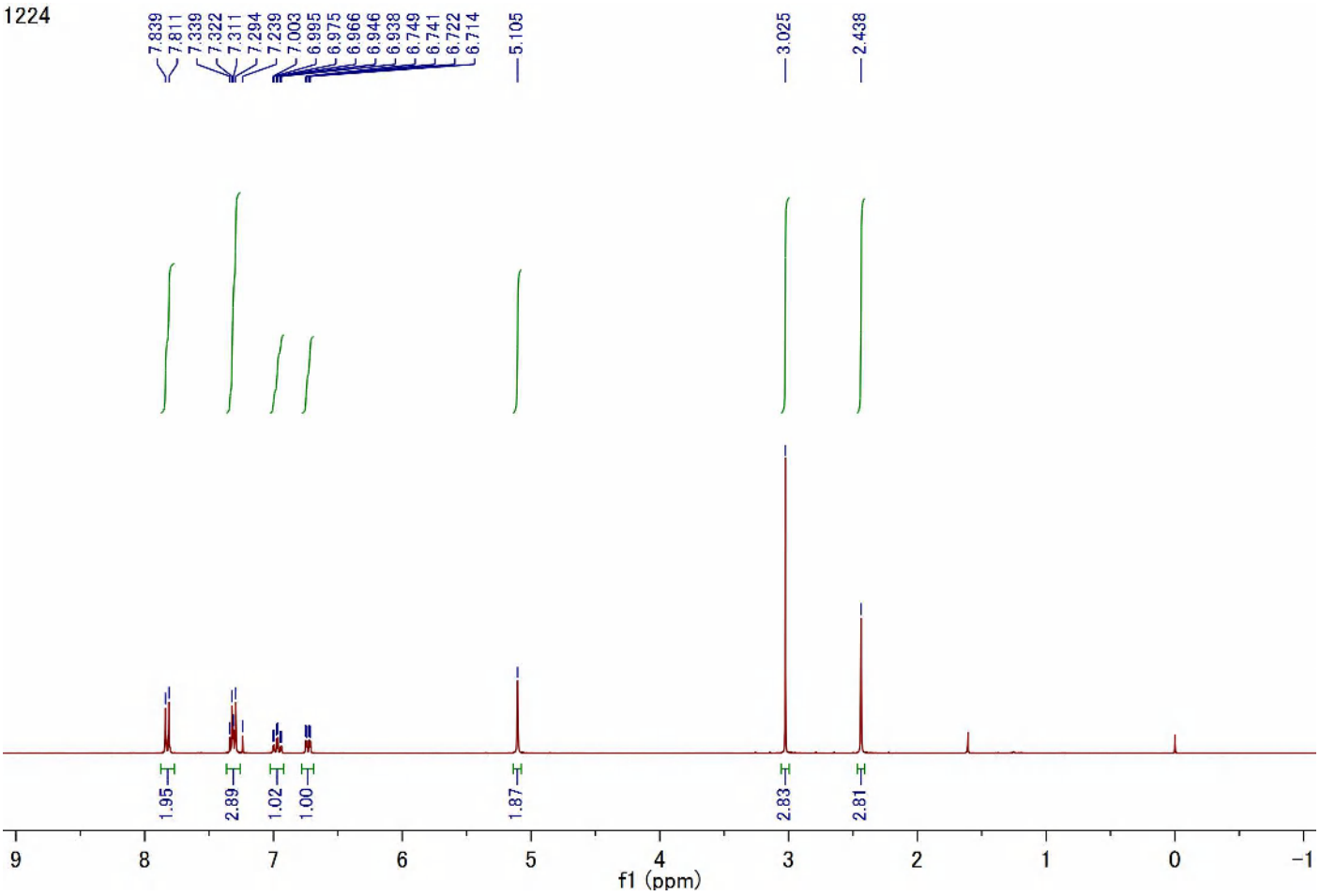
Compound **2i** (^{1}H NMR, 300 MHz, $CDCl_3$)



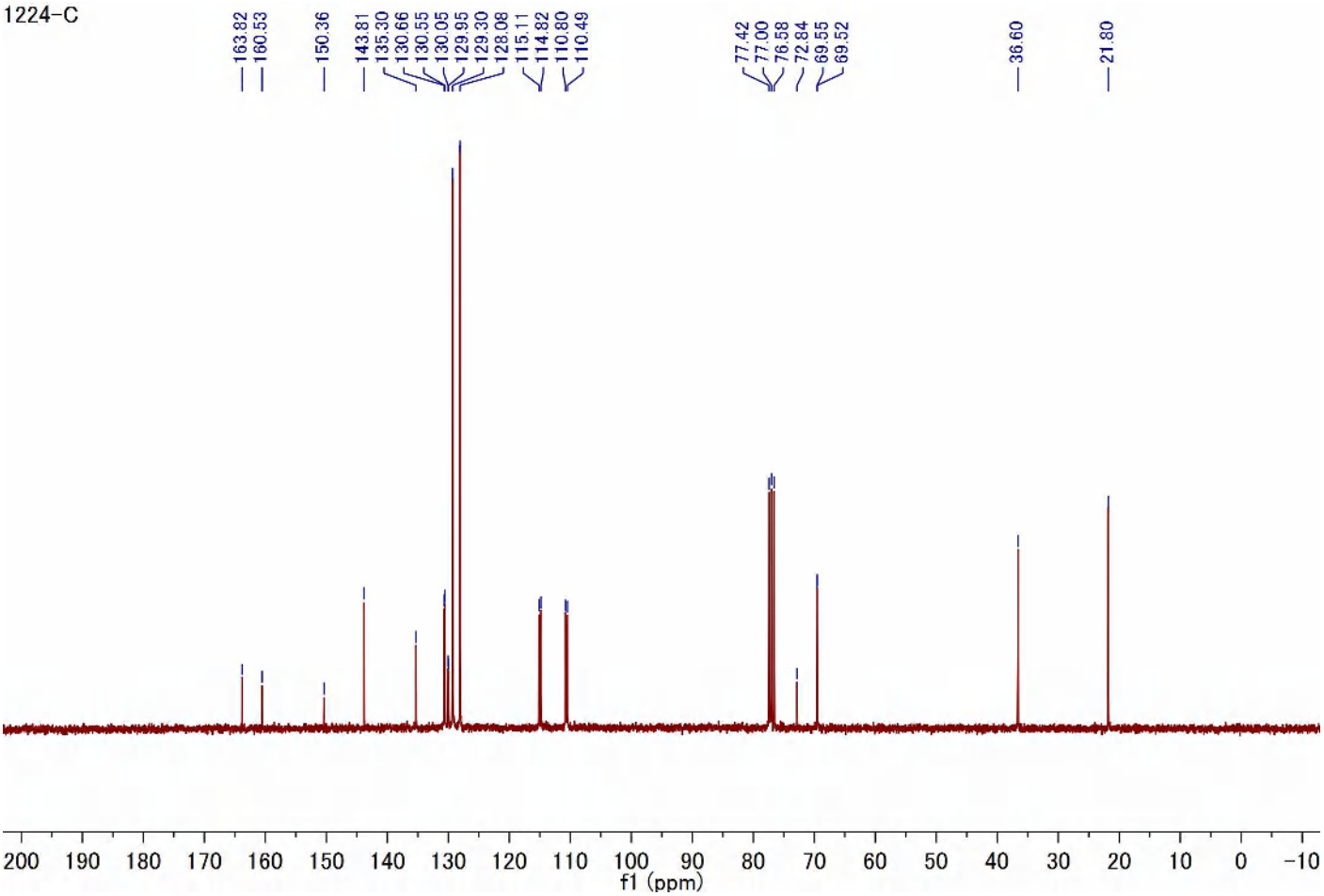
Compound **2i** (^{13}C NMR, 75 MHz, $CDCl_3$)



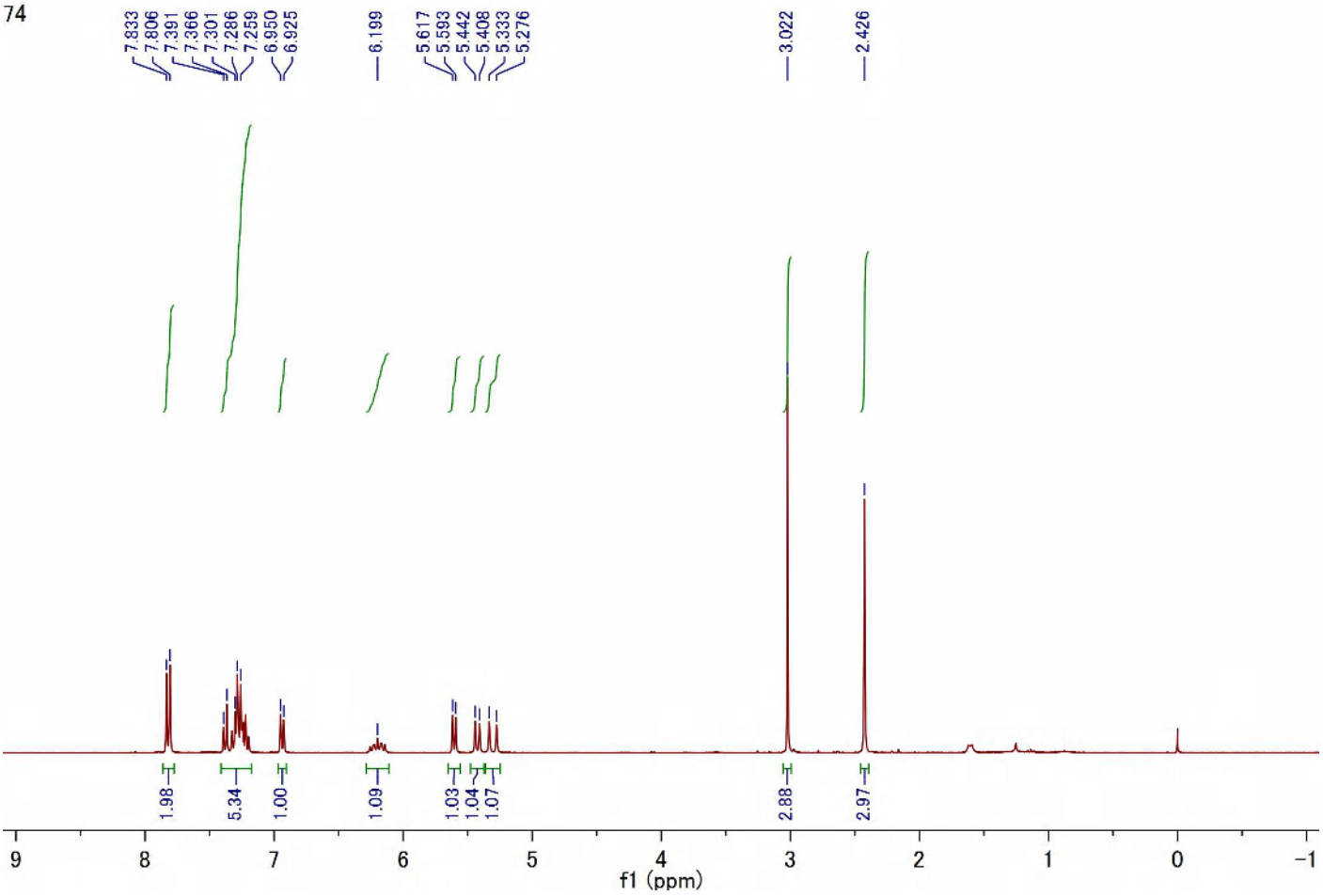
Compound **2j** (^{1}H NMR, 300 MHz, $CDCl_3$)



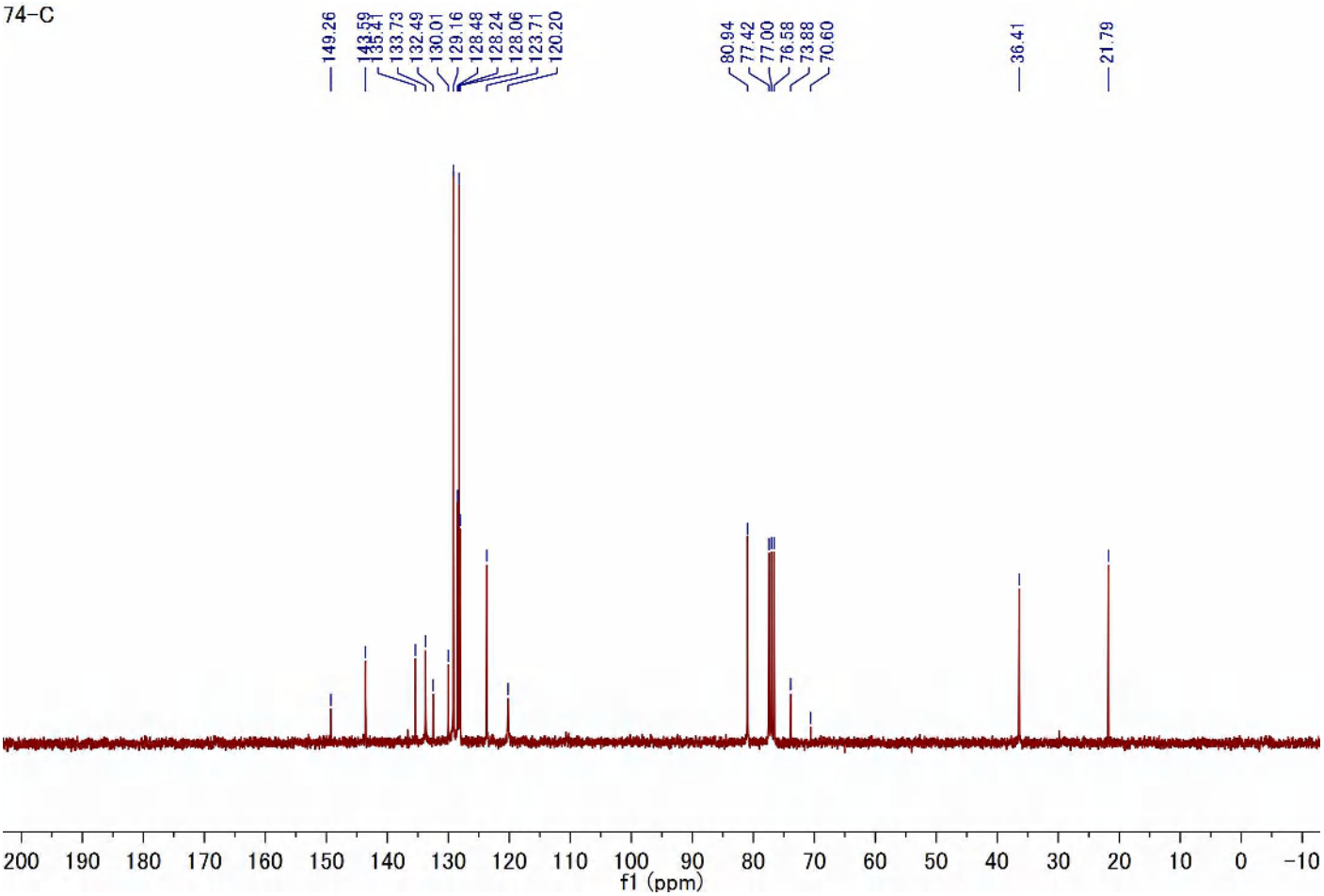
Compound **2j** (^{13}C NMR, 75 MHz, $CDCl_3$)



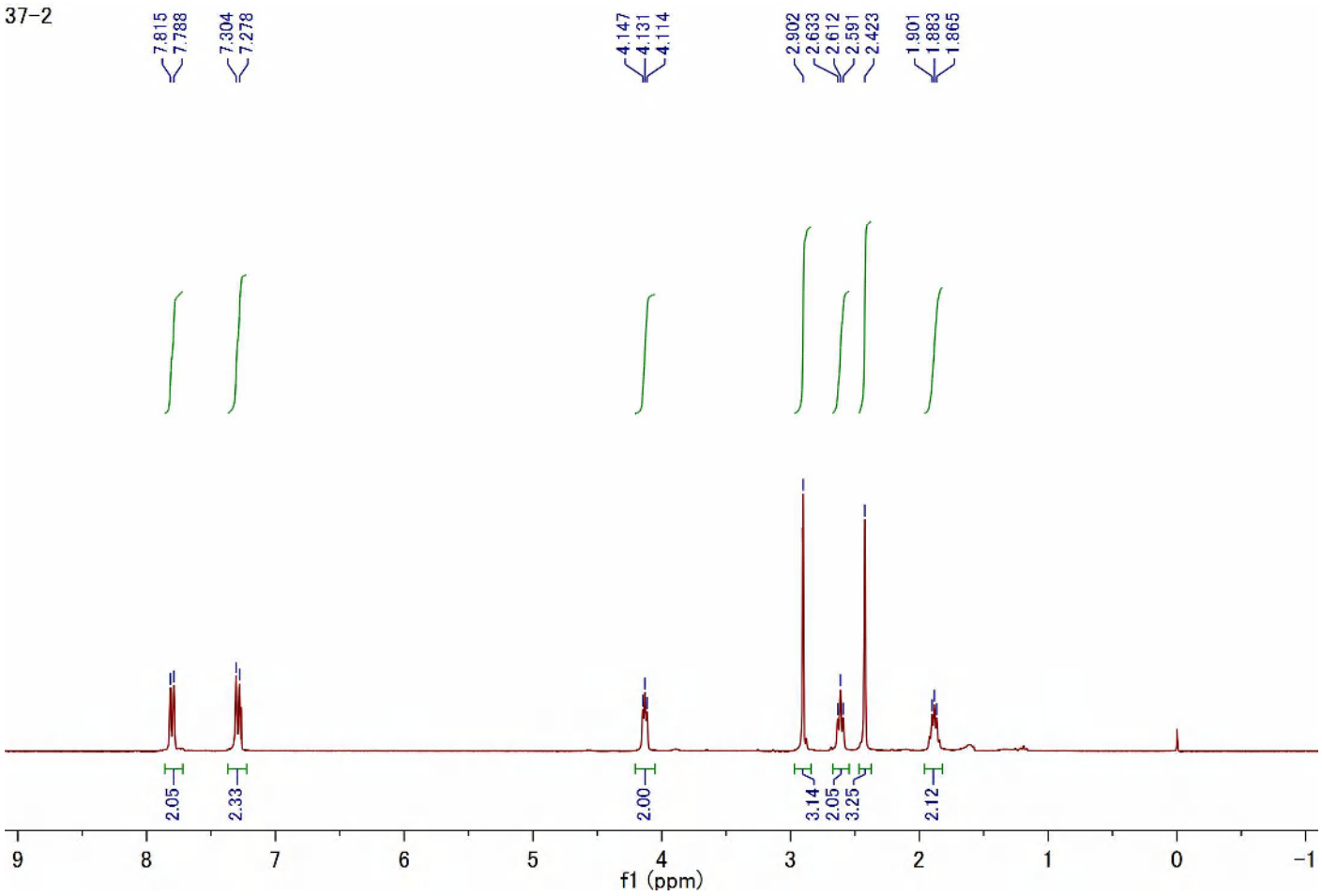
Compound **2k** (^{1}H NMR, 300 MHz, $CDCl_3$)



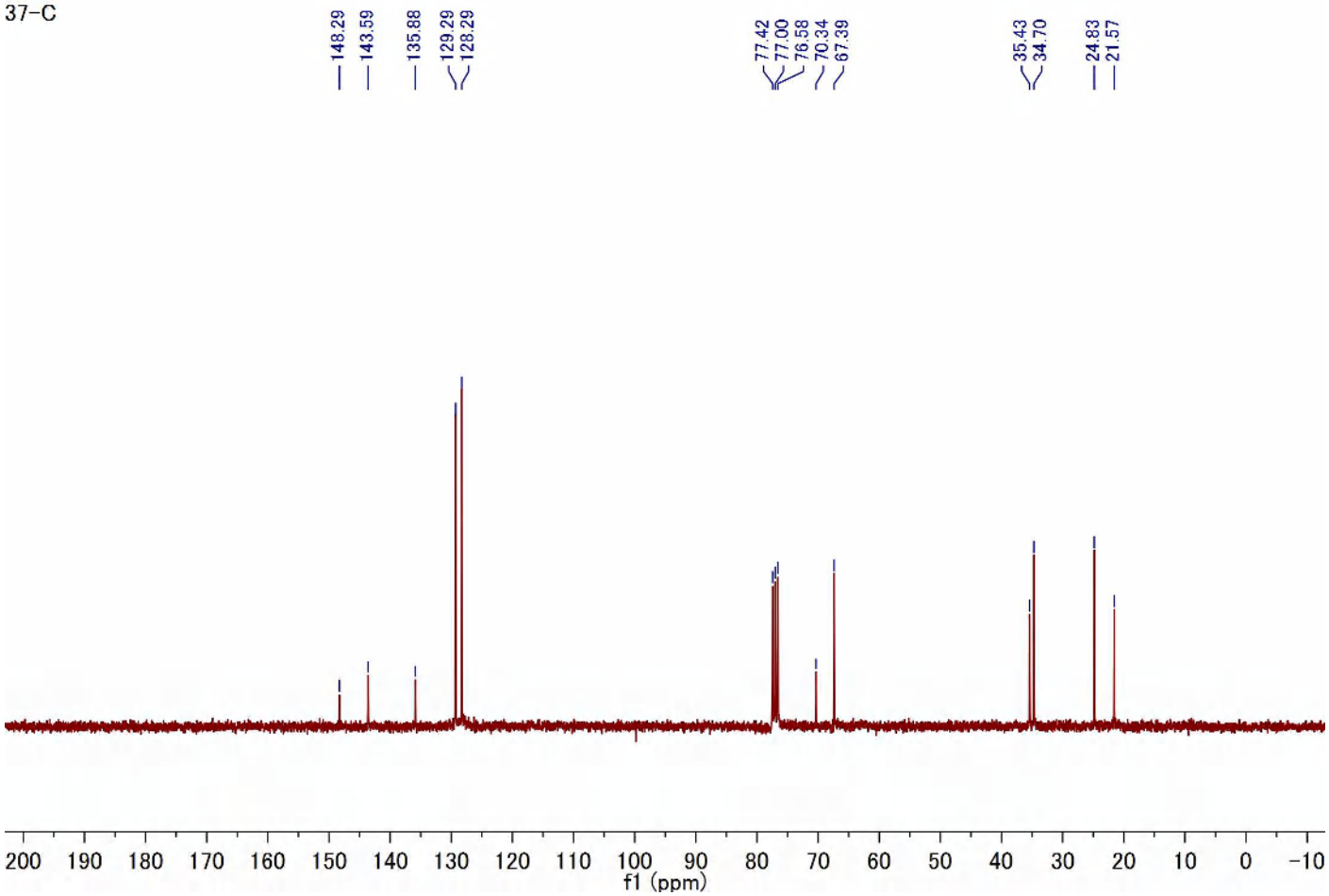
Compound **2k** (^{13}C NMR, 75 MHz, $CDCl_3$)



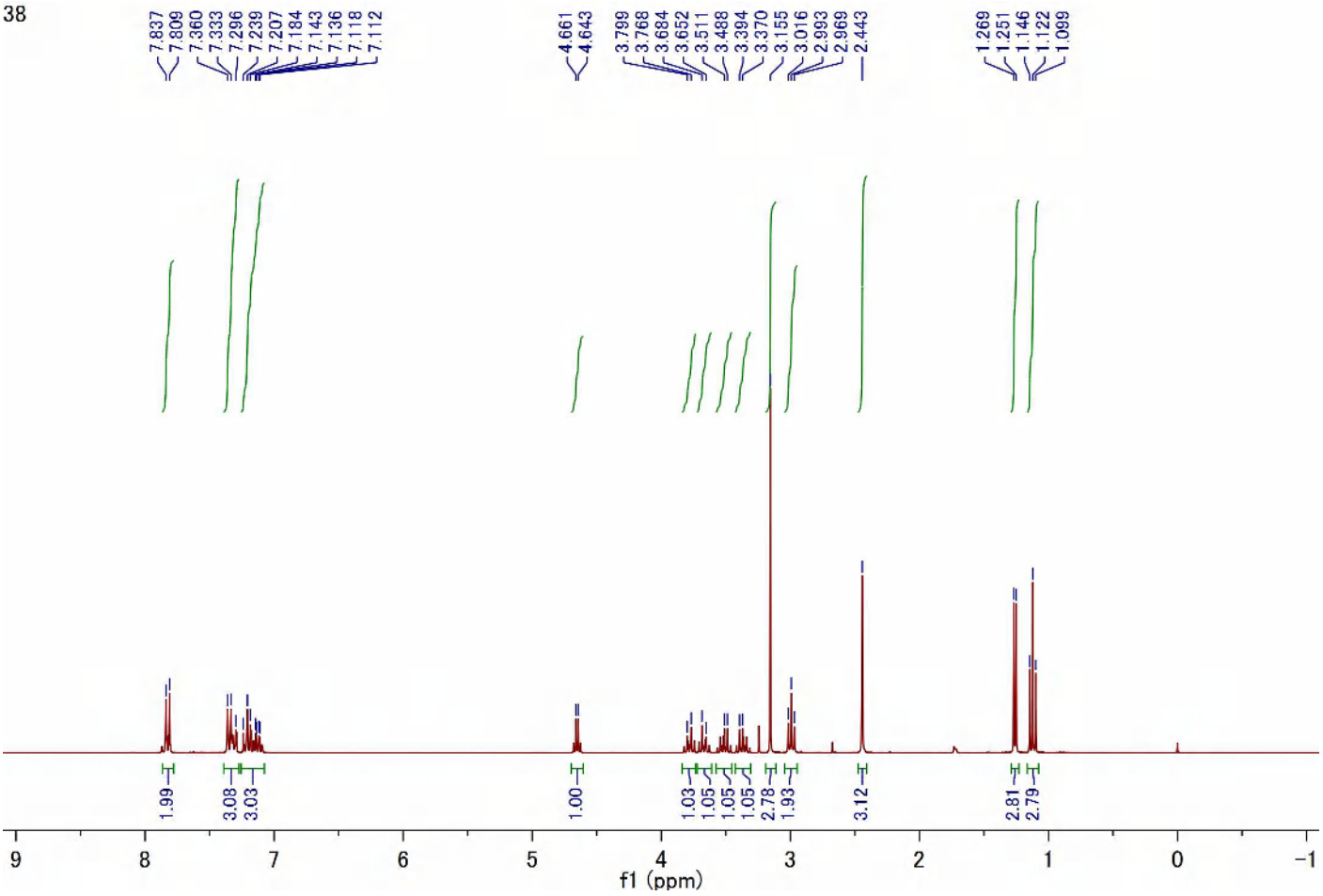
Compound **2l** (^{1}H NMR, 300 MHz, $CDCl_3$)



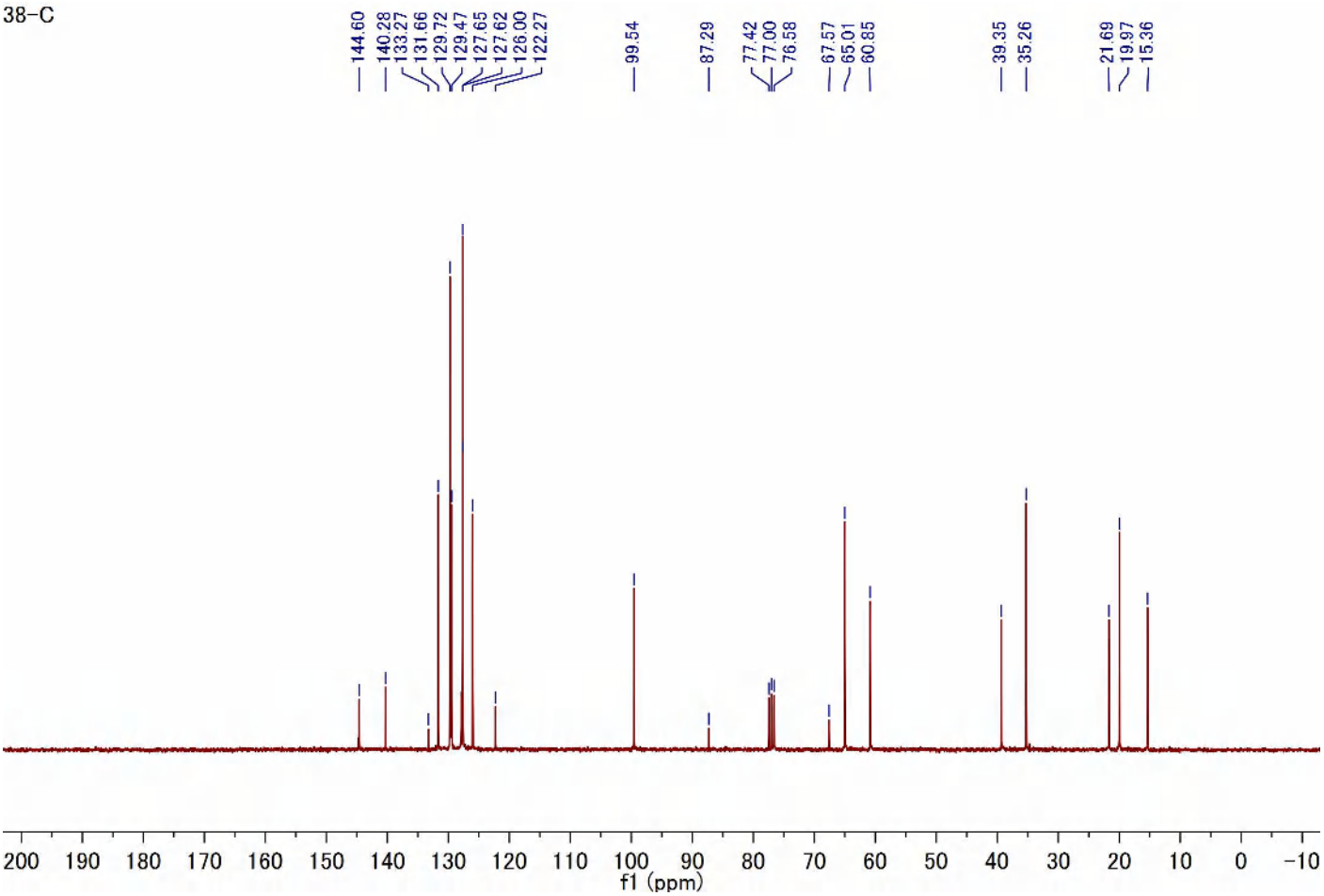
Compound **2l** (^{13}C NMR, 75 MHz, $CDCl_3$)



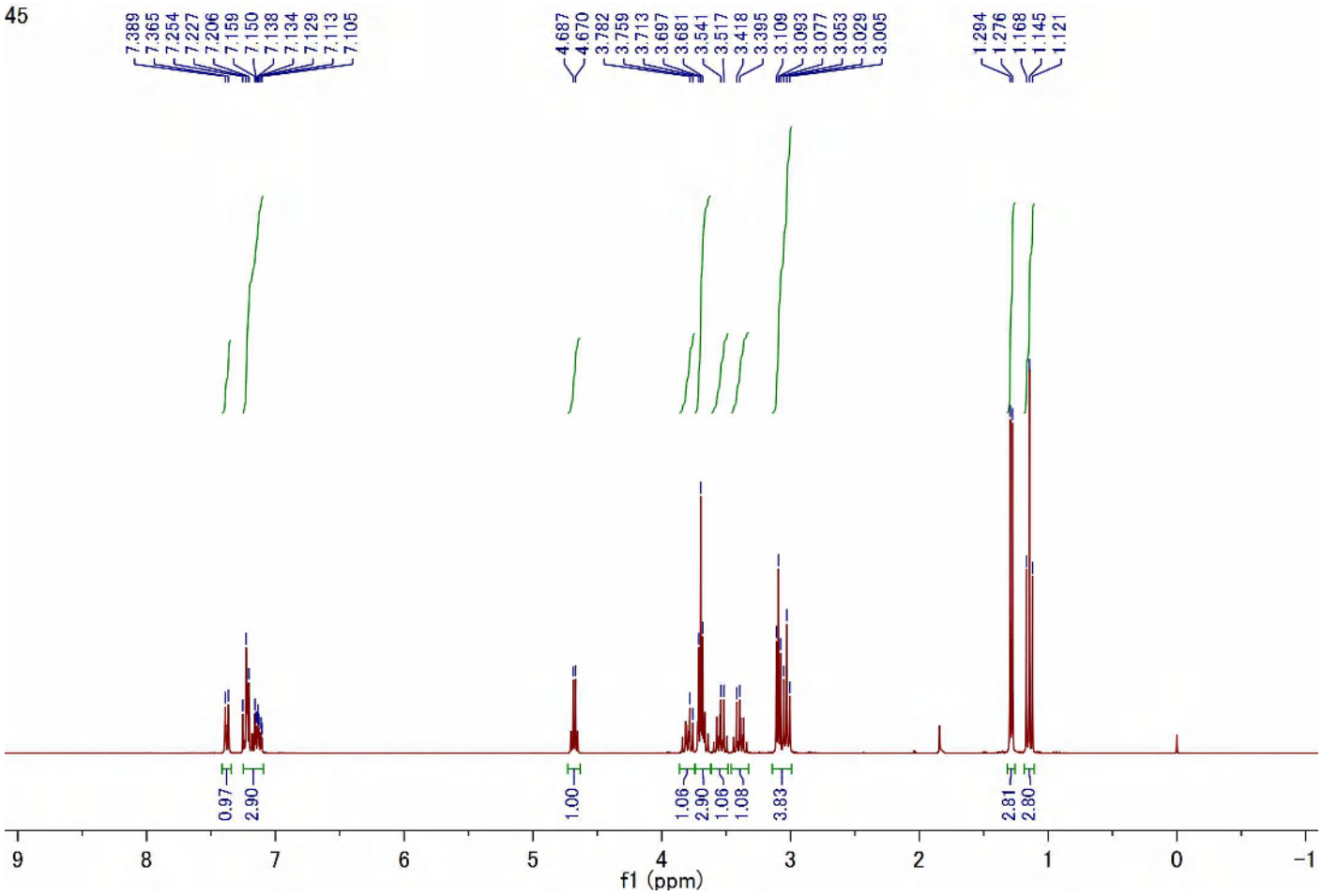
Compound **3a** (^{1}H NMR, 300 MHz, $CDCl_3$)



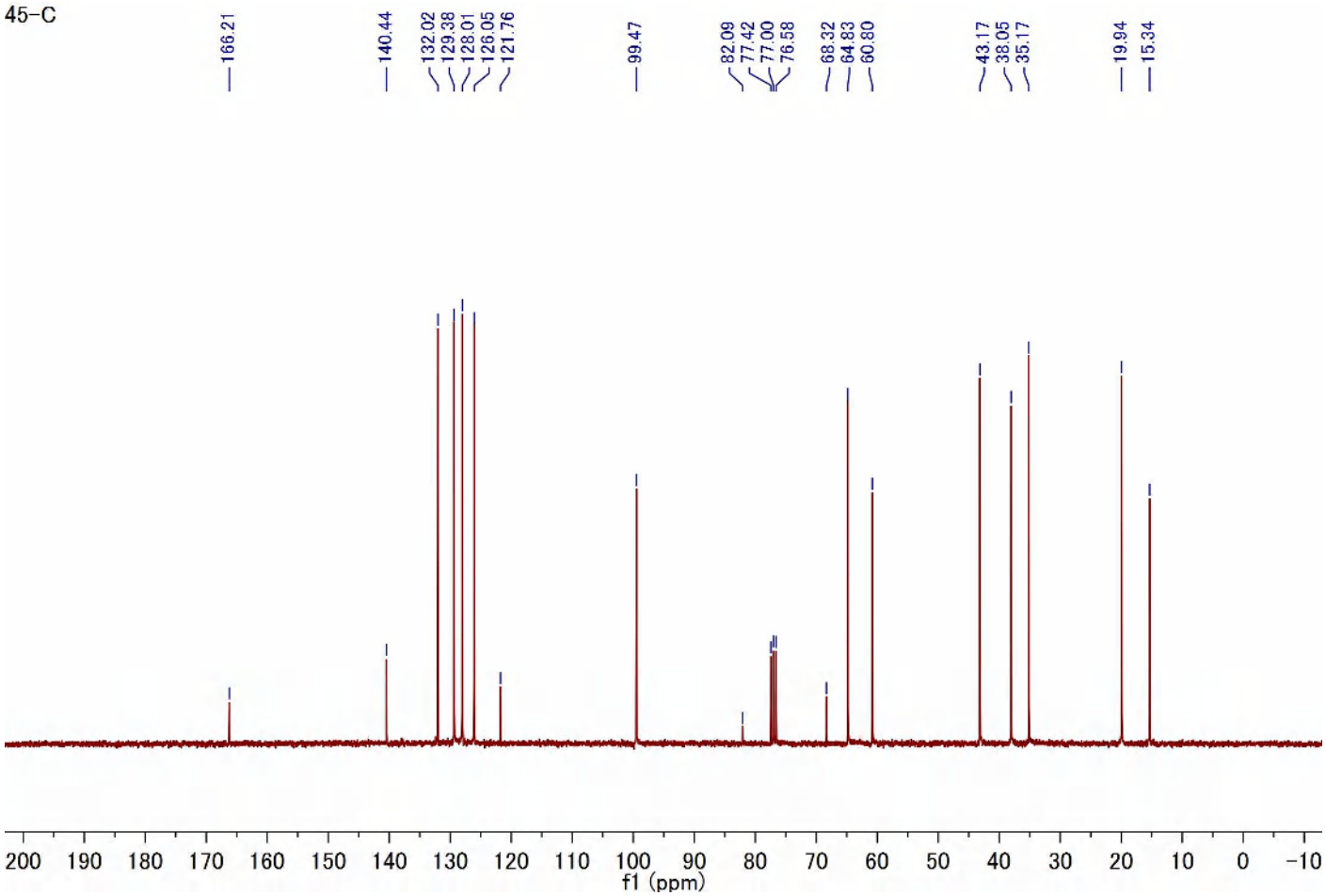
Compound **3a** (^{13}C NMR, 75 MHz, $CDCl_3$)



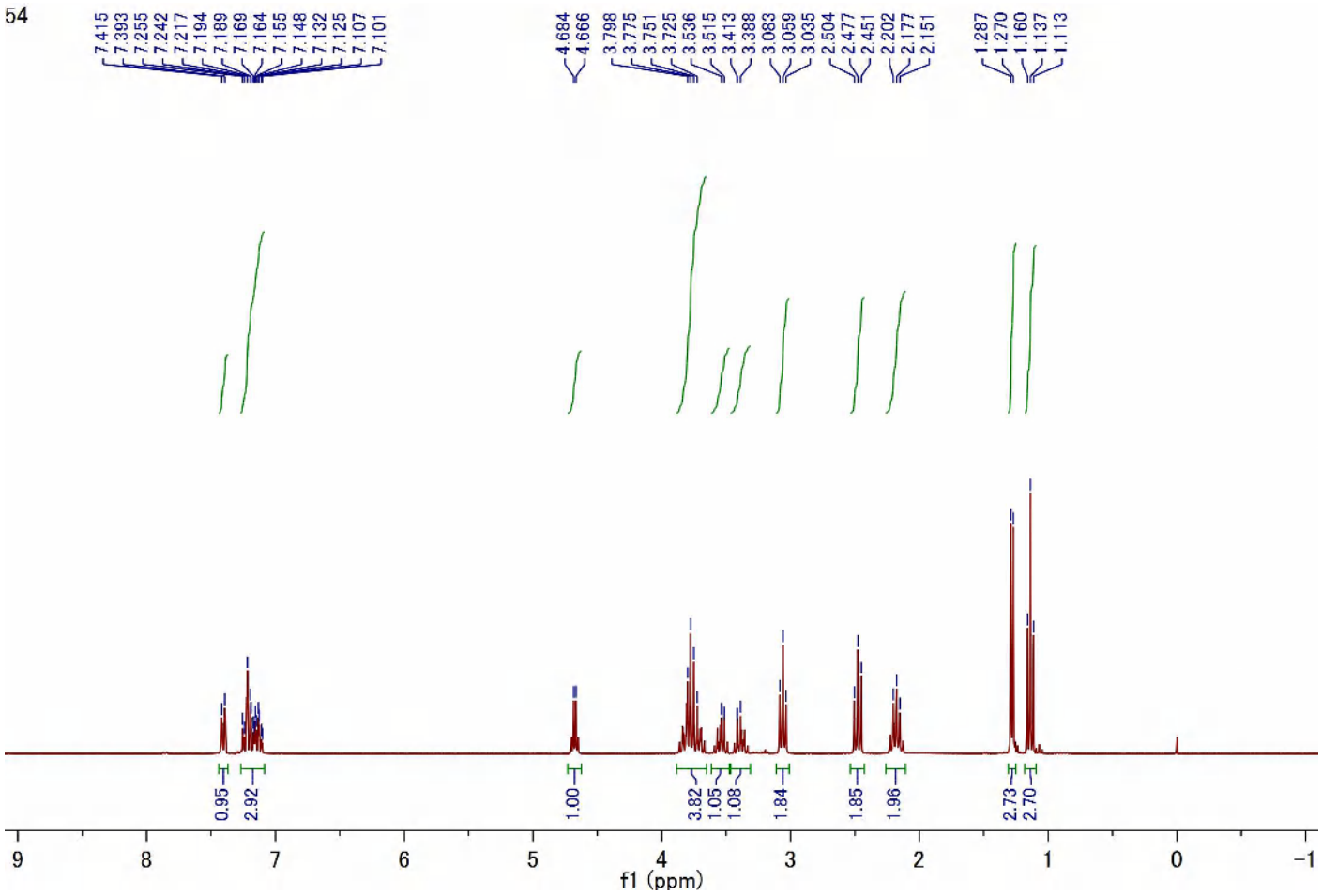
Compound **3b** (^{1}H NMR, 300 MHz, $CDCl_3$)



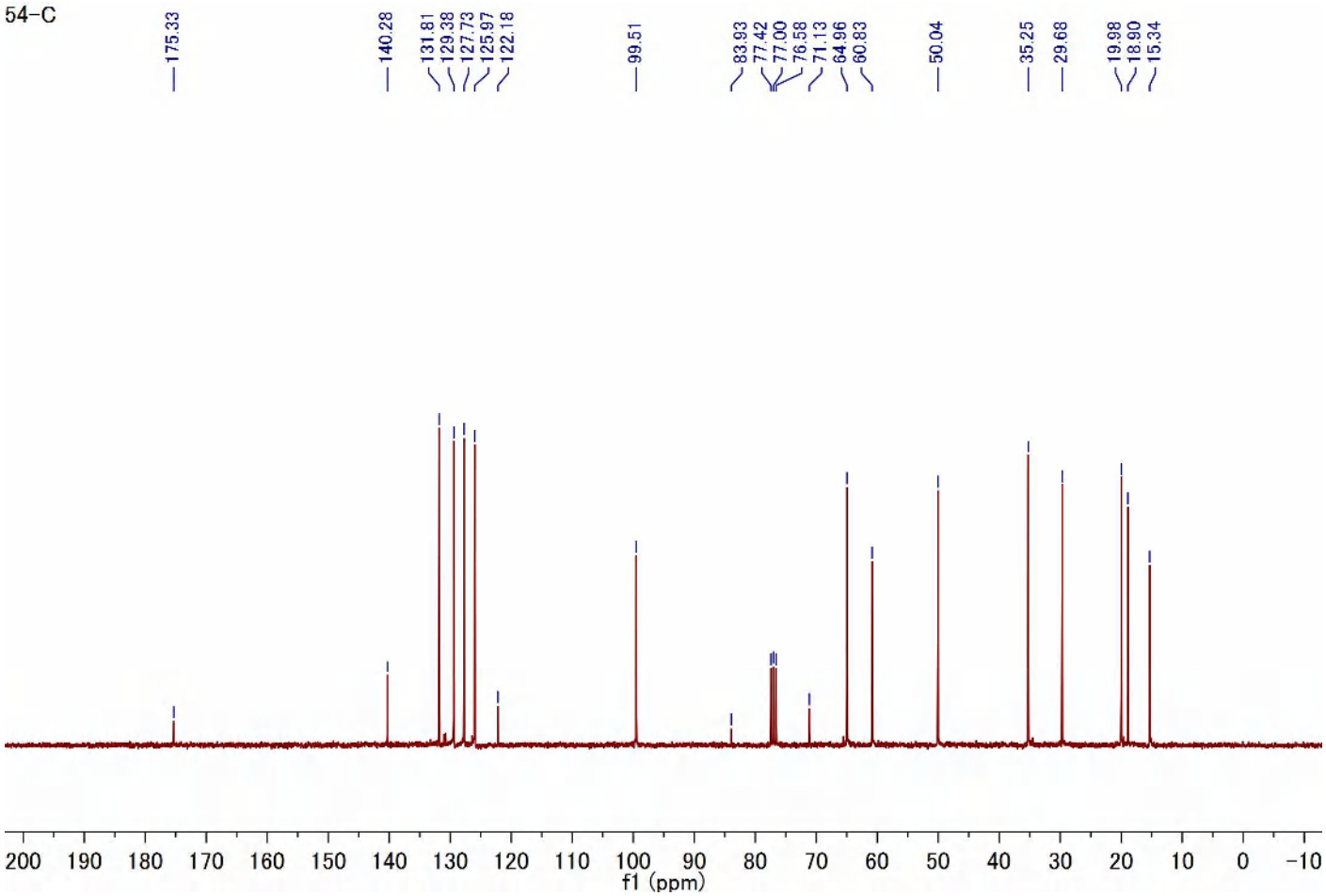
Compound **3b** (^{13}C NMR, 75 MHz, $CDCl_3$)



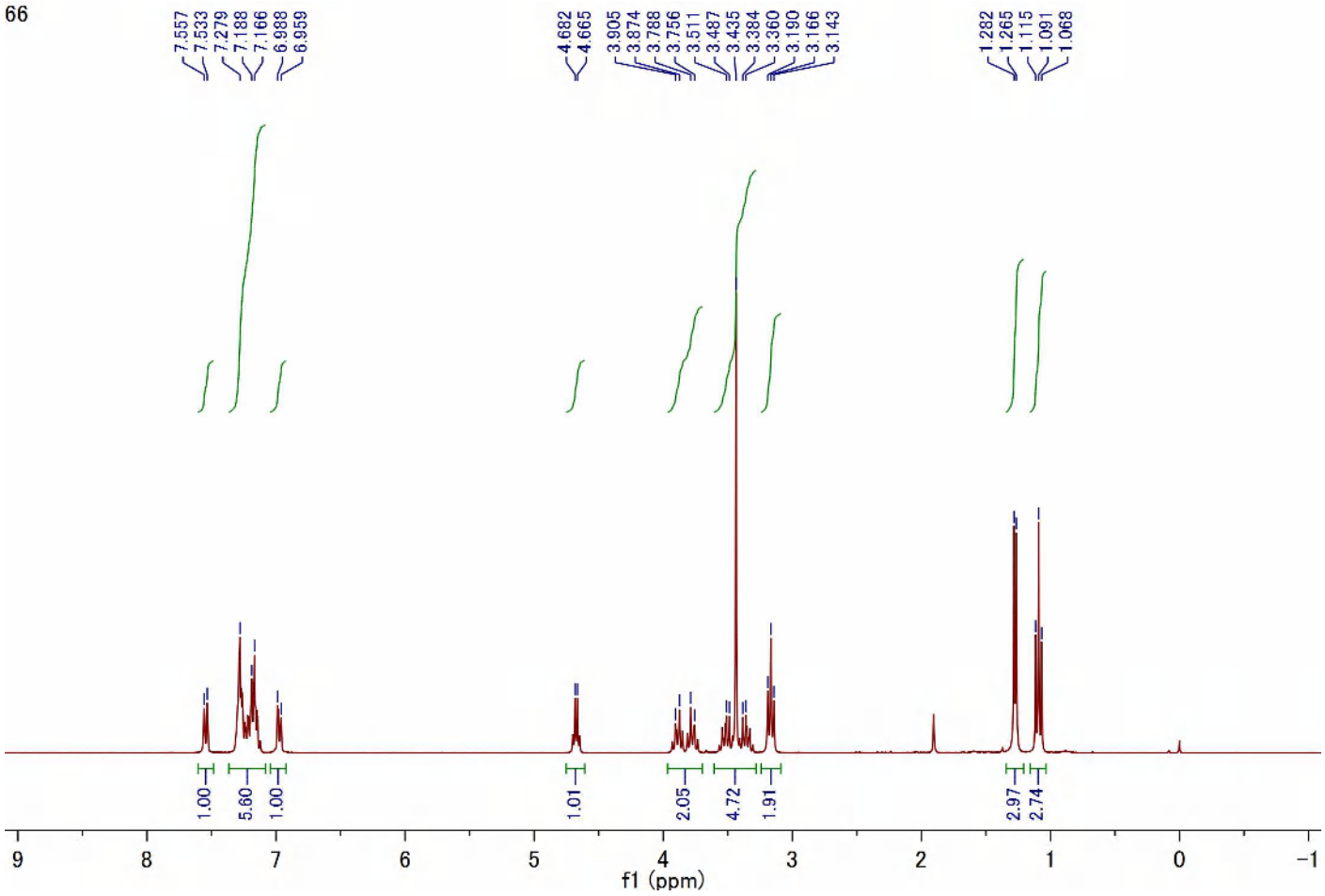
Compound **3c** (^{1}H NMR, 300 MHz, $CDCl_3$)



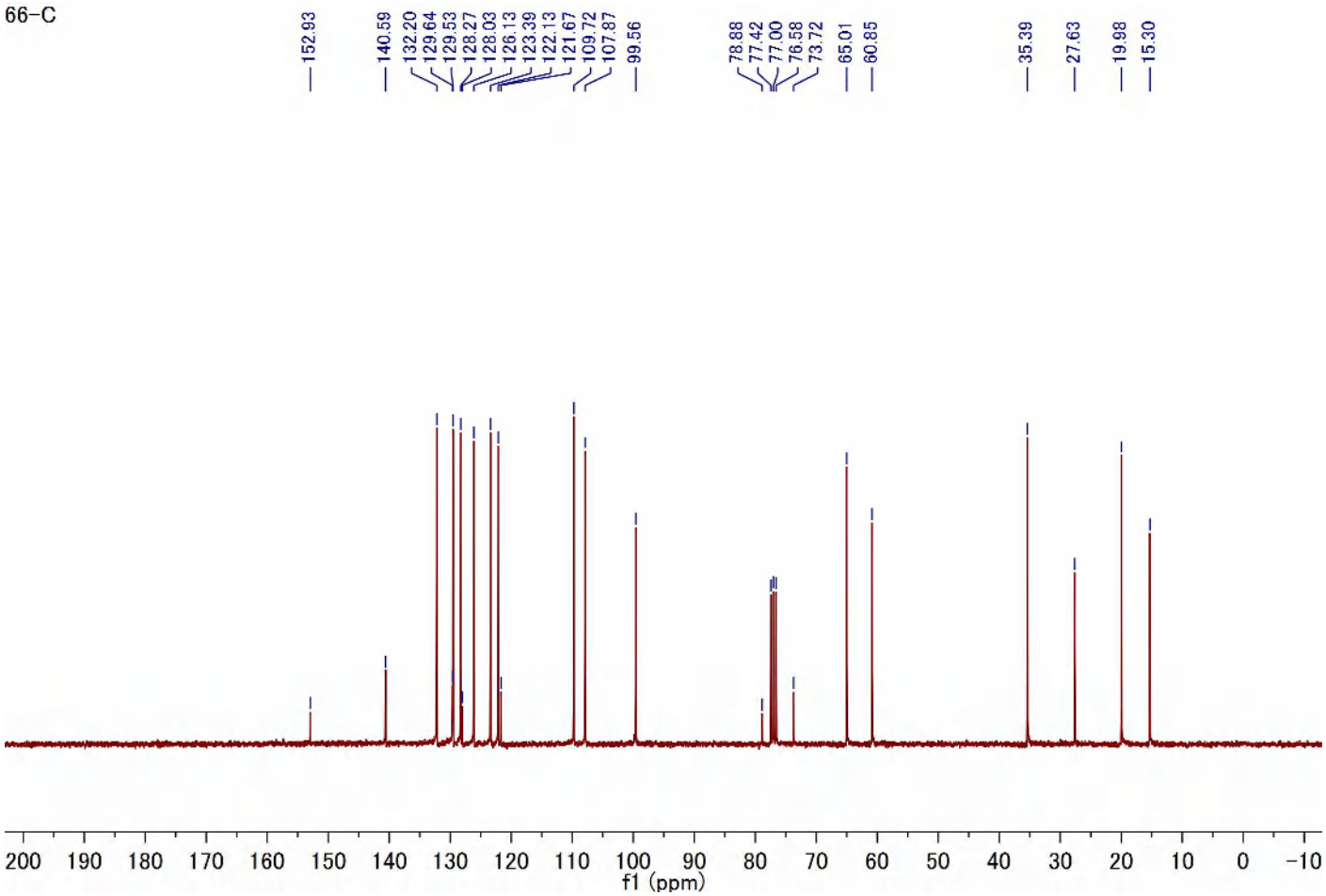
Compound **3c** (^{13}C NMR, 75 MHz, $CDCl_3$)



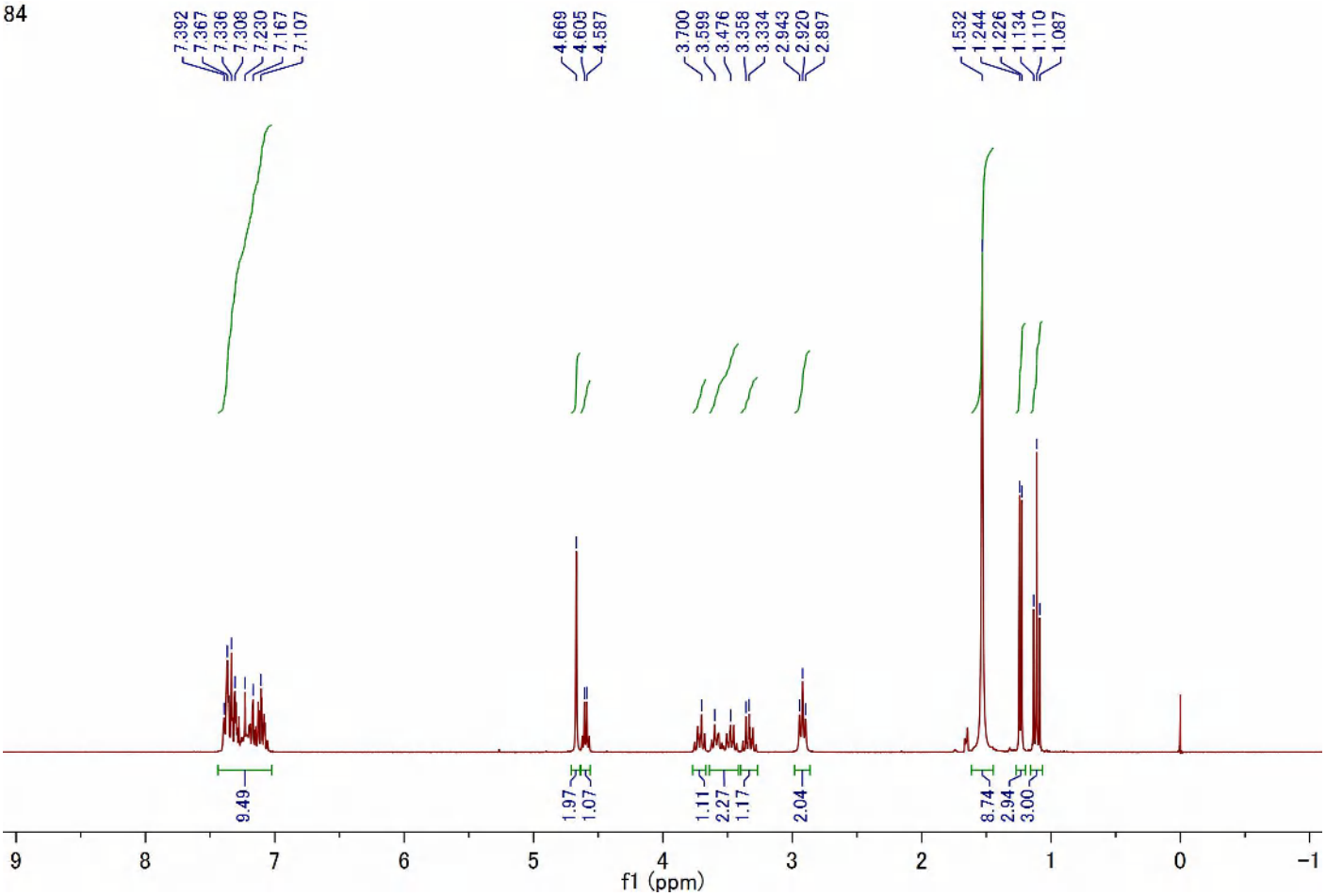
Compound **3d** (^{1}H NMR, 300 MHz, $CDCl_3$)



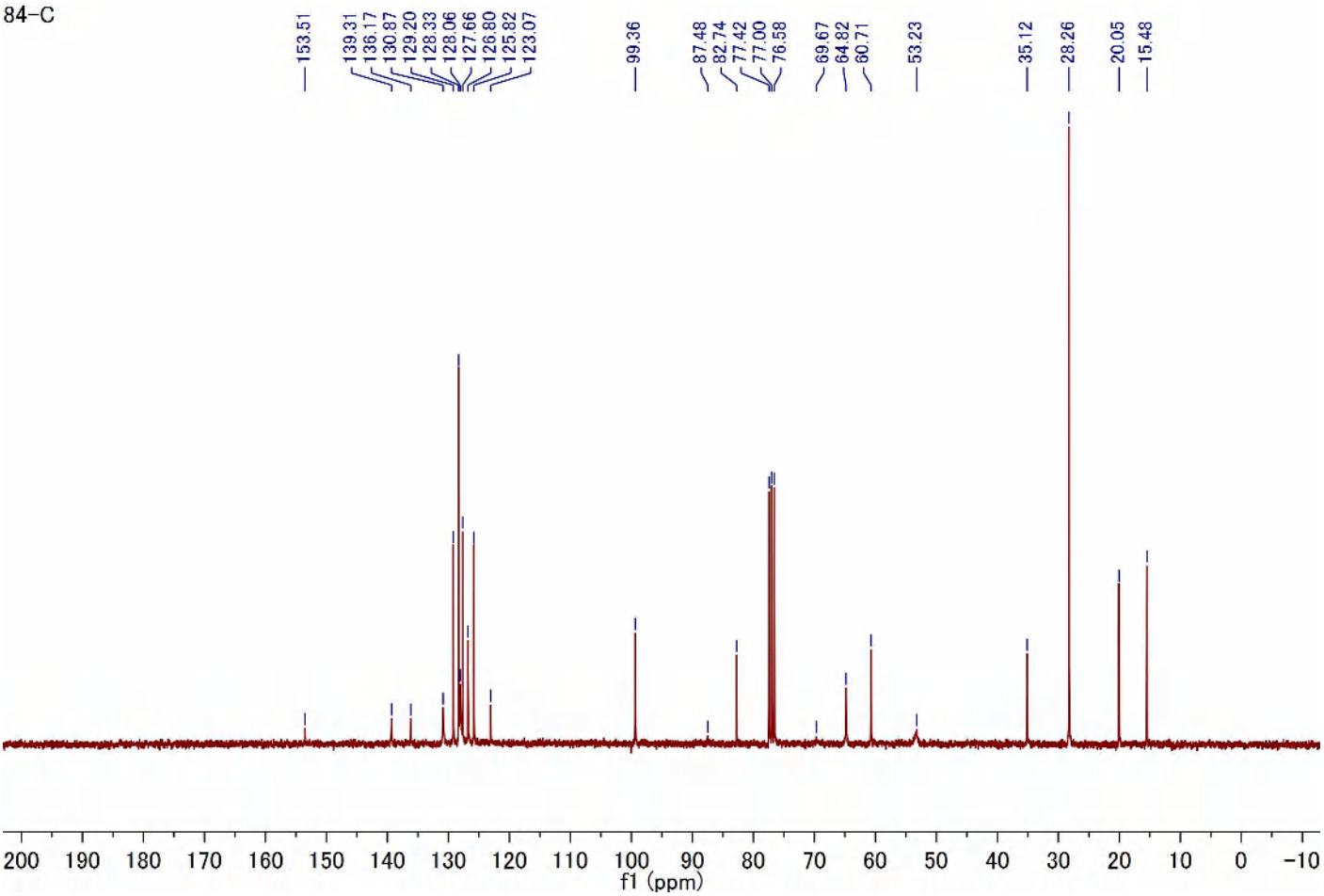
Compound **3d** (^{13}C NMR, 75 MHz, $CDCl_3$)



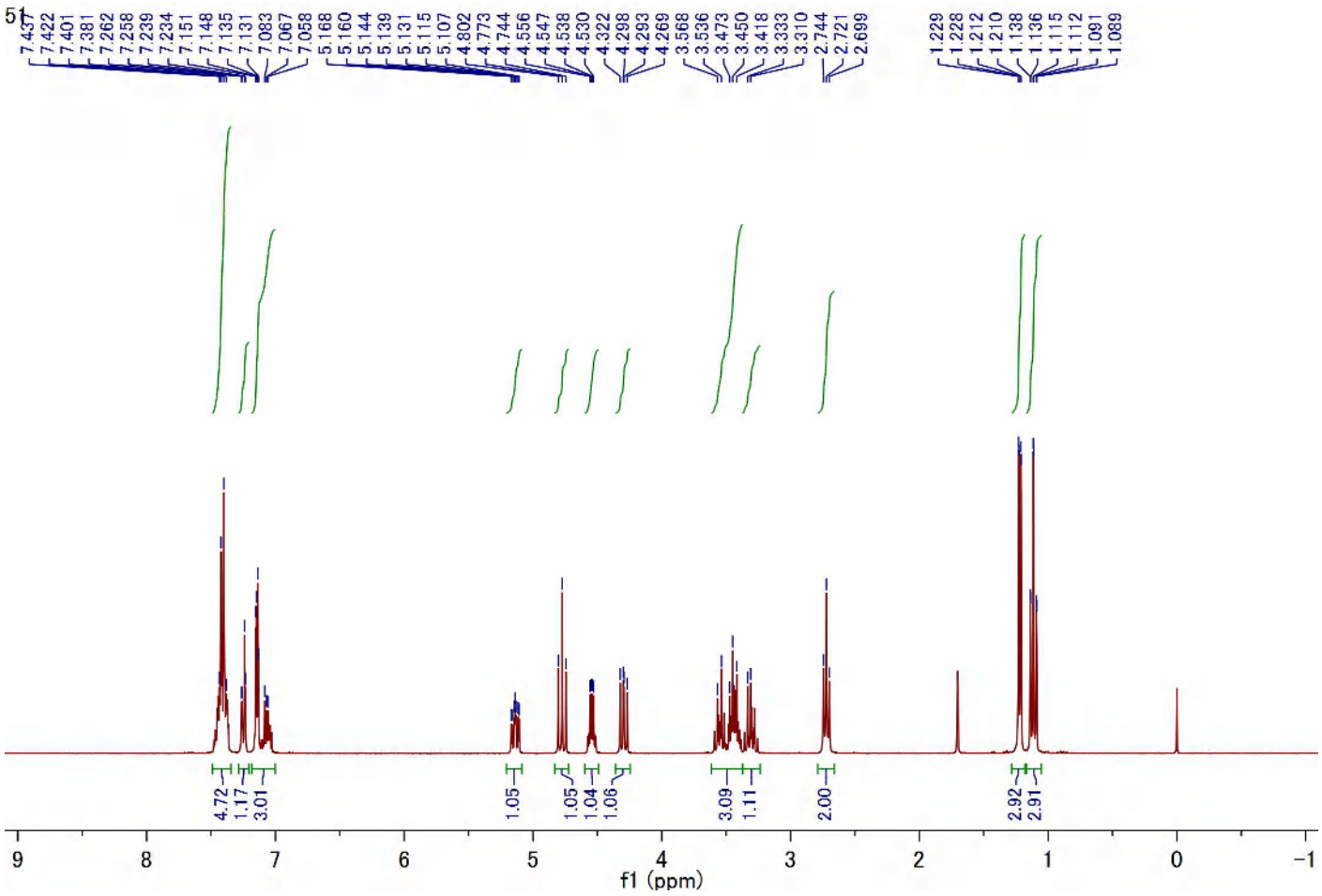
Compound **3e** (^{1}H NMR, 300 MHz, $CDCl_3$)



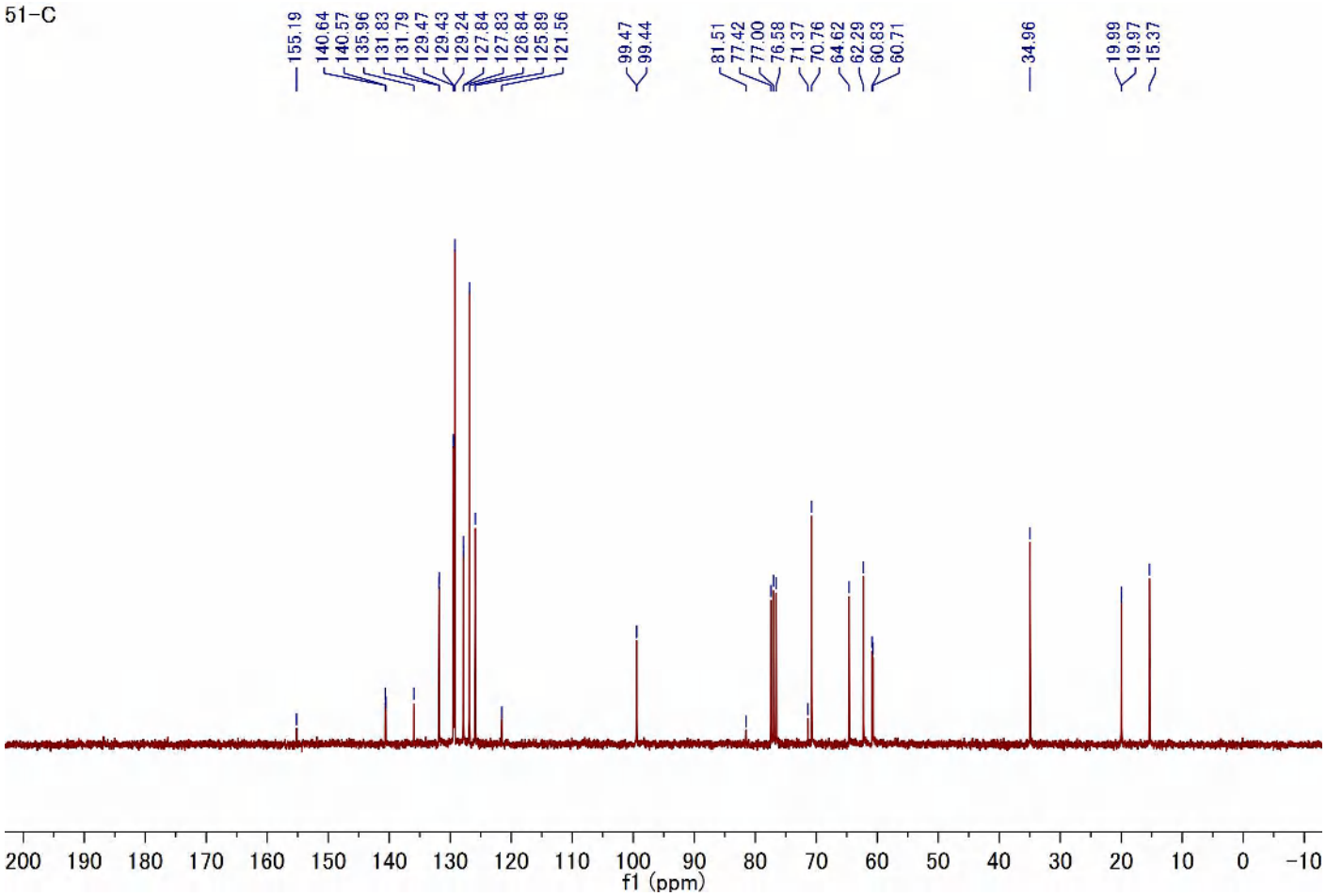
Compound **3e** (^{13}C NMR, 75 MHz, $CDCl_3$)



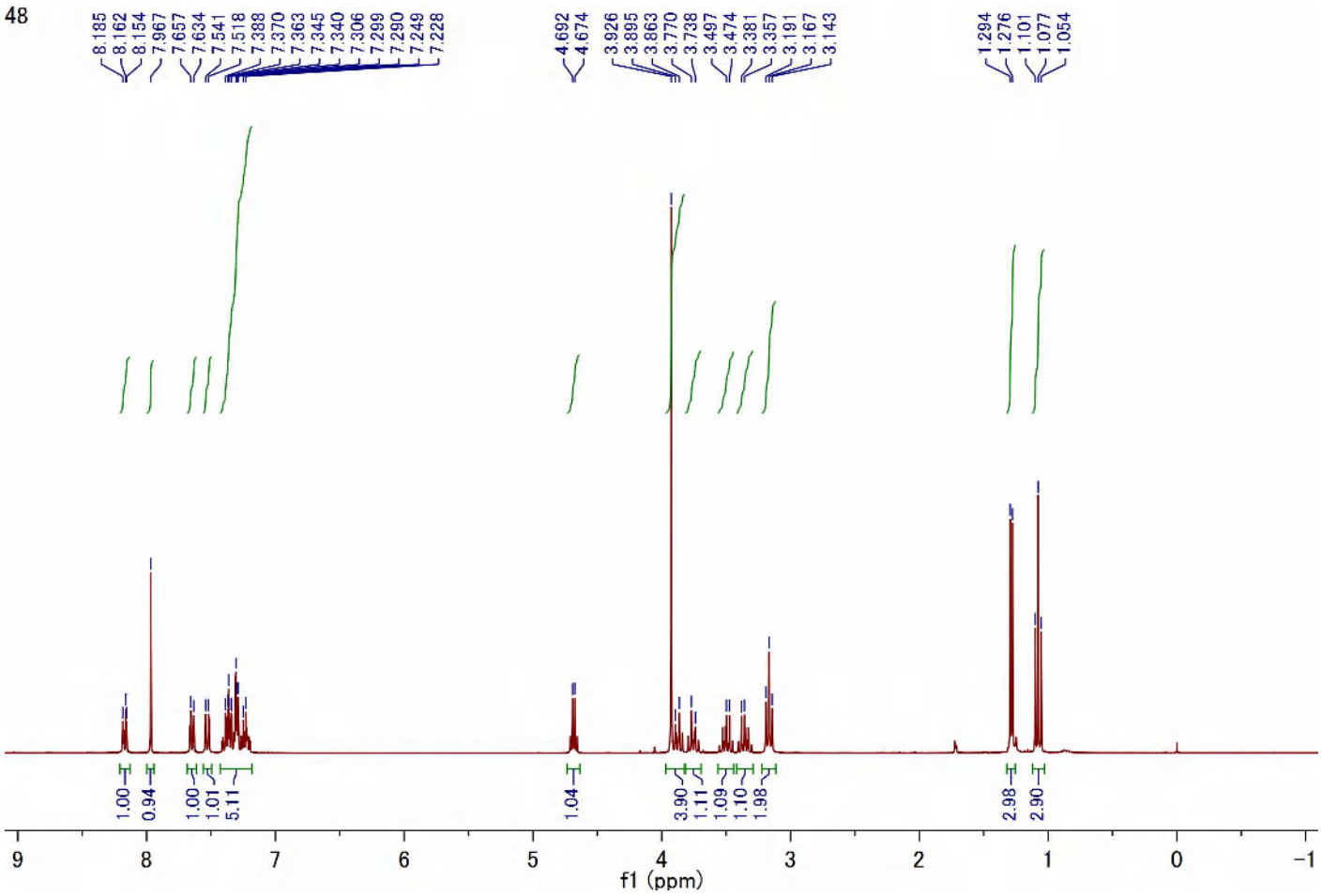
Compound **3f** (^{1}H NMR, 300 MHz, $CDCl_3$)



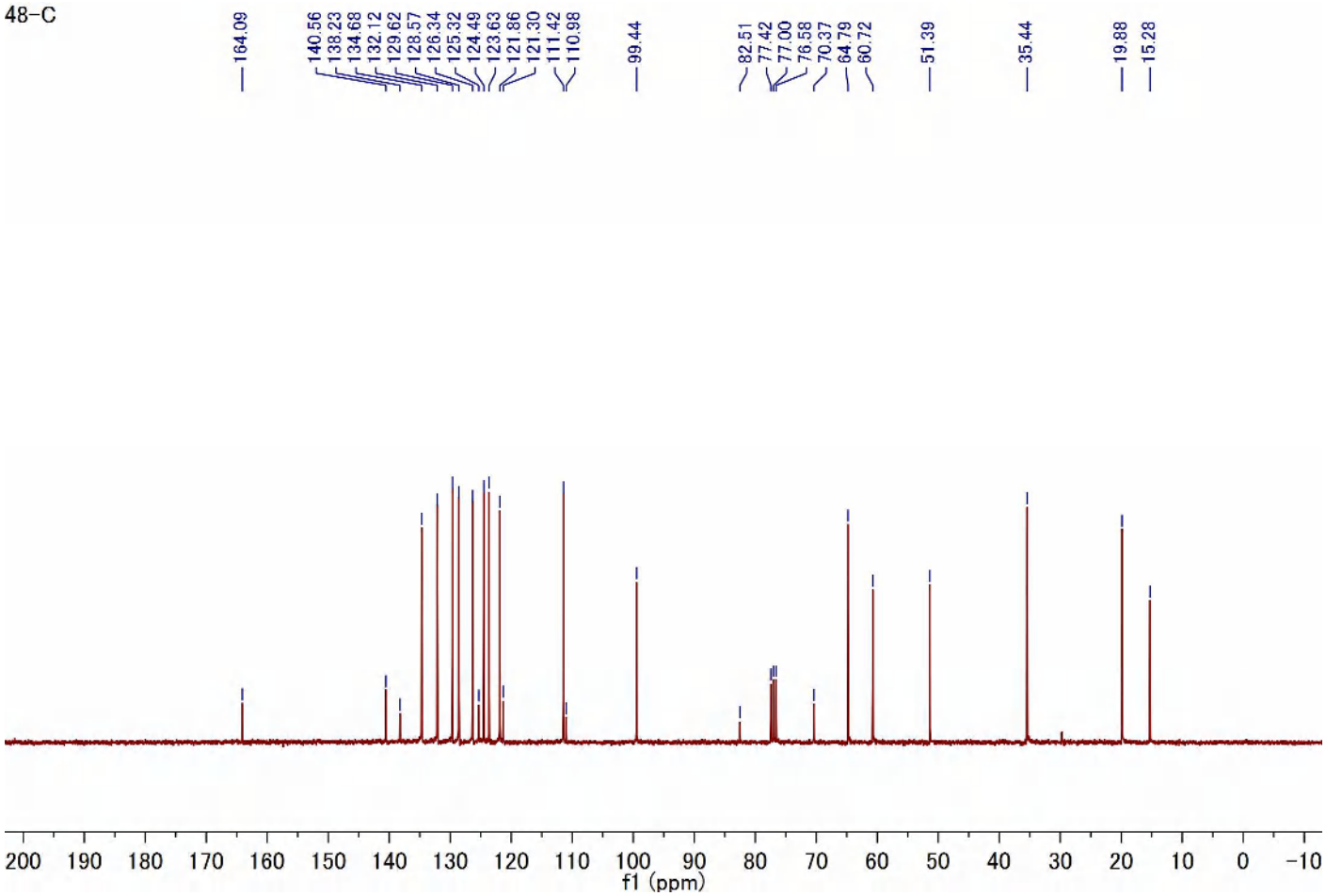
Compound **3f** (^{13}C NMR, 75 MHz, $CDCl_3$)



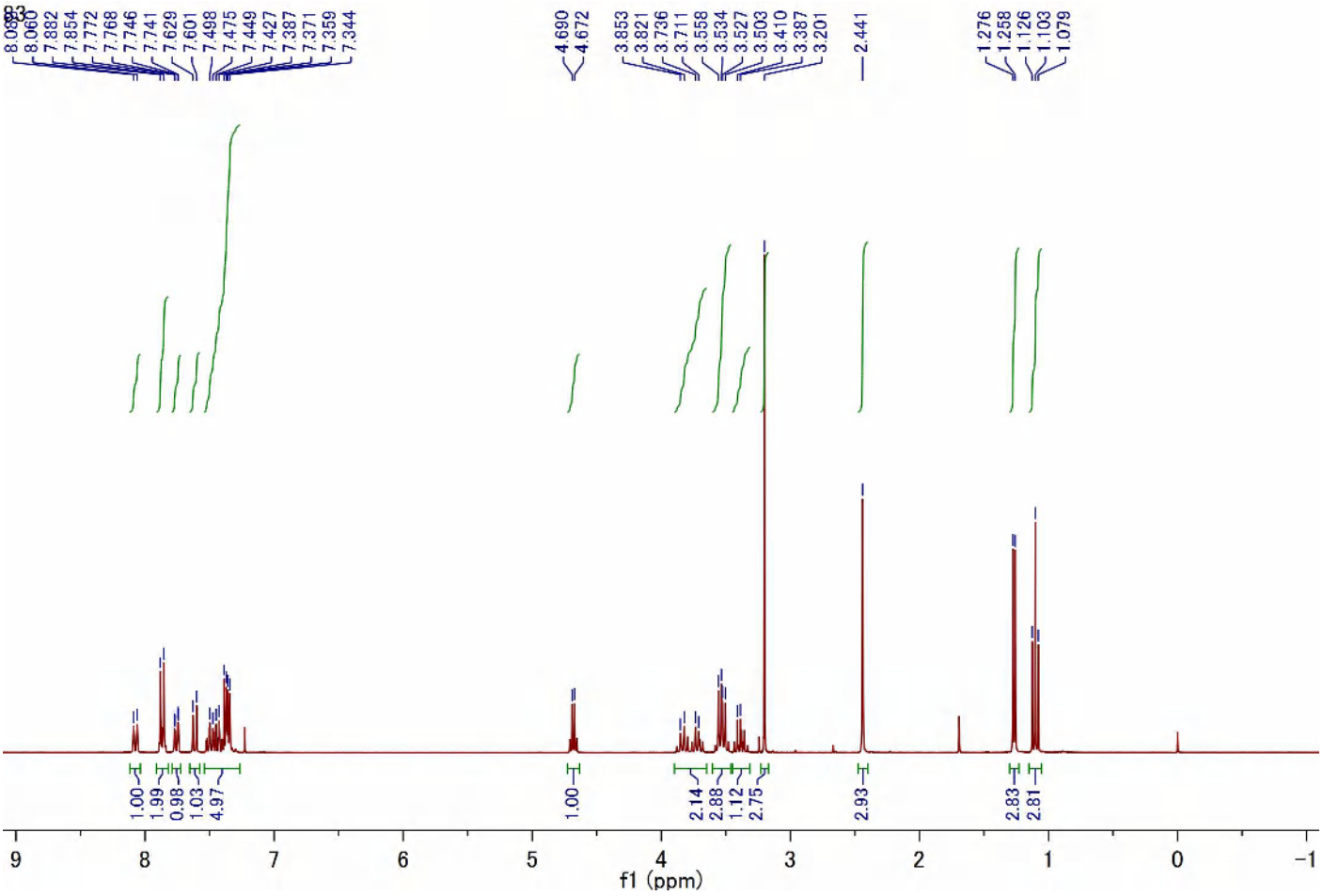
Compound **3g** (^{1}H NMR, 300 MHz, $CDCl_3$)



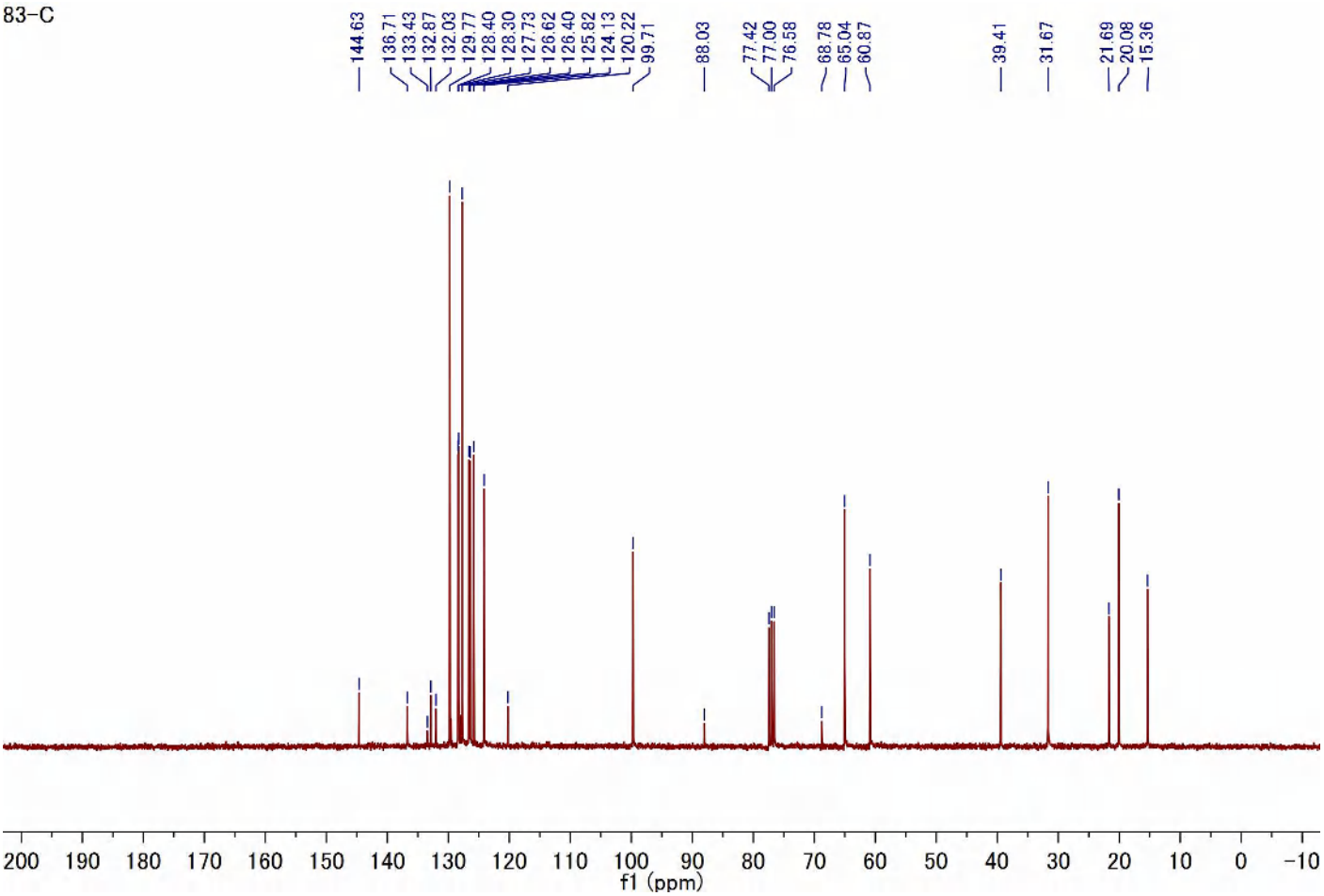
Compound **3g** (^{13}C NMR, 75 MHz, $CDCl_3$)



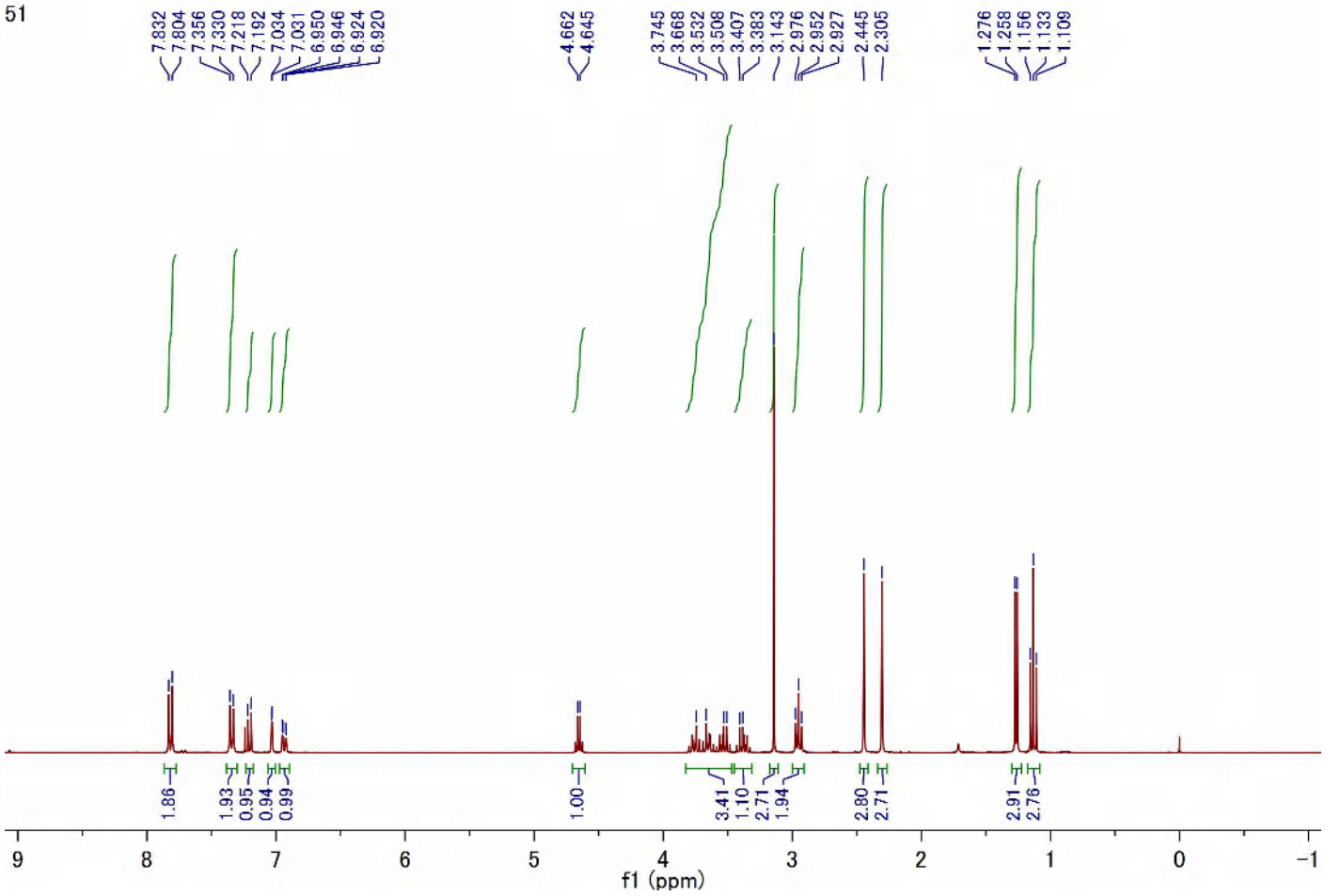
Compound **3h** (^{1}H NMR, 300 MHz, $CDCl_3$)



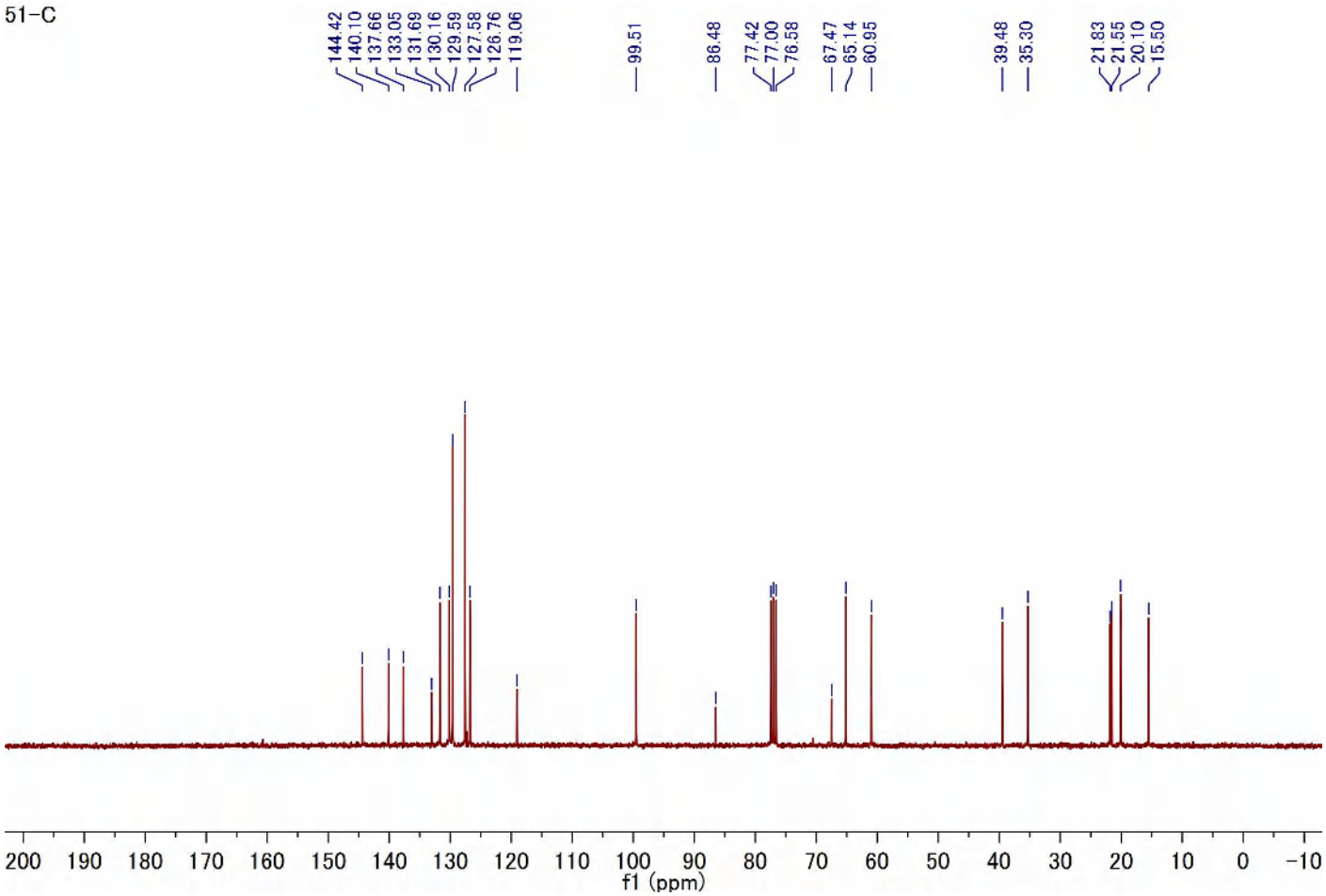
Compound **3h** (^{13}C NMR, 75 MHz, $CDCl_3$)



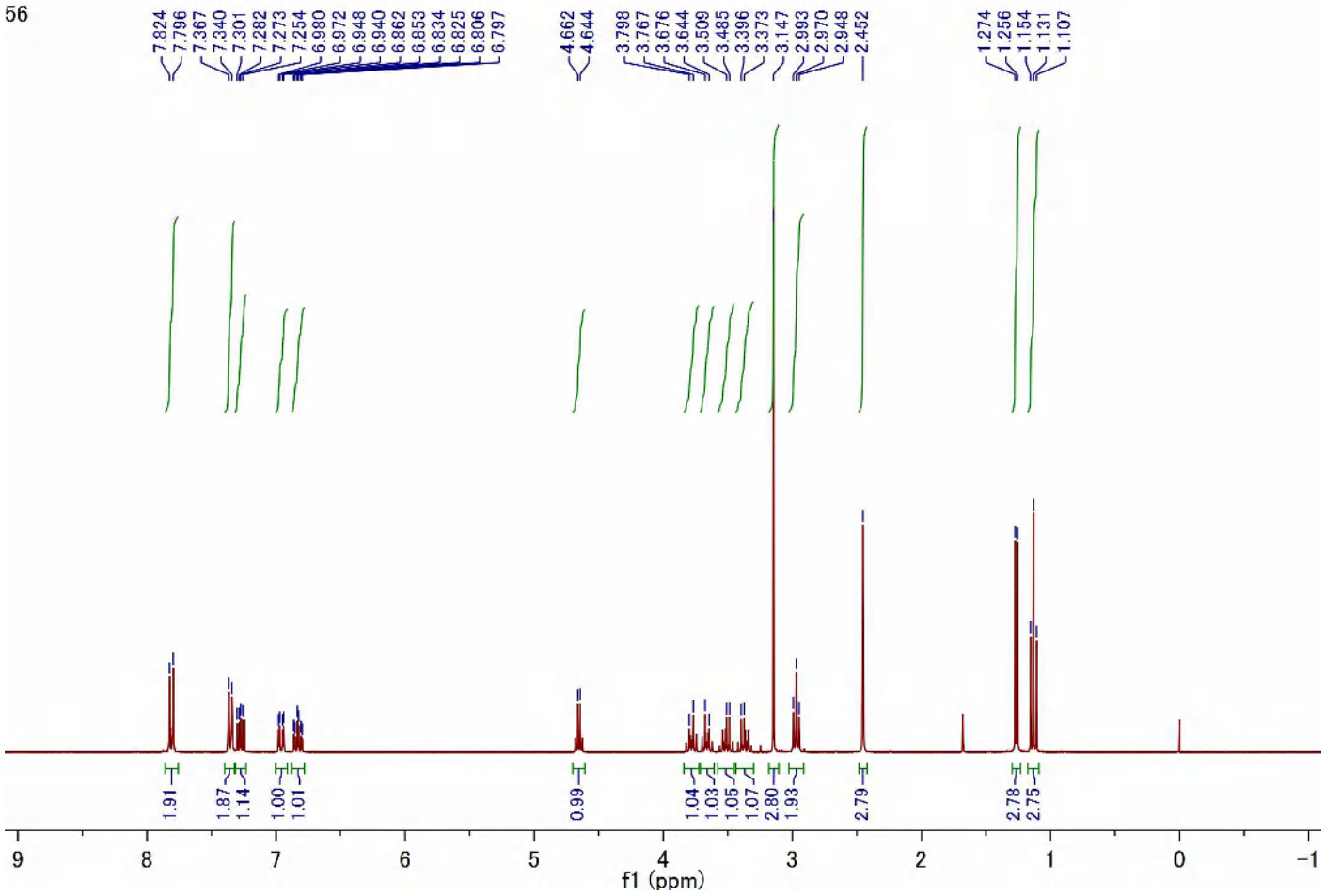
Compound **3i** (^{1}H NMR, 300 MHz, $CDCl_3$)



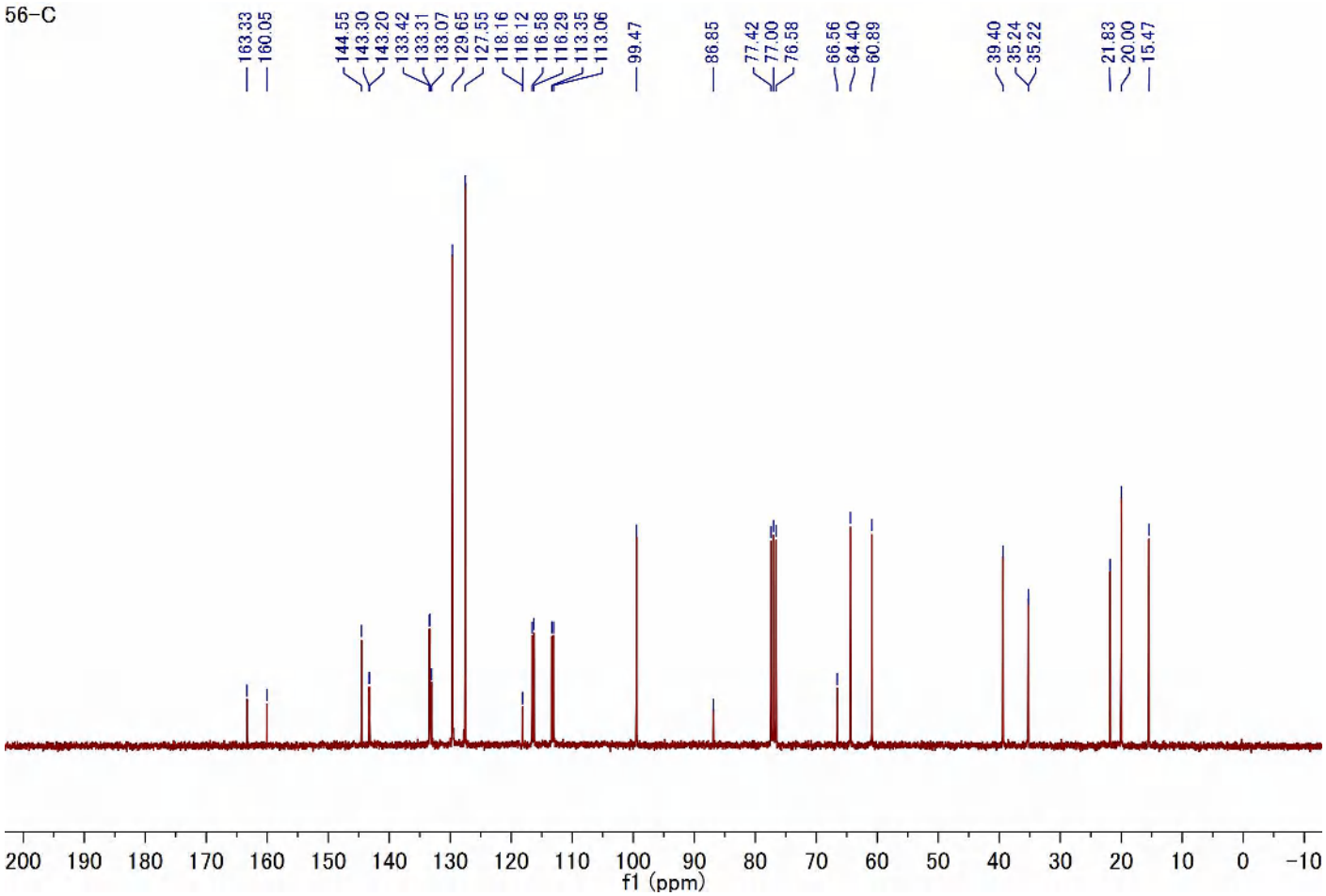
Compound **3i** (^{13}C NMR, 75 MHz, $CDCl_3$)



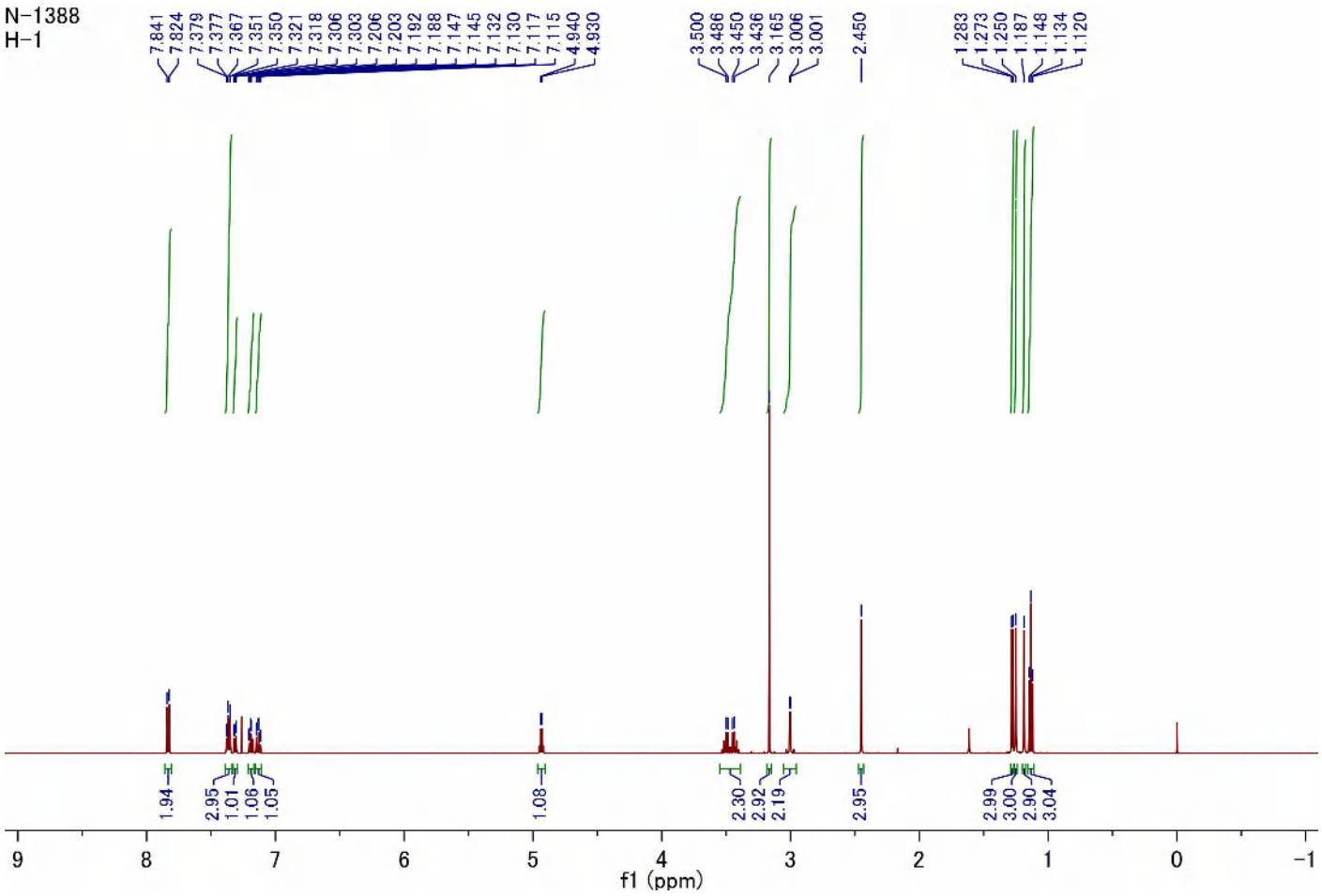
Compound **3j** (^{1}H NMR, 300 MHz, $CDCl_3$)



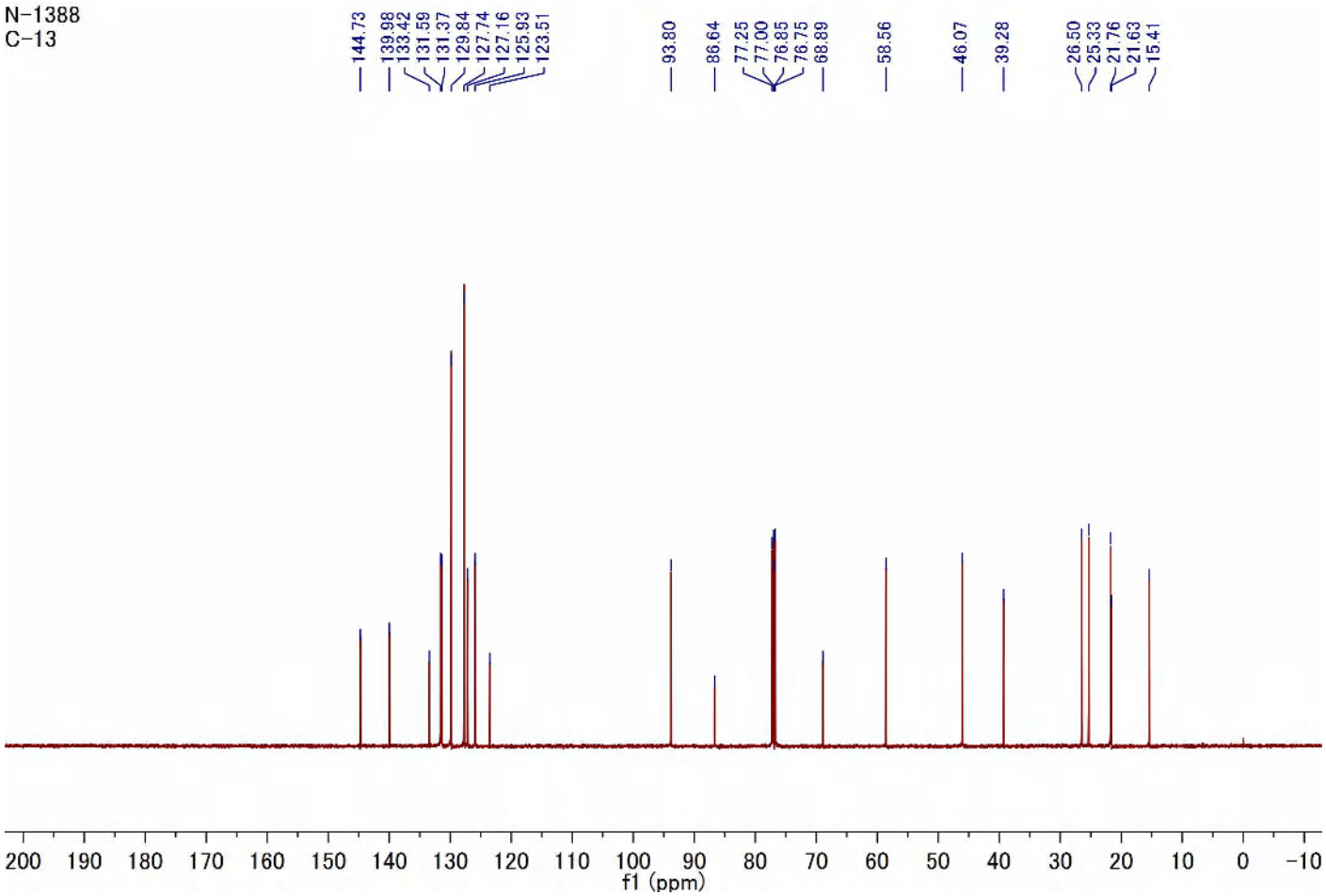
Compound **3j** (^{13}C NMR, 75 MHz, $CDCl_3$)



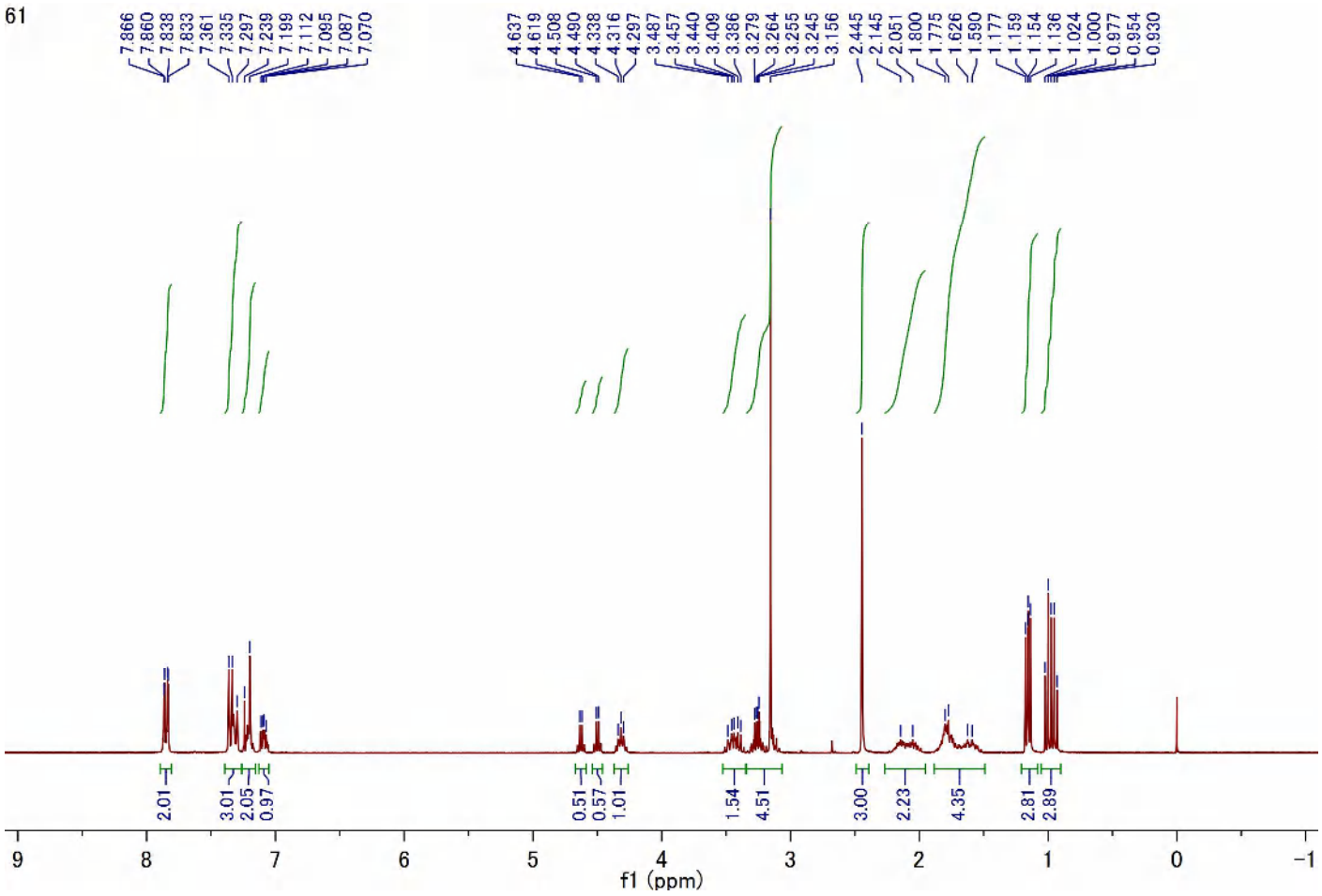
Compound **3k** (^{1}H NMR, 500 MHz, $CDCl_3$)



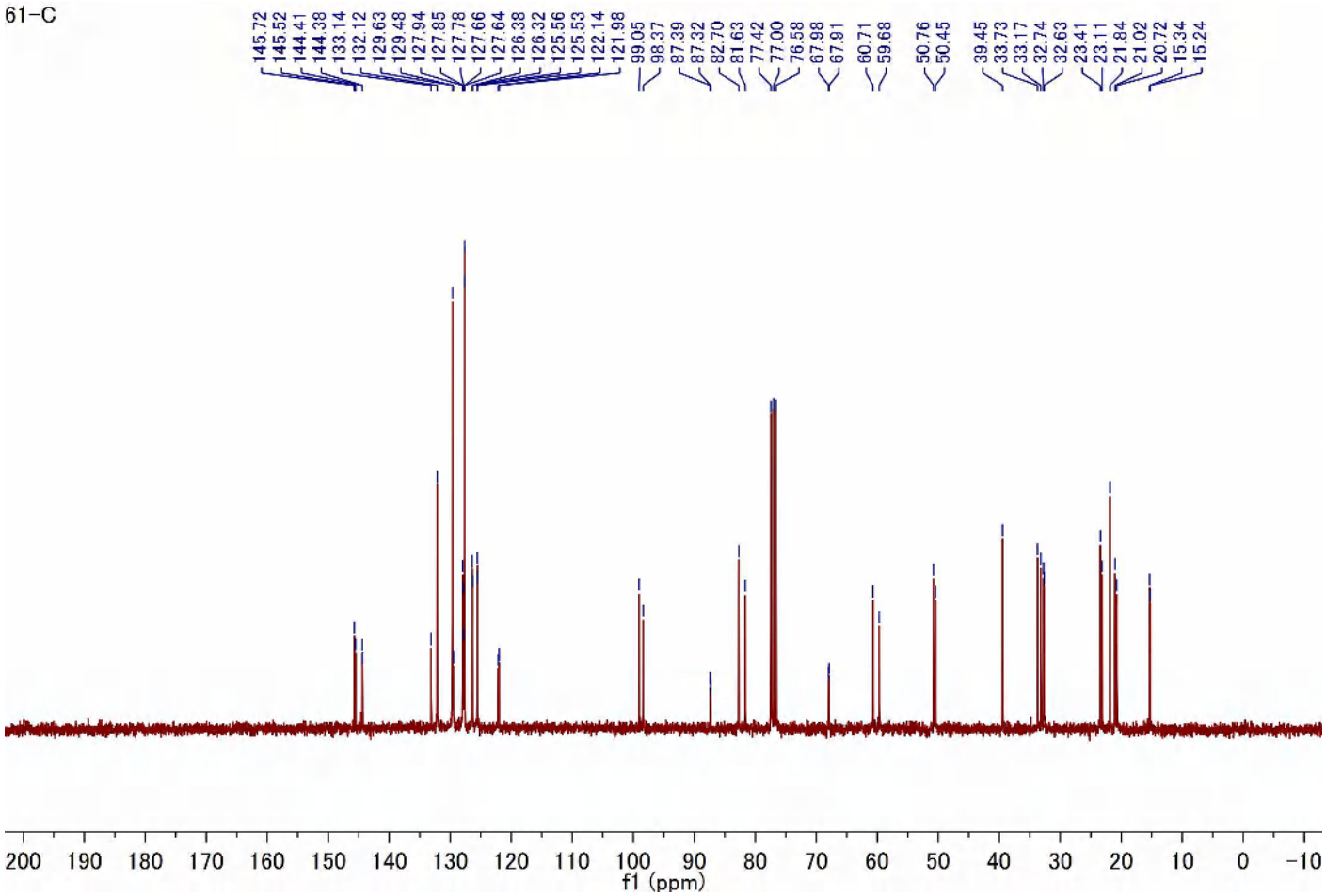
Compound **3k** (^{13}C NMR, 125 MHz, $CDCl_3$)



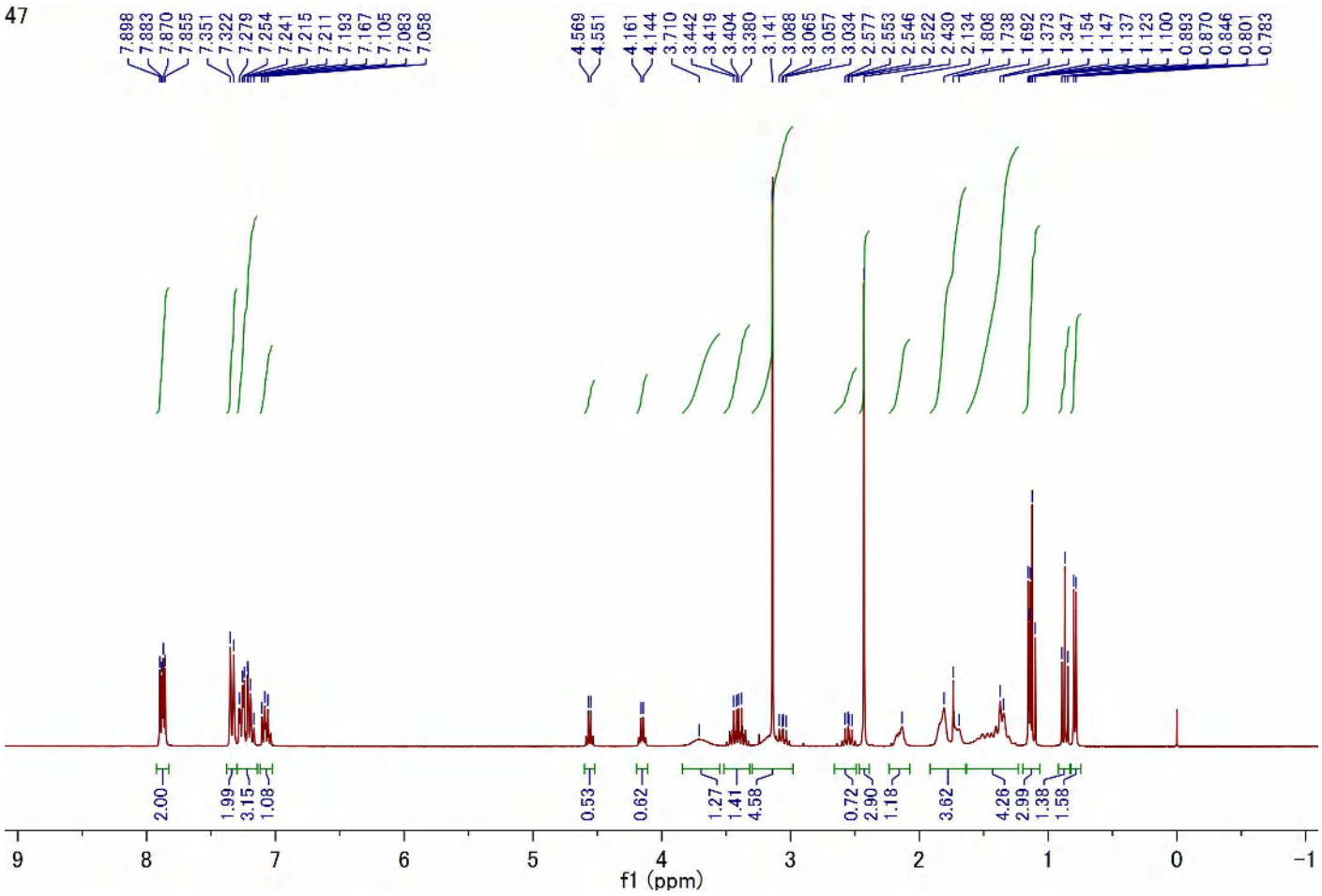
Compound **3l** (^{1}H NMR, 300 MHz, $CDCl_3$)



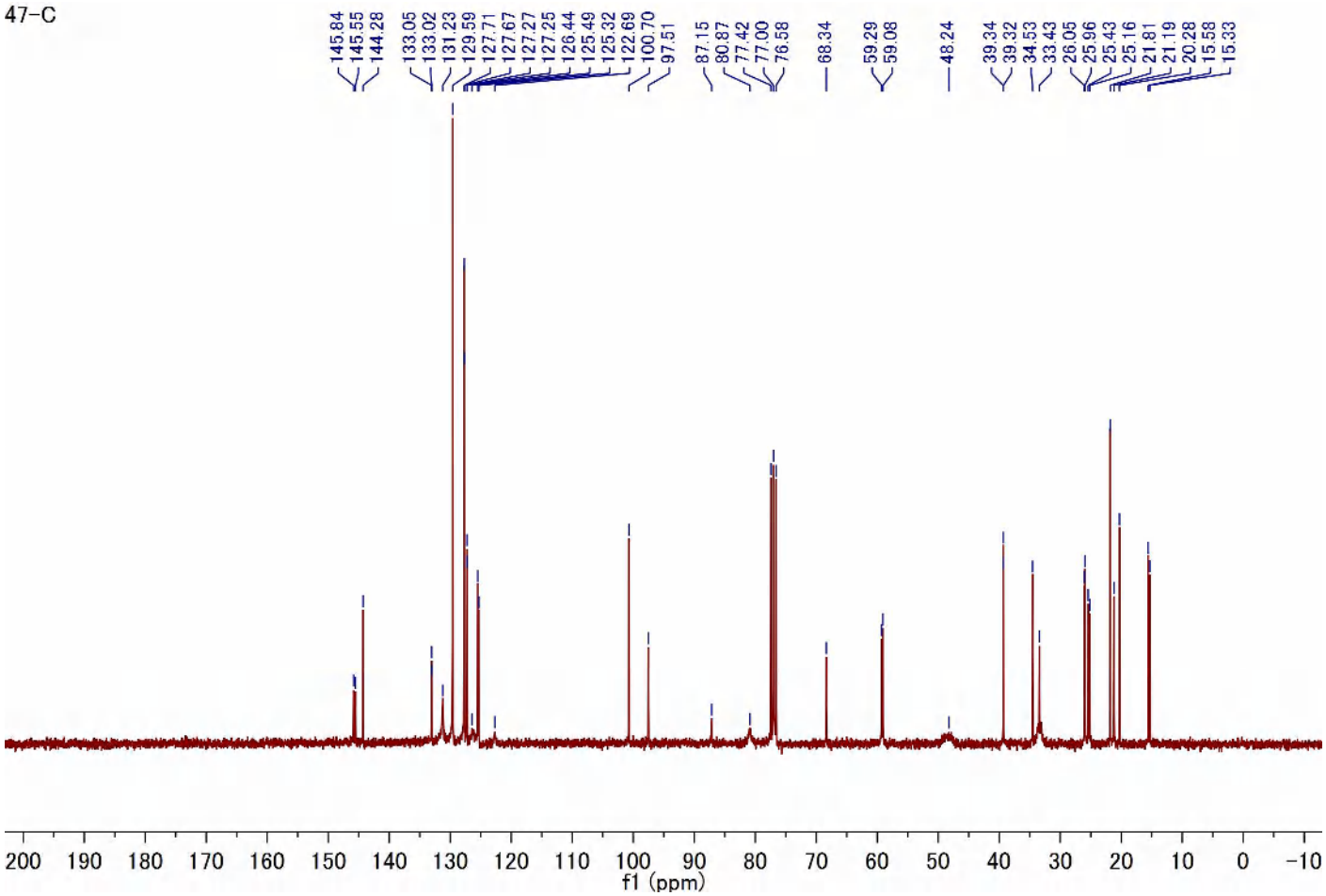
Compound **3l** (^{13}C NMR, 75 MHz, $CDCl_3$)



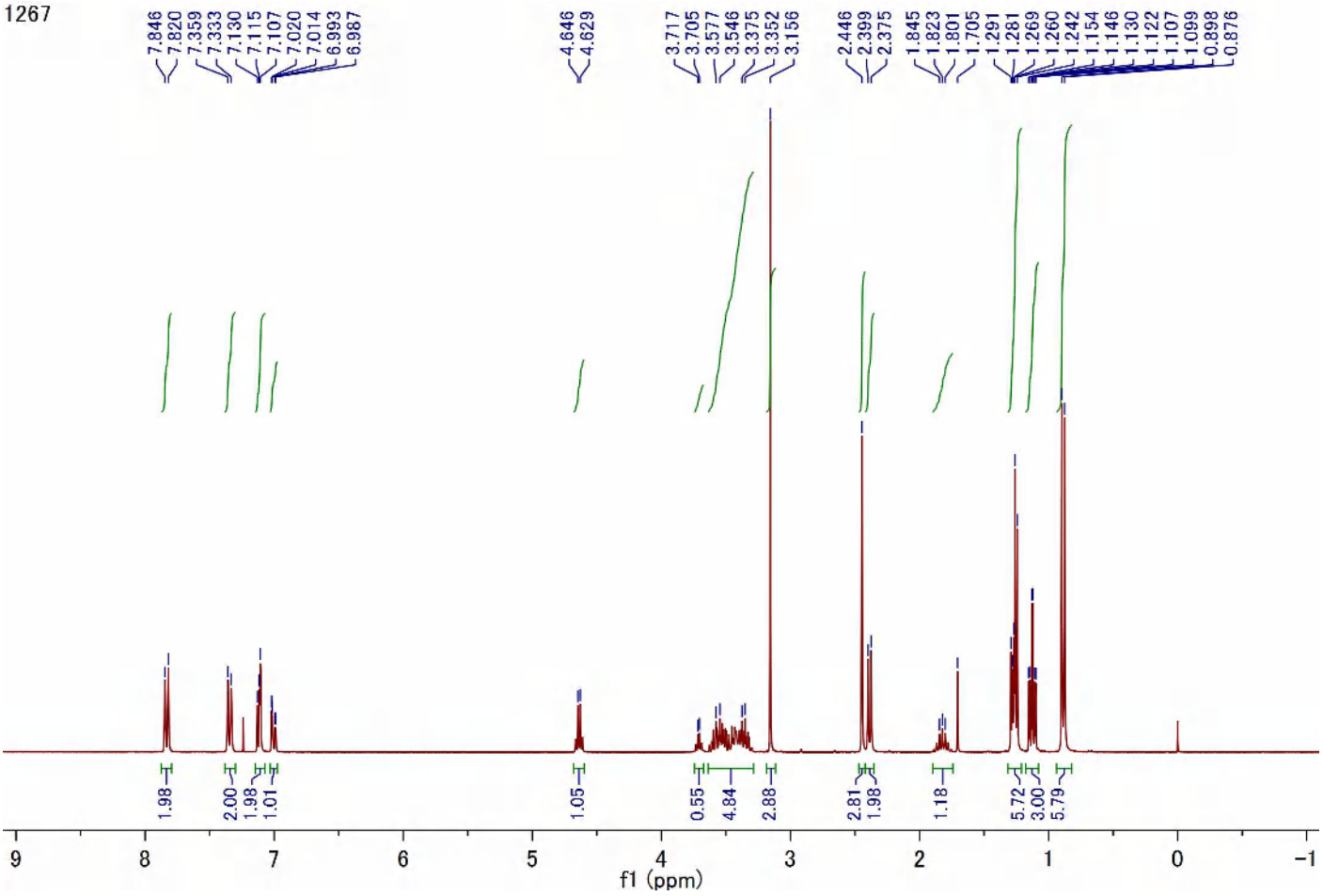
Compound **3m** (^{1}H NMR, 300 MHz, $CDCl_3$)



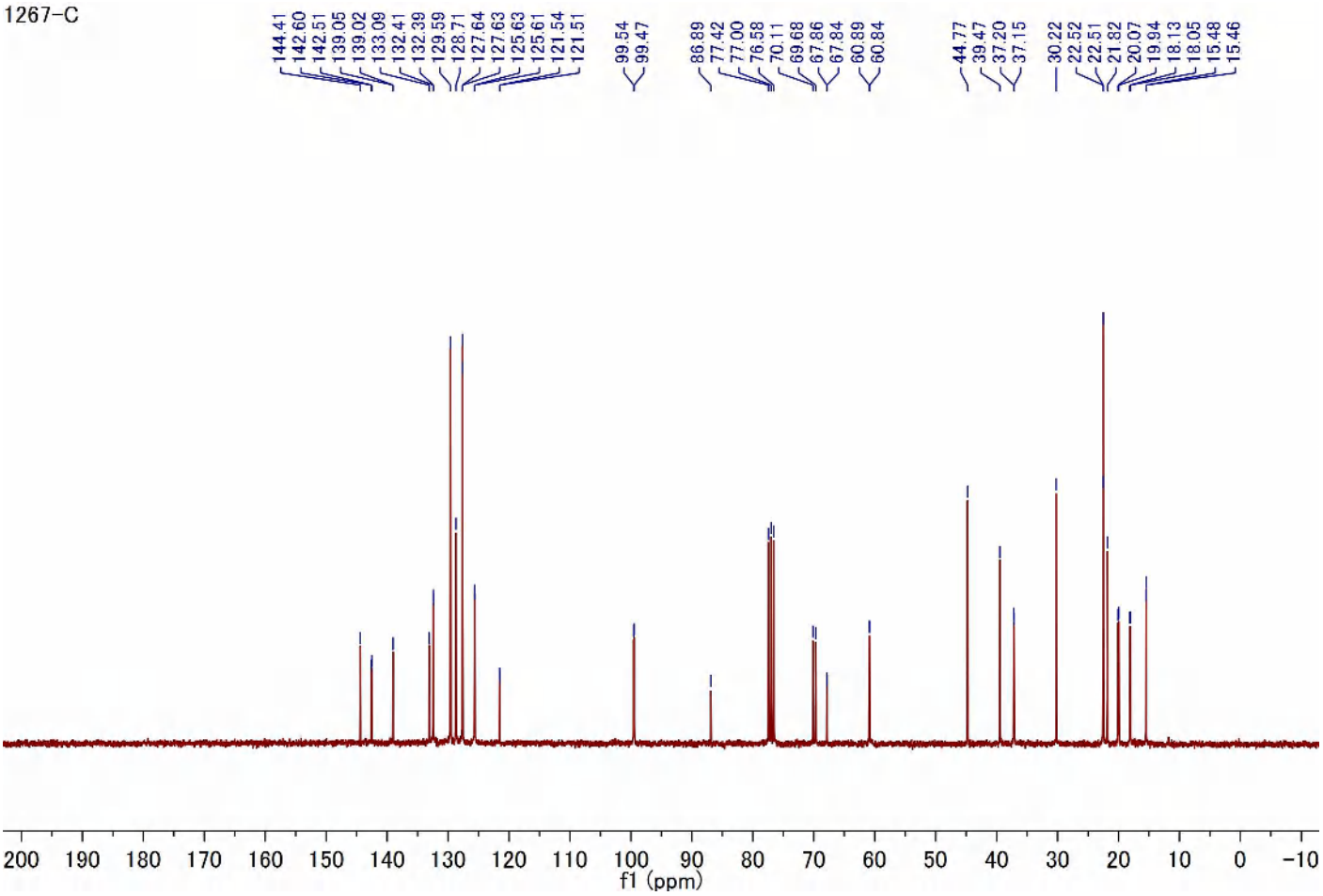
Compound **3m** (^{13}C NMR, 75 MHz, $CDCl_3$)



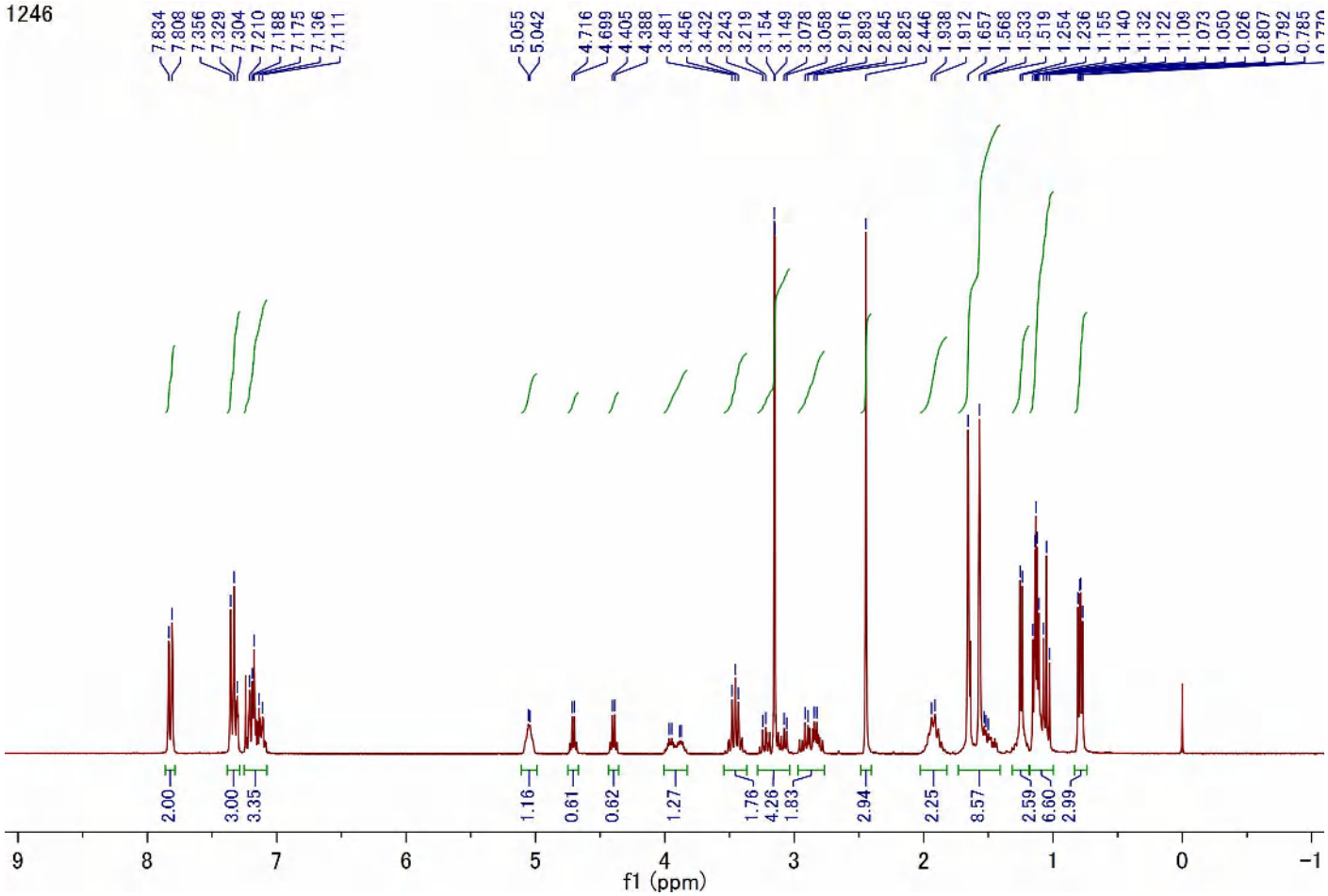
Compound **3n** (^{1}H NMR, 300 MHz, $CDCl_3$)



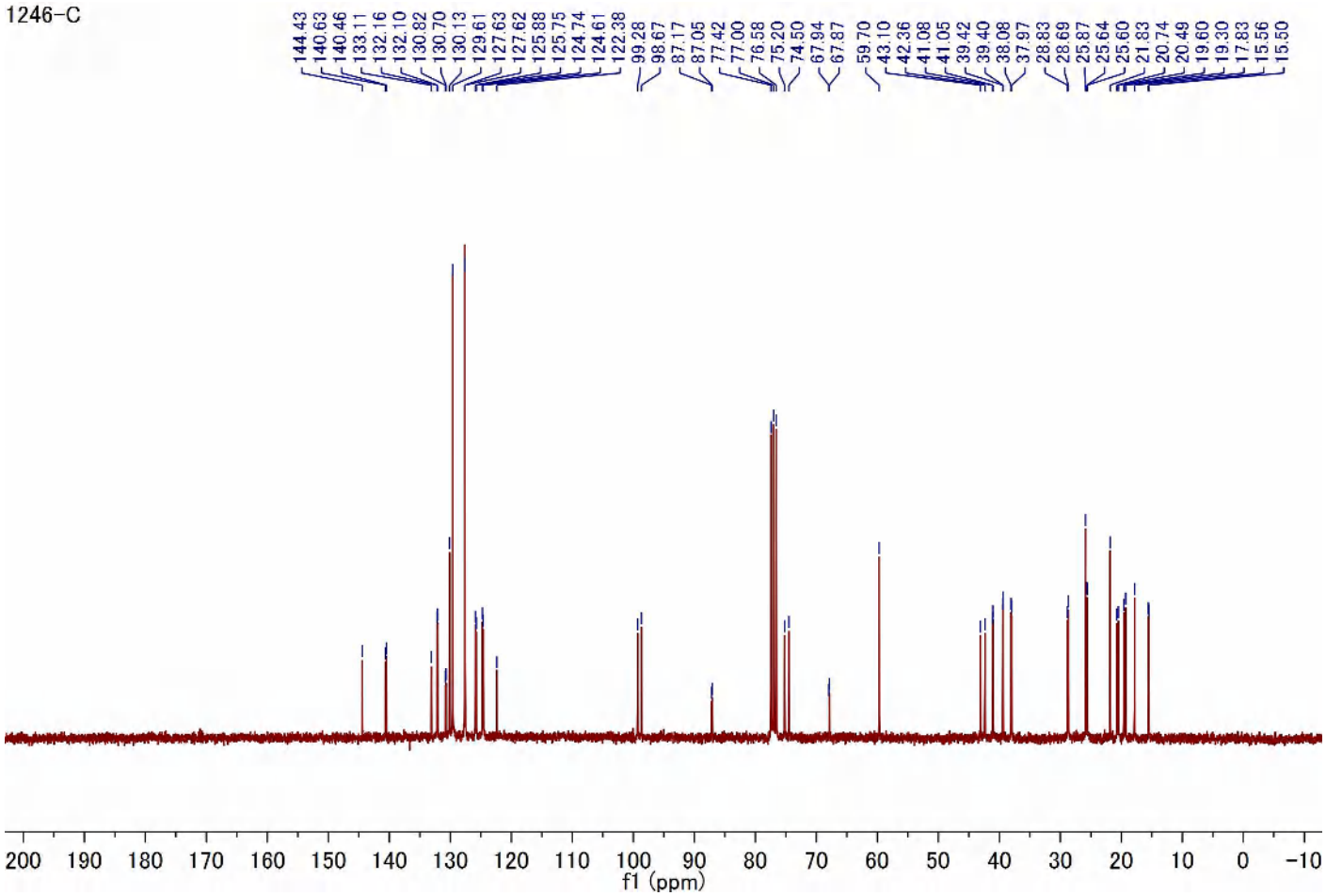
Compound **3n** (^{13}C NMR, 75 MHz, $CDCl_3$)



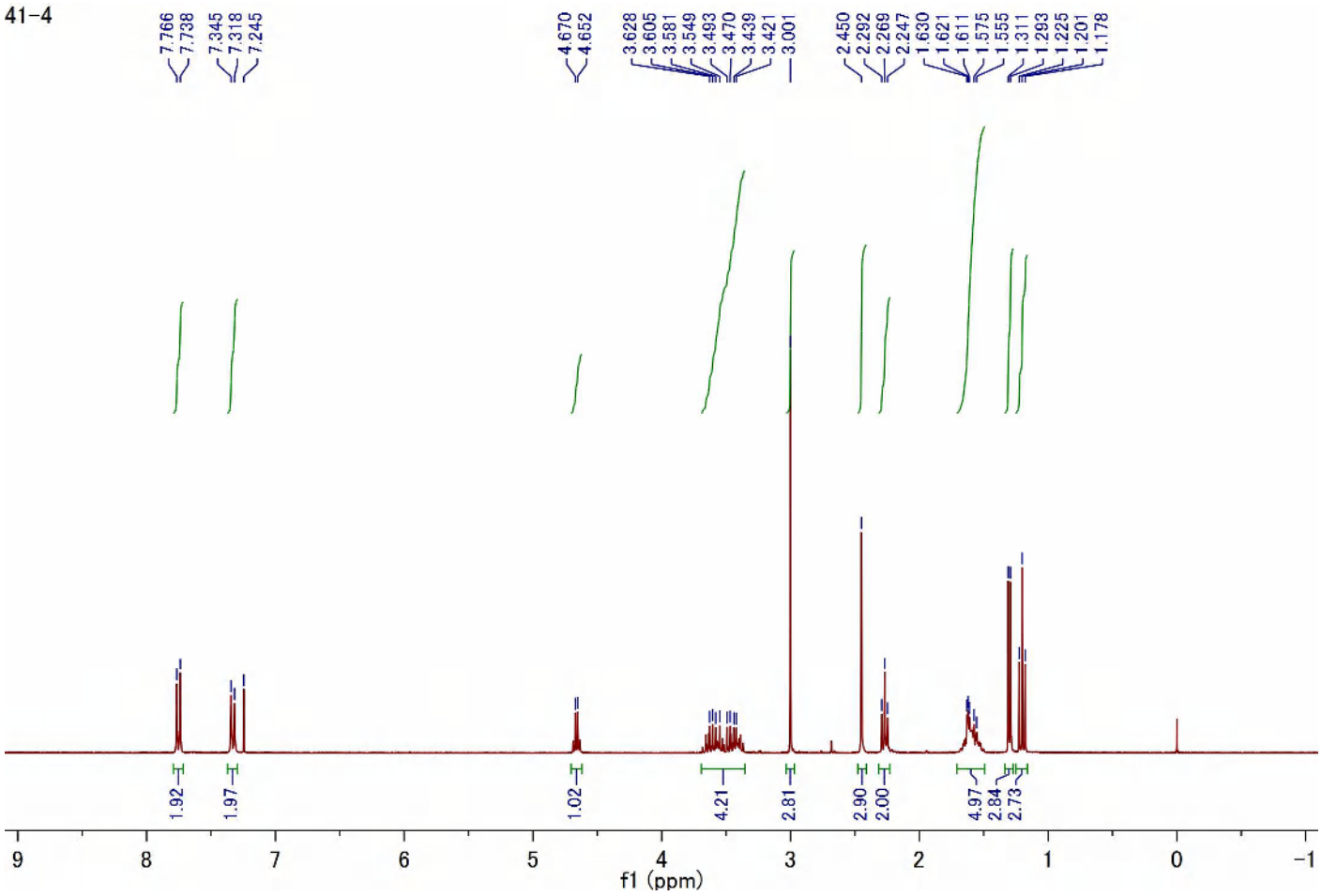
Compound **3o** (^{1}H NMR, 300 MHz, $CDCl_3$)



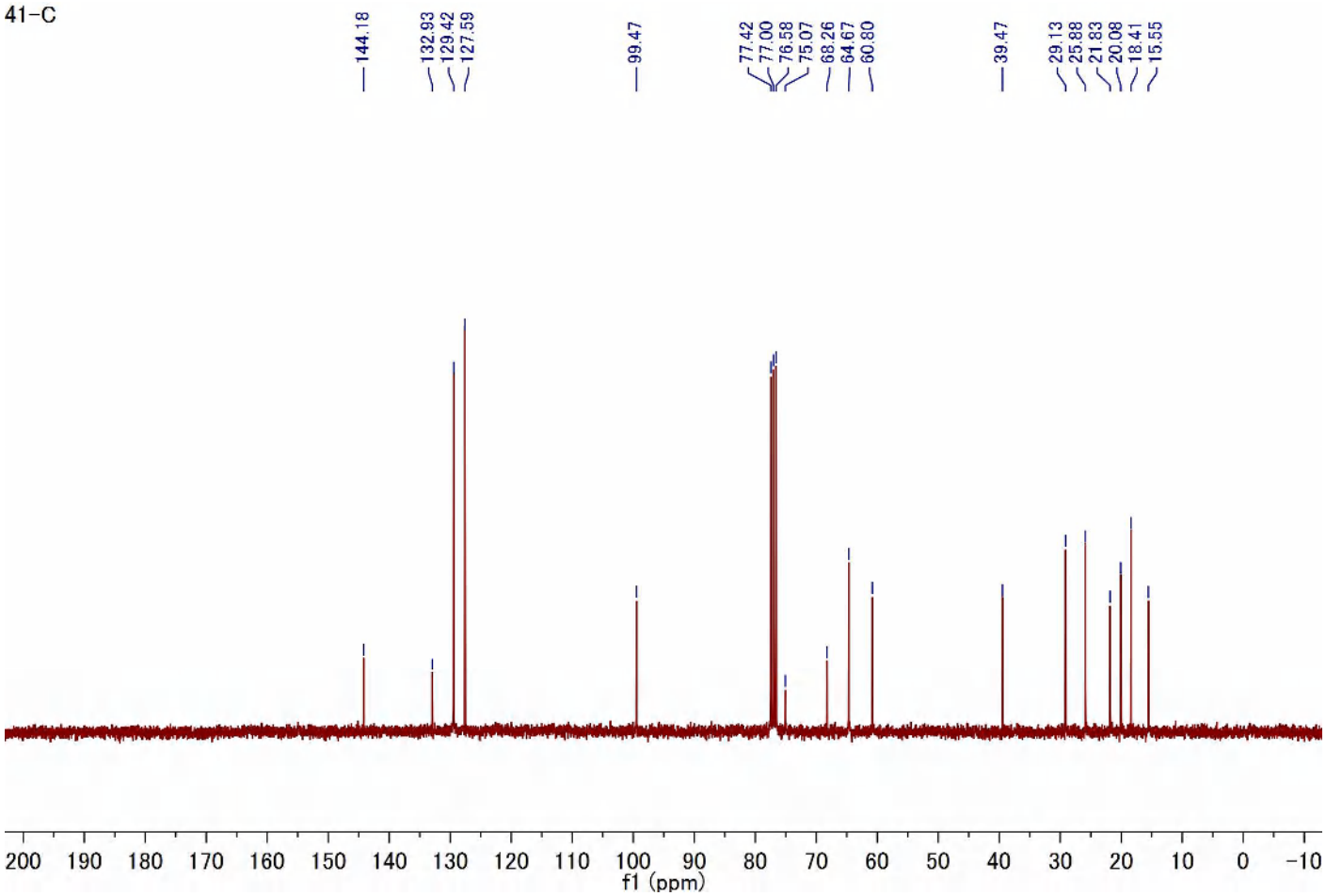
Compound **3o** (^{13}C NMR, 75 MHz, $CDCl_3$)



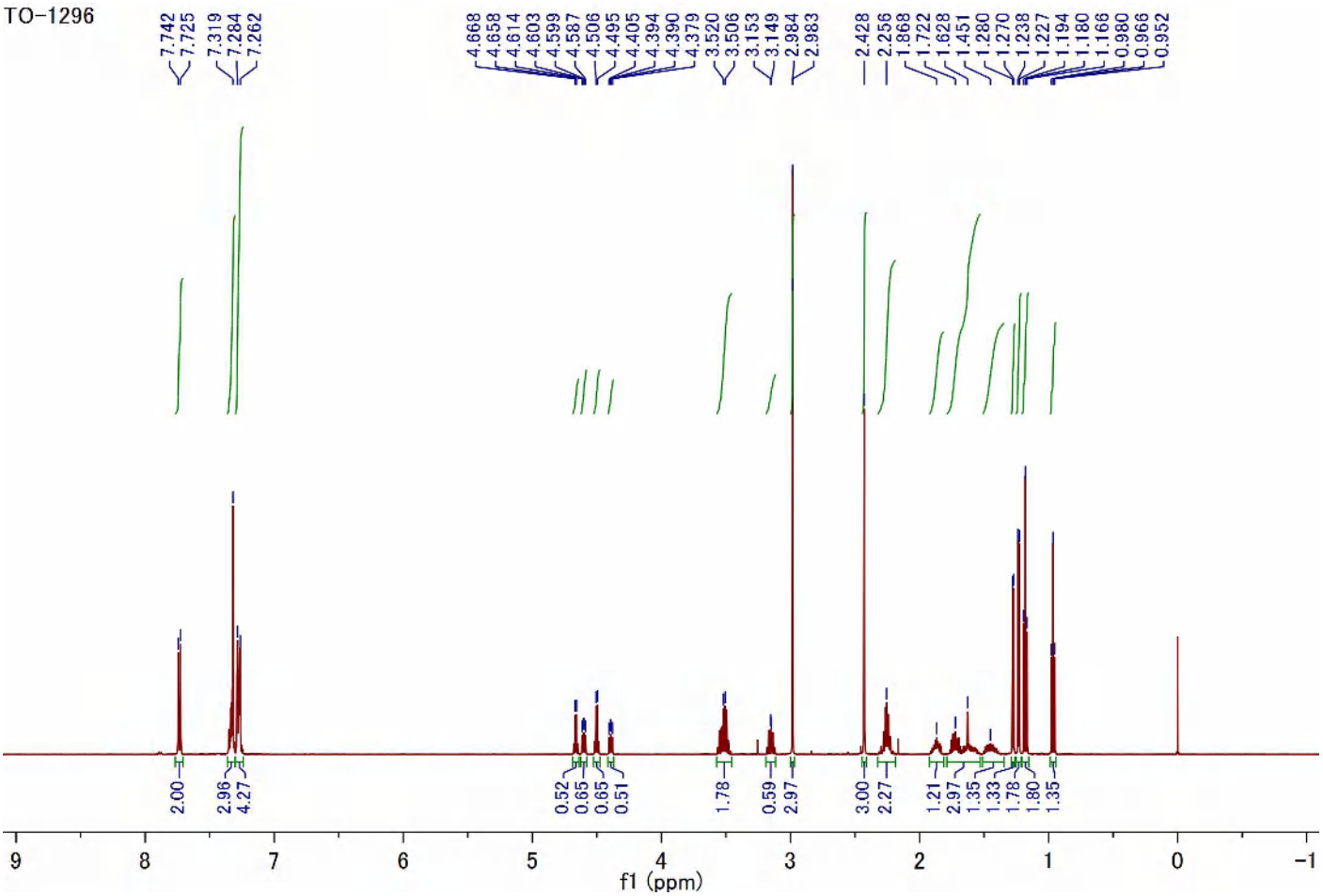
Compound **3p** (^{1}H NMR, 300 MHz, $CDCl_3$)



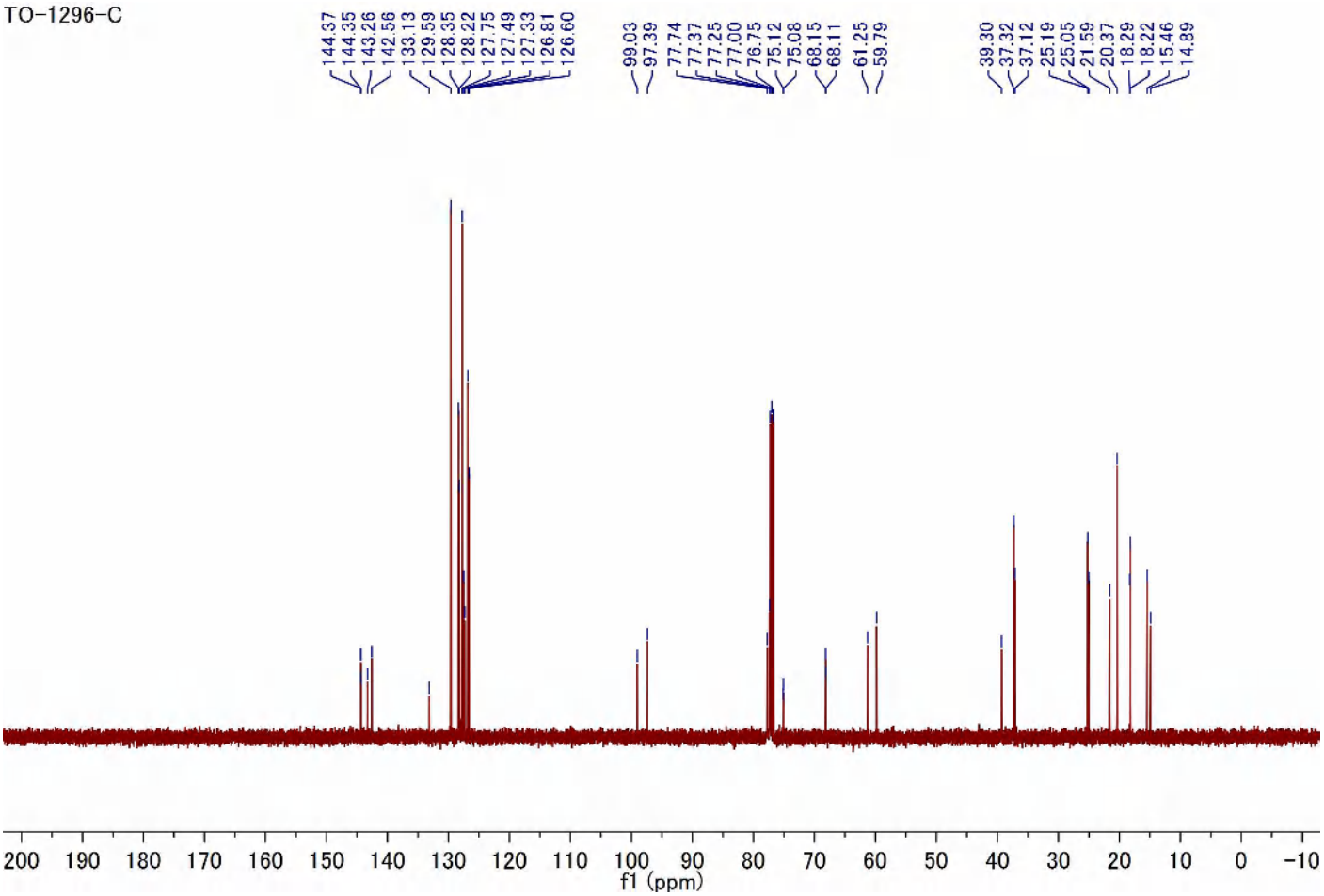
Compound **3p** (^{13}C NMR, 75 MHz, $CDCl_3$)



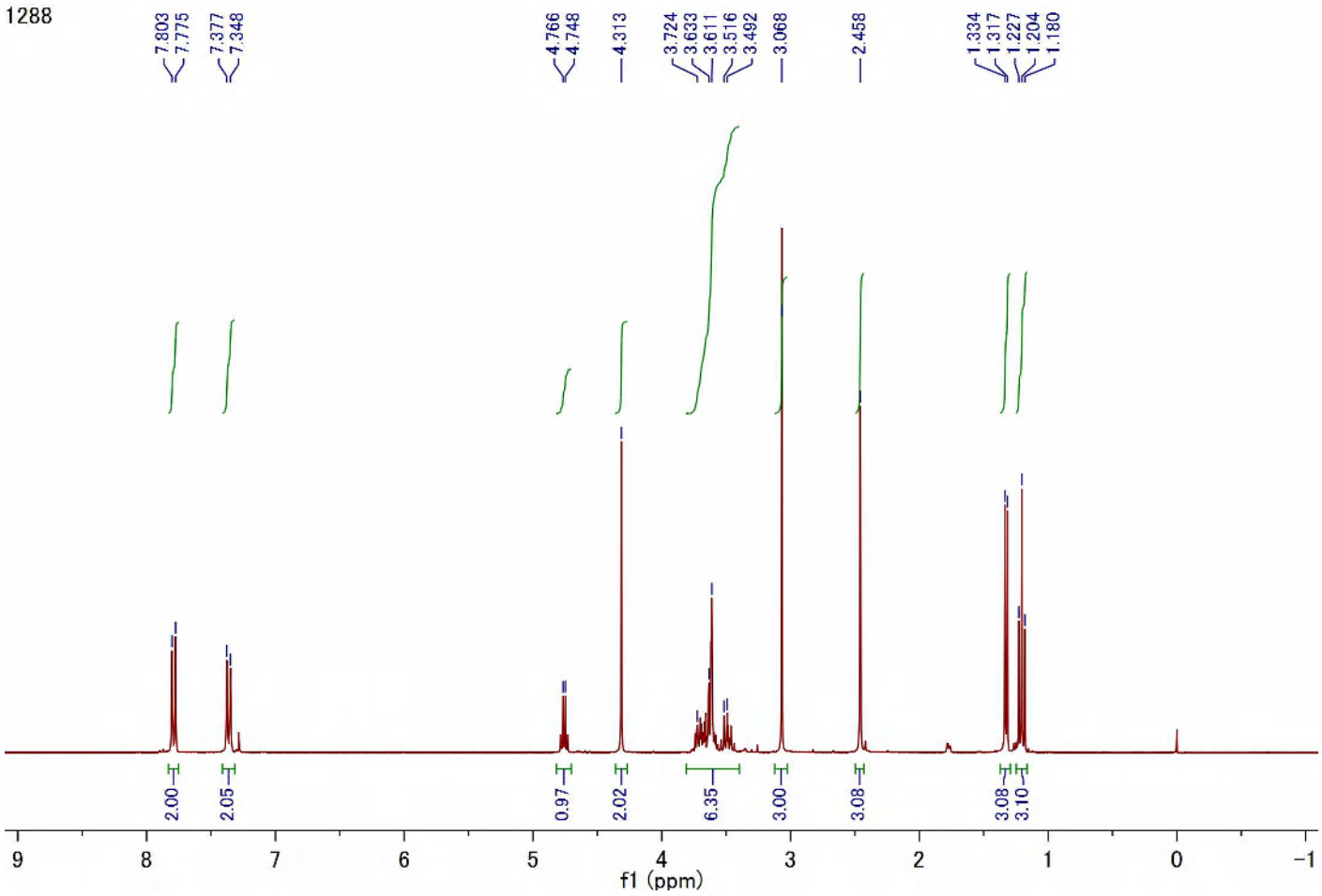
Compound **3q** (^{1}H NMR, 300 MHz, $CDCl_3$)



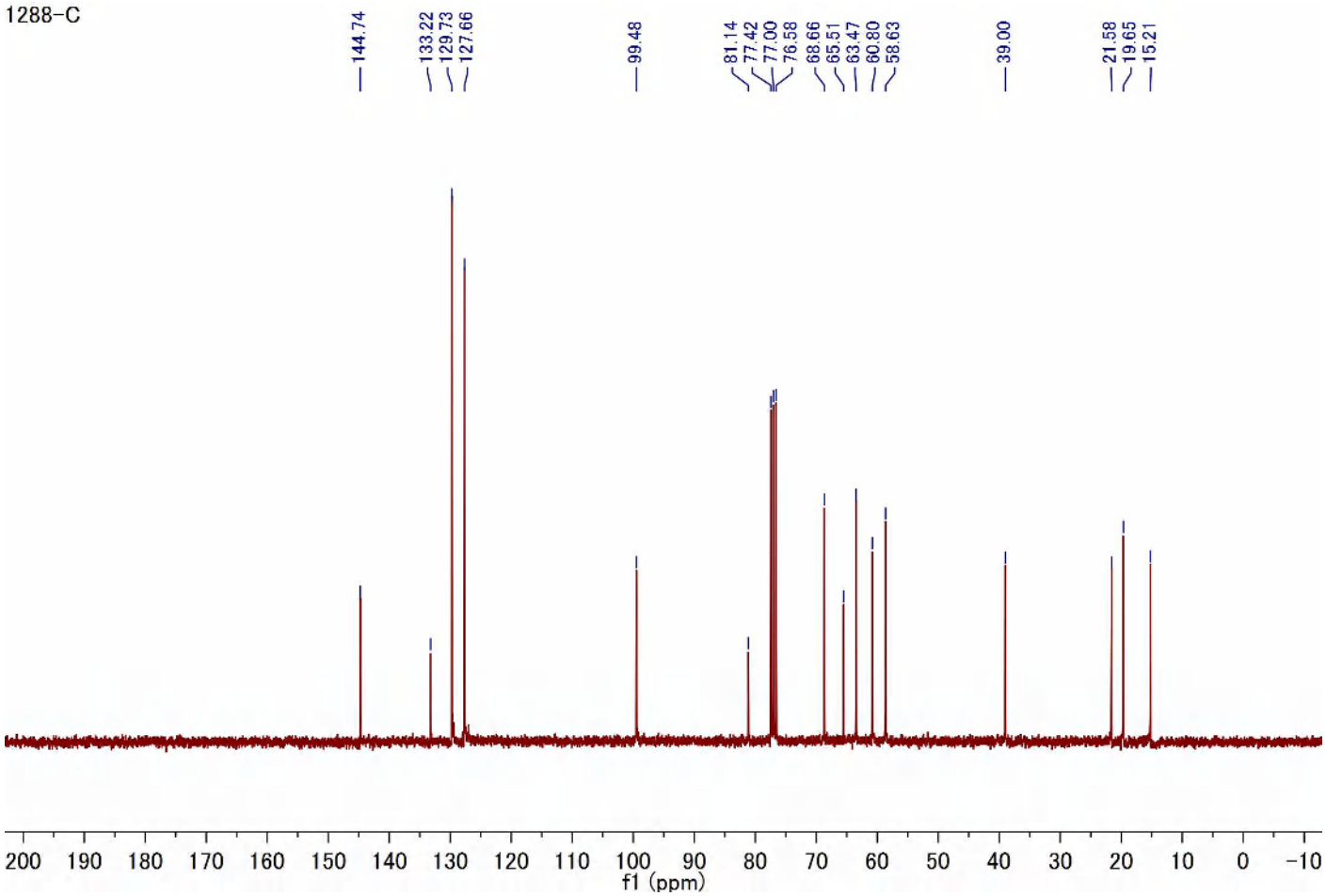
Compound **3q** (^{13}C NMR, 75 MHz, $CDCl_3$)



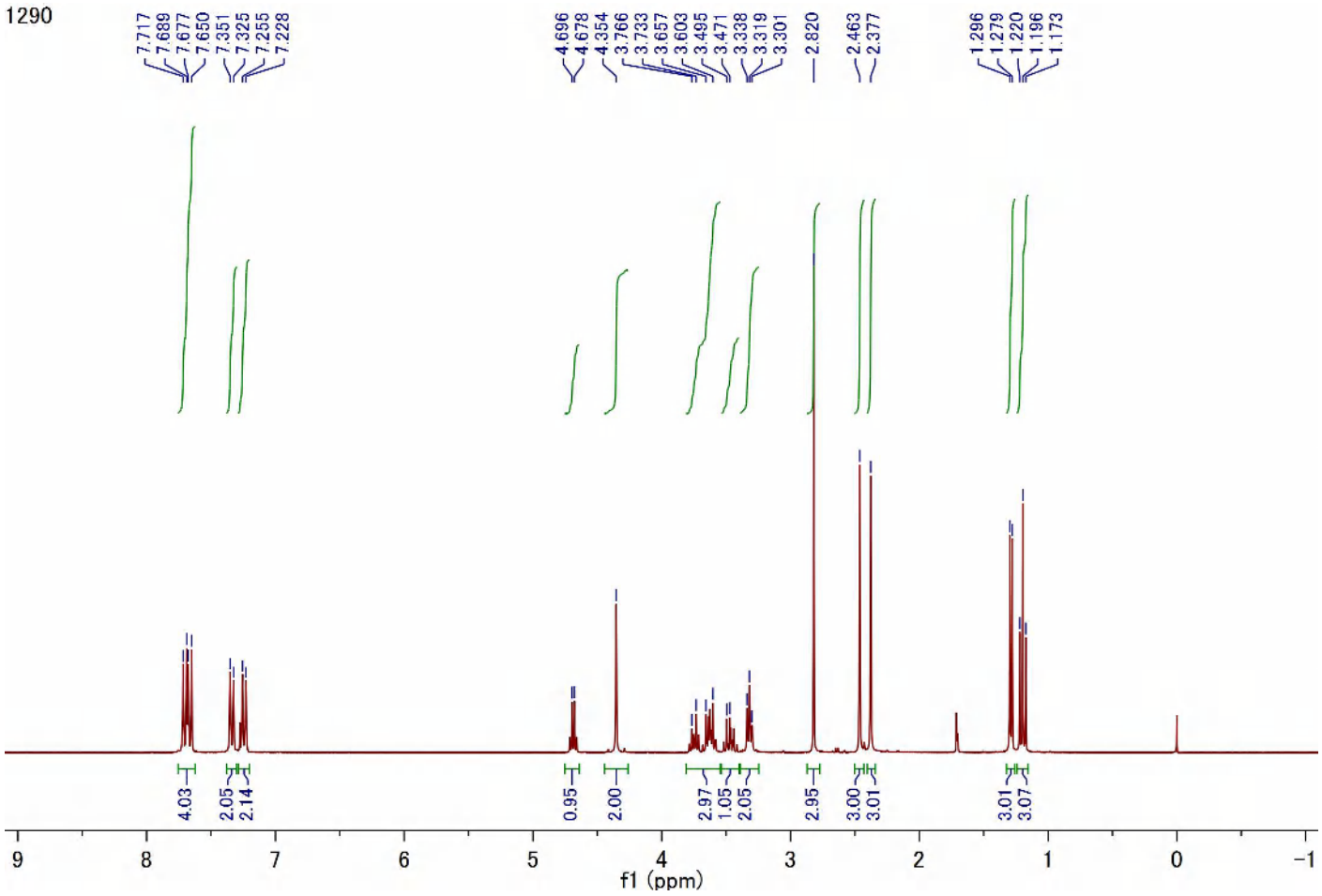
Compound **3r** (^{1}H NMR, 300 MHz, $CDCl_3$)



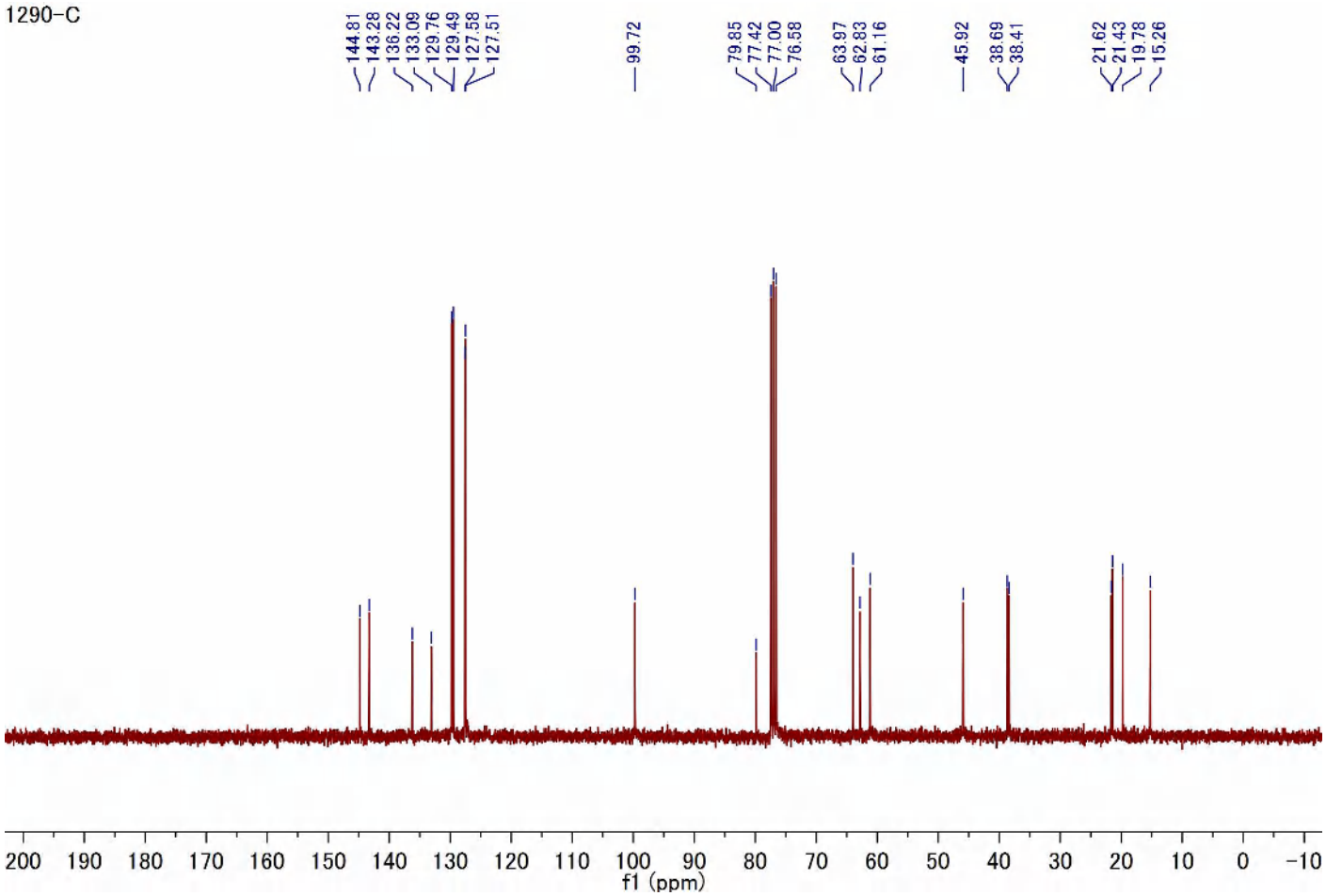
Compound **3r** (^{13}C NMR, 75 MHz, $CDCl_3$)



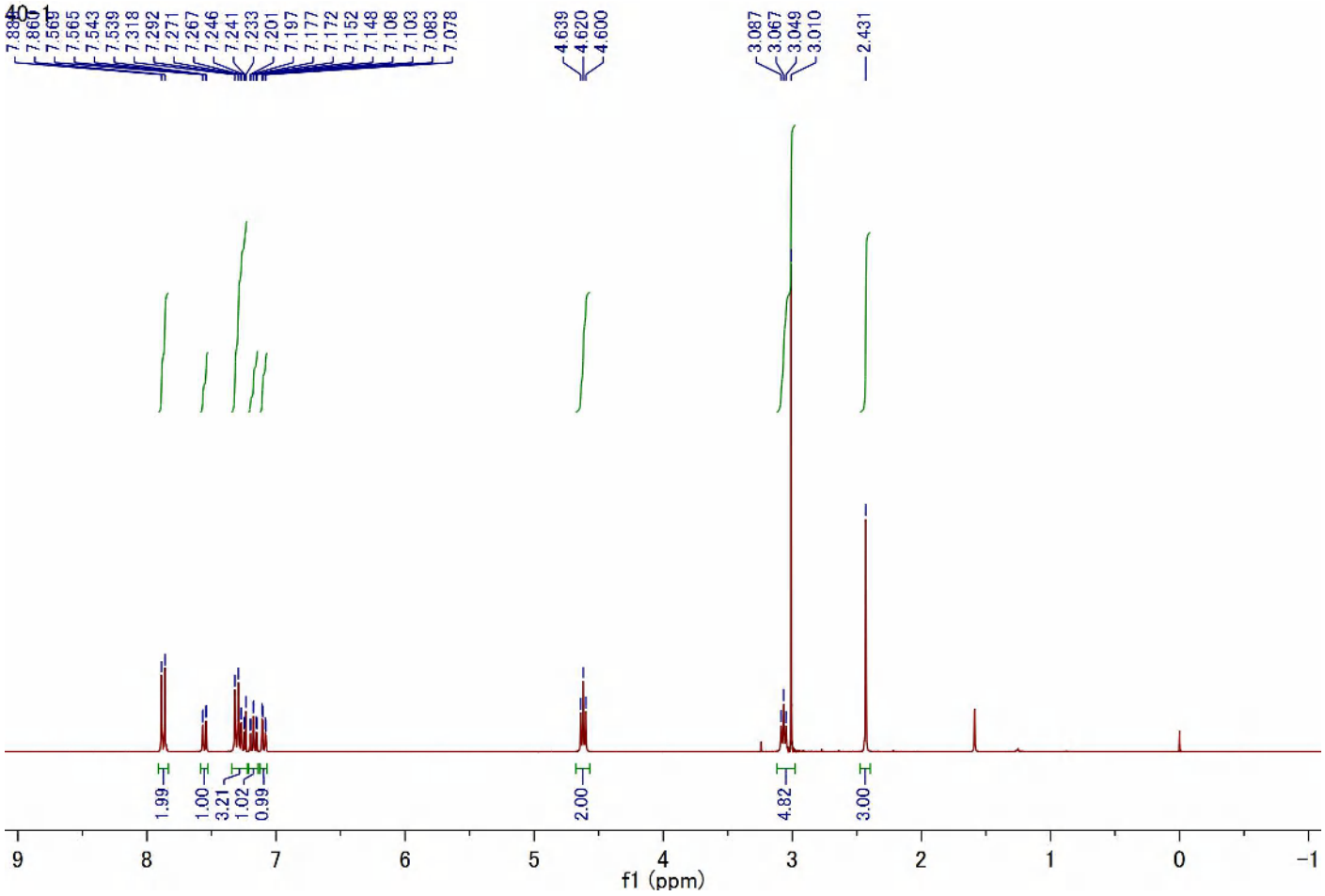
Compound **3s** (^{1}H NMR, 300 MHz, $CDCl_3$)



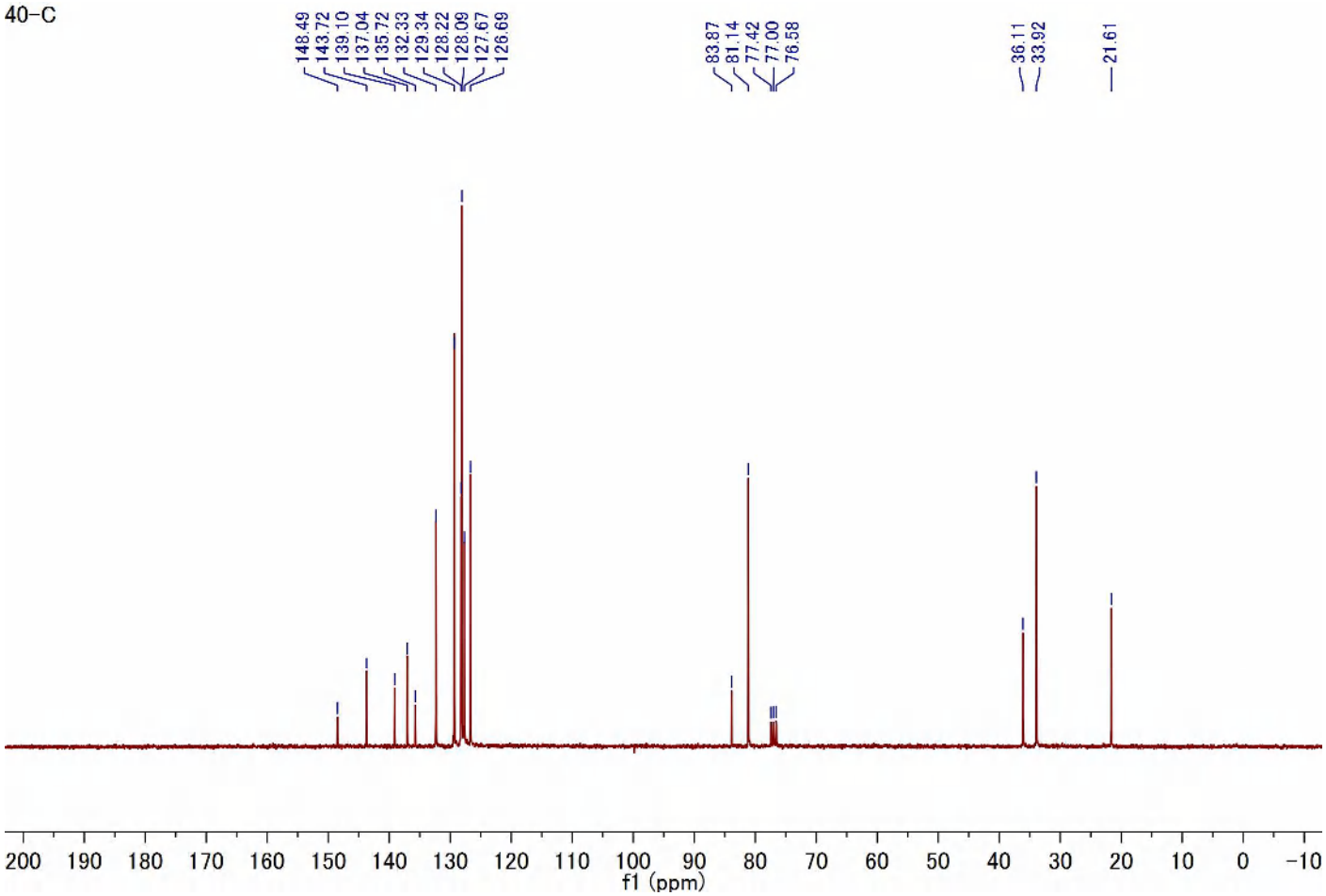
Compound **3s** (^{13}C NMR, 75 MHz, $CDCl_3$)



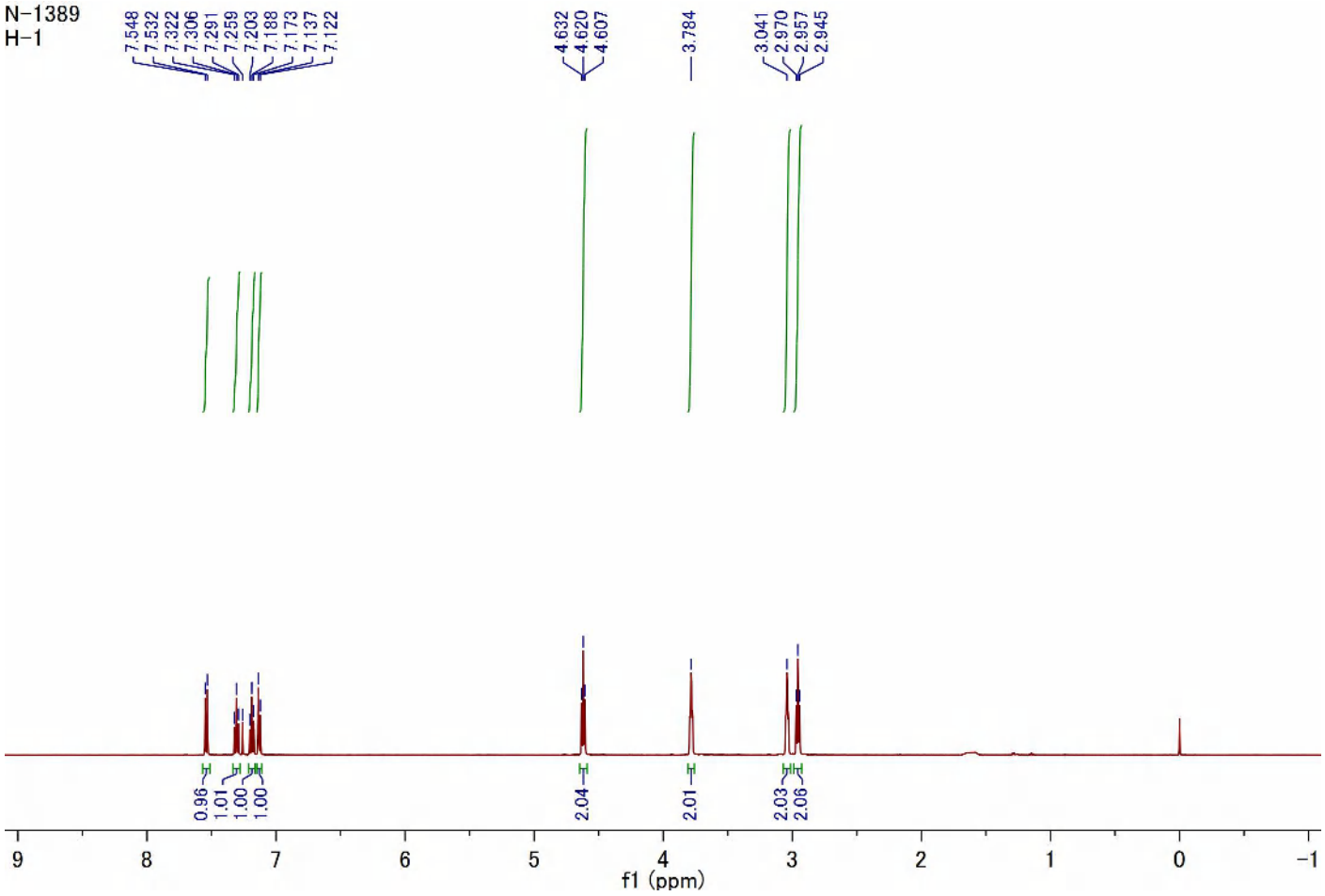
Compound **4a** (^{1}H NMR, 300 MHz, $CDCl_3$)



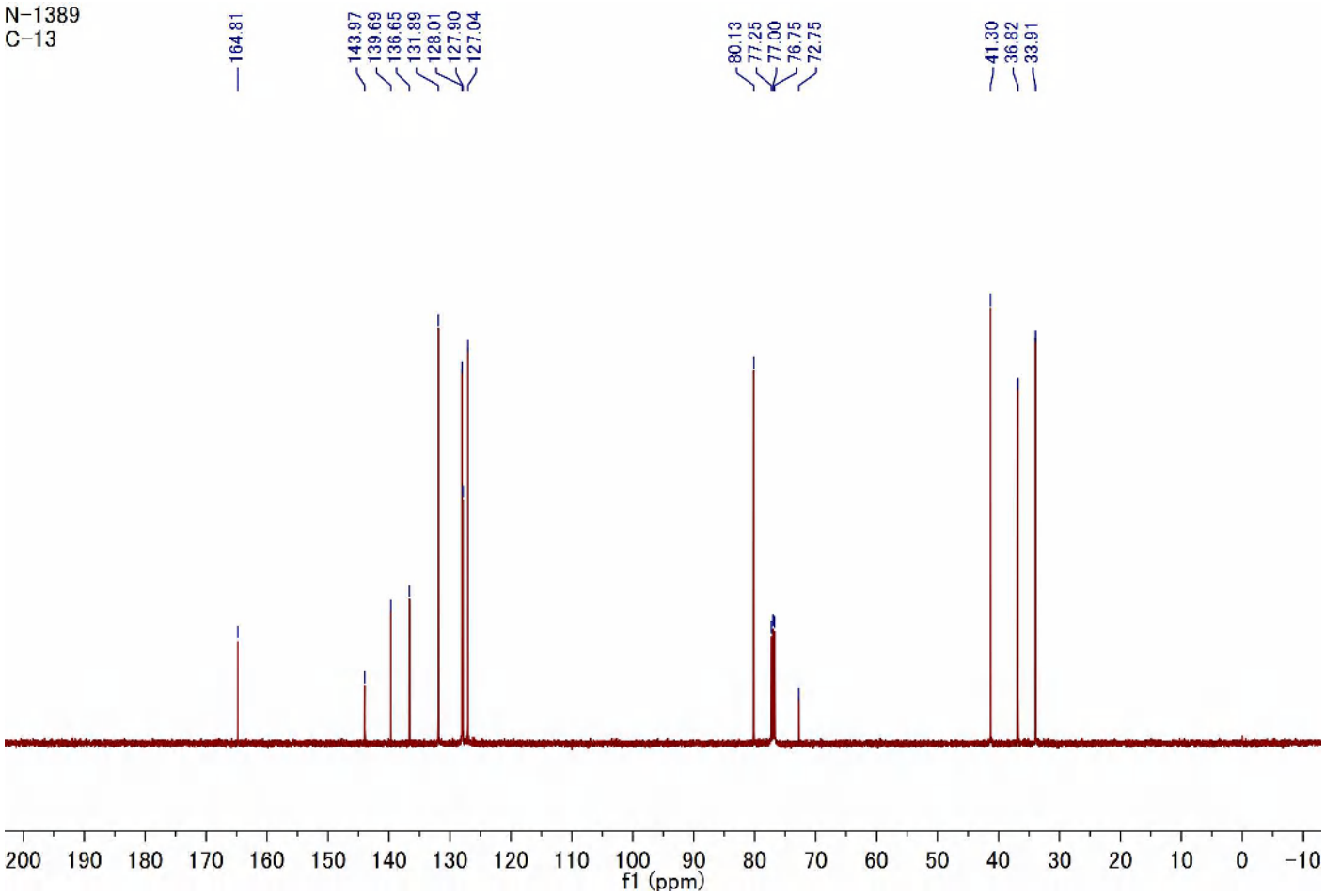
Compound **4a** (^{13}C NMR, 75 MHz, $CDCl_3$)



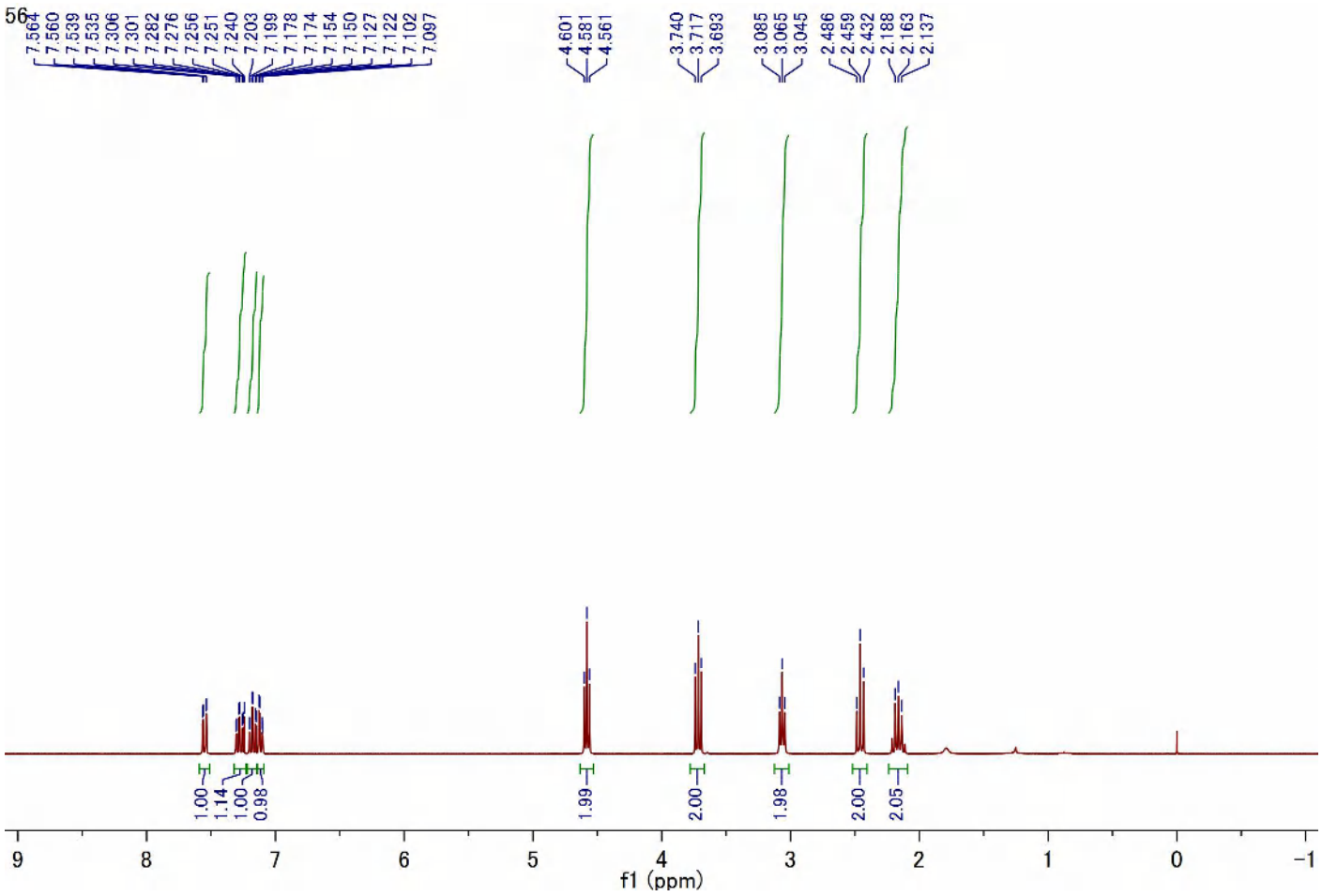
Compound **4b** (^{1}H NMR, 500 MHz, $CDCl_3$)



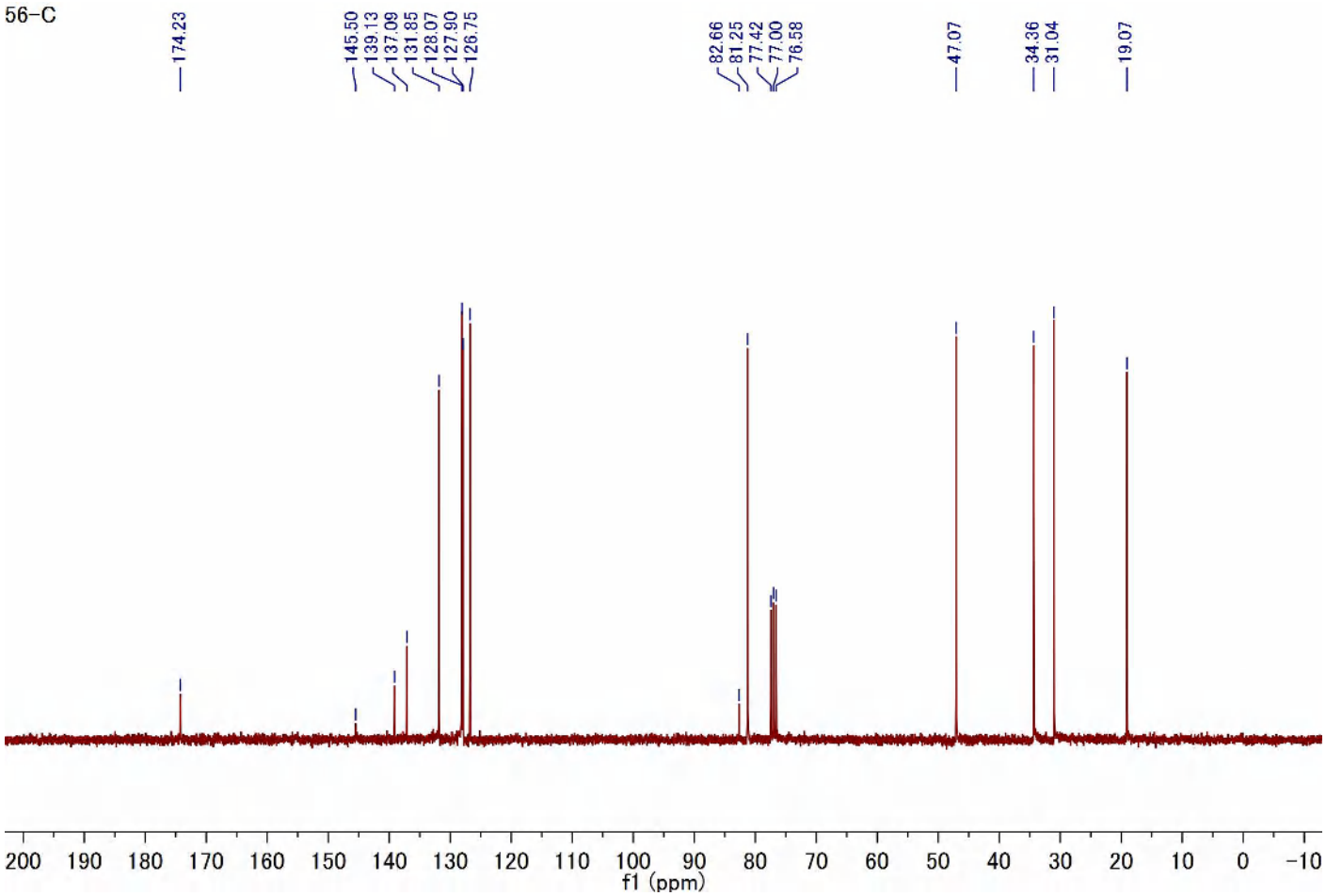
Compound **4b** (^{13}C NMR, 125 MHz, $CDCl_3$)



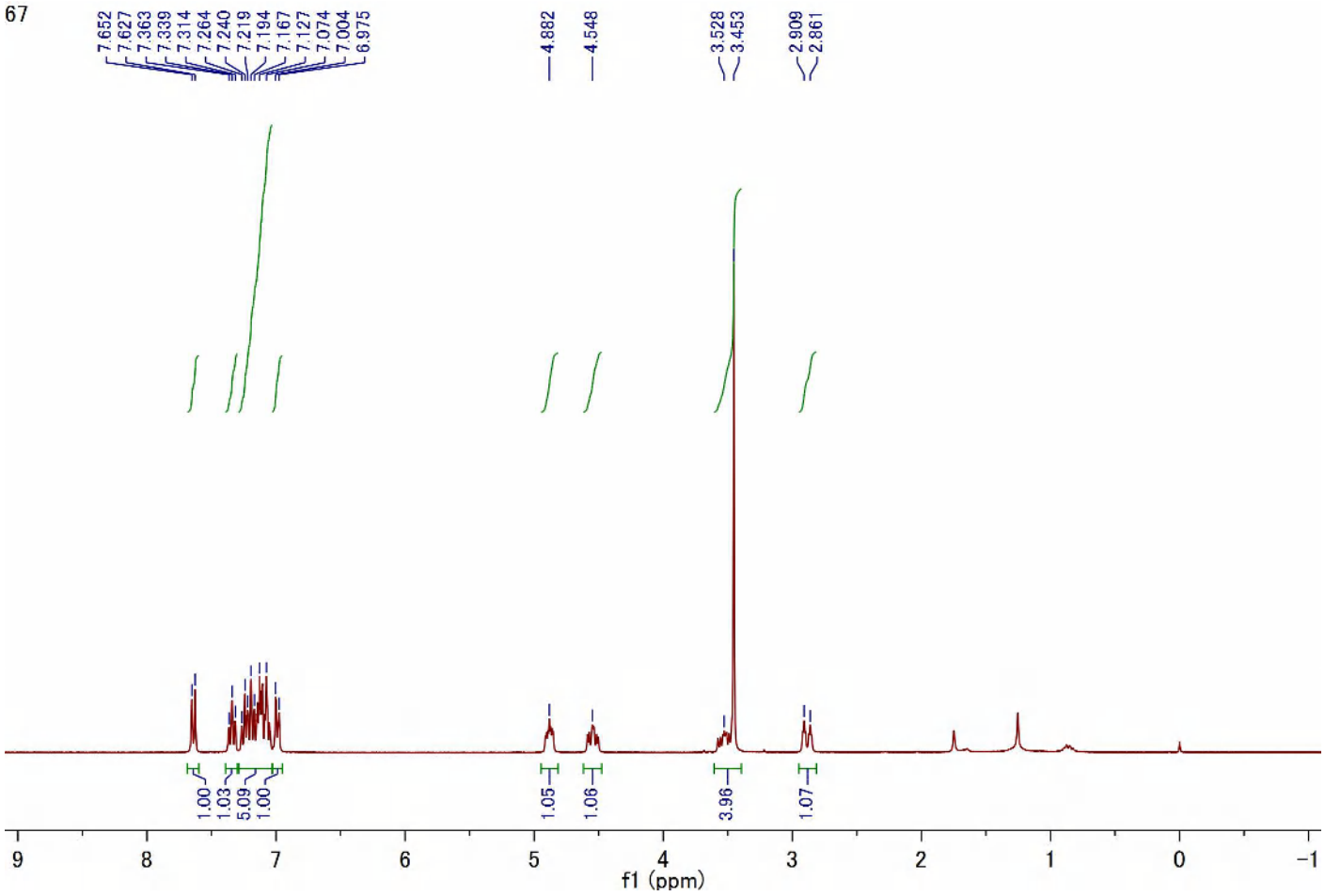
Compound **4c** (^{1}H NMR, 300 MHz, $CDCl_3$)



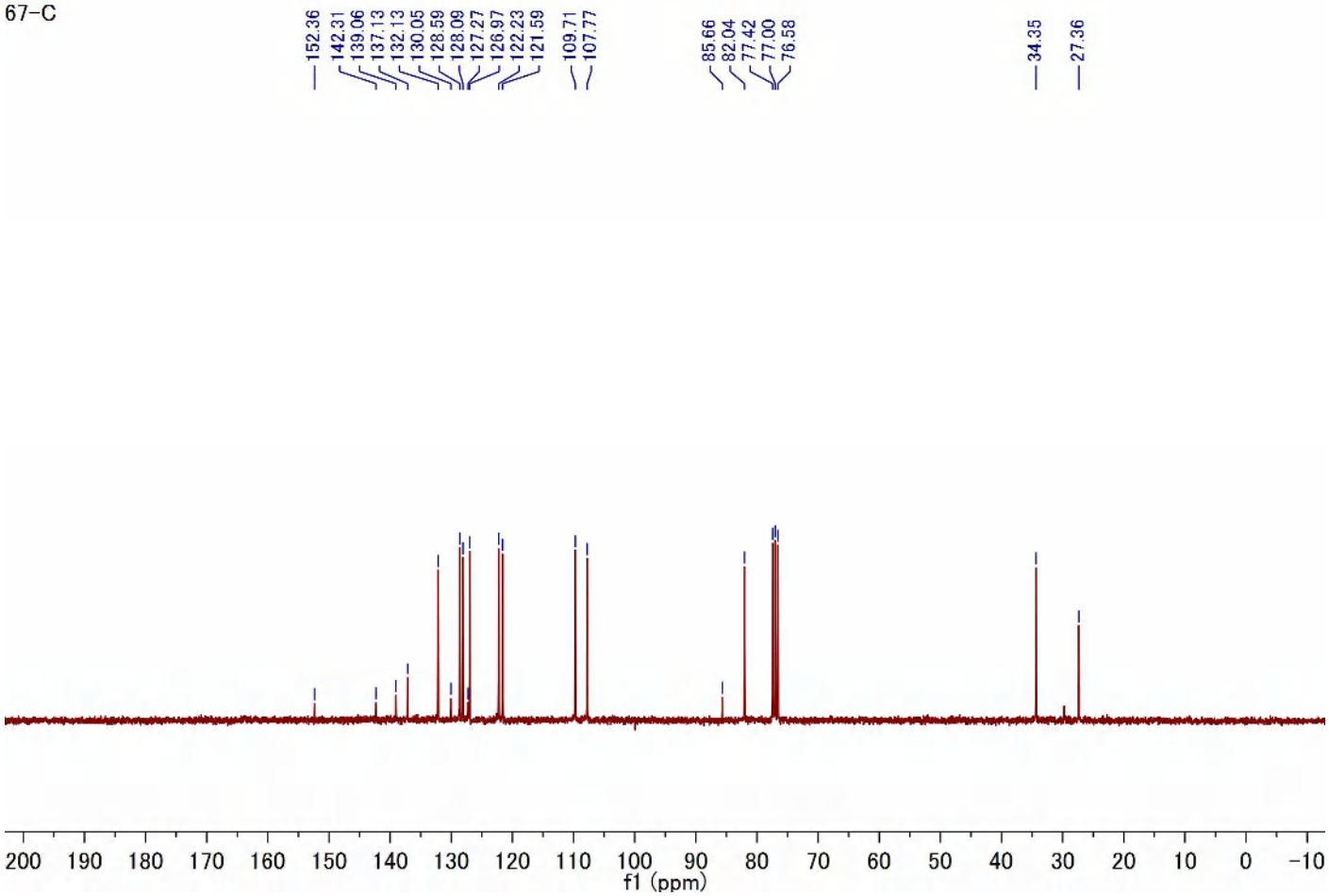
Compound **4c** (^{13}C NMR, 75 MHz, $CDCl_3$)



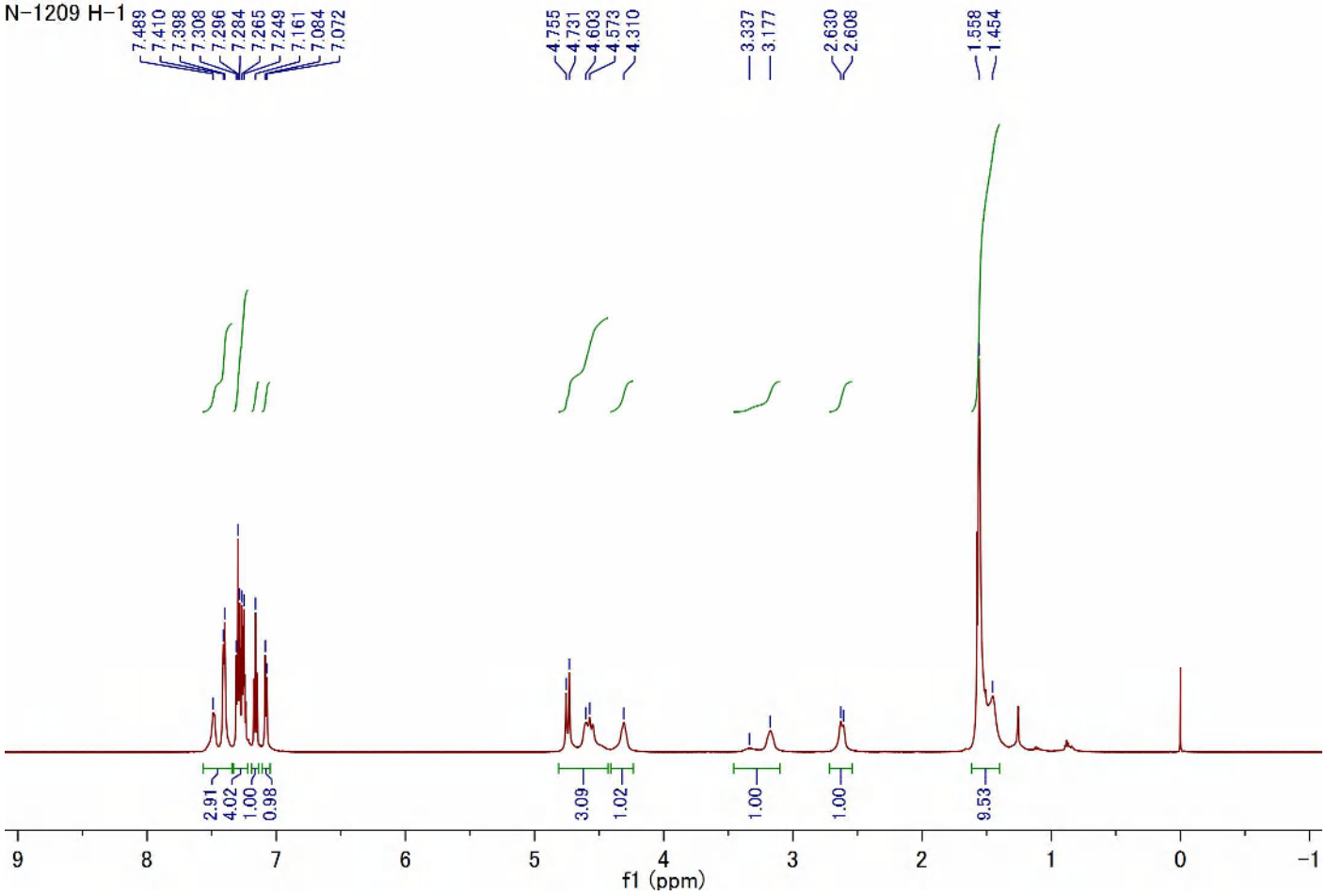
Compound **4d** (^{1}H NMR, 300 MHz, $CDCl_3$)



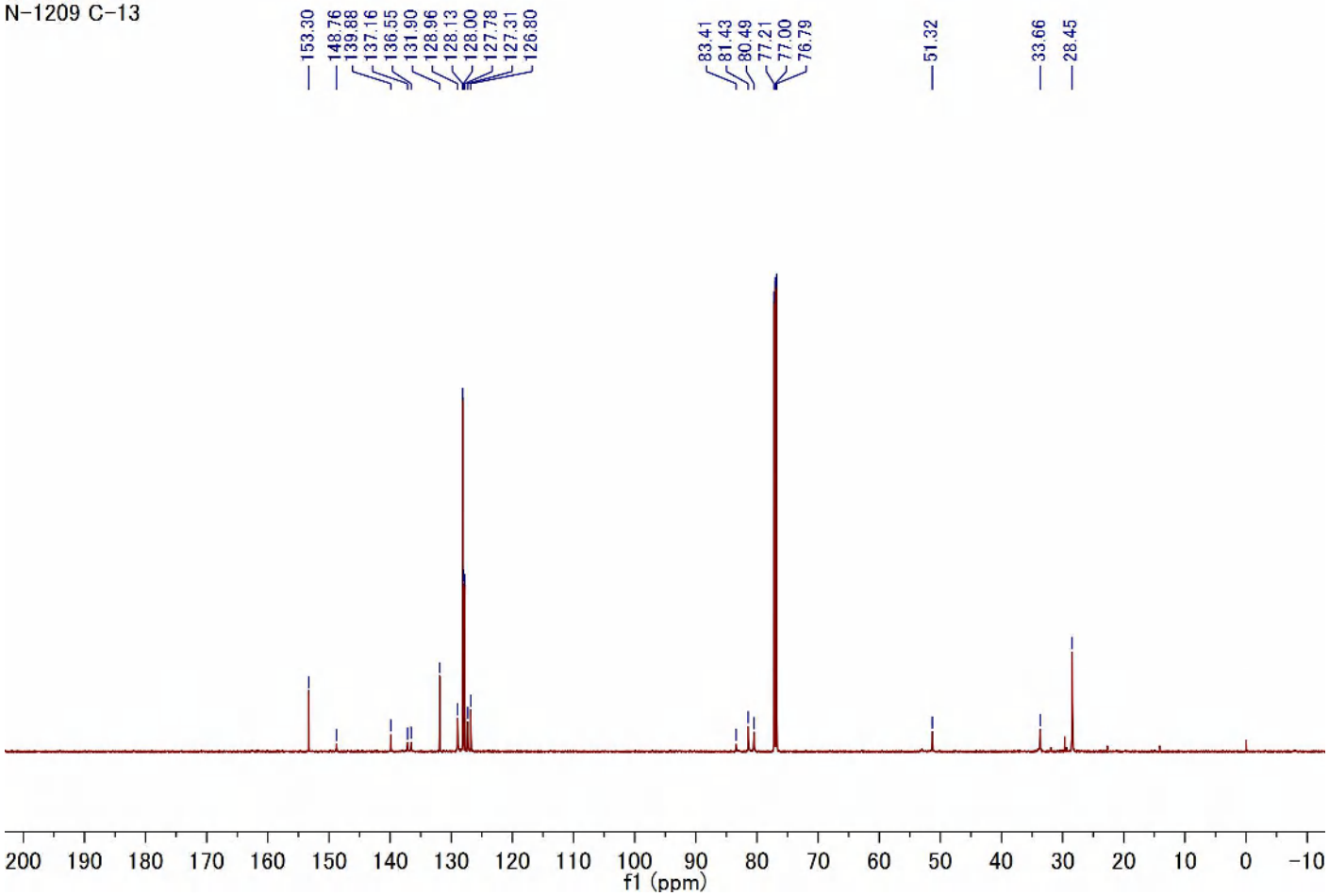
Compound **4d** (^{13}C NMR, 75 MHz, $CDCl_3$)



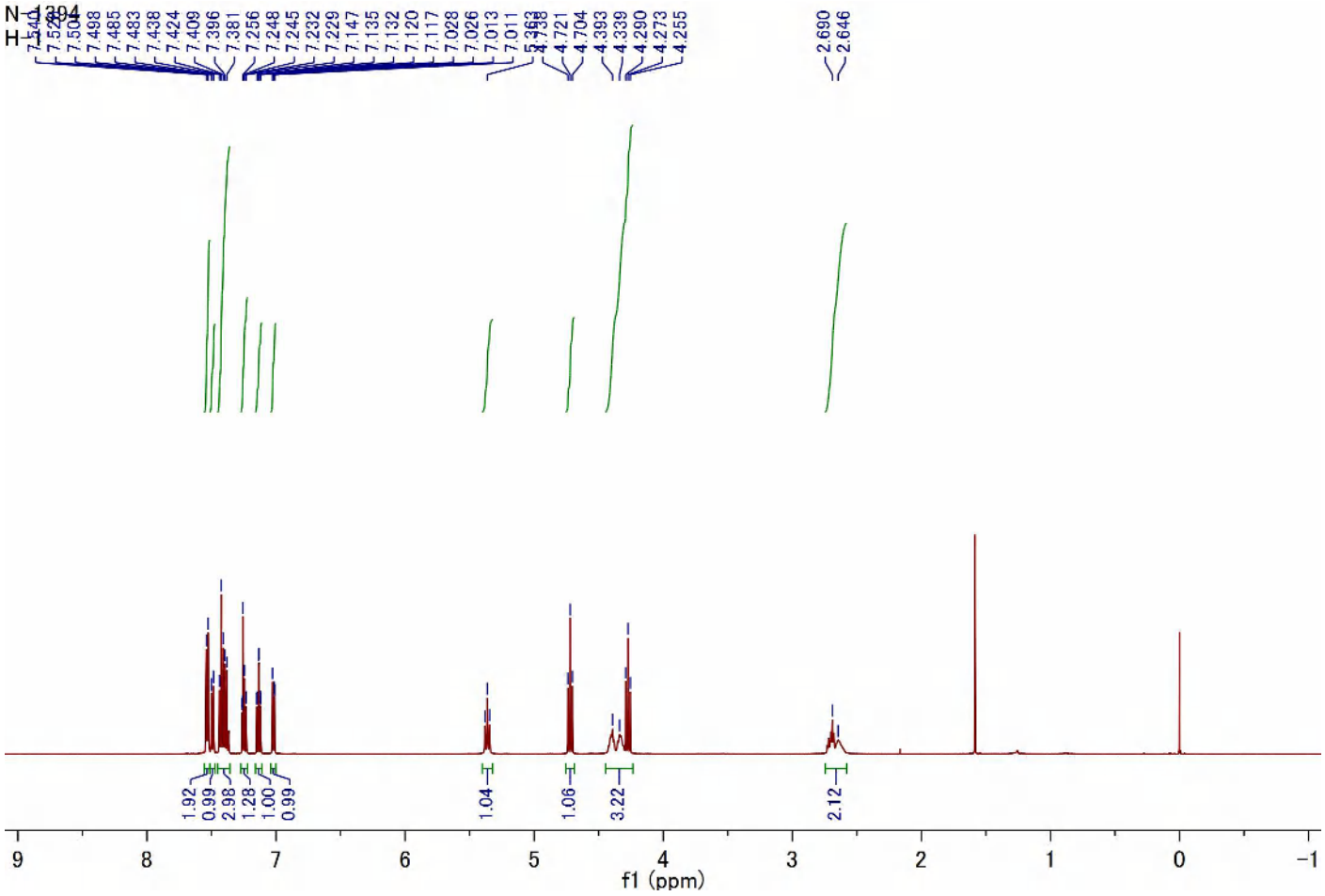
Compound **4e** (^{1}H NMR, 600 MHz, $CDCl_3$)



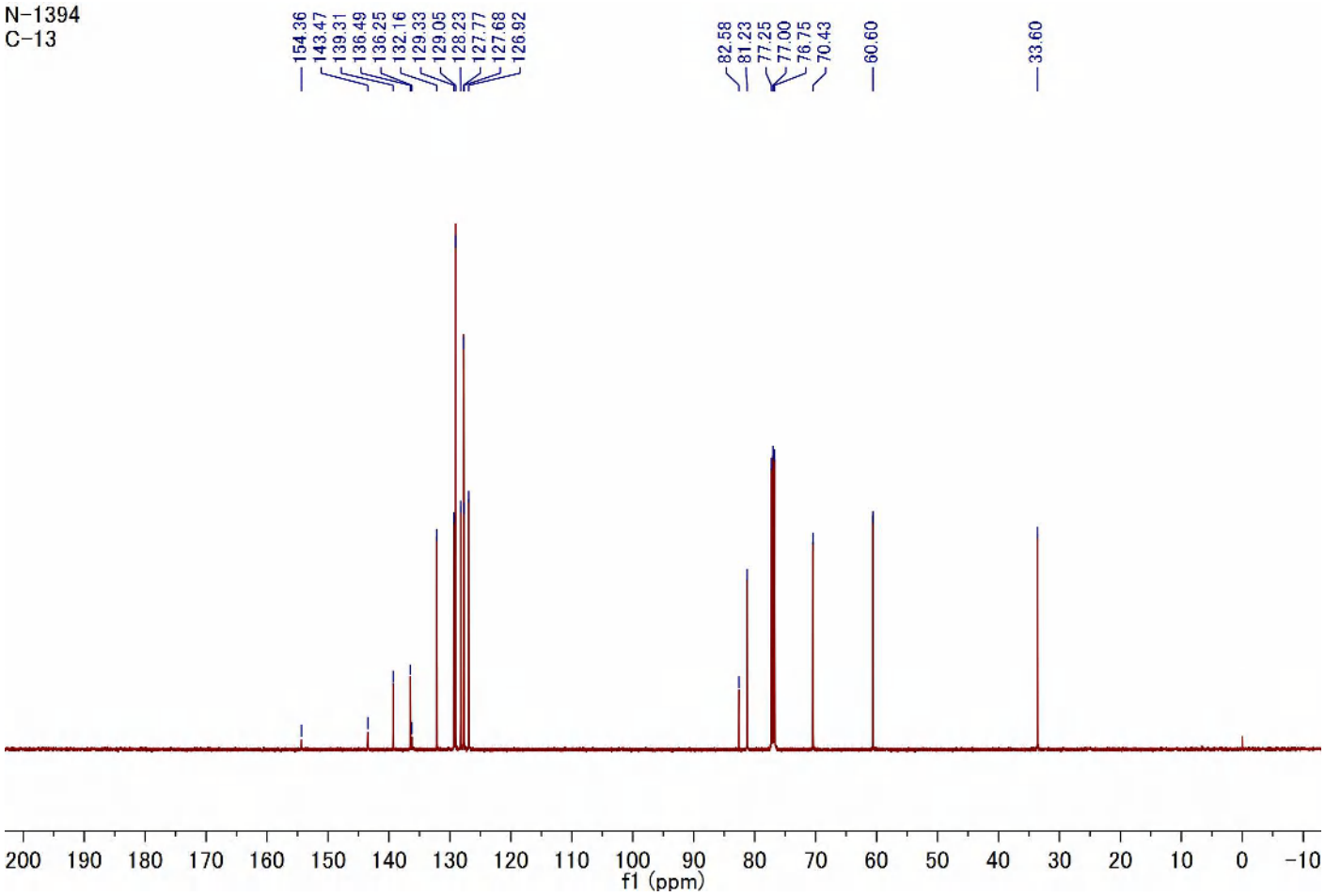
Compound **4e** (^{13}C NMR, 150 MHz, $CDCl_3$)



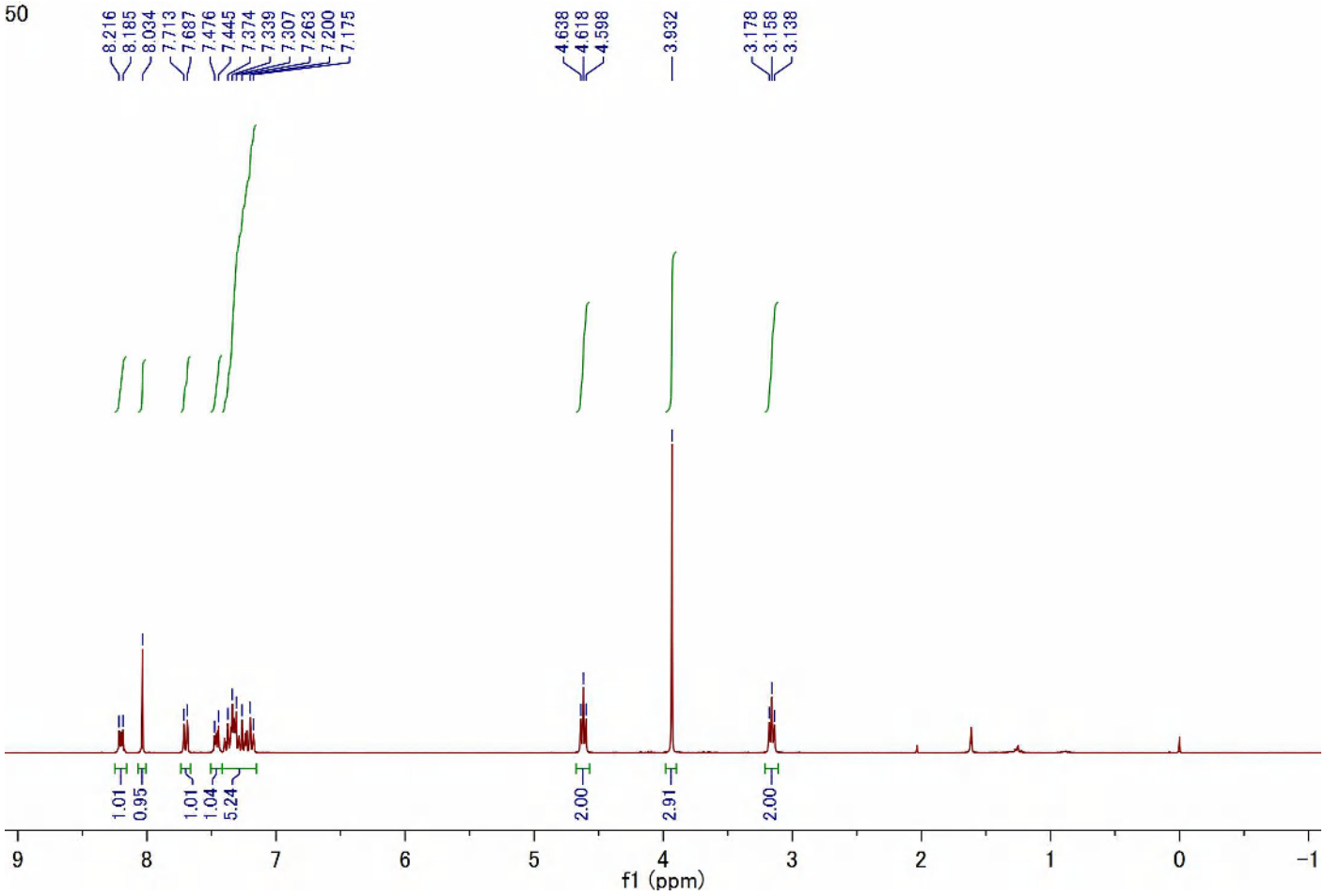
Compound **4f** (^{1}H NMR, 500 MHz, $CDCl_3$)



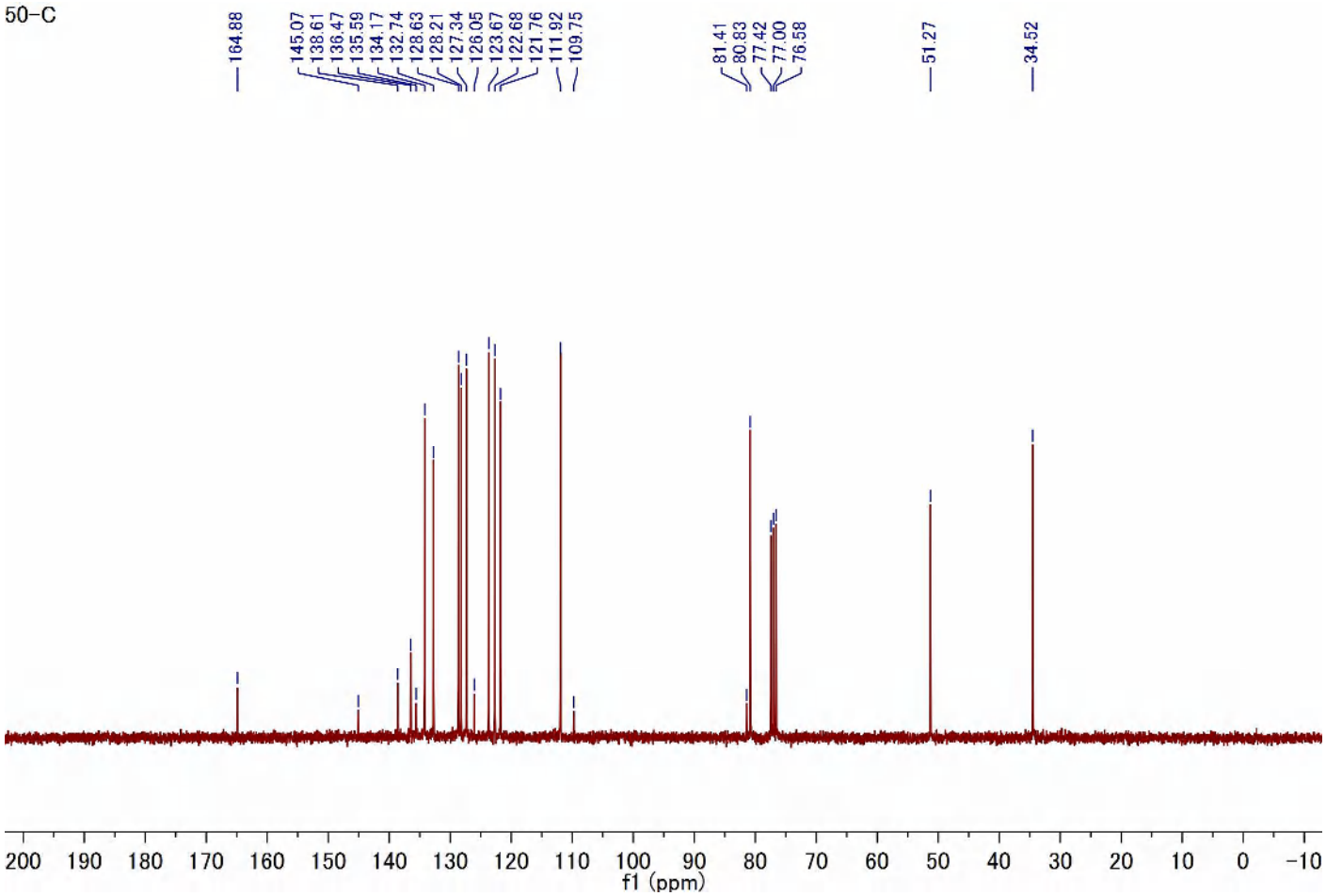
Compound **4f** (^{13}C NMR, 125 MHz, $CDCl_3$)



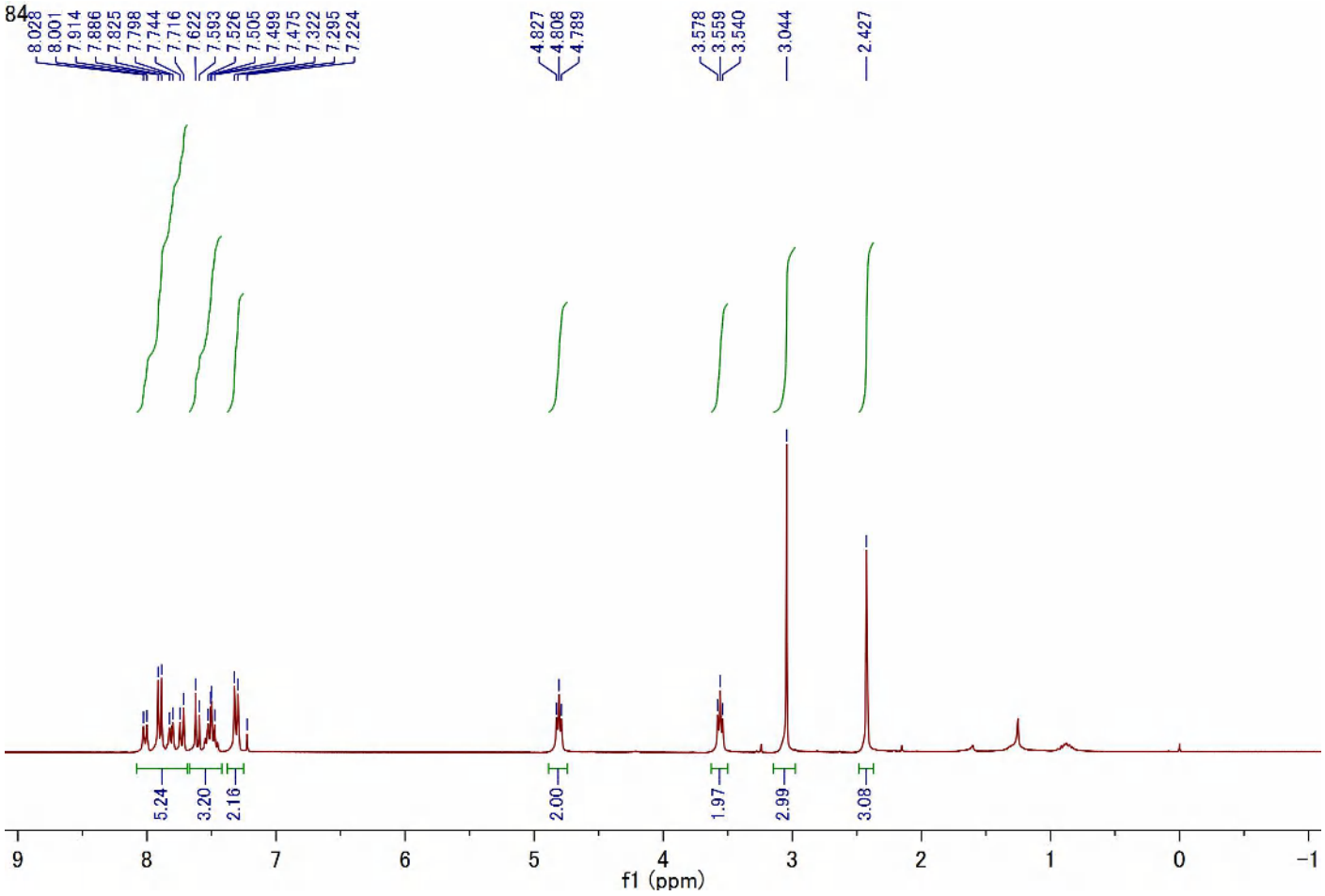
Compound **4g** (^{1}H NMR, 300 MHz, $CDCl_3$)



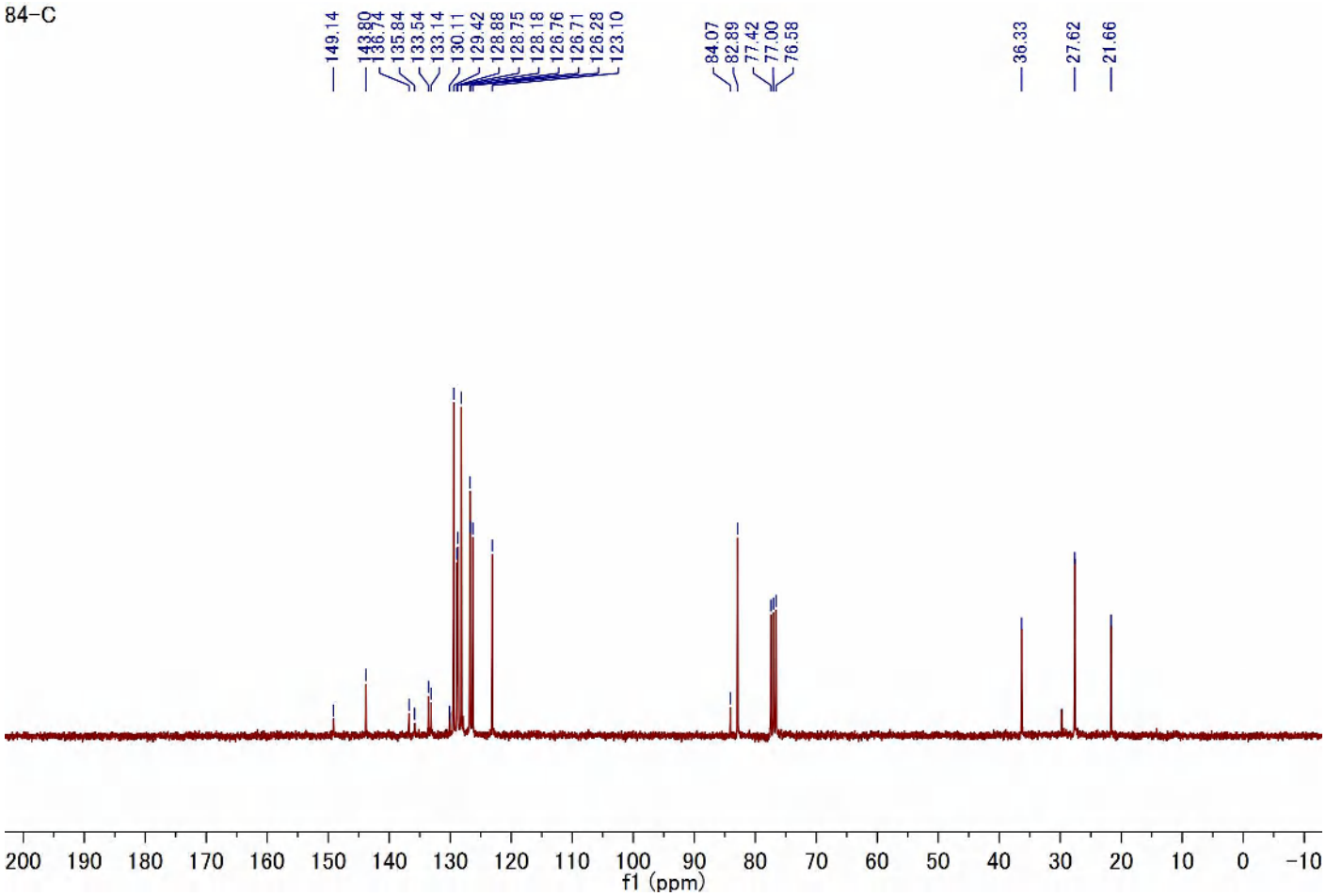
Compound **4g** (^{13}C NMR, 75 MHz, $CDCl_3$)



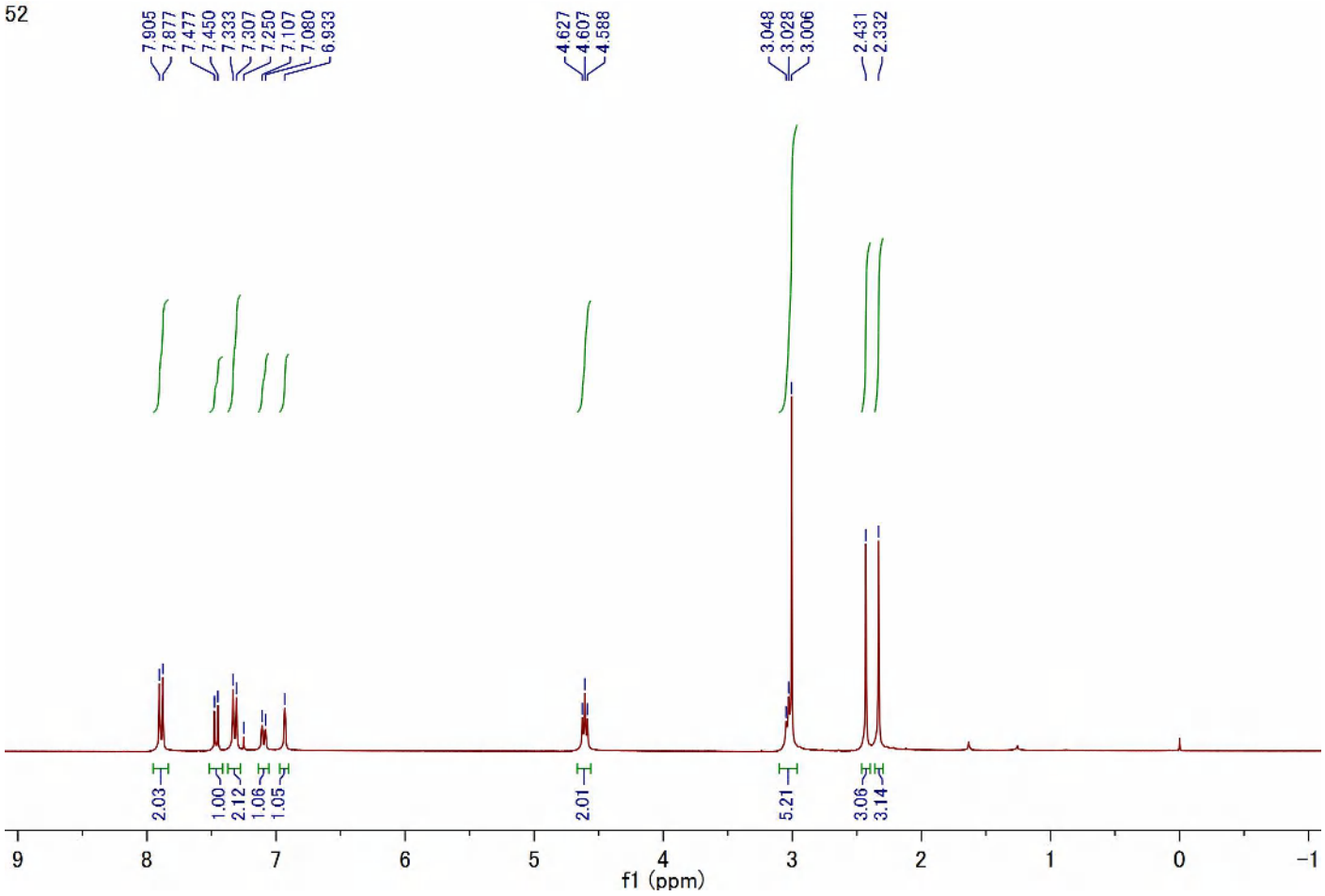
Compound **4h** (^{1}H NMR, 300 MHz, $CDCl_3$)



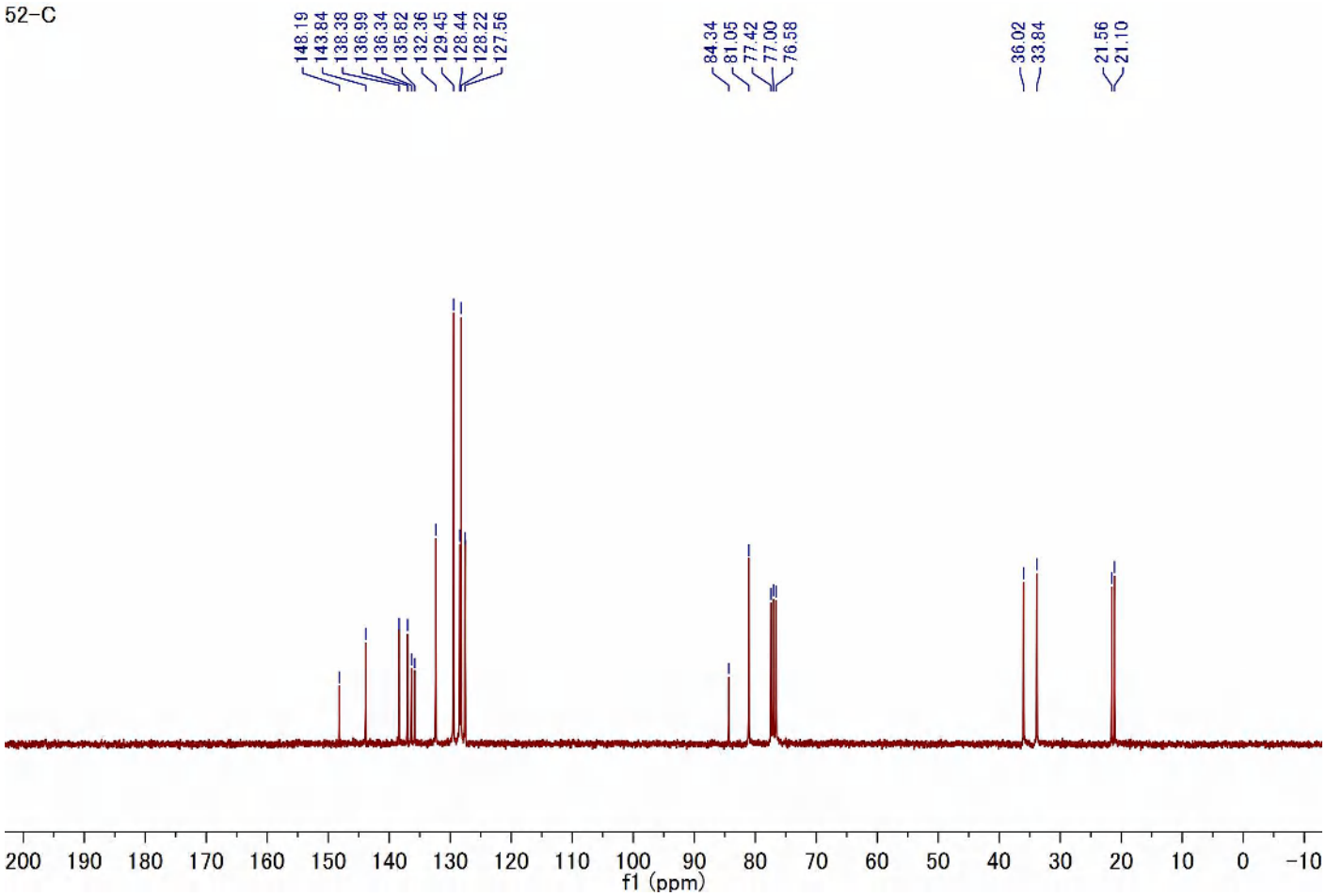
Compound **4h** (^{13}C NMR, 75 MHz, $CDCl_3$)



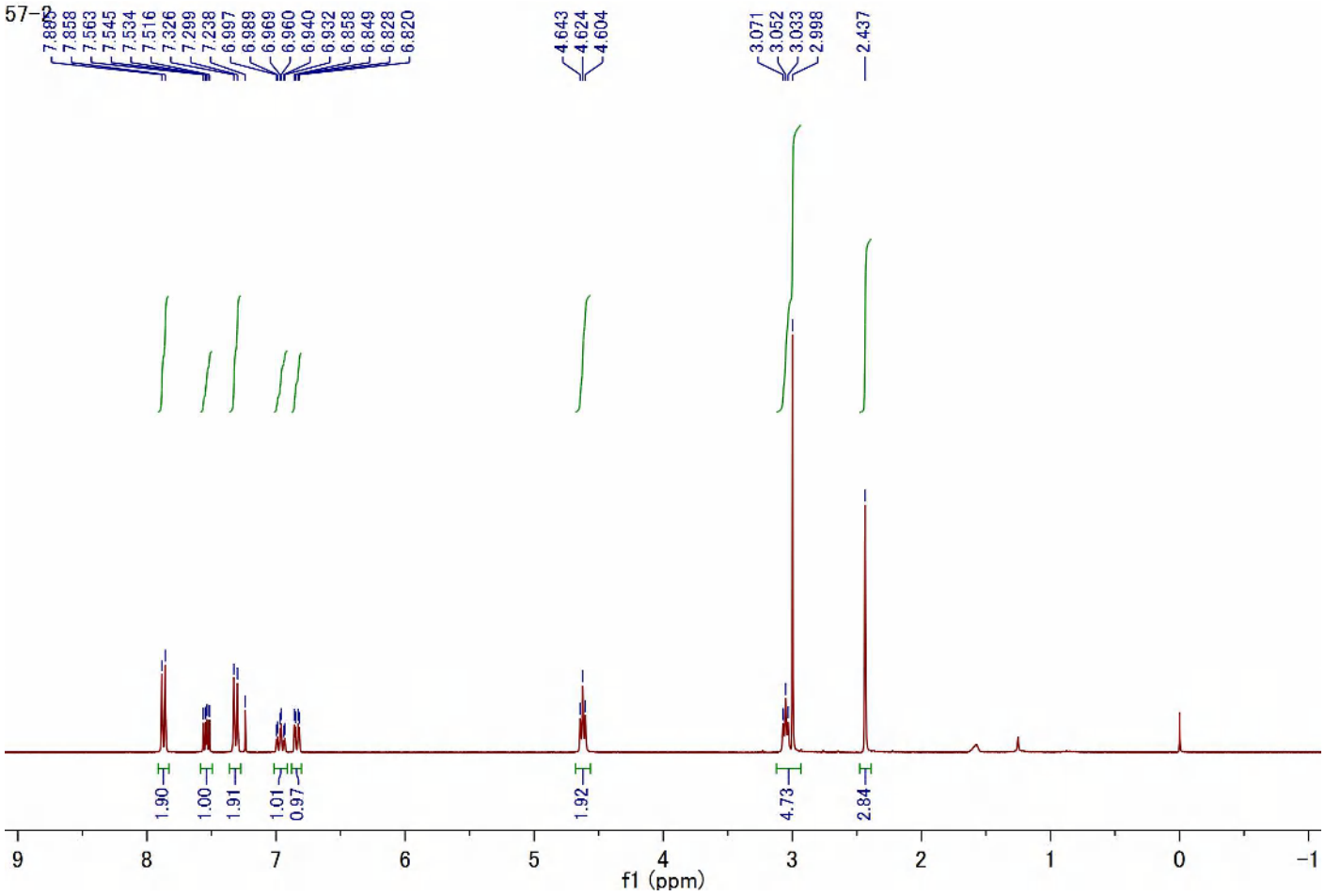
Compound **4i** (^{1}H NMR, 300 MHz, $CDCl_3$)



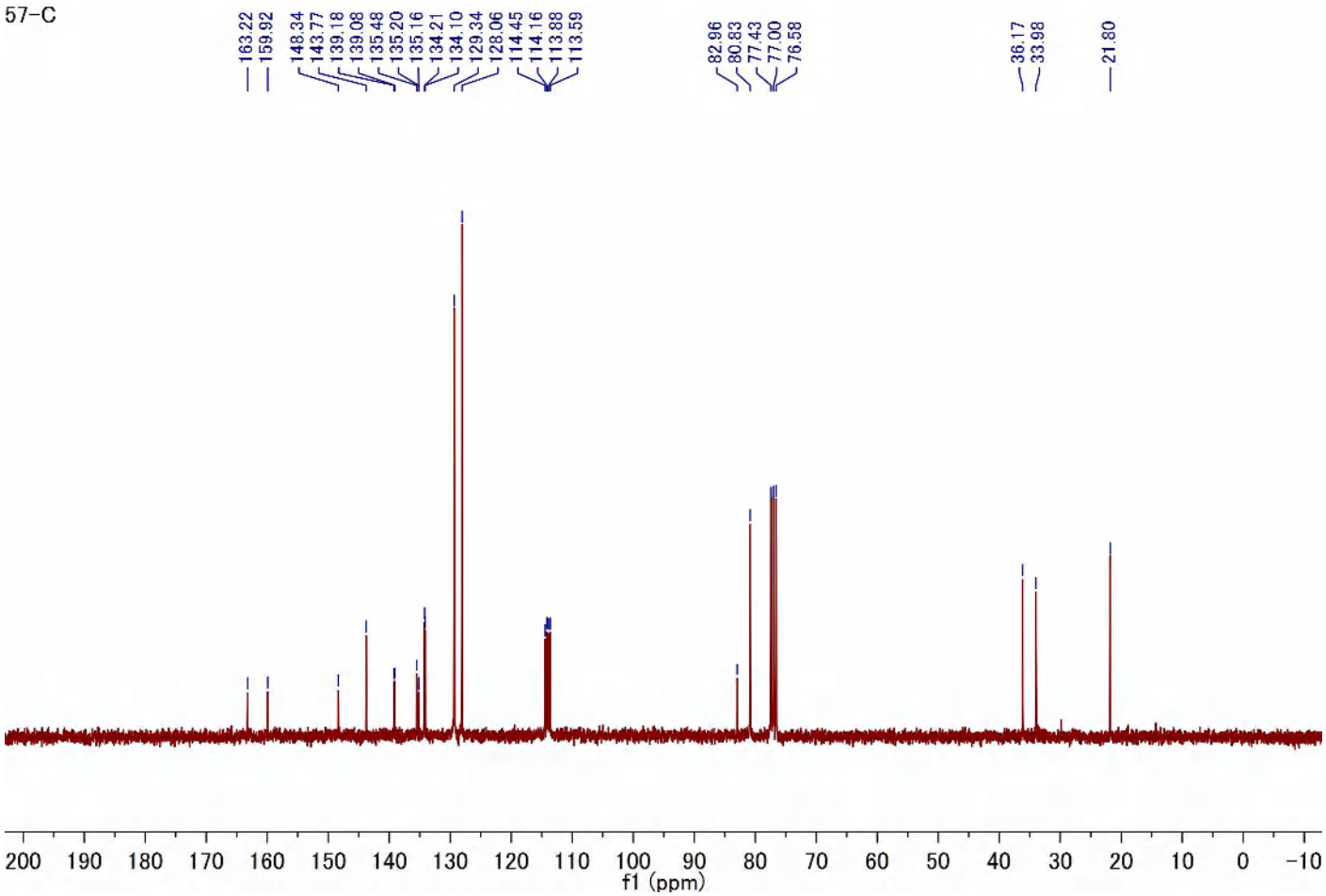
Compound **4i** (^{13}C NMR, 75 MHz, $CDCl_3$)



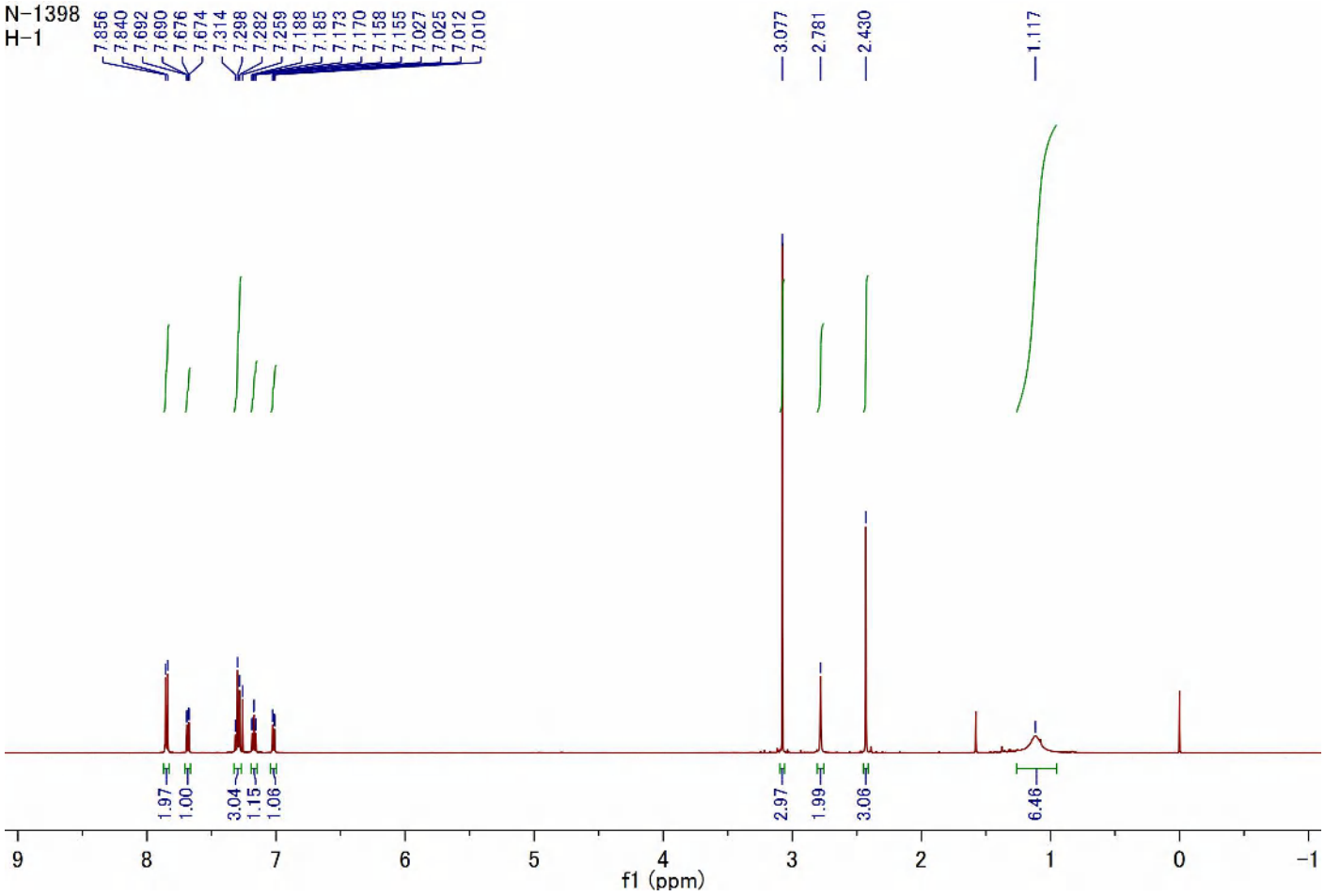
Compound **4j** (^{1}H NMR, 300 MHz, $CDCl_3$)



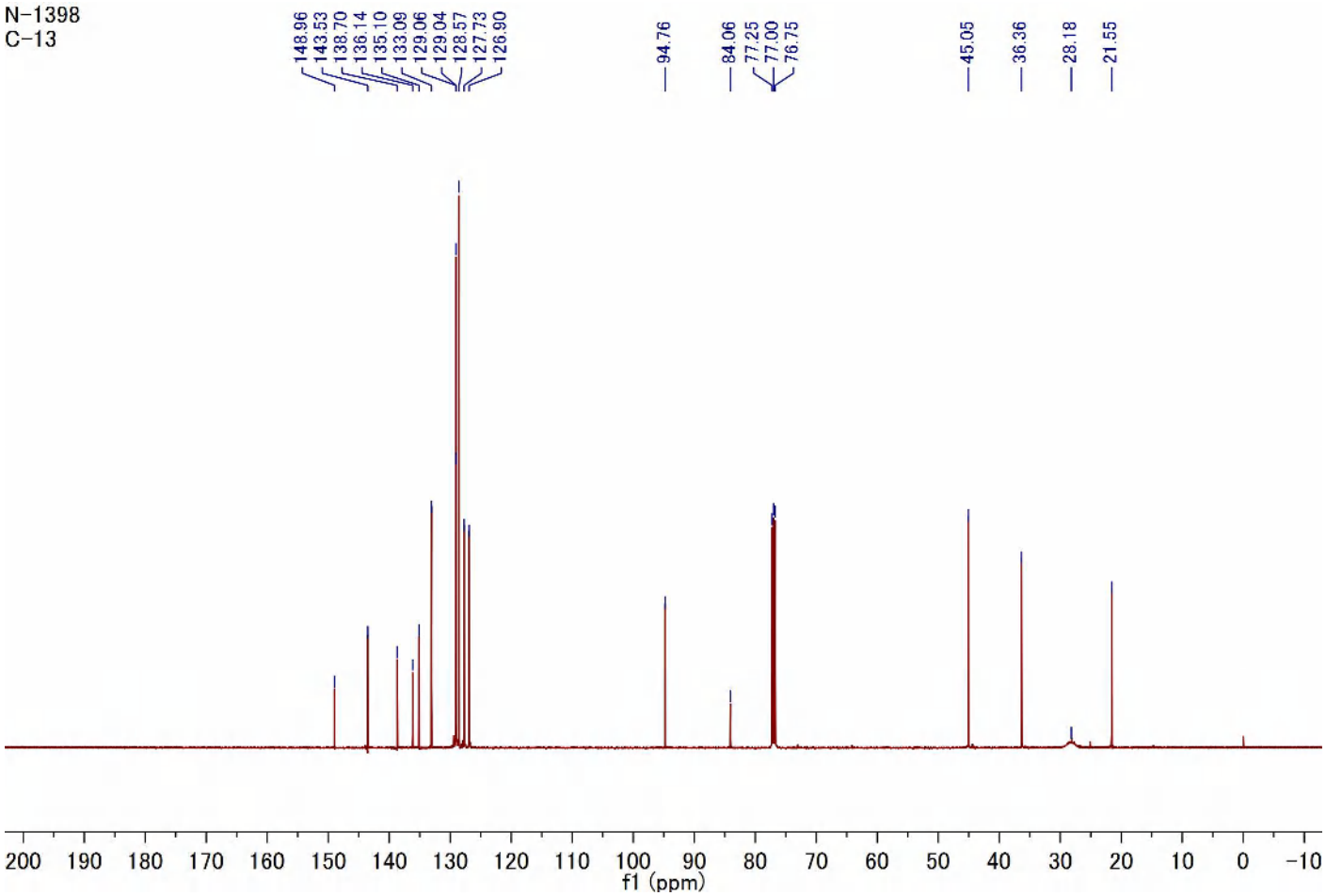
Compound **4j** (^{13}C NMR, 75 MHz, $CDCl_3$)



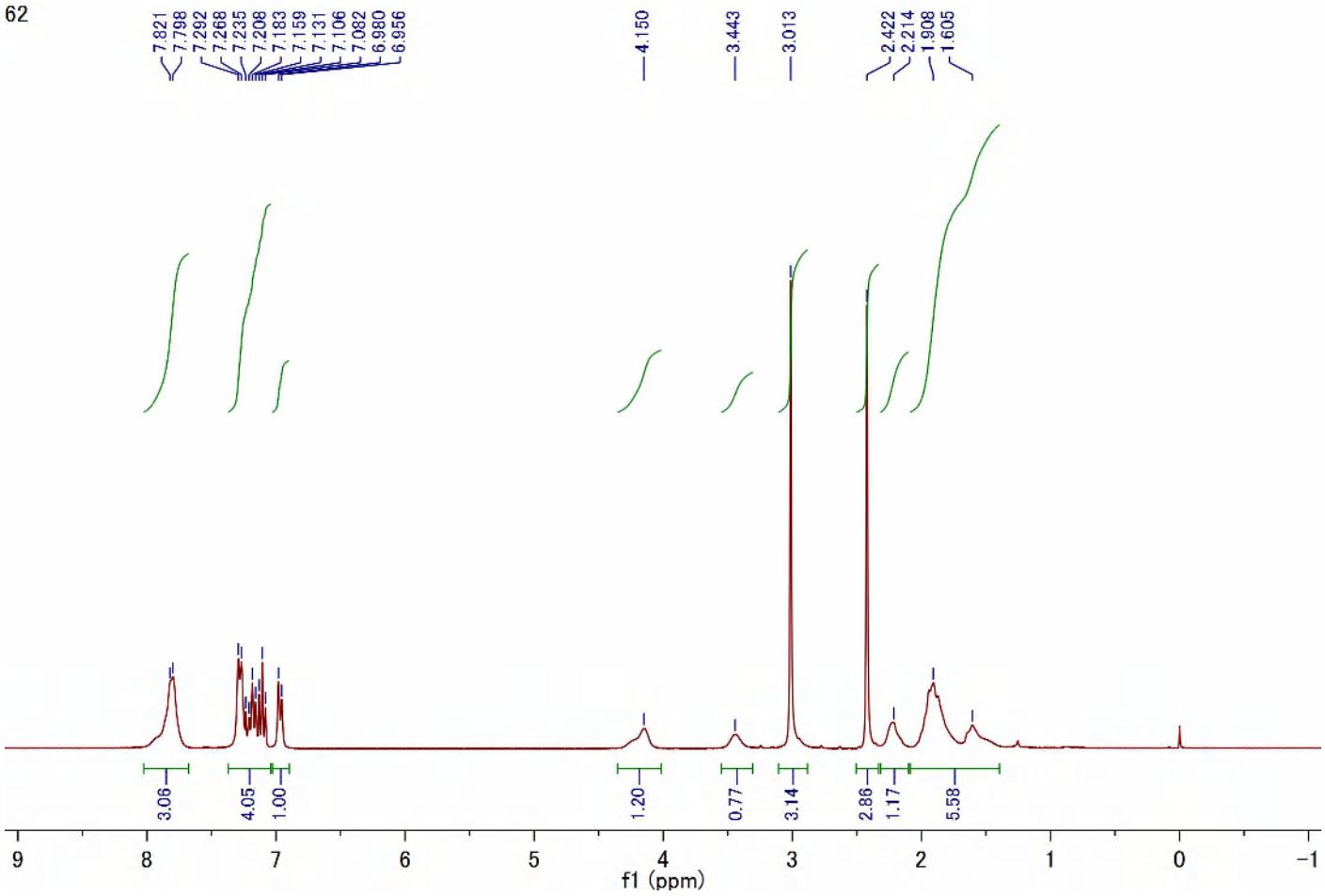
Compound **4k** (^{1}H NMR, 500 MHz, $CDCl_3$)



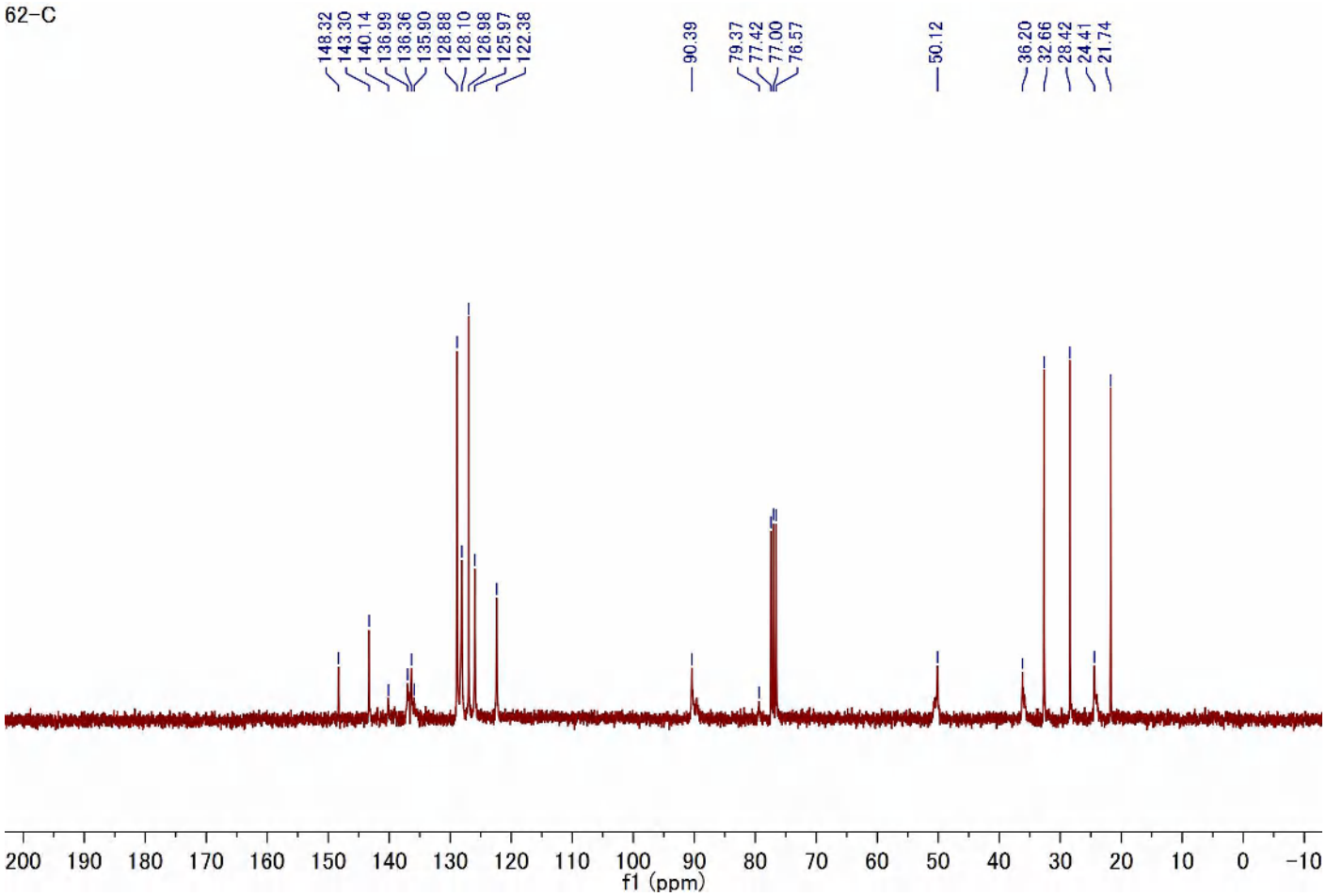
Compound **4k** (^{13}C NMR, 125 MHz, $CDCl_3$)



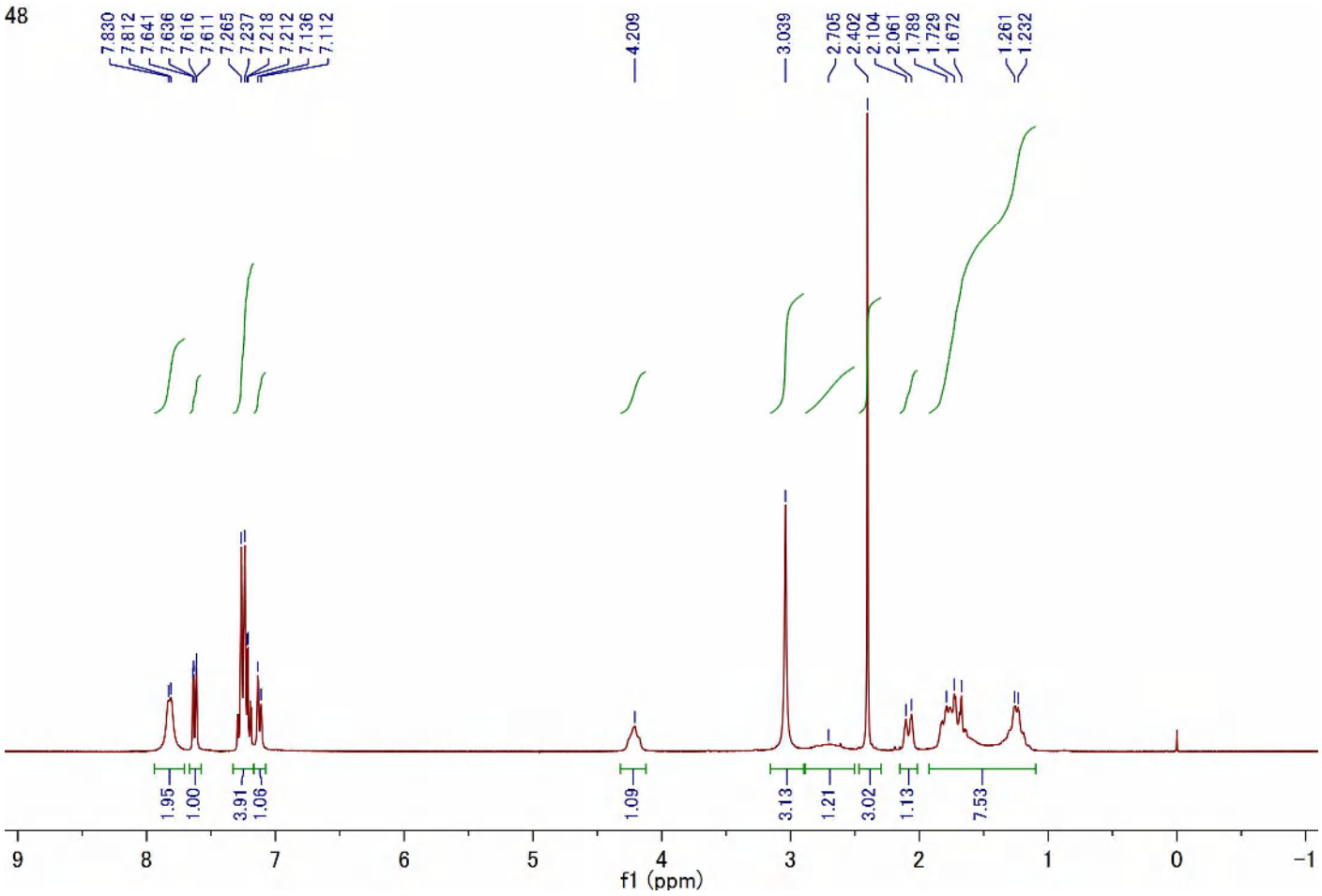
Compound **4l** (^{1}H NMR, 300 MHz, $CDCl_3$)



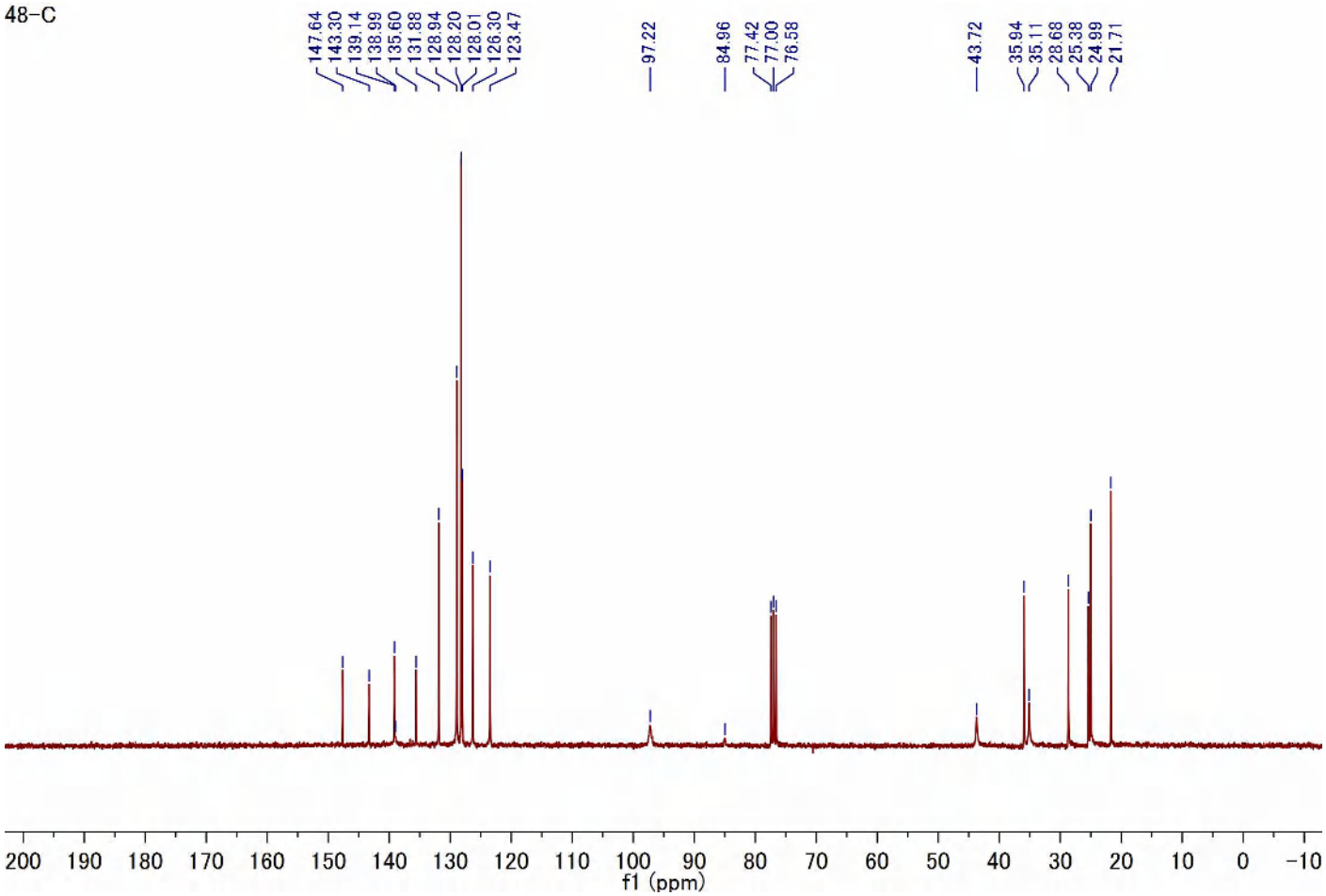
Compound **4l** (^{13}C NMR, 75 MHz, $CDCl_3$)



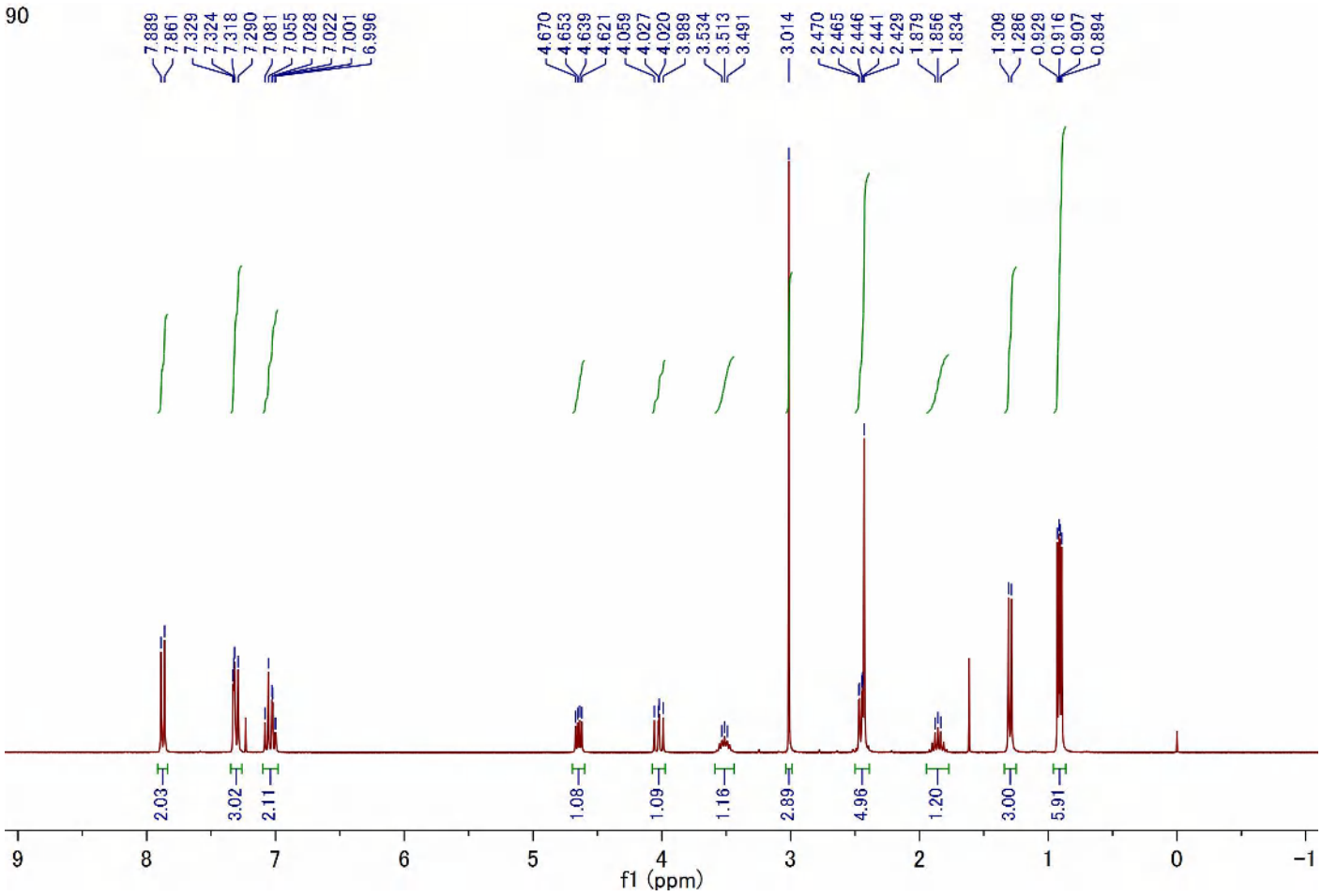
Compound **4m** (^{1}H NMR, 300 MHz, $CDCl_3$)



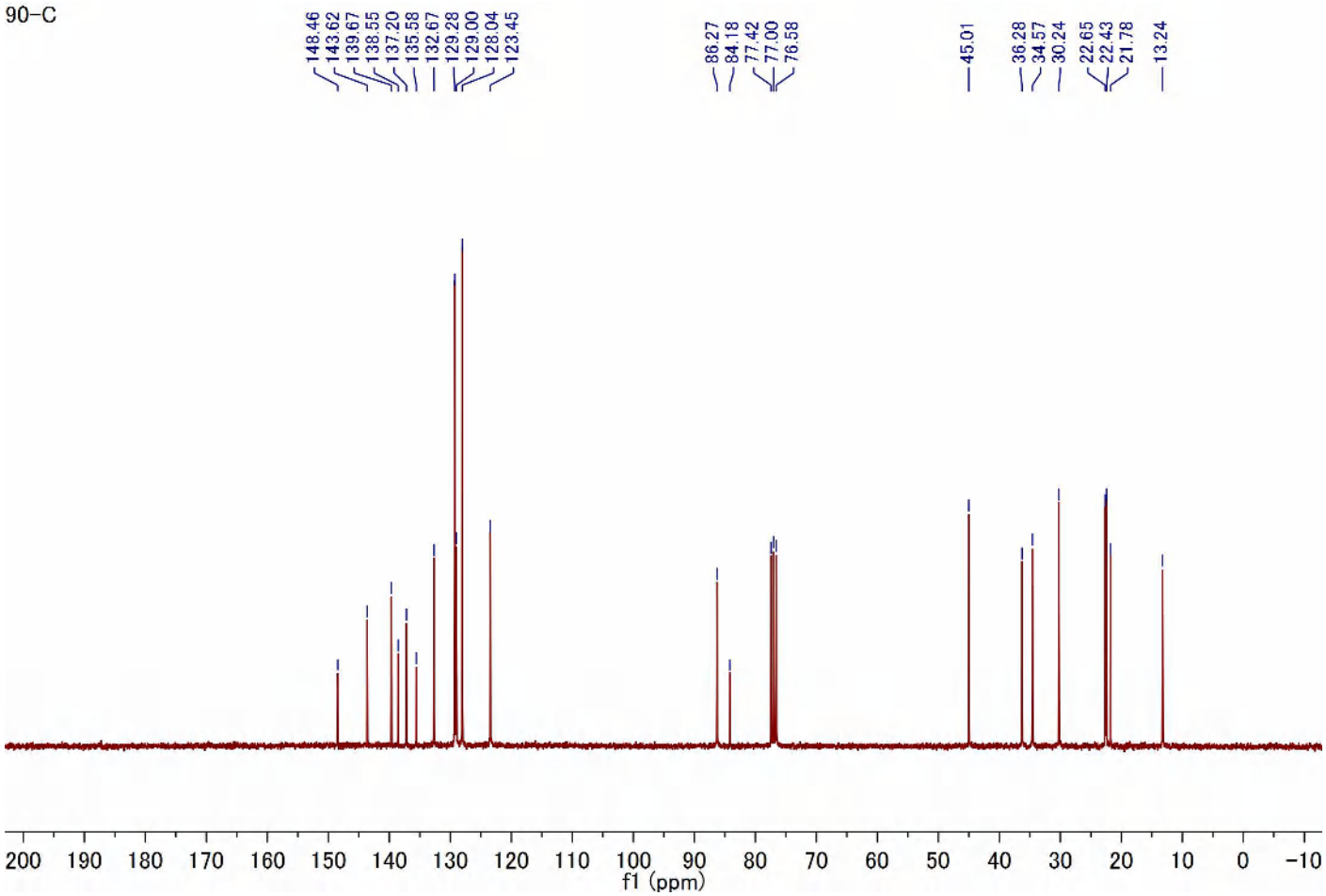
Compound **4m** (^{13}C NMR, 75 MHz, $CDCl_3$)



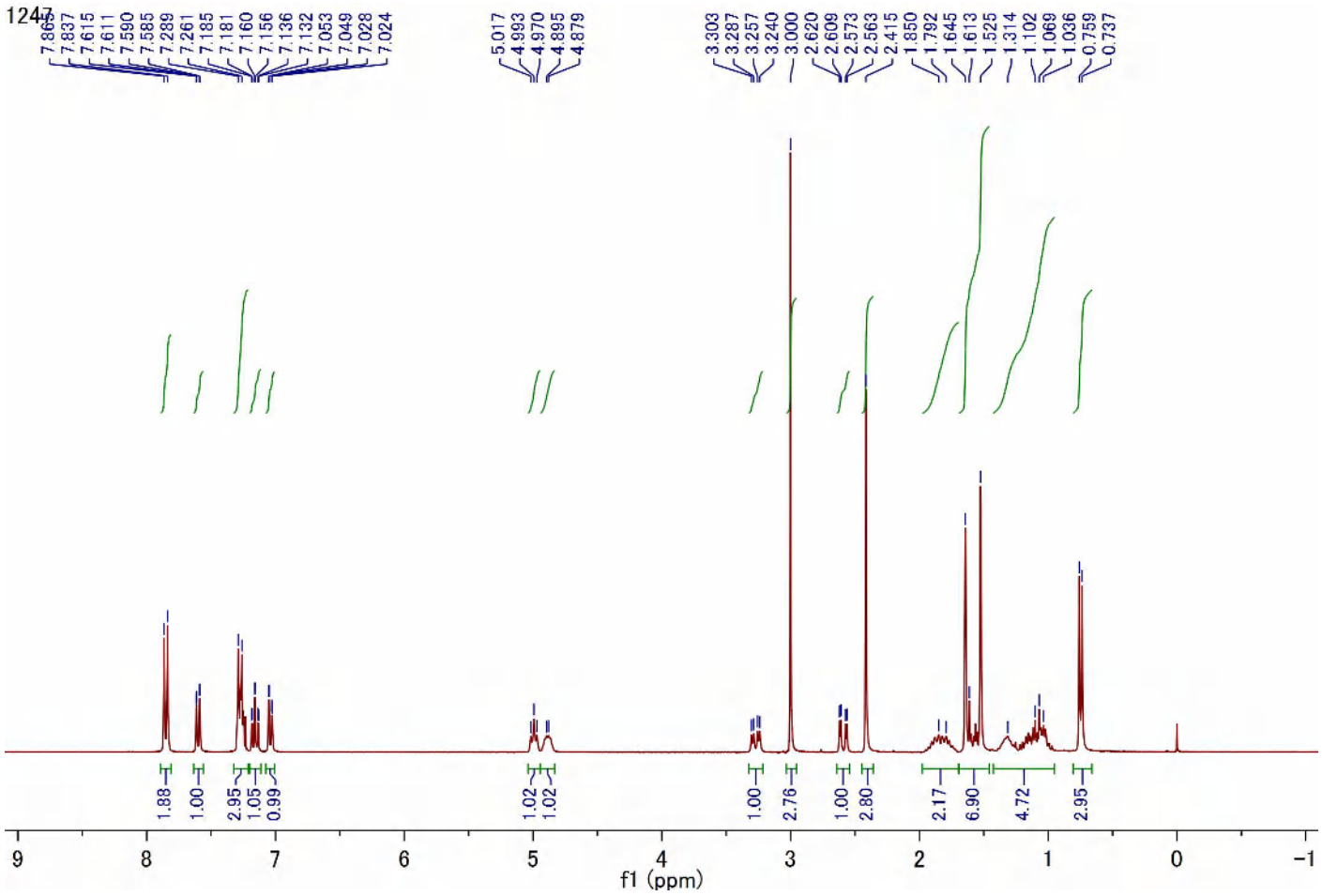
Compound **4n** (^{1}H NMR, 300 MHz, $CDCl_3$)



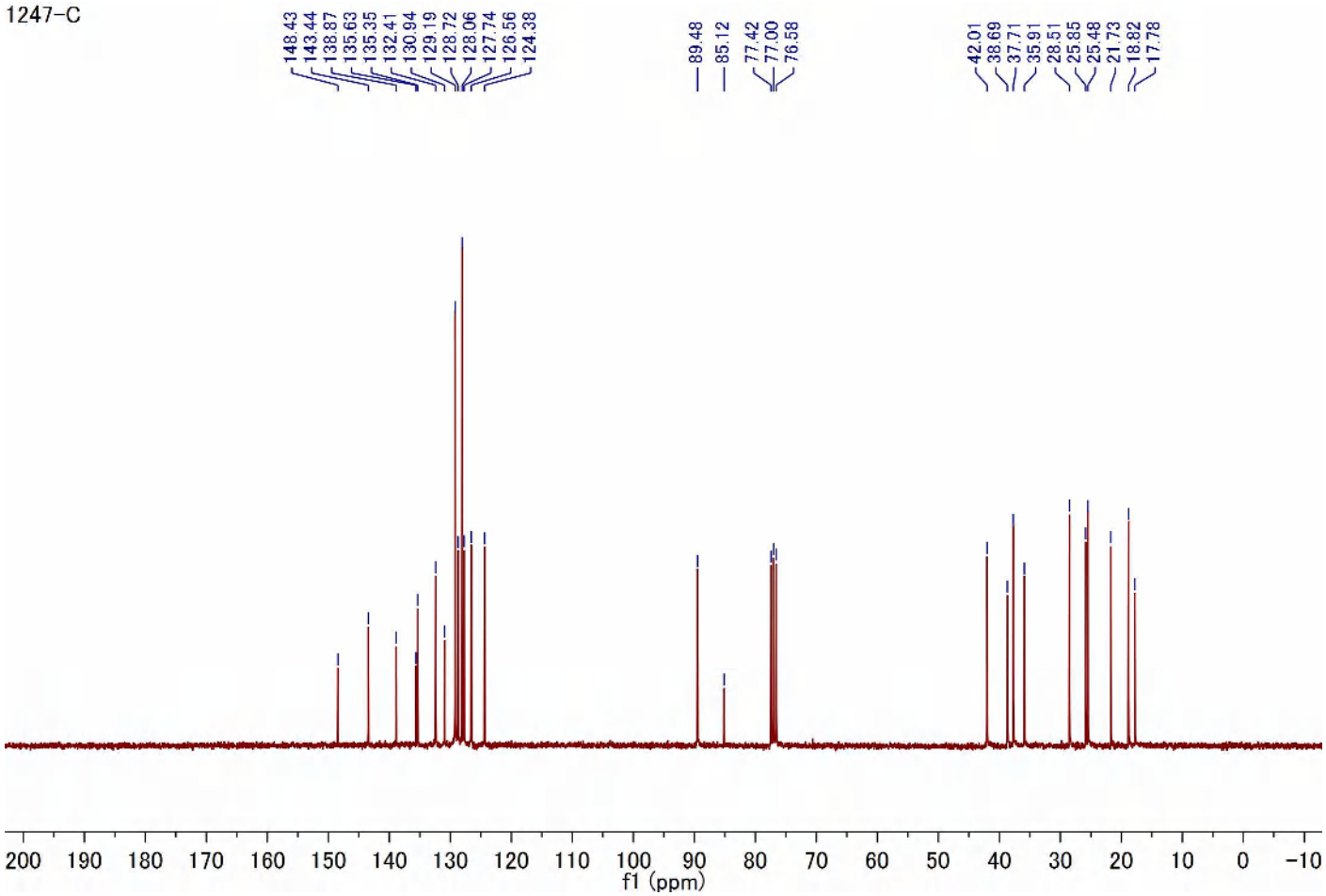
Compound **4n** (^{13}C NMR, 75 MHz, $CDCl_3$)



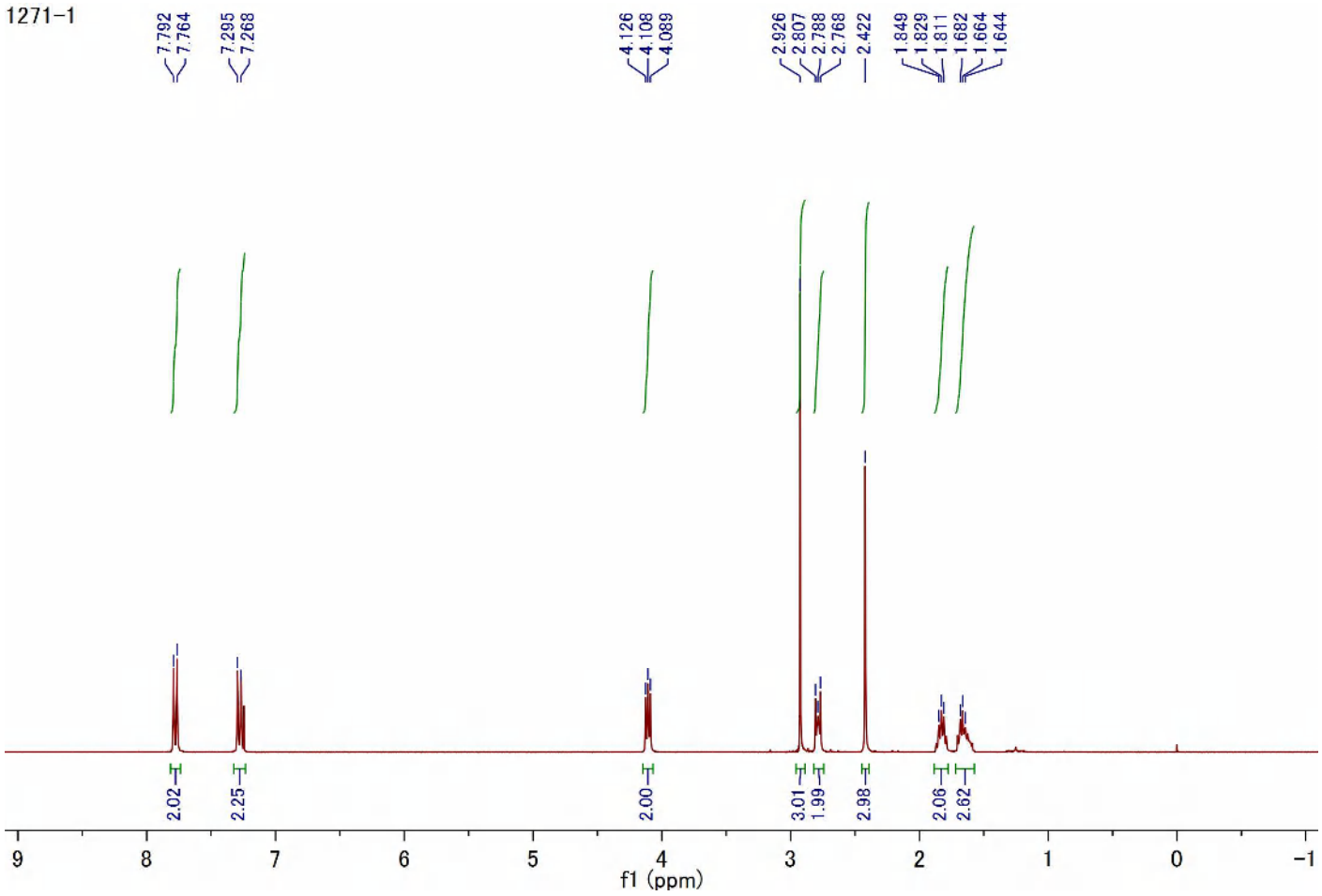
Compound **4o** (^{1}H NMR, 300 MHz, $CDCl_3$)



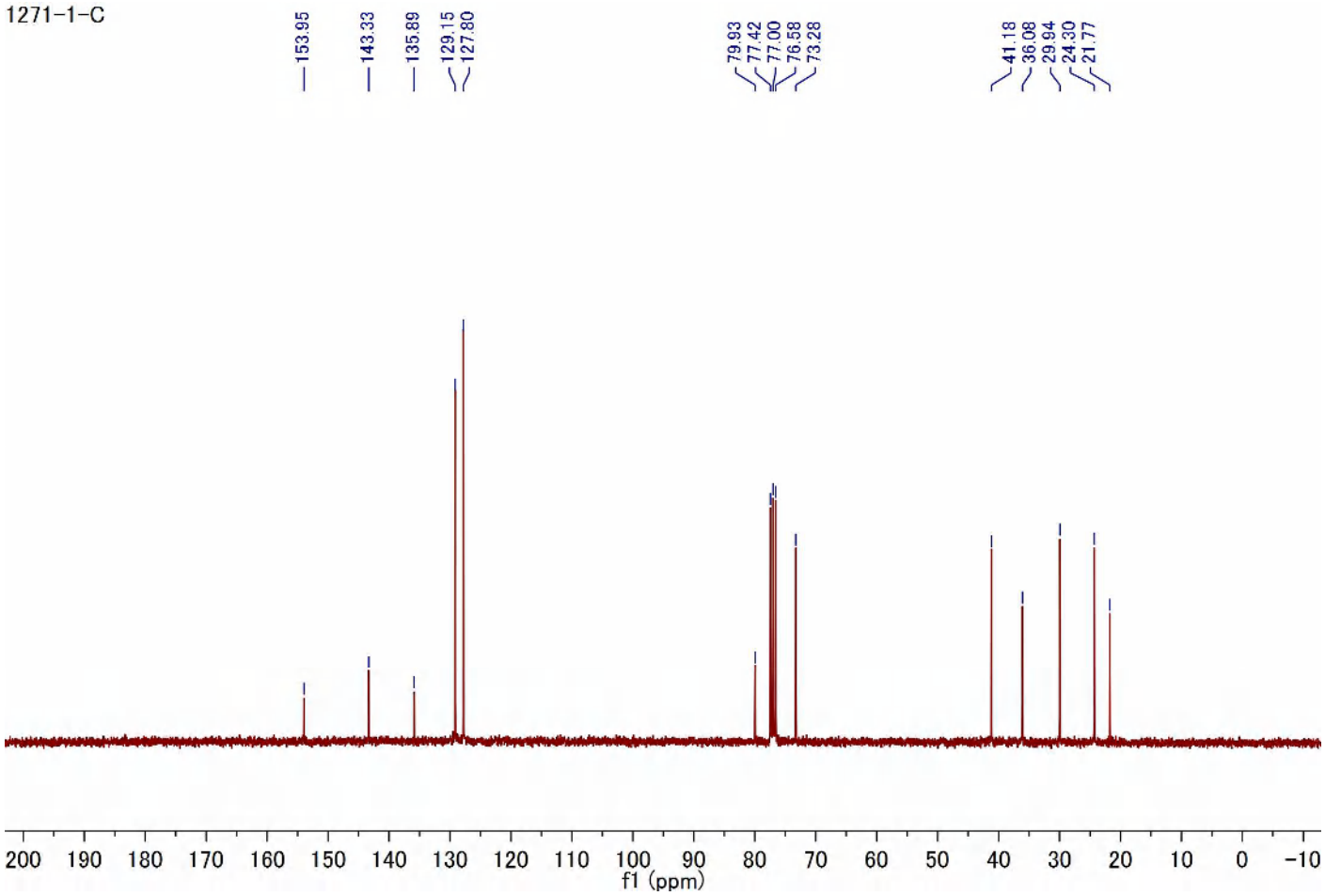
Compound **4o** (^{13}C NMR, 75 MHz, $CDCl_3$)



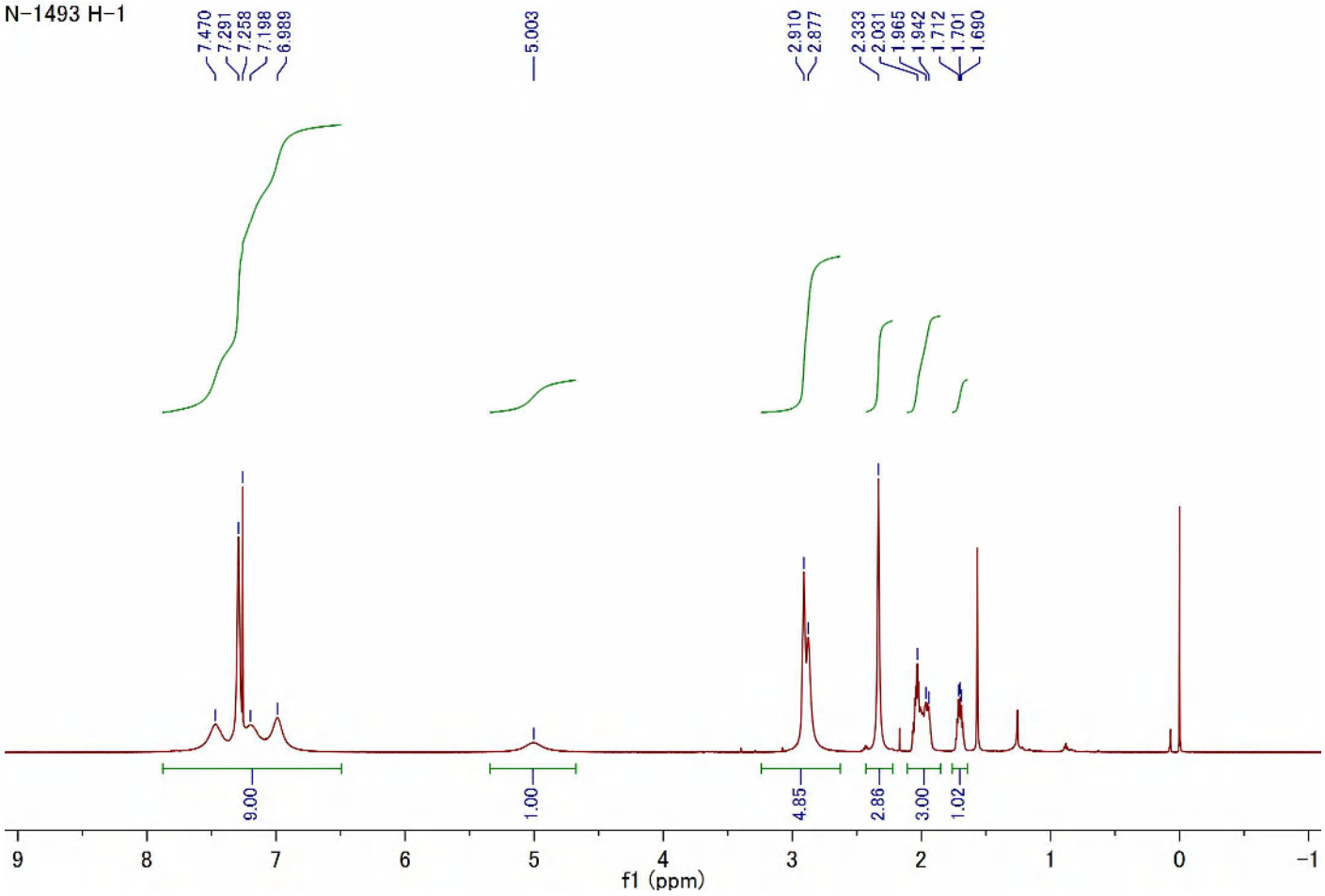
Compound **4p** (^{1}H NMR, 300 MHz, $CDCl_3$)



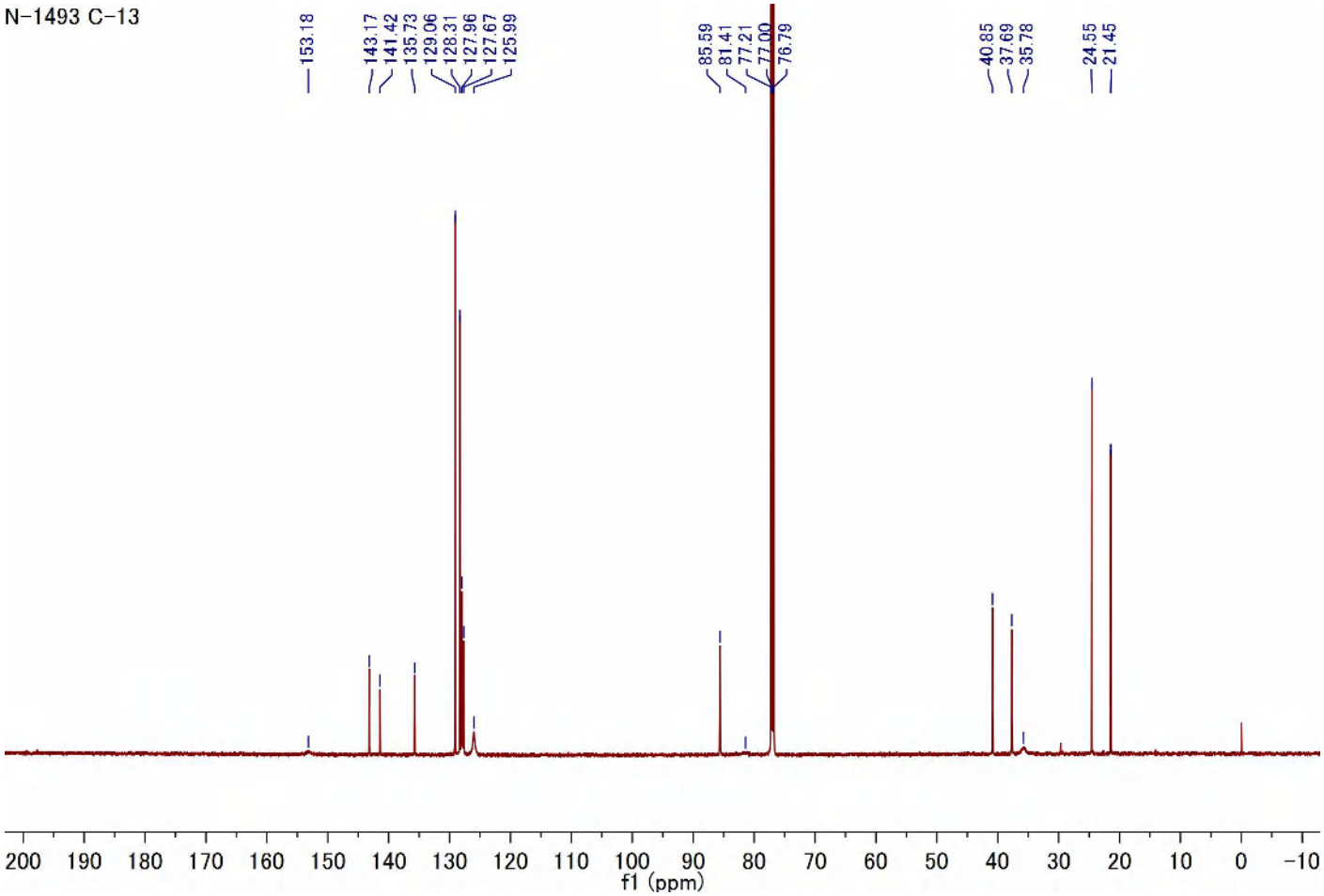
Compound **4p** (^{13}C NMR, 75 MHz, $CDCl_3$)



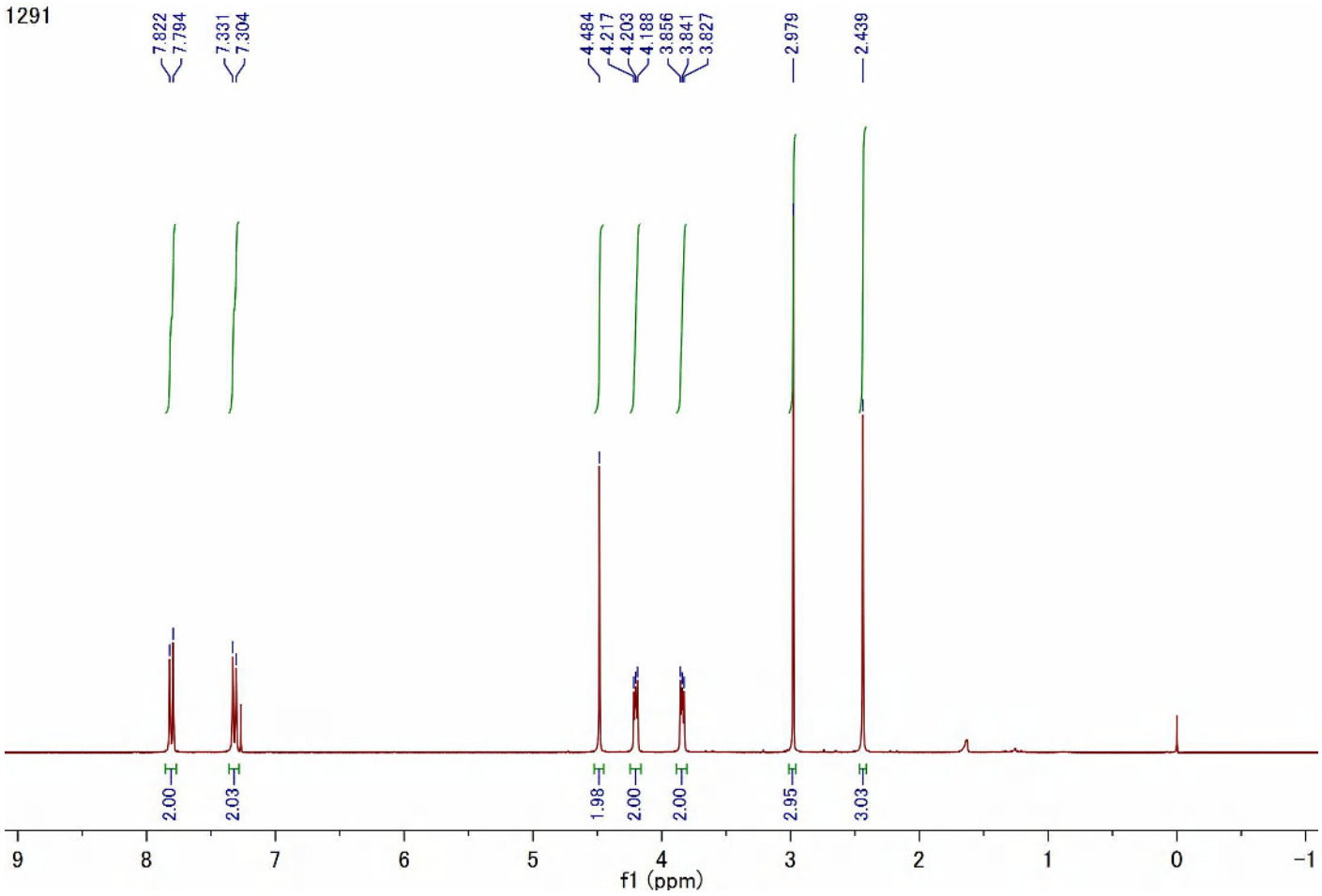
Compound **4q** (^{1}H NMR, 600 MHz, $CDCl_3$)



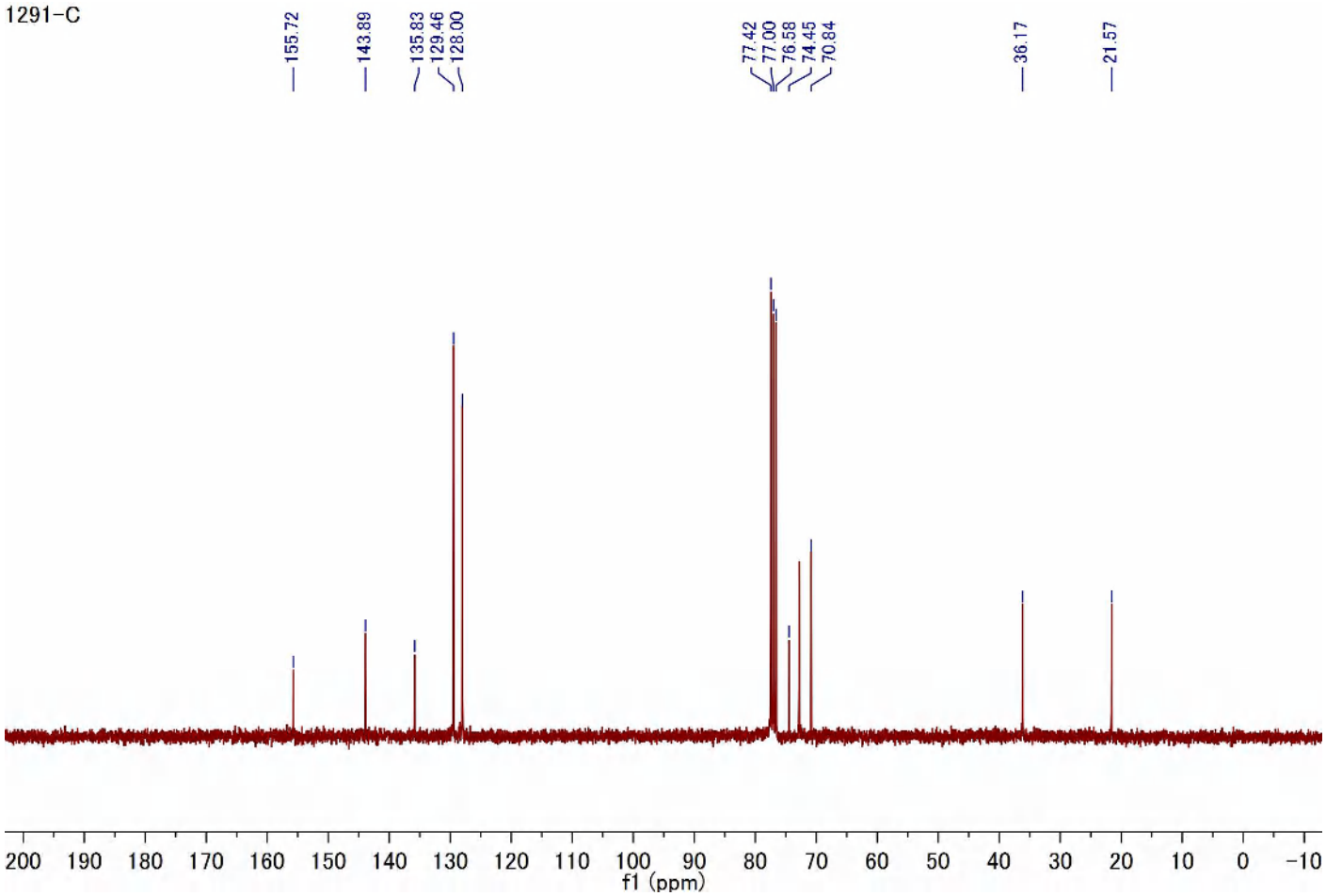
Compound **4q** (^{13}C NMR, 150 MHz, $CDCl_3$)



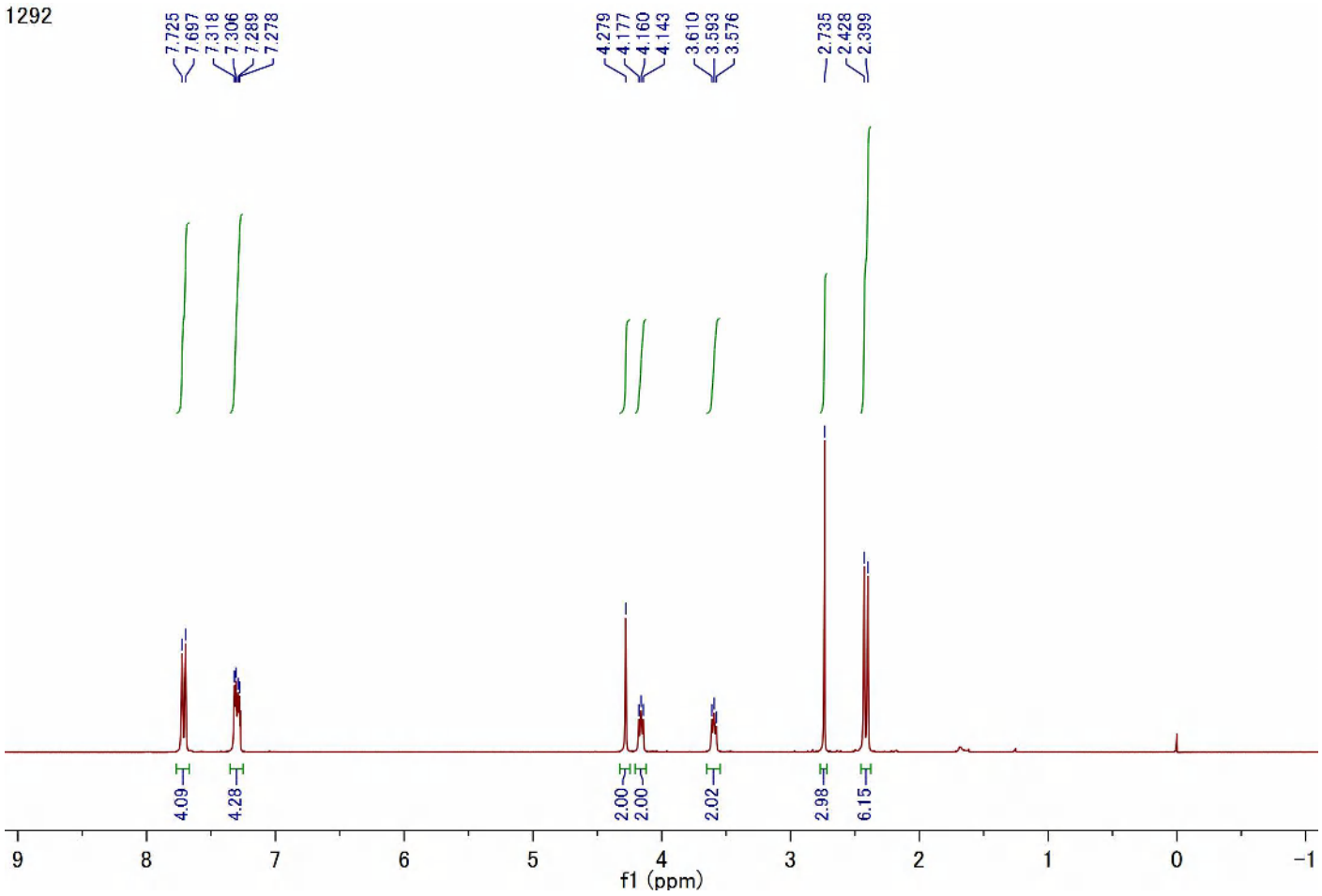
Compound **4r** (^{1}H NMR, 300 MHz, $CDCl_3$)



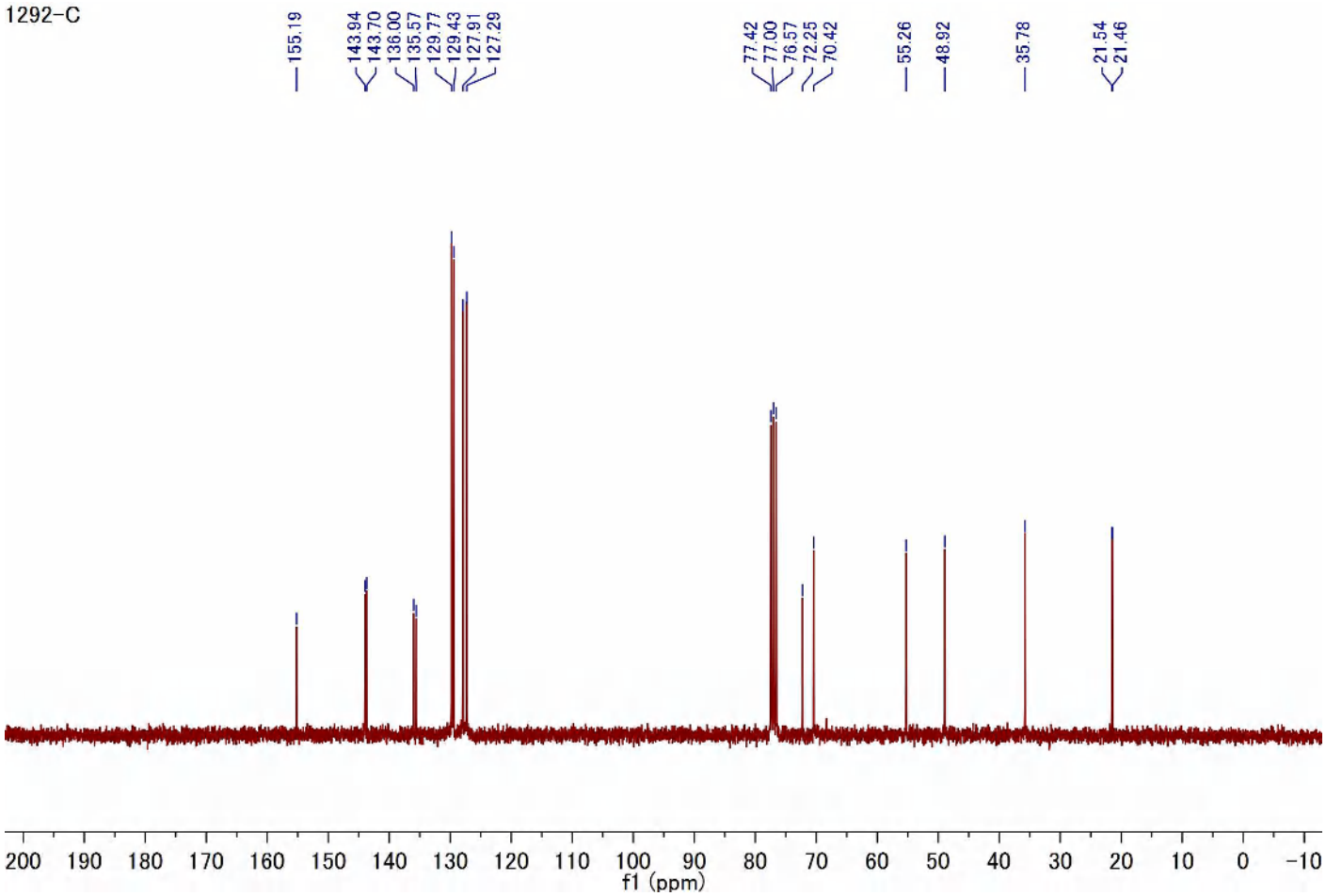
Compound **4r** (^{13}C NMR, 75 MHz, $CDCl_3$)



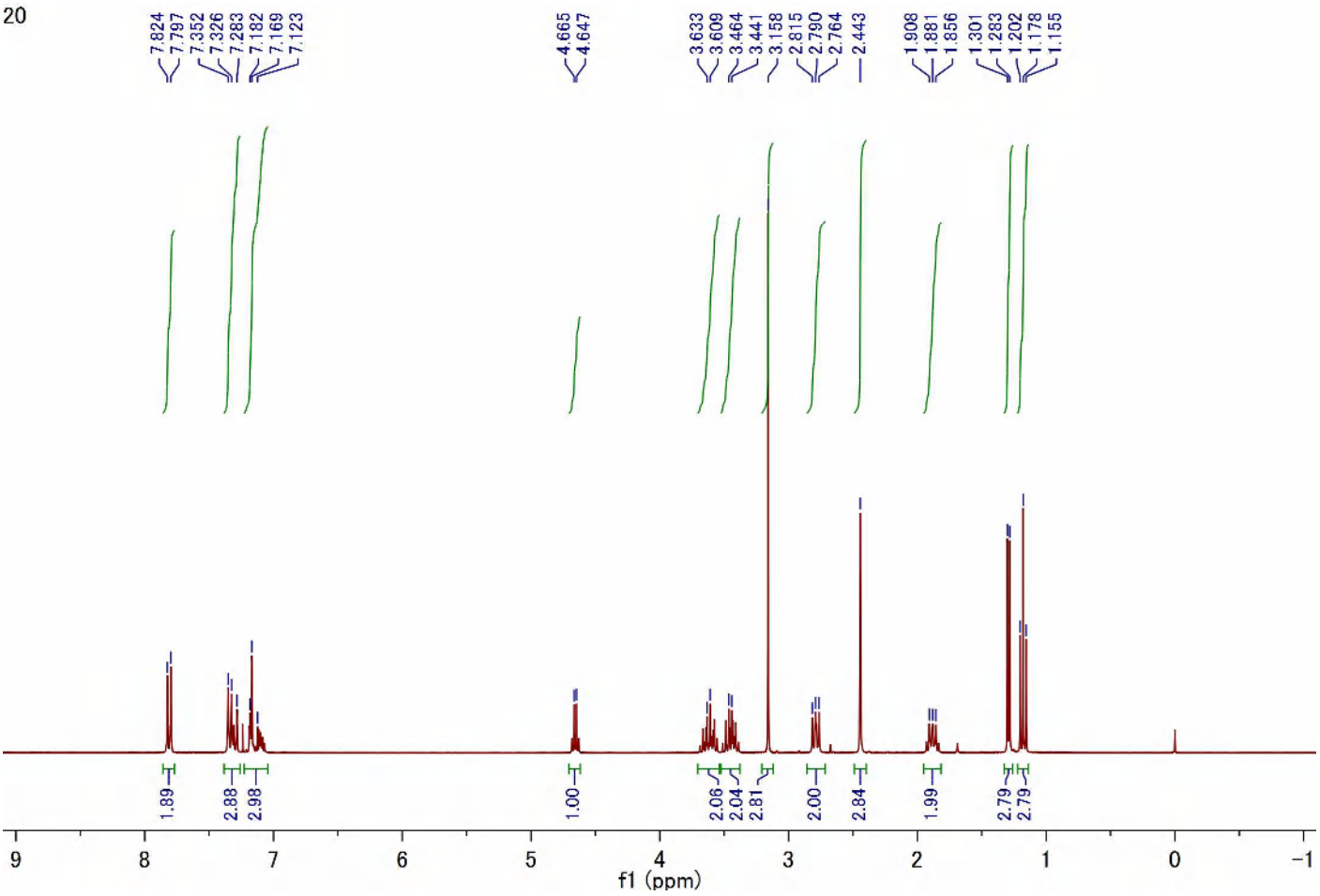
Compound **4s** (^{1}H NMR, 300 MHz, $CDCl_3$)



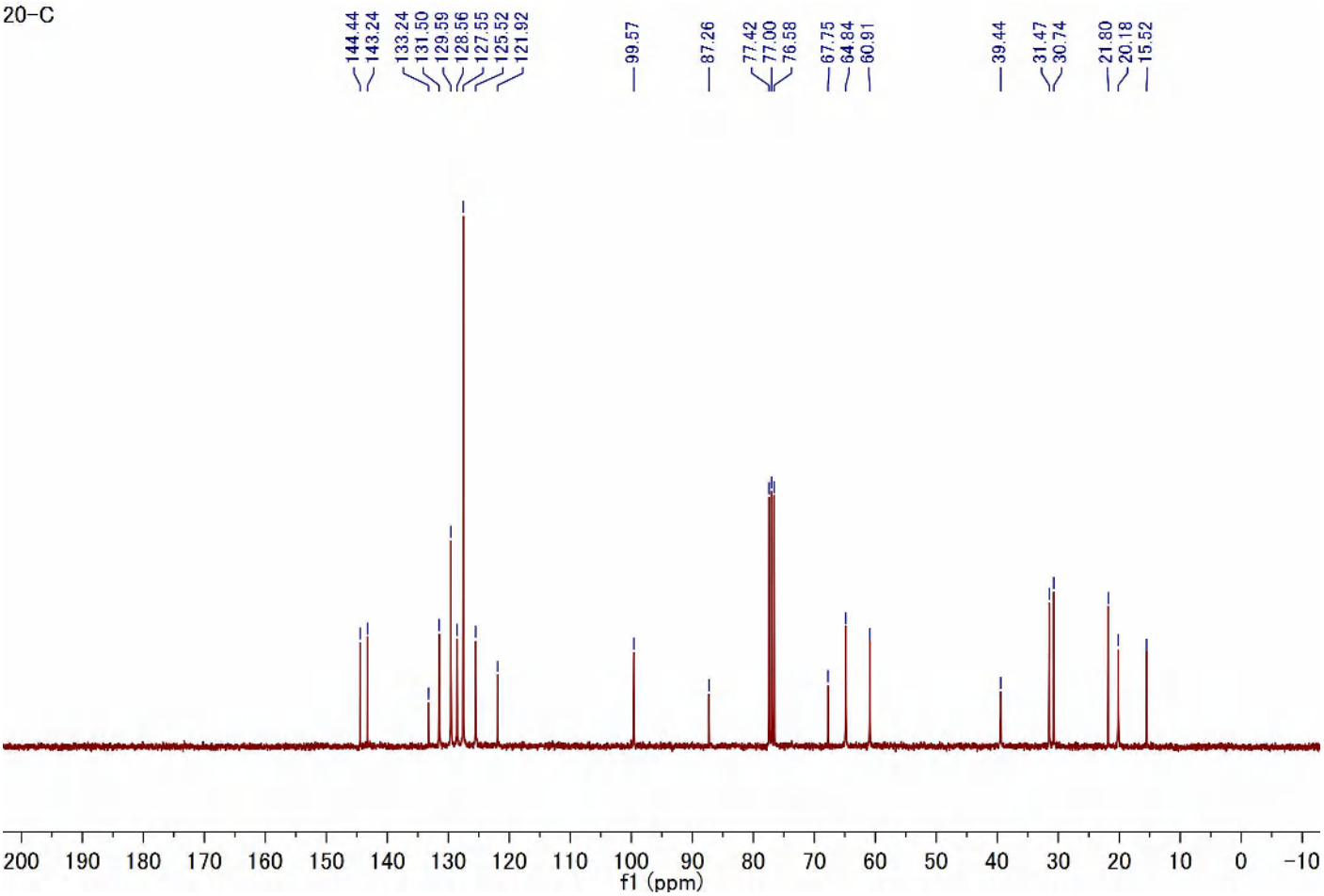
Compound **4s** (^{13}C NMR, 75 MHz, $CDCl_3$)



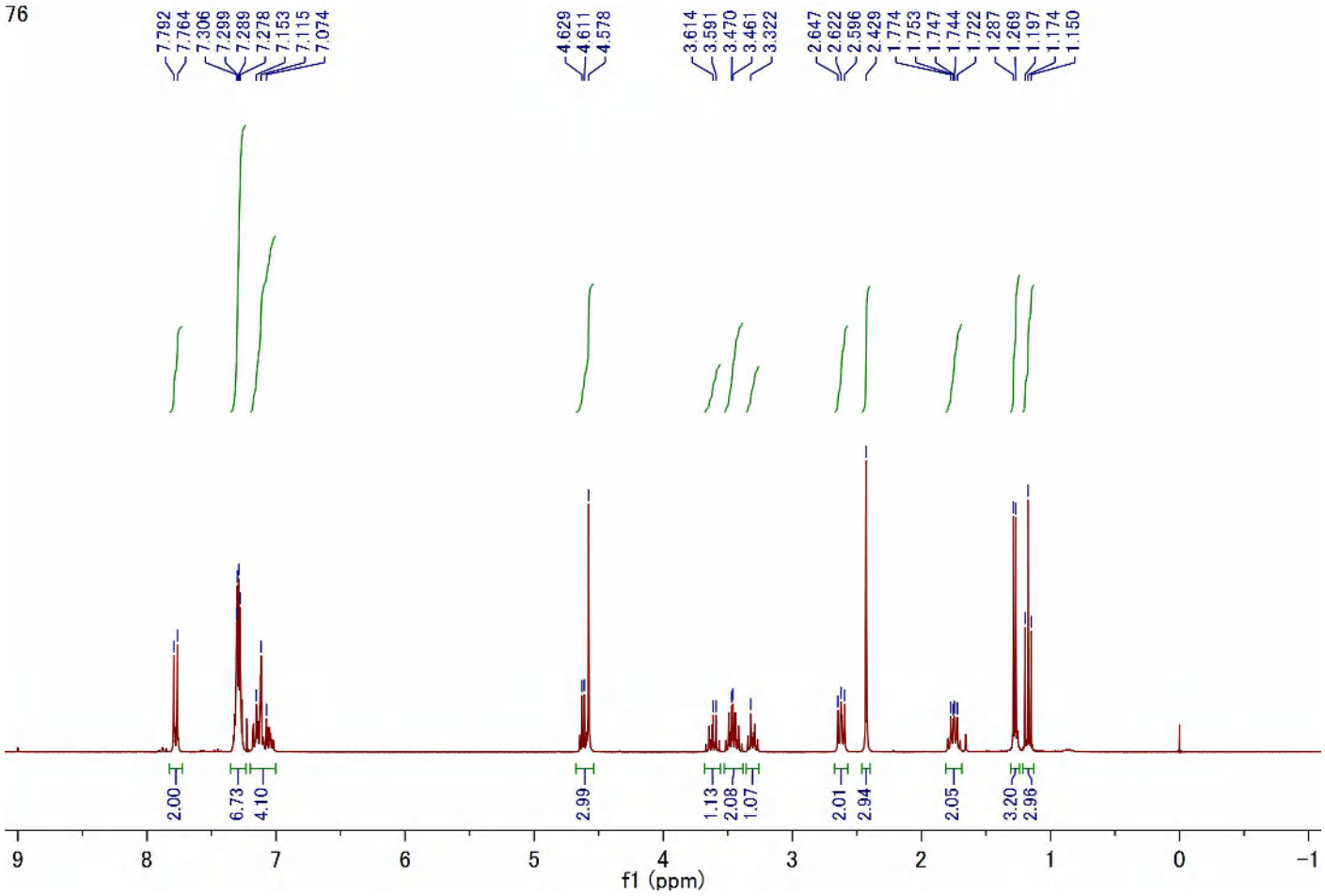
Compound **5a** (^{1}H NMR, 300 MHz, $CDCl_3$)



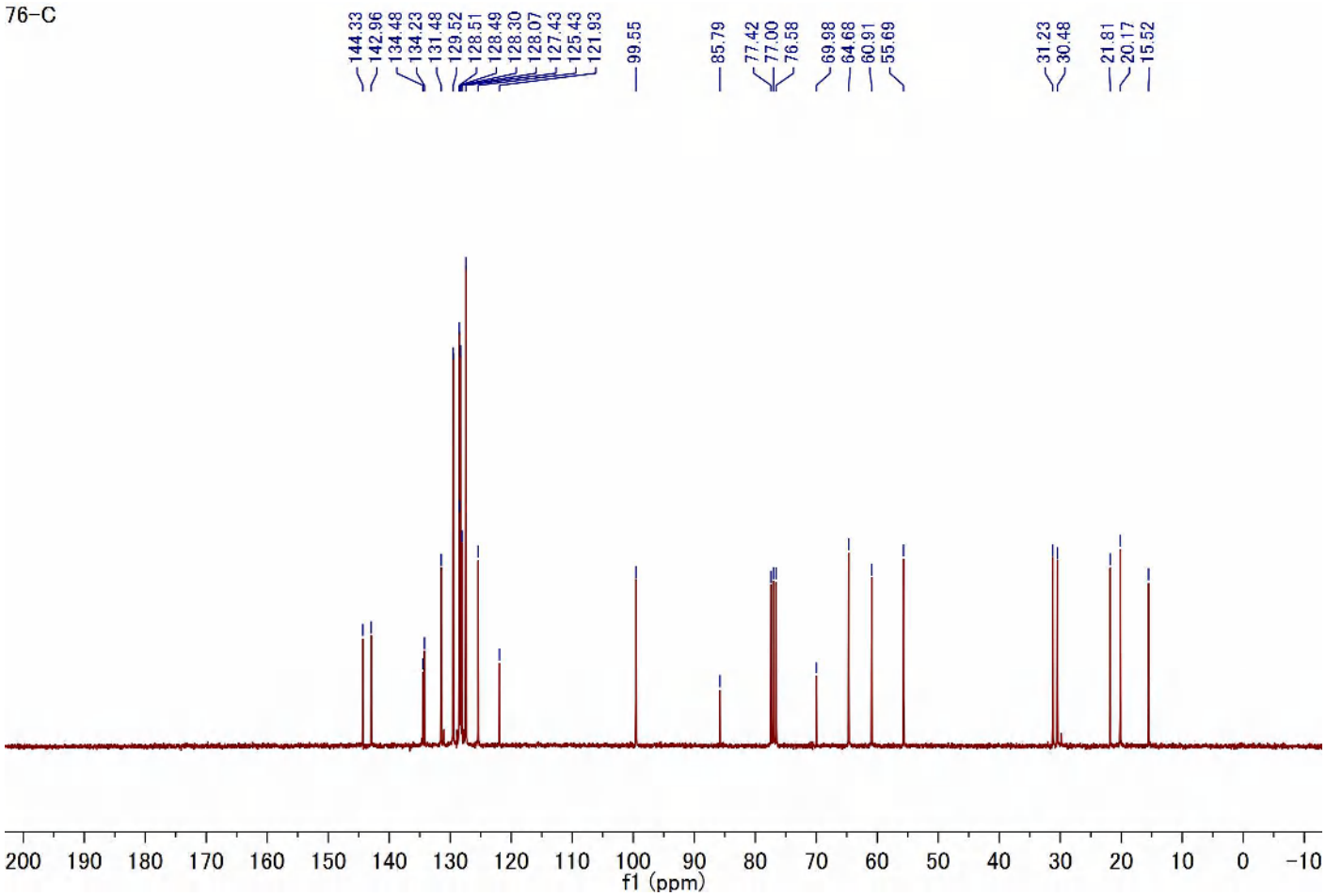
Compound **5a** (^{13}C NMR, 75 MHz, $CDCl_3$)



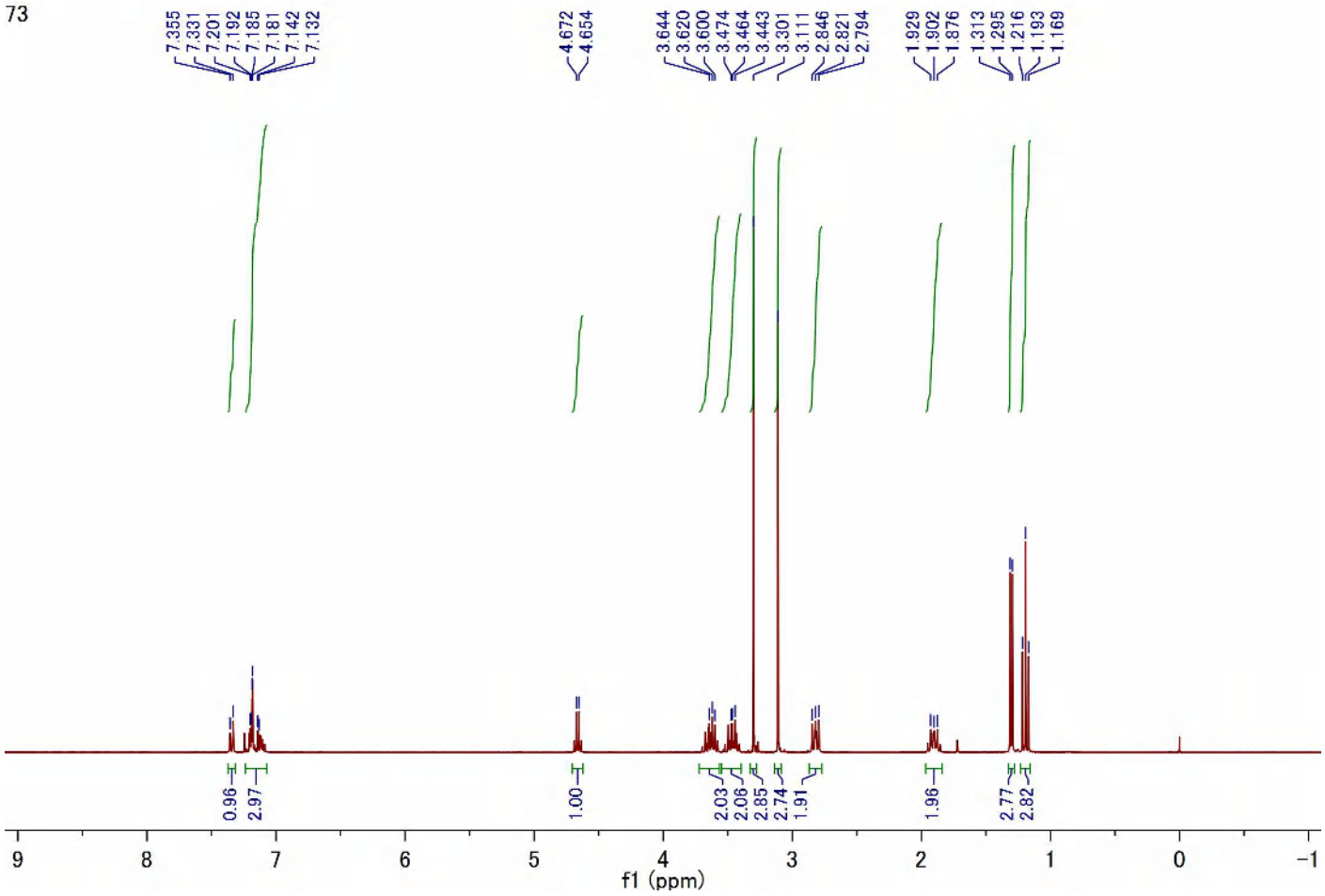
Compound **5b** (^{1}H NMR, 300 MHz, $CDCl_3$)



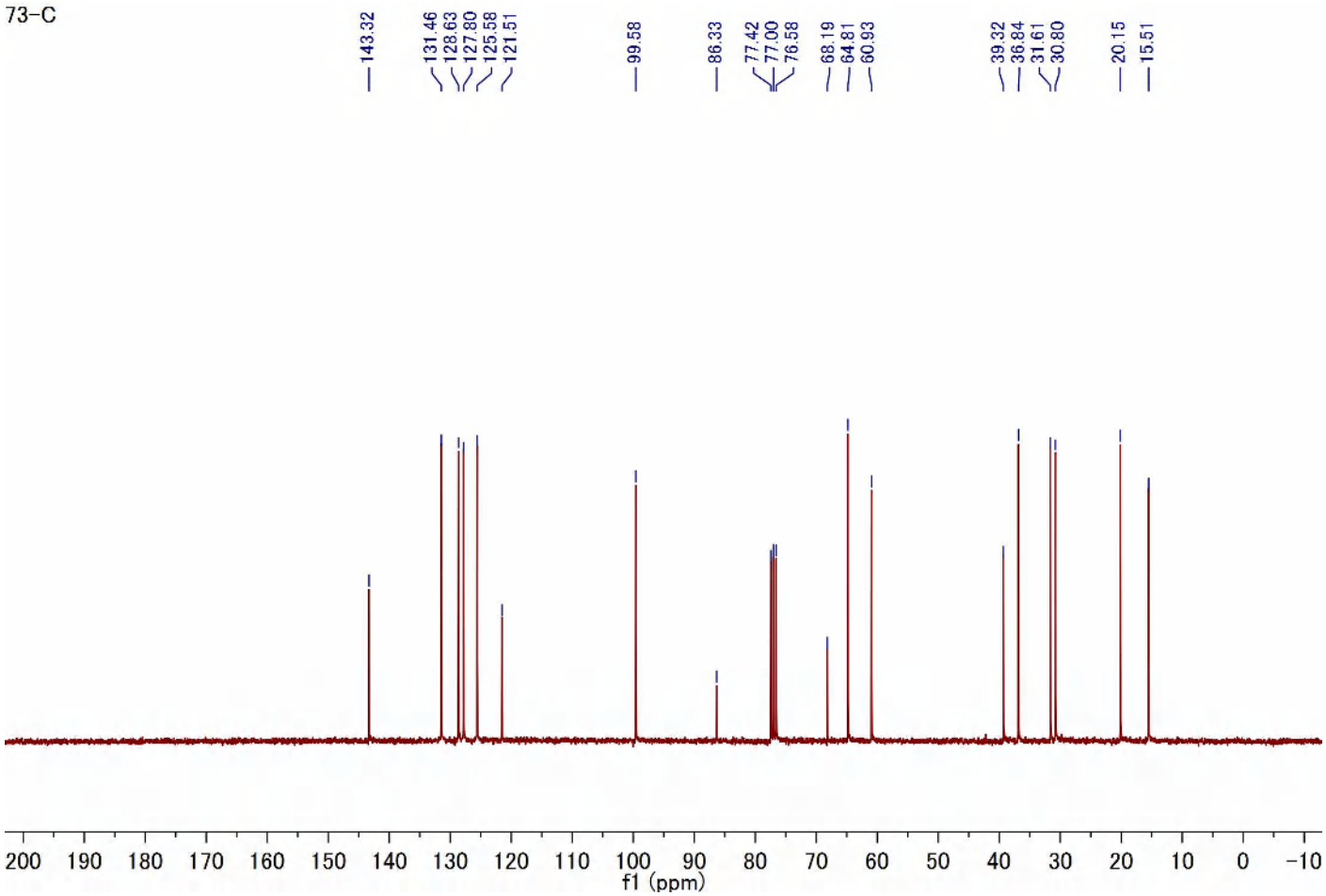
Compound **5b** (^{13}C NMR, 75 MHz, $CDCl_3$)



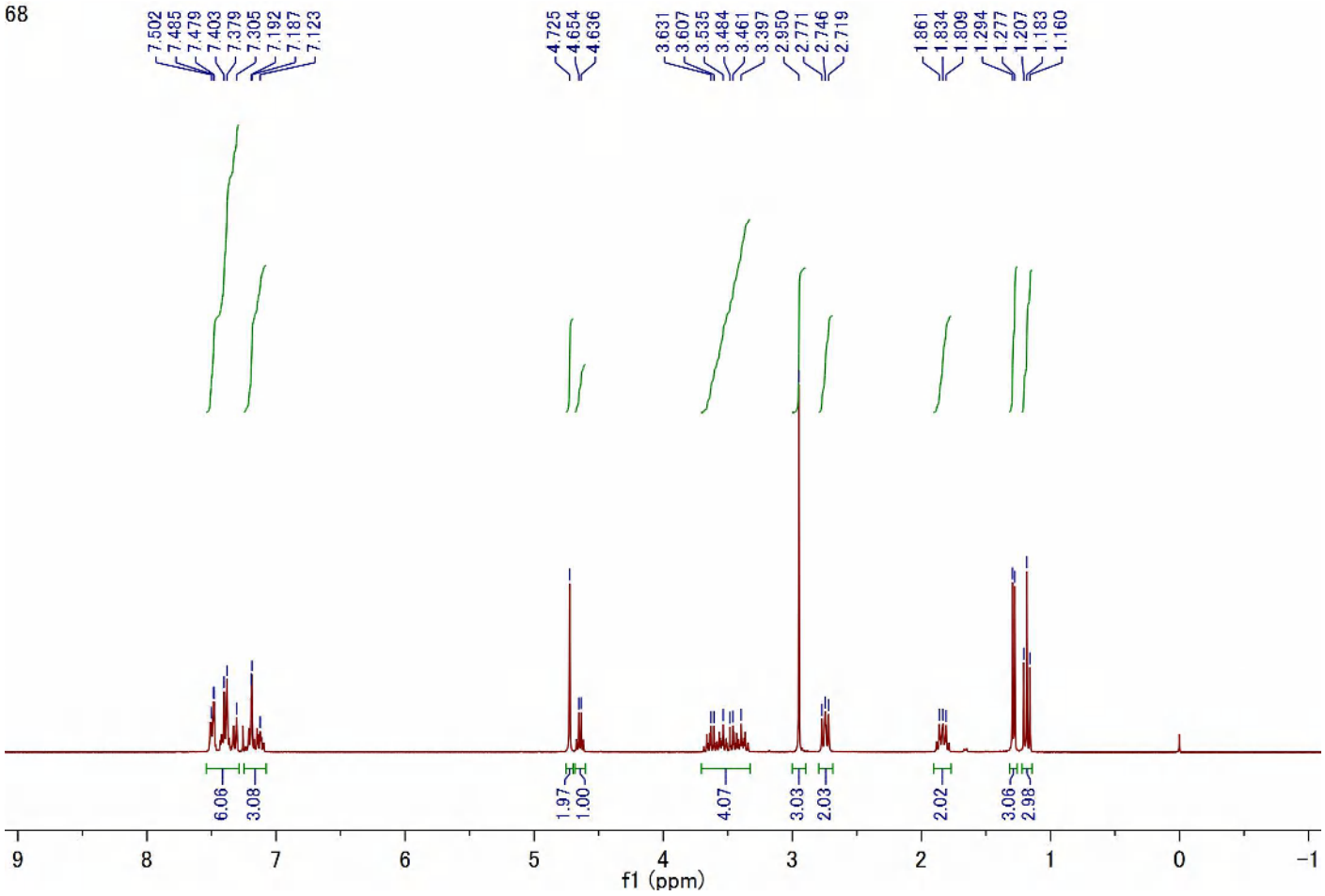
Compound **5c** (^{1}H NMR, 300 MHz, $CDCl_3$)



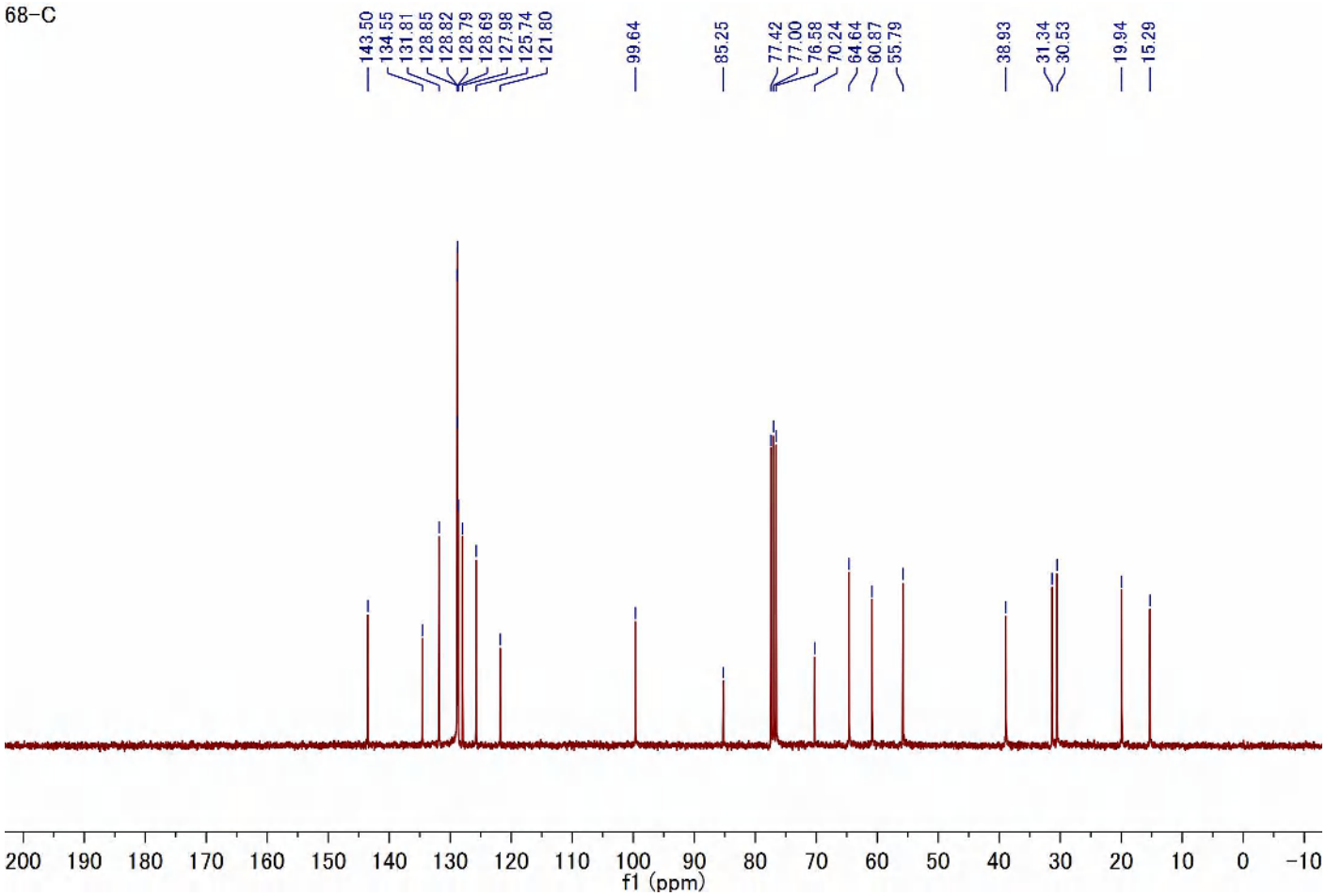
Compound **5c** (^{13}C NMR, 75 MHz, $CDCl_3$)



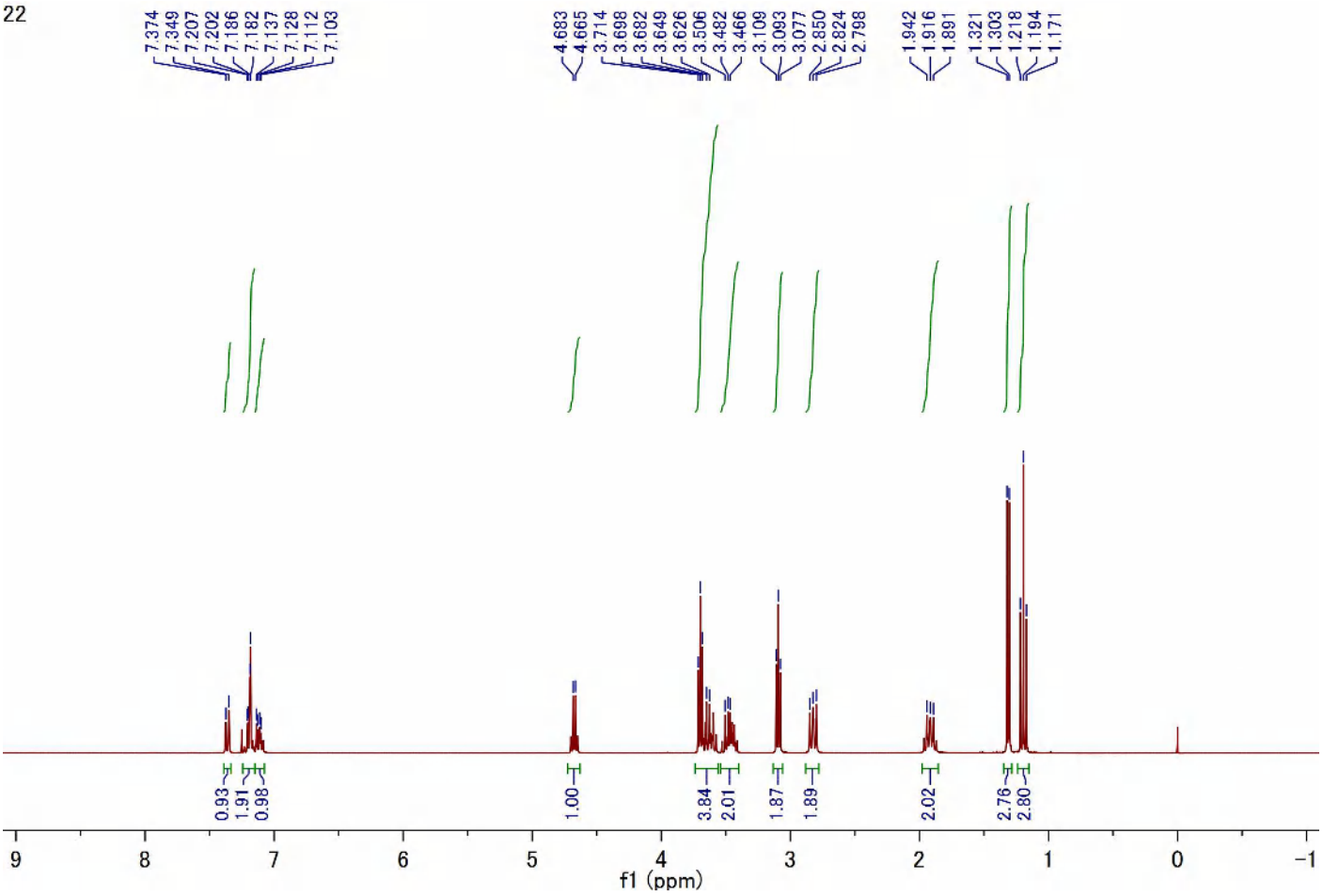
Compound **5d** (^{1}H NMR, 300 MHz, $CDCl_3$)



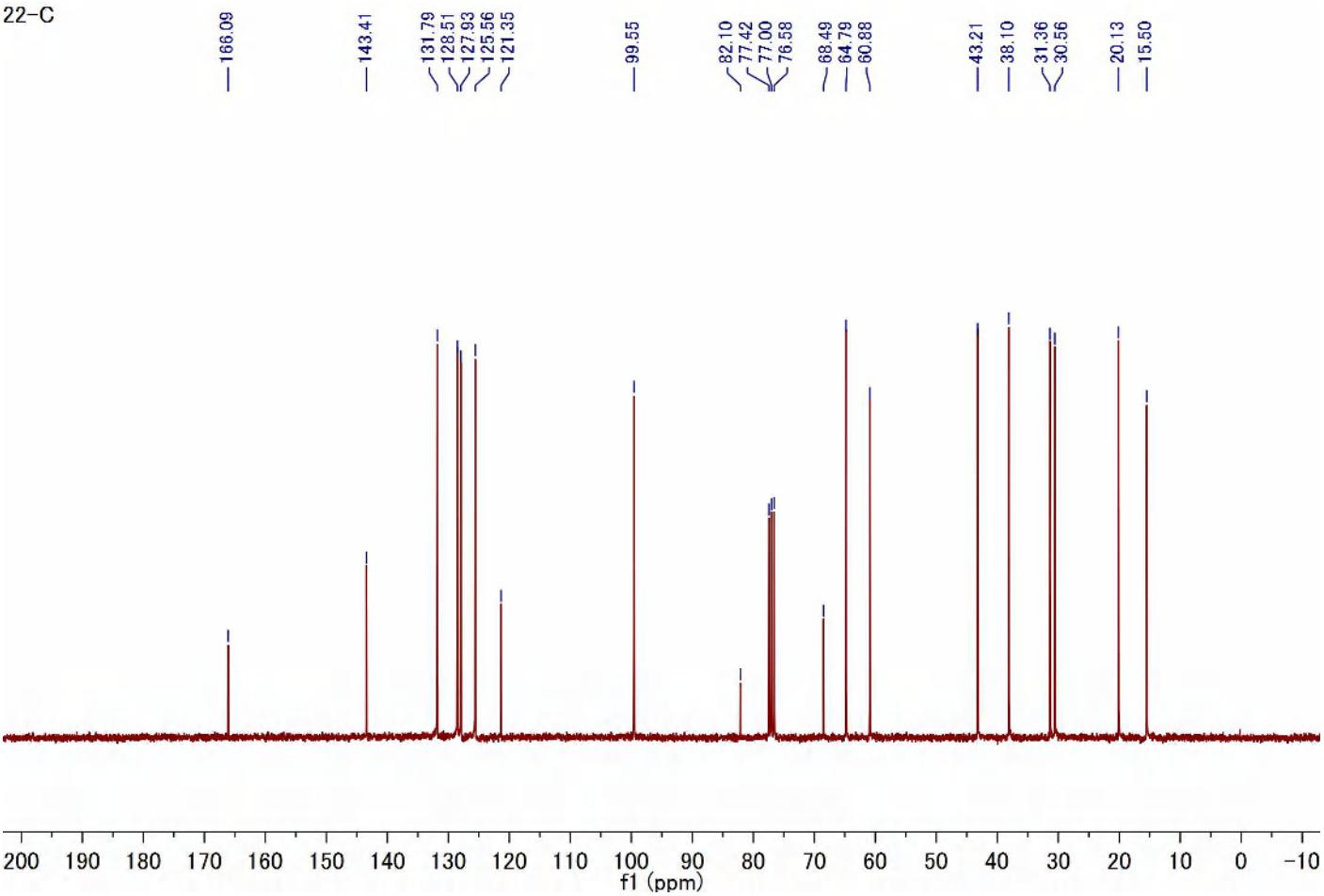
Compound **5d** (^{13}C NMR, 75 MHz, $CDCl_3$)



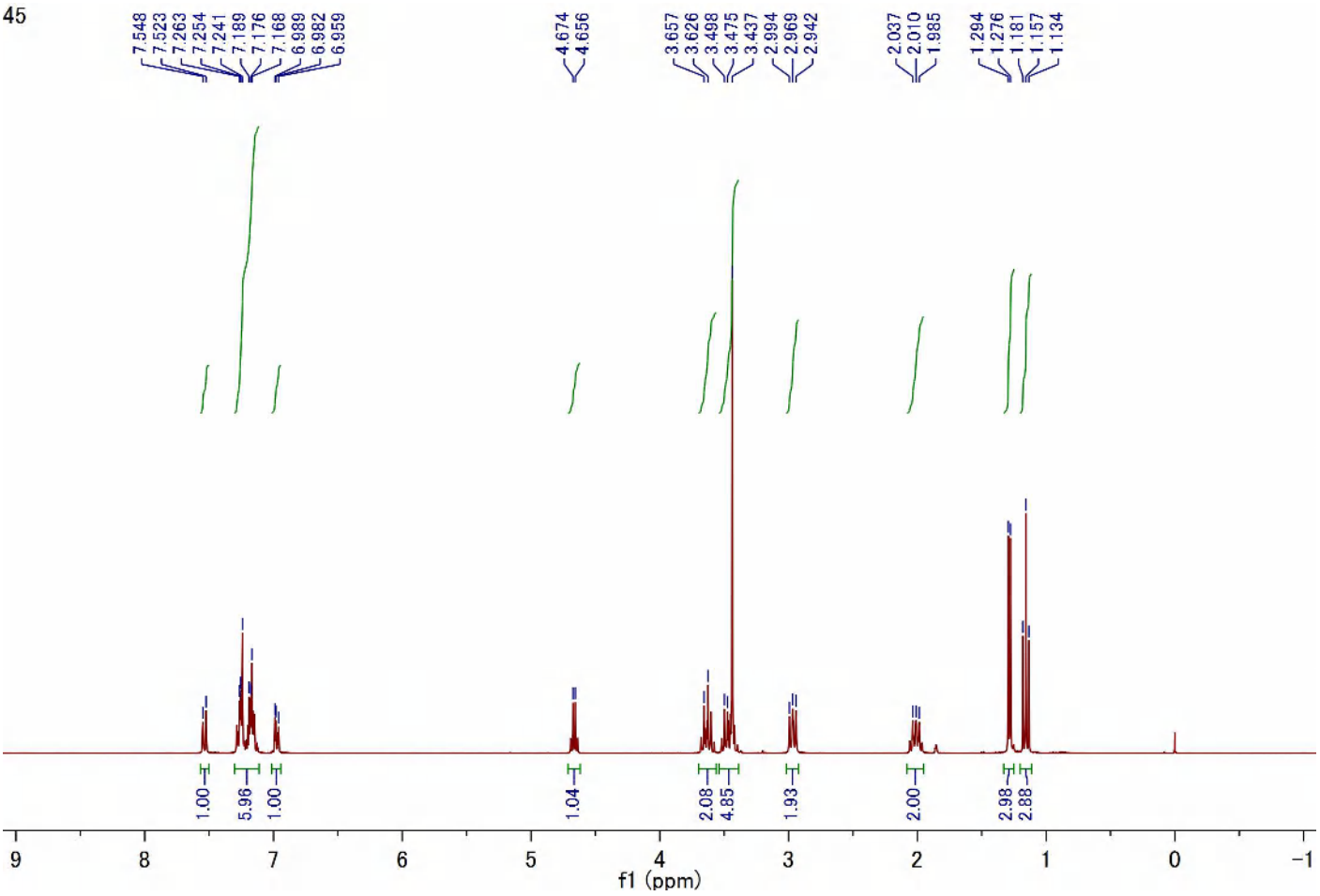
Compound **5e** (^{1}H NMR, 300 MHz, $CDCl_3$)



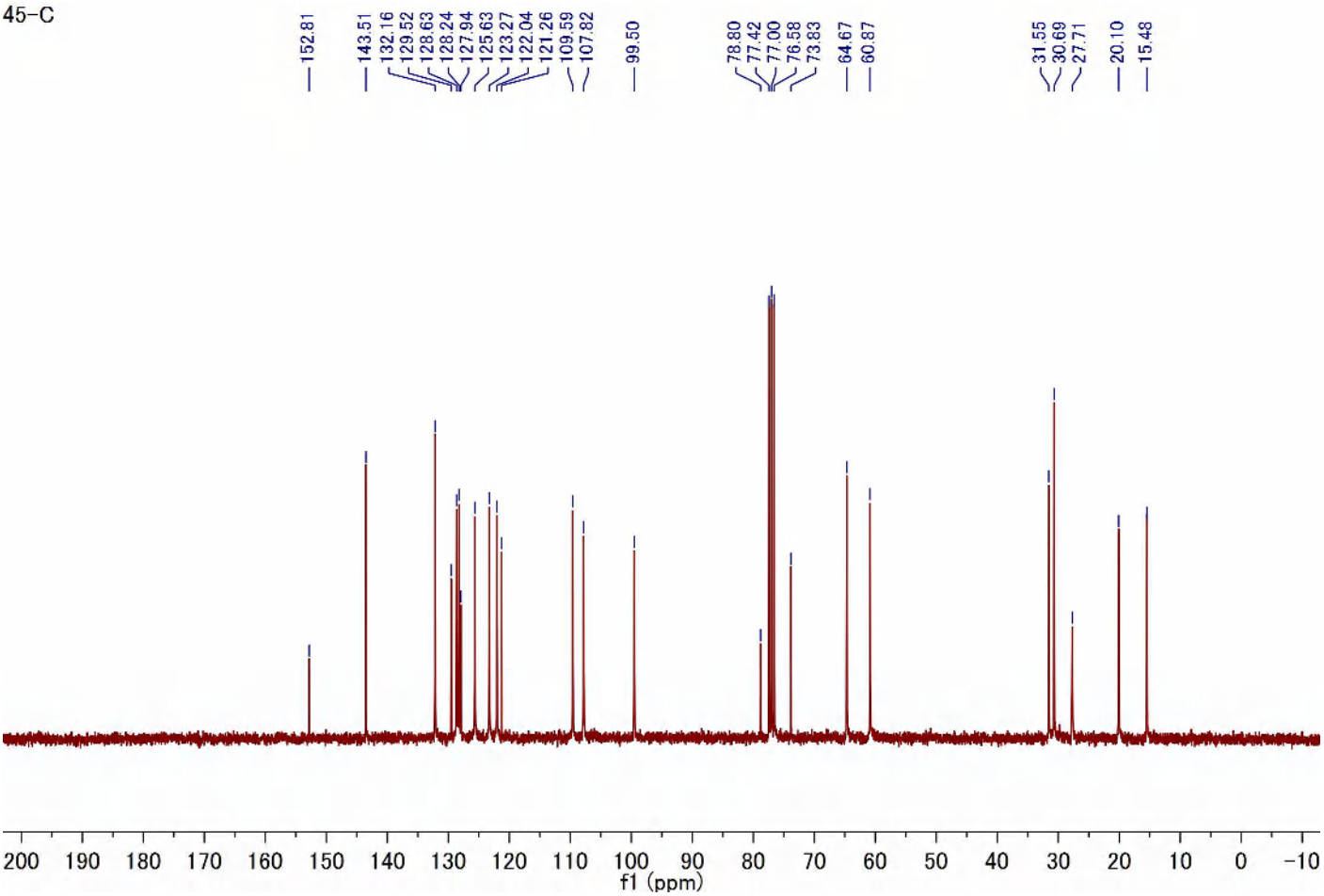
Compound **5e** (^{13}C NMR, 75 MHz, $CDCl_3$)



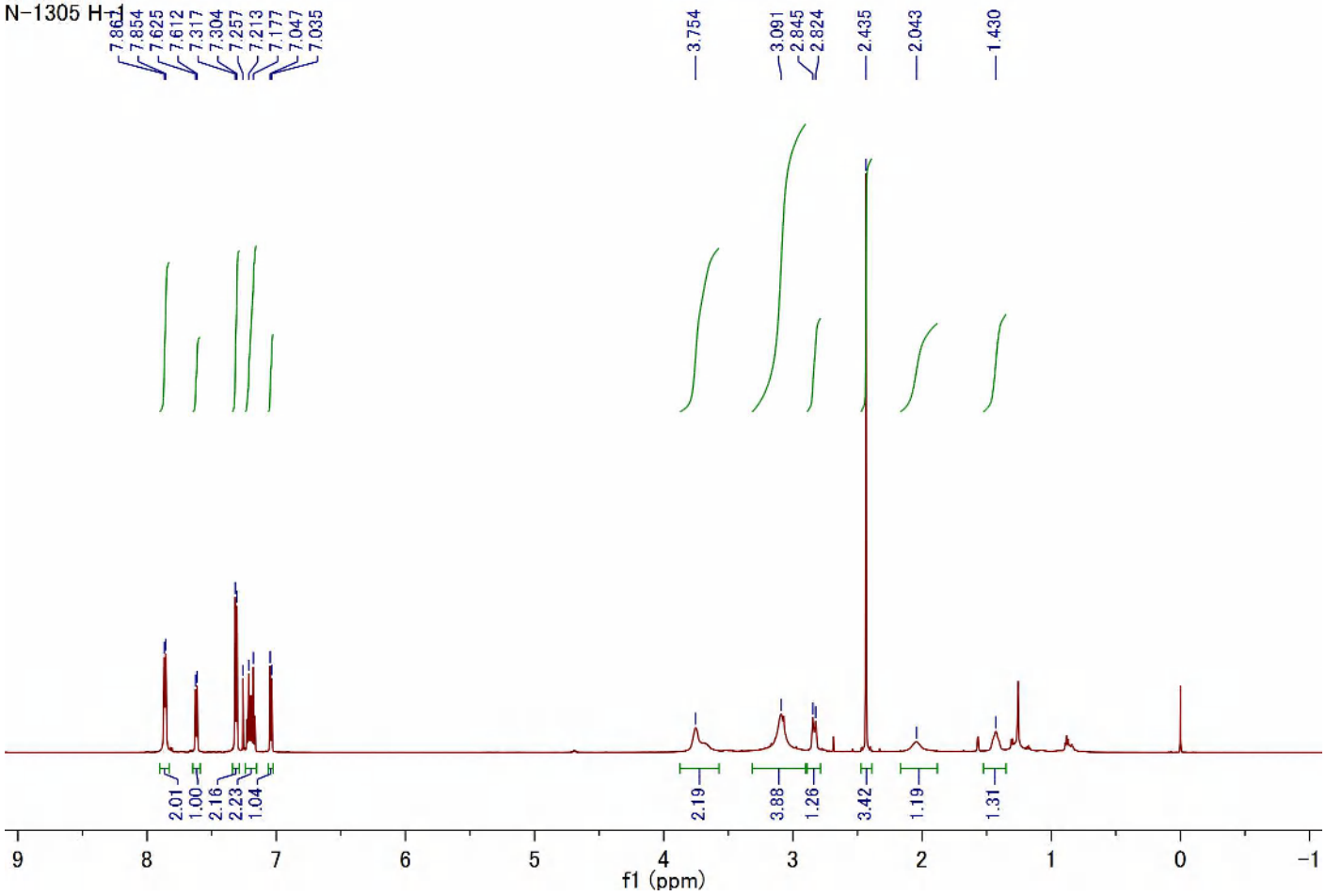
Compound **5f** (^{1}H NMR, 600 MHz, $CDCl_3$)



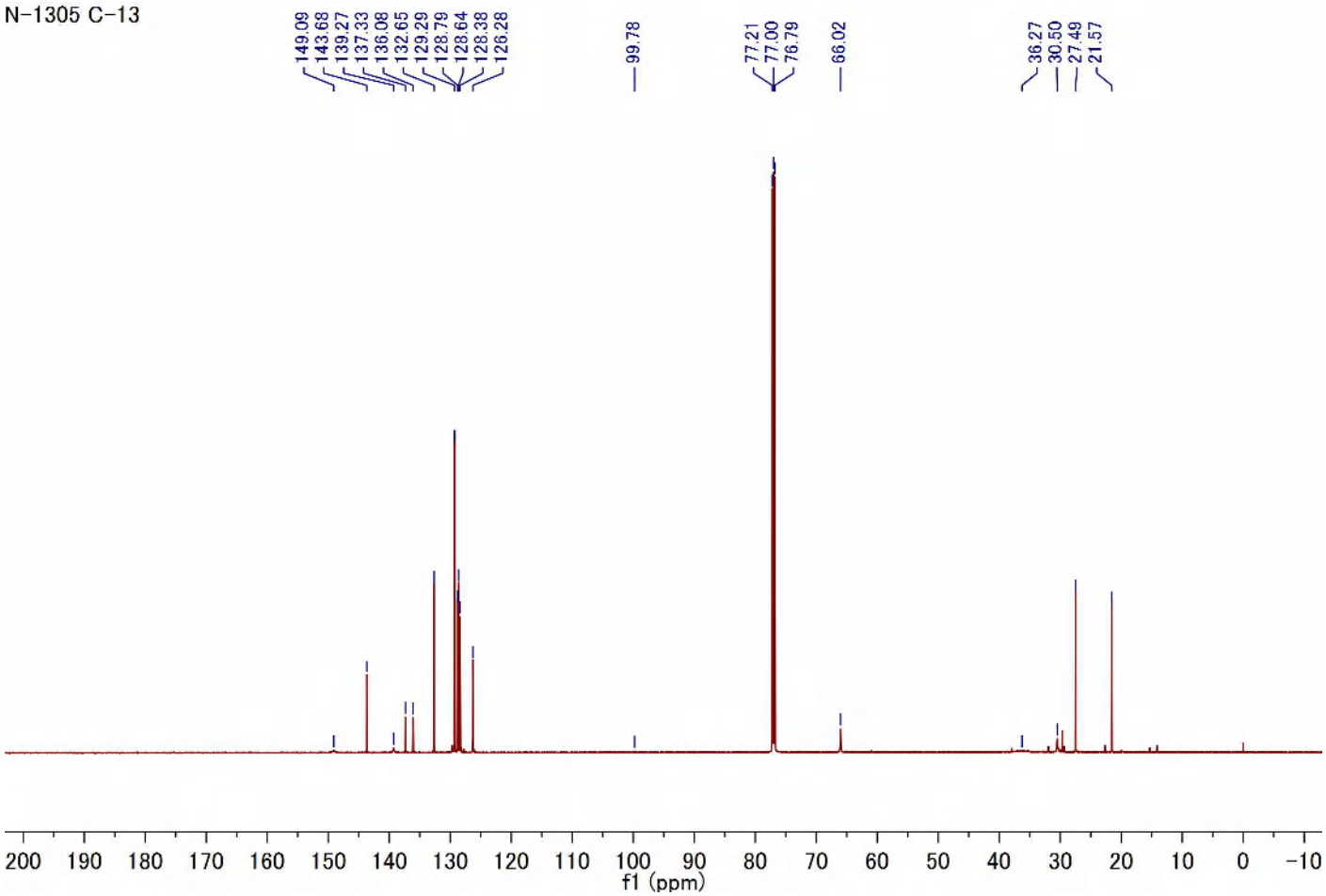
Compound **5f** (^{13}C NMR, 150 MHz, $CDCl_3$)



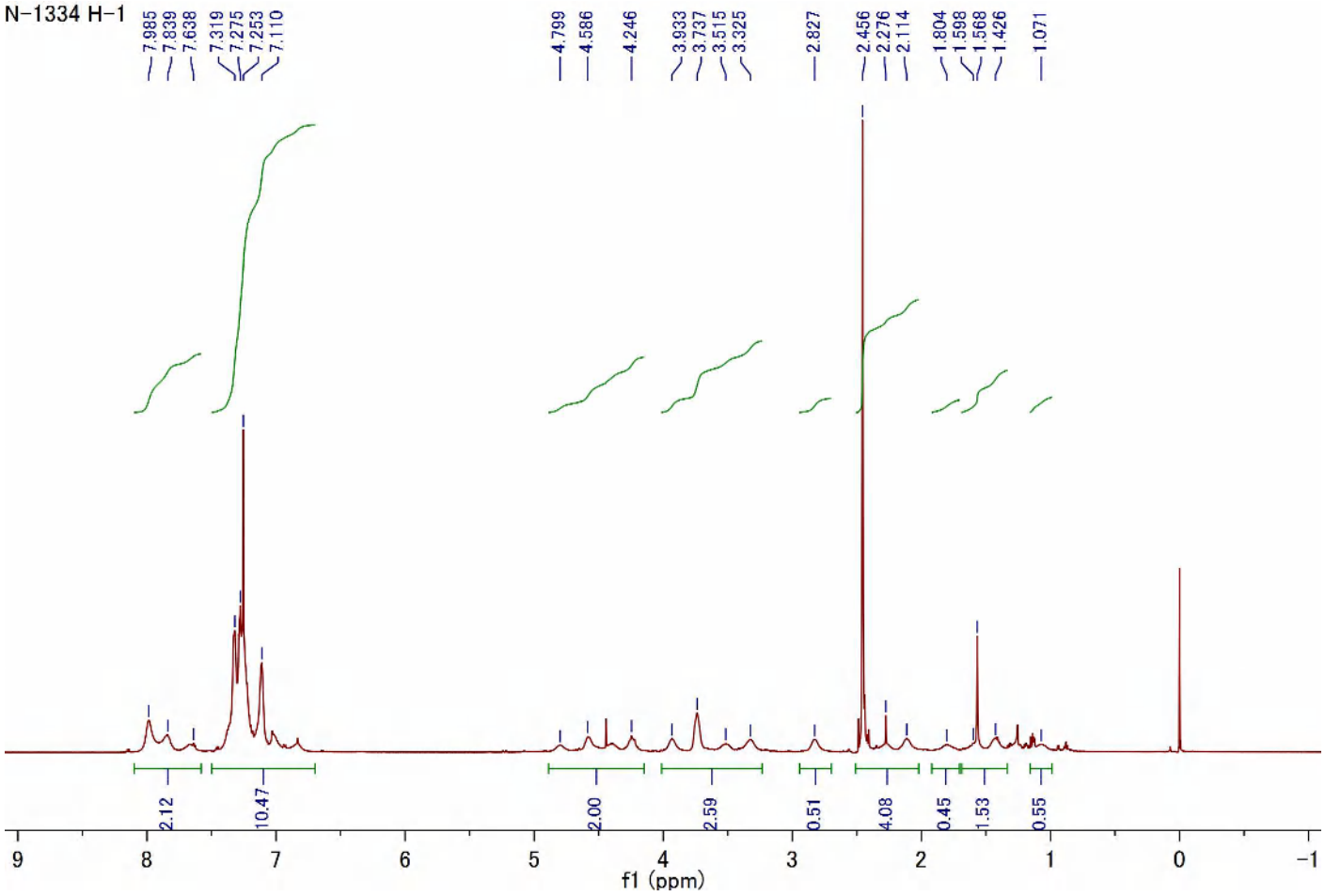
Compound **6a** (^{1}H NMR, 600 MHz, $CDCl_3$)



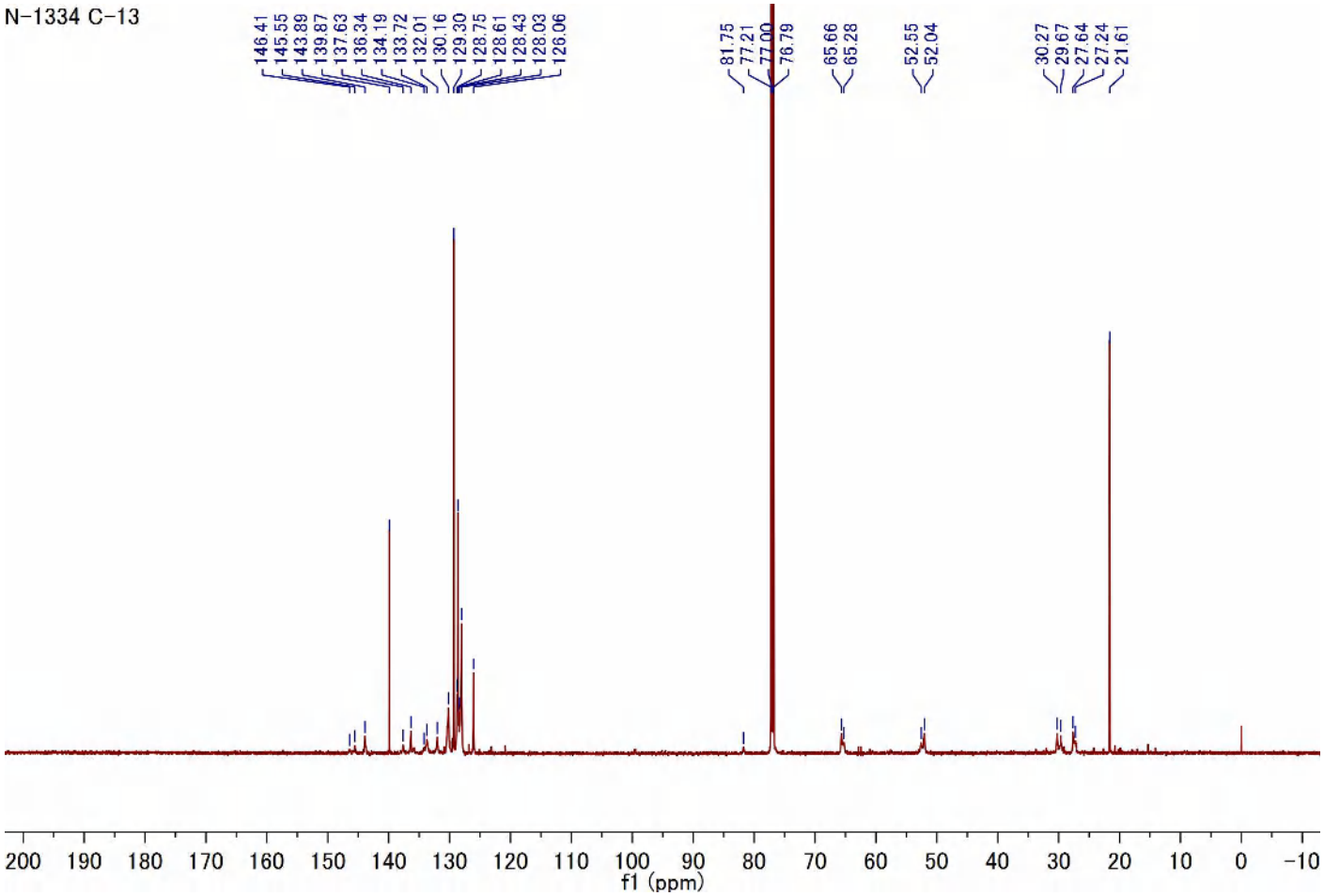
Compound **6a** (^{13}C NMR, 150 MHz, $CDCl_3$)



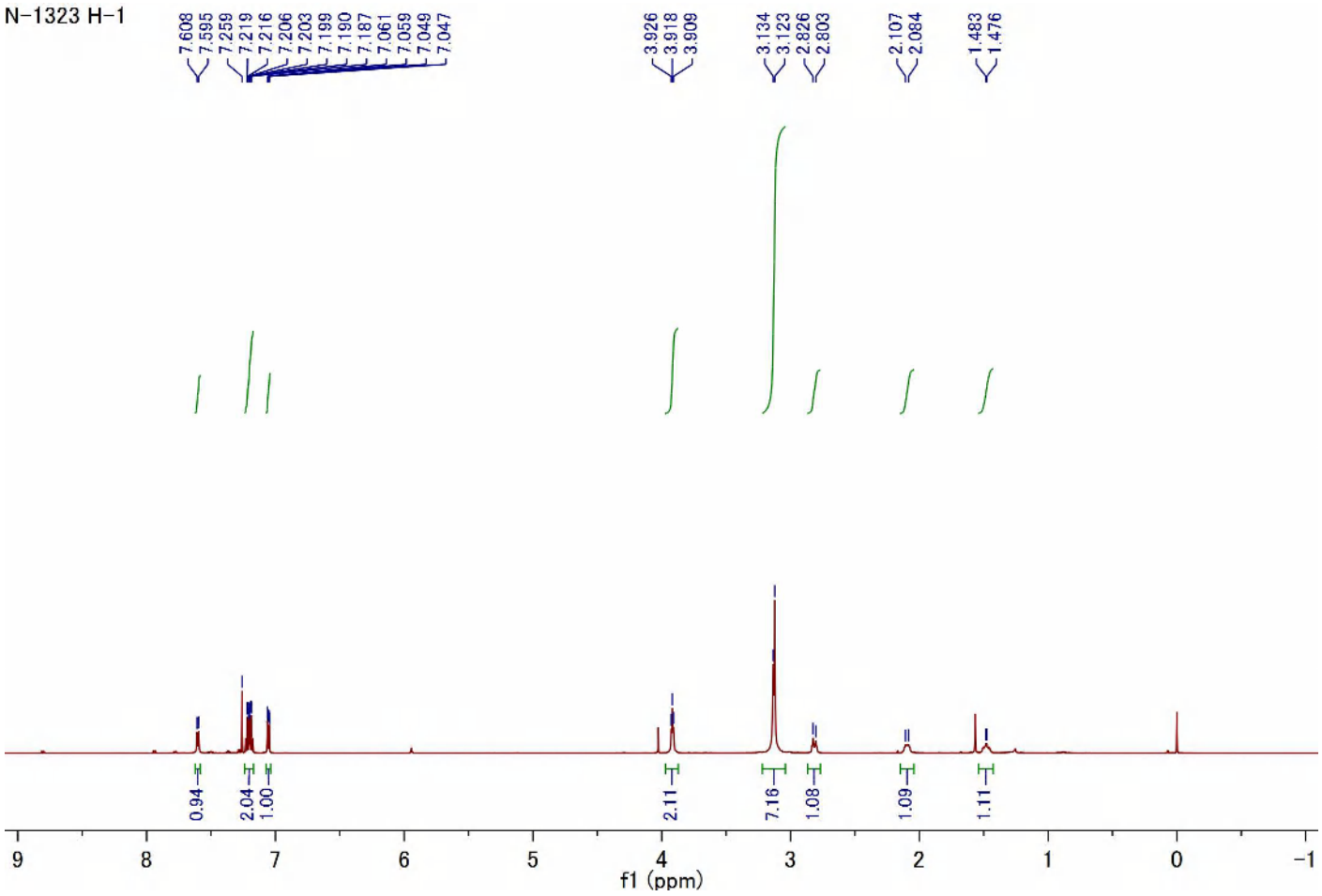
Compound **6b** (^{1}H NMR, 600 MHz, $CDCl_3$)



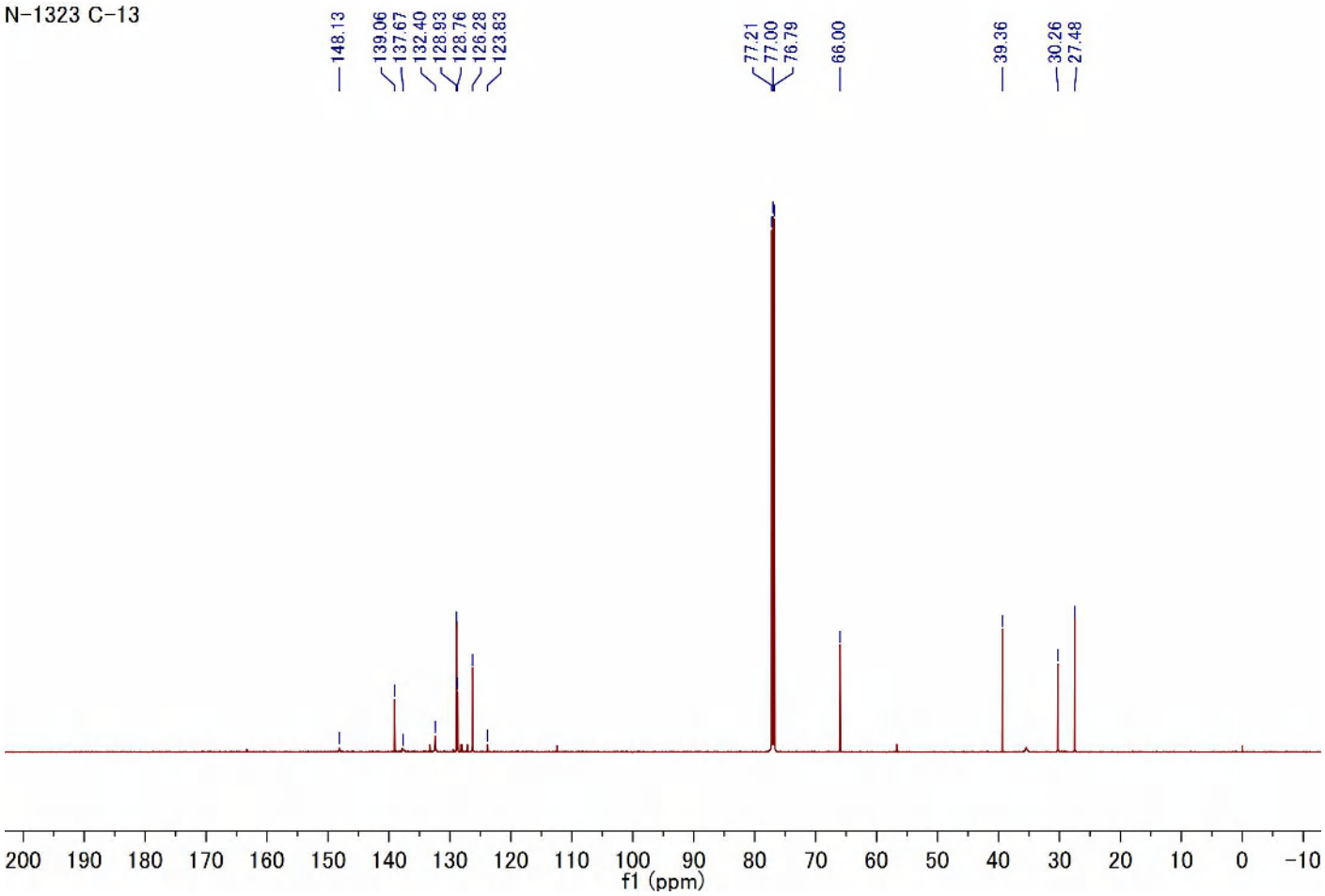
Compound **6b** (^{13}C NMR, 150 MHz, $CDCl_3$)



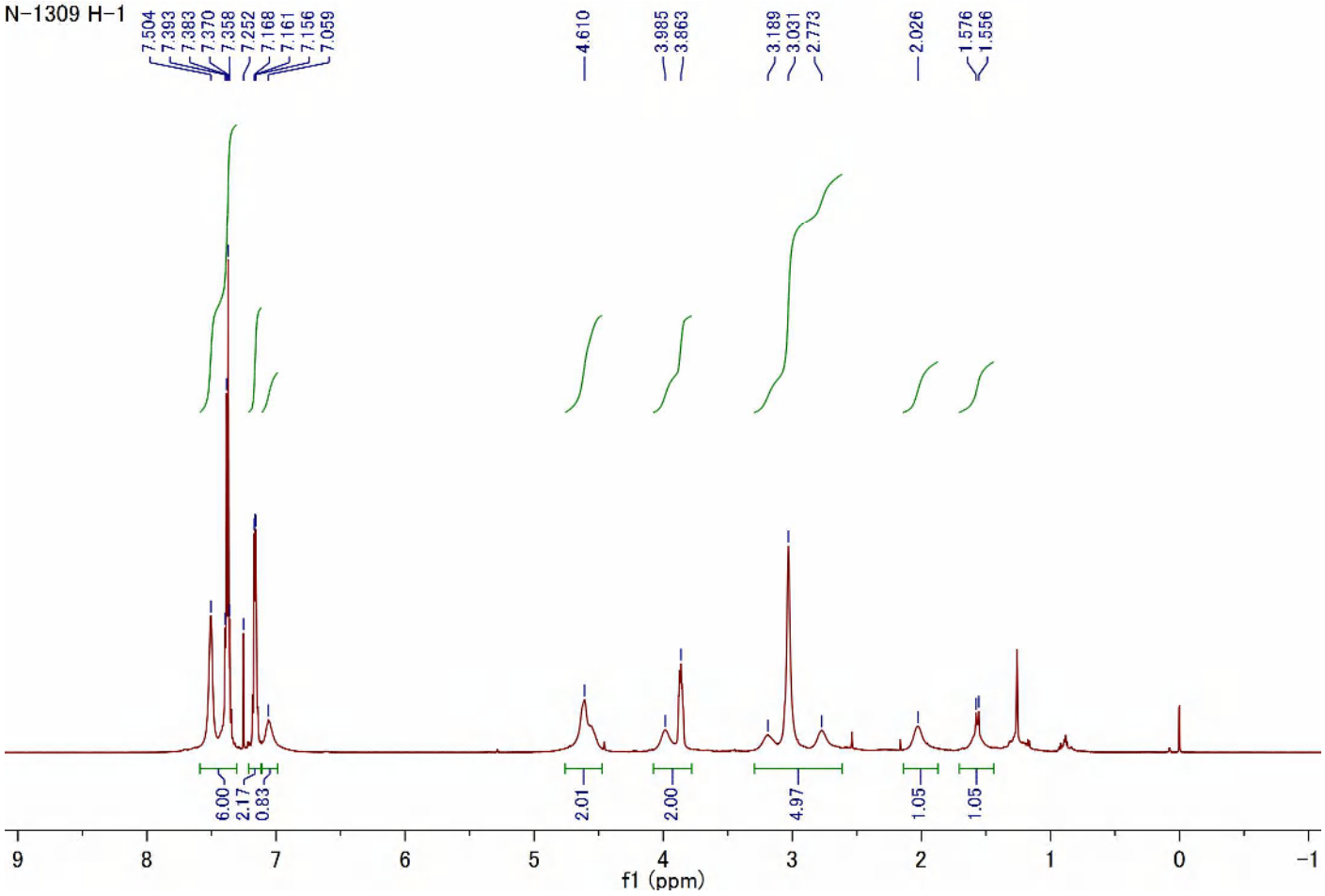
Compound **6c** (^{1}H NMR, 600 MHz, $CDCl_3$)



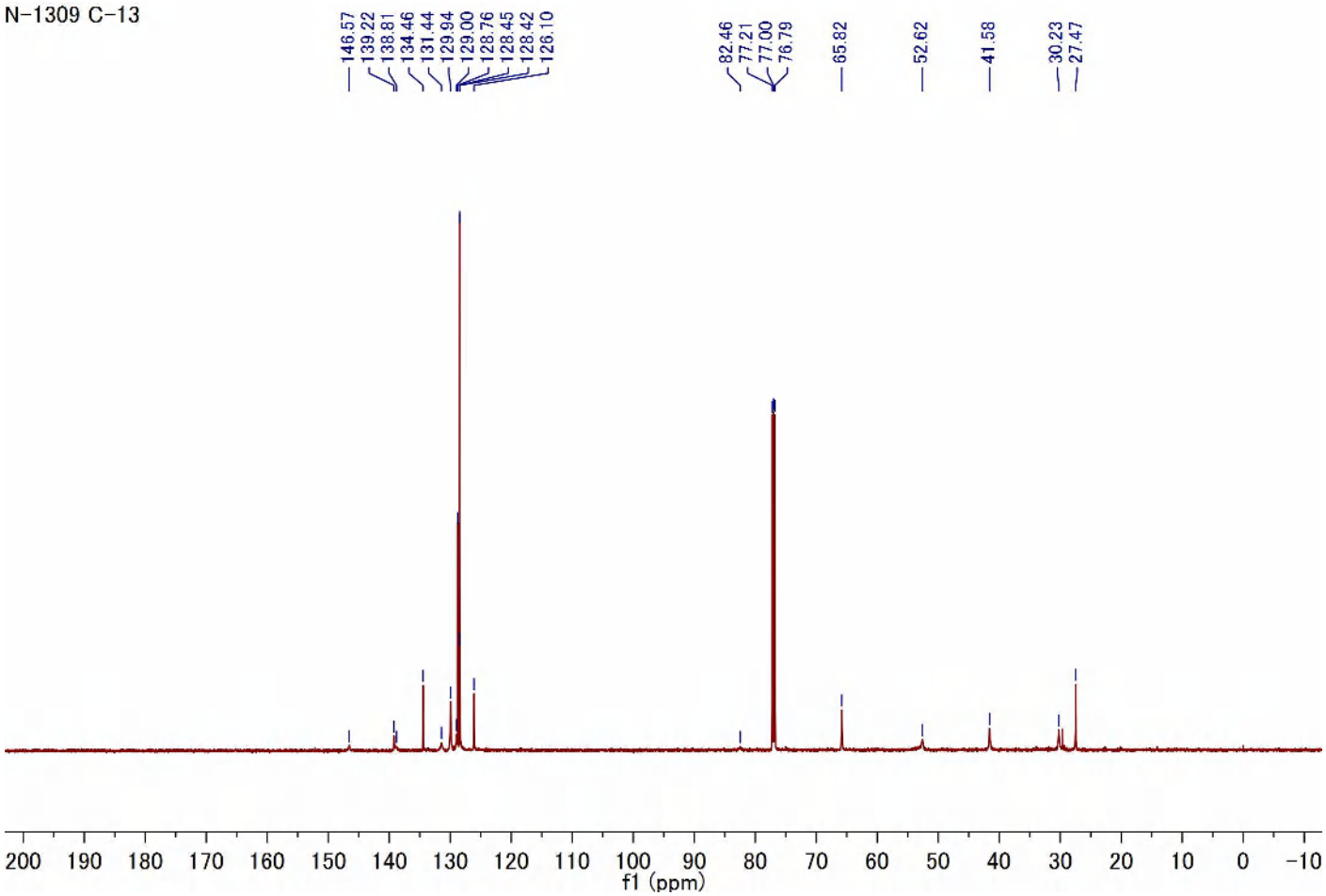
Compound **6c** (^{13}C NMR, 150 MHz, $CDCl_3$)



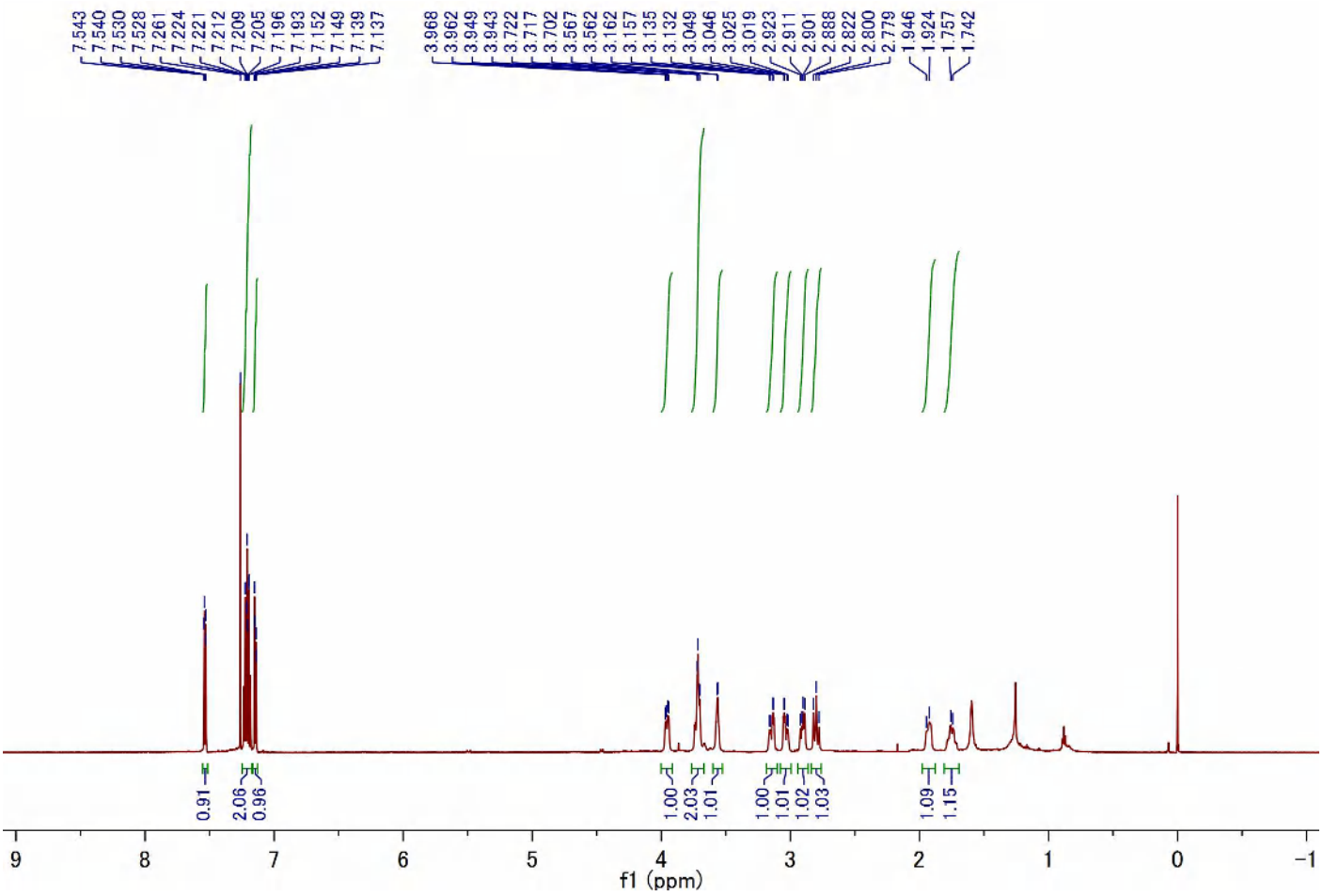
Compound **6d** (^{1}H NMR, 600 MHz, $CDCl_3$)



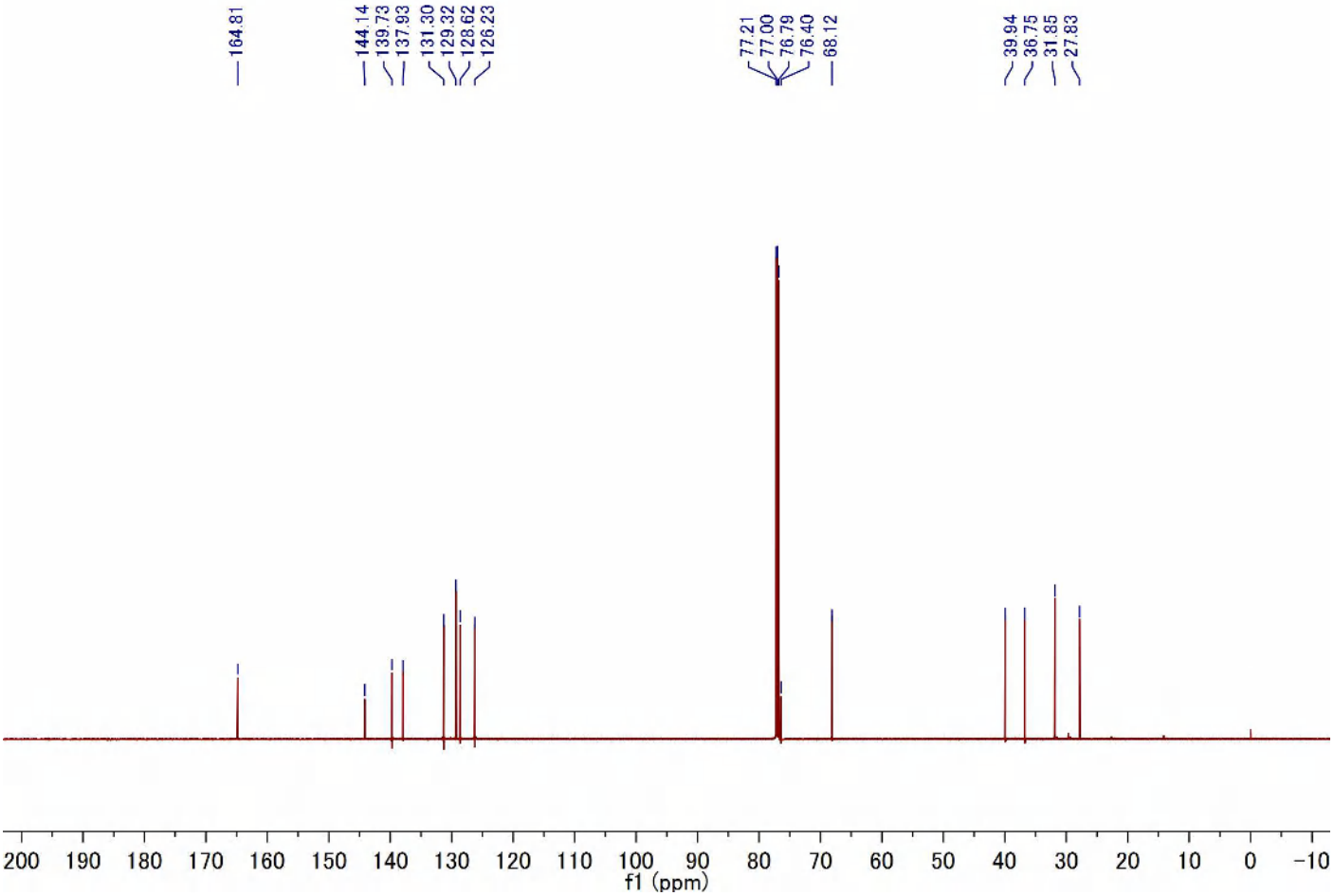
Compound **6d** (^{13}C NMR, 150 MHz, $CDCl_3$)



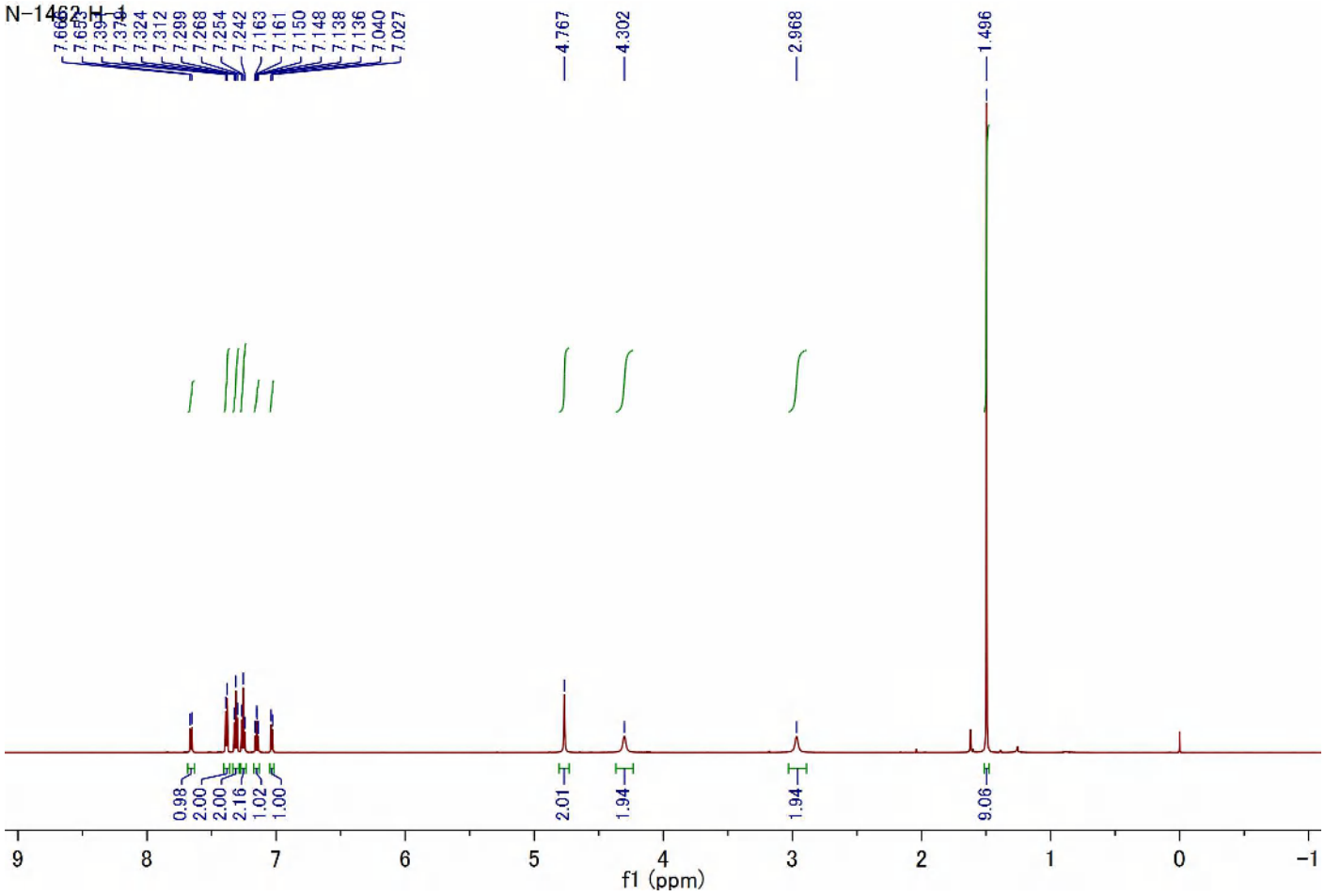
Compound **6e** (^{1}H NMR, 600 MHz, $CDCl_3$)



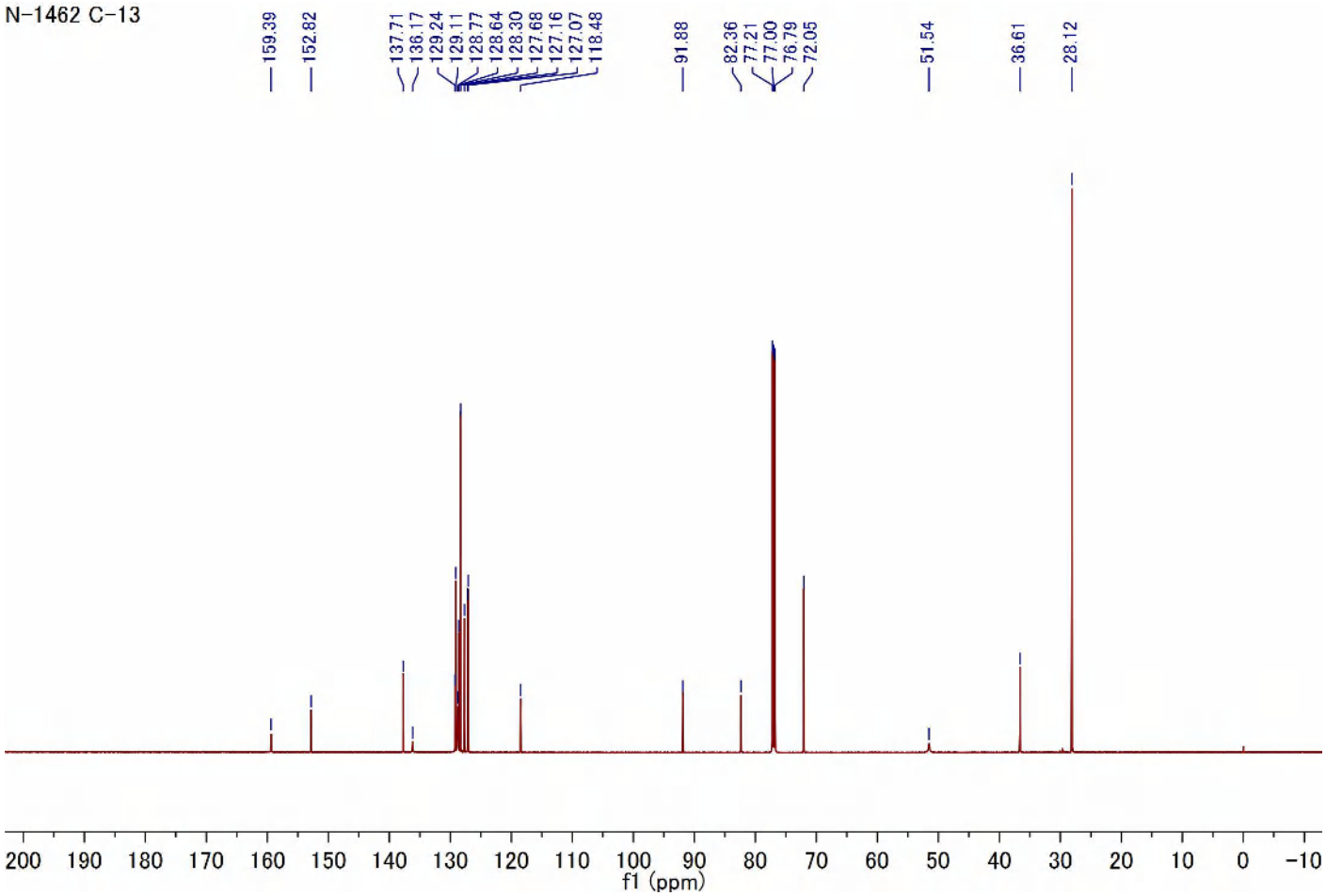
Compound **6e** (^{13}C NMR, 150 MHz, $CDCl_3$)



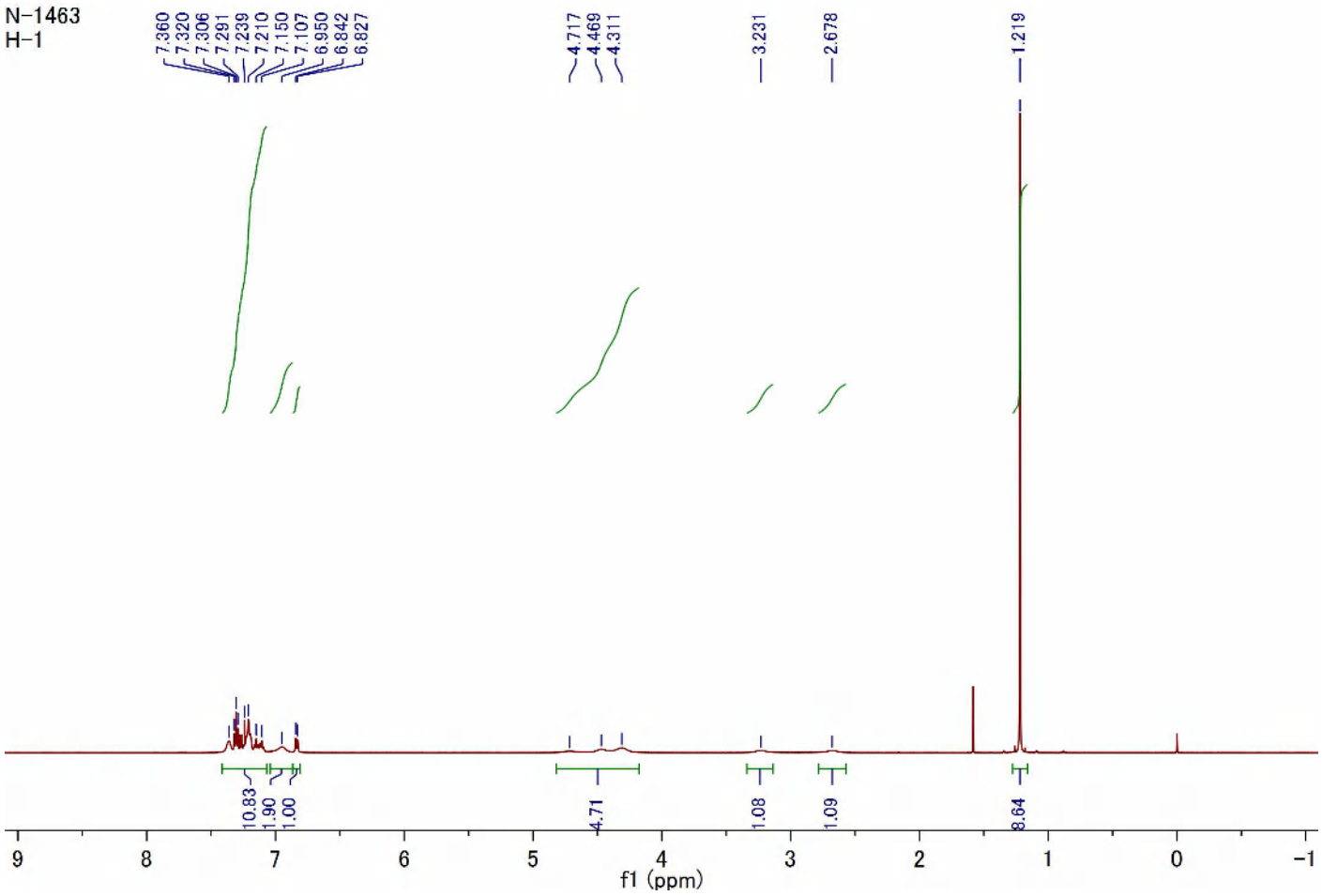
Compound **7** (^{1}H NMR, 600 MHz, $CDCl_3$)



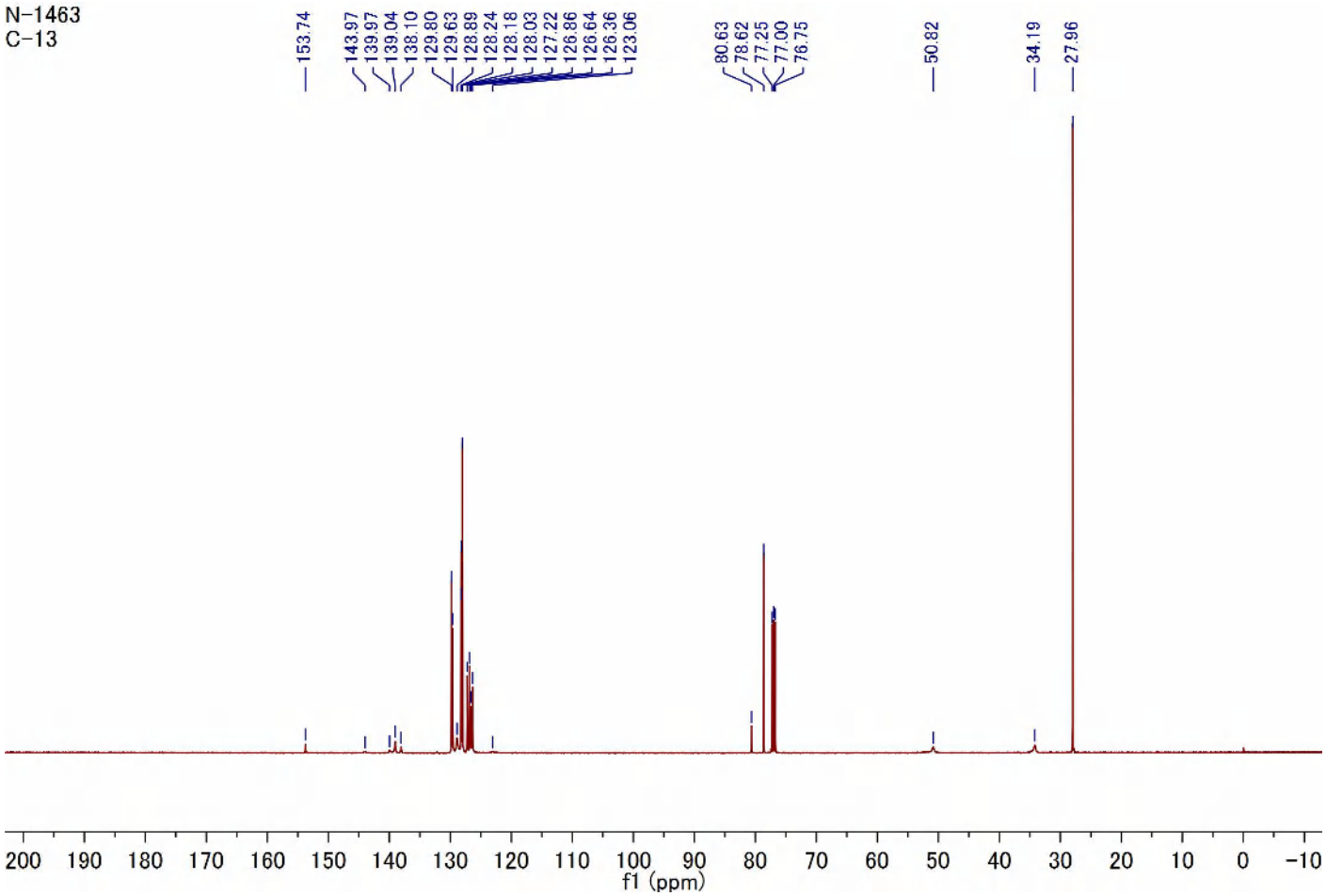
Compound **7** (^{13}C NMR, 150 MHz, $CDCl_3$)



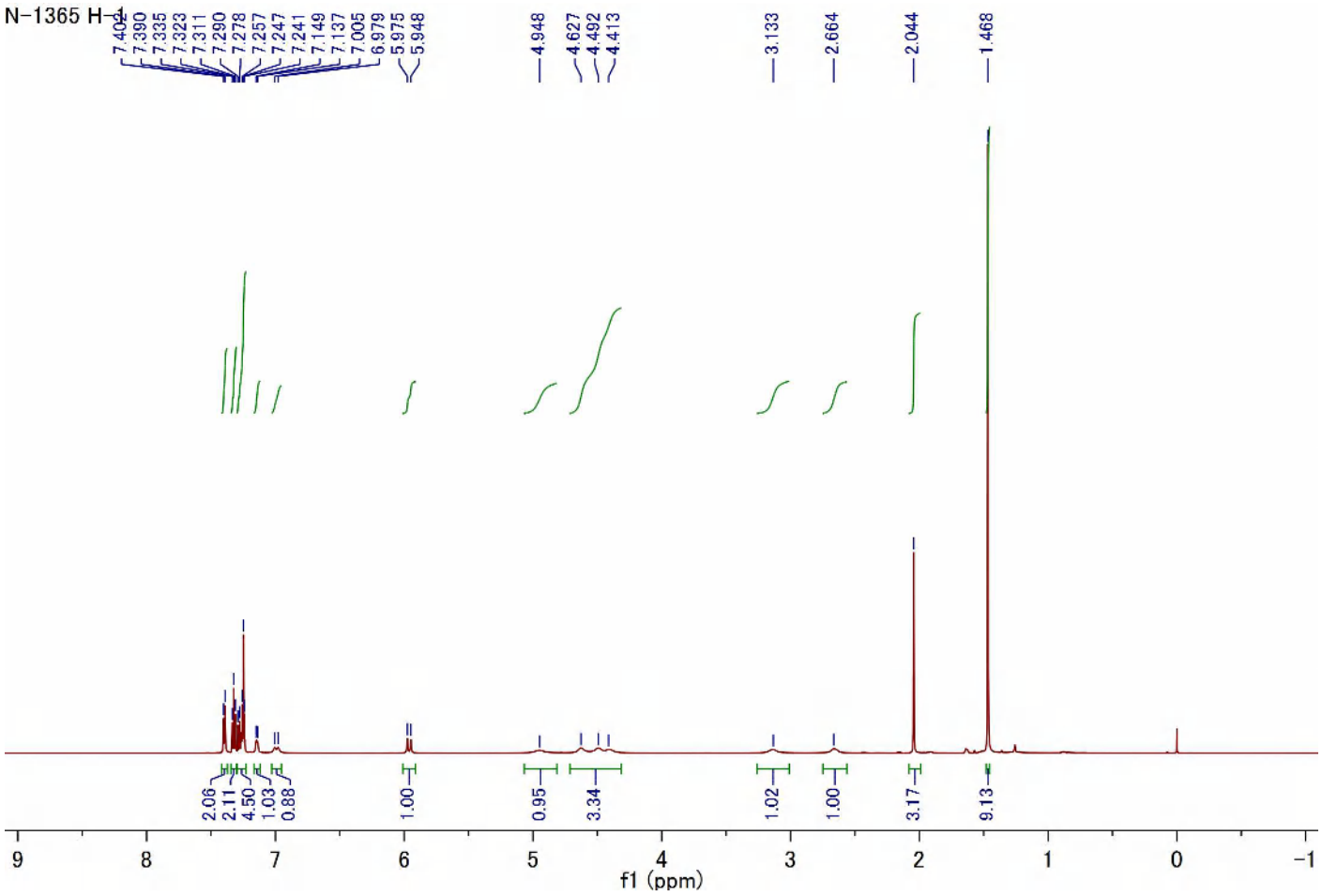
Compound **8** (^{1}H NMR, 500 MHz, $CDCl_3$)



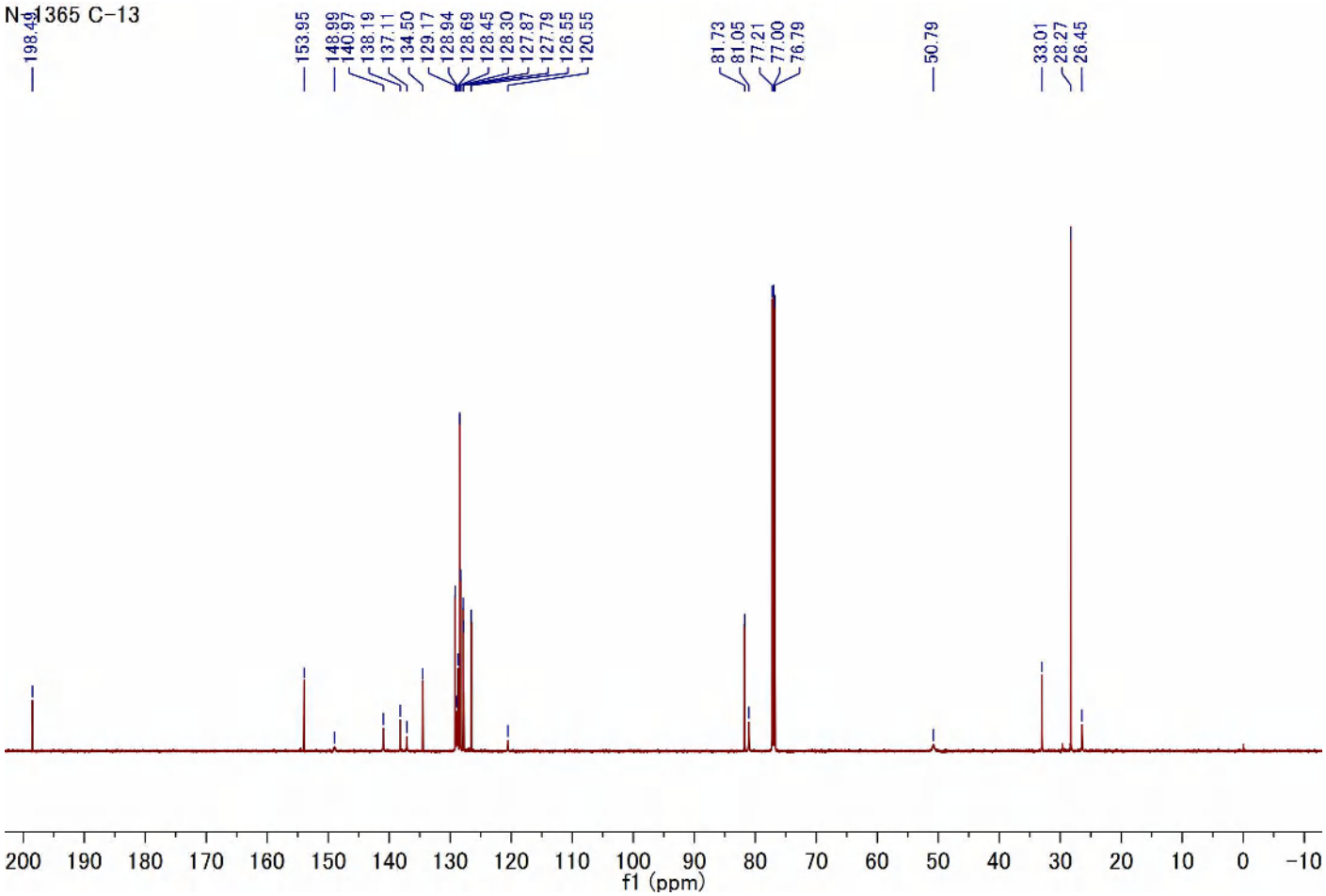
Compound **8** (^{13}C NMR, 125 MHz, $CDCl_3$)



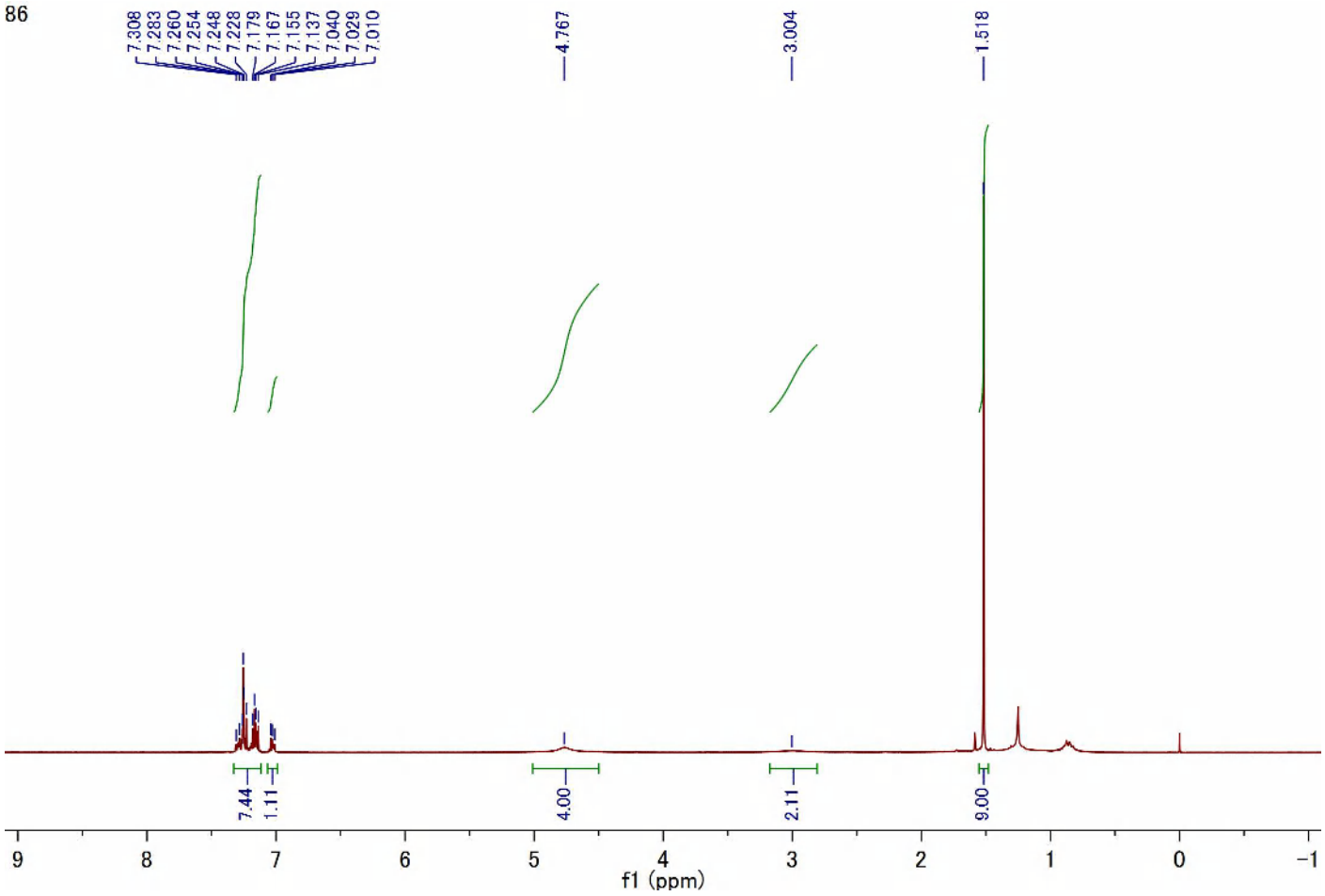
Compound **9** (^{1}H NMR, 600 MHz, $CDCl_3$)



Compound **9** (^{13}C NMR, 150 MHz, $CDCl_3$)



Compound **10** (^{1}H NMR, 300 MHz, $CDCl_3$)



Compound **10** (^{13}C NMR, 75 MHz, $CDCl_3$)