Electronic supplementary materials *Mendeleev Commun.*, 2014, **24**, 269−271

Synthesis of trifluoromethylated [1,4]diazepines from 1,1,1-trifluoroalk-3-yn-2-ones

Alexey R. Romanov, Alexander Yu. Rulev, Igor A. Ushakov, Vasiliy M. Muzalevskiy and Valentine G. Nenajdenko

Table of contents

General remarks.

3.1. General remarks. ^{1}H (400.1 MHz), ^{13}C (101.6 MHz), ^{19}F (376.5 MHz) NMR spectra were recorded on Bruker AVANCE 400 MHz spectrometer. Chemical shifts (δ) in ppm are reported as quoted relative to the residual signals of chloroform-*d* (7.24 for ^{1}H NMR and 77.2 for ^{13}C NMR), acetone-d_6 (2.05 for ^{1}H NMR and 29.9 for ^{13}C NMR), or DMSO-d_6 (2.50 for ^{1}H NMR and 39.5 for ^{13}C NMR) as external references. The coupling constants (*J*) are given in Hertz. The IR spectra were recorded with a Bruker Vertex 70 FT-IR spectrometer and with a portable Varian 3100 diamond ATR/FT-IR spectrometer. The GC/MS analyses were performed with a Shimadzu GCMS-QP5050A instrument (EI, 70 eV). ESI-MS spectra were measured with a MicroTof Bruker Daltonics instrument.

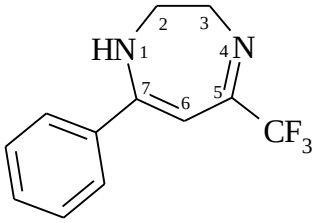
The silica gel used for column chromatography was 230-400 Mesh. All reagents were of reagent grade and were used as such or distilled prior to use. All the solvents were dried according to standard procedures and freshly distilled prior to use.

The NMR tubes (5 mm) were used for the monitoring of the reactions. The amount of each species was determined by integration of the corresponding fluorine signal (with an error of ± 1 %). The initial ynones **1** were prepared according to published procedure [T. Kitazume, T. Sato, *J. Fluor. Chem.* **1985**, *30*, 189].

General procedure

A mixture of ynone **(1a,c,d)** (1.0 mmol) and *o*-phenylenediamine (1.0 mmol) (in the case of **7a-c**) or ethylenediamine (**2a,b**) in ethanol or benzene (2 mL) was stirred at room temperature for 24 h. Volatiles were evaporated *in vacuo*, the residue was purified by column chromatography [silica gel, ether/hexane (1:3) or $CHCl_3$/MeOH (95:5)]. The following heterocycles **2a,b**, **7a-c** were obtained by this method. Products **7c** and **8** were described earlier [N.N. Chipanina, L.P. Oznobikhina, T.N. Aksamentova, A.R. Romanov, A.Yu. Rulev, *Tetrahedron*, **2014**, *70*, 1207-1213].

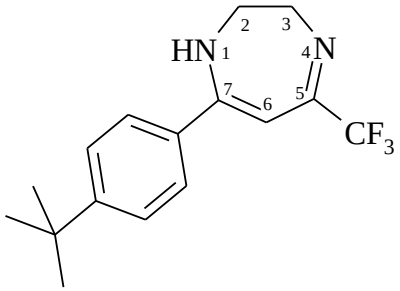
7-Phenyl-5-trifluoromethyl-2,3-dihydro-1H-[1,4]diazepine **(2a)**



Brownish viscous oil, m = 139 mg (58%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.42 (s, 2H, C^2H_2), 3.86 (s, 2H, C^3H_2), 5.29 (br. s., 1H, NH), 6.57 (s, 1H, C^6H), 7.37-7.52 (m, 5H, Ph). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 48.7, 56.0 (C^2, C^3), 87.5 (C^6), 121.3 (q, J = 279.8 Hz, CF_3), 127.4, 129.0, 130.7, 138.0 (Ph), 156.6 (q, J = 31.0 Hz, C^5), 158.7

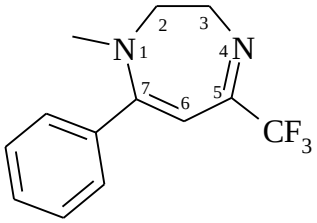
(C^7).^{19}F NMR (376.5 MHz, $CDCl_3$): δ -71.3. MS (EI) *m/z* (relative intensity): m/z (%):240 (100, M^+), 212 (33), 192 (26), 172 (26), 143 (50), 115(31). HRMS (ESI): m/z calcd for $C_{12}H_{11}F_3N_2Na^+$ [M+Na^+]: 263.0767; found: 263.0774.

7-(4-tert-Butylphenyl)-5-trifluoromethyl-2,3-dihydro-1H-[1,4]diazepine **(2b)**



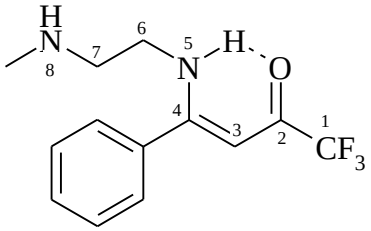
Light yellow solid, m = 55 mg (37%), mp 178-179 °C. IR (KBr, cm^{-1}): *v* 1185 (C-F), 1531, 1567, 1613 (Ph, C=C, C=N). ^{1}H NMR (400 MHz, acetone-d_6): δ 2.81 (s, 9H, *t*-Bu), 4.28 (br. s., 2H, C^2H_2), 4.75 (br. s., 2H, C^3H_2), 5.98 (s, 1H, C^6H), 8.00-8.35 (m, 4H, Ar). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 30.9 ((CH_3)$_3$), 34.5 (C, *t*-Bu), 47.8, 56.1 (C^2, C^3), 84.5 (C^6), 121.4 (q, *J* = 279.3 Hz, CF_3), 125.4, 127.1, 134.7, 153.0 (Ar), 154.8 (q, *J* = 26.7 Hz, C^5), 157.8 (C^7). Anal. Calcd for $C_{16}H_{19}F_3N_2$: C 64.85, H 6.46, N 9.45. Found: C 64.64; H 6.33; N 9.27.

1-Methyl-7-phenyl-5-trifluoromethyl-2,3-dihydro-1H-[1,4]diazepine **(3)**



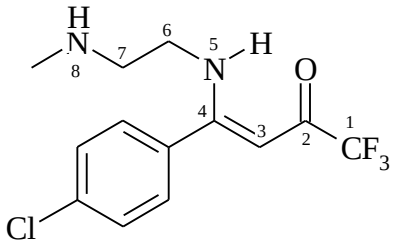
Light yellow oil, m = 85 mg (33%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.75 (s, 3H, Me), 3.20 (br. s., 2H, C^3H_2), 3.98 (br. s., 2H, C^2H_2), 5.22 (s, 1H, C^6H), 7.30-7.45 (m, 5H, Ph). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 43.8 (NCH_3), 55.5, 56.2 (C^2, C^3), 92.1 (C^6), 121.5 (q, *J* = 279.1 Hz, CF_3), 128.6, 128.9, 129.9, 138.5 (Ph), 155.6 (q, *J* = 30.3 Hz, C^5), 161.1 (C^7). Anal. Calcd for $C_{13}H_{13}F_3N_2$: C 61.41; H 5.15; N 11.02. Found: C 61.27; H 4.85; N 10.44.

1,1,1-Trifluoro-4-(2methylamino-ethylamino)-4-phenylbut-3-en-2-one **(4a)**



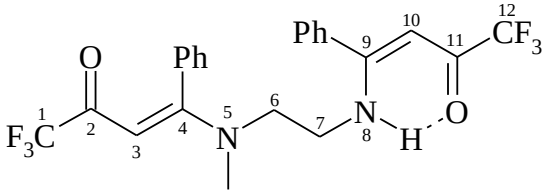
Brown oil, m = 75 mg (28%). IR (cm^{-1}): *v* 1096, 1137, 1190 (C-F), 1585, 1609, 1659 (Ph, C=C, C=O). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.15 (br. s., 1H, NH), 2.38 (s, 3H, NCH_3); 2.74 (m, 2H, C^6H_2), 3.34 (m, 2H, C^7H_2); 5.39 (s, 1H, C^3H); 7.25-7.55 (m, 5H, Ph), 11.26 (br. s., 1H, NH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 36.0 (NCH_3); 44.9, 51.0 (C^6, C^7); 90.3 (C^3), 117.8 (q, *J* = 287.9 Hz, CF_3); 127.5, 128.9, 130.5, 134.1 (Ph); 170.7 (C^4); 176.1 (q, *J* = 33.0 Hz, C^2). Anal. Calcd for $C_{13}H_{15}F_3N_2O \cdot 0.5\ H_2O$: C 55.51; H 5.73; N 9.96. Found: C 55.39; H 5.44; N 9.83.

4-(4-Chlorophenyl)-1,1,1-trifluoro-4-(2-methylamino-ethylamino)-but-3-en-2-one **(4b)**



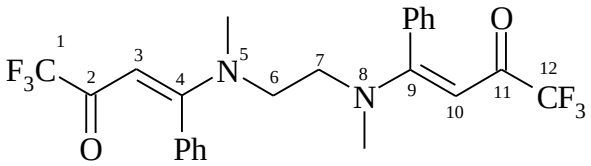
Oil, m = 267 mg (87%). IR (cm^{-1}): *v* 1090, 1138, 1190 (C-F), 1583, 1602, 1662 (Ph, C=C, C=O). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.07 (br. s., 1H, NH), 2.35 (s, 3H, NCH_3); 2.71 (m, 2H, C^6H_2), 3.30 (m, 2H, C^7H_2); 5.33 (s, 1H, C^3H); 7.29 (d, *J* = 8.6 Hz, 2H, CH_{Ar}), 7.39 (d, *J* = 8.6 Hz, 2H, CH_{Ar}), 11.17 (br. s., 1H, NH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 36.0 (NCH_3); 45.0, 51.0 (C^6, C^7); 90.2 (C^3), 117.6 (q, *J* = 288.8 Hz, CF_3); 129.0, 129.2, 132.5, 136.7 (Ph); 169.2 (C^4); 176.3 (q, *J* = 32.8 Hz, C^2). Anal. Calcd for $C_{13}H_{14}ClF_3N_2O$: C 50.91; H 4.60; N 9.13. Found: C 51.24; H 4.79; N 8.81.

1,1,1,12,12,12-Hexafluoro-5-methyl-4,9-diphenyl-5,8-diazadodeca-3,9-diene-2,11-dione **(5)**



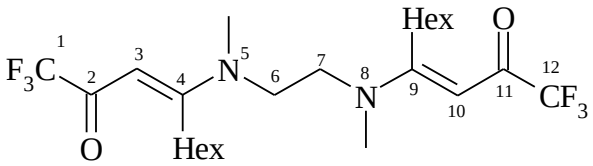
White solid, m = 34 mg (15%). IR (KBr, cm^{-1}): *v* 1175, 1188 (C-F), 1524, 1615, 1656 (C=O, C=C, Ph). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.88 (s, 3H, NCH_3); 3.36 (br. s., 4H, $C^{6}H_2$, $C^{7}H_2$); 5.28, 5.46 (2s, 2H, $C^{3}H$, $C^{10}H$); 6.65-7.60 (m, 10H, 2Ph), 10.97 (br. s., 1H, NH). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -76.7. ^{15}N NMR (40.6 MHz, $CDCl_3$): δ -267.1. Anal. Calcd for $C_{23}H_{20}F_6N_2O_2$: C 58.73; H 4.29; N 5.95. Found: C 59.03; H 4.12; N 5.97. MS (EI) *m/z* (relative intensity): m/z (%): 471 (M^++1, 1), 253 (54), 242 (34), 184 (100), 146 (40).

1,1,1,12,12,12-Hexafluoro-5,8-dimethyl-4,9-diphenyl-5,8-diazadodeca-3,9-diene-2,11-dione **(6a)**



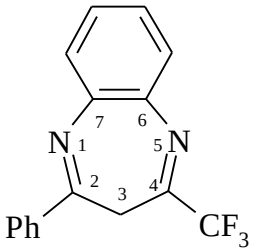
White solid, m = 163 mg (67%), mp 212 °C. IR (cm^{-1}): *v* 1131, 1151, 1177 (C-F), 1524 (C=C), 1605 (Ph), 1657 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.74 (br. s, 6H, NCH_3); 3.16 (br. s, 4H, $C^{6}H_2$, $C^{7}H_2$); 5.30 (br. s, 2H, $C^{3}H$, $C^{10}H$); 6.90-7.50 (m, 10H, Ph). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 38.5 (C^{13}, C^{14}); 50.8 (C^{6}, C^{7}); 88.9 (C^{3}, C^{10}), 117.6 (q, *J* = 293 Hz, $(CF_3)_2$); 127.4, 129.4, 129.8, 134.6 (2Ph); 167.3 (C^{4}, C^{9}); 175.6 (q, *J* = 31 Hz, C^{2}, C^{11}). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -75.1. ^{15}N NMR (40.6 MHz, $CDCl_3$): δ -267.1. Anal. Calcd for $C_{24}H_{22}F_6N_2O_2$: C 59.50; H 4.58; N 5.78; F 23.53. Found: C 59.40; H 4.48; N 5.85; F 23.67. MS (EI) *m/z* (relative intensity): m/z (%): 242 (100, M^+/2), 172 (17), 158 (71), 149 (36).

1,1,1,12,12,12-Hexafluoro-4,9-dihexyl-5,8-dimethyl-5,8-diazadodeca-3,9-diene-2,11-dione **(6b)**



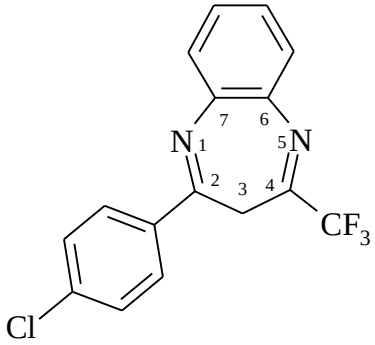
Colorless oil, m = 197 mg (79%). IR (CCl_4, cm^{-1}): *v* 1104, 1137, 1191 (C-F), 1543 (C=C), 1667 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.82 (s, 6H, CH_3), 1.15-1.55 (m, 10H, CH_2, Hex), 2.70-3.25 (m, 6H, NCH_3); 3.40-3.75 (m, 4H, $C^{6}H_2$, $C^{7}H_2$); 5.15 (br. s, 2H, $C^{3}H$, $C^{10}H$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 14.0 ($(CH_3)_2$), 22.6, 27.4, 28.2, 29.6, 30.2, 31.4 ($(CH_2)_{10}$), 39.3 (C^{13}, C^{14}); 50.3 (C^{6}, C^{7}); 86.8 (C^{3}, C^{10}); 117.9 (q, *J* = 292.8 Hz, $(CF_3)_2$); 171.8 (C^{4}, C^{9}); 175.3 (q, *J* = 28.0 Hz, C^{2}, C^{11}). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -76.8. NMR (40.6 MHz, $CDCl_3$): δ -255.1. Anal. Calcd for $C_{24}H_{38}F_6N_2O_2$: C 57.59; H 7.65; N 5.60. Found: C 57.62; H 7.28; N 5.94. MS (EI) *m/z* (relative intensity): m/z (%):261 (30), 250 (100, M^+/2), 192 (44), 190 (55).

2-Phenyl-4-trifluoromethyl-3H-benzo[b][1,4]diazepine **(7a)**



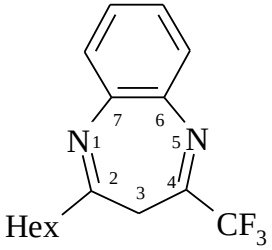
Light yellow solid, m = 182 mg (63%), mp 75-76 °C. IR (KBr, cm^{-1}): *v* 1170, 1183, 1194 (C-F), 1590 (Ar), 1611 (Ph), 1640 (C=N). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.47 (br. s., 2H, $C^{3}H_2$), 7.3-8.08 (m, 9H, Ar). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 32.2 (C^{3}), 121.9 (q, *J* = 266.0 Hz, CF_3), 126.1, 127.9, 128.8, 129.0, 131.5, 136.2, 137.3 (Ar), 144.7 (q, *J* = 35.5 Hz, C^{4}), 153.7 (C^{2}). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -70.9. ^{15}N NMR (40.6 MHz, $CDCl_3$): δ -69.2, -54.6. Anal. Calcd for $C_{16}H_{11}F_3N_2$: C 66.67; H 3.85; N 9.72. Found: C 66.20; H 4.14; N 9.57. MS (EI) *m/z* (relative intensity): m/z (%): 288 (100, M^+), 219 (78), 89 (10).

2-(4-Chloro-phenyl)-4-trifluoromethyl-3H-benzo[b][1,4]diazepine **(7b)**



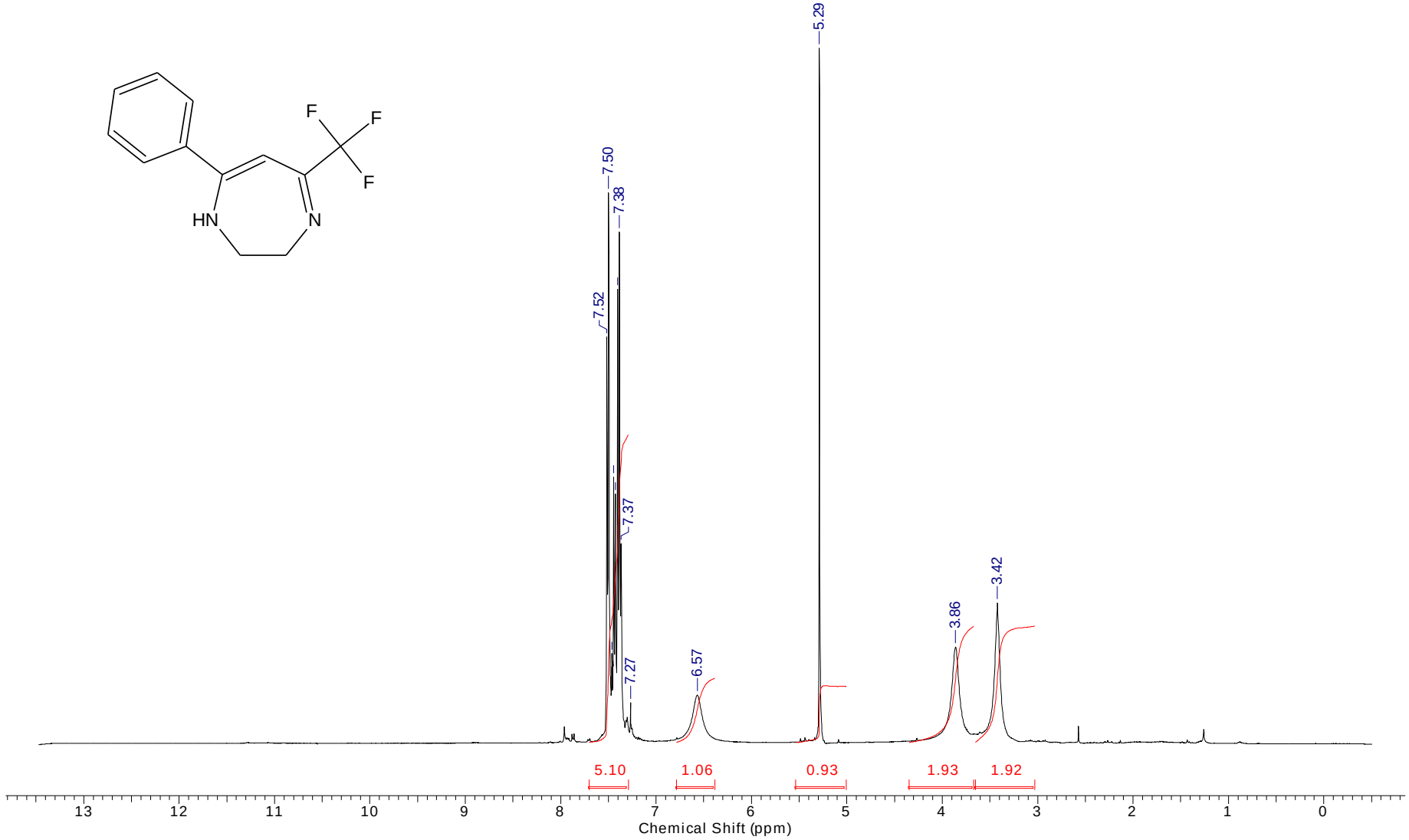
Light yellow solid, m = 232 mg (72%). IR (KBr, cm^{-1}): *v* 1117, 1141 (C-F), 1565 (C=C, $C=N^{1}$), 1586, 1609 ($Cl\text{-}C_6H_4$), 1644 ($C=N^{5}$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.41 (br. s., 2H, $C^{3}H_2$), 7.25-7.70 (m, 6H, Ar), 7.90-8.10 (m, 2H, Ar). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 32.0 (C^{3}), 119.2 (q, *J* = 277 Hz, CF_3), 126.3, 128.0, 129.1, 129.3, 130.0, 134.6, 137.3, 137.9, 141.2 (Ar), 144.4 (q, *J* = 35.5 Hz, C^{2}), 152.2 (C^{4}). Anal. Calcd for $C_{16}H_{10}ClF_3N_2$: C 59.55; H 3.12; N 8.68. Found: C 59.39; H 3.08; N 8.46. MS (EI) *m/z* (relative intensity): m/z (%):322 (49, M^+), 239 (100).

***2-Hexyl-4-trifluoromethyl-3H-benzo[b][1,4]diazepine* (7c)**



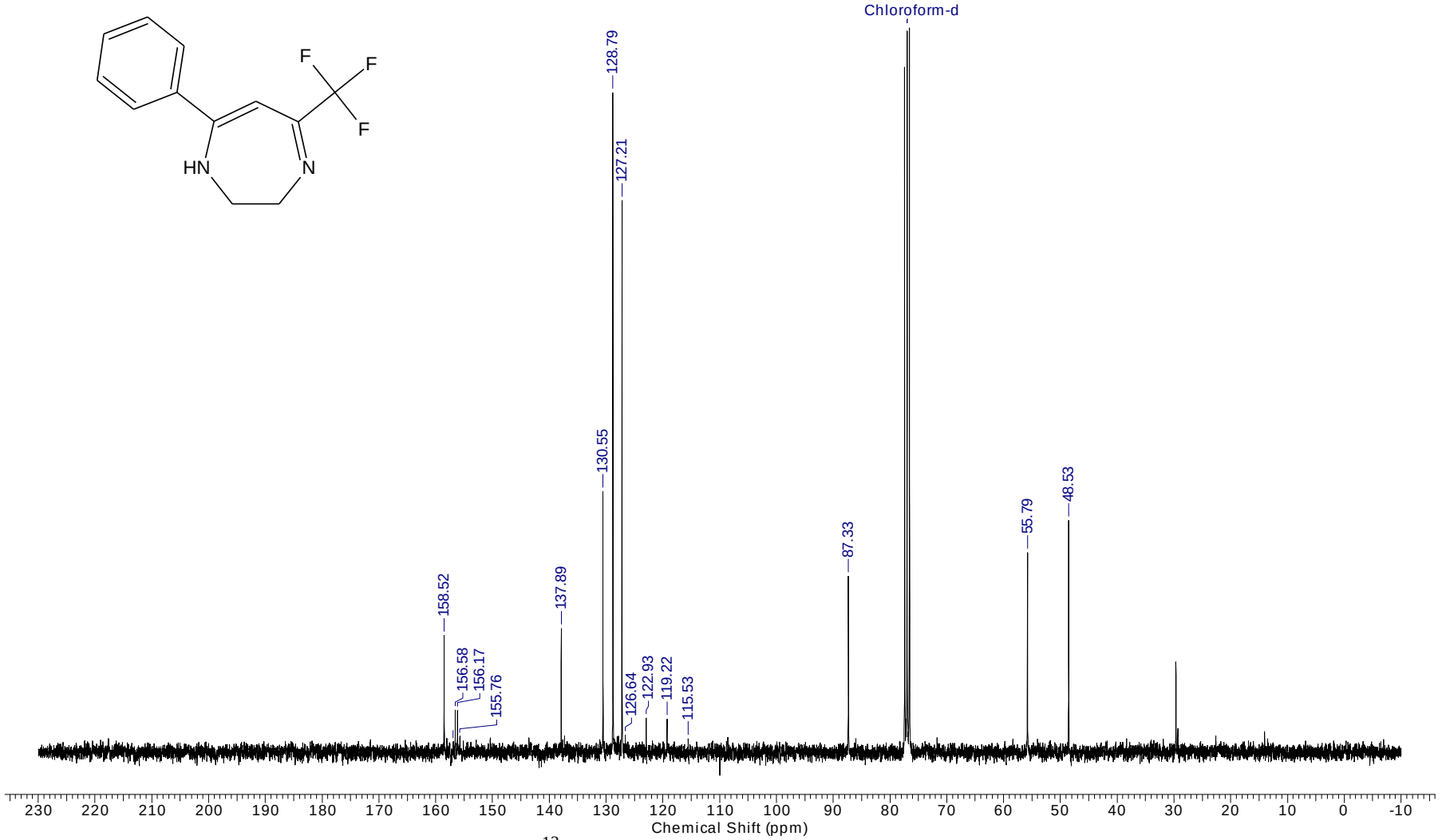
Yellow oil, m = 100 mg (34%). IR (film, cm^{-1}) *v* 1116, 1130, 1143 (C-F), 1598 (Ar), 1640 (C=N). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (t, 3H, CH_3); 1.20-1.45 (m, 6H, CH_2); 1.76 (m, 2H, CH_2); 2.61 (m, 2H, CH_2); 2.96 (br. s., 2H, C^3H_2); 7.31, 7.38, 7.45, 7.53 (m, 4H, Ar). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 14.2 (CH_3); 22.7, 26.2, 29.0, 31.7, 40.4 ((CH_2)$_5$); 35.7 (C^3H_2); 119.2 (q, *J* = 276.8 Hz, CF_3); 125.6, 127.6, 128.3, 129.1, 137.2, 141.2 (Ar); 144.3 (q, *J* = 35.7 Hz, C^4); 161.3 (C^2). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -70.9. ^{15}N NMR (40.6 MHz, $CDCl_3$): δ -71.0, -56.4. Anal. Calcd for $C_{16}H_{19}F_3N_2$: C 64.85; H 6.46; N 9.45. Found: C 64.71; H 6.11; N 9.04. MS (EI) *m/z* (relative intensity): m/z (%):296 (2, M^+), 239 (19), 226 (100).

Acquisition Time (sec)	2.9295	***Comment***	Imported from UXNMR.			***Date***	08 Nov 2011 14:35:46
File Name	D:\BN\output\2011\ноябрь\BM-157.H_001001r			***Frequency (MHz)***	400.13	***Nucleus***	1H
Original Points Count	16384	***Points Count***	65536	***Pulse Sequence***	zg30	***Solvent***	CHLOROFORM-D
Sweep Width (Hz)	5592.84	***Temperature (degree C)***	21.760				



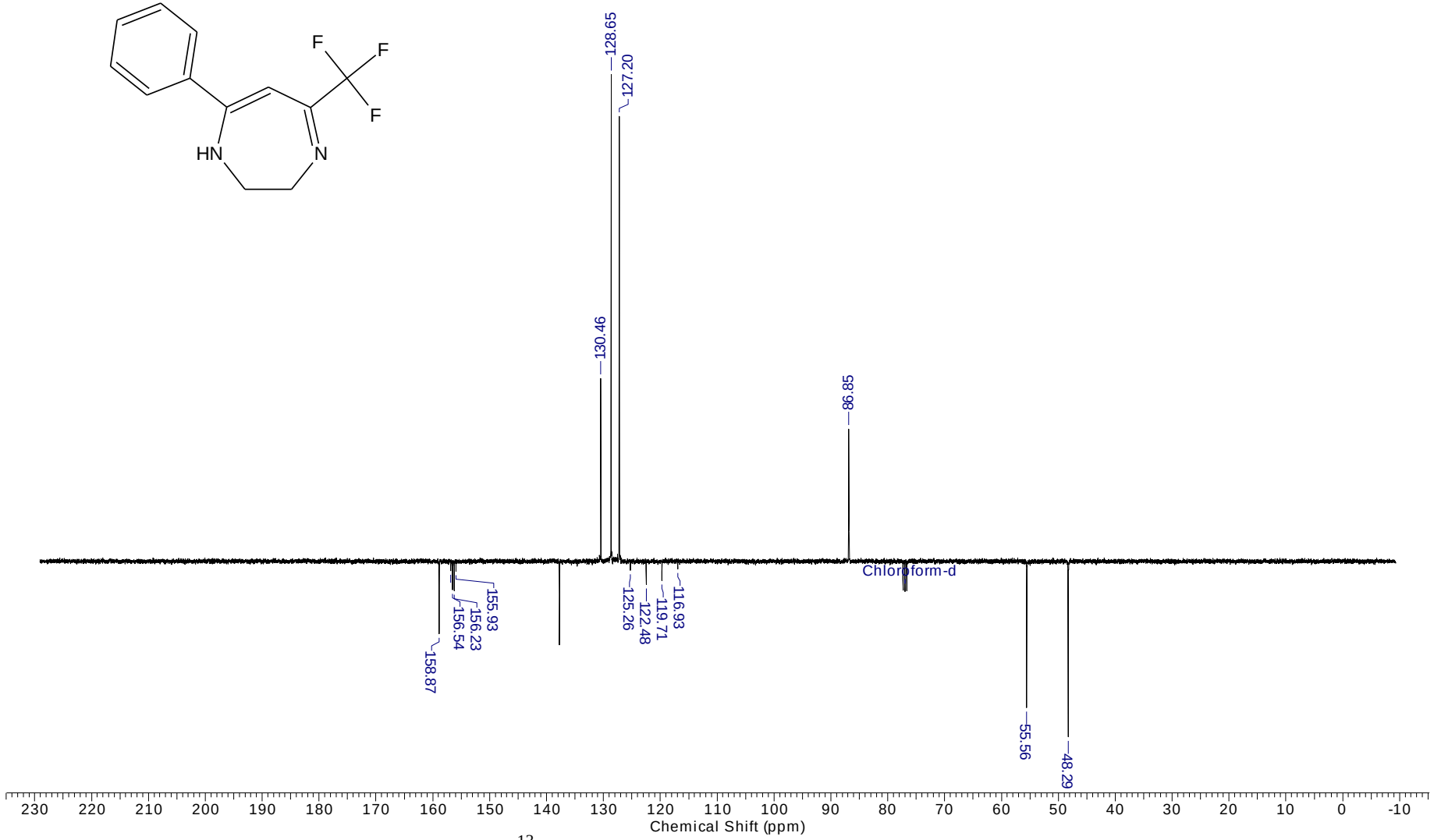
^{1}H NMR spectrum of diazepine **2a**

Acquisition Time (sec)	0.9002	***Comment***	Avance-300, C-13, CDCl3			***Date***	20 Jul 2011 15:17:20
File Name	D:\BN\output\2011\лето\19.07.11\BM-125.{13C}\50541664.{13C}\50541664.{13C}_013000fid					***Frequency (MHz)***	75.48
Nucleus	13C	***Number of Transients***	497	***Original Points Count***	16308	***Points Count***	16384
Pulse Sequence	zgpg30base	***Solvent***	CHLOROFORM-D	***Sweep Width (Hz)***	18115.94	***Temperature (degree C)***	28.300



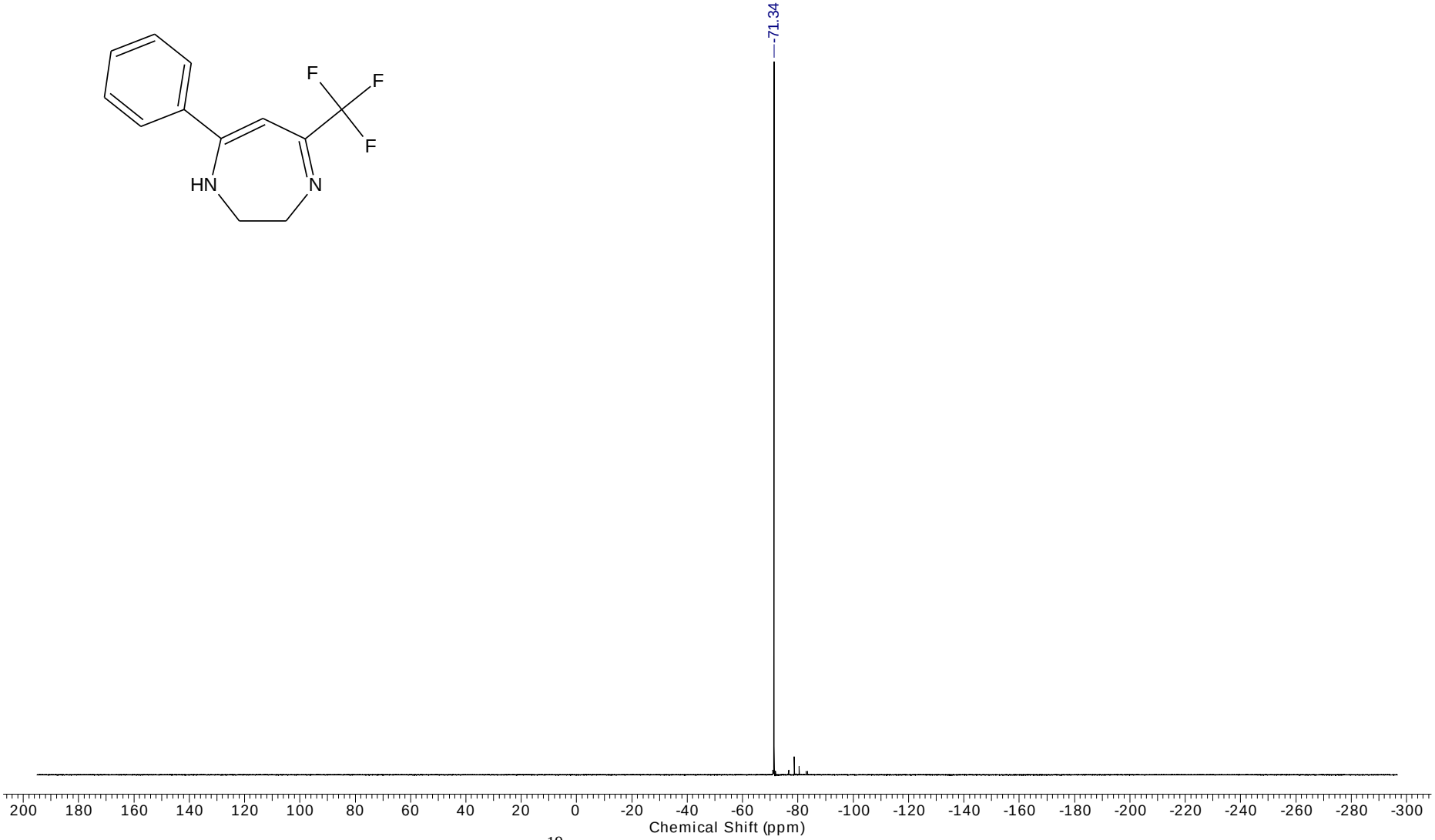
^{13}C NMR spectrum of diazepine **2a**

Acquisition Time (sec)	1.3664	***Comment***	Imported from UXNMR.			***Date***	08 Nov 2011 14:47:28
File Name	D:\BN\output\2011\ноябрь\BM-157.C_004001r			***Frequency (MHz)***	100.61	***Nucleus***	13C	***Number of Transients***	104
Original Points Count	32768	***Points Count***	65536	***Pulse Sequence***	jmod	***Solvent***	CHLOROFORM-D		
Sweep Width (Hz)	23980.81	***Temperature (degree C)***	21.960						

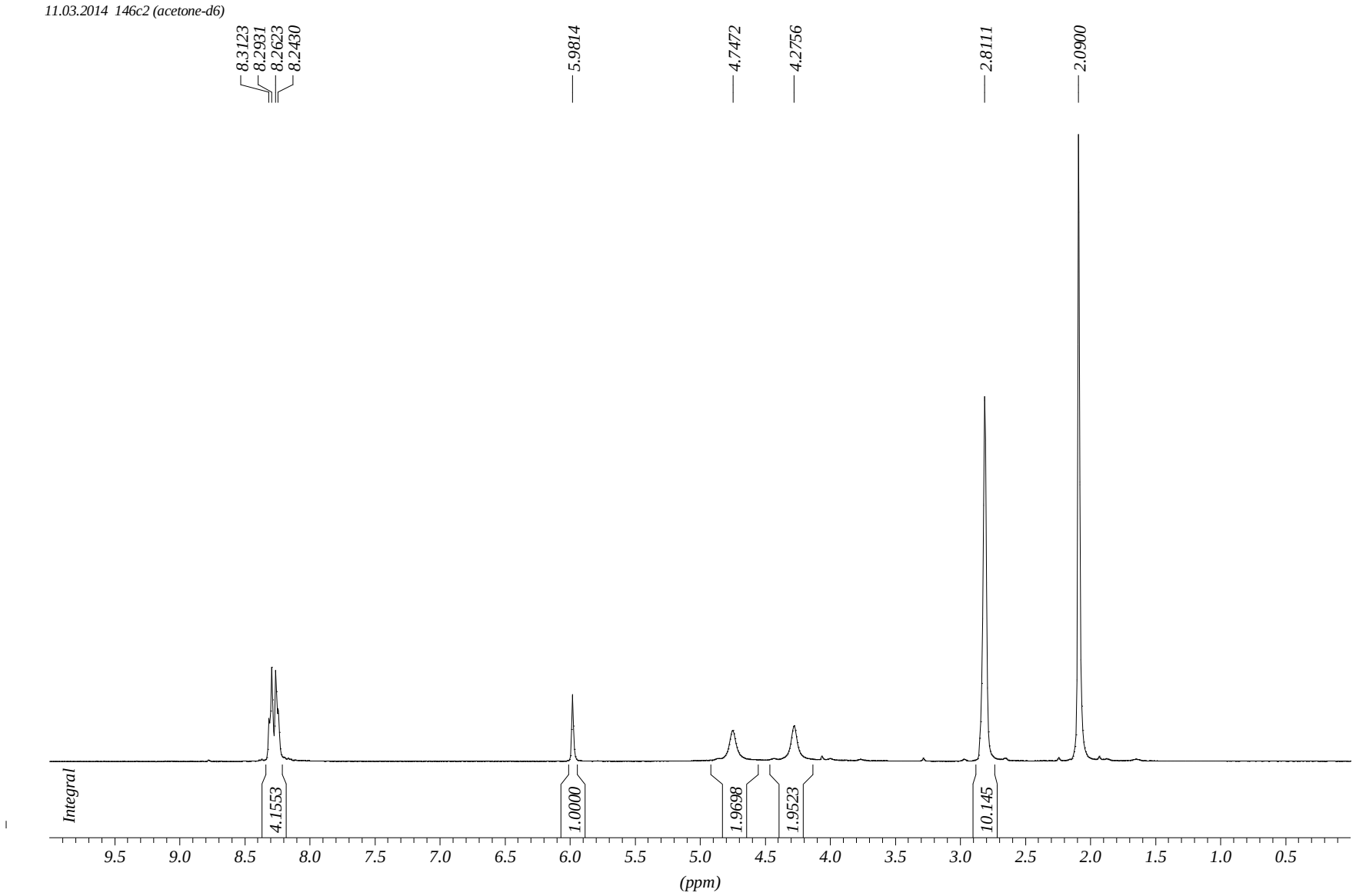


^{13}C APT NMR spectrum of diazepine **2a**

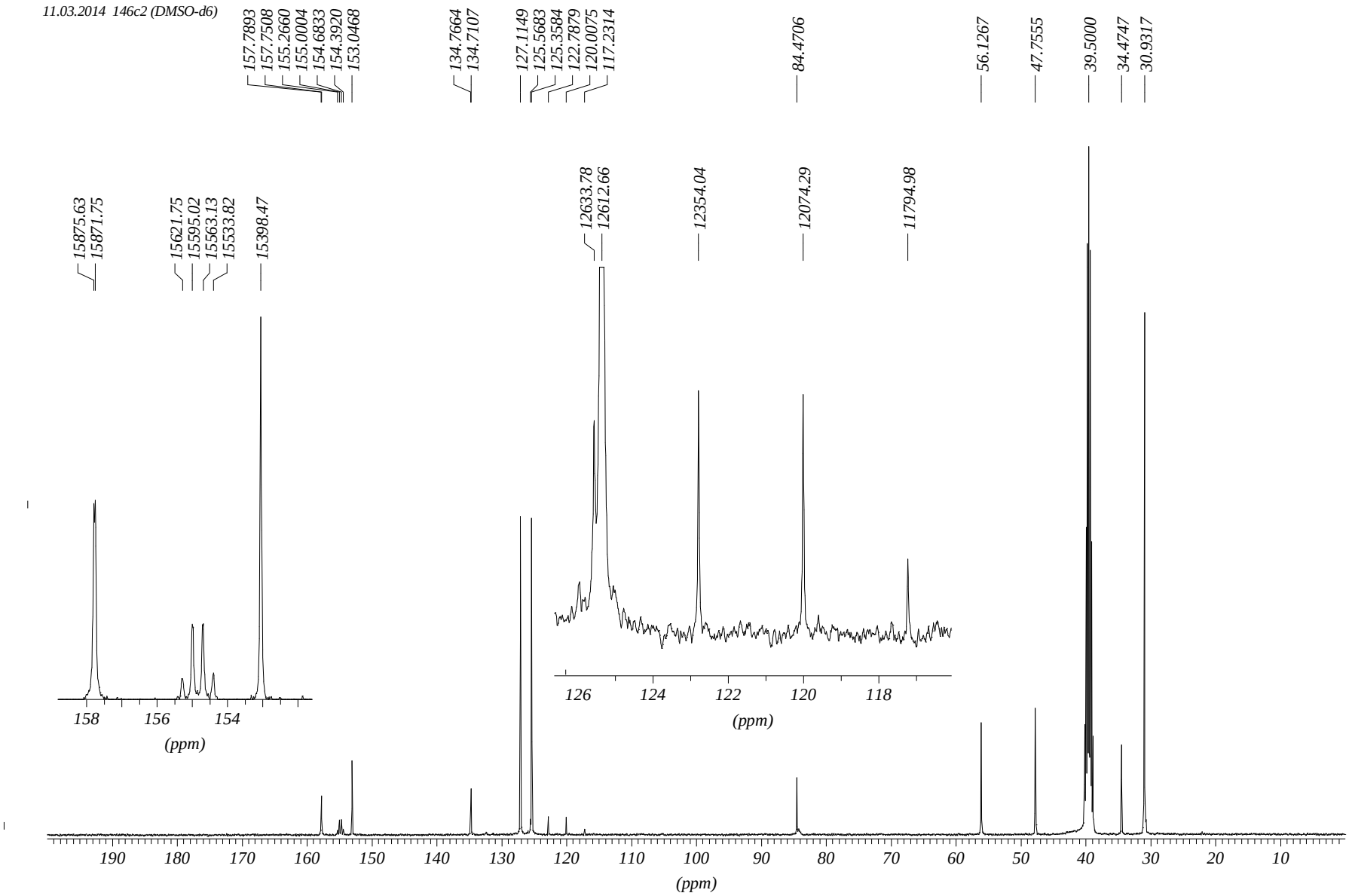
Acquisition Time (sec)	0.2449	***Comment***	19F with CPD	***Date***	14 Jul 2011 13:43:28		
File Name	D:\BN\output\2011\nero\14.07.11\BM-125{19F}\50541523.{19F}\50541523.{19F}_019000fid					***Frequency (MHz)***	282.39
Nucleus	19F	***Number of Transients***	1	***Original Points Count***	34018	***Points Count***	65536
Pulse Sequence	zg	***Solvent***	CHLOROFORM-D			***Sweep Width (Hz)***	138888.89
Temperature (degree C)	27.400						



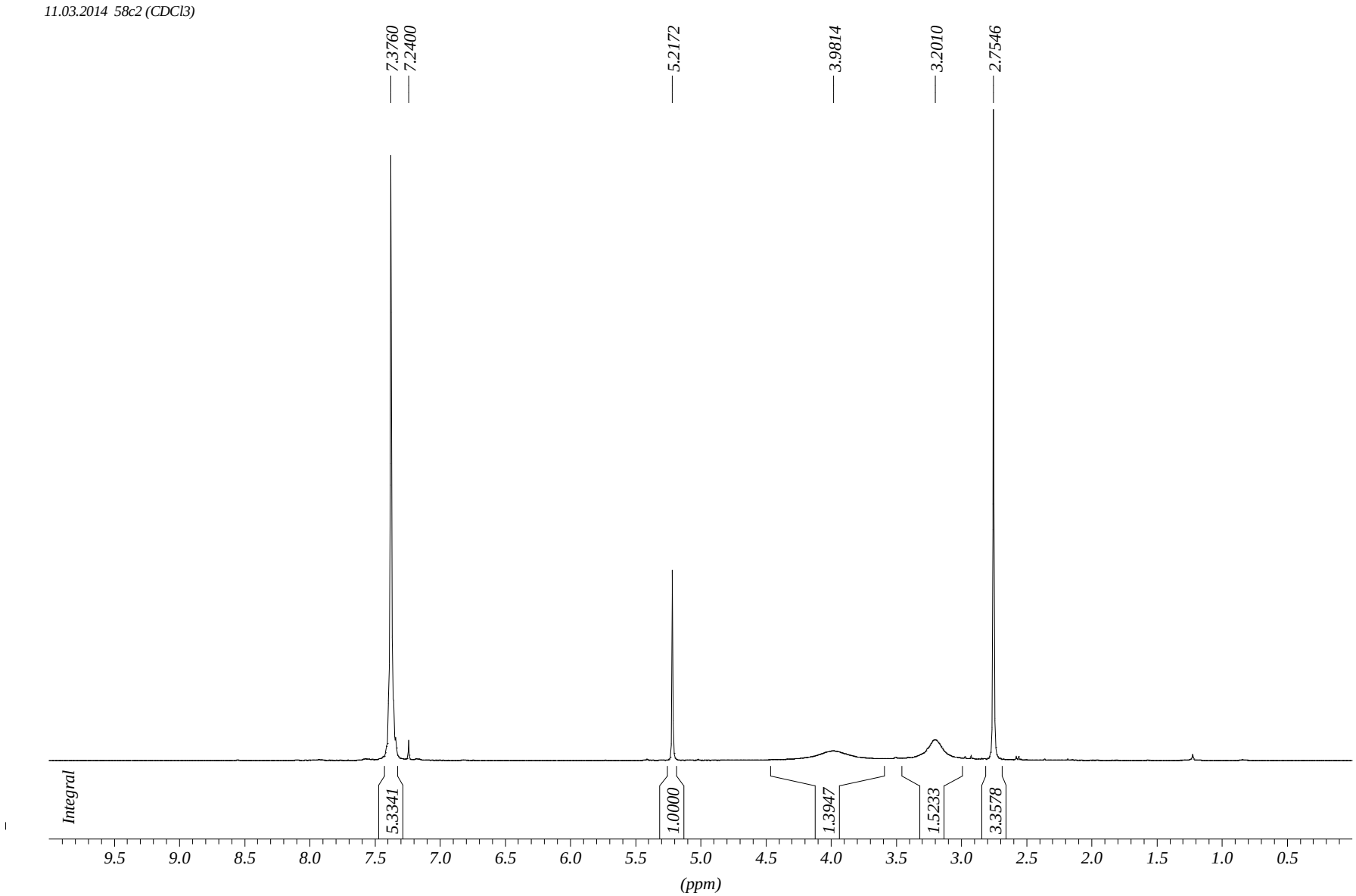
^{19}F NMR spectrum of diazepine **2a**



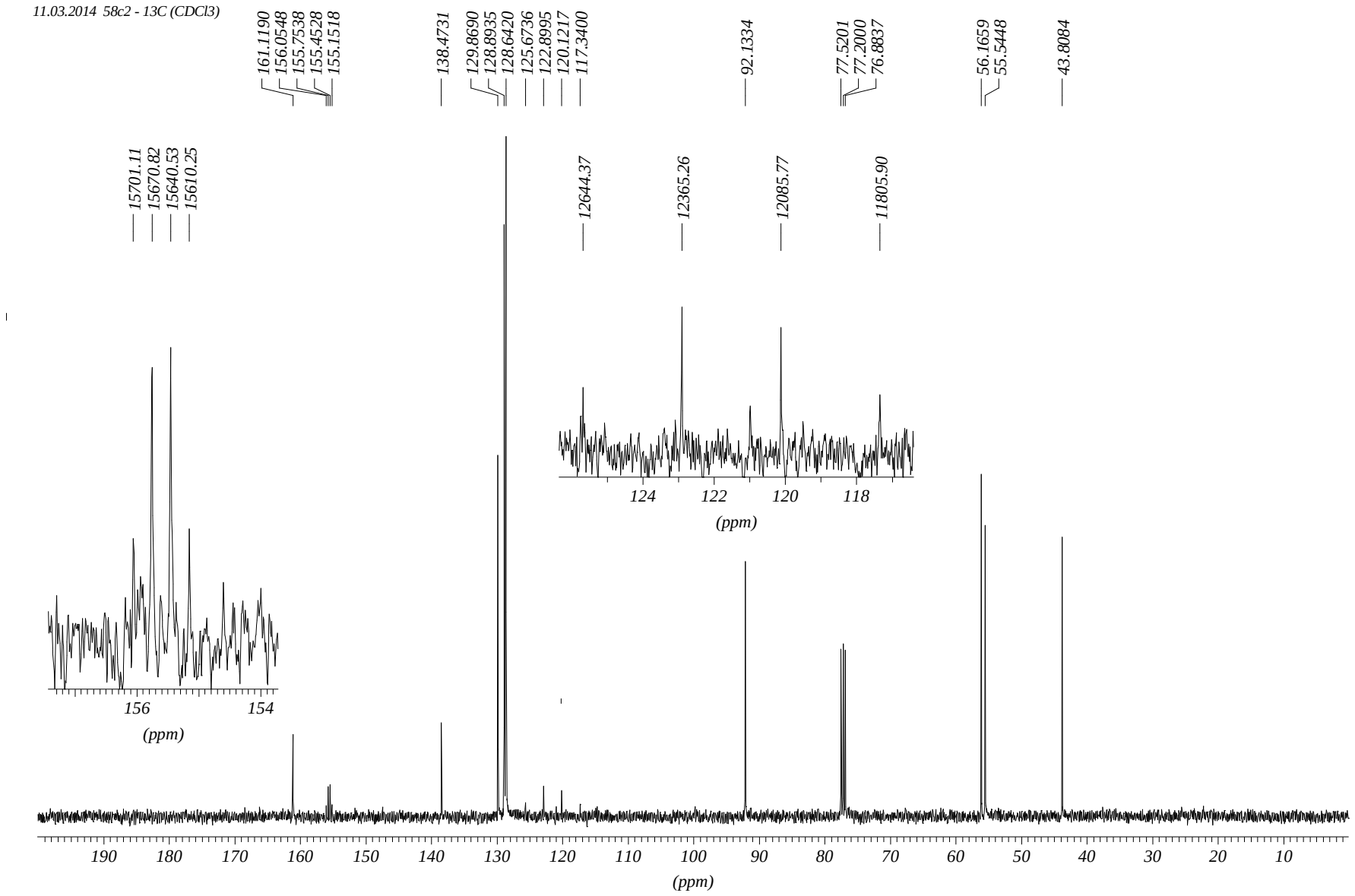
^{1}H NMR spectrum of diazepine **2b**



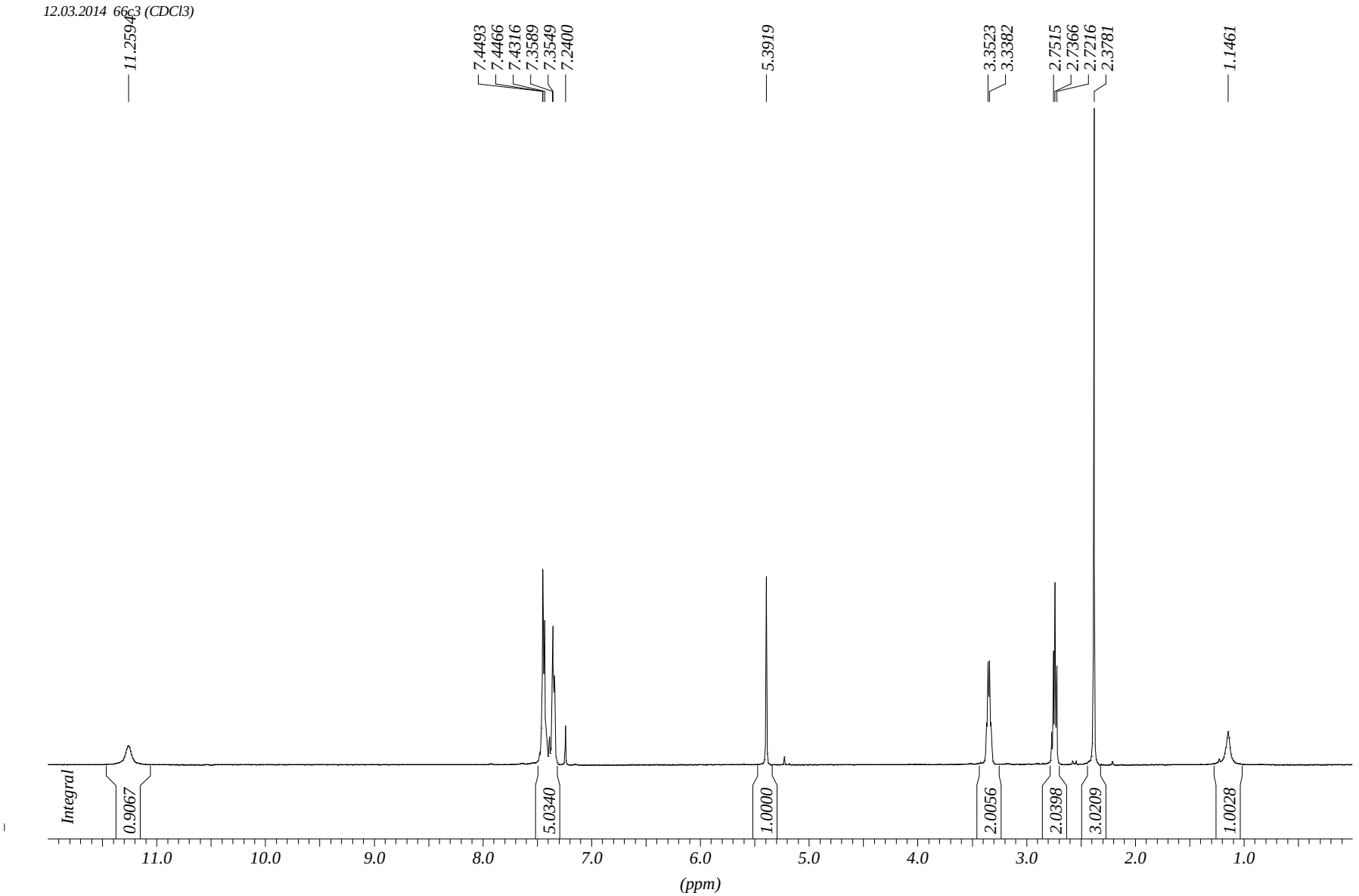
^{13}C NMR spectrum of diazepine **2b**



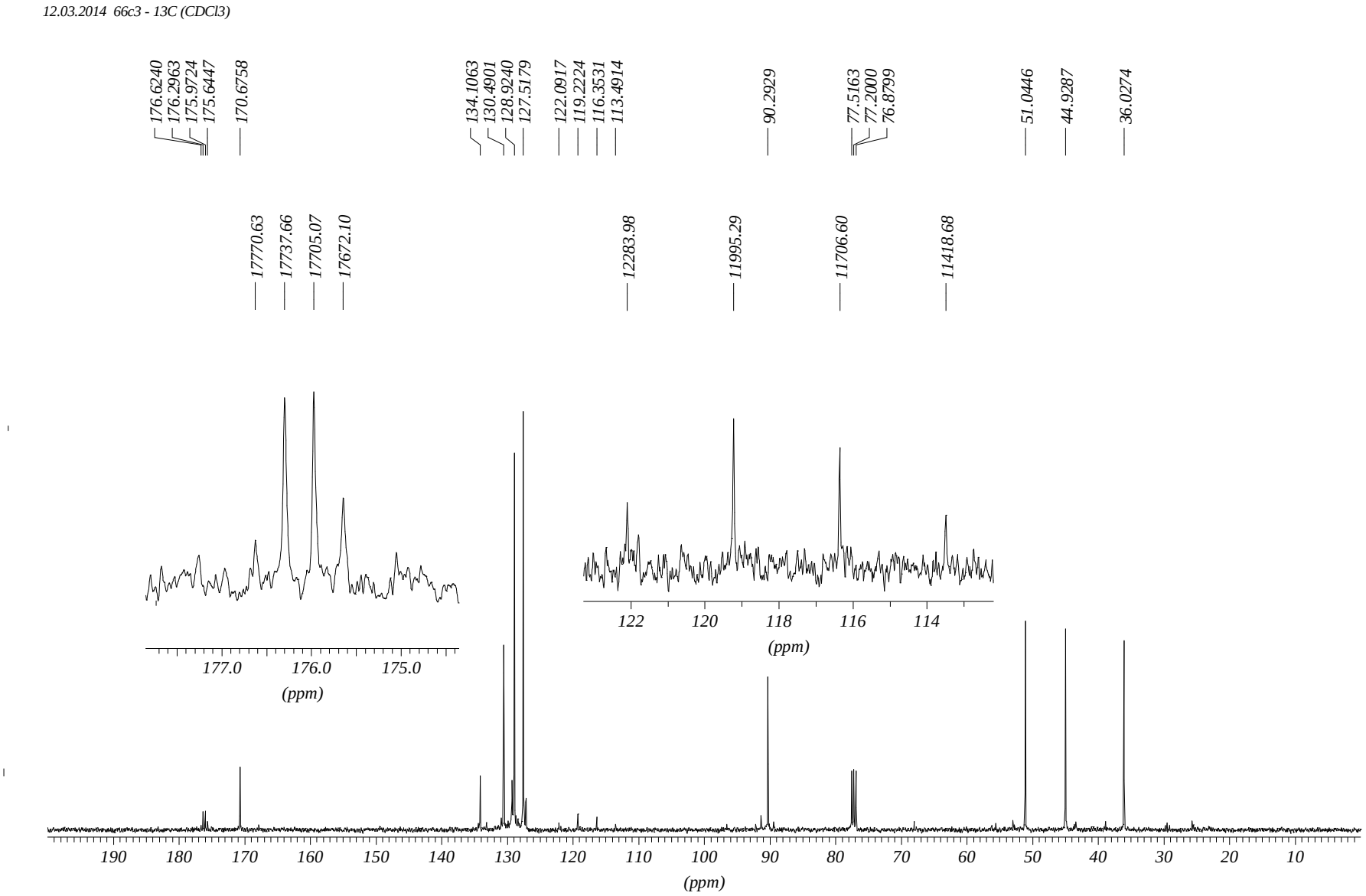
^{1}H NMR spectrum of diazepine **3**



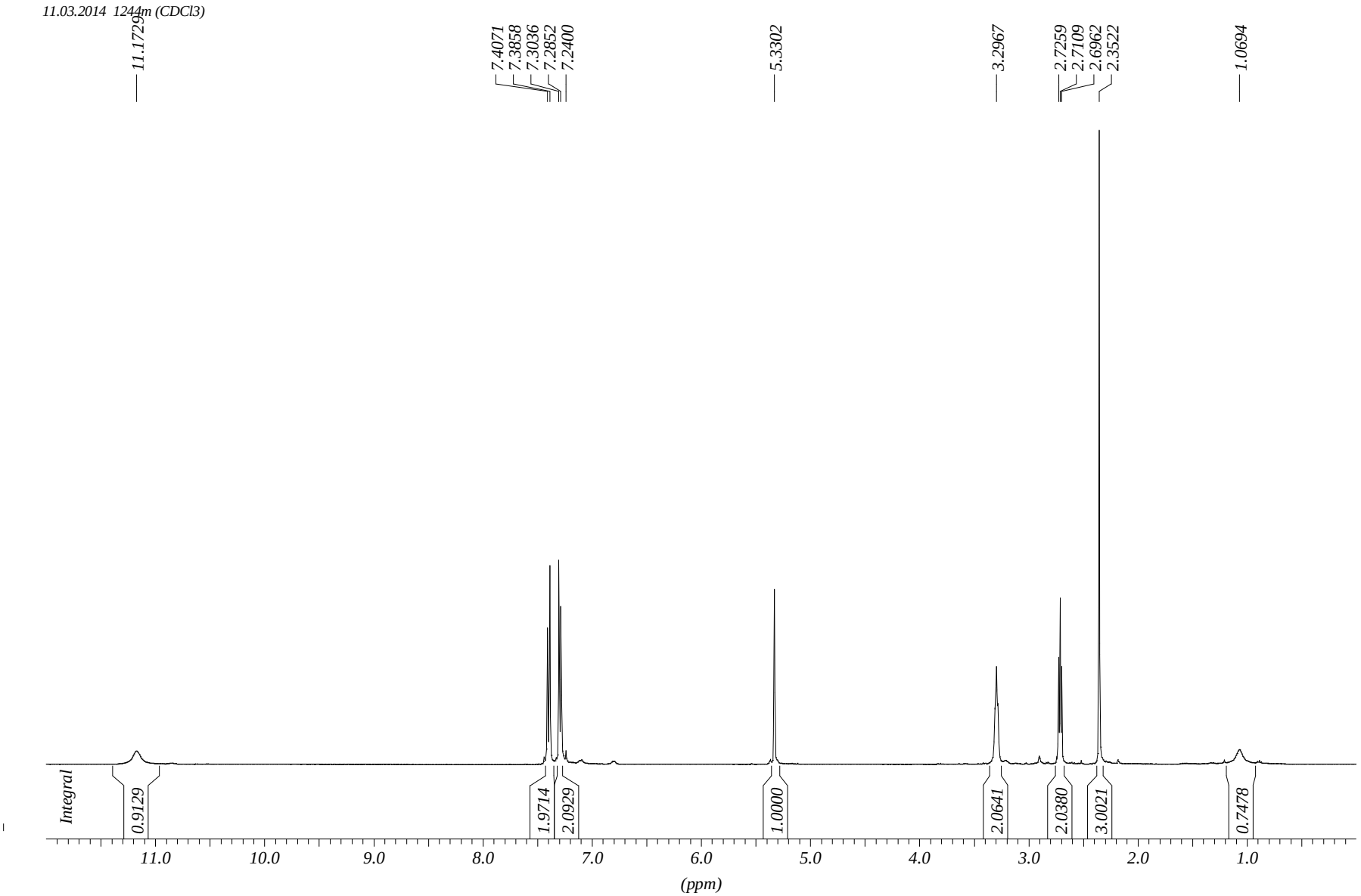
^{13}C NMR spectrum of diazepine **3**



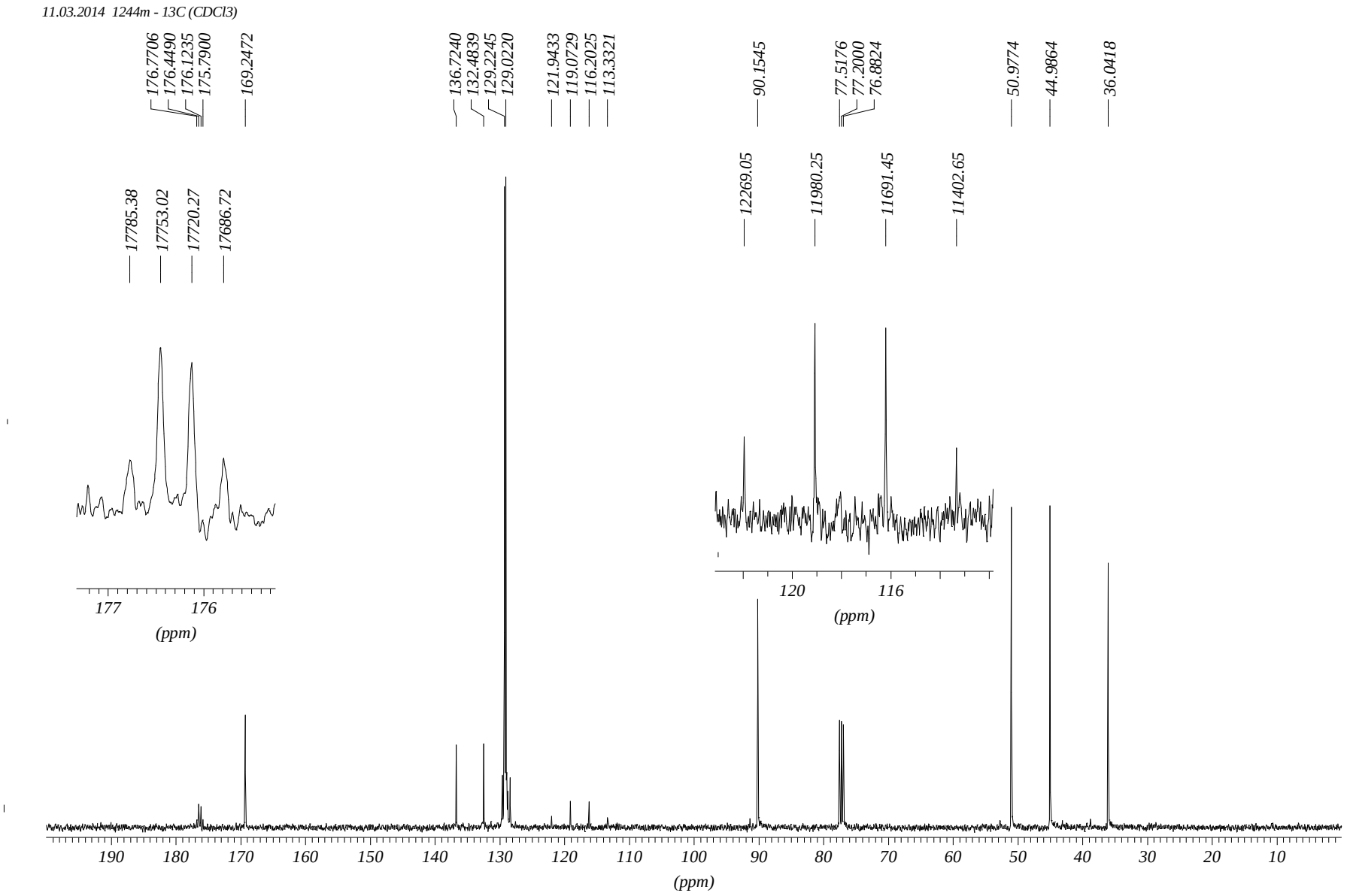
^{1}H NMR spectrum of aminoenone **4a**



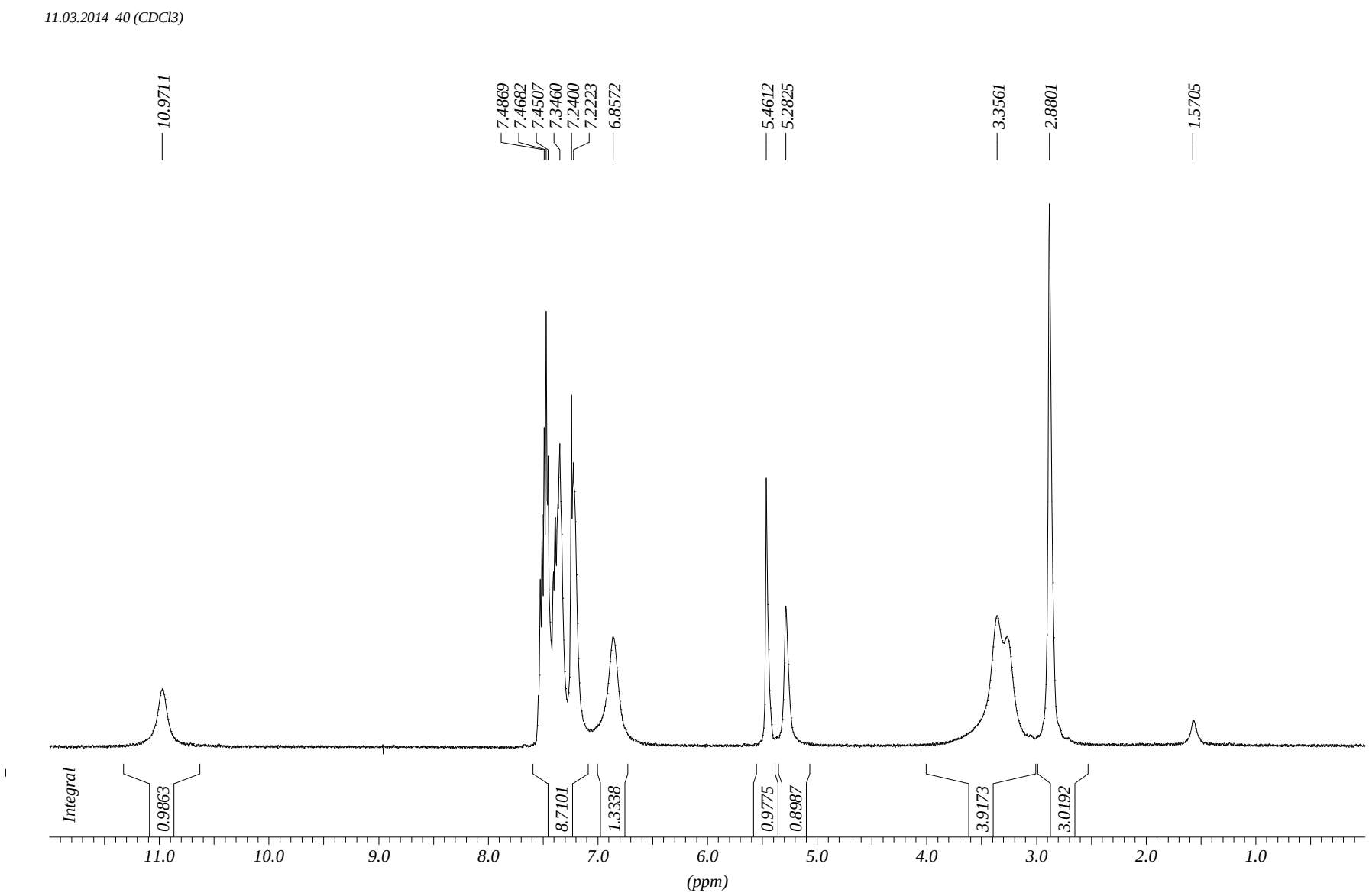
^{13}C NMR spectrum of aminoenone **4a**



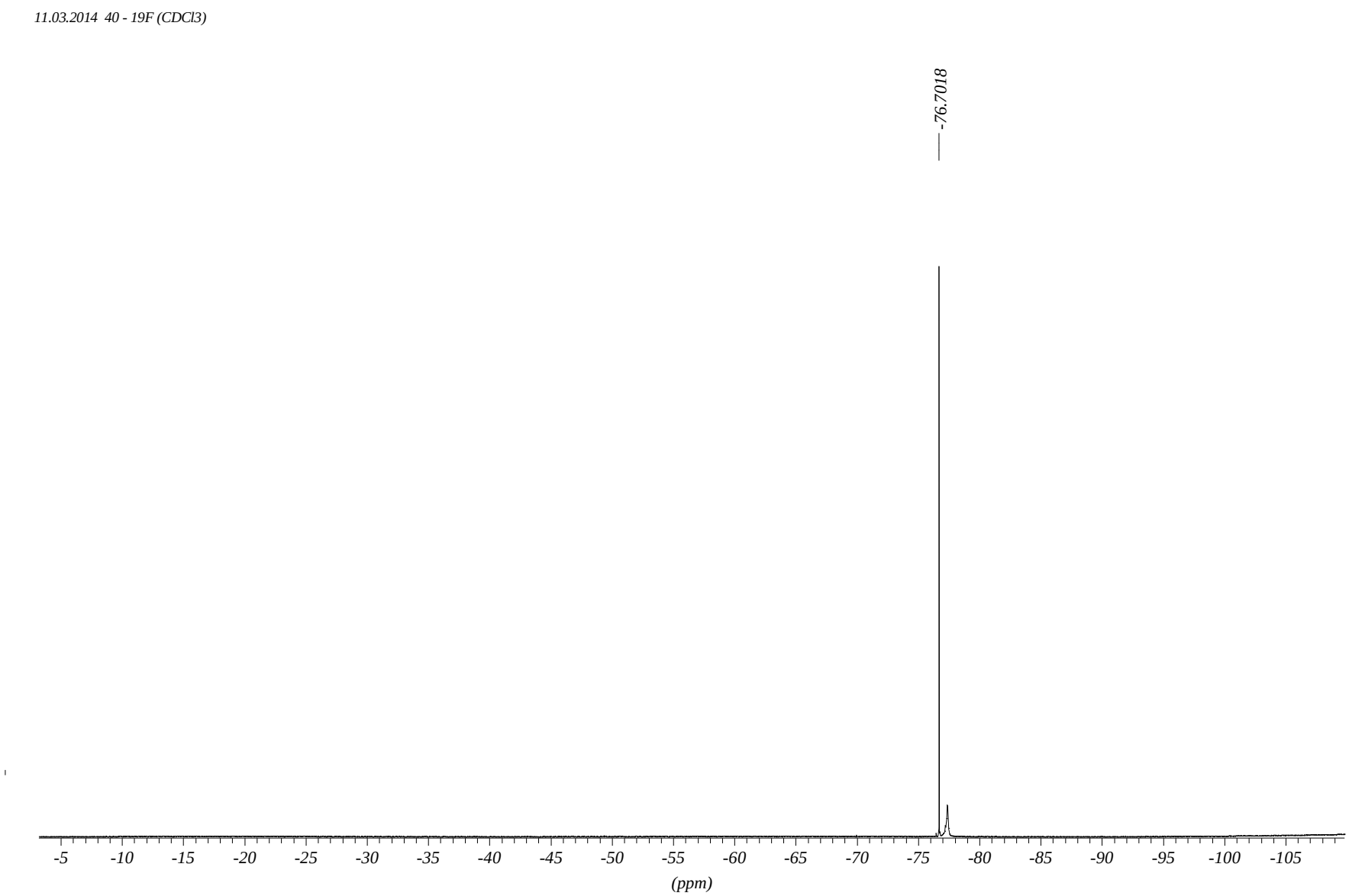
^{1}H NMR spectrum of aminoenone **4b**



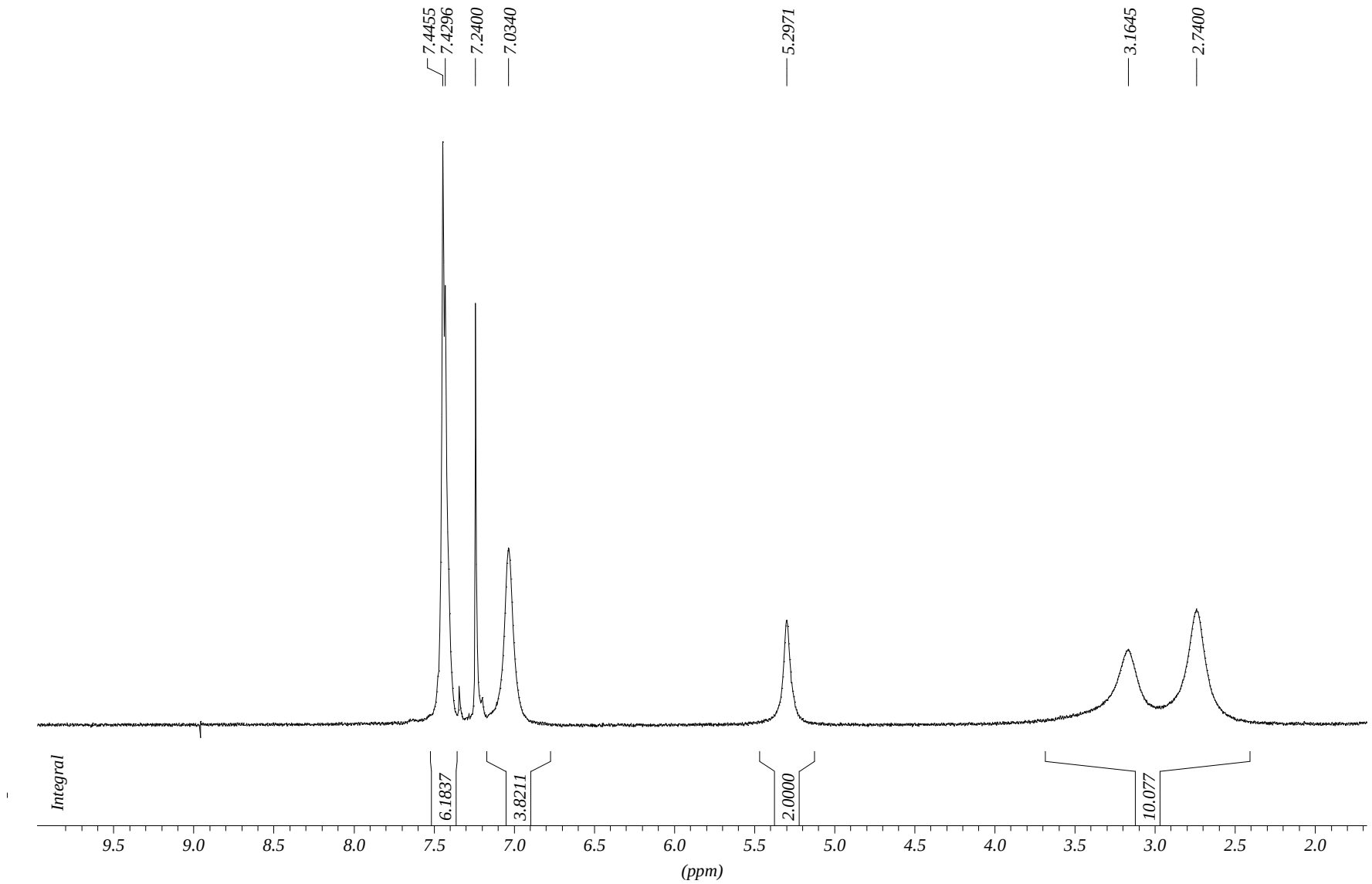
^{13}C NMR spectrum of aminoenone **4b**



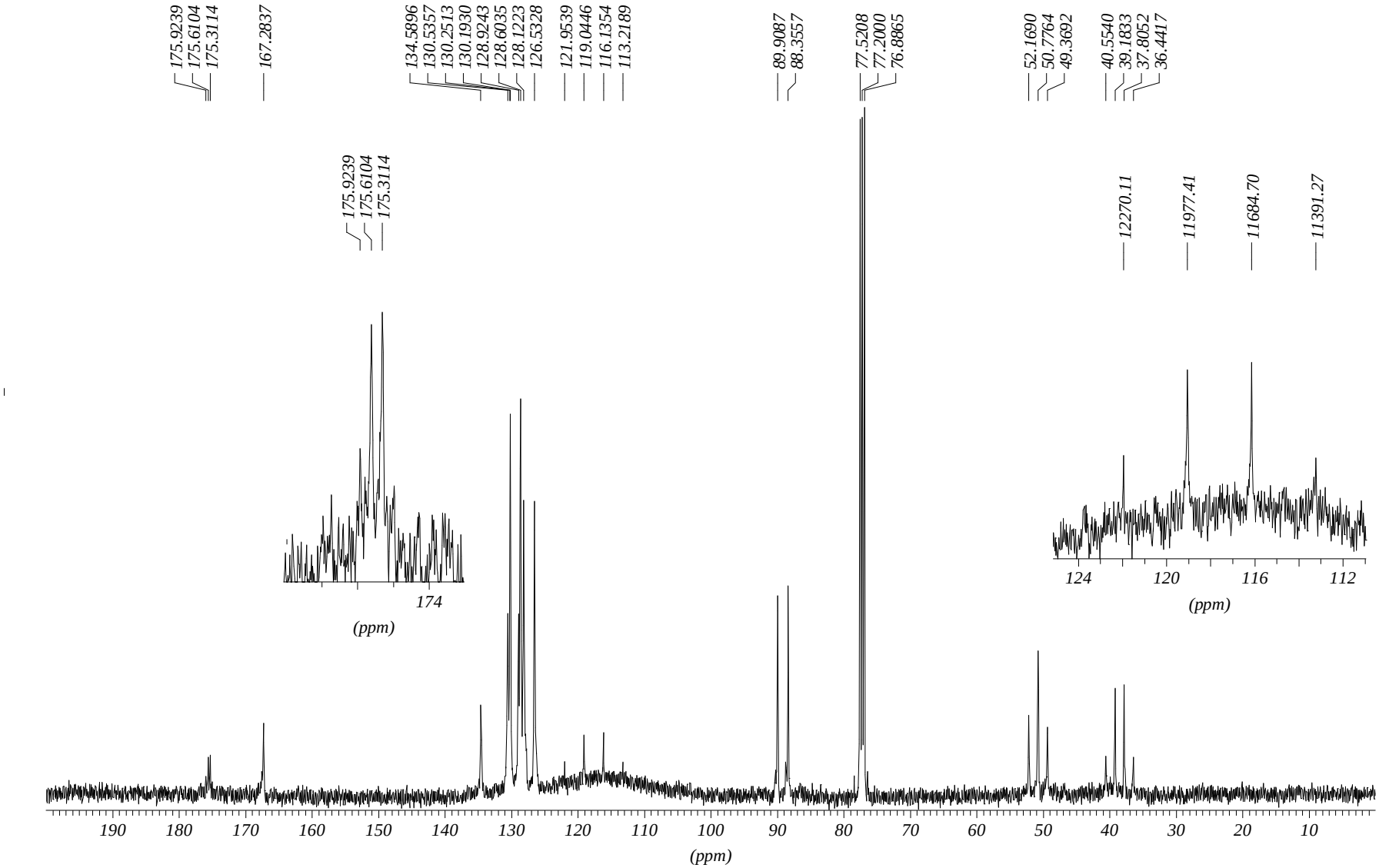
^{1}H NMR spectrum of bis-β-aminoenone **5**



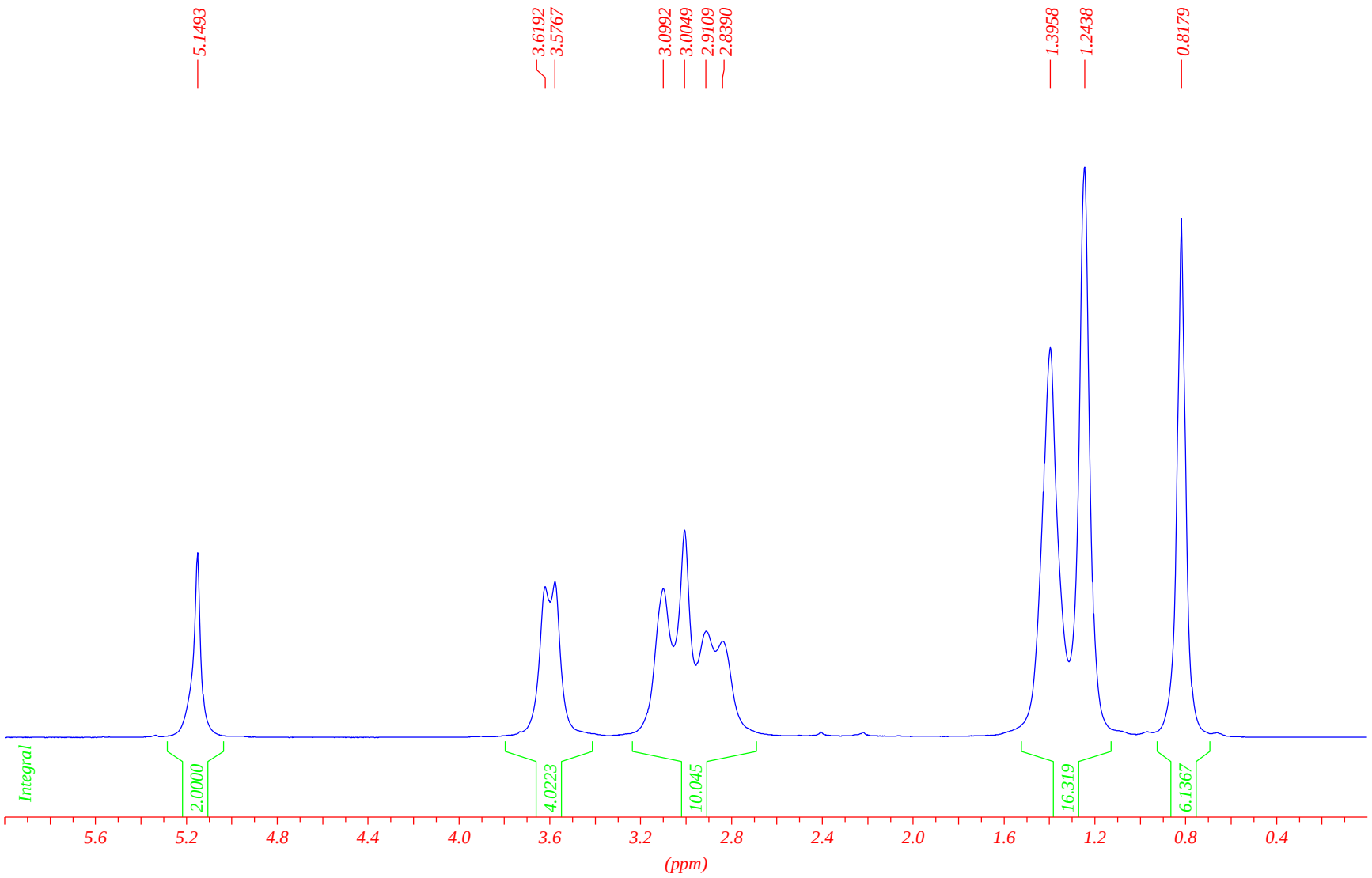
^{19}F NMR spectrum of bis-β-aminoenone **5**



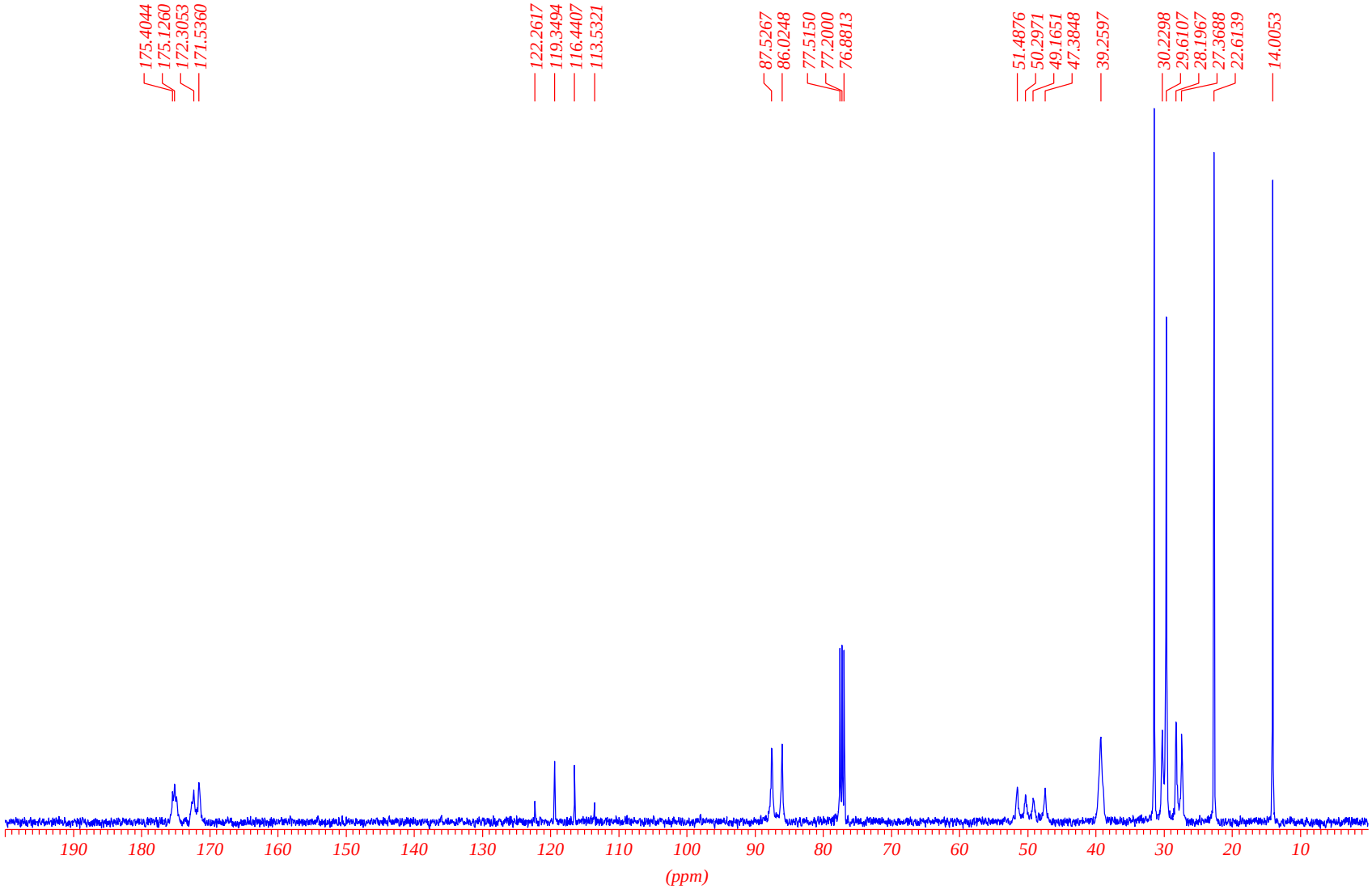
^{1}H NMR spectrum of bis-β-aminoenone **6a**



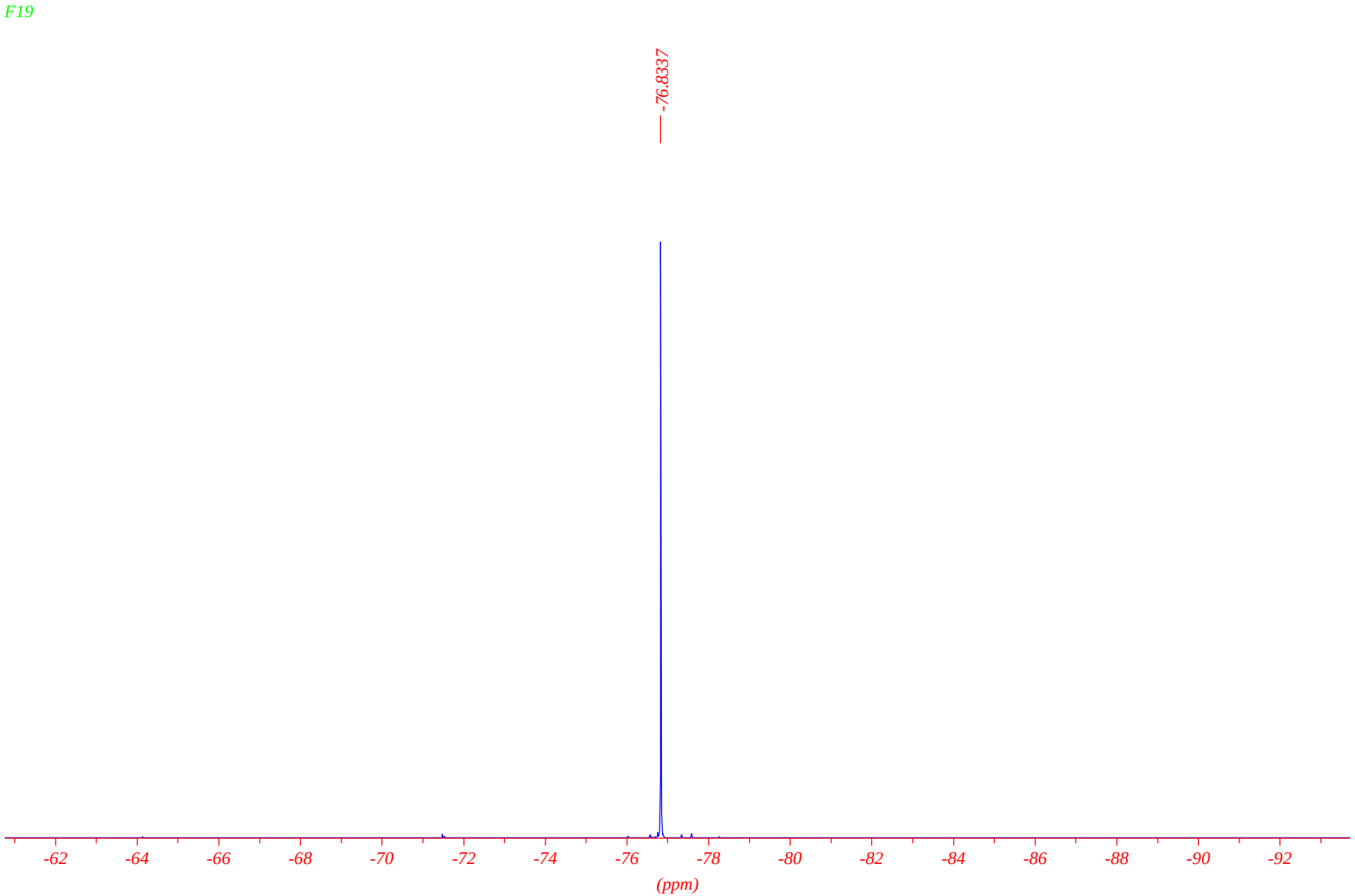
^{13}C NMR spectrum without proton decoupling of bis-*β*-aminoenone **6a**



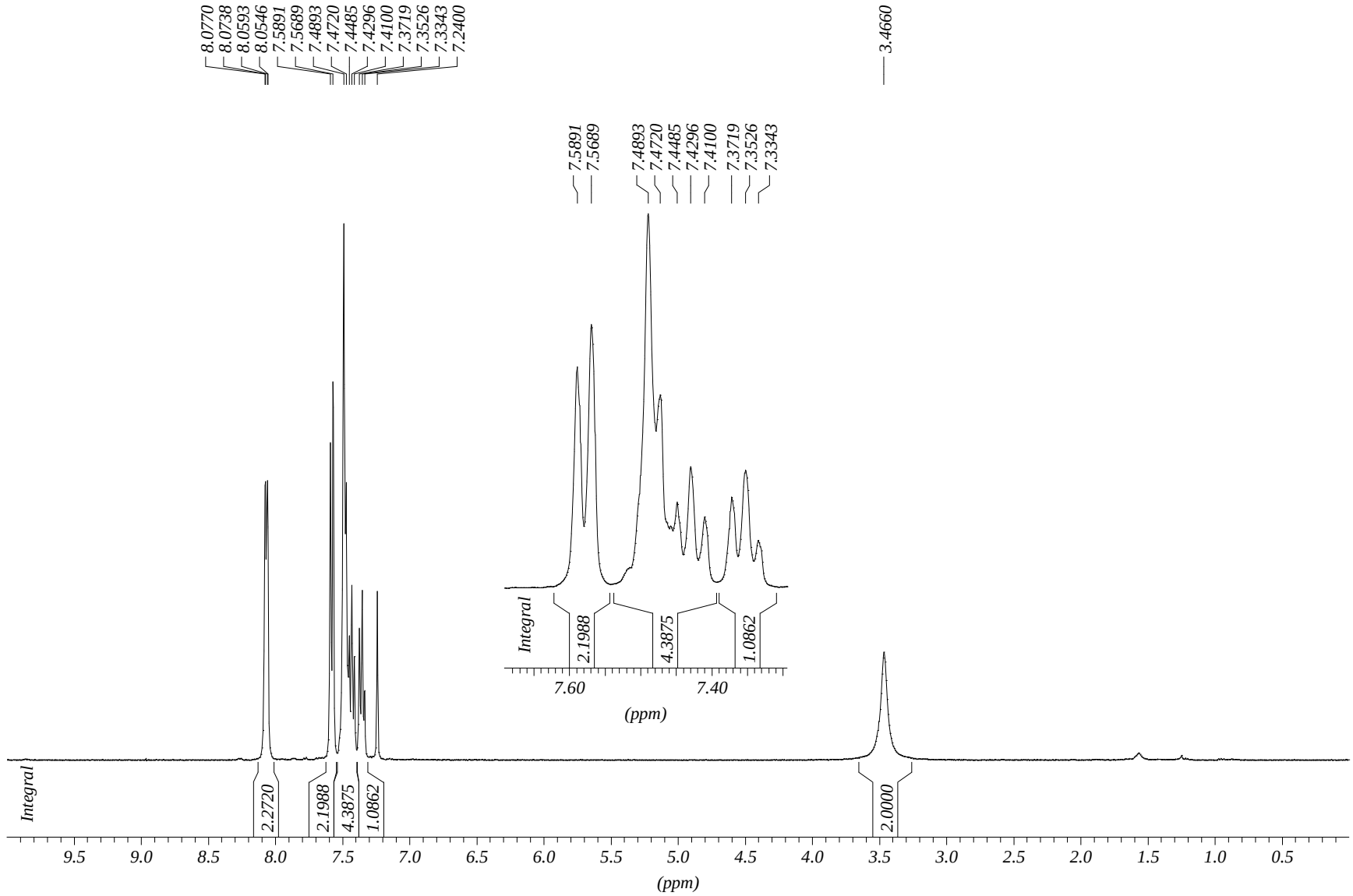
^{1}H NMR spectrum of bis-β-aminoenone **6b**



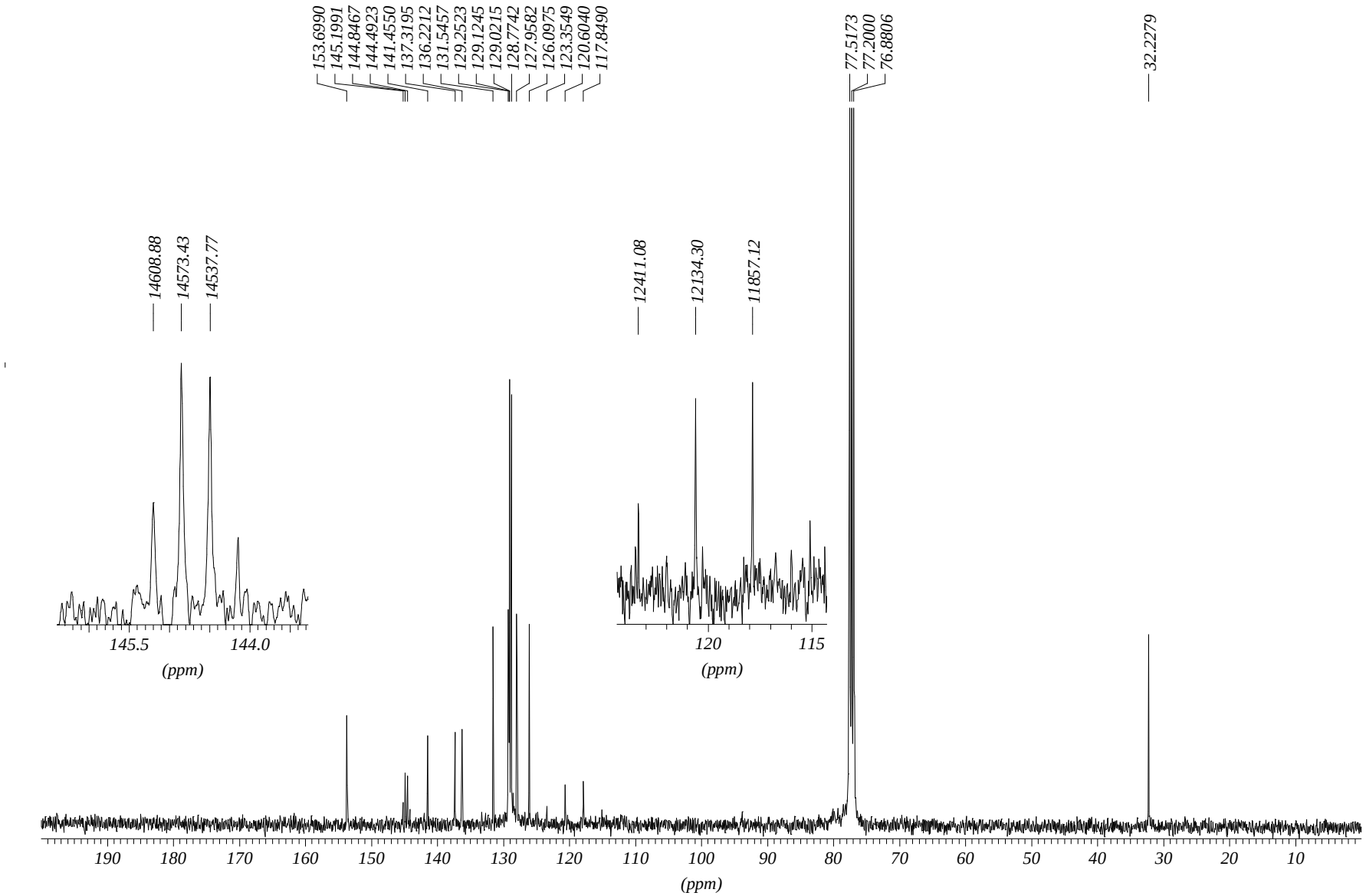
^{13}C NMR spectrum of bis-β-aminoenone **6b**



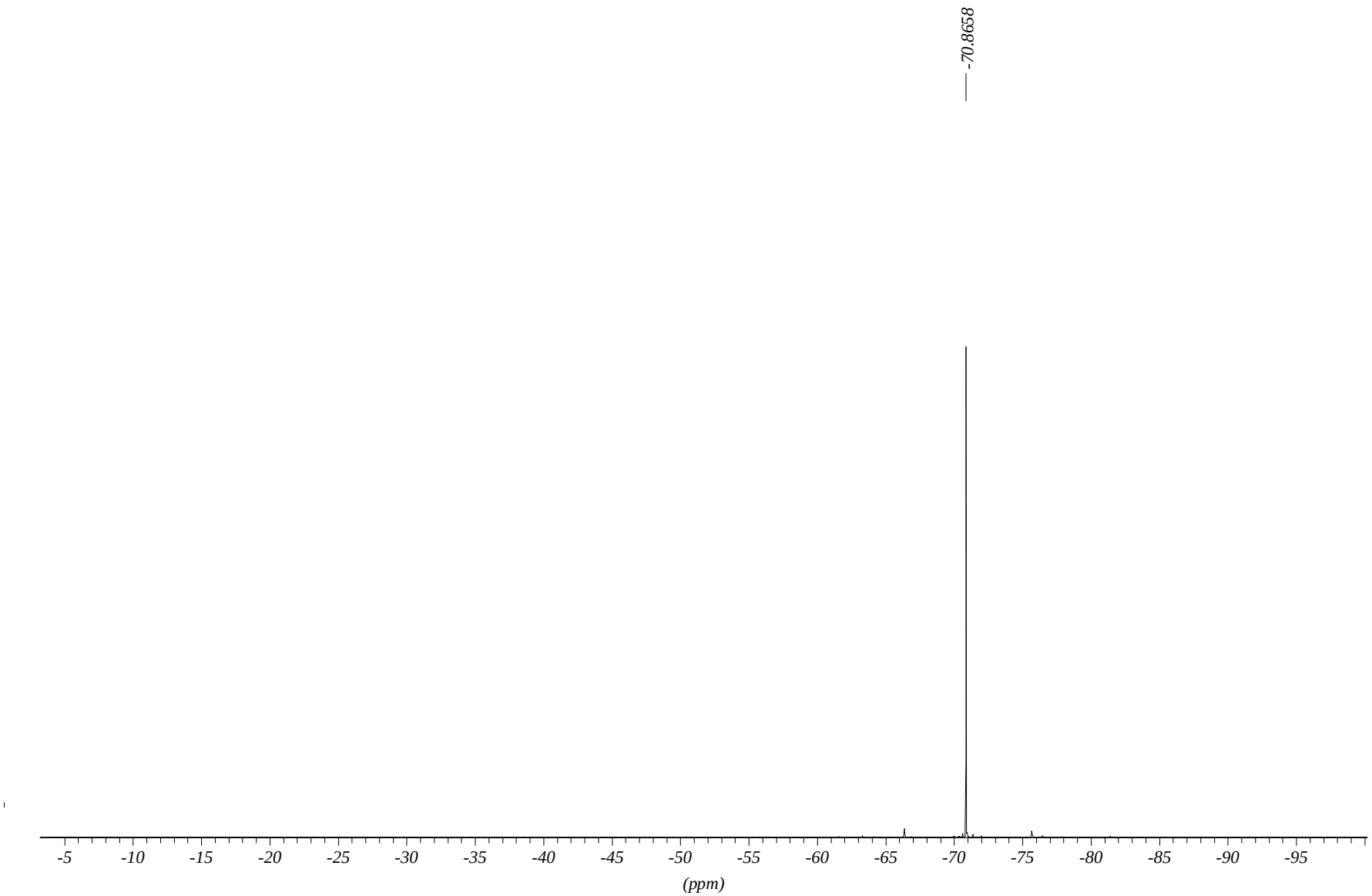
^{19}F NMR spectrum of bis-β-aminoenone **6b**



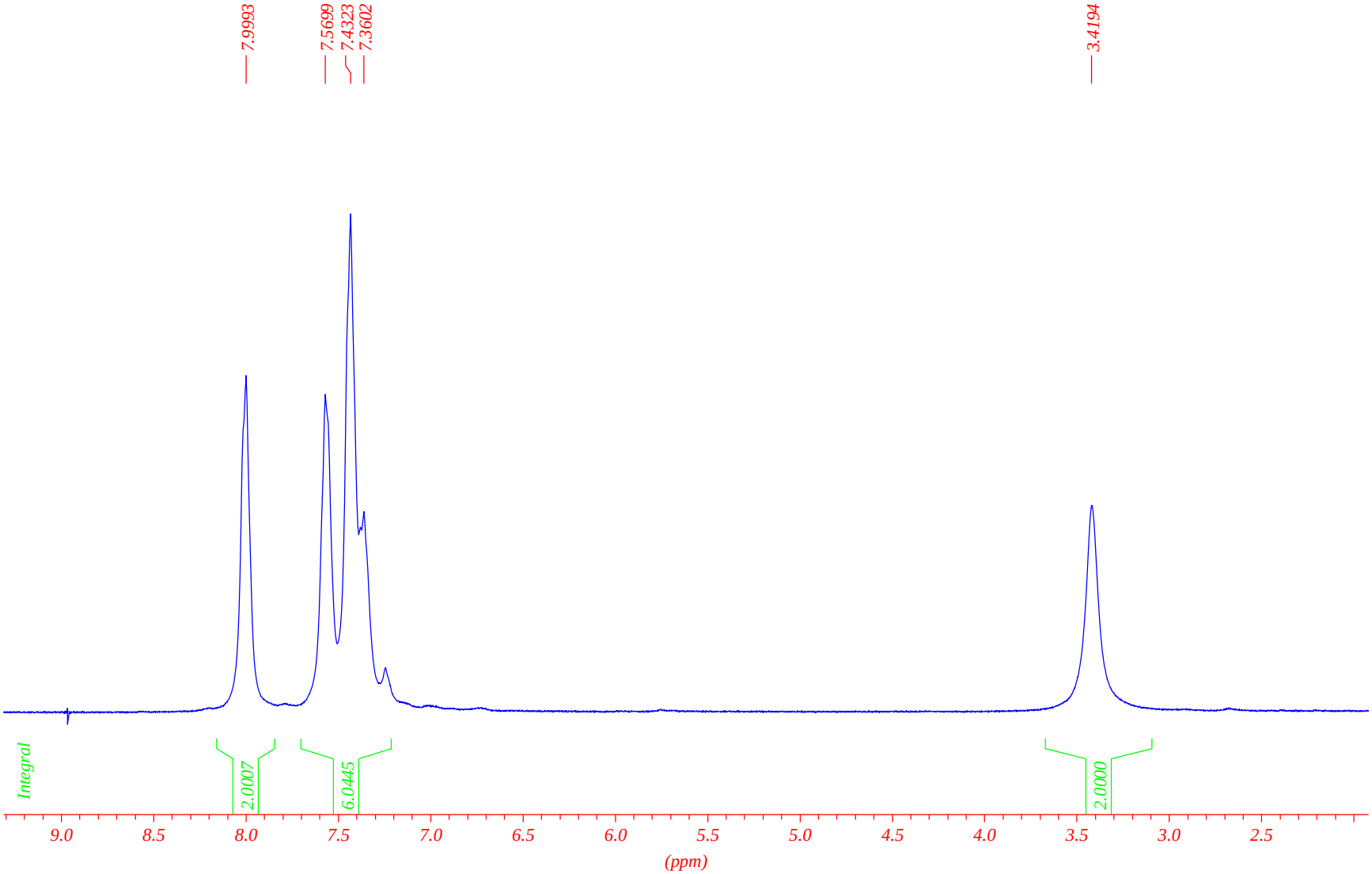
^{1}H NMR spectrum of diazepine **7a**



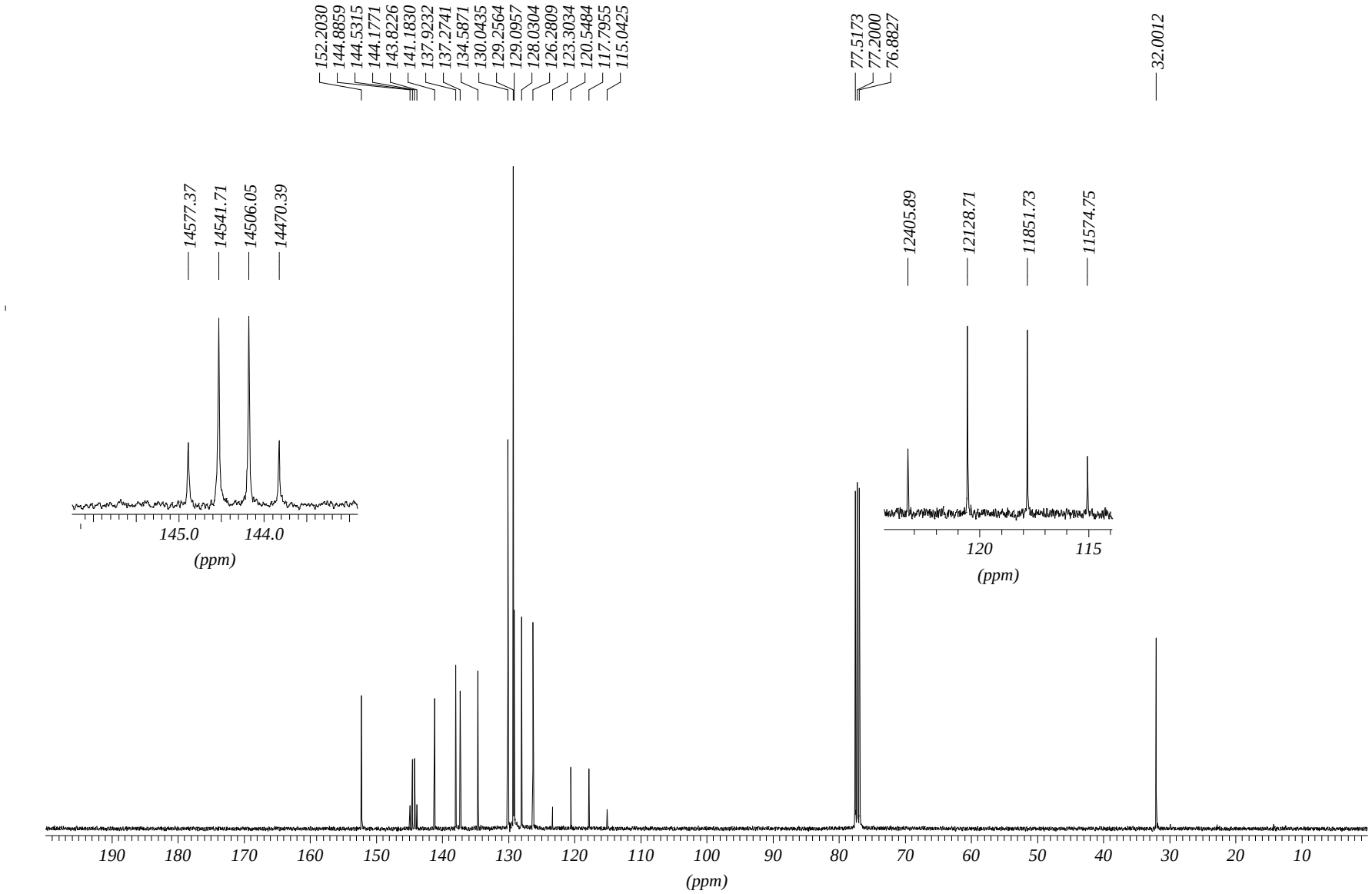
^{13}C NMR spectrum of diazepine **7a**



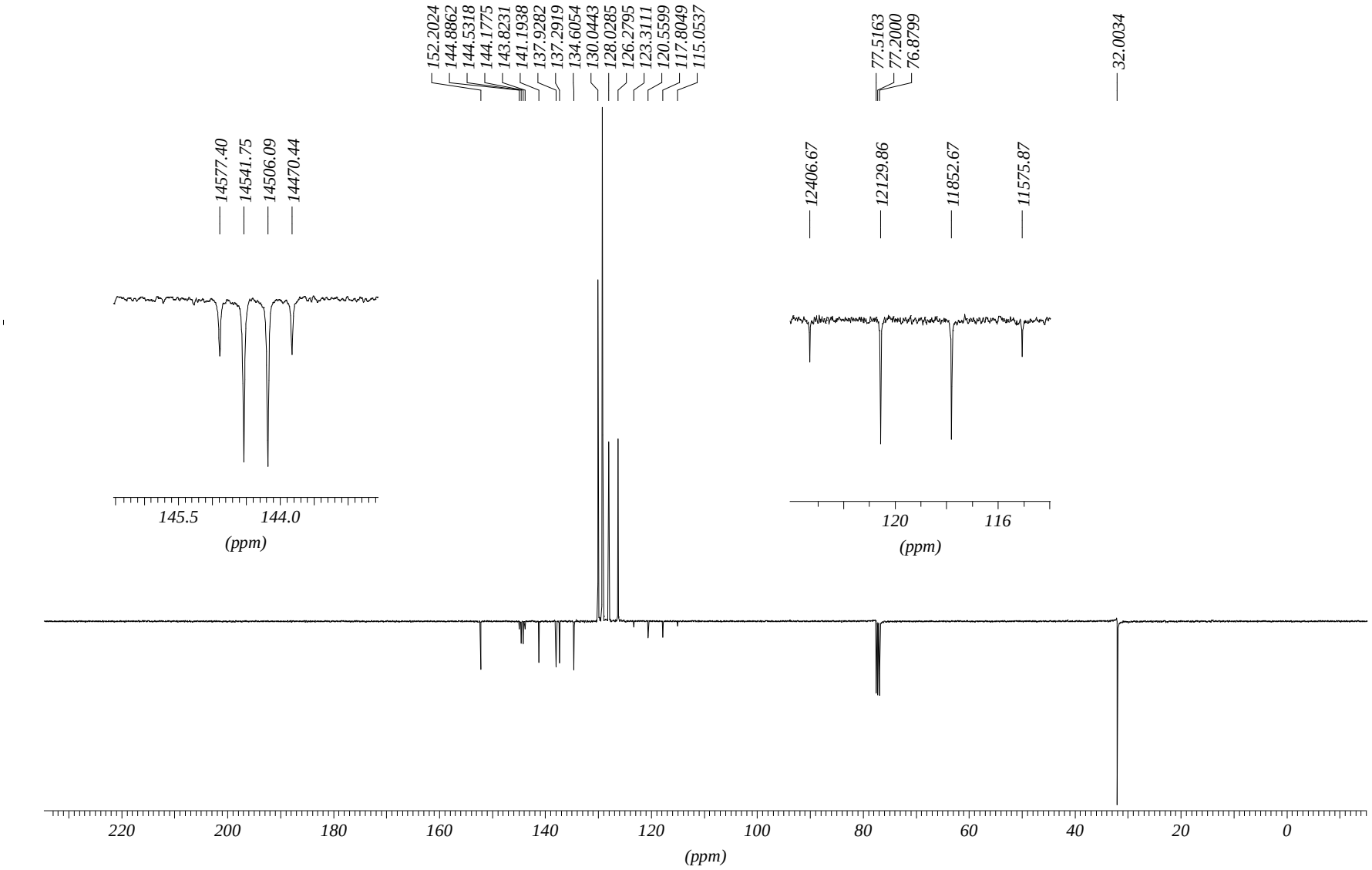
^{19}F NMR spectrum of diazepine **7a**



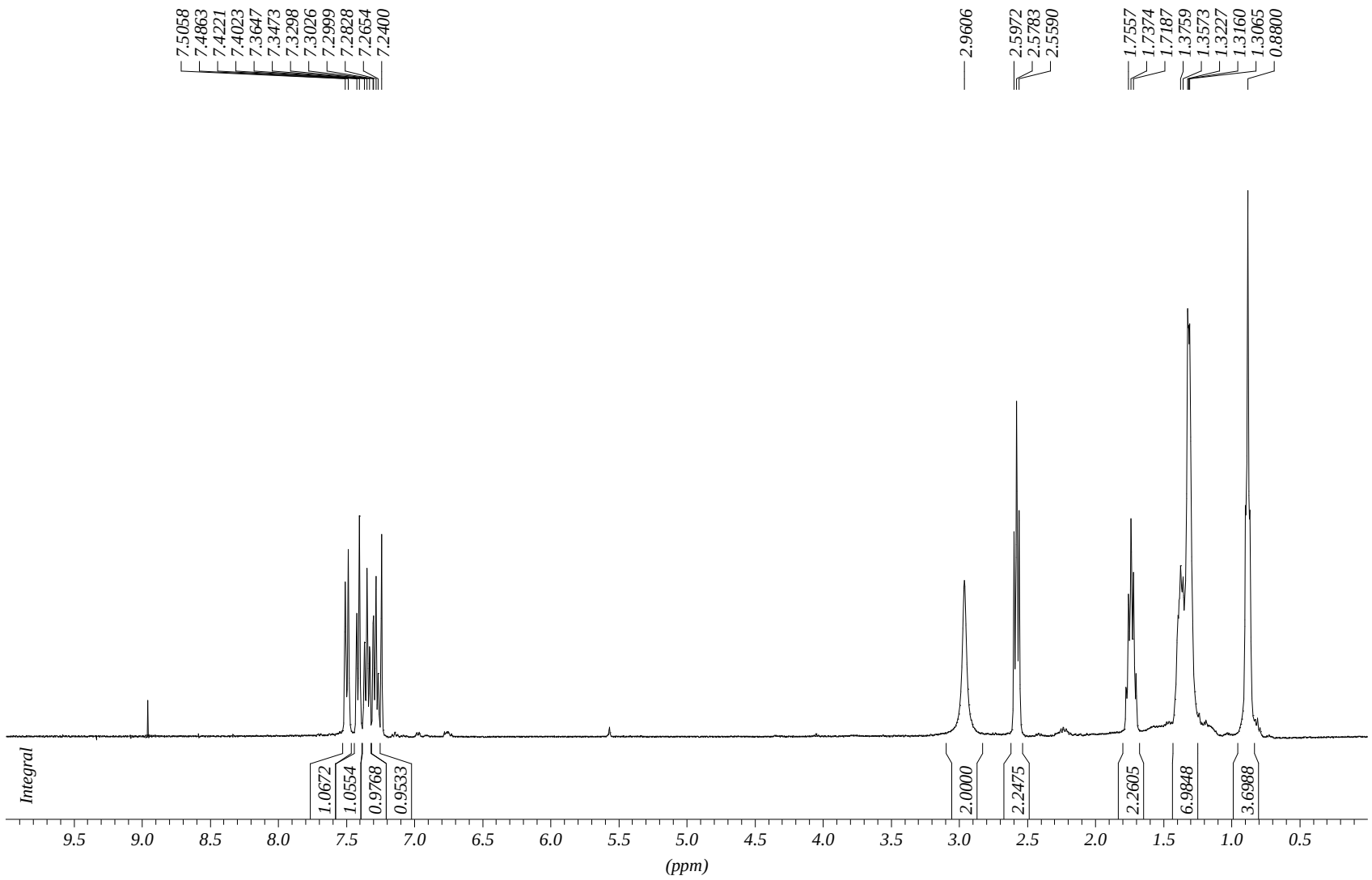
^{1}H NMR spectrum of diazepine **7b**



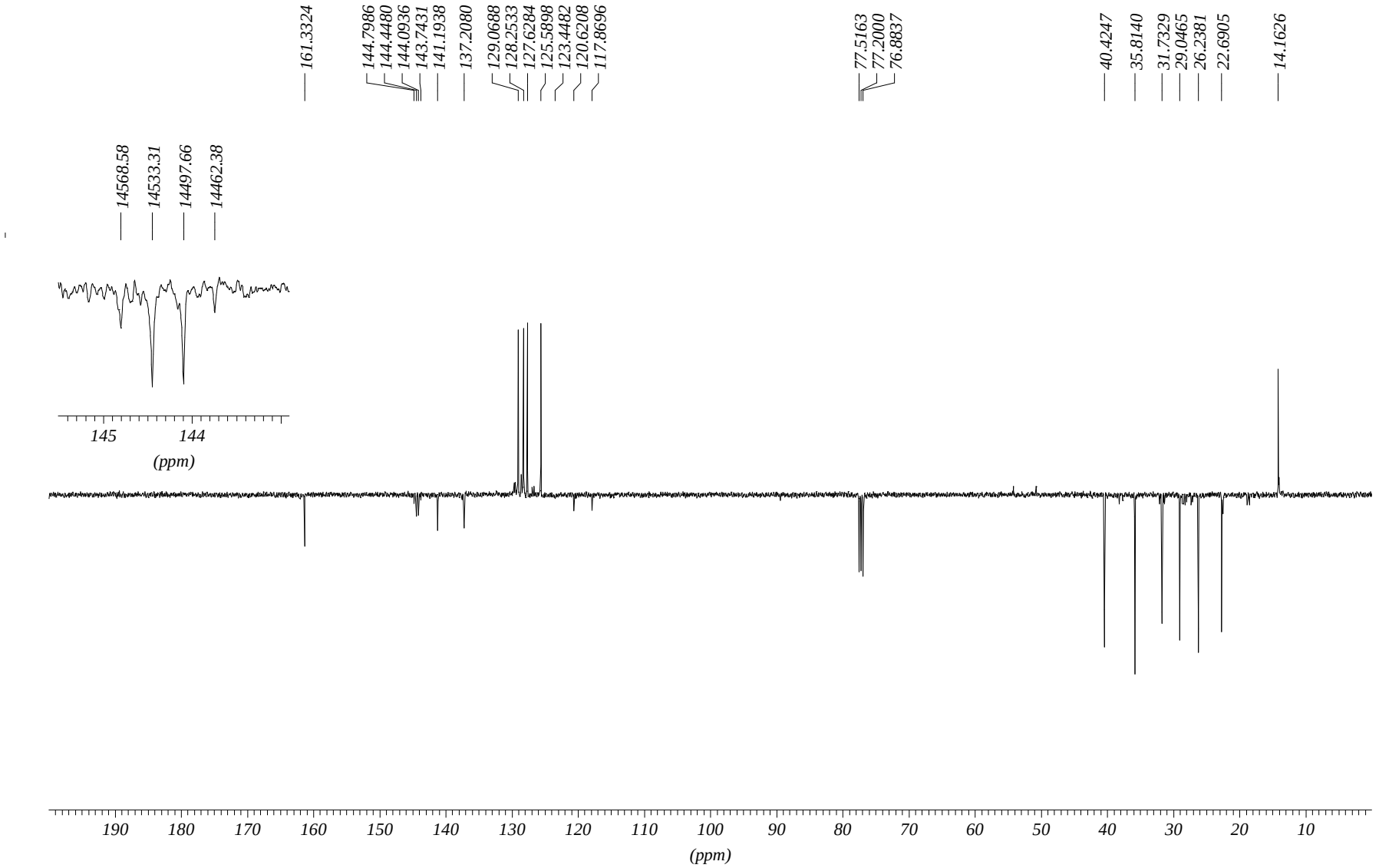
^{13}C NMR spectrum of diazepine **7b**



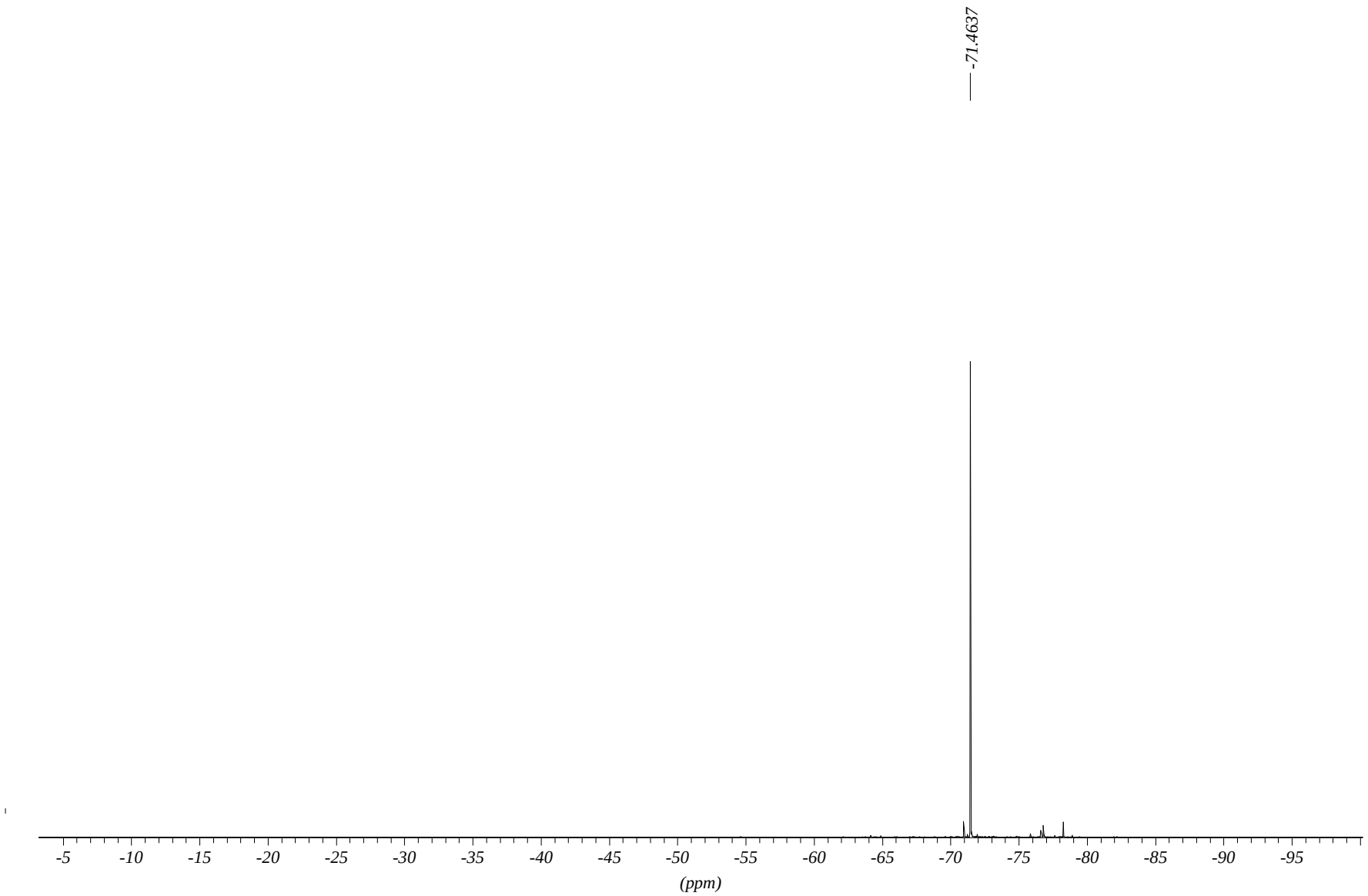
^{13}C NMR spectrum (j-modulation) of diazepine **7b**



^{1}H NMR spectrum of diazepine **7c**



^{13}C NMR spectrum (j-modulation) of diazepine **7c**



^{19}F NMR spectrum of diazepine **7c**