## Supporting Information

# Design and synthesis of atorvastatin derivatives with enhanced water solubility, hepatoselectivity and stability

Svetlana Yu. Maklakova,*[a] Anton V. Lopukhov,[a] Alexandr D. Khudyakov,[a] Sergey V. Kovalev,[a] Maria P. Mazhuga,[a] Olga E. Chepikova,[b] Andrey A. Zamyatnin Jr.,[b,c,d,e] Alexander G. Majouga,[a,f] Natalia L. Klyachko,[a] Elena K. Beloglazkina[a]

[a] *Chemistry Department, Lomonosov Moscow State University, GSP-1, Leninskie Gory 1/3, Moscow 119991, Russian Federation*

[b] *Department of Biotechnology, Sirius University of Science and Technology, Olympic Avenue 1, Sochi 354340, Russian Federation*

[c] *Institute of Molecular Medicine, Sechenov First Moscow State Medical University, Trubetskaya Street 8/2, Moscow 119991, Russian Federation.*

[d] *Belozersky Institute of Physico-Chemical Biology, Lomonosov Moscow State University, GSP-1, Leninskie Gory, Moscow 119992, Russian Federation.*

[e] *Faculty of Health and Medical Sciences, University of Surrey, Guildford GU2 7XH, U.K.*

∗ Corresponding author. E-mail: maklakovaSU@yandex.ru

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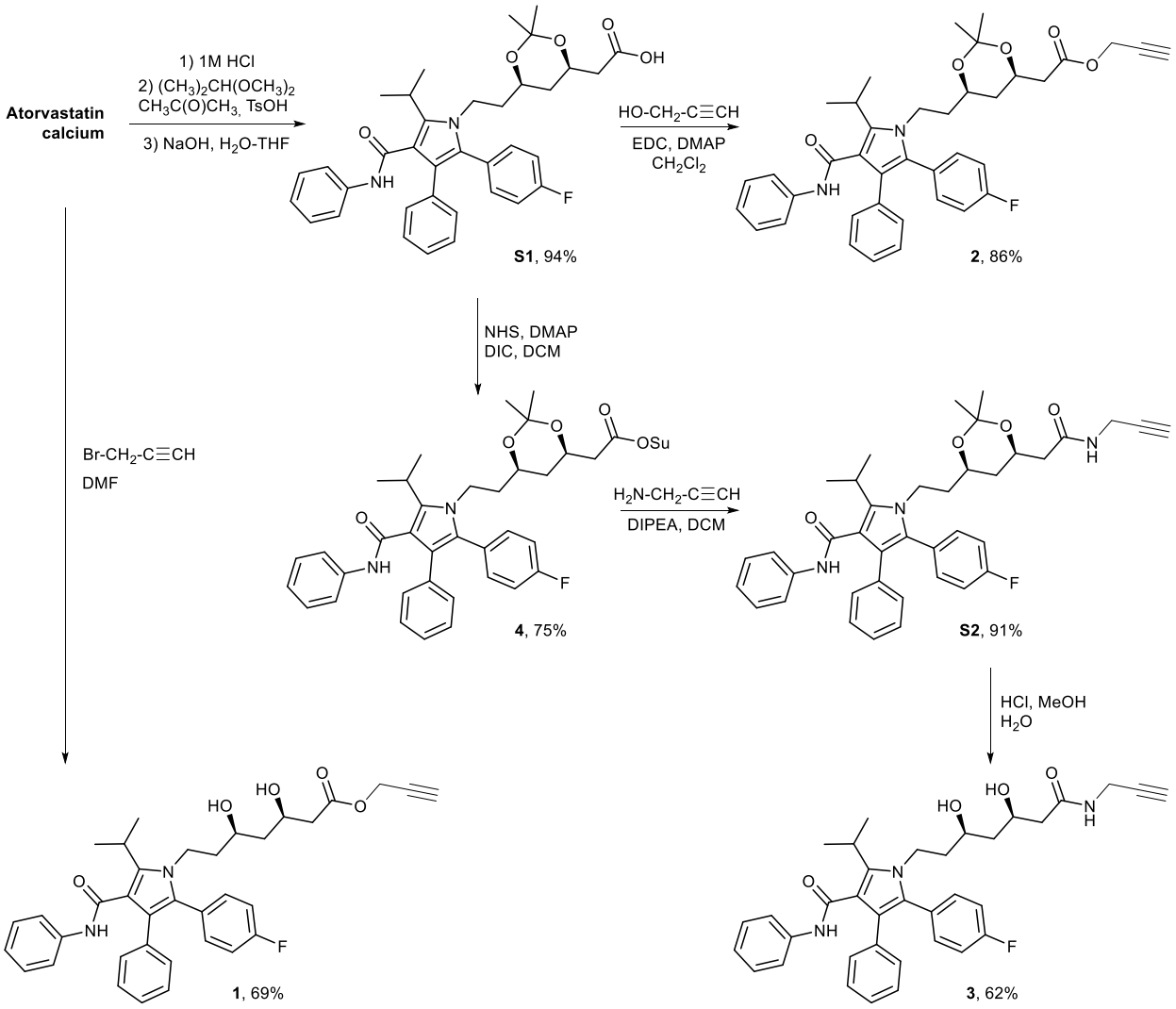
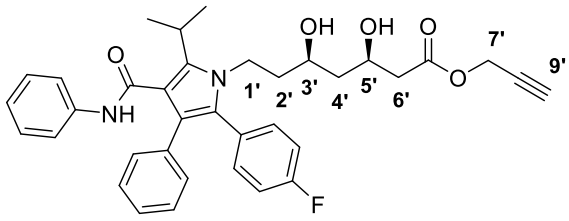
# Synthesis of compounds 1-4

**Scheme S1.** Synthesis of the atorvastatin derivatives 1-4



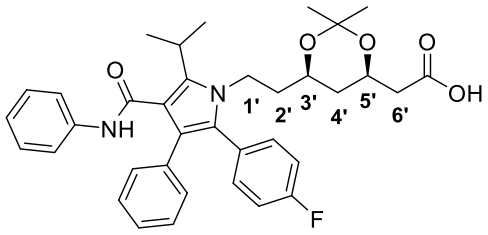

**Prop-2-yn-1-yl (3R,5R)-7-(2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)-1H-pyrrol-1-yl)-3,5-dihydroxyheptanoate (1)**




Atorvastatin calcium trihydrate (0.100 g, 0.083 mmol) and a 80% solution of propargyl bromide (49 µL, 0.51 mmol) in toluene were dissolved in 2 mL of DMF. The mixture was stirred at room temperature for 4 days. After that, it was poured into water. The product was extracted with

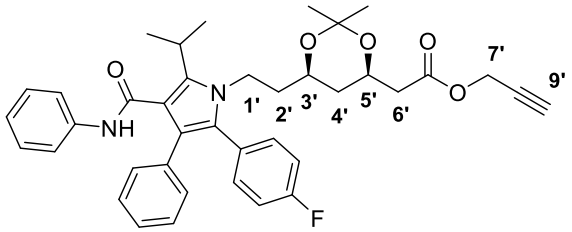
ethyl acetate and purified by column chromatography (Hex:EtOAc=1:2, v/v). Pure compound **1** was obtained as a white solid in 69% yield (0.068 g). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ ppm: 1.43-1.75 (m, 4H, $CH_2$-4', $CH_2$-2'), 1.55 (d, 6H, $CH_3$-$^i$Pr, $J$=7.1 Hz), 2.47-2.49 (m, 2H, $CH_2$-6'), 2.51 (t, 1H, CH-9', $J$=2.5 Hz), 3.43 (br.s, 1H, OH), 3.48 (br.s, 1H, OH), 3.55-3.62 (m, 1H, CH-$^i$Pr), 3.72-3.78 (m, 1H, CH-3'), 3.92-3.99 (m, 1H, CH-5'), 4.16-4.24 (m, 2H, $CH_2$-1'), 4.72 (dd, 2H, $CH_2$-7', $J_1$=2.5, $J_2$=0.9 Hz), 6.86 (br. s, 1H, PhN<u>H</u>), 6.99-7.03 (m, 3H, ArH), 7.07 (d, 2H, ArH, $J$=7.7 Hz), 7.15-7.23 (m, 9H, ArH).

**2-((4*R*,6*R*)-6-(2-(2-(4-Fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)-1*H*-pyrrol-1-yl)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetic acid (S1)[1]**



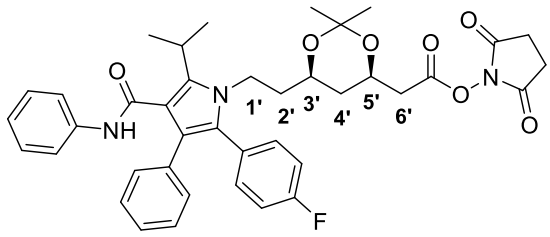

Atorvastatin calcium trihydrate (1.0 g, 0.8 mmol) was stirred for 15 minutes in 40 ml of 1M HCl solution, and then atorvastatin acid was extracted with dichloromethane (3 x 40 ml). The combined organic extracts were dried over $Na_2SO_4$. The solvent was removed under reduced pressure. The resulting residue was dissolved in 10 ml of acetone, and 2,2-dimethoxypropane (2.5 ml, 20.0 mmol) and p-toluenesulfonic acid monohydrate (0.02 g, 0.1 mmol) were added. The resulting mixture was stirred for 24 hours. After that triethylamine (0.075 ml, 0.5 mmol) was added, and the solvent was removed under reduced pressure. To the residue 5 ml of THF and 1 ml of 1 M NaOH solution were added, and the mixture was left to stir overnight. The next day, 1.2 ml of a 1 M HCl solution was added. THF was removed under reduced pressure. The product was extracted with diethyl ether. The organic fraction was dried over $Na_2SO_4$, the solvent was removed under reduced pressure. Compound **S1** was obtained as a white solid in 94% yield (0.9 g). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm: 0.87-0.95 (m, 1H, C<u>H$_A$</u>H$_B$-4'), 1.17, 1.31 (2 s, both 3H, $C(CH_3)_2$), 1.36 (d, 6H, $CH_3$-$^i$Pr, $J$=7.0 Hz), 1.38-1.42 (m, 1H, CH$_A$<u>H$_B$</u>-4'), 1.49-1.65 (m, 2H, $CH_2$-2'), 2.25-2.28 (m, 2H, $CH_2$-6'), 3.21 (m, 1H, CH-$^i$Pr), 3.73-3.82 (m, 2H, $CH_2$-1'), 3.88-3.97 (m, 1H, CH-3'), 4.09-4.17 (m, 1H, CH-5'), 6.96-7.02 (m, 2H, ArH), 7.06-7.10 (m, 4H, ArH), 7.17-7.27 (m, 6H, ArH), 7.51 (d, 2H, ArH, $J$=7.9 Hz), 9.81 (br. s, 1H, PhN<u>H</u>), 12.17 (br. s, 1H, COOH) [1].

**Prop-2-yn-1-yl 2-((4R,6R)-6-(2-(2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)-1H-pyrrol-1-yl)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate (2)**



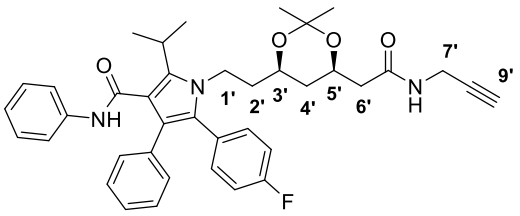

Compound **S1** (600 mg, 1.0 mmol) was dissolved in 10 mL of dichloromethane and EDCl (383 mg, 2.0 mmol), DMAP (60 mg, 0.5 mmol), and propargyl alcohol (190 µL, 3.2 mmol) were added. The reaction mixture was stirred overnight. The product was isolated using column chromatography (Hex:EtOAc, 1:1, v/v). Compound **2** was obtained as a white solid in 86% yield (545 mg). $^{1}$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm: 0.90-0.98 (m, 1H, C$\underline{H_A}H_B$-4'), 1.16, 1.31 (2 s, both 3H, C($CH_3$)$_2$), 1.36 (d, 6H, $CH_3$-$^{i}$Pr, $J$=7.0 Hz), 1.38-1.41 (m, 1H, C$H_A\underline{H_B}$-4'), 1.46-1.65 (m, 2H, $CH_2$-2'), 2.36 (dd, 1H, C$\underline{H_A}H_B$-6', $J_1$=15.6, $J_2$=7.9 Hz), 2.41 (dd, 1H, C$H_A\underline{H_B}$-6', $J_1$=15.6, $J_2$=4.7 Hz), 3.21 (m, 1H, CH-$^{i}$Pr), 3.55 (t, 1H, CH-9', $J$=2.4 Hz), 3.73-3.83 (m, 2H, $CH_2$-1'), 3.88-3.96 (m, 1H, CH-3'), 4.14-4.21 (m, 1H, CH-5'), 4.66 (dd, 1H, C$\underline{H_A}H_B$-7', $J_1$=15.8, $J_2$=2.4 Hz), 4.71 (dd, 1H, C$H_A\underline{H_B}$-7', $J_1$=15.8, $J_2$=2.4 Hz), 6.96-7.03 (m, 2H, ArH), 7.05-7.10 (m, 4H, ArH), 7.17-7.27 (m, 6H, ArH), 7.51 (d, 2H, ArH, $J$=8.1 Hz), 9.82 (br. s, 1H, PhN$\underline{H}$). $^{19}$F {$^{1}$H} NMR (100 MHz, DMSO-$d_6$) $\delta$ ppm: -114.1. $^{13}$C NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm: 19.6, 22.1, 22.4, 25.6, 29.7, 35.1, 37.7, 40.3, 51.6, 65.3, 65.8, 77.6, 78.4, 98.1, 115.4 (d, $^{2}J_{CF}$=21.4 Hz), 117.4, 119.4, 120.6, 123.0, 125.4, 127.3, 127.7, 128.4, 128.3 (d, $^{4}J_{CF}$=2.9 Hz), 129.1, 133.4 (d, $^{4}J_{CF}$=8.1 Hz), 134.8, 135.9, 139.4, 161.7 (d, $^{1}J_{CF}$=245.1 Hz), 166.1, 169.6. HRMS (ESI) *m/z* calcd for $C_{39}H_{41}FN_2O_5$ $[M+H]^+$ *m/z* 637.3072, found: 637.3074.

**2,5-Dioxopyrrolidin-1-yl 2-((4R,6R)-6-(2-(2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)-1H-pyrrol-1-yl)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate (4)**



DMAP (0.009 g, 0.075 mmol), DIC (131 µL, 0.82 mmol), and N-hydroxysuccinimide (0.088 g, 0.75 mmol) were added to a solution of compound **S1** (0.450 g, 0.75 mmol) in 5 mL of $CH_2Cl_2$. The reaction completeness was monitored by TLC. The solvent was removed under reduced pressure. The product was purified by column chromatography (Hex:EtOAc=1:1, v/v). Compound **4** was obtained as a white solid in 75% yield (0.390 g). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm: 0.99-1.12 (m, 1H, C$\underline{H_A}H_B$-4'), 1.19, 1.33 (2 s, both 3H, C($CH_3$)$_2$), 1.37 (d, 6H, $CH_3$-$^i$Pr, $J$=7.0 Hz), 1.47 (d, 1H, $CH_A\underline{H_B}$-4', $J$=12.5 Hz), 1.53-1.66 (m, 2H, $CH_2$-2'), 2.67 (dd, 1H, C$\underline{H_A}H_B$-6', $J_1$=15.9, $J_2$=8.4 Hz), 2.80 (s, 4H, 2$CH_2$-NHS), 2.85 (dd, 1H, $CH_A\underline{H_B}$-6', $J_1$=15.9, $J_2$=4.3 Hz), 3.17-3.27 (m, 1H, CH-$^i$Pr), 3.76-3.85 (m, 2H, $CH_2$-1'), 3.90-3.99 (m, 1H, CH-3'), 4.20-4.26 (m, 1H, CH-5'), 6.96-7.04 (m, 2H, ArH), 7.05-7.11 (m, 4H, ArH), 7.18-7.28 (m, 6H, ArH), 7.51 (d, 2H, ArH, $J$=7.8 Hz), 9.81 (br. s, 1H, PhN$\underline{H}$). $^{13}$C NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm: 19.5, 22.1, 22.4, 25.5, 25.6, 29.6, 34.9, 37.4, 37.7, 65.2, 65.8, 98.4, 115.1 (d, $^2J_{CF}$=20.4 Hz), 117.6, 119.4, 120.6, 123.0, 125.4, 127.3, 127.7, 128.5, 128.6 (d, $^4J_{CF}$=8.3 Hz), 129.1, 133.4 (d, $^3J_{CF}$=8.3 Hz), 134.8, 136.0, 139.5, 161.7 (d, $^1J_{CF}$=246.8 Hz), 166.1, 166.3, 170.1. HRMS (ESI) *m/z* calcd for $C_{40}H_{43}FN_3O_7$ $[M+H]^+$ *m/z* 696.3079, found: 696.3102.

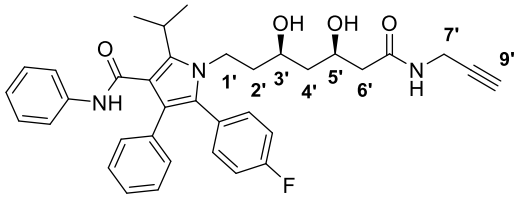
**1-(2-((4R,6R)-2,2-Dimethyl-6-(2-oxo-2-(prop-2-yn-1-ylamino)ethyl)-1,3-dioxan-4-yl)ethyl)-5-(4-fluorophenyl)-2-isopropyl-N,4-diphenyl-1H-pyrrole-3-carboxamide (S2)[2]**




Compound **4** (0.150 g, 0.022 mmol) was dissolved in 5 mL of $CH_2Cl_2$ and DIPEA (45 µL, 0.26 mmol) and propargylamine (14 µL, 0.022 mmol) was added. The mixture was stirred for 24 hours, and then it was poured into water. The product was extracted with $CH_2Cl_2$ and was purified by column chromatography (Hex:EtOAc=1:1, v/v). Compound **S2** was obtained as a colorless oil in 91% yield (0.125 g). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ ppm: 1.06-1.15 (m, 1H, C$\underline{H_A}H_B$-4'), 1.29-1.31 (m, 1H, $CH_A\underline{H_B}$-4'), 1.35, 1.39 (2 s, both 3H, C($CH_3$)$_2$)), 1.54 (d, 6H, $CH_3$-$^i$Pr, $J$=7.1 Hz), 1.64-1.71 (m, 2H, $CH_2$-2'), 2.23 (t, 1H, CH-9', $J$=2.6 Hz), 2.30 (dd, 1H, C$\underline{H_A}H_B$-6', $J_1$=15.2, $J_2$=4.3 Hz), 2.85 (dd, $CH_A\underline{H_B}$-6', $J_1$=15.2, $J_2$=7.2 Hz), 3.59 (m, 1H, CH-$^i$Pr), 3.67-3.73 (m, 1H, CH-3'), 3.79-3.87 (m, 1H, CH-5'), 4.02-4.04 (m, 2H, $CH_2$-7', $J_1$=5.2, $J_2$=2.6 Hz), 4.06-4.18 (m, 2H, $CH_2$-1'),

6.42 (t, 1H, N<u>H</u>$CH_2$, *J*=4.9 Hz), 6.87 (br. s, 1H, PhN<u>H</u>), 6.97-7.03 (m, 3H, ArH), 7.07 (d, 2H, ArH, *J*=7.8 Hz), 7.13-7.23 (m, 9H, ArH).

**1-((3R,5R)-3,5-Dihydroxy-7-oxo-7-(prop-2-yn-1-ylamino)heptyl)-5-(4-fluorophenyl)-2-isopropyl-N,4-diphenyl-1H-pyrrole-3-carboxamide (3)**




Compound **S2** (0.060 g, 0.094 mmol) was dissolved in 7 ml of methanol, 3 ml of 1 M HCl were added, and the mixture was stirred for 20 hours at room temperature. The product was extracted with dichloromethane, washed with saturated $NaHCO_3$ solution, and brine. The product was purified by column chromatography ($CH_2Cl_2$:MeOH=15:1). Compound **3** was obtained as a colorless oil in 62% yield (0.035 g). $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ ppm: 1.39-1.56 (m, 2H, $CH_2$-4'), 1.48 (d, 6H, $CH_3$-$^i$Pr, *J*=7.1), 1.61-1.76 (m, 2H, $CH_2$-2'), 2.29 (d, 2H, $CH_2$-6', *J*=6.5 Hz), 2.58 (t, 1H, CH-9', *J*=2.5 Hz), 3.33-3.40 (m, 1H, CH-$^i$Pr), 3.62-3.68 (m, 1H, CH-3'), 3.87-3.92 (m, 1H, C<u>H$_A$</u>H$_B$-1'), 3.95 (dd, 2H, $CH_2$-7', $J_1$=6.8, $J_2$=2.5 Hz), 3.99-4.12 (m, 2H, CH-5', CH$_A$<u>H$_B$</u>-1'), 7.01-7.15 (m, 8H, ArH), 7.20-7.26 (m, 4H, ArH), 7.30 (d, 2H, ArH, *J*=8.1 Hz). $^{13}$C NMR (400 MHz, $CD_3OD$) $\delta$ ppm: 22.9, 23.0, 27.8, 29.5, 40.3, 42.3, 44.4, 44.5, 68.3, 68.7, 72.4, 80.7, 116.5 (d, $^2J_{CF}$=21.8 Hz), 118.2, 121.6, 123.4, 125.3, 127.0, 129.0, 129.8, 130.4 (d, $^4J_{CF}$=3.3 Hz), 131.0, 134.9 (d, $^3J_{CF}$=8.1 Hz), 136.5, 139.1, 140.0, 164.0 (d, $^1J_{CF}$=246.3 Hz), 169.7, 173.5. HRMS (ESI) *m/z* calcd for $C_{46}H_{56}FN_6O_{11}$ $[M+H]^+$ *m/z* 887.3986, found: 887.3970.

**References**

1. Mizoi K., Takahashi M., Haba M., Hosokawa M. Synthesis and evaluation of atorvastatin esters as prodrugs metabolically activated by human carboxylesterases. // Bioorganic & Medicinal Chemistry Letters. 2016. V.26. P. 921-923

2. Poh J.-S., Makai S., von Keutz T., Tran D. N., Battilocchio C., Pasau P., Ley S. V. Rapid Asymmetric Synthesis of Disubstituted Allenes by Coupling of Flow-Generated Diazo Compounds and Propargylated Amines. // Angewandte Chemie International Edition. 2017. V.56. P. 1-6.

## Quantification of Water Solubility

***Table S1.*** *Substances' molar solubility calculations*

| Compound | Calibration curve coefficient[1] | Absorption intensity of test-solution | Concentration, mmol/L |
|---|---|---|---|
| **Atorvastatin calcium** | 0.012 ± 0.001 | 0.062 | 0.11 ± 0.01 |
| **1a** | 0.009 ± 0.001 | 0.139 | 0.32 ± 0.02 |
| **1b** | 0.012 ± 0.001 | 0.116 | 0.20 ± 0.01 |
| **2a** | 0.010 ± 0.001 | 0.026 | 0.05 ± 0.01 |
| **2b** | 0.008 ± 0.001 | 0.011 | 0.03 ± 0.01 |
| **3a** | 0.010 ± 0.001 | 0.267 | 0.54 ± 0.01 |
| **3b** | 0.010 ± 0.001 | 0.225 | 0.45 ± 0.01 |
| **4c** | 0.009 ± 0.001 | 0.209 | 0.43 ± 0.02 |

[1]y = kx, y - absorption intensity at 290 nm, x – concentration, µmol/L

## Hydrolysis assays

Chromatograms of substances were obtained on a Shimadzu Nexera X2 chromatograph with an AB Sciex QTrap 5500 detector in the multiple reaction monitoring (MRM) mode using electrospray ionization. Separation was carried out on a Waters Acquity C18 column (2.1*100 mm, grain size 1.8 µm) with a Waters Acquity C18 guard column (2.1*5 mm, grain size 1.8 µm) at 60 °C under gradient elution conditions. Mobile phase A - 0.1% solution of formic acid in water, phase B - 0.1% solution of formic acid in methanol. The injection volume is 1 µl. The gradient parameters of MRM transitions are shown in **Table S2**. The MS spectra were recorded using the Analyst 1.7.2 program, and the Sciex OS 1.6.2 program was used to quantify the obtained data.

**Figure S1**. Concentrations of conjugate **1a** and released atorvastatin (Atv) in PBS and in PBS with porcine liver esterase or Pronase®

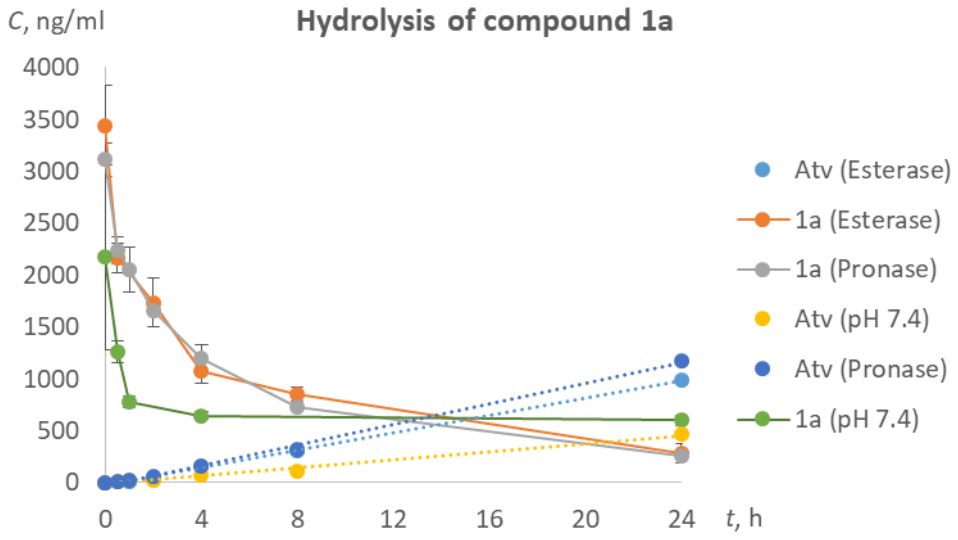


**Figure S2**. Concentrations of conjugate **1b** and released atorvastatin (Atv) in PBS and in PBS with porcine liver esterase or Pronase®

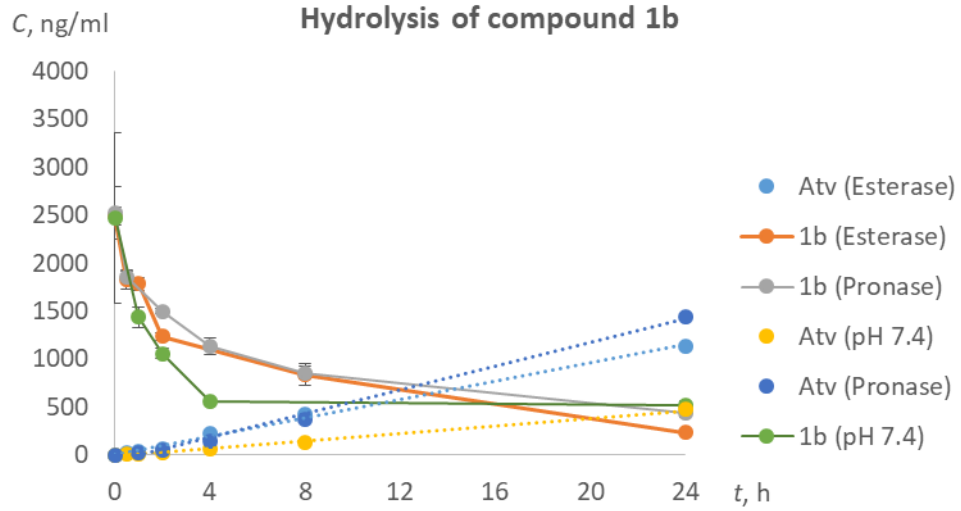



**Figure S3**. Concentrations of conjugate **3a** and released atorvastatin (Atv) in buffer solutions (pH 7.4 and 5.0) and in PBS with porcine liver esterase or Pronase®

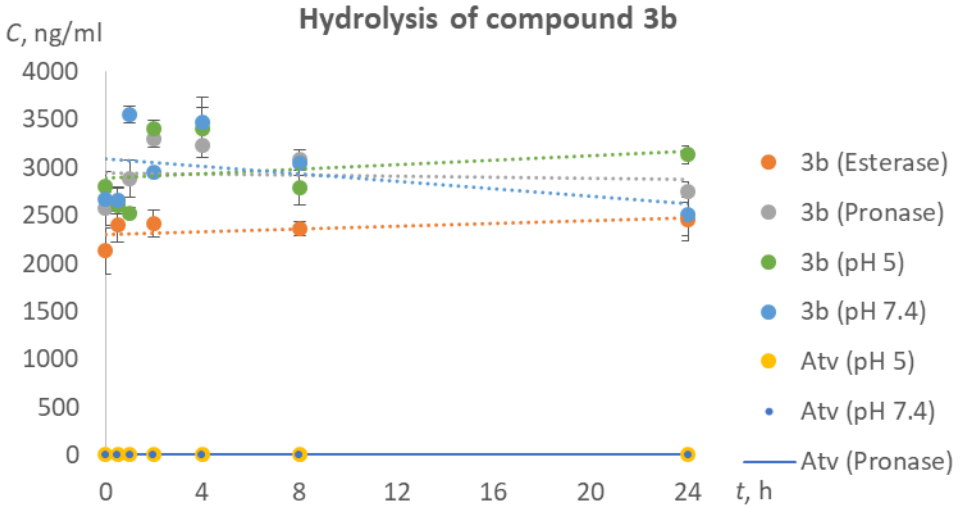



**Figure S4**. Concentrations of conjugate **3b** and released atorvastatin (Atv) in buffer solutions (pH 7.4 and 5.0) and in PBS with porcine liver esterase or Pronase®

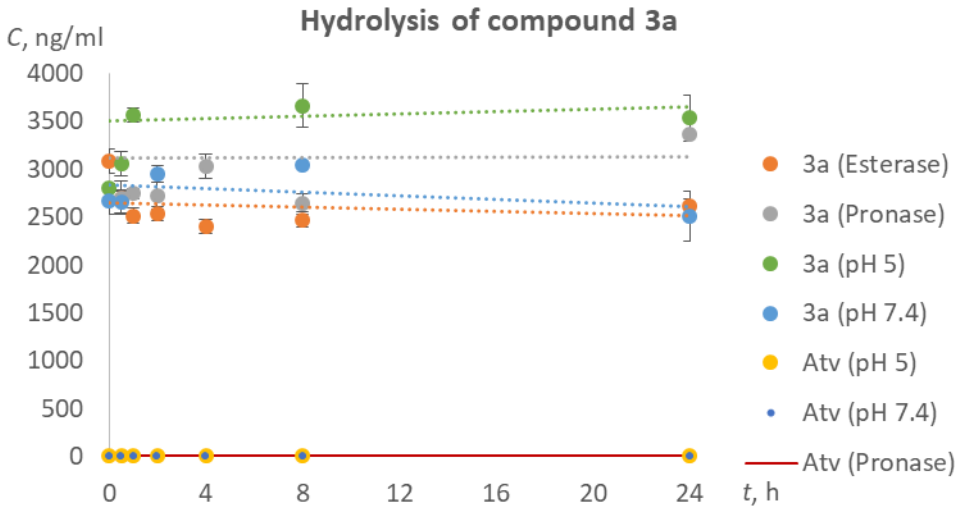


**Figure S5**. Concentrations of conjugate **4c** and released atorvastatin (Atv) in buffer solutions (pH 7.4 and 5.0) and in PBS with porcine liver esterase

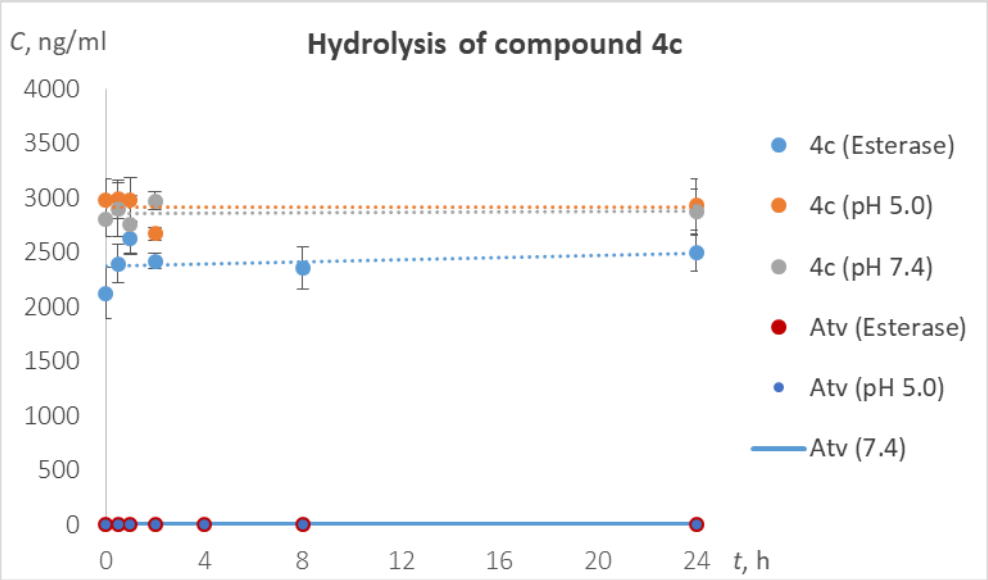



***Table S2.*** *Parameters of MRM transitions*

| Compound | MRM-transition | Precursor mass (Q1), Da | Fragment mass (Q3), Da |
|---|---|---|---|
| Atorvastatin | Atorvastatin pos_1 | 559.148 | 440.2 |
| Atorvastatin | Atorvastatin pos_2 | 559.148 | 250 |
| Atorvastatin | Atorvastatin pos_3 | 559.148 | 292 |
| **3b** | **3b** 1 | 842.285 | 546.3 |
| **3b** | **3b** 2 | 842.285 | 639.3 |
| **3b** | **3b** 3 | 842.285 | 528.2 |
| **1b** | **1b** 1 | 843.383 | 547.2 |
| **1b** | **1b** 2 | 843.383 | 640.3 |
| **1b** | **1b** 3 | 843.383 | 485.3 |
| **1a** | **1a** 1 | 887.293 | 794.3 |
| **1a** | **1a** 2 | 887.293 | 591.3 |
| **1a** | **1a** 3 | 887.293 | 466.1 |
| **3a** | **3a** 1 | 886.26 | 793.3 |
| **3a** | **3a** 2 | 886.26 | 590.3 |
| **3a** | **3a** 3 | 886.26 | 572.3 |
| Atorvastatin | Atorvastatin_neg_1 | 557.177 | 278.1 |
| Atorvastatin | Atorvastatin_neg_2 | 557.177 | 397 |
| Atorvastatin | Atorvastatin_neg_3 | 557.177 | 453.1 |

## Cathepsin B hydrolysis

Expression and purification procedures for human recombinant cathepsin B were described previously.[1] For reaction, the enzyme was preincubated in 0.2M sodium acetic buffer pH 4.6 containing 100 mM NaCl, 1 mM EDTA for 45 min at 37°C for its activation. The activity of

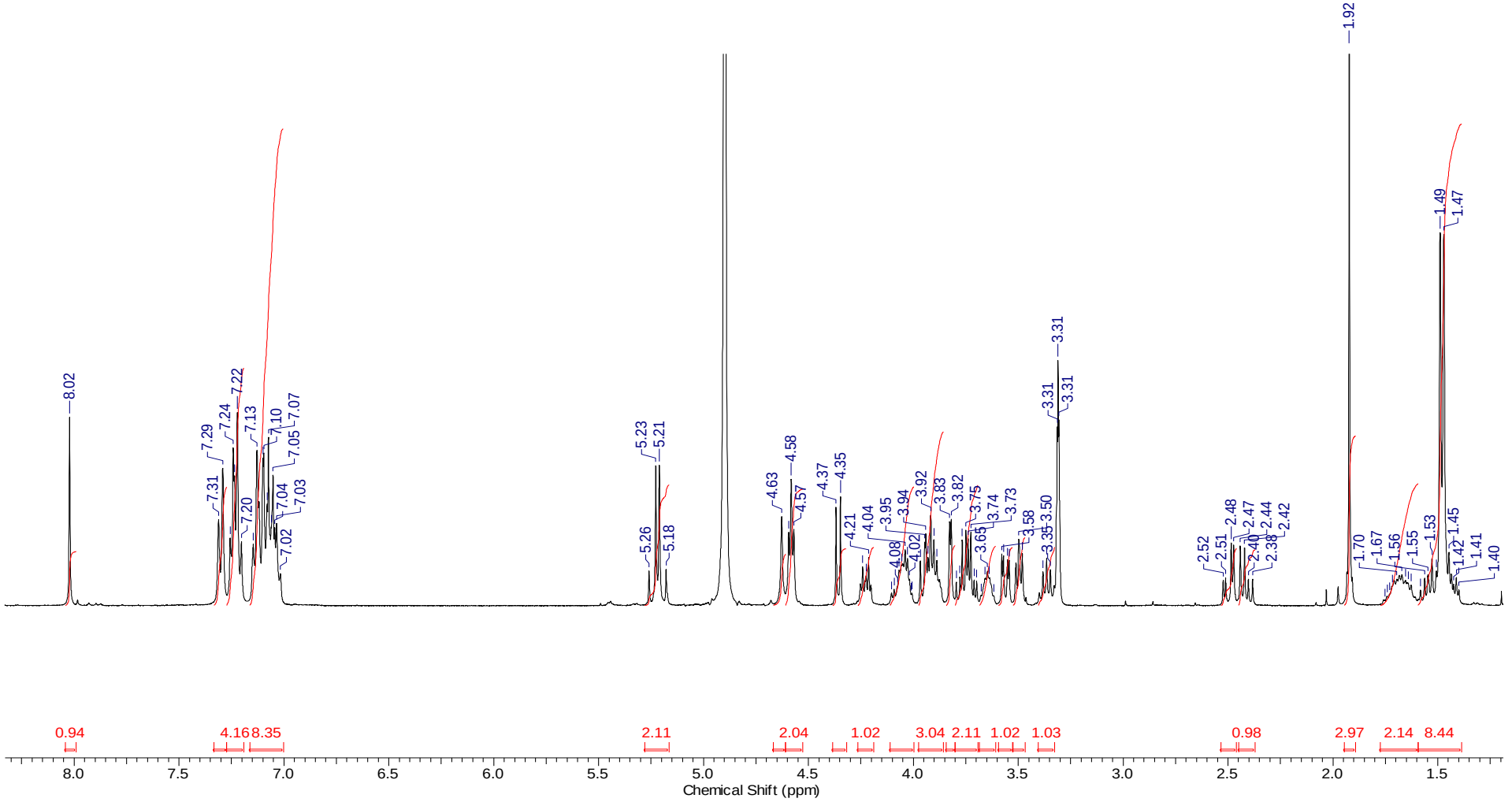
recombinant cathepsin B was detected by the hydrolysis of the fluorogenic substrate Ac-Pro-Leu-Val-Gln-7-amino-4-methylcoumarin (Ac-PLVQ-AMC) (PepTech, Russia). A total for 20 nM of the protein was mixed in 96-well plate with 0.1M sodium acetate buffer (100 mM NaCl, 1 mM EDTA, 0.6% DMSO, pH 3.6), and the substrate was added to a final concentration of 50 µM. The substrate hydrolysis was continuously measured for 12 min using a CLARIOstar® Plus plate reader (BMG Labtech Ortenberg Baden-Württemberg, Germany) at excitation and emission wavelengths of 353 and 442 nm, respectively.

**References**

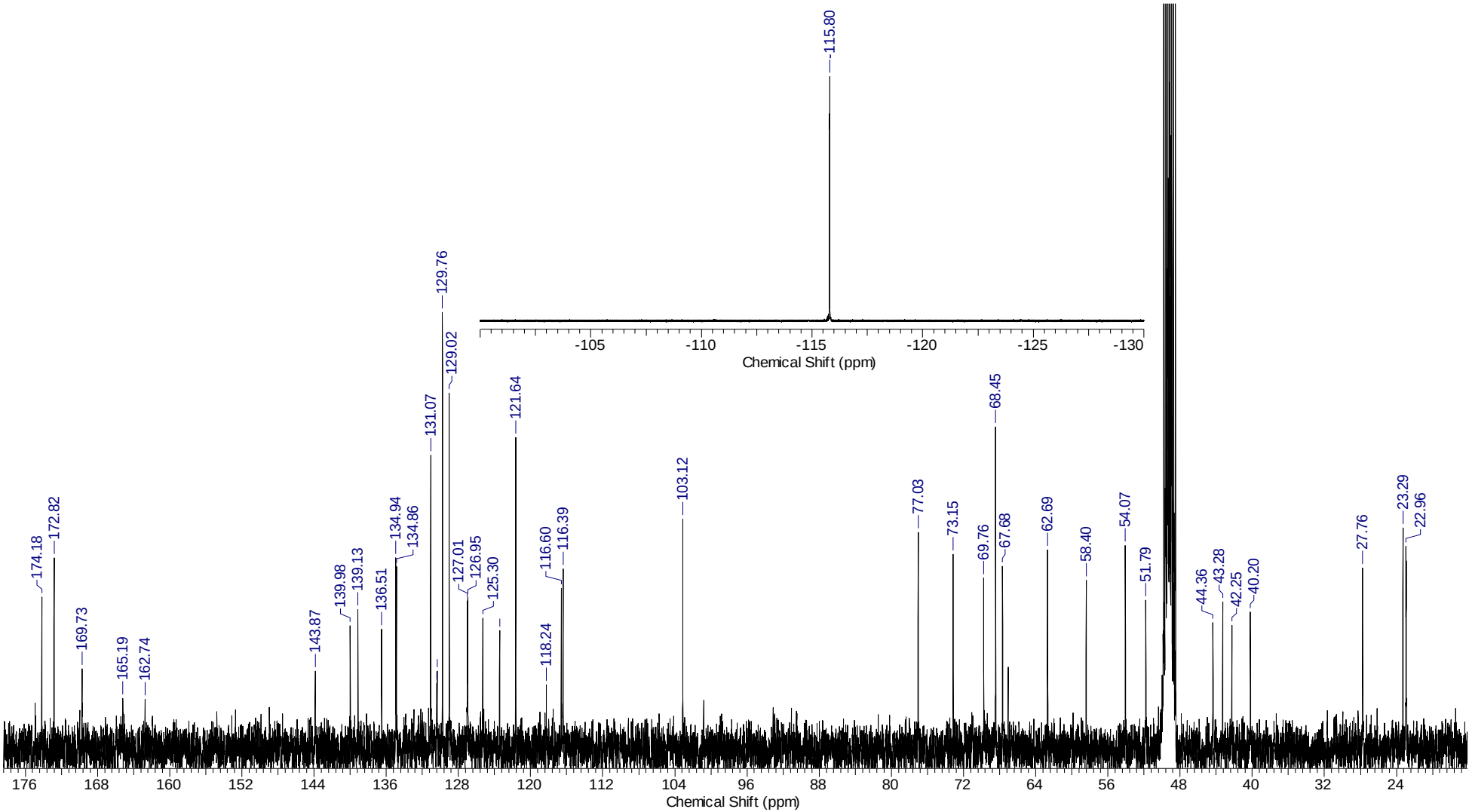
1. M. Rudzińska, A. Parodi, V.D. Maslova, Y.M. Efremov, N.V. Gorokhovets, V.A. Makarov , V.A. Popkov , A.V. Golovin, E.Y. Zernii, A.A. Zamyatnin, Jr. Cysteine cathepsins inhibition affects their expression and human renal cancer cell phenotype // *Cancers*. **2020**. V.12. P.1310.

# NMR spectra of the conjugates

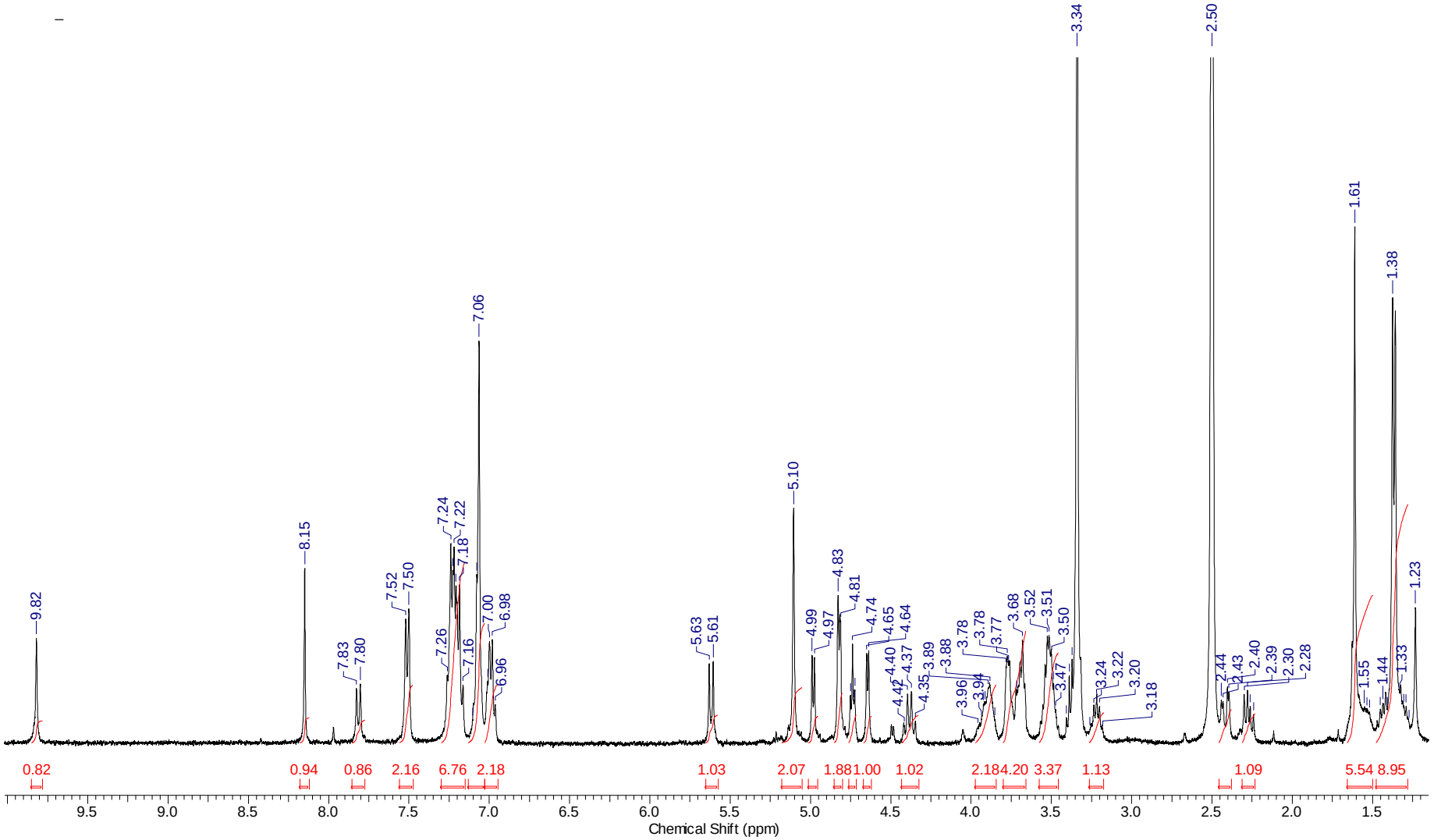
**$^1$H NMR spectrum of compound 1a ($CD_3OD$)**



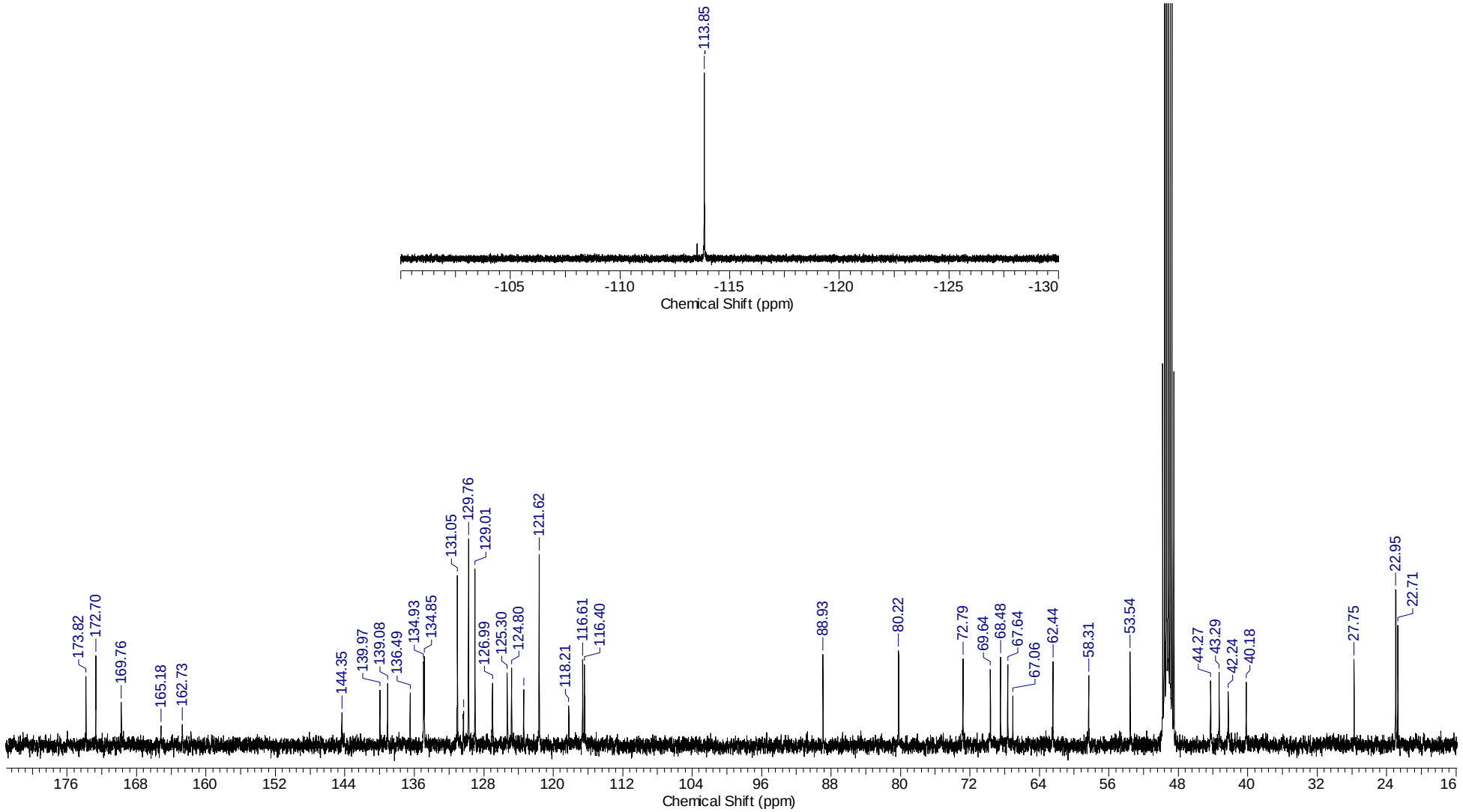
**$^{13}C$ and $^{19}F$ NMR spectra of compound 1a ($CD_3OD$)**



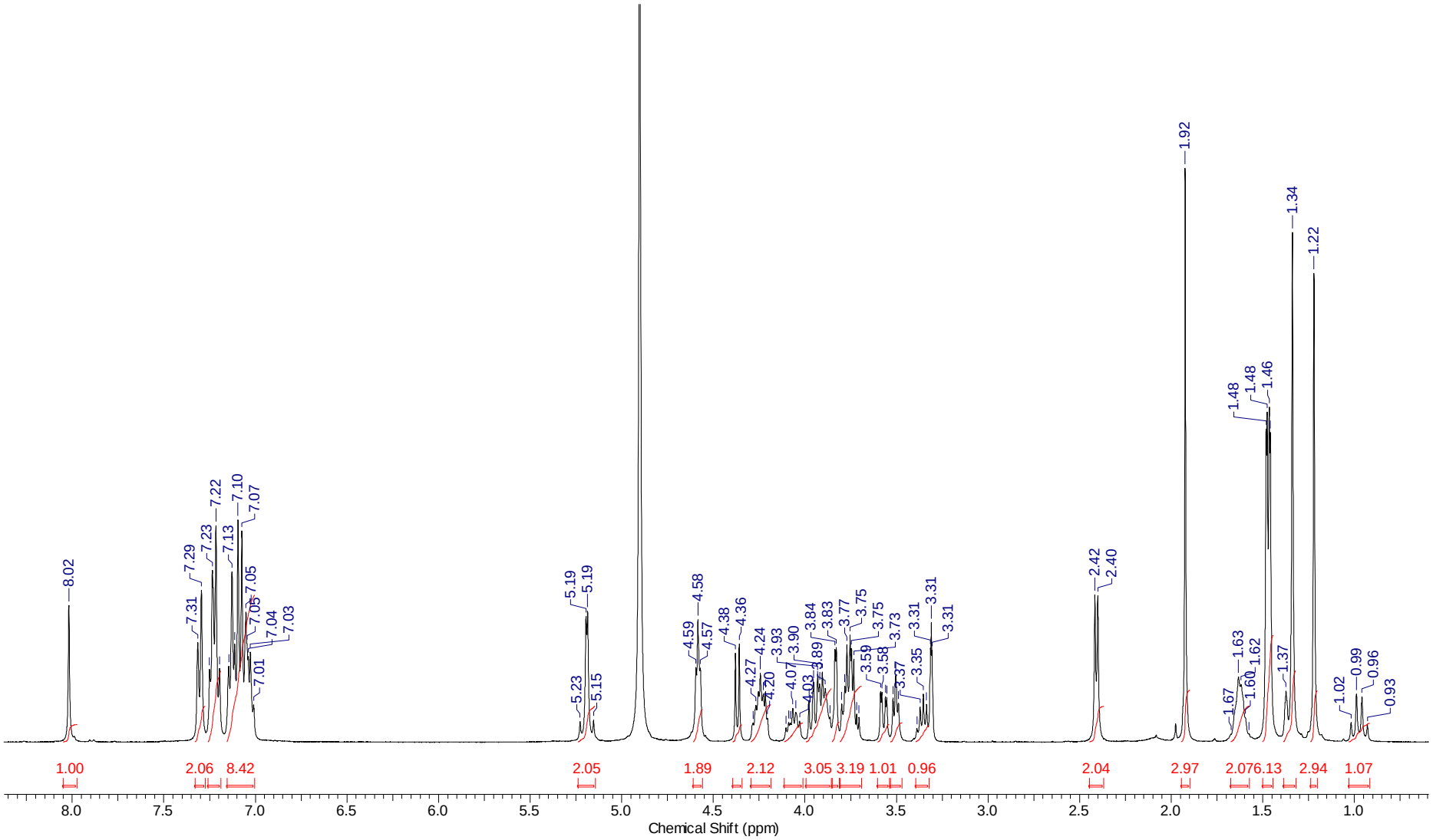
**$^{1}$H NMR spectrum of compound 1b (DMSO-d6)**



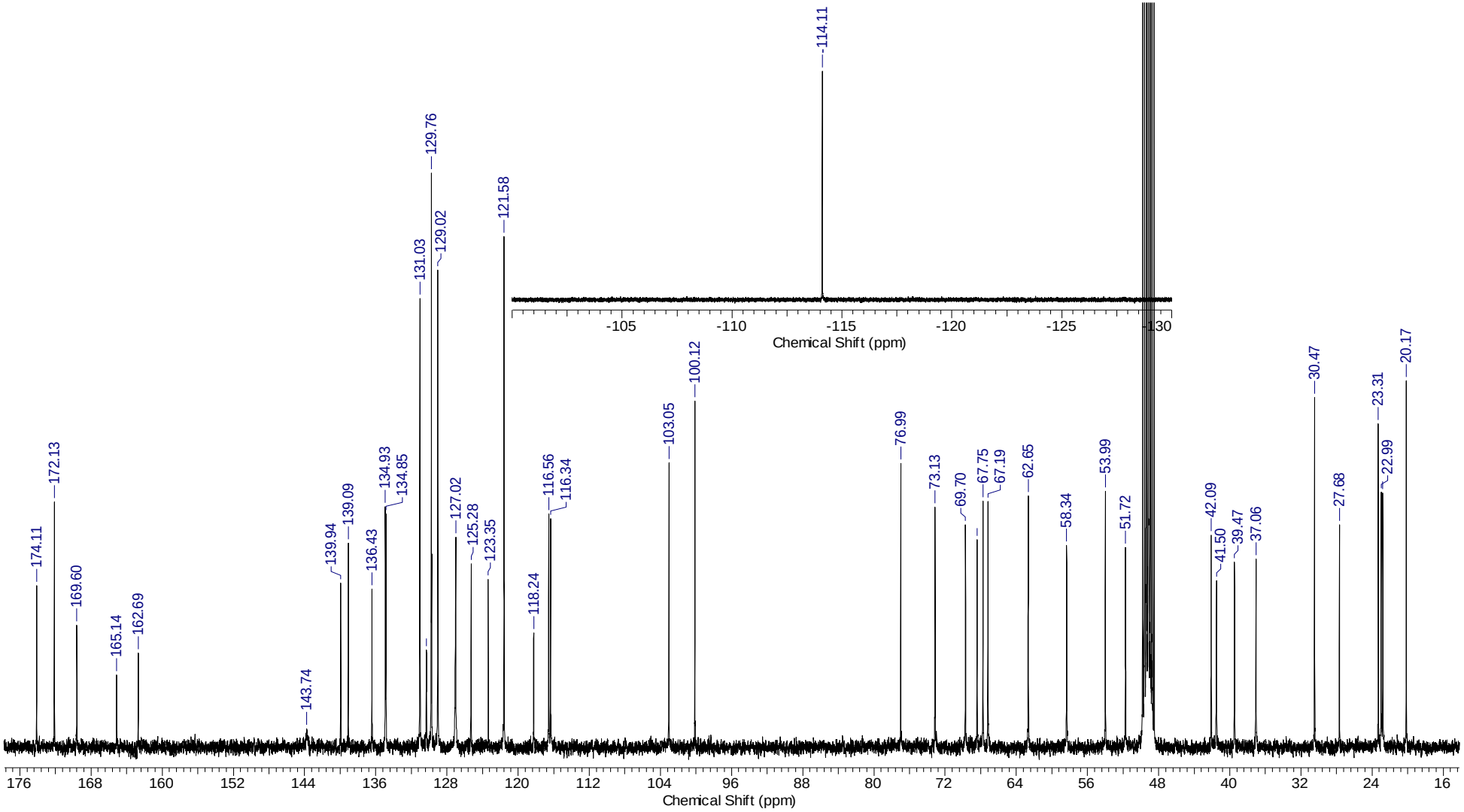
**$^{13}C$ and $^{19}F$ NMR spectra of compound 1b ($CD_3OD$)**



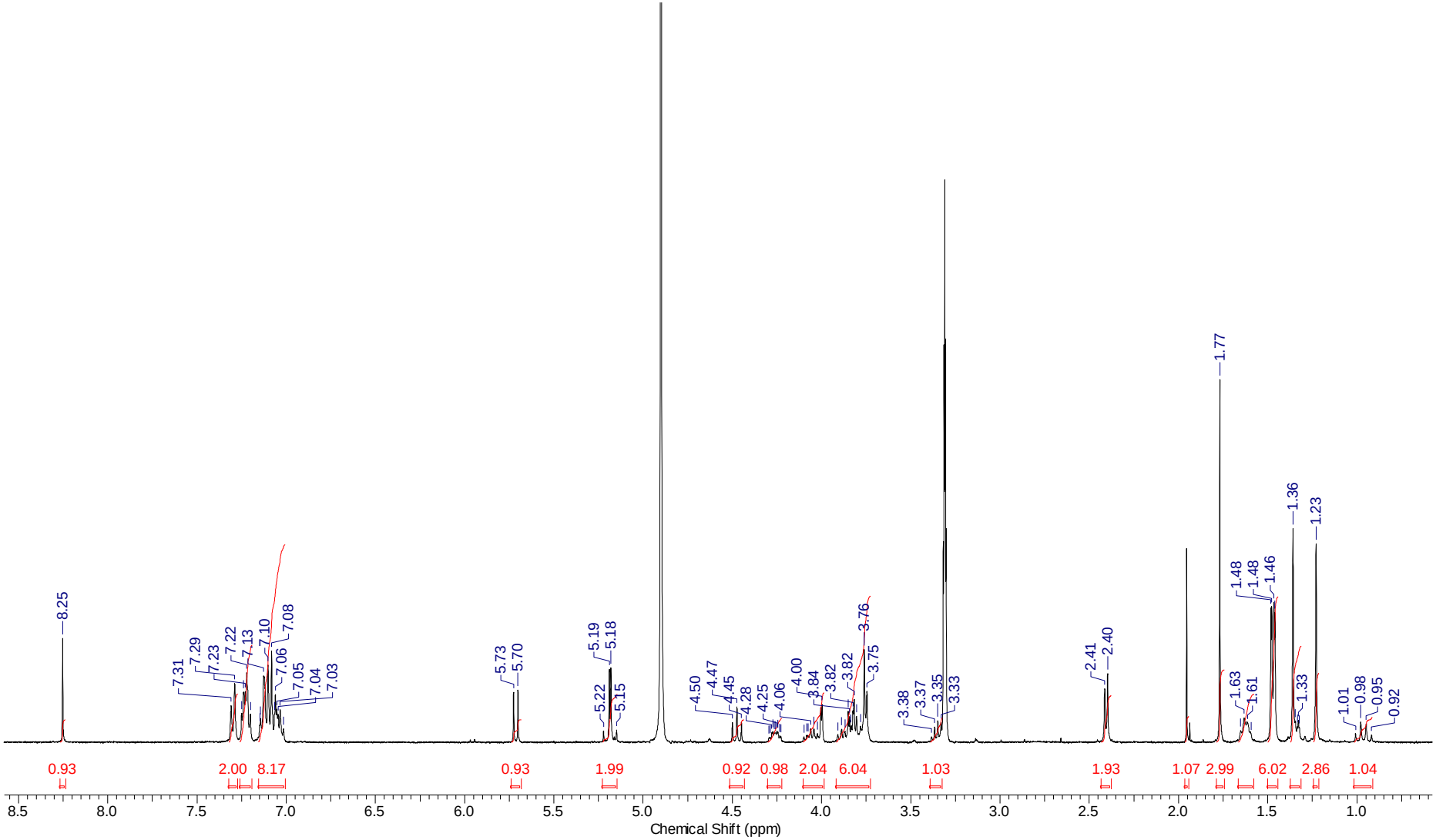
**$^{1}$H NMR spectrum of compound 2a ($CD_3OD$)**



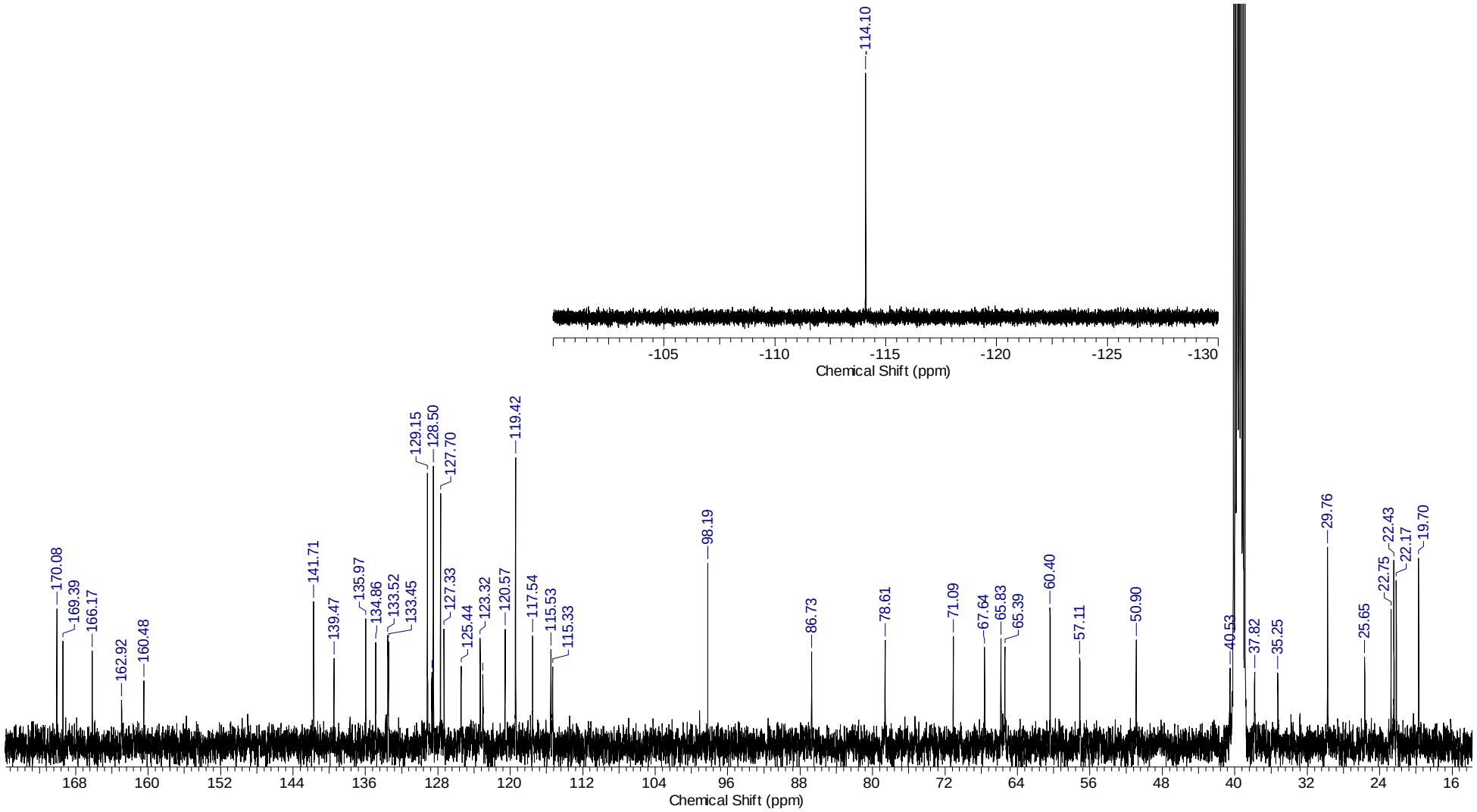
**$^{13}C$ and $^{19}F$ NMR spectra of compound 2a ($CD_3OD$)**



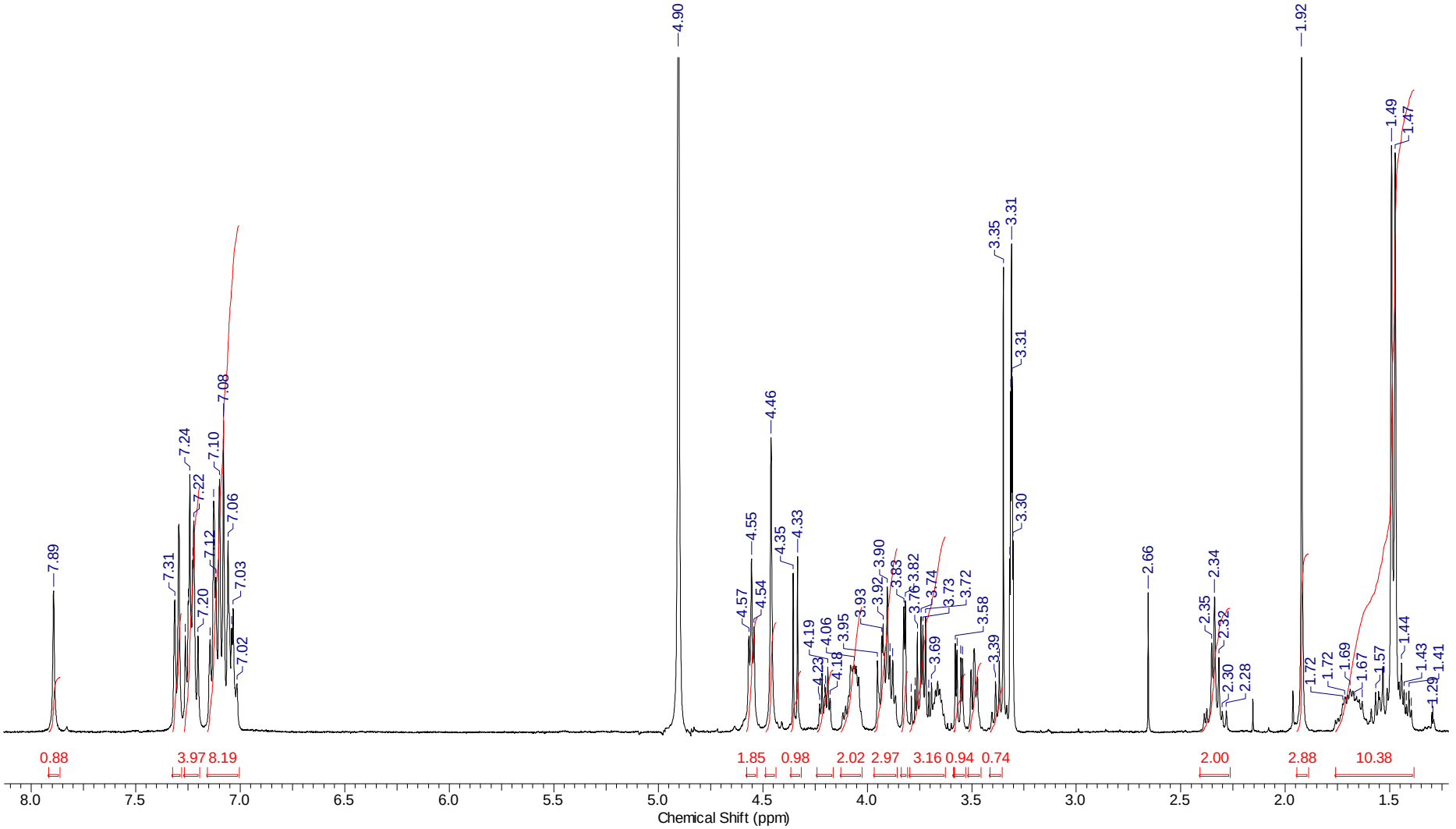
**$^{1}$H NMR spectrum of compound 2b ($CD_3OD$)**



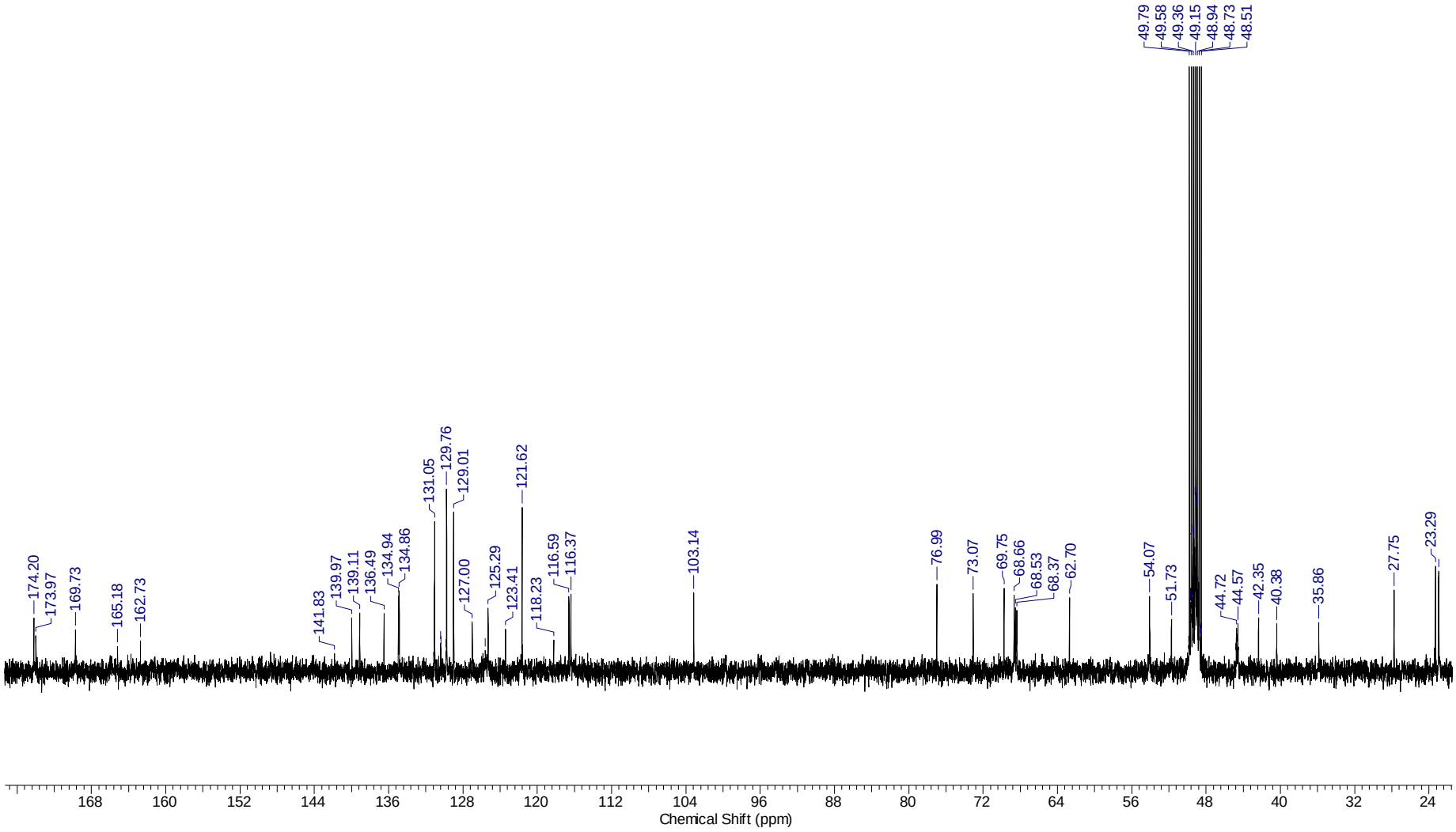
**$^{13}C$ and $^{19}F$ NMR spectra of compound 2b (DMSO-d6)**



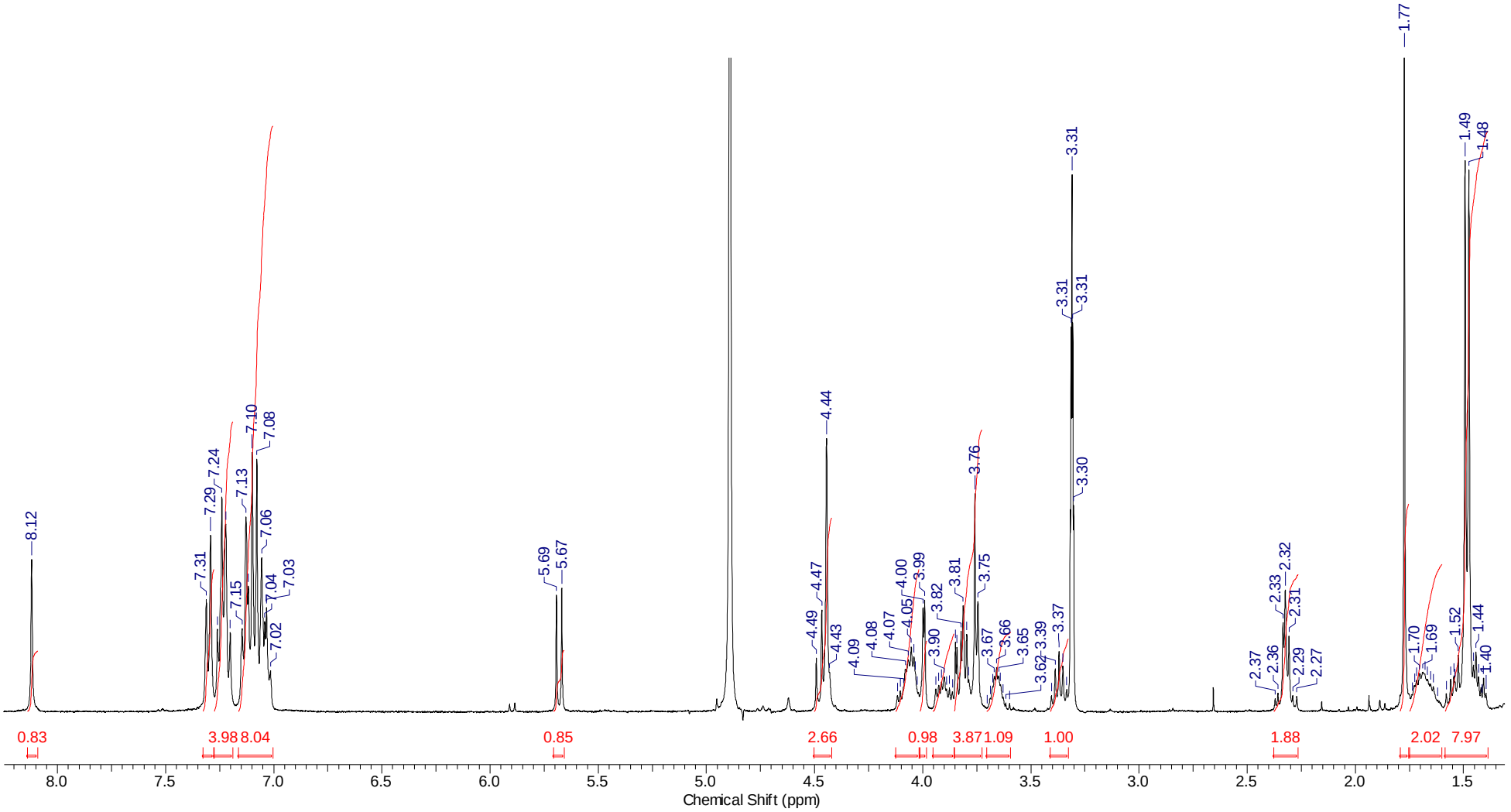
**$^{1}$H NMR spectrum of compound 3a ($CD_3OD$)**



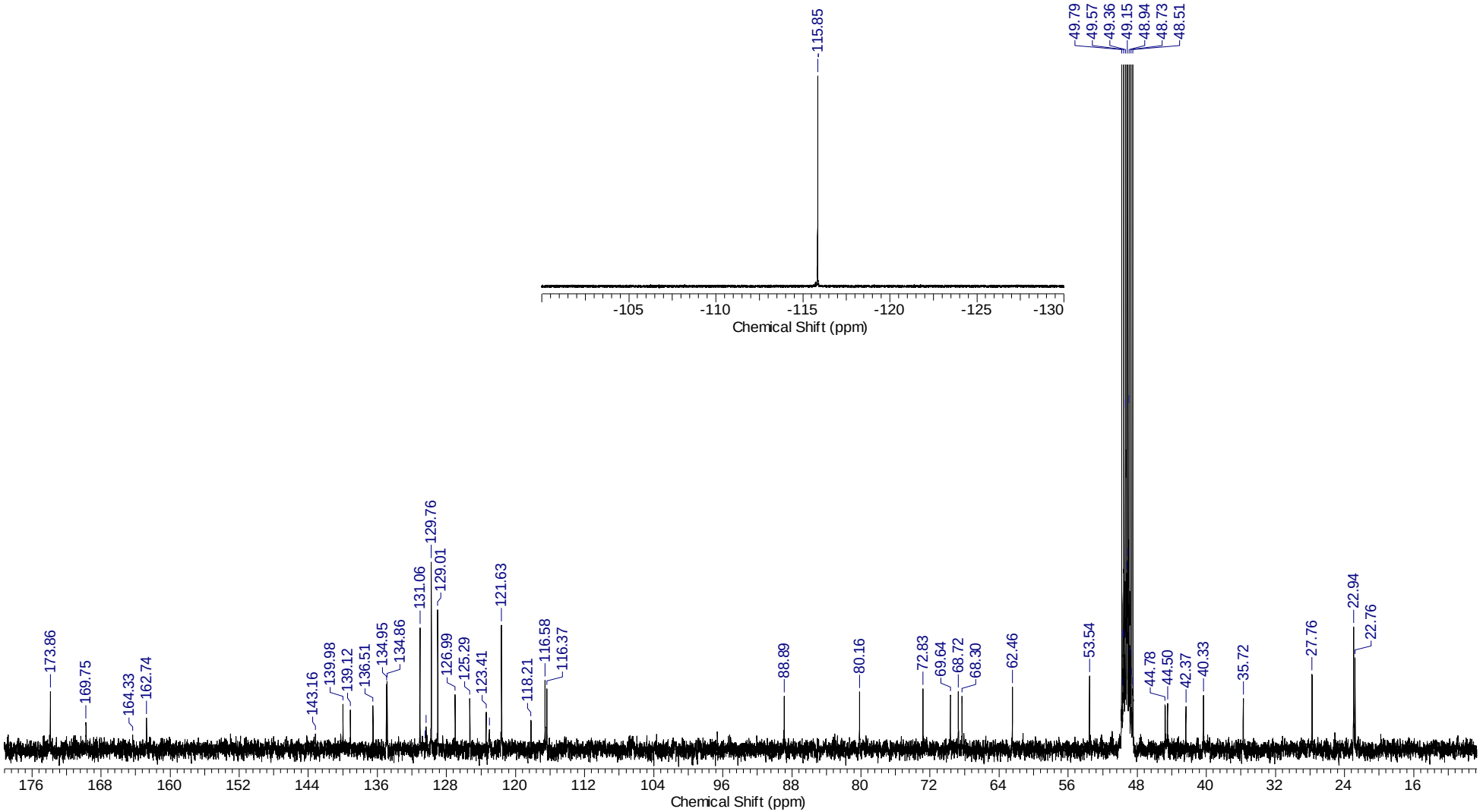
**$^{13}$C NMR spectrum of compound 3a ($CD_3OD$)**



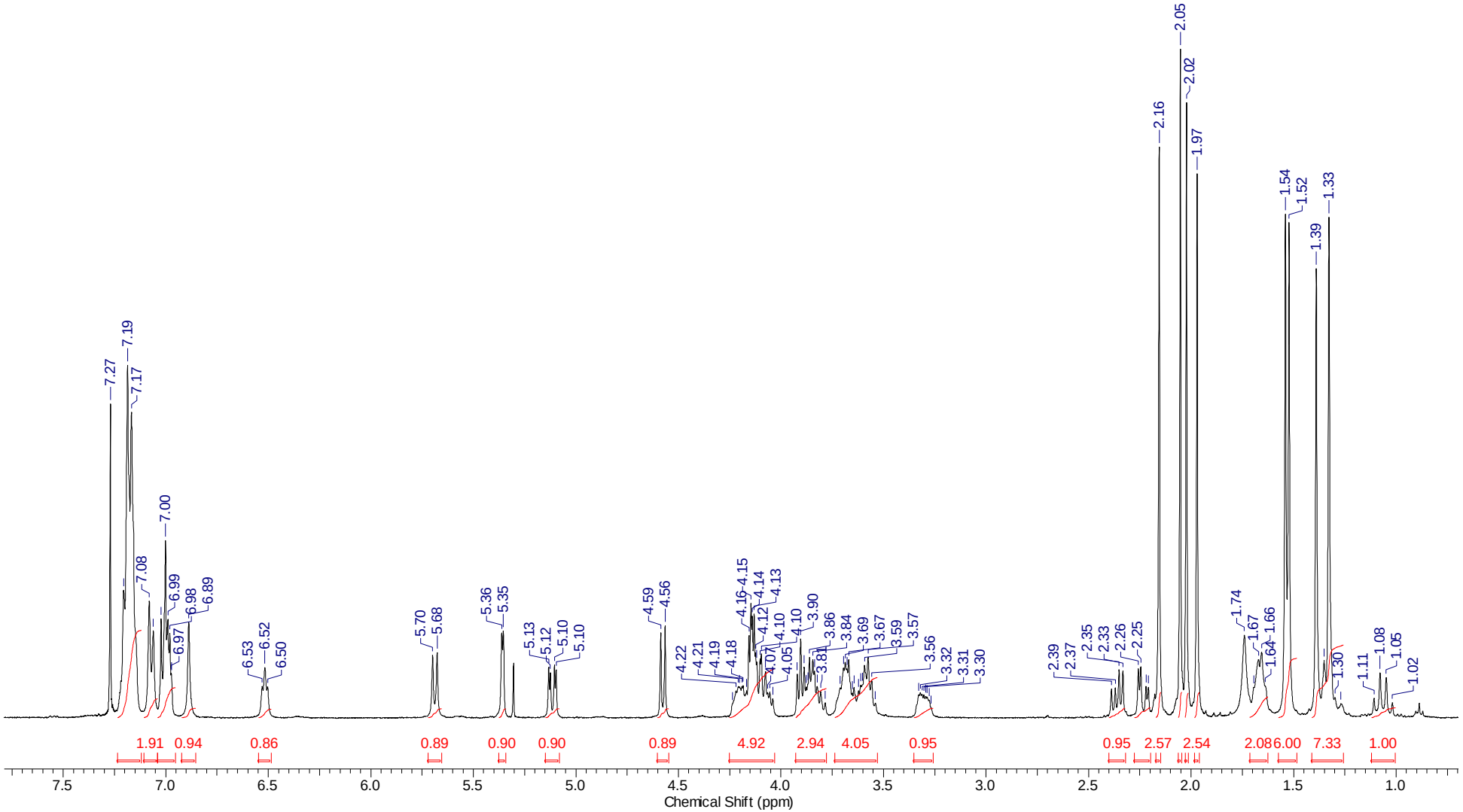
**$^{1}$H NMR spectrum of compound 3b ($CD_3OD$)**



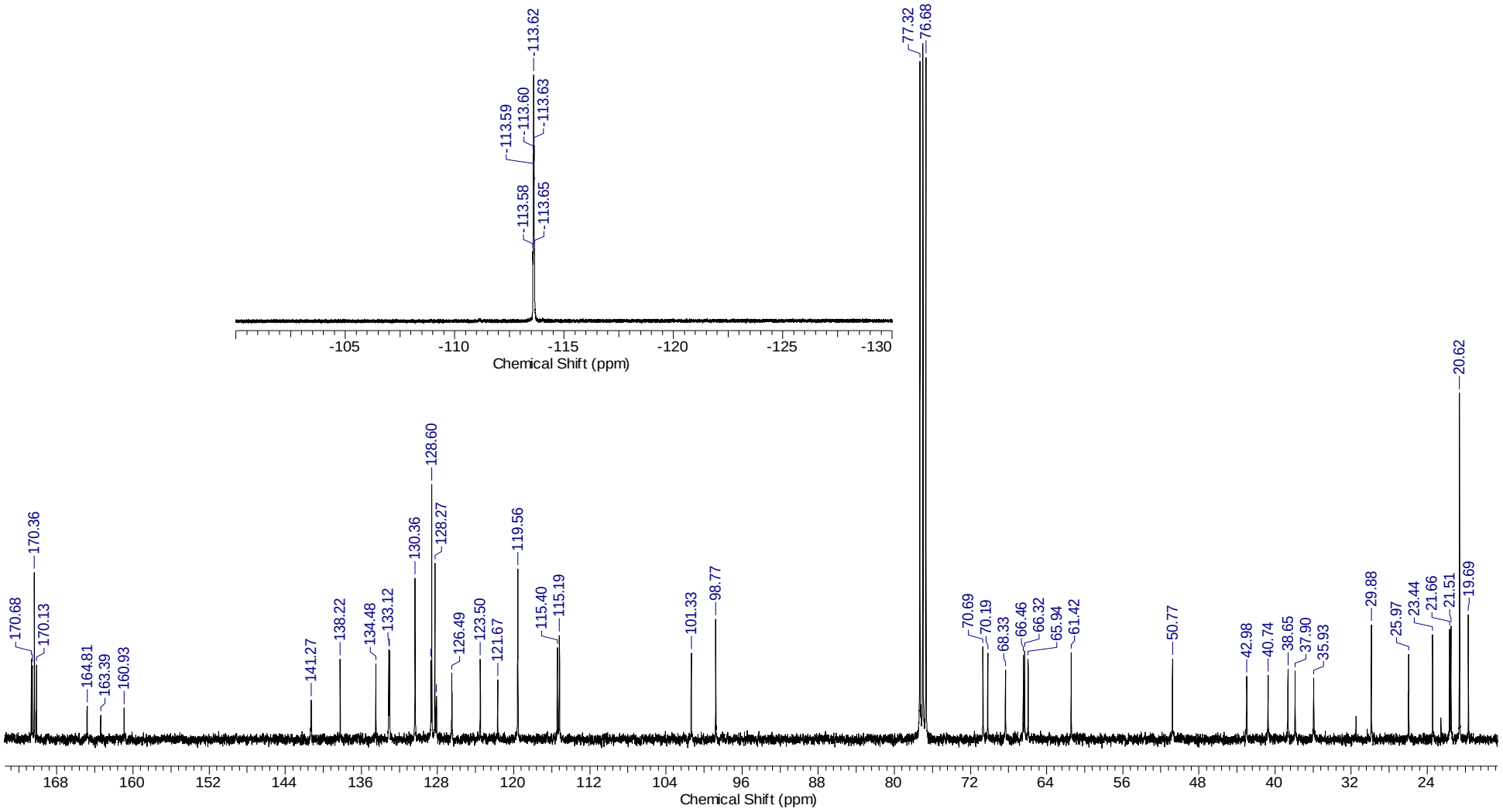
**$^{13}C$ and $^{19}F$ NMR spectra of compound 3b ($CD_3OD$)**



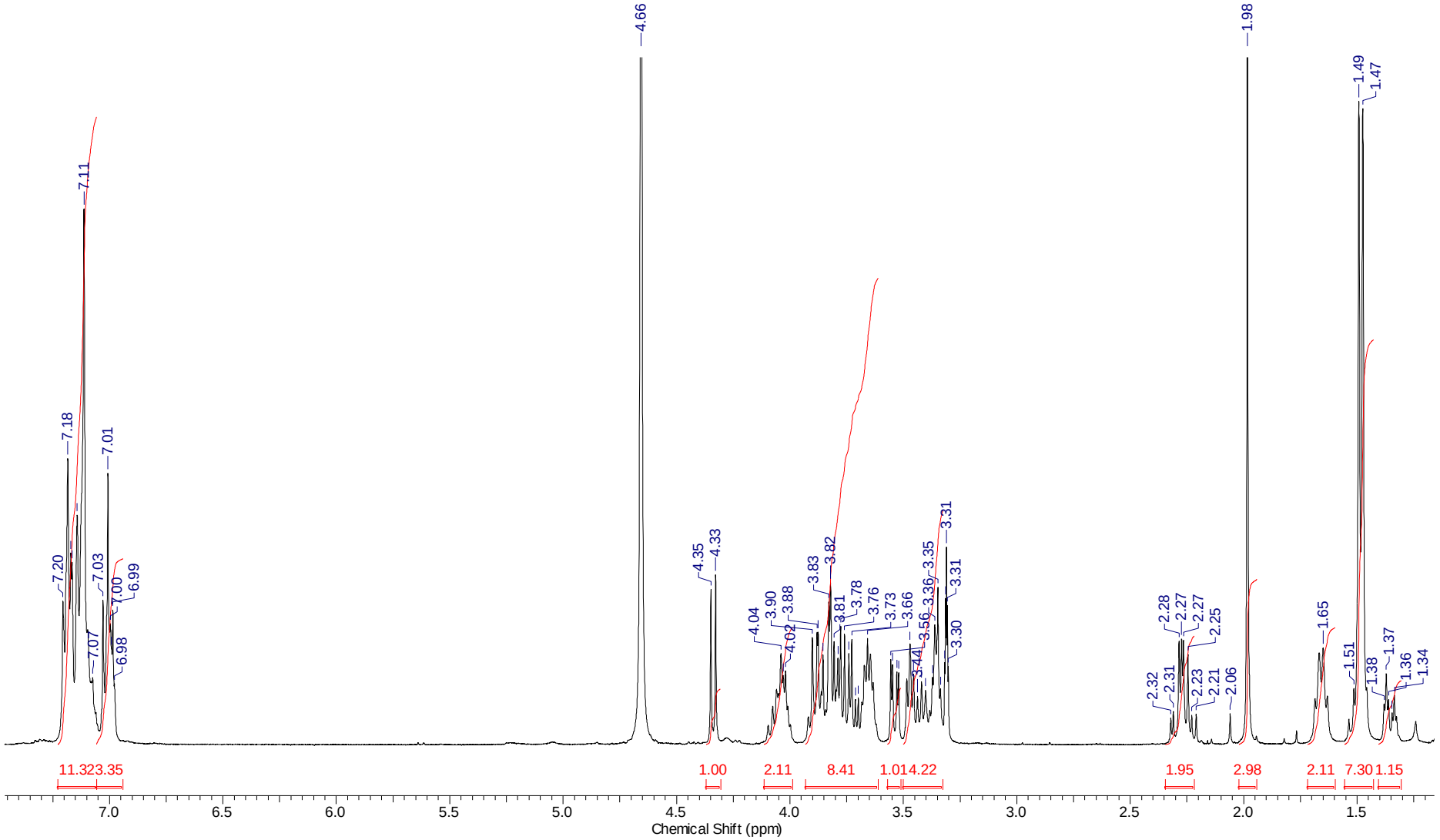
**$^{1}$H NMR spectrum of compound 4c' ($CDCl_3$)**



**$^{13}C$ and $^{19}F$ NMR spectra of compound 4c' ($CDCl_3$)**



**$^{1}$H NMR spectrum of compound 4c ($CD_3OD$)**



**$^{13}C$ and $^{19}F$ NMR spectra of compound 4c ($CD_3OD+CDCl_3$)**