

Synthesis of chiral α -(tetrazol-1-yl)-substituted carboxylic acids

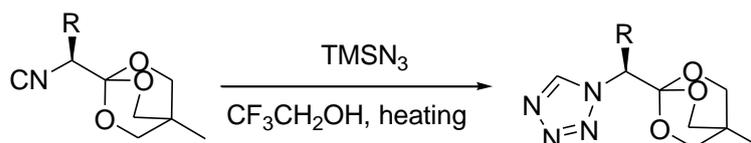
Danil P. Zarezin, Olga I. Shmatova and Valentine G. Nenajdenko

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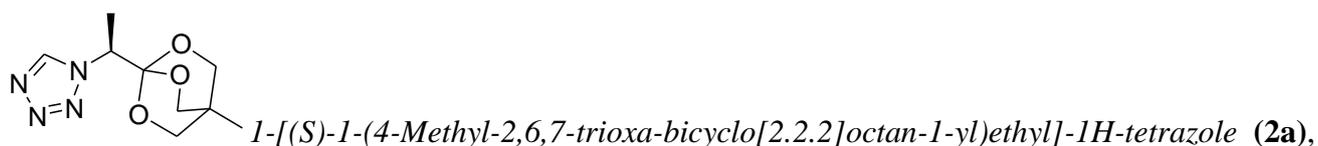
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GENERAL. 1D NMR (^1H and ^{13}C) spectra were obtained on 400 MHz spectrometers. Chemical shifts are reported in parts per million downfield from TMS. Deuterated solvent peaks were used as internal references: CDCl_3 at 7.27 and 77.00 ppm, DMSO-d_6 at 2.50 and 39.50 ppm, and CD_3OD at 3.31 and 49.00 ppm. High-resolution mass spectrometry (HRMS) was performed using a MicroTOF-Q instrument. Electrospray ionization (ESI) mass spectrometry (MS) was performed using dichloromethane or methanol solutions. Melting points are uncorrected. The silica gel used for flash chromatography was 230–400 mesh.

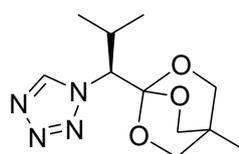
General Procedure for α -tetrazolyl-substituted carboxylic acid OBO-esters **2**



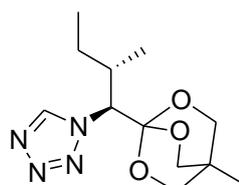
Isocyano OBO-ester **1a-f** (1 mmol) was dissolved in $\text{CF}_3\text{CH}_2\text{OH}$ (5 mL) in a sealed vial. Then TMSN_3 (1.7 mmol) was added. The mixture was heated at 70 °C for 1-2 days (TLC control). When the reaction was complete, the solvent was evaporated and the product was purified by flash column chromatography (eluent: dichloromethane).



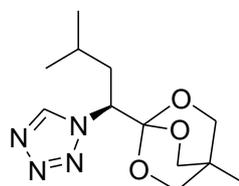
160 mg, 75 %, white solid m.p. 151 – 153 °C; ^1H NMR (400 MHz, CDCl_3): δ 0.79 (s, 3H), 1.61 (d, $J_{\text{HH}} = 7.1$ Hz, 3H), 3.87 (s, 6H), 4.87 (q, $J_{\text{HH}} = 7.1$ Hz, 6H), 8.71 (s, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ 14.0, 15.2, 30.7, 58.8, 72.8, 106.8, 142.3. IR (ZnSe, ATR, cm^{-1}): 709, 1091, 2925. HRMS (ESI): calcd. for $\text{C}_9\text{H}_{15}\text{N}_4\text{O}_3$ $[\text{M}+\text{H}]^+$ 227.1139, found 227.1139. $[\alpha]_{\text{D}}^{25} = -19.2^\circ$ (c 1.0, CH_2Cl_2).



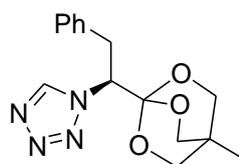
1-[(*S*)-2-Methyl-1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)propyl]-1H-tetrazole (**2b**), 208 mg, 82 %, white solid m.p. 142 – 143 °C; ¹H NMR (400 MHz, CDCl₃): δ 0.76 (d, *J*_{HH} = 6.8 Hz, 3H), 0.80 (s, 3H), 0.99 (d, *J*_{HH} = 6.9 Hz, 3H), 2.44 – 2.53 (m, 1H), 3.85 – 3.91 (m, 6H), 4.66 (d, *J*_{HH} = 6.2 Hz, 1H), 8.75 (s, 1H). ¹³C NMR (100 MHz, CDCl₃): δ 14.1, 18.3, 20.7, 28.7, 30.7, 68.2, 72.6, 107.3, 142.6. IR (ZnSe, ATR, cm⁻¹): 991, 1049, 1468, 2942. HRMS (ESI): calcd. for C₁₁H₁₉N₄O₃ [M+H]⁺ 255.1452, found 255.1453. [α]²⁰_D = -31.7° (c 0.83, CH₂Cl₂).



1-[(*1S,2S*)-2-Methyl-1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)butyl]-1H-tetrazole (**2c**), 225 mg, 84 %, white solid m.p. 111 – 113 °C; ¹H NMR (400 MHz, CDCl₃): δ 0.60 – 0.65 (m, 1H), 0.68 (d, *J*_{HH} = 7.0 Hz, 3H), 0.71 (s, 3H), 0.91 (d, *J*_{HH} = 6.8 Hz, 3H), 1.28 – 1.34 (m, 1H), 2.09 – 2.15 (m, 1H), 3.74 – 3.81 (m, 6H), 4.58 (d, *J*_{HH} = 7.1 Hz, 1H), 8.65 (s, 1H). ¹³C NMR (100 MHz, CDCl₃): δ 10.5, 13.8, 16.3, 24.3, 30.4, 35.1, 67.1, 72.3, 107.1, 142.3. IR (ZnSe, ATR, cm⁻¹): 991, 1056, 1470, 2967. HRMS (ESI): calcd. for C₁₂H₂₁N₄O₃ [M+H]⁺ 269.1608, found 269.1609. [α]²⁰_D = +5.4° (c 1.0, CH₂Cl₂).

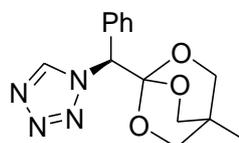


1-[(*S*)-3-Methyl-1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)butyl]-1H-tetrazole (**2d**), 190 mg, 71 %, white solid 112 – 114 °C; ¹H NMR (400 MHz, CDCl₃): δ 0.80 – 0.83 (m, 6H), 0.87 (d, *J*_{HH} = 6.6 Hz, 3H), 1.11 – 1.17 (m, 1H), 1.82 – 1.89 (m, 1H), 1.93 – 2.01 (m, 1H), 3.84 – 3.90 (m, 6H), 4.85 (dd, *J*_{HH} = 3.3 Hz, *J*_{HH} = 8.5 Hz, 1H), 8.70 (s, 1H). ¹³C NMR (100 MHz, CDCl₃): δ 14.1, 20.7, 23.1, 24.0, 30.7, 37.7, 61.5, 72.8, 107.0, 142.2. IR (ZnSe, ATR, cm⁻¹): 1041, 1286, 1471, 2964. HRMS (ESI): calcd. for C₁₂H₂₁N₄O₃ [M+H]⁺ 269.1608, found 269.1609. [α]²⁰_D = -27.4° (c 0.83, CH₂Cl₂).



1-[(*S*)-1-(4-Methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)-2-phenylethyl]-1H-tetrazole (**2e**), 278 g, 92 %, white solid m.p. 147 – 149 °C ¹H NMR (400 MHz, CDCl₃): δ 0.77 (s, 3H), 3.26 (dd, *J*_{HH} = 3.0 Hz, *J*_{HH} = 11.7 Hz, 1H), 3.50 (dd, *J*_{HH} = 3.0 Hz, *J*_{HH} = 11.7 Hz, 1H), 3.88 (s,

6H), 4.96 (dd, $J_{HH} = 3.3$ Hz, $J_{HH} = 8.5$ Hz, 1H), 6.93 (bd, $J_{HH} = 6.2$ Hz, 2H), 7.07 – 7.14 (m, 3H), 8.66 (s, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ 13.8, 30.6, 35.0, 64.5, 72.7, 106.6, 126.8, 128.4, 128.5, 135.4, 142.6. IR (ZnSe, ATR, cm^{-1}): 1006, 1049, 1294, 2894. HRMS (ESI): calcd. for $\text{C}_{15}\text{H}_{19}\text{N}_4\text{O}_3$ $[\text{M}+\text{H}]^+$ 303.1452, found 303.1453. $[\alpha]_{\text{D}}^{20} = -103.2^\circ$ (c 0.83, CH_2Cl_2).

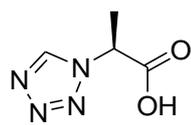


1-[(S)-(4-Methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)(phenyl)methyl]-1H-

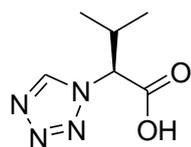
tetrazole (2f), 248 mg, 86 %, white solid m.p. 152 – 154 °C; ^1H NMR (400 MHz, CDCl_3): δ 0.82 (s, 3H), 3.94 (s, 6H), 5.98 (s, 1H), 7.33 – 7.35 (m, 3H), 7.41 – 7.45 (m, 2H), 8.96 (s, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ 13.7, 30.6, 66.1, 72.5, 107.0, 128.2, 128.5, 128.8, 132.4, 142.2. IR (ZnSe, ATR, cm^{-1}): 730, 1047, 1201, 1471, 2885. HRMS (ESI): calcd. for $\text{C}_{14}\text{H}_{17}\text{N}_4\text{O}_3$ $[\text{M}+\text{H}]^+$ 289.1295, found 289.1295. $[\alpha]_{\text{D}}^{20} = +101.6^\circ$ (c 1.0, CH_2Cl_2).

General Procedure for chiral α -tetrazolyl-substituted carboxylic acids **3**

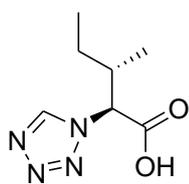
The appropriate tetrazole OBO ester **2a-f** (0.5 mmol) was dissolved in the H_2O /dioxane (3 ml, 1:2) mixture in a sealed vial. Then trifluoroacetic acid was added. Stirring was continued at room temperature for one day (TLC control). Thereafter, 6 *M* hydrochloric acid (3 ml) was added, and the reaction mixture was heated at 90 °C for one day. When the reaction was complete, the solvent was evaporated and the residue was dissolved in ethyl acetate. The organic phase was filtered through Celite, washed with ethyl acetate, and concentrated to give products **3a-f**.



(S)-2-(1H-Tetrazol-1-yl)propanoic acid (3a), 59 mg, 83 %, colourless oil; ^1H NMR (400 MHz, D_2O): δ 1.90 (d, $J_{HH} = 7.4$ Hz, 3H), 5.73 (q, $J_{HH} = 7.4$ Hz, 1H), 9.34 (s, 1H). ^{13}C NMR (100 MHz, D_2O): δ 16.0, 59.9, 143.7, 171.6. ^{13}C NMR (100 MHz, CDCl_3): δ 16.0, 59.9, 143.7, 171.6. IR (ZnSe, ATR, cm^{-1}): 679, 1035, 1234, 1745, 2954, 3342. HRMS (ESI): calcd. for $\text{C}_4\text{H}_7\text{N}_4\text{O}_2$ $[\text{M}+\text{H}]^+$ 143.0564, found 143.0563. $[\alpha]_{\text{D}}^{20} = -8.4^\circ$ (c 1.0, MeOH).

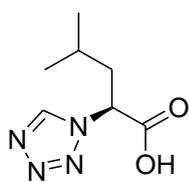


(S)-3-Methyl-2-(1H-tetrazol-1-yl)butanoic acid (3b), 67 mg, 79 %, colourless oil; ^1H NMR (400 MHz, D_2O): δ 1.90 (dd, $J_{HH} = 5.3$ Hz, $J_{HH} = 6.9$ Hz, 6H), 2.56 – 2.64 (m, 1H), 5.45 (d, $J_{HH} = 5.7$ Hz, 1H), 9.35 (s, 1H). ^{13}C NMR (100 MHz, D_2O): δ 16.9, 17.8, 30.5, 59.8, 144.1, 170.1. IR (ZnSe, ATR, cm^{-1}): 627, 1035, 1267, 1471, 1736, 2970, 3330. HRMS (ESI): calcd. for $\text{C}_6\text{H}_9\text{N}_4\text{O}_2$ $[\text{M}-\text{H}]^-$ 169.0731, found 169.0739. 170.0804. $[\alpha]_{\text{D}}^{20} = +7.8^\circ$ (c 1.0, MeOH).



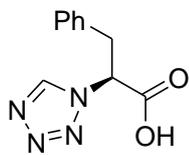
(2*S*,3*S*)-3-Methyl-2-(1*H*-tetrazol-1-yl)pentanoic acid (**3c**), 65 mg, 71%, colourless oil;

¹H NMR (400 MHz, acetone-*d*₆): δ 0.91 (t, *J*_{HH} = 7.3 Hz, 3H), 1.01 (d, *J*_{HH} = 6.6 Hz, 3H), 1.11 – 1.22 (m, 1H), 1.38 – 1.51 (m, 1H), 2.38 – 2.50 (m, 1H), 5.50 (d, *J*_{HH} = 6.6 Hz, 1H), 6.87 (bs, 1H), 9.30 (s, 1H). ¹³C NMR (100 MHz, acetone-*d*₆): δ 11.5, 15.9, 26.0, 38.4, 67.1, 144.6, 169.9. IR (ZnSe, ATR, cm⁻¹): 1039, 1467, 1740, 2970, 3394. HRMS (ESI): calcd. for C₇H₁₁N₄O₂ [M-H]⁺ 183.0887, found 183.0888. [α]_D²⁰ = +18.8° (c 1.0, MeOH).



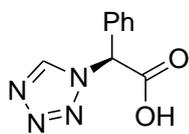
(*S*)-4-Methyl-2-(1*H*-tetrazol-1-yl)pentanoic acid (**3d**), 69 mg, 75 %, colourless oil; ¹H

NMR (400 MHz, D₂O): δ 0.68 – 0.88 (m, 6H), 1.24 – 1.28 (m, 1H), 2.09 – 2.15 (m, 1H), 2.22 – 2.30 (m, 1H), 5.69 – 5.72 (m, 1H), 9.41 (bs, 1H) ¹³C NMR (100 MHz, D₂O): δ 19.9, 21.5, 23.8, 39.1, 64.1, 144.0, 171.4. IR (ZnSe, ATR, cm⁻¹): 1041, 1471, 1747, 2960, 3386. HRMS (ESI): calcd. for C₇H₁₁N₄O₂ [M-H]⁺ 183.0887, found 183.0888. [α]_D²⁰ = +1.8° (c 1.0, MeOH).



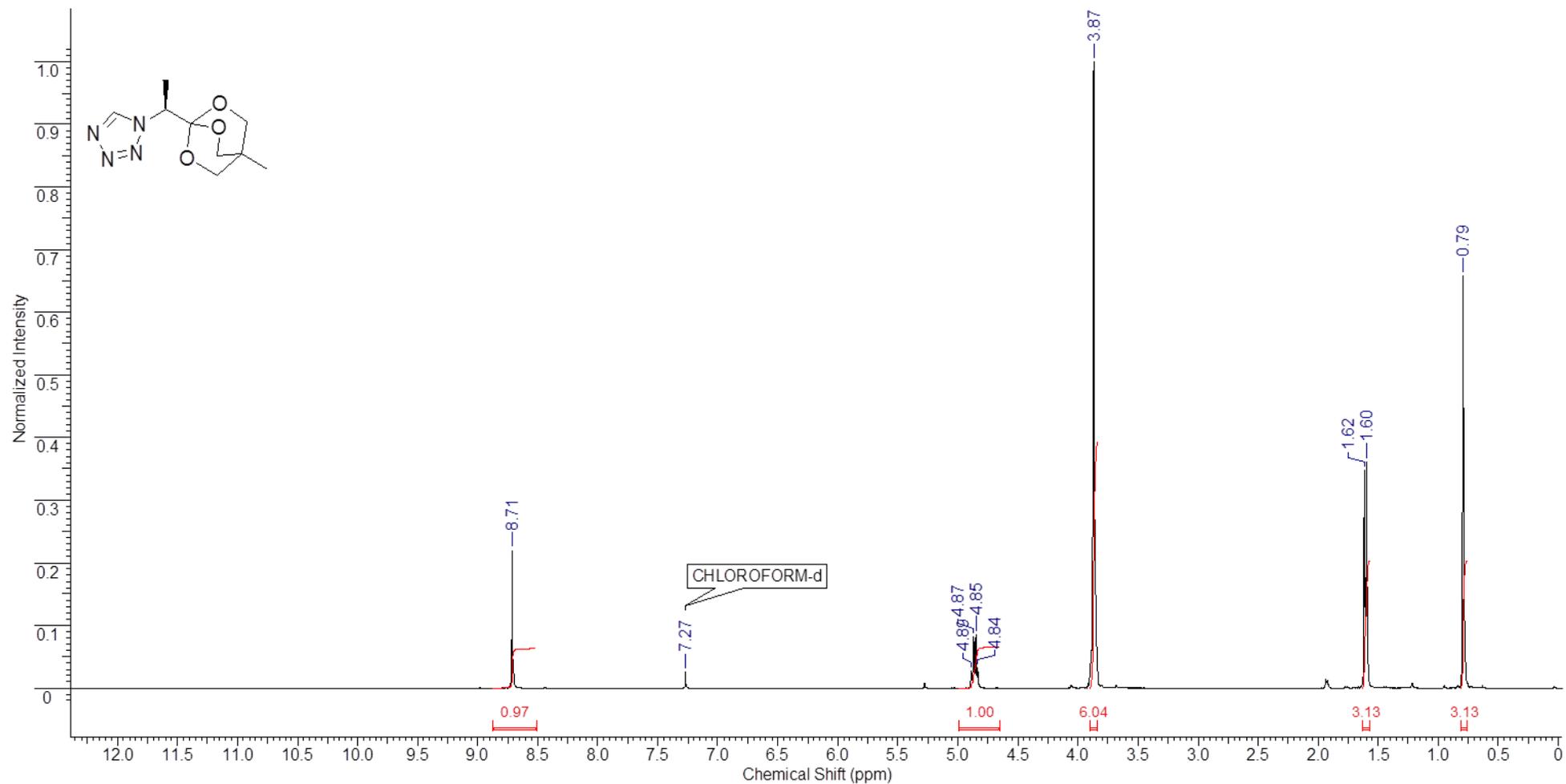
(*S*)-3-Phenyl-2-(1*H*-tetrazol-1-yl)propanoic acid (**3e**), 97 mg, 89 %, colourless oil; ¹H

NMR (400 MHz, CDCl₃): δ 3.47 – 3.65 (m, 2H), 5.71 (dd, *J*_{HH} = 5.1 Hz, *J*_{HH} = 3.6 Hz, 1H), 6.94 – 7.21 (m, 1H), 7.84 (bs, 1H), 8.67 (s, 1H). ¹³C NMR (100 MHz, CDCl₃): δ 38.1, 61.5, 127.8, 128.8, 129.0, 134.0, 146.2, 169.1. IR (ZnSe, ATR, cm⁻¹): 702, 1036, 1741, 2939, 3336. HRMS (ESI): calcd. for C₁₀H₉N₄O₂ [M-H]⁻ 217.0731, found 217.0731. [α]_D²⁰ = +8.2° (c 1.0, MeOH).

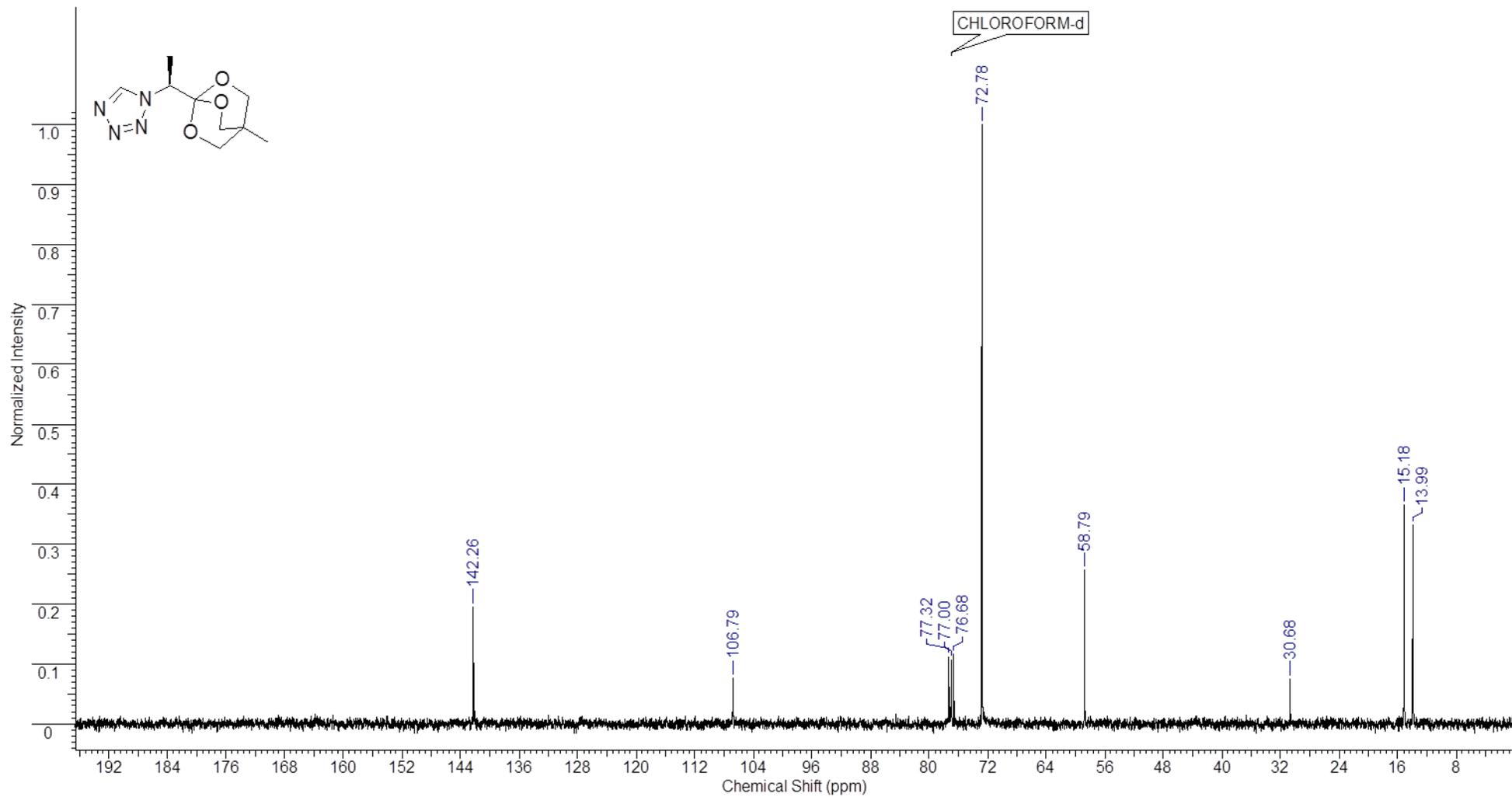


(*S*)-2-Phenyl-2-(1*H*-tetrazol-1-yl)acetic acid (**3f**), 82 mg, 80 %, yellow oil; ¹H NMR

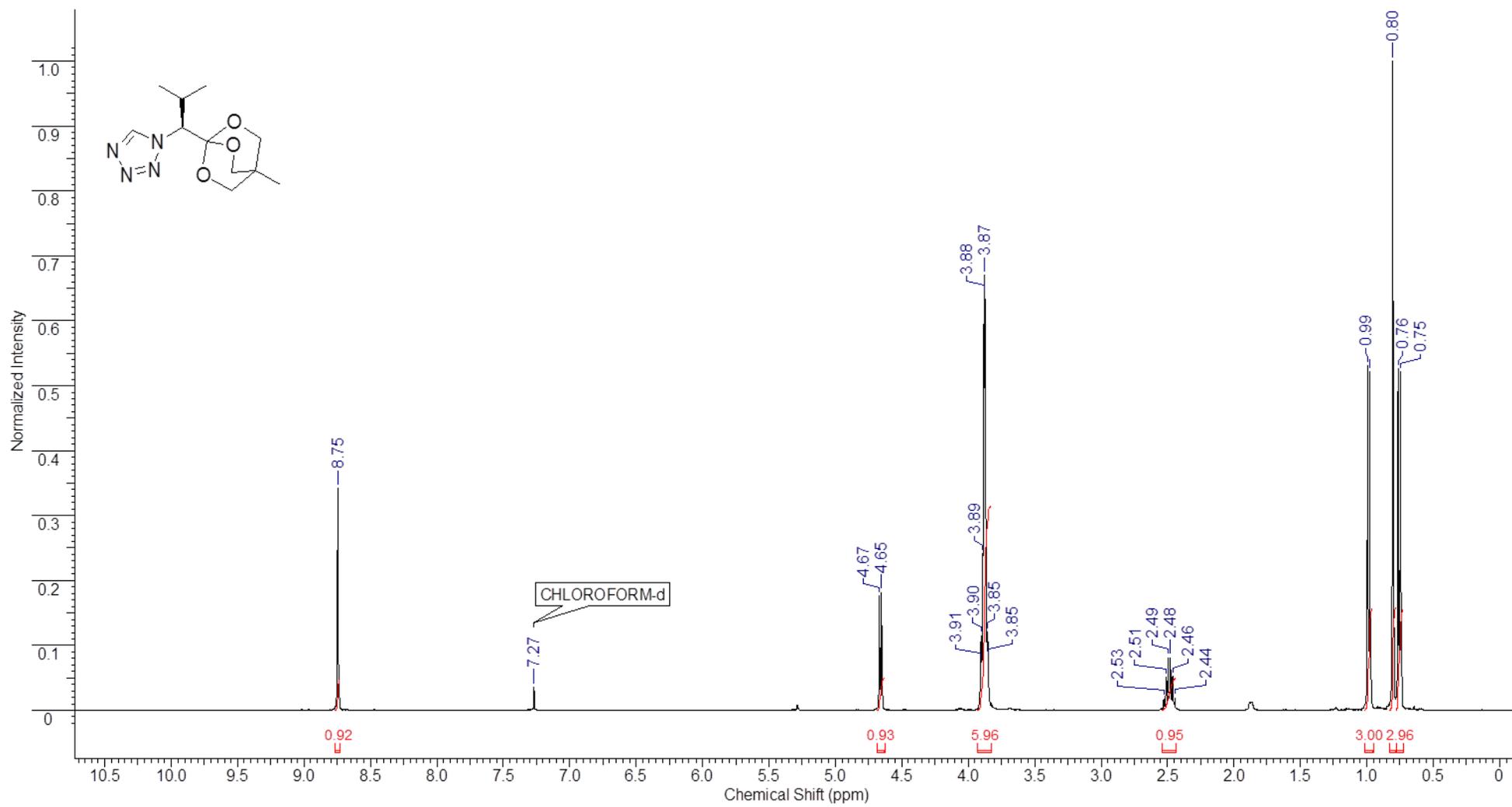
(400 MHz, CDCl₃): δ 6.56 (s, 1H), 6.63 (bs, 1H), 7.35 – 7.45 (m, 5H), 8.91 (s, 1H). ¹³C NMR (100 MHz, CDCl₃): δ 61.5, 128.2, 129.6, 130.2, 131.8, 142.7, 168.5. IR (ZnSe, ATR, cm⁻¹): 714, 1100, 1455, 1753, 2956, 3382. HRMS (ESI): calcd. for C₉H₉N₄O₂ [M+H]⁺ 205.0726, found 205.0720. [α]_D²⁰ = -56.6° (c 1.0, MeOH).



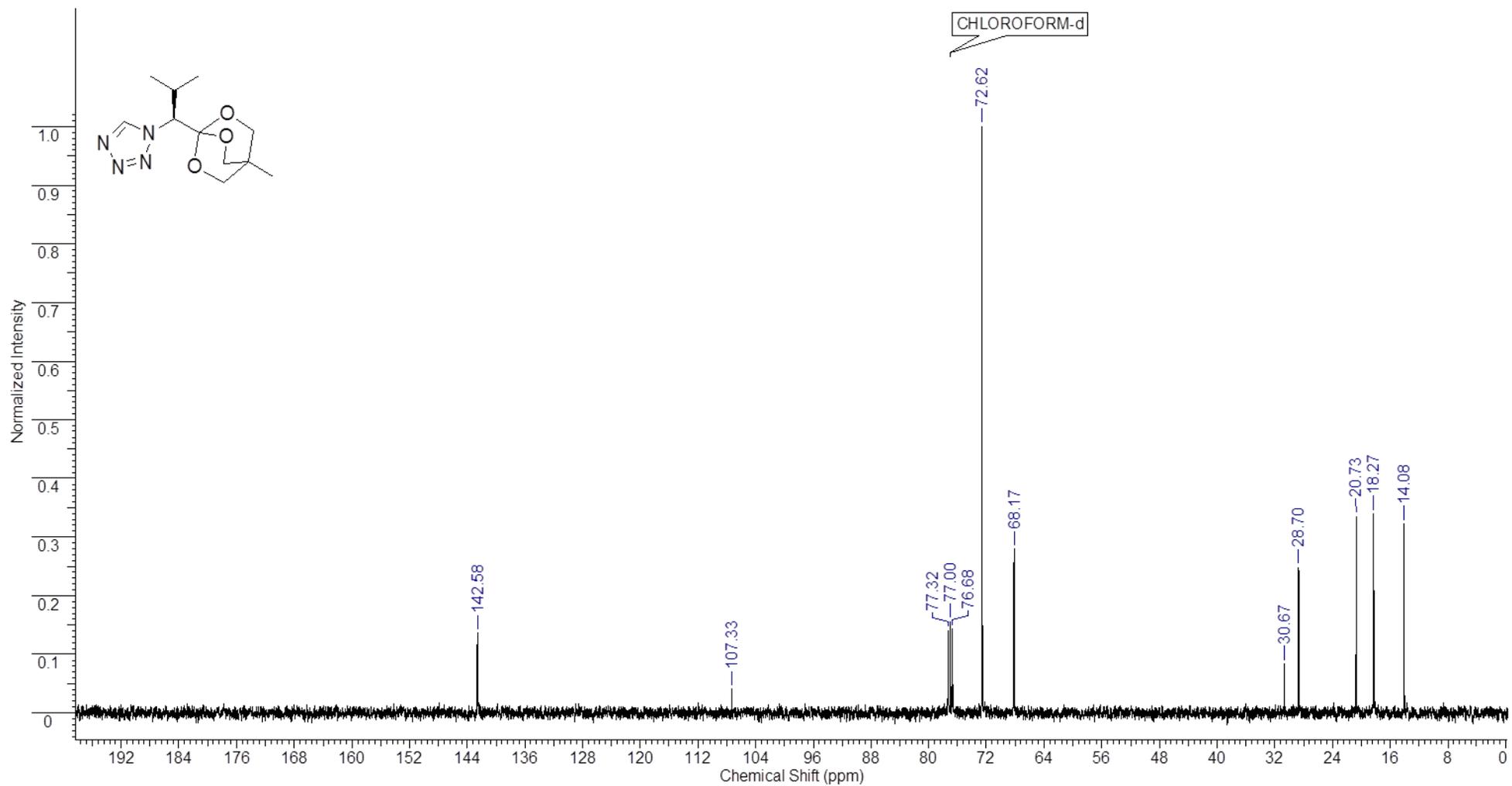
^1H NMR (400 MHz) spectrum of **2a** in CDCl_3



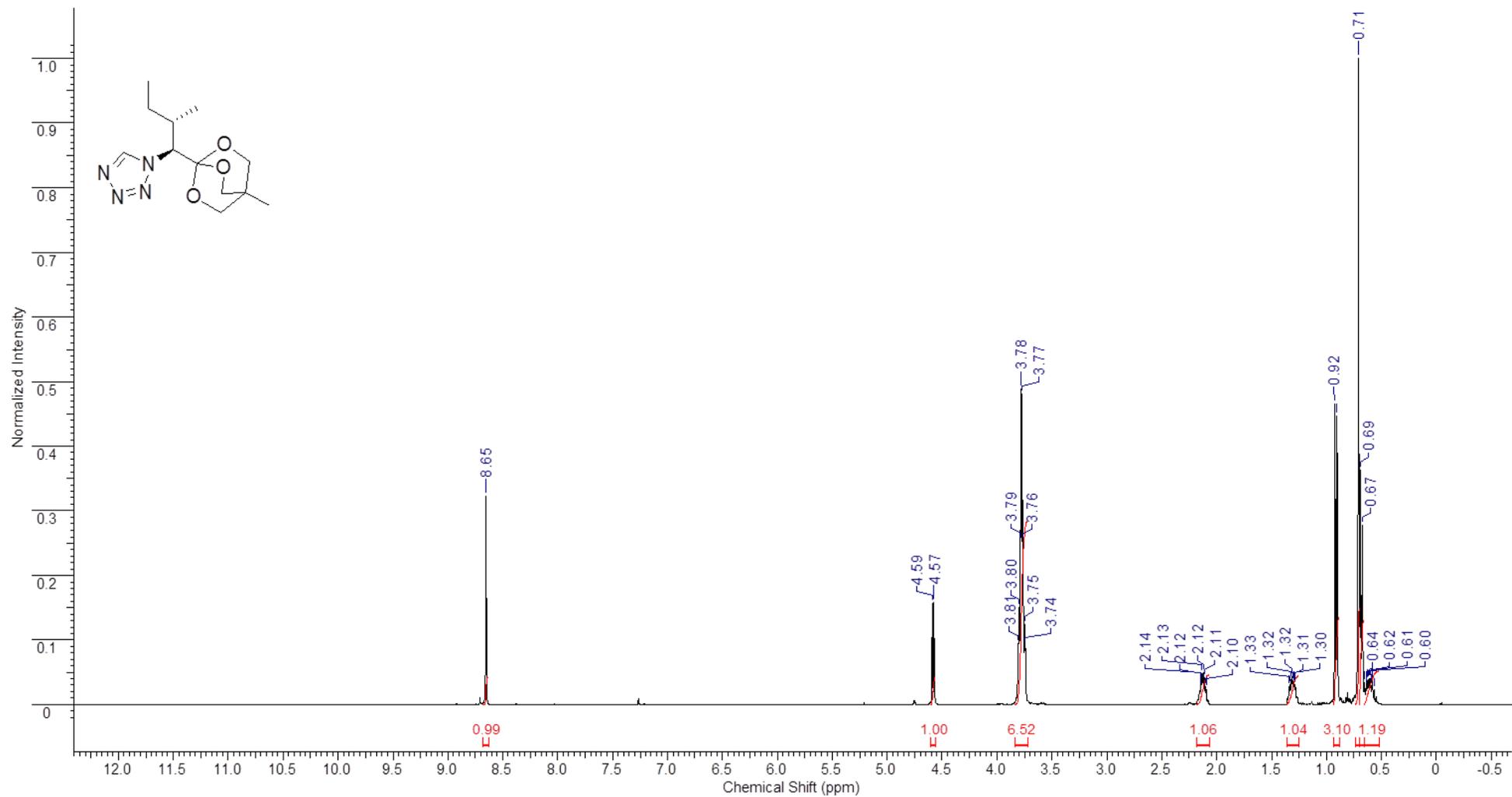
^{13}C NMR (100 MHz) spectrum of **2a** in CDCl_3



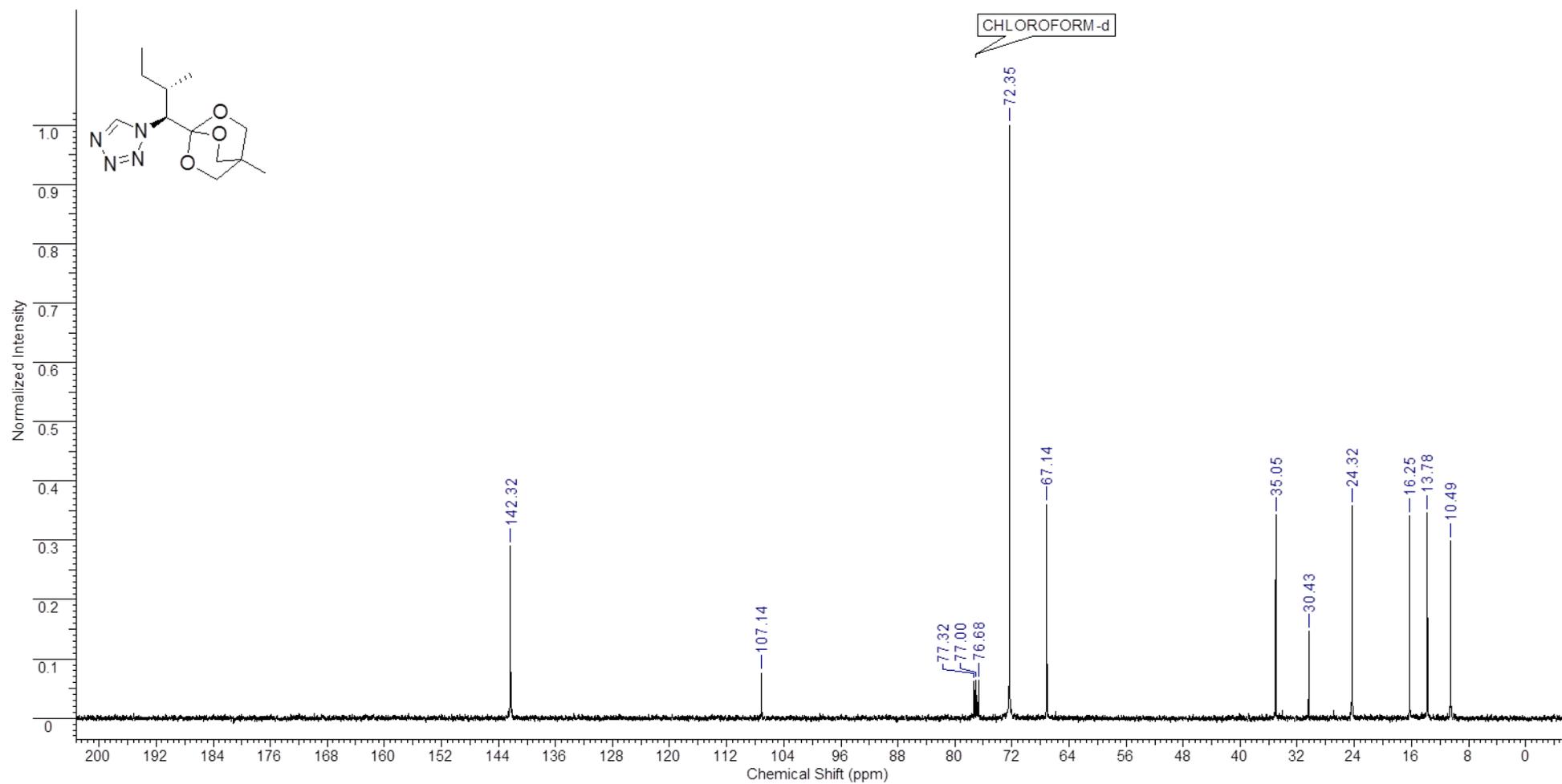
¹H NMR (400 MHz) spectrum of **2b** in CDCl₃



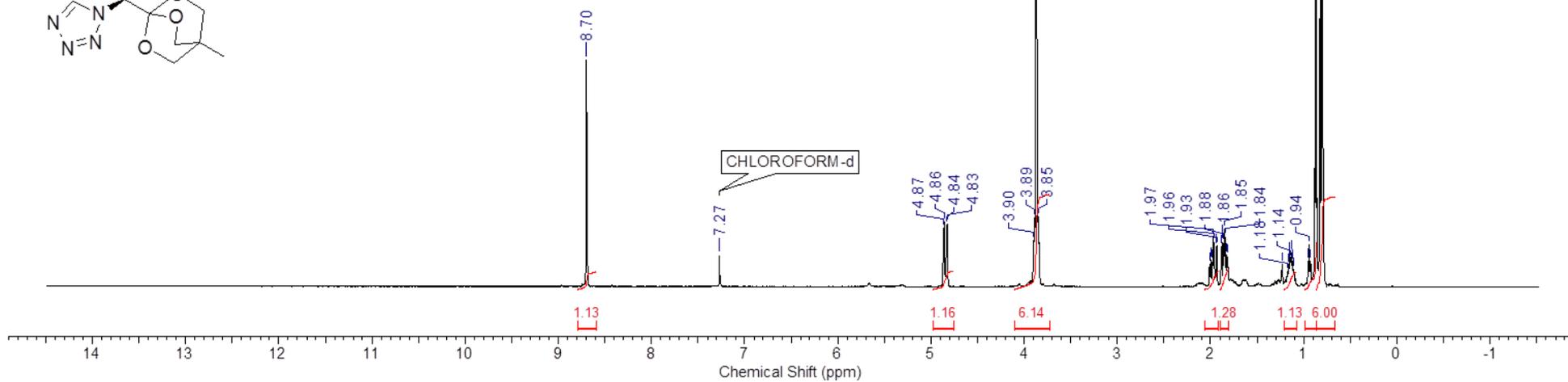
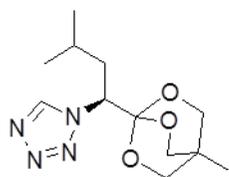
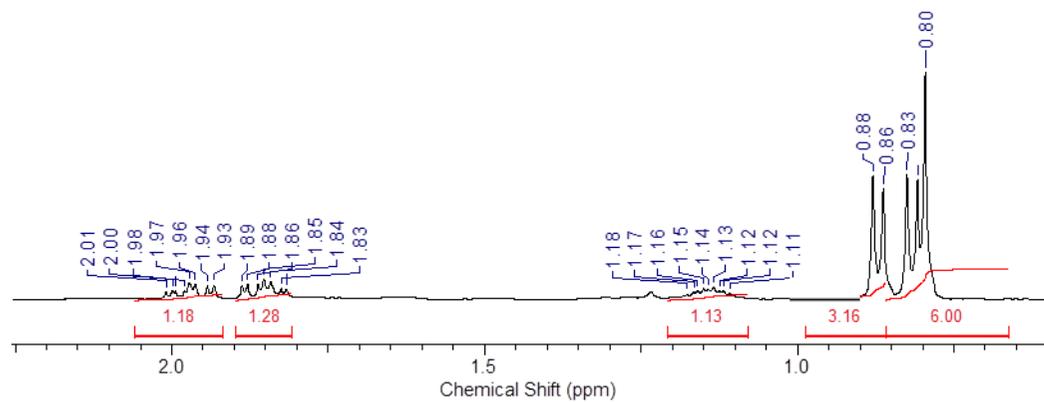
¹³C NMR (100 MHz) spectrum of **2b** in CDCl₃



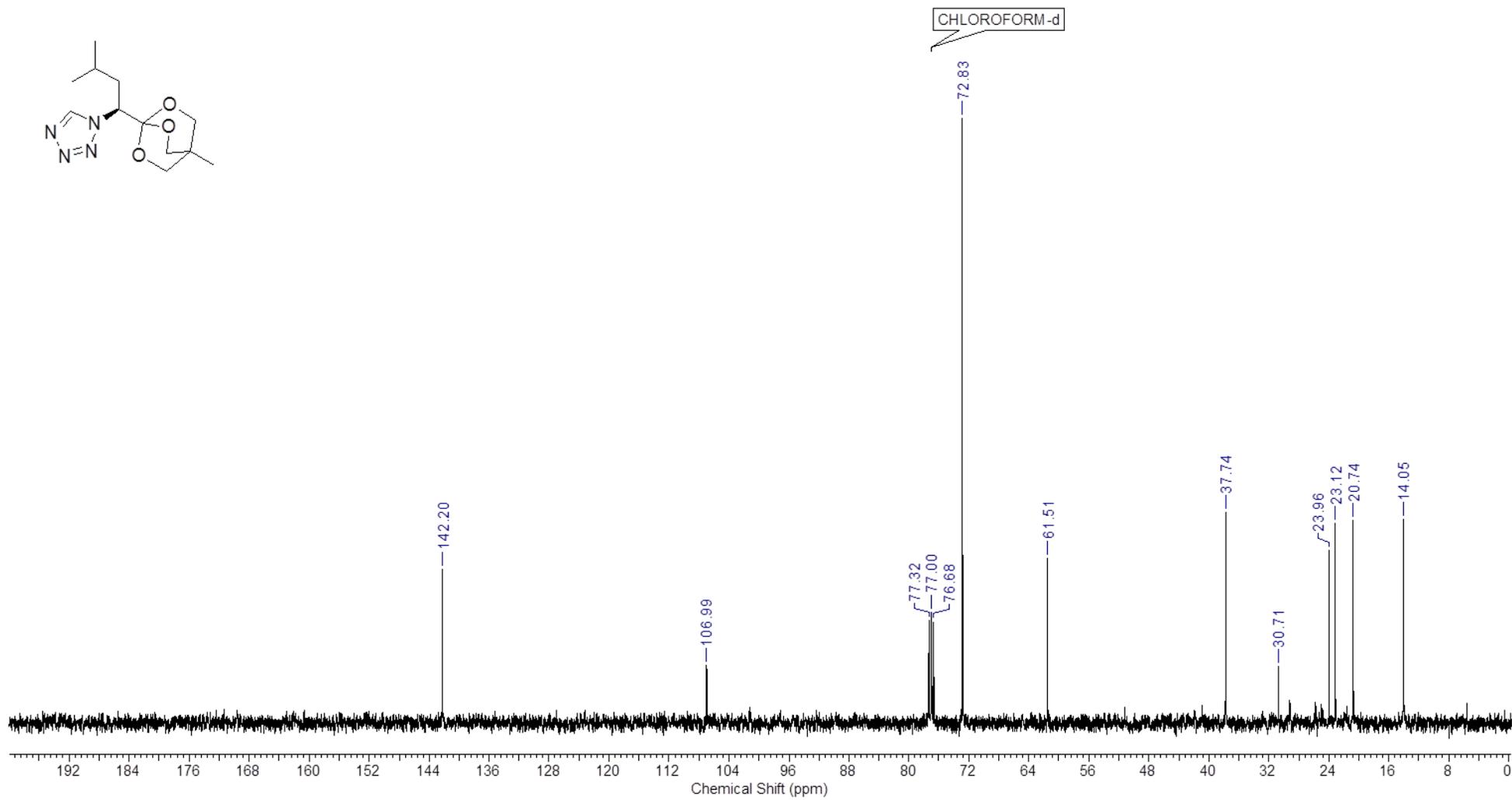
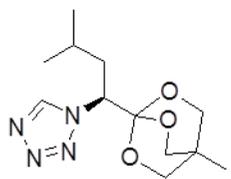
^1H NMR (400 MHz) spectrum of **2c** in CDCl_3



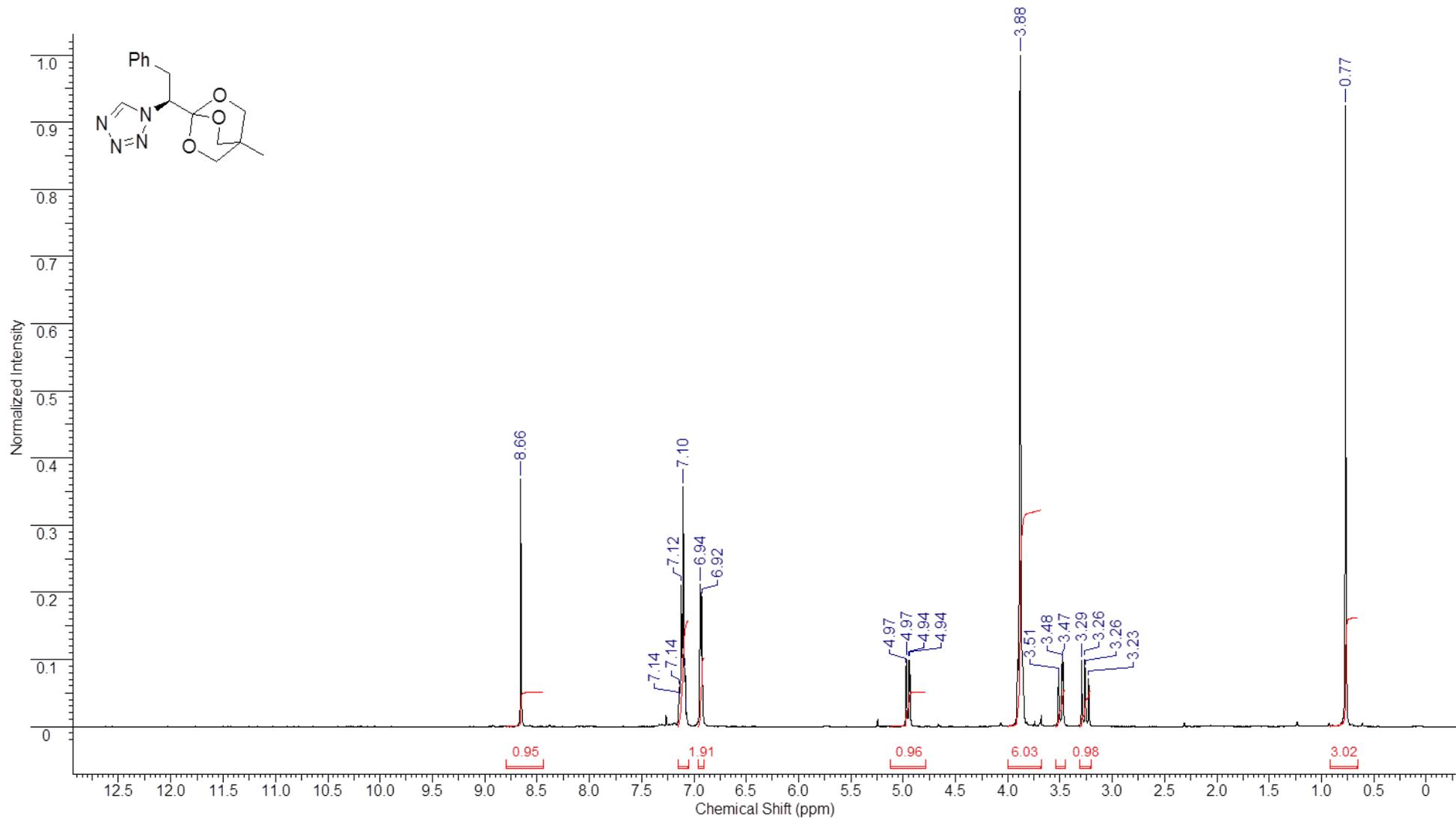
^{13}C NMR (100 MHz) spectrum of **2c** in CDCl_3



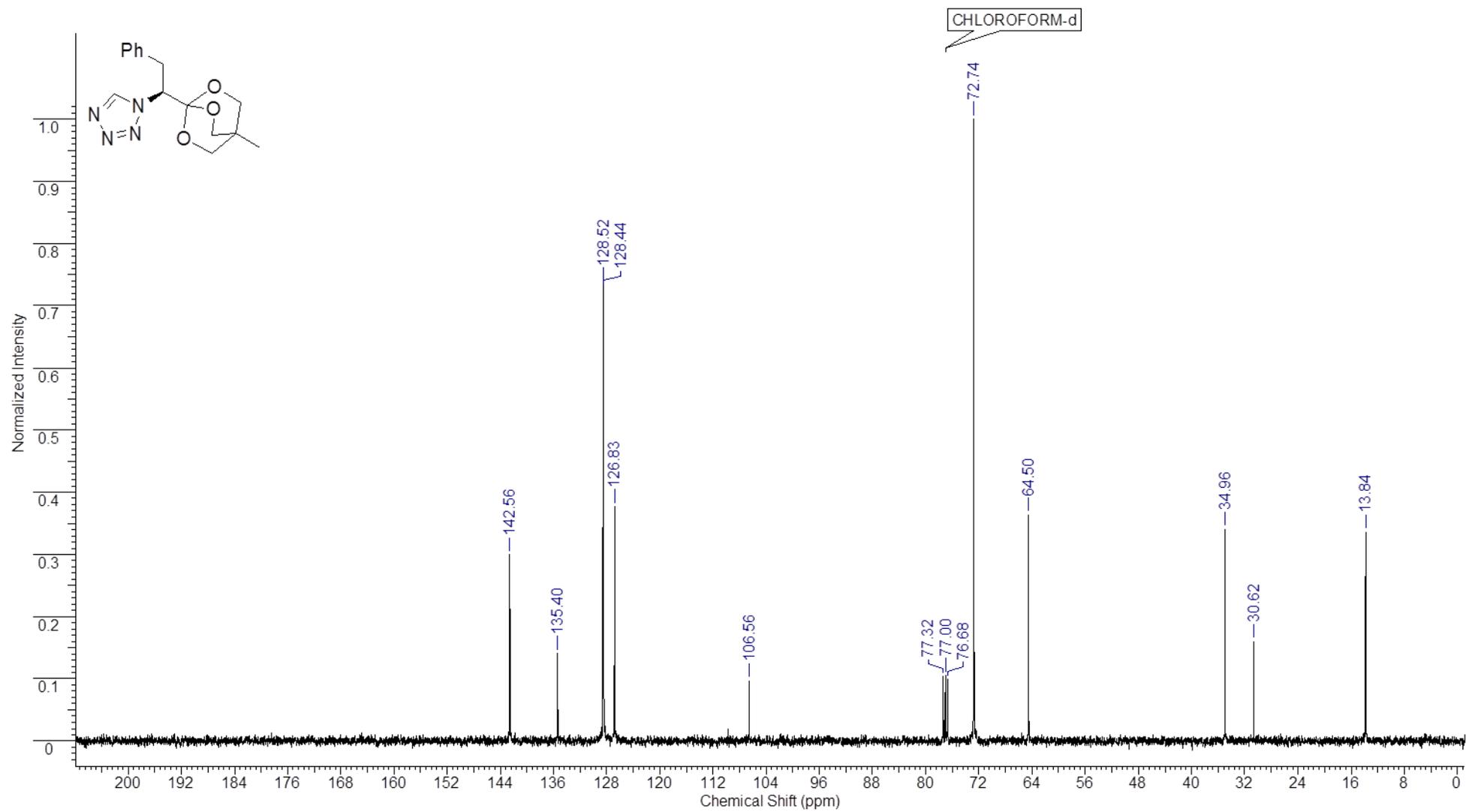
^1H NMR (400 MHz) spectrum of **2d** in CDCl_3



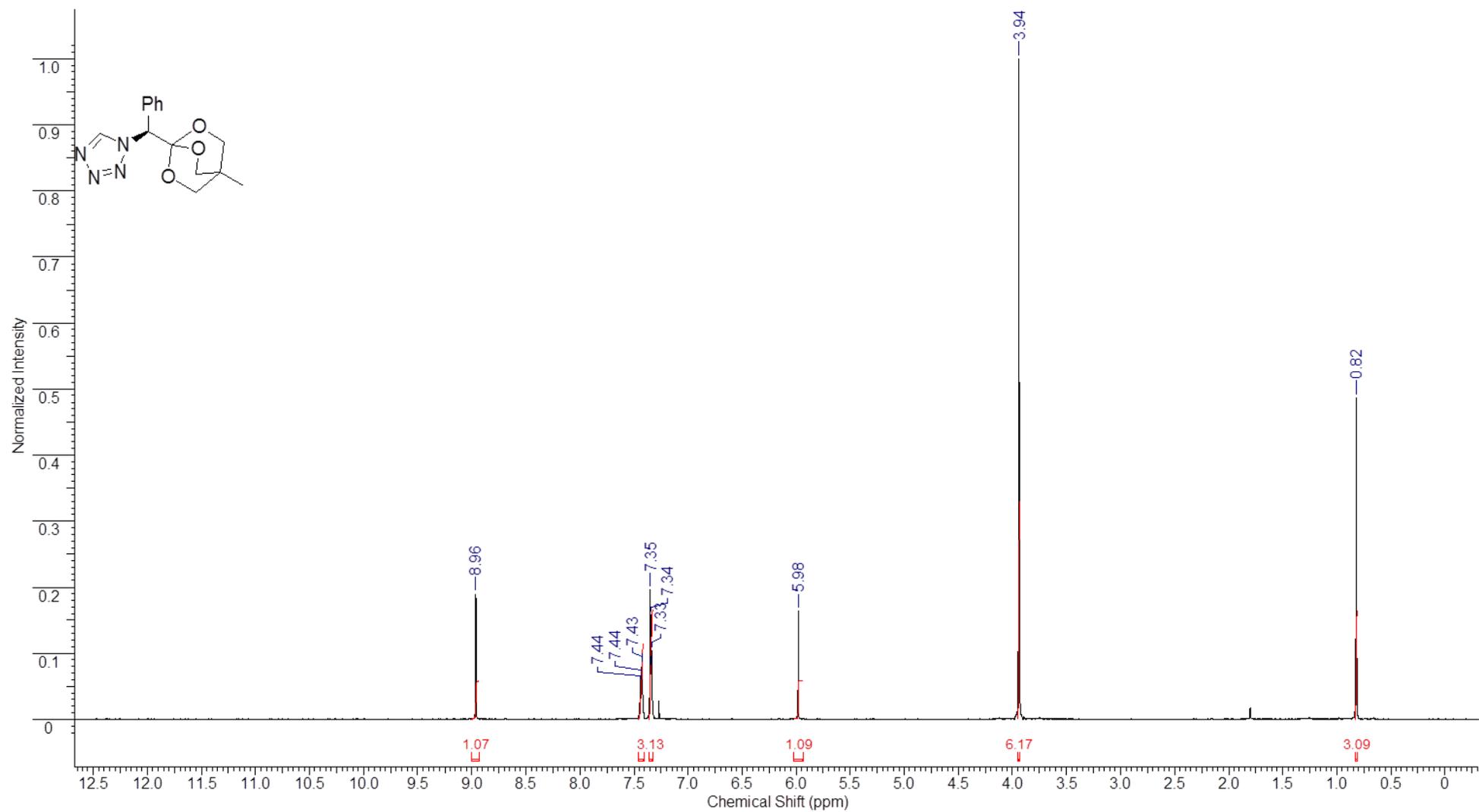
^{13}C NMR (100 MHz) spectrum of **2d** in CDCl_3



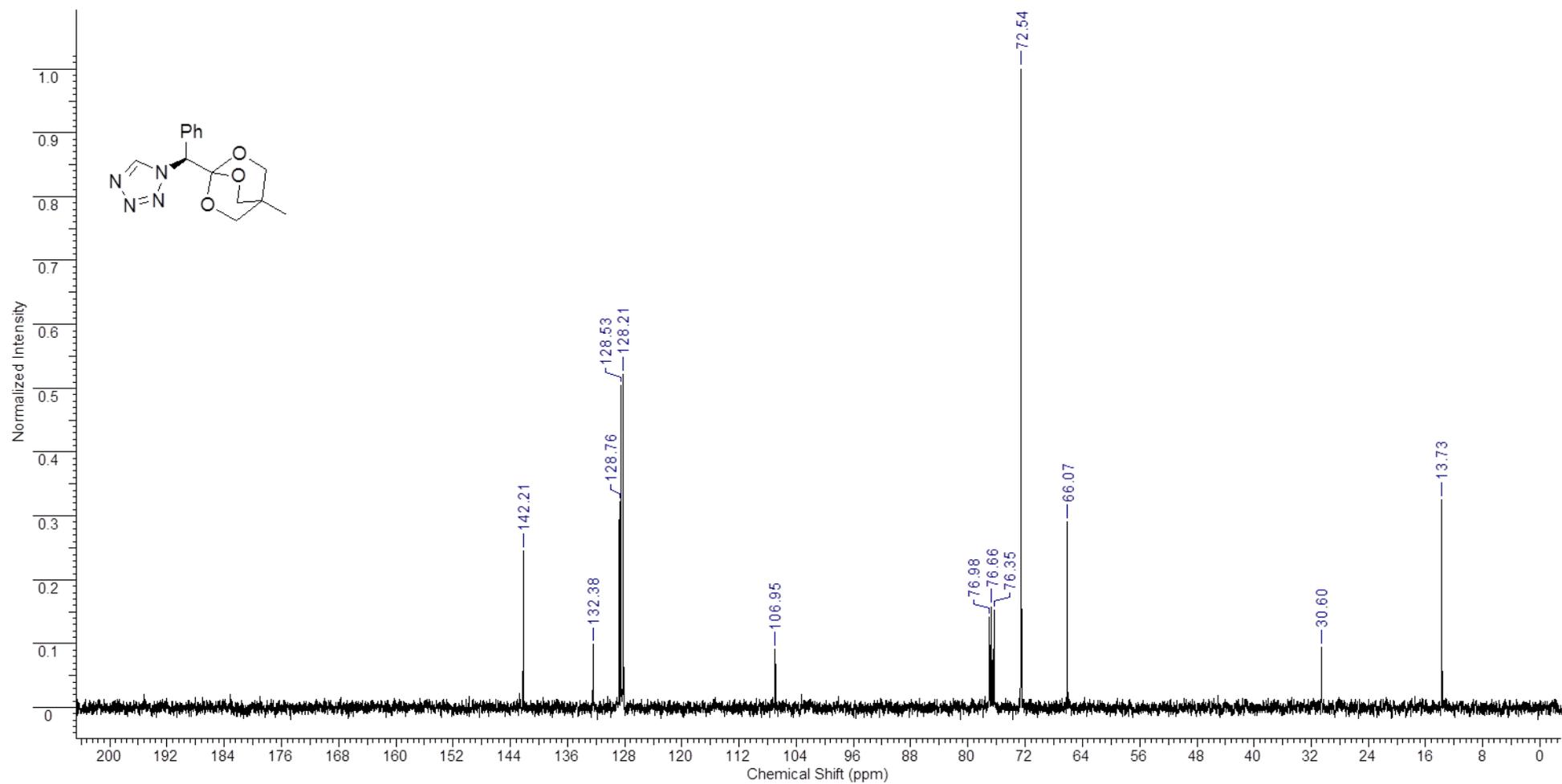
^1H NMR (400 MHz) spectrum of **2e** in CDCl_3



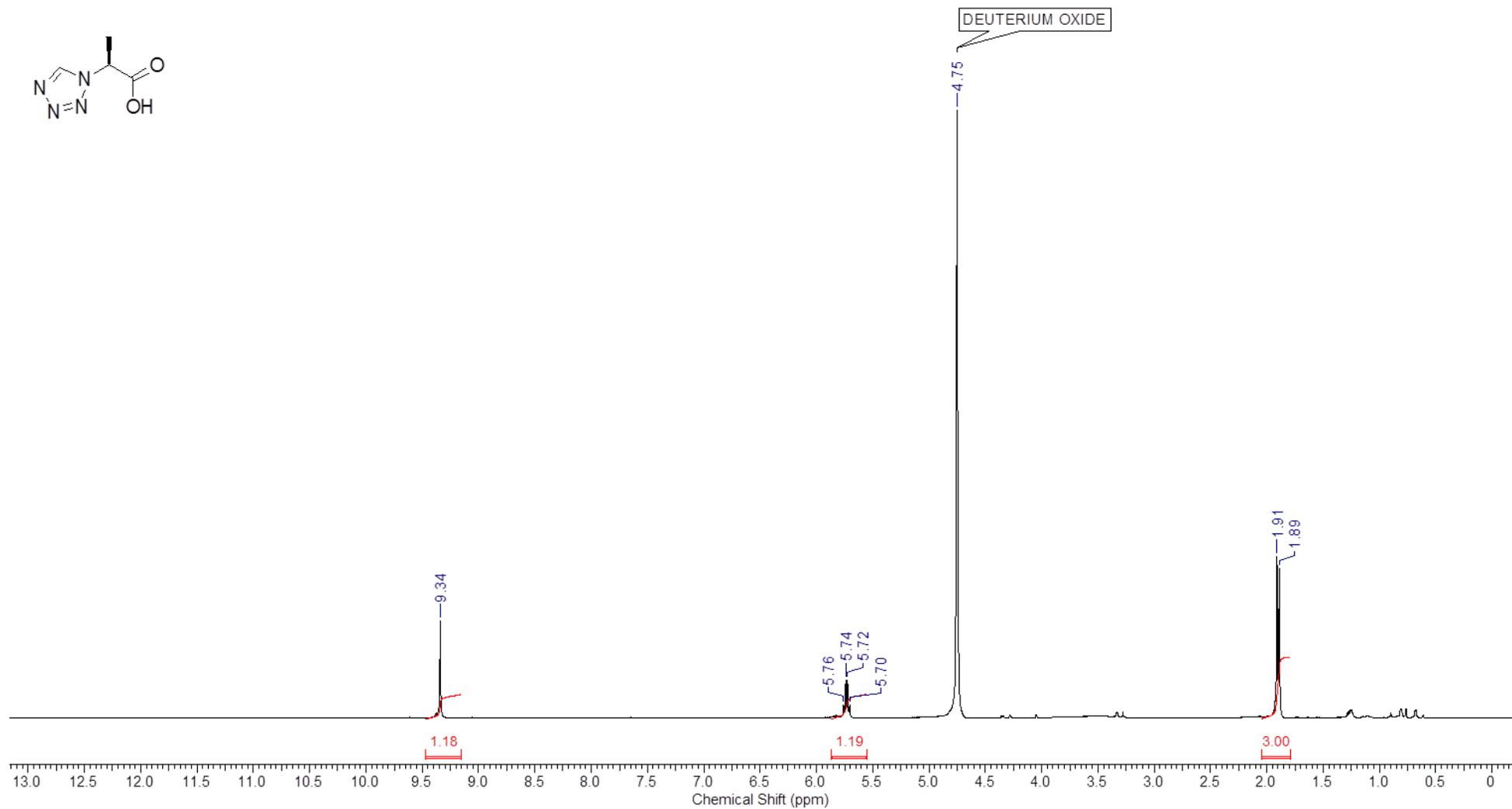
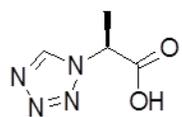
^{13}C NMR (100 MHz) spectrum of **2e** in CDCl_3



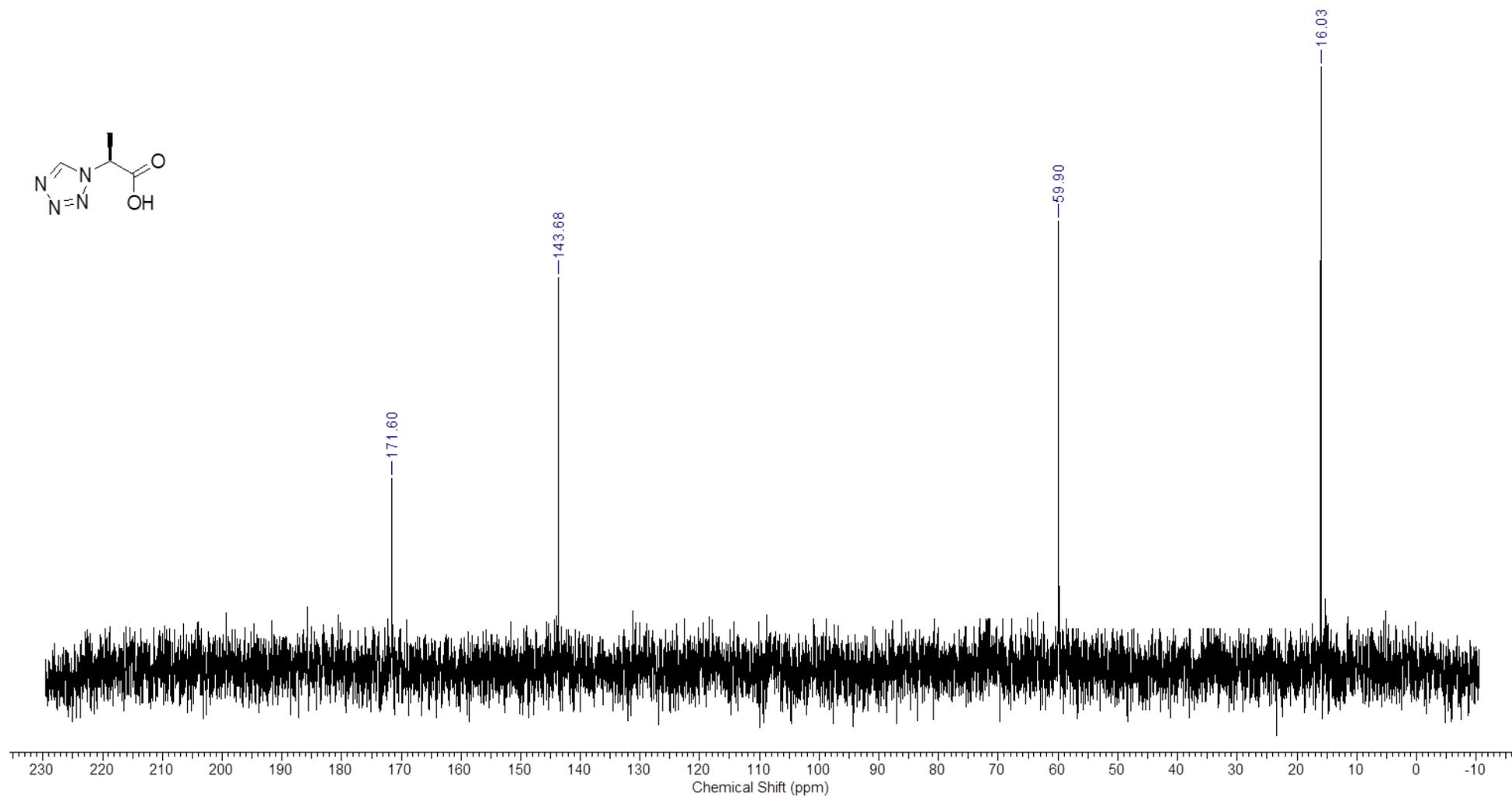
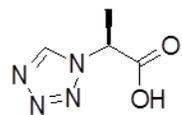
¹H NMR (400 MHz) spectrum of **2f** in CDCl₃



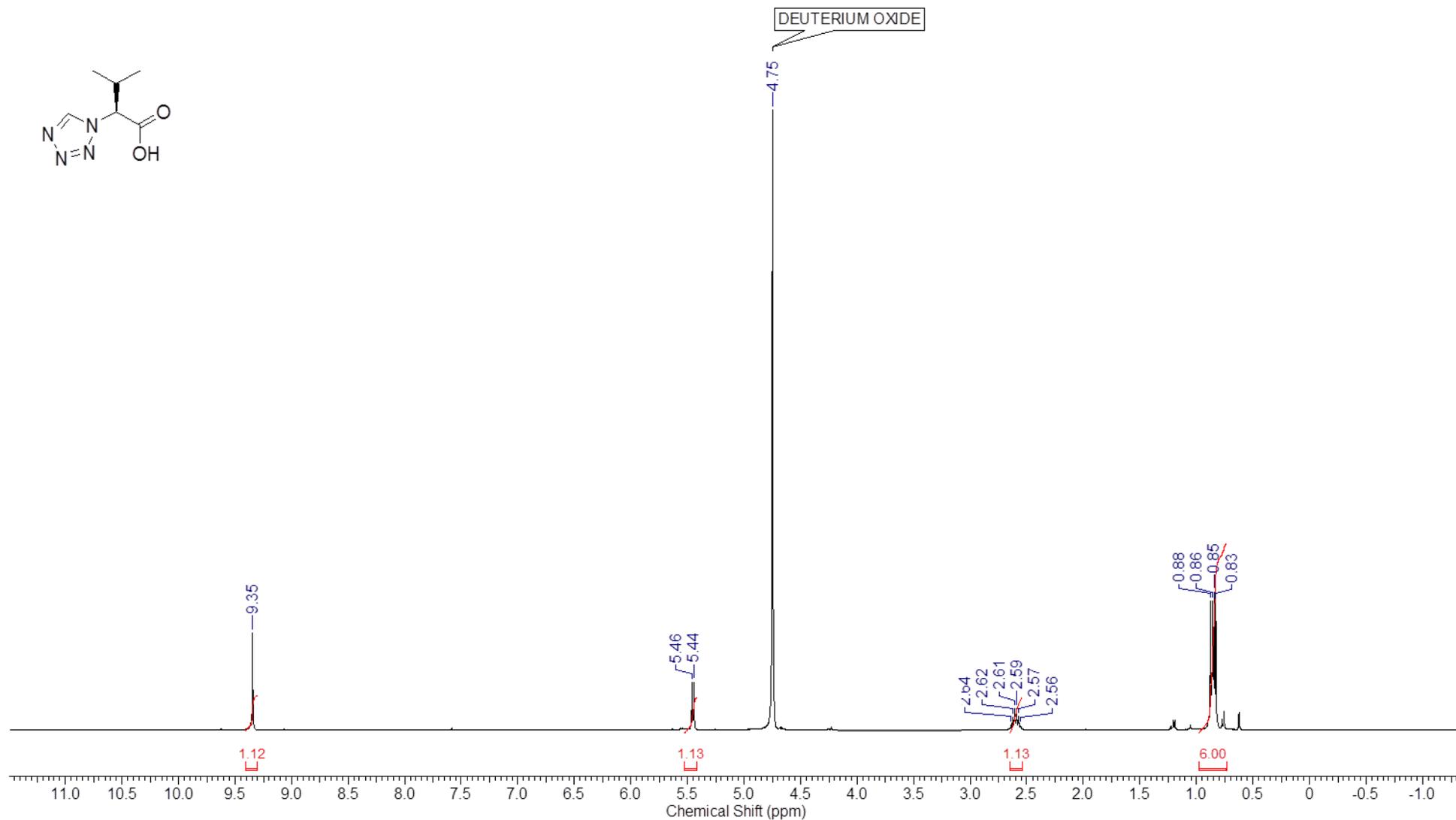
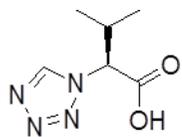
^{13}C NMR (100 MHz) spectrum of **2f** in CDCl_3



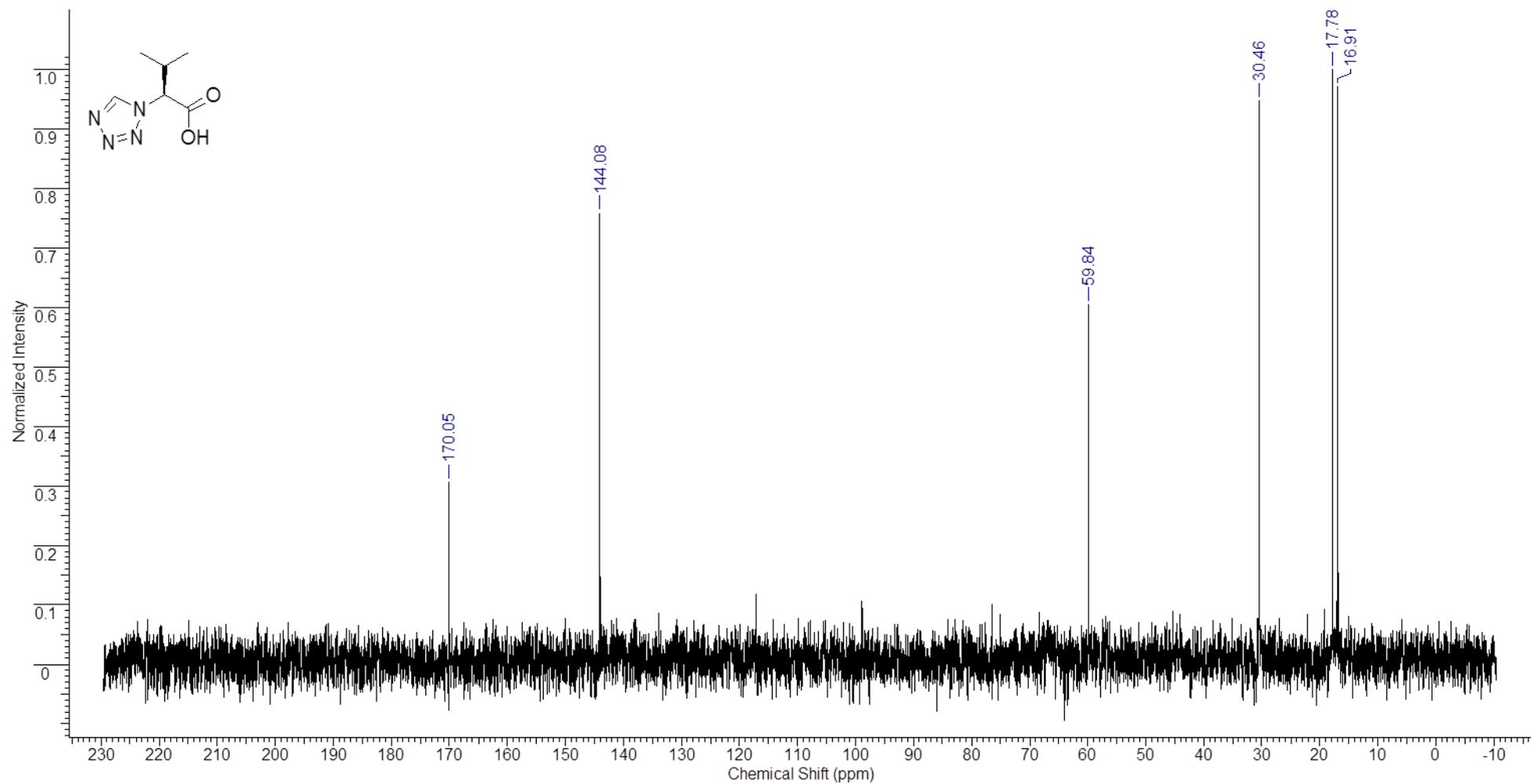
^1H NMR (400 MHz) spectrum of **3a** in D_2O



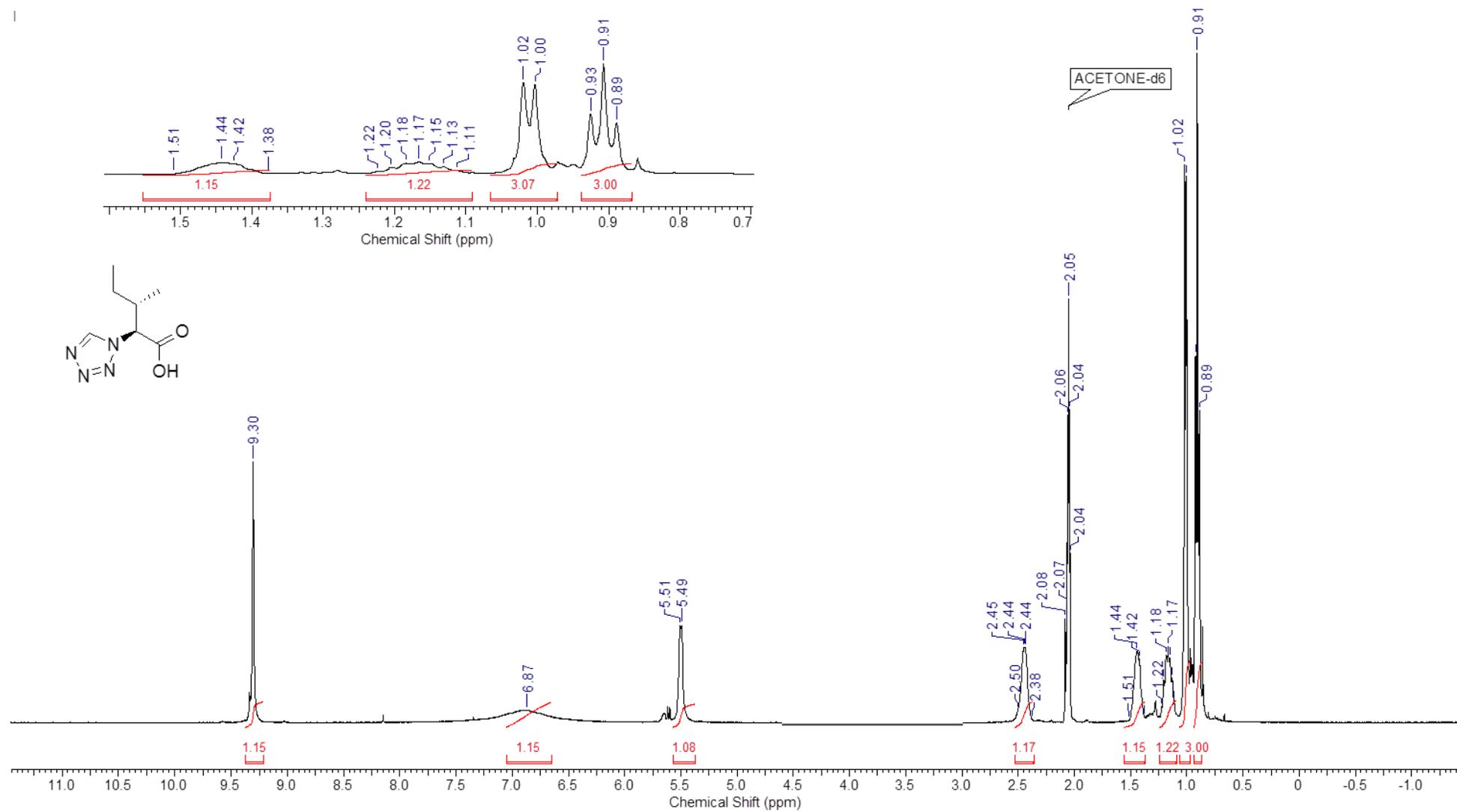
^{13}C NMR (100 MHz) spectrum of **3a** in D_2O



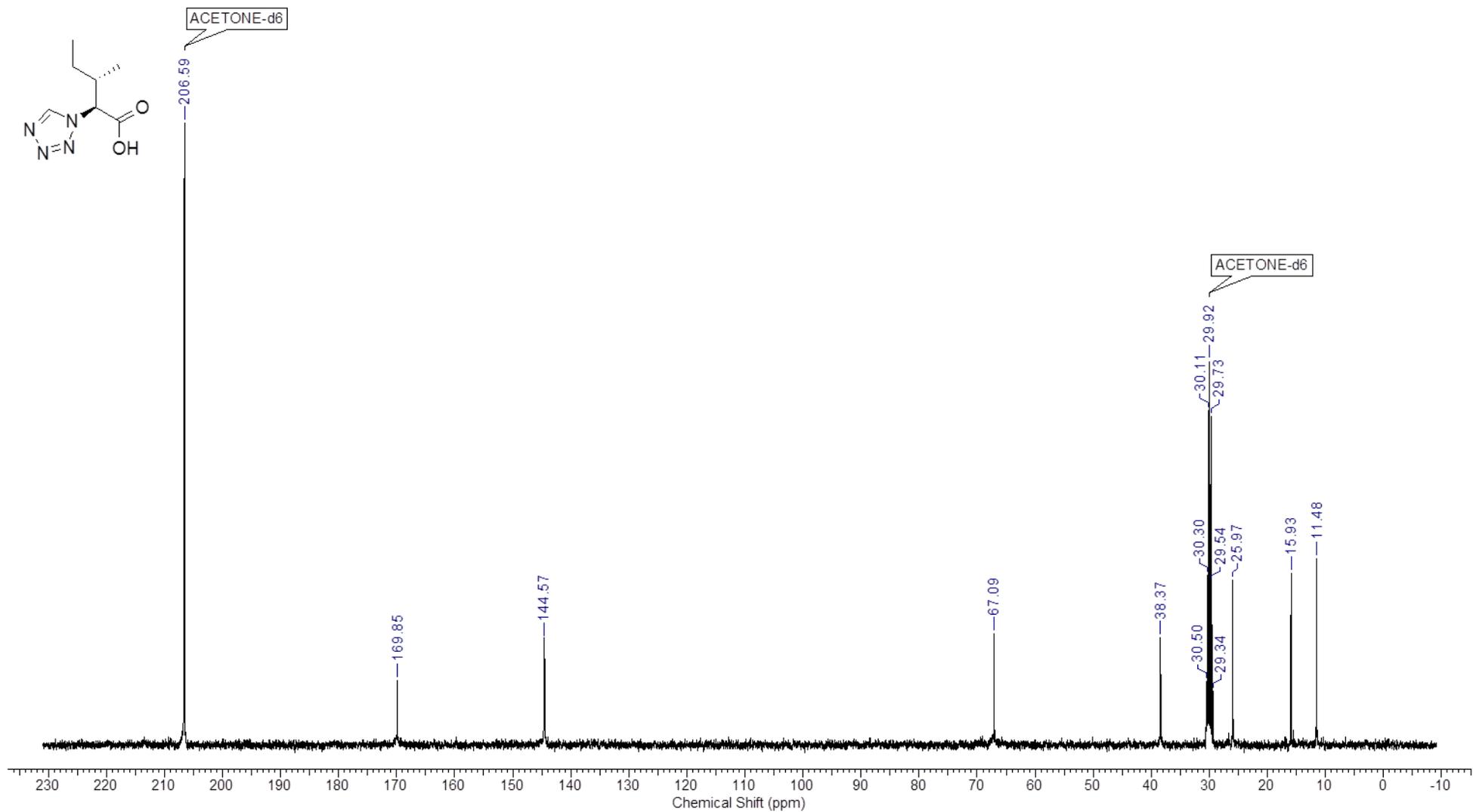
^1H NMR (400 MHz) spectrum of **3b** in D_2O



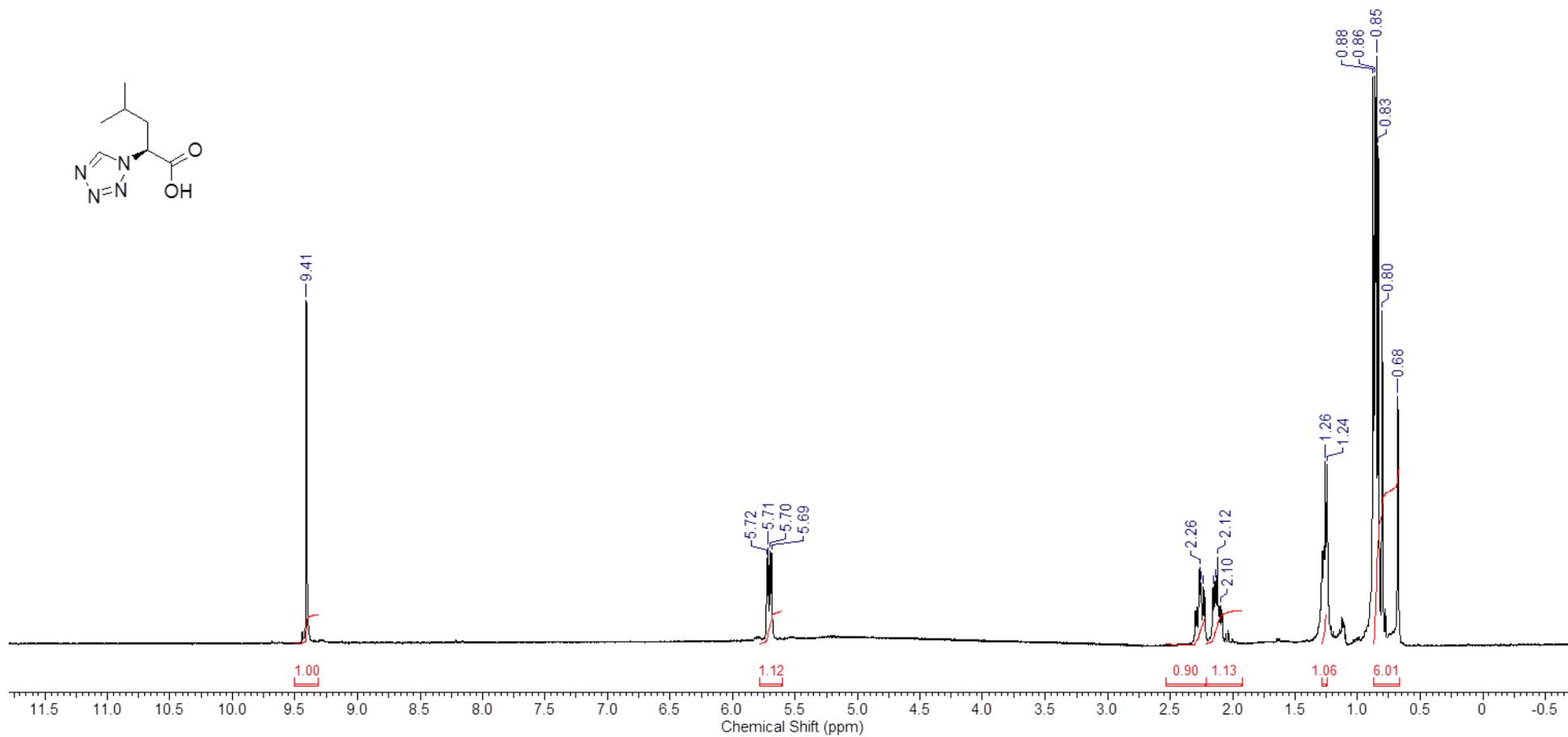
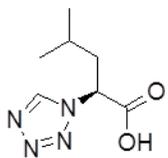
^{13}C NMR (100 MHz) spectrum of **3b** in D_2O



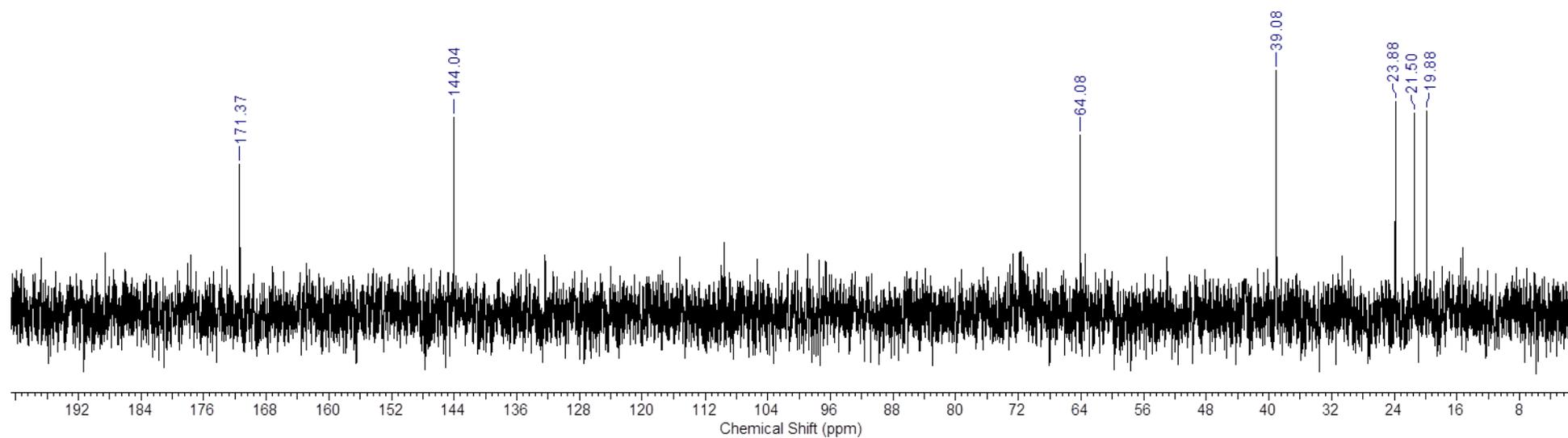
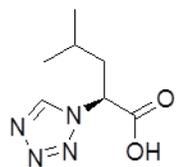
^1H NMR (400 MHz) spectrum of **3b** in acetone- d_6



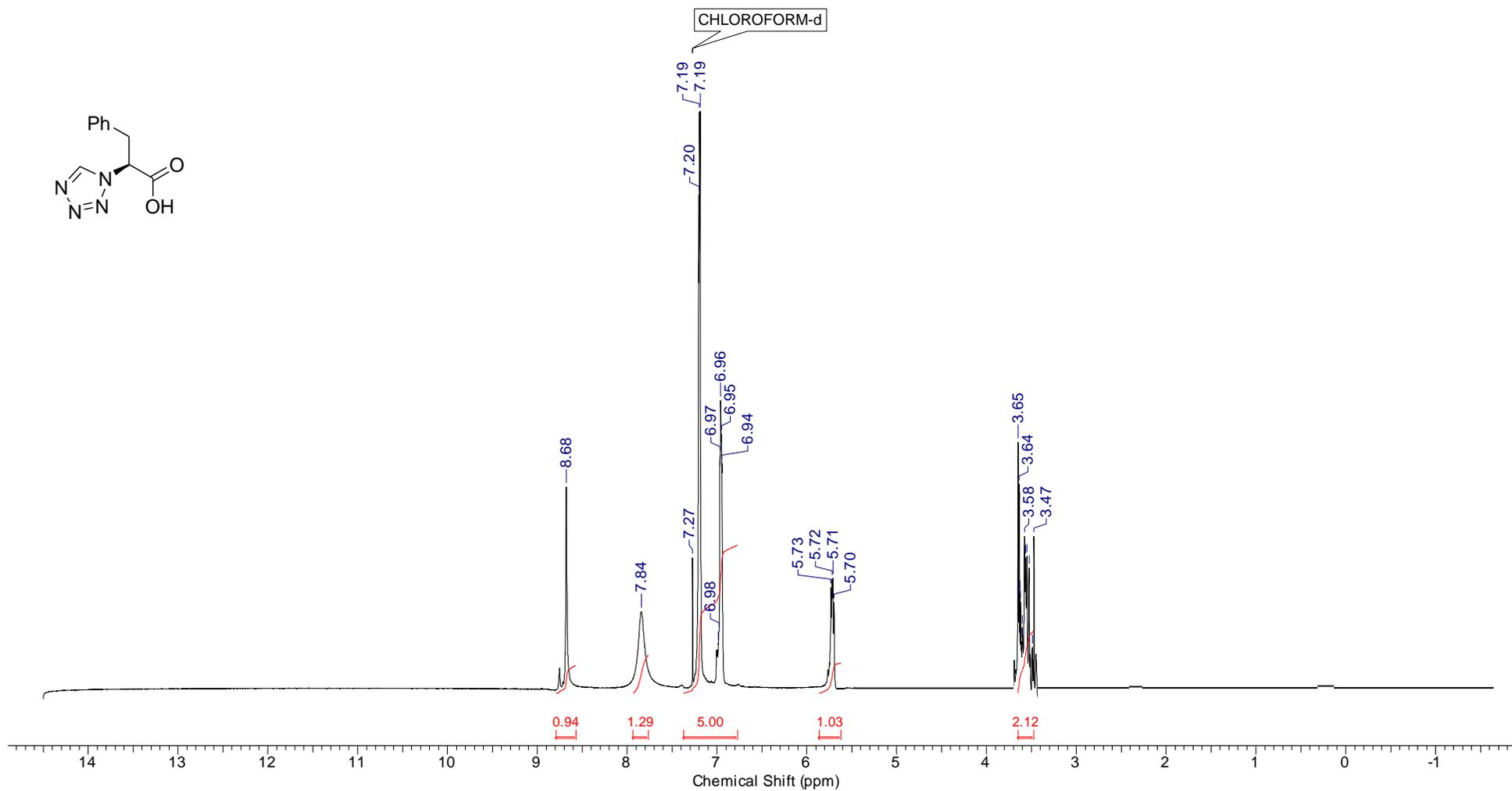
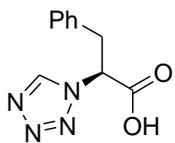
^{13}C NMR (100 MHz) spectrum of **3c** in acetone- d_6



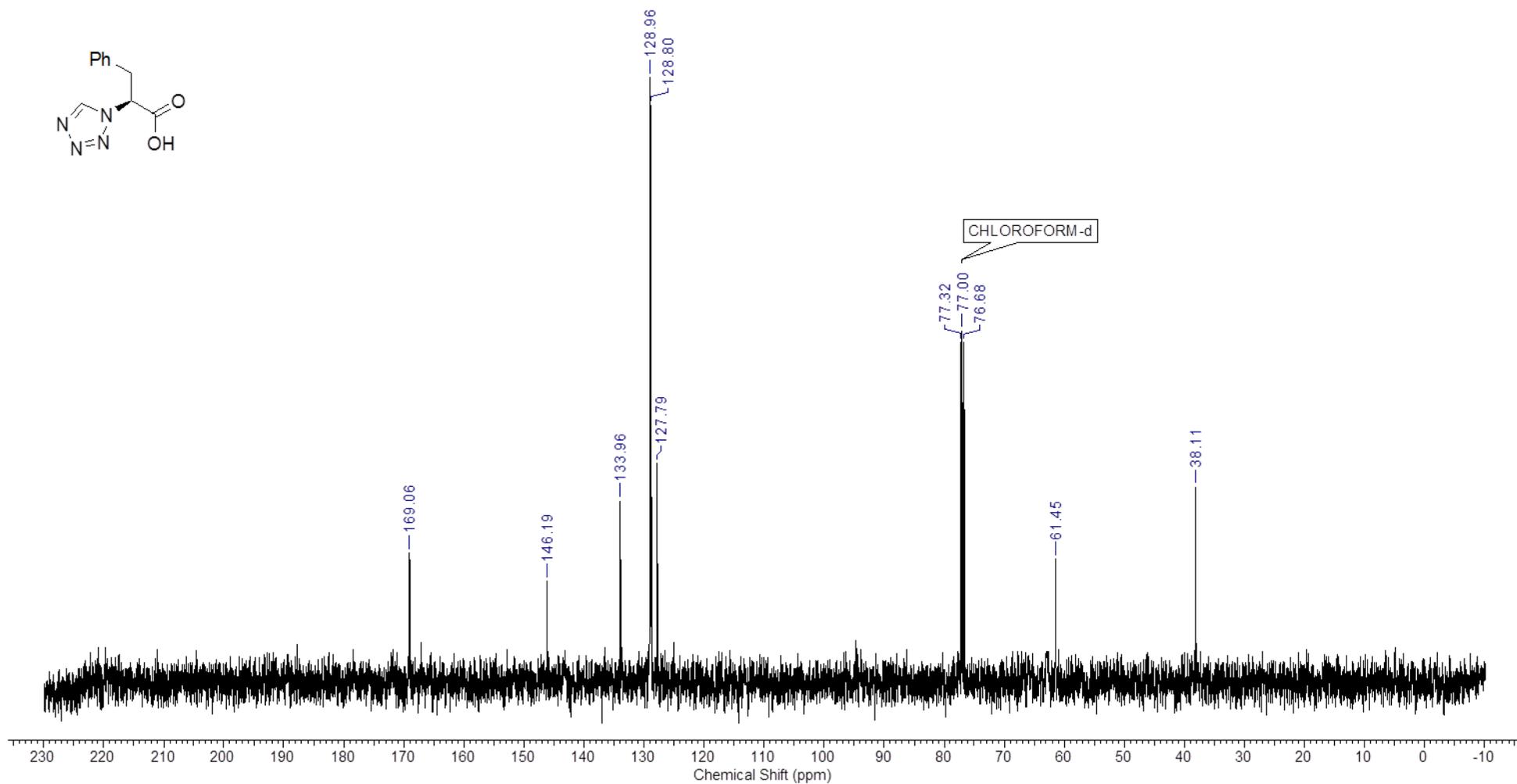
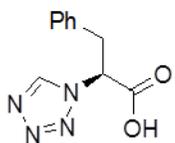
^1H NMR (400 MHz) spectrum of **3d** in D_2O



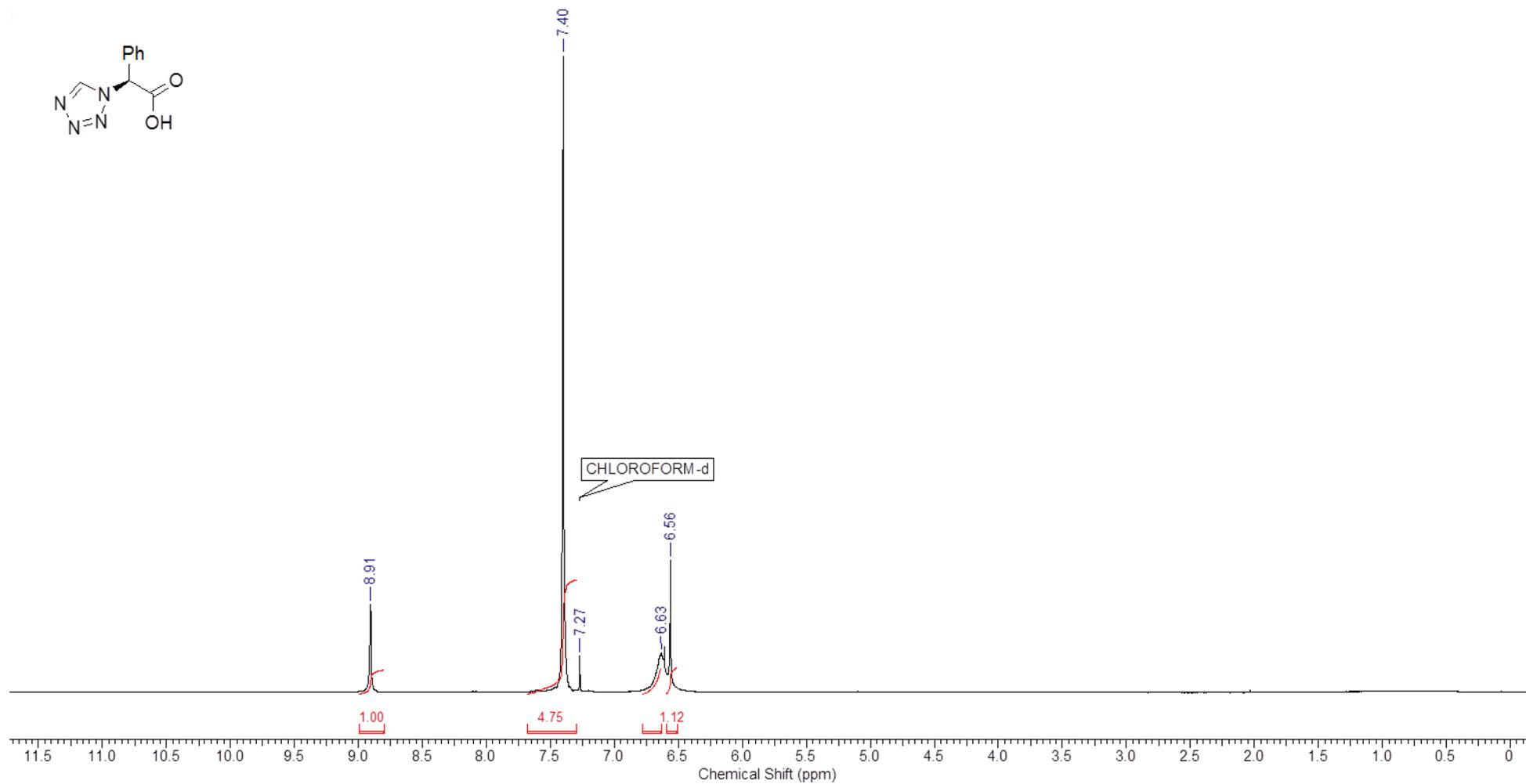
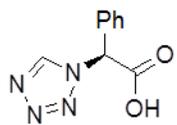
^{13}C NMR (100 MHz) spectrum of **3d** in D_2O



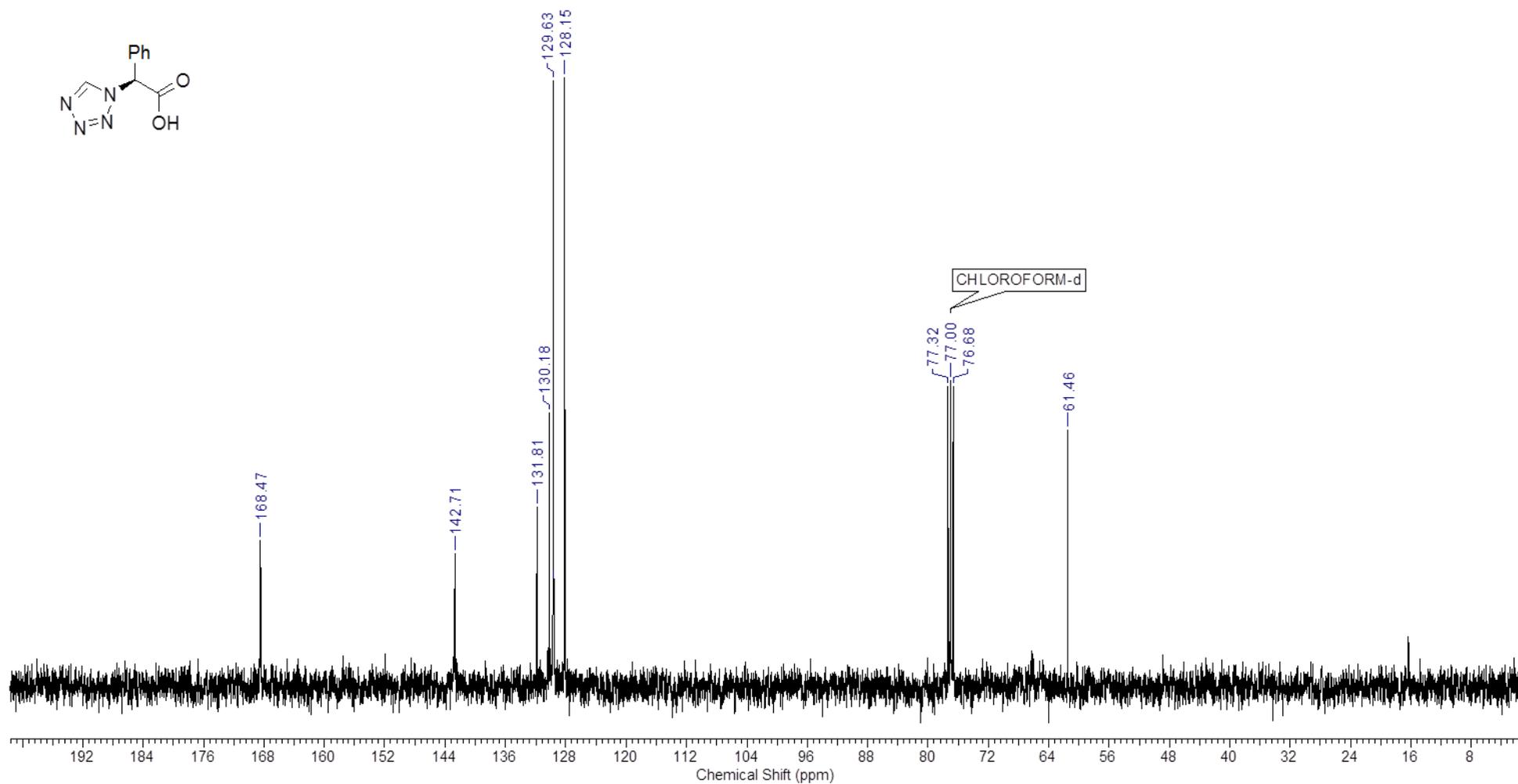
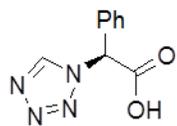
^1H NMR (400 MHz) spectrum of **3e** in CDCl_3



^{13}C NMR (100 MHz) spectrum of **3e** in CDCl_3



¹H NMR (400 MHz) spectrum of **3f** in CDCl₃



^{13}C NMR (100 MHz) spectrum of **3f** in CDCl_3