

# Exploring the relationship between conformation and $pK_a$ : Can a $pK_a$ value be used to determine the conformational equilibrium?

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## Supporting information

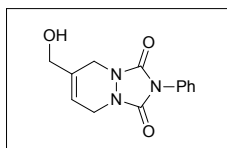
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## Experimental details

All purchased reagents in this study were used without further purification. Dry solvents were tapped from a solvent purification system. Glassware for use in water free reactions, were flame dried under vacuum before use. Flash columns were packed with silica gel 60Å (40-63 µm) as the stationary phase. TLC plates (Merck, 60, F<sub>254</sub>) were stained with either vanillin in EtOH or cerium molybdate in H<sub>2</sub>SO<sub>4</sub> followed by heating. <sup>1</sup>H-NMR and <sup>13</sup>C-NMR spectra were recorded on a Bruker 500 MHz spectrometer with a cryo probe. Chemical shifts (δ) are reported in ppm relative to the residual solvent signal (CDCl<sub>3</sub>: δ = 7.26 for <sup>1</sup>H-NMR and 77.16 for <sup>13</sup>C-NMR. DMSO-d<sub>6</sub>: δ = 2.50 for <sup>1</sup>H-NMR and 39.52 for <sup>13</sup>C-NMR. D<sub>2</sub>O: δ = 4.79 for <sup>1</sup>H-NMR). NMR experiments on compound **1a**, **8**, **15** and **21** were conducted in D<sub>2</sub>O with an external reference (DMSO-d<sub>6</sub>). High-resolution mass spectral (HRMS) data were obtained using either ESI or MALDI on a Bruker Solarix XR mass spectrometer analyzing TOF.

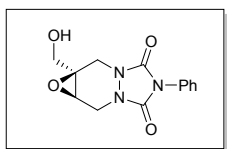
## Experimental procedures

### 6-(hydroxymethyl)-2-phenyl-5,8-dihydro-1H-[1,2,4]triazolo[1,2-a]pyridazine-1,3(2H)-dione (**4**)



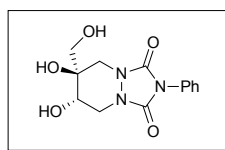
Under inert atmosphere, a flame dried flask was charged with 35mL anhydrous Et<sub>2</sub>O and HMDS (6.5 mL, 30.9 mmol) and then cooled to -78 °C. *n*-BuLi (17.8 mL, 1.6 M, 28.5 mmol) was then added via syringe over 15 min. The cooling bath was removed and the mixture was stirred for 35 mins at 25°C. 2-methyl-2-vinylloxirane (2.33 mL, 23.8 mmol) was then added slowly via syringe over 5 mins and the reaction was refluxed for 22h. After reflux the mixture was cooled in an ice bath, slowly poured into 55 mL 2 M HCl(aq) and stirred for 1 h at 25 °C. The mixture was separated and the aqueous layer extracted with 3x25 mL Et<sub>2</sub>O. The organic layers were combined and washed with 50 mL NaHCO<sub>3</sub>, 50 mL brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated at 30 °C (670 mbar) down to approximately 50 mL of volume. In a separate flask, 4-phenylurazole (4.25 g, 24 mmol) was suspended in 15 mL EtOAc and cooled to 0°C. *t*-BuOCl (3.4 mL, 30 mmol) was added to give a strong red solution that was stirred for 20 mins. The 50 mL solution of crude isoprenol that was prepared above was now added to the red mixture and stirred at 0 °C for 15 mins, then at 25 °C for 18 h. The reaction mixture was filtered, and the precipitate was washed with 50 mL Et<sub>2</sub>O, then dissolved in CHCl<sub>3</sub>, filtered once more and concentrated *in vacuo* to afford 2.33 g (38%) of **4** as a white solid. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.56 – 7.34 (m, 5H, ArH), 5.97 – 5.92 (bs, 1H, CHCH<sub>2</sub>), 4.23 (s, 2H, CH<sub>2</sub>OH), 4.20 (s, 4H, CHCH<sub>2</sub>NN, CCH<sub>2</sub>NN), 1.80 (s, 1H, CH<sub>2</sub>OH). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 152.6(CO), 152.5(CO), 133.1(C), 131.3, 129.3, 128.4, 125.6(Ar), 116.4(CH), 64.0(CH<sub>2</sub>OH), 43.9(CCH<sub>2</sub>), 43.3 (CHCH<sub>2</sub>). M.p. 134-135 °C MS (ESP): *m/z*: 282.0850 [M+Na]<sup>+</sup>, calcd for C<sub>13</sub>H<sub>13</sub>N<sub>3</sub>NaO<sub>3</sub>: 282.0855.

### 1a-(hydroxymethyl)-5-phenyldihydro-1aH-oxireno[2,3-d][1,2,4]triazolo[1,2-a]pyridazine-4,6(2H,5H)-dione (**5**)



Allylic alcohol **4** (5.4 g, 20.8 mmol) and *m*-CPBA (10.78 g, 62.5 mmol) was dissolved in 160 mL 1,2-Dichloroethane and heated to 50 °C for 18 h. The mixture was cooled on ice and filtered. The precipitate was washed with cold DCM and the combined filtrates were washed with 200 mL (sat.) NaHCO<sub>3</sub> followed by extraction of the aqueous layer with 100 mL DCM. The combined organic layers were dried over MgSO<sub>4</sub>, filtered and evaporated. The crude product was purified by flash chromatography (4:1 → 1:0 EtOAc:PE) to afford 4.12 g (72%) of **5** as a white solid. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.49 – 7.44 (m, 4H, ArH), 7.37 (m, 1H, ArH), 4.21 (d, *J* = 13.9, 1H, CHCH<sub>2a</sub>N), 4.12 (d, *J* = 13.5 Hz, 1H, CCH<sub>2a</sub>N), 3.97 – 3.93 (dd, *J* = 12.6 Hz, 5.1 Hz, 1H, CH<sub>2a</sub>OH), 3.91 (dd, *J* = 13.9, 2.7 Hz, 1H, CHCH<sub>2b</sub>N), 3.88 (d, *J* = 13.5 Hz, 1H, CCH<sub>2b</sub>N), 3.83 (dd, *J* = 12.6, 7.8 Hz, 1H, CH<sub>2b</sub>OH), 3.65 (d, *J* = 2.7 Hz, 1H, OCHCH<sub>2</sub>), 1.86 (dd, *J* = 7.8, 5.1 Hz, 1H, CH<sub>2</sub>OH). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 152.9(CO), 152.8(CO), 131.0, 129.4, 128.5, 125.5 (Ar), 62.4(CH<sub>2</sub>OH), 58.3(C), 52.2 (CH), 43.6(CCH<sub>2</sub>N), 43.0 (CHCH<sub>2</sub>N). M.p. 157-159 °C. MS (ESP): *m/z*: 298.0798 [M+Na]<sup>+</sup>, calcd for C<sub>13</sub>H<sub>13</sub>N<sub>3</sub>NaO<sub>4</sub>: 298.0804

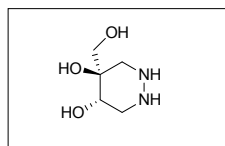
### 6,7-dihydroxy-6-(hydroxymethyl)-2-phenyltetrahydro-1H-[1,2,4]triazolo[1,2-a]pyridazine-1,3(2H)-dione (6)



Epoxide **5** (408 mg, 1.5 mmol) was suspended in 25 mL H<sub>2</sub>O and HClO<sub>4</sub> (1 mL, 70%, 12 mmol) was added. The suspension was then refluxed for 3 h then cooled to 25 °C. The reaction was quenched by adding KHCO<sub>3</sub> (1.6 g, 16 mmol) and stirring for 10 min. The suspension was then concentrated *in vacuo* and purified by flash chromatography (19:1 →18:2→17:3→16:4→15:5

DCM:MeOH) to afford 377 mg (86%) of **6** as an off-white solid. <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 7.54 – 7.36 (m, 5H, ArH), 5.42 (d, *J* = 4.6 Hz, 1H, CHOH), 5.09 (s, 1H, COH), 4.69 (t, *J* = 5.9 Hz, 1H, CH<sub>2</sub>OH), 3.73 (dd, *J* = 11.9, 3.0 Hz, 1H, HOCHCH<sub>2a</sub>N), 3.71 – 3.68 (m, 1H, CHOH), 3.68 (d, *J* = 12.3 Hz, 1H, CCH<sub>2a</sub>N), 3.59 (dd, *J* = 11.9, 1.8 Hz, 1H, HOCHCH<sub>2b</sub>N), 3.54 (dd, *J* = 11.3, 5.9 Hz, 1H, CH<sub>2a</sub>OH), 3.49 (dd, *J* = 11.3, 5.9 Hz, 1H, CH<sub>2b</sub>OH), 3.32 (d, *J* = 12.3 Hz, 1H, CCH<sub>2b</sub>N). <sup>13</sup>C NMR (126 MHz, DMSO) δ 151.7(CO), 151.4(CO), 131.7, 128.9, 127.9, 126.1(Ar), 70.6(C), 65.7(CH), 64.2(CH<sub>2</sub>OH), 46.1(CHCH<sub>2</sub>), 45.9(CCH<sub>2</sub>). M.p. 247-248 °C. MS (ESP): *m/z*: 316.0904 [M+Na]<sup>+</sup>, calcd for C<sub>13</sub>H<sub>15</sub>N<sub>3</sub>NaO<sub>5</sub>: 316.0909

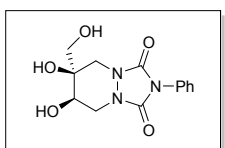
### (4*RS*,5*SR*)-4-(hydroxymethyl)hexahydropyridazine-4,5-diol (1a)



Compound **6** (1 g, 3.4 mmol) was dissolved in 50 mL NH<sub>2</sub>NH<sub>2</sub>•H<sub>2</sub>O and heated to 100 °C for 24 h. The reaction was evaporated, dissolved in H<sub>2</sub>O and applied to a column of ion-exchange resin (Amberlyst IR120), washed with H<sub>2</sub>O, eluted with 2.5% NH<sub>4</sub>OH and concentrated. The crude product was purified by flash chromatography (8:2→7:3 MeCN:H<sub>2</sub>O with a few drops of 24%

NH<sub>4</sub>OH) to afford 222 mg (44%) of **1** as colorless oil that solidified overnight. <sup>1</sup>H NMR (500 MHz, D<sub>2</sub>O) δ 3.74 – 3.51 (m, 3H, CH<sub>2</sub>OH, CHOH), 3.20 (d, *J* = 14.0 Hz, 1H, CHCH<sub>2a</sub>NH), 3.00 (d, *J* = 14.1 Hz, 1H, CCH<sub>2a</sub>NH), 2.76 (dd, *J* = 14.0, 3.7 Hz, 1H, CHCH<sub>2b</sub>NH), 2.60 (d, *J* = 14.0 Hz, 1H, CCH<sub>2b</sub>NH). <sup>13</sup>C NMR (75 MHz, D<sub>2</sub>O, 50°C) δ 70.4(C), 67.6(CH), 64.3(CH<sub>2</sub>OH), 49.4(CHCH<sub>2</sub>), 49.2(CCH<sub>2</sub>). M.p. 167-169 °C. MS (ESP): *m/z*: 149.0926 [M+H]<sup>+</sup>, calcd for C<sub>5</sub>H<sub>13</sub>N<sub>2</sub>O<sub>3</sub>: 149.0926

### (6*R*,7*R*)-6,7-dihydroxy-6-(hydroxymethyl)-2-phenyltetrahydro-1H-[1,2,4]triazolo[1,2-a]pyridazine-1,3(2H)-dione (7)

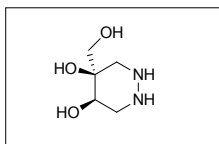


Allylic alcohol **4** (1.5 g, 5.79 mmol) was dissolved in 6 mL acetone and 3 mL H<sub>2</sub>O. Then NMO (0.95 g, 8.1 mmol) and OsO<sub>4</sub> (1.45 mL, 2.5 wt % in *t*-butanol, 0.116 mmol) was added, and the mixture was stirred at 25 °C for 24 h. 7 mL H<sub>2</sub>O was added along with solid Na<sub>2</sub>S<sub>2</sub>O<sub>5</sub> (1.5g, 79 mmol) and stirring continued for 2 h followed by concentration *in vacuo*. The residue was subjected to Soxhlet extraction with acetone for 20 h. The acetone extract was concentrated *in*

*vacuo* and purified by flash chromatography (8:2 →6:4 DCM:MeOH) to afford 0.944 g (59%) of **7** as an oil that solidified upon standing overnight.

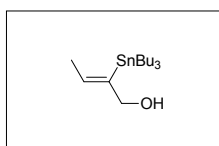
<sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 7.57 – 7.27 (m, 5H, ArH), 5.16 (d, *J* = 6.2 Hz, 1H, CHOH), 4.85 (dd, *J* = 5.7, 5.1 Hz, 1H, CH<sub>2</sub>OH), 4.82 (s, 1H, COH), 3.83 (ddd, *J* = 10.5, 6.2, 4.8 Hz, 1H, CHOH), 3.73 (dd, *J* = 11.1, 4.8 Hz, 1H, CHCH<sub>2a</sub>), 3.67 (d, *J* = 12.4 Hz, 1H, CCH<sub>2a</sub>), 3.58 (dd, *J* = 11.0, 5.7 Hz, 1H, CH<sub>2a</sub>OH), 3.41 (dd, *J* = 11.0, 5.1 Hz, 1H, CH<sub>2b</sub>OH), 3.35 (d, *J* = 12.4 Hz, 1H, CCH<sub>2b</sub>), 3.29 (dd, *J* = 11.1, 10.5 Hz, 1H, CHCH<sub>2b</sub>). <sup>13</sup>C NMR (126 MHz, DMSO-*d*<sub>6</sub>) δ 151.6(CO), 151.2(CO), 131.7, 128.9, 127.9, 126.1(Ar), 70.8(C), 65.5(CH), 63.3(CH<sub>2</sub>OH), 48.4 (CCH<sub>2</sub>), 44.4(CHCH<sub>2</sub>). M.p. could not be obtained because of product decomposition at 207-211 °C. MS (ESP): *m/z*: 316.0910 [M+Na]<sup>+</sup>, calcd for C<sub>13</sub>H<sub>15</sub>N<sub>3</sub>NaO<sub>5</sub>: 316.0909

### (4R,5R)-4-(hydroxymethyl)hexahydropyridazine-4,5-diol(8)



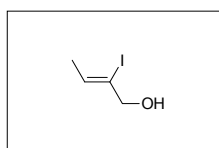
Triol **7** (990 mg, 3.38 mmol) was dissolved in 50 mL  $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$  and heated to 110 °C for 18 h. The reaction was evaporated, dissolved in  $\text{H}_2\text{O}$  and applied to a column of ion-exchange resin (Amberlyst IR120), washed with 400 mL  $\text{H}_2\text{O}$ , eluted with 500 mL 2.5%  $\text{NH}_4\text{OH}$  and concentrated. The crude product was purified by flash chromatography (8:2 MeCN: $\text{H}_2\text{O}$  with a few drops of 24%  $\text{NH}_4\text{OH}$ ) to afford 322 mg (64%) of **8** as an orange oil that solidified upon standing overnight.  $^1\text{H}$  NMR (500 MHz,  $\text{D}_2\text{O}$ )  $\delta$  3.77 (dd,  $J = 10.2, 5.0$  Hz, 1H,  $\text{CHOH}$ ), 3.64 (d,  $J = 11.8$  Hz, 1H,  $\text{CH}_{2a}\text{OH}$ ), 3.60 (d,  $J = 11.8$  Hz, 1H,  $\text{CH}_{2b}\text{OH}$ ), 2.93 (dd,  $J = 12.7, 5.0$  Hz, 1H,  $\text{CHCH}_{2a}\text{NH}$ ), 2.90 (d,  $J = 14.3$  Hz, 1H,  $\text{CCH}_{2a}\text{NH}$ ), 2.82 (dd,  $J = 12.7, 10.2$  Hz, 1H,  $\text{CHCH}_{2b}\text{NH}$ ), 2.77 (d,  $J = 14.3$  Hz, 1H,  $\text{CCH}_{2b}\text{NH}$ ).  $^{13}\text{C}$  NMR (126 MHz,  $\text{D}_2\text{O}$ )  $\delta$  70.8(C), 66.5(CH), 64.1( $\text{CH}_2\text{OH}$ ), 51.6( $\text{CCH}_2$ ), 47.6( $\text{CHCH}_2$ ). M.p. could not be obtained because of product decomposition at 150-154 °C. MS (ESP):  $m/z$ : 149.0926 [ $\text{M}+\text{H}$ ] $^+$ , calcd for  $\text{C}_5\text{H}_{13}\text{N}_2\text{O}_3$ : 149.0926

### (E/Z)2-(tributylstannyl)but-2-en-1-ol (9)<sup>1</sup>



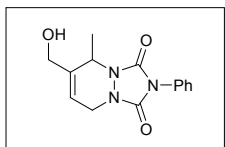
2-butyne-1-ol (6.4 mL, 85.5 mmol) was dissolved in 80 mL dry toluene (4Å Sieves). Then  $\text{SnBu}_3\text{H}$  (25.1 mL, 93.3 mmol) and AIBN (630 mg, 3.8 mmol) was added. The mixture was then heated to 85 °C under nitrogen for 1.5 h. The reaction mixture was concentrated *in vacuo*, and the residue was purified by flash chromatography (Heptane  $\rightarrow$  PE  $\rightarrow$  1:19  $\rightarrow$  1:9  $\rightarrow$  3:7 EtOAc:PE) to afford 20 g (65% - E/Z mixture of 1/3) of **9** as a colorless oil. *Major isomer (Z)*:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  6.32 (q,  $J = 6.6$  Hz, 1H,  $\text{CH}_3\text{CH}=\text{}$ ), 4.17 (d,  $J = 5.6$  Hz, 2H,  $\text{CH}_2\text{OH}$ ), 1.74 (d,  $J = 6.6$  Hz, 3H,  $\text{CH}_3\text{CH}=\text{}$ ), 1.54 – 1.44 (m, 6H,  $\text{SnBu}_3$ ), 1.41 – 1.25 (m, 9H,  $\text{SnBu}_3$ ), 1.15 (t,  $J = 5.6$  Hz, 1H,  $\text{CH}_2\text{OH}$ ), 1.00 – 0.94 (m, 3H,  $\text{SnBu}_3$ ), 0.92 – 0.84 (m, 9H,  $\text{SnBu}_3$ ). The  $^3J_{\text{SnC}=\text{CH}}$  coupling is found to be 123 Hz.  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  144.6( $\text{C}=\text{CSnBu}_3$ ), 136.2( $\text{C}=\text{CSnBu}_3$ ), 70.7( $\text{CH}_2\text{OH}$ ), 29.4( $\text{SnBu}_3$ ), 27.5( $\text{SnBu}_3$ ), 19.7( $\text{CH}_3\text{C}=\text{}$ ), 13.9( $\text{SnBu}_3$ ), 10.2( $\text{SnBu}_3$ ). *Minor isomer (E)*:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  5.66 (m, 1H,  $\text{CH}_3\text{CH}=\text{}$ ), 4.38 (m, 2H,  $=\text{CCH}_2\text{OH}$ ), 1.69 (d,  $J = 6.5$  Hz, 3H,  $\text{CH}_3\text{CH}=\text{}$ ). The remaining signals are overlapped by the major isomer.  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  138.9( $\text{C}=\text{CSnBu}_3$ ), 134.3( $\text{C}=\text{CSnBu}_3$ ), 63.7( $\text{CH}_2\text{OH}$ ), 29.5( $\text{SnBu}_3$ ), 27.6 ( $\text{SnBu}_3$ ), 15.3( $\text{CH}_3\text{C}=\text{}$ ), 13.9( $\text{SnBu}_3$ ), 10.2( $\text{SnBu}_3$ ). MS (ESP):  $m/z$ : 385.1520 [ $\text{M}+\text{Na}$ ] $^+$ , calcd for  $\text{C}_{16}\text{H}_{34}\text{OSn}$ : 385.1529

### 2-iodo-2-buten-1-ol (10)<sup>1</sup>



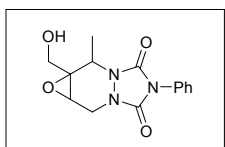
Compound **7** (20 g, 55.4 mmol) was dissolved in 330 mL  $\text{CCl}_4$  and cooled to 0°C.  $\text{I}_2$  (30 g, 118 mmol) was added and the mixture was stirred for 30 min. The reaction was quenched with 250 mL  $\text{Na}_2\text{S}_2\text{O}_3$  (sat.) and the two layers were separated. The aqueous layer was extracted with 1x100 mL  $\text{Et}_2\text{O}$ . The combined organic layers were dried over  $\text{MgSO}_4$ , filtered and evaporated. The crude product was purified by flash chromatography (2:8  $\text{Et}_2\text{O}$ :PE  $\rightarrow$  1:1 EtOAc:PE) to afford 9.94 g (91%) of **8** (1:4 mixture of E/Z isomers along with 10% of the inseparable regio-isomer) as a brown oil. *Major isomer (Z)*:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  5.97 (qt,  $J = 6.4, 1.2$  Hz, 1H,  $\text{CH}_3\text{CH}=\text{}$ ), 4.26 – 4.24 (m, 2H,  $=\text{CCH}_2\text{OH}$ ), 1.80 (dt,  $J = 6.4, 1.2$  Hz, 3H,  $\text{CH}_3\text{CH}=\text{}$ ).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  131.6( $\text{CH}=\text{C}$ ), 109.9( $\text{CH}=\text{C}$ ), 71.9( $\text{CH}_2\text{OH}$ ), 21.6( $\text{CH}_3\text{CH}=\text{}$ ). *Minor Isomer (E)*:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  6.38 (qt,  $J = 7.2, 0.8$  Hz, 1H,  $\text{CH}_3\text{CH}=\text{}$ ), 4.23 (s, 2H,  $=\text{CCH}_2\text{OH}$ ), 1.74 (dt,  $J = 7.2, 0.8$  Hz, 3H,  $\text{CH}_3\text{CH}=\text{}$ ).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  138.2( $\text{CH}=\text{C}$ ), 103.0( $\text{CH}=\text{C}$ ), 64.7( $\text{CH}_2\text{OH}$ ), 16.7( $\text{CH}_3\text{CH}=\text{}$ ). *3-iodo-2-buten-1-ol*:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  5.78 (tq,  $J = 6.0, 1.5$  Hz, 1H,  $\text{CH}_3\text{C}=\text{CH}$ ), 4.17 (dq,  $J = 6.0, 1.2$  Hz, 2H,  $\text{CH}_2\text{OH}$ ), 2.54 (dt,  $J = 1.2, 1.5$  Hz, 3H,  $\text{CH}_3\text{Cl}=\text{C}$ ).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  134.2 ( $\text{CH}_3\text{C}=\text{CH}$ ), 102.5( $\text{CH}_3\text{C}=\text{}$ ), 67.5( $\text{CH}_2\text{OH}$ ), 33.8( $\text{CH}_3\text{Cl}=\text{}$ ). MS (ESP):  $m/z$ : 220.9411 [ $\text{M}+\text{Na}$ ] $^+$ , calcd for  $\text{C}_4\text{H}_7\text{INO}$ : 220.9439

## 6-(hydroxymethyl)-5-methyl-2-phenyl-5,8-dihydro-1H-[1,2,4]triazolo[1,2-a]pyridazine-1,3(2H)-dione (12)



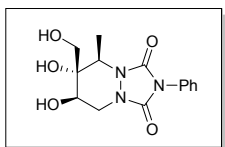
The iodoalcohol **10** (2.02 g, 10.2 mmol),  $\text{PPh}_3$  (0.268 g, 1.02 mmol) and  $\text{Pd}(\text{dba})_2$  (0.293 g, 0.51 mmol) was dissolved in 20 mL dry THF and cooled to 0 °C. Freshly prepared vinyl magnesiumbromide (30.7 mL, 0.83 M, 25.5 mmol) was added by syringe, and the mixture was stirred at 0 °C for 2.5 h. The reaction mixture was then hydrolyzed by addition of 50 mL  $\text{NH}_4\text{Cl}$  (sat.) and extracted with 2x25 mL  $\text{Et}_2\text{O}$ . The collected organic fractions were dried over  $\text{MgSO}_4$  and filtered. In another flask, 4-phenylurazole (1.8 g, 10.2 mmol) was suspended in 30 mL  $\text{EtOAc}$  and cooled to 0 °C.  $t\text{-BuOCl}$  (1.16 mL, 10.2 mmol) was added and stirred for 15 mins to give a strongly red mixture. Then added was the dried organic fractions from the Pd-coupling, and the mixture was stirred for 30 mins. At this point another charge of  $t\text{-BuOCl}$  (0.5 mL, 4.4 mmol) was added, and the mixture was stirred for 30 min at 0 °C followed by 50 min at 25 °C. The mixture was then concentrated *in vacuo* and purified by flash chromatography (1:1 → 4:1 → 9:1  $\text{EtOAc}:\text{PE}$ ) to afford 1.08 g (39% over two steps) of **12** as a light orange solid (contains traces of 4-phenylurazole, these traces can be removed by recrystallization from hot  $\text{EtOAc}$ , though the yield is reduced).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.56 – 7.34 (m, 5H, ArH), 5.90 – 5.86 (m, 1H, =CHCH<sub>2</sub>), 4.70 (bq,  $J$  = 6.5 Hz, 1H, CHCH<sub>3</sub>), 4.40 – 4.31 (m, 1H, CHCH<sub>2a</sub>N), 4.24 (bs, 2H, CH<sub>2</sub>OH), 4.07 – 3.98 (dm, 1H, CHCH<sub>2b</sub>N), 1.70 (s, 1H, CH<sub>2</sub>OH), 1.41 (d,  $J$  = 6.5 Hz, 3H, CH<sub>3</sub>).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  153.4(CO), 151.6(CO), 138.4(C), 131.2, 129.3, 128.3, 125.5(Ar), 115.8(=CHCH<sub>2</sub>), 63.2(CH<sub>2</sub>OH), 50.1(CHCH<sub>3</sub>), 43.8(CHCH<sub>2</sub>), 16.3(CH<sub>3</sub>). M.p. 157-158 °C, MS (ESP):  $m/z$ : 296.1007[M+Na]<sup>+</sup>, calcd for  $\text{C}_{14}\text{H}_{15}\text{N}_3\text{NaO}_3$ : 296.1011

## 1a-(hydroxymethyl)-2-methyl-5-phenyldihydro-1aH-oxireno[2,3-d][1,2,4]triazolo[1,2-a]pyridazine-4,6(2H,5H)-dione (13)



Allylic alcohol **12** (813 mg, 2.98 mmol) and *m*-CPBA (1.54 g, 8.93 mmol) was dissolved in 50 mL DCE and heated to 85 °C for 2.5 h. The mixture was then washed with  $\text{KHCO}_3$  (sat.) and extracted with 2x25 mL DCM, dried over  $\text{MgSO}_4$ , filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (1:1 → 7:3 → 4:1 → 1:0 -  $\text{EtOAc}:\text{PE}$ ) to afford 570 mg (66%) of **13** (1:2 mixture of “cis/trans”) as a light yellow oil that solidified overnight. *Major isomer (13t)*:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.58 – 7.33 (m, 7.5H, ArH(cis/trans)), 4.75 (q,  $J$  = 6.6 Hz, 1H, CHCH<sub>3</sub>), 4.11 (dd,  $J$  = 14.0, 3.3 Hz, 1H, CHCH<sub>2a</sub>), 4.05 (d,  $J$  = 14.0 Hz, 1H, CHCH<sub>2b</sub>), 4.04 (d,  $J$  = 12.8 Hz, 1H, CH<sub>2a</sub>OH), 3.74 (d,  $J$  = 12.8 Hz, 1H, CH<sub>2b</sub>OH), 3.62 (d,  $J$  = 3.3 Hz, 1H, CHCH<sub>2</sub>), 1.43 (d,  $J$  = 6.6 Hz, 3H, CH<sub>3</sub>).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  152.7(CO), 151.6(CO), 131.2, 129.3, 128.4, 125.5(Ar), 61.4(CH<sub>2</sub>OH), 61.4(C), 51.4(CHCH<sub>2</sub>), 49.5(CHCH<sub>3</sub>), 42.3(CHCH<sub>2</sub>), 14.1(CH<sub>3</sub>). *Minor isomer (13c)*:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  4.41 (q,  $J$  = 6.4 Hz, 1H, CHCH<sub>3</sub>), 4.39 (dd,  $J$  = 13.6, 1.0 Hz, 1H, CHCH<sub>2a</sub>) 3.87 (d,  $J$  = 12.6 Hz, 1H, CH<sub>2a</sub>OH), 3.84 (d,  $J$  = 12.6 Hz, 1H, CH<sub>2b</sub>OH), 3.66 (bs, 1H, CHCH<sub>2</sub>), 3.58 (dd,  $J$  = 13.6, 1.6 Hz, 1H, CHCH<sub>2b</sub>), 1.38 (d,  $J$  = 6.4 Hz, 3H, CH<sub>3</sub>).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  154.40(CO), 152.06(CO), 131.06, 129.34, 128.44, 125.40(Ar), 61.87(CH<sub>2</sub>OH), 61.35(C), 53.61(CHCH<sub>2</sub>), 49.17 (CHCH<sub>3</sub>), 44.25(CHCH<sub>2</sub>), 12.15(CH<sub>3</sub>). M.p. could not be obtained because of product decomposition at 151-157 °C. MS (ESP):  $m/z$ : 312.0954 [M+Na]<sup>+</sup>, calcd for  $\text{C}_{14}\text{H}_{15}\text{N}_3\text{NaO}_4$ : 312.0960

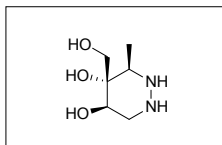
## (5R,6S,7R)-6,7-dihydroxy-6-(hydroxymethyl)-5-methyl-2-phenyltetrahydro-1H-[1,2,4]triazolo[1,2-a]pyridazine-1,3(2H)-dione (14)



The mixture of isomeric epoxides **13** (567 mg, 1.96 mmol) was suspended in 50 mL  $\text{H}_2\text{O}$ ,  $\text{HClO}_4$  (1.35 mL, 70%, 15.7 mmol) was added, and the mixture refluxed for 2.5 h.  $\text{KHCO}_3$  (2 g, 20 mmol) was added, and the mixture was stirred for 10 min followed by concentration *in vacuo*. The crude product was purified by flash chromatography ( $\text{EtOAc}$ ) to afford 542 mg (90%) as a 1:8 mixture of two triols **14a** and **14**. Recrystallized from hot  $\text{MeOH}:\text{PE}$  to afford 395 mg of **14** as a white solid. A second recrystallization afforded another 26 mg of equal purity. This afforded **14** in a total yield of 421mg(70%).  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ )  $\delta$  7.58 – 7.33 (m, 5H, ArH), 5.42 (d,  $J$  = 3.4 Hz, 1H, CHO), 4.94 (s, 1H, COH), 4.69 (dd,  $J$  = 6.4, 4.7 Hz, 1H, CH<sub>2</sub>OH), 4.07 (q,  $J$  = 6.8 Hz, 1H, CHCH<sub>3</sub>), 3.75 (dd,  $J$  = 12.1, 2.1 Hz, 1H, CHCH<sub>2a</sub>), 3.71 (m, 2H, CH<sub>2a</sub>OH, HOCHCH<sub>2</sub>), 3.58 (dd,  $J$

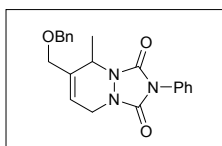
12.1, 2.1 Hz, 1H, CHCH<sub>2b</sub>), 3.54 (dd, *J* = 11.4, 4.7 Hz, 1H, CH<sub>2b</sub>OH), 1.27 (d, *J* = 6.8 Hz, 3H, CHCH<sub>3</sub>). <sup>13</sup>C NMR (126 MHz, DMSO) δ 152.9(CO), 151.0(CO), 131.6, 128.9, 127.9, 126.0(Ar), 72.0(C), 67.0(CHOH), 63.7(CH<sub>2</sub>OH), 55.3(CHCH<sub>3</sub>), 47.0(CHCH<sub>2</sub>), 12.7(CH<sub>3</sub>). M.p. 239-241 °C. MS (ESP): *m/z*: 308.1249 [M+H]<sup>+</sup>, calcd for C<sub>14</sub>H<sub>18</sub>N<sub>3</sub>O<sub>5</sub>: 308.1246

### (3R,4S,5R)-4-(hydroxymethyl)-3-methylhexahydropyridazine-4,5-diol (15)



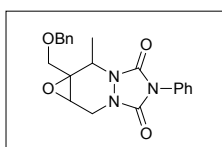
Compound **14** (379 mg, 1.23 mmol) in 17 mL NH<sub>2</sub>NH<sub>2</sub>•H<sub>2</sub>O(65%) was heated to 115 °C for 2 days. The mixture was concentrated *in vacuo*, dissolved in H<sub>2</sub>O and applied to a column of ion-exchange resin (Amberlyst IR120). The column was first washed with H<sub>2</sub>O and then eluted with 2.5% NH<sub>4</sub>OH and concentrated *in vacuo*. The crude product was purified by flash chromatography (8:2 MeCN:H<sub>2</sub>O – made basic with drops of 25% NH<sub>4</sub>OH) to afford 71 mg (36%) of **15** as an oil that solidified overnight. <sup>1</sup>H NMR (500 MHz, D<sub>2</sub>O) δ 3.87 (s, 2H, CH<sub>2</sub>OH), 3.72 (dd, *J* = 9.5, 4.8 Hz, 1H, HOCHCH<sub>2</sub>), 3.10 (dd, *J* = 13.5, 4.8 Hz, 1H, CHCH<sub>2a</sub>), 2.84 (dd, *J* = 13.5, 9.5 Hz, 1H, CHCH<sub>2b</sub>), 2.78 (q, *J* = 7.0 Hz, 1H, CHCH<sub>3</sub>), 1.15 (d, *J* = 7.0 Hz, 3H, CHCH<sub>3</sub>). <sup>13</sup>C NMR (DCl salt) (126 MHz, DMSO-*d*<sub>6</sub>/D<sub>2</sub>O) δ 70.17(C), 60.5(bs, CH<sub>2</sub>OH, CHCH<sub>2</sub>), 56.5(bs, CHCH<sub>3</sub>), 47.2(CHCH<sub>2</sub>), 10.2(CH<sub>3</sub>). M.p. could not be obtained because of product decomposition at 150 °C. (decompose). MS (ESP): *m/z*: 163.1083 [M+H]<sup>+</sup>, calcd for C<sub>6</sub>H<sub>15</sub>N<sub>2</sub>O<sub>3</sub>: 163.1083

### 6-((benzyloxy)methyl)-5-methyl-2-phenyl-5,8-dihydro-1H-[1,2,4]triazolo[1,2-a]pyridazine-1,3(2H)-dione (16)



Allylic alcohol **12** (184 mg, 0.67 mmol, containing trace amounts of 4-phenyl-urazole) and TriBOT (94 mg, 0.24 mmol) was dissolved in 5mL dry 1,4-dioxane with 100 mg 3 Å MS and stirred for 5 mins. TfOH (0.021 mL, 0.24 mmol) was added via syringe, and the reaction was stirred for 2 h at 25 °C. The reaction was quenched with Et<sub>3</sub>N, filtered through silica, eluted with 50 mL 1,4-dioxane and concentrated *in vacuo*. The crude product was purified by flash chromatography (1:9 → 1:4 → 1:3 → 3:7 EtOAc:PE) to afford 203 mg (84%) of **16** as white solid. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.56 – 7.51 (m, 2H, ArH), 7.47 (m, 2H, ArH), 7.42 – 7.29 (m, 6H, ArH), 5.89 (bm, 1H, CH=CH<sub>2</sub>), 4.70 (bq, *J* = 6.5 Hz, 1H, CHCH<sub>3</sub>), 4.58 (d, *J* = 11.9 Hz, 1H, OCH<sub>2a</sub>Ph), 4.50 (d, *J* = 11.9 Hz, 1H, OCH<sub>2b</sub>Ph), 4.35 (dm, 1H, CH<sub>2a</sub>NN), 4.18 – 4.09 (m, 1H, CH<sub>2a</sub>OBn), 4.08 – 3.99 (m, 2H, CH<sub>2b</sub>NN, CH<sub>2b</sub>OBn), 1.39 (d, *J* = 6.5 Hz, 3H, CH<sub>3</sub>). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 153.5(CO), 151.6(CO), 137.6(CH<sub>2</sub>C=CH), 136.1, 131.4, 129.3, 128.7, 128.2, 128.1, 128.0, 125.5(Ar), 117.7(CH=C), 72.7(C<sub>Bn</sub>), 70.3(CH<sub>2</sub>OBn), 50.5(CHCH<sub>3</sub>), 43.9(CHCH<sub>2</sub>N), 16.2(CH<sub>3</sub>). M.p. 127-128 °C, MS (MALDI): *m/z*: 364.1655 [M+H]<sup>+</sup>, calcd for C<sub>21</sub>H<sub>22</sub>N<sub>3</sub>O<sub>3</sub>: 364.1661

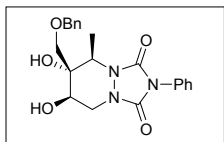
### 1a-((benzyloxy)methyl)-2-methyl-5-phenyldihydro-1aH-oxireno[2,3-d][1,2,4]triazolo[1,2-a]pyridazine-4,6(2H,5H)-dione (17c:17t)



Allylic **16** (203 mg, 0.56 mmol) was dissolved in 15 mL DCE and added *m*CPBA (289 mg, 1.68 mmol). The reaction mixture was then stirred overnight at 60 °C followed by 2 h at 80 °C. The reaction mixture was washed with sat. NaHCO<sub>3</sub>, brine, dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (1:4 → 3:7 → 2:3 → 1:1 EtOAc:PE) to afford the two epoxides: **17c**: 77 mg (36%) as a light orange gum and **17t**: 67 mg (32%) as a white amorphous solid. **17c** <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.51 – 7.29 (m, 10H, ArH), 4.63 – 4.55 (m, 3H, OCH<sub>2</sub>Ph, CHCH<sub>3</sub>), 4.34 (dd, *J* = 13.4, 1.1 Hz, 1H, CHCH<sub>2a</sub>), 3.69 (d, *J* = 11.0 Hz, 1H, CH<sub>2a</sub>OBn), 3.56 (d, *J* = 11.0 Hz, 1H, CH<sub>2b</sub>OBn), 3.55 – 3.51 (dd, *J* = 13.4, 1.5 Hz, 1H, CHCH<sub>2b</sub>), 3.46 (m, 1H, CHCH<sub>2</sub>), 1.38 (d, *J* = 6.5 Hz, 3H, CH<sub>3</sub>). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 154.4(CO), 151.9(CO), 137.3, 131.1, 129.3, 128.8, 128.4, 128.3, 128.0, 125.4(Ar), 74.0 (OCH<sub>2</sub>Ph), 71.3 (CH<sub>2</sub>OBn), 60.0(C), 54.9(CHCH<sub>2</sub>), 49.3 (CHCH<sub>3</sub>), 44.2(CHCH<sub>2</sub>), 12.1(CH<sub>3</sub>). MS (MALDI): *m/z*: 380.1605 [M+H]<sup>+</sup>, calcd for C<sub>21</sub>H<sub>22</sub>N<sub>3</sub>O<sub>4</sub>: 380.1610. **17t** <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.52 – 7.29 (m, 10H, ArH), 4.86 (q, *J* = 6.6 Hz, 1H, CHCH<sub>3</sub>), 4.68

(d,  $J = 11.9$  Hz, 1H,  $\text{OCH}_{2a}\text{Ph}$ ), 4.55 (d,  $J = 11.9$  Hz, 1H,  $\text{OCH}_{2b}\text{Ph}$ ), 4.08 (dd,  $J = 13.9, 3.3$  Hz, 1H,  $\text{CHCH}_{2a}$ ), 4.03 (d,  $J = 13.9$  Hz, 1H,  $\text{CHCH}_{2b}$ ), 4.02 (d,  $J = 11.7$  Hz, 1H,  $\text{CH}_{2a}\text{OBn}$ ), 3.43 (d,  $J = 3.3$  Hz, 1H,  $\text{CHCH}_2$ ), 3.40 (d,  $J = 11.7$  Hz, 1H,  $\text{CH}_{2b}\text{OBn}$ ), 1.41 (d,  $J = 6.6$  Hz, 3H,  $\text{CH}_3$ ).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  152.7(CO), 151.5(CO), 137.2, 131.2, 129.3, 128.7, 128.3, 128.3, 128.1, 125.5(Ar), 73.8( $\text{OCH}_2\text{Ph}$ ), 69.9 ( $\text{CH}_2\text{OBn}$ ), 60.6(C), 50.8( $\text{CHCH}_2$ ), 49.5( $\text{CHCH}_3$ ), 42.0 ( $\text{CHCH}_2$ ), 14.2( $\text{CH}_3$ ). MS (MALDI):  $m/z$ : 380.1605  $[\text{M}+\text{H}]^+$ , calcd for  $\text{C}_{21}\text{H}_{22}\text{N}_3\text{O}_4$ : 380.1610

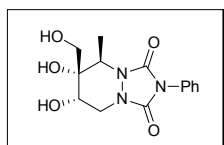
### 6,7-dihydroxy-1a-((benzyloxy)methyl)-5-methyl-2-phenyltetrahydro-1H-[1,2,4]triazolo[1,2-a]pyridazine-1,3(2H)-dione (18a:18)



Epoxide **17c** (56 mg, 0.15 mmol) and epoxide **17t** (70 mg, 0.18 mmol) was each suspended in 20 mL  $\text{H}_2\text{O}$  in separate flasks, added  $\text{HClO}_4$  (70% - 0.1 mL, 1.18 mmol for **17c** - 0.12 mL, 1.44 mmol for **17t**) and refluxed overnight. The mixtures were then extracted with EtOAc (2x15 mL) and evaporated. This provided crude yields from **17c** - 52 mg (87%) and from **17t** - 47 mg (65%).

**17c** provided a 1:3 mixture of **18a:18** whereas **17t** provided almost exclusively **18**.  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ )  $\delta$  7.52 - 7.10 (m, 10H, ArH), 4.62 (d,  $J = 12.1$  Hz, 1H,  $\text{OCH}_{2a}\text{Ph}$ ), 4.54 (d,  $J = 12.1$  Hz, 1H,  $\text{OCH}_{2b}\text{Ph}$ ), 4.14 (q,  $J = 6.8$  Hz, 1H,  $\text{CHCH}_3$ ), 3.80 (d,  $J = 9.9$  Hz, 1H,  $\text{CH}_{2a}\text{OBn}$ ), 3.78 - 3.72 (m, 2H,  $\text{CHCH}_{2a}$ ,  $\text{CHCH}_2$ ), 3.61 (d,  $J = 10.3$  Hz, 1H,  $\text{CHCH}_{2b}$ ), 3.55 (d,  $J = 9.9$  Hz, 1H,  $\text{CH}_{2b}\text{OBn}$ ), 1.25 (d,  $J = 6.8$  Hz, 3H,  $\text{CH}_3$ ).  $^{13}\text{C}$  NMR (126 MHz,  $\text{DMSO}$ )  $\delta$  153.0(CO), 151.1(CO), 138.4, 128.9, 128.9, 128.3, 128.2, 127.6, 127.5, 126.0, (Ar), 72.8( $\text{OCH}_2\text{Ph}$ ), 72.6( $\text{CH}_2\text{OBn}$ ), 71.7(C), 67.3( $\text{CHCH}_2$ ), 55.3( $\text{CHCH}_3$ ), 47.0( $\text{CHCH}_2$ ), 12.7( $\text{CH}_3$ ). MS (MALDI):  $m/z$ : 420.1532  $[\text{M}+\text{Na}]^+$ , calcd for  $\text{C}_{21}\text{H}_{23}\text{N}_3\text{NaO}_5$ : 420.1535

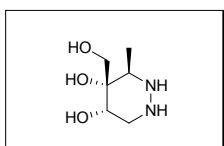
### (5R,6S,7S)-6,7-dihydroxy-6-(hydroxymethyl)-5-methyl-2-phenyltetrahydro-1H-[1,2,4]triazolo[1,2-a]pyridazine-1,3(2H)-dione (20)



Compound **12** (2.88 g, 10.5 mmol) was dissolved in 56 mL acetone and 24 mL  $\text{H}_2\text{O}$ . NMO (1.7 g, 14.7 mmol) was added followed by  $\text{OsO}_4$  (2.6 mL, 2.5% in *t*-BuOH, 0.21 mmol), and the reaction was stirred overnight.  $\text{Na}_2\text{S}_2\text{O}_5$  (2.88 g, 15 mmol) was added, and the mixture was stirred for 10 min. followed by concentration *in vacuo*, and then co-evaporated with toluene. The crude mixture was purified by flash chromatography (1:19 MeOH:DCM). The collected fractions were concentrated *in vacuo*, then dissolved in hot MeOH and applied to an IR120 amberlite ion exchange resin column. The product was eluted off the column using MeOH. The collected fractions were concentrated *in vacuo* to afford 2.4 g (74%) of **20** as a white solid.

$^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ )  $\delta$  7.52 - 7.38 (m, 5H, ArH), 4.15 (q,  $J = 6.8$  Hz, 1H,  $\text{CHCH}_3$ ), 3.94 (dd,  $J = 10.7, 5.4$  Hz, 1H,  $\text{HOCHCH}_2$ ), 3.74 (dd,  $J = 10.8, 5.4$  Hz, 1H,  $\text{CHCH}_{2a}$ ), 3.72 (d,  $J = 11.8$  Hz, 1H,  $\text{CH}_{2a}\text{OH}$ ), 3.48 (d,  $J = 11.8$  Hz, 1H,  $\text{CH}_{2b}\text{OH}$ ), 3.20 (dd,  $J = 10.8, 10.7$  Hz, 1H,  $\text{CHCH}_{2b}$ ), 1.16 (d,  $J = 6.8$  Hz, 3H,  $\text{CH}_3$ ).  $^{13}\text{C}$  NMR (126 MHz,  $\text{DMSO}$ )  $\delta$  151.7(CO), 150.7(CO), 131.5, 128.9, 127.9, 126.0(Ar), 73.3(C), 64.4(CHOH), 63.7 ( $\text{CH}_2\text{OH}$ ), 55.4( $\text{CHCH}_3$ ), 44.5( $\text{CHCH}_2$ ), 12.4( $\text{CH}_3$ ). M.p. 210-213 $^\circ\text{C}$  (decomposition). MS (ESP):  $m/z$ : 330.1066  $[\text{M}+\text{Na}]^+$ , calcd for  $\text{C}_{14}\text{H}_{17}\text{N}_3\text{NaO}_5$ : 330.1066

### (3R,4S,5S)-4-(hydroxymethyl)-3-methylhexahydropyridazine-4,5-diol (21)



Compound **20** (300 mg, 0.98 mmol) in 15 mL  $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$  (65%) was heated to 115  $^\circ\text{C}$  for 4 days. The mixture was then concentrated *in vacuo*, dissolved in  $\text{H}_2\text{O}$  and applied to an IR 120 amberlite ion exchange resin column. The column was first washed with  $\text{H}_2\text{O}$  and then eluted with 2.5%  $\text{NH}_4\text{OH}$ . The eluted fractions were concentrated *in vacuo* and the crude product was purified by flash chromatography (2:8  $\text{H}_2\text{O}$ :MeCN made basic with drops of 25%  $\text{NH}_4\text{OH}$ ) to afford 113 mg (71%) of **21** as a colorless oil.  $^1\text{H}$  NMR (500 MHz,  $\text{D}_2\text{O}$ )  $\delta$  3.92 (dd,  $J = 6.4, 3.5$  Hz, 1H,  $\text{HOCHCH}_2$ ), 3.87 (d,  $J = 12.3$  Hz, 1H,  $\text{CH}_{2a}\text{OH}$ ), 3.70 (d,  $J = 12.3$  Hz, 1H,  $\text{CH}_{2b}\text{OH}$ ), 3.09 (q,  $J = 7.0$  Hz, 1H,  $\text{CHCH}_3$ ), 3.00 - 2.85 (m, 2H,  $\text{CHCH}_2$ ), 1.08 (d,  $J = 7.0$

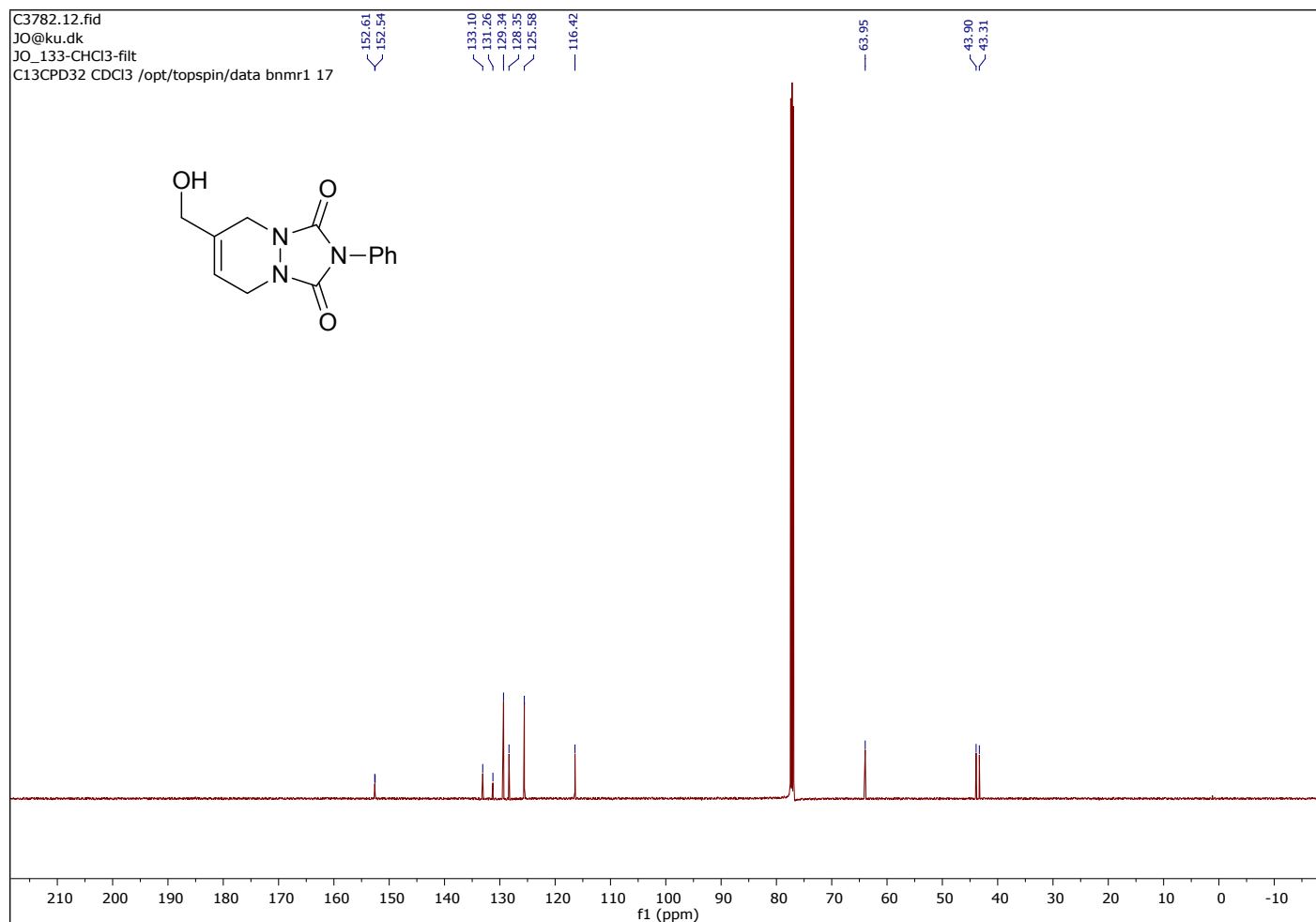
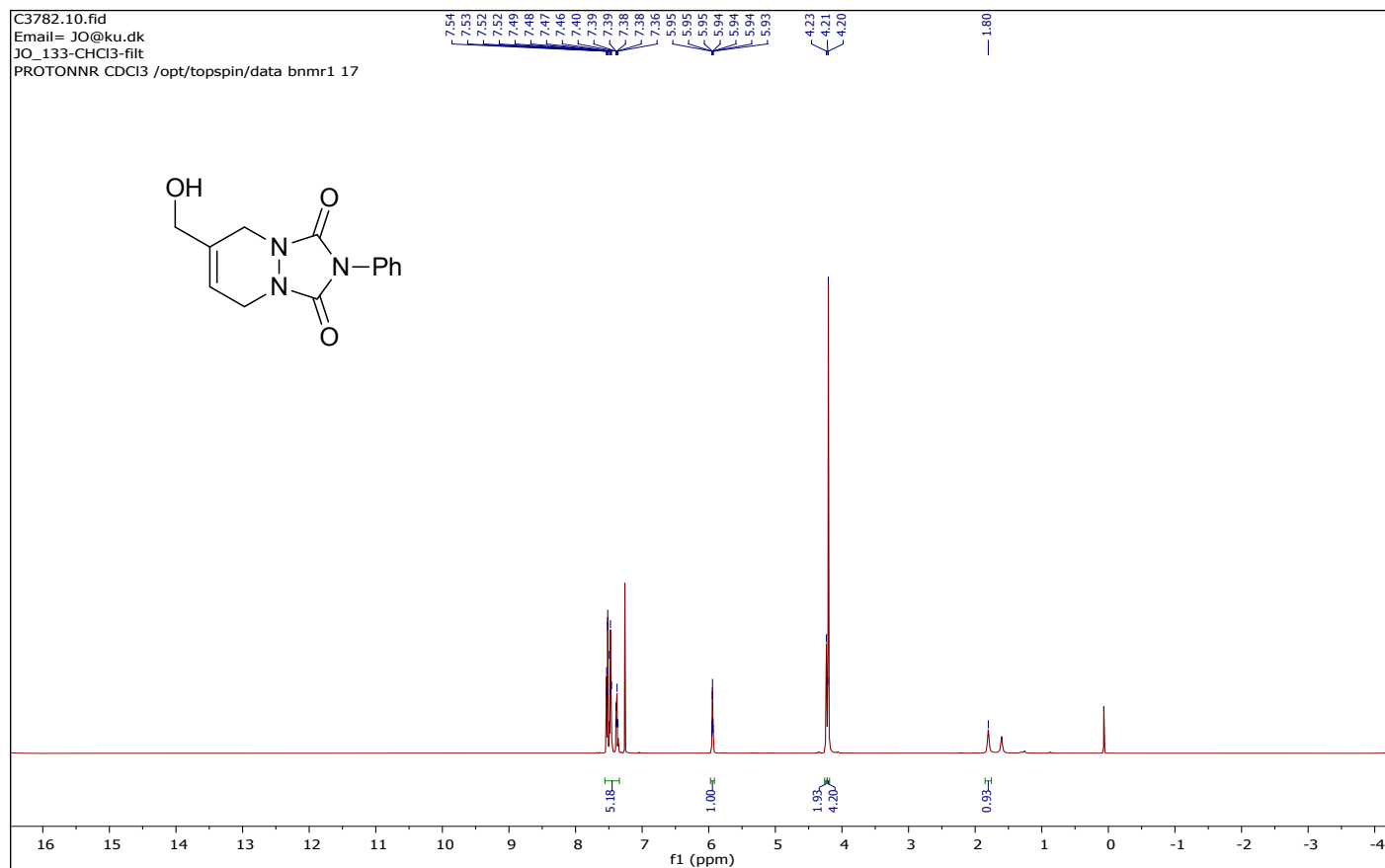
Hz, 3H, CH<sub>3</sub>). <sup>13</sup>C NMR DCl salt (126 MHz, DMSO-*d*<sub>6</sub>/D<sub>2</sub>O) δ 70.9(C), 62.6(CHCH<sub>2</sub>), 61.2(CHCH<sub>2</sub>), 54.2(CHCH<sub>3</sub>), 45.9(CH<sub>2</sub>OH), 9.5(CH<sub>3</sub>). MS (ESP): m/z: 163.1077 [M+H]<sup>+</sup>, calcd for C<sub>6</sub>H<sub>15</sub>N<sub>2</sub>O<sub>3</sub>: 163.1083

### General procedure for the conformational NMR study

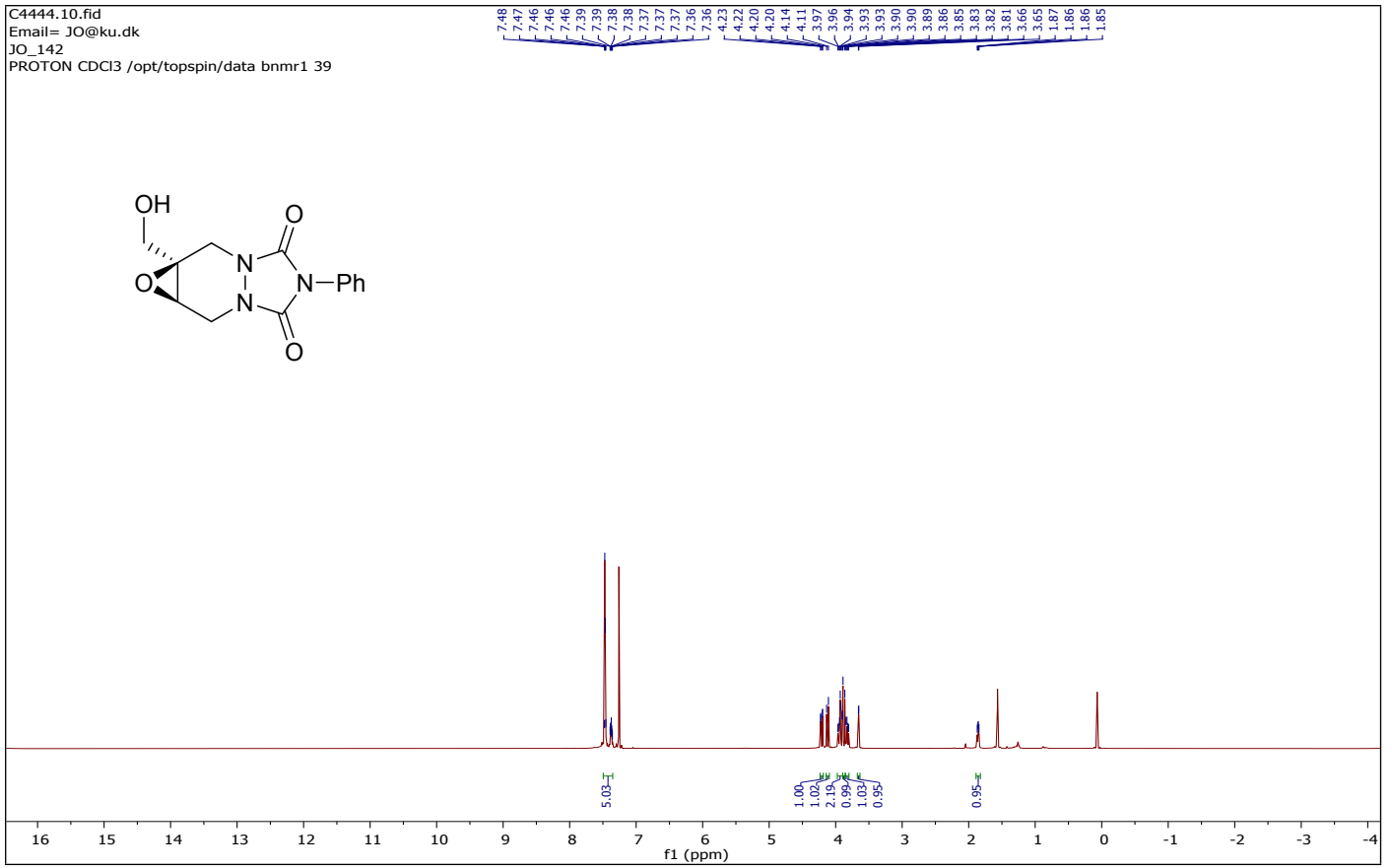
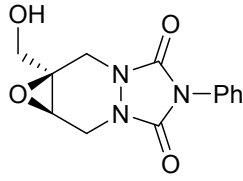
Compound **1a**, **8**, **15** and **21** were each dissolved in D<sub>2</sub>O and the pH adjusted with NaOD (30 wt %) until basic. The NMR was then recorded and the same sample was then added conc. DCl until acidic and again the NMR was recorded. The recorded NMR spectra of the basic solutions were assigned with coupling constants and compared to their corresponding acidic solution NMR spectra.



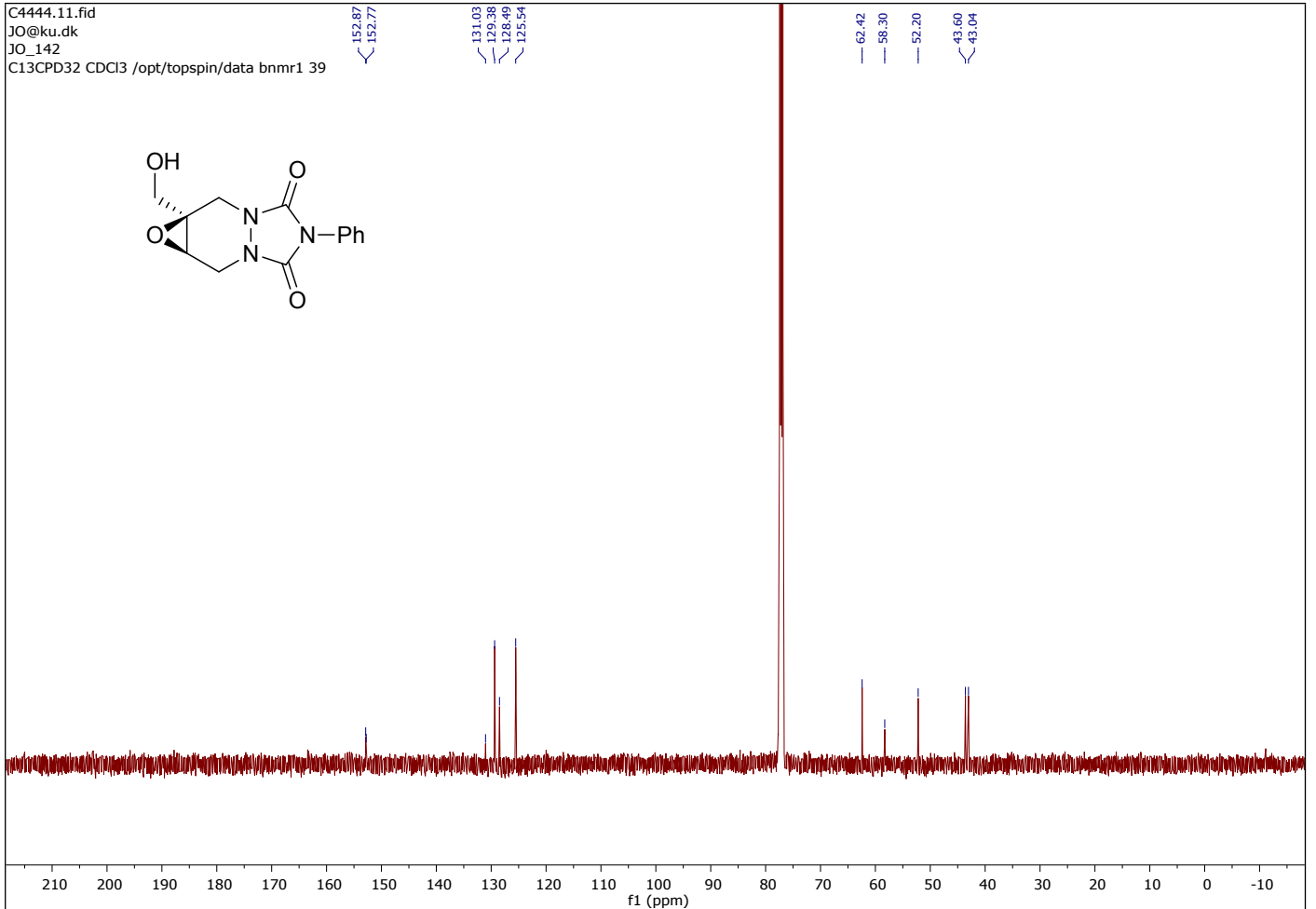
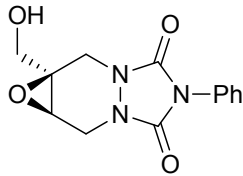
# <sup>1</sup>H and <sup>13</sup>C NMR Spectra

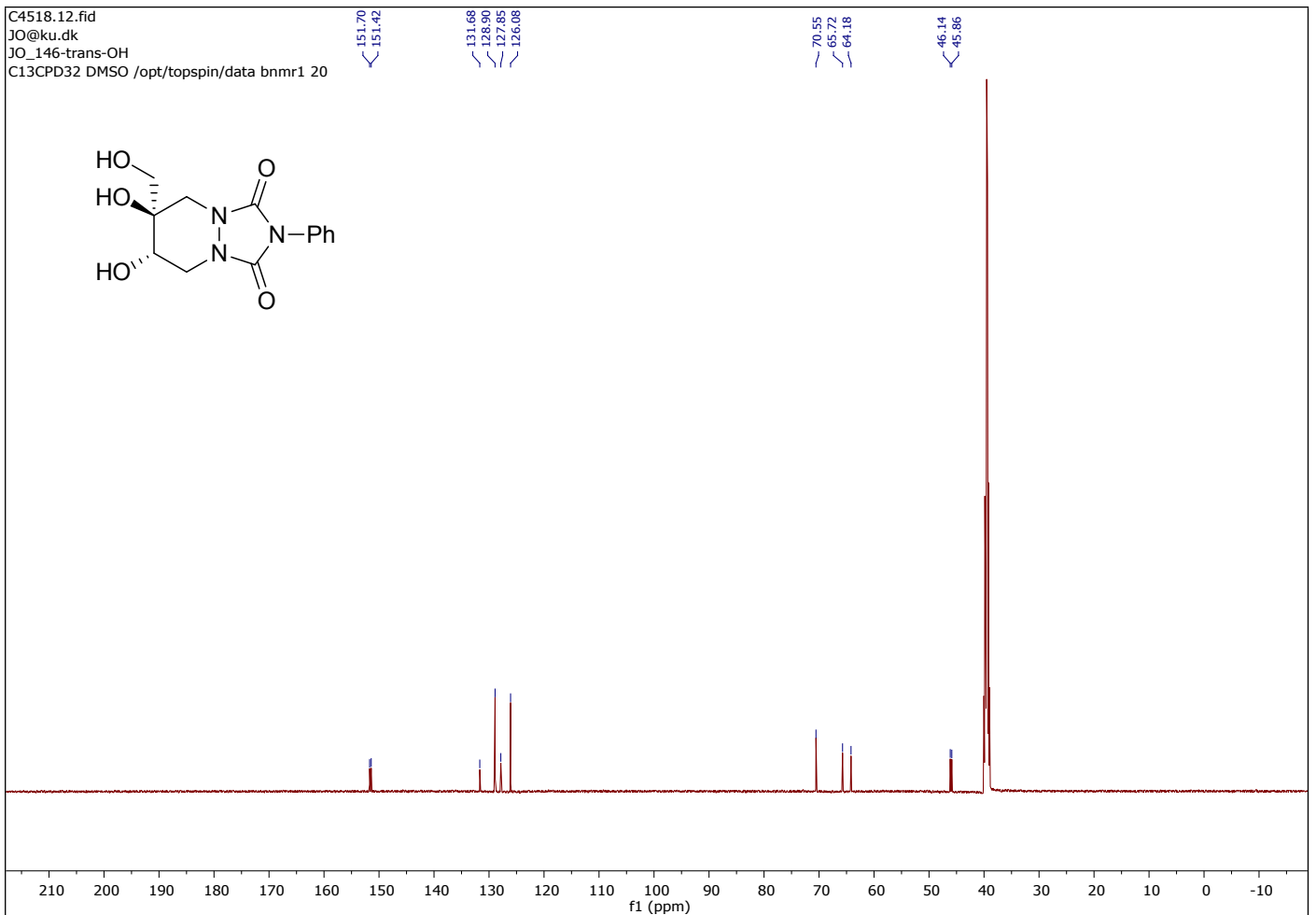
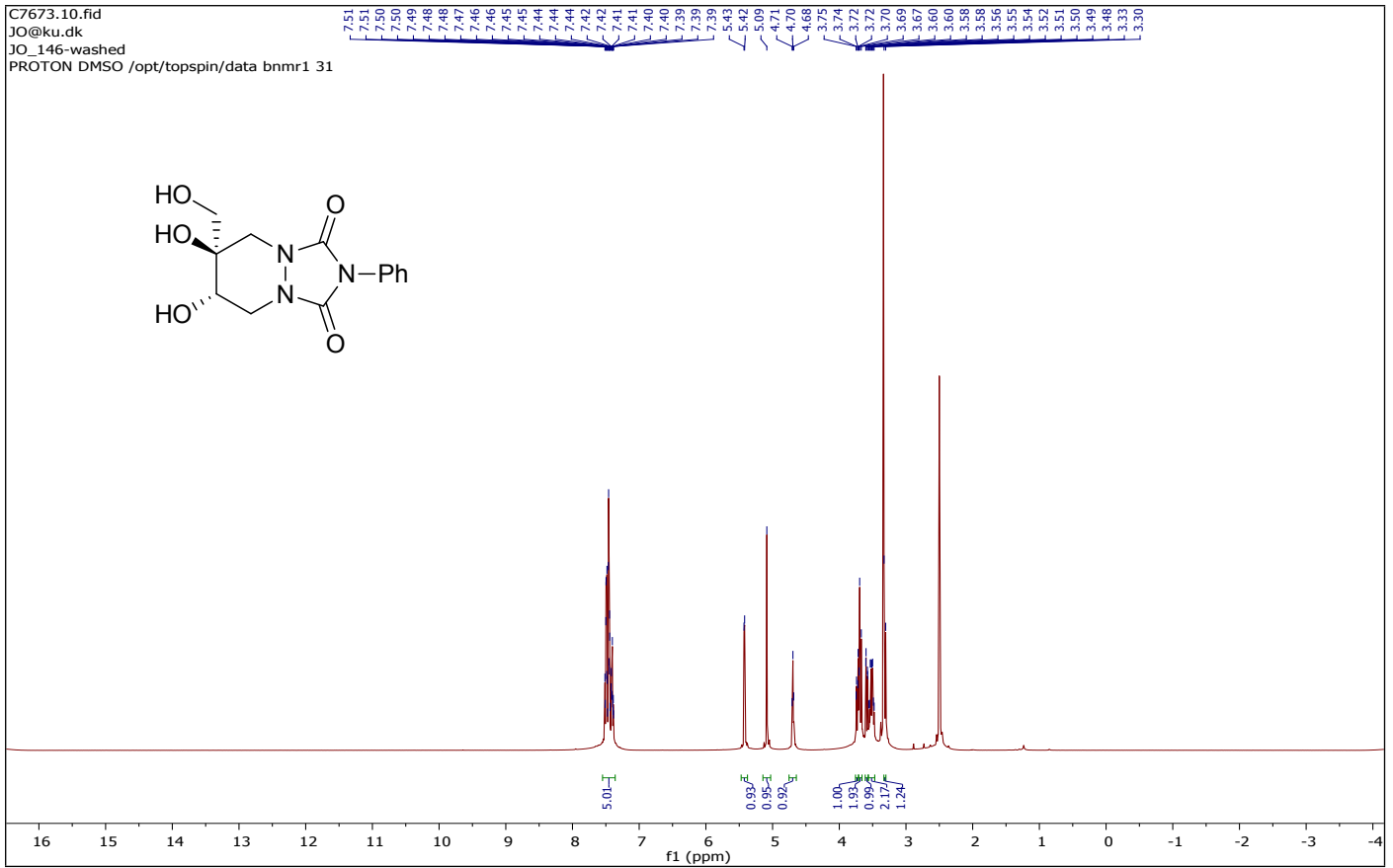


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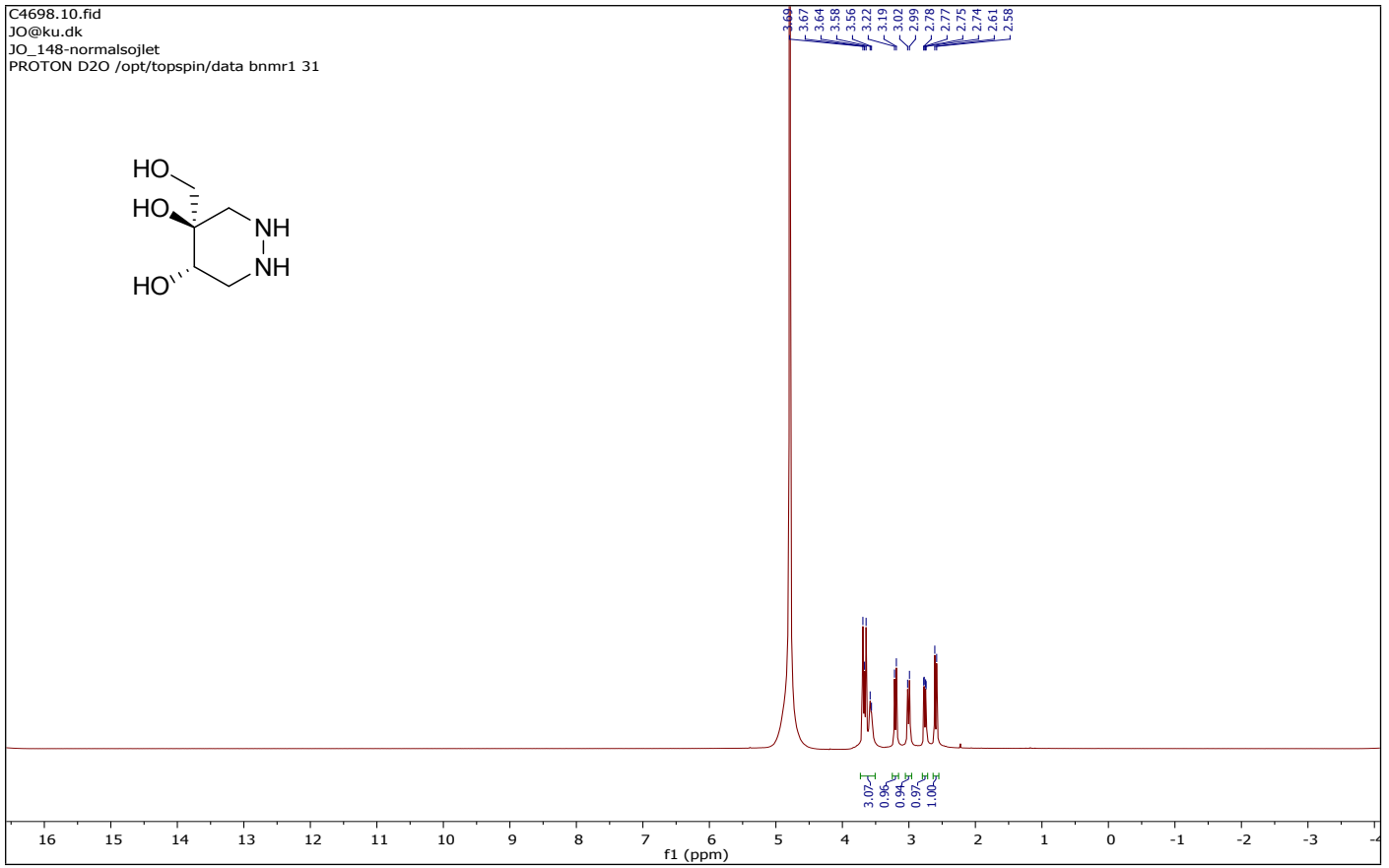
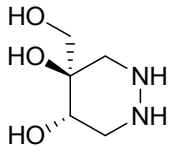


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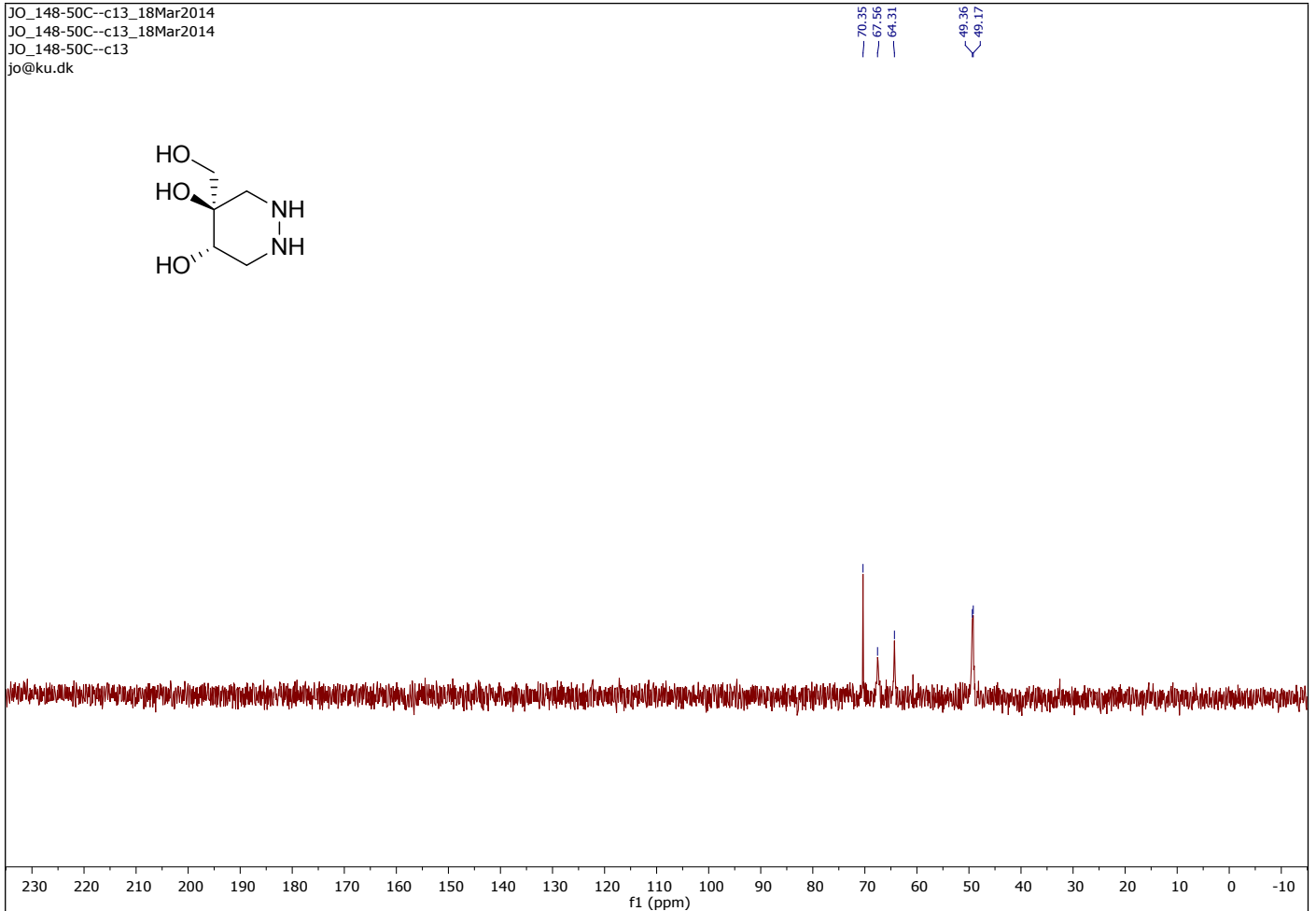
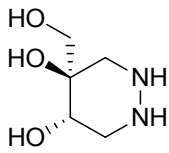




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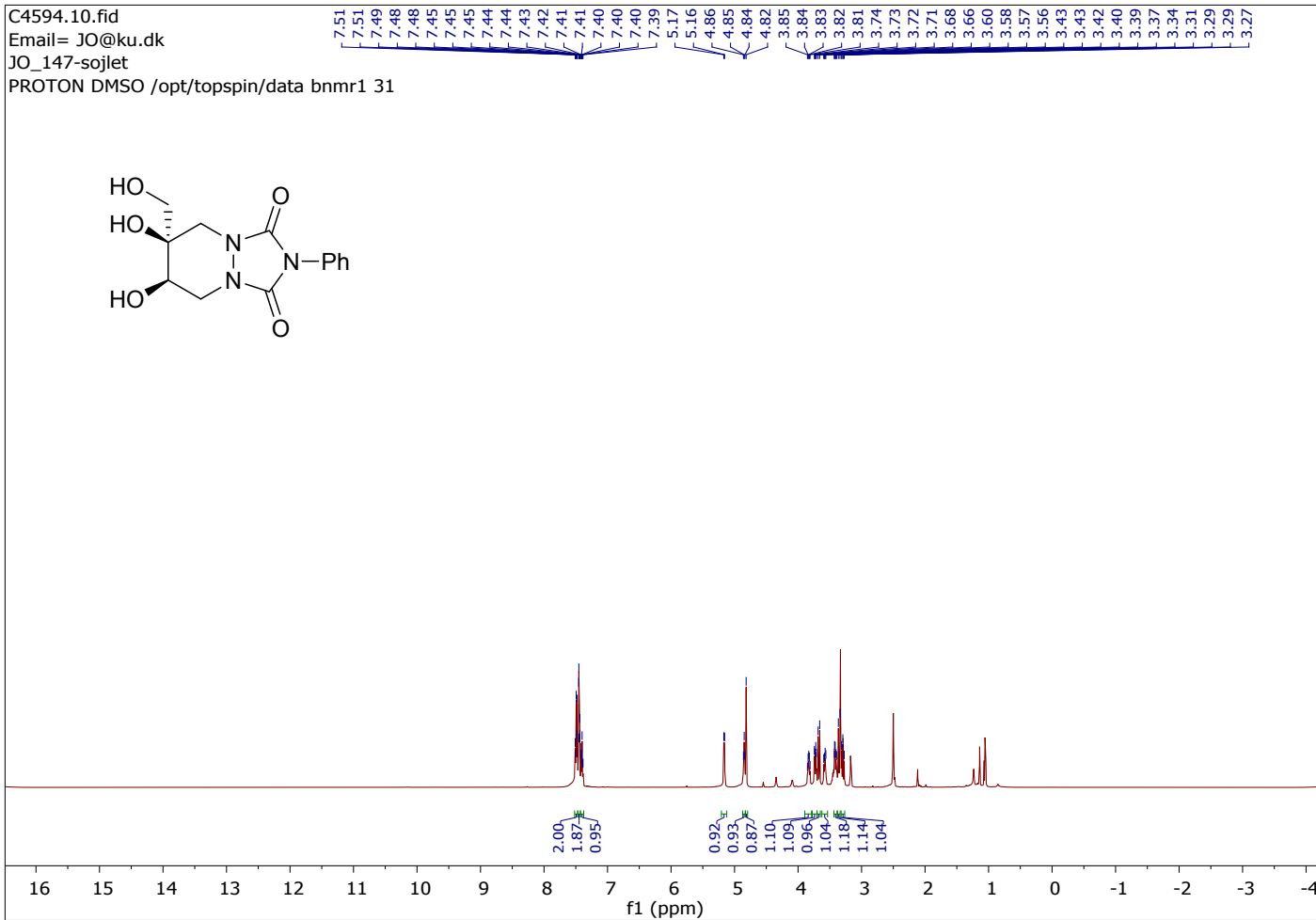
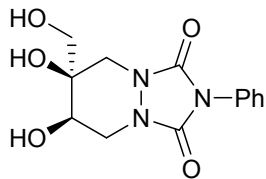


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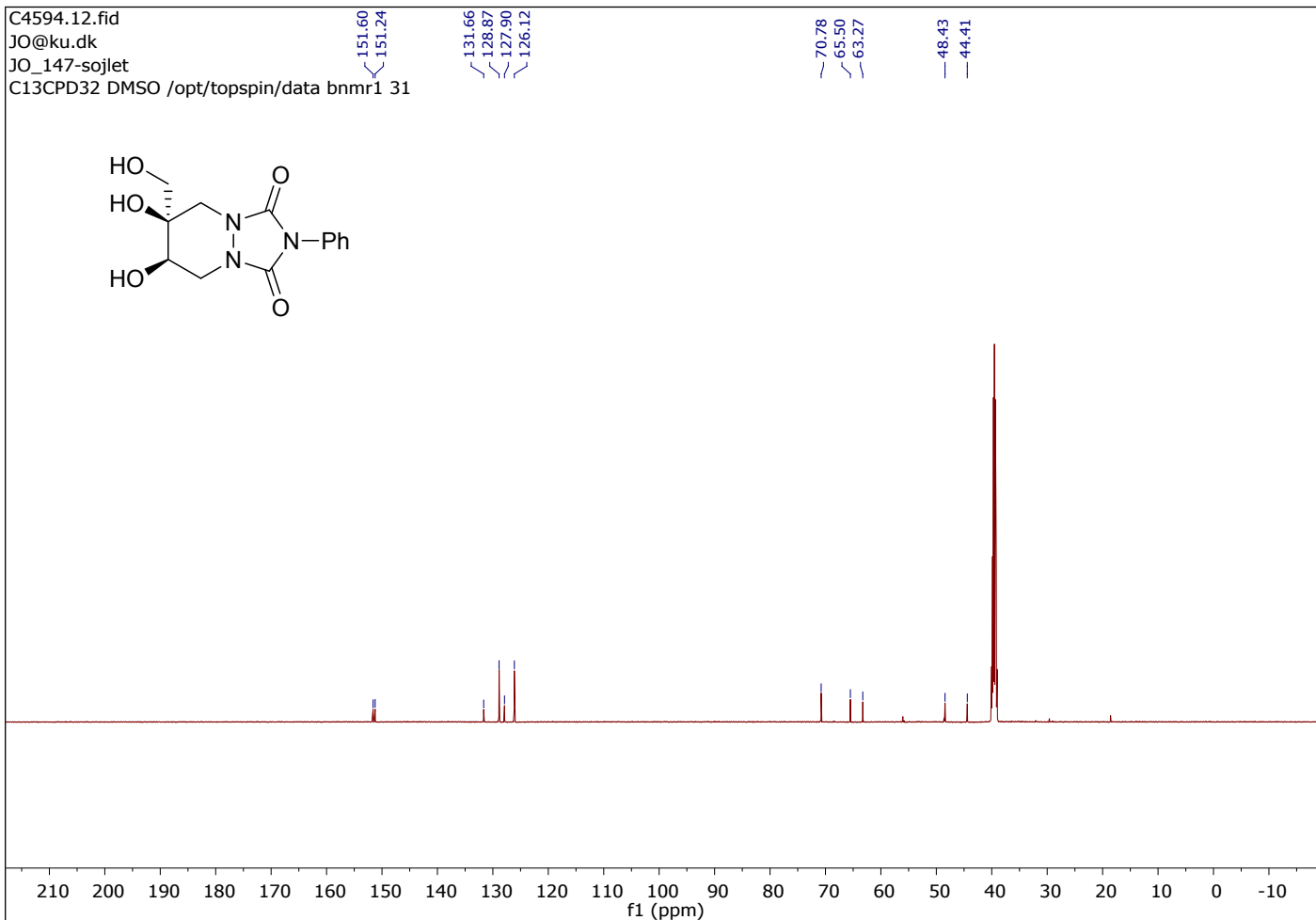
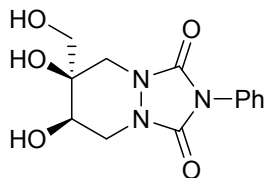


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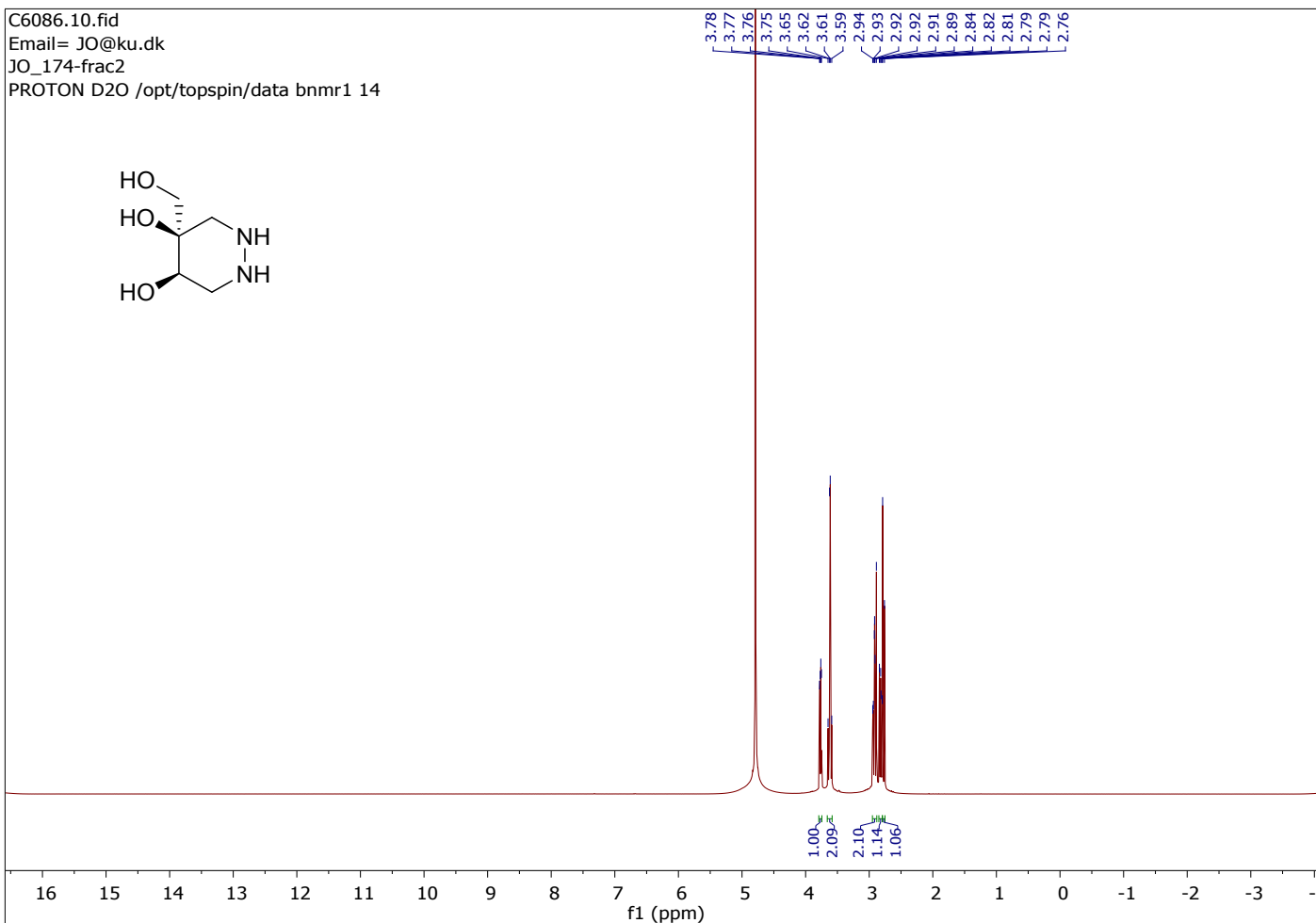
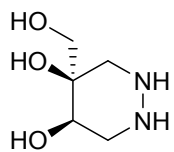
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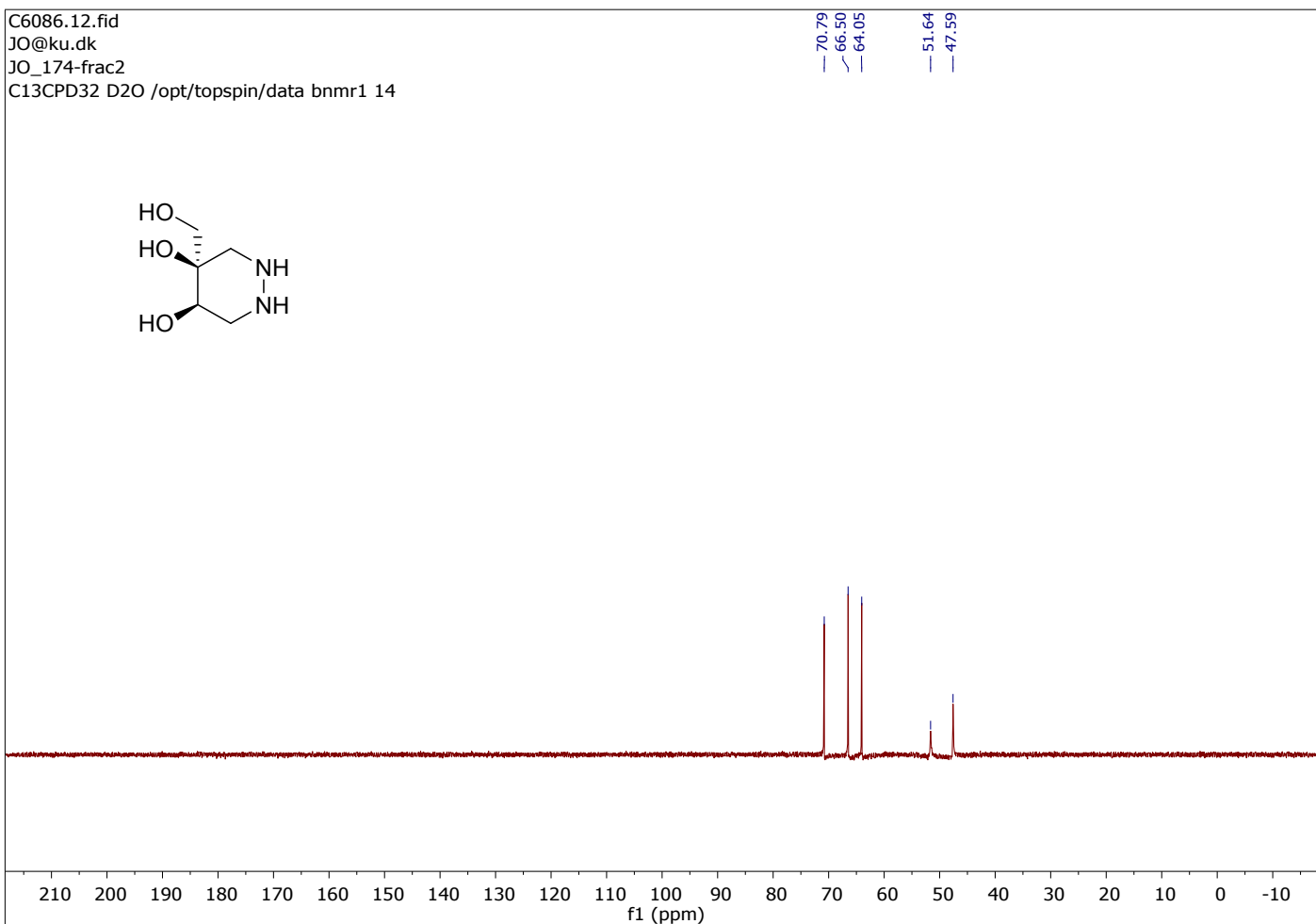
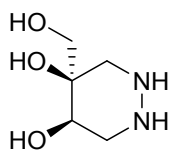
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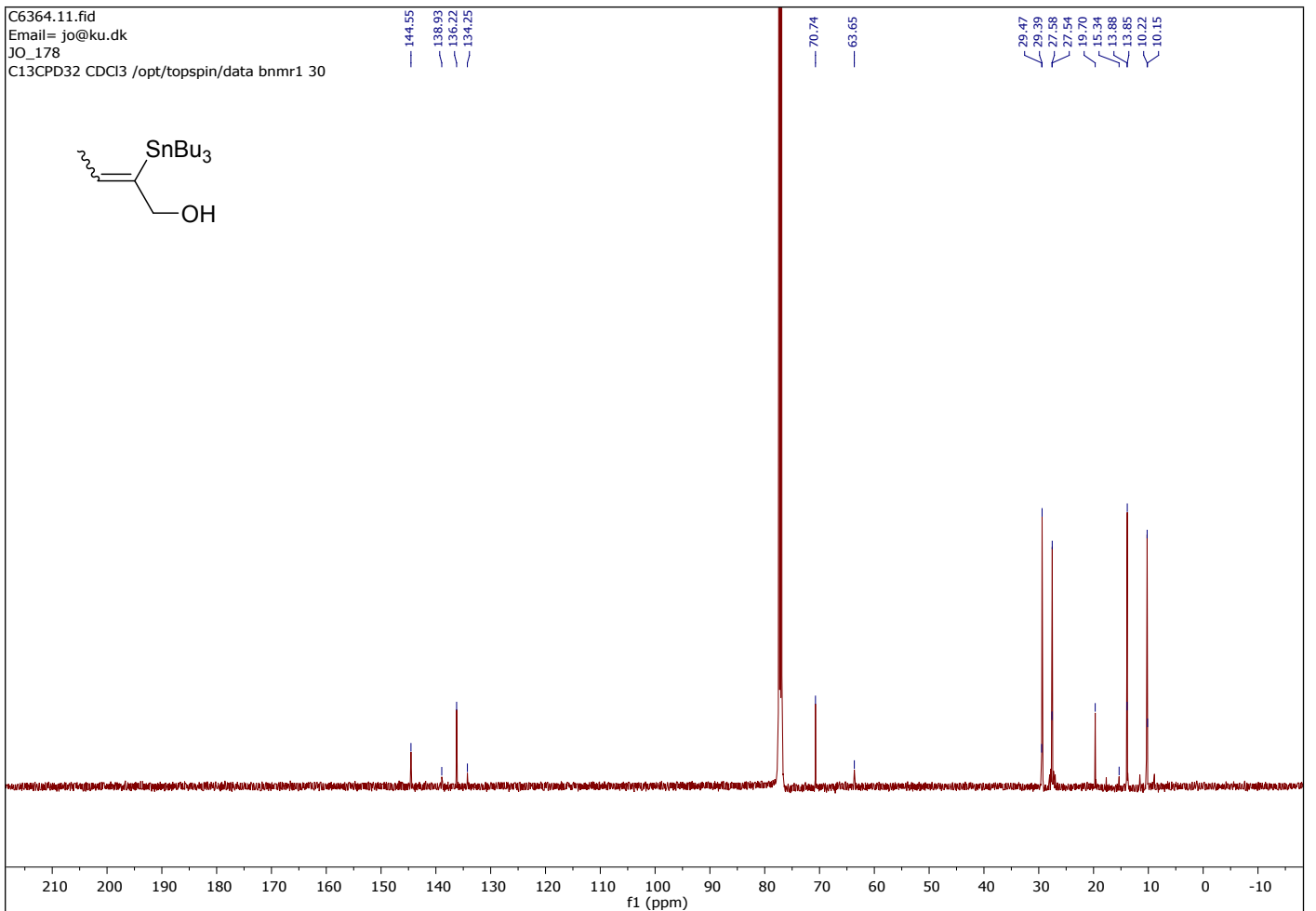
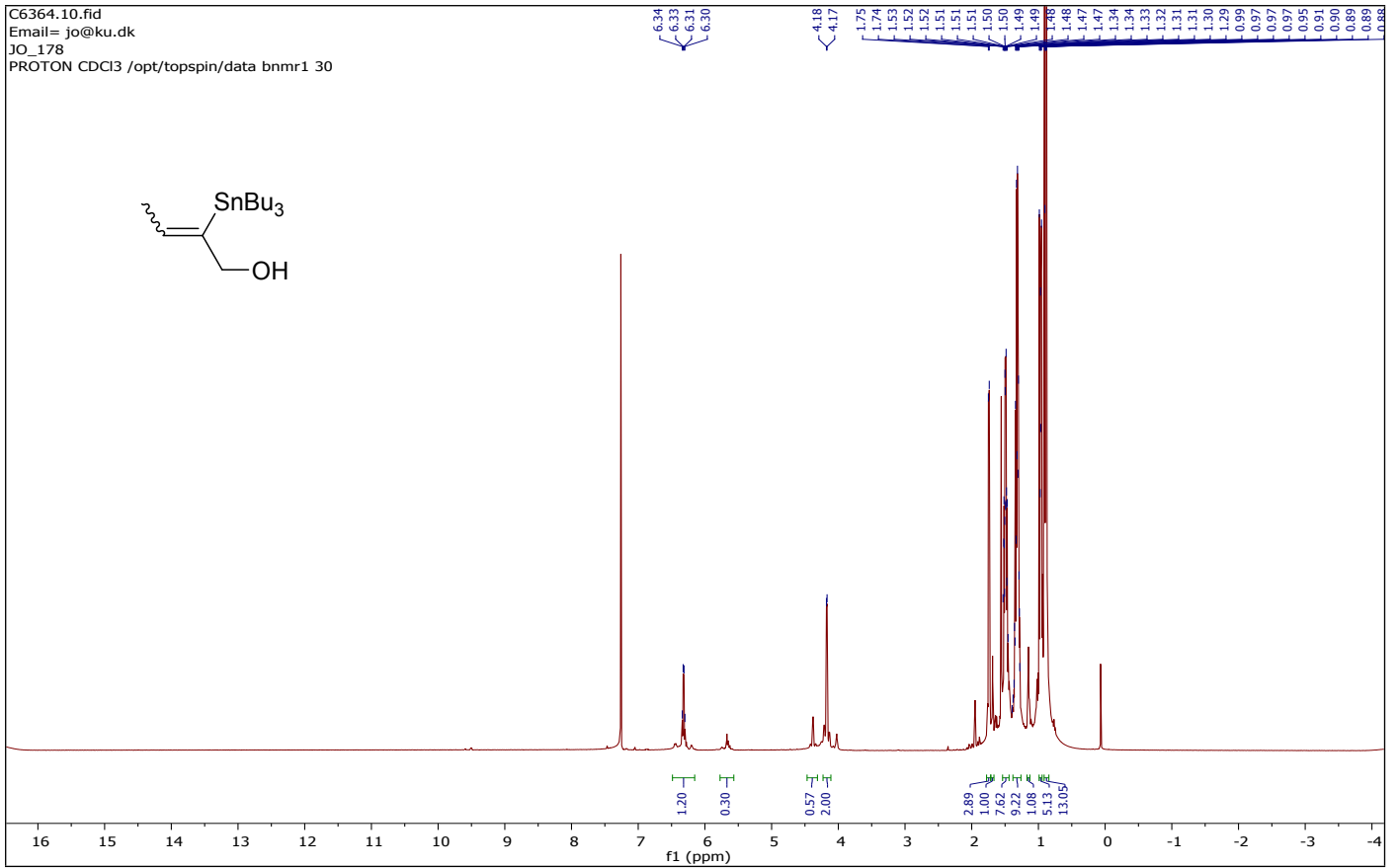


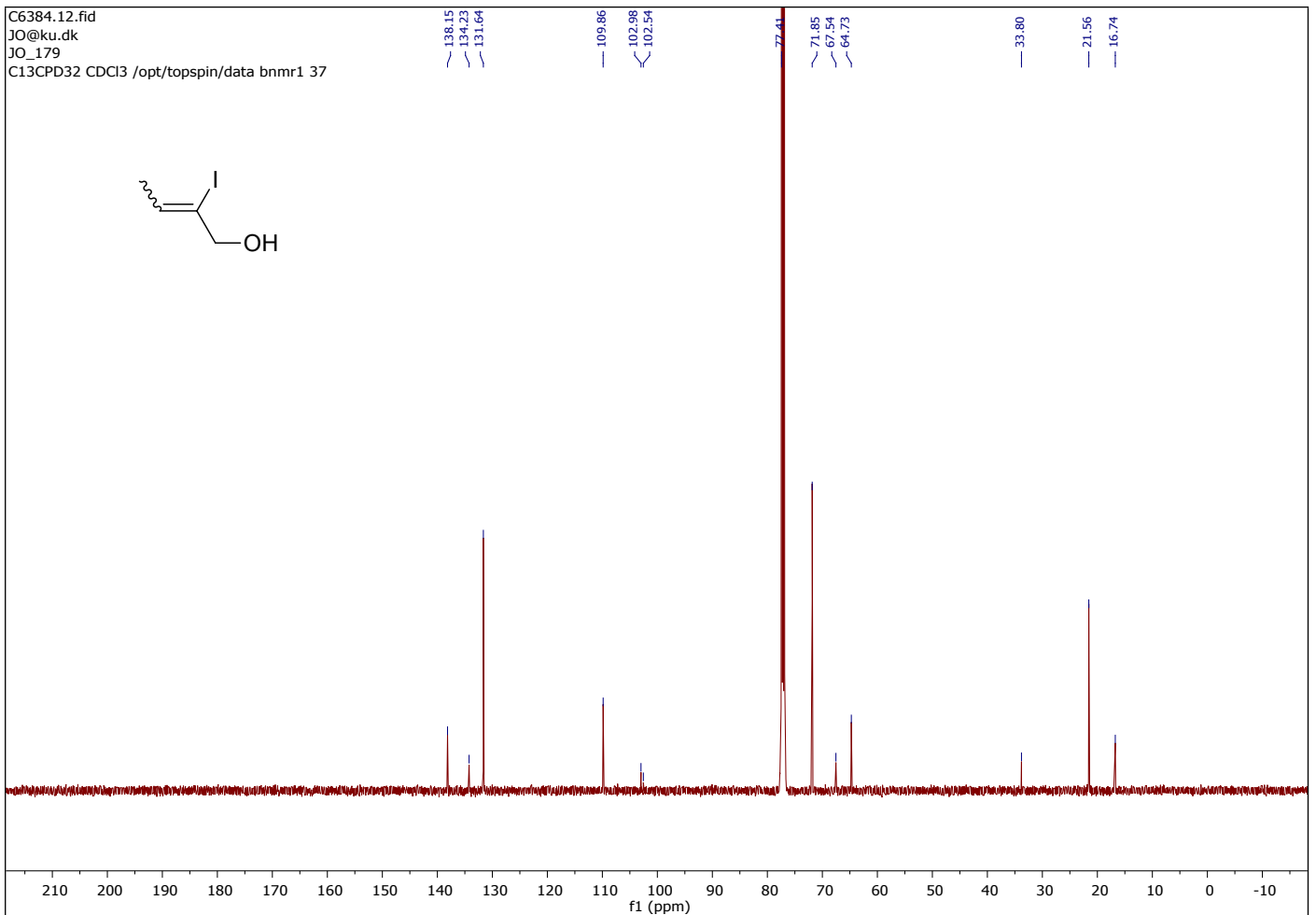
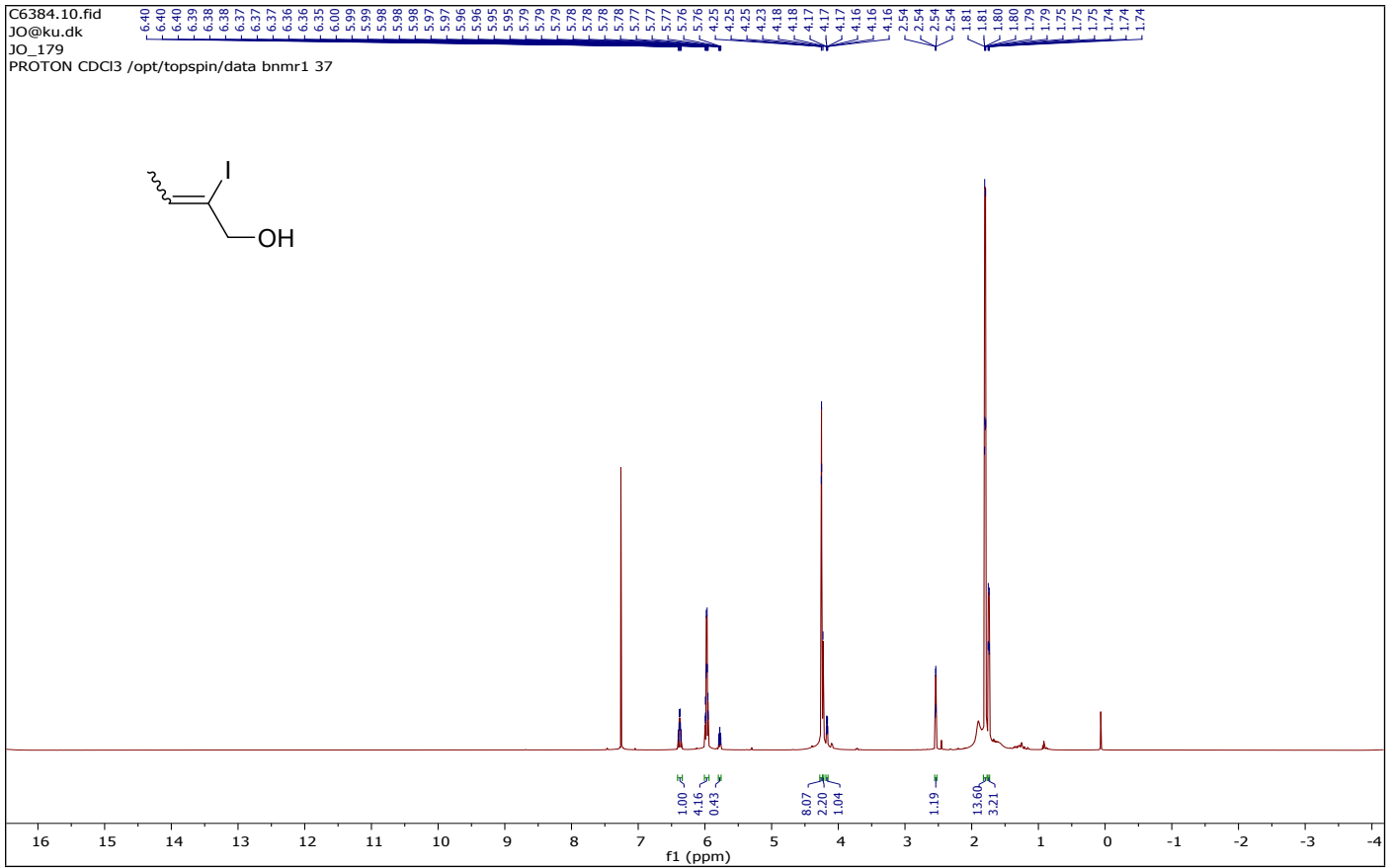
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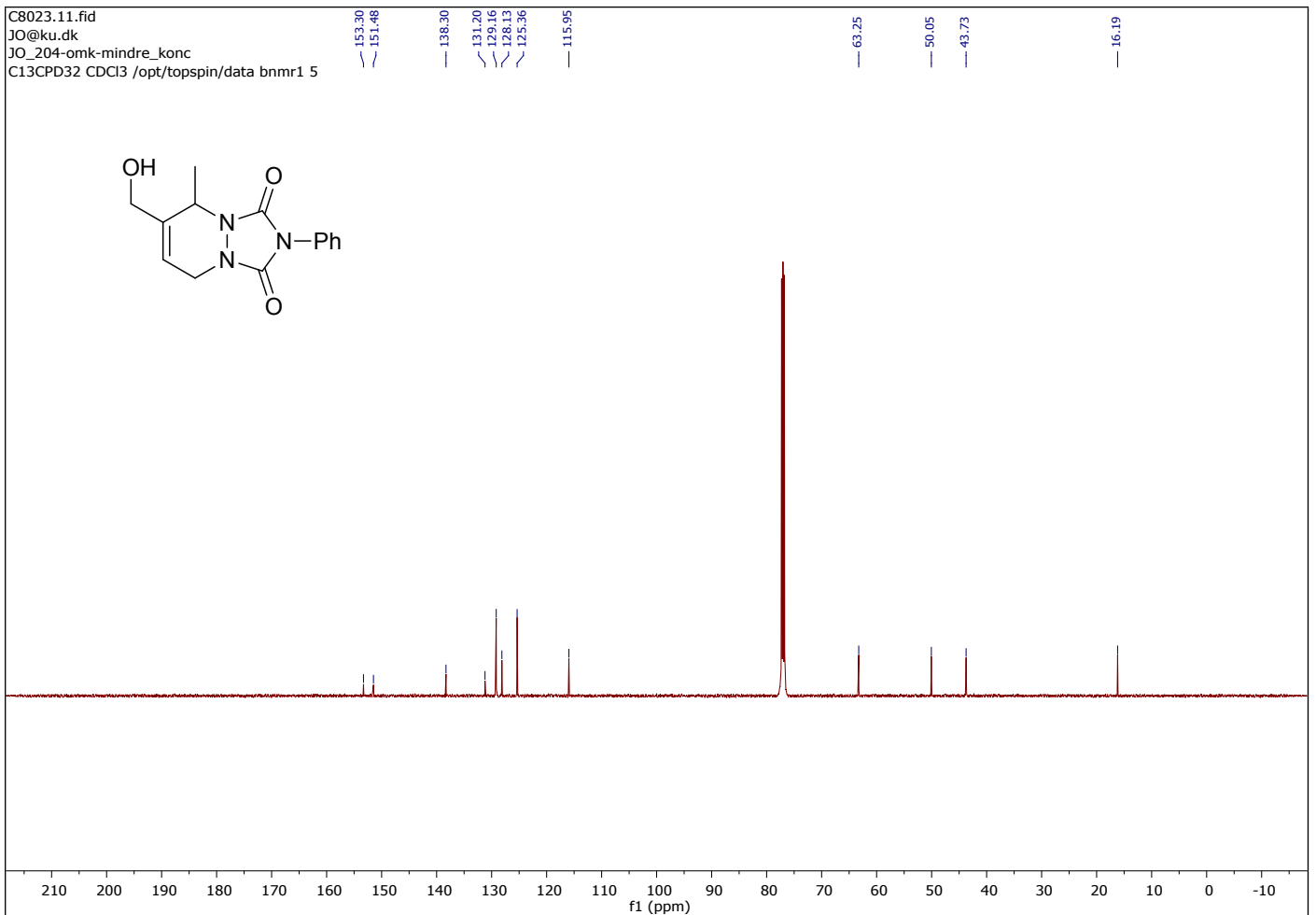
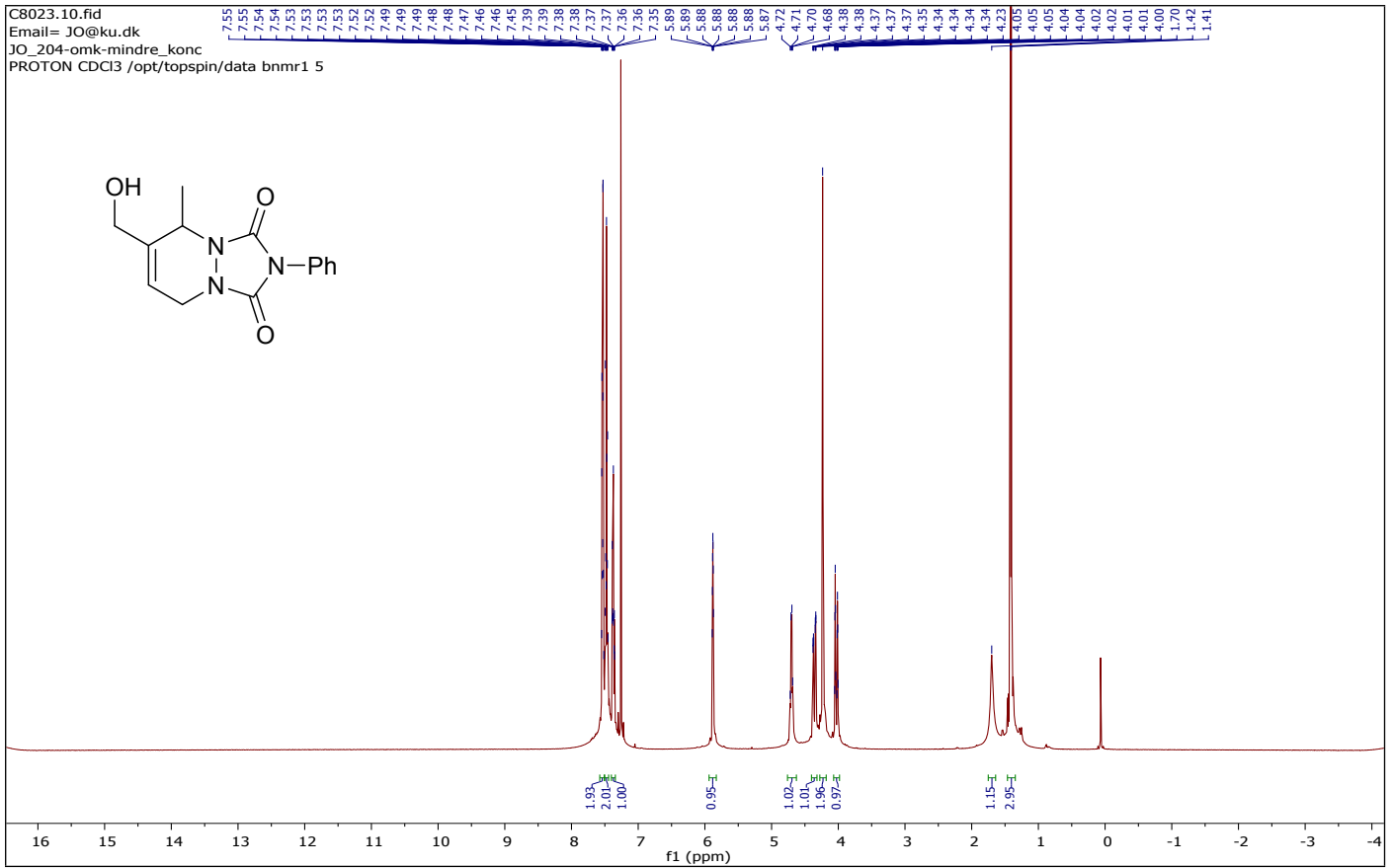
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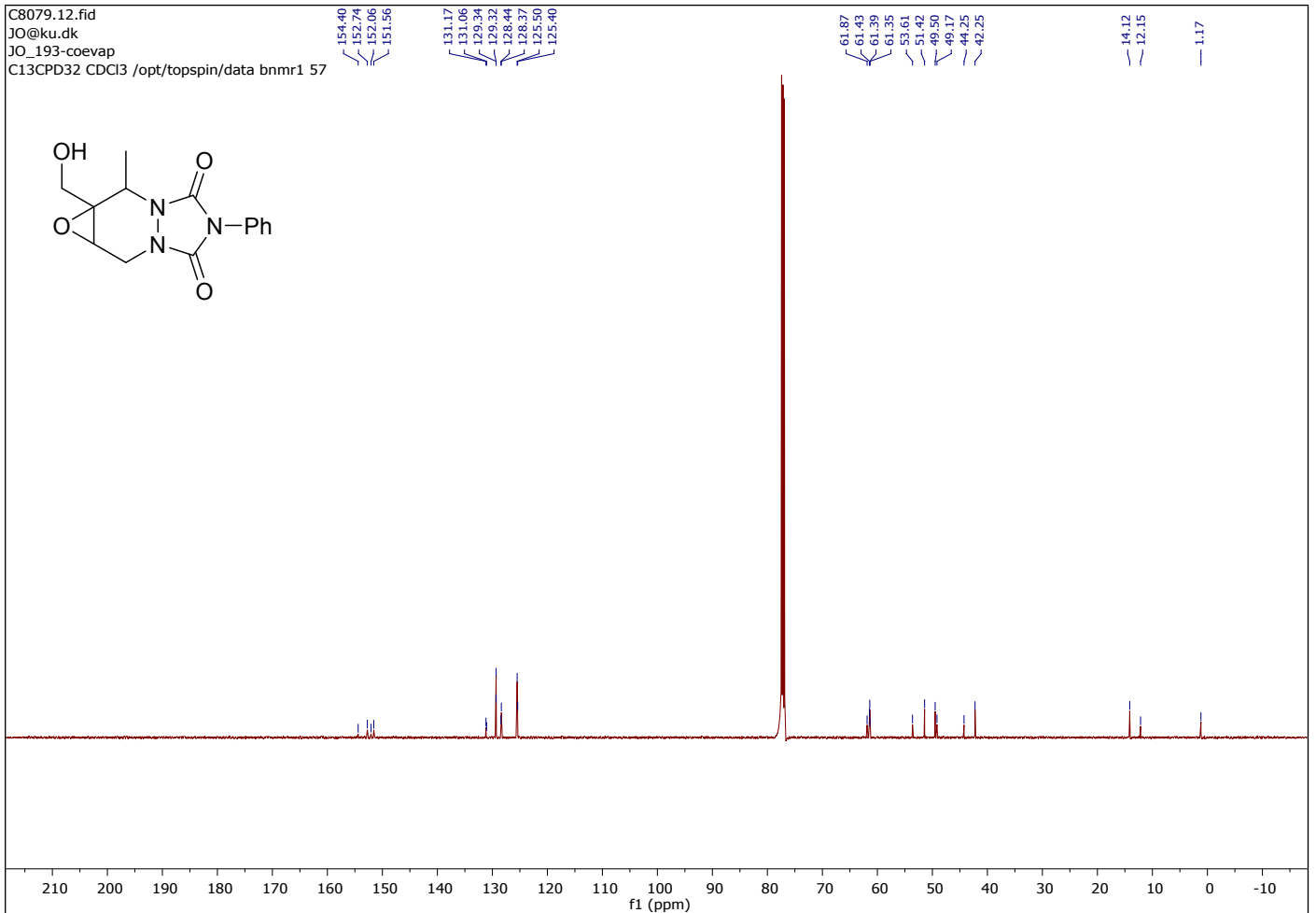
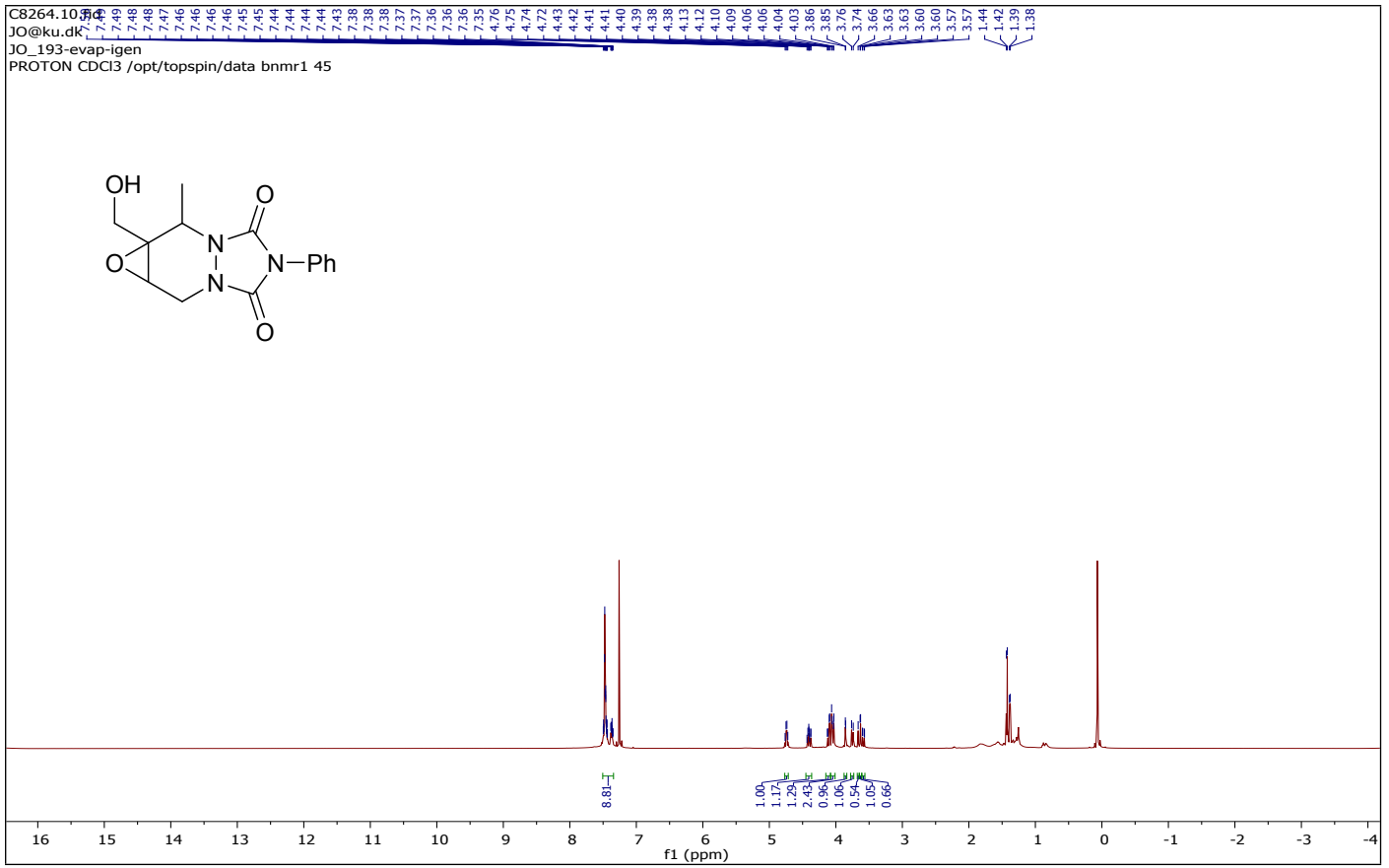


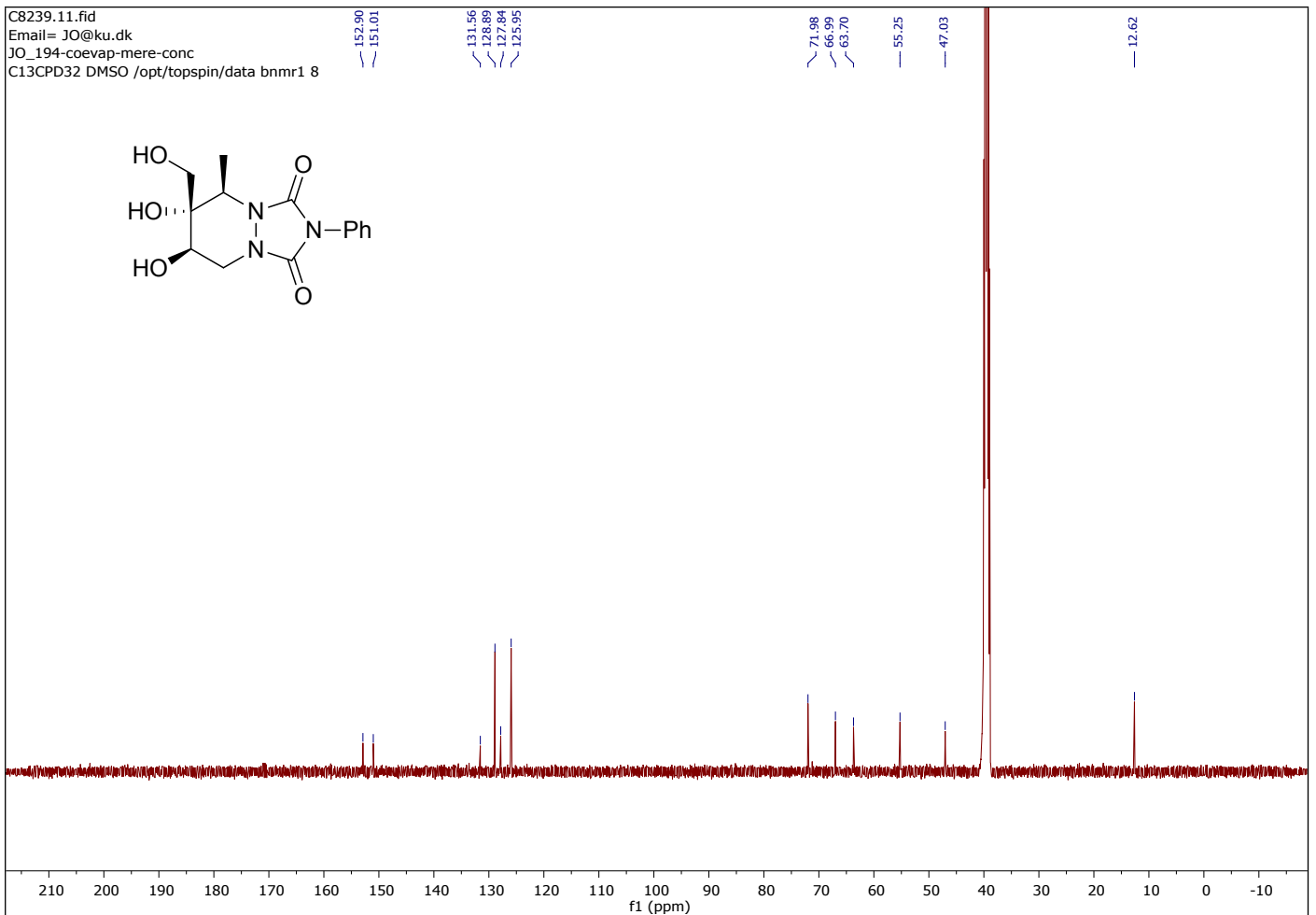
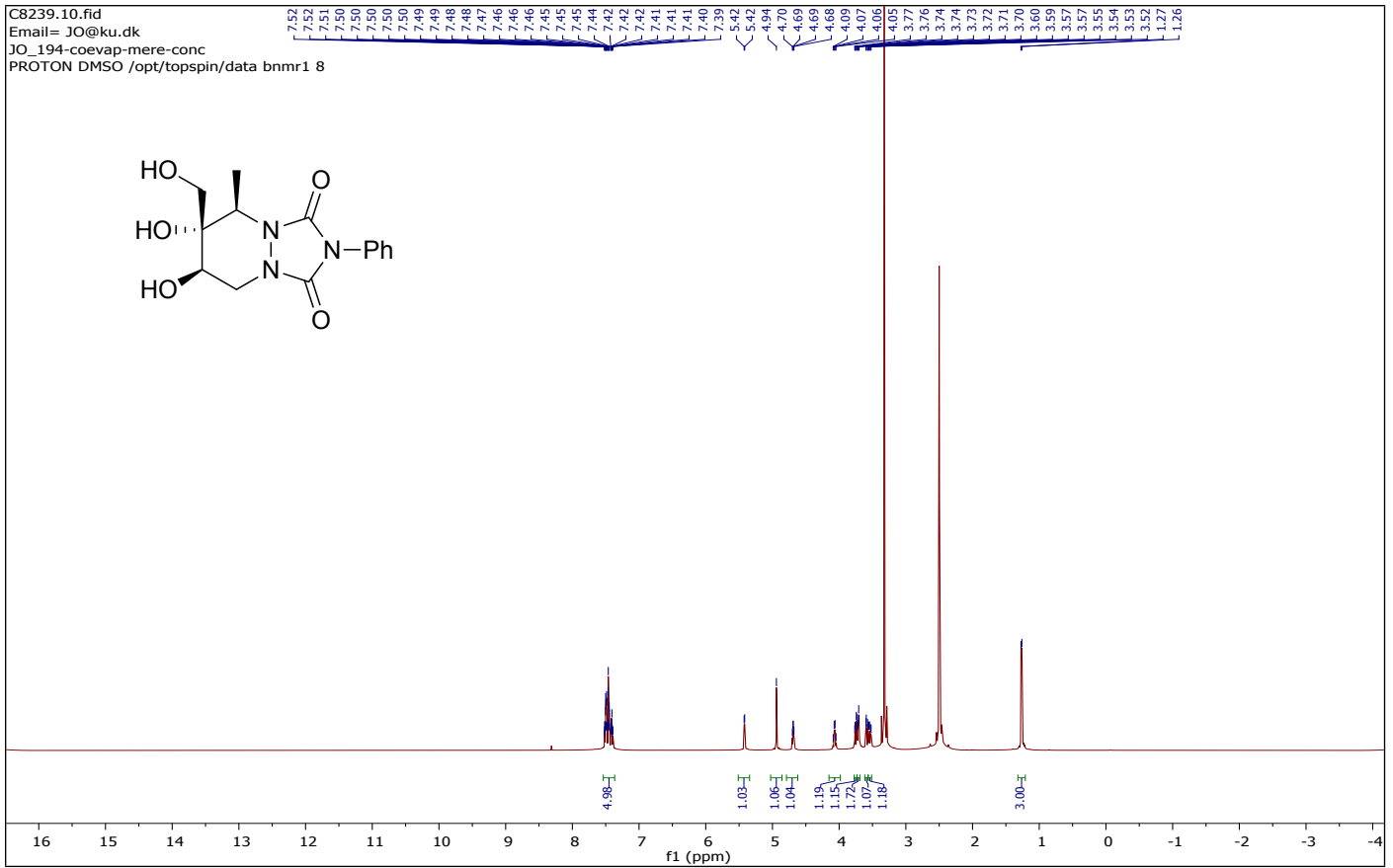




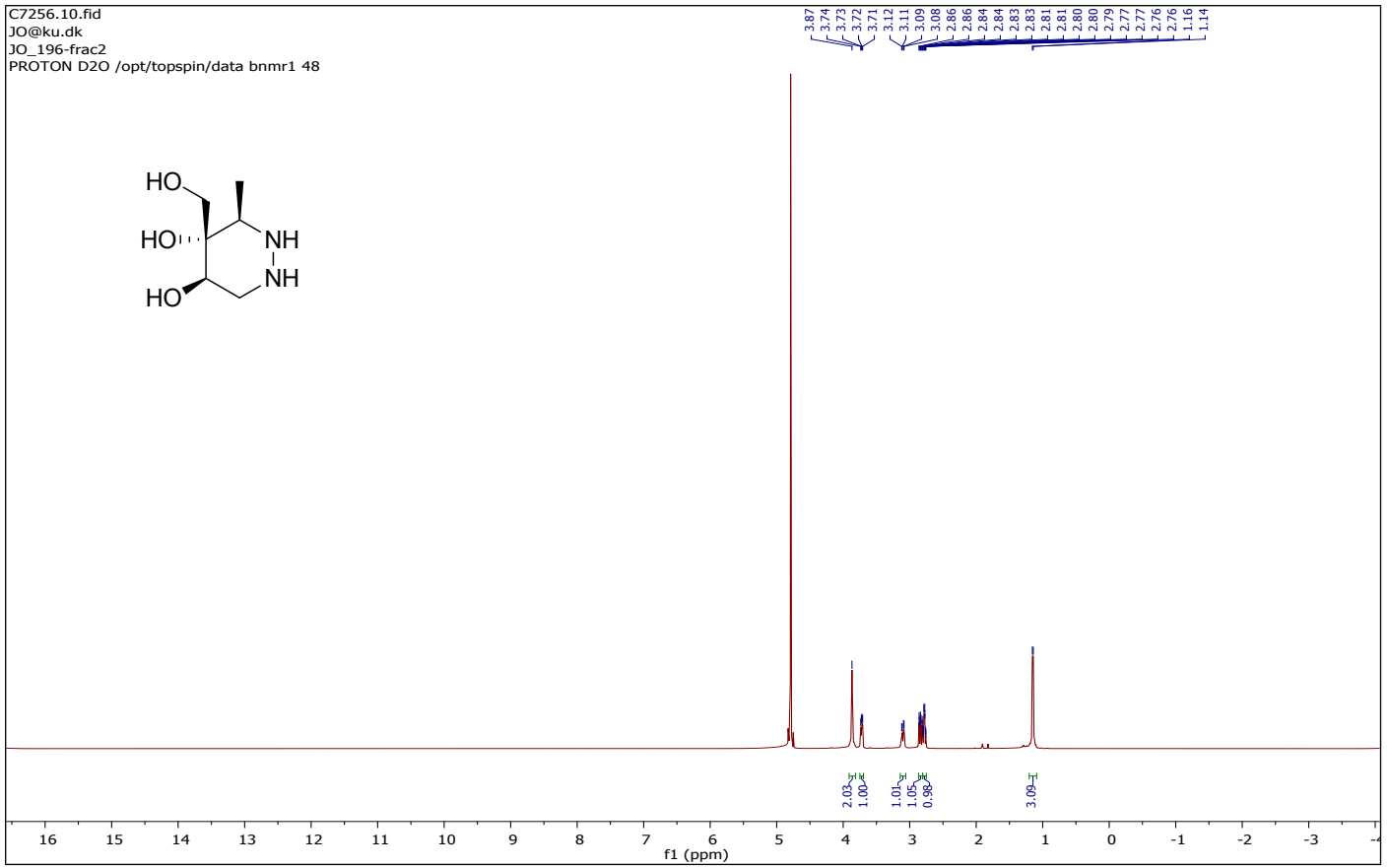
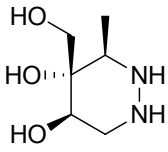




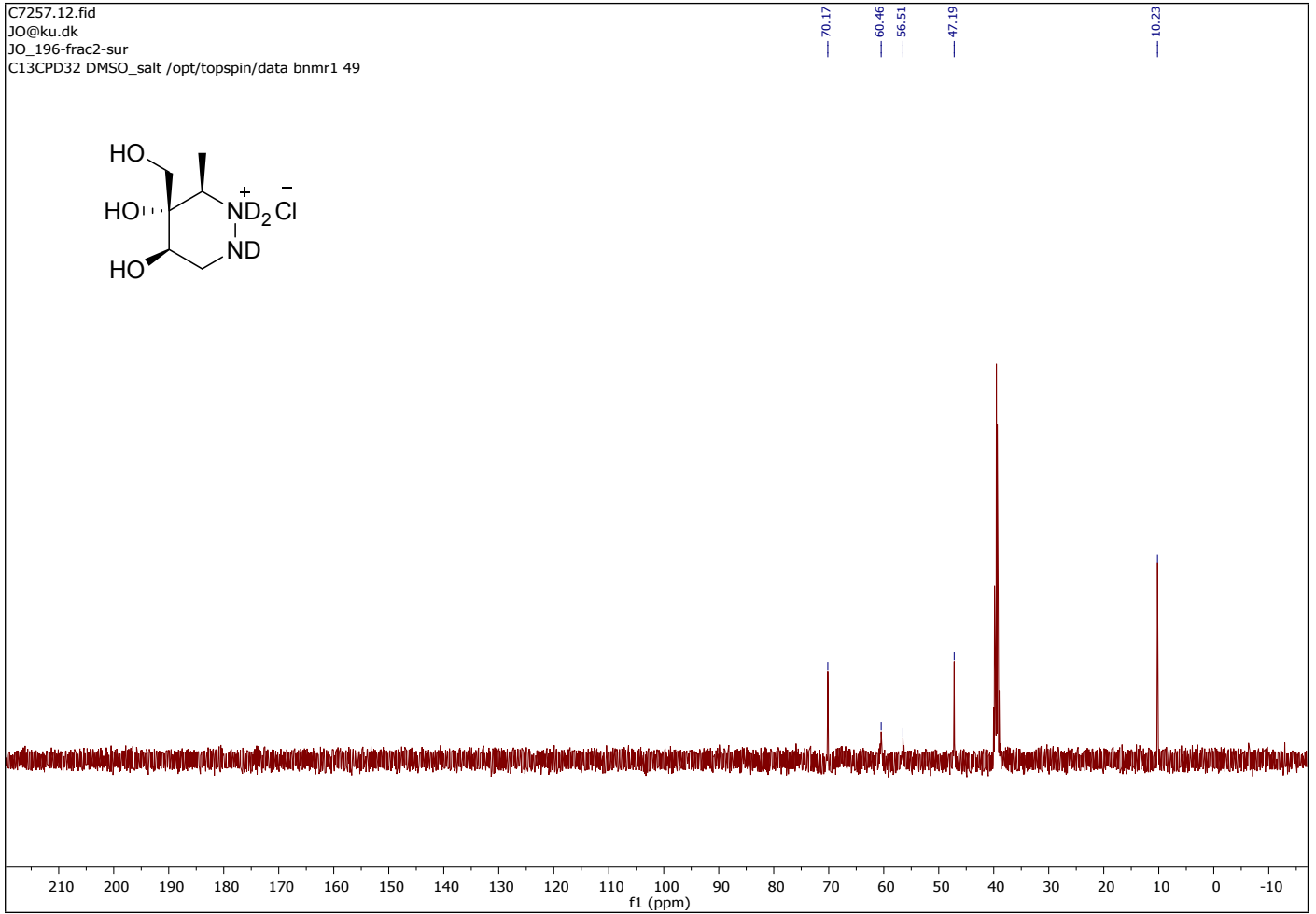
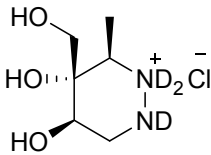


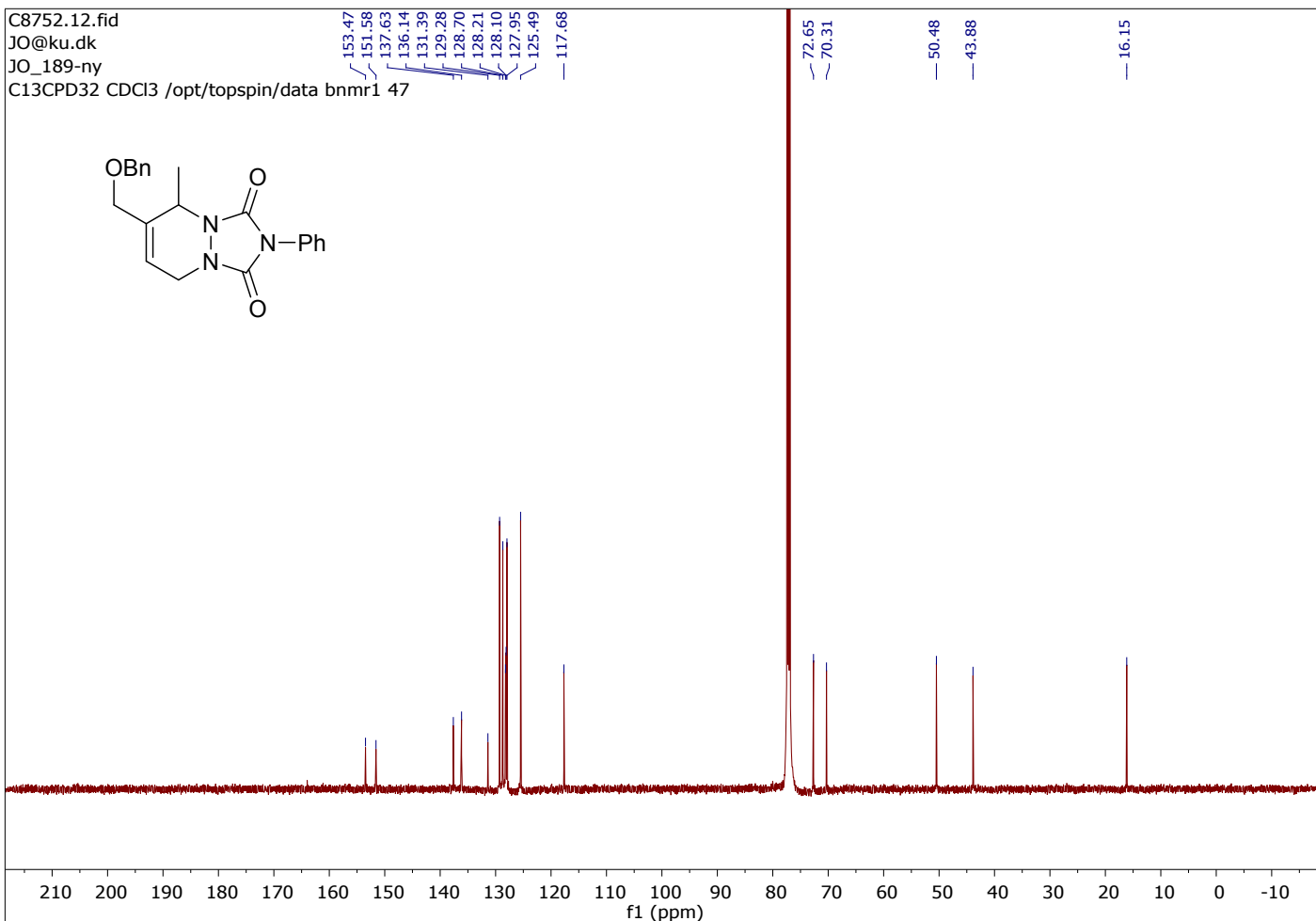
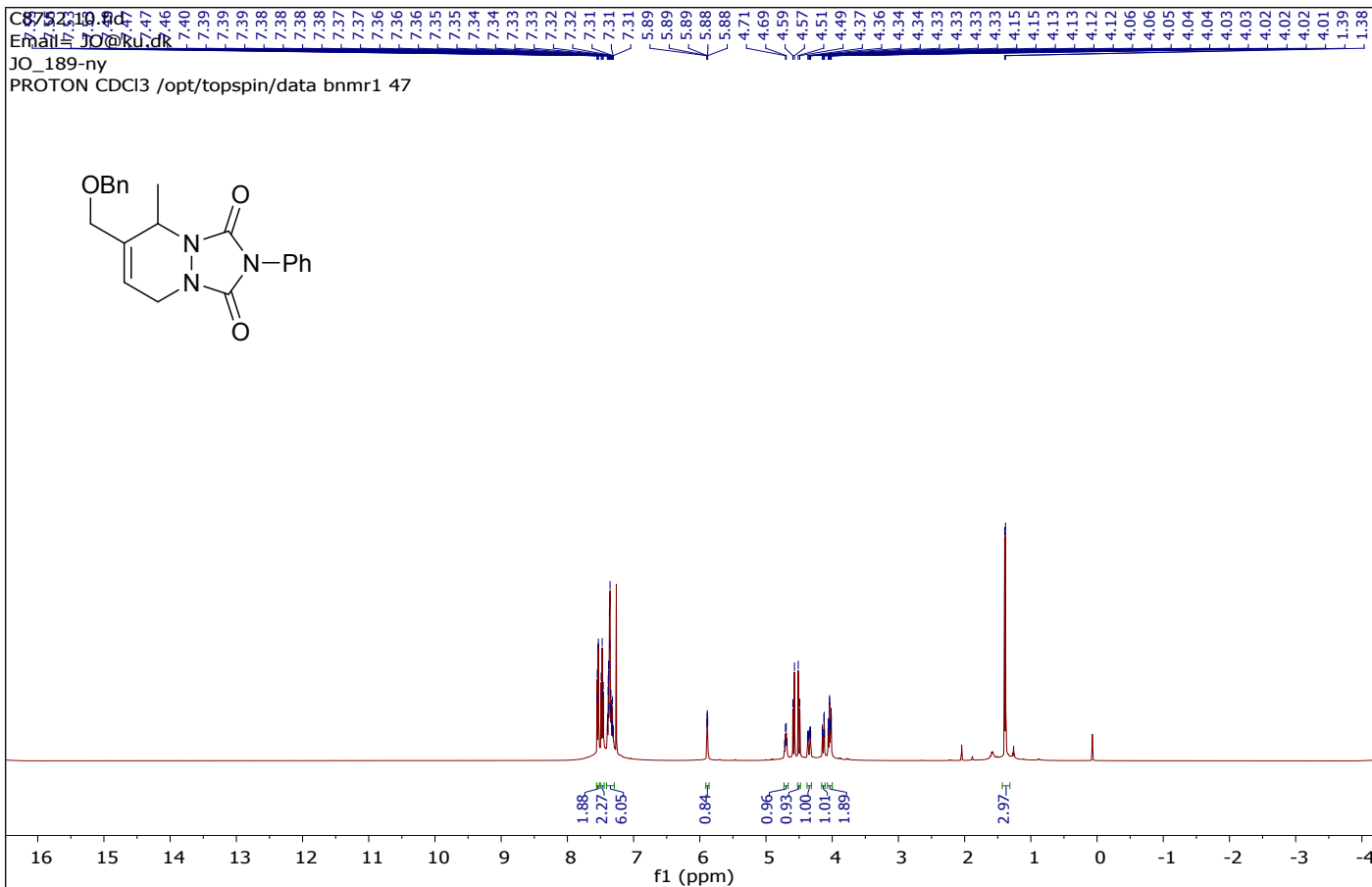


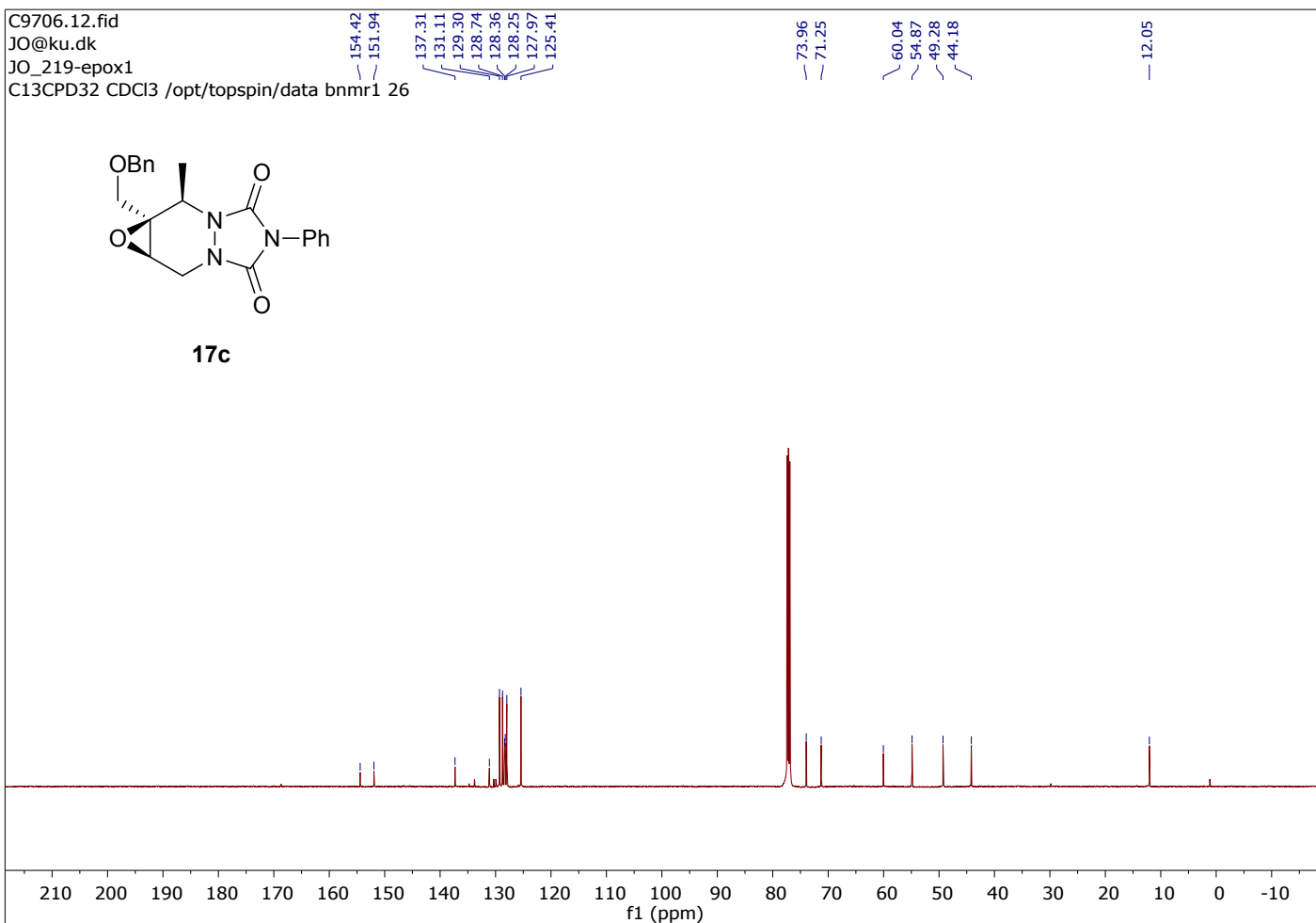
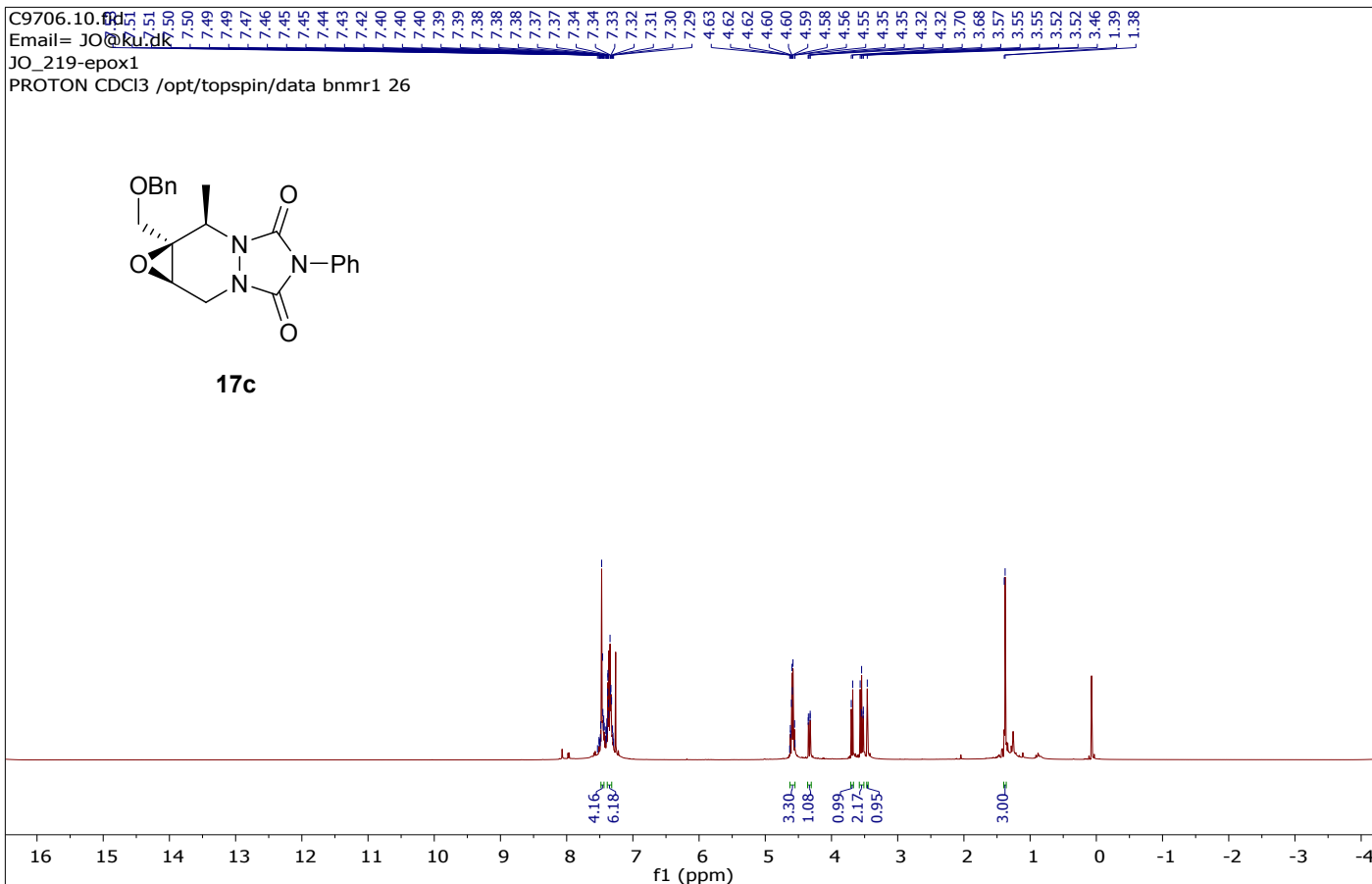
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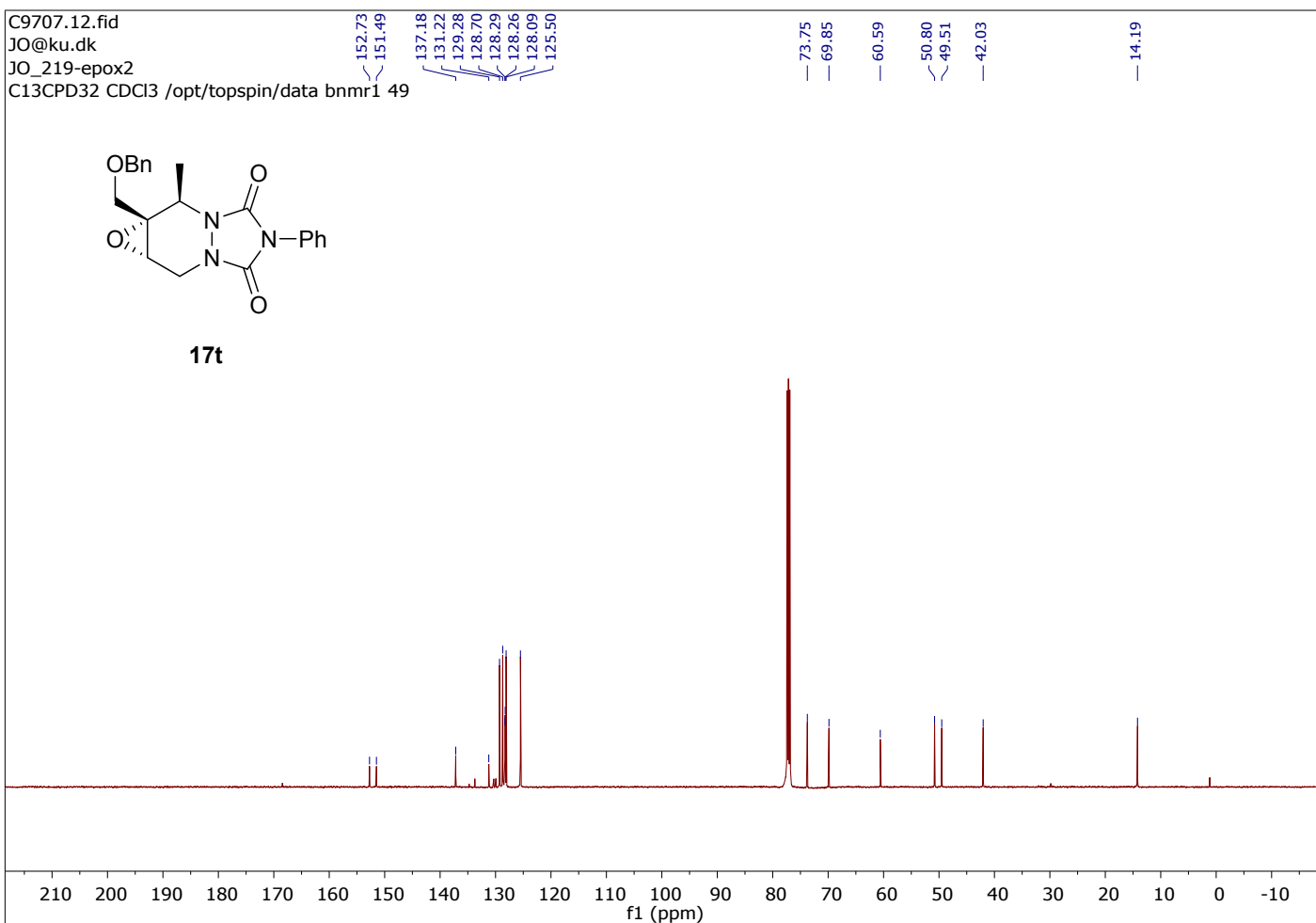
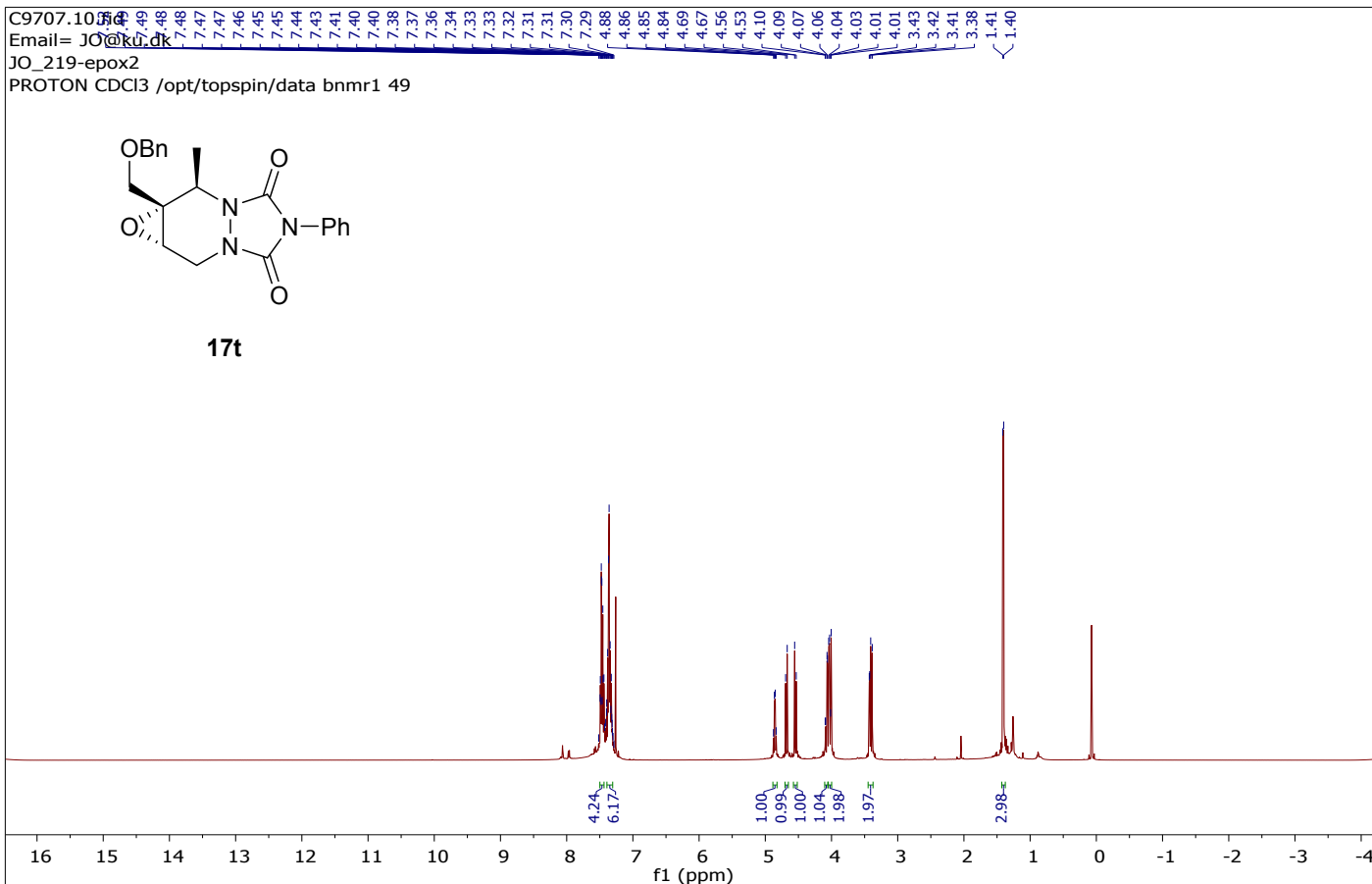


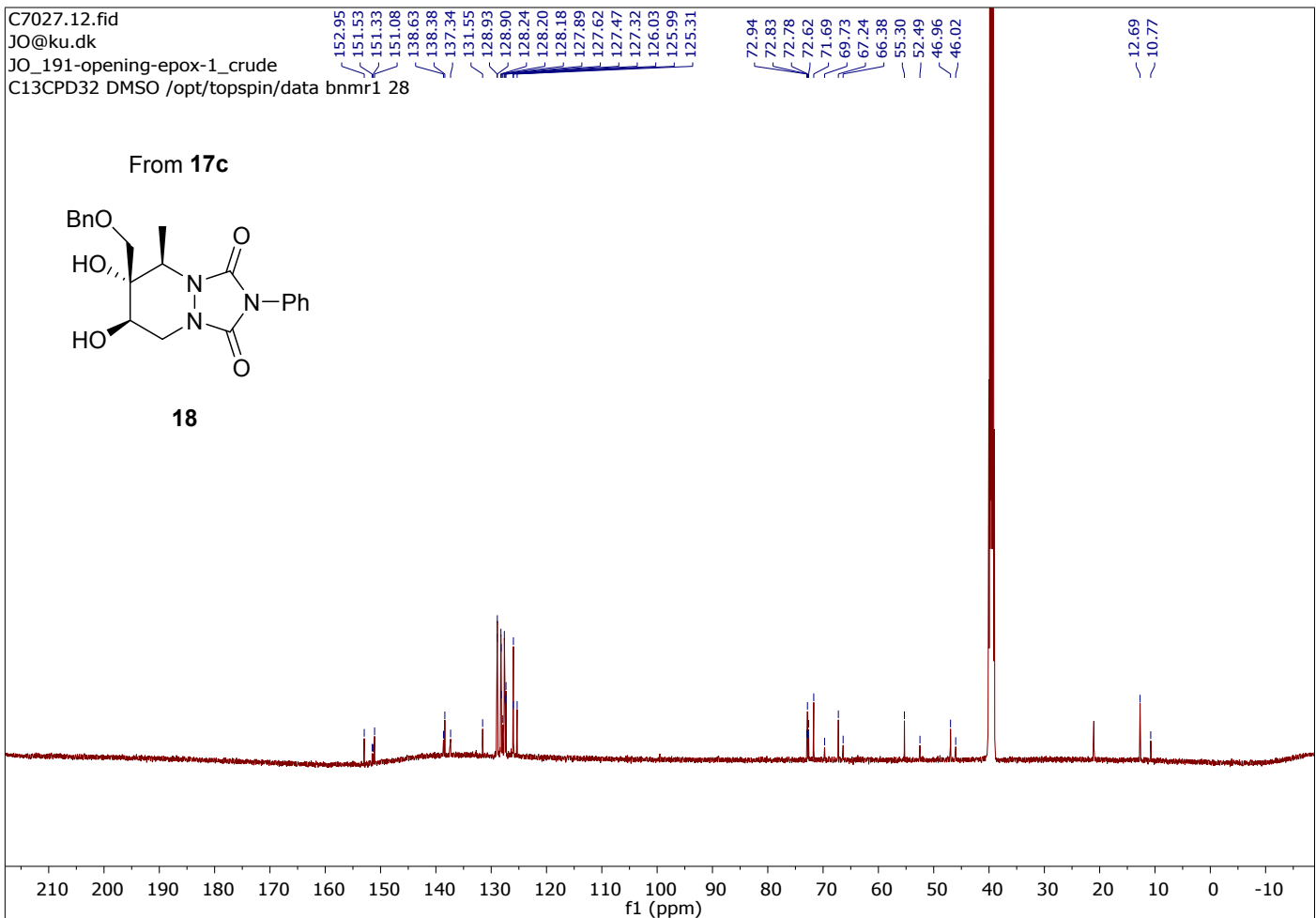
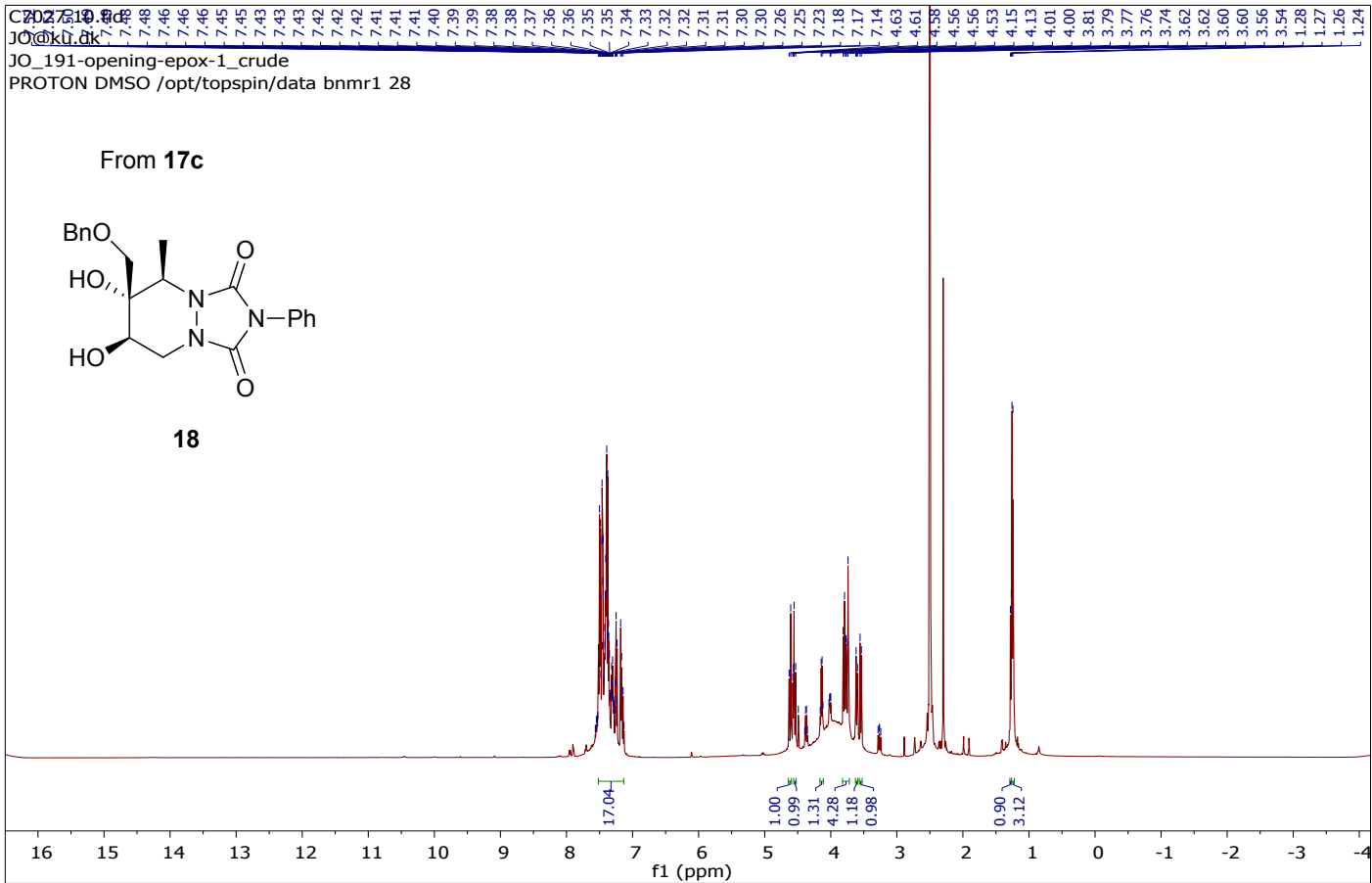
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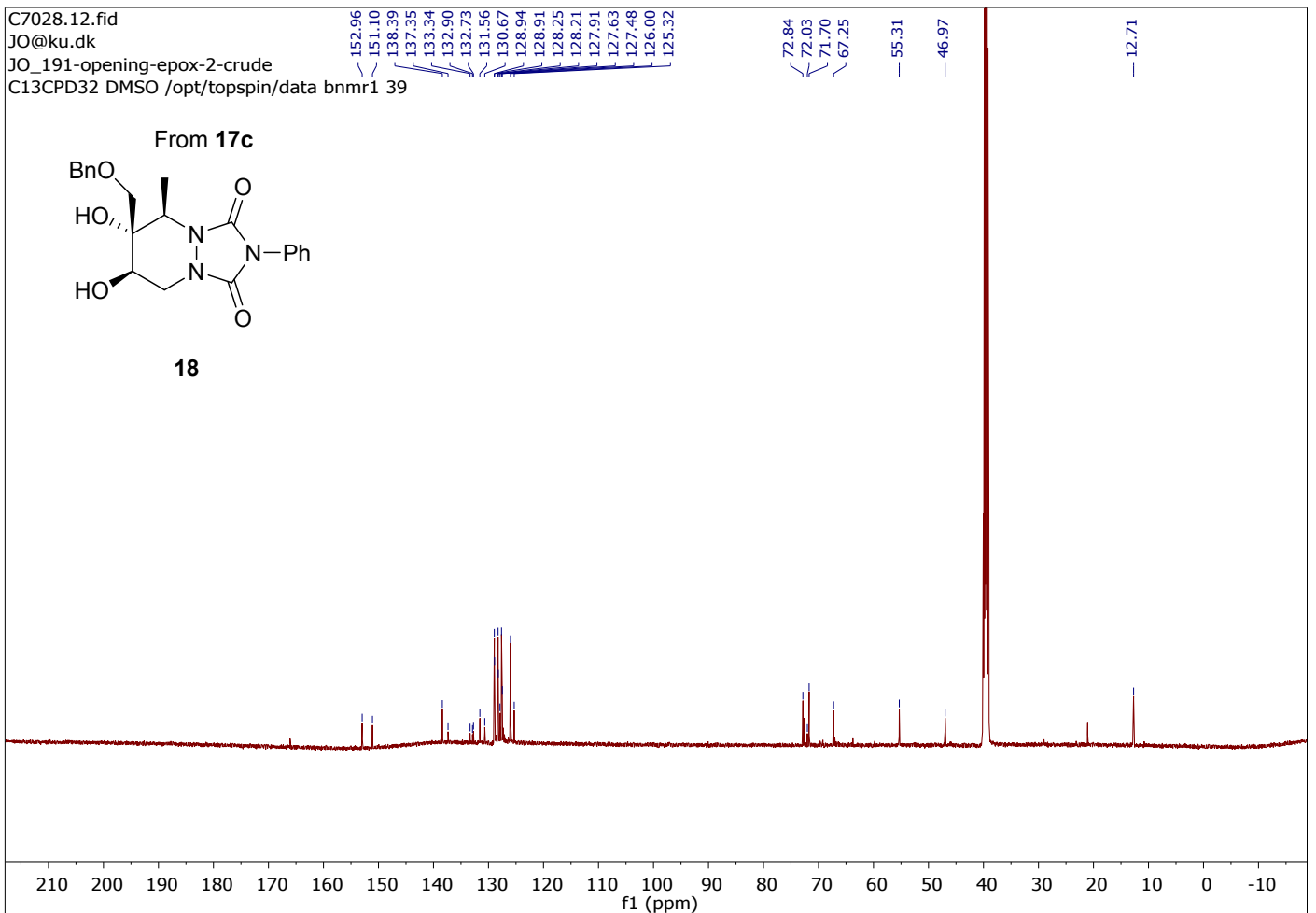
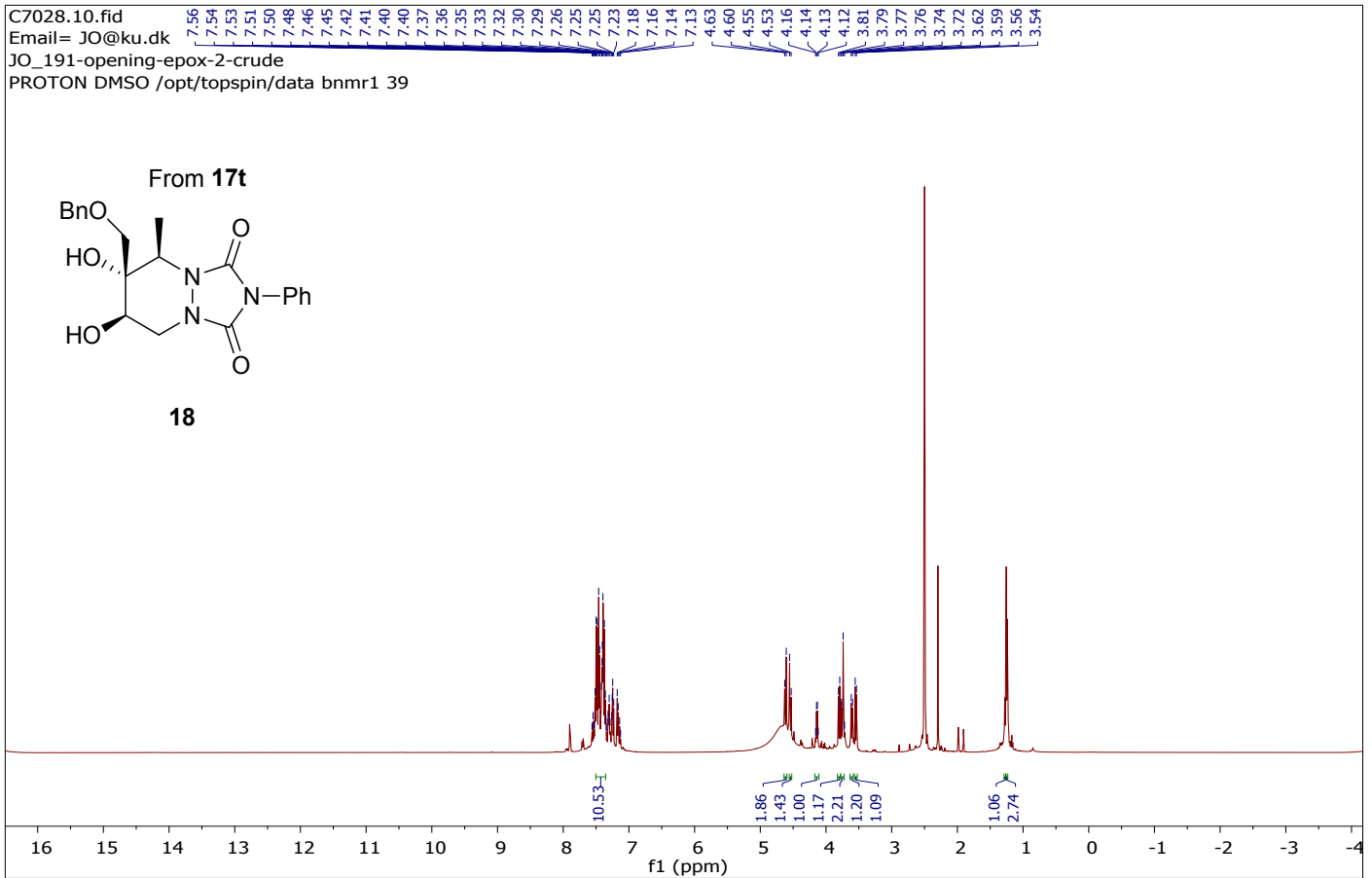


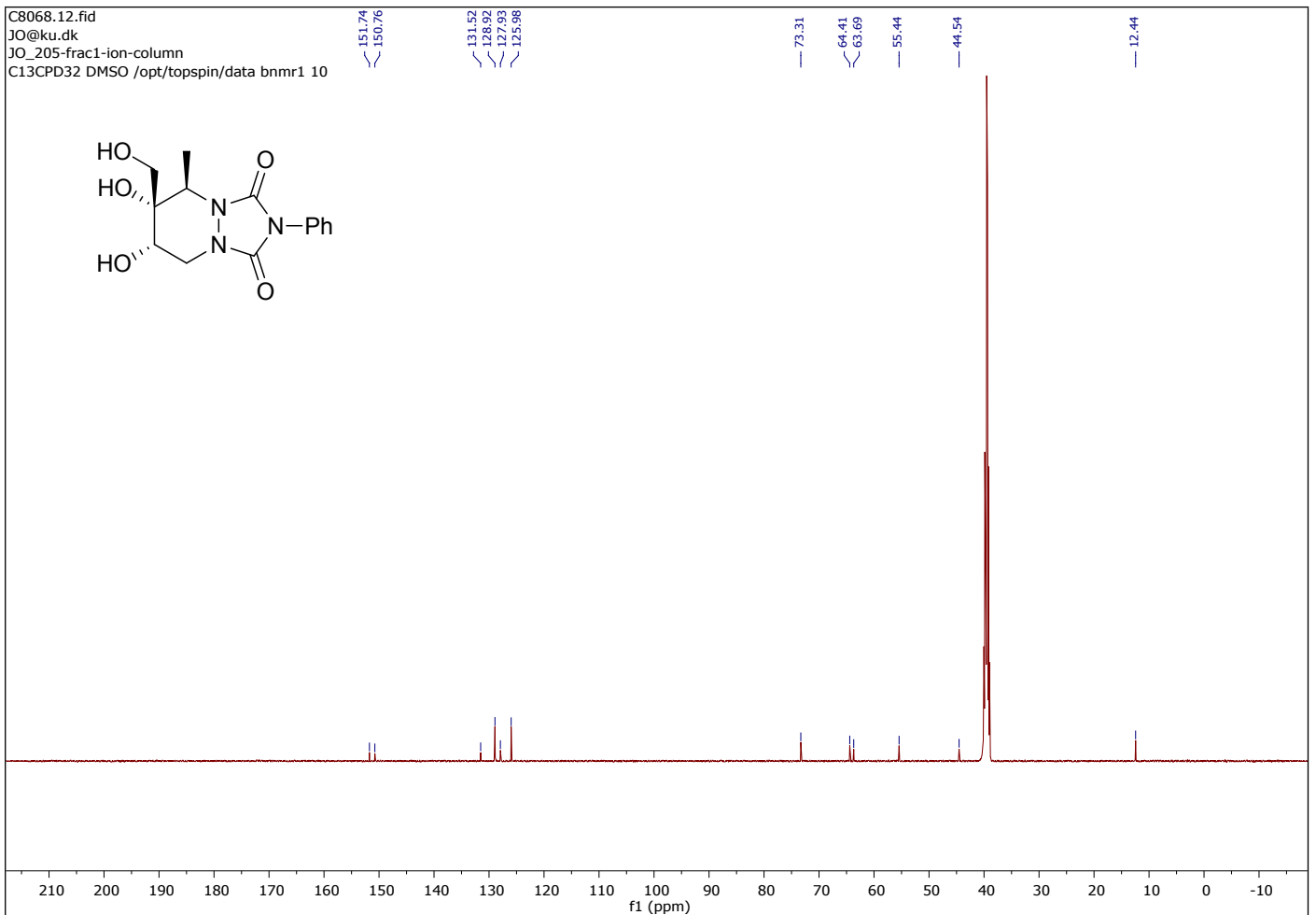
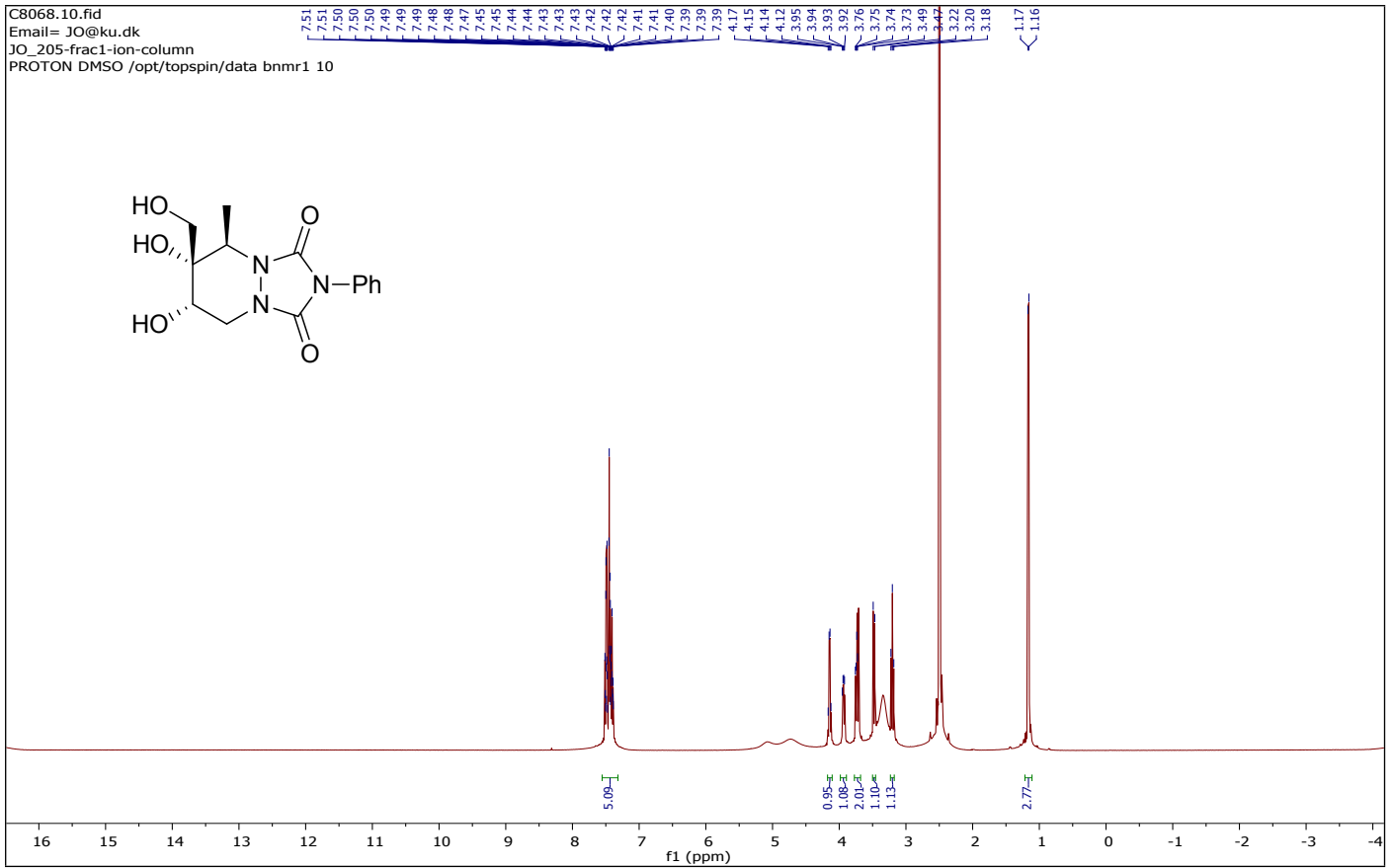




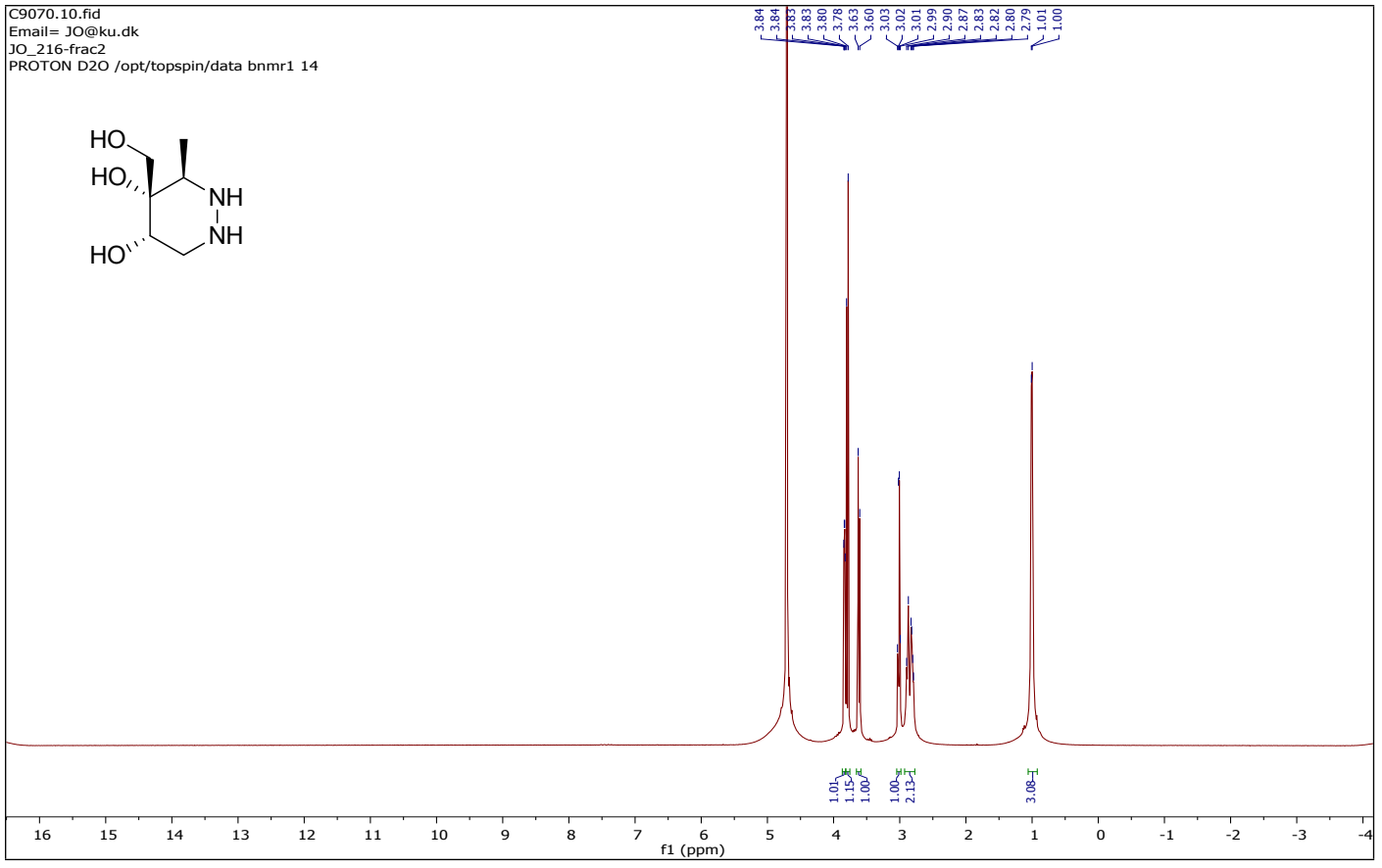
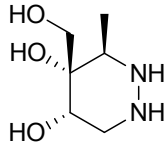




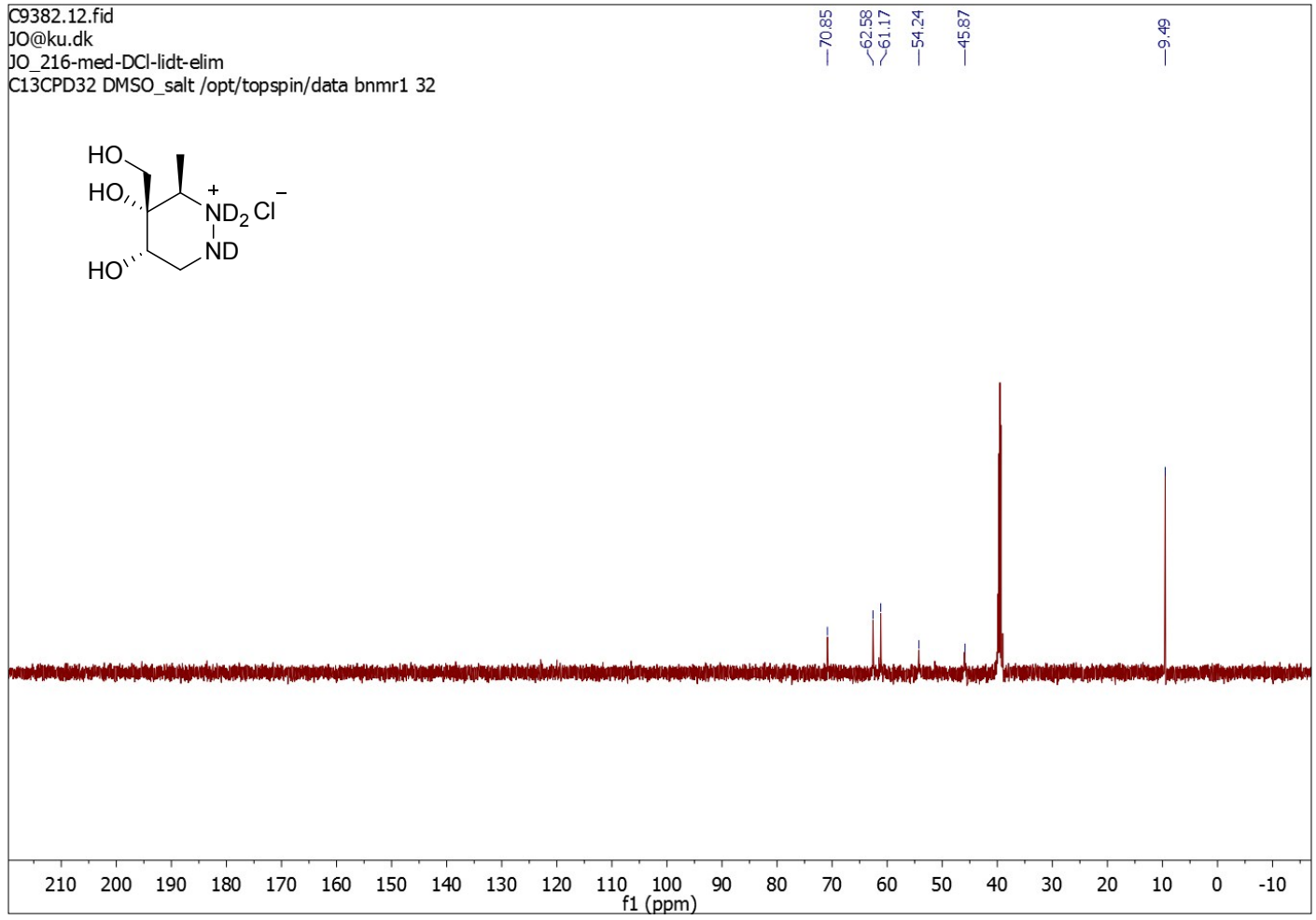
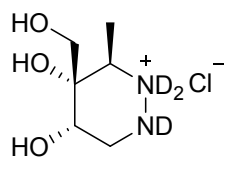




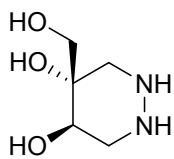
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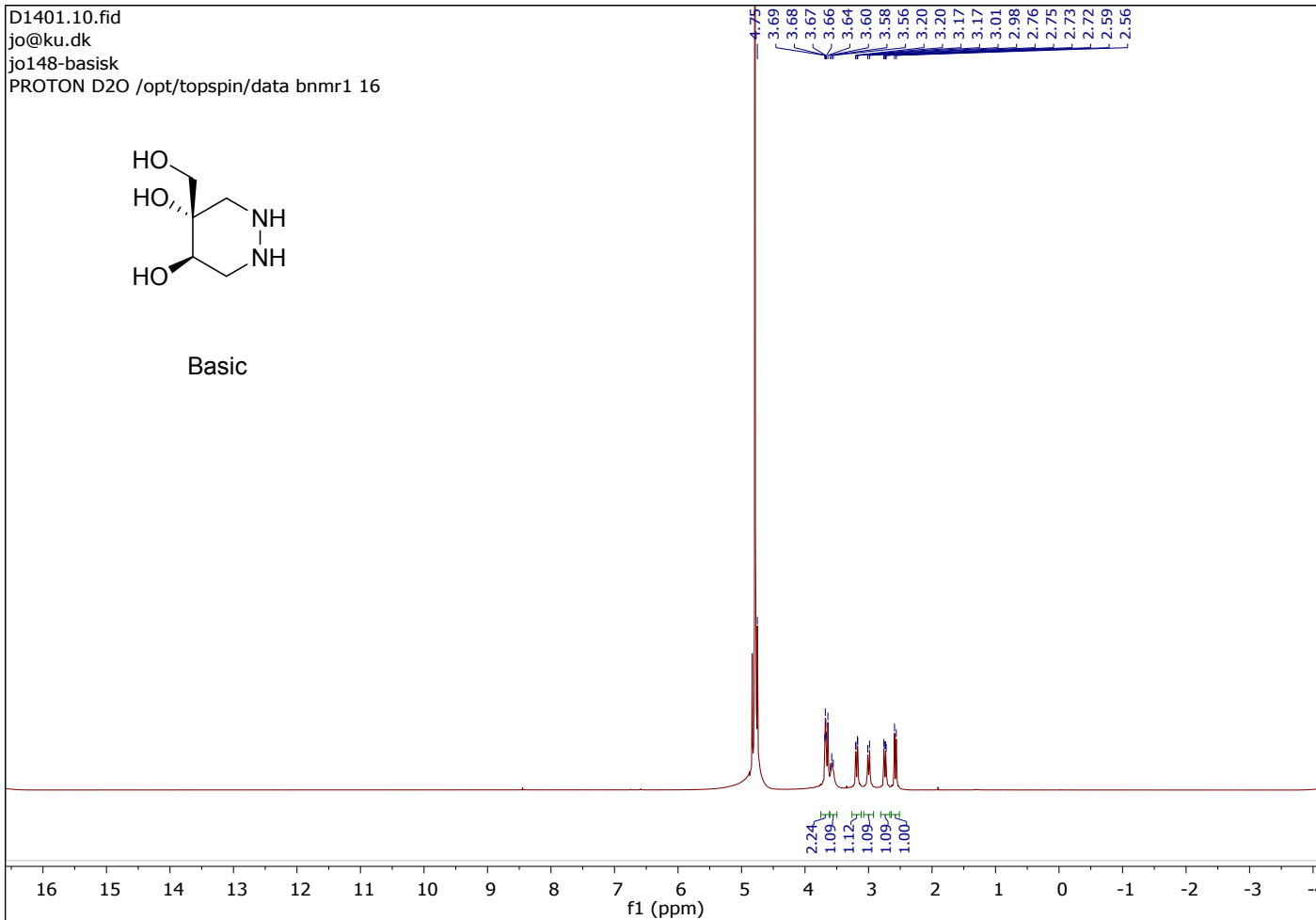
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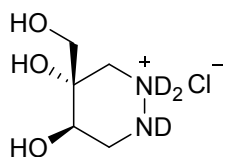
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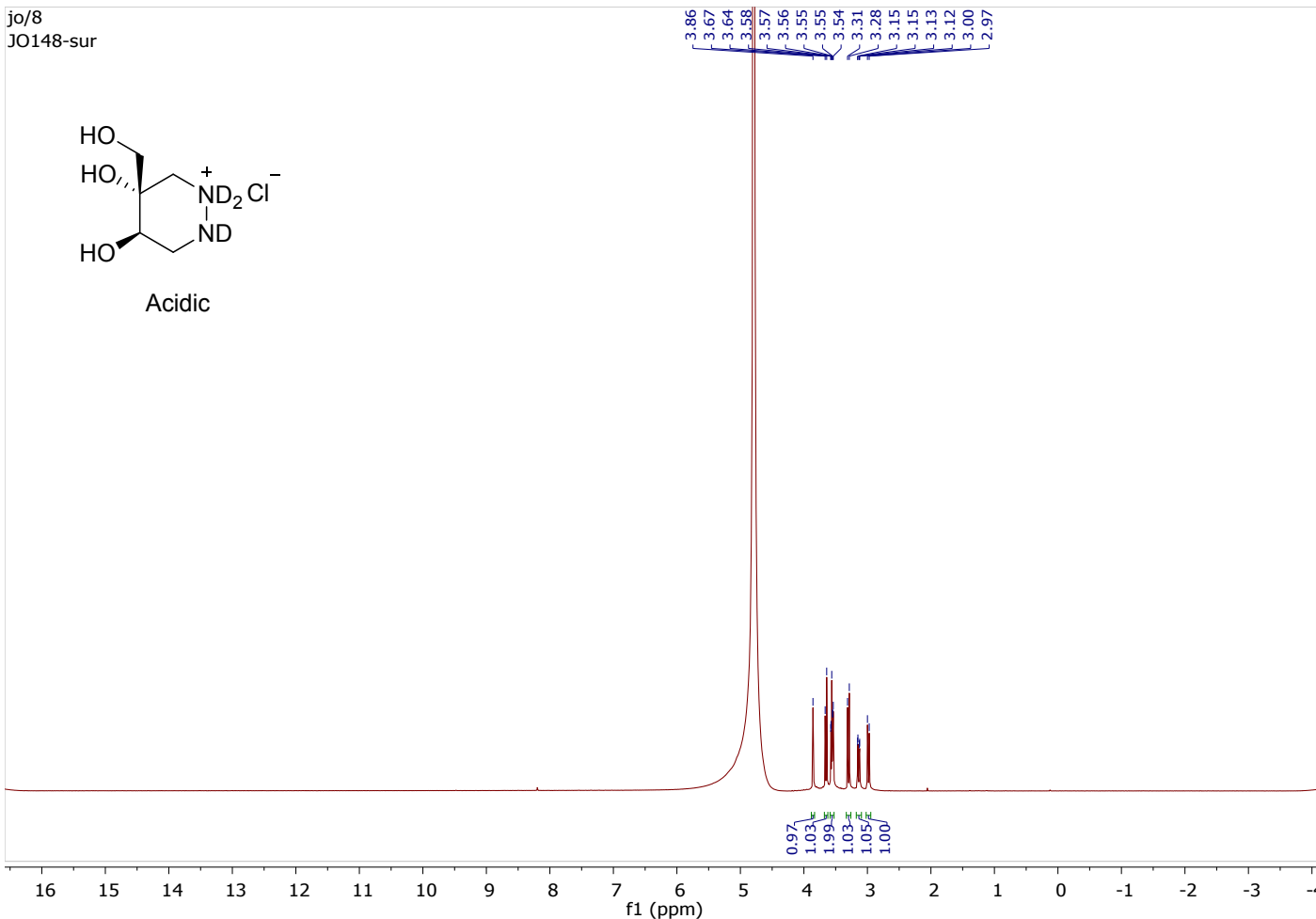
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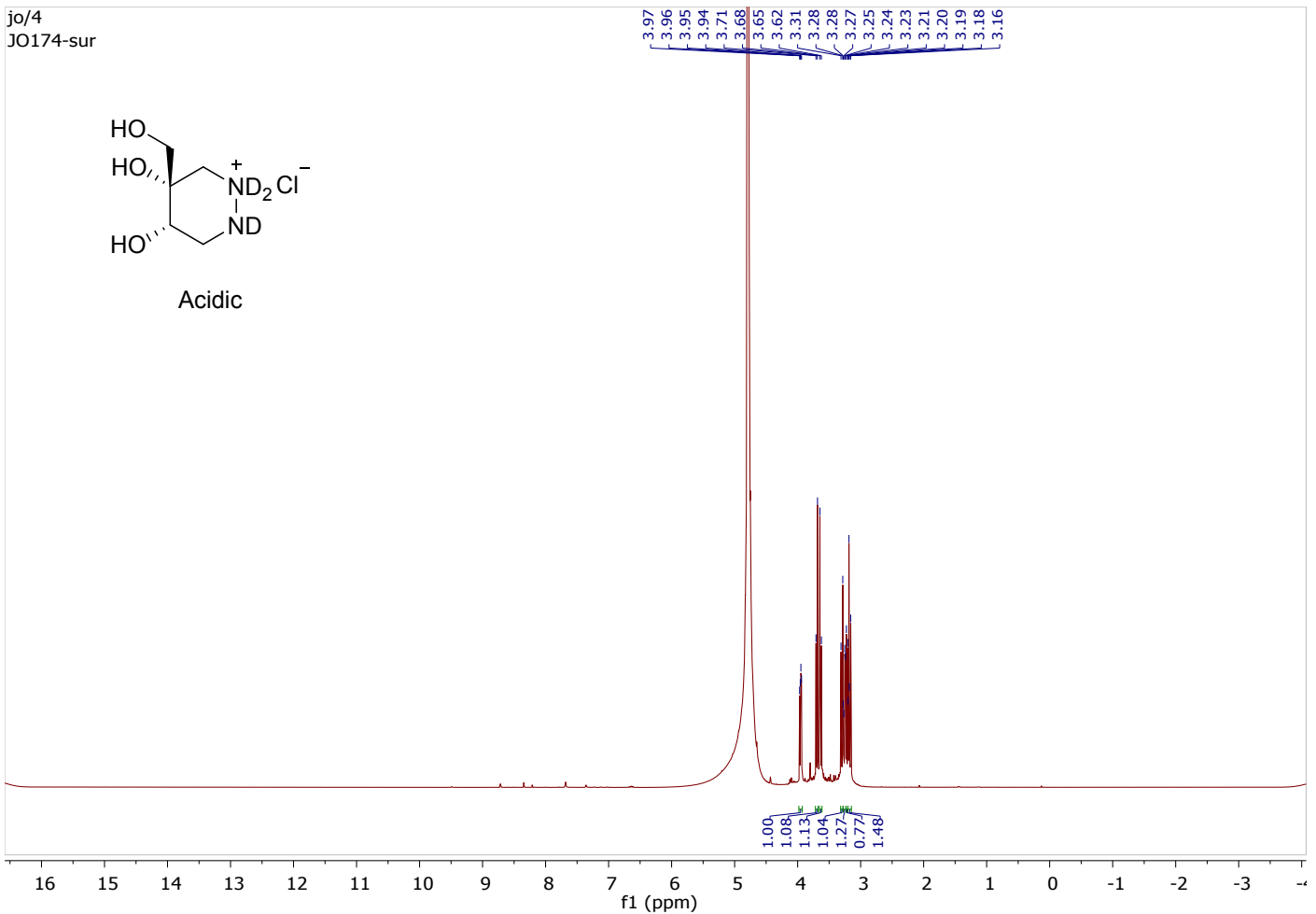
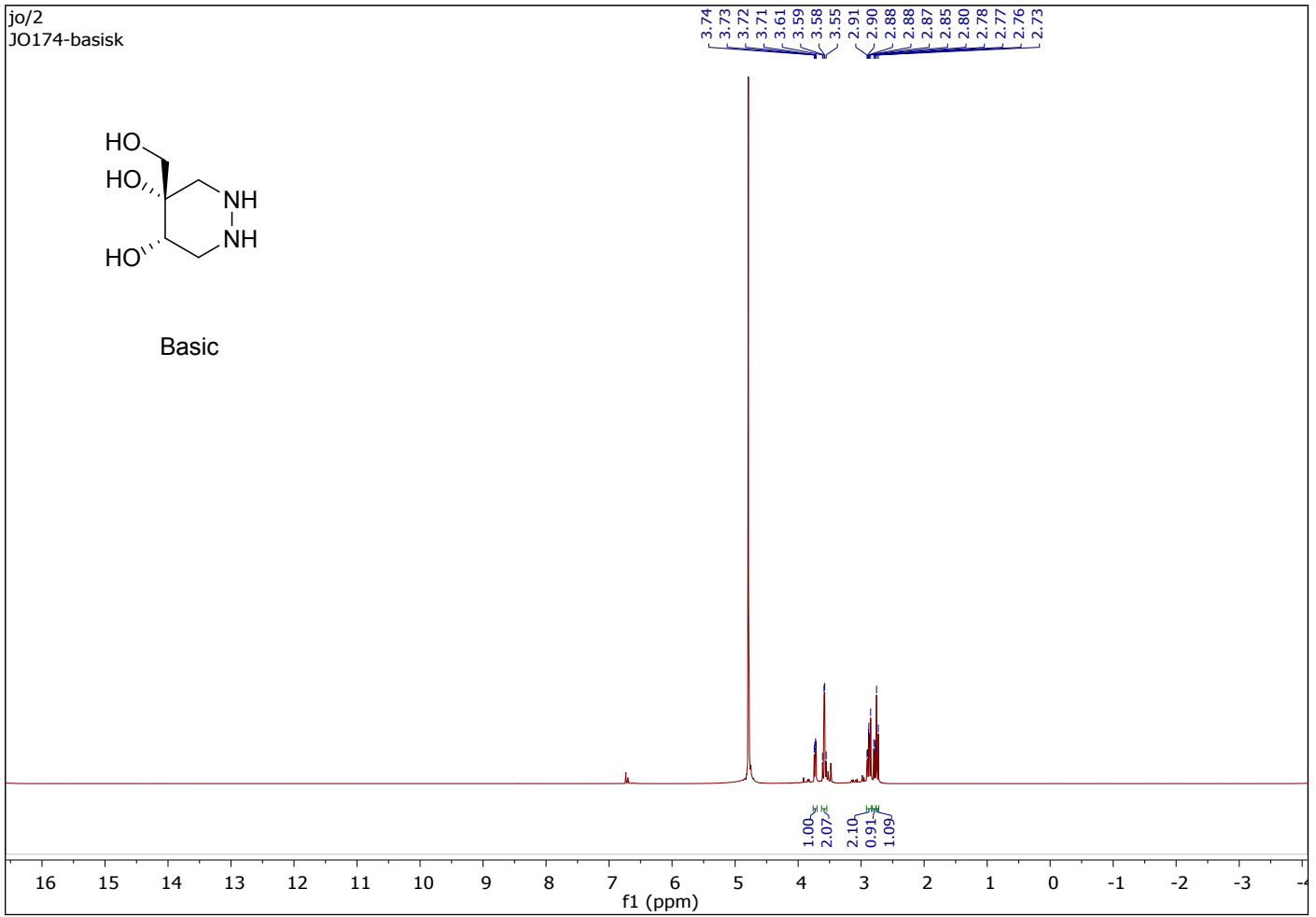


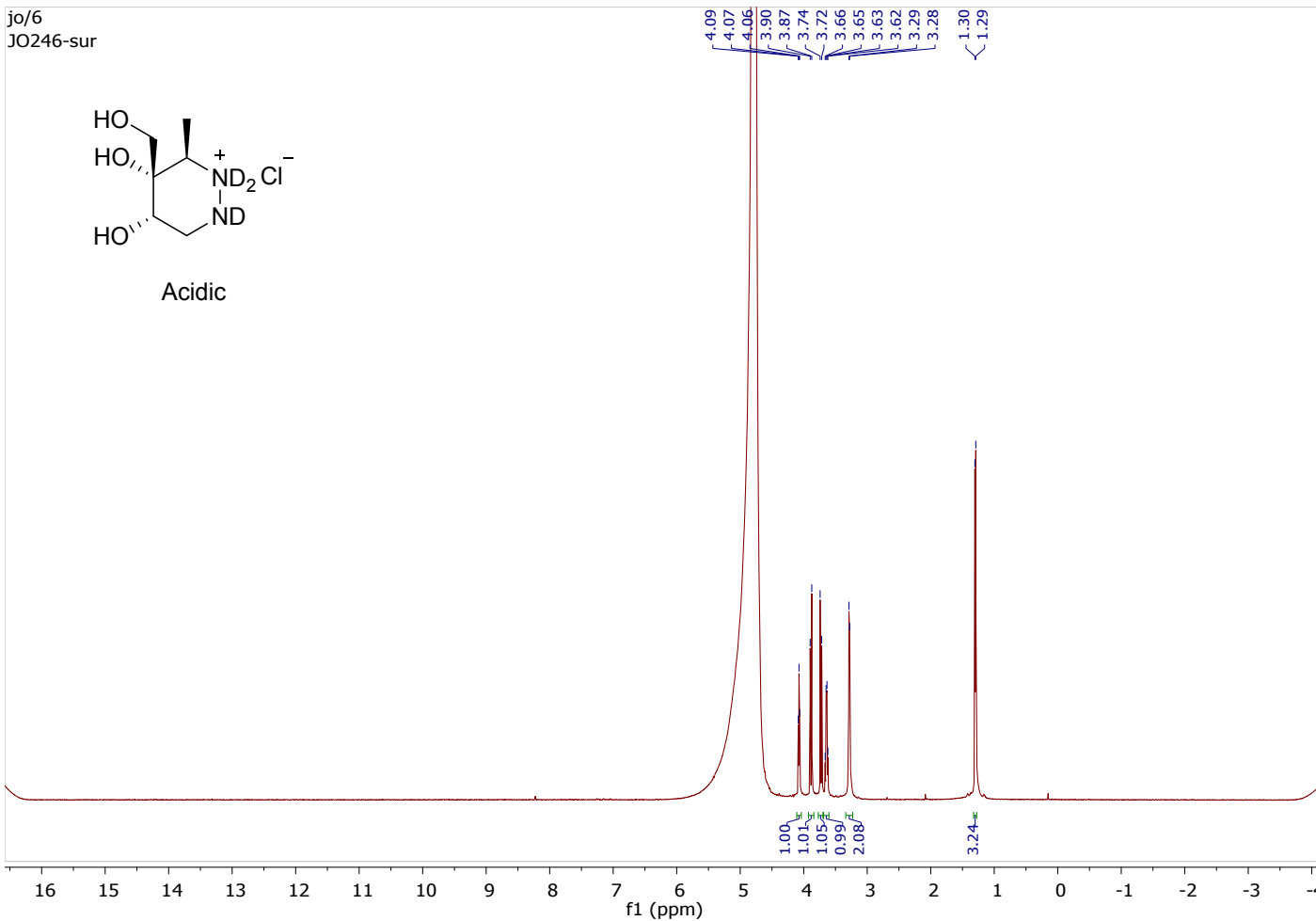
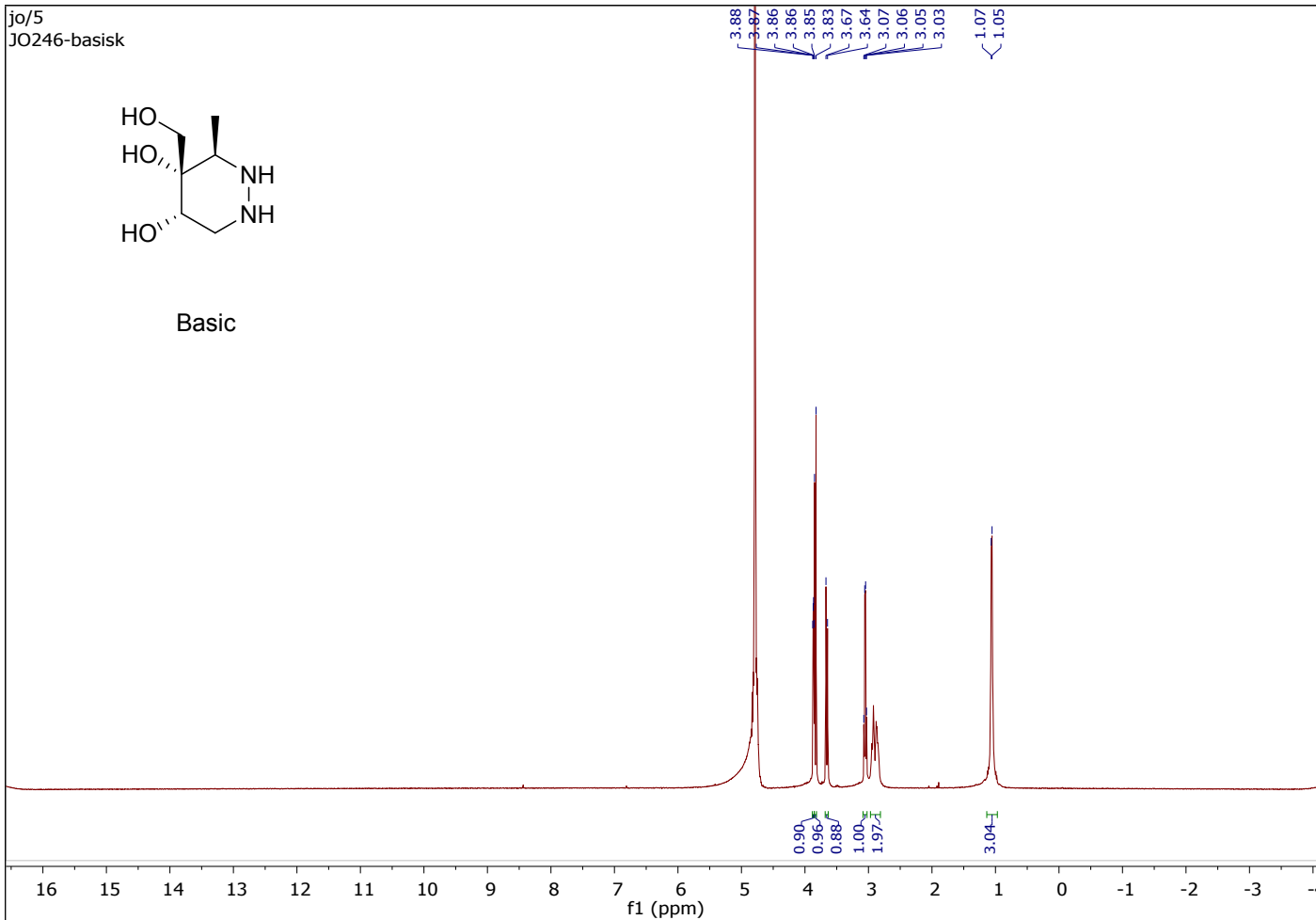
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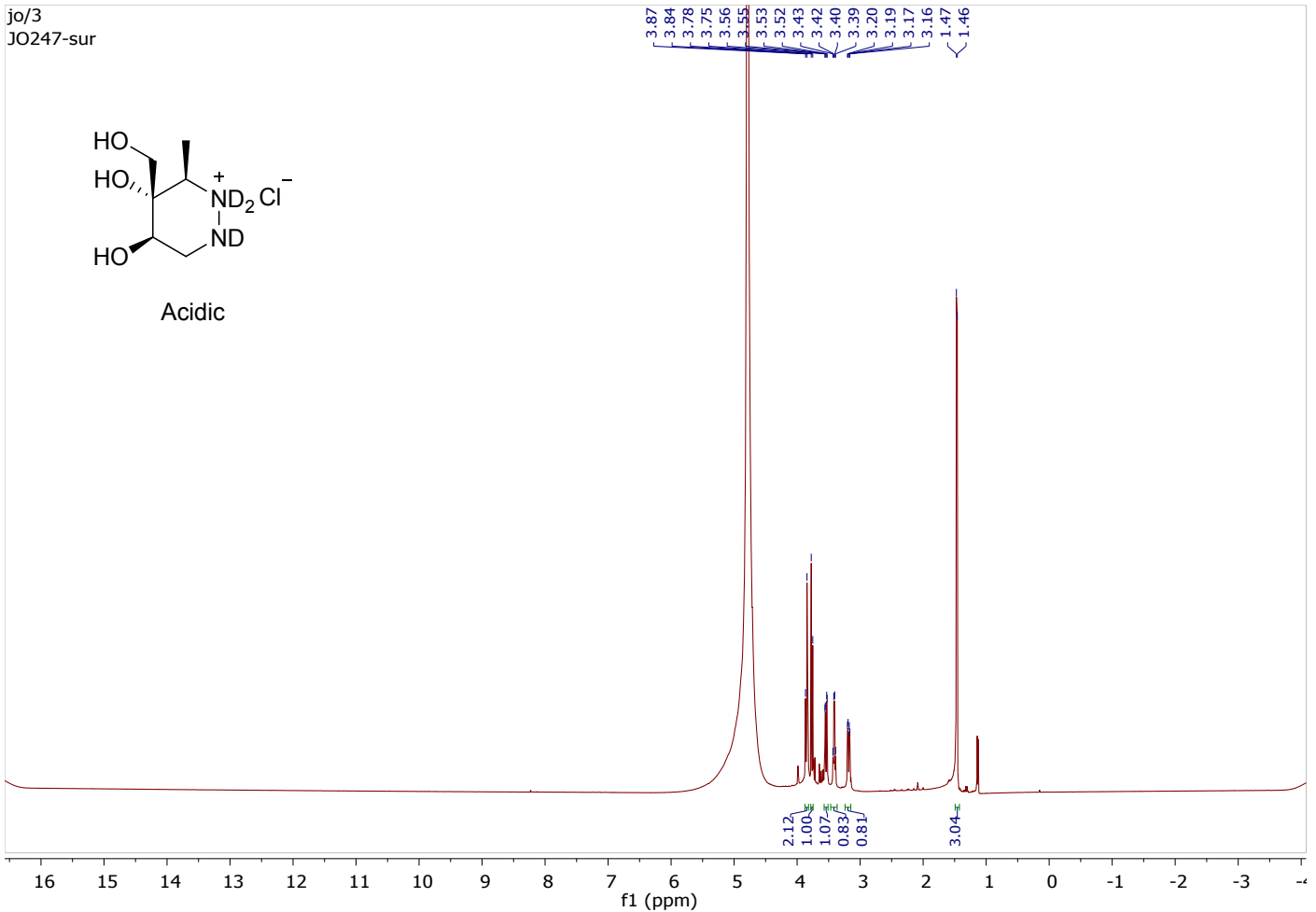
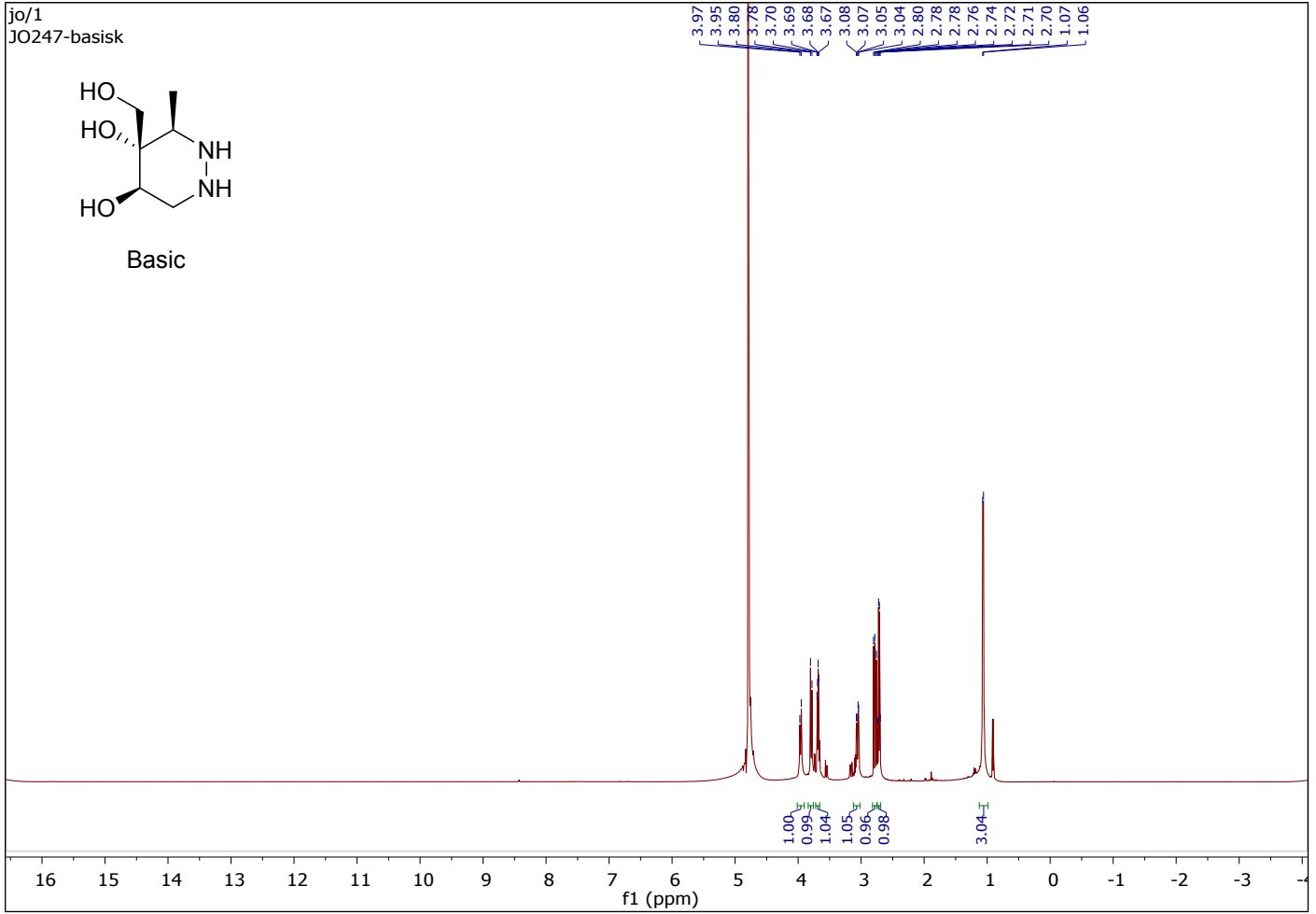


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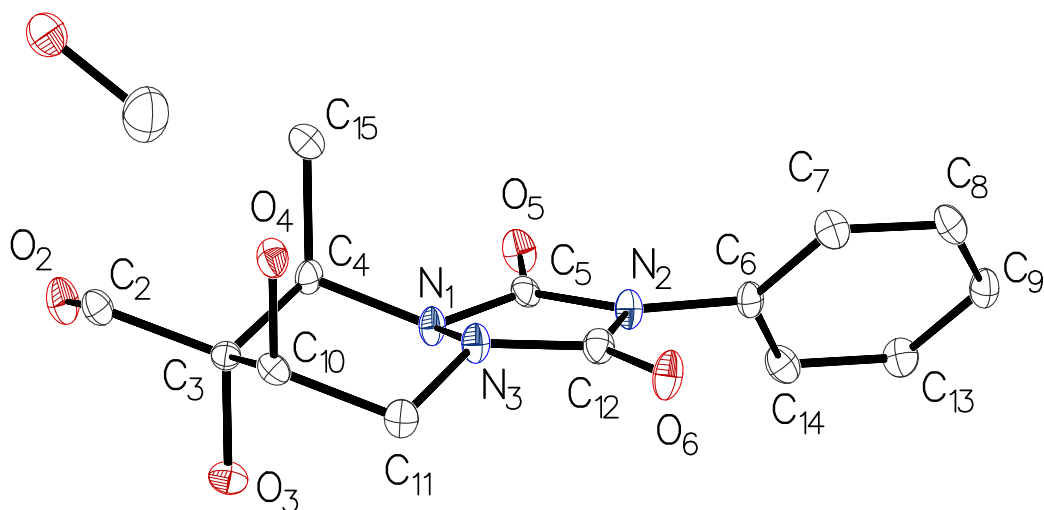






## Crystal Structure Data:

Single crystal X-ray diffraction studies were performed using a Bruker D8 Venture diffractometer monochromated with a doubly curved silicon crystal (Mo  $K\alpha$ ). The dataset was collected and processed using Bruker Apex 2, with the SAINT<sup>2</sup> and SADABS<sup>3</sup> programs and refined using Olex2.<sup>4</sup> All hydrogens were added using a riding model and refined with an isotropic displacement factor of  $1.2U_{eq}$  of the parent atom except for methyl H's and H atoms on heteroatoms which were constrained to  $1.5U_{eq}$  of the parent atom.



**Table 1.** Crystallographic data for **14**

Compound	<b>14</b>
Formula	$C_{15}H_{21}N_3O_6$
$M / g\ mol^{-1}$	339.35
Crystal system	Monoclinic
Space group	$P2_1/c$
$a / \text{\AA}$	10.1672(17)
$b / \text{\AA}$	6.8153(14)
$c / \text{\AA}$	22.813(5)
$\beta / ^\circ$	93.975(7)
$V / \text{\AA}^3$	1577.0(5)
$\rho / Mg\ m^{-3}$	1.429
$\mu / mm^{-1}$	0.111
$\theta_{max} / ^\circ$	25.03
Refl. collected/unique	10403/2771
$R_{int}$	0.0929
Parameters/restraints	230/32
$R_1 (F_o > 2\sigma(F_o))$	0.0461
$R_1$ (all data)	0.0919
$wR_2$	0.1019
GoF	1.050



**Table 2** Selected bond distances and angles

Bond	Bond distance / Å	Bond angle	Angle / °
O1 C1	1.421(3)	C4 N1 N3	116.35(16)
O2 C2	1.436(3)	C5 N1 N3	108.43(18)
O3 C3	1.433(3)	C5 N1 C4	123.70(19)
O4 C10	1.428(3)	C6 N2 C5	124.71(19)
O5 C5	1.223(3)	C12 N2 C5	110.37(19)
O6 C12	1.219(3)	C12 N2 C6	124.77(19)
N1 N3	1.410(3)	C11 N3 N1	116.14(19)
N1 C4	1.471(3)	C12 N3 N1	107.96(17)
N1 C5	1.356(3)	C12 N3 C11	124.9(2)
N2 C5	1.385(3)	C3 C2 O2	107.62(17)
N2 C6	1.434(3)	C2 C3 O3	109.76(19)
N2 C12	1.391(3)	C4 C3 O3	109.29(17)
N3 C11	1.464(3)	C4 C3 C2	109.85(19)
N3 C12	1.361(3)	C10 C3 O3	102.21(18)
C2 C3	1.516(3)	C10 C3 C2	112.68(17)
C3 C4	1.547(3)	C10 C3 C4	112.75(19)
C3 C10	1.543(3)	C3 C4 N1	107.14(18)
C4 C15	1.522(3)	C15 C4 N1	111.5(2)
C6 C7	1.374(3)	C15 C4 C3	116.34(18)
C6 C14	1.386(3)	N1 C5 O5	126.7(2)
C7 C8	1.388(3)	N2 C5 O5	127.5(2)
C8 C9	1.382(3)	N2 C5 N1	105.8(2)
C9 C13	1.382(3)	C7 C6 N2	119.2(2)
C10 C11	1.513(3)	C14 C6 N2	119.3(2)
C13 C14	1.384(3)	C14 C6 C7	121.5(2)
		C8 C7 C6	119.1(2)

C9 C8 C7	120.1(2)
C13 C9 C8	120.2(2)
C3 C10 O4	112.90(18)
C11 C10 O4	109.1(2)
C11 C10 C3	110.02(17)
C10 C11 N3	109.06(19)
N2 C12 O6	127.0(2)
N3 C12 O6	127.3(2)
N3 C12 N2	105.7(2)
C14 C13 C9	120.2(2)
C13 C14 C6	119.0(2)

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References:

1. H. E. Ensley, R. R. Buescher, K. Lee, *J. Org. Chem.*, 1982, **47**, 404-408
2. Bruker AXS Inc., *SAINT*, Version 7.68A Madison, WI, 2009
3. G. Sheldrick, *SADABS*, Version 2008/2 University of Göttingen, 2003
4. O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. Howard and H. Puschmann, *J. Appl. Cryst.*, 2009, **42**, 339–341