Supporting Information

For

Reactivity of Damaged Pyrimidines: Formation of a Schiff Base Intermediate at the Glycosidic Bond of Saturated Dihydrouridine

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Abbreviations used

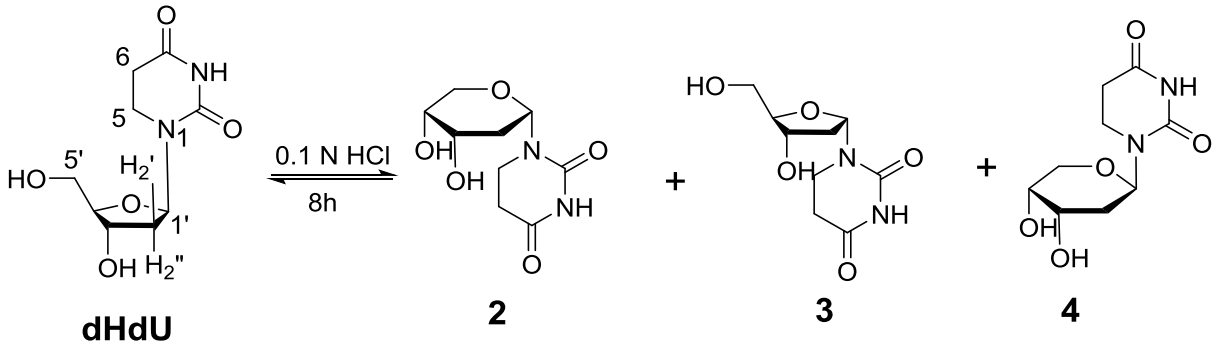
Abbreviations for NMR signal coupling are as follows: s, singlet; d, doublet; m, multiplet.

General Methods

All reagent grade chemicals were purchased from Sigma, Fisher, or VWR and used without further purification. The ^{1}H NMR spectra were obtained on a Bruker 500 MHz NMR Fourier transform spectrometer. NMR spectra were recorded in d_4-methanol, with residual methanol (δ3.31 ppm for ^{1}H NMR and δ49.0 ppm for ^{13}C NMR), in d_6-dimethyl sulfoxide, with residual dimethyl sulfoxide (δ 2.50 ppm for ^{1}H NMR and δ39.5 ppm for ^{13}C NMR), or in deuterated water (D_2O), with residual H_2O (δ4.79 ppm for ^{1}H NMR) taken as standards. The chemical shifts on NMR spectra were reported in parts per million (ppm).

HPLC analysis was performed at room temperature with a Waters (Milford, MA) breeze HPLC system coupled to a 2489 UV/Visible detector at 230 nm, while an Agilent ZORBAX Bonus-RP column (5 μm particle size, 250 × 4.6 mm i.d.) was used for separation. Semi-preparative HPLC was performed at room temperature with the same Waters HPLC setup and an XBridge^{TM} OST C18 column (2.5 μm particle size, 50 × 10 mm i.d.). The LC/MS and MS/MS analyses were conducted via the Agilent 6520 Accurate Mass Q-TOF LC/MS spectrometer.

Preparation of dHdU isomerization products



200 mg dHdU was dissolved in 0.1 M HCl and the reaction was allowed to proceed for 8 hours at ambient temperature. HPLC analysis reveals that four products, including three dHdU isomers **2**, **3** and **4** were formed. The products were separated via semi-preparative HPLC. Briefly, an XBridge^{TM} OST C18 column (2.5 μm particle size, 50 × 10 mm i.d.) was equilibrated with buffer A (10 mM ammonium acetate aqueous solution, pH 7.0); compounds were eluted with an ascending gradient (0% ~ 5%) of acetonitrile (buffer B) in 20 minutes at a flow rate of 4.73 mL/min. The four isomers including dHdU were eluted at 11.0 (**2**), 14.0 (**dHdU**), 14.7 (**3**), and 17.0 (**4**) min respectively. The compounds were desalted by reinjection into HPLC using H_2O-acetonitrile as elution buffers, then dried by rotary evaporation to afford isomer **2** (30 mg, colorless oil), **3**(18 mg, colorless oil), and **4** (23 mg, colorless oil) respectively.

2: ^{1}H NMR (methanol-d_4): δ1.65-1.70 (m, 1H, $H_{2'}$), 2.07 (q, J = 11.6 Hz, 1H, $H_{2''}$), 2.61 (dd, J = 1.4, 6.5 Hz, 1H, H_5), 2.63 (dd, J = 2.4, 6.0 Hz, 1H, H_5), 3.50 (ddd, J = 6.2, 8.0, 12.8 Hz, 1H, H_6), 3.62 (ddd, J = 6.0, 6.9, 12.8 Hz, 1H, H_6), 3.63 (dd, J = 1.0, 12.7 Hz, 1H, $H_{5''}$), 3.67-3.70 (m, 1H, $H_{4'}$), 3.84 (ddd, J = 3.2, 4.7, 11.7 Hz, 1H, $H_{3'}$), 3.95 (dd, J = 2.1, 12.7 Hz, 1H, $H_{5'}$), 5.43 (dd, J = 2.2, 11.4 Hz, 1H, $H_{1'}$); ^{13}C NMR (methanol-d_4): δ32.0, 32.4, 37.5, 68.4, 69.6, 70.2, 81.6, 154.7, 172.8; ESI-MS (positive ion) calcd for $C_9H_{15}N_2O_5^+$: (M + H^+) 231.0975, found 231.0972.

dHdU: ^{1}H NMR (methanol-d_4): δ1.98 (ddd, J = 3.2, 6.4, 13.5, 1H, $H_{2''}$), 2.19 (ddd, J = 6.6, 7.9, 13.5 Hz, 1H, $H_{2'}$), 2.56-2.67 (m, 2H, H_5),3.41 (ddd, J = 5.6, 8.2, 12.6, 1H, H_6), 3.57 (ddd, J = 6.2, 6.8, 12.5 Hz, 1H, H_6), 3.62 (dd, J = 4.6, 11.9 Hz, 1H, $H_{5''}$), 3.68 (dd, J = 4.0, 11.9 Hz, 1H, $H_{5'}$), 3.77 (dd, J = 4.0, 8.0 Hz, 1H, $H_{4'}$), 4.25-4.30 (m, 1H, $H_{3'}$), 6.26 (dd, J = 6.4, 8.0 Hz, 1H, $H_{1'}$); ^{13}C NMR (methanol-d_4): δ31.9, 36.9, 37.5, 63.3, 72.4, 85.3, 87.4, 154.9, 172.9; ESI-MS (positive ion) calcd for $C_9H_{15}N_2O_5^+$: ($M + H^+$) 231.0975, found: 231.0969.

3: ^{1}H NMR (methanol-d_4): δ1.93 (ddd, J = 5.0, 5.0, 10.0, 1H, $H_{2''}$), 2.52 (ddd, J = 7.1, 7.2, 14.1 Hz, 1H, $H_{2'}$), 2.63 (t, J = 6.7 Hz, 2H, H_5), 3.52 (dd, J = 5.0, 12.0 Hz, 1H, $H_{5''}$), 3.56-3.67 (m, 3H, $H_{5'}$ and H_6), 4.00 (dd, J = 4.0, 8.5 Hz, 1H, $H_{4'}$), 4.29 (ddd, J = 4.1, 4.3, 6.9 Hz, 1H, $H_{3'}$), 6.16 (dd, J = 5.5, 7.6 Hz, 1H, $H_{1'}$); ^{13}C NMR (methanol-d_4): δ32.0, 37.4, 39.1, 63.4, 72.2, 86.1, 88.6, 154.9, 173.0; ESI-MS (positive ion) calcd for $C_9H_{15}N_2O_5^+$: ($M + H^+$) 231.0975, found: 231.0975.

4: ^{1}H NMR (methanol-d_4): δ1.81 (ddd, J = 2.4, 3.8, 13.8Hz, 1H, $H_{2''}$), 2.52 (ddd, J = 2.4, 11.2, 13.6 Hz, 1H, $H_{2'}$), 2.60 (t, J = 6.9 Hz, 2H, H_5), 3.40-3.53 (m, 2H, H_6), 3.63-3.71 (m, 2H, $H_{4'}$ and $H_{5''}$), 3.75-3.81 (m, 1H, $H_{5'}$), 4.11-4.15 (m, 1H, $H_{3'}$), 5.84 (dd, J = 2.2, 11.4 Hz, 1H, $H_{1'}$); ^{13}C NMR (methanol-d_4): δ32.0, 35.3, 37.4, 66.8, 68.0, 68.4, 78.4, 154.7, 172.8; ESI-MS (positive ion) calcd for $C_9H_{15}N_2O_5^+$: ($M + H^+$) 231.0975, found: 231.0973.

dHdU isomerization reaction at 90 °C in a pH 7.4 buffer dHdU was dissolved in 200 µL pH 7.4 sodium phosphate buffer containing 150 mM NaCl to a final concentration of 85 mM. The solution was heated to 90 °C using a PCR device with a cap heating function to minimize water evaporation. At various reaction times, 5 µL solution was aliquotted out, immediately frozen in liquid N_2, and saved in –20 °C freezer for future HPLC analysis. In HPLC analysis,

briefly, an Agilent ZORBAX Bonus-RP column (5 μm particle size, 250 × 4.6 mm i.d.) was equilibrated with buffer A (10 mM ammonium acetate aqueous solution, pH 7.0); compounds were eluted with an ascending gradient (0% ~ 5%) of acetonitrile (buffer B) in 20 minutes at a flow rate of 0.5 mL/min. Under such a condition, **1** (5,6-dihydrouracil), **2** , dHdU, **3** and **4** eluted at 8.6, 11.0, 14.0, 14.7, and 17.0 min respectively.

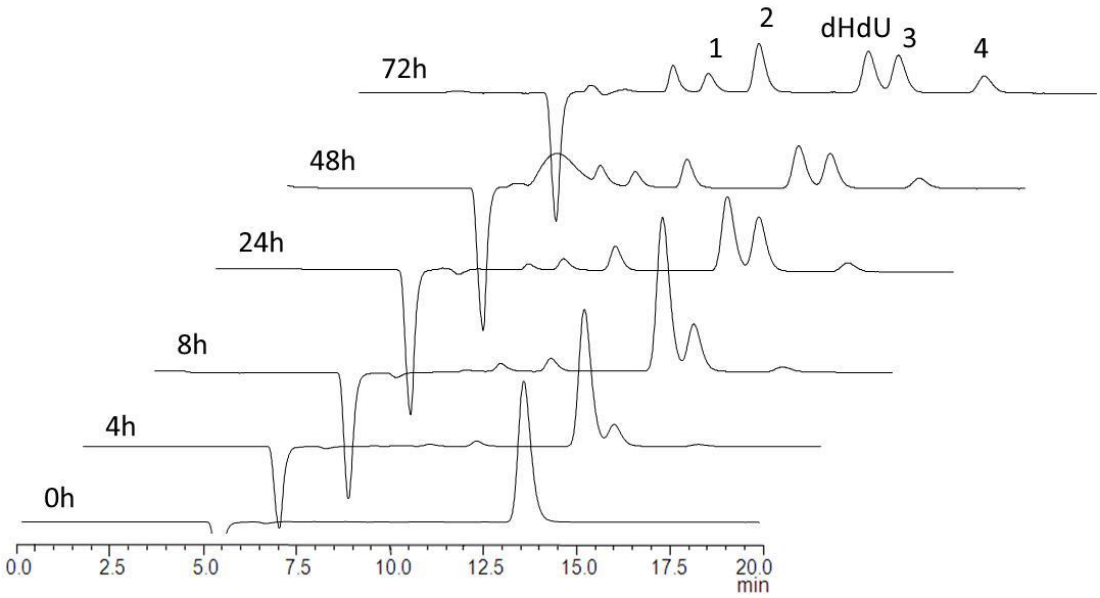


Figure S1. HPLC chromatogram (monitored at 230 nm) of the dHdU isomerization reaction in a pH 7.4 buffer at 90°C for 72 hrs.

Isomerization of 2′-deoxyuridine (dU) and thymidine (T) at pH 1 dU and T were dissolved respectively in 200 μL 0.1 M HCl to a final concentration of 85 mM. The resulting solutions were kept at room temperature for ~ 3 days. At various times, 5 μL of the reaction solution was aliquotted out, immediately frozen in liquid N_2 and saved in –20 °C freezer for future HPLC analysis. In HPLC analysis, an Agilent ZORBAX Bonus-RP column (5 μm particle size, 250 × 4.6 mm i.d.) was equilibrated with buffer A (10 mM ammonium acetate aqueous solution, pH 7.0). For **dU** isomerization reaction, an ascending gradient (0% ~ 5%) of

acetonitrile (buffer B) in 20 minutes at a flow rate of 1 mL/min was used and **dU** was eluted at 10.3 min. For **T** isomerization reaction, an ascending gradient (0% ~ 20%) of acetonitrile (buffer B) in 20 minutes at a flow rate of 1 mL/min was used and **T** was eluted at 11.4 min. No product was observed in either reaction.

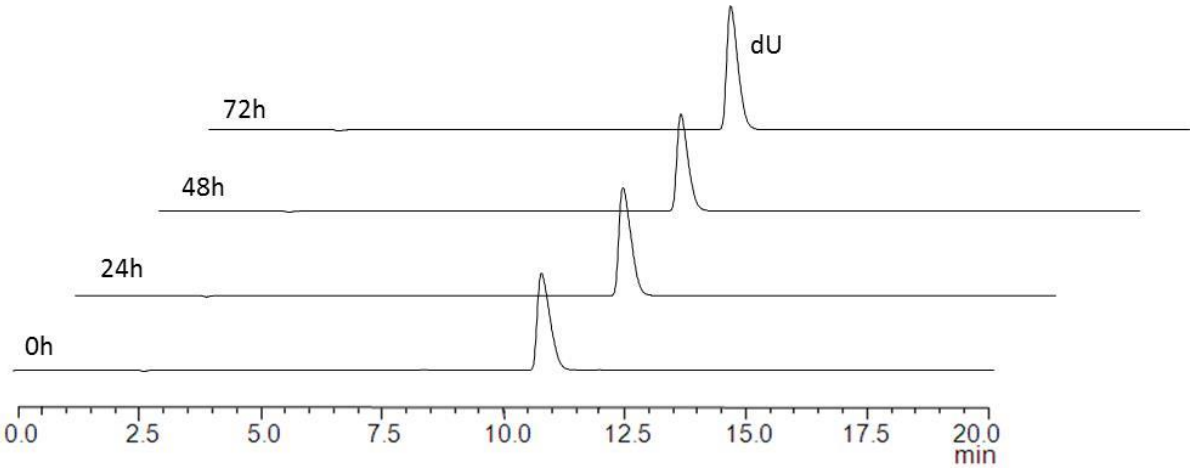


Figure S2. HPLC chromatogram (monitored at 230 nm) of the dU isomerization reaction in the presence of 0.1 M HCl at ambient temperature for 72 hrs.

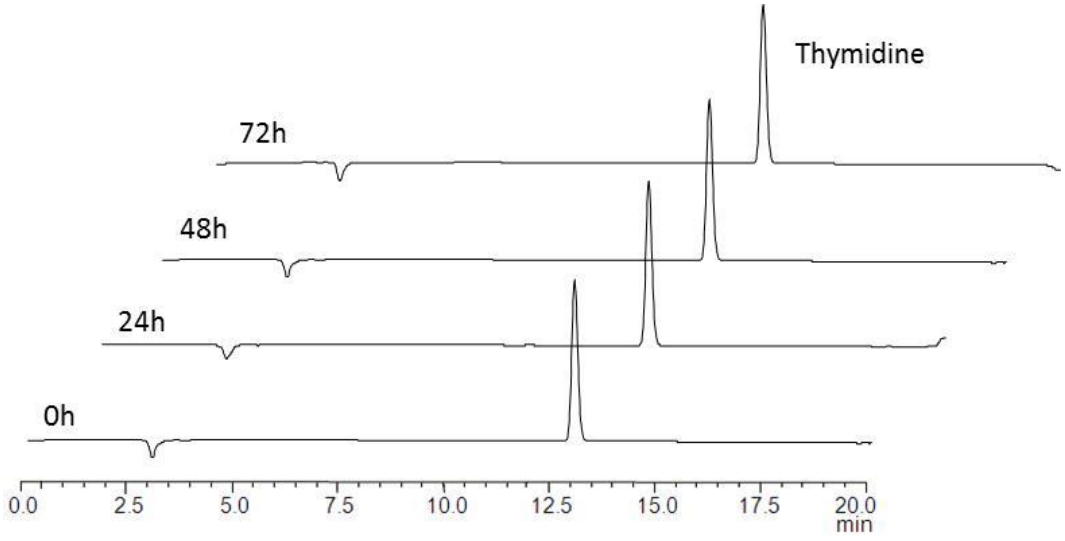


Figure S3. HPLC chromatogram (monitored at 230 nm) of the **T** isomerization reaction in the presence of 0.1 M HCl at ambient temperature for 72 hrs.

Isomerization of dU and T at 90 °C in a pH 7.4 buffer dU and T were dissolved respectively in 200 µL pH 7.4 sodium phosphate buffer containing 150 mM NaCl to a final concentration of 85 mM. The solution was heated to 90 ºC using a PCR device with a cap heating function to minimize water evaporation. At various reaction times, 5 µL solution was aliquotted out, immediately frozen in liquid N_2, and saved in –20 °C freezer for future HPLC analysis. In HPLC analysis, briefly, an Agilent ZORBAX Bonus-RP column (5 µm particle size, 250 × 4.6 mm i.d.) was equilibrated with buffer A (10 mM ammonium acetate aqueous solution, pH 7.0). For **dU** isomerization reaction, an ascending gradient (0% ~ 5%) of acetonitrile (buffer B) in 20 minutes at a flow rate of 1 mL/min was used; **uracil** and **dU** were eluted at 5.1 and 10.3 min respectively. For **T** isomerization reaction, an ascending gradient (0% ~ 20%) of acetonitrile (buffer B) in 20 minutes at a flow rate of 1 mL/min was used; **thymine** and **T** were eluted at 8.3 and 11.4 min respectively. No isomers of dU or T were observed.

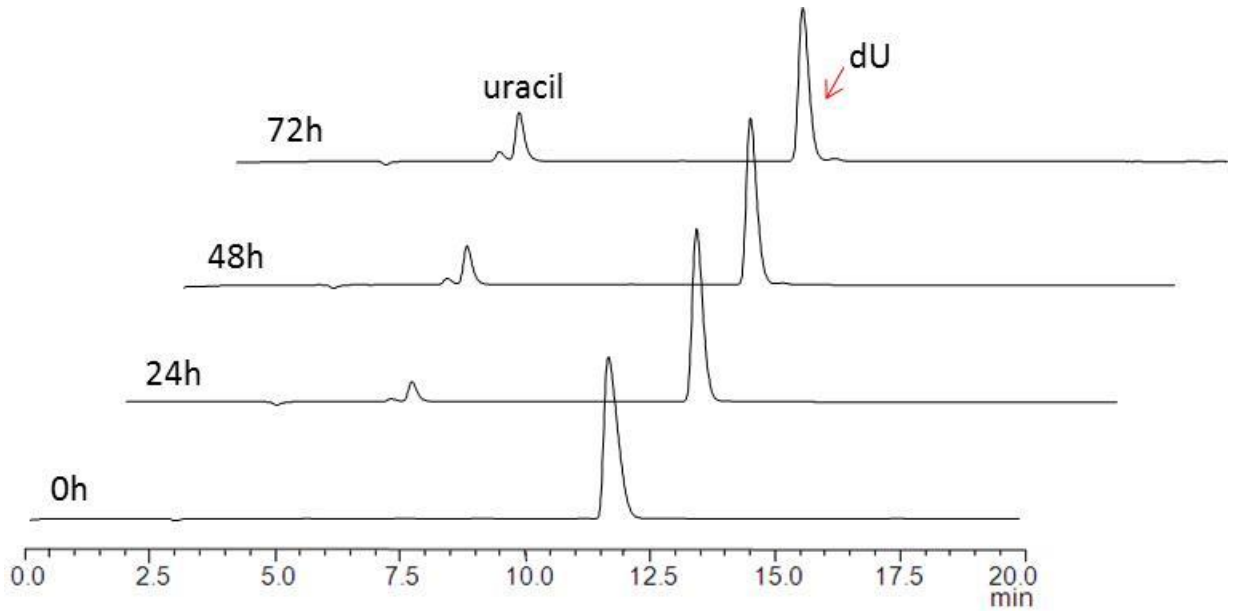


Figure S4. HPLC chromatogram (monitored at 230 nm) of the **dU** isomerization reaction in a pH 7.4 buffer at 90°C for 72 hrs.

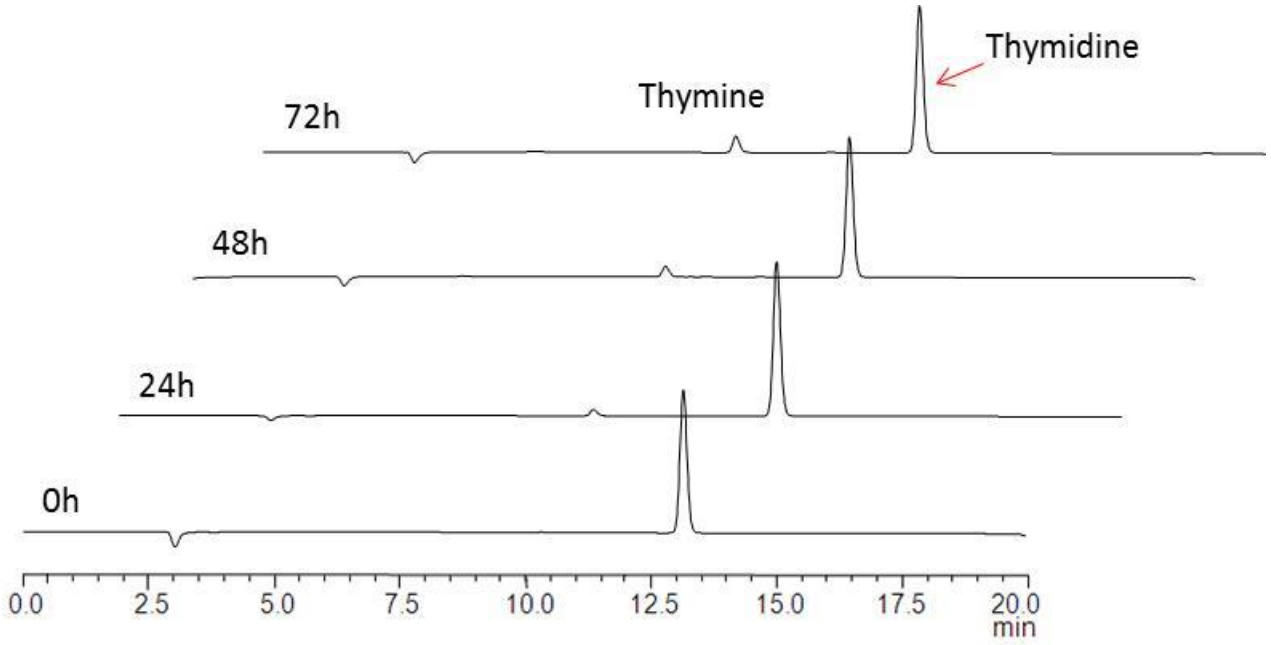


Figure S5. HPLC chromatogram (monitored at 230 nm) of the **T** isomerization reaction in a pH 7.4 buffer at 90°C for 72 hrs.

Preparation of compound 5

dHdU (50 mg, 0.22 mmol) was dissolved in 0.1 M HCl in MeOH:H_2O (1:1, v/v) solution to a final concentration of 5 mM (44 mL); 50 mg Pd-C was then added to the solution. The resulting suspension was stirred under 1 atm H_2 for 8 days at ambient temperature. At various time points, 5 µl of the reaction mixture was extracted, and immediately analyzed by HPLC until ~85% dHdU was consumed. After removing the Pd-C catalyst by filtration, the product was purified by semi-preparative HPLC. Briefly, an XBridge^{TM} OST C18 column (2.5 µm particle size, 50 × 10 mm i.d.) was equilibrated with buffer A (10 mM ammonium acetate aqueous solution, pH 7.0). Compounds were eluted with an ascending gradient (0% ~ 5%) of acetonitrile (buffer B) in 20 minutes at a flow rate of 4.73 mL/min. The dHdU Schiff base hydrogenation product **5** was eluted at 6.1 min. After removing solvent via rotary evaporation, **5** was obtained as a white solid (38 mg, 75%). ^{1}H NMR (methanol-d_4): δ1.58-1.67 (m, 1H), 1.98-2.08 (m, 1H), 2.62-2.73 (m,

2H), 3.44-3.58 (m, 5H), 3.59-3.68 (m, 2H), 3.73 (dd, J = 3.9, 11.3 Hz, 1H);^{13}C NMR (methanol-d_4): δ31.81, 31.87, 43.4, 45.6, 64.7, 70.9, 76.3, 155.3, 173.1; ESI-MS (positive ion) calcd for $C_9H_{17}N_2O_5^+$: (M + H^+) 233.1132, found: 233.1129.

Nucleophilic addition reaction between cysteine and dHdU dHdU was dissolved in H_2O to a final concentration of 85mM. To this solution, 75-fold cysteine·HCl was added followed by the addition of 1 N HCl to adjust the pH to 3. The resulting solution was allowed to react at 37 ºC. At various times, 5 µl of the reaction mixture was extracted, and immediately analyzed by HPLC. Briefly, an Agilent ZORBAX Bonus-RP column (5 µm particle size, 250 × 4.6 mm i.d.) was equilibrated with buffer A (10 mM triethylamine-Acetic Acid aqueous solution, pH 7.0); compounds were eluted with an ascending gradient (0% ~ 5%) of acetonitrile in 20 minutes at a flow rate of 0.5 mL/min. The cysteine-dHdU adducts **6** and **7,** and dHdU deglycosylation product **1**, were eluted at 6.3, 7.1, and 8.7 min respectively.

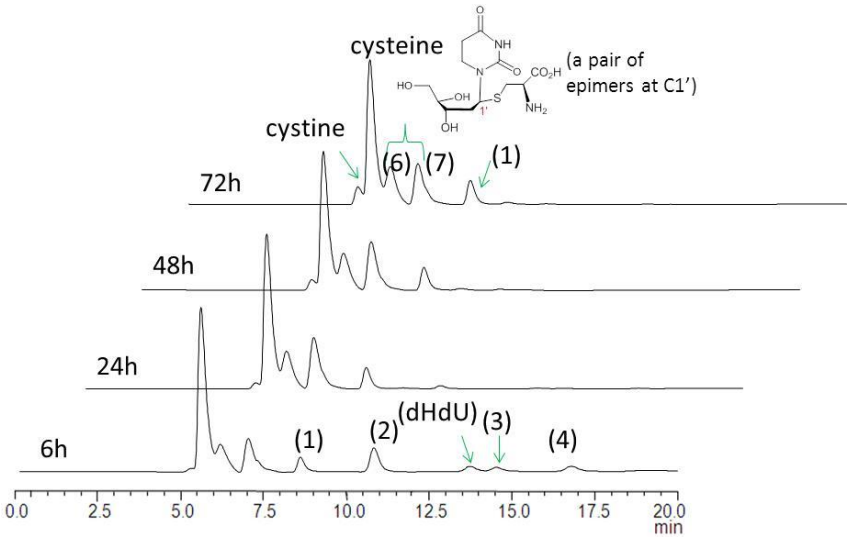
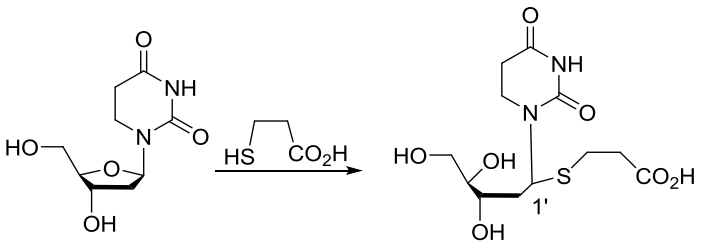


Figure S6. HPLC chromatogram (monitored at 230 nm) of Schiff base intermediate-mediated nucleophilic addition reaction between cysteine and dHdU at 37 ºC for 72 hrs.

Preparation of compounds 8 and 9



dHdU (20 mg, 85μmol) was dissolved in H_2O to a final concentration of 60 mM. To this solution, 3-mercaptopropionic acid $HSCH_2CH_2CO_2H$ (75X) was added. The resulting solution was kept at 60°C for 24 h. 5 μl of the reaction mixture was extracted and immediately analyzed by HPLC to confirm that 85% of the dHdU added has reacted.

The resulting mixture was then purified by preparative HPLC. Briefly, an XBridge^{TM} OST C18 column (2.5 μm particle size, 50 × 10 mm i.d.) was equilibrated with buffer A (triethylamine-Acetic Acid aqueous solution, pH 7.0). Compounds were eluted with an ascending gradient (0% ~ 5%) of acetonitrile in 20 minutes at a flow rate of 2.37 mL/min. Under such a condition, **dHdU-MPA** adducts **8** and **9** were eluted at 15.8 and 16.4 min respectively. After removing solvent via rotary evaporation, **8** (10 mg, 30%) and **9** (18 mg, 56%) were obtained both as colorless gel**.**

8: ^{1}H NMR (methanol-d_4): δ1.66(ddd, J = 3.5, 9.8, 14.6 Hz, 1H, $H_{2'}$), 2.14 (dd, J = 12.5, 14.6 Hz, 1H, $H_{2'}$), 2.42 (ddd, J = 7.5, 7.5, 15.3 Hz, 1H, H_b), 2.52 (ddd, J = 6.3, 8.0, 14.1 Hz, 1H, H_b), 2.61-2.76 (m, 3H, H_c and H_5), 2.80 (ddd, J = 6.2, 8.0, 13.1 Hz, 1H, H_c), 3.34 (ddd, J = 5.3, 8.7, 13.1 Hz, 1H, H_6), 3.37-3.44 (m, 2H, $H_{3'}$ and $H_{4'}$), 3.57 (dd, J = 5.4, 11.2 Hz, 1H, $H_{5'}$), 3.66 (dd, J

= 6.7, 12.5 Hz, 1H, H_6), 3.68 (dd, *J* = 3.2, 11.0 Hz, 1H, $H_{5'}$), 5.97 (dd, *J* = 3.1, 11.9 Hz, 1H, $H_{1'}$);^{13}C NMR (methanol-d_4): δ28.4, 31.8, 36.8, 37.0, 38.7, 57.8, 64.5, 69.9, 75.9, 155.5, 172.8, 179.7; ESI-MS (negative ion) calcd for $C_{12}H_{19}N_2O_7S(M–H)^-$: 335.0918, found: 335.0916;

9: ^{1}H NMR (methanol-d_4): δ1.70 (ddd, *J* = 6.0, 9.7, 11.2 Hz, 1H, $H_{2'}$), 2.07 (ddd, *J* = 2.5, 8.9, 11.5 Hz, 1H, $H_{2'}$), 2.40-2.55 (m, 2H, H_b), 2.61-2.77 (m, 3H, H_a and 2 H_5), 2.80 (ddd, *J* = 6.8, 6.8, 13.0 Hz, 1H, H_a), 3.37-3.44 (m, 2H, $H_{4'}$ and H_6), 3.56 (dd, *J* = 6.3, 11.3Hz, 1H, $H_{5'}$), 3.65-3.75 (m, 3H, $H_{3'}$, $H_{5'}$ and H_6), 5.94 (dd, *J* = 6.1, 8.9 Hz, 1H, $H_{1'}$);^{13}C NMR (methanol-d_4): δ28.3, 31.9, 37.5, 37.8, 38.5, 59.2, 64.6, 71.0, 76.4, 154.9, 172.9, 179.5; ESI-MS (negative ion) calcd for $C_{12}H_{19}N_2O_7S(M–H)^-$: 335.0918, found: 335.0916.

dHT isomerization reaction dHT was dissolved in 200 µL 0.1 M HCl to a final concentration of 85 mM. The resulting solution was kept at room temperature for ~ 3 days. At various times, 5 µL of the reaction solution was aliquotted out, immediately frozen in liquid N_2 and saved in –20 °C freezer for future HPLC analysis. For HPLC analysis, briefly, an Agilent ZORBAX Bonus-RP column (5 µm particle size, 250 × 4.6 mm i.d.) was equilibrated with buffer A (10 mM ammonium acetate aqueous solution, pH 7.0). Compounds were eluted with an ascending gradient (0% ~ 5%) of acetonitrile (buffer B) in 20 minutes at a flow rate of 1 mL/min. The four isomers of **dHT** were eluted at 8.8 (**10**), 10.8 (**dHT**), 11.6 (**11**), and 14.1 (**12**) min respecitively. These products were characterized by MS/MS analysis.

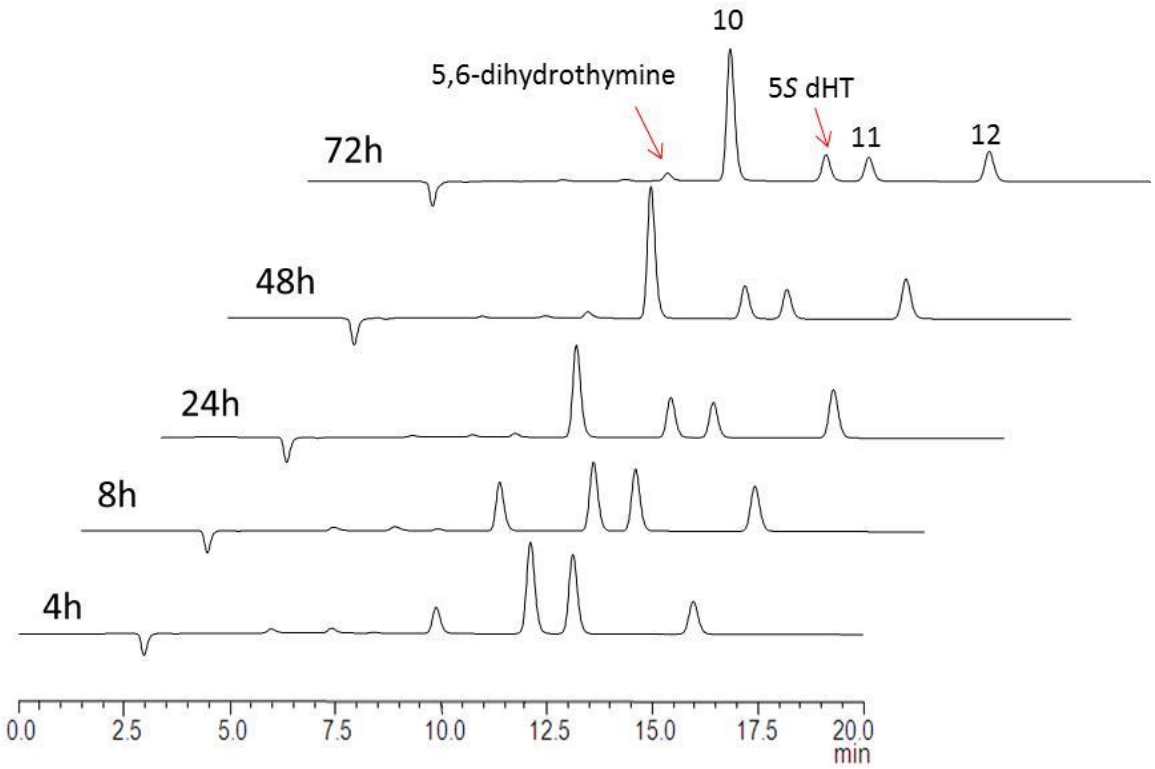


Figure S7. HPLC chromatogram (monitored at 230 nm) of the **dHT** isomerization reaction in the presence of 0.1 M HCl at ambient temperature for 72 hrs.

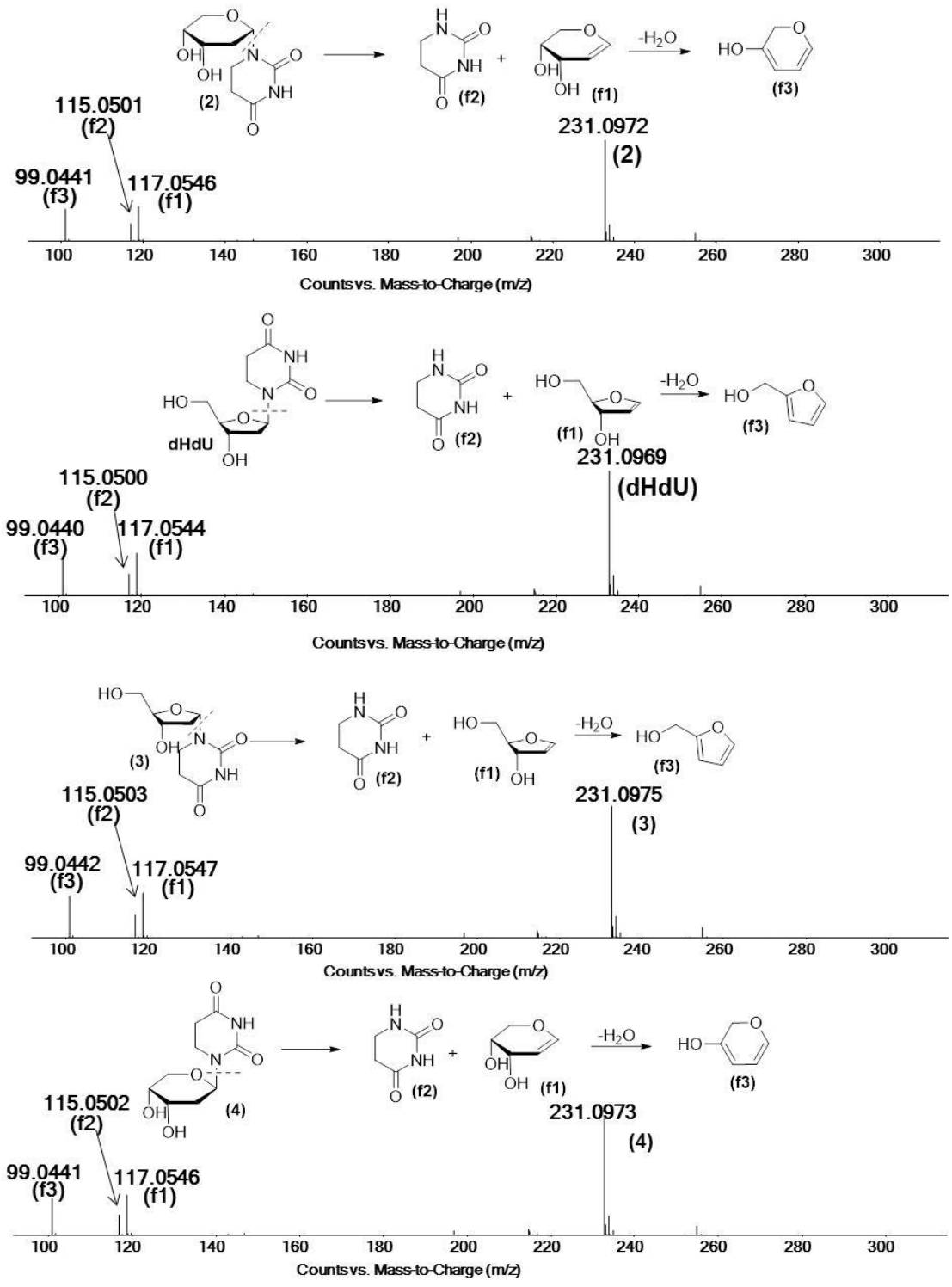


Figure S8. MS-MS spectra and the fragment structures of compounds **2**, **dHdU**, **3** and **4** under positive ion mode.

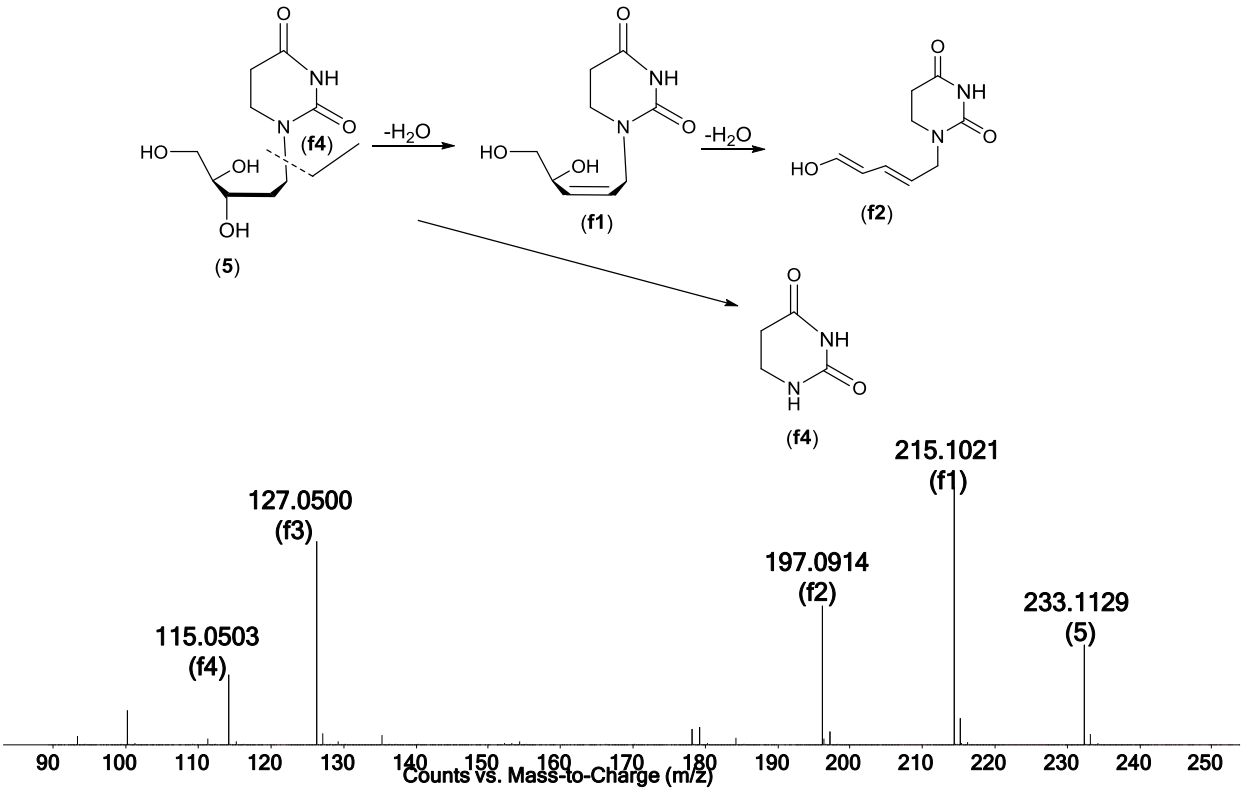


Figure S9. MS-MS spectrum and the fragment structures of compound **5** under positive ion mode.

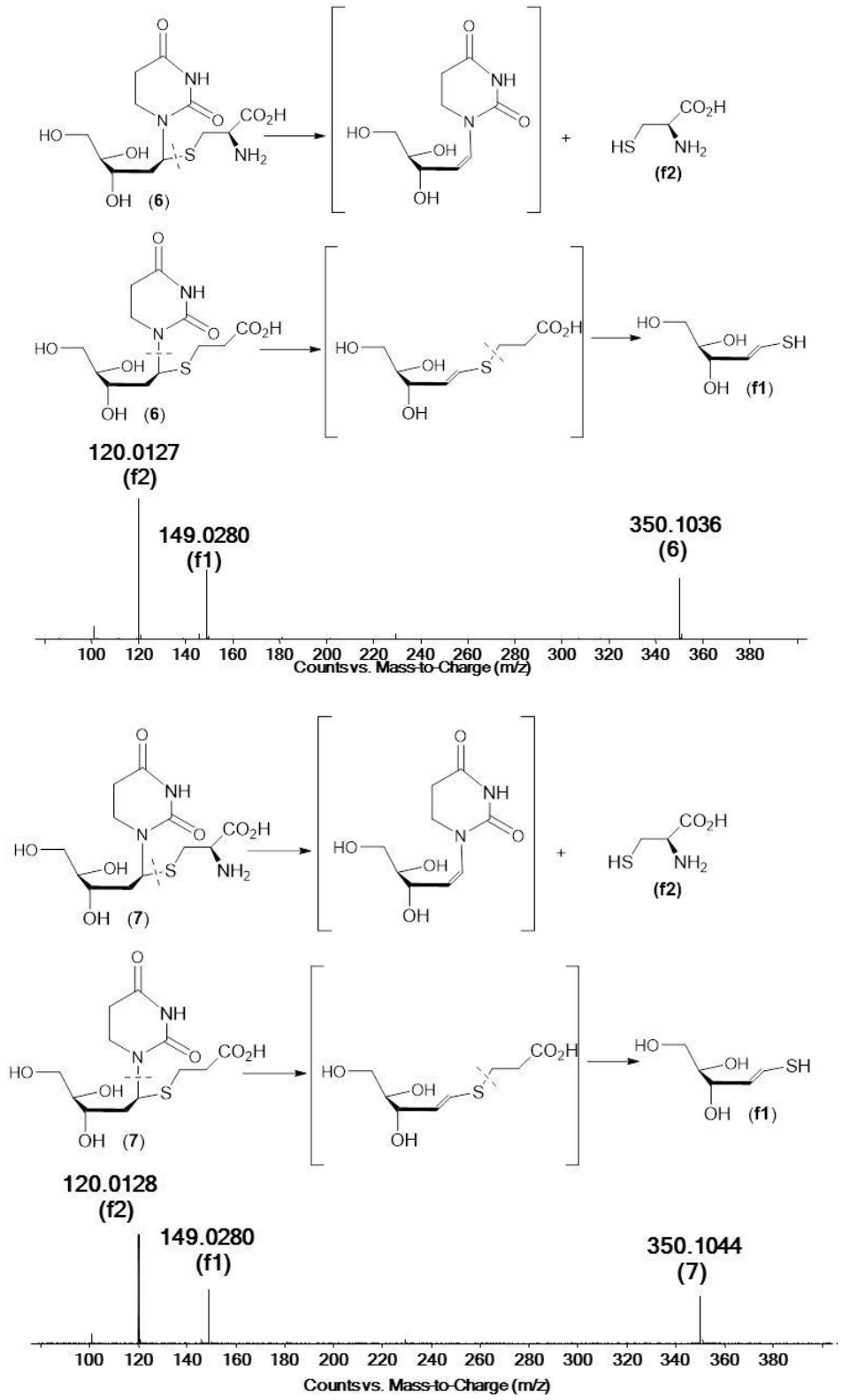


Figure S10. MS-MS spectrum and fragment structures of compounds **6** and **7** under negative ion mode.

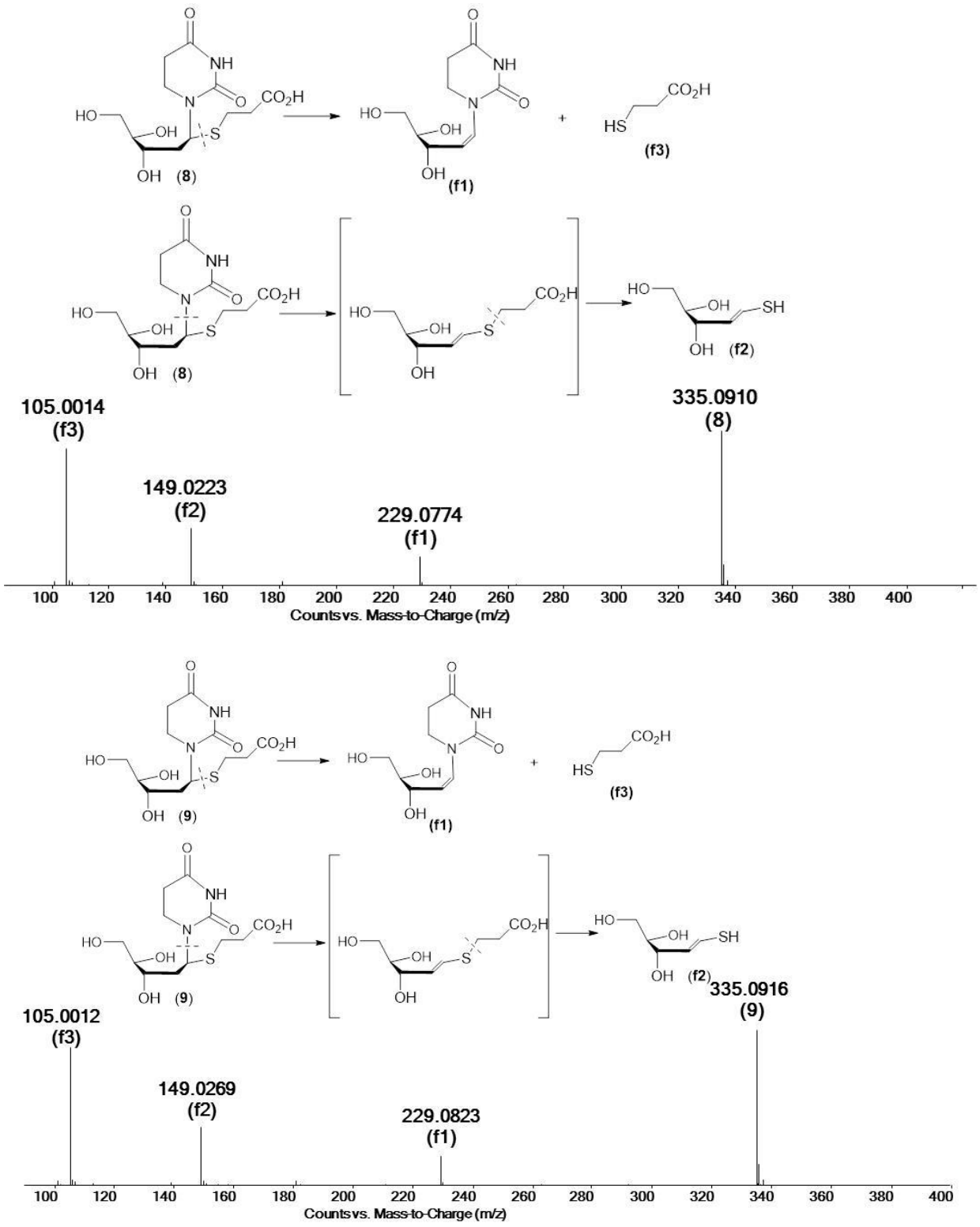


Figure S11. MS-MS spectrum and fragment structures of compounds **8** and **9** under negative ion mode.

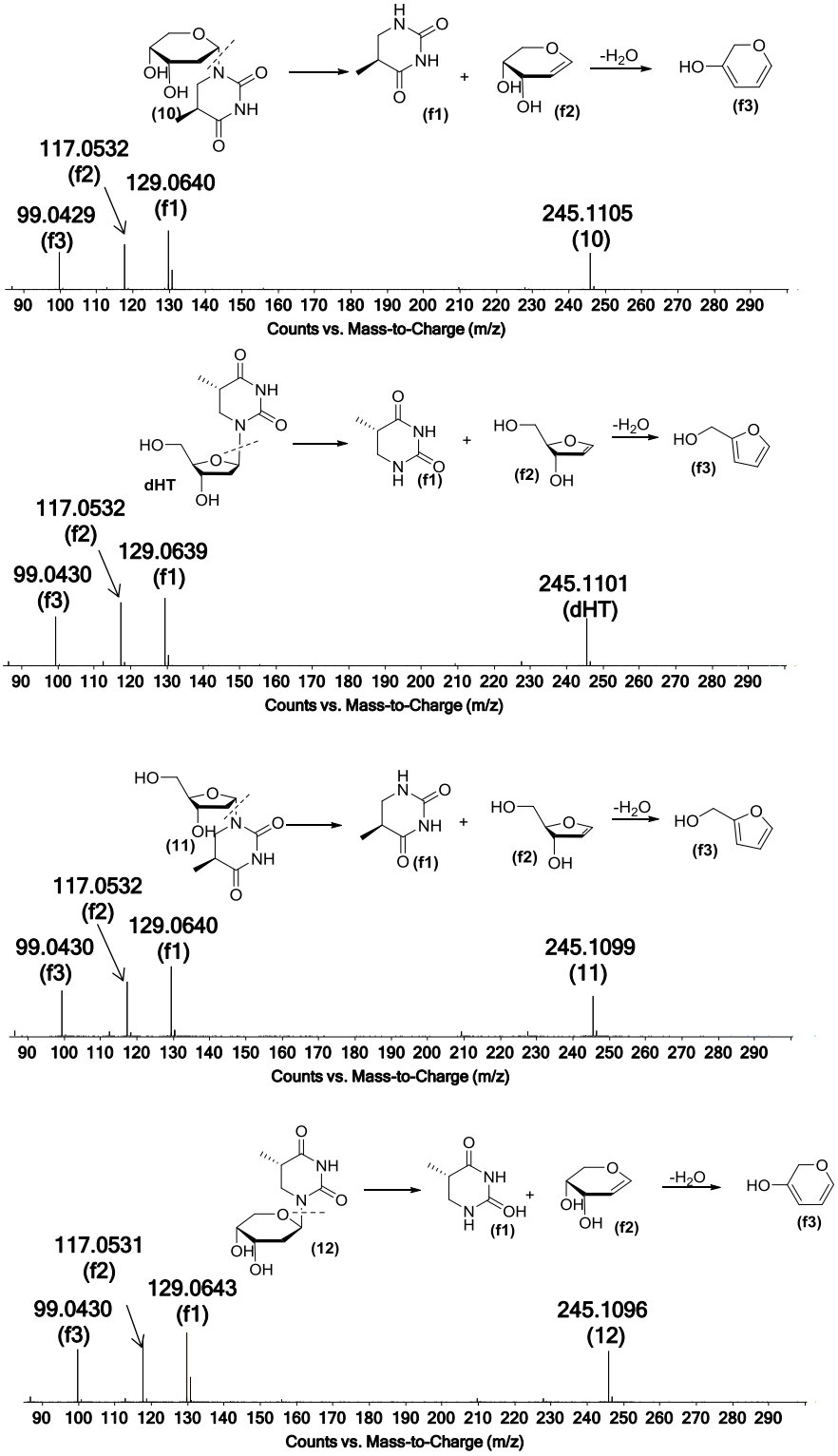


Figure S12. MS/MS spectrum and the fragment structures of dHT and its 3 isomers (formed under acidic conditions) under positive ion mode.

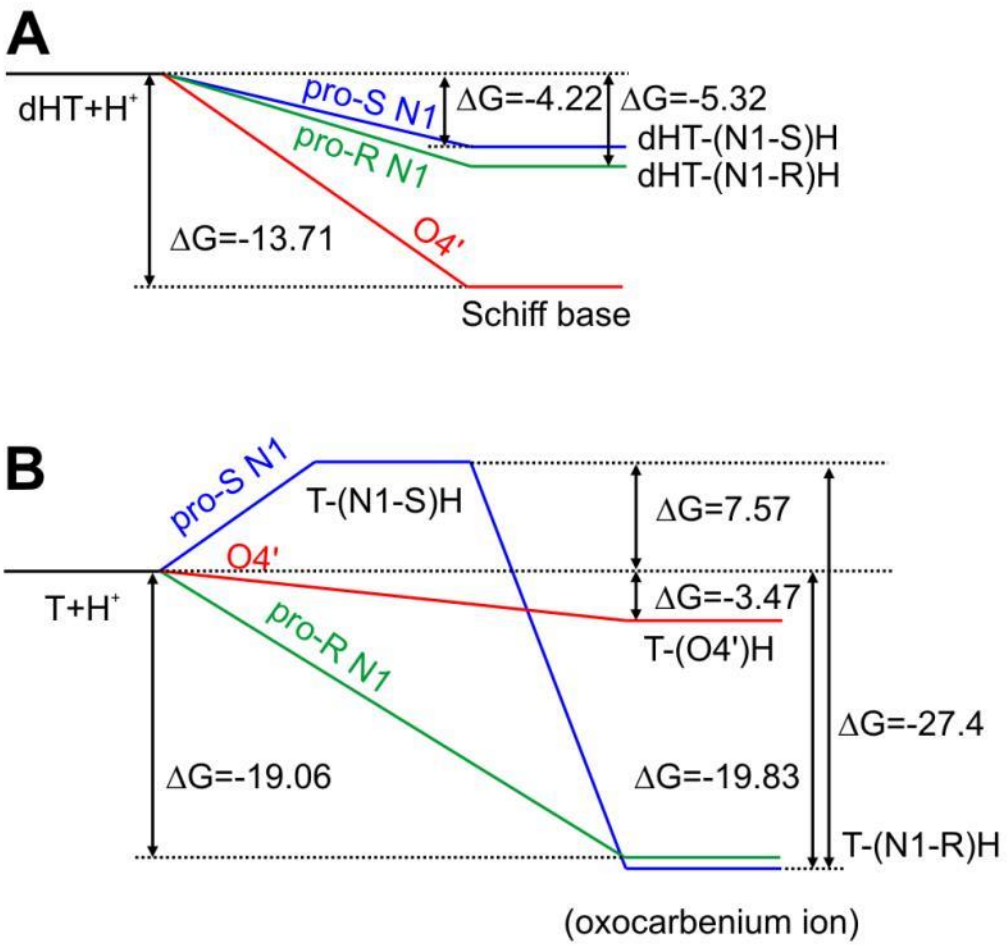


Figure S13. (A) Gibbs Free Energy changes (kcal/mol) for dHT protonation and decomposition. The N1 protonation may result in two putative species **(N1-*R*)H** and **(N1-*S*)H**, which are much higher in Gibbs Free Energy than the **(O4′)H,** suggesting that in dHT, protonation at O4′ is preferred. The **(O4′)H** re-arranges into a Schiff base species via a barrier-free decomposition during the structure optimization. (B) Gibbs Free Energy changes (kcal/mol) for T protonation and decomposition. The N1-*R* protonation is preferred, the resulting **(N1-*R*)H** is unstable, which decays into the oxocarbenium ion via a barrier-free transformation process. In contrast, the T-**(O4′)H** is much higher in Gibbs Free Energy, implying that T deglycosylation is mediated by the oxocarbenium ion pathway via **(N1-*R*)H.** The putative **(N1-*S*)H** intermediate however is found to be metastable as a local minimum on the potential energy surface. The **(N1-*S*)H** pathway however is considered to be irrelevant to the oxocarbenium ion formation because of the high Gibbs Free Energy barrier en route to **(N1-*S*)H**.

Table S1. Rate constants ($\times 10^{-9}$ s^{-1}) for the formations of **1**, **2**, **3**, and **4** in the dHdU isomerization reaction determined via HPLC integration. The respective rate constants at 37 °C and pH 7.4 were then deduced from the Arrhenius plots below.

Temperature	**1**	**2**	**3**	**4**
70	26.5	267	1.69×10^3	115
75	31.3	395	2.51×10^3	190
80	51.3	673	3.55×10^3	299
85	105	1.07×10^3	6.22×10^3	585
90	126	1.68×10^3	9.72×10^3	919
37	0.819	6.98	53.6	1.86

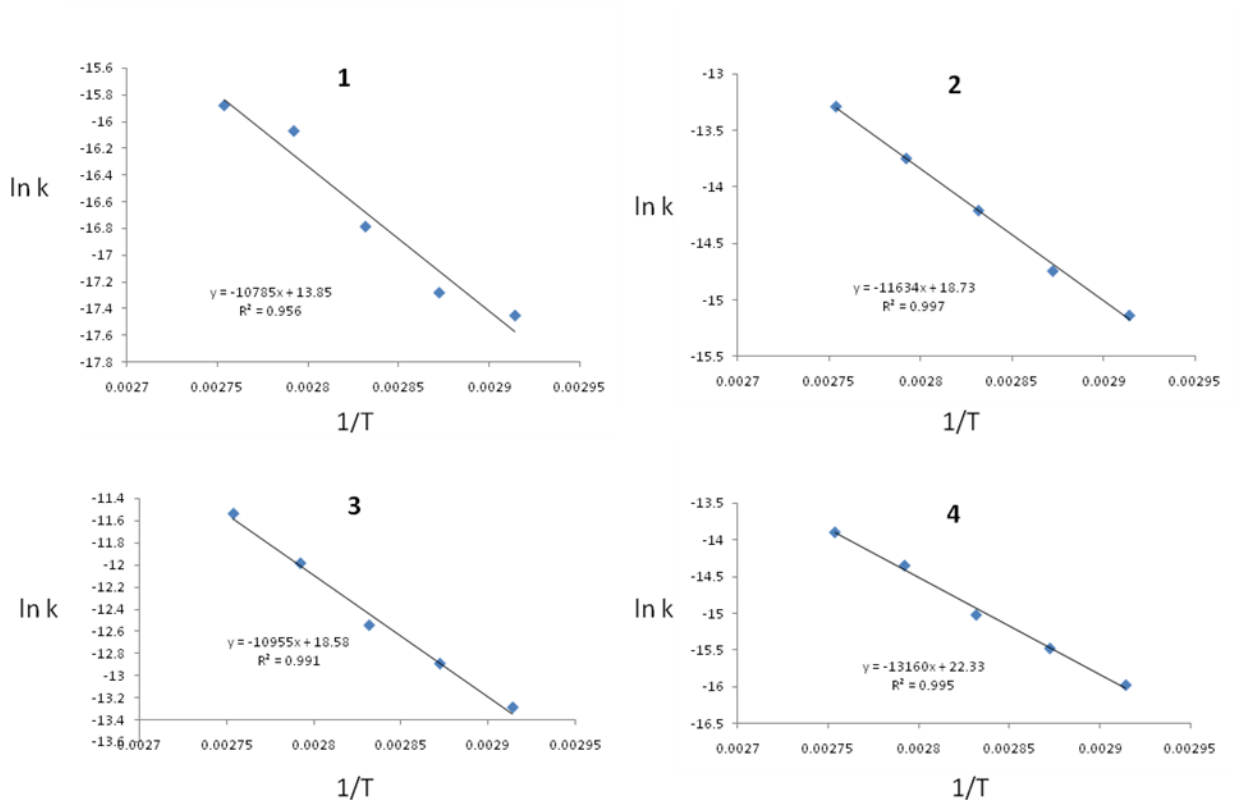


Figure S14. Arrhenius plots for the formations of **1**, **2**, **3**, and **4** in the dHdU isomerization reaction (lnk *vs* 1/T).

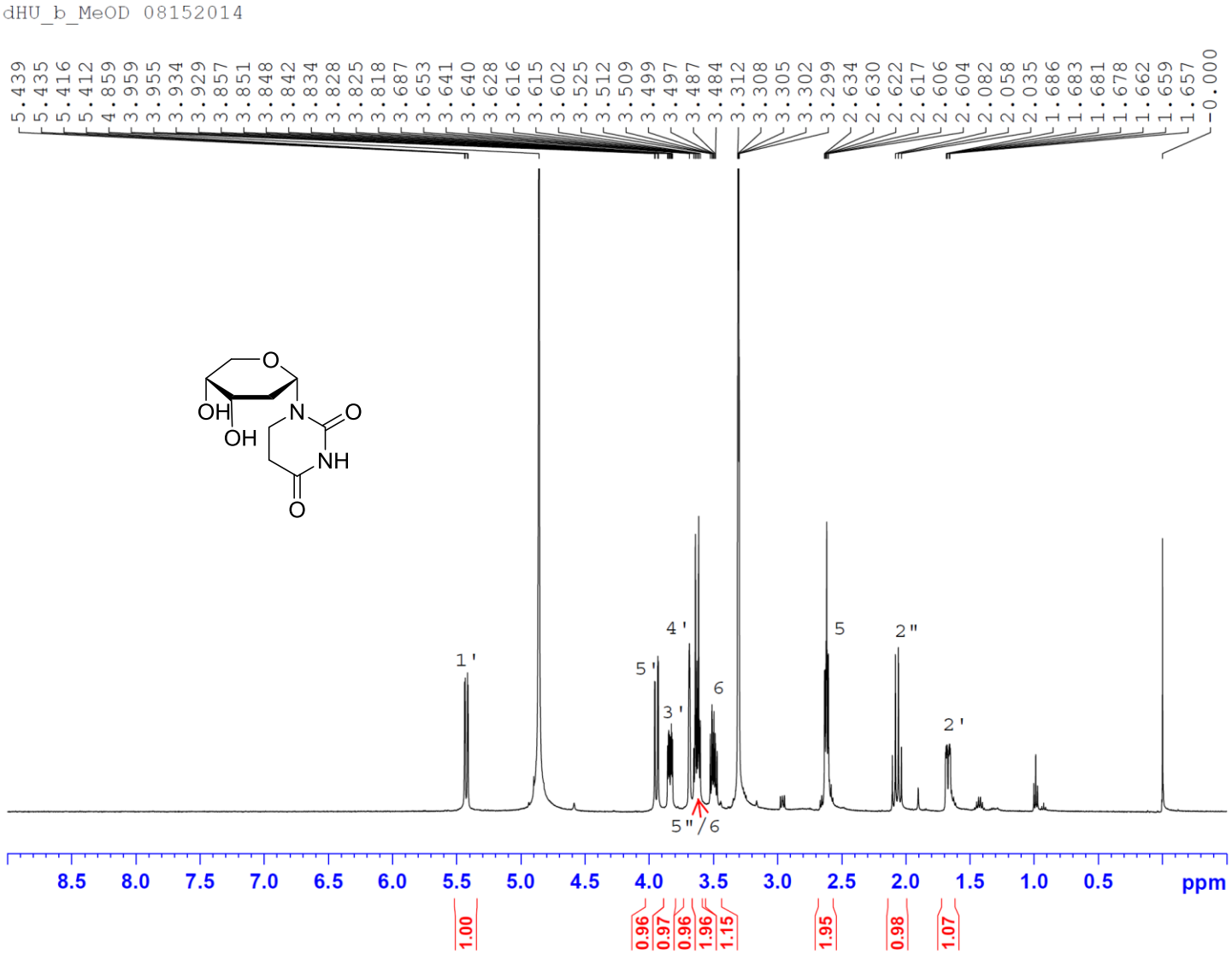


Figure S15. ^{1}H NMR spectrum of compound **2**.

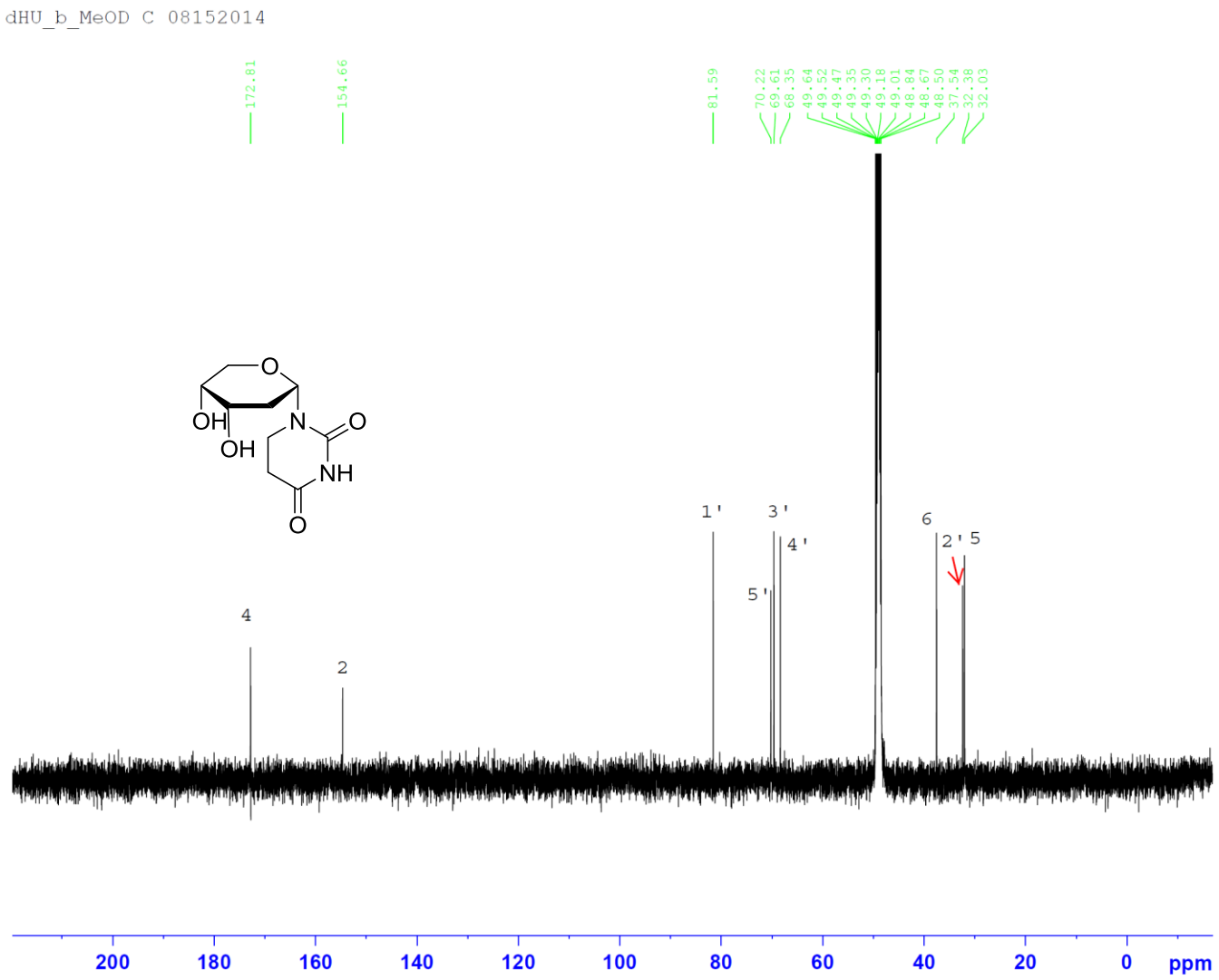


Figure S16. ^{13}C NMR spectrum of compound **2**.

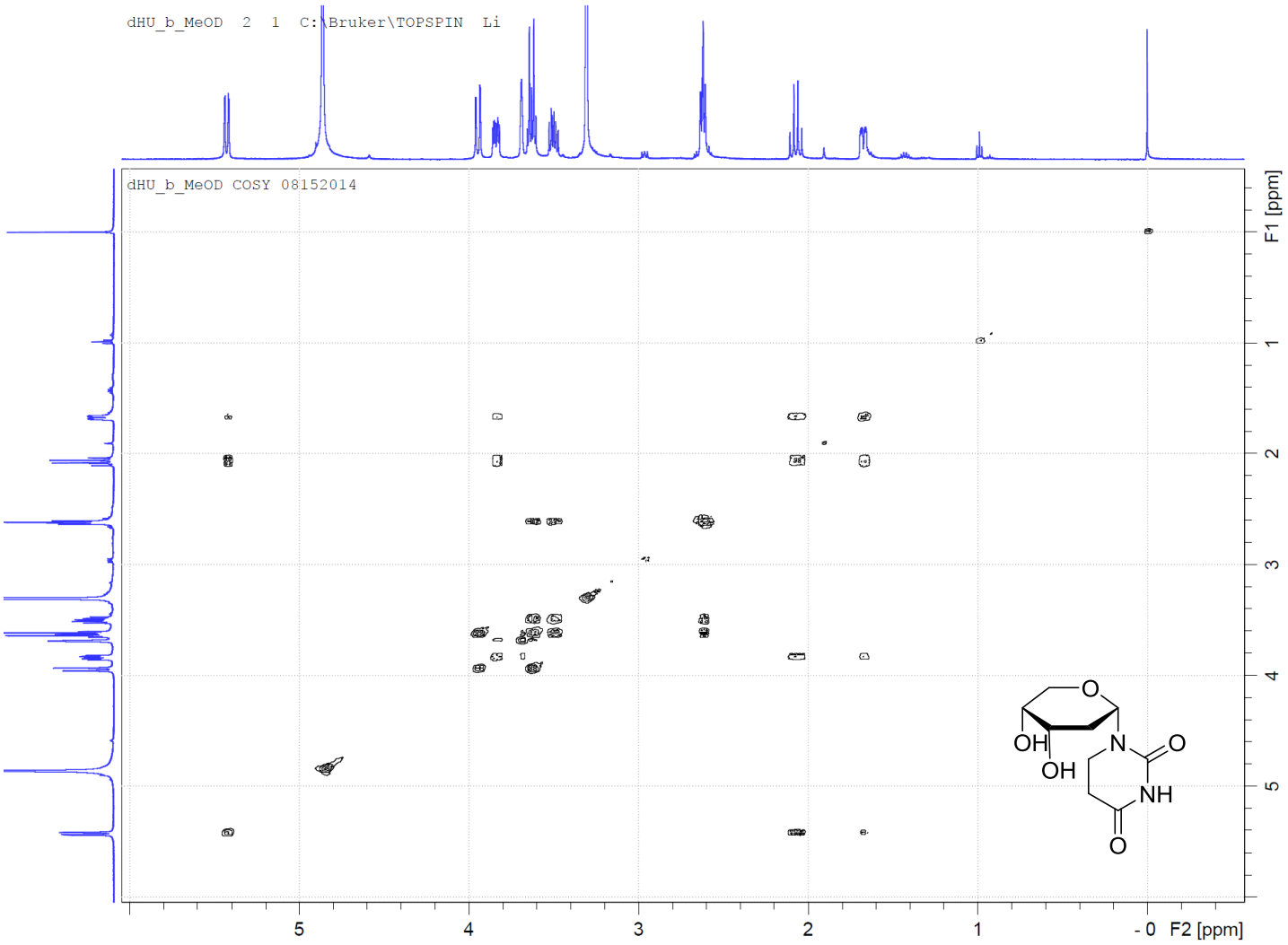


Figure S17. COSY spectrum of compound **2**.

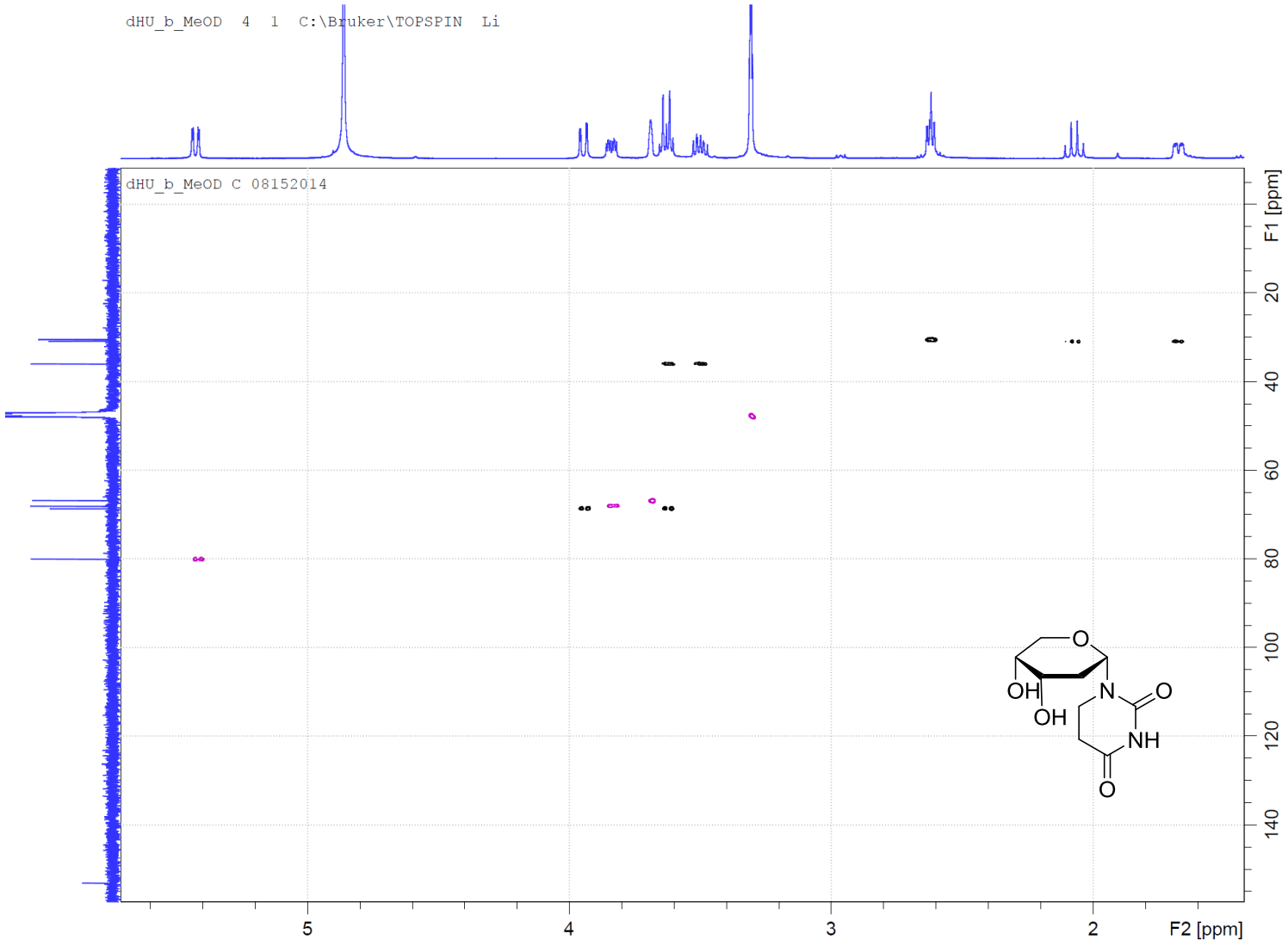


Figure S18. HSQC spectrum of compound **2**.

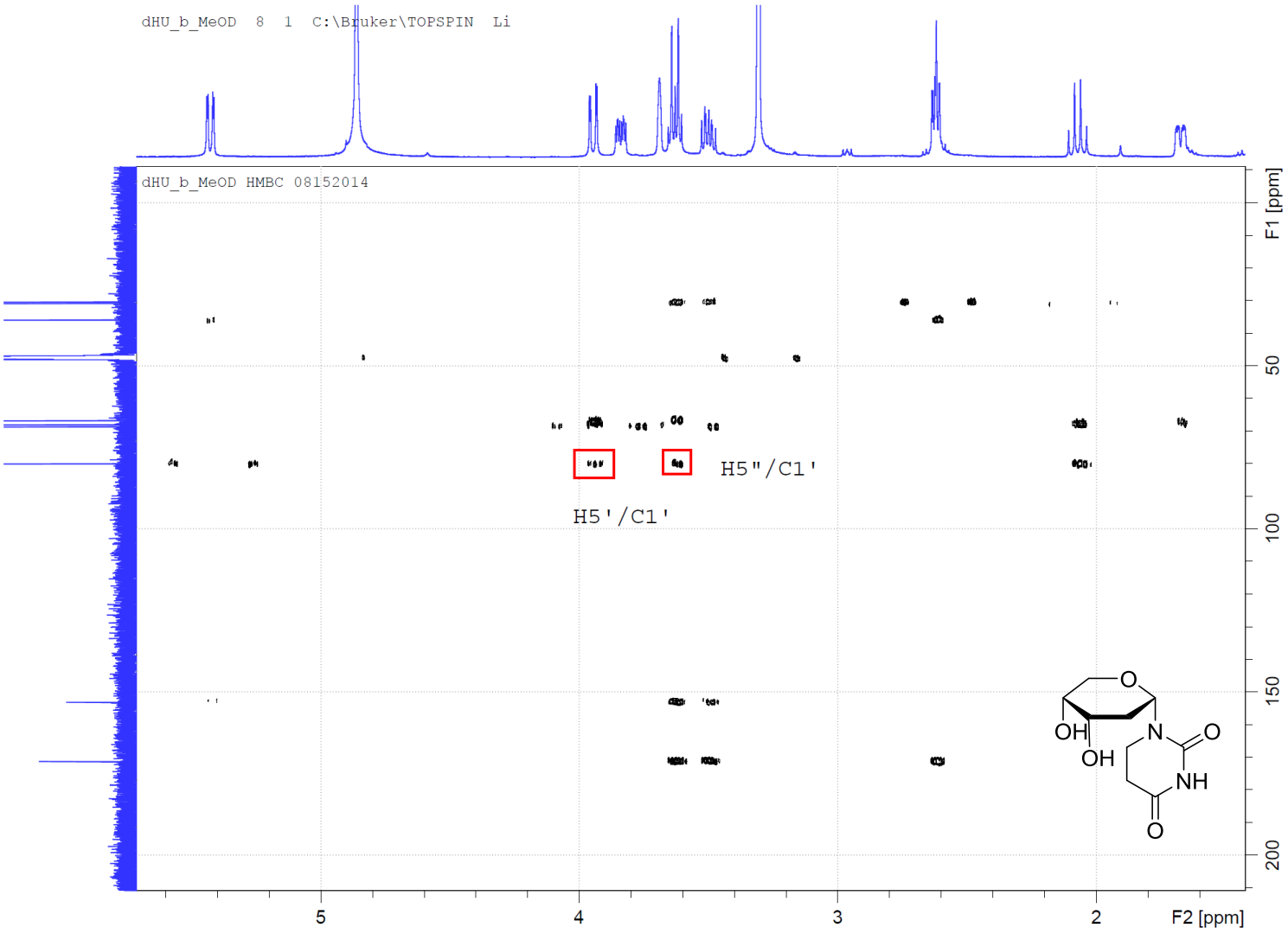


Figure S19. HMBC spectrum of compound **2**.

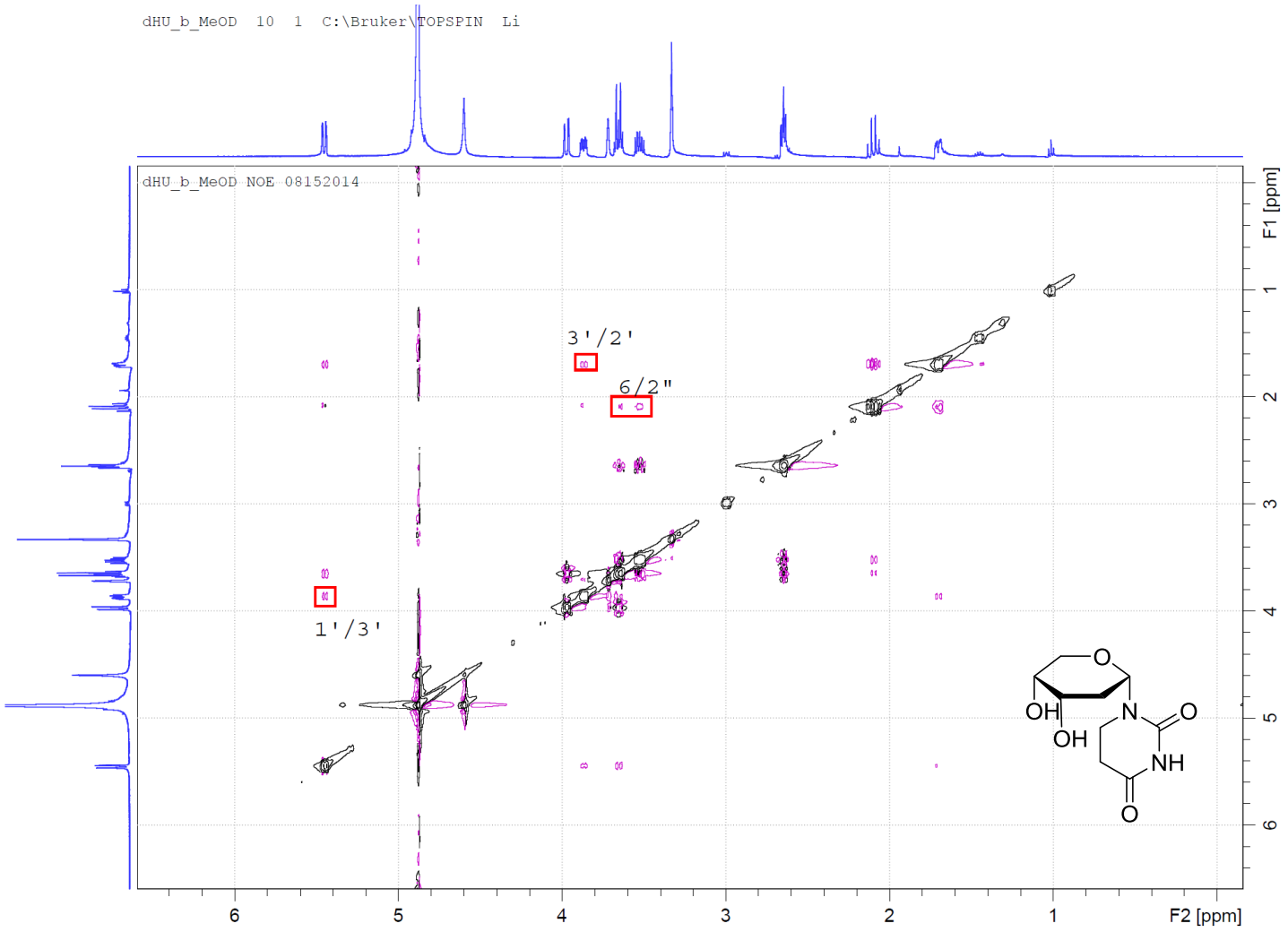


Figure S20. NOE spectrum of compound **2**.

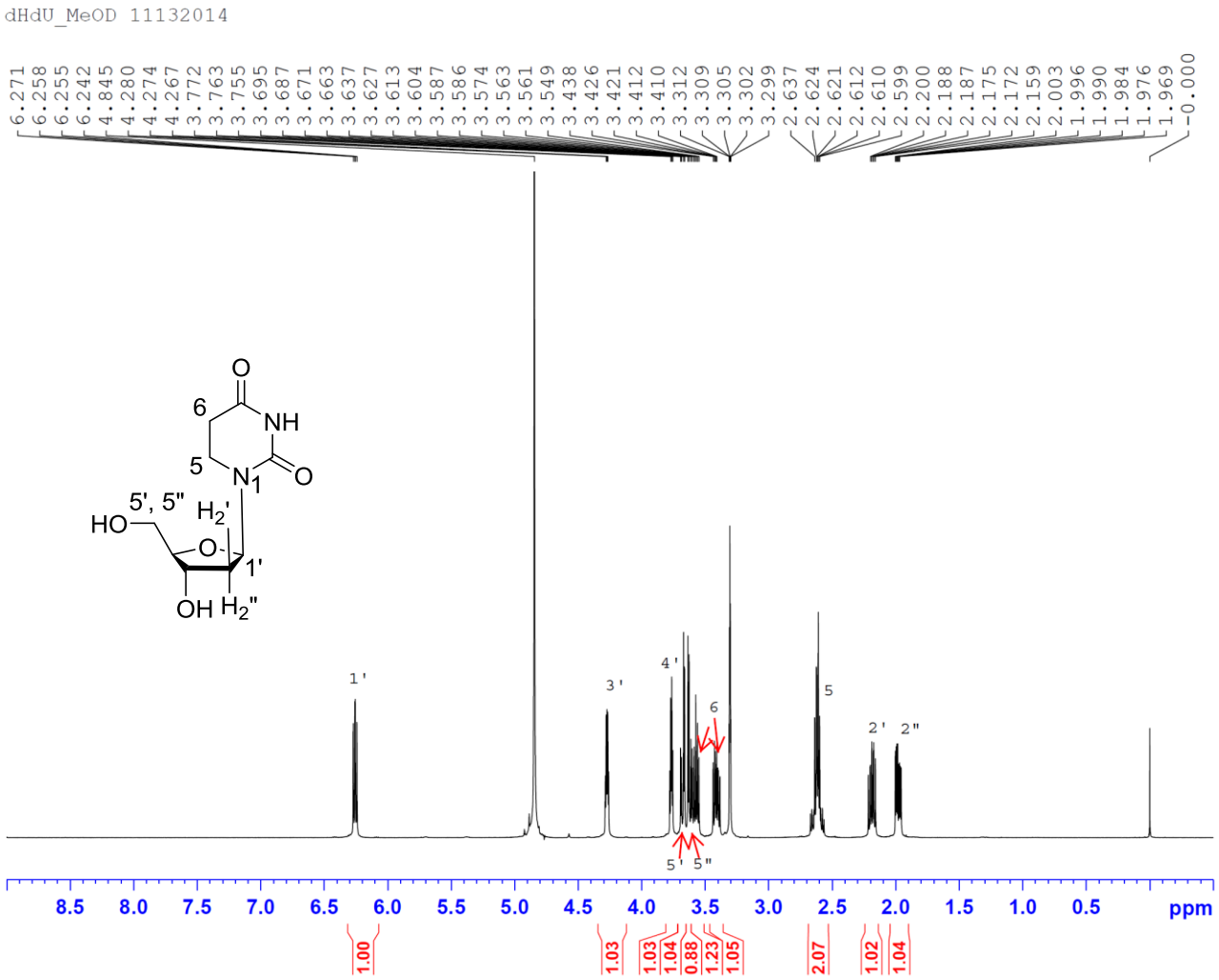


Figure S21. ^{1}H NMR spectrum of **dHdU**.

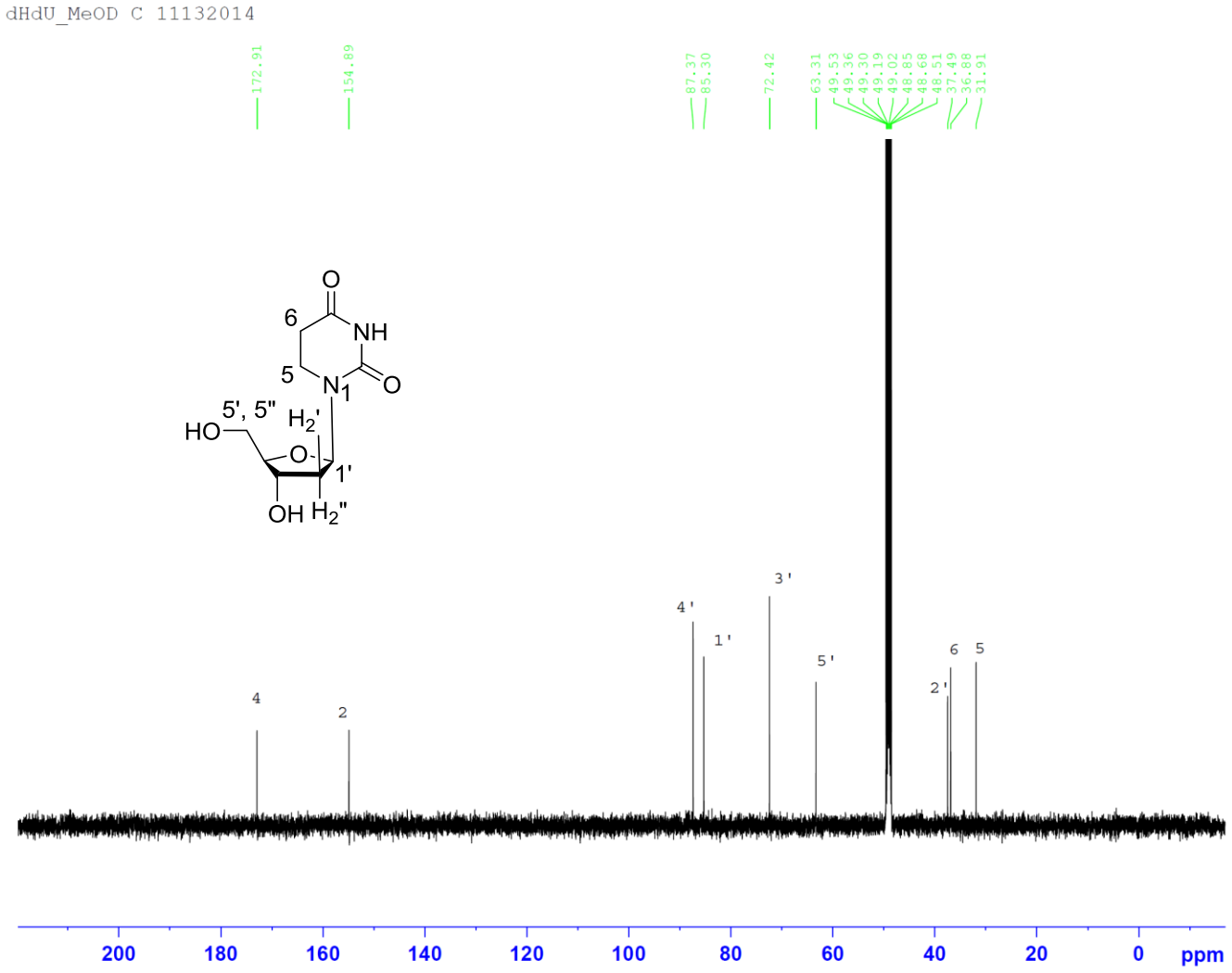


Figure S22. ^{13}C NMR spectrum of **dHdU**.

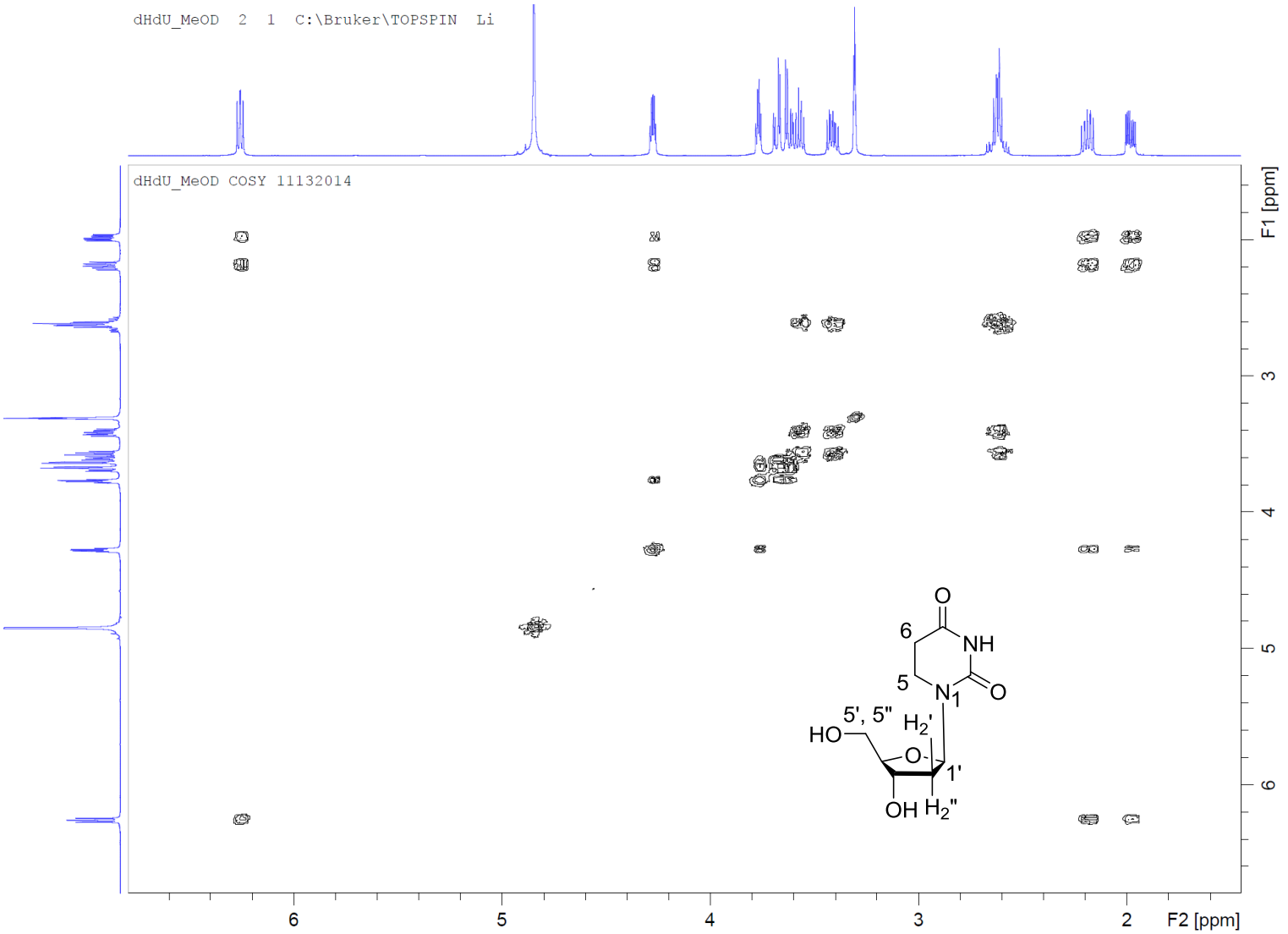


Figure S23. COSY spectrum of **dHdU**.

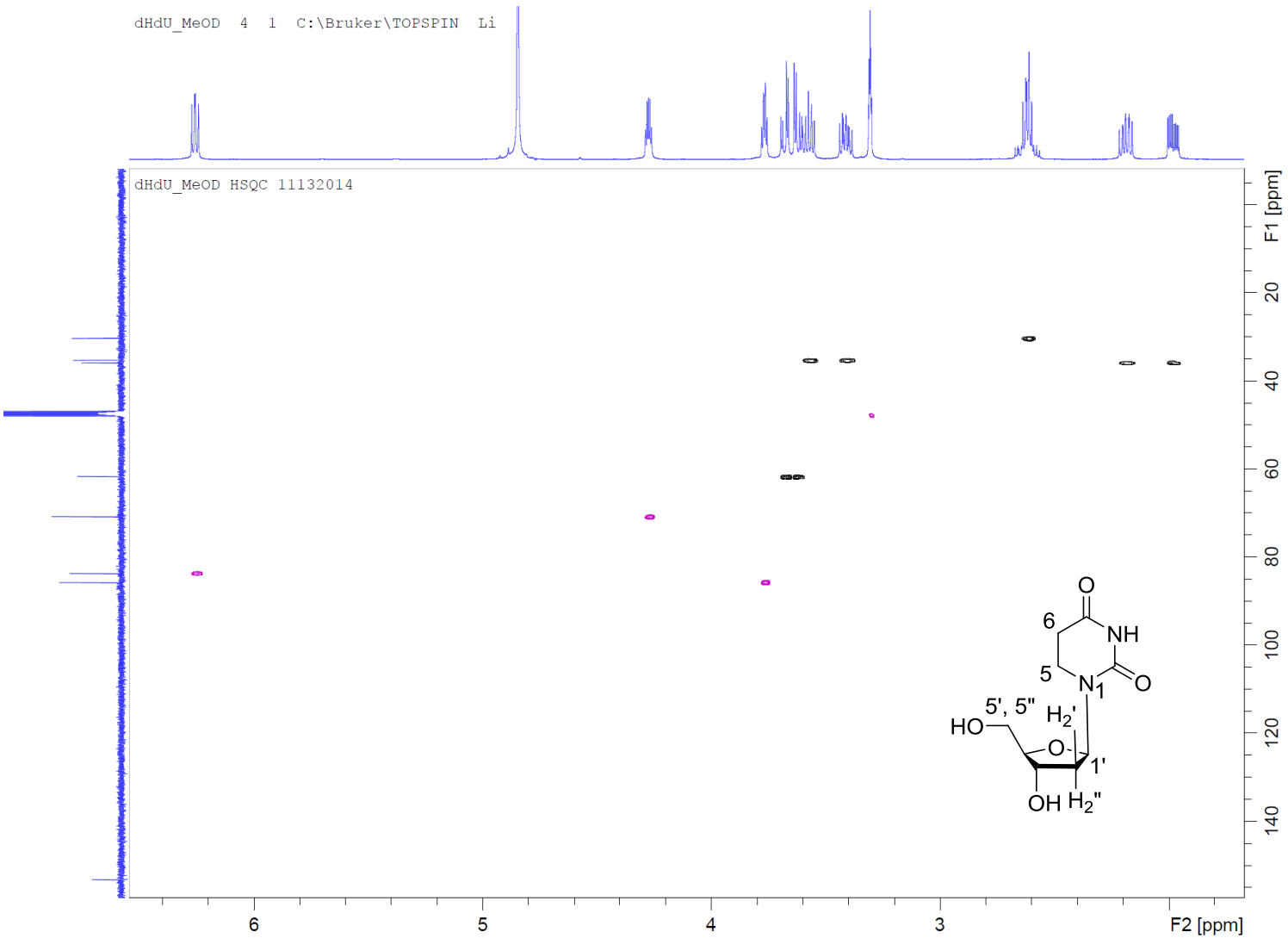


Figure S24. HSQC spectrum of **dHdU**.

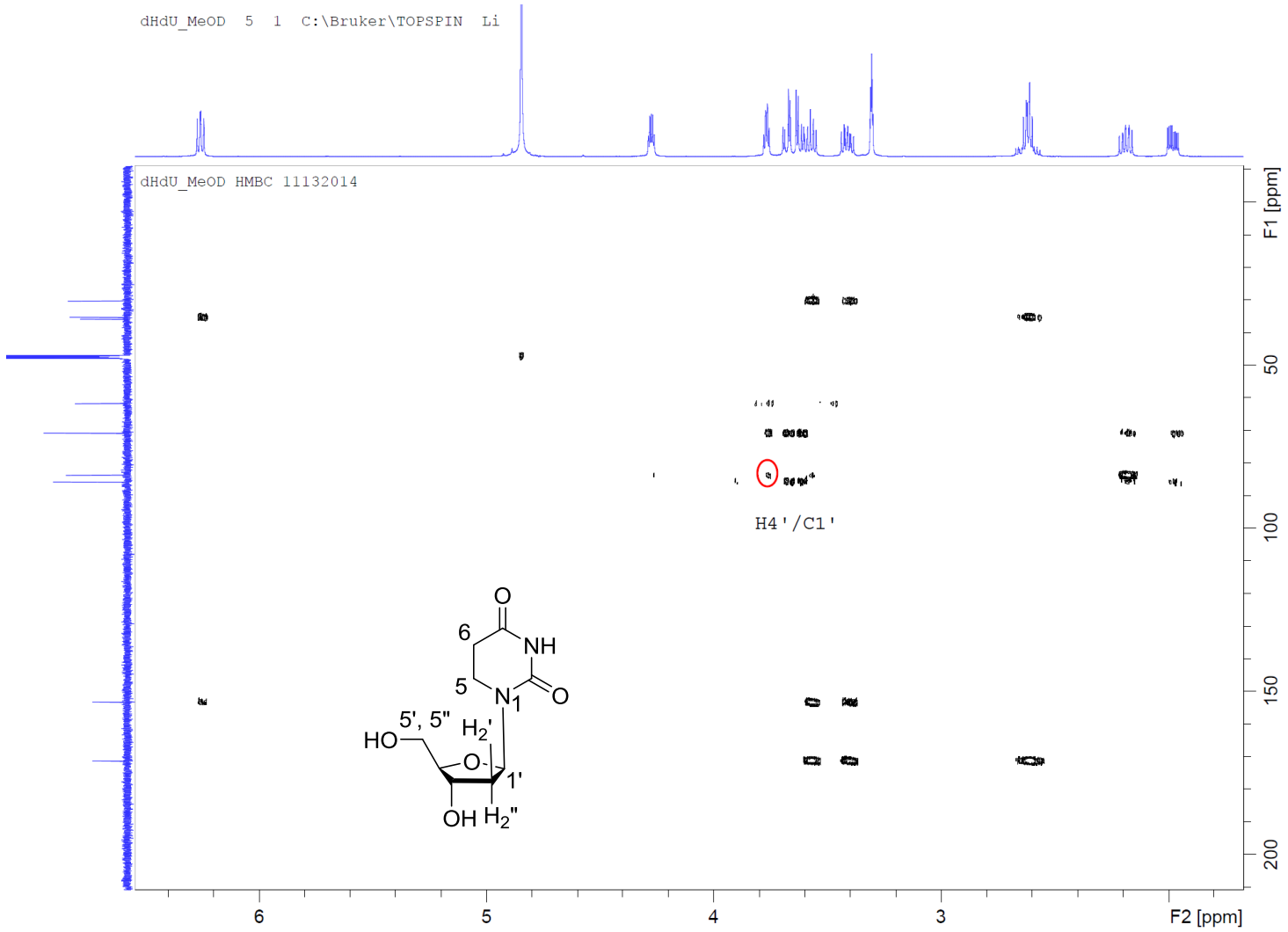


Figure S25. HMBC spectrum of **dHdU.**

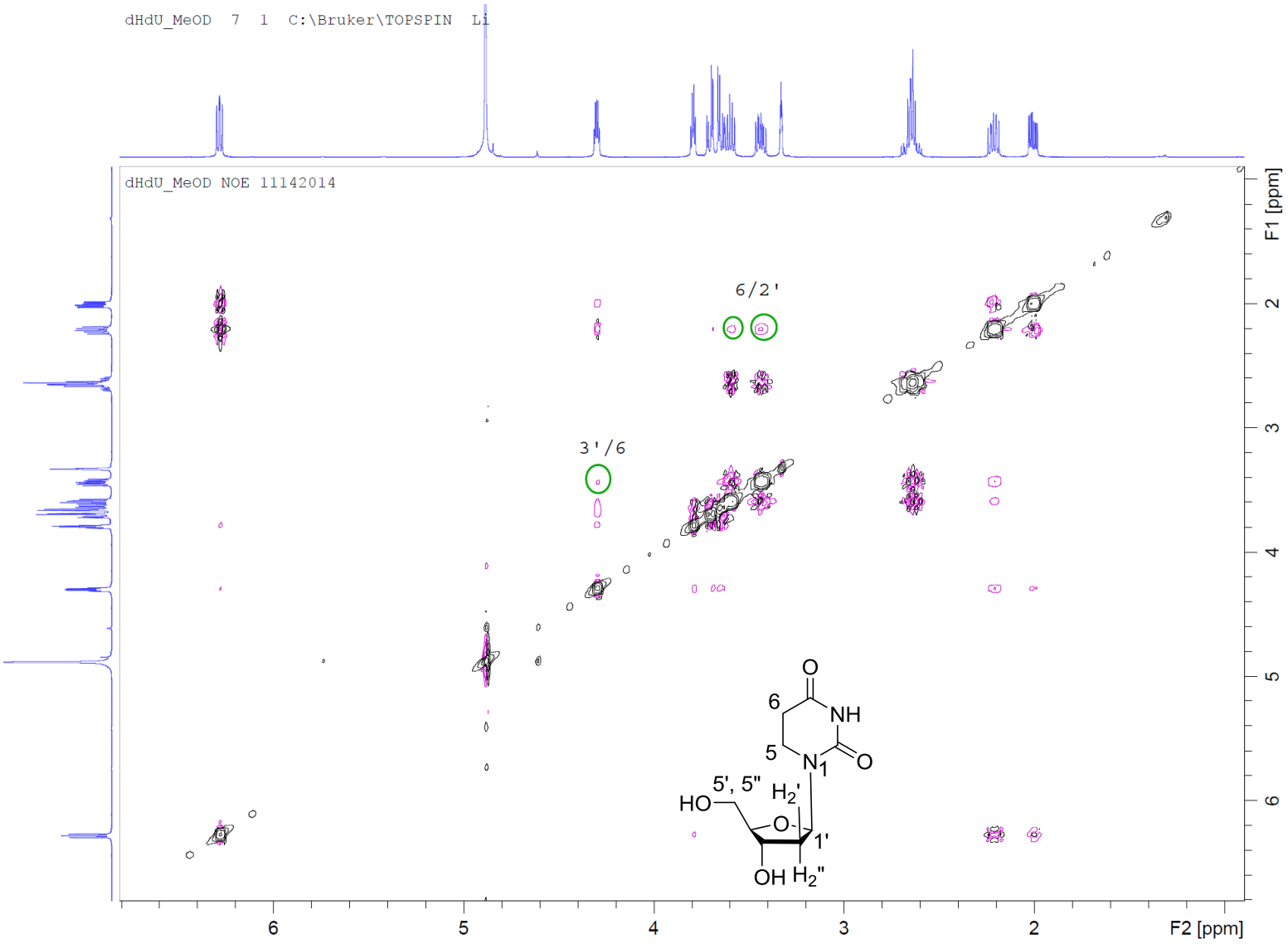


Figure S26. NOESY spectrum of **dHdU.**

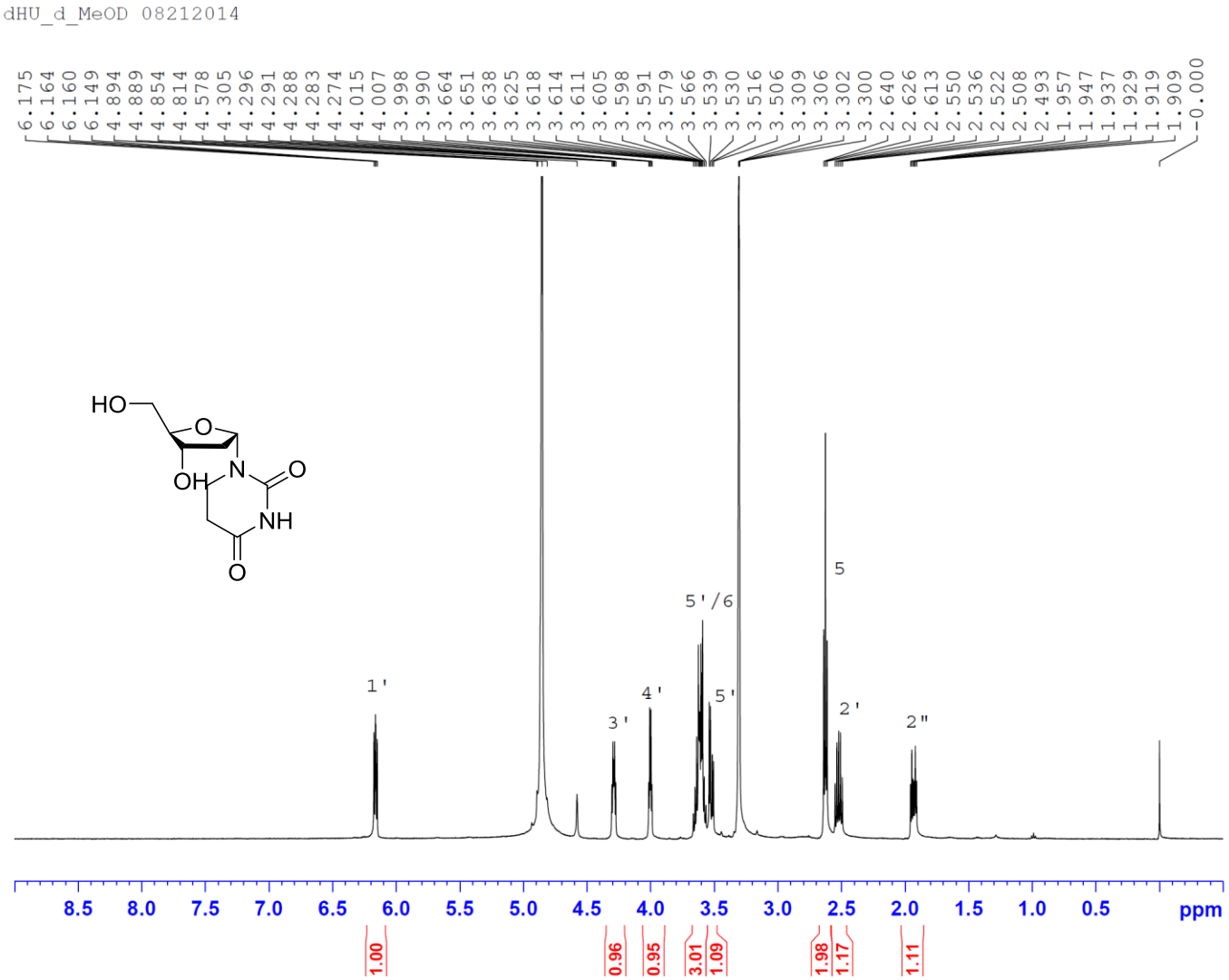


Figure S27. ^{1}H NMR spectrum of compound **3**.

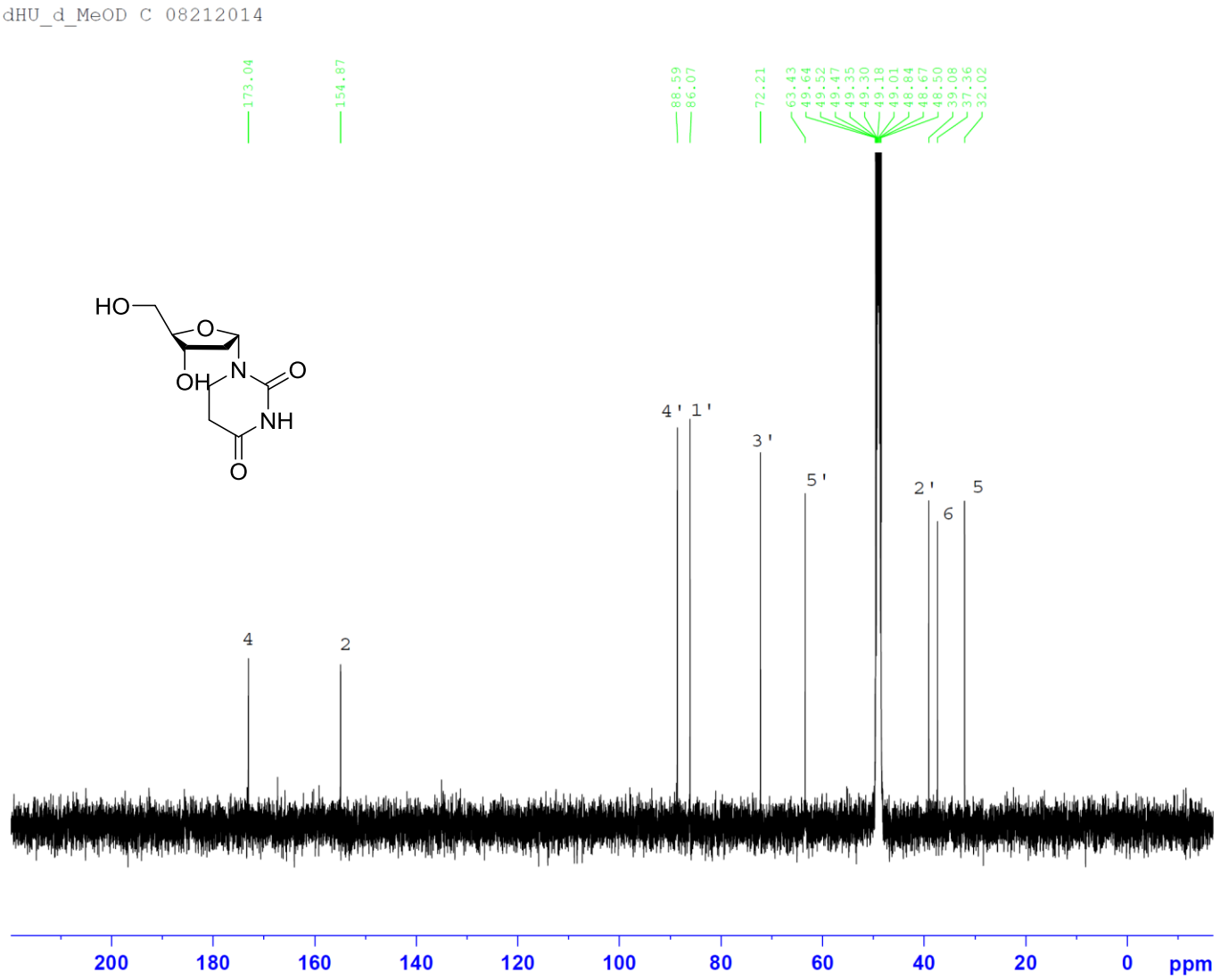


Figure S28. ^{13}C NMR spectrum of compound **3**.

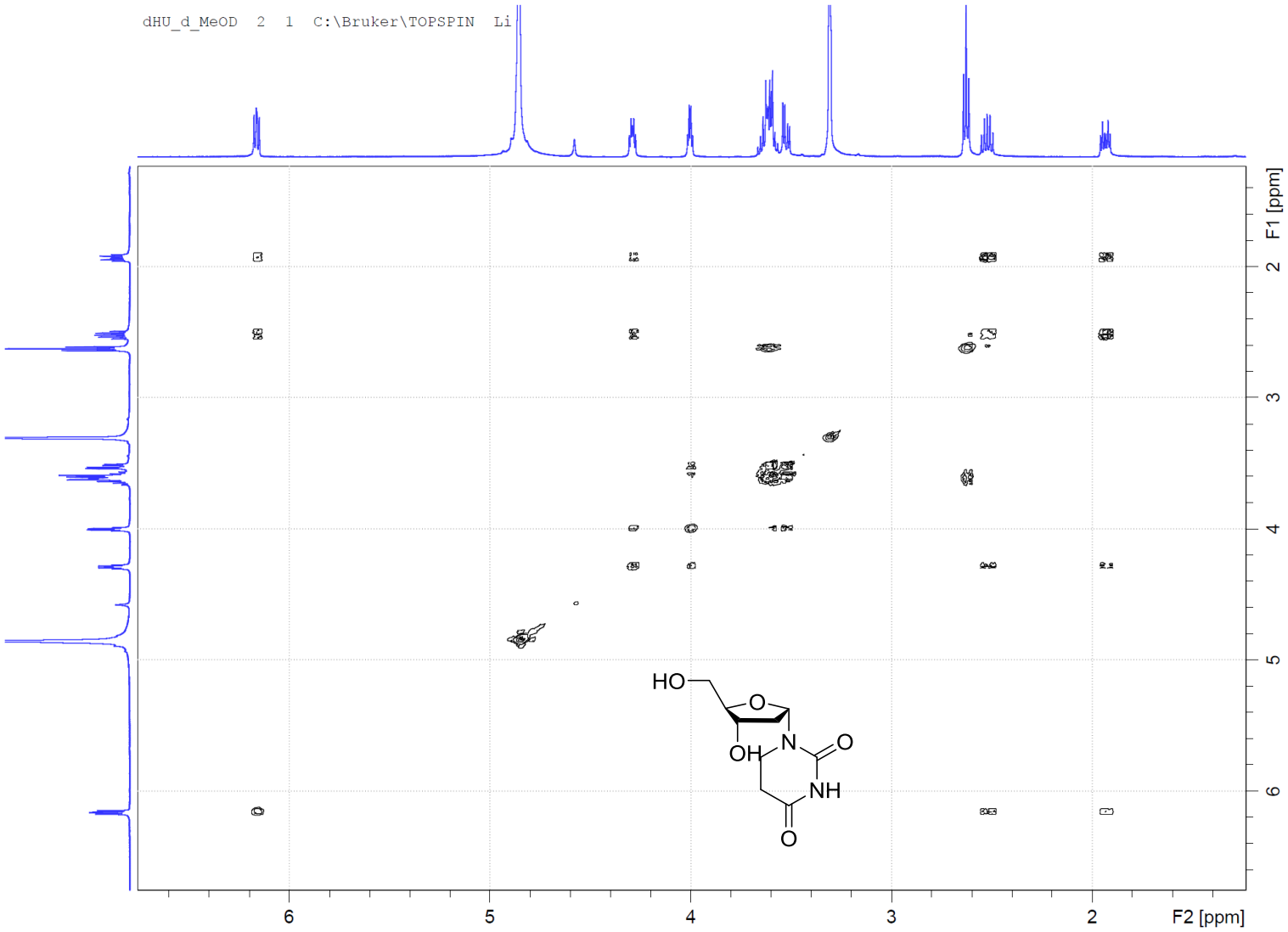


Figure S29. COSY spectrum of compound **3**.

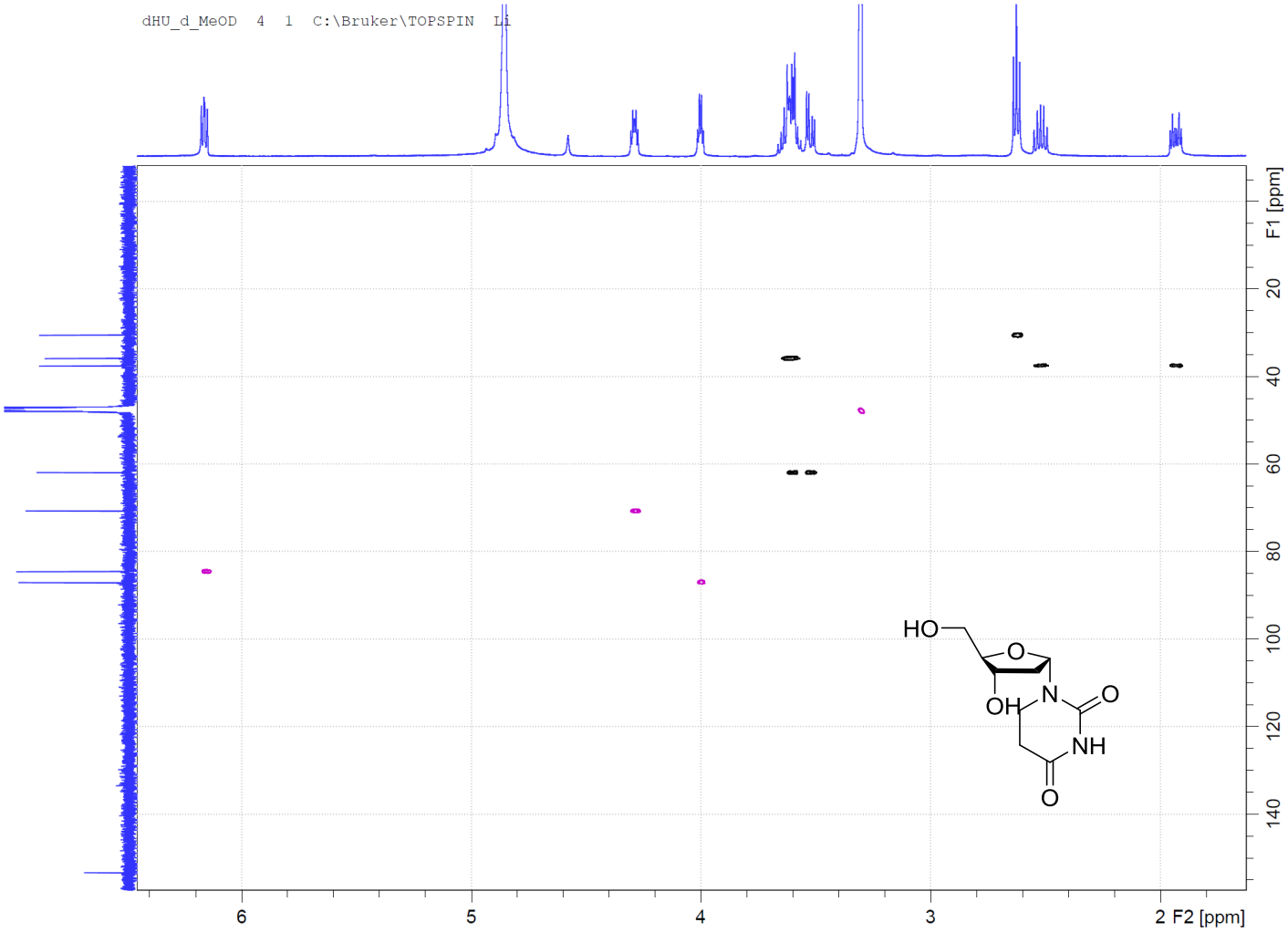


Figure S30. HSQC spectrum of compound **3**.

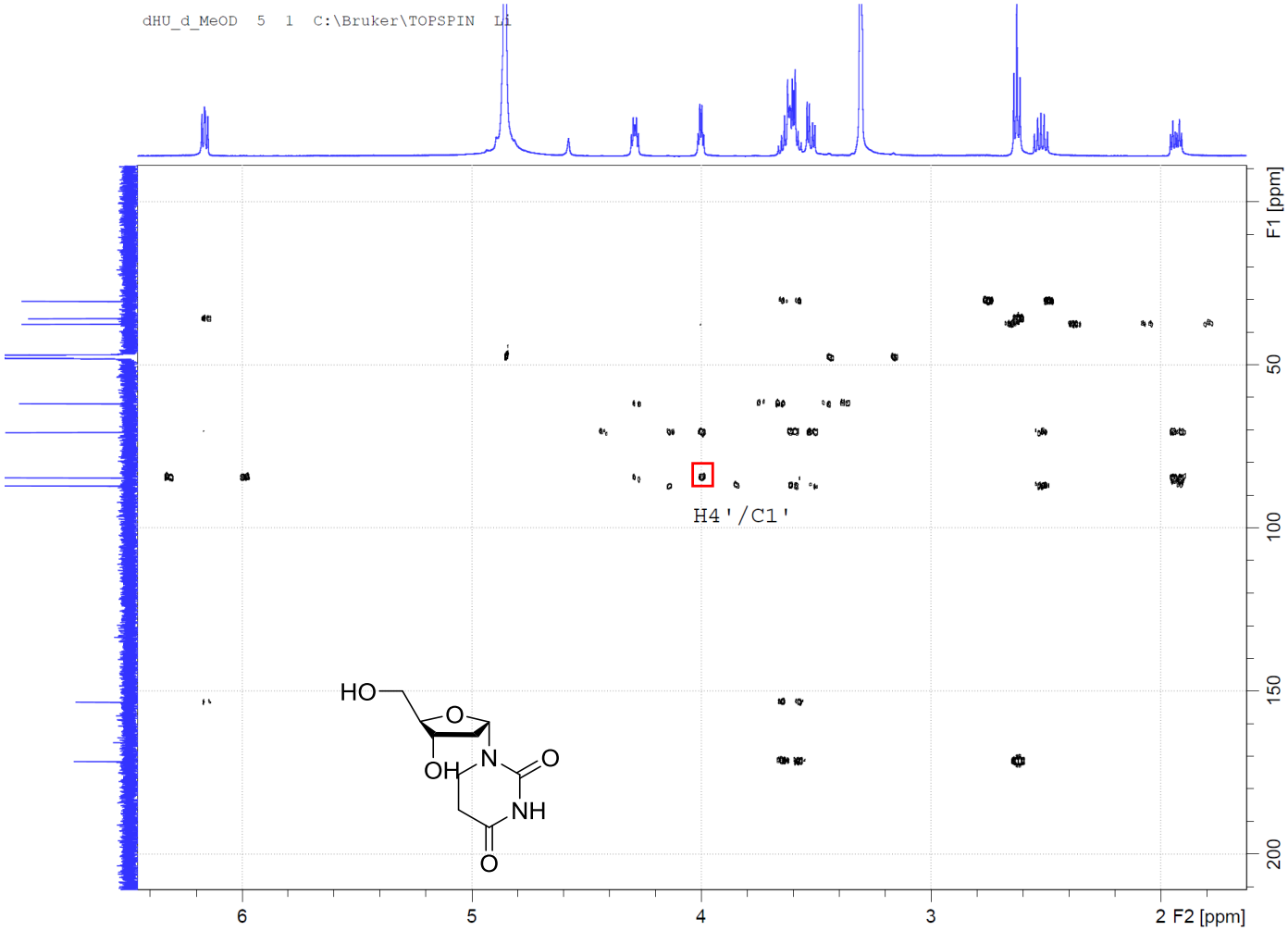


Figure S31. HMBC spectrum of compound **3**.

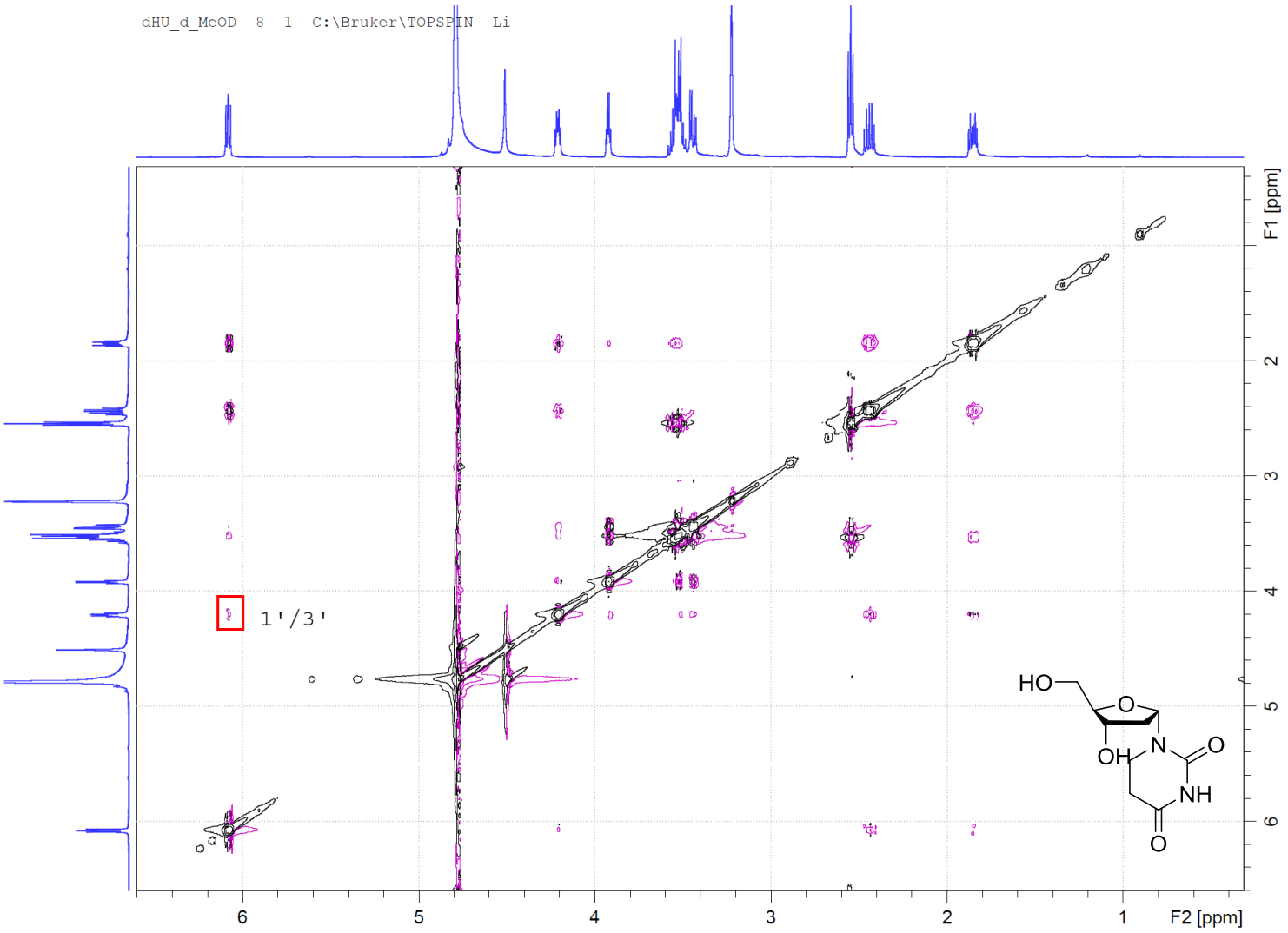


Figure S32. NOESY spectrum of compound **3.**

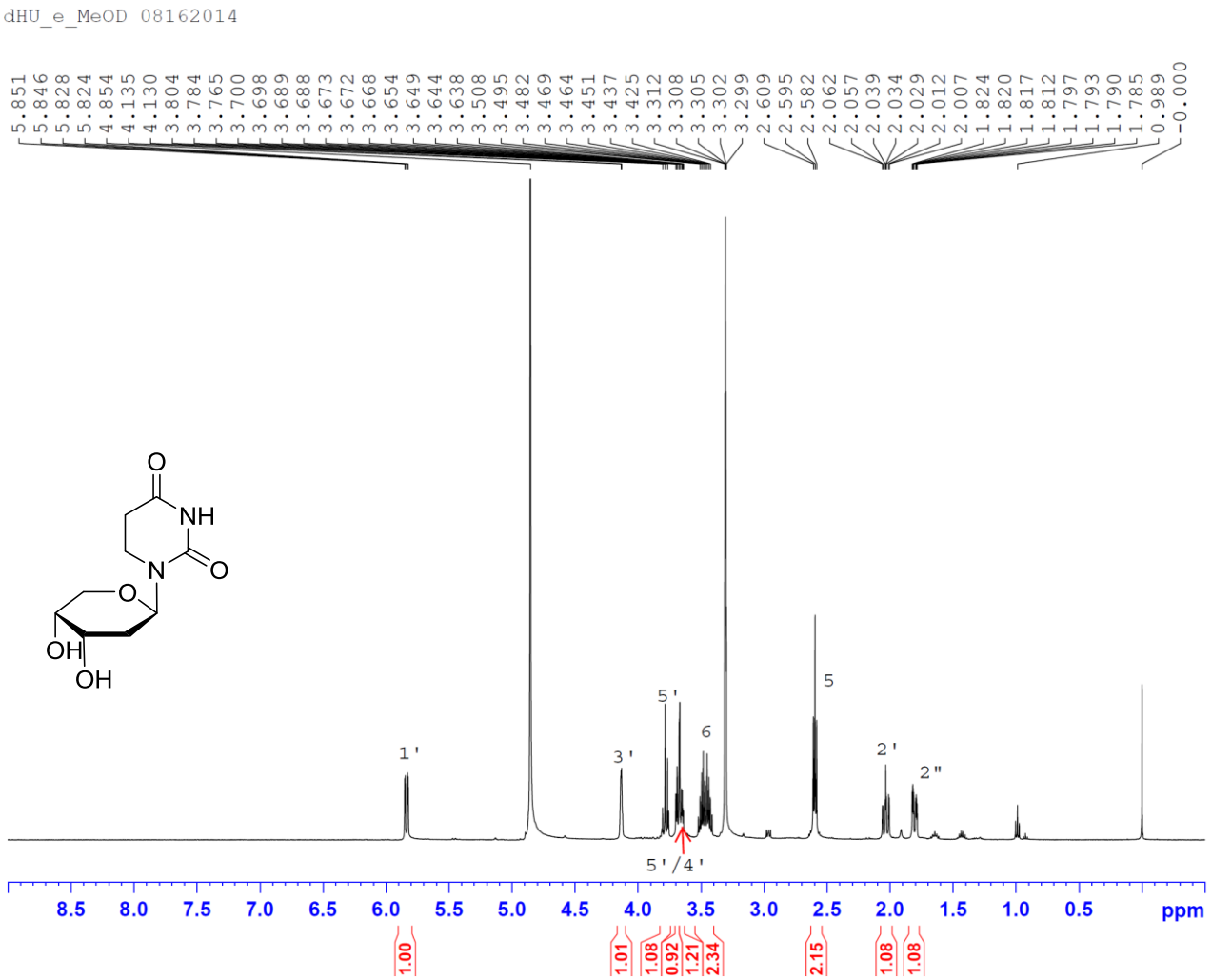


Figure S33. ^{1}H NMR spectrum of compound **4**.

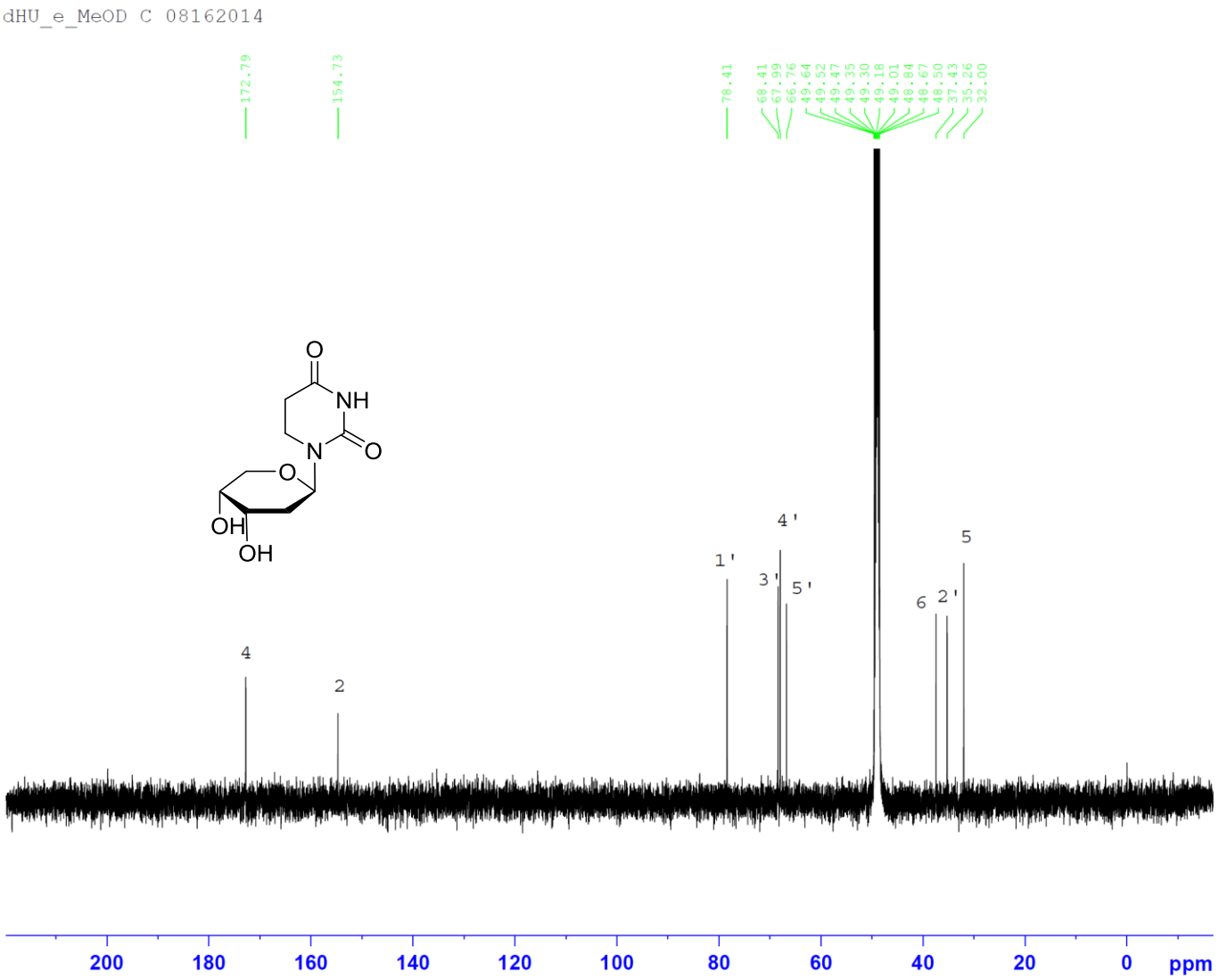


Figure S34. ^{13}C NMR spectrum of compound **4**.

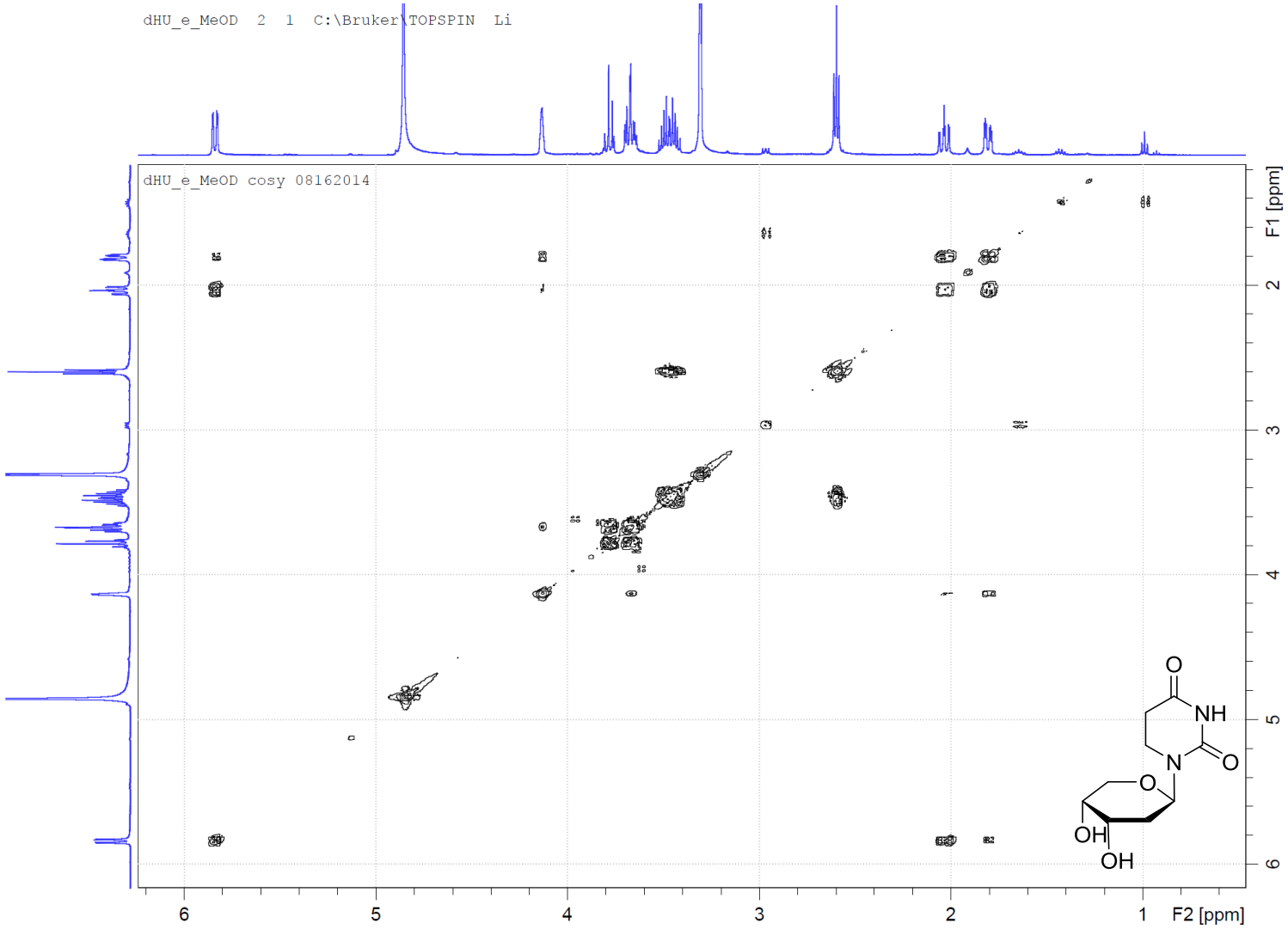


Figure S35. COSY spectrum of compound **4**.

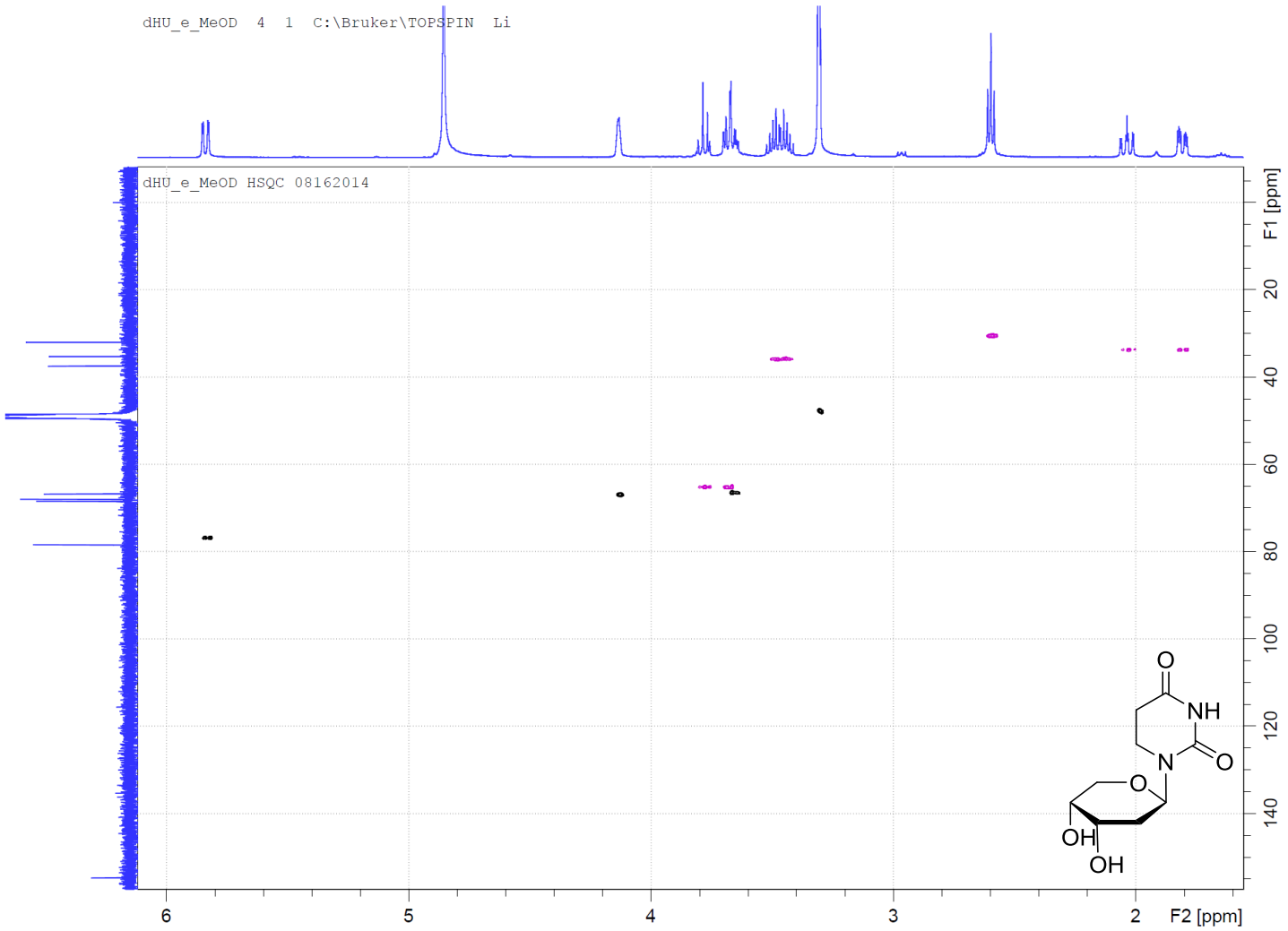


Figure S36. HSQC spectrum of compound **4**.

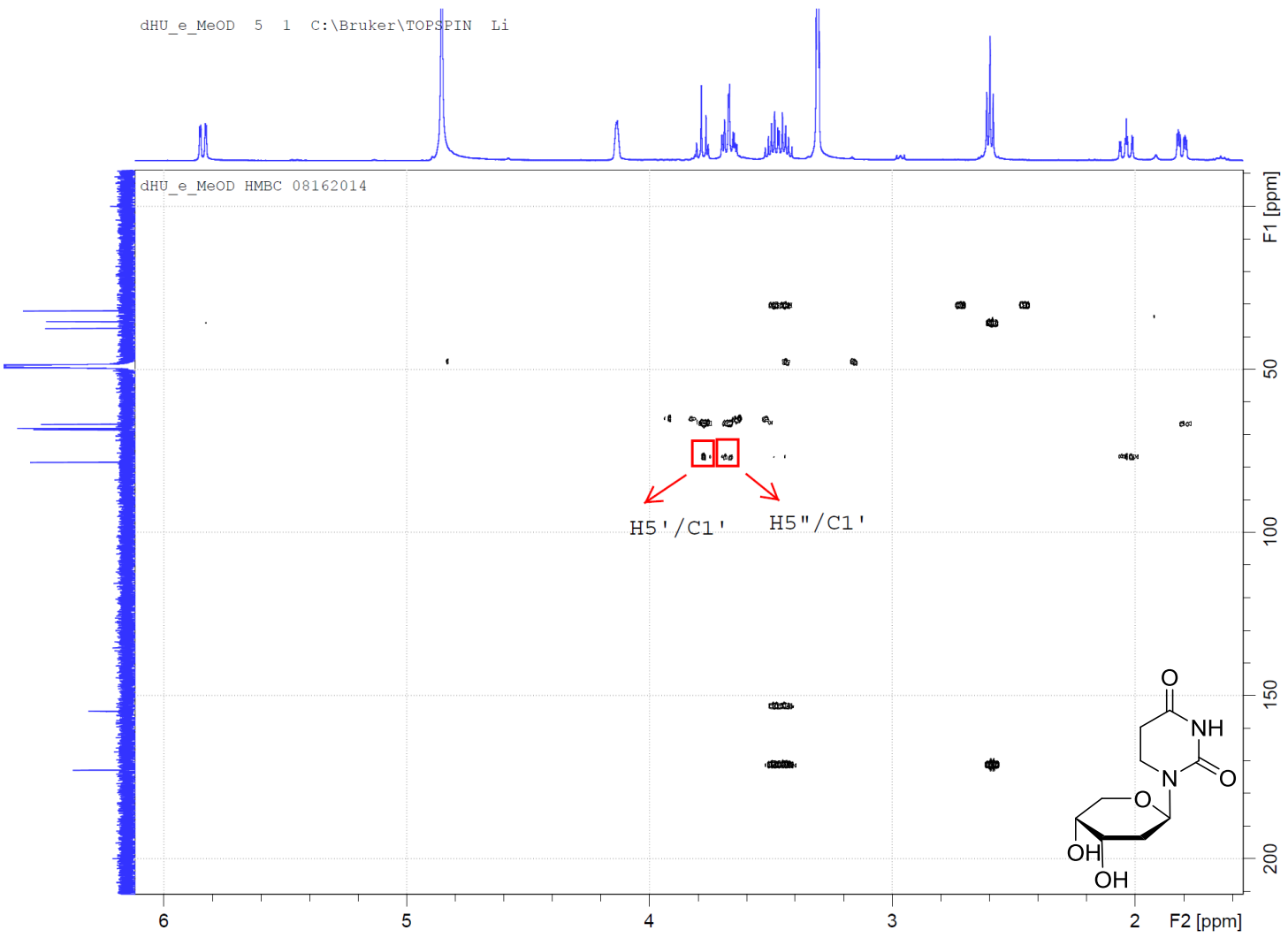


Figure S37. HMBC spectrum of compound **4**.

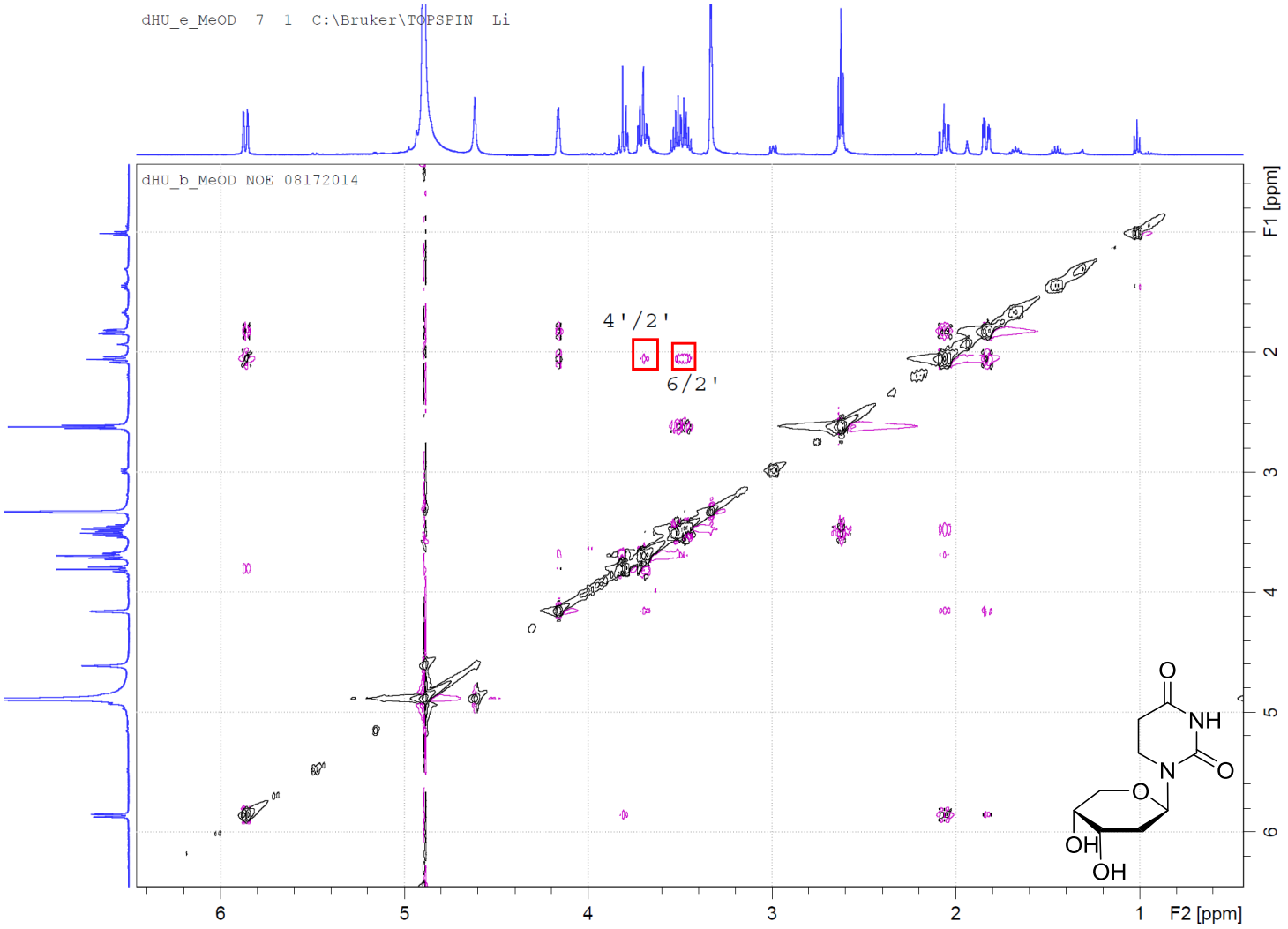


Figure S38. NOESY spectrum of compound **4**.

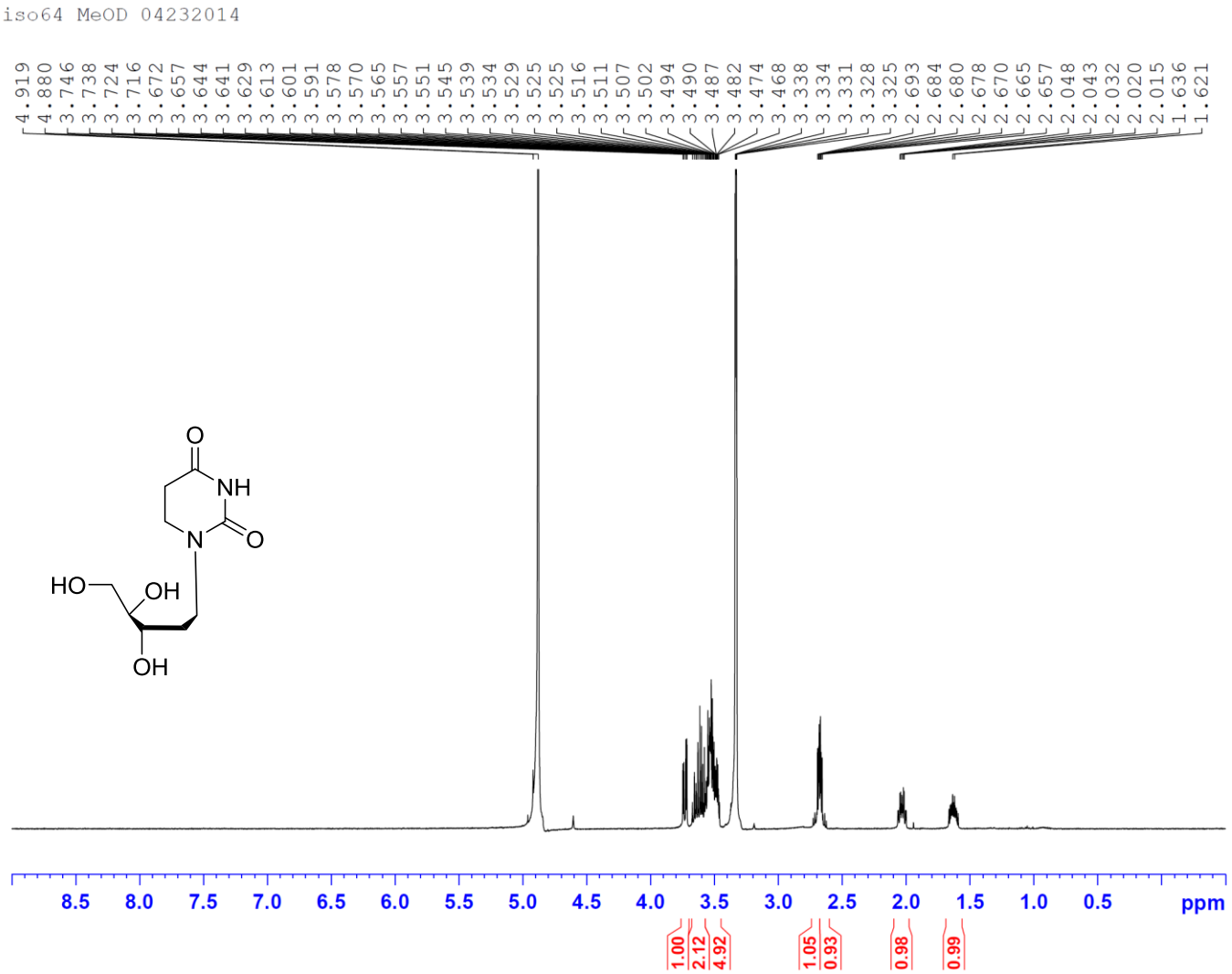


Figure S39. ^{1}H NMR spectrum of compound **5** in Methanol-d_4.

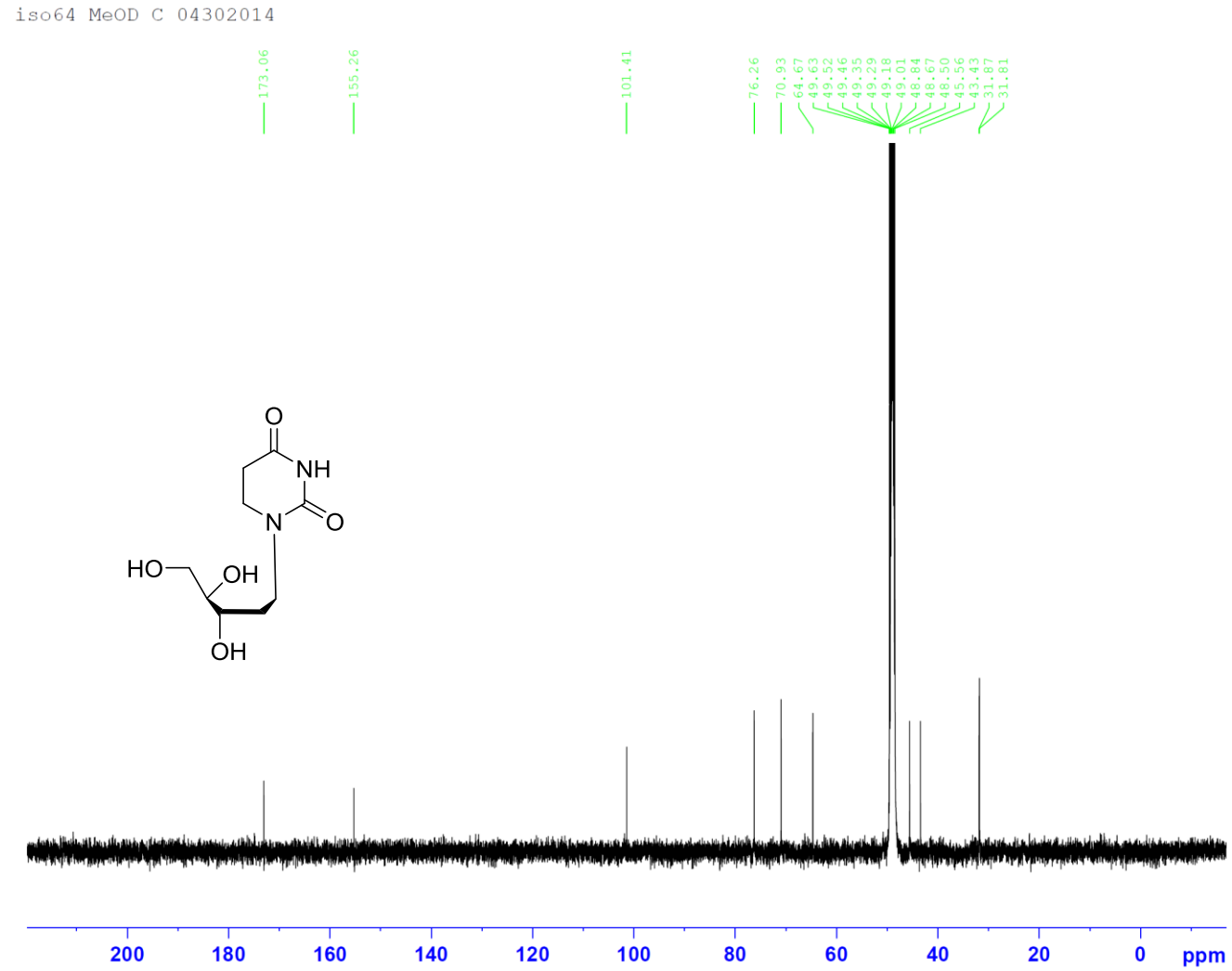


Figure S40. ^{13}C NMR spectrum of compound **5** in Methanol-d_4.

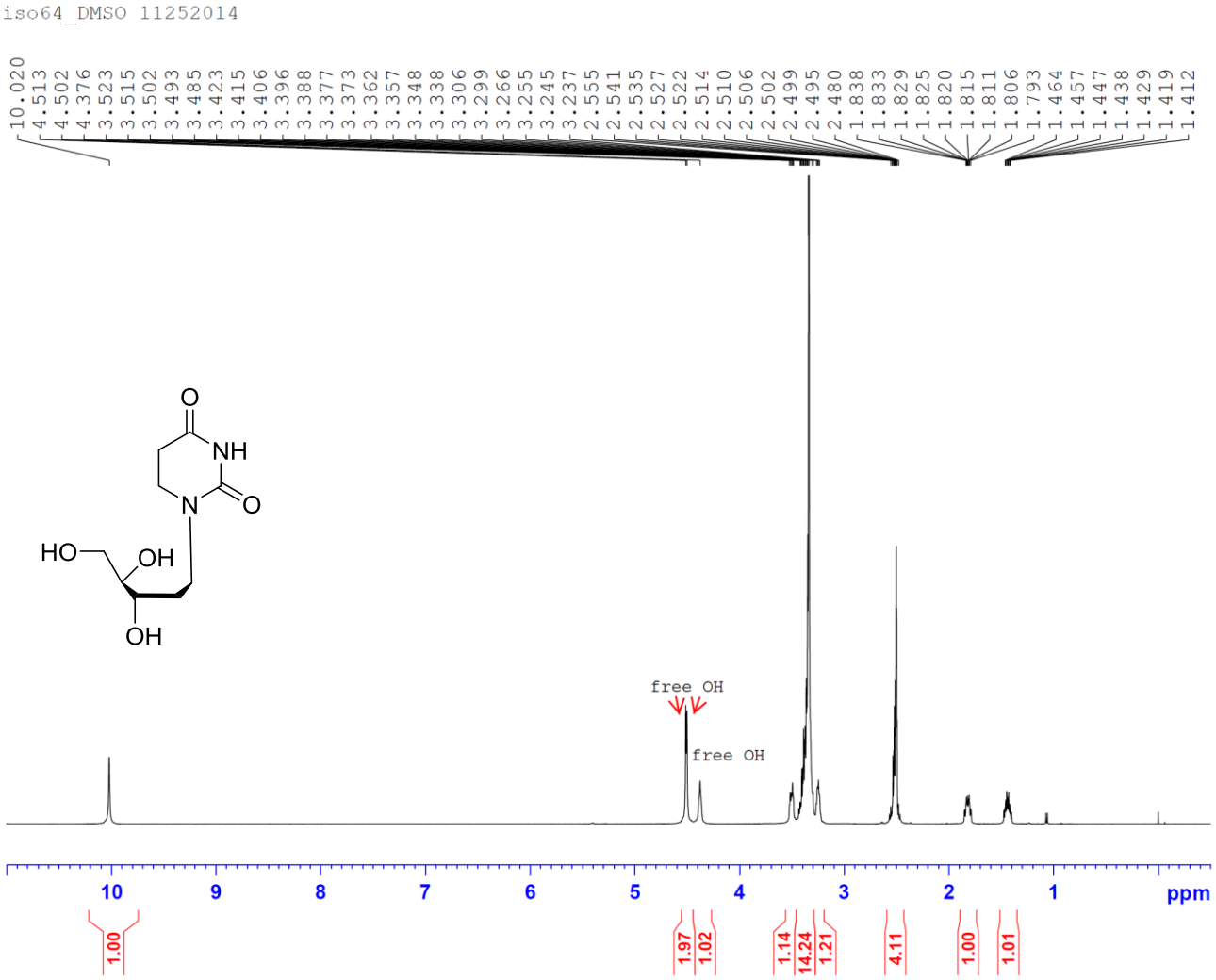


Figure S41. ^{1}H NMR spectrum of compound **5** in DMSO-d_6.

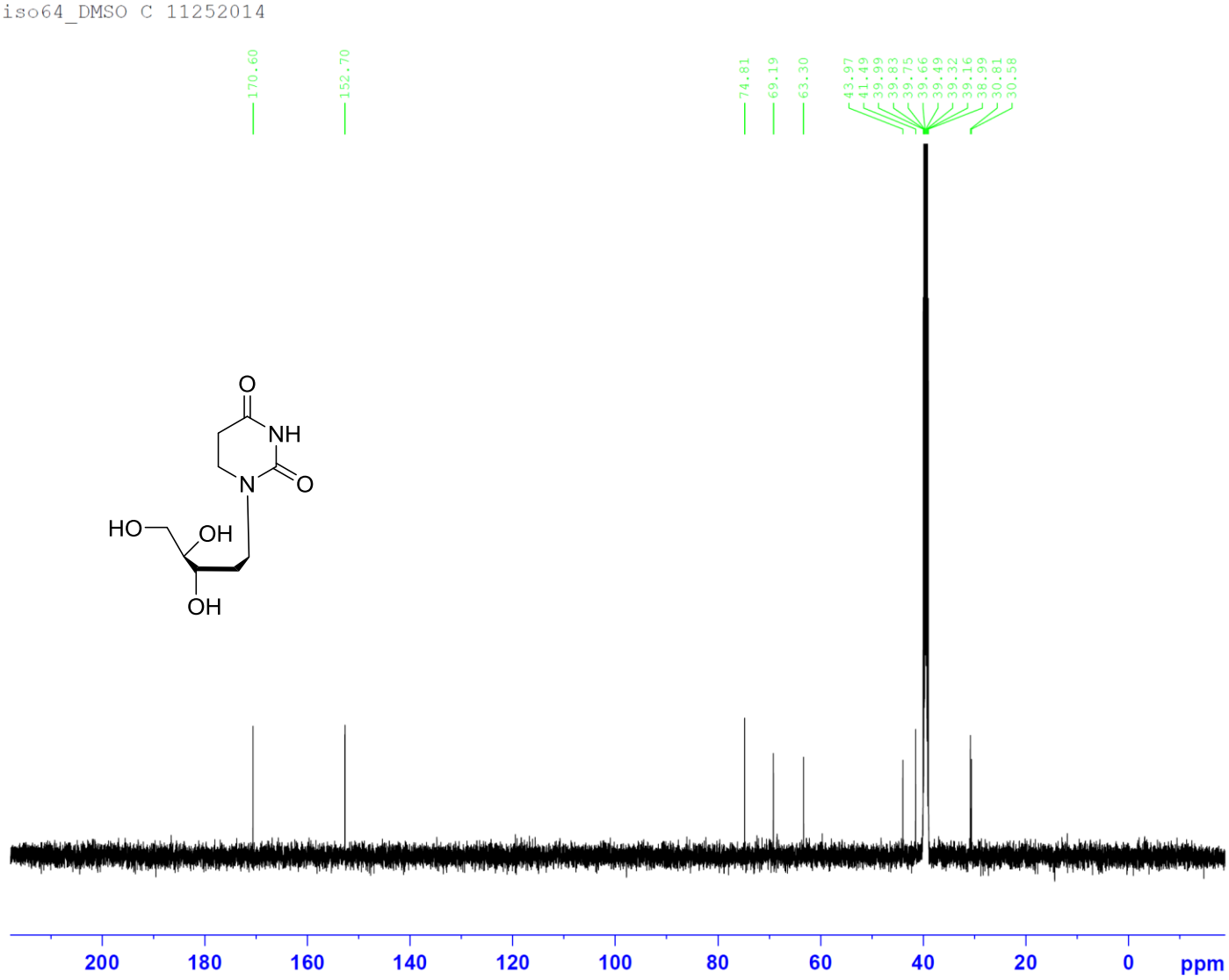


Figure S42. ^{13}C NMR spectrum of compound **5** in DMSO-d_6.

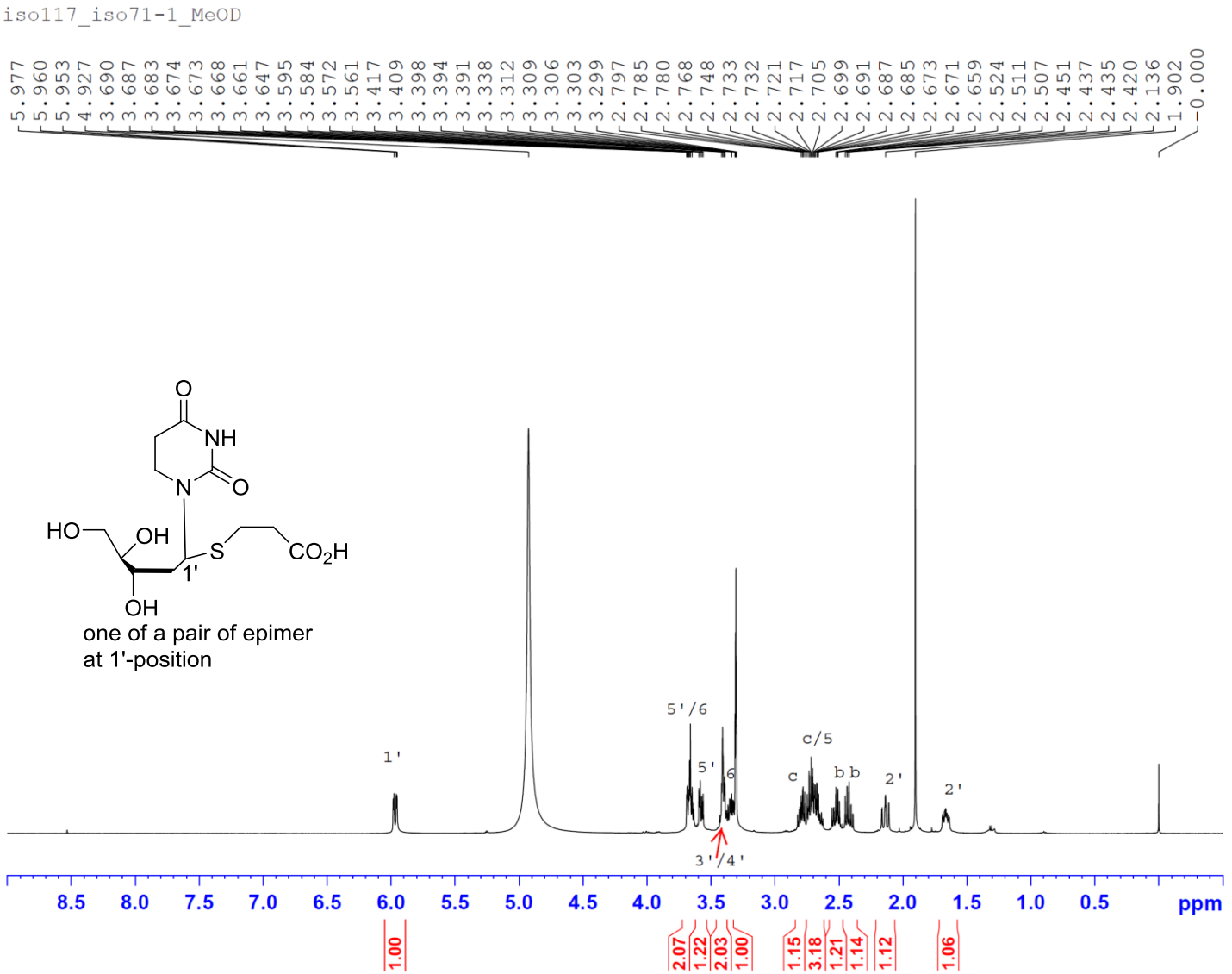


Figure S43. ^{1}H NMR spectrum of compound **8**.

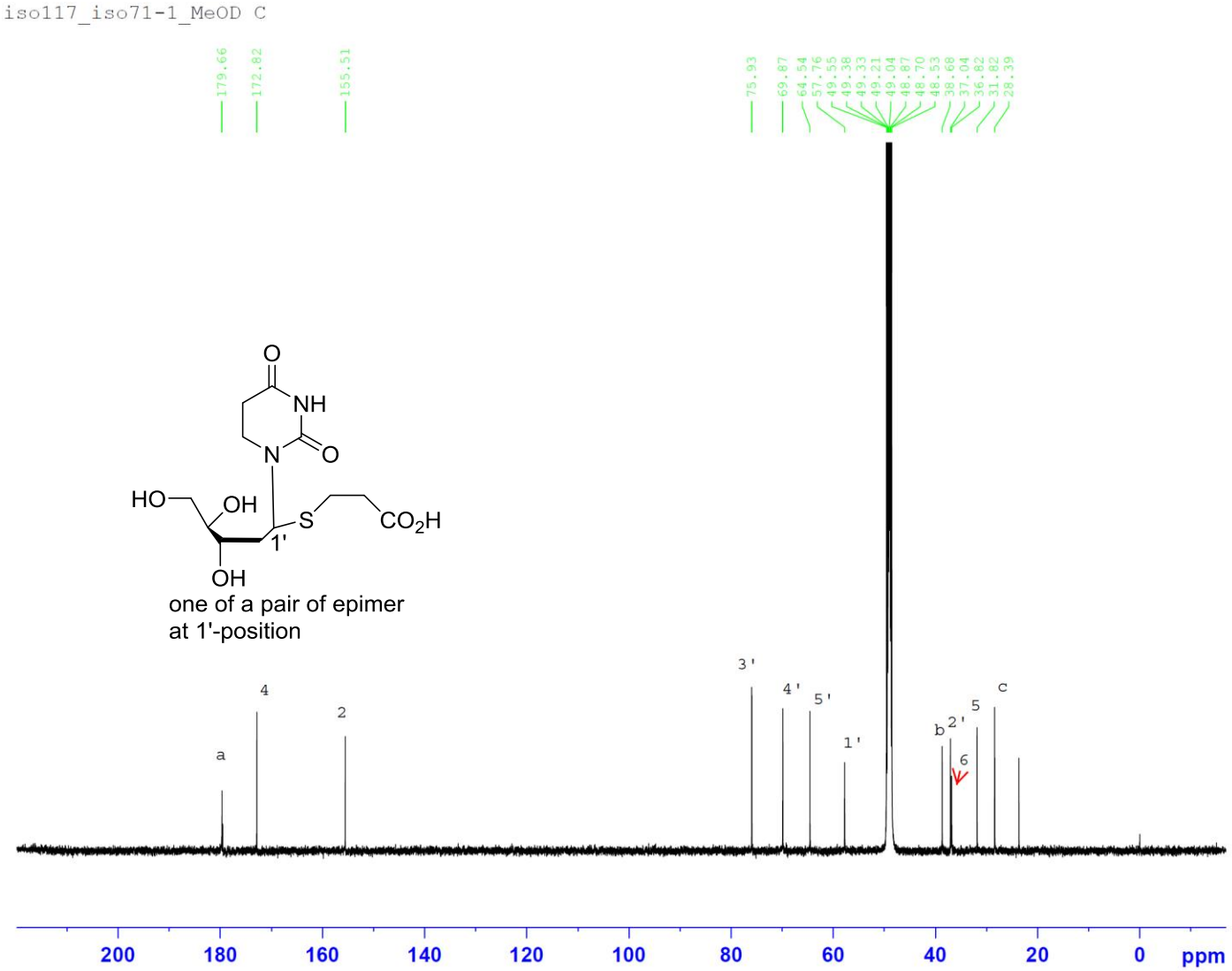


Figure S44. ^{13}C NMR spectrum of compound **8**.

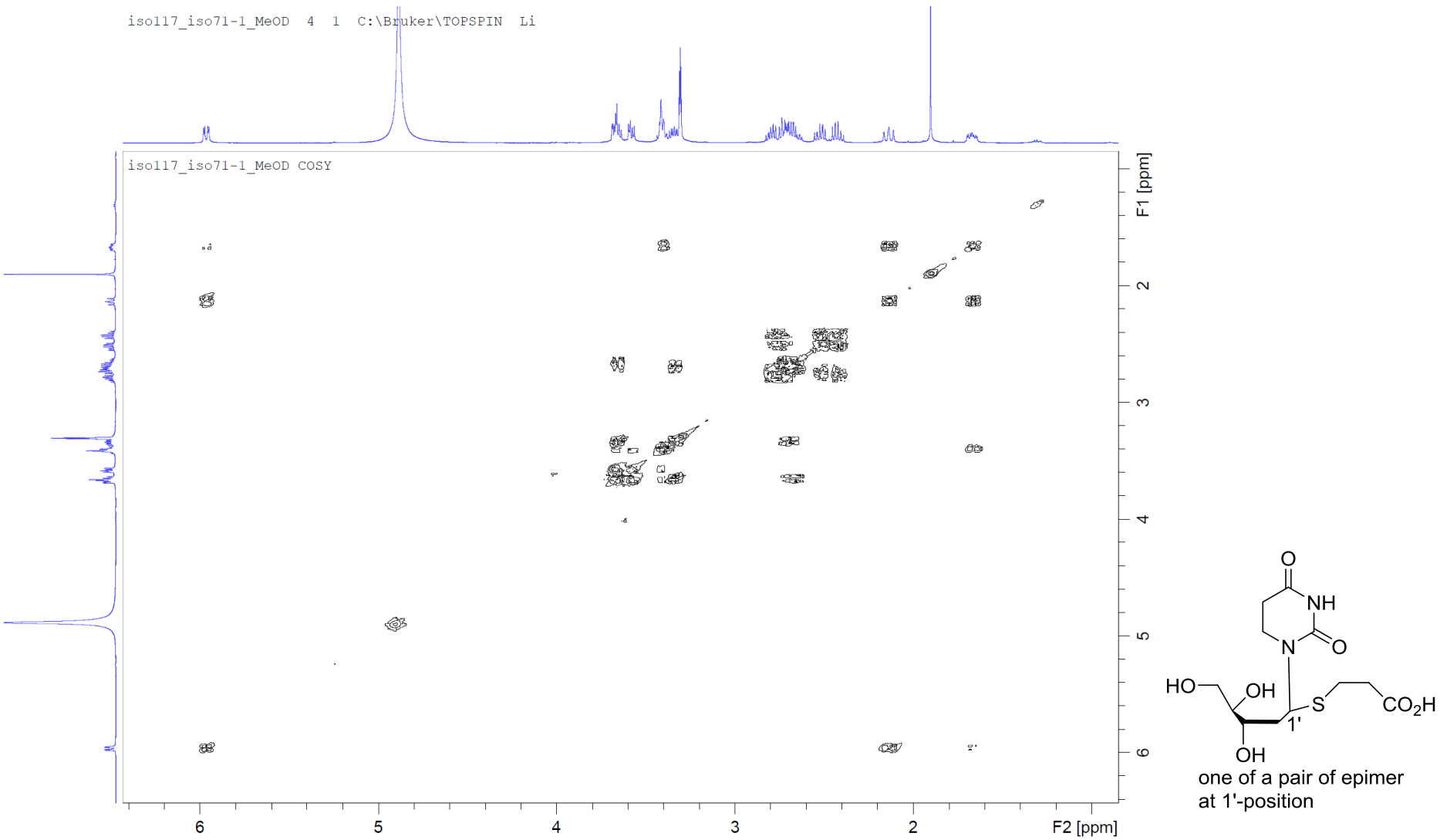


Figure S45. COSY spectrum of compound **8**.

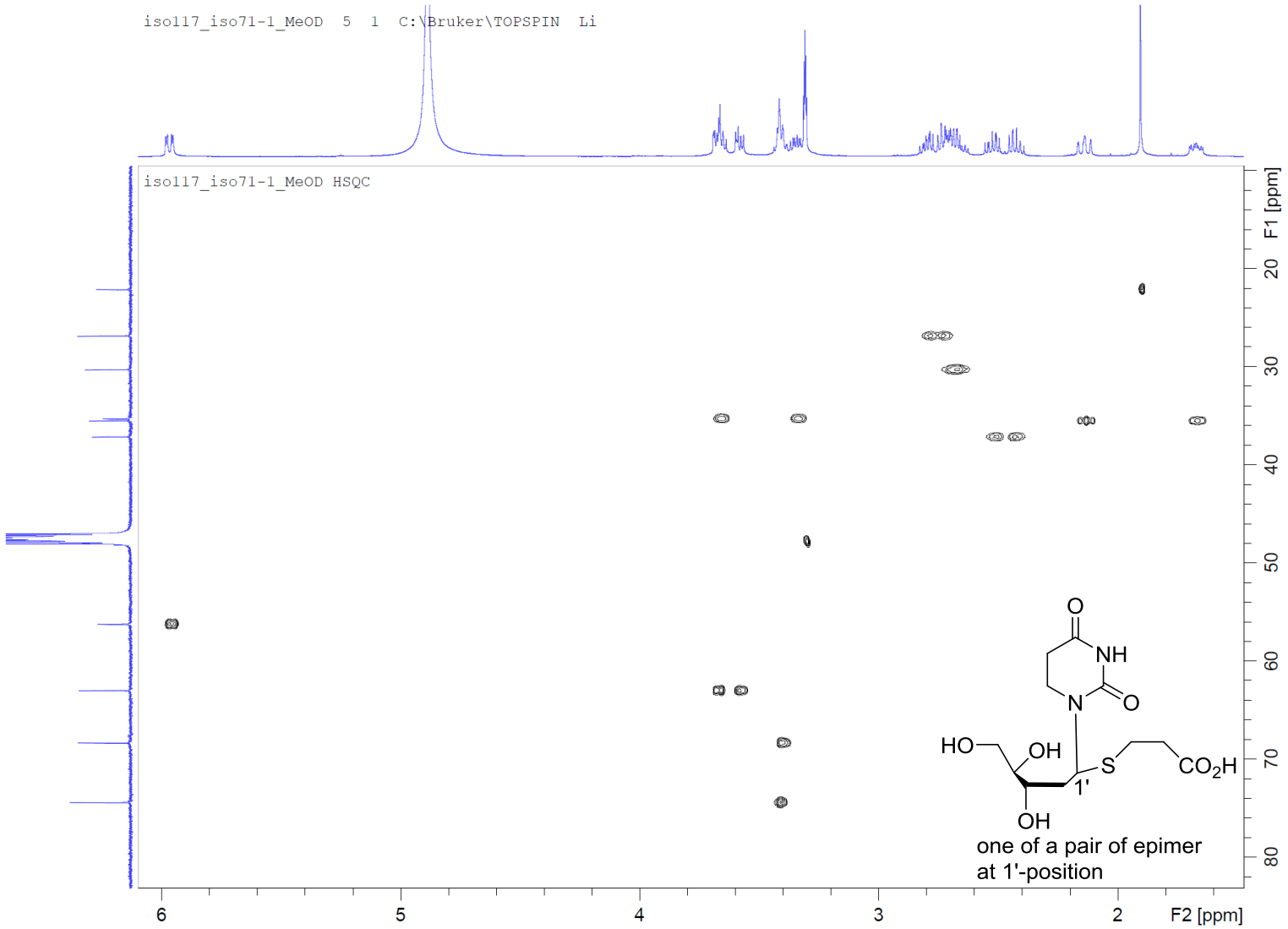


Figure S46. HSQC spectrum of compound **8**.

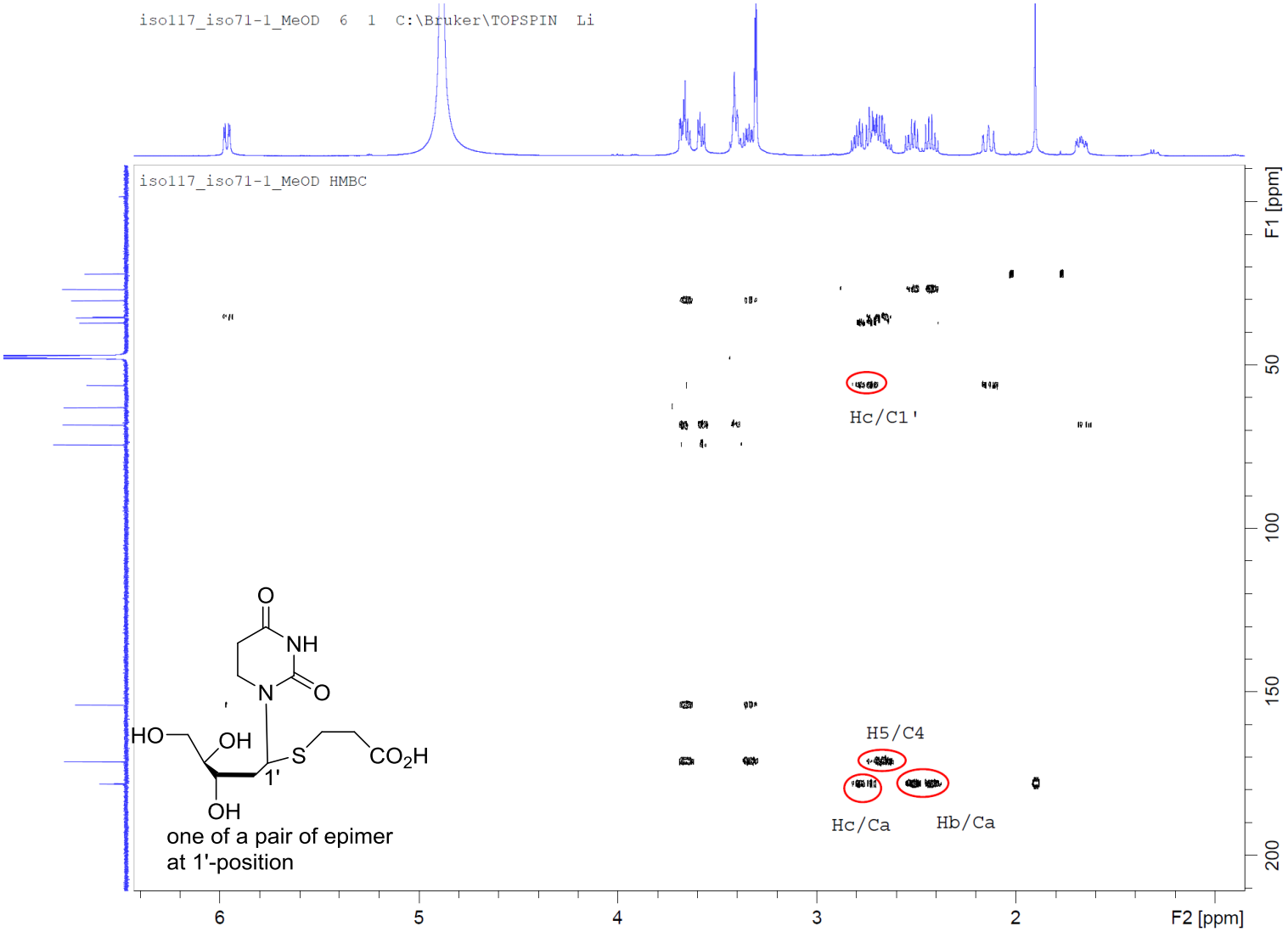


Figure S47. HMBC spectrum of compound **8**.

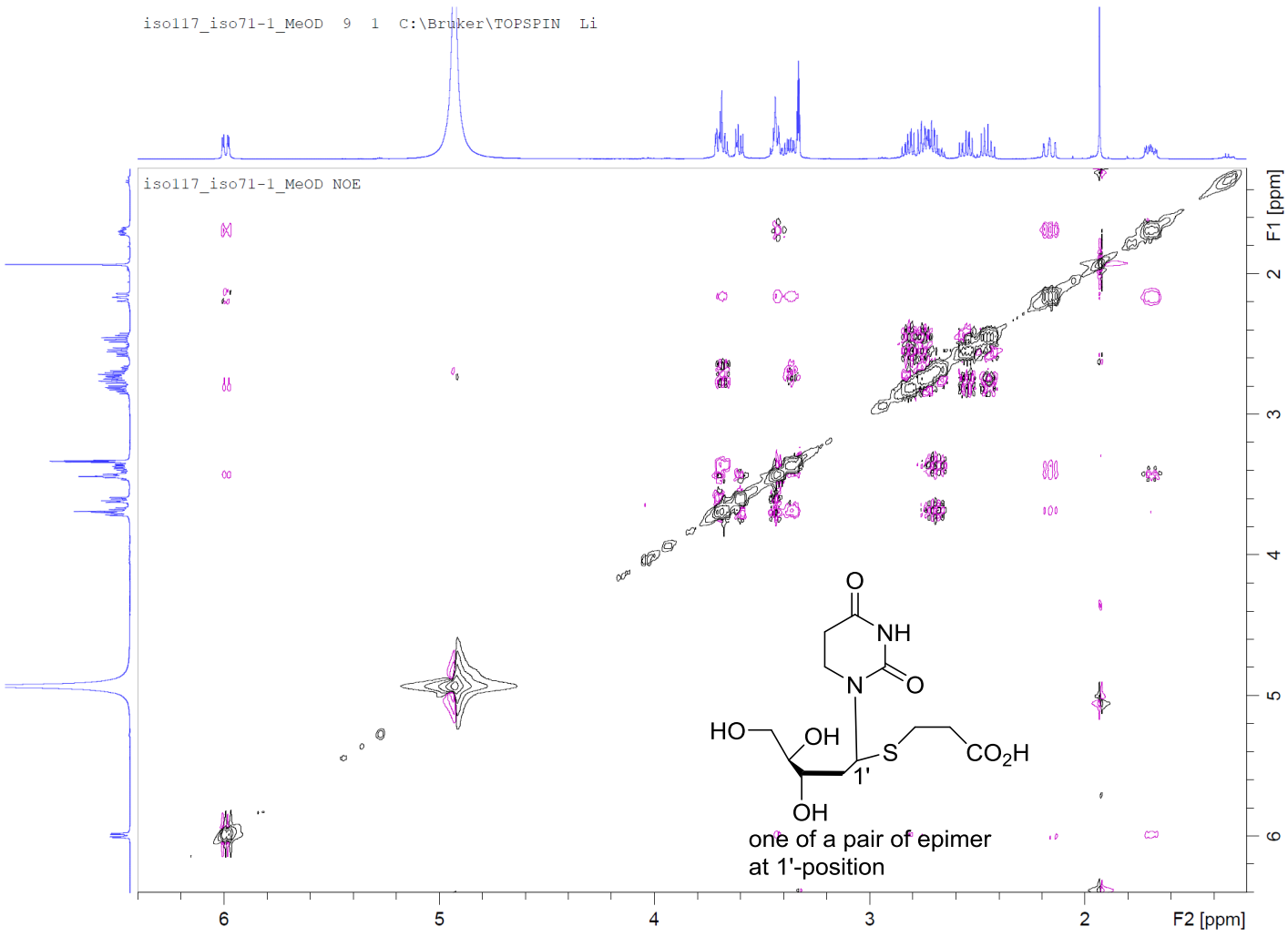


Figure S48. NOESY spectrum of compound **8**.

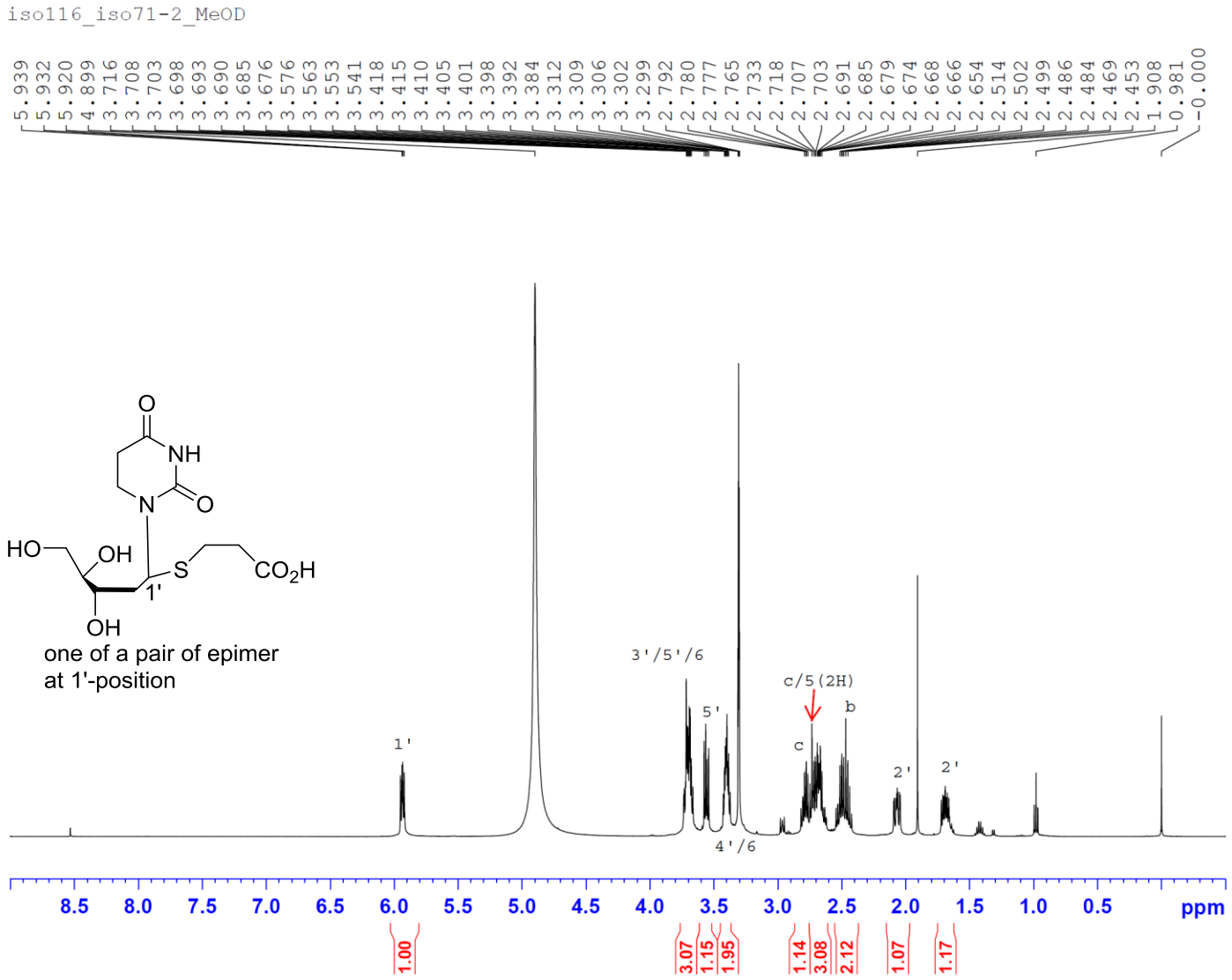


Figure S49. ^{1}H NMR spectrum of compound **9**.

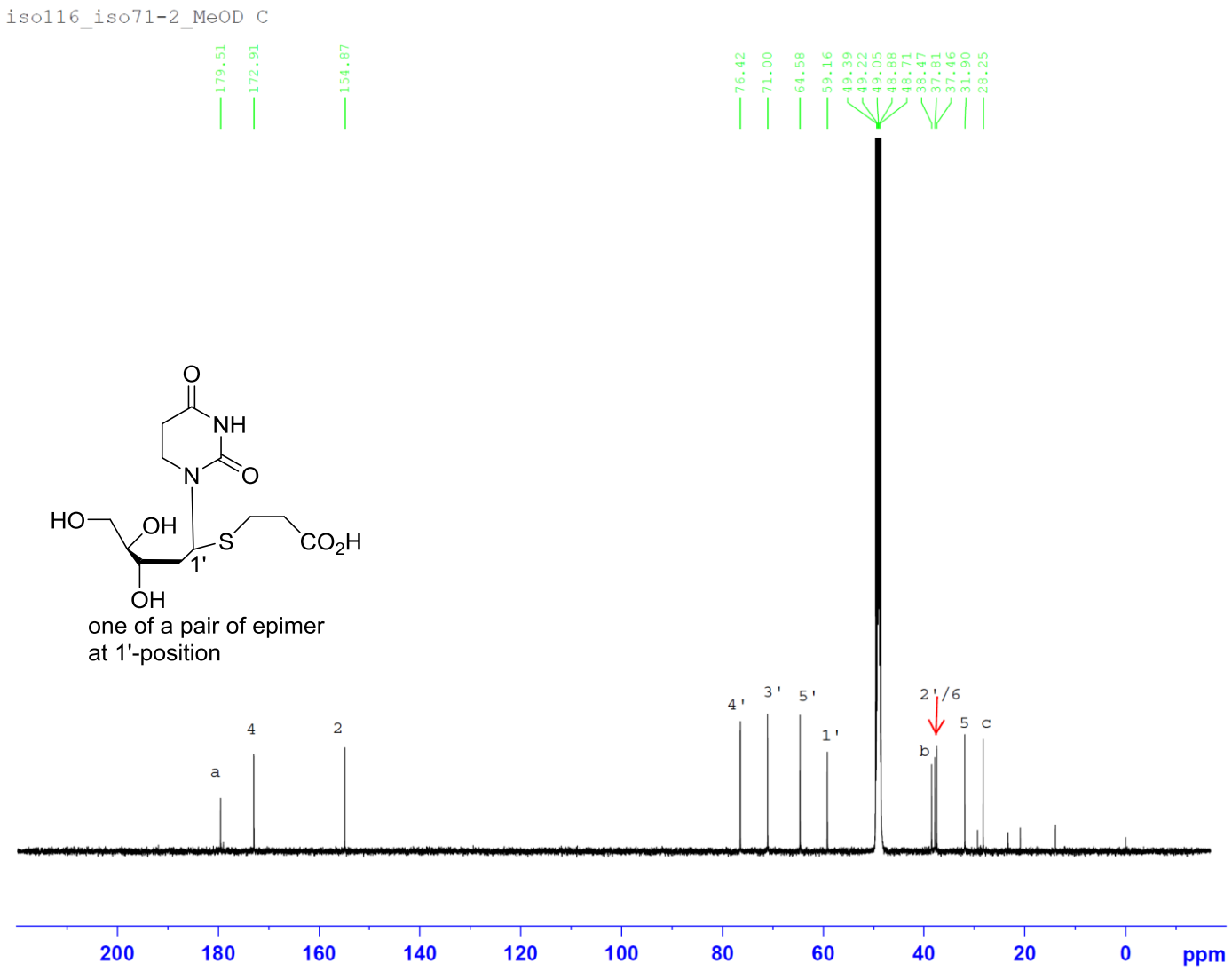


Figure S50. ^{13}C NMR spectrum of compound **9**.

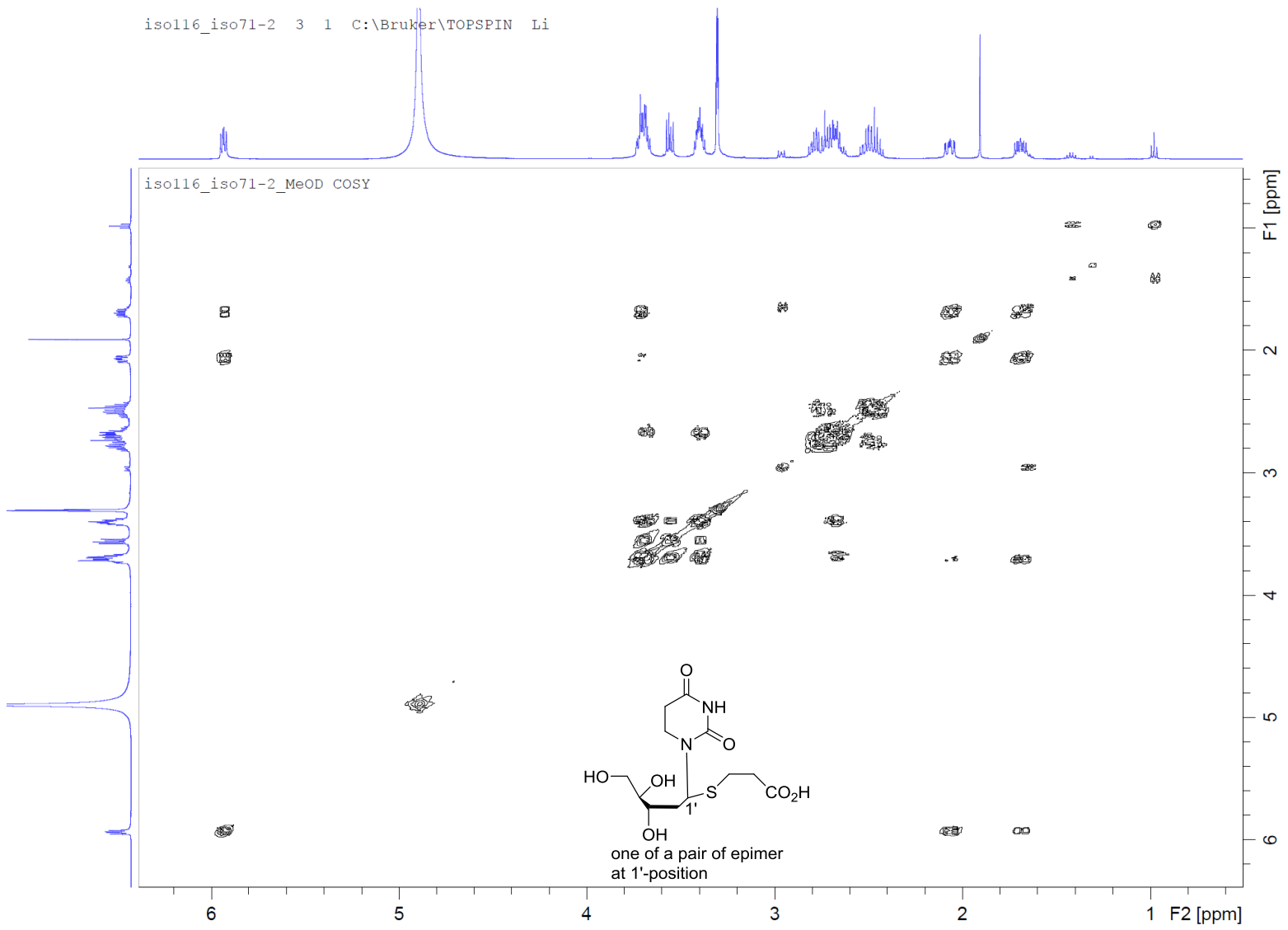


Figure S51. COSY spectrum of compound **9**.

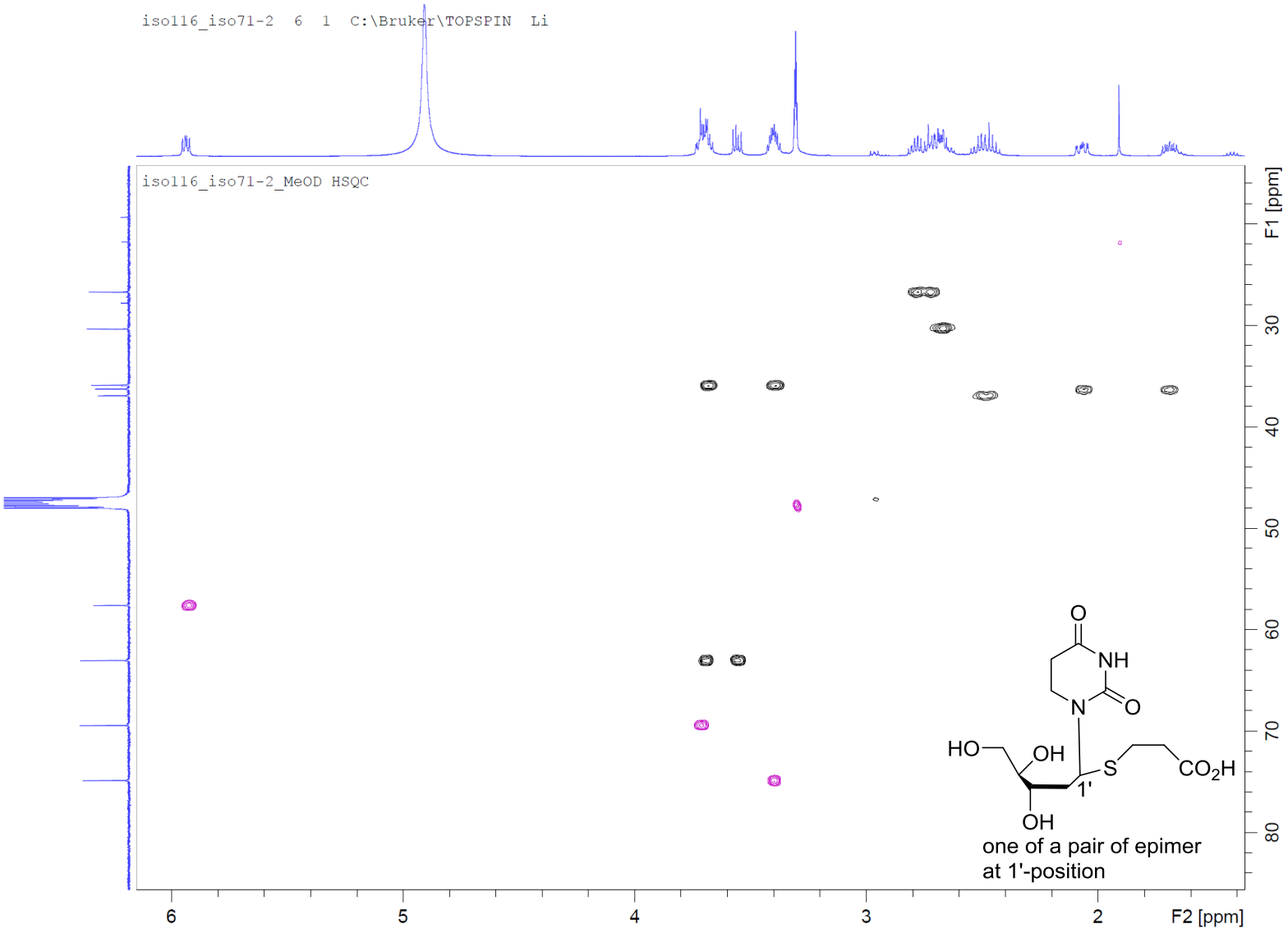


Figure S52. HSQC spectrum of compound **9**.

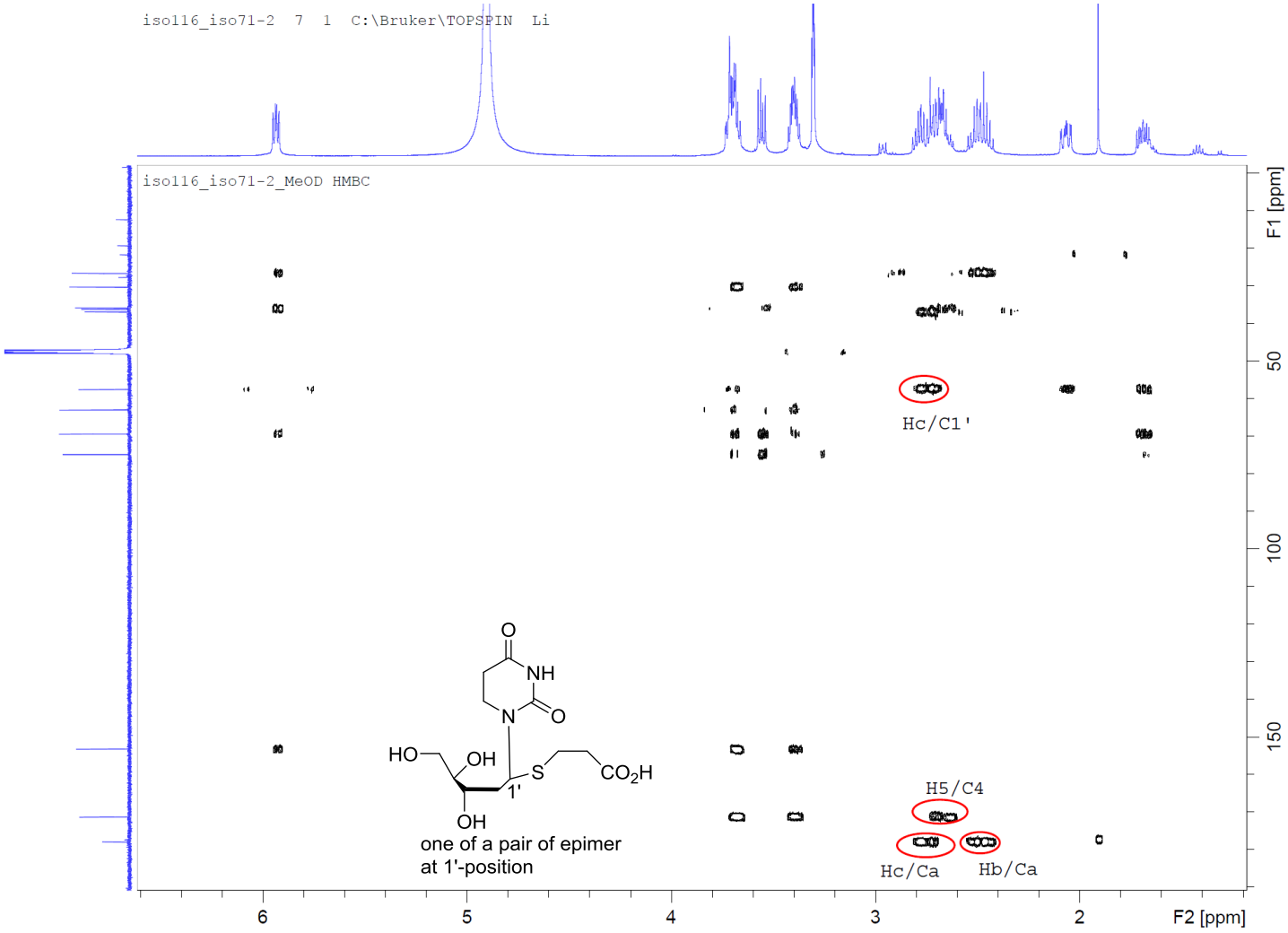


Figure S53. HMBC spectrum of compound **9**.

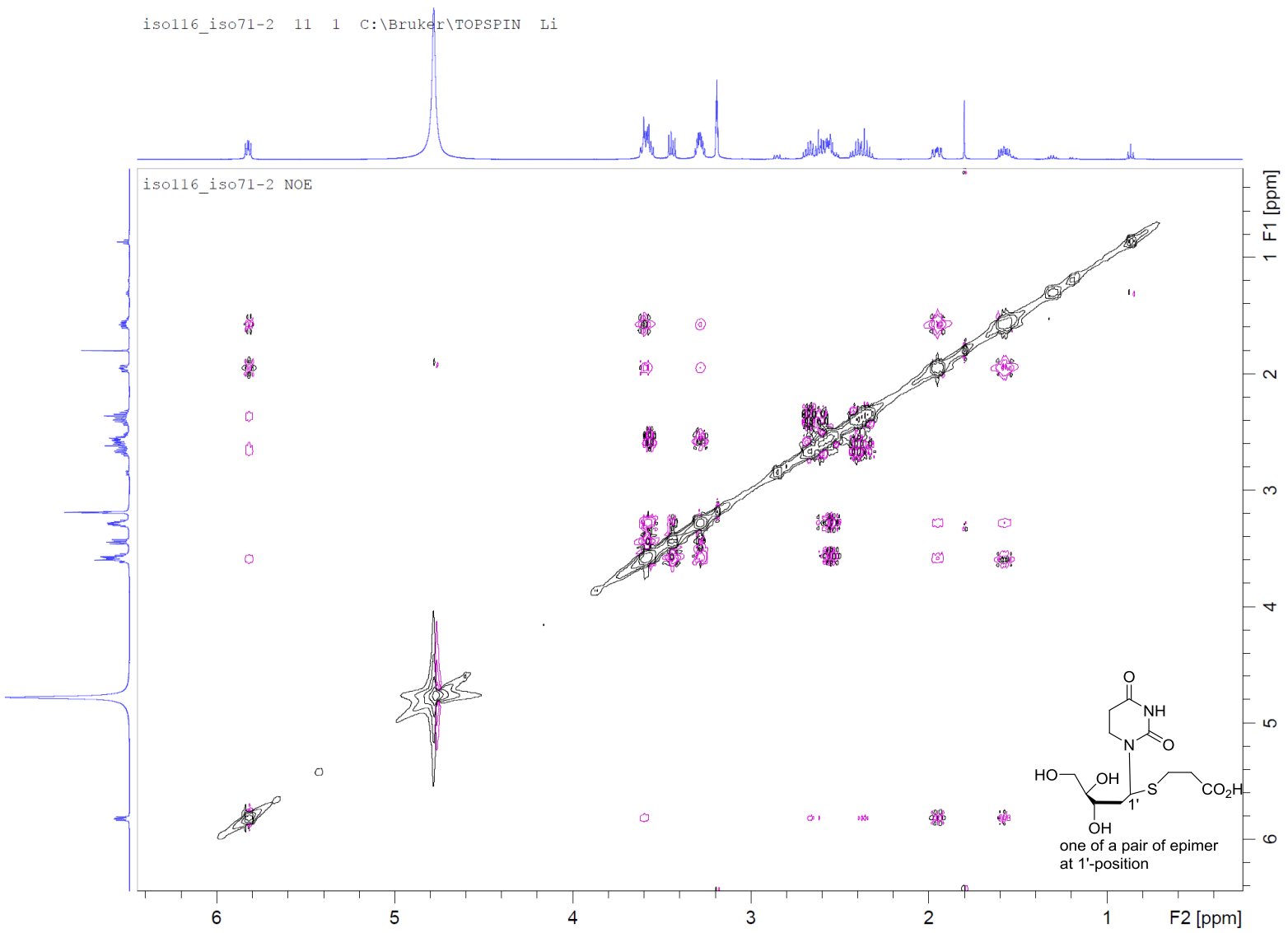


Figure S54. NOESY spectrum of compound **9**.