**Supporting Information**

# Development of Novel Bacterial Topoisomerase Inhibitors Assisted by Computational Screening

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## Safety Statement

***Caution!*** Hydrogen is classified as a GHS Flammable Gas, Category 1. Hydrogen and the hydrogen balloon were handled using flame-resistant PPE, and all open flames were avoided.

***Caution!*** Blue lights can cause damage to eyesight. While the lights were in use, orange safety glasses were worn, and the lights were shielded by either orange light shields or cardboard boxes.

## Assay Methods

*Staphylococcus aureus* DNA gyrase supercoiling assays were performed using an Inspiralis Ltd. (Norwich, UK) kit with modifications. DNA gyrase was added to initiate reactions and was present at a level that was just able to supercoil all relaxed pBR322 under the experimental conditions utilized. DNA gyrase was incubated with 250 ng of relaxed pBR322 DNA, DMSO vehicle control (2.5% final), and varying concentrations of drugs/compounds diluted in DMSO (2.5% final) in 30 µL total reaction volume at 37 °C for 30 min under the following conditions: 40 mM HEPES-KOH (pH 7.6), 10 mM magnesium acetate, 10 mM DTT, 2 mM ATP, 500 mM potassium glutamate and 0.05 mg/mL BSA. Each reaction was stopped with 30 µL STEB buffer (40% sucrose, w/v; 100 mM Tris-HCl (pH 8); 10 mM EDTA (pH 8); 0.5 mg/mL bromophenol blue) followed by the addition of 30 µL chloroform/iso-amyl alcohol (24:1) and loaded on a 1% agarose gel run at 70 V for 2 hours. Gels were stained with ethidium bromide (1µg/mL) followed by UV visualization.

*Staphylococcus aureus* topoisomerase IV decatenation assays were performed using an Inspiralis Ltd. (Norwich, UK) kit according to protocol with slight modifications. Decatenation of 100 ng of kDNA was assessed after 20 min incubation at 37 0C in a final 30 µL reaction volume with DMSO vehicle control (2.5% final) and varying concentrations of drugs/compounds diluted in DMSO in a buffer containing 50 mM Tris-HCl (pH 7.5), 5 mM magnesium chloride, 5 mM DTT, 1.5 mM ATP, 350 mM potassium glutamate, 0.05 mg/mL BSA. Topo IV was added to initiate reactions and was present at a level that was just able to decatenate 80-100% of the kDNA under the experimental conditions utilized. Reactions were stopped with 30 µL STEB buffer (40% sucrose, w/v;

100 mM Tris-HCl (pH 8); 10 mM EDTA (pH 8); 0.5 mg/mL bromophenol blue) followed by the addition of 30 µL chloroform/iso-amyl alcohol (24:1). After mixing and centrifugation, aqueous fractions (20 µL) were loaded on a 1% agarose gel and run at 70 V for 2 hours. Gels were stained with ethidium bromide (1µg/mL) for UV visualization and quantitation of the percent decatenation in the presence or absence of various concentrations of test compounds for the assessment of 50% inhibitory concentrations.

*Escherichia coli* DNA gyrase supercoiling assays were performed according to the procedures of Aldred et al. and Ashley et al.[1,2] Relaxed DNA was prepared with 1 mg/mL pBR322 and 5X Topo I relaxation buffer (250 mM Tris-HCl pH 7.5, 250 mM KCl, 50 mM $MgCl_2$, 2.5 mM DTT, 0.5 mM $Na_2EDTA$ pH 8.0, 150 µg/mL BSA) and calf thymus topoisomerase I. The volume of topoisomerase I used was calculated based on previously established activity of the stock. Samples were incubated at 37°C for 30-45 minutes followed by incubation at 75°C for 10 minutes. DNA concentration was determined by optical density at 260 nm and checked for full relaxation by gel electrophoresis.

Time course experiments were conducted prior to running supercoiling experiments with corresponding compounds to determine the optimal concentration of enzyme to be used and length of incubation. DNA gyrase supercoiling experiments were carried out in 20 µL total reaction volume with varying concentrations of compound diluted in 40% DMSO (final 4%), a DMSO enzyme control, and DMSO DNA control. Master mix was prepared on ice with 5X Gyrase Supercoiling buffer (final 1X) (250 mM Tris-HCl, pH 7.5, 875 mM KGlu, 25 mM $MgCl_2$ and 0.25 mg/mL BSA), 20 mM ATP (1.5 mM/condition), relaxed pBR322 (0.3 µg/condition) and H2O. The DNA control received Master Mix without enzyme. 20X enzyme dilutions were prepared in dilution buffer (40 mM HEPES-KOH, pH 7.6, 1 mM $Na_2EDTA$, 150 mM KGlu, 40% glycerol) on ice with E. coli GyrA and GyrB for a final reaction concentration of 7.5 nM Gyr A/B. Diluted enzyme was added to the Master Mix and subsequently added to reaction tubes containing varying concentrations of compound and the DMSO control in a time dependent manner. Reactions were stopped after 30 minutes with stop solution (10% SDS, 250 mM $Na_2EDTA$). Loading dye (sucrose, 1M Tris-HCl, pH 7.9, bromophenol blue, xylene cyanole) was added to each sample and loaded onto 1% TBE gel. DNA was separated by gel electrophoresis (150 volts, ~2.5 hr.). Gels were stained with 10 mg/mL EtBr 0.75 µg/mL for 30 minutes and destained for 10 minutes. Results were quantified using AlphaImager. DNA cleavage plots were generated using Prism (Dotmatics, Boston, MA).

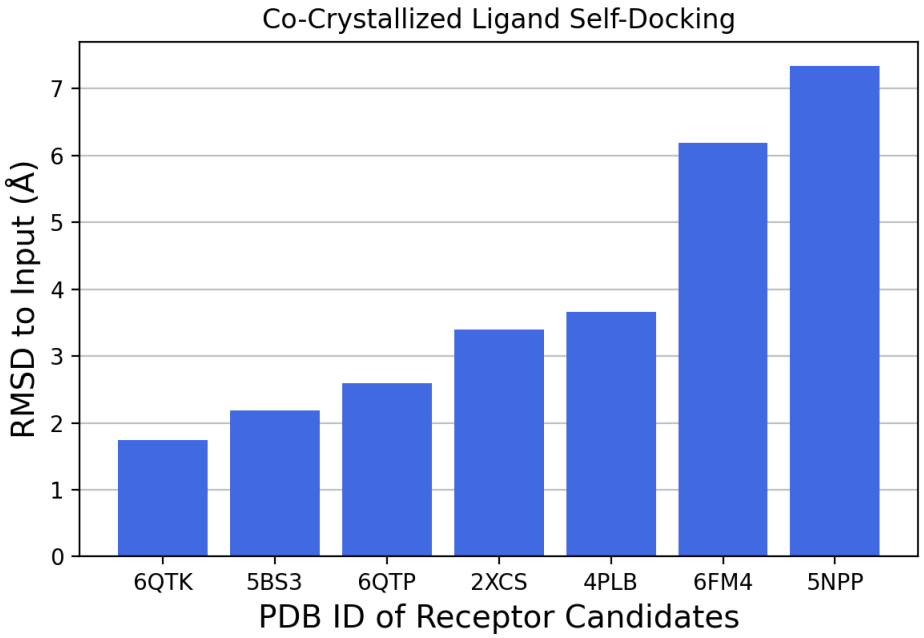
*Staphylococcus aureus* DNA gyrase and topoisomerase IV cleavage assays were performed using modifications of a kit from Inspiralis Ltd. (Norwich, UK). Reactions in 30 µL total volume were incubated with varying concentrations of drug/compound diluted in DMSO (3% final DMSO concentrations) at 37 °C for 30 min in assay buffer (40 mM HEPES-KOH (pH 7.6), 10mM magnesium acetate, 10 mM DTT, 100 mM potassium glutamate and 0.05 mg/mL albumin) containing pBR322 (250 ng/condition) and DNA gyrase (15 nM). Complexes were trapped with the addition of 2% (w/v) SDS (3µL) and proteinase K (10 mg/mL) (1.5 µL) and incubated at 45 °C for an additional 30 minutes to digest enzyme and reveal single-strand (Nick) and double-strand (Lin) breaks. STEB buffer (30 µL) (40 % (w/v) sucrose, 100 mM Tris-HCl (pH 8), and 10 mM EDTA, 0.5 mg/mL bromophenol blue) and chloroform:isoamyl alcohol (24:1) (30 µL) were added

followed by vigorous mixing and centrifugation for 2 min. The aqueous phase (20 µL) was loaded onto a 1% agarose gel containing 0.7 µg/mL ethidium bromide. Gel electrophoresis was conducted (60 V, 2 hours) in 1X TAE buffer containing 0.7 µg/mL ethidium bromide. DNA bands were visualized using ImageLab software (Bio-Rad Laboratories, Hercules, Ca). DNA gyrase cleavage experiments utilized total fluorescence in each lane, determined as previously reported,[3] using corrections for differential emission[4] in supercoiled DNA compared to linearized and nicked DNA bands according to followed by calculation of percent total fluorescence in these bands as a measure of DNA cleavage. Topo IV DNA cleavage products were calculated based on total fluorescence in each lane relative to the linearized EcoR1 digested pBR322 sample that contained equal amounts of DNA. Percent cleavage in enzyme alone controls were subtracted (DNA gyrase experiments) and final results were plotted using Sigmaplot 14.5 (Systat Software, Inc., San Jose, Ca).

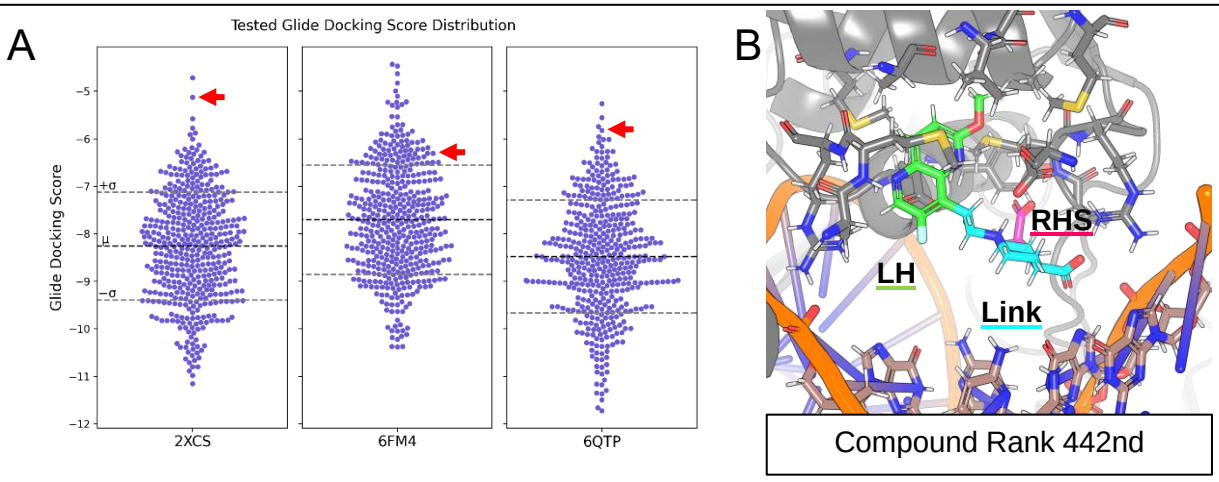
## Computational Model Methods

The benchmark compounds were initially converted from SMILES strings to 3D structure-data files (SDF), and subsequently evaluated for Pan-assay interference compounds (PAINS) and Lipinski's rule violators using the RDKit Python package.[5] We used Schrödinger's LigPrep tool to generate all tautomers, protomers, and stereoisomers for each ligand.[6] This operation used default parameters apart from the EPIK pH range, which was set to 7.4 ± 1.0.[7] Seven Protein Data Bank entries (2XCS, 5BS3, 6FM4, 6QTP, 6QTK, 4PLB, 5NPP) served as docking targets.[8-14] Each of these crystal structures included a heterotetramer of two complete GyrA subunits and two GyrB TOPRIM domains of S. aureus DNA Gyrase, complexed with an NBTI inhibitor and double-stranded DNA. Resolutions ranged between 2.10 Å and 2.70 Å. These structures were prepared with Schrödinger's Protein Preparation Wizard, which added missing hydrogens and set protonation states with EPIK, adhering to the parameters used in the LigPrep stage.[15] Receptor grids, centered on each structure's co-crystalized inhibitor, were generated and compounds were docked using Glide SP with default parameters.[16] Least square linear regressions between ln IC50 values and docking scores were calculated for each system using the linear regression model from the Scikit-Learn python package.[17] Bounds for experimental rank were defined previously as Excellent (ln IC50 <= 4.6), Good (4.6 < ln IC50 <= 6.2), Fair (6.2 < ln IC50 <= 7.8), and poor (7.8 < ln IC50). Ranks for Glide docking scores were then set where the regression line intersected these experimental rank boundaries.

Structures of candidate inhibitors were processed similarly: SMILES strings were converted to 3D SDF format, screened for PAINS and Lipinski violations, and prepared using Schrödinger's LigPrep tool. The configurations for each of these preparation steps were identical to the settings used for preparing the benchmark set. Candidate inhibitors were then docked into the top three gyrase receptors based on our benchmarks using Glide SP with default parameters. Docking scores were averaged for ligands that had multiple variants generated during the LigPrep step. Final docking scores were converted to Z-scores to demonstrate the relative performance of each compound across different systems.




**Supplemental Figure S1.** Self-docking results of the 7 initial receptor candidates in ascending RMSD to input order. Lower values represent a receptor better able to recapitulate the crystallographic binding pose of the original ligand, and this serves as an initial evaluation of the physical representativeness of a receptor.




**Supplemental Figure S2. Bad pose example (A)** Swarm plot distributions of blind docking scores in the three systems selected after benchmarking. System mean scores are marked by the black dashed line with ±1 standard deviation being marked by the grey dashed line. Red arrows show the position of a single poorly performing compound across the three systems (2XCS: 442$^{nd}$ | 6FM4: 394$^{th}$ | 6QTP: 440$^{th}$). **(B)** Docked pose, in 2XCS, of the marked compound. The poor score can be attributed to a non-preferential binding posture perpendicular to normal NBTI binding orientation seen in Figure 2 of the manuscript.

$$ZScore = \frac{x_{GlideScore} - \mu}{\sigma}$$

**Supplemental Equation S1.** Where $X_{GlideScore}$ is the raw Glide docking score for a compound, μ is the mean docking score of all NBTIs tested in that receptor, and σ is the standard deviation of all NBTIs tested in that receptor.

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**General Chemistry:**

Commercially sourced reactants and solvents were used without additional purification. Tetrahydrofuran (THF), N,N-dimethylformamide (DMF), and dichloromethane (DCM) were purchased as anhydrous solvents. Air- and/or moisture-sensitive reactions were conducted in oven-dried glassware under nitrogen protection unless otherwise noted. Reaction progress was monitored using thin-layer chromatography (TLC) with Merck TLC Silica gel 60 F254. Flash chromatography was performed with a Teledyne-ISCO combiflash Rf+ .

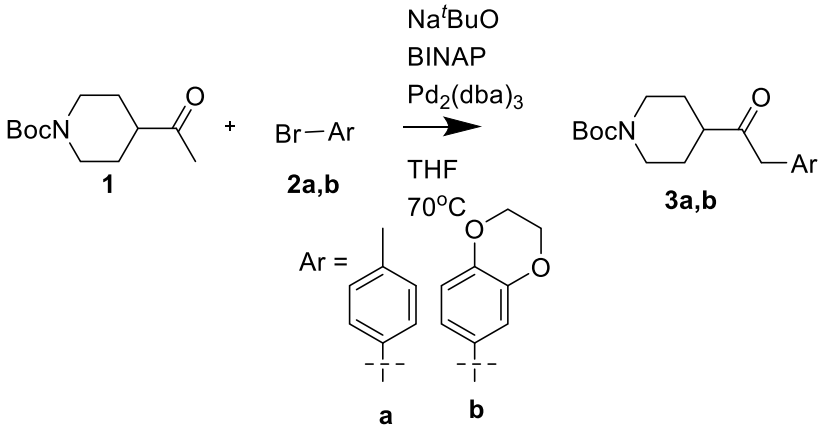
$^{1}$H NMR spectra were obtained at 400 MHz using residual protiated solvent as the internal reference: $CDCl_3$ (7.26 ppm), $CD_3OD$ (3.31 ppm), DMSO-$d_6$ (2.50 ppm). $^{13}$C NMR spectra were obtained at 100 MHz using the solvent as the internal reference: $CDCl_3$ (77.16 ppm), $CD_3OD$ (49.00 ppm), DMSO-$d_6$ (39.52 ppm). Some compounds were synthesized multiple times. In such cases, experimental and characterization data are provided for a representative example.

High resolution mass spectrometry was performed using electrospray ionization. Measurements of purity were carried out using a Acquity UPLC BEH C18 column (2.1 x 50 mm i.d., 1.7 µm). The separations were carried out at 40℃ at a flow rate of 0.7 mL/min in gradient mode of mobile phases of water + 0.1% formic acid and acetonitrile + 0.1% formic acid. The concentration of tested compounds was ~0.5 mg/mL with 2 µl injection volume. Peak detection was accomplished using a UV detector scanning from 210-500nm. Compounds are >95% pure by UPLC, with the exception of **16a,b**; **22c**; and **23a** for which the purity ranged from 93.3-94.3%.

Measurements of enantiomeric excess (ee) were carried out using a CHIRALPAK® IB N-3 column (150 * 4.6 mm i.d., 3 µm) at 25℃ with a flow rate of 1 mL/min in isocratic mode of mobile phases containing hexane and reagent alcohol, with diethylamine as an additive. The concentration of tested compounds was ~250 µg/ml in ethanol with 30 µl injection volume. Peak detection was accomplished using a UV detector at 220 nm.

## General Procedures and Synthesis

1) Methyl Ketone Arylation: (±)-BINAP (0.036 eq), $Pd_2(dba)_3$ (0.015 eq) and $Na^tBuO$ (1.3 eq) were added to a round bottom flask and purged with nitrogen. THF (0.17 M) was added, followed by the requisite bromide (1 eq) and commercially available **1** (1.2 eq). The reaction was stirred at 70°C overnight then cooled to room temperature and diluted with water. The aqueous layer was extracted 5x15 mL ethyl acetate, and the combined organic layers were dried over sodium sulfate, decanted, and concentrated *in vacuo*. The crude mixtures were purified by flash chromatography.

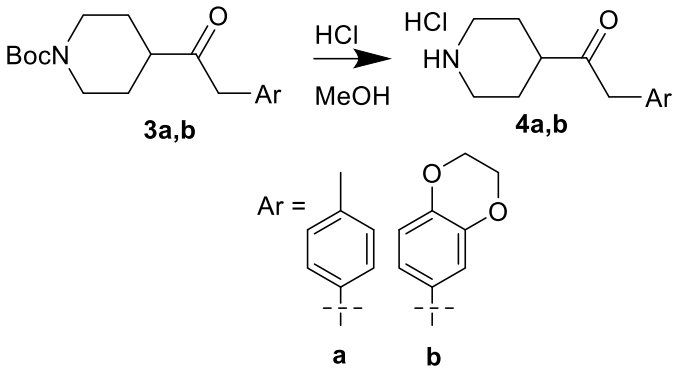



***tert*-butyl 4-(2-(*p*-tolyl)acetyl)piperidine-1-carboxylate (3a)**
The title compound was synthesized using commercially available **2a** according to General Procedure 1. Purification by flash chromatography (compound eluted in 0-10% ethyl acetate in hexanes) and concentration *in vacuo* afforded the title compound (260 mg, 0.819 mmol, 82% yield).
$^1$HNMR ($CDCl_3$, 400 MHz) δ: 7.13 (d, *J* = 8.0 Hz, 2H), 7.07 (d, *J* = 8.0 Hz, 2H), 4.12-4.00 (m, 2H), 3.70 (s, 2H), 2.73 (t, *J* = 12.3 Hz, 2H), 2.58 (tt, *J* = 3.8, 11.3 Hz, 1H), 2.33 (s, 3H), 1.80-1.71 (m, 2H), 1.60-1.49 (m, 2H, obscured by water), 1.44 (s, 9H).

***tert*-butyl 4-(2-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)acetyl)piperidine-1-carboxylate (3b)**
The title compound was synthesized using commercially available **2b** according to General Procedure 1. Purification by flash chromatography (compound eluted in 5-15% ethyl acetate in hexanes) and concentration *in vacuo* afforded the title compound as a yellow oil (180 mg, 0.498 mmol, 50% yield).
$^1$HNMR ($CDCl_3$, 400 MHz, contaminated w/ ethyl acetate and acetone) δ: 6.81 (d, *J* = 8.2 Hz, 1H), 6.69 (d, *J* = 2.0 Hz, 1H), 6.64 (dd, *J* = 2.1, 8.2 Hz, 1H), 4.24 (s, 4H), 4.13-4.02 (m, 2H), 3.62 (s, 2H), 2.77-2.70 (m, 2H), 2.57 (tt, *J* = 3.7, 11.2 Hz, 1H), 1.60-1.48 (m, 4H, obscured by water), 1.45 (s, 9H).

2) Deprotection of Boc Group: The requisite Boc-protected piperidine (1 eq) was dissolved in methanol (0.25 M), and 4 M HCl in 1,4-dioxane (2-2.5 eq) was added dropwise. The reaction was stirred for 4 hours, whereupon the stir bar was

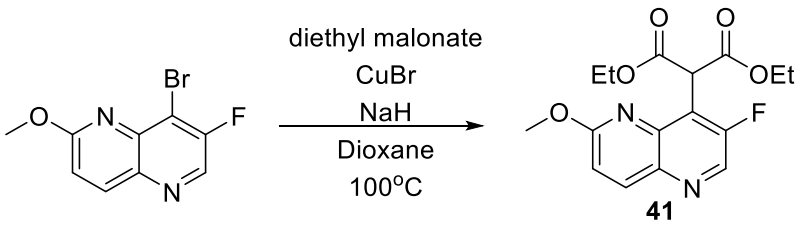
removed, and the reaction was concentrated to afford the crude product as a hydrochloride salt. No further purification was carried out at this stage.




3a,b 4a,b

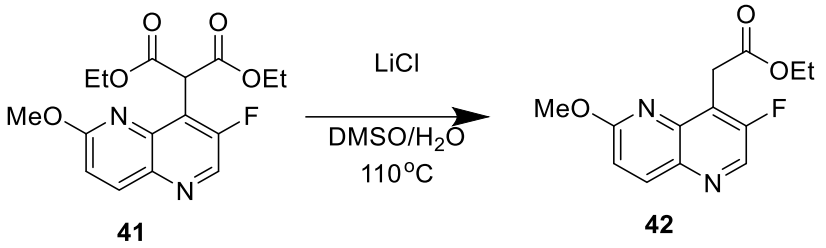
**1-(piperidin-4-yl)-2-(*p*-tolyl)ethan-1-one*hydrochloride (4a)**
The title compound was synthesized using **3a** according to General Procedure 2. The crude product was used directly in the next step.

**2-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-(piperidin-4-yl)ethan-1-one*hydrochloride (4b)**
The title compound was synthesized using **3b** according to General Procedure 2. The crude product was used directly in the next step.



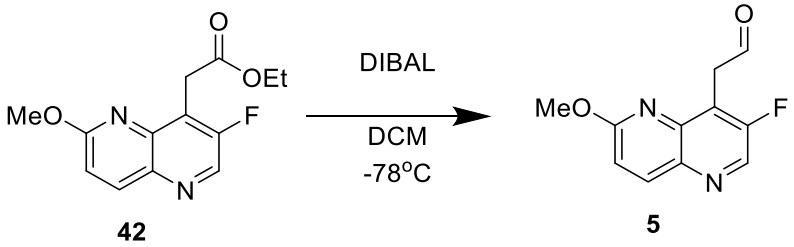

41

**diethyl 2-(3-fluoro-6-methoxy-1,5-naphthyridin-4-yl)malonate (41)**
Sodium hydride (2.4 g, 60 mmol, 3 eq) was added to 3-neck flask. Base was dissolved in 1,4-dioxane (41 mL). A reflux condenser was attached, and the flask was capped. Diethyl malonate (9.15 mL, 60 mmol, 3 eq) was added dropwise by syringe. Once all malonate was added, the flask was heated to 80°C for 1 hour. After 1 hour, copper (I) bromide (1 g, 7 mmol, 0.35 eq) and commercially available 8-bromo-7-fluoro-2-methoxy-1,5-naphthyridine (5.14 g, 20 mmol, 1 eq) were added to the flask. Reaction was heated to 100°C overnight. Upon return, reaction was cooled to room temperature and filtered through a celite plug washing with excess ethyl acetate. Organics were concentrated via rotary evaporation to afford a crude mixture that was purified via flash chromatography eluting in 5% ethyl acetate in hexanes. The title compound was afforded as a clear oil (5.7 g, 16.9 mmol, 84.74%). The reaction was run multiple times with an average yield of 75%.
$^1$HNMR ($CDCl_3$, 400 MHz) δ: 1HNMR (CDCl3, 400 MHz, contaminated with dioxane, impure) δ: 8.71 (d, J = 1.1 Hz, 1H), 8.21 (d, J = 9.0 Hz, 1H), 7.10 (d, J = 9.1 Hz, 1H), 5.79 (s, 1H), 4.26 (q, J = 7.1 Hz, 4H), 4.04 (s, 3H), 1.25 (t, J = 7.1 Hz, 6H).




**41** **42**

**ethyl 2-(3-fluoro-6-methoxy-1,5-naphthyridin-4-yl)acetate (42)**
**41** (1 eq), lithium chloride (4 eq), DMSO (0.2 M), and water (1.2 eq) were added to a round bottom flask. Reaction was heated to 110°C overnight. Upon return, reaction was cooled to room temperature and diluted with water. Tye aqueous layer was extracted 5x15 mL ethyl acetate. Organics were dried over sodium sulfate, decanted, and concentrated via rotary evaporation to afford a crude mixture that was purified via flash chromatography (eluting 0-5% ethyl acetate in hexanes) to afford the title compound as a clear oil. The reaction was run multiple times with an average yield of 70%.
$^1$HNMR ($CDCl_3$, 400 MHz, impure) δ: 8.68 (s, 1H), 8.19 (d, *J* = 9.0 Hz, 1H), 7.08 (d, *J* = 9.0 Hz, 1H), 4.20-4.14 (m, 4H), 4.05 (s, 3H), 1.22 (t, *J* = 7.1 Hz, 3H).

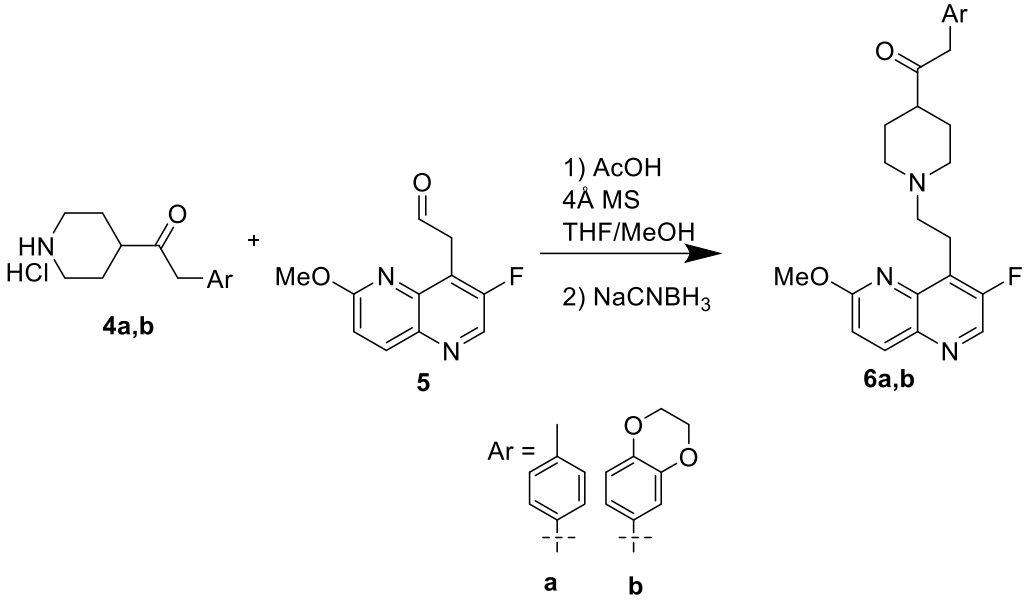



**42** **5**

**2-(3-fluoro-6-methoxy-1,5-naphthyridin-4-yl)acetaldehyde (5)**
**42** (1eq) was dissolved in DCM (0.2 M) and cooled to -78°C. Diisobutylaluminum hydride (DIBAL)(2 eq) was then added dropwise, maintaining a temperature less than -75°C. Once addition was complete, reaction stirred an additional 2 hrs. Reaction was quenched with dropwise addition of methanol, maintaining temperature less than -75°C. Once quenched, reaction was warmed to room temperature and saturated, and aqueous Rochelle's salt was added. Reaction stirred until aqueous layer was separable from organics. Reaction was further diluted with water and extracted 5x15 mL ethyl acetate. Organics were dried over sodium sulfate, decanted, and concentrated via rotary evaporation to afford a crude mixture that was purified via flash chromatography (eluting 0-5% ethyl acetate in hexanes) to afford the title compound as a yellow solid. The reaction was run multiple times with an average yield of 40%.
$^1$HNMR ($CDCl_3$, 400 MHz, impure) δ: 9.86 (d, *J* = 1.2 Hz, 1H), 8.71 (s, 1H), 8.25 (d, *J* = 9.1 Hz, 1H), 7.11 (d, *J* = 9.1 Hz, 1H), 4.21 (t, *J* = 1.4 Hz, 2H), 4.02 (s, 3H).

3) Reductive Amination of Aldehyde: Compound **5** (1.0 eq), the requisite piperidine (1.1 eq), and 4Å molecular sieves (350 mg/mmol of aldehyde) were added to a round bottom flask. Methanol and THF (1:1, 0.25 M) were added, followed by acetic acid (1.5 eq). The reaction was stirred for 4 hours. Sodium

cyanoborohydride (1.2 or 2.0 eq) was added and the reaction was stirred for one additional hour. The reaction was diluted with saturated aqueous sodium carbonate, and the aqueous layer was extracted 5x15 mL ethyl acetate. The combined organic layers were dried with sodium sulfate, decanted, and concentrated *in vacuo*. The crude mixtures were purified by flash chromatography.




**1-(1-(2-(3-fluoro-6-methoxy-1,5-naphthyridin-4-yl)ethyl)piperidin-4-yl)-2-(*p*-tolyl)ethan-1-one (6a)**

The title compound was synthesized using **4a** according to General Procedure 3. Purification by flash chromatography (compound eluted in 0-20% ethyl acetate in hexanes) and concentration *in vacuo* afforded the title compound as a yellow solid (175 mg, 0.415 mmol, 65% yield).

$^{1}$HNMR ($CDCl_3$, 400 MHz) δ: 8.63 (s, 1H), 8.19 (d, *J* = 9.0 Hz, 1H), 7.15 (d, *J* = 7.9 Hz, 2H), 7.11-7.07 (m, 3H), 4.10 (s, 3H), 3.73 (s, 2H), 3.47-3.36 (m, 2H), 3.15-3.06 (m, 2H), 2.82-2.71 (m, 2H), 2.50-2.40 (m, 1H), 2.35 (s, 3H), 2.23-2.10 (m, 2H), 1.94-1.68 (m, 4H). HRMS (ESI) m/z calc'd for $C_{25}H_{29}FN_3O_2$ $[M+H]^+$: 422.22383; found: 422.22263. UPLC: rt: 3.60 min, purity: 95.5%.

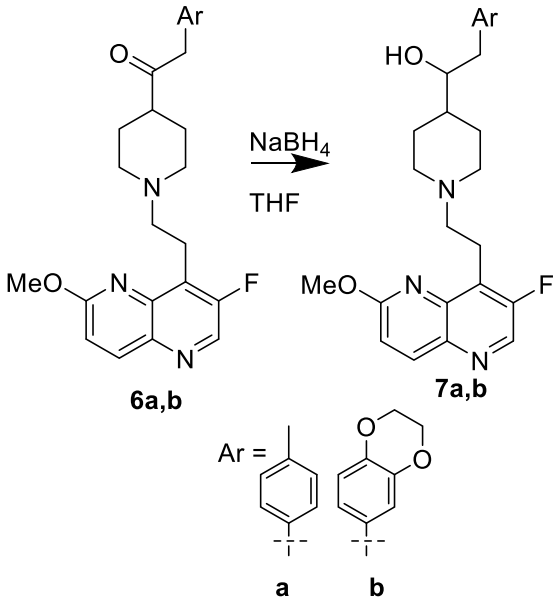
**2-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-(1-(2-(3-fluoro-6-methoxy-1,5-naphthyridin-4-yl)ethyl)piperidin-4-yl)ethan-1-one (6b)**

The title compound was synthesized using **4b** according to General Procedure 3. Purification by flash chromatography (compound eluted in 5-15% ethyl acetate in hexanes) and concentration *in vacuo* afforded the title compound as a yellow solid (55 mg, 0.118 mmol, 22% yield).

$^{1}$HNMR (DMSO-$d_6$, 400 MHz) δ: 8.77 (s, 1H), 8.28 (d, *J* = 9.0 Hz, 1H), 7.24 (d, J = 9.0 Hz, 1H), 6.75 (d, *J* = 8.2 Hz, 1H), 6.65 (d, *J* = 2.0 Hz, 1H), 6.59 (dd, *J* = 2.0, 8.2 Hz, 1H), 4.20 (s, 4H), 4.04 (s, 3H), 3.67 (s, 2H), 3.31-3.27 (m, 2H, obscured by water), 3.10-2.94 (m, 2H), 2.70-2.63 (m, 2H), 2.46-2.38 (m, 1H), 2.10-2.00 (m, 2H), 1.80-1.72 (m, 2H), 1.45-1.33 (m, 2H). $^{13}$CNMR (DMSO-d6, 100 MHz) δ: 210.08, 162.01, 156.82 (d, *J* =

254.1 Hz), 143.00, 142.00, 140.89 (d, *J* = 7.1 Hz), 140.43, 138.09 (d, *J* = 2.0 Hz), 137.88 (d, *J* = 27.8 Hz), expected 130 peak is lost in baseline noise, 127.68, 122.31, 118.10, 116.70, 115.31 (d, *J* = 2.3 Hz), 64.00, 63.95, 56.63, 53.58, 52.25, 47.27, 45.85, 27.43, 20.55.. HRMS (ESI) m/z calc'd for $C_{26}H_{29}FN_3O_4$ $[M+H]^+$: 466.21366; found: 466.2128. UPLC: rt: 3.399 min, purity: 96.9%.

4) Ketone Reduction: The requisite ketone (1.0 eq) was dissolved in methanol (0.2 M). Sodium borohydride (1.2 eq) was added, and the reaction was allowed to stir, monitoring by TLC for consumption of starting material. Once starting material was consumed, the reaction was diluted with saturated aqueous sodium carbonate and extracted 5x10 mL 10% methanol in dichloromethane. The combined organic layers were dried over sodium sulfate, decanted, and concentrated *in vacuo*. The crude mixtures were purified by flash chromatography.




**6a,b** **7a,b**

**a** **b**

**1-(1-(2-(3-fluoro-6-methoxy-1,5-naphthyridin-4-yl)ethyl)piperidin-4-yl)-2-(*p*-tolyl)ethan-1-ol (7a)**

The title compound was synthesized using **6a** according to General Procedure 4. Purification by flash chromatography (compound eluted in 0-0.5% methanol in DCM) and concentration *in vacuo* afforded the title compound as a clear oil (23 mg, 0.054 mmol, 15% yield).

$^1$HNMR ($CDCl_3$, 400 MHz) δ: 8.61 (s, 1H), 8.17 (d, *J* = 9.0 Hz, 1H), 7.13 (d, *J* = 8.3 Hz, 2H), 7.11 (d, *J* = 8.4 Hz, 2H), 7.07 (d, *J* = 9.0 Hz, 1H), 4.09 (s, 3H), 3.68-3.55 (m, 1H), 3.47-3.39 (m, 2H), 3.22-3.13 (m, 2H), 2.89 (dd, *J* = 3.2, 13.7 Hz, 1H), 2.80-2.71 (m, 2H), 2.54 (dd, *J* = 9.6, 13.7 Hz, 1H), 2.33 (s, 3H), 2.19-2.07 (m, 2H), 1.98-1.91 (m, 1H), 1.81-1.73 (m, 1H), 1.60-1.41 (m, 4H). $^{13}$CNMR (CDCl3, 100 MHz) δ: 162.56, 157.42 (d, *J* = 255.4 Hz), 141.78 (d, *J* = 7.1 Hz), 140.29, 138.66 (d, *J* = 2.0 Hz), 138.20, 137.92, 136.22, 135.61, 129.50, 129.41, 115.35 (d, *J* = 2.1 Hz), 76.33, 57.48, 53.98, 53.65 (overlapping signals), 41.55, 40.50, 28.55, 28.07, 21.15, 21.02. HRMS (ESI) m/z calc'd

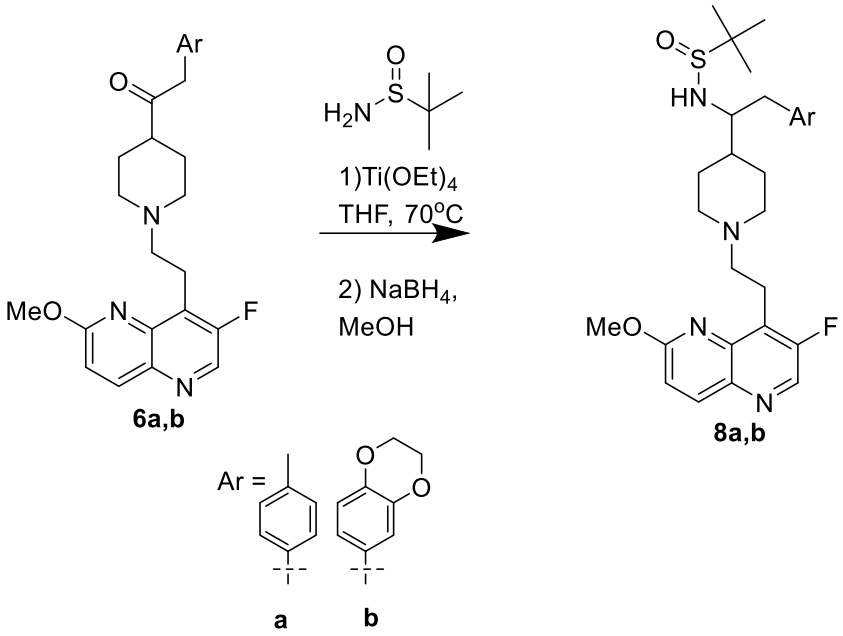
for $C_{25}H_{31}FN_3O_2$ $[M+H]^+$: 424.23948; found: 424.23825. UPLC: rt: 3.49 min, purity: 96.6%.

**2-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-(1-(2-(3-fluoro-6-methoxy-1,5-naphthyridin-4-yl)ethyl)piperidin-4-yl)ethan-1-ol (7b)**

The title compound was synthesized using **6b** according to General Procedure 4. Purification by flash chromatography (compound eluted in 0-0.5% methanol in DCM) and concentration *in vacuo* afforded the title compound as a white solid (5 mg, 0.011 mmol, 10% yield).

$^1$HNMR (DMSO-$d_6$, 400 MHz) δ: 8.77 (s, 1H), 8.28 (d, *J* = 9.0 Hz, 1H), 7.24 (d, *J* = 9.0 Hz, 1H), 6.71 (d, *J* = 8.2 Hz, 1H), 6.69 (d, *J* = 1.8 Hz, 1H), 6.63 (dd, *J* = 1.9, 8.2 Hz, 1H), 4.35-4.30 (m, 1H), 4.19 (s, 4H), 4.04 (s, 3H), 3.38-3.28 (m, 2H, obscured by water), 3.09-2.98 (m, 2H), 2.7-2.61 (m, 2H), 2.59 (dd, *J* = 3.7, 11.2 Hz, 1H), 2.41 (dd, *J* = 8.1, 13.7 Hz, 1H), 2.00-1.88 (m, 2H), 1.74-1.67 (m, 1H), 1.55-1.47 (m, 1H), 1.39-1.31 (m, 4H). HRMS (ESI) m/z calc'd for $C_{26}H_{31}FN_3O_4$ $[M+H]^+$: 468.22931; found: 468.22876. UPLC: rt: 3.322 min, purity: 97.7%.

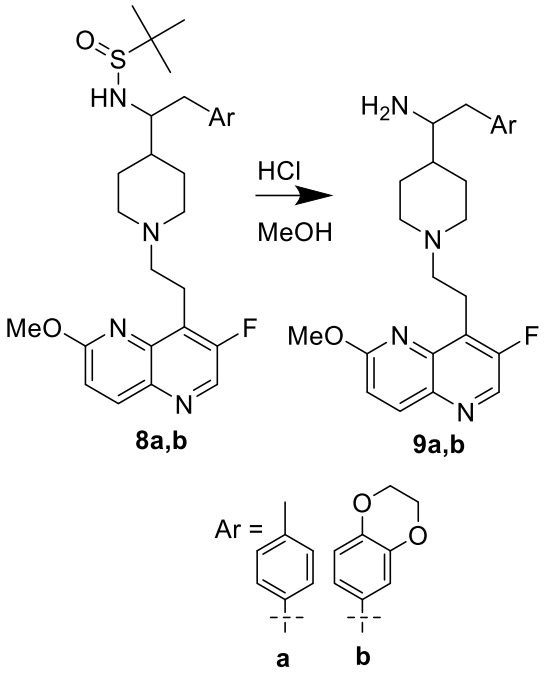
5) Reductive Amination on Ketone: The requisite ketone (1.0 eq) and racemic *tert*-butylsulfinamide (1.2 eq) were added to a round bottom flask. The flask was sparged with nitrogen followed by the addition of THF (0.2 M) and titanium ethoxide (1 eq). The reaction was stirred at 70°C overnight. Upon return, the reaction was cooled to room temperature, and methanol (equal volume to THF) was added followed by sodium borohydride (1.2 eq). The reaction was stirred an additional 30 minutes before diution with saturated aqueous sodium carbonate. The aqueous layer was extracted 5x15 mL ethyl acetate, and the combined organic layers were dried over sodium sulfate, decanted, and concentrated by rotary evaporation. The crude mixtures were used directly in the next step without purification.




**N-(1-(1-(2-(3-fluoro-6-methoxy-1,5-naphthyridin-4-yl)ethyl)piperidin-4-yl)-2-(*p*-tolyl)ethyl)-2-methylpropane-2-sulfinamide (8a)**
The title compound was synthesized using **6a** according to General Procedure 5 and used directly in the next step.

**N-(2-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-(1-(2-(3-fluoro-6-methoxy-1,5-naphthyridin-4-yl)ethyl)piperidin-4-yl)ethyl)-2-methylpropane-2-sulfinamide (8b)**
Title compound was synthesized using **6b** according to General Procedure 5 and directly in the next step.

6) Deprotection of Sulfinamide: The requisite sulfinamide (1 eq) was dissolved in methanol (0.2 M). 4 M HCl (2 eq) was added, and the reaction was allowed to stir, monitoring by TLC. Once starting material was consumed, reaction was basified to pH of ~12 with 1M aqueous sodium hydroxide. This mixture was extracted 5x10 mL 10% methanol in dichloromethane. The combined organic layers were dried over sodium sulfate, decanted, and concentrated by rotary evaporation. The crude mixtures were purified by flash chromatography.




**1-(1-(2-(3-fluoro-6-methoxy-1,5-naphthyridin-4-yl)ethyl)piperidin-4-yl)-2-(*p*-tolyl)ethan-1-amine (9a)**

The title compound was synthesized using **8a** according to General Procedure 6. Purification by flash chromatography (compound eluted in 0-1% methanol in DCM) and concentration *in vacuo* afforded the title compound as a white solid (8 mg, 0.0189 mmol, 25% yield).

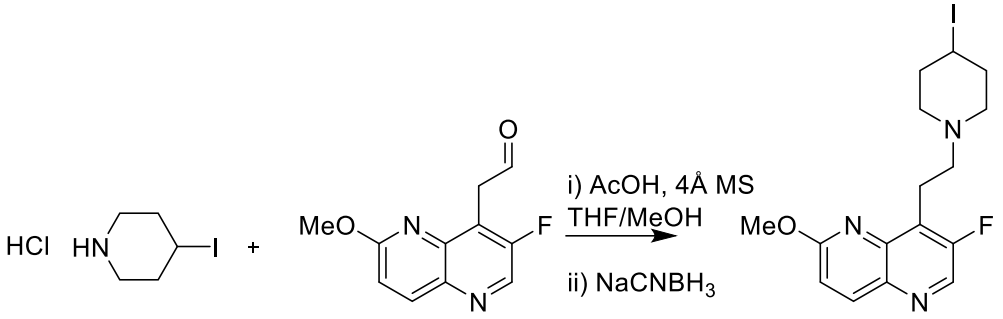
$^{1}$HNMR (DMSO-$d_6$, 400 MHz, contaminated w/ methanol) δ: 8.77 (s, 1H), 8.28 (d, *J* = 9.0 Hz, 1H), 7.24 (d, *J* = 9.0 Hz, 1H), 7.12 (s, 4H), 4.04 (s, 3H), 3.33-3.26 (m, 3H), 3.09-3.00 (m, 3H), 2.78 (dd, *J* = 6.4, 13.9 Hz, 1H), 2.69-2.62 (m, 3H), 2.27 (s, 3H), 1.95-1.86 (m, 2H), 1.69-1.63 (m, 1H), 1.59-1.55 (m, 1H), 1.43-1.18 (m, 4H). $^{13}$CNMR (DMSO-$d_6$, 100 MHz, contaminated w/ $CDCl_3$) δ: 162.38, 156.67 (d, *J* = 256.7 Hz), 140.55 (d, *J* = 6.3 Hz), 140.49, 138.23 (d, *J* = 10.9 Hz), 138.09 (d, *J* = 14.5 Hz), 135.87, 133.28, 129.29, 129.22, 126.31 (d, *J* = 12.6 Hz), 115.67 (d, *J* = 2.3 Hz), 55.00, 54.21, 53.66, 51.04 (d, *J* = 10.4 Hz), 35.16, 34.53, 24.74, 24.44, 20.64, 18.02. HRMS (ESI) m/z calc'd for $C_{25}H_{32}FN_4O$ $[M+H]^+$: 423.25547; found: 423.25473. UPLC: rt: 2.824 min, purity: 95.9%.

**2-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-(1-(2-(3-fluoro-6-methoxy-1,5-naphthyridin-4-yl)ethyl)piperidin-4-yl)ethan-1-amine (9b)**

The title compound was synthesized using **8b** according to General Procedure 6. Purification by flash chromatography (compound eluted in 0.6% methanol in DCM) and concentration *in vacuo* afforded the title compound as an off-white solid (8 mg, 0.0171 mmol, 33% yield).

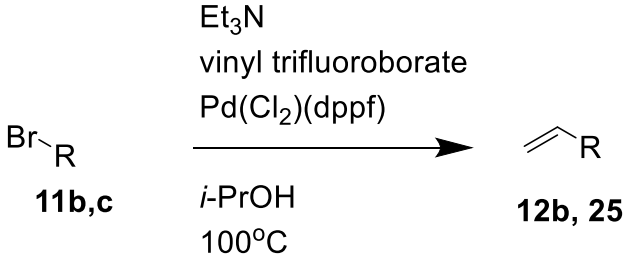
$^{1}$HNMR (DMSO-$d_6$, 400 MHz, contaminated with DMSO) δ: 8.77 (s, 1H), 8.28 (d, *J* = 9.0 Hz, 1H), 7.24(d, *J* = 9.0 Hz, 1H), 6.76 (d, *J* = 8.2 Hz, 1H), 6.72 (d, *J* = 1.9 Hz, 1H), 6.66 (dd, *J* = 2.0, 8.2 Hz, 1H), 4.98 (br s, 2H), 4.20 (s, 4H), 4.04 (s, 3H), 3.37-3.26 (m, 2H), 3.08-3.00(m, 2H), 2.90-2.83 (m, 1H), 2.71-2.63(m, 3H), 2.47-2.40 (m, 1H), 1.98-1.88 (m, 2H), 1.69-1.63(m, 1H), 1.60-1.54 (m, 1H), 1.40-1.18 (m, 3H). $^{13}$CNMR (DMSO-$d_6$, 100

MHz, contaminated with $CDCl_3$ and DMSO) δ: 161.98, 156.84 (d, *J* = 254.09), 143.09, 141.81, 140.92 (d, *J* = 7.1 Hz), 140.43, 138.09 (d, *J* = 1.8 Hz), 137.87 (d, *J* = 27.7 Hz), 131.55, 130.09 (d, *J* = 13.0 Hz), 121.89, 117.63, 116.81, 115.30 (d, *J* = 2.4 Hz), 63.97 (d, *J* = 8.3 Hz), 56.74, 56.22, 53.55, 53.09 (d, *J* = 3.5 Hz), 37.63, 28.21, 26.70, 20.69. HRMS (ESI) m/z calc'd for $C_{26}H_{32}FN_4O_3$ $[M+H]^+$: 467.24530; found: 467.24423. UPLC: rt: 2.735 min, purity: 98.2%.




**7-fluoro-8-(2-(4-iodopiperidin-1-yl)ethyl)-2-methoxy-1,5-naphthyridine (11)**
The title compound was synthesized using commercially available **10** according to General Procedure 3. Purification by flash chromatography (compound eluted in 5-15% ethyl acetate in hexanes) and concentration *in vacuo* afforded the title compound as a yellow solid (265 mg, 0.6396 mmol, 64% yield).
$^1$HNMR ($CDCl_3$, 400 MHz) δ: 8.62 (s, 1H), 8.18 (d, *J* = 9.0 Hz, 1H), 7.08 (d, *J* = 9.1 Hz, 1H), 4.34 (br s, 1H), 4.08 (s, 3H), 3.50-3.32 (br s, 2H), 2.94-2.66 (m, 4H), 2.57-2.30 (m, 2H), 2.25-2.09 (m, 4H).

7) **Suzuki Reaction.** The requisite aryl bromide (1eq), triethylamine (1.5 eq), $Pd(dppf)Cl_2$ (0.1 eq), and isopropanol (0.2 eq) were added to a pressure vial. The reaction was heated to 100°C overnight then cooled to room temperature and filtered through a celite plug, washing with ethyl acetate. The ethyl acetate solution was dried over sodium sulfate, decanted, and concentrated by rotary evaporation to afford crude mixtures that were purified by flash chromatography.

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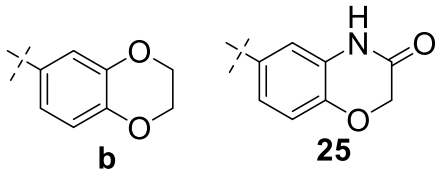
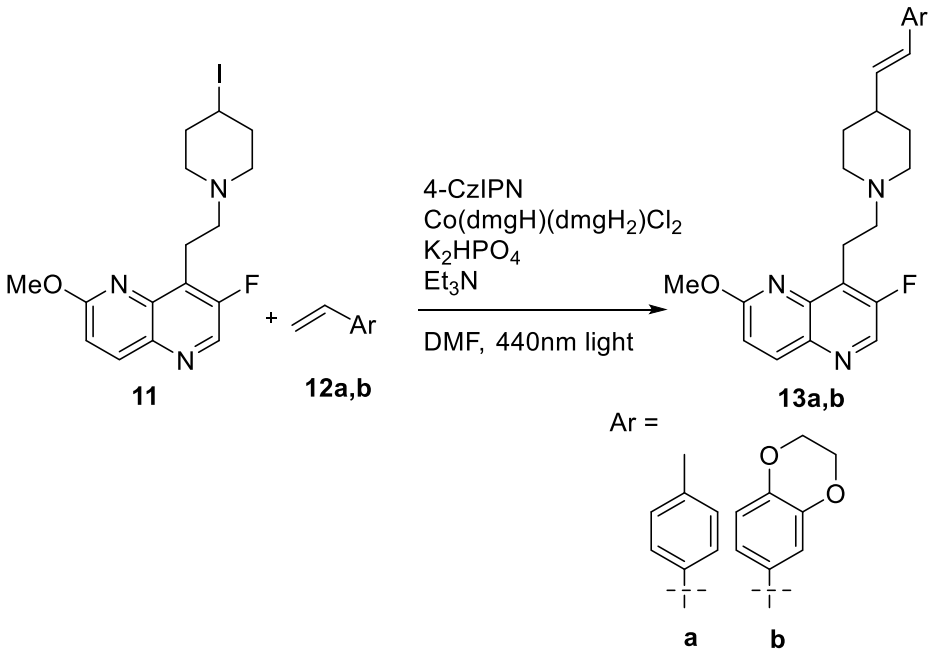


**6-vinyl-2,3-dihydrobenzo[b][1,4]dioxine (12b)**
The title compound was synthesized using commercially available **11b** according to general procedure 7. Purification by flash chromatography (compound eluted in 0-5% ethyl acetate in hexanes) and concentration *in vacuo* afforded the title compound (contaminated by residual starting material) as a clear oil (140 mg, 0.863 mmol, 43%).
**6-vinyl-2H-benzo[b][1,4]oxazin-3(4H)-one (25)**
The title compound was synthesized using commercially available **11c** according to general procedure 7. Purification by flash chromatography (compound eluted in 0-10% ethyl acetate in hexanes) and concentration *in vacuo* afforded the title compound as a white solid (320 mg, 1.83 mmol, 91%).
$^1$HNMR ($CDCl_3$, 400 MHz) δ: 7.75 (s, 1H), 7.03 (dd, *J* = 1.9, 8.4 Hz, 1H), 6.93 (d, *J* = 8.3 Hz, 1H), 6.83 (d, *J* = 1.9 Hz, 1H), 6.62 (dd, *J* = 10.8, 17.6 Hz, 1H), 5.63 (dd, *J* = 0.6, 17.5 Hz, 1H), 5.21 (dd, *J* = 0.5, 10.9 Hz, 1H), 4.62 (s, 2H).

8) <u>Photo-Heck Coupling:</u> 4-CZIPN (0.05 eq), Co(dmgH)(dmgH$_2$)Cl$_2$ (0.03 eq), the requisite iodo-piperidine (1.0 or 2.0 eq), dibasic potassium phosphate (2.0 eq), and aromatic vinyl groups (1.0 eq) were added to a round bottom flask. DMF (0.1 M) was added, followed by triethylamine (2 eq), and the reaction was irradiated with 440 nm blue light, positioned 5-20 cm from the flask, for 17-24 hours. The reaction was stirred for 17-24 hours, monitoring by TLC. Once alkene starting material was consumed, the reaction was stopped by turning off the light. The reaction was diluted with water and extracted 5x15 mL ethyl acetate. The combined organic layers dried over sodium sulfate, decanted, and concentrated by rotary evaporation. The crude mixtures were purified by flash chromatography.



**(*E*)-7-fluoro-2-methoxy-8-(2-(4-(4-methylstyryl)piperidin-1-yl)ethyl)-1,5-naphthyridine (13a)**

The title compound was synthesized using **11** and commercially available **12a** according to General Procedure 8. Purification by flash chromatography (compound eluted in 5-40% ethyl acetate in hexanes) and concentration *in vacuo* afforded the title compound as a yellow solid (158 mg, 0.390 mmol, 40% yield).

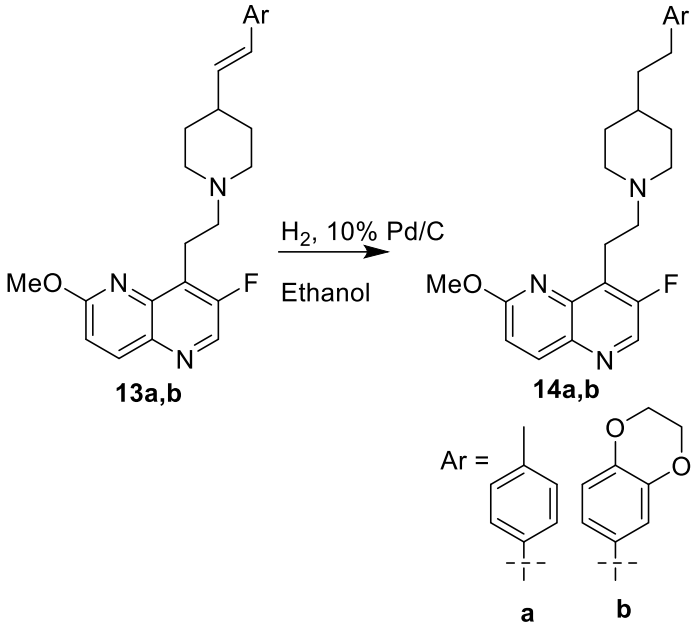
$^{1}$HNMR ($CD_3OD$, 400 MHz) δ: 8.64 (s, 1H), 8.21 (d, *J* = 9.1 Hz, 1H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.18 (d, *J* = 9.1 Hz, 1 H), 7.08 (d, *J* = 8.0 Hz, 2H), 6.38 (d, *J* = 16.0 Hz, 1H), 6.15 (dd, *J* = 16.0, 6.9 Hz, 1H), 4.12 (s, 3H), 3.53-3.47 (m, 2H), 3.22-3.15 (m, 2H), 2.84-2.77 (m, 2H), 2.32-2.14 (m, 3H), 2.29 (s, 3H), 1.88-1.79 (m, 2H), 1.63-1.51 (m, 2H). $^{13}$CNMR ($CDCl_3$, 100 MHz) δ: 162.55, 157.43 (d, *J* = 255.2 Hz), 141.80 (d, *J* = 7.1 Hz), 140.29, 138.66 (d, *J* = 2.0 Hz), 138.06 (d, *J* = 28.1 Hz), 136.83, 135.05, 134.21, 130.72 (d, *J* = 12.6 Hz), 129.33, 128.16, 126.03, 115.33 (d, *J* = 2.6 Hz), 57.59, 53.97, 53.52, 39.47, 32.34, 21.27, 21.06. HRMS (ESI) m/z calc'd for $C_{25}H_{29}FN_3O$ $[M+H]^+$: 406.22892; found: 406.2283. UPLC: rt: 3.93 min, purity: 95.7%.

**(*E*)-8-(2-(4-(2-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)vinyl)piperidin-1-yl)ethyl)-7-fluoro-2-methoxy-1,5-naphthyridine (13b)**

The title compound was synthesized using **47** and **46b** according to General Procedure 8. Purification by flash chromatography (compound eluted in 5-20% ethyl acetate in hexanes) and concentration *in vacuo* afforded the title compound as a white solid (105 mg, 0.234 mmol, 28% yield).

$^{1}$HNMR ($CDCl_3$, 400 MHz) δ: 8.61, (s, 1H), 8.17 (d, *J* = 9.0 Hz, 1H), 7.07 (d, *J* = 9.0 Hz, 1H), 6.87 (d, *J* = 1.9 Hz, 1H), 6.83 (dd, *J* = 2.0, 8.4 Hz, 1H), 6.78 (d, *J* = 8.3 Hz, 1H), 6.26 (d, *J* = 15.9 Hz, 1H), 6.02 (d, *J* = 7.0, 15.9 Hz, 1H), 4.24 (s, 4H), 4.09 (s, 3H), 3.47-3.38 (m, 2H), 3.16-3.07 (m, 2H), 2.80-2.71 (m, 2H), 2.25-2.06 (m, 3H), 1.83-1.73 (m, 2H), 1.67-1.48 (m, partially obscured by water, 2H). $^{13}$CNMR ($CDCl_3$, 100 MHz) δ: 162.56, 157.43 (d, *J* = 255.5 Hz), 143.64, 142.92, 141.81 (d, *J* = 7.0 Hz), 140.30, 138.67 (d, *J* = 2.0 Hz), 138.21, 137.93, 133.79, 131.75, 127.59, 119.52, 117.36, 115.34 (d, *J* = 2.6 Hz), 114.64, 64.59, 64.54, 57.61, 53.98, 53.53, 39.40, 32.39, 29.85, 21.08. HRMS (ESI) m/z calc'd for $C_{26}H_{29}FN_3O_3$ $[M+H]^+$: 450.21875; found: 450.21744. UPLC: rt: 3.66 min, purity: 98.76%.

9) Alkene Hydrogenation: The alkene starting material (1 eq) was dissolved in methanol (0.2 M), and 10% Pd/C (0.1 eq) was added. The reaction was sparged once with a nitrogen balloon, followed by once with a hydrogen balloon. A hydrogen balloon was the attached to the reaction flask by needle through a septum and allowed to stir overnight. Upon return, the reaction was sparged once with a nitrogen balloon and filtered through a celite plug, washing with methanol. The organics were concentrated by rotary evaporation to afford crude mixtures that were purified by flash chromatography.




**7-fluoro-2-methoxy-8-(2-(4-(4-methylphenethyl)piperidin-1-yl)ethyl)-1,5-naphthyridine (14a)**

The title compound was synthesized using **13a** according to General Procedure 9. Purification by flash chromatography (compound eluted in 0-20% ethyl acetate in hexanes) and concentration *in vacuo* afforded the title compound (4 mg, 0.010 mmol, 16% yield).

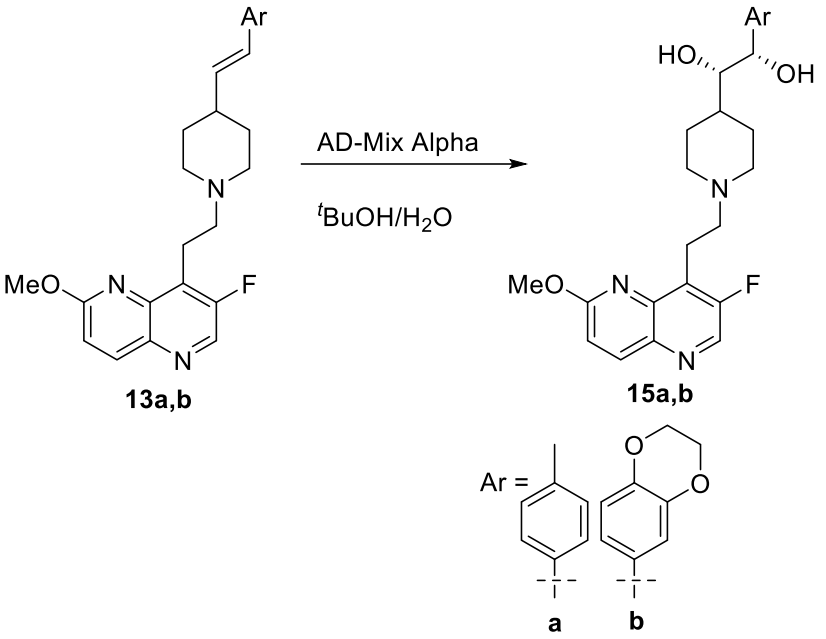
$^{1}$HNMR ($CDCl_3$, 400 MHz) δ: 8.61 (s, 1H), 8.17 (d, *J* = 9.0 Hz, 1H), 7.12-7.03 (m, 5H), 4.08 (s, 3H), 3.45-3.36 (m, 2H), 3.12-3.04 (m, 2H), 2.76-2.67 (m, 2H), 2.64-2.55 (m, 2H), 2.32 (s, 3H), 2.16-2.03 (m, 2H), 1.83-1.72 (m, 2H), 1.61-1.51 (m, 2H), 1.40-1.27 (m, 3H). HRMS (ESI) m/z calc'd for $C_{25}H_{31}FN_3O$ $[M+H]^+$: 408.24457; found: 408.24403. UPLC: rt: 3.97 min, purity: 96.9%.

**8-(2-(4-(2-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)ethyl)piperidin-1-yl)ethyl)-7-fluoro-2-methoxy-1,5-naphthyridine (14b)**

The title compound was synthesized using **13b** according to General Procedure 9. Purification by flash chromatography (compound eluted in 5-15% ethyl acetate in hexanes) and concentration *in vacuo* afforded the title compound (15 mg, 0.033 mmol, 17% yield).

$^{1}$HNMR (DMSO-$d_6$, 400 MHz, contaminated w/ DCM) δ: 8.76 (s, 1H), 8.27 (d, *J* = 9.0 Hz, 1H), 7.23 (d, *J* = 9.0 Hz, 1H), 6.71 (d, *J* = 8.1 Hz, 1H), 6.64 (d, *J* = 1.8 Hz, 1H), 6.60 (dd, J = 1.9, 8.2 Hz, 1H), 4.18 (s, 4H), 4.03 (s, 3H), 3.31-3.27 (m, 2H), 2.97-2.94 (m, 2H), 2.68-2.60 (m, 2H), 2.46-2.42 (m, 2H), 2.02-1.92 (m, 2H), 1.68-1.61 (m, 2H), 1.44-1.37 (m, 2H), 1.22-1.03 (m, 2H). $^{13}$CNMR (DMSO-d6, 100 MHz) δ: 161.97, 156.80 (d, *J* = 254.2 Hz), 143.02, 141.25, 140.89 (d, *J* = 6.8 Hz), 140.39, 138.07 (d, *J* = 1.6 Hz), 137.85 (d, *J* = 27.8 Hz), 135.34, expected 130 peak is lost in baseline noise, 120.80, 116.65, 116.52, 115.27, 64.00, 63.89, 56.83, 53.52, 53.02, 37.98, 34.65, 31.90, 31.50, 20.62. HRMS (ESI) m/z calc'd for $C_{26}H_{31}FN_3O_3$ $[M+H]^+$: 452.2344; found: 452.23306. UPLC: rt: 3.694 min, purity: 98.0%.

10) Asymmetric Dihydroxylation: The alkene starting material (1 eq) was dissolved in *tert*-butanol (0.1 M) and diluted with water (0.1 M), and the respective AD-mix (1.2 g/mmol starting material) was added. The reaction was stirred overnight, monitoring by TLC. Once starting material was consumed, the reaction was quenched with aqueous, saturated sodium sulfite and allowed to stir for 15 minutes. The reaction was diluted with water and extracted 5x10 mL 10% methanol in dichloromethane. The combined organic layers were dried over sodium sulfate, decanted, and concentrated by rotary evaporation to afford crude mixtures that were purified by flash chromatography.




**(1*S*,2*S*)-1-(1-(2-(3-fluoro-6-methoxy-1,5-naphthyridin-4-yl)ethyl)piperidin-4-yl)-2-(*p*-tolyl)ethane-1,2-diol (15a)**

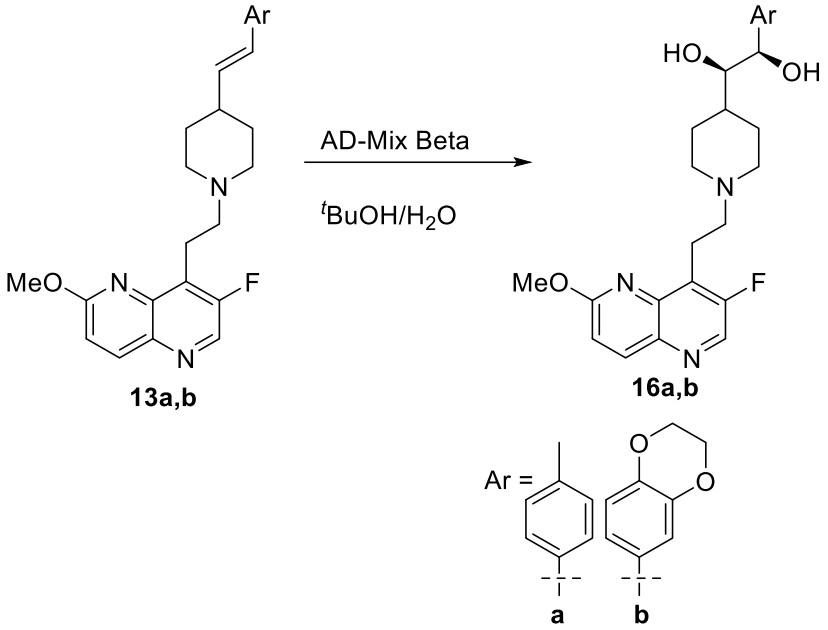
The title compound was synthesized using **13a** according to General Procedure 10 with AD-mix α. Purification by flash chromatography (compound eluted in ethyl acetate) and concentration *in vacuo* afforded the title compound as a clear oil (65 mg, 0.148 mmol, 60% yield).

$^1$HNMR ($CD_3OD$, 400 MHz) δ: 8.63 (s, 1H), 8.20 (d, *J* = 9.1 Hz, 1H), 7.25 (d, *J* = 8.0, 2H), 7.19-7.13 (m, 3H), 4.59 (d, *J* = 5.7 Hz, 1H), 4.10 (s, 3H), 3.50-3.40 (m, 3H), 3.21-3.11 (m, 2H), 2.79-2.71 (m, 2H), 2.32 (s, 3H), 2.14-2.02 (m, 2H), 1.90-1.82 (m, 1H), 1.68-1.47 (m, 3H), 1.41-1.31 (m, 1H). $^{13}$CNMR (DMSO-d6, 100 MHz, contaminated w/ ethyl acetate) δ: 161.95, 156.82 (d, *J* = 254.1 Hz), 140.91 (d, *J* = 7.1 Hz), 140.75, 140.39, 138.07 (d, *J* = 2.2 Hz), 137.84 (d, *J* = 27.8 Hz), 135.59, 130.16 (d, *J* = 13.0 Hz), 128.30, 126.64, 115.25 (d, *J* = 2.0 Hz), 78.09, 73.20, 56.86, 53.52, 53.18, 37.57, 29.09, 26.49, 20.74, 20.69, 20.67. HRMS (ESI) m/z calc'd for $C_{25}H_{31}FN_3O_3$ $[M+H]^+$: 440.2344; found: 440.23407. UPLC: rt: 3.271 min, purity: 95.6%. Enantiomeric excess (ee) determined to be 96.3% by chiral HPLC (98/2 hexane/reagent alcohol).

**(1*S*,2*S*)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-(1-(2-(3-fluoro-6-methoxy-1,5-naphthyridin-4-yl)ethyl)piperidin-4-yl)ethane-1,2-diol (15b)**

The title compound was synthesized using **13b** according to General Procedure 10 with AD-mix α. Purification by flash chromatography (compound eluted in 0-1% methanol in DCM) and concentration *in vacuo* afforded the title compound as a clear oil (15 mg, 0.031 mmol, 12% yield).

$^1$HNMR (DMSO-$d_6$, 400 MHz, contaminated with DMSO) δ: 8.76 (s, 1H), 8.27 (d, *J* = 9.0 Hz, 1H), 7.23 (d, *J* = 9.0 Hz, 1H), 6.80 (s, 1H), 6.77-6.72 (m, 2H), 4.92 (d, *J* = 4.9 Hz, 1H), 4.36 (t, *J* = 5.2 Hz, 1H), 4.26 (br d, J = 5.5 Hz, 1H), 4.2 (s, 4H), 4.03 (s, 3H), 3.31-3.23 (m, 2H, partially obscured by water), 3.18-3.12 (m, 1H, partially obscured by methanol), 3.03-2.92 (m, 2H), 2.69-2.57 (m, 2H), 1.96-1.77 (m, 2H), 1.72-1.63 (m, 1H), 1.49-1.11 (m, 4H). $^{13}$CNMR (DMSO-d6, 100 MHz) δ: 161.98, 156.84 (d, *J* = 254.2 Hz), 142.77, 142.08, 140.93 (d, *J* = 7.1 Hz), 140.43, 138.09 (d, *J* = 2.2 Hz), 137.88 (d, *J* = 27.7 Hz), 136.98, expected 130 peak is lost in baseline noise, 119.48, 116.20, 115.41, 115.30 (d, *J* = 2.1 Hz), 77.98, 72.77, 64.02, 63.98, 56.84, 53.57, 53.16, 37.55, 29.00, 26.54, 20.65 (overlapping signals).HRMS (ESI) m/z calc'd for $C_{26}H_{31}FN_3O_5$ $[M+H]^+$: 484.22423; found: 484.22348. UPLC: rt: 3.103 min, purity: 97.6%. Enantiomeric excess (ee) determined to be 97.8% by chiral HPLC (90/10 hexane/reagent alcohol with 0.1% diethylamine as an additive).




**(1*R*,2*R*)-1-(1-(2-(3-fluoro-6-methoxy-1,5-naphthyridin-4-yl)ethyl)piperidin-4-yl)-2-(*p*-tolyl)ethane-1,2-diol (16a)**

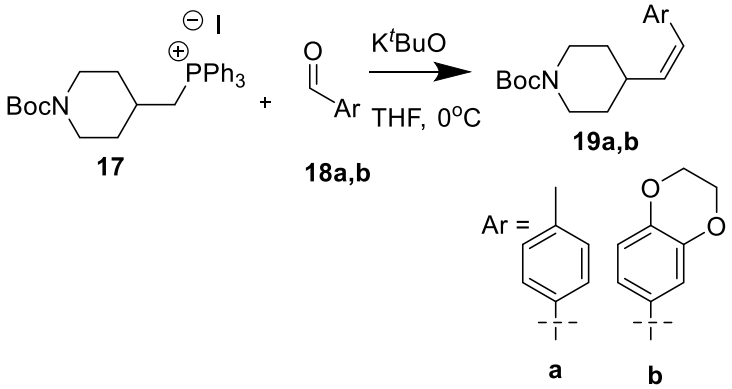
The title compound was synthesized using **13a** according to General Procedure 10 with AD-mix β. Purification by flash chromatography (compound eluted in DCM) and concentration *in vacuo* afforded the title compound as a clear oil (55 mg, 0.148 mmol, 60% yield).

$^1$HNMR ($CD_3OD$, 400 MHz) δ: 8.63 (s, 1H), 8.20 (d, *J* = 9.1 Hz, 1H), 7.25 (d, *J* = 8.0 Hz, 2H), 7.19-7.13 (m, 3H) 4.59 (d, *J* = 5.8 Hz, 1H), 4.10 (s, 3H), 3.50-3.40 (m, 3H), 3.23-3.14 (m, 2H), 2.83-2.73 (m, 2H), 2.32 (s, 3H), 2.19-2.04 (m, 2H), 1.91-1.83 (m, 1H), 1.70-1.49 (m, 3H), 1.42-1.32 (m, 1H). HRMS (ESI) m/z calc'd for $C_{25}H_{31}FN_3O_3$

[M+H]$^+$: 440.2344; found: 440.23349. UPLC: rt: 3.27 min, purity: 93.3%. Enantiomeric excess (ee) determined to be 100% by chiral HPLC (98/2 hexane/reagent alcohol).

**(1*R*,2*R*)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-(1-(2-(3-fluoro-6-methoxy-1,5-naphthyridin-4-yl)ethyl)piperidin-4-yl)ethane-1,2-diol (16b)**
The title compound was synthesized using **13b** according to General Procedure 10 with AD-mix β. Purification by flash chromatography (compound eluted in ethyl acetate) and concentration *in vacuo* afforded the title compound as a clear oil (16 mg, 0.033 mmol, 20% yield).
$^1$HNMR (DMSO-$d_6$, 400 MHz, contaminated with ethyl acetate) δ: 8.76 (s, 1H), 8.27 (d, *J* = 9.0 Hz, 1H), 7.23 (d, *J* = 9.0 Hz, 1H), 6.80 (s, 1H), 6.77-6.72 (m, 2H), 4.92 (d, *J* = 5.0 Hz, 1H), 4.36 (t, *J* = 5.2 Hz, 1H), 4.25 (d, *J* = 5.9 Hz, 1H), 4.20 (s, 4H), 4.03 (s, 3H), 3.30-3.24 (m, 2H), 3.14 (q, J = 5.4 Hz, 1H), 3.01-2.92 (m, 2H), 2.61 (t, *J* = 7.4 Hz, 2H), 1.92-1.78 (m, 2H), 1.71-1.63 (m, 1H), 1.47-1.20 (m, 4H). $^{13}$CNMR (DMSO-d6, 100 MHz, contaminated w/ ethyl acetate) δ: 161.96, 156.83 (d, *J* = 254.2 Hz), 142.75, 142.07, 140.93 (d, *J* = 7.0 Hz), 140.41, 138.08 (d, *J* = 2.1 Hz), 137.86 (d, *J* = 27.8 Hz), 136.98, expected 130 peak is lost in baseline noise, 119.46, 116.18, 115.39, 115.27 (d, *J* = 2.2 Hz), 78.00, 72.75, 64.00, 63.97, 56.89, 53.54, 53.20, 37.61, 29.05, 26.60, 20.74, 20.68. HRMS (ESI) m/z calc'd for $C_{26}H_{31}FN_3O_5$ [M+H]$^+$: 484.22423; found: 484.2233. UPLC: rt: 3.073 min, purity: 94.2%. Enantiomeric excess (ee) determined to be 99% by chiral HPLC (90/10 hexane/reagent alcohol with 0.1% diethylamine as an additive).

11) Wittig Reaction: Commercially available **17** (2.0 eq) was suspended in THF (0.2 M), and potassium *tert*-butoxide (1 M solution in THF, 2.0 eq) was added. This mixture was stirred for 1 hour, becoming orange in color. The reaction was then cooled to 0°C and stirred an additional 5 mins. Aldehyde (1.0 eq) was added, and the reaction was stirred overnight, warming to room temperature. Upon return, reaction was quenched with saturated aqueous ammonium chloride and filtered through a celite plug, washing with 3 volumes of ethyl acetate. The organics were dried over sodium sulfate, decanted, and concentrated by rotary evaporation to afford crude mixtures that were purified by flash chromatography.



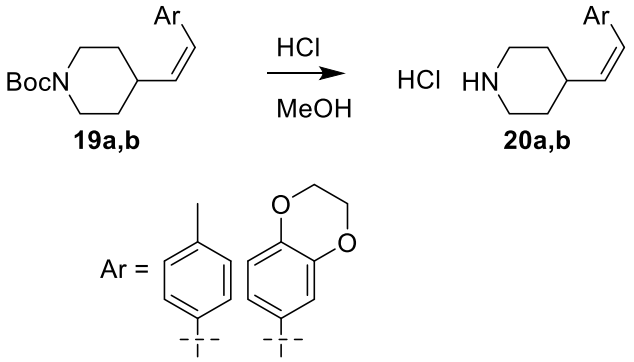

***tert*-butyl (*Z*)-4-(4-methylstyryl)piperidine-1-carboxylate (19a)**
The title compound was synthesized using commercially available **18a** using General Procedure 11. Purification by flash chromatography (compound eluted in 0-2% ethyl acetate in hexanes) and concentration *in vacuo* afforded the title compound as a clear oil (440 mg, 1.46 mmol, 73% yield).

$^1$HNMR ($CDCl_3$, 400 MHz) δ: 7.14 (s, 4H), 6.36 (d, *J* = 11.7 Hz, 1H), 5.41 (dd, *J* = 10, 11.6 Hz, 1H), 4.10-4.05 (m, 2H), 2.77-2.66 (m, 3H), 2.35 (s, 3H), 1.70-1.64 (m, 2H), 1.46 (s, 9H), 1.41-1.30 (m, 2H).

**_tert_-butyl (_Z_)-4-(2-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)vinyl)piperidine-1-carboxylate (19b)**

The title compound was synthesized using commercially available **18b** according to General Procedure 11. Purification by flash chromatography (compound eluted in 0-5% ethyl acetate in hexanes) and concentration *in vacuo* afforded the title compound as a yellow oil (65% average yield).

$^1$HNMR ($CDCl_3$, 400 MHz) δ: 6.83 (d, *J* = 8.3 Hz, 1H), 6.77 (d, *J* = 2.0 Hz, 1H), 6.73 (dd, *J* = 2.0, 8.2 Hz, 1H), 6.27 (d, *J* = 11.6 Hz, 1H), 5.36 (dd, *J* = 10.0, 11.6 Hz, 1H), 4.27 (s, 4H), 4.13-4.01 (m, 2H), 2.80-2.67 (m, 3H), 1.70-1.63 (m, 2H), 1.46 (s, 9H), 1.40-1.28 (m, 2H).

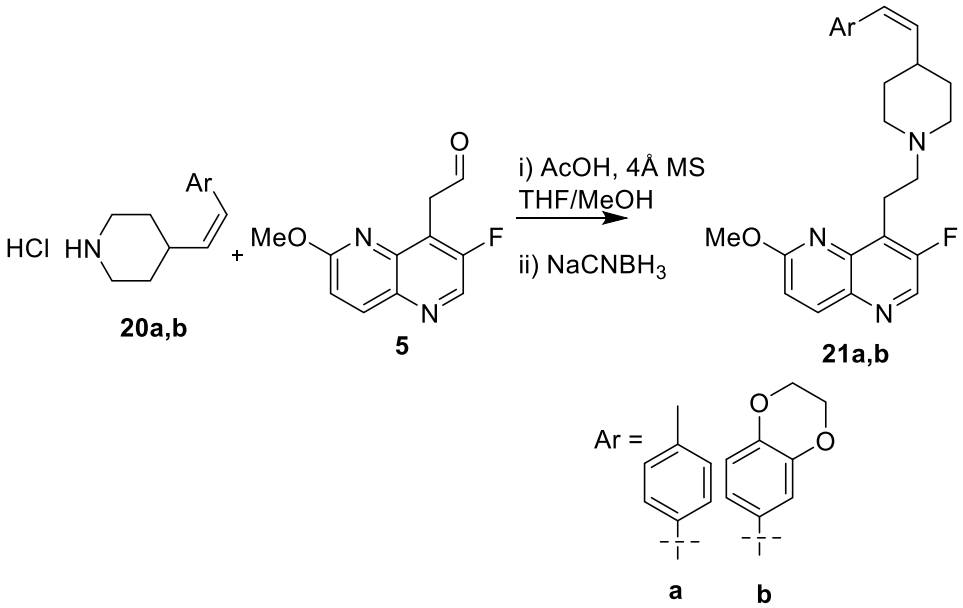



**(_Z_)-4-(4-methylstyryl)piperidine*hydrogen chloride (20a)**

The title compound was synthesized using **19a** according to General Procedure 2 and used directly in the next step.

**(_Z_)-4-(2-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)vinyl)piperidine*hydrogen chloride (20b)**

The title compound was synthesized using **19b** according to General Procedure 2 and used directly in the next step.




**(*Z*)-7-fluoro-2-methoxy-8-(2-(4-(4-methylstyryl)piperidin-1-yl)ethyl)-1,5-naphthyridine (21a)**

The title compound was synthesized using **20a** according to General Procedure 3. Purification by flash chromatography (compound eluted in 0-10% ethyl acetate in hexanes) and concentration *in vacuo* afforded the title compound as a yellow oil (91 mg, 0.224 mmol, 62% yield).

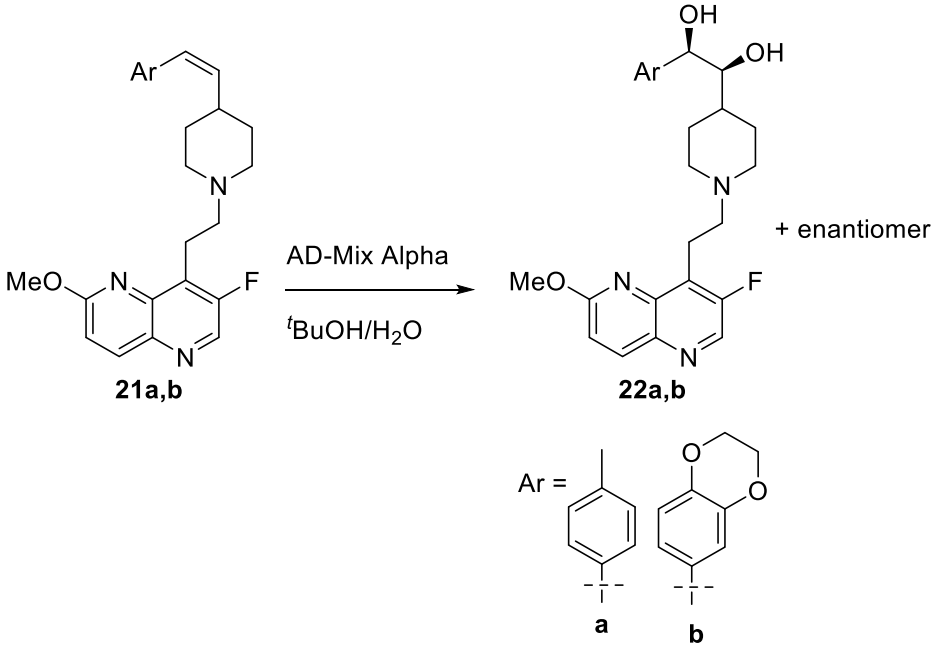
$^{1}$HNMR (DMSO-$d_6$, 400 MHz) δ: 8.77 (s, 1H), 8.27 (d, *J* = 9.0 Hz, 1H), 7.23 (d, *J* = 9.1 Hz, 1H), 7.16 (d, *J* = 8.5 Hz, 2H), 7.13 (d, *J* = 8.6 Hz, 2H), 6.30 (d, *J* = 11.6 Hz, 1H), 5.42 (dd, *J* = 10.2, 11.2 Hz, 1H), 4.03 (s, 3H), 3.31-3.28 (m, 3H) 2.98-2.95 (m, 2H), 2.68-2.63 (m, 2H), 2.28 (s, 3H), 2.07-2.02 (m, 2H), 1.62-1.59 (m, 2H), 1.40-1.30 (m, 2H). $^{13}$CNMR (DMSO-d6, 100 MHz) δ: 161.98, 156.80 (d, *J* = 254.3 Hz), 140.90 (d, *J* = 7.0 Hz), 140.39, 138.08 (d, *J* = 1.4 Hz), 137.85 (d, *J* = 27.8 Hz),136.59, 135.89, 134.19, expected 130 peak is lost in baseline noise, 128.91, 128.17, 127.54, 115.27, 56.87, 53.55, 52.41, 34.65, 31.96, 20.68, 20.60. HRMS (ESI) m/z calc'd for $C_{25}H_{29}FN_3O$ $[M+H]^+$: 406.22892; found: 406.22882. UPLC: rt: 3.92 min, purity: 97.7%.

**(*Z*)-8-(2-(4-(2-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)vinyl)piperidin-1-yl)ethyl)-7-fluoro-2-methoxy-1,5-naphthyridine (21b)**

The title compound was synthesized using **20b** according to General Procedure 3. Purification by flash chromatography (compound eluted in 0-10% ethyl acetate in hexanes) and concentration *in vacuo* afforded the title compound as a clear oil (197 mg, 0.438 mmol, 58% yield).

$^{1}$HNMR ($CDCl_3$, 400 MHz) δ: 8.61 (s, 1H), 8.17 (d, *J* = 9.0 Hz, 1H), 7.07 (d, *J* = 9.0 Hz, 1H), 6.82 (d, *J* = 8.3 Hz, 1H), 6.78 (d, *J* = 1.9 Hz, 1H), 6.74 (dd, *J* = 1.9, 8.3 Hz, 1H), 6.25 (d, *J* = 11.6 Hz, 1H), 5.39 (dd, *J* = 10.0, 11.6 Hz, 1H), 4.26 (s, 4H, 4.08 (s, 3H), 3.46-3.38 (m, 2H), 3.13-3.04 (m, 2H), 2.79-2.70 (m, 2H), 2.67-2.55 (m, 1H), 2.25-2.13 (m, 2H), 1.78-1.70 (m, 2H), 1.62-1.47 (m, partially obscured by water, 2H). $^{13}$CNMR ($CDCl_3$, 100 MHz) δ: 162.56, 157.42 (d, *J* = 255.4 Hz), 143.29, 142.54, 141.80 (d, *J* = 6.8 Hz), 140.29, 138.66 (d, *J* = 2.1 Hz), 138.20, 137.92, 136.56, 131.43, 127.48, 122.13, 117.34, 117.14, 115.34 (d, *J* = 2.6 Hz), 64.57, 64.55, 57.64, 54.00, 53.17,

35.04, 32.57, 20.99. HRMS (ESI) m/z calc'd for $C_{26}H_{29}FN_3O_3$ $[M+H]^+$: 450.21875; found: 450.21753. UPLC: rt: 3.70 min, purity: 98.57%.




**(1*S*,2*R*)-1-(1-(2-(3-fluoro-6-methoxy-1,5-naphthyridin-4-yl)ethyl)piperidin-4-yl)-2-(p-tolyl)ethane-1,2-diol (22a)**

The title compound was synthesized using **21a** according to General Procedure 10 with AD-mix α. Purification by flash chromatography (compound eluted in 0-1% methanol in DCM) and concentration *in vacuo* afforded the title compound white solid (14 mg, 0.032 mmol, 16% yield).

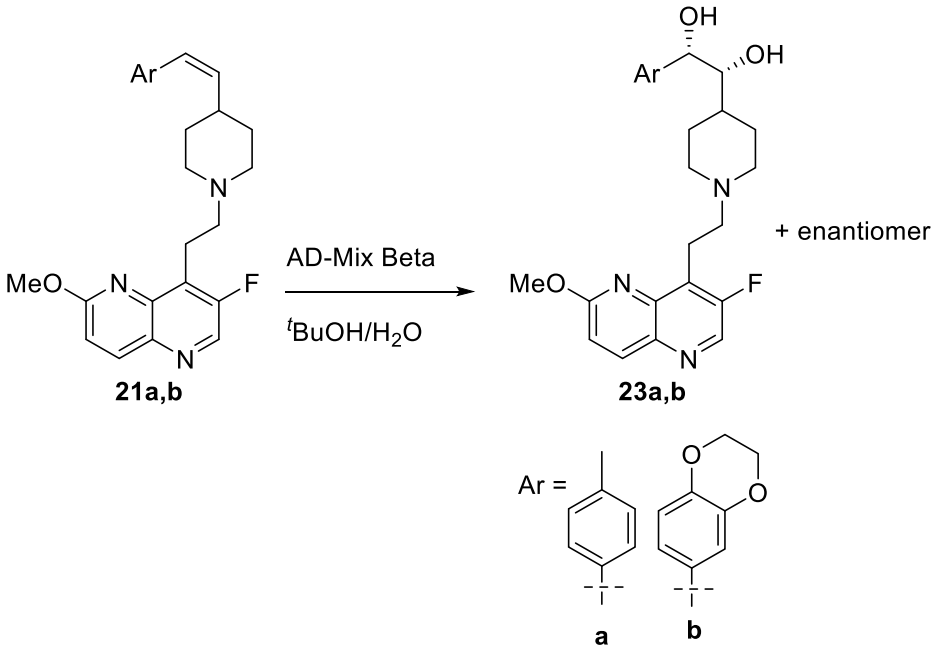
$^1$HNMR (DMSO-$d_6$, 400 MHz, contaminated w/ DCM) δ: 8.76 (s, 1H), 8.27 (d, *J* = 9.0 Hz, 1H), 7.23 (d, *J* = 9.0 Hz, 1H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.07 (d, *J* = 7.8 Hz, 2H), 5.04 (d, *J* = 4.8 Hz, 1H), 4.31 (dd, *J* = 5.0, 6.9 Hz, 1H), 4.15 (d, *J* = 6.1 Hz, 1H), 4.04 (s, 3H), 3.32-3.27 (m, 2H, partially obscured by water), 3.05-2.95 (m, 2H), 2.65-2.59 (m, 2H), 2.27 (s, 3H), 1.99-1.86 (m, 2H), 1.68-1.61 (m, 1H), 1.56-1.45 (m, 1H), 1.44-1.37 (m, 2H), 1.37-1.25 (m, 2H). $^{13}$CNMR (DMSO-d6, 100 MHz) δ: 161.95, 156.82 (d, *J* = 254.2 Hz), 141.29, 140.93 (d, *J* = 7.1 Hz), 140.40, 138.08 (d, *J* = 1.4 Hz), 137.86 (d, *J* = 27.8), 135.37, 130.19 (d, *J* = 13.0 Hz), 127.95, 127.36, 115.25 ( d, *J* = 2.5 Hz), 77.14, 73.29, 56.95 53.54, 53.45, 53.27, 37.27, 29.11, 25.38, 20.69 (overlapping signals). HRMS (ESI) m/z calc'd for $C_{25}H_{31}FN_3O_3$ $[M+H]^+$: 440.2344; found: 440.23389. UPLC: rt: 3.188 min, purity: 95.9%. Enantiomeric excess (ee) determined to be 43.3% by chiral HPLC (99/1 hexane/reagent alcohol).

**(1*R*,2*S*)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-(1-(2-(3-fluoro-6-methoxy-1,5-naphthyridin-4-yl)ethyl)piperidin-4-yl)ethane-1,2-diol (22b)**

The title compound was synthesized using **21b** according to General Procedure 10 with AD-mix α. Purification by flash chromatography (compound eluted in 0-2% methanol in DCM) and concentration *in vacuo* afforded the title compound as a white solid (7 mg, 0.015 mmol, 11% yield).

$^1$HNMR (DMSO-$d_6$, 400 MHz; contaminated w/ DCM) δ: 8.76 (s, 1H), 8.27 (d, *J* = 9.0 Hz, 1H), 7.23 (d, *J* = 9.0 Hz, 1H), 6.82 (d, *J* = 1.8 Hz, 1H), 6.77 (dd, *J* = 1.8, 8.3 Hz, 1H),

6.73 (d, *J* = 8.2 Hz, 1H), 5.00 (d, *J* = 4.9 Hz, 1H). 4.24-4.20 (m, 1H), 4.20 (s, 4H), 4.15 (d, *J* = 6.1 Hz, 1H), 4.04 (s, 3H), 3.31-3.27 (m, 2H, obscured by water), 3.26-3.21 (m, 1H), 3.05-2.96 (m, 2H), 2.65-2.61 (m, 2H), 1.98-1.87 (m, 2H), 1.66-1.60 (m, 1H), 1.54-1.45 (m, 1H), 1.43-1.39 (m, 2H), 1.36-1.23 (m, 1H). $^{13}$CNMR (DMSO-$d_6$, 100 MHz, contaminated w/ DMSO) δ: 161.96, 156.84 (d, *J* = 254.0 Hz), 142.50, 142.02, 140.94 (d, *J* = 7.1 Hz), 140.41, 138.08 (d, *J* = 1.9 Hz), 137.86 (d, *J* = 27.9 Hz), 137.48, 130.21 (d, *J* = 13.0 Hz), 120.26, 116.08, 115.81, 115.27 (d, *J* = 2.4 Hz), 77.11, 72.94, 64.00, 56.95, 53.55, 53.46, 53.27, 37.27, 29.09, 25.36, 20.72. HRMS (ESI) m/z calc'd for $C_{26}H_{31}FN_3O_5$ $[M+H]^+$: 484.22342; found: 484.22305. UPLC: rt: 3.037 min, purity: 96.6%. Enantiomeric excess (ee) could not be determined due to peaks not resolving under standard conditions.



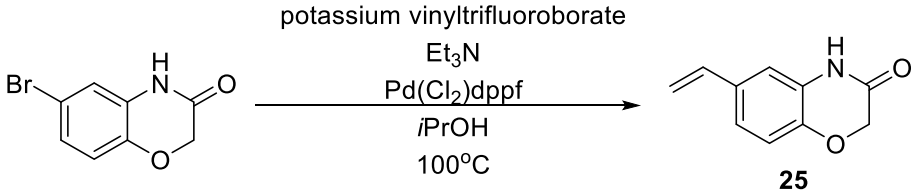

**(1*R*,2*S*)-1-(1-(2-(3-fluoro-6-methoxy-1,5-naphthyridin-4-yl)ethyl)piperidin-4-yl)-2-(p-tolyl)ethane-1,2-diol (23a)**

The title compound was synthesized using **21a** according to General Procedure 10 with AD-mix β. Purification by flash chromatography (compound eluted in ethyl acetate) and concentration *in vacuo* afforded the title compound (14 mg, 0.033 mmol, 87% yield). $^1$HNMR (DMSO-$d_6$, 400 MHz) δ: 8.76 (s, 1H), 8.27 (d, *J* = 9.0 Hz, 1H), 7.25-7.19 (m, 3H), 7.07 (d, *J* = 7.9 Hz, 2H), 5.03 (d, *J* = 4.9 Hz, 1H), 4.31 (dd, *J* = 6.7, 5.1 Hz, 1H), 4.15 (d, *J* = 6.1 Hz, 1H), 4.04 (s, 3H), 3.31-3.25 (m, 3H, partially obscured by water), 3.00 (br t, *J* = 11.6 Hz Hz, 2H), 2.67-2.58 (m, 2H), 2.27 (s, 3H), 1.98-1.86 (m, 2H), 1.69-1.61 (m, 1H), 1.55-1.45 (m, 1H), 1.44-1.37 (m, 2H), 1.37-1.25 (m, 1H). $^{13}$CNMR (DMSO-d6, 100 MHz, contaminated with ethyl acetate) δ: 161.95, 156.83 (d, *J* = 254.0 Hz), 141.29, 140.93 (d, *J* = 7.0 Hz), 140.40, 138.08 (d, *J* = 1.4 Hz), 137.86 (d, *J* = 27.8), 135.37, 130.20 (d, *J* = 13.0 Hz) 127.95, 127.36, 115.26 (d, *J* = 1.8 Hz), 77.14, 73.29, 56.95 53.54, 53.45, 53.27, 37.27, 29.11, 25.38, 20.69 (overlapping signals). HRMS (ESI) m/z calc'd for $C_{25}H_{31}FN_3O_3$ $[M+H]^+$: 440.2344; found: 440.23337. UPLC: rt: 3.259 min, purity: 93.4%. Enantiomeric excess (ee) determined to be 62.0% by chiral HPLC (98/2 hexane/reagent alcohol).

**(1*S*,2*R*)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-(1-(2-(3-fluoro-6-methoxy-1,5-naphthyridin-4-yl)ethyl)piperidin-4-yl)ethane-1,2-diol (23b)**

The title compound was synthesized using **21b** according to General Procedure 10 with AD-mix β. Purification by flash chromatography (compound eluted in 0-2% methanol in DCM) and concentration *in vacuo* afforded the title compound as a white solid (8 mg, 0.016 mmol, 11% yield).

$^1$HNMR (DMSO-$d_6$, 400 MHz; contaminated w/ DMSO) δ: 8.76 (s, 1H), 8.27 (d, *J* = 9.0 Hz, 1H), 7.23 (d, *J* = 9.0 Hz, 1H), 6.82 (d, *J* = 1.8 Hz, 1H), 6.77 (dd, *J* = 1.8, 8.3 Hz, 1H), 6.73 (d, *J* = 8.2 Hz, 1H), 5.00 (d, *J* = 4.9 Hz, 1H). 4.24-4.20 (m, 1H), 4.21 (s, 4H), 4.15 (d, *J* = 6.1 Hz, 1H), 4.04 (s, 3H), 3.31-3.27 (m, 2H, obscured by water), 3.26-3.21 (m, 1H), 3.05-2.96 (m, 2H), 2.65-2.61 (m, 2H), 1.98-1.87 (m, 2H), 1.66-1.60 (m, 1H), 1.54-1.45 (m, 1H), 1.43-1.39 (m, 2H), 1.37-1.23 (m, 1H). $^{13}$CNMR (DMSO-d6, 100 MHz, contaminated w/ DMSO) δ: 161.96, 156.84 (d, *J* = 254.0 Hz), 142.50, 142.02, 140.94 (d, *J* = 7.1 Hz), 140.41, 138.08 (d, *J* = 1.9 Hz), 137.86 (d, *J* = 27.9 Hz), 137.48, 130.21 (d, *J* = 13.0 Hz), 120.26, 116.08, 115.81, 115.27 (d, *J* = 2.4 Hz), 77.11, 72.94, 64.00, 56.95, 53.55, 53.46, 53.27, 37.27, 29.09, 25.36, 20.72 (overlapping signals). HRMS (ESI) m/z calc'd for $C_{26}H_{31}FN_3O_5$ $[M+H]^+$: 484.2248; found: 484.22342. UPLC: rt: 3.035 min, purity: 99%. Enantiomeric excess (ee) could not be determined due to peaks not resolving under standard conditions.

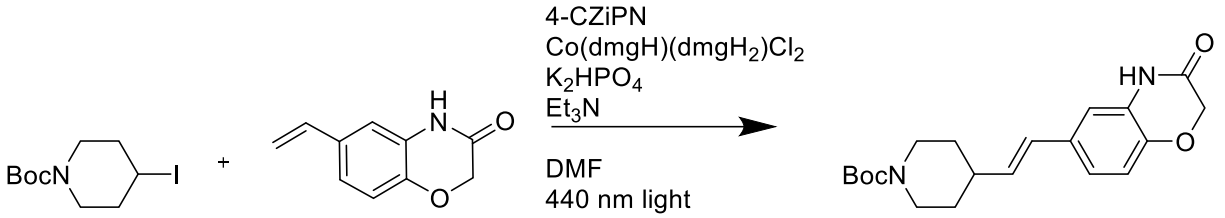



**25**

**6-vinyl-2H-benzo[b][1,4]oxazin-3(4H)-one (25)**

Commercially available 6-bromo-2H-benzo[b][1,4]oxazin-3(4H)-one (456 mg, 2 mmol, 1eq), triethylamine (0.558 mL, 4 mmol, 2 eq), Pd(dppf)$Cl_2$ (73 mg, 0.1 mmol, 0.05 eq), potassium vinyltrifluoroborate (402 mg, 3 mmol, 1.5 eq), and isopropanol (30 mL) were added to a pressure vial. Reaction was heated to 100°C overnight. Upon return, the reaction was cooled to room temperature and filtered through a celite plug, washing with excess ethyl acetate. Organics were dried over sodium sulfate, decanted, and concentrated by rotary evaporation to afford a crude mixture that was purified by flash chromatography. The title compound eluted in 0-10% ethyl acetate in hexanes, and concentration *in vacuo* afforded the title compound as a white solid (200 mg, 1.14 mmol, 57%). The reaction was run multiple times with an average yield of 65%.

$^1$HNMR ($CDCl_3$, 400 MHz) δ: 7.75 (s, 1H), 7.03 (dd, *J* = 1.9, 8.4 Hz, 1H), 6.93 (d, *J* = 8.3 Hz, 1H), 6.83 (d, *J* = 1.9 Hz, 1H), 6.62 (dd, *J* = 10.8, 17.6 Hz, 1H), 5.63 (dd, *J* = 0.6, 17.5 Hz, 1H), 5.21 (dd, *J* = 0.5, 10.9 Hz, 1H), 4.62 (s, 2H).

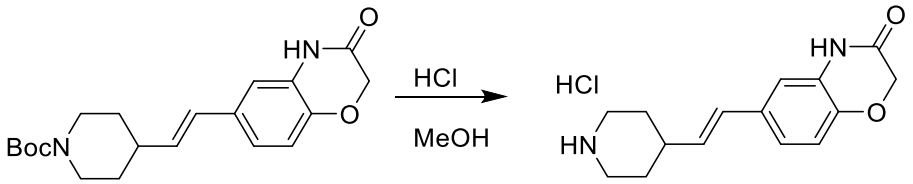



**24** **25** **26**

***tert*-butyl (*E*)-4-(2-(3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)vinyl)piperidine-1-carboxylate (26)**

The title compound was synthesized using commercially available **24** and **25** according to General Procedure 8. Purification by flash chromatography (compound eluted in 0-10% ethyl acetate in hexanes) and concentration *in vacuo* afforded the title compound as a yellow oil (750 mg, 2.09 mmol, 39% yield).

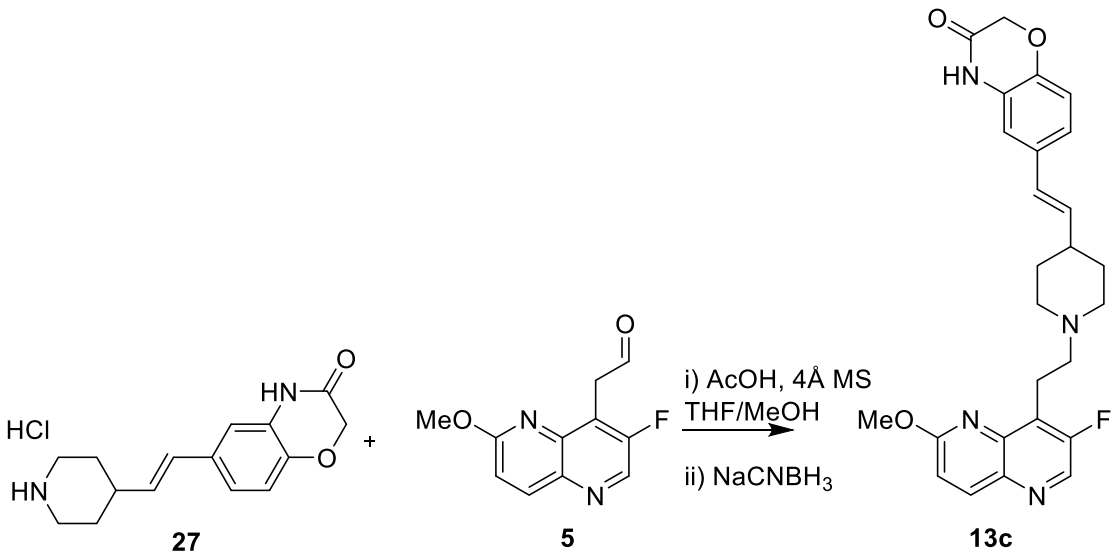
$^1$HNMR ($CDCl_3$, 400 MHz, contaminated w/ DCM and ethyl acetate) δ: 7.44 (s, 1H), 6.96 (dd, *J* = 1.8, 8.4 Hz, 1H), 6.91 (d, J = 8.3 Hz, 1H), 6.75 (d, *J* = 1.9 Hz, 1H), 6.28 (d, *J* = 16 Hz, 1H), 6.02 (dd, *J* = 6.9, 16 Hz, 1H), 4.60 (s, 2H), 4.18-4.06 (m, 2H), 2.82-2.73 (m, 2H), 2.32-2.22 (m, 1H), 1.77-1.70 (m, 2H), 1.47 (s, 9H), 1.42-1.31 (m, 2H).




**26** **27**

**(*E*)-6-(2-(piperidin-4-yl)vinyl)-2H-benzo[b][1,4]oxazin-3(4H)-one*hydrogen chloride (27)**

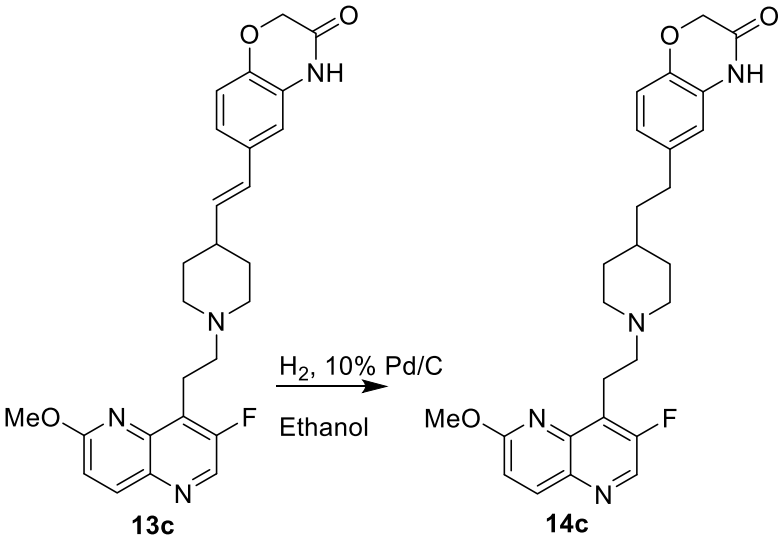
The title compound was synthesized using **26** according to General Procedure 2 and used directly in the next step.



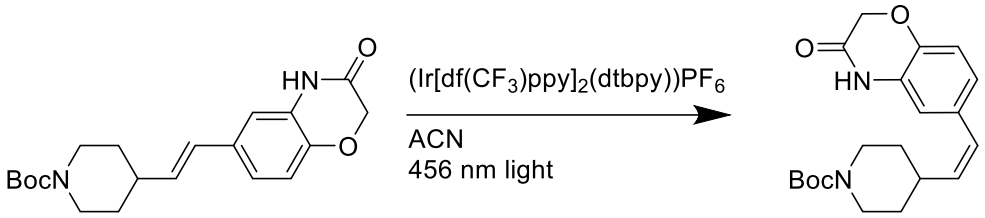

**27** **5** **13c**

**(*E*)-6-(2-(1-(2-(3-fluoro-6-methoxy-1,5-naphthyridin-4-yl)ethyl)piperidin-4-yl)vinyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (13c)**

The title compound was synthesized using **27** according to General Procedure 3. Purification by flash chromatography (compound eluted in 0-20% ethyl acetate in hexanes) and concentration *in vacuo* afforded the title compound as a yellow solid (66 mg, 0.143 mmol, 31% yield).
$^1$HNMR ($CDCl_3$, 400 MHz) δ: 8.62 (s, 1H), 8.18 (d, *J* = 9.0 Hz, 1H), 7.84 (s, 1H), 7.07 (d, *J* = 9.0 Hz, 1H), 6.96 (dd, *J* = 1.8, 8.3 Hz, 1H), 6.90 (d, J = 8.3 H, 1H), 6.77 (d, *J* = 1.8 Hz, 1H), 6.28 (d, *J* = 15.9 Hz, 1H), 6.05 (dd, *J* = 7.0, 15.9 Hz, 1H), 4.60 (s, 2H), 4.09 (s, 3H), 3.44-3.40 (m, 2H), 3.13-3.11 (m, 2H), 2.77-2.74 (m, 2H), 2.19 (td, *J* = 2.1, 15.9 Hz, 2H), 2.18-2.10 (m, 1H), 1.81-1.75 (m, 2H), 1.60-1.50 (obscured by water, m, 2H). HRMS (ESI) m/z calc'd for $C_{26}H_{28}FN_4O_3$ $[M+H]^+$: 463.21400; found: 463.21280. UPLC: rt: 3.37 min, purity: 96.8%.



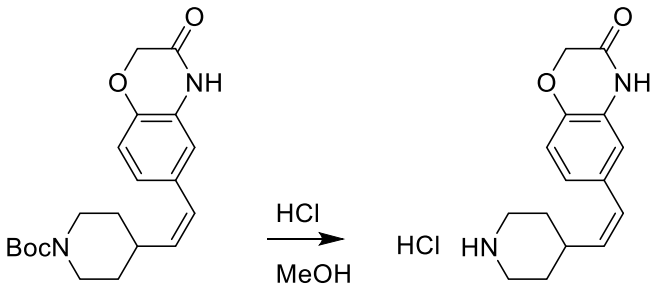

**6-(2-(1-(2-(3-fluoro-6-methoxy-1,5-naphthyridin-4-yl)ethyl)piperidin-4-yl)ethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (14c)**
The title compound was synthesized using **13c** according to General Procedure 8. Purification by flash chromatography (compound eluted in DCM) and concentration *in vacuo* afforded the title compound off-white solid (3 mg, 0.006 mmol, 6% yield).
$^1$HNMR ($CDCl_3$, 400 MHz) δ: 8.61 (s, 1H), 8.17 (d, *J* = 9.0 Hz, 1H), 7.99 (s, 1H), 7.07 (d, *J* = 9.0 Hz, 1H), 6.89 (d, *J* = 8.2 Hz, 1H), 6.79 (dd, *J* = 1.9, 8.2 Hz, 1H), 6.60 (d, *J* = 1.9 Hz, 1H), 4.59 (s, 2H), 4.08 (s, 3H), 3.43-3.38 (m, 2H), 3.11-3.05 (m, 2H), 2.76-2.70 (m, 2H), 2.59-2.53 (m, 2H), 2.13-2.05 (m, 2H), 1.78-1.71 (m, 2H), 1.57-1.50 (m, 2H), 1.37-1.25 (m, 3H). $^{13}$CNMR ($CDCl_3$, 100 MHz) δ: 165.81, 162.54, 157.43 (d, *J* = 255.3 Hz), 141.86, 141.79, 140.30, 138.67 (d, *J* = 2.1 Hz), 138.07 (d, *J* = 28.1 Hz), 137.76, 130.82 (d, *J* = 12.9 Hz), 126.02, 124.09, 116.82, 115.66, 115.32 (d, *J* = 2.8 Hz), 67.57, 57.64, 53.95, 53.81, 38.62, 35.48, 32.55, 32.52, 21.12. HRMS (ESI) m/z calc'd for $C_{26}H_{30}FN_4O_3$ $[M+H]^+$: 465.22965; found: 465.22867. UPLC: rt: 3.369 min, purity: 96.8%.




**26** **28**

***tert*-butyl (*Z*)-4-(2-(3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)vinyl)piperidine-1-carboxylate (28)**

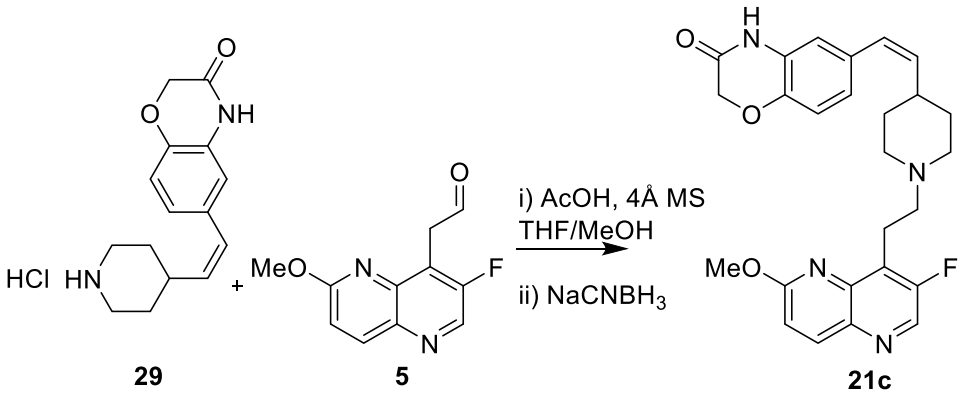
Compound **26** (1 g) was added to a round bottom flask and dissolved in acetonitrile (10 mL). [4,4′-Bis(1,1-dimethylethyl)-2,2′-bipyridine-N1,N1′]bis[3,5-difluoro-2-[5-(trifluoromethyl)-2-pyridinyl-N]phenyl-C] Iridium(III) hexafluorophosphate was added (31 mg). The reaction was irradiated with 456 nm blue light, positioned 5-20 cm from the flask, overnight. Upon return, the reaction was stopped, and the solvent was removed by rotary evaporation. The crude product was purified by flash chromatography (compound eluted in 0-15% ethyl acetate in hexanes) and concentration *in vacuo* afforded the title compound as a yellow oil (340 mg, 0.949 mmol, 34% yield).
$^1$HNMR ($CDCl_3$, 400 MHz, contaminated w/ DCM) δ: 8.09 (s, 1H), 6.95 (d, *J* = 8.3 Hz, 1H), 6.86 (dd, *J* = 1.8, 8.4 Hz, 1H), 6.65 (d, *J* = 1.7 Hz, 1H), 6.29 (d, *J* = 11.6 Hz, 1H), 5.43 (dd, *J* = 10.0, 11.5 Hz, 1H), 4.62 (s, 2H), 4.15-4.02 (m, 2H), 2.74 (t, *J* = 12.5 Hz, 2H), 2.70-2.59 (m, 1H), 1.69-1.61 (m, 2H), 1.46 (s, 9H), 1.36 (qd, *J* = 4.3, 12.6 Hz, 2H).




**28** **29**

**(*Z*)-6-(2-(piperidin-4-yl)vinyl)-2H-benzo[b][1,4]oxazin-3(4H)-one*hydrogen chloride (29)**

The title compound was synthesized using **28** according to General Procedure 2 and used directly in the next step.

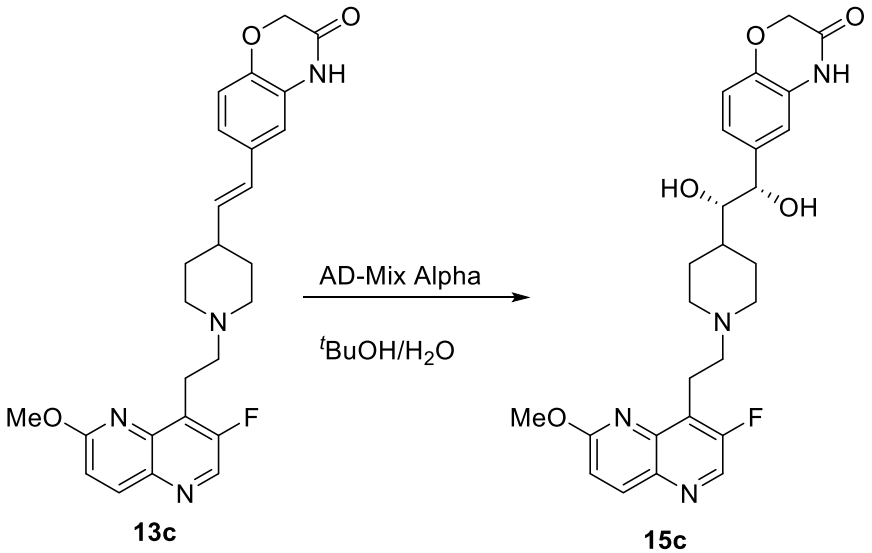



**(*Z*)-4-benzyl-6-(2-(1-(2-(3-fluoro-6-methoxy-1,5-naphthyridin-4-yl)ethyl)piperidin-4-yl)vinyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (21c)**

The title compound was synthesized using **29** according to General Procedure 3. Purification by flash chromatography (compound eluted in 5-50% ethyl acetate in hexanes) and concentration *in vacuo* afforded the title compound as a yellow solid (20 mg, 0.043 mmol, 38% yield).

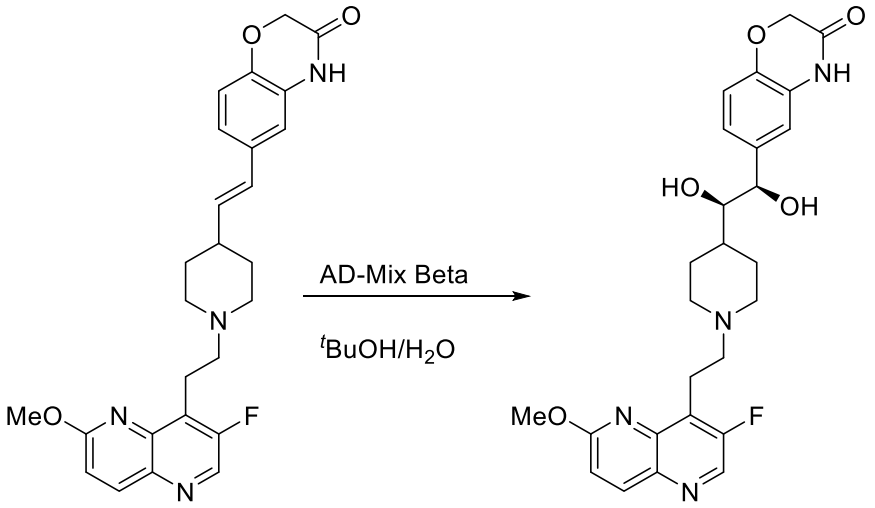
$^{1}$HNMR ($CDCl_3$, 400 MHz, contaminated w/ ethyl acetate) δ: 8.61 (s, 1H), 8.52 (s, 1H), 8.17 (d, *J* = 9.0 Hz, 1H), 7.07 (d, *J* = 9.0 Hz, 1H), 6.94 (d, *J* = 8.3 Hz, 1H), 6.87 (dd, *J* = 1.6, 8.3 Hz, 1H), 6.69 (d, *J* = 1.6 Hz, 1H), 6.27 (d, *J* = 11.6 Hz, 1H), 5.48 (dd, *J* = 10.1, 11.4 Hz, 1H), 4.62 (s, 2H), 4.07 (s, 3H), 3.43-3.37 (m, 2H), 3.10-3.04 (m, 2H), 2.75-2.71 (m, 2H), 2.58-2.47 (m, 1H), 2.17-2.11 (m, 2H), 1.73-1.69 (m, 2H), 1.59-1.49 (m, 2H).

$^{13}$CNMR ($CDCl_3$, 100 MHz) δ: 165.83, 162.54, 157.43 (d, *J* = 255.2 Hz), 142.49, 141.80 (d, *J* = 6.8 Hz), 140.29, 138.66 (d, *J* = 2.4 Hz), 138.04 (d, *J* = 28.0 Hz), 137.67, 132.81, 130.75 (d, *J* = 13.1 Hz), 126.83, 125.99, 124.56, 116.75, 115.98, 115.34 (d, *J* = 2.6 Hz), 67.48, 57.67, 53.94, 53.15, 35.21, 32.58, 21.10. HRMS (ESI) m/z calc'd for $C_{26}H_{28}FN_4O_3$ $[M+H]^+$: 463.21400; found: 463.21304. UPLC: rt: 3.38 min, purity: 97.7%.




**6-((1*S*,2*S*)-2-(1-(2-(3-fluoro-6-methoxy-1,5-naphthyridin-4-yl)ethyl)piperidin-4-yl)-1,2-dihydroxyethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (15c)**

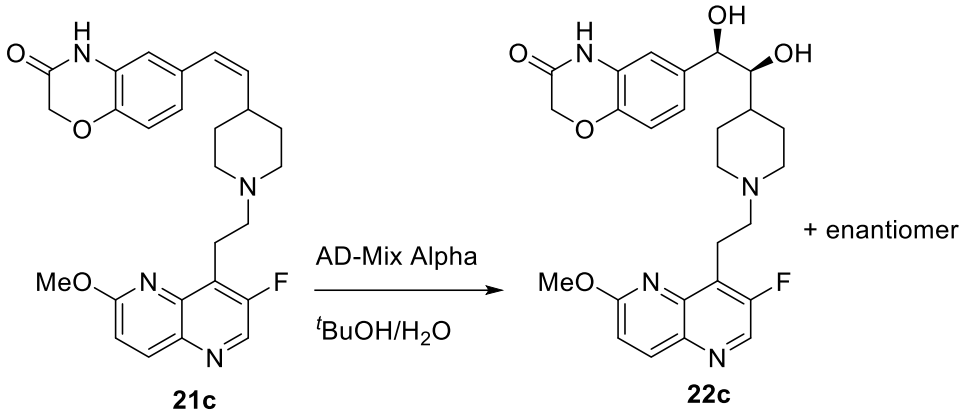
The title compound was synthesized using **13c** according to General Procedure 10 with AD-mix α. Purification by flash chromatography (compound eluted in 0-5% methanol in DCM) and concentration *in vacuo* afforded the title compound as a white solid (11 mg, 0.022 mmol, 20% yield).
$^1$HNMR (DMSO-$d_6$, 400 MHz) δ: 10.64 (s, 1H), 8.77 (s, 1H), 8.27 (d, *J* = 9.0 Hz, 1H), 7.23 (d, *J* = 9.0 Hz, 1H), 6.90 (m, 1H), 6.85 (m, 2H), 5.04 (d, *J* = 4.1 Hz, 1H), 4.52 (s, 2H), 4.41 (t, *J* = 4.9 Hz, 1H), 4.35-4.30 (m, 1H), 4.03 (s, 3H), 3.33-3.27 (m, 1H, obscured by water), 3.14 (q, *J* = 5.0 Hz, 1H), 3.03-2.95 (m, 2H), 2.68-2.60 (m, 2H), 1.95-1.83 (m, 2H), 1.69-1.67 (m, 1H), 1.49-1.43 (m, 1H), 1.42-1.31 (m, 2H), 1.28-1.17 (m, 2H). HRMS (ESI) m/z calc'd for $C_{26}H_{30}FN_4O_5$ $[M+H]^+$: 497.21947; found: 497.2186. UPLC: rt: 2.915 min, purity: 95.8%. Enantiomeric excess (ee) determined to be 99% by chiral HPLC (90/10 hexane/reagent alcohol with 0.1% diethylamine as an additive).




**13c** **16c**

**6-((1*R*,2*R*)-2-(1-(2-(3-fluoro-6-methoxy-1,5-naphthyridin-4-yl)ethyl)piperidin-4-yl)-1,2-dihydroxyethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (16c)**
The title compound was synthesized using **13c** according to General Procedure 10 with AD-mix β. Purification by flash chromatography (compound eluted in 0-1% methanol in DCM) and concentration *in vacuo* afforded the title compound as a white solid (12 mg, 0.024 mmol, 22% yield).
$^1$HNMR (DMSO-$d_6$, 400 MHz) δ: 10.63 (s, 1H), 8.77 (s, 1H), 8.28 (d, *J* = 9.0 Hz, 1H). 7.24 (d, *J* = 9.0 Hz, 1H), 6.90 (m, 1H), 6.85 (m, 2H), 5.02 (d, *J* = 4.8 Hz, 1H), 4.53 (s, 2H), 4.41 (t, *J* = 4.8 Hz, 1H), 4.31-4.30 (m, 1H), 4.03 (s, 3H), 3.33-3.26 (m, 2H, obscured by water), 3.15-3.11 (m, 1H), 2.98-2.95 (m, 2H), 2.63-2.59 (m, 2H), 1.90-1.82 (m, 2H), 1.68-1.65 (m, 1H), 1.46-1.34 (m, 2H), 1.27-1.19 (m, 2H). $^{13}$CNMR (DMSO-d6, 100 MHz) δ: 164.93, 161.96, 156.82 (d, *J* = 254.1 Hz), 141.98, 140.91 (d, *J* = 7.1 Hz), 140.40, 138.20, 138.08 (d, *J* = 1.5 Hz), 137.86 (d, *J* = 27.8 Hz), 130.08 (d, *J* = 12.2 Hz), 126.65, 121.30, 115.28 (overlapping signals), 114.28, 78.04, 72.71, 66.76, 56.80, 53.54, 53.12 (overlapping signals), 37.51, 29.00, 26.68, 20.61. HRMS (ESI) m/z calc'd for $C_{26}H_{30}FN_4O_5$ $[M+H]^+$: 497.21947; found: 497.21884. UPLC: rt: 2.917 min, purity: 95.6%.

Enantiomeric excess (ee) determined to be 99% by chiral HPLC (90/10 hexane/reagent alcohol with 0.1% diethylamine as an additive).

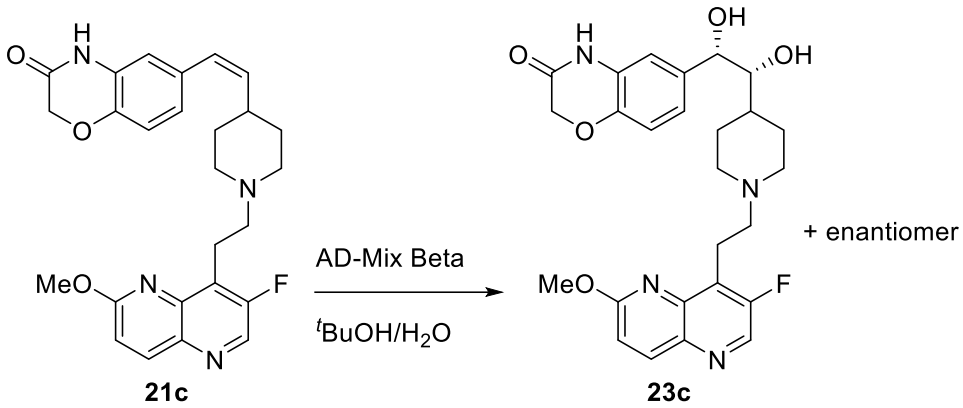



**21c** **22c**

**6-((1*R*,2*S*)-2-(1-(2-(3-fluoro-6-methoxy-1,5-naphthyridin-4-yl)ethyl)piperidin-4-yl)-1,2-dihydroxyethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (22c)**

The title compound was synthesized using **21c** according to General Procedure 10 with AD-mix α. Purification by flash chromatography (compound eluted in 0-1% methanol in DCM) and concentration *in vacuo* afforded the title compound as a white solid (20 mg, 0.040 mmol, 25% yield).

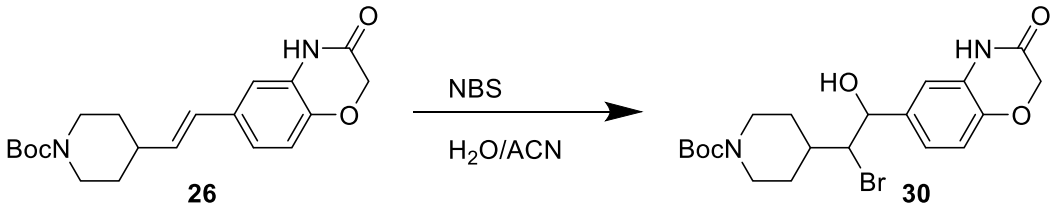
$^1$HNMR (DMSO-$d_6$, 400 MHz) δ: 10.64 (s, 1H), 8.77 (s, 1H), 8.27 (d, *J* = 9.0 Hz, 1H), 7.23 (d, *J* = 9.0 Hz, 1H), 6.92 (d, *J* = 1.6 Hz, 1H), 6.87 (dd, *J* = 1.7, 8.3 Hz, 1H), 6.83 (d, *J* = 8.2 Hz, 1H), 5.13 (d, *J* = 4.4 Hz, 1H), 4.51 (s, 2H), 4.23 (dd, *J* = 4.4, 7.1 Hz, 2H), 4.04 (s, 3H), 3.34-3.28 (m, 2H, obscured by water), 3.26-3.20 (m, 1H), 3.08-2.96 (m, 2H), 2.68-2.60 (m, 2H), 2.10-1.89 (m, 2H), 1.69-1.62 (m, 1H), 1.62-1.52 (m, 1H), 1.51-1.28 (m, 3H). $^{13}$CNMR (DMSO-d6, 100 MHz) δ: 164.97, 161.95, 156.82 (d, *J* = 254.0 Hz), 141.96, 140.92 (d, *J* = 7.0 Hz), 140.40, 138.89, 138.07 (d, *J* = 1.2 Hz), 137.85 (d, *J* = 27.8 Hz), 130.18, 126.36, 122.08, 115.26 (d, *J* = 2.0 Hz), 114.99, 114.97, 77.07, 72.93, 66.77, 56.89, 53.54, 53.43, 53.24, 37.20, 29.08, 25.12, 20.67. HRMS (ESI) m/z calc'd for $C_{26}H_{30}FN_4O_5$ $[M+H]^+$: 497.21947; found: 497.21942. UPLC: rt: 2.866 min, purity: 94.3%. Enantiomeric excess (ee) determined to be 17.9% by chiral HPLC (90/10 hexane/reagent alcohol with 0.1% diethylamine as an additive).




**6-((1*S*,2*R*)-2-(1-(2-(3-fluoro-6-methoxy-1,5-naphthyridin-4-yl)ethyl)piperidin-4-yl)-1,2-dihydroxyethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (23c)**

Title compound was synthesized using **21c** according to General Procedure 10 with AD-mix β. Purification by flash chromatography (compound eluted in 0-1% methanol in DCM) and concentration *in vacuo* afforded the title compound as a white solid (20 mg, 0.040 mmol, 25% yield).

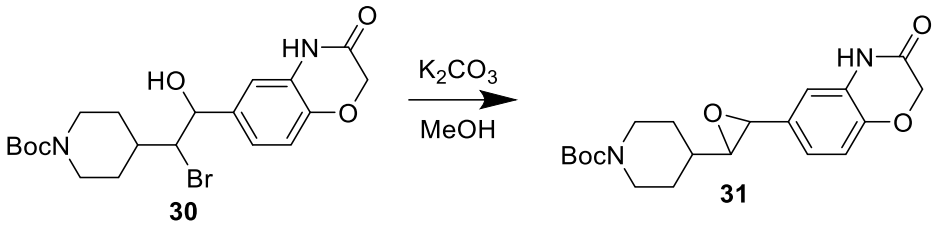
$^{1}$HNMR (DMSO-$d_6$, 400 MHz) δ: 10.64 (s, 1H), 8.77 (s, 1H), 8.27 (d, *J* = 9.0 Hz, 1H), 7.23 (d, *J* = 9.0 Hz, 1H), 6.92 (d, *J* = 1.6 Hz, 1H), 6.87 (dd, *J* = 1.7, 8.3 Hz, 1H), 6.83 (d, *J* = 8.2 Hz, 1H), 5.13 (d, *J* = 4.4 Hz, 1H), 4.51 (s, 2H), 4.23 (dd, *J* = 4.4, 7.1 Hz, 2H), 4.04 (s, 3H), 3.34-3.28 (m, 2H, obscured by water), 3.26-3.20 (m, 1H), 3.11-2.99 (m, 2H), 2.74-2.60 (m, 2H), 2.10-1.89 (m, 2H), 1.69-1.62 (m, 1H), 1.62-1.52 (m, 1H), 1.51-1.29 (m, 3H). $^{13}$CNMR (DMSO-d6, 100 MHz) δ: 164.97, 161.98, 156.81 (d, *J* = 254.2 Hz), 141.97, 140.89 (d, *J* = 7.1 Hz), 140.40, 138.88, 138.08 (d, *J* = 1.2 Hz), 137.86 (d, *J* = 27.8 Hz), expected 130 peak is lost in baseline noise, 126.37, 122.07, 115.28 (d, *J* = 1.8 Hz), 114.98 (overlapping signals), 77.01, 72.94, 66.77, 56.75, 53.56, 53.34, 53.17, 37.09, 28.93, 24.99, 20.55. HRMS (ESI) m/z calc'd for $C_{26}H_{30}FN_4O_5$ $[M+H]^+$: 497.21947; found: 497.21863. UPLC: rt: 2.867 min, purity: 97.8%. Enantiomeric excess (ee) determined to be 14.0% by chiral HPLC (90/10 hexane/reagent alcohol with 0.1% diethylamine as an additive).




***tert*-butyl 4-(1-bromo-2-hydroxy-2-(3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)ethyl)piperidine-1-carboxylate (30)**

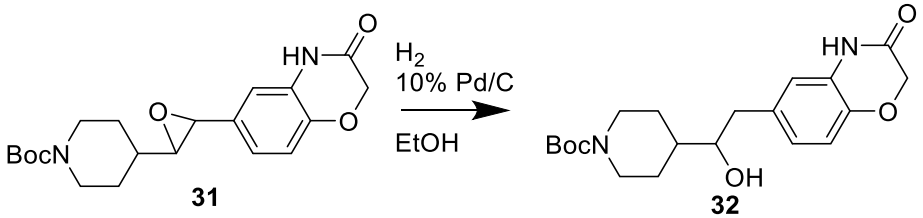
Compound **26** (200 mg) was added to a round bottom flask and dissolved in acetonitrile (1 mL). Water (1 mL) was added, and the solution was sparged once with a nitrogen balloon. The reaction was cooled to 0°C and N-bromosuccinimide (120 mg) was added. The reaction was covered in foil and allowed to stir overnight. Upon return, reaction was quenched with aqueous, saturated sodium thiosulfate, whereupon it became yellow. The reaction was diluted with ethyl acetate and phases separated. The aqueous layer was extracted 5x5 mL ethyl acetate, and the combined organic layers were dried over

sodium sulfate, decanted, and concentrated by rotary evaporation to afford crude mixtures. Crude mixtures were then purified via flash chromatography (compound eluted in 5-40% ethyl acetate in hexanes) and concentration *in vacuo* afforded the title compound as a white solid (180 mg, 0.395 mmol, 71% yield).
$^1$HNMR ($CDCl_3$, 400 MHz, contaminated w/ ethyl acetate and DCM) δ: 7.67 (s, 1H), 7.04-6.89 (m, 2H), 6.87 (d, *J* = 1.4 Hz, 1H), 4.89 (dd, *J* = 3.3, 7.5 Hz, 1H), 4.66 (s, 2H), 4.18-4.14 (m, 2H, obscured by ethyl acetate), 2.78-2.66 (m, 2H), 2.25 (d, *J* = 3.3 Hz, 1H), 2.05-1.96 (m, 1H), 1.92-1.90 (m, 1H), 1.70-1.56 (m, 2H, obscured by water), 1.56-1.48 (m, 2H, obscured by water and next peak), 1.48 (s, 9H).



**30** **31**

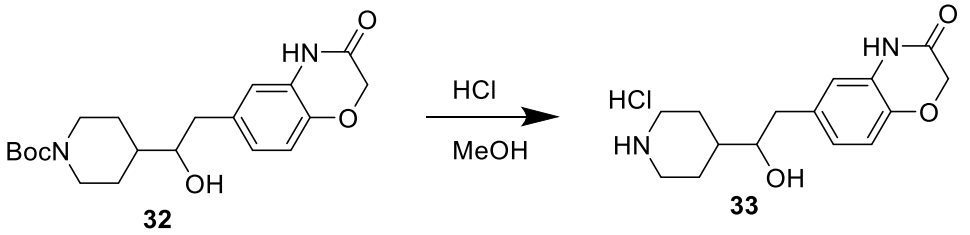
***tert*-butyl 4-(3-(3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)oxiran-2-yl)piperidine-1-carboxylate (31)**
Compound **30** (175 mg) was dissolved in methanol (2 mL). Potassium carbonate (107 mg) was added and allowed to stir until consumption of starting material was observed by TLC. Upon completion of reaction, reaction was quenched with saturated aqueous ammonium chloride and filtered through a celite plug, washing with ethyl acetate. After separation of phases, the organic layer was dried over sodium sulfate, decanted, and concentrated by rotary evaporation to afford desired epoxide, which was used without further purification. Title compound was afforded as a yellow solid (145 mg, 0.385 mmol, 100% yield).
$^1$HNMR ($CDCl_3$, 400 MHz, contaminated w/ ethyl acetate) δ:6.96-6.85 (m, 2H), 6.62 (s, 1H), 4.59 (s, 2H), 4.21-4.07 (m, 2H, obscured by ethyl acetate), 3.63 (s, 1H), 2.78-2.65 (m, 3H), 1.89-1.80 (m, 1H), 1.73-1.65 (m, 1H), 1.59-1.50 (m,1H), 1.46 (s, 9H), 1.42-1.28 (m, 4H, obscured by ethyl acetate).



**31** **32**

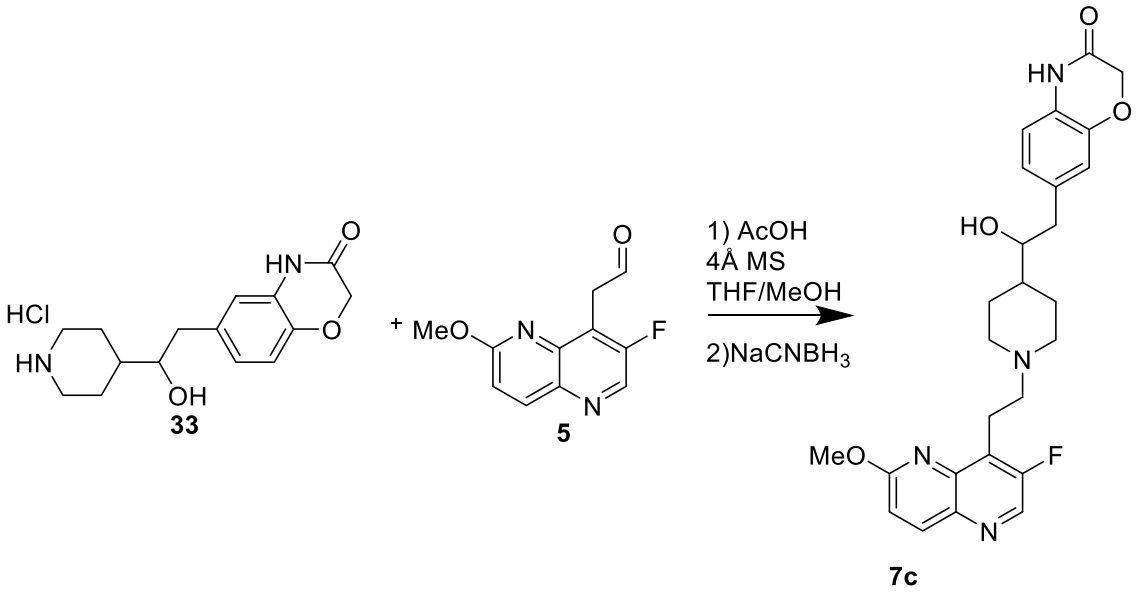
***tert*-butyl 4-(1-hydroxy-2-(3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)ethyl)piperidine-1-carboxylate (32)**
Compound **31** (144 mg) was dissolved in ethanol (2 mL), and 10% Pd/C (5 mg) was added. The reaction was sparged once with a nitrogen balloon and once with a hydrogen balloon. A hydrogen balloon was attached to reaction by needle through a septum, and the reaction was allowed to stir overnight. Upon return, reaction was sparged once with a nitrogen balloon, filtered through a celite plug, and washed with ethyl acetate. The solvent was removed by rotary evaporation to afford the crude

product as a white solid (140 mg, 0.372 mmol, 97% yield) which was used without additional purification.
$^1$HNMR ($CDCl_3$, 400 MHz, contaminated w/ DCM) δ: 6.93 (d, *J* = 8.2 Hz, 1H), 6.84-6.80 (m, 1H), 6.67-6.64 (m, 1H), 4.61 (s, 2H), 4.23-4.12 (m, 2H), 3.59-3.51 (m, 1H), 2.85-2.77 (m, 1H), 2.73-2.61 (m, 2H), 2.57-2.48 (m, 1H), 1.89-1.81 (m, 1H), 1.71-1.64 (m, 1H), 1.60-1.51 (m, 1H), 1.46 (s, 9H), 1.43-1.27 (m, 4H).




**32** **33**

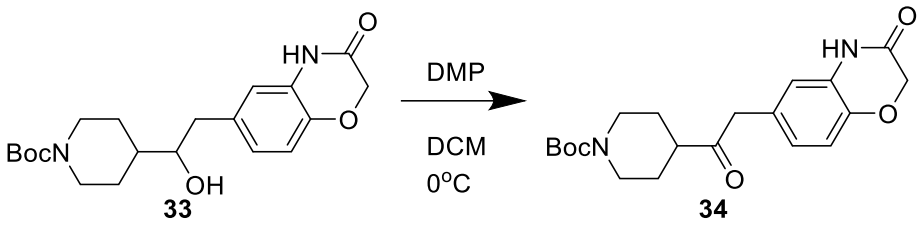
**6-(2-hydroxy-2-(piperidin-4-yl)ethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one hydrochloride (33)**
The title compound was synthesized using **32** according to General Procedure 2 and used directly in the next step.




**33** **5** **7c**

**7-(2-(1-(2-(3-fluoro-6-methoxy-1,5-naphthyridin-4-yl)ethyl)piperidin-4-yl)-2-hydroxyethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (7c)**
The title compound was synthesized using **33** according to General Procedure 3. Purification by flash chromatography (compound eluted in 0-1% methanol in DCM) and concentration *in vacuo* afforded the title compound as a white solid (7 mg, 0.015 mmol, 21% yield).
$^1$HNMR (DMSO-$d_6$, 400 MHz, contaminated w/ DCM and DMSO) δ: 8.62 (s, 1H), 8.17 (d, *J* = 9.0 Hz, 1H), 7.43 (s, 1H), 7.07 (d, *J* = 9.0 Hz, 1H), 6.93 (d, *J* = 8.2 Hz, 1H), 6.83 (dd, *J* = 1.9, 8.2 Hz, 1H), 6.65 (d, *J* = 1.8 Hz, 1H), 4.60 (s, 2H), 4.09 (s, 3H), 3.60-3.54 (m, 1H), 3.45-3.39 (m, 2H), 3.21-3.12 (m, 2H), 2.84 (dd, *J* = 2.8, 13.8 Hz, 1H), 2.78-2.71 (m, 2H), 2.52 (dd, *J* = 9.6, 13.8 Hz, 1H), 2.16-2.06 (m, 2H), 1.93-1.87 (m, 1H), 1.77-1.71

(m, 1H), 1.56-1.40 (m, 4H, obscured by water). $^{13}$CNMR (DMSO-d6, 100 MHz, contaminated w/ DMSO) δ: 165.00, 161.97, 156.83 (d, *J* = 254.0 Hz), 141.32, 140.92 (d, *J* = 7.1 Hz), 140.41, 138.08 (d, *J* = 1.8 Hz), 137.87 (d, *J* = 27.7 Hz), 134.30, expected 130 peak is lost in baseline noise, 126.70, 123.76, 116.66, 115.53, 115.28 (d, *J* = 1.7 Hz), 74.65, 66.77, 56.92, 56.85, 53.55, 53.16, 30.17, 28.53, 28.01, 26.66, 20.67. HRMS (ESI) m/z calc'd for $C_{26}H_{30}FN_4O_4$ $[M+H]^+$: 481.22456; found: 481.22397. UPLC: rt: 3.069 min, purity: 96.5%.

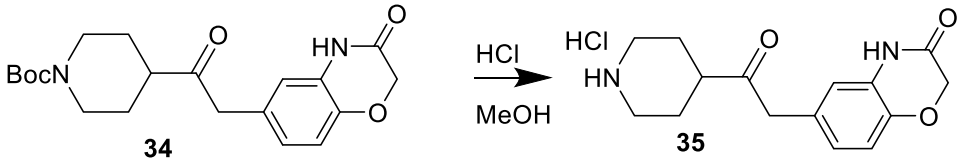


**33** **34**

***tert*-butyl 4-(2-(3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)acetyl)piperidine-1-carboxylate (34)**

Compound **33** (105 mg) was dissolved in DCM (1.4 mL) and cooled to 0°C. Dess-Martin Periodinane (DMP, 142 mg) was added in one portion. The reaction began bubbling upon addition and was allowed to stir overnight. Upon return, reaction was diluted with water and 1M aqueous NaOH. After separation of phases, the aqueous layer was extracted 5x10 mL ethyl acetate. The combined organic layers were dried over sodium sulfate, decanted, and concentrated by rotary evaporation to afford the title compound as a clear oil (110 mg, 0.278 mmol, 100% yield).

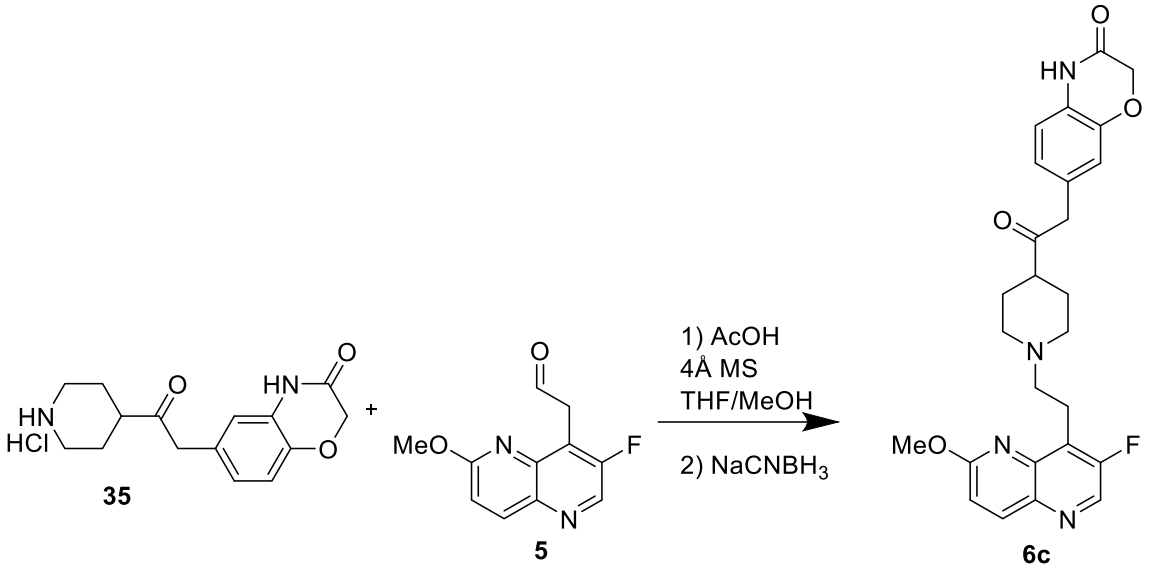
$^1$HNMR ($CDCl_3$, 400 MHz, contaminated w/ ethyl acetate) δ: 7.77 (s, 1H), 6.93 (d, *J* = 8.2 Hz, 1H), 6.77 (dd, *J* = 2.0, 8.2 Hz, 1H), 6.62 (d, *J* = 2.0 Hz, 1H), 4.61 (s, 2H), 4.14-4.04 (m, 2H, obscured by ethyl acetate), 3.68 (s, 2H), 2.81-2.72 (m, 2H), 2.57 (tt, *J* = 3.8, 11.4 Hz, 1H), 1.84-1.75 (m, 2H), 1.61-1.50 (m, 2H, obscured by water), 1.46-1.43 (m, 9H).



**34** **35**

**6-(2-oxo-2-(piperidin-4-yl)ethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one*hydrochloride (35)**

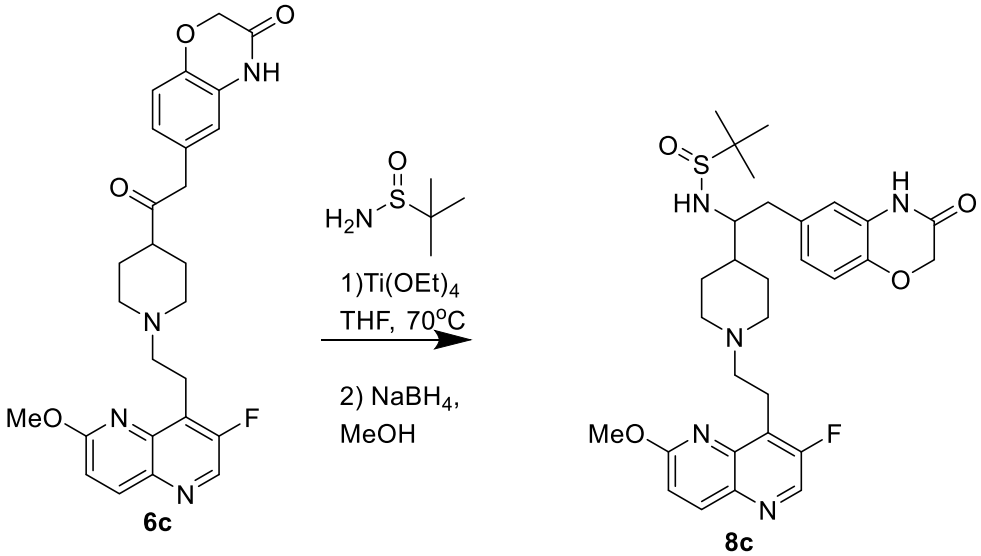
The title compound was synthesized using **34** according to General Procedure 2 and used directly in the next step.



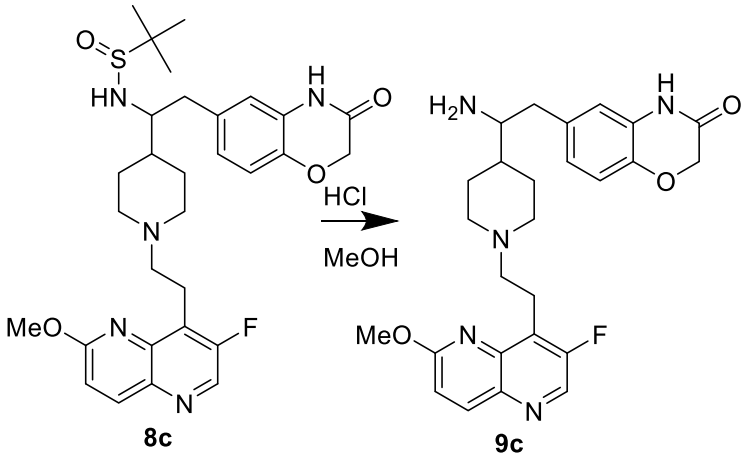

**4-benzyl-6-(2-(1-(2-(3-fluoro-6-methoxy-1,5-naphthyridin-4-yl)ethyl)piperidin-4-yl)-2-oxoethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (6c)**

The title compound was synthesized using **35** according to General Procedure 3. Purification by flash chromatography (compound eluted in 0-15% ethyl acetate in hexanes) and concentration *in vacuo* afforded the title compound as a yellow solid (50 mg, 0.104 mmol, 42% yield).

$^1$HNMR ($CDCl_3$, 400 MHz, contaminated with ethyl acetate) δ: 8.61 (s, 1H), 8.17 (d, *J* = 9.0 Hz, 1H), 8.11 (s, 1H), 7.07 (d, *J* = 9.0 Hz, 1H), 6.92 (d, J = 8.2 Hz, 1H), 6.77 (dd, *J* = 2.0, 8.2 Hz, 1H), 6.64 (d, *J* = 1.9 Hz, 1H), 4.60 (s, 2H), 4.08 (s, 3H), 3.68 (s, 2H), 3.49-3.83 (m, 2H), 3.18-3.07 (m, 2H), 2.86-2.73 (m, 2H), 2.53-2.39 (m, 1H), 2.29-2.12 (m, 2H), 1.96-1.70 (m, 4H). HRMS (ESI) m/z calc'd for $C_{26}H_{28}FN_4O_4$ $[M+H]^+$: 479.20891; found: 479.20773. UPLC: rt: 3.07 min, purity: 95.16%.

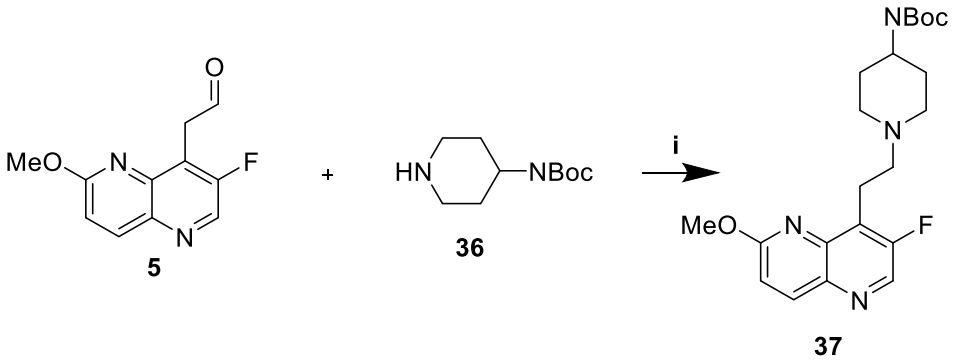


***N*-(1-(1-(2-(3-fluoro-6-methoxy-1,5-naphthyridin-4-yl)ethyl)piperidin-4-yl)-2-(3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)ethyl)-2-methylpropane-2-sulfinamide (8c)**
The title compound was synthesized using **6c** according to General Procedure 5 and used directly in the next step.




**8c** **9c**

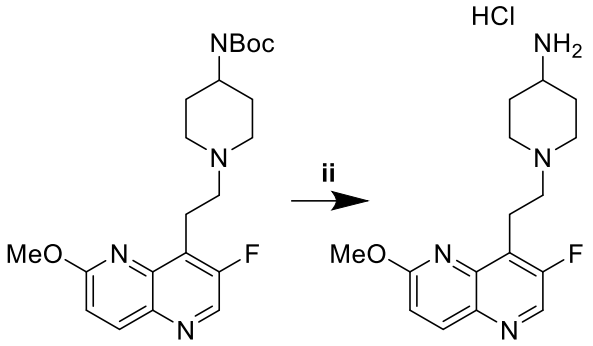
**6-(2-amino-2-(1-(2-(3-fluoro-6-methoxy-1,5-naphthyridin-4-yl)ethyl)piperidin-4-yl)ethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (9c)**
The title compound was synthesized using **8c** according to General Procedure 6. Purification by flash chromatography (compound eluted in 0-1% methanol in DCM) and concentration *in vacuo* afforded the title compound as a white solid (5 mg, 0.0104 mmol, 17% yield).
$^1$HNMR (DMSO-$d_6$, 400 MHz) δ: 10.61 (s, 1H), 8.77 (s, 1H), 8.28 (d, *J* = 9.0 Hz, 1H), 7.24 (d, *J* = 9.0 Hz, 1H), 6.84 (d, *J* = 8.2 Hz, 1H), 6.74-6.70 (m, 2H), 4.51 (s, 2H), 4.04 (s, 3H), 3.33-3.26 (m, 2H, obscured by water), 3.06-2.99 (m, 2H), 2.68-2.54 (m, 4H), 2.24 (dd, J = 8.4, 12.9 Hz, 1H), 2.00-1.90 (m, 2H), 1.70-1.63 (m, 1H), 1.60-1.52 (m, 1H), 1.37-1.09 (m, 5H). HRMS (ESI) m/z calc'd for $C_{26}H_{31}FN_5O_3$ $[M+H]^+$: 480.24054; found: 480.24045. UPLC: rt: 2.600 min, purity: 97.9%.




**5** **36** **37**

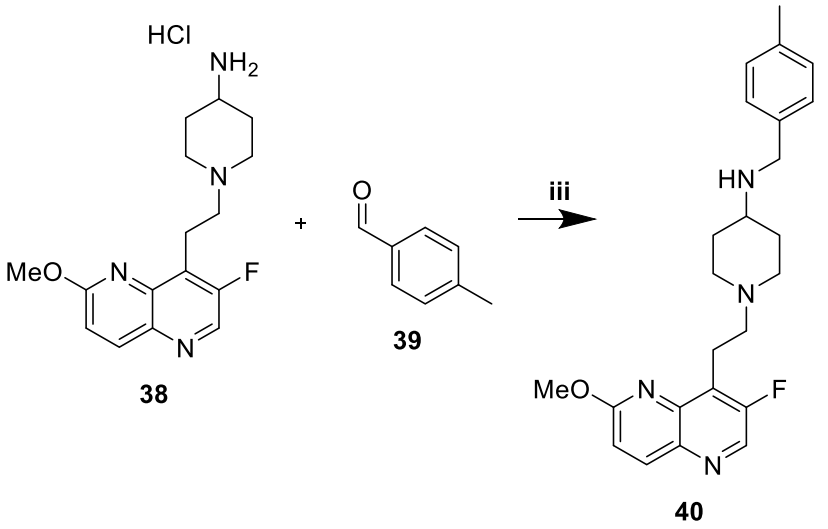
***tert*-butyl (1-(2-(3-fluoro-6-methoxy-1,5-naphthyridin-4-yl)ethyl)piperidin-4-yl)-λ$^2$-azanecarboxylate (37)**
The title compound was synthesized using commercially available **36** according to General Procedure 3. Purification by flash chromatography (compound eluted in 5-40%

ethyl acetate in hexane) and concentration *in vacuo* afforded the title compound as a yellow solid (120 mg, 0.297 mmol, 65% yield).
$^1$HNMR ($CDCl_3$, 400 MHz, contaminated w/ ethyl acetate) δ: 8.61 (s, 1H), 8.17 (d, *J* = 9.0 Hz, 1H), 7.07 (d, J = 9.0 Hz, 1H), 4.47-4.38 (m, 1H), 4.07 (s, 3H), 3.54-3.44 (m, 1H), 3.43-3.35 (m, 2H), 3.06-2.94 (m, 2H), 2.78-2.69 (m, 2H), 2.31-2.20 (m, 2H), 2.00-1.91 (m,2H), 1.44 (s, 9H).




**37** **38**

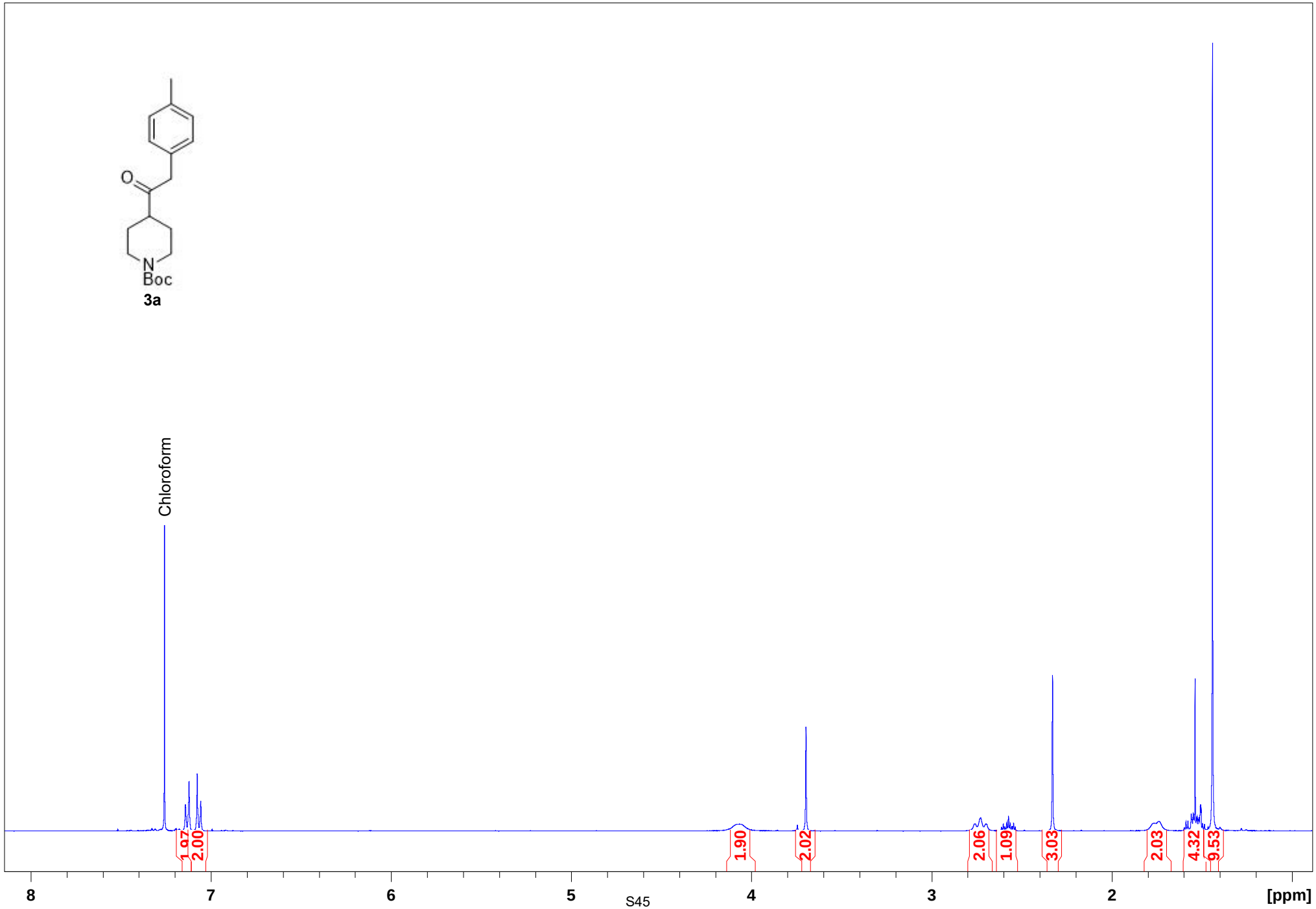
**1-(2-(3-fluoro-6-methoxy-1,5-naphthyridin-4-yl)ethyl)piperidin-4-amine hydrochloride (38)**
The title compound was synthesized using **37** according to General Procedure 2 and used directly in the next step.




**38** **39** **40**

**1-(2-(3-fluoro-6-methoxy-1,5-naphthyridin-4-yl)ethyl)-*N*-(4-methylbenzyl)piperidin-4-amine (40)**
The title compound was synthesized using commercially available **39** according to General Procedure 3. Purification by flash chromatography (compound eluted in 0-1% methanol in DCM) and concentration *in vacuo* afforded the title compound as a white solid (20 mg, 0.0490 mmol, 20% yield).
$^1$HNMR ($CDCl_3$, 400 MHz) δ: 8.61 (s, 1H), 8.17 (d, *J* = 9.0 Hz, 1H), 7.22 (d, *J* = 7.9 Hz, 2H), 7.13 (d, *J* = 7.8 Hz, 2H), 7.07 (d, *J* = 9.0 Hz, 1H), 4.08 (s, 3H), 3.79 (s, 2H), 3.45-3.36 (m, 2H), 3.09-3.01 (m, 2H), 2.78-2.70 (m, 2H), 2.60-2.50 (m, 1H), 2.33 (s, 3H),

2.24-2.12 (m, 2H), 1.99-1.89 (m, 2H), 1.60-1.41 (m, partially obscured by water, 3H). $^{13}$CNMR (CDCl3, 100 MHz) δ: 162.50, 157.41 (d, *J* = 255.3 Hz), 141.78 (d, *J* = 7.1 Hz), 140.25, 138.61 (d, *J* = 2.0 Hz), 138.02 (d, *J* = 28.2 Hz), 137.75, 136.57, 130.76 (d, *J* = 13.0 Hz), 129.22, 128.13, 115.29 (d, *J* = 2.7 Hz), 57.24, 54.12, 53.92, 52.30, 50.60, 32.87, 21.20 (overlapping signals). HRMS (ESI) m/z calc'd for $C_{24}H_{30}FN_4O$ $[M+H]^+$: 409.23982; found: 409.23935. UPLC: rt: 2.669 min, purity: 97.02%.


O
N
Boc
3a
Chloroform
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2.03
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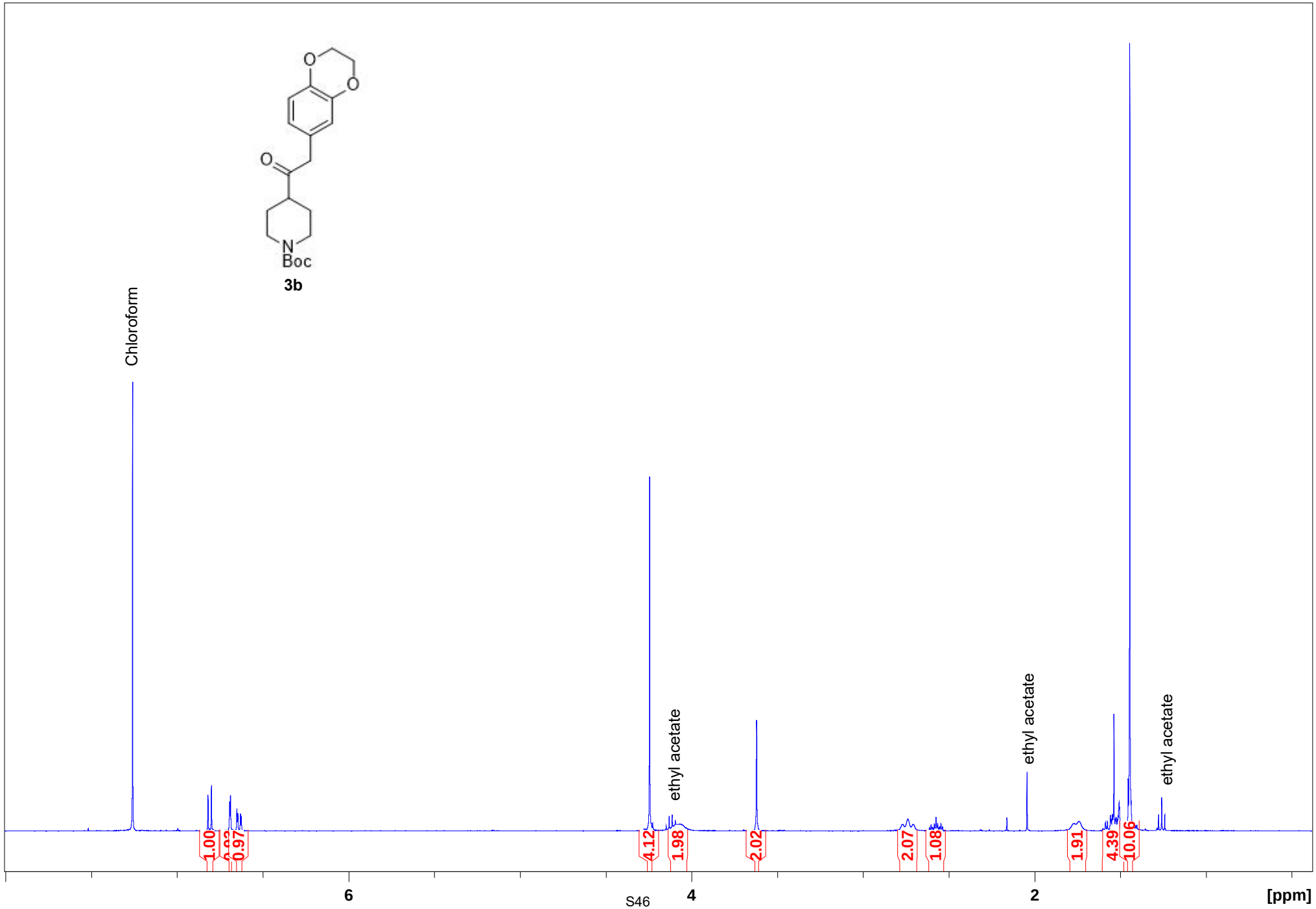
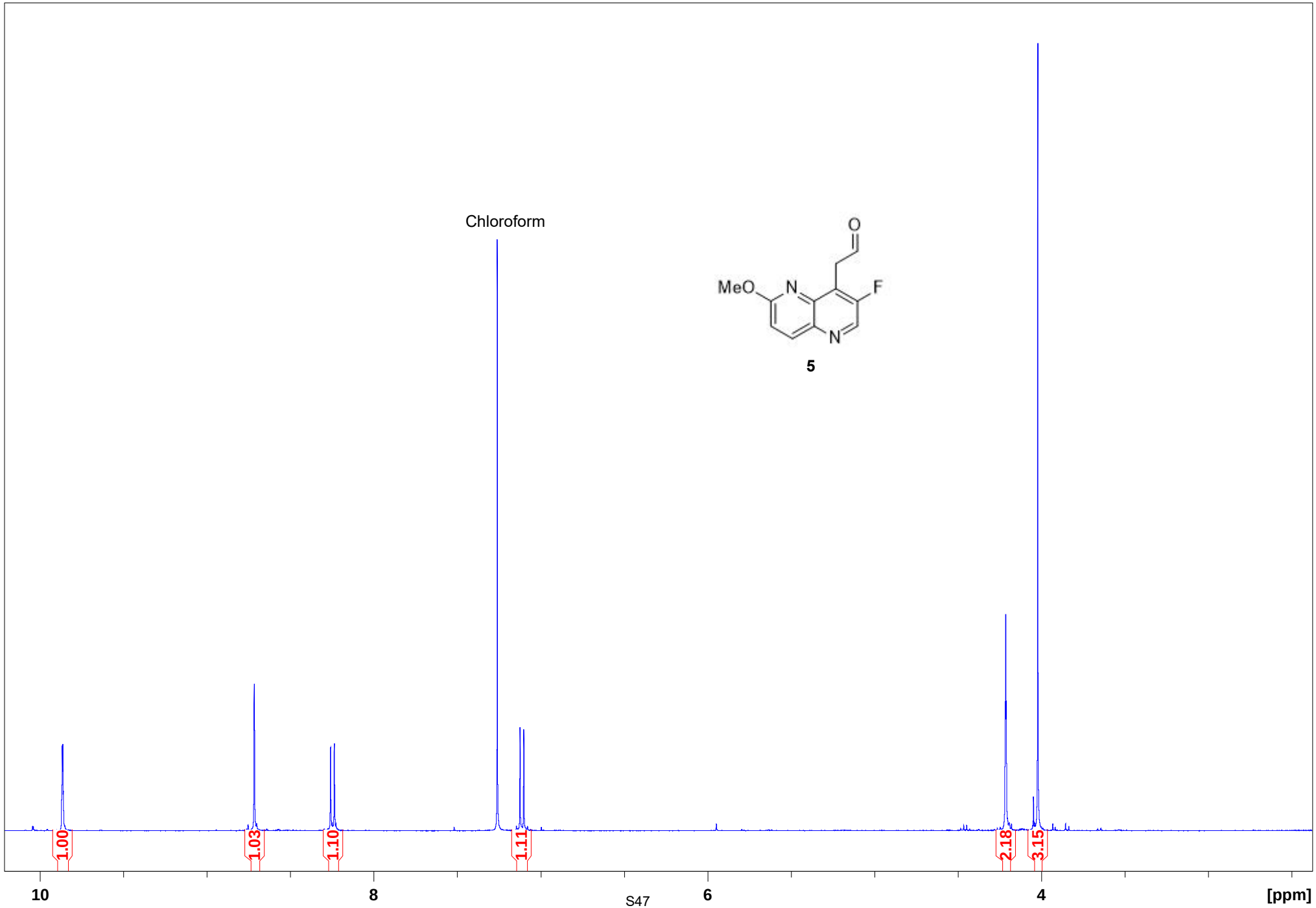
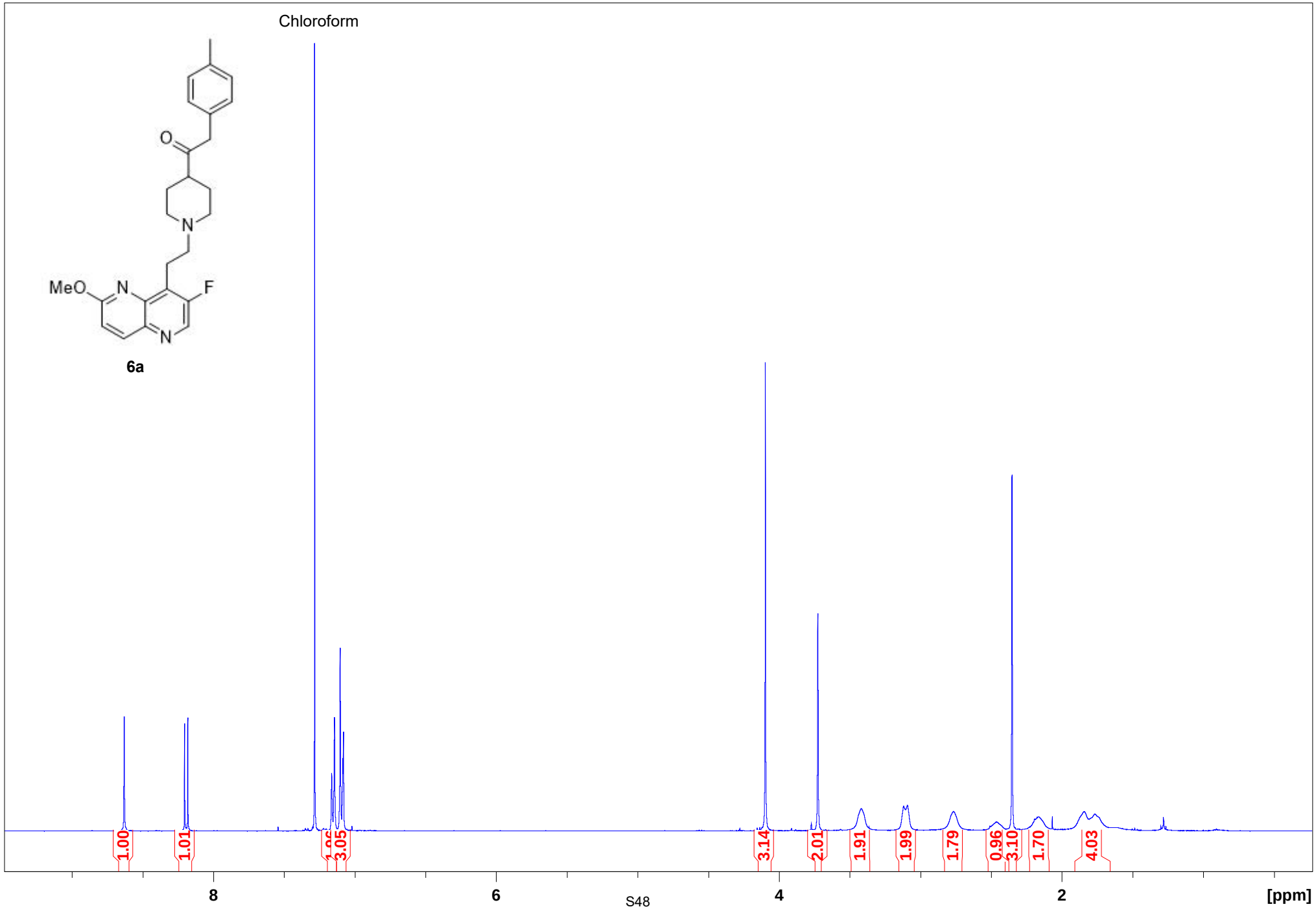
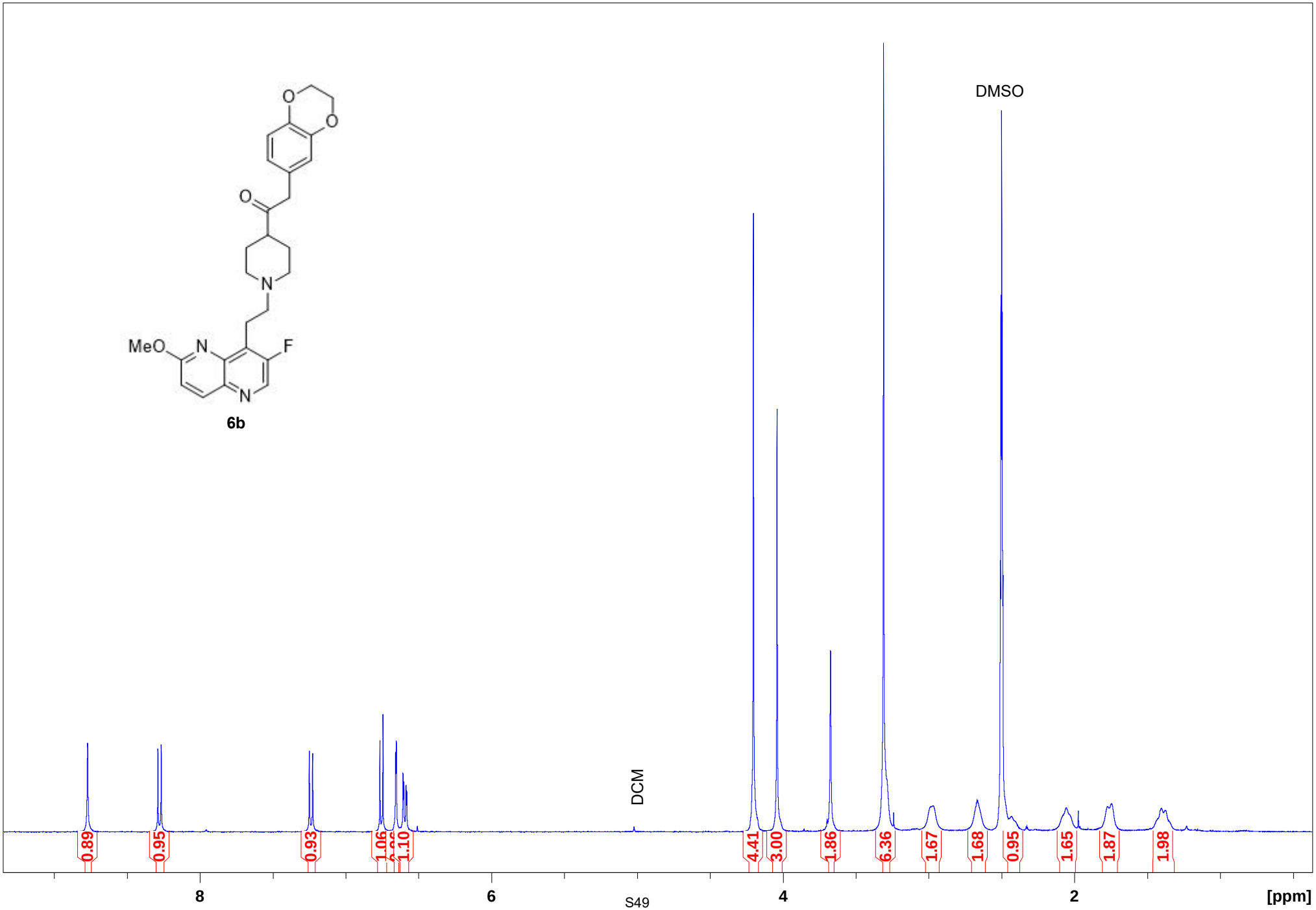
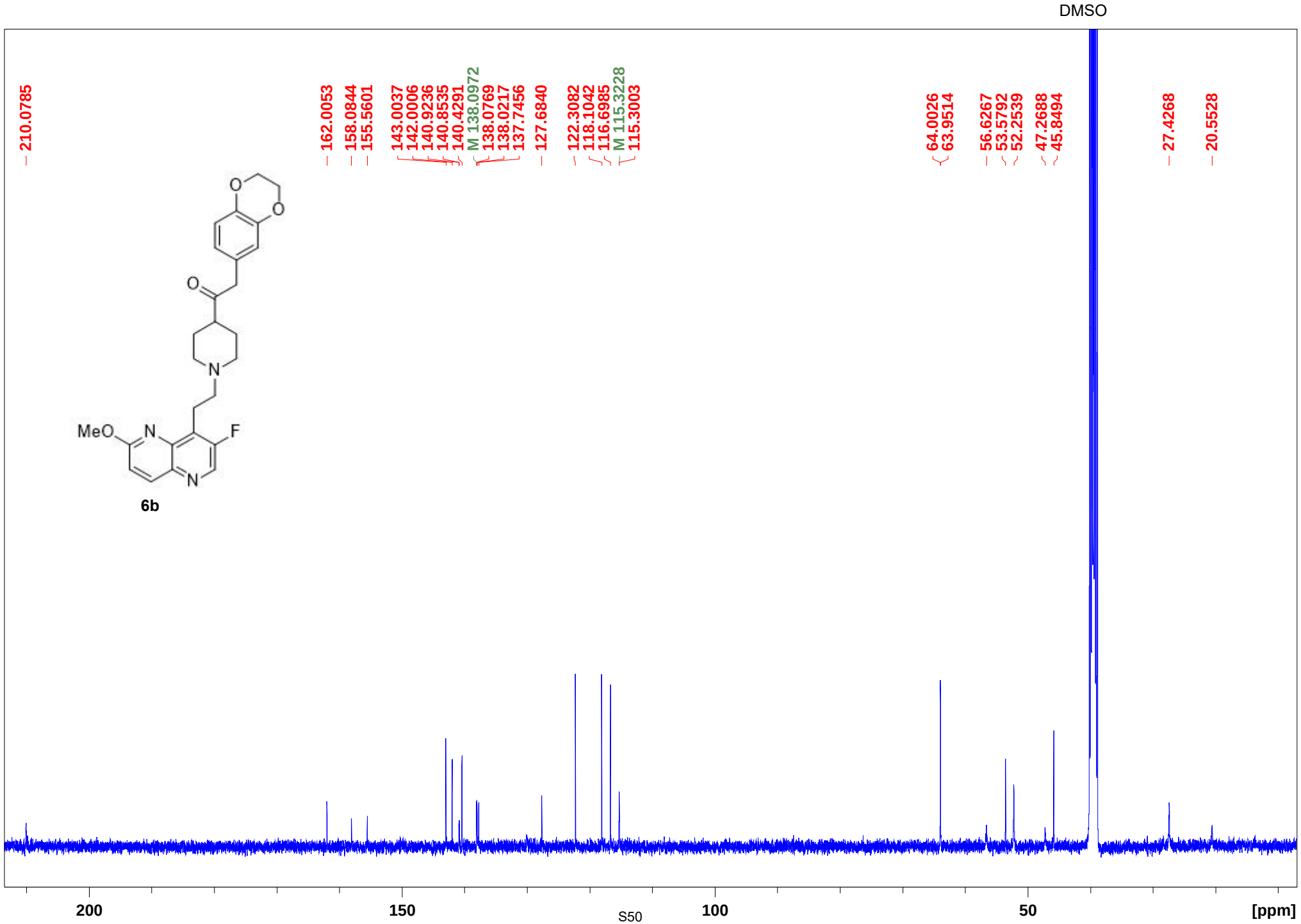
2
[ppm]


O
O
O
N
Boc
3b
Chloroform
ethyl acetate
ethyl acetate
ethyl acetate
1.00
0.97
4.12
1.98
2.02
2.07
1.08
1.91
4.39
10.06
6
4
2
[ppm]

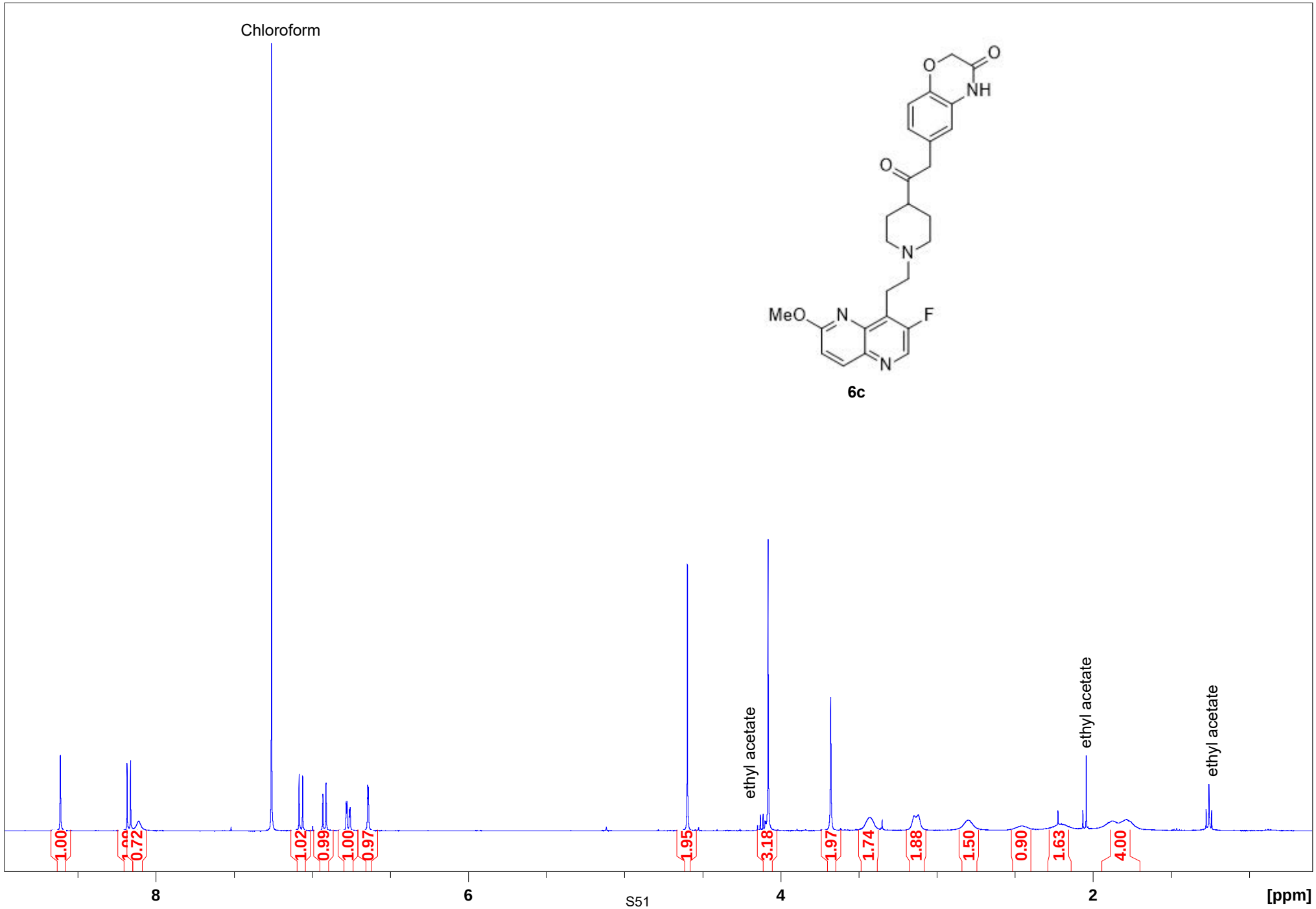

Chloroform
MeO
N
F
O
N
5
1.00
1.03
1.10
1.11
2.18
3.15
10
8
6
4
[ppm]

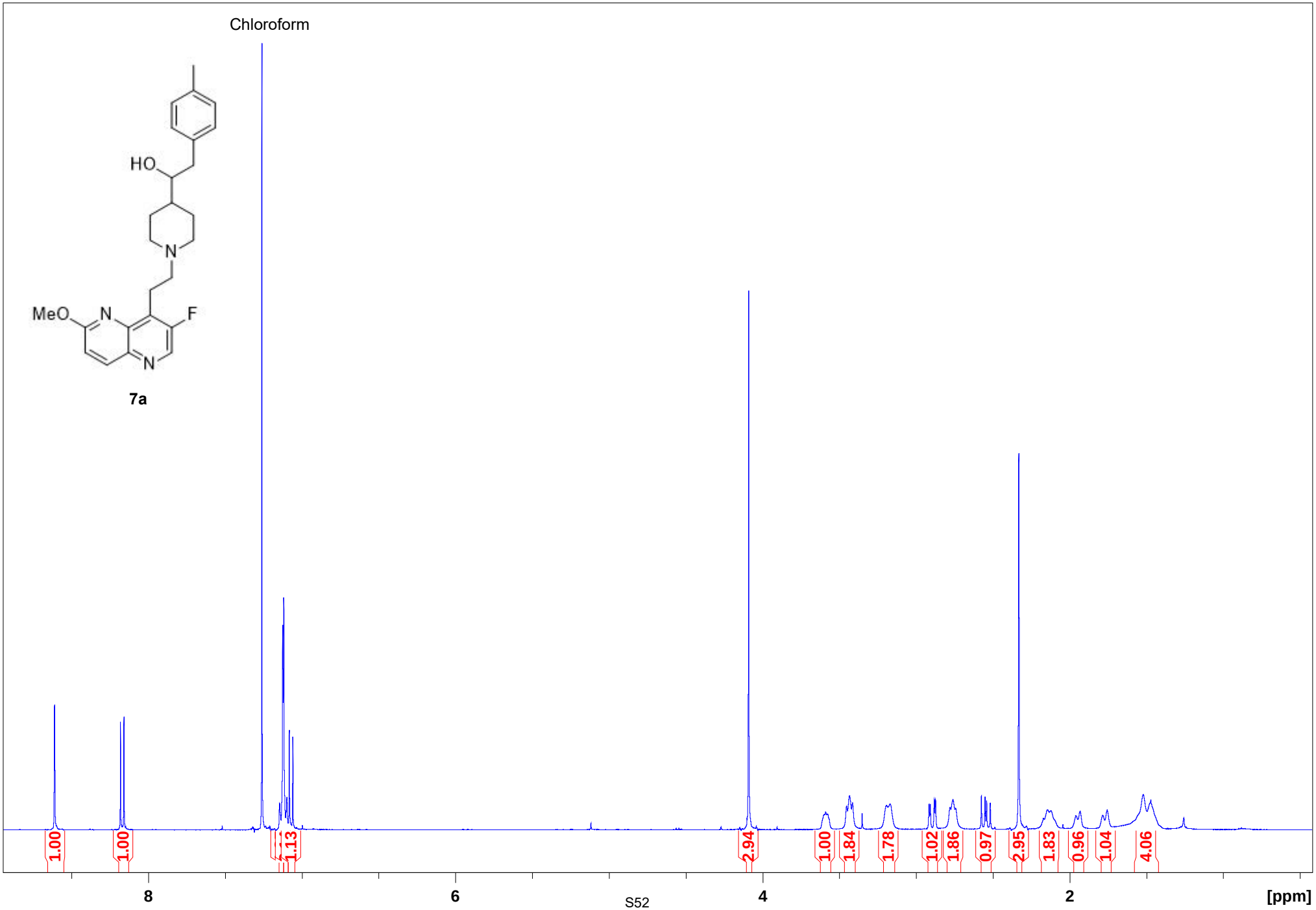

Chloroform
O
N
MeO
N
F
N
6a
1.00
1.01
3.05
3.14
2.01
1.91
1.99
1.79
0.96
3.10
1.70
4.03
8
6
4
2
[ppm]

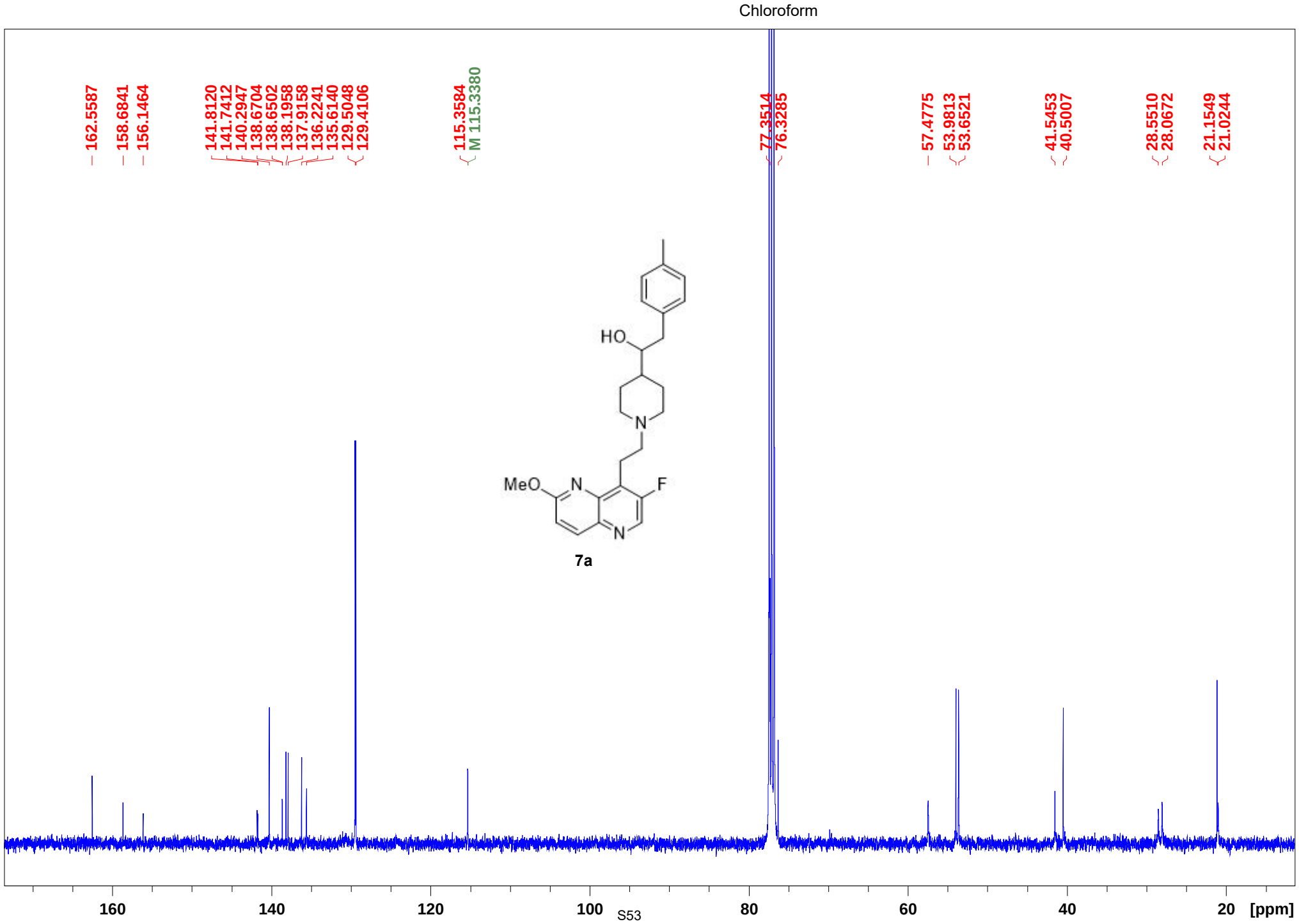

O
O
O
N
MeO
N
F
N
6b
DMSO
DCM
0.89
0.95
0.93
1.06
1.10
4.41
3.00
1.86
6.36
1.67
1.68
0.95
1.65
1.87
1.98
8
6
4
2
[ppm]

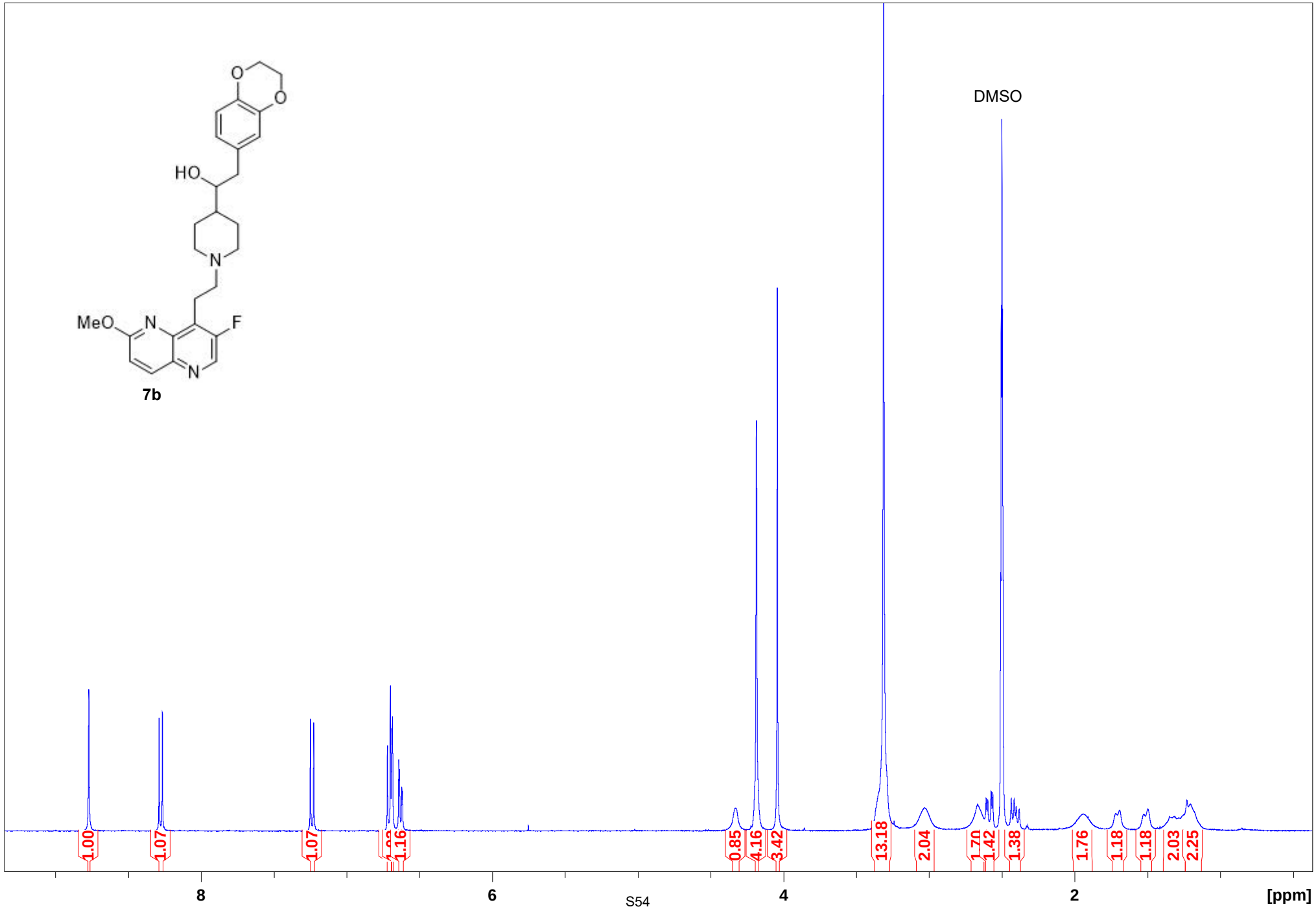

DMSO
210.0785
162.0053
158.0844
155.5601
143.0037
142.0006
140.9236
140.8535
140.4291
M 138.0972
138.0769
138.0217
137.7456
127.6840
122.3082
118.1042
116.6985
M 115.3228
115.3003
64.0026
63.9514
56.6267
53.5792
52.2539
47.2688
45.8494
27.4268
20.5528
O
O
O
N
MeO
N
F
N
200
150
100
50
[ppm]

**6b**

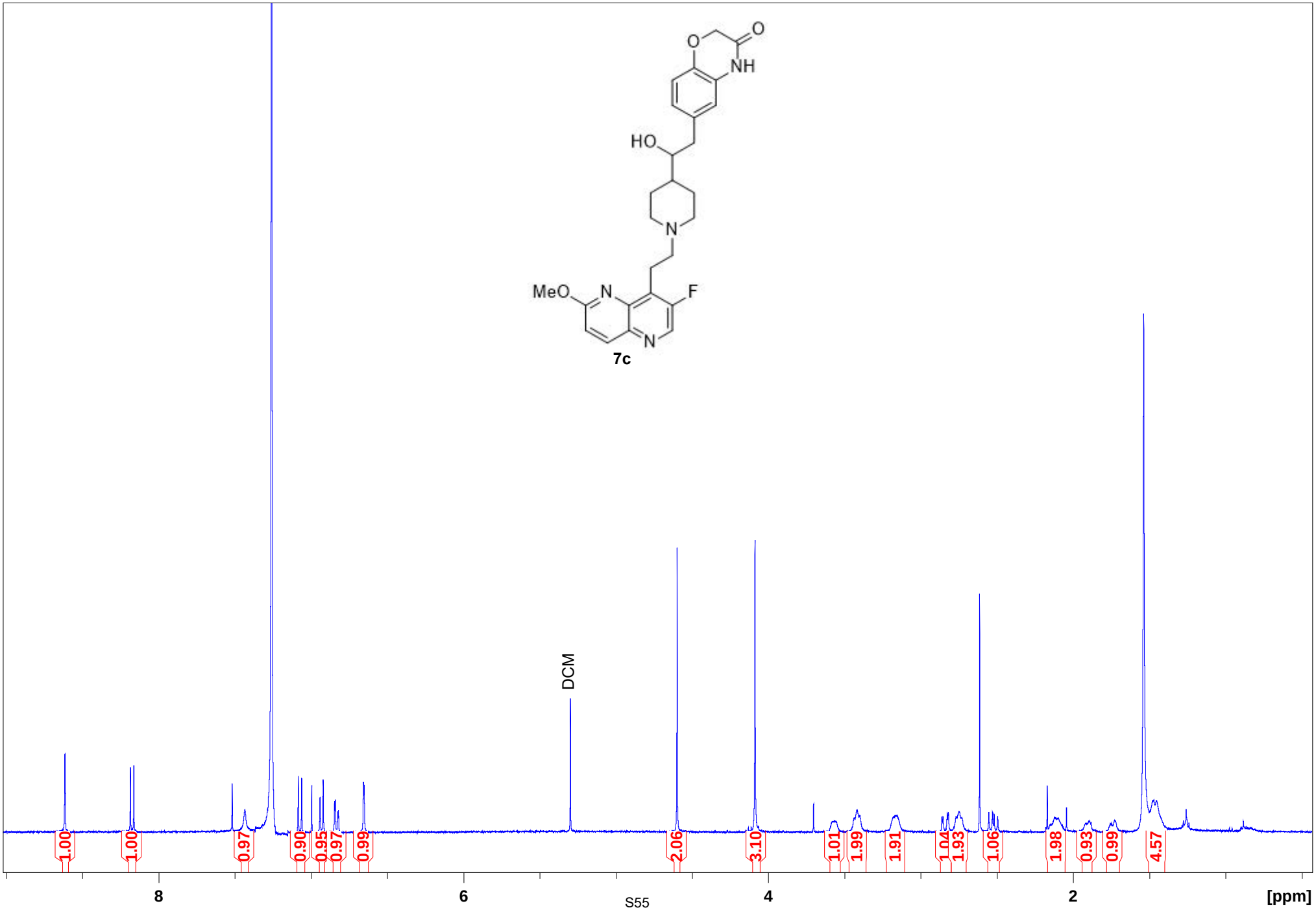

Chloroform
O
O
NH
O
N
MeO
N
F
N
6c
ethyl acetate
ethyl acetate
ethyl acetate
1.00
1.99
0.72
1.02
0.99
1.00
0.97
1.95
3.18
1.97
1.74
1.88
1.50
0.90
1.63
4.00
8
6
4
2
[ppm]

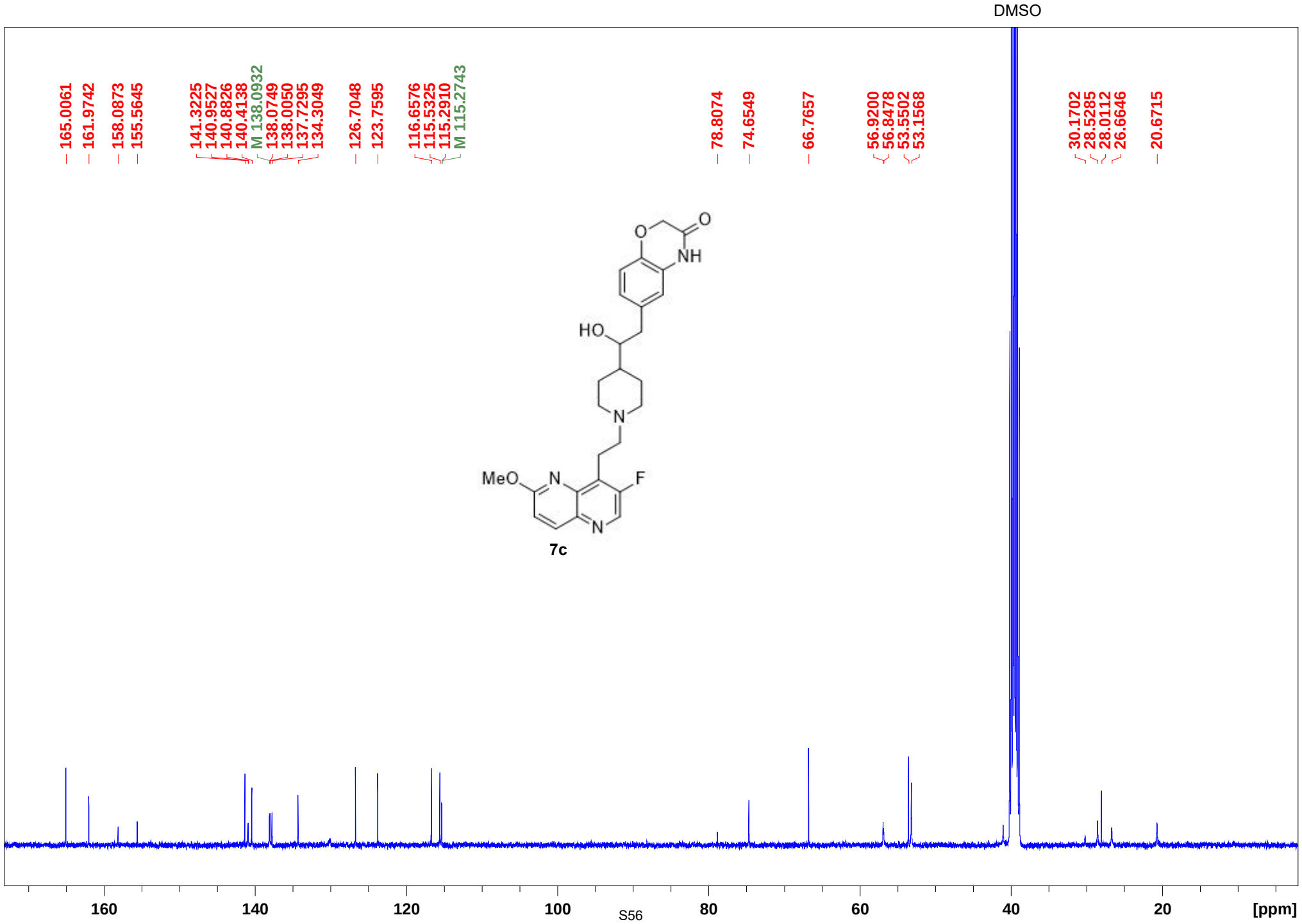

Chloroform
HO
N
MeO
N
F
N
7a
1.00
1.00
1.13
2.94
1.00
1.84
1.78
1.02
1.86
0.97
2.95
1.83
0.96
1.04
4.06
8
6
4
2
[ppm]


Chloroform
162.5587
158.6841
156.1464
141.8120
141.7412
140.2947
138.6704
138.6502
138.1958
137.9158
136.2241
135.6140
129.5048
129.4106
115.3584
M 115.3380
77.3514
76.3285
57.4775
53.9813
53.6521
41.5453
40.5007
28.5510
28.0672
21.1549
21.0244
HO
N
MeO
N
F
N
7a
160
140
120
100
80
60
40
20
[ppm]

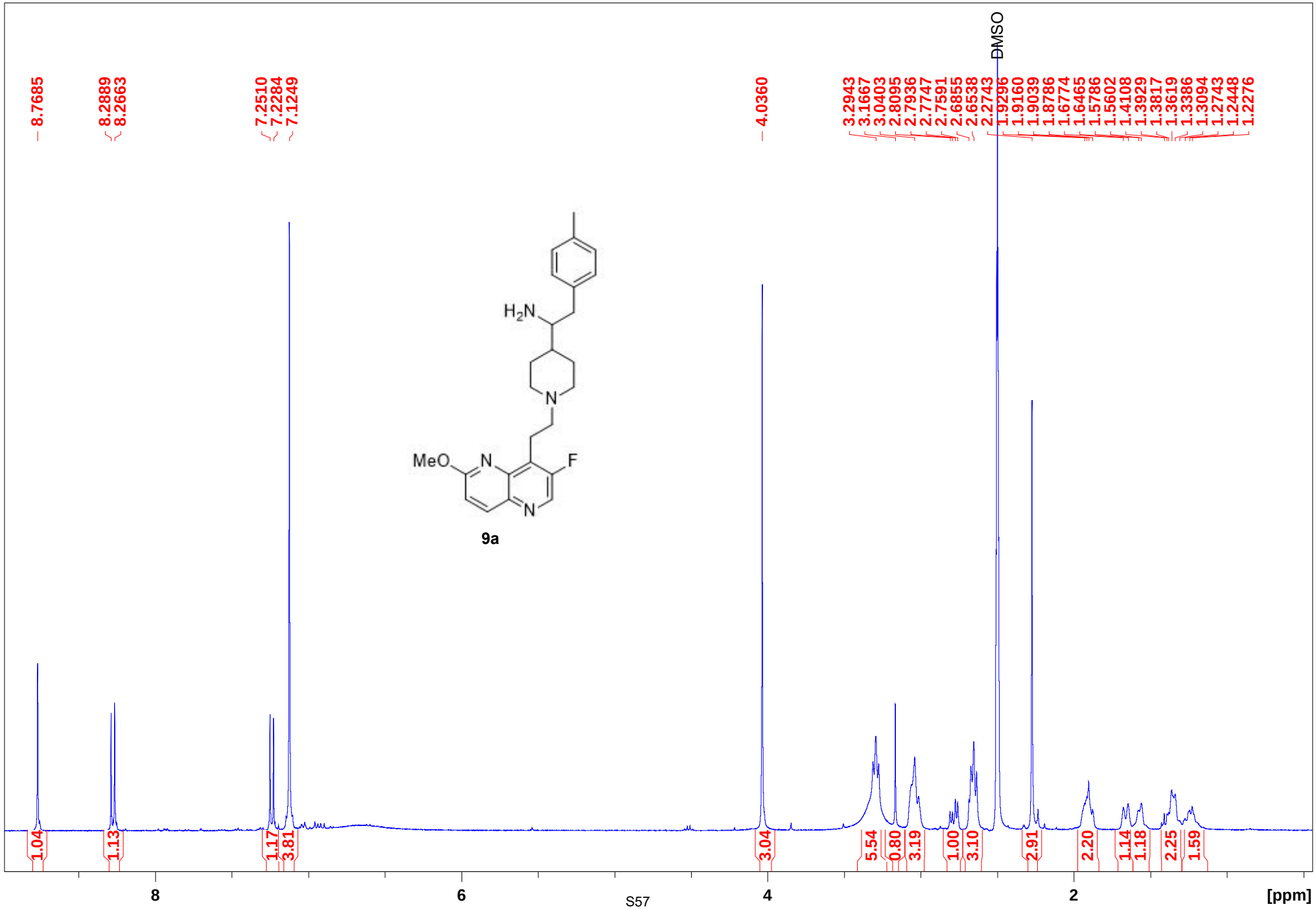

HO
O
O
N
MeO
N
F
N
7b
DMSO
1.00
1.07
1.07
1.16
0.85
4.16
3.42
13.18
2.04
1.70
1.42
1.38
1.76
1.18
1.18
2.03
2.25
8
6
4
2
[ppm]

Chloroform

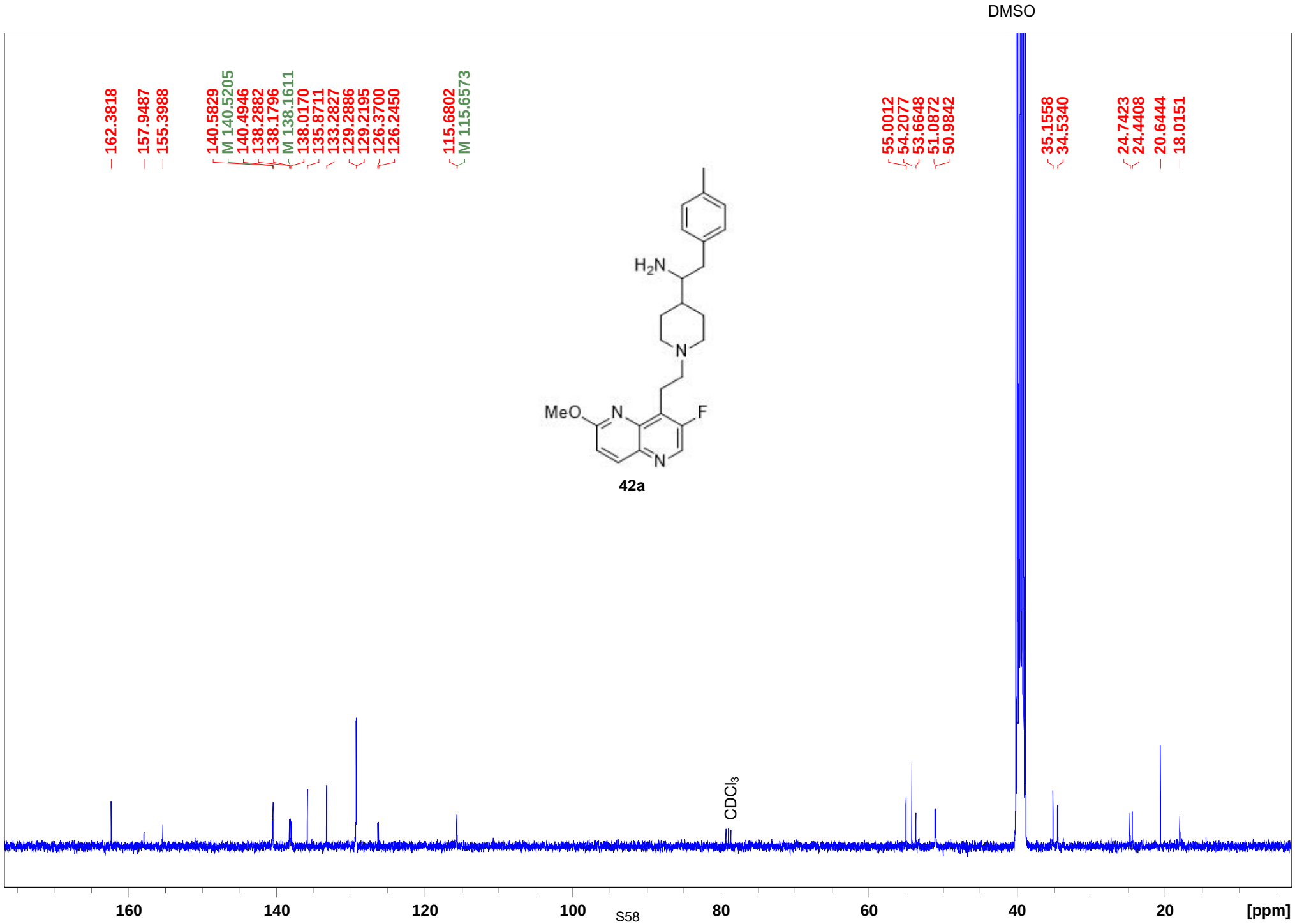

O
O
NH
HO
N
MeO
N
F
N
7c
DCM
1.00
1.00
0.97
0.90
0.95
0.97
0.99
2.06
3.10
1.01
1.99
1.91
1.04
1.93
1.06
1.98
0.93
0.99
4.57
8
6
4
2
[ppm]

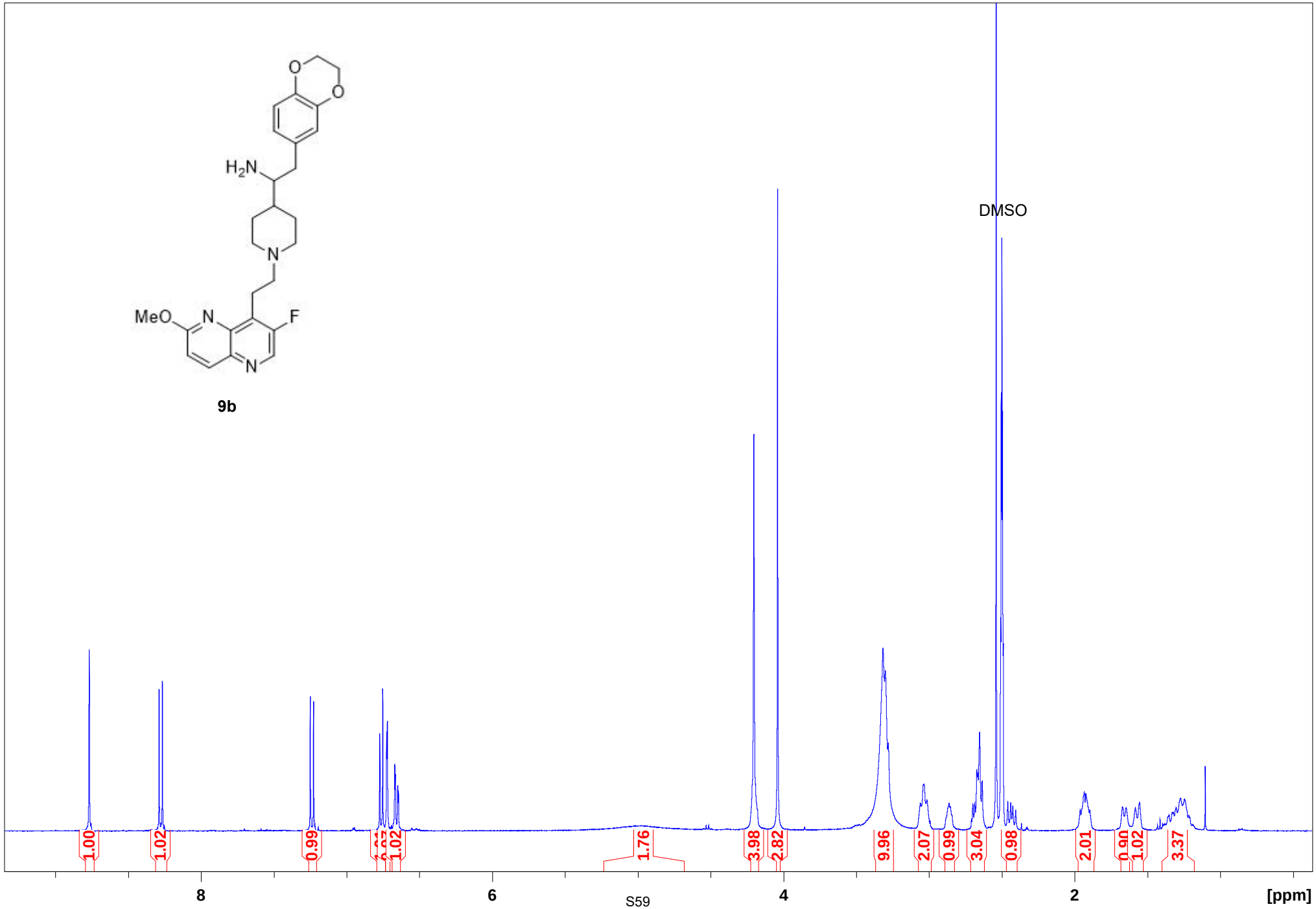

DMSO
165.0061
161.9742
158.0873
155.5645
141.3225
140.9527
140.8826
140.4138
M 138.0932
138.0749
138.0050
137.7295
134.3049
126.7048
123.7595
116.6576
115.5325
115.2910
M 115.2743
78.8074
74.6549
66.7657
56.9200
56.8478
53.5502
53.1568
30.1702
28.5285
28.0112
26.6646
20.6715
O
O
NH
HO
N
MeO
N
F
N
160
140
120
100
80
60
40
20
[ppm]

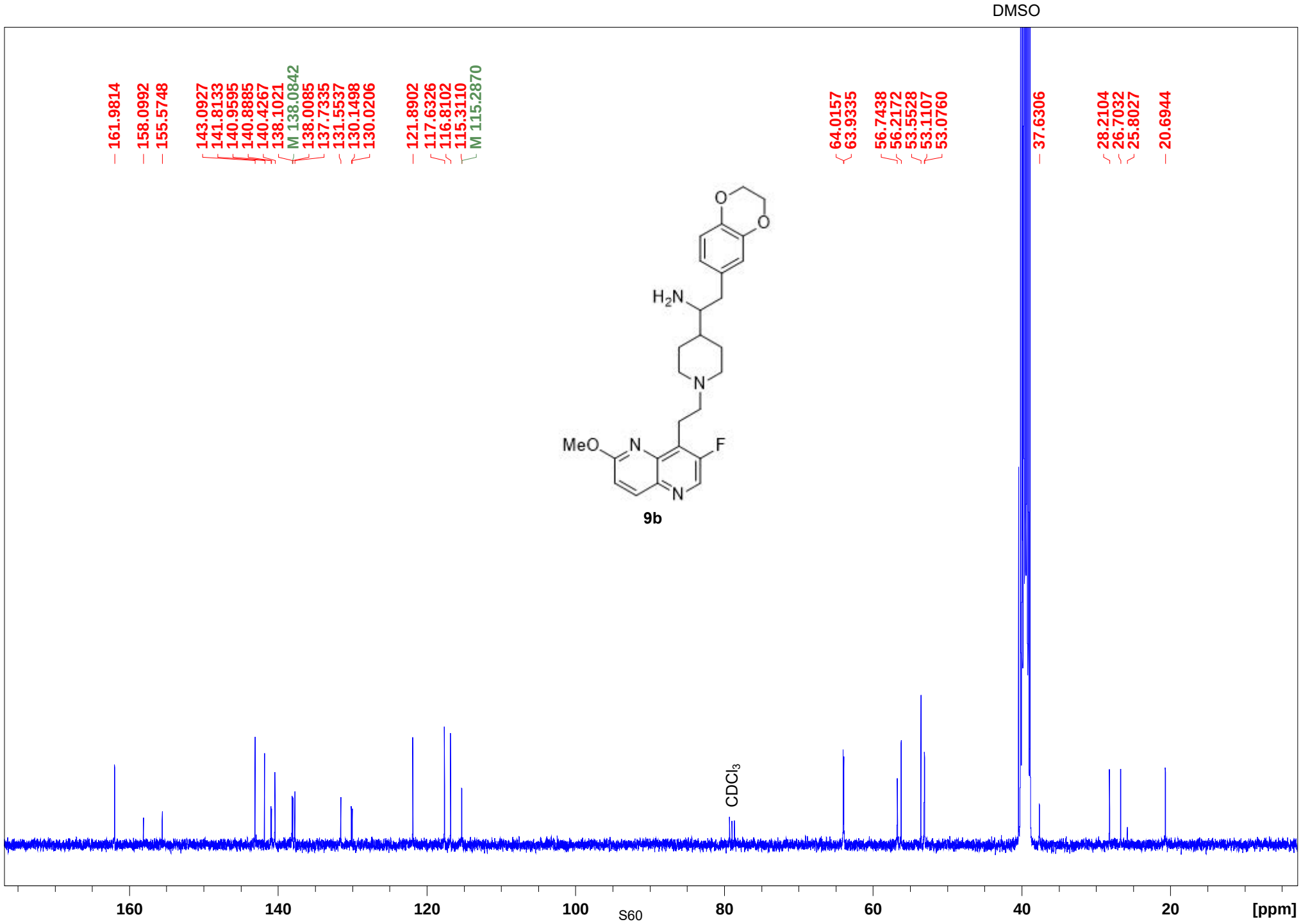
**7c**

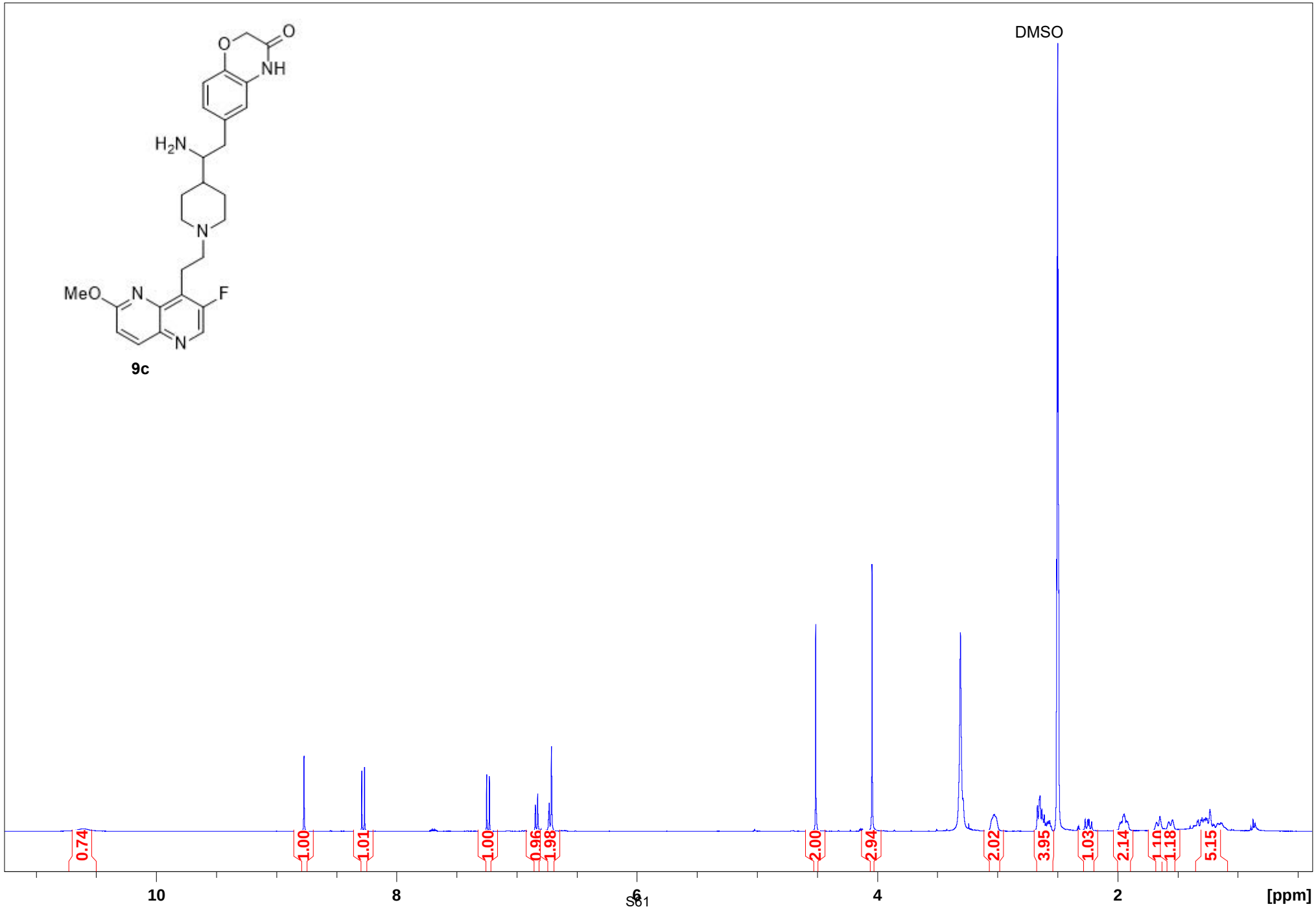

8.7685
8.2889
8.2663
7.2510
7.2284
7.1249
4.0360
3.2943
3.1667
3.0403
2.8095
2.7936
2.7747
2.7591
2.6855
2.6538
2.2743
1.9296
1.9160
1.9039
1.8786
1.6774
1.6465
1.5786
1.5602
1.4108
1.3929
1.3817
1.3619
1.3386
1.3094
1.2743
1.2448
1.2276
DMSO
1.04
1.13
1.17
3.81
3.04
5.54
0.80
3.19
1.00
3.10
2.91
2.20
1.14
1.18
2.25
1.59
8
6
4
2
[ppm]

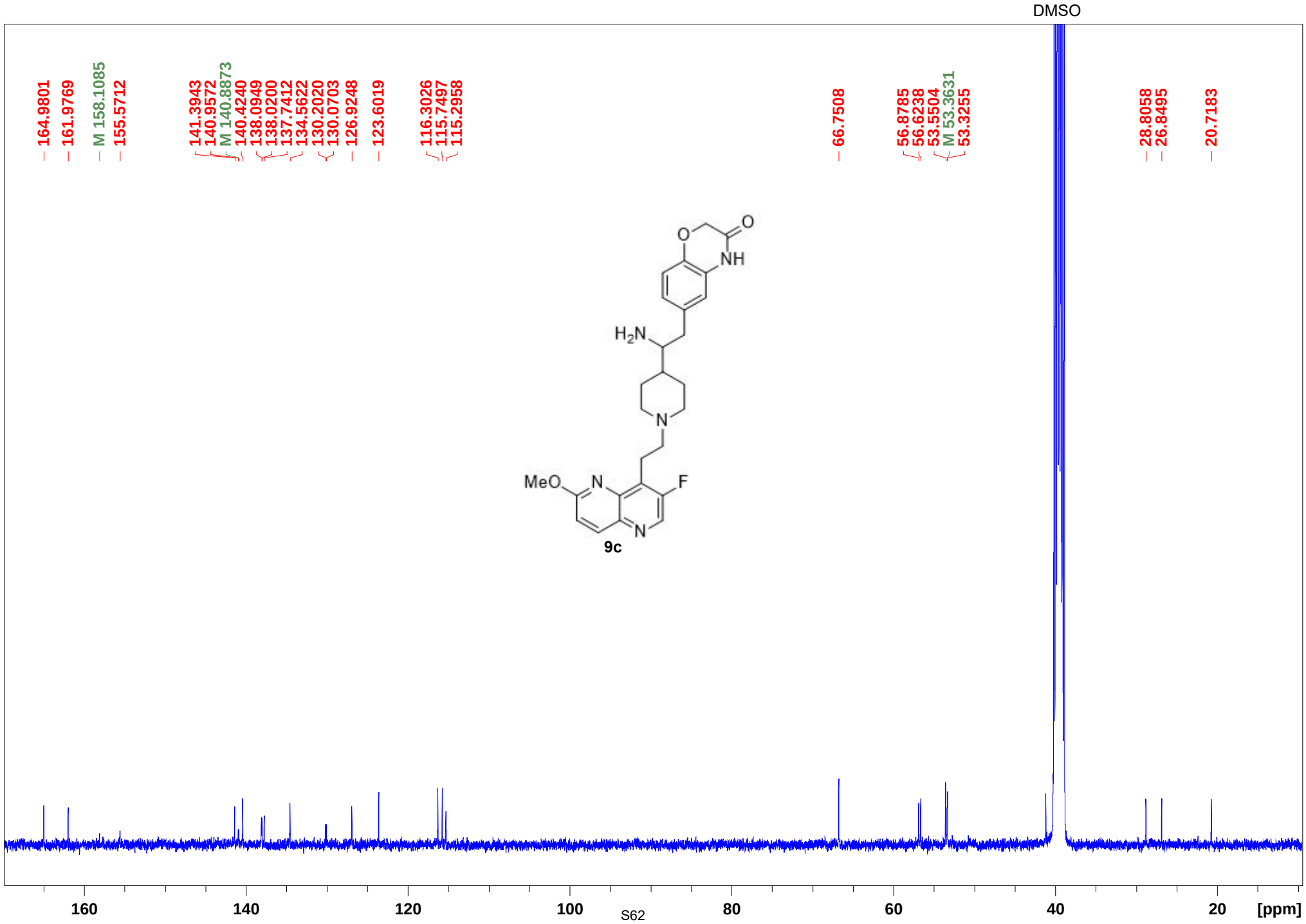
9a

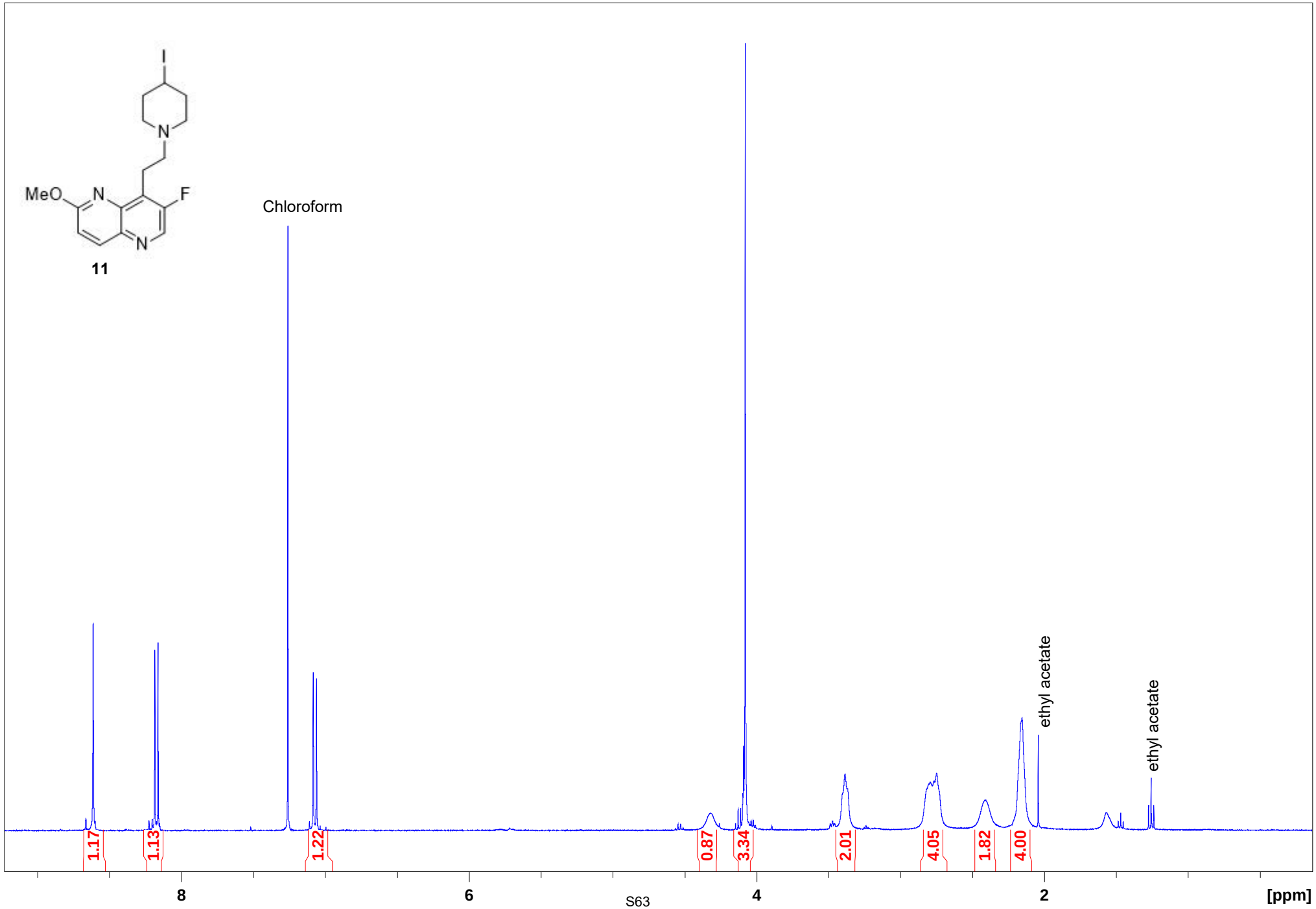

DMSO
162.3818
157.9487
155.3988
140.5829
M 140.5205
140.4946
138.2882
138.1796
M 138.1611
138.0170
135.8711
133.2827
129.2886
129.2195
126.3700
126.2450
115.6802
M 115.6573
55.0012
54.2077
53.6648
51.0872
50.9842
35.1558
34.5340
24.7423
24.4408
20.6444
18.0151
H2N
N
MeO
N
F
N
42a
CDCl3
160
140
120
100
80
60
40
20
[ppm]

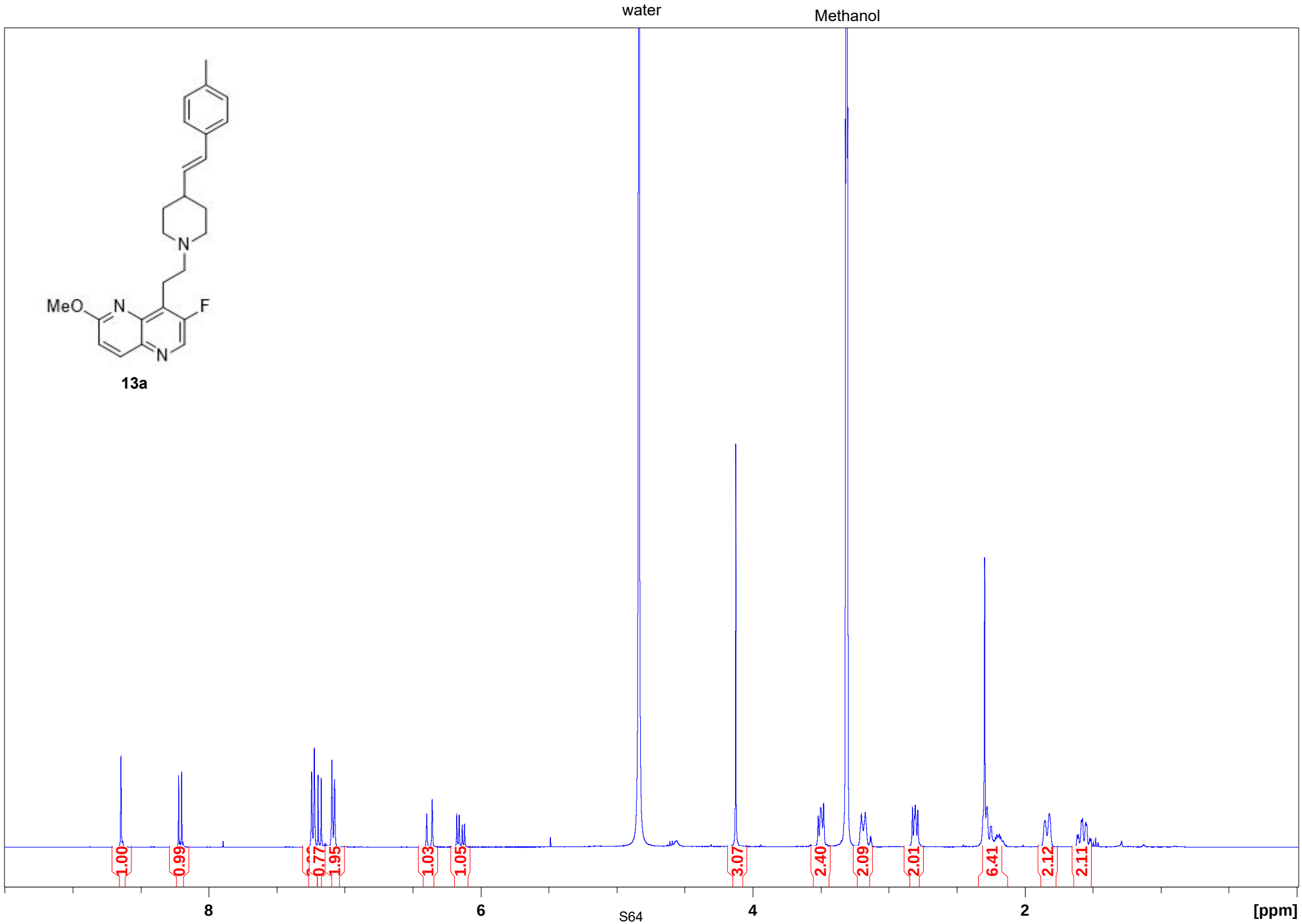

O
O
H2N
N
MeO
N
F
N
9b
DMSO
1.00
1.02
0.99
1.02
1.76
3.98
2.82
9.96
2.07
0.99
3.04
0.98
2.01
0.90
1.02
3.37
8
6
4
2
[ppm]

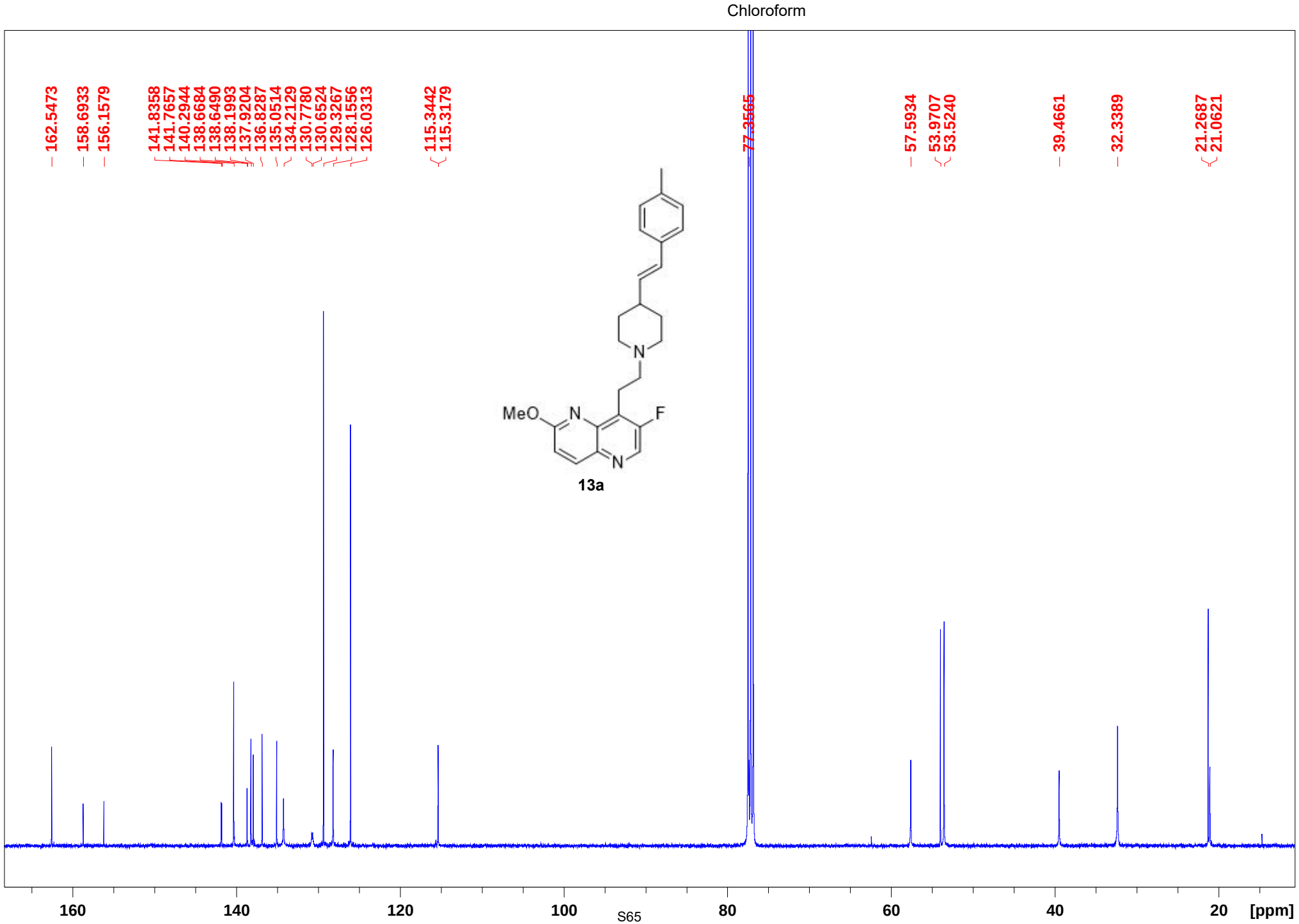

DMSO
161.9814
158.0992
155.5748
143.0927
141.8133
140.9595
140.8885
140.4267
138.1021
M 138.0842
138.0085
137.7335
131.5537
130.1498
130.0206
121.8902
117.6326
116.8102
115.3110
M 115.2870
64.0157
63.9335
56.7438
56.2172
53.5528
53.1107
53.0760
37.6306
28.2104
26.7032
25.8027
20.6944
H2N
N
MeO
N
F
N
9b
CDCl3
160
140
120
100
80
60
40
20
[ppm]

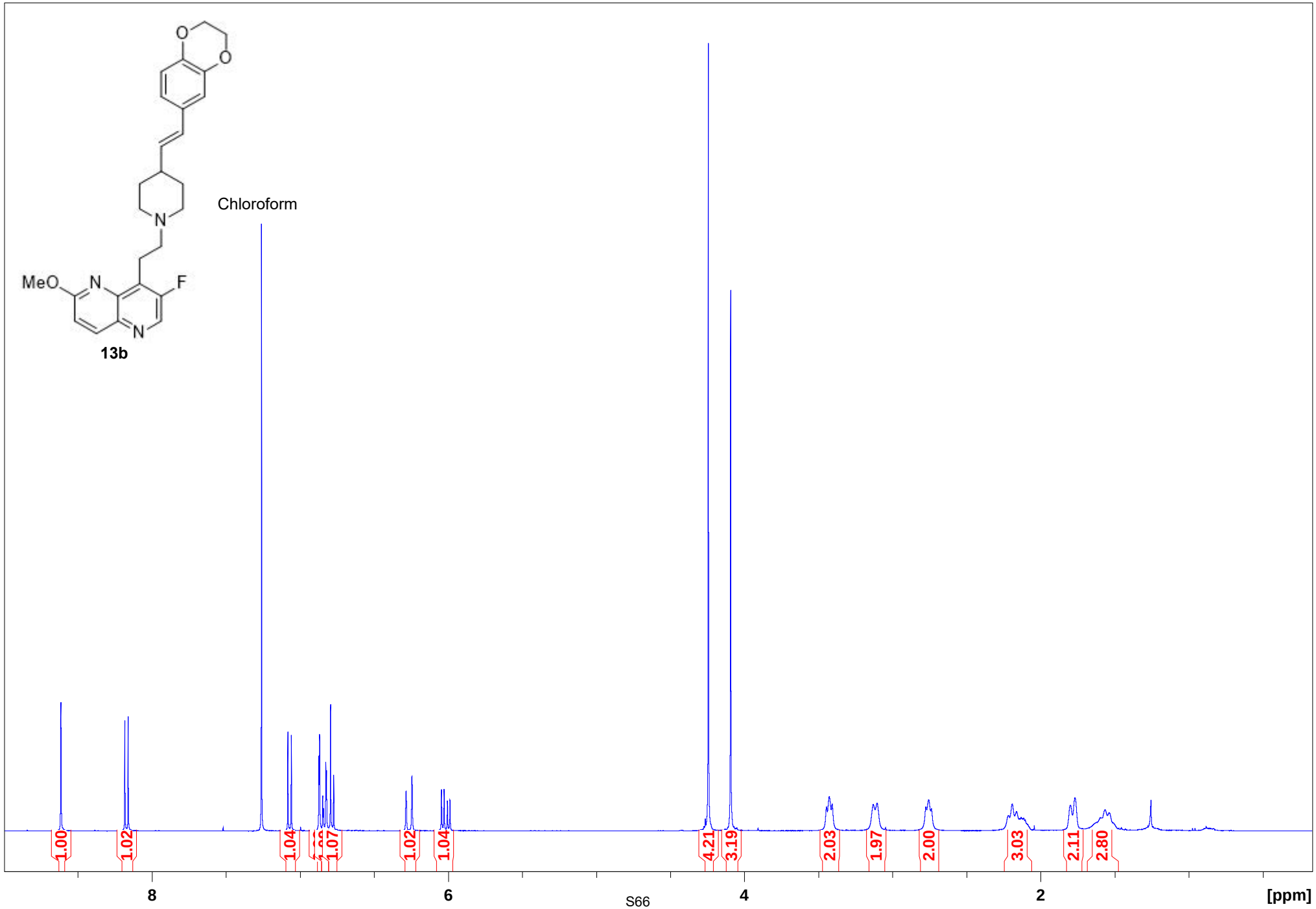

O
O
NH
$H_2N$
N
MeO
N
F
N
9c
DMSO
0.74
1.00
1.01
1.00
0.96
1.98
2.00
2.94
2.02
3.95
1.03
2.14
1.10
1.18
5.15
10
8
6
4
2
[ppm]

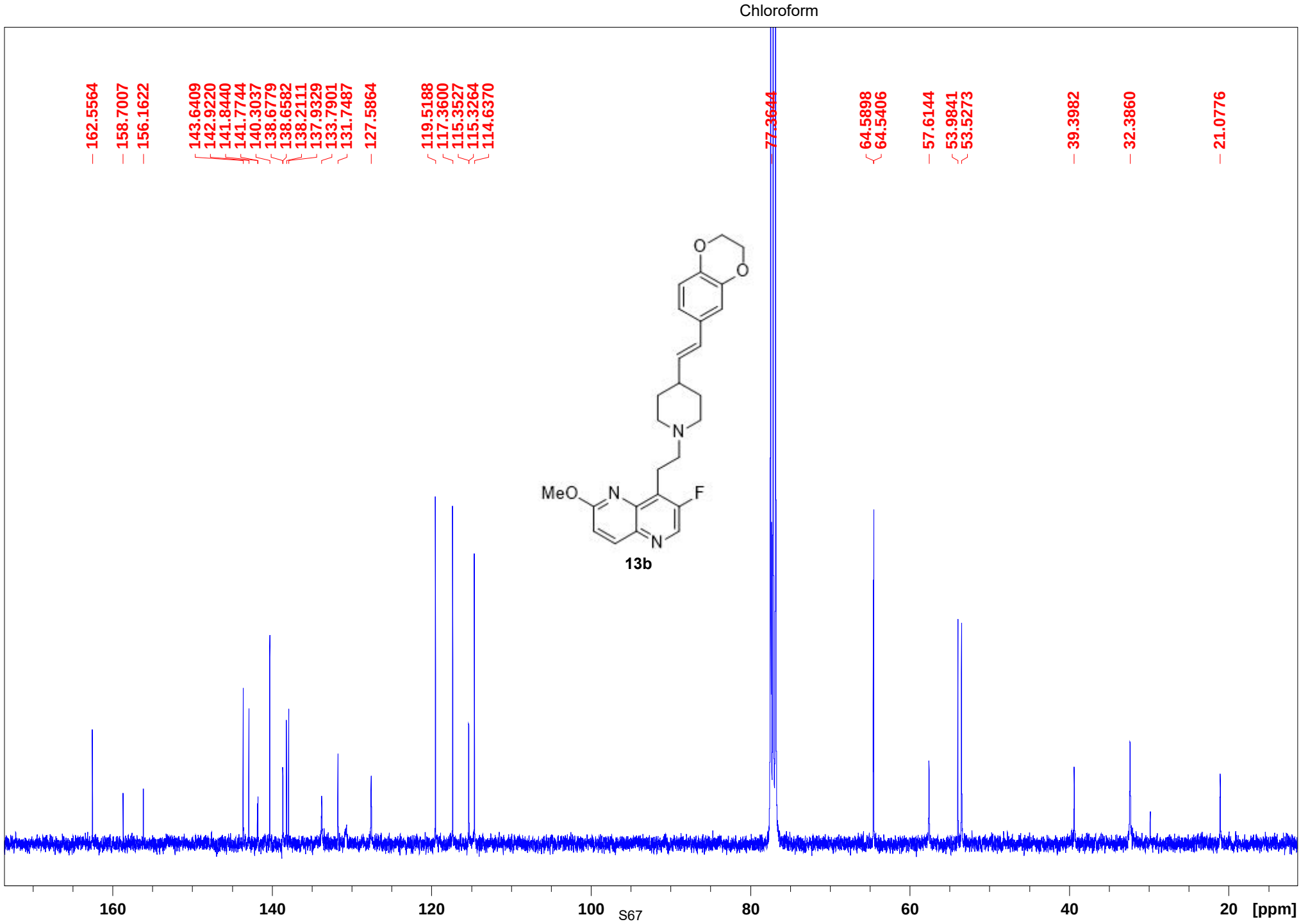

DMSO
164.9801
161.9769
M 158.1085
155.5712
141.3943
140.9572
M 140.8873
140.4240
138.0949
138.0200
137.7412
134.5622
130.2020
130.0703
126.9248
123.6019
116.3026
115.7497
115.2958
66.7508
56.8785
56.6238
53.5504
M 53.3631
53.3255
28.8058
26.8495
20.7183
O
O
NH
H2N
N
MeO
N
F
N
9c
160
140
120
100
80
60
40
20
[ppm]


I
N
MeO
N
F
N
11
Chloroform
ethyl acetate
ethyl acetate
1.17
1.13
1.22
0.87
3.34
2.01
4.05
1.82
4.00
8
6
4
2
[ppm]

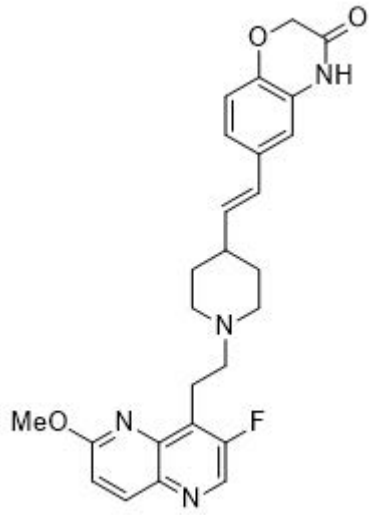

water
Methanol
MeO
N
F
N
N
13a
1.00
0.99
2.22
0.77
1.95
1.03
1.05
3.07
2.40
2.09
2.01
6.41
2.12
2.11
8
6
4
2
[ppm]


Chloroform
162.5473
158.6933
156.1579
141.8358
141.7657
140.2944
138.6684
138.6490
138.1993
137.9204
136.8287
135.0514
134.2129
130.7780
130.6524
129.3267
128.1556
126.0313
115.3442
115.3179
77.3565
57.5934
53.9707
53.5240
39.4661
32.3389
21.2687
21.0621
MeO
N
F
N
N
13a
160
140
120
100
80
60
40
20
[ppm]


Chloroform
MeO
N
F
N
N
O
O
13b
1.00
1.02
1.04
1.07
1.02
1.04
4.21
3.19
2.03
1.97
2.00
3.03
2.11
2.80
8
6
4
2
[ppm]


Chloroform
162.5564
158.7007
156.1622
143.6409
142.9220
141.8440
141.7744
140.3037
138.6779
138.6582
138.2111
137.9329
133.7901
131.7487
127.5864
119.5188
117.3600
115.3527
115.3264
114.6370
77.3644
64.5898
64.5406
57.6144
53.9841
53.5273
39.3982
32.3860
21.0776
MeO
N
F
N
O
O
N
13b
160
140
120
100
80
60
40
20
[ppm]

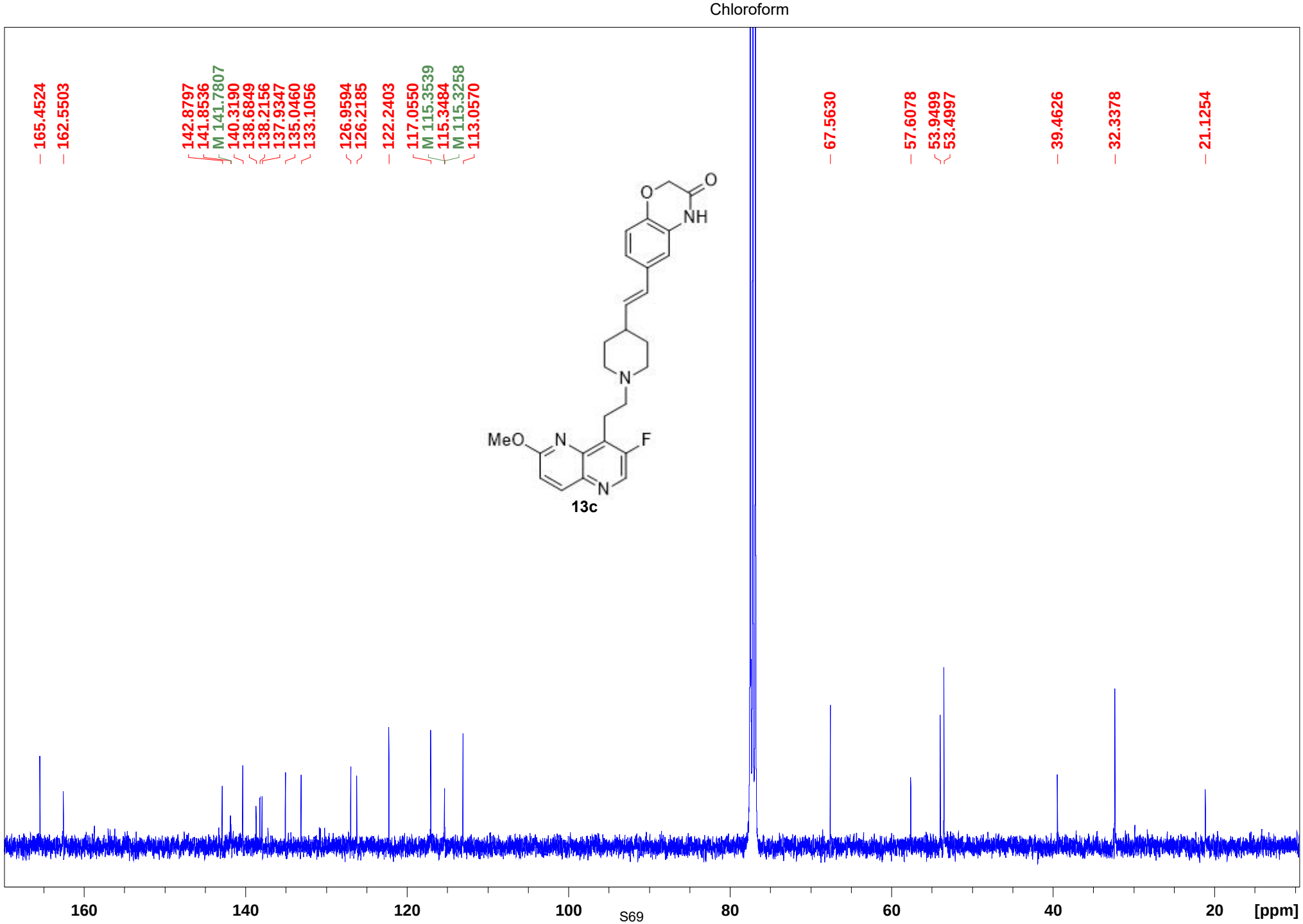
Chloroform

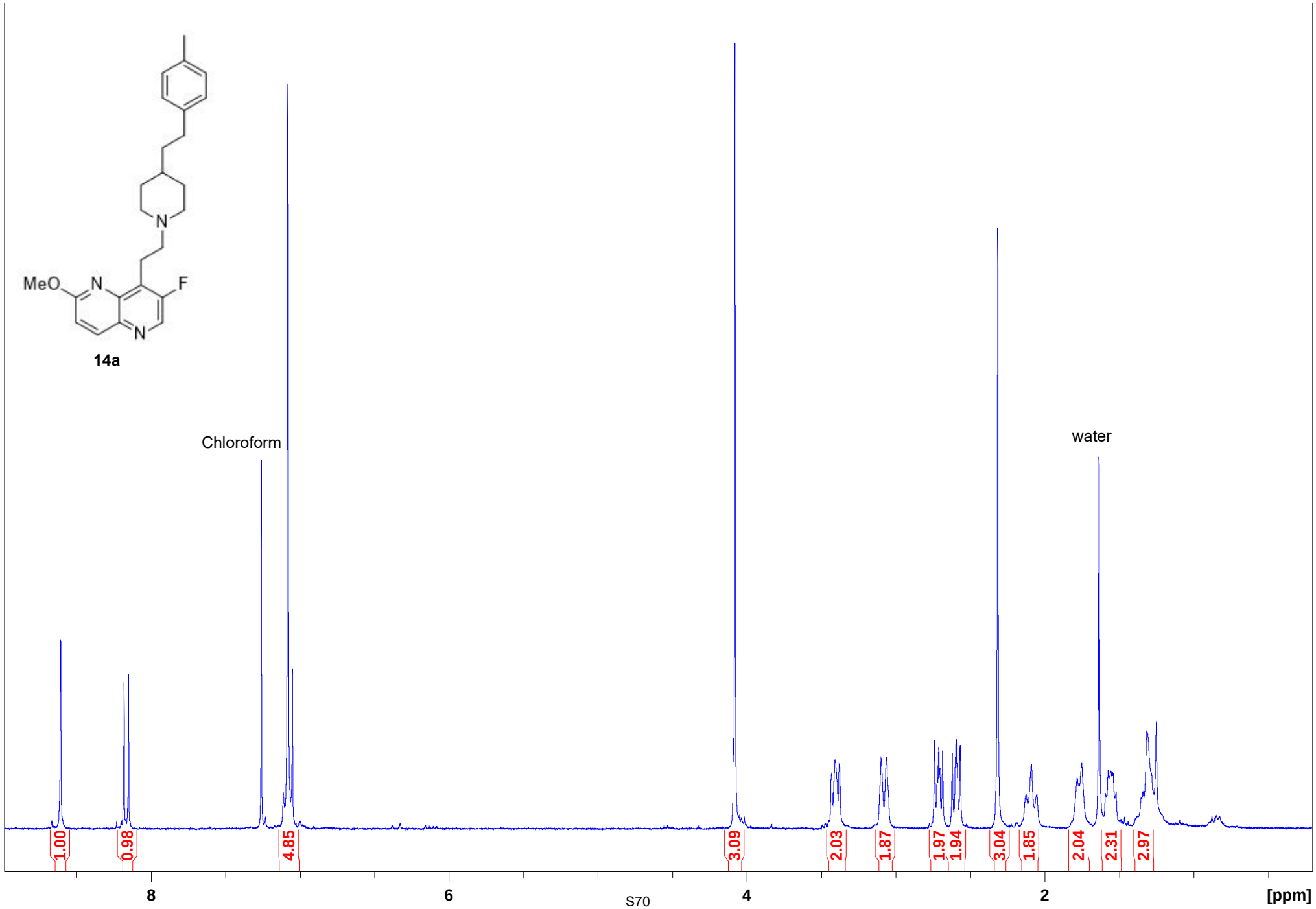


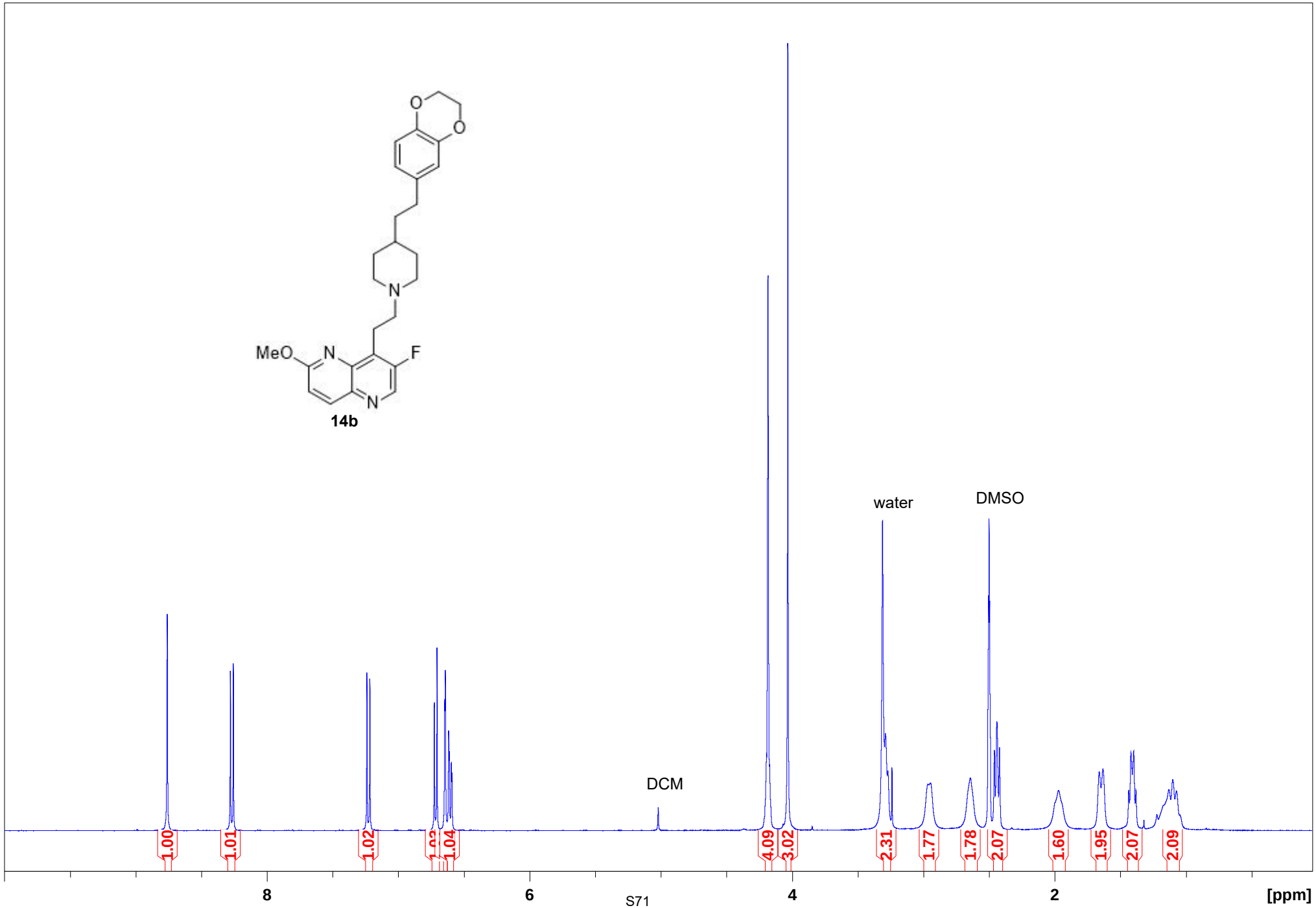

**13c**

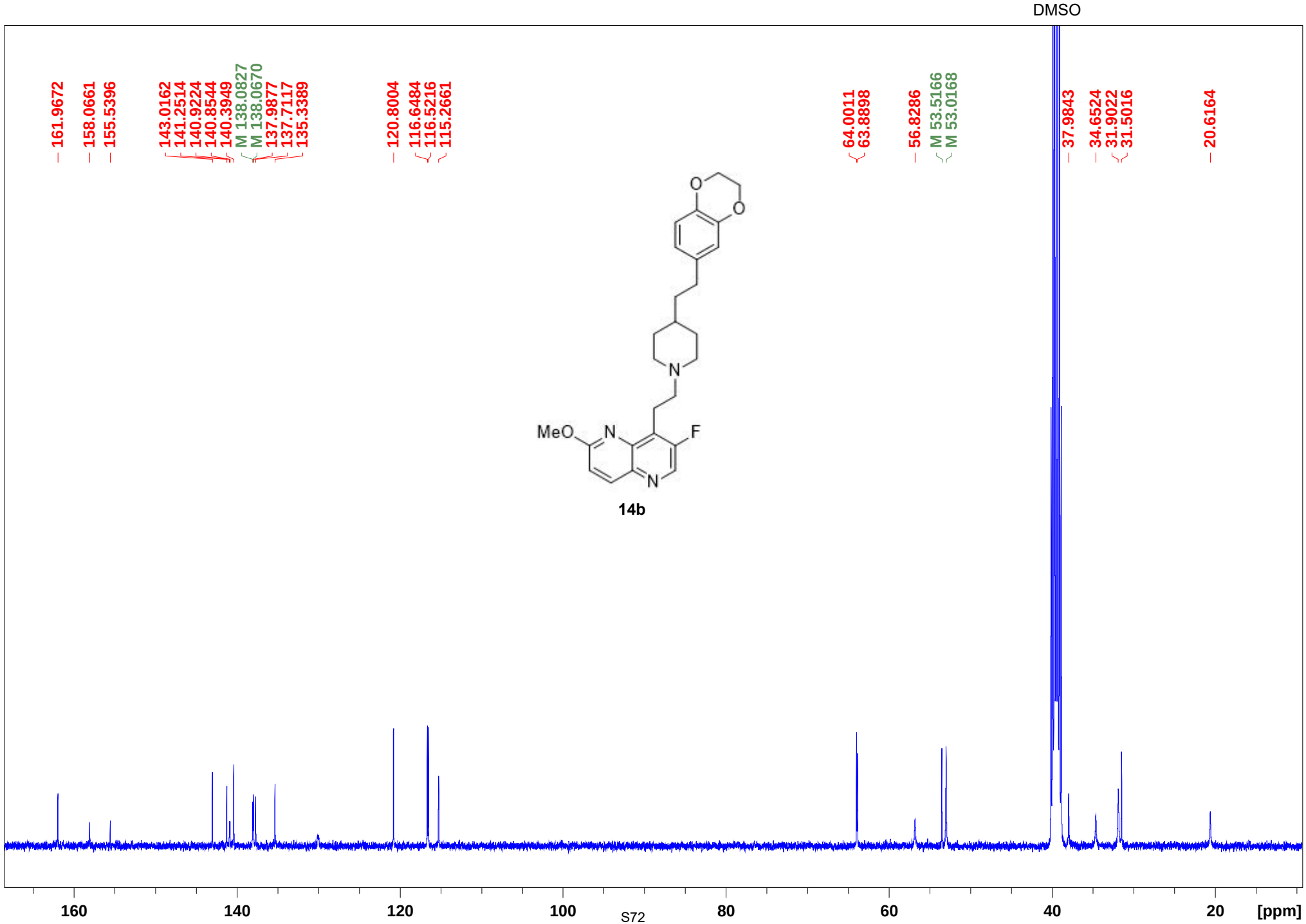
1.00 1.04 0.91 1.11 1.08 1.08 1.09 2.10 3.16 2.13 2.16 2.21 2.24 2.18 2.17 2.30 3.59

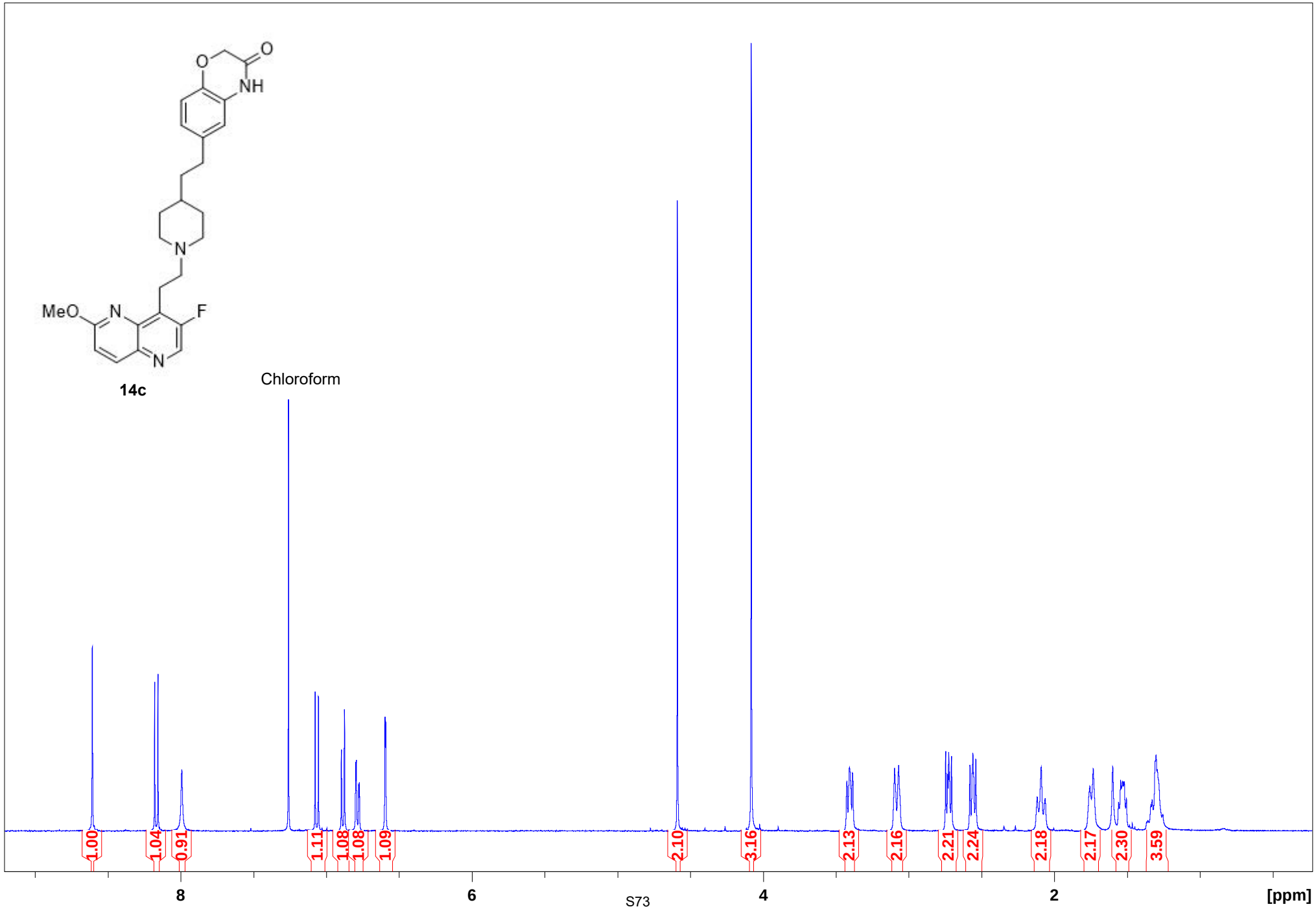
8 6 4 2 [ppm]

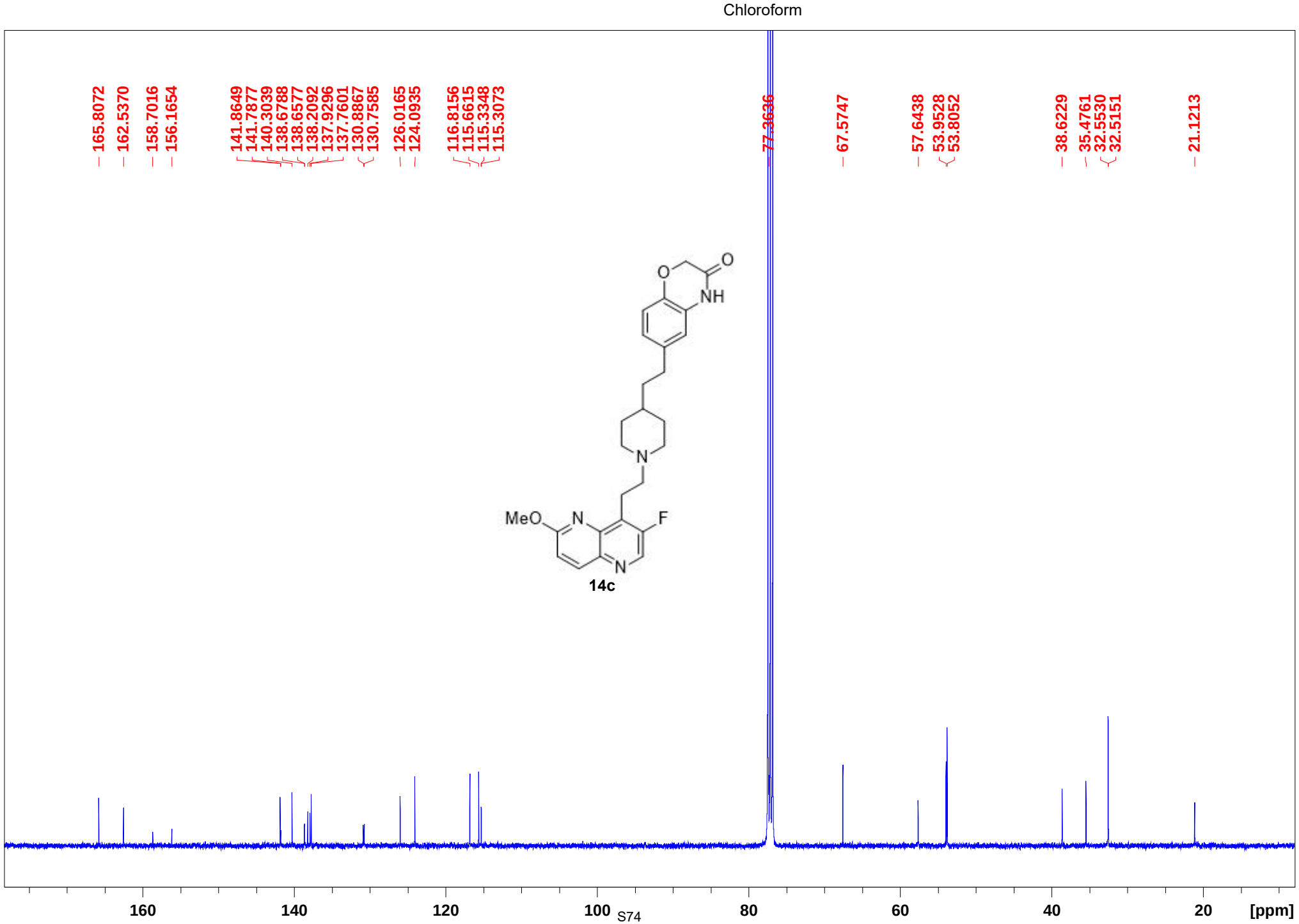

Chloroform
165.4524
162.5503
142.8797
141.8536
M 141.7807
140.3190
138.6849
138.2156
137.9347
135.0460
133.1056
126.9594
126.2185
122.2403
117.0550
M 115.3539
115.3484
M 115.3258
113.0570
67.5630
57.6078
53.9499
53.4997
39.4626
32.3378
21.1254
O
O
NH
N
MeO
N
F
N
13c
160
140
120
100
80
60
40
20
[ppm]

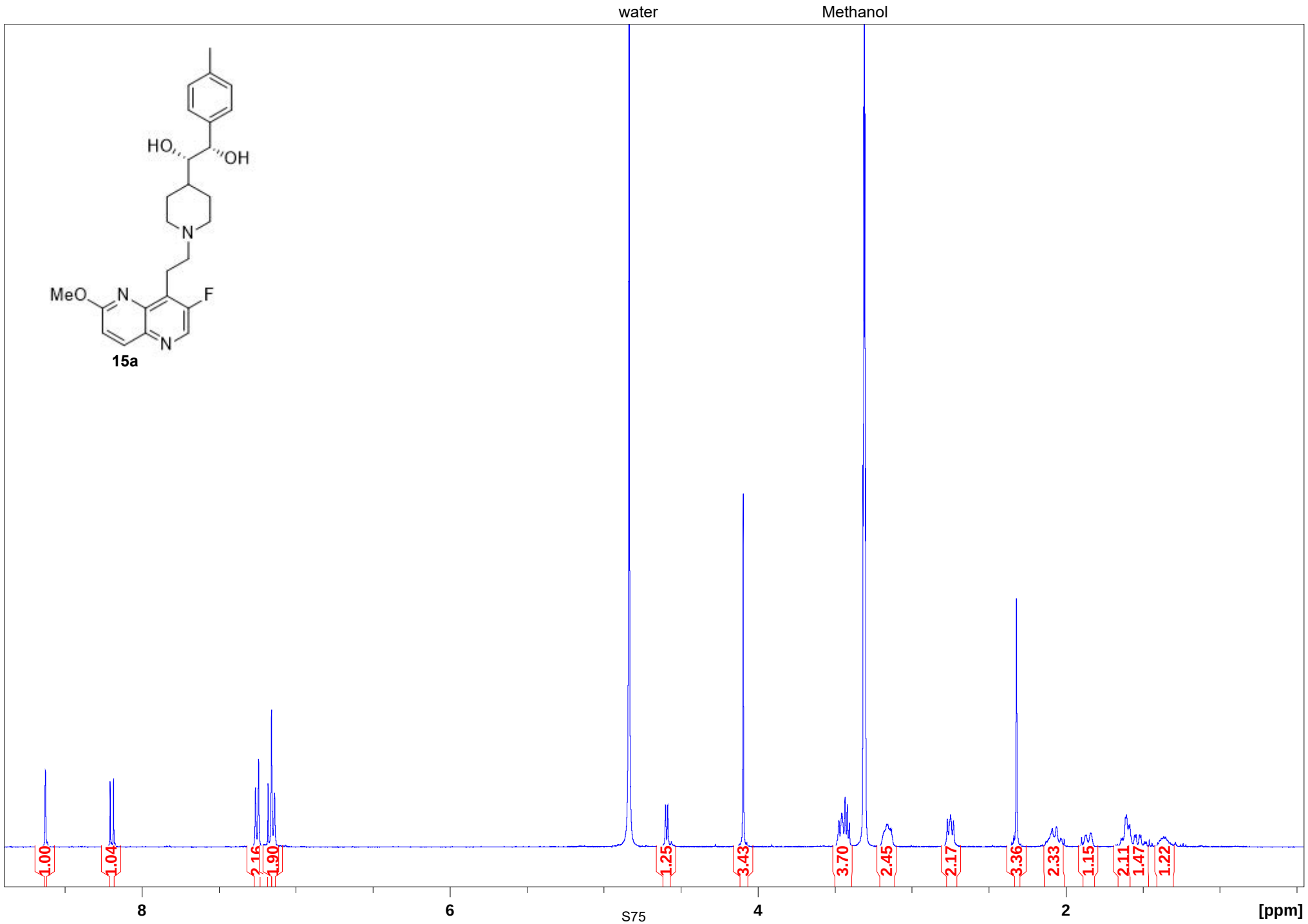

MeO
N
F
N
N
14a
Chloroform
water
1.00
0.98
4.85
3.09
2.03
1.87
1.97
1.94
3.04
1.85
2.04
2.31
2.97
8
6
4
2
[ppm]

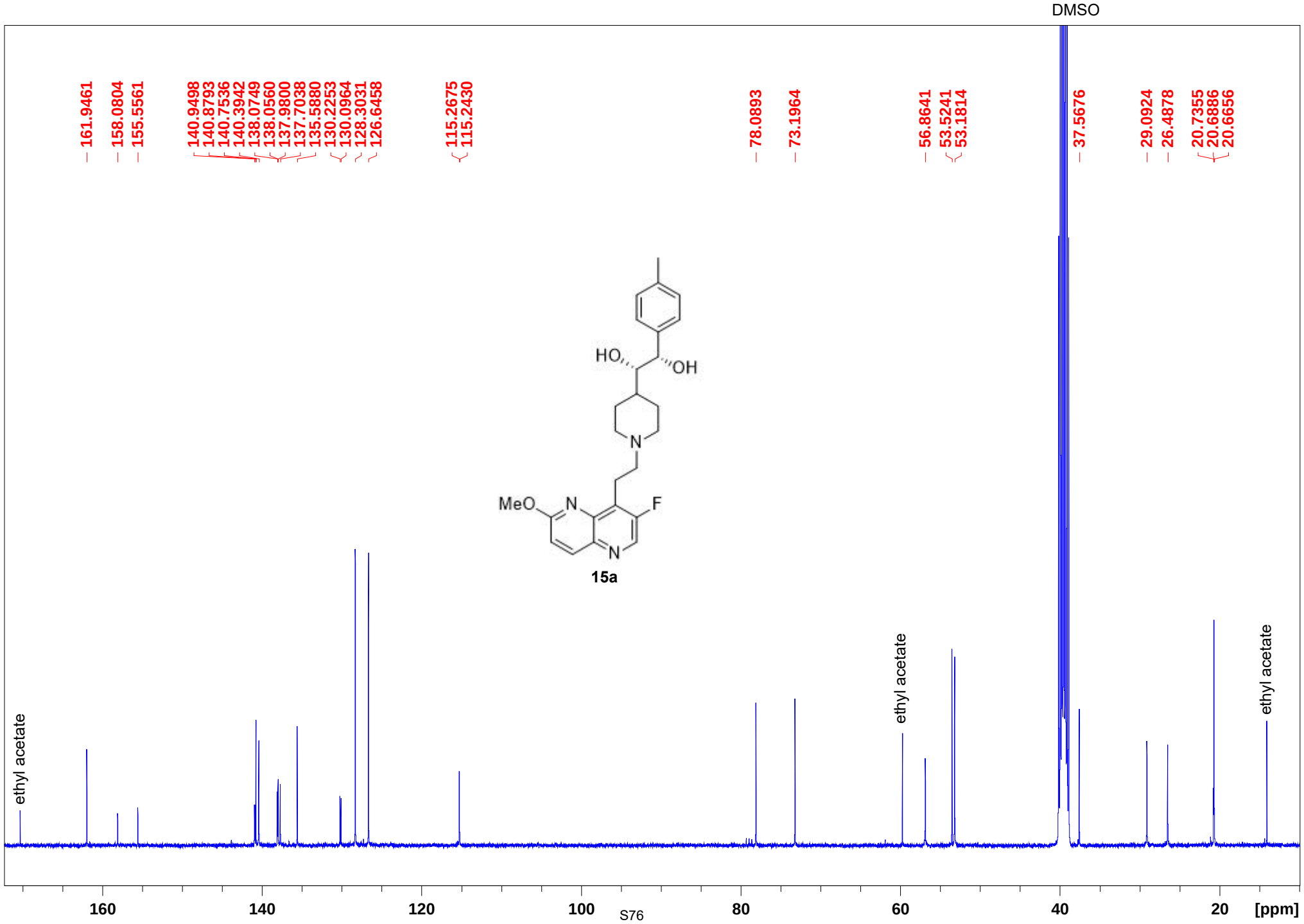

MeO
N
F
N
O
O
N
14b
water
DMSO
DCM
1.00
1.01
1.02
1.03
1.04
4.09
3.02
2.31
1.77
1.78
2.07
1.60
1.95
2.07
2.09
8
6
4
2
[ppm]

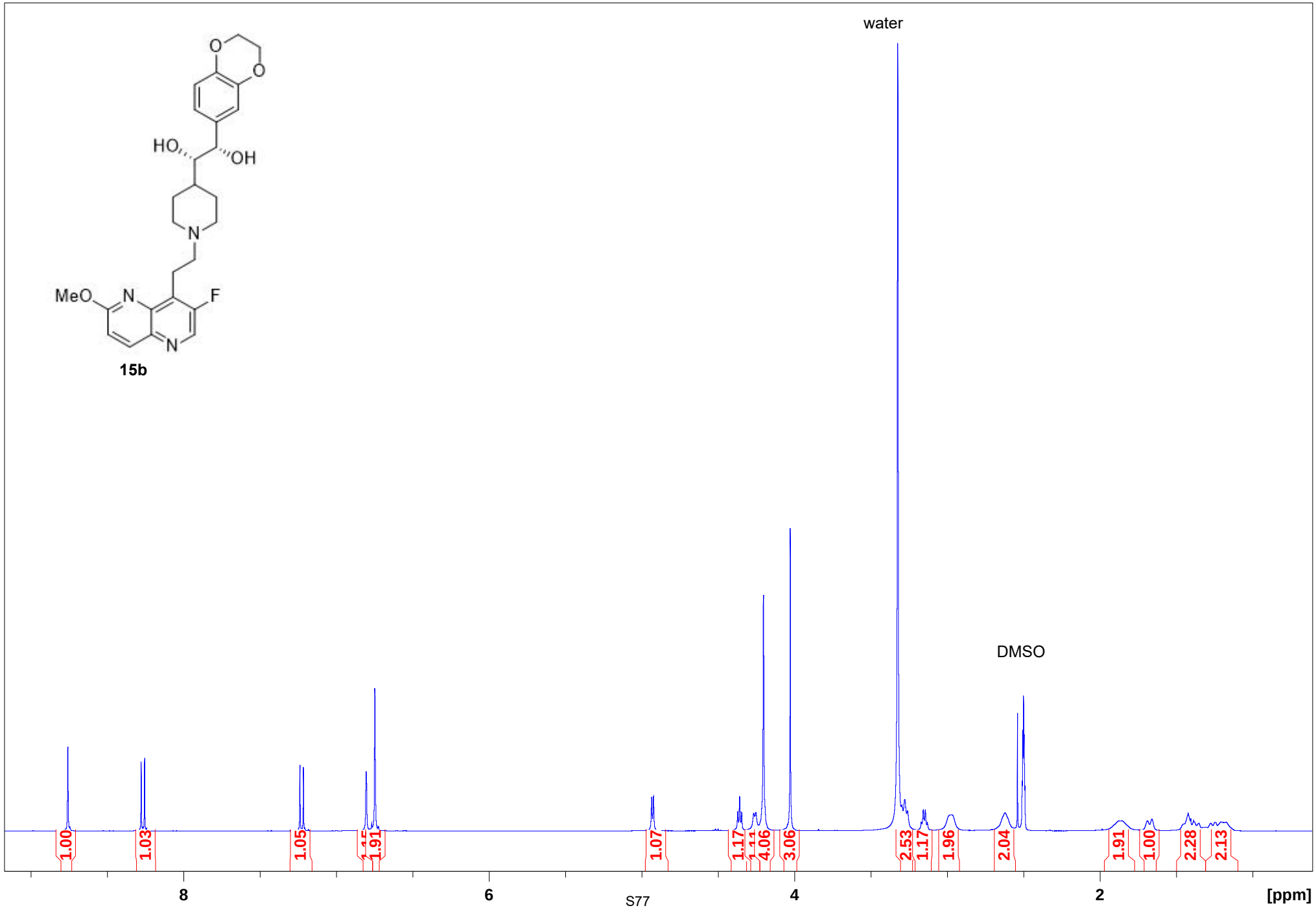

DMSO
161.9672
158.0661
155.5396
143.0162
141.2514
140.9224
140.8544
140.3949
M 138.0827
M 138.0670
137.9877
137.7117
135.3389
120.8004
116.6484
116.5216
115.2661
64.0011
63.8898
56.8286
M 53.5166
M 53.0168
37.9843
34.6524
31.9022
31.5016
20.6164
MeO
N
F
N
O
O
N
14b
160
140
120
100
80
60
40
20
[ppm]

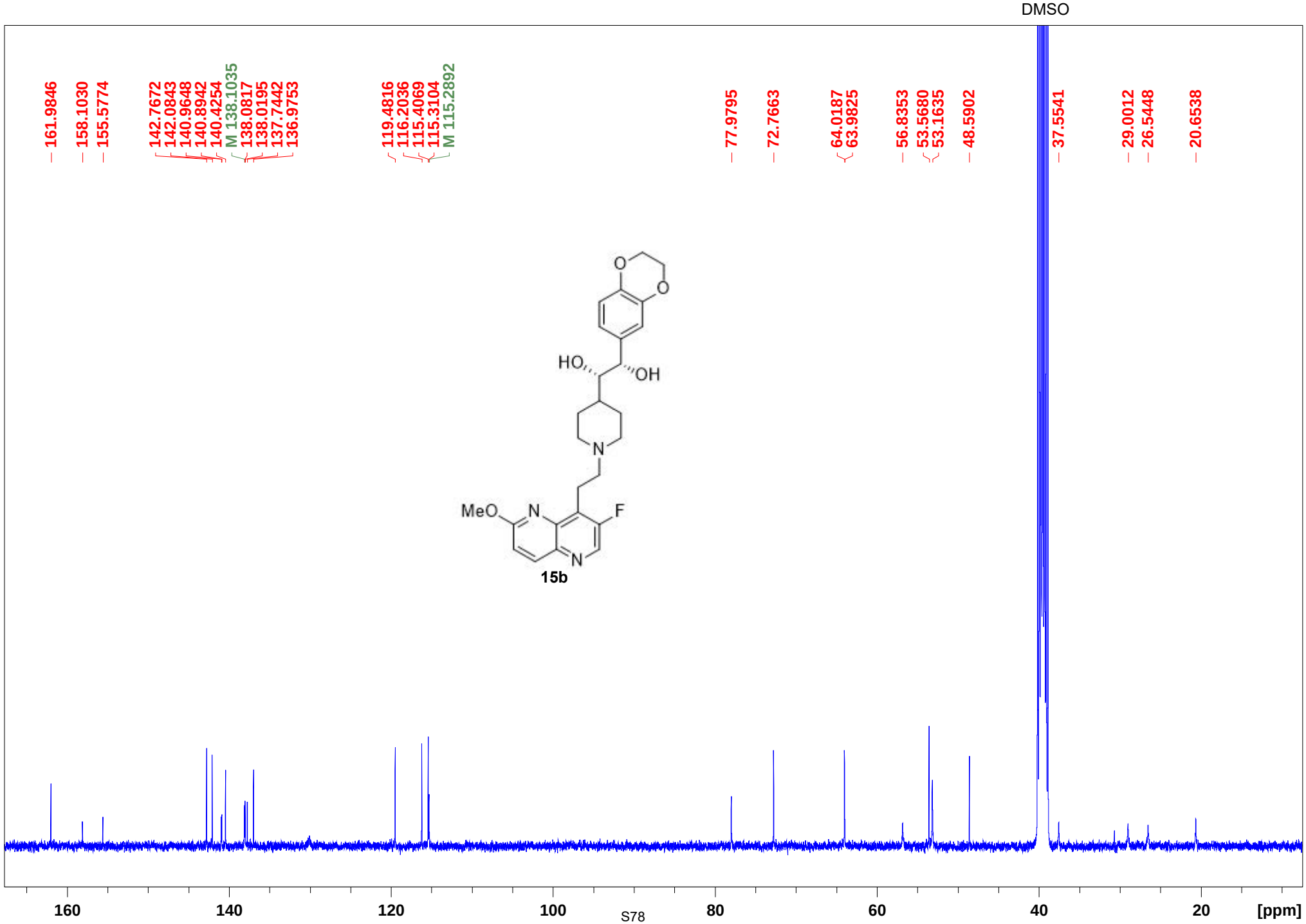

O
O
NH
N
MeO
N
F
N
14c
Chloroform
1.00
1.04
0.91
1.11
1.08
1.08
1.09
2.10
3.16
2.13
2.16
2.21
2.24
2.18
2.17
2.30
3.59
8
6
4
2
[ppm]

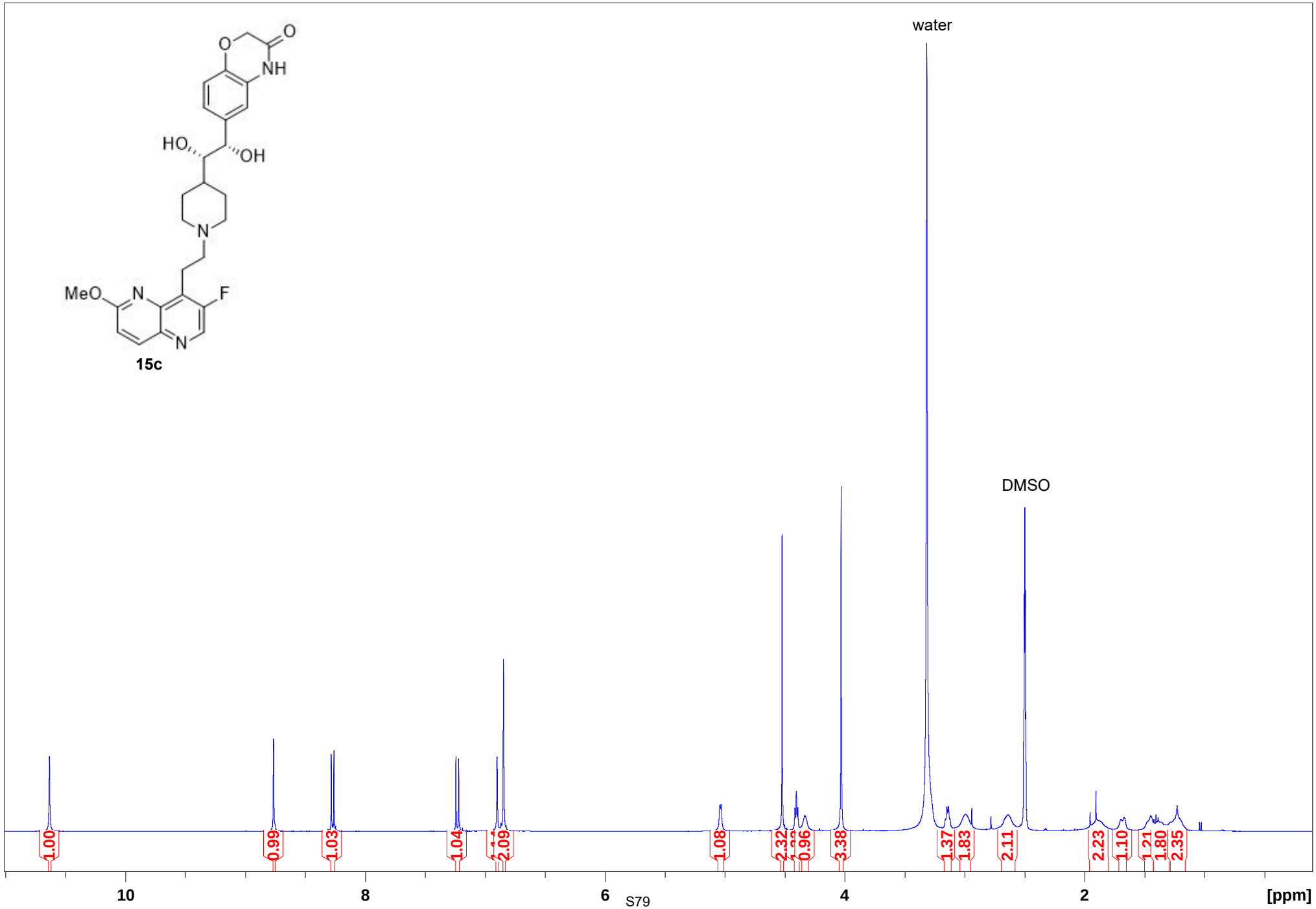

Chloroform
165.8072
162.5370
158.7016
156.1654
141.8649
141.7877
140.3039
138.6788
138.6577
138.2092
137.9296
137.7601
130.8867
130.7585
126.0165
124.0935
116.8156
115.6615
115.3348
115.3073
77.3636
67.5747
57.6438
53.9528
53.8052
38.6229
35.4761
32.5530
32.5151
21.1213
O
O
NH
N
MeO
N
F
N
14c
160
140
120
100
80
60
40
20
[ppm]

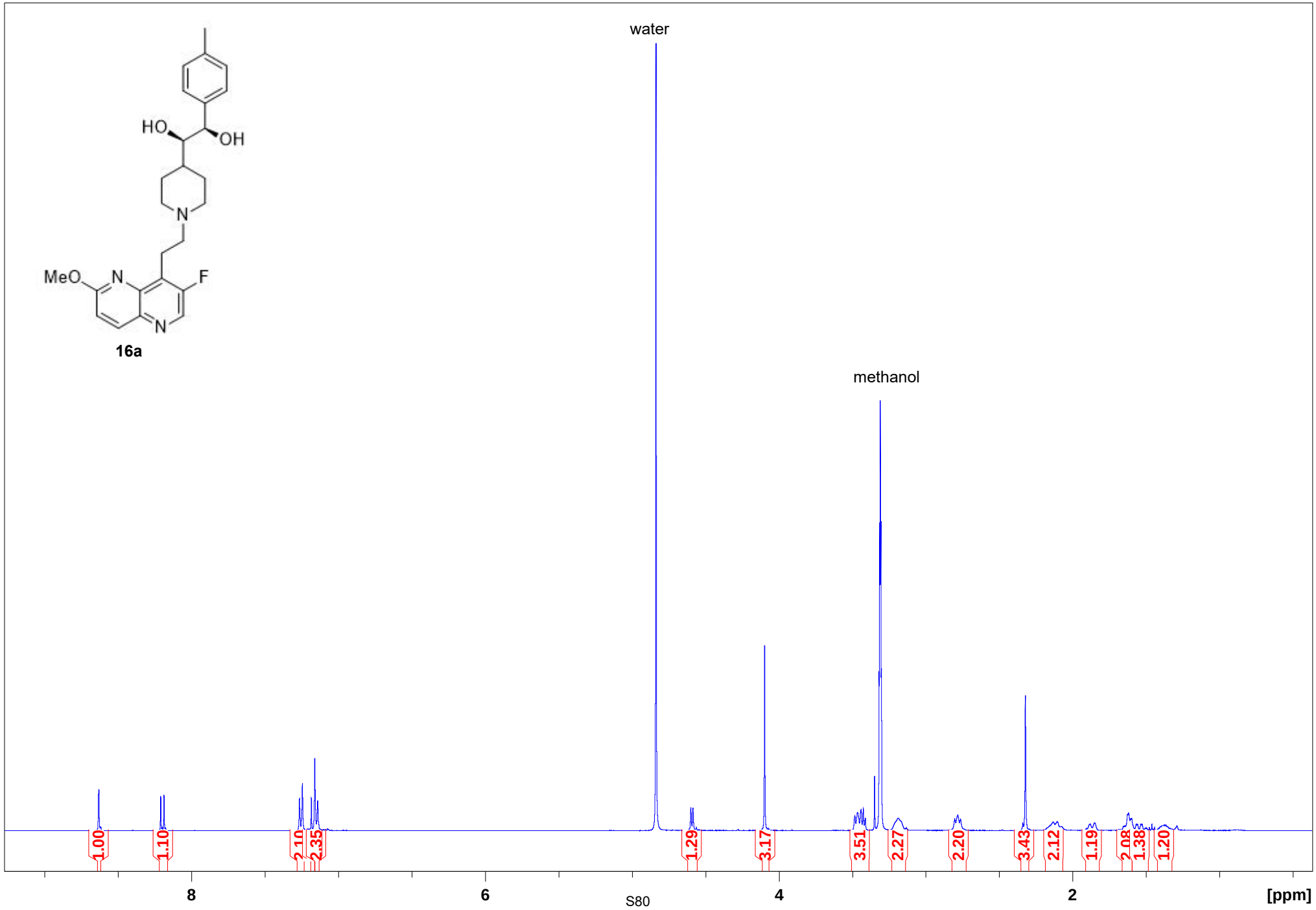

water
Methanol
HO
OH
N
MeO
N
F
N
15a
1.00
1.04
2.16
1.90
1.25
3.43
3.70
2.45
2.17
3.36
2.33
1.15
2.11
1.47
1.22
8
6
4
2
[ppm]

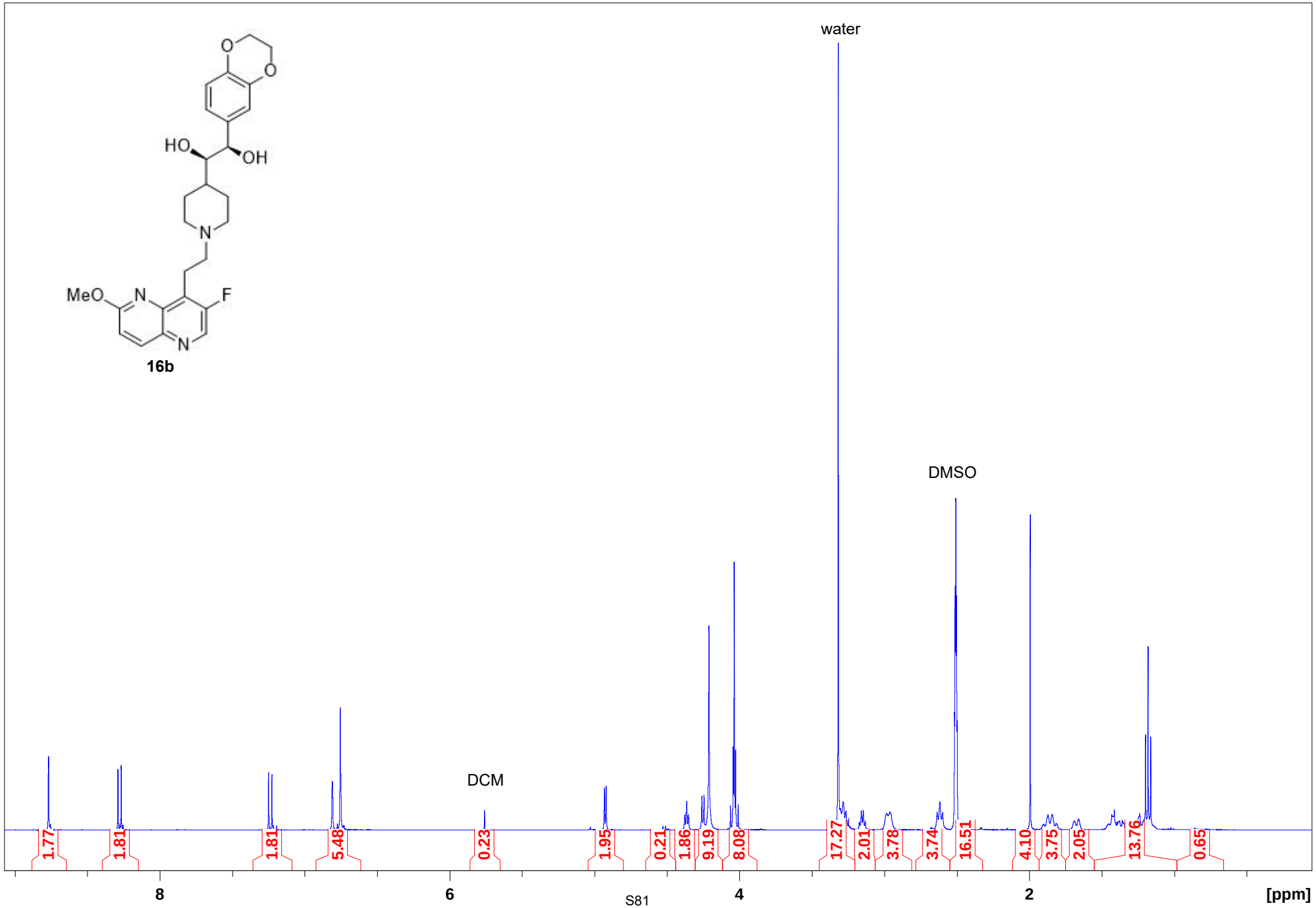

DMSO
161.9461
158.0804
155.5561
140.9498
140.8793
140.7536
140.3942
138.0749
138.0560
137.9800
137.7038
135.5880
130.2253
130.0964
128.3031
126.6458
115.2675
115.2430
78.0893
73.1964
56.8641
53.5241
53.1814
37.5676
29.0924
26.4878
20.7355
20.6886
20.6656
HO
OH
N
MeO
N
F
N
15a
ethyl acetate
ethyl acetate
ethyl acetate
160
140
120
100
80
60
40
20
[ppm]

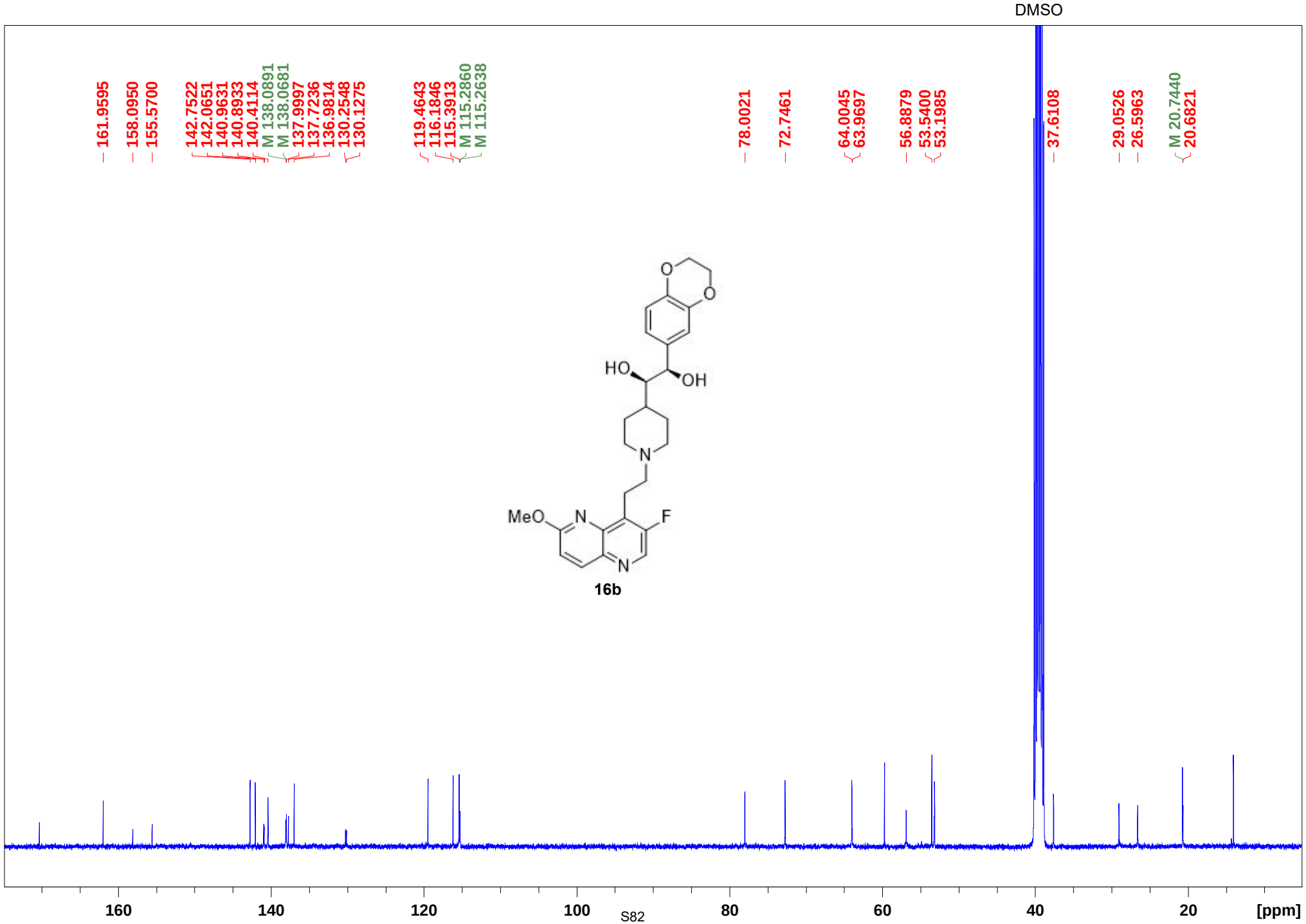

water
DMSO
HO
OH
O
O
N
MeO
N
F
N
15b
1.00
1.03
1.05
1.91
1.07
1.17
4.06
3.06
2.53
1.17
1.96
2.04
1.91
1.00
2.28
2.13
8
6
4
2
[ppm]

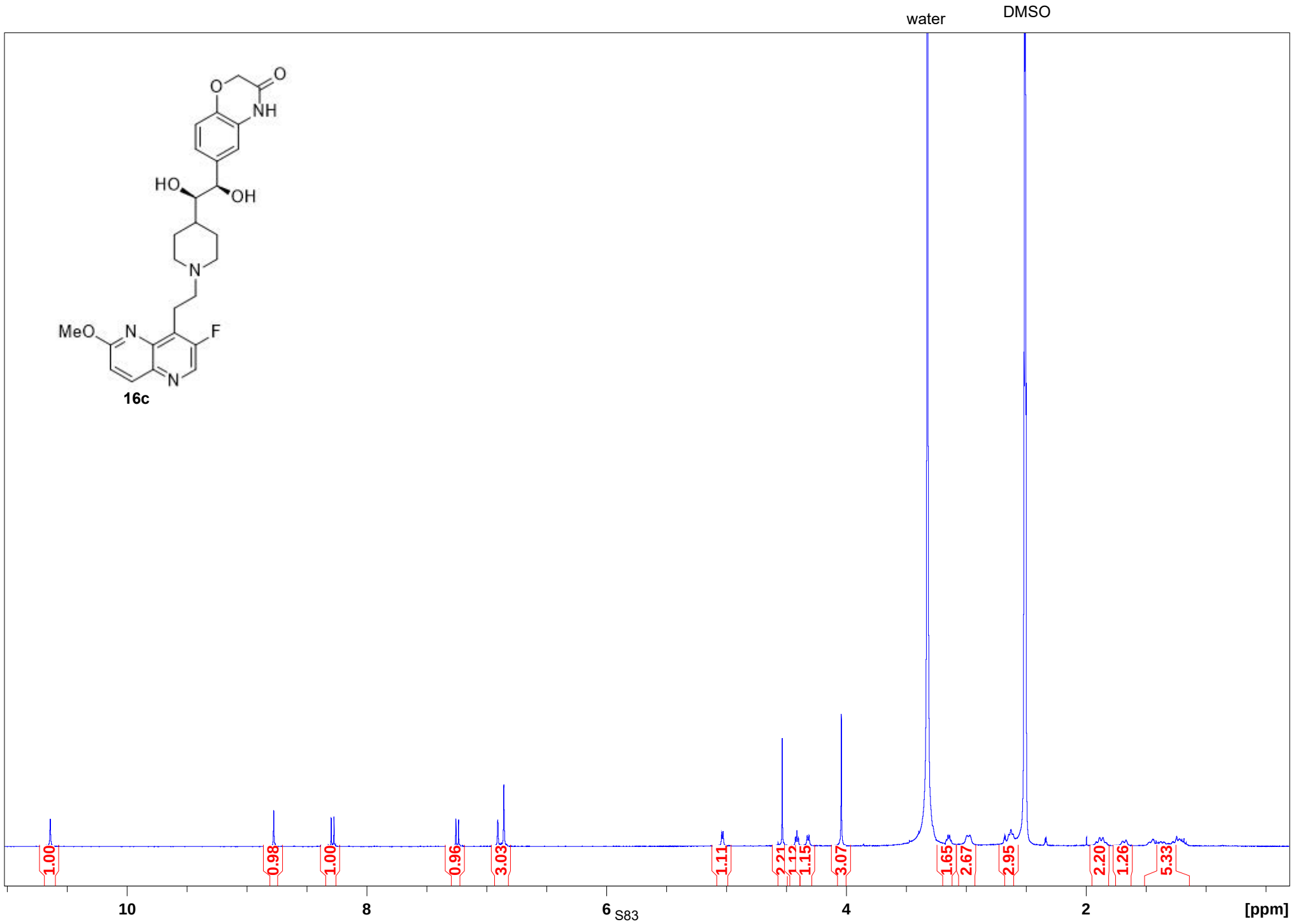

DMSO
161.9846
158.1030
155.5774
142.7672
142.0843
140.9648
140.8942
140.4254
M 138.1035
138.0817
138.0195
137.7442
136.9753
119.4816
116.2036
115.4069
115.3104
M 115.2892
77.9795
72.7663
64.0187
63.9825
56.8353
53.5680
53.1635
48.5902
37.5541
29.0012
26.5448
20.6538
HO
OH
O
O
N
MeO
N
F
N
15b
160
140
120
100
80
60
40
20
[ppm]

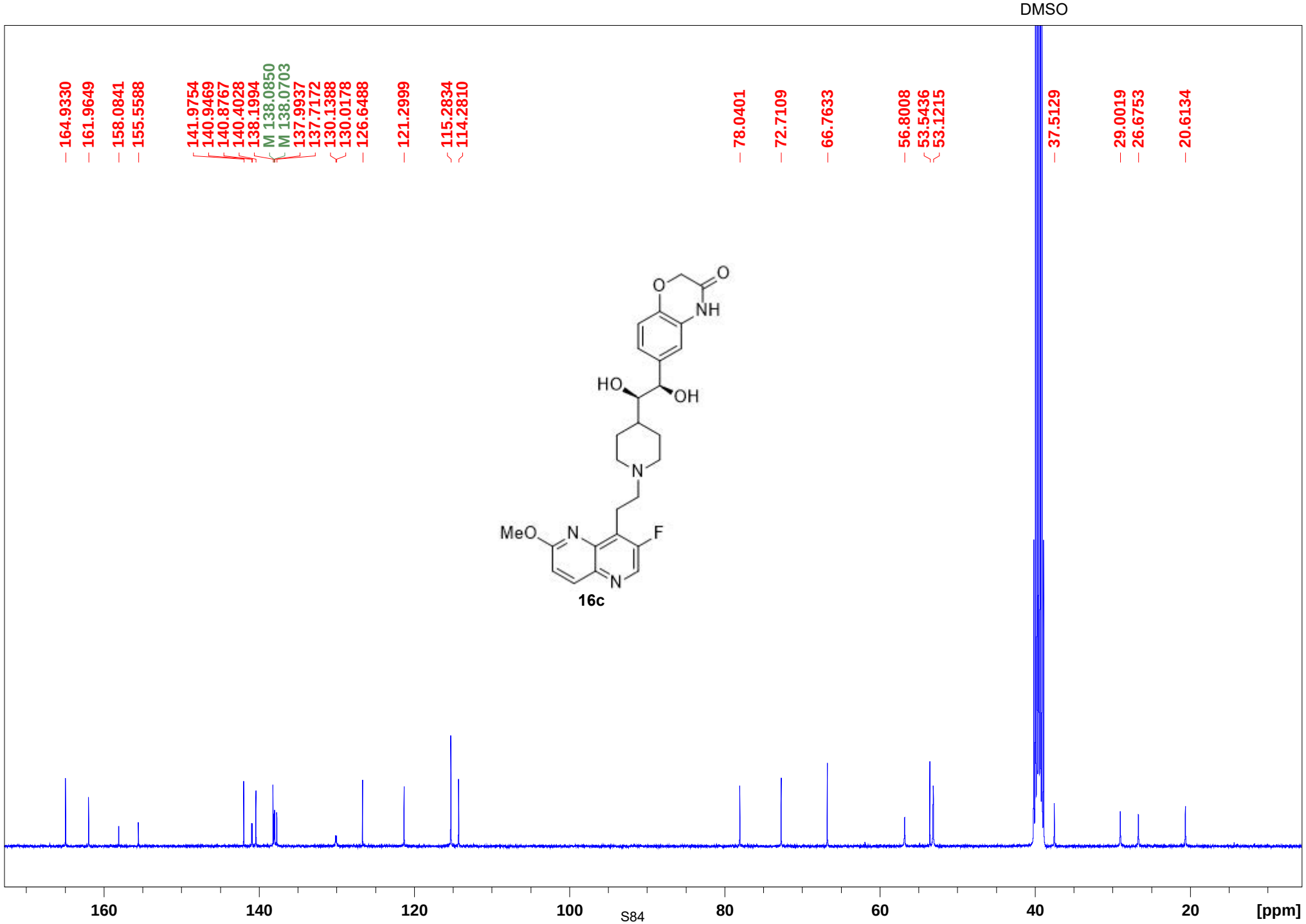

water
DMSO
MeO
N
F
HO
OH
O
NH
15c
1.00
0.99
1.03
1.04
2.09
1.08
2.32
0.96
3.38
1.37
1.83
2.11
2.23
1.10
1.21
1.80
2.35
10
8
6
4
2
[ppm]

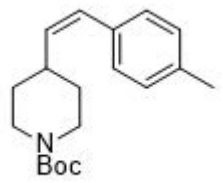

water
methanol
HO
OH
N
MeO
N
F
N
16a
1.00
1.10
2.10
2.35
1.29
3.17
3.51
2.27
2.20
3.43
2.12
1.19
2.08
1.38
1.20
8
6
4
2
[ppm]


water
DMSO
DCM
HO
OH
O
O
N
MeO
N
F
N
16b
1.77
1.81
1.81
5.48
0.23
1.95
0.21
1.86
9.19
8.08
17.27
2.01
3.78
3.74
16.51
4.10
3.75
2.05
13.76
0.65
8
6
4
2
[ppm]


DMSO
161.9595
158.0950
155.5700
142.7522
142.0651
140.9631
140.8933
140.4114
M 138.0891
M 138.0681
137.9997
137.7236
136.9814
130.2548
130.1275
119.4643
116.1846
115.3913
M 115.2860
M 115.2638
78.0021
72.7461
64.0045
63.9697
56.8879
53.5400
53.1985
37.6108
29.0526
26.5963
M 20.7440
20.6821
HO
OH
O
O
N
MeO
N
F
N
16b
160
140
120
100
80
60
40
20
[ppm]


water
DMSO
O
O
NH
HO
OH
N
MeO
N
F
N
16c
1.00
0.98
1.00
0.96
3.03
1.11
2.21
1.12
1.15
3.07
1.65
2.67
2.95
2.20
1.26
5.33
10
8
6
4
2
[ppm]


DMSO
164.9330
161.9649
158.0841
155.5588
141.9754
140.9469
140.8767
140.4028
138.1994
M 138.0850
M 138.0703
137.9937
137.7172
130.1388
130.0178
126.6488
121.2999
115.2834
114.2810
78.0401
72.7109
66.7633
56.8008
53.5436
53.1215
37.5129
29.0019
26.6753
20.6134
O
O
NH
HO
OH
N
MeO
N
F
N
16c
160
140
120
100
80
60
40
20
[ppm]

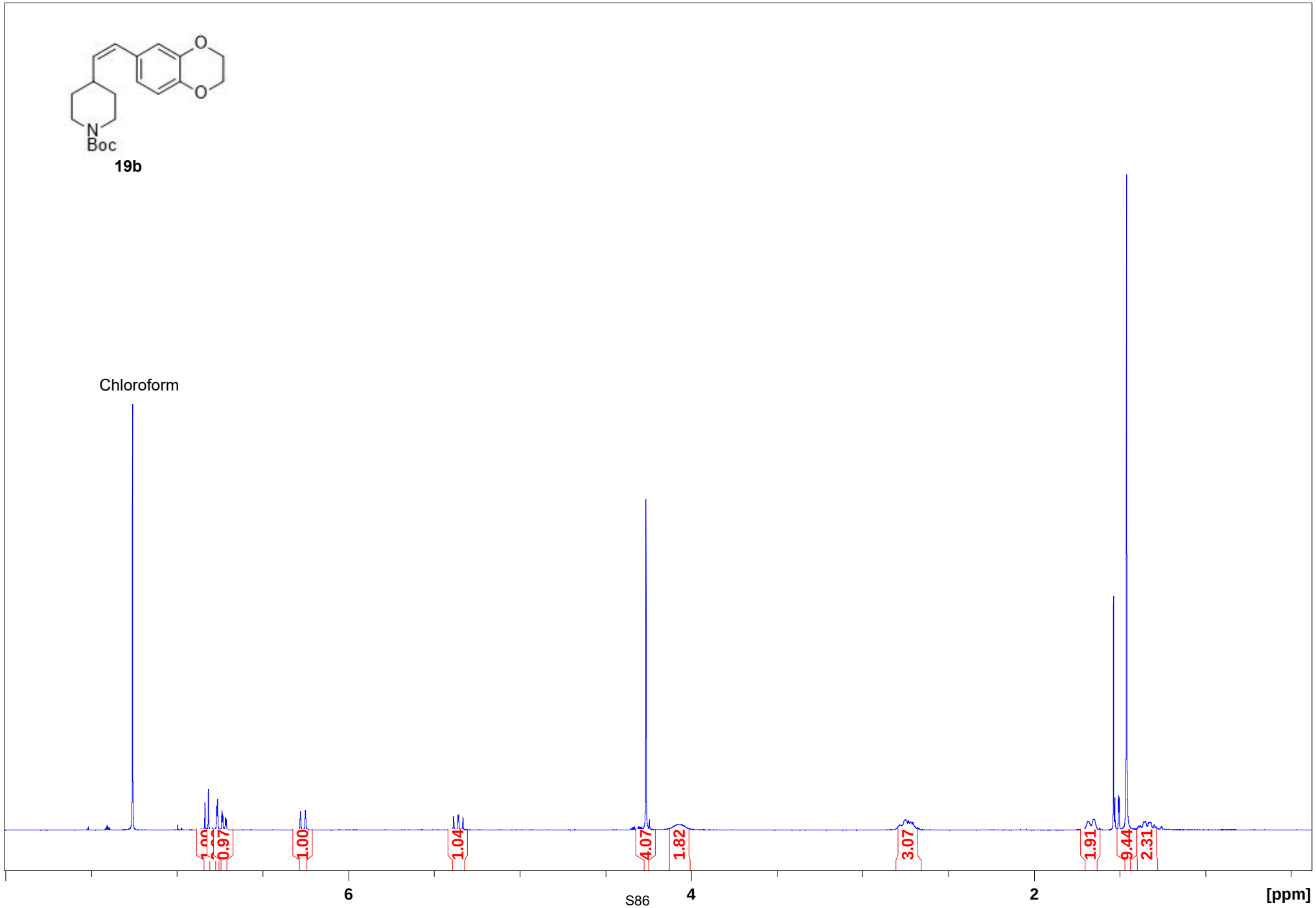


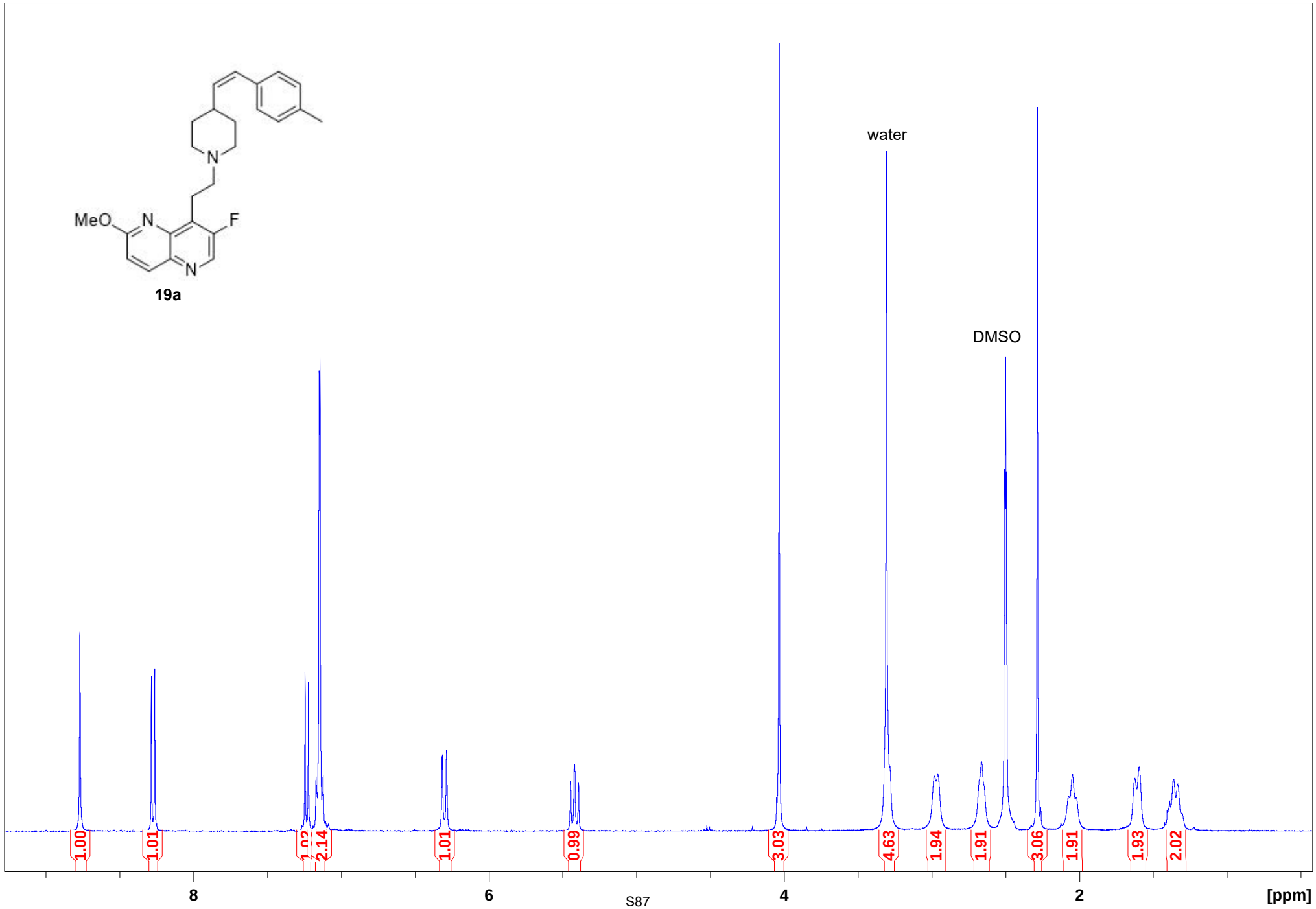

**19a**

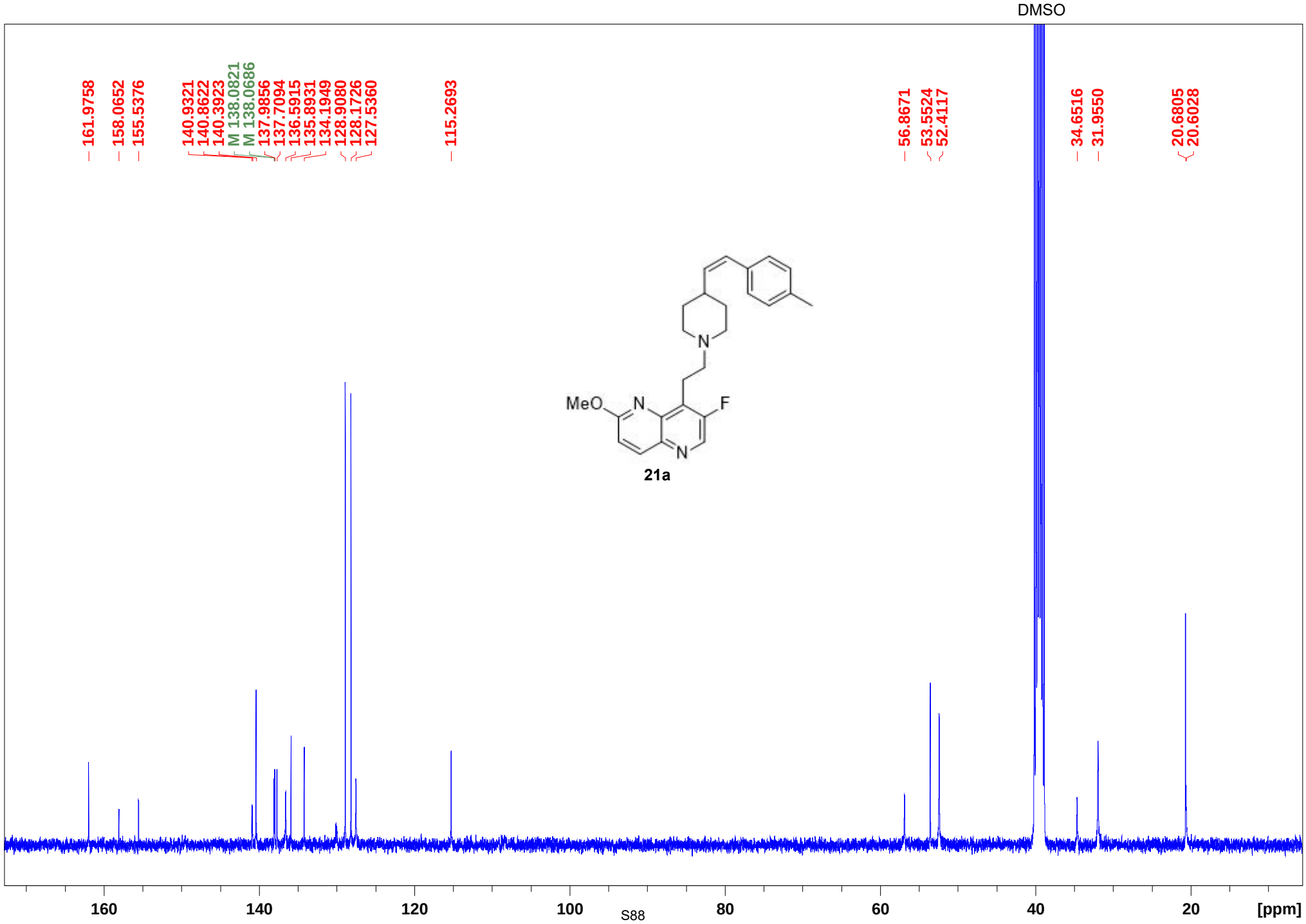
Chloroform

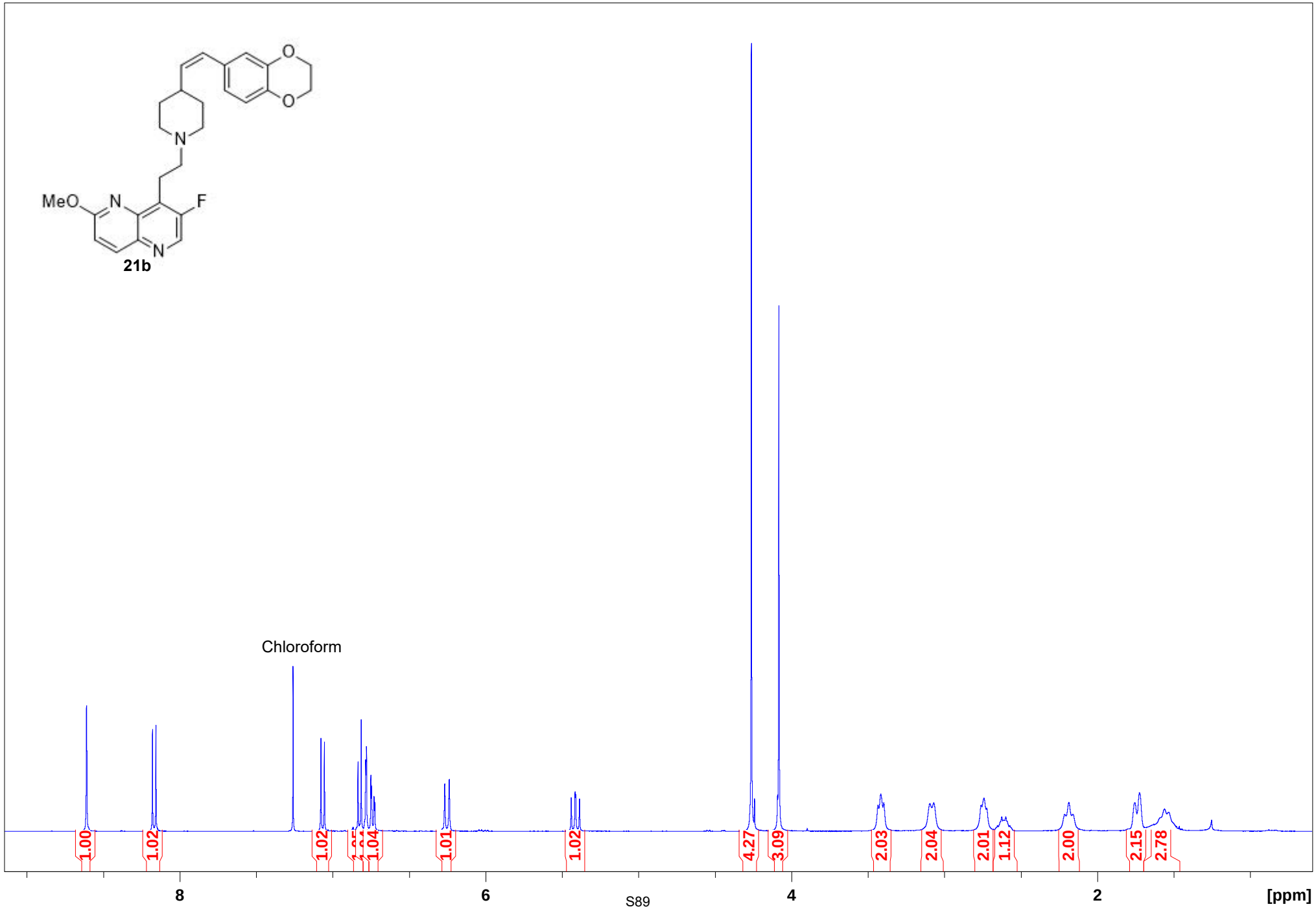
4.00 0.96 1.00 2.04 3.15 2.96 2.08 9.99 2.32

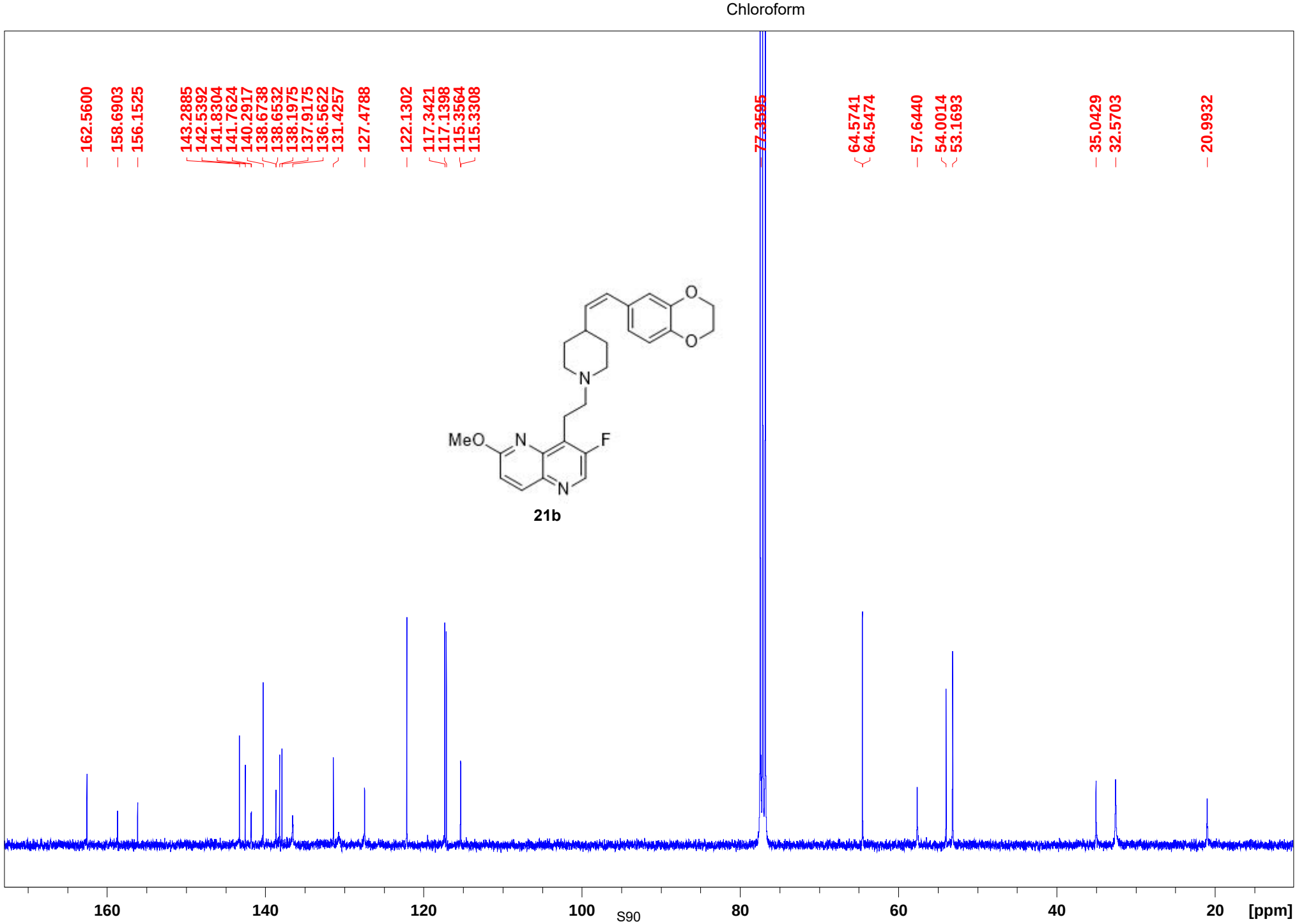
7 6 5 4 3 2 1 [ppm]

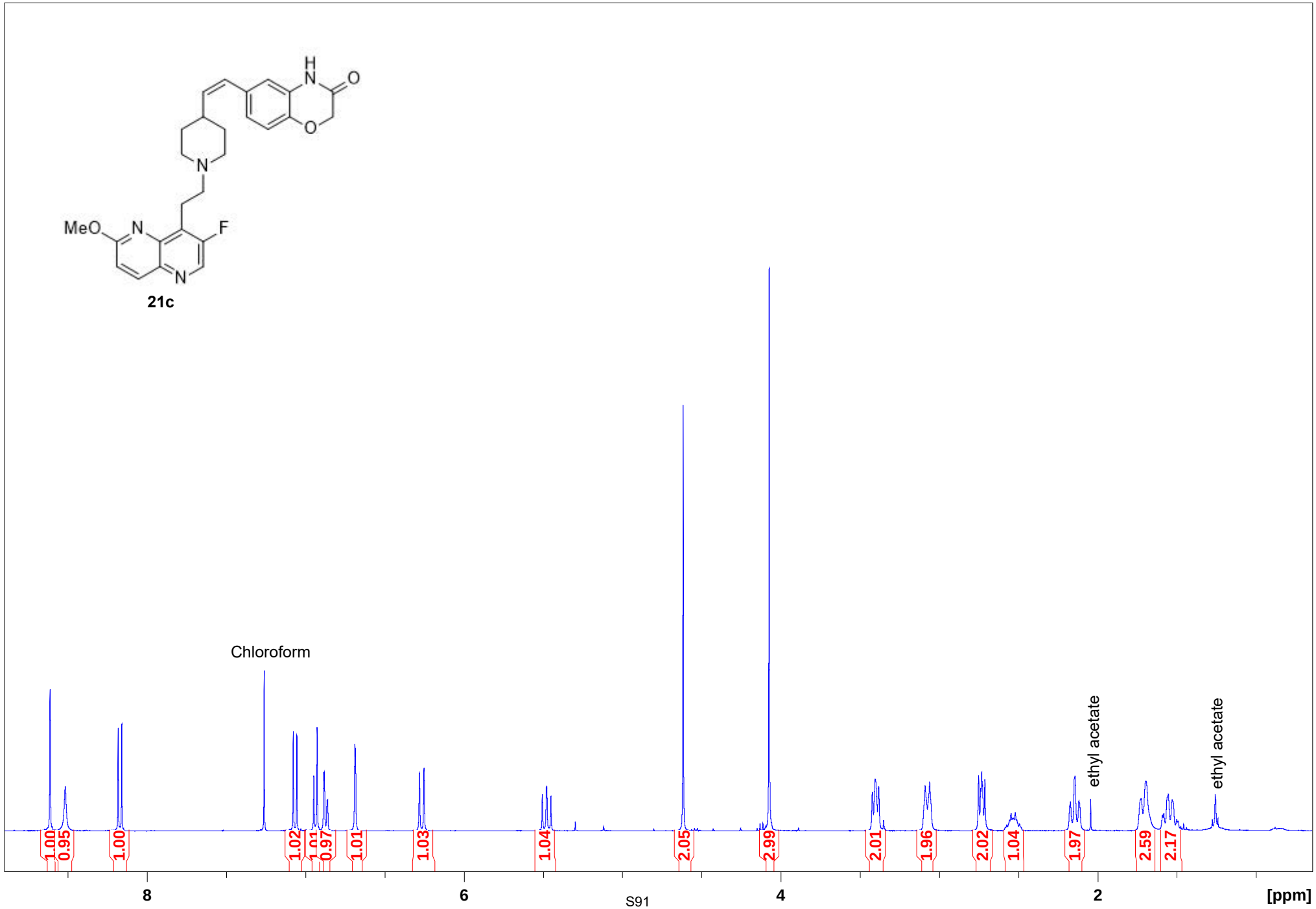

O
O
N
Boc
19b
Chloroform
1.00
1.22
0.97
1.00
1.04
4.07
1.82
3.07
1.91
9.44
2.31
6
4
2
[ppm]

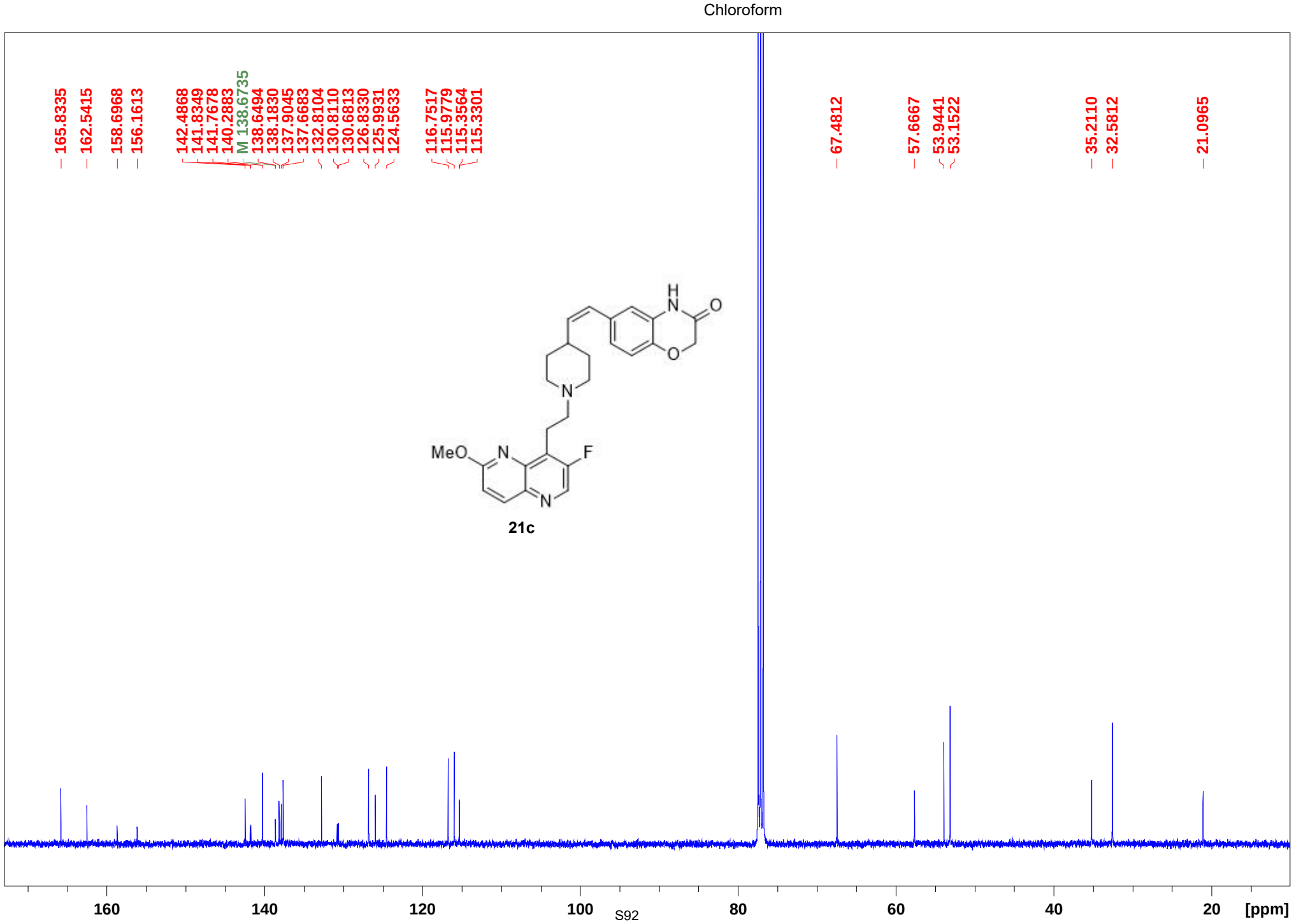

MeO
N
F
N
N
19a
water
DMSO
1.00
1.01
1.02
2.14
1.01
0.99
3.03
4.63
1.94
1.91
3.06
1.91
1.93
2.02
8
6
4
2
[ppm]


DMSO
161.9758
158.0652
155.5376
140.9321
140.8622
140.3923
M 138.0821
M 138.0686
137.9856
137.7094
136.5915
135.8931
134.1949
128.9080
128.1726
127.5360
115.2693
56.8671
53.5524
52.4117
34.6516
31.9550
20.6805
20.6028
MeO
N
F
N
N
21a
160
140
120
100
80
60
40
20
[ppm]


MeO
N
F
N
O
O
N
21b
Chloroform
1.00
1.02
1.02
1.01
1.02
4.27
3.09
2.03
2.04
2.01
1.12
2.00
2.15
2.78
8
6
4
2
[ppm]


Chloroform
162.5600
158.6903
156.1525
143.2885
142.5392
141.8304
141.7624
140.2917
138.6738
138.6532
138.1975
137.9175
136.5622
131.4257
127.4788
122.1302
117.3421
117.1398
115.3564
115.3308
77.3595
64.5741
64.5474
57.6440
54.0014
53.1693
35.0429
32.5703
20.9932
MeO
N
F
O
O
N
N
21b
160
140
120
100
80
60
40
20
[ppm]


MeO
N
F
N
H
N
O
O
N
21c
Chloroform
ethyl acetate
ethyl acetate
1.00
0.95
1.00
1.02
1.01
0.97
1.01
1.03
1.04
2.05
2.99
2.01
1.96
2.02
1.04
1.97
2.59
2.17
8
6
4
2
[ppm]


Chloroform
165.8335
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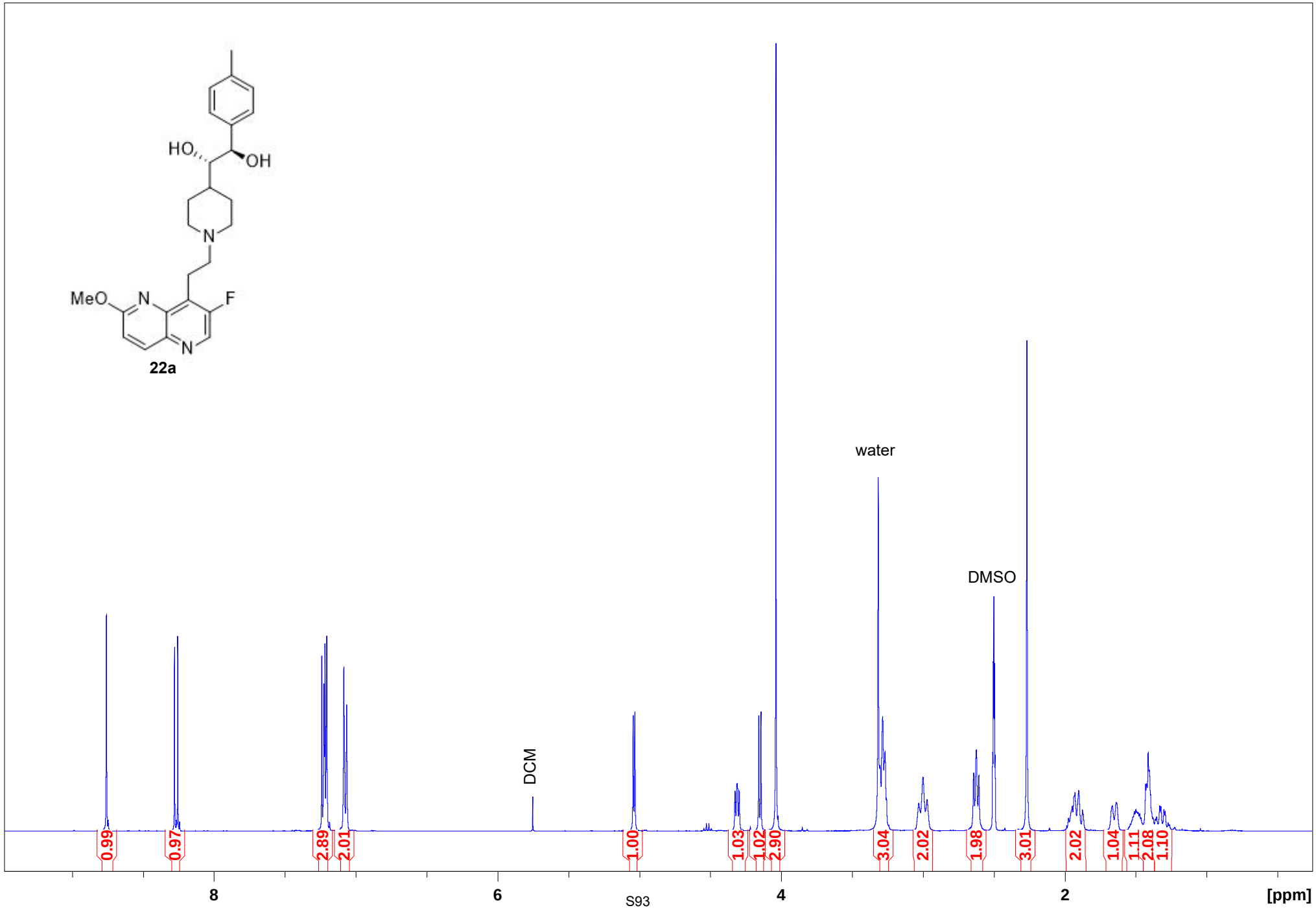
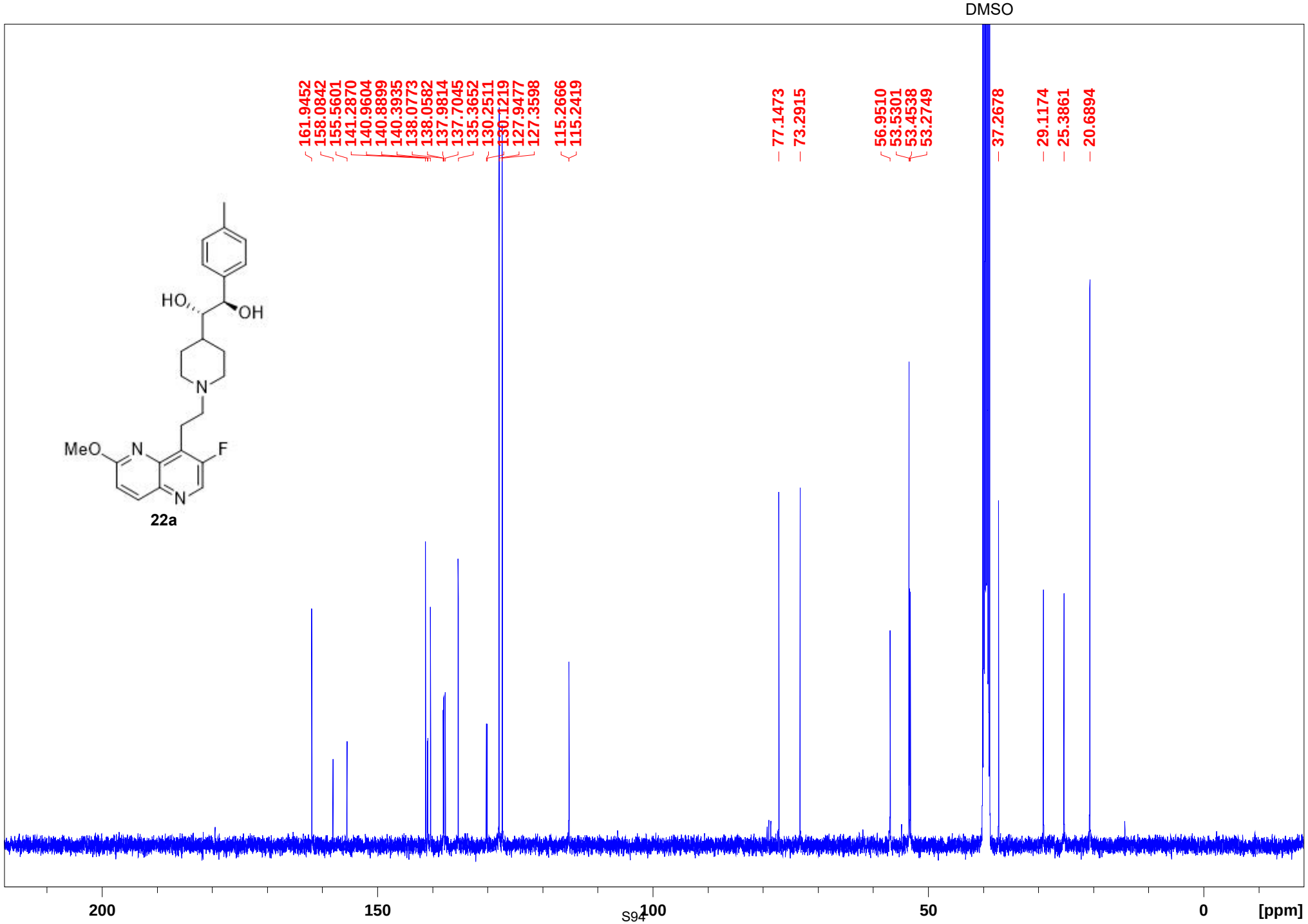
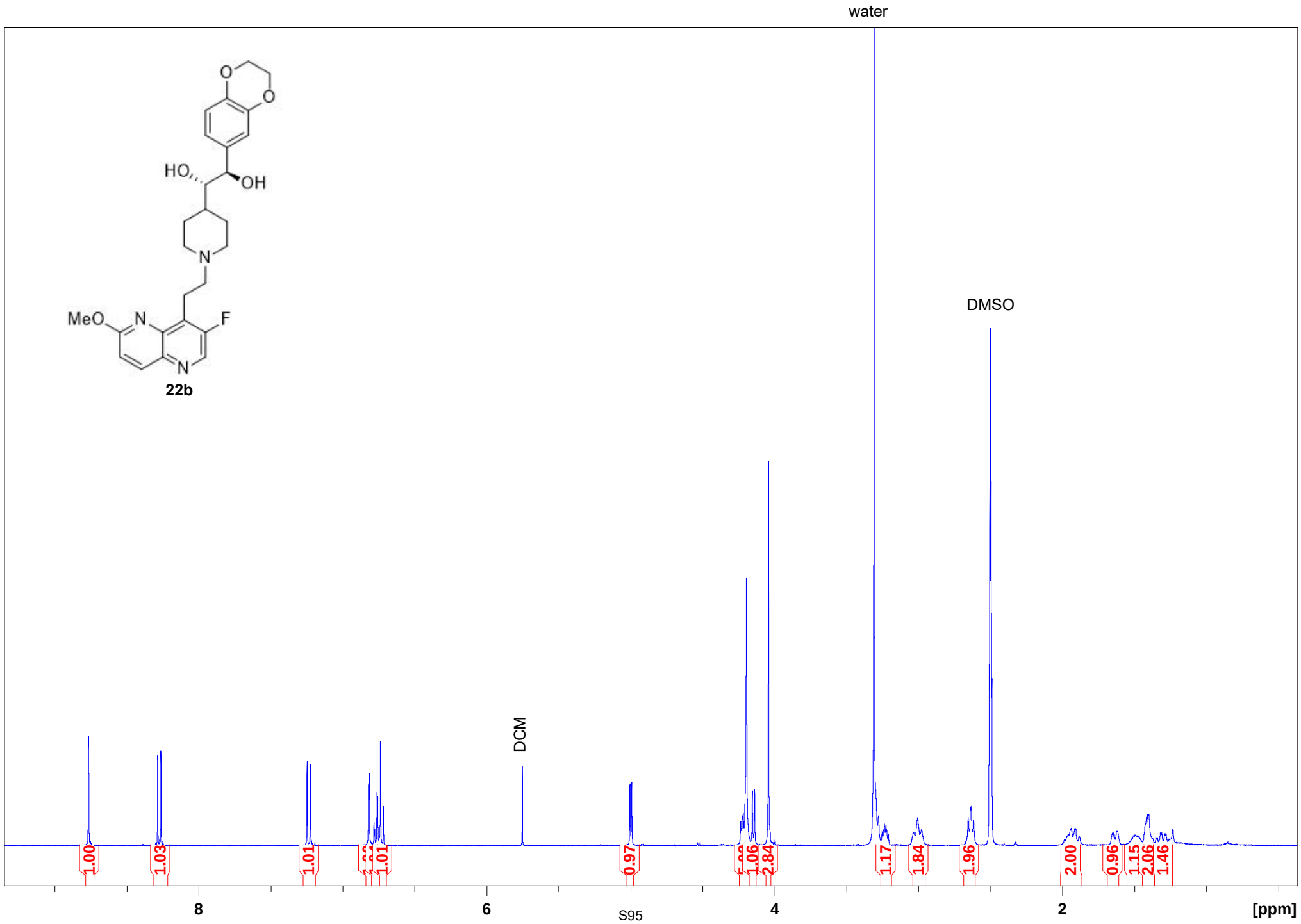
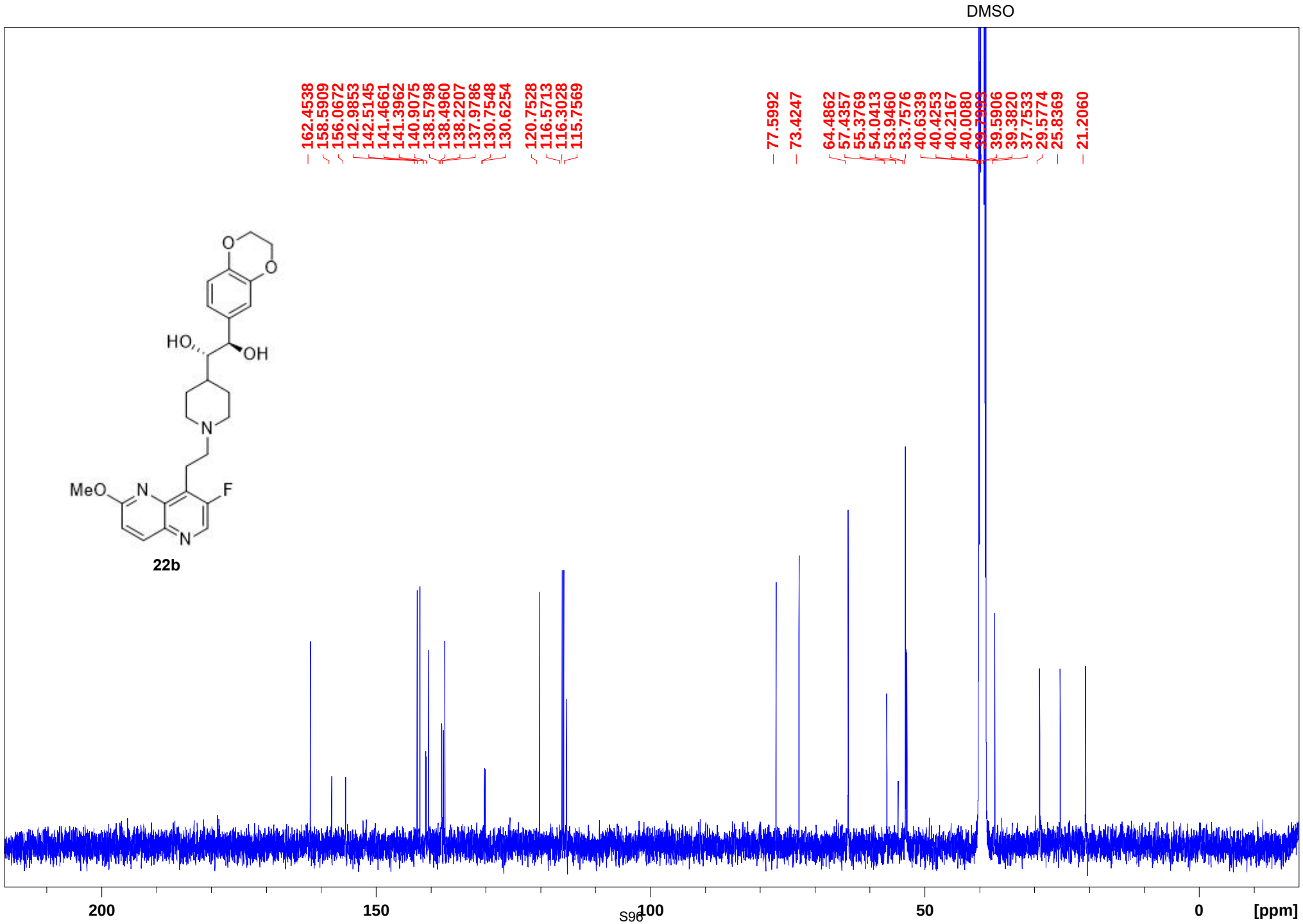
158.6968
156.1613
142.4868
141.8349
141.7678
140.2883
M 138.6735
138.6494
138.1830
137.9045
137.6683
132.8104
130.8110
130.6813
126.8330
125.9931
124.5633
116.7517
115.9779
115.3564
115.3301
67.4812
57.6667
53.9441
53.1522
35.2110
32.5812
21.0965
MeO
N
F
H
N
O
O
N
N
160
140
120
100
80
60
40
20
[ppm]

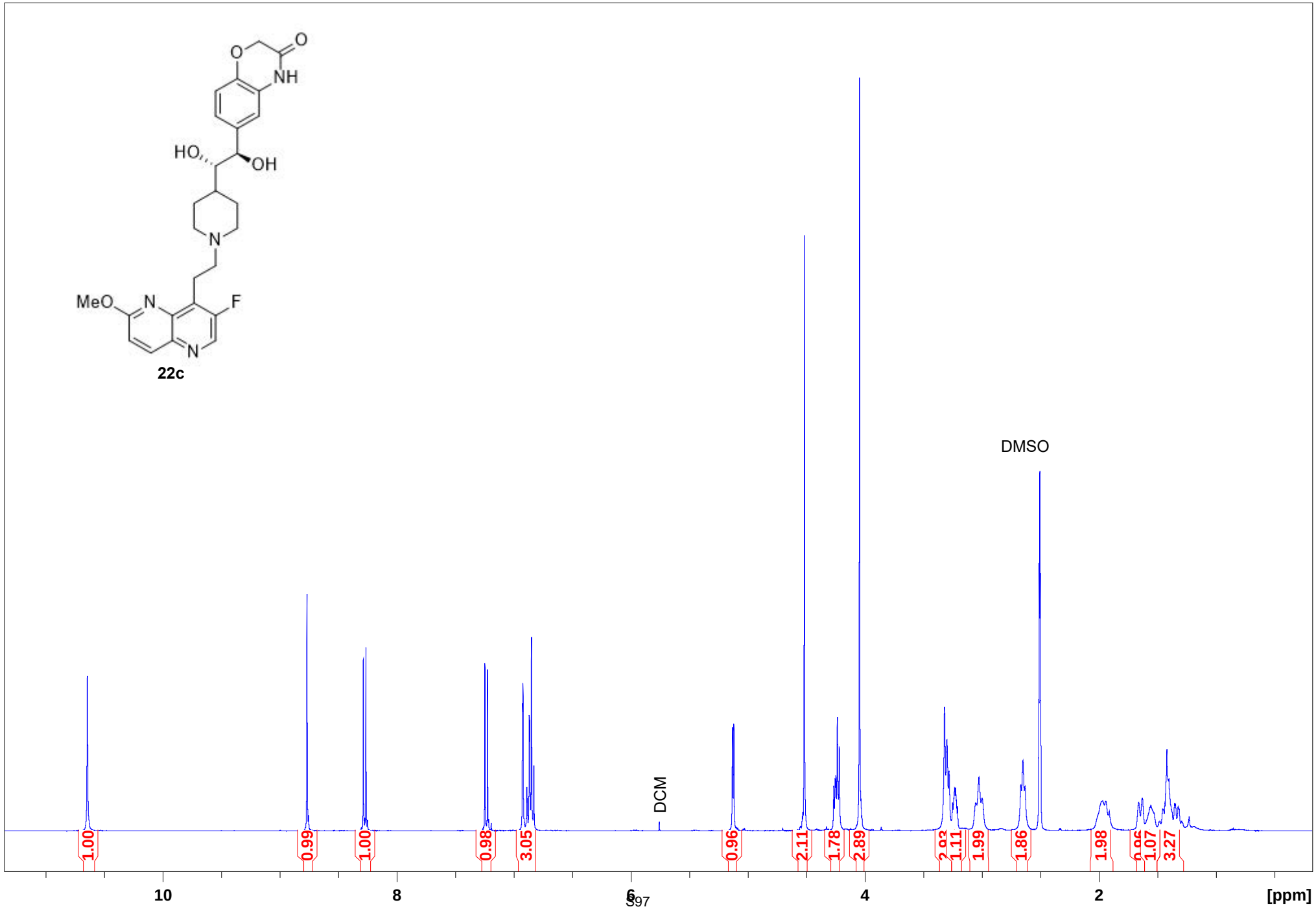
**21c**

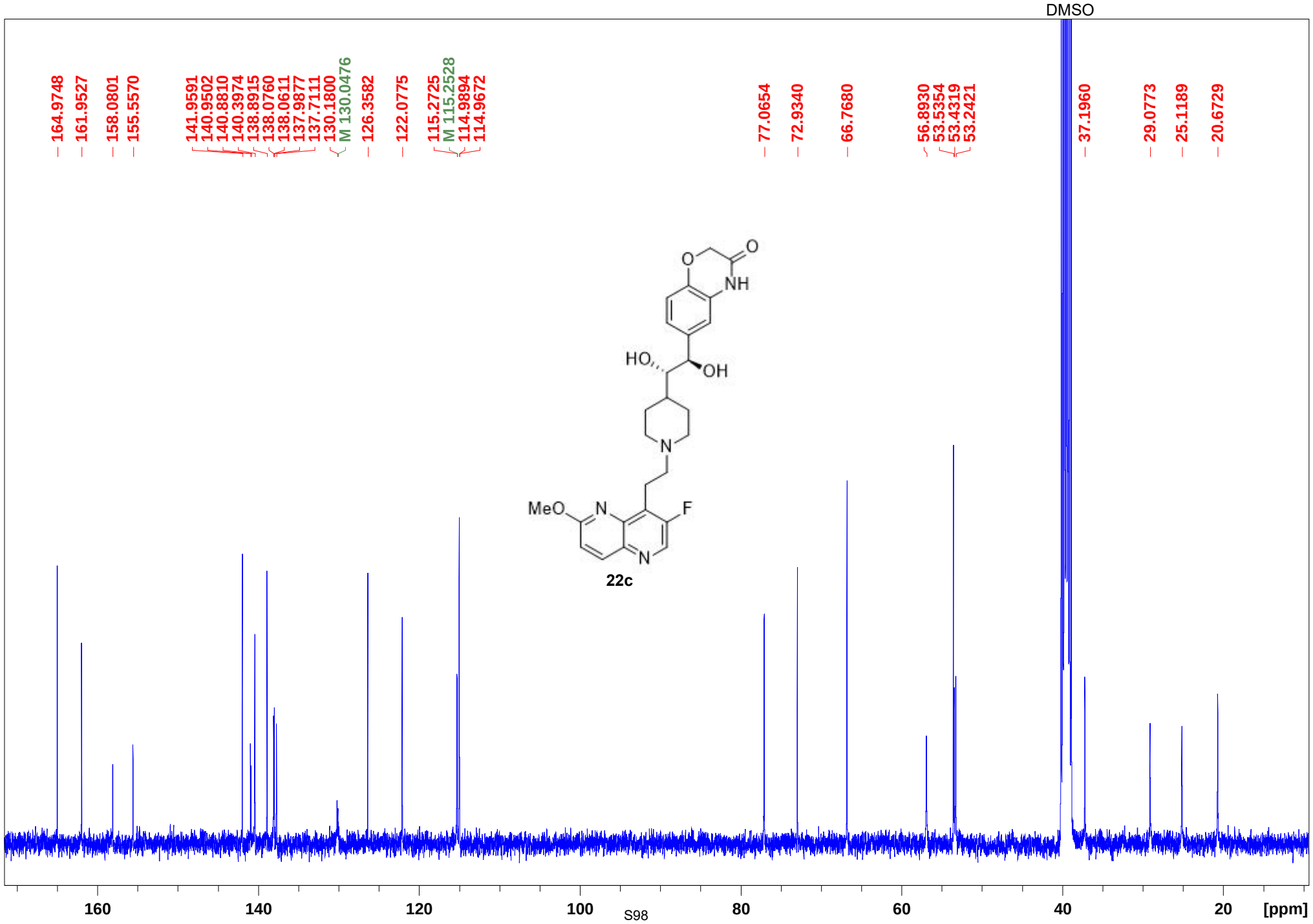

HO
OH
N
MeO
N
F
N
22a
water
DMSO
DCM
0.99
0.97
2.89
2.01
1.00
1.03
1.02
2.90
3.04
2.02
1.98
3.01
2.02
1.04
1.11
2.08
1.10
8
6
4
2
[ppm]

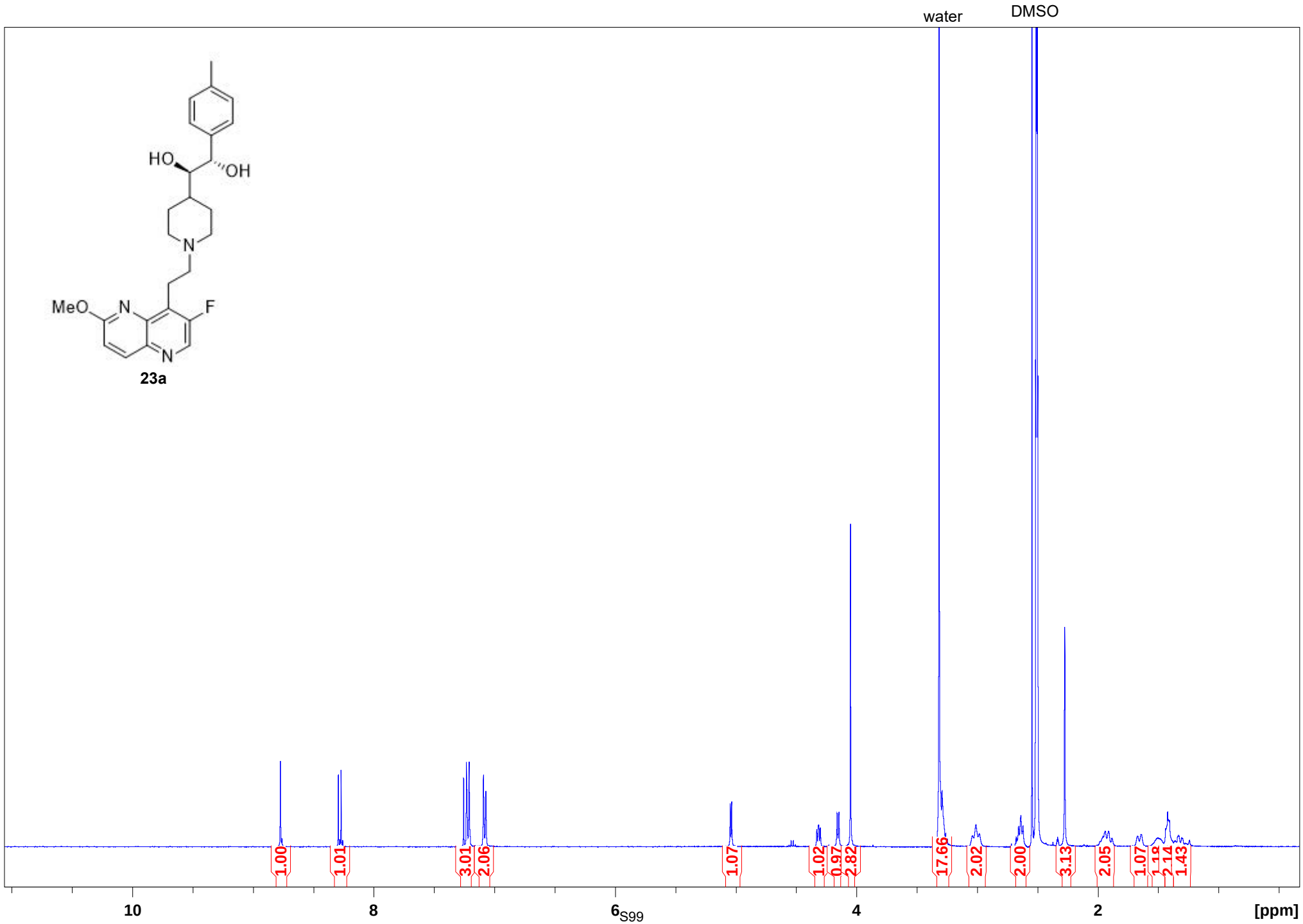

DMSO
161.9452
158.0842
155.5601
141.2870
140.9604
140.8899
140.3935
138.0773
138.0582
137.9814
137.7045
135.3652
130.2511
130.1219
127.9477
127.3598
115.2666
115.2419
77.1473
73.2915
56.9510
53.5301
53.4538
53.2749
37.2678
29.1174
25.3861
20.6894
HO
OH
N
MeO
N
F
N
22a
200
150
100
50
0
[ppm]

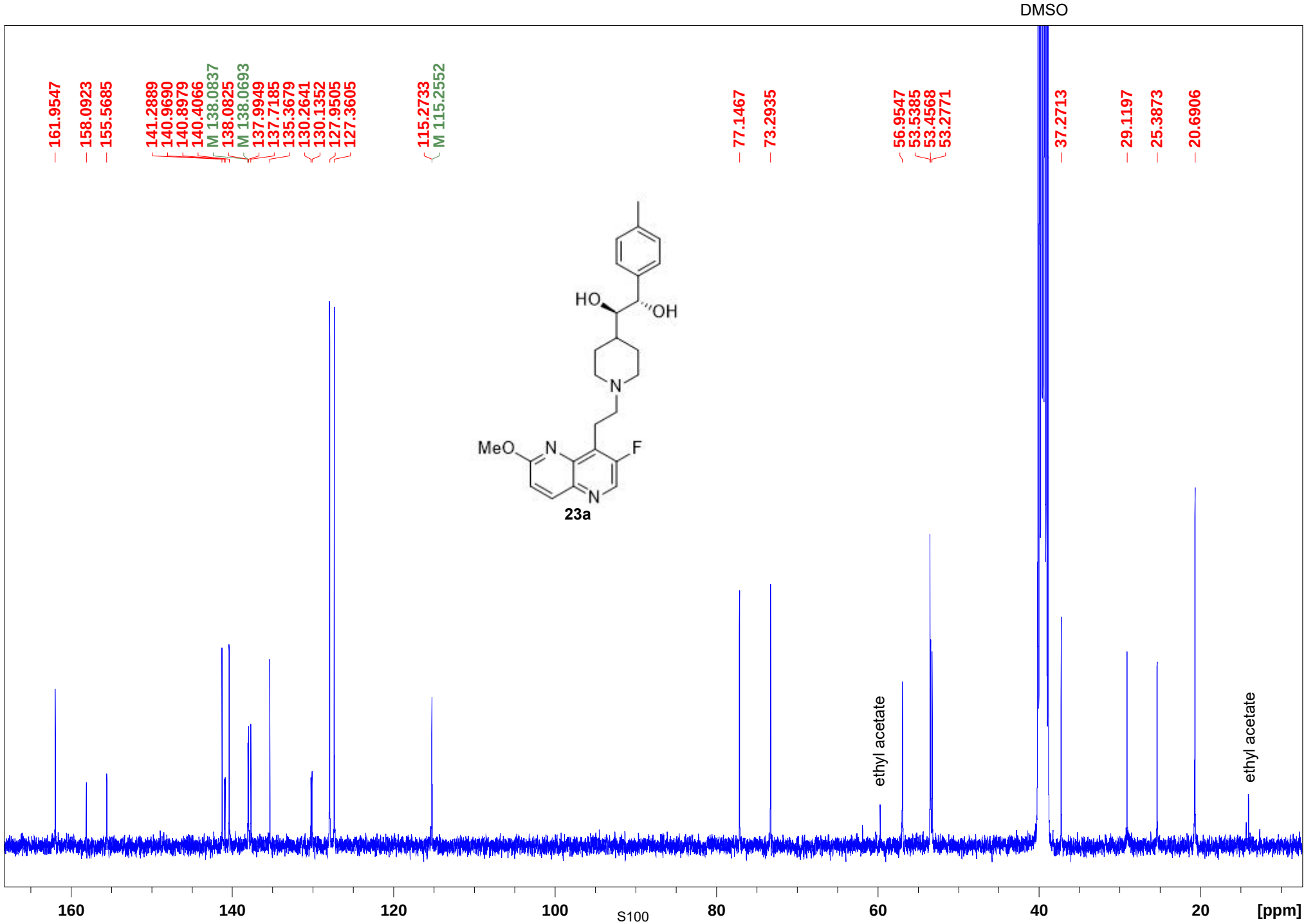

water
DMSO
DCM
HO
OH
N
MeO
N
F
N
O
O
22b
1.00
1.03
1.01
1.01
0.97
1.06
2.84
1.17
1.84
1.96
2.00
0.96
1.15
2.06
1.46
8
6
4
2
[ppm]

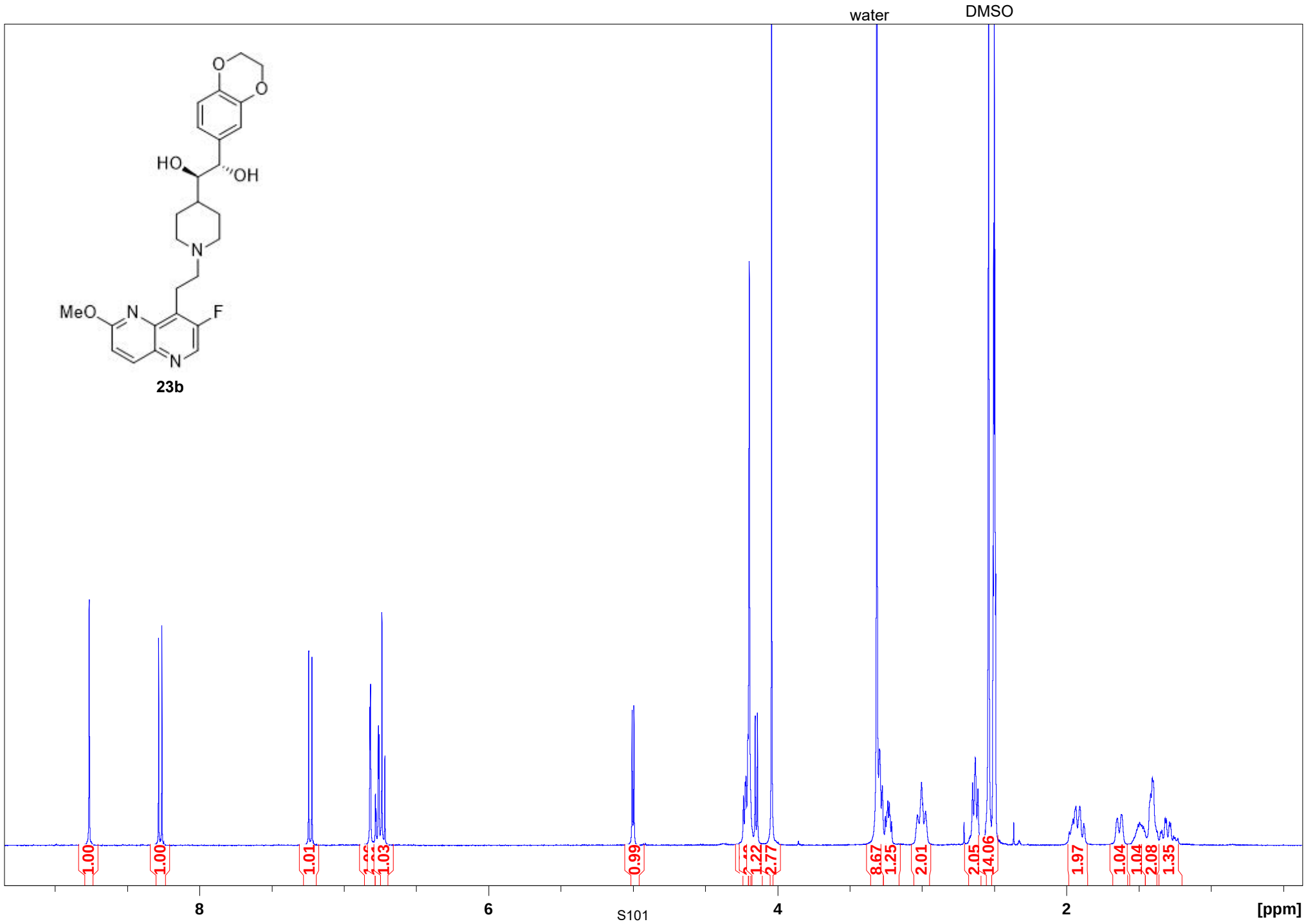

DMSO
162.4538
158.5909
156.0672
142.9853
142.5145
141.4661
141.3962
140.9075
138.5798
138.4960
138.2207
137.9786
130.7548
130.6254
120.7528
116.5713
116.3028
115.7569
77.5992
73.4247
64.4862
57.4357
55.3769
54.0413
53.9460
53.7576
40.6339
40.4253
40.2167
40.0080
39.7993
39.5906
39.3820
37.7533
29.5774
25.8369
21.2060
HO
OH
O
O
N
MeO
N
F
N
22b
200
150
100
50
0
[ppm]

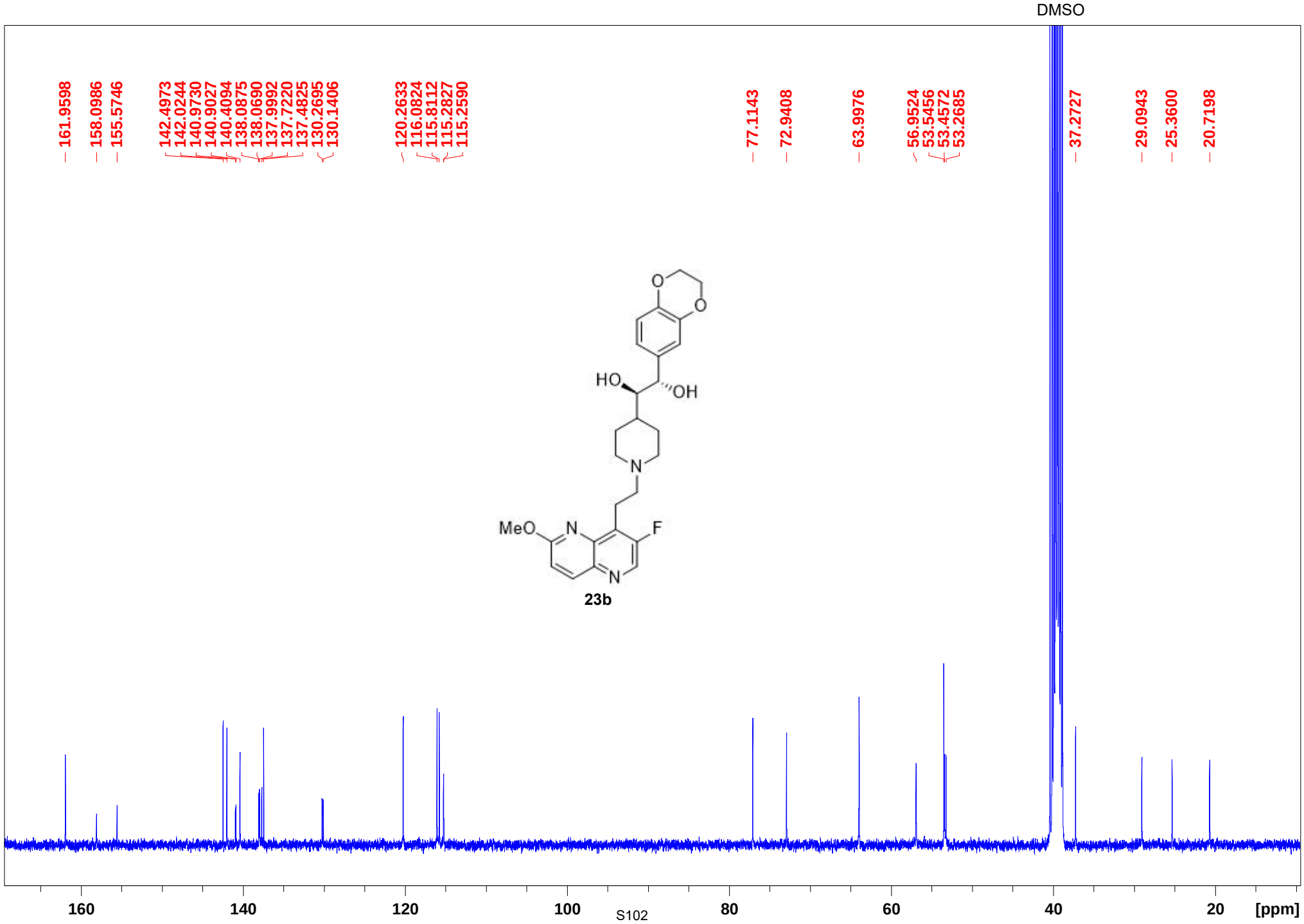

O
O
NH
HO
OH
N
MeO
N
F
N
22c
DMSO
DCM
1.00
0.99
1.00
0.98
3.05
0.96
2.11
1.78
2.89
2.02
1.11
1.99
1.86
1.98
1.07
3.27
10
8
6
4
2
[ppm]


DMSO
164.9748
161.9527
158.0801
155.5570
141.9591
140.9502
140.8810
140.3974
138.8915
138.0760
138.0611
137.9877
137.7111
130.1800
M 130.0476
126.3582
122.0775
115.2725
M 115.2528
114.9894
114.9672
77.0654
72.9340
66.7680
56.8930
53.5354
53.4319
53.2421
37.1960
29.0773
25.1189
20.6729
O
O
NH
HO
OH
N
MeO
N
F
N
22c
160
140
120
100
80
60
40
20
[ppm]

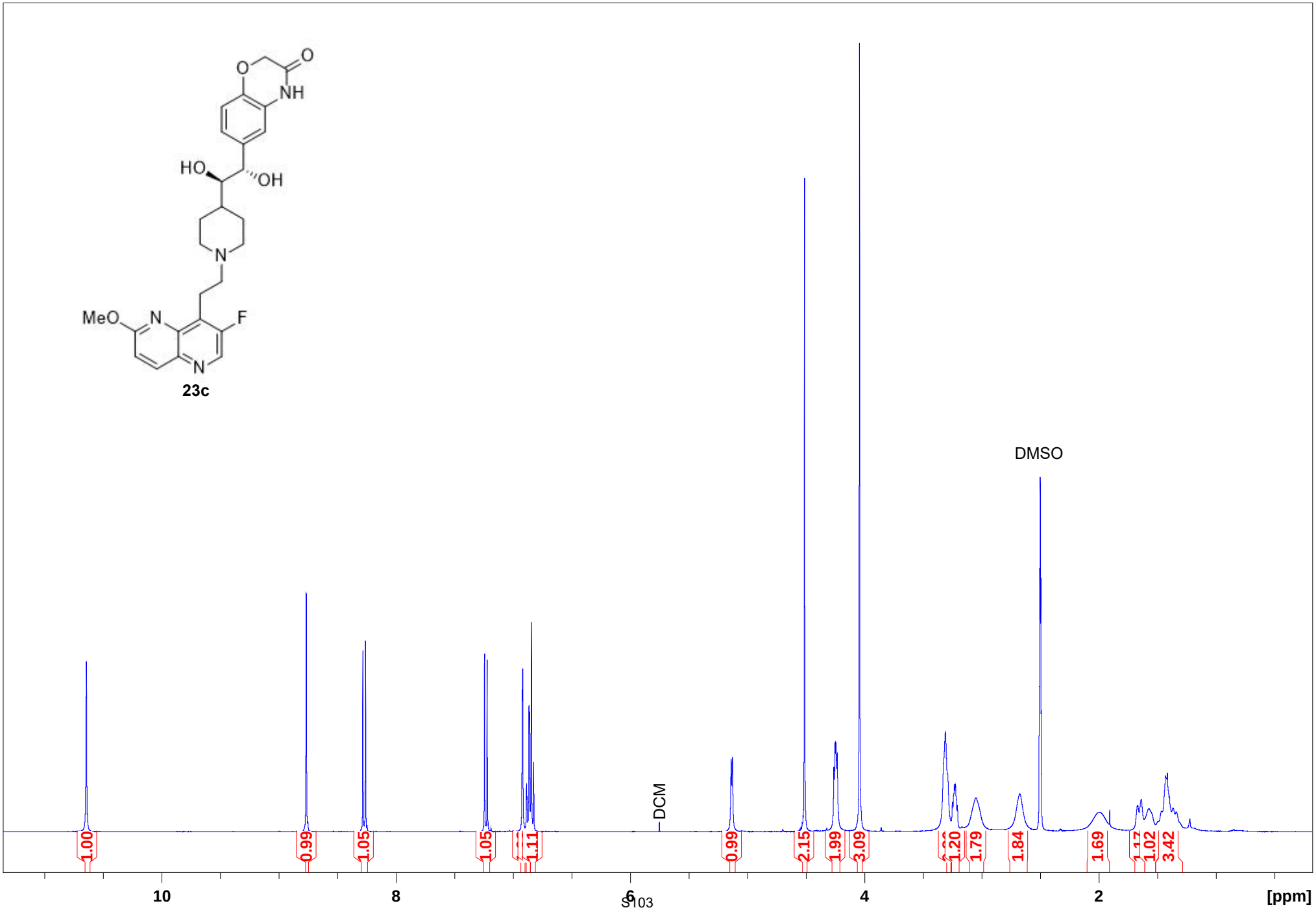

water
DMSO
HO
OH
N
MeO
N
F
N
23a
1.00
1.01
3.01
2.06
1.07
1.02
0.97
2.82
17.66
2.02
2.00
3.13
2.05
1.07
1.19
2.14
1.43
10
8
6
S99
4
2
[ppm]

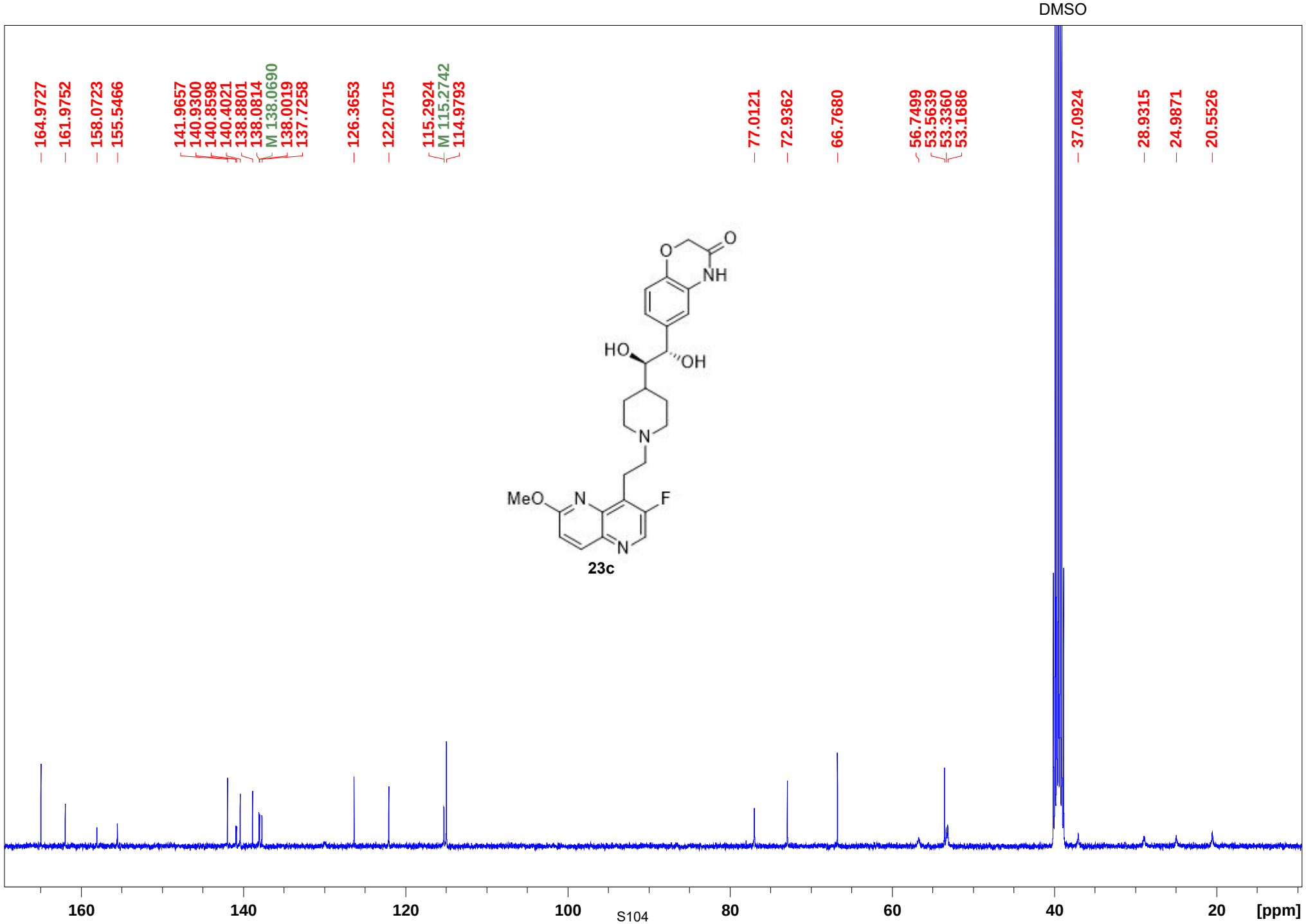

DMSO
161.9547
158.0923
155.5685
141.2889
140.9690
140.8979
140.4066
M 138.0837
138.0825
M 138.0693
137.9949
137.7185
135.3679
130.2641
130.1352
127.9505
127.3605
115.2733
M 115.2552
77.1467
73.2935
56.9547
53.5385
53.4568
53.2771
37.2713
29.1197
25.3873
20.6906
HO
OH
N
MeO
N
F
N
23a
ethyl acetate
ethyl acetate
160
140
120
100
S100
80
60
40
20
[ppm]

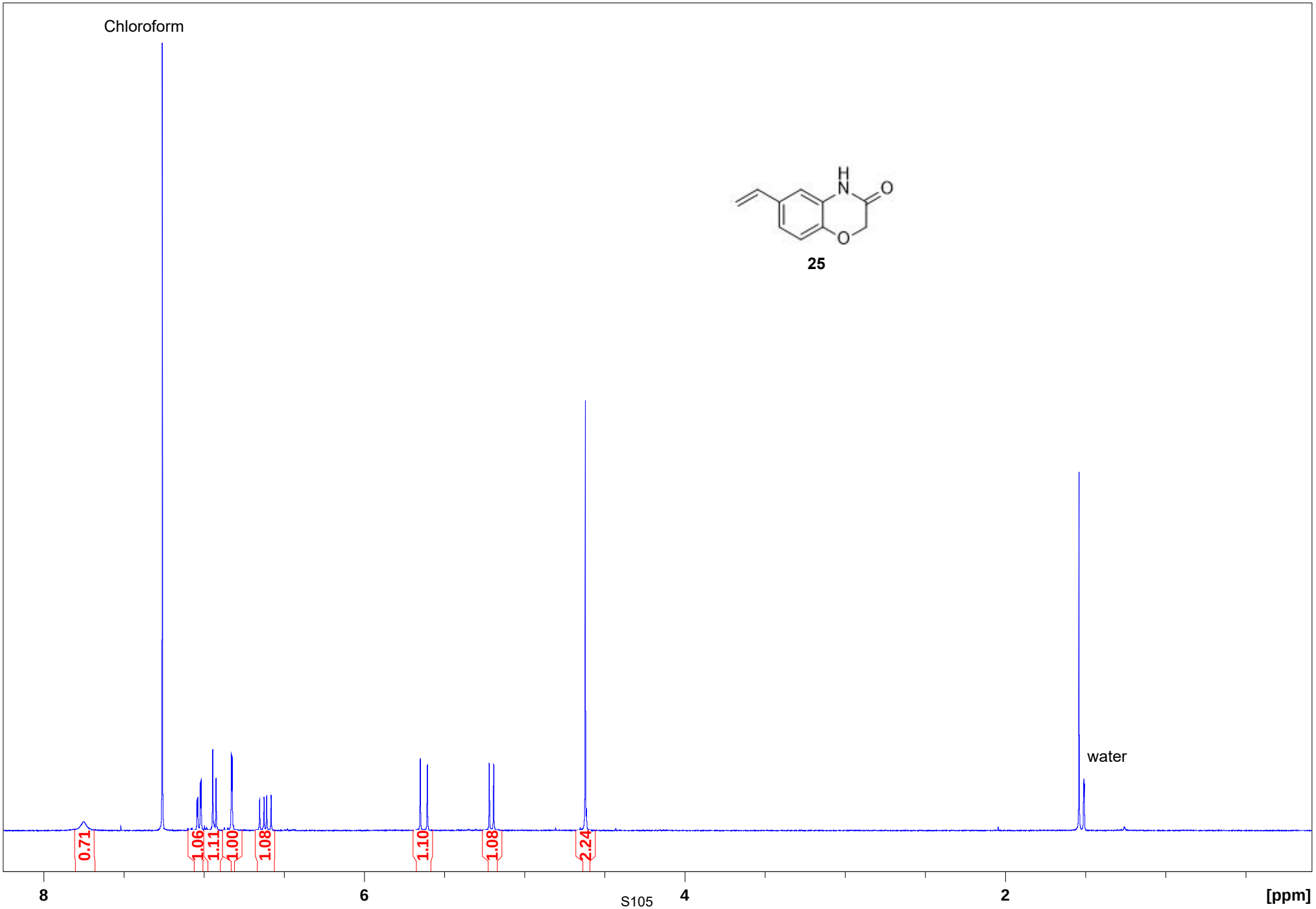

water
DMSO
HO
OH
O
O
N
MeO
N
F
N
23b
1.00
1.00
1.01
1.03
0.99
1.22
2.77
8.67
1.25
2.01
2.05
14.06
1.97
1.04
1.04
2.08
1.35
8
6
4
2
[ppm]


DMSO
161.9598
158.0986
155.5746
142.4973
142.0244
140.9730
140.9027
140.4094
138.0875
138.0690
137.9992
137.7220
137.4825
130.2695
130.1406
120.2633
116.0824
115.8112
115.2827
115.2590
77.1143
72.9408
63.9976
56.9524
53.5456
53.4572
53.2685
37.2727
29.0943
25.3600
20.7198
HO
OH
O
O
N
MeO
N
F
N
160
140
120
100
80
60
40
20
[ppm]

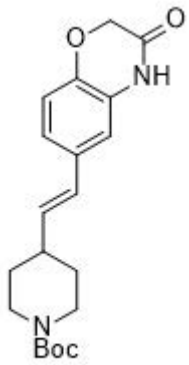
**23b**


O
O
NH
HO
OH
N
MeO
N
F
N
23c
DMSO
DCM
1.00
0.99
1.05
1.05
1.11
0.99
2.15
1.99
3.09
1.20
1.79
1.84
1.69
1.02
3.42
10
8
6
4
2
[ppm]


DMSO
164.9727
161.9752
158.0723
155.5466
141.9657
140.9300
140.8598
140.4021
138.8801
138.0814
M 138.0690
138.0019
137.7258
126.3653
122.0715
115.2924
M 115.2742
114.9793
77.0121
72.9362
66.7680
56.7499
53.5639
53.3360
53.1686
37.0924
28.9315
24.9871
20.5526
O
O
NH
HO
OH
N
MeO
N
F
N
23c
160
140
120
100
80
60
40
20
[ppm]


Chloroform
H
N
O
O
25
0.71
1.06
1.11
1.00
1.08
1.10
1.08
2.24
water
8
6
4
2
[ppm]

Chloroform

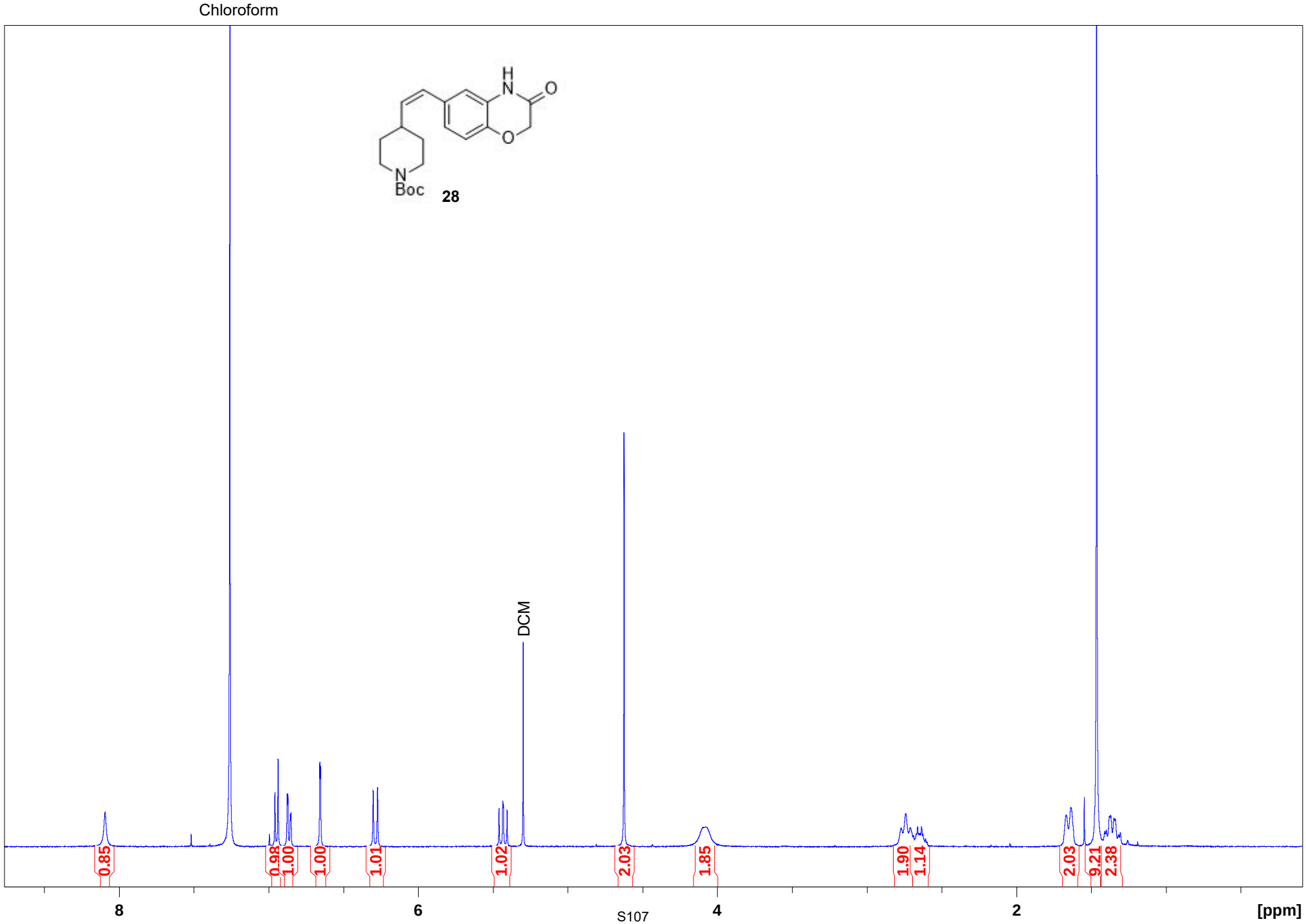


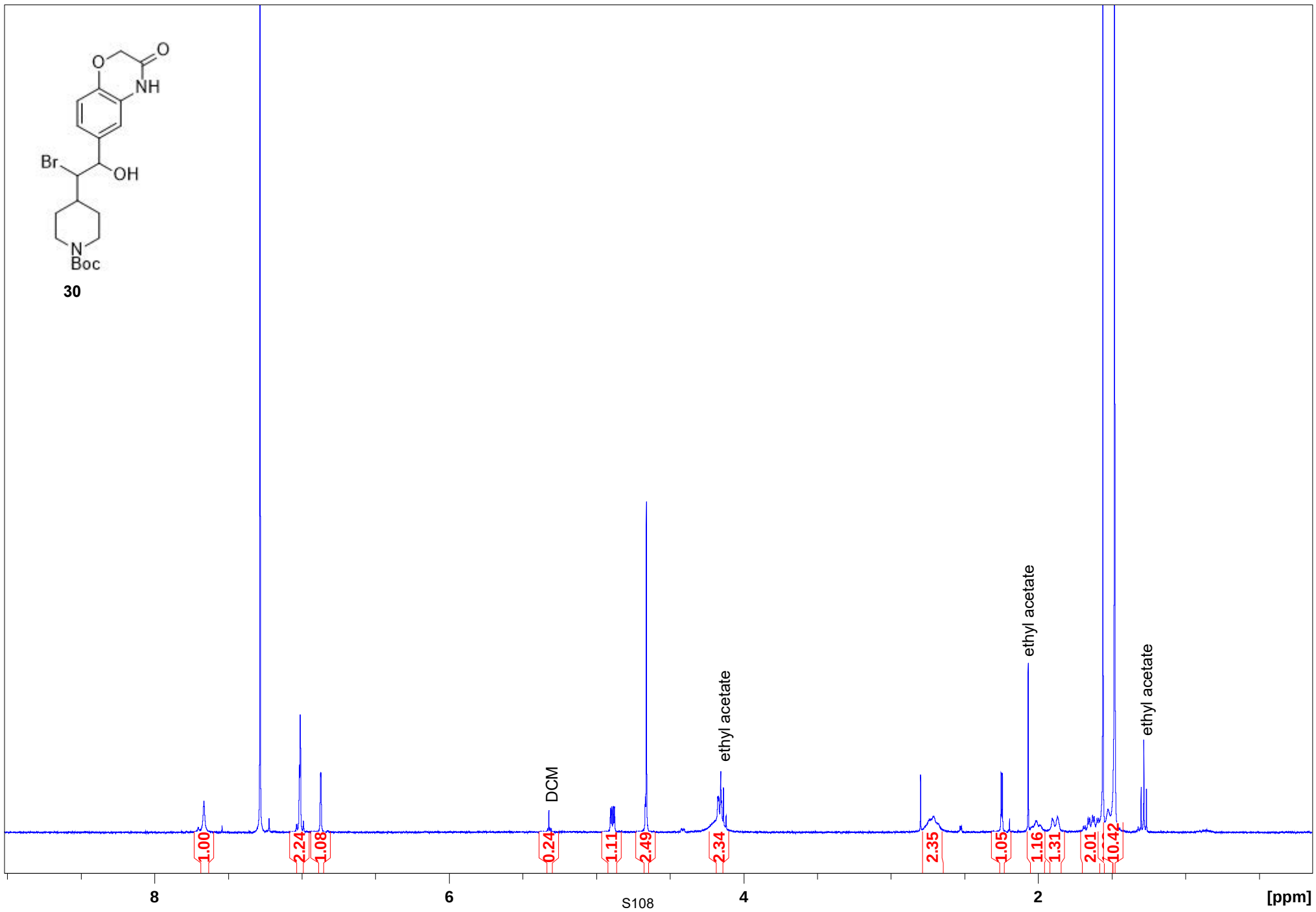

**26**

DCM

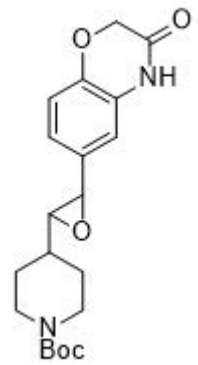
0.91 1.00 0.99 0.97 1.04 1.02 2.00 1.98 1.95 1.00 2.01 10.36 2.41

6 4 2 [ppm]


Chloroform
H
N
O
O
N
Boc
28
DCM
0.85
0.98
1.00
1.00
1.01
1.02
2.03
1.85
1.90
1.14
2.03
9.21
2.38
8
6
4
2
[ppm]


Chloroform
O
O
NH
Br
OH
N
Boc
30
DCM
ethyl acetate
ethyl acetate
ethyl acetate
1.00
2.24
1.08
0.24
1.11
2.49
2.34
2.35
1.05
1.16
1.31
2.01
10.42
8
6
4
2
[ppm]

Chloroform

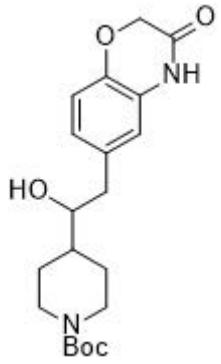



**31**

1.98 1.00 1.96 2.17 0.92 3.25 1.33 1.09 0.93 9.99 3.89

6 4 2 [ppm]

Chloroform

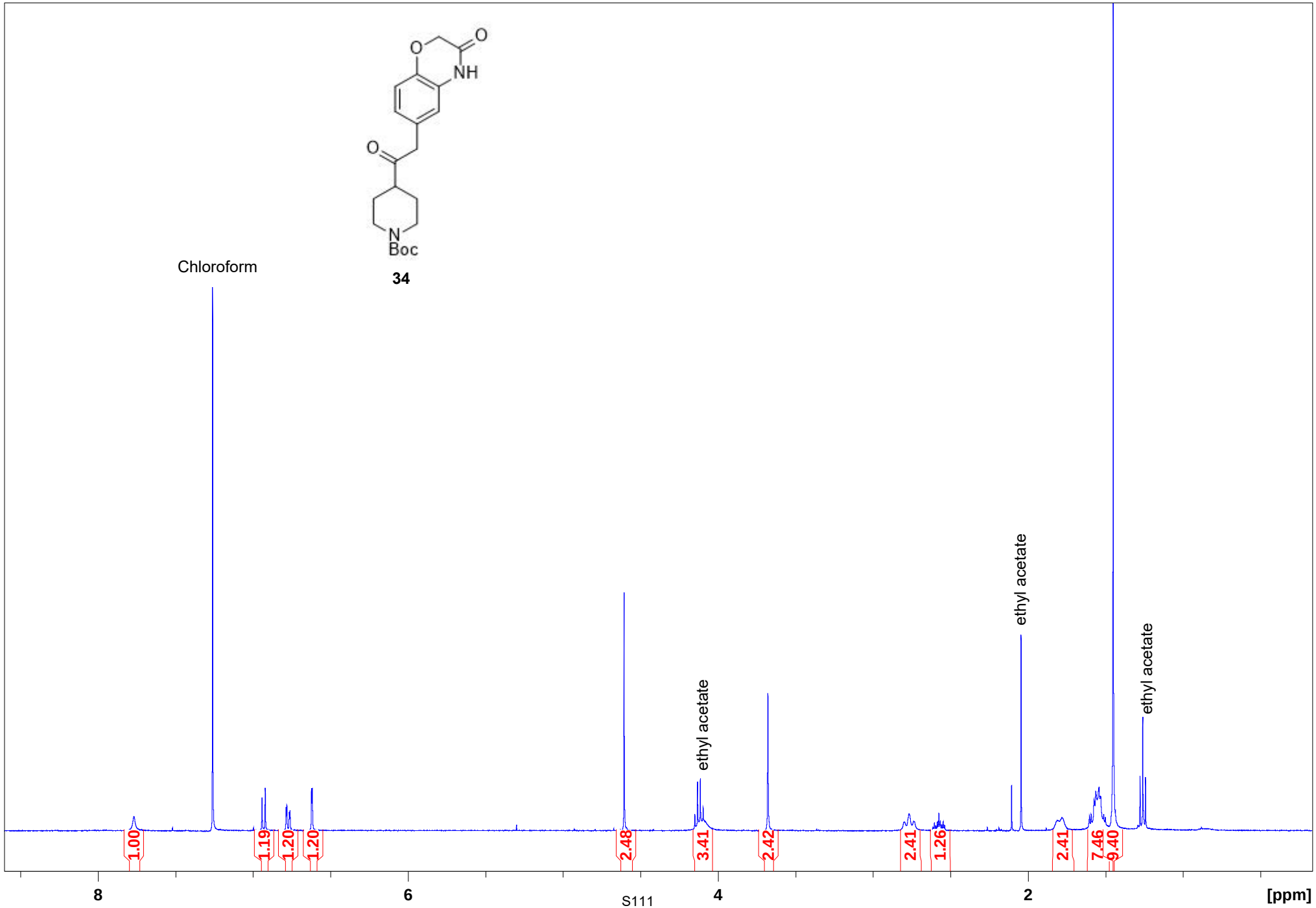


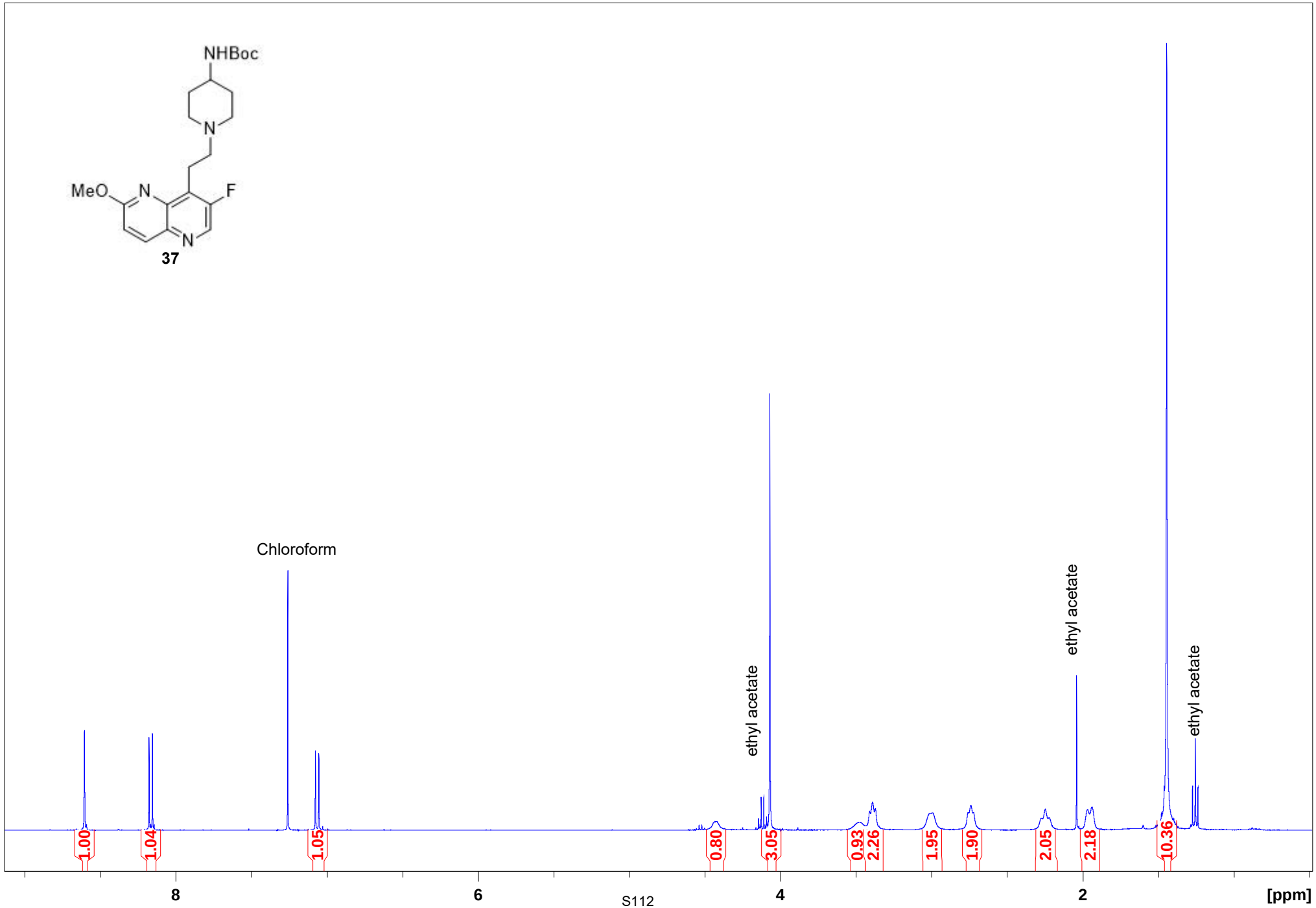

**32**

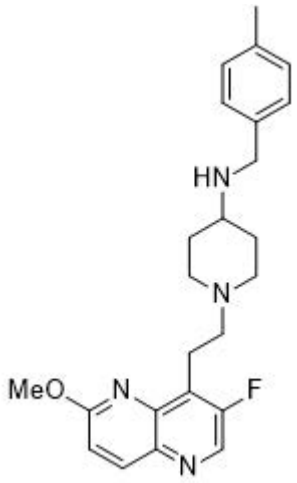
DCM

1.00 0.95 0.89 1.94 1.71 0.97 0.95 1.91 1.09 1.21 1.18 1.36 9.60 4.01

7 6 5 4 3 2 1 [ppm]


O
O
NH
O
N
Boc
34
Chloroform
ethyl acetate
ethyl acetate
ethyl acetate
1.00
1.19
1.20
1.20
2.48
3.41
2.42
2.41
1.26
2.41
7.46
9.40
8
6
4
2
[ppm]


NHBoc
N
MeO
N
F
N
37
Chloroform
ethyl acetate
ethyl acetate
ethyl acetate
1.00
1.04
1.05
0.80
3.05
0.93
2.26
1.95
1.90
2.05
2.18
10.36
8
6
4
2
[ppm]

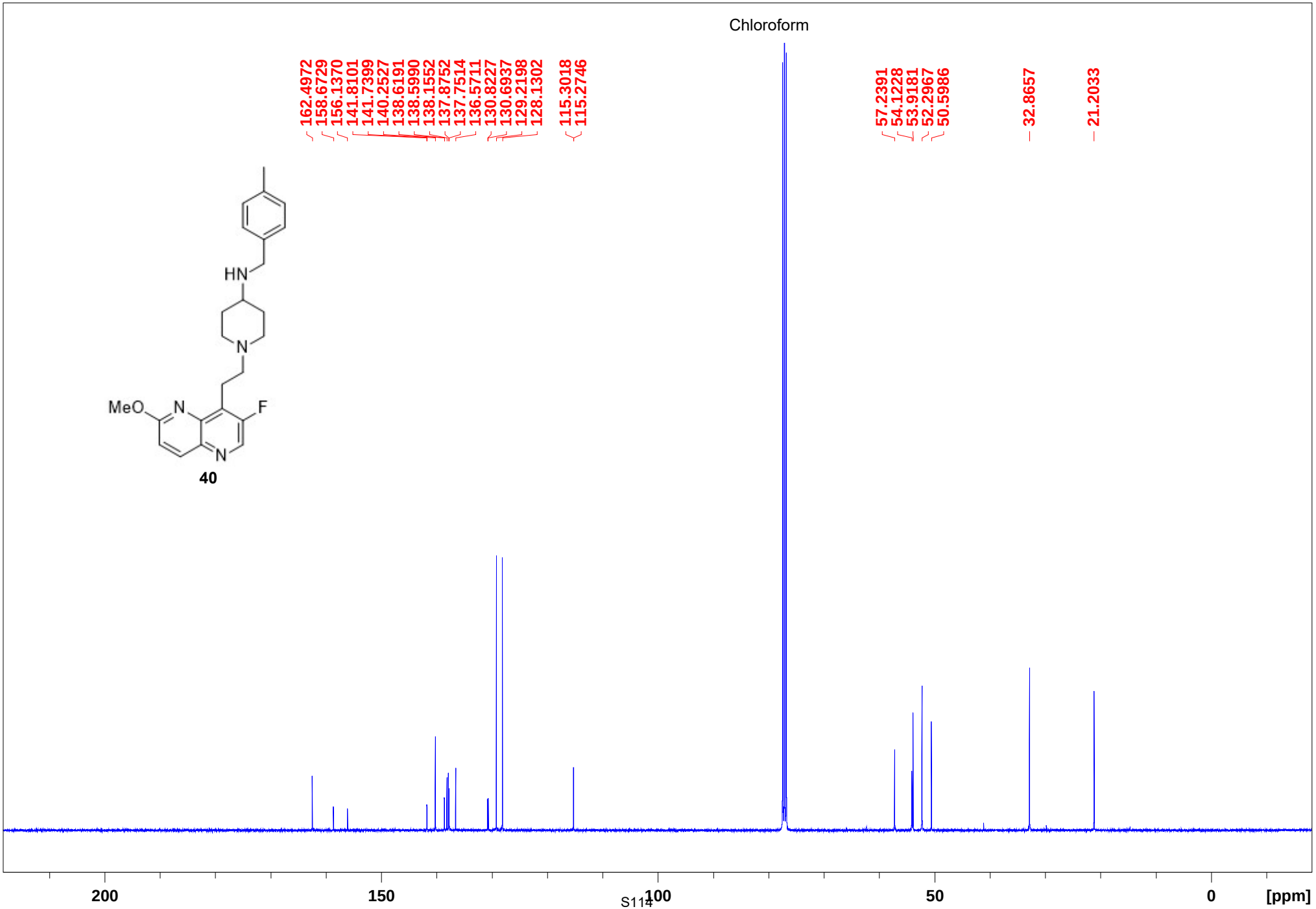


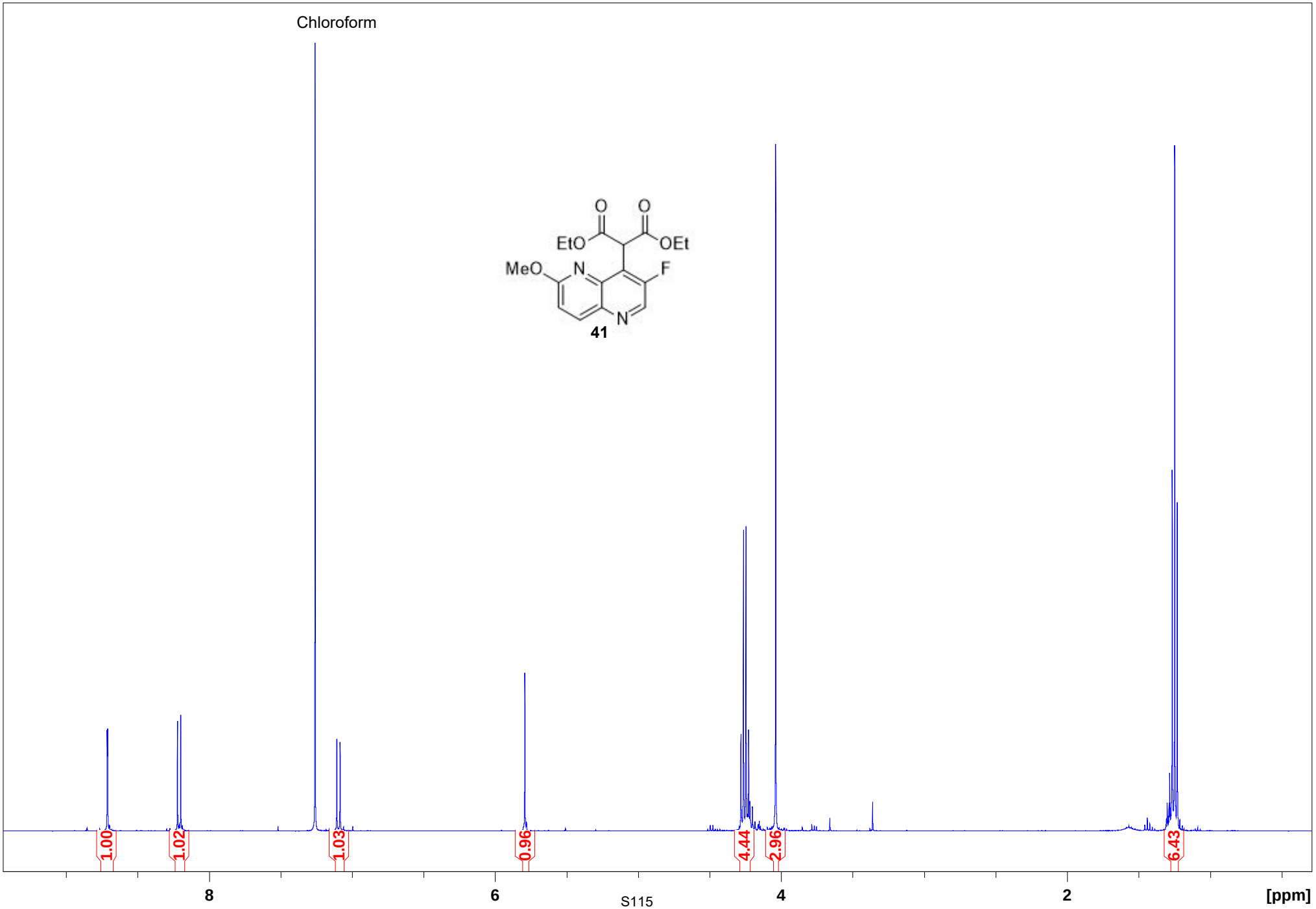

**40**

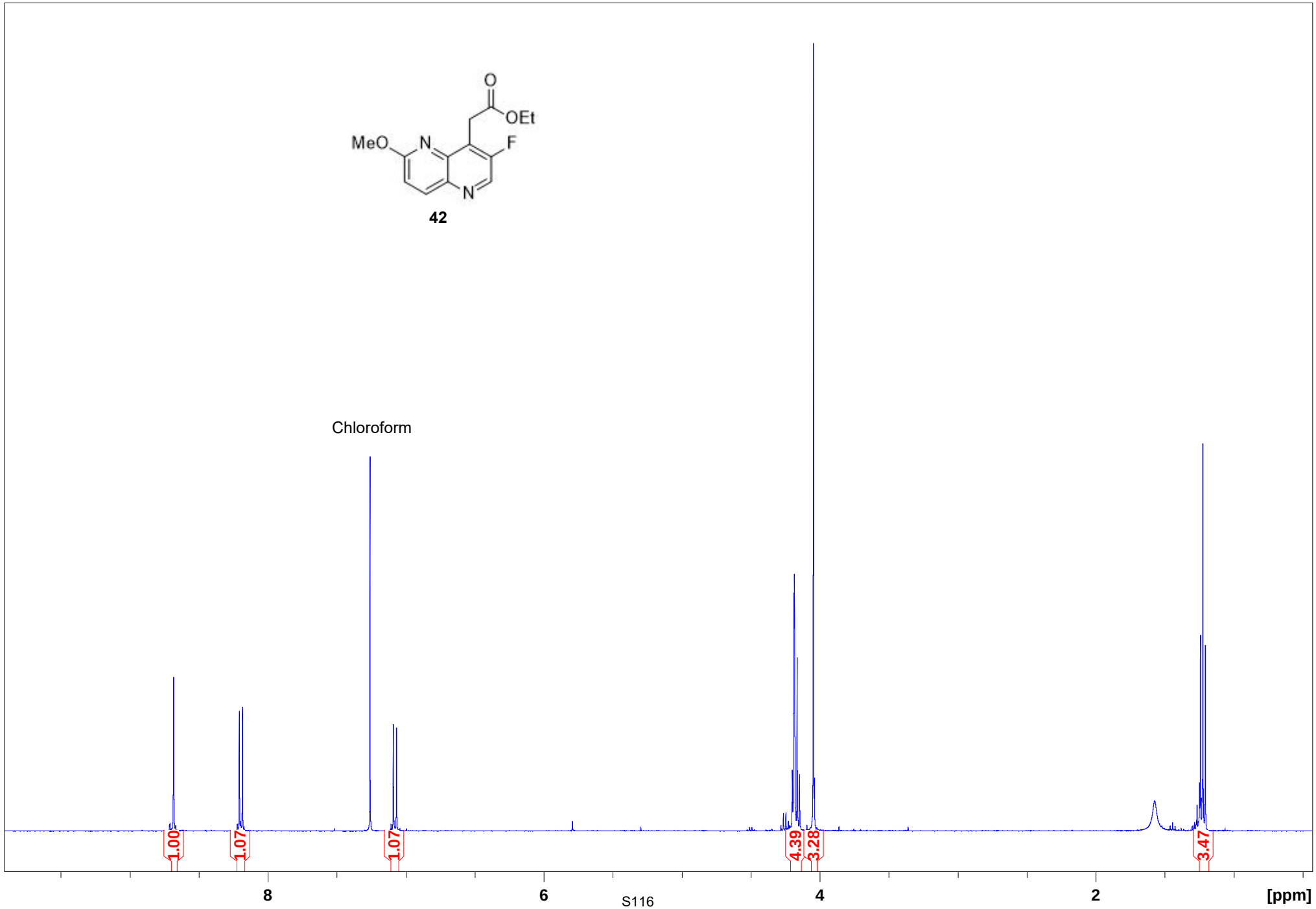
Chloroform

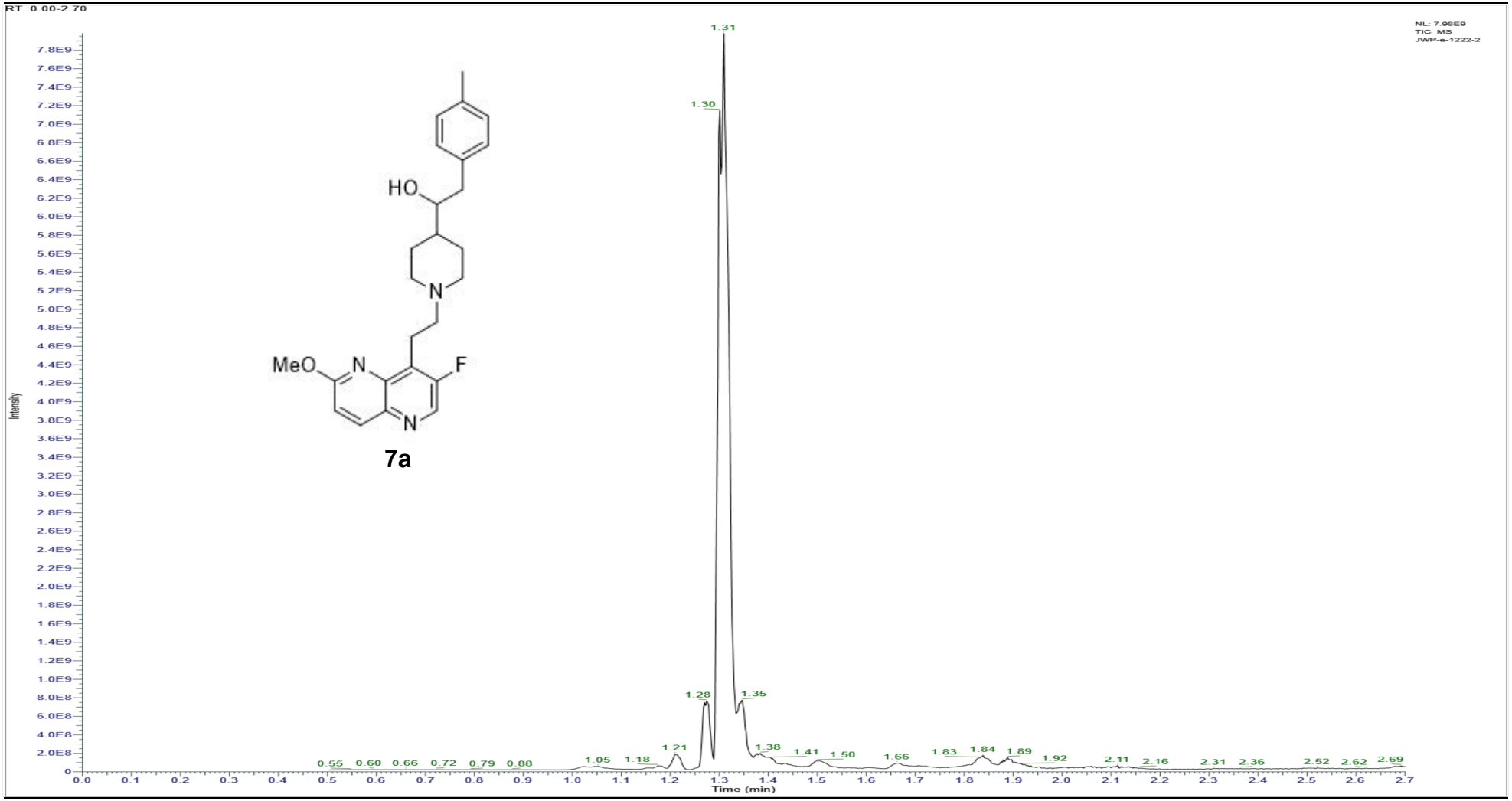
1.00 0.99 2.14 2.02 1.01 3.11 1.91 1.82 1.83 1.84 0.88 3.07 1.85 1.93 4.43

8 6 4 2 [ppm]

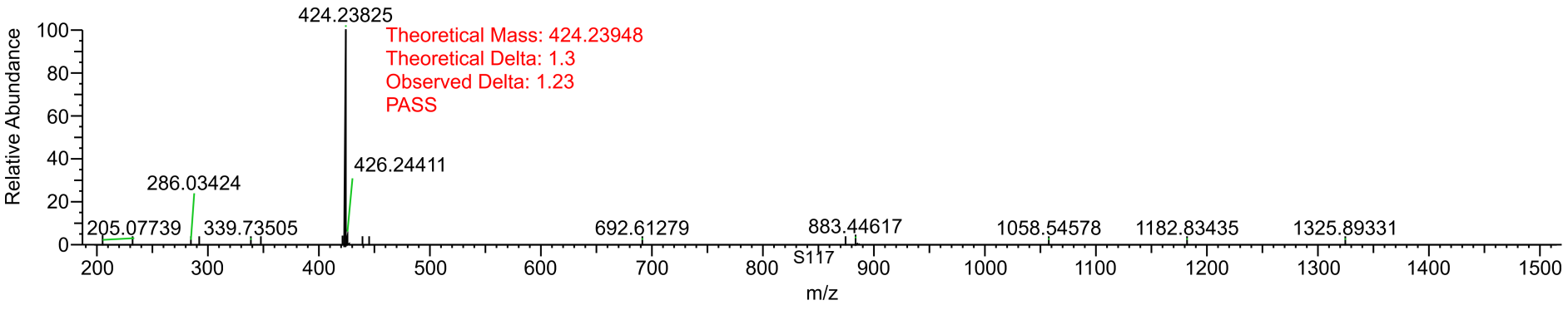

Chloroform
162.4972
158.6729
156.1370
141.8101
141.7399
140.2527
138.6191
138.5990
138.1552
137.8752
137.7514
136.5711
130.8227
130.6937
129.2198
128.1302
115.3018
115.2746
57.2391
54.1228
53.9181
52.2967
50.5986
32.8657
21.2033
HN
N
MeO
N
F
N
40
200
150
100
50
0
[ppm]


Chloroform
O
O
EtO
OEt
MeO
N
F
N
41
1.00
1.02
1.03
0.96
4.44
2.96
6.43
8
6
4
2
[ppm]


O
OEt
MeO
N
F
N
42
Chloroform
1.00
1.07
1.07
4.39
3.28
3.47
8
6
4
2
[ppm]




JWP-e-1222-2 #342 RT: 1.31 AV: 1 NL: 5.06E9
T: FTMS + p ESI Full ms [200.0000-1500.0000] TIC: 7263578100.00000
BPI: 5199437312.00000 BPM: 424.23824 IIT (ms): 0.09100

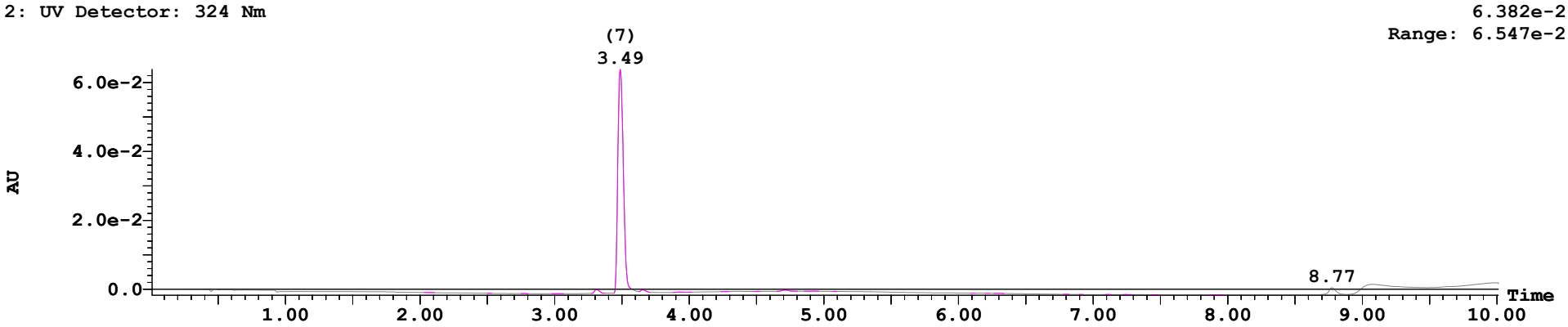


Vial:1:4 ID: File:JWP-e-1222-2
Date:09-Dec-2023 Time:13:30:14 Description:JWP-e-1222-2
Method:C:\MassLynx\OpenLynx_Methods\Mitton-Fry_10min_150-600_Test01.olp Instrument:ACQ-QDA#KBD6021
MS Method:10_min_150-600 Inlet Method:10_min_150-600 Detectors:Waters Acquity PDA

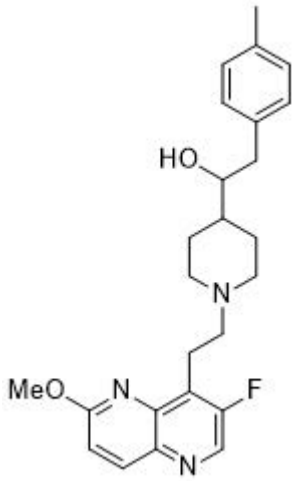
Printed: Sat Dec 09 13:42:31 2023

**Sample Report (continued):**

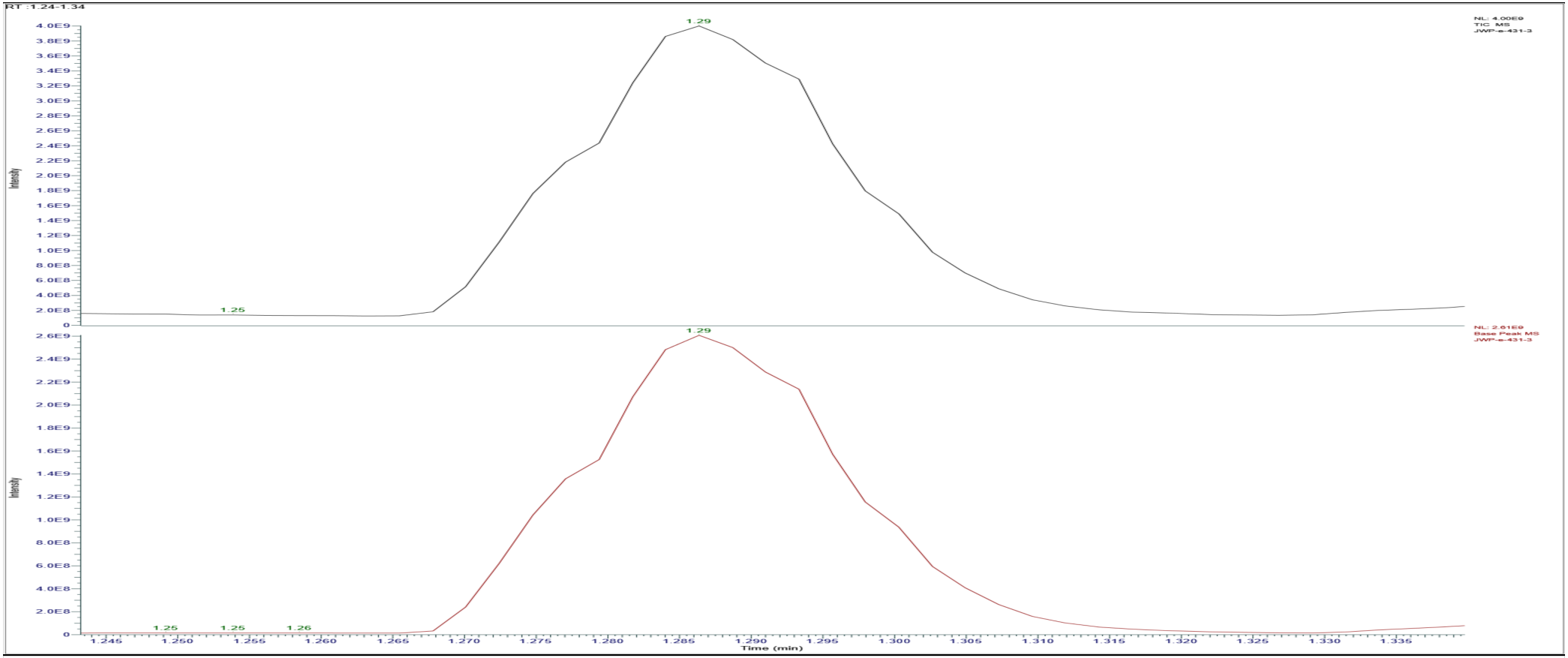
| | |
|---|---|
| 9 | 3.76 |
| 10 | 3.89 |



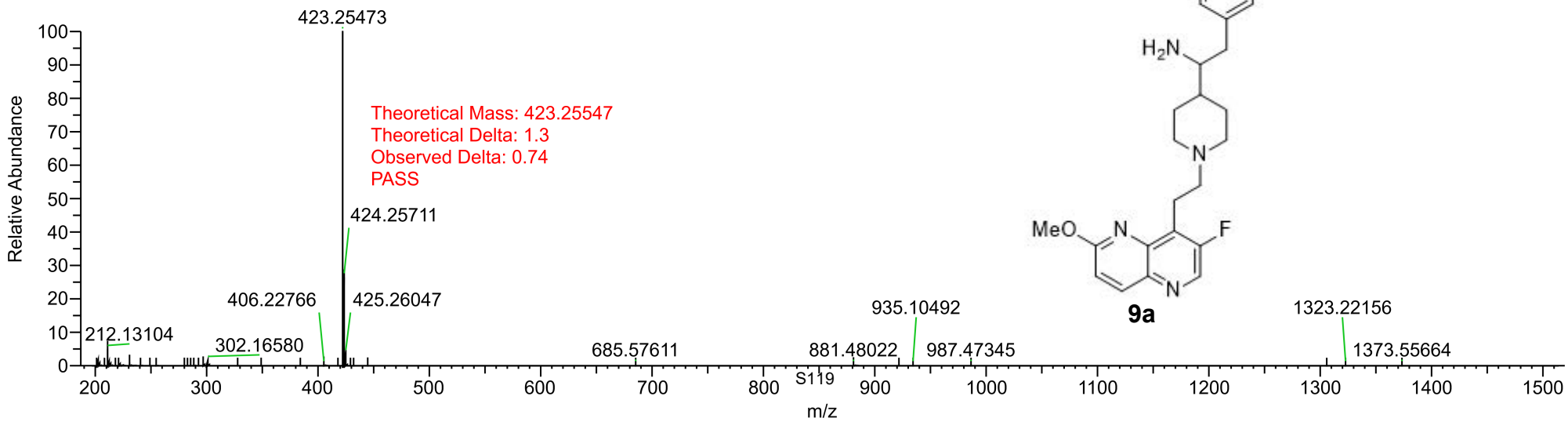

| Peak Number | Time | AreaAbs | Area %Total |
|---|---|---|---|
| 1 | 2.03 | 6e-001 | 0.02 |
| 2 | 2.51 | 2e-001 | 0.01 |
| 3 | 2.77 | 5e-001 | 0.02 |
| 5 | 3.03 | 8e-001 | 0.02 |
| 6 | 3.31 | 5e+001 | 1.50 |
| 7 | 3.49 | 3e+003 | 96.60 |
| 8 | 3.65 | 2e+001 | 0.80 |
| 11 | 3.93 | 3e+000 | 0.11 |
| 12 | 4.29 | 5e-001 | 0.02 |
| 13 | 4.51 | 5e-001 | 0.02 |
| 14 | 4.71 | 2e+001 | 0.61 |
| 15 | 4.88 | 6e-001 | 0.02 |
| 16 | 4.92 | 1e+000 | 0.05 |
| 17 | 5.08 | 3e-001 | 0.01 |
| 18 | 6.11 | 2e-001 | 0.01 |
| 19 | 6.21 | 2e-001 | 0.01 |
| 20 | 6.28 | 1e+000 | 0.04 |
| 21 | 6.80 | 3e-001 | 0.01 |
| 22 | 6.91 | 3e-001 | 0.01 |
| 23 | 7.11 | 9e-001 | 0.03 |
| 24 | 7.24 | 7e-001 | 0.02 |
| 25 | 7.46 | 6e-001 | 0.02 |
| 26 | 7.88 | 1e+000 | 0.04 |




**7a**




JWP-e-431-3 #343 RT: 1.29 AV: 1 NL: 2.56E9
T: FTMS + p ESI Full ms [200.0000-1500.0000] TIC: 4001273600.00000
BPI: 2608272128.00000 BPM: 423.25473 IIT (ms): 0.27700





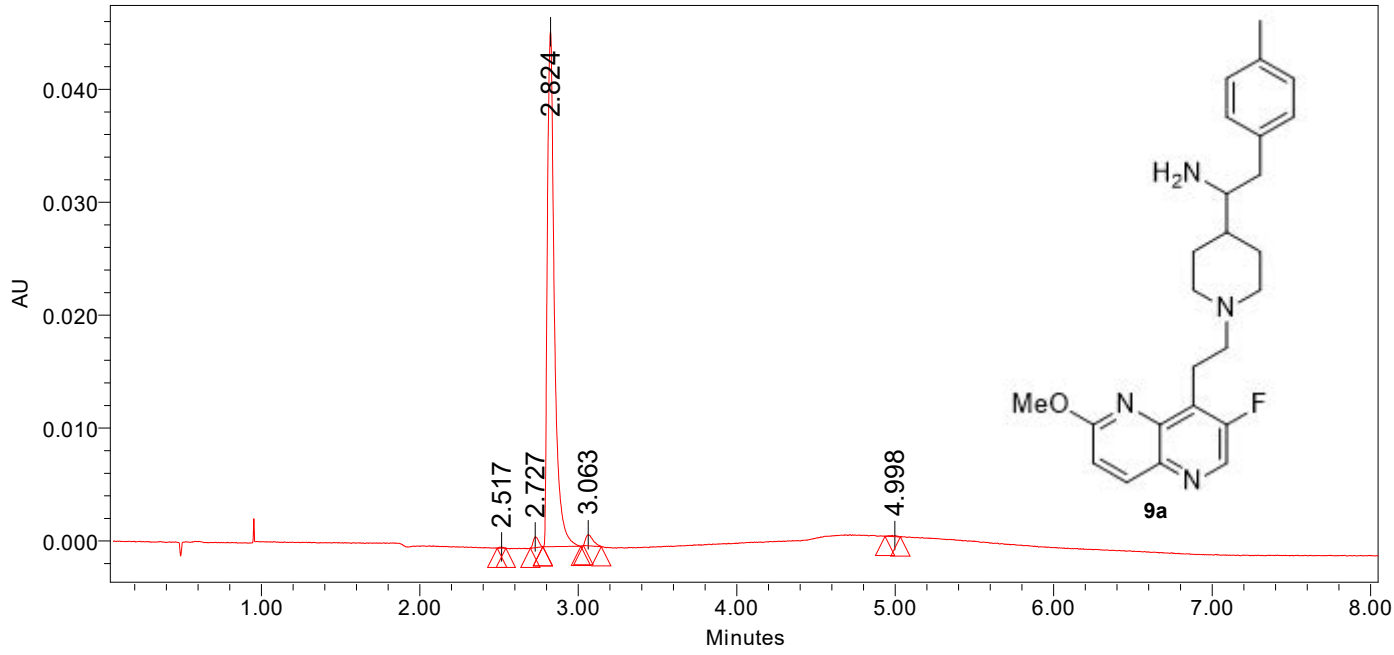


**9a**

# SAMPLE INFORMATION

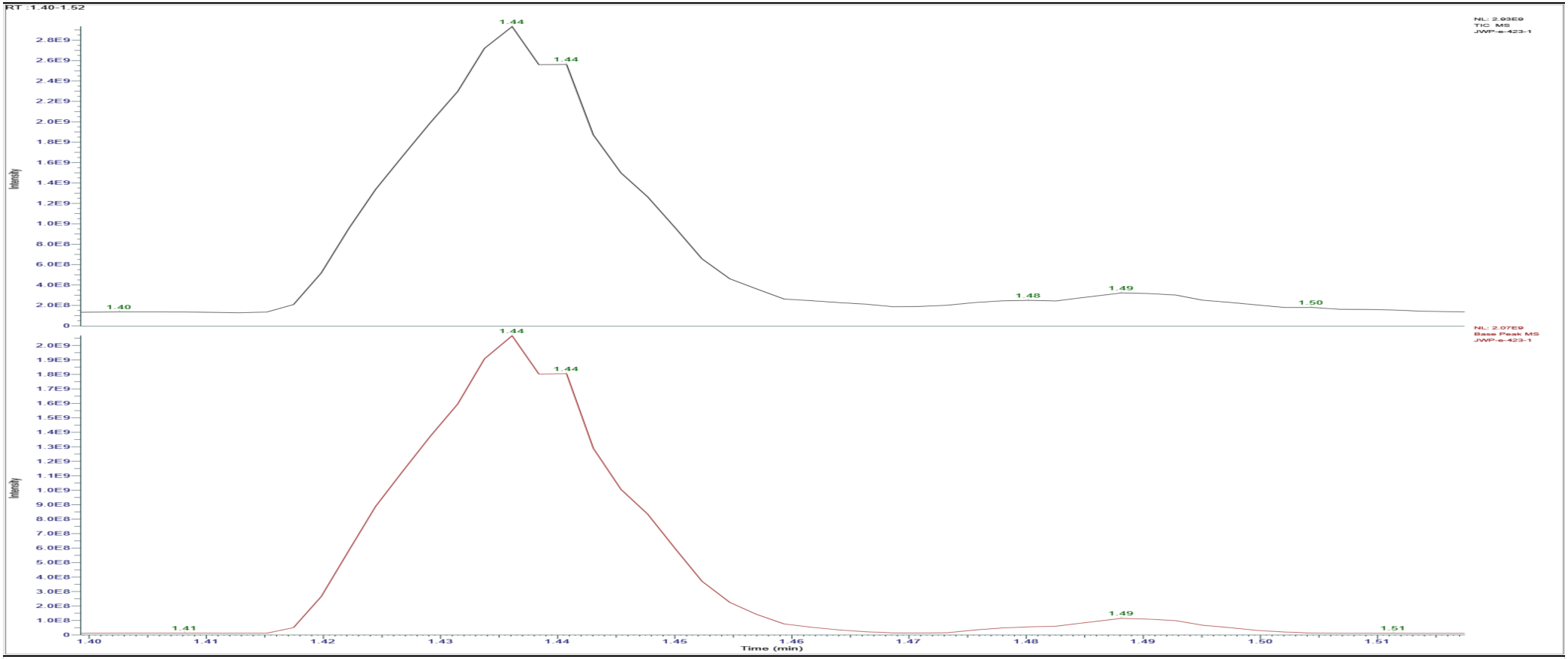
| | | | |
|---|---|---|---|
| Sample Name: | JWP-e-431-3 | Acquired By: | Developer |
| Sample Type: | Unknown | Sample Set Name: | default |
| Vial: | 2:F,2 | Acq. Method Set: | PDA_QDA_Def |
| Injection #: | 1 | Processing Method | PDA_PM_Def |
| Injection Volume: | 2.00 ul | Channel Name: | 323.9 |
| Run Time: | 8.0 Minutes | Proc. Chnl. Descr.: | PDA Spectrum PDA 323.9 nm, |
| Date Acquired: | 8/31/2022 11:22:30 AM EDT | | |
| Date Processed: | 8/31/2022 1:36:06 PM EDT | | |

**Auto-Scaled Chromatogram**

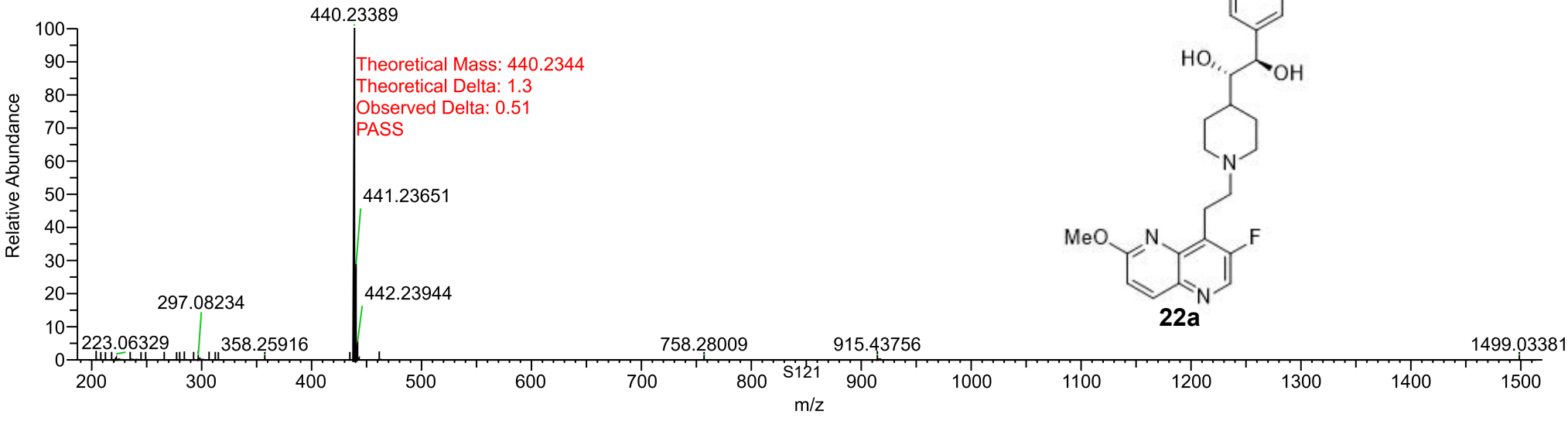



Peak Results

| | RT | % Area |
|---|---|---|
| 1 | 2.517 | 0.1 |
| 2 | 2.727 | 1.5 |
| 3 | 2.824 | 95.9 |
| 4 | 3.063 | 2.2 |
| 5 | 4.998 | 0.2 |




JWP-e-423-1 #407 RT: 1.44 AV: 1 NL: 2.02E9
T: FTMS + p ESI Full ms [200.0000-1500.0000] TIC: 2933029900.00000
BPI: 2067483008.00000 BPM: 440.23388 IIT (ms): 0.31300





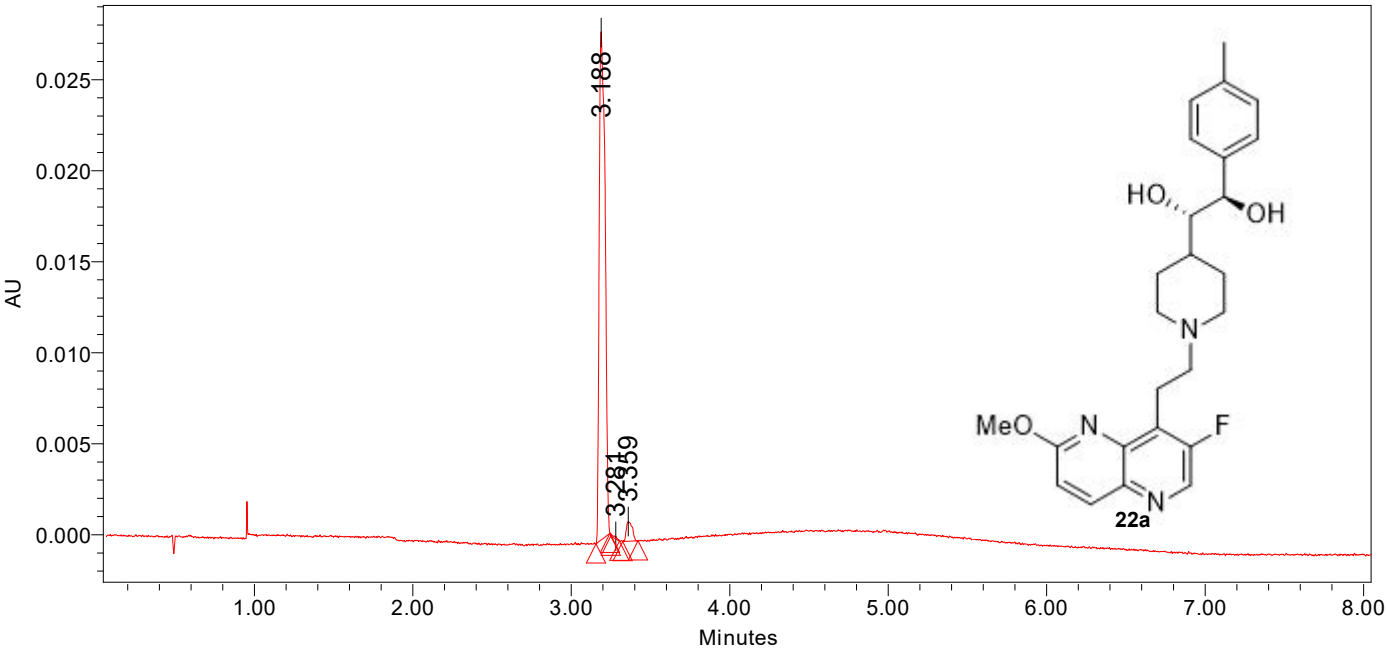


**22a**

# SAMPLE INFORMATION

| | | | |
|---|---|---|---|
| Sample Name: | JWP-e-423-1 | Acquired By: | Developer |
| Sample Type: | Unknown | Sample Set Name: | dfeault |
| Vial: | 2:F,2 | Acq. Method Set: | PDA_QDA_Def |
| Injection #: | 1 | Processing Method | PDA_PM_Def |
| Injection Volume: | 2.00 ul | Channel Name: | 323.9 |
| Run Time: | 8.0 Minutes | Proc. Chnl. Descr.: | PDA Spectrum PDA 323.9 nm, |
| Date Acquired: | 8/31/2022 3:37:07 PM EDT | | |
| Date Processed: | 8/31/2022 5:21:12 PM EDT | | |

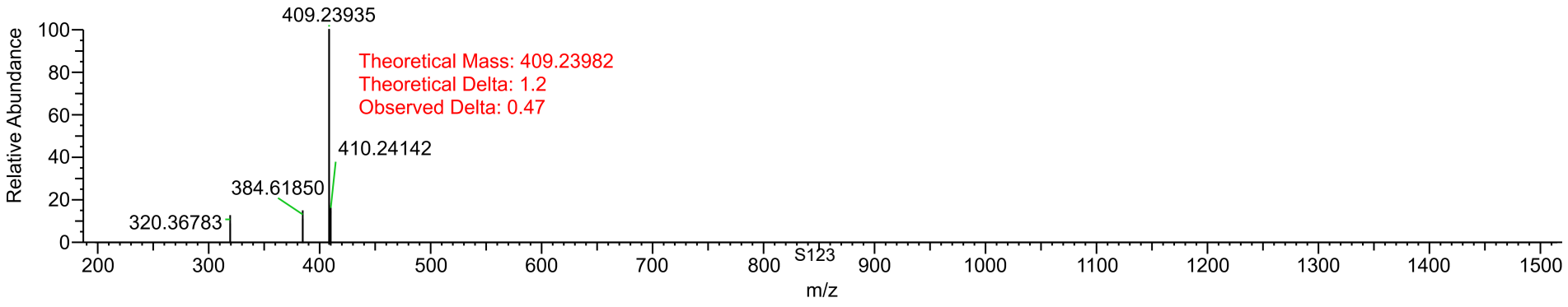
**Auto-Scaled Chromatogram**




Peak Results

| | RT | % Area |
|---|---|---|
| 1 | 3.188 | 95.9 |
| 2 | 3.281 | 0.4 |
| 3 | 3.359 | 3.8 |


JWP-e-223-2 #267 RT: 1.14 AV: 1 NL: 1.02E8
T: FTMS + p ESI Full ms [200.0000-1500.0000] TIC: 150367630.00000
BPI: 102735800.00000 BPM: 409.23936 IIT (ms): 0.16200

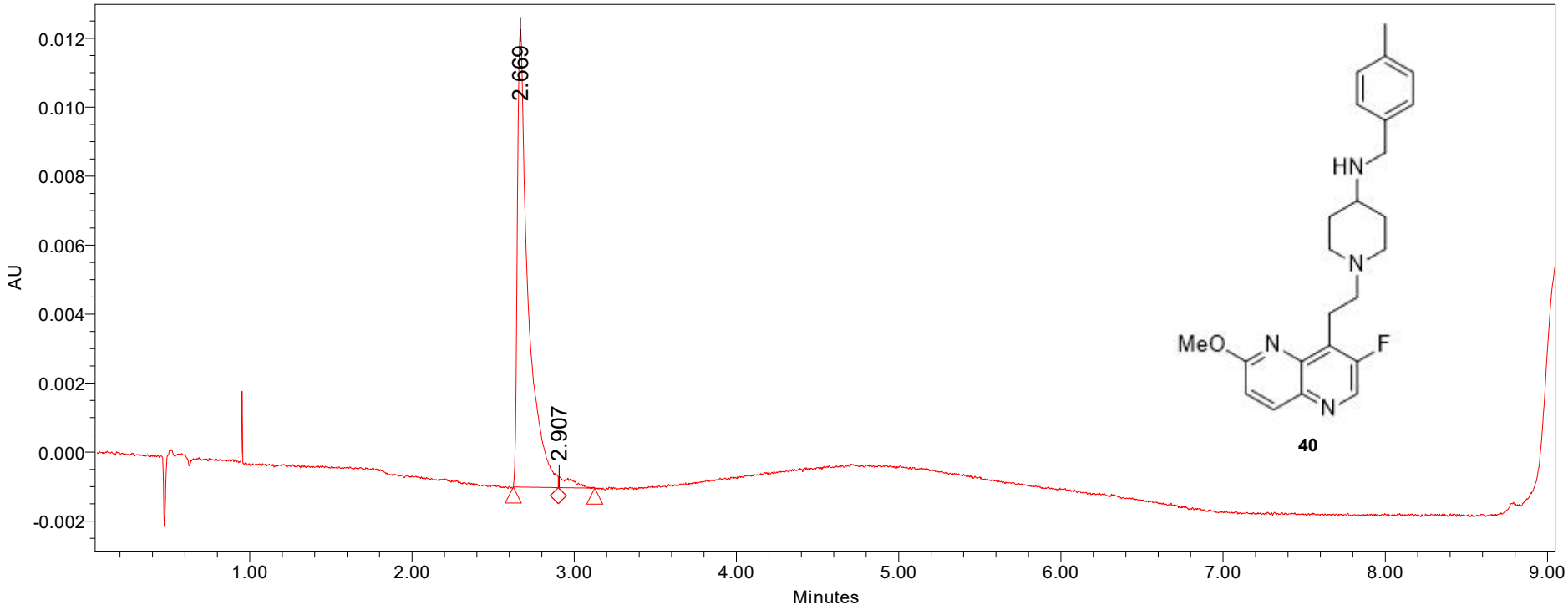


# SAMPLE INFORMATION

Acquired at OSU College of Pharmacy Shared Instrumentation Lab R151

| | | | |
|---|---|---|---|
| Sample Name: | JWP-e-223-2 | Acquired By: | Developer |
| Sample Type: | Unknown | Date Acquired: | 7/27/2023 11:02:05 AM EDT |
| Vial: | 1:A,2 | Acq. Method Set: | PDA_QDA_Def |
| Injection #: | 1 | Date Processed: | 7/27/2023 4:15:59 PM EDT |
| Injection Volume: | 2.00 ul | Processing Method: | PDA_PM_Def |
| Sample Set Name: | default | Channel Name: | 323.9nm |
| | | Proc. Chnl. Descr.: | PDA Spectrum PDA 323.9 nm, Time offset by 0.046 |

**Auto-Scaled Chromatogram**

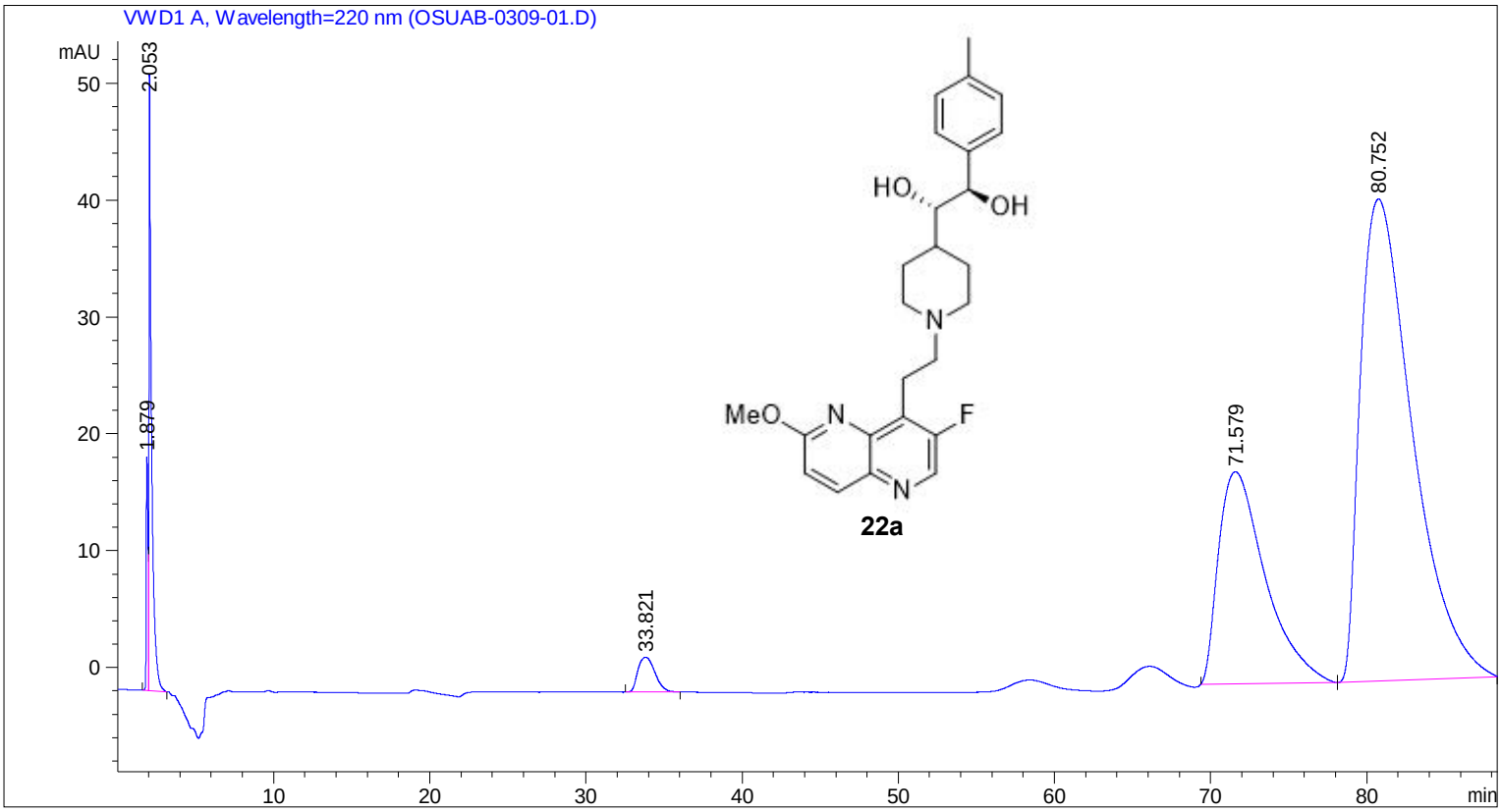



PDA Result Table

| | Name | RT | % Area |
|---|---|---|---|
| 1 | | 2.669 | 97.02 |
| 2 | | 2.907 | 2.98 |

Data File C:\Chem32\1\Data\OSUAB-0309-01.D
Sample Name: OSUAB-0309-01

```
==========================================================================
Acq. Operator   : SYSTEM
Sample Operator : SYSTEM
Acq. Instrument : OSU_Rm331-ELSD                Location :   1
Injection Date  : 12/21/2023 1:47:19 PM
                                                Inj Volume : Manually
Acq. Method     : C:\Chem32\1\Methods\Hex-EtOH-6040_Isocratic.M
Last changed    : 12/21/2023 1:45:10 PM by SYSTEM
                  (modified after loading)
Analysis Method : C:\Chem32\1\Methods\Hex-EtOH-6040_Isocratic.M
Last changed    : 12/21/2023 4:45:38 PM by SYSTEM
Sample Info     : OSUAB-0309-01
                  method 99 hex. 1 RA.
```




```
==========================================================================
                        Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=220 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   1.879 BV    0.1148  154.00912   20.00095   1.0749
   2   2.053 VB    0.1474  603.60779   52.80570   4.2130
   3  33.821 BB    0.9038  226.58345    2.97755   1.5815
   4  71.579 BB    2.5643 3778.73071   18.16215  26.3743
```

Data File C:\Chem32\1\Data\OSUAB-0309-01.D
Sample Name: OSUAB-0309-01

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 5 | 80.752 | BBA | 2.9484 | 9564.38672 | 41.25961 | 66.7563 |
| Totals : | | | | 1.43273e4 | 135.20596 | |

*** End of Report ***