Incorporation of a chiral *gem*-disubstituted nitrogen heterocycle yields an oxazolidinone antibiotic with reduced mitochondrial toxicity

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Materials and Methods

Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon. Commercially obtained reagents were used as received. Chemicals were purchased from Sigma Aldrich/Strem/Alfa Aesar/Combi-Blocks/Enamine/PharmaBlock and used as received. From Combi-Blocks: (S)-epichlorohydrin, 2,2-dimethylmorpholine. From Enamine: 1,8-dioxa-4-azaspiro[5.5]undecane, *tert*-butyl 1-oxa-4,8-diazaspiro[5.5]undecane-8-carboxylate, 6-oxa-2,9-diazaspiro[4.5]decane, 2,6-dioxa-9-azaspiro[4.5]decane. From PharmaBlock: *tert*-butyl 8-oxo-6-oxa-2,9-diazaspiro[4.5]decane-2-carboxylate.

Reaction temperatures were controlled by an IKAmag temperature modulator. Glove box manipulations were performed under a nitrogen atmosphere. Thin-layer chromatography (TLC) and preparatory TLC was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching or $KMnO_4$ staining. Silia*Flash* P60 Academic Silica gel (particle size 0.040–0.063 mm) was used for flash chromatography.

Analytical SFC was performed with a Mettler SFC supercritical CO_2 analytical chromatography system utilizing a Chiralpak IC column (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. with visualization at 254 nm. Reverse Phase Preparatory HPLC was performed with a Teledyne ISCO ACCQPrep HP125 preparative liquid chromatography system equipped with a RediSep Prep C18 5 μm column (20 x 250 mm).

^{1}H NMR spectra were recorded on a Varian Inova 600 MHz or 500 MHz spectrometer or a Bruker Avance HD 400 MHz spectrometer and are reported relative to residual $CHCl_3$ (δ 7.26 ppm) or CH_3OH (δ 3.31 ppm). ^{13}C NMR spectra were recorded on a Varian Inova 500 MHz spectrometer or a Bruker Avance HD 400 MHz spectrometer and are reported relative to residual $CDCl_3$ (δ 77.16 ppm) or CD_3OD (δ 49.00 ppm). Data for ^{1}H NMR are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sept = septuplet, m = multiplet, br s = broad singlet. Data for ^{13}C NMR are reported in terms of chemical shifts (δ ppm). Some reported spectra include minor solvent impurities of water (δ 1.56 or 4.87 ppm), ethyl acetate (δ 4.12, 2.05, 1.26 ppm), methylene chloride (δ 5.30 ppm), acetone (δ 2.17 ppm), grease (δ 1.26, 0.86 ppm), and/or silicon grease (δ 0.07 ppm), which do not impact product assignments.

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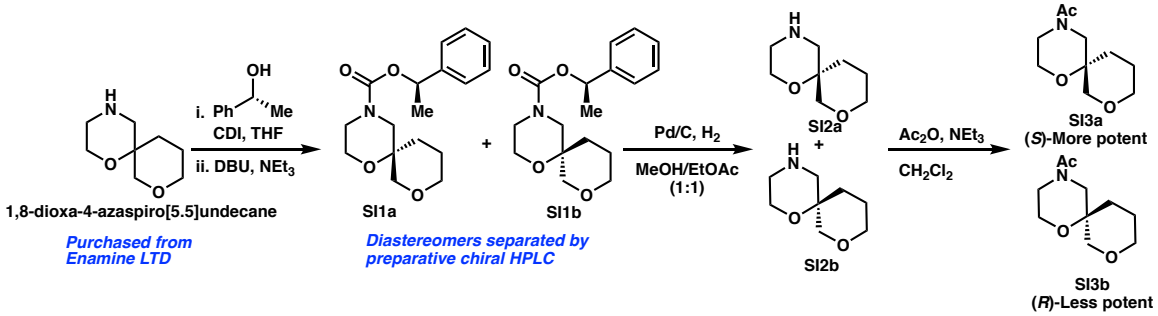
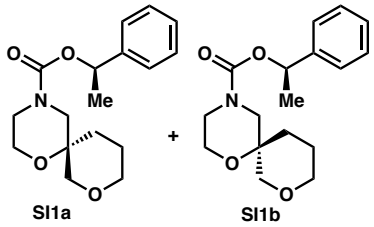
IR spectra were obtained using a Perkin Elmer Paragon 1000 spectrometer using thin films deposited on NaCl plates and reported in frequency of absorption (cm^{-1}). High resolution mass spectra (HRMS) were obtained from an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI+), atmospheric pressure chemical ionization (APCI+), or mixed ionization mode (MM: ESI-APCI+). Optical rotations were measured with a Jasco P-2000 polarimeter operating on the sodium D-line (589 nm), using a 100 mm pathlength cell and are reported as: $[\alpha]_D^T$ (concentration in g/100 mL, solvent).

MIC values were obtained in collaboration with UCLA (P.L.B. and J.F.M.) and the CO-ADD. Pharmacokinetic data was obtained with WuXi AppTec, a contract research organization.

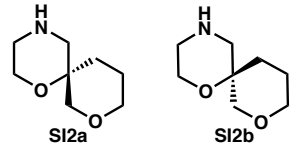
List of Abbreviations: ee – enantiomeric excess, DBU - 1,8-Diazabicyclo[5.4.0]undec-7-ene, HPLC – high-performance liquid chromatography, SFC – supercritical fluid chromatography, TLC – thin-layer chromatography, EtOAc – ethyl acetate, THF – tetrahydrofuran, MeOH – methanol, MeCN – acetonitrile, Et_2O – diethyl ether, CH_2Cl_2 – methylene chloride, IPA – isopropanol, AcOH – acetic acid.

Determination of Absolute Configuration of 19a and 19b.

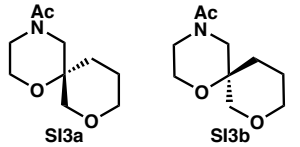




Diastereomers SI1a and SI1b: To a solution of (*S*)-(−)-1-Phenylethanol (599 uL, 1.1 equiv) in THF (4.5 mL, 1M), was added CDI (794 mg, 1.1 equiv). The solution was stirred for 1 h at room temperature. Then NEt_3 (686 uL, 1.1 equiv) and DBU (732 uL, 1.1 equiv) were added and the solution was stirred for 5 min. Then 1,8-dioxa-4-azaspiro[5.5]undecane was added and the solution was stirred for 16 h before quenching with NH_4Cl. Following extraction with EtOAc (3x10 mL) and backwashing with $NaHCO_3$ (5 mL), the combined organic layers were dried over Na_2SO_4 and concentrated. The crude product was purified by silica gel flash chromatography (33% EtOAc:Hexanes). The diastereomers were then separated by chiral preparative HPLC (CHIRALPAK IC Column 20 x 150 mm), 30% *i*PrOH:Hexanes. The diastereomer **SI1a** which results in the more potent analogue **19a** elutes first from the chiral column.



***(R)* and *(S)*-1,8-dioxa-4-azaspiro[5.5]undecane, enantiopure SI2a and SI2b:** To a solution of carbamate **SI1a** or **SI1b** (460 mg, 1 equiv) in 1:1 EtOAc/MeOH (16 mL, 0.1 M) under nitrogen was added Pd/C (10%, 80 mg, 0.05 equiv). The reaction vessel was evacuated and filled with hydrogen three times and then left to stir for 12 h at room temperature. Following completion as determined by TLC, the reaction was filtered through celite, rinsed with EtOAc, and then concentrated to afford the enantiopure amines **SI2a** or **SI2b**, which were used in subsequent reactions without further purification.



(*R*) and **(*S*)-1-(1,8-dioxa-4-azaspiro[5.5]undecan-4-yl)ethan-1-one** (Acylated enantiomers **SI3a** and **SI3b**): To a solution of **SI2a** or **SI2b** in CH_2Cl_2 (5 mL, 0.1 M) was added NEt_3 (106 uL, 1.5 equiv) and Ac_2O (53 uL, 1.1 equiv). The reaction was stirred at rt for 1 h and then purified by automated silica gel flash chromatography (Teledyne ISCO): $MeOH/CH_2Cl_2$ (0 → 30%) to afford the acylated amine **SI3a** or **SI3b** as a clear oil (65 mg, 65% yield); **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 3.84 – 3.21 (m, 10H), 2.09 (d, *J* = 5.2 Hz, 3H), 1.88 – 1.48 (m, 4H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ (169.6 & 169.4 appear as two peaks due to hindered rotation), (71.1 & 70.9 appear as two peaks due to hindered rotation), (70.2 & 69.4 appear as two peaks due to hindered rotation), (68.5 & 68.4 appear as two peaks due to hindered rotation), (60.4 & 60.1 appear as two peaks due to hindered rotation), (51.1 & 41.7 appear as two peaks due to hindered rotation) (46.8 & 46.6 appear as two peaks due to hindered rotation), (30.9 & 29.8 appear as two peaks due to hindered rotation), (22.8 & 22.0 appear as two peaks due to hindered rotation), (21.2 & 21.11 appear as two peaks due to hindered rotation). **IR:** See VCD section; **HRMS (MM: ESI-APCI)** *m/z* calc'd for $C_{10}H_{21}N_2O_3$ $[M+NH_4]^+$: 217.1547, found 217.1552. **$[\alpha]_D^{22.7}$** –22.00 (c 1.0, $CHCl_3$) for (*S*) ent. **$[\alpha]_D^{22.4}$** +17.38 (c 21.0, $CHCl_3$) for (*R*) ent.

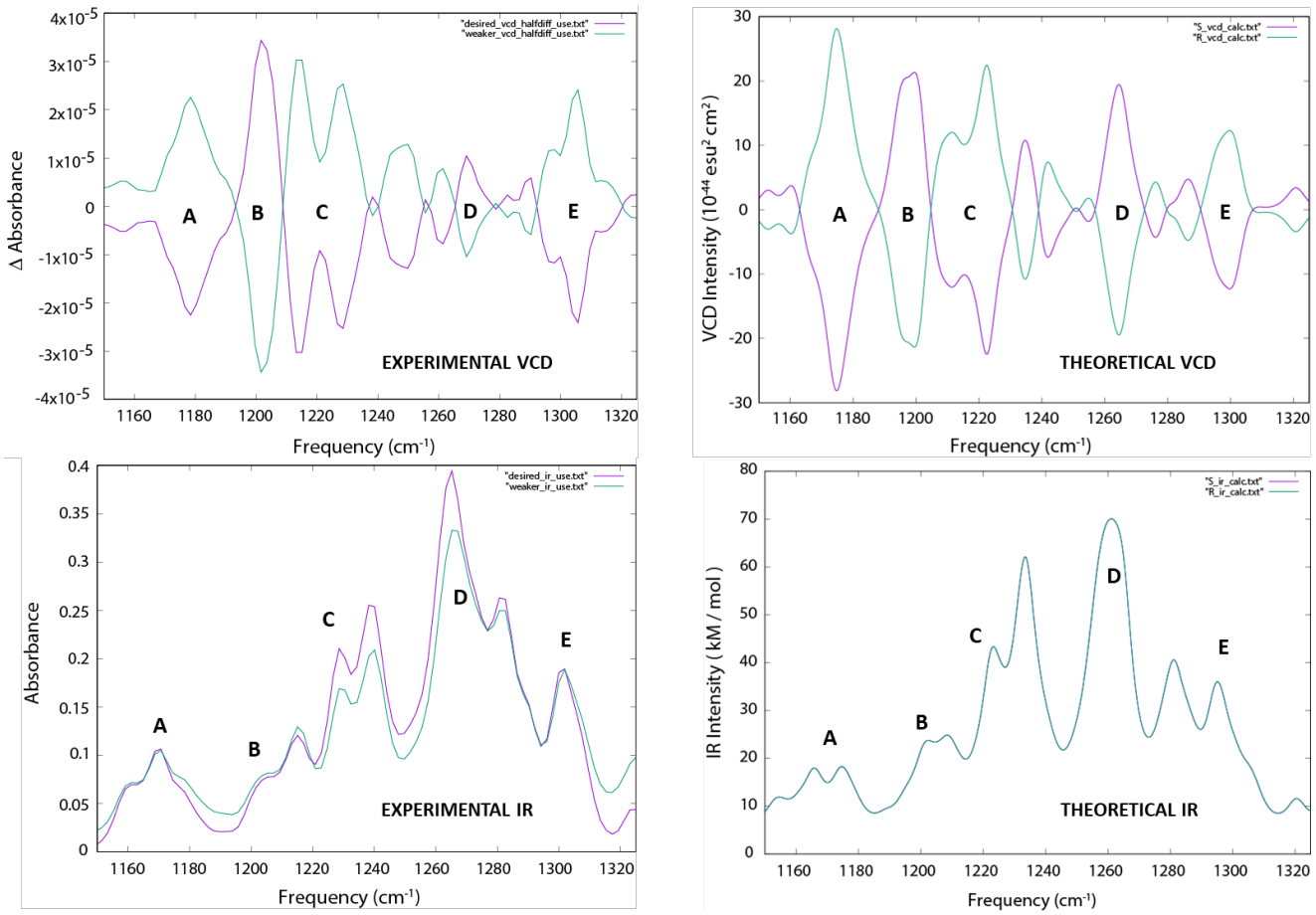
Note: We elected to acylate these amines to facilitate absolute stereochemistry determination by both VCD and optical rotations.

Method 1 – Vibrational Circular Dichroism (VCD)

Experimental Protocol. Solutions of **SI3a** and **SI3b** (65 mg/mL) were prepared in $CDCl_3$ and loaded into a front-loading SL-4 cell (International Crystal Laboratories) possessing BaF_2 windows and 100 μm path length. Infrared (IR) and VCD spectra were acquired on a BioTools ChiralIR-2X VCD spectrometer as a one-hour block of 3120 scans for each enantiomer. A 15-minute acquisition of neat (+)-α-pinene control (separate 75 μm BaF_2 cell) yielded a VCD spectrum in agreement with literature spectra. IR and VCD spectra were background-corrected using a 5-minute block acquisition of the empty instrument chamber under gentle N_2 purge. The resultant VCD spectra of **SI3a** and **SI3b** were enantiomer subtracted (half-difference).

Computational Protocol. The arbitrarily chosen (*R*) enantiomer of compound **SI3b** was subjected to an exhaustive initial molecular mechanics-based conformational search (MMFF94 force field, 0.08 Å geometric RMSD cutoff, and 30 kcal/mol energy window)

as implemented in MOE 2018.1 (Chemical Computing Group, Montreal, CA). All conformers retained the (*R*) configuration. All MMFF94 conformers were then subjected to geometry optimization, harmonic frequency calculation, and VCD rotational strength evaluation using density functional theory. All quantum mechanical calculations utilized the B3PW91 functional, cc-pVTZ basis, and implicit IEFPCM chloroform solvation model as implemented in the *Gaussian 16* program system (Rev. B.01; Frisch *et al*., Gaussian, Inc., Wallingford, CT). Resultant harmonic frequencies were scaled by 0.98. All structurally unique conformers were Boltzmann weighted by relative free energy at 298.15 K. The predicted IR and VCD frequencies and intensities were convolved using Lorentzian line shapes (γ = 4 cm^{-1}) and summed using the respective Boltzmann weights to yield the final predicted IR and VCD spectra of the (*R*) enantiomer of **SI3b**. The predicted VCD of the corresponding (*S*) enantiomer was generated by inversion of sign. From the agreement between the predicted and measured IR and VCD spectra in the useful range (1150-1325 cm^{-1}; see below) the absolute configuration of the *N*-acylated derivative of the desired, more active spirocyclic amine tail group was established as (*S*).



Experimental (left) and computed (right) IR and VCD spectra for **SI3a** and **SI3b.**

Method 2 – Optical Rotation (OR)

Computational Protocol. The ensemble of unique B3PW91/cc-PVTZ conformers of the (R) enantiomer of **SI3b** generated in Method 1 above were subjected to optical rotation calculation at 589.0 nm using the B3LYP hybrid density functional, the large and diffuse 6-311++G(2df,2pd) basis set, and the IEFPCM implicit chloroform solvent model. From the computed B3PW91/cc-pVTZ free energies at 298.15 K and IEFPCM-B3LYP/6-31++G(2df,2pd) optical rotations, a Boltzmann-weighted OR value of +33.6° was determined for the *(R)*-configuration of the above *N*-acylated derivative. (Thus -33.6° for the (*S*) configuration). As the measured specific rotations ($CHCl_3$ solvent, 22.7 °C, c = 1.0, 100 mm path length) were found to be +17.4° (less potent enantiomer) and -20.0° (more potent enantiomer) the OR-based assignment is therefore accord with the VCD-based assignment above (more active = *(S)*, less active = *(R)*. Individual free energies and optical rotational signatures are provided in the accompanying Microsoft Excel file.

Experimental Procedures for Biological Assays

Broth microdilution method A (Performed by the CO-ADD)

Samples were provided by the collaborator and stored frozen at -20 °C. Samples were prepared in DMSO and water to a final testing concentration of 32 μg/mL or 20 μM

(unless otherwise indicated in the data sheet) and serially diluted 1:2 fold 8 times. Each sample concentration was prepared in 384-well plates, non-binding surface plate (NBS; Corning 3640) for each bacterial/fungal strain or Tissue-culture treated (TC-treated; Corning 3712/3764) black for mammalian cell types, all in duplicate (n=2), and keeping the final DMSO concentration to a maximum of 0.5% DMSO. All sample preparation was done using liquid handling robots.

Whole cell growth inhibition assays against S. aureus ATCC 43300 MRSA were conducted as an 8-point dose response to determine the Minimum Inhibitory Concentration (MIC), in duplicate (n=2). All bacteria were cultured in Cation-adjusted Mueller Hinton broth (CAMHB) at 37 °C overnight. A sample of each culture was then diluted 40-fold in fresh broth and incubated at 37 °C for 1.5-3 h. The resultant mid-log phase cultures were diluted (CFU/mL measured by OD_{600}), then added to each well of the compound containing plates, giving a cell density of 5Å~10^5 CFU/mL and a total volume of 50 µL. All the plates were covered and incubated at 37 °C for 18 h without shaking.

Inhibition of bacterial growth was determined measuring absorbance at 600 nm (OD_{600}), using a Tecan M1000 Pro monochromator plate reader. The percentage of growth inhibition was calculated for each well, using the negative control (media only) and positive control (bacteria without inhibitors) on the same plate as references. The percentage of growth inhibition was calculated for each well, using the negative control (media only) and positive control (bacteria without inhibitors) on the same plate. The MIC was determined as the lowest concentration at which the growth was fully inhibited, defined by an inhibition ≥ 80%. In addition, the maximal percentage of growth inhibition is reported as D_{Max} , indicating any compounds with partial activity.

Broth microdilution method B (Performed by UCLA, P.L.B and J.F.M.)

A broth microdilution method was used to estimate the MIC of synthesized compounds against Staphylococcus aureus ATCC 8235-4 (MSSA), 43300 (MSSA), 29213 (MRSA), and 25293 (MSSA). Compounds were diluted in Luria-Bertani (LB) broth to concentrations ranging from 4 µM to 22 µM (in 2 µM steps) in 96 well plates (100 µl per well). DMSO-treated wells (carrier-only) were used as negative controls, and linezolid-treated wells were used as positive controls. Wells at the edge of the plate were not used to avoid broth evaporation during incubation. Overnight cultures of S. aureus 8235-4 were diluted 1:200 in experimental plates, and plates were sealed with a plastic cover and tape. Inoculated plates were gently shaken (150 RPM) at 37 °C for 16hrs, at which point the optical density at 600nm (OD_{600}) for each well was determined using an Epoch microplate spectrophotometer (BioTek Instruments). MIC was defined as the concentration at which at least 90% of S. aureus growth was inhibited, relative to DMSO-treated controls. *For consistency with conventional reporting, µM values were converted to µg/mL by multiplying the compound's MW by its µM value (uM x MW)/1000 = µg/mL. ug/mL values were then rounded to the nearest integer.*

Simulated Gastric Fluid Assay (low pH) (Performed by WuXi AppTec): Please see accompanying Microsoft Excel file.

Cytochrome DDI Assay (Performed by WuXi AppTec): Please see accompanying Microsoft Excel file.

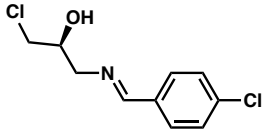
Kinetic Solubility Assay (Performed by WuXi AppTec): Please see accompanying Microsoft Excel file.

Hepatocyte Stability Assay (Performed by WuXi AppTec): Please see accompanying Microsoft Excel file.

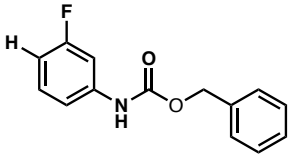
HepG2 Cell Toxicity Assay (Performed by WuXi AppTec): Please see accompanying Microsoft Excel file.

Mitochondrial Protein Synthesis Inhibition Assay (Performed by WuXi AppTec): Please see accompanying Microsoft Excel file.

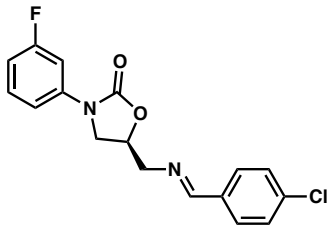
Procedures and Spectroscopic Data for the Synthesis of Linezolid Analogues



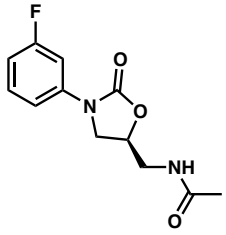
(*S*)-1-chloro-3-((4-chlorobenzylidene)amino)propan-2-ol (3). To a solution of benzaldehyde (25 g, 1 equiv) in THF (180 mL, 1M) was added aqueous ammonia (28 wt %, 18 mL, 1.5 equiv). The mixture was stirred at rt for 20 min. Then, (*S*)-epichlorohydrin (13.9 mL, 1.0 equiv) was added. The reaction was stirred at 30 °C for 4 h, then at 40 °C for 12 h. with a reflux condenser attached. Then, another 18 mL aq. NH_3 was added and stirring was continued at 40 °C for another 12 h. The solvent was concentrated under reduced pressure. 50 mL PhMe was added and then removed under reduced pressure to azeotrope remaining volatiles. The aqueous solution was then extracted with EtOAc (3x50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was recrystallized using hot hexanes, rinsed with hexanes, and isolated as white needles (22.7 g, 55% yield). Product identity matched previously reported characterization data.[1]



benzyl (3-fluorophenyl)carbamate (4). To a solution of 3-fluoroaniline (5 g, 1 equiv) and K_2CO_3 (7.46 g, 1.2 equiv) in THF at rt was added CbzCl (7 mL, 1.1 equiv). The solution was stirred at rt for 5 h and then quenched with 200 mL sat. Na_2CO_3. The layers were separated and the organic layer was washed with Na_2CO_3 (2x). The combined aqueous layers were extracted with CH_2Cl_2 (4x). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude mixture was triturated with hexanes at rt: after cooling at -20 °C, the white precipitate was isolated by filtration and used in the next step. Product identity matched previously reported characterization data.[2]



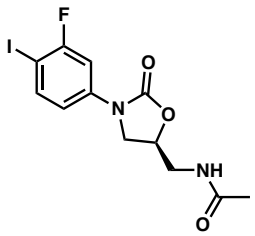
(*S*)-5-(((4-chlorobenzylidene)amino)methyl)-3-(3-fluorophenyl)oxazolidin-2-one (5). To a solution of carbamate **4** (4 g, 1 equiv) and LiOtBu (3.27 g, 2.5 equiv) in CH_2Cl_2 (22 mL, 0.75 M) was added a solution of imine **3** in CH_2Cl_2 (11 mL, 2.27 M). The reaction was refluxed for 16 h, and then allowed to cool to rt before being quenched with half saturated brine. The solution was extracted with CH_2Cl_2 (4x30 mL). Addition H_2O and CH_2Cl_2 were added to clear emulsions formed in the separatory funnel. The combined organic layers were dried over Na_2SO_4, filtered over celite to remove suspended particles, and then concentrated under reduced pressure. The crude product was triturated by adding hot Et_2O, which solvated the byproduct, but left the product unsolvated. The hot Et_2O was allowed to cool to rt and then the product was isolated by filtration and rinsed with cold Et_2O to provide the imine **5** as a white fluffy solid (4.73 g, 87% yield); **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 8.35 (s, 1H), 7.62 (d, J = 8.3 Hz, 2H), 7.54 – 7.14 (m, 5H), 6.84 (td, J = 8.2, 2.5 Hz, 1H), 4.97 (dq, J = 8.9, 5.2 Hz, 1H), 4.29 – 4.04 (m, 2H), 4.04 – 3.79 (m, 2H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 163.21 (d, J_{CF} = 245.0 Hz), 163.68, 154.45, 139.94 (d, J_{CF} = 10.7 Hz), 137.44, 134.09, 130.35 (d, J_{CF} = 9.4 Hz), 129.66, 129.10, 113.43 (d, J_{CF} = 3.0 Hz), 110.85 (d, J_{CF} = 21.2 Hz), 105.90 (d, J_{CF} = 26.9 Hz), 71.90, 63.28, 48.27; **IR (Neat Film, NaCl)** 3746, 2360, 1748, 1646, 1614, 1495, 1456, 1405, 1224, 1195, 1168, 1087, 837 cm^{-1}; **HRMS (MM: ESI-APCI)** *m/z* calc'd for $C_{17}H_{15}FN_2O_2$ $[M+H]^+$: 333.0801, found 333.0803. **$[\alpha]_D^{22.7}$** –99.9 (c 2.0, $CHCl_3$).



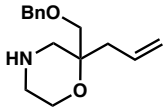
(*S*)-*N*-((3-(3-fluorophenyl)-2-oxooxazolidin-5-yl)methyl)acetamide (6). To a solution of imine **5** in a 1:1 mixture of EtOAc/H_2O (80 mL, 0.17 M) was added concentrated HCl (2.26 mL, 2 equiv). The reaction was stirred at rt for 5 h and then slowly quenched with $NaHCO_3$(aq). Then, KOH was added until pH = 14. The solution was extracted with EtOAc (4x40 mL) and CH_2Cl_2 (4x40 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was triturated with Et_2O to afford crude amine, which was used in the next step without purification.

To a solution of crude amine in CH_2Cl_2 (45 mL, 0.3 M) was added NEt_3 (3.78 mL, 2 equiv) followed by Ac_2O (2.55 mL, 2 equiv). The reaction was stirred for 2 h at rt and then quenched with H_2O. Following extraction with EtOAc (3x20 mL) and drying with Na_2SO_4, the combined organic layers were concentrated under reduced pressure. The crude product was dissolved in a minimal amount of hot CH_2Cl_2 and then Et_2O was added. The solution was left overnight at -20 °C, resulting in crystallization of pure **6**. The solid product

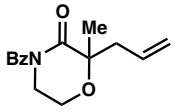
(3.28 g, was isolated by filtration and rinsed with Et_2O. Product identity matched previously reported characterization data.



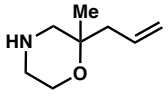
(S)-N-((3-(3-fluoro-4-iodophenyl)-2-oxooxazolidin-5-yl)methyl)acetamide (7). To a solution of **(*S*)-*N*-((3-(3-fluorophenyl)-2-oxooxazolidin-5-yl)methyl)acetamide (6)** (2.9 g, 1 equiv) in TFA (12 mL, 1M) was added NIS (2.72 g, 1.05 equiv) portion-wise. The reaction was stirred for 1 h at rt. While stirring, the exothermic reaction turned pinked. Next, the TFA was concentrated off under reduced pressure. The crude mixture was diluted with $Na_2S_2O_3$ (10%), and then KOH was added until pH = 14. Next the solution was diluted to ~700 mL volume with H_2O. Extraction with CH_2Cl_2 (4x50 mL) and EtOAc (4x50 mL) was followed by drying with Na_2SO_4 and concentration of the combined organic layers under reduced pressure. The crude product was then purified by silica gel flash chromatography (5 → 10% MeOH/CH_2Cl_2) to afford the desired iodinated compound **7** (4 g, 92% yield). Product identity matched previously reported characterization data.[4]



2-allyl-2-((benzyloxy)methyl)morpholine (11). Prepared according to literature procedure.[5] Product identity matched previously reported characterization data.[5]



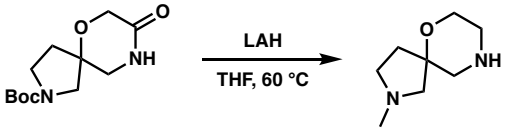
2-allyl-4-benzoyl-2-methylmorpholin-3-one.[5] Prepared according to an adapted procedure from our publications:[5,6] In the glove box, in a 100 mL Schlenck bomb, Pd(OAc) (2.7 mg, 0.005 equiv), GlyPHOX[7,8] (16 mg, 0.02 equiv), and MTBE (5 mL) were added. The solution was stirred at rt for 30 min. Then, allyl 4-benzoyl-2-methyl-3-oxomorpholine-2-carboxylate[5] dissolved in 10 mL toluene was added. The reaction was heated to 60 °C for 5 h, at which time TLC analysis showed complete consumption of starting material. The solution was loaded onto a silica gel flash column and purified (10 → 20% EtOAc/Hexanes) to afford racemic **2-allyl-4-benzoyl-2-methylmorpholin-3-one** as a white solid (620 mg, 98% yield). Product identity matched previously reported characterization data.[5]



2-allyl-2-methylmorpholine (10). To a solution of **2-allyl-4-benzoyl-2-methylmorpholin-3-one** (620 mg, 1 equiv) in iPrOH (60 mL, 0.04 M) was added LiOH-H_2O (150 mg, 1.5 equiv) dissolved in H_2O (16 mL, 0.15 M). The reaction was stirred at

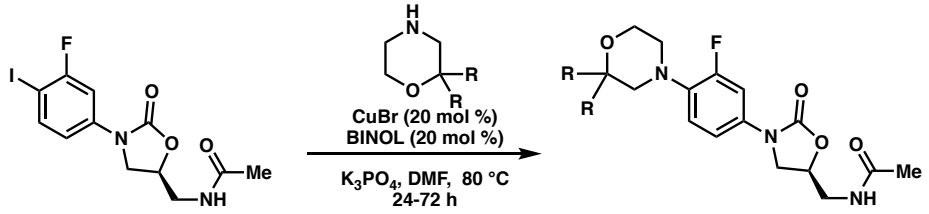
room temperature for 2 h and then concentrated into SiO2. The dry-loaded crude product was purified by silica gel flash chromatography (2.5 → 5% MeOH/CH_2Cl_2) to afford the deprotected lactam, which was carried onto the next step:

To a solution of deprotected lactam (370 mg, 1 equiv) in THF (24 mL, 0.1 M) was added LAH (271 mg, 3 equiv) portionwise at 0 °C. The reaction was then heated to 50 °C for 2 h. A Fieser workup was performed: the reaction was diluted with Et_2O (12 mL) at 0 °C, then the following were slowly and sequentially added at 0 °C: 270 uL H_2O, 270 uL 15% aq. NaOH, and lastly 800 uL H_2O. The suspension was stirred at 0 °C for 15 min and then $MgSO_4$ was added. The mixture was allowed to warm to rt and then filtered over celite, rinsing with EtOAc. The solvent was concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography (5 → 10% MeOH/CH_2Cl_2) to yield racemic **10** as a clear oil (305 mg, 90% yield over two steps); **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 5.80 (dddd, *J* = 14.6, 12.9, 6.1, 3.8 Hz, 1H), 5.14 – 5.02 (m, 2H), 3.67 (dq, *J* = 5.7, 3.3, 2.7 Hz, 2H), 2.79 (q, *J* = 4.4, 4.0 Hz, 2H), 2.74 – 2.57 (m, 2H), 2.48 (dt, *J* = 12.1, 5.5 Hz, 1H), 2.21 (dt, *J* = 12.7, 5.9 Hz, 1H), 2.06 (d, *J* = 7.5 Hz, 1H), 1.26 – 1.10 (m, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 133.6, 117.9, 72.1, 61.6, 54.3, 46.0, 41.7, 22.0; **IR (Neat Film, NaCl)** 3335, 3074,2973, 2938, 2868, 2818, 2741,2360, 1639, 1455, 1375, 1324, 1259, 1200, 1177, 1130, 1084, 997, 914, 852, 797, 750, 669 cm^{-1}; **HRMS (MM: ESI-APCI)** *m/z* calc'd for $C_8H_{16}NO$ $[M+H]^+$: 142.1226, found 142.1229.



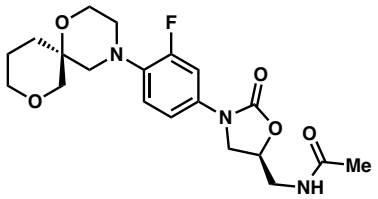
2-methyl-6-oxa-2,9-diazaspiro[4.5]decane (SI5). To a solution of *tert*-butyl 8-oxo-6-oxa-2,9-diazaspiro[4.5]decane-2-carboxylate (100 mg, 1 equiv) in THF (3.9 mL, 0.1 M) at 0 °C was slowly added LAH (59 mg, 4 equiv). The reaction was stirred at 60 °C for 6 h and then allowed to cool to ambient temperature. A Fieser workup was performed: the reaction was diluted two-fold with Et_2O at 0 °C, then the following were slowly and sequentially added at 0 °C: 60 uL H_2O, 60 uL 15% aq. NaOH, and lastly 180 uL H_2O. The suspension was stirred at 0 °C for 15 min and then $MgSO_4$ was added. The mixture was allowed to warm to rt and then filtered over celite, rinsing with EtOAc. The solvent was concentrated under reduced pressure. The crude product was used without further purification.

Preparation of linezolid analogues via Cu-Catalyzed Ullman Coupling

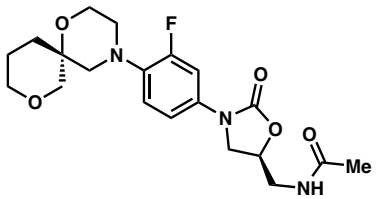


To a flame-dried one-dram vial equipped with a Teflon screw cap and a stir bar was added CuBr (0.1 - 0.3 equiv), BINOL (0.1 - 0.3 equiv), aryl iodide **7** (1 equiv), and K_3PO_4 (2 equiv). The vial was cycled into a glovebox and then DMF (0.2 M final concentration) was

added to the vial, followed by the amine (2 equiv). The reaction was stirred at 80 °C for 24-72 hours until complete consumption of starting material was noted by LC-MS analysis. In some cases, conversion of the starting material stopped, at which point 0.2 equiv of CuBr and 0.2 equiv of BINOL was added to the reaction, which then proceeded to completion. The reaction was diluted with EtOAc and filtered through a plug of silica, rinsing with 10% MeOH/EtOAc. The solution was concentrated in vacuo until all DMF solvent was removed. The crude material was purified by by silica gel flash chromatography or reverse phase prep HPLC to afford the desired linezolid analog.

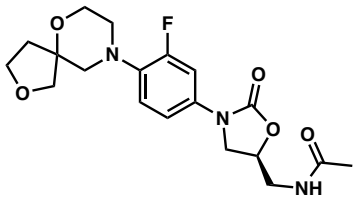


N-(((*S*)-3-(3-fluoro-4-((*S*)-1,8-dioxa-4-azaspiro[5.5]undecan-4-yl)phenyl)-2-oxooxazolidin-5-yl)methyl)acetamide (**19a**). Prepared according to the general procedure using: CuBr (2.3 mg, 0.016 mmol, 0.2 equiv), BINOL (4.5 mg, 0.016 mmol, 0.2 equiv), aryl iodide **7** (30 mg, 0.079 mmol, 1 equiv), K_3PO_4 (34 mg, 0.16 mmol, 2 equiv), enantiopure **(*S*)-1,8-dioxa-4-azaspiro[5.5]undecane (SI2a)** (18 mg, 0.16 mmol, 2 equiv), and 400 uL DMF. The crude residue was purified by silica gel flash chromatography (2 → 3 → 5% MeOH/CH_2Cl_2) to yield spirotetrahydropyran analogue **19a** (8 mg, 28% yield) as a clear oil: **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.40 (dd, *J* = 14.1, 2.6 Hz, 1H), 7.04 (ddd, *J* = 8.8, 2.6, 1.1 Hz, 1H), 6.88 (t, *J* = 9.1 Hz, 1H), 6.39 (t, *J* = 6.2 Hz, 1H), 4.76 (dddd, *J* = 8.8, 6.7, 5.5, 3.3 Hz, 1H), 4.00 (t, *J* = 9.0 Hz, 1H), 3.91 (t, *J* = 4.9 Hz, 2H), 3.85 – 3.77 (m, 1H), 3.74 (dd, *J* = 9.2, 6.7 Hz, 1H), 3.71 – 3.54 (m, 5H), 3.09 – 2.94 (m, 2H), 2.92 (s, 2H), 2.01 (s, 3H), 1.95 – 1.78 (m, 3H), 1.58 (dddd, *J* = 14.3, 11.4, 6.8, 2.4 Hz, 1H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 171.3, 155.6 (d, J_{CF} = 246.5 Hz), 154.5, 136.9 (d, J_{CF} = 9.0 Hz), 133.0 (d, J_{CF} = 10.3 Hz), 119.2 (d, J_{CF} = 4.0 Hz), 114.0 (d, *J* = 3.4 Hz), 107.6 (d, *J* = 26.1 Hz), 72.1, 71.7, 70.0, 68.7, 61.0, 56.9, 50.8, 47.8, 42.0, 31.0, 23.2, 22.4; **IR (Neat Film, NaCl)** 3312, 3073, 2953, 2846, 2244, 1748, 1660, 1517, 1486, 1446, 1416, 1374, 1324, 1279, 1225, 1196, 1097, 1044, 985, 910, 871, 809, 732, 674, 646 cm^{-1}; **HRMS (MM: ESI-APCI)** *m/z* calc'd for $C_{20}H_{27}FN_3O_5$ $[M+H]^+$: 408.1929, found 408.1909 **$[\alpha]_D^{22.7}$** –20.8 (c 1.5, $CHCl_3$).

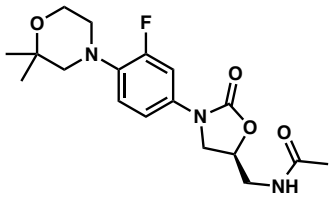


***N*-(((*S*)-3-(3-fluoro-4-((*R*)-1,8-dioxa-4-azaspiro[5.5]undecan-4-yl)phenyl)-2-oxooxazolidin-5-yl)methyl)acetamide (19b)**. Prepared according to the general procedure using: CuBr (2.3 mg, 0.016 mmol, 0.2 equiv), BINOL (4.5 mg, 0.016 mmol, 0.2 equiv), aryl iodide **7** (30 mg, 0.079 mmol, 1 equiv), K_3PO_4 (34 mg, 0.16 mmol, 2 equiv), enantiopure **(*R*)-1,8-dioxa-4-azaspiro[5.5]undecane (SI2b)** (18 mg, 0.16 mmol, 2 equiv), and 400 uL DMF. The crude residue was purified by silica gel flash chromatography (2 → 3 → 5% MeOH/CH_2Cl_2) to yield spirotetrahydropyran analogue **19b** (10 mg, 32% yield) as a clear oil: **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.43 (dd, *J* = 14.1, 2.6 Hz, 1H), 7.06

(ddd, *J* = 8.8, 2.7, 1.1 Hz, 1H), 6.91 (t, *J* = 9.1 Hz, 1H), 6.06 (t, *J* = 6.2 Hz, 1H), 4.76 (dddd, *J* = 8.9, 6.7, 5.8, 3.2 Hz, 1H), 4.02 (t, *J* = 9.0 Hz, 1H), 3.93 (t, *J* = 4.9 Hz, 2H), 3.81 (d, *J* = 11.7 Hz, 1H), 3.78 – 3.55 (m, 6H), 3.08 – 2.96 (m, 2H), 2.94 (s, 2H), 2.02 (s, 3H), 1.96 – 1.77 (m, 3H), 1.59 (dddd, *J* = 15.1, 12.8, 6.9, 2.4 Hz, 2H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 171.1, 155.6 (d, *J* = 246.6 Hz), 154.3, 136.81 (d, *J* = 8.9 Hz), 133.06 (d, *J* = 10.4 Hz), 119.27 (d, *J* = 4.0 Hz), 113.99 (d, *J* = 3.5 Hz), 107.62 (d, *J* = 26.2 Hz), 71.9, 71.7, 70.0, 68.7, 60.9, 56.9, 50.8, 47.7, 42.1, 31.0, 23.3, 22.5; **IR (Neat Film, NaCl)** 3318, 3067, 2927, 2850, 1748, 1667, 1516, 1486, 1416, 1374, 1326, 1277, 1225, 1097, 939, 870, 815, 733 cm^{-1}; **HRMS (MM: ESI-APCI)** *m/z* calc'd for $C_{20}H_{27}FN_3O_5$ $[M+H]^+$: 408.1929, found 408.1932. **$[\alpha]_D^{22.7}$** +1.7 (c 1.0, $CHCl_3$).

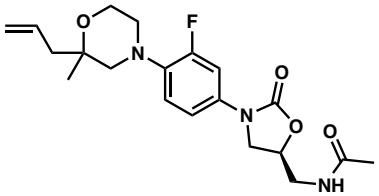


***N*-(((5*S*)-3-(3-fluoro-4-(2,6-dioxa-9-azaspiro[4.5]decan-9-yl)phenyl)-2-oxooxazolidin-5-yl)methyl)acetamide (18).** Prepared according to the general procedure using: CuBr (7.5 mg, 0.052 mmol, 0.3 equiv), BINOL (15.0 mg, 0.052 mmol, 0.3 equiv), aryl iodide **7** (66 mg, 0.17 mmol, 1 equiv), K_3PO_4 (74 mg, 0.35 mmol, 2 equiv), **2,6-dioxa-9-azaspiro[4.5]decane (**50 mg, 0.35 mmol, 2 equiv), and 873 uL DMF. The crude residue was purified by reverse phase preparatory HPLC (0 → 100% MeCN/H_2O gradient over 10 minutes, 30x250 mm C_{18} column, 60 mL/min flow rate) to yield spirotetrahydrofuran analogue **18** (35 mg, 51% yield) as a clear oil. Note: HPLC H_2O solvent contained 0.25% TFA: **^{1}H NMR (400 MHz, Chloroform-*d*)** δ (Note TFA appears in the ^{1}H and ^{13}C NMR) 7.41 (dd, *J* = 14.0, 2.6 Hz, 1H), 7.05 (ddd, *J* = 8.8, 2.6, 1.1 Hz, 1H), 6.92 (t, *J* = 9.0 Hz, 1H), 4.82 (dddd, *J* = 8.8, 6.4, 5.1, 3.6 Hz, 1H), 4.14 – 3.83 (m, 7H), 3.79 (dd, *J* = 9.3, 6.4 Hz, 1H), 3.75 – 3.65 (m, 2H), 3.03 (d, *J* = 5.2 Hz, 4H), 2.24 – 2.13 (m, 2H), 2.13 – 2.00 (m, 4H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 171.4, 155.6 (d, *J* = 246.6 Hz), 154.5, 136.4 (d, *J* = 9.0 Hz), 133.3 (d, *J* = 10.4 Hz), 119.1 (d, *J* = 4.0 Hz), 114.0 (d, *J* = 3.3 Hz), 107.6 (d, *J* = 26.1 Hz), 82.6, 75.5, 72.1, 67.6, 63.1, 57.9, 50.1, 47.7, 42.0, 36.4, 23.2; **IR (Neat Film, NaCl)** 3304, 3070, 2955, 2870, 1751, 1662, 1517, 1446, 1415, 1374, 1326, 1278, 1227, 1195, 1083, 1060, 992, 919, 731 cm^{-1}; **HRMS (MM: ESI-APCI)** *m/z* calc'd for $C_{19}H_{25}FN_3O_5$ $[M+H]^+$: 394.1773 found 394.1779. **$[\alpha]_D^{2.8}$** –5.54 (c 1.0, $CHCl_3$).

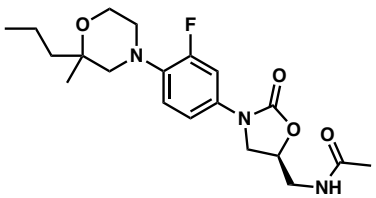


(S)-N-((3-(4-(2,2-dimethylmorpholino)-3-fluorophenyl)-2-oxooxazolidin-5-yl)methyl)acetamide (12). Prepared according to the general procedure using: CuBr (2.3 mg, 0.016 mmol, 0.2 equiv), BINOL (4.5 mg, 0.016 mmol, 0.2 equiv), aryl iodide **7** (30 mg, 0.079 mmol, 1 equiv), K_3PO_4 (34 mg, 0.16 mmol, 2 equiv), dimethyl morpholine (18 mg, 0.16 mmol, 2 equiv), and 400 uL DMF. The crude residue was purified by silica gel

flash chromatography (2 → 3 → 5% MeOH/CH_2Cl_2) to yield dimethyl analogue **12** (8 mg, 28% yield) as a clear oil: **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.42 (dd, *J* = 14.2, 2.6 Hz, 1H), 7.05 (ddd, *J* = 8.8, 2.6, 1.1 Hz, 1H), 6.88 (t, *J* = 9.1 Hz, 1H), 6.16 (t, *J* = 6.2 Hz, 1H), 4.76 (dddd, *J* = 8.9, 6.7, 5.7, 3.3 Hz, 1H), 4.01 (t, *J* = 9.0 Hz, 1H), 3.92 – 3.85 (m, 2H), 3.80 – 3.65 (m, 2H), 3.61 (dt, *J* = 14.7, 6.1 Hz, 1H), 3.01 – 2.93 (m, 2H), 2.81 (s, 2H), 2.02 (s, 3H), 1.34 (s, 6H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 171.2, 155.6 (d, J_{CF} = 247.5 Hz), 154.45, 137.1 (d, J_{CF} = 9.1 Hz), 132.71 (d, J_{CF} = 10.1 Hz), 119.02 (d, J_{CF} = 4.0 Hz), 114.03 (d, J_{CF} = 4.0 Hz), 107.7 (d, J_{CF} = 133.3 Hz), 72.0, 71.6, 61.4, 60.89, 60.86, 50.5, 47.8, 42.1, 24.8, 23.3; δ **IR (Neat Film, NaCl)** 3300, 2971, 1748, 1659, 1517, 1415, 1366, 1325, 1272, 1224, 1194, 1100, 987, 862, 752 cm^{-1}; **HRMS (MM: ESI-APCI)** *m/z* calc'd for $C_{18}H_{25}FN_3O_4$ $[M+H]^+$: 366.1824, found 366.1827 **$[\alpha]_D^{22.8}$** –5.60 (c 0.5, $CHCl_3$).

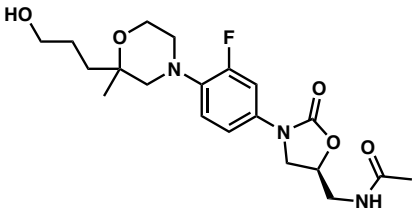


***N*-(((5*S*)-3-(4-(2-allyl-2-methylmorpholino)-3-fluorophenyl)-2-oxooxazolidin-5-yl)methyl)acetamide (13).** Prepared according to the general procedure using: CuBr (9.1 mg, 0.064 mmol, 0.3 equiv), BINOL (18 mg, 0.064 mmol, 0.3 equiv), aryl iodide **7** (80 mg, 0.21 mmol, 1 equiv), K_3PO_4 (90 mg, 0.42 mmol, 2 equiv), methallyl morpholine **10** (60 mg, 0.42 mmol, 2 equiv), and 1.1 mL DMF. The crude residue was purified by reverse phase preparatory HPLC (50 → 70% MeCN/H_2O gradient over 7 minutes, 30x250 mm C_{18} column, 60 mL/min flow rate) to yield methallyl analogue **13** (45 mg, 54% yield) as a light brown oil; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.40 (dd, *J* = 14.1, 2.6 Hz, 1H), 7.04 (dd, *J* = 8.8, 2.6 Hz, 1H), 6.90 (t, *J* = 9.1 Hz, 1H), 6.74 (t, *J* = 6.2 Hz, 1H), 5.93 – 5.78 (m, 1H), 5.17 – 5.07 (m, 2H), 4.85 – 4.75 (m, 1H), 4.05 (t, *J* = 9.0 Hz, 1H), 3.91 (td, *J* = 4.6, 2.8 Hz, 2H), 3.81 – 3.59 (m, 3H), 3.05 – 2.95 (m, 2H), 2.90 (dd, *J* = 11.6, 1.1 Hz, 1H), 2.79 (dd, *J* = 11.6, 1.0 Hz, 1H), 2.66 (dd, *J* = 14.1, 7.1 Hz, 1H), 2.34 (ddt, *J* = 14.1, 7.5, 1.2 Hz, 1H), 2.07 (s, 3H), 1.29 (s, 3H): **^{13}C NMR (101 MHz, $CDCl_3$)** δ 172.9 (C=O), 155.6 (d, J_{CF} = 247.5 Hz), 154.9 (C=O), 137.1 (d, J_{CF} = 8.1 Hz), 133.4, 132.5 (d, J_{CF} = 10.1 Hz), 119.2 (d, J_{CF} = 4.0 Hz), 118.3, 114.3 (d, J_{CF} = 4.0 Hz), 107.9 (d, J_{CF} = 26.3 Hz), 73.5, 72.0, 61.1, 59.7, 50.4, 47.9, 42.3, 41.5, 22.9, 22.4; δ **IR (Neat Film, NaCl)** 3300, 3077, 2976, 2822, 1752, 1662, 1546, 1517, 1486, 1445, 1415, 1377, 1326, 1269, 1222, 1196, 1172, 1086, 995, 918, 867, 817, 750, 703 cm^{-1}; **HRMS (MM: ESI-APCI)** *m/z* calc'd for $C_{20}H_{27}FN_3O_4$ $[M+H]^+$: 392.1980, found 392.1976 **$[\alpha]_D^{23.0}$** –4.55 (c 1.0, $CHCl_3$).

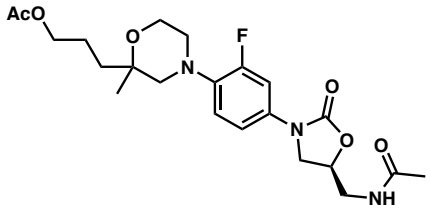


N-(((5*S*)-3-(3-fluoro-4-(2-methyl-2-propylmorpholino)phenyl)-2-oxooxazolidin-5-yl)methyl)acetamide (22). To a solution of methallyl analogue **13** (12 mg, 0.031 mmol, 1 equiv) in MeOH (300 uL, 0.1 M) was added Pd/C (10% wt/wt, 3.3 mg, 0.1 equiv). The

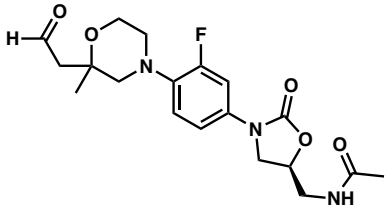
reaction vial was evacuated and backfilled with H_2 three times, and then sparged with H_2 for 5 min. The reaction was stirred for 7 h and then the Pd/C was filtered off through a plug of celite, rinsing with EtOAc. The solution was concentrated under reduced pressure and purified by silica gel flash chromatography (2 → 5% MeOH/CH_2Cl_2) to yield the methyl-propyl analogue **22** as a clear oil (10 mg, 83% yield); **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.41 (ddd, *J* = 14.2, 2.5, 0.9 Hz, 1H), 7.04 (ddq, *J* = 8.8, 2.6, 1.0 Hz, 1H), 6.89 (t, *J* = 9.1 Hz, 1H), 6.52 – 6.28 (m, 1H), 4.78 (dddd, *J* = 8.9, 6.6, 5.8, 3.2 Hz, 1H), 4.03 (t, *J* = 9.0 Hz, 1H), 3.86 (tdd, *J* = 11.6, 5.7, 4.3 Hz, 2H), 3.79 – 3.67 (m, 2H), 3.63 (dt, *J* = 14.7, 6.1 Hz, 1H), 3.05 – 2.92 (m, 2H), 2.83 (q, *J* = 11.5 Hz, 2H), 2.06 (s, 3H), 1.84 (ddd, *J* = 12.9, 10.3, 6.0 Hz, 1H), 1.55 – 1.31 (m, 3H), 1.29 (s, 3H), 0.95 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 172.2, 155.6 (d, J_{CF} = 246.7 Hz), 154.6, 137.2 (d, J_{CF} = 8.8 Hz), 132.5 (d, J_{CF} = 10.3 Hz), 119.1 (d, J_{CF} = 4.2 Hz), 114.1 (d, J_{CF} = 3.3 Hz), 107.8 (d, J_{CF} = 26.3 Hz), 73.6, 71.9, 61.0, 60.1, 60.1, 50.4, 50.4, 47.8, 42.2, 39.6, 23.0, 22.0, 16.4, 14.8. **IR (Neat Film, NaCl)** 3297, 3074, 2957, 2872, 1753, 1659, 1517, 1485, 1448, 1414, 1377, 1326, 1278, 1226, 1195, 1101,1087, 994, 919, 867, 750 cm^{-1}; **HRMS (MM: ESI-APCI)** *m/z* calc'd for $C_{20}H_{29}FN_3O_4$ $[M+H]^+$: 394.2137, found 394.2147 **$[\alpha]_D^{22.0}$** –8.45 (c 0.7, $CHCl_3$).



N-(((5S)-3-(3-fluoro-4-(2-(3-hydroxypropyl)-2-methylmorpholino)phenyl)-2-oxooxazolidin-5-yl)methyl)acetamide (20). In a glovebox, to a solution of methallyl analogue **13** (20 mg, 0.051 mmol, 1 equiv) in THF (500 uL, 0.1 M), was added 9-BBN dimer (25 mg, 0.10 mmol, 2 equiv). The reaction was stirred for 3 h at ambient temperature amd then taken out of the glovebox. Then, a solution of $NaBO_3 \cdot 4H_2O$ in H_2O (500 uL) was added and the mixture was stirred for 2 h before being concentrated down. The crude residue was purified by reverse phase preparatory HPLC (0 → 100% MeCN/H_2O gradient over 10 minutes, 30x250 mm C_{18} column, 60 mL/min flow rate) to yield hydroxyl analogue **20** (4 mg, 19% yield) as a clear oil; **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.42 (dd, *J* = 14.2, 2.6 Hz, 1H), 7.05 (ddq, *J* = 8.8, 2.5, 1.1 Hz, 1H), 6.89 (td, *J* = 9.1, 1.3 Hz, 1H), 6.31 (q, *J* = 6.0 Hz, 1H), 4.83 – 4.73 (m, 1H), 4.47 – 4.32 (m, 1H), 4.03 (t, *J* = 9.0 Hz, 1H), 3.96 – 3.80 (m, 2H), 3.80 – 3.68 (m, 3H), 3.68 – 3.56 (m, 1H), 2.87 (q, *J* = 6.8, 5.0 Hz, 5H), 2.05 (s, 3H), 1.95 – 1.81 (m, 2H), 1.75 – 1.69 (m, 1H), 1.64 – 1.52 (m, 1H), 1.33 (d, *J* = 23.0 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 172.0, 155.6 (d, *J* = 246.7 Hz), 154.6, 137.0 (d, *J* = 8.9 Hz), 132.7 (d, *J* = 10.4 Hz), 119.1 (dd, *J* = 4.1, 1.9 Hz), 114.1 (d, *J* = 3.3 Hz), 107.7 (d, *J* = 26.1 Hz), 73.6, 72.9, 71.9, 68.6, 63.4, 61.2, 61.1, 60.3, 60.3, 60.1, 60.1, 50.3, 50.2, 50.3, 47.8, 42.2, 34.8, 32.6, 26.3, 23.1, 22.2, 22.1, 21.4. **IR (Neat Film, NaCl)** 3314, 2937, 1783, 1747, 1666, 1517, 1486, 1416, 1379, 1223, 1168, 1100, 866, 820, 745, 667 cm^{-1}; **HRMS (MM: ESI-APCI)** *m/z* calc'd for $C_{20}H_{29}FN_3O_4$ $[M+H]^+$: 410.2086, found 410.2084 **$[\alpha]_D^{24.3}$** –6.35 (c 0.33, $CHCl_3$).

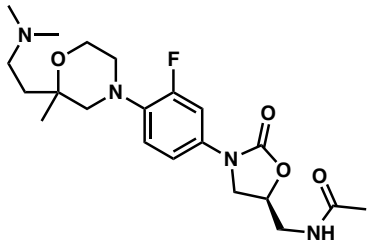


3-(4-(4-((*S*)-5-(acetamidomethyl)-2-oxooxazolidin-3-yl)-2-fluorophenyl)-2-methylmorpholin-2-yl)propyl acetate (**21**). To a solution of hydroxyl analogue **20** (4 mg, 1 equiv) in CH_2Cl_2 (200 uL, 0.05 M) was added NEt_3 (4 uL, 3 equiv) and AcCl (1 uL, 2 equiv). The solution was stirred at rt for 4 h, then concentrated, and purified by silica gel flash chromatography (3 → 5% MeOH/CH_2Cl_2) to give acetylated analogue **21** as a clear oil (3 mg, 68% yield). **1H NMR (400 MHz, Chloroform-*d*)** δ 7.42 (ddd, *J* = 14.2, 2.5, 0.9 Hz, 1H), 7.06 (dddt, *J* = 8.7, 2.7, 1.9, 1.0 Hz, 1H), 6.88 (t, *J* = 9.1 Hz, 1H), 6.11 (t, *J* = 6.3 Hz, 1H), 4.76 (dddd, *J* = 8.9, 6.6, 5.7, 3.2 Hz, 1H), 4.47 – 4.32 (m, 1H), 4.10 (td, *J* = 6.6, 5.2 Hz, 1H), 4.02 (t, *J* = 9.0 Hz, 1H), 3.88 – 3.80 (m, 2H), 3.76 – 3.66 (m, 2H), 3.65 – 3.58 (m, 1H), 2.97 (t, *J* = 4.9 Hz, 2H), 2.86 (d, *J* = 11.6 Hz, 1H), 2.80 (dd, *J* = 11.5, 1.6 Hz, 1H), 2.04 (d, *J* = 11.9 Hz, 6H), 1.86 (d, *J* = 6.7 Hz, 2H), 1.75 – 1.70 (m, 1H), 1.57 – 1.51 (m, 1H), 1.30 (d, *J* = 2.6 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 171.0, 171.2, 156.8, 154.4, 136.9 (dd, J_{CF} = 12.6, 9.0 Hz), 132.8 (t, J_{CF} = 10.5 Hz), 119.1 (t, J_{CF} = 3.5 Hz), 114.0 (d, J_{CF} = 3.3 Hz), 107.6 (d, J_{CF} = 26.2 Hz), 73.0, 71.9, 68.7, 65.0, 61.1, 60.1, 50.3, 47.8, 42.1, 23.2, 22.6, 22.1, 21.1. **IR (Neat Film, NaCl)** 3311, 3063, 2962, 1747, 1667, 1516, 1415, 1371, 1222,1169, 1087, 1036, 919, 867, 803, 737, 703 cm^{-1}; **HRMS (MM: ESI-APCI)** *m/z* calc'd for $C_{22}H_{31}FN_3O_6$ $[M+H]^+$: 452.2191, found 452.2185 **$[\alpha]_D^{24.0}$** +3.67 (c .33, $CHCl_3$).

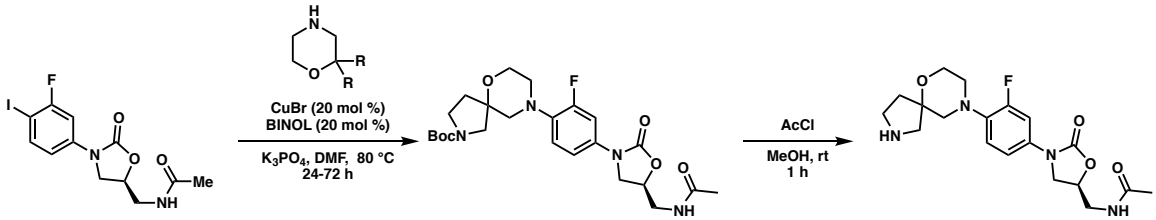


***N*-(((5*S*)-3-(3-fluoro-4-(2-methyl-2-(2-oxoethyl)morpholino)phenyl)-2-oxooxazolidin-5-yl)methyl)acetamide** (**SI4**). To a solution of methallyl analogue **13** (54 mg, 1 equiv) in 2:1 THF/H_2O (14 mL, 0.01 M) was added a solution of OsO_4 in PhMe (87 uL, 0.079 M, 0.05 equiv) followed by NaIO4 (89 mg, 3 equiv) The reaction was stirred for 16 h at ambient temperature, and was then quenched with $Na_2S_2O_3$. The mixture was extracted with EtOAc (5x) and the combined organic layers were dried over Na_2SO_4. The residue was purified by silica gel chromatography (10 → 20% → 30% MeOH/CH_2Cl_2) to yield dimethylamino analogue **SI4** (15 mg, 94% yield) as a yellow oil. **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 9.89 (t, *J* = 2.9 Hz, 1H), 7.42 (dd, *J* = 14.1, 2.6 Hz, 1H), 7.06 (ddd, *J* = 8.8, 2.6, 1.2 Hz, 1H), 6.89 (t, *J* = 9.1 Hz, 1H), 6.21 (t, *J* = 6.2 Hz, 1H), 4.76 (dddd, *J* = 8.9, 6.7, 5.7, 3.3 Hz, 1H), 4.07 – 3.78 (m, 3H), 3.78 – 3.56 (m, 3H), 3.10 – 3.02 (m, 2H), 3.02 – 2.89 (m, 2H), 2.82 (d, *J* = 11.7 Hz, 1H), 2.63 (dd, *J* = 15.4, 2.9 Hz, 1H), 2.02 (s, 3H), 1.44 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 201.9, 171.2, 155.7 (d, *J* = 246.5 Hz), 154.4, 136.4 (d, *J* = 9.1 Hz), 133.2 (d, *J* = 10.4 Hz), 119.3 (d, *J* = 3.9 Hz), 114.0 (d, *J* = 3.3 Hz),

107.6 (d, J = 26.1 Hz), 72.7, 72.0, 61.4, 60.0, 50.3, 49.5, 47.7, 42.0, 23.7, 23.2; **IR (Neat Film, NaCl)** 3316, 2937, 1748, 1659, 1517, 1415,1379,1279, 1225,1085, 868, 751 cm^{-1}; **HRMS (MM: ESI-APCI)** *m/z* calc'd for $C_{19}H_{25}FN_3O_5$ $[M+H]^+$: 394.1773, found 394.1770 $[\alpha]_D^{25.3}$ +3.97 (c .47, $CHCl_3$).

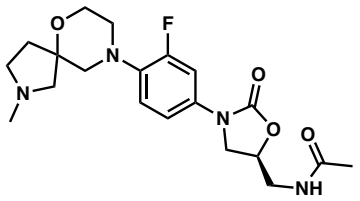


N-(((5S)-3-(4-(2-(2-(dimethylamino)ethyl)-2-methylmorpholino)-3-fluorophenyl)-2-oxooxazolidin-5-yl)methyl)acetamide (23). To a solution of aldehyde **SI4** (15 mg, 0.038 mmol, 1 equiv) in THF (400 uL, 0.1 M) was added dimethylamine (95 uL, 0.19 mmol, 5 equiv) and AcOH (2 uL, 0.038 mmol, 1 equiv). The solution was stirred for 5 min, and then $NaBH(OAc)_3$ (16 mg, 0.076 mmol, 2 equiv) was added. The reaction was stirred for 3 h at ambient temperature, and was then concentrated onto SiO_2. The silica loaded crude residue was purified by silica gel chromatography (10 → 20% → 30% $MeOH/CH_2Cl_2$) to yield dimethylamino analogue **23** (15 mg, 94% yield) as a clear oil; **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.41 (dt, J = 14.1, 2.8 Hz, 1H), 7.05 (dt, J = 9.0, 2.7 Hz, 1H), 6.86 (t, J = 9.1 Hz, 1H), 6.43 (t, J = 6.2 Hz, 1H), 4.76 (dtd, J = 9.3, 6.2, 3.4 Hz, 1H), 4.00 (t, J = 8.9 Hz, 1H), 3.84 (h, J = 6.8 Hz, 2H), 3.75 (dd, J = 9.1, 6.6 Hz, 1H), 3.68 (ddd, J = 14.6, 6.2, 3.4 Hz, 1H), 3.60 (dt, J = 14.6, 6.1 Hz, 1H), 3.02 – 2.92 (m, 4H), 2.86 (d, J = 11.6 Hz, 1H), 2.80 (d, J = 11.6 Hz, 1H), 2.66 (s, 6H), 2.46 – 2.38 (m, 1H), 2.01 (d, J = 8.8 Hz, 3H), 1.91 – 1.82 (m, 1H), 1.32 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 171.38, 155.62 (d, J = 246.1 Hz), 154.49, 136.54 (d, J = 9.1 Hz), 133.13 (d, J = 10.5 Hz), 119.19 (d, J = 4.0 Hz), 114.05 (d, J = 3.2 Hz), 107.60 (d, J = 26.3 Hz), 72.2, 72.0, 61.3, 60.1, 53.0, 50.25, 47.8, 43.2, 42.1, 31.3, 23.2, 22.3. **IR (Neat Film, NaCl)** 3250, 2924, 2270, 1750, 1669, 1554, 1517, 1484, 1413, 1381, 1325, 1278, 1226,1195, 1097, 993, 867,749, 674 cm^{-1}; **HRMS (MM: ESI-APCI)** *m/z* calc'd for $C_{21}H_{32}FN_4O_4$ $[M+H]^+$: 423.2402, found 423.2393 $[\alpha]_D^{24.0}$ –3.59 (c 1.0, $CHCl_3$).

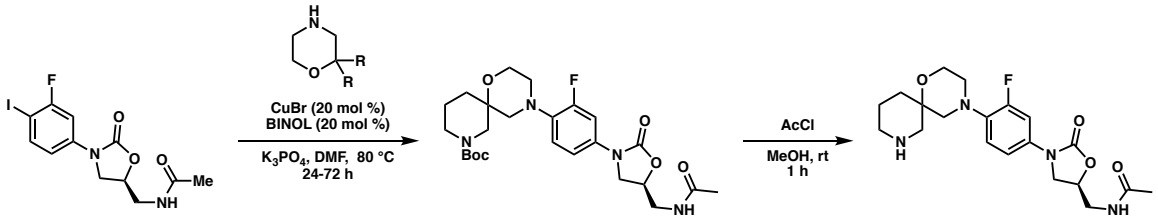


N-(((5S)-3-(3-fluoro-4-(6-oxa-2,9-diazaspiro[4.5]decan-9-yl)phenyl)-2-oxooxazolidin-5-yl)methyl)acetamide (**27**). Prepared according to the general procedure using: CuBr (2.3 mg, 0.016 mmol, 0.2 equiv), BINOL (4.5 mg, 0.016 mmol, 0.2 equiv), aryl iodide **7** (30 mg, 0.079 mmol, 1 equiv), K_3PO_4 (34 mg, 0.16 mmol, 2 equiv), 6-oxa-2,9-diazaspiro[4.5]decane (38 mg, 0.16 mmol, 2 equiv), and 400 uL DMF. The crude residue was filtered through a silica column (2 → 3 → 5 → 10% $MeOH/CH_2Cl_2$) to yield a mixture

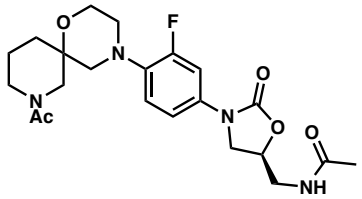
of Boc-protected spirocyclic analogue **15** and starting material aryl iodide **7**, which was carried forward to the next step: To 2.3 mL MeOH at 0 °C was added AcCl (230 uL), generating HCl *in situ*. This HCl solution was stirred for 5 min at 0°C and then transferred by syringe into a 20 mL scintillation vial containing Boc analogue **15**. The reaction was stirred for 1 h at ambient temperature and then the solvent was concentrated under reduced pressure onto SiO_2. The silica-loaded residue was purified by silica gel flash chromatography (5 → 10 → 20% MeOH/CH_2Cl_2) to yield spiropyrrolidine analogue **27** as a light yellow oil (12 mg, 40% yield over 2 steps). **^{1}H NMR (400 MHz, CD_3OD)** δ 7.53 (dd, *J* = 14.5, 2.5 Hz, 1H), 7.19 (ddd, *J* = 8.8, 2.6, 1.0 Hz, 1H), 7.08 (t, *J* = 9.2 Hz, 1H), 4.83 – 4.73 (m, 1H), 4.12 (t, *J* = 9.0 Hz, 1H), 3.94 (dd, *J* = 5.4, 4.3 Hz, 2H), 3.80 (dd, *J* = 9.2, 6.3 Hz, 1H), 3.72 (dd, *J* = 12.6, 1.6 Hz, 1H), 3.56 (d, *J* = 5.0 Hz, 2H), 3.50 – 3.40 (m, 2H), 3.26 (d, *J* = 12.6 Hz, 1H), 3.17 (d, *J* = 11.8 Hz, 1H), 3.13 – 2.97 (m, 3H), 2.42 – 2.29 (m, 1H), 2.17 – 2.00 (m, 2H), 1.96 (s, 3H); **^{13}C NMR (101 MHz, CD_3OD)** δ 174.1, 156.9 (d, *J* = 244.3 Hz), 156.6, 137.2 (d, *J* = 10.1 Hz), 135.5 (d, *J* = 10.6 Hz), 120.7 (d, *J* = 4.0 Hz), 115.5 (d, *J* = 3.0 Hz), 108.4 (d, *J* = 26.3 Hz), 82.2, 73.5, 63.5, 57.5, 52.6, 51.5, 49.2, 45.3, 43.1, 34.5, 22.4 (Note: A ^{1}H-^{13}C HSQC experiment revealed the chemical shift of a methylene carbon to be at 49.2 ppm, obscured by MeOD resonance); **IR (Neat Film, NaCl)** 3287, 2924, 2282, 1754, 1667, 1548, 1516, 1415, 1377, 1325, 1278, 1226, 1083, 989, 869, 751 cm^{-1}; **HRMS (MM: ESI-APCI)** *m/z* calc'd for $C_{19}H_{26}FN_4O_4$ $[M+H]^+$: 393.1933, found 393.1937 **$[\alpha]_D^{24.2}$** –3.78 (c 0.5, MeOH).



***N*-(((5*S*)-3-(3-fluoro-4-(2-methyl-6-oxa-2,9-diazaspiro[4.5]decan-9-yl)phenyl)-2-oxooxazolidin-5-yl)methyl)acetamide (17)**. Prepared according to the general procedure using: CuBr (2.3 mg, 0.2 equiv), BINOL (4.6 mg, 0.2 equiv), aryl iodide **7** (30 mg, 1 equiv), K_3PO_4 (34 mg, 2 equiv), **2-methyl-6-oxa-2,9-diazaspiro[4.5]decane (SI5)** (25 mg, 2 equiv), and 400 uL DMF. The crude residue was purified by silica gel flash chromatography (5 → 10 → 20 MeOH/CH_2Cl_2) to yield *N*-methyl spiropyrrolidine analogue **17** (15 mg, 47% yield) as a light yellow oil; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.45 (dd, *J* = 14.1, 2.6 Hz, 1H), 7.08 (ddd, *J* = 8.8, 2.6, 1.1 Hz, 1H), 6.90 (t, *J* = 9.0 Hz, 1H), 6.05 (t, *J* = 6.2 Hz, 1H), 4.77 (dddd, *J* = 8.9, 6.7, 5.9, 3.3 Hz, 1H), 4.02 (td, *J* = 9.0, 0.8 Hz, 1H), 3.95 – 3.81 (m, 2H), 3.79 – 3.66 (m, 2H), 3.60 (dt, *J* = 14.7, 6.1 Hz, 1H), 3.25 (s, 1H), 3.11 (d, *J* = 11.6 Hz, 2H), 3.01 (t, *J* = 10.5 Hz, 5H), 2.66 (s, 3H), 2.20 (m, 2H), 2.02 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 171.1, 155.8 (d, *J* = 246.5 Hz), 154.4, 136.0 (d, *J* = 9.1 Hz), 133.6 (d, *J* = 10.4 Hz), 119.4 (d, *J* = 3.7 Hz), 114.0 (d, *J* = 3.4 Hz), 107.6 (d, *J* = 26.2 Hz), 81.7, 72.0, 63.4, 62.8, 57.84, 55.0, 50.4, 47.8, 42.4, 42.1, 35.4, 23.3; **IR (Neat Film, NaCl)** 3264, 2925, 2283, 1747, 1666, 1516, 1444, 1377, 1325, 1225, 1082, 869, 752 cm^{-1}; **HRMS (MM: ESI-APCI)** *m/z* calc'd for $C_{20}H_{28}FN_4O_4$ $[M+H]^+$: 407.2089, found 407.2095; **$[\alpha]_D^{24.8}$** –6.65 (c 1.0, MeOH).

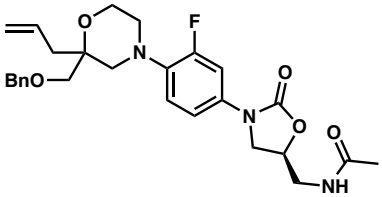


N-(((5S)-3-(3-fluoro-4-(1-oxa-4,8-diazaspiro[5.5]undecan-4-yl)phenyl)-2-oxooxazolidin-5-yl)methyl)acetamide (25). Prepared according to the general procedure using: CuBr (2.1 mg, 0.015 mmol, 0.2 equiv), BINOL (4.2 mg, 0.015 mmol, 0.2 equiv), aryl iodide **7** (28 mg, 0.074 mmol, 1 equiv), K_3PO_4 (31 mg, 0.15 mmol, 2 equiv), *tert*-butyl 1-oxa-4,8-diazaspiro[5.5]undecane-8-carboxylate (38 mg, 0.15 mmol, 2 equiv), and 370 uL DMF. The crude residue was filtered through a silica column (40% MeCN/CH_2Cl_2) to yield a mixture of Boc-protected spirocyclic analogue **16** and starting material aryl iodide **7**, which was carried forward to the next step: To 2.2 mL MeOH at 0 °C was added AcCl (220 uL), generating HCl *in situ*. This HCl solution was stirred for 5 min at 0°C and then transferred by syringe into a 20 mL scintillation vial containing Boc analogue **16**. The reaction was stirred for 1 h at ambient temperature and then the solvent was concentrated under reduced pressure onto SiO_2. The silica-loaded residue was purified by silica gel flash chromatography (1 → 2 → 5 → 10 → 100% MeOH/CH_2Cl_2 with 1% NH_4OH) to yield spiropiperidine analogue **25** as a light yellow oil (12 mg, 32% yield over two steps): **^{1}H NMR (600 MHz, CD_3OD)** δ 7.51 (dd, *J* = 14.4, 2.5 Hz, 1H), 7.18 (ddd, *J* = 8.8, 2.6, 1.0 Hz, 1H), 7.06 (t, *J* = 9.2 Hz, 1H), 4.83 – 4.77 (m, 1H), 4.14 (t, *J* = 9.0 Hz, 1H), 3.98 (ddd, *J* = 11.4, 8.0, 3.2 Hz, 1H), 3.91 (ddd, *J* = 11.9, 5.0, 3.4 Hz, 1H), 3.88 – 3.80 (m, 2H), 3.56 (d, *J* = 5.1 Hz, 2H), 3.38 – 3.32 (m, 2H), 3.13 – 3.06 (m, 1H), 3.06 – 2.97 (m, 4H), 2.86 (d, *J* = 12.0 Hz, 1H), 2.20 – 2.14 (m, 1H), 2.14 – 2.01 (m, 1H), 1.97 (s, 3H), 1.81 – 1.76 (m, 1H), 1.63 (td, *J* = 13.7, 4.3 Hz, 1H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 171.3, 155.6 (d, *J* = 246.3 Hz), 154.6, 136.8 (d, *J* = 9.0 Hz), 133.0 (d, *J* = 10.4 Hz), 119.2 (d, *J* = 5.6 Hz), 114.0 (t, *J* = 3.8 Hz), 107.6 (d, *J* = 26.1 Hz), 72.1, 69.8, 60.9, 58.5, 50.7, 47.8, 46.13, 42.1, 31.6, 29.8, 23.3, 21.3; **IR (Neat Film, NaCl)** 3275, 2931, 2359, 1748, 1668, 1540, 1517, 1417, 1374, 1286, 1224, 1195, 1084, 867, 732 cm^{-1}; **HRMS (MM: ESI-APCI)** *m/z* calc'd for $C_{20}H_{28}FN_4O_4$ $[M+H]^+$: 407.2089, found 407.2080 **$[\alpha]_D^{25.2}$** –5.83 (c 0.8, $CHCl_3$).

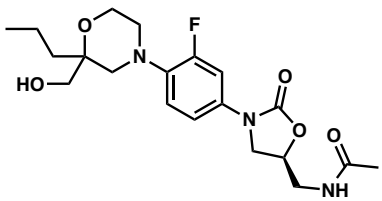


***N*-(((5*S*)-3-(4-(8-acetyl-1-oxa-4,8-diazaspiro[5.5]undecan-4-yl)-3-fluorophenyl)-2-oxooxazolidin-5-yl)methyl)acetamide (26)**. To a solution of spiropiperidine **25** (12 mg, 1 equiv) in MeCN was added NEt_3 (12 uL, 3 equiv) followed by DMAP (0.4 mg, 0.1 equiv), and then Ac_2O (4 uL, 1.5 equiv). The reaction was stirred at rt for 2 h, concentrated, and then purified by silica gel flash chromatography (2 → 5 → 10% MeOH/CH_2Cl_2) to afford acetylated analogue **26** as a clear oil (10 mg, 77% yield). **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.42 (dddd, *J* = 20.9, 14.2, 2.6, 1.6 Hz, 1H), 7.05 (ttd, *J* = 8.8, 2.6, 1.1 Hz, 1H), 6.94 – 6.82 (m, 1H), 6.34 – 6.17 (m, 1H), 4.86 (dd, *J* = 14.0, 6.1 Hz, 1H), 4.81 –

4.70 (m, 1H), 4.11 (ddd, *J* = 12.0, 8.9, 3.0 Hz, 1H), 4.05 – 3.82 (m, 2H), 3.82 – 3.43 (m, 6H), 3.23 – 2.64 (m, 5H), 2.15 – 2.05 (m, 3H), 2.02 (s, 3H), 1.89 – 1.83 (m, 1H), 1.74 – 1.66 (m, 2H), 1.60 – 1.50 (m, 1H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ (Note: multiple peaks observed due to the presence of rotamers) 171.2, 171.2, 169.9, 169.3, 156.9, 156.8, 154.5, 154.4, 136.8, 136.7, 136.7, 136.6, 136.4, 136.3, 133.5, 133.4, 132.9, 132.8, 119.4, 119.4, 119.2, 114.0, 114.0, 113.9, 107.7, 107.6, 107.5, 107.4, 107.3, 72.0, 71.9, 71.2, 70.8, 61.6, 61.3, 58.3, 56.5, 51.4, 51.1, 51.1, 50.3, 47.7, 47.3, 45.9, 45.8, 42.3, 42.1, 42.1, 42.1, 33.1, 33.0, 23.2, 21.7, 21.4, 20.9; **IR (Neat Film, NaCl)** cm^{-1}; **HRMS (MM: ESI-APCI)** *m/z* calc'd for $C_{22}H_{30}FN_4O_5$ $[M+H]^+$: 449.2195, found 449.2193 **$[\alpha]_D^{24.4}$** –11.08 (c 0.7, $CHCl_3$).



N-(((5*S*)-3-(4-(2-allyl-2-((benzyloxy)methyl)morpholino)-3-fluorophenyl)-2-oxooxazolidin-5-yl)methyl)acetamide (14). Prepared according to the general procedure using: CuBr (2.3 mg, 0.016 mmol, 0.2 equiv), BINOL (4.5 mg, 0.016 mmol, 0.2 equiv), aryl iodide **7** (30 mg, 0.079 mmol, 1 equiv), K_3PO_4 (34 mg, 0.16 mmol, 2 equiv), benzyloxy morpholine[5] (18 mg, 0.16 mmol, 2 equiv), and 400 uL DMF. The crude residue was purified by silica gel flash chromatography (2 → 3 → 5% MeOH/CH_2Cl_2) to yield benzyloxy analogue **14** (8 mg, 28% yield) as a clear oil: **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.46 – 7.34 (m, 1H), 7.33 (d, *J* = 4.4 Hz, 3H), 7.33 – 7.23 (m, 1H), 7.04 (dd, *J* = 8.8, 1.8 Hz, 1H), 6.88 (t, *J* = 9.1 Hz, 1H), 6.29 (t, *J* = 6.1 Hz, 1H), 5.82 (ddt, *J* = 17.5, 10.3, 7.3 Hz, 1H), 5.15 – 5.04 (m, 2H), 4.76 (qd, *J* = 7.8, 6.6, 5.0 Hz, 1H), 4.56 (s, 2H), 4.05 – 3.49 (m, 7H), 3.06 – 2.87 (m, 4H), 2.77 (dt, *J* = 15.0, 7.5 Hz, 1H), 2.46 (dd, *J* = 14.3, 7.6 Hz, 1H), 2.01 (m, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 171.4, 155.7 (d, *J* = 246.7 Hz), 154.5, 138.4, 137.0 (d, *J* = 9.0 Hz), 133.3, 132.9 (d, *J* = 10.3 Hz), 128.5, 127.8, 127.7, 119.3 (d, *J* = 4.0 Hz), 118.3, 114.0 (d, *J* = 3.3 Hz), 107.6 (d, *J* = 26.1 Hz), 74.9, 73.7, 72.0, 71.0, 61.4, 56.1, 50.5, 47.8, 42.1, 37.2, 23.2; **IR (Neat Film, NaCl)** 3288, 2921, 2364, 1749, 1654, 1516, 1416, 1373, 1324, 1274, 1224, 1103, 747 cm^{-1}; **HRMS (MM: ESI-APCI)** *m/z* calc'd for $C_{27}H_{33}FN_3O_5$ $[M+H]^+$: 498.2399, found 498.2393 **$[\alpha]_D^{22.6}$** –3.54 (c 1.0, $CHCl_3$).



***N*-(((5*S*)-3-(4-(2-allyl-2-((benzyloxy)methyl)morpholino)-3-fluorophenyl)-2-oxooxazolidin-5-yl)methyl)acetamide** (**24**). In a 1 dram vial open to the air, benzyloxy analogue **14** (20 mg, 0.04 mmol, 1 equiv) was dissolved in MeOH (400 uL, 0.1M). $Pd(OH)_2/C$ (20 wt. %, 4.2 mg, 0.006 mmol, 0.15 equiv) was then added. The vial was then sealed with a septum cap and evacuated and filled using a balloon containing H_2 three times. The solvent was then sparged with H_2 for 5 min and stirred for 16 h until TLC analysis showed the starting material had been consumed. The $Pd(OH)_2/C$ was filtered off

using a Celite plug and rinsed with EtOAc. The solvent was concentrated under reduced pressure onto SiO_2. The silica-loaded residue was purified by silica gel flash chromatography (2 → 3 → 10% MeOH/CH_2Cl_2) to yield hydroxyl analogue **24** (14 mg, 88% yield) as a clear oil: **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.42 (dt, *J* = 14.1, 2.4 Hz, 1H), 7.05 (dtd, *J* = 8.9, 2.4, 1.1 Hz, 1H), 6.90 (t, *J* = 9.1 Hz, 1H), 6.27 (t, *J* = 6.3 Hz, 1H), 4.77 (dddd, *J* = 8.9, 6.7, 5.6, 3.3 Hz, 1H), 4.01 (t, *J* = 9.0 Hz, 1H), 3.92 (t, *J* = 4.9 Hz, 2H), 3.79 – 3.70 (m, 2H), 3.74 – 3.63 (m, 2H), 3.61 (dt, *J* = 14.7, 6.0 Hz, 1H), 3.07 – 2.97 (m, 2H), 2.99 – 2.85 (m, 2H), 2.02 (s, 3H), 1.83 (ddd, *J* = 14.0, 11.6, 5.6 Hz, 1H), 1.60 (ddd, *J* = 14.0, 11.1, 5.8 Hz, 1H), 1.44 – 1.21 (m, 2H), 0.94 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 171.3, 155.7 (d, *J* = 246.4 Hz), 154.5, 136.9 (d, *J* = 9.1 Hz), 133.1 (d, *J* = 10.4 Hz), 119.3 (d, *J* = 4.0 Hz), 114.0 (d, *J* = 2.5 Hz), 107.6 (d, *J* = 26.2 Hz), 75.3, 72.0, 64.8, 61.42, 55.4, 50.4, 47.8, 42.1, 35.3, 23.3, 16.4, 14.9; **IR (Neat Film, NaCl)** 3316, 2957, 1747,1659, 1547, 1516, 1416, 1375, 1268, 1229, 1090, 743 cm^{-1}; **HRMS (MM: ESI-APCI)** *m/z* calc'd for $C_{20}H_{29}FN_3O_5$ $[M+H]^+$: 410.2086, found 410.2086 **$[\alpha]_D^{22.3}$** –11.50 (c 1.0, $CHCl_3$).

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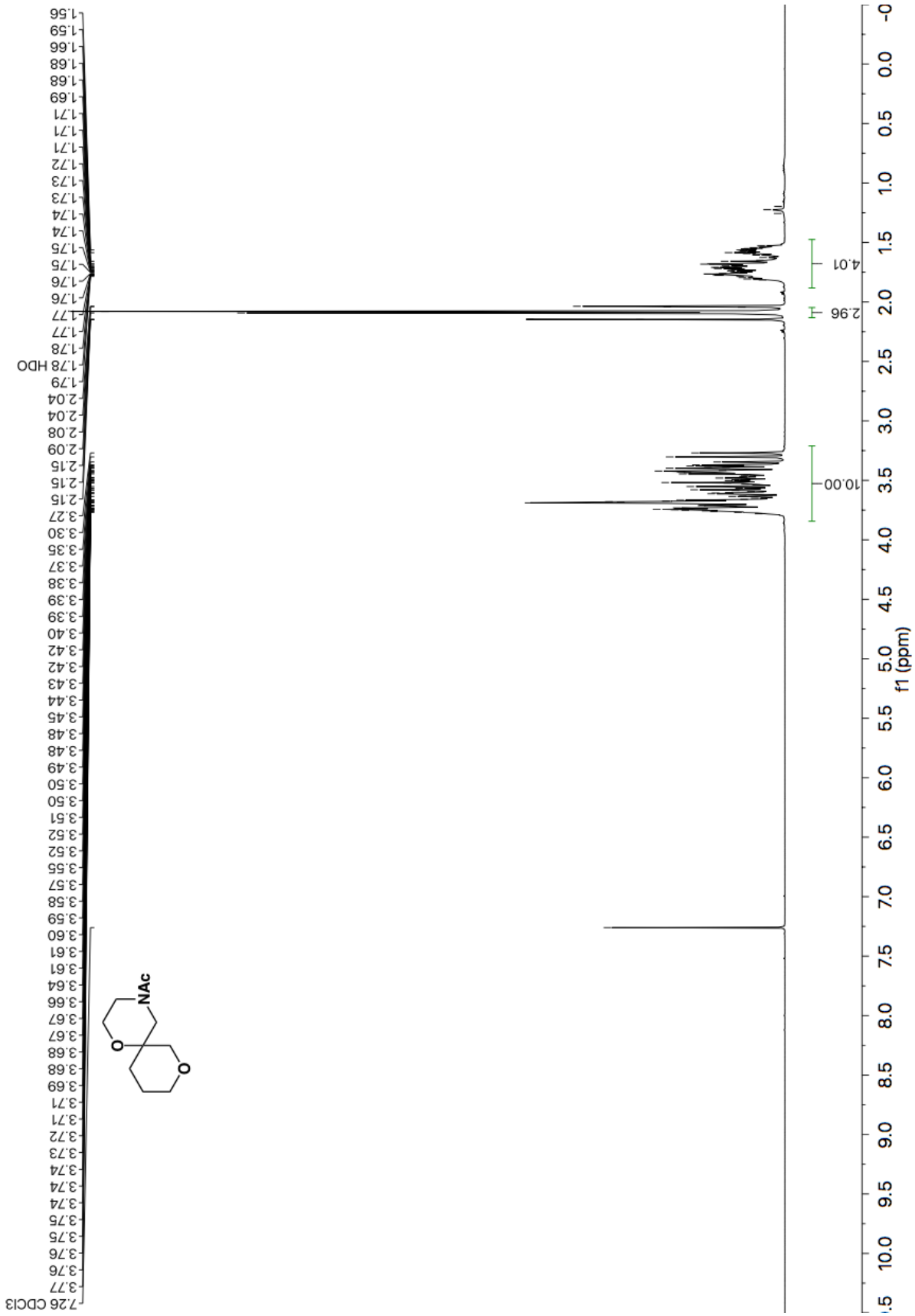
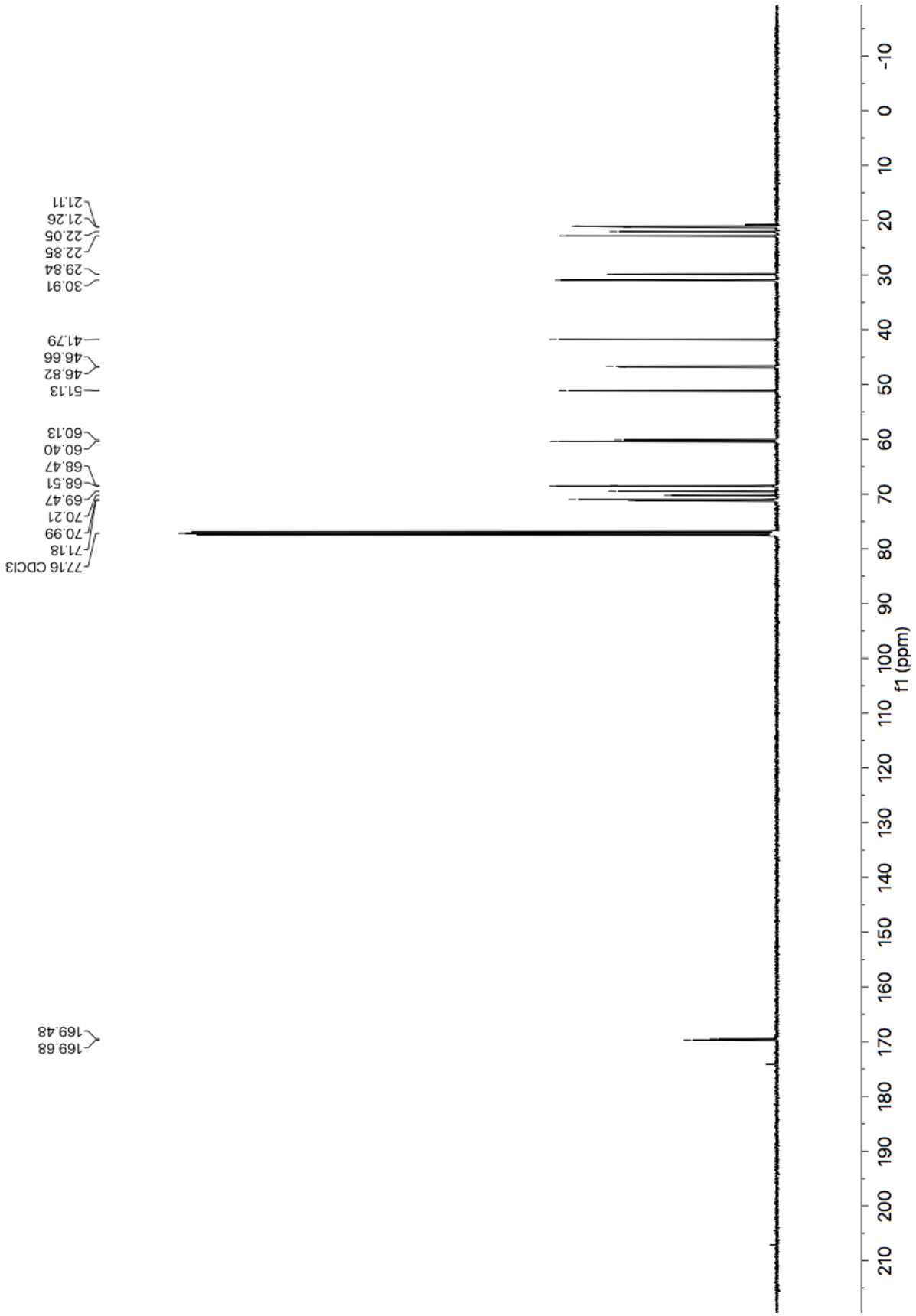
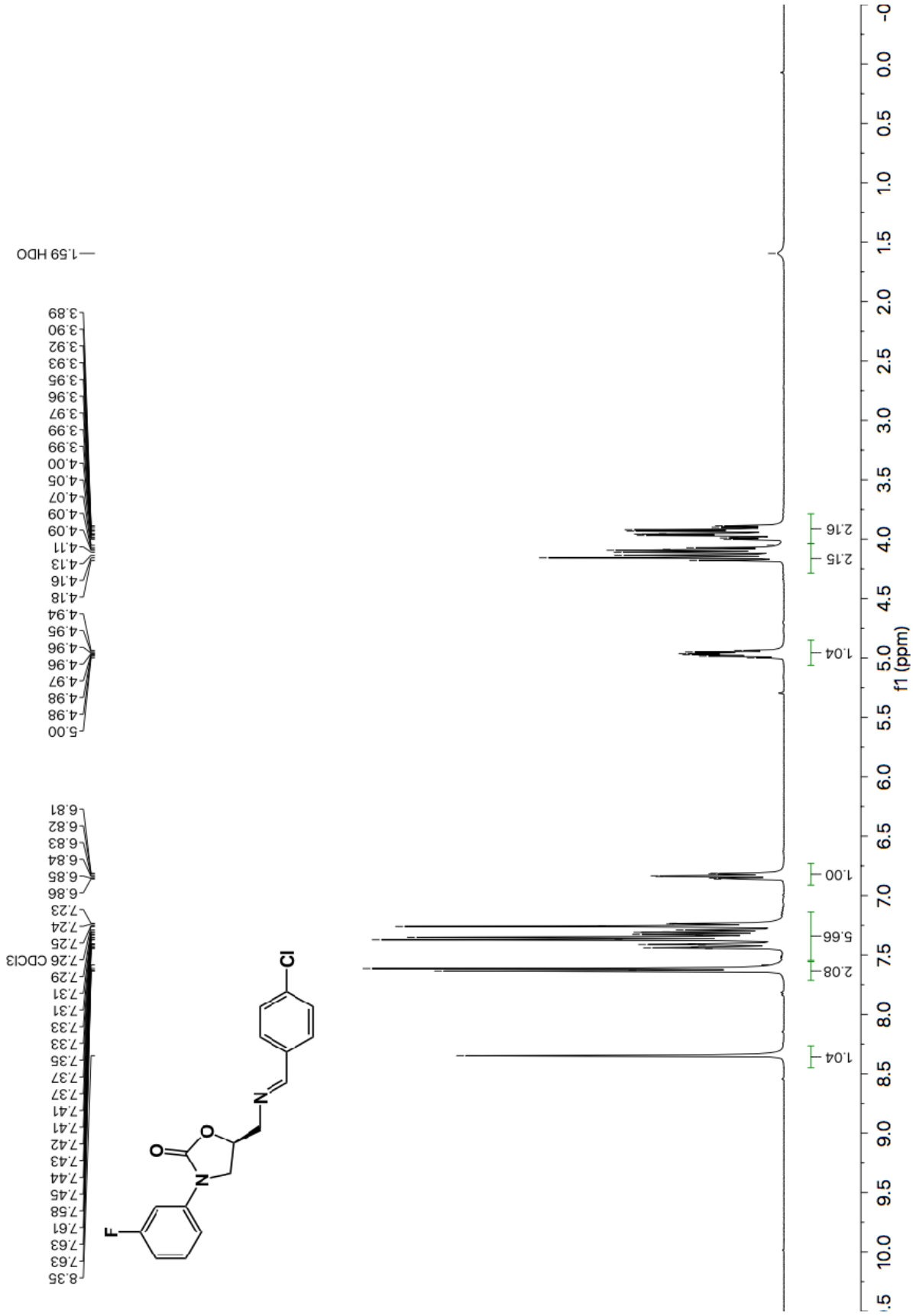


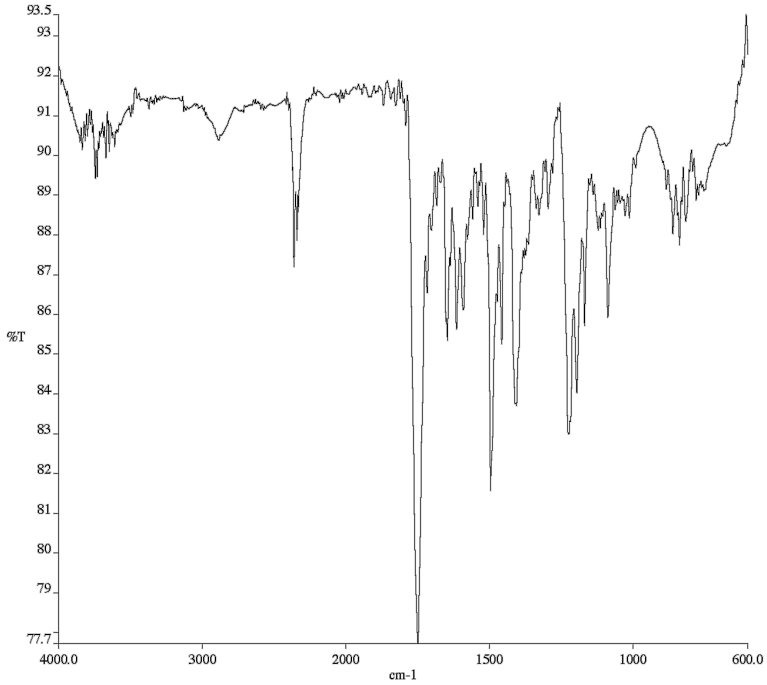
^{1}H NMR (400 MHz, $CDCl_3$) of compound **SI3a.**



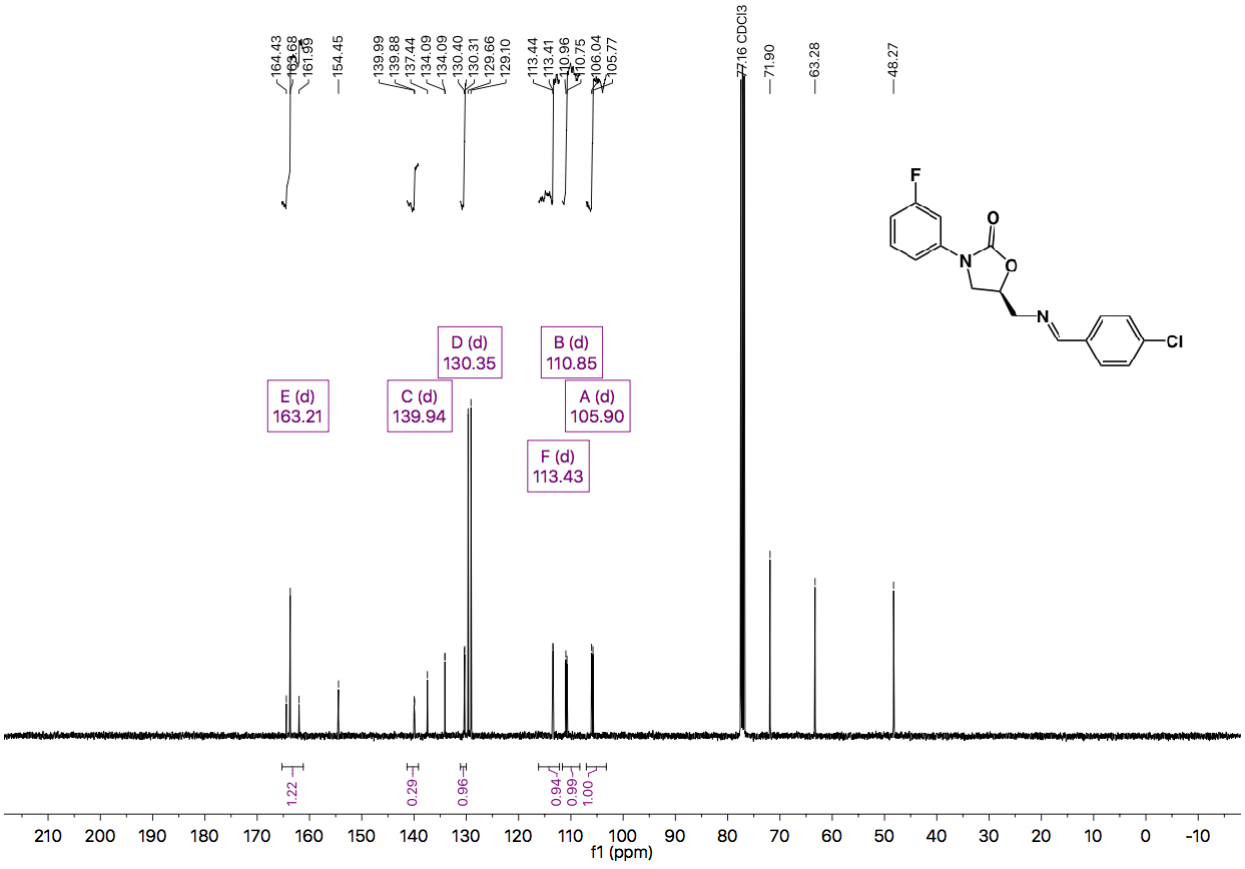
^{13}C NMR (101 MHz, $CDCl_3$) of compound



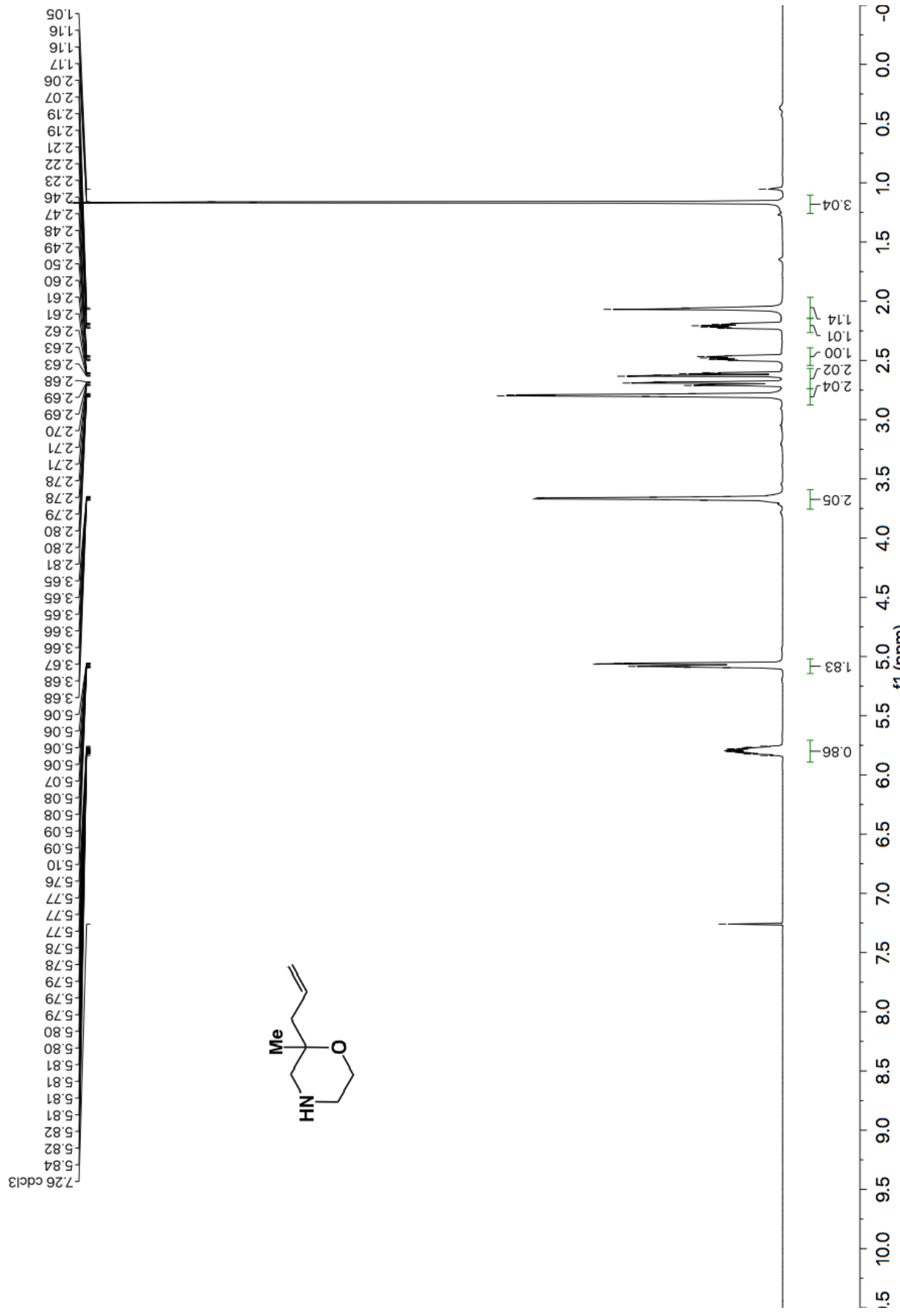
^{1}H NMR (400 MHz, $CDCl_3$) of compound **5.**



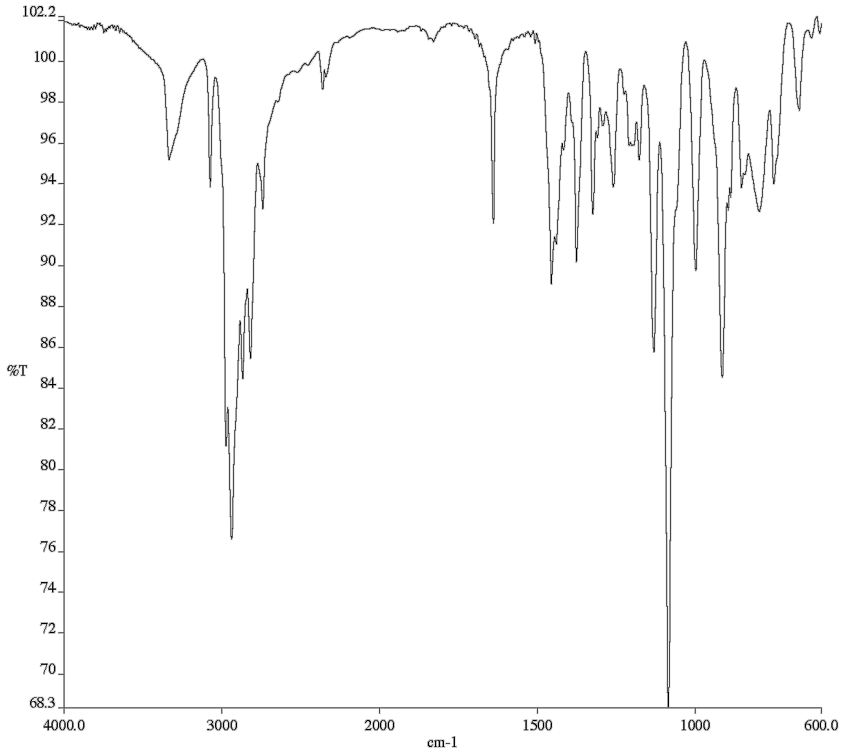
Infrared spectrum (Thin Film, NaCl) of compound **5**.



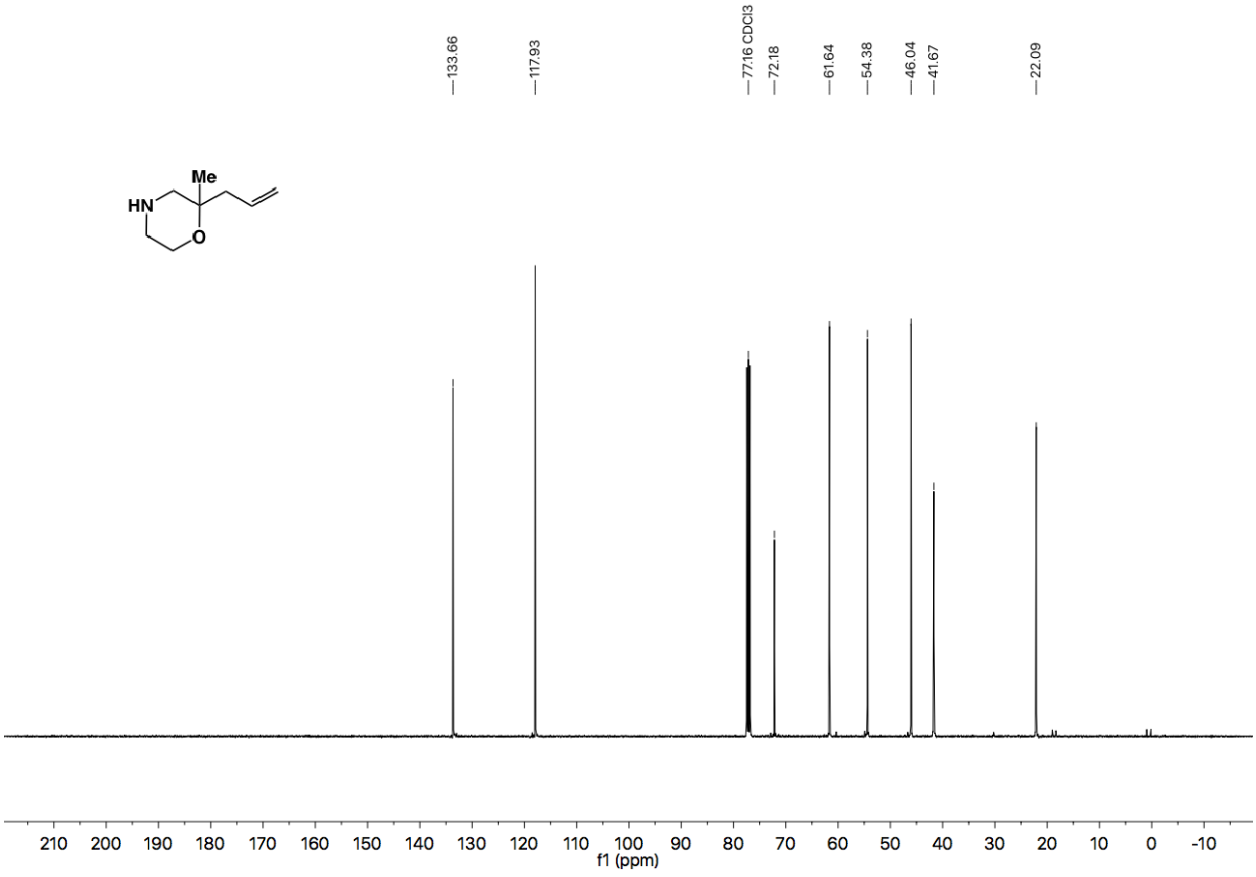
^{13}C NMR (101 MHz, $CDCl_3$) of compound **5**.



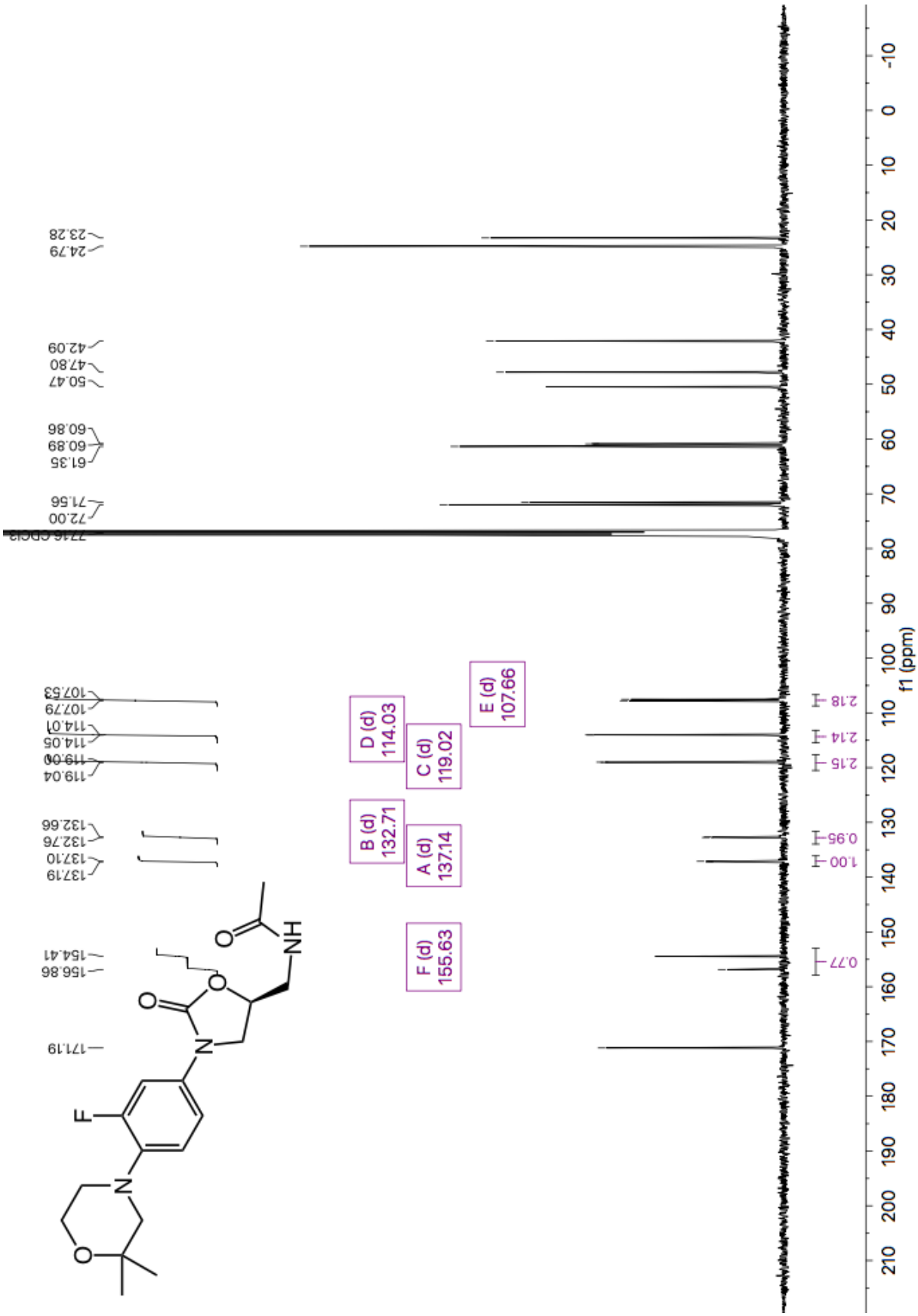
^{1}H NMR (600 MHz, $CDCl_3$) of compound **10.**



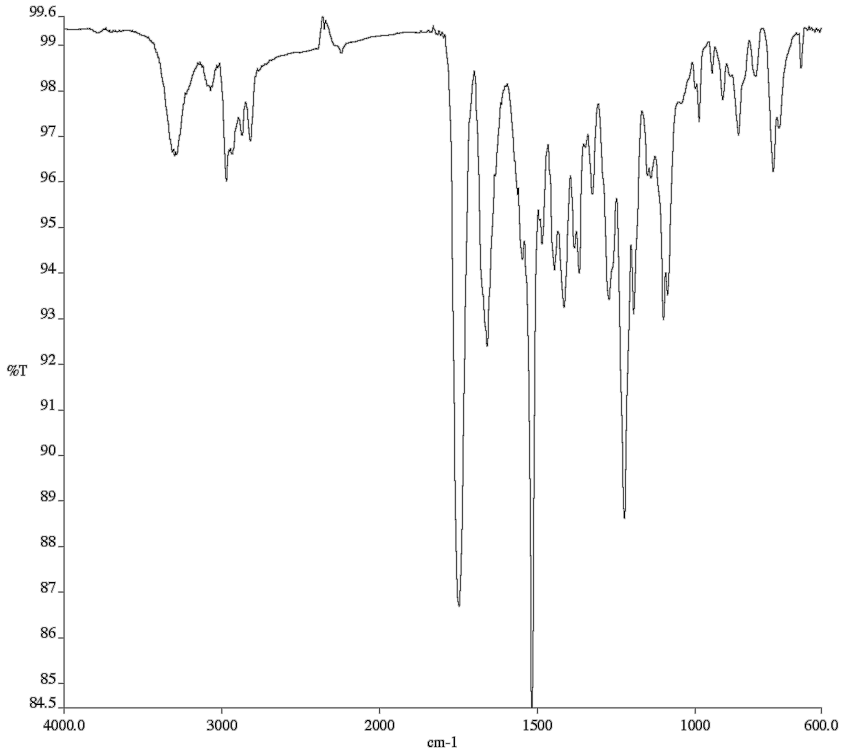
Infrared spectrum (Thin Film, NaCl) of compound **10**.



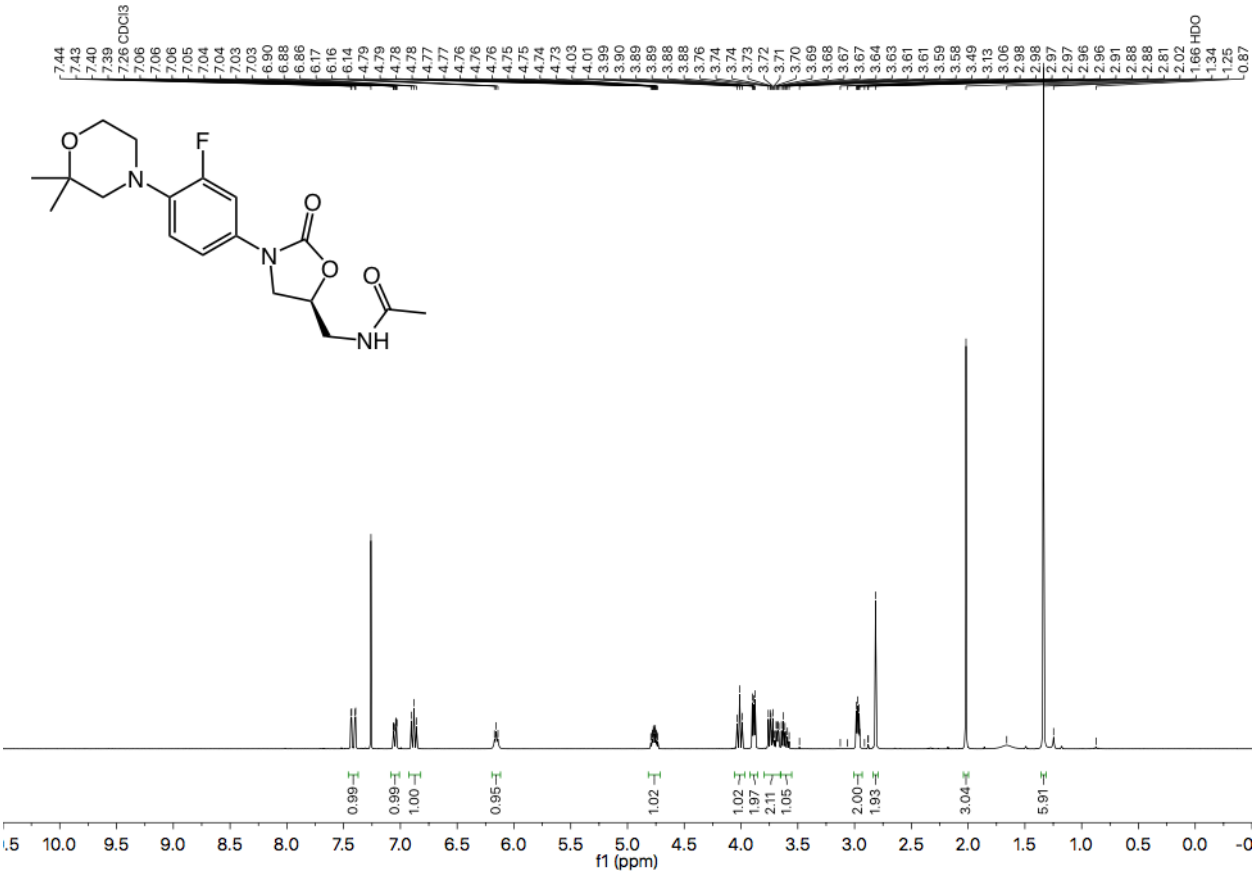
^{13}C NMR (101 MHz, $CDCl_3$) of compound **10**.



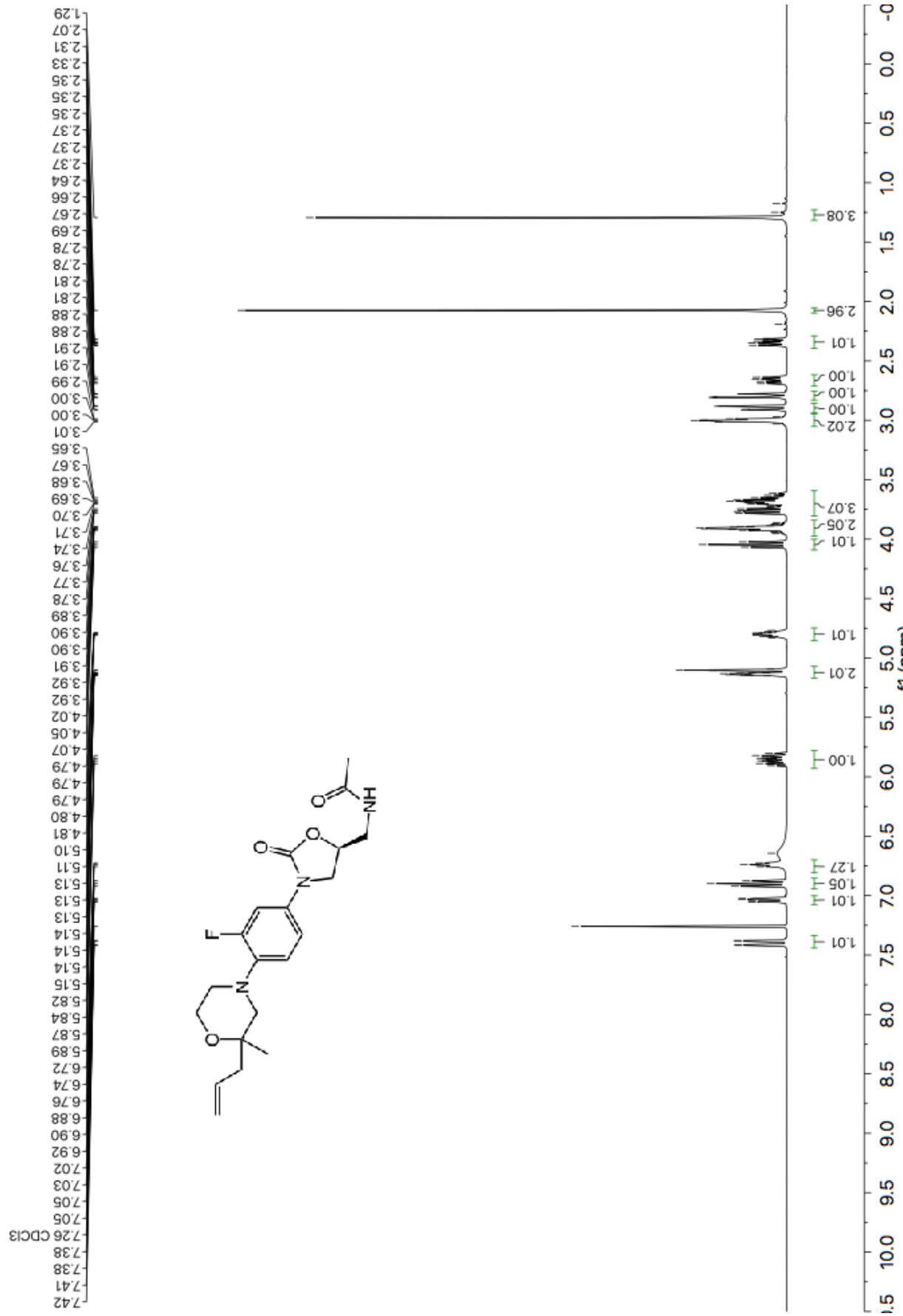
^{1}H NMR (400 MHz, $CDCl_3$) of compound **12.**



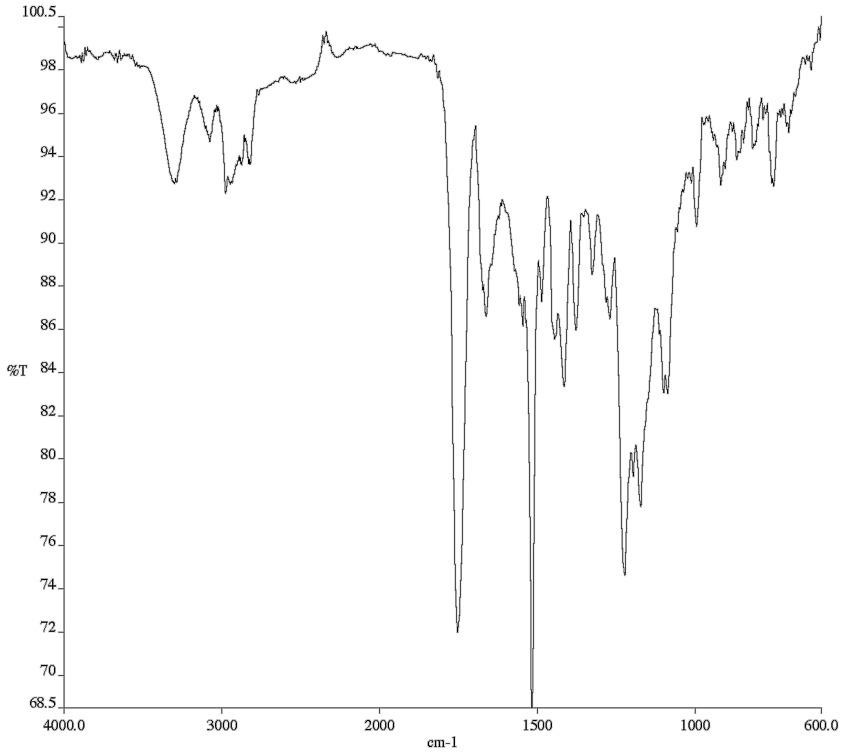
Infrared spectrum (Thin Film, NaCl) of compound **12**.



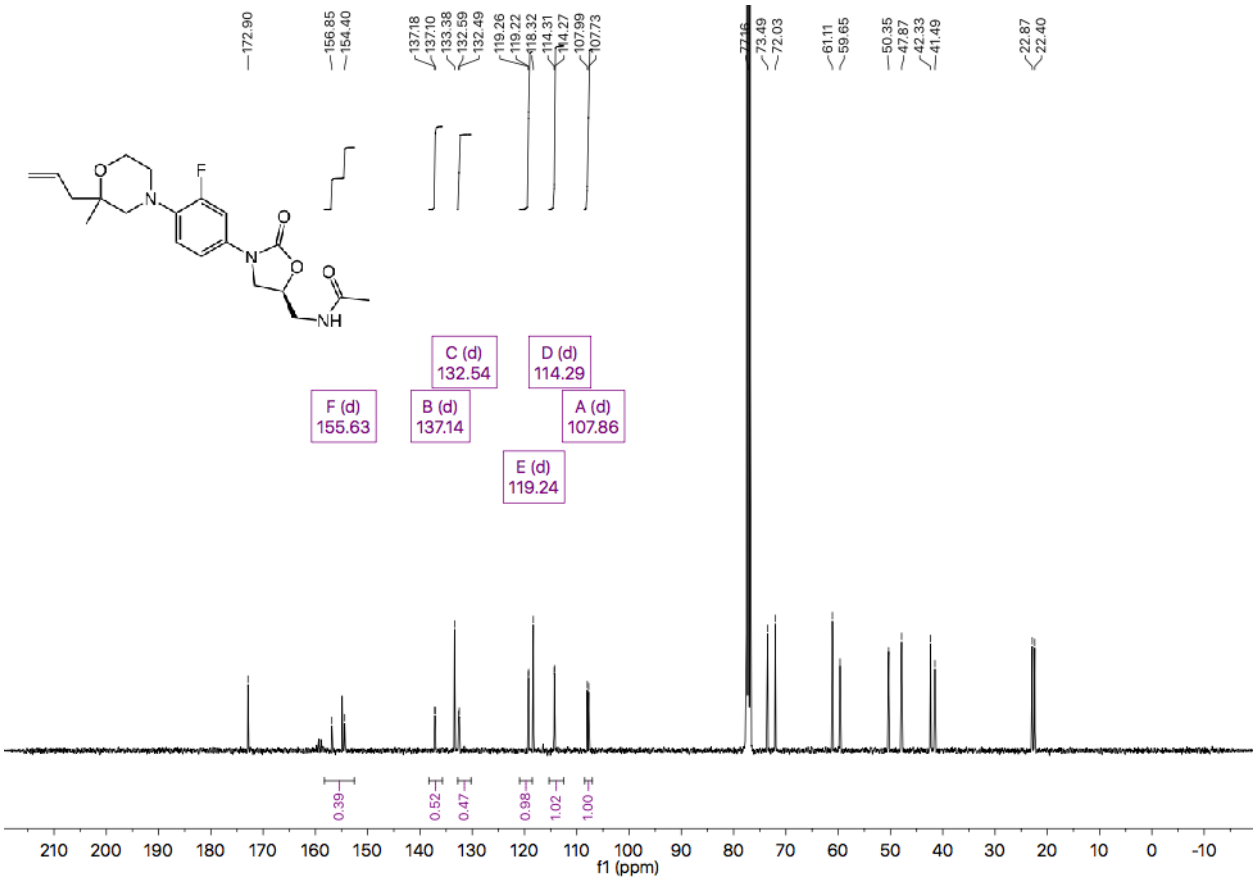
^{13}C NMR (101 MHz, $CDCl_3$) of compound **12**.



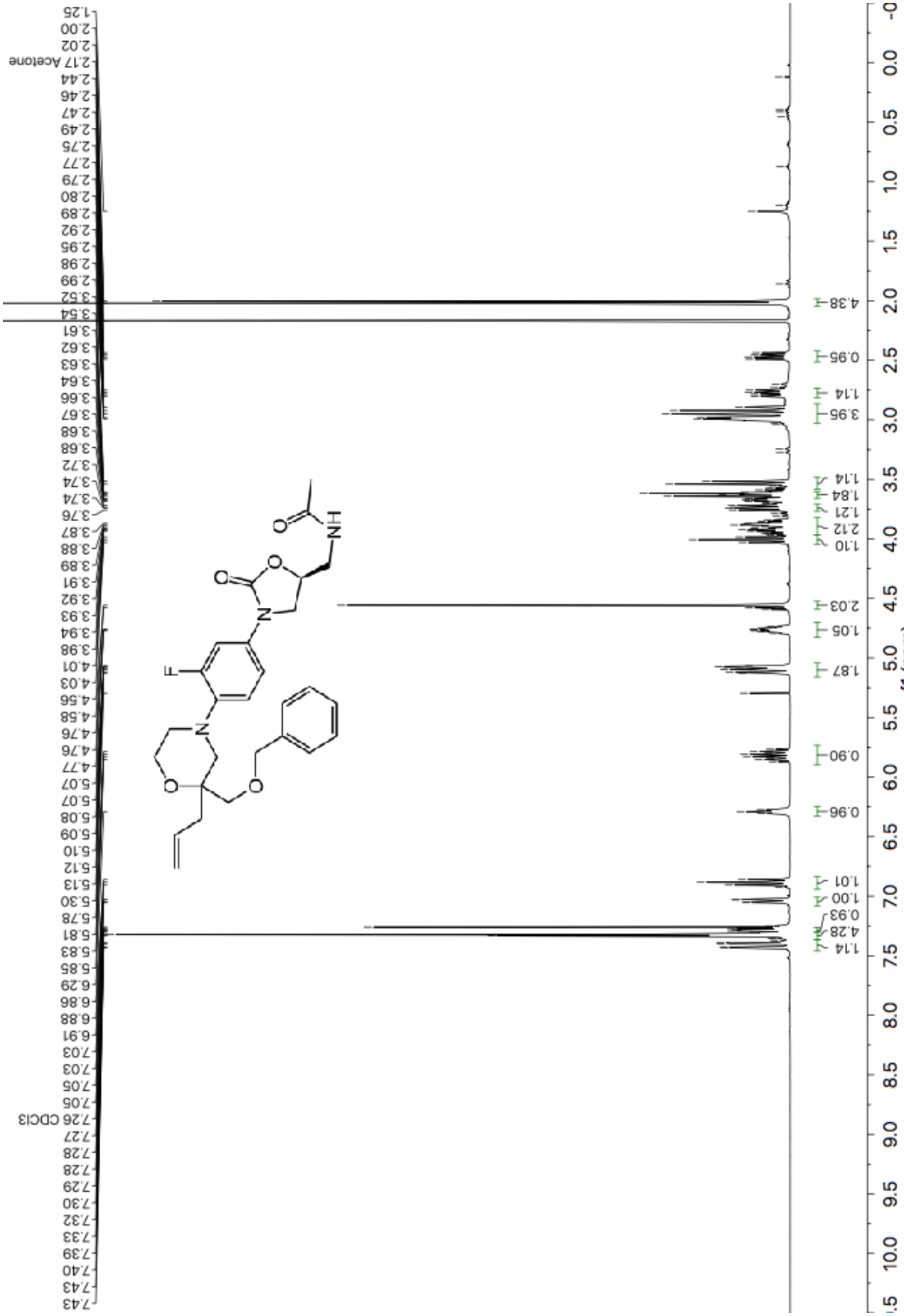
^{1}H NMR (400 MHz, $CDCl_3$) of compound **13.**



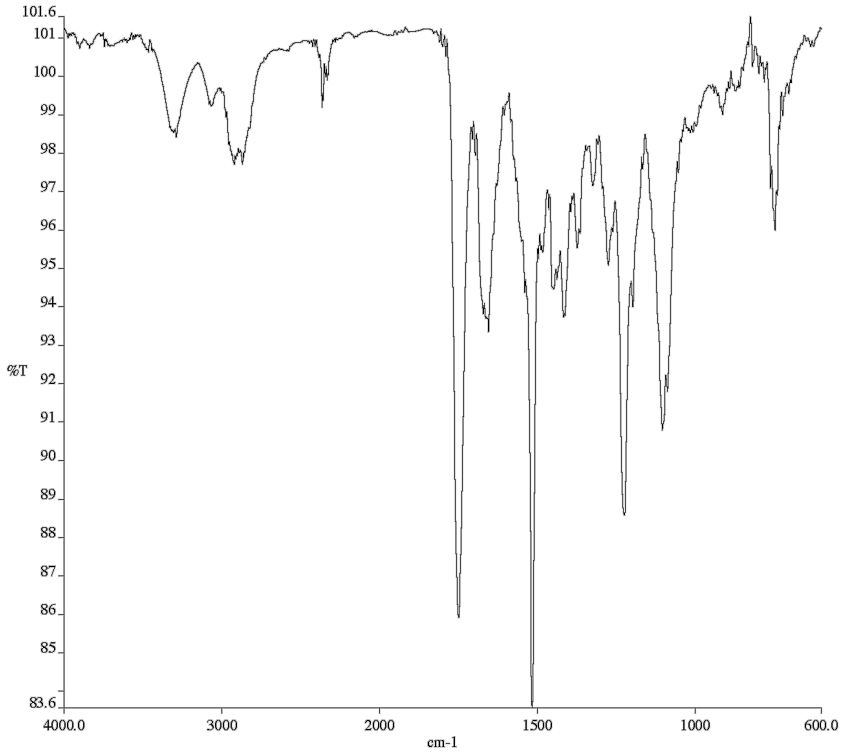
Infrared spectrum (Thin Film, NaCl) of compound **13**.



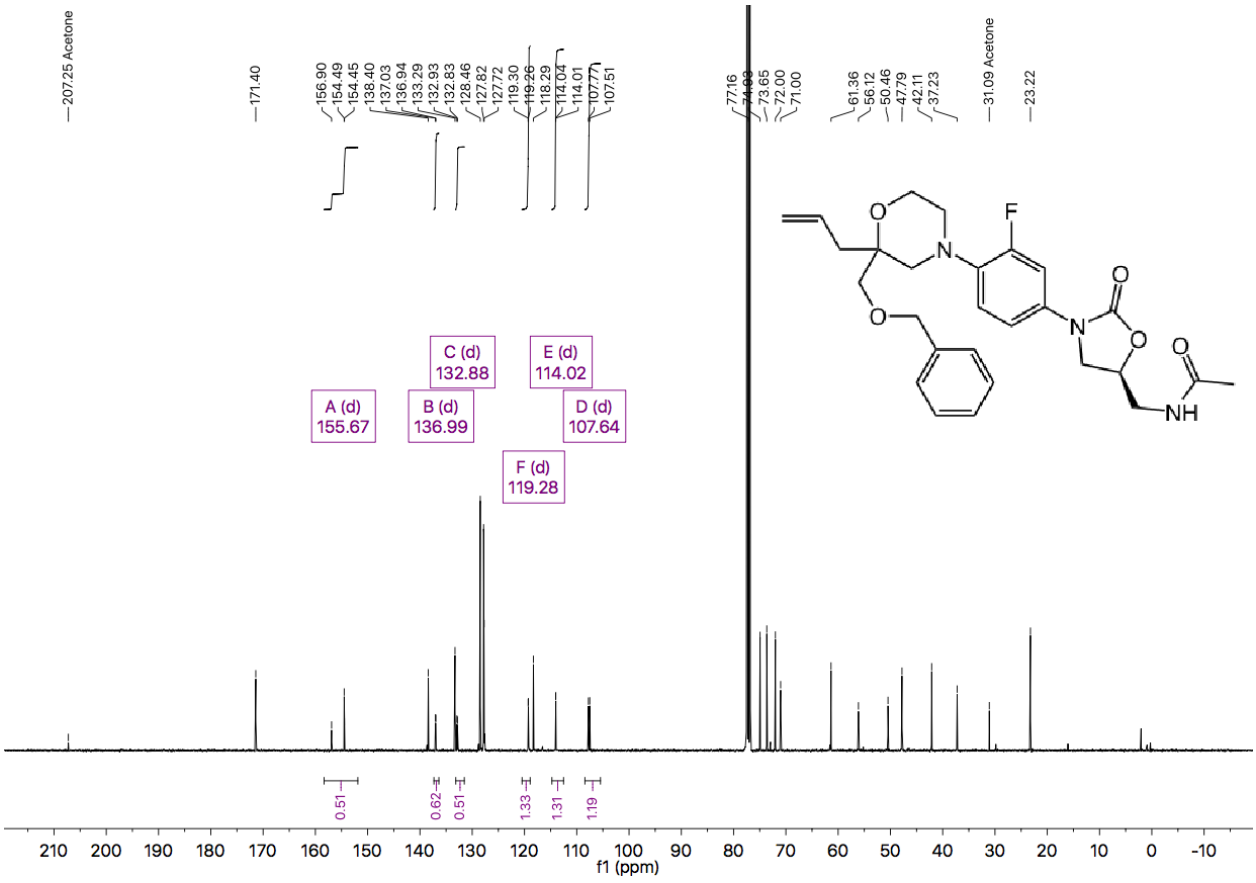
^{13}C NMR (101 MHz, $CDCl_3$) of compound **13**.



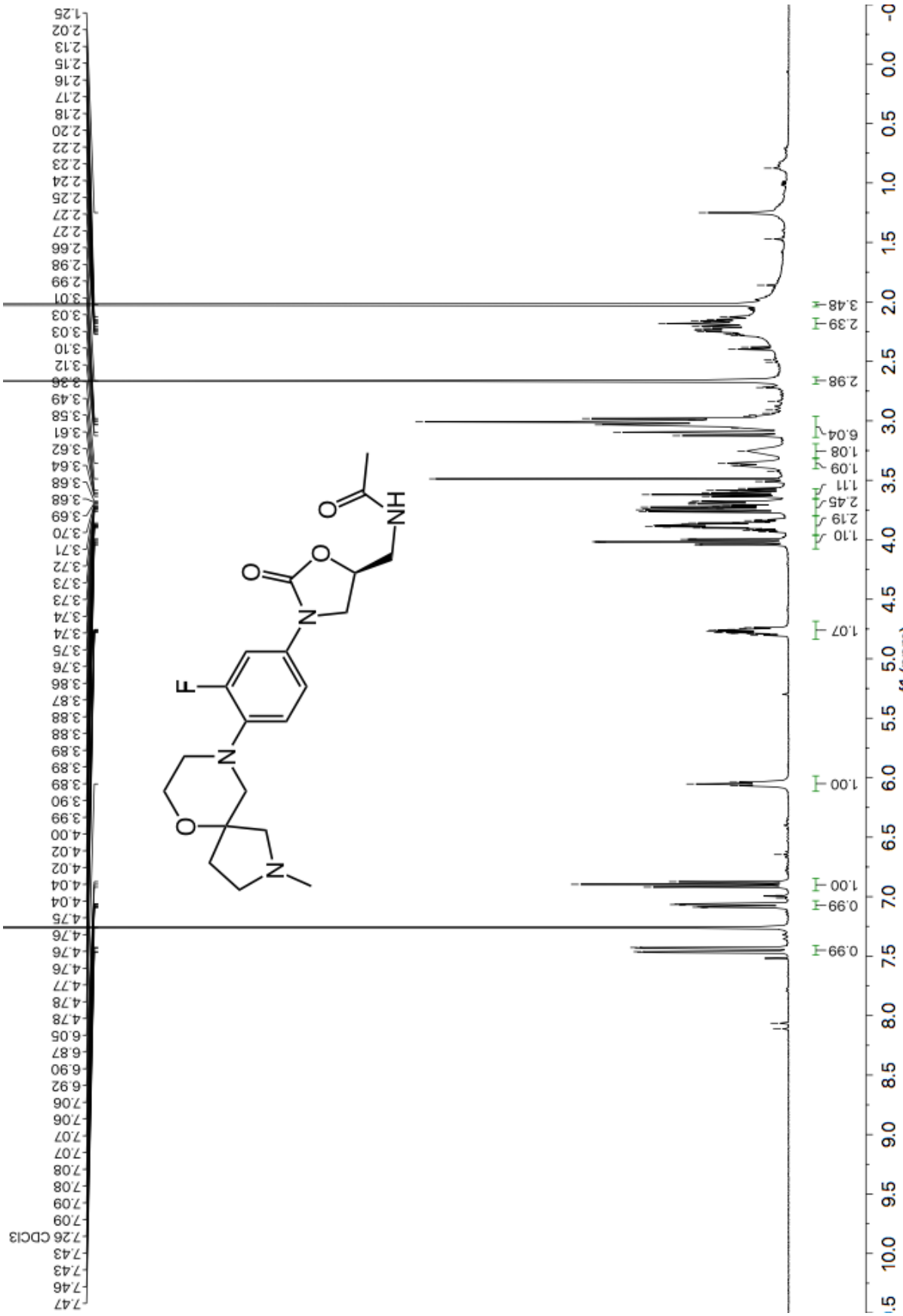
^{1}H NMR (400 MHz, $CDCl_3$) of compound **14.**



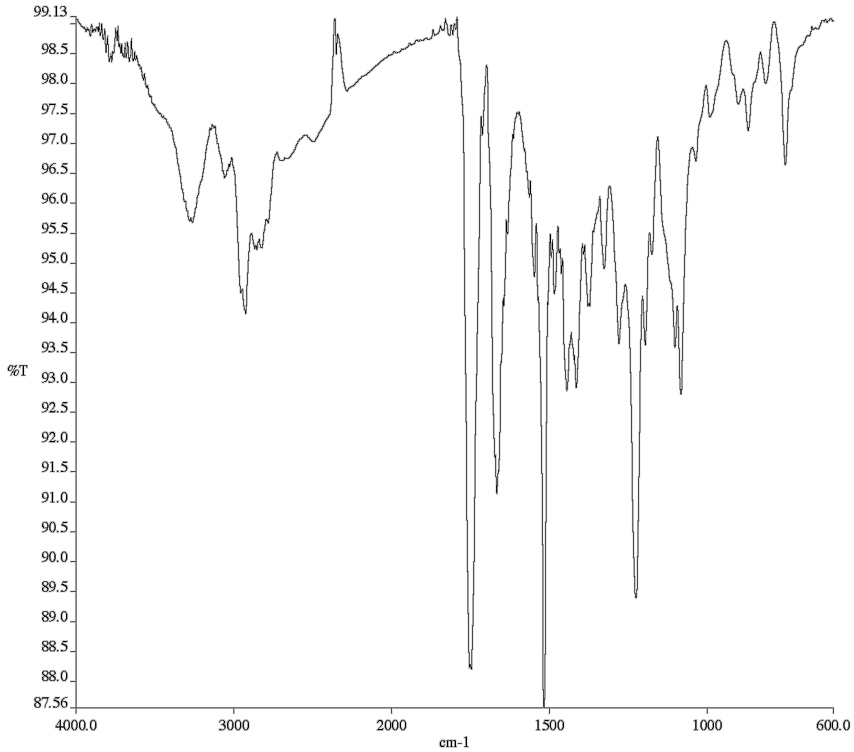
Infrared spectrum (Thin Film, NaCl) of compound **14**.



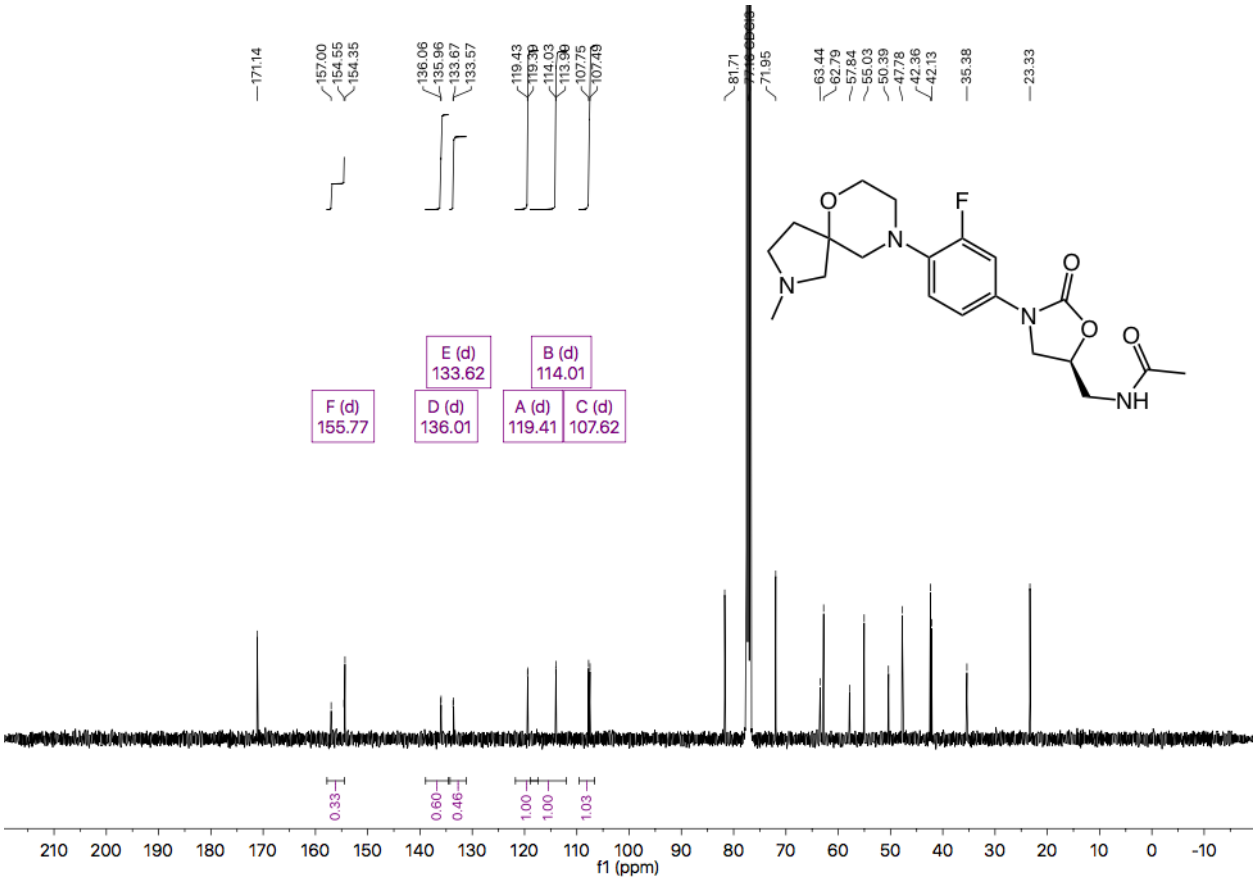
^{13}C NMR (101 MHz, $CDCl_3$) of compound **14**.



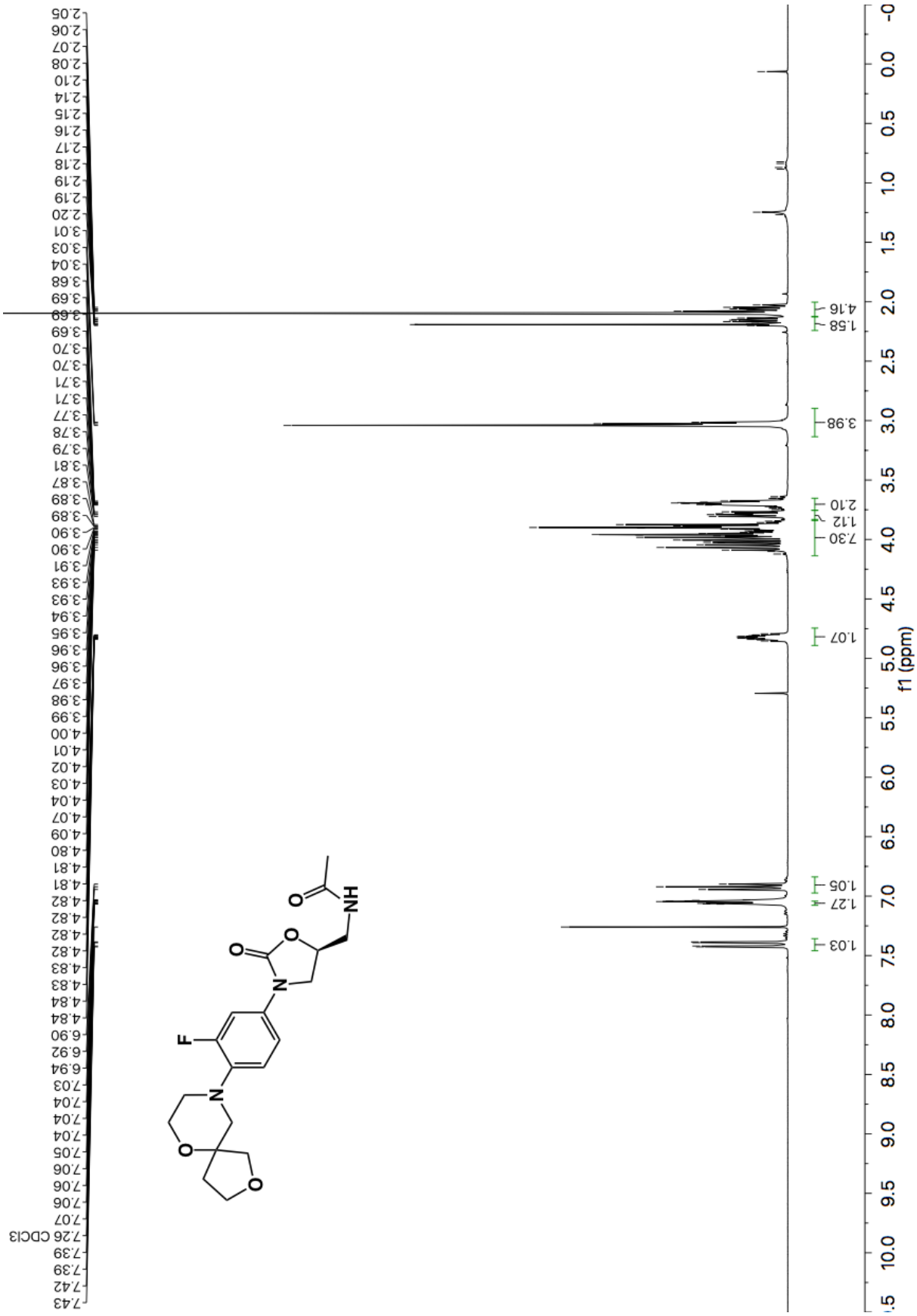
^{1}H NMR (400 MHz, $CDCl_3$) of compound **17.**



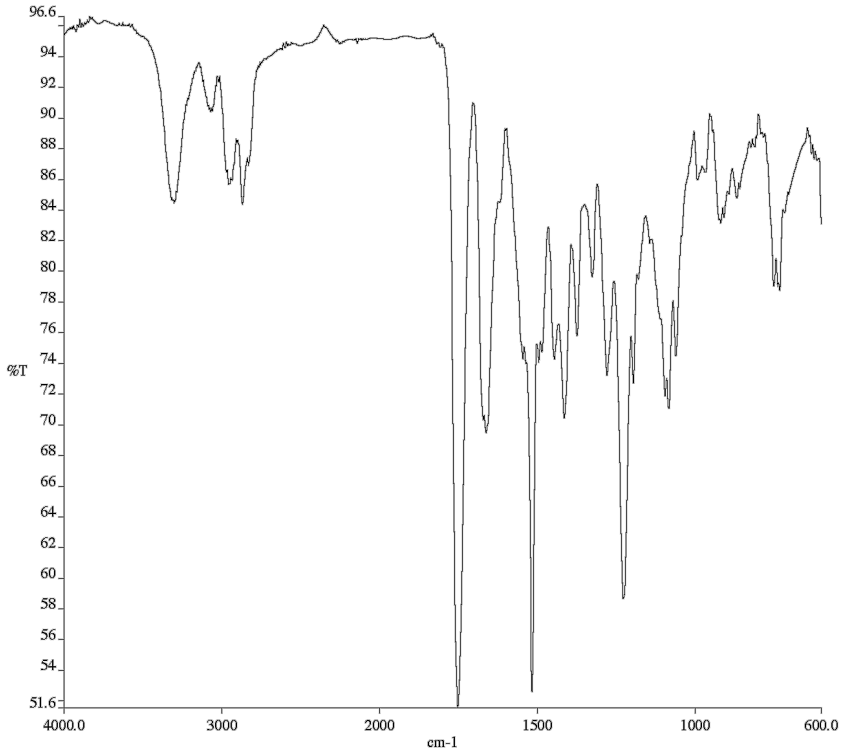
Infrared spectrum (Thin Film, NaCl) of compound **17**.



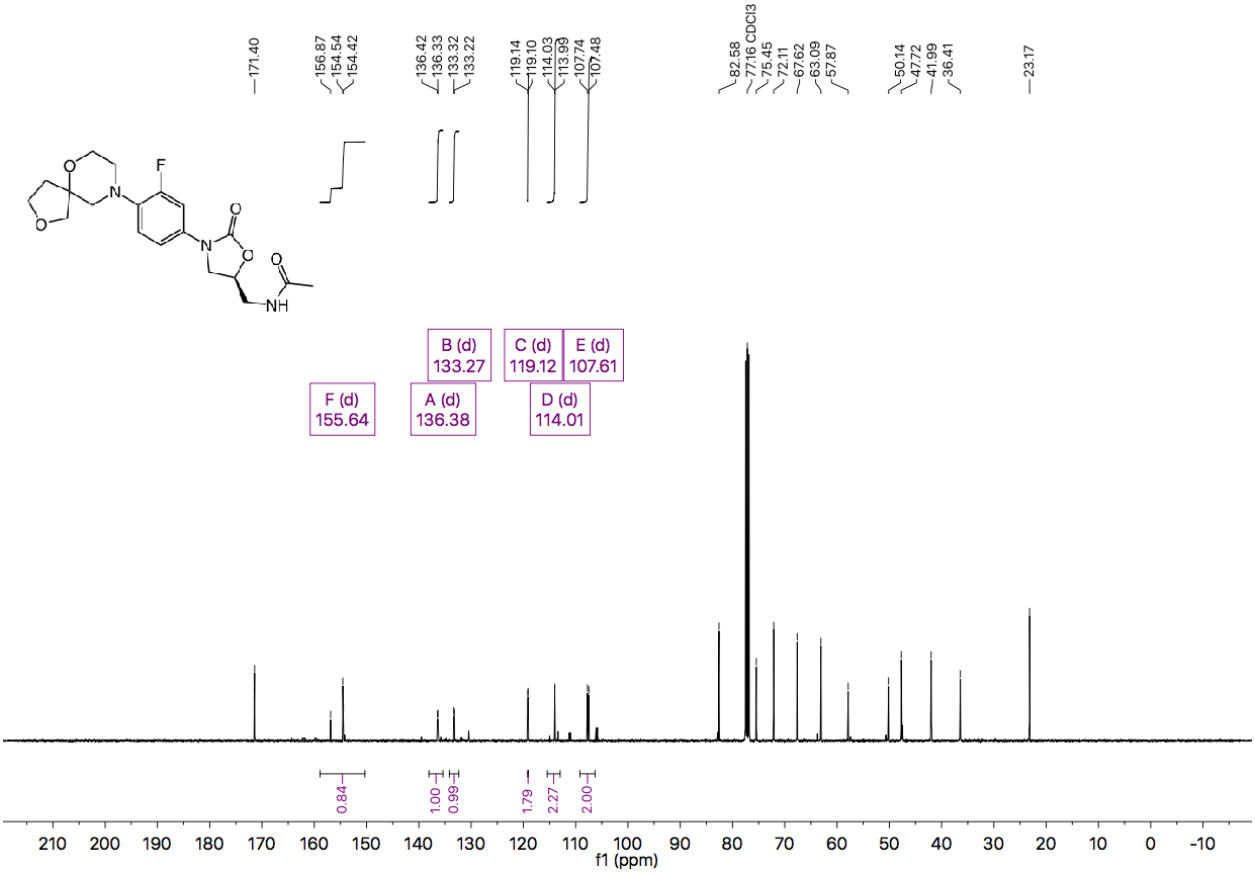
^{13}C NMR (101 MHz, $CDCl_3$) of compound **17**.



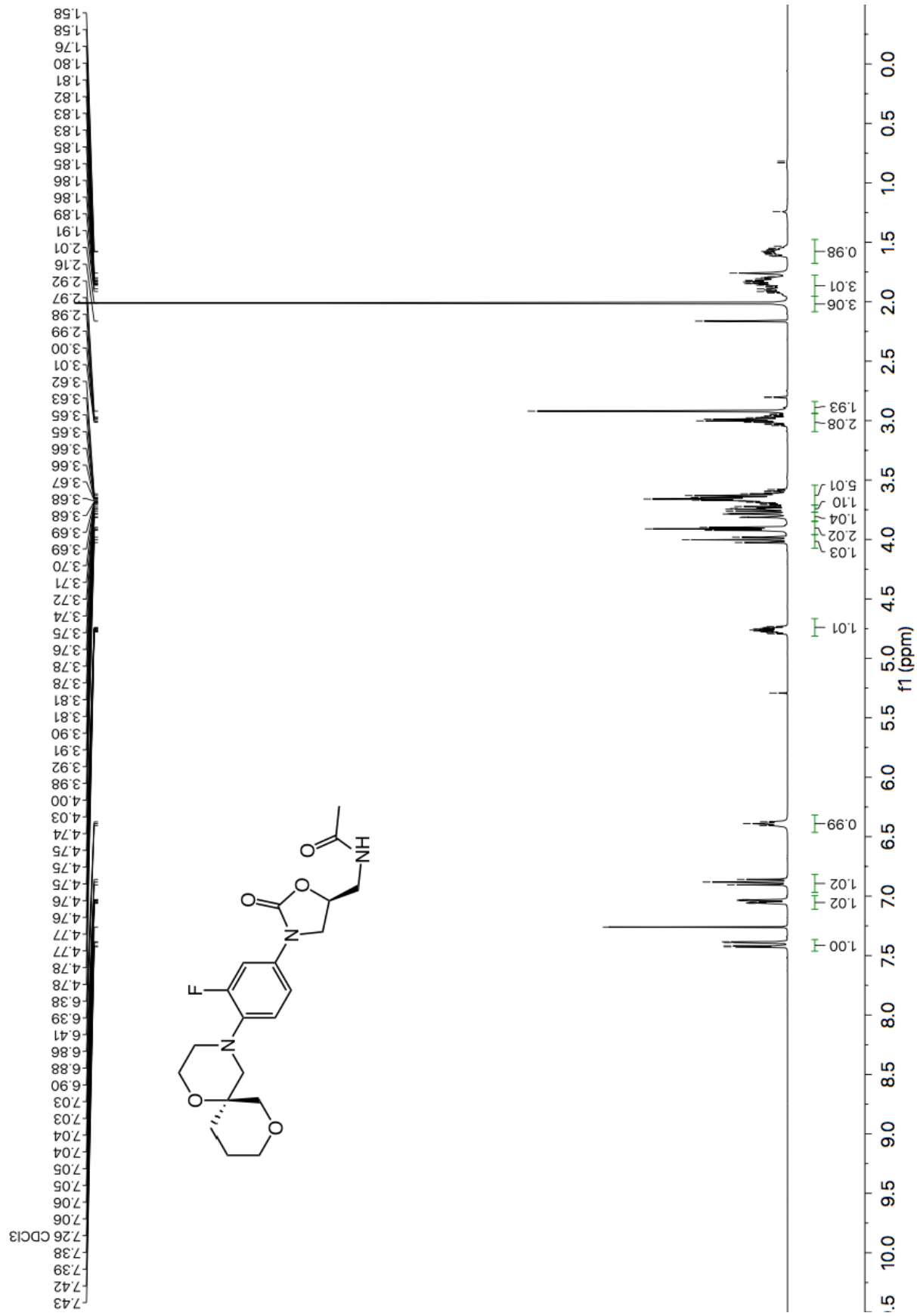
^{1}H NMR (400 MHz, $CDCl_3$) of compound **18.**



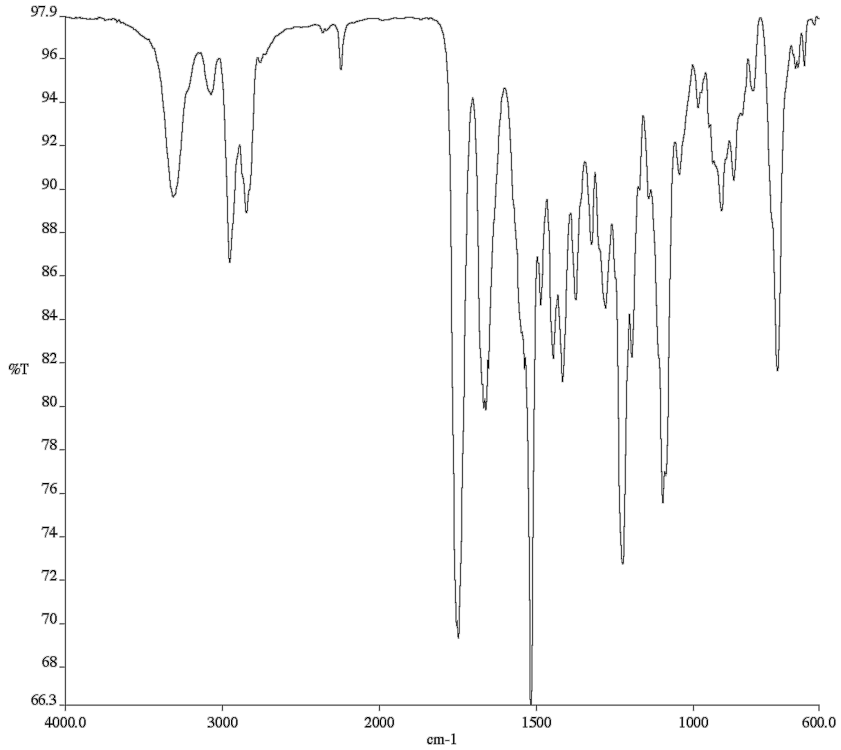
Infrared spectrum (Thin Film, NaCl) of compound **18**.



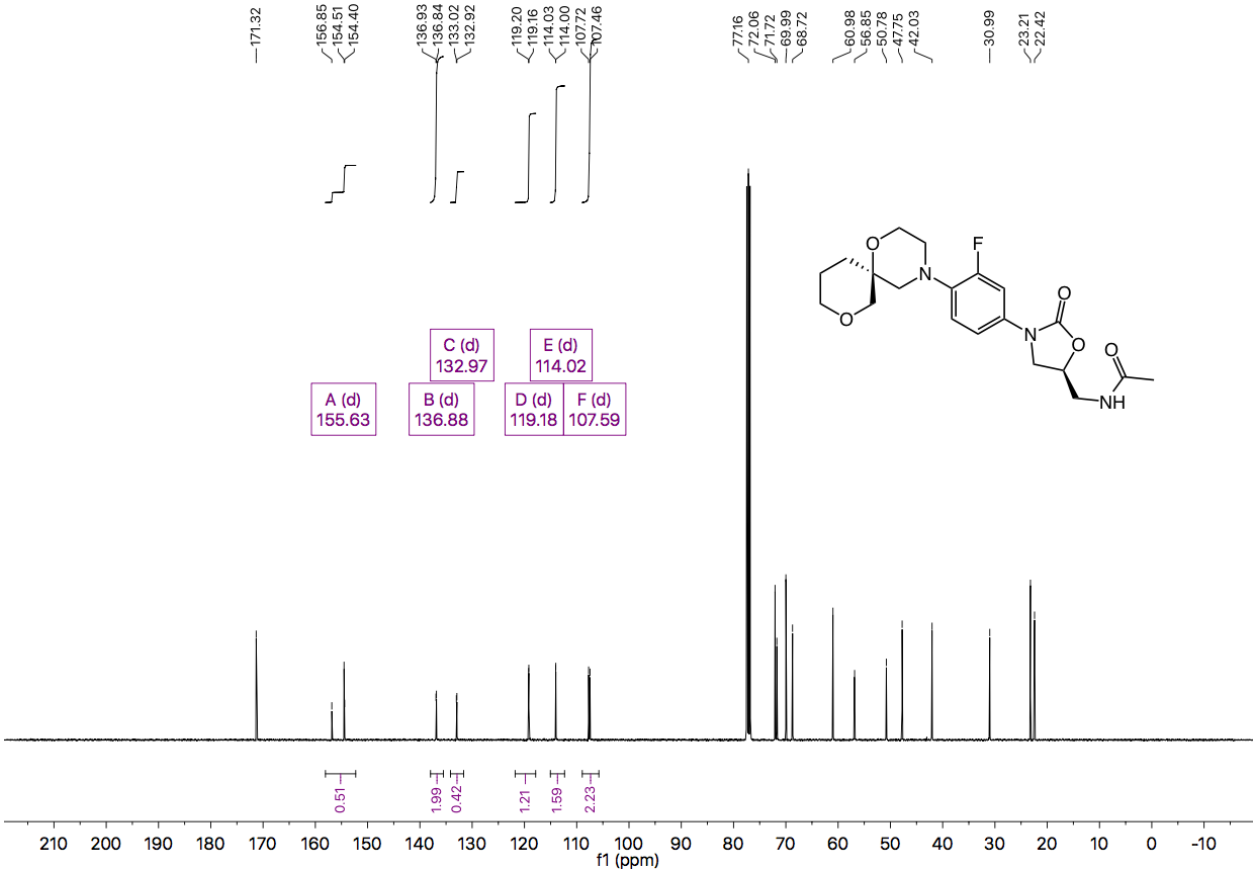
^{13}C NMR (101 MHz, $CDCl_3$) of compound **18**.



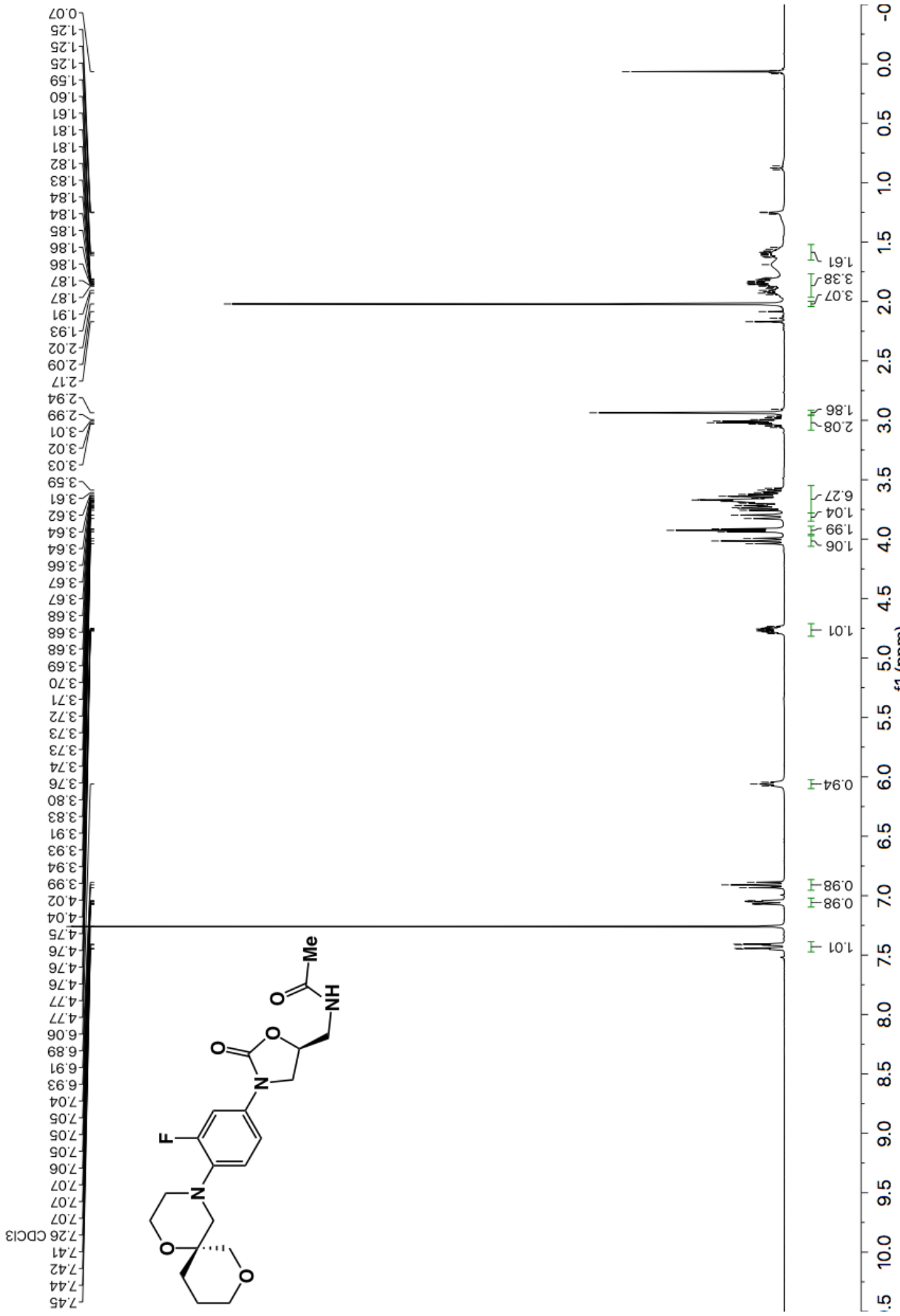
^{1}H NMR (400 MHz, $CDCl_3$) of compound **19a.**



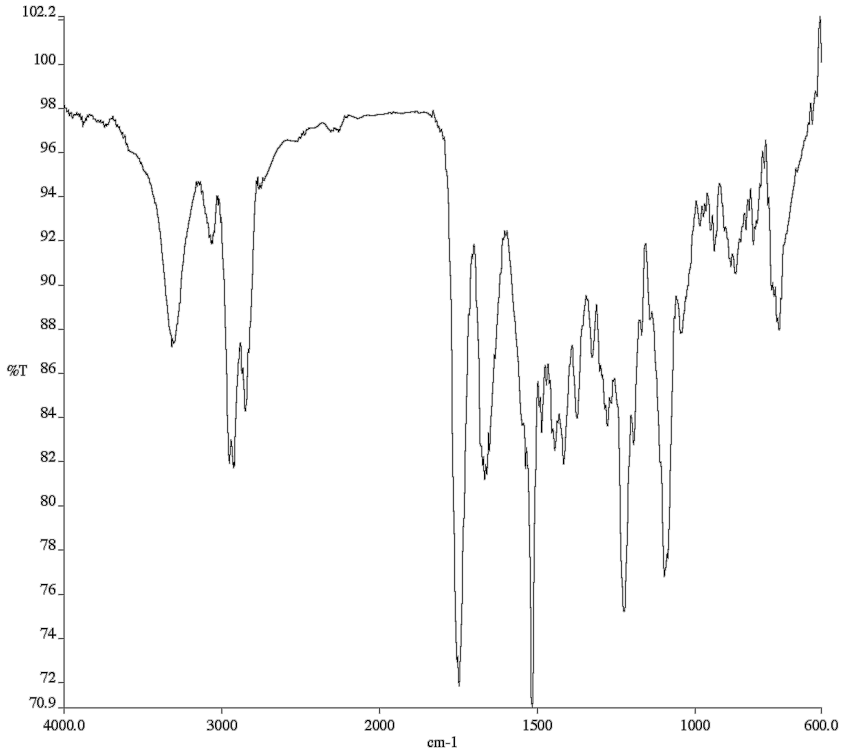
Infrared spectrum (Thin Film, NaCl) of compound **19a**.



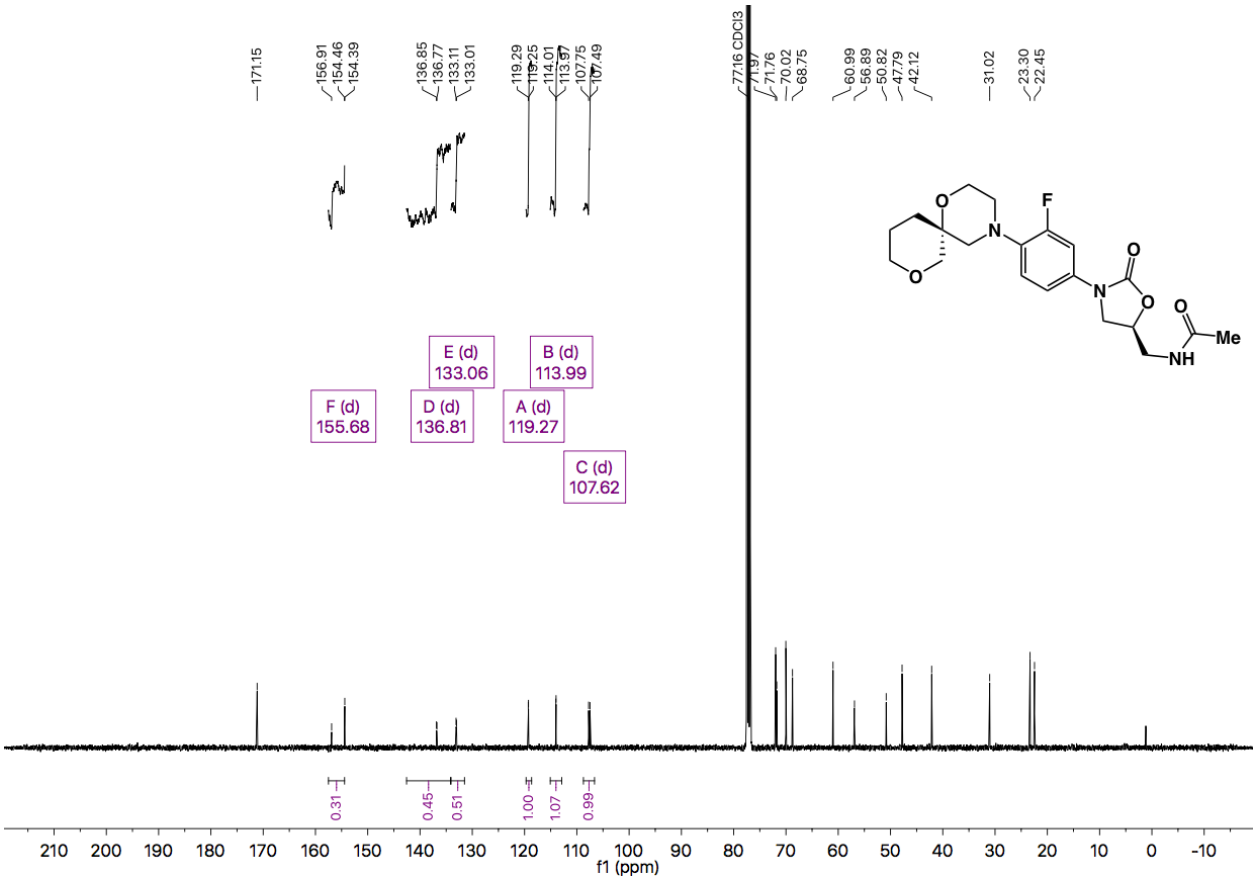
^{13}C NMR (101 MHz, $CDCl_3$) of compound **19a**.



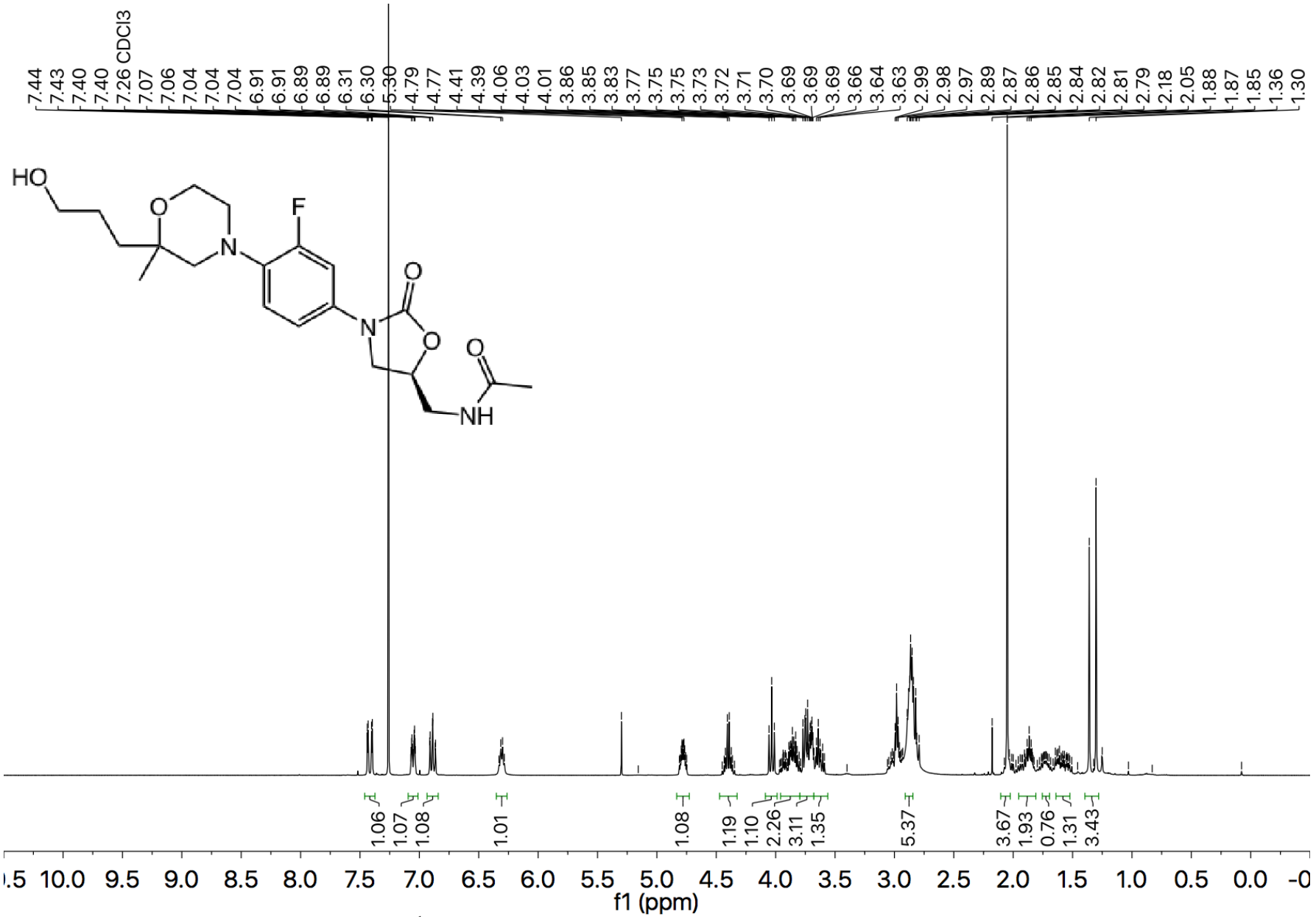
^{1}H NMR (400 MHz, $CDCl_3$) of compound **19b.**



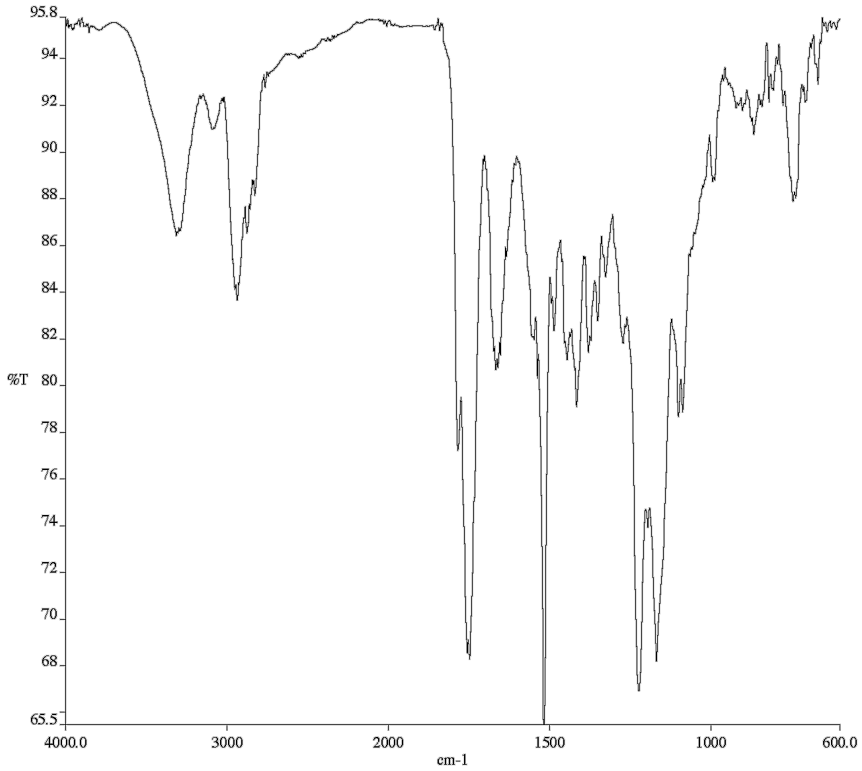
Infrared spectrum (Thin Film, NaCl) of compound **19b**.



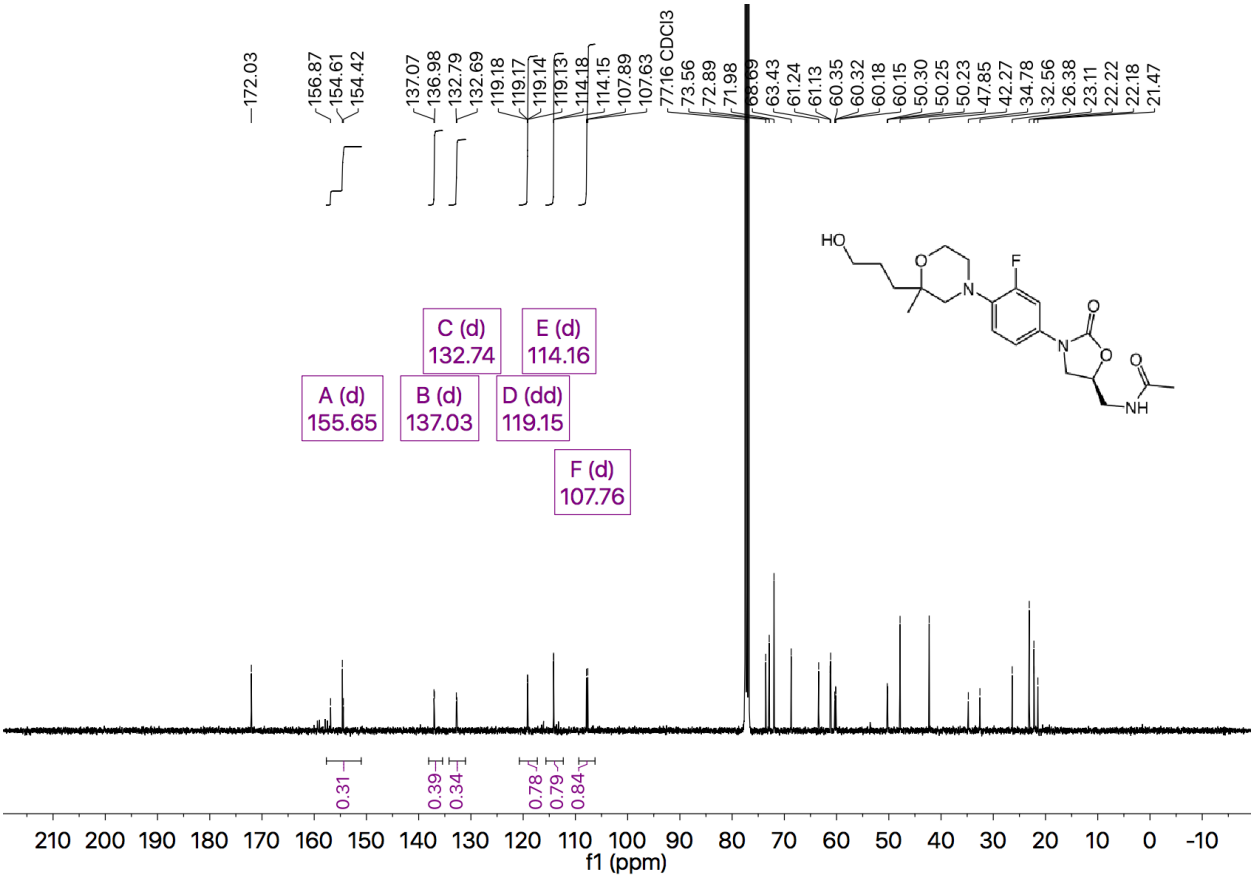
^{13}C NMR (101 MHz, $CDCl_3$) of compound **19b**.



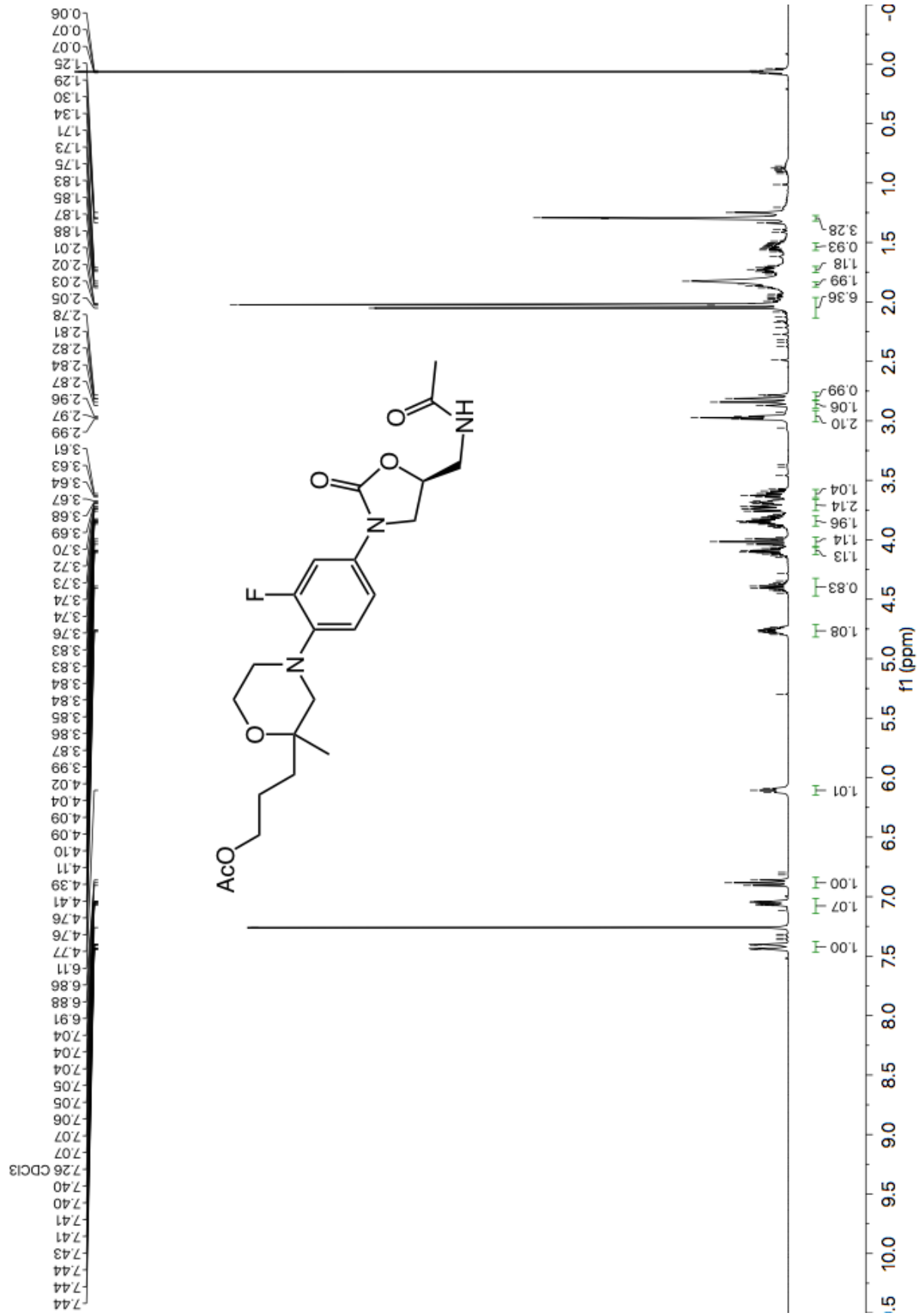
^{1}H NMR (400 MHz, $CDCl_3$) of compound **20.**



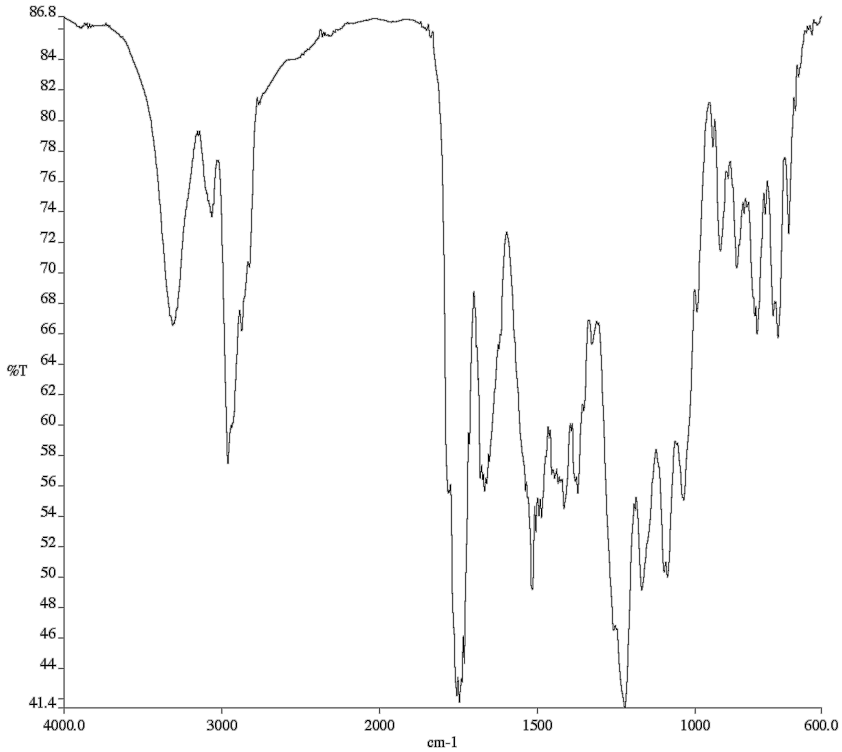
Infrared spectrum (Thin Film, NaCl) of compound **20**.



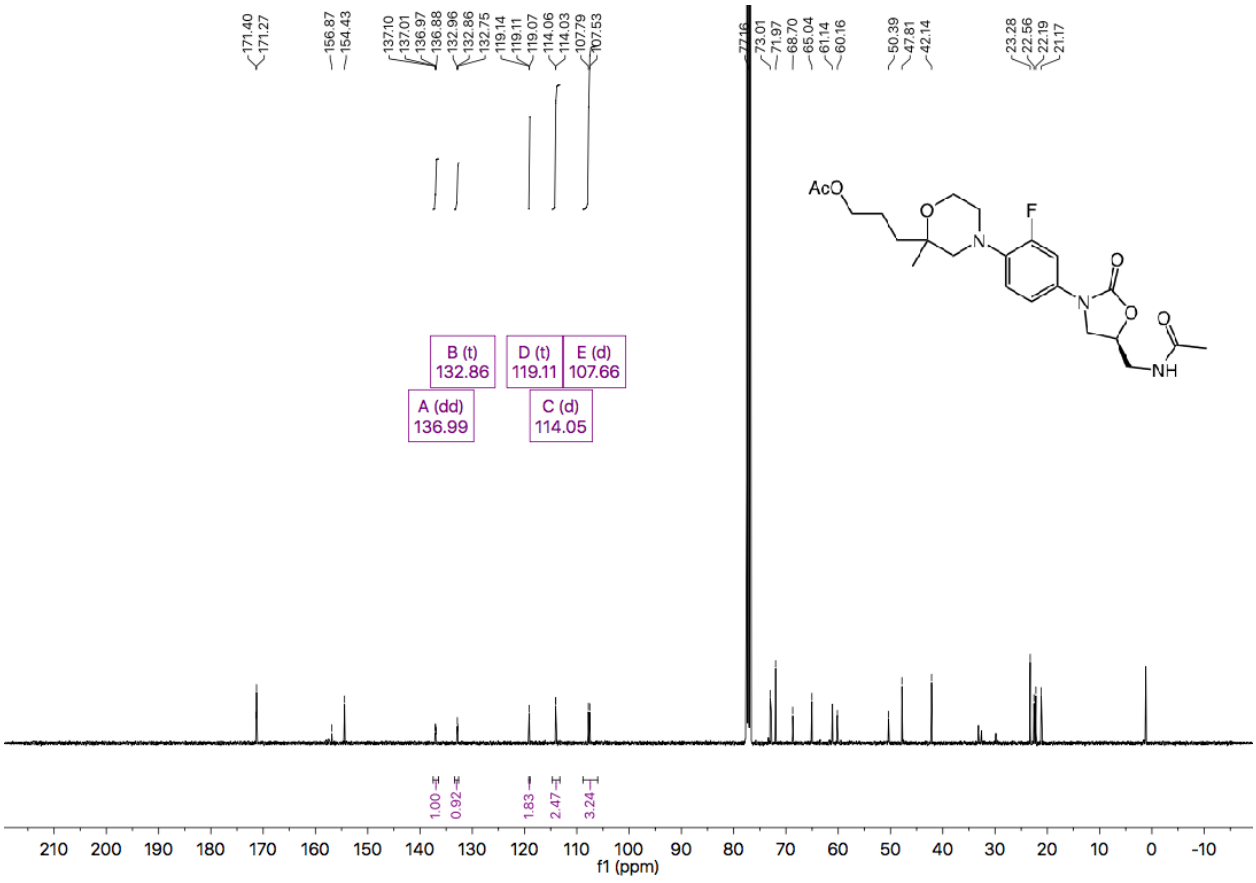
^{13}C NMR (101 MHz, $CDCl_3$) of compound **20**.



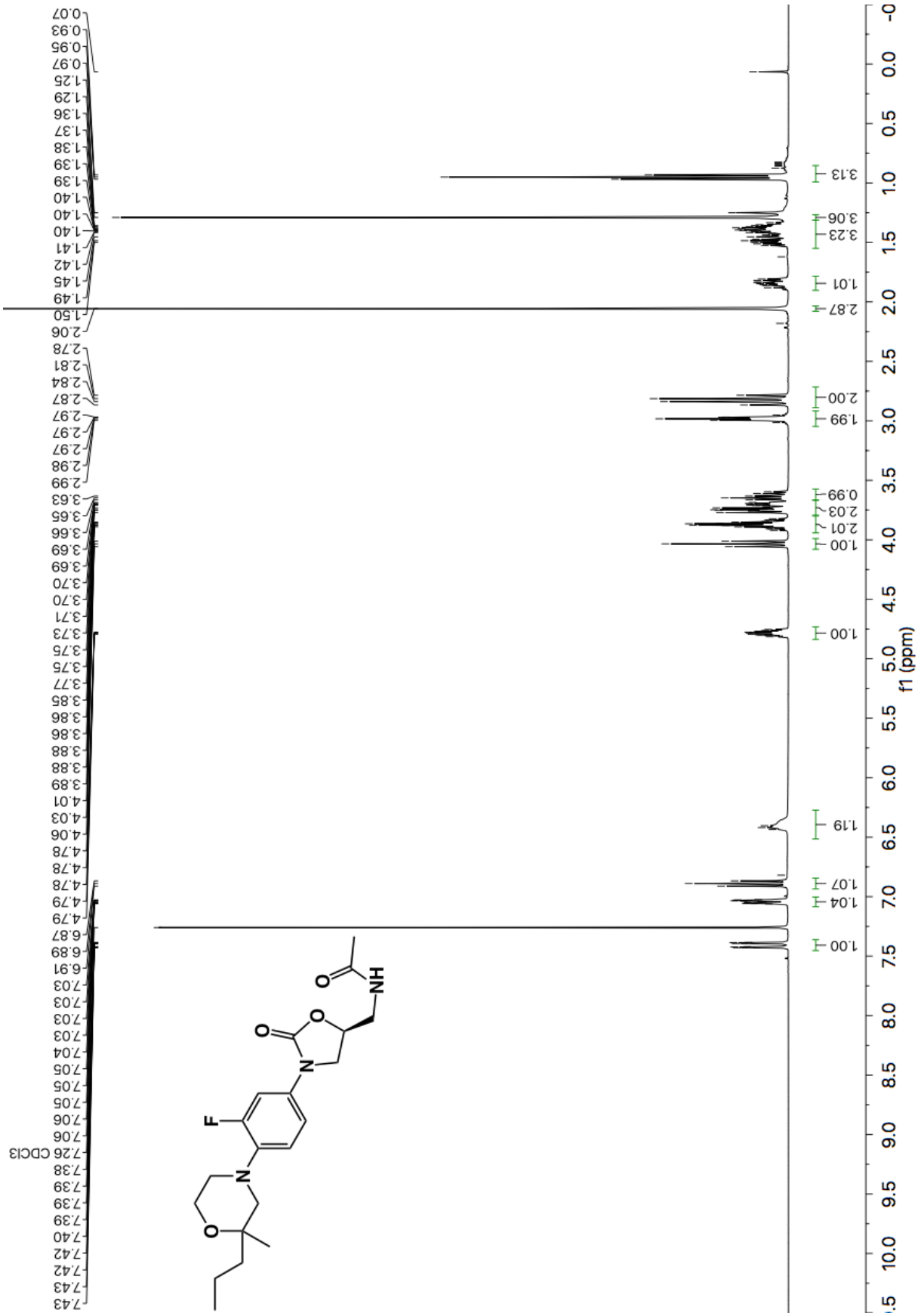
^{1}H NMR (400 MHz, $CDCl_3$) of compound **21.**



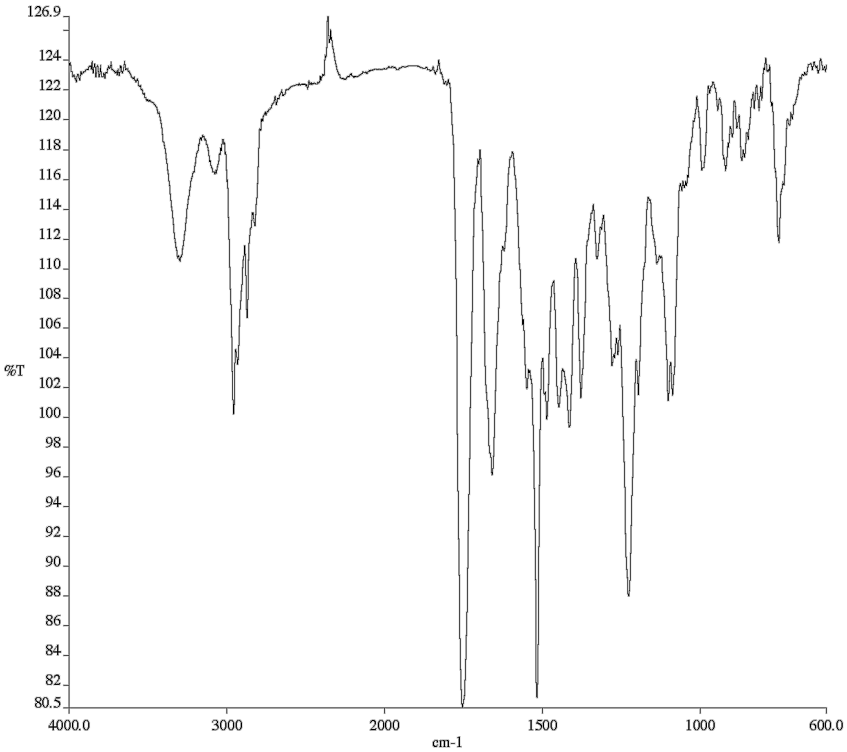
Infrared spectrum (Thin Film, NaCl) of compound **21**.



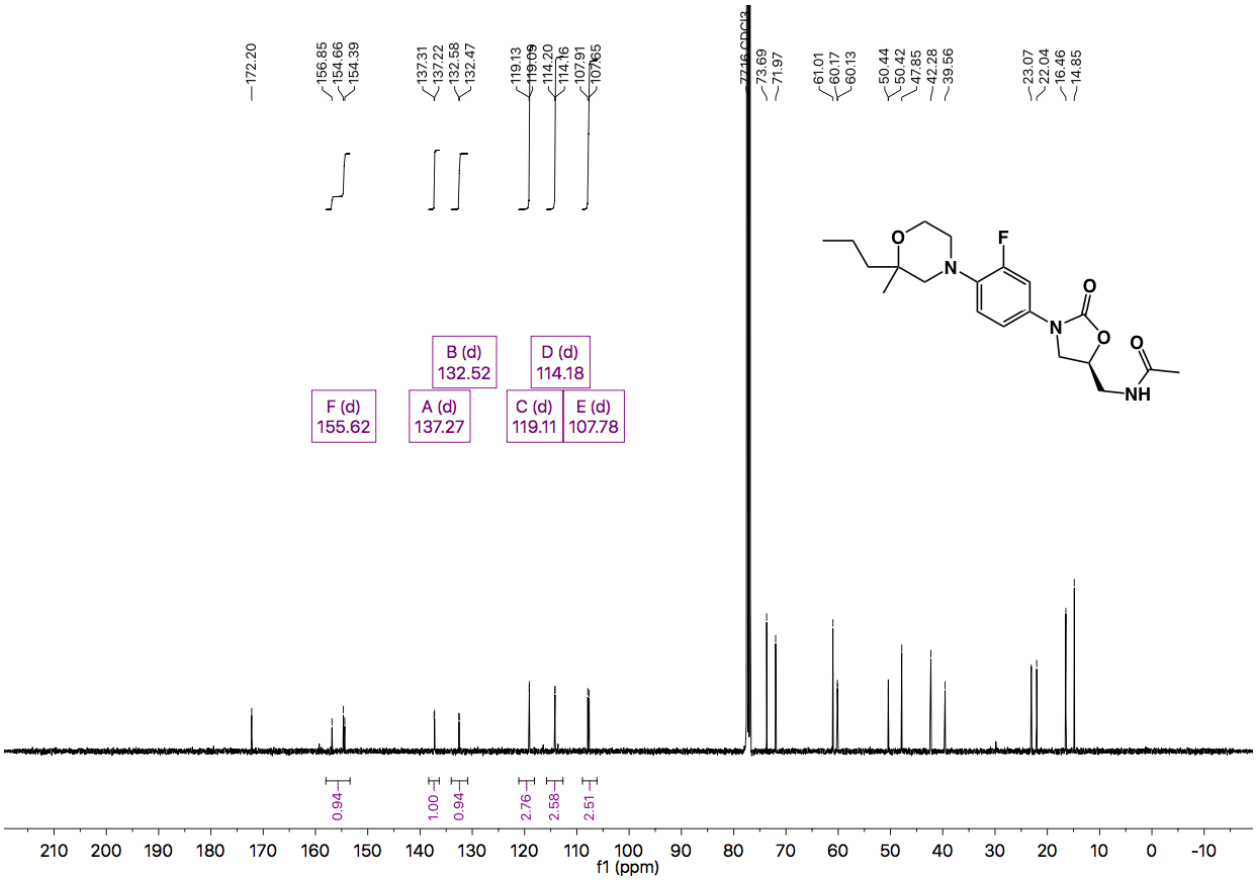
^{13}C NMR (101 MHz, $CDCl_3$) of compound **21**.



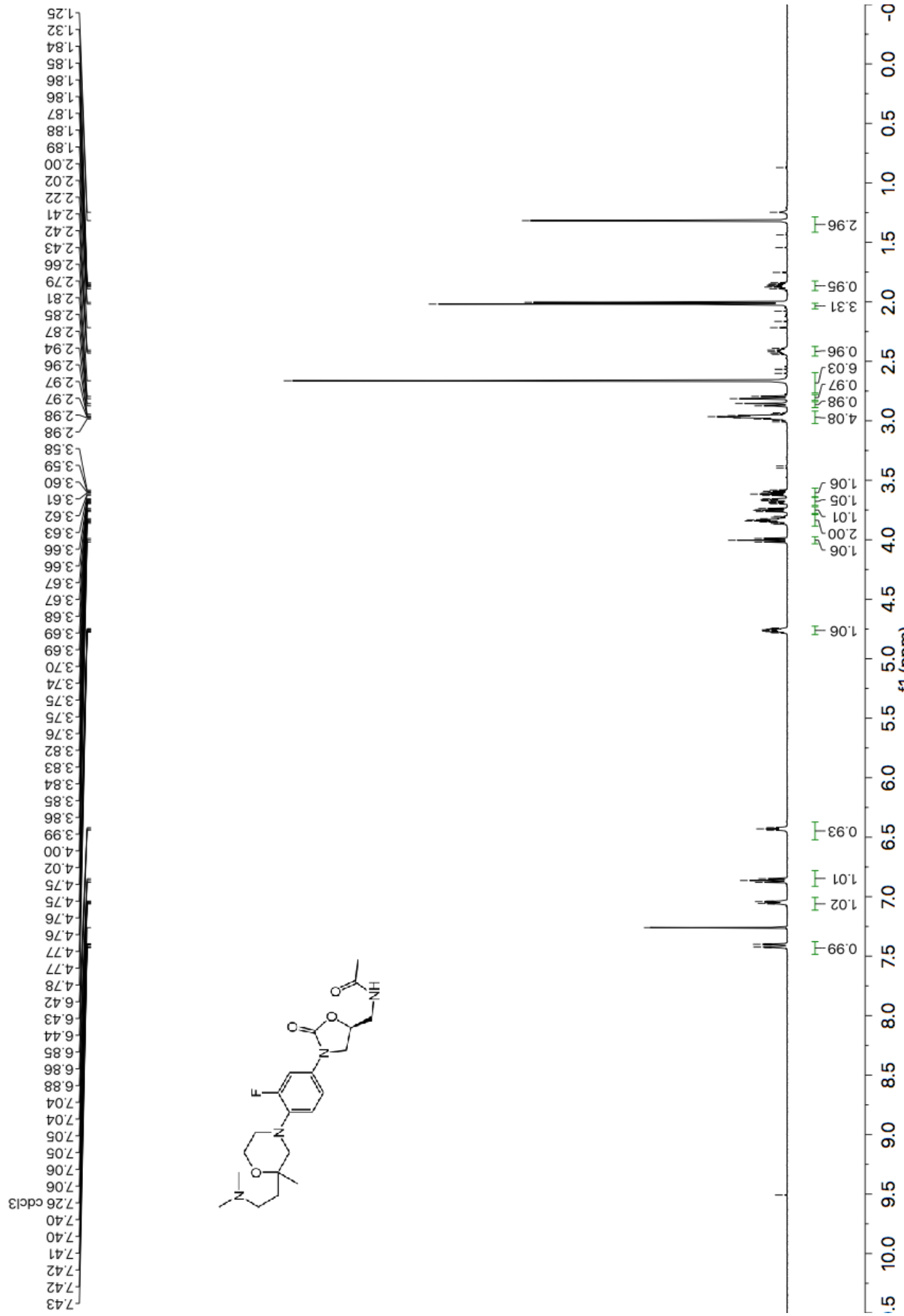
^{1}H NMR (400 MHz, $CDCl_3$) of compound **22.**



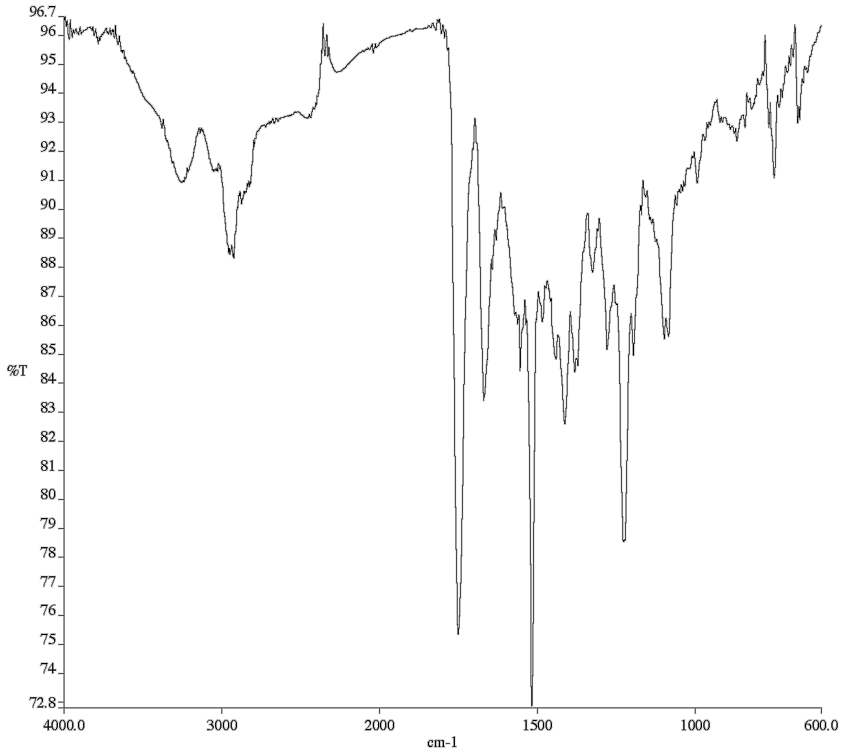
Infrared spectrum (Thin Film, NaCl) of compound **22**.



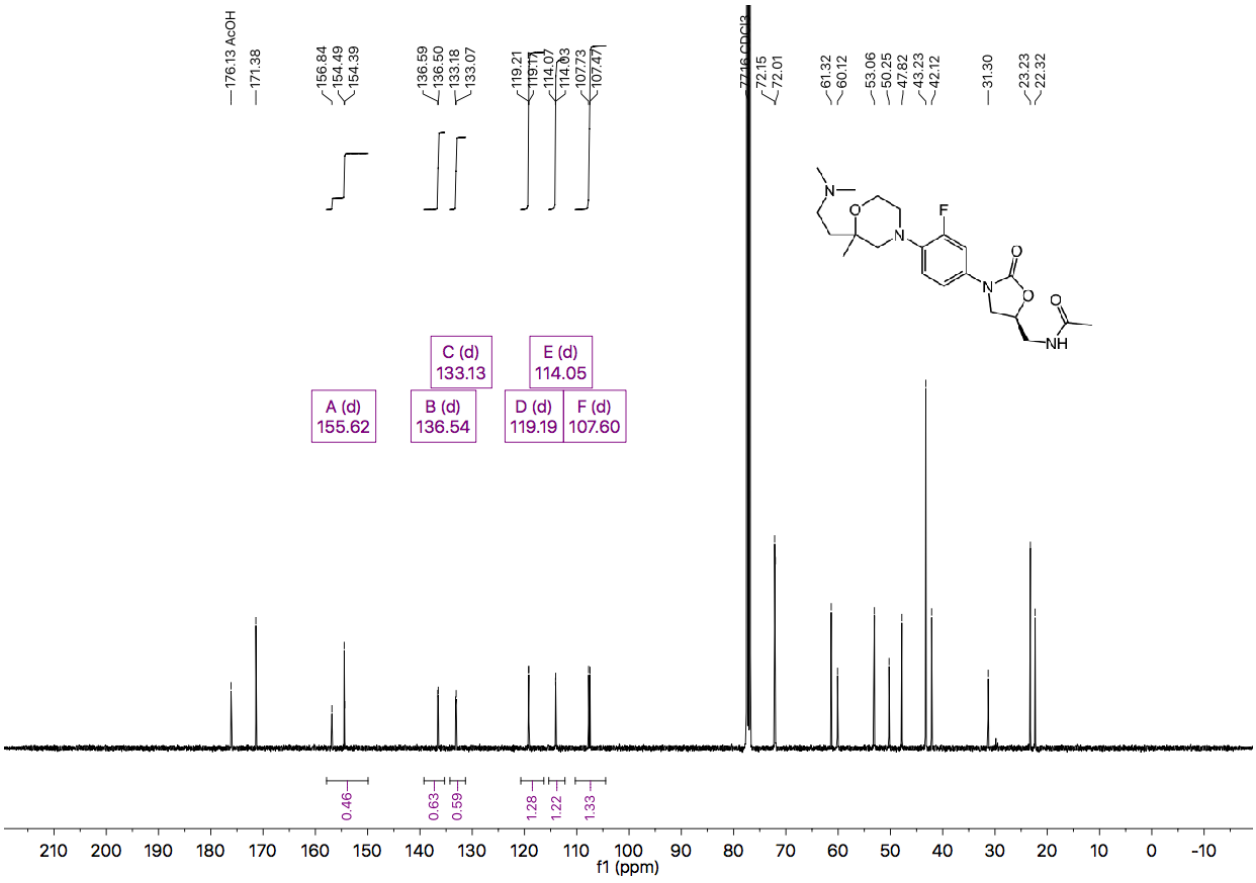
^{13}C NMR (101 MHz, $CDCl_3$) of compound **22**.



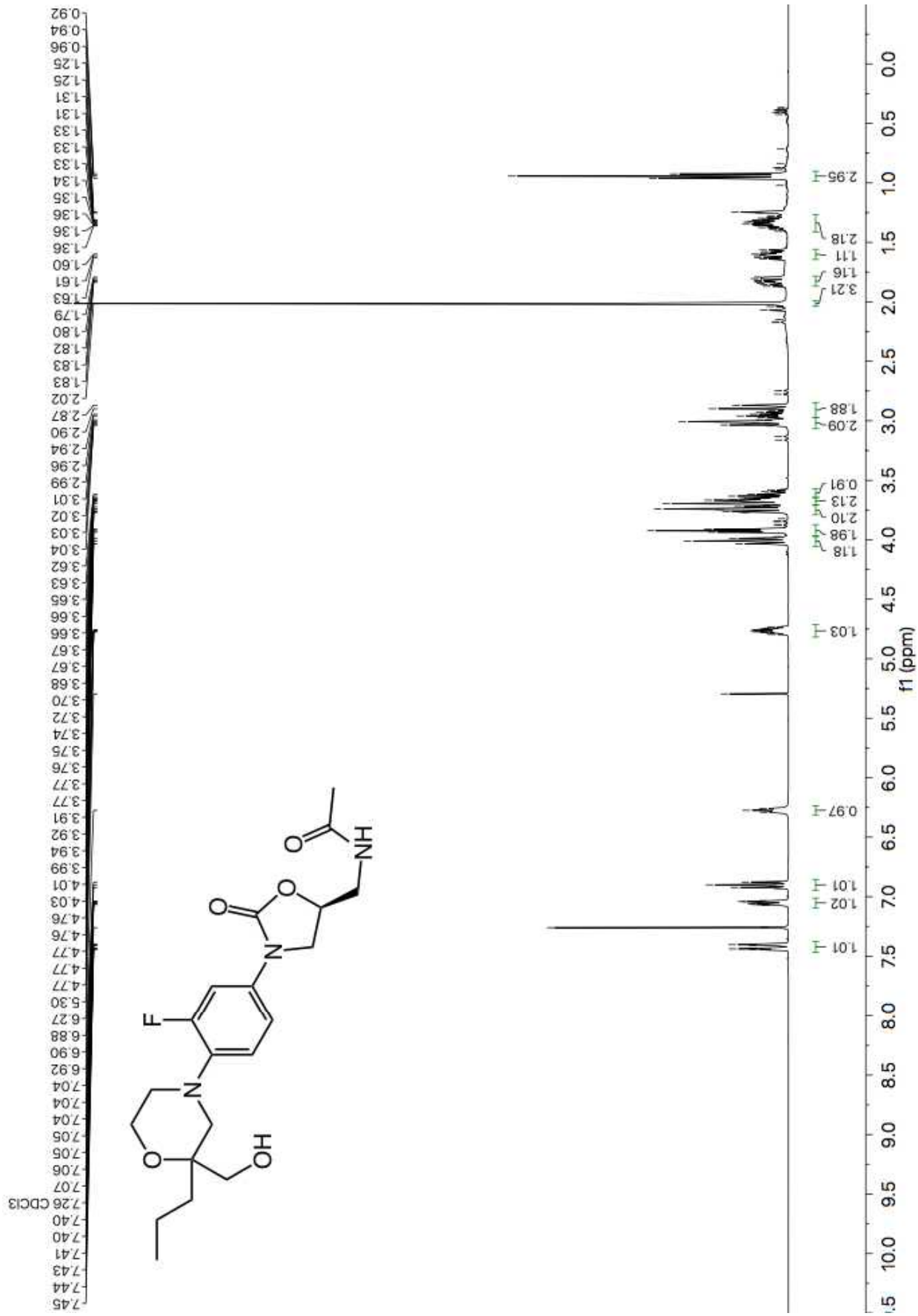
^{1}H NMR (600 MHz, $CDCl_3$) of compound **23.**



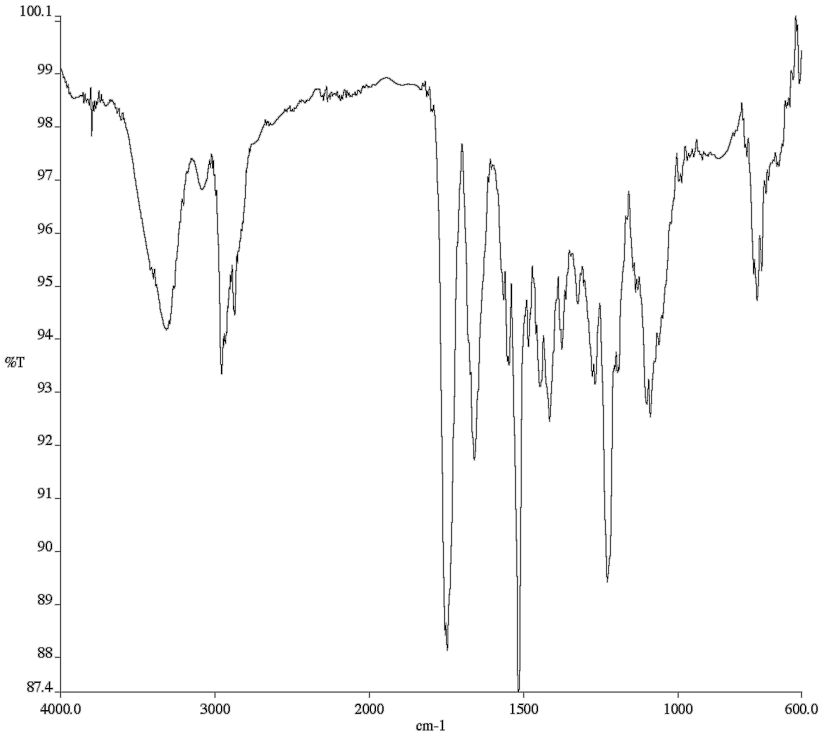
Infrared spectrum (Thin Film, NaCl) of compound **23**.



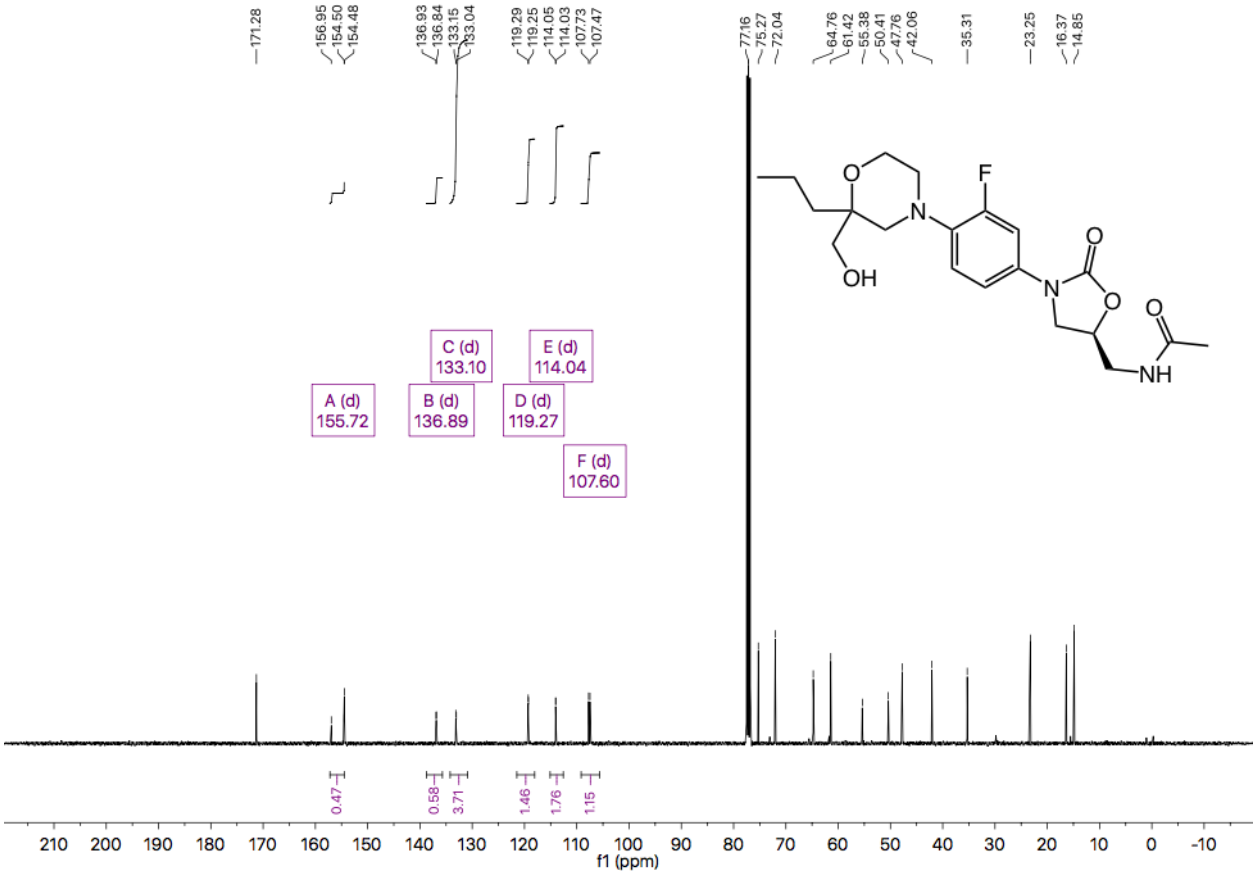
^{13}C NMR (101 MHz, $CDCl_3$) of compound **23**.



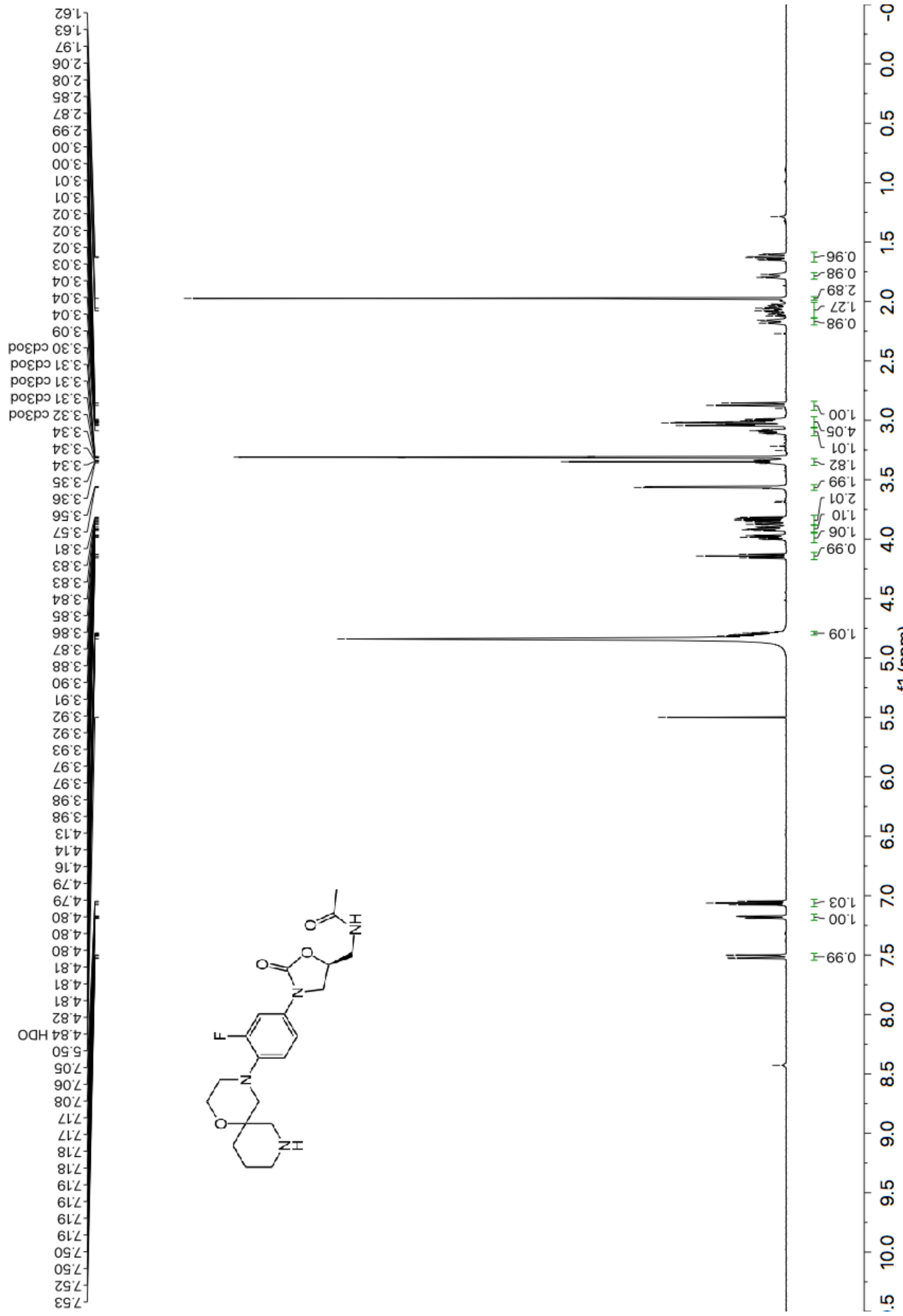
^{1}H NMR (400 MHz, $CDCl_3$) of compound **24.**



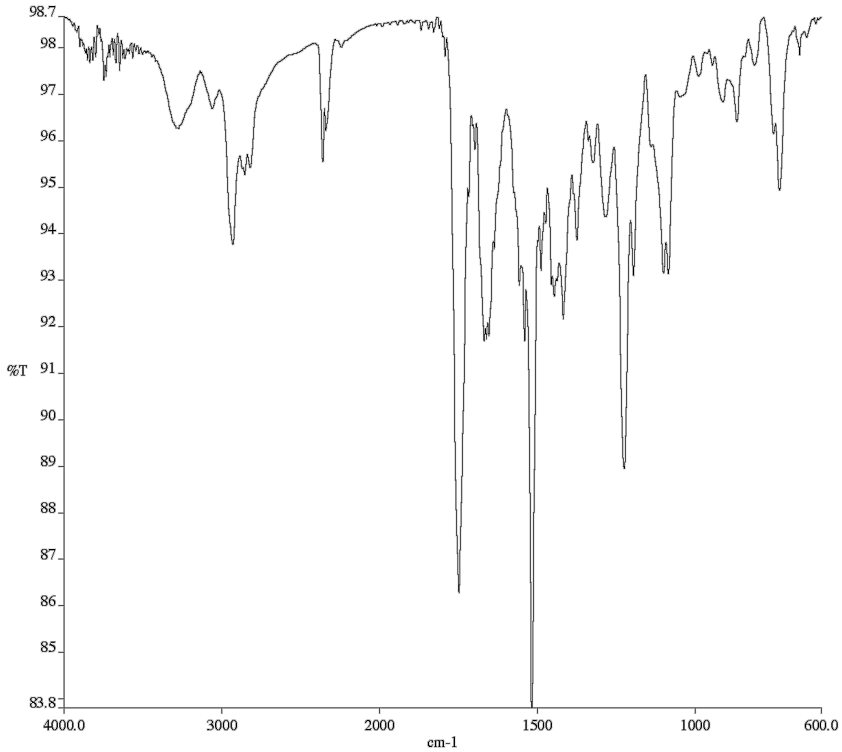
Infrared spectrum (Thin Film, NaCl) of compound **24**.



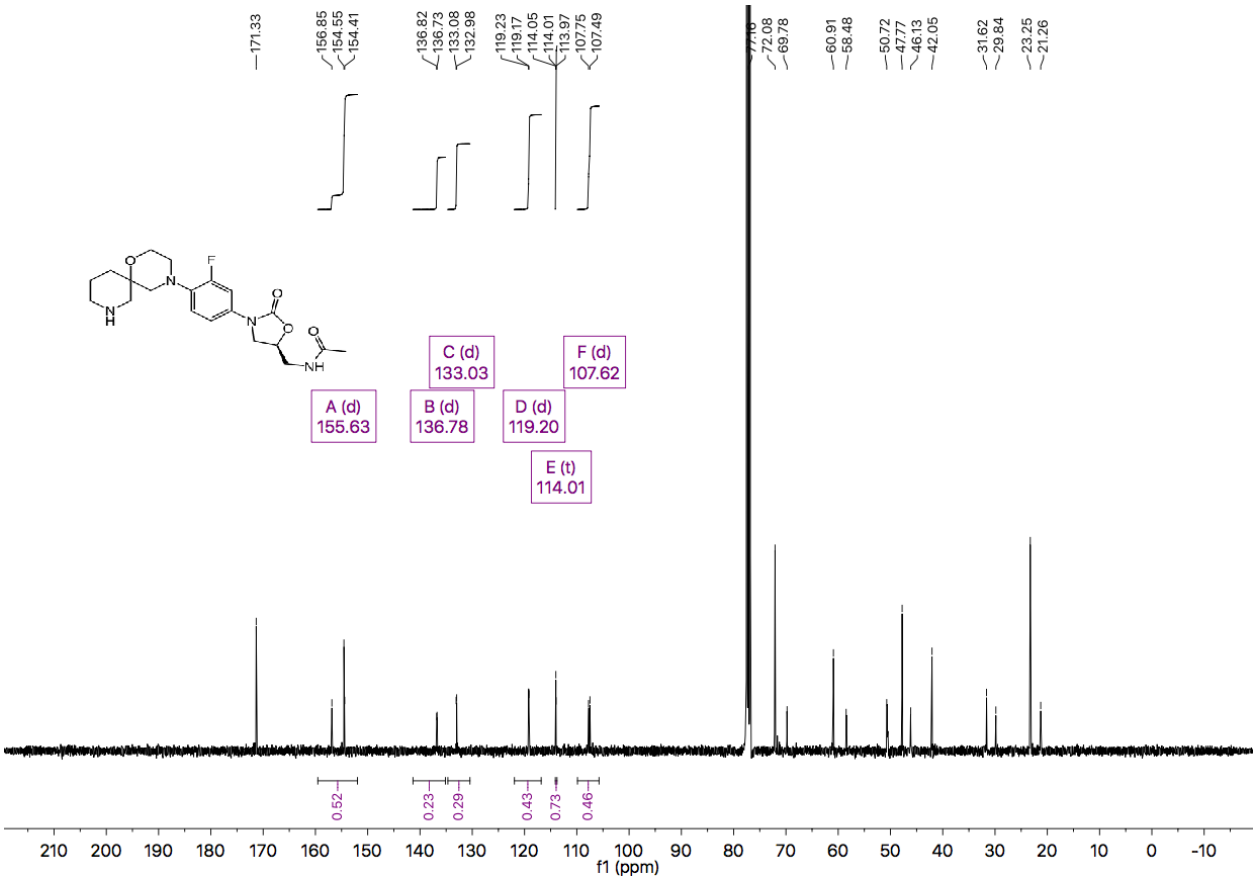
^{13}C NMR (101 MHz, $CDCl_3$) of compound **24**.



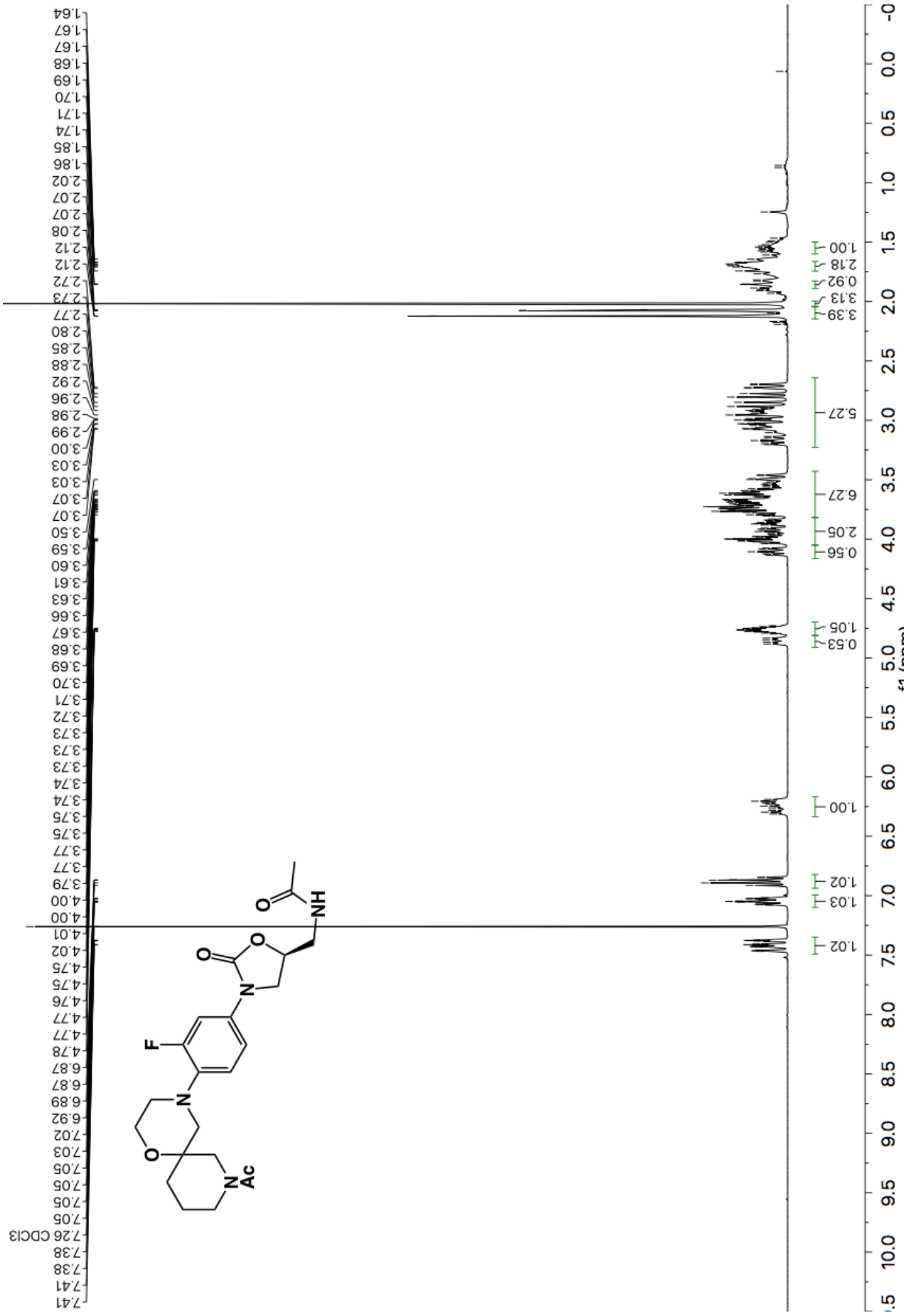
^{1}H NMR (600 MHz, CD_3OD) of compound **25.**



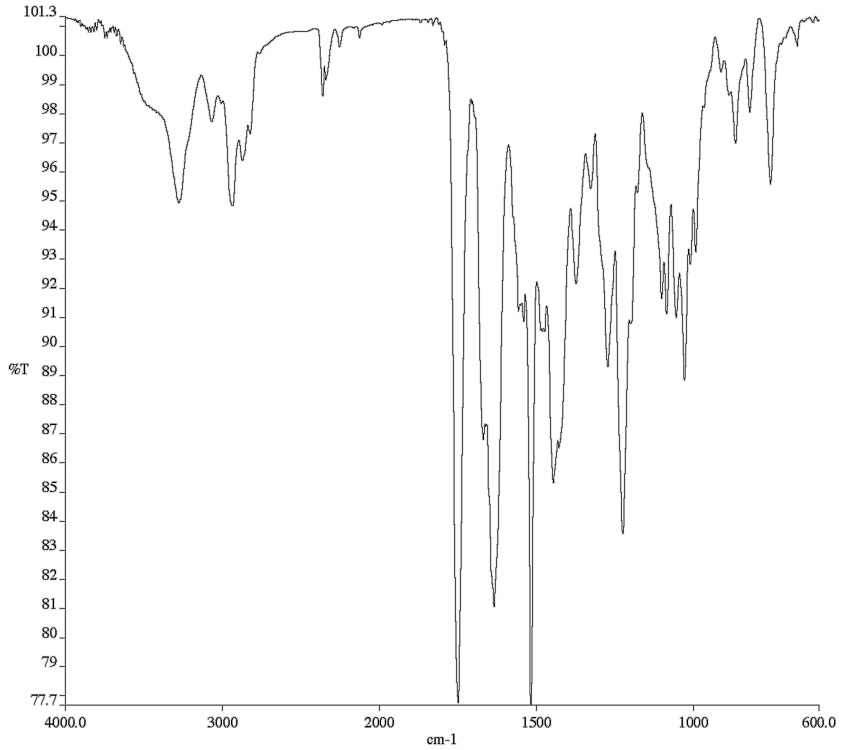
Infrared spectrum (Thin Film, NaCl) of compound **25**.



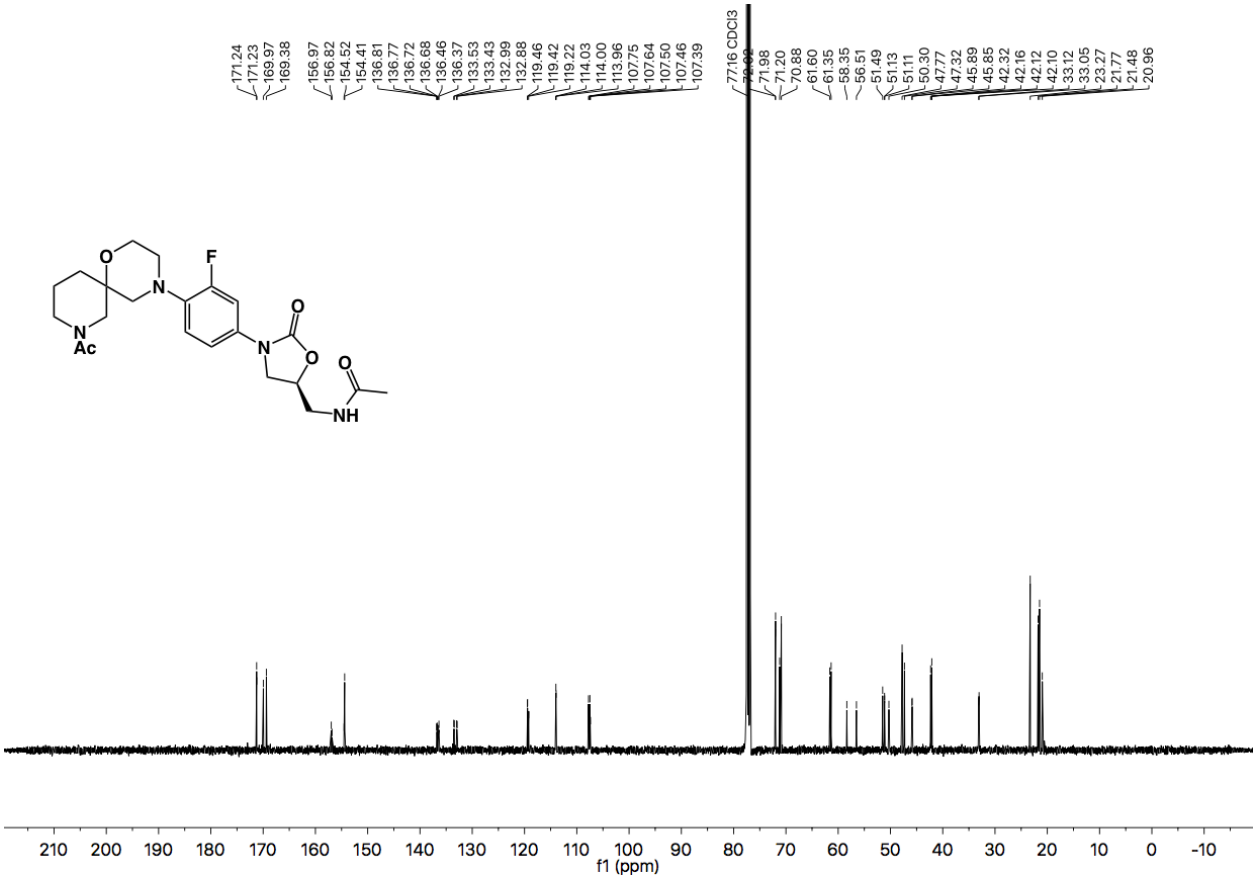
^{13}C NMR (101 MHz, $CDCl_3$) of compound **25**.



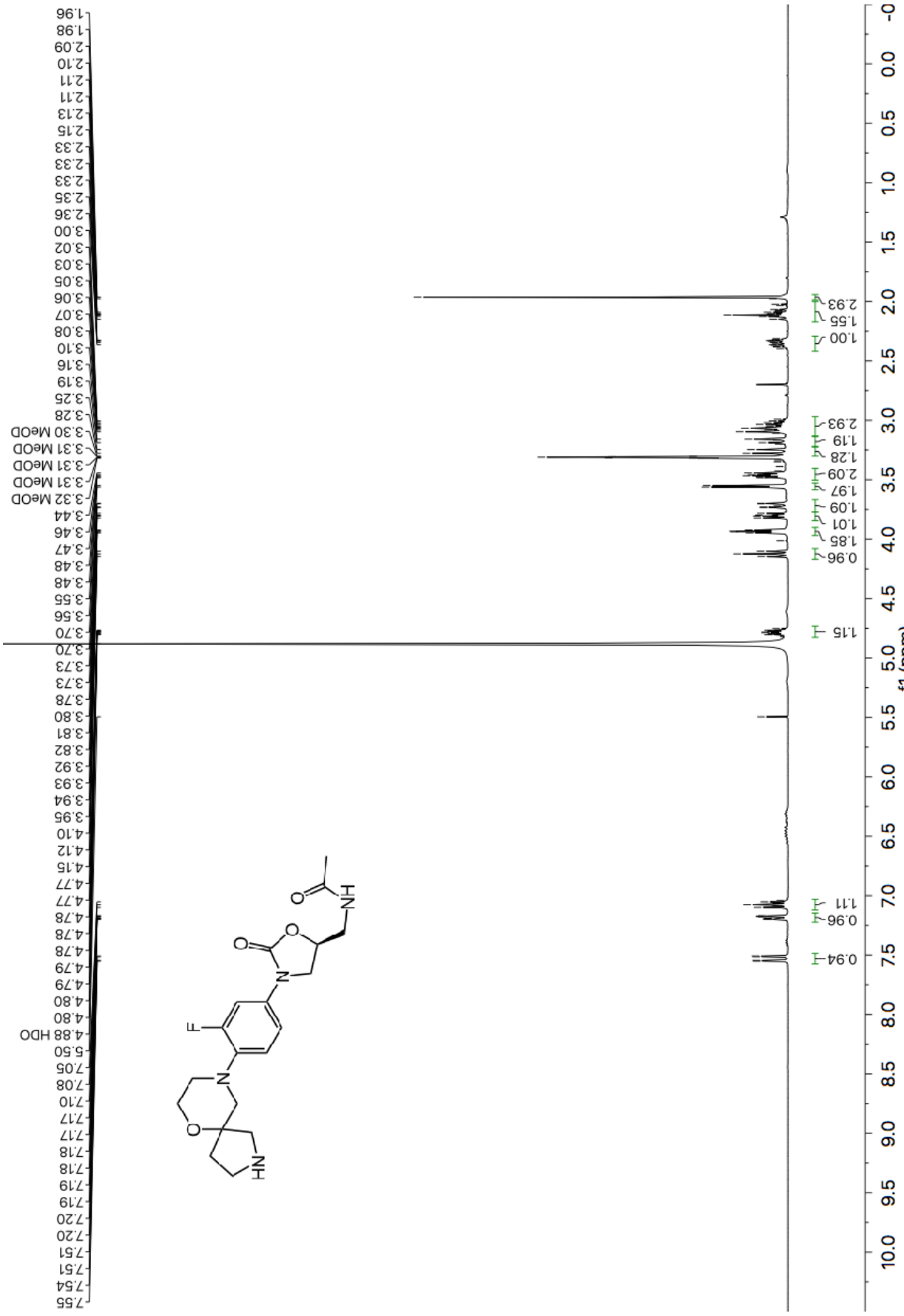
^{1}H NMR (400 MHz, $CDCl_3$) of compound **26.**



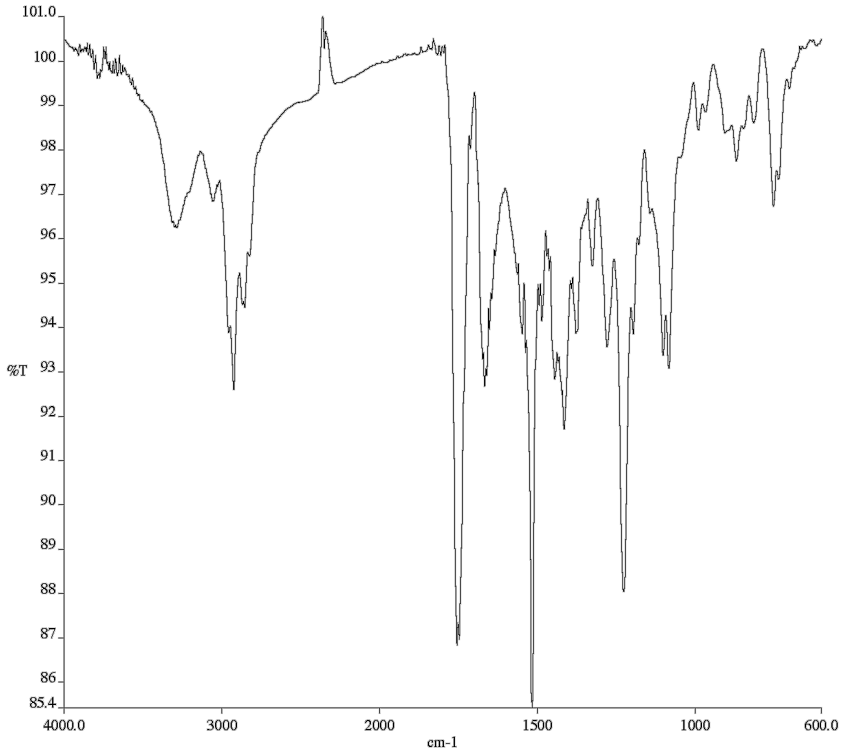
Infrared spectrum (Thin Film, NaCl) of compound **26**.



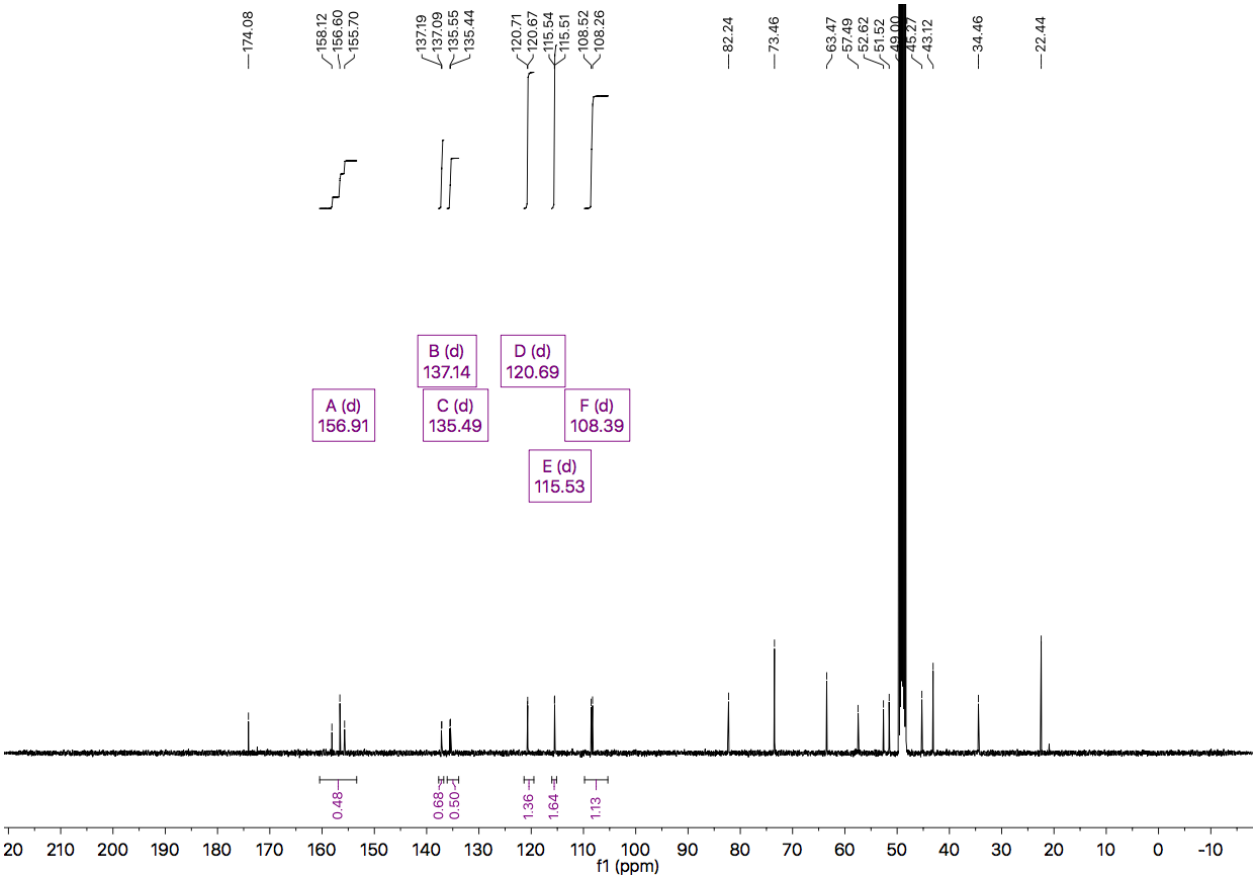
^{13}C NMR (101 MHz, $CDCl_3$) of compound **26**.



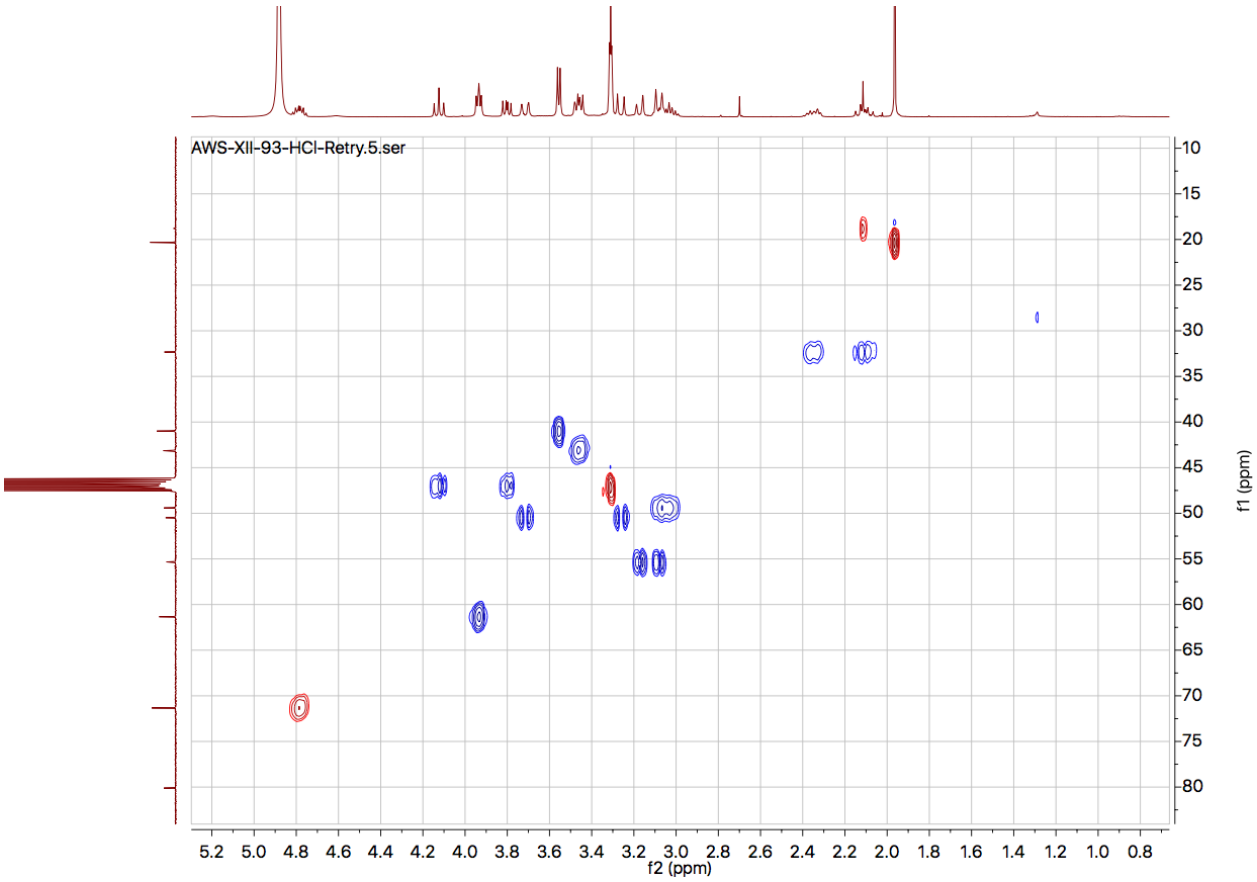
^{1}H NMR (400 MHz, CD_3OD) of compound **27.**



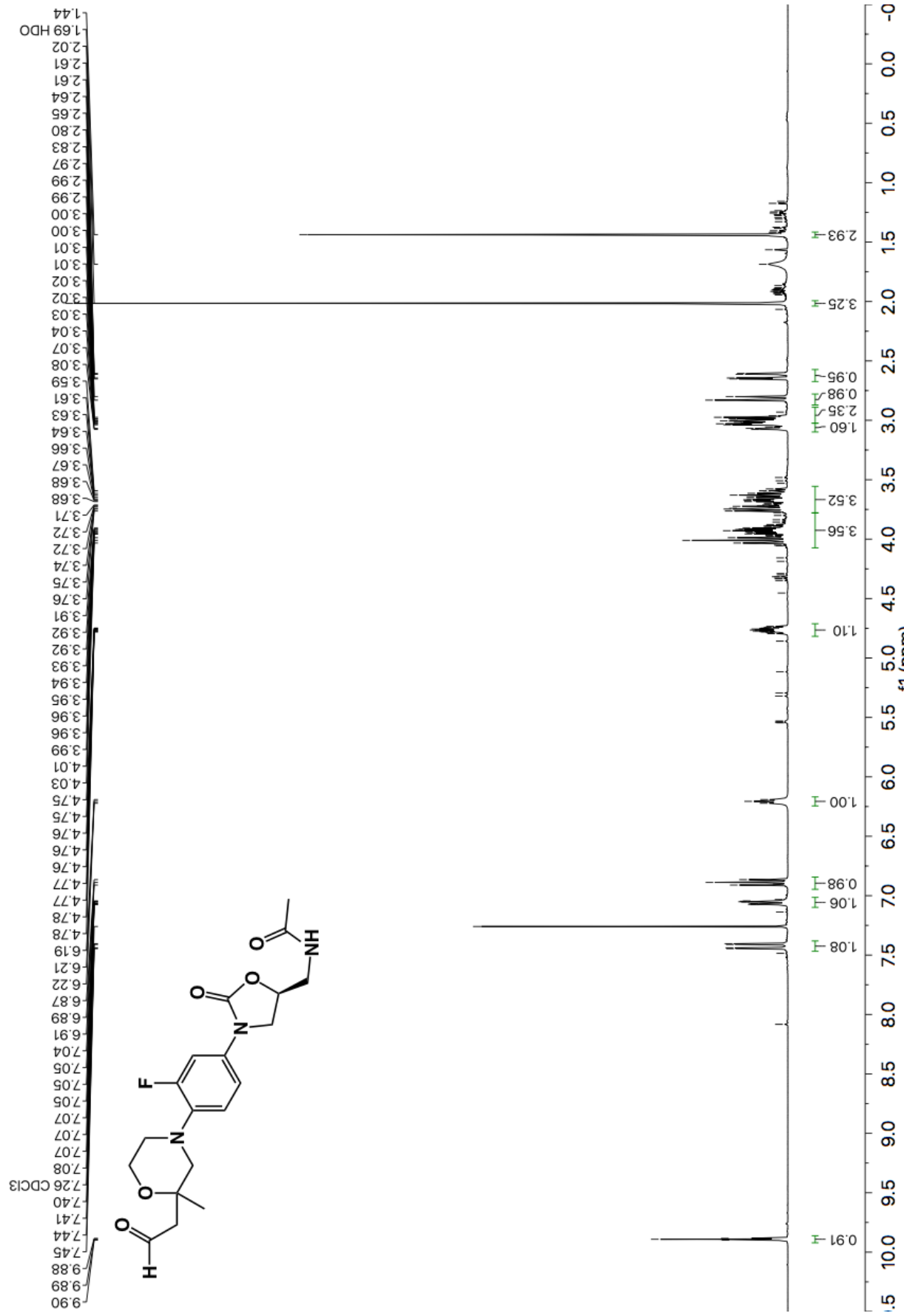
Infrared spectrum (Thin Film, NaCl) of compound **27**.



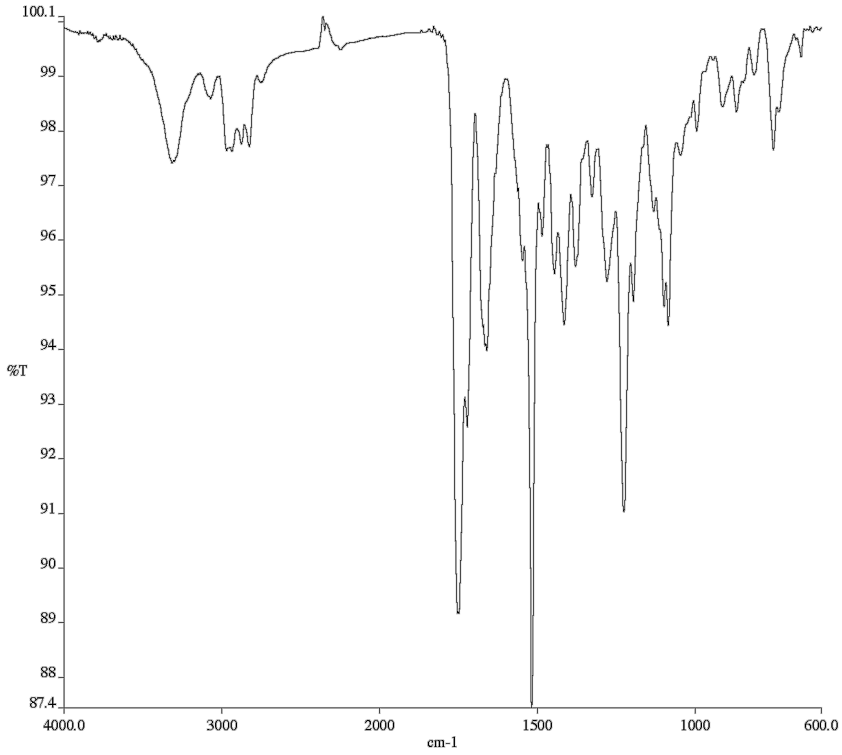
^{13}C NMR (101 MHz, CD_3OD) of compound **27**.



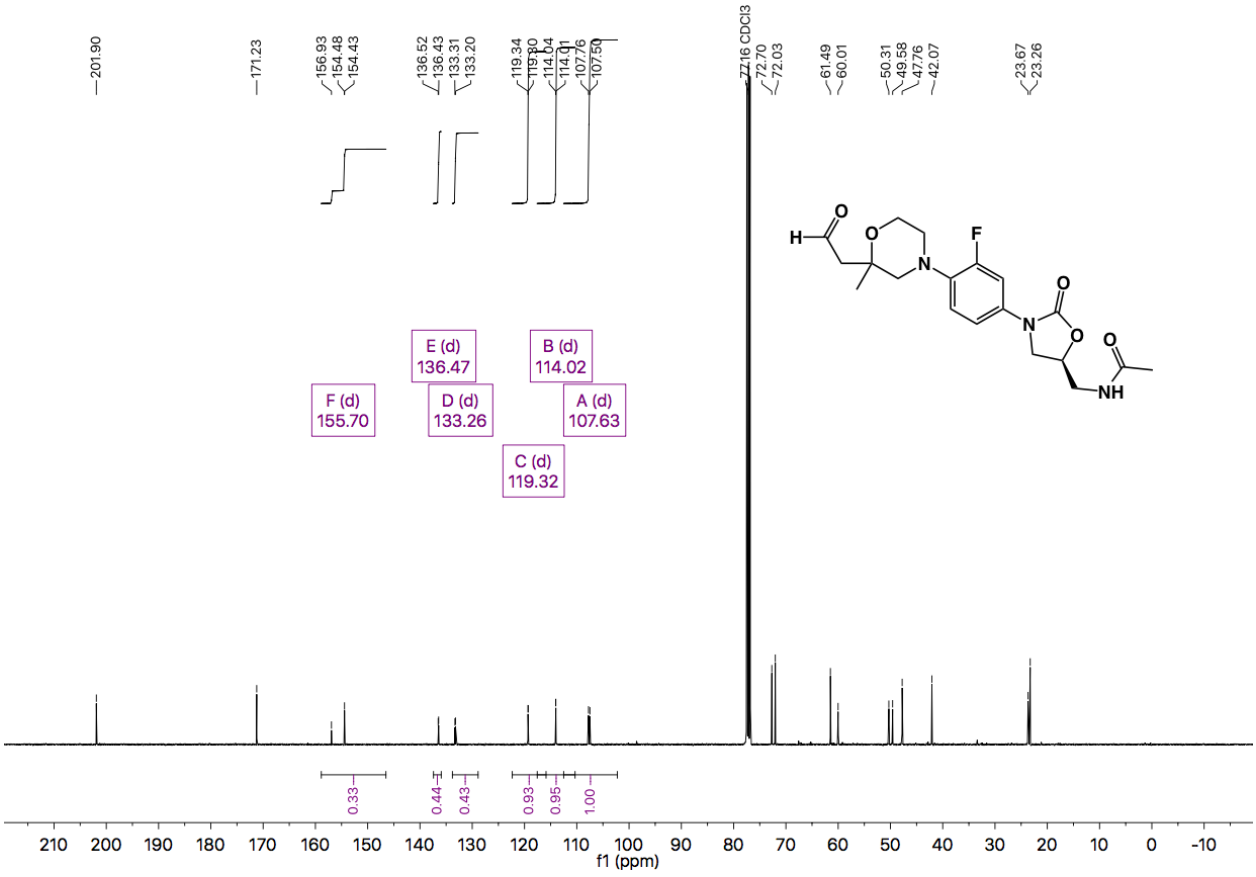
HSQC of compound **27** revealing one peak obscured by CD_3OD.



^{1}H NMR (400 MHz, $CDCl_3$) of compound **SI4.**



Infrared spectrum (Thin Film, NaCl) of compound **SI4**.



^{13}C NMR (101 MHz, $CDCl_3$) of compound **SI4**.