Angewandte Chemie
Eine Zeitschrift der Gesellschaft Deutscher Chemiker

Supporting Information

A Rapid Total Synthesis of Ciprofloxacin Hydrochloride in Continuous Flow

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Supporting Information

Table of Contents

General Experimental Methods

Reactions were carried out in reactors made with coils of extreme-purity PFA tubing (IDEX Health & Science). The tubing was wrapped around an aluminum cylinder and embedded in aluminum shells with cartridge heaters (Omega Engineering) embedded in the central aluminum cylinder for reactions at elevated temperatures. A thermocouple was inserted in those reactors for temperature monitoring and control (Omega Engineering).[1]

The phrase "X was concentrated" refers to removal of solvents by means of a rotary evaporator attached to a Büchi V-700 vacumn pump (bled to 40-1000 mbar as needed). SiliaFlash® F60 (230-400 mesh) from SiliCycle® was used for flash column chromatography. Analytical thin layer chromatography (TLC) was performed using EMD Millipore glass backed plates (Cat# 105715). TLC plates were analyzed by short wave UV illumination.

^1H, ^{13}C and ^{19}F NMR spectra were recorded on a Bruker Avance 400 MHz or a Varian Inova-500 spectrometer in $CDCl_3$ at ambient temperature unless otherwise indicated. Chemical shifts are reported in δ (ppm downfield from tetramethylsilane) and referenced to residual undeuterated solvents (7.26 for ^1H NMR and 77.0 for ^{13}C NMR). Referencing of ^{19}F NMR spectra was calculated by the instruments using the default methods. Coupling constants are reported in Hz with multiplicities denoted as s (singlet), d (doublet), dd (doublet of doublets), ddd (doublet of doublet of doublets), t (triplet), q (quartet), m (multiplet) and br (broad). High resolution mass spectra (HRMS) were performed by the Department of Chemistry Instrumentation Facility at Massachusetts Institute of Technology on a Bruker Daltonics APEXIV 4.7 Tesla Fourier Transform Ion Cyclotron Resonance Mass Spectrometer (FT-ICR-MS), using direct analysis in real time (DART).

Screen of Conditions for acylation of 7

Table S1. Screen of conditions for acylation of **7**.

Solvent \ Base	Triethylamine	Diethylisopropylamine	DBU[h]
THF[a]	Full conversion, precipitation	Full conversion, precipitation	N/A
MeCN[b]	Full conversion, precipitation	Full conversion, clear	No desired product
Acetone	Full conversion, precipitation	Full conversion, precipitation	No desired product
1,4-Dioxane	Full conversion, precipitation	Full conversion, precipitation	N/A
Chloroform	Full conversion, clear	Full conversion, clear	No desired product
DCM[c]	Full conversion, precipitation	N/A	N/A
1,2-DCE[d]	Full conversion, precipitation	N/A	N/A
Toluene	Full conversion, precipitation	Full conversion, precipitation	No desired product
DMSO[e]	Full conversion, precipitation, low yield	No desired product	N/A
DMF[f]	Full conversion, precipitation, low yield	N/A	N/A
DMA[g]	Full conversion, precipitation, low yield	N/A	N/A

[a] Tetrahydrofuran. [b] Acetonitrile. [c] Dichloromethane. [d] 1,2-dichloroethane. [e] Dimethylsulfoxide. [f] *N,N*-dimethylfomamide. [g] *N,N*-dimethylacetamide. [h] 1,8-Diazabicyclo[5.4.0]undec-7-ene.

Optimization of one-pot cyclization−S_NAr reaction of crude 4

Table S2. Solvent effect of optimization of cyclization−S_NAr with crude 4 in batch.[a]

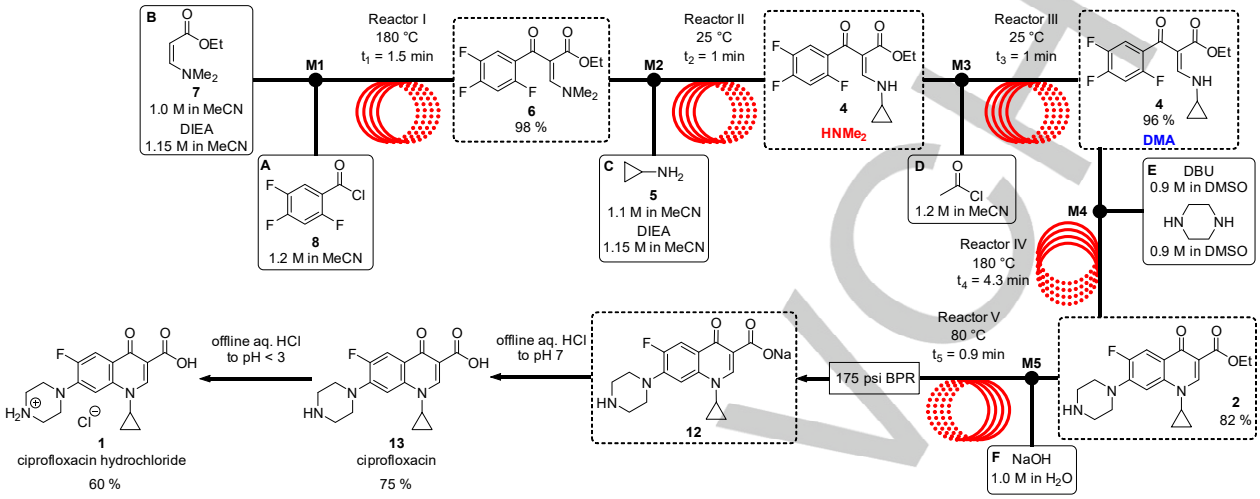
Solvent added	Concentration (M)	Yield of **4** (%)[b]	Observation
DMSO	0.15	70	Emulsion after reaction
DMSO	0.075	73	Clear after reaction
DMSO	0.09	86[c]	Clear after reaction
MeCN	0.15	78	Precipitated after reaction
MeCN	0.075	64	Precipitated after reaction
1:1 DMSO/MeCN	0.15	81[d]	Clear after reaction, precipitated upon standing
1:1 DMSO/MeCN	0.075	81	Clear after reaction, precipitated upon standing

[a] Reactions were run at 180 °C in sealed vessels for 5 min with 3.5 equiv. of DBU and 3.5 equiv. of piperazine. [b] ^{1}H NMR yields. 1,3,5-Trimethoxybenzene was used as standard except otherwise noted. [c] Isolated yield in flow, Scheme 4b, started from pure **4**. [d] Isolated yield in flow.

SUPPORTING INFORMATION

Procedure of Continuous Synthesis of Ciprofloxacin Hydrochloride 1

Scheme S1. Flow scheme of continuous total synthesis of ciprofloxacin



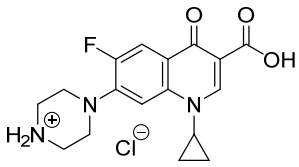
Solutions A-D were prepared in oven-dried 10 mL screw cap volumetric flasks (Kimberly Chase 621600-0010) and loaded into oven-dried 8 mL stainless steel syringes (Harvard Apparatus 70-2267) under a nitrogen atmosphere. Syringes were then mounted onto and driven by syringe pumps (PHD 22/2000 Syringe Pump or PHD ULTRA™ Syringe Pump). Without any precautions, solution E was prepared in a 25 mL volumetric flask and loaded into a 20 mL stainless steel syringe (Harvard Apparatus 70-2251). The syringe was then mounted onto and driven by a PHD ULTRA™ high pressure syringe pump. Solution F was pumped by a Knauer HPLC pump. Back pressure was regulated with a back pressure regulator (BPR).[1] Mixing was done by combining two streams into a tee (IDEX Health & Science P-712) followed by a short piece of modified PFA tubing with repeated constraints (0.50 mm ID, 1.59 mm OD for M1 and 0.75 mm ID, 1.59 mm OD for M2-5).[2]

Table S3. Solution preparation list for the synthesis

Solution stream	Composition	Pump	Flow rate (µL/min)
A	**8** (1.2 M in MeCN)	Syringe pump A	148.13
B	**7** (1.0 M in MeCN) DIEA (1.15 M in MeCN)	Syringe pump B	148.13
C	**5** (1.25 M in MeCN) DIEA (1.15 M in MeCN)	Syringe pump C	148.13
D	Acetyl chloride (1.2 M in MeCN)	Syringe pump C	148.13
E	DBU (0.9 M in DMSO) Piperazine (0.9 M in DMSO)	High pressure syringe pump D	576.07
F	NaOH (1.0 M in H_2O)	Knauer pump	888.8

The whole sequence was run as follows: before pumping, all reactors were primed with anhydrous acetonitrile. Solutions A and B were mixed into Reactor I (0.50 mm ID, 1.59 mm OD, 444 µL) at 180 °C for a residence time of 1.5 min. The outlet stream was mixed with solution C and passed through coiled PFA Reactor II (0.75 mm ID, 1.59 mm OD, 444 µL) at ambient temperature for a residence time of 1 min. The outlet stream was mixed with solution D into Reactor III (0.75 mm ID, 1.59 mm OD, 593 µL) at ambient temperature for a residence time of 1 min. The outlet stream was mixed with solution E into Reactor IV (1.55 mm ID, 3.18 mm OD, 5 mL) at 180 °C for a residence time of 4.3 min. The outlet stream was mixed with solution F into Reactor V (1.0 mm ID, 1.59 mm OD, 1.8 mL) at 80 °C for a residence time of 0.9 min. The outlet stream was passed through a 175 psi BPR. The outlet stream was collected for 2 min after running the sequence for 27 min (3 residence times). **It is critical to wrap the mixer and the tubing from the outlet of Reactor IV to the inlet of Reactor V and the back pressure regulator with insulation to prevent clogging**. Then syringe pumps A-C were stopped. Remaining solutions of **2** and **12** in Reactor IV and V were expelled by pumping either remaining solution E or a separate stream of DMSO to prevent clogging upon cooling down.

4 N HCl was added to the mixture collected to adjust pH to 7. Ciprofloxacin **13** was allowed to gradually precipitate in a 4 °C fridge. The solid was filtered, washed three times with water and three times with acetone and dried, affording 74.0 mg (75 % overall) yellow solid. A minimal amount of 2 N HCl was added to the solid to adjust pH to 1. All solid dissolved upon gentle heating and acetone was added to the solution until the first sign of cloudiness. The solution was cooled down to 4 °C. The needle crystal was filtered, washed three times with a cold mixture of 20:1 acetone/water and dried, affording 65.0 mg (60 % overall) yellowish crystal.



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NMR spectra are identical to those of commercial product. ^{1}H NMR (500 MHz, D_2O, referenced to residual H_2O peak at 4.79 ppm) δ 8.62 (s, 1H), 7.53-7.47 (m, 2H), 3.72-3.65 (m, 1H), 3.63-3.56 (m, 4H), 3.51-3.44 (m, 4H), 1.42-1.35 (m, 2H), 1.20-1.13 (m, 2H). ^{13}C NMR (126 MHz, D_2O, referenced to 3-(trimethylsilyl)propionic-2,2,3,3-d_4 acid, sodium salt (TSP) as an external standard at 0 ppm) δ 177.9 (d, J = 2.4), 171.1, 155.8 (d, J = 252.0), 150.6, 147.3 (d, J = 10.1), 141.4, 120.8 (d, J = 8.1), 113.0 (d, J = 23.3), 109.0, 108.0, 49.0 (d, J = 5.4), 46.0, 38.9, 10.3. ^{19}F NMR (470 MHz, D_2O) δ −120.8. HRMS (DART) calcd for $C_{17}H_{19}FN_3O_3$ $(M-Cl)^+$ 332.1405, found 332.1400.

Figure S1. Left view of system setup.

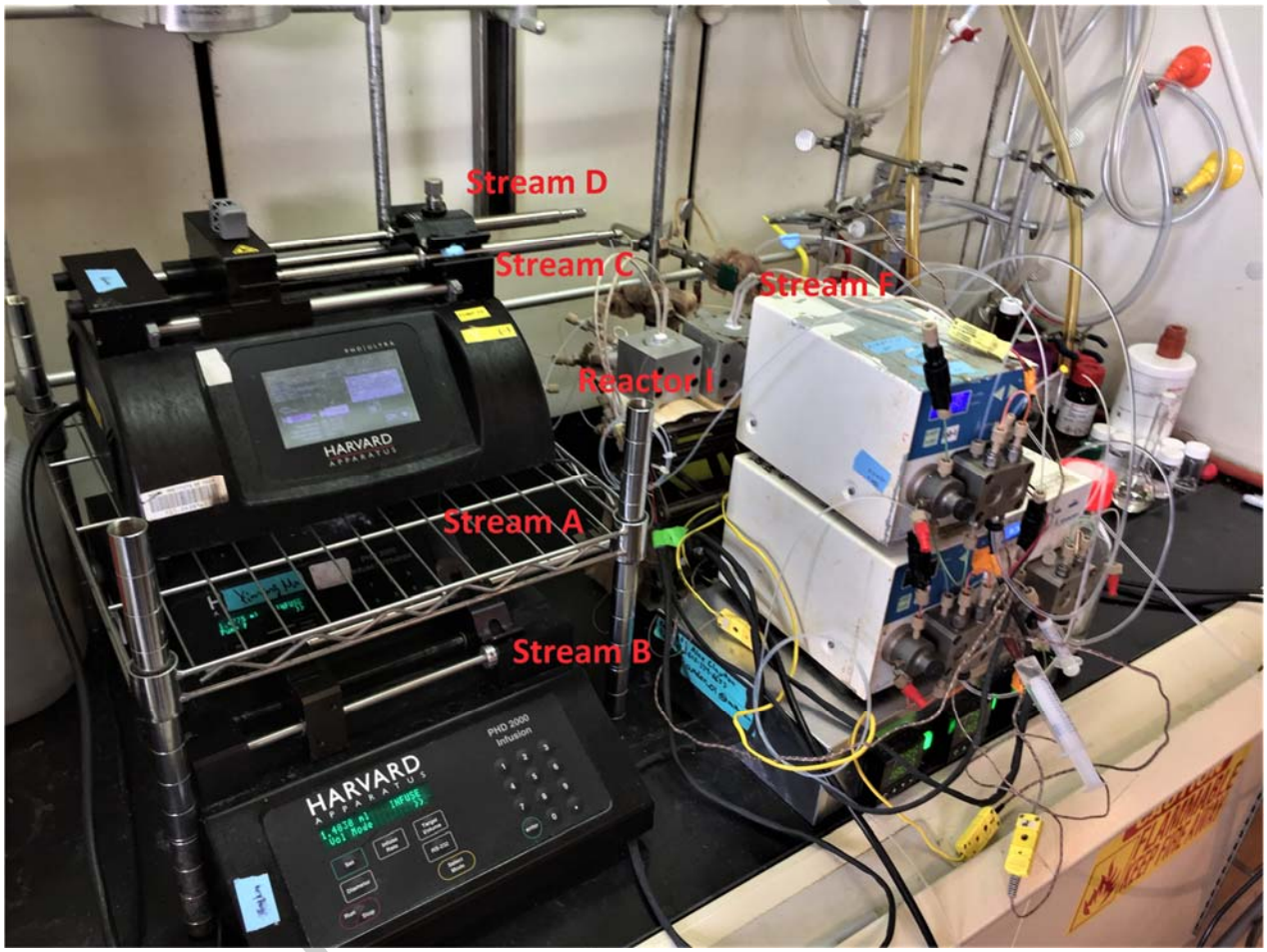
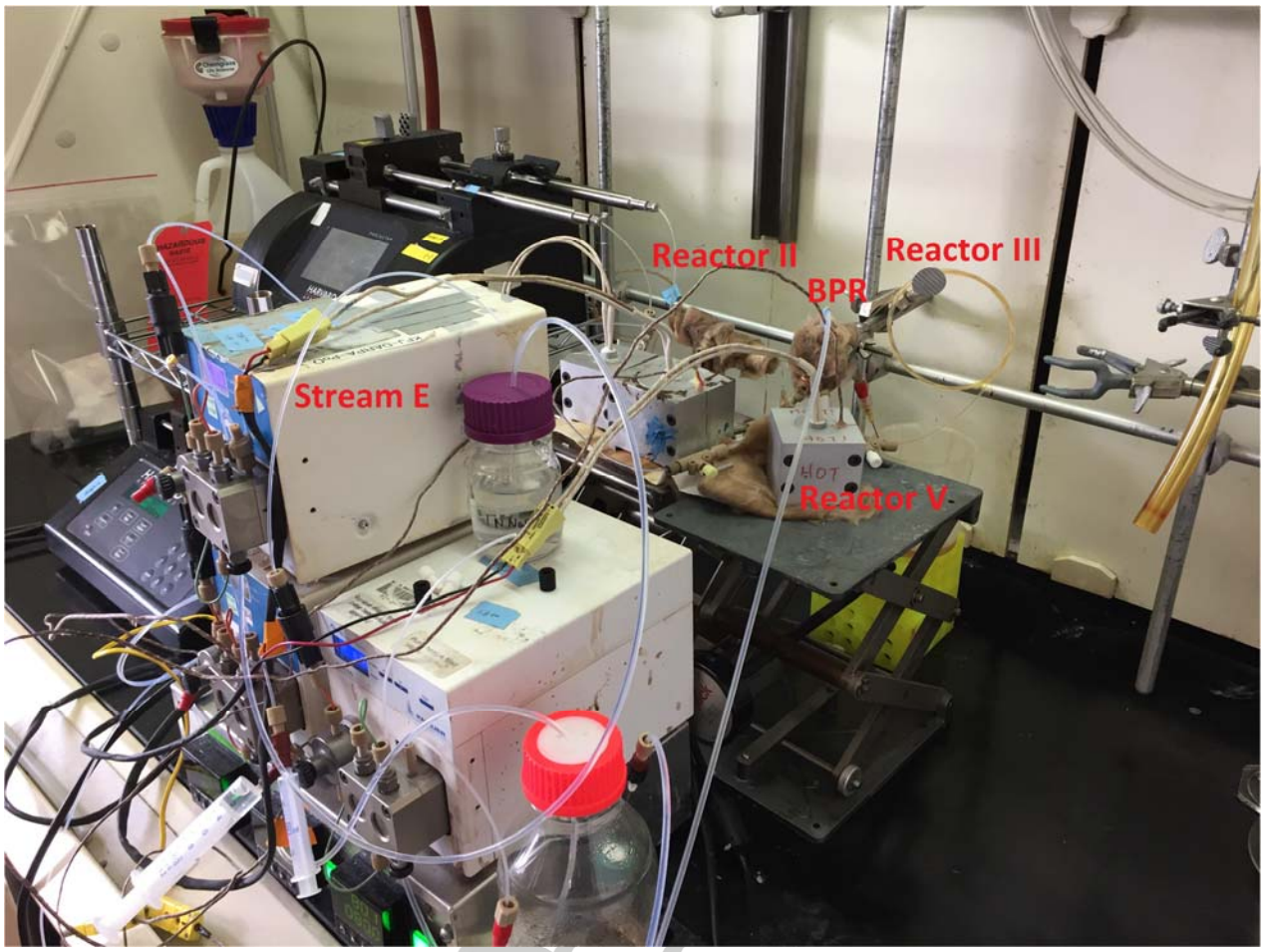
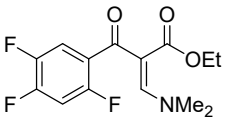


Figure S2. Right view of system setup.



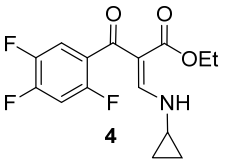
Note that in small scale preparation, Stream E was pumped by a syringe pump. However, shown in the pictures, it was pumped by a knauer pump for longer runs.

Isolation and Characterization of Intermediates



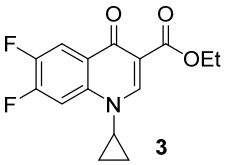
6

Solutions A and B were loaded and pumped through Reactor I. The outlet of Reactor I was connected to the BPR. After running for 4.5 min, the crude solution of **6** was collected for 2 min and 1 s. It was diluted with DCM and washed with saturated aqueous solution of NH_4Cl. The aqueous phase was extracted with DCM three times. The combined organic phases were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography (3:1 hexanes/acetone) to afford **6** (88.5 mg, 98 %) as yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.47 (br dd, 1H, *J* = 16.0, 9.0), 6.88 (ddd, 1H, *J* = 15.8, 9.6, 6.2), 4.02 (q, 2H, *J* = 7.1), 3.34 (br s, 3H), 2.86 (br s, 3H), 1.01 (t, 3H, *J* = 7.1). ^{13}C NMR (126 MHz, $CDCl_3$) δ 184.8, 167.4, 158.1, 155.2 (br d, *J* = 245.8), 151.1 (br ddd, *J* = 254.6, 11.5, 11.5), 146.5 (ddd, *J* = 245.7, 12.7, 3.6), 127.0 (ddd, *J* = 15.8, 4.0, 4.0), 117.8 (dd, *J* = 19.7, 4.0), 105.2 (dd, *J* = 29.0, 21.0), 102.2 (br), 59.8, 47.8 (br), 42.7 (br), 13.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ −115.4, −130.1 (br), −142.8. HRMS (DART) calcd for $C_{14}H_{15}F_3NO_3$ $(M+H)^+$ 302.0999, found 302.0989.



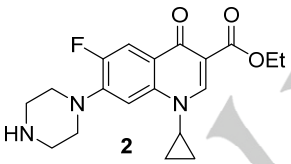
4

Solutions A-D were loaded and pumped through Reactors I-III. The outlet of Reactor III was connected to the BPR. After running for 10.5 min, the crude solution of **4** was collected for 2 min. It was diluted with DCM and washed with saturated aqueous solution of NH_4Cl. The aqueous phase was extracted with DCM three times. The combined organic phases were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography (5:1 hexanes/ethyl acetate) to afford **4** (89.0 mg, 96 %) as yellowish oil. ^{1}H NMR (two rotamers, 400 MHz, $CDCl_3$) δ 10.86 (br d, 0.84H, *J* = 12.4), 9.41 (br d, 0.14H, *J* = 13.6), 8.19 (dd, 0.84H, *J* = 13.8, 0.5), 8.14 (dd, 0.16H, *J* = 14.3, 0.5), 7.31 (ddd, 0.16H, *J* = 15.2, 8.9, 6.4), 7.17 (ddd, 0.85H, *J* = 15.0, 8.8, 6.2), 6.85 (ddd, 1H, *J* = 15.4, 9.1, 6.2), 4.04 (q, 1.69H, *J* = 7.1), 3.98 (q, 0.32H, *J* = 7.2), 3.04-2.89 (m, 1H), 1.06 (t, 2.59H, *J* = 7.2), 0.96-0.76 (m, 4.52H). ^{13}C NMR (two rotamers, 101 MHz, $CDCl_3$) δ 188.1 (major), 185.9 (minor), 168.3 (minor), 166.5 (major), 160.7 (major), 160.4 (minor), 154.8 (minor, ddd, *J* = 247.7, 9.8), 154.1 (major, ddd, *J* = 247.0, 9.6, 2.9), 150.9 (minor, ddd, *J* = 253.0, 10.6), 150.4 (major, ddd, *J* = 253.0, 14.8, 12.2), 146.5 (ddd, *J* = 245.2, 12.6, 3.6), 127.4 (ddd, *J* = 19.2, 4.4, 4.4), 117.6 (minor, ddd, *J* = 20.5, 5.1, 1.5), 116.7 (major, ddd, *J* = 20.6, 5.2, 1.5), 105.0 (major, dd, *J* = 28.6, 20.7), 104.9 (minor, dd, *J* = 28.6, 21.0), 101.65 (minor), 101.60 (major), 59.8 (major), 59.5 (minor), 30.4 (major), 30.1 (minor), 14.0 (major), 13.6 (minor), 6.51 (minor), 6.49 (major). ^{19}F NMR (two rotamers, 376 MHz, $CDCl_3$) δ −115.6 (minor), −116.7 (major), −131.3 (minor), −132.1 (major), −143.2. HRMS (DART) calcd for $C_{15}H_{15}F_3NO_3$ $(M+H)^+$ 314.0999, found 314.1004.



3

Solutions A-D were loaded and pumped through Reactors I-III. A 0.9 M DMSO solution of DBU was pumped by syringe pump D. The outlet stream of Reactor IV was mixed with a dilution stream of DMSO, pumped by a Knauer pump at a flow rate of 3.77 mL/min and passed through our tubing mixer (1.0 mm ID, 1.59 mm OD)[2] and the BPR sequentially. After running for 24 min, the crude solution of **3** was collected for 2 min. It was diluted with DCM and washed with 1.0 M aqueous solution of NaOH. The aqueous phase was extracted with DCM three times. The combined organic phases were washed with brine twice. The organic phase was dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography (40:1 DCM/MeOH). The fractions containing **3** were combined, dried and washed with Et_2O three times to afford **3** (71.3 mg, 82 %) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (s, 1H), 8.19 (dd, 1H, *J* = 10.4, 8.8), 7.71 (dd, 1H, *J* = 11.2, 6.4), 4.37 (t, 2H, *J* = 7.1), 3.51-3.37 (m, 1H), 1.45-1.30 (t+m, 3H+2H, *J* = 7.1), 1.20-1.10 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.6, 165.2, 153.2 (dd, *J* = 256.2, 15.2), 148.8, 148.6 (dd, *J* = 251.3, 13.4), 137.5 (d, *J* = 9.4), 125.7 (d, *J* = 4.7), 115.3 (dd, *J* = 18.9, 2.2), 110.9, 105.5 (d, *J* = 22.9), 61.0, 34.7, 14.3, 8.2. ^{19}F NMR (376 MHz, $CDCl_3$) δ −127.4, −138.9. HRMS (DART) calcd for $C_{15}H_{14}F_2NO_3$ $(M+H)^+$ 294.0936, found 294.0915.



2

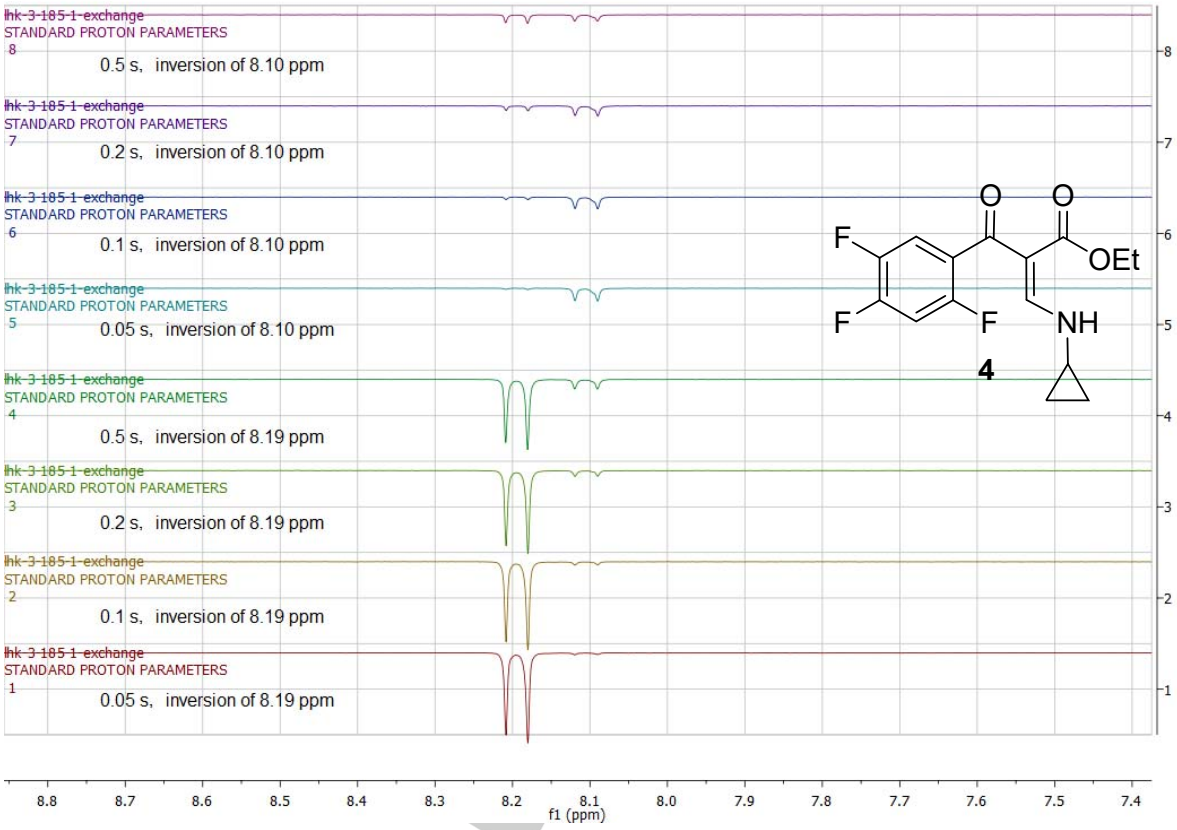
Solutions A-E were loaded and pumped through Reactors I-IV. The outlet stream of Reactor IV was mixed with a dilution stream of DMSO, pumped by a Knauer pump at a flow rate of 3.77 mL/min and passed through our tubing mixer (1.0 mm ID, 1.59 mm OD)[2] and the BPR sequentially. After running for 24 min, the crude solution of **2** was collected for 2 min. It was diluted with DCM and washed with 1.0 M aqueous solution of NaOH. The aqueous phase was extracted with DCM three times. The combined organic phases were washed with H_2O twice. The organic phase was dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography (12:1:0.02 DCM/MeOH/NH_4OH). The fractions containing **2** were combined, dried and washed with Et_2O three times to afford **2** (87.1 mg, 82 %) as off white solid. ^{1}H NMR (400 MHz, CD_3OD, referenced to residual MeOH peak at 3.31 ppm) δ 8.53 (s, 1H), 7.73 (d, 1H, *J* = 13.6), 7.42 (d, 1H, *J* = 7.4), 4.31 (q, 2H, *J* = 7.1), 3.66-3.58 (m, 1H), 3.29-3.23 (m, 4H), 3.07-3.00 (m, 4H), 1.41-1.30 (t+m, 3H+2H, *J* = 7.1), 1.20-1.13 (m, 2H). ^{13}C NMR (101 MHz, CD_3OD, referenced to residual MeOH peak at 49.00 ppm) δ 175.2 (d, *J* = 2.2), 166.0, 154.8 (d, *J* = 248.1), 149.8, 146.5 (d, *J* = 10.3), 139.8, 123.1 (d, *J* = 7.2), 112.9 (d, *J* = 23.5), 110.3, 106.9 (d, *J* = 3.2), 61.6, 51.7 (d, *J* = 4.4), 46.4, 36.2, 14.7, 8.5. ^{19}F NMR (376 MHz, CD_3OD) δ −124.8. HRMS (DART) calcd for $C_{19}H_{23}FN_3O_3$ $(M+H)^+$ 360.1718, found 360.1699.

1D NOESY Selective Inversion Experiment of 4

This experiment was done in a 1:1 mixture of DMSO-d_6 and MeCN-d_3 with various mixing times (50, 100, 200 and 500 ms). The doublets at 8.19 and 8.10 ppm (N−**H**) were selectively inverted. Take excitation of the doublet at 8.19 ppm as an example. The same peak would appear as a negative peak. If there were no exchange between the two doublets, the doublet at 8.10 ppm would not appear, rather than appearing as a negative peak. Therefore we conclude that the two doublets belong to two interchangeable species of **4** in this solvent mixture.

This result indicates that rapid E/Z isomerization of the double bond occurs in the 1:1 mixture of DMSO-d_6 and MeCN-d_3.[3] This solution structural information and the solvent screening results in Table S2 led us to select DMSO and MeCN as solvent for the one-pot cyclization-S_NAr in Reactor IV.

Figure S1. 1D NOESY selective inversion of **4** with various mixing times (0.05, 0.1, 0.2, 0.5 s).



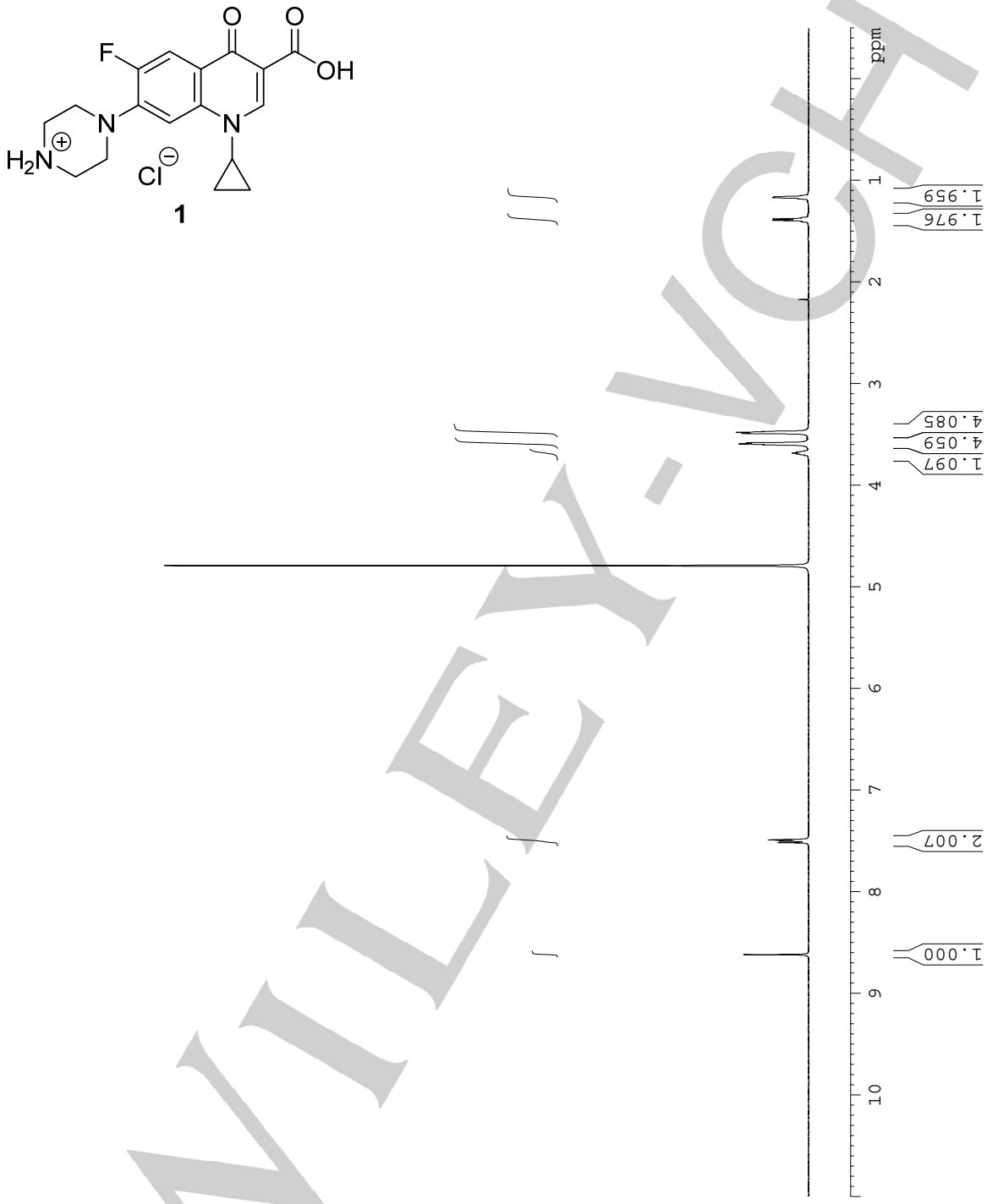
References and Notes

[1] A. Adamo, R. L. Beingessner, M. Behnam, J. Chen, T. F. Jamison, K. F. Jensen, J.-C. M. Monbaliu, A. S. Myerson, E. M. Revalor, D. R. Snead, T. Stelzer, N. Weeranoppanant, S. Y. Wong, P. Zhang, *Science* **2016**, *352*, 61-67.

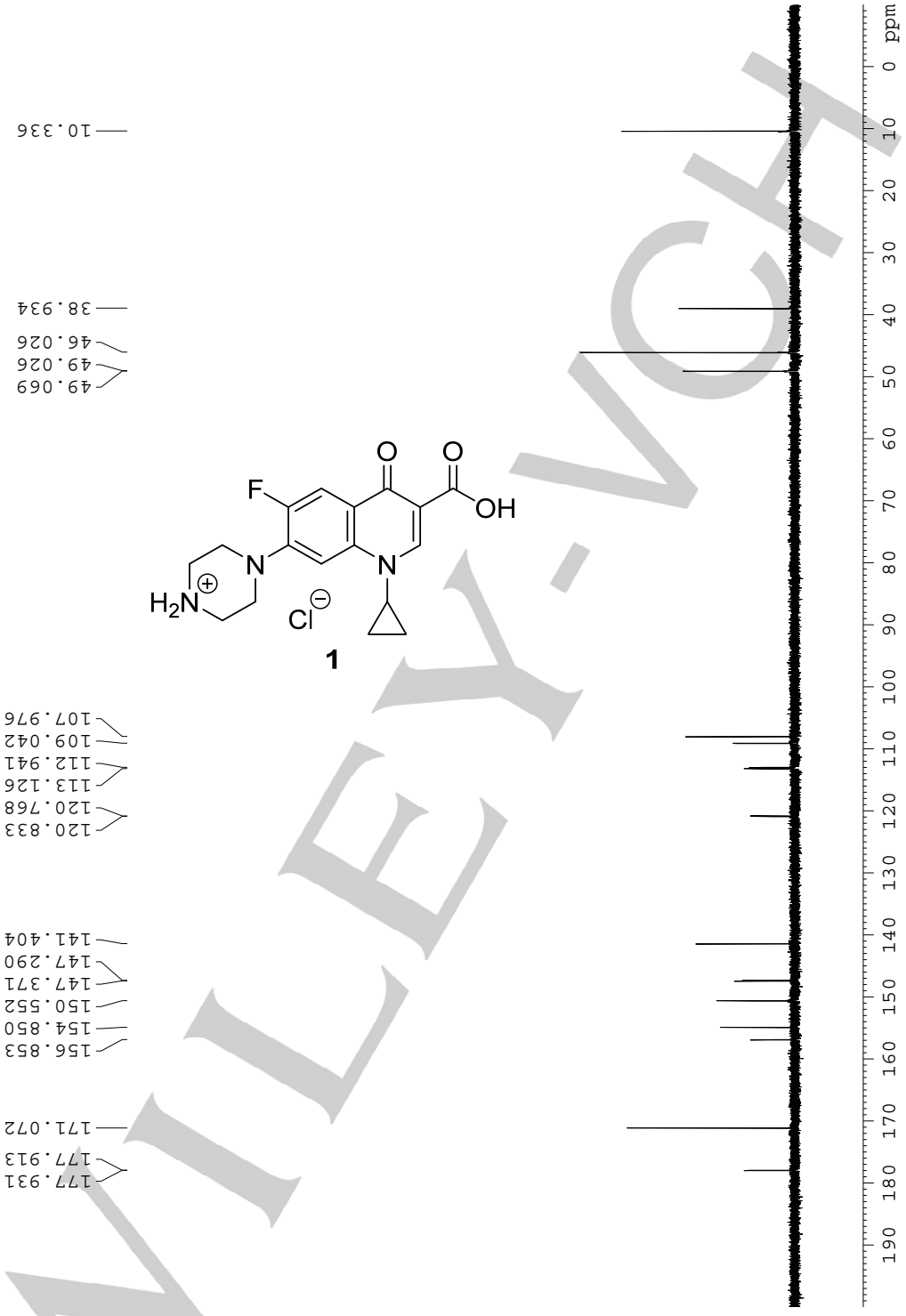
[2] Unpublished design.

[3] For similar isomerization, see (a) H. Egawa, M. Kataoka, K.-I. Shibamori, T. Miyamoto, J. Nakano, J.-I. Matsumoto, *J. Heterocyclic. Chem.* **1987**, *24*, 181-185. (b) D. T. W. Chu, *J. Heterocyclic. Chem.* **1985**, *22*, 1033-1034.

^{1}H NMR (500 MHz) of 1



^{13}C NMR (126 MHz) of 1



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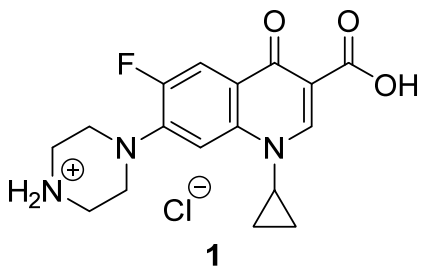
^{19}F NMR (470 MHz) of 1



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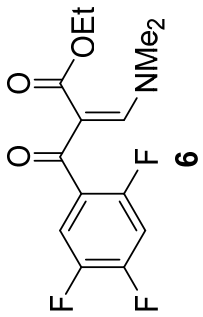
^{1}H NMR (500 MHz) of 6



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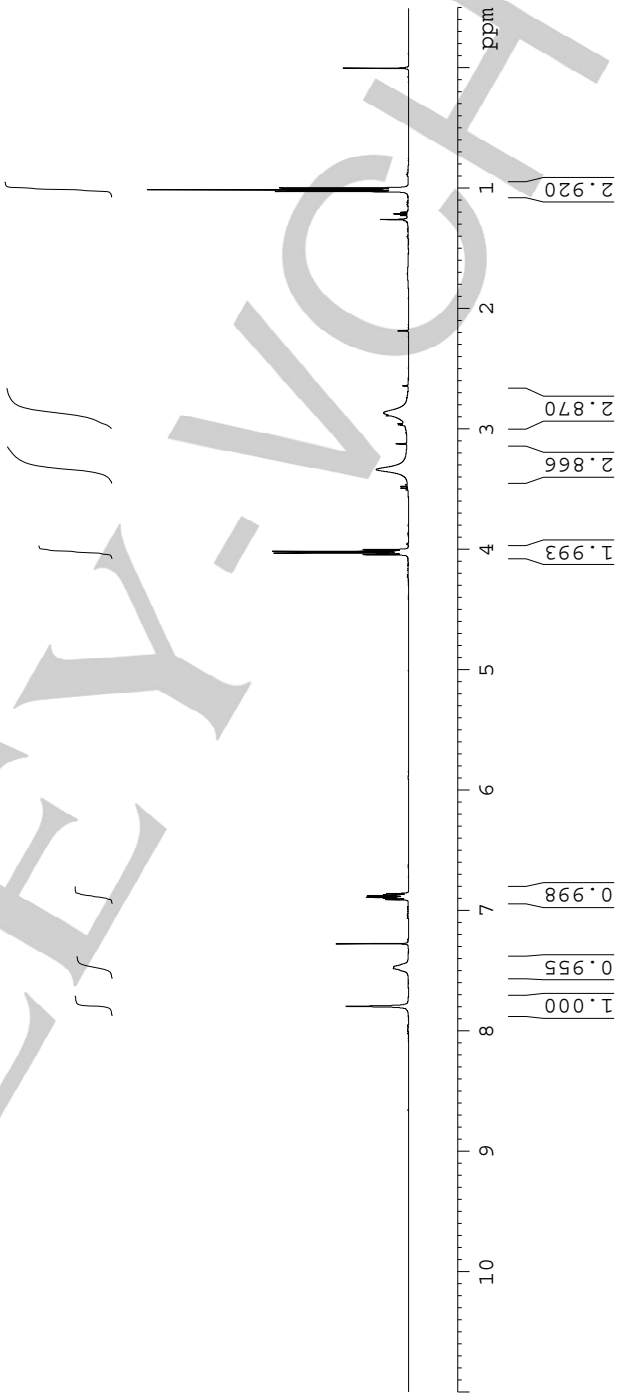
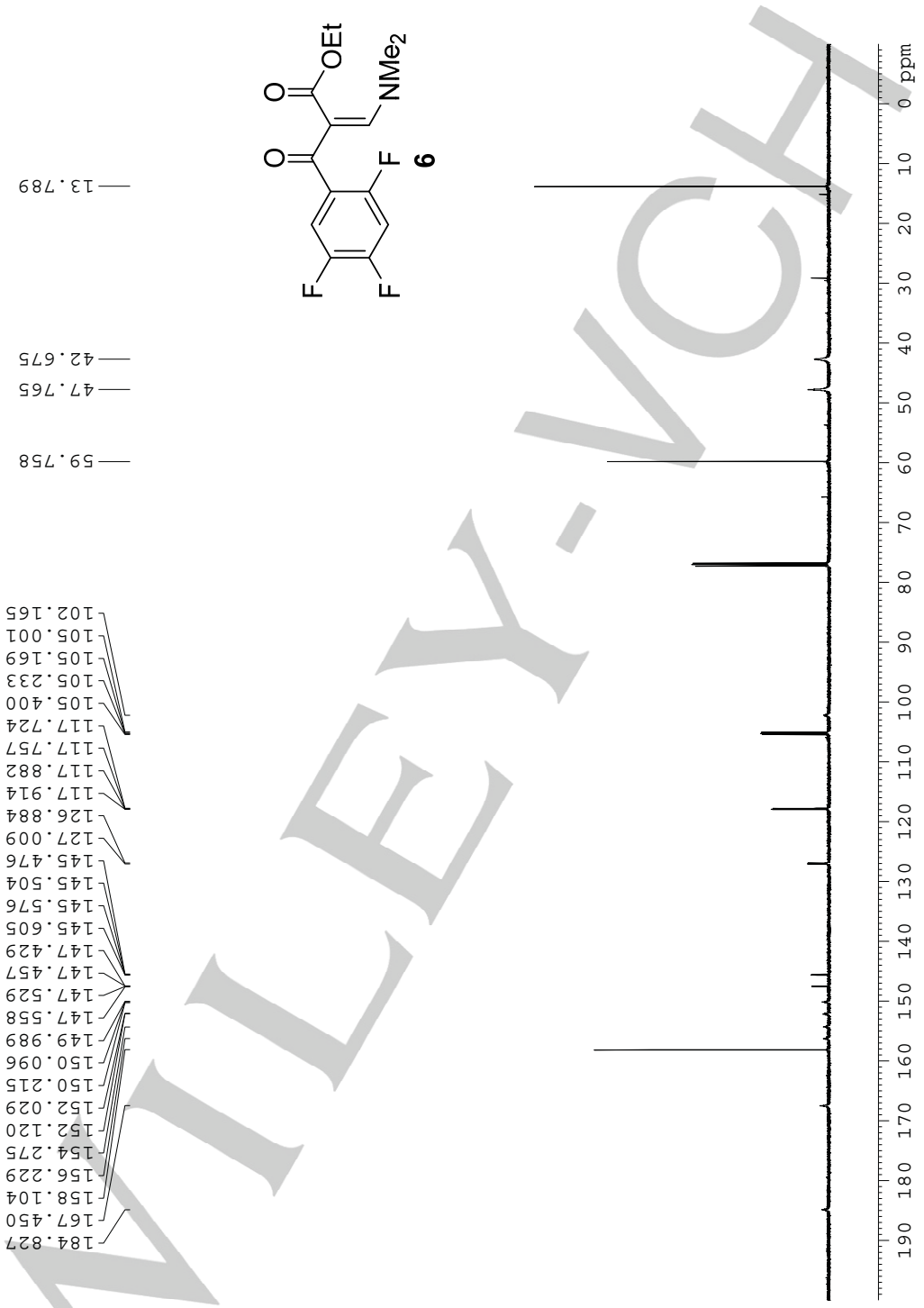
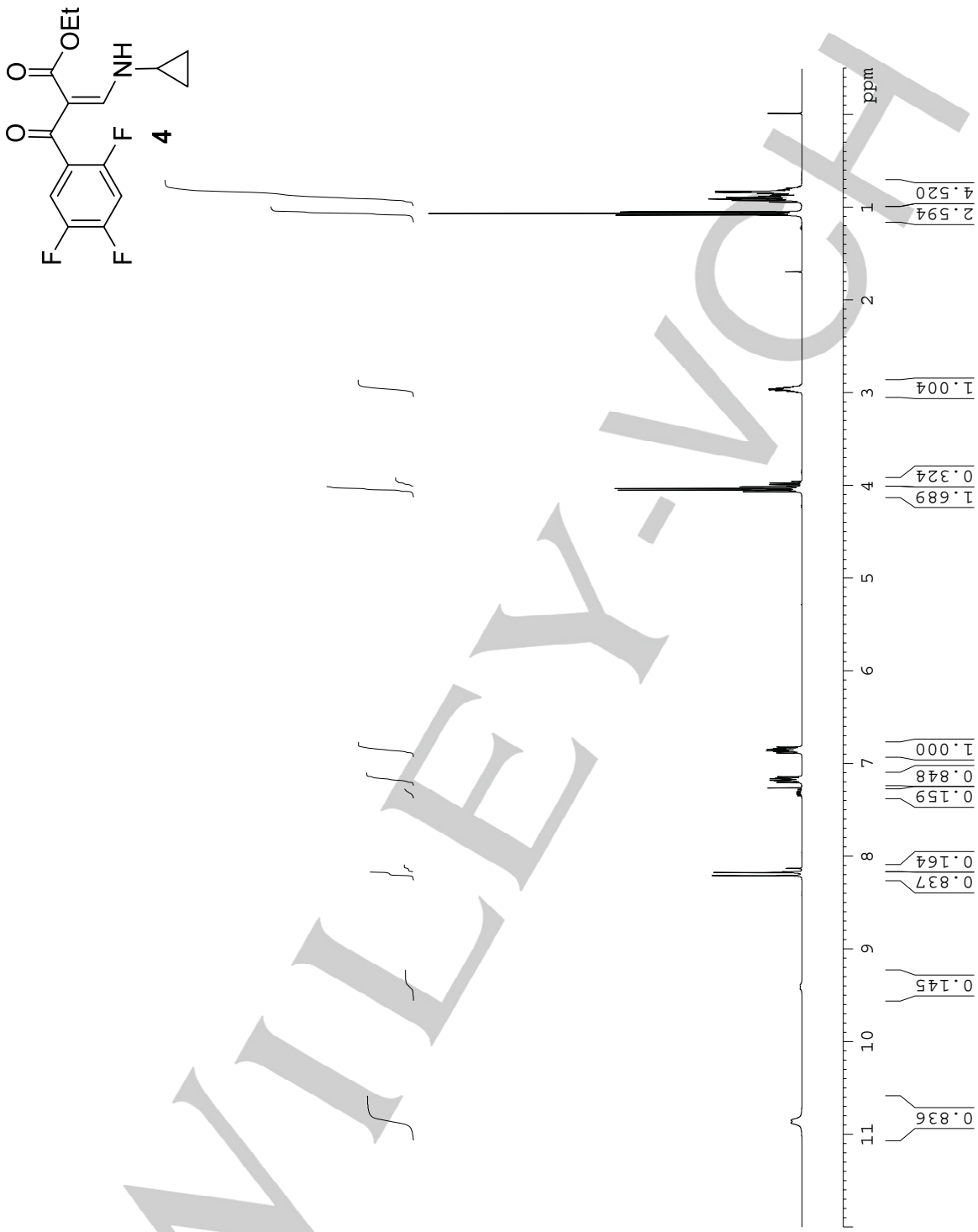


^{13}C NMR (126 MHz) of 6

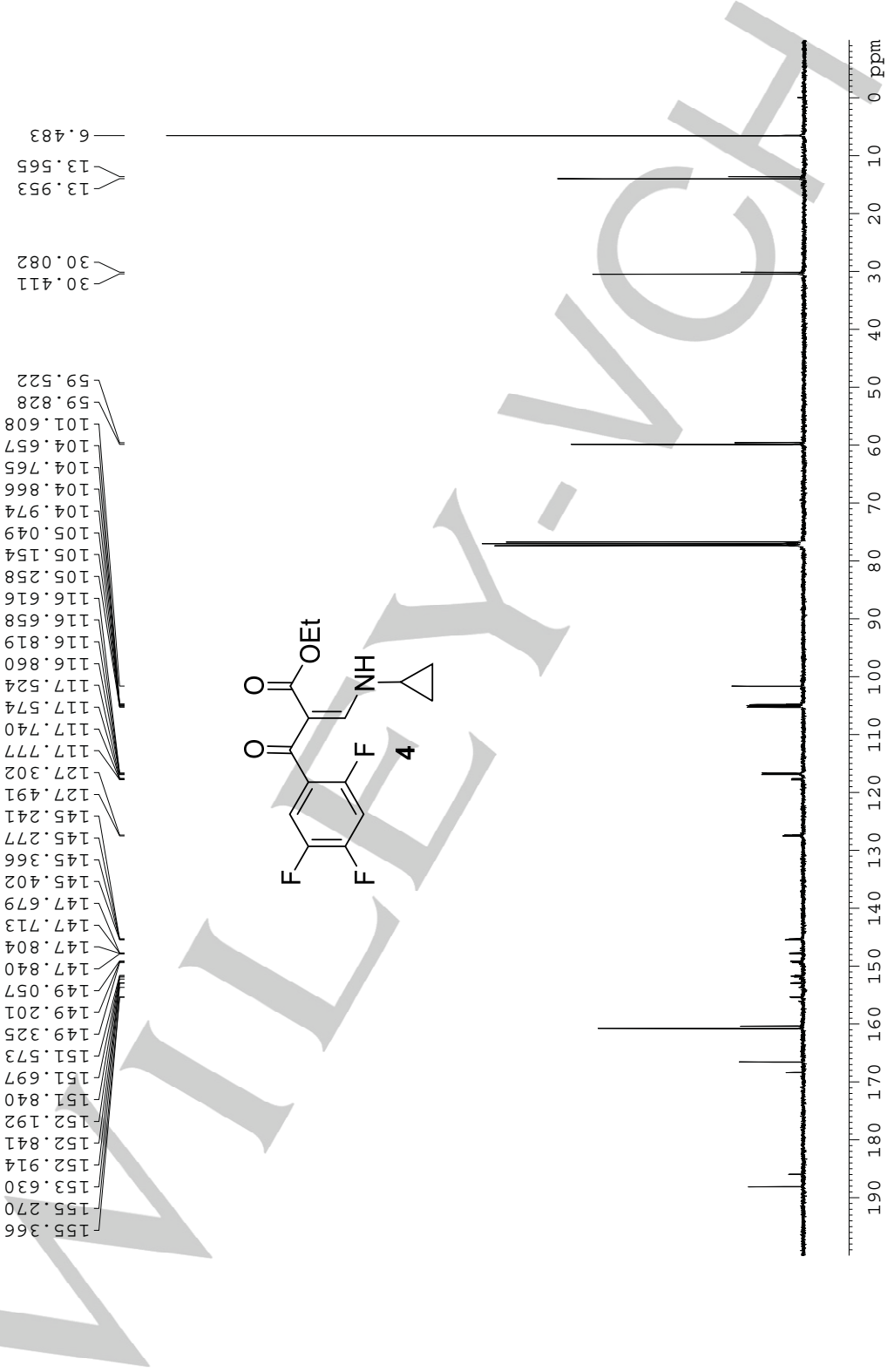


^{19}F NMR (376 MHz) of 6

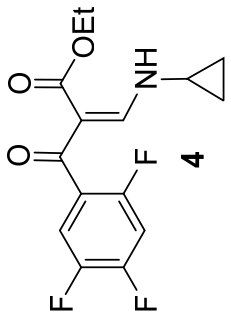
^{1}H NMR (400 MHz) of 4

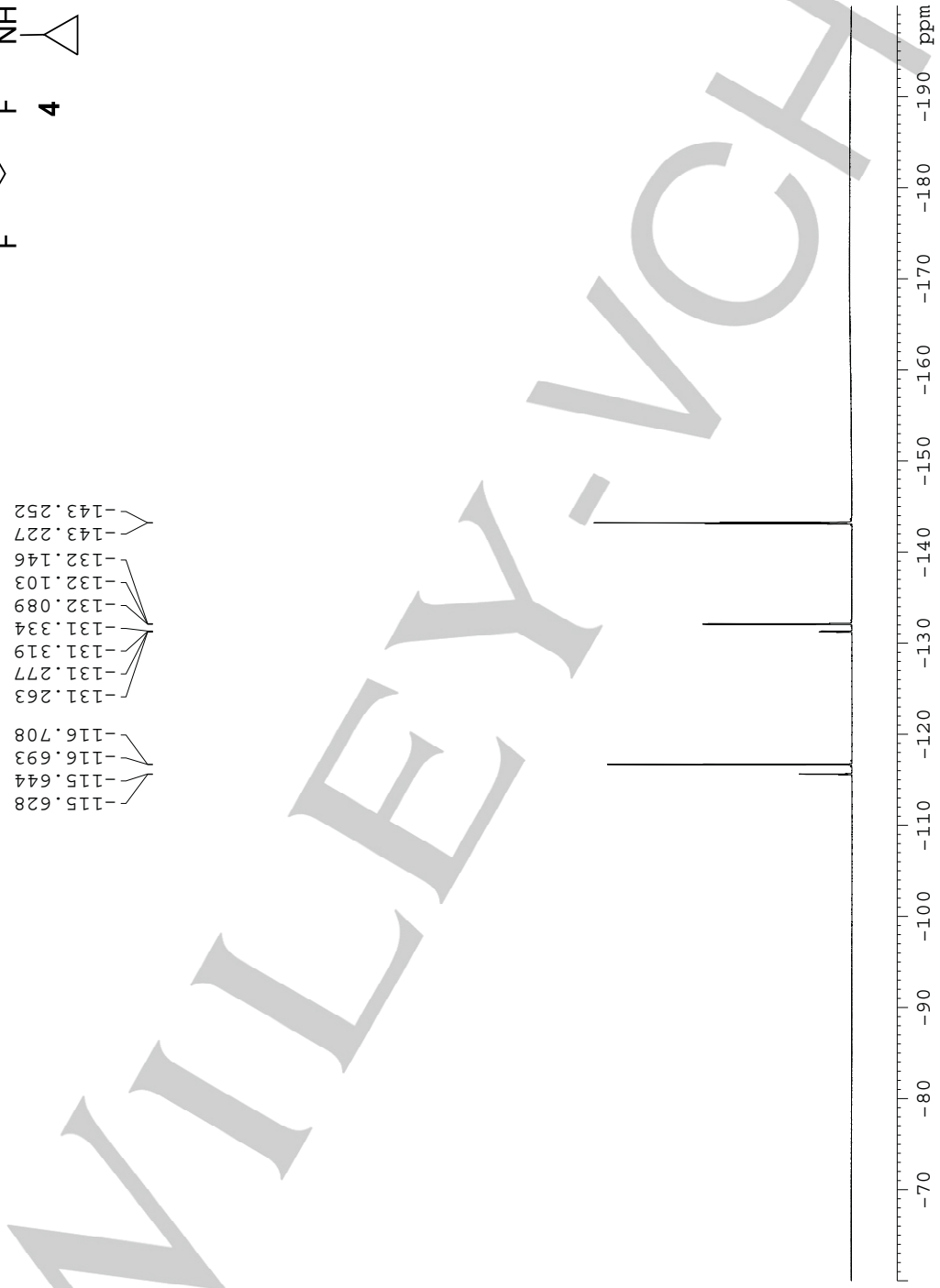


^{13}C NMR (101 MHz) of 4

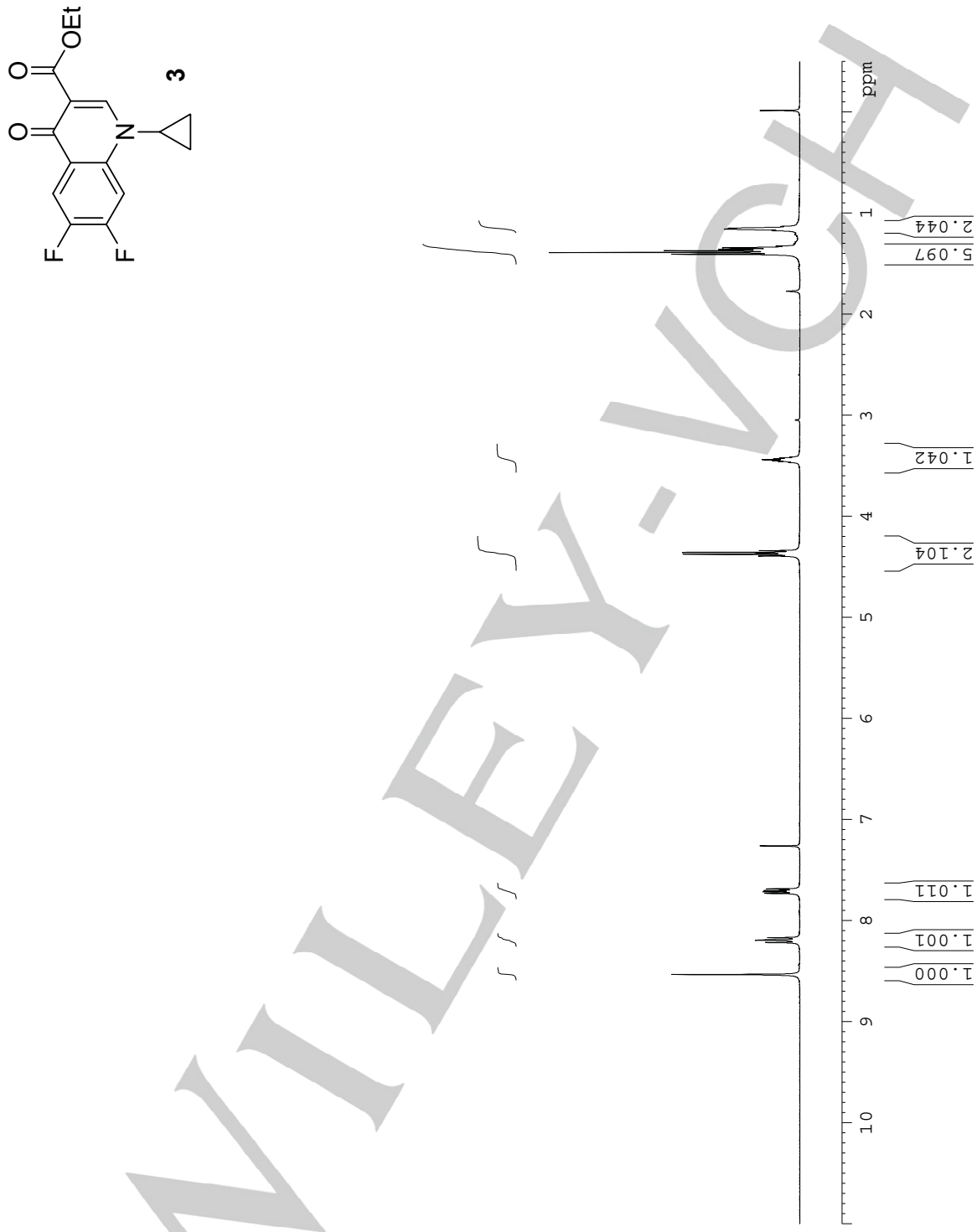


^{19}F NMR (376 MHz) of 4

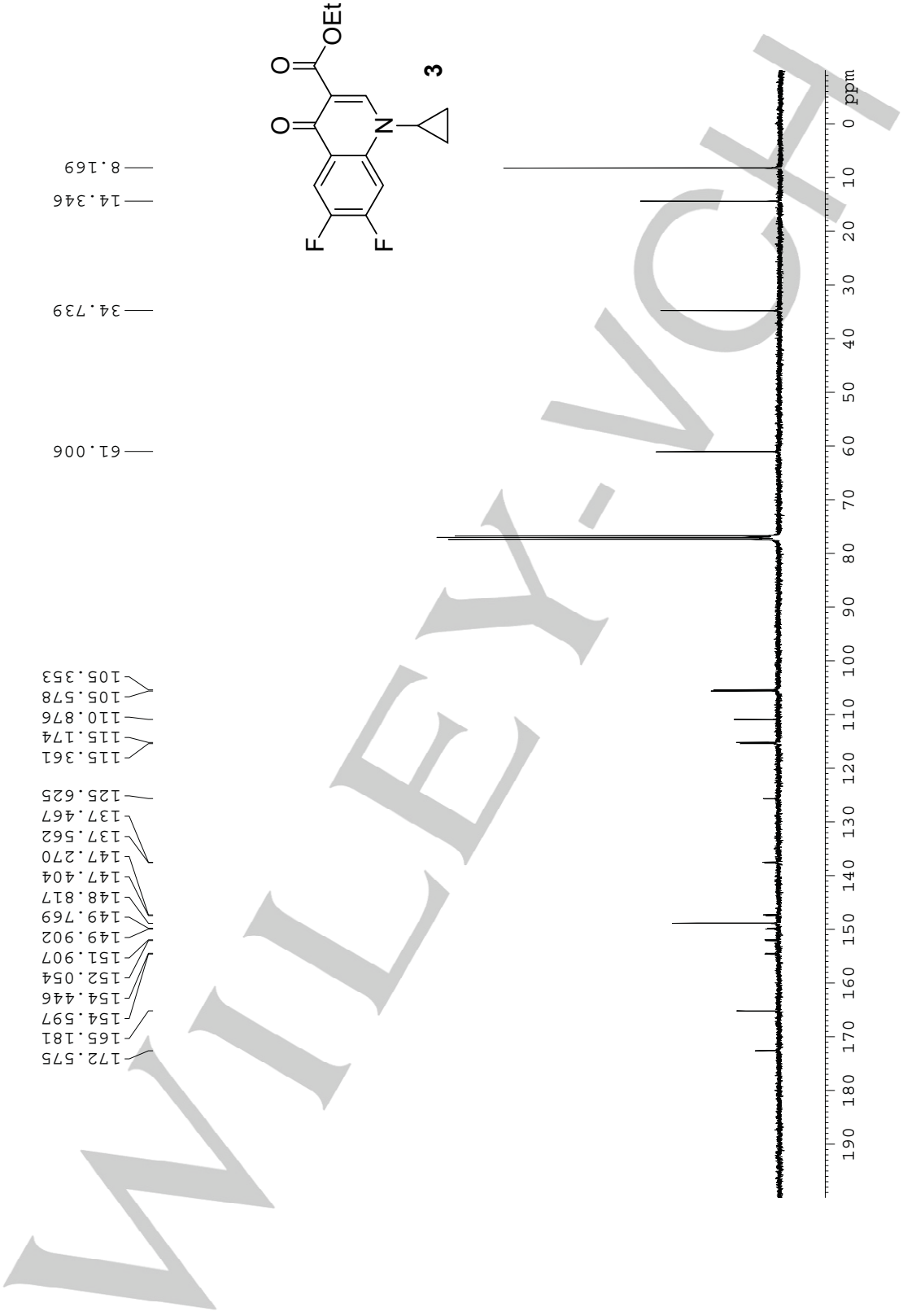




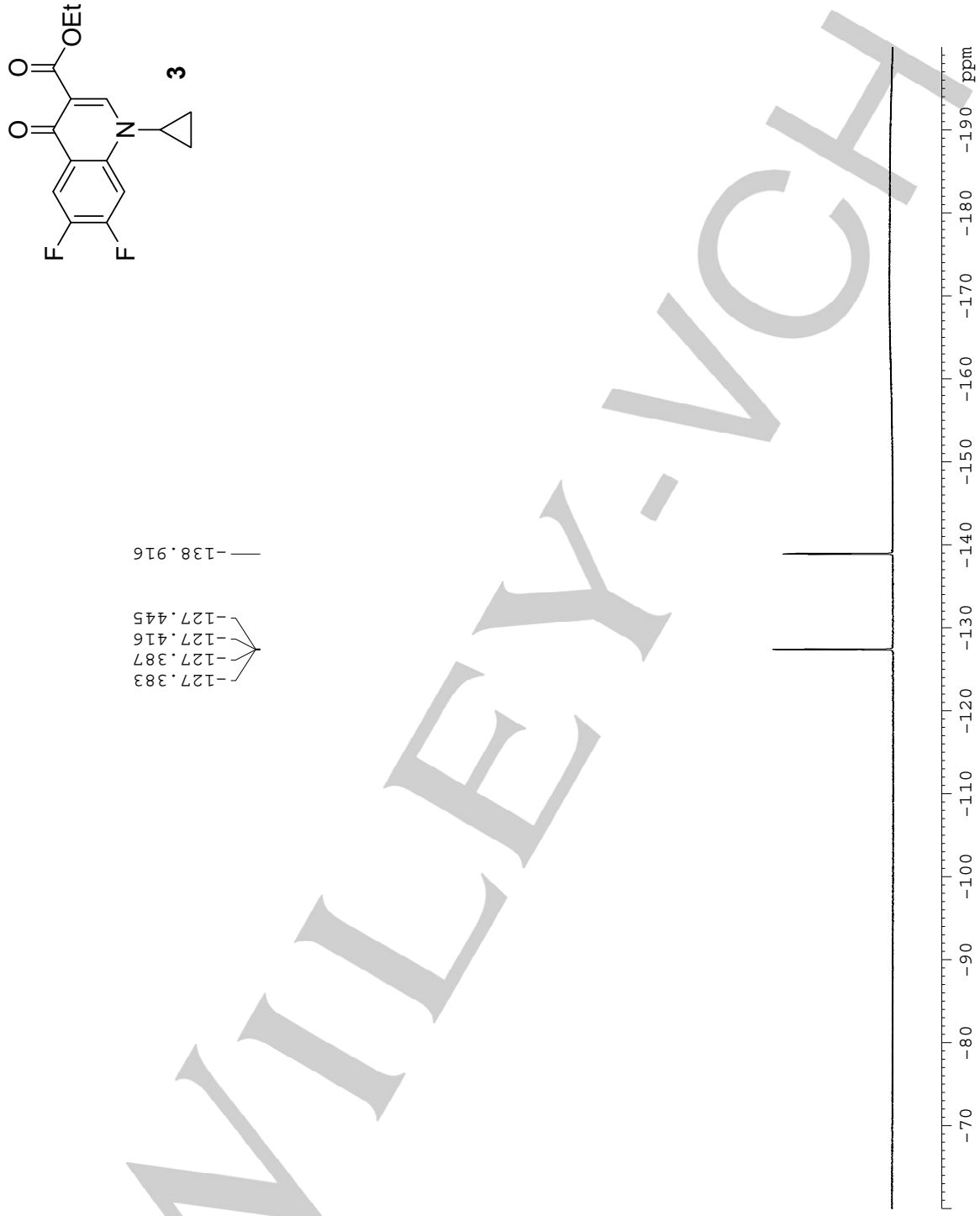
^{1}H NMR (400 MHz) of 3



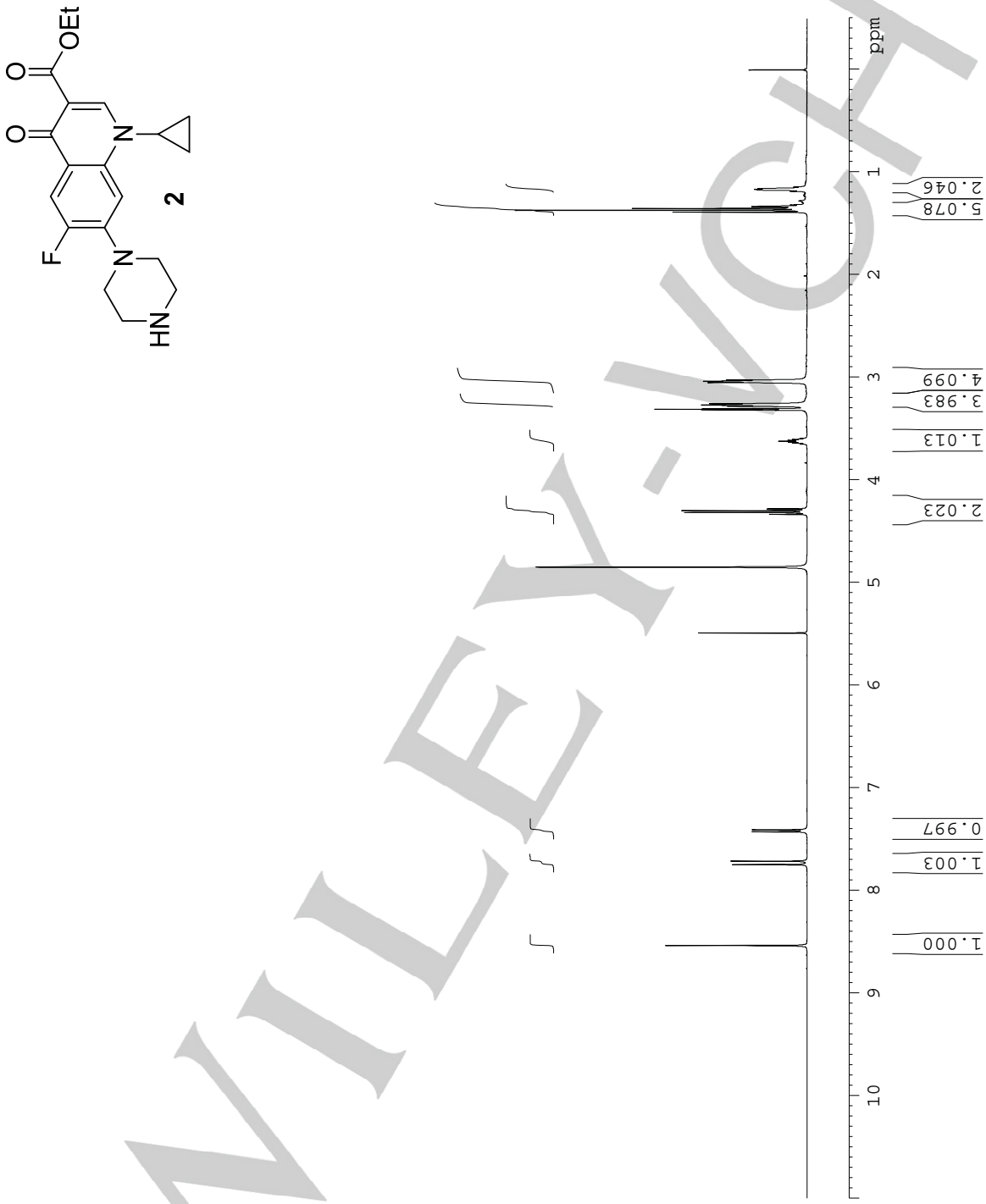
^{13}C NMR (101 MHz) of 3



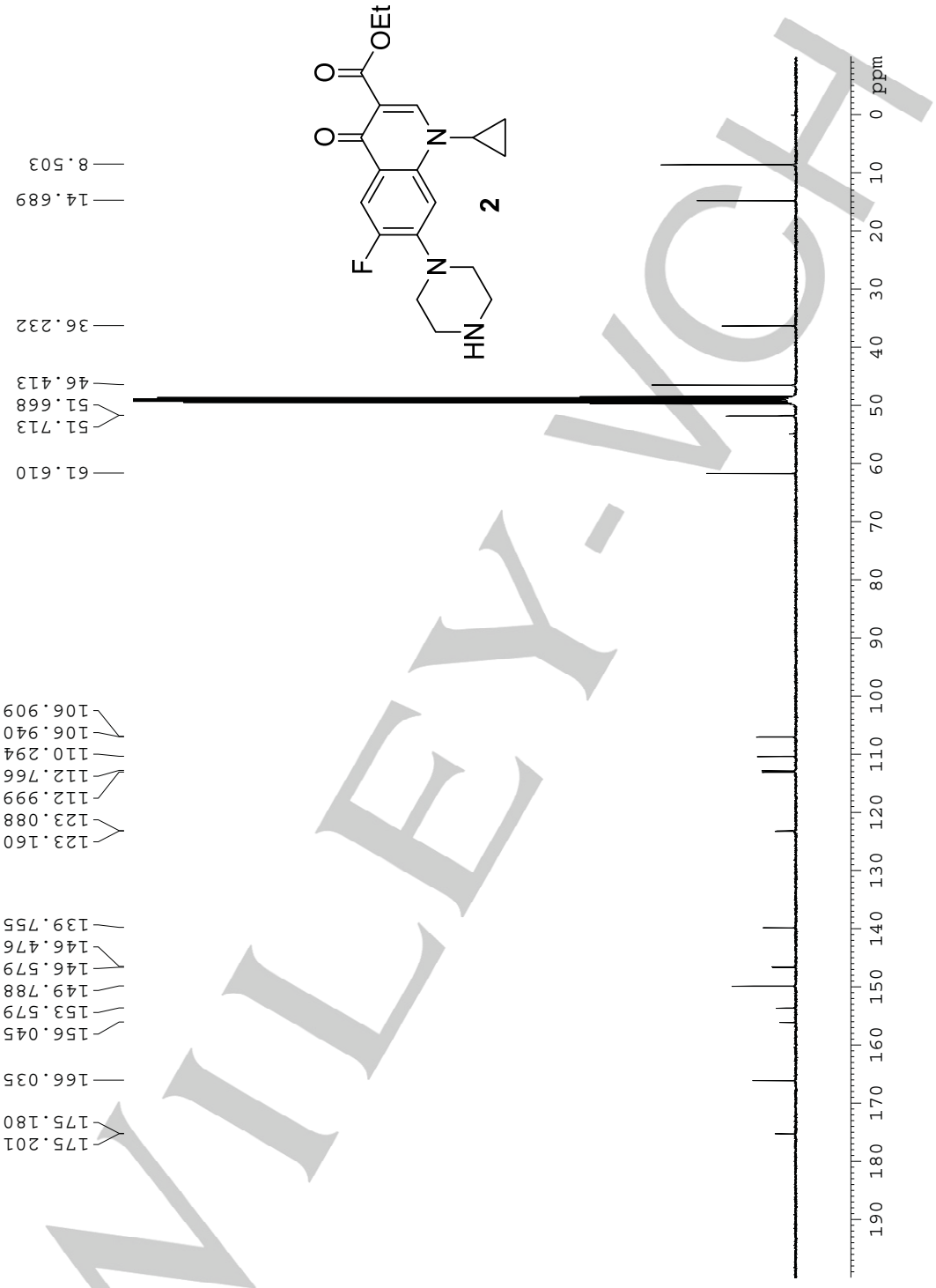
^{19}F NMR (376 MHz) of 3



^{1}H NMR (400 MHz) of 2



^{13}C NMR (101 MHz) of 2



^{19}F NMR (376 MHz) of 2