Supporting Information

Photocatalytic reductive radical-radical coupling of *N*, *N'*-cyclicazomethine imines with difluorobromo derivatives

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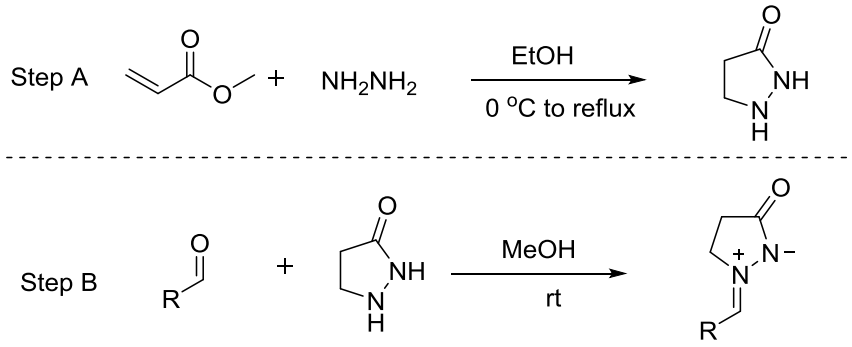
1. General Experimental Methods.

Unless otherwise noted, all the reagents were purchased from commercial suppliers and used without further purification. ^{1}H NMR spectra were recorded at 400 MHz. The chemical shifts were recorded in ppm relative to tetramethylsilane and with the solvent resonance as the internal standard. Data were reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz), integration. ^{13}C NMR data were collected at 100 MHz with complete proton decoupling. Chemical shifts were reported in ppm from the tetramethylsilane with the solvent resonance as internal standard. ^{19}F NMR data were collected at 376 MHz with complete proton decoupling. UV–Vis spectra were recorded using a shimadzu UV-2600. Infrared spectra (IR) were measured by FT-IR apparatus. High resolution mass spectroscopy (HRMS) was recorded on TOF MS ES+ mass spectrometer and acetonitrile was used to dissolve the sample. Cyclic Voltammetry (CV) experiments were recorded on a CHI650D Electrochemical workstation. Emission intensities were recorded using Perkin-Elemer LS 55 Fluorescence Spectrometer. Column chromatography was carried out on silica gel (200-300 mesh).

General procedure A: the synthesis of azomethine imines[1]

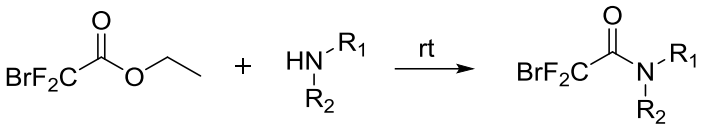


Step A: To a mixture of hydrazine monohydrate (100 mmol, 1 eq) in anhydrous EtOH (30 mL) cooled to 0 ℃ was added methyl acrylate (1000 mmol, 1 eq) dropwise over 5 min. And then the mixture was heated to reflux until the reaction was judged to be complete by TLC analysis. The

resulting solution was concentrated in vacuum and purified by column chromatography on silica gel to give the corresponding product pyrazolidin-3-one as yellow oil (40-60% yield).

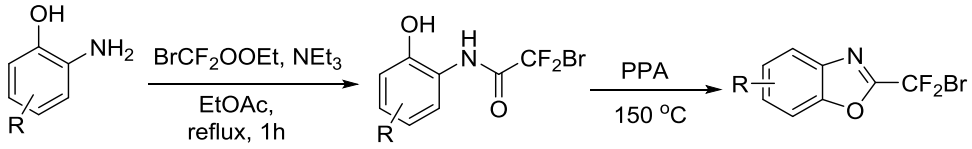
Step B: The corresponding aldehyde (5 mmol, 1 equiv.) was added to a solution of pyrazolidin-3-one (5 mmol, 1 equiv.) in methanol (2 mL) and the mixture was stirred overnight at room temperature. Thereafter, the precipitate was collected by filtration, washed with a mixed solvent of n-hexane and CH_2Cl_2 (9:1), and dried under vacuum to afford the desired azomethine imine as a solid (40-70% yield).

General procedure B: the synthesis of bromodifluoroamides[2]



A mixture of amine (10 mmol, 1 equiv.) and bromodifluoroacetate (10 mmol, 1 equiv.) was stirred under air overnight or until the reaction was judged to be complete by TLC analysis. Then, the reaction mixture was purified by column chromatography on silica gel to give the corresponding amide (40%-50% yield).

General procedure C: the synthessis of 2-(bromodifluoromthyl)benzoxazole[3]



A solution of 2-aminophenol (10 mmol, 1 equiv.), bromodifluoroacluoacetate (10 mmol, 1 equiv.), and Et_3N (11mmol, 1.1 eq) in EtOAc (15 mL) was heated to reflux for 1 h. After cooling to room temperature, the reaction mixture was washed once with 10 mL HCl (1 M) and then concentrated in vacuum to afford the crude product 2-bromo-2,2-difluoro-N-(2-hydroxyphenyl)acetamide. To this crude product was added polyphosphoric acid (24 mmol, 2.4 eq)

and the obtaining mixture was heated rapidly to 150 ℃. After reacting for 1 h, the mixture was allowed to cool to room temperature and ice water (30 mL) and $NH_3.H_2O$ (6 mL, 30% aq) were added. The aqueous solution was extracted with CH_2Cl_2 (50 mL). The organic layer was dried over Na_2SO_4, concentrated in vacuum and purified by column chromatography on silica gel to give the corresponding 2-(bromodifluoromthyl)benzoxazole (45-78% yield).

General procedure D: the synthesis of compound 3a-3x and 4a-4q

N, *N*'-cyclicazomethine imines **1** (0.20 mmol), Cs_2CO_3 (0.30 mmol, 1.5 eq.) (K_2HPO_4 for **3x**), Asc-H (0.30mmol, 1.5 eq.) and $Ir(ppy)_3$ (2.00 mmol%) and $BrCF_2CO_2Et$ or bromodifluoroamides **2** (0.60 mmol, 3 eq.) in DMSO (1 mL) were placed in a 5 mL flask and the reaction mixture was stirred at room temperature for 2 h (12h for **3x**) under irradiation of 30 W blue LEDs (distance app. 3 cm). Then, it was diluted with EtOAc (60 mL), and washed with brine (3×20 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The obtained crude product was then purified by flash chromatography using silica gel (EtOAc/PE = 1:9-1:1).

2. Mechanistic studies

Time profile of the transformation with the light ON/OFF over time[4]

Two standard reactions were set up parallel on a 0.20 mmol scale according to the general procedure D and extra 3 equiv. of benzotrifluoride was added as the internal standard. After being irradiated for 10 min, an aliquot (300 μL) from the reaction mixture was transferred into a nuclear magnetic tube charged with 0.5 mL of DMSO-d_6. The yield of product was determined by ^{19}F NMR. Then the reaction mixture was stirred for 10 min with light-off. All of the following yields were analyzed in the identical way after a 10 min light on or off.

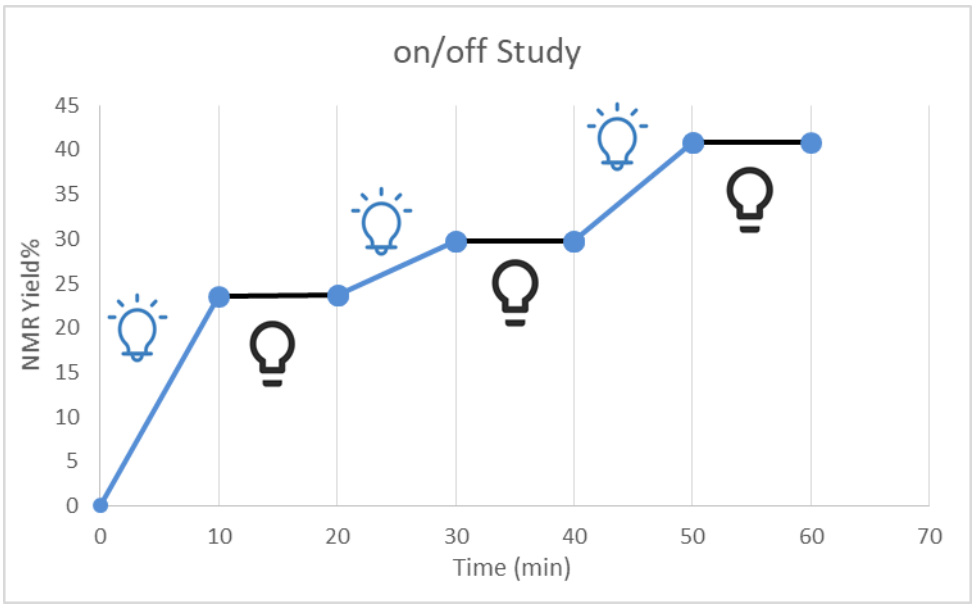


Figure S1: Time profile of the transformation with the light ON/OFF over time.

UV–Vis spectrum of 1a

The UV–Vis spectrum of **1a** features a maximum absorption (λ_{max}) at 351 nm.

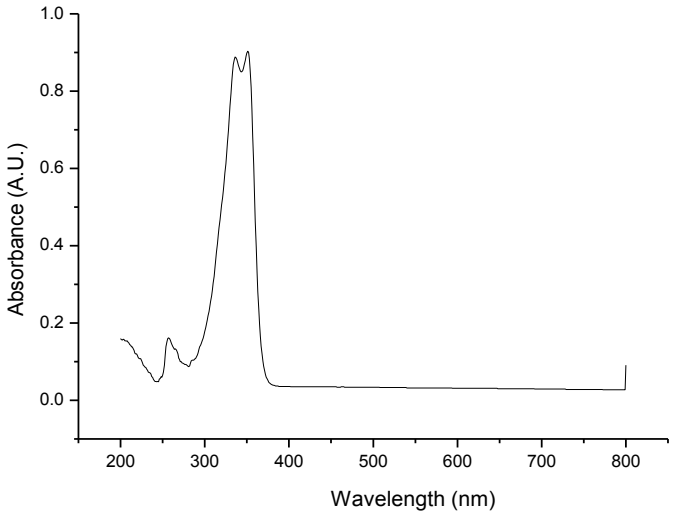


Figure S2. Absorbance of 1×10^{-4} M solution of **1a** in DMSO

Emission Quenching Experiments (Stern–Volmer Studies)

All fluorescence measurements were recorded using a Hitachi FL-7000 Fluorometer. Quenching studies were conducted in CH_3CN and DMSO respectively. All *fac*-Ir(ppy)$_3$ solutions (concentration of 5 µM) were excited at 320 nm and the emission intensity was collected at 517 nm. Measurements using corresponding quenchers were taken in triplicate at different concentrations.

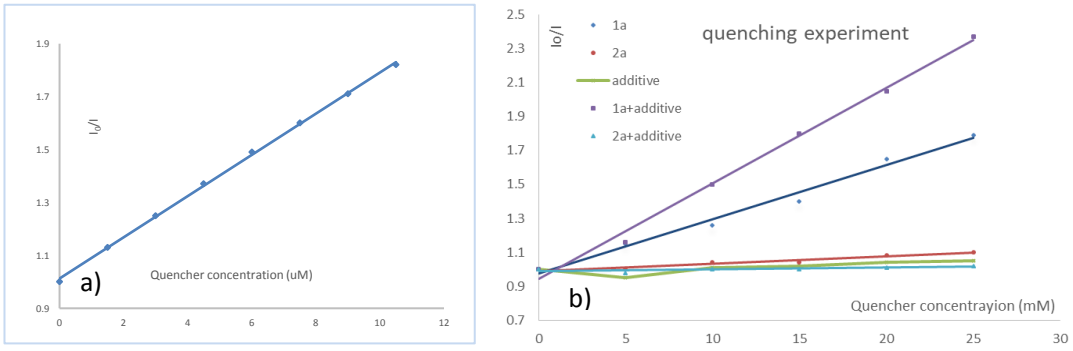


Figure S3. Stern-Volmer experiment of **1a** in MeCN b) Stern-Volmer experiments in DMSO

Cyclic voltammetry[5]

Cyclic Voltammetry was performed using a CHI650D Electrochemical workstation using a glassycarbon working electrode, Ag/AgCl in 3 M NaCl reference electrode, and a platinum counter electrode. The solution for test of **1a** was prepared by dissolving the sample (0.2 mmol) into a 0.1 M solution of tetrabutylammonium hexafluorophosphate ($TBAPF_6$) in MeCN (10 mL). Otherwise, $Ir(ppy)_3$ (0.2 mmol), Asc-H (88.1 mg, 0.5 mmol)/Cs_2CO_3 (162.9 mg, 0.5mmol), $BrCF_2COOEt$ (0.2 mmol) or *N, N'*-cyclicazomethine imines (0.2 mmol) were well dissolved in a 0.1 M ($TBAPF_6$) solution in DMSO (ca. 10 mL) respectively for CV study . The potential range scanned was typically -3V and 3V at a 100mV/s.

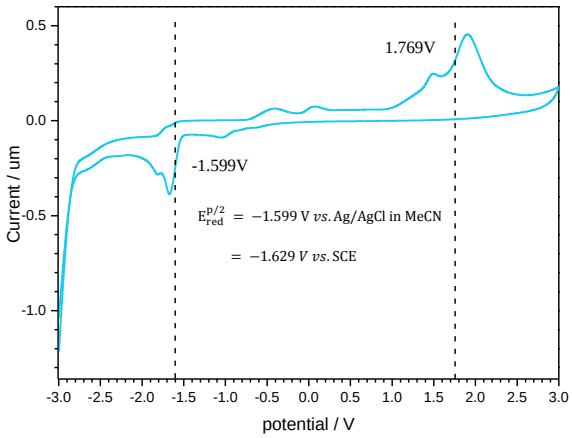


Figure S3: CV study of **1a** in MeCN, $E_{red}^{p/2}$ = -1.629 V *vs.* SCE (the obtained value was referenced to Ag/AgCl and converted to SCE by subtracting 0.03V).

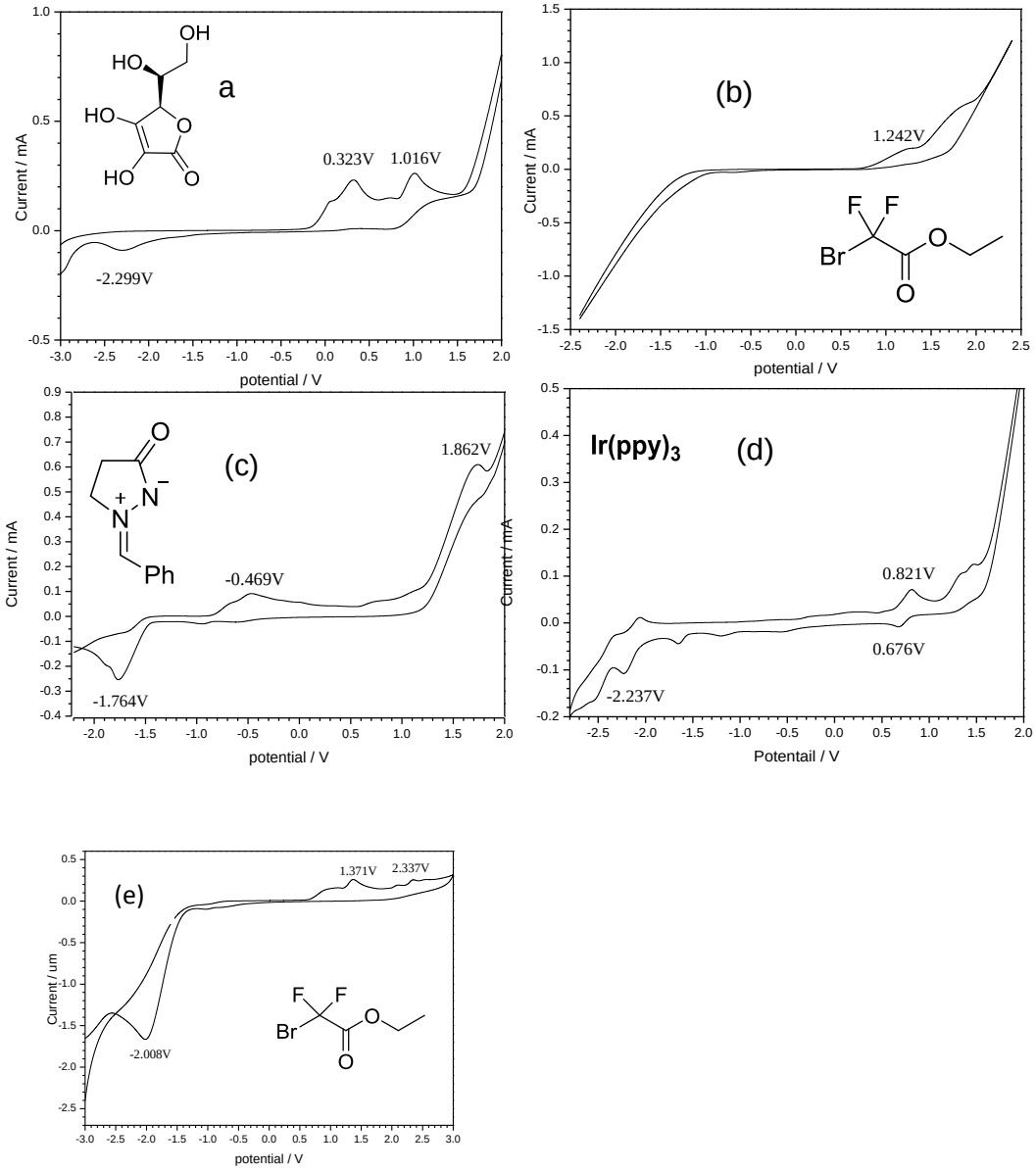
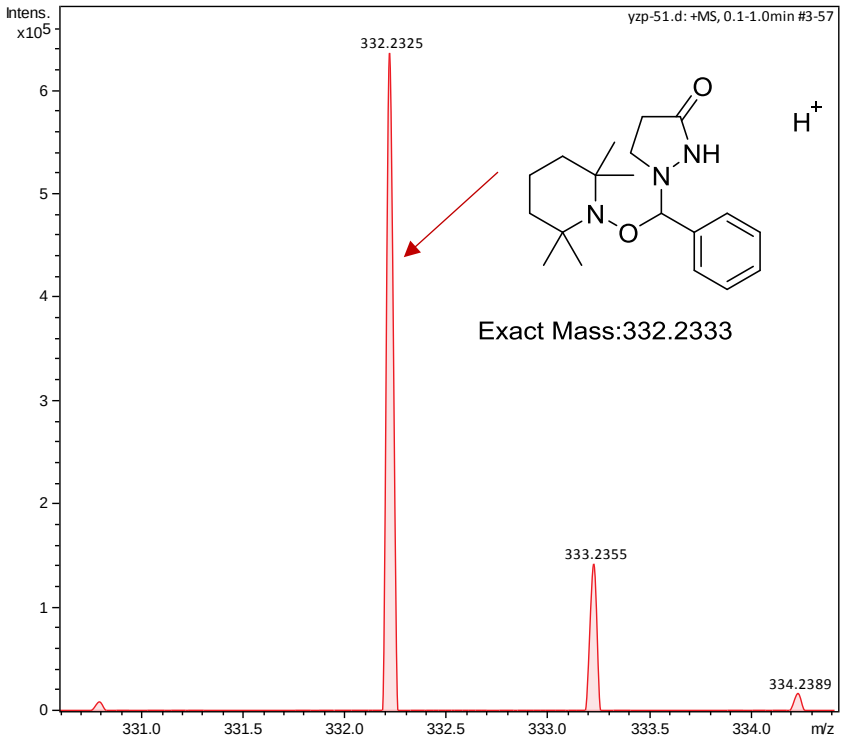


Figure S4: CV studies in DMSO for (a) Asc-H + Cs_2CO_3, $E_p^C = E_{red}$ = -2.30 V; (b) $BrCF_2COOEt$, $E_p^C = E_{red}$ = -2.40 V (c) *N*, *N*'-cyclicazomethine imines **1a**, $E_p^C = E_{red}$ = -1.764 V; (d) $Ir(ppy)_3$, $E_p(Ir^{IV}/Ir^{III})$ = 0.68 V and excited state redox potential was calculated using the Rehm-Weller equation $E(Ir^{III*}/Ir^{IV})$ = -1.82 V. CV studies in CH_3CN for (e) $BrCF_2CO_2Et$, $E_p^C = E_{red}$ = -2.01 V.

Trapping Experiment

Verification of the formation of an *N, N*'-cyclicazomethine imines **1a** radical generated through oxidative quenching of the photocatalyst and subsequent free-radical coupling with•CF_2COOEt. 3-Pyrazolidinone **1a** radical and •CF_2COOEt were tried respectively *via* the radical-trapping experiment through the addition of TEMPO and BHT (0.6 mmol, 3 eq.).

N, N'-Cyclicazomethine imines **1a** (0.20 mmol), Cs_2CO_3 (0.30 mmol, 1.5 eq.), Asc-H (0.30 mmol, 1.5 eq.) and $Ir(ppy)_3$ (2.00 mmol%) and $BrCF_2CO_2Et$ **2a** (0.60 mmol, 3 eq.) in DMSO (1 mL) were placed in a 5 mL flask and the reaction mixture was stirred at room temperature for 2 h under irradiation of 30 W blue LEDs (distance app. 3 cm). In order to ensure whether the putative *N, N*'-cyclicazomethine imines **1a** was trapped by TEMPO and •CF2COOEt was trapped by BHT. ESI-MS analysis of the crude reaction mixture was performed (see Figure S6). The resulting mass spectrum clearly shows a peak corresponding to the coupled product between TEMPO radical and *N, N*'-cyclicazomethine imines **1a** (HRMS (ESI): $C_{19}H_{30}N_3O_2^+$ $[M+H]^+$ Calcd 332.2333, Found 332.2325) and BHT radical and the expected •CF_2COOEt (HRMS (ESI) : $C_{19}H_{28}F_2NaO_3^+$ $[M + Na]^+$Calcd 365.1899, Found 365.1877). Simultaneously, we also observed the dimer of *N, N*'-cyclicazomethine imine **1a** (HRMS (ESI): $C_{20}H_{20}N_4NaO_2^+$ $[M+H]^+$ Calcd 371.1478, Found 371.1490).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333.2355
334.2389
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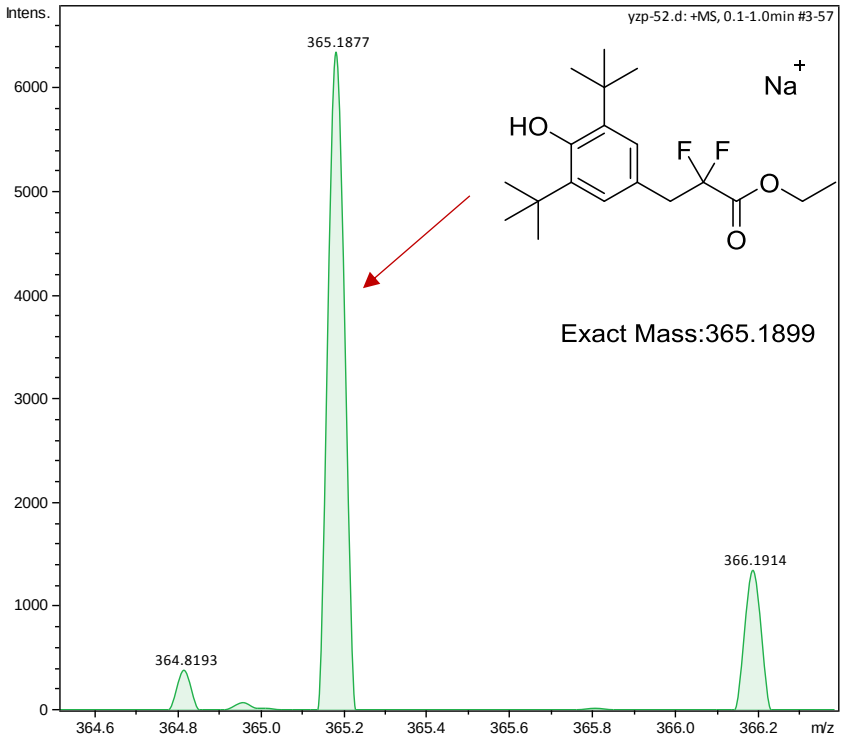
NH
N
N
O
H+
Exact Mass:332.2333
m/z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Na+
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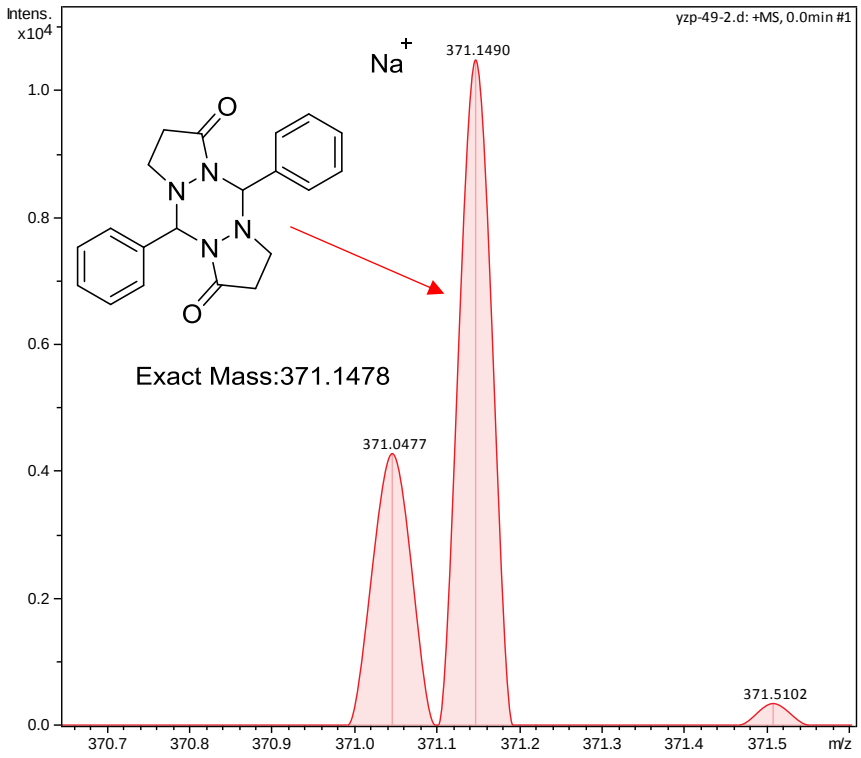


Figure S5. Crude ESI-MS of the species **I**, **II** and **C**.

Ref:

[1] (a) H. C. Guo, H. L. Liu, F. L. Zhu, R. S. Na, H. Jiang, Y. Wu, L. Zhang, Z. Li, H. Yu, B. Wang, Y. M. Xiao, X. P. Hu, M. Wang; *Angew. Chem. Int. Ed.* 2013, **52**, 12641; (b) S. E. Winterton, J. M. Ready; *Org. Let*t. 2016, **18**, 2608; (c) S. J. Shen, Y. L. Yang, J. Y. Duan, Z. H. Jia, J. Y. Liang; *Org. Biomol. Chem*., 2018, **16**, 1068.

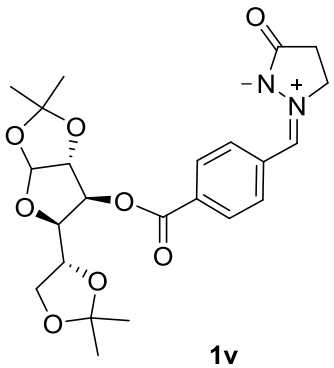
[2] (a) C. P. Chen, R. S. Zeng, J. Y. Zhang, Y. S. Zhao; *Eur. J. Org. Chem*. 2017, **46**, 6947; (b) Atsushi Tarui, S. Shinohara, K. Sato, M. Omote, A. Ando; *Org. Lett*. 2016, **18**, 1128.

[3] (a) T. Meiresonne, G. Verniest, N. D. Kimpe, S. Mangelinckx; *J. Org. Chem*. 2015, **80**, 5111.

[4] M. A. Cismesiaa, T. P. Yoon; *Chem. Sci***. 2015**, **6**, 5426.

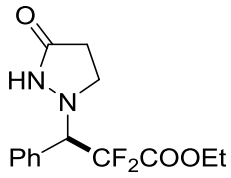
[5] D. Rehm, A. Weller; *Isr. J. Chem*. 1970, **8**, 259.

3. Characterization data of compound 1v, 3a-3x, 4a-4q.



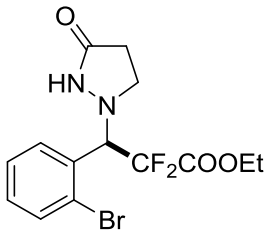
1v

N, N'-cyclicazomethine imines **1v**: Pale yellow solid (Yield 50%); m.p. 130-132 ℃; IR (KBr) ν 667, 762, 843, 960, 1069, 1161, 1257 1656, 1719 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, *J* = 8.4 Hz, 2H), 8.09 (d, *J* = 8.4 Hz, 2H), 7.14 (s, 1H), 5.96 (d, *J* = 3.6 Hz, 1H), 5.50 (d, *J* = 2.4 Hz, 1H), 4.65 (d, *J* = 3.6 Hz, 1H), 4.58 (t, *J* = 8.0 Hz, 3H), 4.31-4.36 (m, 2H), 4.13-4.15 (m, 1H), 4.07-4.10 (m, 1H), 2.86 (t, *J* = 8 Hz, 2H), 1.56 (s, 3H), 1.42 (s, 3H), 1.33 (s, 3H), 1.27 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.5, 164.3, 133.3, 131.4, 131.2, 130.7, 129.9, 112.4, 109.5, 105.1, 83.3, 79.9, 77.4, 72.5, 67.3, 58.5, 29.2, 26.8, 26.2, 25.2. HRMS (ESI): $C_{23}H_{28}N_2NaO_8^+$ $[M+Na]^+$ Calcd 483.1738, Found 483.1727.



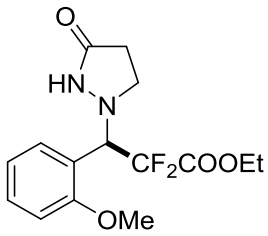
3a

difluorinated 3-pyrazolidinone **3a**: pale yellow solid (52.0 mg, 0.176 mmol, yield 88%); m.p. 108-110 ℃; IR (KBr) ν 650, 735, 822, 1052, 1221, 1369, 1677, 1759, 3188 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66 (*br*, s, 1H), 7.38-7.48 (m, 5H), 4.37 (dd, *J* = 18.0, 10.4 Hz, 1H), 4.28 (q, *J* = 7.2 Hz, 2H), 3.45-3.53 (m, 1H), 3.29-3.36 (m, 1H), 2.05-2.13 (m, 1H), 1.83-1.92 (m, 1H), 1.26 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 163.3 (t, $^2J_{C-F}$ = 31.5 Hz), 130.5, 130.1, 129.8, 128.9, 115.1 (dd, $^1J_{C-F}$ = 256.0, 258.2 Hz), 72.0 (dd, $^2J_{C-F}$ = 24.5, 20.9 Hz), 63.23, 51.64, 29.7, 13.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ -108.68 (d, *J* = 260.3 Hz), -112.35 (d, *J* = 260.7 Hz); HRMS (ESI): $C_{14}H_{17}F_2N_2O_3^+$ $[M+H]^+$ Calcd 299.1202, Found 299.1177.



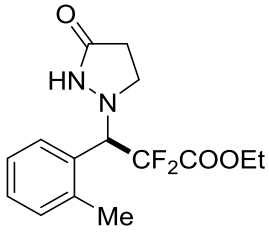
3b

difluorinated 3-pyrazolidinone **3b**: pale yellow solid (60.0 mg, 0.160 mmol, yield 80%); m.p. 112-114 ℃; IR (KBr) ν 650, 725, 967, 1060, 1134, 1305, 1689, 1762, 3182 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66-7.71 (m, 2H), 7.54 (*br* s, 1H), 7.38 (t, *J* = 7.6 Hz, 1H), 7.27-7.30 (m, 1H), 5.30 (dd, *J* =18.1, 10.4 Hz, 1H), 4.24-4.36 (m, 2H), 3.45 (t, *J* = 8.0 Hz, 2H), 2.21-2.29 (m, 1H), 1.89-1.98 (m, 1H), 1.29 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1, 163.0 (t, $^{2}J_{C-F}$ = 31.6 Hz), 133.4, 131.7, 131.1, 130.3, 128.0, 126.7, 114.9 (dd, $^{1}J_{C-F}$ = 259.1, 255.5 Hz), 68.7 (dd, $^{2}J_{C-F}$ = 24.7, 20.9 Hz), 63.4, 52.0, 29.8, 13.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ -108.62 (d, *J* = 261.1 Hz), -111.76 (d, *J* = 261.3 Hz); HRMS (ESI): $C_{14}H_{16}BrF_2N_2O_3^+$ $[M+H]^+$ Calcd 377.0307, Found 377.0328.



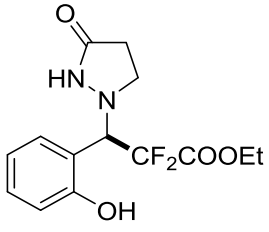
3c

difluorinated 3-pyrazolidinone **3c**: pale yellow solid (65.1 mg, 0.198 mmol, yield 99%); m.p. 101-103 ℃; IR (KBr) *v* 644, 730, 799, 1019, 1179, 1229, 1792, 1768, 2921 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.0 Hz, 1H), 7.28-7.33 (m, 2H), 6.87-6.94 (m, 2H), 5.18 (dd, *J* = 20.1, 11.1 Hz, 1H), 4.21 (q, *J* = 7.2Hz, 2H), 3.81 (s, 3H), 3.40-3.49 (m, 1H), 3.29-3.36 (m,1H), 1.95-2.03 (m, 1H), 1.75-1.83 (m, 1H), 1.18 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 162.5 (t, $^{1}J_{C-F}$ = 31.5 Hz), 157.0, 130.1, 129.8, 120.0, 117.4, 114.6 (dd, $^{1}J_{C-F}$ = 258.0, 255.3 Hz), 109.8, 62.0, 61.0 ($^{2}J_{C-F}$ = 24.7, 21.0 Hz). 54.8, 50.9, 28.9, 12.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ -108.31 (d, *J* = 259.4 Hz), -111.85 (d, *J* = 260.1 Hz); HRMS (ESI): $C_{15}H_{19}F_2N_2O_4^+$ $[M+H]^+$ Calcd 329.1307, Found 329.1326.



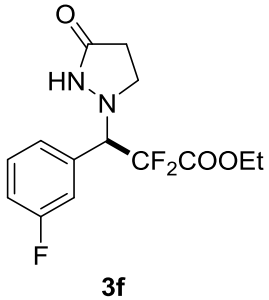
3d

difluorinated 3-pyrazolidinone **3d**: pale yellow solid (46.2 mg, 0.148 mmol, yield 74%); m.p. 111-112 ℃; IR (KBr) *v* 653, 732, 887, 1059, 1132, 1203, 1695, 1753, 3125 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.6 Hz, 1H), 7.21-7.30 (m, 3H), 7.05 (*br* s, 1H), 4.72 (t, *J* = 13.2 Hz, 1H), 4.19-4.27 (m, 2H), 3.29 (t, *J* = 8.0 Hz, 2H), 2.43 (s, 3H), 2.33-2.41 (m, 1H), 2.12-2.20 (m, 1H), 1.20 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 163.3 (t, $^{2}J_{C-F}$ = 31.4 Hz), 137.9, 131.0, 129.5, 129.4, 129.3, 126.6, 115.2 (t, $^{1}J_{C-F}$ = 257.4 Hz), 63.3, 51.6, 50.8, 29.8, 20.2, 13.7; ^{19}F NMR (376 MHz, $CDCl_3$) -108.37 (d, *J* = 258.3 Hz), -109.40 (d, *J* = 257.9 Hz); HRMS (ESI): $C_{15}H_{18}F_2KN_2O_3^+$ $[M+K]^+$ Calcd 351.0917, Found 351.0891.



3e

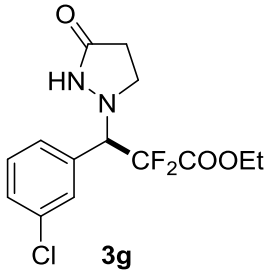
difluorinated 3-pyrazolidinone **3e**: pale brown oil (37.0 mg, 0.118 mmol, yield 59%); IR (KBr) ν 651, 825, 1056, 1219, 1309, 1457, 1669, 1757, 3125 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.61 (s, 1H), 9.43 (s, 1H), 7.37 (d, *J* = 7.6 Hz, 1H), 7.20-7.24 (m, 1H), 6.92 (d, *J* = 8.4 Hz, 1H), 6.91 (t, *J* = 7.6 Hz, 1H), 5.20 (dd, *J* = 22.8, 10.4 Hz, 1H), 4.18-4.29 (m, 2H), 3.58 (t, *J* = 7.2 Hz, 1H), 1.79-1.99 (m, 2H), 1.65-1.74 (m, 1H), 1.17 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 175.8, 163.5 (t, ^{2}J = 31.2 Hz), 156.9, 131.4, 130.6, 119.3, 117.5, 115.7, 62.1 (dd, J_{C-F} = 24.7, 19.6 Hz), 61.9, 52.8, 30.0, 14.0; ^{19}F NMR (376 MHz, DMSO-d_6) δ -107.69 (d, *J* = 258.2 Hz), -112.90 (d, *J* = 258.2 Hz). HRMS (ESI): $C_{14}H_{17}F_2N_2O_4^+$ $[M+H]^+$ Calcd 315.1151, Found 315.1123.



3f

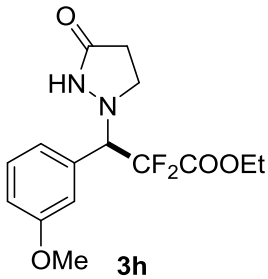
difluorinated 3-pyrazolidinone **3f**: pale yellow oil (30.3 mg, 0.096 mmol, yield 48%); IR (KBr) *v* 657, 803, 1031, 1179, 1226, 1304, 1678, 1720, 2923 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.3 Hz, 2H), 7.33 (*br* s, 1H), 7.11 (t, *J* = 8.4 Hz, 2H), 4.33-4.40 (m, 1H), 4.30 (q, *J* = 7.2 Hz,

2H), 3.43- 3.51 (m, 1H), 3.27-3.33 (m, 1H), 2.11-2.22 (m, 1H), 1.87-2.00 (m, 1H)， 1.23 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ 175.5 , 163.6 (d, $^{1}J_{C\text{-}F}$ = 250.1 Hz), 163.2 (t, $^{2}J_{C\text{-}F}$ = 31.4 Hz), 132.4 (d, $^{3}J_{C\text{-}F}$ = 8.1 Hz), 126.0 , 116.0 (d, $^{2}J_{C\text{-}F}$ = 21.5 Hz), 71.3 (dd, $^{2}J_{C\text{-}F}$ = 25.2, 20.8 Hz), 63.3, 51.7, 29.6, 13.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ -108.22 (d, J = 260.9 Hz), -110.94, -112.95 (d, J = 261.3 Hz). HRMS (ESI): $C_{14}H_{16}F_3N_2O_3^+$ $[M+H]^+$ Calcd 317.1108, Found 317.1079.



3g

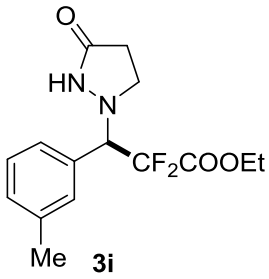
difluorinated 3-pyrazolidinone **3g**: pale yellow oil (41.2 mg, 0.124 mmol, yield 62%); IR (KBr) *v* 694, 788, 1063, 1217, 1302, 1421, 1681, 1723, 2922 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.40 (m, 4H), 4.27-4.34 (m, 1H), 4.24 (q, J = 7.2 Hz, 2H), 3.36-3.42 (m, 1H), 3.24-3.30 (m, 1H), 2.10-2.18 (m,1H), 1.89-1.97 (m, 1H), 1.22 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 162.1 (t, $^{2}J_{C\text{-}F}$ = 30.8 Hz), 133.8, 131.2, 129.5, 129.1, 129.0, 127.6, 113.6 (dd, $^{1}J_{C\text{-}F}$ = 259.1, 255.2 Hz), 70.44 (dd, $^{2}J_{C\text{-}F}$ = 25.7, 20.9 Hz), 62.4, 50.6, 28.7, 12.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ -107.64 (d, J = 262.1 Hz), -112.90 (d, J = 262.0 Hz). HRMS (ESI): $C_{14}H_{16}ClF_2N_2O_3^+$ $[M+H]^+$ Calcd 333.0812, Found 333.0837.



3h

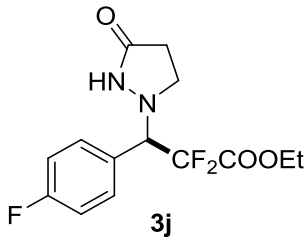
difluorinated 3-pyrazolidinone **3h**: pale yellow solid (45.3 mg, 0.138mmol, yield 69%); m.p. 103-105 ℃; IR (KBr) *v* 654, 729, 789, 1055, 1232, 1302, 1680, 1768, 2924 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, J = 8.1 Hz, 1H), 7.21 (d, J = 8.0 Hz, 1H), 6.88-6.96 (m, 3H), 4.23-4.28 (m, 1H), 4.22 (q, J = 7.2 Hz, 2H), 3.74 (s, 3H), 3.38-3.45 (m, 1H), 3.23-3.30 (m, 1H), 2.04-2.12 (m, 1H), 1.83-1.92 (m, 1H), 1.20 (t, J = 7.2Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5, 162.4 (t, $^{2}J_{C\text{-}F}$ = 31.6 Hz), 158.7, 130.6, 128.9, 121.8, 115.3 (dd, $^{1}J_{C\text{-}F}$ = 257.3, 256.0 Hz), 115.1, 114.2, 71.1 (dd, $^{2}J_{C\text{-}F}$ = 23.9, 21.5 Hz), 62.2, 54.3, 50.6, 28.7, 12.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ

-108.53 (d, J = 260.1 Hz), -111.91 (d, J = 260.9 Hz). HRMS (ESI): $C_{15}H_{18}F_2N_2NaO_4^+$ $[M+Na]^+$ Calcd 351.1127, Found 351.1121.



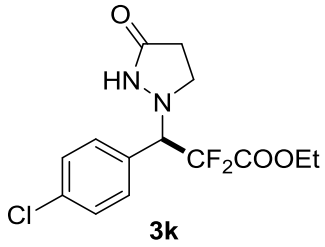
3i

difluorinated 3-pyrazolidinone **3i**: pale yellow solid (46.2 mg, 0.148 mmol, yield 74%); m.p. 85-87 ℃; IR (KBr) v 657, 713, 781, 1063, 1213, 1302, 1695, 1762, 2930 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (*br* s, 1H), 7.22-7.30 (m, 4H), 4.25-4.35 (m, 3H), 3.43-3.51 (m, 1H), 3.28-3.35 (m, 1H), 2.37 (s, 3H), 2.09-2.18 (m, 1H), 1.88-1.97 (m, 1H), 1.26 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 163.3 (t, $^2J_{C-F}$ = 31.5 Hz), 138.6, 131.2, 130.5, 130.1, 128.7, 127.5, 115.1 (t, $^1J_{C-F}$ = 256.9 Hz), 72.2 (dd, $^2J_{C-F}$ = 23.7, 21.6 Hz), 63.2, 51.7, 29.7, 21.4, 13.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ -108.70 (d, J = 259.9 Hz), -111.77 (d, J = 260.4 Hz). HRMS (ESI): $C_{15}H_{18}F_2NaN_2O_3^+$ $[M+Na]^+$ Calcd 335.1178, Found 335.1159.



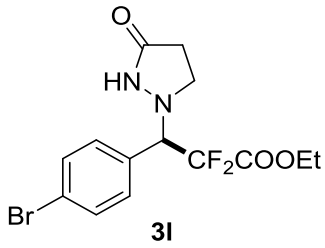
3j

difluorinated 3-pyrazolidinone motif **3j**: pale yellow oil (40.5 mg, 0.128 mmol, yield 64%); IR (KBr) v 657, 702, 785, 1063, 1229, 1304, 1693, 1710, 2925 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 (*br* s, 1H), 7.36-7.41 (m, 1H), 7.21-7.27 (m, 2H), 7.12-7.17 (m, 1H), 4.38 (dd, J = 18.1, 9.5 Hz, 1H), 4.31 (t, J = 7.2 Hz, 2H), 3.43-3.50 (m, 1H), 3.31-3.37 (m, 1H), 2.14-2.22 (m, 1H), 1.94-2.04 (m, 1H), 1.29 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6, 163.3 (d, $^2J_{C-F}$ = 30.9 Hz), 162.6 (d, $^1J_{C-F}$ = 247.9 Hz), 132.6 (d, $^3J_{C-F}$ = 7.1 Hz), 130.4 (d, $^3J_{C-F}$ = 8.2 Hz), 126.4, 117.5 (d, $^2J_{C-F}$ = 22.4 Hz), 116.8 (d, $^2J_{C-F}$ = 20.9 Hz), 114.7 (dd, $^1J_{C-F}$ = 259.2, 255.5 Hz), 71.5 (dd, $^2J_{C-F}$ = 24.5, 21.3 Hz), 63.4, 51.6, 29.6, 13.82; ^{19}F NMR (376 MHz, $CDCl_3$) δ -107.84 (d, J = 261.9 Hz), -111.43 , -112.95 (d, J = 262.0 Hz). HRMS (ESI): $C_{14}H_{16}F_3N_2O_3^+$ $[M+H]^+$ Calcd 317.1108, Found 317.1078.



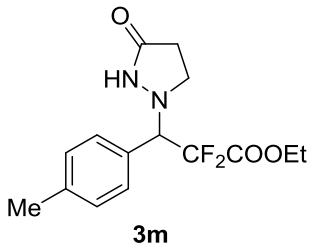
3k

difluorinated 3-pyrazolidinone **3k**: pale yellow solid (36.5 mg, 0.110 mmol, yield 55 %); m.p. 99-101 ℃; IR (KBr) *v* 660, 743, 823, 1052, 1181, 1236, 1694, 1755, 2917 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.43 (m, 4H), 7.12 (*br* s,1H), 4.29-4.38 (m, 3H), 3.43-3.51 (m, 1H), 3.27-3.33 (m, 1H), 2.13-2.20 (m, 1H), 1.89-1.97 (m, 1H), 1.30 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 136.2, 131.8, 129.2, 128.6, 71.5 (dd, $^{2}J_{C-F}$ = 25.5, 20.7 Hz), 63.4, 51.8, 29.6, 13.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ -107.70 (d, *J* = 261.2 Hz), -113.12 (d, *J* = 261.5 Hz); HRMS (ESI): $C_{14}H_{16}ClF_2N_2O_3^+$ $[M+H]^+$ Calcd 333.0812, Found 333.0782.



3l

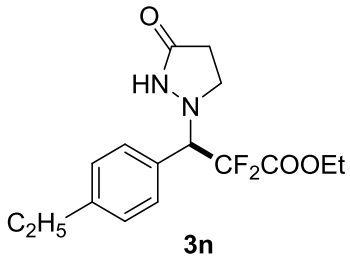
difluorinated 3-pyrazolidinone motif **3l**: pale yellow solid (55.7 mg, 0.146 mmol, yield 73%); m.p. 112-114 ℃; IR (KBr) *v* 592, 656, 741, 893, 1051, 1109, 1696, 1746, 2933 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* =8.4 Hz, 2H), 7.30 (br s, 1H), 4.29-4.37 (m, 3H), 3.43-3.50 (m, 1H), 3.27-3.34 (m, 1H), 2.12-2.20 (m, 1H), 1.89-1.98 (m, 1H), 1.30 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6, 163.2 (t, $^{2}J_{C-F}$ = 31.3 Hz), 132.1, 129.2, 124.4, 71.5 (dd, $^{2}J_{C-F}$ = 25.4, 20.7 Hz), 63.4, 51.8, 29.6, 13.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ -107.67 (d, *J* = 261.6 Hz), -113.25 (d, *J* = 261.8 Hz). HRMS (ESI): $C_{14}H_{15}BrF_2KN_2O_3^+$ $[M+K]^+$ Calcd 414.9866, Found 414.9846.



3m

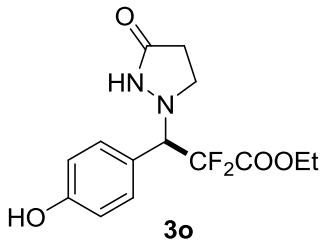
difluorinated 3-pyrazolidinone **3m**: pale yellow solid (45.6 mg, 0.146 mmol, yield 73%); m.p. 111-113 ℃; IR (KBr) *v* 653, 731, 826, 1063, 1179, 1228, 1689, 1771, 2934 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 7.6 Hz, 2H), 7.13 (d, *J* = 8.0 Hz, 2H), 4.19-4.29 (m, 3H), 3.39-3.46 (m, 1H), 3.21-3.27 (m, 1H), 2.92 (s, 3H), 1.97-2.05 (m, 1H), 1.77-1.85 (m, 1H), 1.20 (t,

J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6, 163.2 (t, $^2J_{C\text{-}F}$ = 31.3 Hz), 139.9, 130.4, 129.6, 126.8, 115.2 (t, $^1J_{C\text{-}F}$ = 257.0 Hz), 71.9 (dd, $^2J_{C\text{-}F}$ = 25.2, 21.3 Hz), 63.3, 51.7, 29.8, 21.2, 13.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ -108.53 (d, J = 259.6 Hz), -112.06 (d, J = 263.7 Hz); HRMS (ESI): $C_{15}H_{18}F_2N_2NaO_3^+$ $[M+Na]^+$ Calcd 335.1178, Found 335.1189.



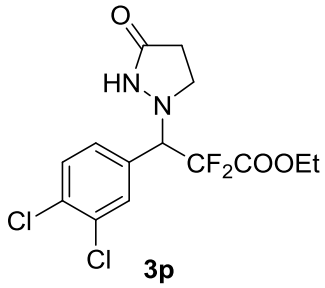
3n

difluorinated 3-pyrazolidinone motif **3n**: pale yellow oil (38.5 mg, 0.118 mmol, yield 59%); IR (KBr) v 649, 766, 833, 968, 1130, 1310,1698, 1753, 2920 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (br s, 1H), 7.36 (d, J = 8.0 Hz, 2H), 7.23 (d, J = 8.0 Hz, 2H), 4.26-4.36 (m, 3H), 3.46-3.53 (m, 1H), 3.28-3.34 (m,1H), 2.60 (q, J = 7.6 Hz, 2H), 2.04-2.12 (m, 1H), 1.83-1.92 (m, 1H), 1.21-1.28 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6, 163.4 (t, $^2J_{C\text{-}F}$ = 31.5 Hz), 146.1, 130.5, 128.4, 127.1, 115.2 (t, $^1J_{C\text{-}F}$ = 257.2 Hz), 71.9 (dd, $^2J_{C\text{-}F}$ = 23.5, 22.0 Hz), 63.2, 51.7, 29.7, 28.5, 15.3, 13.8; ^{19}F NMR (376 MHz, Chloroform-d) δ -108.68 (d, J = 259.5 Hz), -112.02 (d, J = 260.4 Hz); HRMS (ESI): $C_{16}H_{21}F_2N_2O_3^+$ $[M+H]^+$ Calcd 327.1515, Found 327.1491.



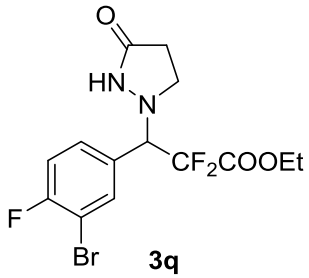
3o

difluorinated 3-pyrazolidinone **3o**: pale yellow solid (37.1 mg, 0.118 mmol, yield 59%); m.p. 162-164 ℃; IR (KBr) v 645, 799, 943, 1015, 1125, 1219,1678, 1763, 3203 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.64 (s, 1H), 9.37 (s, 1H), 7.29 (d, J = 8.4 Hz, 2H), 6.76 (d, J = 8.8 Hz, 2H), 4.53 (dd, J = 21.6, 10.4 Hz, 1H), 4.18-4.26 (m, 2H), 3.33-3.38 (m, 2H), 1.72-1.80 (m, 1H), 1.55-1.63 (m, 1H), 1.17 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, DMSO) δ 175.8, 163.5 (t, $^2J_{C\text{-}F}$ = 30.7 Hz), 158.6, 132.5, 121.0, 115.8 (t, $^1J_{C\text{-}F}$ = 255.2 Hz), 115.7, 69.9 (dd, $^2J_{C\text{-}F}$ = 24.4, 19.2 Hz), 63.2, 51.3, 29.9, 14.1; ^{19}F NMR (376 MHz, DMSO-d_6) δ -108.06 (d, J = 257.8 Hz), -113.13 (d, J = 257.6 Hz); HRMS (ESI): $C_{14}H_{16}F_2N_2NaO_4^+$ $[M+Na]^+$ Calcd 337.0970, Found 337.0995.



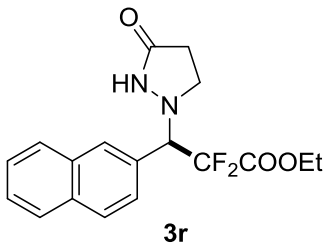
3p

difluorinated 3-pyrazolidinone **3p**: pale yellow oil (62.2 mg, 0.170 mmol, yield 85%); IR (KBr) ν 669, 718, 1064, 1217, 1300, 1467, 1692, 1710, 2925 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 1.6 Hz, 1H), 7.50 (d, *J* = 8.4 Hz, 1H), 7.35 (d, *J* = 8.4 Hz, 1H), 4.30-4.39 (m, 3H), 3.40-3.47 (m, 1H), 3.29-3.36 (m, 1H), 2.20-2.30 (m, 1H), 2.00-2.08 (m, 1H), 1.32 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 163.0 (dd, $^{2}J_{C-F}$ = 30.7, 30.4 Hz), 134.4, 133.1, 132.4, 130.9, 130.5, 129.6, 114.5 (dd, $^{1}J_{C-F}$ = 259.8, 254.7 Hz), 70.87 (dd, $^{2}J_{C-F}$ = 25.9, 20.8 Hz), 63.6, 51.7, 29.6, 13.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ -106.86 (d, *J* = 263.3 Hz), -113.60 (d, *J* = 263.2 Hz); HRMS (ESI): $C_{14}H_{15}Cl_2F_2N_2O_3^+$ $[M+H]^+$ Calcd 367.0422, Found 367.0402.



3q

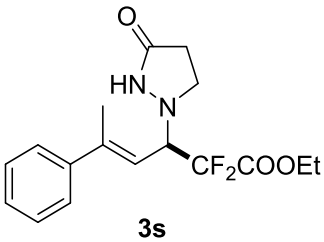
difluorinated 3-pyrazolidinone **3q**: pale yellow oil (67.1 mg, 0.118 mmol, yield 94%); IR (KBr) ν 666, 721, 827, 1190, 1254, 1302, 1694, 1723, 2927 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 7.4 Hz, 1H), 7.64 (br s, 1H), 7.43-7.46 (m, 1H), 7.17 (t, *J* = 8.4 Hz, 1H), 4.30-4.40 (m, 3H), 3.40-3.47 (m, 1H), 3.29-3.36 (m, 1H), 2.21-2.29 (m, 1H), 1.99-2.07 (m, 1H), 1.31 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 175.8, 163.1 (t, $^{2}J_{C-F}$ = 31.2 Hz), 159.9 (d, $^{1}J_{C-F}$ = 251.3 Hz), 135.6, 131.2, 127.9, 116.9 (d, $^{2}J_{C-F}$ = 22.5 Hz), 114.6 (t, $^{1}J_{C-F}$ = 259.6 Hz), 109.6 (d, $^{2}J_{C-F}$ = 21.2 Hz), 70.7 (dd, $^{2}J_{C-F}$ = 26.0, 20.8 Hz), 63.5, 51.7, 29.6, 13.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ -104.95, -107.22 (d, *J* = 262.8 Hz), -113.60 (d, *J* = 262.7 Hz); HRMS (ESI): $C_{14}H_{14}BrF_3KN_2O_3^+$ $[M+K]^+$ Calcd 432.9737, Found 432.9710.



3r

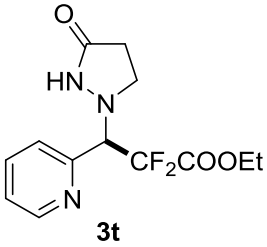
difluorinated 3-pyrazolidinone **3r**: pale yellow oil (29.9 mg, 0.086 mmol, yield 43%); IR (KBr) *ν* 746, 800, 1061, 1206, 1293, 1680, 1760, 2922 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (*br* s, 1H),

7.85-7.89 (m, 3H), 7.49-7.59 (m, 4H), 4.53 (dd, *J* = 16.8, 11.2 Hz, 1H), 4.27 (q, *J* = 7.2 Hz, 2H), 3.46-3.53 (m, 1H), 3.34-3.41 (m, 1H), 2.10-2.18 (m, 1H), 1.87-1.96 (m, 1H), 1.23 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 163.2 (t, $^2J_{C\text{-}F}$ = 31.6 Hz), 133.6, 130.7, 130.0, 128.7, 128.3, 127.71, 127.68, 127.2, 126.9, 126.7, 113.9 (t, $^1J_{C\text{-}F}$ = 257.2 Hz), 72.9-71.7 (t, $^2J_{C\text{-}F}$ = 23.2 Hz), 63.3, 51.8, 29.7, 13.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ -108.38 (d, *J* = 260.2 Hz), -111.51 (d, *J* = 260.8 Hz); HRMS (ESI): $C_{18}H_{18}F_2N_2NaO_3^+$ $[M+Na]^+$ Calcd 371.1178, Found 371.1179.



3s

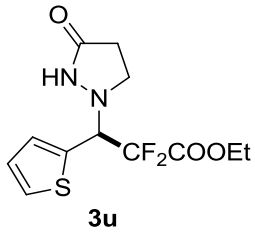
difluorinated 3-pyrazolidinone **3s**: pale yellow oil (29.8 mg, 0.088 mmol, yield 44%); IR (KBr) *v* 698, 746, 1017, 1189, 1296, 1371 1697, 1762, 2922 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.38 (m, 2H), 7.25-7.30 (m, 3H), 7.03 (*br* s, 1H), 6.65 (s, 1H), 4.31 (q, *J* = 7.2 Hz, 2H), 3.88 (t, *J* = 12.8 Hz, 1H), 3.41-3.50 (m, 2H), 2.42-2.60 (m, 2H), 2.00 (s, 3H), 1.31 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.1, 163.3 (t, *J* = 31.6 Hz), 136.0, 135.5, 129.8, 129.0, 128.4, 127.6, 117.9-112.7 (m), 76.1-75.7 (m), 63.3, 51.2, 29.8, 16.0, 14.0. HRMS (ESI): $C_{17}H_{20}F_2N_2NaO_3^+$ $[M+Na]^+$ Calcd 361.1334, Found 361.1356.



3t

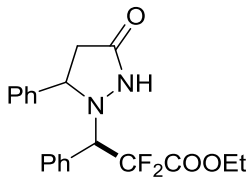
difluorinated 3-pyrazolidinone **3t**: pale yellow solid (41.3 mg, 0.138 mmol, yield 69%); m.p. 104-106 ℃; IR (KBr) *v* 656, 745, 1055, 1207, 1307, 1371, 1686, 1763, 2927 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58-8.59 (d, *J* = 4.1 Hz, 1H), 7.71 (td, *J* = 8.0, 1.6 Hz, 1H), 7.54 (d, *J* = 7.6 Hz, 1H), 7.30-7.33 (m, 1H), 4.72 (dd, *J* = 20.8, 8.0 Hz, 1H), 4.24-4.30 (m, 2H), 3.47-3.61 (m, 2H), 1.98-2.06 (m, 1H), 1.69-1.77 (m, 1H), 1.24 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.8, 163.1 (dd, $^2J_{C\text{-}F}$ = 32.7, 30.3 Hz), 151.0, 149.6, 137.1, 125.36 (d, $^3J_{C\text{-}F}$ = 3.7 Hz), 124.4, 114.8 (dd, $^1J_{C\text{-}F}$ = 258.1, 254.8 Hz), 72.9 (dd, $^2J_{C\text{-}F}$ = 26.3, 20.1 Hz), 63.4, 51.9, 29.7, 13.9; ^{19}F NMR (376

MHz, $CDCl_3$) δ -107.17 (d, *J* = 265.0 Hz), -114.32 (d, *J* = 264.9 Hz). HRMS (ESI): $C_{13}H_{16}F_2N_3O_3^+$ $[M+H]^+$ Calcd 300.1154, Found 300.1150.



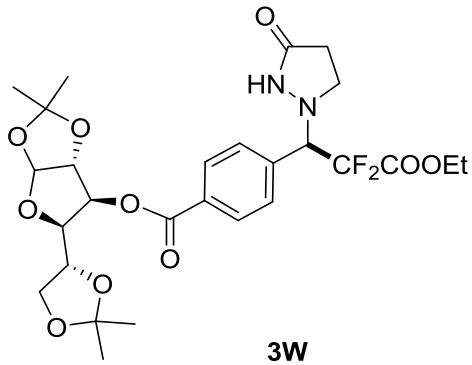
3u

difluorinated 3-pyrazolidinone motif **3u**: pale yellow solid (38.9 mg, 0.128 mmol, yield 64%); m.p. 118-120 ℃; IR (KBr) *v* 657, 716, 800, 1012, 1176, 1294, 1675, 1761, 3193 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 5.2 Hz, 1H), 7.17 (d, *J* = 4.8 Hz, 1H), 7.02-7.04 (m, 1H), 4.66 (dd, *J* = 21.3, 8.1 Hz, 1H), 4.29 (q, *J* = 6.8 Hz, 2H), 3.54-3.62 (m, 1H), 3.22-3.29 (m, 1H), 1.90-1.98 (m, 1H), 1.72-1.81 (m, 1H), 1.27 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0, 163.3 (dd, $^2J_{C-F}$ = 32.1, 30.3 Hz), 131.1, 128.8, 128.4, 127.2, 114.4 (dd, $^1J_{C-F}$ = 259.2, 254.6 Hz), 67.4 (dd, $^2J_{C-F}$ = 27.4, 20.6 Hz), 63.4, 51.6, 29.8, 13.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ -106.88 (d, *J* = 260.2 Hz), -115.54 (d, *J* = 260.2 Hz); HRMS (ESI): $C_{12}H_{14}F_2N_2NaO_3S^+$ $[M+Na]^+$ Calcd 327.0585, Found 327.0555.



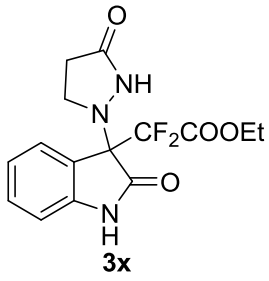
3V

difluorinated 3-pyrazolidinone motif **3w**: pale yellow solid (52.4 mg, 0.140 mmol, yield 70%); m.p. 132-134 ℃; IR (KBr) *v* 697, 1058, 1224, 1305, 1370, 1456, 1693, 1750, 2925 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (br s, 1H), 7.43-7.45 (m, 2H), 7.33-7.40 (m, 3H), 7.25-7.30 (m, 3H), 7.19-7.20 (m, 2H), 4.68 (dd, *J* = 17.2, 8.9 Hz, 1H), 4.51-4.53 (m, 1H), 4.22-4.28 (m, 2H), 2.72 (dd, *J* = 16.8, 8.4 Hz, 1H), 2.22 (dd, *J* = 16.8, 2.4 Hz, 1H), 1.21 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 163.5 (t, $^2J_{C-F}$ = 31.2 Hz), 140.2, 131.4, 130.0, 129.7, 128.9, 128.6, 127.7, 126.3, 114.7 (dd, $^1J_{C-F}$ = 260.4, 254.2 Hz), 71.7 (dd, $^2J_{C-F}$ = 24.6, 20.4 Hz), 63.4, 36.0, 13.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ -107.13 (d, *J* = 262.5 Hz), -112.88 (d, *J* = 262.9 Hz); HRMS (ESI): $C_{20}H_{20}F_2KN_2O_3^+$ $[M+K]^+$ Calcd 413.1074, Found 413.1048.



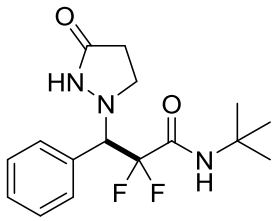
3W

difluorinated 3-pyrazolidinone motifs **3v**: Pale yellow solid (101.8 mg, 0.174 mmol, yield 87%); m.p. 162-164 ℃; IR (KBr) *v* 669, 873, 1162, 1215, 1307, 1652, 1683, 1791,2930 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.0 Hz, 2H), 7.59 (d, *J* = 8.0 Hz, 2H), 7.53 (*br* s, 1H), 5.94-5.97 (m, 1H), 5.51 (s, 1H), 4.63 (d, *J* = 3.6 Hz, 1H), 4.47 (dd, *J* = 18.4, 8.4 Hz, 1H), 4.30-4.39 (m, 4H), 4.08-4.16 (m, 2H), 3.44-3.51 (m, 1H), 3.31-3.37 (m, 1H), 2.11-2.22 (m, 1H), 1.81-1.98 (m, 1H), 1.56 (s, 3H), 1.42 (s, 3H), 1.33 (s, 3H), 1.26-1.29 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 164.5, 163.1 (t, $^{2}J_{C\text{-}F}$ = 31.6 Hz), 135.8, 135.7, 130.8-130.9 (m), 130.0, 112.4, 112.3, 109.5, 109.4, 105.1, 105.0, 83.3, 79.9, 72.5, 72.4, 71.6 (dd, $^{2}J_{C\text{-}F}$ = 25.6, 20.3 Hz), 67.3 (d, $J_{C\text{-}F}$ = 1.0 Hz), 63.5, 51.8, 51.7, 29.6, 29.5, 26.9, 26.8, 26.7, 26.2, 25.2, 13.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ -106.94 (d, *J* = 263.2 Hz), -113.50 (d, *J* = 263.2 Hz); HRMS (ESI): $C_{27}H_{34}F_2N_2NaO_{10}^{+}$ $[M+Na]^{+}$ Calcd 607.2074, Found 607.2064.



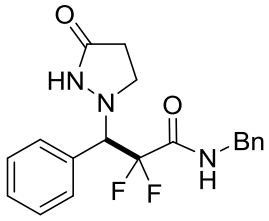
3x

difluorinated 3-pyrazolidinone **3x**: pale yellow solid (40 mg, 0.058mmol, yield 46%), mp: 170-172 ℃; IR (KBr) 627, 731, 953, 1113, 1246, 1367, 1469, 1672, 2918 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.95 (s, 1H), 9.38 (s, 1H), 7.36-7.39 (m, 2H), 7.04 (t, *J* = 7.6, Hz, 1H), 6.90 (d, *J* = 8.0 Hz, 1H), 4.11 (q, *J* = 7.0 Hz, 2H), 3.55 (t, *J* = 7.6 Hz, 2H). 1.97-2.61 (m, 2H), 1.03 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 180.5, 175.7, 166.1 (t, $^{2}J_{C\text{-}F}$ = 31.1 Hz), 148.5 136.4, 132.4, 127.4, 126.9, 118.9 (t, $^{1}J_{C\text{-}F}$ = 247.4 Hz), 115.4, 77.3 (t, $^{2}J_{C\text{-}F}$ = 21.2 Hz), 68.3, 53.6, 35.2, 18.5; ^{19}F NMR (376 MHz, DMSO-d_6) δ -108.78 (d, *J* = 258.4 Hz), -109.92 (d, *J* = 258.2 Hz); HRMS (ESI): $C_{15}H_{16}F_2N_3O_4^{+}$ $[M+H]^{+}$ Calcd 340.1103, Found 340.1083.



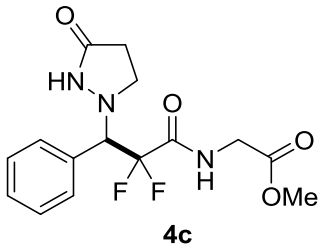
4a

difluorinated 3-pyrazolidinone **4a**: pale yellow solid (26.0 mg, 0.080 mmol, yield 40%); m.p. 179-181 ℃; IR (KBr) ν 650, 701, 822, 1057, 1144, 1229, 1679, 1768, 2924 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.59 (br s, 1H), 7.39-7.48 (m, 5H), 6.32 (br s, 1H), 4.45 (t, *J* = 6.4 Hz, 1H), 3.43-3.50 (m, 1H), 3.28-3.35 (m, 1H), 2.11-2.19 (m, 1H), 1.86-1.95 (m, 1H), 1.26 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 162.1 (t, $^2J_{C-F}$ = 26.2 Hz), 131.0, 130.5, 129.5, 128.8, 117.6 (t, $^1J_{C-F}$ = 259.5 Hz), 71.62 (t, $^2J_{C-F}$ = 22.6 Hz), 52.1, 51.9, 29.9, 28.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ -109.39 (d, *J* = 253.2 Hz), -112.06 (d, *J* = 256.4 Hz); HRMS (ESI): $C_{16}H_{21}F_2N_3NaO_2^+$ $[M+Na]^+$ Calcd 348.1494, Found 348.1493.



4b

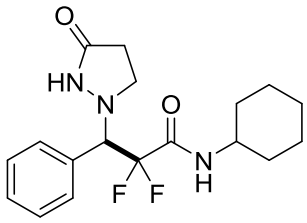
difluorinated 3-pyrazolidinone **4b**: pale yellow solid (62.5 mg, 0.174 mmol, yield 87%); m.p. 143-145 ℃; IR (KBr) *v* 610, 741, 1060, 1155, 1365, 1460, 1680, 1771, 2924 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) *δ* 9.37 (s, 1H), 9.09 (t, *J* = 6.0 Hz, 1H), 7.54 (d, *J* = 7.0 Hz, 2H), 7.38-7.48 (m, 3H), 7.20-7.29 (m, 3H), 7.12 (d, *J* = 6.9 Hz, 2H), 4.67 (dd, *J* = 22.4, 10.4 Hz, 1H), 4.35 (d, *J* = 6.0 Hz, 2H), 3.39-3.51 (m, 2H), 1.64-1.71 (m, 1H), 1.33-1.42 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.6, 163.7 (t, $^1J_{C-F}$ = 27.5 Hz), 137.0, 130.8, 130.3, 129.6, 128.8, 128.6, 127.6, 127.5, 119.53, 117.0 (dd, $^1J_{C-F}$ = 261.3, 255.2 Hz), 71.0 (dd, $^2J_{C-F}$ = 27.2, 19.8 Hz), 51.8, 43.5, 29.9; ^{19}F NMR (376 MHz, DMSO-d_6) δ -107.60 (d, *J* = 253.9 Hz), -113.36 (d, *J* = 254.1 Hz); HRMS (ESI): $C_{19}H_{19}F_2N_3NaO_2^+$ $[M+Na]^+$ Calcd 382.1338, Found 382.1336.



4c

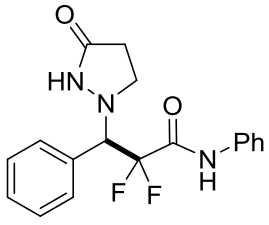
difluorinated 3-pyrazolidinone **4c**: pale yellow solid (67.5 mg, 0.198 mmol, yield 99%); m.p. 122-124 ℃; IR (KBr) *v* 655, 747, 987, 1207, 1366, 1669, 1699, 1730, 2924 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ

8.80 (*br* s, 1H), 7.63 (*br* s, 1H), 7.50-7.51 (m, 2H), 7.40-7.42 (m, 3H), 4.52 (dd, *J* = 21.9, 7.8 Hz, 1H), 4.07 (d, *J* = 4.8 Hz, 2H), 3.75 (s, 3H), 3.51-3.58 (m, 1H), 3.29-3.35 (m, 1H), 2.01-2.08 (m, 1H), 1.73-1.81 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.6, 169.3, 163.9 (t, $^2J_{C\text{-}F}$ = 28.4 Hz), 130.6, 130.3, 129.6, 128.8, 116.5 (dd, $^1J_{C\text{-}F}$ = 261.2, 254.7 Hz), 71.3 (dd, $^2J_{C\text{-}F}$ = 27.1, 19.9 Hz), 52.6, 51.9, 41.1, 29.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ -105.12 (d, *J* = 262.5 Hz), -116.13 (d, *J* = 258.3 Hz); HRMS (ESI): $C_{15}H_{17}F_2N_3NaO_4^+$ $[M+Na]^+$ Calcd 364.1079, Found 364.1076.



4d

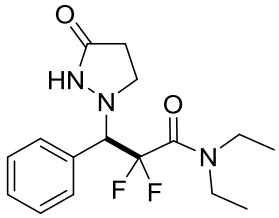
difluorinated 3-pyrazolidinone **4d**: pale yellow solid (56.9 mg, 0.162 mmol, yield 81%); m.p. 165-167 ℃; IR (KBr) ν 656, 789, 1056, 1149, 1231, 1303, 1680, 1769, 2923 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (br s, 1H), 7.48 (d, *J* = 6.8 Hz, 2H), 7.36-7.42 (m, 3H), 6.56 (br s, 1H), 4.46 (dd, *J* = 17.2, 12.0 Hz 1H), 3.68-3.76 (m, 1H), 3.45-3.52 (m, 1H), 3.28-3.34 (m, 1H), 2.09-2.16 (m, 1H), 1.83-1.91 (m, 2H), 1.57-1.71 (m, 4H), 1.28-1.38 (m, 2H), 1.10-1.16 (m, 2H), 0.95-1.05 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.8, 162.2 (t, $^2J_{C\text{-}F}$ = 27.0 Hz), 130.9, 130.5, 129.5, 128.8, 116.6 (t, $^1J_{C\text{-}F}$ = 261.4 Hz), 72.1 (t, $^2J_{C\text{-}F}$ = 22.9 Hz), 51.8, 48.7, 32.3, 30.0, 25.3, 24.7, 24.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ -108.52 (d, *J* = 253.0 Hz), -113.29 (d, *J* = 260.4 Hz); HRMS (ESI): $C_{18}H_{23}F_2N_3NaO_2^+$ $[M+Na]^+$ Calcd 374.1651, Found 374.1652.



4e

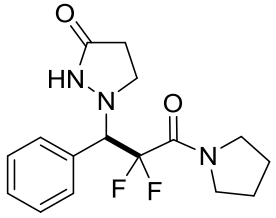
difluorinated 3-pyrazolidinone motif **4e**: pale yellow solid (62.1 mg, 0.180 mmol, yield 90%); m.p. 175-177 ℃; IR (KBr) *v* 651, 751, 1059, 1137, 1219, 1551, 1686, 1712, 2920cm^{-1}; ^{1}H NMR (400 MHz , DMSO-d_6) *δ* 10.28 (s, 1H), 9.49 (s, 1H), 7.59-7.65 (m, 4H), 7.43-7.45 (m, 3H), 7.36-7.39 (m, 2H), 7.15-7.19 (m, 1H), 4.76 (dd, J = 24.4, 7.6 Hz, 1H), 3.42-3.46 (m, 2H), 1.66-1.73 (m, 1H), 1.35-1.41 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 175.75, 162.1 (t, $^2J_{C\text{-}F}$ = 28.2 Hz),

137.6, 131.5, 131.3, 129.5, 129.3, 128.8, 125.4, 121.2, 69.9 (dd, $^{2}J_{C\text{-}F}$ = 27.2, 18.9 Hz), 55.5, 29.9; ^{19}F NMR (376 MHz, DMSO-d_6) δ -105.03 (d, *J* = 254.7 Hz), -114.50 (d, *J* = 254.8 Hz); HRMS (ESI): $C_{18}H_{17}F_2N_3NaO_2^+$ $[M+Na]^+$ Calcd 368.1181, Found 368.1181.



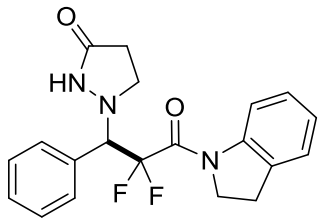
4f

difluorinated 3-pyrazolidinone **4f**: pale yellow oil (55.9 mg, 0.172 mmol, yield 86%); IR (KBr) *v* 652, 702, 802, 969, 1043, 1181, 1643, 1698, 2924 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (*br* s, 1H), 7.45-7.47 (m, 2H), 7.37-7.39 (m, 3H), 4.59 (dd, *J* = 15.5, 11.6 Hz, 1H), 3.30-3.41 (m, 4H), 3.23-3.28 (m, 1H), 3.12-3.19 (m, 1H), 2.12-2.22 (m, 1H), 1.97-2.07 (m, 1H), 1.13 (t, *J* = 7.2 Hz, 3H), 1.07 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.8, 161.9 (t, $^{2}J_{C\text{-}F}$ = 27.7 Hz), 131.3, 130.5, 129.4, 128.7, 117.5 (t, $^{1}J_{C\text{-}F}$ = 260.8 Hz), 72.7 (dd, $^{2}J_{C\text{-}F}$ = 23.4, 21.0 Hz), 51.7, 42.3, 42.2 (t, $^{3}J_{C\text{-}F}$ = 6.8 Hz), 29.9, 14.5, 12.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ -101.23 (d, *J* = 272.5 Hz), -104.14 (d, *J* = 272.3 Hz); HRMS (ESI): $C_{16}H_{21}F_2N_3NaO_2^+$ $[M+Na]^+$ Calcd 348.1494, Found 348.1470.



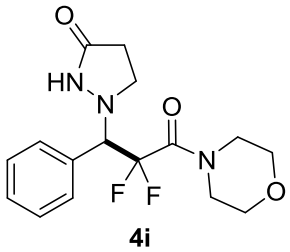
4g

difluorinated 3-pyrazolidinone **4g**: pale yellow solid (47.8 mg, 0.148 mmol, yield 74%); m.p. 151-153 ℃; IR (KBr) ν 644, 741, 822, 1052, 1122, 1446,1630, 1695, 3310 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48-7.50 (m, 2H), 7.39-7.42 (m, 3H), 4.50 (t, *J* = 12.4 Hz, 1H), 3.43-3.56 (m, 2H), 3.31-3.42 (m, 3H), 3.20-3.21 (m, 1H), 2.23-2.31 (m, 1H), 2.05-2.14 (m, 1H), 1.70-1.83 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 161.2 (t, $^{2}J_{C\text{-}F}$ = 28.4 Hz), 131.4, 130.3, 129.5, 128.7, 117.1 (t, $^{1}J_{C\text{-}F}$ = 261.2 Hz), 72.6 (t, $^{2}J_{C\text{-}F}$ = 22.3 Hz), 51.7, 47.9, 46.9 (dd, $^{3}J_{C\text{-}F}$ = 7.8, 6.0 Hz), 29.8, 26.5, 23.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ -103.13 (d, *J* = 268.0 Hz), -105.64 (d, *J* = 267.9 Hz); HRMS (ESI): $C_{16}H_{19}F_2N_3NaO_2^+$ $[M+Na]^+$ Calcd 346.1338, Found 346.1340.



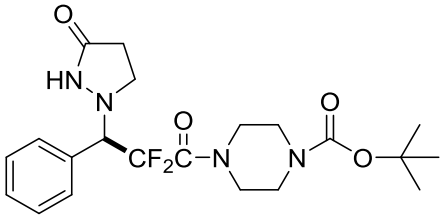
4h

difluorinated 3-pyrazolidinone **4h**: pale yellow solid (73.5 mg, 0.198 mmol, yield 99%); m.p. 164-166 ℃; IR (KBr) ν 646, 763, 863, 1030, 1140, 1174, 1661, 1698, 3201 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.0 Hz, 1H), 7.49-7.51 (m, 3H), 7.37-7.41 (m, 3H), 7.19-7.24 (m, 2H), 7.10 (t, *J* = 7.2 Hz, 1H), 4.65 (dd, *J* = 15.5, 11.0 Hz, 1H), 4.03-4.09 (m, 1H), 3.89-3.96 (m, 1H), 3.38 (t, *J* = 7.6 Hz, 2H), 3.04 (t, *J* = 8.4 Hz, 2H), 2.16-2.24 (m, 1H), 1.99-2.08 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 160.6 (t, $^{2}J_{C-F}$ = 28.9 Hz), 142.4, 131.6, 131.2, 130.5, 129.5, 128.8, 127.6, 125.4, 124.6, 118.4, 72.5 (dd, $^{2}J_{C-F}$ = 23.4, 21.0 Hz), 51.8, 48.2-48.4 (m), 29.9, 28.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ -101.82 (d, *J* = 272.7 Hz), -106.27 (d, *J* = 272.7 Hz); HRMS (ESI): $C_{20}H_{19}F_2N_3NaO_2^+$ $[M+Na]^+$ Calcd 394.1338, Found 394.1334.



4i

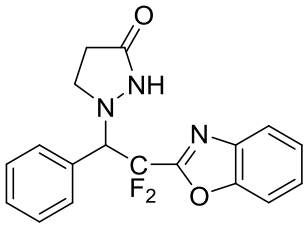
difluorinated 3-pyrazolidinone **4i**: pale yellow solid (38.0 mg, 0.112 mmol, yield 56%); m.p. 164-166 ℃; IR (KBr) ν 696, 749, 847, 965, 1067, 1112, 1623, 1729, 2921 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.46 (m, 5H), 4.09 (dd, *J* = 20.7, 15.3 Hz, 1H), 3.60-3.67 (m, 6H), 3.36-3.46 (m, 2H), 3.06 (t, *J* = 5.2 Hz, 2H), 2.53-2.70 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 158.6 (t, $^{2}J_{C-F}$ = 29.6 Hz), 129.6, 129.1, 128.8, 115.1 (t, $^{1}J_{C-F}$ = 260.3 Hz), 73.4 (t, $^{2}J_{C-F}$ = 22.6 Hz), 66.7, 66.3, 52.1, 45.9, 42.2, 32.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ -115.32 (d, *J* = 253.1 Hz), -116.49 (d, *J* = 269.7 Hz); HRMS (ESI): $C_{16}H_{19}F_2N_3NaO_3^+$ $[M+Na]^+$ Calcd 362.1287, Found 362.1281.



4j

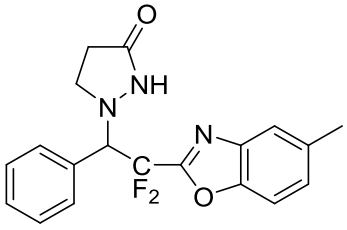
difluorinated 3-pyrazolidinone **4j**: pale yellow solid (81.0 mg, 0.186 mmol, yield 93%); m.p. 143-145 ℃; IR (KBr) ν 657, 869, 1058, 1173, 1245, 1419, 1654, 1683, 2923 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.47 (m, 2H), 7.38-

7.42 (m, 3H), 4.57 (dd, *J* = 10.9, 16.6 Hz, 1H), 3.62-3.64 (m, 1H), 3.32-3.53 (m, 8H), 3.23-3.28 (m, 1H), 2.10-2.20 (m, 1H), 1.98-2.04 (m, 1H), 1.46 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.0, 161.4 (t, $^2J_{C\text{-}F}$ = 28.1 Hz), 154.4, 130.9, 130.6, 129.5, 128.8, 118.2 (t, $^1J_{C\text{-}F}$ = 259.3 Hz), 80.5, 72.5 (dd, $^2J_{C\text{-}F}$ = 23.4, 20.0 Hz), 51.8, 45.8, 43.5, 29.9, 29.7, 28.3, 22.7, 14.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ -99.60 (d, *J* = 261.2 Hz), -103.70 (d, *J* = 276.3 Hz); HRMS (ESI): $C_{21}H_{28}F_2N_4NaO_4^+$ $[M+Na]^+$ Calcd 461.1971, Found 461.1966.



4k

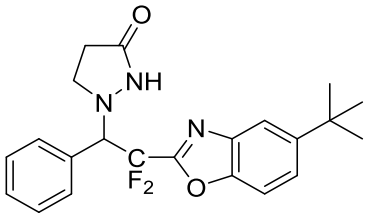
difluorinated 3-pyrazolidinone **4k**: pale yellow solid (50 mg, 0.146 mmol, yield 73%); m.p. 172-174 ℃; IR (KBr) ν 605, 845, 957, 1101, 1222, 1351, 1454, 1696, 2918 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80-7.82 (m, 1H), 7.59-7.61 (m, 1H), 7.37-7.50 (m, 7H), 4.80 (dd, *J* = 18.0, 9.6 Hz, 1H), 3.44-3.52 (m, 1H), 3.31-3.38 (m, 1H), 2.04-2.12 (m, 1H), 1.85-1.93 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 150.5, 140.0, 130.5, 130.3, 129.8, 129.0, 126.9, 125.4, 121.3, 111.4, 73.6 (dd, $^2J_{C\text{-}F}$ = 26.8, 21.5 Hz), 51.9, 29.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ -98.05 (d, *J* = 277.0 Hz), -106.98 (d, *J* = 276.9 Hz); HRMS (ESI): $C_{18}H_{15}F_2N_3NaO_2^+$ $[M+Na]^+$ Calcd 366.1025, Found 366.0999.



4l

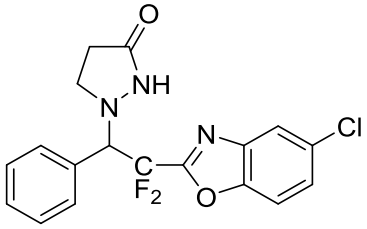
difluorinated 3-pyrazolidinone **4l**: pale yellow solid (24 mg, 0.068 mmol, yield 34%); m.p. 155-157 ℃; IR (KBr) ν 653, 804, 931, 1041, 1179, 1295, 1459, 1700, 2920 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (*br* s, 1H), 7.51, (s, 1H), 7.37-7.41 (m, 3H), 7.28-7.33 (m, 3H), 7.17-7.19 (m, 1H), 4.59 (dd, *J* = 17.6, 9.9 Hz, 1H), 3.36-3.43 (m, H), 3.23-3.30 (m, 1H), 2.41 (s, 3H), 2.00-2.08 (m, 1H), 1.80-1.89 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 157.1 (t, $^2J_{C\text{-}F}$ = 32.5 Hz), 148.8, 140.2, 135.4, 130.4, 129.7, 128.9, 128.0, 121.0, 116.1 (t, $^1J_{C\text{-}F}$ =

250.2 Hz), 110.7, 74.0 (t, $^{2}J_{C\text{-}F}$ = 26.4, 21.7 Hz), 51.9, 29.7, 21.5; ^{19}F NMR (376 MHz, Chloroform-*d*) δ -98.37 (d, *J* = 276.8 Hz), -106.39 (d, *J* = 277.3 Hz); HRMS (ESI): $C_{19}H_{17}F_2N_3NaO_2^+$ $[M+Na]^+$ Calcd 380.1181, Found 380.1159.



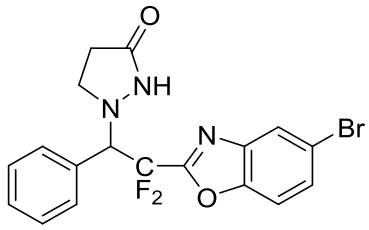
4m

difluorinated 3-pyrazolidinone **4m**: pale yellow oil (22 mg, 0.056 mmol, yield 28%); IR (KBr) ν 652, 812, 931, 1042, 1178, 1271, 1480, 1695, 2958 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.48-7.51 (m, 4H), 7.36-7.41 (m, 3H), 4.67 (dd, *J* = 17.6, 9.9 Hz, 1H), 3.43-3.51 (m, 1H), 3.30-3.37 (m, 1H), 2.05-2.12 (m, 1H), 1.86-1.94 (m, 1H), 1.38 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 157.3 (t, $^{2}J_{C\text{-}F}$ = 32.8 Hz), 149.1, 148.6, 140.0, 130.5, 129.7, 129.0, 124.8, 117.6, 116.0 (t, $^{1}J_{C\text{-}F}$ = 249.5 Hz), 110.5, 73.0 (dd, $^{2}J_{C\text{-}F}$ = 25.9, 21.4 Hz), 51.9, 35.0, 31.7, 29.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ -97.35 (d, *J* = 277.3 Hz), -106.61 (d, *J* = 276.3 Hz); HRMS (ESI): $C_{22}H_{23}F_2N_3NaO_2^+$ $[M+Na]^+$ Calcd 422.1651, Found 422.1661.



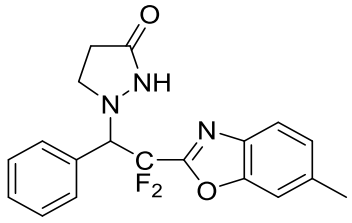
4n

difluorinated 3-pyrazolidinone **4n**: pale yellow solid (28 mg, 0.074 mmol, yield 37%); mp. 170-172 ℃; IR (KBr) ν 652, 850, 924, 1044, 1104, 1284, 1452, 1696, 2921 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 1.6 Hz, 1H), 7.36-7.53 (m, 8H), 4.60 (dd, *J* = 18.0, 9.6 Hz, 1H), 3.44-3.51 (m, 1H), 3.32-3.38 (m, 1H), 2.05-2.13 (m, 1H), 1.86-1.94 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 158.6 (t, $^{2}J_{C\text{-}F}$ = 33.1 Hz), 149.1, 141.0, 131.1, 130.4, 130.1, 129.8, 129.0, 127.3, 121.2, 115.9 (t, $^{1}J_{C\text{-}F}$ = 261.1 Hz), 112.1, 73.9 (dd, $^{2}J_{C\text{-}F}$ = 26.6, 21.6 Hz), 53.4, 52.0, 29.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ -98.67 (d, *J* = 277.4 Hz), -107.05 (d, *J* = 277.5 Hz); HRMS (ESI): $C_{18}H_{14}ClF_2N_3NaO_2^+$ $[M+Na]^+$ Calcd 400.0635, Found 400.0639.



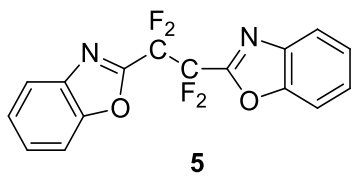
4o

difluorinated 3-pyrazolidinone **4o**: pale yellow solid (27 mg, 0.064 mmol, yield 32%); mp. 165-167 ℃; IR (KBr) ν 651, 809, 908, 1034, 1179, 1298, 1447, 1684, 2926 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 1.6 Hz, 1H), 7.56-7.59 (m, 1H), 7.36-7.49 (m, 7H), 4.66 (dd, *J* = 17.9, 9.8 Hz, 1H), 3.44-3.51 (m, 1H), 3.31-3.38 (m, 1H), 2.04-2.12 (m, 1H), 1.85-1.94 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4, 158.4 (t, $^{2}J_{C-F}$ = 33.4 Hz), 149.5, 141.5, 130.4, 130.1, 130.0, 129.8, 129.0, 124.3, 118.3, 115.9 (t, $^{1}J_{C-F}$ = 250.9 Hz), 112.6, 73.8 (dd, $^{2}J_{C-F}$ = 26.4, 21.4 Hz), 52.0, 29.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ -98.66 (d, *J* = 277.2 Hz), -107.10 (d, *J* = 277.5 Hz); HRMS (ESI): $C_{18}H_{14}BrF_2N_3NaO_2^+$ $[M+Na]^+$ Calcd 444.0130, Found 444.0117.



4p

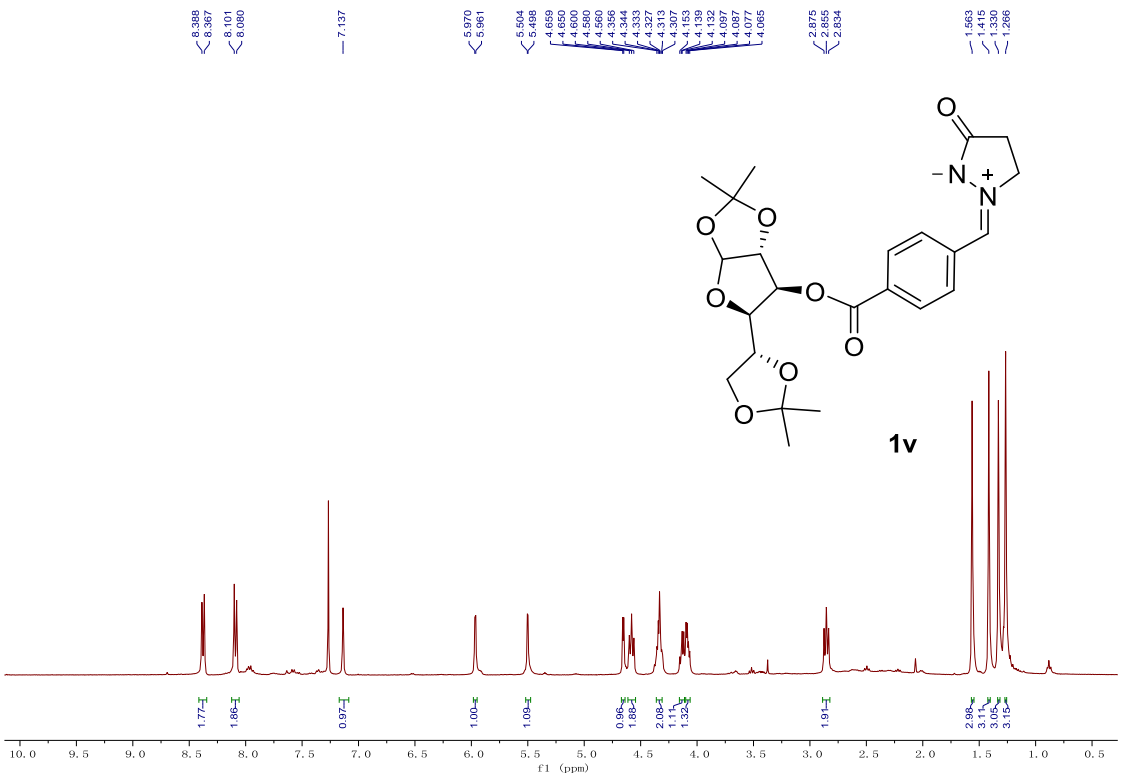
difluorinated 3-pyrazolidinone **4p**: pale yellow solid (34 mg, 0.096 mmol, yield 48%); mp. 164-1667 ℃; IR (KBr) ν 654, 748, 806, 930, 1178, 1218, 1457, 1699, 2921 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.4 Hz, 1H), 7.47-7.49 (m ,2H), 7.35-7.40 (m ,4H), 7.22 (d, *J* = 8.4 Hz, 1H), 4.66 (dd, *J* = 10, 17.6 Hz, 1H), 3.43-3.50 (m, 1H), 3.31-3.37 (m, 1H), 2.50 (s, 3H), 2.05-2.12 (m, 1H), 1.86-1.94 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 156.7 (t, $^{2}J_{C-F}$ = 32.8 Hz), 150.9, 137.8, 137.5, 130.4, 129.7, 128.9, 126.7, 120.6, 116.1 (t, $^{1}J_{C-F}$ = 249.9 Hz), 111.3, 74.0 (dd, $^{2}J_{C-F}$ = 26.7, 21.6 Hz), 51.9, 29.7, 21.8; ^{19} FNMR (376 MHz, $CDCl_3$) δ -98.22 (d, *J* = 276.4 Hz), -106.38 (d, *J* = 276.2 Hz); HRMS (ESI): $C_{19}F_2N_3NaO_2^+$ $[M+Na]^+$ Calcd 380.1181, Found 380.1166.



5

Dimer **5**: pale yellow solid (12 mg, 0.036 mmol, yield 36%), mp: 132-134 ℃; IR (KBr) ν 427, 584, 671, 751, 865, 967, 1106, 1242, 1352, 1569, 1615, 1727, cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86

(d, *J* = 7.8 Hz, 2H), 7.66 (d, *J* = 8.2 Hz, 2H), 7.52 (t, *J* = 7.7 Hz, 2H), 7.46 (t, *J* = 7.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.9, 139.9, 127.6, 125.7, 121.8, 111.60; ^{19}F NMR (376 MHz, $CDCl_3$) δ -112.95; HRMS (ESI): $C_{16}H_8F_4N_2NaO_2^+$ $[M+Na]^+$ Calcd 359.0414, Found 359.0427.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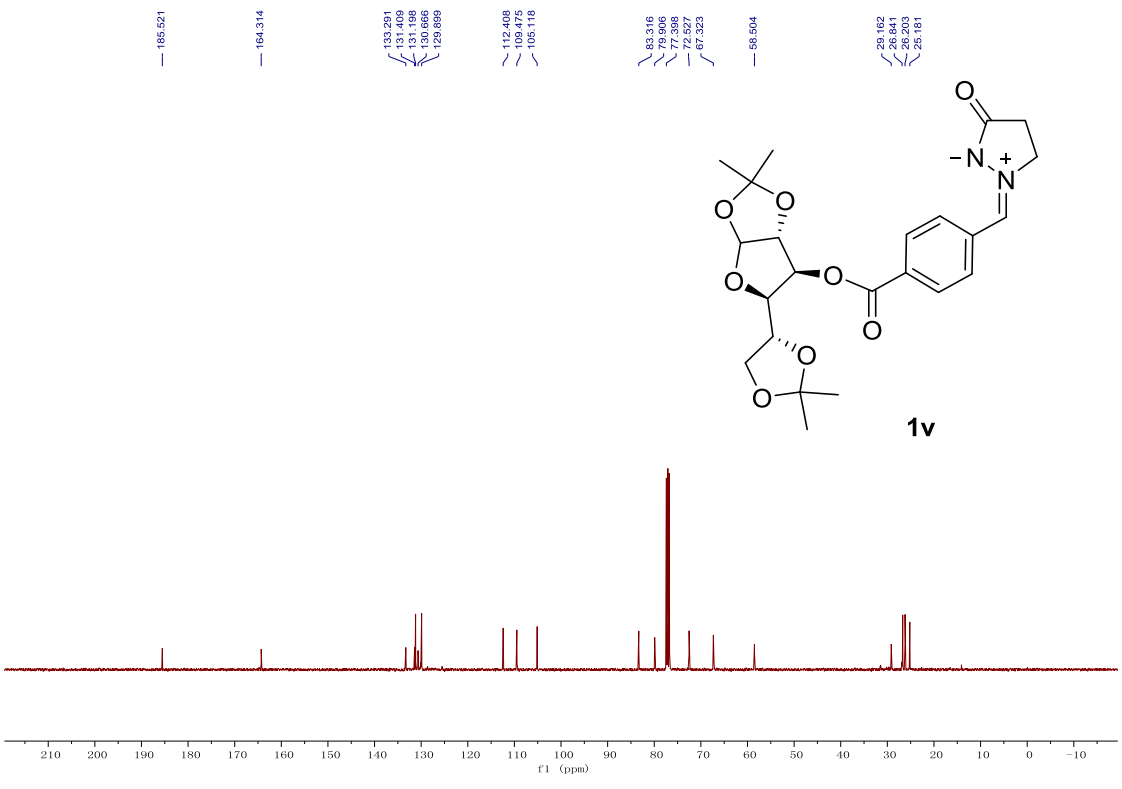
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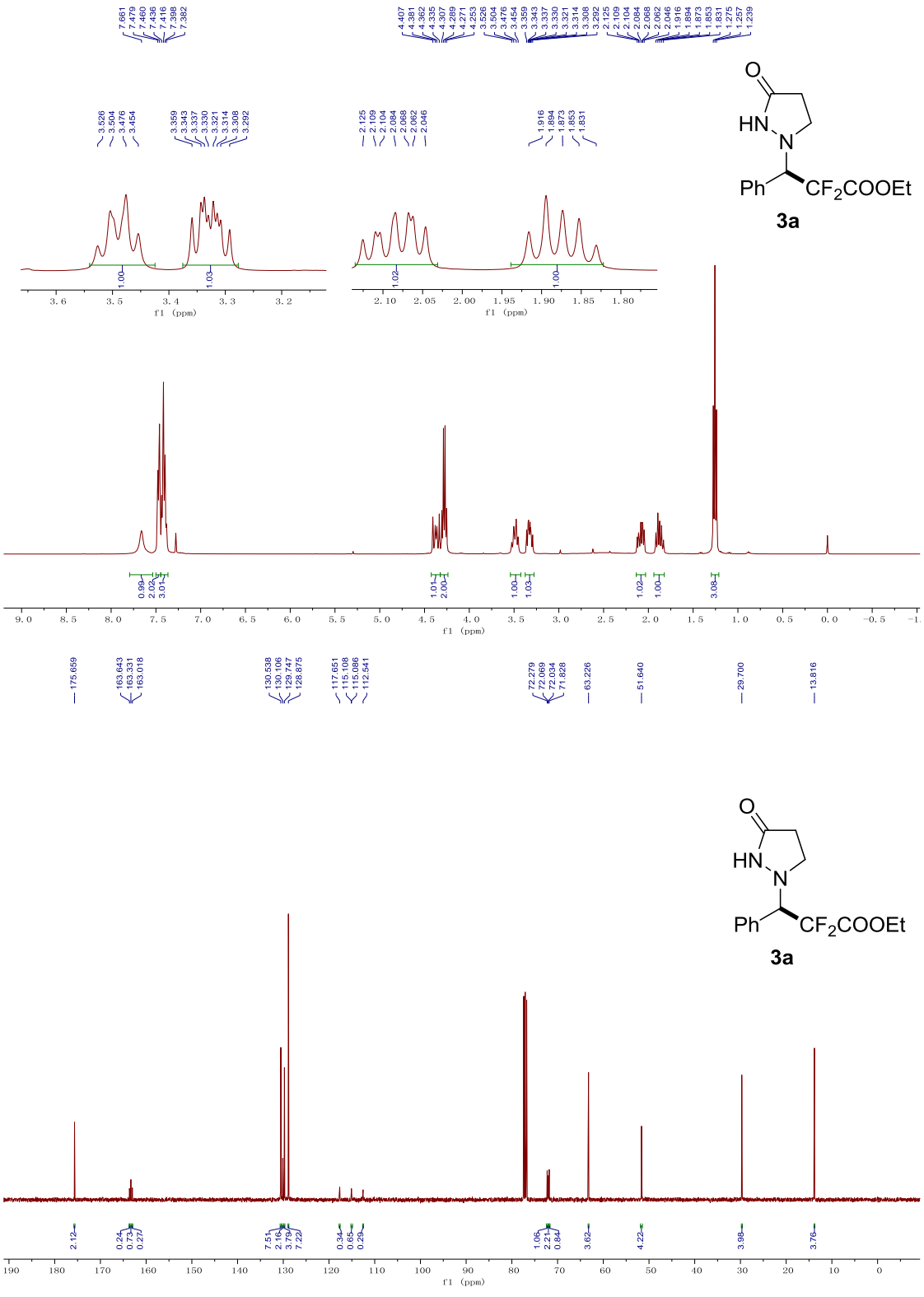
1v
f1 (ppm)


3a
3a
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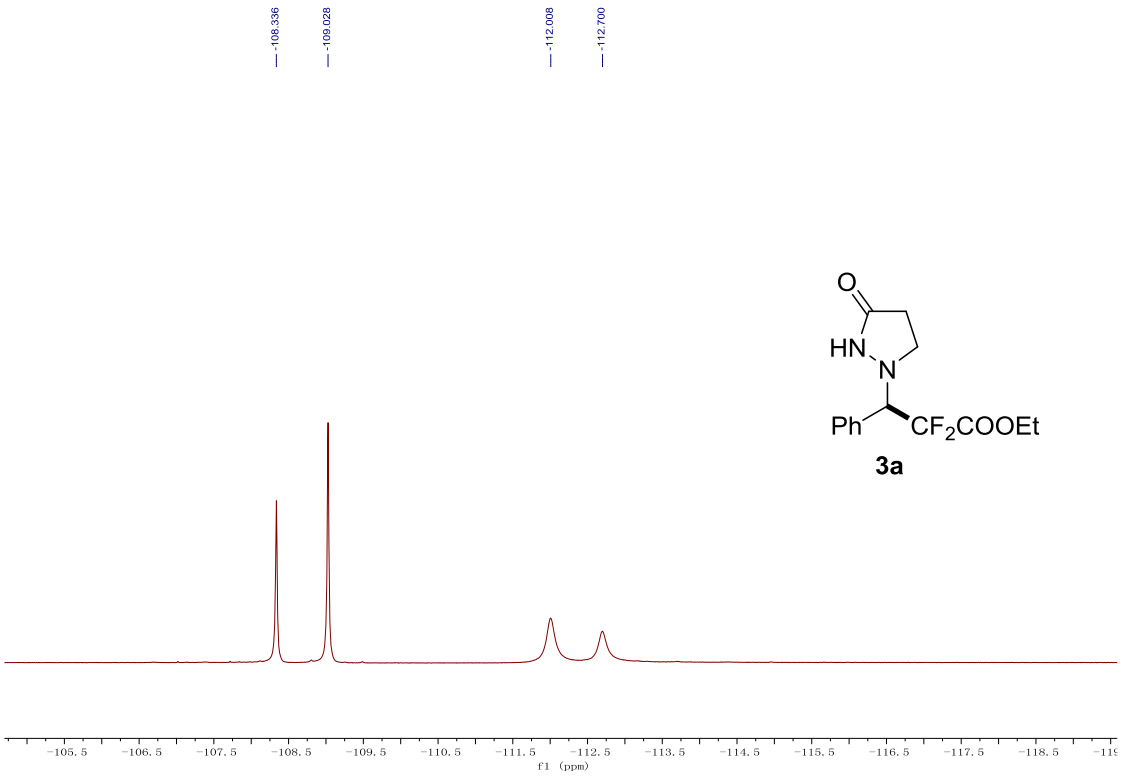
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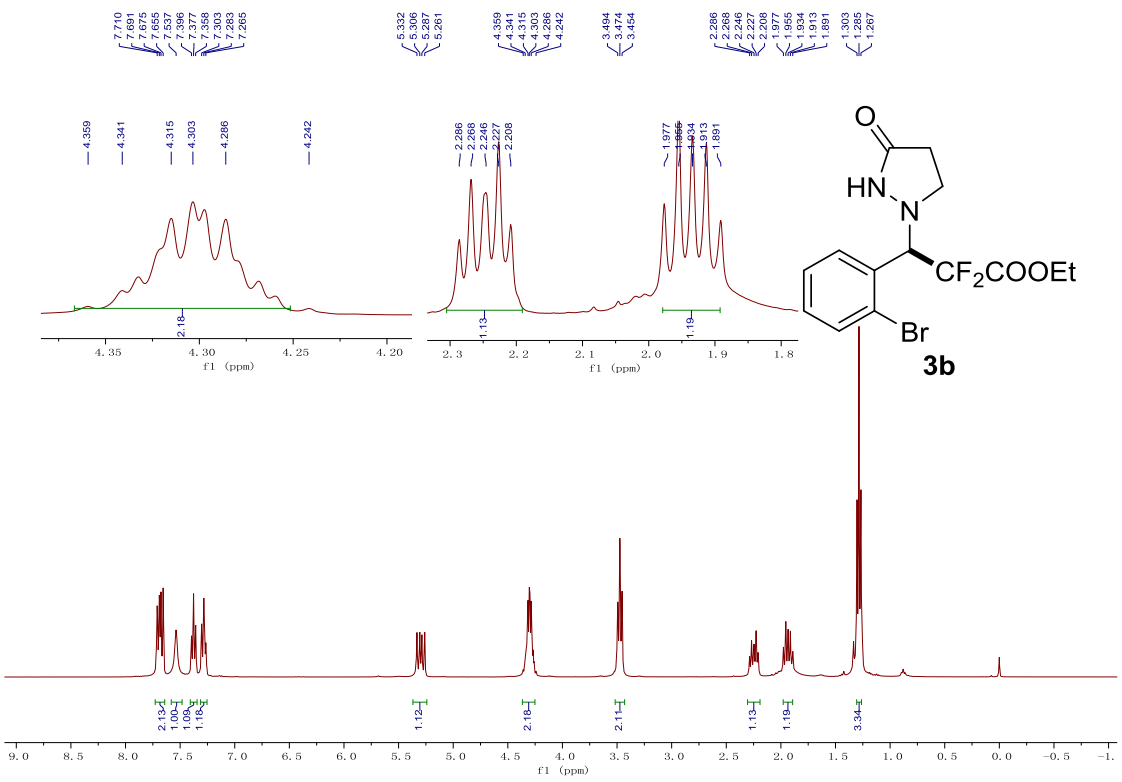
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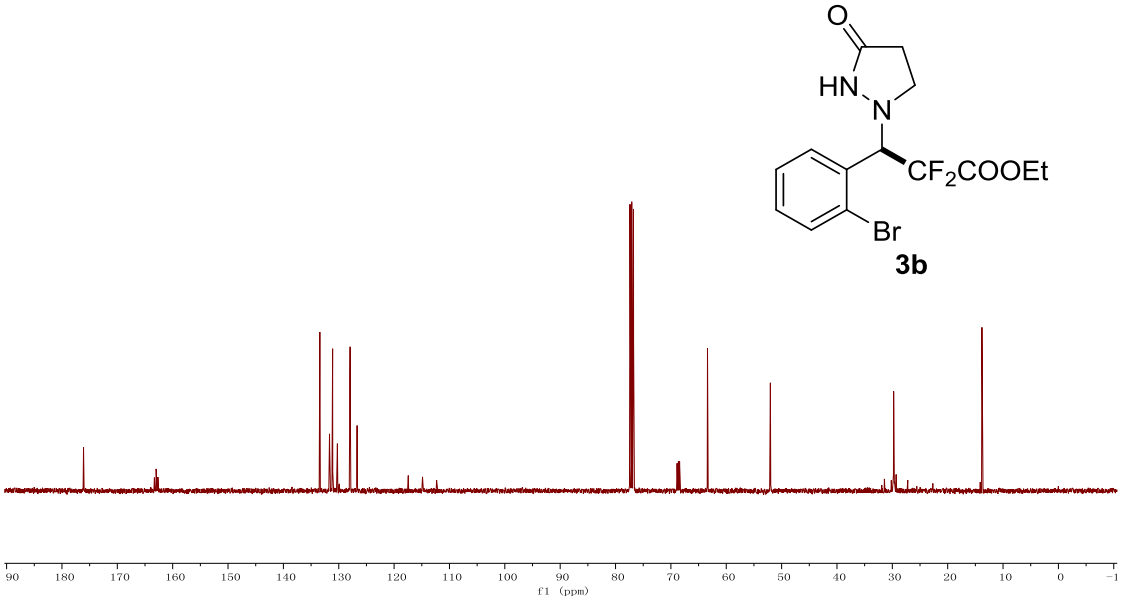
Br
3b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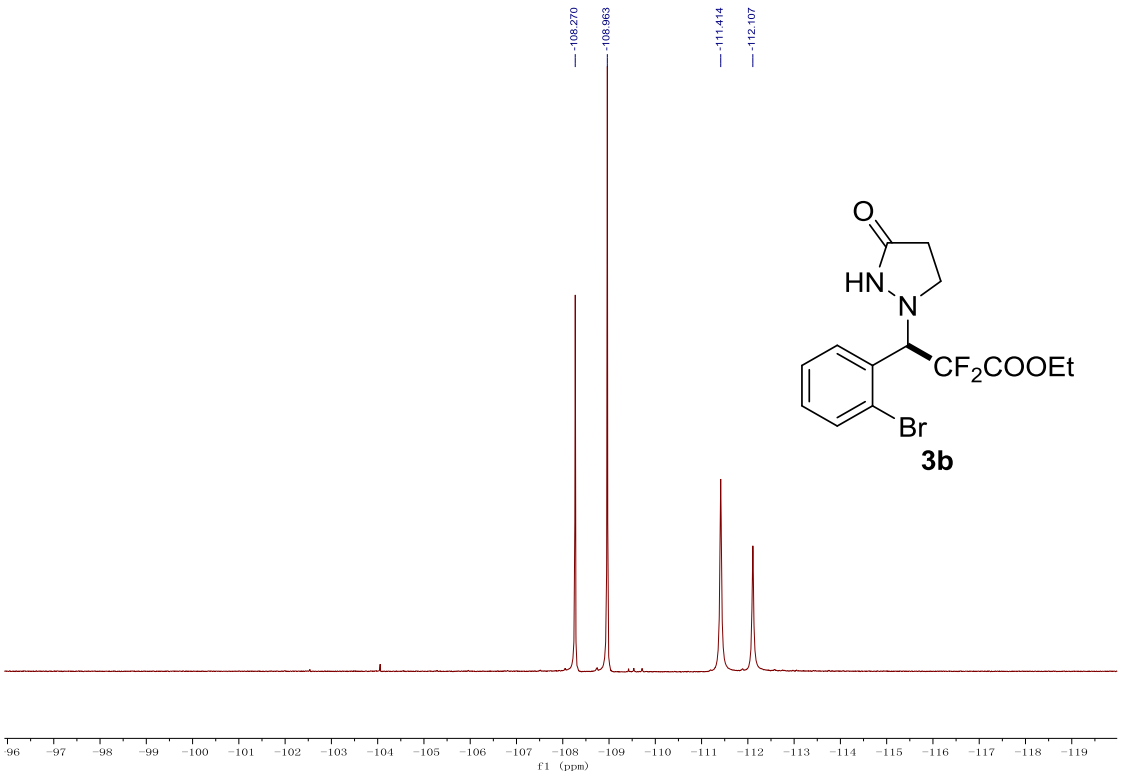
CF2COOEt
Br
3b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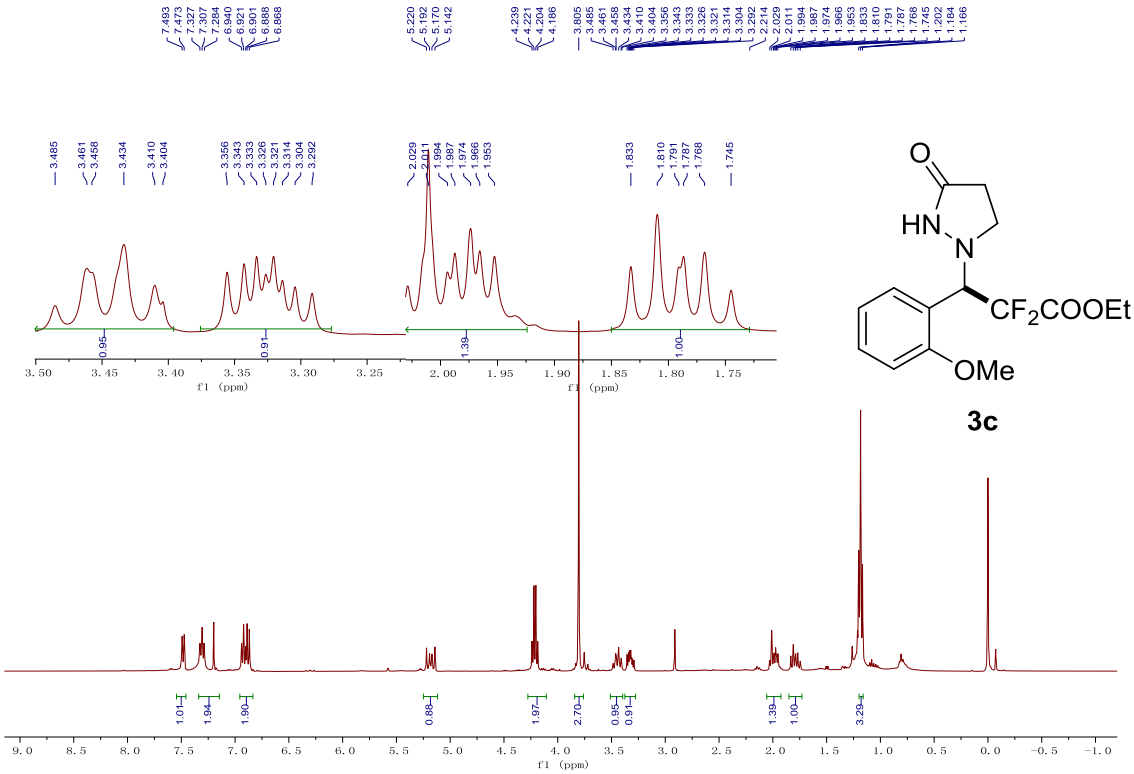
f1 (ppm)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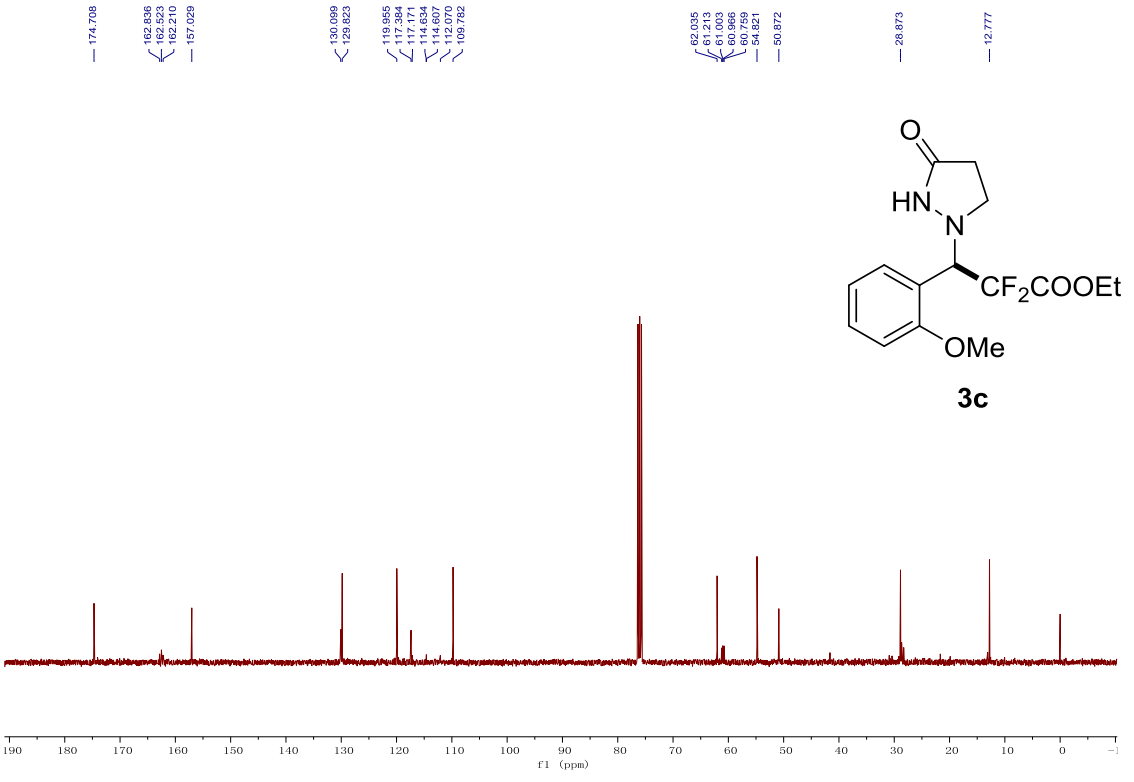
7.307
7.284
6.940
6.921
6.901
6.888
6.868
5.220
5.192
5.172
5.142
4.239
4.221
4.204
4.186
3.805
3.485
3.461
3.458
3.434
3.410
3.404
3.356
3.343
3.333
3.326
3.321
3.314
3.304
3.292
2.214
2.029
2.011
1.994
1.987
1.974
1.966
1.953
1.833
1.810
1.791
1.787
1.768
1.745
1.202
1.184
1.166
0.95
0.91
1.39
1.00
f1 (ppm)
1.01
1.94
1.90
0.88
1.97
2.70
0.95
0.91
1.39
1.00
3.29
f1 (ppm)
O
HN
N
CF2COOEt
OMe
3c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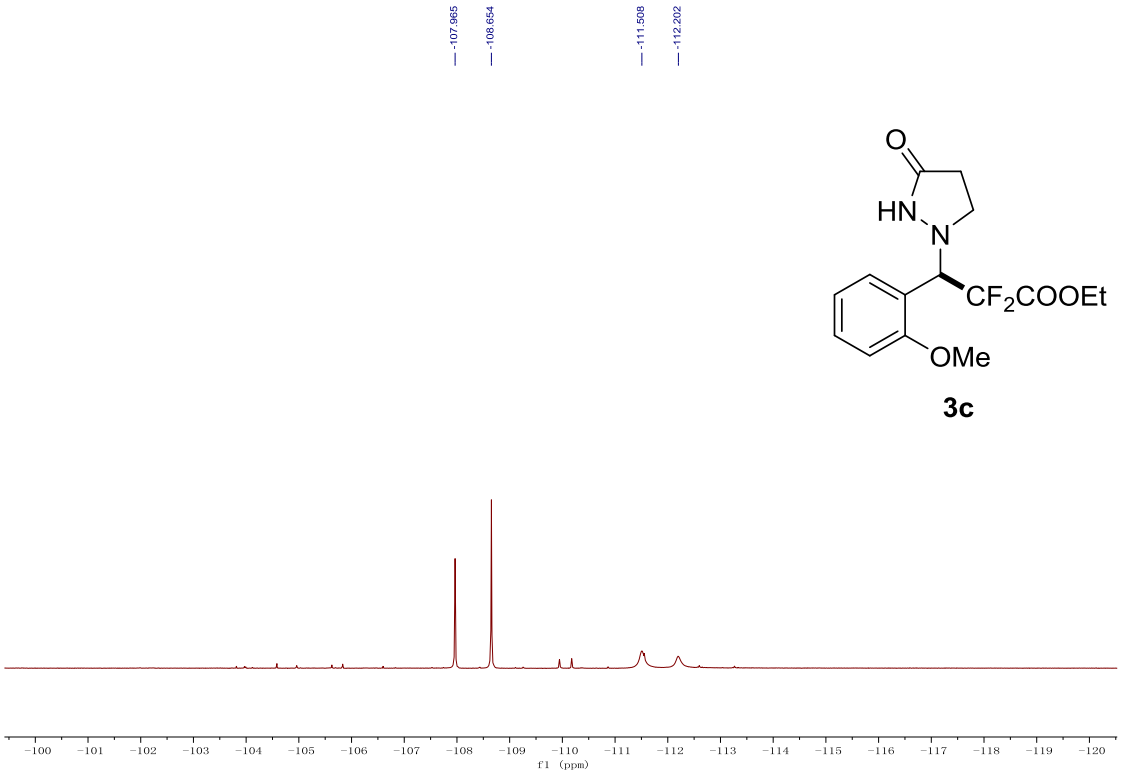
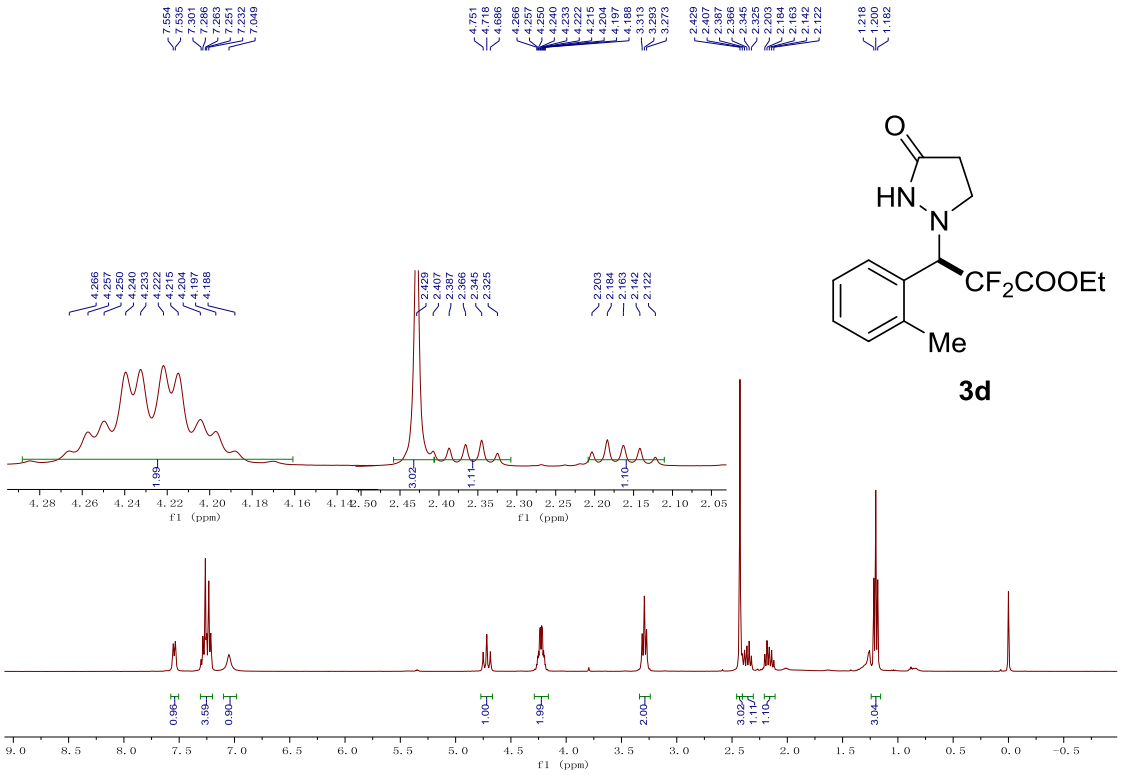
162.836
162.523
162.210
157.029
130.099
129.823
119.955
117.384
117.171
114.634
114.407
112.070
109.782
62.035
61.213
61.003
60.966
60.729
54.821
50.872
28.873
12.777
f1 (ppm)
O
HN
N
CF2COOEt
OMe
3c

.


-107.965
-108.654
-111.508
-112.202
O
HN
N
CF2COOEt
OMe
3c
−100 −101 −102 −103 −104 −105 −106 −107 −108 −109 −110 −111 −112 −113 −114 −115 −116 −117 −118 −119 −120
f1 (ppm)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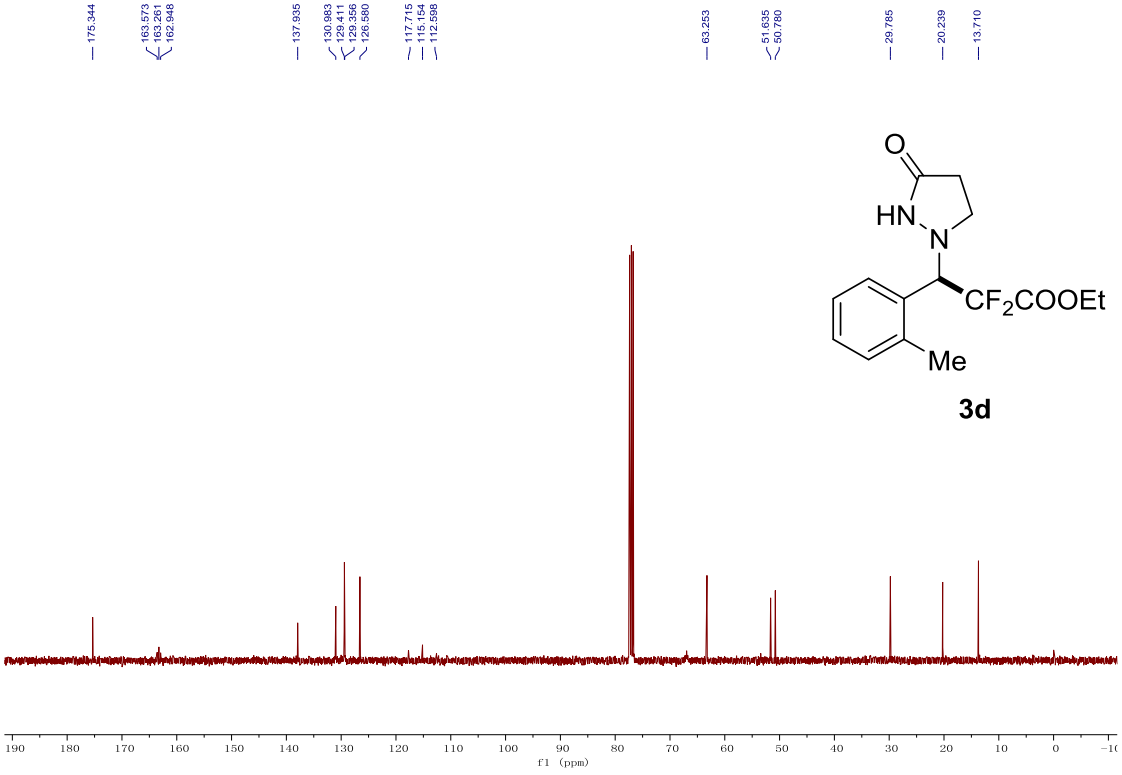
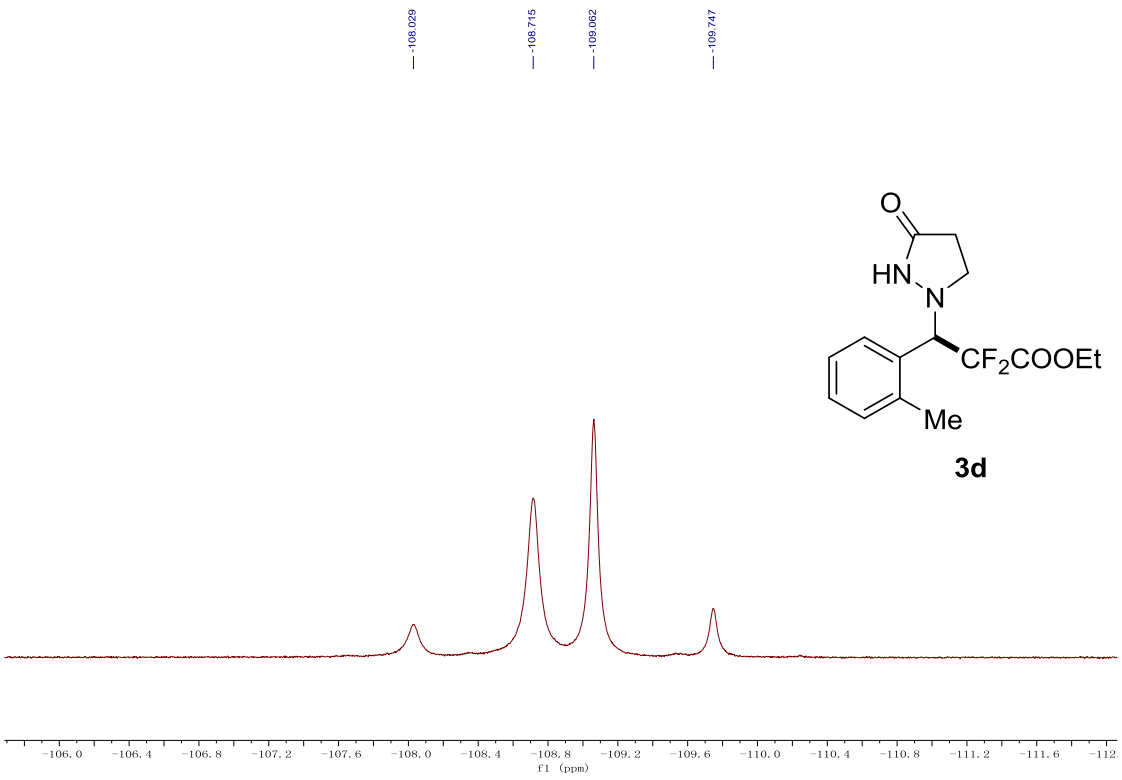
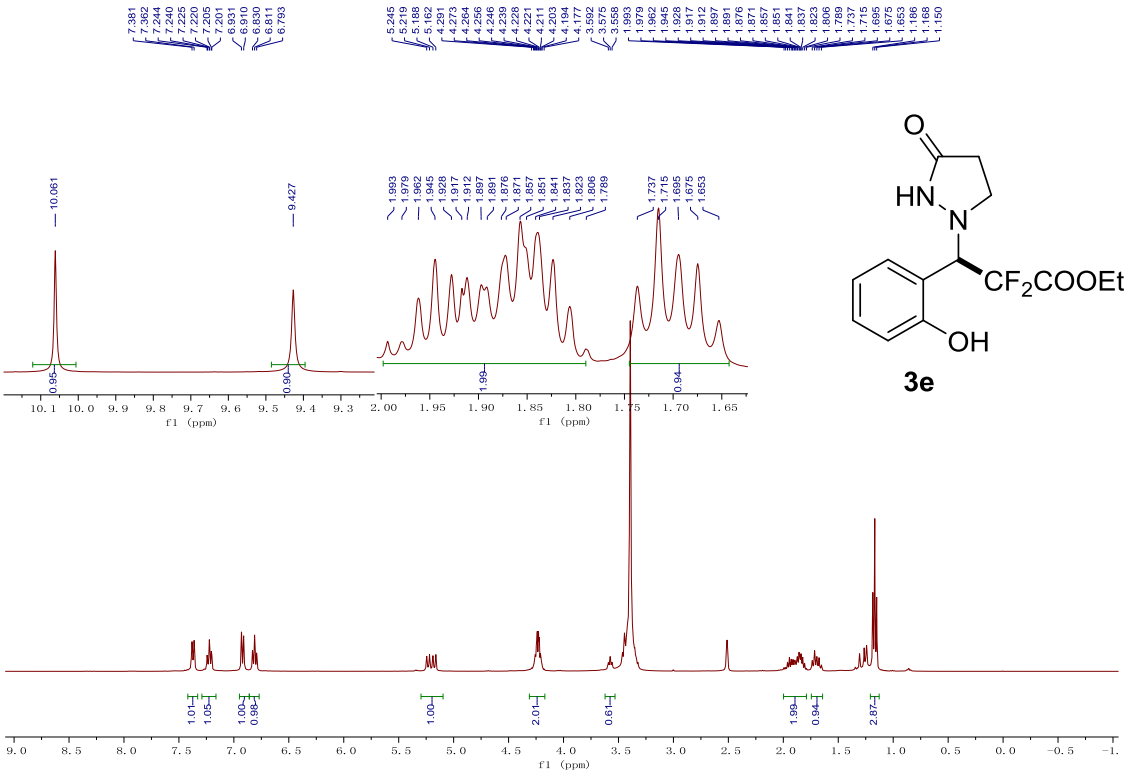
7.301
7.286
7.263
7.251
7.232
7.049
4.751
4.718
4.686
4.266
4.257
4.250
4.240
4.233
4.222
4.215
4.204
4.197
4.188
3.313
3.293
3.273
2.429
2.407
2.387
2.366
2.345
2.325
2.203
2.184
2.163
2.142
2.122
1.218
1.200
1.182
O
HN
N
CF2COOEt
Me
3d
f1 (ppm)


175.344
163.573
163.261
162.948
137.935
130.983
129.411
128.356
126.580
117.715
115.154
112.598
63.253
51.635
50.780
29.785
20.239
13.710
O
HN
N
CF2COOEt
Me
3d
f1 (ppm)


-108.029
-108.715
-109.062
-109.747
O
HN
N
CF2COOEt
Me
3d
-106.0
-106.4
-106.8
-107.2
-107.6
-108.0
-108.4
-108.8
-109.2
-109.6
-110.0
-110.4
-110.8
-111.2
-111.6
-112.
f1 (ppm)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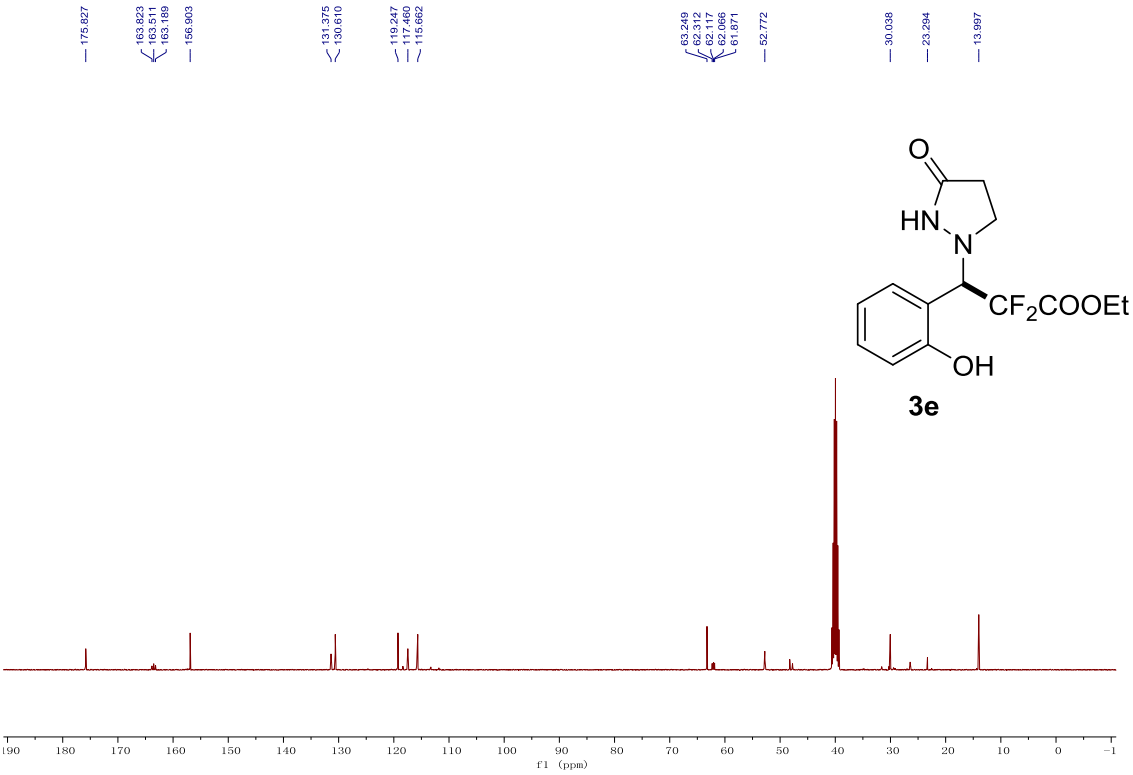
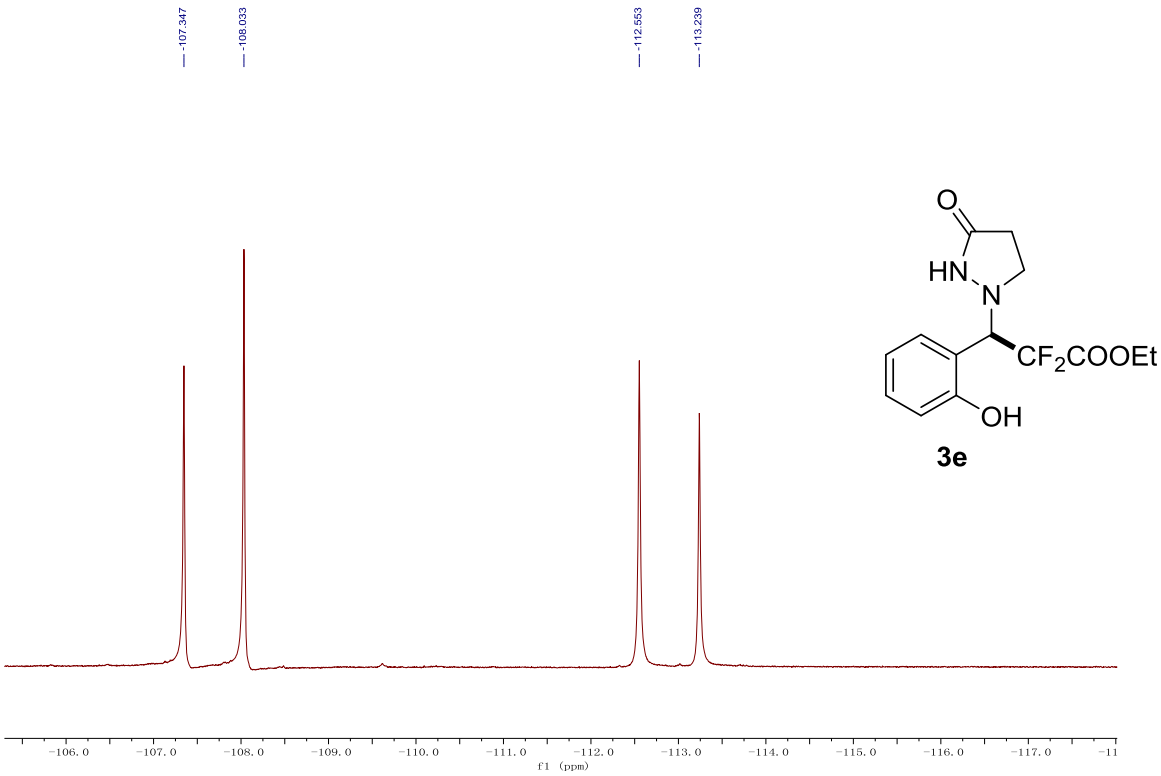
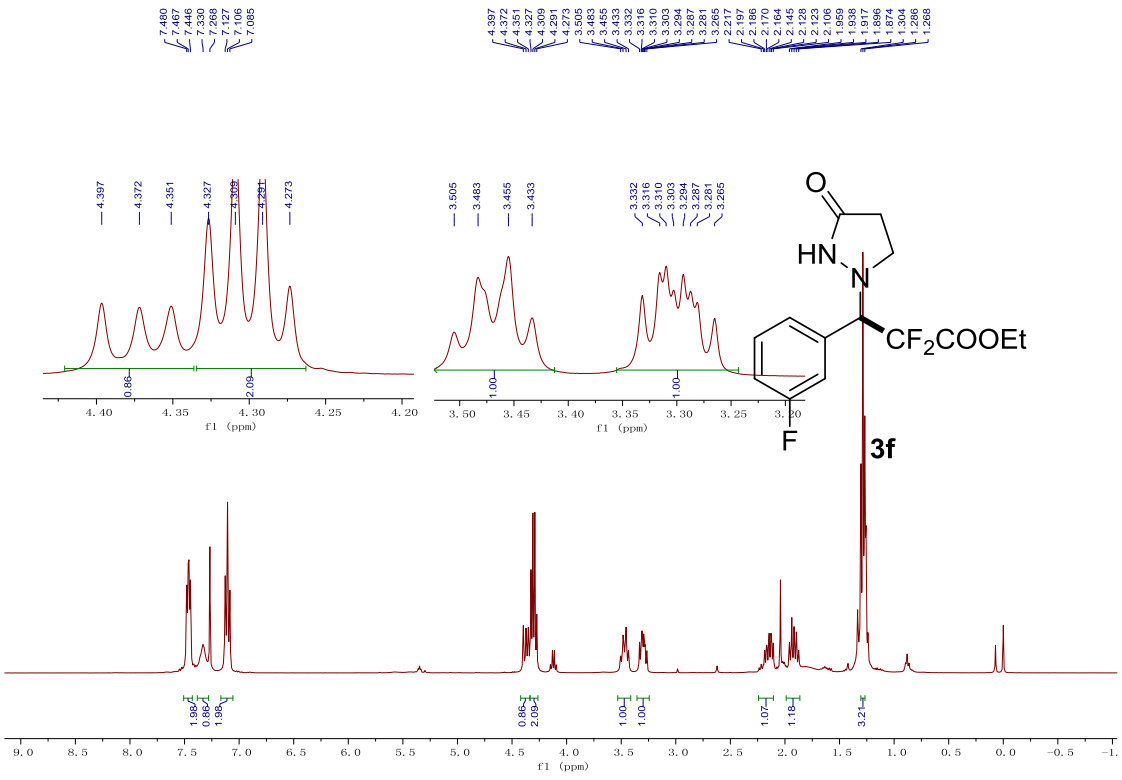
7.362
7.244
7.240
7.225
7.220
7.205
7.201
6.931
6.910
6.830
6.811
6.793
5.245
5.219
5.188
5.162
4.291
4.273
4.264
4.256
4.246
4.239
4.228
4.221
4.211
4.203
4.194
4.177
3.592
3.575
3.558
1.993
1.979
1.962
1.945
1.928
1.917
1.912
1.897
1.891
1.876
1.871
1.857
1.851
1.841
1.837
1.823
1.806
1.789
1.737
1.715
1.695
1.675
1.653
1.186
1.168
1.150
10.061
9.427
0.95
0.90
1.98
0.94
f1 (ppm)
HN
N
O
CF2COOEt
OH
3e
1.01
1.05
1.00
0.98
1.00
2.01
0.61
1.99
0.94
2.87


175.827
163.823
163.511
163.189
156.903
131.375
130.610
119.247
117.460
115.662
63.249
62.312
62.117
62.066
61.871
52.772
30.038
23.294
13.997
f1 (ppm)
HN
N
O
CF2COOEt
OH
3e


-107.347
-108.033
-112.553
-113.239
O
HN
N
CF2COOEt
OH
3e
-106.0
-107.0
-108.0
-109.0
-110.0
-111.0
-112.0
-113.0
-114.0
-115.0
-116.0
-117.0
f1 (ppm)


7.480
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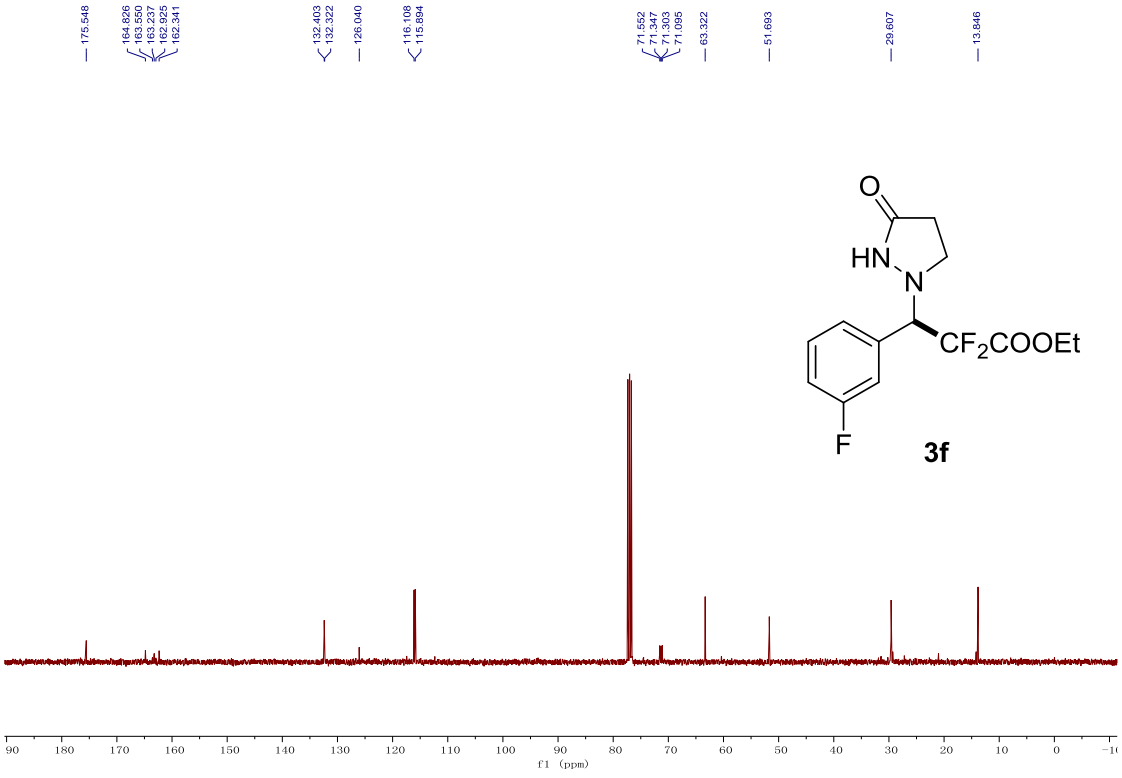
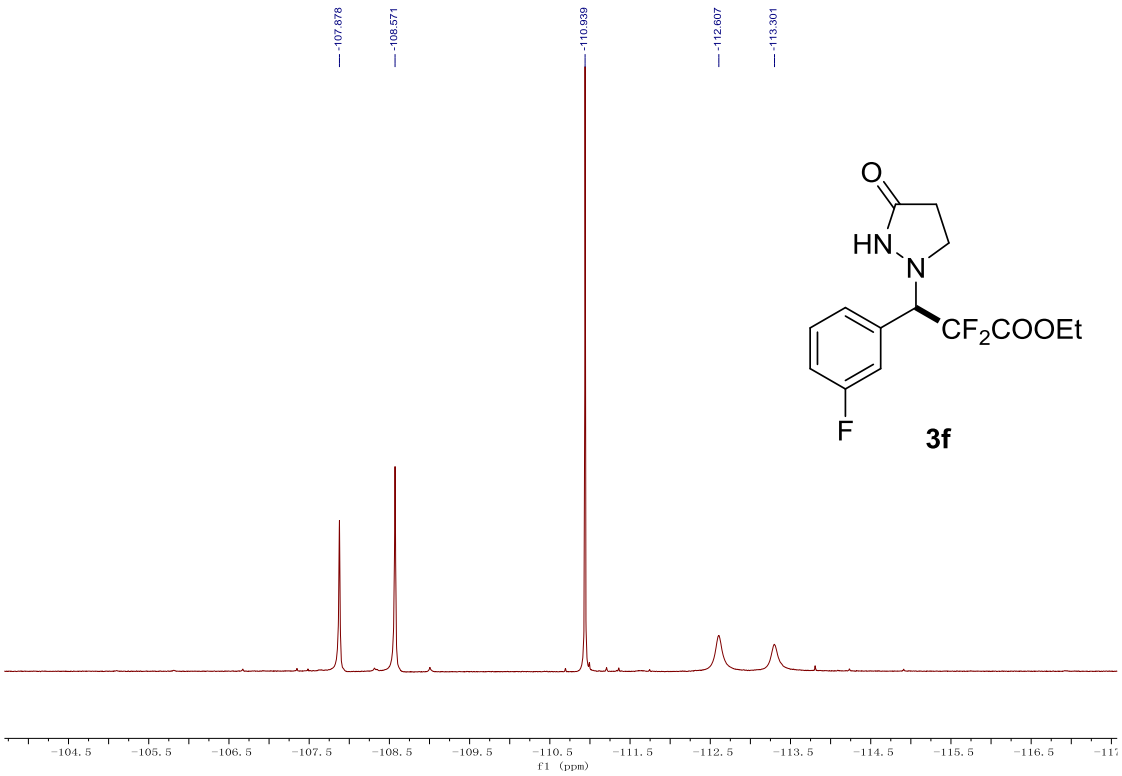
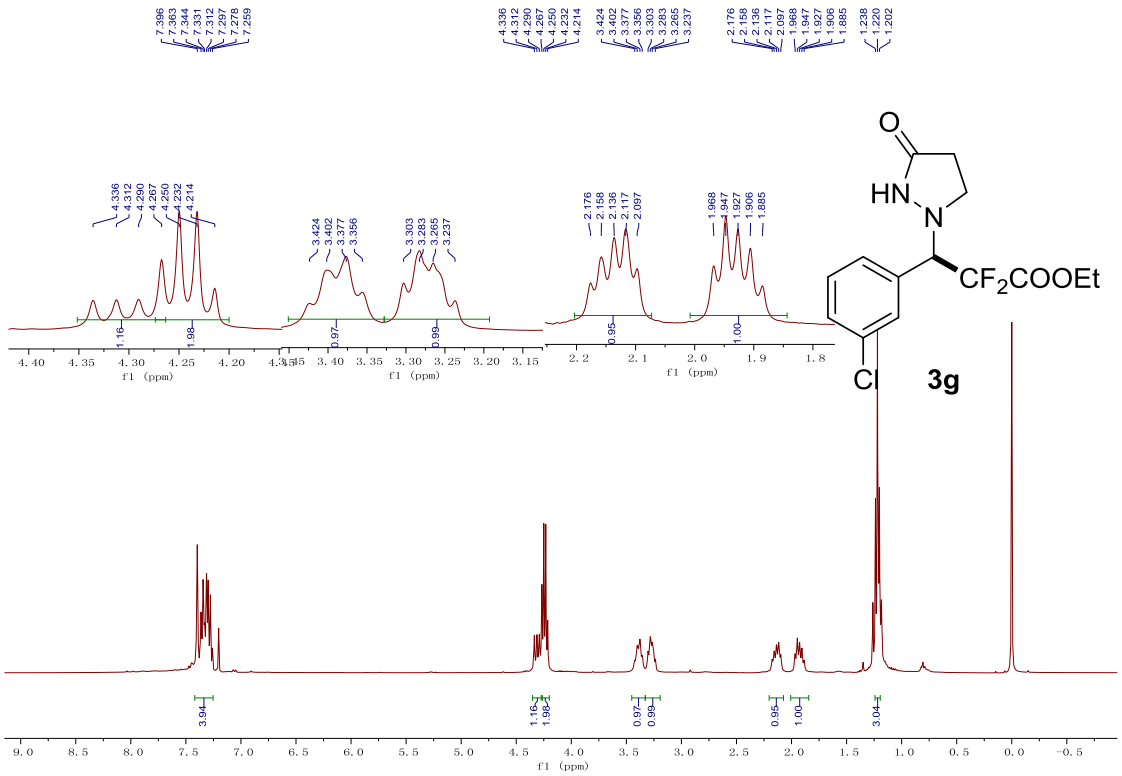
7.446
7.330
7.268
7.227
7.106
7.085
4.397
4.372
4.351
4.327
4.309
4.291
4.273
3.505
3.483
3.455
3.433
3.332
3.316
3.310
3.303
3.294
3.287
3.281
3.265
2.217
2.197
2.186
2.170
2.164
2.145
2.128
2.123
2.106
1.959
1.938
1.917
1.896
1.874
1.304
1.286
1.268
0.86
2.09
1.00
1.00
f1 (ppm)
HN
N
O
CF2COOEt
F
3f
1.98
0.86
1.98
0.86
2.09
1.00
1.00
1.07
1.18
3.21
f1 (ppm)


175.548
164.826
163.550
163.237
162.925
162.341
132.403
132.322
126.040
116.108
115.894
71.552
71.347
71.303
71.095
63.322
51.693
29.607
13.846
HN
N
O
CF2COOEt
F
3f
f1 (ppm)


-107.878
-108.571
-110.939
-112.607
-113.301
O
HN
N
CF2COOEt
F
3f
-104.5
-105.5
-106.5
-107.5
-108.5
-109.5
-110.5
-111.5
-112.5
-113.5
-114.5
-115.5
-116.5
f1 (ppm)


7.396
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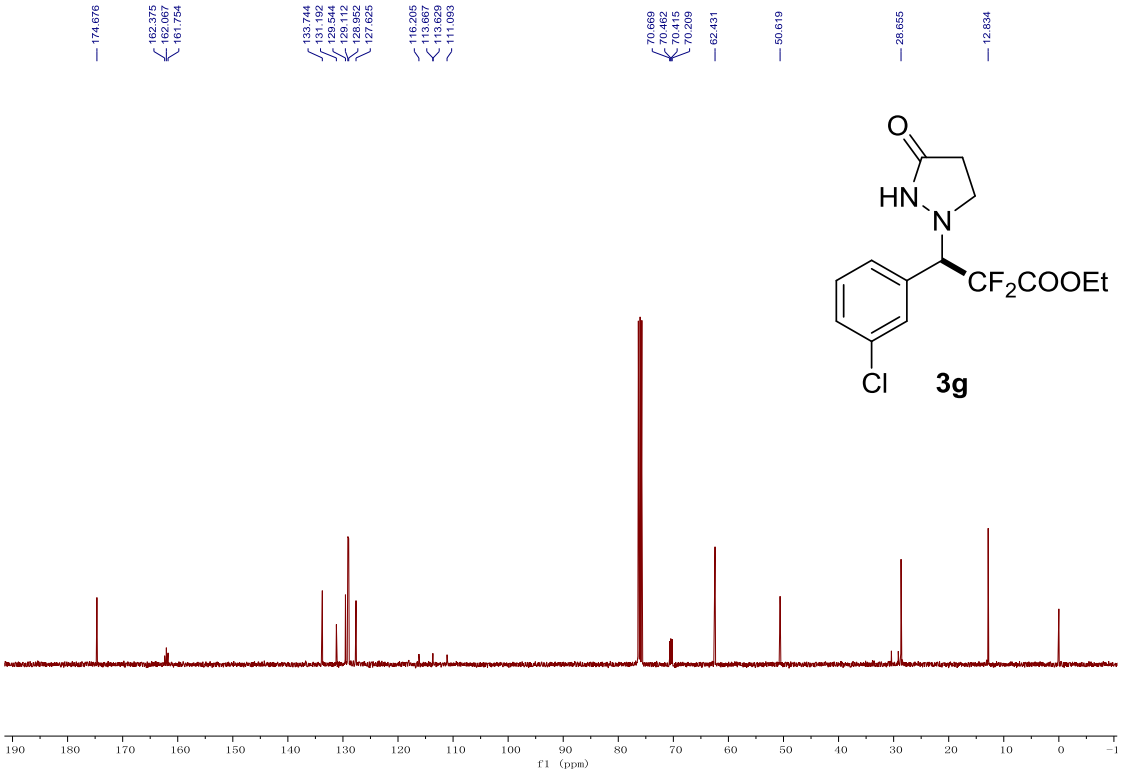
7.344
7.331
7.312
7.297
7.278
7.259
4.336
4.312
4.290
4.267
4.250
4.232
4.214
3.424
3.402
3.377
3.356
3.303
3.283
3.265
3.237
2.176
2.158
2.136
2.117
2.097
1.968
1.947
1.927
1.906
1.885
1.238
1.220
1.202
f1 (ppm)
HN
N
O
CF2COOEt
Cl
3g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162.375
162.067
161.754
133.744
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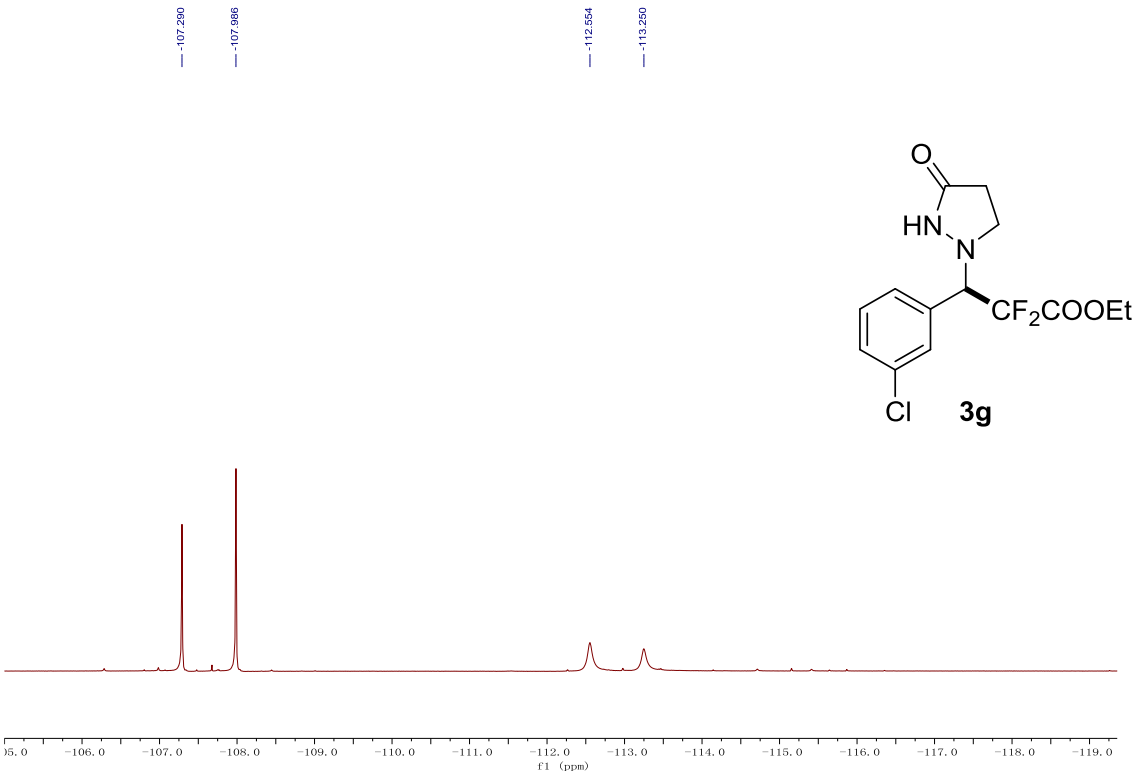
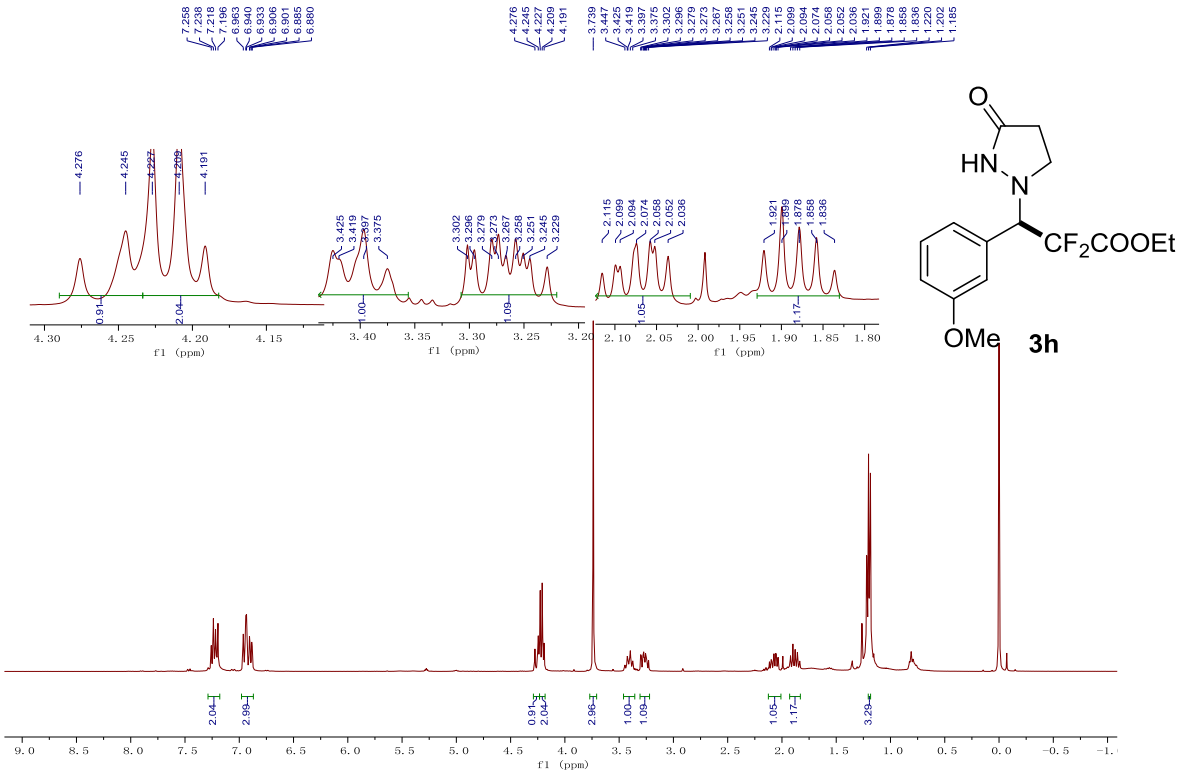
129.544
129.112
128.952
127.625
116.205
113.667
113.629
111.093
70.669
70.462
70.415
70.209
62.431
50.619
28.655
12.834
f1 (ppm)
HN
N
O
CF2COOEt
Cl
3g


-107.290
-107.986
-112.554
-113.250
O
HN
N
CF2COOEt
Cl
3g
−106.0
−107.0
−108.0
−109.0
−110.0
−111.0
−112.0
−113.0
−114.0
−115.0
−116.0
−117.0
−118.0
−119.0
f1 (ppm)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7.238
7.218
7.196
6.963
6.940
6.933
6.906
6.901
6.885
6.880
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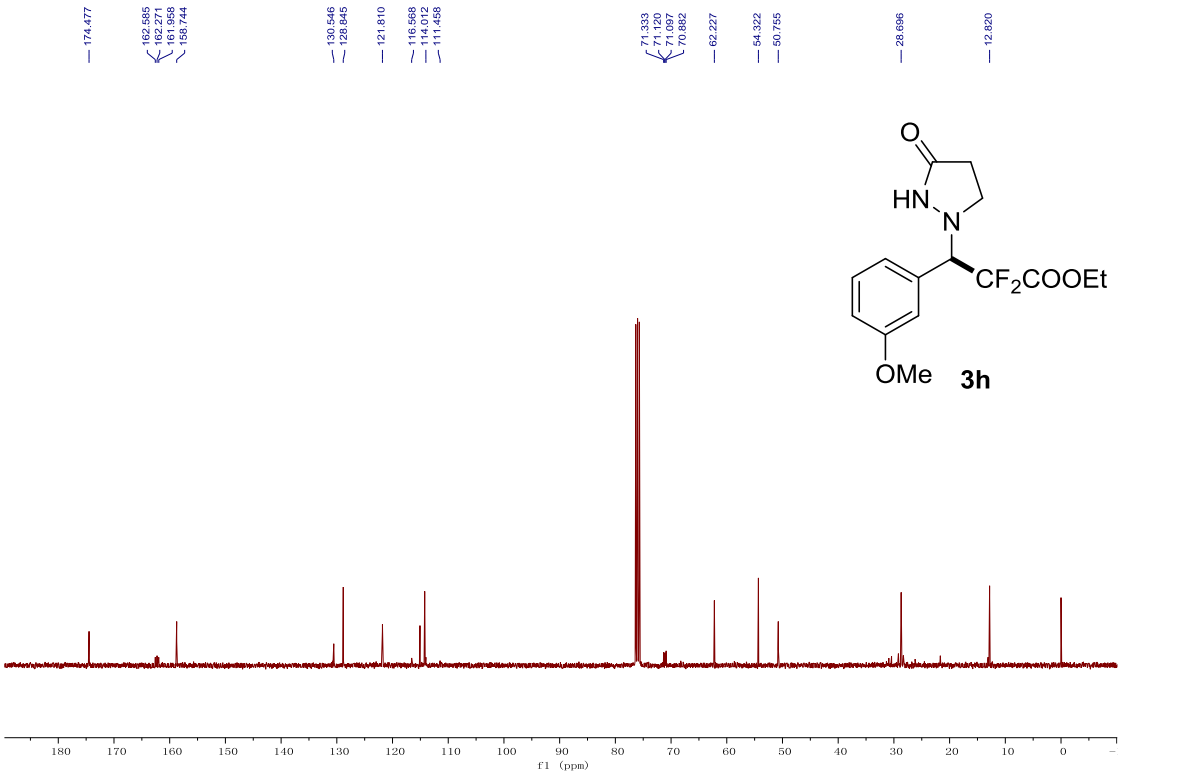
4.245
4.227
4.209
4.191
3.739
3.447
3.425
3.419
3.397
3.375
3.302
3.296
3.279
3.273
3.267
3.258
3.251
3.245
3.229
2.115
2.099
2.094
2.074
2.058
2.052
2.036
1.921
1.899
1.878
1.858
1.836
1.220
1.202
1.185
f1 (ppm)
O
HN
N
CF2COOEt
OMe
3h


174.477
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162.271
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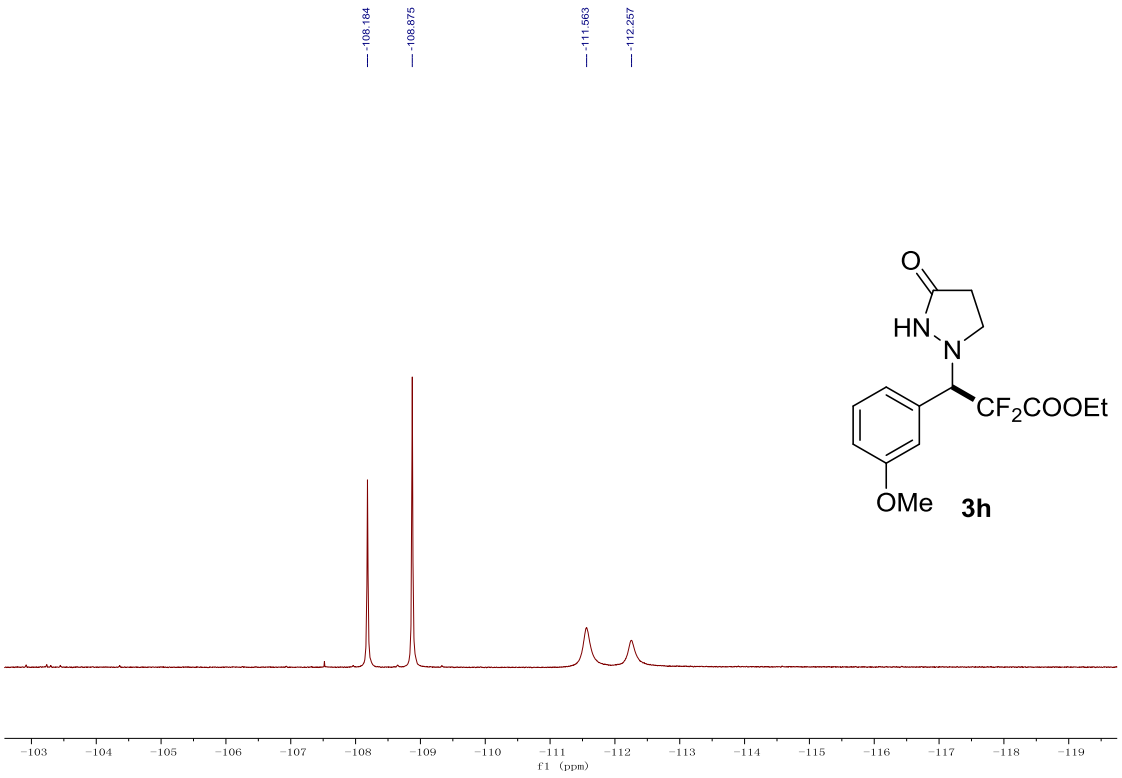
160.744
130.546
128.845
121.810
116.568
114.012
111.458
71.333
71.120
71.097
70.882
62.227
54.322
50.755
28.696
12.820
f1 (ppm)
O
HN
N
CF2COOEt
OMe
3h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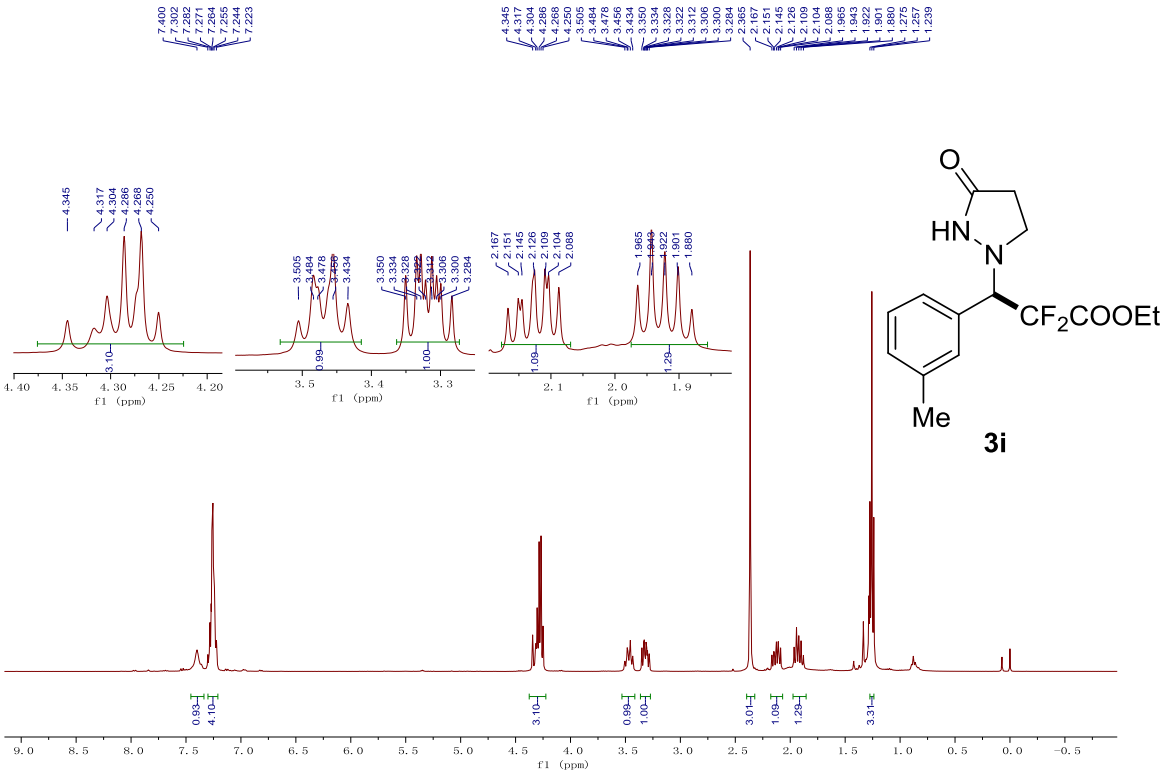
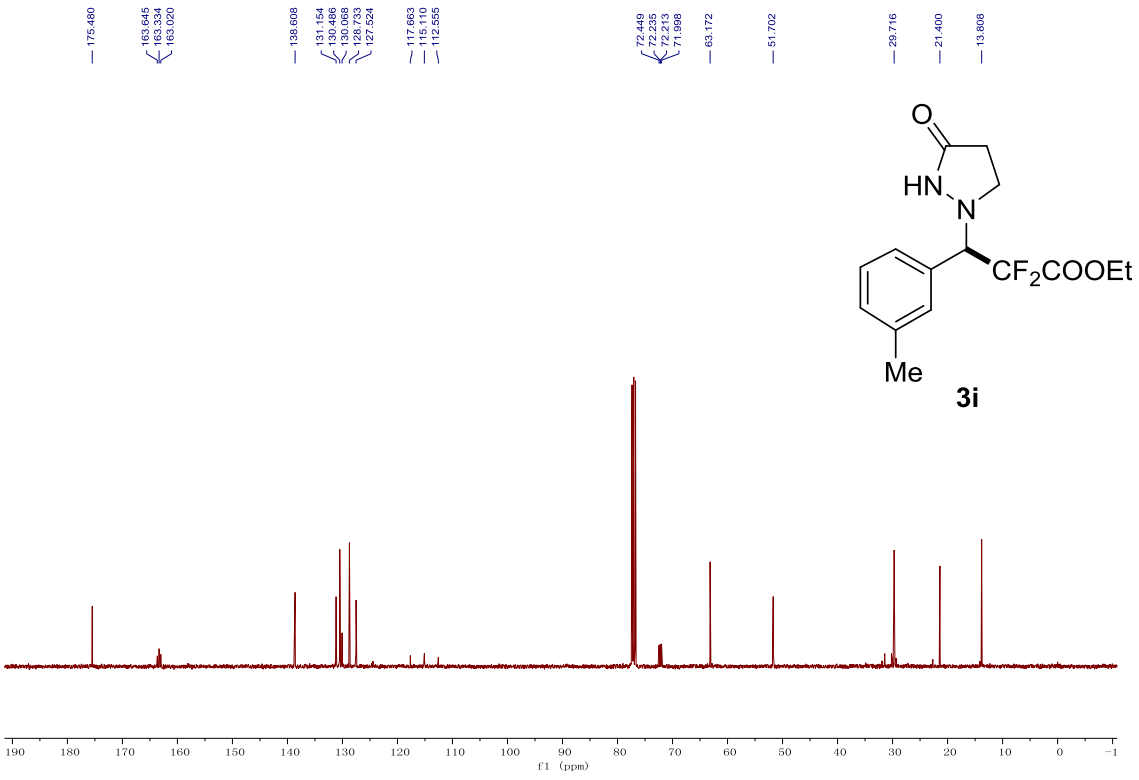
-108.875
-111.563
-112.257
O
HN
N
CF2COOEt
OMe
3h
−103
−104
−105
−106
−107
−108
−109
−110
−111
−112
−113
−114
−115
−116
−117
−118
−119
f1 (ppm)


7.400
7.302
7.282
7.271
7.264
7.255
7.244
7.223
4.345
4.317
4.304
4.286
4.268
4.250
3.505
3.484
3.478
3.456
3.434
3.350
3.334
3.328
3.322
3.312
3.306
3.300
3.284
2.365
2.167
2.151
2.145
2.126
2.109
2.104
2.088
1.965
1.943
1.922
1.901
1.880
1.275
1.257
1.239
f1 (ppm)
HN
N
O
CF2COOEt
Me
3i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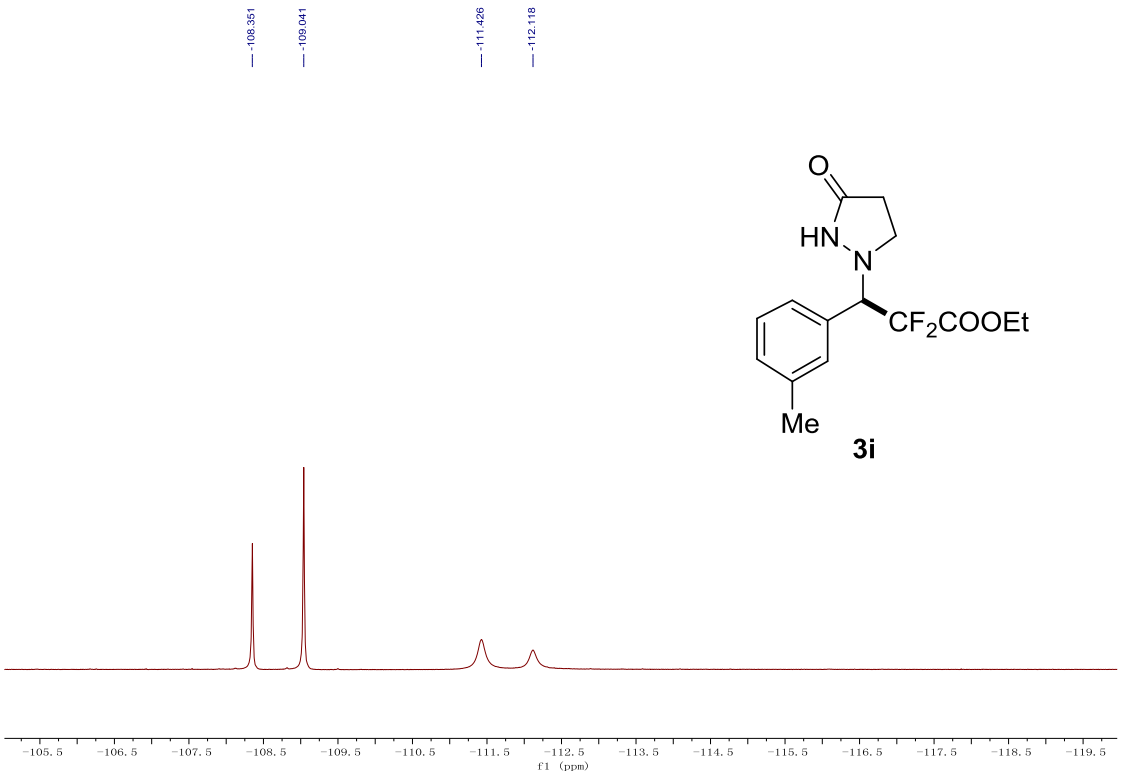
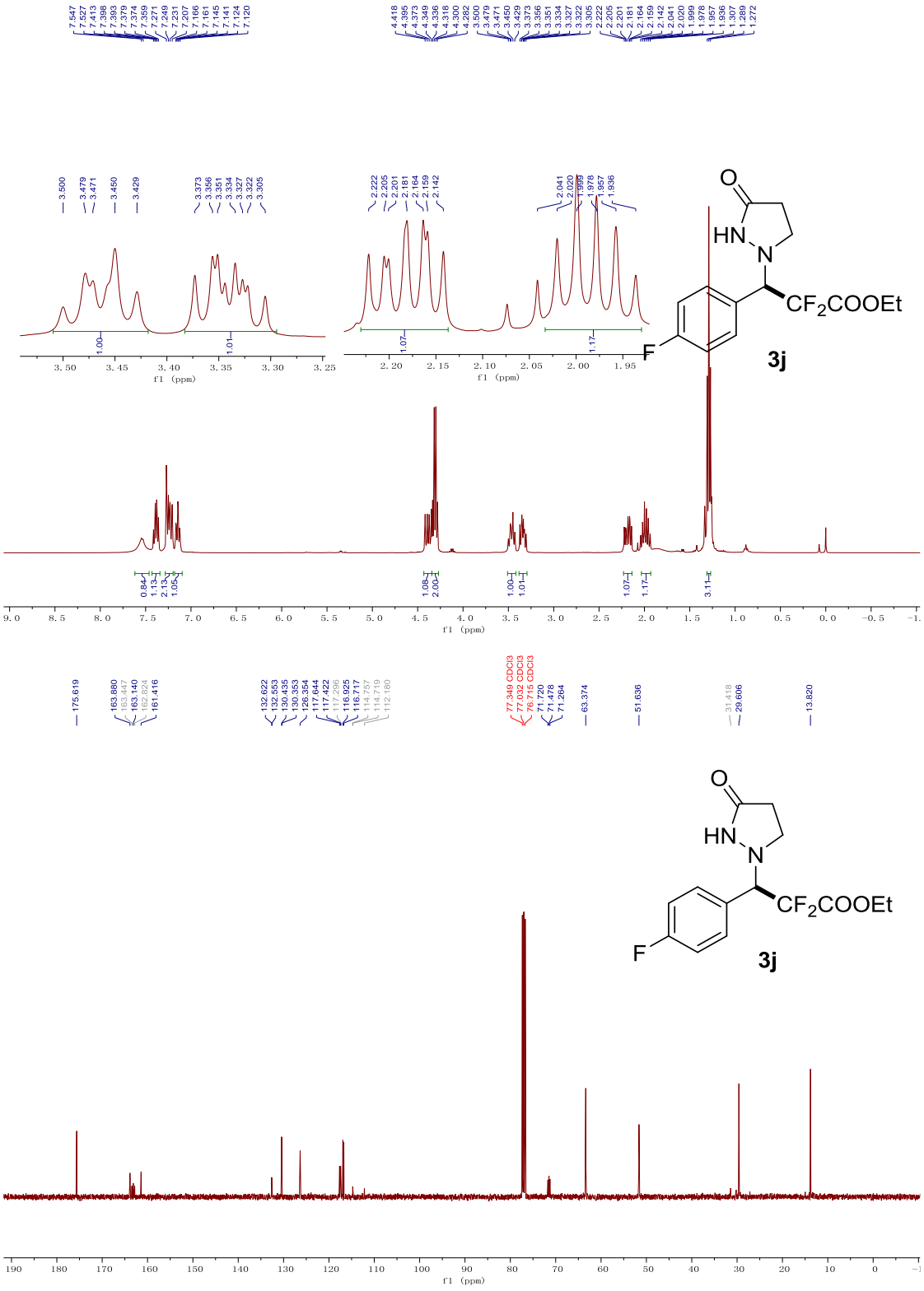
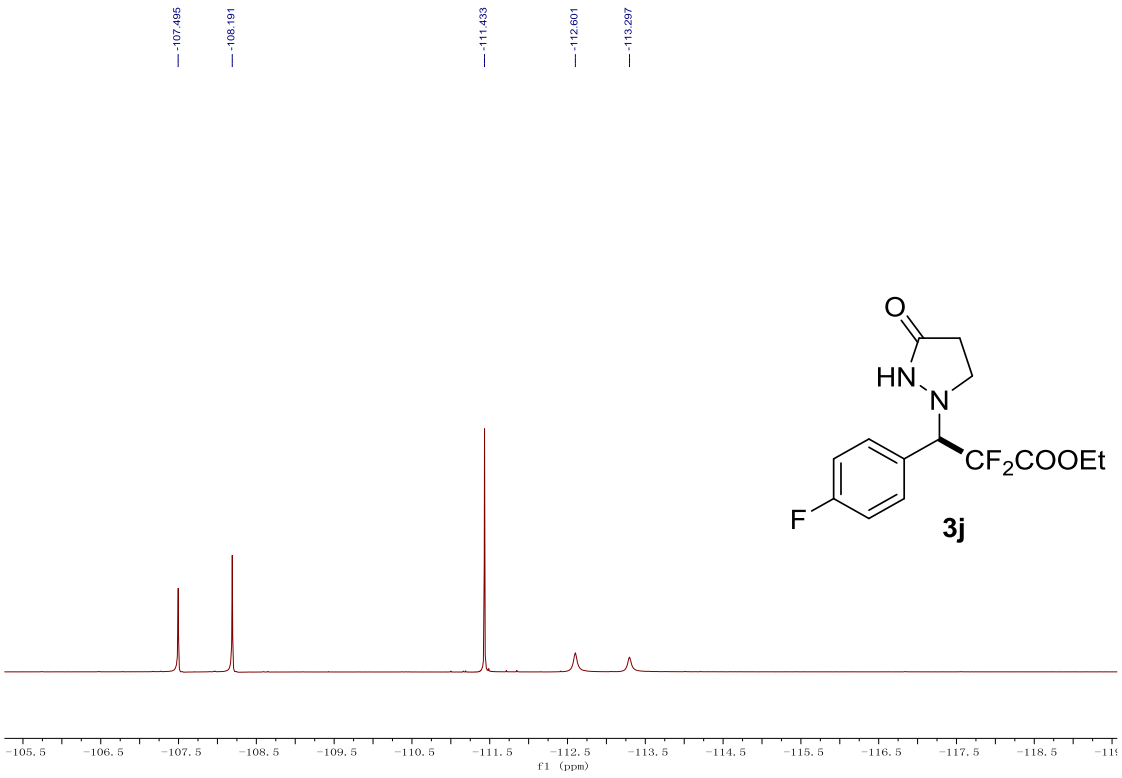
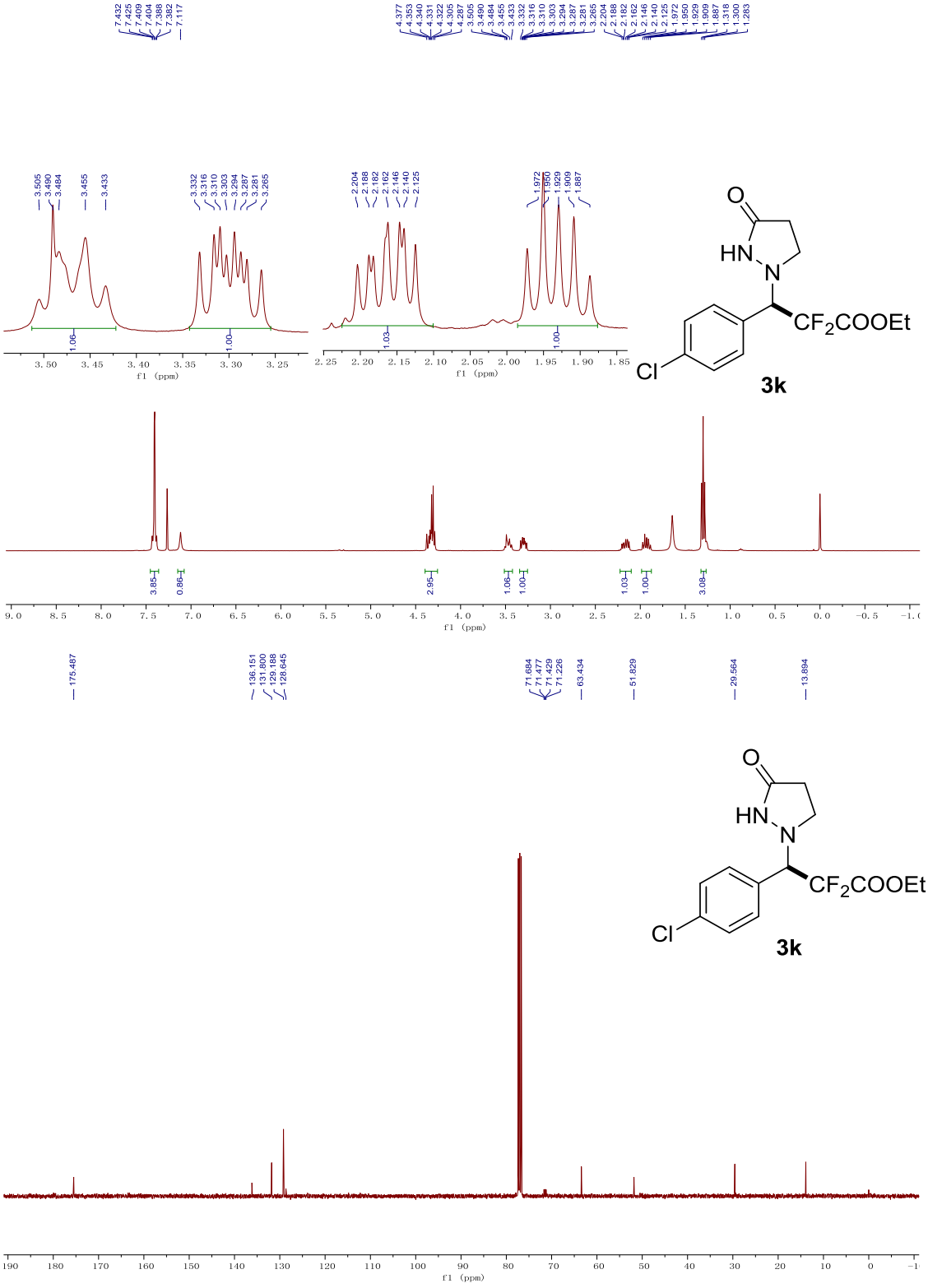
163.334
163.020
138.608
131.154
130.486
130.068
128.733
127.524
117.663
115.410
112.555
72.449
72.235
72.213
71.998
63.172
51.702
29.716
21.400
13.808
f1 (ppm)
HN
N
O
CF2COOEt
Me
3i


-108.351
-109.041
-111.426
-112.118
O
HN
N
CF2COOEt
Me
3i
−105.5
−106.5
−107.5
−108.5
−109.5
−110.5
−111.5
−112.5
−113.5
−114.5
−115.5
−116.5
−117.5
−118.5
−119.5
f1 (ppm)


HN
N
O
CF2COOEt
F
3j
f1 (ppm)


-107.495
-108.191
-111.433
-112.601
-113.297
O
HN
N
CF2COOEt
F
3j
−105.5
−106.5
−107.5
−108.5
−109.5
−110.5
−111.5
−112.5
−113.5
−114.5
−115.5
−116.5
−117.5
−118.5
f1 (ppm)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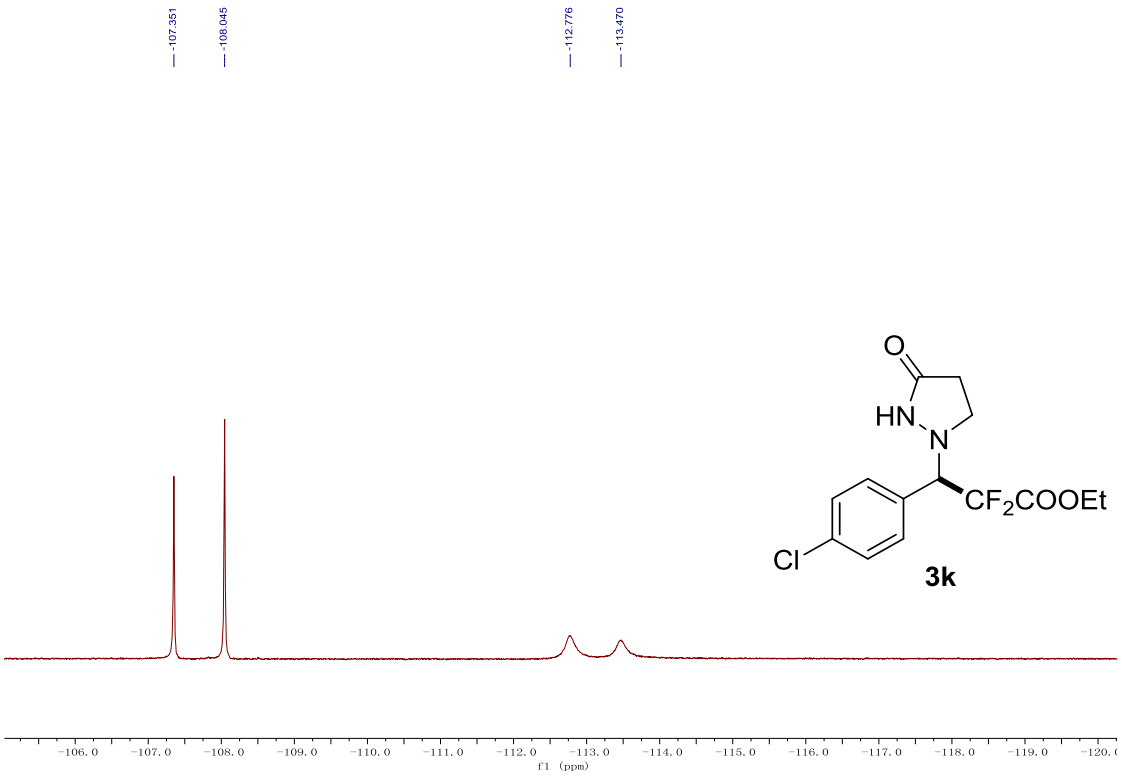
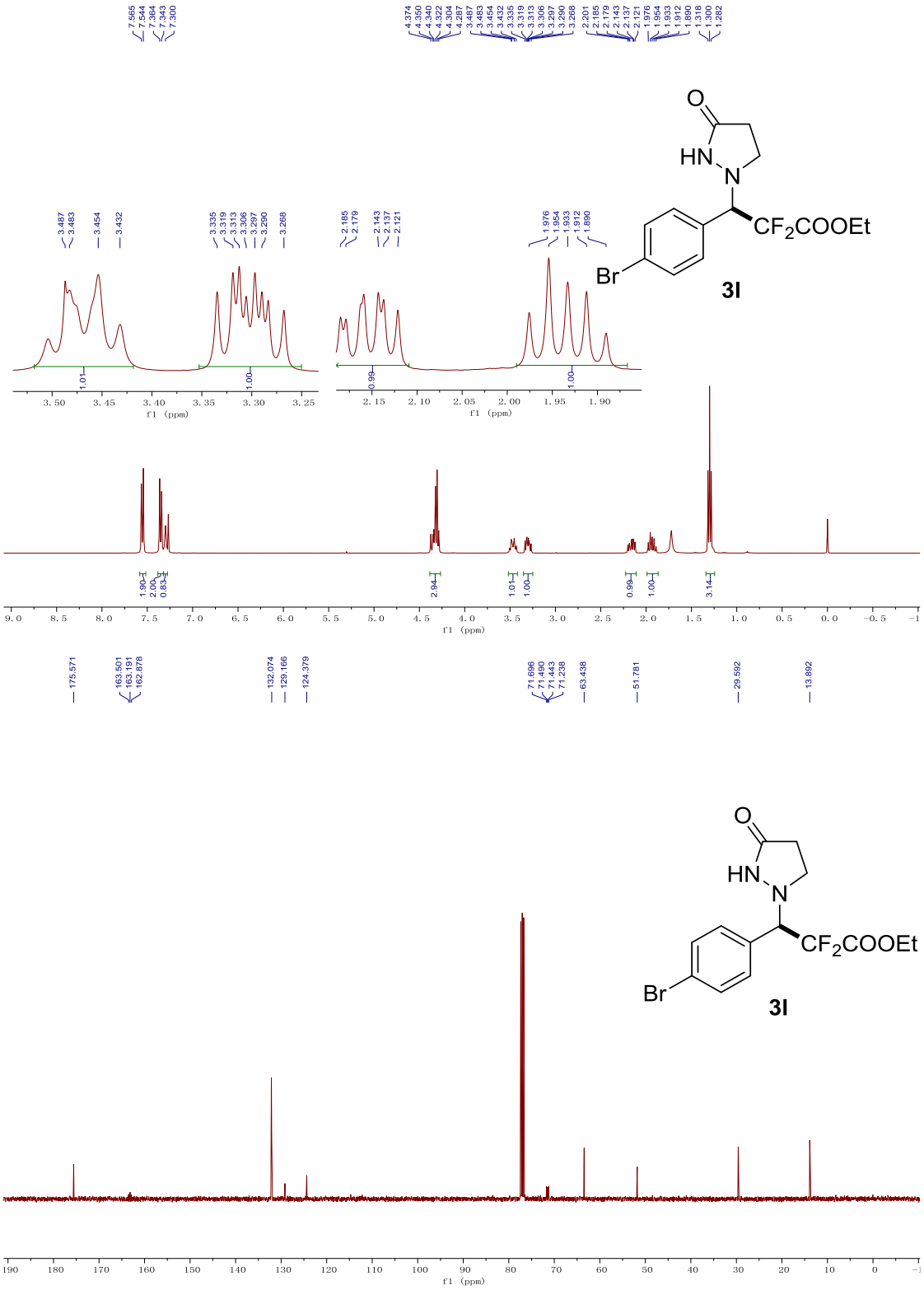
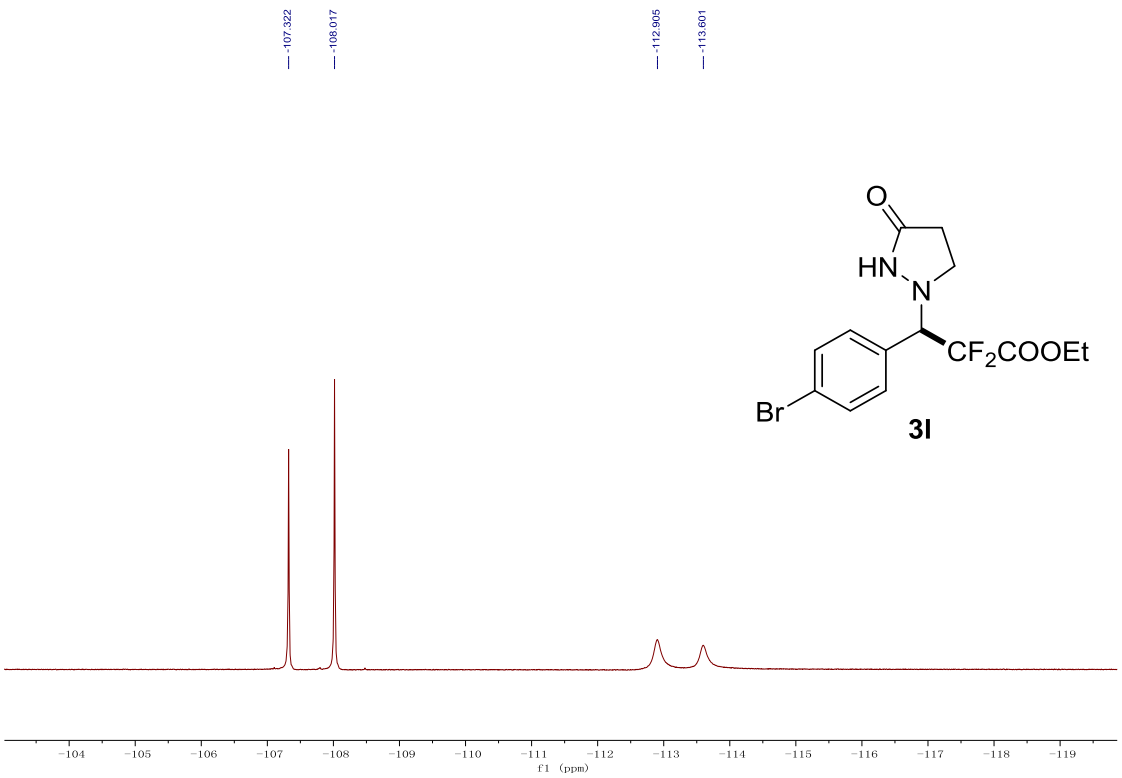
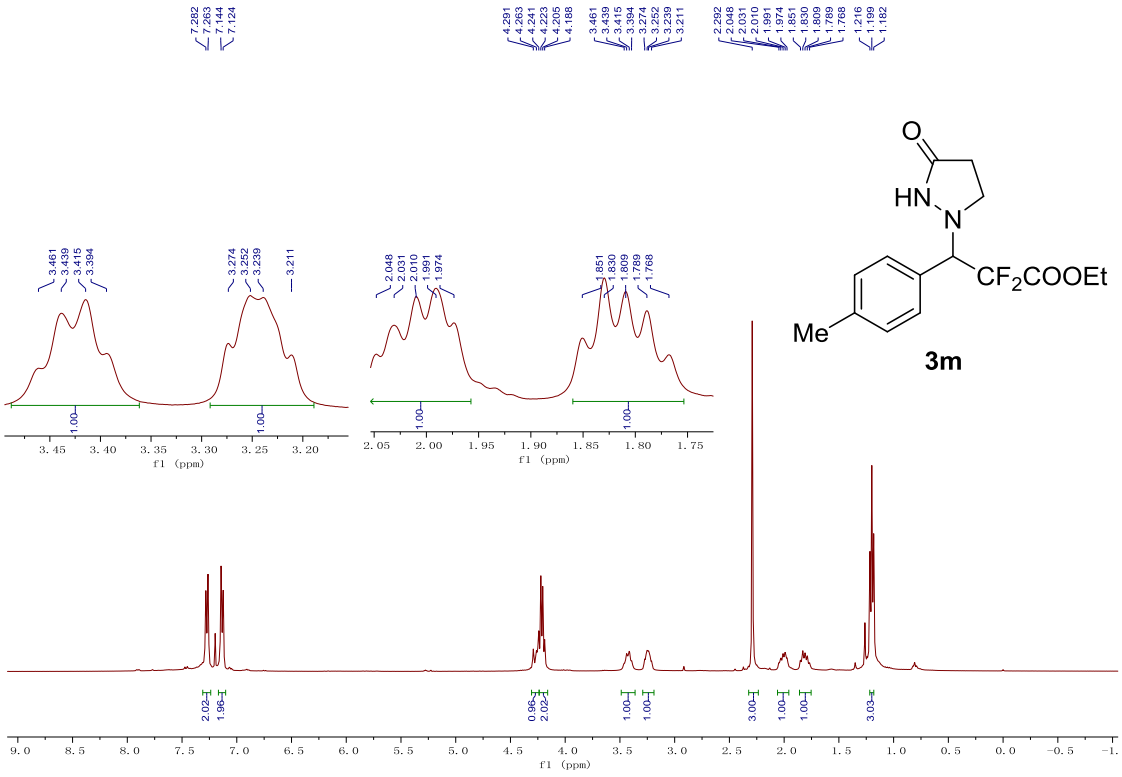
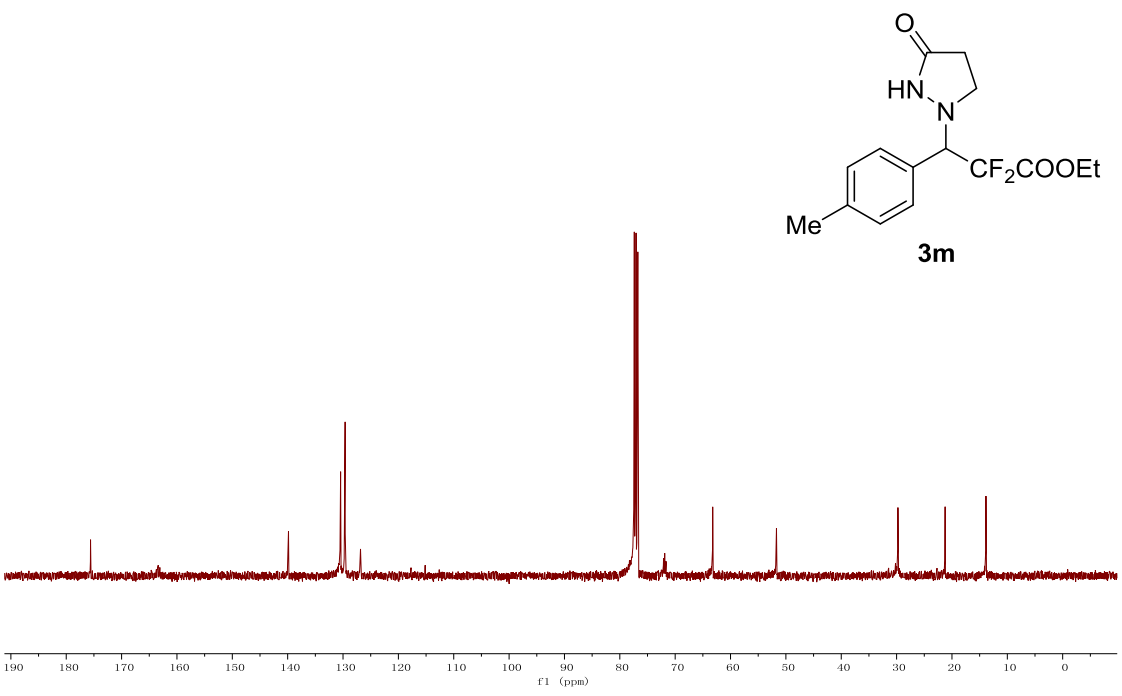
7.405
7.404
7.388
7.382
7.117
4.377
4.353
4.340
4.331
4.322
4.305
4.287
3.505
3.490
3.484
3.455
3.433
3.332
3.316
3.310
3.303
3.294
3.287
3.281
3.265
2.204
2.188
2.182
2.162
2.146
2.140
2.125
1.972
1.950
1.929
1.909
1.887
1.316
1.300
1.283
f1 (ppm)
HN
N
O
CF2COOEt
Cl
3k
175.487
136.151
131.800
129.188
128.645
71.684
71.477
71.429
71.226
63.434
51.829
29.564
13.894

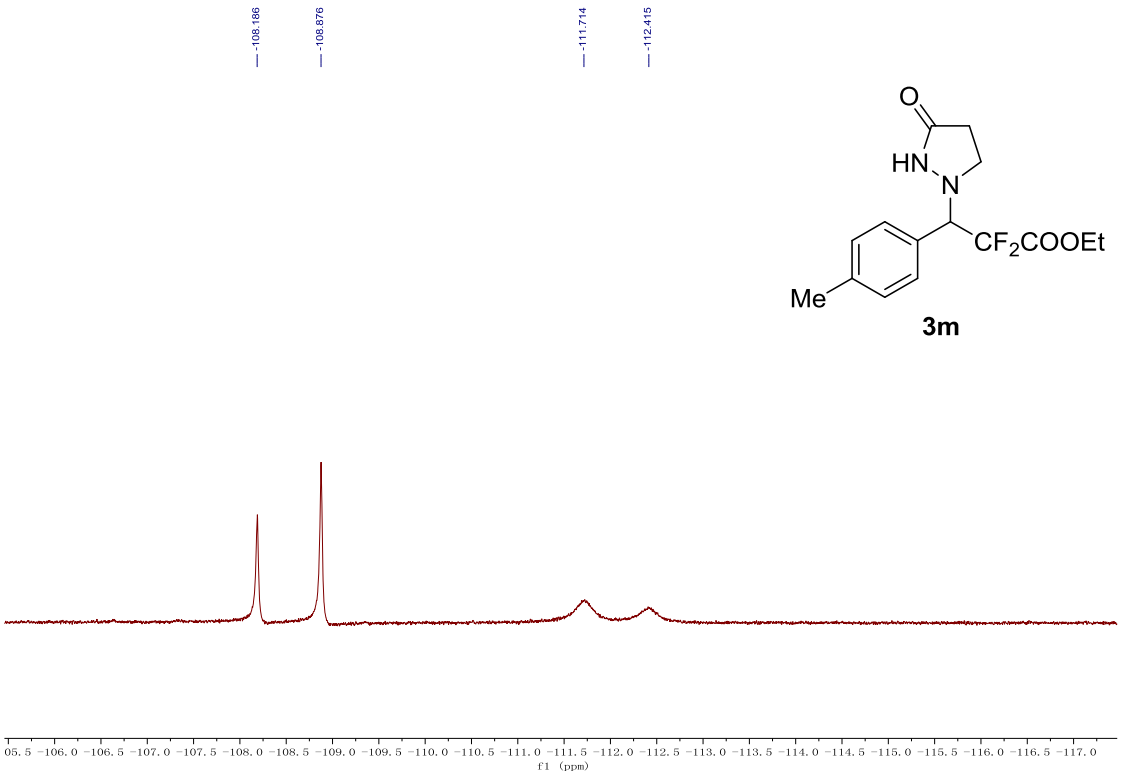

-107.351
-108.045
-112.776
-113.470
O
HN
N
CF2COOEt
Cl
3k
-106.0
-107.0
-108.0
-109.0
-110.0
-111.0
-112.0
-113.0
-114.0
-115.0
-116.0
-117.0
-118.0
-119.0
f1 (ppm)

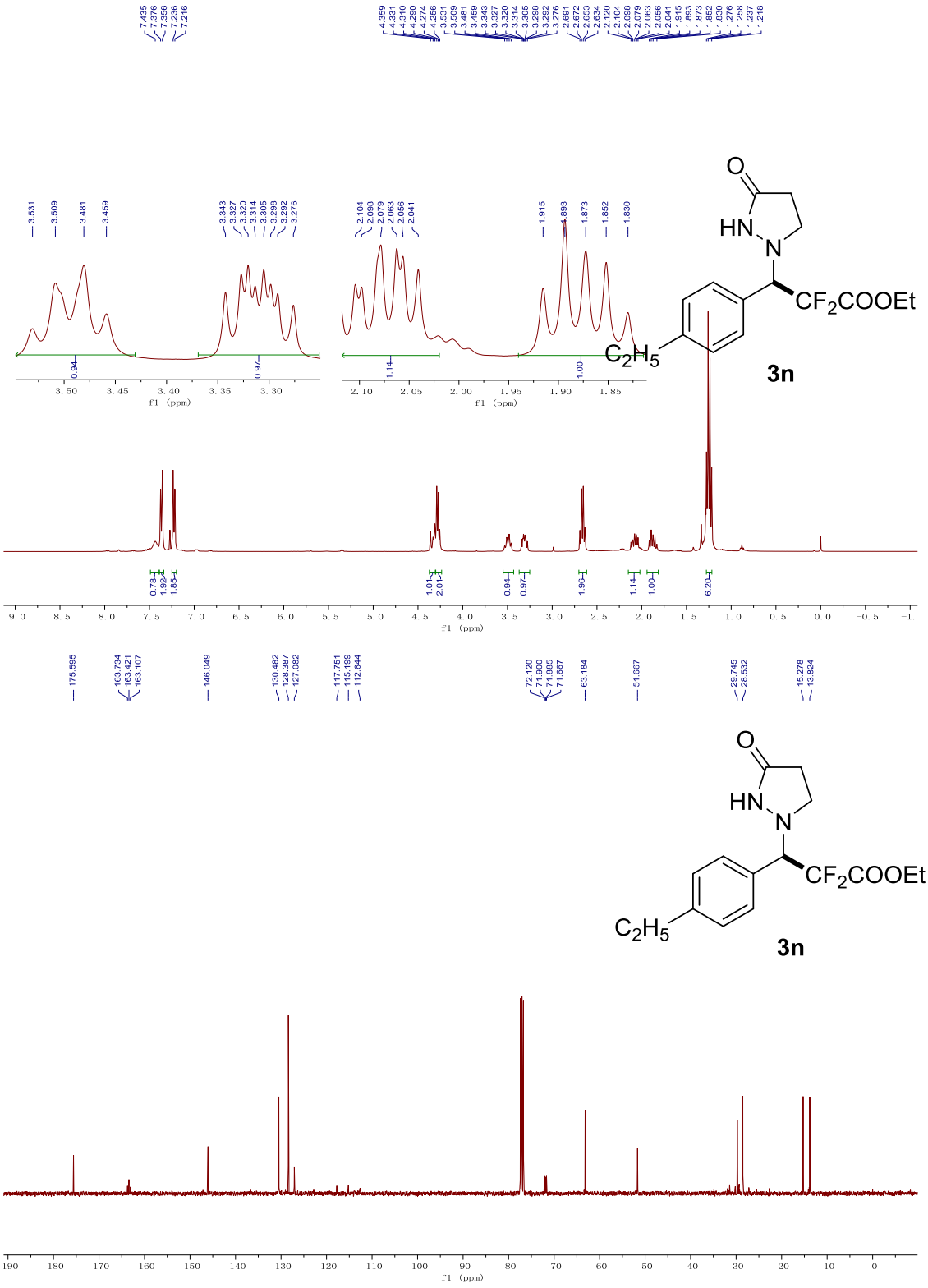

7.565
7.544
7.384
7.343
7.300
4.374
4.350
4.340
4.322
4.304
4.287
3.487
3.483
3.454
3.432
3.335
3.319
3.313
3.306
3.297
3.290
3.268
2.201
2.185
2.179
2.143
2.137
2.121
1.976
1.954
1.933
1.912
1.890
1.318
1.300
1.282
O
HN
N
CF2COOEt
Br
3I
f1 (ppm)
175.571
163.501
163.191
162.878
132.074
129.166
124.379
71.696
71.490
71.443
71.238
63.438
51.781
29.592
13.892

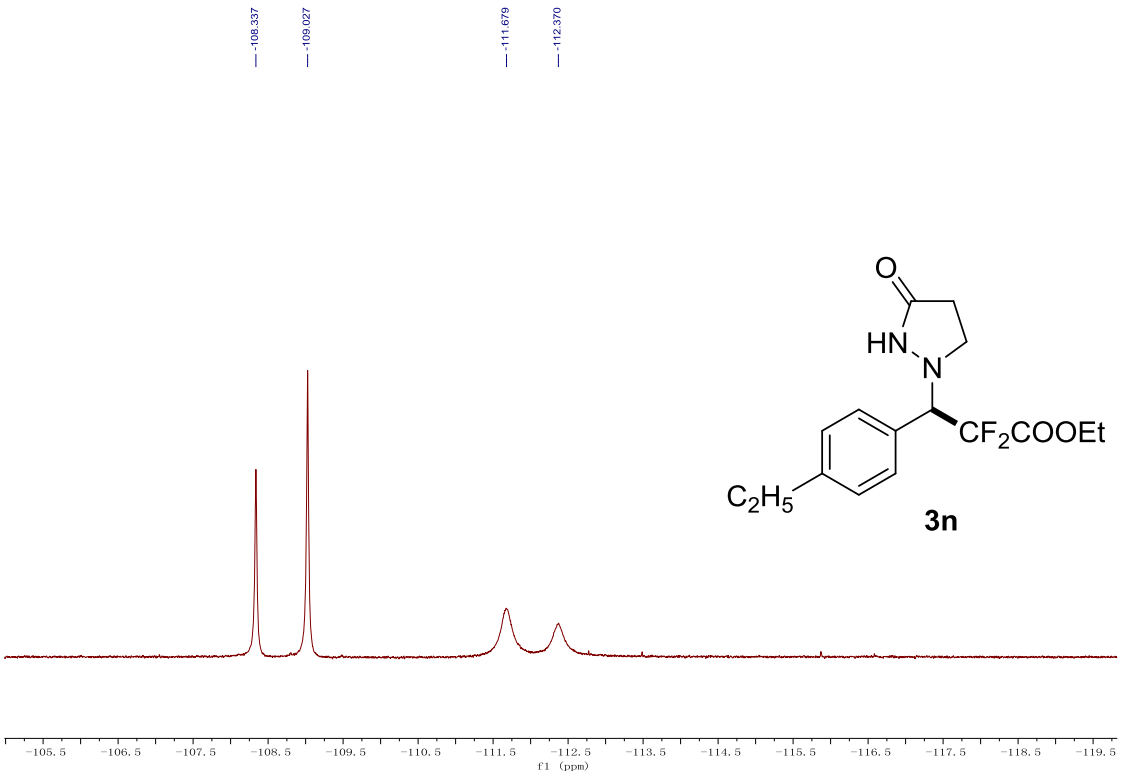

-107.322
-108.017
-112.905
-113.601
O
HN
N
CF2COOEt
Br
3l
−104
−105
−106
−107
−108
−109
−110
−111
−112
−113
−114
−115
−116
−117
−118
−119
f1 (ppm)

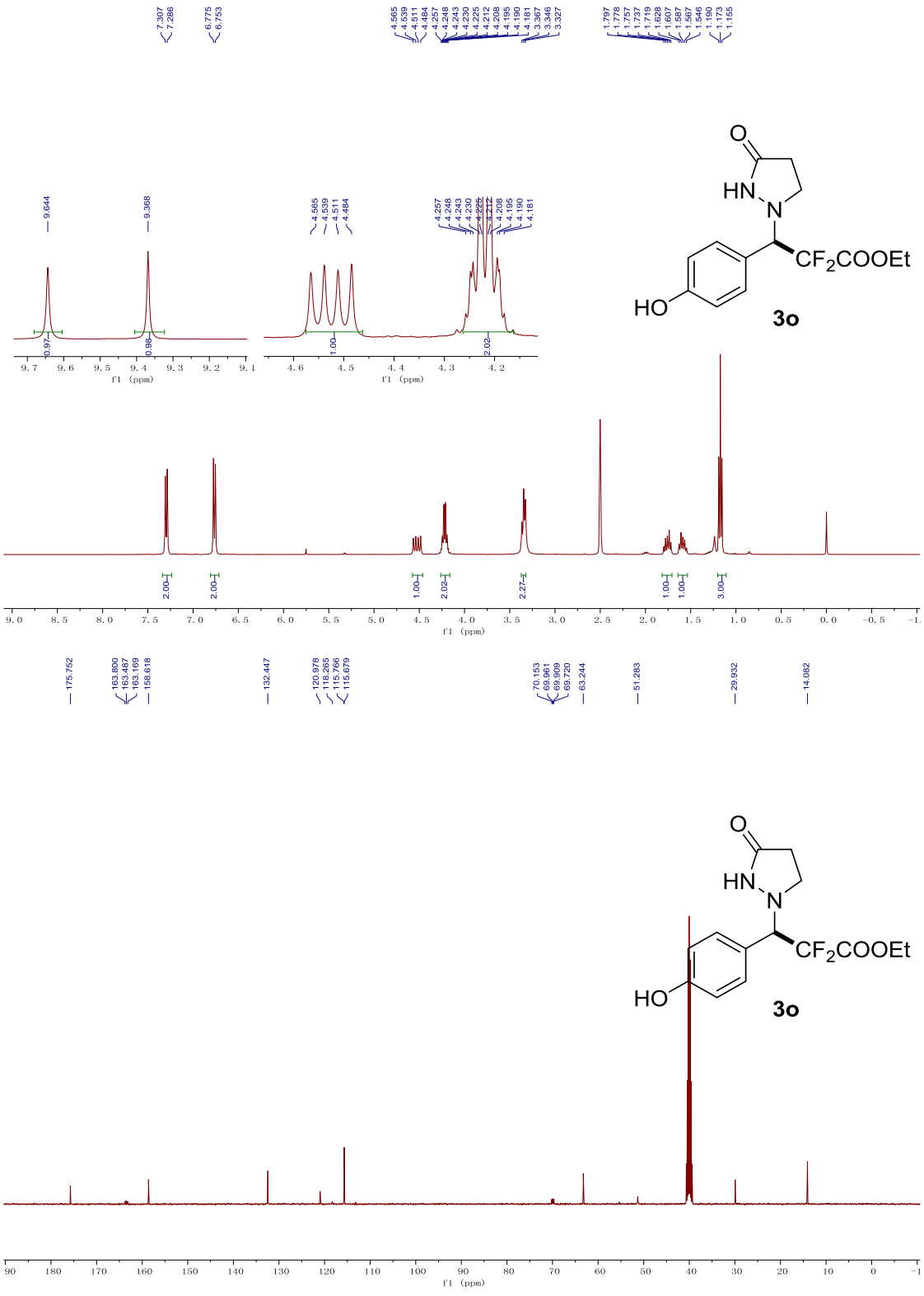

7.282
7.263
7.144
7.124
4.291
4.263
4.241
4.223
4.205
4.188
3.461
3.439
3.415
3.394
3.274
3.252
3.239
3.211
2.292
2.048
2.031
2.010
1.991
1.974
1.851
1.830
1.809
1.789
1.768
1.216
1.199
1.182
HN
N
O
CF2COOEt
Me
3m
f1 (ppm)

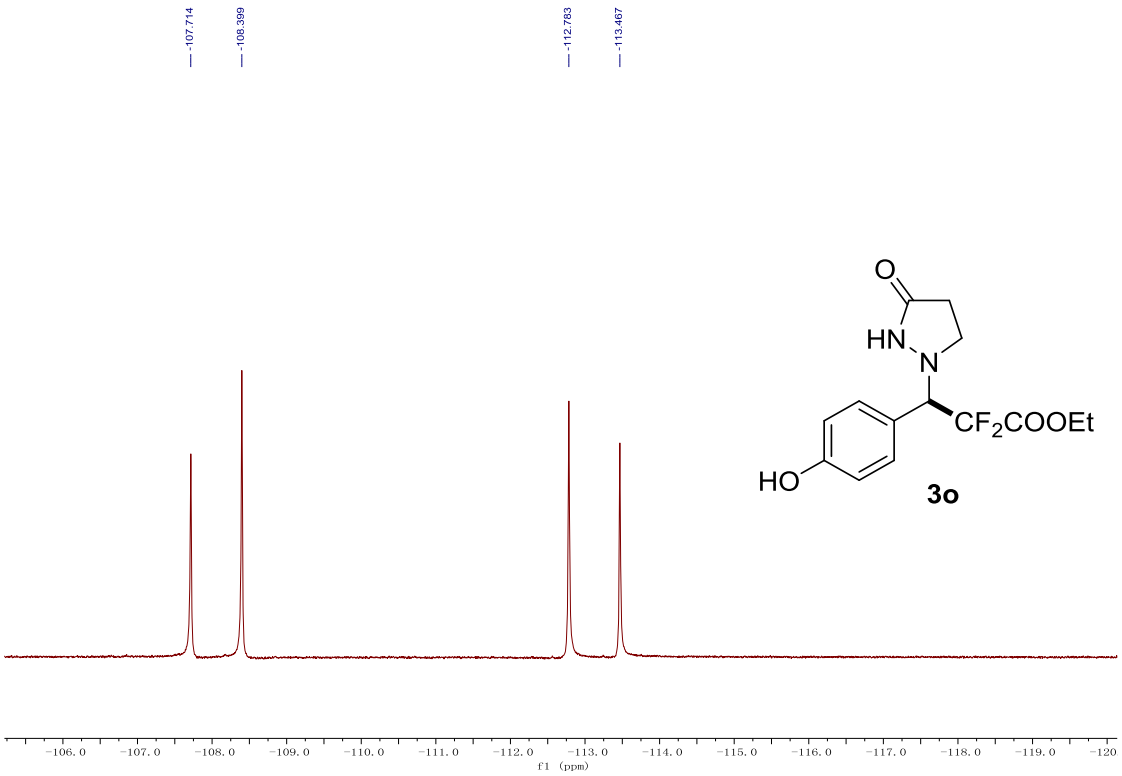

175.612
163.709
163.389
163.069
139.850
130.436
129.620
126.840
117.716
115.183
115.162
112.616
72.097
71.892
71.645
63.270
51.701
29.808
21.234
13.859
HN
N
O
CF2COOEt
Me
3m
f1 (ppm)

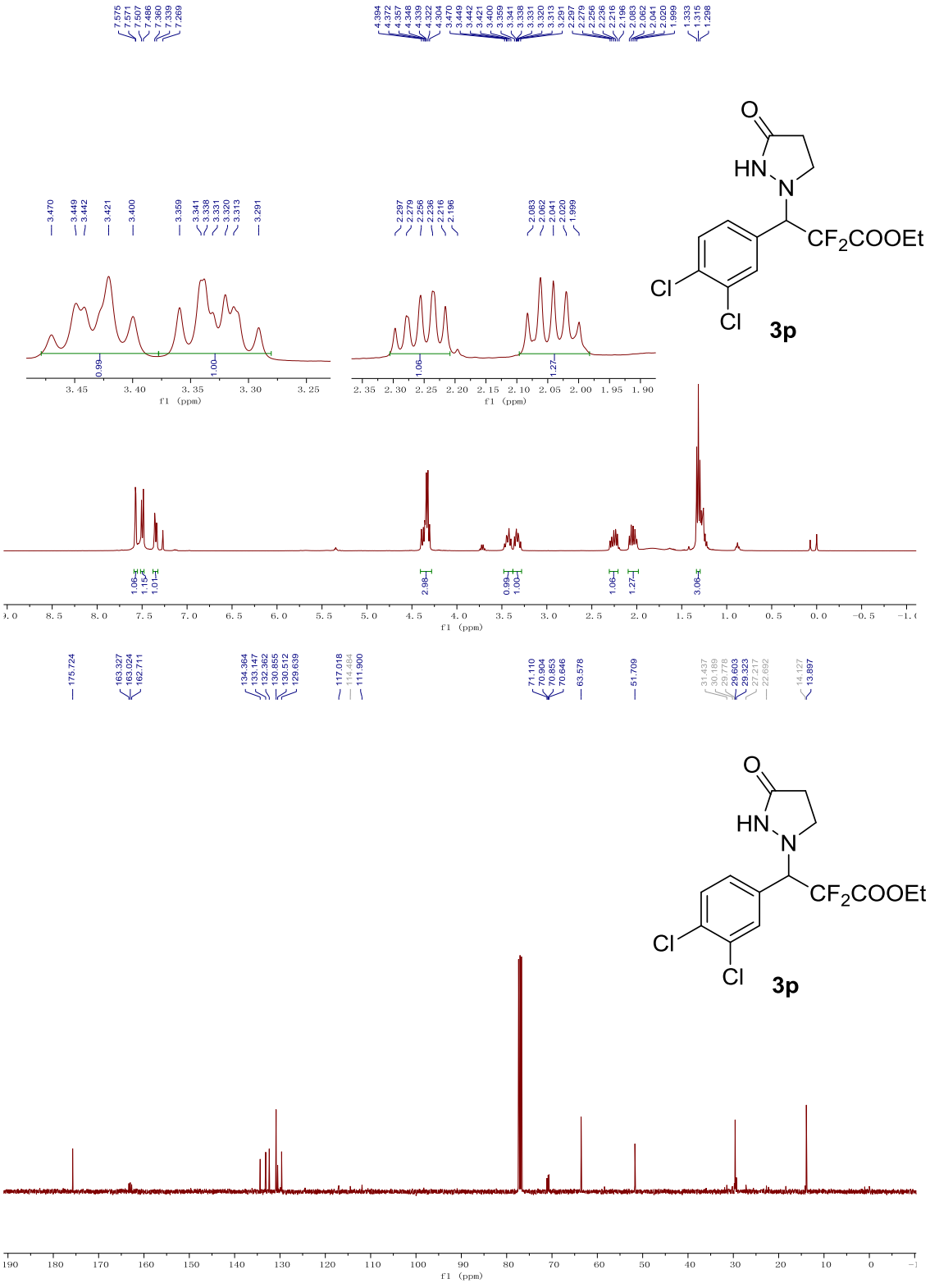

-108.186
-108.876
-111.714
-112.415
O
HN
N
CF2COOEt
Me
3m
05.5 -106.0 -106.5 -107.0 -107.5 -108.0 -108.5 -109.0 -109.5 -110.0 -110.5 -111.0 -111.5 -112.0 -112.5 -113.0 -113.5 -114.0 -114.5 -115.0 -115.5 -116.0 -116.5 -117.0
f1 (ppm)

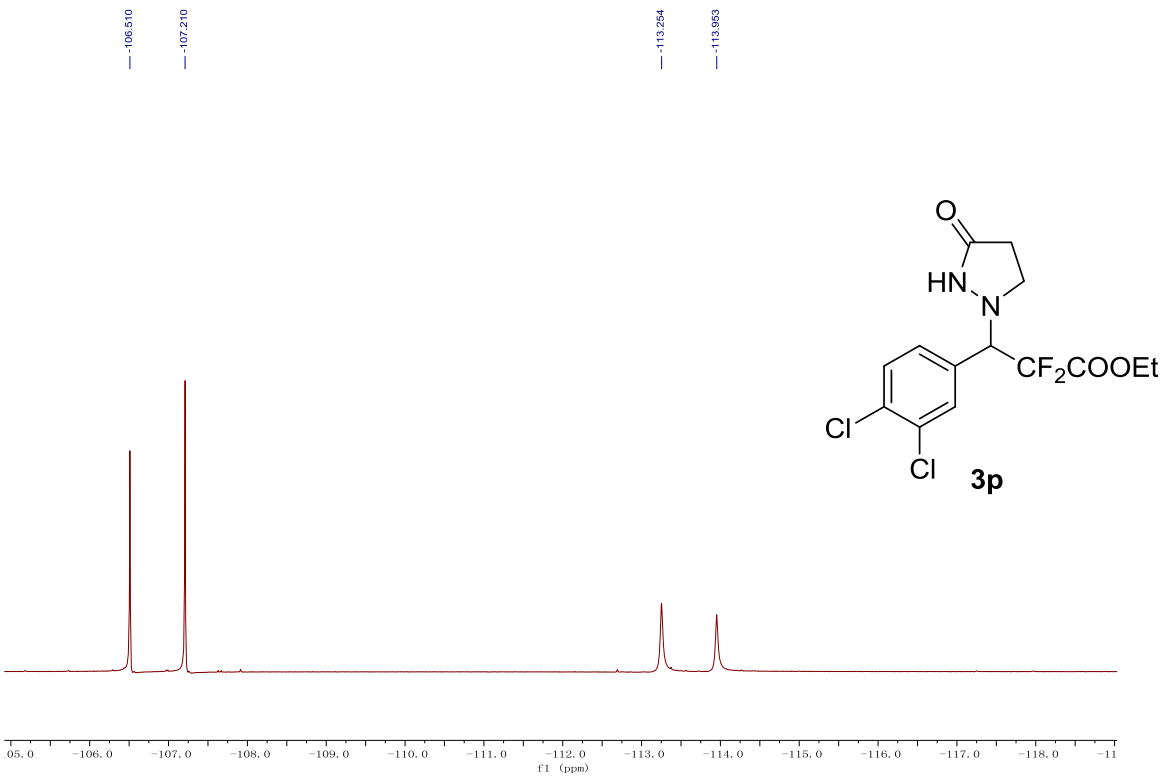

7.435
7.376
7.356
7.296
7.216
4.359
4.331
4.310
4.290
4.274
4.256
3.531
3.509
3.481
3.459
3.343
3.327
3.320
3.314
3.305
3.298
3.292
3.276
2.691
2.672
2.655
2.634
2.120
2.104
2.098
2.079
2.063
2.056
2.041
1.915
1.893
1.873
1.852
1.830
1.276
1.258
1.237
1.218
O
HN
N
CF2COOEt
C2H5
3n
f1 (ppm)
O
HN
N
CF2COOEt
C2H5
3n
f1 (ppm)

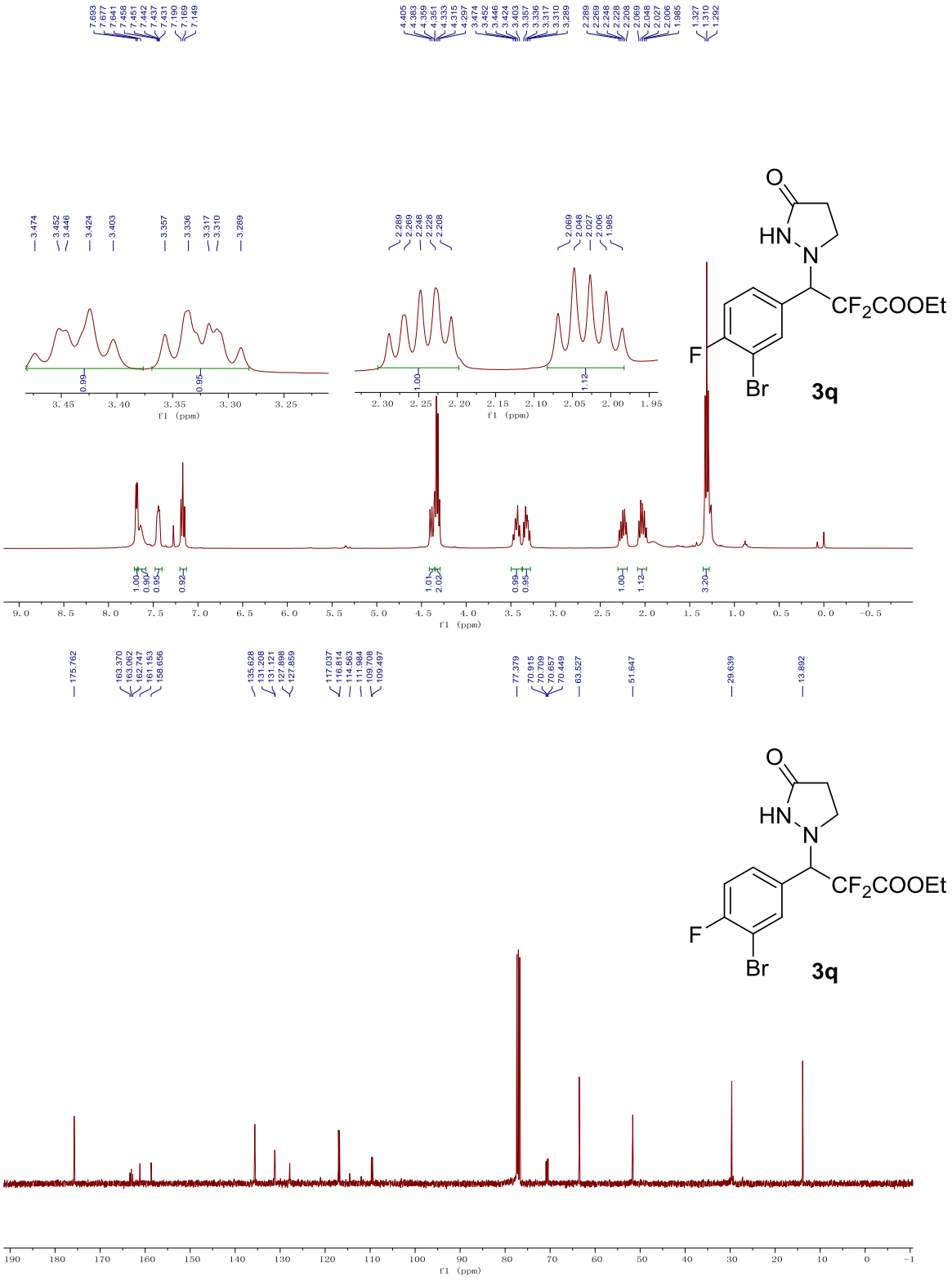

-108.337
-109.027
-111.679
-112.370
O
HN
N
CF2COOEt
C2H5
3n
−105.5
−106.5
−107.5
−108.5
−109.5
−110.5
−111.5
−112.5
−113.5
−114.5
−115.5
−116.5
−117.5
−118.5
−119.5
f1 (ppm)

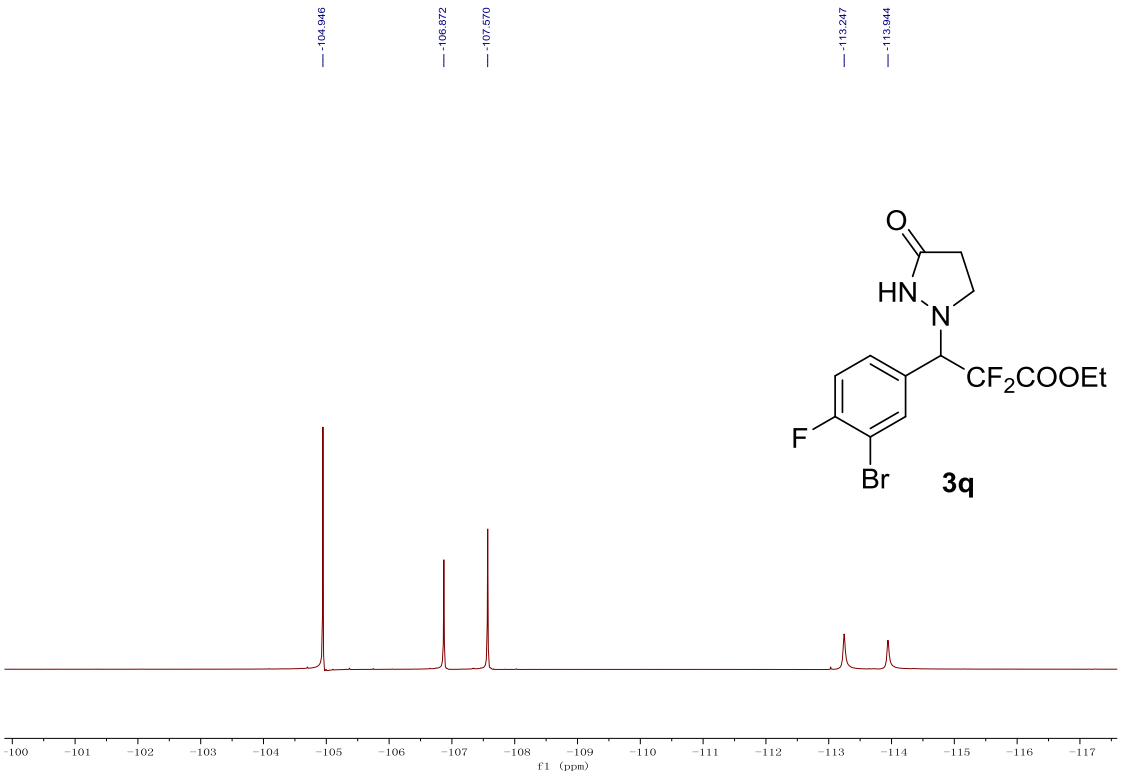

7.307
7.286
6.775
6.753
4.565
4.539
4.511
4.484
4.257
4.248
4.243
4.230
4.225
4.212
4.208
4.195
4.190
4.181
3.367
3.346
3.327
1.797
1.778
1.757
1.737
1.719
1.628
1.607
1.587
1.567
1.546
1.190
1.173
1.155
9.644
9.368
f1 (ppm)
0.97
0.98
1.00
2.02
O
HN
N
CF2COOEt
HO
3o
2.00
2.00
1.00
2.02
2.27
1.00
1.00
3.00
175.752
163.800
163.487
163.169
158.618
132.447
120.978
118.265
115.766
115.679
70.153
69.961
69.909
69.720
63.244
51.263
29.932
14.082

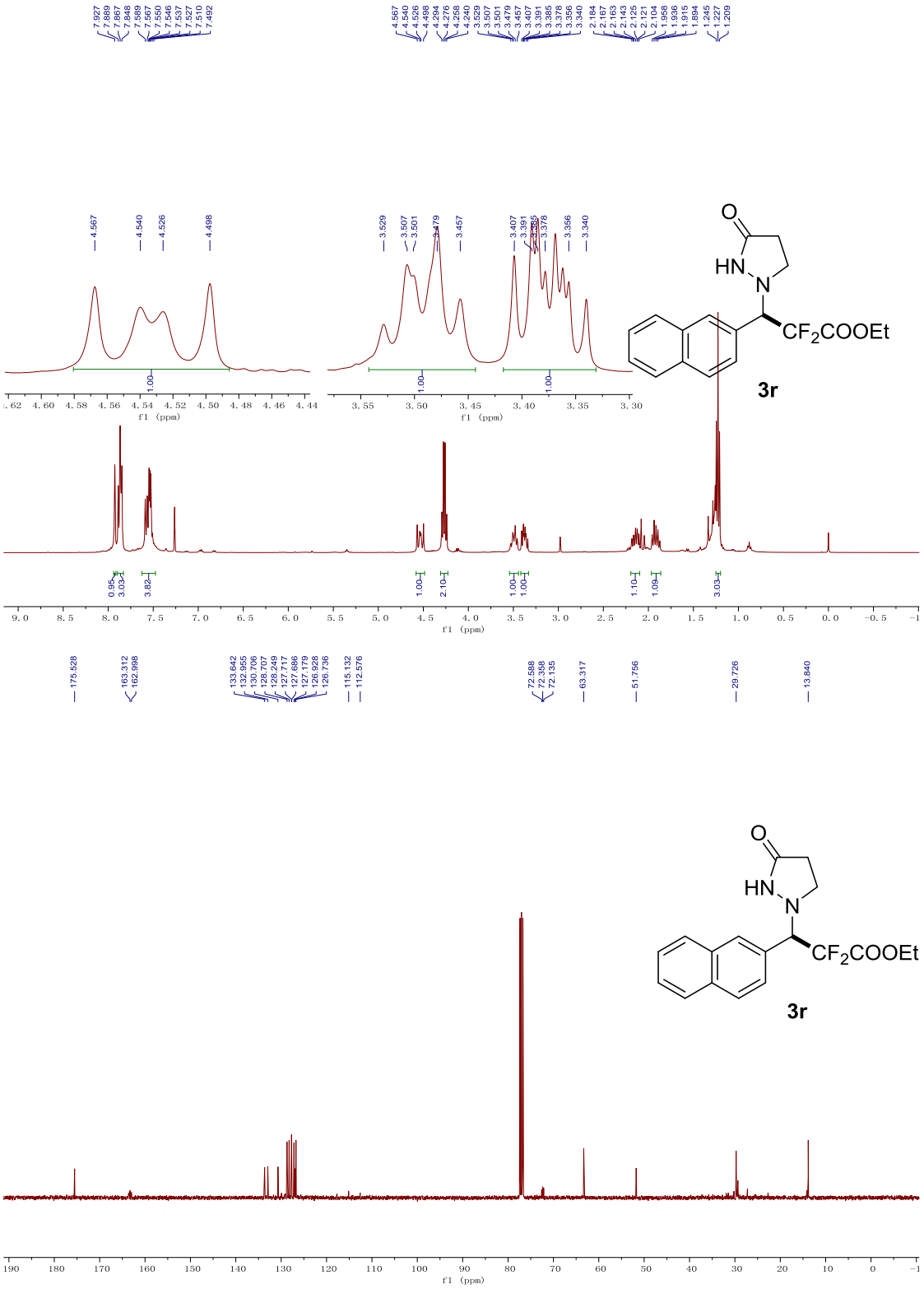

-107.714
-108.399
-112.783
-113.467
O
HN
N
CF2COOEt
HO
3o
-106.0
-107.0
-108.0
-109.0
-110.0
-111.0
-112.0
-113.0
-114.0
-115.0
-116.0
-117.0
-118.0
-119.0
-120
f1 (ppm)

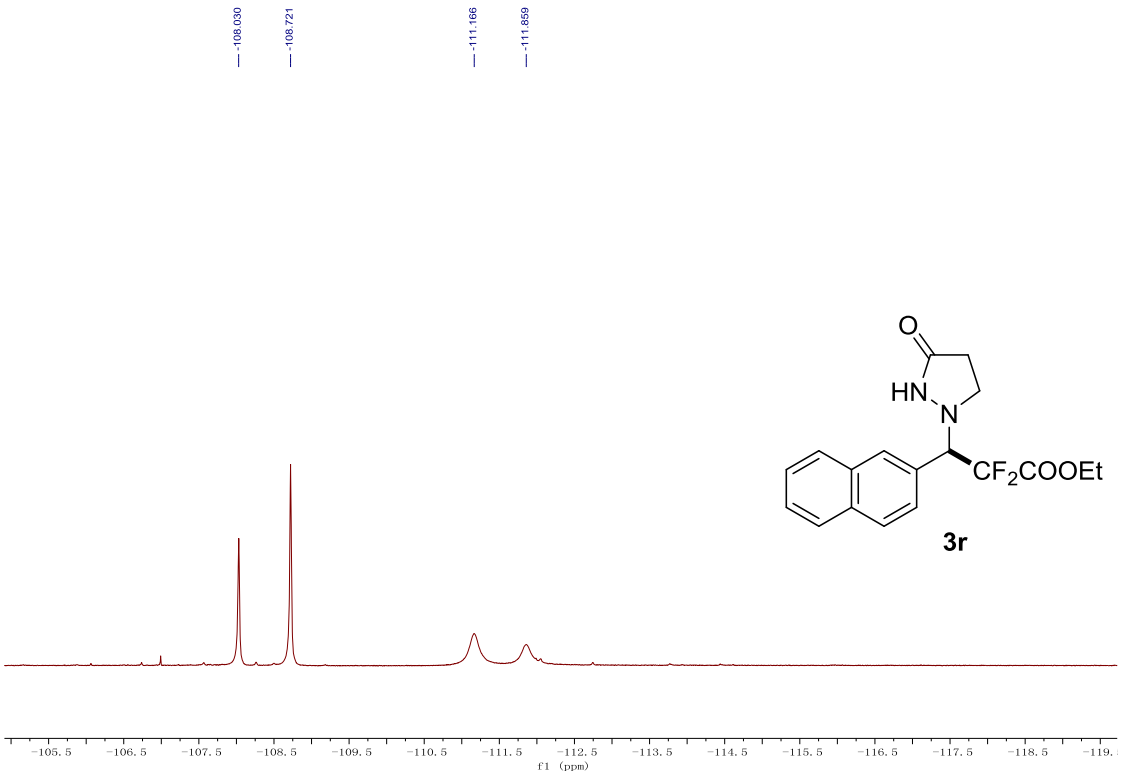

7.575
7.571
7.507
7.486
7.360
7.339
7.269
4.394
4.372
4.357
4.348
4.339
4.322
4.304
4.270
3.449
3.442
3.421
3.400
3.359
3.341
3.338
3.331
3.320
3.313
3.291
2.297
2.279
2.256
2.236
2.216
2.196
2.083
2.062
2.041
2.020
1.999
1.333
1.315
1.298
O
HN
N
CF2COOEt
Cl
Cl
3p
f1 (ppm)
175.724
163.327
163.024
162.711
134.364
133.147
132.362
130.855
130.512
129.639
117.018
114.484
111.900
71.110
70.904
70.853
70.646
63.578
51.709
31.437
30.169
29.778
29.603
29.323
27.217
22.692
14.127
13.897

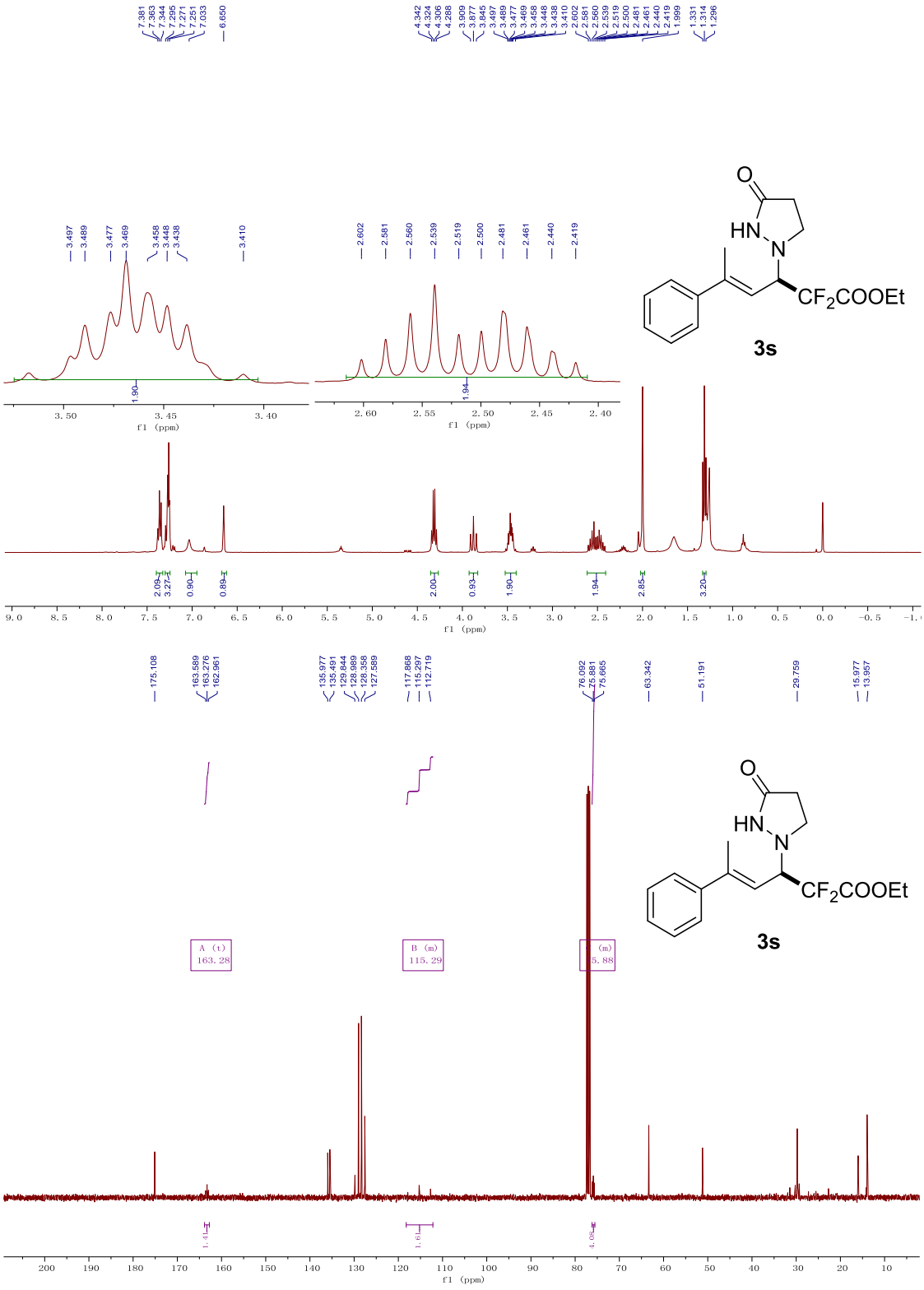

-106.510
-107.210
-113.254
-113.953
O
HN
N
CF2COOEt
Cl
Cl
3p
f1 (ppm)

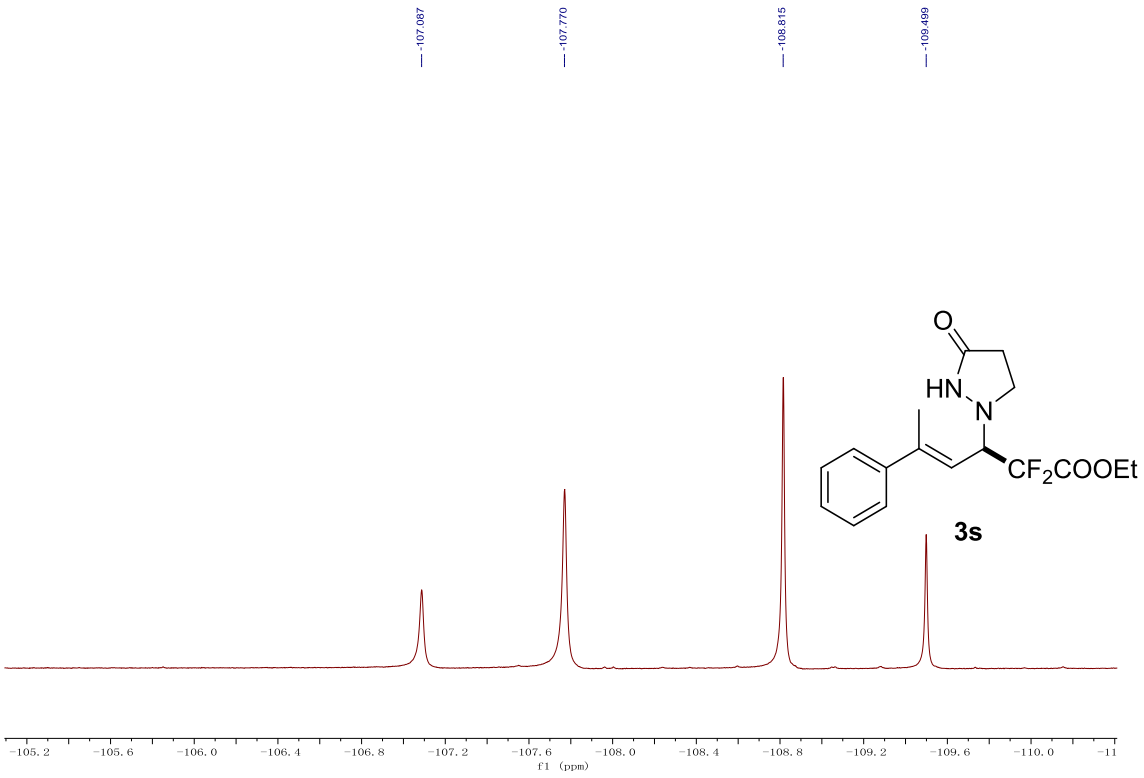

3q
3q

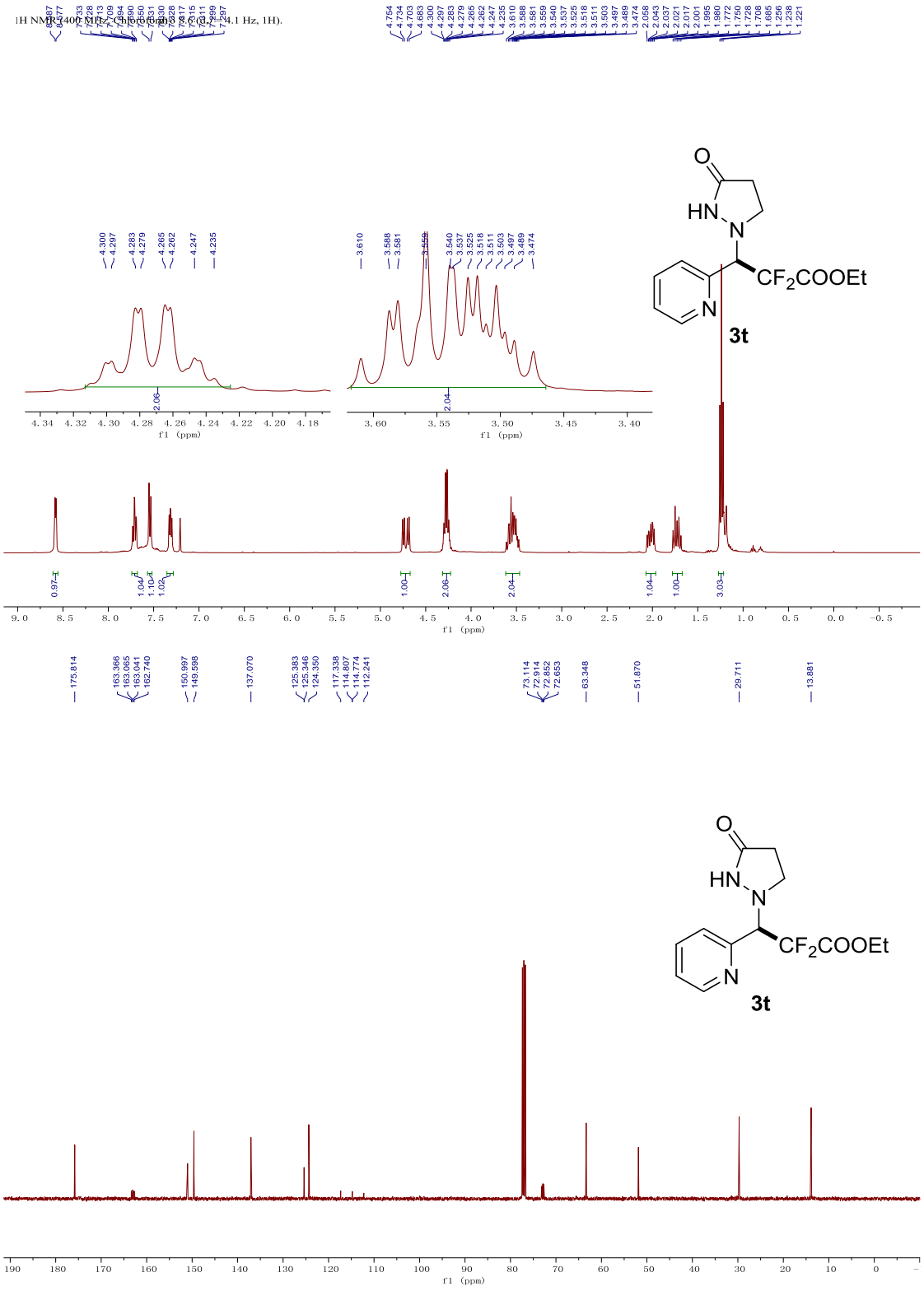

-104.946
-106.872
-107.570
-113.247
-113.944
O
HN
N
CF2COOEt
F
Br
3q
-100
-101
-102
-103
-104
-105
-106
-107
-108
-109
-110
-111
-112
-113
-114
-115
-116
-117
f1 (ppm)

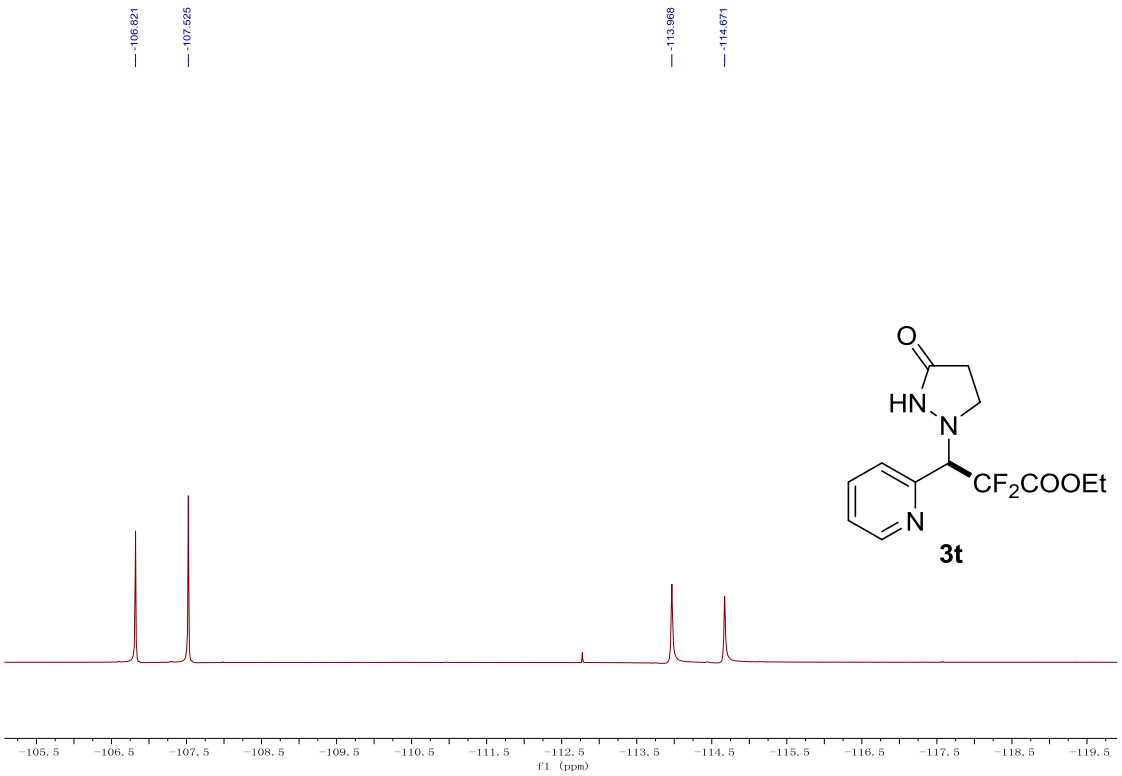

7.927
7.889
7.867
7.848
7.589
7.567
7.550
7.546
7.537
7.527
7.510
7.492
4.567
4.540
4.526
4.498
4.294
4.276
4.258
4.240
3.529
3.507
3.501
3.479
3.457
3.407
3.391
3.385
3.378
3.356
3.340
2.184
2.167
2.163
2.143
2.125
2.121
2.104
1.958
1.936
1.915
1.894
1.245
1.227
1.209
HN
N
O
CF2COOEt
3r
f1 (ppm)
175.528
163.312
162.998
133.642
132.955
130.706
128.707
128.249
127.717
127.686
127.179
126.928
126.736
115.132
112.576
72.588
72.358
72.135
63.317
51.756
29.726
13.840

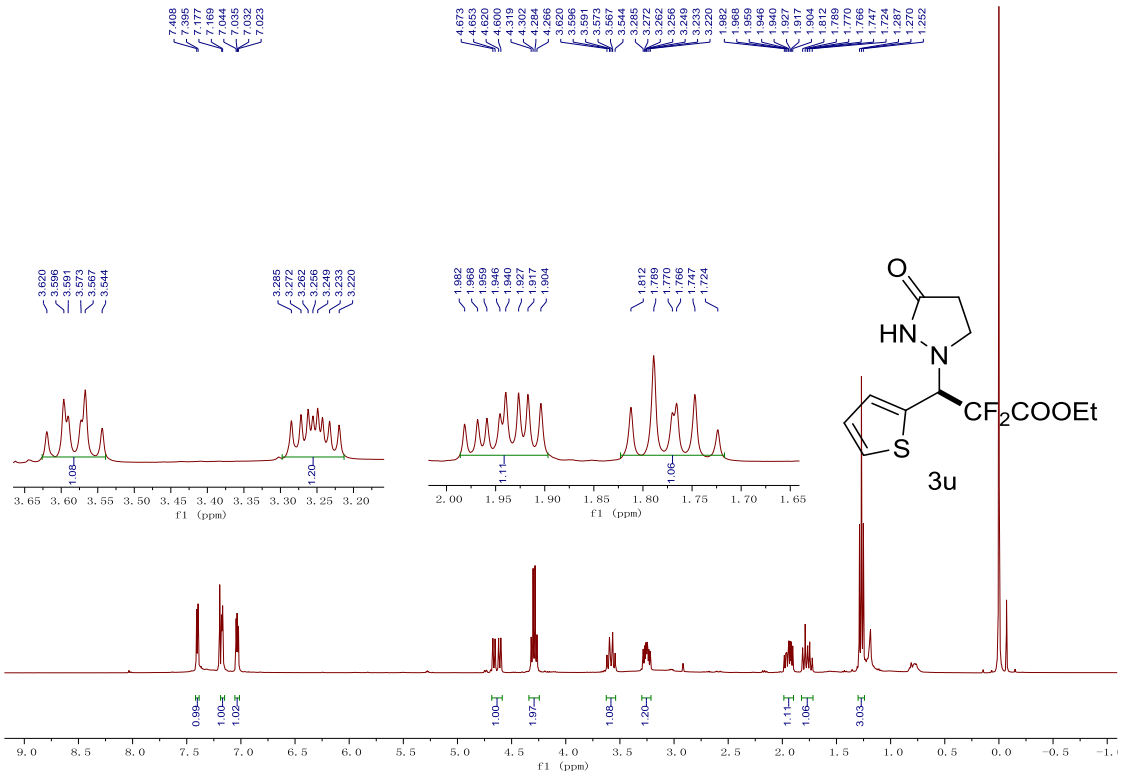

-108.030
-108.721
-111.166
-111.859
O
HN
N
CF2COOEt
3r
-105.5
-106.5
-107.5
-108.5
-109.5
-110.5
-111.5
-112.5
-113.5
-114.5
-115.5
-116.5
-117.5
-118.5
f1 (ppm)

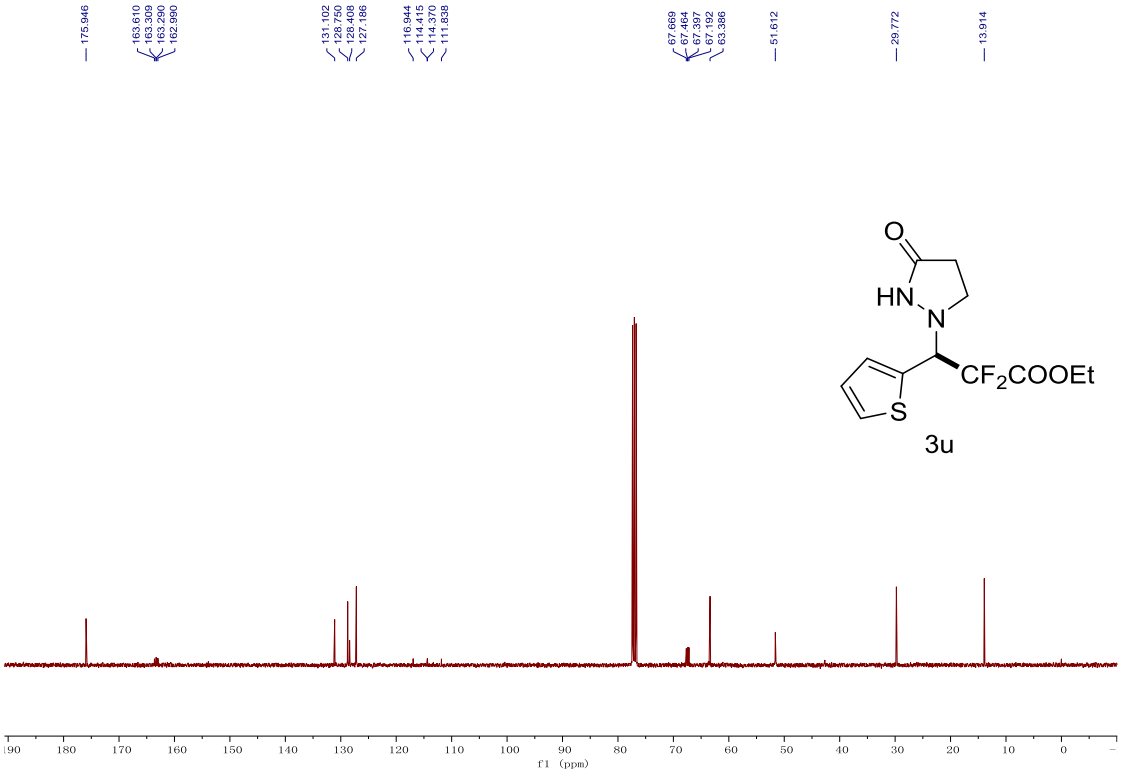

7.381
7.363
7.344
7.295
7.271
7.251
7.033
6.650
4.342
4.324
4.306
4.288
3.909
3.877
3.845
3.497
3.489
3.477
3.469
3.458
3.446
3.438
3.410
2.602
2.581
2.560
2.539
2.519
2.500
2.481
2.461
2.440
2.419
1.999
1.331
1.314
1.296
O
HN
N
CF2COOEt
3s
f1 (ppm)
f1 (ppm)
f1 (ppm)
175.108
163.589
163.276
162.961
135.977
135.491
129.844
128.989
128.358
127.589
117.868
115.297
112.719
76.092
75.881
75.665
63.342
51.191
29.759
15.977
13.957
A (t)
163.28
B (m)
115.29
(m)
5.88
f1 (ppm)

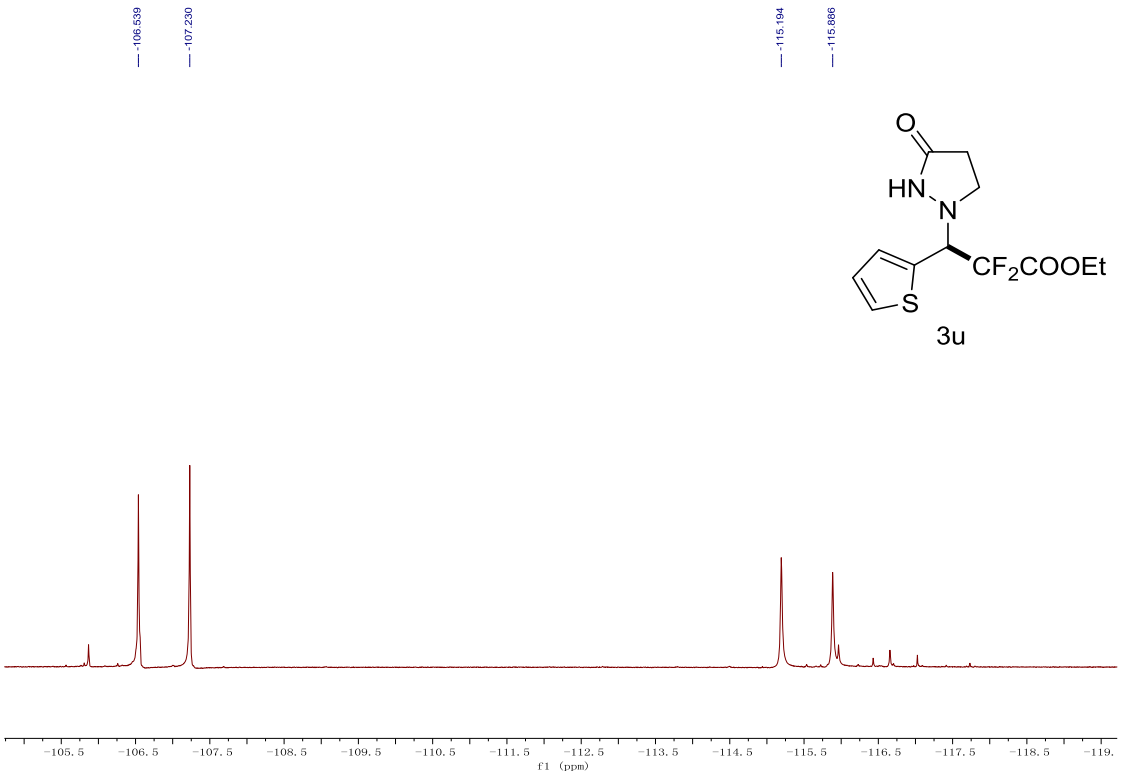

-107.087
-107.770
-108.815
-109.499
O
HN
N
CF2COOEt
3s
-105.2
-105.6
-106.0
-106.4
-106.8
-107.2
-107.6
-108.0
-108.4
-108.8
-109.2
-109.6
-110.0
f1 (ppm)


1H NMR (400 MHz, CDCl3)
4.754
4.734
4.703
4.683
4.300
4.297
4.283
4.279
4.265
4.262
4.247
4.235
3.610
3.588
3.581
3.559
3.540
3.537
3.525
3.518
3.511
3.503
3.497
3.489
3.474
2.058
2.043
2.037
2.021
2.017
2.001
1.995
1.980
1.772
1.750
1.728
1.708
1.685
1.256
1.238
1.221
O
HN
N
CF2COOEt
N
3t
f1 (ppm)
0.97
1.04
1.10
1.02
1.00
2.06
2.04
1.04
1.00
3.03
175.814
163.366
163.065
163.041
162.740
150.997
149.598
137.070
125.383
125.346
124.350
117.338
114.807
114.774
112.241
73.114
72.914
72.852
72.653
63.348
51.870
29.711
13.881

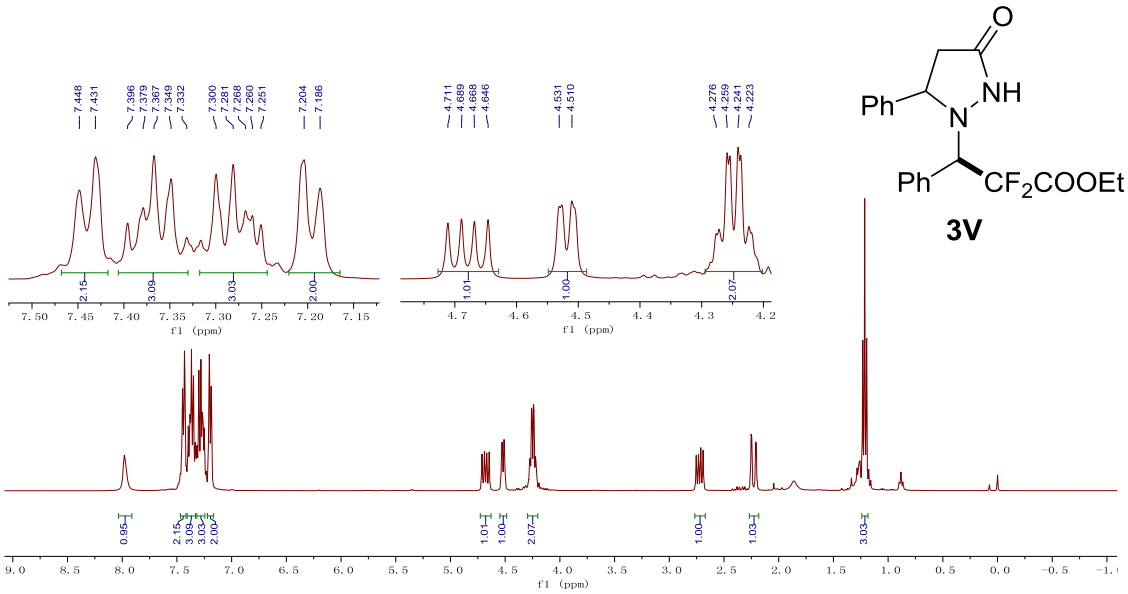

-106.821
-107.525
-113.968
-114.671
O
HN
N
CF2COOEt
N
3t
−105.5
−106.5
−107.5
−108.5
−109.5
−110.5
−111.5
−112.5
−113.5
−114.5
−115.5
−116.5
−117.5
−118.5
−119.5
f1 (ppm)


3u

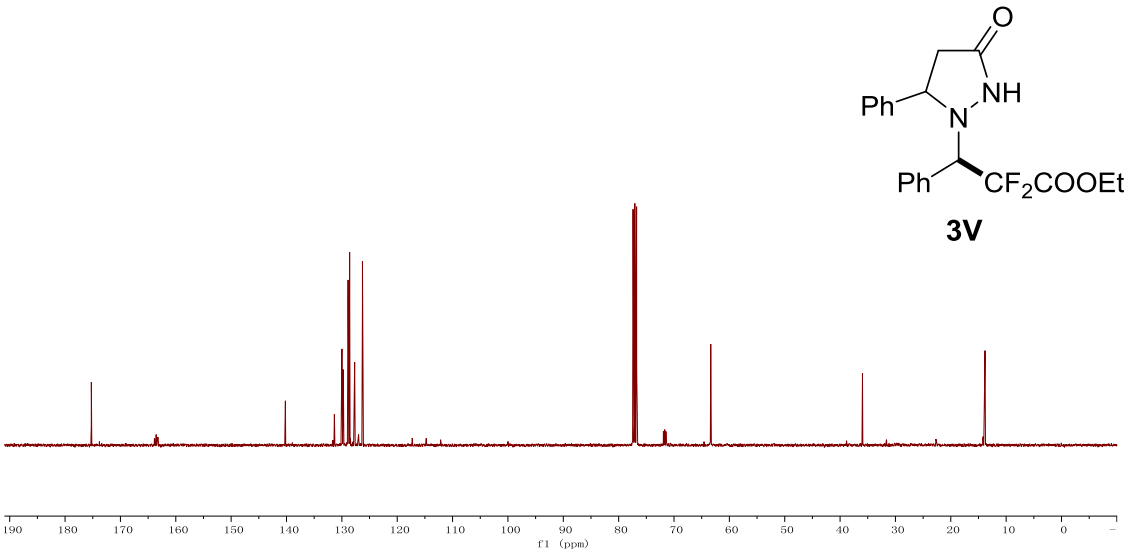

3u


-106.539
-107.230
-115.194
-115.886
O
HN
N
CF2COOEt
S
3u
−105.5
−106.5
−107.5
−108.5
−109.5
−110.5
−111.5
−112.5
−113.5
−114.5
−115.5
−116.5
−117.5
−118.5
−119.
f1 (ppm)

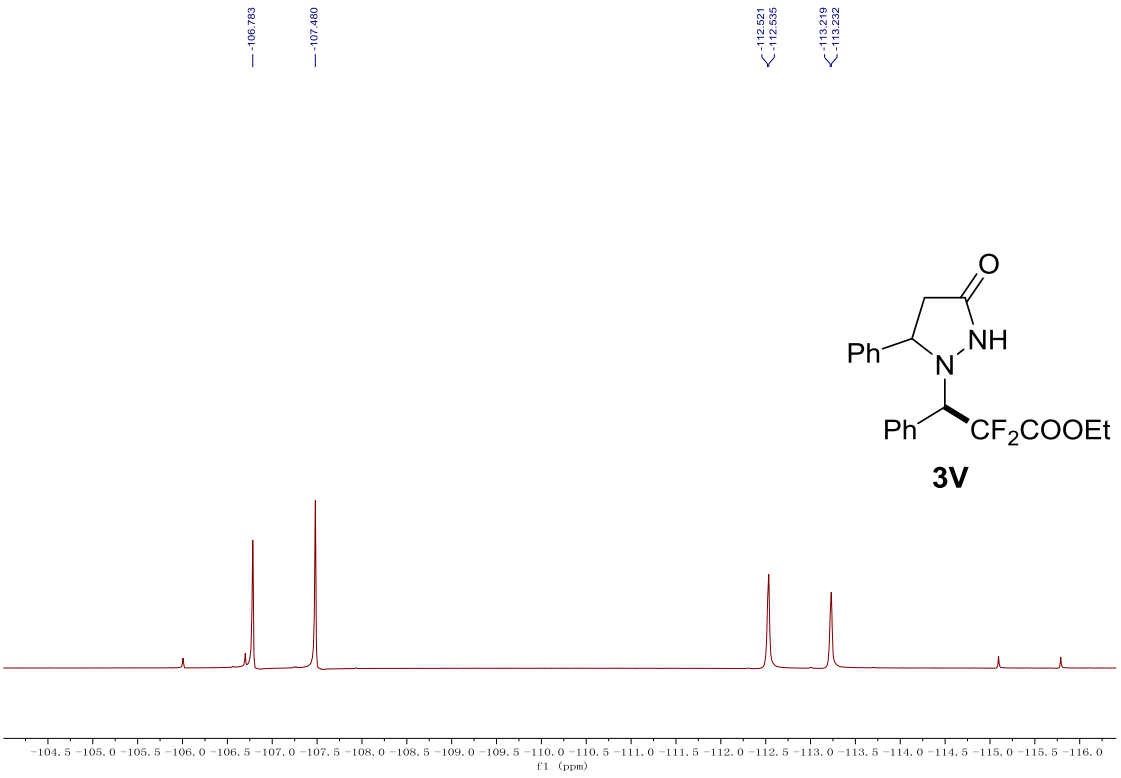
1H NMR (400 MHz, Chloroform-d) δ 7.7 (dd, J = 7.2, 8.9 Hz, 1H), 2.7 (dd, J = 7.1, 11.

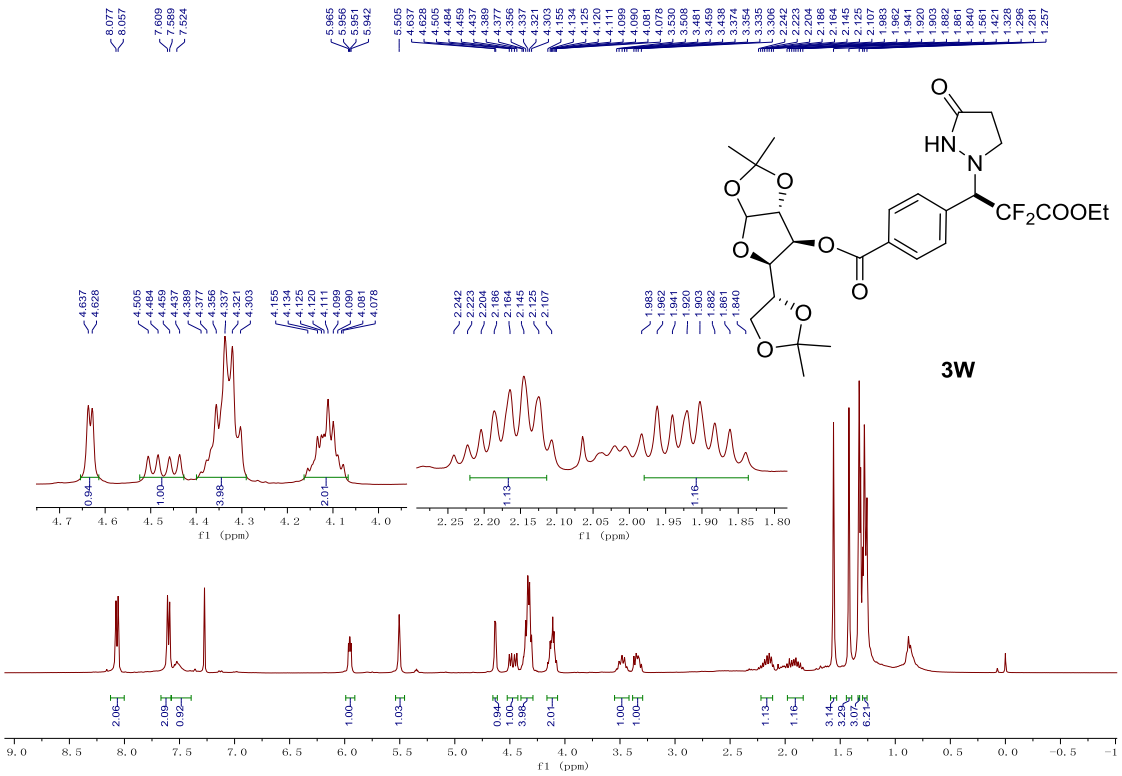


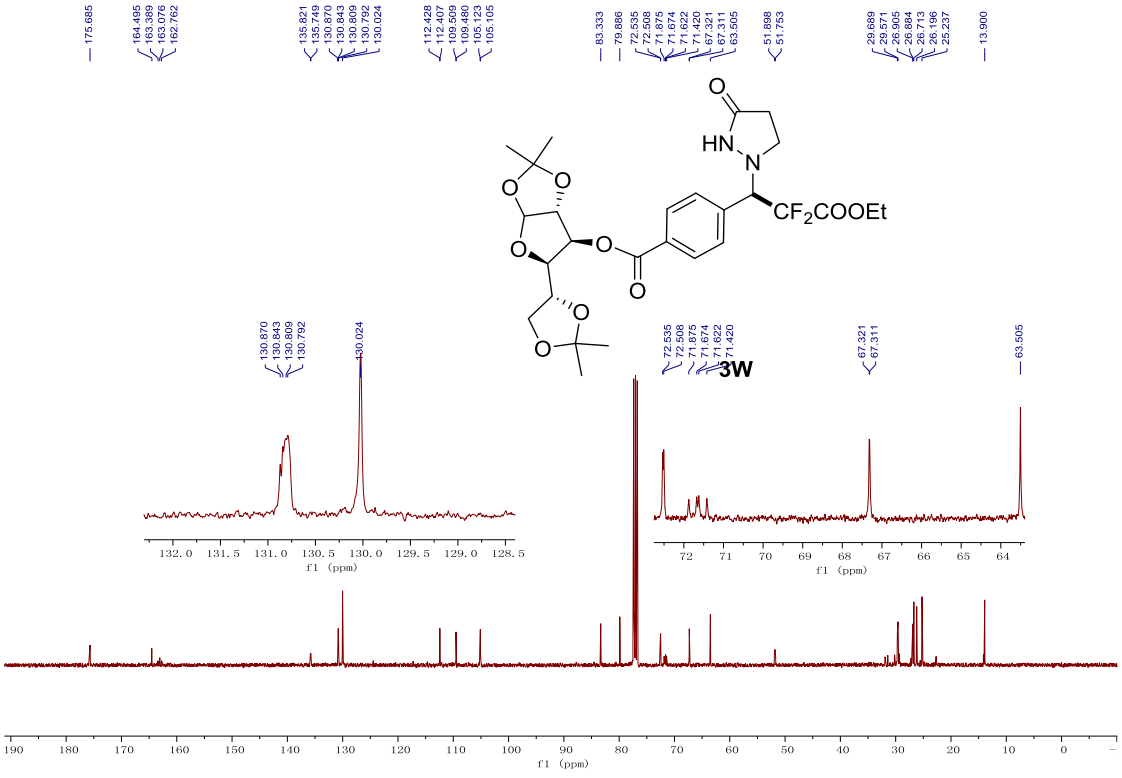
3V

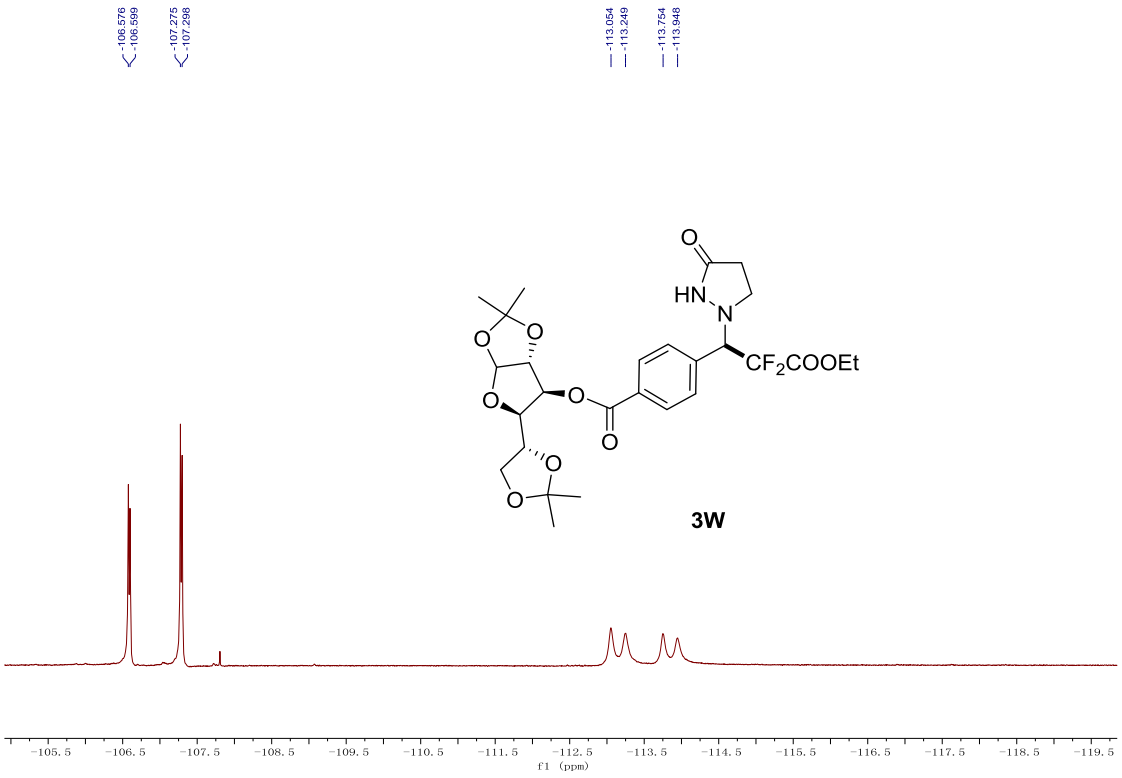


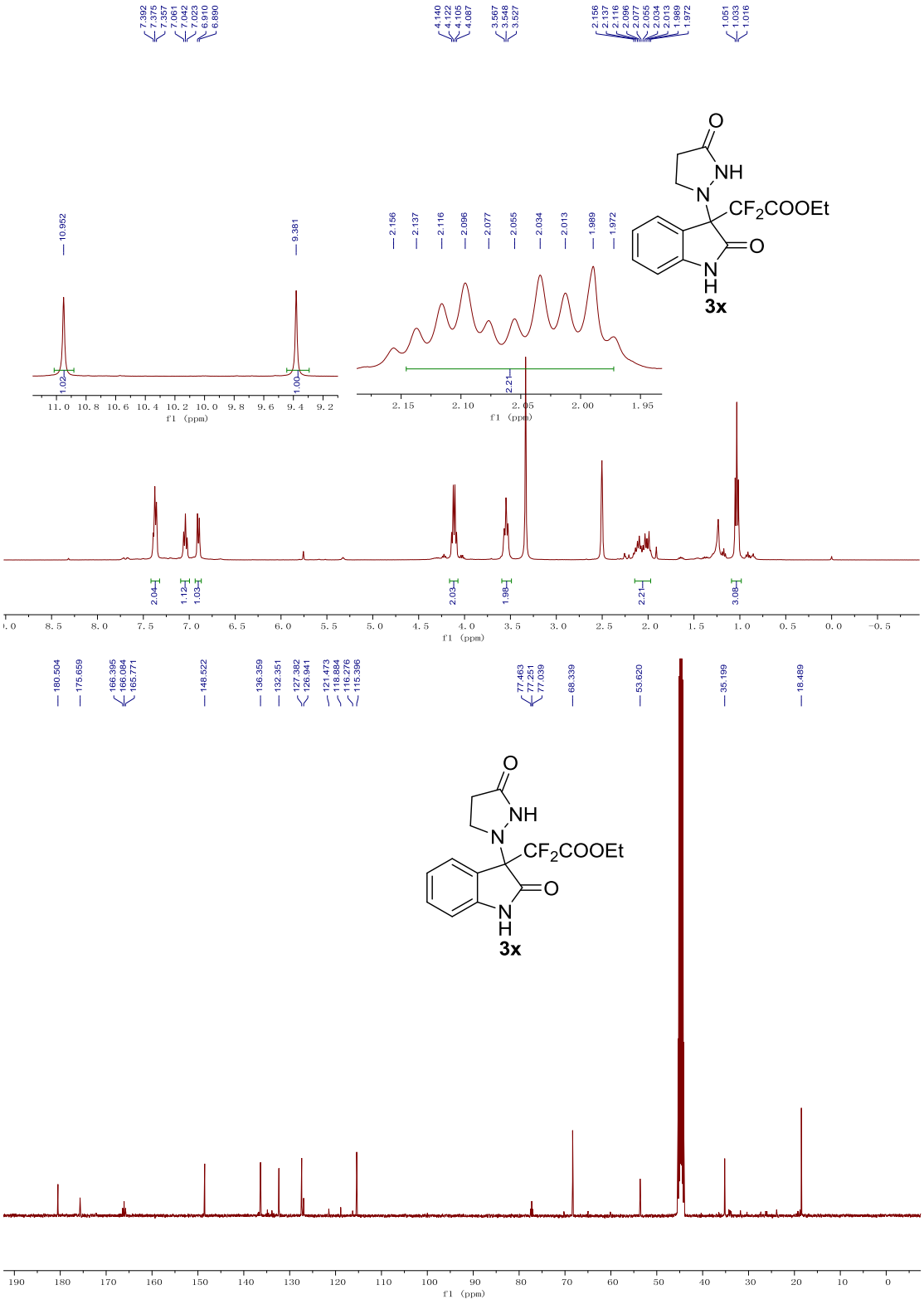
3V

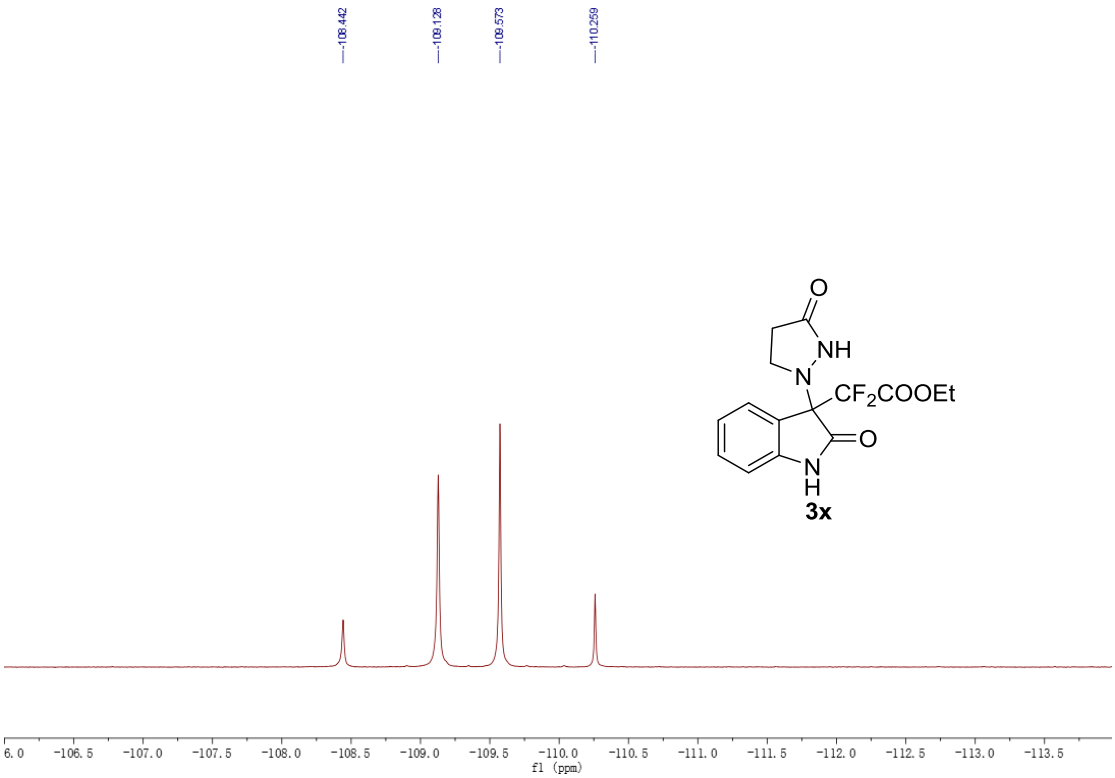

-106.783
-107.480
-112.521
-112.535
-113.219
-113.232
O
NH
Ph
N
Ph
CF2COOEt
3V
−104.5 −105.0 −105.5 −106.0 −106.5 −107.0 −107.5 −108.0 −108.5 −109.0 −109.5 −110.0 −110.5 −111.0 −111.5 −112.0 −112.5 −113.0 −113.5 −114.0 −114.5 −115.0 −115.5 −116.0
f1 (ppm)

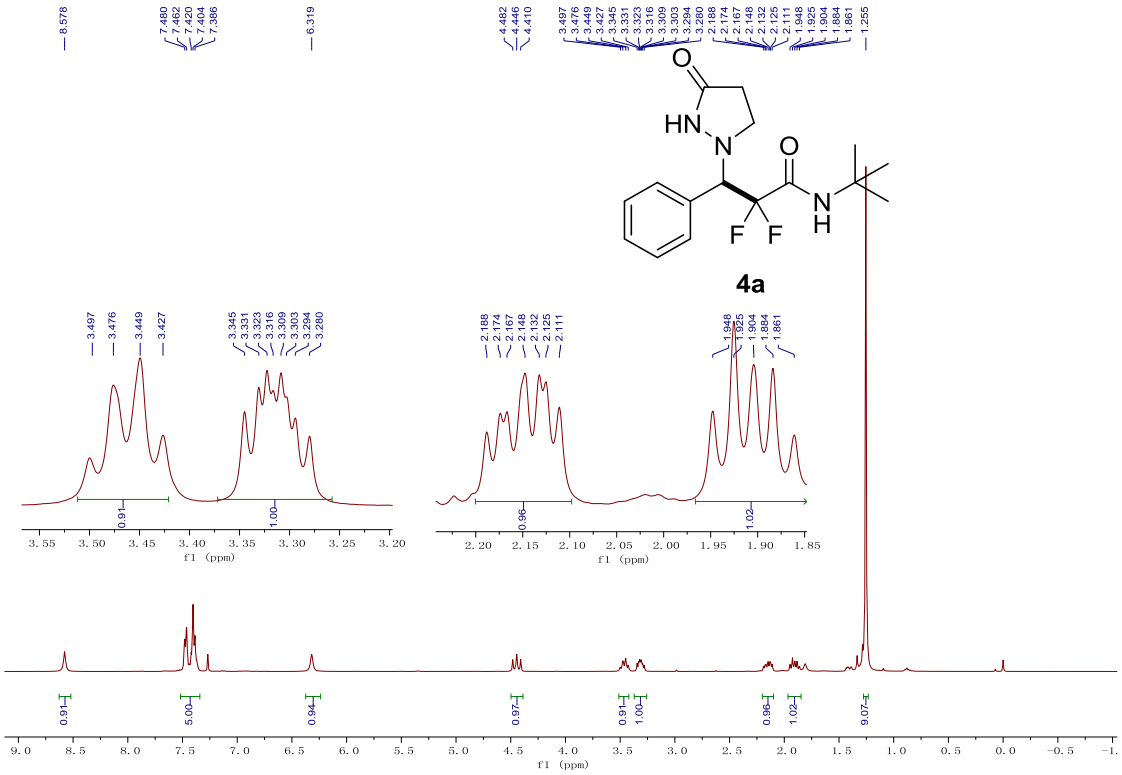

3W

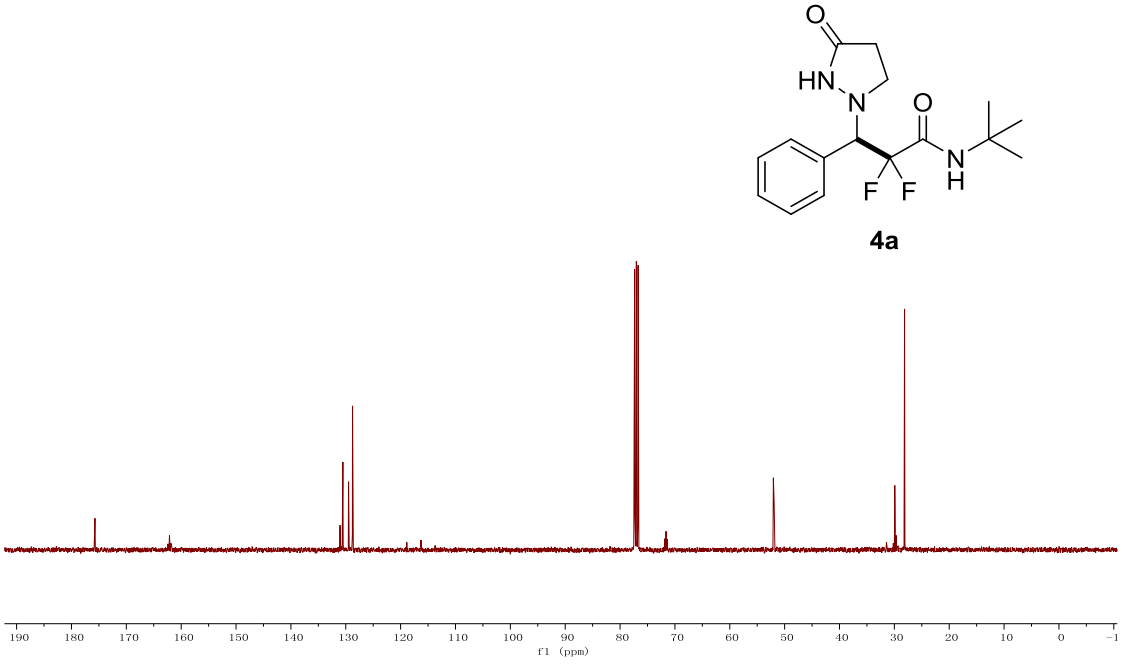

3W

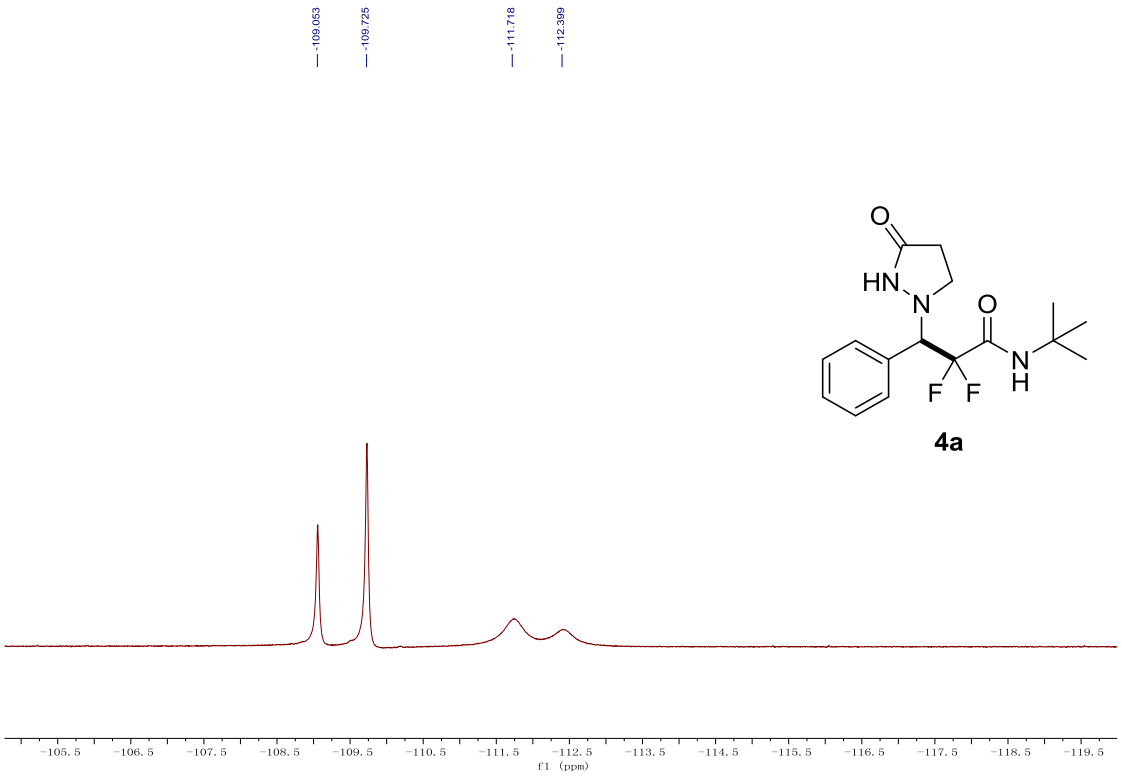

-106.576
-106.599
-107.275
-107.298
-113.054
-113.249
-113.754
-113.948
O
HN
N
O
O
O
O
O
O
O
O
CF2COOEt
3W
−105.5
−106.5
−107.5
−108.5
−109.5
−110.5
−111.5
−112.5
−113.5
−114.5
−115.5
−116.5
−117.5
−118.5
−119.5
f1 (ppm)

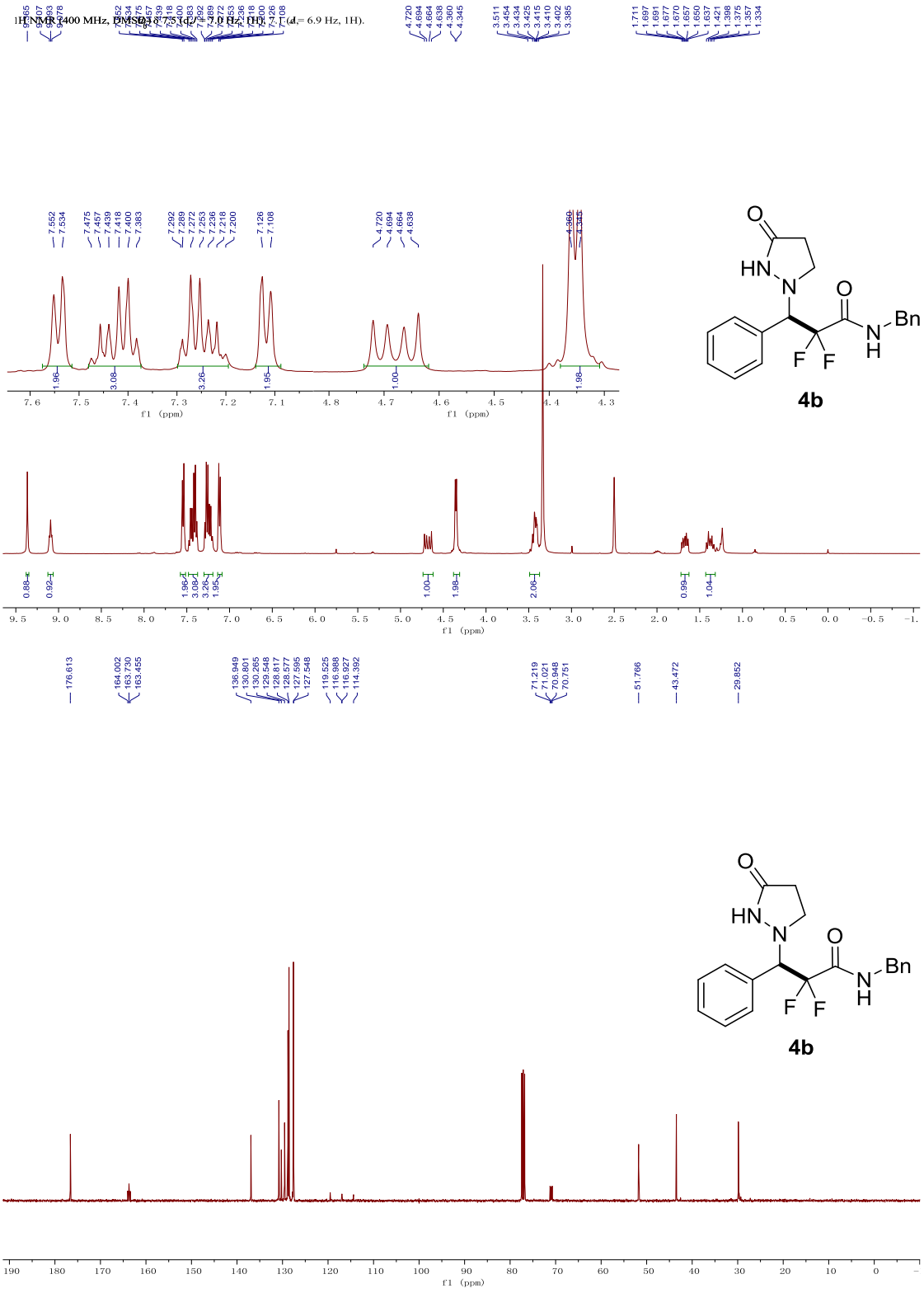

7.392
7.376
7.357
7.061
7.042
7.023
6.910
6.890
4.140
4.122
4.105
4.087
3.567
3.548
3.527
2.156
2.137
2.116
2.096
2.077
2.055
2.034
2.013
1.989
1.972
1.051
1.033
1.016
10.952
9.381
1.02
1.00
f1 (ppm)
2.21
2.04
1.12
1.03
2.03
1.98
2.21
3.08
180.504
175.659
166.395
166.084
165.771
148.522
136.359
132.351
127.382
126.941
121.473
118.884
116.276
115.396
77.463
77.251
77.039
68.339
53.620
35.199
18.489
CF2COOEt
3x

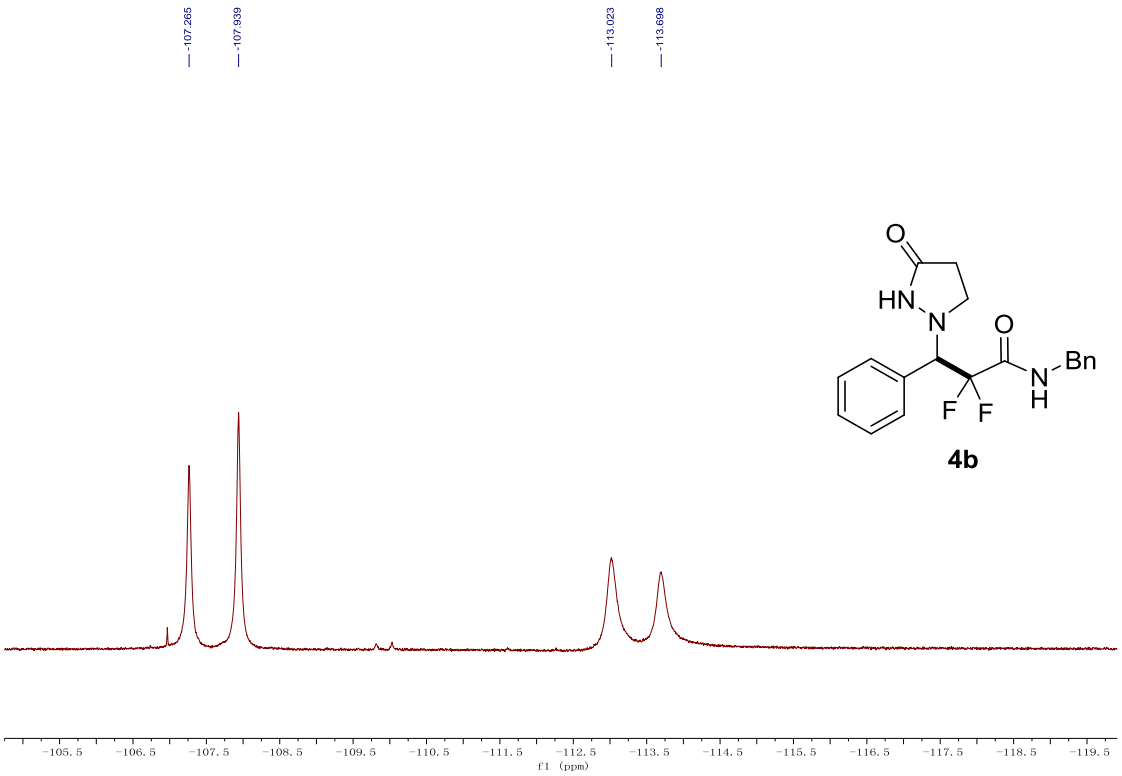

-108.442
-109.128
-109.573
-110.259
O
NH
N
CF2COOEt
O
N
H
3x
6.0
-106.5
-107.0
-107.5
-108.0
-108.5
-109.0
-109.5
-110.0
-110.5
-111.0
-111.5
-112.0
-112.5
-113.0
-113.5
f1 (ppm)

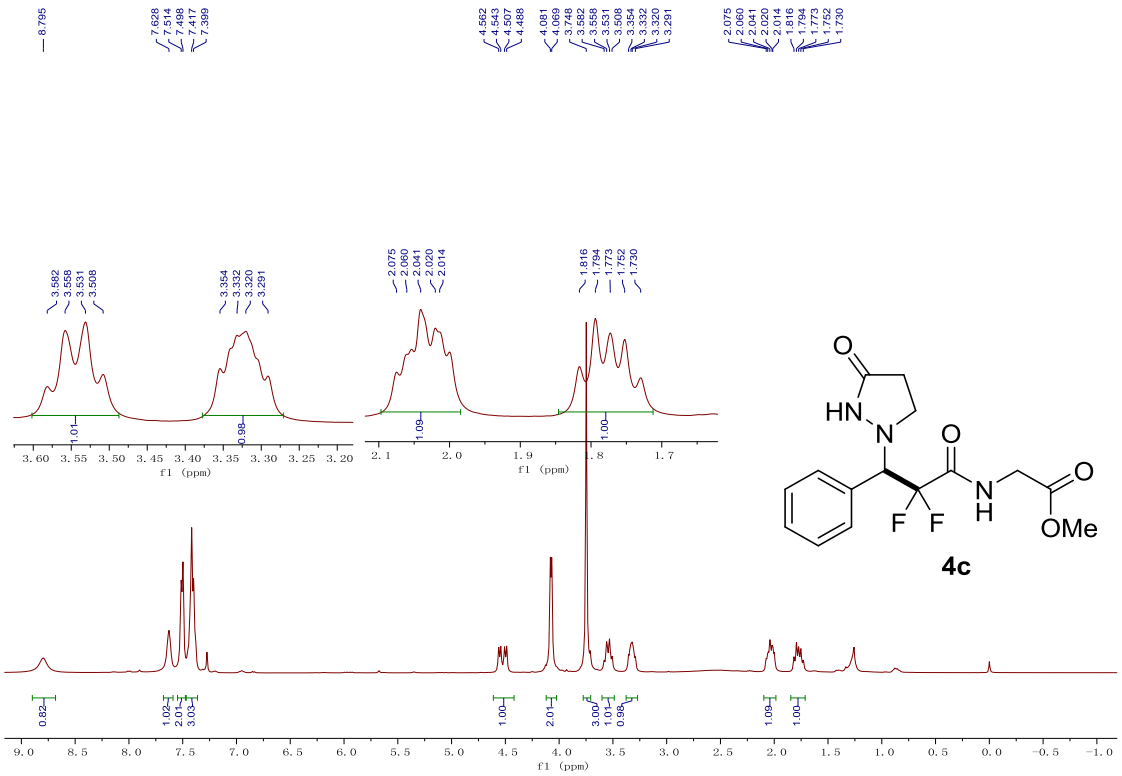

8.578
7.480
7.462
7.420
7.404
7.386
6.319
4.482
4.446
4.410
3.497
3.476
3.449
3.427
3.345
3.331
3.323
3.316
3.309
3.303
3.294
3.280
2.188
2.174
2.167
2.148
2.132
2.125
2.111
1.948
1.925
1.904
1.884
1.861
1.255
HN
N
O
O
N
H
F F
4a
f1 (ppm)

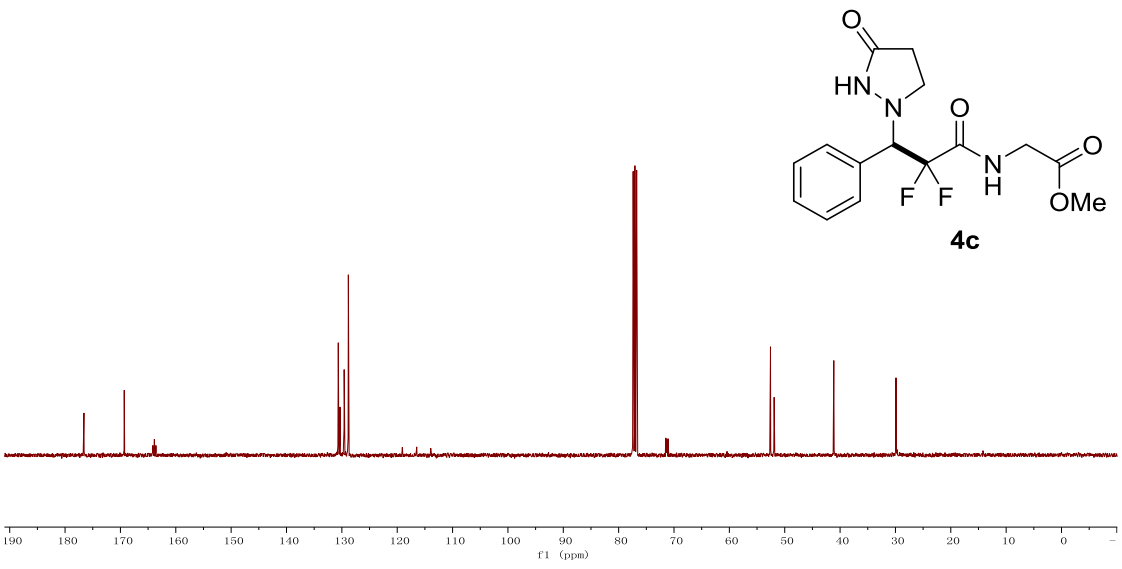

175.718
162.398
162.136
161.877
131.037
130.522
129.487
128.765
118.871
116.292
71.845
71.622
71.395
52.054
51.913
29.921
28.140
HN
N
O
O
N
H
F F
4a
f1 (ppm)

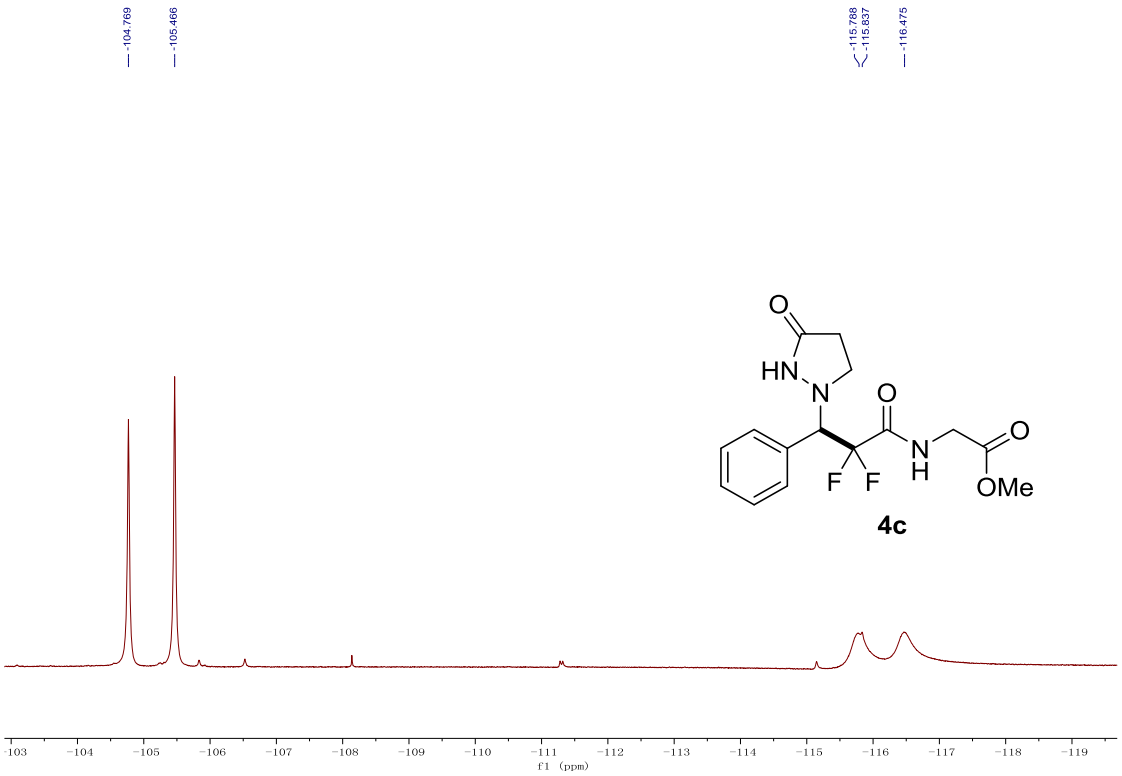

-109.053
-109.725
-111.718
-112.399
O
HN
N
O
N
H
F F
4a
-105.5
-106.5
-107.5
-108.5
-109.5
-110.5
-111.5
-112.5
-113.5
-114.5
-115.5
-116.5
-117.5
-118.5
-119.5
f1 (ppm)

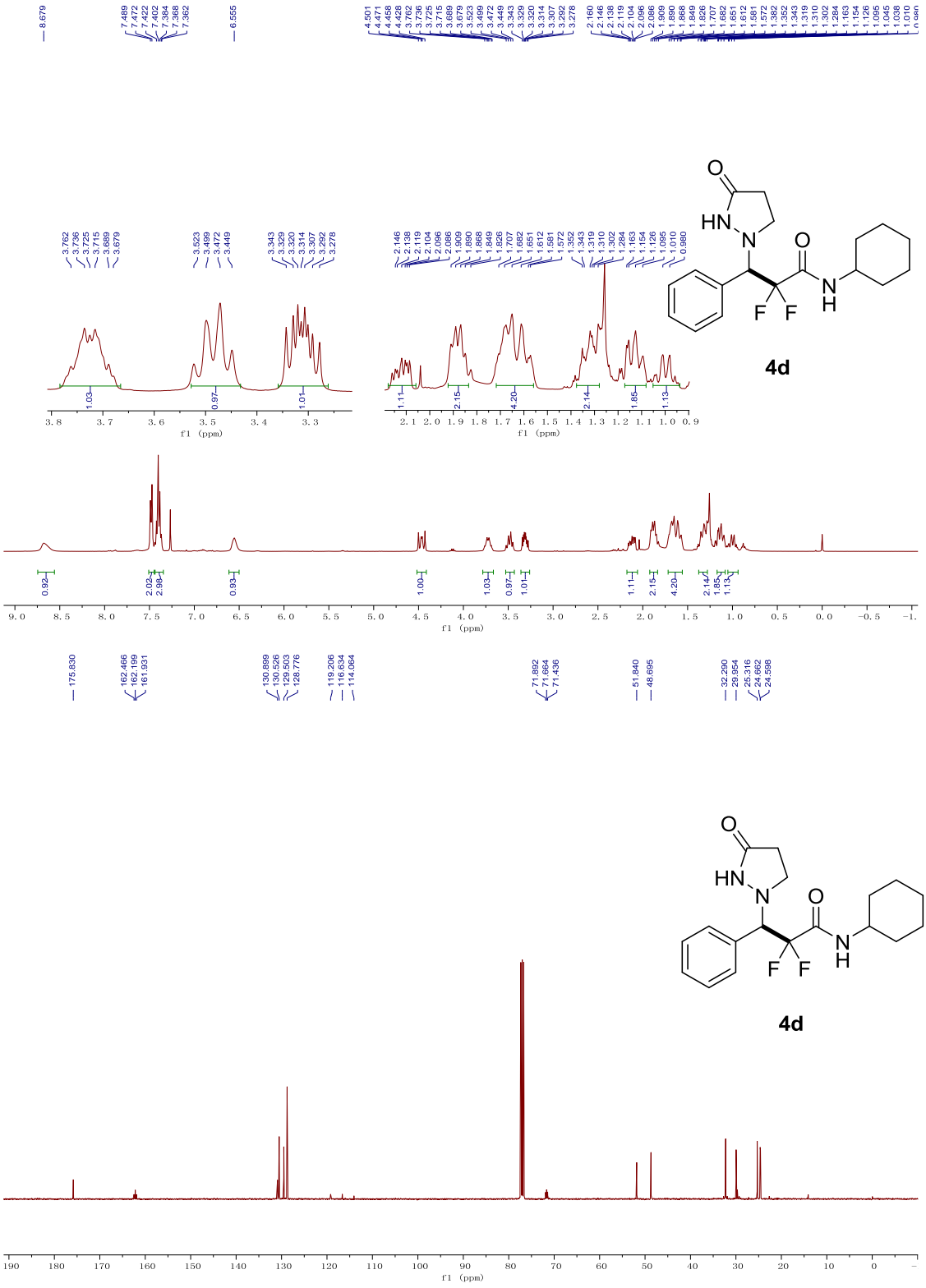

4b
4b

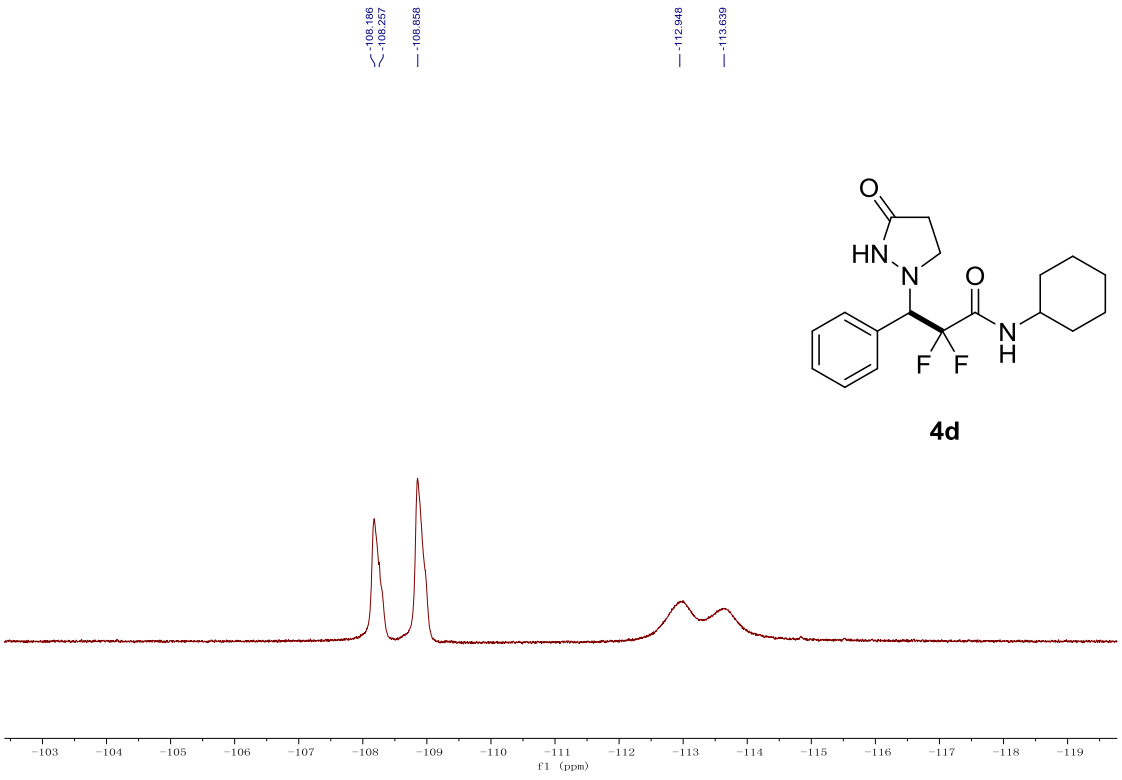

-107.265
-107.939
-113.023
-113.698
O
HN
N
O
N
H
Bn
F
F
4b
−105.5
−106.5
−107.5
−108.5
−109.5
−110.5
−111.5
−112.5
−113.5
−114.5
−115.5
−116.5
−117.5
−118.5
−119.5
f1 (ppm)

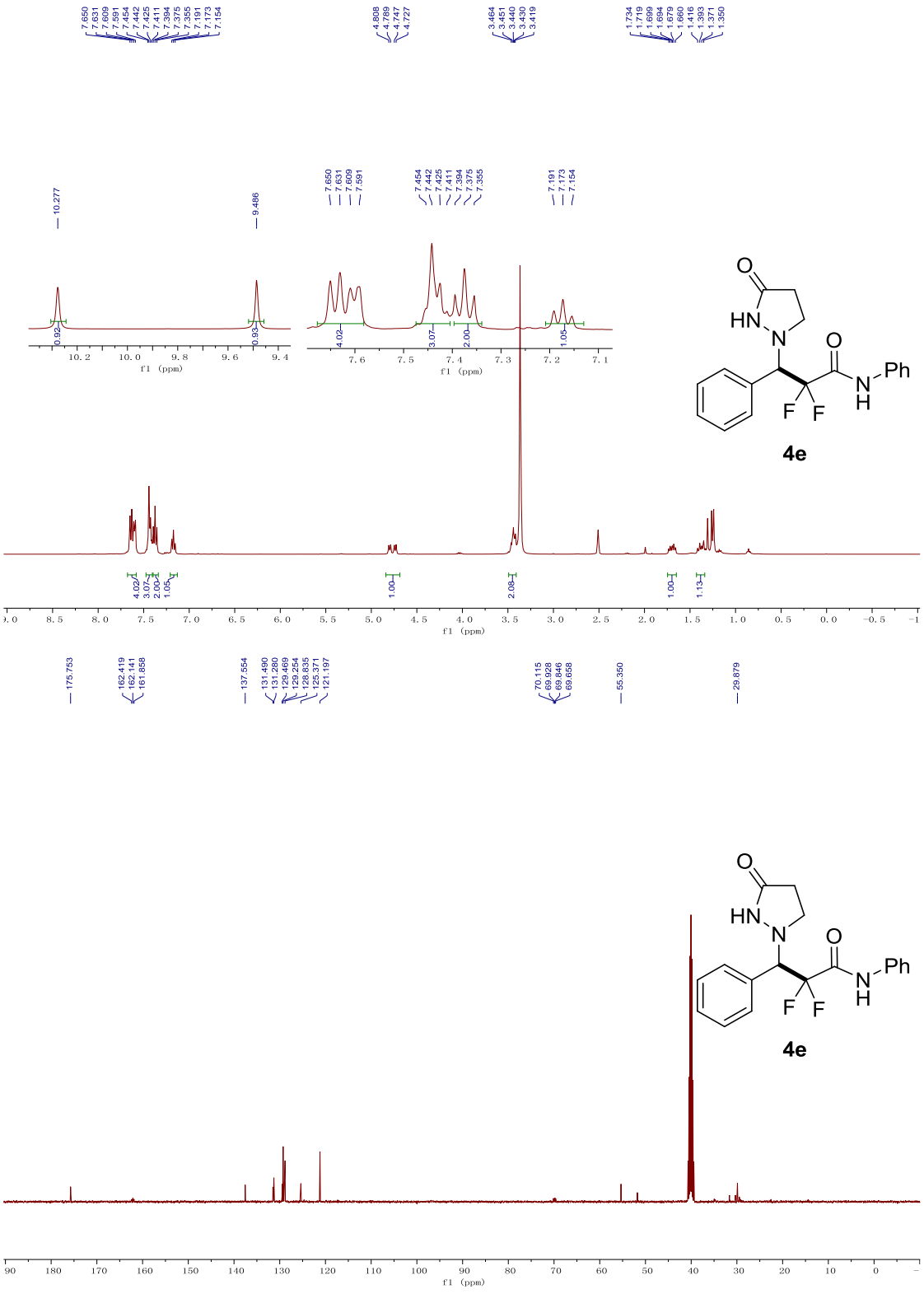

8.795
7.628
7.514
7.498
7.417
7.399
4.562
4.543
4.507
4.488
4.081
4.069
3.748
3.582
3.558
3.531
3.508
3.354
3.332
3.320
3.291
2.075
2.060
2.041
2.020
2.014
1.816
1.794
1.773
1.752
1.730
f1 (ppm)
4c

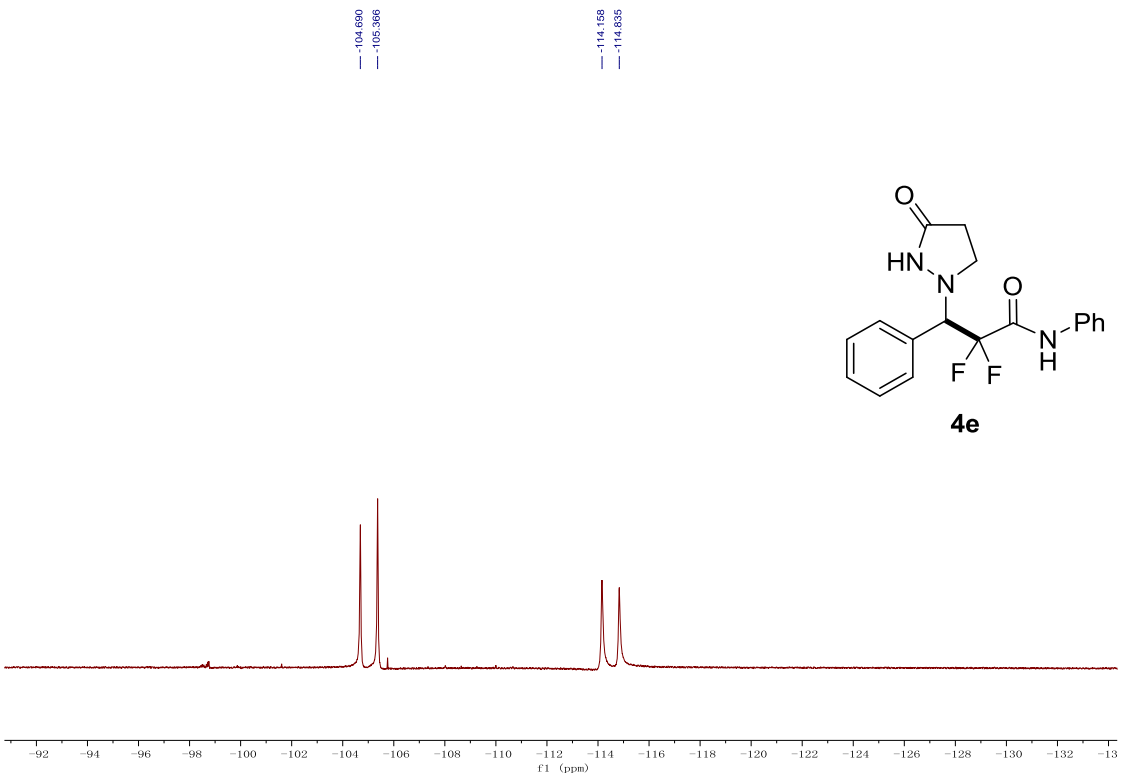

176.594
169.312
164.153
163.872
163.589
130.648
130.328
129.587
128.827
119.075
116.546
115.451
113.948
71.506
71.307
71.236
71.038
52.571
51.911
41.132
29.900
f1 (ppm)
4c


-104.769
-105.466
-115.788
-115.837
-116.475
O
HN
N
O
N
H
O
OMe
F
F
4c
-103
-104
-105
-106
-107
-108
-109
-110
-111
-112
-113
-114
-115
-116
-117
-118
-119
f1 (ppm)

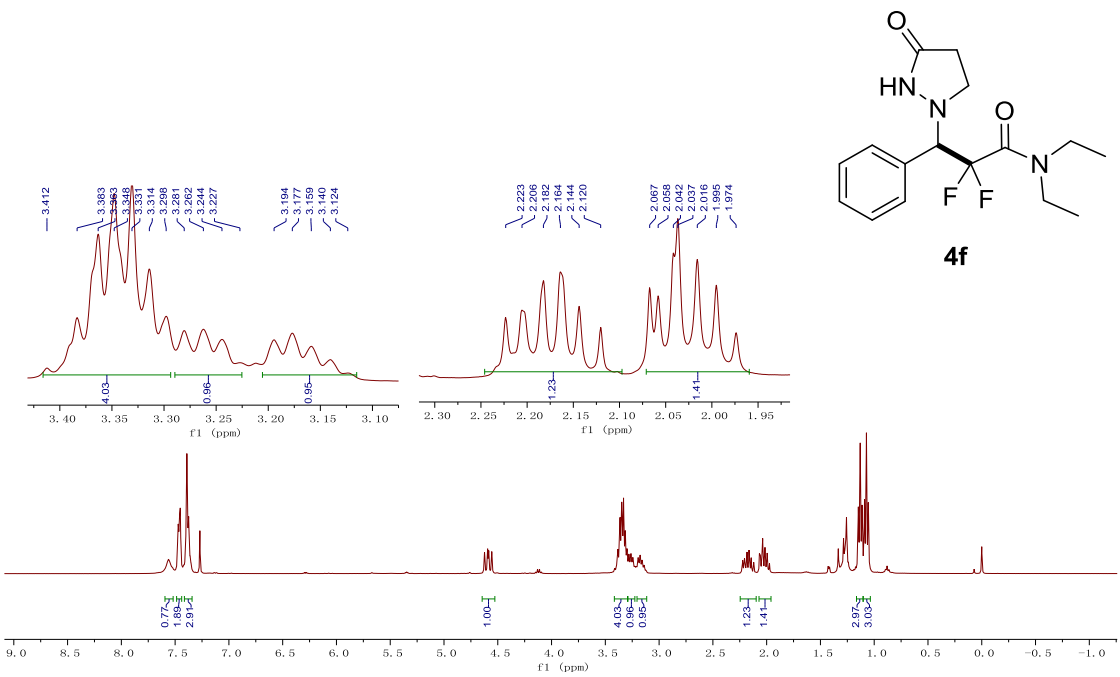

4d
f1 (ppm)
4d
f1 (ppm)


-108.186
-108.257
-108.658
-112.948
-113.639
O
HN
N
O
N
H
F
F
4d
−103
−104
−105
−106
−107
−108
−109
−110
−111
−112
−113
−114
−115
−116
−117
−118
−119
f1 (ppm)

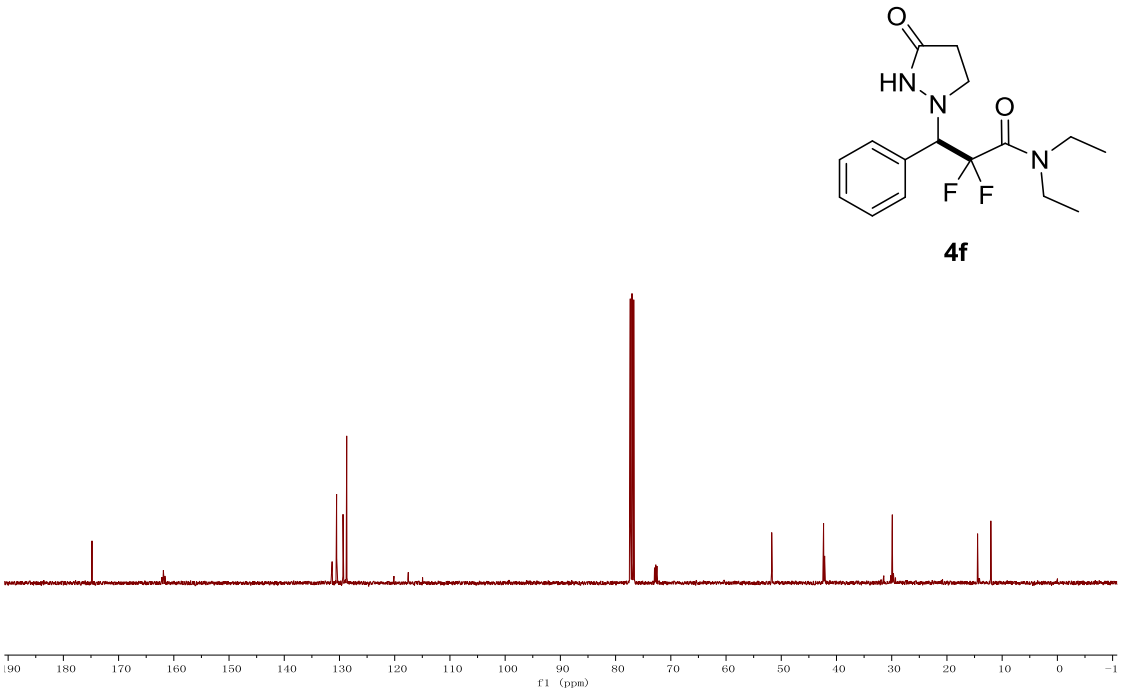

7.650
7.631
7.609
7.591
7.454
7.442
7.425
7.411
7.394
7.375
7.355
7.191
7.173
7.154
4.808
4.789
4.747
4.727
3.464
3.451
3.440
3.430
3.419
1.734
1.719
1.699
1.694
1.679
1.660
1.416
1.393
1.371
1.350
10.277
9.486
0.92
0.93
4.02
3.07
2.00
1.05
1.00
2.08
1.00
1.13
f1 (ppm)
HN
N
O
O
N
H
Ph
F
F
4e
175.753
162.419
162.141
161.858
137.554
131.490
131.280
129.469
129.254
128.835
125.371
121.197
70.115
69.928
69.846
69.658
55.350
29.879
f1 (ppm)
HN
N
O
O
N
H
Ph
F
F
4e


-104.690
-105.366
-114.158
-114.835
O
HN
N
O
N
H
Ph
F
F
4e
-92
-94
-96
-98
-100
-102
-104
-106
-108
-110
-112
-114
-116
-118
-120
-122
-124
-126
-128
-130
-132
-13
f1 (ppm)

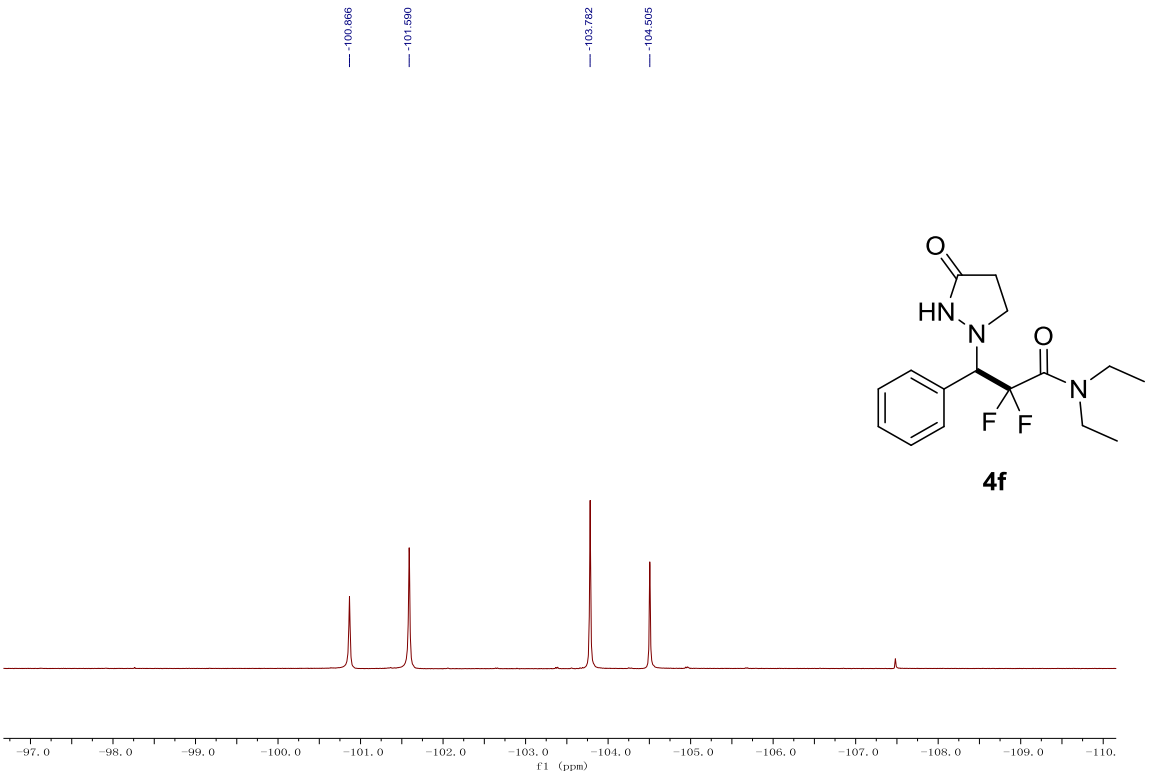
¹H NMR (400 MHz, CDCl₃) δ 4.6 (dd, *J* = 15.5, 11.6 Hz, 1H).

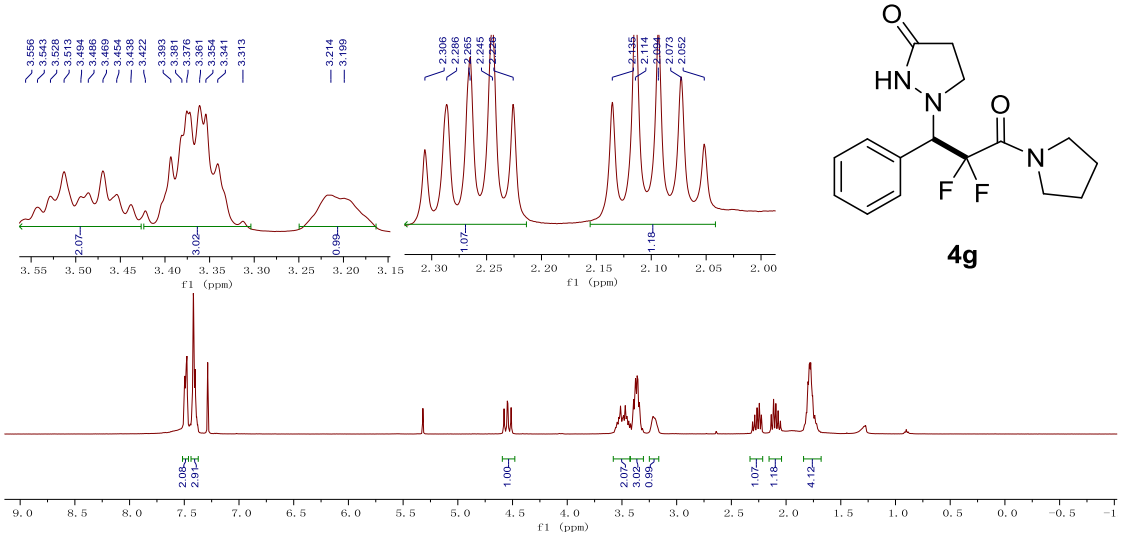


4f

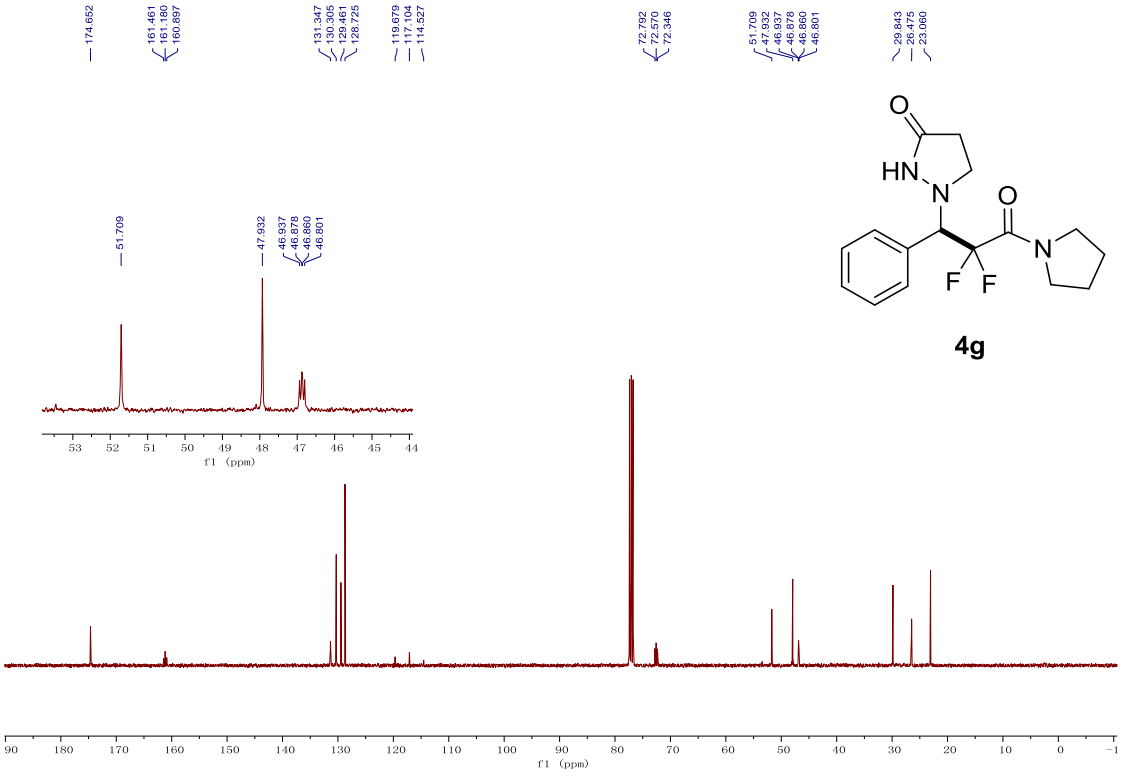


4f

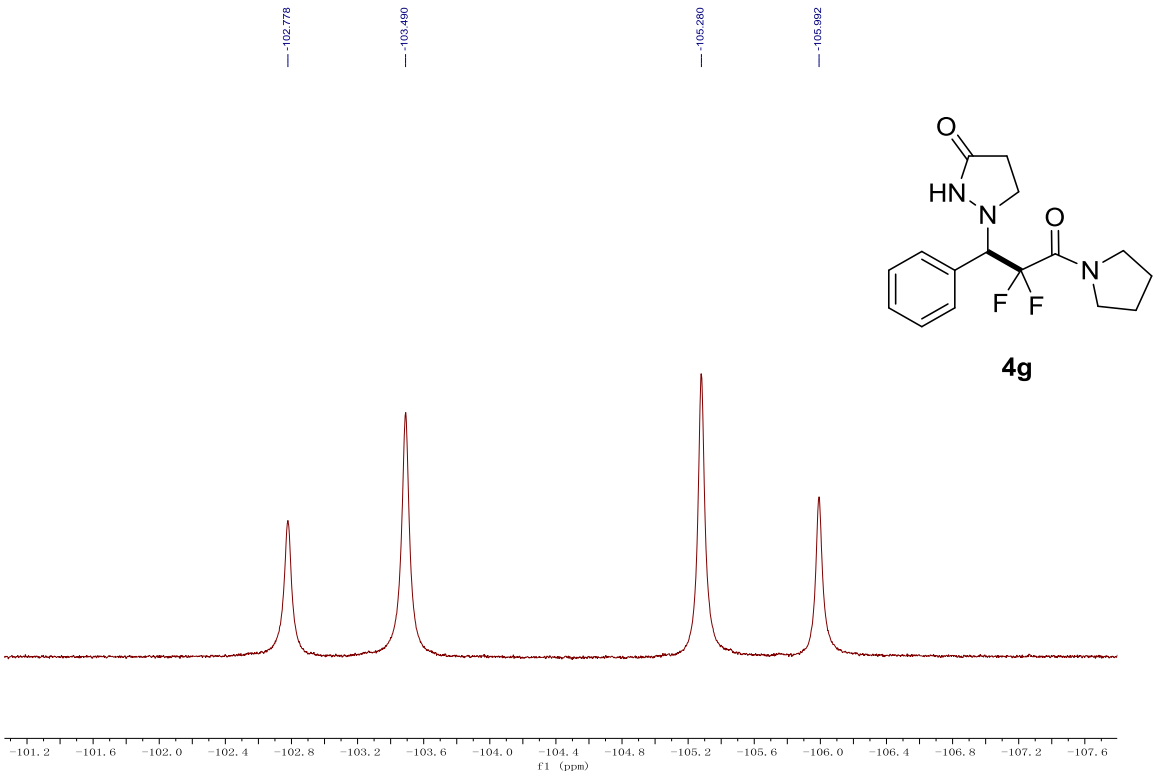

-100.866
-101.590
-103.782
-104.505
O
HN
N
O
N
F
F
4f
-97.0
-98.0
-99.0
-100.0
-101.0
-102.0
-103.0
-104.0
-105.0
-106.0
-107.0
-108.0
-109.0
-110.
f1 (ppm)

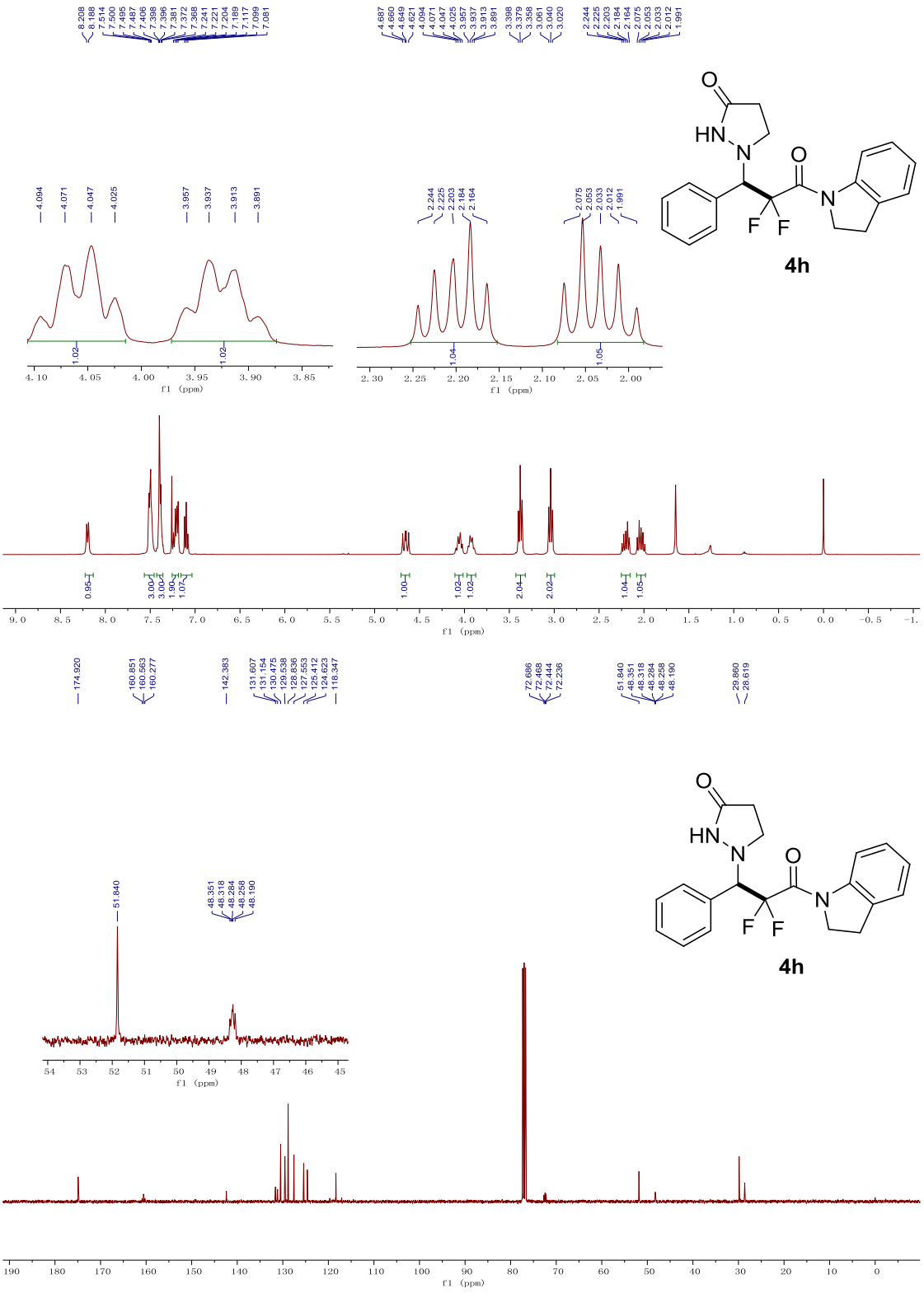


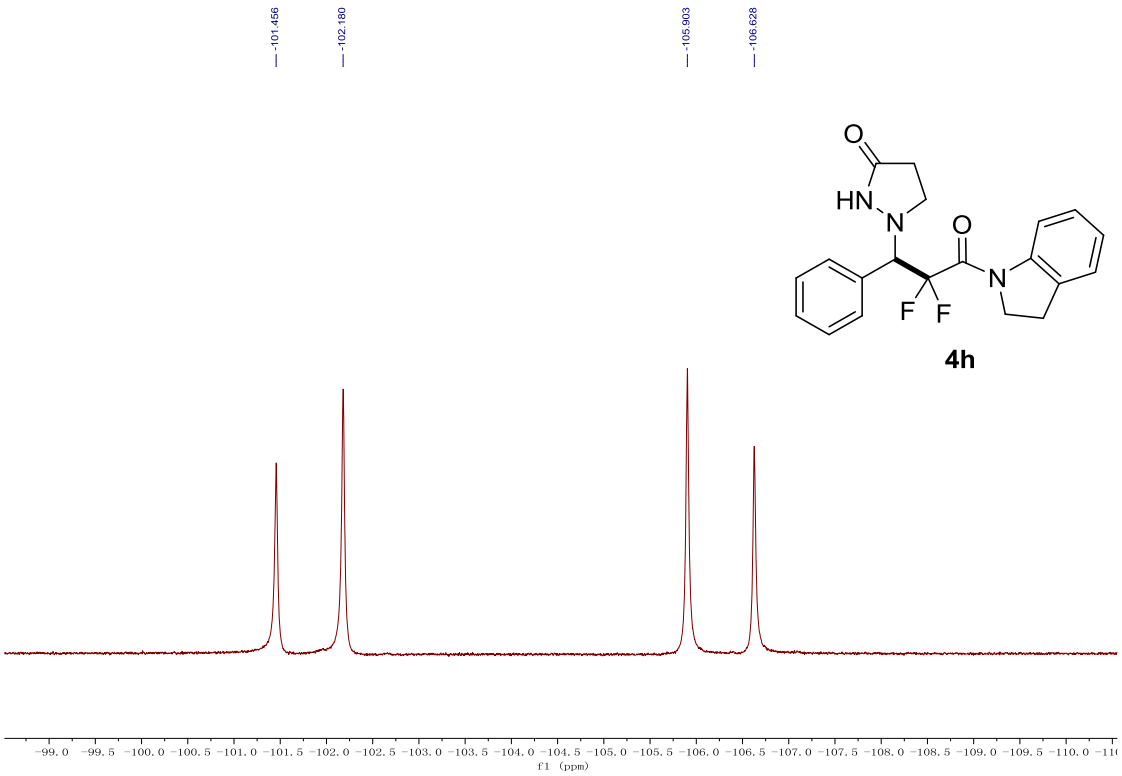
4g



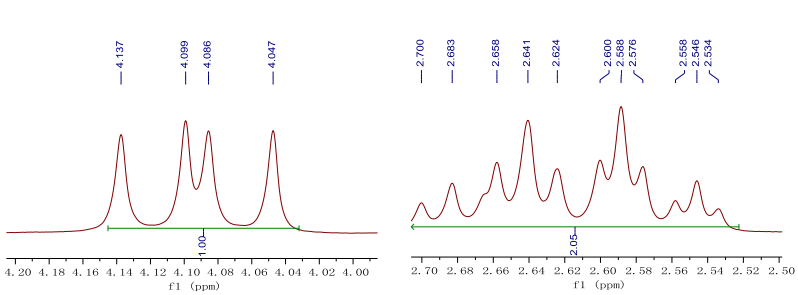
4g

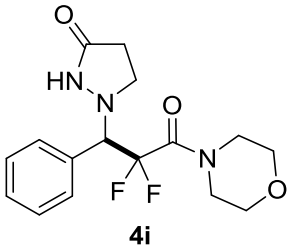

-102.778
-103.490
-105.280
-105.992
O
HN
N
O
N
F
F
4g
−101.2
−101.6
−102.0
−102.4
−102.8
−103.2
−103.6
−104.0
−104.4
−104.8
−105.2
−105.6
−106.0
−106.4
−106.8
−107.2
−107.6
f1 (ppm)


4h
4h

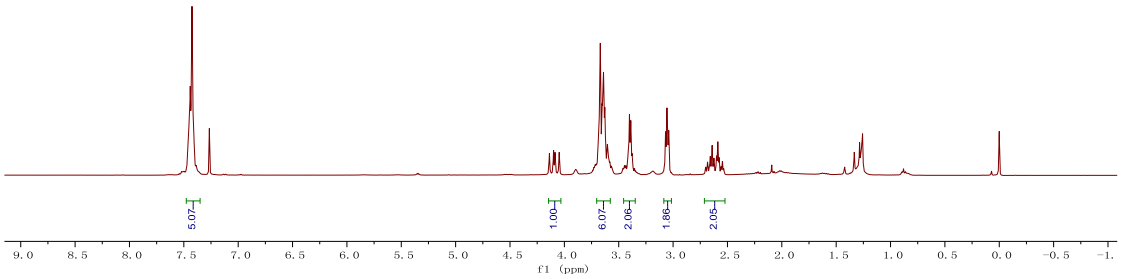

-101.456
-102.180
-105.903
-106.628
O
HN
N
O
N
F
F
4h
-99.0 -99.5 -100.0 -100.5 -101.0 -101.5 -102.0 -102.5 -103.0 -103.5 -104.0 -104.5 -105.0 -105.5 -106.0 -106.5 -107.0 -107.5 -108.0 -108.5 -109.0 -109.5 -110.0
f1 (ppm)


7.459
7.450
7.441
7.425
7.419
7.388
4.137
4.099
4.086
4.047
3.669
3.652
3.640
3.628
3.604
3.596
3.461
3.447
3.412
3.401
3.389
3.377
3.356
3.069
3.056
3.040
2.700
2.683
2.658
2.641
2.624
2.600
2.588
2.576
2.558
2.546
2.534

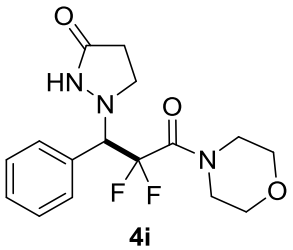

4.137
4.099
4.086
4.047
1.00
4.20 4.18 4.16 4.14 4.12 4.10 4.08 4.06 4.04 4.02 4.00
f1 (ppm)
2.700
2.683
2.658
2.641
2.624
2.600
2.588
2.576
2.558
2.546
2.534
2.05
2.70 2.68 2.66 2.64 2.62 2.60 2.58 2.56 2.54 2.52 2.50
f1 (ppm)


O
HN
N
O
N
O
F F

4i

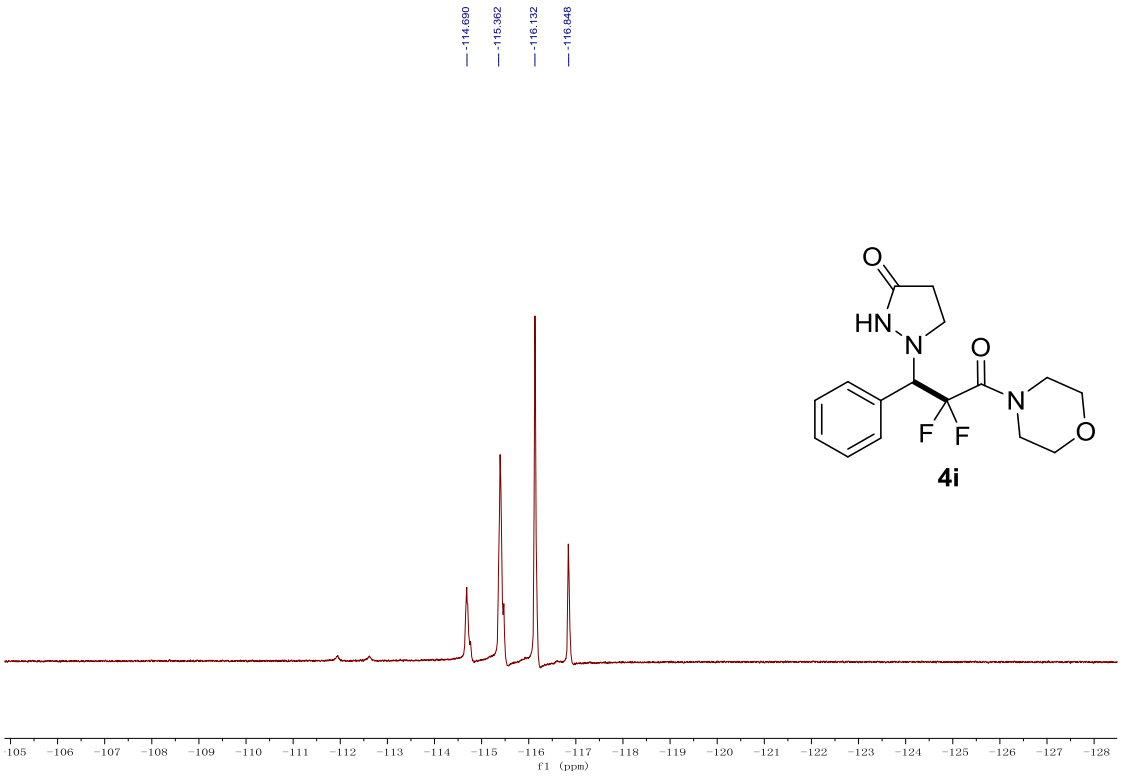

5.07
1.00
6.07
2.06
1.86
2.05
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5 −1.
f1 (ppm)

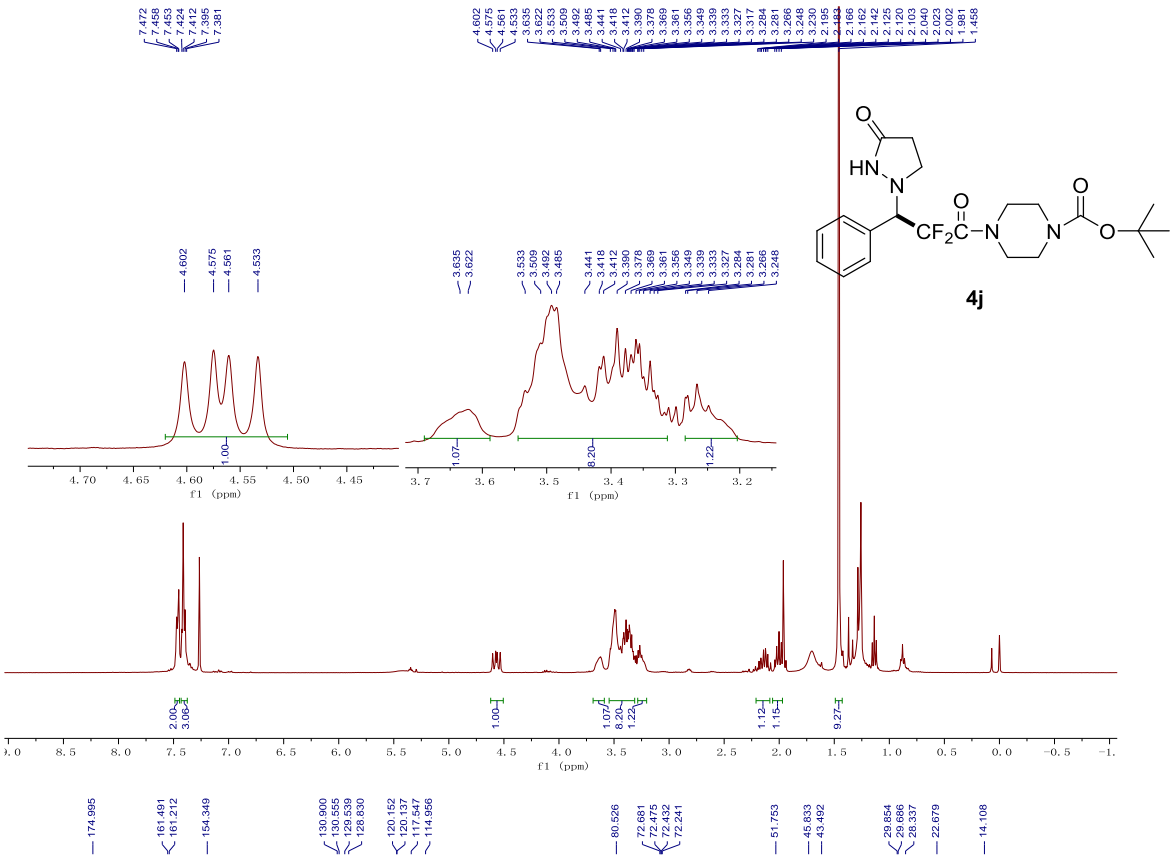

170.196
158.894
158.600
158.306
129.615
129.123
128.767
117.620
115.097
112.577
73.598
73.372
73.149
66.679
66.318
52.117
45.884
42.172
32.929
29.687

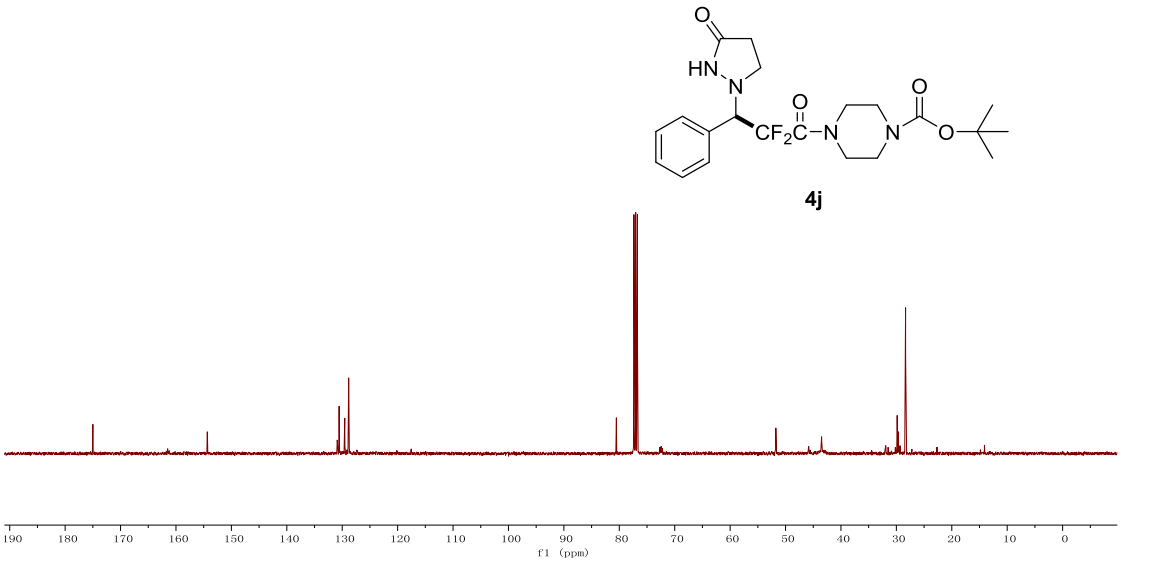

O
HN
N
O
N
O
F F

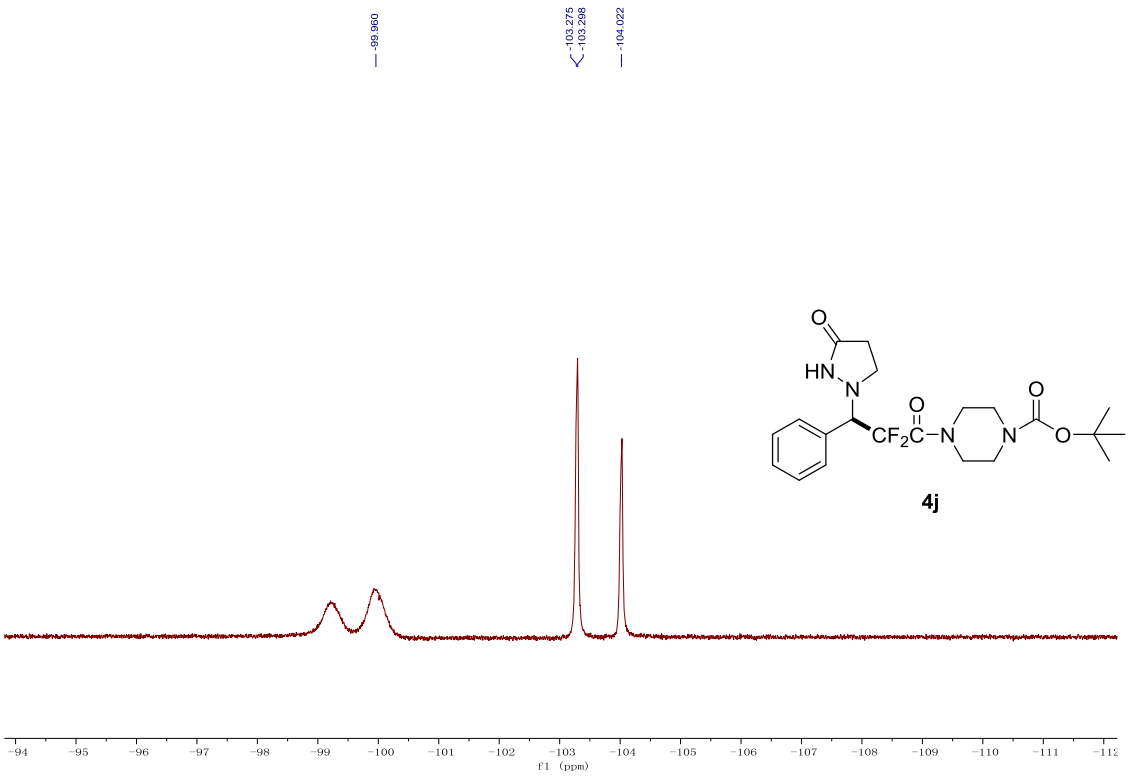
4i

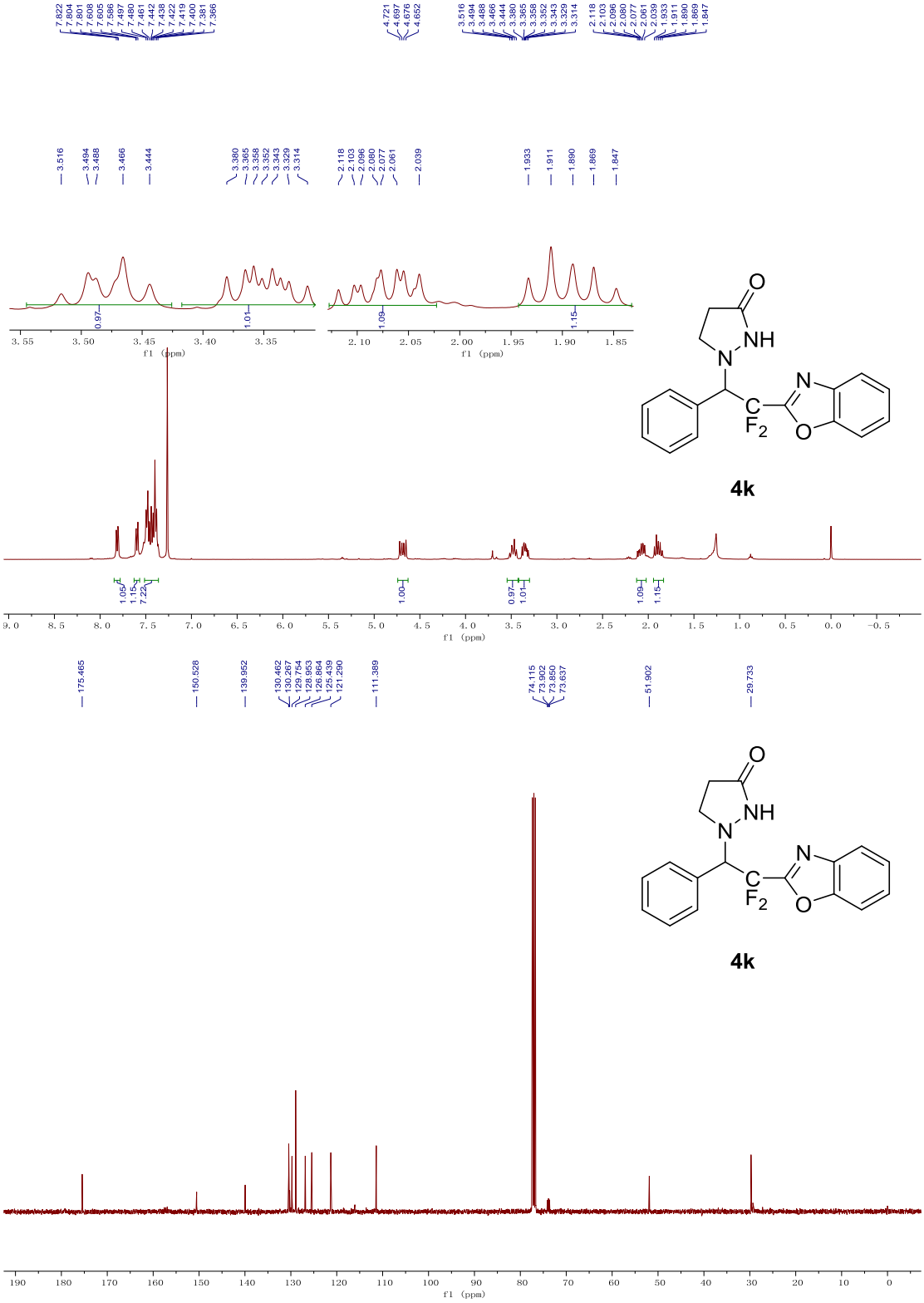
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −1
f1 (ppm)

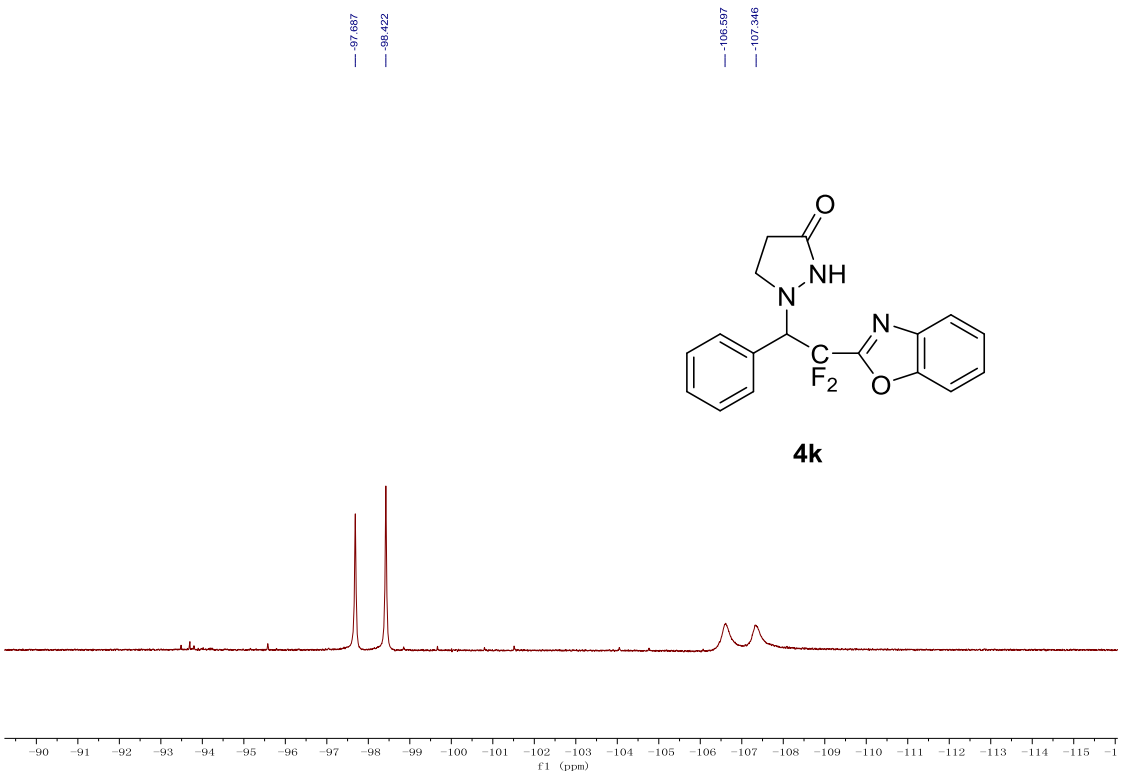

-114.690
-115.362
-116.132
-116.848
O
HN
N
O
N
F
F
O
4i
105 −106 −107 −108 −109 −110 −111 −112 −113 −114 −115 −116 −117 −118 −119 −120 −121 −122 −123 −124 −125 −126 −127 −128
f1 (ppm)

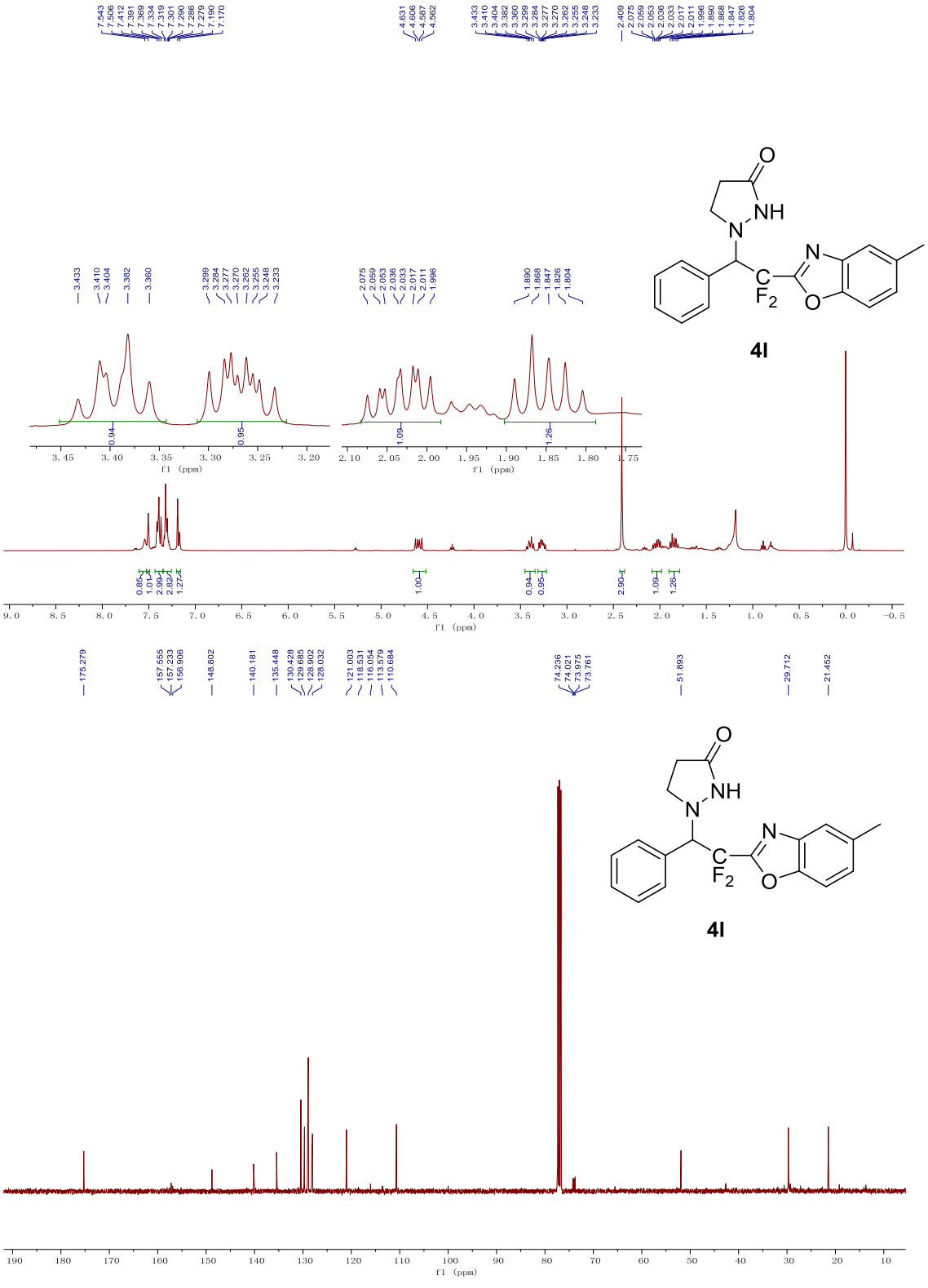

4j
f1 (ppm)

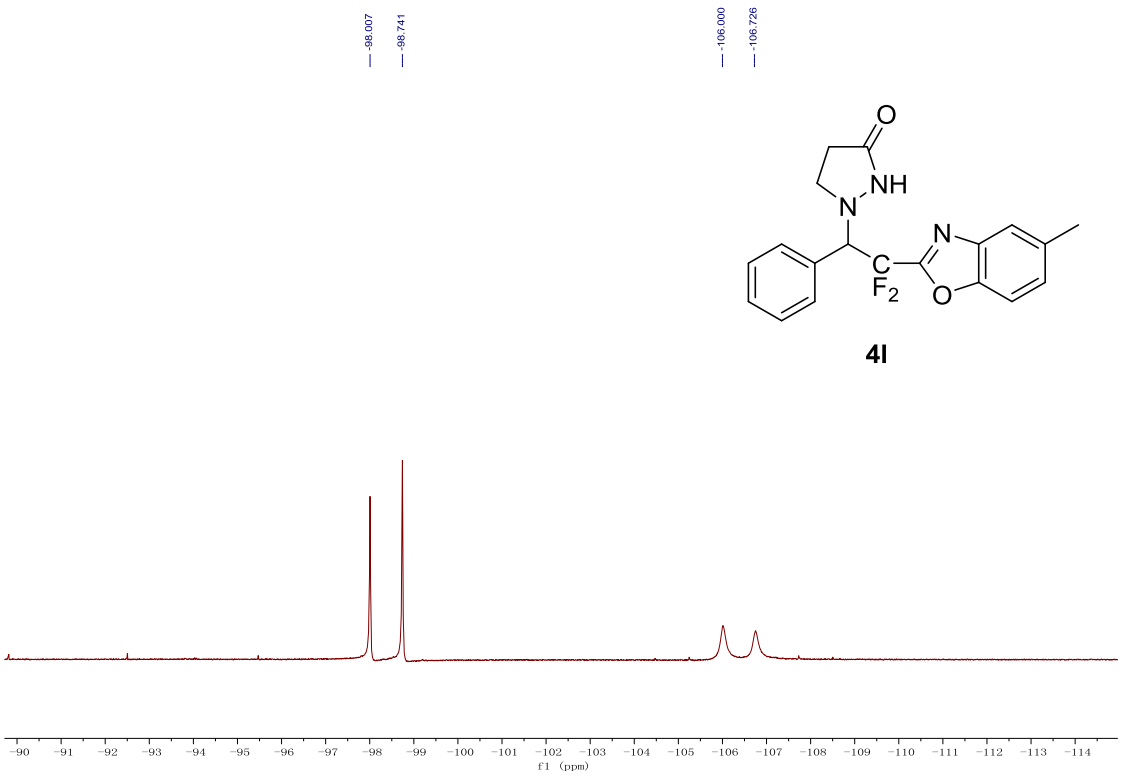

4j
f1 (ppm)

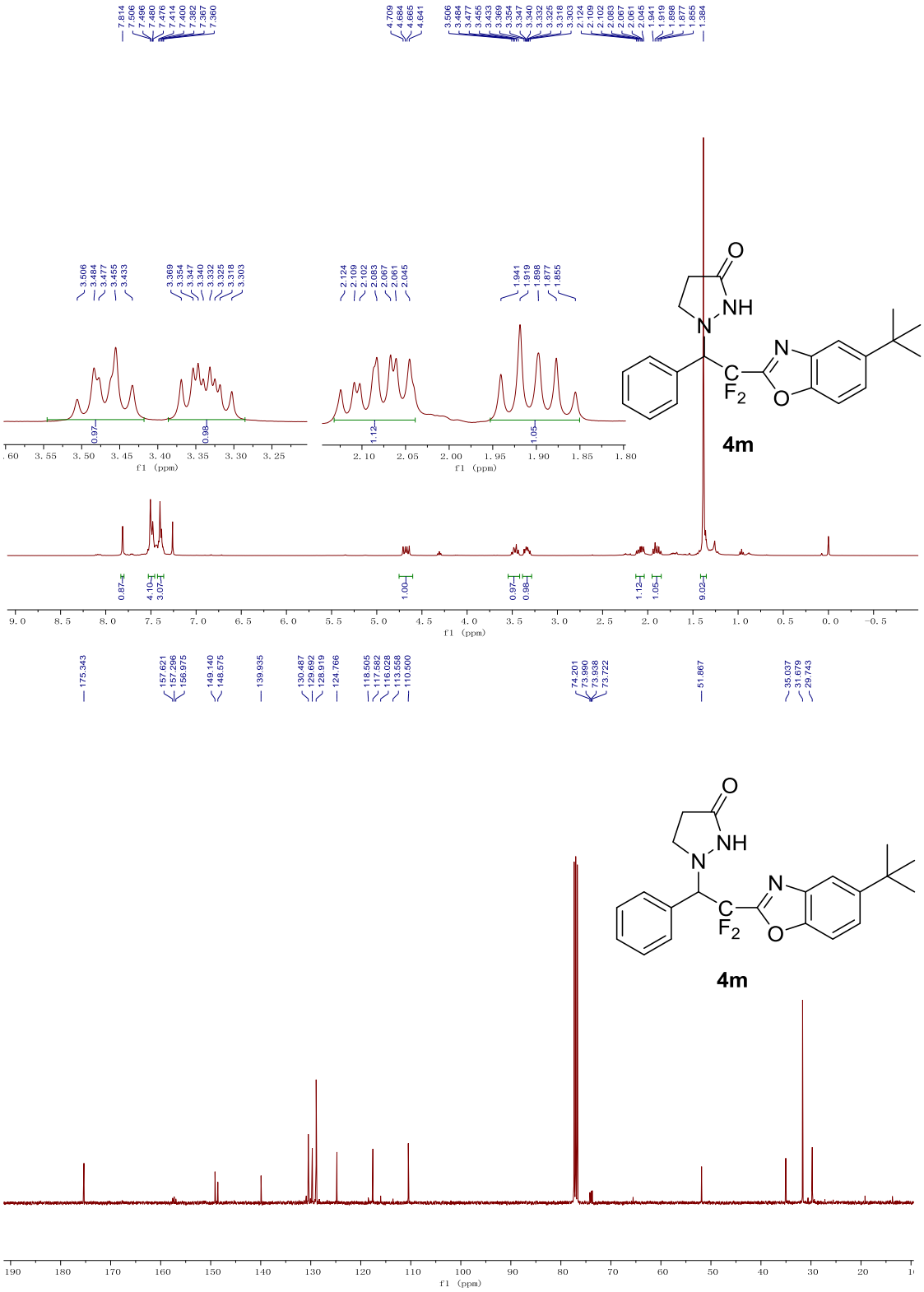

-99.960
-103.275
-103.298
-104.022
O
HN
N
O
CF2C
N
N
O
O
4j
−94
−95
−96
−97
−98
−99
−100
−101
−102
−103
−104
−105
−106
−107
−108
−109
−110
−111
f1 (ppm)

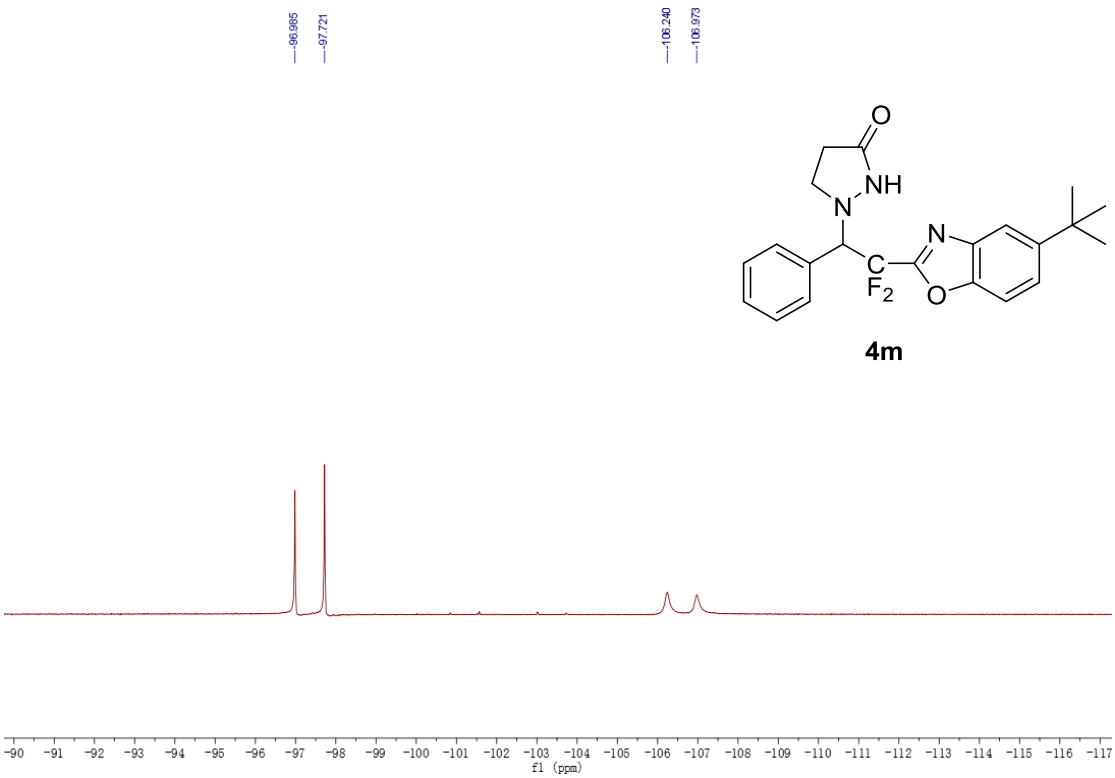

7.822
7.804
7.801
7.608
7.605
7.586
7.497
7.480
7.461
7.442
7.438
7.422
7.419
7.400
7.381
7.366
4.721
4.697
4.676
4.652
3.516
3.494
3.488
3.466
3.444
3.380
3.365
3.358
3.352
3.343
3.329
3.314
2.118
2.103
2.096
2.080
2.077
2.061
2.039
1.933
1.911
1.890
1.869
1.847
0.97
1.01
1.09
1.15
f1 (ppm)
O
NH
N
C
F2
N
O
4k
1.05
1.15
7.22
1.00
0.97
1.01
1.09
1.15
f1 (ppm)
175.465
150.528
139.952
130.462
130.267
129.754
128.953
126.864
125.439
121.290
111.389
74.115
73.902
73.850
73.637
51.902
29.733
O
NH
N
C
F2
N
O
4k
f1 (ppm)

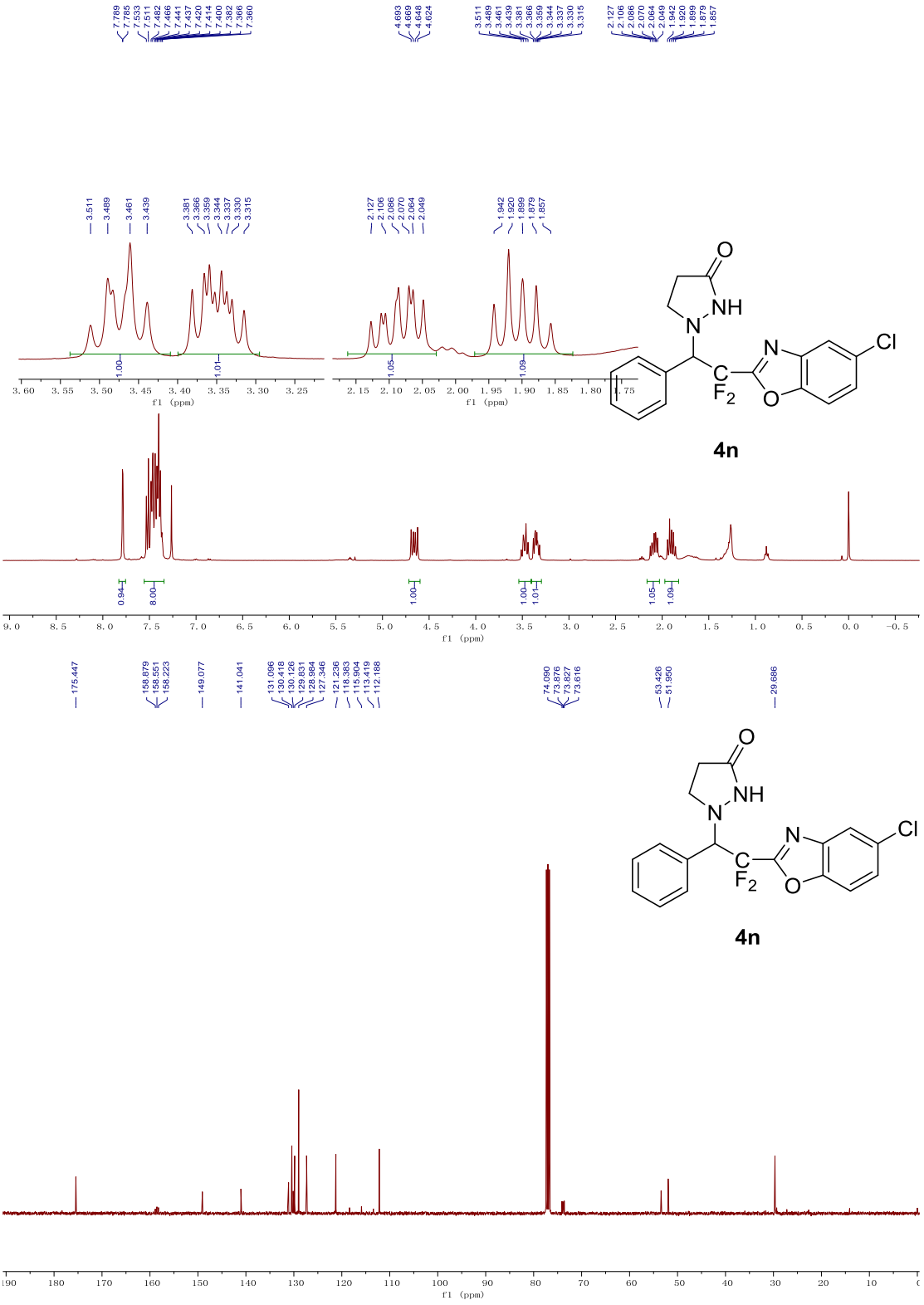

-97.687
-98.422
-106.597
-107.346
O
NH
N
N
C
F2
O
4k
−90 −91 −92 −93 −94 −95 −96 −97 −98 −99 −100 −101 −102 −103 −104 −105 −106 −107 −108 −109 −110 −111 −112 −113 −114 −115
f1 (ppm)

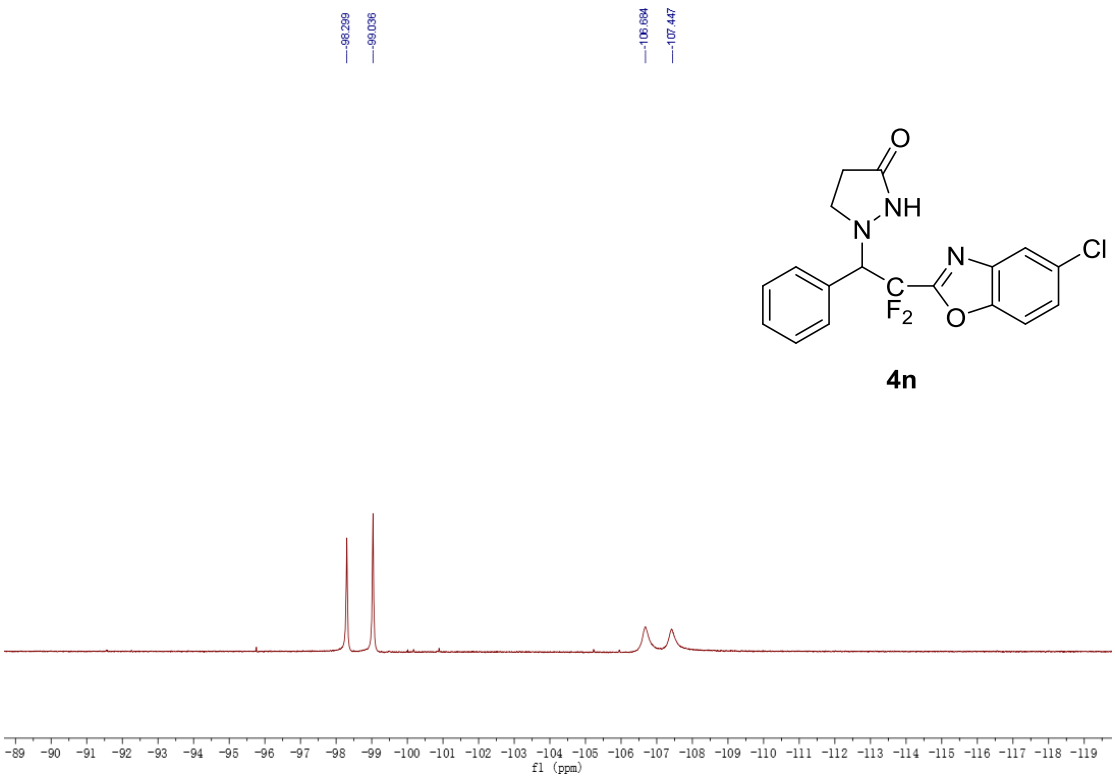

4l
4l
f1 (ppm)

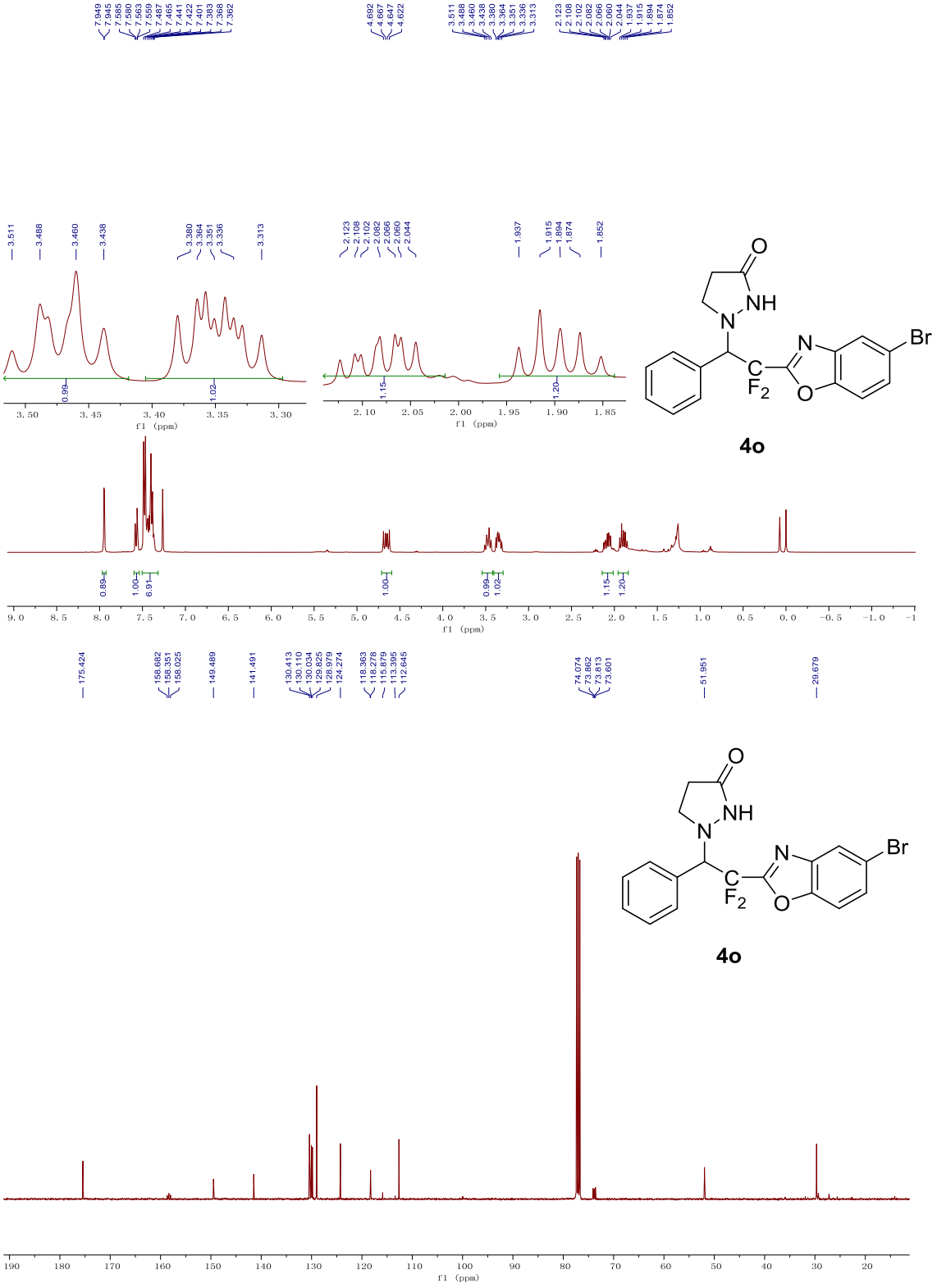

-98.007
-98.741
-106.000
-106.726
O
NH
N
N
C
F2
O
4l
−90 −91 −92 −93 −94 −95 −96 −97 −98 −99 −100 −101 −102 −103 −104 −105 −106 −107 −108 −109 −110 −111 −112 −113 −114
f1 (ppm)

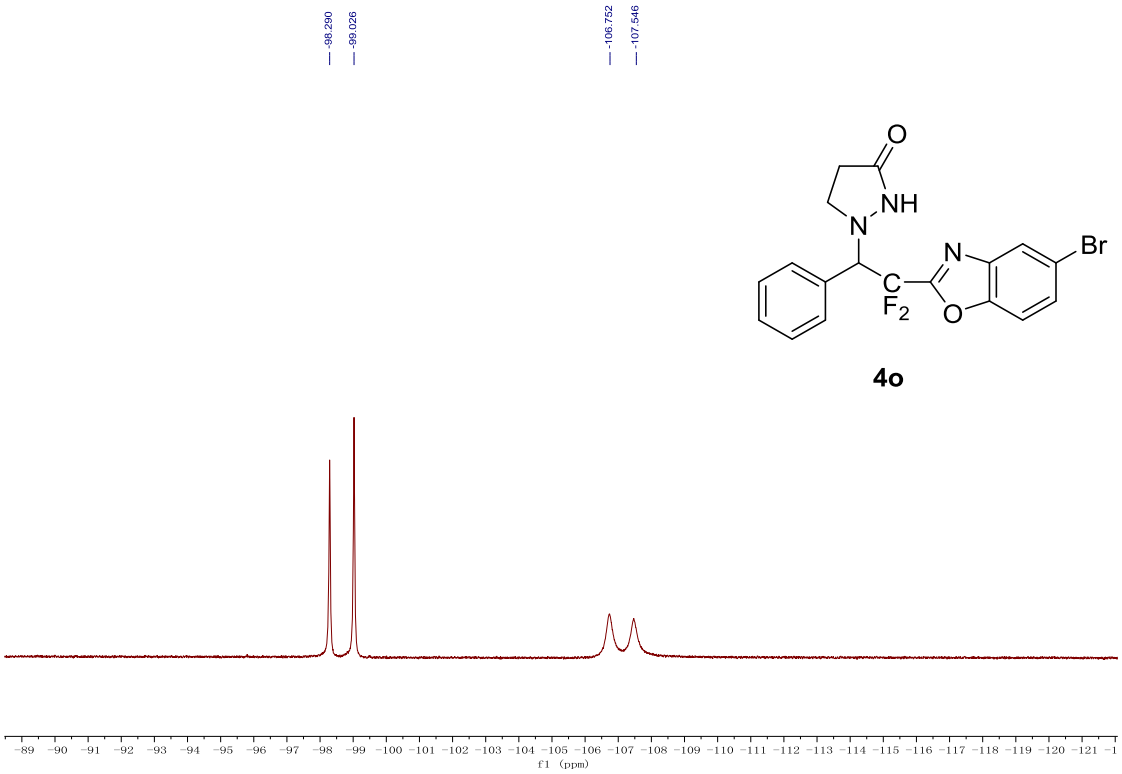

4m
4m
f1 (ppm)

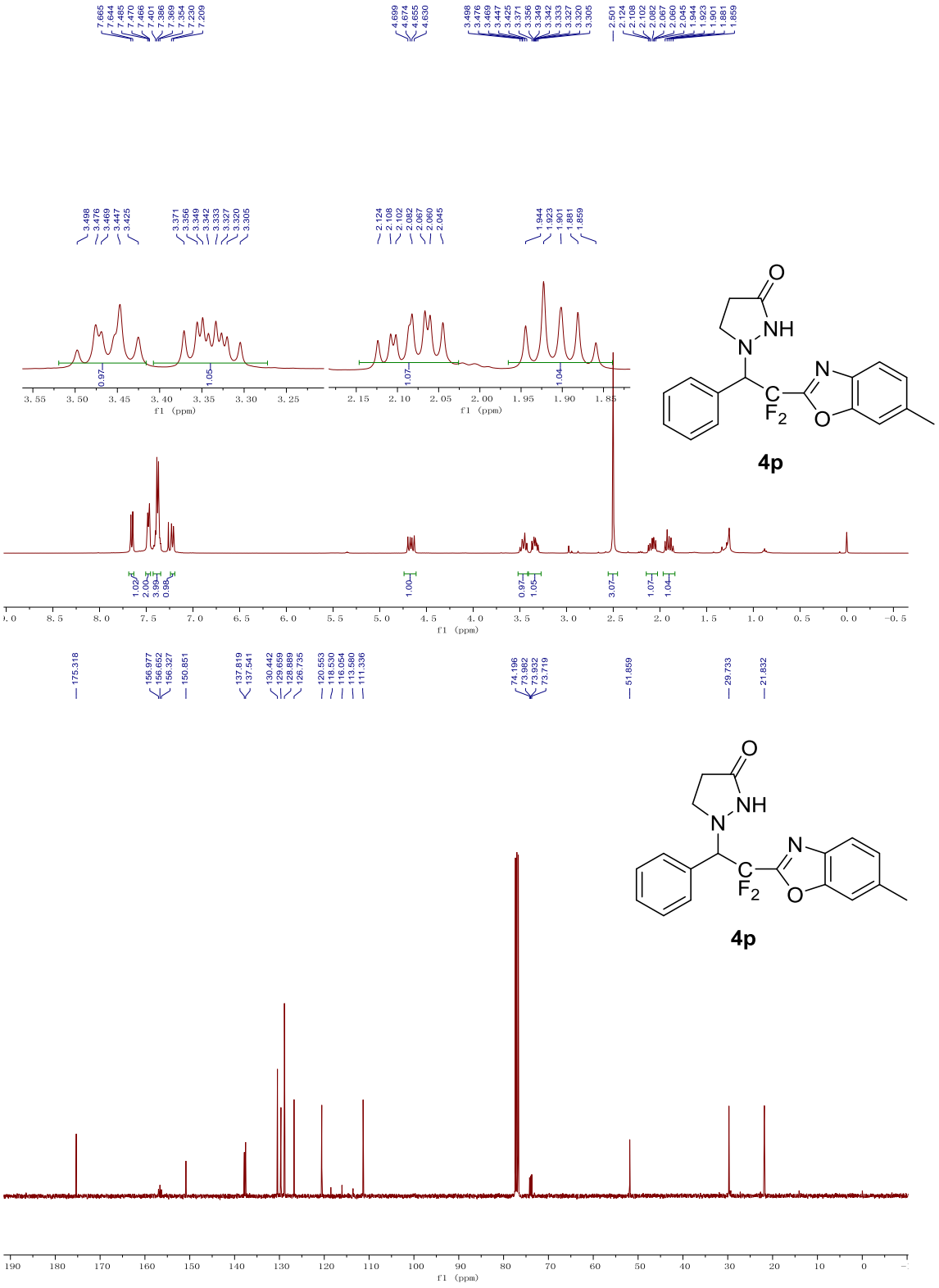

-96.985
-97.721
-106.240
-106.973
O
NH
N
N
C
F2
O
4m
-90 -91 -92 -93 -94 -95 -96 -97 -98 -99 -100 -101 -102 -103 -104 -105 -106 -107 -108 -109 -110 -111 -112 -113 -114 -115 -116 -117
f1 (ppm)

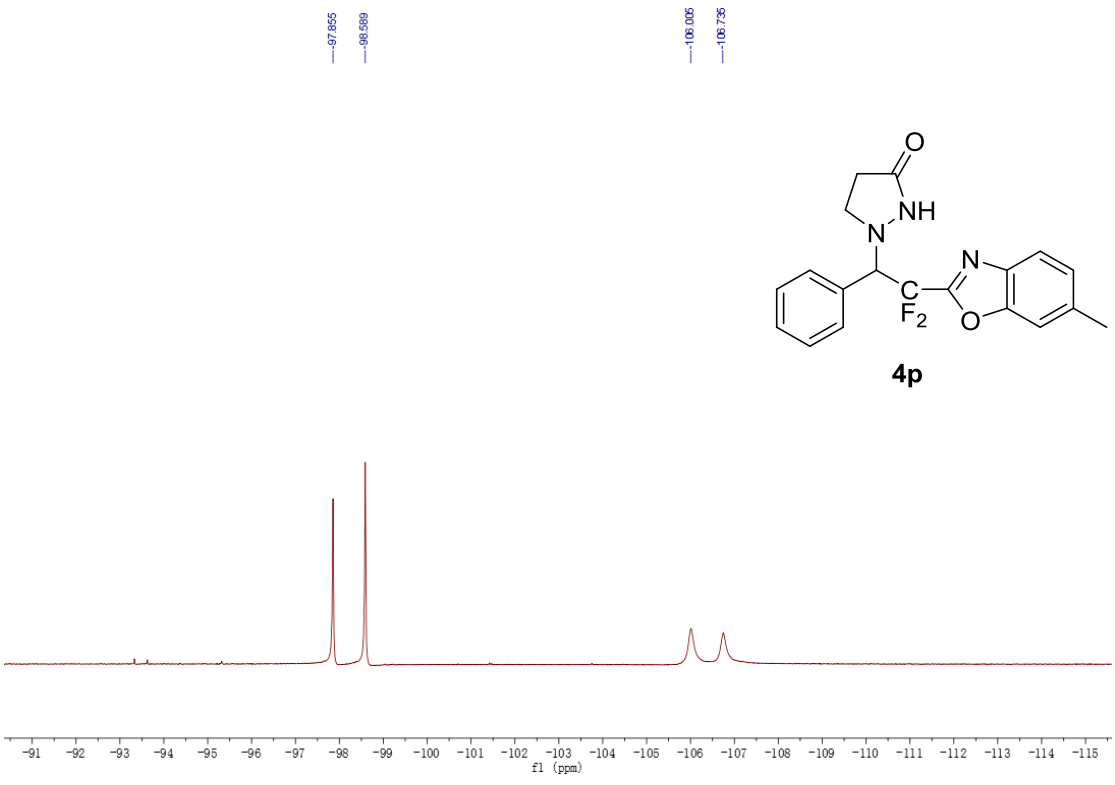

4n
4n

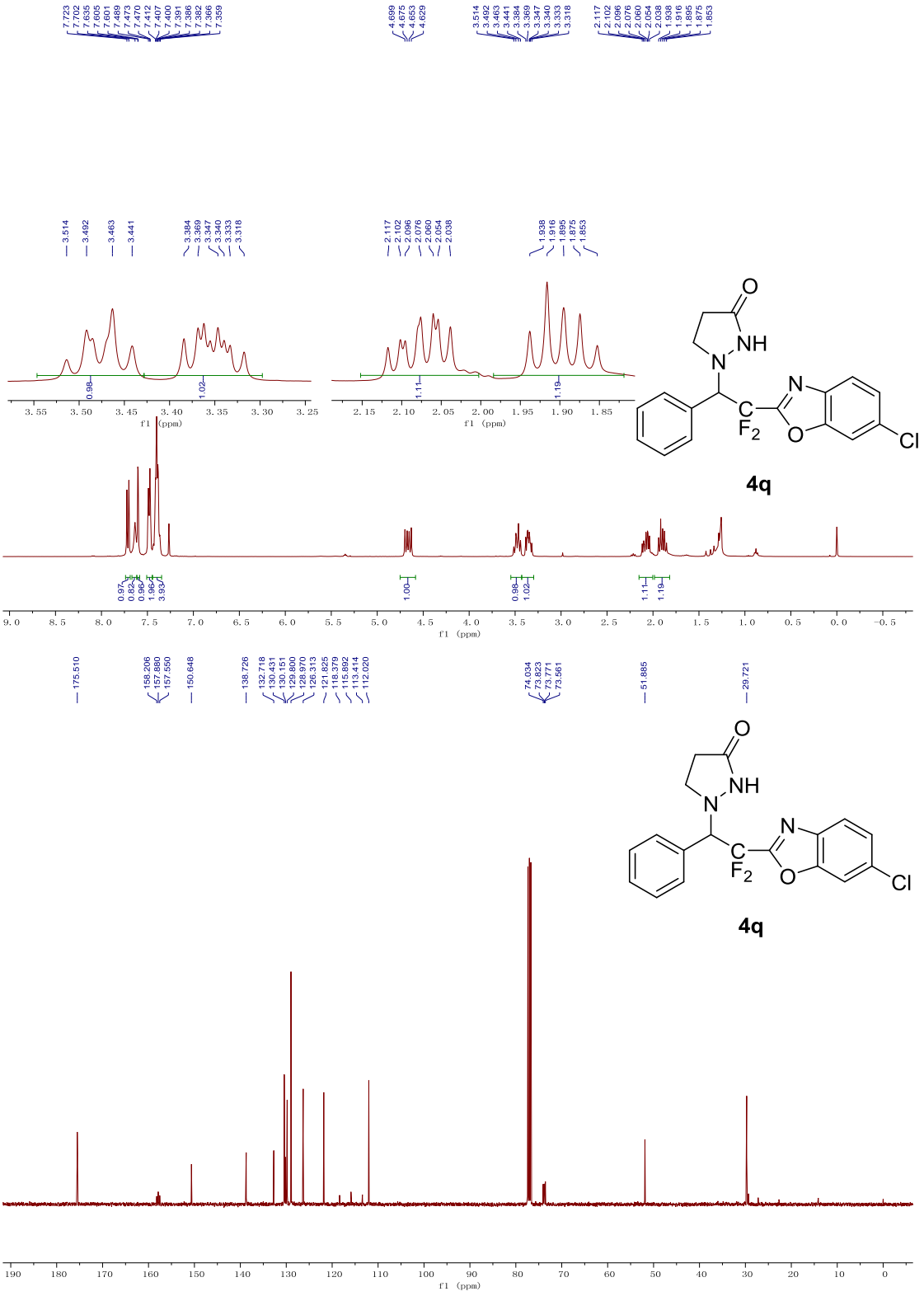

-98.299
-99.036
-106.684
-107.447
O
NH
N
N
Cl
C
F2
O
4n
-89 -90 -91 -92 -93 -94 -95 -96 -97 -98 -99 -100 -101 -102 -103 -104 -105 -106 -107 -108 -109 -110 -111 -112 -113 -114 -115 -116 -117 -118 -119
f1 (ppm)

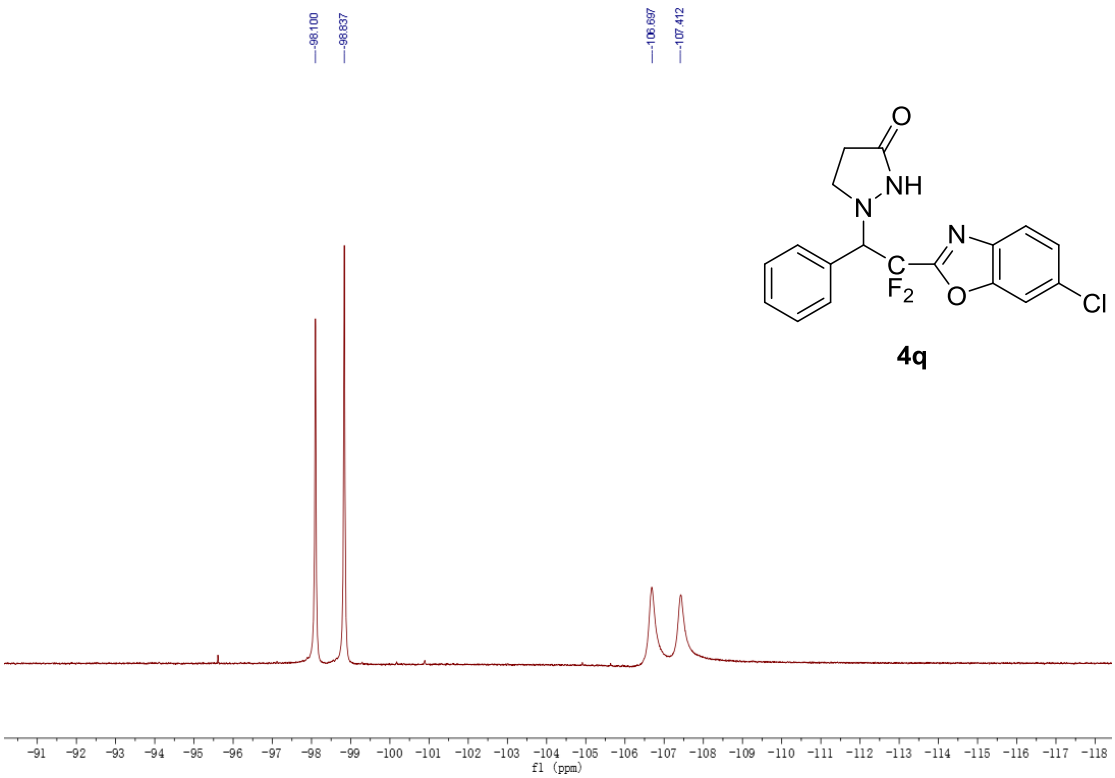

7.949
7.945
7.585
7.580
7.565
7.559
7.487
7.465
7.441
7.422
7.401
7.383
7.368
7.362
4.692
4.667
4.647
4.622
3.511
3.488
3.460
3.438
3.380
3.364
3.351
3.336
3.313
2.123
2.108
2.102
2.082
2.066
2.060
2.044
1.937
1.915
1.894
1.874
1.852
f1 (ppm)
O
NH
N
C
F2
N
O
Br
4o
175.424
158.682
158.351
158.025
149.489
141.491
130.413
130.110
130.034
129.825
128.979
124.274
118.363
118.278
115.879
113.395
112.645
74.074
73.862
73.813
73.601
51.951
29.679


-98.290
-99.026
-106.752
-107.546
O
NH
N
N
Br
C
F2
O
4o
-89 -90 -91 -92 -93 -94 -95 -96 -97 -98 -99 -100 -101 -102 -103 -104 -105 -106 -107 -108 -109 -110 -111 -112 -113 -114 -115 -116 -117 -118 -119 -120 -121 -1
f1 (ppm)

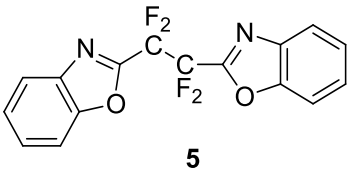

4p
4p


-97.855
-98.589
-106.005
-106.735
O
NH
N
N
C
F2
O
4p
-91 -92 -93 -94 -95 -96 -97 -98 -99 -100 -101 -102 -103 -104 -105 -106 -107 -108 -109 -110 -111 -112 -113 -114 -115
f1 (ppm)

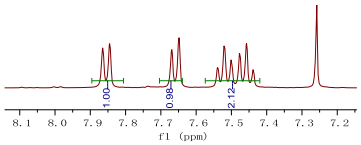

7.723
7.702
7.635
7.605
7.601
7.489
7.473
7.470
7.412
7.407
7.400
7.391
7.386
7.382
7.366
7.359
4.699
4.675
4.653
4.629
3.514
3.492
3.463
3.441
3.384
3.369
3.347
3.340
3.333
3.318
2.117
2.102
2.096
2.076
2.060
2.054
2.038
1.938
1.916
1.895
1.875
1.853
0.98
1.02
1.11
1.19
f1 (ppm)
O
NH
N
C
F2
O
N
Cl
4q
0.97
0.82
0.98
1.96
3.93
1.00
0.98
1.02
1.11
1.19
f1 (ppm)
175.510
158.206
157.880
157.550
150.648
138.726
132.718
130.431
130.151
129.800
128.970
128.313
121.625
118.879
115.892
113.414
112.020
74.034
73.823
73.771
73.561
51.885
29.721
O
NH
N
C
F2
O
N
Cl
4q
f1 (ppm)

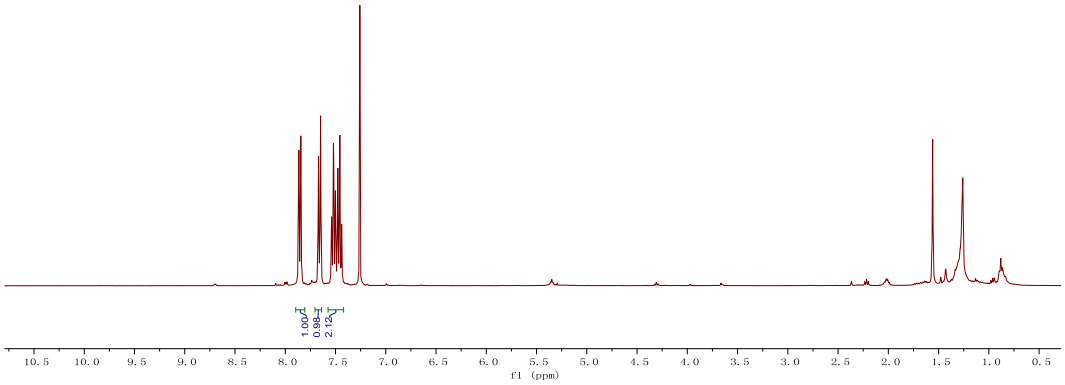

-98.100
-98.837
-106.697
-107.412
O
NH
N
N
C
F2
O
Cl
4q
-91 -92 -93 -94 -95 -96 -97 -98 -99 -100 -101 -102 -103 -104 -105 -106 -107 -108 -109 -110 -111 -112 -113 -114 -115 -116 -117 -118
f1 (ppm)


7.865
7.845
7.810
7.754
7.738
7.732
7.669
7.648
7.602
7.540
7.521
7.501
7.477
7.457
7.439
7.258
7.184

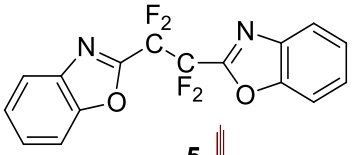

F2
C
C
F2
N
O
N
O

5

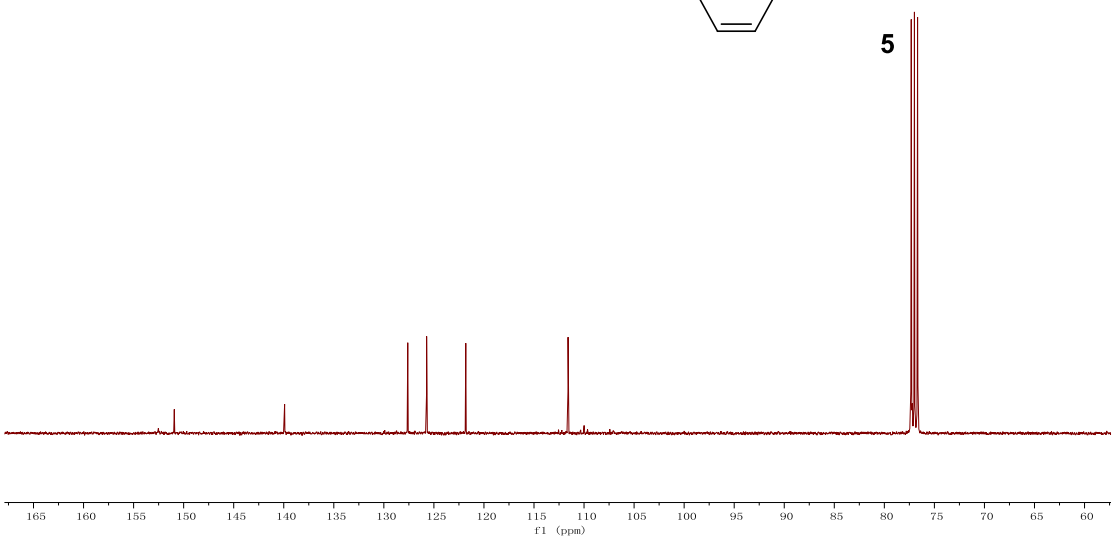

1.00
0.98
2.12
8.1 8.0 7.9 7.8 7.7 7.6 7.5 7.4 7.3 7.2
f1 (ppm)

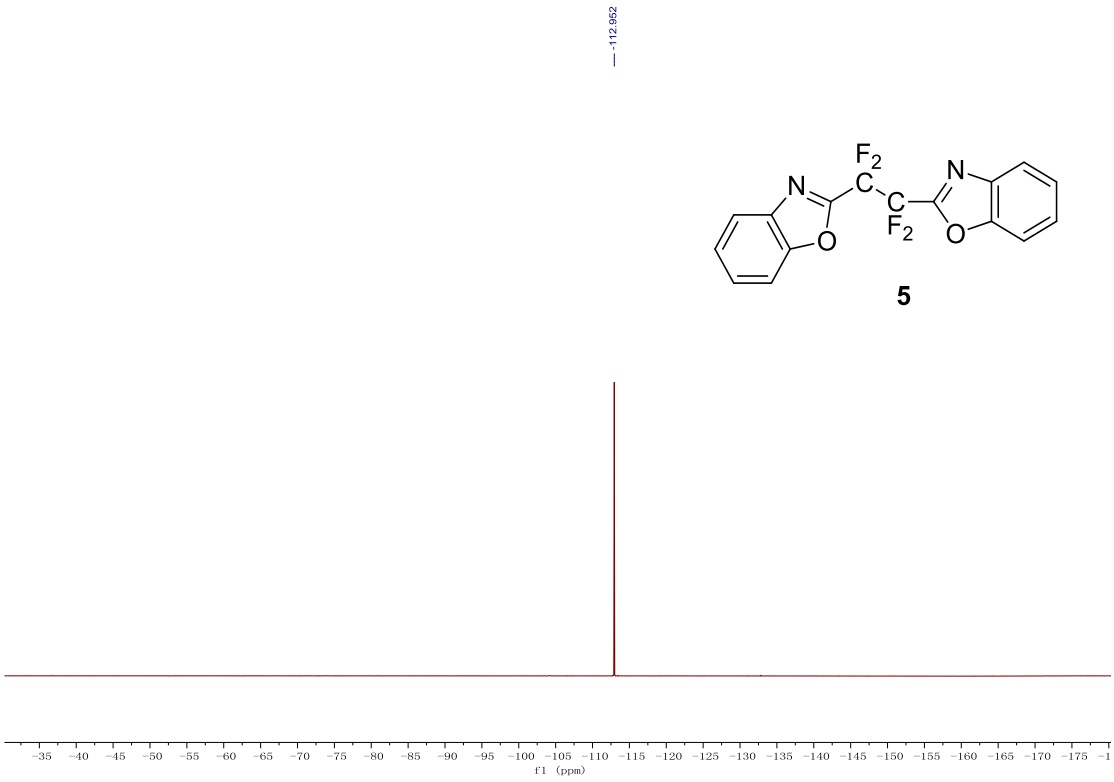

1.00
0.98
2.12
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)


150.937
139.911
127.610
125.726
121.813
111.598


F2
C
C
F2
N
O
N
O

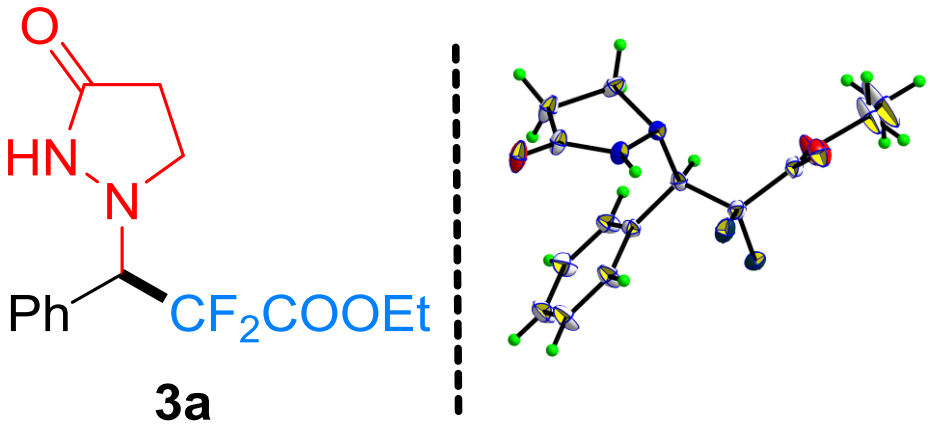
5


165 160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60
f1 (ppm)


-112.952
F2
C
C
F2
N
O
N
O
5
−35 −40 −45 −50 −55 −60 −65 −70 −75 −80 −85 −90 −95 −100 −105 −110 −115 −120 −125 −130 −135 −140 −145 −150 −155 −160 −165 −170 −175 −1
f1 (ppm)

X-ray crystallographic data of compound

1. X-Ray crystallographic analysis of dispirooxindole-piperazine **3a** (CCDC 1858543) showing the thermal ellipsoids at 30% probability level.



Bond precision: C-C = 0.0037 A Wavelength=0.71073

Cell: a=13.8602(6) b=11.4447(6) c=9.3074(4)
alpha=90 beta=101.885(1) gamma=90
Temperature: 293 K

	Calculated	Reported
Volume	1444.75(12)	1444.74(12)
Space group	P 21/c	P2(1)/c
Hall group	-P 2ybc	?
Moiety formula	C14 H16 F2 N2 O3	?
Sum formula	C14 H16 F2 N2 O3	C13.50 H16 F2 N2 O3
Mr	298.29	292.28
Dx,g cm-3	1.371	1.344
Z	4	4
Mu (mm-1)	0.114	0.112
F000	624.0	612.0
F000'	624.39	
h,k,lmax	18,14,12	18,14,12
Nref	3323	3312
Tmin,Tmax	0.973,0.978	
Tmin'	0.967	

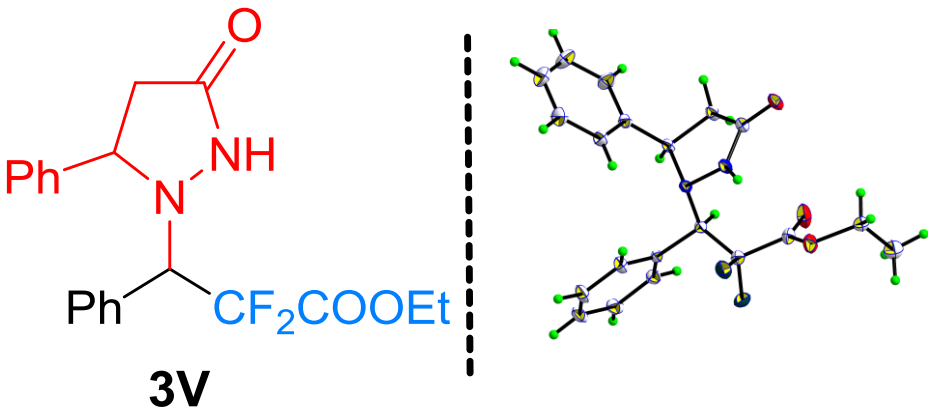
Correction method= Not given

Data completeness= 0.997 Theta(max)= 27.540

R(reflections)= 0.0618(2295) wR2(reflections)= 0.1823(3312)

S = 1.029 Npar= 190

2. X-Ray crystallographic analysis of dispirooxindole-piperazine **3v** (CCDC 1858544) showing the thermal ellipsoids at 30% probability level.



3V

Bond precision: C-C = 0.0036 A Wavelength=0.71073

Cell: a=11.6732(7) b=16.7833(11) c=10.3207(7)
alpha=90 beta=115.021(2) gamma=90
Temperature: 293 K

	Calculated	Reported
Volume	1832.2(2)	1832.2(2)
Space group	P 21/c	P2(1)/c
Hall group	-P 2ybc	?
Moiety formula	C19.88 H19.70 F2 N2 O3	?
Sum formula	C19.88 H19.70 F2 N2 O3	C20 H20 F2 N2 O3
Mr	372.64	374.38
Dx,g cm-3	1.351	1.357
Z	4	4
Mu (mm-1)	0.105	0.105
F000	779.9	784.0
F000'	780.37	
h,k,lmax	15,21,13	15,21,13
Nref	4232	4220
Tmin,Tmax	0.975,0.979	
Tmin'	0.969	

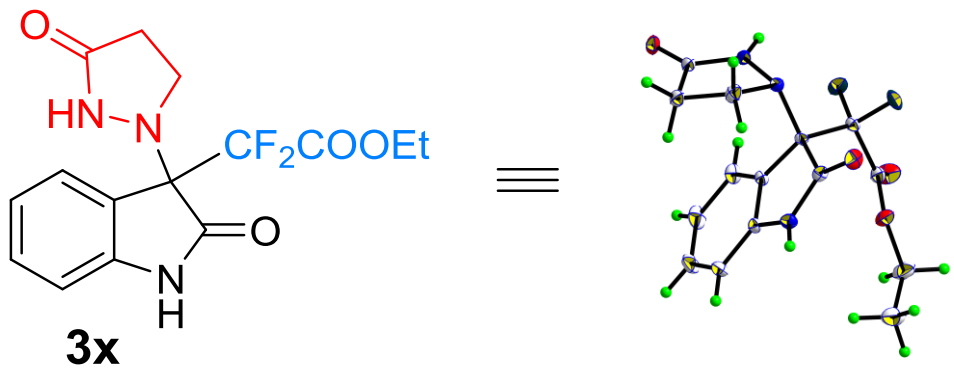
Correction method= Not given

Data completeness= 0.997 Theta(max)= 27.540

R(reflections)= 0.0656(3156) wR2(reflections)= 0.1894(4220)

S = 1.055 Npar= 242

3. X-Ray crystallographic analysis of dispirooxindole-piperazine **3x** (CCDC 1877660) showing the thermal ellipsoids at 30% probability level.



Bond precision: C-C = 0.0021 A Wavelength=0.71073

Cell: a=8.3068(4) b=14.1708(8) c=13.3787(6)
alpha=90 beta=98.617(3) gamma=90
Temperature: 296 K

	Calculated	Reported
Volume	1557.08(14)	1557.08(14)
Space group	P 21/n	P2(1)/n
Hall group	-P 2yn	?
Moiety formula	C15 H15 F2 N3 O4	?
Sum formula	C15 H15 F2 N3 O4	C15 H15 F2 N3 O4
Mr	339.30	339.30
Dx,g cm-3	1.447	1.447
Z	4	4
Mu (mm-1)	0.122	0.122
F000	704.0	704.0
F000'	704.45	
h,k,lmax	10,18,17	10,18,17
Nref	3643	3584
Tmin,Tmax	0.971,0.976	
Tmin'	0.964	

Correction method= Not given

Data completeness= 0.984 Theta(max)= 27.660

R(reflections)= 0.0403(3027) wR2(reflections)= 0.1113(3584)

S = 1.034 Npar= 218