Supporting information:

Can a C-H···O interaction be a determinant of conformation?

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1. **General synthetic experimental procedures.**
2. **Experimental procedures and data for all compounds.**
3. **^{1}H and ^{13}C NMR spectra for all compounds; ^{19}F spectra where appropriate.**
4. **Coordinates for 4A-4F**

1. General synthetic experimental procedures.

1.1 Solvents and Reagents

THF was distilled under an atmosphere of dry nitrogen from lithium aluminium hydride and calcium hydride in the presence of triphenylmethane; dichloromethane was distilled from calcium hydride; triethylamine was distilled from calcium hydride and stored over potassium hydroxide. pH 7 Buffer was prepared by dissolving KH_2PO_4 (85 g) and NaOH (14.5 g) in distilled water (950 mL). Petrol refers to the fraction of petroleum ether boiling between 40 and 60 ˚C. Aldehydes were purified by distillation or recrystallization. All other reagents and solvents were used as supplied, without prior purification.

1.2 Chromatography

Thin layer chromatography (TLC) was performed on glass or aluminium plates coated with Merck 60 F_{254} silica and visualization was achieved by UV light or by staining with ceric ammonium molybdate or potassium permanganate. Flash column chromatography was carried out using Merck Kieselgel (230-400 mesh).

1.3 Nuclear Magnetic Resonance Spectroscopy

NMR spectra were recorded on a Bruker DPX 400 (^{1}H: 400 MHz and ^{13}C: 100 MHz), a Bruker Avance Cryo 500 (^{1}H: 500 MHz and ^{13}C: 125 MHz), a Bruker AVB 500 (^{1}H: 500 MHz and ^{13}C: 125 MHz) or a Bruker DPX 250 (^{1}H: 250 MHz and ^{13}C: 63 MHz) spectrometer. Chemical shifts are quoted in ppm and are referenced to the residual non-deuterated solvent peak, and are reported (based on appearance rather than interpretation) as follows: chemical shift δ/ppm (number of protons, multiplicity, coupling constant *J*/Hz, assignment) [br, broad; s, singlet; d, doublet; t, triplet; q, quartet; qui, quintet; sept, septet; m, multiplet]. ^{19}F spectra were run at 376 MHz on a Bruker Avance 400 with a QNP probe.

1.4 Infrared Spectroscopy

Infrared spectra were recorded neat on a Perkin-Elmer Spectrum One spectrometer fitted with an attenuated total reflectance attachment with internal referencing or a Bruker Tensor 27 FTIR with internal calibration.

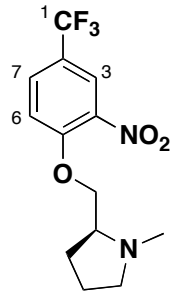
1.5 Mass Spectrometry

Accurate mass measurements were performed on a Finnigan MAT 900 XLT (ES+) at the EPSRC National Mass Spectrometry Service Centre at Swansea, or on a Bruker microTOF (ES+) at the University of Oxford. LCMS were performed on an Agilent MSD LC-MS APCI 120-1000 full gradient machine or an Agilent LC-MS APCI 1100.

1.6 Polarimetry

Optical rotations were recorded on a Perkin-Elmer 241 polarimeter with a path length of 1 dm.

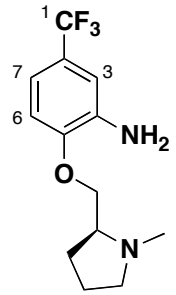
(*S*)-1-Methyl-2-((2-nitro-4-(trifluoromethyl)phenoxy)methyl)pyrrolidine



KHMDS (0.5 M solution in toluene, 56.1 mL, 28.1 mmol) was added dropwise over 1 h to a stirred solution of *N*-methyl-L-prolinol (3.08 g, 26.7 mmol) and 4-fluoro-3-nitrobenzotrifluoride (3.93 mL, 28.1 mmol) in THF (180 mL) at 0 ˚C. The solution was allowed to warm to rt over 1 h then diluted with dichloromethane (400 mL), washed with NH_4Cl (aq) (400 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (8 % CH_3OH in $CHCl_3$, R_f 0.30) to afford the turn precursor as a yellow solid (5.29 g, 17.4 mmol, 65 %).

Mp 60-61 ˚C; $[\alpha]_D^{25}$ – 24.8 (c = 1.0, $CHCl_3$); δ_H (500 MHz, $CDCl_3$): 8.10 (1H, d, *J* 2.0, Ar-H^3), 7.76 (1H, dd, *J* 8.5, 2.0, Ar-H^7), 7.17 (1H, d, *J* 8.5, Ar-H^6), 4.13 (1H, dd, *J* 9.0, 6.0, CH_2OAr), 4.03 (1H, dd, *J* 9.0, 5.5, CH_2OAr), 3.09 (1H, m, CH_2NMe), 2.78 (1H, br m, CHNMe), 2.48 (3H, s, CH_3), 2.33 (1H, m, CH_2NMe), 2.07 (1H, m, C$H_2$$CH_2CH_2NMe$), 1.85-1.77 (2H, m, C$H_2$$CH_2NMe$), 1.70 (1H, m, C$H_2$$CH_2CH_2NMe$); δ_C (125 MHz, $CDCl_3$): 154.7 (C^5), 139.3 (C^4), 130.9 (q, $J_{C\text{-}F}$ 4.0, C^7), 123.3 (q, $J_{C\text{-}F}$ 3.5, C^3), 123.0 (q, $J_{C\text{-}F}$ 270.1, C^1), 122.4 (q, $J_{C\text{-}F}$ 34.3, C^2), 114.6 (C^6), 73.4 (*C*H_2OAr), 63.6 (*C*HNMe), 57.8 (*C*H_2NMe), 42.0 (NCH_3), 28.7 (*C*$H_2CH_2CH_2NMe$), 23.3 (*C*H_2CH_2NMe); υ_{max} (neat) cm^{-1}: 2952 (m) & 2790 (m) (C-H), 1627 (s) & 1578 (w) (Ar C=C), 1541 (s) & 1323 (s) (NO_2), 1282 (s) & 1127 (s) (C-O); HRMS calcd for $C_{13}H_{15}F_3N_2O_3$ $[M+H]^+$: 305.1108. Found: 305.1111.

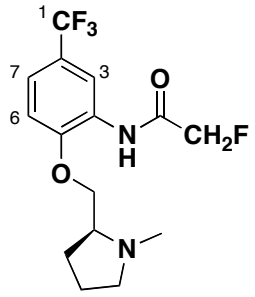
(*S*)-2-((1-Methylpyrrolidin-2-yl)methoxy)-5-(trifluoromethyl)aniline



(*S*)-1-Methyl-2-((2-nitro-4-(trifluoromethyl)phenoxy)methyl)pyrrolidine (3.1 g, 10.2 mmol), ammonium formate (4.50 g, 71.3 mmol) and palladium (10 wt.% on carbon, 0.300 g) were dissolved in methanol:ethyl acetate (9:1 by volume, 80 mL total) and stirred at 50 ˚C for 2 h. The reaction mixture was allowed to cool to rt then filtered through a pad of Celite™ and the solids washed with methanol (250 mL). The solvent was removed *in vacuo* and the residue dissolved in dichloromethane (300 mL), washed with brine (300 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to yield the aniline (2.77 g, 10.1 mmol, 99 %, 17:3 $CHCl_3$:CH_3OH, R_f 0.18) as a pale brown solid which was used in subsequent reactions without purification.

Mp 177-178 °C; $[\alpha]_D^{25}$ – 6.4 (c = 1.0, $CHCl_3$); δ_H (500 MHz, CD_3OD): 7.01 (1H, d, *J* 2.1, Ar-H^3), 6.99 (1H, d, *J* 8.4, Ar-H^6), 6.93 (1H, dd, *J* 8.4, 2.1, Ar-H^7), 4.36 (1H, dd, *J* 11.0, 3.5, CH_2OAr), 4.28 (1H, dd, *J* 11.0, 5.5, CH_2OAr), 3.65 (1H, br m, CHNMe), 3.59 (1H, m, CH_2NMe), 3.07 (1H, m, CH_2NMe), 2.92 (3H, s, NCH_3), 2.32 (1H, m, C$H_2$$CH_2CH_2NMe$), 2.13-2.01 (3H, m, C$H_2CH_2CH_2NMe$); δ_C (125 MHz, CD_3OD): 149.4 (C^5), 139.2 (C^4), 126.0 (q, $J_{C\text{-}F}$ 268.9, C^1), 125.3 (q, $J_{C\text{-}F}$ 31.9, C^2), 115.7 (q, $J_{C\text{-}F}$ 4.3, C^7), 112.6 (q, $J_{C\text{-}F}$ 3.8, C^3), 112.4 (C^6), 68.3 (*C*HNMe), 67.6 (*C*H_2OAr), 58.3 (*C*H_2NMe), 41.2 (NCH_3), 27.6 (*C*$H_2CH_2CH_2NMe$), 23.3 (*C*H_2CH_2NMe); υ_{max} (neat) cm^{-1}: 3379 (br) (N-H), 2976 (w) (C-H), 1611 (s) (N-H), 1520 (s) (Ar C=C), 1218 (s) & 1117 (s) (C-O); HRMS calcd for $C_{13}H_{17}F_3N_2O$ $[M+H]^+$: 275.1366. Found: 275.1367.

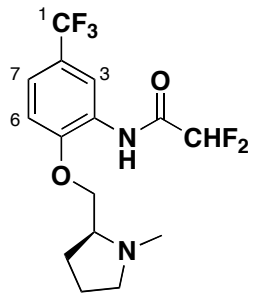
(*S*)-2-Fluoro-*N*-(2-((1-methylpyrrolidin-2-yl)methoxy)-5-(trifluoromethyl)phenyl)ethanamide



Sodium fluoroacetate (0.164 g, 1.64 mmol) was dissolved in dichloromethane (16 mL). *N*,*N*'-dicyclohexylcarbodiimide (0.338 g, 1.64 mmol) and 4-dimethylaminopyridine (0.013 g, 0.109 mmol) were added and the solution stirred at rt for 5 min. (*S*)-2-((1-methylpyrrolidin-2-yl)methoxy)-5-(trifluoromethyl)aniline (0.300 g, 1.09 mmol) in dichloromethane (4.0 mL) was added dropwise and the reaction mixture left to stir overnight. The solvent was removed *in vacuo* and the crude product purified by column chromatography (19:1 $CHCl_3$:CH_3OH, R_f 0.12) to afford a pale crystalline solid (0.219 g, 0.656 mmol, 60 %).

Mp 93-94 ˚C; $[\alpha]_D^{25}$ - 27.3 (c = 1.0, $CHCl_3$); δ_H (500 MHz, $CDCl_3$): 8.80 (1H, br s, N-H), 8.68 (1H, d, *J* 2.0, Ar-H^3), 7.34 (1H, dd, *J* 8.5, 2.0, Ar-H^7), 6.95 (1H, d, *J* 8.5, Ar-H^6), 4.91 (2H, d, *J* 47.0, CH_2F), 4.10 (1H, dd, *J* 9.0, 5.0, CH_2OAr), 3.98 (1H, dd, *J* 9.0, 5.0, CH_2OAr), 3.10 (1H, m, CH_2NMe), 2.71 (1H, m, CHNMe), 2.46 (3H, s, NCH_3), 2.33 (1H, m, CH_2NMe), 2.05 (1H, m, $CH_2CH_2CH_2NMe$), 1.85-1.78 (2H, m, CH_2CH_2NMe), 1.74 (1H, m, $CH_2CH_2CH_2NMe$); δ_C (125 MHz, $CDCl_3$): 165.5 (d, $J_{C\text{-}F}$ 16.4, C=O), 149.8 (C^5), 126.9 (C^4), 124.1 (q, $J_{C\text{-}F}$ 270.1, C^1), 123.5 (q, $J_{C\text{-}F}$ 32.8, C^2), 121.8 (q, $J_{C\text{-}F}$ 3.9, C^7), 117.0 (q, $J_{C\text{-}F}$ 3.9, C^3), 111.1 (C^6), 80.2 (d, $J_{C\text{-}F}$ 186.9, CHF_2), 72.1 (CH_2OAr), 64.2 (CHNMe), 57.7 (CH_2NMe), 41.7 (NCH_3), 28.5 ($CH_2CH_2CH_2NMe$), 23.1 (CH_2CH_2NMe); υ_{max} (neat) cm^{-1}: 3403 (s) (N-H), 2953 (m) & 2799 (m) (C-H), 1687 (s) (C=O), 1604 (m) (N-H), 1547 (s) & 1495 (s) (Ar C=C), 1276 (s) & 1124 (s) (C-O); HRMS calcd for $C_{15}H_{18}F_4N_2O_2$ $[M+H]^+$: 335.1377. Found: 335.1375.

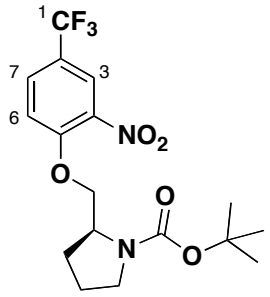
(*S*)-2,2-Difluoro-*N*-(2-((1-methylpyrrolidin-2-yl)methoxy)-5-(trifluoromethyl)phenyl)ethanamide



4-Dimethylaminopyridine (0.011 g, 0.093 mmol) was added to a solution of (*S*)-2-((1-methylpyrrolidin-2-yl)methoxy)-5-(trifluoromethyl)aniline (0.254 g, 0.926 mmol) in dichloromethane (2.0 mL). The mixture was cooled to 0 ˚C and pyridine (127 µL) and difluoroacetic anhydride (127 µL, 1.02 mmol) were added. The reaction mixture was stirred for 2 h, allowed to warm to rt and the solvents removed *in vacuo*. The crude product was purified by column chromatography (17:3 $CHCl_3$:CH_3OH, R_f 0.48) to afford a pale brown crystalline solid (0.313 g, 0.887 mmol, 96 %).

Mp 90-91 ˚C; $[\alpha]_D^{25}$ - 29.1 (c = 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$): 9.13 (1H, br s, N-H), 8.64 (1H, d, *J* 2.0, Ar-H^3), 7.39 (1H, dd, *J* 8.4, 2.0, Ar-H^7), 7.00 (1H, d, *J* 8.4, Ar-H^6), 6.02 (1H, t, *J* 54.0, CHF_2), 4.14 (1H, dd, *J* 9.6, 4.8, CH_2OAr), 4.01 (1H, dd, *J* 9.6, 4.8, CH_2OAr), 3.13 (1H, m, CH_2NMe), 2.67 (1H, m, CHNMe), 2.44 (3H, s, NCH_3), 2.33 (1H, m, CH_2NMe), 2.05 (1H, m, $CH_2CH_2CH_2NMe$), 1.83-1.75 (3H, m, $CH_2CH_2CH_2NMe$); δ_C (125 MHz, $CDCl_3$): 160.4 (t, J_{C-F} 24.8, C=O), 150.5 (C^5), 126.7 (C^4), 123.9 (q, J_{C-F} 270.3, C^1), 123.9 (q, J_{C-F} 32.9, C^2), 122.6 (q, J_{C-F} 3.9, C^7), 117.6 (q, J_{C-F} 3.8, C^3), 112.4 (C^6), 108.5 (t, J_{C-F} 252.4, CHF_2), 72.0 (CH_2OAr), 64.4 (CHNMe), 57.6 (CH_2NMe), 41.4 (NCH_3), 28.1 ($CH_2CH_2CH_2NMe$), 22.9 (CH_2CH_2NMe); υ_{max} (neat) cm^{-1}: 3411 (w) (N-H), 2955 (m) & 2798 (w) (C-H), 1711 (s) (C=O), 1607 (m) (N-H), 1551 (s) & 1497 (s) (Ar C=C), 1275 (s) & 1110 (s) (C-O); HRMS calcd for $C_{15}H_{17}F_5N_2O_2$ $[M+H]^+$: 353.1283. Found: 353.1282.

(*S*)-*tert*-Butyl 2-((2-nitro-4-(trifluoromethyl)phenoxy)methyl)pyrrolidine-1-carboxylate



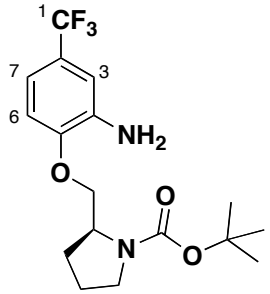
Reaction performed on a 1.06 mmol scale utilizing the same procedure for the preparation of (*S*)-1-methyl-2-((2-nitro-4-(trifluoromethyl)phenoxy)methyl)pyrrolidine. The crude product was purified by column chromatography (7:1 Pet:EtOAc, R_f 0.36) to afford the turn precursor as a yellow oil (0.201 g, 0.515 mmol, 49 %).

$[\alpha]_D^{25}$ – 50.0 (c = 1.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$): 8.09 (1H, d, *J* 1.9, Ar-H^3), 7.77 (1H, dd, *J* 8.8, 1.9, Ar-H^7), 7.38 (1H, d, *J* 8.8, Ar-H^6), 4.36-4.27 (2H, br m, CH_2OAr), 4.15 (1H, br m, C*H*NBoc), 3.38 (2H, br m, CH_2NBoc), 2.08-1.97 (3H, br m, CH_2CH_2CH_2NBoc), 1.86 (1H, br m, CH_2CH_2CH_2NBoc), 1.45 (9H, s, $CO_2C(CH_3)_3$); *Major rotamer*: δ_C (125 MHz, $CDCl_3$): 154.8 (C=O), 154.5 (C^5), 139.3 (C^4), 130.9 (q, $J_{C\text{-}F}$ 3.2, C^7), 123.2 (q, $J_{C\text{-}F}$ 3.8, C^3), 123.1 (q, $J_{C\text{-}F}$ 270.3, C^1), 122.7 (q, $J_{C\text{-}F}$ 34.6, C^2), 115.2 (C^6), 79.7 ($CO_2C(CH_3)_3$), 69.6 (CH_2OAr), 55.5 (*C*HNBoc), 47.1 (*C*H_2NBoc), 28.4 ($CO_2C(CH_3)_3$), 28.0 (*C*H_2CH_2CH_2NBoc), 23.8 (*C*H_2CH_2NBoc); *Minor rotamer*: δ_C (125 MHz, $CDCl_3$): 154.4 (C=O), 154.1 (C^5), 139.4 (C^4), 130.8 (q, $J_{C\text{-}F}$ 3.2, C^7), 123.4 (q, $J_{C\text{-}F}$ 3.8, C^3), 123.1 (q, $J_{C\text{-}F}$ 270.3, C^1), 122.7 (q, $J_{C\text{-}F}$ 34.6, C^2), 114.6 (C^6), 80.1 ($CO_2C(CH_3)_3$), 70.1 (CH_2OAr), 55.4 (*C*HNBoc), 46.7 (*C*H_2NBoc), 28.7 (*C*H_2CH_2CH_2NBoc), 28.6 ($CO_2C(CH_3)_3$), 22.8 (*C*H_2CH_2NBoc); υ_{max} (neat) cm^{-1}: 2977 (m) & 2882 (m) (C-H), 1687 (s) (C=O), 1627 (s) (N-H), 1584 (w) (Ar C=C), 1541 (s) & 1322 (s) (NO_2), 1284 (s) & 1125 (s) (C-O); HRMS calcd for $C_{17}H_{21}F_3N_2O_5$ $[M+H]^+$: 391.1475. Found: 391.1477.

The data was in accordance with the literature.[Δ]

[Δ] Jones, C. R.; Qureshi, M. K. N.; Truscott, F. R.; Hsu, S.-T. D.; Morrison, A. J.; Smith; M. D. *Angew. Chem. Int. Ed.* **2008**, *47*, 7099.

(*S*)-*tert*-Butyl 2-((2-amino-4-(trifluoromethyl)phenoxy)methyl)pyrrolidine-1-carboxylate



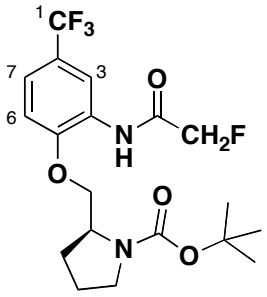
Reaction performed on a 0.069 mmol scale utilizing the same procedure for the preparation of (*S*)-2-((1-methylpyrrolidin-2-yl)methoxy)-5-(trifluoromethyl)aniline to yield the crude aniline (0.022 g, 0.062 mmol, 90 %, 4:1 Pet:EtOAc, R_f 0.28) as a pale brown oil which was used in subsequent reactions without purification.

$[\alpha]_D^{25}$ – 15.0 (c = 1.0, $CHCl_3$); δ_H (500 MHz, $CDCl_3$): 6.95 (1H, br d, *J* 8.4, Ar-H^7), 6.90 (1H, br s, Ar-H^3), 6.86 (1H, d, *J* 8.4, Ar-H^6), 4.26-4.12 (2H, br m, CH_2OAr), 3.97-3.88 (3H, br m, C*H*NBoc & Ar-NH_2), 3.38 (2H, br m, CH_2NBoc), 2.04-1.97 (3H, br m, CH_2CH_2CH_2NBoc), 1.86 (1H, br m, CH_2CH_2CH_2NBoc), 1.47 (9H, s, $CO_2C(CH_3)_3$); *Major rotamer*: δ_C (125 MHz, $CDCl_3$): 154.9 (C=O), 148.5 (C^5), 136.5 (C^4), 124.5 (q, $J_{C\text{-}F}$ 271.1, C^1), 123.3 (q, $J_{C\text{-}F}$ 34.2, C^2), 115.4 (q, $J_{C\text{-}F}$ 4.0, C^7), 111.0 (C^3), 110.7 (C^6), 79.5 ($CO_2C(CH_3)_3$), 68.8 (CH_2OAr), 55.8 (*C*HNBoc), 46.9 (CH_2NBoc), 28.5 ($CO_2C(CH_3)_3$), 27.9 ($CH_2CH_2CH_2$NBoc), 23.9 (CH_2CH_2NBoc); *Minor rotamer*: δ_C (125 MHz, $CDCl_3$): 154.4 (C=O), 148.3 (C^5), 136.5 (C^4), 124.5 (q, $J_{C\text{-}F}$ 271.1, C^1), 123.3 (q, $J_{C\text{-}F}$ 34.2, C^2), 115.4 (q, $J_{C\text{-}F}$ 4.0, C^7), 111.3 (C^3), 110.7 (C^6), 80.0 ($CO_2C(CH_3)_3$), 68.7 (CH_2OAr), 55.6 (*C*HNBoc), 46.6 (CH_2NBoc), 28.8 ($CH_2CH_2CH_2$NBoc), 28.5 ($CO_2C(CH_3)_3$), 22.9 (CH_2CH_2NBoc); υ_{max} (neat) cm^{-1}: 3471 (br) & 3354 (br) (N-H), 2976 (m) & 2929 (w) (C-H), 1681 (s) (C=O), 1623 (s) (N-H), 1521 (s) (Ar C=C), 1220 (s) & 1107 (s) (C-O); HRMS calcd for $C_{17}H_{23}F_3N_2O_3$ $[M+H]^+$: 361.1734. Found: 361.1734.

The data was in accordance with the literature.[Δ]

[Δ] Jones, C. R.; Qureshi, M. K. N.; Truscott, F. R.; Hsu, S.-T. D.; Morrison, A. J.; Smith; M. D. *Angew. Chem. Int. Ed.* **2008**, *47*, 7099.

(*S*)-*tert*-Butyl 2-((2-(2-fluoroethanamido)-4-(trifluoromethyl)phenoxy)methyl)pyrrolidine-1-carboxylate

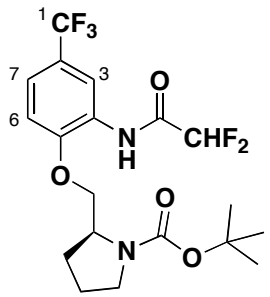


Sodium fluoroacetate (0.200 g, 2.00 mmol) was dissolved in a solution of HCl in ether (2 M, 1.0 mL) and stirred for 30 min. Dioxane (1.0 mL) was added followed by thionyl chloride (0.153 mL, 2.10 mmol) and the reaction mixture heated at 90 ˚C for 2 h.

Sodium hydride (60 % dispersion in mineral oil, 0.043 g, 1.08 mmol) was added to a solution of (*S*)-*tert*-butyl 2-((2-amino-4-(trifluoromethyl)phenoxy)methyl)pyrrolidine-1-carboxylate (0.240 g, 0.666 mmol) in dioxane (1.0 mL) and stirred at rt for 5 min. The cooled acid chloride solution was added dropwise over 5 min. The reaction mixture turned a dark brown and was left to stir overnight. The solution was washed with pH 7 buffer solution (15 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (4:1 Pet:EtOAc, R_f 0.24) to afford a pale crystalline solid (0.275 g, 0.654 mmol, 60 %).

Mp 57-58 ˚C; $[\alpha]_D^{25}$ - 35.7 (c = 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$): 8.71 (1H, br s, Ar-H^3), 8.62 (1H, br s, N-H), 7.36 (1H, dd, *J* 7.9, 1.4, Ar-H^7), 7.06 (1H, br d, *J* 7.9, Ar-H^6), 5.00 (2H, d, *J* 47.3, CH_2F), 4.25 (2H, br m, CH_2OAr & C*H*NBoc), 4.09 (1H, br m, CH_2OAr), 3.46-3.40 (2H, br m, CH_2NBoc), 2.14-2.03 (1H, br m, C$H_2CH_2CH_2$NBoc), 1.99-1.88 (3H, br m, CH_2CH_2NBoc), 1.47 (9H, s, $CO_2C(CH_3)_3$); *Major rotamer*: δ_C (125 MHz, $CDCl_3$): 171.1 (d, $J_{C\text{-}F}$ 16.8, C=O amide), 154.9 (C=O carbamate), 149.5 (C^5), 126.7 (C^4), 124.0 (q, $J_{C\text{-}F}$ 270.4, C^1), 123.3 (q, $J_{C\text{-}F}$ 32.4, C^2), 121.8 (q, $J_{C\text{-}F}$ 3.9, C^7), 116.9 (q, $J_{C\text{-}F}$ 3.6, C^3), 110.9 (C^6), 80.2 (d, $J_{C\text{-}F}$ 186.3, CH_2F), 79.7 ($CO_2C(CH_3)_3$), 69.4 (CH_2OAr), 55.7 (*C*HNBoc), 47.0 (CH_2NBoc), 28.3 ($CO_2C(CH_3)_3$), 27.9 ($CH_2CH_2CH_2$NBoc), 24.0 (CH_2CH_2NBoc); *Minor rotamer*: δ_C (125 MHz, $CDCl_3$): 171.1 (d, $J_{C\text{-}F}$ 16.8, C=O amide), 154.2 (C=O carbamate), 149.3 (C^5), 126.7 (C^4), 124.0 (q, $J_{C\text{-}F}$ 270.4, C^1), 123.3 (q, $J_{C\text{-}F}$ 32.4, C^2), 121.8 (q, $J_{C\text{-}F}$ 3.9, C^7), 117.0 (q, $J_{C\text{-}F}$ 3.6, C^3), 110.7 (C^6), 80.2 (d, $J_{C\text{-}F}$ 186.3, CH_2F), 79.7 ($CO_2C(CH_3)_3$), 69.4 (CH_2OAr), 55.5 (*C*HNBoc), 46.7 (CH_2NBoc), 28.3 ($CO_2C(CH_3)_3$), 27.9 ($CH_2CH_2CH_2$NBoc), 23.0 (CH_2CH_2NBoc); υ_{max} (neat) cm^{-1}: 3418 (s) (N-H), 2977 (m) & 2882 (w) (C-H), 1688 (br s) (C=O), 1615 (m) (N-H), 1544 (s) (Ar C=C), 1276 (s) & 1113 (s) (C-O); HRMS calcd for $C_{19}H_{24}F_4N_2O_4$ $[M+H]^+$: 421.1745. Found: 421.1745.

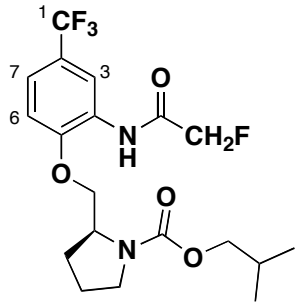
(*S*)-*tert*-Butyl 2-((2-(2,2-difluoroethanamido)-4-(trifluoromethyl)phenoxy)methyl)pyrrolidine-1-carboxylate



Reaction performed on a 0.832 mmol scale utilizing the same procedure for the preparation of (*S*)-2,2-difluoro-*N*-(2-((1-methylpyrrolidin-2-yl)methoxy)-5-(trifluoromethyl)phenyl)ethanamide. The crude product was purified by column chromatography (2:1 Pet:EtOAc, R_f 0.51) to afford a pale crystalline solid (0.321 g, 0.732 mmol, 88 %).

Mp 89-90 ˚C; $[\alpha]_D^{25}$ – 9.8 (c = 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$): 9.11 (1H, s, N-H), 8.66 (1H, br s, Ar-H^3), 7.37 (1H, br d, *J* 8.1, Ar-H^7), 7.00 (1H, br d, *J* 8.3, Ar-H^6), 6.13 (1H, t, *J* 54.0, CHF_2), 4.29 (1H, br m, C*H*NBoc), 4.16 (1H, br m, CH_2OAr), 4.06 (1H, br m, CH_2OAr), 3.53-3.35 (2H, br m, CH_2NBoc), 2.14-2.04 (1H, br m, C$H_2CH_2CH_2$NBoc), 1.97-1.90 (2H, br m, CH_2CH_2NBoc), 1.87 (1H, br m, C$H_2CH_2CH_2$NBoc), 1.44 (9H, s, $CO_2C(CH_3)_3$); δ_C (125 MHz, $CDCl_3$): 160.5 (t, $J_{C\text{-}F}$ 25.3, C=O amide), 155.3 (C=O carbamate), 150.0 (C^5), 126.4 (C^4), 124.0 (q, $J_{C\text{-}F}$ 272.0, C^1), 123.4 (q, $J_{C\text{-}F}$ 32.7, C^2), 122.5 (q, $J_{C\text{-}F}$ 3.9, C^7), 117.3 (q, $J_{C\text{-}F}$ 3.7, C^3), 110.9 (C^6), 108.2 (t, $J_{C\text{-}F}$ 251.1, CHF_2), 80.0 ($CO_2C(CH_3)_3$), 70.5 (CH_2OAr), 55.8 ($CHNBoc$), 47.1 (CH_2NBoc), 28.4 ($CO_2C(CH_3)_3$), 27.8 ($CH_2CH_2CH_2NBoc$), 23.9 (CH_2CH_2NBoc); υ_{max} (neat) cm^{-1}: 3247 (br) (N-H), 2979 (m) (C-H), 1719 (s) (C=O amide), 1674 (s) (C=O carbamate), 1618 (m) (N-H), 1498 (s) (Ar C=C), 1270 (s) & 1110 (s) (C-O); HRMS calcd for $C_{19}H_{23}F_5N_2O_4$ $[M+H]^+$: 439.1651. Found: 439.1655.

(*S*)-Isopropyl 2-((2-(2-fluoroacetamido)-4-(trifluoromethyl)phenoxy)methyl)pyrrolidine-1-carboxylate



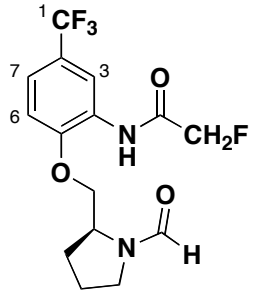
(*S*)-*tert*-Butyl 2-((2-(2-fluoroethanamido)-4-(trifluoromethyl)phenoxy)methyl)pyrrolidine-1-carboxylate (0.100 g, 0.238 mmol), was dissolved in dichloromethane:TFA (1:1 by volume, total volume 1.0 mL) and stirred at 0 ˚C for 1 h. The solvent was removed *in vacuo* and the residue redissolved in dichloromethane (5 mL) and washed with $NaHCO_3$ (aq) (5 mL). The organic layer was dried over Na_2SO_4, filtered and the solvent removed *in vacuo* to give the crude amine that was used without purification in the subsequent reaction.

Isobutyl chloroformate (34 μL, 0.262 mmol) was added dropwise to a solution of the crude amine in dichloromethane (1.0 mL) and triethylamine (36 μL, 0.262 mmol) at 0 ˚C. The reaction was stirred at rt for 3 h, then diluted with dichloromethane (10 mL), washed with brine (15 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (4:1 Pet:EtOAc, R_f 0.33) to afford a white solid (0.095 g, 0.226 mmol, 95 %).

Mp 75-77 ˚C; $[\alpha]_D^{25}$ - 48.0 (c = 0.5, $CHCl_3$); δ_H (500 MHz, $CDCl_3$): 8.79-8.74 (1H, br s, NH), 8.71 (1H, s, ArH^3), 7.36 (1H, br d, *J* 8.2, ArH^7), 7.06 (1H, br d, *J* 8.2, ArH^6), 4.97 (2H, d, *J* 47.3, CH_2F), 4.33-4.23 (2H, br m, CH_2OAr & $CHNCO_2{}^iBu$), 4.17-4.10 (1H, br m, CH_2OAr), 3.91-3.82 (2H, br m, $CH_2CH(CH_3)_2$), 3.53-3.42 (2H, br m, $CH_2NCO_2{}^iBu$), 2.20-2.06 (1H, br m, $CH_2CH_2CH_2NCO_2{}^iBu$), 2.04-1.89 (4H, br m, $CH_2CH_2CH_2NCO_2{}^iBu$, $CH_2CH_2NCO_2{}^iBu$ & $CH(CH_3)_2$), 0.95 (6H, d *J* 6.2, $CH(CH_3)_2$); *Major rotamer*: δ_C (125 MHz, $CDCl_3$): 165.5 (d, $J_{C\text{-}F}$ 17.0, C=O amide), 155.7 (C=O carbamate), 149.4 (C^5), 126.7 (C^4), 124.0 (q, $J_{C\text{-}F}$ 271.8, C^1), 123.4 (q, $J_{C\text{-}F}$ 33.4, C^2), 121.8 (q, $J_{C\text{-}F}$ 3.8, C^7), 116.9 (C^3), 110.8 (C^6), 80.2 (d, $J_{C\text{-}F}$ 186.9, CH_2F), 71.4 ($CH_2CH(CH_3)_2$), 69.2 (CH_2OAr), 56.0 ($CHNCO_2{}^iBu$), 46.7 ($CH_2NCO_2{}^iBu$), 28.0 ($CH_2CH_2CH_2NCO_2{}^iBu$), 27.9 ($CH(CH_3)_2$), 24.0 ($CH_2CH_2NCO_2{}^iBu$), 19.0 ($CH(CH_3)_2$); *Minor rotamer*: δ_C (125 MHz, $CDCl_3$): 165.5 (d, $J_{C\text{-}F}$ 17.0, C=O amide), 155.1 (C=O carbamate), 149.3 (C^5), 126.7 (C^4), 124.0 (q, $J_{C\text{-}F}$ 271.8, C^1), 123.4 (q, $J_{C\text{-}F}$ 33.4, C^2), 121.8 (q, $J_{C\text{-}F}$ 3.8, C^7), 116.9 (C^3), 110.6 (C^6), 80.2 (d, $J_{C\text{-}F}$ 186.9, CH_2F), 71.6 ($CH_2CH(CH_3)_2$), 69.4 (CH_2OAr), 55.7 ($CHNCO_2{}^iBu$), 47.1 ($CH_2NCO_2{}^iBu$), 28.9

($CH_2CH_2CH_2NCO_2{}^iBu$), 27.9 ($CH(CH_3)_2$), 24.0 ($CH_2CH_2NCO_2{}^iBu$), 19.1 ($CH(CH_3)_2$); υ_{max} (neat) cm^{-1}: 3417 (s) (N-H), 2962 (m) & 2879 (w) (C-H), 1693 (br s) (C=O), 1612 (m) (N-H), 1547 (s) (Ar C=C), 1275 (s) & 1116 (s) (C-O); HRMS calcd for $C_{19}H_{24}F_4N_2O_4$ $[M+Na]^+$: 443.1564. Found: 443.1561.

(*S*)-2-Fluoro-*N*-(2-((1-formylpyrrolidin-2-yl)methoxy)-5-(trifluoromethyl)phenyl)acetamide



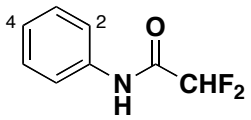
(*S*)-*tert*-Butyl 2-((2-(2-fluoroethanamido)-4-(trifluoromethyl)phenoxy)methyl)pyrrolidine-1-carboxylate (0.100 g, 0.238 mmol), was dissolved in dichloromethane:TFA (1:1 by volume, total volume 1.0 mL) and stirred at 0 ˚C for 1 h. The solvent was removed *in vacuo* and the residue redissolved in dichloromethane (5 mL) and washed with $NaHCO_3$ (aq) (5 mL). The organic layer was dried over Na_2SO_4, filtered and the solvent removed *in vacuo* to give the crude amine that was used without purification in the subsequent reaction.

TBTU (0.084g, 0.262 mmol) was added to a solution of the crude amine, formic acid (10 μL, 0.262 mmol) and triethylamine (36 μL, 0.262 mmol) in dichloromethane (1.0 mL) at 0 ˚C. The reaction was stirred at rt for 12 h, then diluted with dichloromethane (10 mL), washed with brine (15 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (97:3 EtOAc:CH_3OH, R_f 0.32 in EtOAc) to afford a white solid (0.063 g, 0.187 mmol, 76 %).

Mp 88-90 ˚C; $[\alpha]_D^{25}$ - 41.4 (c = 0.2, $CHCl_3$); *Major rotamer*: δ_H (500 MHz, $CDCl_3$): 8.78-8.74 (2H, br s, ArH^3 & NH), 8.38 (1H, br s, CHO), 7.41 (1H, br d, *J* 8.5, ArH^7), 7.06 (1H, br d, *J* 8.5, ArH^6), 5.02 (2H, d, *J* 47.3, CH_2F), 4.54-4.48 (1H, m, C*H*NCHO), 4.36-4.32 (1H, br m, CH_2OAr), 4.31-4.26 (1H, br m, CH_2OAr), 3.76-3.70 (1H, br m, C*H*$_2$NCHO), 3.62-3.54 (1H, br m, C*H*$_2$NCHO), 2.34-2.24 (1H, br m, C*H*$_2$CH$_2$CH$_2$NCHO), 2.16-2.04 (2H, br m, C*H*$_2$CH$_2$CH$_2$NCHO & C*H*$_2$CH$_2$NCHO), 2.02-1.94 (1H, br m, C*H*$_2$CH$_2$NCHO); *Minor rotamer*: δ_H (500 MHz, $CDCl_3$): 8.78-8.74 (1H, br s, ArH^3), 8.61-8.56 (1H, br s, NH), 8.46 (1H, s, CHO), 7.48 (1H, br d, *J* 8.5, ArH^7), 6.99 (1H, br d, *J* 8.5, ArH^6), 5.01 (2H, d, *J* 47.3, CH_2F), 4.41-4.36 (1H, m, C*H*NCHO), 4.15-4.07 (2H, br m CH_2OAr), 3.82-3.75 (1H, br m, C*H*$_2$NCHO), 3.53-3.46 (1H, br m, C*H*$_2$NCHO); *Major rotamer*: δ_C (125 MHz, $CDCl_3$): 165.5 (d, $J_{C\text{-}F}$ 17.3, *C*=O aromatic amide), 161.8 (*C*=O aliphatic amide), 149.2 (C^5), 126.8 (C^4), 124.0 (q, $J_{C\text{-}F}$ 273.5, C^1), 123.7 (q, $J_{C\text{-}F}$ 32.8, C^2), 121.7 (q, $J_{C\text{-}F}$ 4.0, C^7), 117.0 (q, $J_{C\text{-}F}$ 4.0, C^3), 110.8 (C^6), 80.2 (d, $J_{C\text{-}F}$ 186.9, CH_2F), 68.8 (CH_2OAr), 54.0 (*C*HNCHO), 47.0 (*C*H$_2$NCHO), 27.7 (*C*H$_2$CH$_2$CH$_2$NCHO), 24.0 (*C*H$_2$CH$_2$NCHO); *Minor rotamer*: δ_C (125 MHz, $CDCl_3$): 165.4 (d, $J_{C\text{-}F}$ 17.2, *C*=O aromatic

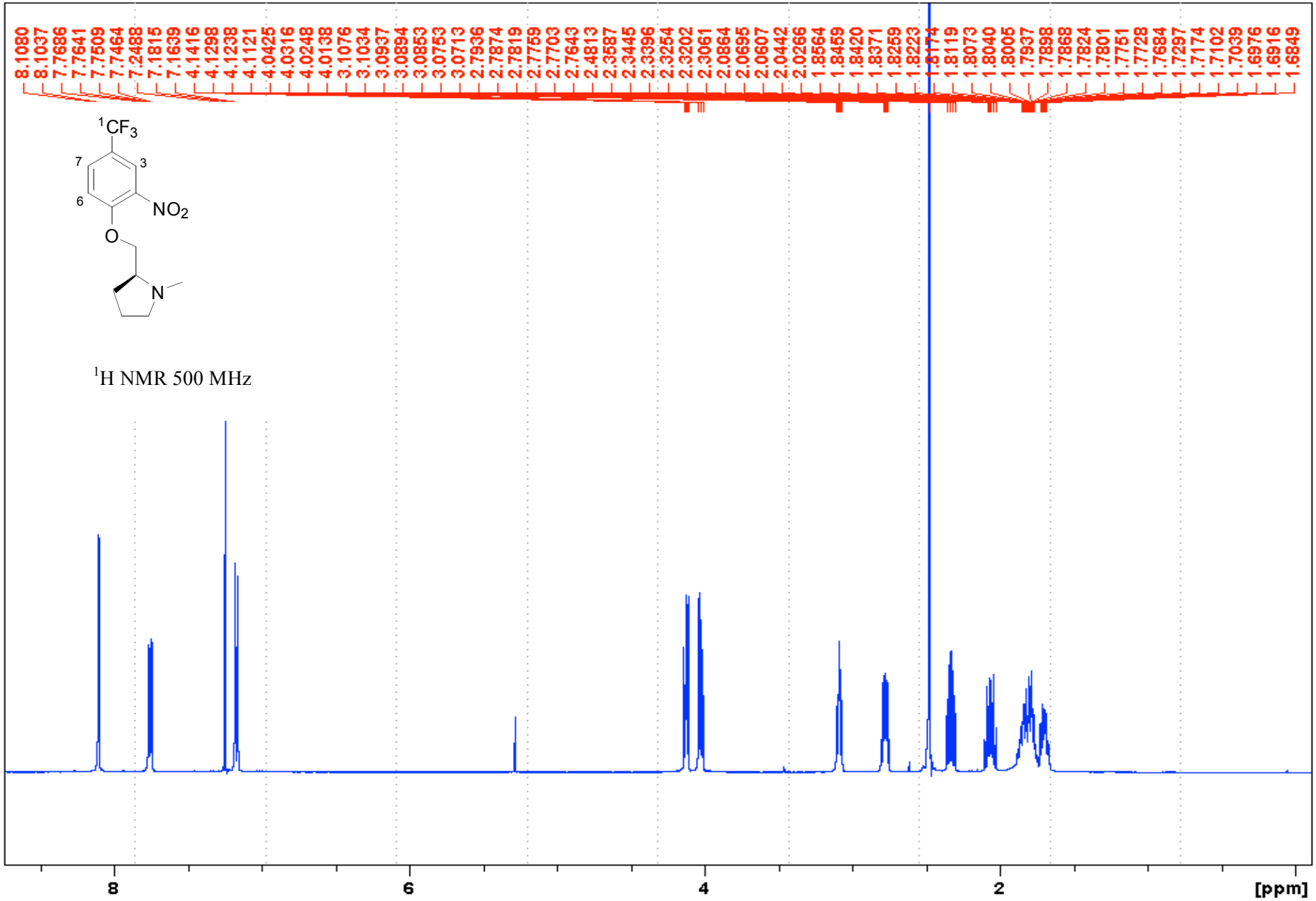
amide), 161.2 (*C*=O aliphatic amide), 148.9 (C_5), 126.6 (C^4), 123.9 (q, $J_{C\text{-}F}$ 273.3, C^1), 124.2 (q, $J_{C\text{-}F}$ 32.8, C^2), 121.9 (q, $J_{C\text{-}F}$ 4.0, C^7), 117.4 (q, $J_{C\text{-}F}$ 4.0, C^3), 110.6 (C^6), 80.3 (d, $J_{C\text{-}F}$ 187.5, CH_2F), 70.7 (CH_2OAr), 56.1 (*C*HNCHO), 43.8 (*C*H_2NCHO), 27.6 (*C*$H_2CH_2CH_2$NCHO), 22.8 (*C*H_2CH_2NCHO); υ_{max} (neat) cm^{-1}: 3417 (s) (N-H), 2959 (m) & 2854 (w) (C-H), 1693 (br s) (C=O), 1612 (m) (N-H), 1548 (s) (Ar C=C), 1275 (s) & 1116 (s) (C-O); HRMS calcd for $C_{15}H_{16}F_4N_2O_3$ $[M+Na]^+$: 371.0989. Found: 371.0987.

2,2-Difluoro-*N*-phenylacetamide



Reaction performed on a 5.49 mmol scale utilizing the same procedure for the preparation of (*S*)-2,2-difluoro-*N*-(2-((1-methylpyrrolidin-2-yl)methoxy)-5-(trifluoromethyl)phenyl)ethanamide **7**. The crude product was purified by column chromatography (4:1 Pet:EtOAc, R_f 0.70) to afford a colourless crystalline solid (0.935 g, 5.46 mmol, 99 %).

Mp 55 ˚C; δ_H (500 MHz, $CDCl_3$): 8.84 (1H, br s, N-H), 7.60 (2H, d, *J* 7.7, Ar^2-H), 7.35 (2H, t, *J* 7.6, Ar^3-H), 7.22 (1H, t, *J* 7.4, Ar^4-H), 6.03 (1H, t, *J* 54.1, CHF_2); δ_C (125 MHz, $CDCl_3$): 161.1 (t, $J_{C\text{-}F}$ 31.2, C=O), 135.9 (C^1), 129.1 (C^3), 125.9 (C^4), 120.9 (C^2), 108.4 (t, $J_{C\text{-}F}$ 313.1, CHF_2); υ_{max} (neat) cm^{-1}: 3264 (br) & 3052 (m) (N-H), 1677 (s) (C=O), 1597 (s) & 1560 (s) (Ar C=C), 1121 (s) & 1053 (s); HRMS calcd for $C_8H_7F_2NO$ $[M+Na]^+$: 194.0388. Found: 194.0394.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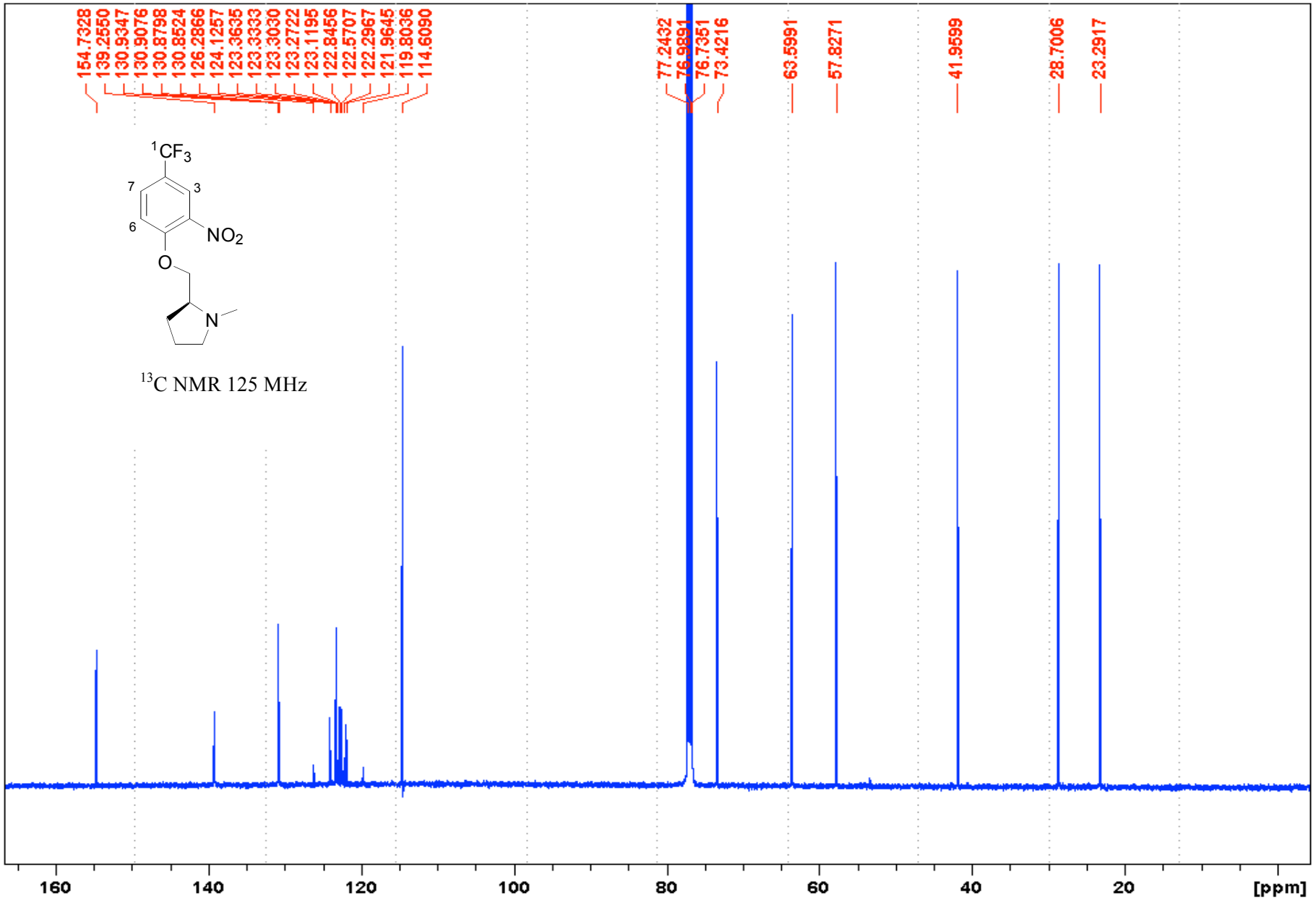
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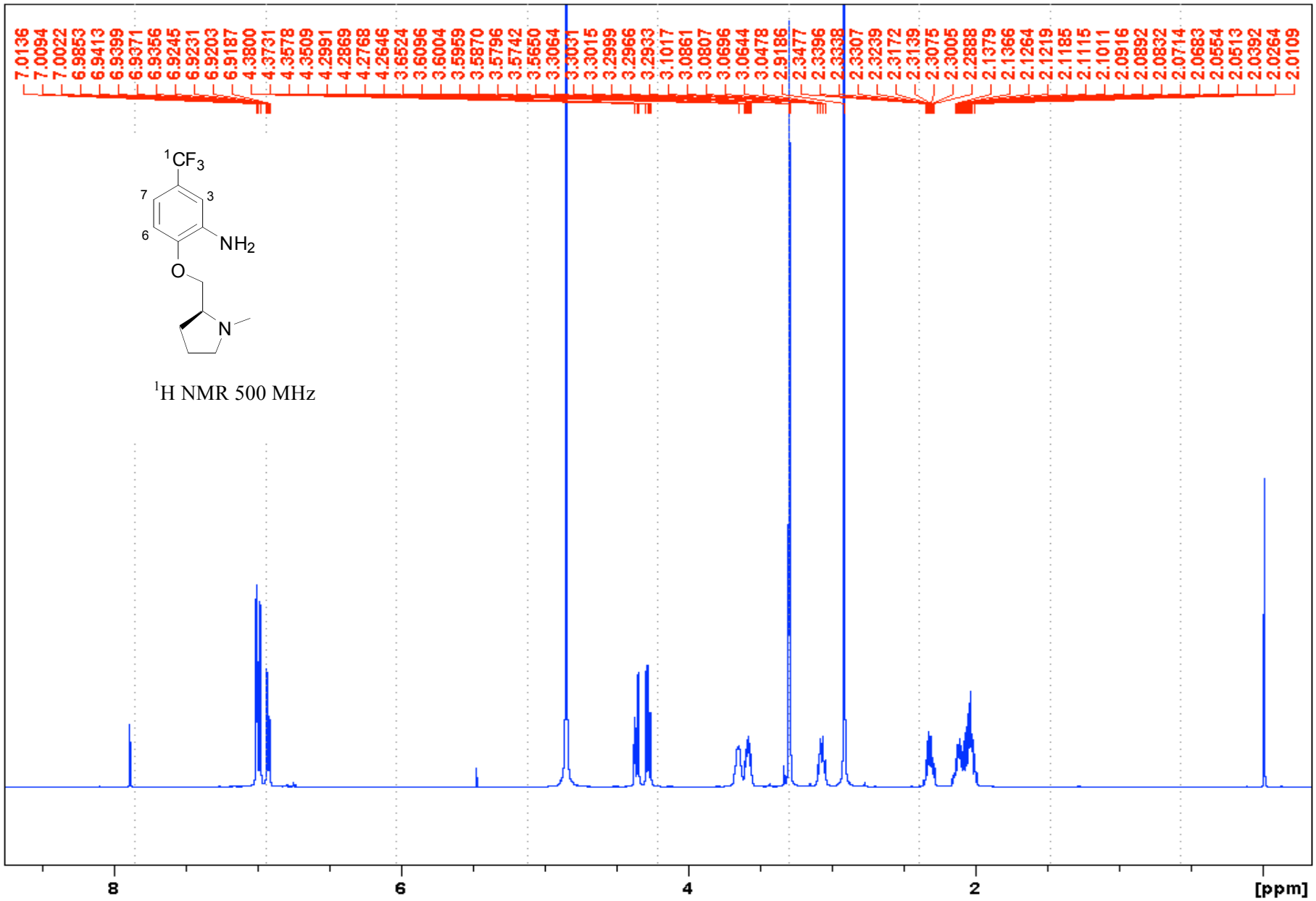
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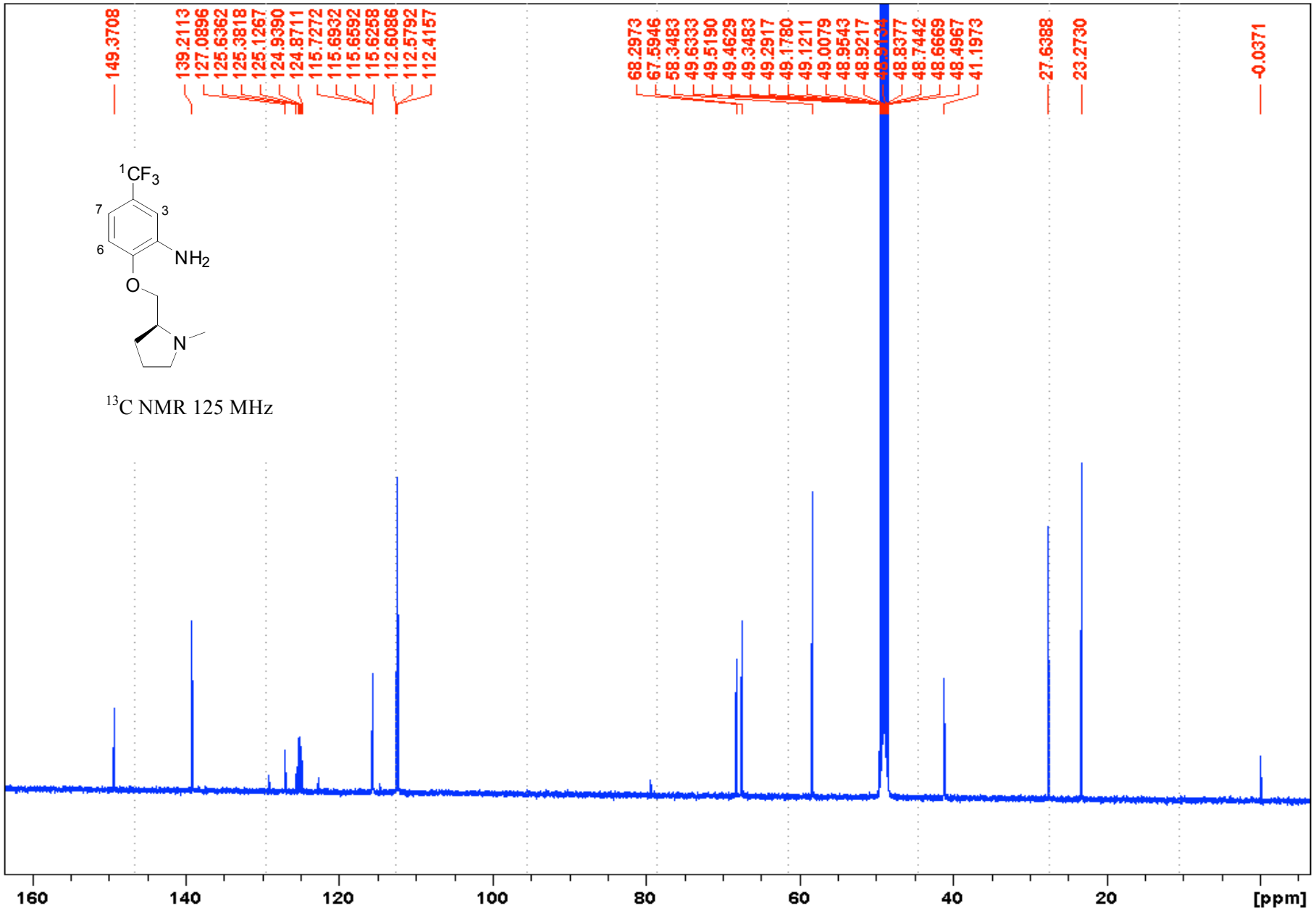
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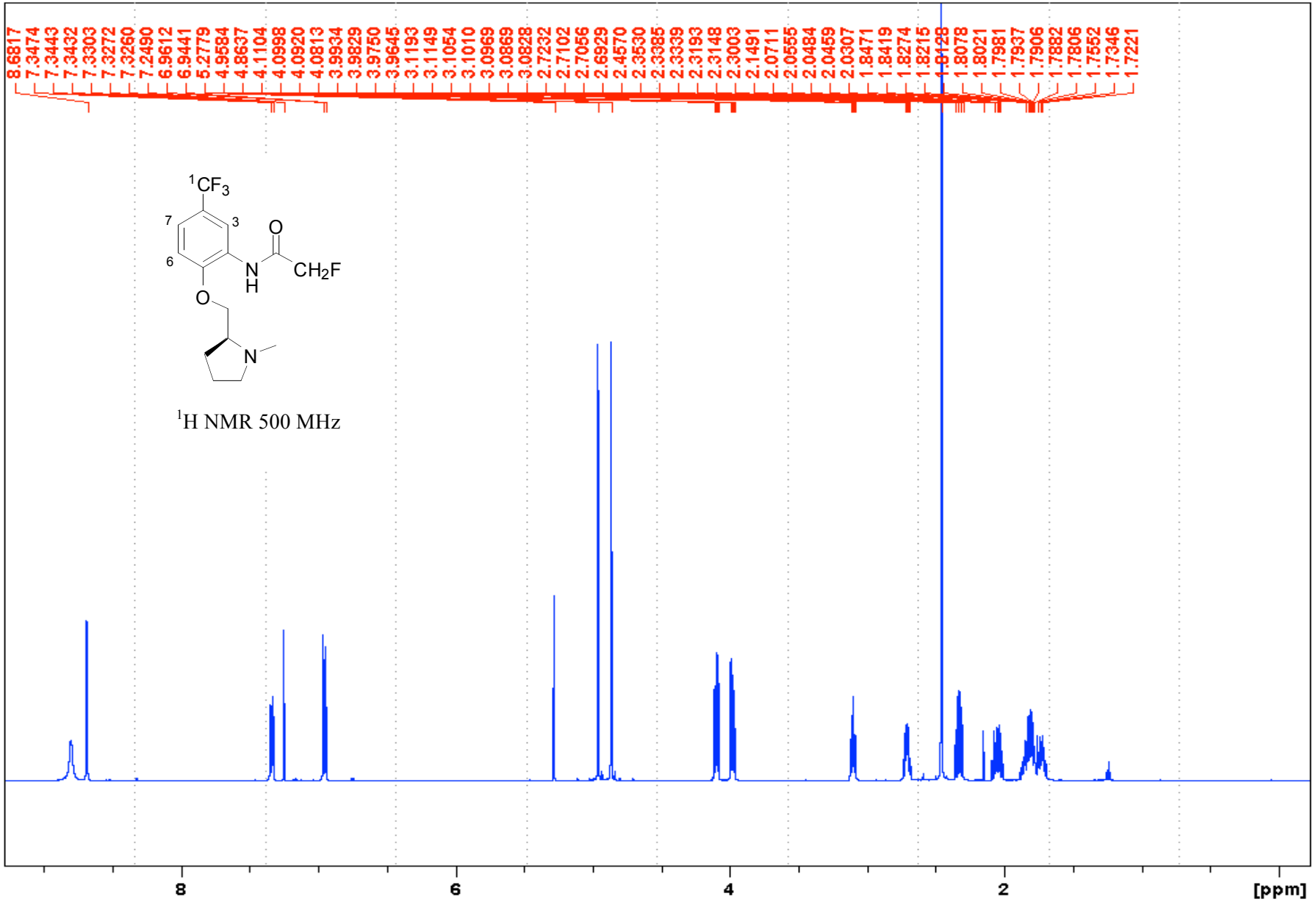
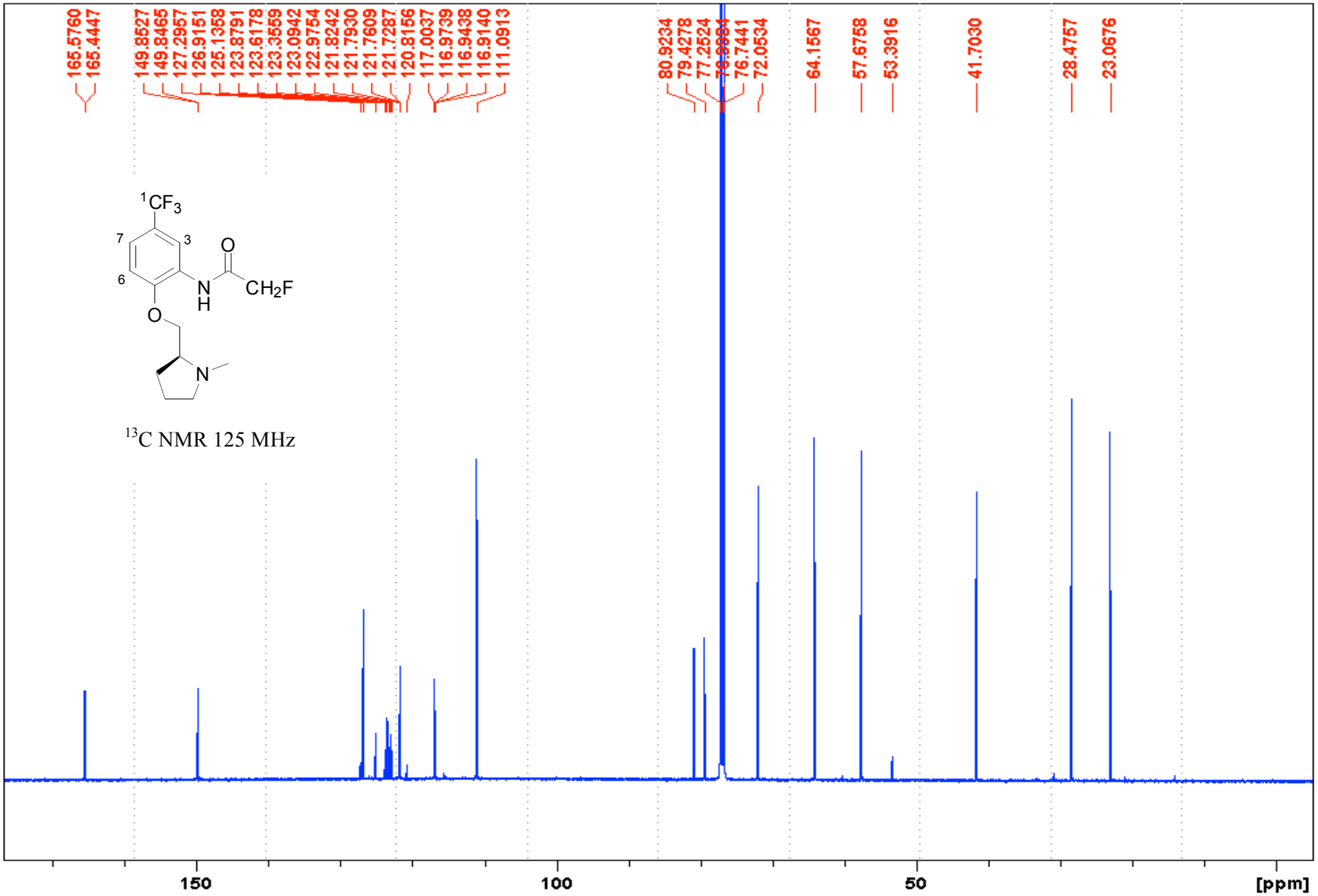
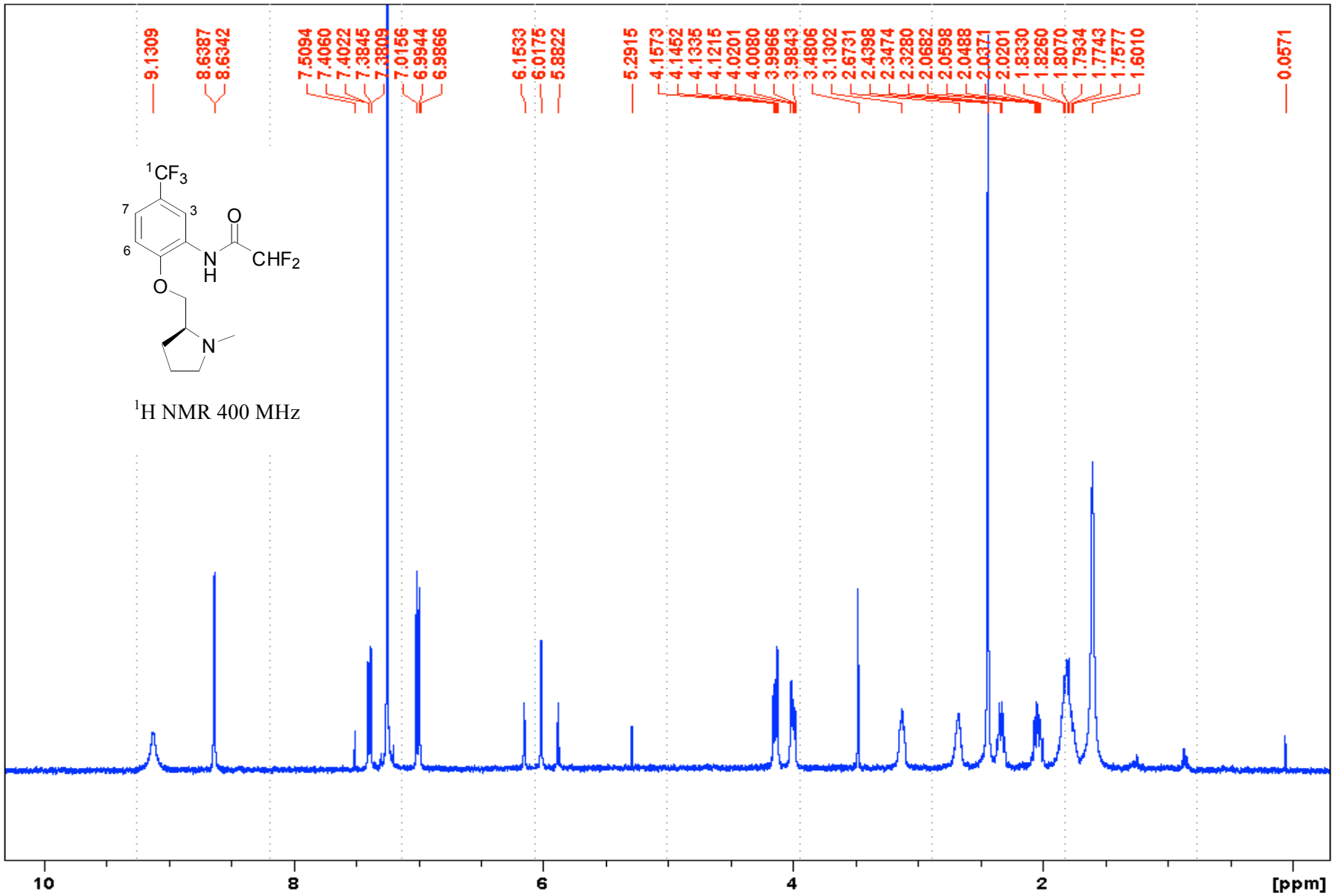
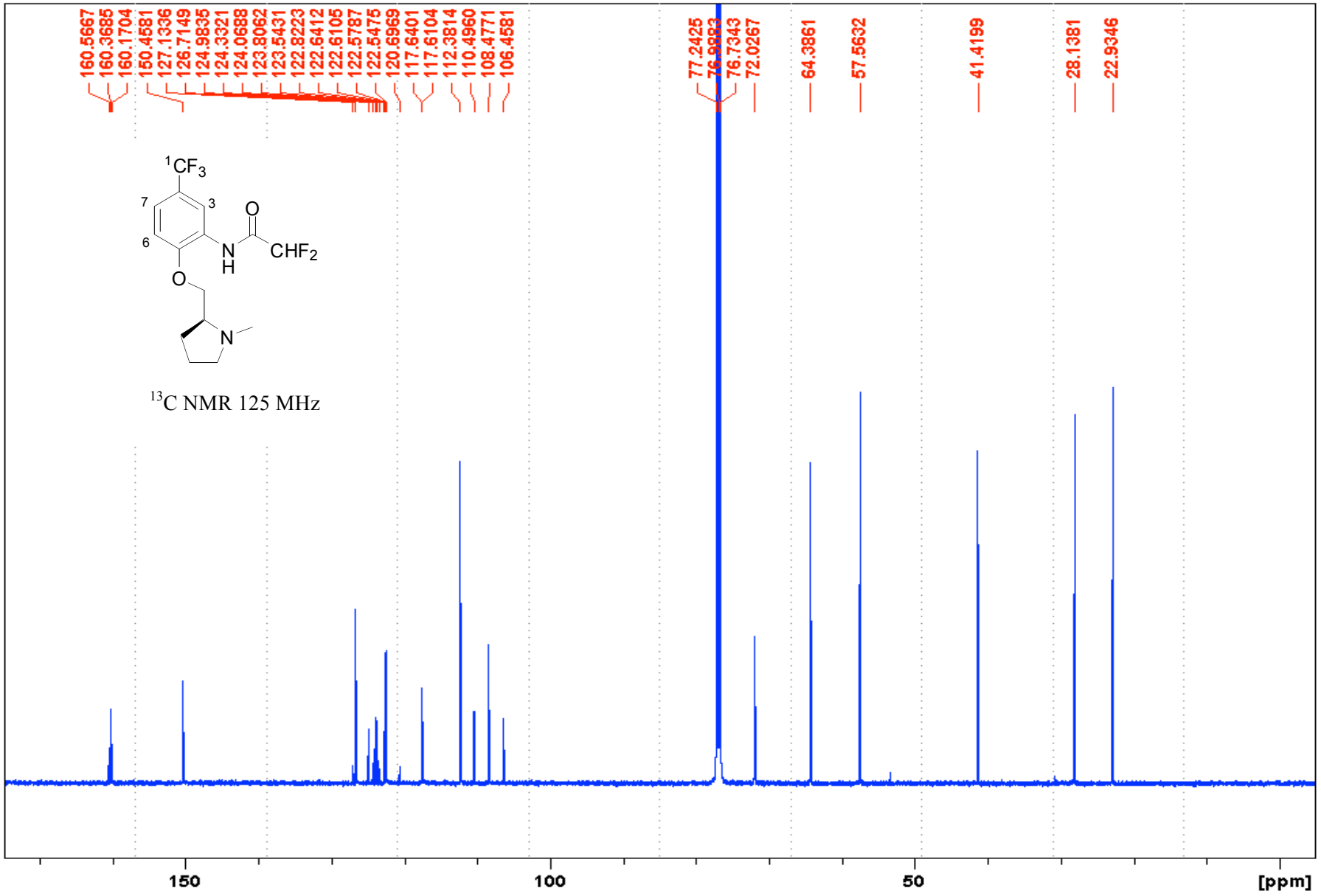
49.1211
49.0079
48.9543
48.9217
48.8377
48.7442
48.6669
48.4967
41.1973
27.6388
23.2730
-0.0371
$^{1}CF_3$
7
3
6
NH_2
O
N
^{13}C NMR 125 MHz
160
140
120
100
80
60
40
20
[ppm]

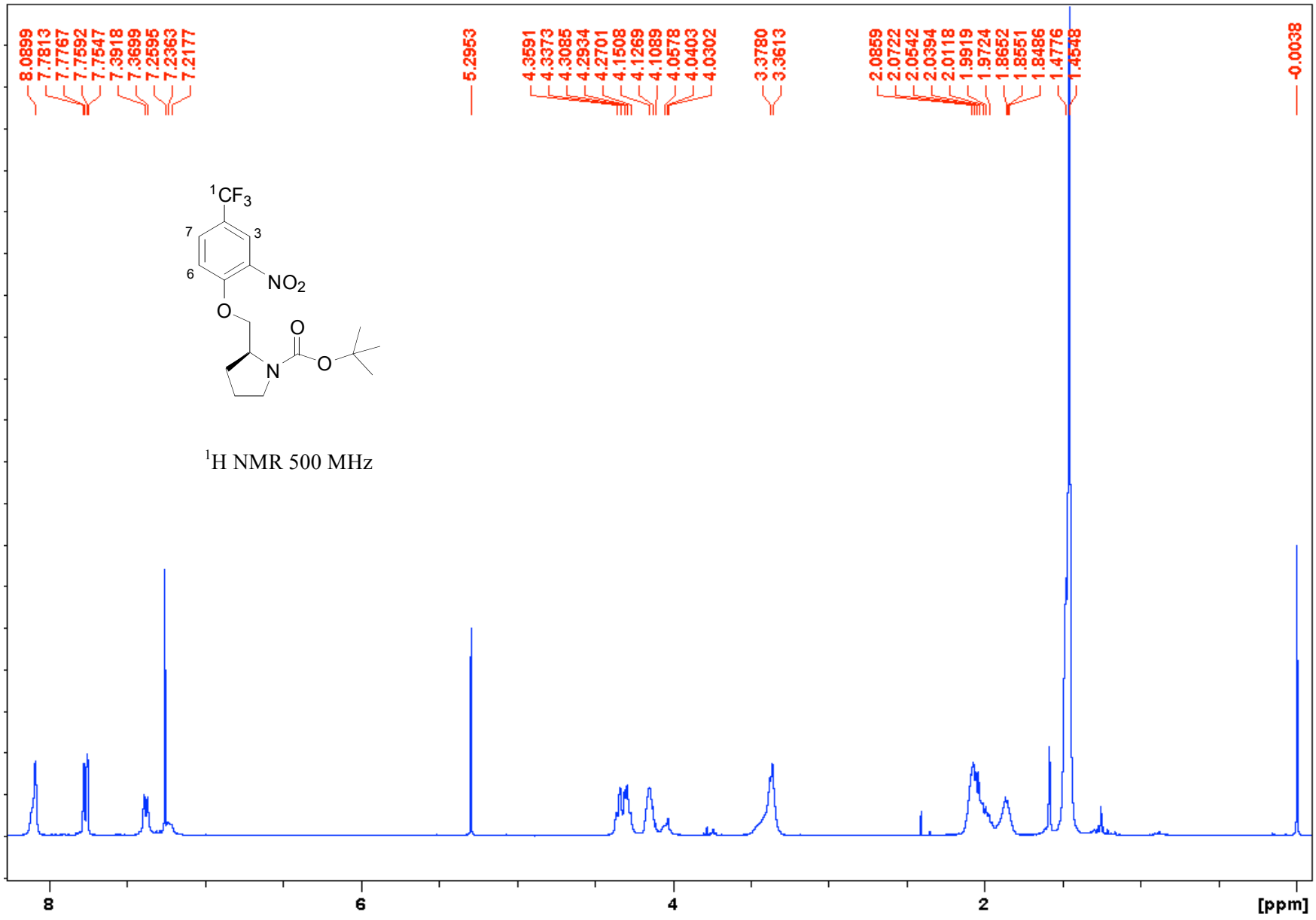


^{1}H NMR 500 MHz

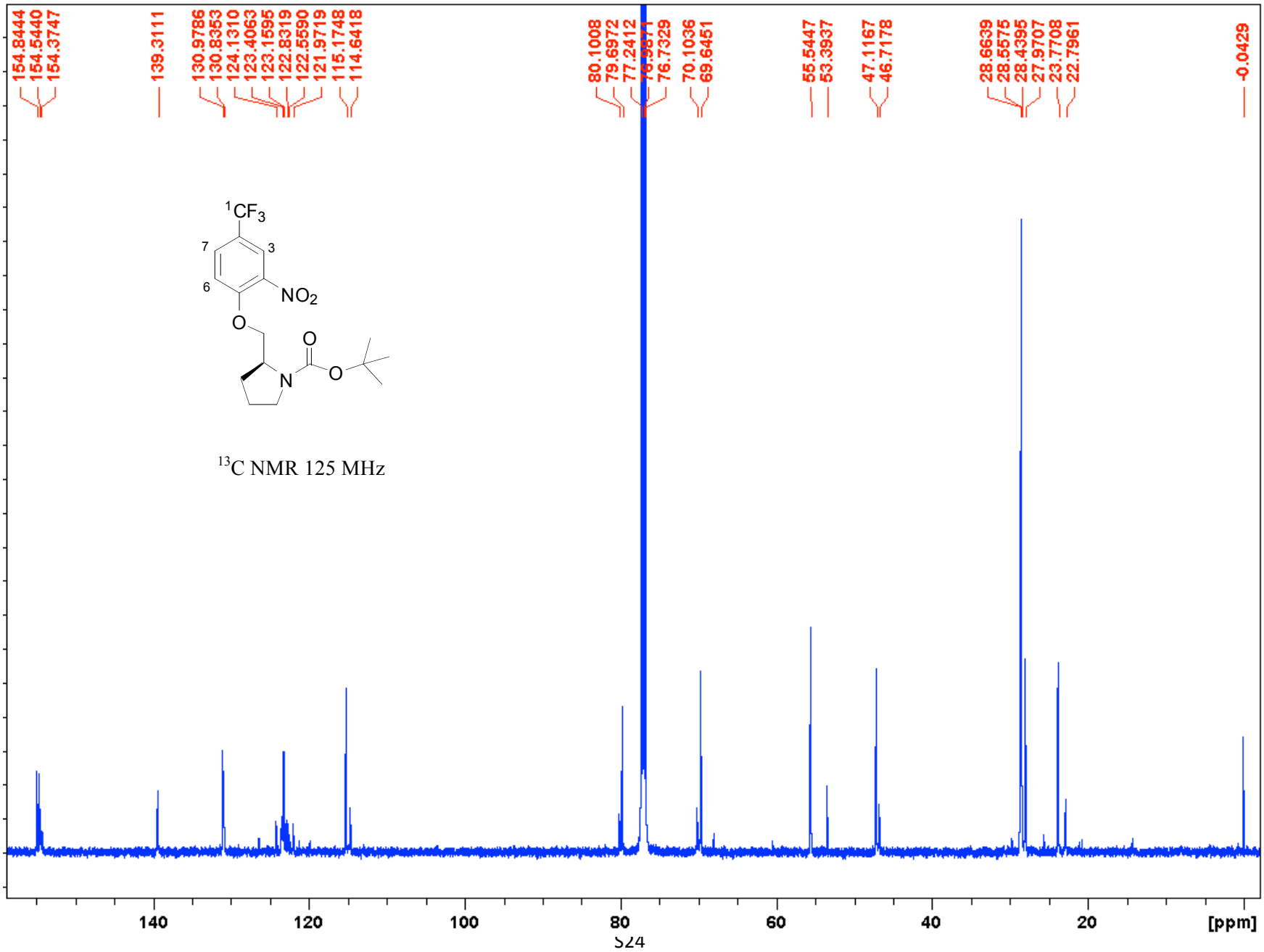

165.5760
165.4447
149.8527
149.8465
127.2957
126.9151
125.1358
123.8791
123.6178
123.3559
123.0942
122.9754
121.8242
121.7930
121.7609
121.7287
120.8156
117.0037
116.9739
116.9438
116.9140
111.0913
80.9234
79.4278
77.2524
76.7441
72.0534
64.1567
57.6758
53.3916
41.7030
28.4757
23.0676
$^{1}CF_3$
7
3
6
O
N
H
CH_2F
O
N
^{13}C NMR 125 MHz
150
100
50
[ppm]


9.1309
8.6387
8.6342
7.5094
7.4060
7.4022
7.3845
7.3809
7.0156
6.9944
6.9866
6.1533
6.0175
5.8822
5.2915
4.1573
4.1452
4.1335
4.1215
4.0201
4.0080
3.9966
3.9843
3.4806
3.1302
2.6731
2.4398
2.3474
2.3280
2.0682
2.0598
2.0488
2.0371
2.0201
1.8330
1.8260
1.8070
1.7934
1.7743
1.7577
1.6010
0.0571
$^1CF_3$
7
3
6
O
N
H
O
CHF_2
N
^{1}H NMR 400 MHz
10
8
6
4
2
[ppm]

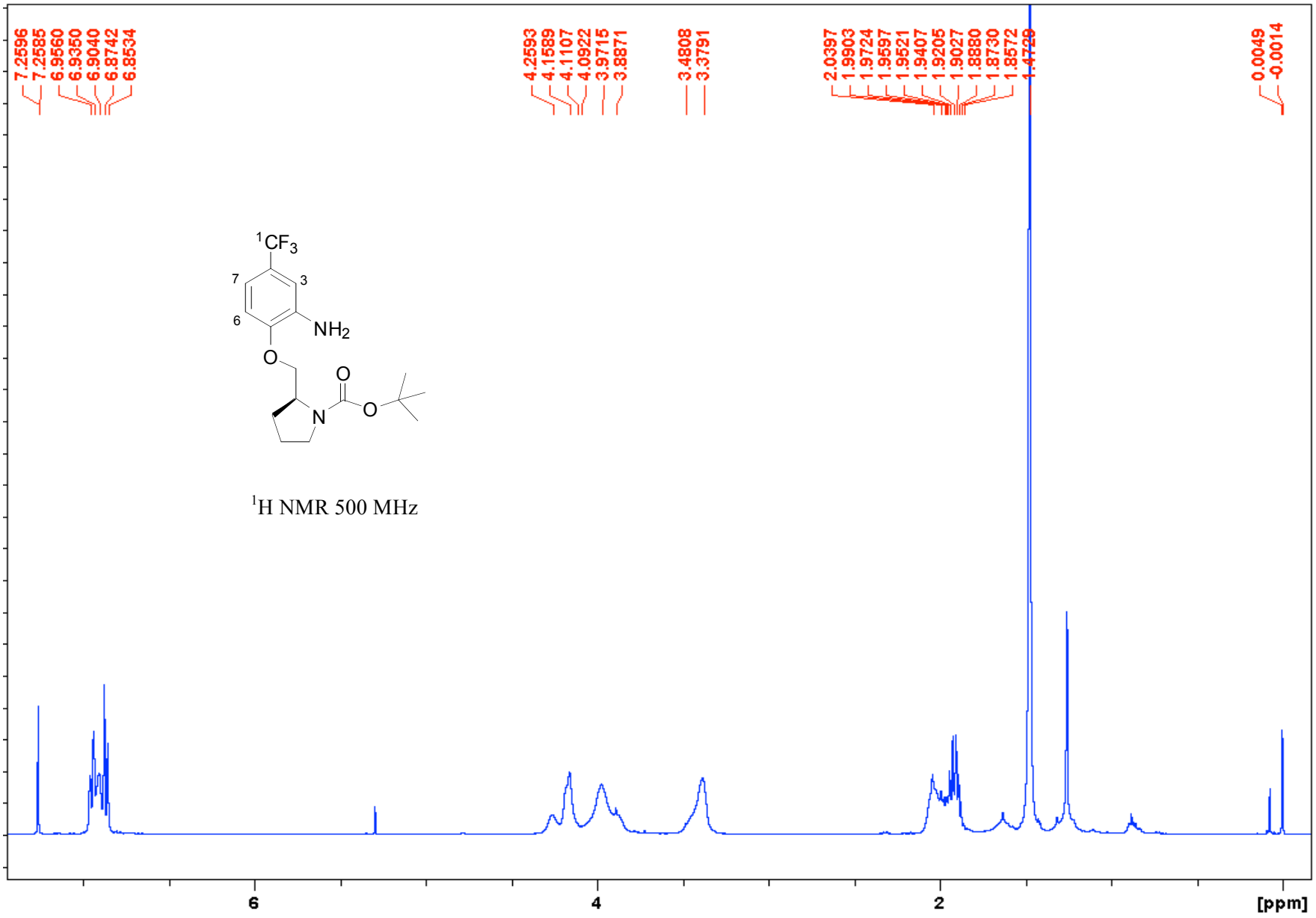

160.5667
160.3685
160.1704
150.4581
127.1336
126.7149
124.9835
124.3321
124.0688
123.8062
123.5431
122.8223
122.6412
122.6105
122.5787
122.5475
120.6969
117.6401
117.6104
112.3814
110.4960
108.4771
106.4581
77.2425
76.9883
76.7343
72.0267
64.3861
57.5632
41.4199
28.1381
22.9346
$^{1}CF_3$
7
3
6
O
N
H
O
CHF_2
N
^{13}C NMR 125 MHz
150
100
50
[ppm]



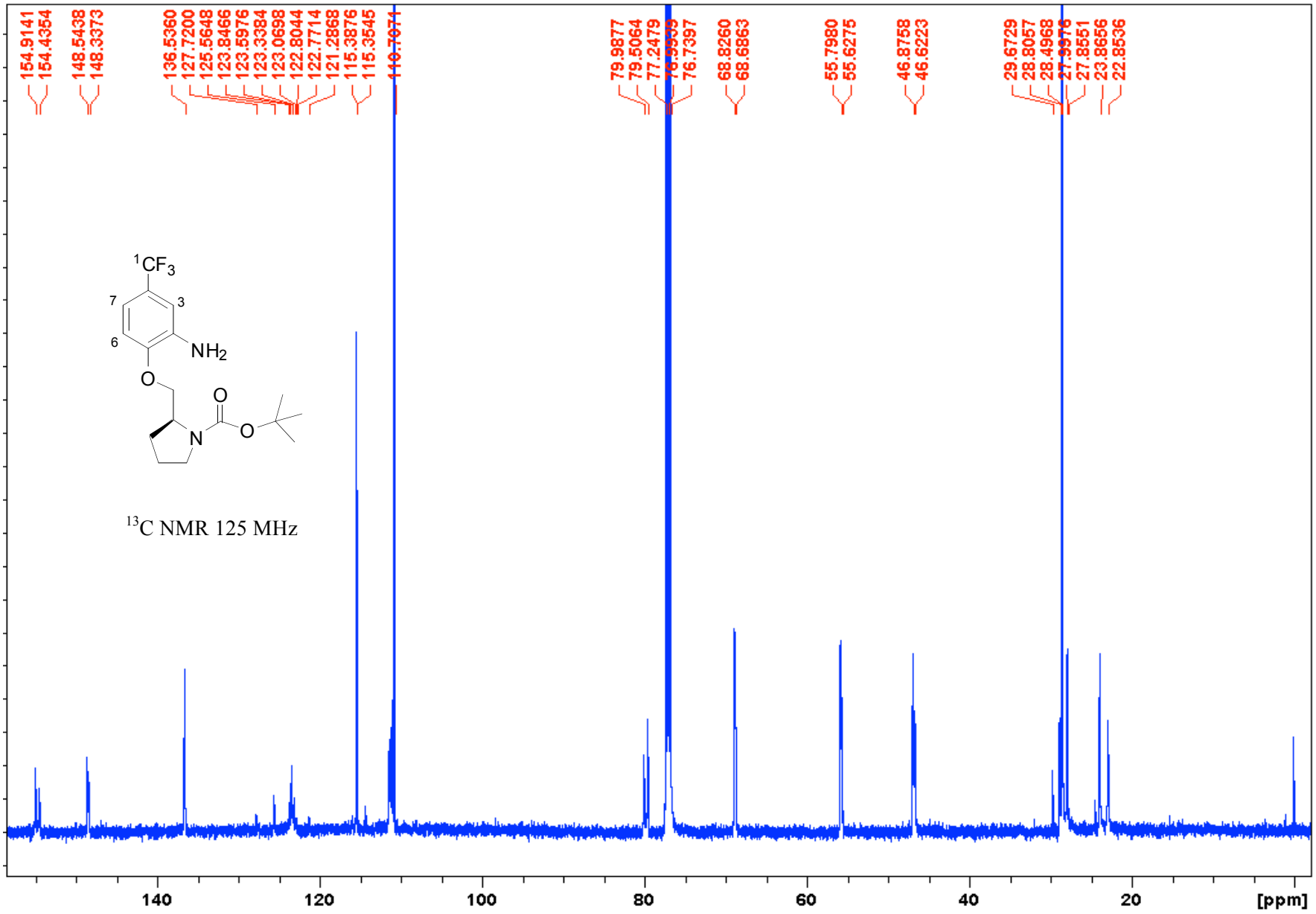
^{1}H NMR 500 MHz

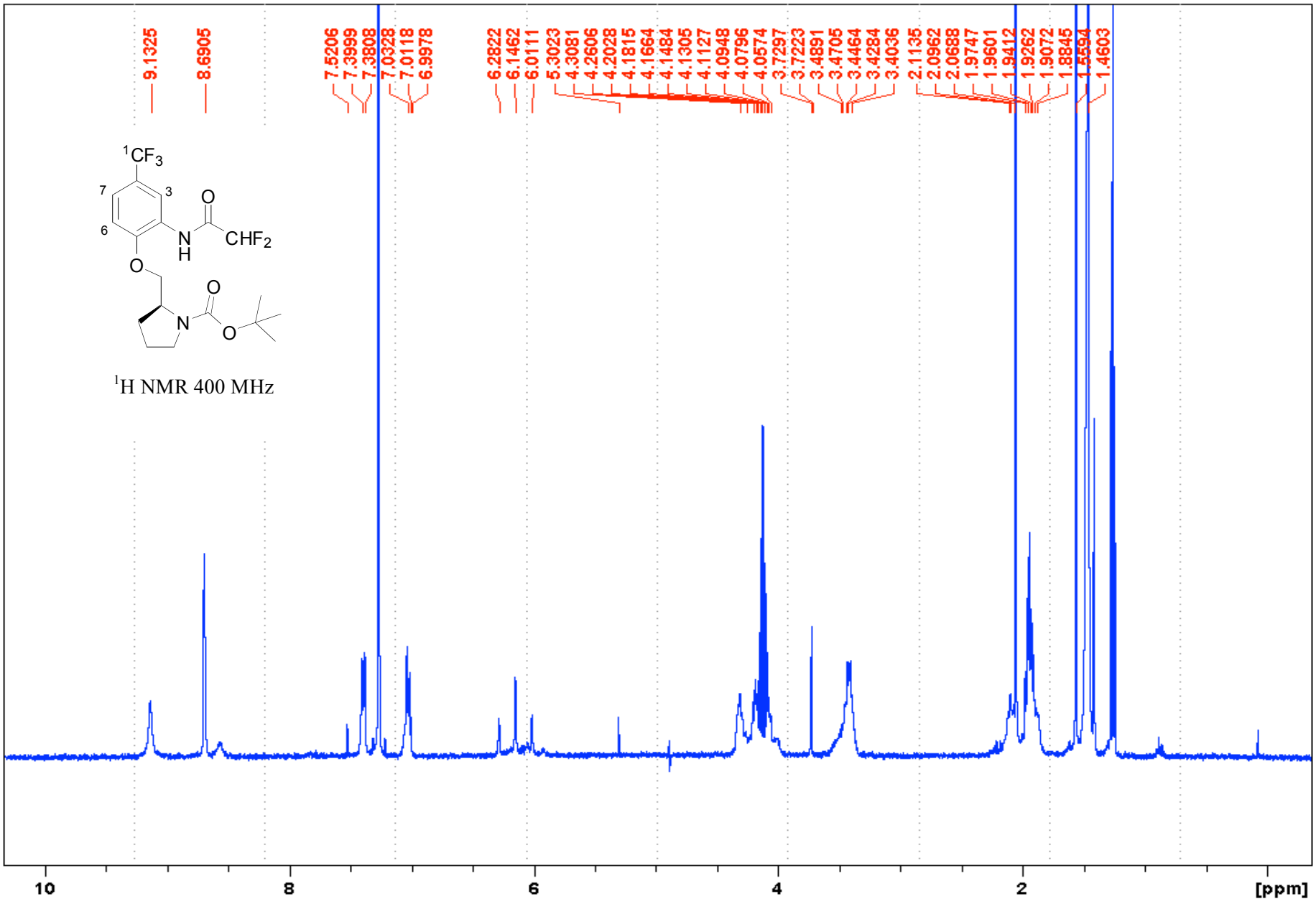


^{13}C NMR 125 MHz

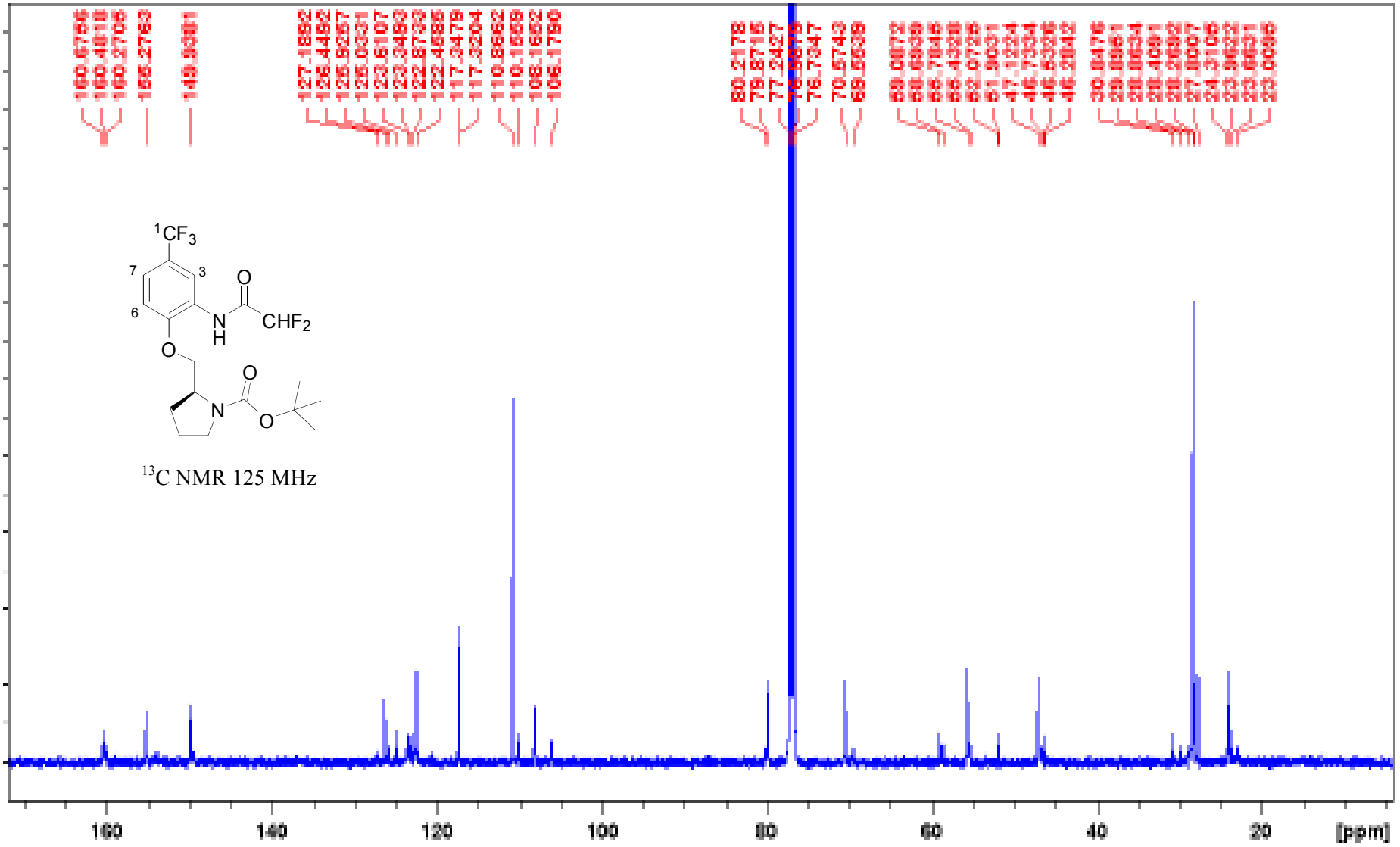


^{1}H NMR 500 MHz

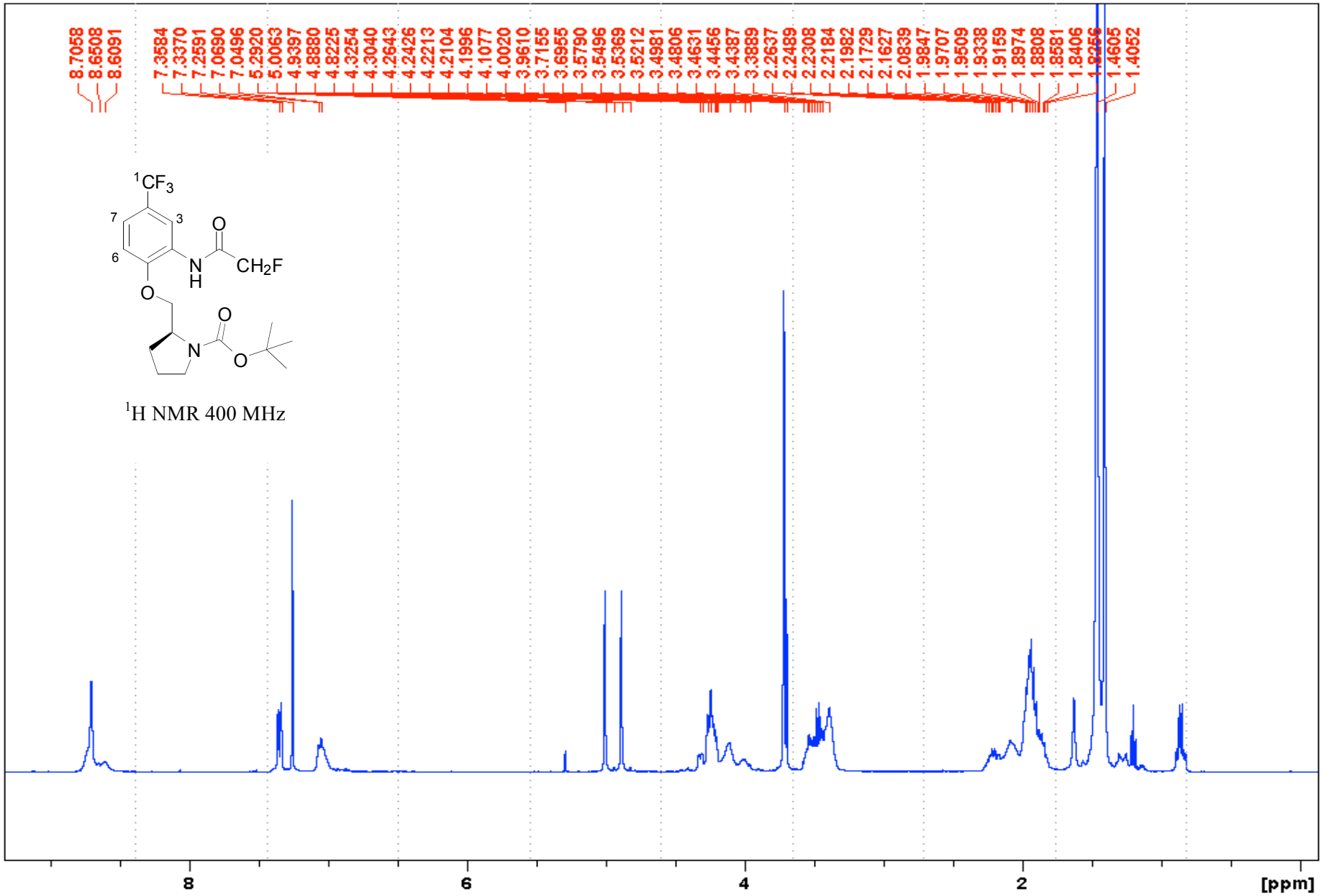

154.9141
154.4354
148.5438
148.3373
136.5360
127.7200
125.5648
123.8466
123.5976
123.3384
123.0698
122.8044
122.7714
121.2868
115.3876
115.3545
110.7071
79.9877
79.5064
77.2479
76.9303
76.7397
68.8260
68.6863
55.7980
55.6275
46.8758
46.6223
29.6729
28.8057
28.4968
27.9976
27.8551
23.8656
22.8536
$^{1}CF_3$
7
3
6
NH_2
O
O
N
O
^{13}C NMR 125 MHz
140
120
100
80
60
40
20
[ppm]



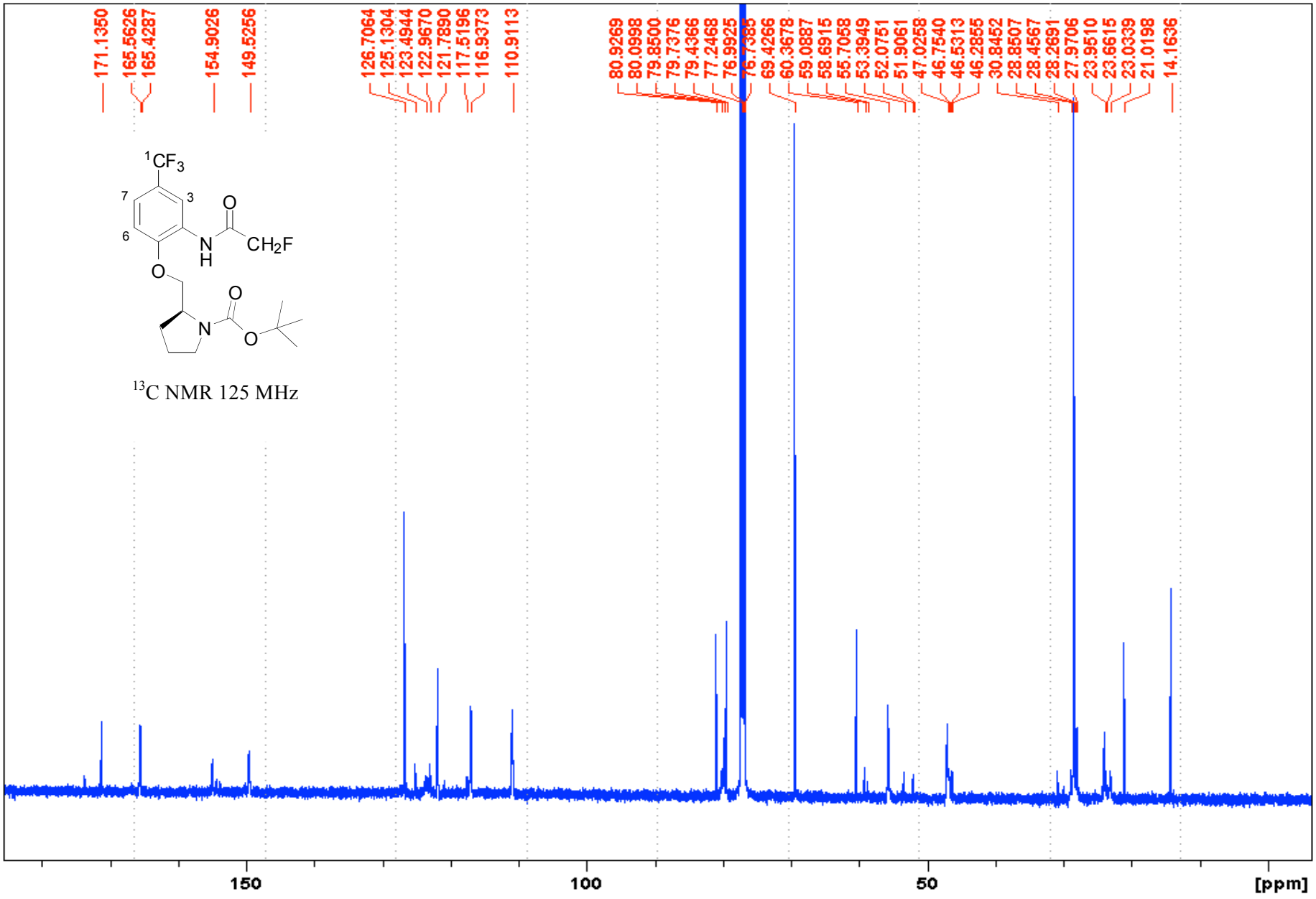
^{1}H NMR 400 MHz



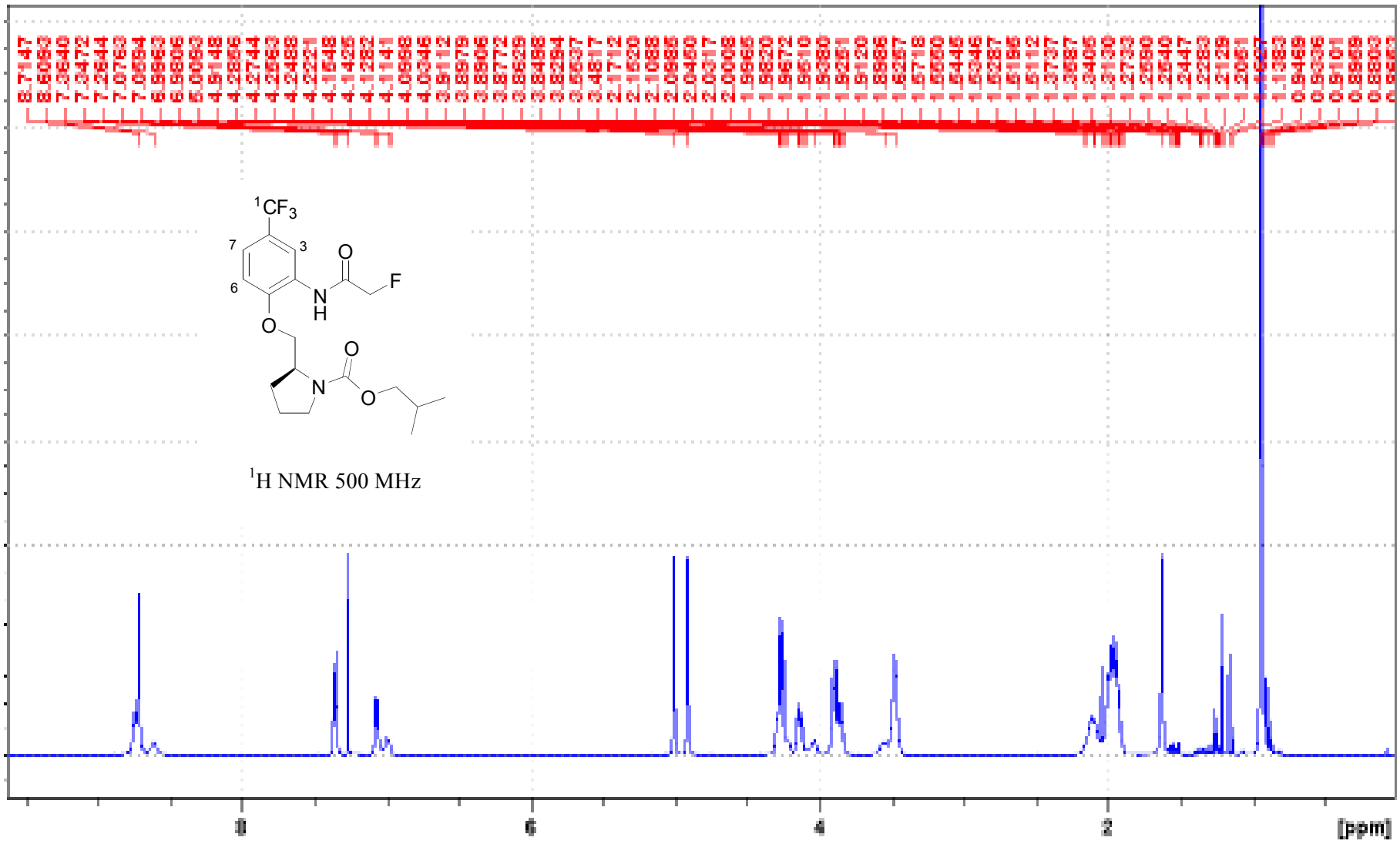
^{13}C NMR 125 MHz



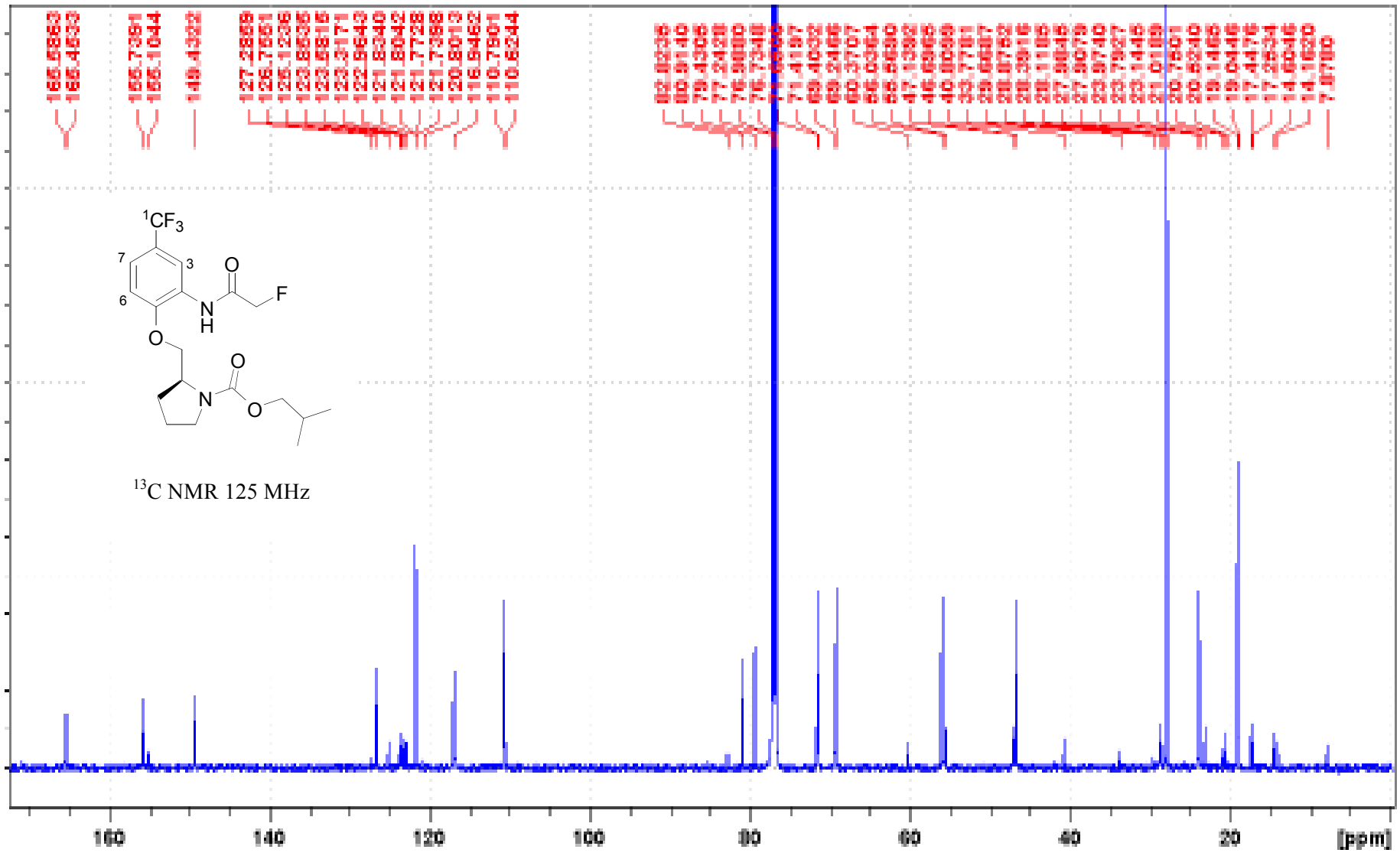
^{1}H NMR 400 MHz

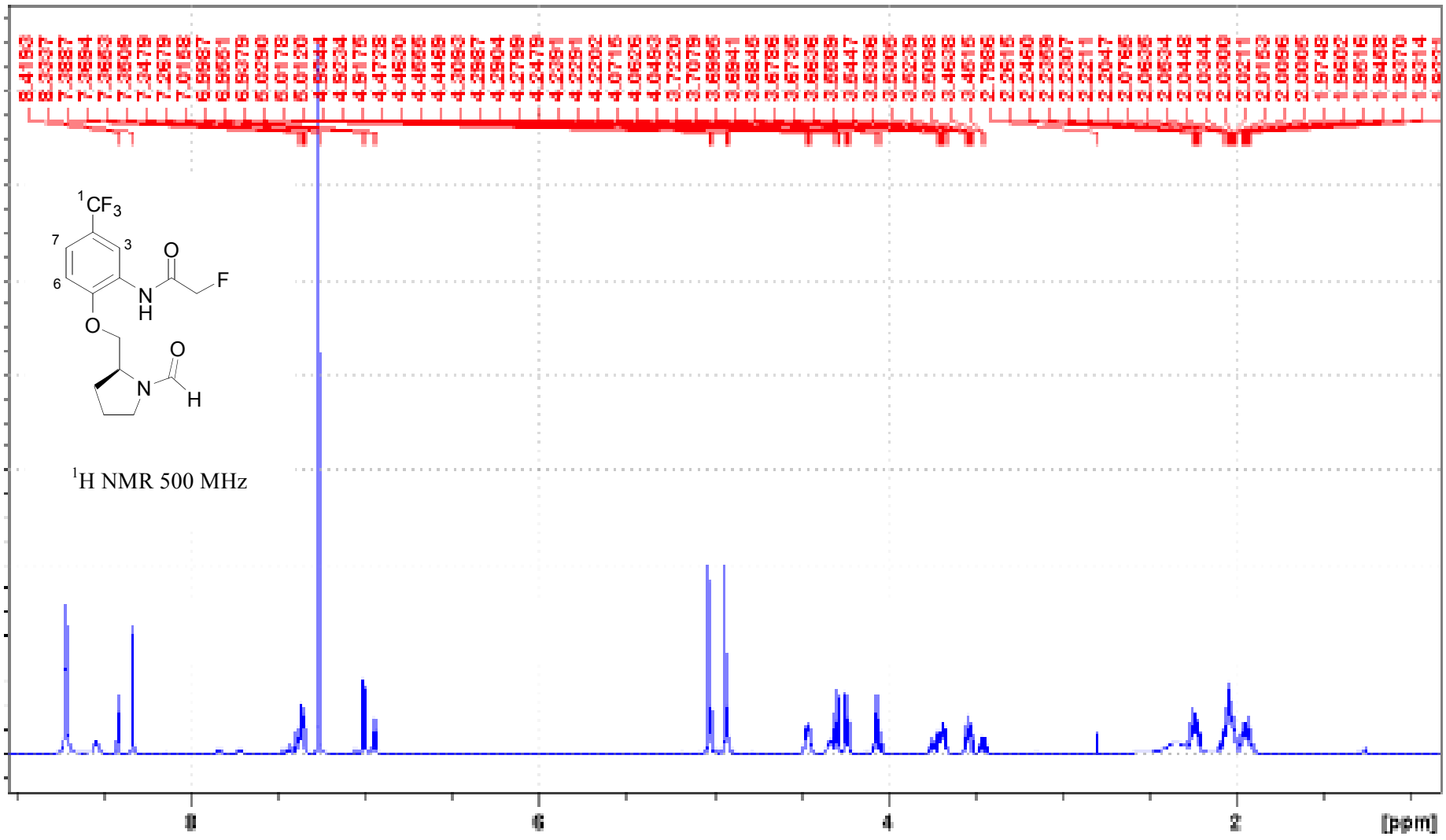


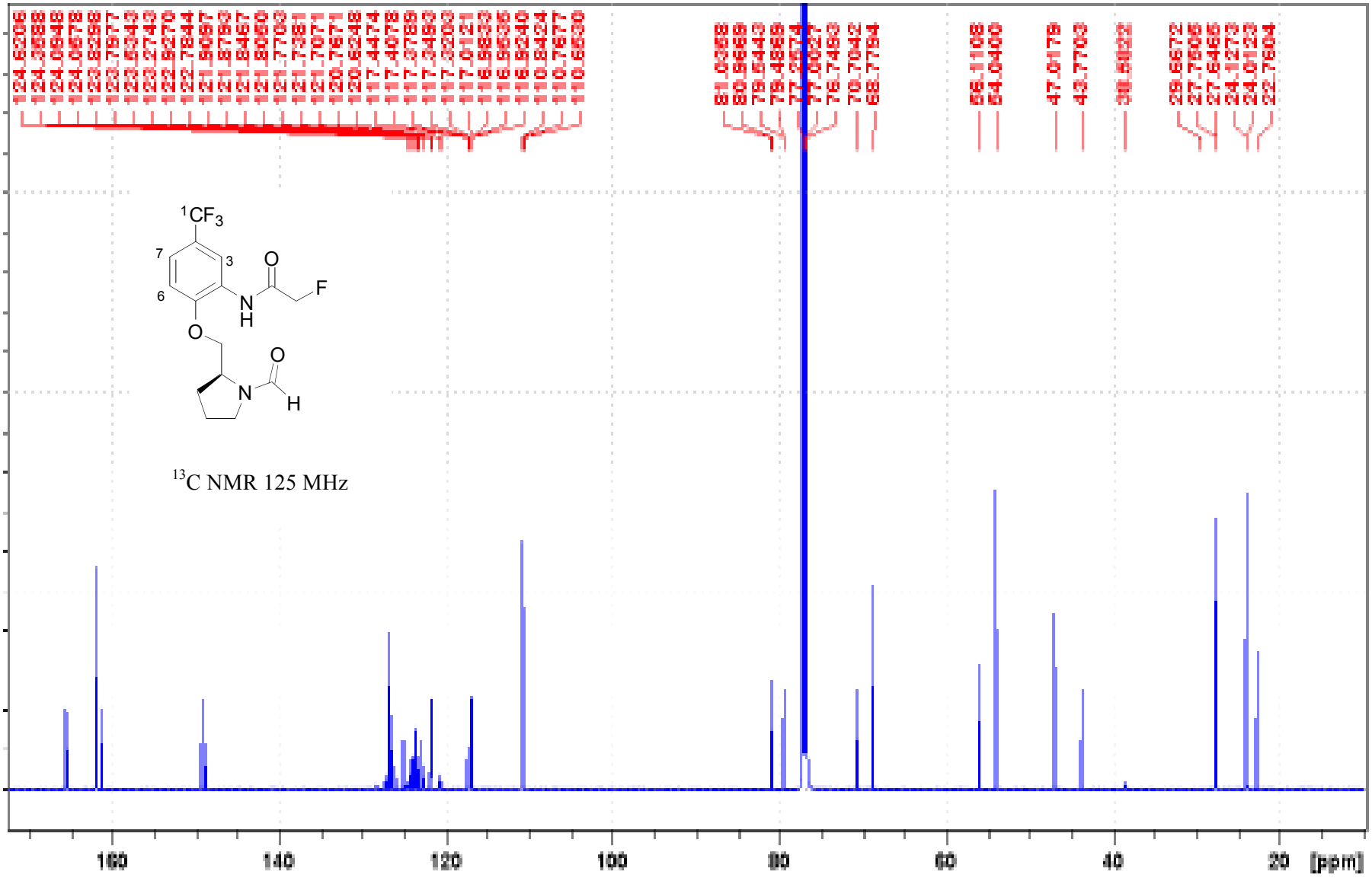
^{13}C NMR 125 MHz

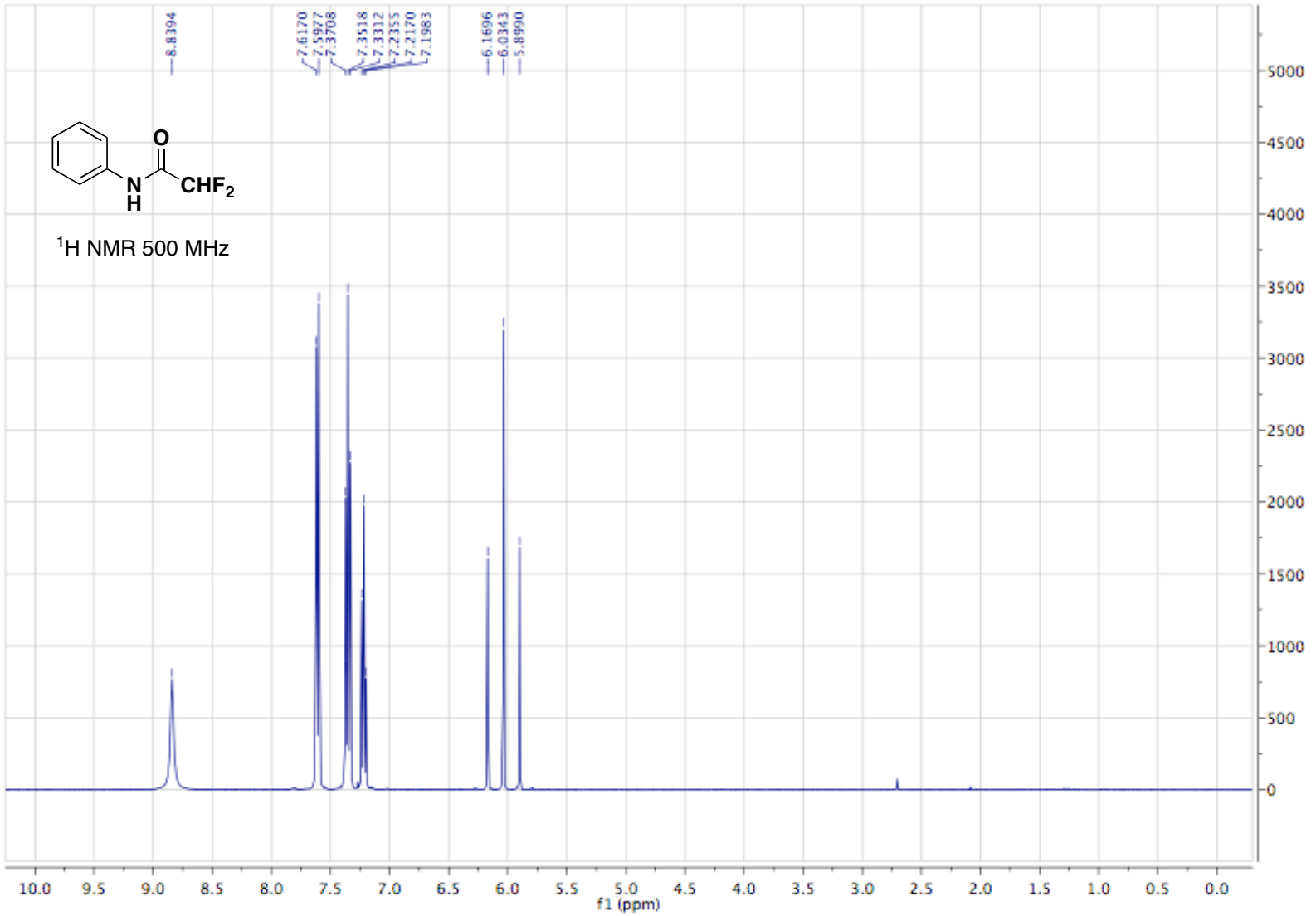


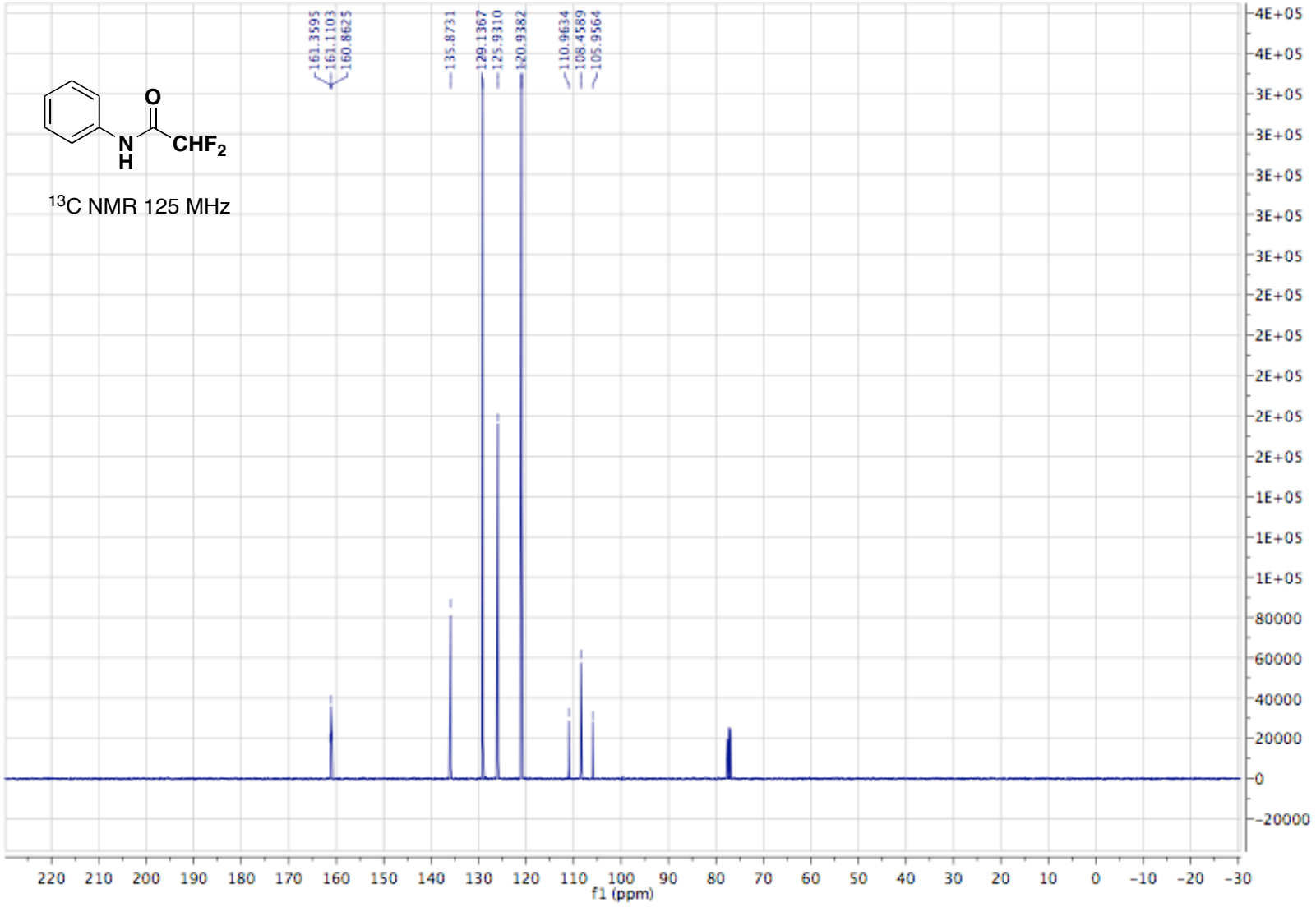
^{1}H NMR 500 MHz


^{13}C NMR 125 MHz
160
140
120
100
80
60
40
20
[ppm]


CF3
F
O
N
H
O
O
N
H
1H NMR 500 MHz
8
6
4
2
[ppm]


124.6206
124.3658
124.0948
124.0678
123.8258
122.7877
123.5343
123.2743
122.5270
122.7844
121.9057
121.8763
121.8457
121.8060
121.7702
121.7381
121.7071
120.7671
120.6248
117.4474
117.4078
117.3789
117.3482
117.3203
117.0121
116.9833
116.9535
116.5240
110.8424
110.7677
110.6630
81.0368
80.9665
79.5443
79.4869
77.3574
77.0027
76.7453
70.7042
68.7764
56.1108
54.0400
47.0178
43.7703
30.5822
29.6672
27.7905
27.6465
24.1272
24.0123
22.7904
$^{1}CF_3$
7
3
6
O
F
N
H
O
O
N
H
^{13}C NMR 125 MHz
160
140
120
100
80
60
40
20
[ppm]


8.8394
7.6170
7.5977
7.3708
7.3518
7.3312
7.2355
7.2170
7.1983
6.1696
6.0343
5.8990
O
N
H
CHF2
1H NMR 500 MHz
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
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
0.0
f1 (ppm)


161.3595
161.1103
160.8625
135.8731
129.1367
125.9310
120.9382
110.9634
108.4589
105.9564
O
N
H
CHF2
13C NMR 125 MHz
4E+05
3E+05
2E+05
1E+05
80000
60000
40000
20000
0
-20000
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30
f1 (ppm)

4. Coordinates for 4A-4F

4A

C 0	-0.687668	1.788330	0.780000
C 0	-1.066376	3.051682	0.324127
C 0	-2.419754	3.334320	0.085678
C 0	-3.399643	2.370575	0.301605
C 0	-3.031006	1.099792	0.754364
C 0	-1.689392	0.803497	0.987030
C 0	-2.791092	4.716095	-0.374496
F 0	-2.032700	5.132355	-1.422012
F 0	-2.624054	5.646683	0.606308
F 0	-4.087875	4.800461	-0.769012
O 0	-1.219315	-0.399033	1.417130
C 0	-2.120605	-1.466827	1.691849
C 0	-1.294983	-2.727676	1.971573
C 0	-2.187210	-3.897049	2.437271
N 0	-0.659439	-3.269119	0.758453
C 0	-2.578705	-4.607437	1.128769
C 0	-1.311783	-4.499756	0.266953
C 0	0.602997	-2.887543	0.388611
O 0	1.237564	-1.986023	0.921570
O 0	1.035889	-3.651733	-0.645264
C 0	2.363266	-3.437561	-1.258621
C 0	3.467819	-3.683853	-0.225266
C 0	2.396667	-4.506683	-2.354202
C 0	2.438324	-2.034103	-1.868912
N 0	0.638733	1.414886	1.070938
C 0	1.739670	2.220291	1.048096
O 0	1.771530	3.391891	0.682541
C 0	3.042465	1.582336	1.519119
F 0	2.855438	0.331741	2.113922
H 0	-0.304962	3.801636	0.161743
H 0	-4.443481	2.596680	0.119003
H 0	-3.796112	0.352661	0.925323
H 0	-2.727921	-1.212738	2.572205
H 0	-2.785751	-1.629791	0.834290
H 0	-0.520981	-2.470673	2.700760
H 0	-3.050064	-3.564728	3.022079

H 0	-1.598389	-4.569046	3.070740
H 0	-3.416214	-4.090942	0.646393
H 0	-2.881271	-5.646667	1.283157
H 0	-1.526581	-4.428543	-0.802582
H 0	-0.649368	-5.361313	0.414734
H 0	3.444855	-2.933350	0.565857
H 0	3.356979	-4.677551	0.221481
H 0	4.443497	-3.643478	-0.721451
H 0	3.347626	-4.457474	-2.893478
H 0	2.294922	-5.507156	-1.922577
H 0	1.583878	-4.353790	-3.070740
H 0	2.411438	-1.266022	-1.095184
H 0	1.604889	-1.872437	-2.560287
H 0	3.371460	-1.932907	-2.433304
H 0	0.778458	0.446472	1.356247
H 0	3.503052	2.251312	2.250809
H 0	3.713806	1.458344	0.663315

4B

C 0	-1.224884	-4.490952	0.115051
N 0	-0.674850	-3.172379	0.497360
C 0	-1.463150	-2.512482	1.553085
C 0	-2.335190	-3.661728	2.096344
C 0	-2.561157	-4.562820	0.869110
C 0	-2.319046	-1.356354	1.021042
O 0	-1.423141	-0.348953	0.578171
C 0	-1.868561	0.822021	0.045654
C 0	-0.826141	1.722946	-0.295654
C 0	-1.156586	2.958527	-0.851395
C 0	-2.505554	3.289139	-1.057693
C 0	-3.523331	2.402267	-0.718567
C 0	-3.201950	1.158035	-0.163528
N 0	0.481125	1.279129	-0.030502
C 0	1.649109	1.986786	-0.172974
C 0	2.870438	1.255142	0.392395
F 0	3.944534	1.390060	-0.486145
C 0	-2.828598	4.641602	-1.629715
F 0	-4.140015	4.765961	-1.959579
C 0	0.596405	-2.778152	0.183792
O 0	1.159622	-3.666351	-0.664856

C 0	2.525513	-3.490585	-1.210571
C 0	2.586197	-2.222748	-2.066330
F 0	-2.112839	4.910797	-2.752075
F 0	-2.552612	5.647491	-0.753906
O 0	1.140808	-1.763748	0.619461
C 0	3.551010	-3.485977	-0.072861
C 0	2.690384	-4.738861	-2.081650
O 0	1.738876	3.108673	-0.650635
H 0	-1.341080	-4.564667	-0.969315
H 0	-0.539581	-5.286407	0.429840
H 0	-0.782257	-2.105240	2.306259
H 0	-3.266495	-3.306747	2.547562
H 0	-1.779297	-4.204056	2.868500
H 0	-3.374008	-4.170151	0.248459
H 0	-2.822662	-5.589523	1.138443
H 0	-2.953979	-0.965088	1.828552
H 0	-2.959763	-1.687119	0.192474
H 0	-0.364853	3.645157	-1.117996
H 0	-4.560516	2.667526	-0.884827
H 0	-3.992310	0.465515	0.101700
H 0	0.547150	0.320724	0.311340
H 0	2.687332	0.188950	0.548584
H 0	3.152008	1.729187	1.339554
H 0	2.466919	-1.323822	-1.462112
H 0	1.805450	-2.240707	-2.833420
H 0	3.556427	-2.169098	-2.570404
H 0	3.432724	-2.611984	0.568161
H 0	3.449066	-4.389664	0.537018
H 0	4.560532	-3.474716	-0.496506
H 0	3.677460	-4.734222	-2.553619
H 0	2.599121	-5.647491	-1.478867
H 0	1.930618	-4.765976	-2.868484

4C

C 0	-2.097458	1.052353	0.419769
C 0	-0.710938	1.077545	0.556534
C 0	-0.039734	2.308655	0.775925
C 0	-0.776779	3.489273	0.848541
C 0	-2.171783	3.448212	0.707733
C 0	-2.830750	2.241226	0.495316

O 0	0.100677	-0.018143	0.496094
C 0	-0.492477	-1.321854	0.372482
C 0	0.592636	-2.391006	0.378189
N 0	1.288422	-2.549667	-0.904892
C 0	1.904816	-3.877869	-0.844864
C 0	0.809509	-4.766739	-0.239639
C 0	-0.018234	-3.791885	0.638824
C 0	2.236847	-1.497650	-1.250854
N 0	1.358856	2.240265	0.911850
C 0	2.237686	3.260895	1.118027
O 0	1.961380	4.451172	1.216843
C 0	-2.933182	4.742371	0.782318
F 0	-2.697815	5.409073	1.943878
C 0	3.699738	2.839371	1.229980
F 0	3.869965	1.449783	1.100769
F 0	-4.275040	4.561340	0.698288
F 0	-2.590393	5.596848	-0.219757
H 0	-2.616653	0.117569	0.250595
H 0	-0.258972	4.423996	1.016068
H 0	-3.908356	2.215744	0.386597
H 0	-1.169250	-1.475937	1.222931
H 0	-1.062561	-1.385574	-0.562698
H 0	1.310974	-2.143494	1.185577
H 0	2.222290	-4.194473	-1.843796
H 0	2.803391	-3.872955	-0.194824
H 0	0.186066	-5.193649	-1.030304
H 0	1.229126	-5.596848	0.335541
H 0	-1.074524	-3.811325	0.347763
H 0	0.026932	-4.039368	1.703339
H 0	1.723663	-0.540848	-1.360535
H 0	3.034882	-1.380905	-0.492355
H 0	2.708588	-1.741700	-2.207687
H 0	1.753860	1.308182	0.858017
H 0	4.275024	3.327255	0.438797
H 0	4.085358	3.139816	2.207672

4D

C 0	3.344742	-3.908768	-2.142349
C 0	2.753235	-1.464432	-2.270309
C 0	2.984818	-2.656372	-1.338425

O 0	1.706741	-3.050308	-0.699219
C 0	4.046341	-2.378006	-0.270050
F 0	-2.928955	5.240555	-2.204224
F 0	3.342804	1.984421	-0.968781
O 0	1.136719	3.840790	-0.413269
C 0	-0.450012	-4.251083	0.230728
F 0	-4.932449	4.555939	-1.674957
C 0	1.020600	-2.231781	0.126495
C 0	-3.657822	4.662200	-1.217621
C 0	1.236984	2.661911	-0.114578
C 0	-1.700775	3.213959	-0.647537
C 0	2.613556	2.033875	0.196793
C 0	-3.091476	3.335815	-0.791092
N 0	-0.141296	-2.834076	0.521912
N 0	0.214462	1.759796	-0.019318
O 0	1.382965	-1.109024	0.481491
C 0	-1.157730	2.005463	-0.211900
C 0	-3.940125	2.270050	-0.501068
C 0	-1.731430	-4.517532	1.033890
C 0	-2.025925	0.921921	0.076218
C 0	-3.403732	1.053467	-0.065475
O 0	-1.375931	-0.203262	0.478729
F 0	-3.691208	5.558594	-0.191864
F 0	3.282440	2.841187	1.070938
C 0	-2.066330	-1.312683	1.033890
C 0	-1.000031	-2.271484	1.579208
C 0	-1.635300	-3.527359	2.208344
H 0	4.288100	-3.749786	-2.673325
H 0	2.567368	-4.134048	-2.878571
H 0	3.460617	-4.773880	-1.482513
H 0	1.953537	-1.688309	-2.983566
H 0	3.667786	-1.263443	-2.837418
H 0	2.493683	-0.562073	-1.717468
H 0	5.012360	-2.208572	-0.756592
H 0	4.149780	-3.238785	0.398743
H 0	3.797424	-1.498230	0.323471
H 0	-0.576187	-4.409424	-0.843262
H 0	0.376251	-4.889206	0.565186
H 0	-1.041611	4.043000	-0.865143
H 0	2.572815	1.023895	0.612473

H 0	0.446808	0.799744	0.240295
H 0	-5.012360	2.375916	-0.617294
H 0	-2.617126	-4.306519	0.424698
H 0	-1.799332	-5.558578	1.360397
H 0	-4.061050	0.219955	0.153748
H 0	-2.683838	-1.799316	0.266861
H 0	-2.714645	-0.977448	1.855331
H 0	-0.378204	-1.712952	2.285080
H 0	-0.969406	-3.920975	2.983582
H 0	-2.601822	-3.320084	2.677383

4E

C 0	-0.811340	1.774002	-0.144104
C 0	-1.146545	2.969009	-0.779770
C 0	-2.485352	3.234741	-1.107162
C 0	-3.490326	2.321243	-0.804932
C 0	-3.165176	1.119736	-0.166519
C 0	-1.839905	0.844238	0.161072
C 0	-2.804459	4.535095	-1.790512
F 0	-2.144257	4.668976	-2.972733
F 0	-2.451141	5.611160	-1.037384
F 0	-4.127151	4.666977	-2.064590
O 0	-1.403412	-0.282211	0.780716
C 0	-2.303528	-1.325470	1.133911
C 0	-1.462402	-2.498825	1.649521
C 0	-2.346039	-3.637680	2.198883
N 0	-0.699219	-3.165009	0.579712
C 0	-2.581375	-4.545593	0.978531
C 0	-1.241455	-4.494690	0.231476
C 0	0.563721	-2.759048	0.236710
O 0	1.097946	-1.732910	0.644547
O 0	1.124451	-3.655746	-0.607529
C 0	2.475113	-3.452866	-1.179900
C 0	3.520370	-3.400345	-0.061188
C 0	2.658615	-4.708923	-2.035965
C 0	2.486664	-2.194641	-2.052612
N 0	0.497772	1.409637	0.233231
C 0	1.595062	2.213409	0.218246
O 0	1.647217	3.375229	-0.170410
C 0	2.893326	1.571304	0.738495

F 0 3.458679 0.801437 -0.251358
F 0 2.664902 0.752563 1.813644
H 0 -0.368027 3.683456 -1.007843
H 0 -4.521729 2.535797 -1.058090
H 0 -3.948990 0.412338 0.076233
H 0 -2.981354 -0.973633 1.924530
H 0 -2.896561 -1.626587 0.260605
H 0 -0.768219 -2.106903 2.399231
H 0 -3.273254 -3.272812 2.650726
H 0 -1.793655 -4.181305 2.972748
H 0 -3.386200 -4.146347 0.350952
H 0 -2.857605 -5.566681 1.254974
H 0 -1.349319 -4.600037 -0.851028
H 0 -0.558624 -5.281540 0.574417
H 0 3.394333 -2.512604 0.559021
H 0 3.448151 -4.292191 0.570343
H 0 4.521744 -3.379578 -0.504211
H 0 3.637741 -4.685181 -2.523972
H 0 2.601089 -5.611160 -1.419327
H 0 1.887527 -4.767487 -2.810242
H 0 2.368744 -1.291916 -1.453476
H 0 1.686295 -2.240677 -2.798553
H 0 3.441895 -2.131790 -2.584457
H 0 0.609802 0.454346 0.579681
H 0 3.604446 2.349518 1.022278

4F

C 0 0.771240 -4.417435 0.599930
N 0 0.479675 -3.093552 0.042862
C 0 -0.625977 -2.571777 0.855072
C 0 -1.535553 -3.808578 1.069900
C 0 -0.614900 -5.035095 0.832825
C 0 -1.403320 -1.438095 0.199387
O 0 -0.675919 -0.203766 0.330170
C 0 -1.218338 0.944595 -0.167374
C 0 -0.460861 2.118652 0.078171
C 0 -0.919586 3.347565 -0.392487
C 0 -2.129120 3.411102 -1.098755
C 0 -2.875092 2.260406 -1.337860
C 0 -2.419083 1.023804 -0.870300

N 0	0.733261	1.945572	0.803925
C 0	1.632156	2.893860	1.180038
C 0	2.858398	2.344910	1.932266
F 0	2.588898	1.128036	2.524429
C 0	-2.582321	4.743576	-1.628600
F 0	-3.875458	4.723770	-2.038757
C 0	1.660614	-2.243988	-0.052811
F 0	-1.841873	5.145798	-2.698486
F 0	-2.474747	5.728683	-0.700836
O 0	1.571640	4.096100	0.961929
F 0	3.875458	2.139160	1.038193
H 0	1.394958	-4.991700	-0.092758
H 0	1.324127	-4.335022	1.557617
H 0	-0.256317	-2.208954	1.835632
H 0	-2.364197	-3.803482	0.353104
H 0	-1.974731	-3.794998	2.071518
H 0	-0.938095	-5.591553	-0.051422
H 0	-0.614929	-5.728683	1.678284
H 0	-2.375427	-1.320206	0.695267
H 0	-1.560013	-1.666824	-0.861893
H 0	-0.337769	4.238892	-0.201126
H 0	-3.809708	2.316788	-1.883270
H 0	-3.004364	0.133484	-1.061310
H 0	0.916931	0.993515	1.100510
H 0	3.197556	3.044464	2.698471
H 0	1.416336	-1.301743	-0.546112
H 0	2.101074	-2.017792	0.937653
H 0	2.420090	-2.753174	-0.653763