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Supporting Information

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Supplementary information:

A nonpeptidic reverse turn that promotes parallel sheet structure stabilized by C-H···O hydrogen bonds in cyclopropane γ-peptides

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1. **General experimental procedures.**
2. **Experimental procedures and data for all compounds.**
3. **DMSO titration experiments for compounds 6, 7, 12, 13, 14 and 15.**
4. **Temperature coefficients in $CDCl_3$ for 12, 13, 14 and 15.**
5. **Solution IR data for 6 and 7.**
6. **^1H and ^{13}C NMR spectra for all compounds.**

1. General 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). All other reagents and solvents were used as supplied, without prior purification.

1.2 Chromatography

Thin layer chromatography (TLC) was performed on glass 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 Avance 700 (^1H: 700 MHz), a Bruker DPX 400 (^1H: 400 MHz and ^{13}C: 100 MHz) or a Bruker Avance Cryo 500 (^1H: 500 MHz and ^{13}C: 125.3 MHz). 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, a, apparent].

Proton resonance assignments within individual residues were derived from combined application of 2D total-correlation spectroscopy (TOCSY), 2D-nuclear Overhauser effect spectroscopy (NOESY), ^1H-^{13}C heteronuclear single quantum correlation (HSQC) spectroscopy, and ^{13}C-semiselective heteronuclear multiple bond correlation (HMBC) spectroscopy with a 2 ms Gaussian pulse to achieve selective excitation of carbonyl carbons. Long-range, through-bond heteronuclear correlations observed in ^{13}C-semiselective HMBC

experiments permitted sequential placement of residues.[1] Thus correlations were observed from H-2^i and H-3^i to the carbonyl carbon C=O^i in the same cyclopropane residue and more importantly the sequential connectivities from NH^{i+1} and H-6^{i+1} in the adjacent cyclopropane residue to the same carbonyl. These $^2J_{CH}$ and $^3J_{CH}$ correlations to the intervening carbonyl carbons firmly established all neighboring cyclopropane residues in the sequence. The ^{13}C selective experiments proved necessary as all the amide carbonyl resonances fell within a 2 ppm range and only the higher resolution of the semiselective approach was able to resolve these resonances and thus provide unambiguous connectivities.

The build-up curves of nOe crosspeak intensities as a function of mixing times in 2D-NOESY spectra were obtained; an optimal mixing time of 800 ms was chosen to yield maximum crosspeak intensities with minimal spin-diffusion effects. Individual nOe crosspeaks were assigned to identify long-range, through-space dipole-dipole interactions, based on which the hydrogen bond networks were confirmed and inter-strand contacts identified.

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.

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.

1.6 Melting points

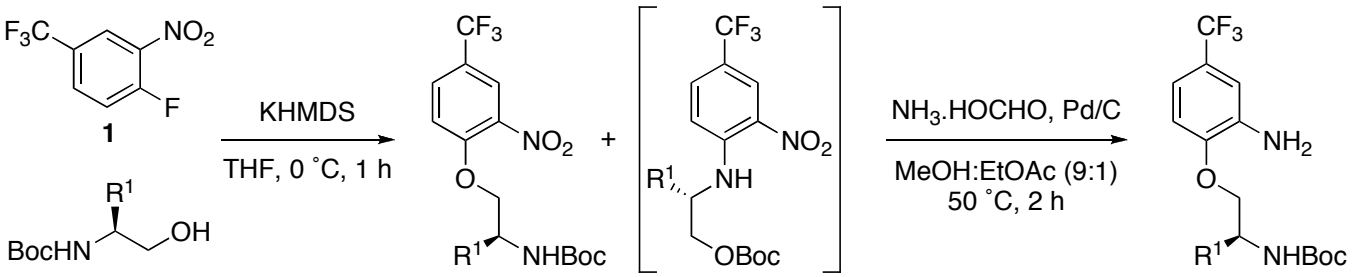
Melting points were recorded on a Kofler hot block and are uncorrected.

1.7 Polarimetry

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

[1] T. D. W. Claridge and I. Perez-Victoria, *Org. Biomol. Chem.*, 2003, 1, 3632

2. Experimental procedures and data.

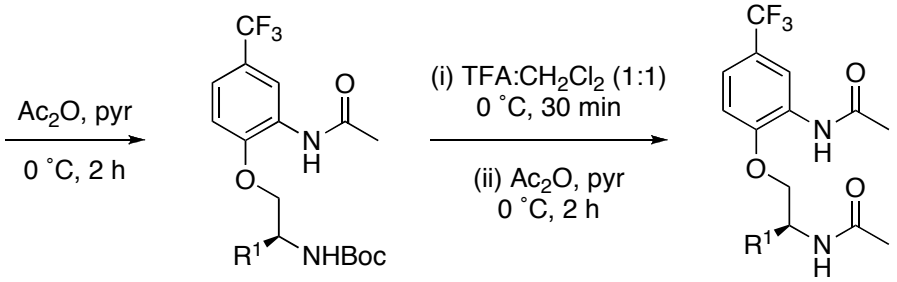


2: $R^1 = {}^{i}Pr$
3: $R^1 = {}^{t}Bu$

4: $R^1 = {}^{i}Pr$
5: $R^1 = {}^{t}Bu$

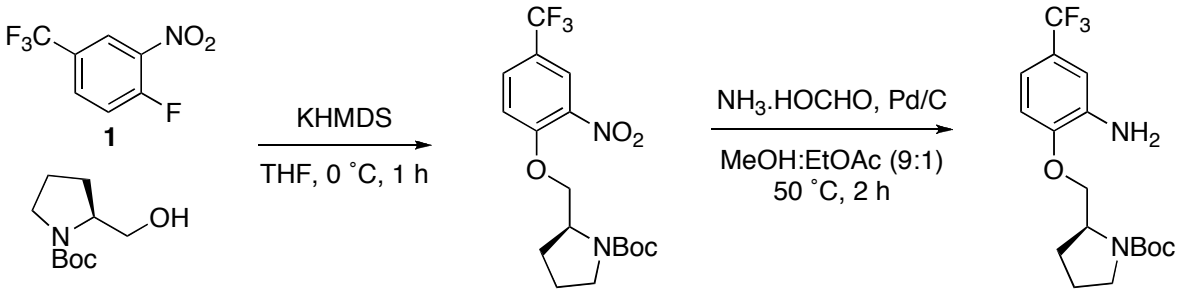
16: $R^1 = {}^{t}Bu$

17: $R^1 = {}^{i}Pr$
18: $R^1 = {}^{t}Bu$



19: $R^1 = {}^{i}Pr$
20: $R^1 = {}^{t}Bu$

6: $R^1 = {}^{i}Pr$
7: $R^1 = {}^{t}Bu$



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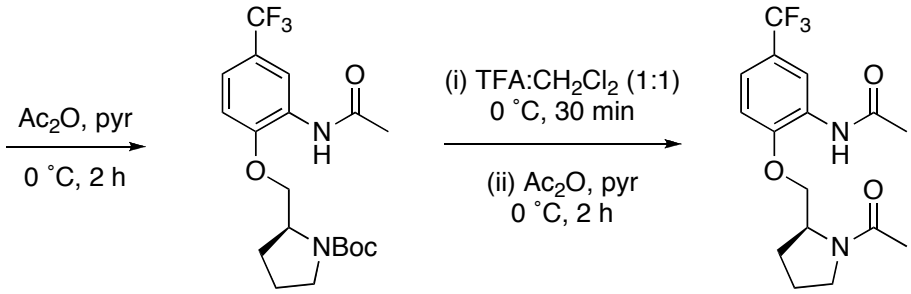

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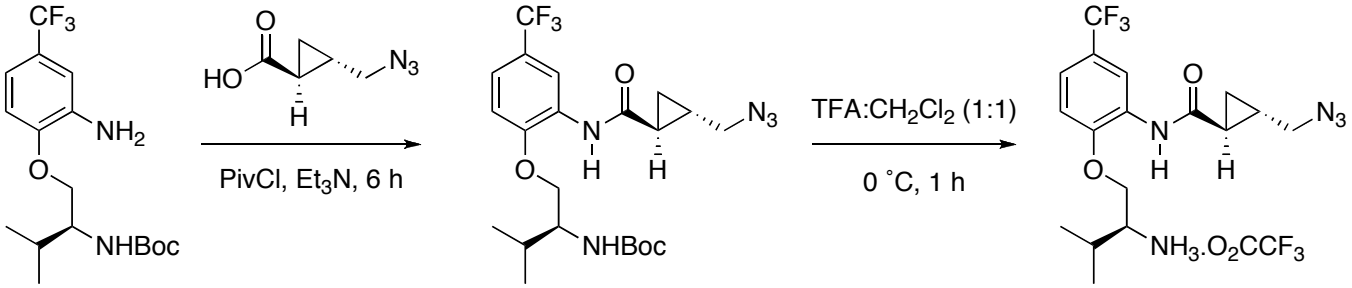
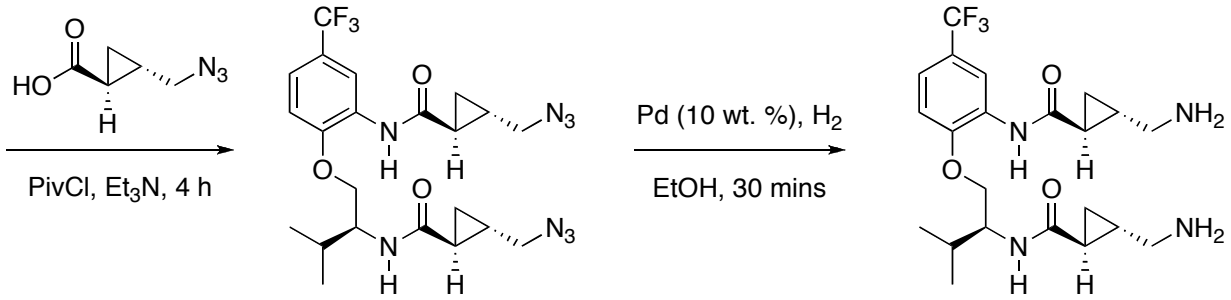


17: *(S)*-^{i}Pr
225: *(R)*-^{i}Pr

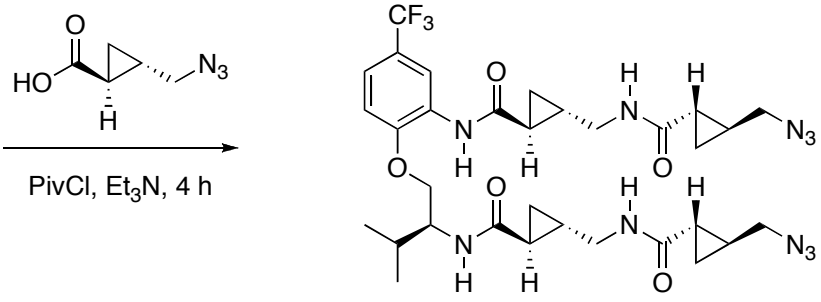
26: *(S)*-^{i}Pr
11: *(R)*-^{i}Pr

27: *(S)*-^{i}Pr
28: *(R)*-^{i}Pr



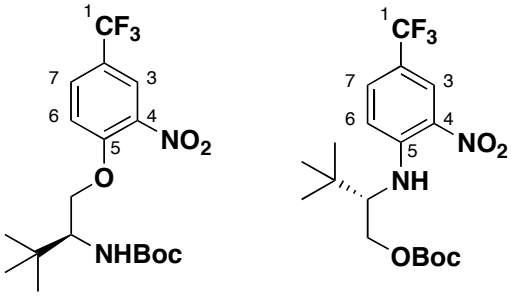
13: *(S)*-^{i}Pr
12: *(R)*-^{i}Pr

29: *(S)*-^{i}Pr
30: *(R)*-^{i}Pr



15: *(S)*-^{i}Pr
14: *(R)*-^{i}Pr

(*S*)-*tert*-butyl 3,3-dimethyl-1-(2-nitro-4-(trifluoromethyl)phenoxy)butan-2-ylcarbamate 5 and **(*S*)-*tert*-butyl 3,3-dimethyl-1-(2-nitro-4-(trifluoromethyl)phenylamino)butan-2-yl carbonate 16**



5 and **16**

KHMDS (0.5 M solution in toluene, 4.60 mL, 2.30 mmol) was added dropwise over 1 h to a stirred solution of Boc-L-*tert* leucinol **3** (0.500 g, 2.30 mmol) and 4-fluoro-3-nitrobenzotrifluoride **1** (0.967 mL, 6.9 mmol) in THF (15 mL) at 0 ˚C. The solution was allowed to warm to rt over 1 h then diluted with dichloromethane (35 mL), washed with NH_4Cl (aq) (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (7:1 Pet:EtOAc), to afford the side product **16** as a bright yellow oil (0.047 g, 0.116 mmol, 5 %, R_f 0.51) and the turn precursor **5** as a dark orange oil (0.762 g, 1.88 mmol, 81 %, R_f 0.22)

Data for (*S*)-*tert*-butyl 3,3-dimethyl-1-(2-nitro-4-(trifluoromethyl)phenoxy)butan-2-ylcarbamate **5**.

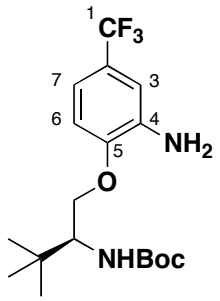
$[\alpha]_D^{25}$ – 5.4 (c = 0.33, $CHCl_3$). δ_H (500 MHz, $CDCl_3$): 8.15 (1H, d, *J* 1.9, Ar-H^3), 7.79 (1H, dd, *J* 8.8, 1.9, Ar-H^7), 7.20 (1H, d, *J* 8.8, Ar-H^6), 5.02 (1H, d, *J* 10.0, N-H), 4.33 (1H, dd, *J* 9.7, 3.3, CH_2OAr), 4.23 (1H, dd, *J* 9.7, 4.4, CH_2OAr), 3.82 (1H, m, C*H*NHBoc), 1.44 (9H, s, $CO_2C(CH_3)_3$), 1.02 (9H, s, $C(CH_3)_3$). δ_C (125 MHz, $CDCl_3$): 155.8 (C=O), 154.4 (C^5), 139.2 (C^4), 131.3 (q, $J_{C\text{-}F}$ 3.4, C^7), 124.1 (q, $J_{C\text{-}F}$ 270.4, C^1), 123.5 (q, $J_{C\text{-}F}$ 3.8, C^3), 123.1 (q, $J_{C\text{-}F}$ 34.3, C^2), 114.6 (C^6), 79.6 ($CO_2C(CH_3)_3$), 69.6 (CH_2OAr), 56.8 (CHNHBoc), 34.4 ($C(CH_3)_3$), 28.3 ($CO_2C(CH_3)_3$), 27.1 ($C(CH_3)_3$). υ_{max} (neat) cm^{-1}: 3336 (m) (N-H), 2966 (m) & 2872 (w) (C-H), 1681 (s) (C=O), 1629 (s) (N-H), 1586 (w) (Ar C=C), 1536 (s) & 1322 (s) (NO_2), 1278 (s) & 1124 (s) (C-O). HRMS (ES+): calcd for $C_{18}H_{25}F_3N_2O_5$ $[M+H]^+$: 407.1788; found: 407.1792.

Data for (*S*)-*tert*-butyl 3,3-dimethyl-1-(2-nitro-4-(trifluoromethyl)phenylamino)butan-2-yl carbonate **16**.

$[\alpha]_D^{25}$ + 68.5 (c = 1.0, $CHCl_3$). δ_H (500 MHz, $CDCl_3$): 8.54 (1H, d, *J* 9.8, N-H), 8.45 (1H, d, *J* 2.1, Ar-H^3), 7.55 (1H, dd, *J* 9.2, 2.1, Ar-H^7), 7.09 (1H, d, *J* 9.2, Ar-H^6), 4.40 (1H, dd, *J* 11.5, 4.1, CH_2OBoc), 4.14 (1H, dd, *J* 11.5, 8.5, CH_2OBoc), 3.81 (1H, ddd, *J* 9.8, 8.5, 4.1, C*H*NH), 1.37 (9H, s, $CO_2C(CH_3)_3$), 1.06 (9H, s,

$C(CH_3)_3$). δ_C (125 MHz, $CDCl_3$): 153.4 (C=O), 147.7 (C^5), 132.0 (q, $J_{C\text{-}F}$ 3.1, C^7), 130.9 (C^4), 125.1 (q, $J_{C\text{-}F}$ 4.1, C^3), 123.5 (q, $J_{C\text{-}F}$ 269.1, C^1), 117.3 (q, $J_{C\text{-}F}$ 34.1, C^2), 115.0 (C^6), 82.6 ($CO_2C(CH_3)_3$), 66.7 (CH_2OBoc), 60.2 (CHNH), 34.5 ($C(CH_3)_3$), 27.5 ($CO_2C(CH_3)_3$), 26.6 ($C(CH_3)_3$). υ_{max} (neat) cm^{-1}: 3348 (m) (N-H), 2968 (m) & 2876 (w) (C-H), 1740 (s) (C=O), 1635 (s) (N-H), 1578 (m) (Ar C=C), 1538 (s) & 1324 (s) (NO_2), 1270 (s) & 1152 (s) (C-O). HRMS (ES+): calcd for $C_{18}H_{25}F_3N_2O_5$ $[M+NH_4]^+$: 424.2054; found: 424.2051.

(*S*)-*tert*-butyl 1-(2-amino-4-(trifluoromethyl)phenoxy)-3,3-dimethylbutan-2-ylcarbamate 18

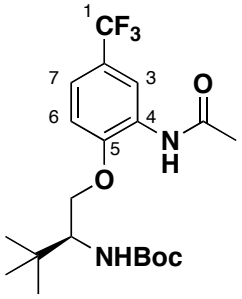


18

5 (0.056 g, 0.152 mmol), ammonium formate (0.067 g, 1.07 mmol) and palladium (10 wt. % on carbon, 0.006 g) were dissolved in methanol:ethyl acetate (9:1 by volume, 1.5 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 (20 mL). The solvent was removed *in vacuo* and the residue dissolved in dichloromethane (10 mL), washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to yield the aniline **18** (0.051 g, 0.135 mmol, 89 %, R_f 0.50 4:1 Pet:EtOAc) as a pale yellow amorphous solid which was used in subsequent reactions without purification.

$[\alpha]_D^{25}$ – 14.5 (c = 0.9, $CHCl_3$). δ_H (400 MHz, $CDCl_3$): 6.93 (1H, dd, *J* 8.4, 1.7, Ar-H^7), 6.89 (1H, d, *J* 1.7, Ar-H^3), 6.74 (1H, d, *J* 8.4, Ar-H^6), 4.65 (1H, d, *J* 9.0, N*H*Boc), 4.20 (1H, dd, *J* 12.6, 5.9, CH_2OAr), 4.04 (2H, br s, Ar-NH_2), 3.91-3.85 (2H, m, C*H*NHBoc & CH_2OAr), 1.45 (9H, s, $CO_2C(CH_3)_3$), 1.03 (9H, s, $C(CH_3)_3$). δ_C (125 MHz, $CDCl_3$): 156.3 (C=O), 148.6 (C^5), 136.9 (C^4), 124.5 (q, $J_{C\text{-}F}$ 269.8, C^1), 123.5 (q, $J_{C\text{-}F}$ 32.0, C^2), 115.1 (q, $J_{C\text{-}F}$ 4.0, C^7), 110.9 (q, $J_{C\text{-}F}$ 3.3, C^3), 110.3 (C^6), 79.4 ($CO_2C(CH_3)_3$), 68.8 (CH_2OAr), 58.1 (*C*HNHBoc), 33.6 ($C(CH_3)_3$), 28.4 ($CO_2C(CH_3)_3$), 27.0 ($C(CH_3)_3$). υ_{max} (neat) cm^{-1}: 3456 (br) & 3360 (br) (N-H), 2968 (s) (C-H), 1694 (s) (C=O), 1623 (s) (N-H), 1520 (s) (Ar C=C), 1220 (s) & 1114 (s) (C-O). HRMS (ES+): calcd for $C_{18}H_{27}F_3N_2O_3$ $[M+H]^+$: 377.2047; found: 377.2053.

(*S*)-*tert*-butyl 1-(2-ethanamido-4-(trifluoromethyl)phenoxy)-3,3-dimethylbutan-2-ylcarbamate 20

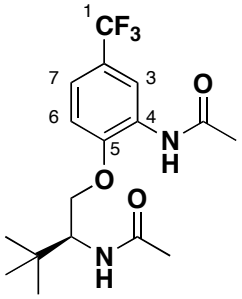


20

4-Dimethylaminopyridine (0.002 g, 0.016 mmol) was added to a solution of **18** (0.036 g, 0.096 mmol) in acetic anhydride (0.5 mL) and pyridine (0.5 mL) at 0 ˚C. 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 (4:1 Pet:EtOAc, R_f 0.30) to afford **20** as a pale crystalline solid (0.039 g, 0.093 mmol, 97 %).

Mp 126-127 ˚C. $[\alpha]_D^{25}$ + 33.3 (c = 1.0, $CHCl_3$). δ_H (400 MHz, $CDCl_3$): 8.77 (1H, d, *J* 1.4, Ar-H^3), 8.58 (1H, br s, C^4NH), 7.24 (1H, dd, *J* 8.4, 1.4, Ar-H^7), 6.81 (1H, d, *J* 8.4, Ar-H^6), 4.66 (1H, d, *J* 8.6, N*H*Boc), 4.03 (1H, dd, *J* 14.3, 8.0, CH_2OAr), 3.93-3.86 (2H, m, CH_2OAr & C*H*NHBoc), 2.28 (3H, s, $COCH_3$), 1.44 (9H, s, $CO_2C(CH_3)_3$), 1.05 (9H, s, $C(CH_3)_3$). δ_C (125 MHz, $CDCl_3$): 169.3 (C=O amide), 157.0 (C=O carbamate), 149.3 (C^5), 128.9 (C^4), 124.2 (q, $J_{C\text{-}F}$ 269.9, C^1), 123.4 (q, $J_{C\text{-}F}$ 32.4, C^2), 120.2 (q, $J_{C\text{-}F}$ 4.0, C^7), 116.5 (q, $J_{C\text{-}F}$ 3.4, C^3), 109.8 (C^6), 79.7 ($CO_2C(CH_3)_3$), 70.2 (CH_2OAr), 58.8 (*C*HNHBoc), 32.7 ($C(CH_3)_3$), 28.4 ($CO_2C(CH_3)_3$), 26.9 ($C(CH_3)_3$), 24.6 ($COCH_3$). υ_{max} (neat) cm^{-1}: 3325 (br) (N-H), 2969 (m) (C-H), 1681 (s) (C=O), 1604 (m) (N-H), 1542 (s) & 1492 (m) (Ar C=C), 1272 (s) & 1118 (s) (C-O). HRMS (ES+): calcd for $C_{20}H_{29}F_3N_2O_4$ $[M+H]^+$: 419.2152; found: 419.2155.

(*S*)-*N*-(2-(2-ethanamido-3,3-dimethylbutoxy)-5-(trifluoromethyl)phenyl)ethanamide 7

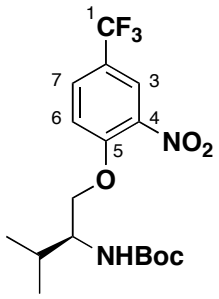


7

20 (0.177 g, 0.423 mmol) was dissolved in dichloromethane:TFA (1:1 by volume, 3.0 mL total) and the resulting solution stirred at 0 ˚C for 30 min. The solvent was removed *in vacuo* and the residue redissolved in dichloromethane (10 mL). The solution was washed with $NaHCO_3$ (aq) (10 mL), brine (10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to yield the crude amine. The amine intermediate was dissolved in acetic anhydride (1.5 mL) and pyridine (1.5 mL), cooled to 0 ˚C and 4-dimethylaminopyridine was added (0.002 g, 0.016 mmol). The solution was stirred for 2 h, allowed to warm to rt and the solvents removed *in vacuo*. The crude product was purified by column chromatography (1:1 Pet:EtOAc, R_f 0.18) to afford **7** as a pale crystalline solid (0.127 g, 0.352 mmol, 84 %).

Mp 160-161 ˚C. $[\alpha]_D^{25}$ – 3.7 (c = 1.0, $CHCl_3$). δ_H (400 MHz, $CDCl_3$): 8.75 (1H, d, *J* 1.9, Ar-H^3), 8.41 (1H, br s, C^4NH), 7.22 (1H, dd, *J* 8.4, 1.9, Ar-H^7), 6.78 (1H, d, *J* 8.4, Ar-H^6), 5.50 (1H, d, *J* 9.9, N*H*$COCH_3$), 4.36-4.28 (2H, m, CH_2OAr), 3.81 (1H, d, *J* 9.9, 8.8, C*H*NHBoc), 2.30 (3H, s, $COCH_3$), 2.06 (3H, s, $COCH_3$), 1.06 (9H, s, $C(CH_3)_3$). δ_C (125 MHz, $CDCl_3$): 171.5 (C=O), 169.7 (C=O), 149.3 (C^5), 128.8 (C^4), 124.2 (q, $J_{C\text{-}F}$ 269.9, C^1), 123.4 (q, $J_{C\text{-}F}$ 32.5, C^2), 120.2 (q, $J_{C\text{-}F}$ 4.0, C^7), 116.5 (q, $J_{C\text{-}F}$ 3.8, C^3), 109.7 (C^6), 69.5 (CH_2OAr), 57.1 (*C*HNHBoc), 32.4 ($C(CH_3)_3$), 29.3 ($CH(CH_3)_2$), 26.8 ($C(CH_3)_3$), 24.1 & 23.7 (2 x $COCH_3$). υ_{max} (neat) cm^{-1}: 3320 (br) & 3085 (br) (N-H), 2966 (m) (C-H), 1652 (s) (C=O), 1615 (m) (N-H), 1542 (s) (Ar C=C), 1271 (s) & 1115 (s) (C-O). HRMS (ES+): calcd for $C_{17}H_{23}F_3N_2O_3$ $[M+H]^+$: 361.1734; found: 361.1733.

(*S*)-*tert*-butyl 3-methyl-1-(2-nitro-4-(trifluoromethyl)phenoxy)butan-2-ylcarbamate 4

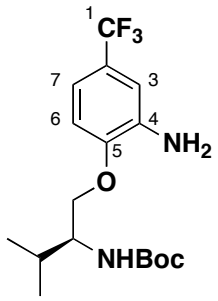


4

KHMDS (0.5 M solution in toluene, 14.8 mL, 7.38 mmol) was added dropwise over 1 h to a stirred solution of Boc-L-valinol **2** (1.5 g, 7.38 mmol) and 4-fluoro-3-nitrobenzotrifluoride **1** (3.10 mL, 22.1 mmol) in THF (45 mL) at 0 ˚C. The solution was allowed to warm to rt over 1 h then diluted with dichloromethane (100 mL), washed with NH_4Cl (aq) (150 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (7:1 Pet:EtOAc, R_f 0.22) to afford the turn precursor **4** as a dark orange oil (2.32 g, 5.90 mmol, 80 %).

$[\alpha]_D^{25}$ – 81.5 (c = 1.0, $CHCl_3$). δ_H (500 MHz, $CDCl_3$): 8.19 (1H, d, *J* 2.1, Ar-H^3), 7.80 (1H, dd, *J* 10.0, 2.1, Ar-H^7), 7.20 (1H, d, *J* 10.0, Ar-H^6), 4.86 (1H, d, *J* 7.9, N-H), 4.31 (1H, dd, *J* 9.3, 6.8, CH_2OAr), 4.18 (1H, dd, *J* 9.3, 3.9, CH_2OAr), 3.71 (1H, m, C*H*NHBoc), 2.03 (1H, septet, *J* 6.8, C*H*$(CH_3)_2$), 1.44 (9H, s, $C(CH_3)_3$), 1.01 (3H, d, *J* 6.8, CH(C*H*$_3)_2$), 0.98 (3H, d, *J* 6.8, CH(C*H*$_3)_2$). δ_C (125 MHz, $CDCl_3$): 156.7 (C=O), 154.6 (C^5), 139.1 (C^4), 131.2 (q, $J_{C\text{-}F}$ 3.1, C^7), 123.5 (q, $J_{C\text{-}F}$ 3.9, C^3), 123.1 (q, $J_{C\text{-}F}$ 34.4, C^2), 123.0 (q, $J_{C\text{-}F}$ 270.1, C^1), 114.8 (C^6), 79.7 ($CO_2C(CH_3)_3$), 70.1 (CH_2OAr), 55.0 (CHNHBoc), 29.2 ($CH(CH_3)_2$), 28.3 ($CO_2C(CH_3)_3$), 19.6 & 19.0 ($CH(CH_3)_2$). υ_{max} (neat) cm^{-1}: 3432 (m) (N-H), 2973 (m) & 2877 (w) (C-H), 1705 (s) (C=O), 1627 (s) (N-H), 1584 (w) (Ar C=C), 1541 (s) & 1327 (s) (NO_2), 1286 (s) & 1127 (s) (C-O). HRMS (ES+): calcd for $C_{17}H_{23}F_3N_2O_5$ $[M+H]^+$: 410.1897; found: 410.1897.

(*S*)-*tert*-butyl 1-(2-amino-4-(trifluoromethyl)phenoxy)-3-methylbutan-2-ylcarbamate 17

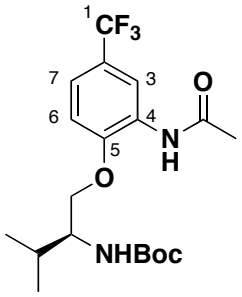


17

4 (1.55 g, 3.95 mmol), ammonium formate (0.748 g, 11.3 mmol) and palladium (10 wt. % on carbon, 0.155 g) were dissolved in methanol:ethyl acetate (9:1 by volume, 40 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 (120 mL). The solvent was removed *in vacuo* and the residue dissolved in dichloromethane (80 mL), washed with brine (80 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to yield the aniline **17** (1.13 g, 3.12 mmol, 79 %, R_f 0.45 4:1 Pet:EtOAc) as a yellow crystalline solid which was used in subsequent reactions without purification.

Mp 104-106 ˚C. $[\alpha]_D^{25}$ – 44.7 (c = 1.0, $CHCl_3$). δ_H (500 MHz, $CDCl_3$): 6.96 (1H, dd, *J* 8.3, 2.0, Ar-H^7), 6.91 (1H, d, *J* 2.0, Ar-H^3), 6.77 (1H, d, *J* 8.3, Ar-H^6), 4.66 (1H, d, *J* 9.6, N-H), 4.07 (1H, dd, *J* 9.7, 4.4, CH_2OAr), 4.00 (1H, dd, *J* 9.7, 5.8, CH_2OAr), 3.84 (1H, br m, C*H*NHBoc), 1.96 (1H, septet, *J* 6.8, C*H*$(CH_3)_2$), 1.45 (9H, s, $C(CH_3)_3$), 1.02 (3H, d, *J* 6.8, $CH(CH_3)_2$), 1.00 (3H, d, *J* 6.8, $CH(CH_3)_2$). δ_C (125 MHz, $CDCl_3$): 156.0 (C=O), 148.4 (C^5), 136.7 (C^4), 124.4 (q, $J_{C\text{-}F}$ 269.6, C^1), 123.5 (q, $J_{C\text{-}F}$ 32.4, C^2), 115.3 (q, $J_{C\text{-}F}$ 4.0, C^7), 111.1 (q, $J_{C\text{-}F}$ 2.6, C^3), 110.5 (C^6), 79.5 ($CO_2C(CH_3)_3$), 69.3 (CH_2OAr), 55.1 (*C*HNHBoc), 29.5 ($CH(CH_3)_2$), 28.4 ($CO_2C(CH_3)_3$), 19.6 & 18.5 ($CH(CH_3)_2$). υ_{max} (neat) cm^{-1}: 3364 (m) (N-H), 2978 (m) (C-H), 1698 (m) (C=O), 1625 (m) (N-H), 1521 (s) (Ar C=C), 1223 (s) & 1115 (s) (C-O). HRMS (ES+): calcd for $C_{17}H_{25}F_3N_2O_3$ $[M+H]^+$: 363.1890; found: 363.1887.

(*S*)-*tert*-butyl 1-(2-ethanamido-4-(trifluoromethyl)phenoxy)-3-methylbutan-2-ylcarbamate 19

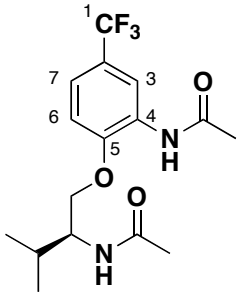


19

4-Dimethylaminopyridine (0.002 g, 0.016 mmol) was added to a solution of **17** (0.030 g, 0.082 mmol) in acetic anhydride (0.5 mL) and pyridine (0.5 mL) at 0 ˚C. 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 (7:1 Pet:EtOAc, R_f 0.10) to afford **19** as a pale crystalline solid (0.032 g, 0.079 mmol, 97 %).

Mp 122-123 ˚C. $[\alpha]_D^{25}$ + 23.2 (c = 1.0, $CHCl_3$). δ_H (400 MHz, $CDCl_3$): 8.76 (1H, d, *J* 1.9, Ar-H^3), 8.58 (1H, br s, C^4NH), 7.25 (1H, dd, *J* 8.4, 1.9, Ar-H^7), 6.82 (1H, d, *J* 8.4, Ar-H^6), 4.61 (1H, d, *J* 7.8, N*H*Boc), 4.09 (1H, dd, *J* 12.1, 5.9, CH_2OAr), 3.96-3.88 (2H, m, C*H*NHBoc & CH_2OAr), 2.28 (3H, s, $COCH_3$), 1.89 (1H, septet, *J* 6.1, C*H*$(CH_3)_2$), 1.45 (9H, s, $CO_2C(CH_3)_3$), 1.04 (3H, d, *J* 6.1, CH(C*H*$_3)_2$), 1.03 (3H, d, *J* 6.1, CH(C*H*$_3)_2$). δ_C (125 MHz, $CDCl_3$): 169.3 (C=O amide), 156.8 (C=O carbamate), 149.3 (C^5), 128.8 (C^4), 124.2 (q, $J_{C\text{-}F}$ 270.1, C^1), 123.4 (q, $J_{C\text{-}F}$ 32.3, C^2), 120.2 (q, $J_{C\text{-}F}$ 3.9, C^7), 116.6 (q, $J_{C\text{-}F}$ 3.3, C^3), 109.9 (C^6), 79.8 ($CO_2C(CH_3)_3$), 71.8 (CH_2OAr), 55.6 (*C*HNHBoc), 34.6 (CH_2CH_3), 29.5 (*C*H$(CH_3)_2$), 28.4 ($CO_2C(CH_3)_3$), 24.7 ($COCH_3$), 19.5 & 18.5 (CH(*C*H$_3)_2$). υ_{max} (neat) cm^{-1}: 3399 (w) & 3353 (br) (N-H), 2969 (m) & 2878 (m) (C-H), 1698 (s) (C=O carbamate), 1673 (s) (C=O amide), 1604 (m) (N-H), 1537 (s) (Ar C=C), 1271 (s) & 1121 (s) (C-O). HRMS (ES+): calcd for $C_{19}H_{27}F_3N_2O_4$ $[M+H]^+$: 405.1996; found: 405.1998.

(*S*)-*N*-(2-(2-ethanamido-3-methylbutoxy)-5-(trifluoromethyl)phenyl)ethanamide 6

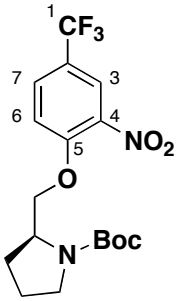


6

19 (0.058 g, 0.143 mmol) was dissolved in dichloromethane:TFA (1:1 by volume, 1.5 mL total) and the resulting solution stirred at 0 ˚C for 30 min. The solvent was removed *in vacuo* and the residue redissolved in dichloromethane (10 mL). The solution was washed with $NaHCO_3$ (aq) (10 mL), brine (10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to yield the crude amine. The amine intermediate was dissolved in acetic anhydride (0.5 mL) and pyridine (0.5 mL), cooled to 0 ˚C and 4-dimethylaminopyridine was added (0.003 g, 0.025mmol). The solution was stirred for 2 h, allowed to warm to rt and the solvents removed *in vacuo*. The crude product was purified by column chromatography (1:2 Pet:EtOAc, R_f 0.22) to afford **6** as a pale crystalline solid (0.024 g, 0.075 mmol, 52 %).

Mp 193-194 ˚C. $[\alpha]_D^{25}$ – 9.1 (c = 0.4, $CHCl_3$). δ_H (500 MHz, $CDCl_3$): 8.71 (1H, d, *J* 1.8, Ar-H^3), 8.40 (1H, br s, C^4NH), 7.22 (1H, dd, *J* 8.5, 1.8, Ar-H^7), 6.79 (1H, d, *J* 8.5, Ar-H^6), 5.53 (1H, d, *J* 9.3, NH), 4.31 (1H, m, C*H*NHCOCH$_3$), 4.18 (1H, dd, *J* 9.2, 3.3, CH_2OAr), 3.83 (1H, dd, *J* 9.6, 9.2, CH_2OAr), 2.28 (3H, s, $COCH_3$), 2.04 (3H, s, $COCH_3$), 1.88 (1H, septet, *J* 6.7, C*H*$(CH_3)_2$), 1.05 (3H, d, *J* 6.7, CH(C*H*$_3)_2$), 1.03 (3H, d, *J* 6.7, CH(C*H*$_3)_2$). δ_C (125 MHz, $CDCl_3$): 171.3 (C=O), 169.6 (C=O), 149.3 (C^5), 128.8 (C^4), 124.2 (q, $J_{C\text{-}F}$ 269.7, C^1), 123.5 (q, $J_{C\text{-}F}$ 32.2, C^2), 120.3 (q, $J_{C\text{-}F}$ 4.0, C^7), 116.7 (q, $J_{C\text{-}F}$ 3.8, C^3), 109.8 (C^6), 70.1 (*C*H_2OAr), 54.2 (*C*HNHBoc), 29.1 (*C*H$(CH_3)_2$), 24.4 (CO*C*H$_3$), 23.7 (CO*C*H$_3$), 19.5 & 18.7 (CH(*C*H$_3)_2$). υ_{max} (neat) cm^{-1}: 3317 (br) (N-H), 2966 (m) & 2877 (w) (C-H), 1699 (s) (C=O), 1634 (s) & 1605 (m) (N-H), 1539 (s) (Ar C=C), 1272 (s) & 1110 (s) (C-O). HRMS (ES+): calcd for $C_{16}H_{21}F_3N_2O_3$ $[M+H]^+$: 347.1577; found: 347.1575.

(*S*)-*tert*-butyl 2-((2-nitro-4-(trifluoromethyl)phenoxy)methyl)pyrrolidine-1-carboxylate 22

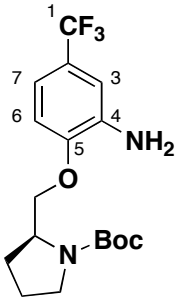


22

KHMDS (0.5 M solution in toluene, 2.12 mL, 1.06 mmol) was added dropwise over 1 h to a stirred solution of Boc-L-proline **21** (0.214 g, 1.06 mmol) and 4-fluoro-3-nitrobenzotrifluoride **1** (0.450 mL, 3.18 mmol) in THF (5 mL) at 0 ˚C. The solution was allowed to warm to rt over 1 h then diluted with dichloromethane (30 mL), washed with NH_4Cl (aq) (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (7:1 Pet:EtOAc, R_f 0.36) to afford the turn precursor **22** as a yellow oil (0.201 g, 0.515 mmol, 49 %).

$[\alpha]_D^{25}$ – 50.0 (c = 1.1, $CHCl_3$). δ_H (500 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 carbamate), 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 (CH_2NBoc), 28.4 ($CO_2C(CH_3)_3$), 28.0 ($CH_2CH_2CH_2NBoc$), 23.8 (CH_2CH_2NBoc). *Minor rotamer*: δ_C (125 MHz, $CDCl_3$): 154.4 (C=O carbamate), 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 (CH_2NBoc), 28.7 ($CH_2CH_2CH_2NBoc$), 28.6 ($CO_2C(CH_3)_3$), 22.8 (CH_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 (ES+): calcd for $C_{17}H_{21}F_3N_2O_5$ $[M+H]^+$: 391.1475; found: 391.1477.

(*S*)-*tert*-butyl 2-((2-amino-4-(trifluoromethyl)phenoxy)methyl)pyrrolidine-1-carboxylate 23

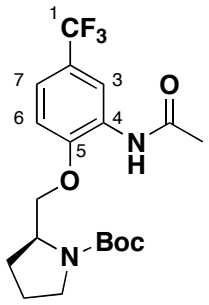


23

22 (0.027 g, 0.069 mmol), ammonium formate (0.030 g, 0.484 mmol) and palladium (10 wt. % on carbon, 0.003 g) were dissolved in methanol:ethyl acetate (9:1 by volume, 1 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 (20 mL). The solvent was removed *in vacuo* and the residue dissolved in dichloromethane (10 mL), washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to yield the aniline **23** (0.022 g, 0.062 mmol, 90 %, R_f 0.28 4:1 Pet:EtOAc) 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 carbamate), 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 ($CH_2CH_2CH_2NBoc$), 23.9 (CH_2CH_2NBoc). *Minor rotamer*: δ_C (125 MHz, $CDCl_3$): 154.4 (C=O carbamate), 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 ($CH_2CH_2CH_2NBoc$), 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 (ES+): calcd for $C_{17}H_{23}F_3N_2O_3$ $[M+H]^+$: 361.1734; found: 361.1734.

(*S*)-*tert*-butyl 2-((2-ethanamido-4-(trifluoromethyl)phenoxy)methyl)pyrrolidine-1-carboxylate 24

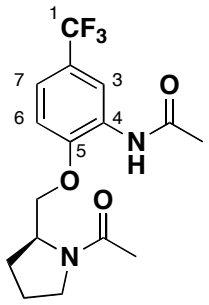


24

4-Dimethylaminopyridine (0.012 g, 0.098 mmol) was added to a solution of **23** (0.120 g, 0.333 mmol) in acetic anhydride (1.0 mL) and pyridine (1.0 mL) at 0 ˚C. 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 (4:1 Pet:EtOAc, R_f 0.56) to afford **24** as a pale crystalline solid (0.127 g, 0.316 mmol, 95 %).

Mp 90-91 ˚C. $[\alpha]_D^{25}$ + 18.4 (c = 1.0, $CHCl_3$). δ_H (400 MHz, $CDCl_3$): 8.92 (1H, br s, N-H), 8.76 (1H, br s, Ar-H^3), 7.24 (1H, br d, *J* 7.7, Ar-H^7), 6.83 (1H, br d, *J* 7.7, Ar-H^6), 4.42 (1H, br m, C*H*NBoc), 3.96 (2H, br m, CH_2OAr), 3.48-3.37 (2H, br m, CH_2NBoc), 2.29 (3H, br s, $COCH_3$), 2.10-2.03 (1H, br m, C$H_2CH_2CH_2$NBoc), 1.99-1.89 (2H, br m, CH_2CH_2NBoc), 1.77 (1H, br m, C$H_2CH_2CH_2$NBoc), 1.47 (9H, s, $CO_2C(CH_3)_3$). δ_C (125 MHz, $CDCl_3$): 169.4 (C=O amide), 155.7 (C=O carbamate), 149.4 (C^5), 128.9 (C^4), 124.3 (q, $J_{C\text{-}F}$ 270.8, C^1), 123.2 (q, $J_{C\text{-}F}$ 32.4, C^2), 120.2 (q, $J_{C\text{-}F}$ 3.9, C^7), 116.6 (q, $J_{C\text{-}F}$ 3.6, C^3), 109.7 (C^6), 79.7 ($CO_2C(CH_3)_3$), 71.4 (CH_2OAr), 55.8 (*C*HNBoc), 47.1 (CH_2NBoc), 28.4 ($CO_2C(CH_3)_3$), 27.5 ($CH_2CH_2CH_2$NBoc), 24.6 ($COCH_3$), 24.0 (CH_2CH_2NBoc). υ_{max} (neat) cm^{-1}: 3289 (br) (N-H), 2977 (m) & 2882 (w) (C-H), 1676 (s) (C=O), 1604 (m) (N-H), 1545 (s) (Ar C=C), 1270 (s) & 1110 (s) (C-O). HRMS (ES+): calcd for $C_{19}H_{25}F_3N_2O_4$ $[M+H]^+$: 403.1839; found: 403.1837.

(*S*)-*N*-(2-((1-ethanoylpyrrolidin-2-yl)methoxy)-5-(trifluoromethyl)phenyl)ethanamide 8

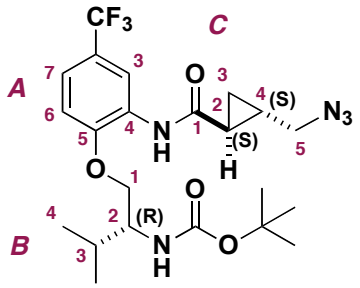


8

24 (0.071 g, 0.197 mmol) was dissolved in dichloromethane:TFA (1:1 by volume, 2.0 mL total) and the resulting solution stirred at 0 ˚C for 30 min. The solvent was removed *in vacuo* and the residue redissolved in dichloromethane (5.0 mL). The solution was washed with $NaHCO_3$ (aq) (5.0 mL), brine (5.0 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to yield the crude amine. The amine intermediate was dissolved in acetic anhydride (1.0 mL) and pyridine (1.0 mL), cooled to 0 ˚C and 4-dimethylaminopyridine was added (0.002 g, 0.016 mmol). The solution was stirred for 2 h, allowed to warm to rt and the solvents removed *in vacuo*. The crude product was purified by column chromatography (EtOAc, R_f 0.20) to afford **8** as a pale crystalline solid (0.054 g, 0.157 mmol, 80 %).

Mp 99-100 ˚C. $[\alpha]_D^{25}$ – 6.2 (c = 1.0, $CHCl_3$). δ_H (400 MHz, $CDCl_3$): 8.76 (1H, d, *J* 1.7, Ar-H^3), 8.68 (1H, br s, C^4NH), 7.24 (1H, dd, *J* 8.5, 1.7, Ar-H^7), 6.85 (1H, d, *J* 8.5, Ar-H^6), 4.75 (1H, d, *J* 9.3, C*H*NCO), 4.04 (1H, dd, *J* 8.5, 2.3, CH_2OAr), 3.94 (1H, t, *J* 8.5, CH_2OAr), 3.55 (2H, br m, CH_2NCO), 2.30 (3H, s, $COCH_3$), 2.11 (3H, s, $COCH_3$), 2.08-2.01 (3H, m, C*H*$_2$C*H*$_2$$CH_2NCO$), 1.83 (1H, m, C*H*$_2$$CH_2CH_2NCO$). δ_C (125 MHz, $CDCl_3$): 171.1 (C=O), 169.6 (C=O), 149.2 (C^5), 128.8 (C^4), 124.3 (q, $J_{C\text{-}F}$ 270.0, C^1), 123.3 (q, $J_{C\text{-}F}$ 32.5, C^2), 120.2 (q, $J_{C\text{-}F}$ 3.9, C^7), 116.5 (q, $J_{C\text{-}F}$ 3.8, C^3), 109.8 (C^6), 70.5 (*C*H_2OAr), 55.2 (*C*HNCO), 47.9 (*C*H_2NBoc), 28.4 (CO*C*H_3), 24.5 (*C*$H_2CH_2CH_2$NBoc), 24.1 (CO*C*H_3), 23.2 (*C*H_2CH_2NBoc). υ_{max} (neat) cm^{-1}: 3284 (br) (N-H), 2964 (m) & 2882 (w) (C-H), 1690 (s) (C=O), 1633 (s) (N-H), 1545 (s) (Ar C=C), 1271 (s) & 1112 (s) (C-O). HRMS (ES+): calcd for $C_{16}H_{19}F_3N_2O_3$ $[M+H]^+$: 345.1421; found: 345.1425.

***tert*-butyl (*R*)-1-(2-((1*S*,2*S*)-2-(azidomethyl)cyclopropanecarboxamido)-4-(trifluoromethyl)phenoxy)-3-methylbutan-2-ylcarbamate 11**



11

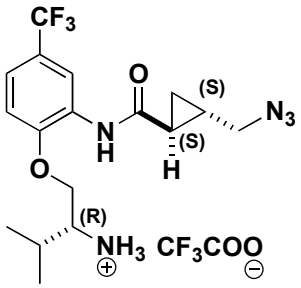
Pivaloyl chloride (192 μL, 1.56 mmol) was added dropwise over 5 mins to a stirring solution of (1*S*, 2*S*)-2-(azidomethyl)cyclopropanecarboxylic acid[2] (220 mg, 1.56 mmol) and triethylamine (657 μL, 4.68 mmol) in THF (5 mL) at room temperature. After 1h, the resulting white suspension was added to a solution of **23** (565 mg, 1.56 mmol) in THF (5 mL). After 5 h, TLC (EtOAc/Pet ether 40-60, 3:17), indicated a small amount of starting material remaining (R_f 0.34). The mixture was concentrated *in vacuo*, dissolved in dichloromethane (20 mL) and washed with pH 7 buffer solution (2 x 5 mL). The collected aqueous layers were extracted with dichloromethane (2 x 10 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (EtOAc/Petroleum ether 40-60, 3:17) to yield **9** (605 mg, 80%) as a colourless oil.

$[\alpha]_D^{25}$ 83.2 (c = 0.5, $CHCl_3$); R_f 0.31 (EtOAc/Pet ether 40-60, 3:17); υ_{max} (film) cm^{-1}: 3388 (NH), 2973, 2880, 2083 (N_3), 1672 (amide I), 1538 (amide II), 1439, 1346, 1270, 1118, 1022; HRMS (ES+): calcd for $C_{22}H_{30}F_3N_5O_4$ $[M+H]^+$: 486.2323; found 486.2315.

[2] Qureshi, M. K. N.; Smith, M. D. *Chem. Commun.*, **2006**, 5006.

Spin system	Position		δ_H (500 MHz, $CDCl_3$, ppm)	multiplicity	*J* (Hz)	δ_C (125 MHz, $CDCl_3$, ppm)
A	C-1		-	-	-	124.2
	C-2		-	-	-	123.5
	C-3		8.77	d	1.2	116.4
	C-4		-	-	-	128.9
	C-5		-	-	-	149.2
	C-6		6.82	d	8.4	109.9
	C-7		7.25	dd	8.4, 1.4	120.2
	NH		8.99	s	-	-
B	C-1		4.00-3.92	m	-	71.9
	C-1’		4.12-4.10	m	-	
	C-2		4.00-3.92	m	-	55.7
	C-3		1.93-1.82	m	-	29.4
	C-4	4	1.05	at	-	18.6
		4'				19.5
	NH		4.64	d	8.8	-
C	C-1		-	-	-	171.0
	C-2		2.07-2.04	m	-	21.2
	C-3	3	0.95	ddd	-	13.1
		3'	1.36	a-td	-	
	C-4		1.93-1.82	m	-	20.4
	C-5	5	3.27	dd	-	53.5
		5'	3.32	dd	-	
Boc	C-1		-	-	-	156.9
	C-2		-	-	-	79.8
	C-3		1.45	s	-	28.4

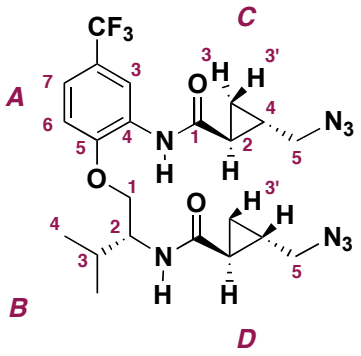
(*R*)-1-(2-((1*S*,2*S*)-2-(azidomethyl)cyclopropanecarboxamido)-4-(trifluoromethyl)phenoxy)-3-methylbutan-2-aminium 2,2,2-trifluoroacetate 28



28

A solution of **9** (205 mg, 0.42 mmol) dichloromethane (1 mL) was added dropwise to a stirring solution of trifluoroacetic acid and dichloromethane (1:1 v/v, 2 mL) at 0 °C. The reaction mixture was stirred and allowed to warm to rt over 1 h. After 1h, TLC (EtOAc/Pet ether 40-60, 1.5:8.5), indicated total consumption of starting material (R_f 0.34) to a single product (R_f 0-0.1). The reaction was concentrated *in vacuo* and coevaporated with toluene (2 x 20 mL) to afford crude **28** that was used without purification in the next step.

(1*S*,2*S*)-2-(azidomethyl)-*N*-(2-((*R*)-2-((1*S*, 2*S*)-2-(azidomethyl)cyclopropanecarboxamido)-3-methylbutoxy)-5-(trifluoromethyl)phenyl)cyclopropanecarboxamide 12



12

Pivaloyl chloride (48 μL, 0.39 mmol) was added dropwise over 5 mins to a stirring solution of (1*S*, 2*S*)-2-(azidomethyl)cyclopropanecarboxylic acid[3] (55 mg, 0.39 mmol) and triethylamine (165 μL, 1.17 mmol) in THF (2 mL) at room temperature. After 1h, the resulting white suspension was added to a solution of **28** (195 mg, 0.39 mmol) in THF (2 mL). After 3 h, TLC (EtOAc/Pet ether 40-60, 3:7), indicated total consumption of starting material (R_f 0-0.1) to a major product (R_f 0.3). The reaction mixture was concentrated *in vacuo*, re-dissolved in dichloromethane (20 mL) and washed with pH 7 buffer solution (2 x 5 mL). The collected aqueous layers were extracted with dichloromethane (2 x 10 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (EtOAc/Pet ether 40-60, 3:7) to yield **12** (140 mg, 70%) as a colourless oil.

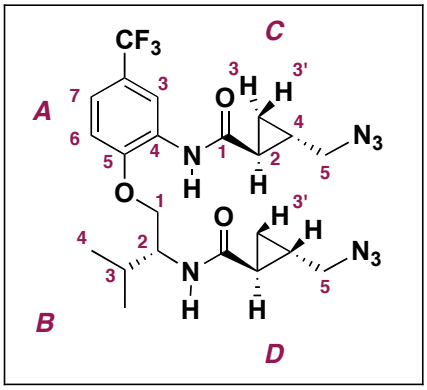
$[\alpha]_D^{25}$ -21.3 (c = 0.46, $CHCl_3$); R_f 0.30 (diethyl ether/Pet ether 40-60, 3:7); υ_{max} (film) cm^{-1}: 3304 (NH), 2966, 2933, 2877, 2096 (N_3), 1652 (Amide I), 1545 (Amide II), 1440, 1325, 1270, 1164, 1118, 1024; HRMS (ES+): calcd for $C_{22}H_{27}F_3N_8O_3$ $[M+H]^+$: 509.5531; found 509.2229.

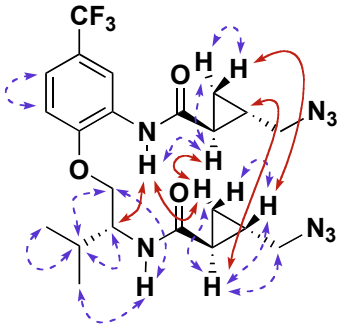
[3] Qureshi, M. K. N.; Smith, M. D. *Chem. Commun.*, **2006**, 5006.

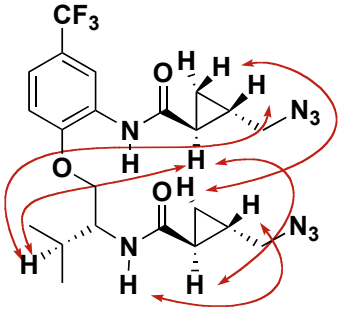
^{1}H NMR: 500 MHz, 2.6 mM in $CDCl_3$ @ 7.27 ppm, 298K

Spin system	Position		δ_H (500 MHz, $CDCl_3$, ppm)	multiplicity	*J* (Hz)	δ_C (125 MHz, $CDCl_3$, ppm)
A	C-1		-	-	-	124.1
	C-2		-	-	-	123.5
	C-3		8.70	d	1.8	116.7
	C-4		-	-	-	128.6
	C-5		-	-	-	149.2
	C-6		7.25	d	1.7, 8.4	109.8
	C-7		6.81	d	8.5	120.4
	NH		8.72	s	-	-
B	C-1		3.92	t	9.2	71.1
	C-1’		4.19	dd	3.0, 9.0	
	C-2		4.34	ddt	2.9, 6.7, 9.4	54.6
	C-3		1.95	Sext.d	6.7, 6.6, 13.4	29.2
	C-4	4	1.08	s	-	18.7
		4'	1.09	s	-	19.6
	NH		5.83	d	9.4	-
C	C-1		-	-	-	171.2
	C-2		2.03	m	-	20.9
	C-3	3	0.91	ddd	4.5, 6.1, 8.3	12.9
		3'	1.37	td	4.6, 9.0	
	C-4		1.84	dddd	4.0, 6.5, 8.7, 12.8	20.5
	C-5	5,5’	3.30	m	-	53.4
D	C-1		-	-	-	173.3
	C-2		1.77	m	-	21.0
	C-3	3	0.82	ddd	4.7, 6.1, 8.3	12.1
		3'	1.26	m	-	
	C-4		1.44	m	-	19.7
	C-5	5	3.11	dd	7.7, 13.1	53.1
		5'	3.37	dd	5.8, 13.1	

NOE data: short-range intraresidue NOEs are indicated by dashed blue line and longer range NOEs by solid red lines.

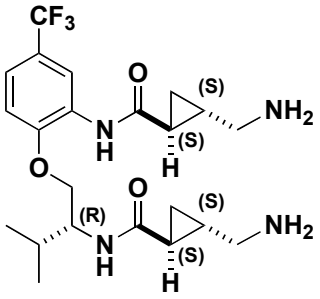






Ref Proton	NOEs						
3'D	5'D (w)	5D	4D	3D			
3C	5,5'C	2C	3'C	4C(w)			
4,4'B	NHB	2B	1B	1'B	3B		
3D	3A, NHA (w)	2C	2D	3'D	3'C		
3'C	4C	3C	4D				
4D	NHB	5'D	5D	2D	3'C	3'D	
2D	5'D	5D	2C	4C	4D	3D	3'D (w)
4C	5C	2C	3'C	2D	3C (w)	3B	
3B	NHB	2B	1B (w)	1'B	4,4'B	2C	4C
2C	3A, NHA	5,5'C	4C	2D	3D	3C	3B
5D	5'D	2D	4D	3D			
5,5'C	2C	4C	3C	NHB (w)			
5'D	5D	2D	4D	3D			
1B	3B	NHB	2B	1'B	3B	4,4'B	7A
1'B	3B	2B	1B	4,4'B	7A		
2B	3A, NHA	NHB	1B	1'B	3B	4,4'B	
NHB	2B	1B	3B	4D	4,4'B		
7A	3A, NHA	6A	1B	1'B	2B		
6A	3A, NHA	7A					
3A, NHA	A6	2B	2C	3D			

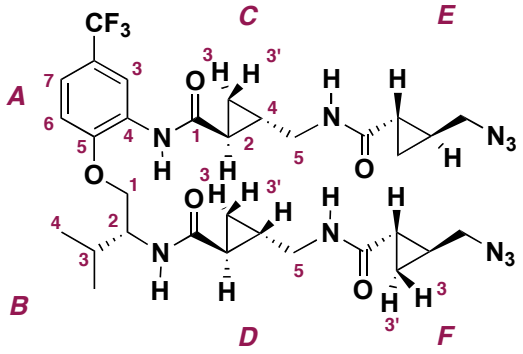
(1*S*,2*S*)-2-(aminomethyl)-*N*-(2-((*R*)-2-((1*S*,2*S*)-2-(aminomethyl)cyclopropanecarboxamido)-3-methylbutoxy)-5-(trifluoromethyl)phenyl)cyclopropanecarboxamide 30



30

A deoxygenated solution of **12** (52 mg, 0.1 mmol) in ethanol (1 mL) was added dropwise to a stirred, suspension of palladium black (10 wt %**,** 5.2 mg) in ethanol (1.5 mL) under an atmosphere of hydrogen. The reaction mixture was stirred for 30 mins when TLC (EtOAc/Pet ether 40-60, 3:7) indicated complete conversion of starting material (R_f 0.34) to a major product (R_f 0-0.1). The reaction mixture was filtered through Celite™ (washing with ethanol) and concentrated *in vacuo* to yield **30 (**44 mg, 0.096 mmol, 96%), which was used without further purification.

(1*S*,2*S*)-2-(azidomethyl)-*N*-(((1*S*,2*S*)-2-(2-((*R*)-2-((1*S*,2*S*)-2-(((1*S*,2*S*)-2-(azidomethyl)cyclopropanecarboxamido)methyl)cyclopropanecarboxamido)-3-methylbutoxy)-5-(trifluoromethyl)phenylcarbamoyl)cyclopropyl)methyl)cyclopropanecarboxamide 14



14

Pivaloyl chloride (32 μL, 0.26 mmol) was added dropwise over 5 mins to a stirring solution of (1*S*, 2*S*)-2-(azidomethyl)cyclopropanecarboxylic acid[4] (37 mg, 0.26 mmol) and triethylamine (101 μL, 0.71 mmol) in THF (2 mL) at room temperature. After 1h, the resulting white suspension was added to a solution of **30** (44 mg, 0.096 mmol) in THF (1 mL). After 3 h TLC (EtOAc), indicated total consumption of starting material (R_f 0-0.1) and the presence of a major product (R_f 0.21). The reaction mixture was concentrated *in vacuo*, re-dissolved in dichloromethane (20 mL) and washed with pH 7 buffer solution (2 x 5 mL). The combined aqueous layers were extracted with dichloromethane (2 x 10mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (methanol/$CHCl_3$, 1:9) to yield **14** (42 mg, 60%) as a colourless oil.

R_f 0.40 (methanol/$CHCl_3$, 1:9); $[\alpha]_D^{25}$ 17.1 (c = 0.56, $CHCl_3$); υ_{max} (film) cm^{-1}: 3296 (NH), 2965, 2932, 2875, 2094 (N_3), 1638 (amide I), 1542 (amide II), 1440, 1325, 1269, 1163, 1119, 1023; HRMS (ES+): calcd for $C_{32}H_{41}F_3N_{10}O_5$ $[M+H]^+$: 703.3286; found 703.3298.

^{1}H NMR: 700 MHz, 2.8 mM in $CDCl_3$@ 7.27 ppm, 298k

[4] Qureshi, M. K. N.; Smith, M. D. *Chem. Commun.*, **2006**, 5006.

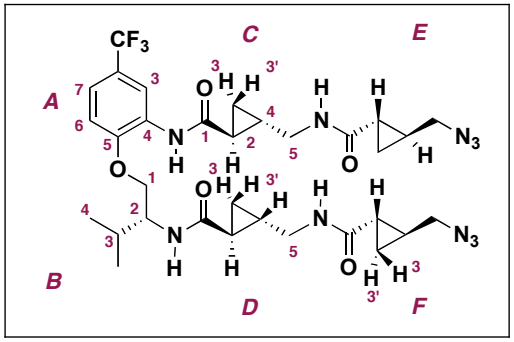
Spin system	Position		δ_H (700 MHz, $CDCl_3$, ppm)	multiplicity	*J* (Hz)	δ_C (125 MHz, $CDCl_3$, ppm)
A	C-1		-	-	-	124.2
	C-2		-	-	-	123.6
	C-3		8.68	d	1.7	116.6
	C-4		-	-	-	128.8
	C-5		-	-	-	149.2
	C-6		6.81	d	8.5	109.9
	C-7		7.24	dd	1.5, 8.5	120.2
	NH		8.70	s	-	-
B	C-1		3.94	t	9.3	71.3
	C-1’		4.17	dd	2.9, 9.0	
	C-2		4.25	ddt	2.9, 6.7, 9.5	54.8
	C-3		1.93	td	6.8, 13.6	29.2
	C-4	4	1.05	t	6.3	18.8
		4'	1.05	t	6.3	19.6
	NH		5.96	d	9.3	-
C	C-1		-	-	-	171.3
	C-2		1.91-1.88	m	-	*
	C-3	3	0.84	ddd	4.0, 5.2, 6.8	*
		3'	1.41-1.34	m	-	
	C-4		1.64-1.60	m	-	*
	C-5	5	2.86	ddd	4.2, 7.8, 13.9	42.8
		5'	3.74	td	6.7, 13.8	
	NH		6.55	dd	4.2, 6.5	-
D	C-1		-	-	-	174.2
	C-2		1.60-1.57	m	-	*
	C-3	3	0.82-0.79	m	-	*
		3'	1.13	td	4.7, 9.1	
	C-4		1.52	dddd	4.2, 6.3,10.3, 13.5	*
	C-5	5	3.15-3.21	m	-	42.5
		5'	3.31-3.27	m	-	
	NH		6.10	t	5.7	-
E	C-1		-	-	-	171.8
	C-2		1.41-1.34	m	-	*
	C-3	3	0.77	ddd	4.4, 5.9, 8.3	*
		3'	1.25	tdd	4.6, 6.9, 9.0	
	C-4		1.73-1.68	m	-	*
	C-5	5	3.15-3.21	ddmd	-	53.3
		5'	3.31-3.27	m	-	
F	C-1		-	-	-	172.1
	C-2		1.41-1.34	m	-	*
	C-3	3	0.82-0.79	m	-	*
		3'	1.25	tdd	4.7, 6.9, 9.0	
	C-4		1.73-1.68	m	-	*

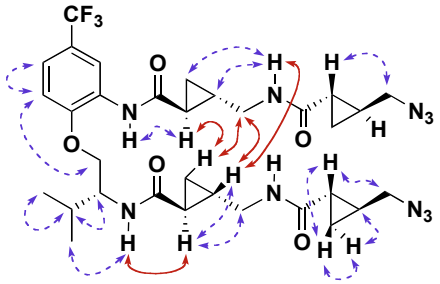
Spin system	Position		δ_H (700 MHz, $CDCl_3$, ppm)	multiplicity	*J* (Hz)	δ_C (125 MHz, $CDCl_3$, ppm)
	C-5	5	3.12	dd	7.5, 13.0	53.4
		5'	3.36	dd	6.0, 13.0	

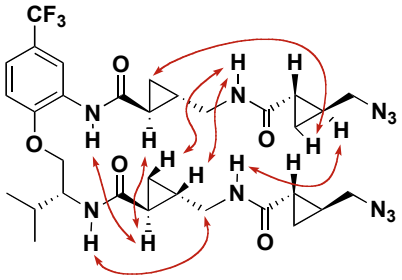
* resonance overlap prevented residue specific unambiguous assignment of all of the ^{13}C signals for some C-2, C-3 and C-4 carbons; their (grouped) values are presented below:

Spin system	Position	δ_C (125 MHz, $CDCl_3$, ppm)
C/D/E/F	C-3	12.0
		12.3
		12.6
C/D/E/F	C-2 and C-4	19.4
		19.7
		20.4
		20.6
		21.1
		21.7
		21.8
		22.1

NOE data: short-range intraresidue NOEs are indicated by dashed blue lines, and longer-range NOEs by solid red lines.



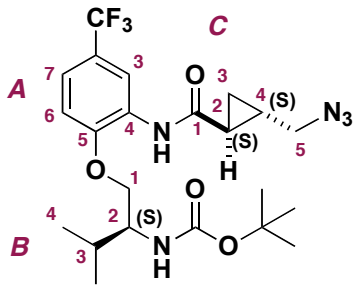




No	Proton	NOEs											
1	**E-3**	D-3 or F-3 *	E-3’	E-2	E-4								
2	**D-3**	D-3’	D-4	D-2									
3	**F-3**	E-3 *	F-3’	F-2	F-4								
4	**C-3**	C-3’	D-4	C-4	C-2								
5	**B-4,4’**	B-3	B-1	B-1’	B-2	NH_B							
6	**D-3’**	D-3	D-4	D-2	C-2								
7	**E-3’**	E-3	E-2	E-4									
8	**F-3’**	F-3	F-2	F-4									
9	**C-3’**	C-3	C-4	C-2									
10	**E-2**	E-3	E-3’	E-4									
11	**F-2**	F-3	F-3’	F-4									
12	**D-4**	D-3	D-3’	C-5	D-5	D-5’	C-5’	B-2	NH_B	NH_D	NH_C	NH_A	
13	**D-2**	D-3	D-3’	D-5	D-5’	B-2	NH_B	NH_D	NH_C				
14	**C-4**	C-3	C-3’	C-2	C-5	C-5’							
15	**F-4**	F-5	E-5	E-5’	F-5’	NH_D	NH_C						
16	**E-4**	F-5	E-5	E-5’	F-5’	NH_D	NH_C	NH_A					
17	**C-2**	C-3	D-3’	C-3’	C-4	C-5	C-5’						
18	**B-3**	B-4,4’	E-3’ or F-3’ or C-3’	B-1	B-1’	B-2	NH_B						
19	**C-5**	C-3	D-3’	D-4	C-4	C-2	C-5’	NH_C					
20	**F-3**	F-3’	F-5	F-2	F-4	F-5’							
21	**E-5**	E-3	E-3’	E-2	E-4	E-5’							
22	**D-5**	D-3	D-4	D-2	D-5’	NH_D							
23	**D-5’**	D-3	D-4	D-2	D-5	NH_D							
24	**E-5’**	E-3	E-3’ v weak	E-2	E-4	E-5							
25	**F-5’**	F-3	F-3’ v weak	F-2	F-4	F-5							
26	**C-5’**	C-3	D-4	C-4	C-2	C-5	NH_C						
27	**B-1**	B-4,4’	B-3	B-1’	B-2	NH_B	A-6						
28	**B-1’**	B-4,4’	B-3	B-1	B-2	A-6	NH_A						
29	**B-2**	B-4,4’	E-2	D-2	B-3	B-1	B-1’	NH_B	NH_A				
30	**NH_B**	B-4,4’	D-3’	E-3’ or F-3’ or C-3’	E-2 or F-2	D-4	D-2	F4 or E-4	B-3	B-1	B-1’	B-2	
31	**NH_D**	D-3	E-3’ or F-3’ or C-3’	F-2 or E-2	D-4	D-2	F4 or E-4	D-5	D-5’	31			
32	**NH_C**	C-3	D-3’	E-3’ or F-3’ or C-3’	E-2 or F-2	D-4	C-4	F4 or E-4	C-2	C-5	C-5’	B-2	NH_A
33	**A-6**	B-1	B1’	A-7									
34	**A-7**	A-6											
36	**D-3’**	E-3’ or F-3’ or C-3’	D-4	C-4	C-2	B-1	B-1’	B-2	NH_B	NH_C	A-6	NH_A	

Note: Resonance overlap of E-3’, F-3’, C-3’, E-2, F-2, F4 and E4 make non-ambiguous assignments difficult
* potentially ambiguous and very weak

***tert*-butyl (*S*)-1-(2-((1*S*,2*S*)-2-(azidomethyl)cyclopropanecarboxamido)-4-(trifluoromethyl)phenoxy)-3-methylbutan-2-ylcarbamate 26**



26

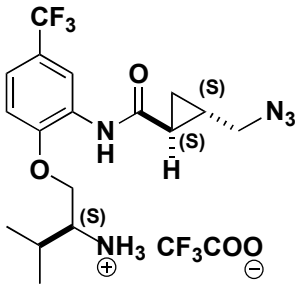
Pivaloyl chloride (170 μL, 1.38 mmol) was added dropwise over 5 mins to a stirring solution of (1*S*, 2*S*)-2-(azidomethyl)cyclopropanecarboxylic acid[5] (195 mg, 1.38 mmol) and triethylamine (582 μL, 4.14 mmol) in THF (5 mL) at room temperature. After 1h, the resulting white suspension was added to a solution of **17** (500 mg, 1.38 mmol) in THF (5 mL). After 5 h, TLC (EtOAc/Pet ether 40-60, 3:17), indicated the presence of a small amount of starting material (R_f 0.34). The reaction mixture was concentrated *in vacuo*, dissolved in dichloromethane (20 mL) and washed with pH 7 buffer solution (5 mL). The collected aqueous layers were extracted with dichloromethane (2 x 10 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (EtOAc/Petroleum ether 40-60, 3:17) to yield **26** (500 mg, 75%) as a colourless oil.

R_f 0.31 (EtOAc/Pet ether 40-60, 1.5:8.5); $[\alpha]_D^{25}$ 83.2 (c = 0.5, $CHCl_3$); υ_{max} (film) cm^{-1}: 3388 (NH), 3361, 2973, 2880, 2083 (N_3), 1672 (amide I), 1538 (amide II), 1439, 1346, 1270, 1118, 1022; HRMS (ES+) calcd for $C_{22}H_{30}F_3N_5O_4$ $[M+H]^+$: 486.2323; found 486.2315.

[5] Qureshi, M. K. N.; Smith, M. D. *Chem. Commun.*, **2006**, 5006.

Spin system	Position		δ_H (500 MHz, $CDCl_3$, ppm)	multiplicity	*J* (Hz)	δ_C (125 MHz, $CDCl_3$, ppm)
A	C-1		-	-	-	124.2
	C-2		-	-	-	123.5
	C-3		8.75	-	-	116.7
	C-4		-	-	-	128.9
	C-5		-	-	-	149.3
	C-6		6.83	d	8.4	110.0
	C-7		7.24	d	8.8	120.2
	NH		8.75	s	-	-
B	C-1		3.96-3.95	m	-	72.0
	C-1’		4.10-4.09	m	-	
	C-2		4.10-4.09	m	-	55.7
	C-3		1.94-1.83	m	-	29.4
	C-4	4	1.05	at	6.4	18.5
		4'				19.6
	NH		4.66	d	7.3	-
C	C-1		-	-	-	171.2
	C-2		2.01-1.99	m	-	20.9
	C-3	3	0.95	ddd	4.5, 6.0, 8.4	13.6
		3'	1.37-1.32	m	-	
	C-4		1.94-1.83	m	-	20.0
	C-5	5	3.24	dd	7.2,12.9	53.3
		5'	3.33	dd	6.2, 12.7	
Boc	C-1		-	-	-	157.0
	C-2		-	-	-	79.7
	C-3		1.45	s	-	28.4

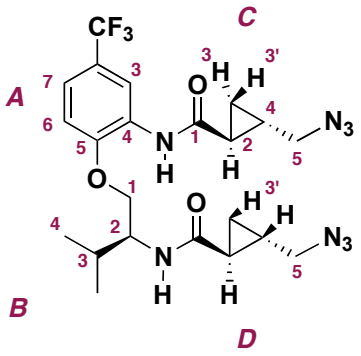
(*R*)-1-(2-((1*S*,2*S*)-2-(azidomethyl)cyclopropanecarboxamido)-4-(trifluoromethyl)phenoxy)-3-methylbutan-2-aminium 2,2,2-trifluoroacetate 27



27

A solution of **26** (205 mg, 0.42 mmol) in dichloromethane (1 mL) was added dropwise to a stirring solution of trifluroacetic acid and dichloromethane (1:1 v/v, 2 mL) at 0 °C. The reaction mixture was stirred and allowed to warm to rt over 1 h when TLC (EtOAc/Pet ether 40-60, 1.5:8.5), indicated consumption of starting material (R_f 0.34) to a single product (R_f 0-0.1). The reaction was concentrated *in vacuo* and coevaporated with toluene (2 x 20 mL) to afford crude **27** that was used without further purification in the next step.

(1*S*,2*S*)-2-(azidomethyl)-*N*-(2-((*S*)-2-((1*S*,2*S*)-2-(azidomethyl)cyclopropanecarboxamido)-3-methylbutoxy)-5-(trifluoromethyl)phenyl)cyclopropanecarboxamide 13



13

Pivaloyl chloride (47 μL, 0.39 mmol) was added dropwise over 5 mins to a stirring solution of (1*S*, 2*S*)-2-(azidomethyl)cyclopropanecarboxylic acid[6] (55 mg, 0.39 mmol) and triethylamine (165 μL, 1.17 mmol) in THF (2 mL) at room temperature. After 1h, the resulting white suspension was added to a solution of **27** (195 mg, 0.39 mmol) in THF (2 mL). After 3 h, TLC (EtOAc/Pet ether 40-60, 3:7), indicated total consumption of starting material (R_f 0-0.1) and appearance of a major product (R_f 0.3). The reaction mixture was concentrated *in vacuo*, dissolved in dichloromethane (20 mL) and washed with pH 7 buffer solution (5 mL). The collected aqueous layers were extracted with dichloromethane (2 x 10mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (EtOAc/Petroleum ether 40-60, 3:7) to yield **13** (149 mg, 75%) as colourless oil.

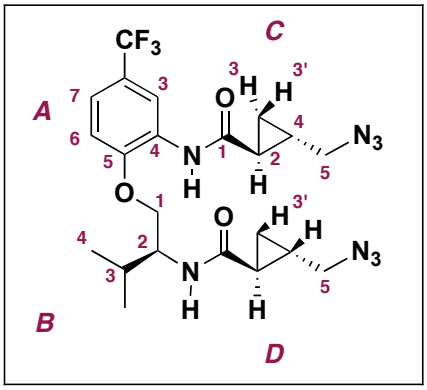
R_f 0.30 (diethyl ether/Pet ether 40-60, 3:7); $[\alpha]_D^{25}$ 58.0 (c = 1, $CHCl_3$); υ_{max} (film) cm^{-1}: 3303 (NH), 2966, 2932, 2877, 2096 (N_3), 1650 (amide I), 1544 (amide II), 1440, 1324, 1270, 1163, 1117, 1024; HRMS (ES+) calcd for $C_{22}H_{27}F_3N_8O_3$ $[M+H]^+$: 509.5531; found 509.2229.

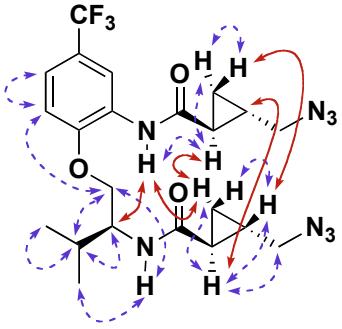
[6] Qureshi, M. K. N.; Smith, M. D. *Chem. Commun.*, **2006**, 5006.

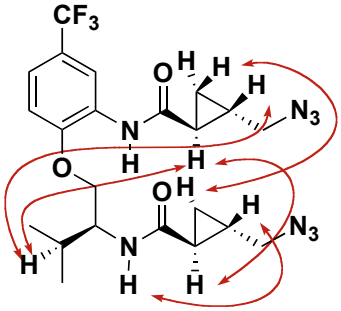
1H NMR: 500 MHz, 3.1 mM in $CDCl_3$ @ 7.27 ppm, 298K.

Spin system	Position		δ_H (500 MHz, $CDCl_3$, ppm)	multiplicity	*J* (Hz)	δ_C (125 MHz, $CDCl_3$, ppm)
A	C-1		-	-	-	124.2
	C-2		-	-	-	123.5
	C-3		8.68	s	-	116.7
	C-4		-	-	-	128.8
	C-5		-	-	-	149.2
	C-6		6.73	d	8.4	109.7
	C-7		7.18	d	8.4	120.2
	NH		8.72	s	-	-
B	C-1		3.88	t	9.3	71.3
	C-1’		4.09	dd	2.9, 8.9	
	C-2		4.25	ddt	2.8, 6.4, 9.4	54.8
	C-3		1.87	m	-	29.1
	C-4	4	1.00	s	-	18.7
		4'	1.01	s	-	19.6
	NH		5.68	d	9.3	-
C	C-1		-	-	-	171.2
	C-2		1.98	td	4.4, 8.5	20.9
	C-3	3	0.86	ddd	4.5, 6.1, 8.5	11.8
		3'	1.27	m	-	
	C-4		1.78	m	-	20.2
	C-5	5	3.18	dd	7.0, 12.9	53.5
		5'	3.35	dd	6.3, 12.9	
D	C-1		-	-	-	173.4
	C-2		1.38	m	-	21.0
	C-3	3	0.81	ddd	4.8, 6.0, 8.3	13.4
		3'	1.27	m	-	
	C-4		1.59	m	-	20.1
	C-5	5	3.06	dd	7.2, 13.1	52.9
		5'	3.27	dd	5.9, 13.2	

NOE data: short-range intraresidue NOEs are indicated by dashed blue line and longer range NOEs by solid red lines.

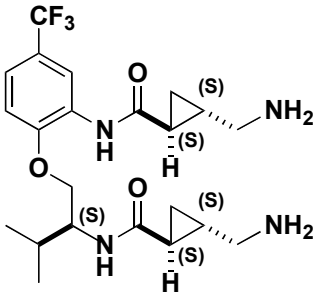






No	Ref Proton	nOes						
1	**3'D**	5'D	5D	4D	3D			
2	**3C**	5,5'C	2C	3'C				
3	**4,4'B**	NHB	2B	1B	1'B	3B		
4	**3D**	3A, NHA	2C	2D	3'D	3'C		
5	**3'C**	4C	3C	4D				
6	**4D**	NHB	5'D	5D	2D	3D	3'C	3'D
7	**2D**	5'D	5D	2C	4C	4D	3D	
8	**4C**	5,5'C	2C	3'C	2D			
9	**3B**	NHB	2B	1B	1'B	4,4'B	2C	4C
10	**2C**	3A, NHA	5,5'C	4C	2D	3D	3C	
11	**5D**	5'D	2D	4D	3D			
12	**5,5'C**	2C	4C	3C				
13	**5'D**	NHB	5D	2D	4D	3D		
14	**1B**	3B	NHB	2B	1B	3B	4,4'B	
15	**1'B**	3B	2B	1'B	3B	4,4'B		
16	**2B**	3A, NHA	NHB	1B	1'B	3B	4,4'B	
17	**NHB**	2B	1'B	3B	4D	4,4'B		
18	**6A**	3A, NHA	A7	1B	1'B			
19	**7A**	3A, NHA	3B					
20	**3A, NHA**	A7	2B	2C	3D			

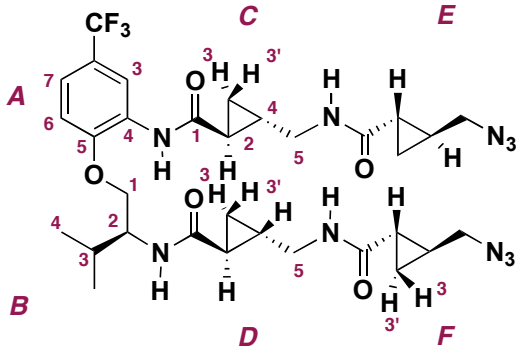
(1*S*,2*S*)-2-(aminomethyl)-*N*-(2-((*R*)-2-((1*S*,2*S*)-2-(aminomethyl)cyclopropanecarboxamido)-3-methylbutoxy)-5-(trifluoromethyl)phenyl)cyclopropanecarboxamide 29



29

A deoxygenated solution of **13** (67 mg, 0.13 mmol) in ethanol (1 mL) was added dropwise to a stirred suspension of palladium black (10 wt %**,** 5 mg) in ethanol (1.5 mL) under an atmosphere of hydrogen. The reaction mixture was stirred for 30 mins when TLC (EtOAc/Pet ether 40-60, 3:7) indicated complete conversion of starting material (R_f 0.34) to a major product (R_f 0-0.1). The reaction mixture was filtered through Celite™ (washing with ethanol) and concentrated *in vacuo* to yield **29** 57.0 mg, 0.125 mmol, 95%), which was used without further purification.

(1*S*,2*S*)-2-(azidomethyl)-*N*-(((1*S*,2*S*)-2-(2-((*S*)-2-((1*S*,2*S*)-2-(((1*S*,2*S*)-2-(azidomethyl)cyclopropanecarboxamido)methyl)cyclopropanecarboxamido)-3-methylbutoxy)-5-(trifluoromethyl)phenylcarbamoyl)cyclopropyl)methyl)cyclopropanecarboxamide 15



15

Pivaloyl chloride (35 μL, 0.28 mmol) was added dropwise over 5 mins to a stirring solution of (1*S*, 2*S*)-2-(azidomethyl)cyclopropanecarboxylic acid[7] (40 mg, 0.28 mmol) and triethylamine (108 μL, 0.77 mmol) in THF (2 mL) at room temperature. After 1h, the resulting white suspension was added to a solution of **29** (50 mg, 0.11 mmol) in THF (1 mL). After 3 h, TLC (EtOAc) indicated total consumption of starting material (R_f 0-0.1) and appearance of a major product (R_f 0.2). The reaction mixture was concentrated *in vacuo*, re-dissolved in dichloromethane (20 mL) and washed with pH 7 buffer solution (2 x 5 mL). The collected aqueous layers were extracted with dichloromethane (2 x 10mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (methanol/$CHCl_3$, 1:9) to yield **15** (50 mg, 65%) as colourless oil.

R_f 0.40 (methanol/$CHCl_3$, 1:9); $[\alpha]_D^{25}$ 82.1 (c = 0.25, $CHCl_3$); υ_{max} (film) cm^{-1}: 3303 (NH), 2965, 2932, 2873, 2096 (N_3), 1641 (amide I), 1543 (amide II), 1440, 1329, 1270, 1164, 1120, 1023; HRMS (ES+): calcd for $C_{32}H_{41}F_3N_{10}O_5$ $[M+H]^+$: 703.3286; found 703.3298.

^{1}H NMR: 700MHz, 2.8 mM in $CDCl_3$ @ 7.27 ppm, 298K.

Spin system	Position	δ_H (500 MHz, $CDCl_3$, ppm)	multiplicity	*J* (Hz)	δ_C (125 MHz, $CDCl_3$, ppm)
A	C-1	-	-	-	124.2
	C-2	-	-	-	123.5
	C-3	8.72	d	1.56	116.5

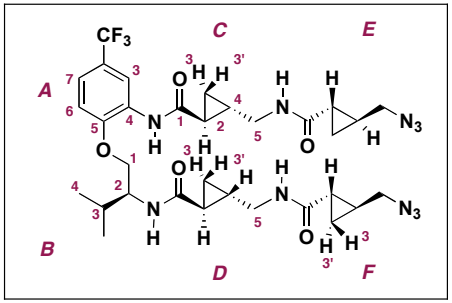
[7] Qureshi, M. K. N.; Smith, M. D. *Chem. Commun.*, **2006**, 5006.

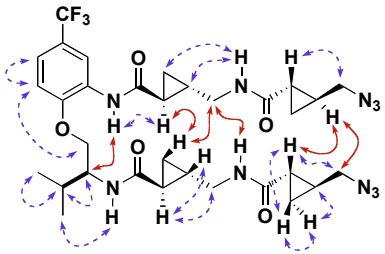
Spin system	Position		δ_H (500 MHz, $CDCl_3$, ppm)	multiplicity	*J* (Hz)	δ_C (125 MHz, $CDCl_3$, ppm)
	C-4		-	-	-	129.0
	C-5		-	-	-	149.5
	C-6		6.83	d	8.4	110.2
	C-7		7.26	dd	1.5, 8.3	120.3
	NH		8.75	s	-	-
B	C-1		3.92	t	9.7	71.8
	C-1’		4.22	dd	2.7, 9.1	
	C-2		4.33	ddt	2.7, 6.3, 9.3	54.9
	C-3		1.92-1.88	m	-	29.3
	C-4	4	1.06-1.05	m	-	18.7
		4'	1.06-1.05	m	-	19.3
	NH		5.81	d	9.3	-
C	C-1		-	-	-	171.5
	C-2		1.98	m	-	*
	C-3	3	0.88-0.83	m	-	13.9
		3'	1.37	td	4.5, 8.8	
	C-4		1.66-1.61	m	-	*
	C-5	5	3.01	ddd	4.1, 7.9, 13.4	43.2
		5'	3.71-3.67	m	-	
	NH		6.54-6.52	m	-	-
D	C-1		-	-	-	174.2
	C-2		1.53-1.49	m	-	*
	C-3	3	0.88-0.83	m	-	13.2
		3'	1.16	td	4.2, 8.5	
	C-4		1.46-1.41	m	-	*
	C-5	5	3.20-3.12	m	-	42.5
		5'	3.20-3.12	m	-	
	NH		6.97	t	4.1	-
E	C-1		-	-	-	172.0
	C-2		1.71-1.67	m	-	*
	C-3	3	0.82-0.78	m	-	12.1
		3'	1.2-1.212	m	-	
	C-4		1.46-1.41	m	-	*
	C-5	5	3.20-3.12	m	-	53.4
		5'	3.31-3.27	m	-	
F	C-1		-	-	-	172.5
	C-2		1.60-1.55	m	-	*
	C-3	3	0.63	ddd	4.7, 5.8, 8.3	11.8
		3'	1.12	td	4.6, 9.0	
	C-4		1.46-1.41	m	-	*
	C-5	5	3.09	dd	7.2, 13.0	53.4
		5'	3.20-3.12	m	-	

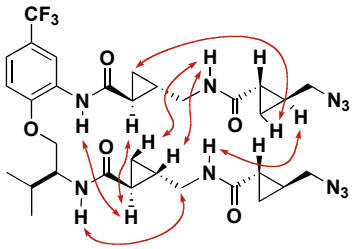
* resonance overlap prevented residue specific unambiguous assignment of all of the ^{13}C signals for some C-2 and C-4 carbons; their (grouped) values are presented below:

Spin System	**Carbon**	**δ_C (125 MHz, $CDCl_3$, ppm)**
C, D, E, F	C-2 and C-4	19.6
		19.9
		20.3
		20.8
		20.9
		21.2
		22.2

NOE data: short-range intraresidue NOEs are indicated by dashed blue lines, and longer-range NOEs by solid red lines.







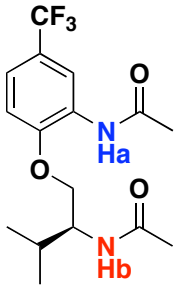
No	Ref Proton	NOEs							
1	**F-3**	F-3’	F-4	F-5	F-5’				
2	**E-3**	E-3’	E-4	E-5	E-5’				
3	**D-3**	D-3’	D-4	D-5,5’	NH_D				
4	**C-3**	C-3’	C-2	C-5 (w)	C-5’	NH_C			
5	**B-4,4’**	NH_B	B2	B1	B1’	B3			
6	**F-3’**	F-4 (vw)	F-2	F-3					
7	**D-3’**	D-3	D-4 (w)	D-2	C-2	C-5 (vw)	NH_C		
8	**E-3’**	E-4 (w)	E-2	E-3	C-3	E-5 (vw)	F-5’ (vw)		
9	**C-3’**	C-2	C-4	C-3					
10	**D-4**	D-3	D-3’	D-2	D-5,5’	NH_B			
11	**E-4**	E-3	E-3’	E-2	E-5	E-5’	F-2	NH_C	
12	**F-4**	F-3	F-3’	F-2	F-5	F-5’	NH_D		
13	**D-2**	C-2	D-3’	D-4	D-5,5’	D-3	NH_D	NH_A	
14	**F-2**	F-3’	F-4	F-3’	E-4	F-5	F-5’	F-3 (vw)	
15	**C-4**	C-2	C-3’	C-5	C-5’	NH_C			
16	**E-2**	E-3’	E-4	E-5	E-5’				
17	**B-3**	B-4,4’	NH_B						
18	**C-2**	C-4	D-2	C-3	C-5	C-5’	NH_C	NH_A	C-3’ (vw)
19	**C-5**	C-2	C-4	C-3	C-5’	NH_C			
20	**F-5**	F-2	F-4	F-3	F-5’				
21	**E-5**	E-2	E-4	E-3	E-5’				
22	**D-5,5’**	D-3	D-4	D-2	NH_D				
23	**F-5’**	F-3	F-4	F-2	F-5				
24	**E-5’**	E-2	E-4	E-3	E-5				
25	**C-5’**	C-2	C-4	D-2	C-3	C-5	NH_C		
26	**B-1**	B-3	B-4,4’	B1’	B-2	NH_B	A-7	A-6	
27	**B-1’**	A-7	B-2	B-1	B-3	B-4,4’	A-6		
28	**B-2**	B-3	B-4,4’	B1	B1’	NH_B	NH_A		
29	**NH_B**	B-1	B-2	B-3	D-4	B-4,4’			
30	**NH_C**	C-3	C-4	C-2	C-5	C-5’	D-3‘	D-4	
31	**A-6**	A-7	B-1	B-1’					
32	**NH_D**	D-3	E-4	D-2	D-5,5’	C-5’			
33	**A-7**	A-6							
34	**A-3**								
35	**NH_A**	C-2	B-2						

w = weak; vw = very weak

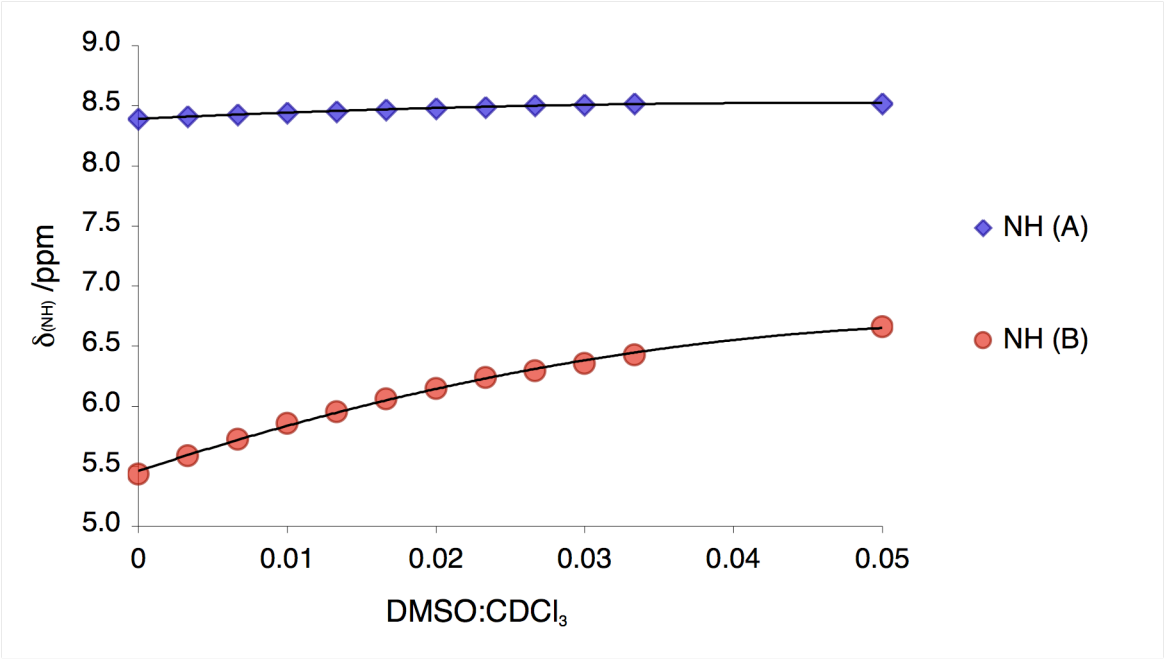
3. DMSO-d_6 titration experiments:

A 1.0 mM sample of compound was prepared in pre-dried $CDCl_3$ (0.60 mL) containing tetramethylsilane (TMS) as an internal standard. The initial ^1H NMR spectrum was taken. A 2.0 µL aliquot of DMSO-d_6 was added and the tube shaken to ensure complete mixing of solvents. The subsequent ^1H NMR spectrum was recorded. A further 2.0 µL aliquot of DMSO-d_6 was added and the process repeated until a total of 20 µL of the hydrogen-bonding solvent had been added. A final 10 µL aliquot of DMSO-d_6 was added, and the ^1H NMR spectrum recorded, so as to establish an upper limit. Chemical shift values were referenced to TMS (δ_H = 0.0000).

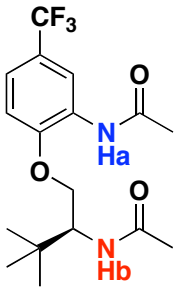
Data for 6



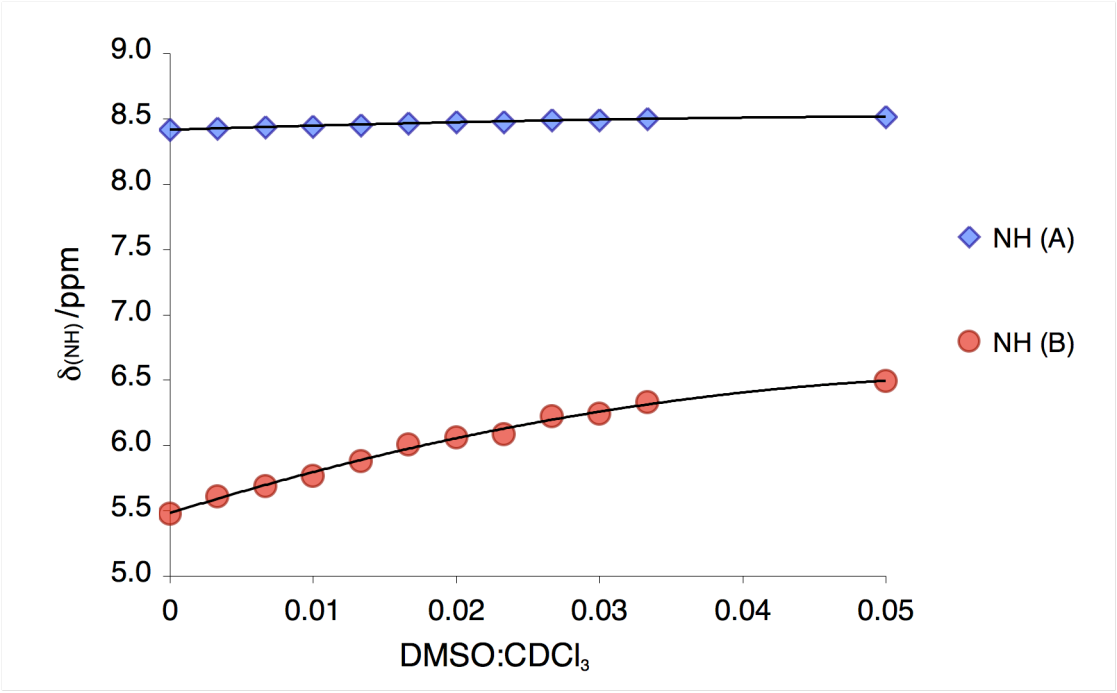
v (DMSO / mL)	v' ($CDCl_3$ mL)	v/v'	$\delta_{(NH)}$ A / ppm	$\delta_{(NH)}$ B / ppm
0.0000	0.6000	0.0000	8.3903	5.4323
0.0020	0.6000	0.0033	8.4090	5.5840
0.0040	0.6000	0.0067	8.4242	5.7240
0.0060	0.6000	0.0100	8.4394	5.8573
0.0080	0.6000	0.0133	8.4527	5.9521
0.0100	0.6000	0.0167	8.4666	6.0591
0.0120	0.6000	0.0200	8.4769	6.1435
0.0140	0.6000	0.0233	8.4867	6.2377
0.0160	0.6000	0.0267	8.5031	6.2933
0.0180	0.6000	0.0300	8.5072	6.3553
0.0200	0.6000	0.0333	8.5149	6.4269
0.0300	0.6000	0.0500	8.5190	6.6615



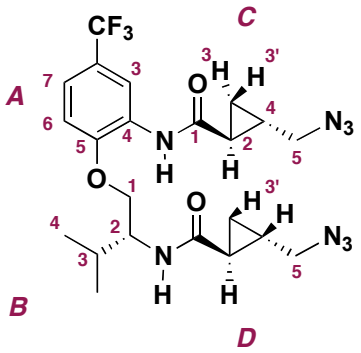
Data for 7



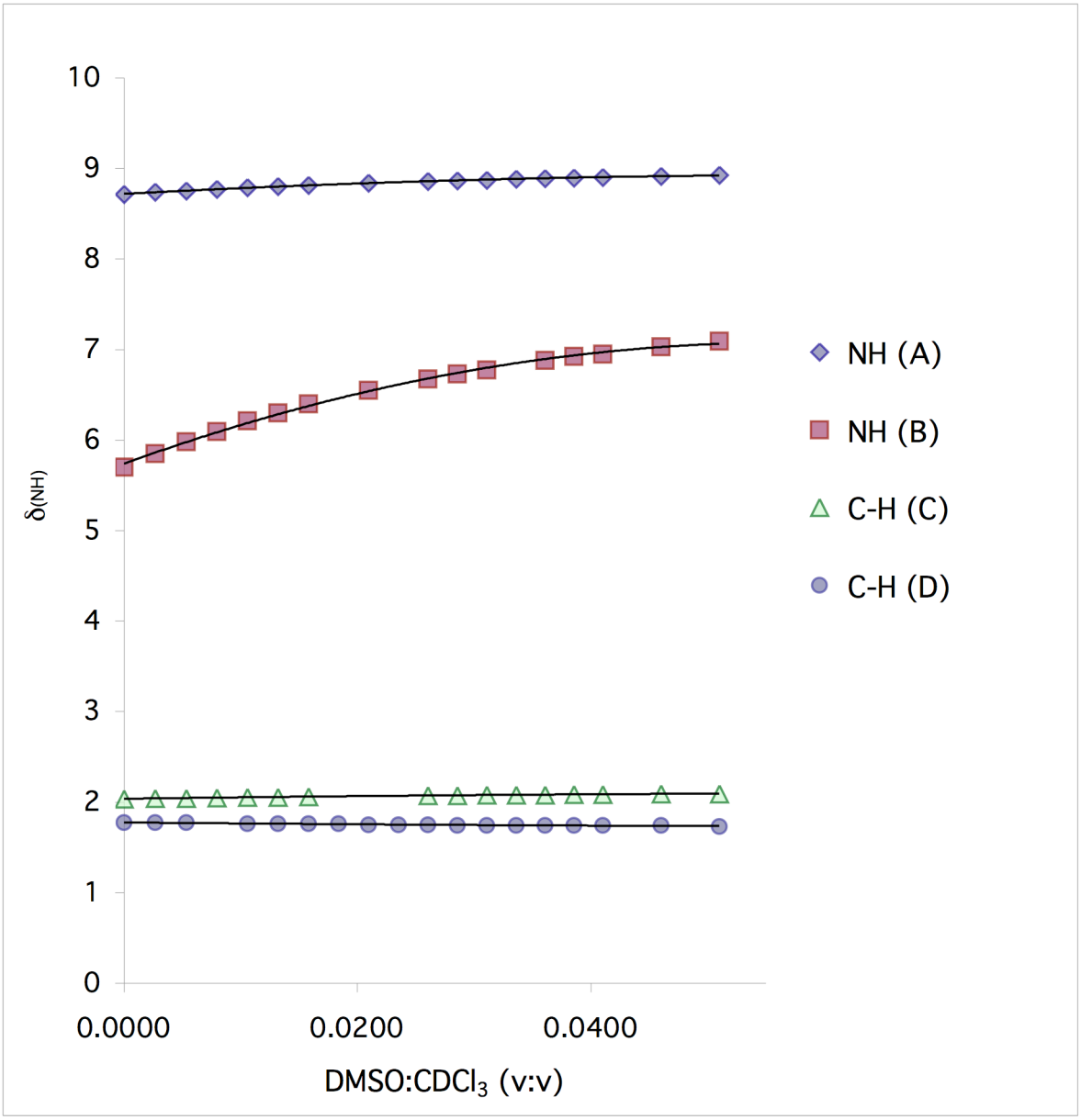
v (DMSO / mL)	v' ($CDCl_3$ mL)	v/v'	$\delta_{(NH)}$ A / ppm	$\delta_{(NH)}$ B / ppm
0.0000	0.6000	0.0000	8.4148	5.4776
0.0020	0.6000	0.0033	8.4262	5.6107
0.0040	0.6000	0.0067	8.4360	5.6888
0.0060	0.6000	0.0100	8.4423	5.7679
0.0080	0.6000	0.0133	8.4515	5.8785
0.0100	0.6000	0.0167	8.4668	6.0055
0.0120	0.6000	0.0200	8.4755	6.0589
0.0140	0.6000	0.0233	8.4738	6.0822
0.0160	0.6000	0.0267	8.4881	6.2223
0.0180	0.6000	0.0300	8.4906	6.2438
0.0200	0.6000	0.0333	8.5002	6.3284
0.0300	0.6000	0.0500	8.5154	6.4898



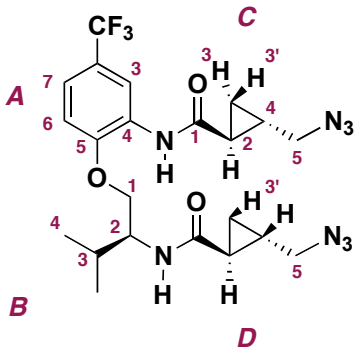
DMSO titration Data for 12 **[breaks in the table indicate resonance overlap that prevented unambiguous assignment].**



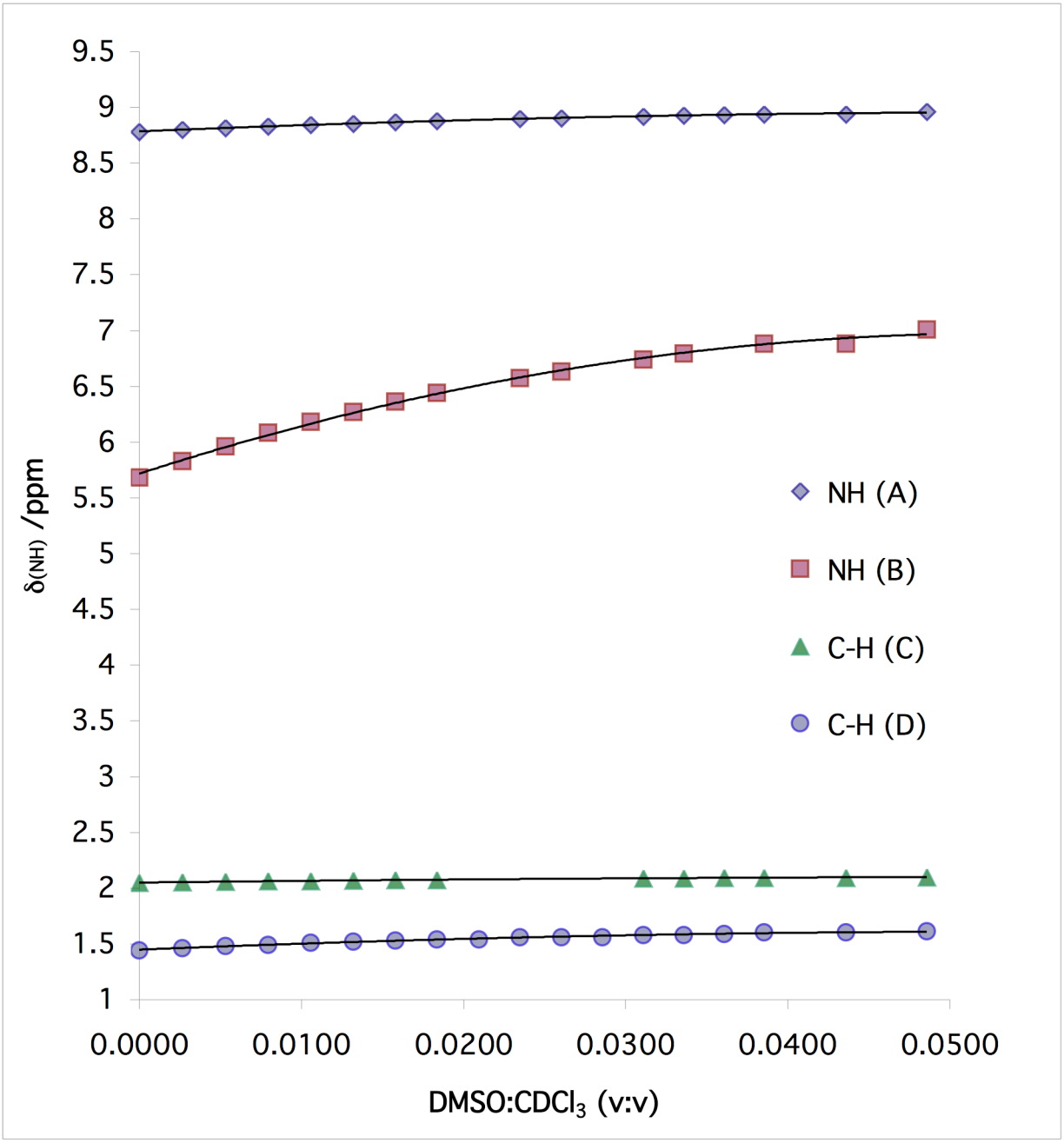
v/v (DMSO:$CDCl_3$)	$\delta_{(NH)}$ A / ppm	$\delta_{(NH)}$ B / ppm	δ $C^{\alpha}H^{C}$	δ $C^{\alpha}H^{D}$
0.0000	8.711	5.7	2.034	1.77
0.0027	8.736	5.85	2.04	1.77
0.0053	8.753	5.98	2.044	1.77
0.0080	8.769	6.09	2.048	
0.0106	8.787	6.21	2.052	1.76
0.0132	8.8	6.3	2.056	1.76
0.0158	8.816	6.4	2.059	1.76
0.0184				1.76
0.0209	8.839	6.55		1.75
0.0235				1.75
0.0260	8.856	6.67	2.071	1.75
0.0286	8.866	6.73	2.074	1.74
0.0311	8.873	6.77	2.076	1.74
0.0336	8.881		2.079	1.74
0.0361	8.888	6.88	2.08	1.74
0.0386	8.895	6.92	2.083	1.74
0.0410	8.901	6.95	2.085	1.74
0.0460	8.914	7.03	2.089	1.74
0.0510	8.924	7.09	2.092	1.73


10
9
8
7
6
5
4
3
2
1
0
δ(NH)
0.0000
0.0200
0.0400
DMSO:CDCl3 (v:v)
NH (A)
NH (B)
C-H (C)
C-H (D)

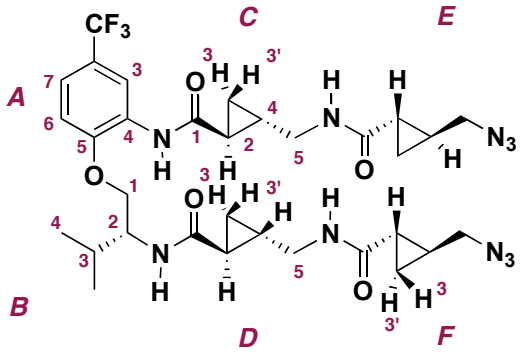
DMSO titration Data for 13



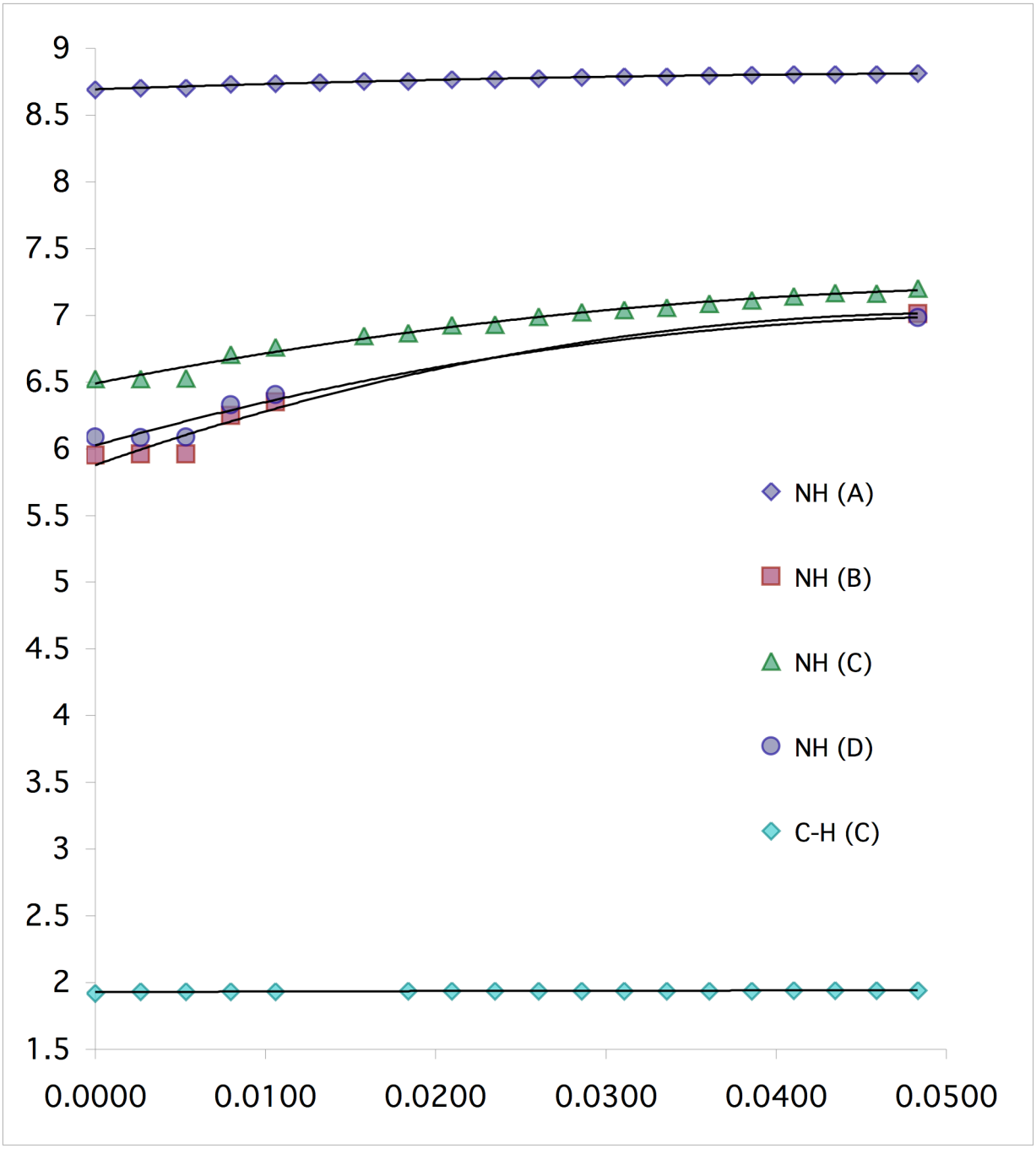
v/v (DMSO:$CDCl_3$)	$\delta_{(NH)}$ A / ppm	$\delta_{(NH)}$ B / ppm	δ $C^{\alpha}H^{C}$	δ $C^{\alpha}H^{D}$
0.0000	8.779	5.68	2.048	1.44
0.0027	8.799	5.83	2.052	1.46
0.0053	8.815	5.96	2.057	1.48
0.0080	8.831	6.08	2.061	1.49
0.0106	8.844	6.18	2.064	1.51
0.0132	8.856	6.27	2.068	1.52
0.0158	8.867	6.36	2.071	1.53
0.0184	8.878	6.44	2.074	1.54
0.0209				1.54
0.0235	8.896	6.57		1.56
0.0260	8.904	6.63		1.56
0.0286				1.56
0.0311	8.919	6.74	2.086	1.58
0.0336	8.926	6.79	2.089	1.58
0.0361	8.933		2.091	1.59
0.0386	8.939	6.88	2.093	1.6
0.0436	8.938	6.88	2.093	1.6
0.0486	8.959	7.01	2.099	1.61


9.5
9
8.5
8
7.5
7
6.5
6
5.5
5
4.5
4
3.5
3
2.5
2
1.5
1
δ(NH) /ppm
0.0000
0.0100
0.0200
0.0300
0.0400
0.0500
DMSO:CDCl3 (v:v)
NH (A)
NH (B)
C-H (C)
C-H (D)

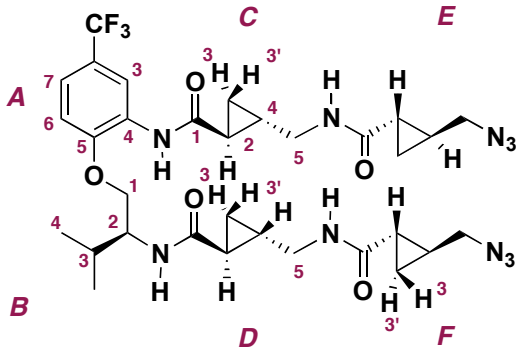
DMSO titration data for 14



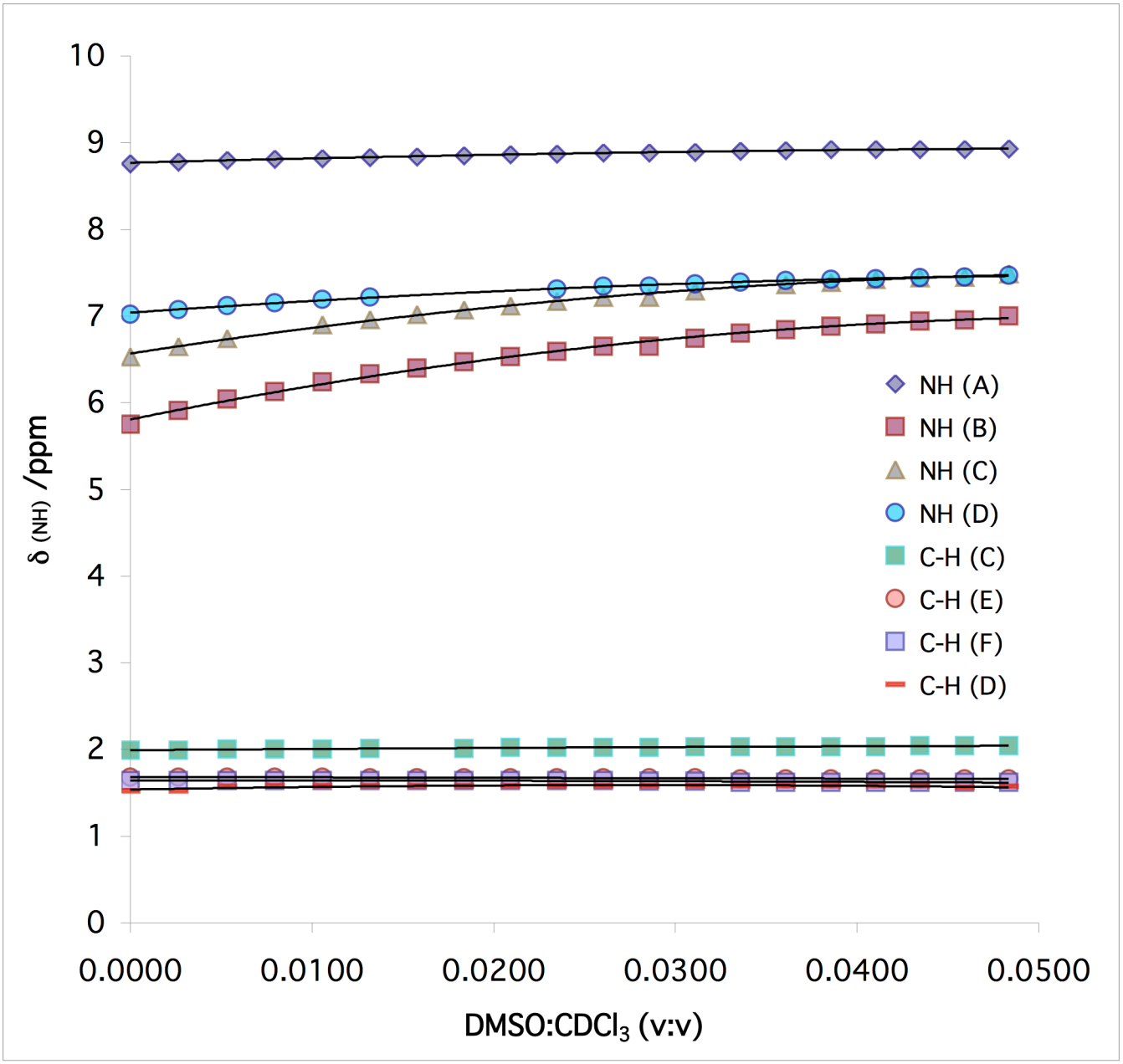
v/v (DMSO:$CDCl_3$)	$\delta_{(NH)}$ A / ppm	$\delta_{(NH)}$ B / ppm	$\delta_{(NH)}$ C / ppm	$\delta_{(NH)}$ D / ppm	δ $C^{\alpha}H^{C}$
0.0000	8.691	5.95	6.523	6.087	1.919
0.0027	8.702	5.96	6.523	6.084	1.932
0.0053	8.702	5.96	6.527	6.087	1.932
0.0080	8.731	6.25	6.705	6.329	1.933
0.0106	8.739	6.35	6.763	6.406	1.934
0.0132	8.746				
0.0158	8.754		6.848		
0.0184	8.756		6.867		1.935
0.0209	8.766		6.928		1.935
0.0235	8.767		6.93		1.935
0.0260	8.777		6.99		1.936
0.0286	8.782		7.025		1.937
0.0311	8.787		7.04		1.937
0.0336	8.79		7.06		1.937
0.0361	8.795		7.09		1.938
0.0386	8.799		7.113		1.938
0.0410	8.803		7.144		1.939
0.0435	8.806		7.168		1.94
0.0459	8.807		7.166		1.94
0.0483	8.814	7.01	7.204	6.981	1.941


9
8.5
8
7.5
7
6.5
6
5.5
5
4.5
4
3.5
3
2.5
2
1.5
0.0000
0.0100
0.0200
0.0300
0.0400
0.0500
NH (A)
NH (B)
NH (C)
NH (D)
C-H (C)

DMSO Titration data for 15



v/v (DMSO:$CDCl_3$)	$\delta_{(NH)}$ A / ppm	$\delta_{(NH)}$ B / ppm	$\delta_{(NH)}$ C / ppm	$\delta_{(NH)}$ D / ppm	δ $C^{\alpha}H^{C}$	δ $C^{\alpha}H^{E}$	δ $C^{\alpha}H^{F}$	δ $C^{\alpha}H^{D}$
0.0000	8.76	5.75	6.53	7.02	1.99	1.68	1.64	1.52
0.0027	8.78	5.91	6.65	7.07	1.99	1.68	1.64	1.52
0.0053	8.8	6.04	6.74	7.12	2	1.68	1.64	1.57
0.0080	8.81	6.13		7.15	2	1.68	1.64	1.58
0.0106	8.82	6.24	6.9	7.19	2	1.68	1.64	1.58
0.0132	8.83	6.33	6.96	7.22	2.01	1.67	1.64	1.58
0.0158	8.84	6.4	7.02			1.67	1.64	1.58
0.0184	8.85	6.47	7.07		2.01	1.67	1.64	1.58
0.0209	8.86	6.53	7.12		2.02	1.67	1.64	1.58
0.0235	8.87	6.59	7.17	7.31	2.02	1.67	1.64	1.58
0.0260	8.88	6.65	7.22	7.34	2.02	1.67	1.64	1.58
0.0286	8.88	6.65	7.22	7.34	2.02	1.67	1.63	1.58
0.0311	8.89	6.74	7.29	7.37	2.03	1.67	1.63	1.58
0.0336	8.9	6.8		7.39	2.03	1.66	1.62	1.58
0.0361	8.91	6.84	7.36	7.41	2.03	1.66	1.62	1.58
0.0386	8.92	6.88	7.39	7.42	2.03	1.66	1.62	1.58
0.0410	8.92	6.91	7.42	7.43	2.03	1.66	1.62	1.58
0.0435	8.92	6.94	7.44	7.44	2.04	1.66	1.62	1.58
0.0459	8.92	6.95	7.45	7.45	2.04	1.66	1.62	1.56
0.0483	8.93	7	7.49	7.47	2.04	1.66	1.62	1.57


10
9
8
7
6
5
4
3
2
1
0
δ (NH) /ppm
0.0000
0.0100
0.0200
0.0300
0.0400
0.0500
DMSO:CDCl3 (v:v)
NH (A)
NH (B)
NH (C)
NH (D)
C-H (C)
C-H (E)
C-H (F)
C-H (D)

4. Temperature coefficients: (500 MHz, 1.5-2 mM in $CDCl_3$, referenced to TMS@0ppm).

Cmpd 12

Temp/K	*δ(NH)^A*	*δ(NH)^B*	*δ(C-2)^C*	*δ(C-2)^D*
290	8.736	5.72	2.047	1.777
295	8.72	5.7	2.039	1.774
300	8.705	5.69	2.032	1.769
305	8.689	5.68	2.024	1.765
310	8.673	5.67	2.017	1.761
315	8.656	5.66	2.009	1.757
Δδ(ppb/K^{-1})	**-3.2**	**-2.4**	**-1.52**	**-0.8**

Cmpd 13

Temp/K	*δ(NH)^A*	*δ(NH)^B*	*δ(C-2)^C*	*δ(C-2)^D*
290	8.811	5.71	2.06	1.451
295	8.796	5.69	2.054	1.448
300	8.779	5.68	2.048	1.446
305		5.67	2.041	1.444
310	8.745	5.67	2.035	1.442
315	8.727	5.66	2.028	1.44
Δδ(ppb/K^{-1})	**-3.36**	**-2**	**-1.28**	**-0.44**

Cmpd 14

Temp/K	*δ(NH)^A*	*δ(NH)^B*	*δ(NH)^C*	*δ(NH)^D*	*δ(C-2)^C*
290	8.726	5.98	6.565	6.113	1.934
295	8.712	5.96	6.534	6.089	1.933
300	8.699	5.94	6.508	6.067	1.933
305		5.92	6.484	6.048	1.932
310	8.672	5.91	6.46	6.028	1.932
315	8.657	5.89	6.43	6.004	1.931
Δδ(ppb/K^{-1})	**-2.76**	**-3.6**	**-5.4**	**-4.36**	**-0.12**

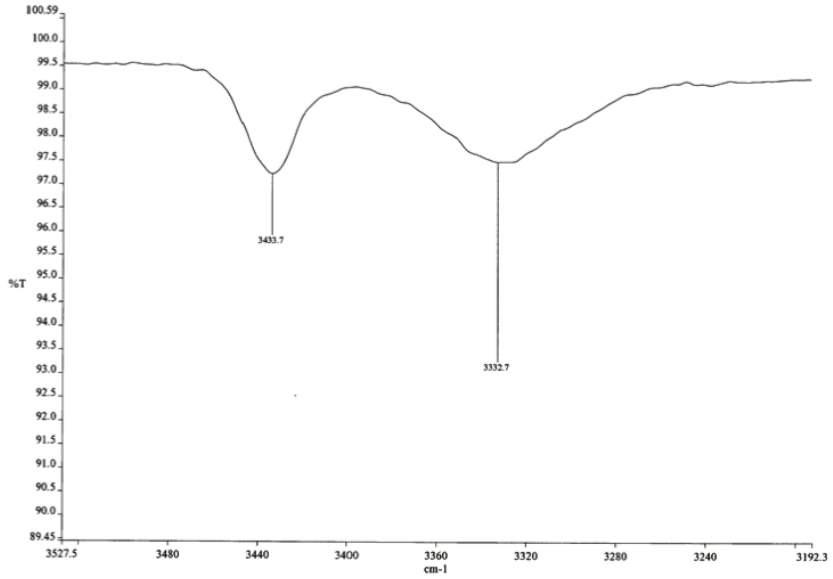
Cmpd 15

Temp/K	*δ(NH)^A*	*δ(NH)^B*	*δ(NH)^C*	*δ(NH)^D*	*δ(C-2)^C*	*δ(C-2)^E*
290	8.795	5.86	6.57	7.099	2.001	1.68
295	8.775	5.83	6.55	7.05	1.993	1.68
300	8.756	5.79	6.53	6.998	1.985	1.68
305	8.736	5.77	6.51	6.948	1.978	1.68
310		5.74	6.48	6.9	1.97	1.68
315	8.699	5.72	6.46	6.852	1.963	1.68
Δδ(ppb/K^{-1})	**-3.84**	**-5.6**	**-4.4**	**-9.88**	**-1.52**	**0**

5. Solution Infrared studies of 6 and 7

A 1.0 mM solution of compound in CH_2Cl_2 (dried over CaH_2 under N_2) was prepared. Baseline corrections were applied to obtain the spectra reproduced in figures **1 & 2**. IR measurements were carried out at 25˚C on a Perkin-Elmer Spectrum One FT-IR spectrometer equipped with a Specac demountable omni-cell GS01800 fitted with NaCl windows and having a pathlength of 1.0 mm. Solvent subtraction was carried out by using a reference spectrum of CH_2Cl_2 obtained at room temperature. Spectra of 60 scans (6 sec per scan) were obtained with 2-cm^{-1} resolution.

Sharp bands at 3430-3440 cm^{-1} are assigned to non-hydrogen-bonded N-H (H_B) and the broad bands at 3330-3340 cm^{-1} are assigned to internally hydrogen-bonded N-H (H_A).



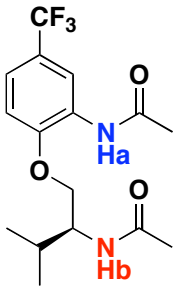
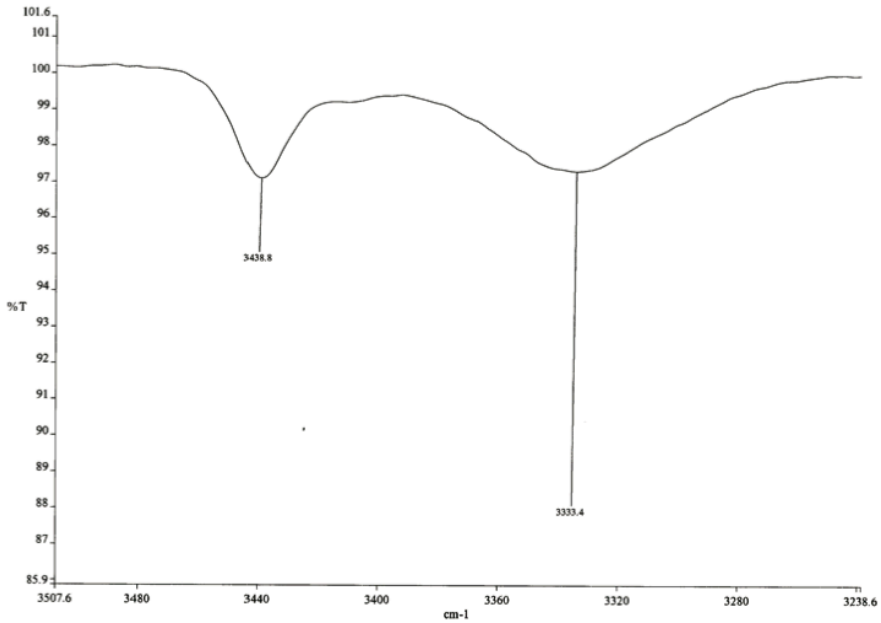


Figure **1**: N-H stretch region of FT-IR spectrum for 1 mM solution of **6** in CH_2Cl_2.



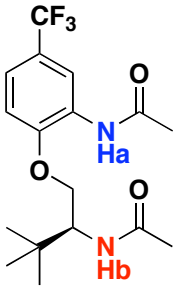
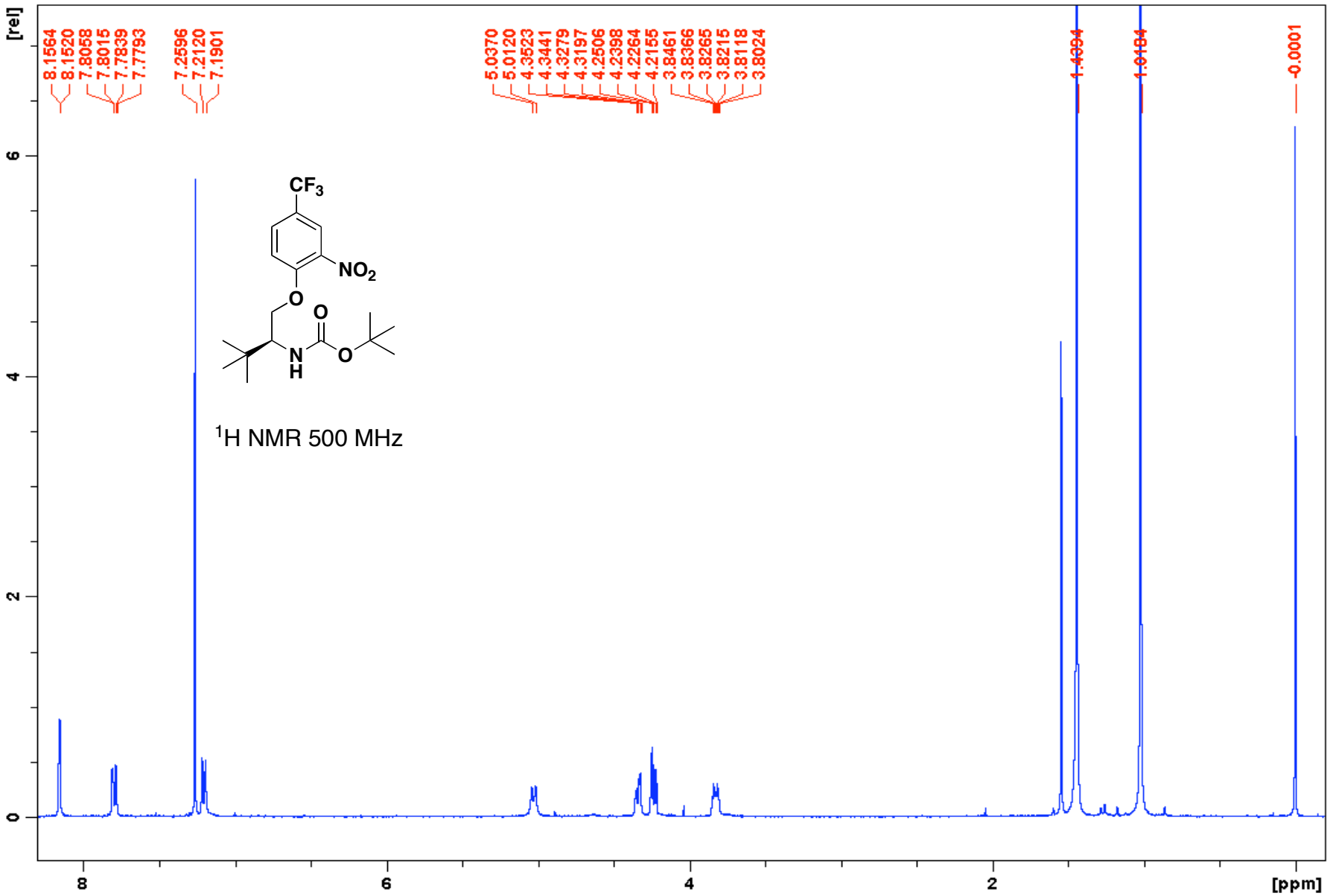
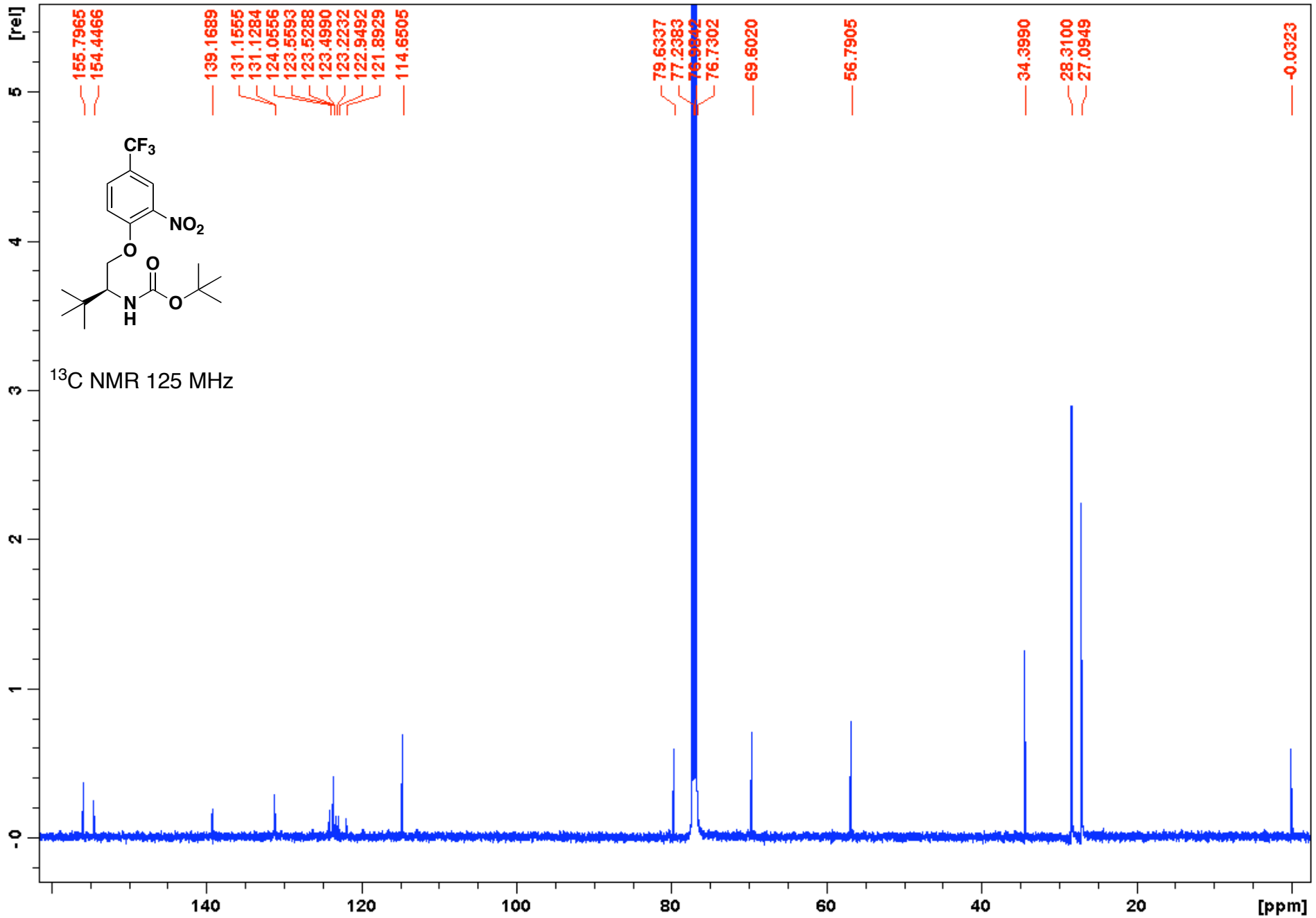


Figure **2**: N-H stretch region of FT-IR spectrum for 1 mM solution of **7** in CH_2Cl_2.

6. ^{1}H and ^{13}C NMR spectra for all compounds.

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154.4466
139.1689
131.1555
131.1284
124.0556
123.5593
123.5288
123.4990
123.2232
122.9492
121.8929
114.6505
79.6337
77.2383
76.7302
69.6020
56.7905
34.3990
28.3100
27.0949
-0.0323
[rel]
5
4
3
2
1
-0
140
120
100
80
60
40
20
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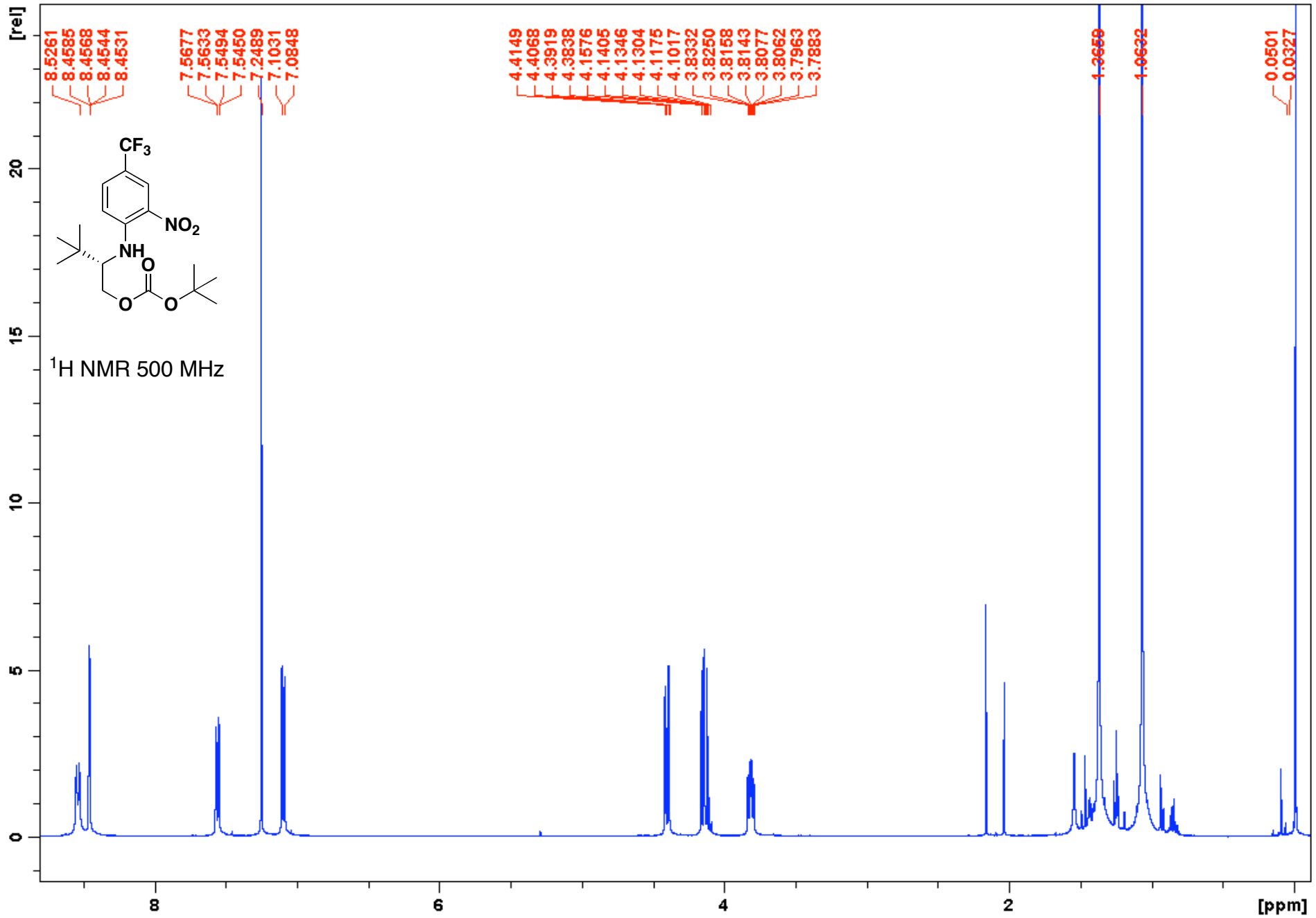
CF3
NO2
O
O
N
H
O
13C NMR 125 MHz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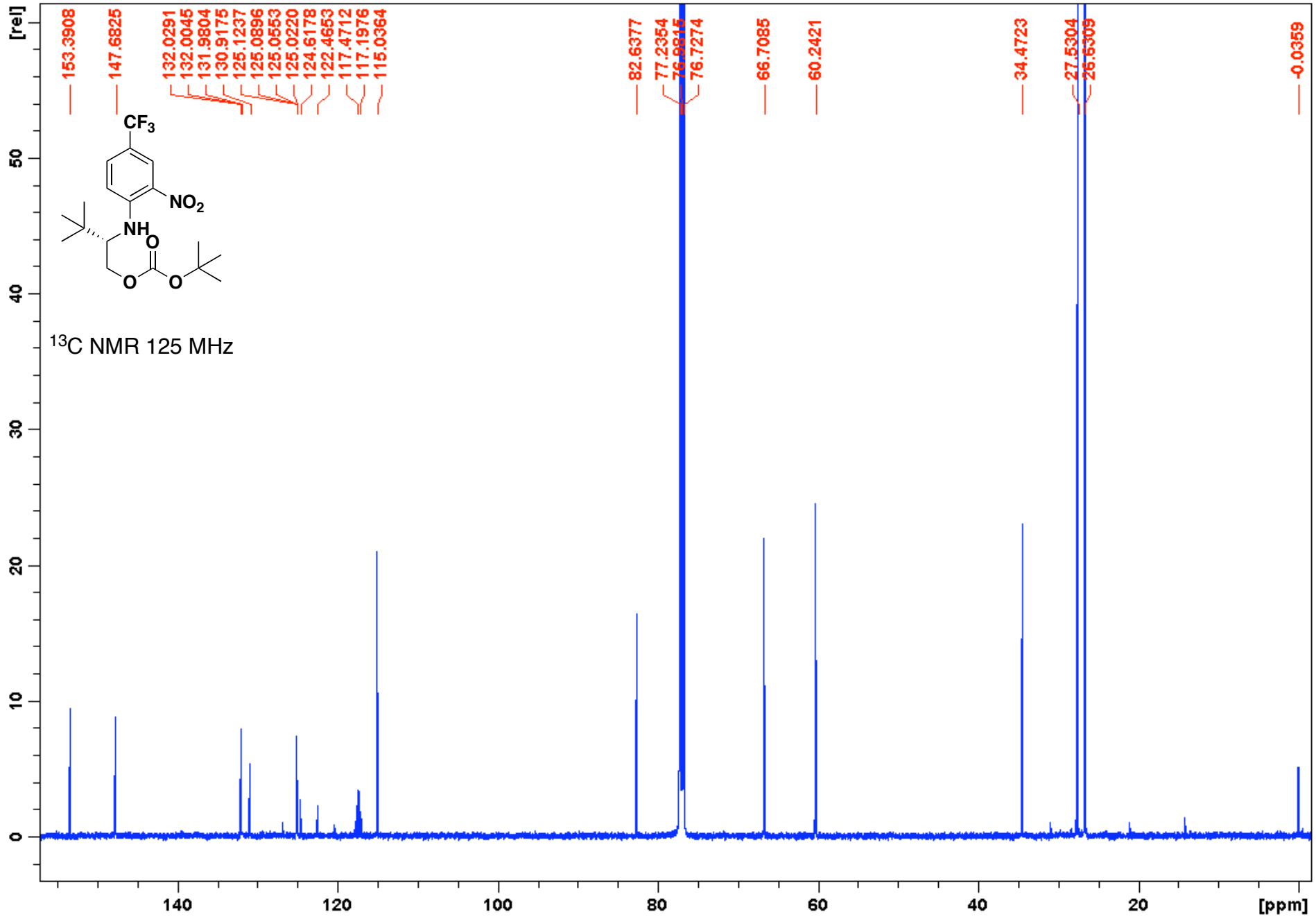
8.4585
8.4568
8.4544
8.4531
7.5677
7.5633
7.5494
7.5450
7.2489
7.1031
7.0848
4.4149
4.4068
4.3919
4.3838
4.1576
4.1405
4.1346
4.1304
4.1175
4.1017
3.8332
3.8250
3.8158
3.8143
3.8077
3.8062
3.7963
3.7883
1.3659
1.0632
0.0501
0.0327
CF3
NO2
NH
O
O
O
1H NMR 500 MHz
0
5
10
15
20
8
6
4
2
[ppm]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131.9804
130.9175
125.1237
125.0896
125.0553
125.0220
124.6178
122.4653
117.4712
117.1976
115.0364
82.6377
77.2354
76.9815
76.7274
66.7085
60.2421
34.4723
27.5304
26.5309
-0.0359
CF3
NO2
NH
O
O
O
13C NMR 125 MHz
[rel]
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20
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60
40
20
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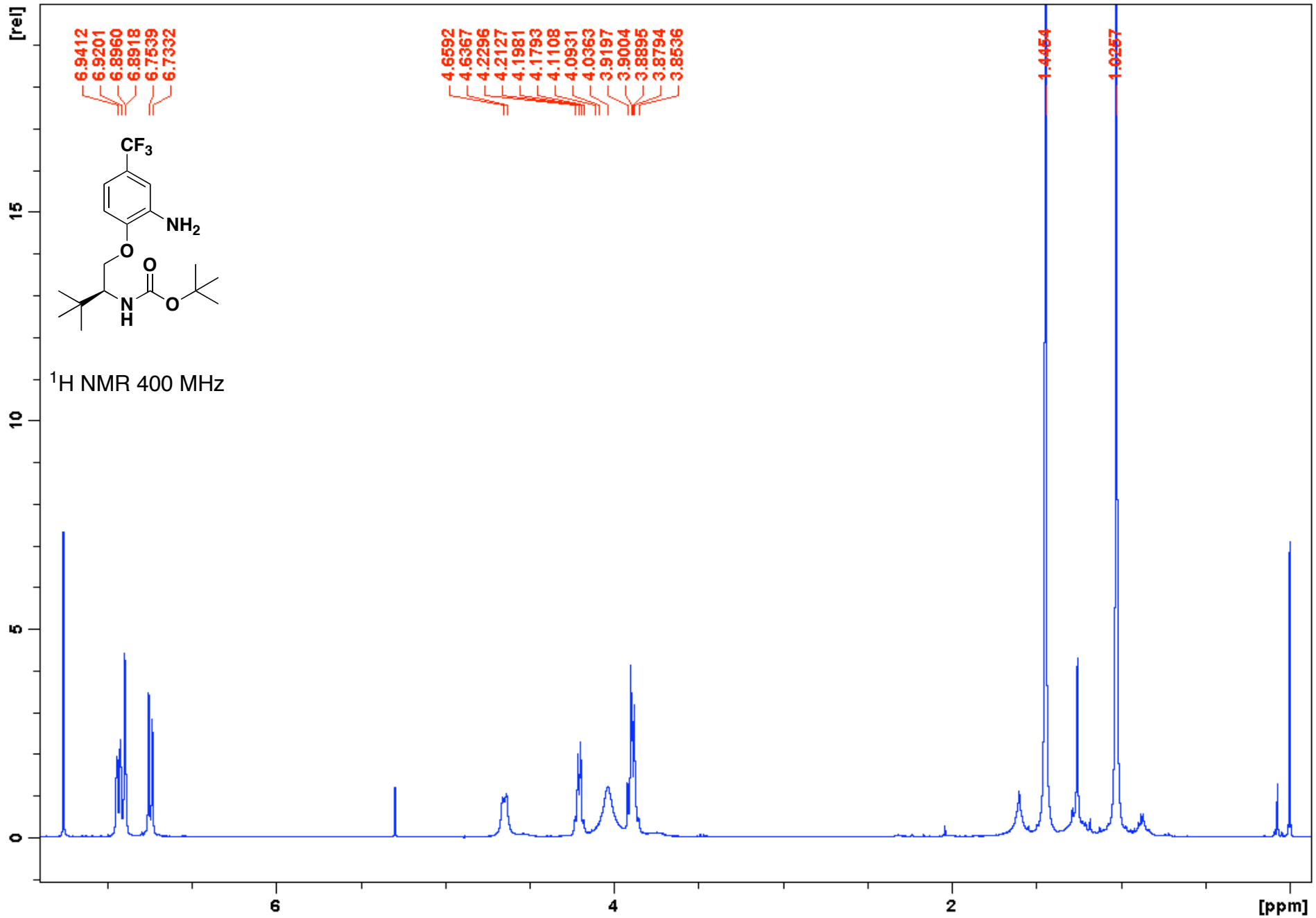
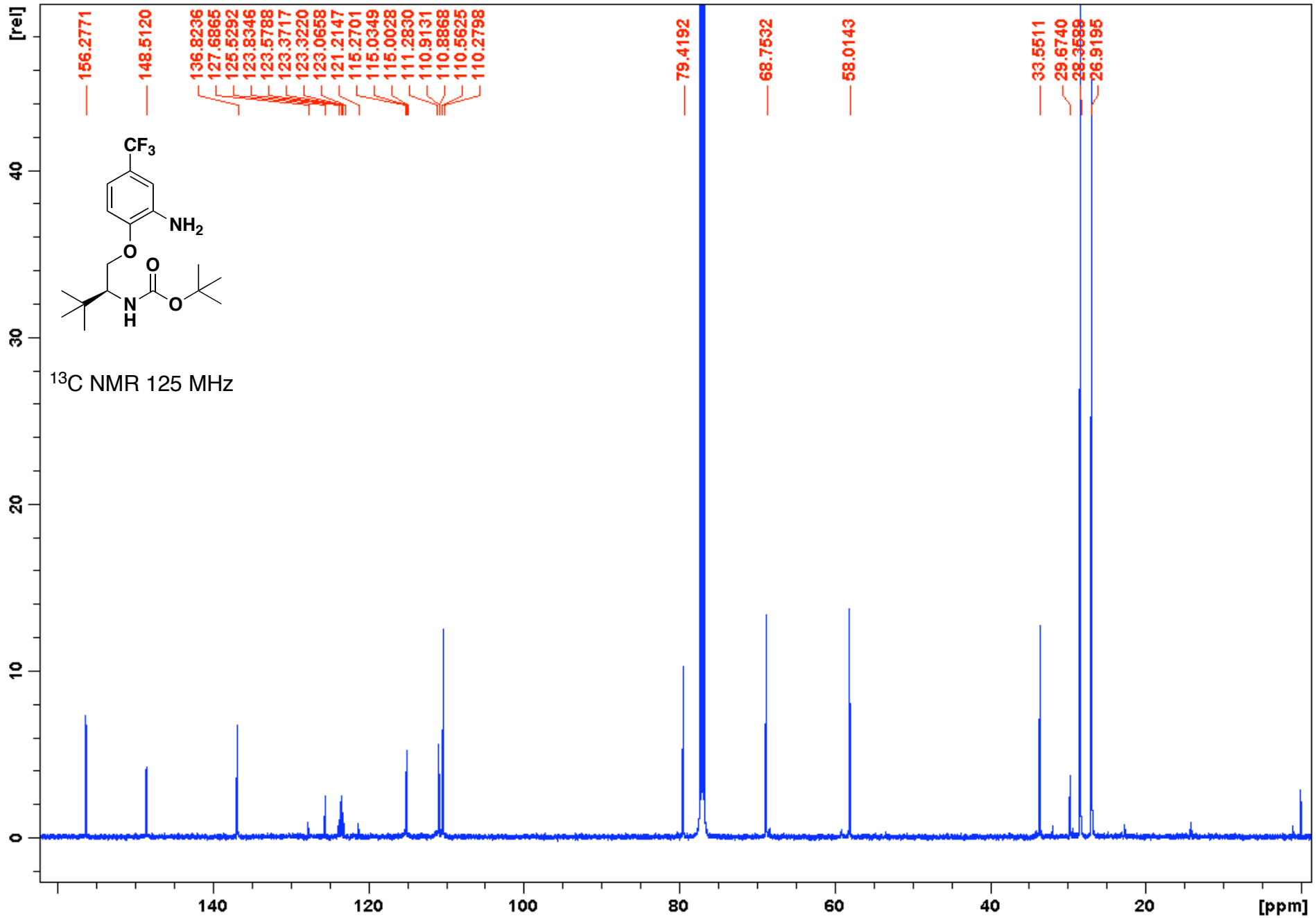


^{1}H NMR 400 MHz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121.2147
115.2701
115.0349
115.0028
111.2830
110.9131
110.8868
110.5625
110.2798
79.4192
68.7532
58.0143
33.5511
29.6740
28.3689
26.9195
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0
10
20
30
40
140
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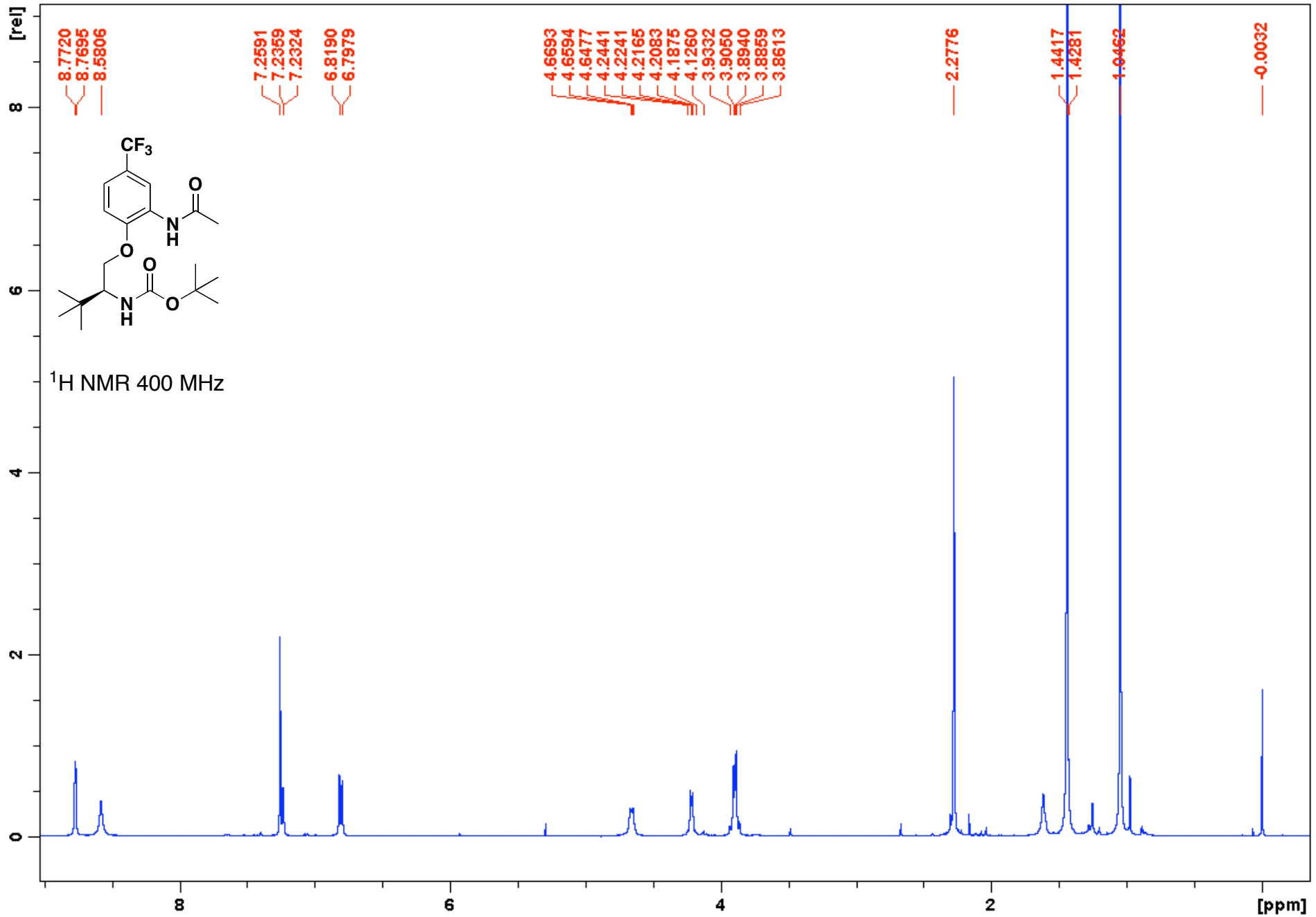
100
80
60
40
20
[ppm]
CF3
NH2
O
O
N
H
O
13C NMR 125 MHz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8.5806
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7.2359
7.2324
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6.7979
4.6693
4.6594
4.6477
4.2441
4.2241
4.2165
4.2083
4.1875
4.1260
3.9332
3.9050
3.8940
3.8859
3.8613
2.2776
1.4417
1.4281
1.0462
-0.0032
CF3
O
N
H
O
O
N
H
O
1H NMR 400 MHz
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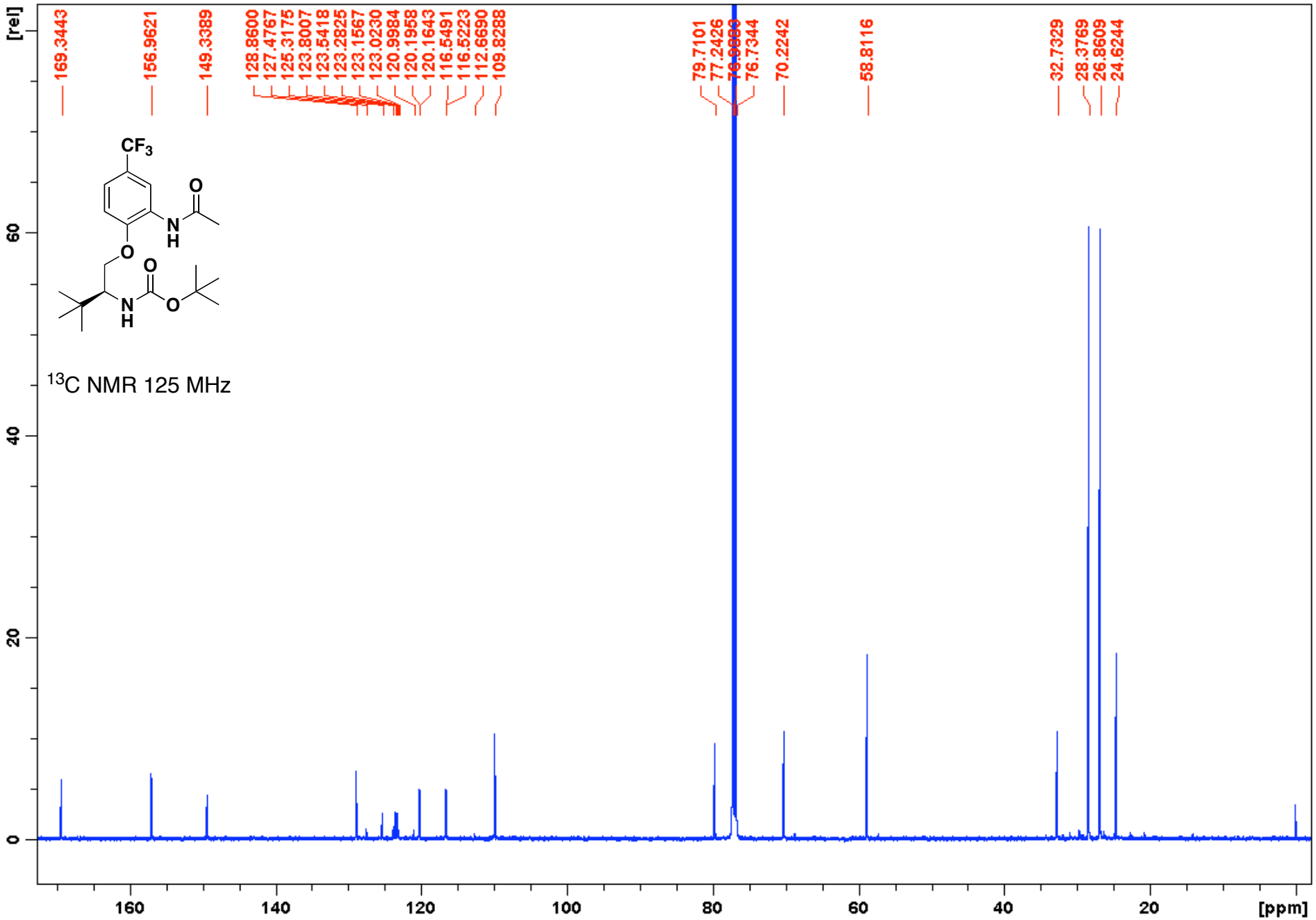
4
6
8
8
6
4
2
[ppm]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123.0230
120.9984
120.1958
120.1643
116.5491
116.5223
112.6690
109.8288
79.7101
77.2426
76.7344
70.2242
58.8116
32.7329
28.3769
26.8609
24.6244
CF3
O
N
H
O
O
N
H
O
13C NMR 125 MHz
0
20
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60
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140
120
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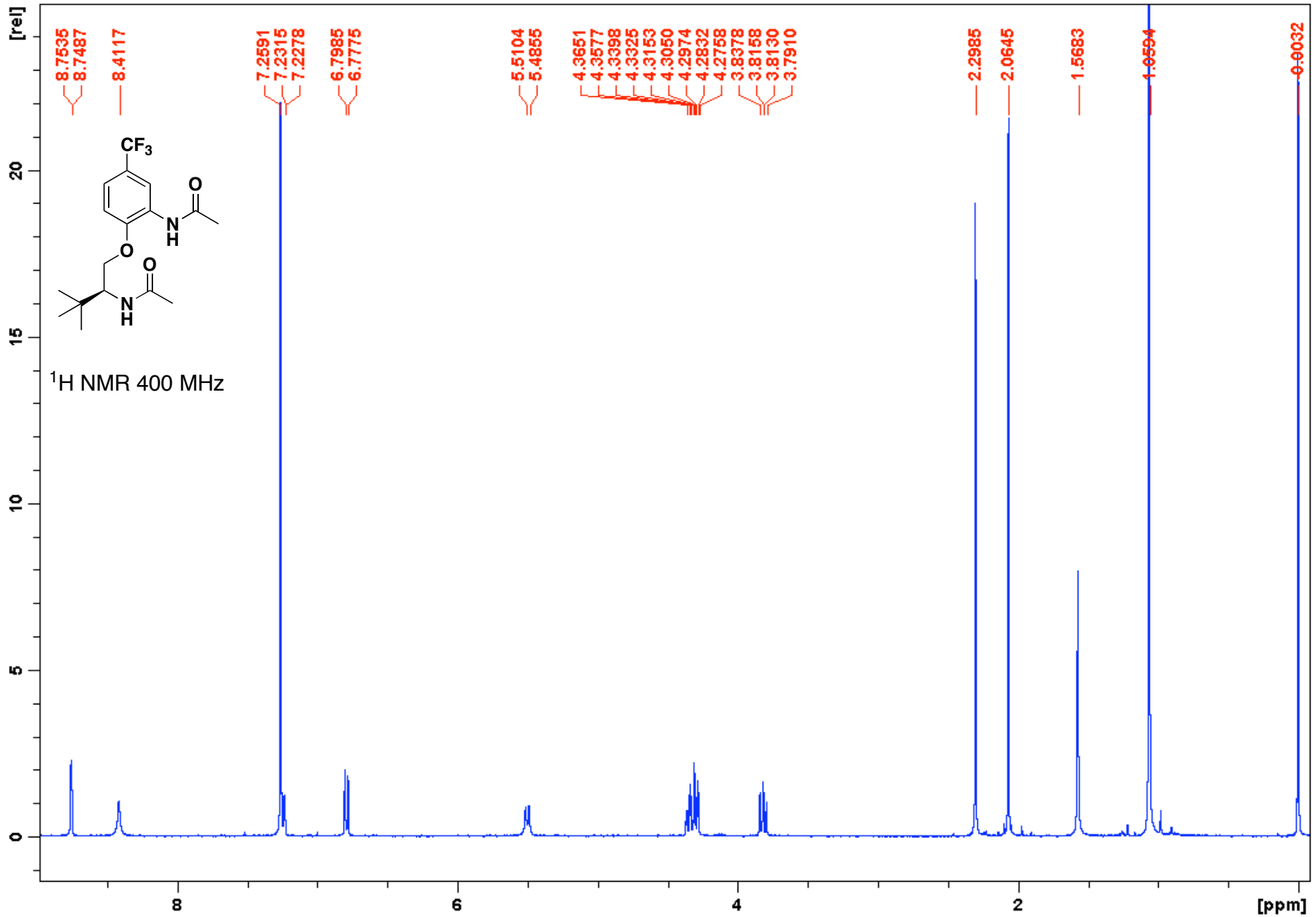
60
40
20
[ppm]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7.2315
7.2278
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6.7775
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5.4855
4.3651
4.3577
4.3398
4.3325
4.3153
4.3050
4.2974
4.2832
4.2758
3.8378
3.8158
3.8130
3.7910
2.2985
2.0645
1.5683
1.0594
0.0032
CF3
O
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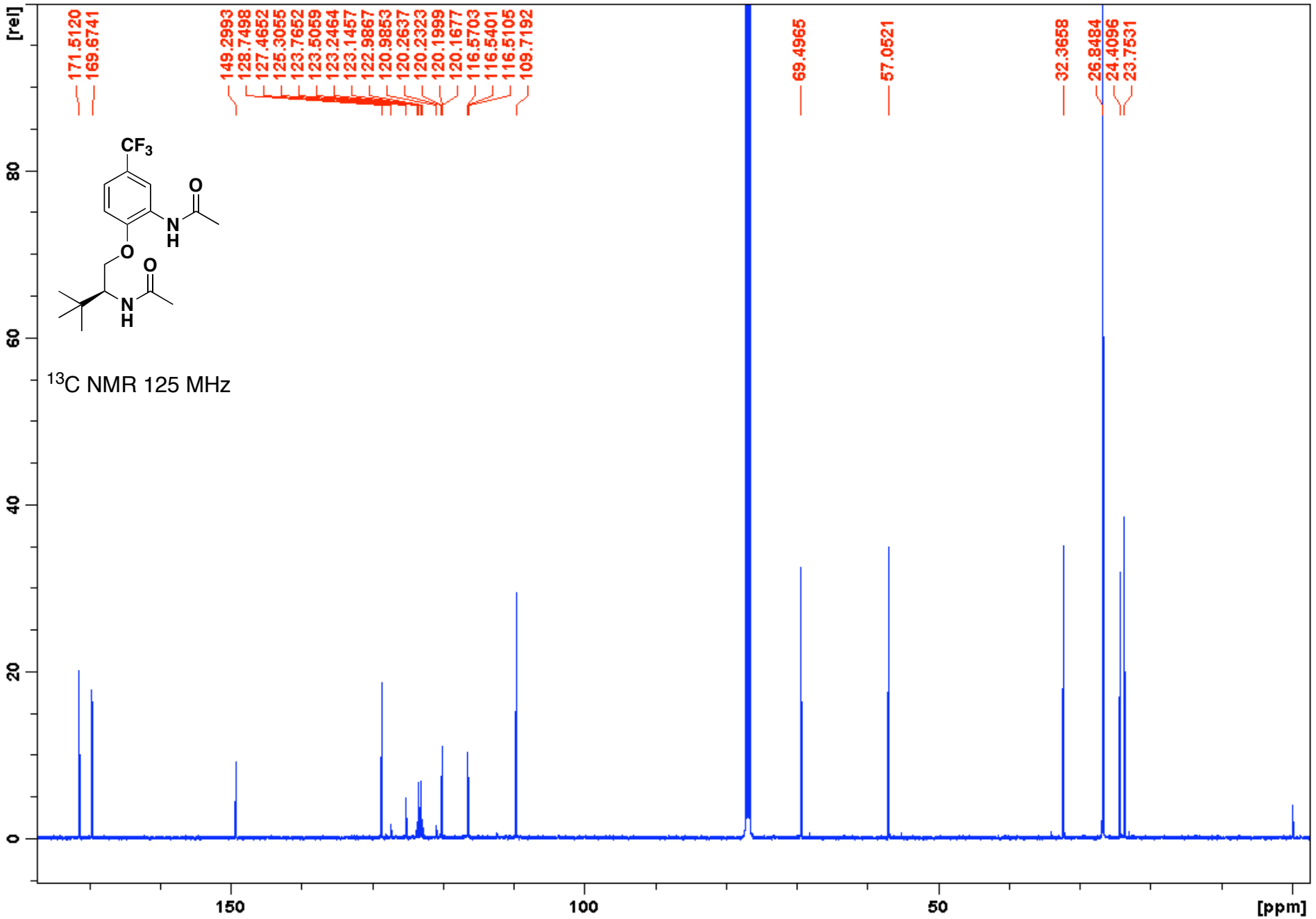
H
O
O
N
H
1H NMR 400 MHz
0
5
10
15
20
8
6
4
2
[ppm]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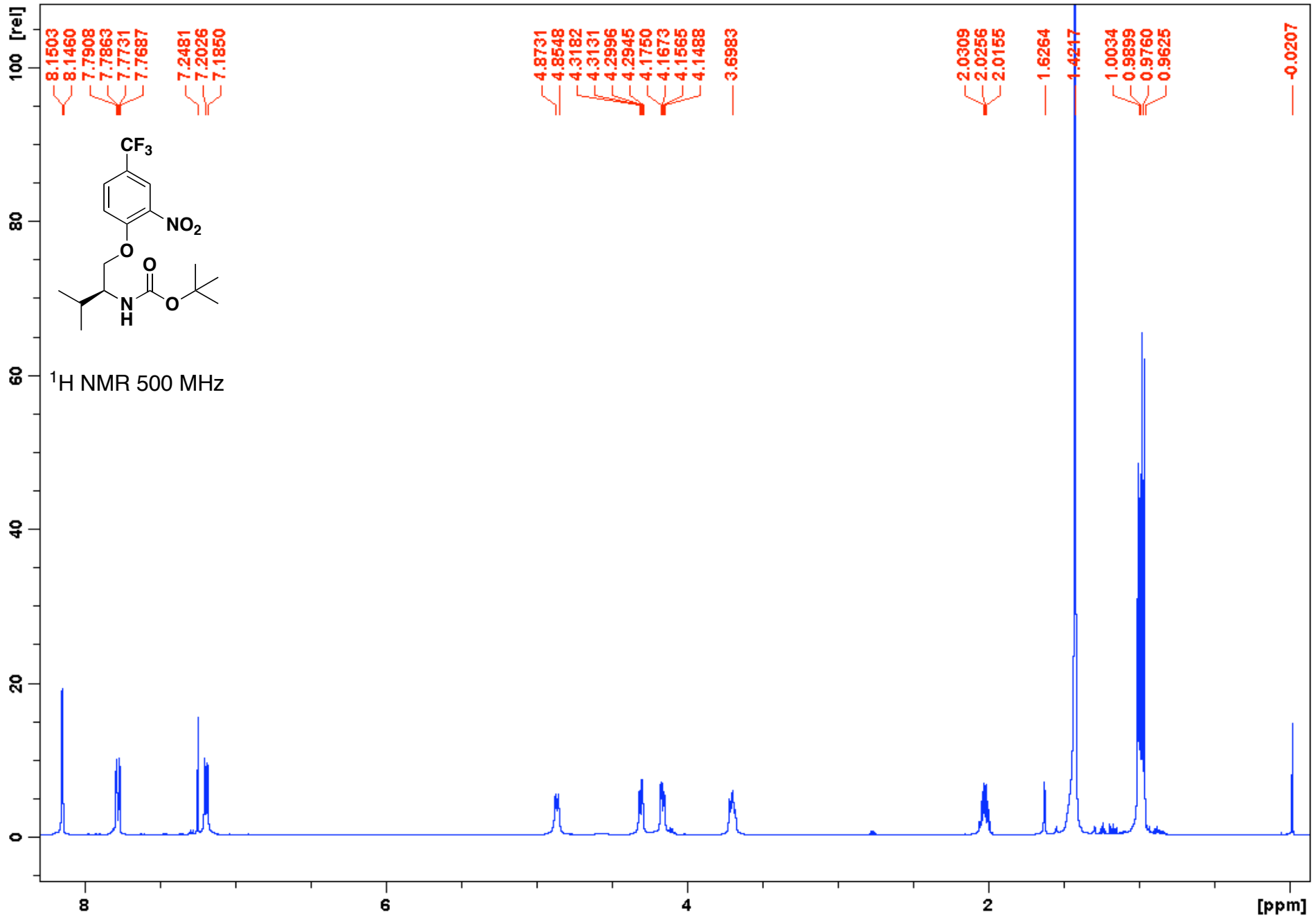
123.1457
122.9867
120.9853
120.2637
120.2323
120.1999
120.1677
116.5703
116.5401
116.5105
109.7192
69.4965
57.0521
32.3658
26.8484
24.4096
23.7531
CF3
O
N
H
O
O
N
H
13C NMR 125 MHz
0
20
40
60
80
150
100
50
[ppm]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40
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7.2026
7.1850
4.8731
4.8548
4.3182
4.3131
4.2996
4.2945
4.1750
4.1673
4.1565
4.1488
3.6983
2.0309
2.0256
2.0155
1.6264
1.4217
1.0034
0.9899
0.9760
0.9625
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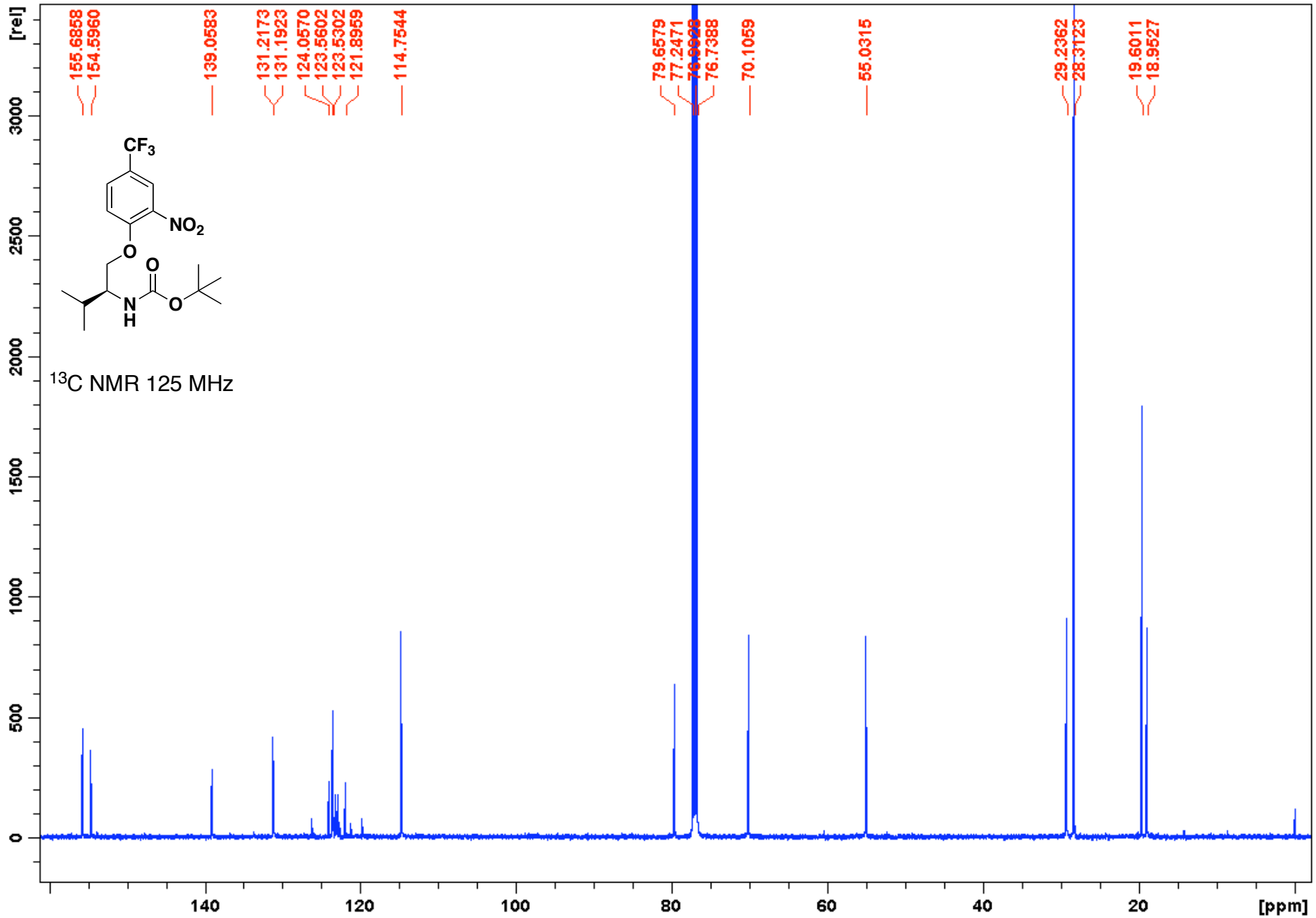
CF3
NO2
O
O
N
H
O
1H NMR 500 MHz
8
6
4
2
[ppm]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131.1923
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121.8959
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77.2471
76.7388
70.1059
55.0315
29.2362
28.3123
19.6011
18.9527
[rel]
3000
2500
2000
1500
1000
500
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140
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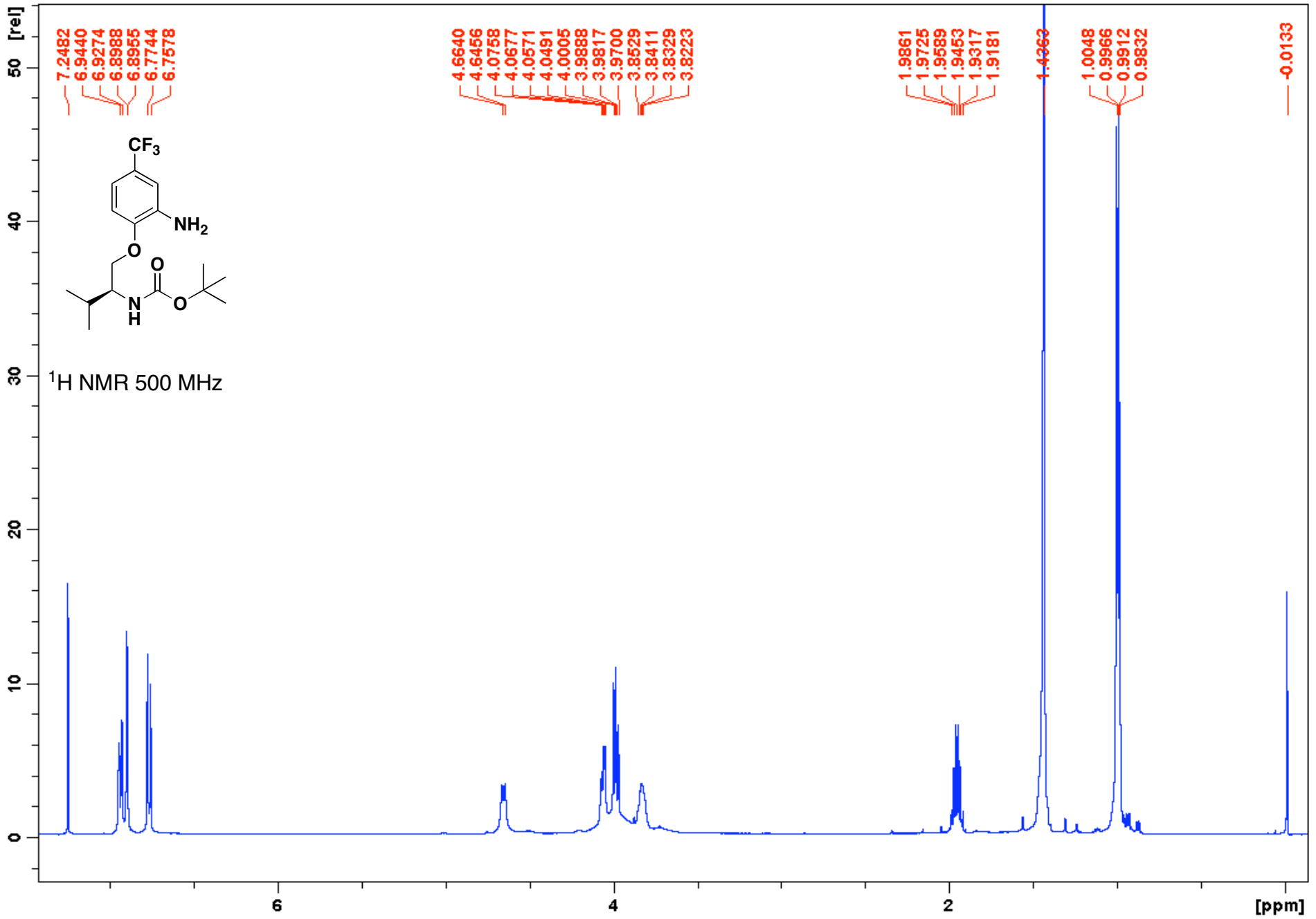
100
80
60
40
20
[ppm]
CF3
NO2
O
O
N
H
O
13C NMR 125 MHz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6.8955
6.7744
6.7578
4.6640
4.6456
4.0758
4.0677
4.0571
4.0491
4.0005
3.9888
3.9817
3.9700
3.8529
3.8411
3.8329
3.8223
1.9861
1.9725
1.9589
1.9453
1.9317
1.9181
1.4363
1.0048
0.9966
0.9912
0.9832
-0.0133
CF3
NH2
O
O
O
N
H
1H NMR 500 MHz
50 [rel]
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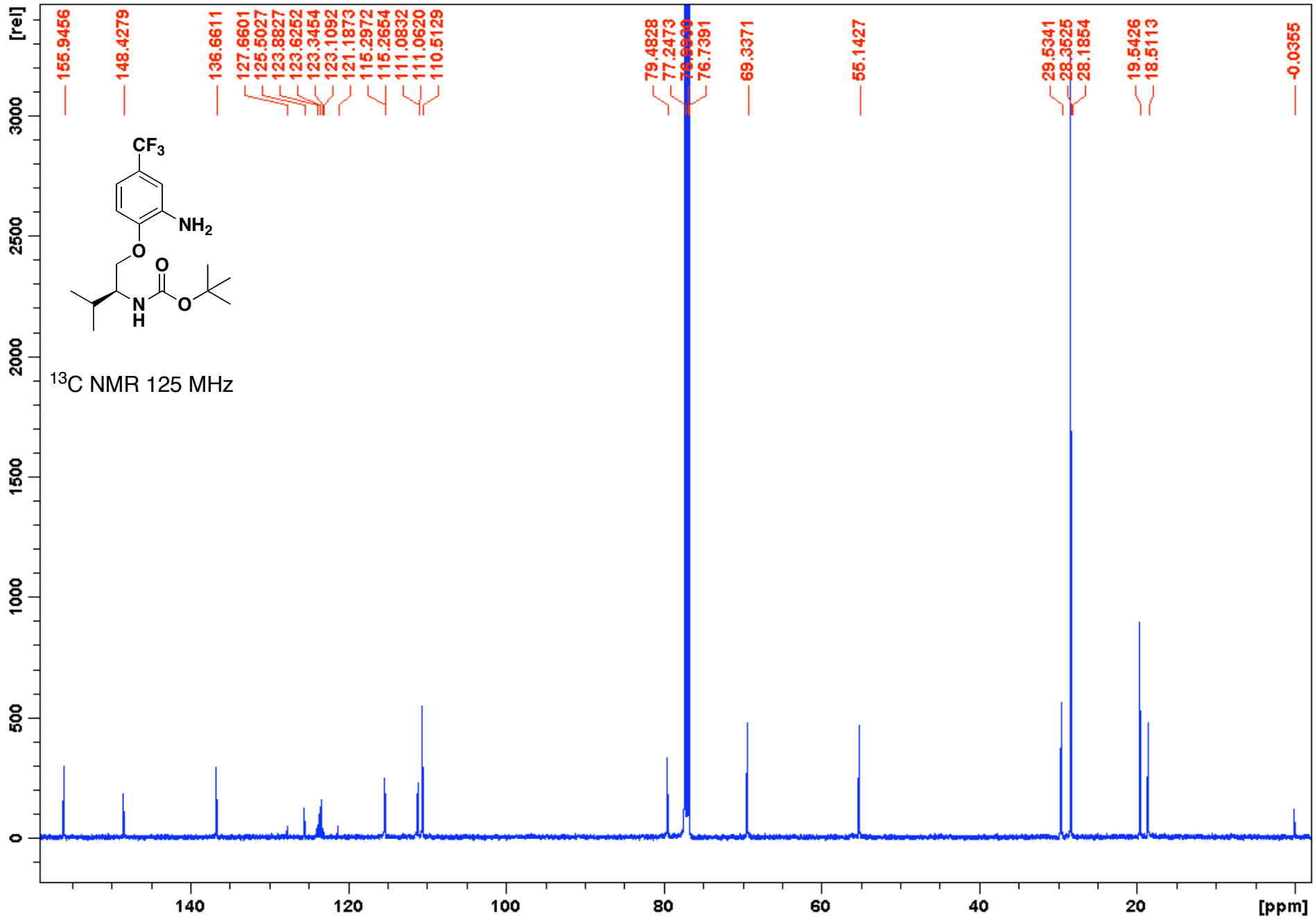
30
20
10
0
6
4
2
[ppm]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125.5027
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123.1092
121.1873
115.2972
115.2654
111.0832
111.0620
110.5129
79.4828
77.2473
76.7391
69.3371
55.1427
29.5341
28.3525
28.1854
19.5426
18.5113
-0.0355
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3000
2500
2000
1500
1000
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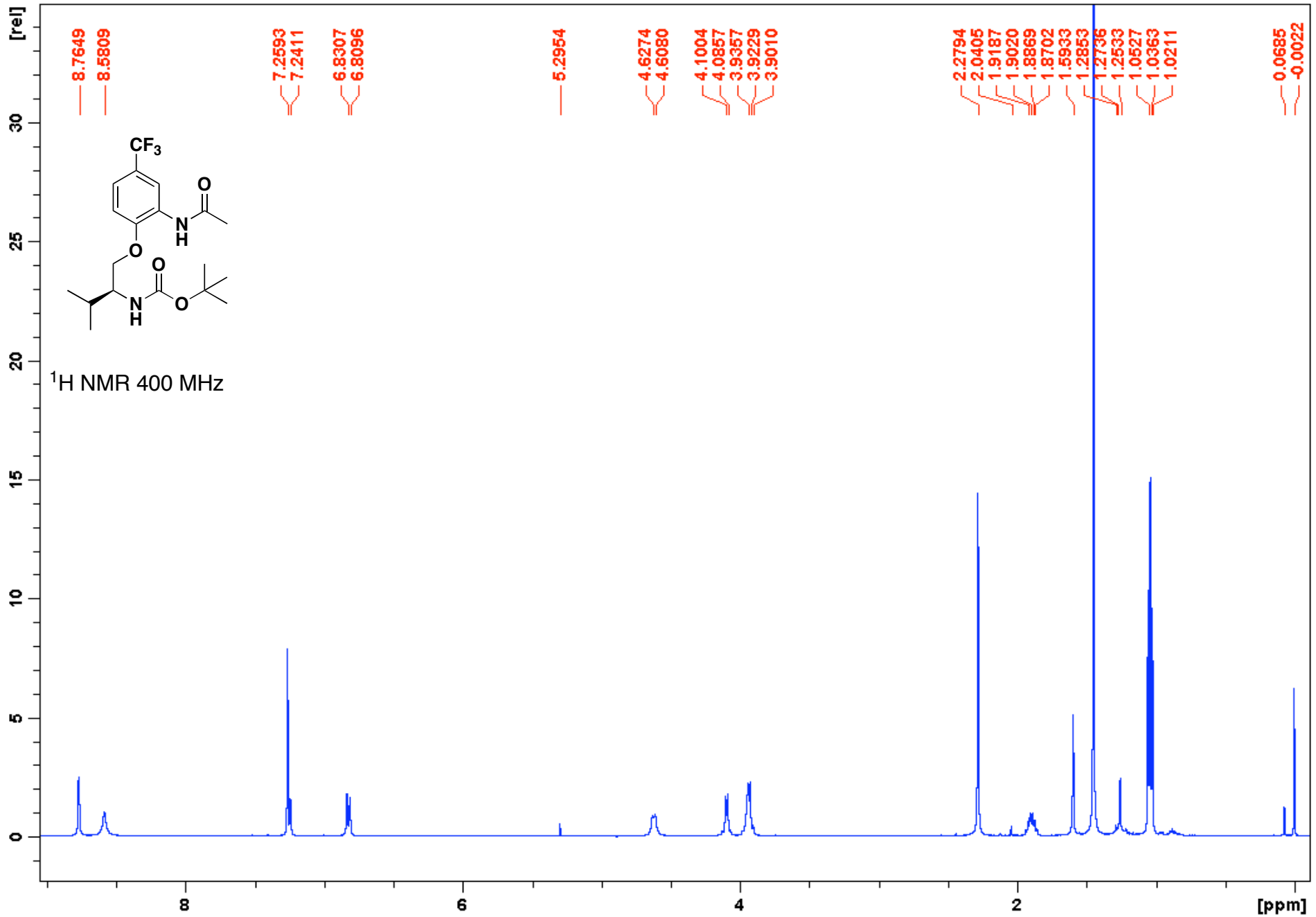
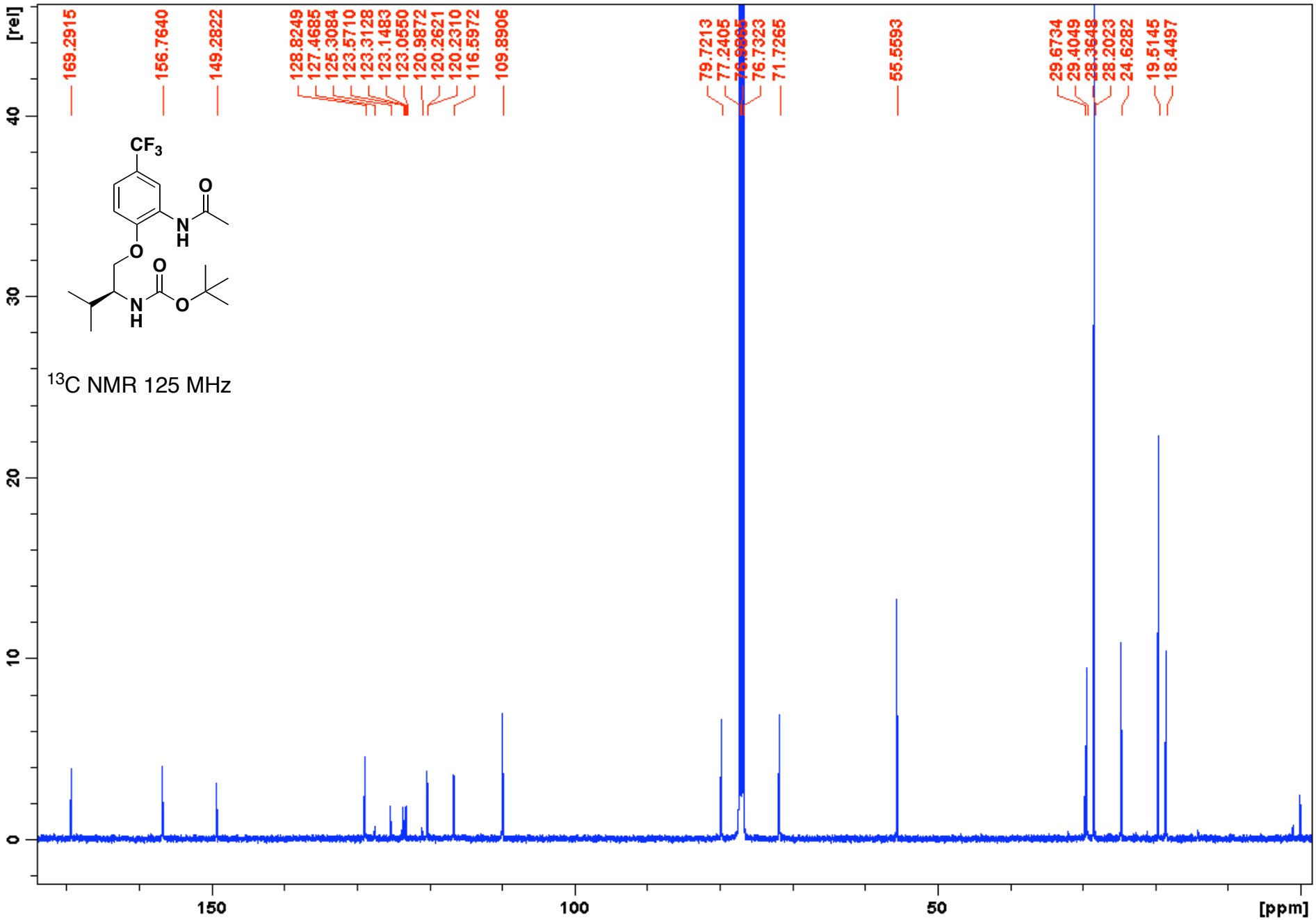
80
60
40
20
[ppm]
CF3
NH2
O
O
N
H
O
13C NMR 125 MHz



^{1}H NMR 400 MHz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120.2621
120.2310
116.5972
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79.7213
77.2405
76.7323
71.7265
55.5593
29.6734
29.4049
28.3648
28.2023
24.6282
19.5145
18.4497
CF3
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N
H
O
O
N
H
O
13C NMR 125 MHz
0
10
20
30
40
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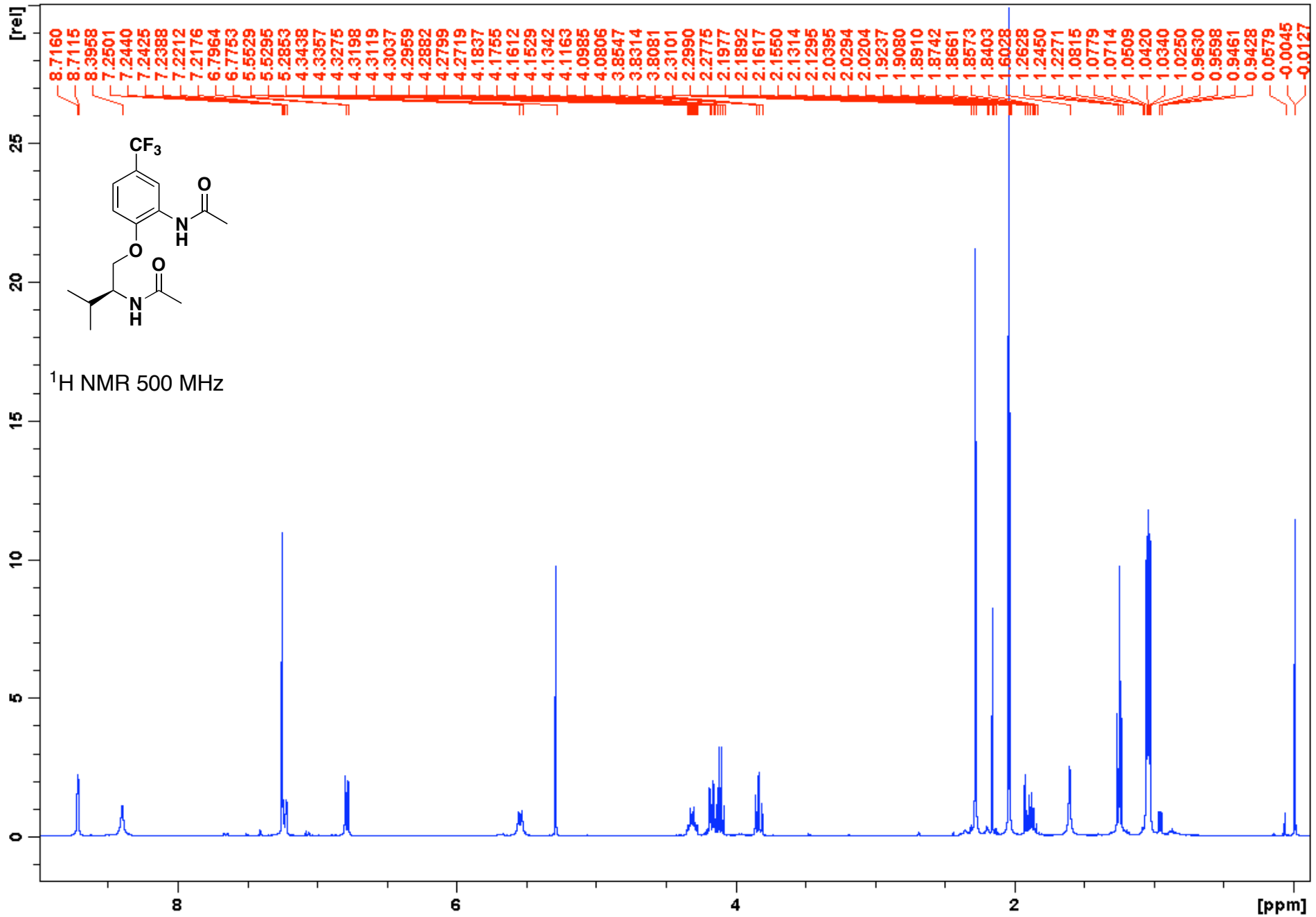
100
50
[ppm]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7.2176
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5.5529
5.5295
5.2853
4.3438
4.3357
4.3275
4.3198
4.3119
4.3037
4.2959
4.2882
4.2799
4.2719
4.1837
4.1755
4.1612
4.1529
4.1342
4.1163
4.0985
4.0806
3.8547
3.8314
3.8081
2.3101
2.2990
2.2775
2.1977
2.1892
2.1617
2.1550
2.1314
2.1295
2.0395
2.0294
2.0204
1.9237
1.9080
1.8910
1.8742
1.8661
1.8573
1.8403
1.6028
1.2628
1.2450
1.2271
1.0815
1.0779
1.0714
1.0509
1.0420
1.0340
1.0250
0.9630
0.9598
0.9461
0.9428
0.0579
-0.0045
-0.0127
CF3
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H
O
O
N
H
1H NMR 500 MHz
25
20
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10
5
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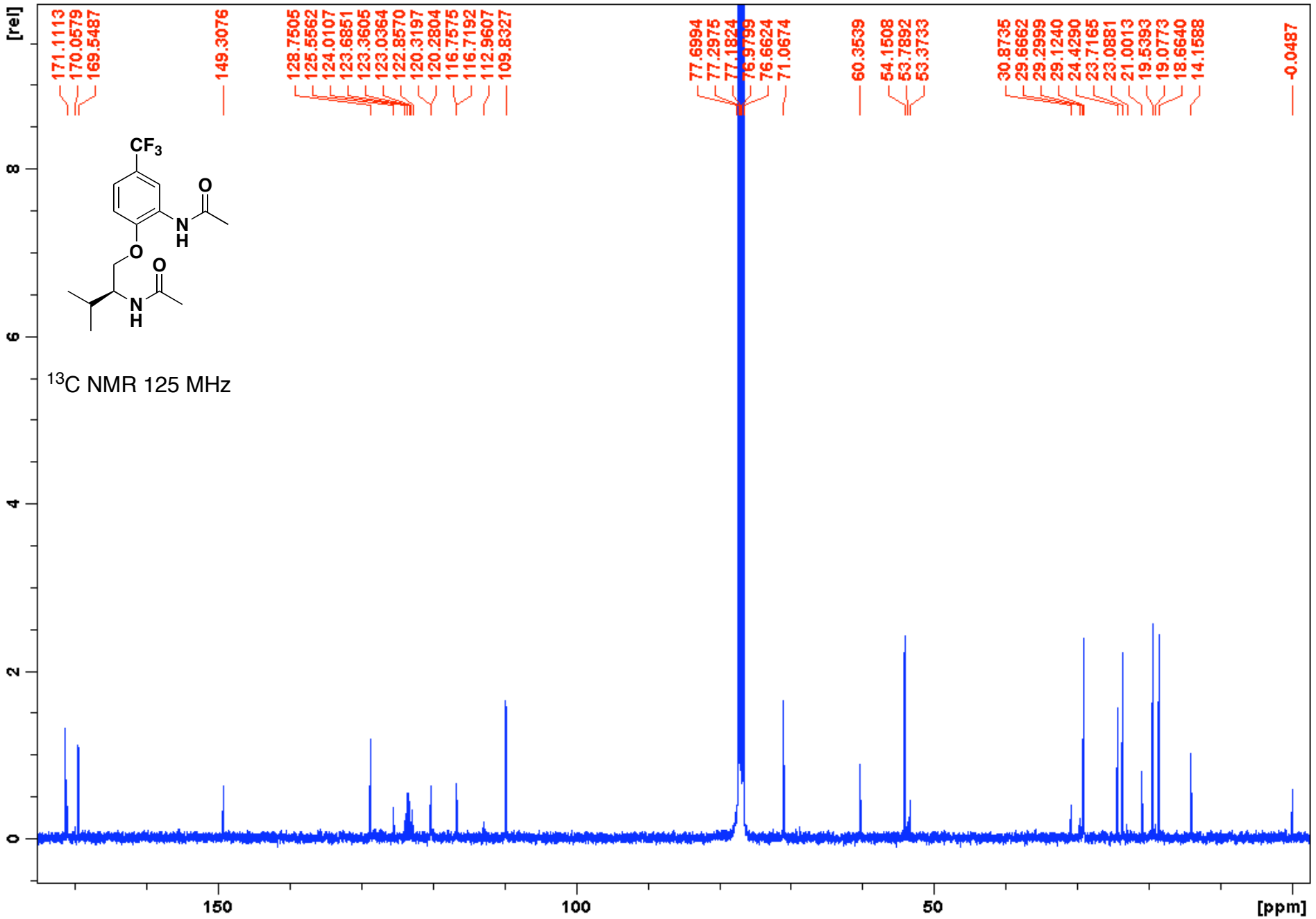
6
4
2
[ppm]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124.0107
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120.3197
120.2804
116.7575
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109.8327
77.6994
77.2975
77.1824
76.9799
76.6624
71.0674
60.3539
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53.7892
53.3733
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29.6662
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24.4290
23.7165
23.0881
21.0013
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19.0773
18.6640
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8
150
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[ppm]
CF3
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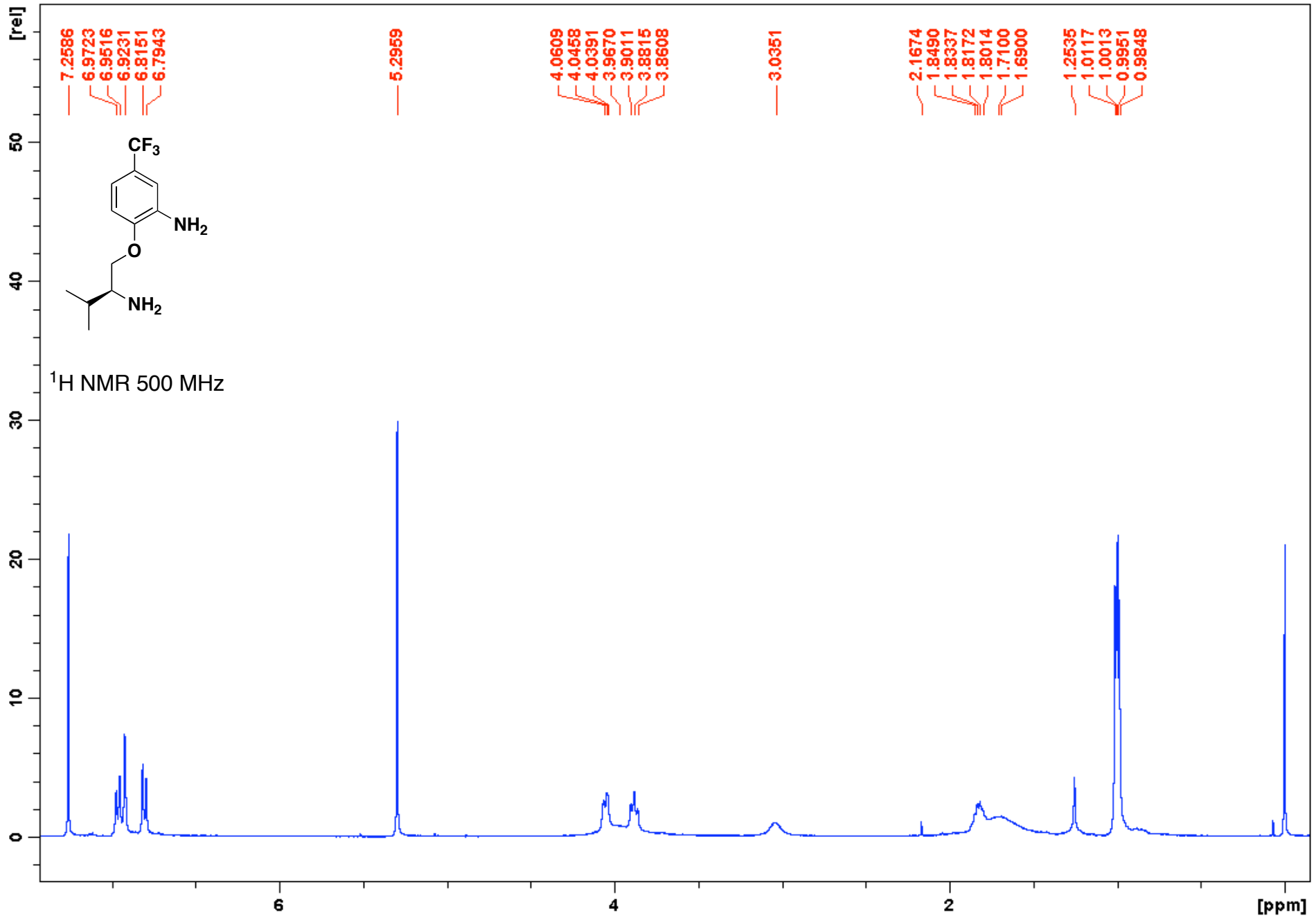
H
O
O
N
H
13C NMR 125 MHz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4.0391
3.9670
3.9011
3.8815
3.8608
3.0351
2.1674
1.8490
1.8337
1.8172
1.8014
1.7100
1.6900
1.2535
1.0117
1.0013
0.9951
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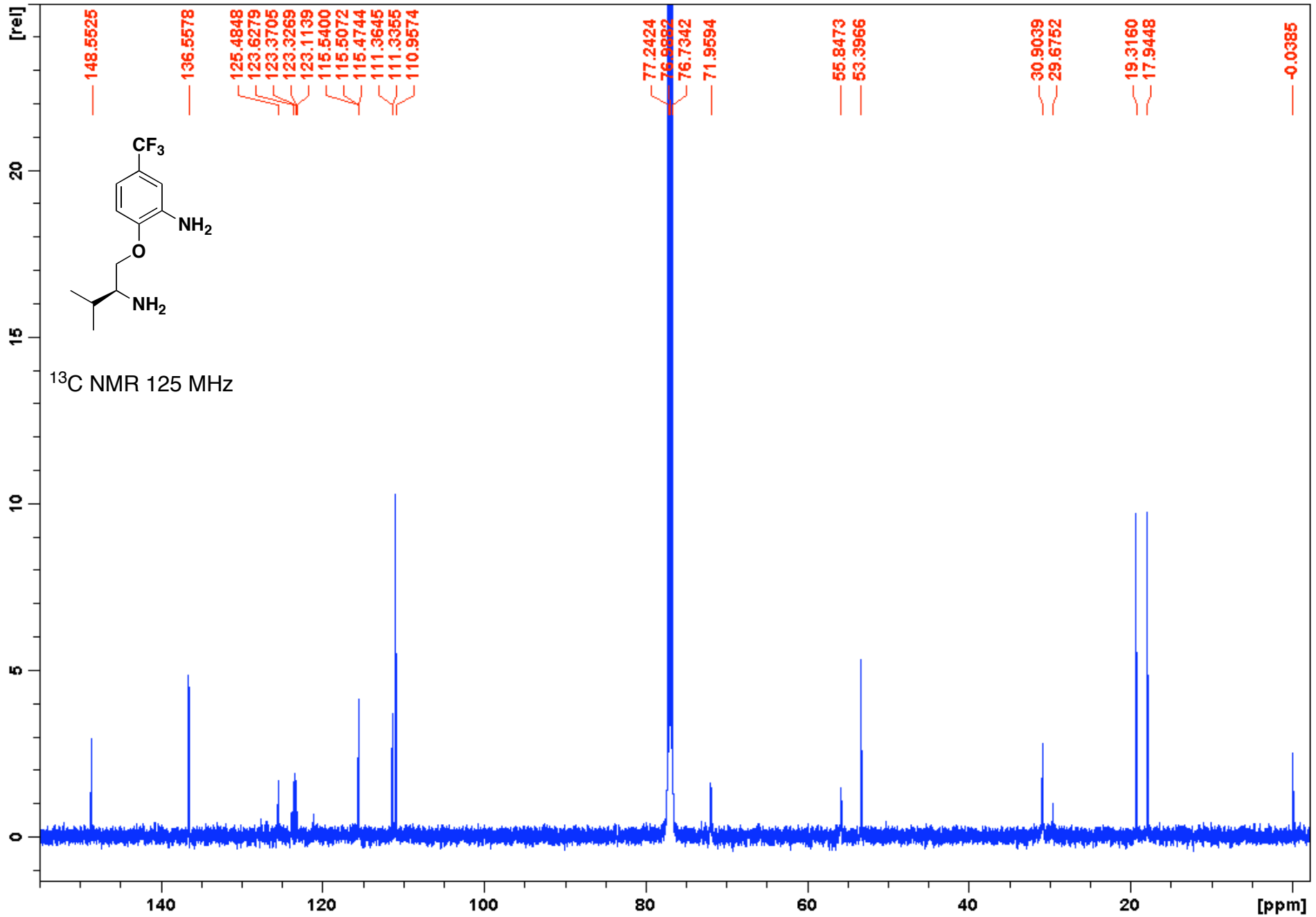
CF3
NH2
O
NH2
1H NMR 500 MHz
0
10
20
30
40
50
6
4
2
[ppm]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77.2424
76.9882
76.7342
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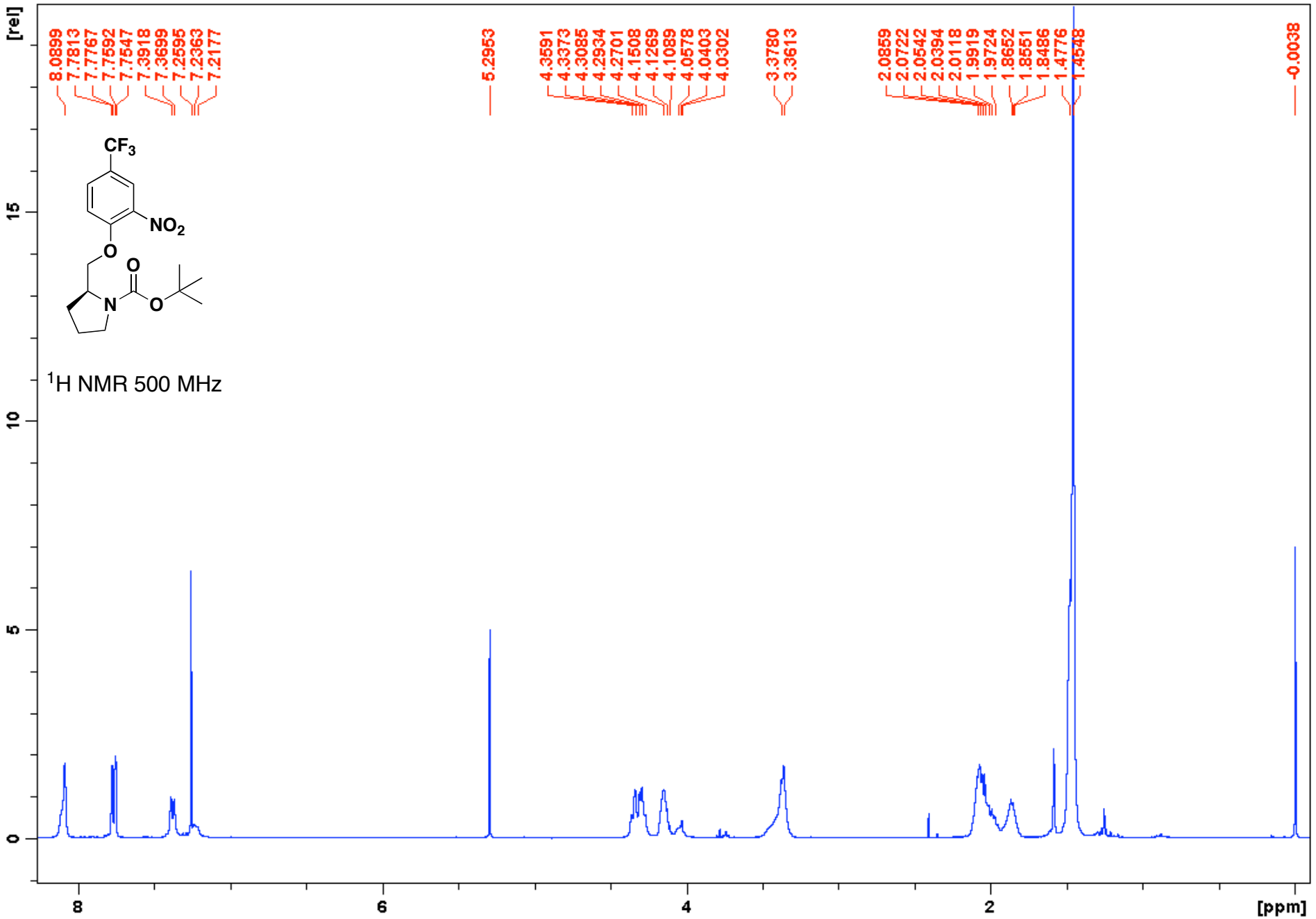
55.8473
53.3966
30.9039
29.6752
19.3160
17.9448
-0.0385
CF3
NH2
O
NH2
13C NMR 125 MHz
0
5
10
15
20
140
120
100
80
60
40
20
[ppm]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7.2177
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4.3591
4.3373
4.3085
4.2934
4.2701
4.1508
4.1269
4.1089
4.0578
4.0403
4.0302
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3.3613
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2.0118
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1.9724
1.8652
1.8551
1.8486
1.4776
1.4548
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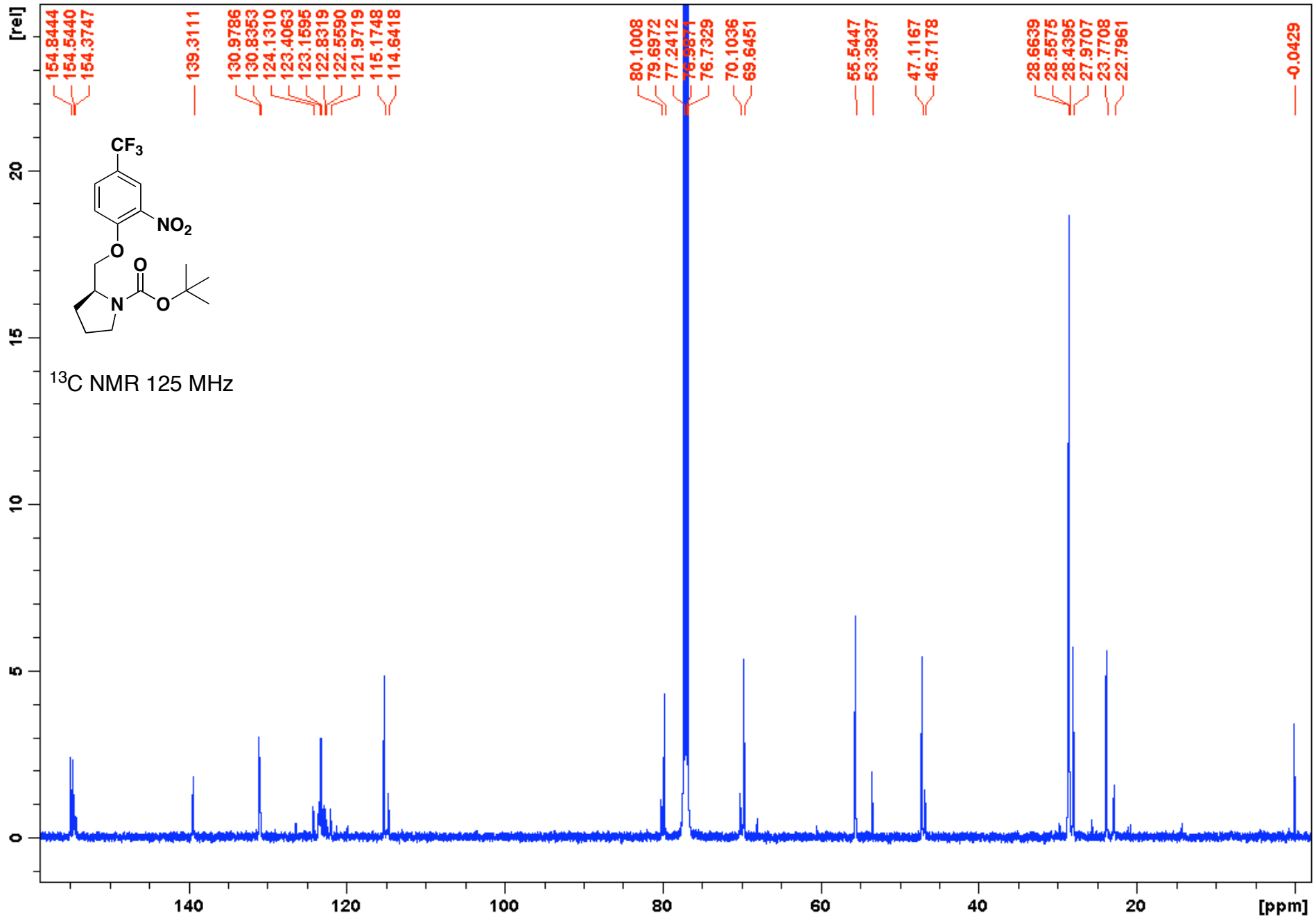
CF3
NO2
O
O
N
O
1H NMR 500 MHz
15
10
5
0
8
6
4
2
[ppm]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114.6418
80.1008
79.6972
77.2412
76.9871
76.7329
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69.6451
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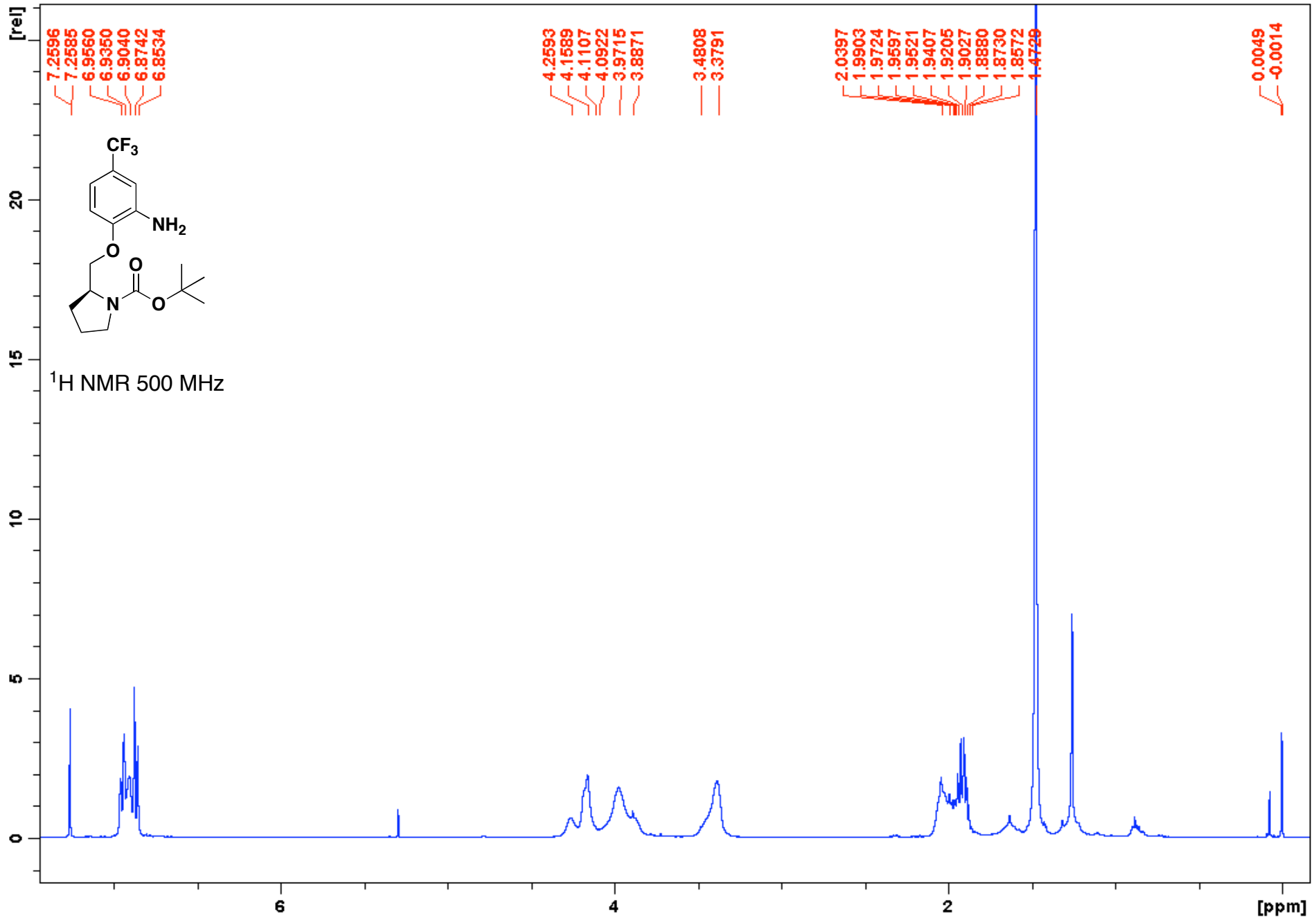
53.3937
47.1167
46.7178
28.6639
28.5575
28.4395
27.9707
23.7708
22.7961
-0.0429
CF3
NO2
O
O
N
O
13C NMR 125 MHz
0
5
10
15
20
140
120
100
80
60
40
20
[ppm]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6.9040
6.8742
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4.1589
4.1107
4.0922
3.9715
3.8871
3.4808
3.3791
2.0397
1.9903
1.9724
1.9597
1.9521
1.9407
1.9205
1.9027
1.8880
1.8730
1.8572
1.4729
0.0049
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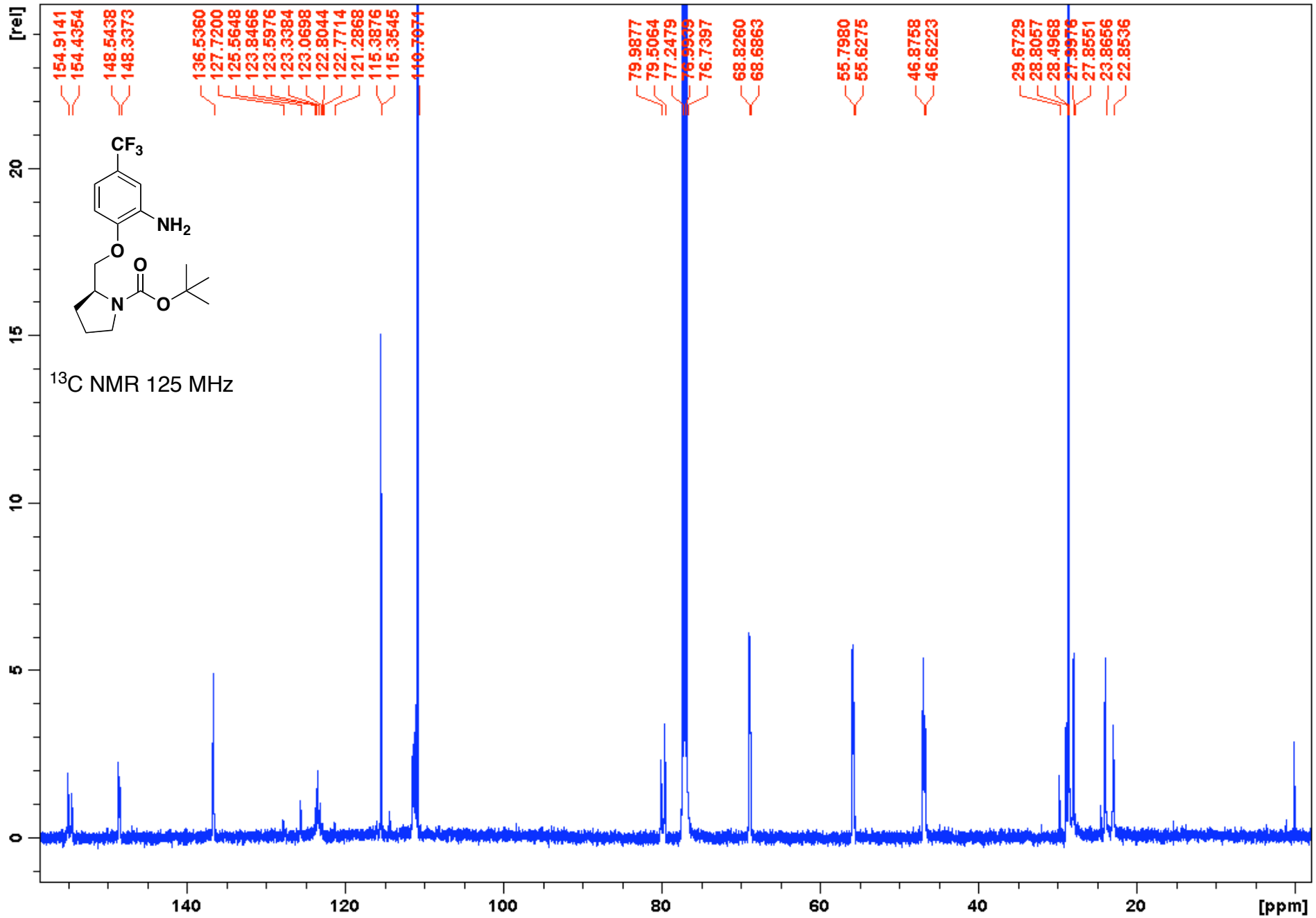
CF3
NH2
O
O
N
O
1H NMR 500 MHz
20
15
10
5
0
6
4
2
[ppm]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115.3545
110.7071
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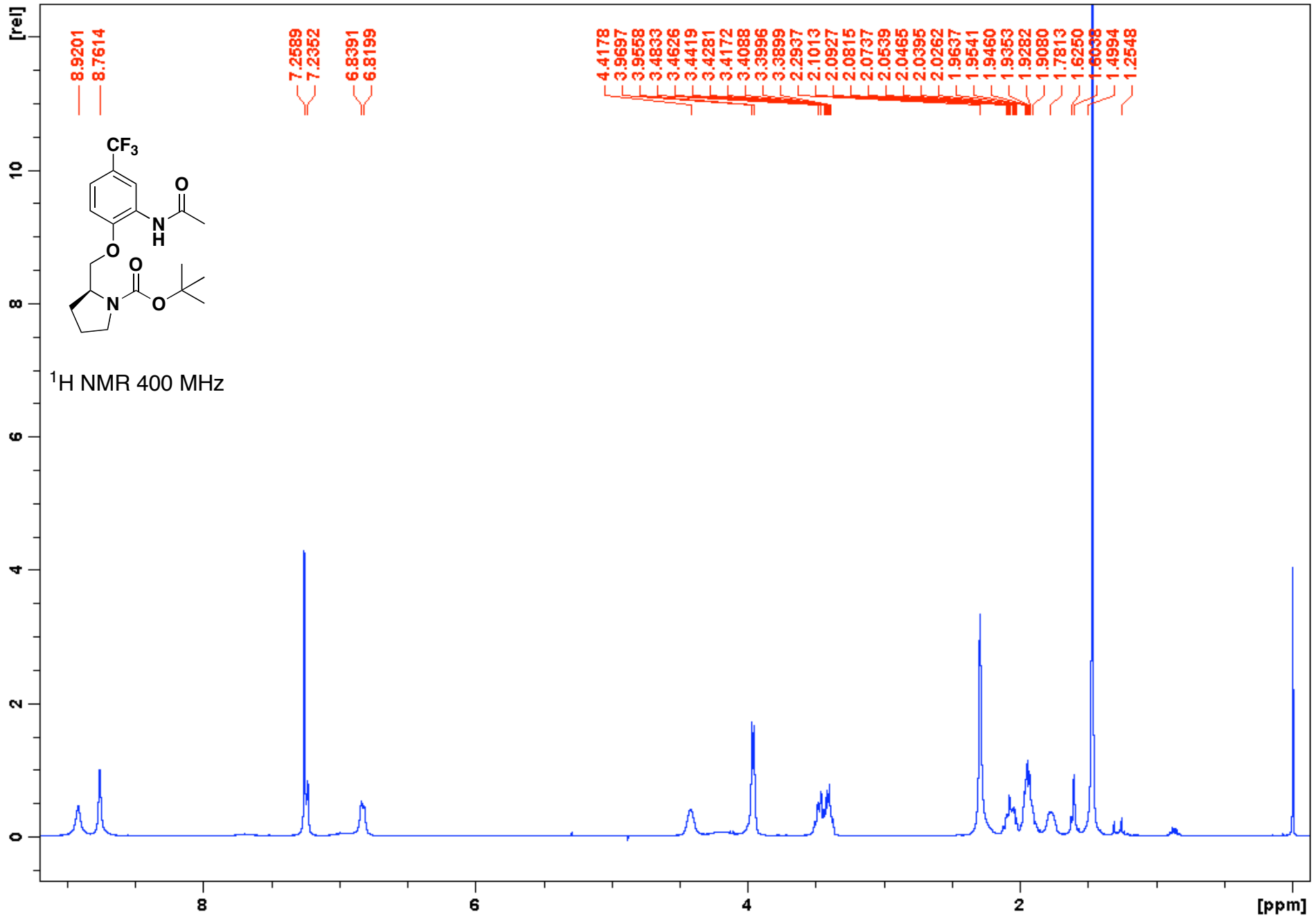
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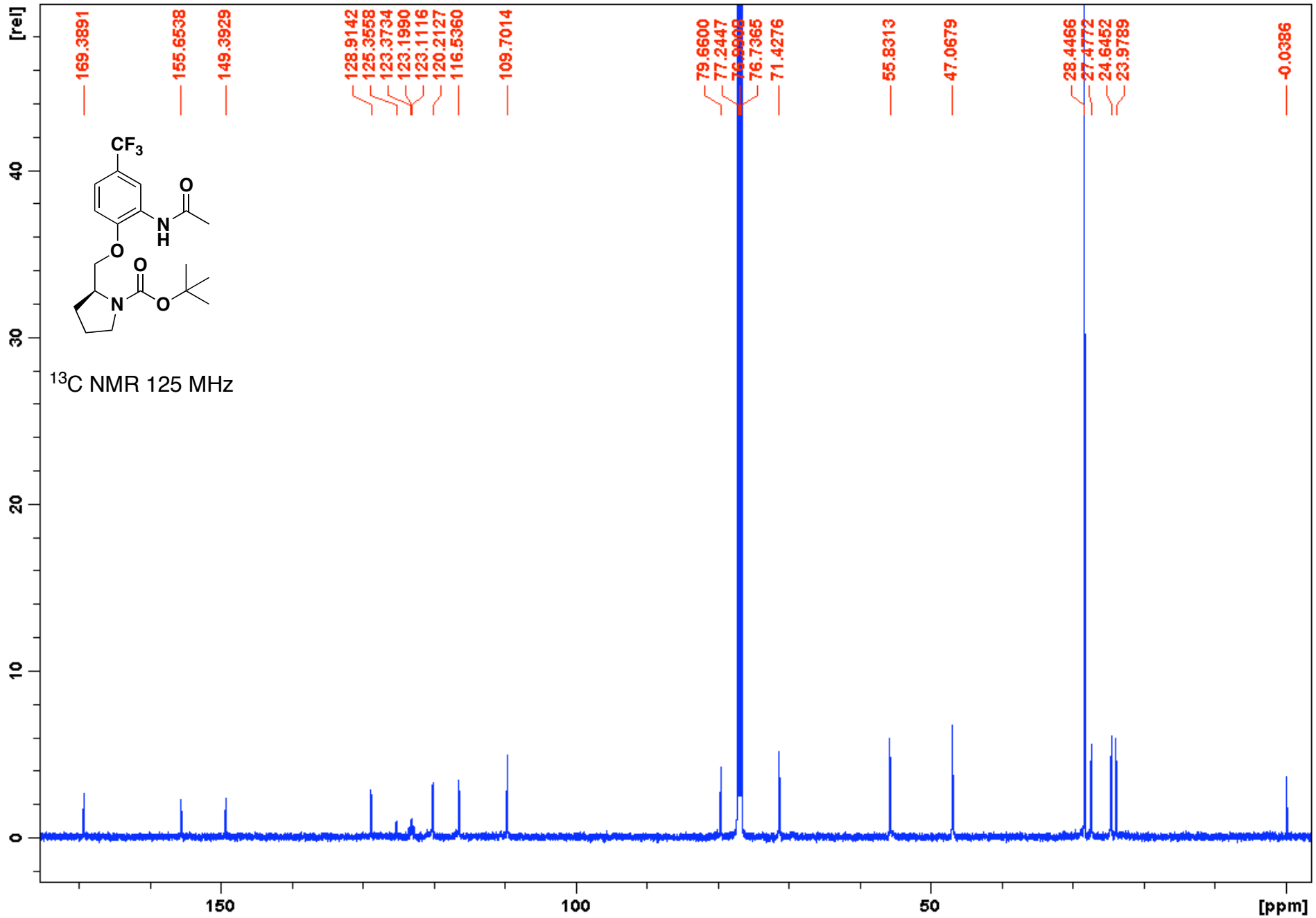
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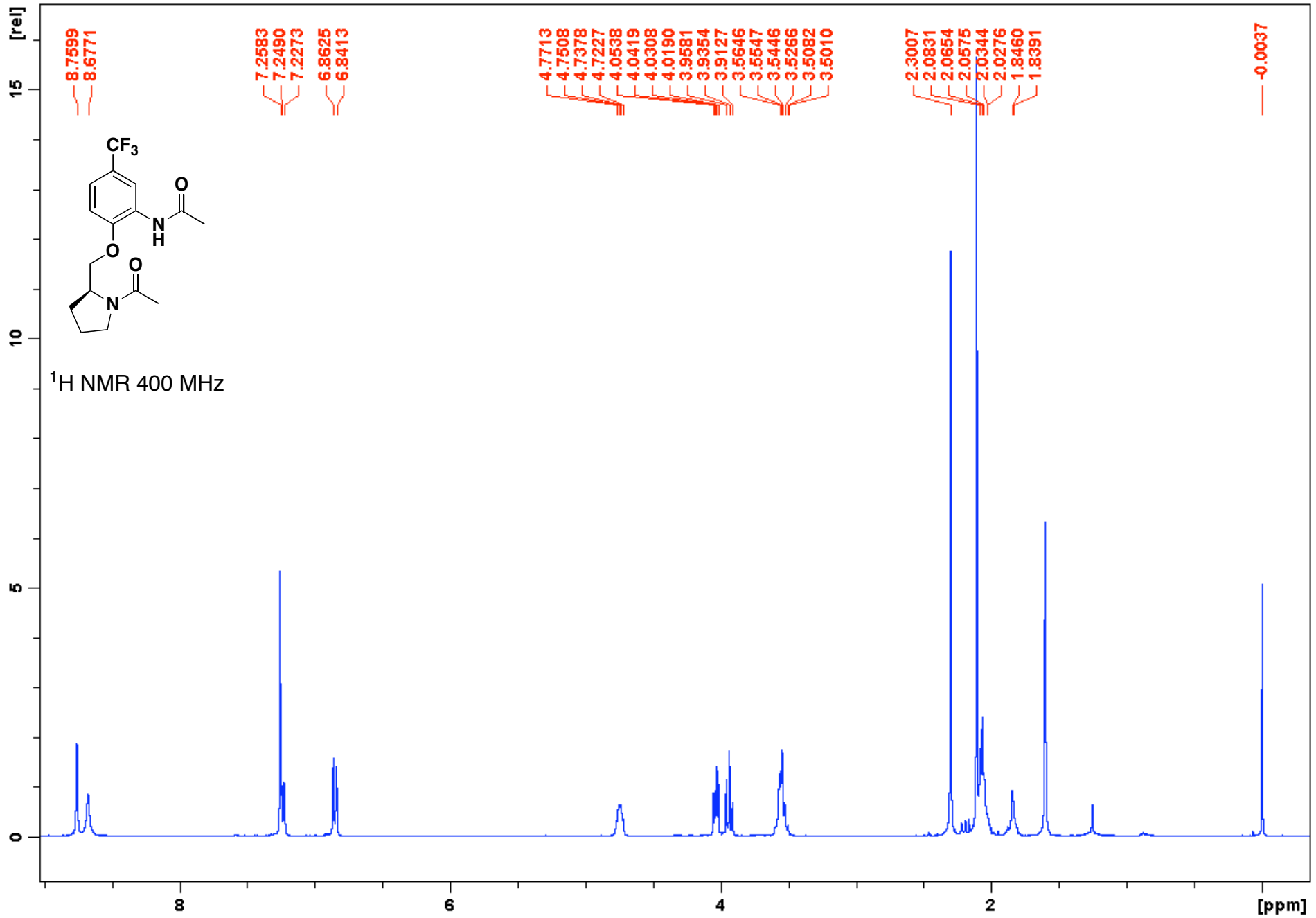
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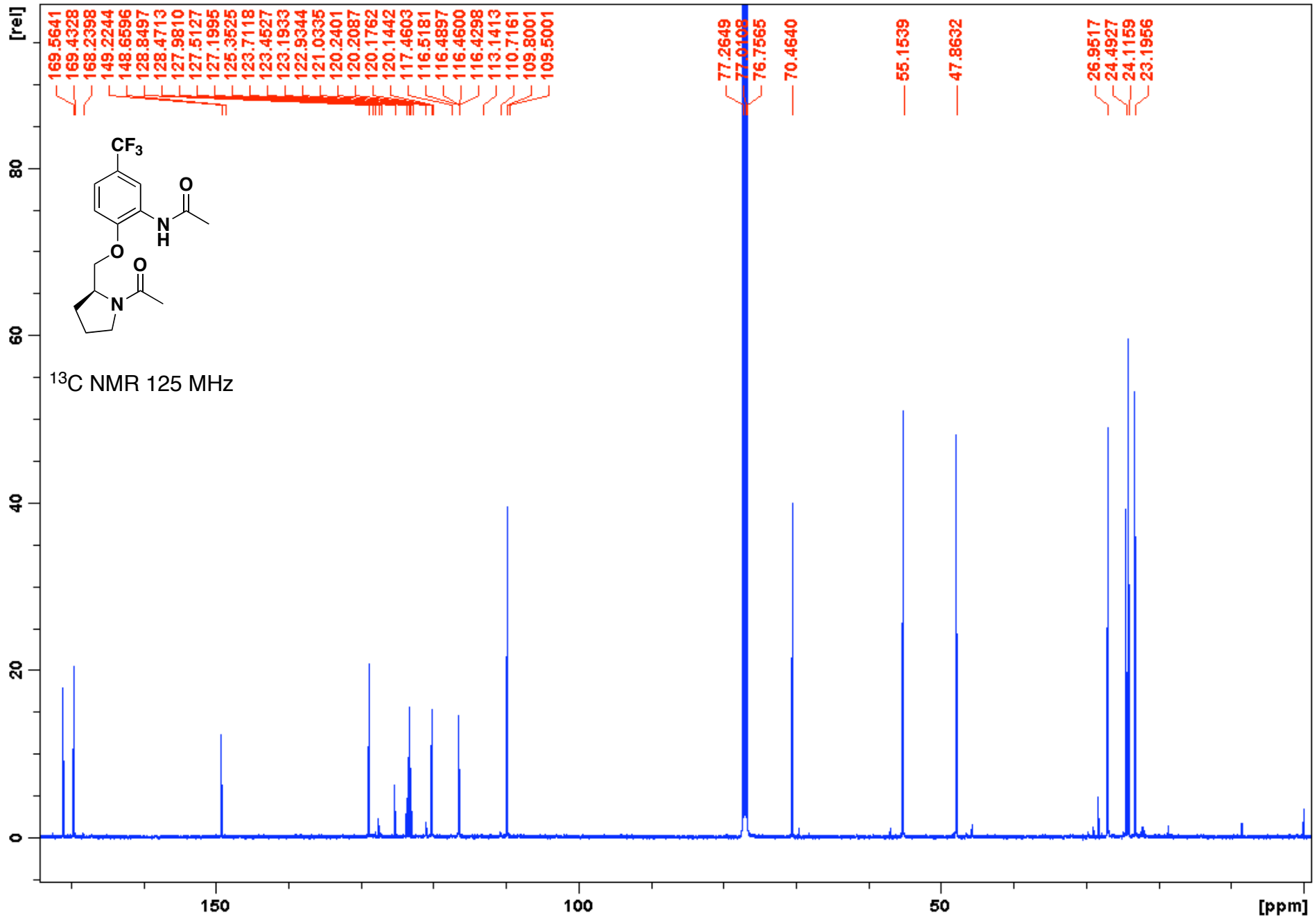
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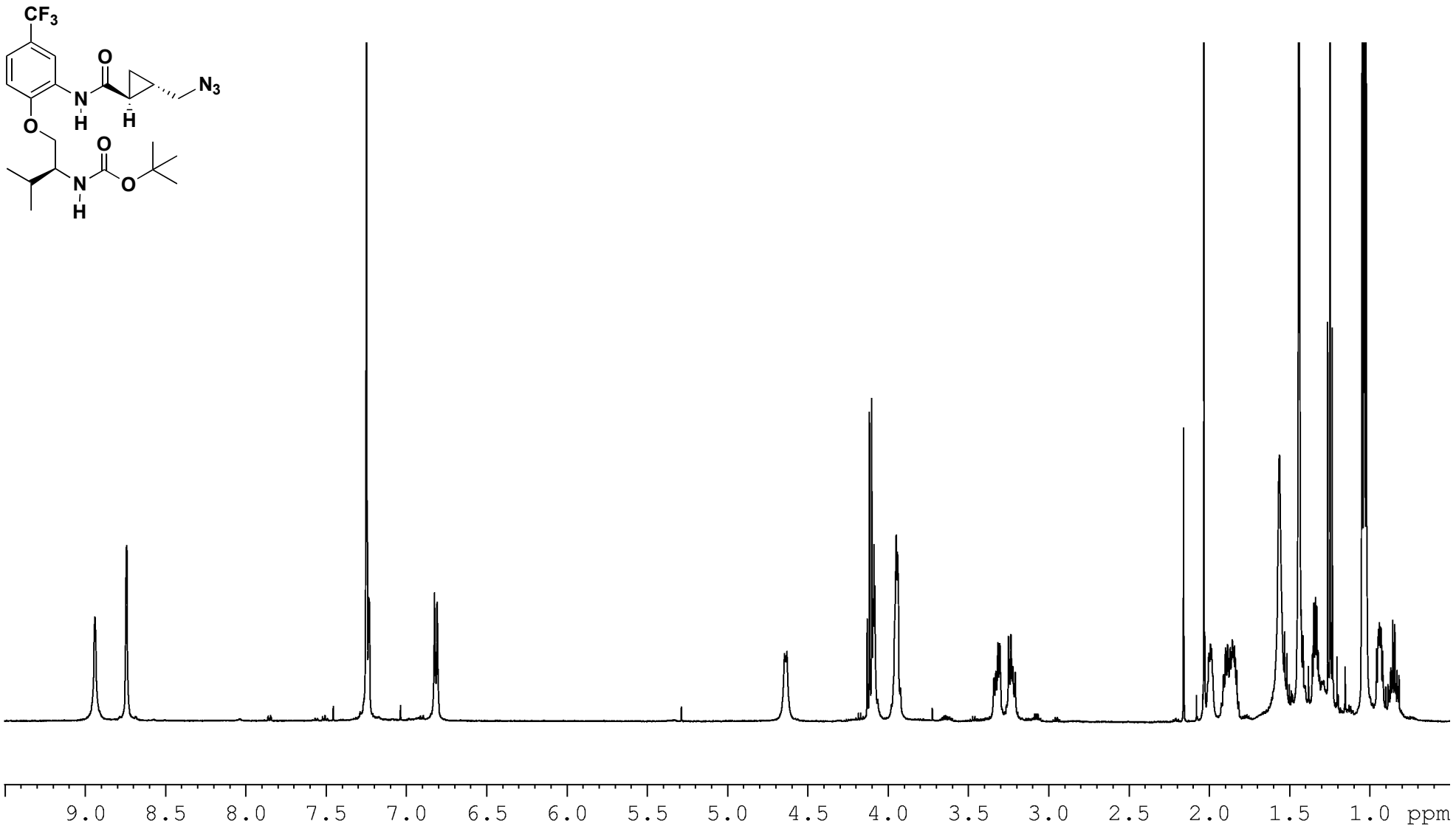
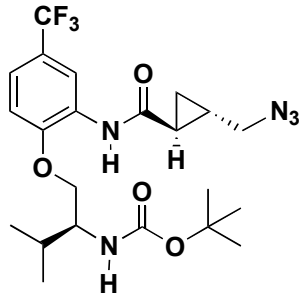
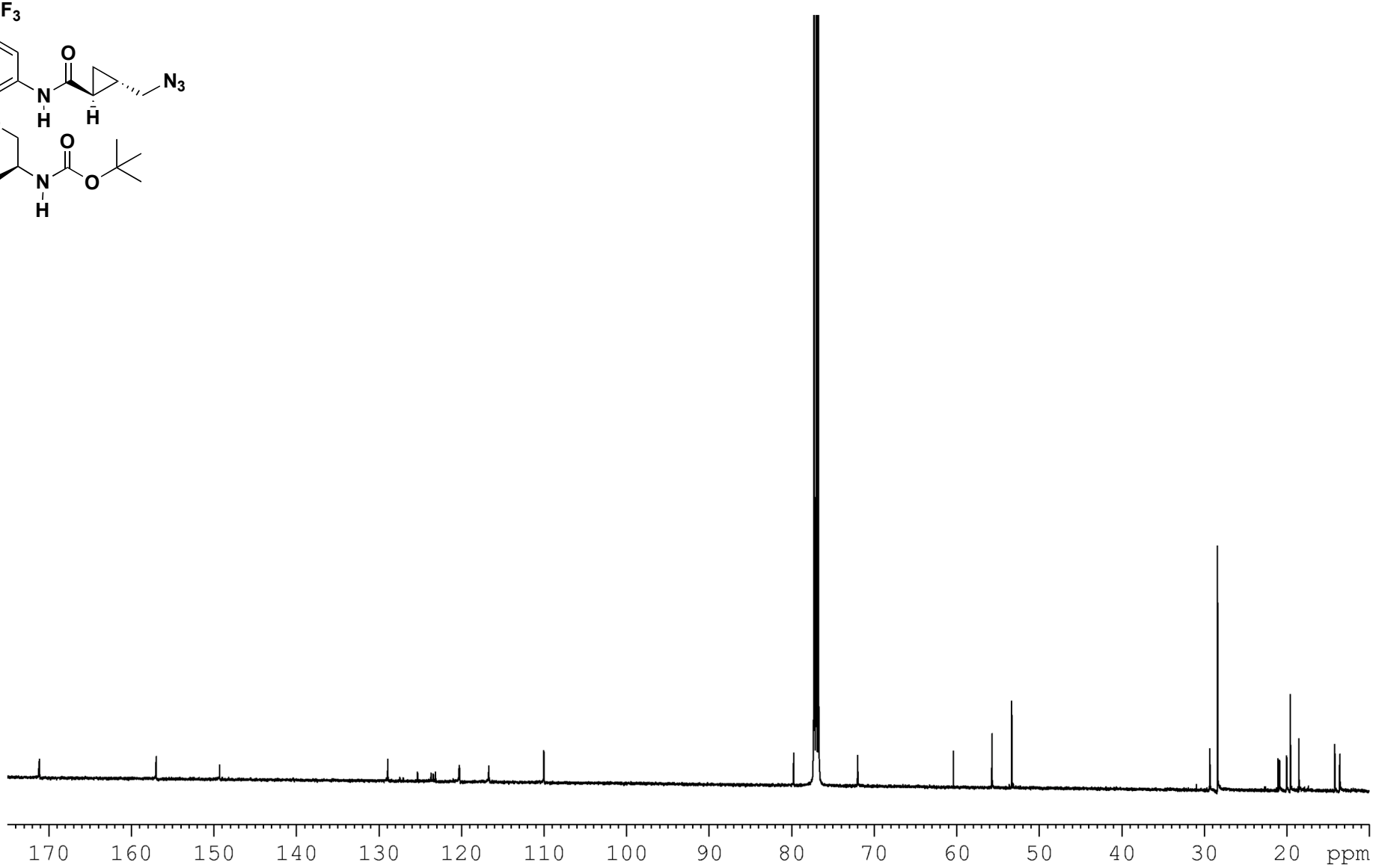
δ_H (500 MHz, d_1-chloroform)

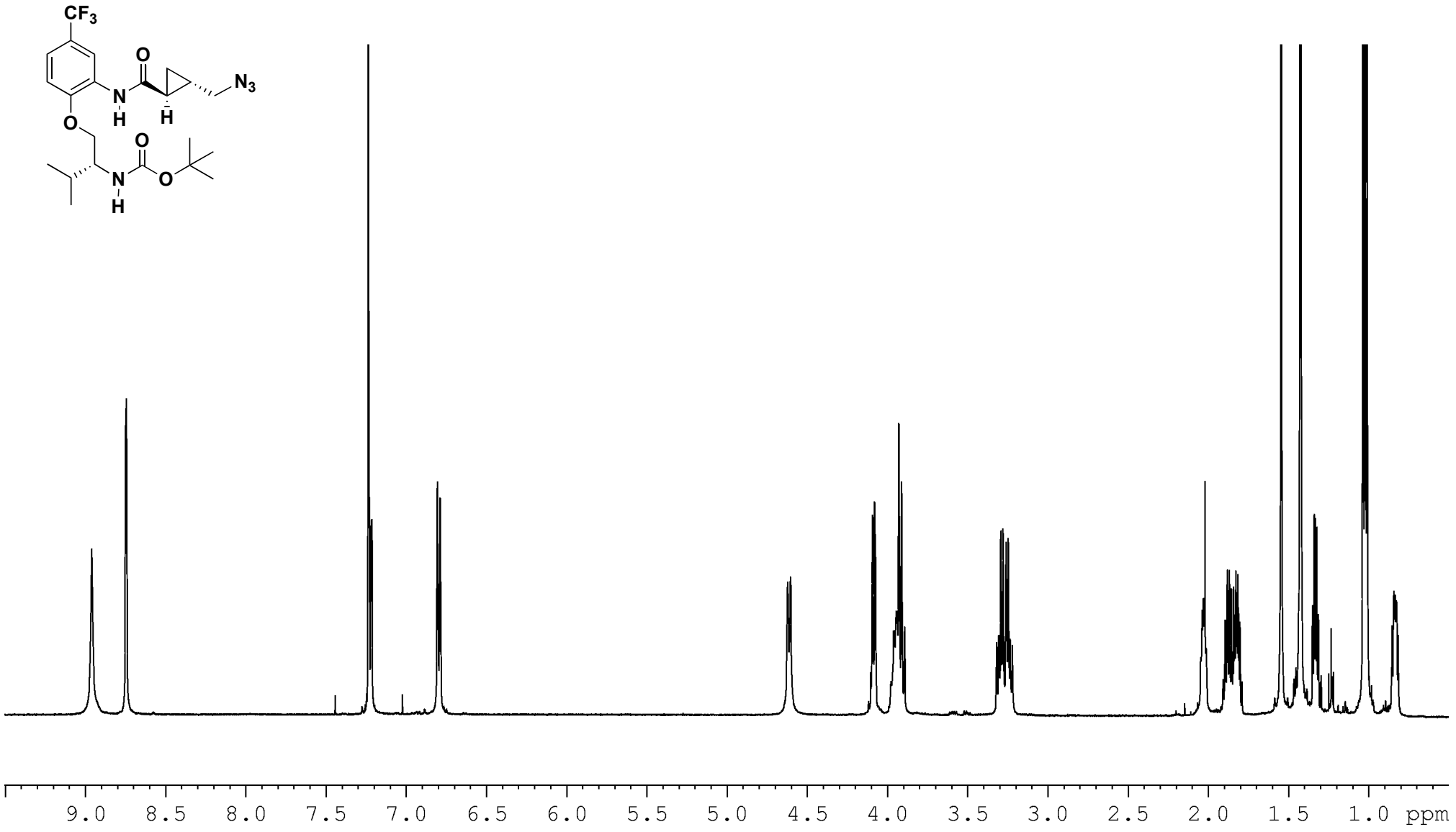


δ_C (125 MHz, d_1-chloroform)

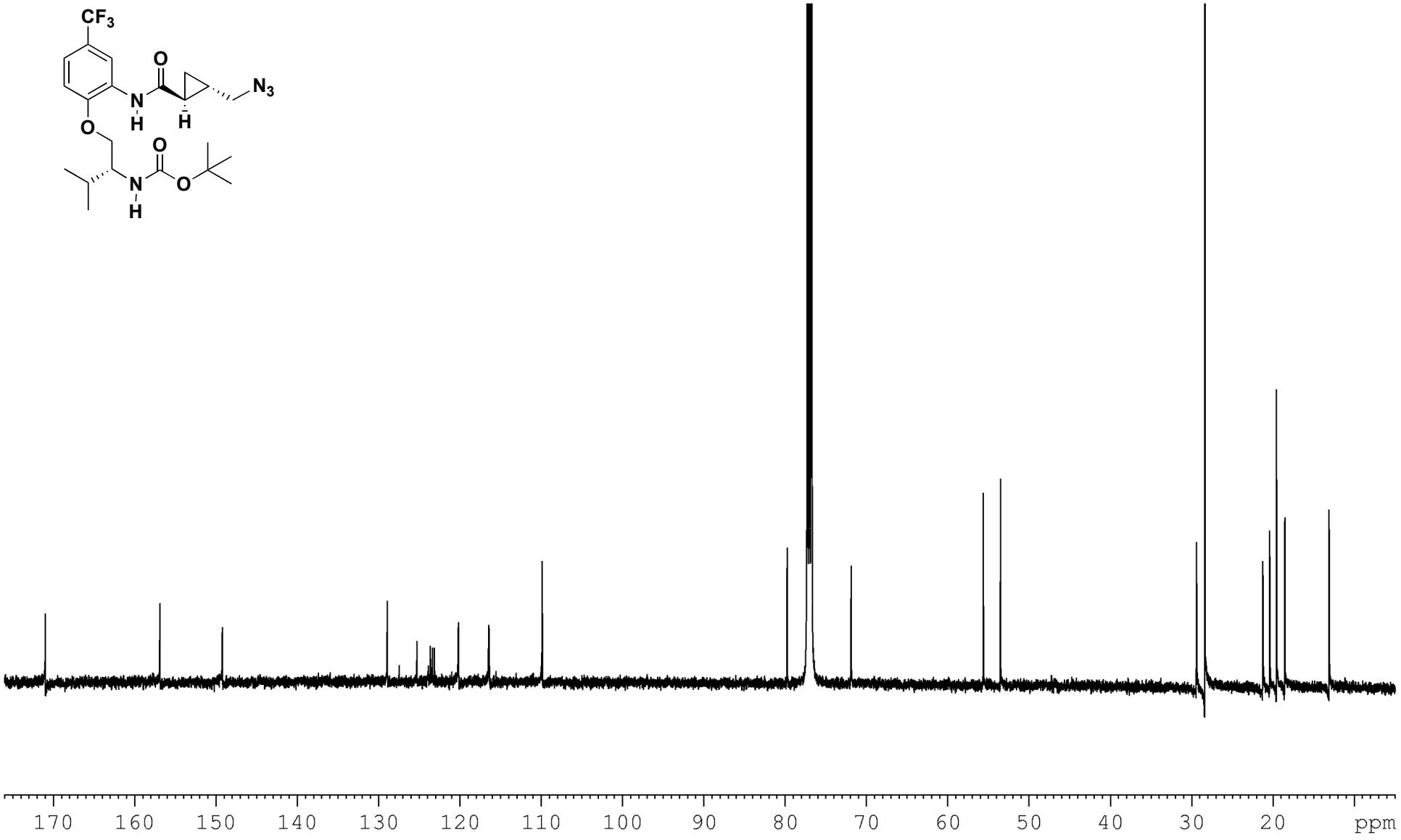




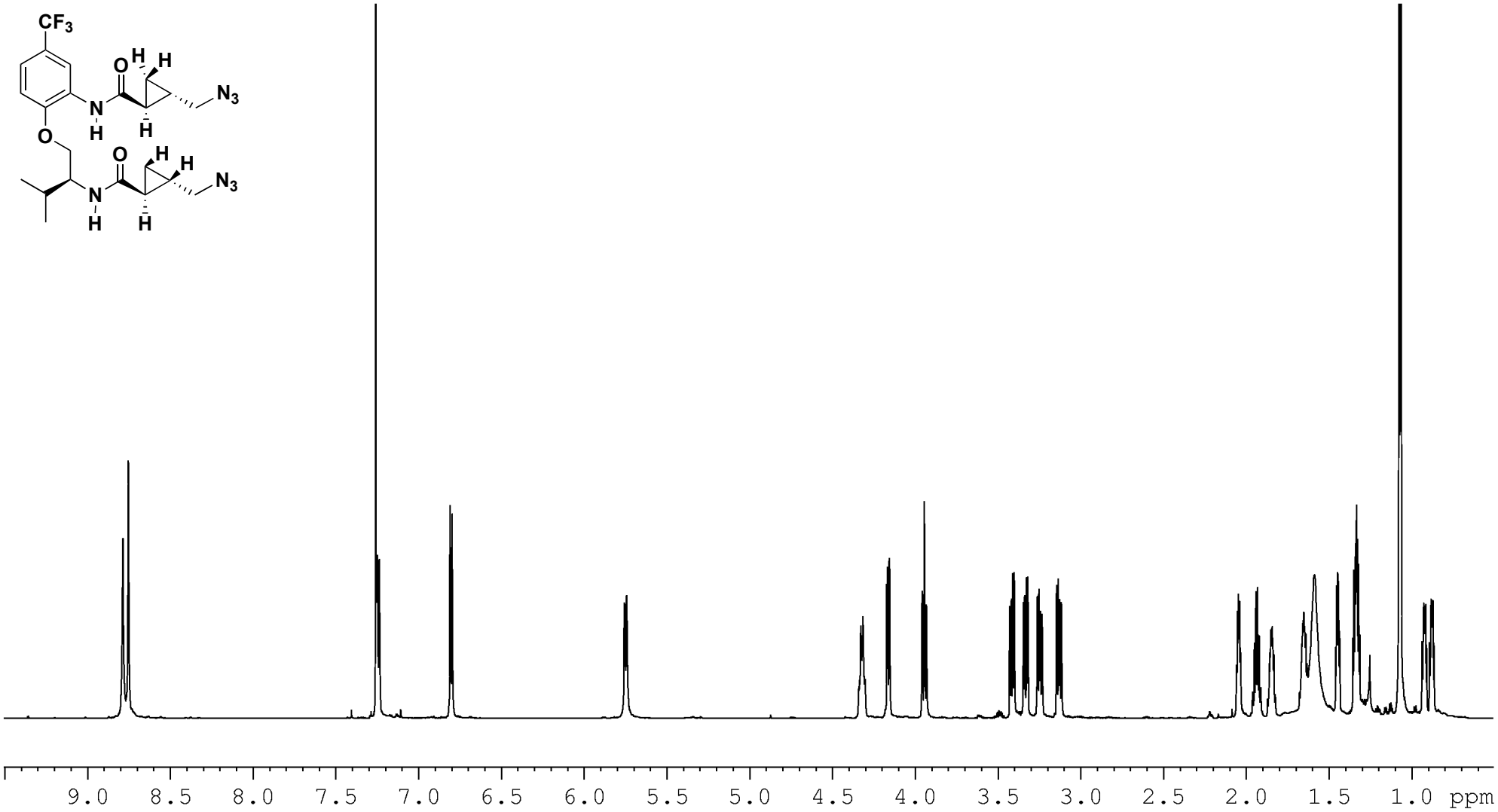
δ_H (700 MHz, d_1-chloroform)



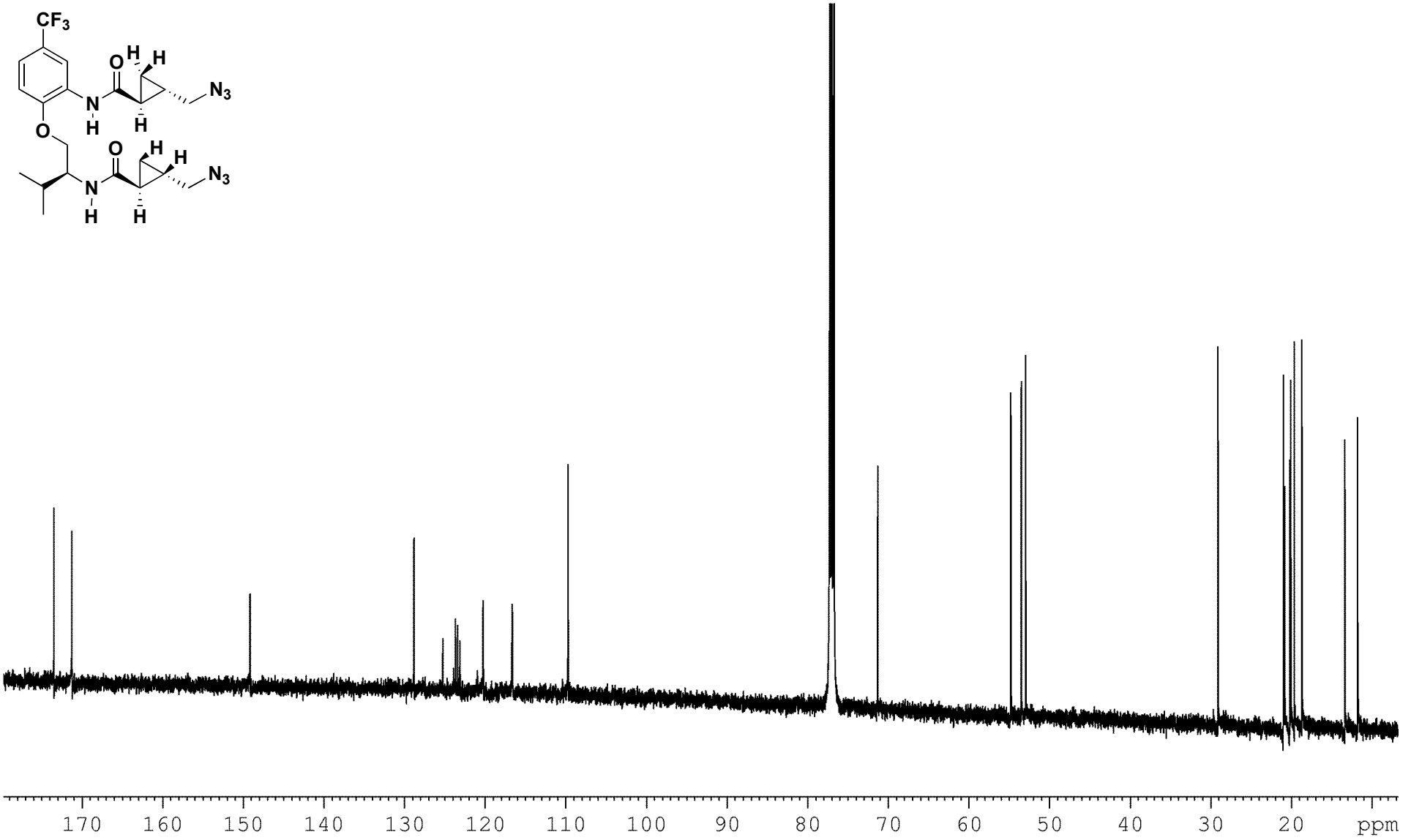
δ_C (125 MHz, d_1-chloroform)



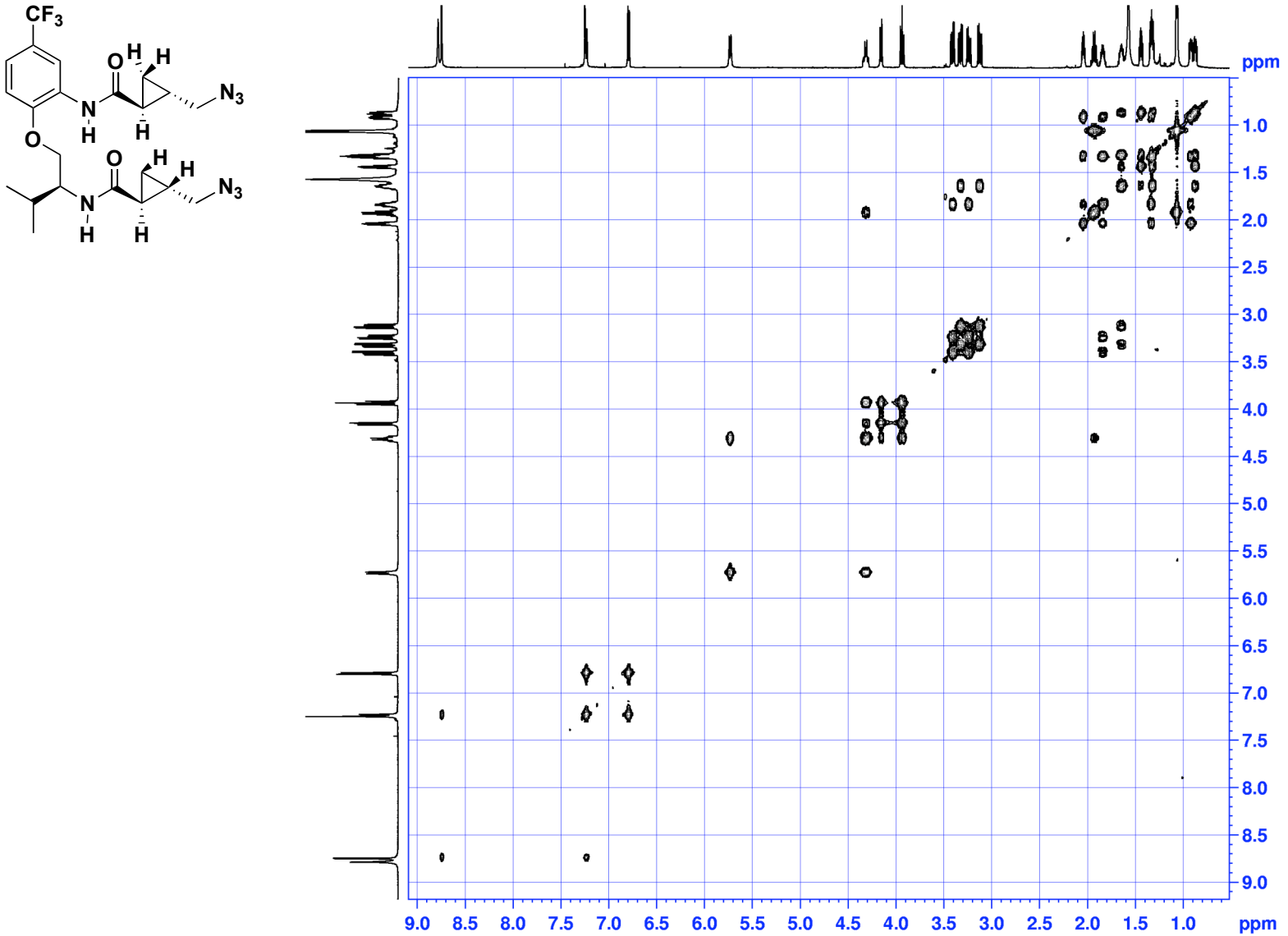
δ_H (700 MHz, d_1-chloroform)



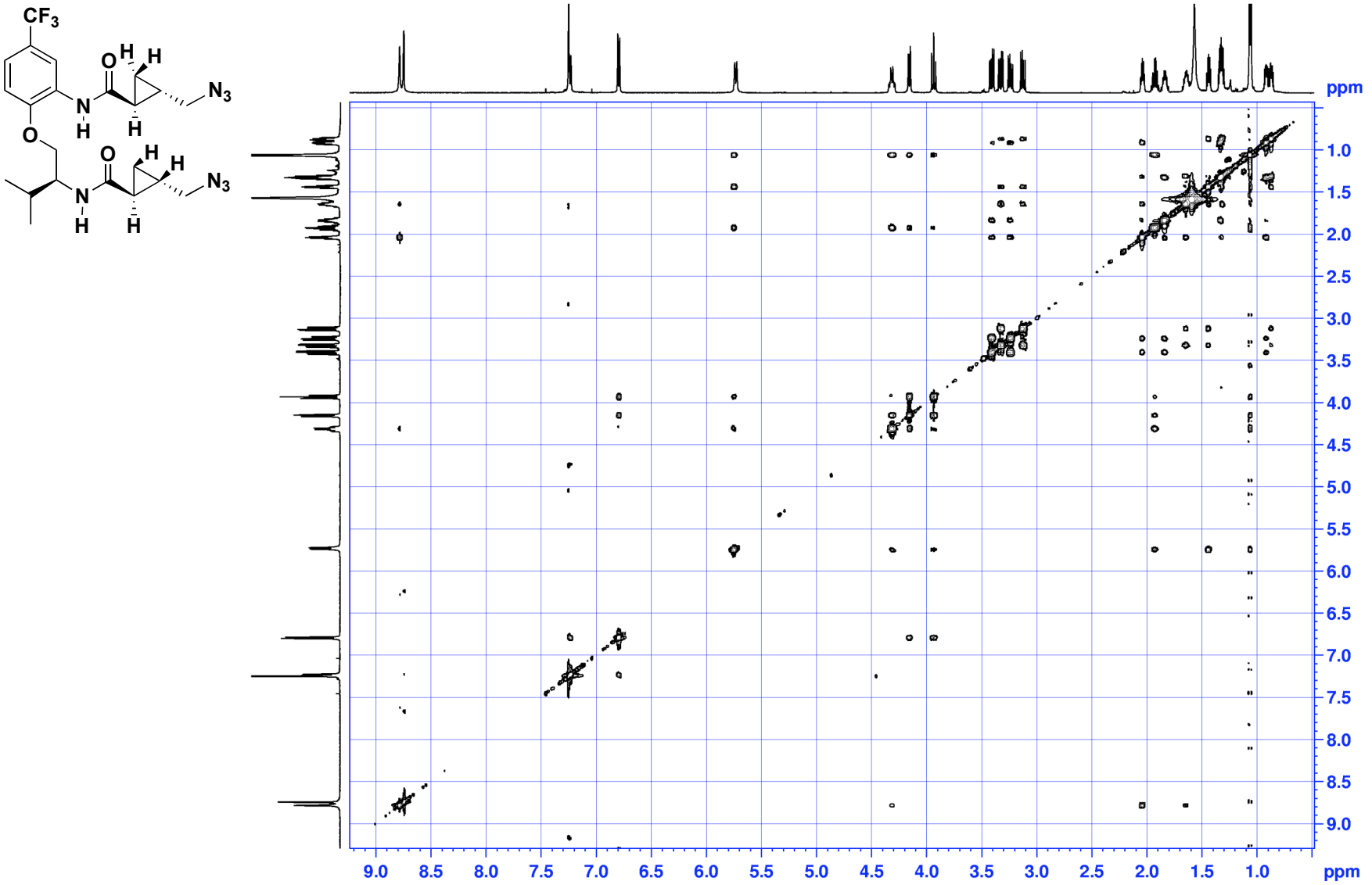
δ_C (125 MHz, d_1-chloroform)



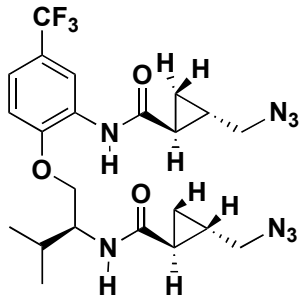
COSY (500 MHz, d_1-chloroform)

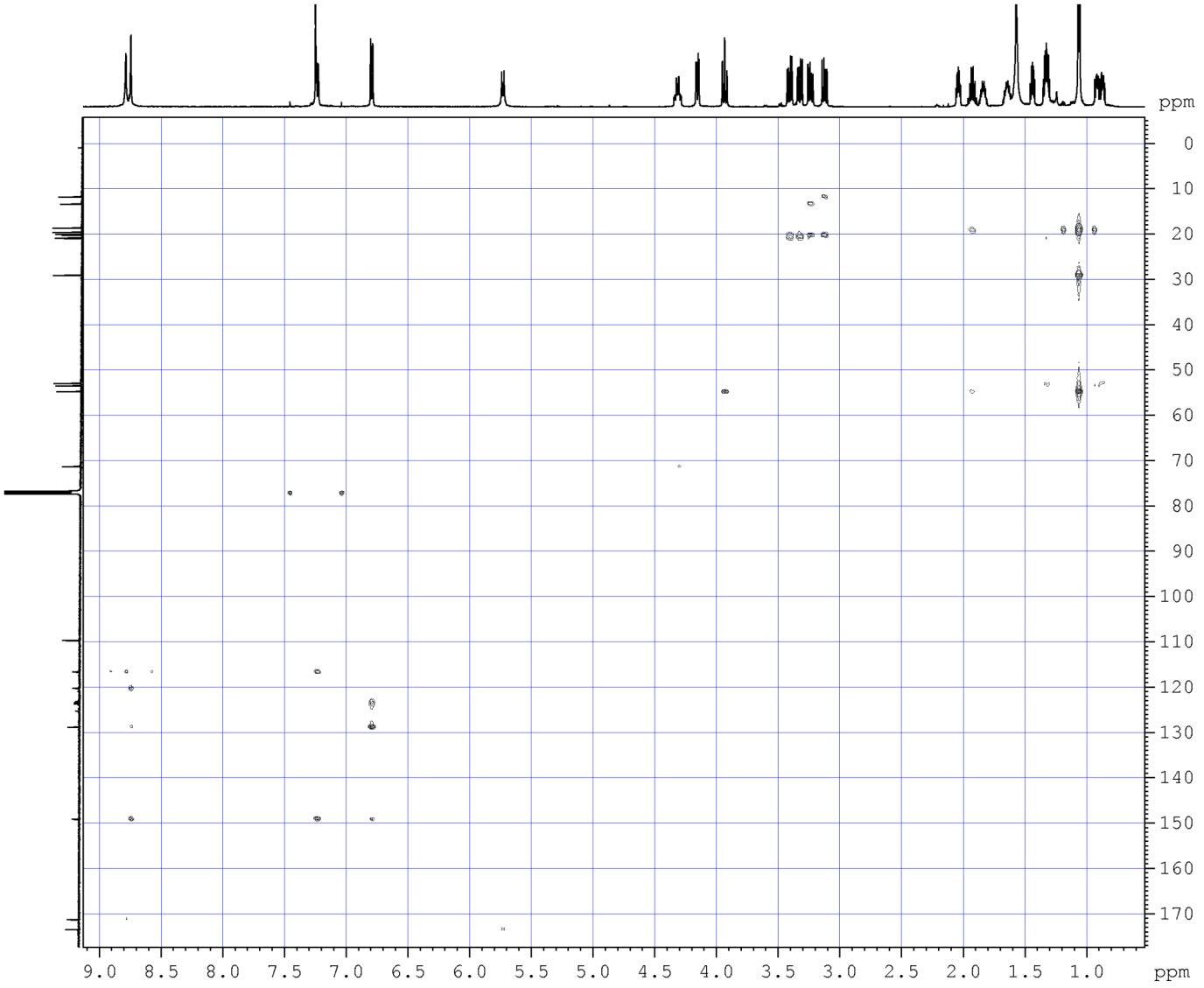


NOESY; 1s mixing time (500 MHz, d_1-chloroform)

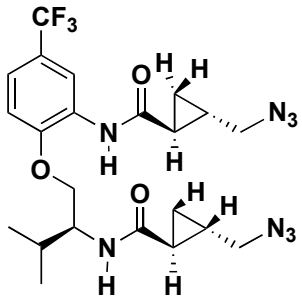


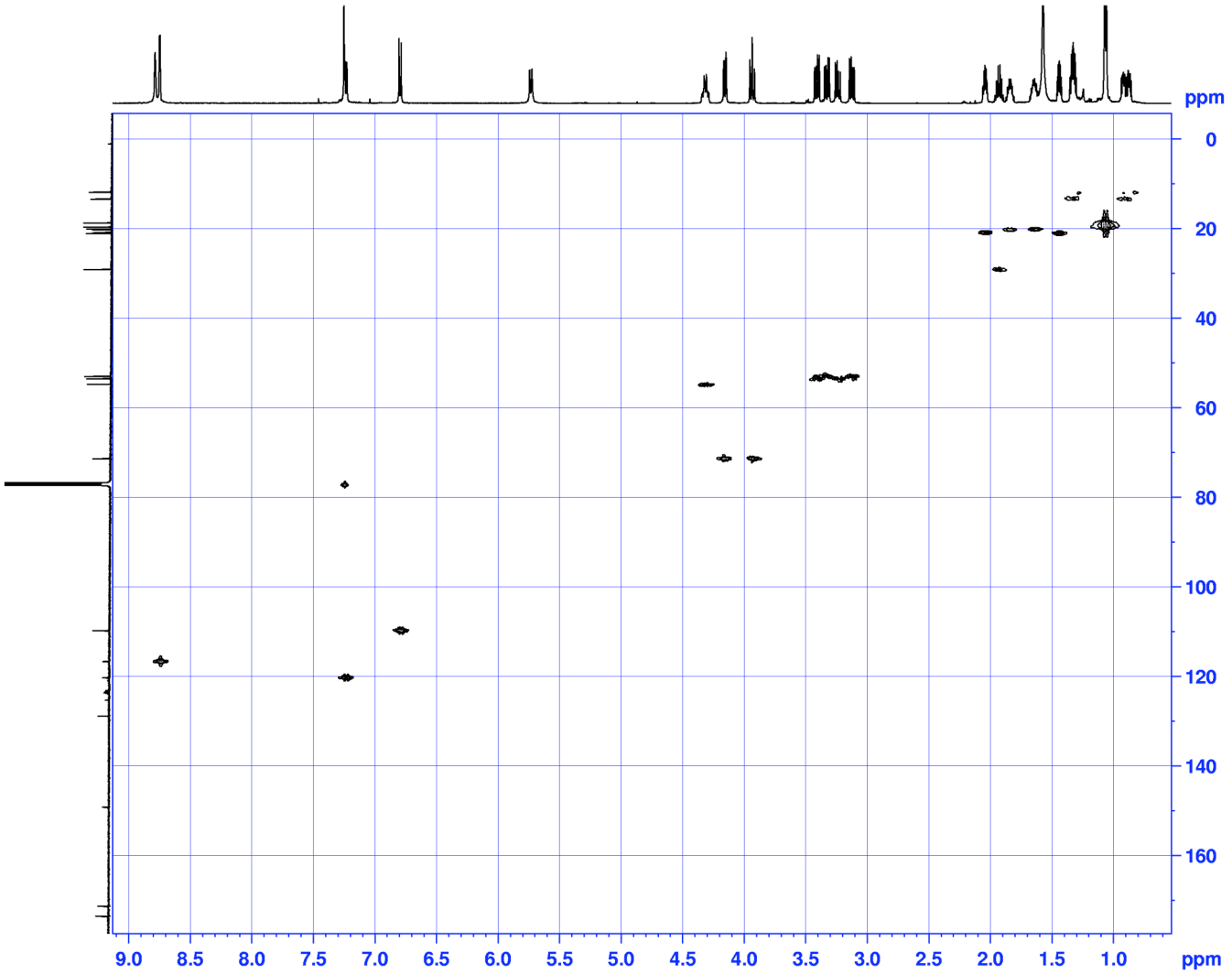
HMBC
(500 MHz, d_1-chloroform)



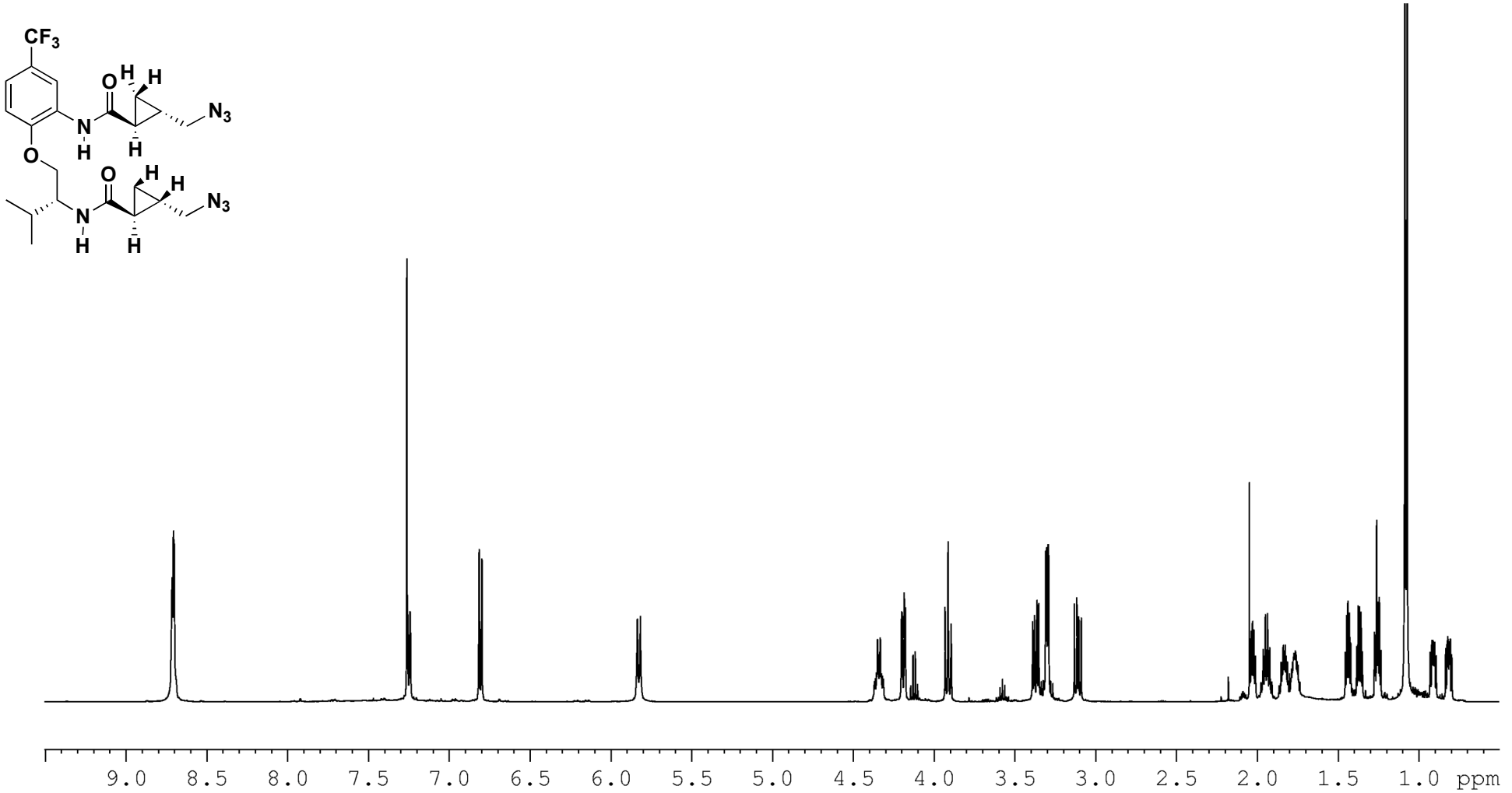


HMQC
(500 MHz, d_1-chloroform)

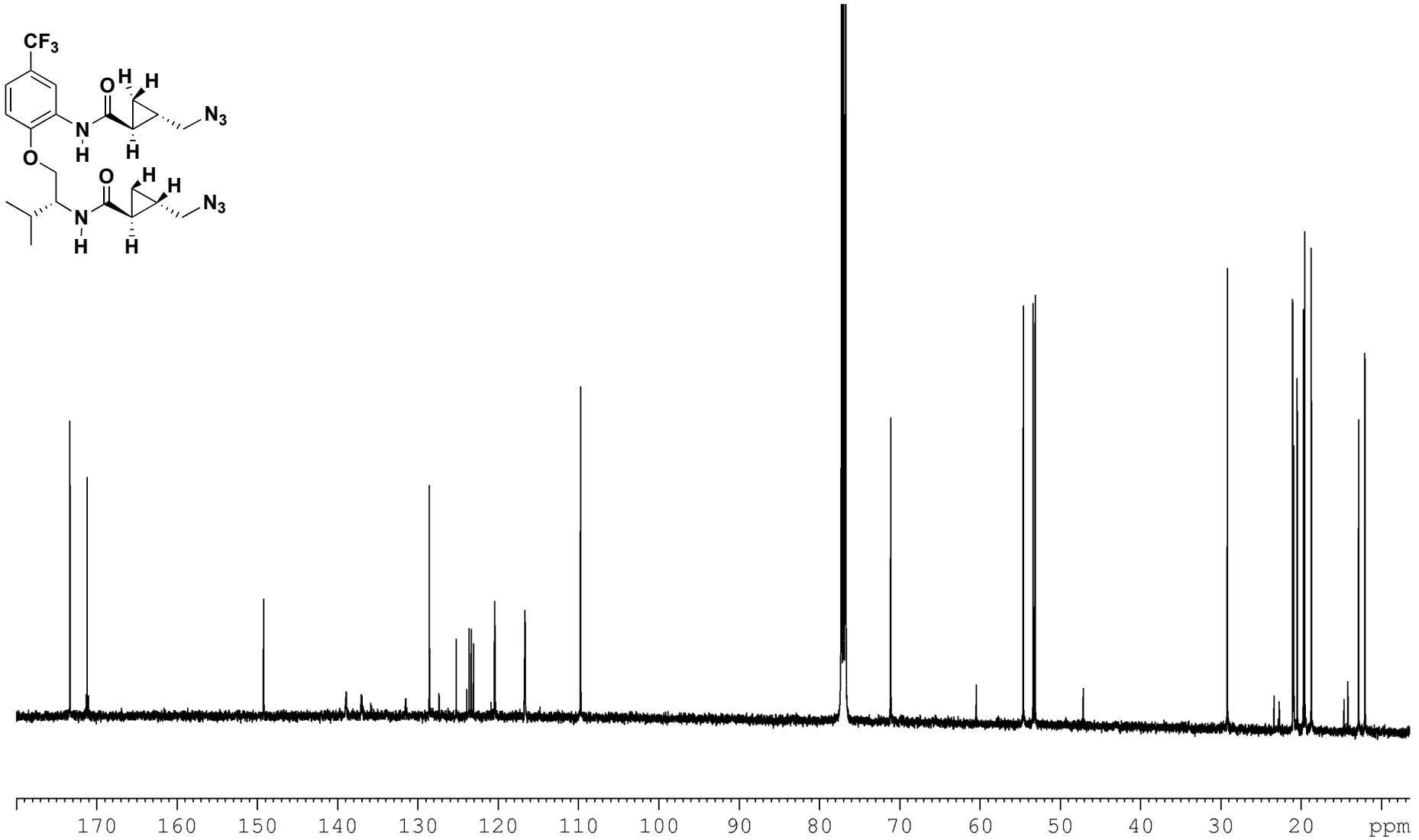




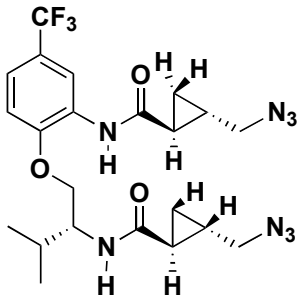
δ_H (700 MHz, d_1-chloroform)

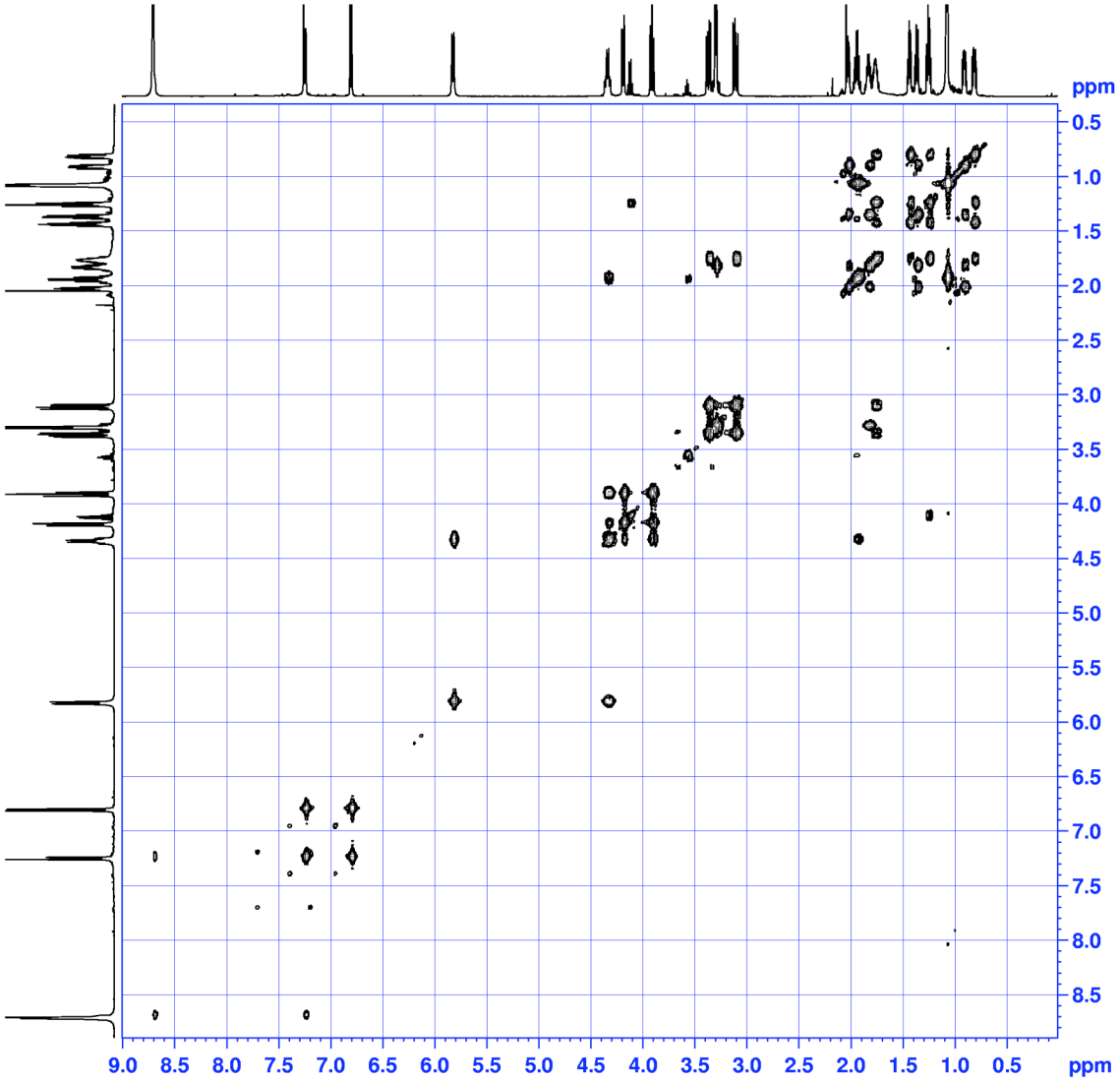


δ_C (125 MHz, d_1-chloroform)

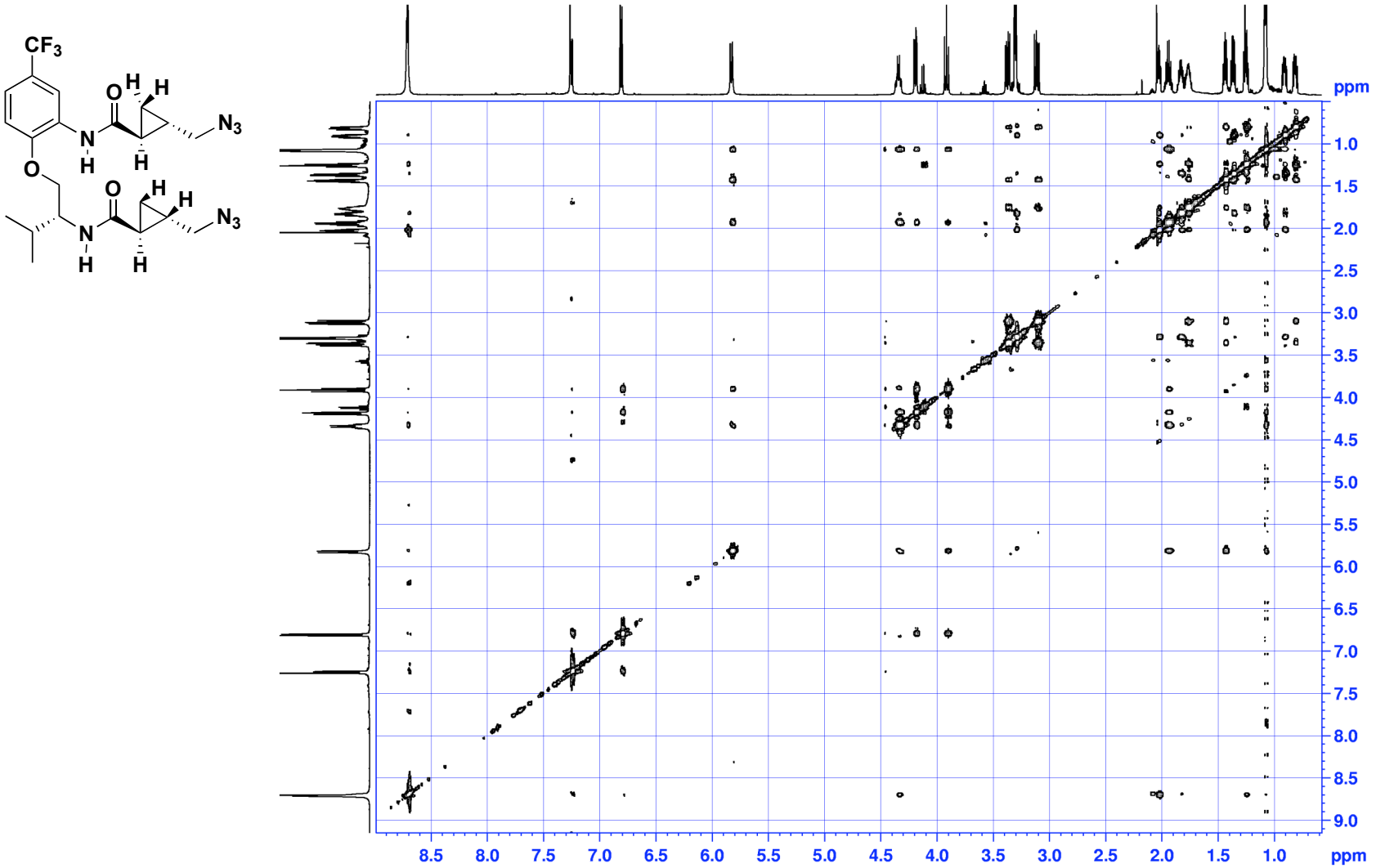


COSY
(500 MHz, d_1-chloroform)

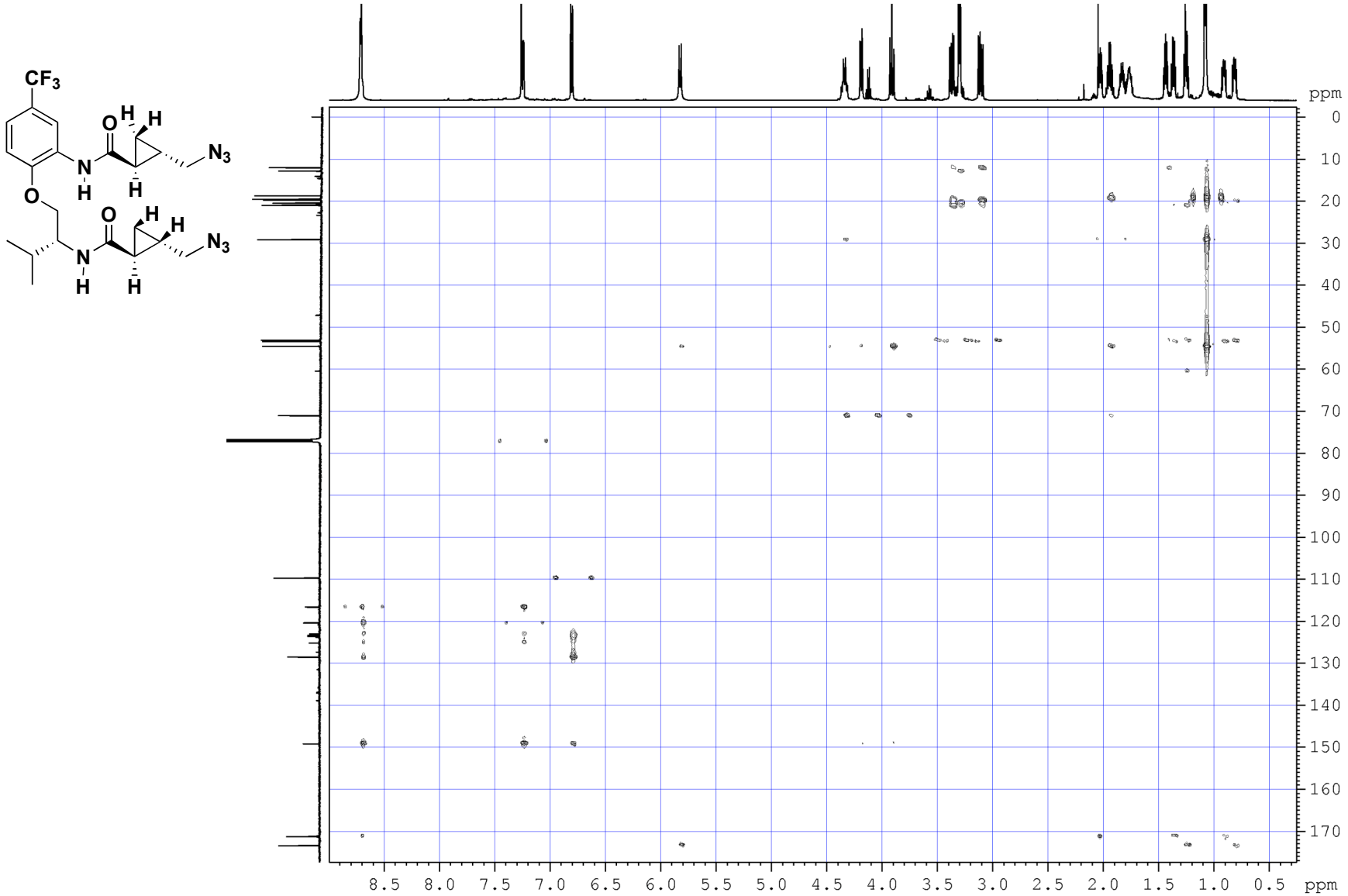




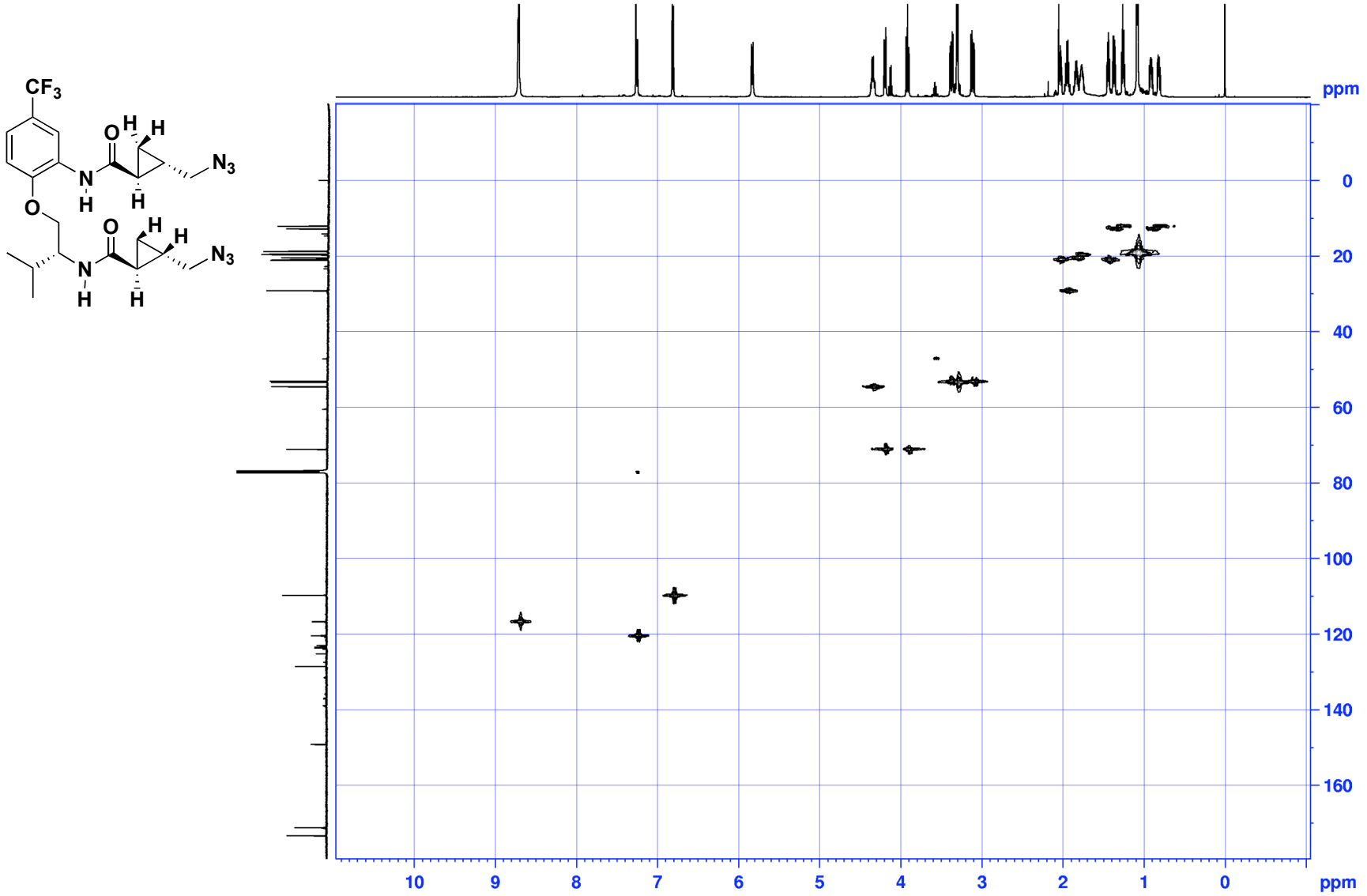
NOESY; 1s mixing time
(500 MHz, d_1-chloroform)



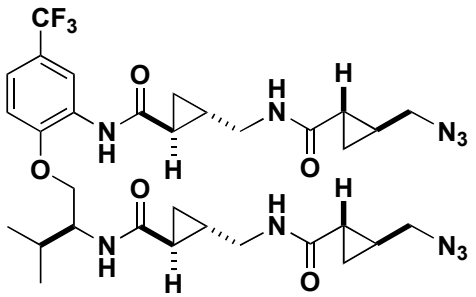
HMBC
(500 MHz, d_1-chloroform)

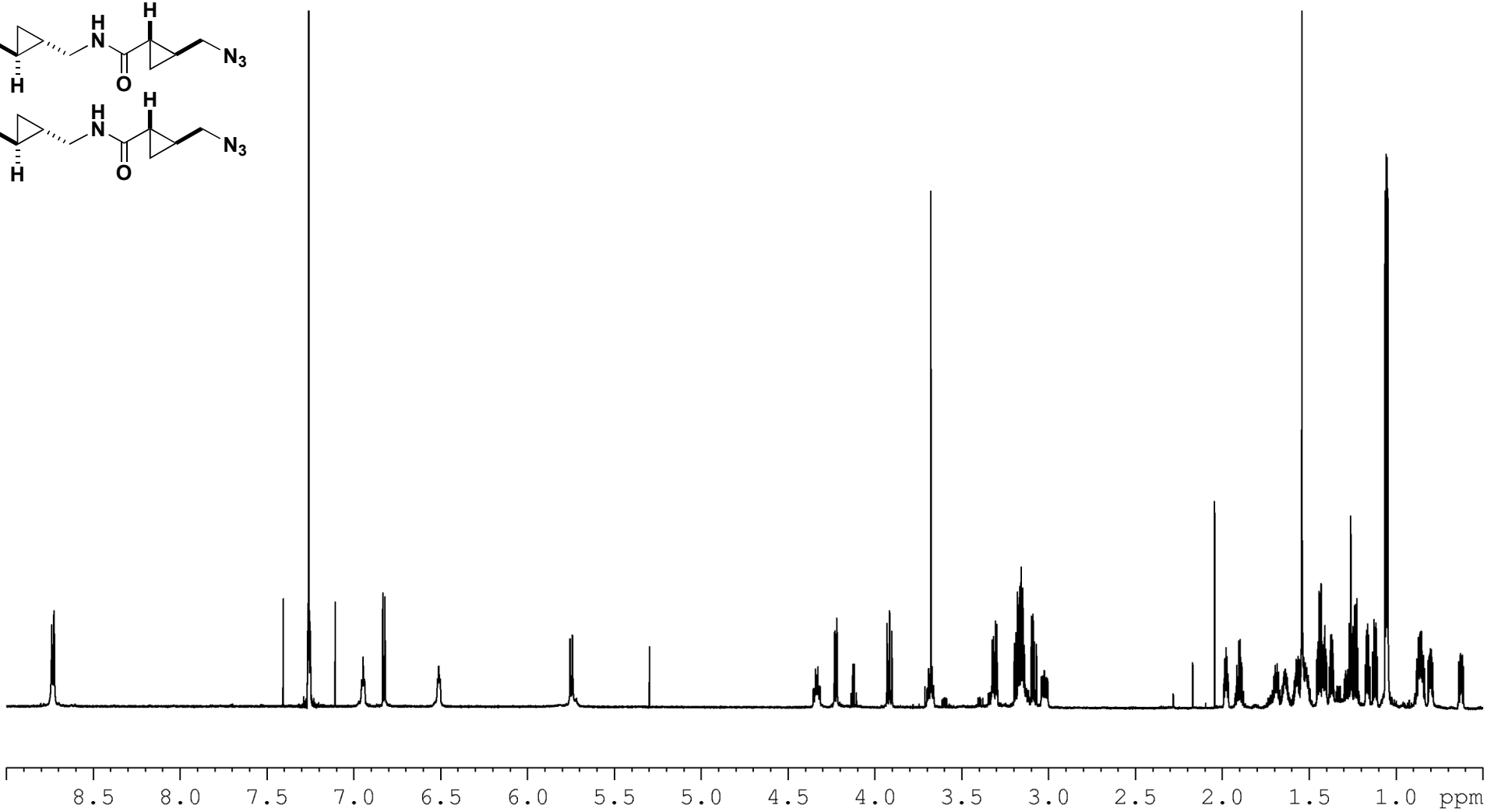


HMQC
(500 MHz, d_1-chloroform)

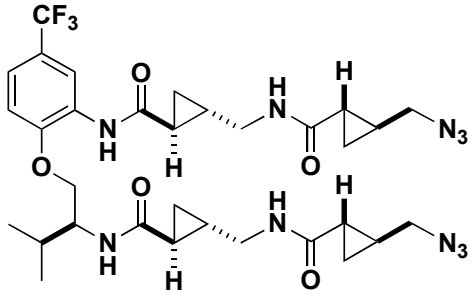


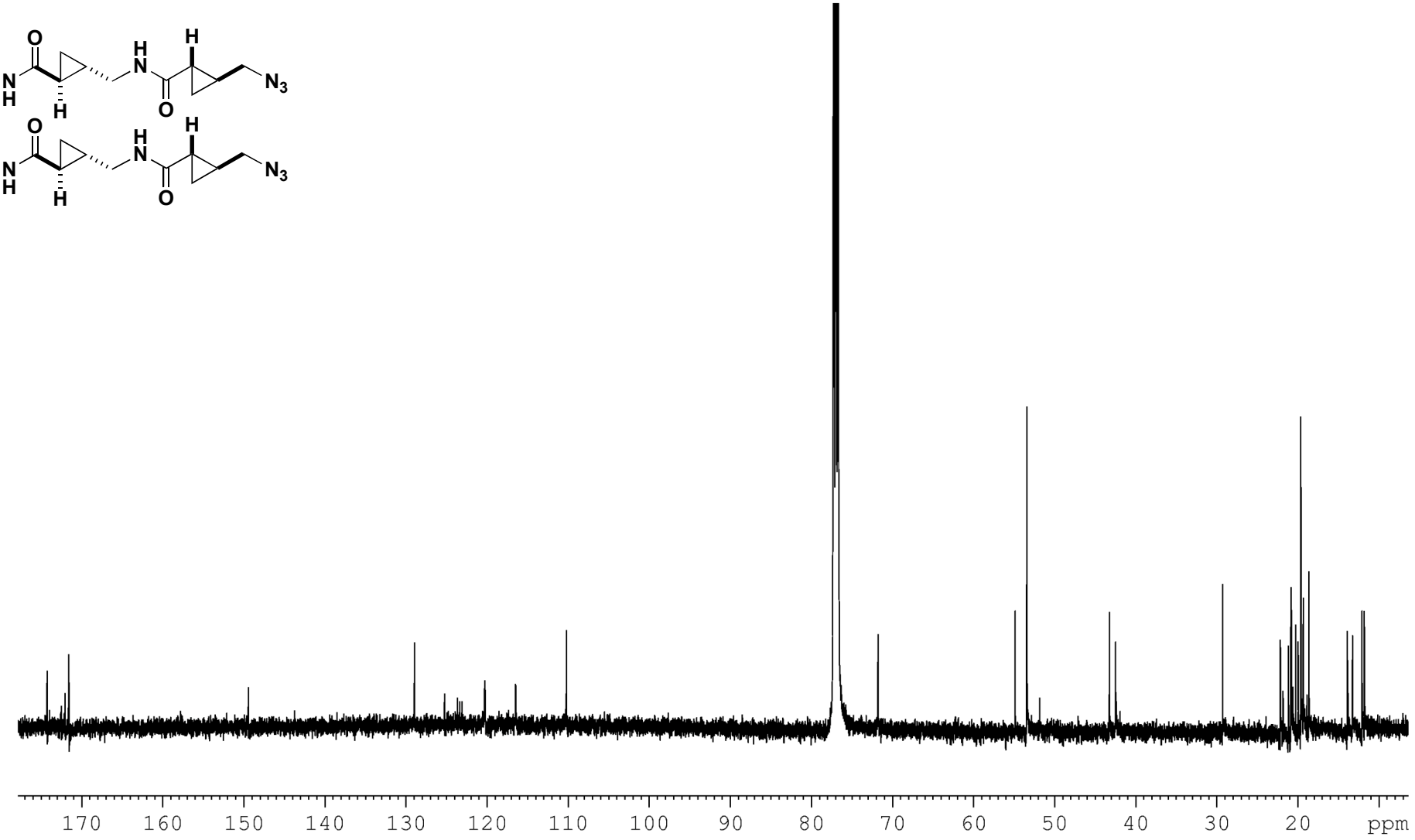
δ_H (700 MHz, d_1-chloroform)



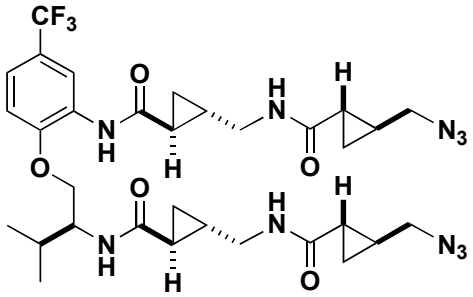


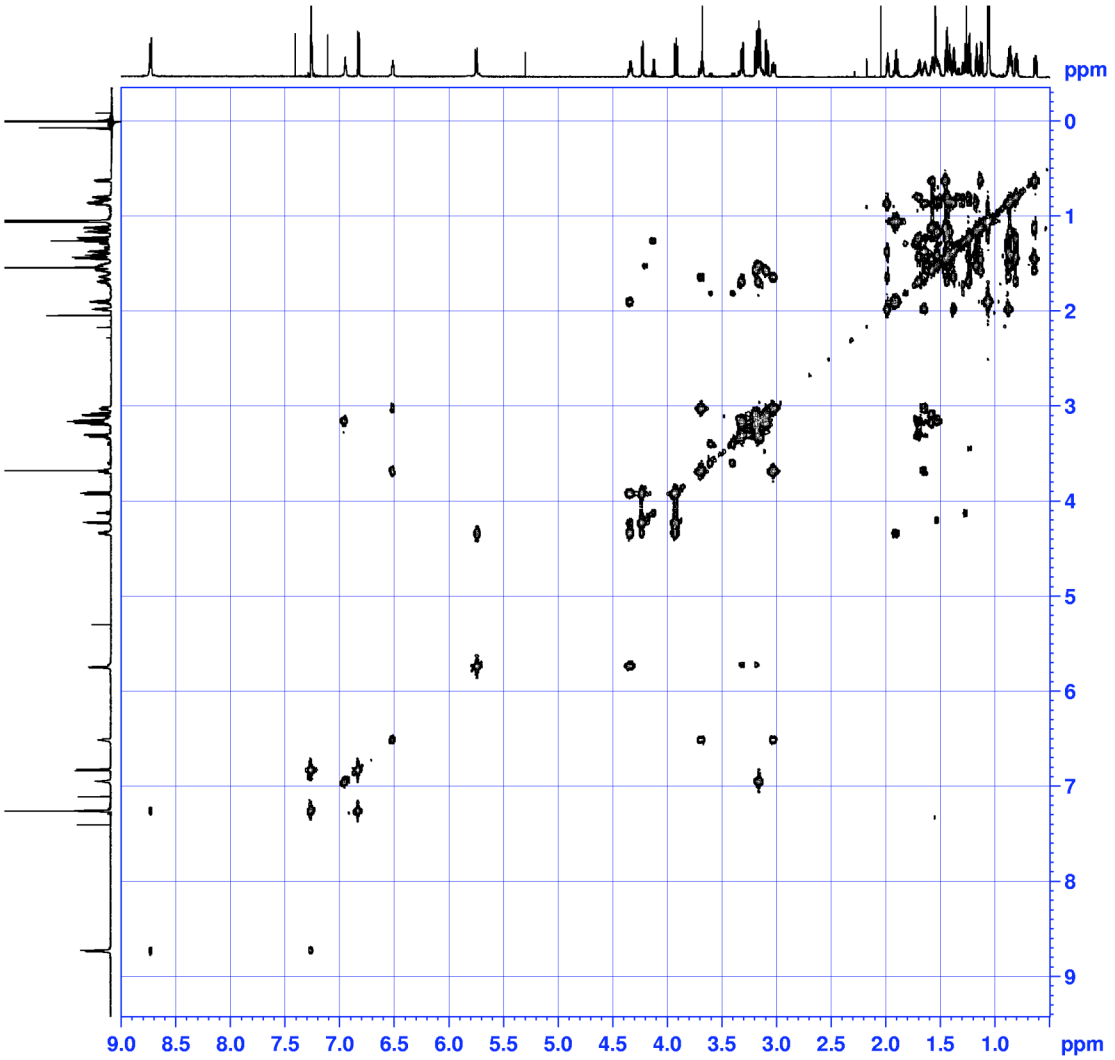
δ_C (125 MHz, d_1-chloroform)



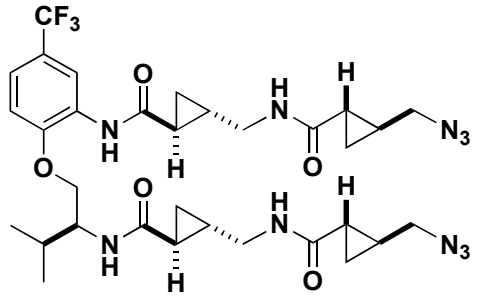


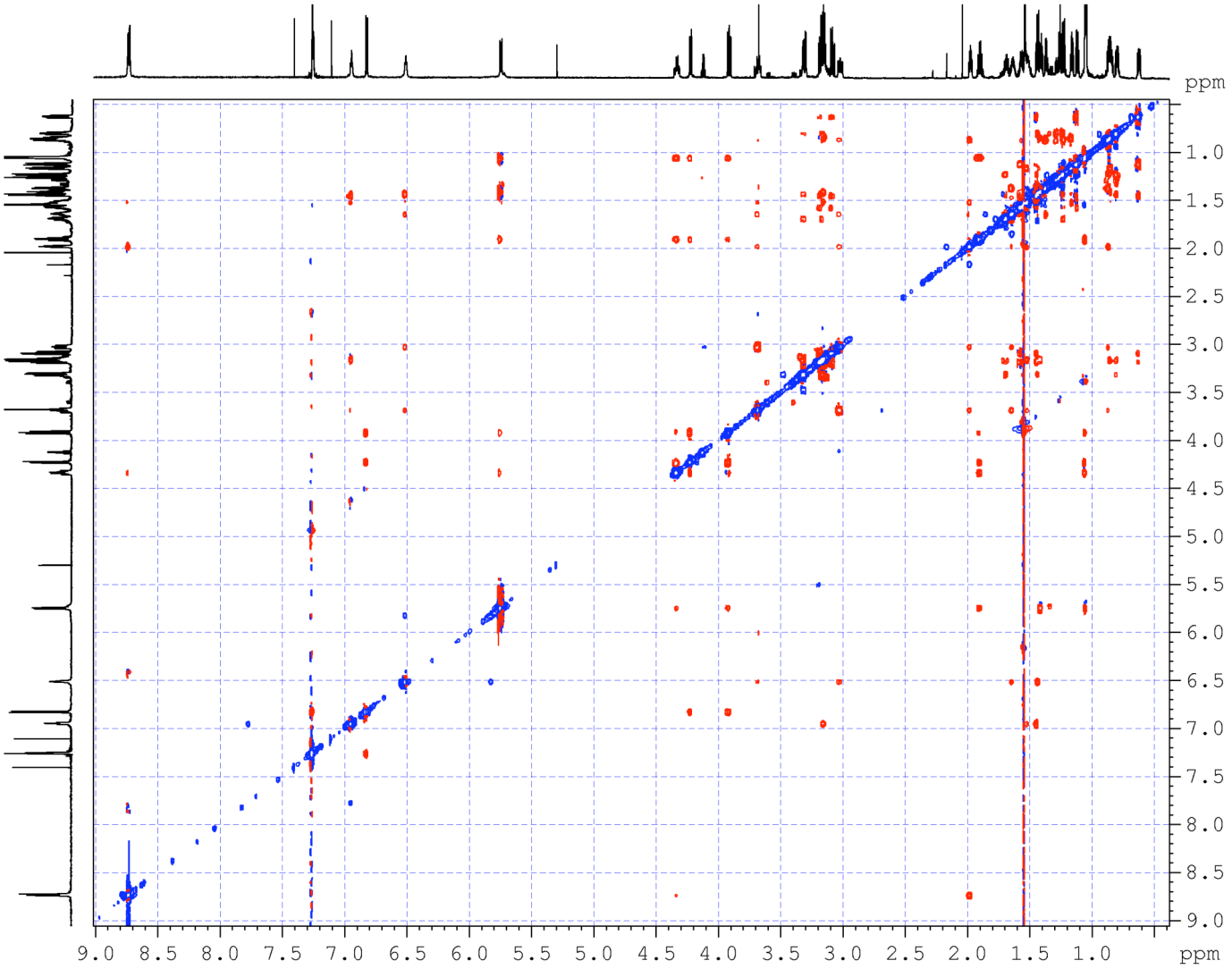
COSY
(700 MHz, d_1-chloroform)



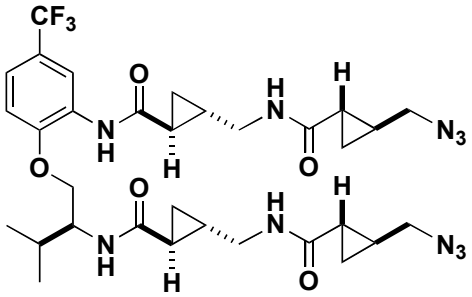


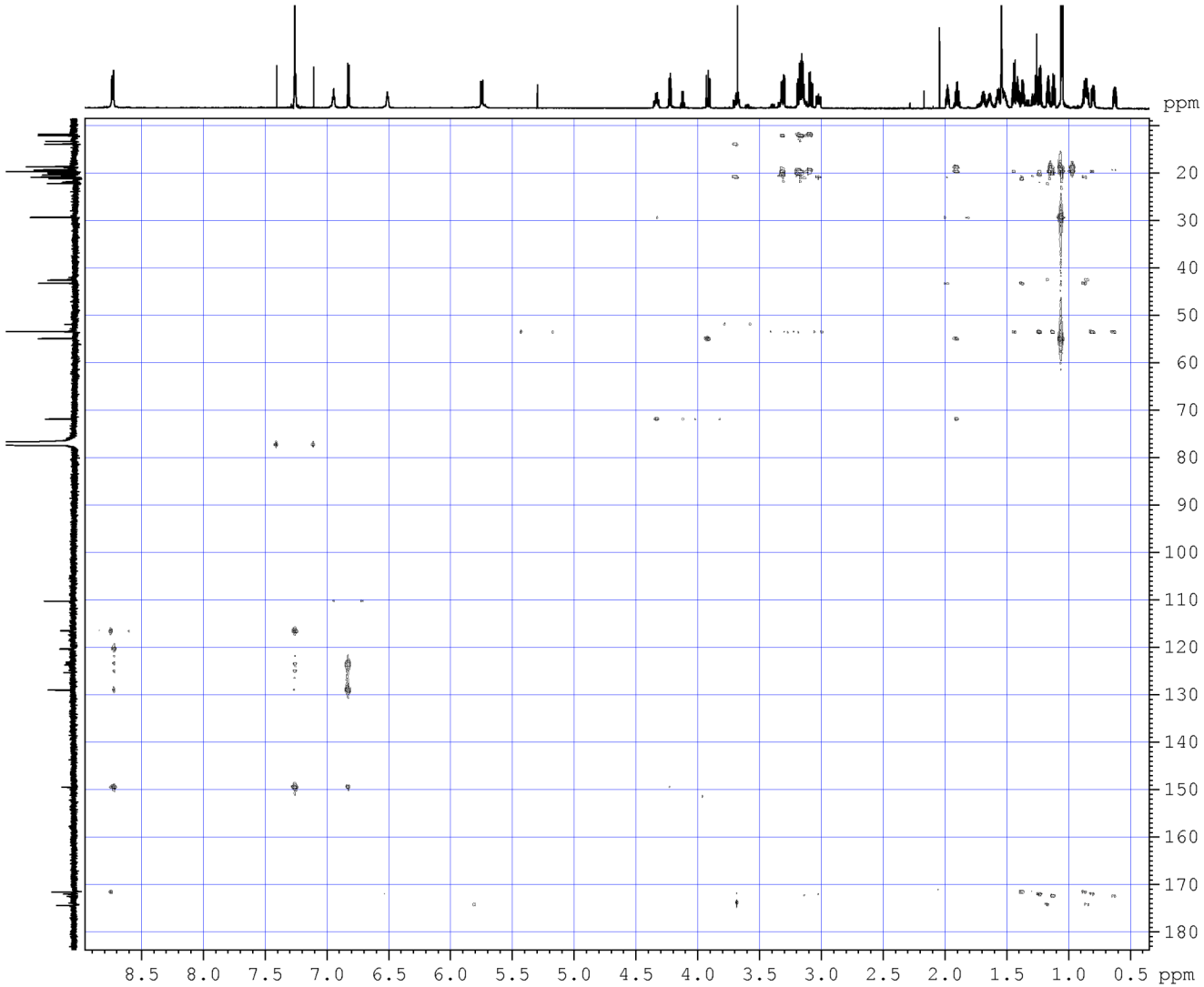
NOESY; 0.8 s mixing time
(700 MHz, d_1-chloroform)



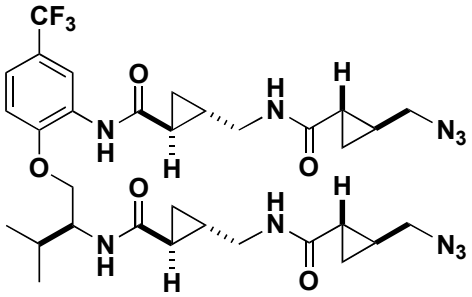


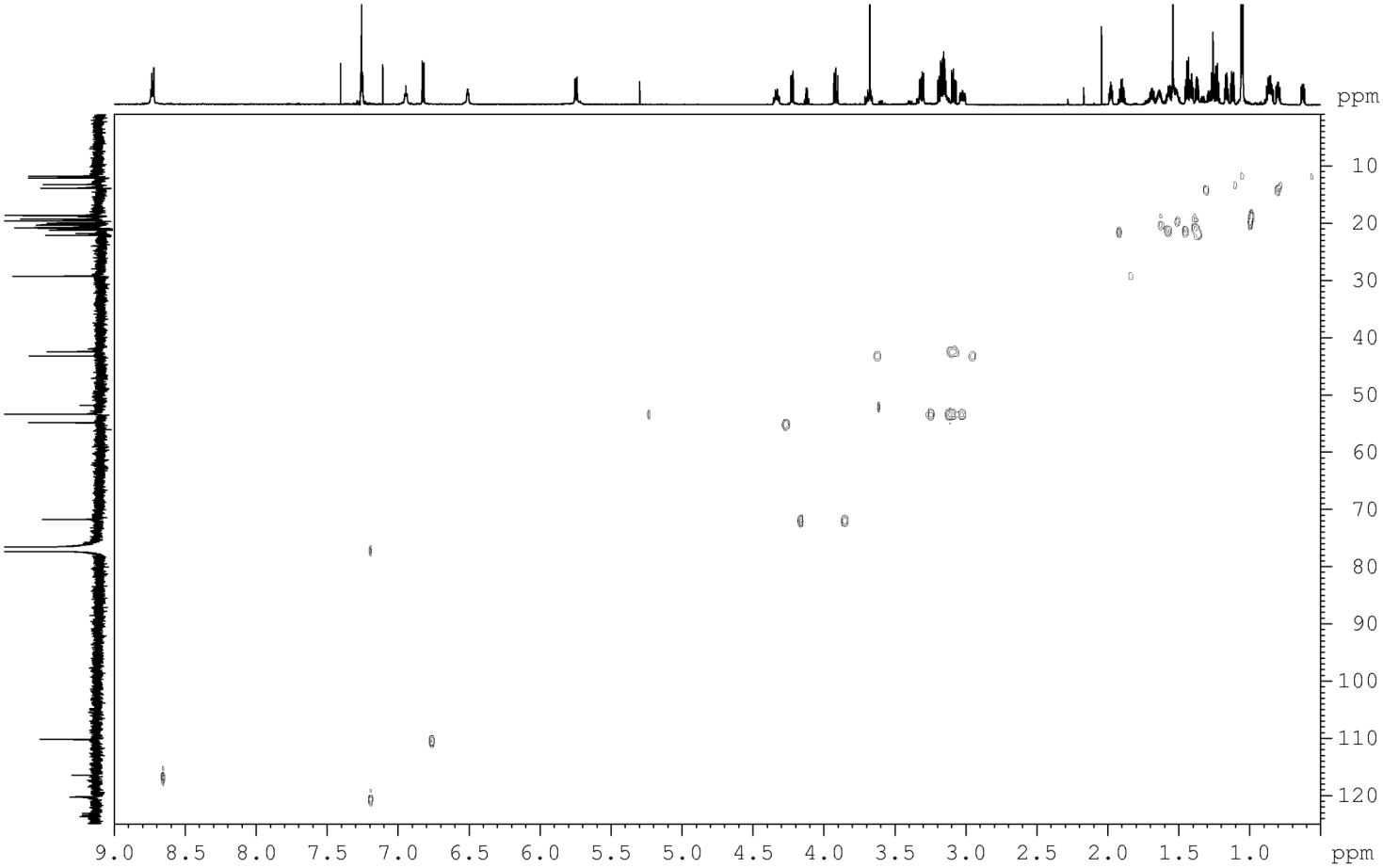
HMBC
(700 MHz, d_1-chloroform)



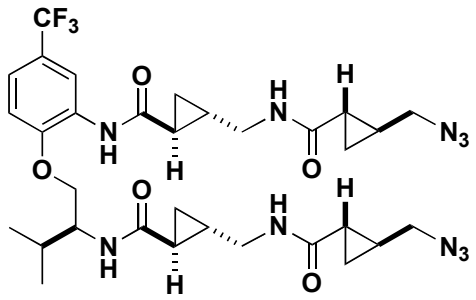


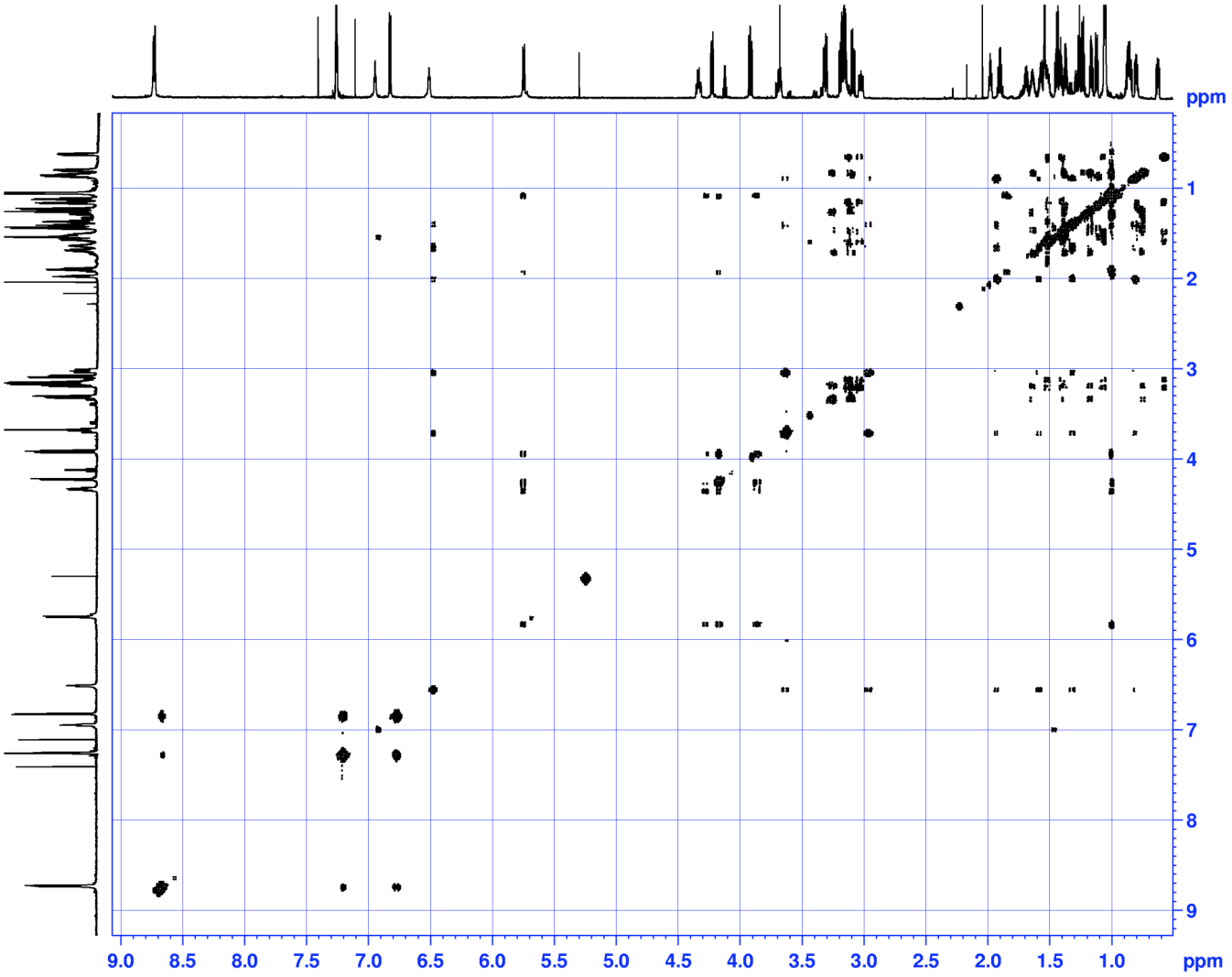
HSQC
(700 MHz, d_1-chloroform)



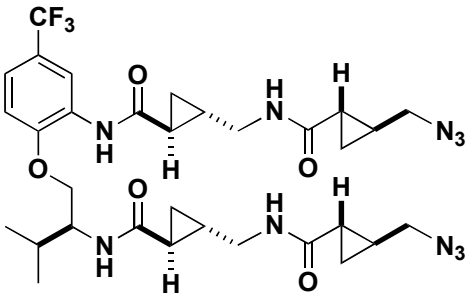


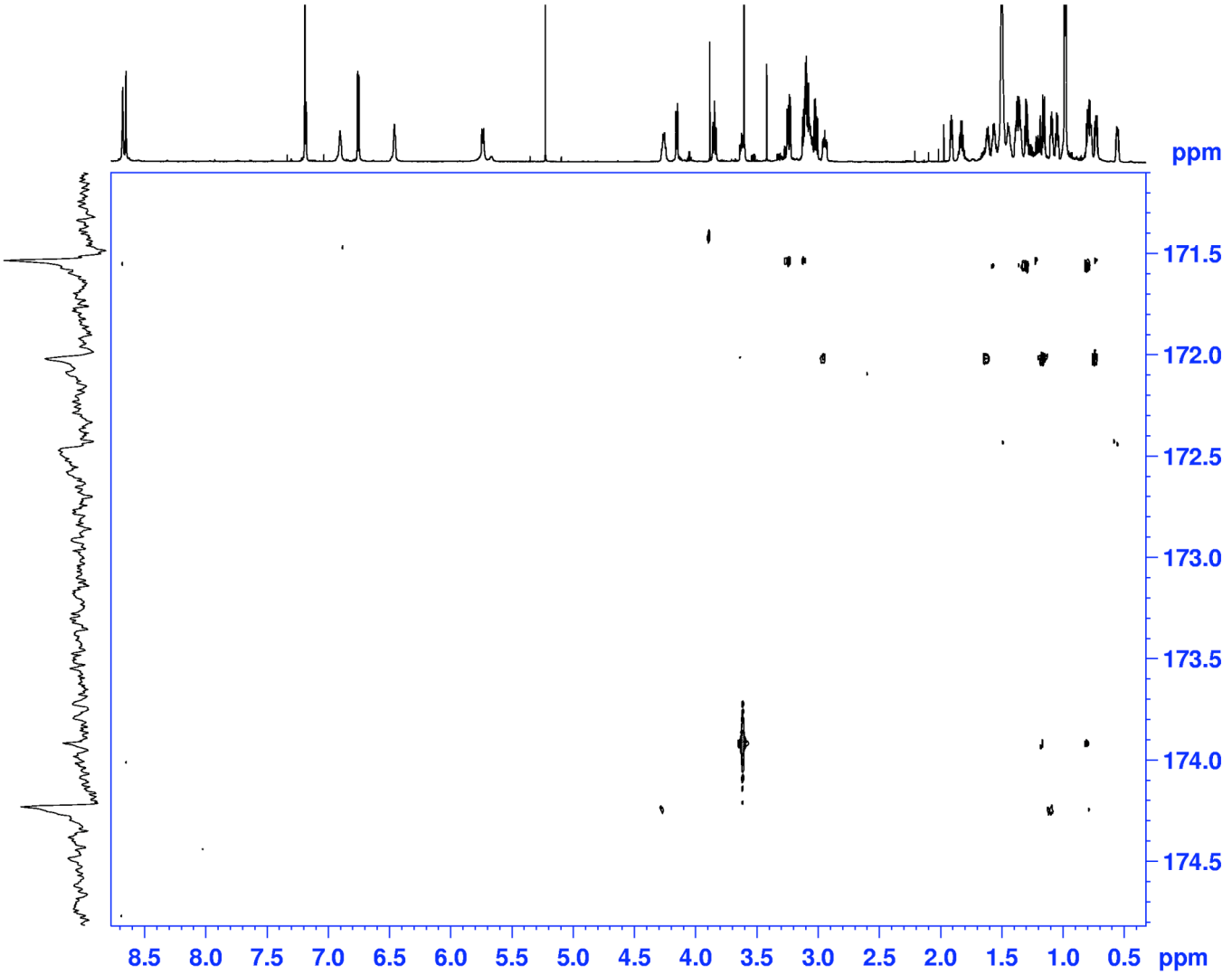
TOCSY
(700 MHz, d_1-chloroform)



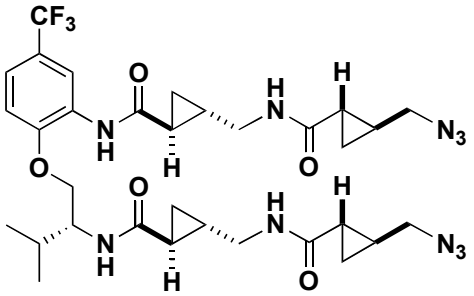


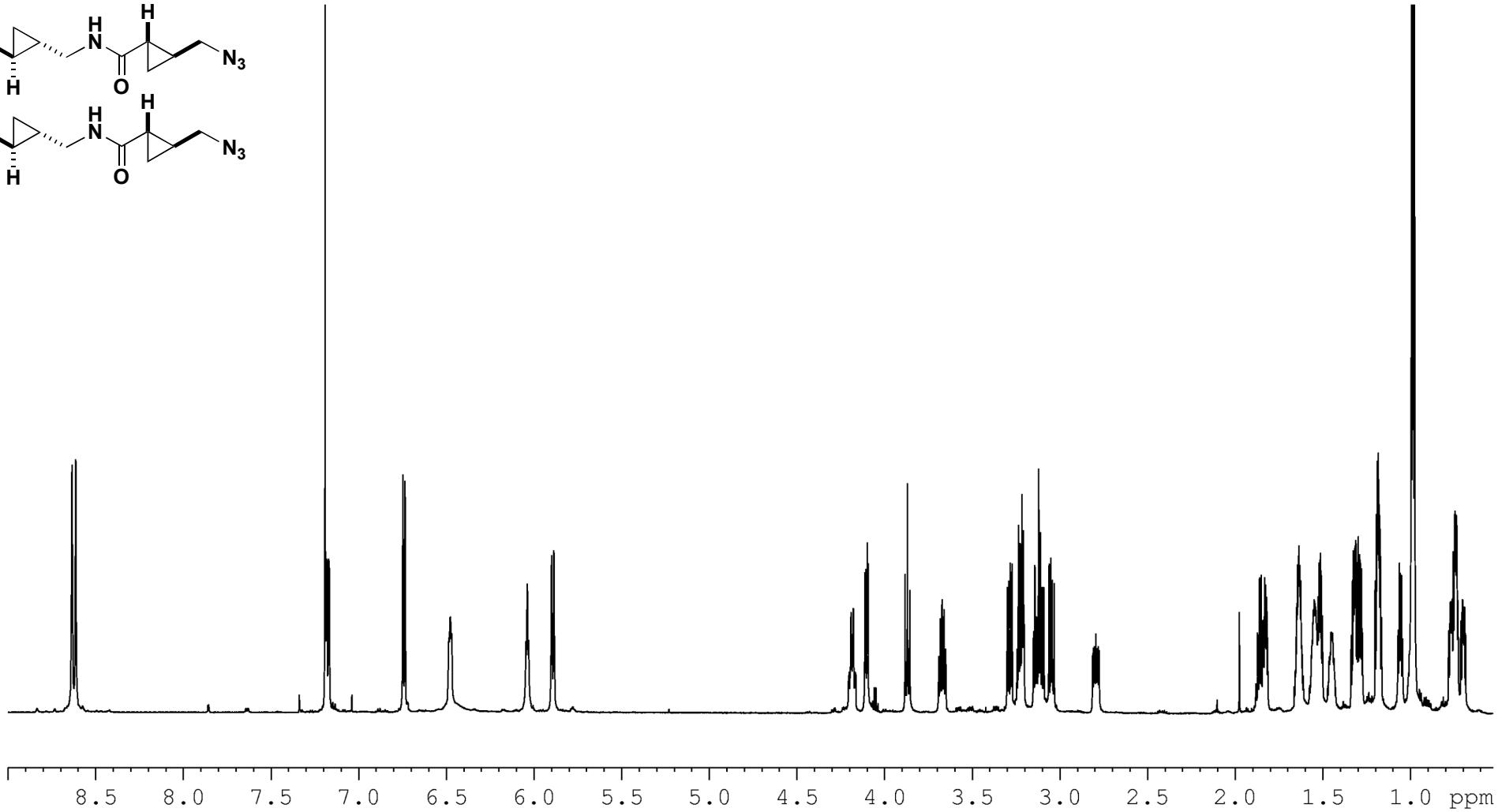
Constant time HMBC
(700 MHz, d_1-chloroform)



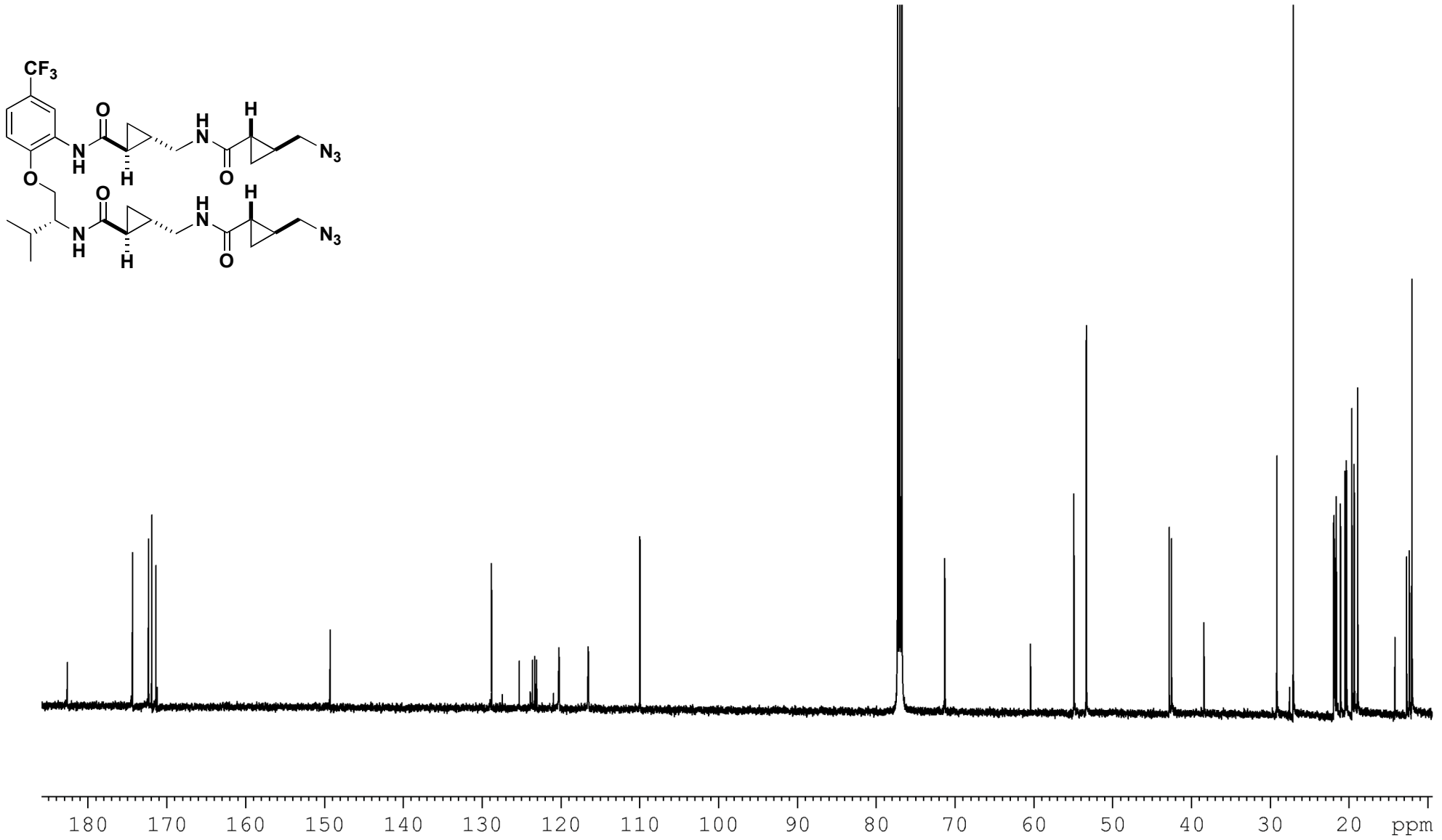


δ_H (700 MHz, d_1-chloroform)

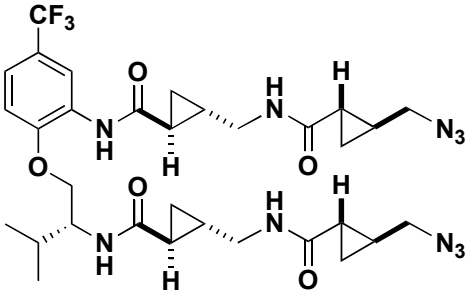


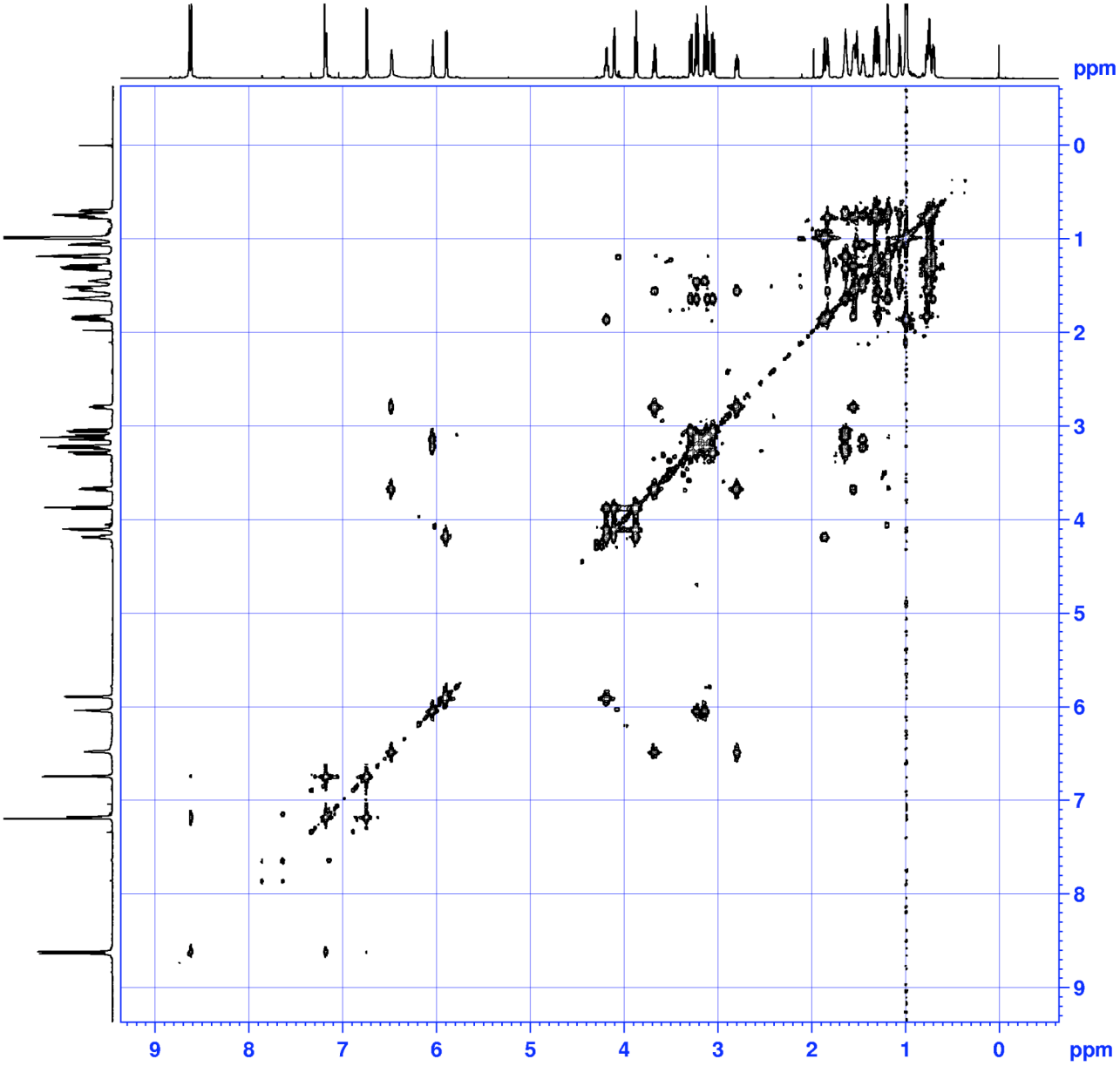


δ_C (125 MHz, d_1-chloroform)

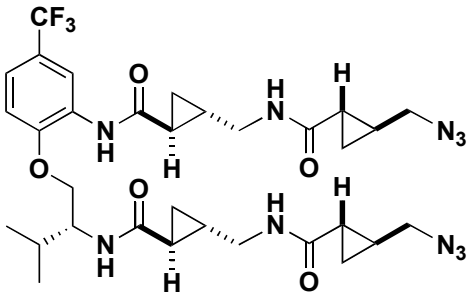


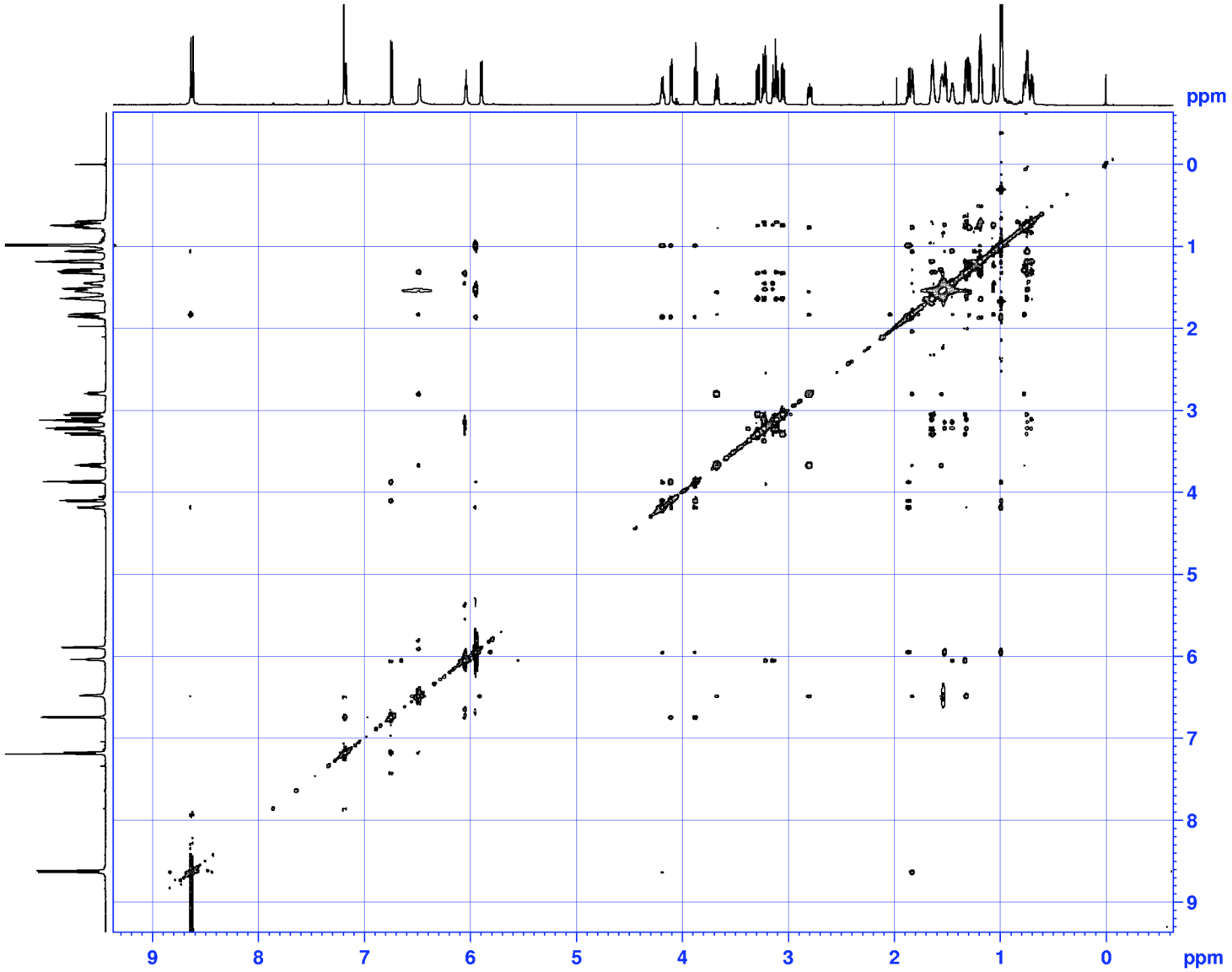
COSY
(700 MHz, d_1-chloroform)



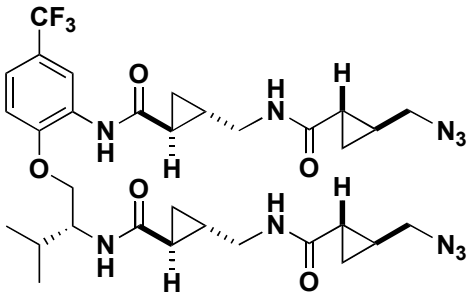


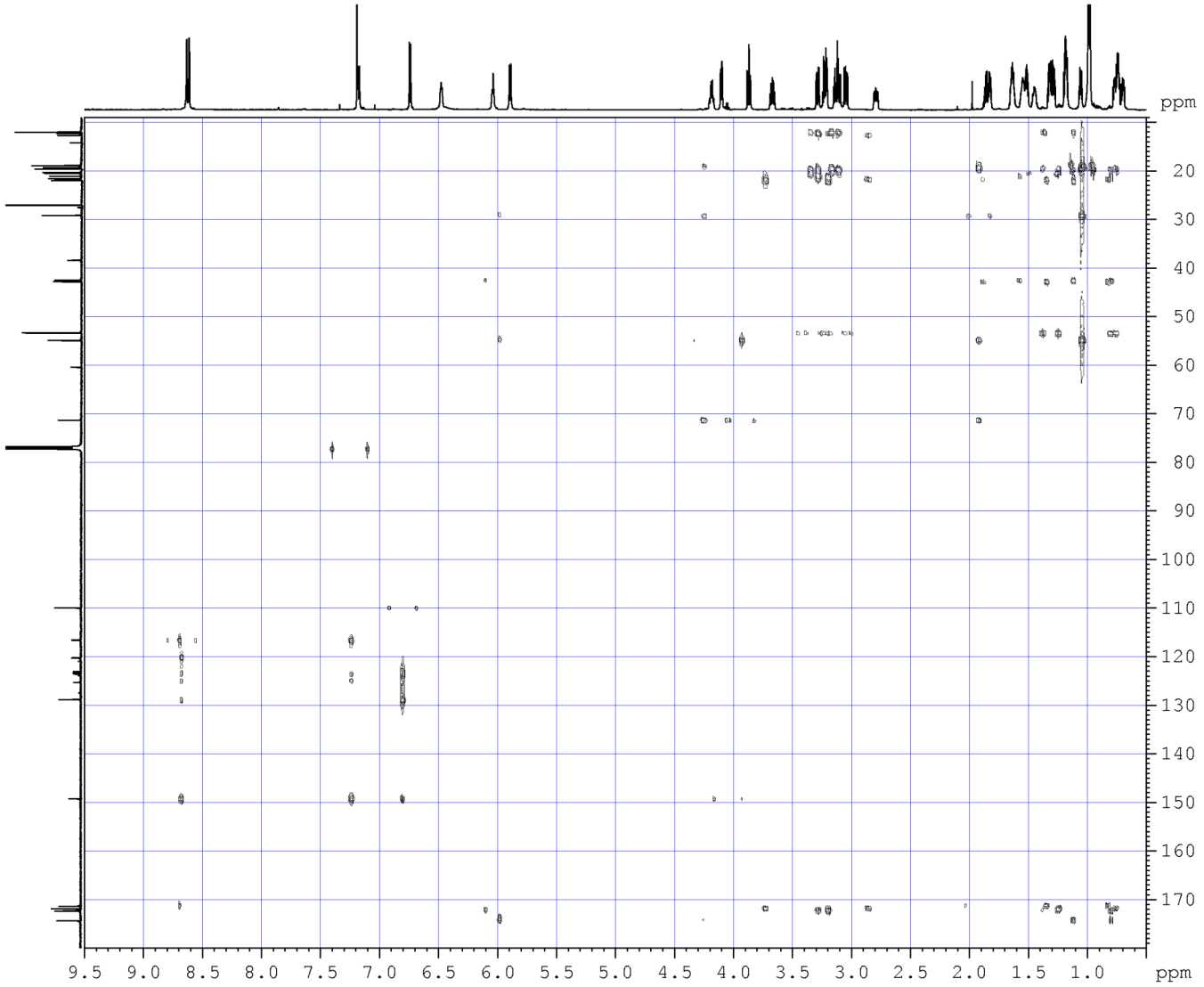
NOESY; 0.8 s mixing time
(700 MHz, d_1-chloroform)



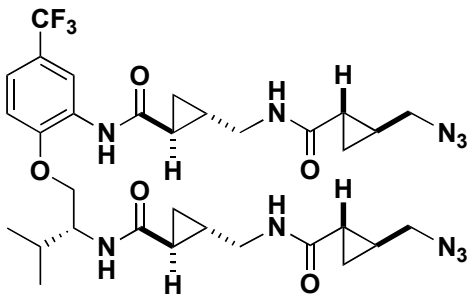


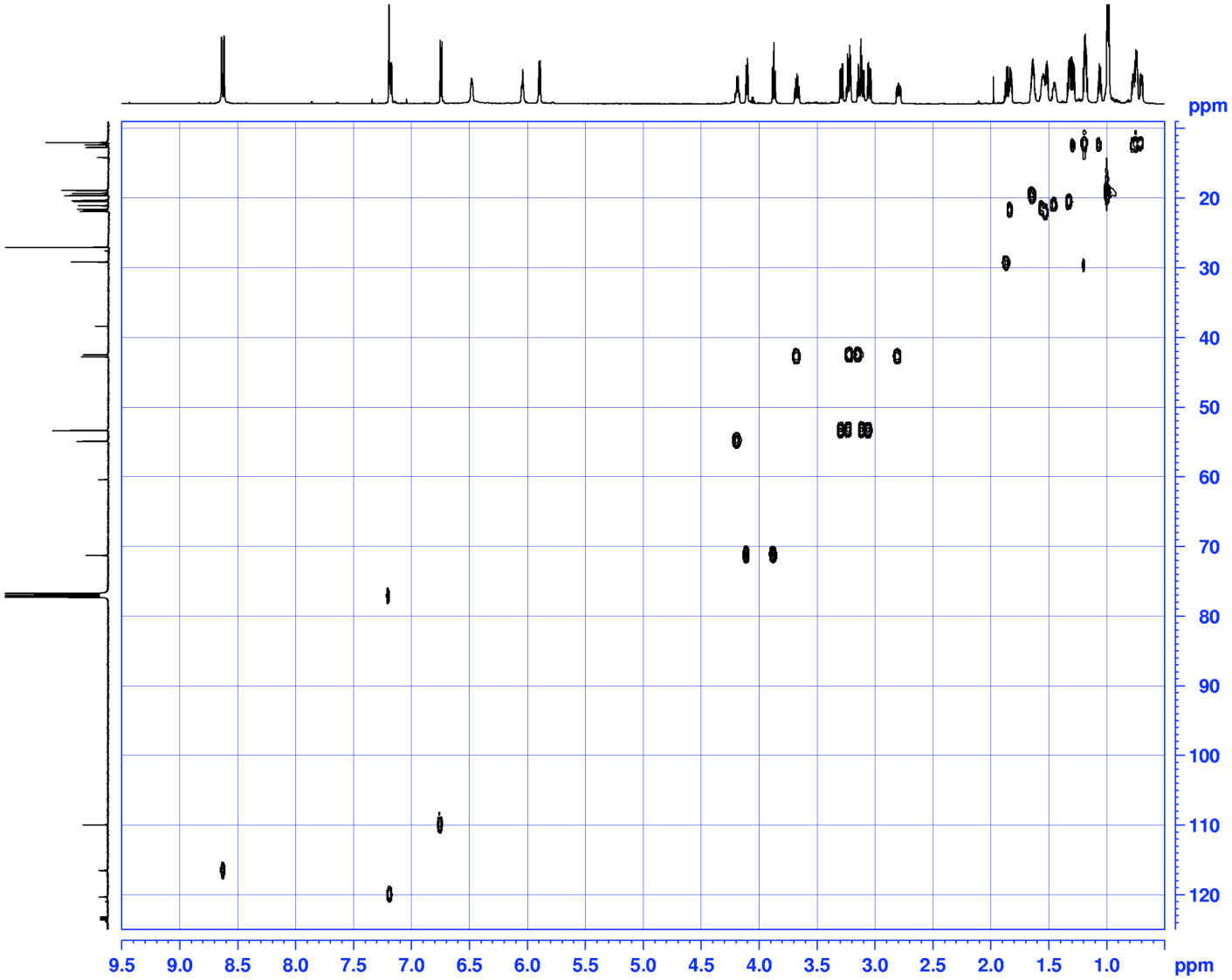
HMBC
(700 MHz, d_1-chloroform)



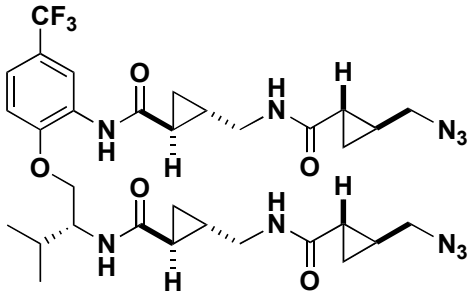


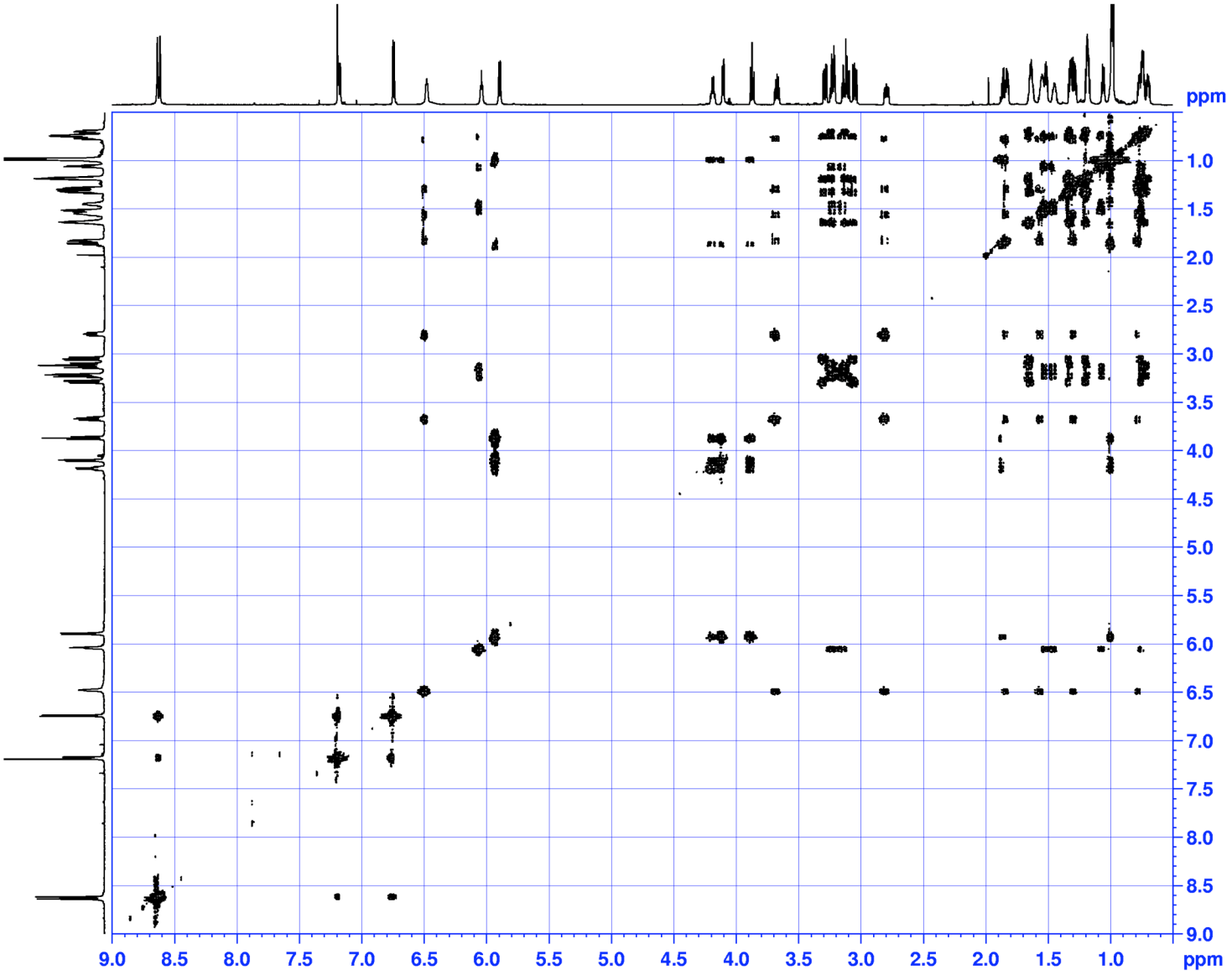
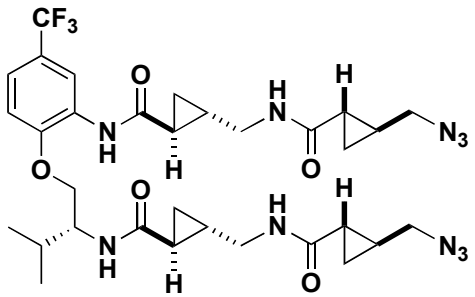
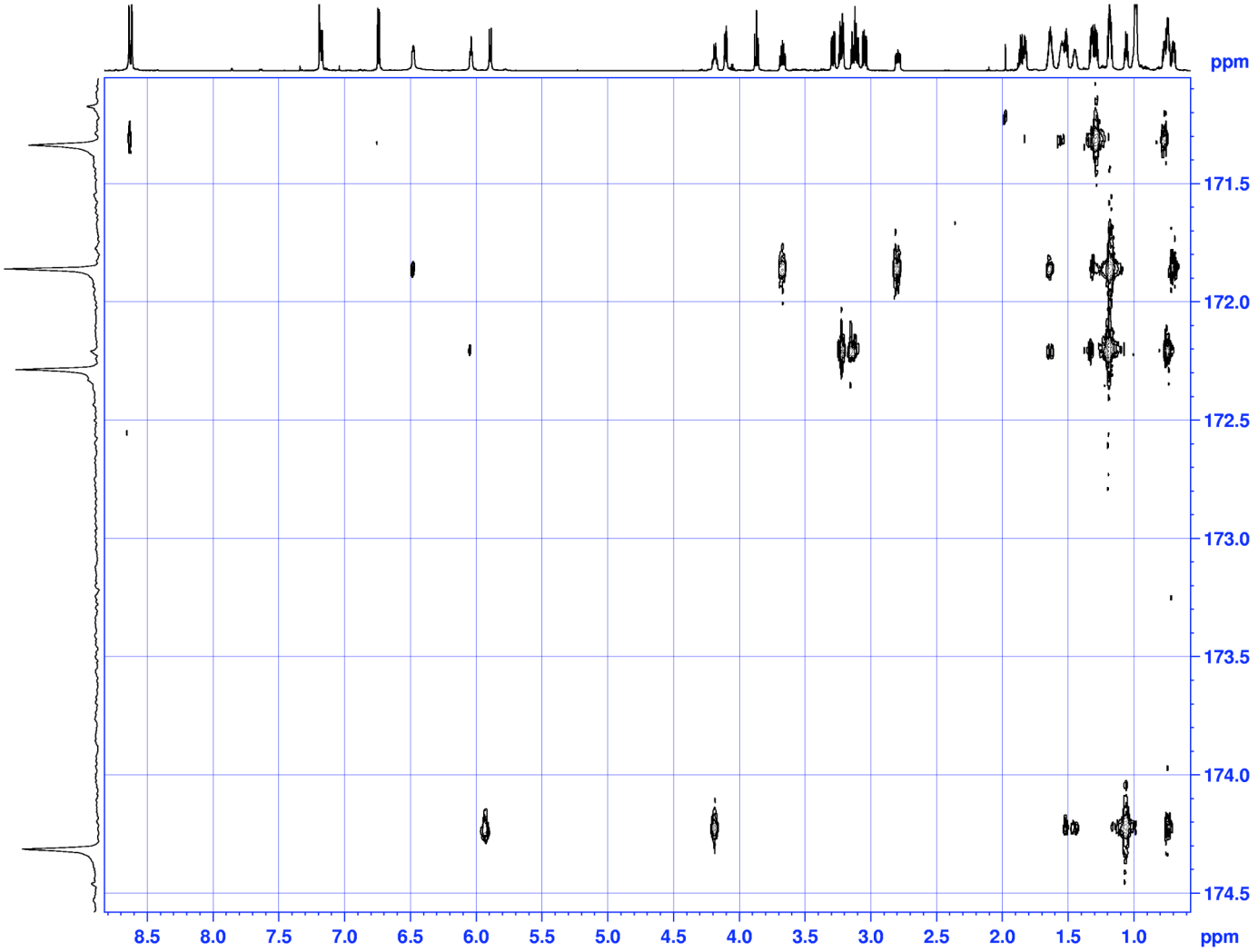
HSQC
(700 MHz, d_1-chloroform)





TOCSY
(700 MHz, d_1-chloroform)





Constant time HMBC
(700 MHz, d_1-chloroform)