SUPPLEMENTARY INFORMATION

Development of Fluorescent Aryltryptophans by Pd Mediated Cross-Coupling of Unprotected Halotryptophans in Water

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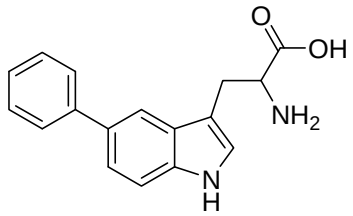
General: All chemicals were obtained commercially and used as received unless stated otherwise. TLC was performed on precoated aluminium plates (Silica Gel 60 F254, Merck). Compounds were visualized by exposure to UV light. NMR spectra were recorded at 298 K on a Varian Inova spectrometer at 500 MHz (1H). Chemical shifts (δ) are reported in ppm and referenced to methanol (^{1}H δ 3.33, ^{13}C δ 39.49). Coupling constants (*J*) are reported in Hz. Accurate electrospray ionisation mass spectra (HR ESI-MS) were obtained on a Finnigan MAT 900 XLT mass spectrometer at the EPSRC National Mass Spectrometry Service Centre, Swansea.

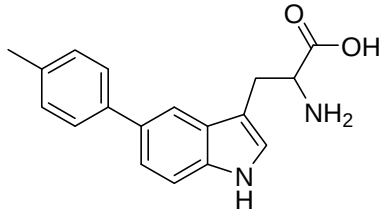
General procedure for the synthesis of aryltryptophans: L-Halotryptophan (0.035mmol), Na_2Cl_4Pd (2.5 mol %), TPPTS (2.5 equiv. to Pd) or TXPTS (10 equiv. to Pd), K_2CO_3 (5 equiv.), and arylboronic acid (1.1 equiv.) were placed in a flask and purged with N_2. Degassed water (6 mL) was added via a syringe, and the reaction was stirred at 80 °C under N_2 for the given time. Upon completion, the aqueous reaction was diluted with H_2O (10 mL) and the pH adjusted to 7 using 10% HCl. The solution was washed with ethyl aceteate (2 × 10 mL) and the aqueous layer was collected and evaporated to dryness. The crude residue was passed through a 0.22μm teflon filter and purified by reverse phase HPLC. Analytical chromatograhy (HPLC) was carried out on an Gilson 800 machine equipped with a Phenomex Synergi Polar-RP80A column (25cm ×15.00 mm, particle size 4μm); gradient: MeOH against 0.1% TFA in Water; detection (diode array detector): 254 / 280 nm.

5-Phenyl tryptophan (3a):



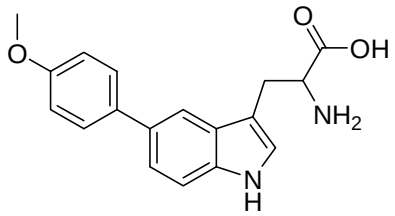
7.62 mg (78% yield using TPPTS) and 8.9 mg (90% yield using TXPTS), ^{1}H NMR (CD_3OD, 500 MHz) δ = 3.36 (dd, 1H, *J*= 7.5 Hz, 15.5 Hz), 3.50 (dd, 1H, *J* = 5.0 Hz, 15.5 Hz), 4.23 (dd, 1H, *J* = 5.0 Hz, 7.5 Hz), 7.21 (s, 1H), 7.24 (tt, *J* = 1.0 Hz, 2.5 Hz, 7.5 Hz), 7.36-7.43 (m, 4H), 7.62 (dd, 2H, *J* = 1.0 Hz, 7.5 Hz), 7.81 (s, 1H): ^{13}C NMR (CD_3OD, 125 MHz) δ = 27.5, 54.6, 108.3, 112.9, 117.4, 112.6, 126.3, 127.2, 128.2, 128.8, 129.6, 134.1, 137.8, 143.9, 171.9: HRMS (ESI) *m/z* 281.1288 $[M+H]^+$ (Calcd. For $C_{17}H_{17}O_2N_2$ 281.1285).

5-Tolyl tryptophan (3b):



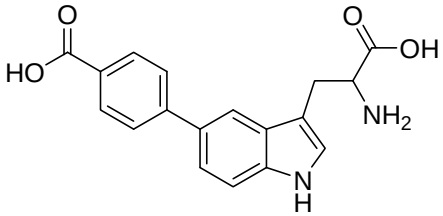
9.85 mg (90% yield), ^{1}H NMR (CD_3OD, 500 MHz) δ = 2.33, (s, 3H), 3.36 (dd, 1H, *J* = 7.5 Hz, 15.5 Hz), 3.48 (dd, 1H, *J* = 5.0 Hz, 15.5 Hz), 4.24 (dd, 1H, *J* = 5.0 Hz, 7.5 Hz), 7.20 (t, 3H, *J* = 11 Hz), 7.37 (dd, 1H, *J* = 1.5 Hz, 8.5 Hz), 7.40 (d, 1H, *J* = 8.5 Hz), 7.50 (d, 2H, *J* = 8.5 Hz), 7.77 (s, 1H): ^{13}C NMR (CD_3OD, 125 MHz) δ = 21.0, 27.5, 54.5, 108.2, 112.8, 117.1, 122.5, 126.2, 128.0, 128.8, 130.3, 130.6, 134.0, 136.9, 137.7, 141.0, 171.8: HRMS (ESI) *m*/*z* 295.1444 $[M+H]^+$ (Calcd. For $C_{18}H_{19}O_2N_2$ 295.1441).

5-(4-Methoxyphenyl) tryptophan (3c):



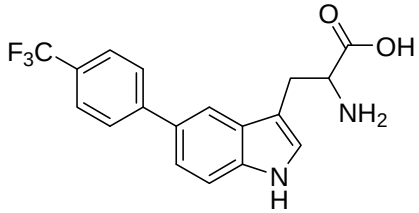
9.55 mg (87% yield), ^{1}H NMR (CD_3OD, 500 MHz) δ = 3.35 (dd, 1H, *J* = 7.5 Hz, 15.5 Hz), 3.48 (dd, 1H, *J* = 4.5 Hz, 15.5 Hz), 3.79 (s, 3H), 4.25 (dd, 1H, *J* = 5.0 Hz, 7.5 Hz), 6.94 (d, 2H, *J* = 7.0 Hz), 7.19 (s, 1H), 7.35 (dd, 1H, *J* = 1.5 Hz, 8.5 Hz), 7.39 (dd, 1H, *J* = 1.0 Hz, 8.5 Hz), 7.55 (d, 2H, *J* = 8.5 Hz), 7.43 (s, 1H): ^{13}C NMR (CD_3OD, 125 MHz) δ = 27.5, 54.5, 55.7, 108.1, 112.8, 115.0, 116.8, 122.4, 126.2, 128.8, 129.1, 133.9, 136.5, 137.5, 160.0, 171.8: HRMS (ESI) *m*/*z* 311.1389 $[M+H]^+$ (Calcd. For $C_{18}H_{19}O_3N_2$ 311.1390).

5-(4-Carboxyphenyl) tryptophan (3d):



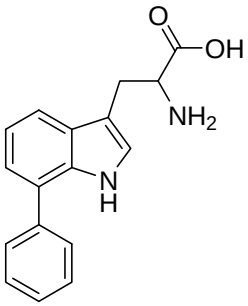
7.80 mg (68% yield), ^{1}H NMR (CD_3OD, 500 MHz) δ = 3.40 (dd, 1H, *J* = 7.0 Hz, 15.0 Hz), 3.50 (dd, 1H, *J* = 5.0 Hz, 15.5 Hz), 4.27 (dd, 1H, *J* = 5.0 Hz, 7.5 Hz), 7.24 (s, 1H), 7.45-7.49 (m, 2H), 7.76 (d, 2H, *J* = 8.5 Hz), 7.90 (s, 1H), 8.05 (d, 2H, *J* = 8.5 Hz): ^{13}C NMR (CD_3OD, 125 MHz) δ = 27.4, 54.6, 108.5, 113.1, 117.9, 122.6, 126.7, 128.0, 128.9, 129.5, 131.2, 132.7, 138.4, 148.6, 170.0, 171.7: HRMS (ESI) *m*/*z* 325.1185 $[M+H]^+$ (Calcd. For $C_{18}H_{17}O_4N_2$ 325.1183).

5-(4-Trifluoromethylphenyl) tryptophan (3e):



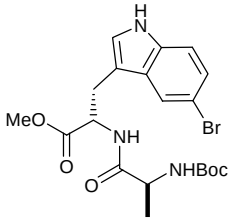
4.3 mg (35% yield), ^{1}H NMR (CD_3OD, 500 MHz) δ = 3.33 (dd, 1H, *J* = 8.0 Hz, 15.5 Hz), 3.50 (dd, 1H, *J* = 5.0 Hz, 15.5 Hz), 4.16 (dd, 1H, *J* = 5.0 Hz, 7.5 Hz), 7.24 (s, 1H), 7.46 (d, 2H, *J* = 1.0 Hz), 7.67 (d, 2H, *J* = 8.0 Hz), 7.83 (d, 2H, *J* = 8.0 Hz), 7.93 (s, 1H): ^{13}C NMR (CD_3OD, 125 MHz) δ = 27.7, 55.0, 109.0, 113.1, 118.1, 122.4, 126.5, 126.7, 128.5, 129.0, 132.2, 138.4, 147.8, 172.4: HRMS (ESI) *m*/*z* 349.1157 $[M+H]^+$ (Calcd. For $C_{18}H_{16}O_2N_2F_3$ 349.1158).

7-Phenyl tryptophan (4):



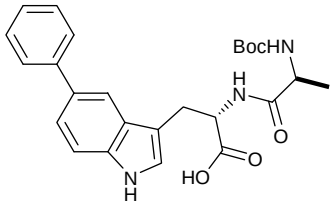
1.5 mg (15% yield using TPPTS), and 8.69 mg (88% yield using TXPTS), ^{1}H NMR (CD_3OD, 500 MHz) δ = 3.33 (dd(o), 1H, *J* = 10.0 Hz, 19.0 Hz), 3.50 (dd, 1H, *J* = 6.0 Hz, 19.0 Hz), 4.25 (dd, 1H, *J* = 6.5 Hz, 9.5 Hz), 7.15 (d, 2H, *J* = 5.5 Hz), 7.20 (s, 1H), 7.35 (t, 1H, *J* = 9.0 Hz), 7.47 (t, 2H, *J* = 9.0 Hz), 7.57-7.59 (m, 3H): ^{13}C NMR (CD_3OD, 125 MHz) δ = 27.6, 54.6, 108.2, 118.3, 120.9, 123.1, 127.5, 128.3, 129.3, 129.9, 130.2, 134.5, 140.5, 171.8: HRMS (ESI) *m*/*z* 281.1284 $[M+H]^+$ (Calcd. For $C_{17}H_{17}O_2N_2$ 281.1285).

***N*-Boc-L-Ala-5-Bromo-L-Trp methyl ester (5):**



58% yield, ^{1}H NMR (CD_3OD, 500 MHz) δ = 1.22 (d, 3H, *J* = 9.0 Hz), 1.37 (s, 9H), 3.17-3.20 (m, 2H), 3.61 (s, 3H), 4.02 (d, 1H, *J* = 8.5 Hz), 4.66 (q, 1H, *J* = 8.0 Hz, 8.5 Hz), 7.14 (d, 2H, *J* = 11.0 Hz), 7.20 (d, 1H, *J* = 11.0 Hz), 7.59 (s, 1H), 7.98 (brs, 1H, *J* = 8.5 Hz). MS (ESI) *m*/*z* 469 $[M+H]^+$.

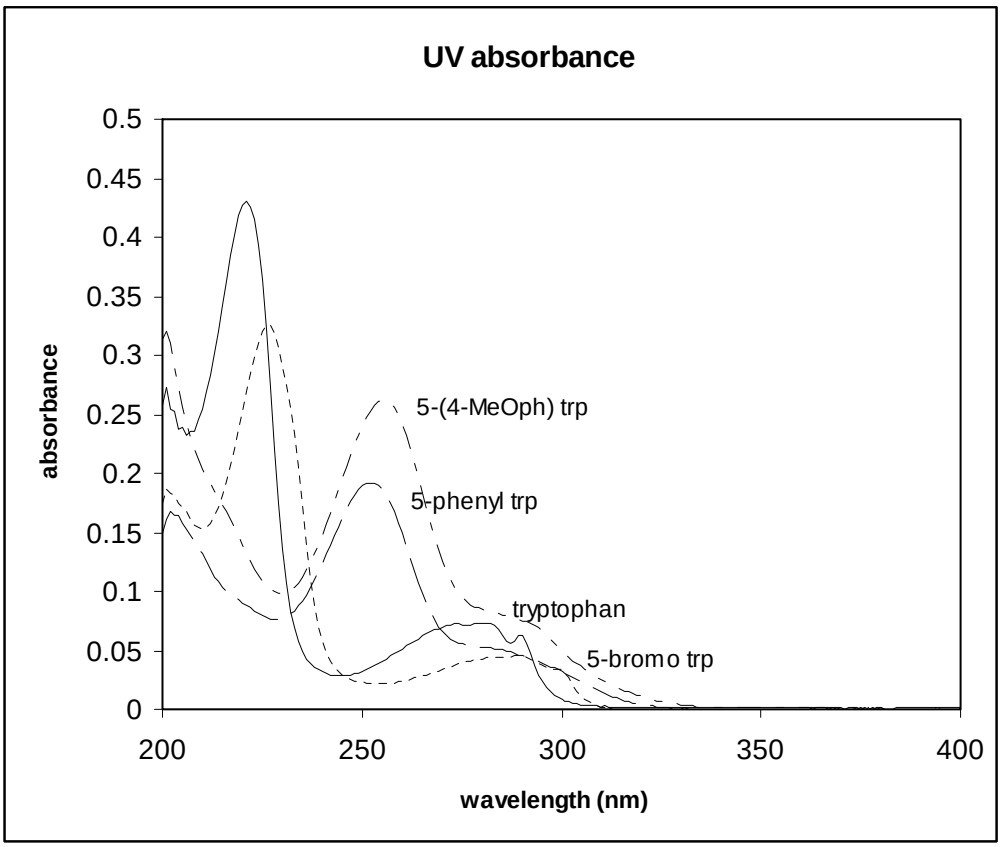
***N*-Boc-L-Ala-5-Phenyl-L-Trp (6):**



62%, ^{1}H NMR (CD_3OD, 500 MHz) δ = 1.17 (d, 3H, *J* = 10.0 Hz), 1.36 (s, 9H), 3.26(m (o), 2H), 4.01 (m, 1H), 4.71 (m, 1H), 7.13 (s, 1H), 7.22 (t, 1H, *J* = 10.0 Hz), 7.35-7.39 (m, 4H), 7.62 (d, 2H, *J* = 10.0 Hz), 7.76 (s, 1H): HRMS (ESI) *m*/*z* 452.2180 $[M+H]^+$ (Calcd. For $C_{25}H_{30}O_5N_3$ 452.2180).

UV absorbance spectra

UV absorbance spectra were recorded on a Perkin Elmer Lambda 25 UV/VIS spectrometer at room temperature. Sample concentration was 100 μM in methanol.



Fluorescence emission spectra

Fluorescence emission spectra were recorded on a Perkin Elmer LS-45 spectrometer at room temperature after excitation at the respective wavelength. Samples were measured in a quartz micro fluorescence cell (path length 1.0 cm) at a concentration of 100 μM (unless otherwise stated) in methanol or water.

Samples:

3a: 5-phenyl tryptophan
3c: 5-(4-methoxyphenyl) tryptophan
3d: 5-(4-carboxyphenyl) tryptophan
4: 7-phenyl tryptophan

Figure S1

Solvent: water
Excitation wavelength λ_{ex}: 254 nm

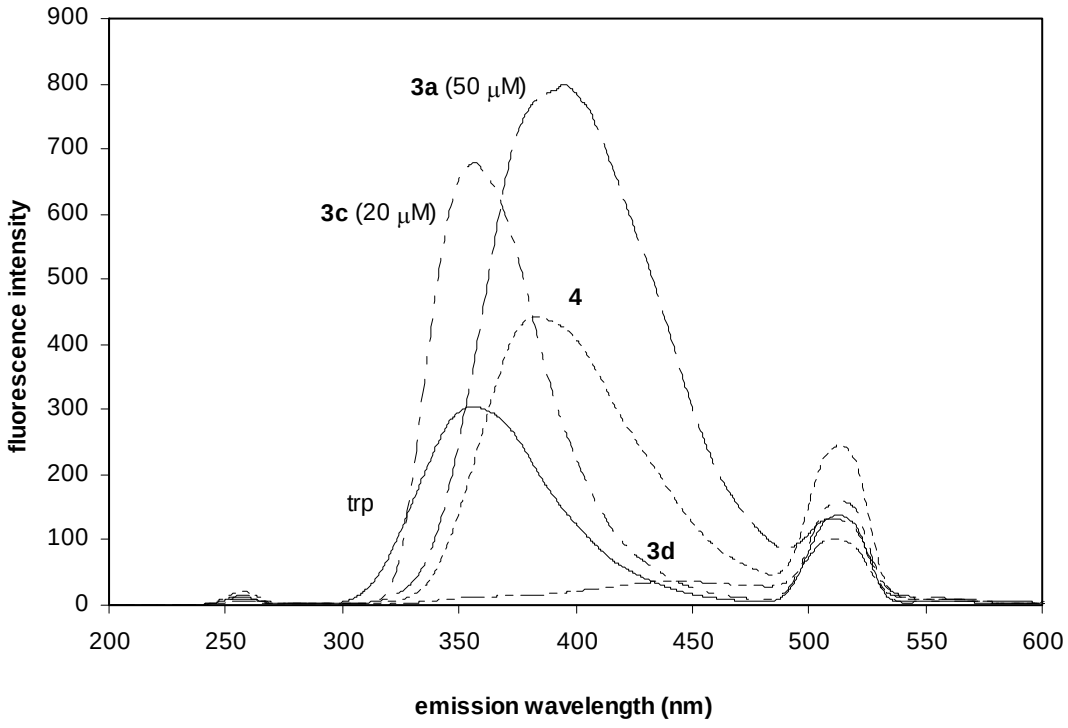


Figure S2

Solvent: water
Excitation wavelength λ_{ex}: 295 nm

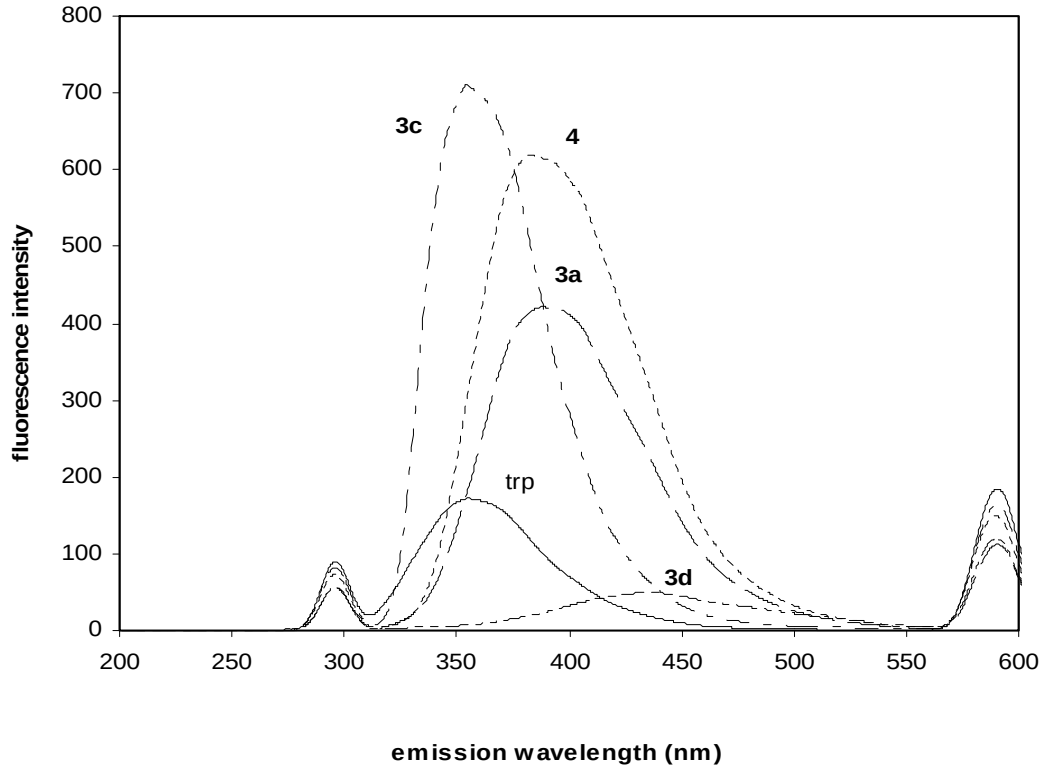
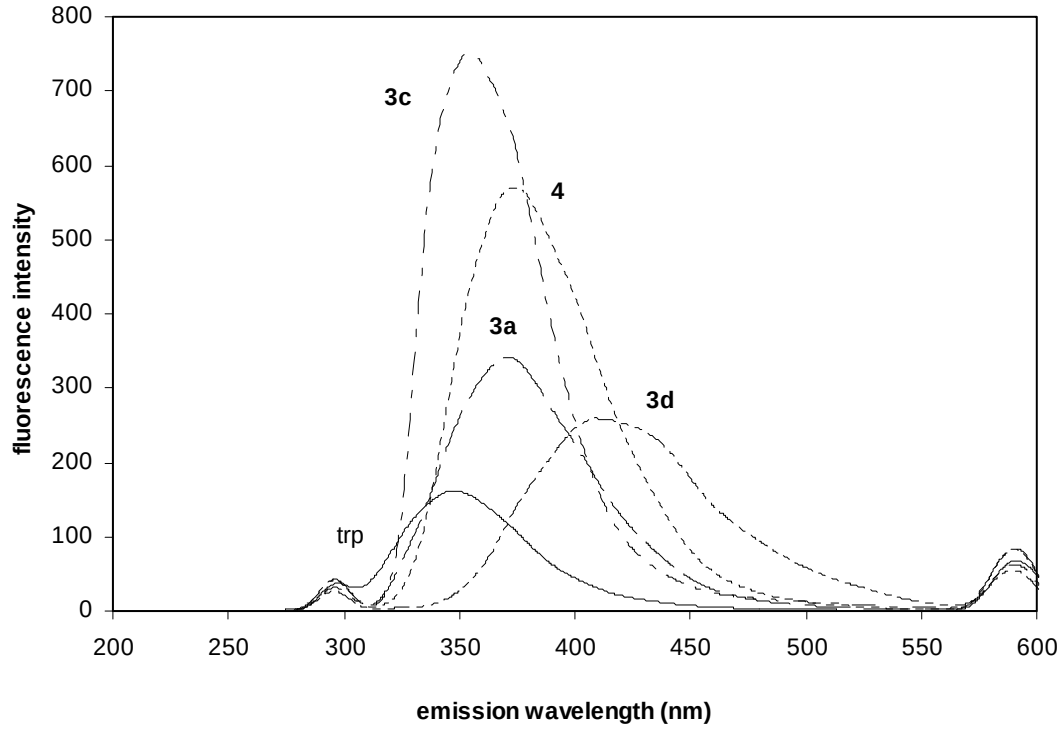
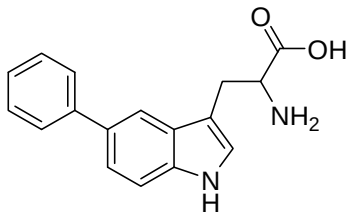


Figure S3

Solvent: methanol
Excitation wavelength λ_{ex}: 295 nm





500 MHz, CD_3OD

Fig 1. ^{1}H NMR spectra of 5-Phenyltryptophan (3a).

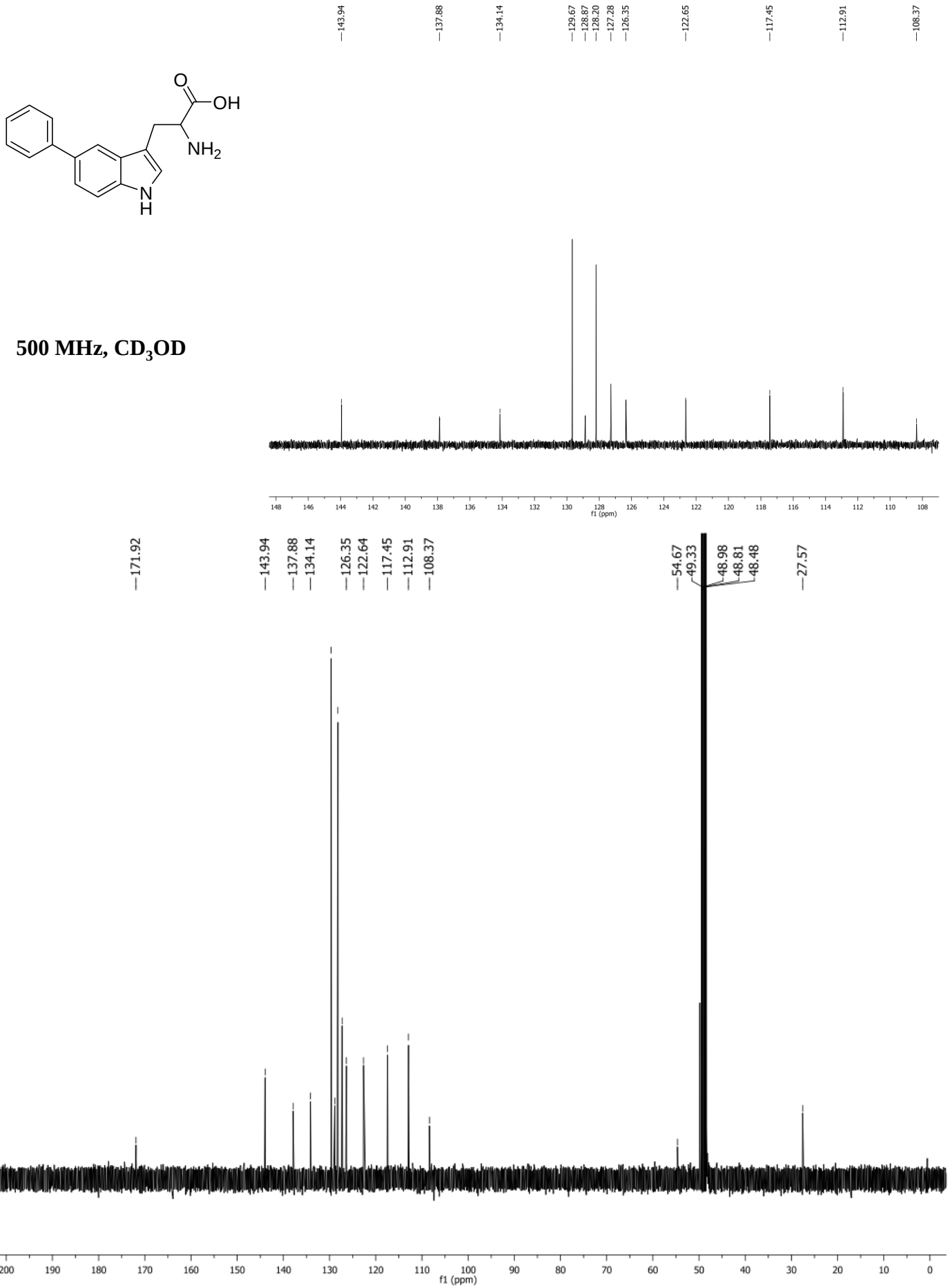
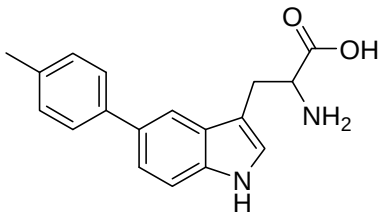
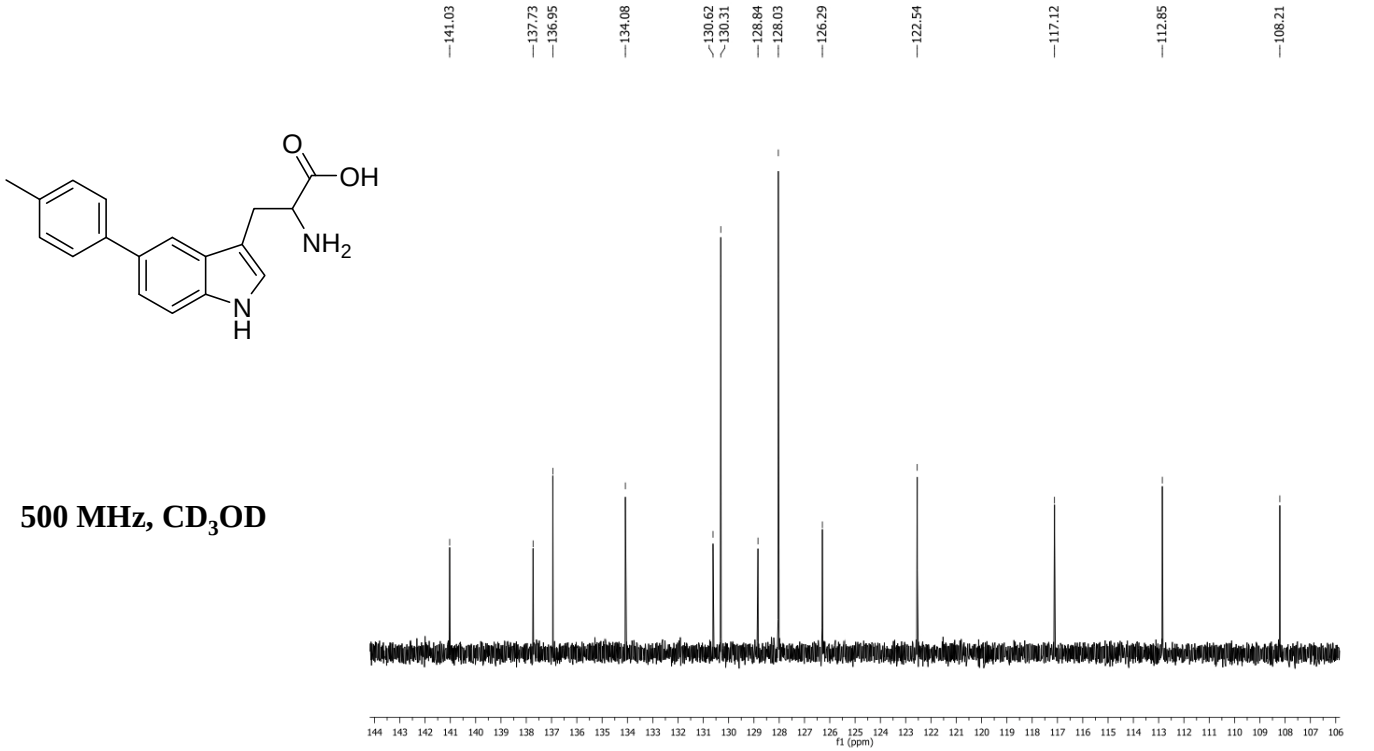


Fig 2. ^{13}C NMR spectra of 5-Phenyltryptophan (3a).



500 MHz, CD_3OD

Fig 3. ^{1}H NMR spectra of 5-Tolyltryptophan (3b).



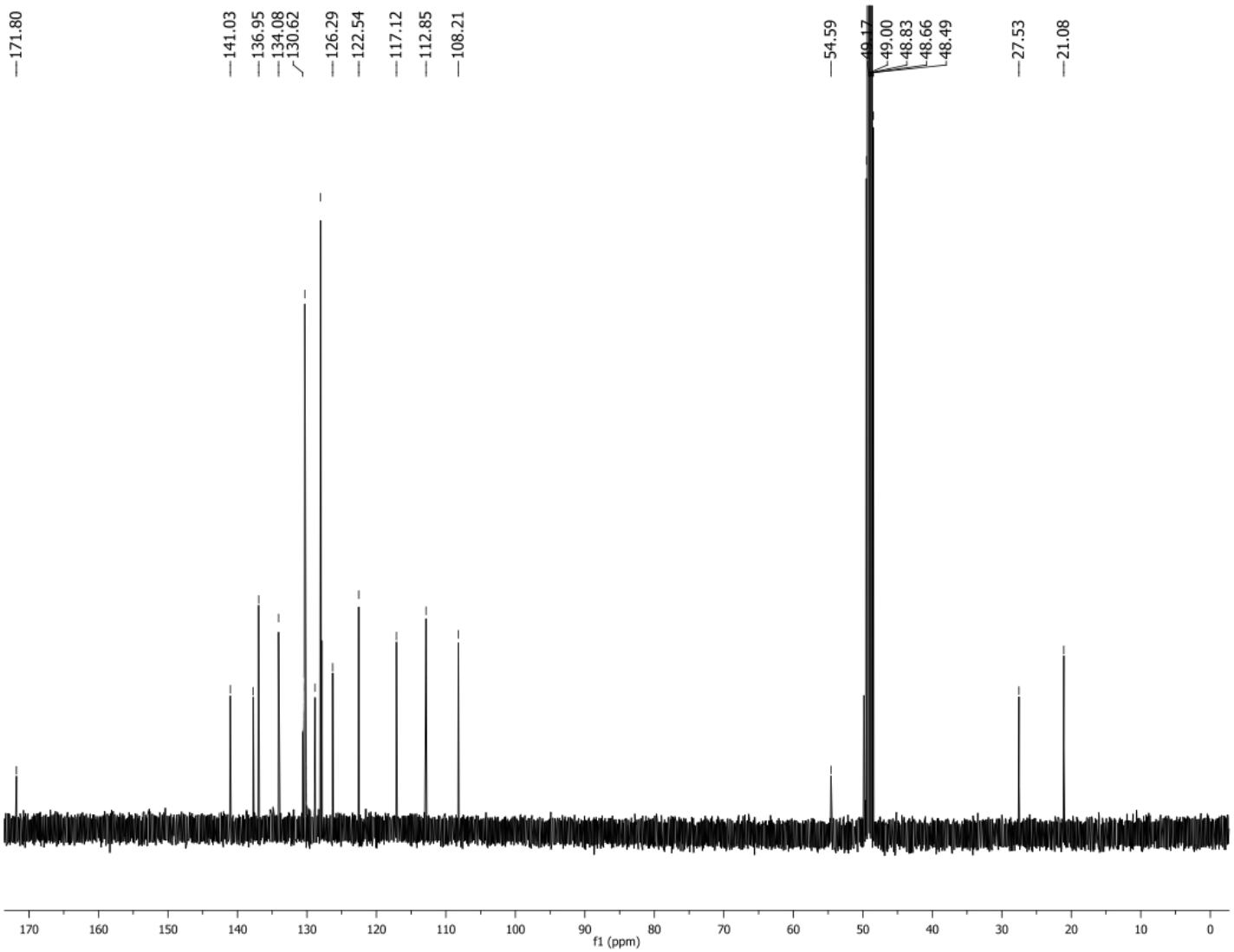
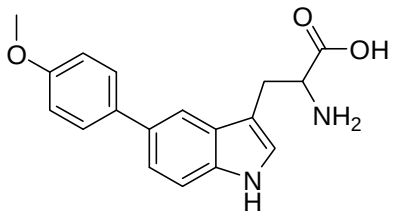
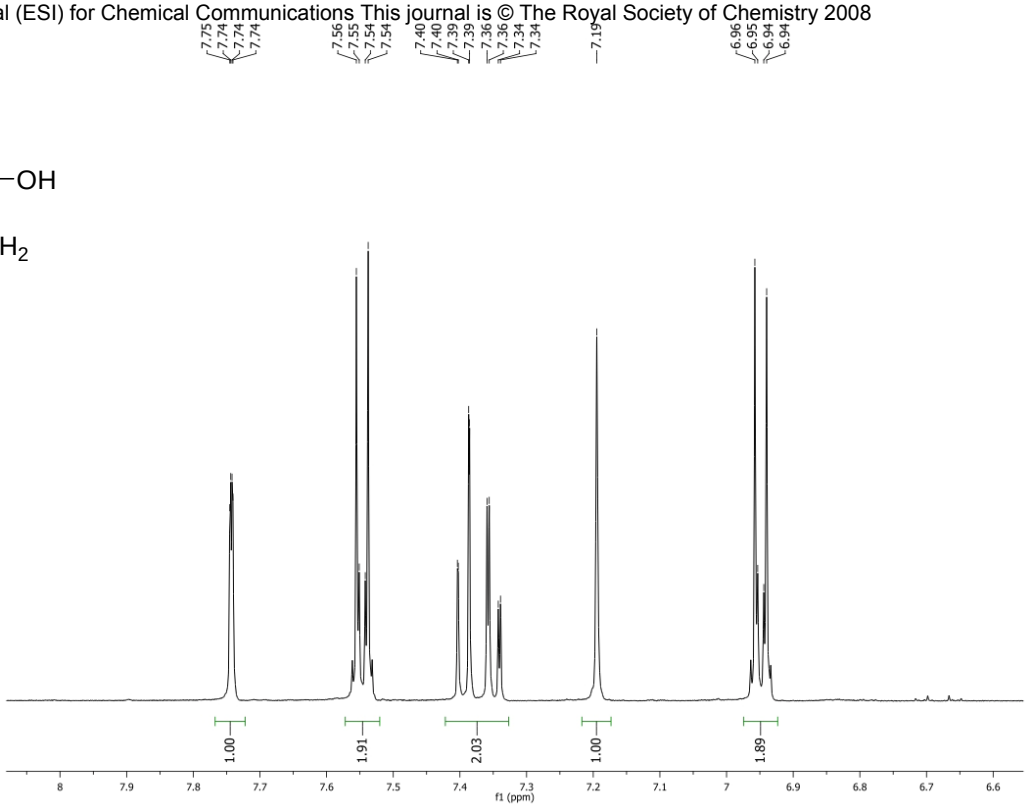


Fig 4. ^{13}C NMR spectra of 5-Tolyltryptophan (3b).



500 MHz, CD_3OD



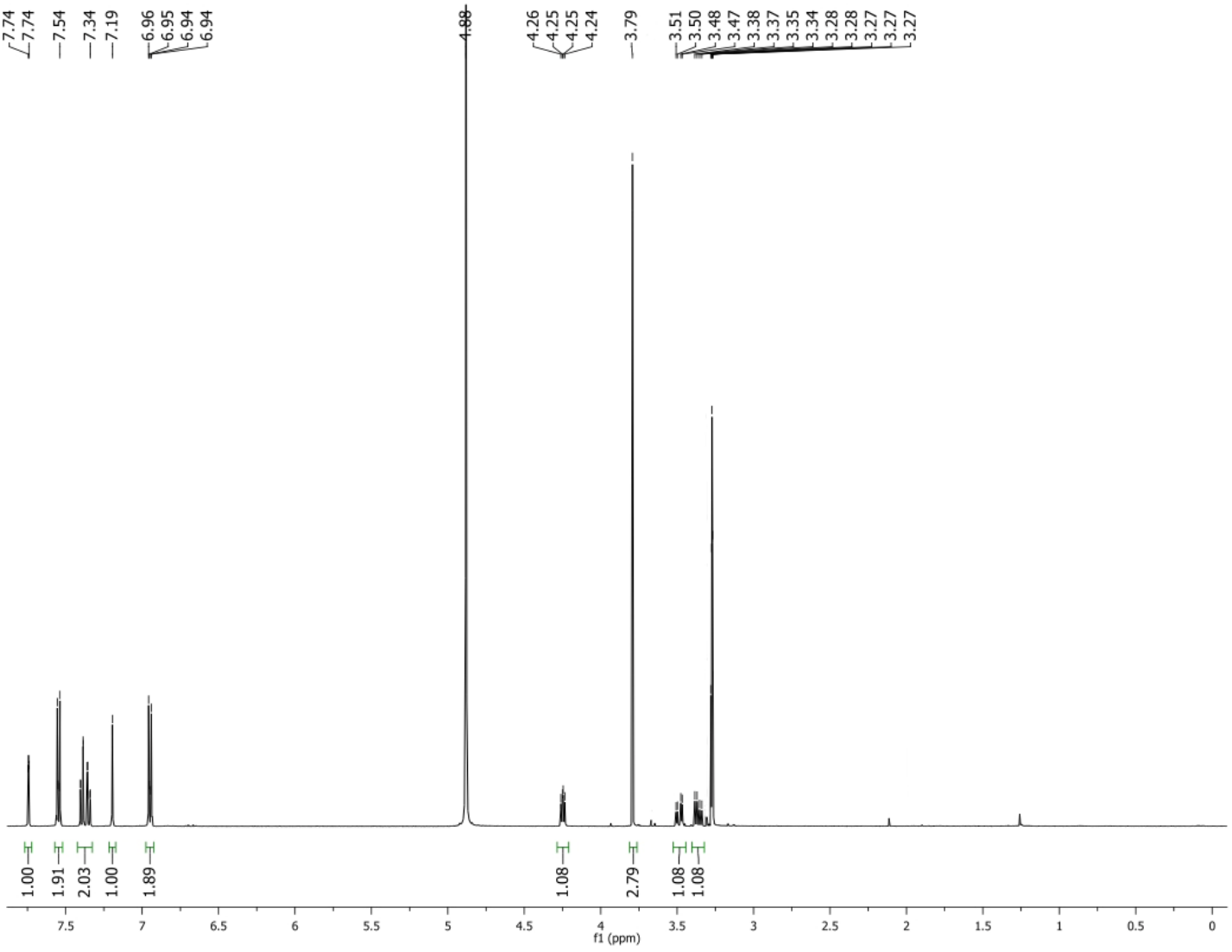
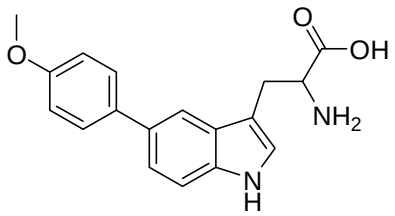
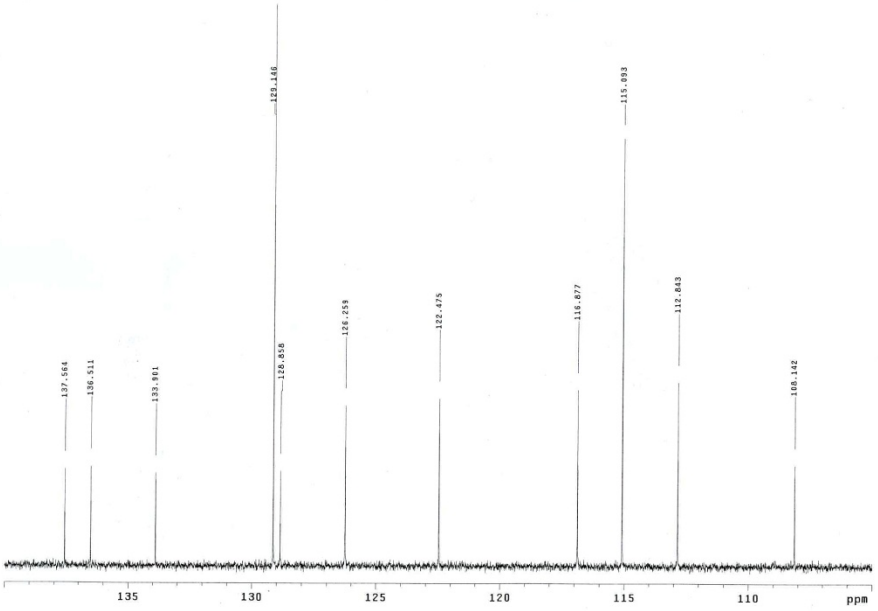


Fig 5. [1]H NMR spectra of 5-(4methoxyphenyl)tryptophan (3c).



500 MHz, CD_3OD



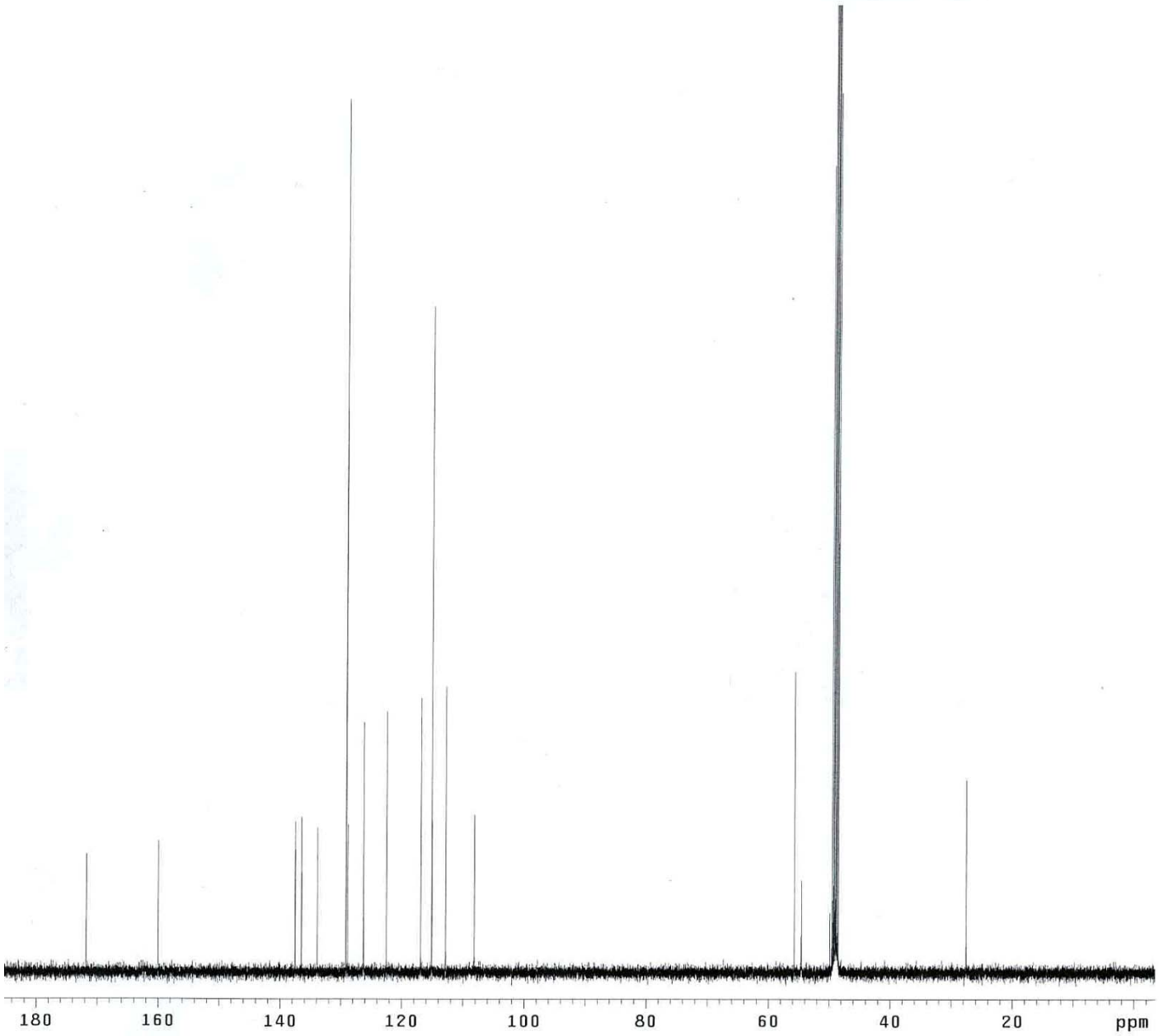
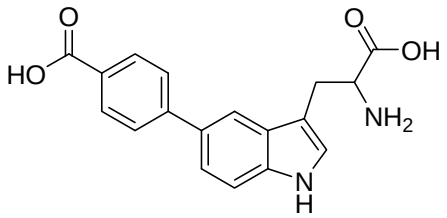


Fig 6. ^{13}C NMR spectra of 5-(4methoxyphenyl)tryptophan (3c).



500 MHz, CD_3OD

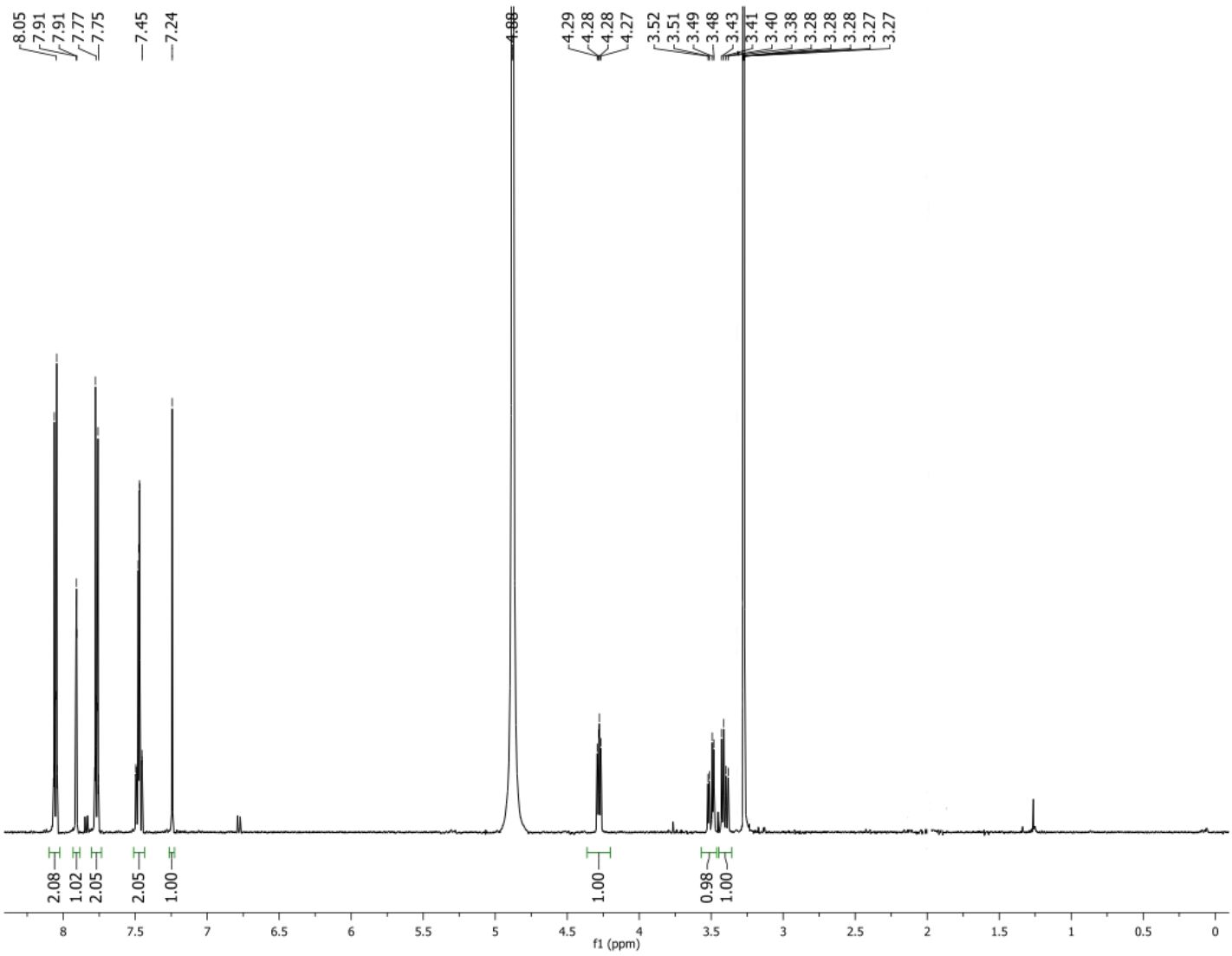
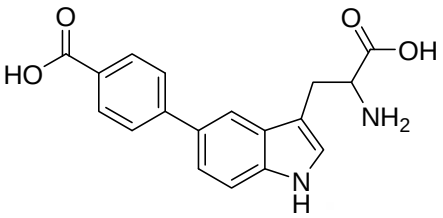
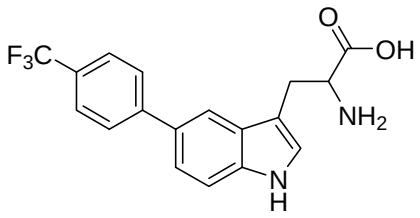


Fig 7. ^{1}H NMR spectra of 5-(4carboxyphenyl)tryptophan (3d).

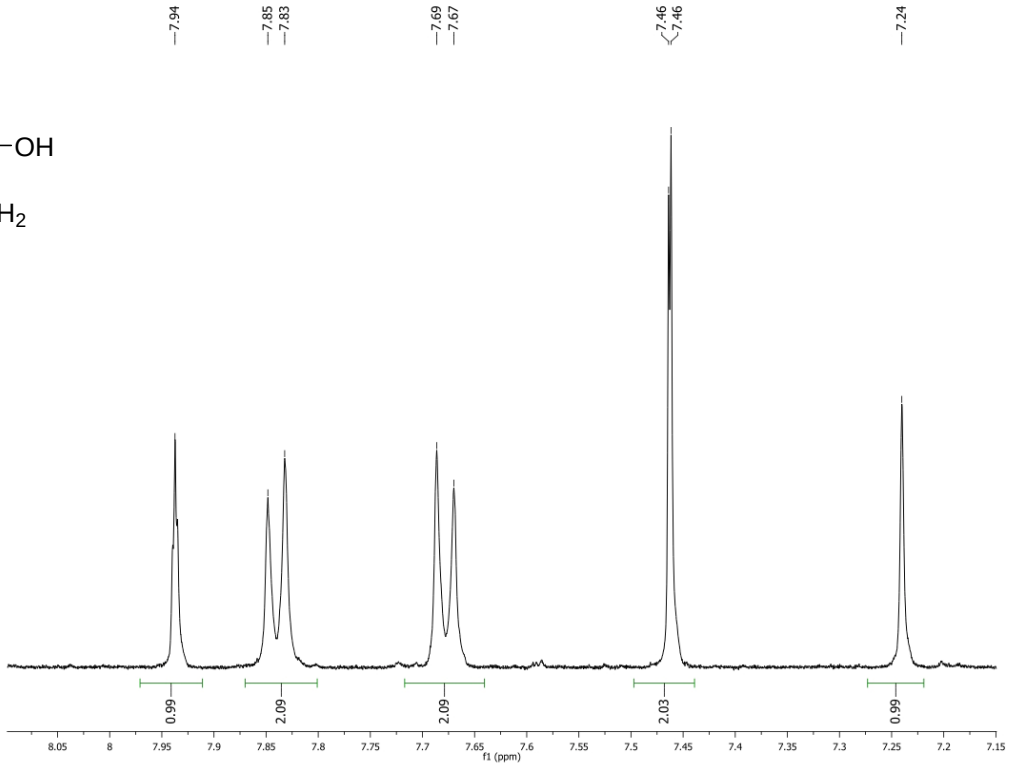


500 MHz, CD_3OD

Fig 8. ^{13}C NMR spectra of 5-(4carboxyphenyl)tryptophan (3d).



500 MHz, CD_3OD



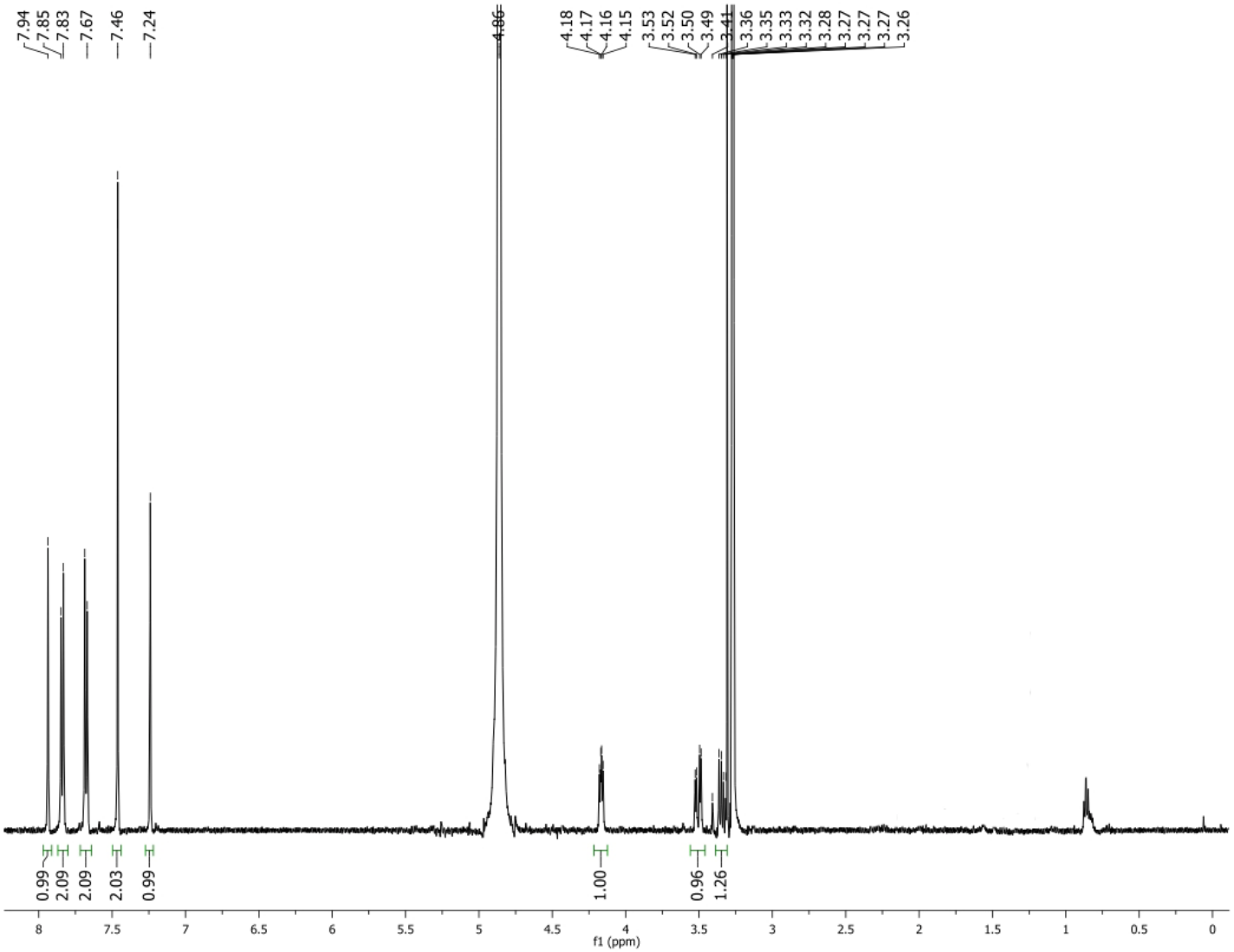
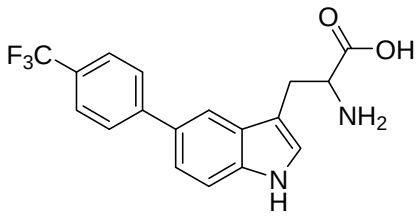
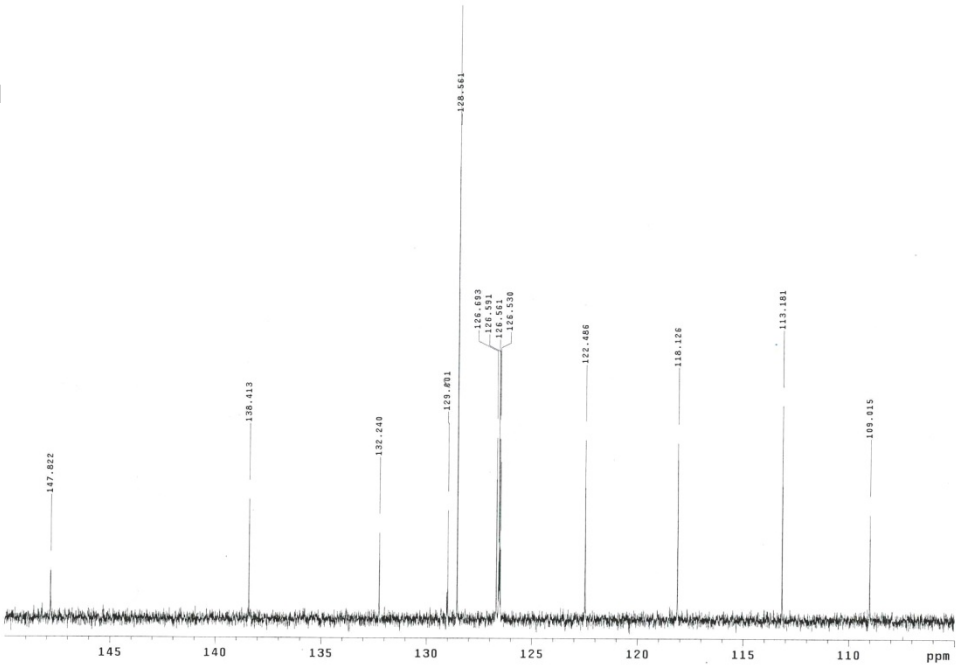


Fig 9. ^{1}H NMR spectra of 5-(trifluoromethylphenyl)tryptophan (3e).



500 MHz, CD_3OD



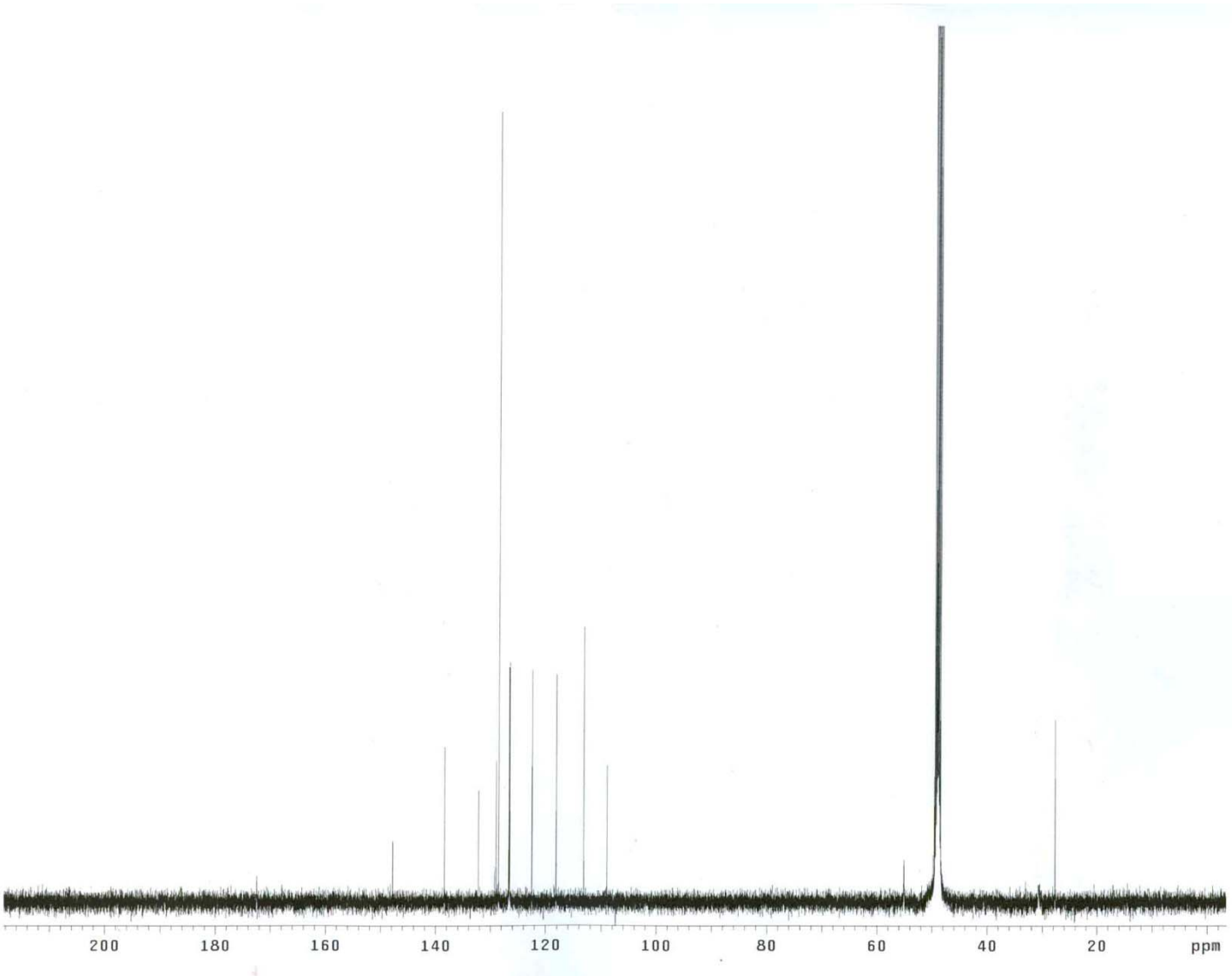
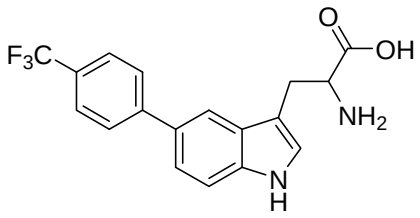


Fig 10. ^{13}C NMR spectra of 5-(trifluoromethylphenyl)tryptophan (3e).



500 MHz, CD_3OD, ^{19}F NMR

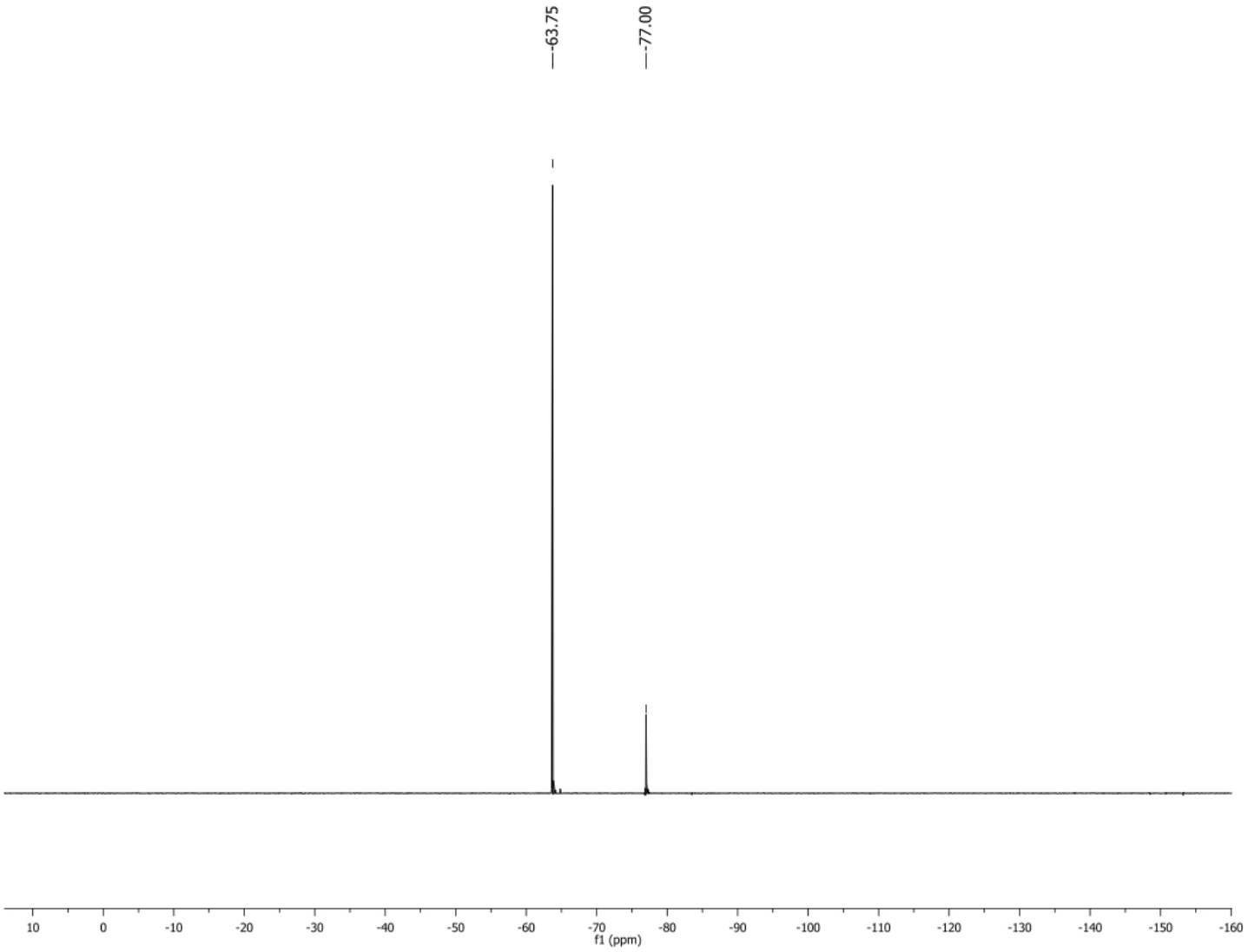
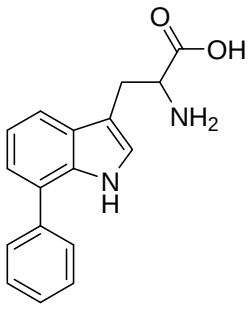
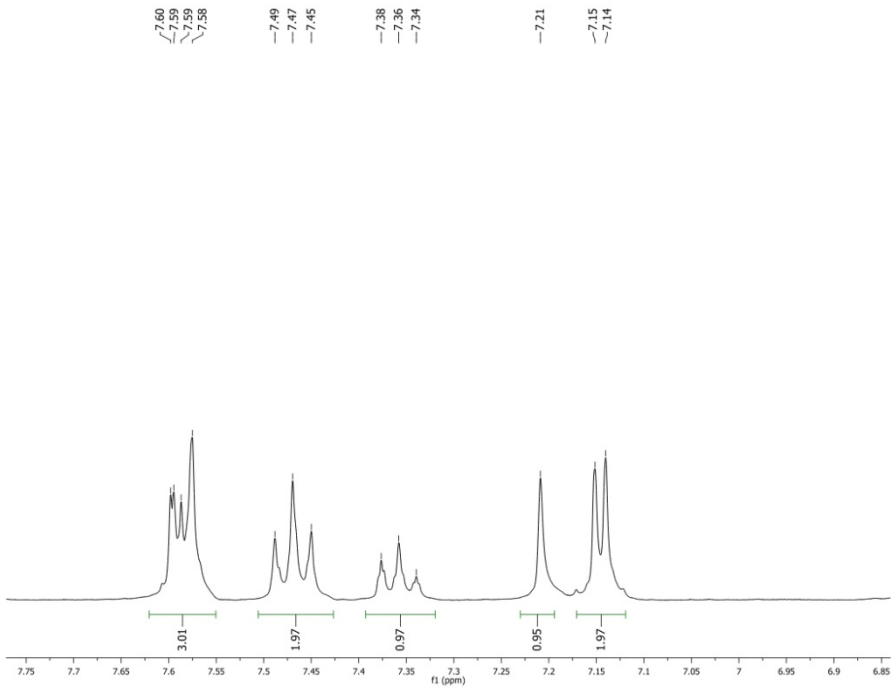


Fig 11. ^{19}F NMR spectra of 5-(trifluoromethylphenyl)tryptophan (3e).



500 MHz, CD_3OD



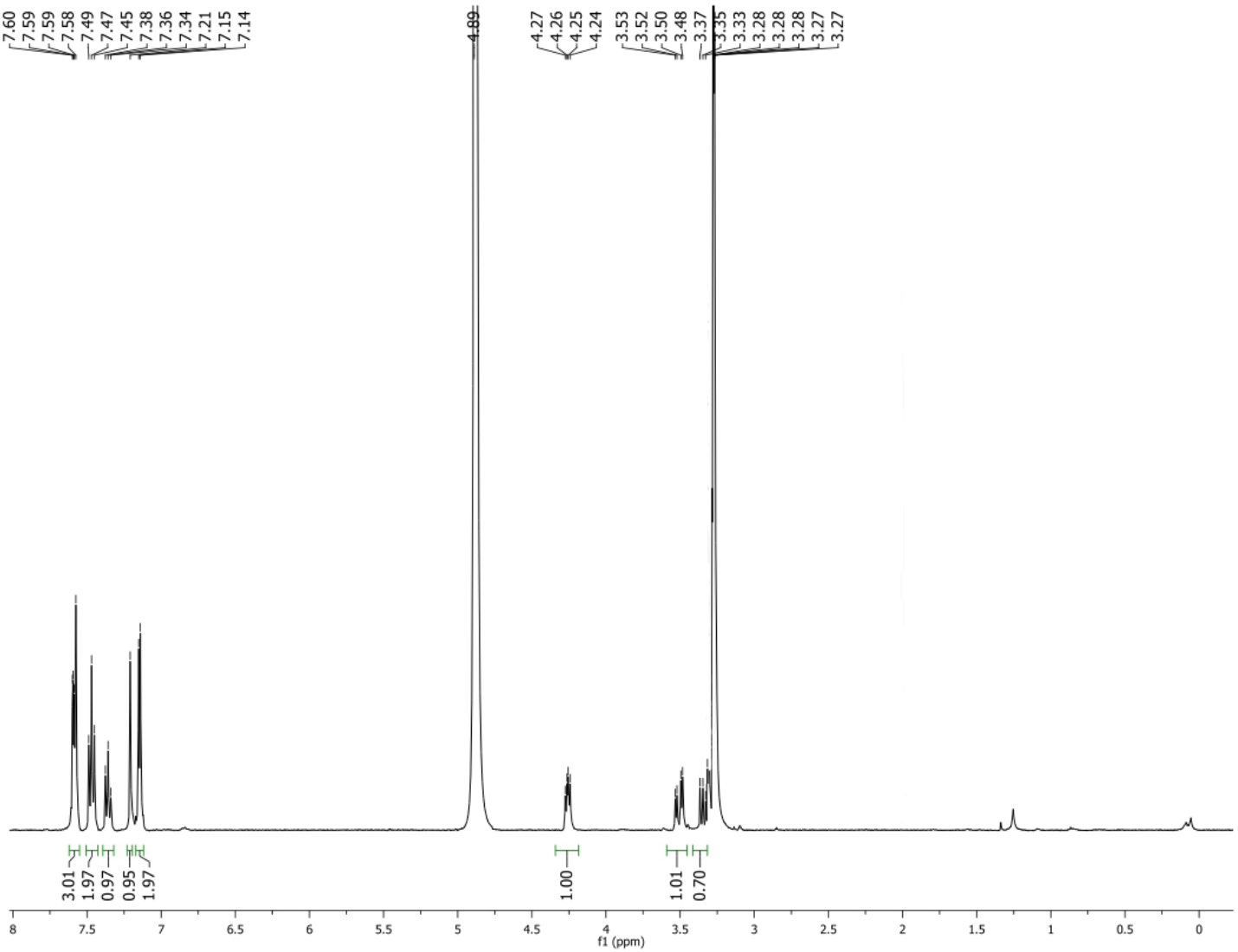
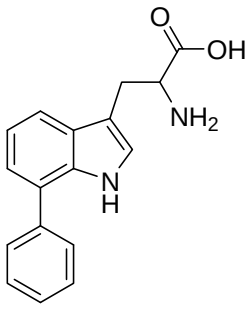
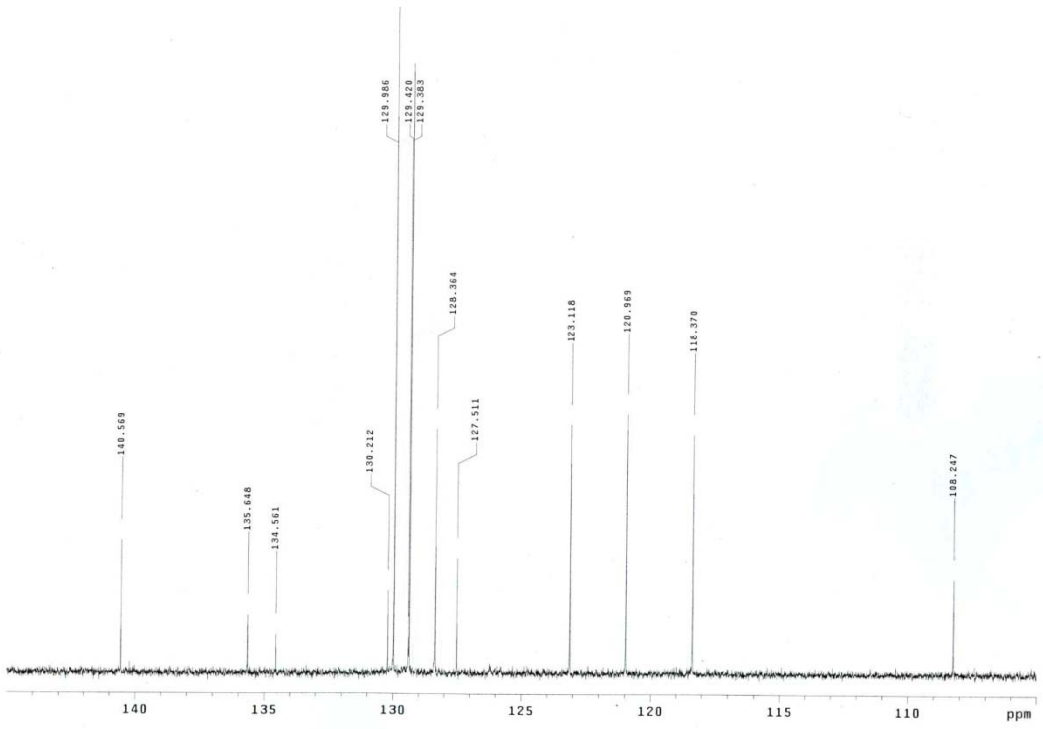


Fig 12. ^{1}H NMR spectra of 7-Phenyltryptophan (4).



500 MHz, CD_3OD



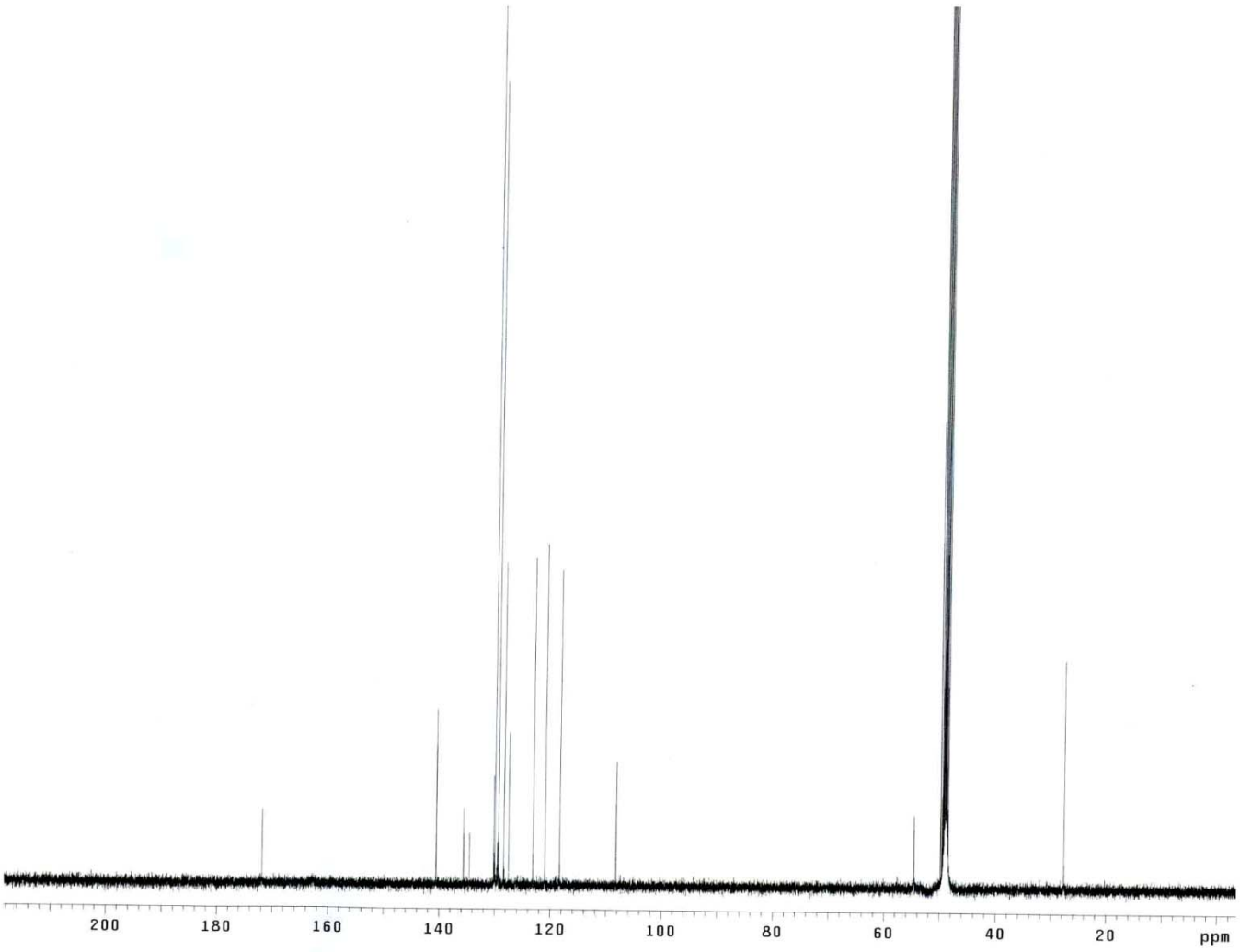
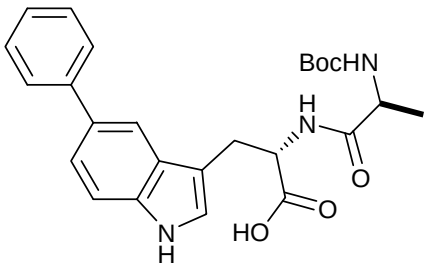
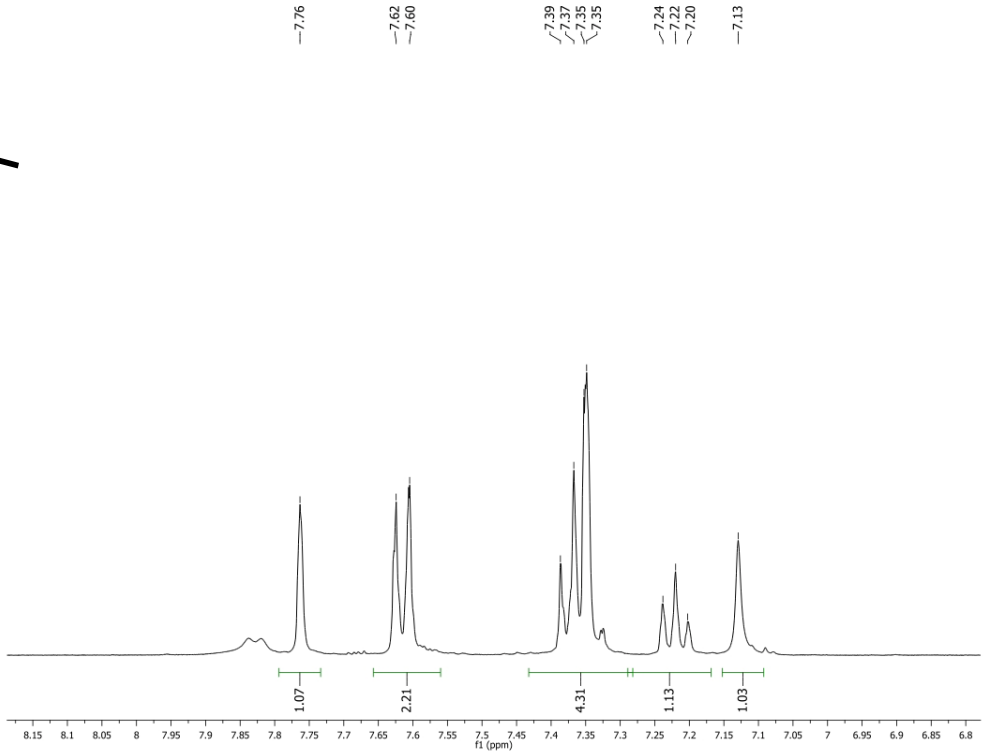


Fig 13. ^{13}C NMR spectra of 7-Phenyltryptophan (4).



400 MHz, CD_3OD



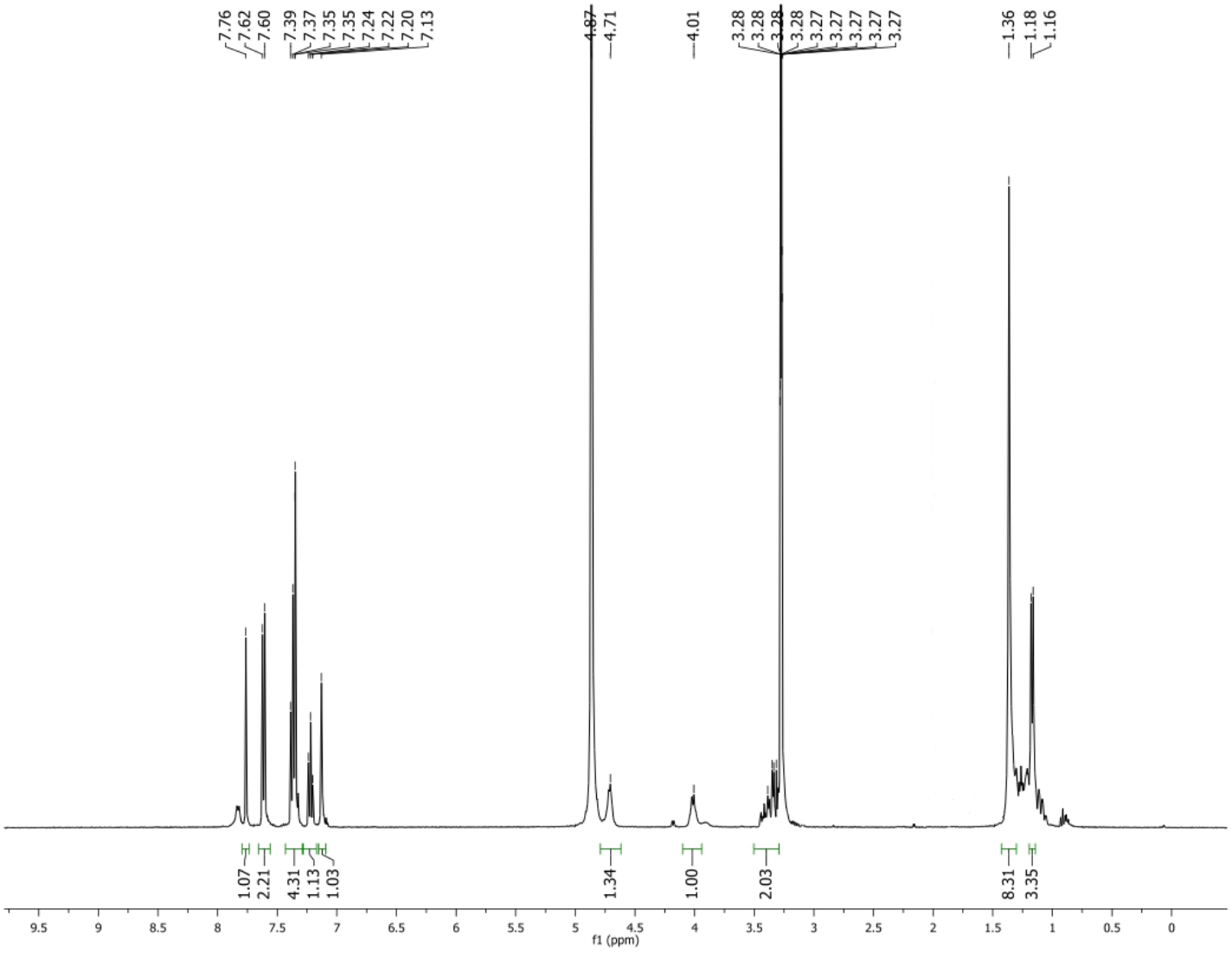


Fig 14. ^{1}H NMR spectra of *N*-Boc-L-Ala-5-Phenyl-L-Trp.