A Simple, Modular Synthesis of C4-Substituted Tryptophan Derivatives

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Supporting Information

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General Procedures:

All reactions were run in air except noted. Column chromatography purifications were performed in flash conditions using 230-400 Mesh silica gel. Analytical thin layer chromatography (TLC) was carried out on silica gel plates (silica gel 60 F254), that were visualized by exposure to ultraviolet light and an aqueous solution of cerium ammonium molybdate (CAM) or *p*-anisaldehyde. Copies of ^{1}H NMR and ^{13}C NMR spectra are provided.

Instrumentation:

^{1}H NMR and ^{13}C NMR spectra were recorded at 400/100 and 200/50 MHz on spectrometer, using $CDCl_3$, CD_3OD or DMSO-d_6 as solvent. Chemical shifts (δ scale) are reported in parts per million (ppm) relative to the central peak of the solvent. Coupling constants (J values) are given in Hertz (Hz). Only molecular ions (M + 1) are given for the ESI-MS analysis. Absorbances are reported in cm^{-1} for the IR analysis. Melting points were determined on a capillary melting point apparatus and are uncorrected. Elemental analyses were within ± 0.4 of the theoretical values (C,H,N).

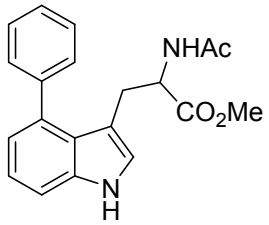
Starting Materials:

Methyl 2-acetamido-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indol-3-yl)propanoate (**1**) was synthesized according to the literature procedure.[1] Other chemicals were purchased from commercial suppliers and were used without further purification.

General Procedure for Suzuki coupling.

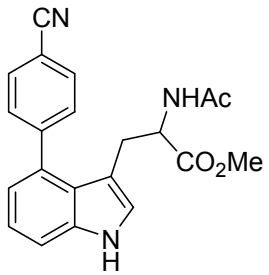
The methyl 2-acetamido-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indol-3-yl)propanoate (**1**) (116 mg, 0.3 mmol), $Pd_2(dba)_3$ (8 mg, 0.009 mmol) and PCy_3 (6 mg, 0.02 mmol) were added to a 10 mL Schlenk flask equipped with a stir bar. The flask was evacuated and refilled with argon five times. Dioxane anhydrous (0.7 mL), (hetero)aryl halide (0.25 mmol, if the halide was a solid was added prior to the evacuation/refill cycle), and aqueous K_3PO_4 (1.27 M, 0.6 mL, 0.51 mmol) were added by syringe. The reaction mixture was stirred at 100 °C for 18 h. The mixture was filtered over Celite and washed with EtOAc. The solvent were concentrated under reduce pressure and to the residue obtained were added H_2O (5 mL) and EtOAc (5 mL). The phases were separated and the aqueous phase was extracted with further EtOAc. The combined organic phase were dried over Na_2SO_4, and the solvent evaporated under reduced pressure. The residue obtained was purified by flash chromatography (DCM/MeOH 98:2).

Methyl 2-acetamido-3-(4-phenyl-1*H*-indol-3-yl)propanoate (2a)



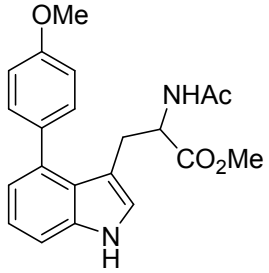
Compound **2a** was prepared according to the general procedure using bromobenzene as aryl halide. Isolated as amorphous solid (54 mg, 64%). MS (ESI): 337 $[M+H]^+$; ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.70 (s, 3H), 2.52 (dd, J_1 = 10.0 and J_2 = 15.0 Hz, 1H), 2.72 (dd, J_1 = 5.0 and J_2=15.0 Hz, 1H), 3.40 (s, 3H), 3.80-3.91 (m, 1H), 6.78 (dd, J_1 = 1.0 and J_2 = 7.0 Hz, 1H), 7.07-7.16 (m, 2H), 7.33-7.43 (m, 6H), 8.04 (d, J = 7.5 Hz, 1H), 11.08 (d, J = 2.0 Hz, 1H); ^{13}C NMR (50 MHz, DMSO-d_6): δ 22.6, 28.8, 51.8, 53.1, 110.3, 111.2, 120.8, 121.1, 124.3, 125.2, 127.1, 128.2, 129.5, 135.1, 137.3, 142.0, 169.4, 173.0; FTIR (film): 3396, 3273, 1721, 1660 cm^{-1}; Anal. calcd. for $C_{20}H_{20}N_2O_3$ (336.15): C, 71.41; H, 5.99; N, 8.33. Found: C, 71.57; H, 6.05; N, 8.27.

Methyl 2-acetamido-3-(4-(4-cyanophenyl)-1*H*-indol-3-yl)propanoate (2b)



Compound **2b** was prepared according to the general procedure using 4-bromobenzonitrile as aryl halide. Isolated as white solid after crystallization from acetone (65 mg, 72%). MS (ESI): 362 $[M+H]^+$; ^1H NMR (200 MHz, DMSO-d_6): δ 1.70 (s, 3H), 2.55 (dd, J_1 = 9.5 and J_2 = 14.5 Hz, 1H), 2.73 (dd, J_1 = 5.0 and J_2 = 14.5 Hz, 1H) 3.44 (s, 3H), 3.71-3.82 (m, 1H) 6.84 (d, J = 7.0 Hz, 1H), 7.15 (t, J = 8.0 Hz, 1H), 7.23 (d, J = 2.0 Hz, 1H) 7.45 (d, J = 8.0 Hz, 1H), 7.56 (d, J = 8.0 Hz, 2H), 7.89 (d, J = 8.0 Hz, 2H), 7.95 (d, J = 8.0 Hz, 1H) 11.13 (br s, 1H); ^{13}C NMR (50 MHz, DMSO-d_6): δ 22.6, 29.0, 51.8, 53.0, 109.9, 110.1, 112.2, 119.5, 120.8, 121.2, 123.8, 126.2, 130.6, 132.3, 133.2, 137.5, 146.9, 169.4, 172.8; m.p.: 254 - 257 °C (acetone); FTIR (film): 3361, 2224, 1725, 1662 cm^{-1}; Anal. calcd. for $C_{21}H_{19}N_3O_3$ (361.14); C, 69.79; H, 5.30; N, 11.63. Found: C, 69.61; H, 5.36; N, 11.70

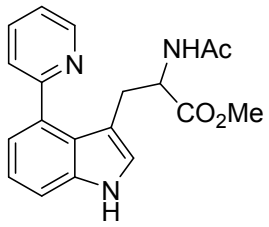
Methyl 2-acetamido-3-(4-(4-methoxyphenyl)-1*H*-indol-3-yl)propanoate (2c)



Compound **2c** was prepared according to the general procedure using 1-bromo-4-methoxybenzene as aryl halide. Isolated as white solid after crystallization from acetone (62 mg, 68%). MS (ESI): 367 $[M+H]^+$; ^1H NMR (200 MHz, DMSO-d_6): δ 1.71 (s, 3H), 2.55 (dd, J_1 = 9.5 and J_2=15.0 Hz, 1H), 2.77 (dd, J_1 = 5.0 and J_2 =15.0 Hz, 1H), 3.43 (s, 3H), 3.82 (s, 3H), 3.82-3.95 (m, 1H), 6.76 (d, J = 7.0 Hz, 1H), 6.98 (d, J=8.5 Hz, 2H), 7.08 (t, J = 8.0 Hz, 1H), 7.13 (d, J = 2.0 Hz, 1H), 7.27 (d, J = 8.5 Hz, 2H), 7.34 (d, J = 8.0 Hz, 1H), 7.92 (d, J = 7.5 Hz, 1H), 10.97 (br s, 1H); ^{13}C NMR (50

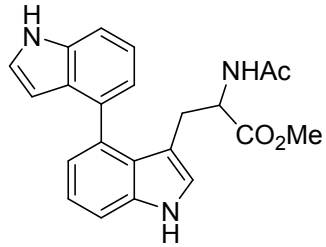
MHz, DMSO-d_6): δ 22.6, 28.8, 51.8, 53.2, 55.5, 110.3,110.9, 113.7, 120.9, 121.1, 124.5, 125.3, 130.6, 134.2, 134.9, 137.3, 158.8, 169.5, 173.1; m.p.: 220-221 °C (acetone); FTIR (film): 3396, 3273, 1721, 1660 cm^{-1}; Anal. calcd. for $C_{21}H_{22}N_2O_4$; C, 68.84; H, 6.05; N, 7.65. Found: C, 68.95; H, 6.01; N, 7.72.

Methyl 2-acetamido-3-(4-(pyridin-2-yl)-1*H*-indol-3-yl)propanoate (2d)



Compound **2d** was prepared according to the general procedure using 2-chloropyridine as heteroaryl halide. Isolated as greyish solid (35 mg, 41%). MS (ESI): 338 $[M+H]^+$; ^1H NMR (200 MHz, DMSO-d_6): δ 1.71 (s, 3H), 2.60 (dd, J_1 = 10.0 and J_2 = 14.5 Hz, 1H), 2.90 (dd, J_1 = 5.0 and J_2 = 14.5 Hz, 1H), 3.46 (s, 3H), 3.90-4.02 (m, 1H), 6.96 (dd, J_1 = 1.0 and J_2 = 7.0 Hz, 1H), 7.15 (t, J = 7.5 Hz,1H), 7.21 (d, J = 2.5 Hz, 1H), 7.36-7.40 (m, 1H), 7.41-7.46 (m, 1H), 7.53 (d, J = 8.0 Hz, 1H), 7.88 (dt, J = 7.5 Hz, 1H), 8.19 (d, J = 7.5 Hz, 1H), 8.60-8.64 (m, 1H), 11.06 (br s, 1H); ^{13}C NMR (50 MHz, DMSO-d_6): δ 22.7, 28.8, 51.8, 53.7, 110.7, 112.3, 120.9, 121.2, 122.2, 124.4, 124.6, 125.9, 134.3, 137.1, 137.6, 148.9, 160.2, 169.4, 173.1; m.p.: 187-188 °C (EtOAc/cyclohexane); FTIR (film): 3394, 3251, 1727, 1665 cm^{-1}; Anal. calcd. for $C_{19}H_{19}N_3O_3$ (337.14); C, 67.64; H, 5.68; N, 12.46. Found: C, 67.48; H, 5.73; N, 12.41.

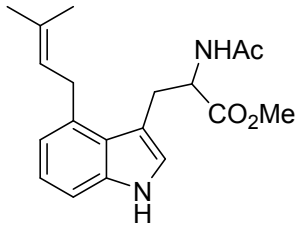
Methyl 3-(1*H*,1'*H*-4,4'-biindol-3-yl)-2-acetamidopropanoate (2e)



Compound **2e** was prepared according to the general procedure using 4-bromo-1*H*-indole as heteroaryl halide. Isolated as white solid after crystallization from acetone (45 mg, 48%). MS (ESI):

376 $[M+H]^+$; ^1H NMR (200 MHz, DMSO-d_6): δ 1.67 (s, 3H), 2.21-2.44 (m, 2H), 3.33 (s, 3H), 3.76-3.87 (m, 1H), 5.94 (br s, 1H), 6.86-6.93 (m, 2H), 7.05-7.18 (m, 2H), 7.24-7.27 (m, 1H), 7.35-7.43 (m, 2H), 7.74 (d, J = 7.5 Hz, 1H) 10.94 (br s, 1H), 11.06 (br s, 1H); ^{13}C NMR (50 MHz, DMSO-d_6): δ 22.6, 28.2, 51.5, 53.2, 101.0, 110.5, 110.8, 110.9, 120.0, 120.7, 121.0, 121.3, 125.1, 125.5, 128.3, 133.7, 133.9, 134.2, 136.1, 137.3, 169.3, 172.9; m.p.: 218 - 219 °C (acetone); FTIR (film): 3391, 1723, 1666 cm^{-1}; Anal. calcd. for $C_{22}H_{21}N_3O_3$ (375.16); C, 70.38; H, 5.64; N, 11.19. Found: C, 70.57; H, 5.71; N, 11.11.

Methyl 2-acetamido-3-(4-(3-methylbut-2-enyl)-1*H*-indol-3-yl)propanoate (3)



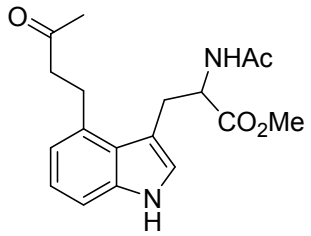
A mixture of $[Pd_2(dba)_3]$ (6.4 mg, 0.007 mmol), prenyl bromide (12 µL, 0.1 mmol), K_2CO_3 (124 mg, 0.9 mmol) and **1** (50 mg, 0.13 mmol) in dry toluene (2 mL) was heated at refluxed under argon for 16 h. Water was added and the mixture was extracted three times with Et_2O. The combined organic layers were washed with water and brine and dried over Na_2SO_4. The solvent was evaportaed under reduced pressure and the residue obtained was purified by flash chromatography (DCM/MeOH, 97:3) to give **3** (28 mg, 85%) as white solid.

MS (ESI): 329 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$): δ 1.76 (s, 6H), 1.96 (s, 3H), 3.33 (dd, J_1 = 15.0 and J_2 = 7.5 Hz, 1H), 3.50 (dd, J_1 = 15.0 and J_2 = 5.0 Hz, 1H), 3.67-3.80 (m, 2H), 3.73 (s, 3H), 4.93-4.98 (m, 1H), 5.30-5.34 (m, 1H), 5.95 (br d, J = 8.0 Hz, 1H), 6.91 (d, J = 7.5 Hz, 1H), 7.01 (s, 1H), 7.12 (t, J = 7.5 Hz, 1H), 7.23 (d, J = 7.5 Hz, 1H), 8.21 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.0, 23.1, 25.7, 29.6, 32.2, 52.3, 53.1, 109.4, 110.8, 120.4, 122.4, 122.5, 123.7, 125.3, 132.5, 134.4, 136.9, 170.0, 172.9; m.p.: 165-166 °C (EtOAc/petroleum ether); FTIR (film): 3410, 3267, 1732, 1643 cm^{-1}; Anal. Calcd. For $C_{19}H_{24}N_2O_3$ (328.18): C, 69.49; H, 7.37; N, 8.53; Found: C, 69.35; H, 7.44; N, 8.49.

General procedure for rhodium catalyzed reaction:

A vial was charged with **1** (39 mg, 0.1 mmol), methyl vinyl ketone or 4-chlorobenzaldehyde (0.12 mmol), $[Rh(COD)OH]_2$ (2 mg, 0.05 mmol) and 1,4 dioxane (0.9 mL). The vial was sealed with a Teflon-lined cap and heated at 80 °C for 16 hours. The reaction mixture was diluted with EtOAc, filtered through a pad of silice and the solvent was removed under reduced pressure. The residue obtained was purified by flash chromatography.

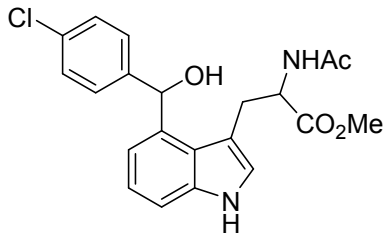
Methyl 2-acetamido-3-(4-(3-oxobutyl)-1*H*-indol-3-yl)propanoate (4)



Compound **4** was prepared according to the general procedure using methyl vinyl ketone as enone. The residue obtained was purified by flash chromatography (cyclohexane/EtOAc 2:8) to give **4** (20 mg, 61%) as white solid.

MS (ESI): 331 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$): δ 1.96 (s, 3H), 2.16 (s, 3H), 2.84 (t, J = 8.0 Hz, 2H), 3.29-3.35 (m, 3H), 3.46 (dd, J_1 = 15.0 and J_2 = 5.5 Hz, 1H), 3.70 (s, 3H), 4.91 – 4.97 (m, 1H,), 6.11 (br d, J = 8.0 Hz, 1H,), 6.87 (d, J = 7.5 Hz, 1H), 7.02 (s, 1H), 7.09 (t, J = 7.5 Hz, 1H), 7.21 (d, J = 7.5 Hz, 1H), 8.34 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.1, 27.0, 29.9, 30.1, 45.3, 52.4, 53.2, 109.7, 110.5, 120.2, 122.3, 122.9, 124.9, 133.6, 136.9, 170.0, 172.8, 208.1; m.p.: 88 - 89 °C (EtOAc/petroleum ether); FTIR (film): 3523, 3284, 1748, 1717, 1654 cm^{-1}; Anal. Calcd. For $C_{18}H_{22}N_2O_4$ (330.16): C, 65.44; H, 6.71; N, 8.48; Found: C, 65.30; H, 6.78; N, 8.42.

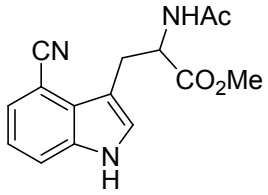
Methyl 2-acetamido-3-(4-((4-chlorophenyl)(hydroxy)methyl)-1*H*-indol-3-yl)propanoate (5)



Compound **5** was prepared according to the general procedure using 4-chlorobenzaldehyde as aldehyde. The residue obtained was purified by flash chromatography (cyclohexane/EtOAc 3:7) to give **5** (27 mg, 68%) as a 1:1 mixture of two diastereomers, as white solid.

MS (ESI): 383 $[M-18+H]^+$; ^1H NMR (400 MHz, $CDCl_3$): δ 1.80 (s, 3H), 1.82 (s, 3H), 3.12 (dd, J_1 = 15.0 and J_2 = 8.5 Hz, 1H),), 3.21 (dd, J_1 = 15.0 and J_2 = 5.0 Hz, 1H),), 3.29 (dd, J_1 = 15.0 and J_2 = 6.5 Hz, 1H),), 3.39 (dd, J_1 = 15.0 and J_2 = 8.5 Hz, 1H), 3.64 (s, 3H), 3.69 (s, 3H), 4.93 - 4.95 (m, 2H), 6.43 (s, 1H), 6.51 (br d, J = 7.5 Hz, 1H), 6.55 (s, 1H), 6.65 (d, J = 7.0 Hz, 1H), 6.85 (br d, J = 7.5 Hz, 1H), 6.93 - 6.98 (m, 2H), 7.03 (t, J = 7.5 Hz, 1H), 7.10 (t, J = 7.5 Hz, 1H), 7.25 - 7.37 (m, 10H), 8.65 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.9, 30.1, 30.2, 52.3, 52.4, 53.5, 54.2, 72.1, 72.9, 110.2, 110.4, 111.67, 111.75, 120.0, 120.2, 121.8, 121.9, 124.0, 124.2, 124.6, 124.9, 128.31, 128.34, 132.9, 135.1, 137.1, 137.2, 142.0, 142.2, 170.6, 170.7, 172.9, 173.2; m.p.: 243 - 244 °C (EtOAc/ cyclohexane); FTIR (film): 3386, 1735, 1654 cm^{-1}; Anal. Calcd. For $C_{21}H_{21}ClN_2O_4$ (400.12): C, 62.92; H, 5.28; N, 6.99; Found: C, 62.74; H, 5.21; N, 7.05.

Methyl 2-acetamido-3-(4-cyano-1*H*-indol-3-yl)propanoate (6)

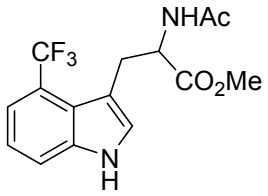


In a sealed tube, **1** (39 mg, 0.1 mmol), CuCN (9 mg, 0.1 mmol) and K_2CO_3 (41 mg, 0.3 mmol) were dissolved in DMF (2 mL). The reaction mixture was then stirred at 60 °C for 16 hours. After cooled to room temperature, to the reaction mixture was added a saturated aqueous solution of NH_4Cl (8 mL), and then extracted with EtOAc (4 x 20 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, and the solvent evaporated under reduced pressure. The residue obtained was purified by flash chromatography (EtOAc) to give **6** (10 mg, 34%) as yellow solid.

MS (ESI): 286 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$): δ 1.95 (s, 3H), 3.49 (dd, J_1 = 15.0 and J_2 = 8.0 Hz, 1H), 3.60 (dd, J_1 = 15.0 and J_2 = 5.0 Hz, 1H), 3.75 (s, 3H), 4.97-5.02 (m, 1H), 6.18 (br d, J = 7.0 Hz, 1H), 7.23 (t, J = 7.5 Hz, 1H), 7.29 (d, J = 2.0 Hz, 1H), 7.49 (d, J = 7.5 Hz, 1H), 7.59 (d, J

= 7.5 Hz, 1H), 8.51 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.1, 27.6, 52.4, 53.3, 101.7, 111.2, 116.3, 121.6, 126.1, 126.7, 126.9, 136.2, 138.5, 169.8, 172.2; m.p.: 202 - 203 °C (EtOAc); FTIR (film): 3384, 3254, 2219, 1736, 1647 cm^{-1}; Anal. Calcd. For $C_{15}H_{15}N_3O_3$ (285.11): C, 63.15; H, 5.30; N, 14.73; Found: C, 62.91; H, 5.36; N, 14.68.

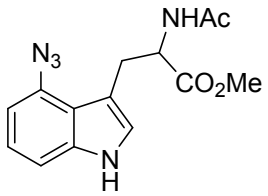
Methyl 2-acetamido-3-(4-(trifluoromethyl)-1*H*-indol-3-yl)propanoate (7)



To a solution of **1** (39 mg, 0.1 mmol), CuCl (10 mg, 0.1 mmol) and $NaSO_2CF_3$ (47 mg, 0.3 mmol) in MeOH (0.2 mL), DCM (0.2 mL) and H_2O (0.16) at 0 °C was slowly added TBHP (70% solution in water, 70 µL, 0.5 mmol). The reaction was allowed to warm to room temperature and was then stirred for 16 hours. EtOAc was added and organic layer was washed with saturated aqueous sodium bicarbonate (2 mL) and potassium sulfite (1 mL) solutions. The organic layer was separated, and the combined aqueous layers were extracted with ethyl acetate (3 x 3 mL). The combined organic layers were dried over Na_2SO_4, and the solvent evaporated under reduced pressure. The residue obtained was purified by flash chromatography (gradient from cyclohexane/EtOAc 2:8 to EtOAc) to give **7** (17 mg, 52%) as white solid.

MS (ESI): 329 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.95 (s, 3H), 3.21 (dd, J_1 = 16.0 and J_2 = 9.0 Hz, 1H), 3.43 (dd, J_1 = 16.0 and J_2 = 5 Hz, 1H), 3.76 (s, 3H), 5.02-5.07 (m, 1H), 5.91 (br d, J = 8.0 Hz, 1H), 7.24 (t, J = 8.0 Hz, 1H), 7.31 (s, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.56 (d, J = 8.0 Hz, 1H), 8.52 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.1, 28.8, 52.4, 52.5, 110.0, 115.64, 115.65, 118.1 (q, J = 25 Hz), 120.7, 122.5, 124.9, 126.3, 137.5, 170.3, 173.0; m.p.: 154 - 155 °C (EtOAc/ petroleum ether); FTIR (film): 3416, 1760, 1630 cm^{-1}; Anal. Calcd. For $C_{15}H_{15}F_3N_2O_3$ (328.10): C, 54.88; H, 4.61; N, 8.53; Found: C, 55.01; H, 4.57; N, 8.59.

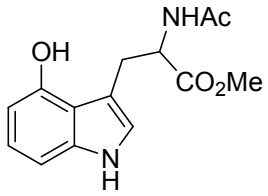
Methyl 2-acetamido-3-(4-azido-1H-indol-3-yl)propanoate (8)



To a solution of **1** (39 mg, 0.1 mmol) in MeOH (1.3 mL) were added NaN_3 (10 mg, 0.15 mmol) and $Cu(OAc)_2$ (1.8 mg, 0.01 mmol). The reaction mixture was stirred at 50 °C open to the air for 16 h. The methanol was removed under reduced pressure. The residue was dissolved in EtOAc and washed with water (1 x 10 mL). The organic layer was washed with brine (1 x 8 mL), dried over Na_2SO_4, and the solvent evaporated under reduced pressure. The residue obtained was purified by flash chromatography (cyclohexane/ EtOAc 3:7) to give **8** (29 mg, 97%) as white solid.

MS (ESI): 324 $[M+23]^+$; ^{1}H NMR (400 MHz, CD_3OD): δ 1.92 (s, 3H), 3.17 (dd, J_1 = 14.0 and J_2 = 9.0 Hz, 1H), 3.46 (dd, J_1 = 14.0 and J_2 = 6.0 Hz, 1H), 3.68 (s, 3H), 4.84 (dd, J_1 = 9.0 and J_2 = 6.0 Hz, 1H), 6.84 (dd, J_1 = 7.0 and J_2 = 1.5 Hz, 1H), 7.03 (s, 1H), 7.12 – 7.18 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD): δ 20.8, 28.2, 51.1, 54.1, 107.4, 108.1, 109.4, 119.0, 121.9, 124.0, 132.0, 138.4, 171.8, 172.9; m.p.: 172 - 174 °C (EtOAc); FTIR (film): 3334, 2110, 1734, 1647 cm^{-1}; Anal. Calcd. for $C_{14}H_{15}N_5O_3$ (301.12): C, 55.81; H, 5.02; N, 23.24; Found: C, 55.92; H, 4.98; N, 23.31.

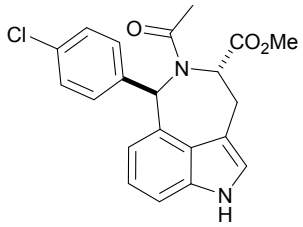
Methyl 2-acetamido-3-(4-hydroxy-1*H*-indol-3-yl)propanoate (9)



To a solution of **1** (39 mg, 0.1 mmol) in THF/H_2O 1:1 (1 mL) was added $NaBO_3 \cdot 4H_2O$ (38 mg, 0.25 mmol). The reaction mixture was vigorously stirred for 10 minutes and then was diluted with water (1 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layer was washed with brine, dried over Na_2SO_4, and the solvent evaporated under reduced pressure. The residue obtained was purified by flash chromatography (EtOAc) to give **9** (27 mg, 96%) as white solid.

MS (ESI): 277 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD): δ 1.88 (s, 3H), 3.25 (dd, J_1 = 14.0 and J_2 = 9.0 Hz, 1H), 3.35 (br s, 1H), 3.39 (dd, J_1 = 14.0 and J_2 = 5.0 Hz, 1H), 3.67 (s, 3H), 4.61 (dd, J_1 = 9.0 and J_2 = 5.0 Hz, 1H), 6.38 (d, J = 7.0 Hz, 1H), 6.83-6.88 (m, 2H), 6.90 (s, 1H); ^{13}C NMR (100 MHz, CD_3OD): δ 22.3, 29.4, 52.5, 56.8, 104.2, 104.7, 110.8, 118.0, 123.3, 123.4, 140.4, 152.1, 173.2, 174.4; m.p.: 193 - 194 °C (EtOAc); FTIR (film): 3291, 1758, 1628 cm^{-1}; Anal. Calcd. for $C_{14}H_{16}N_2O_4$ (276.11): C, 60.86; H, 5.84; N, 10.14; Found: C, 60.99; H, 5.87; N, 10.21.

***Trans*-methyl 2-acetyl-1-(4-chlorophenyl)-2,3,4,6-tetrahydro-1*H*-azepino[5,4,3-cd]indole-3-carboxylate (10)**



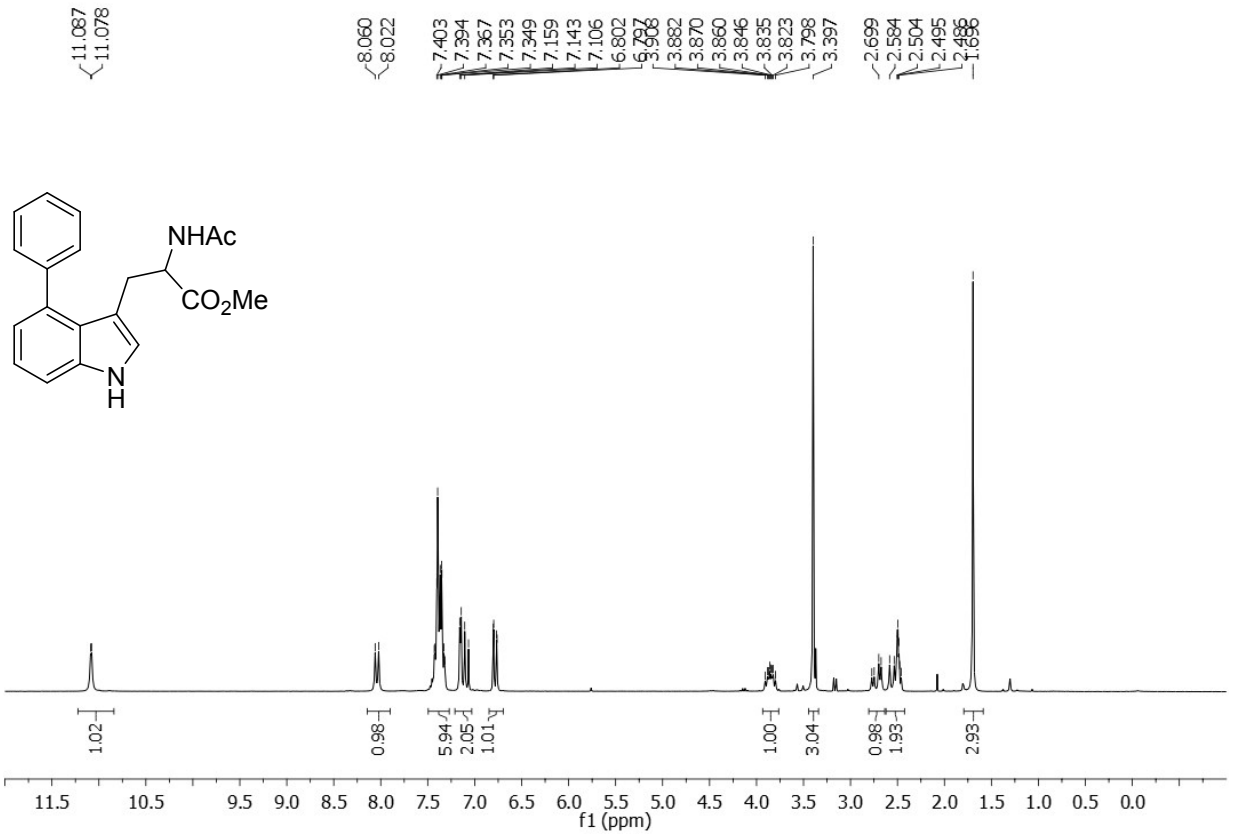
To a solution of methyl 2-acetamido-3-(4-((4-chlorophenyl)(hydroxy)methyl)-1*H*-indol-3-yl)propanoate (**5**) (40 mg, 0.1 mmol) in CH_3CN (1.2 mL) was added bis(benzonitrile)palladium(II) chloride (6 mg, 0.015 mmol). The reaction mixture was stirred at 80 °C for 20 h. The solvent was removed under reduced pressure and the residue obtained was purified by flash chromatography (cyclohexane/ EtOAc 3:7) to give **10** (17 mg, 45%) as white solid.

MS (ESI): 383 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$): δ 2.39 (s, 3H) 2.74 (dd, J = 15.0 and 14.0 Hz, 1H), 3.07 (dd, J = 15.0 and 4.0 Hz, 1H), 3.72 (s, 3H), 5.06 (dd, J = 14.0 and 4.0 Hz, 1H), 6.33 (s, 1H), 6.95 - 6.98 (m, 2H), 7.19 - 7.24 (m, 5H), 7.39 (d, J = 8.0 Hz, 1H), 8.19 (br s, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.1, 25.9, 52.1, 61.3, 64.0, 111.4, 112.9, 118.5, 120.8, 122.5, 128.3, 129.7, 130.5, 131.0, 133.5, 136.5, 138.9, 171.8, 172.1; m.p.: 171 - 173 °C; FTIR (film): 3324, 1745, 1636 cm^{-1}. Anal. Calcd. for $C_{21}H_{19}ClN_2O_3$ (382.11): C, 65.88; H, 5.00; N, 7.32; Found: C, 66.07; H, 4.94; N, 7.39.

References:

[1] S. Bartolucci, F. Bartoccini, M. Righi and G. Piersanti, *Org. Lett.*, 2012, **14**, 600.

Compound **2a**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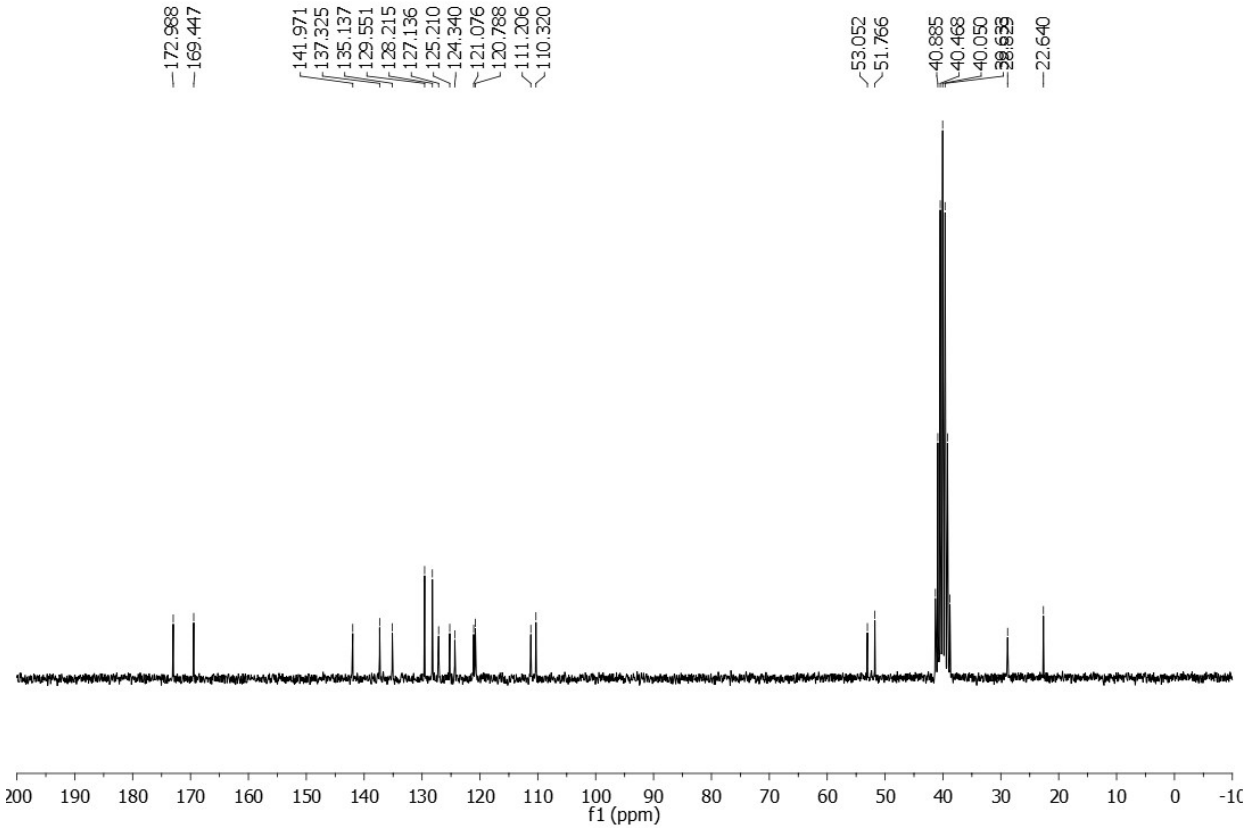
8.060
8.022
7.403
7.394
7.367
7.353
7.349
7.159
7.143
7.106
6.802
3.908
3.882
3.870
3.860
3.846
3.835
3.823
3.798
3.397
2.699
2.584
2.504
2.495
NHAc
CO2Me
N
H
1.02
0.98
5.94
2.05
1.01
1.00
3.04
0.98
1.93
2.93
f1 (ppm)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141.971
137.325
135.137
129.551
128.215
127.136
125.210
124.340
121.076
120.788
111.206
110.320
53.052
51.766
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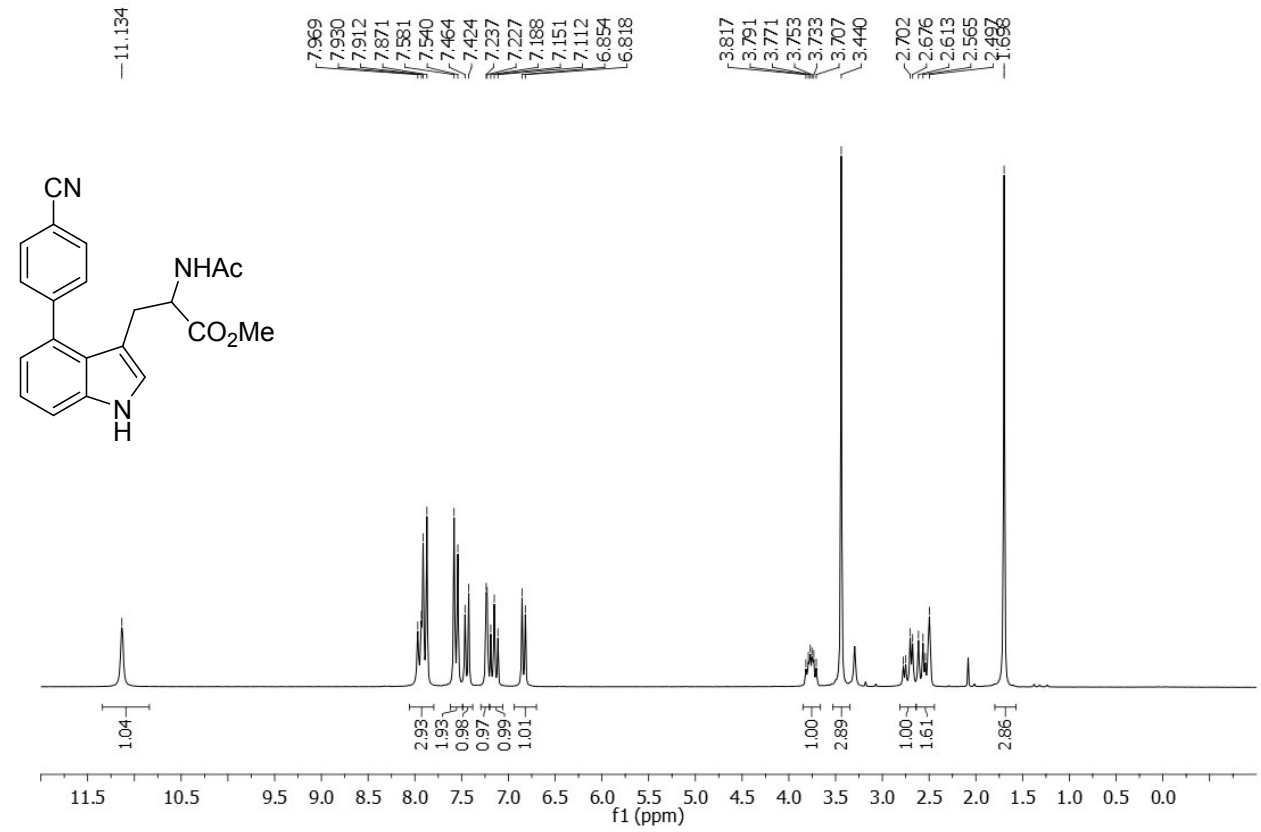
40.468
40.050
22.640
f1 (ppm)

Compound **2b**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7.969
7.930
7.912
7.871
7.581
7.540
7.464
7.424
7.237
7.227
7.188
7.151
7.112
6.854
6.818
3.817
3.791
3.771
3.753
3.733
3.707
3.440
2.702
2.676
2.613
2.565
2.497
1.698
CN
NHAc
CO2Me
N
H
1.04
2.93
1.93
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0.97
0.99
1.01
1.00
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1.00
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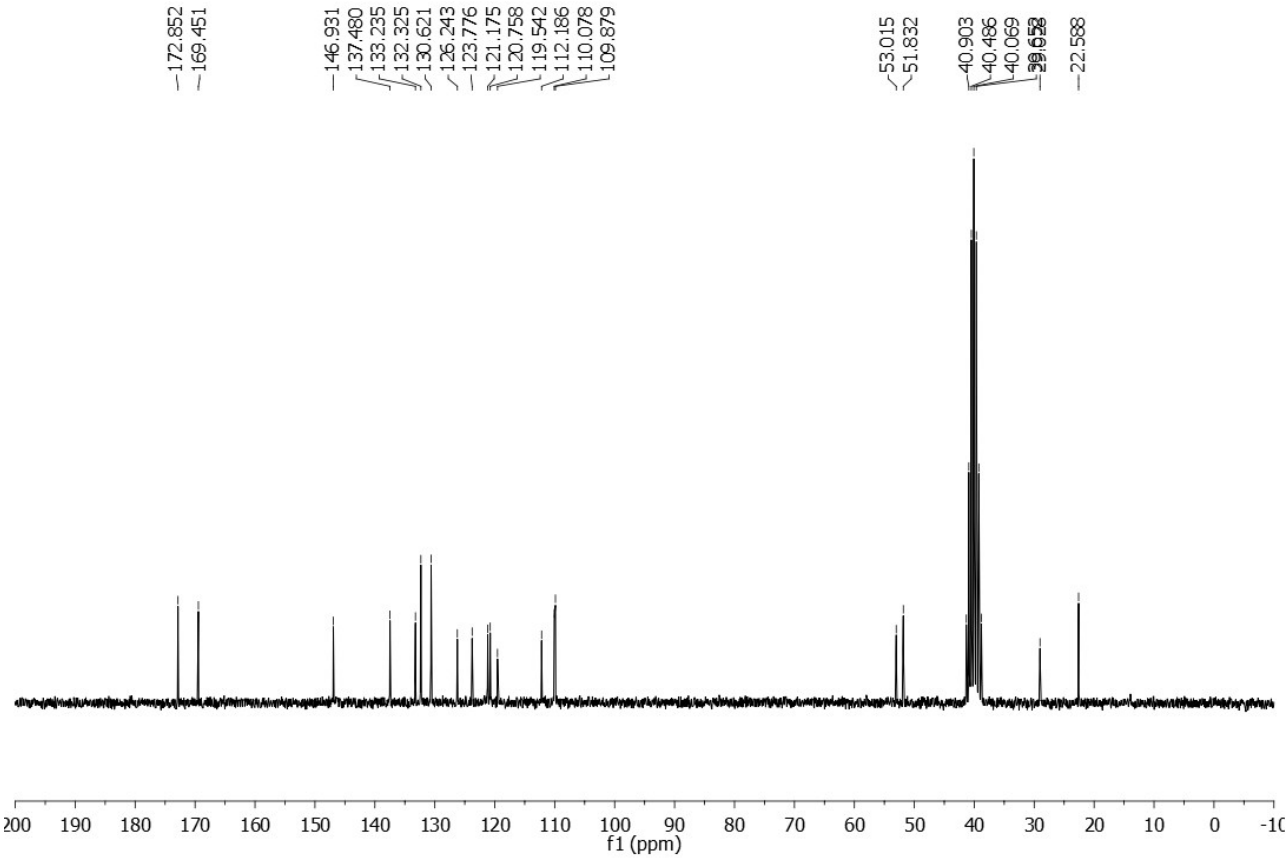
2.86
f1 (ppm)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121.175
120.758
119.542
112.186
110.078
109.879
53.015
51.832
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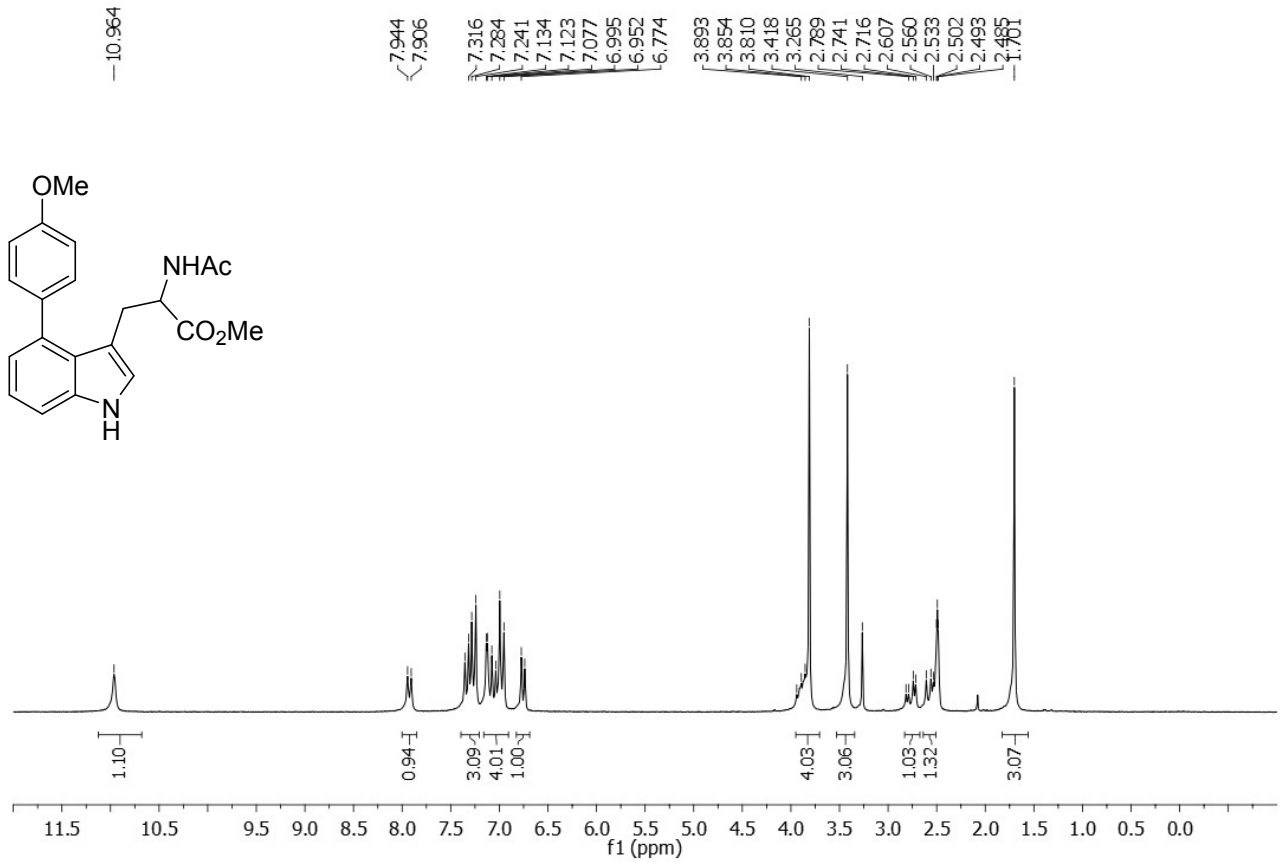
40.486
40.069
22.588
f1 (ppm)

Compound **2c**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7.316
7.284
7.241
7.134
7.123
7.077
6.995
6.952
6.774
3.893
3.854
3.810
3.418
3.265
2.789
2.741
2.716
2.607
2.560
2.533
2.502
2.493
1.701
OMe
NHAc
CO2Me
N
H
1.10
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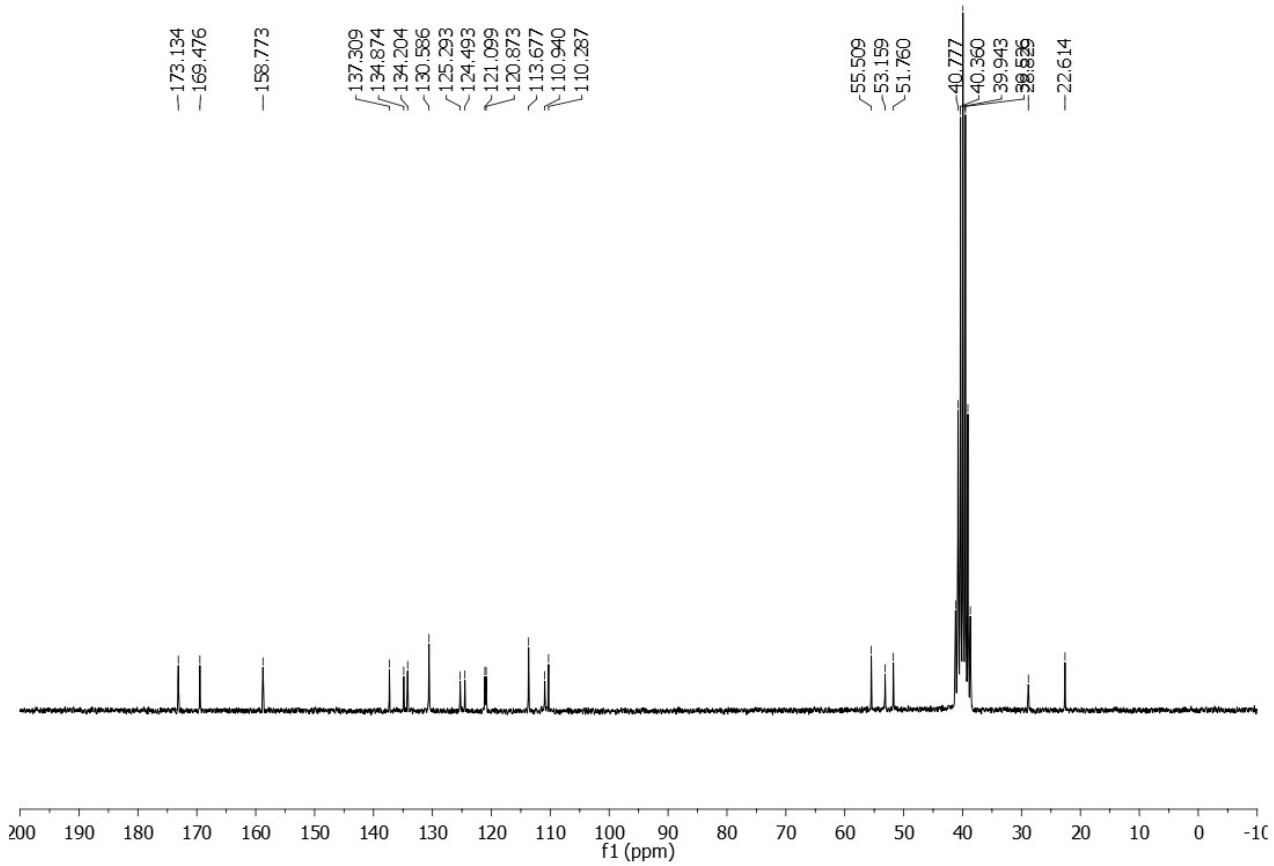
4.01
1.00
4.03
3.06
1.03
1.32
3.07
f1 (ppm)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134.204
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121.099
120.873
113.677
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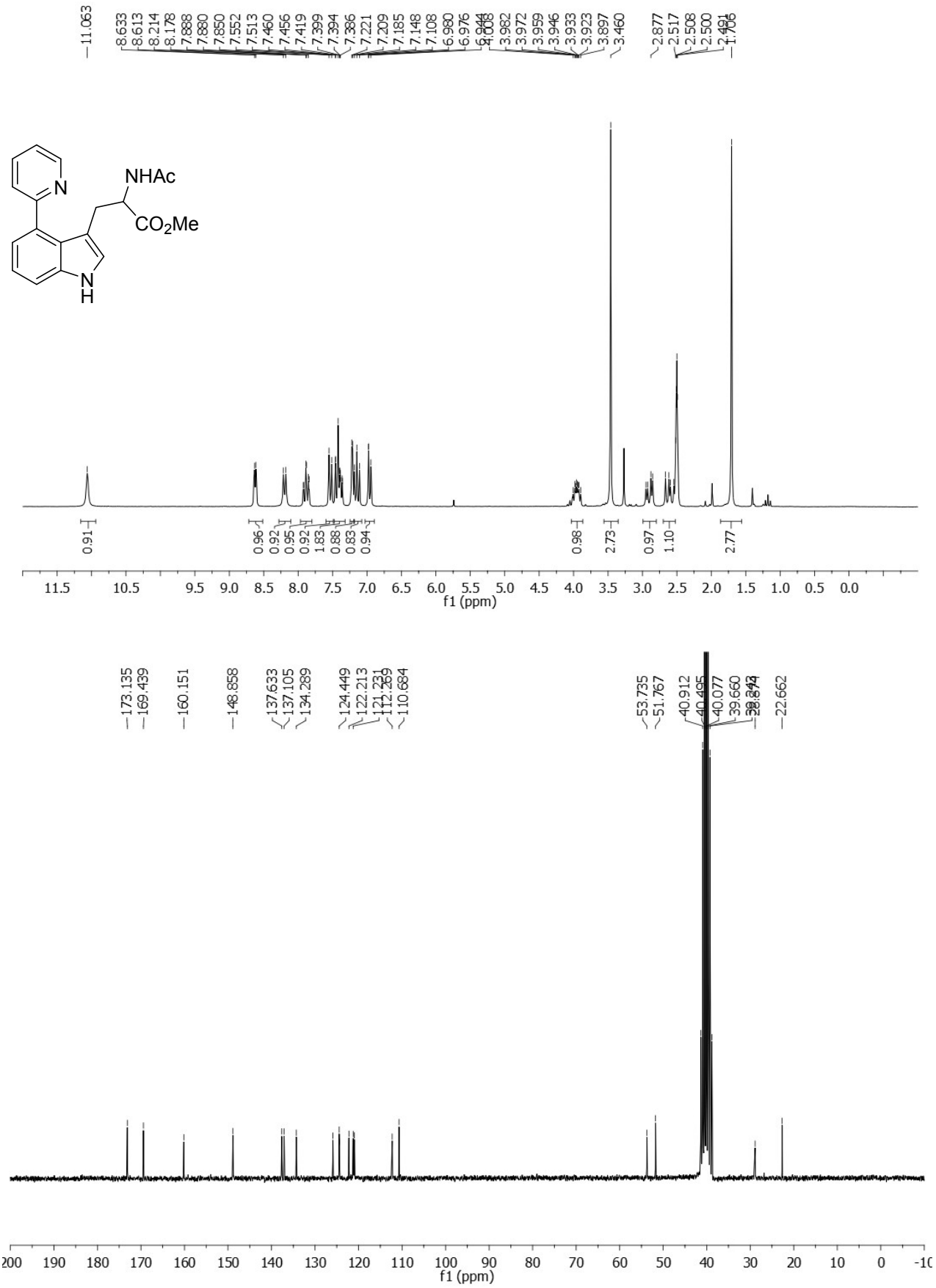
110.287
55.509
53.159
51.760
40.777
40.360
39.943
22.614
f1 (ppm)

Compound **2d**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8.613
8.214
8.178
7.888
7.880
7.850
7.552
7.513
7.460
7.456
7.419
7.399
7.394
7.386
7.221
7.209
7.185
7.148
7.108
6.980
6.976
6.944
4.008
3.982
3.972
3.959
3.946
3.933
3.923
3.897
3.460
2.877
2.517
2.508
2.500
2.491
1.706
NHAc
CO2Me
N
N
H
0.91
0.96
0.92
0.95
0.92
1.83
0.88
0.83
0.94
0.98
2.73
0.97
1.10
2.77
f1 (ppm)
173.135
169.439
160.151
148.858
137.633
137.105
134.289
124.449
122.213
121.231
112.289
110.684
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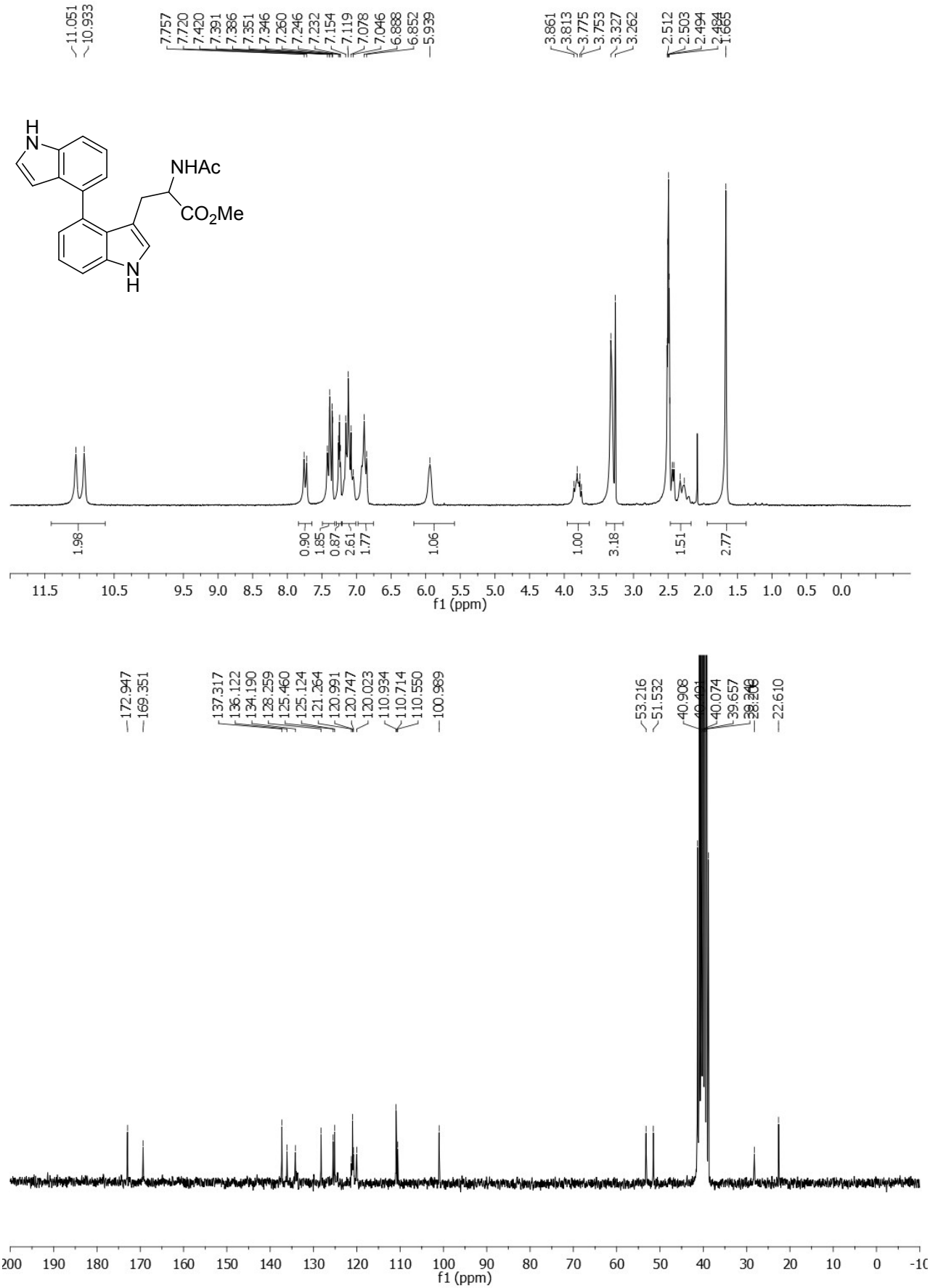
51.767
40.912
40.077
39.660
22.662
f1 (ppm)

Compound **2e**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7.260
7.246
7.232
7.154
7.119
7.078
7.046
6.888
6.852
5.939
3.861
3.813
3.775
3.753
3.327
3.262
2.512
2.503
2.494
2.484
1.685
H
N
NHAc
CO2Me
N
H
1.98
0.90
1.85
0.87
2.61
1.77
1.06
1.00
3.18
1.51
2.77
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
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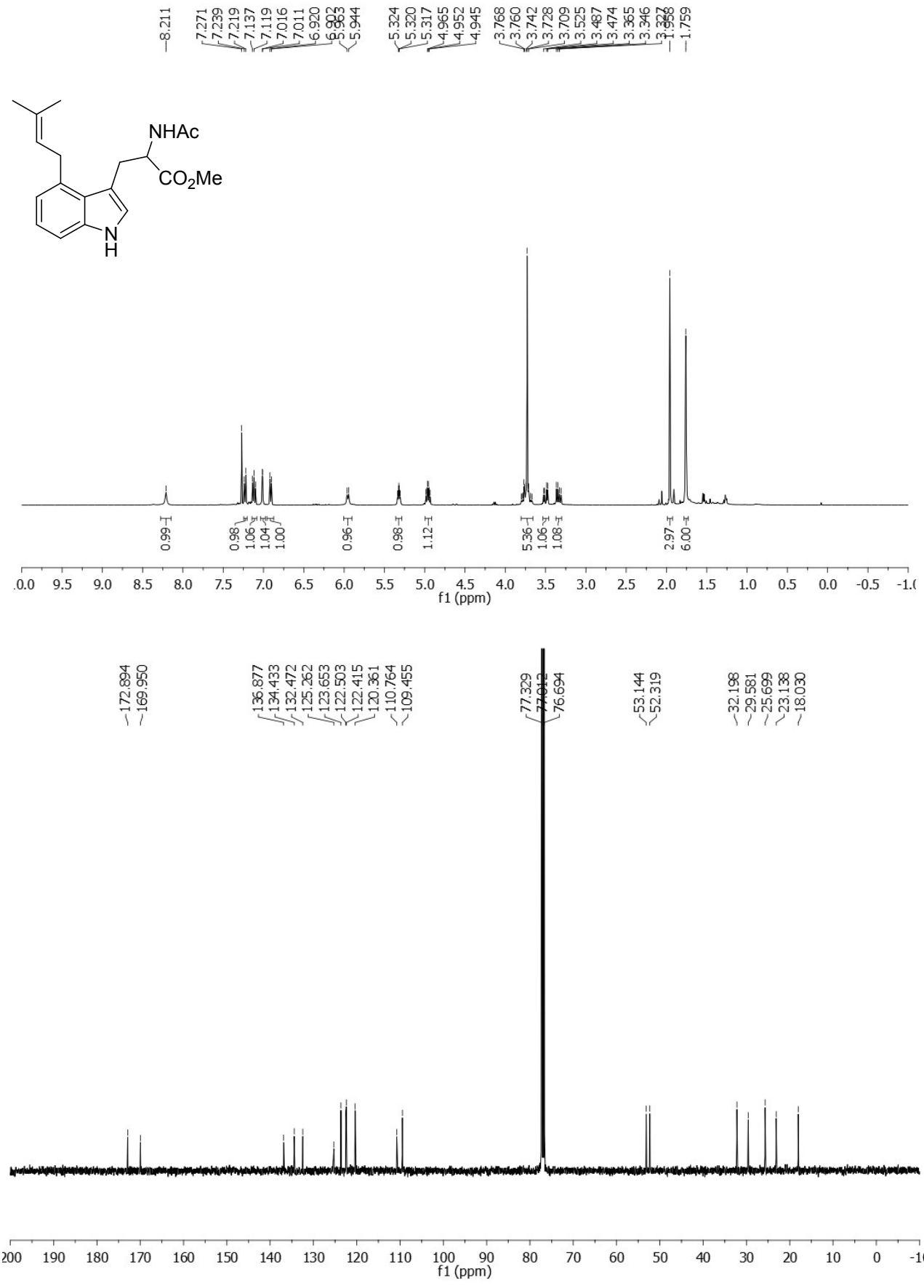
169.351
137.317
136.122
134.190
128.259
125.460
125.124
121.264
120.991
120.747
120.023
110.934
110.714
110.550
100.989
53.216
51.532
40.908
40.074
39.657
22.610
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

Compound **3**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7.219
7.137
7.119
7.016
7.011
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6.902
6.863
5.944
5.324
5.320
5.317
4.965
4.952
4.945
3.768
3.760
3.742
3.728
3.709
3.525
3.487
3.474
3.365
3.346
1.958
1.759
NHAc
CO2Me
N
H
0.99
0.98
1.06
1.04
1.00
0.96
0.98
1.12
5.36
1.06
1.08
2.97
6.00
f1 (ppm)
172.894
169.950
136.877
134.433
132.472
125.262
123.653
122.503
122.415
120.361
110.764
109.455
77.329
77.012
76.694
53.144
52.319
32.198
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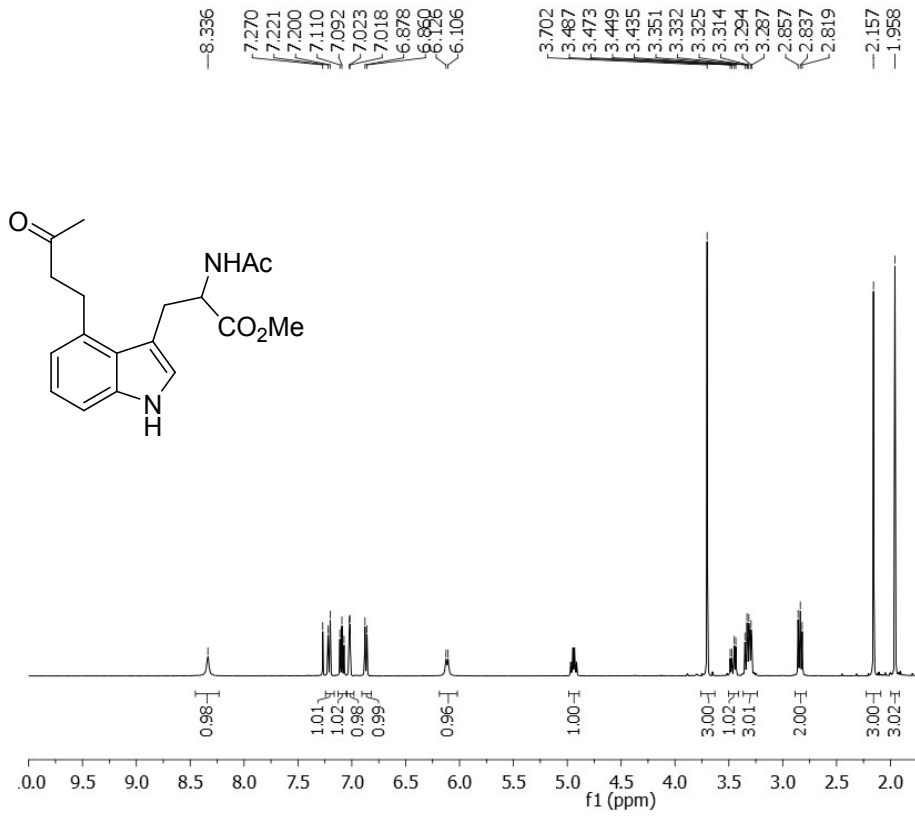
23.138
18.030
f1 (ppm)

Compound **4**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7.221
7.200
7.110
7.092
7.023
7.018
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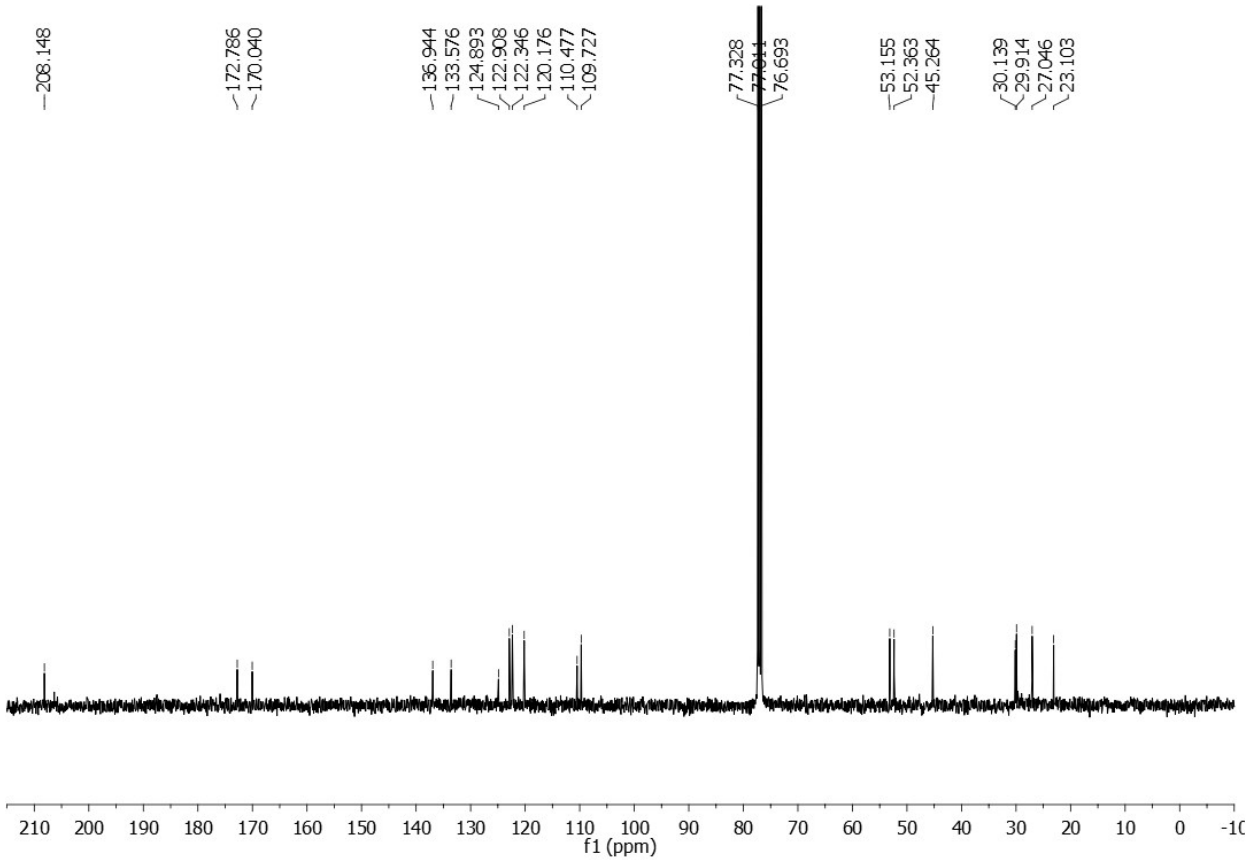
6.860
6.128
6.106
3.702
3.487
3.473
3.449
3.435
3.351
3.332
3.325
3.314
3.294
3.287
2.857
2.837
2.819
2.157
1.958
O
NHAc
CO2Me
N
H
0.98
1.01
1.02
0.98
0.99
0.96
1.00
3.00
1.02
3.01
2.00
3.00
3.02
f1 (ppm)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122.346
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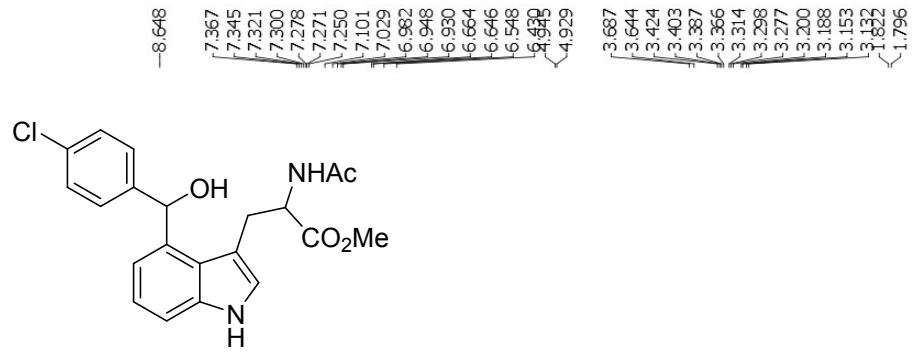
109.727
77.328
77.011
76.693
53.155
52.363
45.264
30.139
29.914
27.046
23.103
f1 (ppm)

Compound **5**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7.278
7.271
7.250
7.101
7.029
6.982
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6.930
6.664
6.646
6.548
4.945
4.929
3.687
3.644
3.424
3.403
3.387
3.366
3.314
3.298
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3.188
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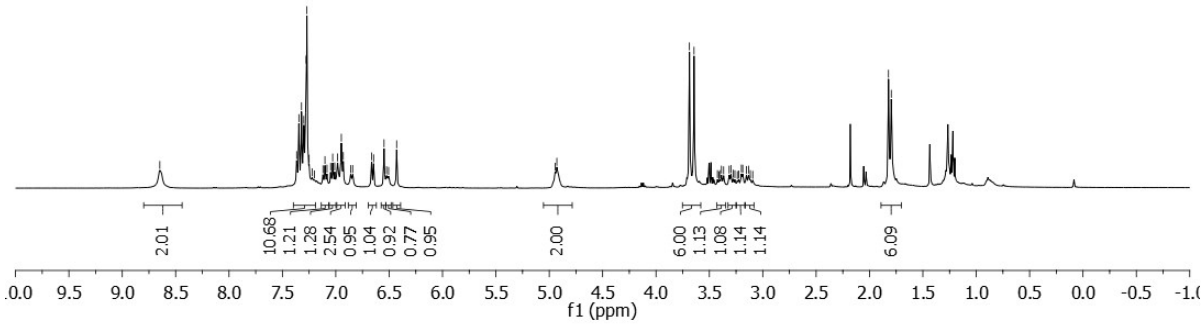
CO2Me
N
H


2.01
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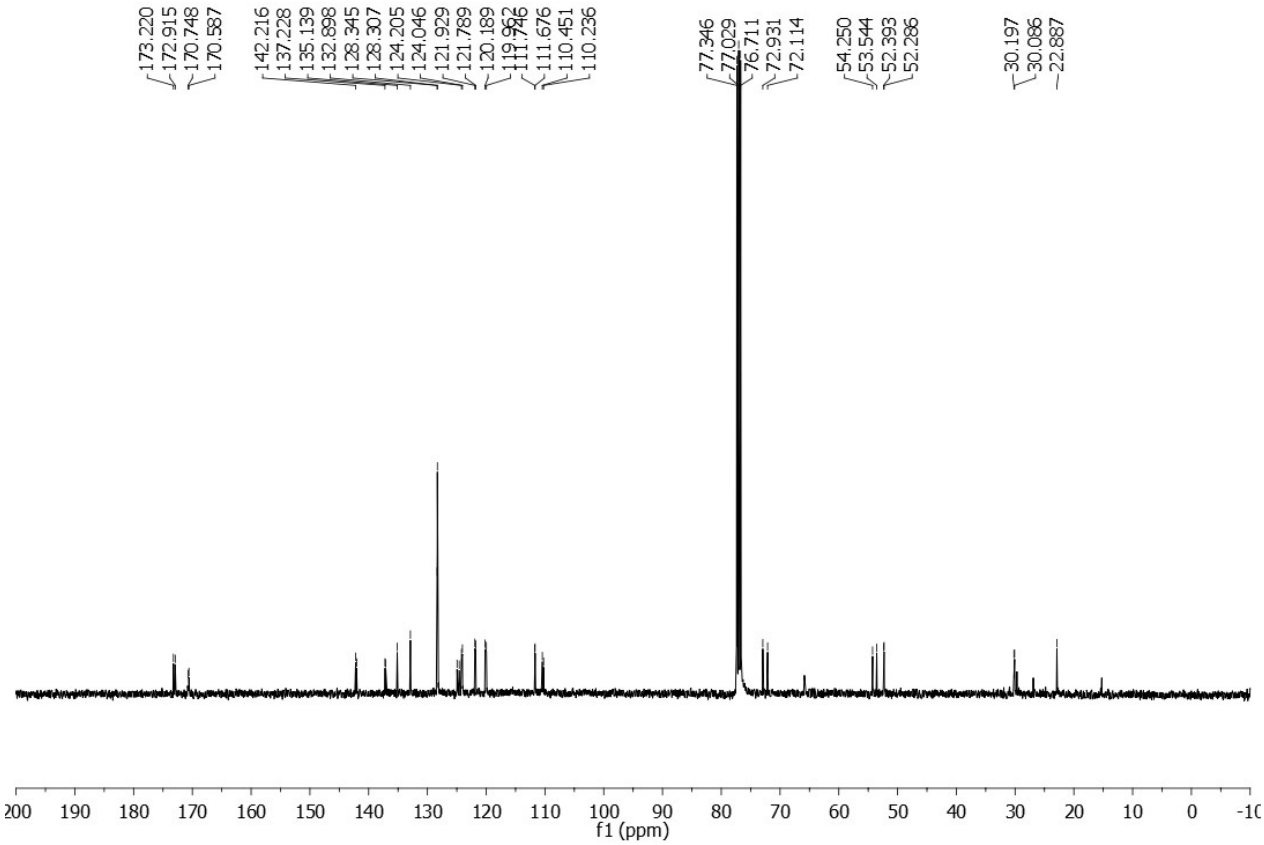
1.21
1.28
2.54
0.95
1.04
0.92
0.77
0.95
2.00
6.00
1.13
1.08
1.14
1.14
6.09
f1 (ppm)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170.587
142.216
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132.898
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128.307
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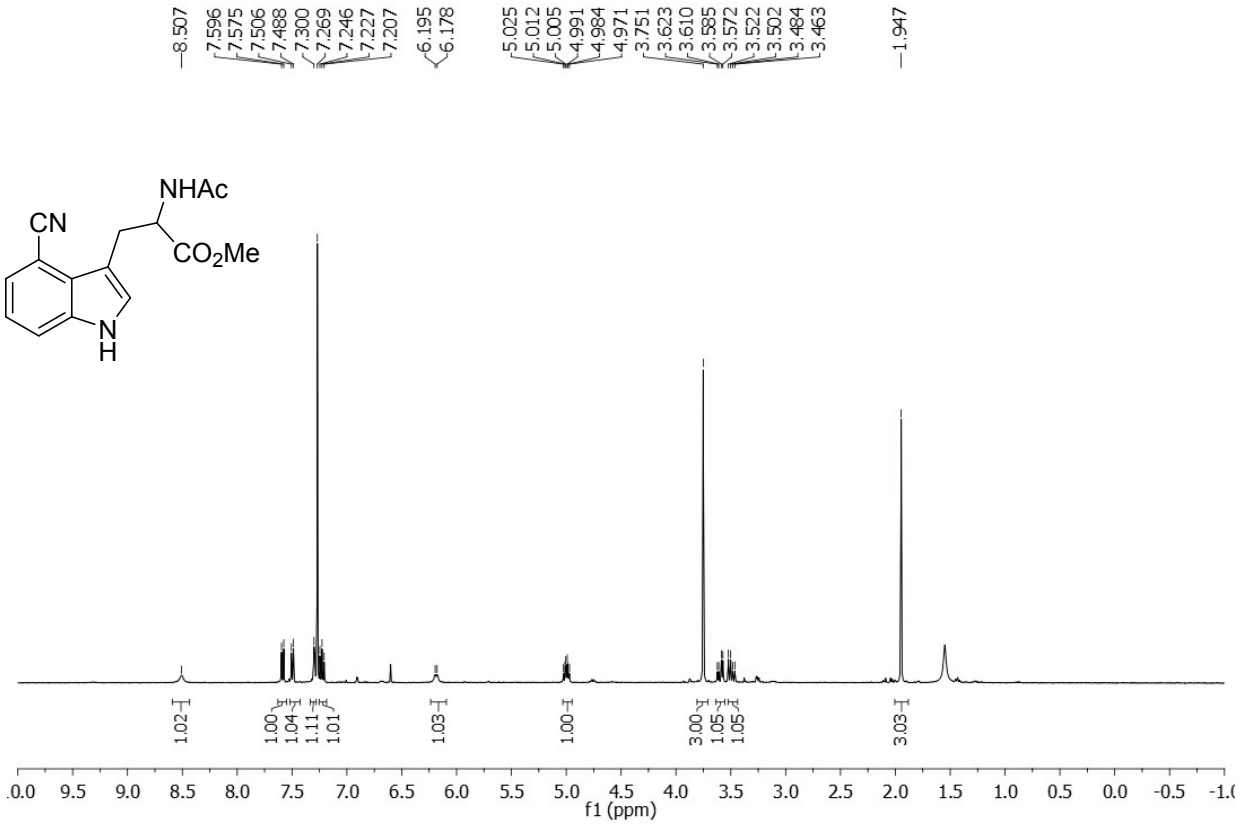
124.046
121.929
121.789
120.189
119.962
111.746
111.676
110.451
110.236
77.346
77.029
76.711
72.931
72.114
54.250
53.544
52.393
52.286
30.197
30.086
22.887
f1 (ppm)

Compound **6**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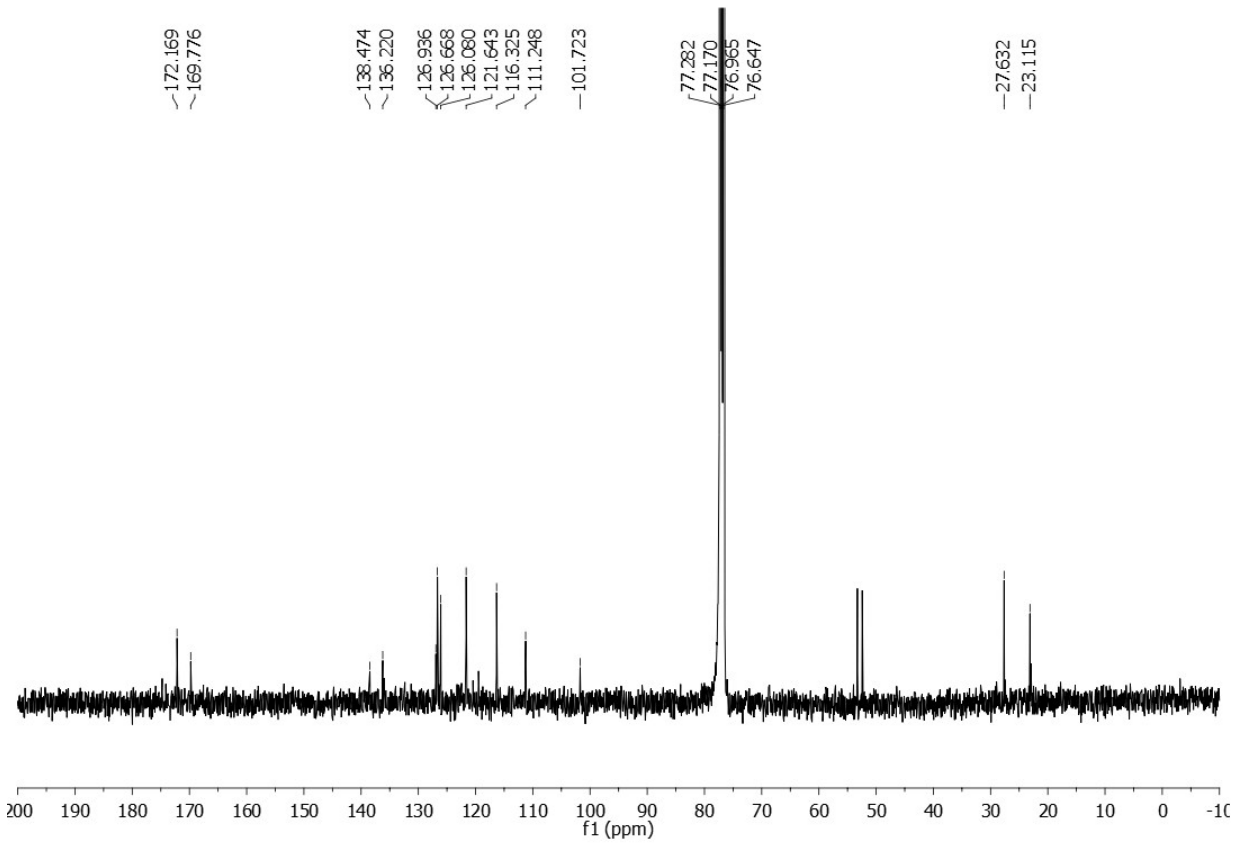
7.227
7.207
6.195
6.178
5.025
5.012
5.005
4.991
4.984
4.971
3.751
3.623
3.610
3.585
3.572
3.522
3.502
3.484
3.463
1.947
NHAc
CN
CO2Me
N
H
1.02
1.00
1.04
1.11
1.01
1.03
1.00
3.00
1.05
1.05
3.03
f1 (ppm)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121.643
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76.965
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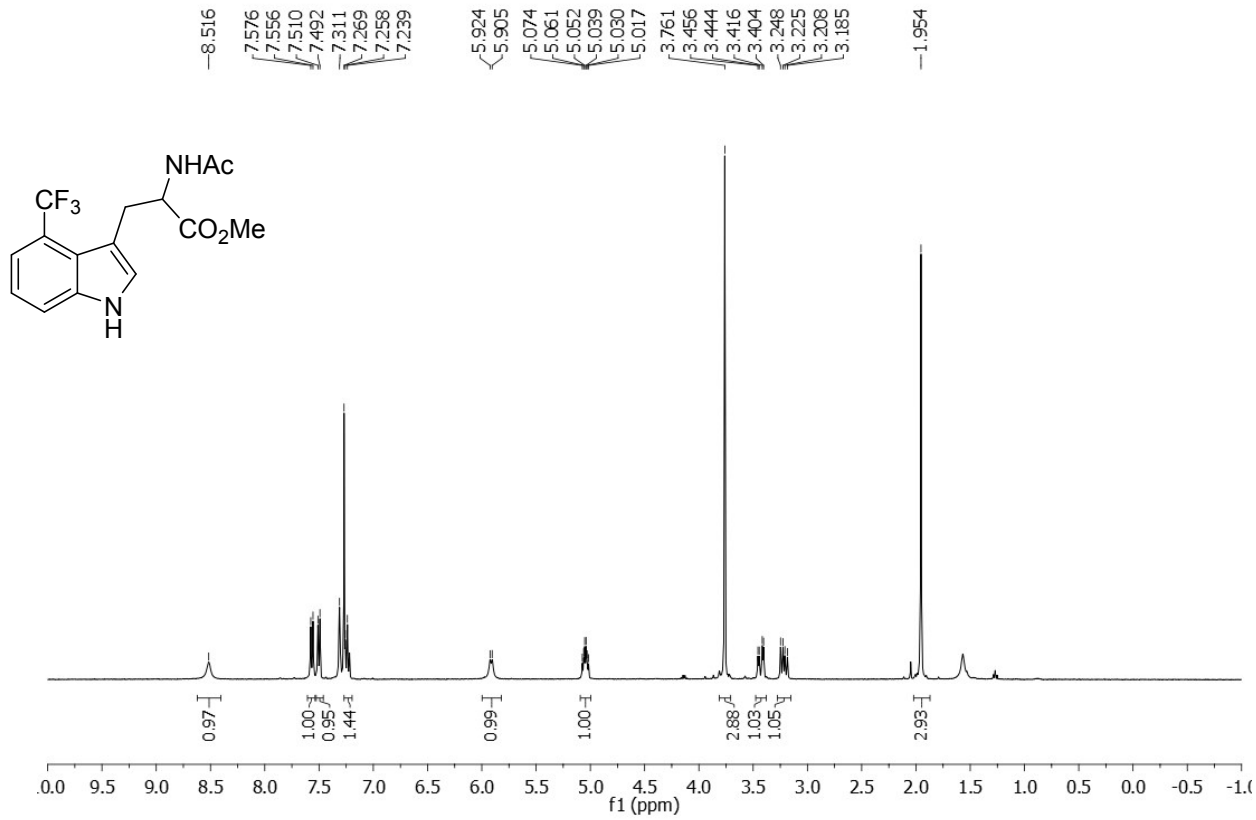
27.632
23.115
f1 (ppm)

Compound **7**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7.492
7.311
7.269
7.258
7.239
5.924
5.905
5.074
5.061
5.052
5.039
5.030
5.017
3.761
3.456
3.444
3.416
3.404
3.248
3.225
3.208
3.185
1.954
NHAc
CF3
CO2Me
N
H
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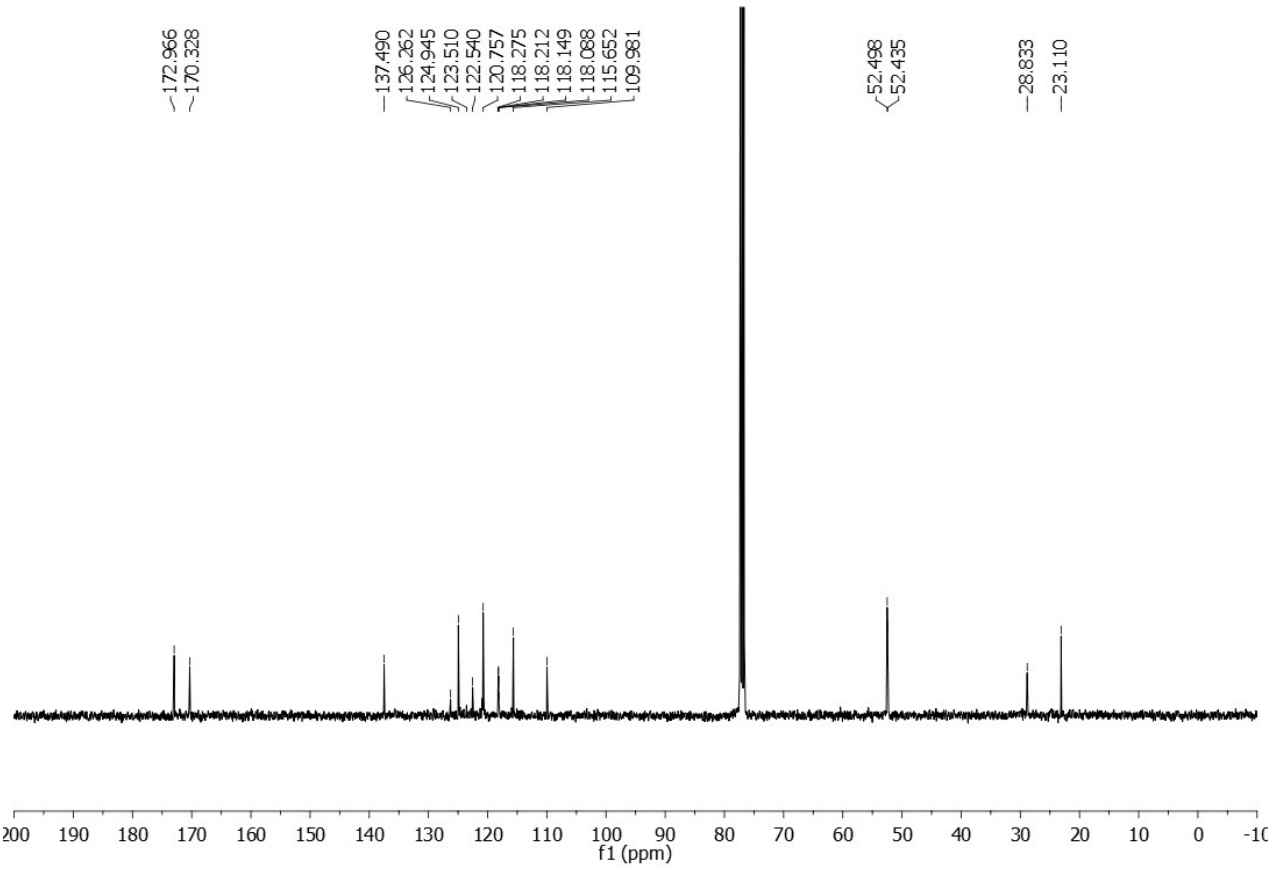
0.95
1.44
0.99
1.00
2.88
1.03
1.05
2.93
f1 (ppm)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124.945
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120.757
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118.212
118.149
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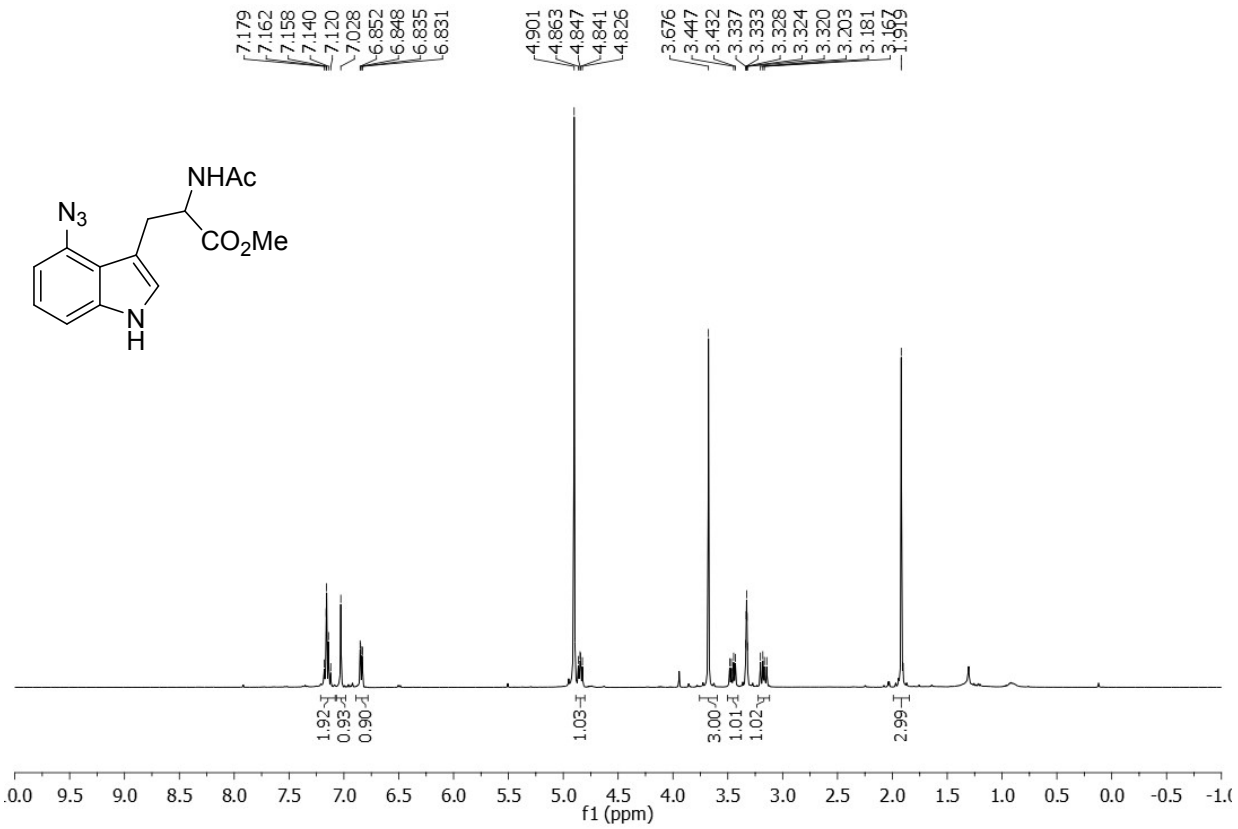
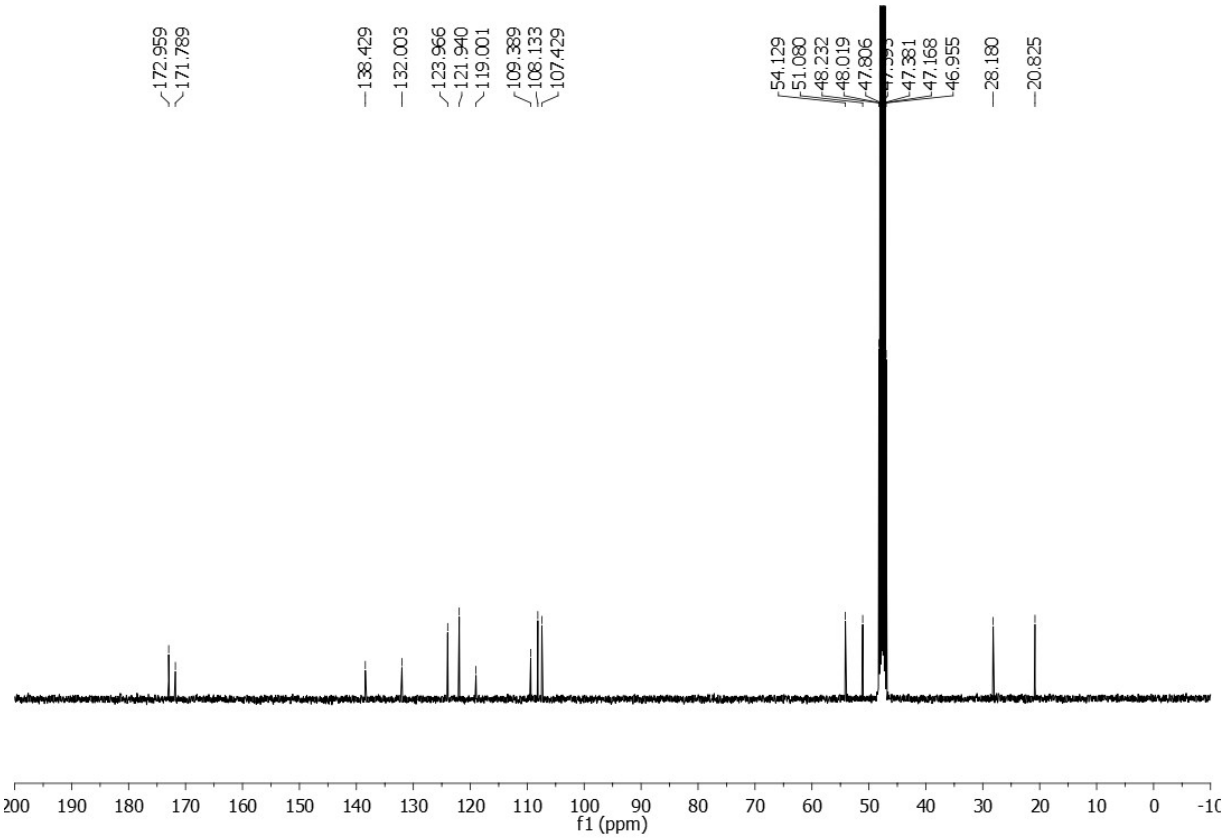
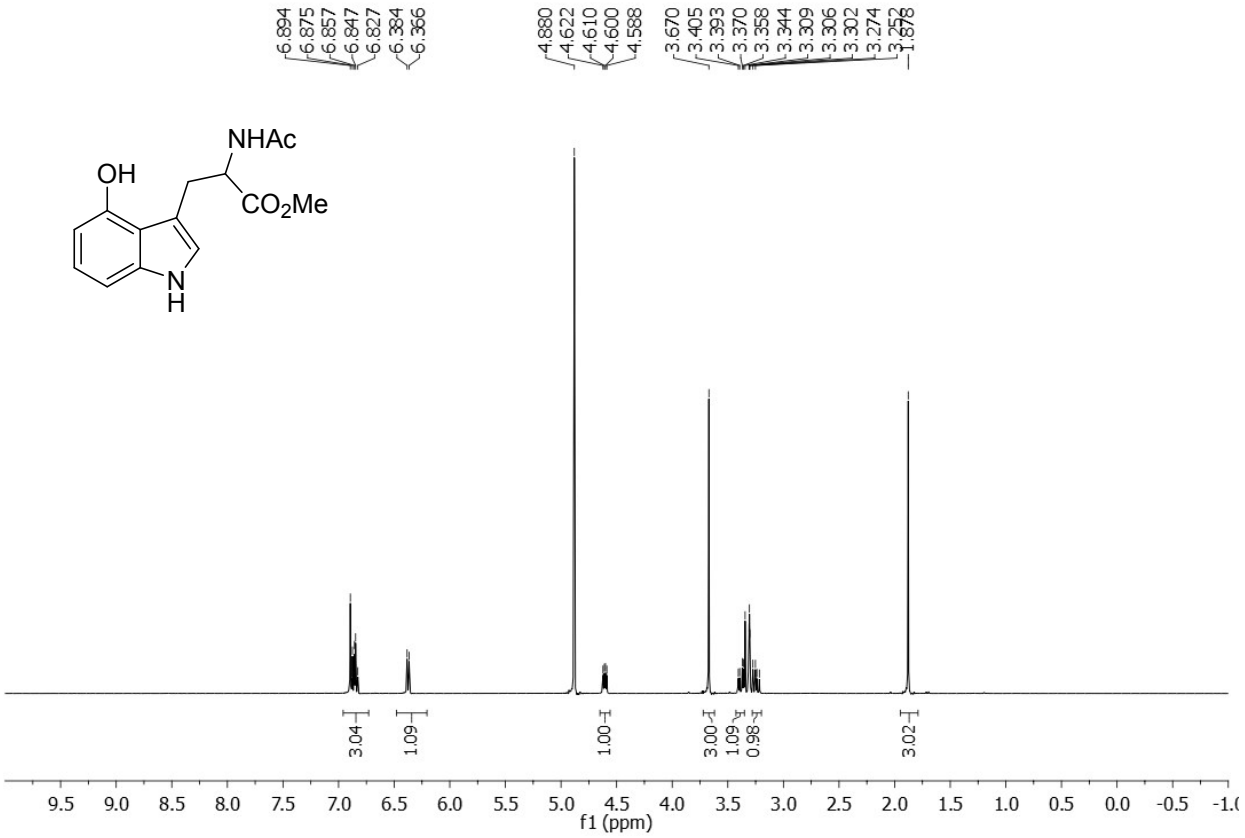
109.981
52.498
52.435
28.833
23.110
f1 (ppm)

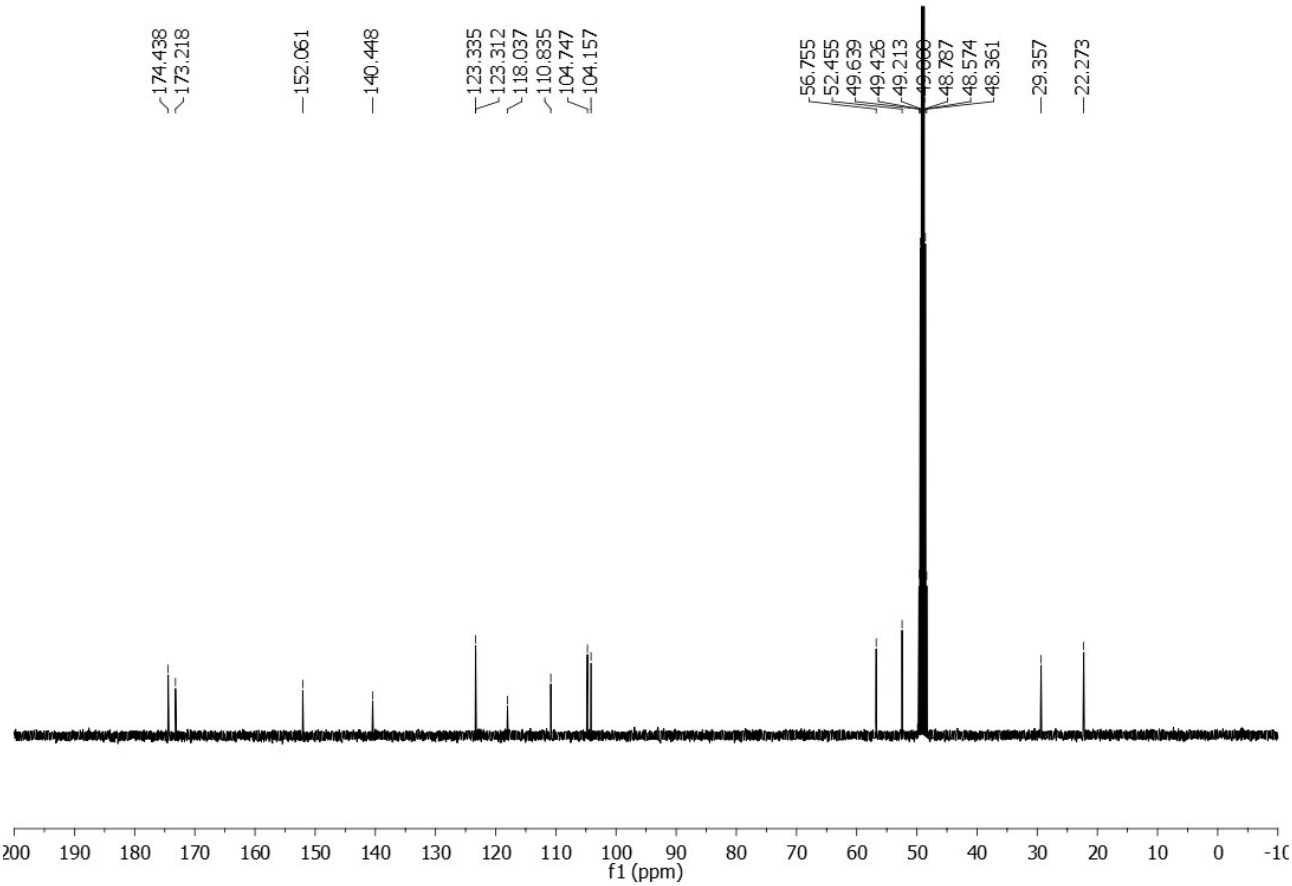
Compound **8**


7.179
7.162
7.158
7.140
7.120
7.028
6.852
6.848
6.835
6.831
4.901
4.863
4.847
4.841
4.826
3.676
3.447
3.432
3.337
3.333
3.328
3.324
3.320
3.203
3.181
3.167
1.919
NHAc
N3
CO2Me
N
H
1.92
0.93
0.90
1.03
3.00
1.01
1.02
2.99
f1 (ppm)

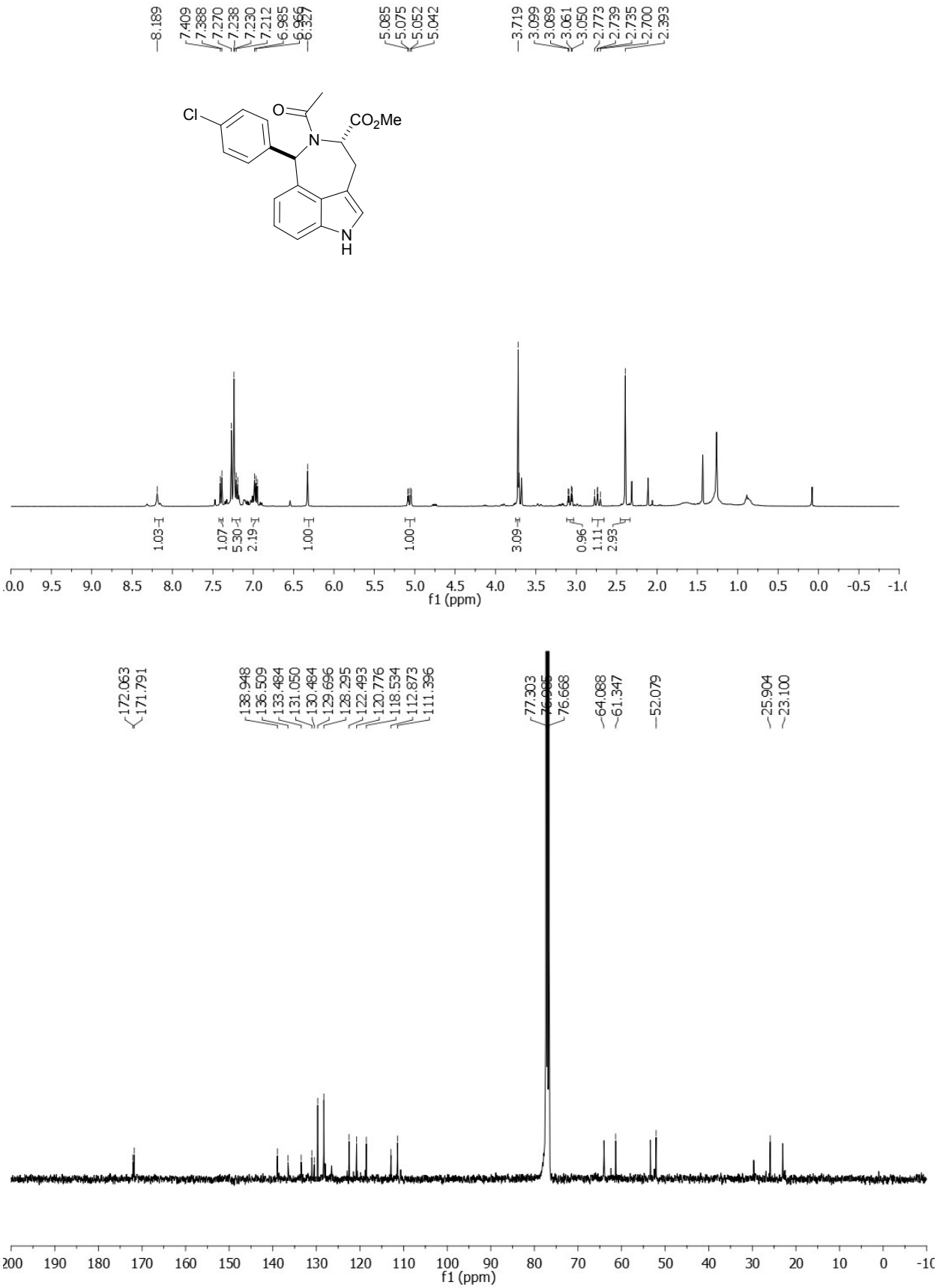

172.959
171.789
138.429
132.003
123.966
121.940
119.001
109.389
108.133
107.429
54.129
51.080
48.232
48.019
47.806
47.381
47.168
46.955
28.180
20.825
f1 (ppm)

Compound **9**


6.894
6.875
6.857
6.847
6.827
6.384
6.366
4.880
4.622
4.610
4.600
4.588
3.670
3.405
3.393
3.370
3.358
3.344
3.309
3.306
3.302
3.274
3.252
1.678
NHAc
OH
CO2Me
N
H
3.04
1.09
1.00
3.00
1.09
0.98
3.02
f1 (ppm)


174.438
173.218
152.061
140.448
123.335
123.312
118.037
110.835
104.747
104.157
56.755
52.455
49.639
49.426
49.213
49.000
48.787
48.574
48.361
29.357
22.273
f1 (ppm)

Compound **10**


8.189
7.409
7.388
7.270
7.238
7.230
7.212
6.985
6.966
6.357
5.085
5.075
5.052
5.042
3.719
3.099
3.089
3.061
3.050
2.773
2.739
2.735
2.700
2.393
Cl
O
N
CO2Me
N
H
1.03
1.07
5.30
2.19
1.00
1.00
3.09
0.96
1.11
2.93
f1 (ppm)
172.063
171.791
138.948
136.509
133.484
131.050
130.484
129.696
128.295
122.493
120.776
118.534
112.873
111.396
77.303
76.985
76.668
64.088
61.347
52.079
25.904
23.100
f1 (ppm)

NOESY of compound **10** ($CDCl_3$, 400MHz)