Electronic Supplementary Material (ESI) for Reaction Chemistry & Engineering.

A Hybrid Machine-Assisted Multistep Continuous Flow - Microwave Approach for Fast-Following Library Preparation of Bioactive Compounds

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1 General Methods

All reagents and solvents were commercially available and were used without further purification unless stated otherwise. Petroleum ether refers to the 40-60 °C fraction.

For the measurement of ^{1}H, ^{13}C and ^{19}F NMR spectra a Bruker Fourier^{300} (300 MHz), 400 UltraShield^{TM} (400 MHz) or Ascend^{TM}500 (500 MHz) were used. The obtained chemical shifts δ are reported in ppm and are referenced to the residual solvent signal or to the standard trifluorotoluene (-63.72 ppm) in ^{19}F NMR. Spin-spin coupling constants J are given in Hz and refer to apparent multiplicities rather than true coupling constants. Data is reported as: chemical shift, multiplicity and integration. Carbon shifts are reported to the nearest 0.5 ppm and the number of signals rounded to the same value is indicated in brackets. Carbons in an identical environment giving one signal are not indicated further.

The flow setup consisted of PFA tubing of an 0.8 mm ID and four pumps. There was little back pressure generated in the system, so that both syringe pumps and HPLC pumps were used successfully in this work. Residence coils were made from the tubing by taking the appropriate length for the desired volume.

Column chromatography was performed using 60 A (40-64 micron) silica and solvent mixtures of petroleum ether and ethyl acetate unless stated otherwise.

High resolution mass spectral (HRMS) data were obtained on a Waters MALDI-TOF mx at Cardiff University or on a Thermo Scientific LTQ Orbitrap XL by the EPSRC UK National Mass Spectrometry Facility at Swansea University.

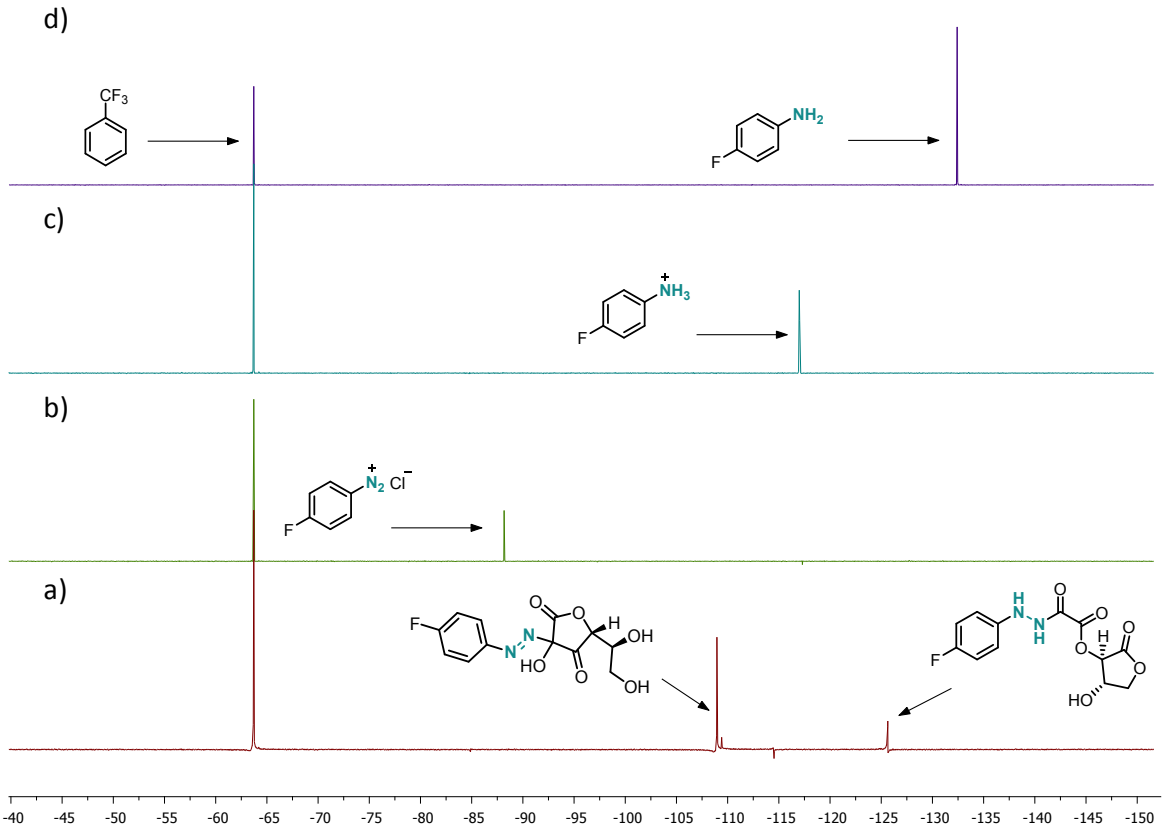
IR spectra were obtained from a Shimadzu IR-Affinity-1S FTIR and melting points using a Gallenkamp apparatus and are reported uncorrected.

References to spectroscopic data are given for known compounds.

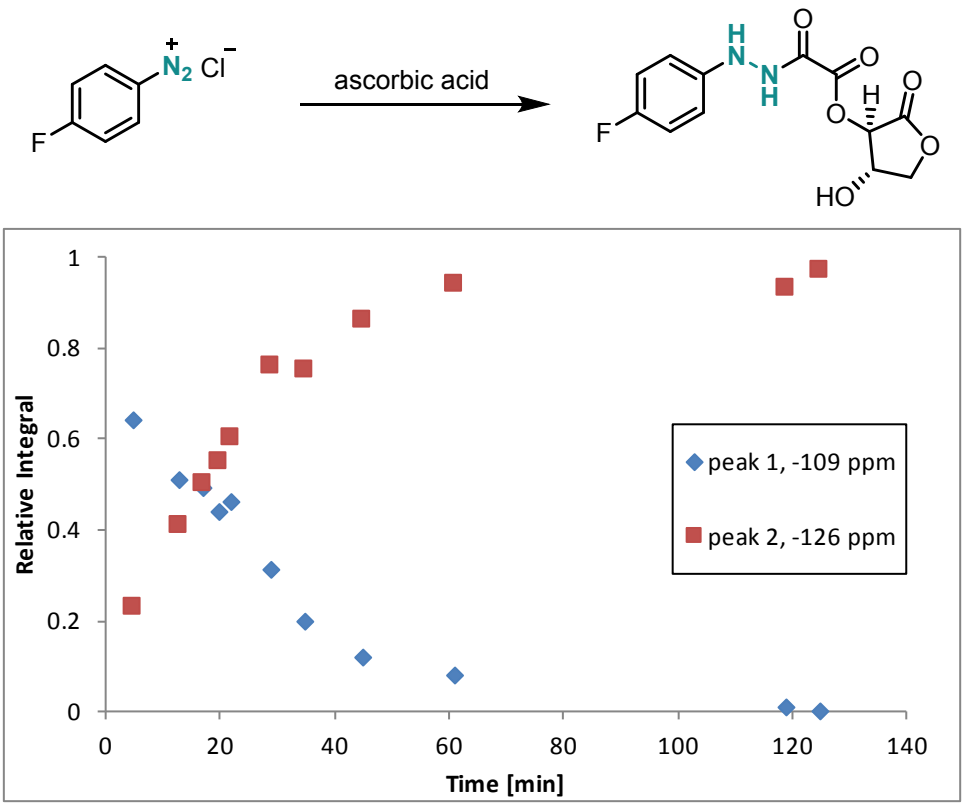
2 Method for the optimization of the multistep indole synthesis

2.1 Investigating the hydrazide formation by ^{19}F NMR

p-Fluoroaniline (0.111 g, 1 mmol) was dissolved in MeCN (5 mL) in a 50 mL RBF equipped with a stirrer bar and trifluorotoluene (41 µL, 0.33 mmol, 0.33 equiv) added as the internal standard. To that reaction solution aqueous HCl (5 mL, 1 M, 5 mmol, 5 equiv) was added and a ^{19}F NMR taken. After recombining the solutions and cooling in ice-water isoamylnitrite (0.117 g, 1 mmol, 1 equiv) in MeCN (5 mL) was added and another ^{19}F NMR was taken. After recombining, ascorbic acid (0.176 g, 1 mmol, 1 equiv) in water (5 mL) was added at room temperature and the reaction monitored over time via ^{19}F NMR.



Scheme 2: ^{19}F NMR monitoring of the reaction with internal standard; a) *p*-fluoroaniline in MeCN; b) after addition of HCl; c) after addition of isoamylnitrite, diazonium salt; d) after addition of ascorbic acid, two new peaks observed



Scheme 3: ^{19}F NMR monitoring of the reaction over time after addition of ascorbic acid

2.2 Optimization of the Microwave Step

To a solution of *p*-fluorophenylhydrazine hydrochloride (0.163 g, 1 mmol) in acetonitrile (10 mL) and aqueous HCl (0.2 M, 5 mL) in a 35 mL microwave vial neat cyclohexanone was added (0.098 g, 1 mmol, 1 equiv). The reaction mixture was heated in the microwave for 10 min at 120 °C. After cooling to room temperature, the product conversion was determined via ^{19}F NMR from the crude reaction mixture (98%). The NMR solution was then combined with the rest of the reaction mixture. This was then diluted with 10 mL H_2O and the product extracted with DCM (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure to give the product in 97% isolated yield (0.184 g, 0.97 mmol).

To a solution of *p*-fluoroaniline (0.111 g, 1 mmol) in acetonitrile (5 mL) in a 35 mL microwave vial a solution of HCl (0.2 M in water, 5 mL, 1 mmol, 1 equiv) was added. After cooling to 0 °C, isoamylnitrite (0.117 g, 1 mmol, 1 equiv) in acetonitrile (5 mL) was added slowly. The ice bath was removed and a solution of ascorbic acid (0.176 g, 1 mmol, 1 equiv) in water (5 mL) was added. The reaction mixture was left to stir for

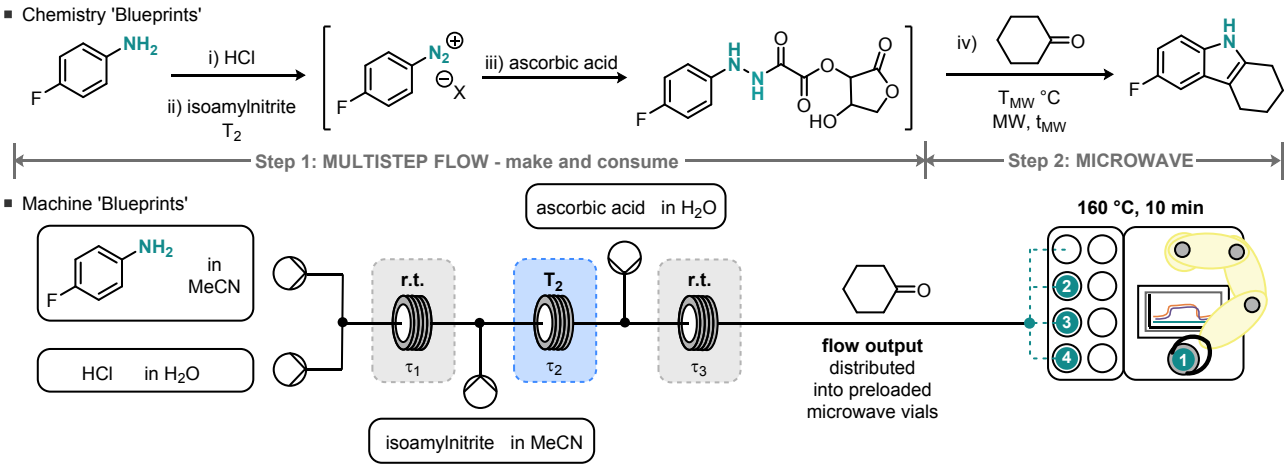
30 min before neat cyclohexanone was added (0.098 g, 1 mmol, 1 equiv). The reaction mixture was heated in the microwave for the appropriate time and temperature. After cooling to room temperature, the product conversion was determined via ^{19}F NMR from the crude reaction mixture.

Table 1: Optimization of the microwave step; a: 5 mL of 1 M HCl added (5 mmol, 5 equiv); b: 1.2 equiv of IAN

entry	hydrazine source	T_{MW} [°C]	t_{MW} [min]	^{19}F yield [%]
1	commercial	120	10	98 (97)
2	in situ prepared	120	10	15
3	in situ prepared	140	10	30
4	in situ prepared	160	10	52 (47)
5	in situ prepared	180	10	46
6	in situ prepared	160	30	48
7[a]	in situ prepared	160	10	67
8[a,b]	**in situ prepared**	**160**	**10**	**73**

2.3 Optimization of the Telescoped Process

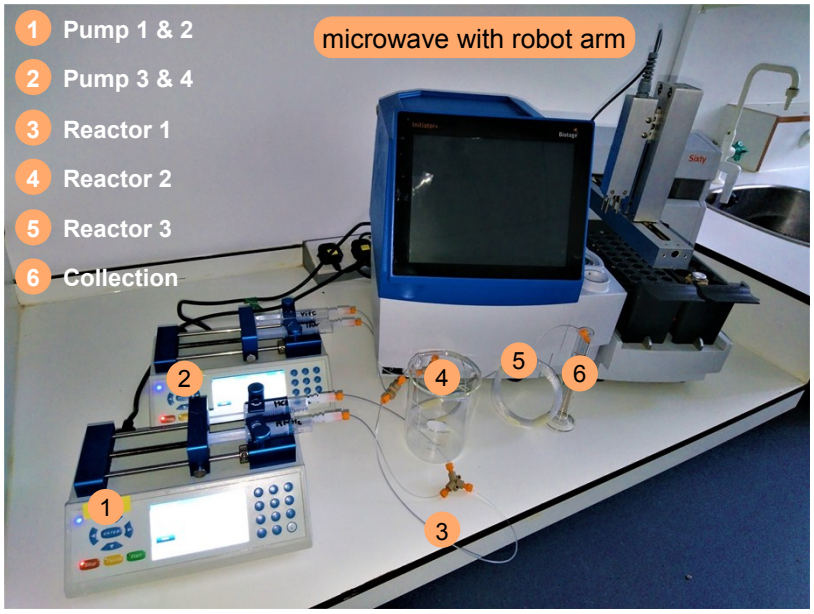
Solutions of *p*-fluoroaniline (0.2 M in acetonitrile), HCl (in water), isoamylnitrite (in acetonitrile) and ascorbic acid (in water) were prepared. These were then pumped through the flow system (see Scheme 1) at a flow rate of 0.2 $mLmin^{-1}$. After waiting for steady state for 20 min, fractions of 20 mL (1 mmol, 25 min) were collected. The neat cyclohexanone (0.098 g, 1 mmol) was added into a 35 mL microwave vial equipped with a stirrer bar and the reaction solution was added. The reaction mixture was heated in the microwave for the 10 min at 160 °C. After cooling to room temperature trifluorotoluene (0.041 mL, 0.33 mmol) was added and yield determined by ^{19}F NMR.



Optimization of Step 1 machine parameters

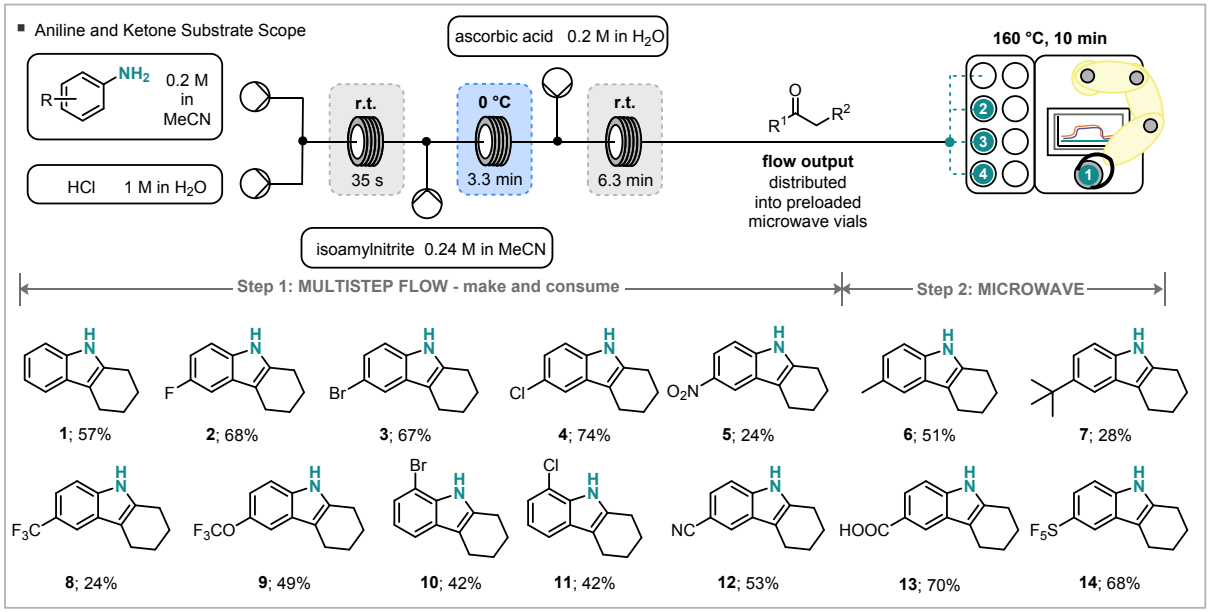
entry	c (HCl) [mol/L]	c (isoamylnitrite) [mol/L]	c (Vit C) [mol/L]	T_2 [°C]	τ_1 [min]	τ_2 [min]	τ_3 [min]	^{19}F yield %
1	0.2	0.24	0.2	0	0.6	3.3	6.3	41
2	1	0.2	0.2	0	0.6	3.3	6.3	72
3	1	0.24	0.24	0	0.6	3.3	6.3	62
4	1	0.24	0.2	rt	0.6	3.3	6.3	53
5	1	0.24	0.2	0	5	3.3	6.3	60
6	1	0.24	0.2	0	0.6	1.7	6.3	64
7	1	0.24	0.2	0	0.6	8.3	6.3	65
8	1	0.24	0.2	0	0.6	3.3	2.5	64
9	1	0.24	0.2	0	0.6	3.3	12.5	64
10	**1**	**0.24**	**0.2**	**0**	**0.6**	**3.3**	**6.3**	**74 (68)**

Table 2: Optimization of the Telescoped Process



Picture 1: Picture of the Optimized Setup

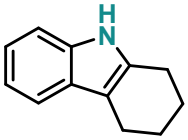
3 General Method for the Synthesis of Indoles 1-14: Aniline Screen



Scheme 4: Aniline Substrate Scope

Solutions of the aniline (2 mmol, 10 mL of 0.2 M solution in acetonitrile), HCl (10 mL of 1 M aqueous solution), isoamylnitrite (0.281 g, 2.4 mmol, 10 mL of 0.24 M solution in acetonitrile) and ascorbic acid (0.352 g, 2 mmol, 10 mL of 0.2 M aqueous solution) were prepared. These were then pumped through the flow system (see Scheme 4) at a flow rate of 0.2 mLmin^{-1}. After waiting for steady state for 20 min, fractions of 20 mL (1 mmol, 25 min) were collected. The neat cyclohexanone (0.098 g, 1 mmol) was added into a 35 mL microwave vial equipped with a stirrer bar and the reaction solution added. The reaction mixture was heated in the microwave (160 °C, 10 min). After cooling to room temperature, the reaction mixture was diluted with 10 mL water and extracted with DCM (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was then further purified via column chromatography (EtOAc in petroleum ether, 0 to 5%).

2,3,4,9-Tetrahydro-1H-carbazole (1)[1]



Following the general procedure, **1** was synthesized from aniline (2 mmol, 0.186 g) and obtained as a yellow solid (57%, 0.097 g, 0.57 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (bs, 1H), 7.48 (d, *J* = 7.4 Hz, 1H), 7.28 (d, *J* =7.9 Hz, 1H), 7.16 - 7.06 (m, 2H), 2.73 - 2.96 (m, 4H), 1.99 - 1.83 (m, 4H) ppm.

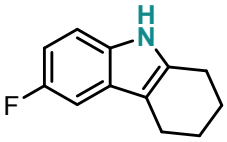
^{13}C NMR (101 MHz, $CDCl_3$) δ 136.0, 134.5, 128.0, 121.0, 119.5, 118.0, 110.5, 110.0, 23.5, 23.5, 23.5, 21.0 ppm.

mp: 106 - 108 °C.

IR: 3394, 3016, 2926, 2846, 1591, 1613, 1467, 1438, 1363, 1325, 1303, 1234, 1143, 1108, 918, 8134, 636, 596, 578, 542, 478, 426 cm^{-1}.

HRMS (EI^+) Calcd. for $[C_{12}H_{13}N]^+$ 170.0970; Found 170.0974.

6-Fluoro-2,3,4,9-tetrahydro-1H-carbazole (2)[1]



Following the general procedure, **2** was synthesized from *p*-fluoroaniline (2 mmol, 0.222 g) and obtained as a yellow solid (68%, 0.128 g, 0.68 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (bs, 1H), 7.17 (dd, *J* =8.6, 4.3 Hz, 1H), 7.10 (d, *J* =9.6 Hz, 1H), 6.84 (t, *J* =9.0 Hz, 1H), 2.74 - 2.69 (m, 4H), 1.96−1.79 (m, 4H) ppm.

^{19}F NMR (376 MHz, $CDCl_3$) δ -125.43 (S) ppm.

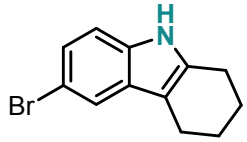
^{13}C NMR (101 MHz, $CDCl_3$) δ 158.0 (d, *J* =233.5 Hz), 136.5, 132.0, 128.0 (d, *J* =9.6 Hz, 111.0 (d, *J* =9.7 Hz), 110.5 (d, *J* =4.4 Hz), 109.0 (d, *J* =26.1 Hz), 103.0 (d, *J* =23.2 Hz), 23.5, 23.5, 23.5, 21.0 ppm.

mp (DCM): 96 - 98 °C.

IR: 3404, 2931, 2850, 1615, 1581, 1479, 1444, 1319, 1251, 1230, 1180, 1128, 1107, 1062, 920, 854, 792, 704, 601, 472 cm^{-1}.

HRMS (AP^+) Calcd. for $[C_{12}H_{12}FN]^+$ 189.0954; Found 189.0953.

6-Bromo-2,3,4,9-tetrahydro-1H-carbazole (3)[2]



Following the general procedure, **3** was synthesized from *p*-bromoaniline (2 mmol, 0.344 g) and obtained as a yellow solid (64%, 0.159 g, 0.64 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (bs, 1H), 7.57 (s, 1H), 7.18 (d, *J* = 8.5 Hz, 1H), 7.13 (d, *J* = 8.5 Hz, 1H), 2.73-2.64 (m, 4H), 1.97 - 1.79 (m, 4H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 136.5, 134.5, 130.0, 123.5, 120.5, 112.5, 112.0, 110.0,

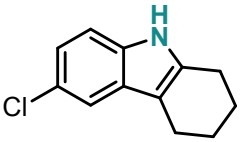
23.5 (2C), 23.0, 21.0 ppm.

mp (DCM): 146 - 147 °C.

IR: 3402, 2937, 2846, 1737, 1433, 1309, 1232, 1045, 975, 862, 796, 743, 640, 584, 478 cm^{-1}.

HRMS (AP^+) Calcd. for $[C_{12}H_{12}BrN]^+$ 250.0231; Found 250.0242.

6-Chloro-2,3,4,9-tetrahydro-1H-carbazole (4)[3]



Following the general procedure, **4** was synthesized from *p*-chloroaniline (2 mmol, 0.254 g) and obtained as a yellow solid (74%, 0.131 g, 0.74 mmol).

^1H NMR (400 MHz, $CDCl_3$) δ 7.66 (bs, 1H), 7.42 (s, 1H), 7.16 (d, *J* = 8.5 Hz, 1H), 7.06 (d, *J* =8.5 Hz, 1H), 2.73 - 2.65 (m, 4H), 1.96 - 1.82 (m, 4H) ppm.

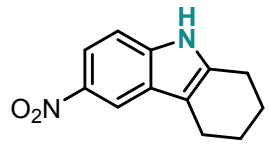
^{13}C NMR (101 MHz, $CDCl_3$) δ 136.0, 134.0, 129.0, 125.0, 121.0, 117.5, 111.0, 110.0, 23.5 (2C), 23.0, 21.0 ppm.

mp (DCM): 140 - 141 °C.

IR: 3400, 2937, 2846, 1737, 1577, 1467, 1435, 1354, 1311, 1230, 1055, 972, 900, 862, 798, 655, 640, 590, 476 cm^{-1}.

HRMS (AP^+) Calcd. for $[C_{12}H_{12}ClN]^+$ 206.0737; Found 206.0745.

6-Nitro-2,3,4,9-tetrahydro-1H-carbazole (5)[1]



Following the general procedure, **5** was synthesized from *p*-nitroaniline (2 mmol, 0.276 g) and obtained as a yellow solid (24%, 0.052 g, 0.24 mmol).

^1H NMR (400 MHz, $CDCl_3$) δ 8.42 (s, 1H), 8.15 - 7.92 (m, 2H), 7.31 - 7.22 (m, 1H), 2.86 - 2.64 (m, 4H), 2.04 - 1.82 (m, 4H).

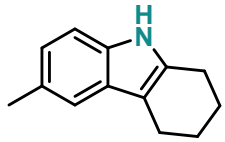
^{13}C NMR (126 MHz, $CDCl_3$) δ 141.5, 139.0, 137.5, 127.5, 117.0, 115.0, 113.0, 110.0, 23.5, 23.0 (2C), 21.0.

mp (DCM): 156 - 158 °C.

IR: 3331, 2924, 2817, 1625, 1579, 1506, 1473, 1438, 1396, 1357, 1307, 1205, 1149, 1078, 881, 823, 651, 599 cm^{-1}.

HRMS (EI^+) Calcd. for $[C_{12}H_{12}N_2O_2]^+$ 216.0899; Found 216.0899.

6-Methyl-2,3,4,9-tetrahydro-1H-carbazole (6)[1]



Following the general procedure, **6** was synthesized from *p*-toluidine (2 mmol, 0.214 g) and obtained as a yellow solid (51%, 0.087 g, 0.51 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (bs, 1H), 7.16 (s, 1H), 7.06 (d, *J* =8.2 Hz, 1H), 6.85 (d, *J* =8.0 Hz, 1H), 2.66 - 2.55 (m, 4H), 2.36 (s, 3H), 1.88 - 1.73 (m, 4H) ppm.

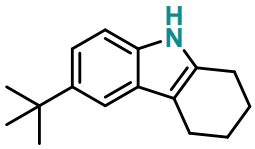
^{13}C NMR (101 MHz, $CDCl_3$) δ 134.5, 134.0, 128.5, 128.0, 122.5, 117.5, 110.0 (2C), 23.5, 23.5, 23.5, 22.0, 21.0 ppm.

mp (DCM): 132 - 133 °C.

IR: 3390, 2927, 2846, 1589, 1436, 1313, 797, 594, 4673 cm^{-1}.

HRMS (AP^+) Calcd. for $[C_{13}H_{14}N]^+$ 184.1121; Found: 184.1120.

6-(Tert-butyl)-2,3,4,9-tetrahydro-1H-carbazole (7)[4]



Following the general procedure, **7** was synthesized from *p*-tertbutylaniline (2 mmol, 0.298 g) and obtained as a yellow solid (28%, 0.064 g, 0.28 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (bs, 1H), 7.44 (s, 1H), 7.23 - 7.16 (m, 2H), 2.71 (t, *J* =5.3 Hz, 4H), 1.94 - 1.83 (m, 4H), 1.38 (s, 9H) ppm.

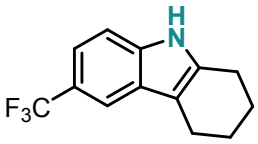
^{13}C NMR (101 MHz, $CDCl_3$) δ 142.5, 134.5, 134.0, 128.0, 119.5, 114.0, 110.5, 110.0, 35.0, 32.0, 23.5 (3C), 21.5 ppm.

mp (DCM): 114 - 115 °C.

IR: 3390, 2929, 2852, 1475, 1361, 1313, 1236, 869, 804, 624, 482, 449 cm^{-1}.

HRMS (EI^+) Calcd. for $[C_{16}H_{21}N]^+$ 227.1674; Found 227.1672.

6-(Trifluoromethyl)-2,3,4,9-tetrahydro-1H-carbazole (8)



Following the general procedure, **8** was synthesized from *p*-(trifluoromethyl)aniline (2 mmol, 0.322 g) and obtained as a yellow solid (24%, 0.057 g, 0.24 mmol).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.54 (s, 1H), 7.51 (d, *J* = 8.3 Hz, 1H), 7.31 (d, *J* = 8.2 Hz, 1H), 2.77 (t, *J* = 5.9 Hz, 2H), 2.72 (t, *J* = 5.8 Hz, 2H), 1.99 – 1.82 (m, 4H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 137.5, 134.5, 130.5, 125.5 (q, *J* = 271.3 Hz), 123.0 (q, *J* = 31.6 Hz), 118.0, 116.0 (q, *J* = 3.6 Hz), 111.0, 108.0 (q, *J* = 4.3 Hz), 23.5 (2C), 23.0, 21.0.

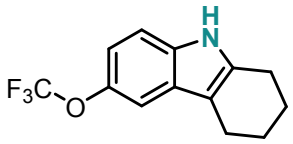
^{19}F-NMR (471 MHz, $CDCl_3$) δ -60.09 (S) ppm.

mp (DCM): 120 - 121 °C.

IR: 3460, 3408, 2931, 2854, 1583, 1478, 1427, 1323, 1267, 1147, 1098, 1051, 908, 873, 813, 711, 813, 711, 640, 463 cm^{-1}.

HRMS (EI$^+$) Calcd. for $[C_{13}H_{12}F_3N]^+$ 239.0922; Found 239.0924.

6-(Trifluoromethoxy)-2,3,4,9-tetrahydro-1H-carbazole (9)[4]



Following the general procedure, **9** was synthesized from *p*-(trifluoromethoxy)aniline (2 mmol, 0.354 g) and obtained as a yellow solid (49%, 0.126 g, 0.49 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.30 (s, 1H), 7.22 (d, *J* = 8.7 Hz, 1H), 6.98 (d, *J* = 8.7 Hz, 1H), 2.71 (dt, *J* = 11.3, 5.4 Hz, 4H), 1.97 – 1.82 (m, 4H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 143.0, 136.5, 134.0, 128.0, 121.0 (q, J = 254.5 Hz), 115.0, 111.0 (2C), 110.5, 23.5 (2C), 23.0, 21.0.

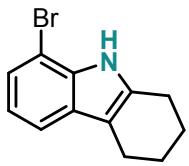
^{19}F NMR (376 MHz $CDCl_3$) δ -58.05 (S) ppm.

mp (DCM): 58 - 60 °C.

IR: 3404, 2958, 2846, 1583, 1479, 1449, 1211, 1151, 869, 798, 688, 599, 482 cm^{-1}.

HRMS (EI$^+$) Calcd. for $[C_{13}H_{12}F_3NO]^+$ 255.0871; Found 255.0868.

8-Bromo-2,3,4,9-tetrahydro-1H-carbazole (10)



Following to the general procedure, **10** was synthesized from *o*-bromoaniline (2 mmol, 0.344 g) and obtained as a yellow solid (42%, 0.106 g, 0.42 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.39 (d, *J* = 7.8 Hz, 1H), 7.25 (d, *J* = 7.1 Hz, 1H), 6.95 (t, *J* = 7.7 Hz, 1H), 2.77 (t, *J* = 5.9 Hz, 2H), 2.69 (t, *J* = 5.7 Hz, 2H), 2.03 – 1.79 (m, 4H).

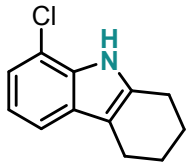
^{13}C NMR (101 MHz, $CDCl_3$) δ 135.0, 134.5, 129.0, 123.5, 120.5, 117.0, 111.5, 104.0, 23.5 (2C), 23.0, 21.0.

mp (DCM): 56 - 57 °C.

IR: 3392, 2933, 2850, 1583, 1548, 1485, 1460, 1438, 1413, 1359, 1312, 1301, 1278, 1205, 1186, 1149, 1124, 954, 896, 769, 732, 640, 572, 426 cm^{-1}.

HRMS (EI^+) Calcd. for $[C_{12}H_{12}BrN]^+$ 250.0231; Found 250.0242.

8-Chloro-2,3,4,9-tetrahydro-1H-carbazole (11)[5]



Following the general procedure, **11** was synthesized from *o*-chloroaniline (2 mmol, 0.254 g) and obtained as a yellow solid (42%, 0.086 g, 0.42 mmol).

^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (bs, 1H), 7.35 (d, *J* =7.7 Hz, 1H), 7.10 (d, *J* =7.6 Hz, 1H), 7.00 (t, *J* =7.8 Hz, 1H), 2.77 (t, *J* = 5.5 Hz, 2H), 2.70 (t, *J* = 5.5 Hz, 2H), 1.97–1.82 (m, 4H) ppm.

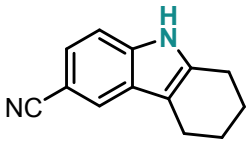
^{13}C NMR (126 MHz, $CDCl_3$) δ 135.0, 133.0, 129.5, 120.5, 120.0, 116.5, 116.0, 111.5, 23.5, 23.0 (2C), 21.0 ppm.

mp (DCM): 57 - 58 °C.

IR: 3394, 2916, 2845, 1891, 1815, 1615, 1585, 1564, 1489, 1457, 1419, 1361, 1325, 1301, 1209, 1123, 1014, 908, 753, 726, 574, 462 cm^{-1}.

HRMS (EI^+) Calcd. for $[C_{12}H_{12}ClN]^+$ 205.0658; Found: 205.0672.

2,3,4,9-tetrahydro-1H-carbazole-6-carbonitrile (12)[4]



Following the general procedure, **12** was synthesized from *p*-aminobenzonitrile (2 mmol, 0.236 g) and obtained as an orange solid (53%, 0.104 g, 0.53 mmol).

^1H NMR (400 MHz, DMSO) δ 11.29 (s, 1H), 7.84 (s, 1H), 7.39 (d, *J* = 8.3 Hz, 1H), 7.33 (dd, *J* = 8.4, 1.3 Hz, 1H), 2.72 (t, *J* = 5.7 Hz, 2H), 2.63 (t, *J* = 5.7 Hz, 2H), 1.90 - 1.71 (m, 4H) ppm.

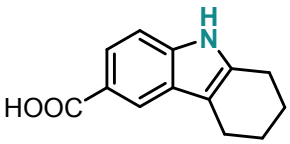
^{13}C NMR (101 MHz, DMSO) δ 137.5 (2C), 127.0, 123.0, 122.5, 121.0, 111.5, 109.5, 100.0, 22.5 (2C), 20.5 ppm.

mp (DCM): 106-108 °C.

IR: 3312, 2922, 2849, 2216, 1622, 1476, 1317, 1179, 799, 621 cm^{-1}.

HRMS (FTMS+ p NSI) Calcd. for $[C_{13}H_{13}N_2]^+$ 197.1073; Found 197.1071.

2,3,4,9-tetrahydro-1H-carbazole-6-carboxylic acid (13)



Following the general procedure, **13** was synthesized from *p*-aminobenzoic acid (2 mmol, 0.274 g) and obtained as an orange solid (70%, 0.150 g, 0.70 mmol).

^{1}H NMR (400 MHz, DMSO) δ 12.31 (s, 1H), 11.02 (s, 1H), 8.01 (s, 1H), 7.63 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.28 (d, *J* = 8.5 Hz, 1H), 2.70 (t, *J* = 5.4 Hz, 2H), 2.65 (t, *J* = 5.4 Hz, 2H), 1.95 - 1.69 (m, 4H).

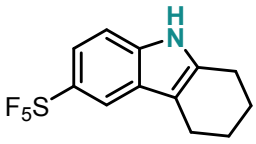
^{13}C NMR (101 MHz, DMSO) δ 168.5, 138.0, 136.0, 127.0, 121.5, 120.5, 119.5, 110.0, 109.5, 23.0, 22.5, 20.5.

mp (DCM): >150 °C (degradation).

IR: 3397, 2941, 2905, 2849, 1668, 1614, 1245, 772, 494 cm^{-1}.

HRMS (FTMS+ p NSI) Calcd. for $[C_{13}H_{14}O_2N_1]^+$ 216.1019; Found 216.1020.

6-(pentafluorothio)-2,3,4,9-tetrahydro-1H-carbazole (14)



Following the general procedure, **14** was synthesized from *p*-pentafluorothio aniline (2 mmol, 0.281 g) and obtained as a light brown solid (68%, 0.181 g, 0.68 mmol).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.87 (d, *J* = 2.1 Hz, 1H), 7.50 (dd, *J* = 8.9, 2.2 Hz, 1H), 7.25 (d, *J* = 9.9 Hz, 1H), 2.78 – 2.65 (m, 4H), 1.98 – 1.82 (m, 4H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 146.5, 137.0, 136.0, 127.0, 119.0 – 118.5 (m), 116.5 – 116.0 (m), 112.0, 109.5, 23.5, 23.0 (2C), 21.0.

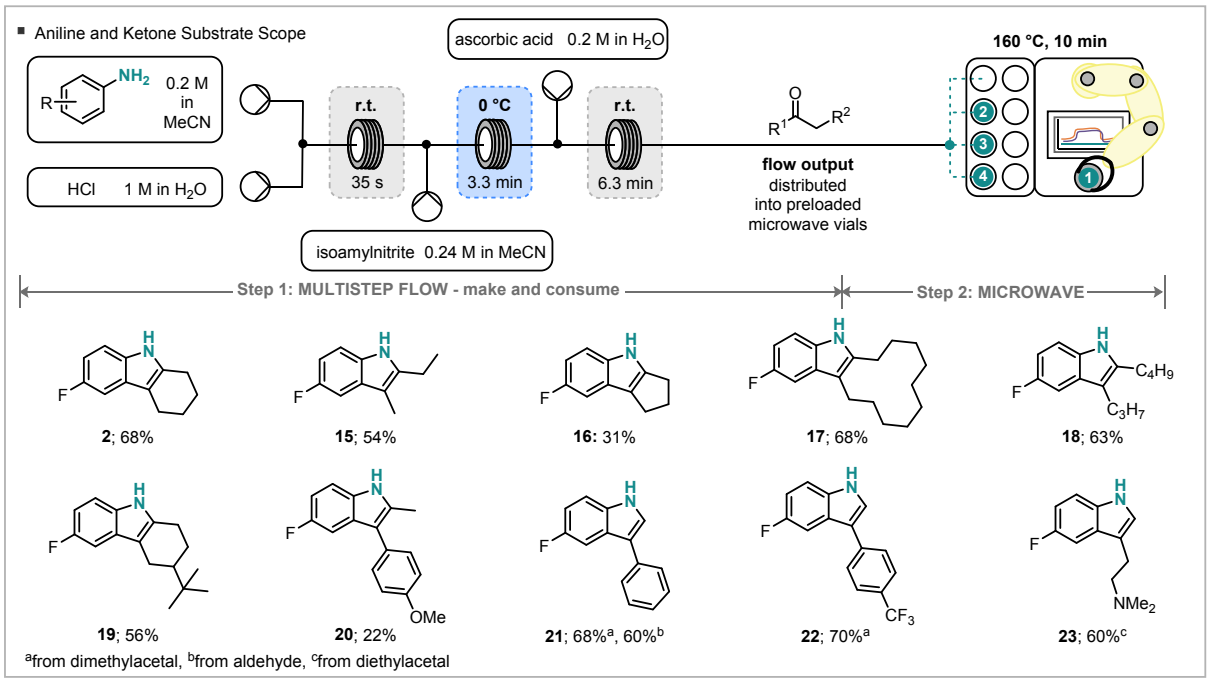
^{19}F NMR (471 MHz, $CDCl_3$) δ 91.85 –83.51 (m, 1F), 65.95 (d, *J* = 150.0 Hz, 4F).

mp (DCM): 66-68 °C

IR: 3482, 2922, 2855, 1474, 1323, 791, 613, 556 cm^{-1}.

HRMS (ASAP+) Calcd. for $[C_{12}H_{13}F_5NS]^+$ 298.0689; Found 298.0683.

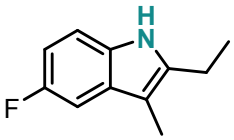
4 General Method for the Synthesis of Indoles 15-23: Ketone Screen



Scheme 5: Ketone Substrate Scope

Solutions of *p*-fluoroaniline (0.2 M in acetonitrile), HCl (1 M in water), isoamylnitrite (0.24 M in acetonitrile) and ascorbic acid (0.2 M in water) were prepared. These were then pumped through the flow system (see Scheme 5) at a flow rate of 0.2 mLmin^{-1}. After waiting for steady state for 20 min, fractions of 20 mL (1 mmol, 25 min) were collected. The neat ketone (1 mmol) was added into a 35 mL microwave vial equipped with a stirrer bar and the reaction solution added. The reaction mixture was heated in the microwave (160 °C, 10 min). After cooling to room temperature trifluorotoluene (0.041 mL, 0.33 mmol) was added and yield determined by ^{19}F NMR. After recombining the NMR sample with the bulk solution, it was diluted with 10 mL water and extracted with DCM (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was then further purified via column chromatography (EtOAc in petroleum ether, 0 to 5%).

3-Ethyl-5-fluoro-2-methyl-1H-indole (15)



Following the general procedure, **15** was synthesized from 3-pentanone (1 mmol, 0.086 g) and obtained as a yellow solid

(54%, 0.096 g, 0.54 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.19 - 7.14 (m, 1H), 7.11 (d, *J* = 9.7 Hz, 1H), 6.84 (t, *J* = 9.1 Hz, 1H), 2.75 (m, *J* =7.6 Hz, 2H), 2.19 (s, 3H), 1.28 (t, *J* =7.6Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.0 (d, *J* = 233.4 Hz), 138.5, 131.5, 130.0 (d, *J* = 9.6 Hz), 110.5 (d, *J* = 9.7 Hz), 109.0 (d, *J* = 26.2 Hz), 106.71 (d, *J* = 4.5 Hz), 103.23 (d, *J* = 23.2 Hz), 19.5, 14.0, 8.5 ppm.

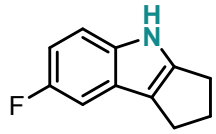
^{19}F NMR (376 MHz, $CDCl_3$) δ -125.49 (S) ppm.

mp (DCM): 58 – 59 °C.

IR: 3392, 2976, 2863, 1842, 1624, 1581, 1483, 1446, 1325, 1288, 1180, 1055, 941, 848, 803, 607, 493 cm^{-1}.

HRMS (EI$^+$) Calcd. for $[C_{11}H_{12}FN_2]^+$ 177.0954; Found 177.0954.

7-fluoro-1,2,3,4-tetrahydrocyclopenta[b]indole (16)



Following the general procedure, **16** was synthesized from cyclopentanone (1 mmol, 0.084 g) and obtained as a yellow solid (31%,0.054 g, 0.31 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.19 (m, 1H), 7.07 (m, 1H), 6.82 (m, 1H), 2.86 (t, *J* = 7.1 Hz, 2H), 2.80 (t, *J* = 6.9 Hz, 2H), 2.60 - 2.48 (m, 2H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.0 (d, *J* = 233.5 Hz), 146.0, 137.5, 125.0 (d, *J* = 10.0 Hz), 120.0 (d, *J* = 4.3 Hz), 111.5 (d, *J* = 9.9 Hz), 108.5 (d, *J* = 26.1 Hz), 104.0 (d, *J* = 23.5 Hz), 28.5, 26.0, 24.5 ppm.

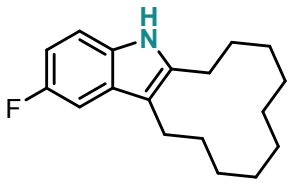
^{19}F NMR (376 MHz, $CDCl_3$) δ -125.19 (S) ppm.

mp (DCM): 80 - 83 °C.

IR: 3410, 2918, 2854, 1662, 1622, 1577, 1473, 1446, 1300, 1074, 850, 801, 599, 478, 413 cm^{-1}.

HRMS (EI$^+$) Calcd. for $[C_{11}H_{10}FN]^+$ 175.0797; Found 175.0799.

2-fluoro-6,7,8,9,10,11,12,13,14,15-decahydro-5H-cyclododeca[b]indole (17)



Following the general procedure, **17** was obtained from cyclododecanone (1 mmol, 0.182 g). The product was isolated as a pale yellow solid (68%, 0.129 g, 0.68 mmol).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.97 (bs, 1H), 7.40 - 7.27 (m, 2H), 7.09 (m, 1H), 3.17 - 2.75 (m, 4H), 1.91 - 1.68 (m, 4H), 1.68 - 1.02 (m, 12H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 194.5, 158.0 (d, *J* = 236.7 Hz), 133.0 (d, *J* = 33.4 Hz), 129.0 (d, *J* = 9.3 Hz), 123.5 (d, *J* = 5.7 Hz), 115.5 (d, *J* = 27.0 Hz), 113.0 (d, *J* = 9.4 Hz), 106.0, 105.5, 41.0, 28.0, 26.5, 26.0, 24.5, 24.0, 23.0, 22.5, 22.0 ppm.

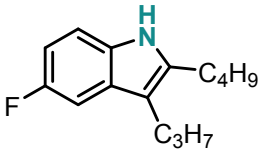
^{19}F NMR (471 MHz, $CDCl_3$) δ -123.21(S) ppm.

mp (hexane): 190 - 192 °C

IR: 3322, 2920, 2359, 1625, 1520, 1508, 1458, 1425, 1265, 1229, 1172, 1092, 1080, 1018, 810, 758, 667, 590, 486, 419 cm^{-1}.

HRMS (ES^+) Calcd. for $[C_{18}H_{25}FN]^+$ 274.1971, Found 274.1981.

2-butyl-5-fluoro-3-propyl-1H-indole (18)



Following the general procedure, compound **18** was obtained from 5-nonanone (1 mmol, 0.142 g) as an orange oil (63%, 0.147 g, 0.63 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.19 – 7.11 (m, 2H), 6.83 (td, *J* = 9.2, 2.5 Hz, 1H), 2.75 – 2.68 (m, 2H), 2.66 – 2.58 (m, 2H), 1.69 – 1.56 (m, 4H), 1.46 – 1.32 (m, 2H), 0.96 (t, *J* = 7.3 Hz, 3H), 0.95 (t, *J* = 7.3 Hz, 3H).

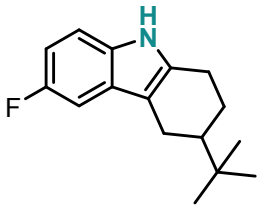
^{13}C NMR (101 MHz, $CDCl_3$) δ 158.0 (d, *J* = 233.2 Hz), 137.5, 132.0, 129.5 (d, *J* = 9.4 Hz), 112.5 (d, *J* = 4.5 Hz), 110.5 (d, *J* = 9.7 Hz), 109.0 (d, *J* = 26.1 Hz), 103.5 (d, *J* = 23.2 Hz), 32.0, 26.5, 26.0, 24.0, 22.5, 14.5, 14.0 ppm.

^{19}F NMR (376 MHz, $CDCl_3$) δ -125.63 (S) ppm.

IR: 3420, 2957, 2930, 2359, 2342, 1608, 1508, 1483, 1456, 1364, 1287, 1236, 1175, 1074, 968, 847, 822, 793, 606, 419 cm^{-1}.

HRMS (FTMS+ p NSI) Calcd. for $[C_{15}H_{20}FN]^+$ 234.1653, Found 234.1654.

3-(tert-butyl)-6-fluoro-2,3,4,9-tetrahydro-1H-carbazole (19)



Following the general procedure, **19** was obtained from 4-tertbutylcyclohexanone (1 mmol, 0.154 g). The product was isolated as a colourless solid (56%, 0.137 g, 0.56 mmol).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.03 (bs, 1H), 7.37 (dd, *J* = 8.3, 4.4 Hz, 1H), 7.12 (dd, *J* = 7.2, 1.9 Hz, 1H), 7.07 - 6.95 (m, 1H), 2.82 - 2.71 (m, 2H), 2.53 (d, *J* = 14.5 Hz, 1H), 2.25 - 2.18 (m, 1H), 1.88 (t, *J* = 12.6 Hz, 1H), 1.24 (qd, *J* = 12.6, 5.6 Hz, 1H), 1.12 (t, *J* = 13.7 Hz, 1H), 0.89 (s, 9H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 185.0 (d, *J* = 3.6 Hz), 161.5 (d, *J* = 245.7 Hz), 150.0 (d, *J* = 2.1 Hz), 139.5 (d, *J* = 8.2 Hz), 121.0 (d, *J* = 8.6 Hz), 116.0 (d, *J* = 23.5 Hz), 110.5 (d, *J* = 24.8 Hz), 92.5, 42.0, 37.0, 32.0, 29.5 (2C), 27.5.

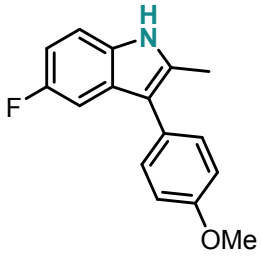
^{19}F NMR (471 MHz, $CDCl_3$) δ -116.56 (S).

mp (hexane): 125 - 126 °C.

IR: 2961, 2359, 1607, 1459, 1172, 1094, 870, 825, 799, 592, 538, 418 cm^{-1}.

HRMS (EI^+) Calcd. for $[C_{16}H_{21}FN]^+$ 246.1658; Found 246.1647.

5-fluoro-3-(4-methoxyphenyl)-2-methyl-1H-indole (20)



Following the general procedure, compound **20** was obtained from 4-methoxyphenyl acetone (1 mmol, 0.164 g) to yield a yellow solid (22%, 0.056 g, 0.22 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.43 – 7.35 (m, 2H), 7.29 – 7.18 (m, 2H), 7.05 – 6.98 (m, 2H), 6.89 (td, *J* = 9.0, 2.5 Hz, 1H), 3.87 (s, 3H), 2.48 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.5 (d, *J* = 233.9 Hz), 158.0, 133.0, 131.5, 130.5, 128.5 (d, *J* = 9.6 Hz), 127.5, 114.5 (d, *J* = 4.4 Hz), 114.0, 111.0 (d, *J* = 9.7 Hz), 110.0 (d, *J* = 26.2 Hz), 104.0 (d, *J* = 24.0 Hz), 55.5, 12.5.

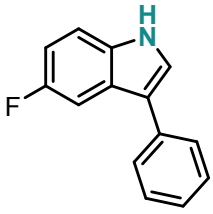
^{19}F NMR (376 MHz, $CDCl_3$) δ -124.67 (S).

mp (DCM): 120-124 °C

IR: 3347, 3001, 2963, 2920, 1510, 1487, 1452, 1236, 795, 615, 577 cm^{-1}.

HRMS (ES^+) Calcd. for $[C_{16}H_{15}FNO]^+$ 256.1138, Found 256.1138.

5-fluoro-3-phenyl-1H-indole (21)[6]



Following the general procedure, compound **21** was obtained as a brown solid from phenyl acetaldehyde (1 mmol, 0.120 g) and the corresponding acetal 2,2-dimethoxyethylbenzene (1 mmol, 0.166 g) in 60% (0.127 g, 0.60 mmol) and 68% (0.143 g, 0.68 mmol) respectively.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (bs, 1H), 7.68 - 7.56 (m, 3H), 7.47 - 7.41 (m, 3H), 7.37 - 7.28 (m, 2H), 7.02 (m, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.5 (d, *J* = 234.9 Hz), 135.0, 133.5, 129.0, 127.5, 126.5, 126.5 (d, *J* = 9.9 Hz), 123.5, 118.5 (d, *J* = 4.7 Hz), 112.0 (d, *J* = 9.7 Hz), 111.0 (d, *J* = 26.4 Hz), 105.0 (d, *J* = 24.2 Hz) ppm.

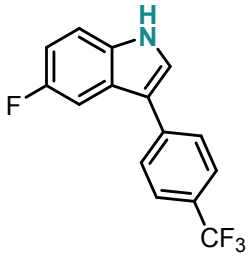
^{19}F NMR (471 MHz, $CDCl_3$) δ -123.91 (S) ppm.

mp (DCM): 94 - 95 °C.

IR: 3454, 3132, 2359, 1599, 1578, 1539, 1458, 1323, 1172, 1161, 1119, 920, 799, 758, 691, 691, 681, 592, 529, 486, 424 cm^{-1}.

HRMS (ASAP^{+}) Calcd. for $[C_{14}H_{10}FN]^{+}$ 212.0876, Found 212.0881.

5-fluoro-3-(4-(trifluoromethyl)phenyl)-1H-indole (22)



Following the general procedure, compound **22** was obtained from 4-trifluoromethylphenyl acetaldehyde dimethyl acetal (1 mmol, 0.234 g) to yield yellow solid (70%, 0.196 g, 0.70 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (s, 1H), 7.71 (q, *J* = 8.5 Hz, 4H), 7.56 (dd, *J* = 9.8, 2.5 Hz, 1H), 7.48 (d, *J* = 2.7 Hz, 1H), 7.38 (dd, *J* = 8.9, 4.4 Hz, 1H), 7.04 (td, *J* = 8.9, 2.4 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.5 (d, *J* = 235.5 Hz), 139.0, 133.0, 128.0 (q, *J* = 32.5 Hz), 127.0, 126.0 (q, *J* = 3.8 Hz), 126.0 (d, *J* = 9.8 Hz), 124.53 (q, *J* = 271.7 Hz), 124.5, 117.5 (d, *J* = 4.7 Hz), 112.5 (d, *J* = 9.7 Hz), 111.5 (d, *J* = 26.4 Hz), 105.0 (d, *J* = 24.3 Hz).

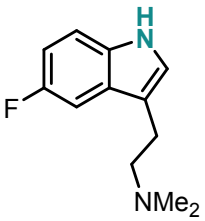
^{19}F NMR (376 MHz, $CDCl_3$) δ -62.28 (s, 3H), -123.02 (s, 1H).

mp (DCM): 55-58 °C.

IR: 3455, 2928,2855, 1612, 1479, 1323, 1103, 924, 845, 800, 594 cm^{-1}.

HRMS (FTMS+ p APCI corona) Calcd. for $[C_{15}H_9F_4N]$ 279.0666, Found 279.0665.

2-(5-fluoro-1H-indol-3-yl)-*N,N*-dimethylethan-1-amine (23)



Following the general procedure, compound **23** was obtained from 4-(dimethylamino)butyraldehyde diethylacetal (1 mmol, 0.189 g) and purified via column chromatography (0 to 10% Et_3N in EtOAc) to yield an orange solid (60%, 0.124 g, 0.70 mmol).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.32 – 7.23 (m, 2H), 7.08 (s, 1H), 6.95 (t, *J* = 9.0 Hz, 1H), 2.97 – 2.89 (m, 2H), 2.69 – 2.61 (m, 2H), 2.38 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 157.5 (d, *J* = 234.1 Hz), 133.0, 128.0 (d, *J* = 9.6 Hz), 123.5, 114.5 (d, *J* = 4.7 Hz), 112.0 (d, *J* = 9.7 Hz), 110.5 (d, *J* = 26.4 Hz), 104.0 (d, *J* = 23.2 Hz), 60.0, 45.5, 24.0.

^{19}F NMR (471 MHz, $CDCl_3$) δ -125.06 (d, *J* = 3.7 Hz).

mp (DCM): 62-64 °C.

IR: 3136, 3049, 2947, 2859, 2822, 2770, 1582, 1464, 1445, 1155, 1032, 937, 843, 795, 713, 615, 422 cm^{-1}.

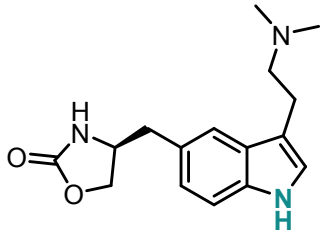
HRMS (FTMS + p NSI) Calcd. for $[C_{12}H_{16}FN_2]^+$ 207.1292, Found 207.1292.

5 General Method for the Synthesis of Indoles 24-33: Zolmitriptan plus Analogues

Scheme 6: Zolmitriptan plus Analogues

Solutions of (*S*)-4-(4-aminobenzyl)-2-oxazolidinone (0.2 M in acetonitrile), HCl (1 M in water), isoamylnitrite (0.24 M in acetonitrile) and ascorbic acid (0.2 M in water) were prepared. These were then pumped through the flow system (see Scheme 6) at a flow rate of 0.2 mLmin^{-1}. After waiting for steady state for 20 min, fractions of 20 mL (1 mmol, 25 min) were collected. The neat ketone (1 mmol) was added into a 35 mL microwave vial equipped with a stirrer bar and the reaction solution added. The reaction mixture was heated in the microwave (160 °C, 10 min). After cooling to room temperature the reaction mixture was neutralised with 20 mL aqueous $NaHCO_3$ and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was then further purified via column chromatography (EtOAc in petroleum ether, 20 to 50%).

(*S*)-4-((3-(2-(dimethylamino)ethyl)-1H-indol-5-yl)methyl)oxazolidin-2-one, Zolmitriptan (24)[7]



Following the general procedure, compound **24** was obtained from 4-aminobutyraldehyde diethylacetal (1 mmol, 0.189 g) and purified via column chromatography (10% Et_3N in EtOH) to yield a slightly brown solid (56%, 0.162 g, 0.56 mmol).

^{1}H NMR (500 MHz, DMSO) δ 10.71 (s, 1H), 7.77 (s, 1H), 7.35 (s, 1H), 7.25 (d, *J* = 8.2 Hz, 1H), 7.11 (d, *J* = 1.5 Hz, 1H), 6.92 (d, *J* = 8.2 Hz, 1H), 4.22 (t, *J* = 7.4 Hz, 1H), 4.10 – 3.94 (m, 2H), 2.95 – 2.72 (m, 4H), 2.55 – 2.46 (m, 2H), 2.22 (s, 6H).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.41 (s, 1H), 7.39 (s, 1H), 7.28 (d, *J* = 8.2 Hz, 1H), 7.02 (s, 1H), 6.95 (d, *J* = 8.2 Hz, 1H), 5.57 (s, 1H), 4.44 (t, *J* = 8.3 Hz, 1H), 4.24 – 4.03 (m, 2H), 3.01 – 2.86 (m, 4H), 2.71 – 2.57 (m, 2H), 2.36 (s, 6H).

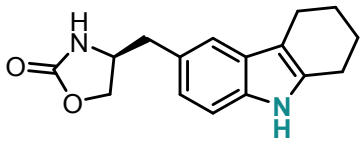
^{13}C NMR (126 MHz, DMSO) δ 158.5, 135.0, 127.5, 126.0, 122.5, 122.5, 119.0, 112.5, 111.0, 68.0, 60.0, 53.0, 45.0 (2C), 40.5, 23.0.

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.5, 135.5, 128.0, 126.5, 123.0, 122.5, 119.0, 114.0, 112.0, 67.0, 60.0, 54.5, 45.5 (2C), 42.0, 23.5.

mp (DCM): 40-45 °C.

IR: 3395, 3285, 2922, 2857, 2824, 2778, 2361, 1732, 1404, 1234, 1022, 727, 637 cm^{-1}.

HRMS (EI^+) Calcd. for $[C_{16}H_{21}N_3O_2]^+$ 287.1634, Found 287.1632.



(*S*)-4-((2,3,4,9-tetrahydro-1H-carbazol-6-yl)methyl)oxazolidin-2-one (25)

Following the general procedure, compound **25** was obtained from cyclohexanone (1 mmol, 0.098 g) to yield an off-white solid (57%, 0.155 g, 0.57 mmol).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.24 (t, *J* = 9.2 Hz, 2H), 6.89 (dd, *J* = 8.1, 1.6 Hz, 1H), 5.14 (s, 1H), 4.46 (t, *J* = 8.4 Hz, 1H), 4.19 (dd, *J* = 8.6, 5.6 Hz, 1H), 4.13 – 4.04 (m, 1H), 3.02 – 2.84 (m, 2H), 2.71 (dt, *J* = 11.4, 5.5 Hz, 4H), 1.99 – 1.79 (m, 4H).

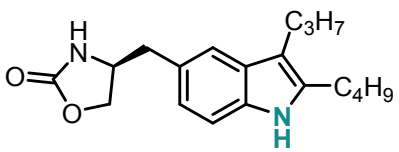
^{13}C NMR (126 MHz, $CDCl_3$) δ 159.5, 135.5, 135.0, 128.5, 126.5, 122.0, 118.0, 111.0, 110.0, 70.0, 54.5, 42.0, 23.5 (3C), 21.0.

mp (DCM): 184-188 °C.

IR: 3391, 2918 ,1753, 1719, 1477, 1396, 1244, 1018, 941, 480 cm^{-1}.

HRMS (FTMS + p NSI) Calcd. for $[C_{16}H_{19}O_2N_2]^+$ 271.1441, Found 271.1444.

(*S*)-4-((2-butyl-3-propyl-1H-indol-5-yl)methyl)oxazolidin-2-one (26)



Following the general procedure, compound **26** was obtained from 5-nonanone (1 mmol, 0.142 g) to yield a light brown oil (52%, 0.164 g, 0.52 mmol).

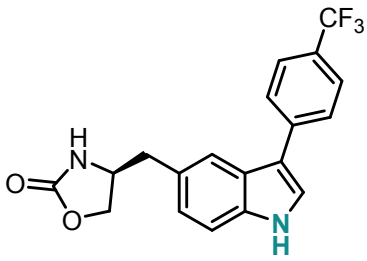
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.31 – 7.20 (m, 2H), 6.89 (dd, *J* = 8.2, 1.6 Hz, 1H), 5.03 (s, 1H), 4.48 (t, *J* = 8.3 Hz, 1H), 4.23 – 4.18 (m, 1H), 4.14 – 4.06 (m, 1H), 3.00 – 2.87 (m, 2H), 2.76 – 2.68 (m, 2H), 2.68 – 2.61 (m, 2H), 1.68 – 1.60 (m, 4H), 1.46 – 1.33 (m, 2H), 0.97 (t, *J* = 5.5 Hz, 3H), 0.94 (t, *J* = 5.5 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.0, 136.5, 134.5, 129.5, 126.5, 121.5, 118.5, 112.0, 111.0, 70.0, 54.5, 42.0, 32.0, 26.5, 26.0, 24.5, 22.5, 14.5, 14.0.

mp (DCM): 64-68 °C.

IR: 3395, 3308, 2955, 2928, 2868, 1736, 1479, 1454, 1404, 1240, 1022 cm^{-1}.

HRMS (FTMS + p NSI) Calcd. for $[C_{19}H_{27}N_2O_2]^+$ 315.2068, Found 315.2067.



(*S*)-4-((3-(4-(trifluoromethyl)phenyl)-1H-indol-5-yl)methyl)oxazolidin-2-one (27)

Following the general procedure, compound **27** was obtained from 4-methoxy phenylacetaldhyde dimethylacetal (1 mmol, 0.196 g) to yield a yellow solid (67%, 0.241 g, 0.67 mmol).

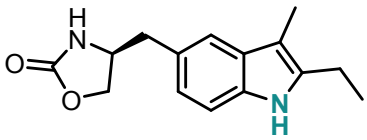
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.44 (s, 1H), 7.77 – 7.66 (m, 5H), 7.48 – 7.40 (m, 2H), 7.08 (d, *J* = 8.2 Hz, 1H), 5.03 (s, 1H), 4.49 (t, *J* = 8.5 Hz, 1H), 4.25 – 4.18 (m, 1H), 4.18 – 4.10 (m, 1H), 3.08 – 2.91 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.5, 139.0, 136.0, 128.5, 128.0 (q, *J* = 32.5 Hz), 127.5, 126.0, 126.0 (q, *J* = 3.7 Hz), 124.5 (q, *J* = 271.5 Hz), 124.0, 123.5, 119.5, 117.0, 112.5, 70.0, 54.5, 42.0.

mp (DCM): 182-186 °C.

IR: 3431, 3265, 2320, 2853, 1745, 1730, 1612, 1325, 1096, 1065, 800, 442 cm^{-1}.

HRMS (FTMS + p NSI) Calcd. for $[C_{25}H_{23}O_2N_2]^+$ 361.1158, Found 361.1164.



(*S*)-4-((2-ethyl-3-methyl-1H-indol-5-yl)methyl)oxazolidin-2-one (28)

Following the general procedure, compound **28** was obtained from 3-pentanone (1 mmol, 0.086 g) to yield a white solid (55%, 0.141 g, 0.55 mmol).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.27 – 7.25 (m, 1H), 7.23 (d, *J* = 8.2 Hz, 1H), 6.90 (dd, *J* = 8.2, 1.7 Hz, 1H), 4.95 (s, 1H), 4.48 (t, *J* = 8.3 Hz, 1H), 4.23 – 4.18 (m, 1H), 4.14 – 4.06 (m, 1H), 3.05 – 2.87 (m, 2H), 2.76 (q, *J* = 7.6 Hz, 2H), 2.22 (s, 3H), 1.28 (t, *J* = 7.6 Hz, 3H).

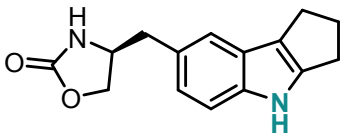
^{13}C NMR (126 MHz, $CDCl_3$) δ 159.0, 137.5, 134.5, 130.0, 126.5, 122.0, 118.5, 111.0, 106.0, 70.0, 54.5, 42.0, 19.5, 14.0, 8.5.

mp (DCM): 60-64 °C

IR: 3387, 3267, 2970, 2914, 2363, 1732, 1404, 1240, 1022, 935, 935, 704 cm^{-1}.

HRMS (FTMS + p NSI) Calcd. for $[C_{15}H_{19}O_2N_2]^+$ 259.1447, Found 259.1449.

(*S*)-4-((1,2,3,4-tetrahydrocyclopenta[b]indol-7-yl)methyl)oxazolidin-2-one (29)



Following the general procedure, compound **29** was obtained from cyclopentanone (1 mmol, 0.084 g) to yield an off-white solid (41%, 0.105 g, 0.41 mmol).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.28 – 7.19 (m, 2H), 6.87 (dd, *J* = 8.2, 1.5 Hz, 1H), 5.10 (s, 1H), 4.47 (t, *J* = 8.4 Hz, 1H), 4.28 – 4.14 (m, 1H), 4.14 – 4.03 (m, 1H), 3.00 – 2.89 (m, 2H), 2.84 (dt, *J* = 26.0, 6.9 Hz, 4H), 2.62 – 2.47 (m, 2H).

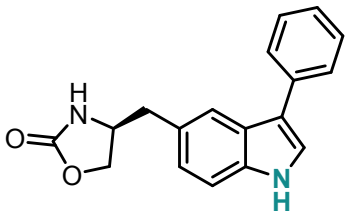
^{13}C NMR (126 MHz, $CDCl_3$) δ 159.0, 145.0, 140.0, 127.0, 125.5, 121.5, 119.5, 119.0, 112.0, 70.0, 54.5, 42.0, 29.0, 26.0, 24.5.

mp (DCM): 180-182 °C.

IR: 3385, 3277, 2980, 2947, 2857, 1755, 1713, 1225, 1022, 1005, 488 cm^{-1}.

HRMS (FTMS + p NSI) Calcd. for $[C_{15}H_{17}O_2N_2]^+$ 257.1290, Found 257.1293.

(*S*)-4-((3-phenyl-1H-indol-5-yl)methyl)oxazolidin-2-one (30)



Following the general procedure, compound **30** was obtained from phenylacetaldhyde dimethylacetal (1 mmol, 0.166 g) to yield a slightly yellow solid (68%, 0.198 g, 0.68 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1H), 7.71 (s, 1H), 7.64 (d, *J* = 7.5 Hz, 2H), 7.47 (t, *J* = 7.6 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.31 (t, *J* = 7.3 Hz, 1H), 7.04 (d, *J* = 8.3 Hz, 1H), 5.15 (s, 1H), 4.47 (t, *J* = 8.3 Hz, 1H), 4.23 – 4.07 (m, 2H), 3.06 – 2.90 (m, 2H).

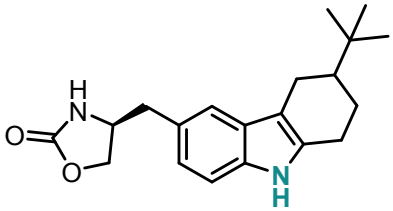
^{13}C NMR (126 MHz, $CDCl_3$) δ 159.5, 136.0, 135.5, 129.0, 127.5 (2C), 126.5, 126.0, 123.5, 123.0, 120.0, 118.0, 112.0, 70.0, 54.5, 42.0.

mp (DCM): 72-77 °C.

IR: 3401, 3275, 2911, 1732, 1601, 1541, 1475, 1414, 1242, 1024, 939, 768, 752, 698 cm^{-1}.

HRMS (FTMS + p NSI) Calcd. for $[C_{18}H_{17}O_2N_2]^+$ 293.1285, Found 293.1288.

(*S*)-4-((3-(tert-butyl)-2,3,4,9-tetrahydro-1H-carbazol-6-yl)methyl)oxazolidin-2-one (31)



Following the general procedure, compound **31** was obtained from 4-tertbutyl cyclohexanone (1 mmol, 0.154 g) to yield a mixture of the diastereomers as an off-white solid (73%, 0.238 g, 0.73 mmol).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.29 – 7.20 (m, *J* = 16.0, 5.8 Hz, 2H), 6.89 (dd, *J* = 8.2, 1.6 Hz, 1H), 5.04 (s, 1H), 4.47 (t, *J* = 8.4 Hz, 1H), 4.25 – 4.16 (m, *J* = 8.6, 5.6 Hz, 1H), 4.15 – 4.04 (m, *J* = 7.9, 4.8, 2.2 Hz, 1H), 3.03 – 2.86 (m, *J* = 22.0, 13.5, 7.1 Hz, 2H), 2.85 – 2.66 (m, 3H), 2.48 – 2.31 (m, *J* = 12.4, 9.9 Hz, 1H), 2.16 – 2.03 (m, *J* = 6.8, 3.8 Hz, 1H), 1.58 – 1.47 (m, 2H), 1.01 (s, 9H).

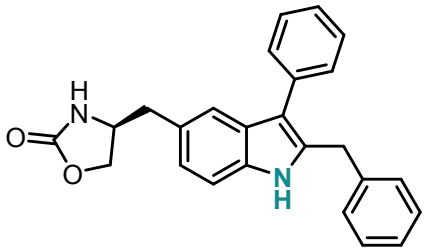
^{13}C NMR (126 MHz, $CDCl_3$) δ 159.5, 135.5 (2C), 129.0 (2C), 128.5, 126.5, 122.0, 118.0, 111.0, 110.5, 70.0, 54.5 (2C), 42.0, 27.5 (2C), 25.0, 22.5 (2C).

mp (DCM): 94-98 °C.

IR: 3387, 3283, 2947, 2909, 2843, 1736, 1476, 1242, 1022, 750 cm^{-1}.

HRMS (FTMS + p NSI) Calcd. for $[C_{20}H_{27}N_2O_2]^+$ 327.2070, Found 327.2067.

(*S*)-4-((2-benzyl-3-phenyl-1H-indol-5-yl)methyl)oxazolidin-2-one (32)



Following the general procedure, compound **32** was obtained from 1,3-diphenylacetone (1 mmol, 0.210 g) to yield an off-white solid (49%, 0.187 g, 0.49 mmol).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.56 – 7.42 (m, 5H), 7.41 – 7.29 (m, 3H), 7.29 – 7.16 (m, 4H), 6.96 (d, *J* = 8.1 Hz, 1H), 4.96 (s, 1H), 4.45 (t, *J* = 8.1 Hz, 1H), 4.24 (s, 2H), 4.17 (t, *J* = 6.9 Hz, 1H), 4.14 – 4.04 (m, 1H), 3.00 – 2.85 (m, 2H).

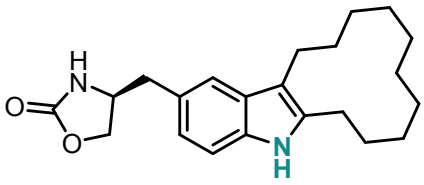
^{13}C NMR (126 MHz, $CDCl_3$) δ 159.0, 138.5, 135.0, 134.5, 129.5, 129.0 (2C), 128.5, 127.5, 127.0, 126.5, 123.0, 119.5, 115.5, 111.5, 70.0, 54.5, 42.0, 33.0.

mp (DCM): 166-168 °C.

IR: 3393, 3238, 2922, 1755, 1730, 1601, 1493, 1404, 1026, 705 cm^{-1}.

HRMS (FTMS + p NSI) Calcd. for $[C_{25}H_{23}O_2N_2]^+$ 383.1755, Found 383.1754.

(*S*)-4-((6,7,8,9,10,11,12,13,14,15-decahydro-5H-cyclododeca[b]indol-2-yl)methyl)oxazolidin-2-one (33)



Following the general procedure, compound **33** was obtained from cyclododecanone (1 mmol, 0.182 g) to yield a white solid (55%, 0.196 g, 0.55 mmol).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.32 (s, 1H), 7.23 (d, *J* = 8.2 Hz, 1H), 6.90 (dd, *J* = 8.2, 1.6 Hz, 1H), 5.00 (s, 1H), 4.48 (t, *J* = 8.3 Hz, 1H), 4.25 – 4.17 (m, 1H), 4.14 – 4.06 (m, 1H), 3.00 – 2.87 (m, 2H), 2.78 – 2.67 (m, 4H), 1.86 – 1.72 (m, 4H), 1.54 – 1.40 (m, 4H), 1.34 (dd, *J* = 6.2, 3.2 Hz, 6H), 1.29 – 1.19 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.0, 137.0, 135.0, 129.0, 126.5, 122.0, 119.0, 112.5, 111.0, 70.0, 54.5, 42.0, 28.0, 27.5, 25.0 (3C), 24.0, 22.5 (2C), 22.0, 21.5.

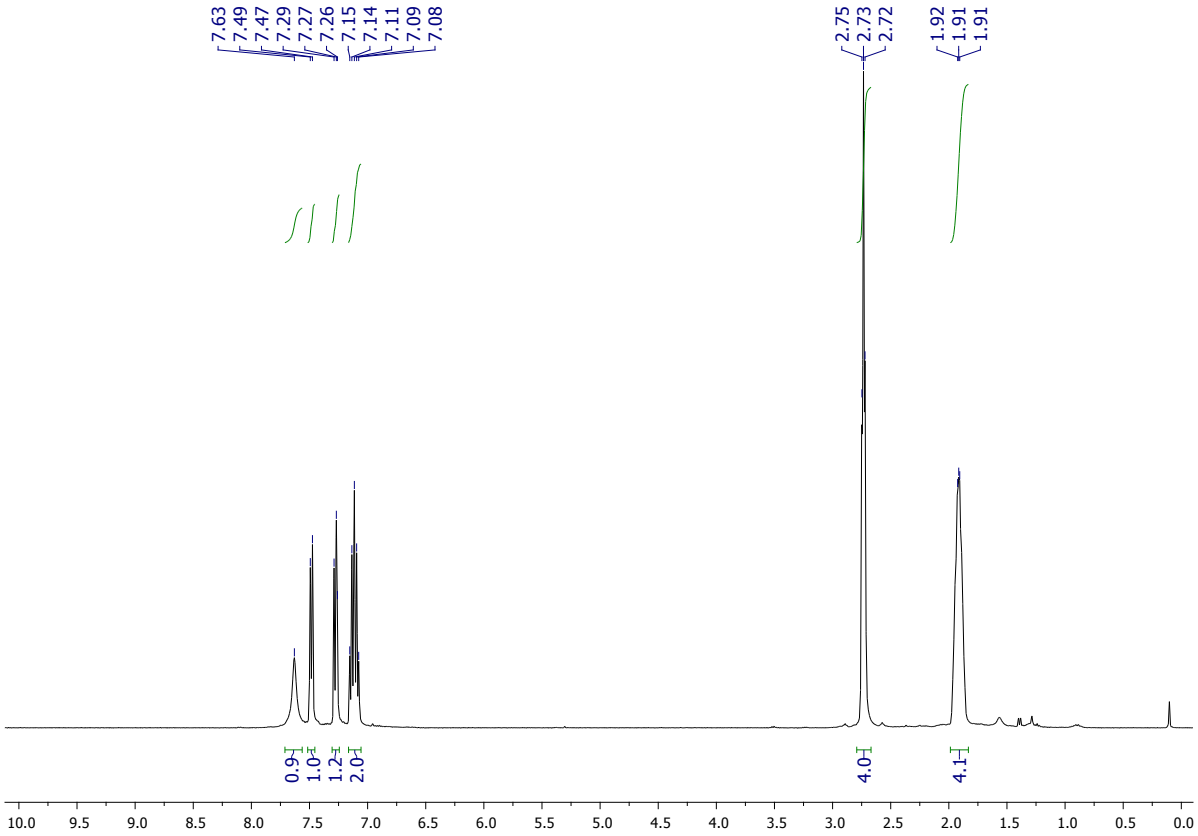
mp (DCM): 96-100 cm^{-1}.

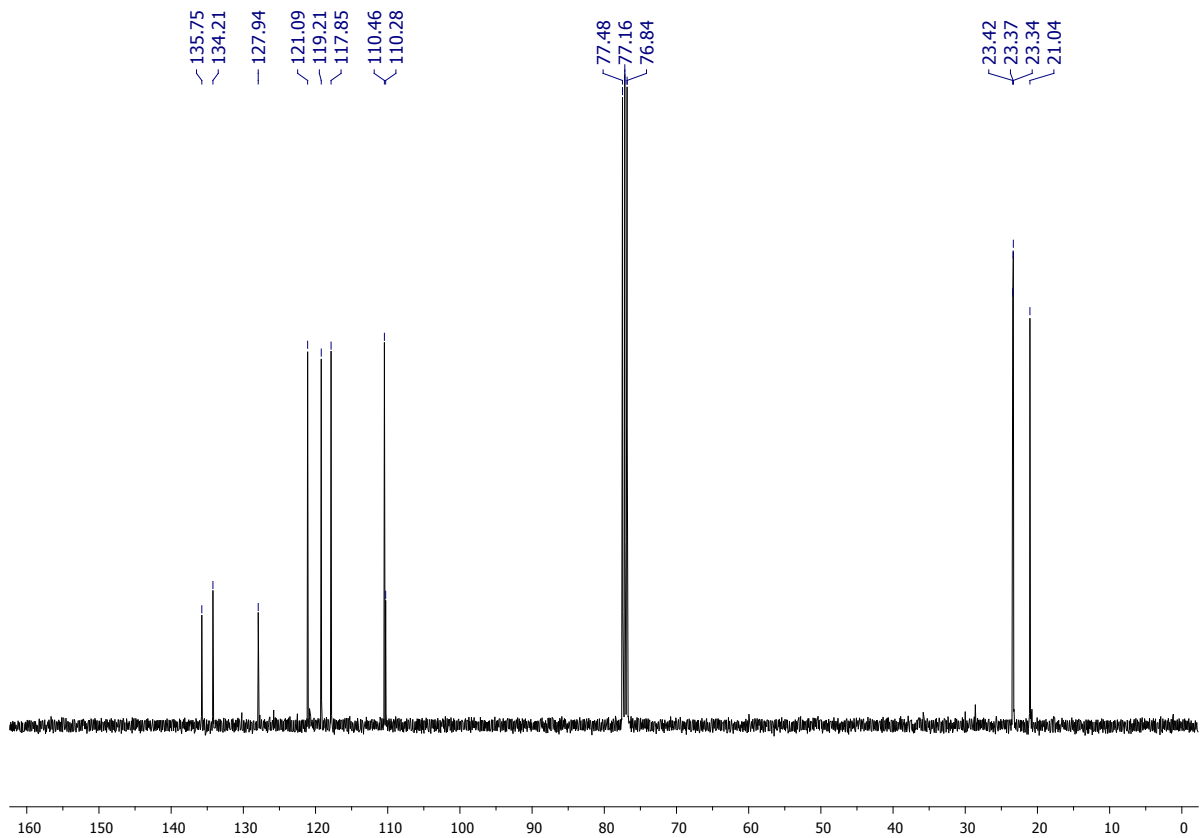
IR: 3393, 3285, 2922, 2851, 2361, 1732, 1614, 1323, 1111, 1067, 702 cm^{-1}.

HRMS (FTMS + p NSI) Calcd. for $[C_{22}H_{31}O_2N_2]^+$ 355.2380, Found 355.2382.

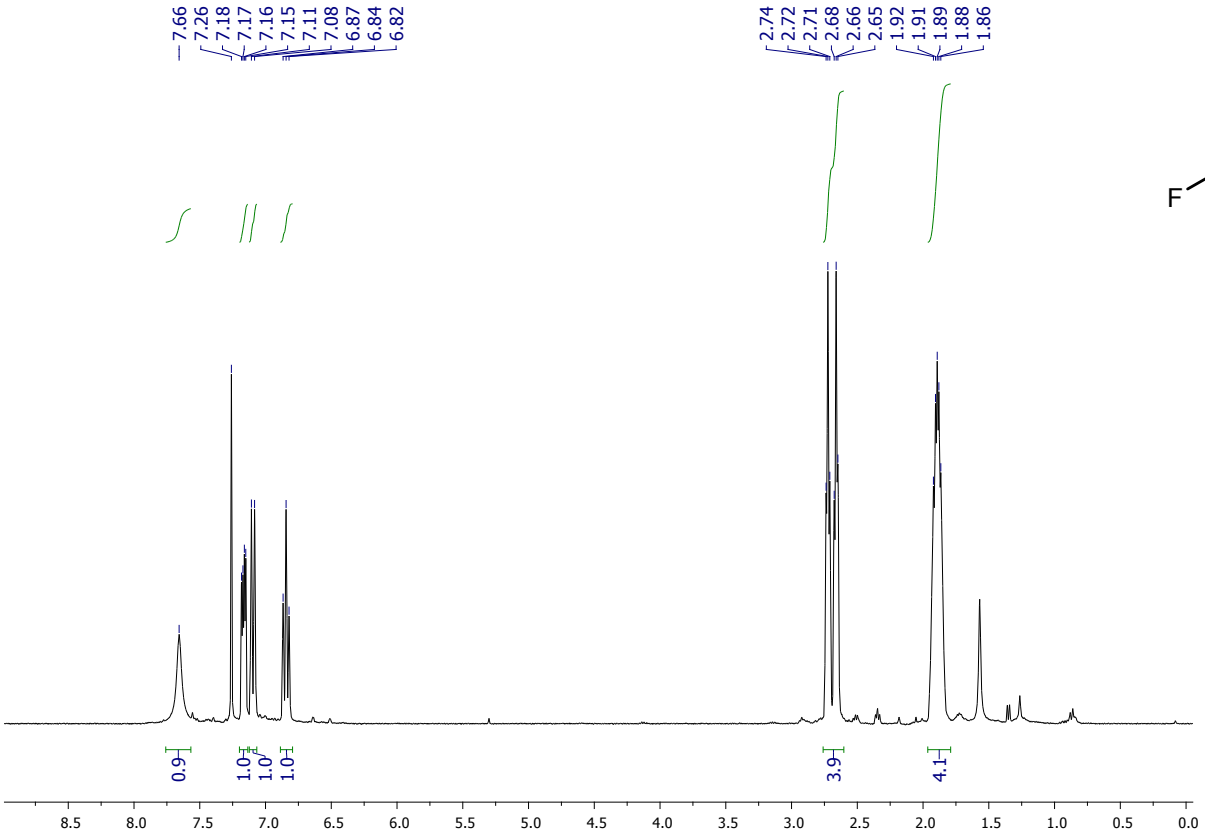
6 Spectroscopic Data

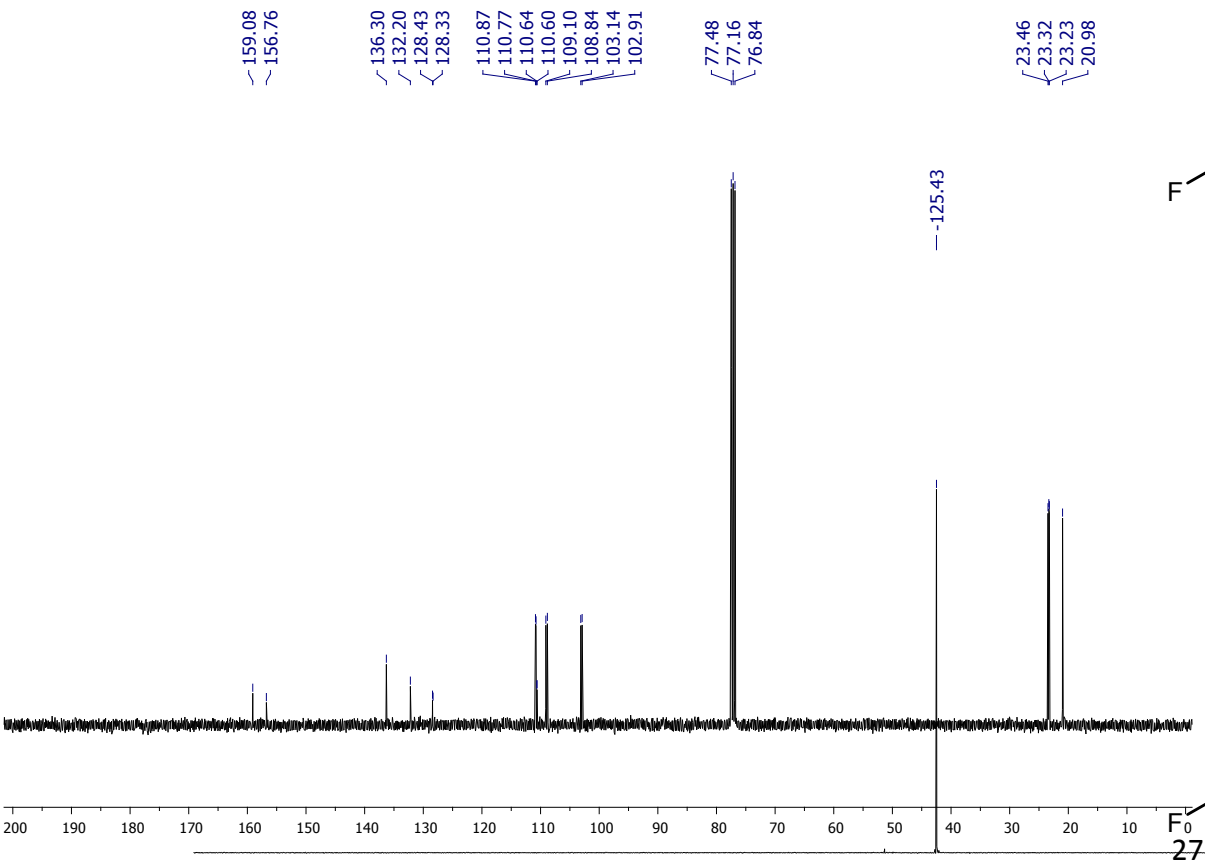
2,3,4,9-Tetrahydro-1H-carbazole (1)



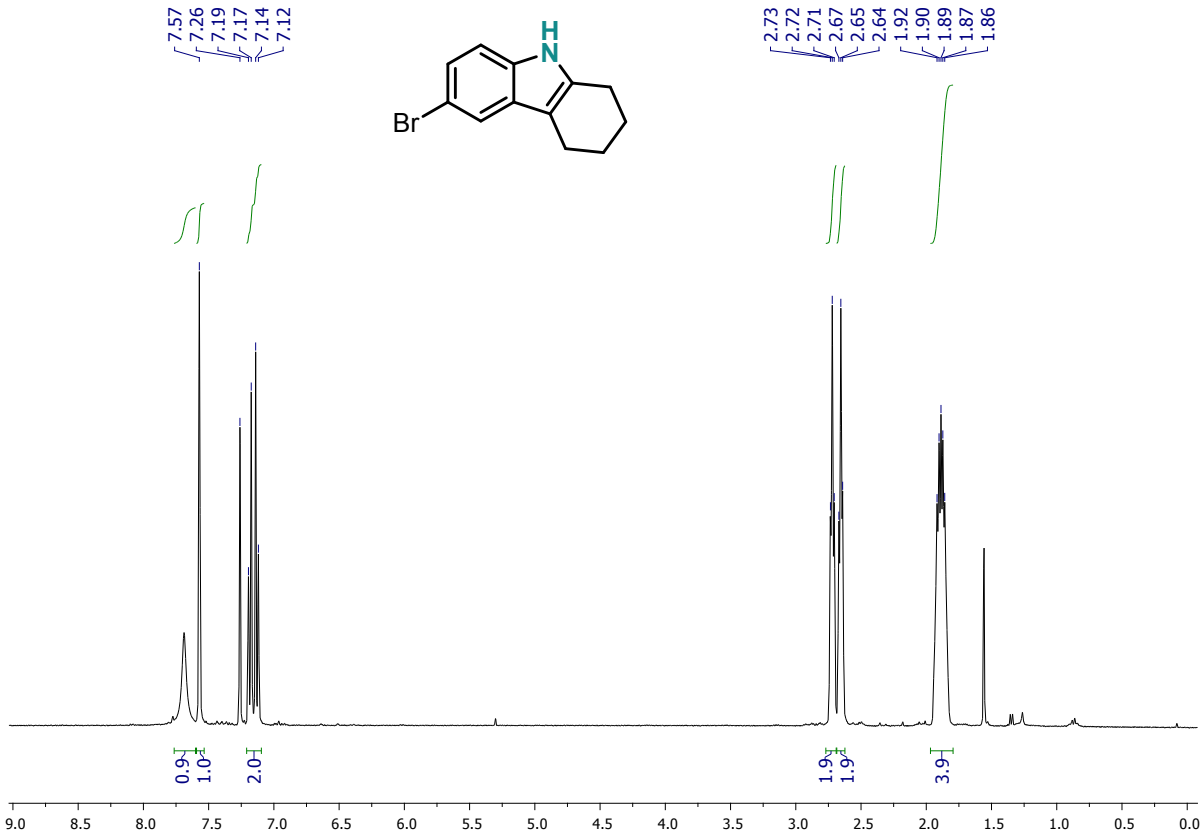


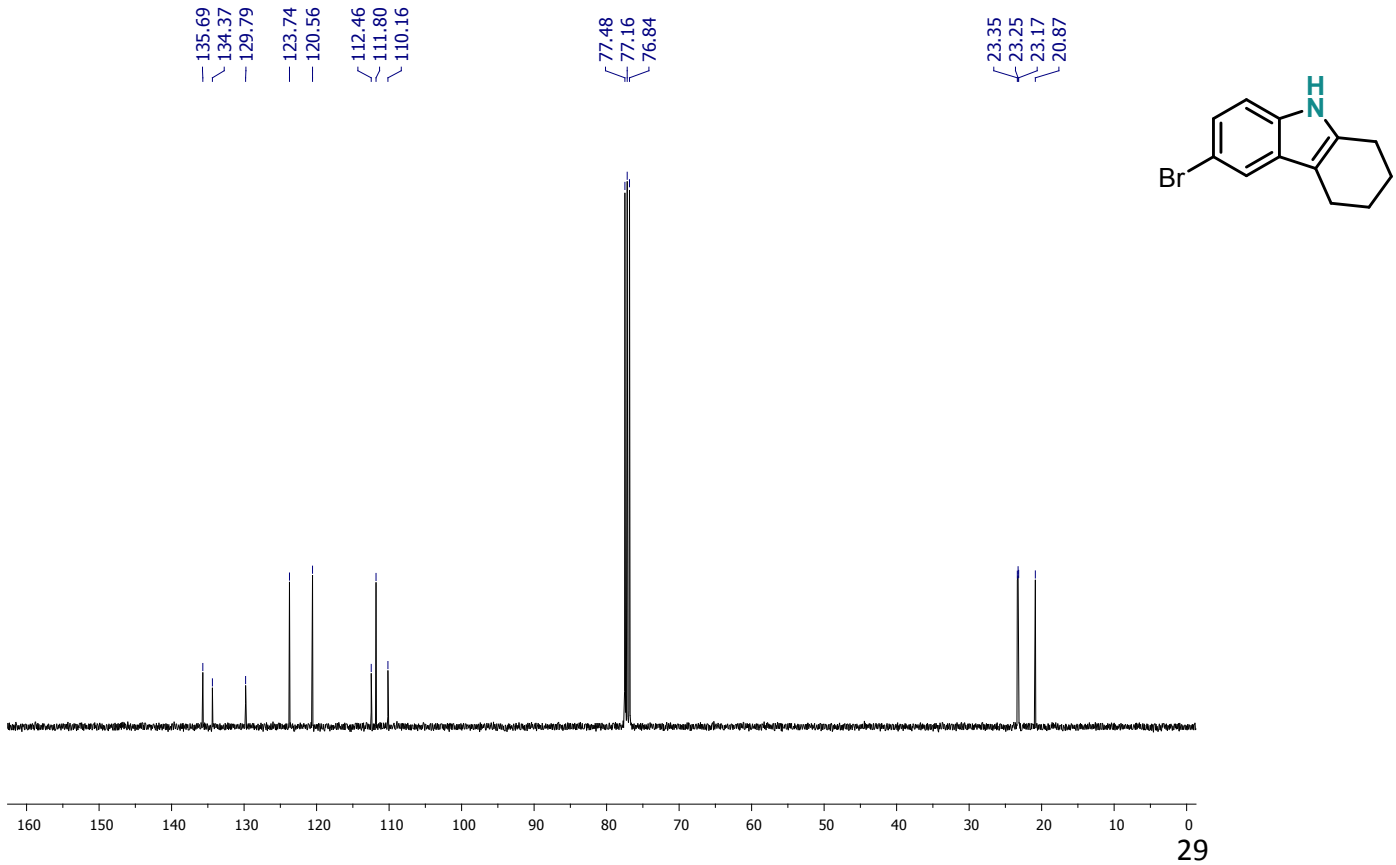
6-Fluoro-2,3,4,9-tetrahydro-1H-carbazole (2)



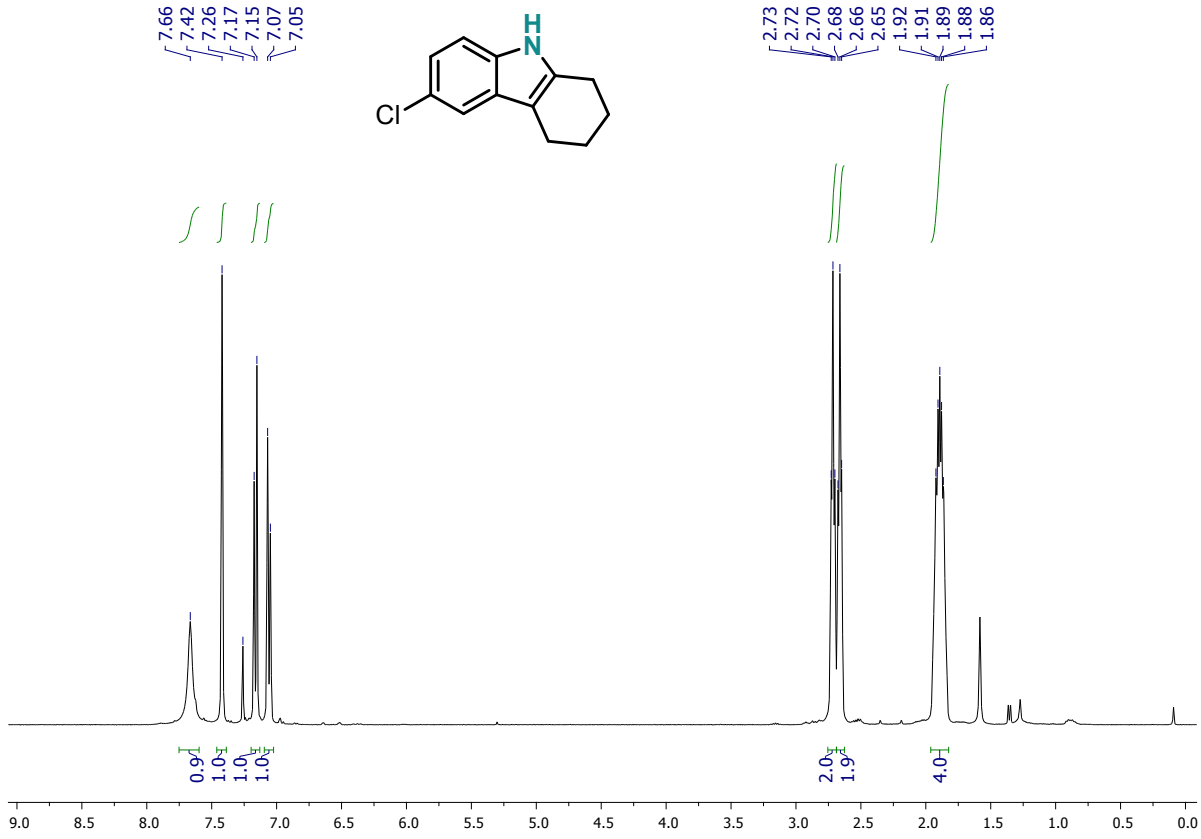


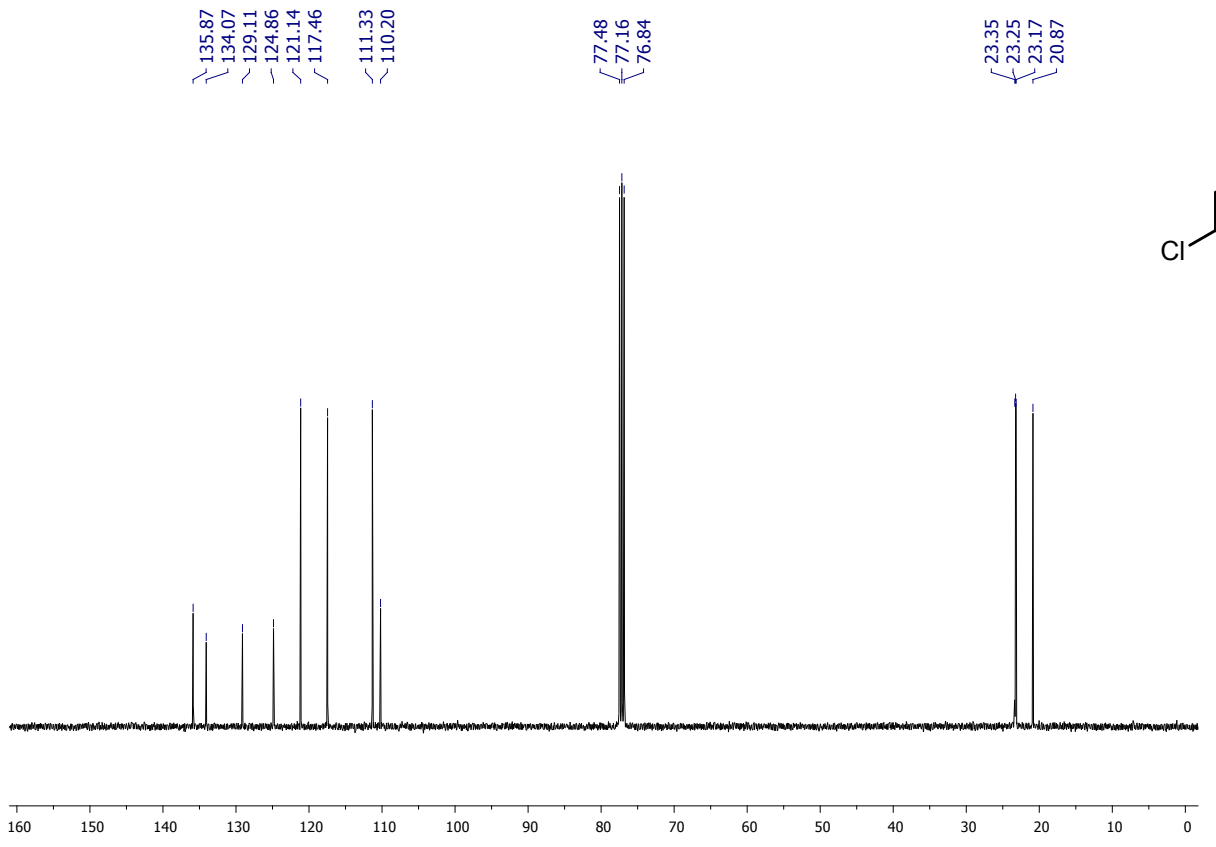
6-Bromo-2,3,4,9-tetrahydro-1H-carbazole (3)



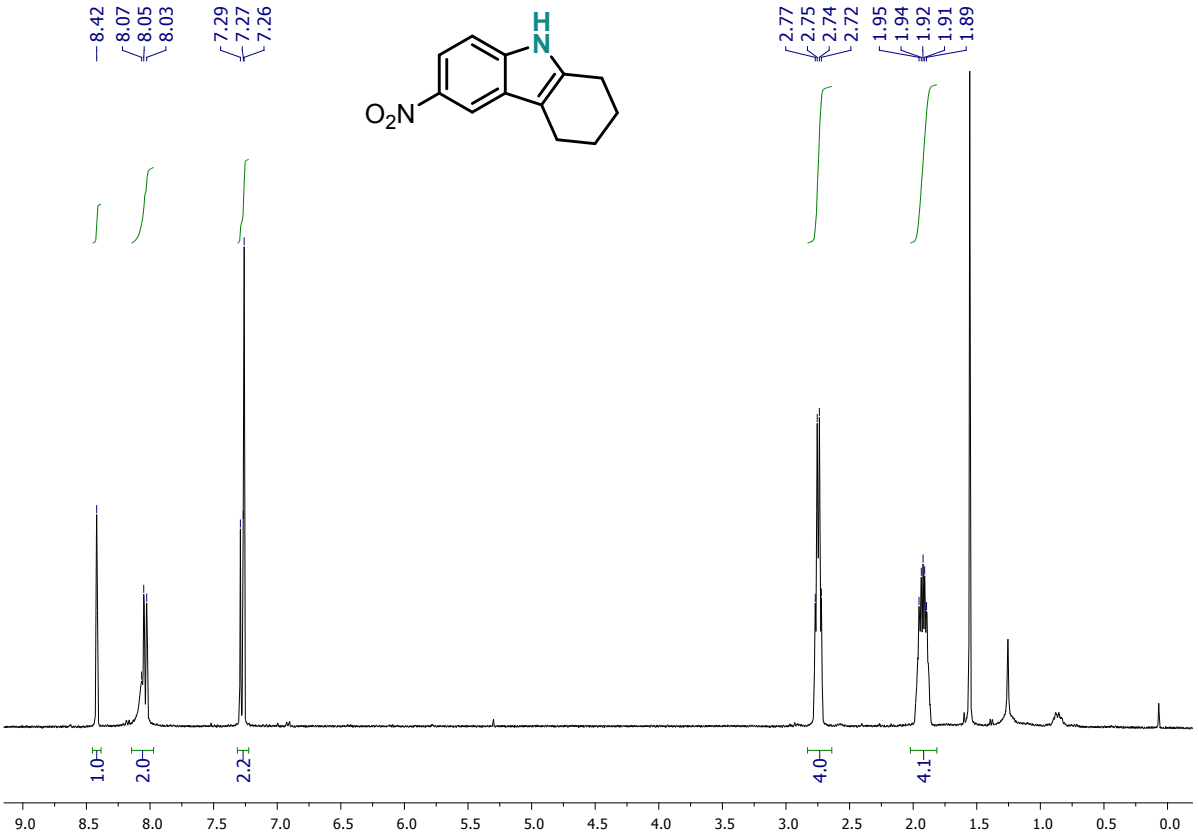


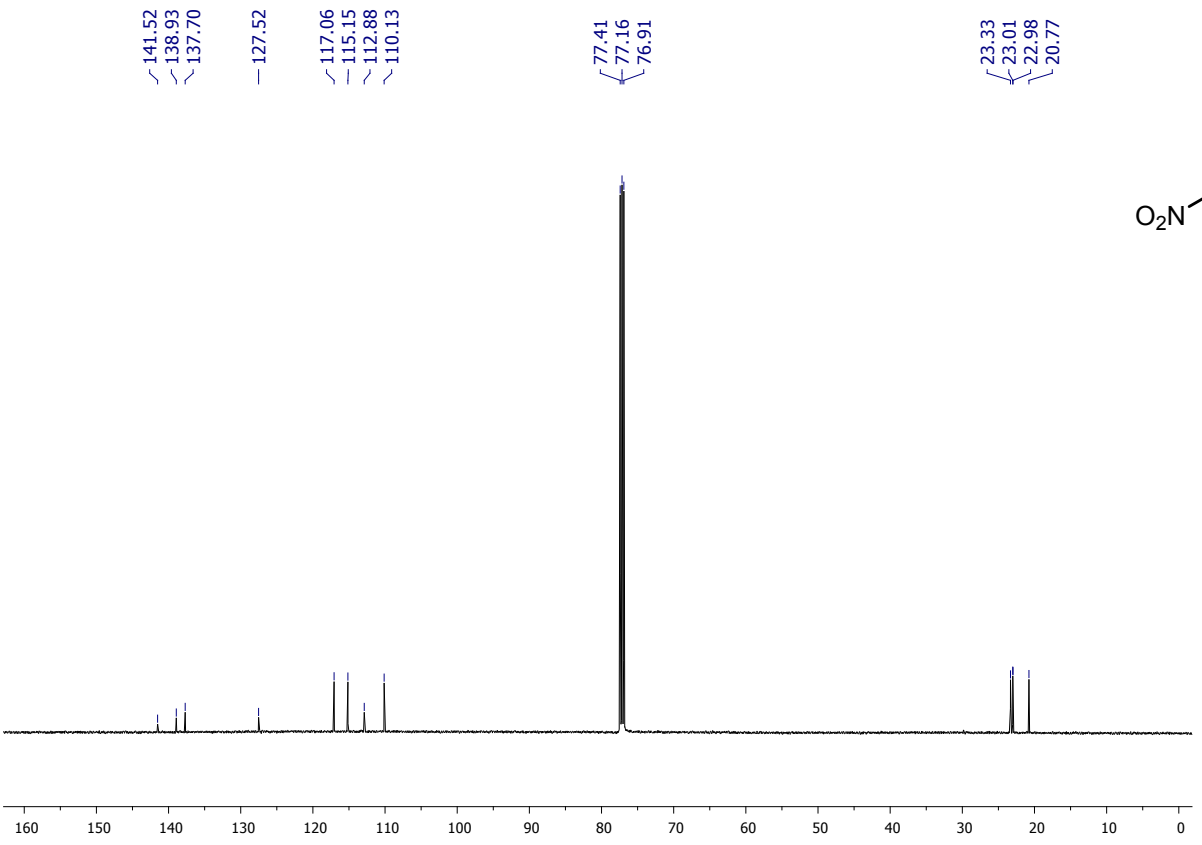
6-Chloro-2,3,4,9-tetrahydro-1H-carbazole (4)



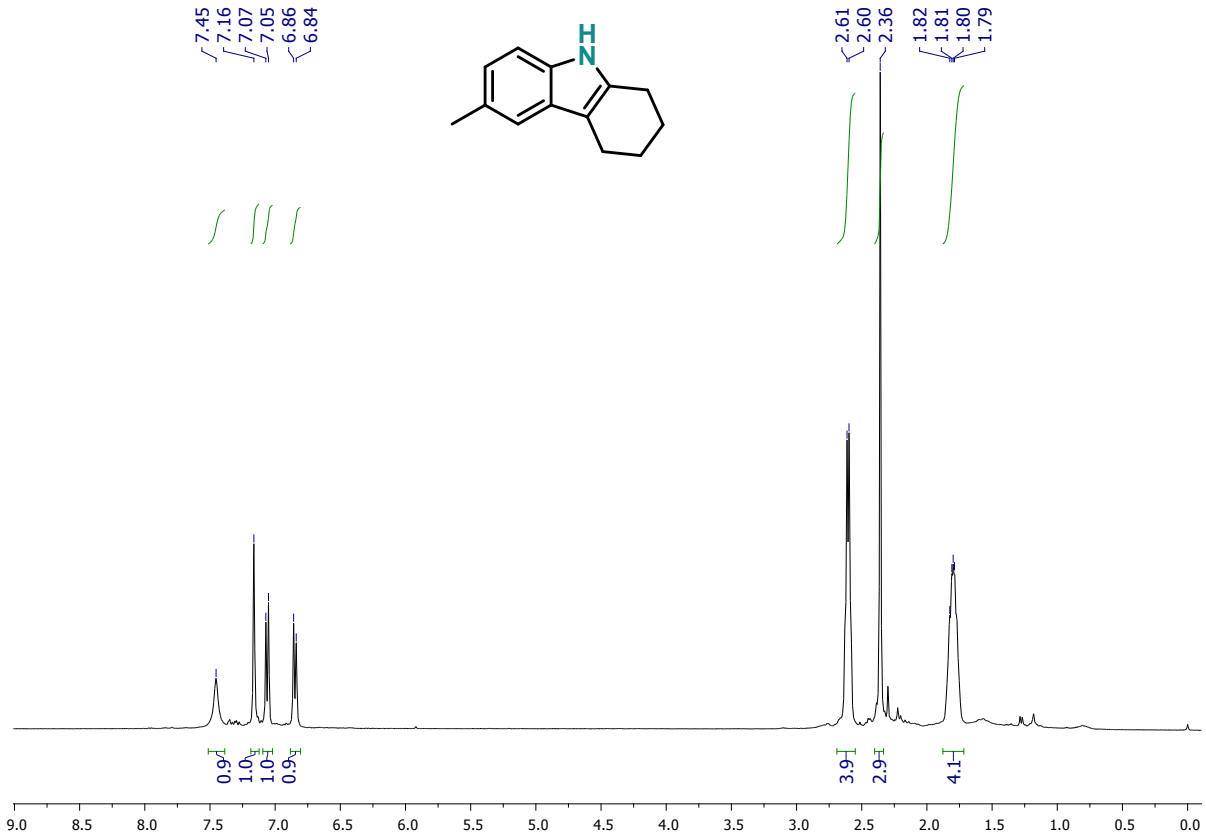


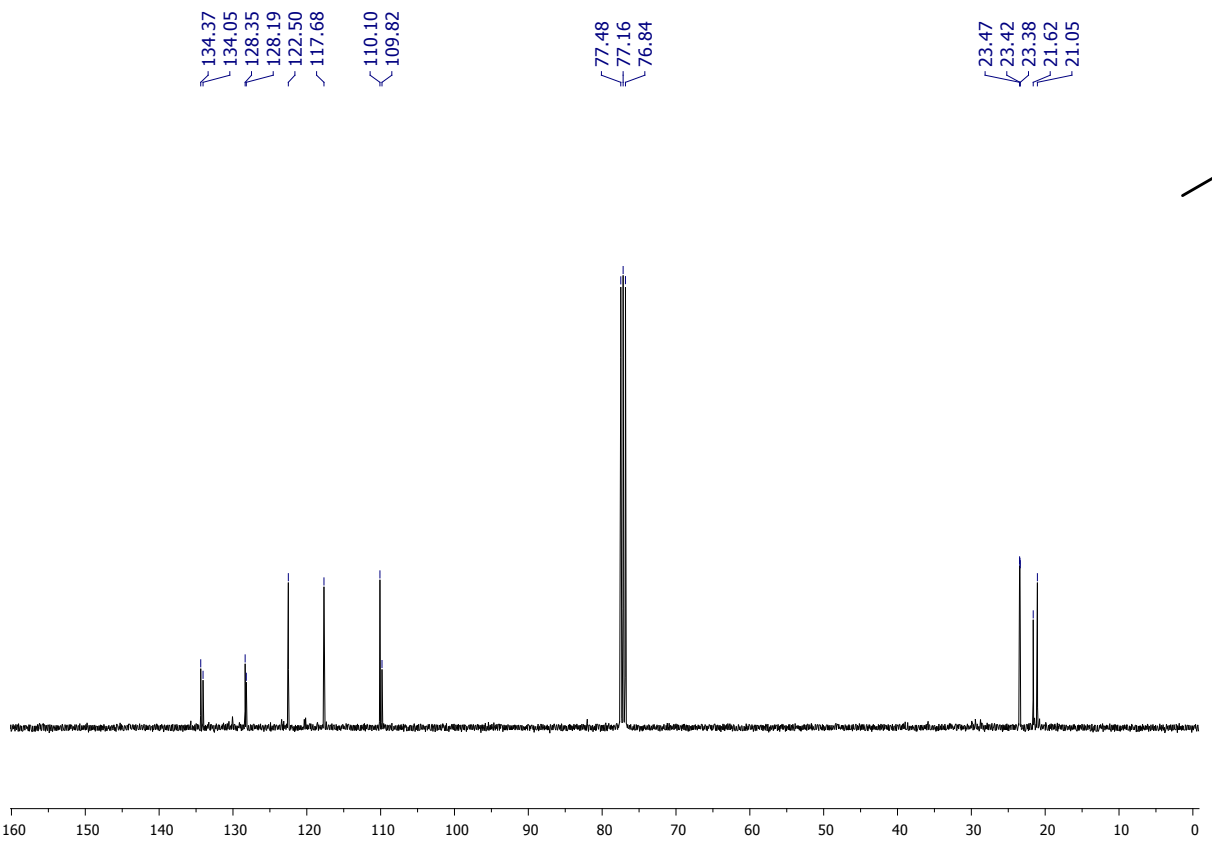
6-Nitro-2,3,4,9-tetrahydro-1H-carbazole (5)



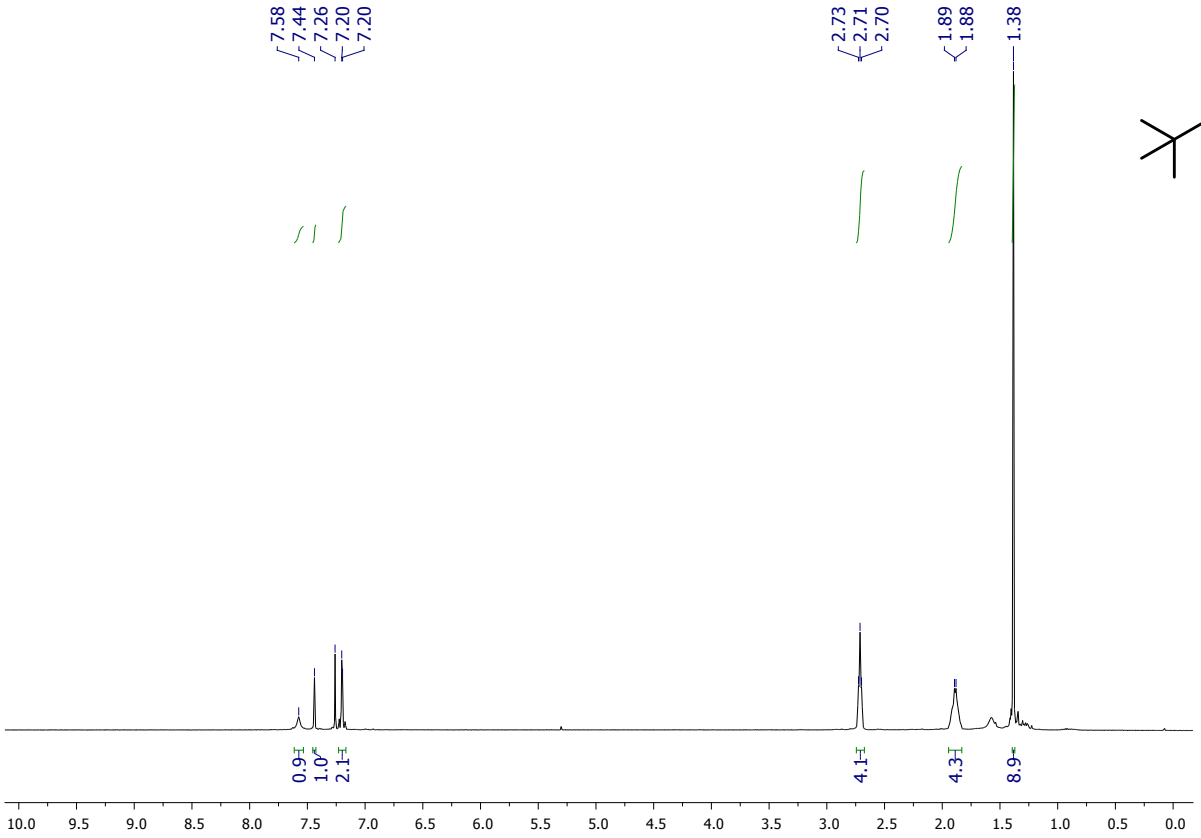


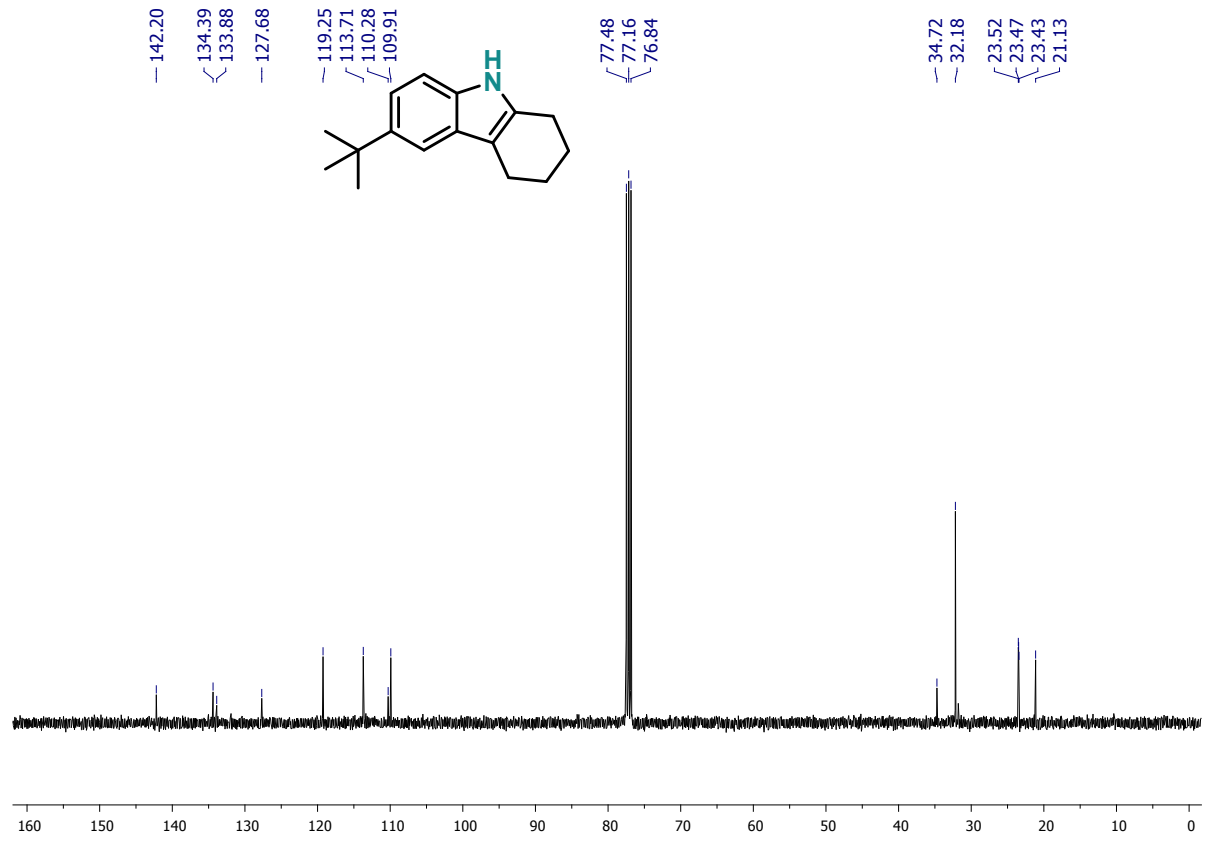
6-Methyl-2,3,4,9-tetrahydro-1H-carbazole (6)



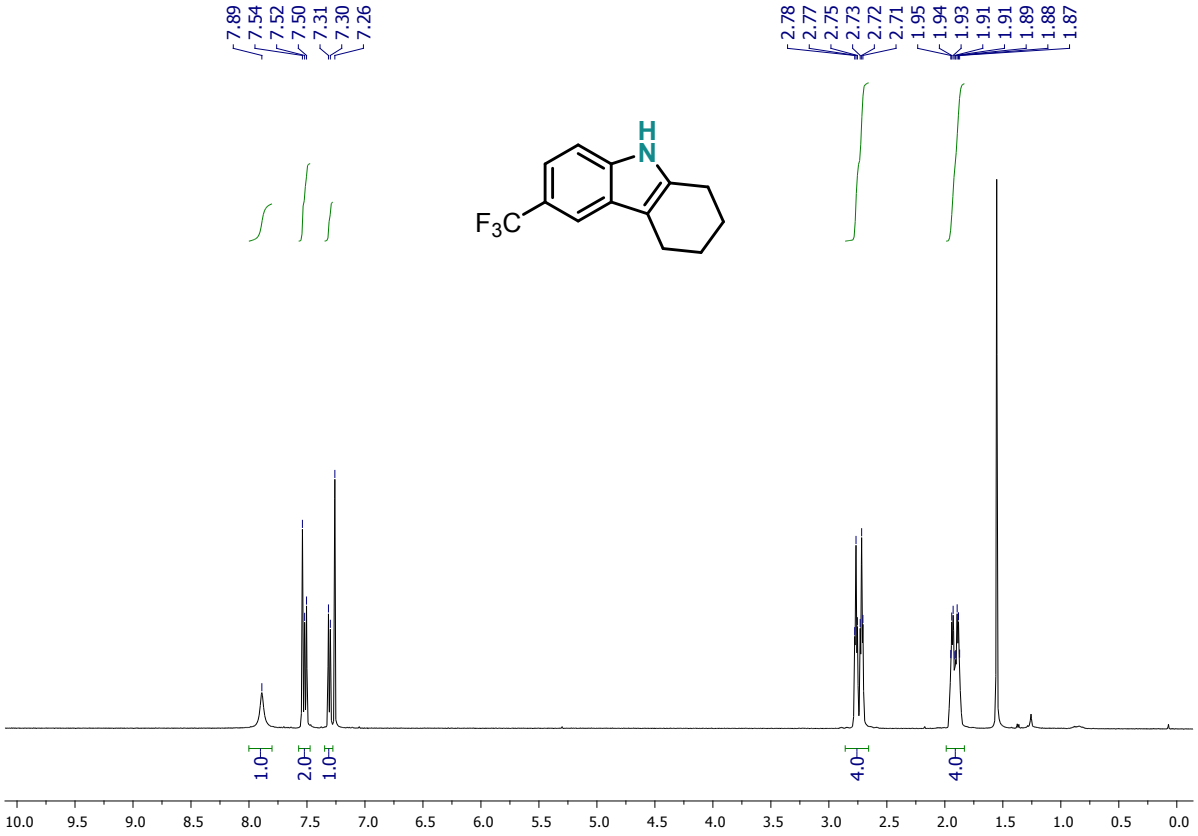


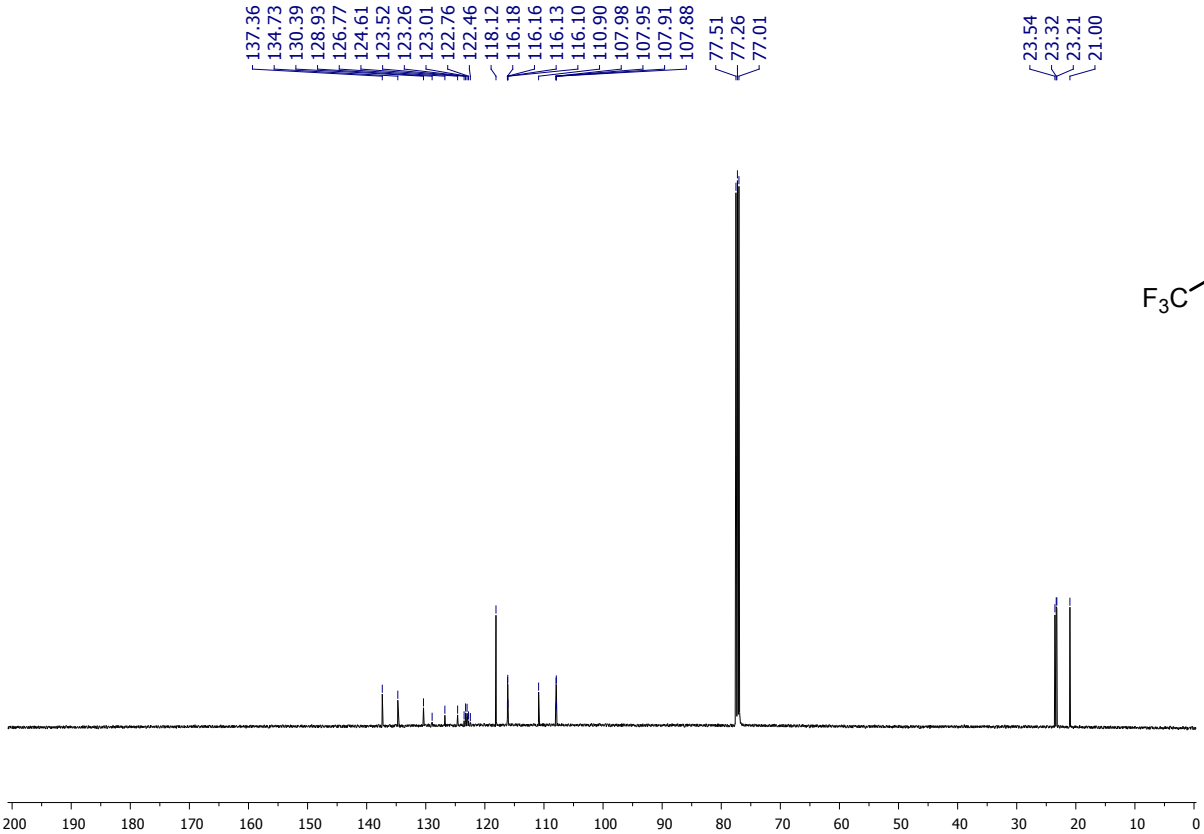
6-(Tert-butyl)-2,3,4,9-tetrahydro-1H-carbazole (7)

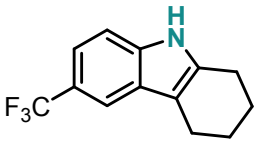


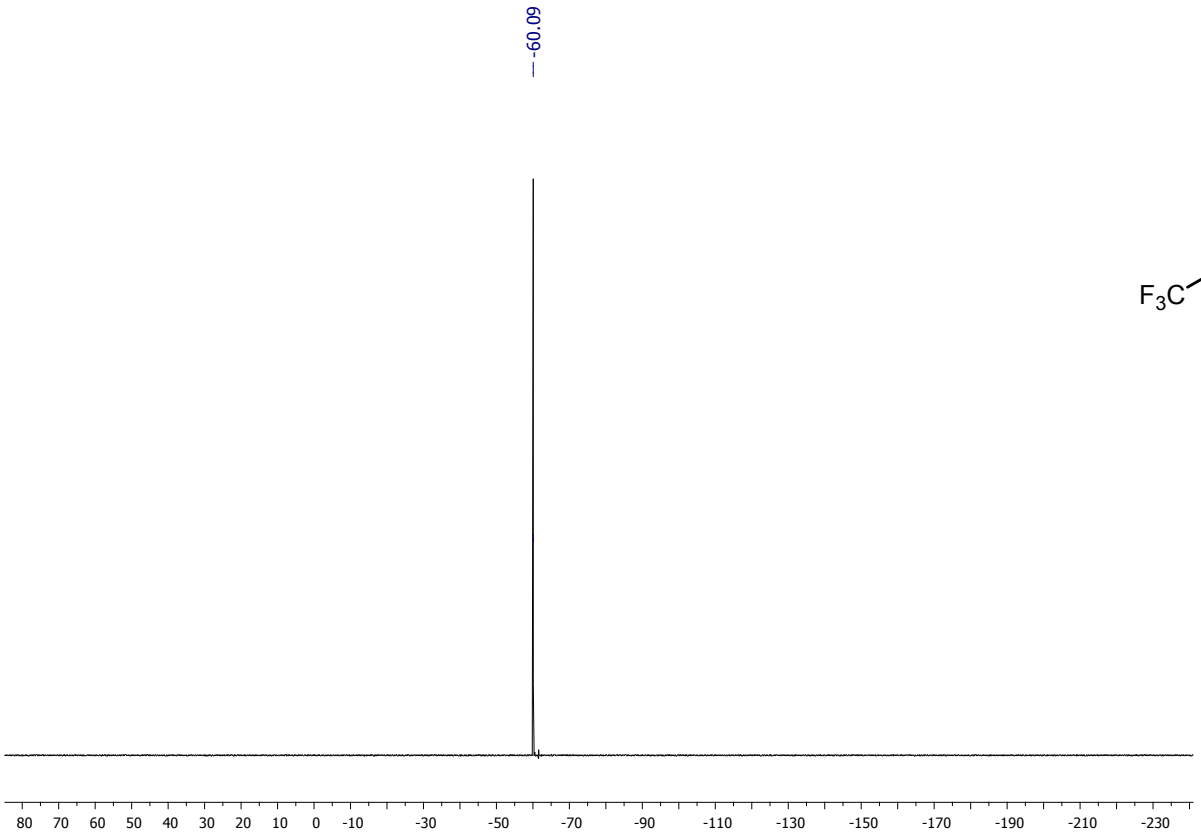


6-(Trifluoromethyl)-2,3,4,9-tetrahydro-1H-carbazole (8)

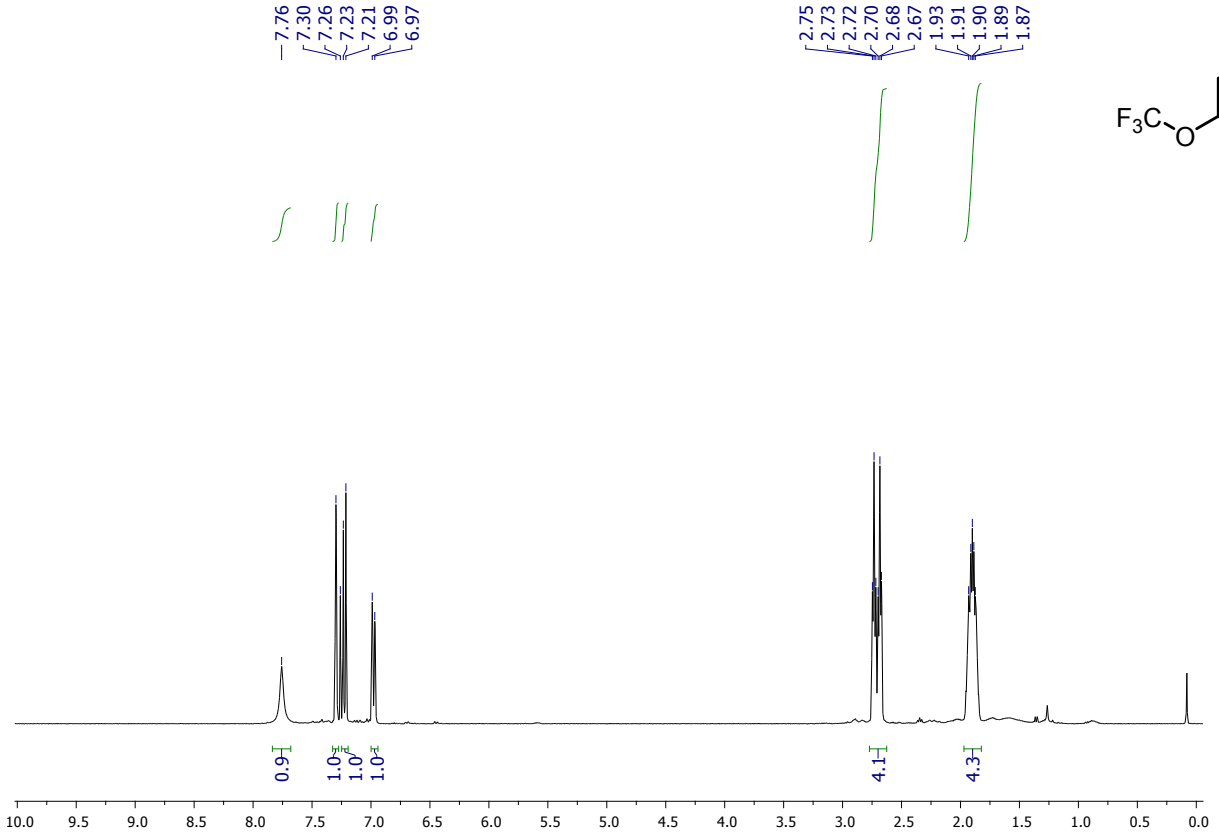


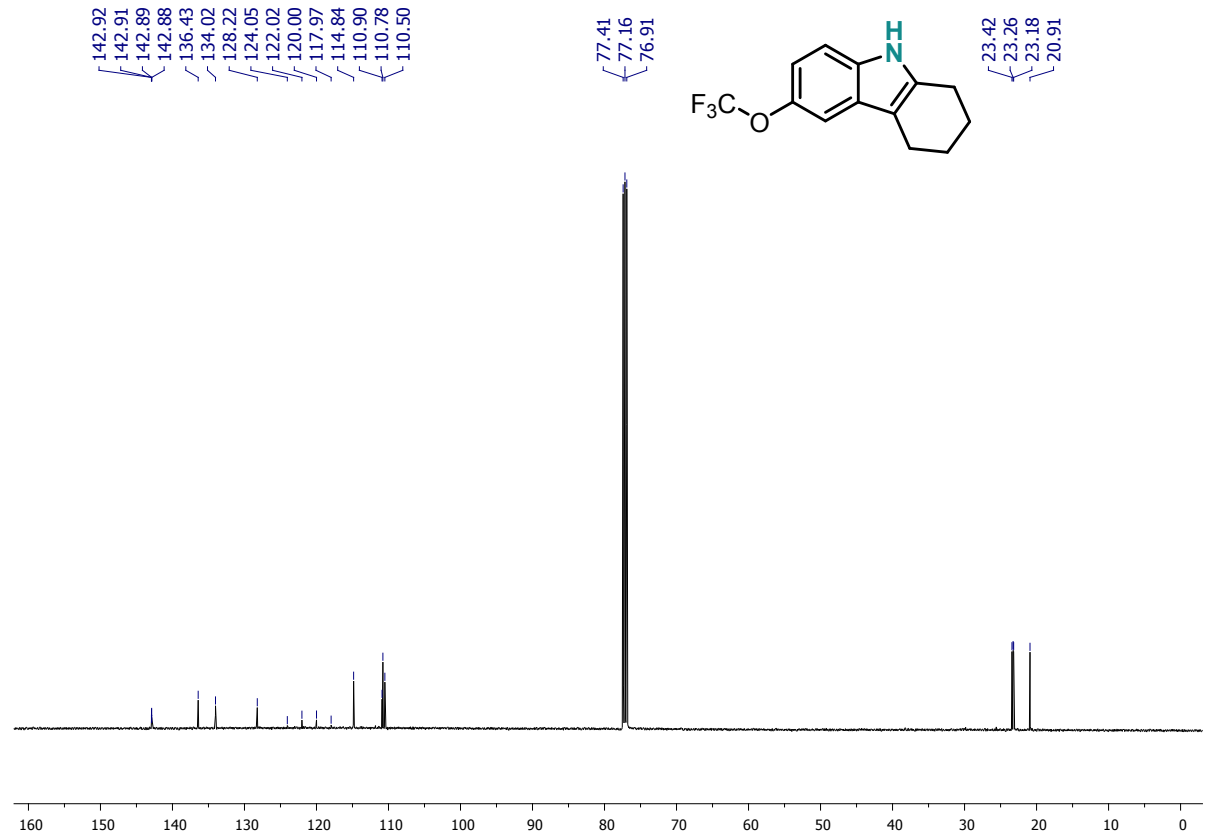


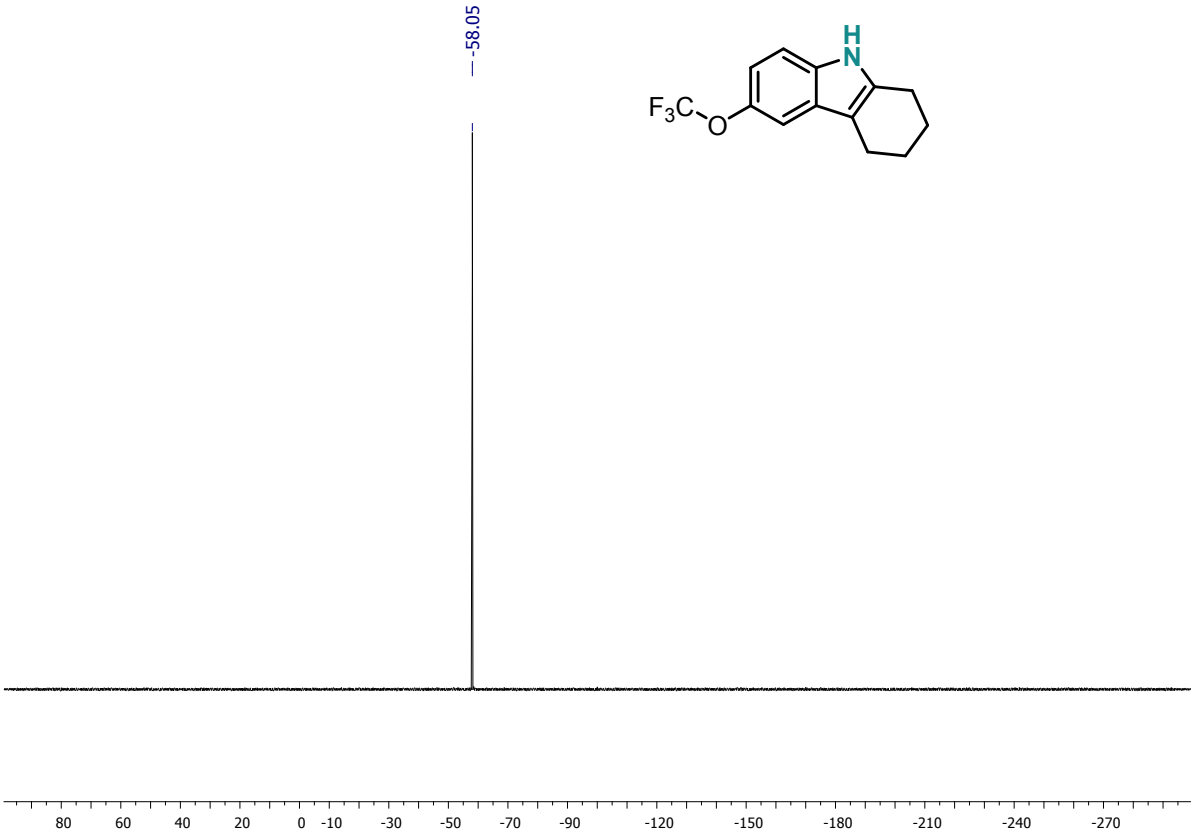



-60.09
H
N
F3C
80 70 60 50 40 30 20 10 0 -10 -30 -50 -70 -90 -110 -130 -150 -170 -190 -210 -230

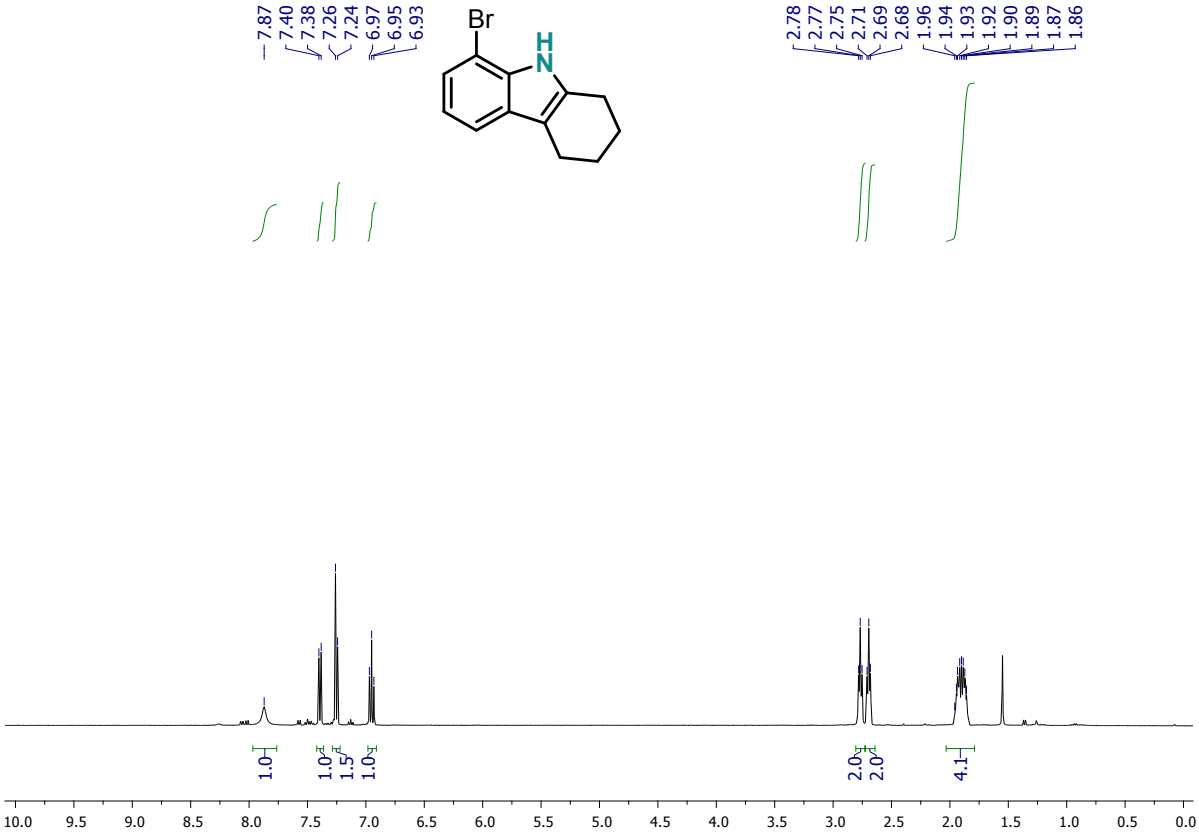
6-(Trifluoromethoxy)-2,3,4,9-tetrahydro-1H-carbazole (9)

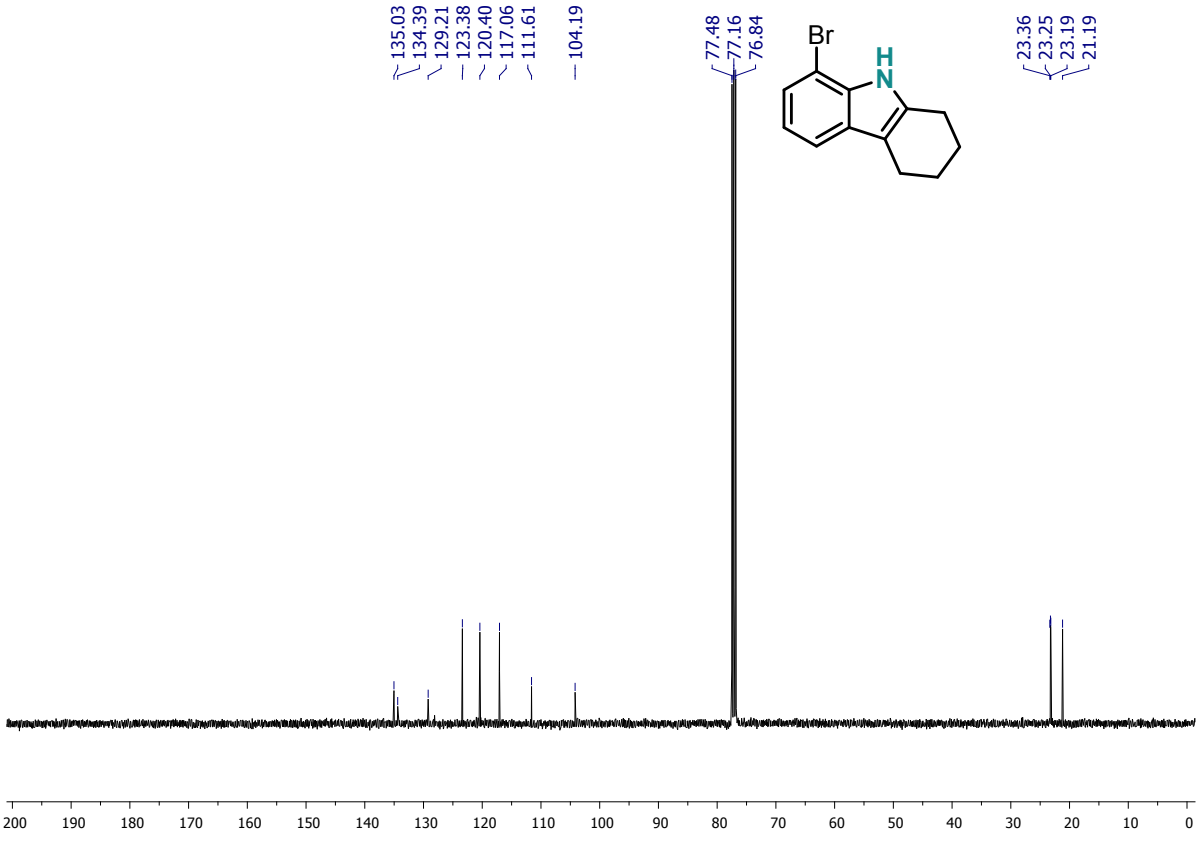




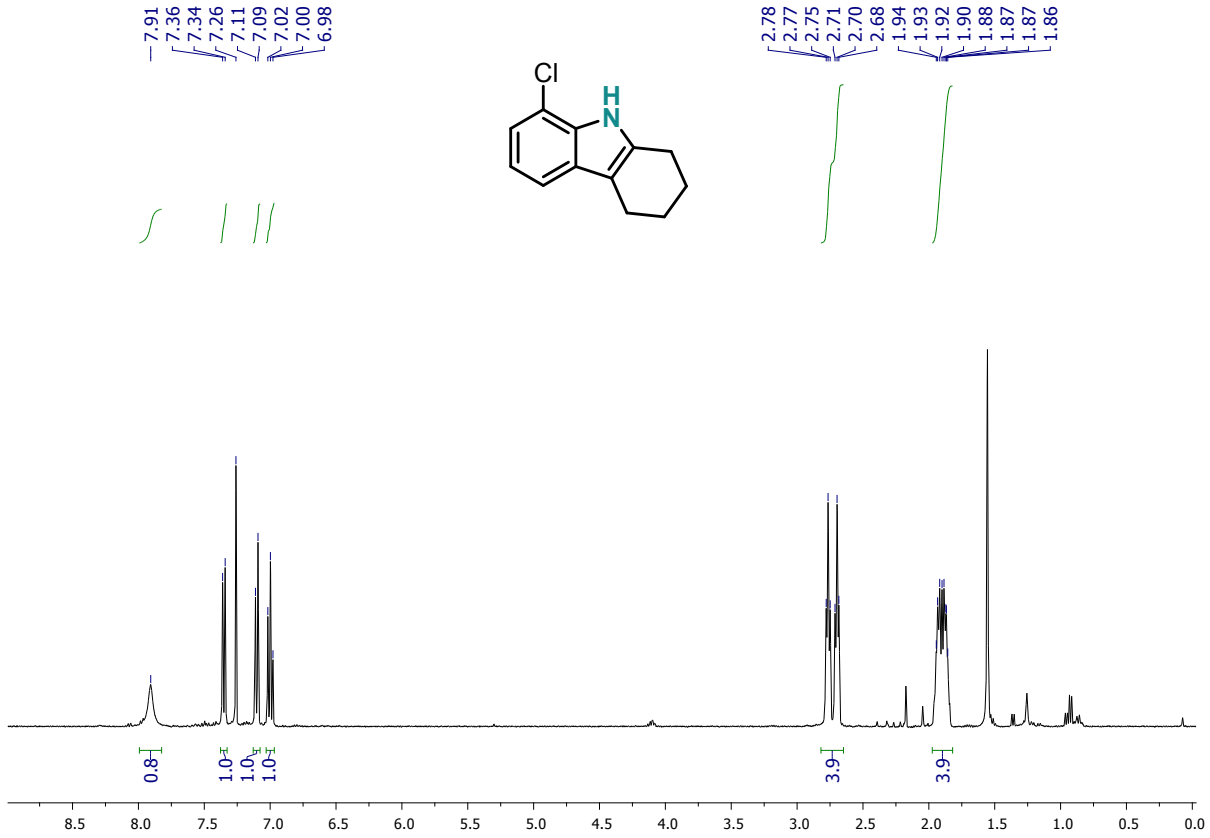

-58.05
H
N
F3C
O
80
60
40
20
0
-10
-30
-50
-70
-90
-120
-150
-180
-210
-240
-270

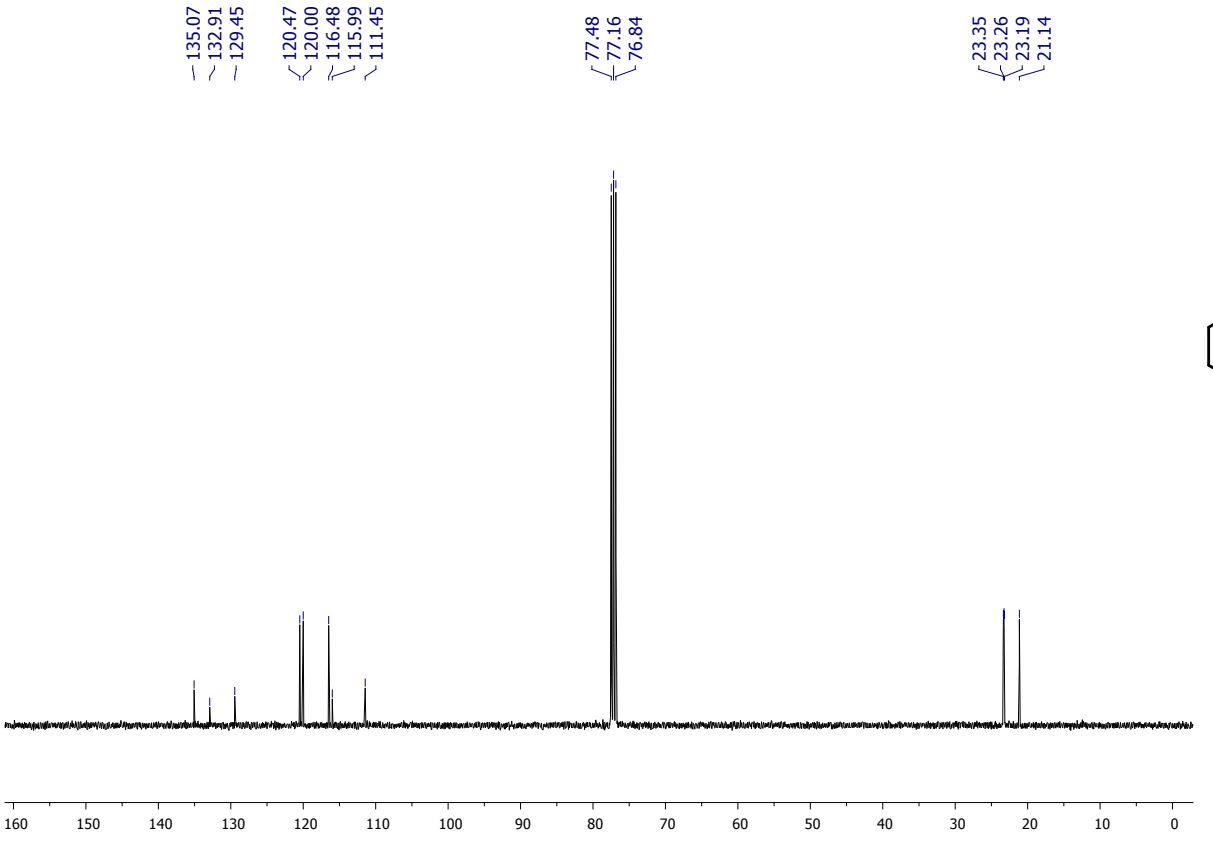
8-Bromo-2,3,4,9-tetrahydro-1H-carbazole (10)

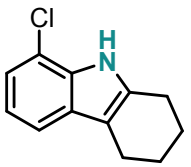




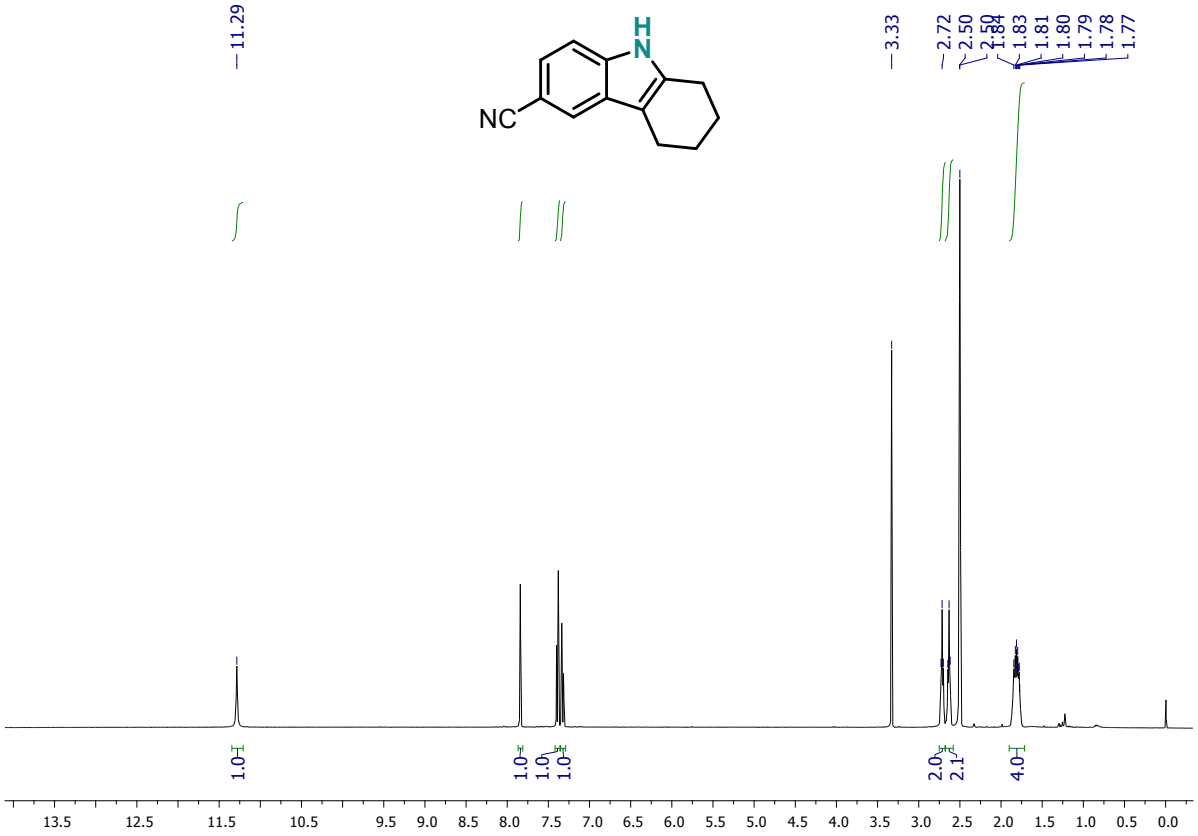
8-Chloro-2,3,4,9-tetrahydro-1H-carbazole (11)

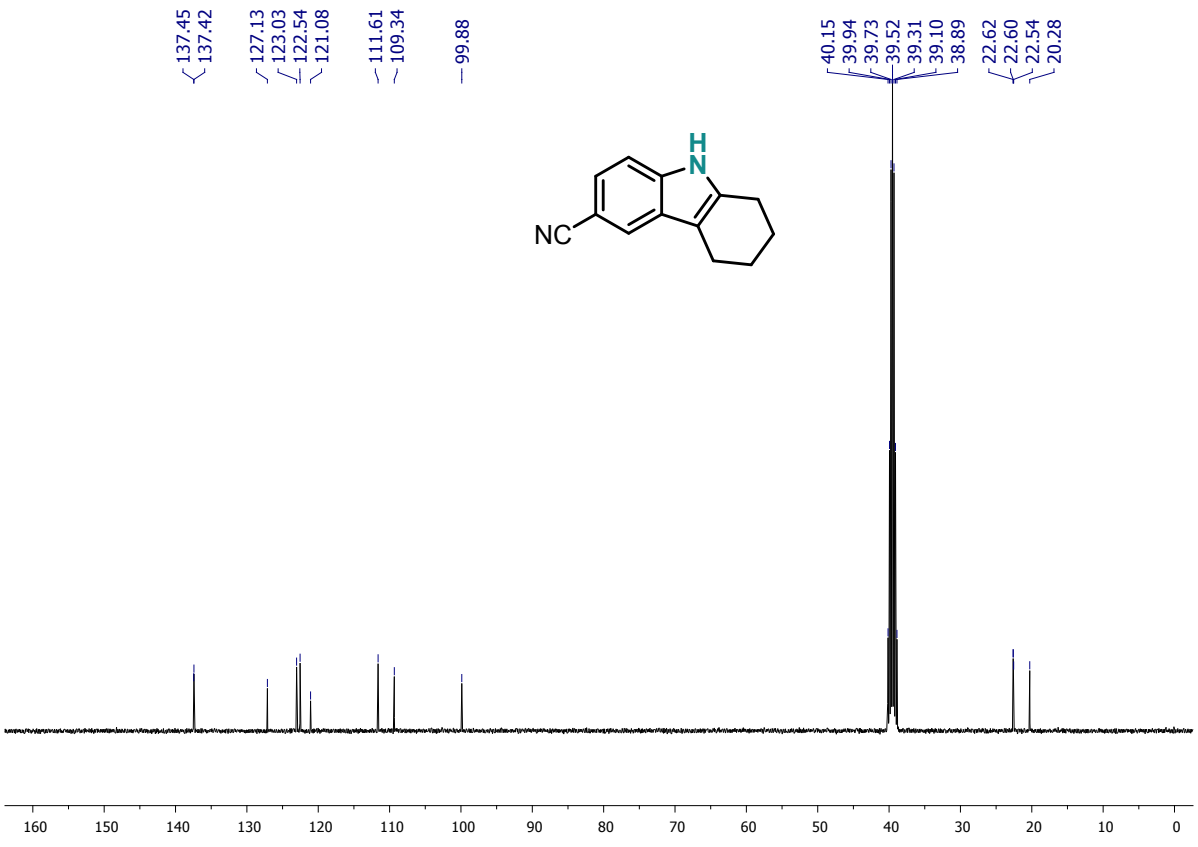




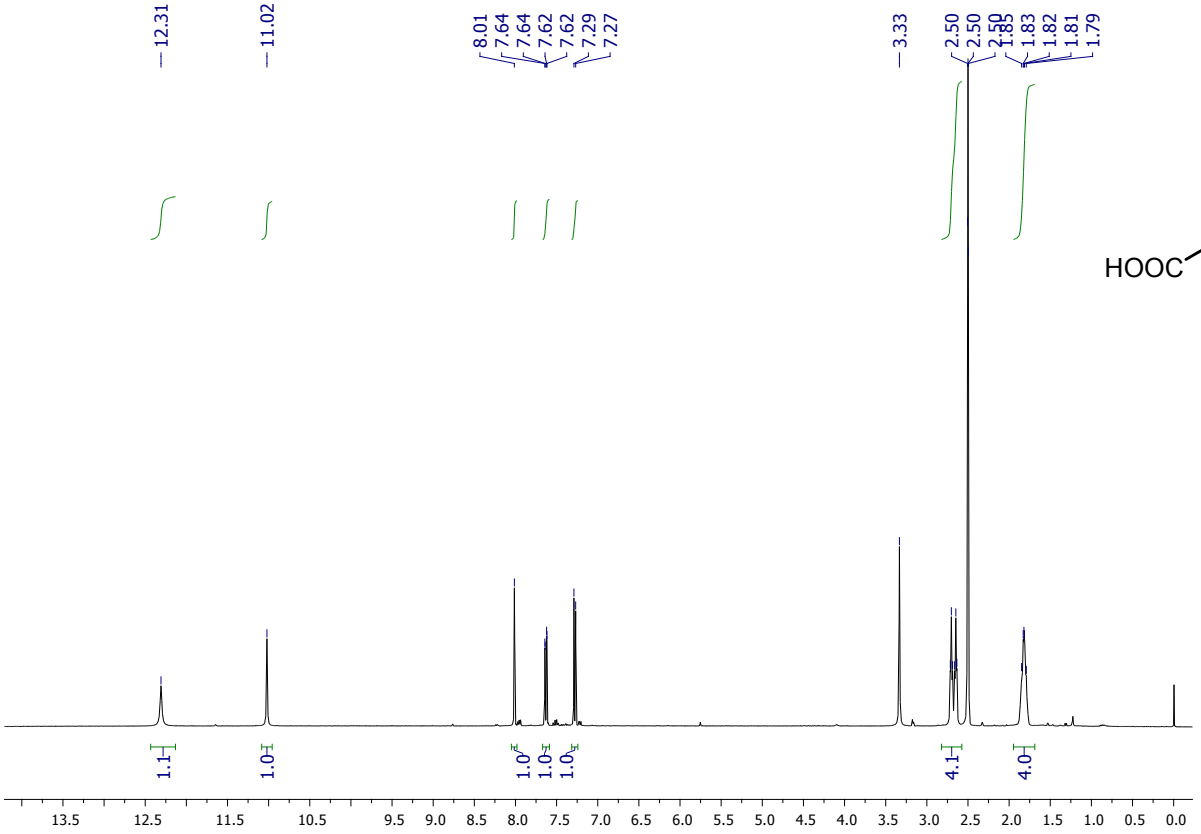


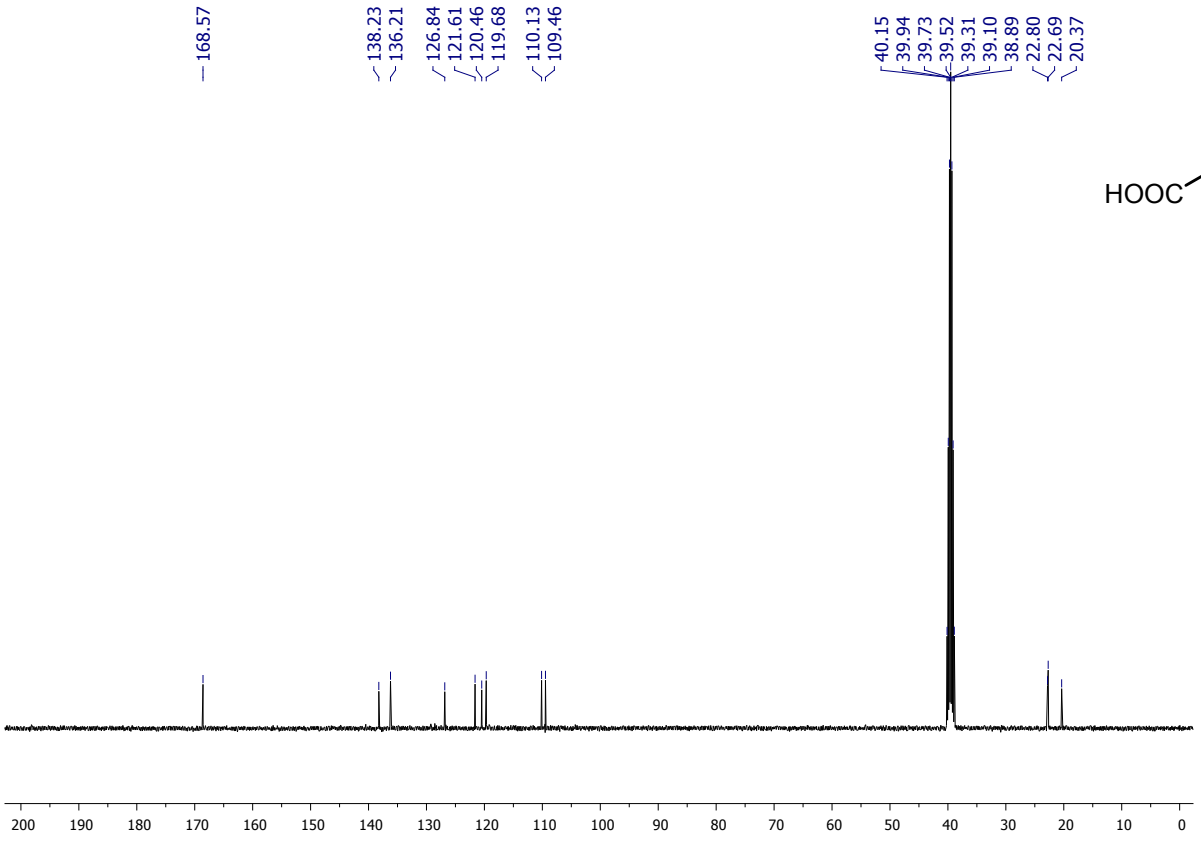
2,3,4,9-tetrahydro-1H-carbazole-6-carbonitrile (12)



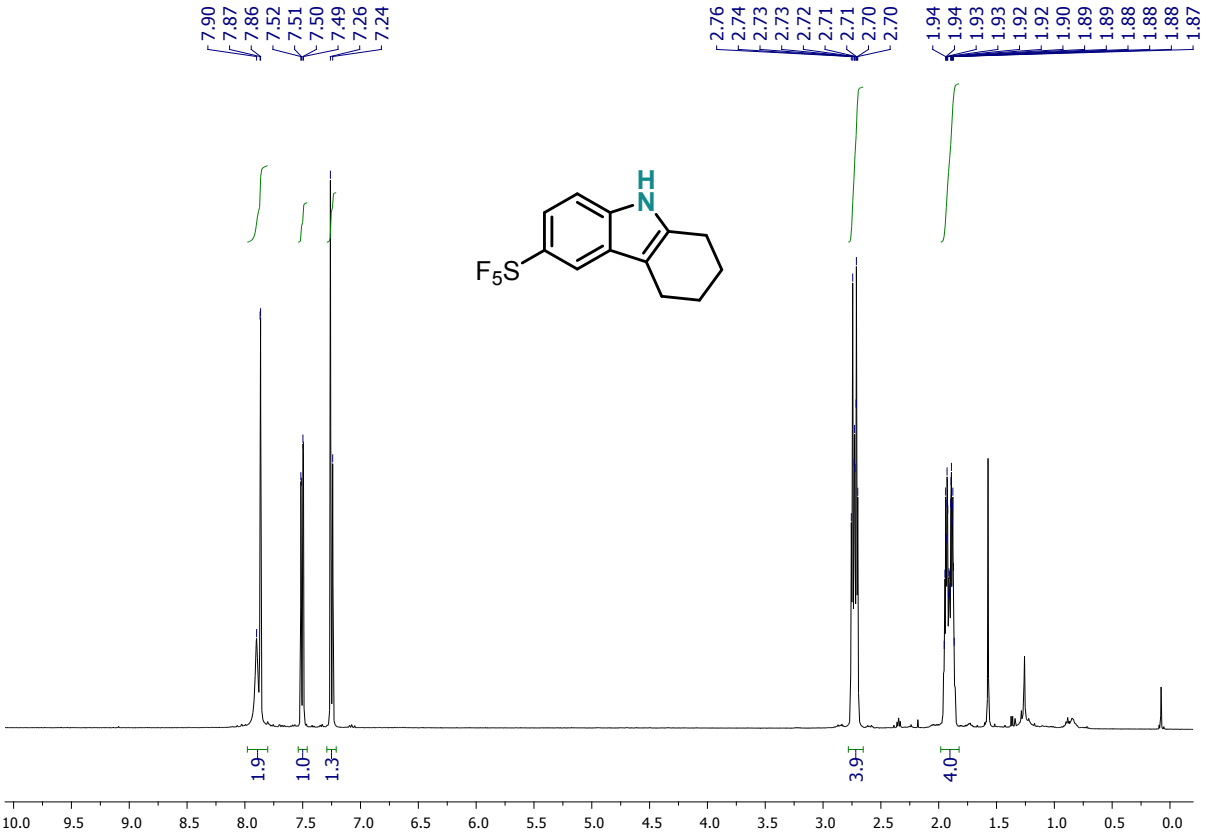


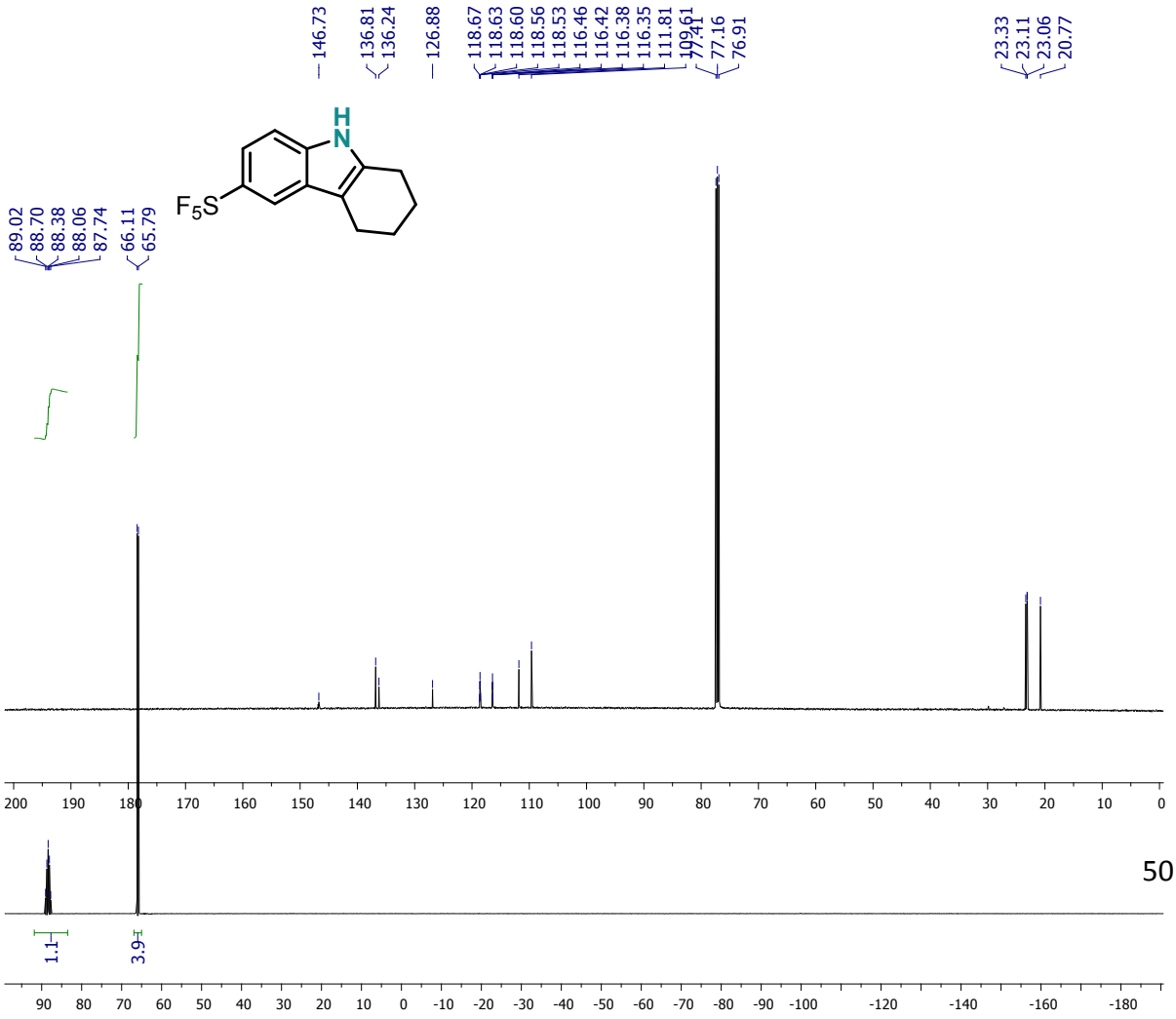
2,3,4,9-tetrahydro-1H-carbazole-6-carboxylic acid (13)

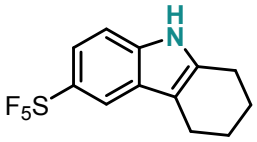




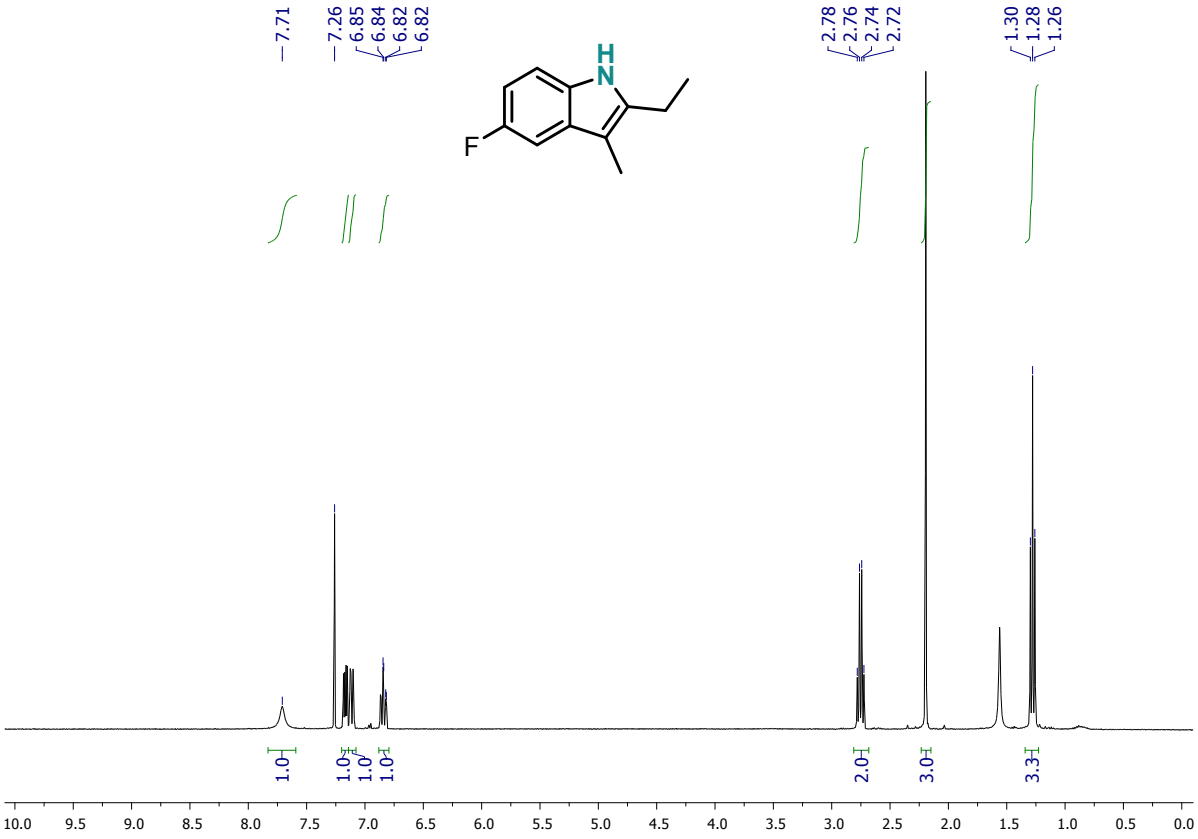
6-(pentafluorothio)-2,3,4,9-tetrahydro-1H-carbazole (14)

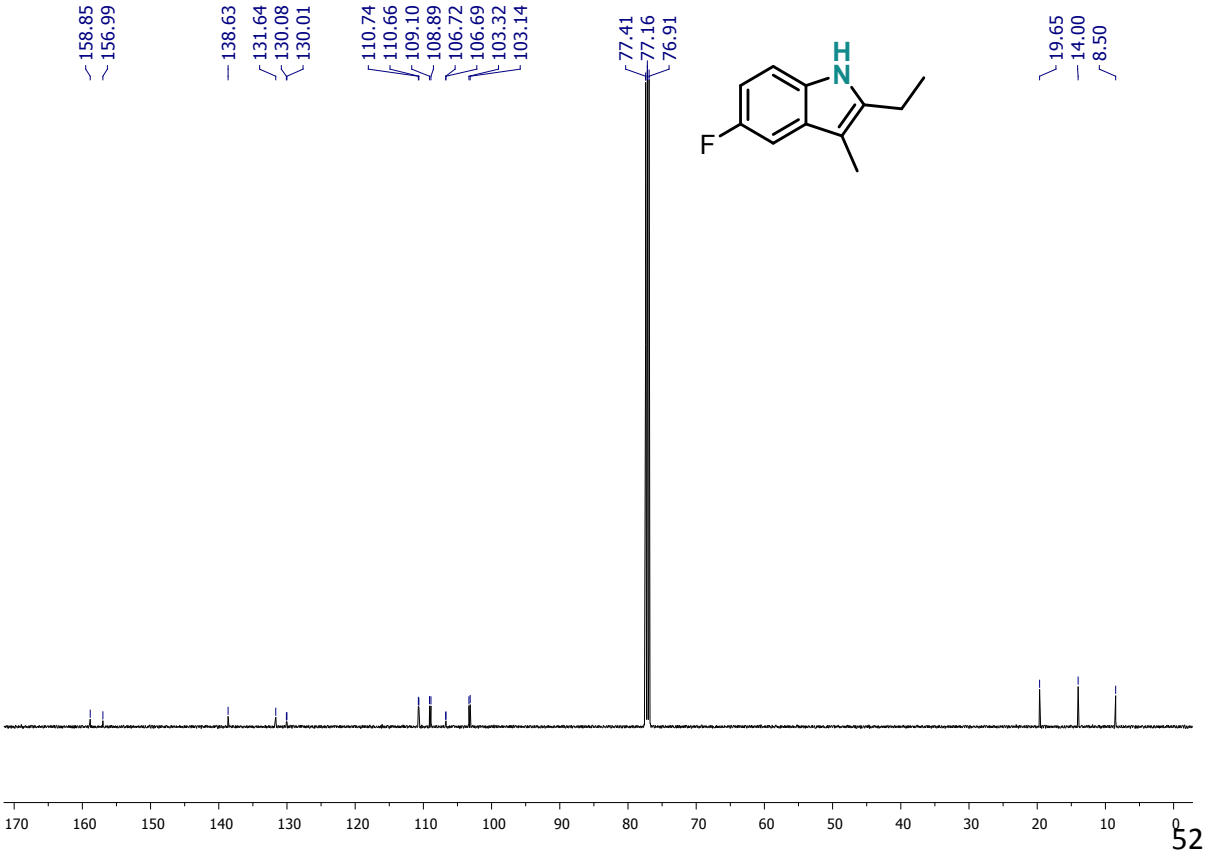


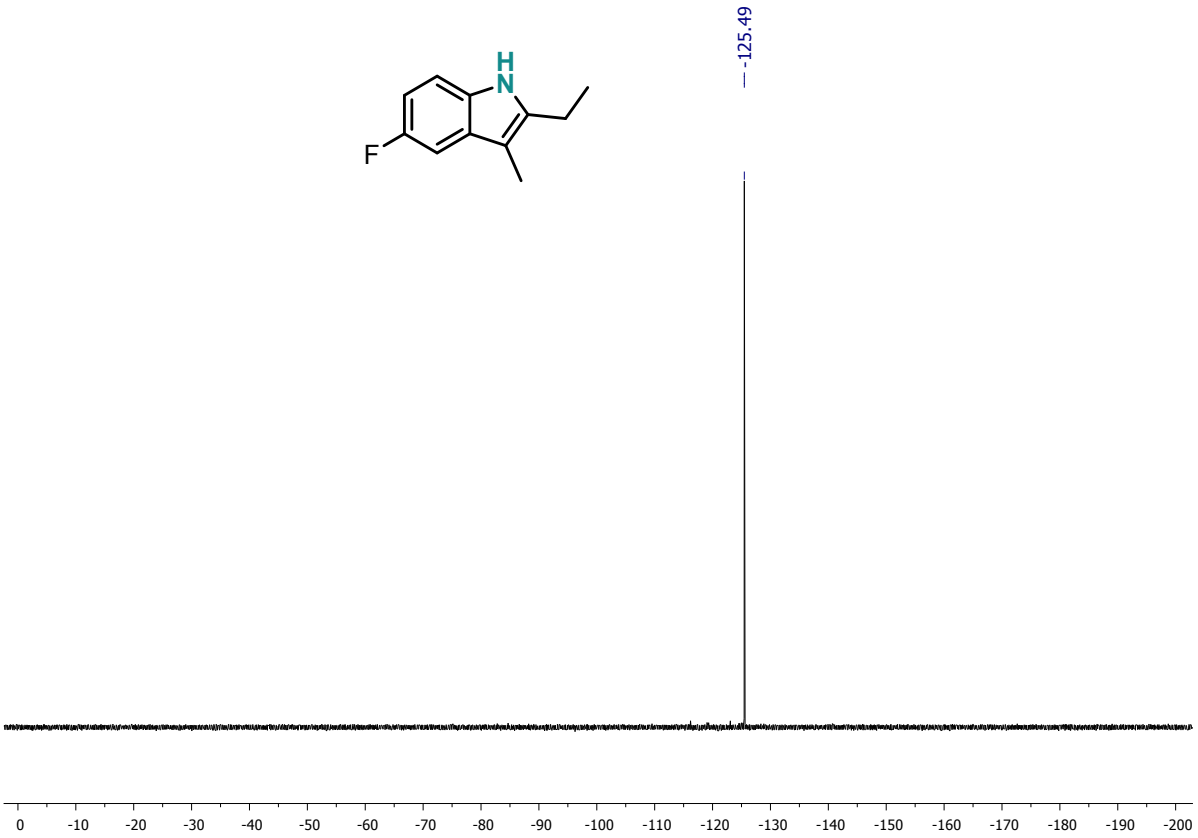



H
N
F5S

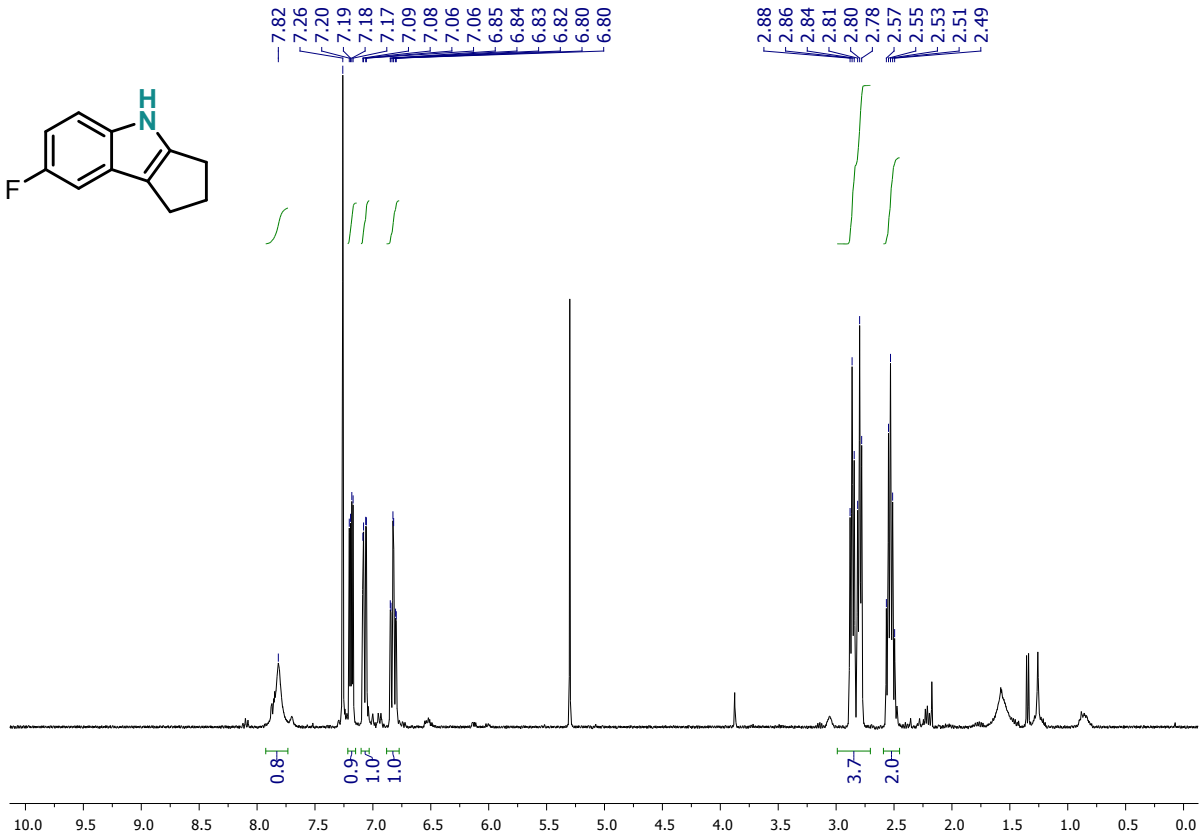
3-Ethyl-5-fluoro-2-methyl-1H-indole (15)

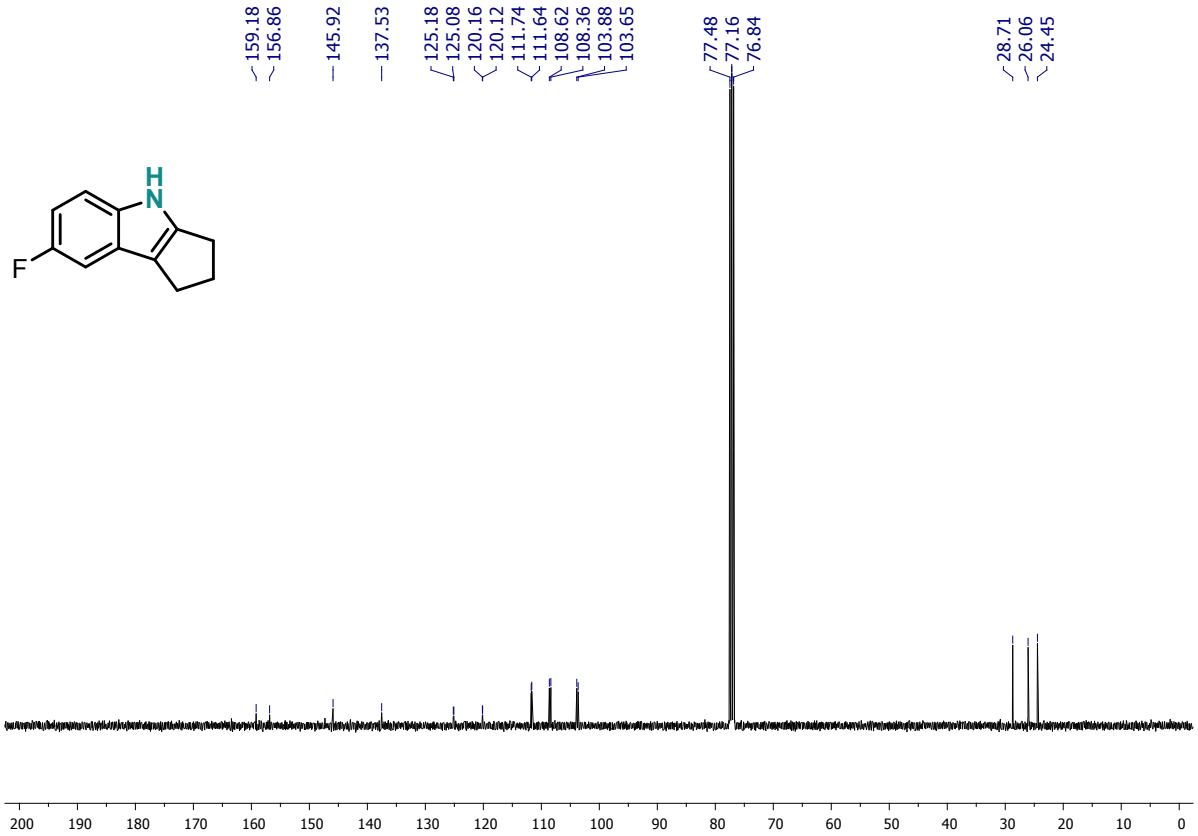


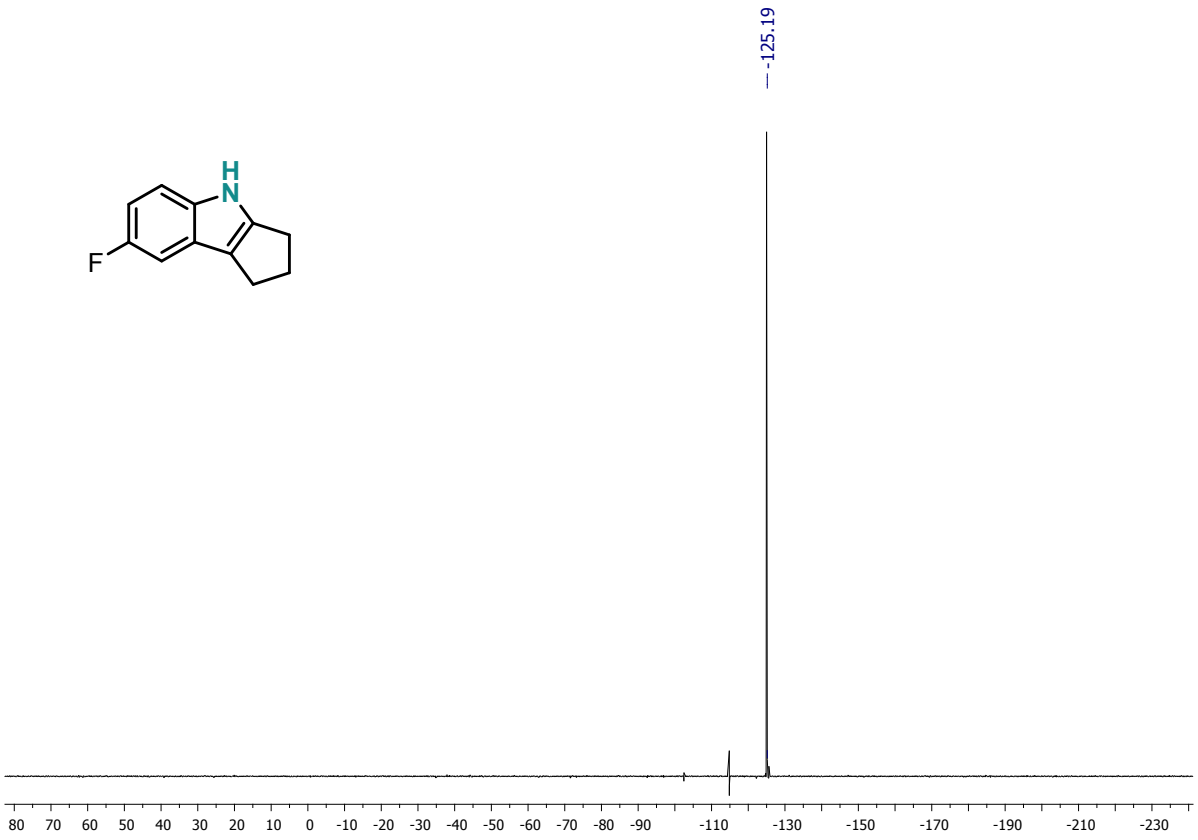



H
N
F
-125.49
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200

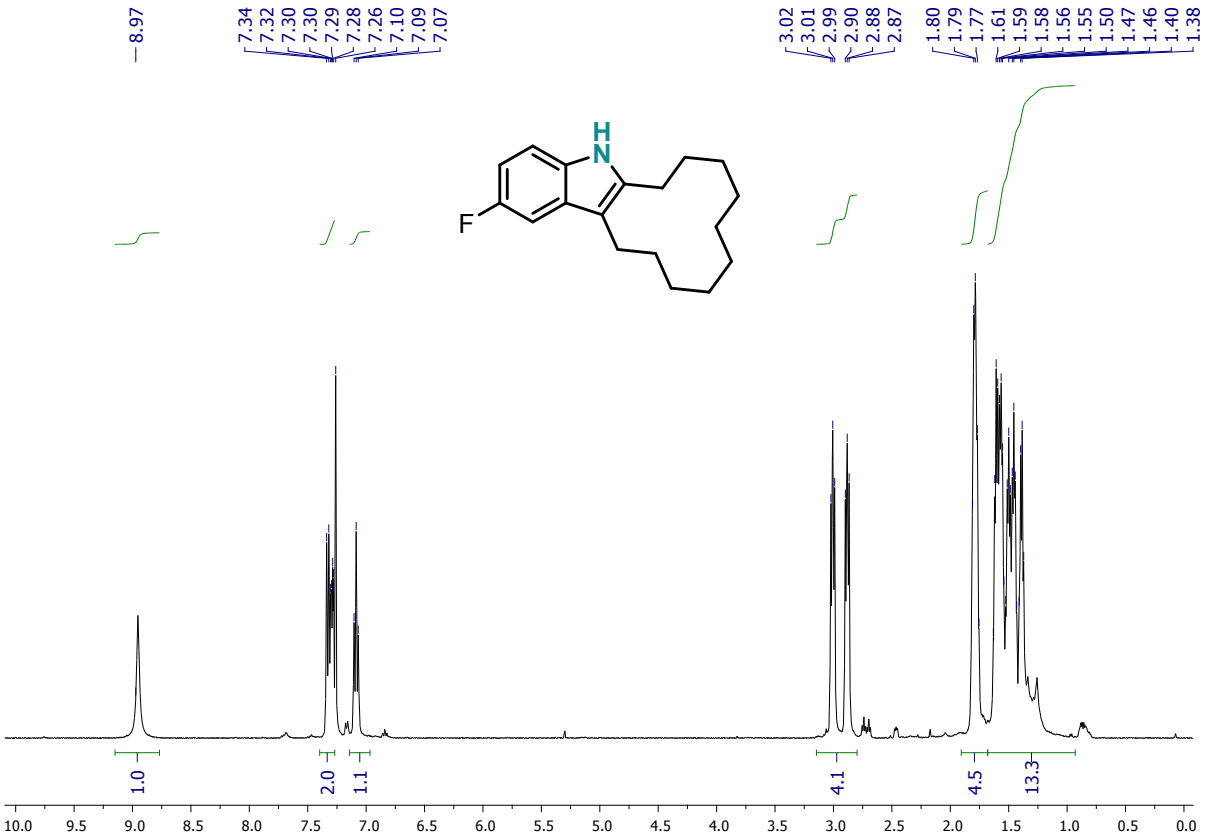
7-fluoro-1,2,3,4-tetrahydrocyclopenta[b]indole (16)

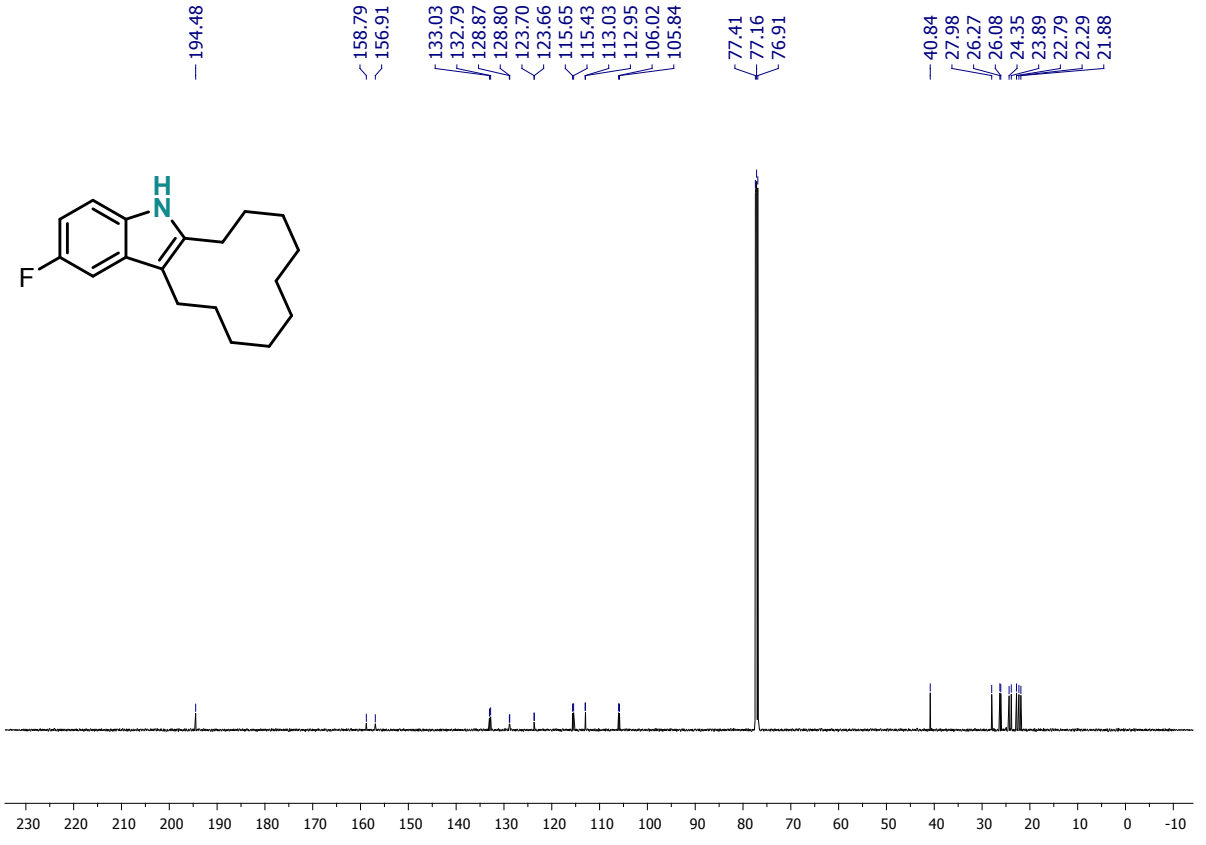


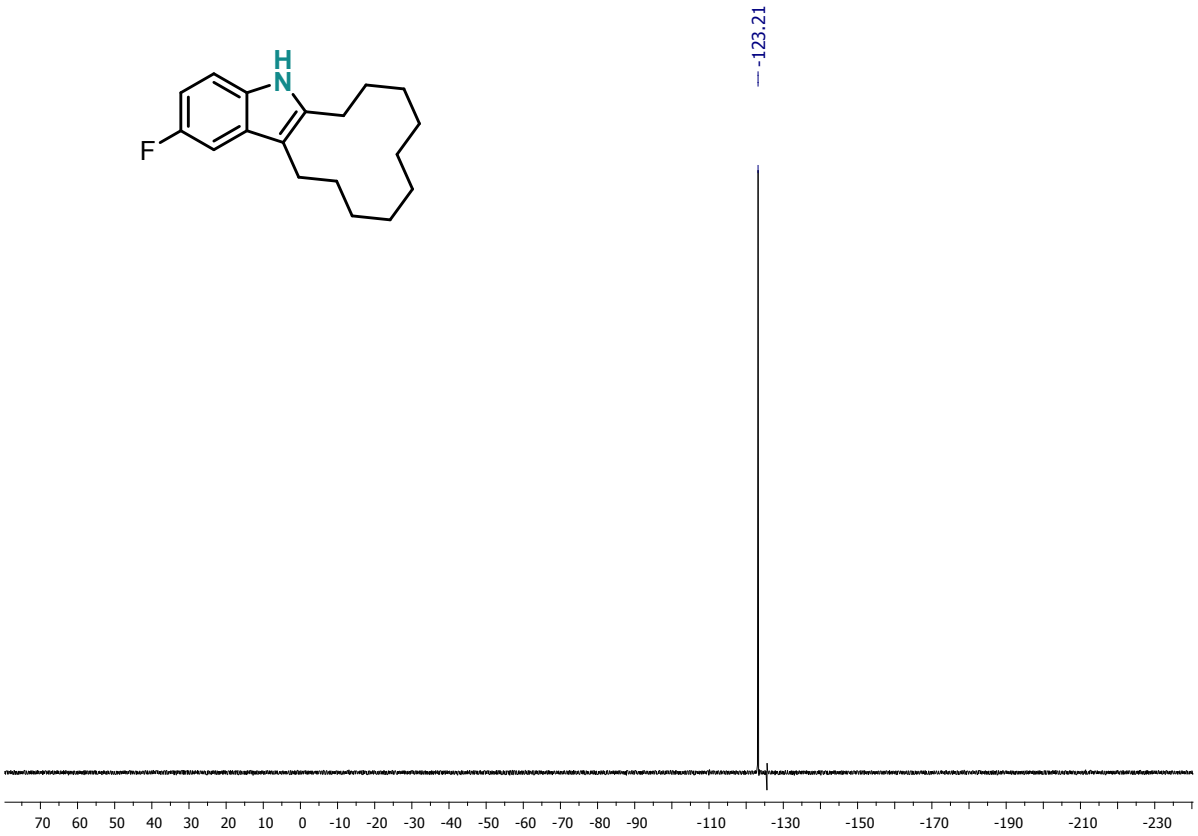



-125.19
H
N
F
80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -110 -130 -150 -170 -190 -210 -230

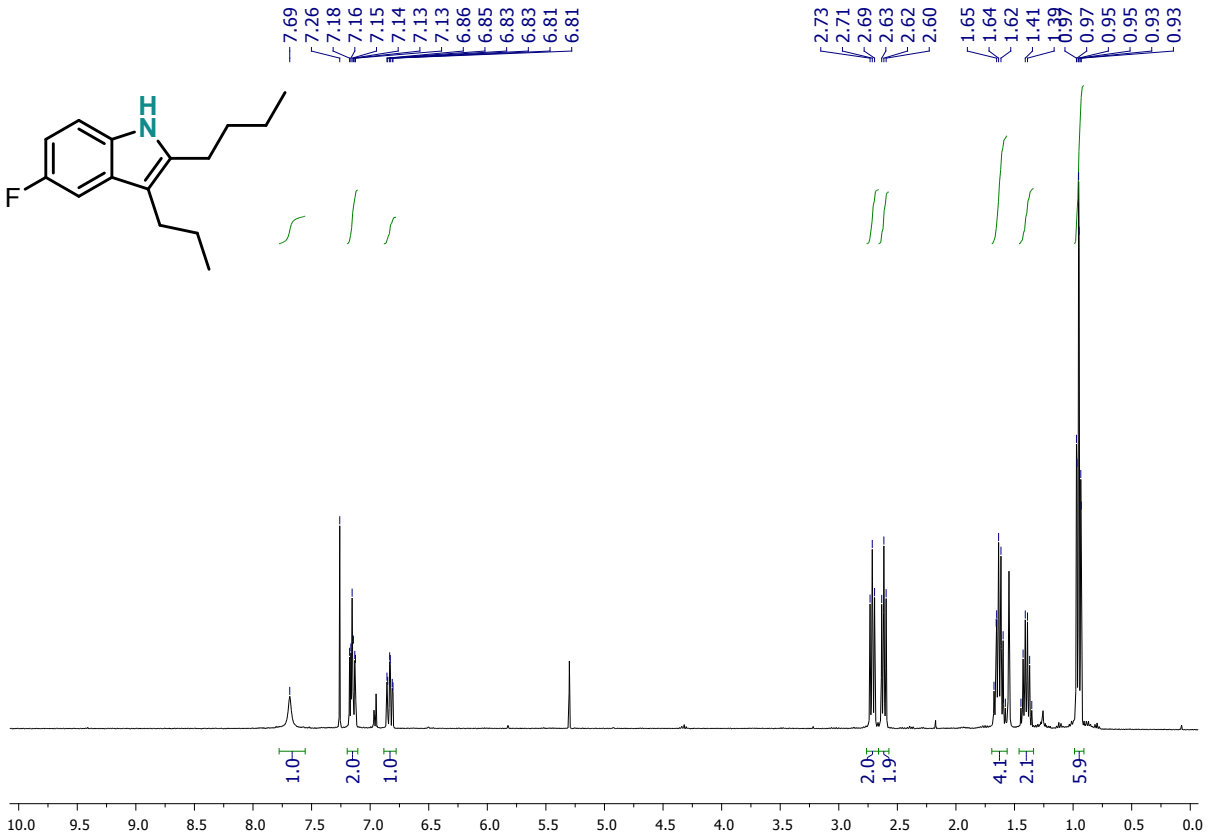
2-fluoro-6,7,8,9,10,11,12,13,14,15-decahydro-5H-cyclododeca[b]indole (17)

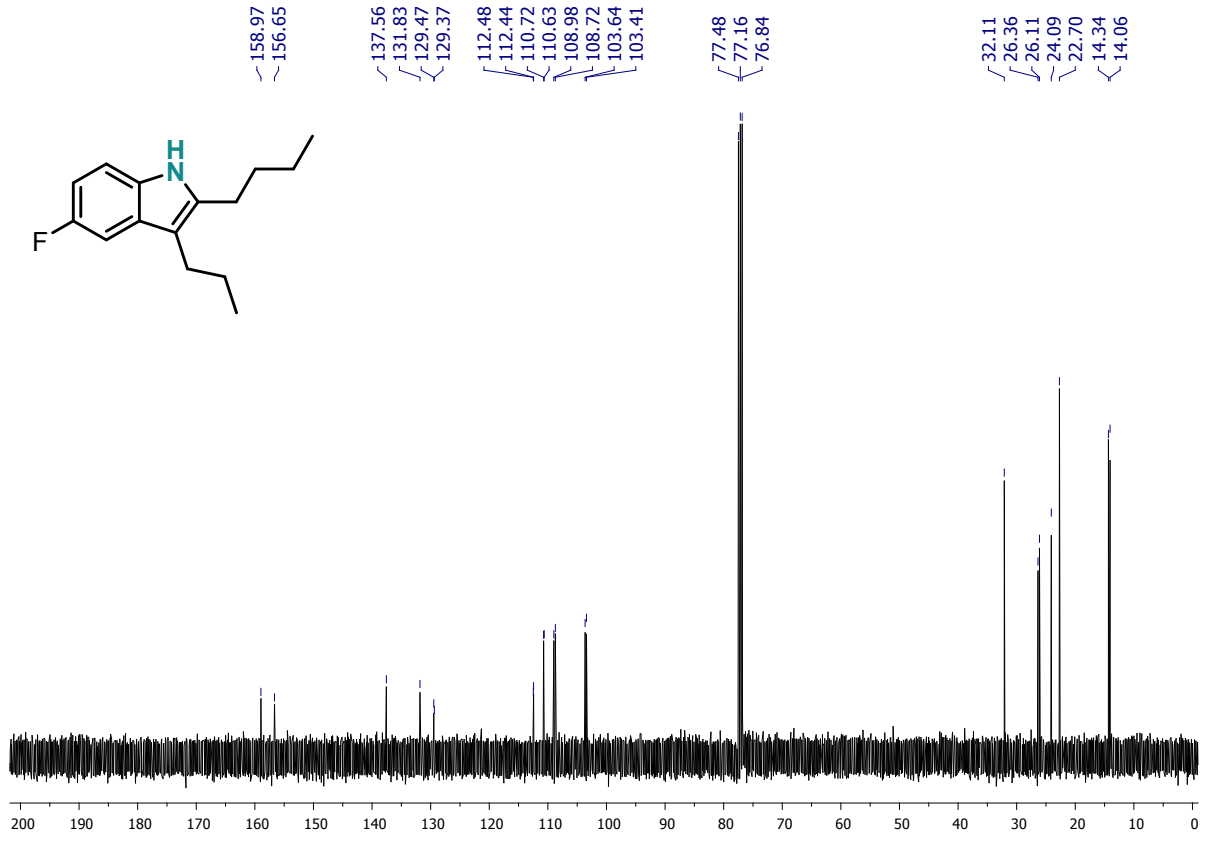


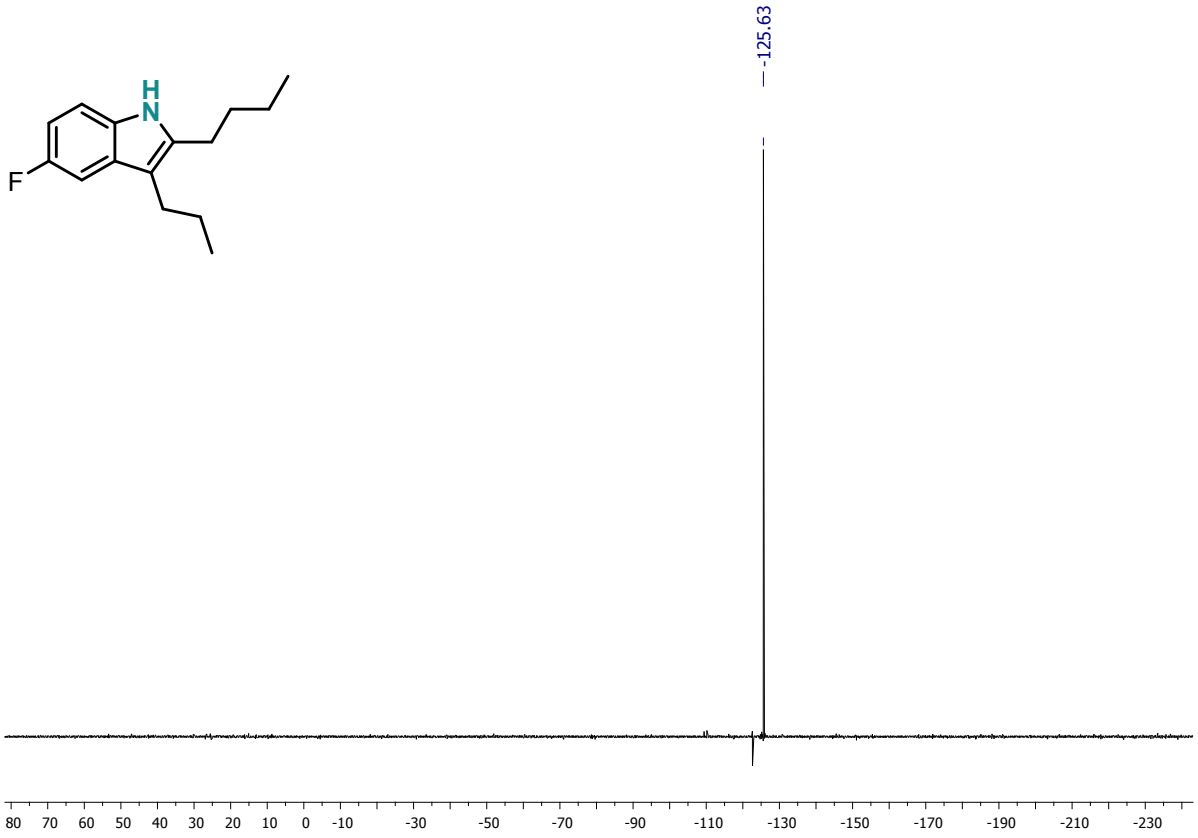



H
N
F
-123.21
70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -110 -130 -150 -170 -190 -210 -230

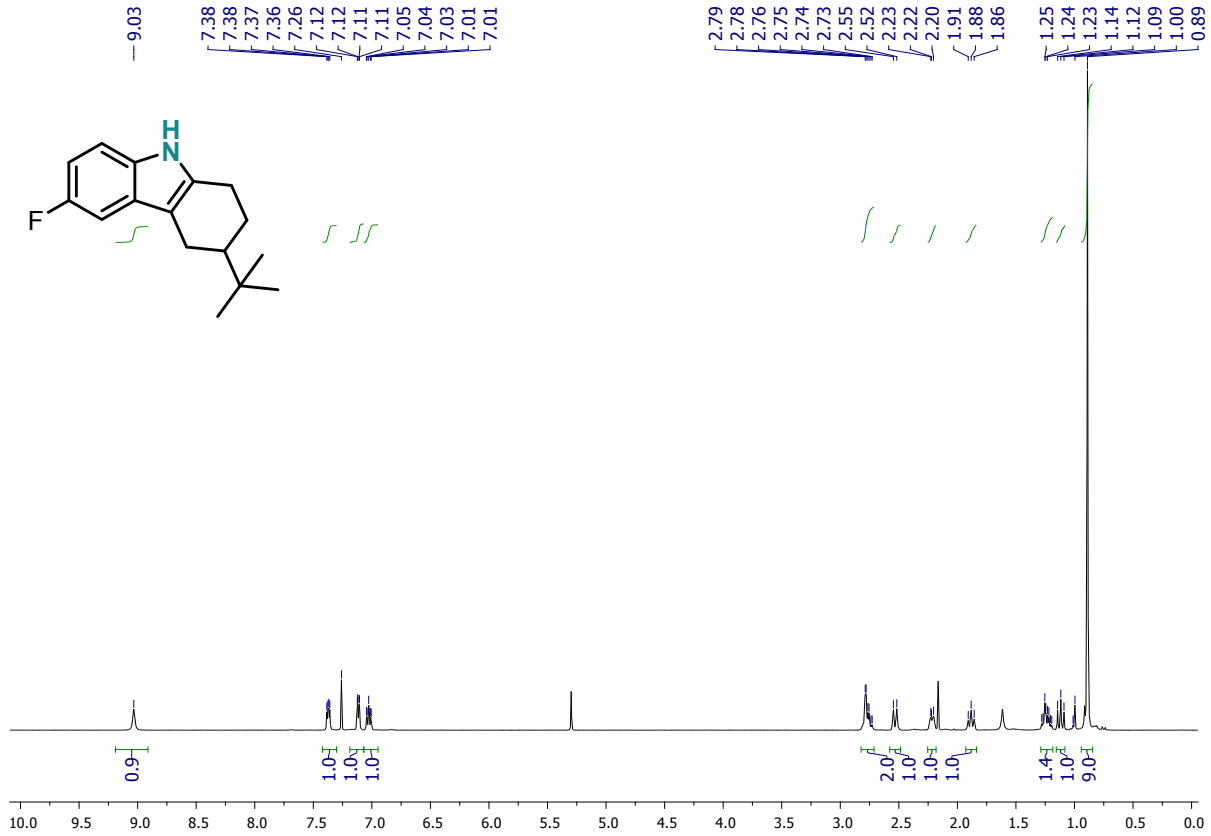
2-butyl-5-fluoro-3-propyl-1H-indole (18)

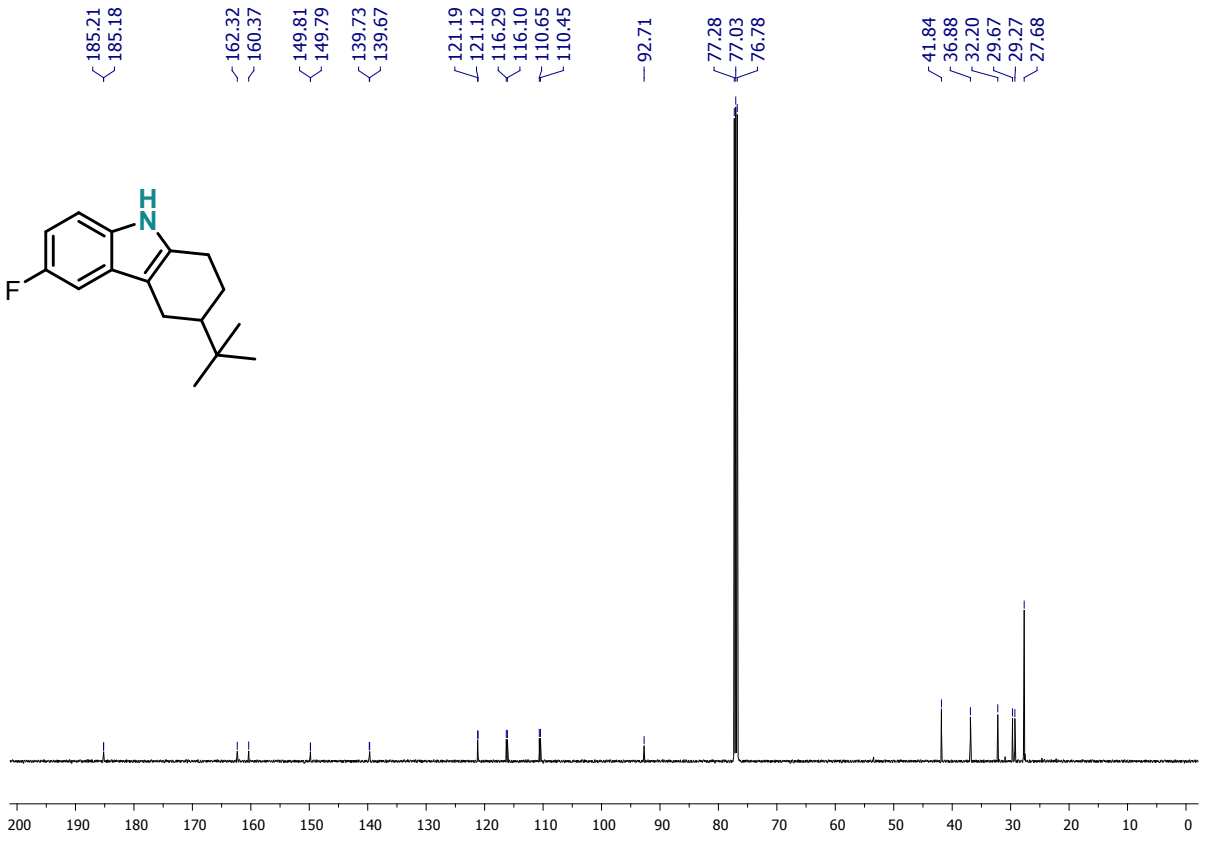


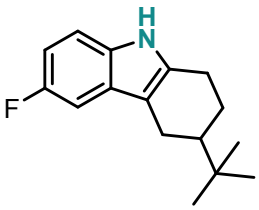



H
N
F
-125.63
80 70 60 50 40 30 20 10 0 -10 -30 -50 -70 -90 -110 -130 -150 -170 -190 -210 -230

3-(tert-butyl)-6-fluoro-2,3,4,9-tetrahydro-1H-carbazole (19)

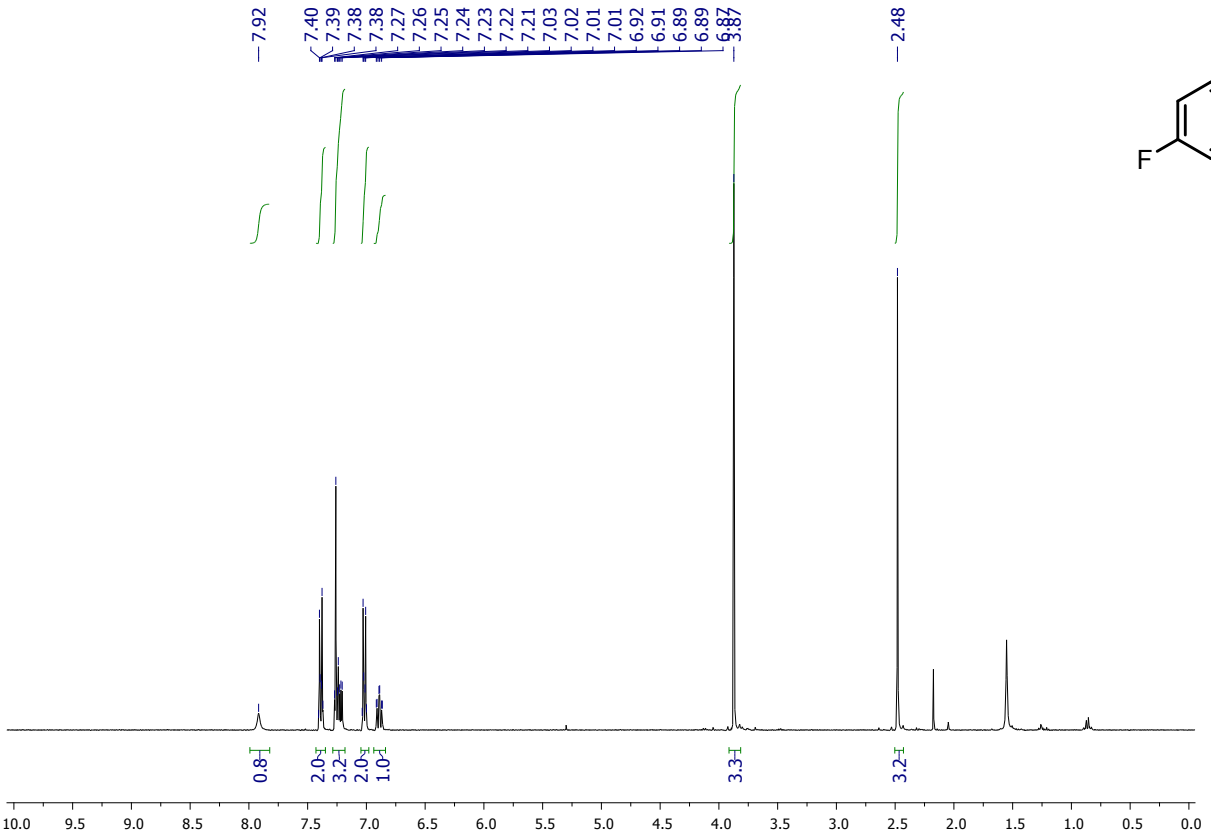


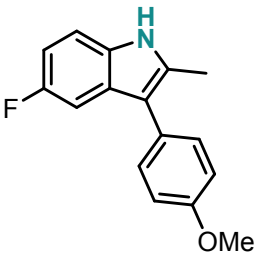


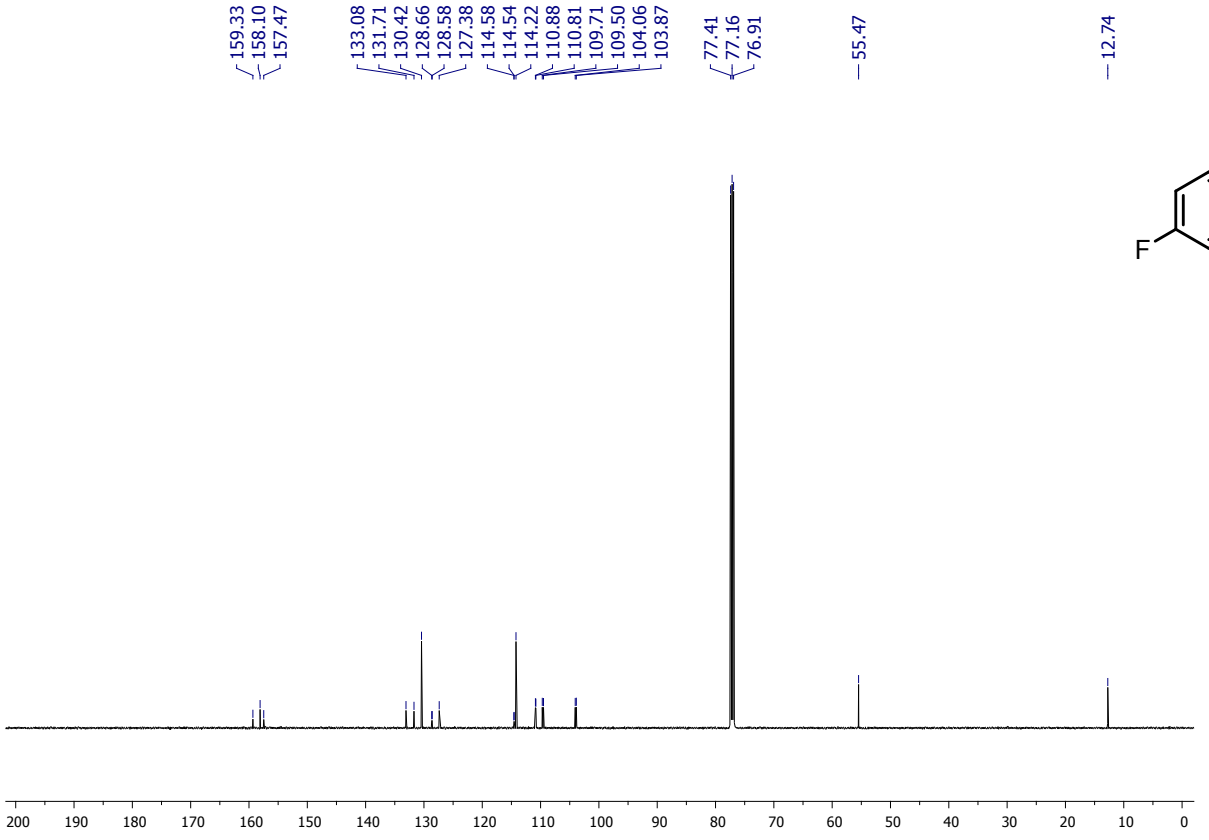

H
N
F

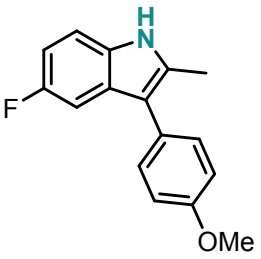
-116.56
80 70 60 50 40 30 20 10 0 -10 -30 -50 -70 -90 -110 -130 -150 -170 -190 -210 -230

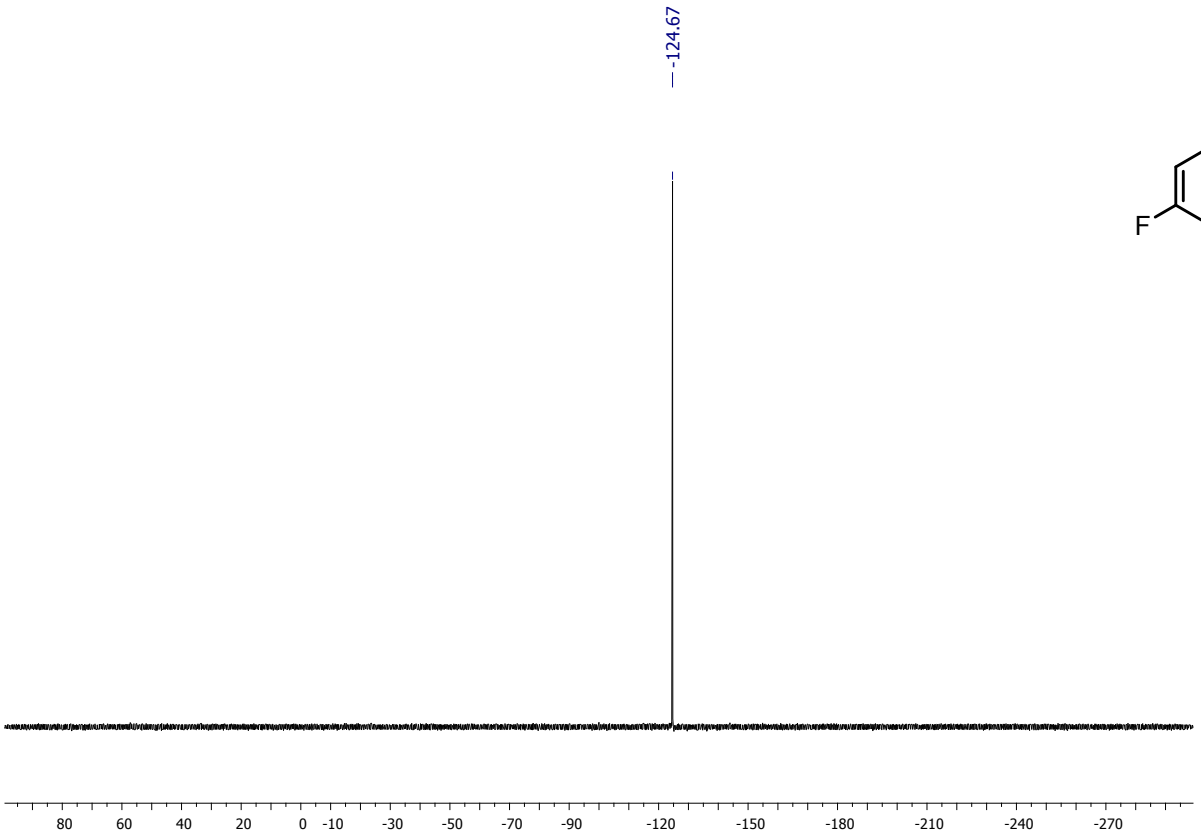
5-fluoro-3-(4-methoxyphenyl)-2-methyl-1H-indole (20)



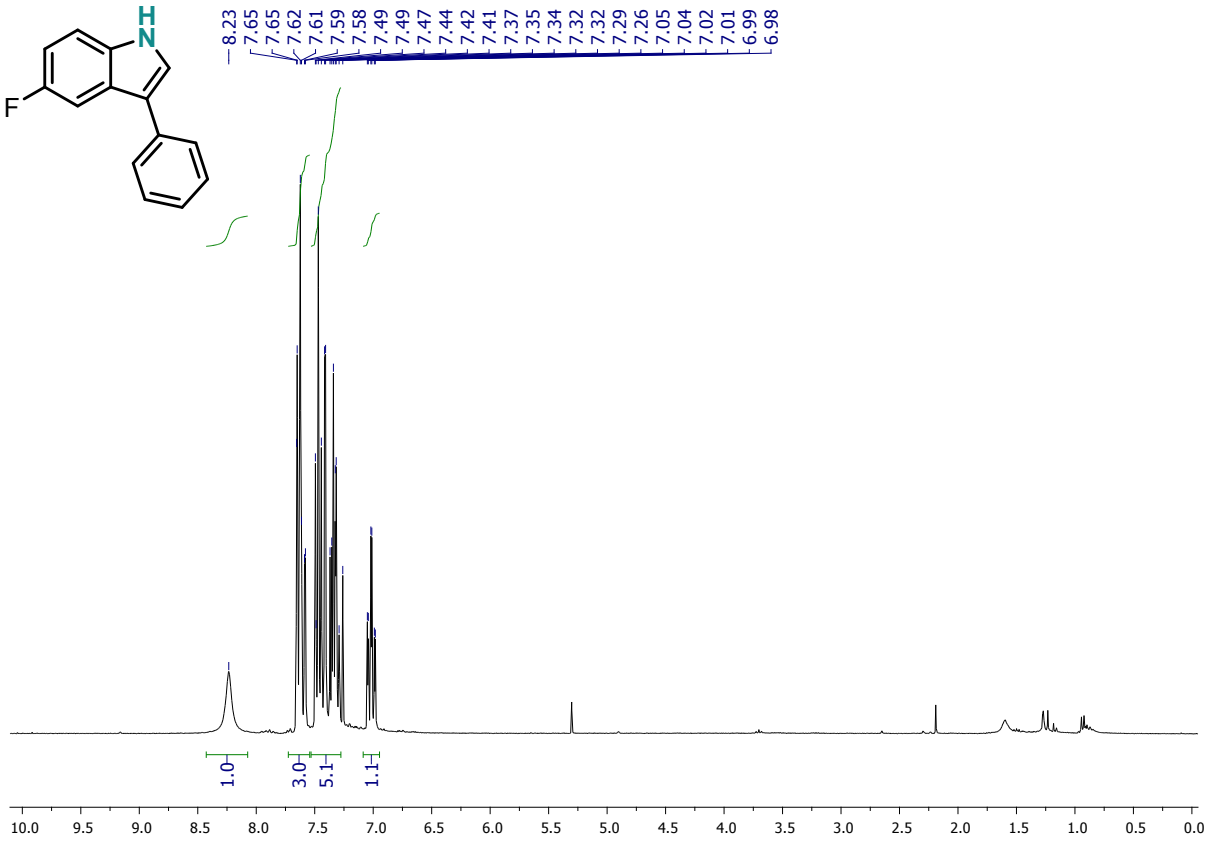


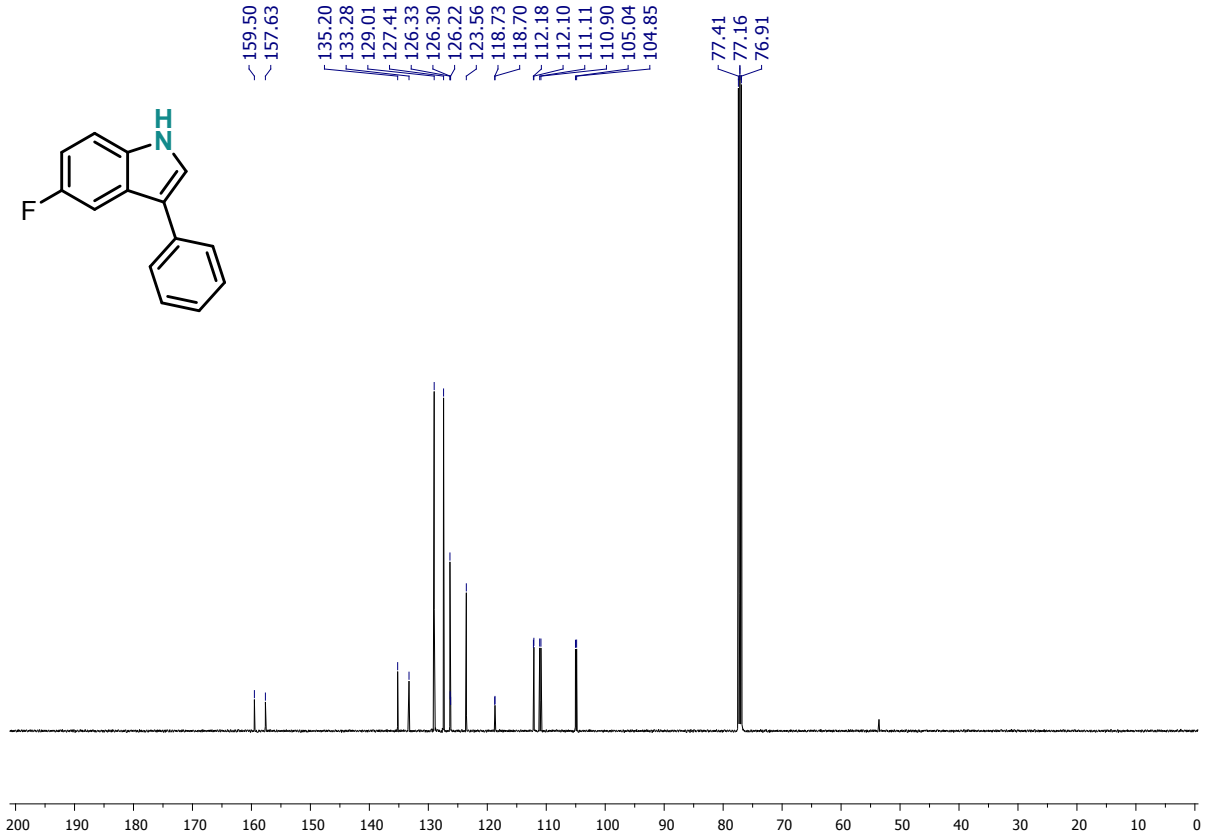


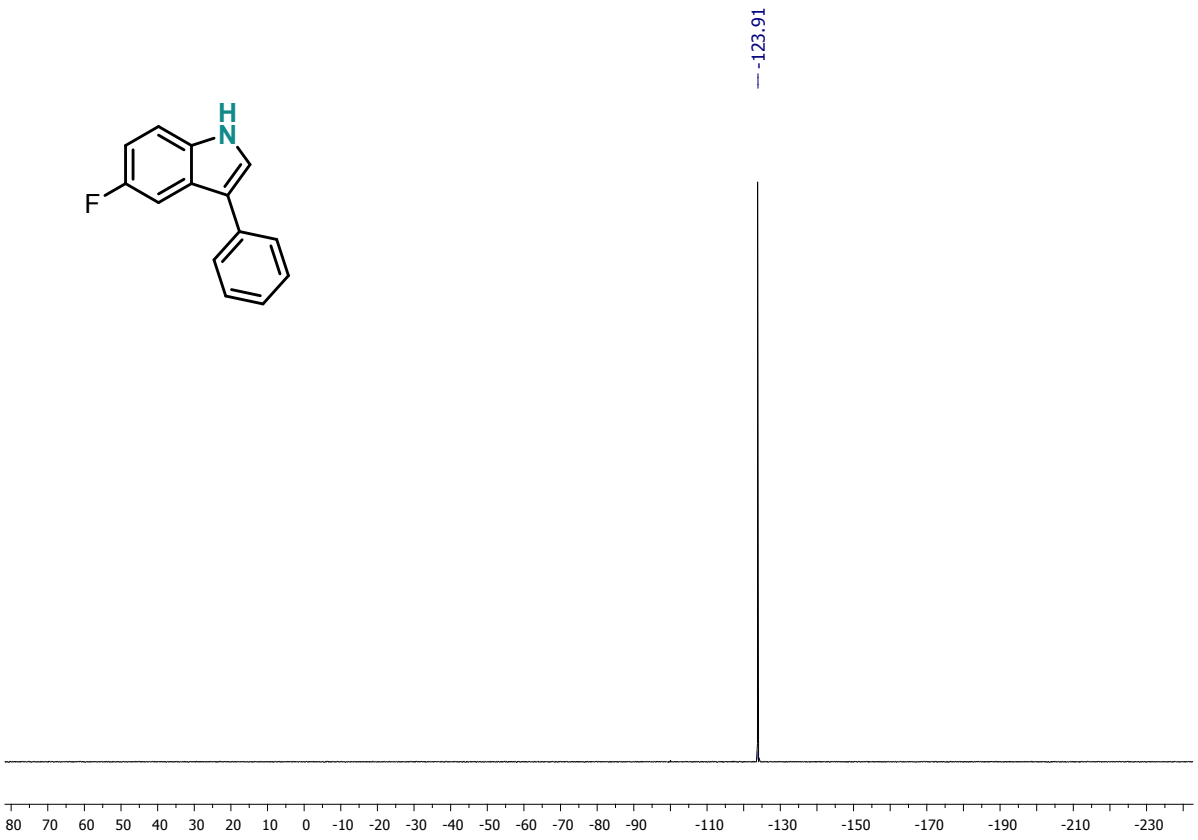



-124.67
H
N
F
OMe
80
60
40
20
0
-10
-30
-50
-70
-90
-120
-150
-180
-210
-240
-270

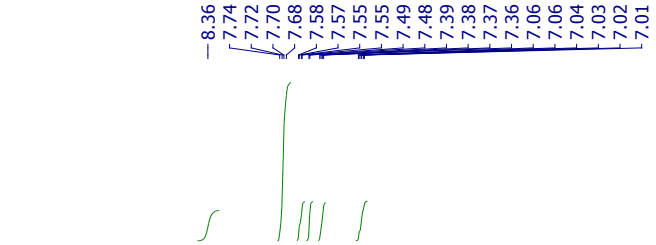
5-fluoro-3-phenyl-1H-indole (21)

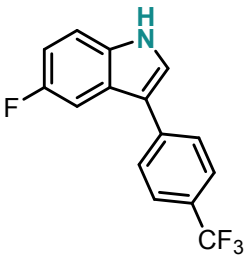


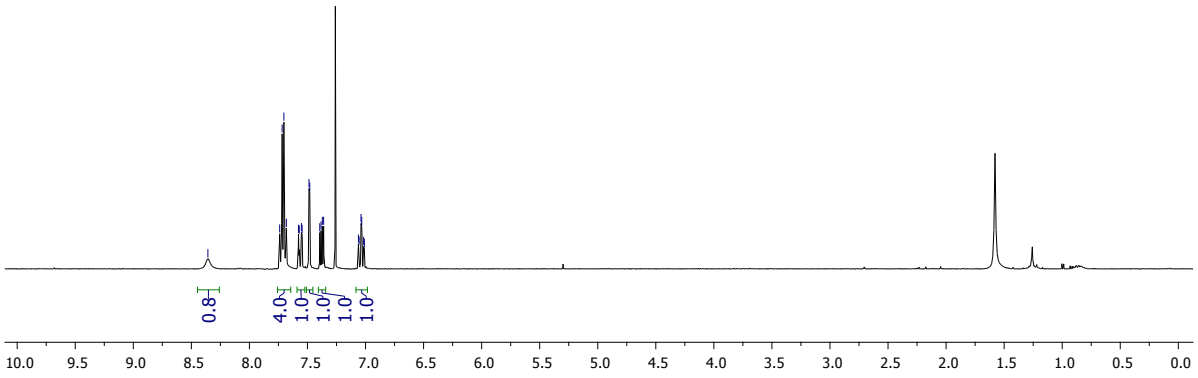


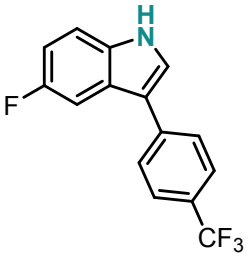

-123.91
H
N
F
80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -110 -130 -150 -170 -190 -210 -230

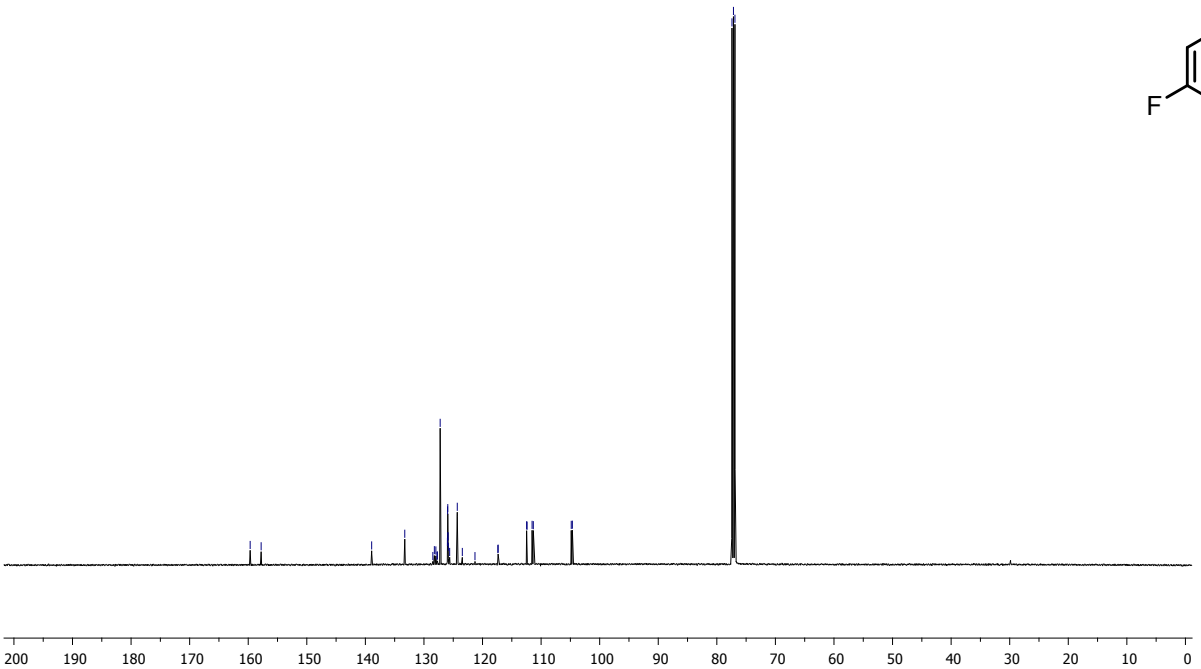
5-fluoro-3-(4-(trifluoromethyl)phenyl)-1H-indole (22)

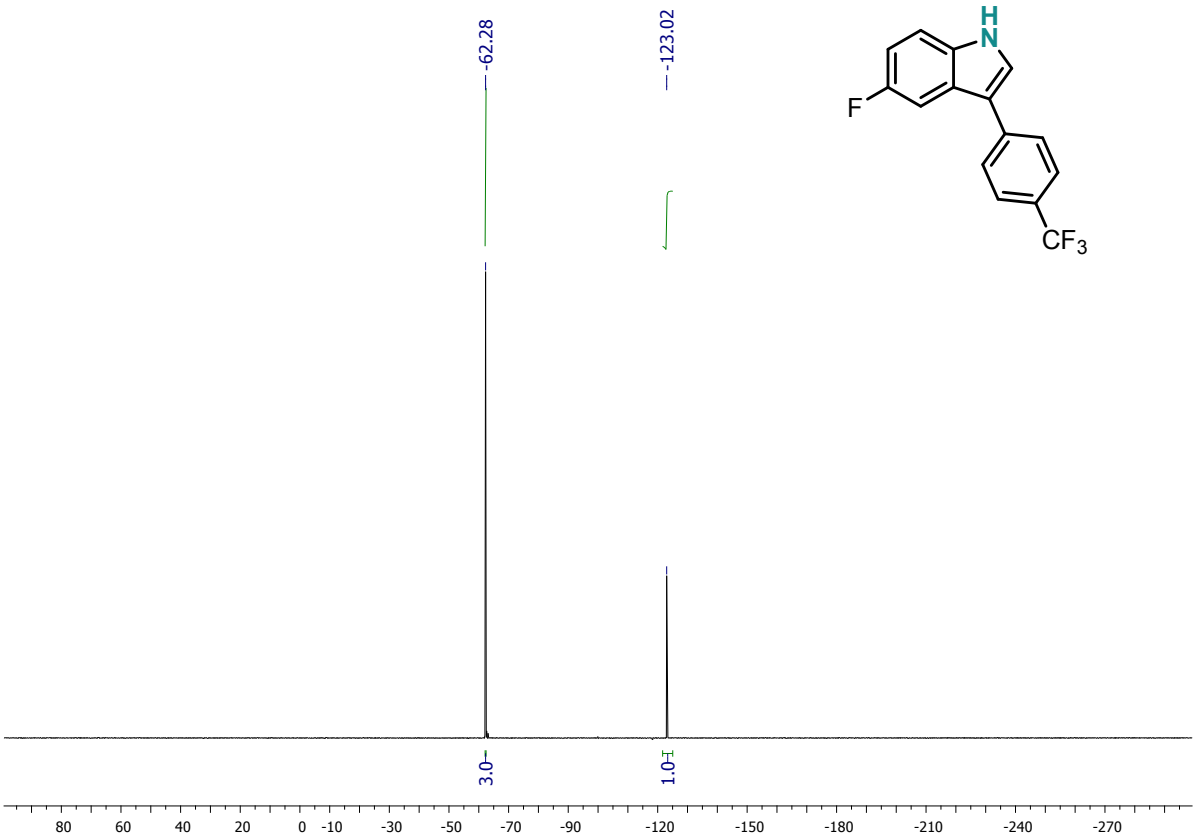








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H
N
F
CF3
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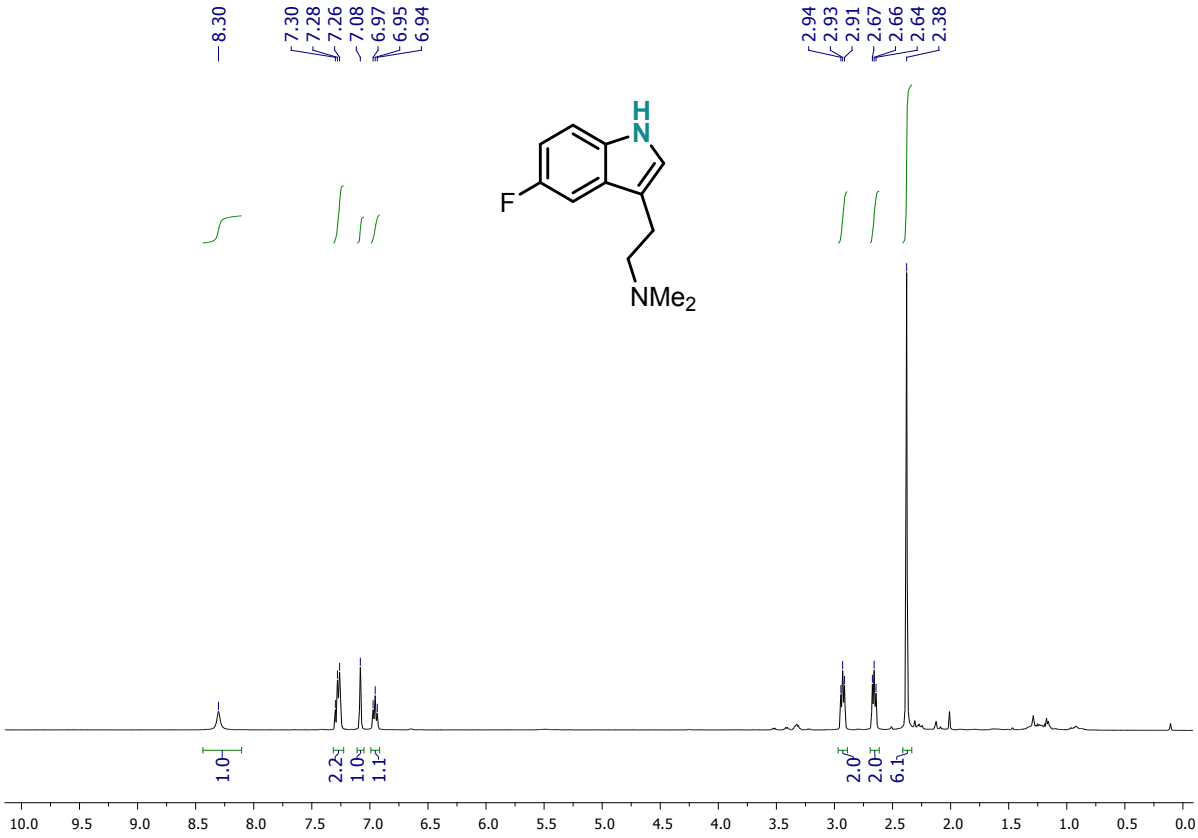
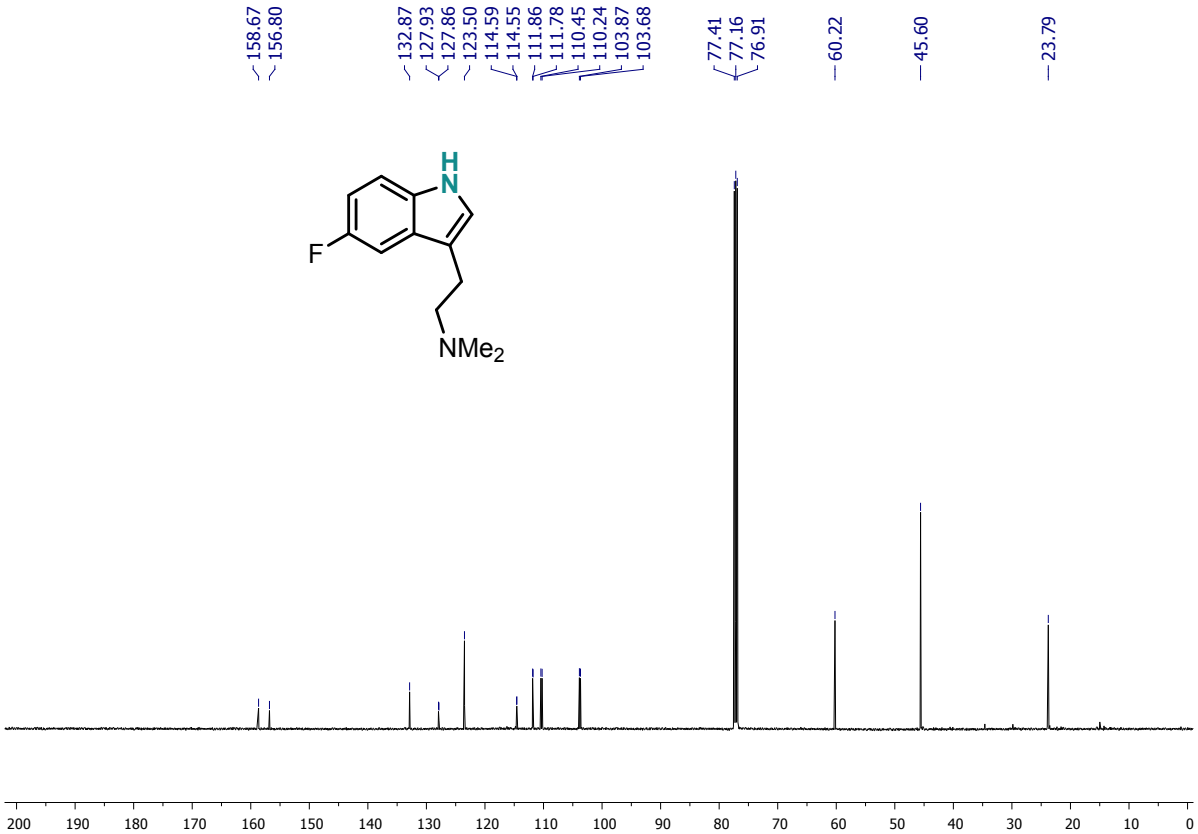
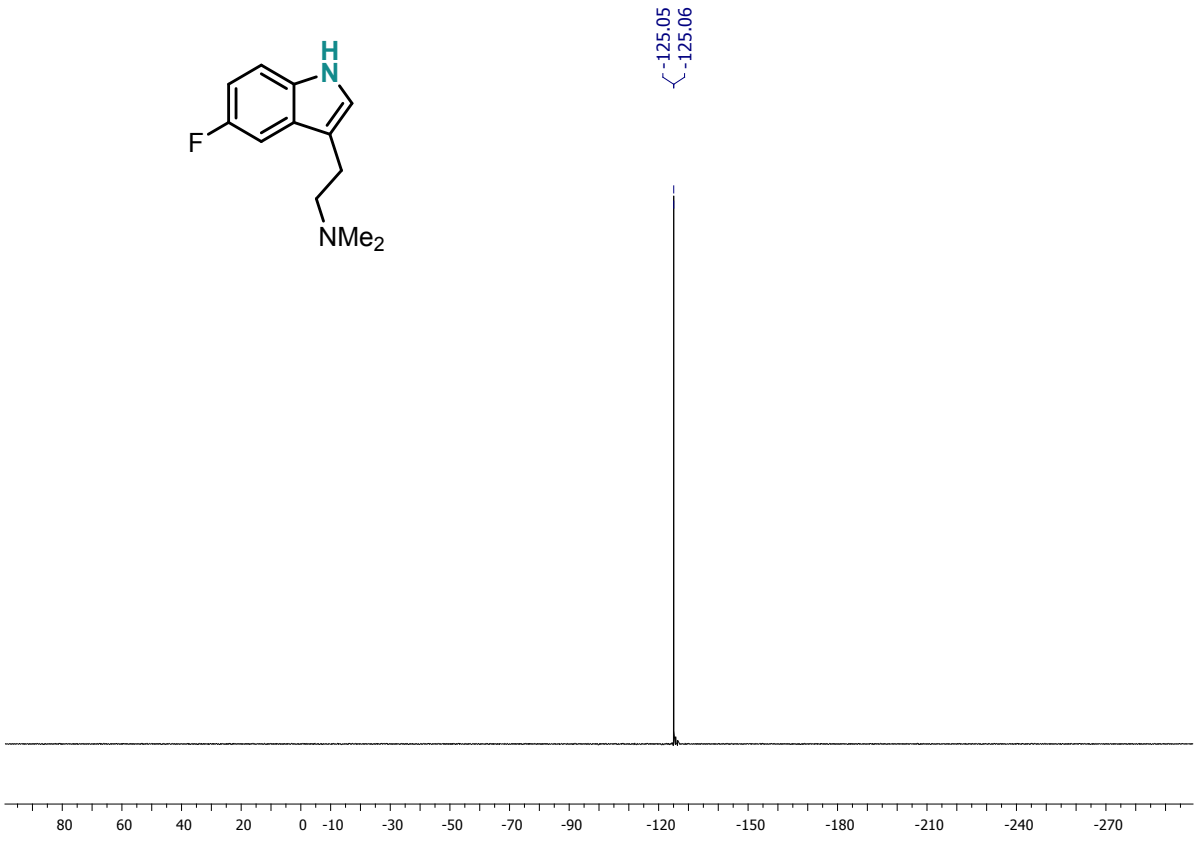
1.0
80
60
40
20
0
-10
-30
-50
-70
-90
-120
-150
-180
-210
-240
-270

2-(5-fluoro-1H-indol-3-yl)-N,N-dimethylethan-1-amine (23)

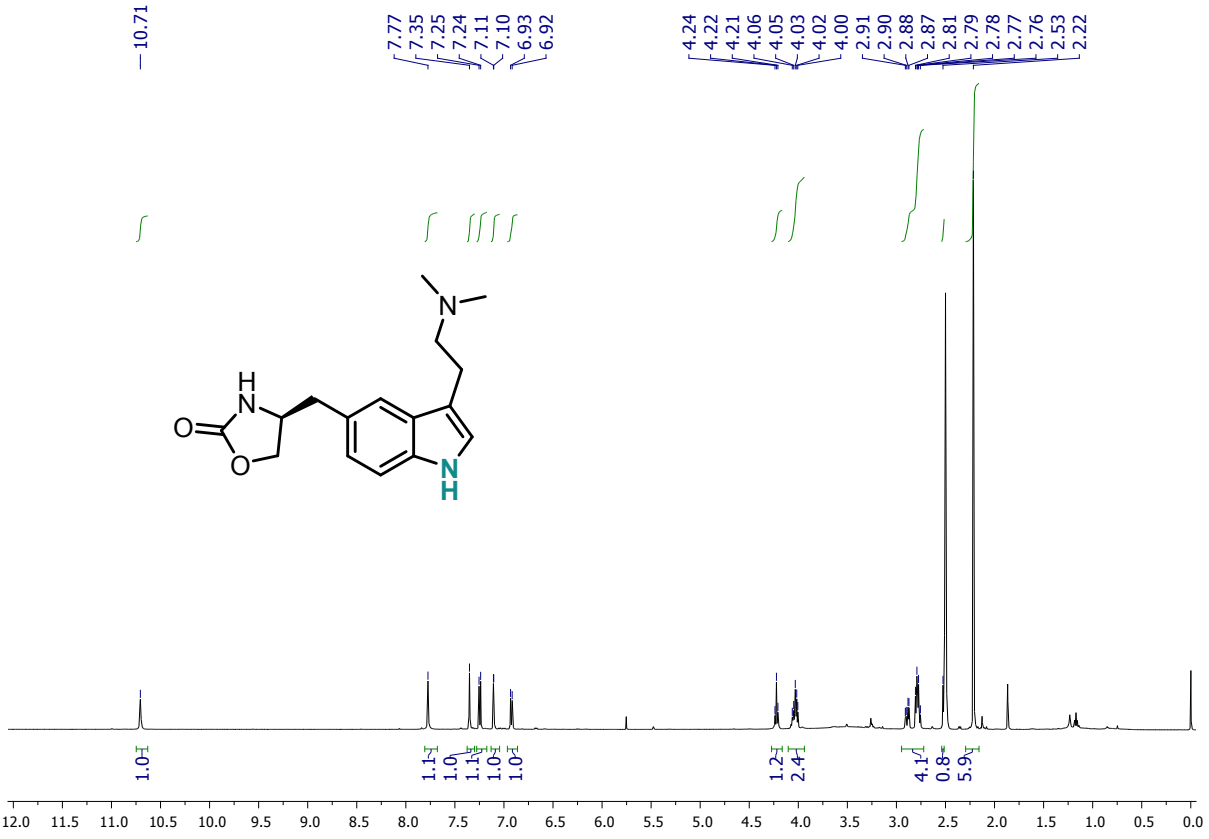


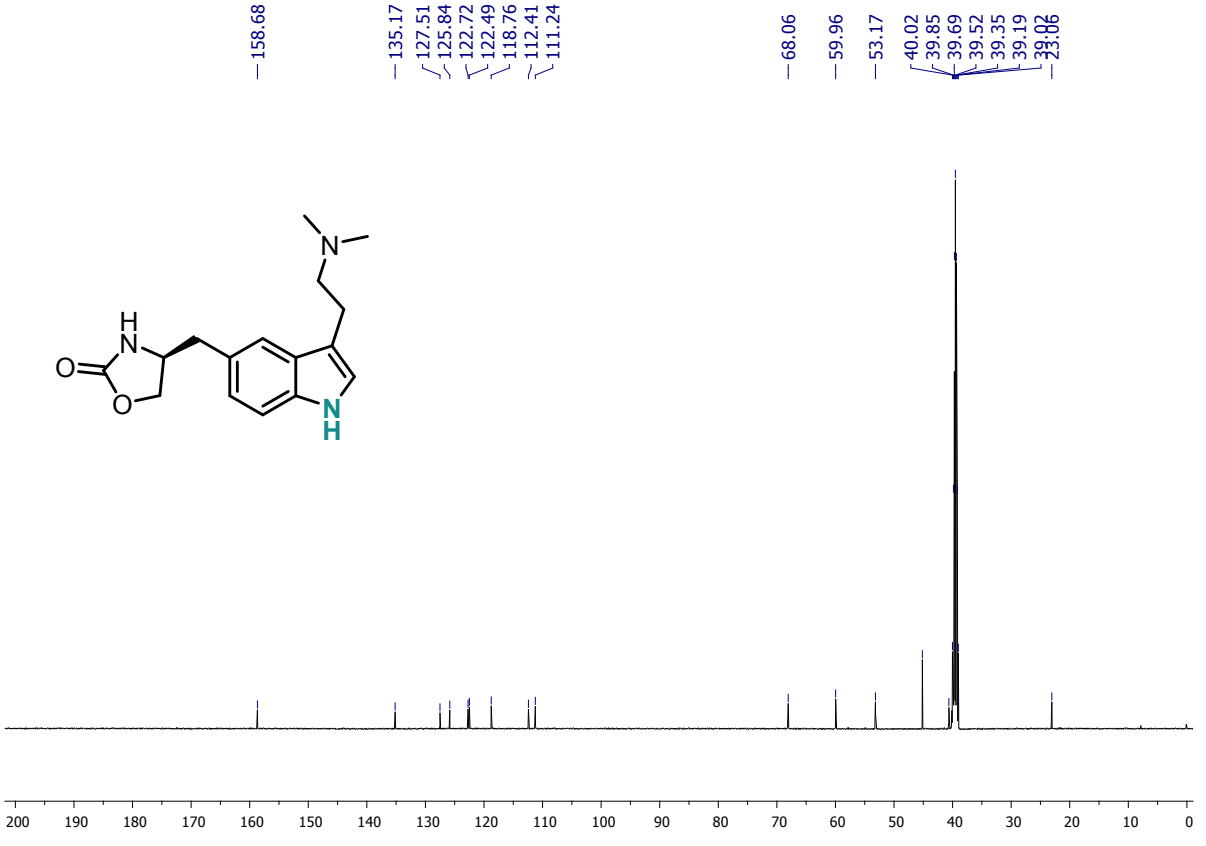



H
N
F
NMe2
-125.05
-125.06
80
60
40
20
0
-10
-30
-50
-70
-90
-120
-150
-180
-210
-240
-270

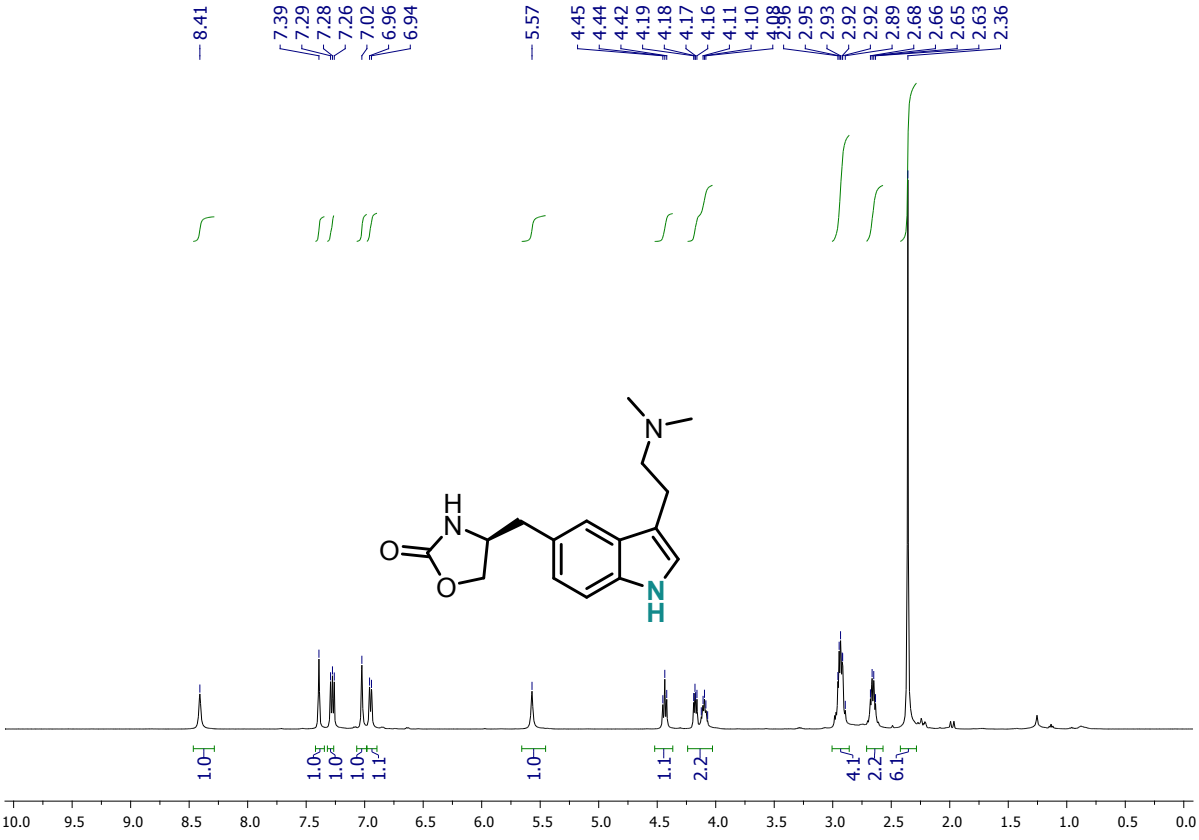
(*S*)-4-((3-(2-(dimethylamino)ethyl)-1H-indol-5-yl)methyl)oxazolidin-2-one, Zolmitriptan (24)

in DMSO-d^6





in $CDCl_3$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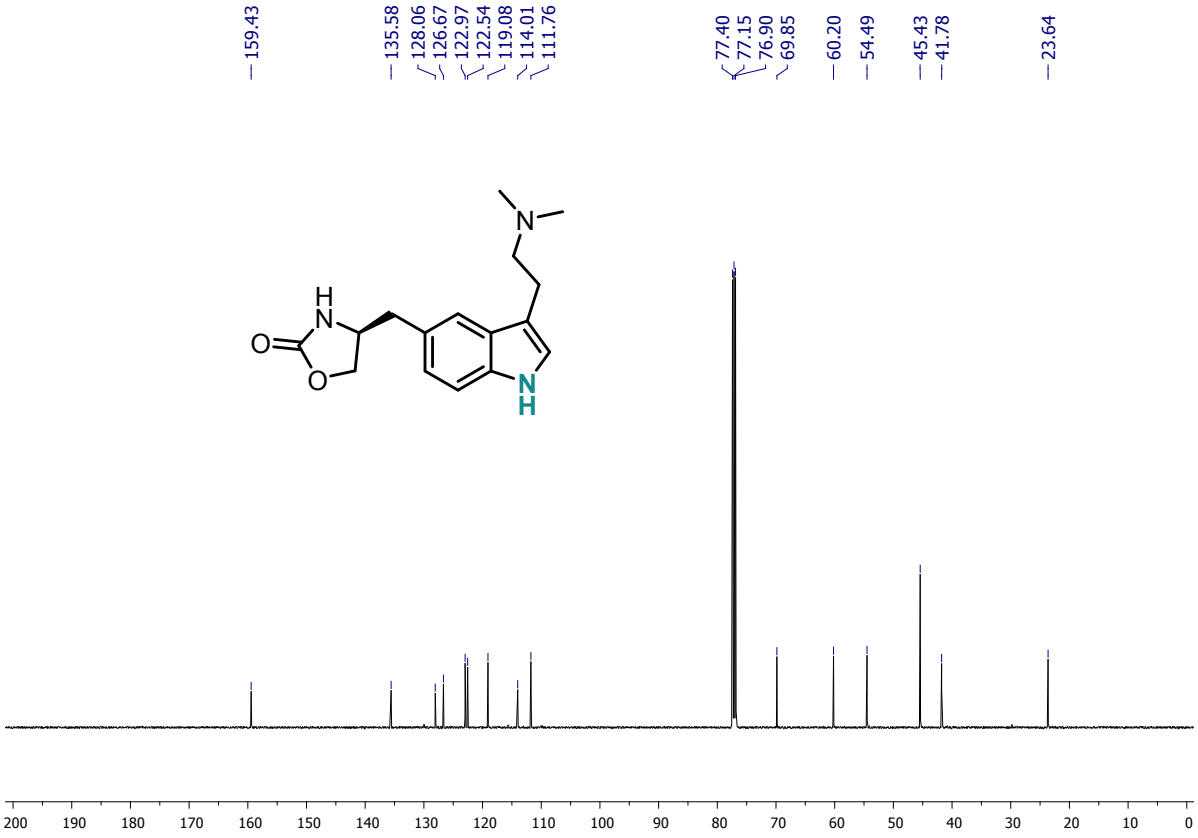
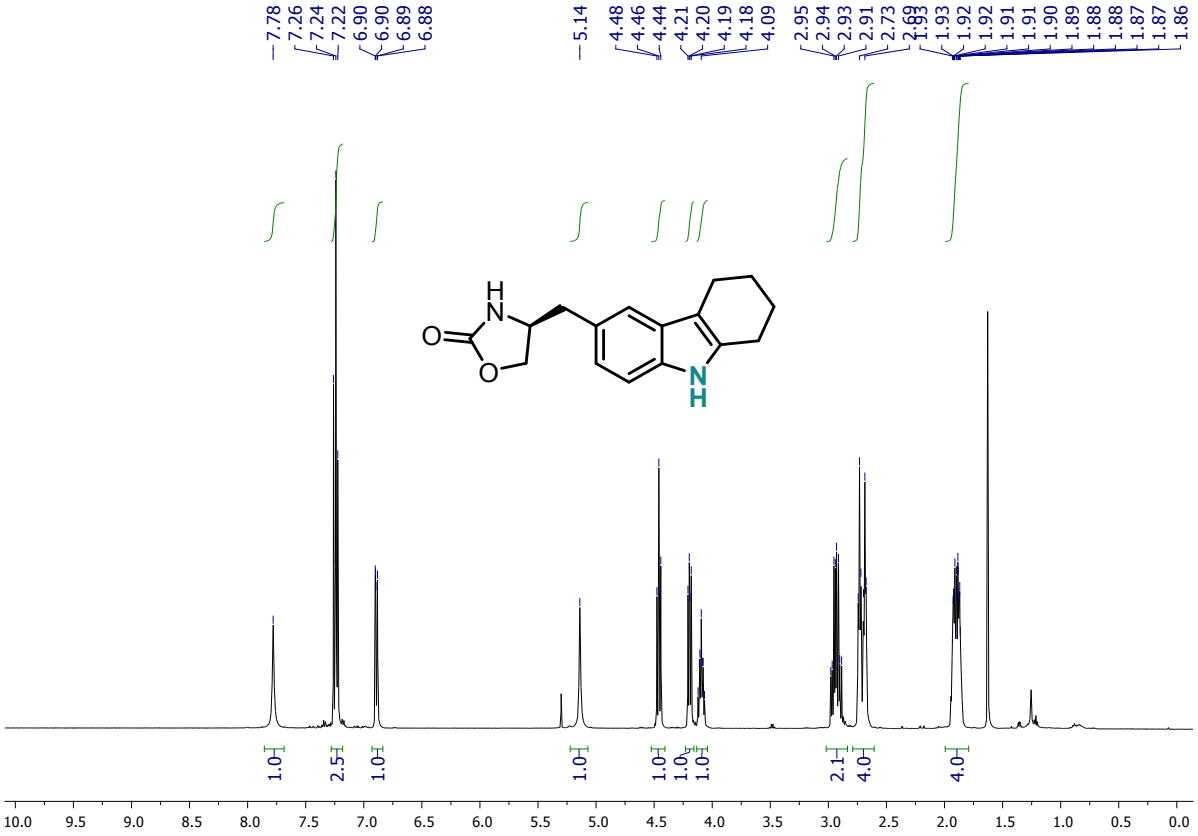
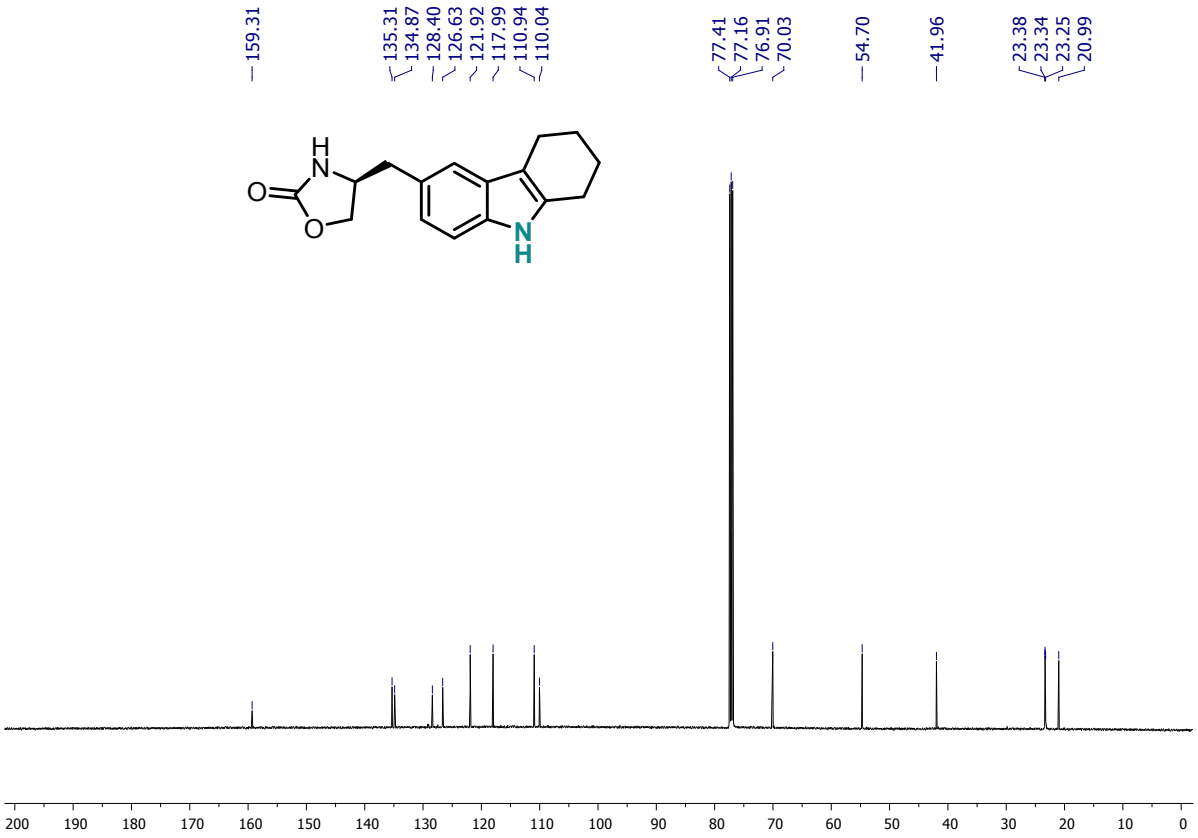
7.39
7.29
7.28
7.26
7.02
6.96
6.94
5.57
4.45
4.44
4.42
4.19
4.18
4.17
4.16
4.11
4.10
2.95
2.93
2.92
2.92
2.89
2.68
2.66
2.65
2.63
2.36
1.0
1.0
1.0
1.0
1.1
1.0
1.1
2.2
4.1
2.2
6.1
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

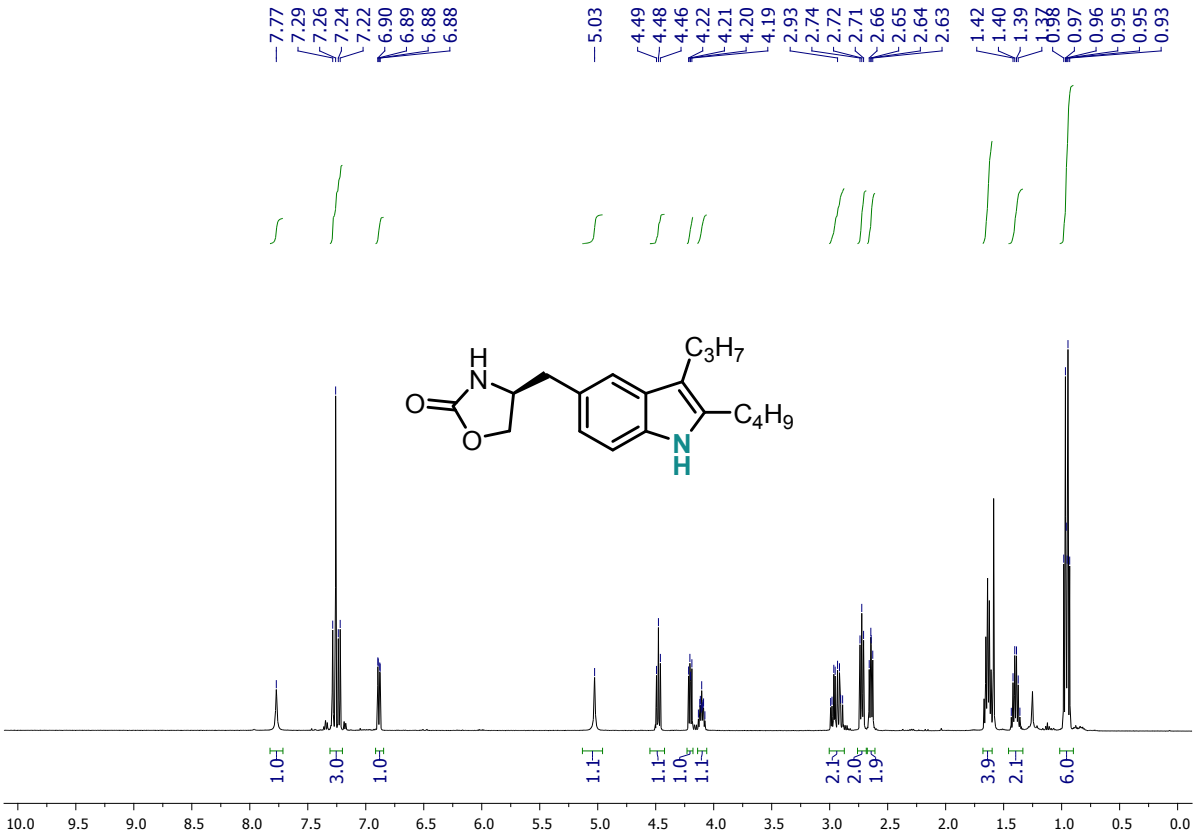

159.43
135.58
128.06
126.67
122.97
122.54
119.08
114.01
111.76
77.40
77.15
76.90
69.85
60.20
54.49
45.43
41.78
23.64
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

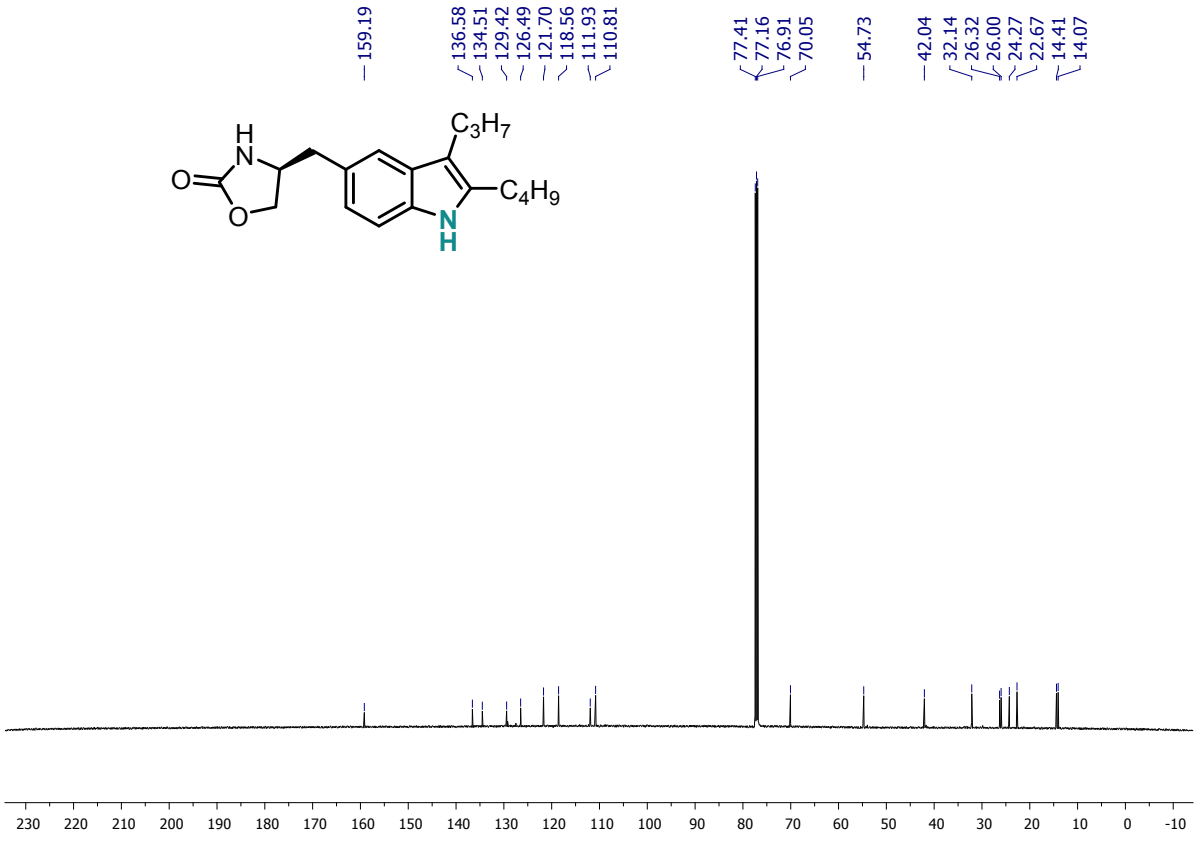
(S)-4-((2,3,4,9-tetrahydro-1H-carbazol-6-yl)methyl)oxazolidin-2-one (25)



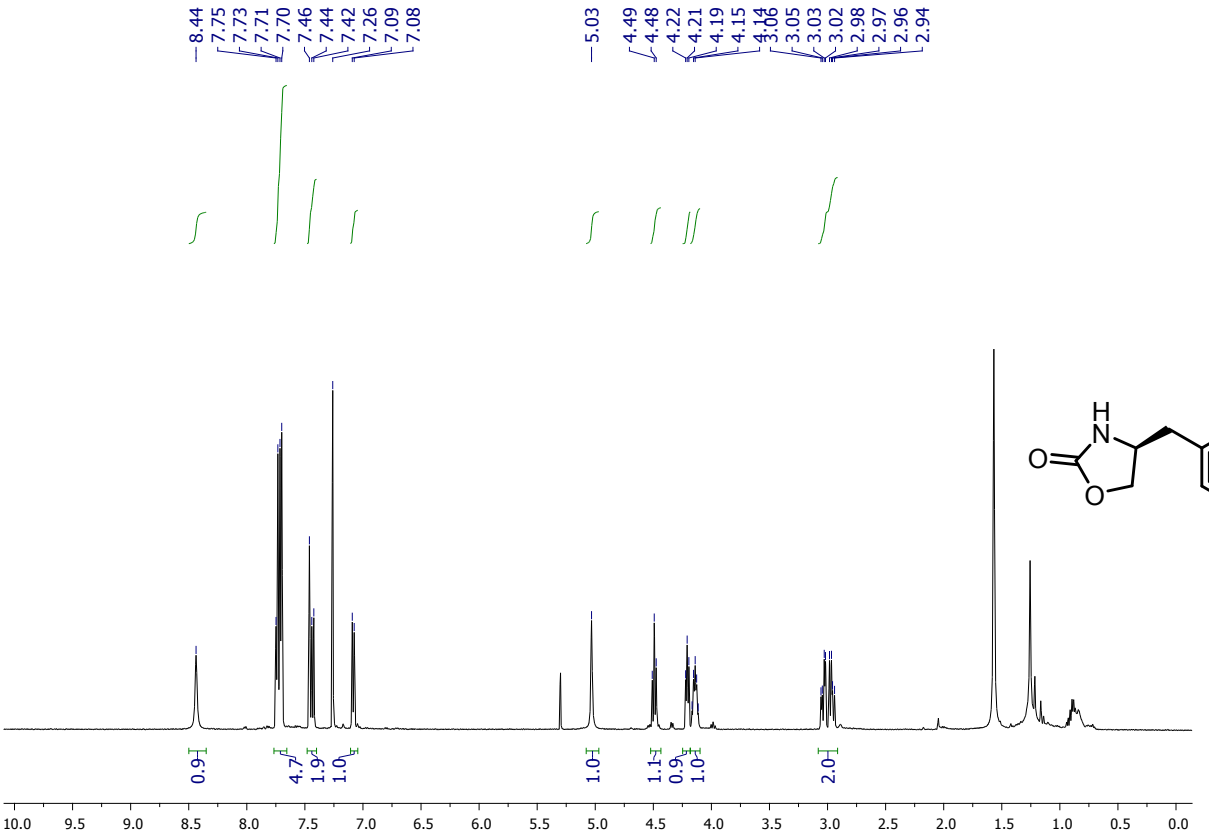


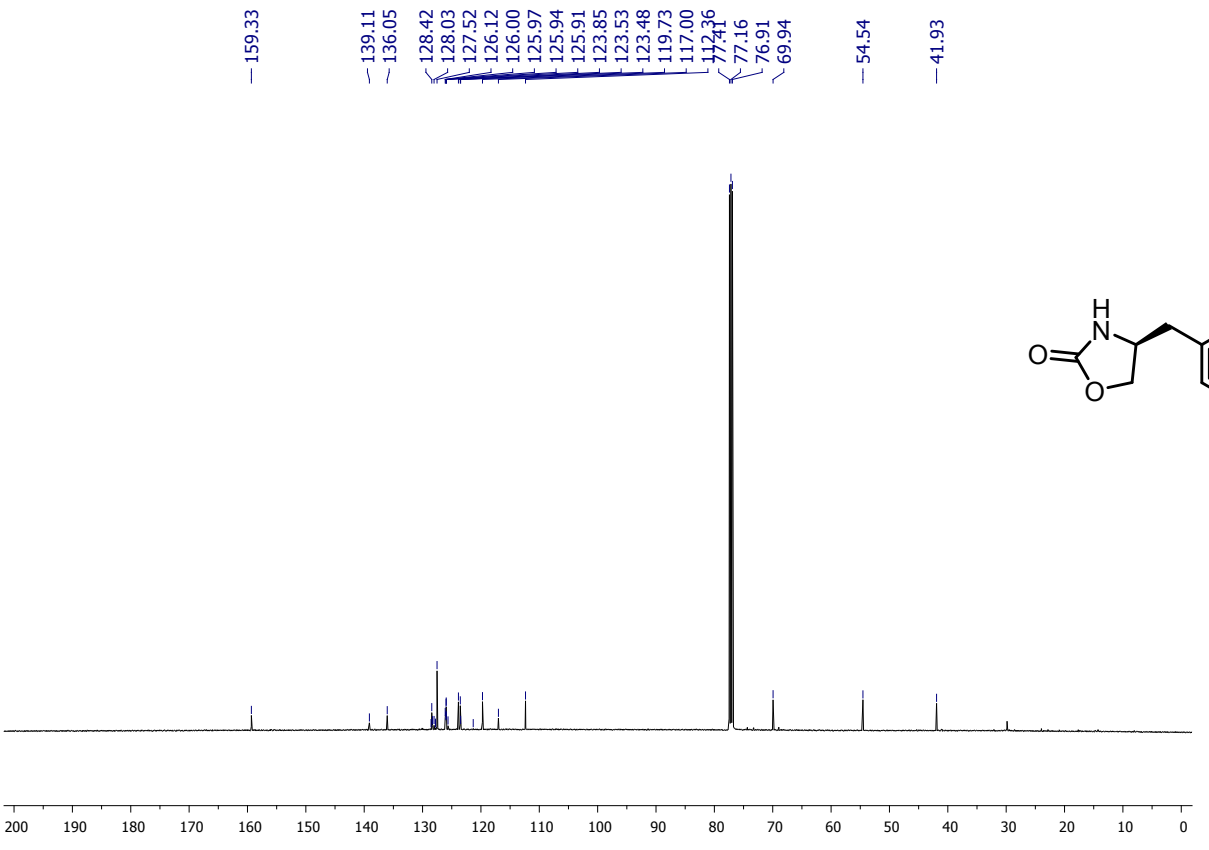
(S)-4-((2-butyl-3-propyl-1H-indol-5-yl)methyl)oxazolidin-2-one (26)



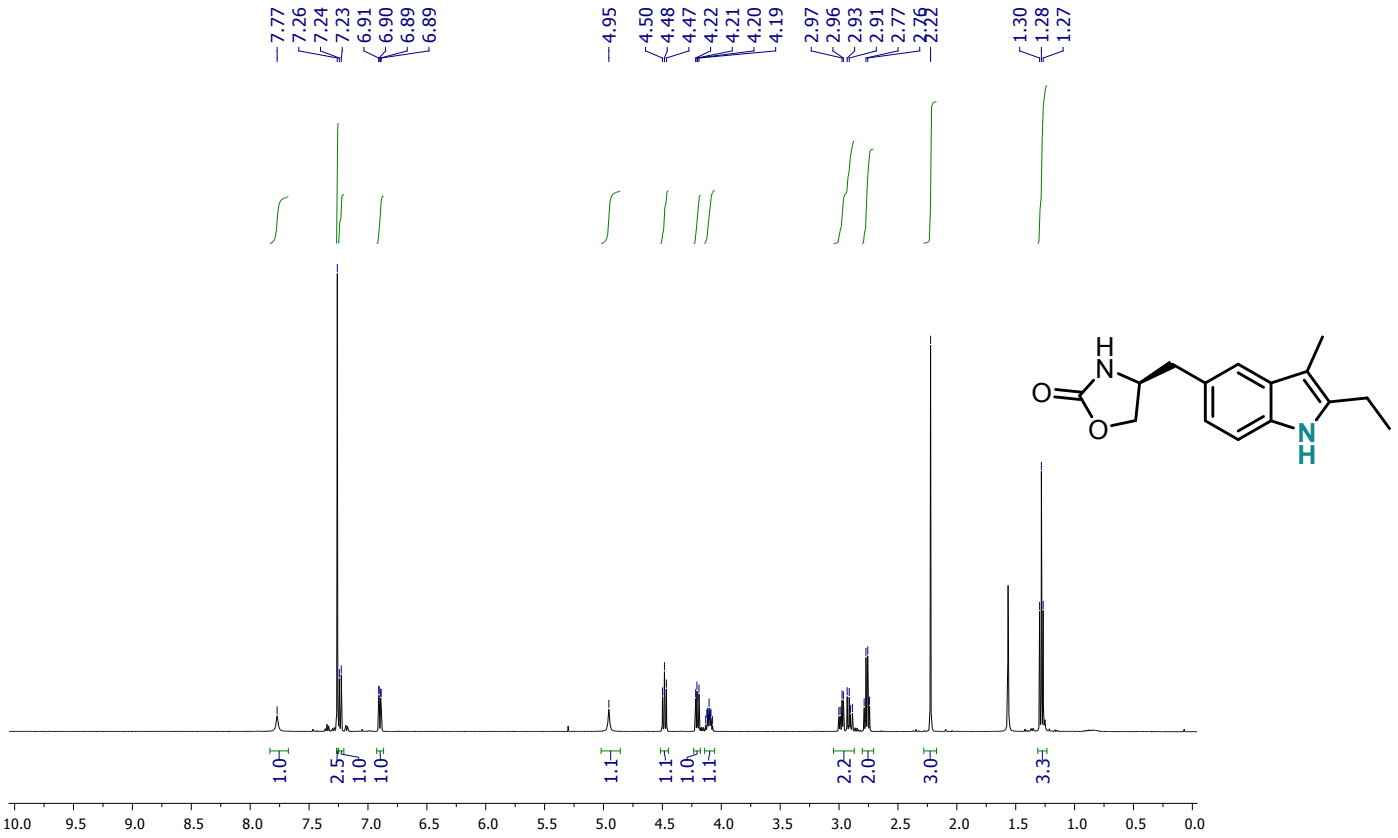


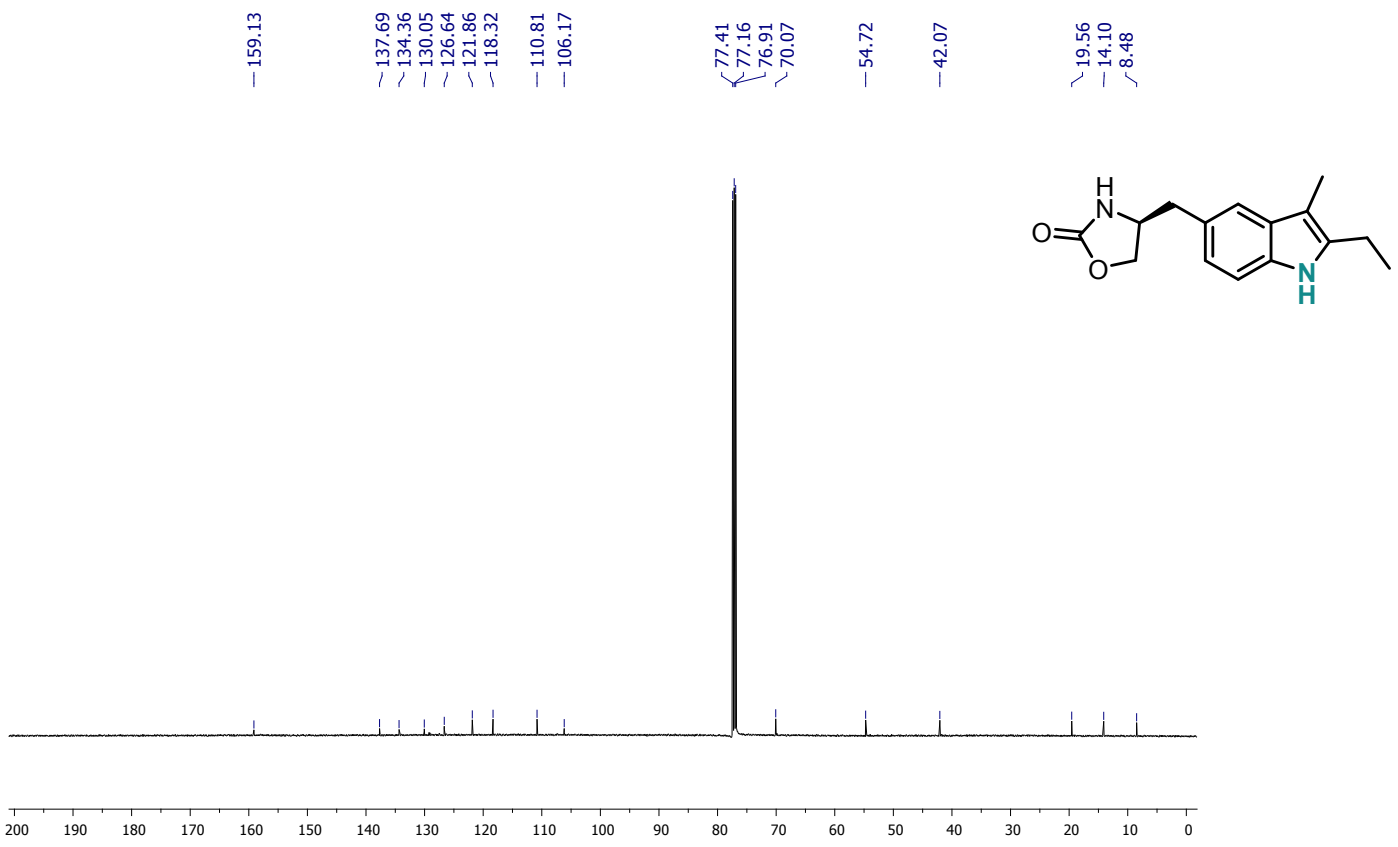
(S)-4-((3-(4-(trifluoromethyl)phenyl)-1H-indol-5-yl)methyl)oxazolidin-2-one (27)



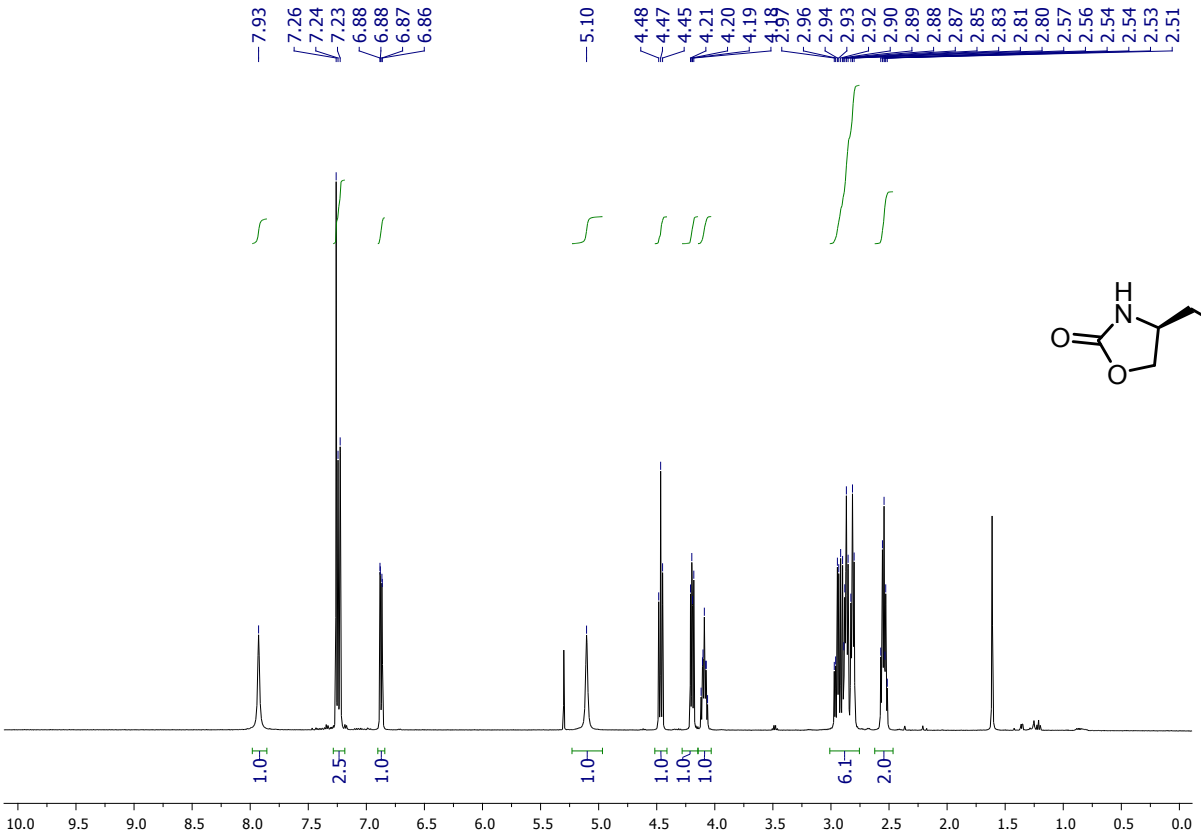


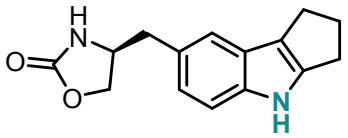
(S)-4-((2-ethyl-3-methyl-1H-indol-5-yl)methyl)oxazolidin-2-one (28)

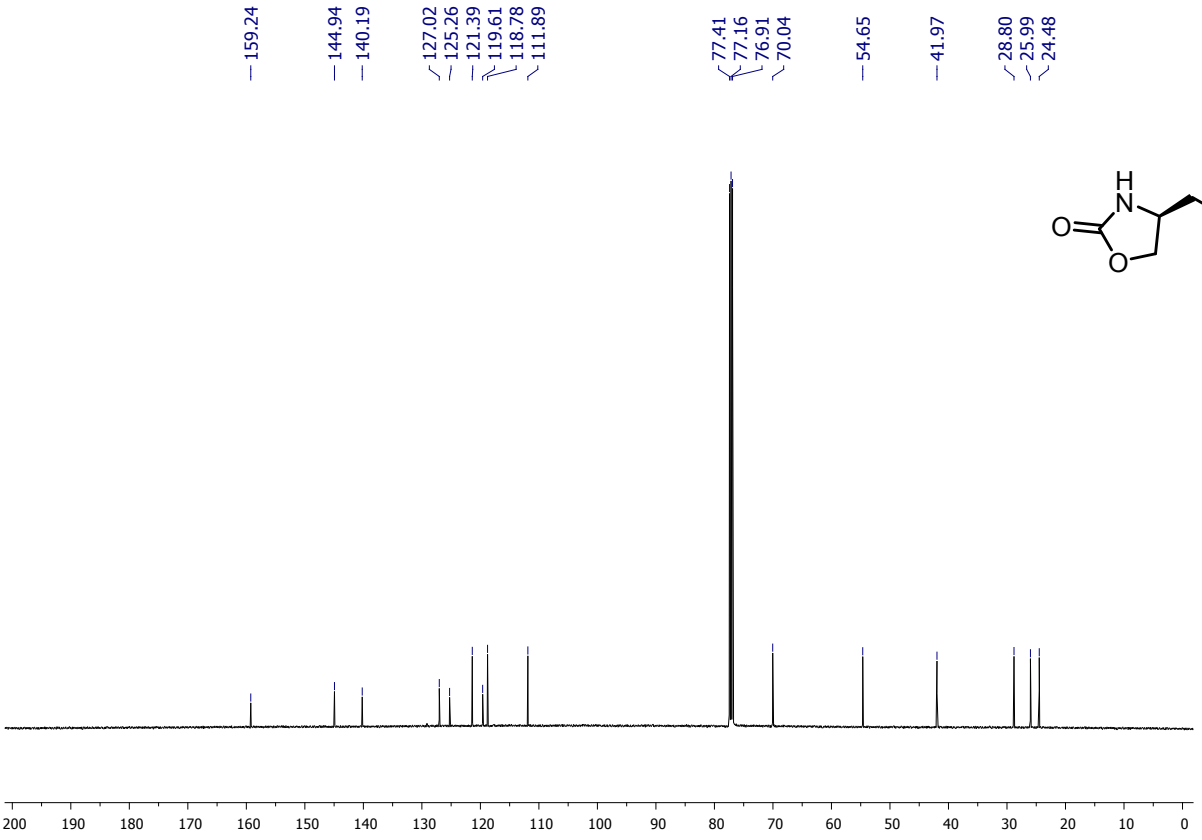


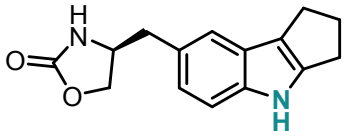


(S)-4-((1,2,3,4-tetrahydrocyclopenta[b]indol-7-yl)methyl)oxazolidin-2-one (29)

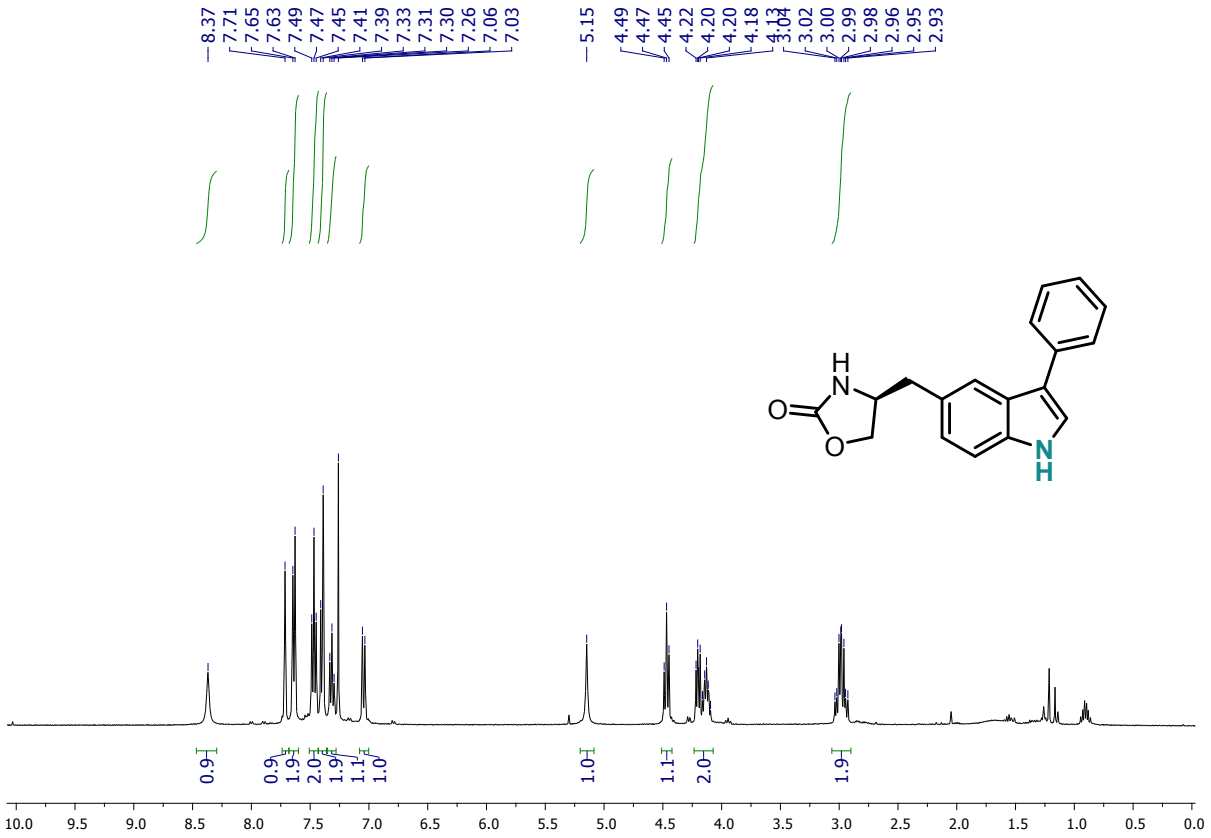


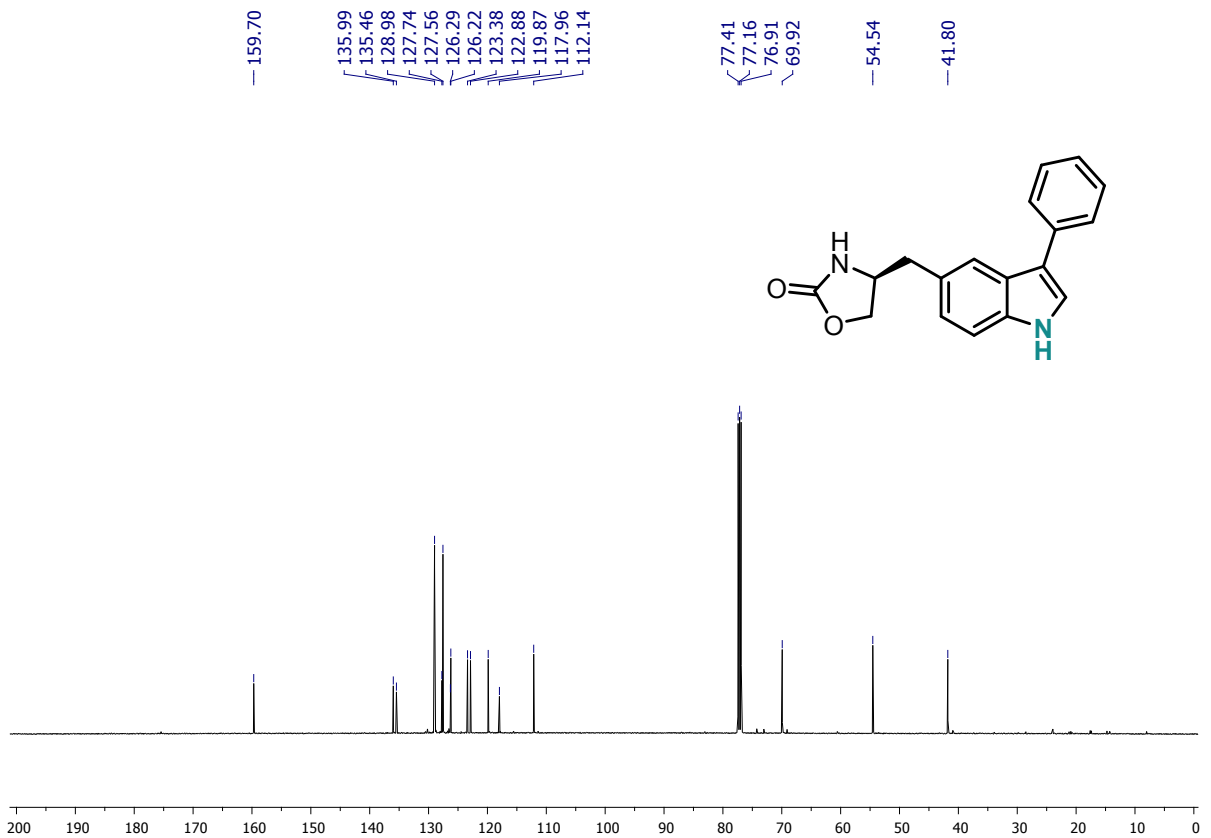




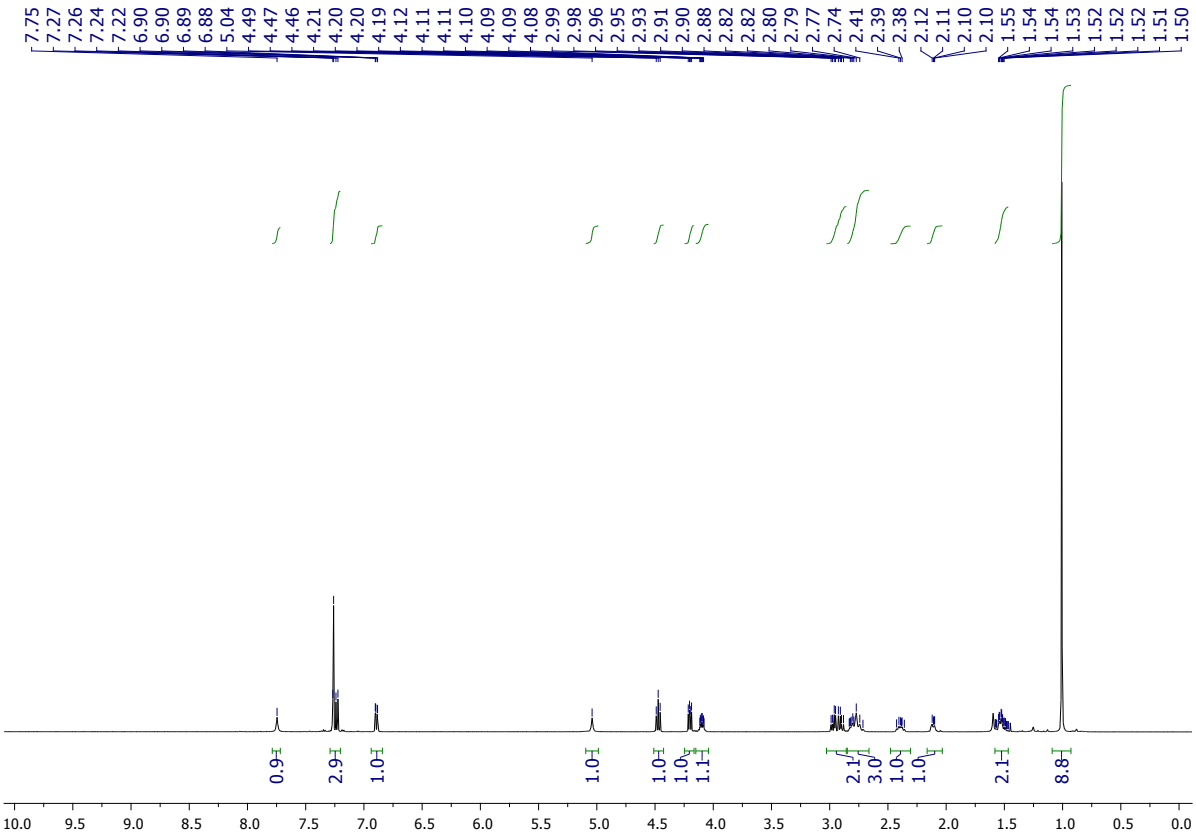


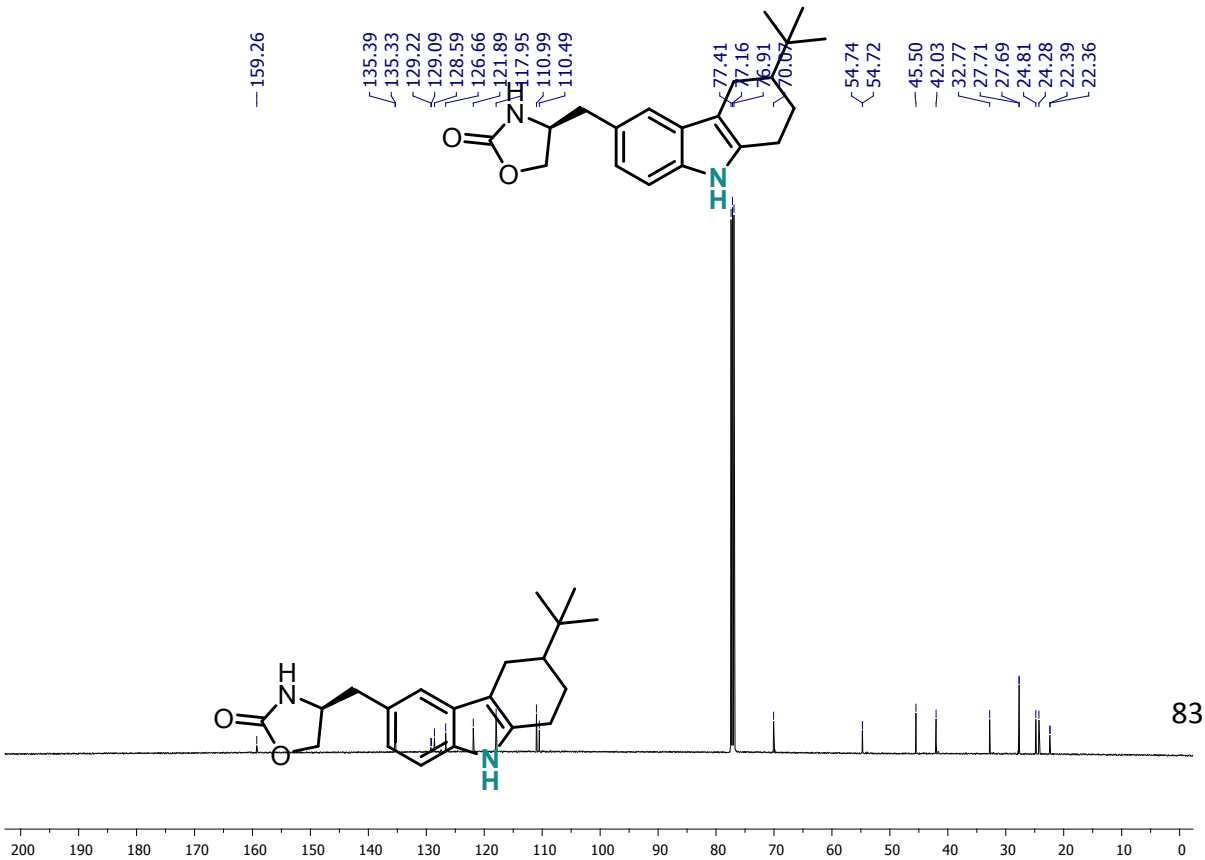
(S)-4-((3-phenyl-1H-indol-5-yl)methyl)oxazolidin-2-one (30)



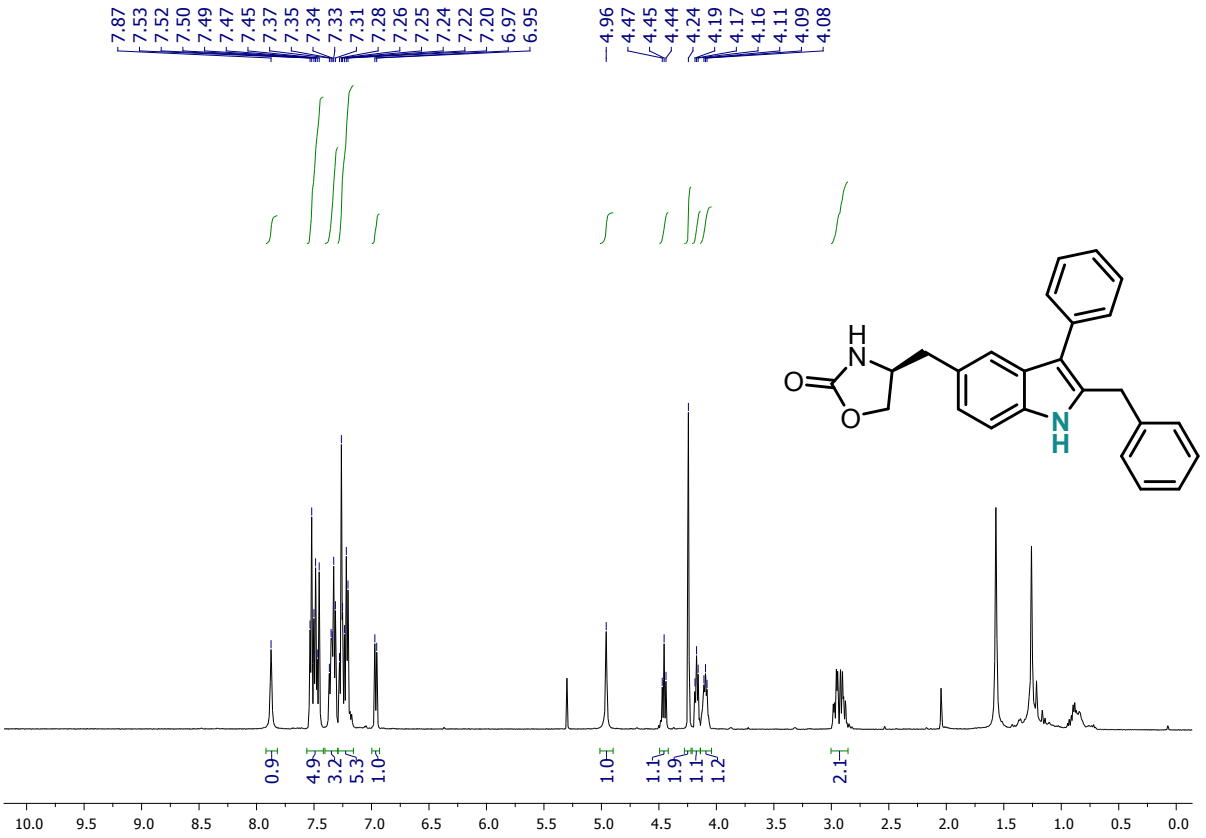


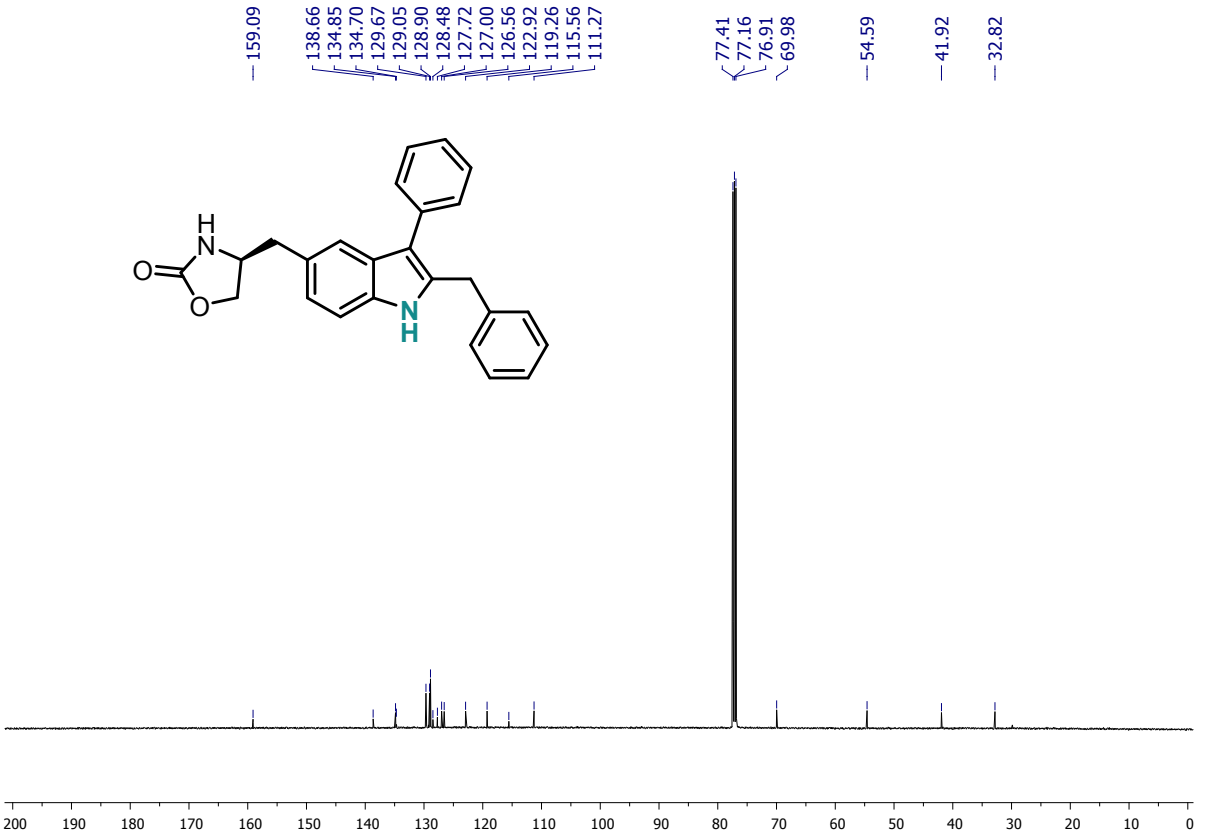
(4S)-4-((3-(tert-butyl)-2,3,4,9-tetrahydro-1H-carbazol-6-yl)methyl)oxazolidin-2-one (31)



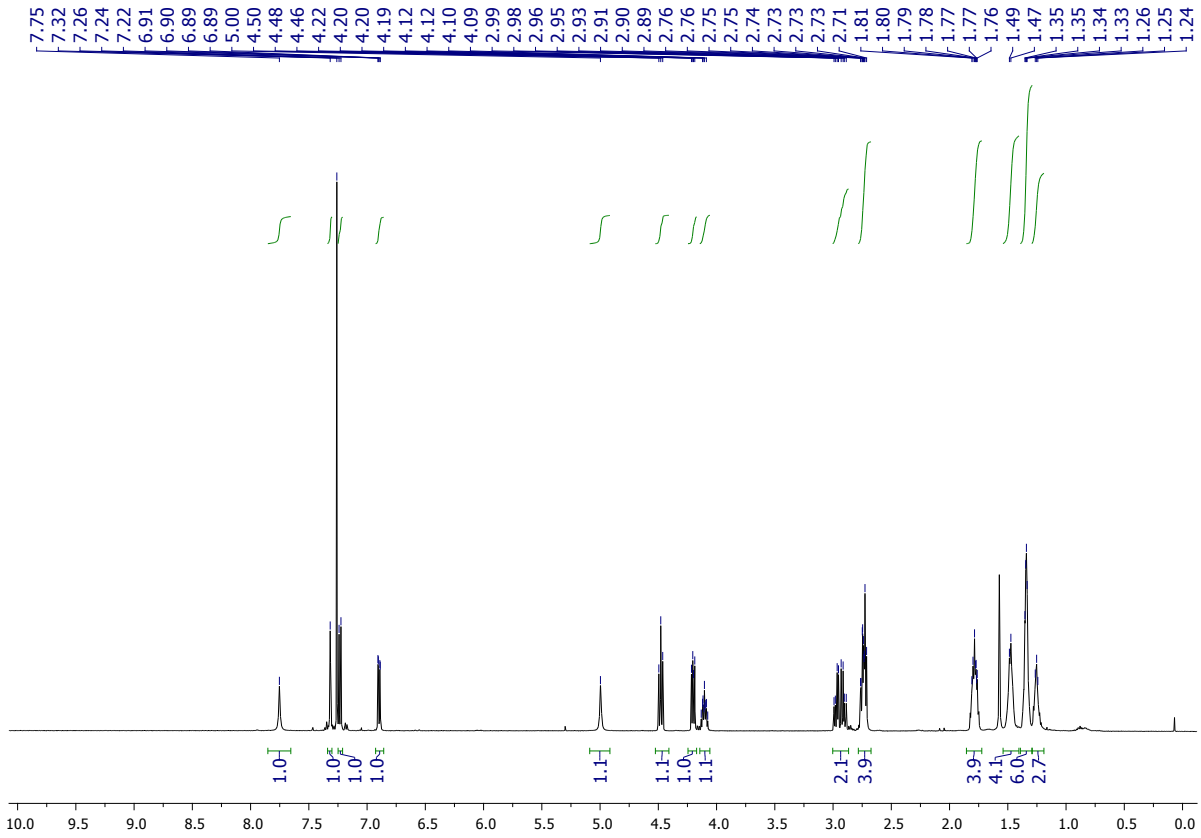


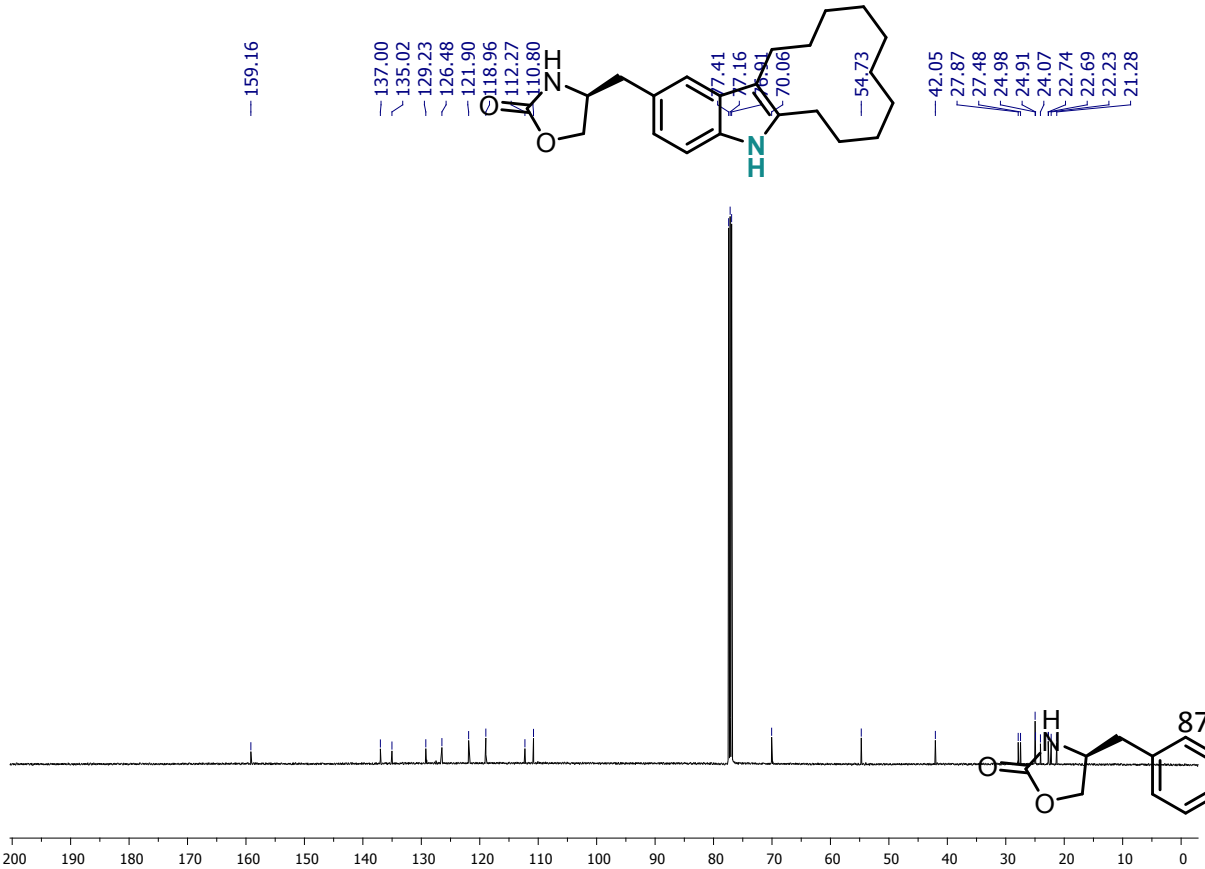
(S)-4-((2-benzyl-3-phenyl-1H-indol-5-yl)methyl)oxazolidin-2-one (32)





(S)-4-((6,7,8,9,10,11,12,13,14,15-decahydro-5H-cyclododeca[b]indol-2-yl)methyl)oxazolidin-2-one (33)





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