Mechanochemical Fischer Indolisation: an Eco-friendly Design for a Timeless Reaction

Andrea Porcheddu,[a] Rita Mocci,[a] Margherita Brindisi,*[b] Federico Cuccu,[a] Claudia Fattuoni,[a] Francesco Delogu,[d] Evelina Colacino,[e] and Maria Valeria D'Auria[b]*

[a]*Dipartimento di Scienze Chimiche e Geologiche, Università degli Studi di Cagliari, Cittadella Universitaria, 09042 Cagliari, Italy.*

[b]*Dipartimento di Farmacia, Università degli studi di Napoli 'Federico II', Via Domenico Montesano 49, 80131, Napoli, Italy.*

[c]Dipartimento di Ingegneria Meccanica, Chimica, e dei Materiali, Università degli Studi di Cagliari, via Marengo 2, 09123 Cagliari, Italy

[e] ICGM, Univ Montpellier CNRS, ENSCM, Montpellier, France

E-mails of corresponding authors: rita.mocci@unica.it (R. Mocci), margherita.brindisi@unina.it (M.Brindisi)

Table of contents

GENERAL METHODS AND MATERIALS

Commercially available reagents were purchased from Acros, Aldrich, Strem Chemicals, Alfa-Aesar, TCI Europe and used as received. All reactions were monitored by thin-layer chromatography (TLC) performed on glass-backed silica gel 60 F254, 0.2 mm plates (Merck), and compounds were visualized under UV light (254 nm) or using cerium ammonium molybdate solution with subsequent heating. The eluents were technical grade. Mechanochemical reactions were carried out using a FormTech FTS-1000 Shaker Mill® apparatus. The reagents were milled using a zirconia SmartSnap™ grinding jar (15 mL) equipped with balls (ϕ = 8 mm or ϕ = 3 mm, m_{tot} 6.5 g) of the same material. Precisely, the zirconium oxide of the vessels and balls used for all reactions accomplished in the mixer mill is yttrium oxide stabilized (ZrO_2-Y). If not stated otherwise, these parameters were applied. ^{1}H and ^{13}C liquid NMR spectra were recorded on a Bruker Avance III HD 600 MHz NMR spectrometer at 298 K. Proton chemical shifts are expressed in parts per million (ppm, δ scale) and are referred to the residual hydrogen in the solvent ($CDCl_3$, 7.27 ppm or DMSO 2.54 ppm) or to internal tetramethylsilane (TMS). Data are represented as follows: chemical shift δ is expressed in ppm, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and/or multiple resonances, br = broad singlet, and combination of thereof), coupling constant (*J*) in Hertz (Hz) and integration. Carbon chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to the carbon resonances of the NMR solvent ($CDCl_3$, δ 77.0 ppm or δ DMSO-d_6 δ 39.5 ppm). Deuterated NMR solvents were obtained from Aldrich. Samples were analyzed using an Agilent 5977B MS interfaced to the GC 7890B equipped with a DB-5ms column (J& W), injector temperature at 230 °C, detector temperature at 280 °C, helium carrier gas flow rate of 1 ml/min. The GC oven temperature program was 100°C initial temperature with 4 min hold time and ramping at 15°C/min to a final temperature of 270°C with 7 min hold time. 1 µL of each sample was injected in split (1:20) mode. After a solvent delay of 3 minutes, mass spectra were acquired in full scan mode using 2.28 scans/s with a 50–500 Amu mass range. Retention times of different compounds were determined by injecting pure compounds under identical conditions. HRMS were recorded on LTQ Orbitrap Elite (Thermofischer) instrument (ESI). All the experiments were carried out in duplicate to ensure the reproducibility of the experimental data. Yields refer to pure isolated materials.

GENERAL EXPERIMENTAL PROCEDURES FOR THE SYNTHESIS OF INDOLES AND INDOLINES

GENERAL EXPERIMENTAL PROCEDURES FOR THE PREPARATION OF INDOLES 3a-3za, 7a-7g

Aldehyde or ketone (1.1 mmol), phenylhydrazine hydrochloride (1.0 mmol), oxalic acid (3.5 mmol), dimethylurea (1.5 mmol) and acetic acid (η = 0.1 μl mg^{-1}) were loaded into a zirconium dioxide grinding jar (15 mL) equipped with 20 balls (ϕ = 3 mm, m_{tot} 6.5g) of the same material. The jar was sealed and shaken at a frequency of 30 Hz in a shaker mill until the complete disappearance of the starting material was observed by TLC (heptane/EtOAc: 9/1) and GC-MS analysis on an aliquot of crude. After completing the reaction, the resulting solid was triturated with water (2x3 mL), filtered through a filter paper, and dried in vacuo, affording the desired indole product. ^{1}H-NMR and ^{13}C spectrometry confirmed its structure. Alternatively, the solid mixture was triturated with EtOAc (2x3 mL), the resulting solution filtered through a short silica plug, and the filtrate dried *in vacuo* to give the indole product. Where necessary, further purification can be achieved by column chromatography (*n*-hexane:EtOAc 9:1 v/v).

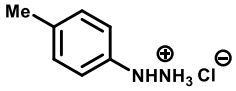
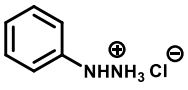
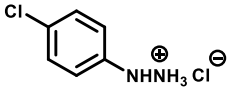
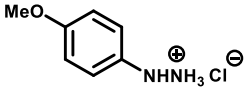
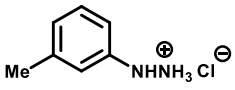
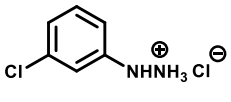
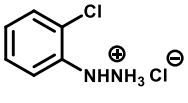
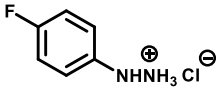
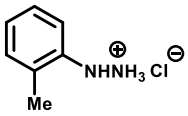
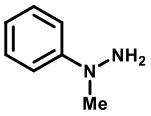
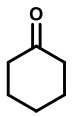
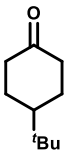
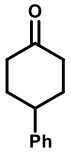
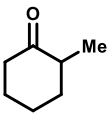
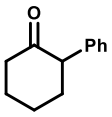
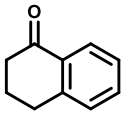
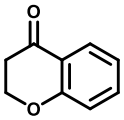
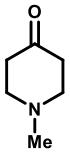
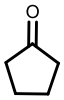
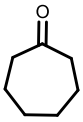
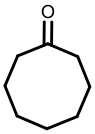
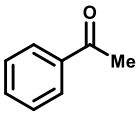
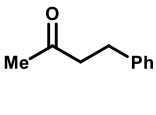
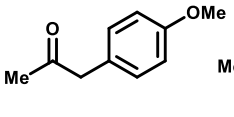
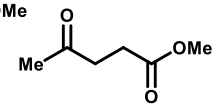
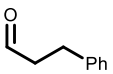
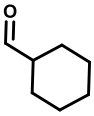
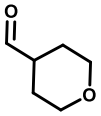
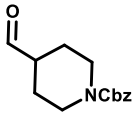
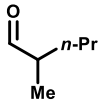
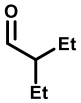
GENERAL EXPERIMENTAL PROCEDURES FOR THE PREPARATION OF INDOLINES 10a-10k

Aldehyde or ketone (1.1 mmol), phenylhydrazine hydrochloride (1.0 mmol), oxalic acid (3.5 mmol), dimethylurea (1.5 mmol) and acetic acid (η = 0.1 μl mg^{-1}) were loaded into a zirconium dioxide grinding jar (15 mL) equipped with 20 balls (ϕ = 3 mm, m_{tot} 6.5g) of the same material. The jar was sealed and shaken at a frequency of 30 Hz in an shaker mill until the complete disappearance of the starting material was observed by TLC (heptane/EtOAc: 9:1 v/v) and GC-MS analysis on an aliquot of crude. At the end of this time, sodium borohydride (2.0 mmol) was added to the resulting reaction mixture and further ball-milled for 60 minutes at 30 Hz. Upon completing the ball-milling process, the content of the jar was treated with water (2x3 mL) and EtOAc (2x3mL). Next, the resulting organic layers were combined and filtered through a short silica plug and dried *in vacuo* to give the corresponding indoline.

ADDITIVE-RECYCLING EXPERIMENTS IN THE PREPARATION OF INDOLE 3a

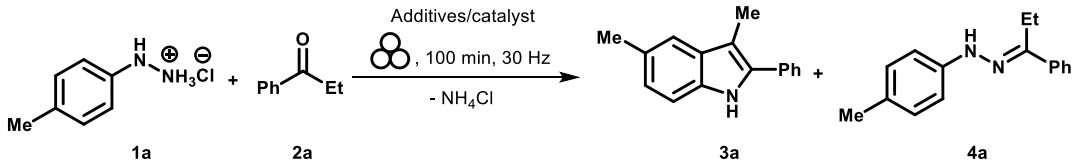
Propiophenone (1.1 mmol), phenylhydrazine hydrochloride (1.0 mmol), oxalic acid (3.5 mmol), dimethylurea (1.5 mmol) and acetic acid (η = 0.1 μl mg^{-1}) were loaded into a zirconium dioxide grinding jar (15 mL) equipped with 20 balls (ϕ = 3 mm, m_{tot} 6.5g) of the same material. The jar was sealed and shaken at a frequency of 30 Hz in a shaker mill until for 300 minutes. After completing the reaction, the resulting solid was triturated with water (2x3 mL), filtered through a filter paper, and dried in vacuo, affording the desired indole product. The wash waters were collected and evaporated under reduced pressure.The recovered solid additive containing oxalic acid and dimethyl urea was dried under vacuum for several hours and then reused for the next cycle with a fresh charge of reagents. Cycle 1: 76%, Cycle 2: 74%, Cycle 3: 73 %, Cycle 4: 70%.

Table S1. List of Starting materials

Phenyhdrazines
 1a  1b  1c  1d  1e
 1f  1g  1h  1i  5a
Ketones
 2a  2b  2c  2d  2e  2f
 2g  2h  2i  2j  2k  2l
 2m  2n  2o  2p  2q
Aldehydes
 6a  6b  6c  6d  6e
 8a  8b  8c  8d  8e

OPTIMIZATION OF THE REACTION CONDITIONS

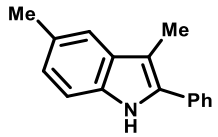
Table S2. Optimization of the reaction conditions for 3a[a]



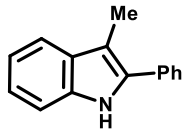
Entry	Catalyst (Equiv.)	Number of balls	3a (%)	Ratio (%)[b] of 3a:4a
1	Tetrabutylammonium bisulfate	2 (ϕ = 8 mm)	-	1:99
2	PTSA/Choline Chloride (2:1)	2 (ϕ = 8 mm)	13	99:1
3	DMU/$ZnCl_2$(7:0.05)	2 (ϕ = 8 mm)	16	17:83
4	DMU/citric acid (6:4)	2 (ϕ = 8 mm)	21	35:65
5	Oxalic acid/imidazole (2:1)	2 (ϕ = 8 mm)	Traces	1:99
6	DMU/tartaric acid (7:3)	2 (ϕ = 8 mm)	46	50:50
7	PTSA/imidazole (2:1)	2 (ϕ = 8 mm)	28	90:10
8	Oxalic acid/ Choline Chloride (2:1)	2 (ϕ = 8 mm)	-	1:99
9	DMU/oxalic acid (7:0.5)	20 (ϕ = 3 mm)	57	65:35
10	DMU/oxalic acid (6:4)	20 (ϕ = 3 mm)	47	83:17
11	DMU/oxalic acid (3.5:3.5)	20 (ϕ = 3 mm)	25	64:36

[a] **1a** (158.6 mg, 1.0 mmol), **2a** (147.6 mg, 1.1 mmol) and catalysts were milled in a 15 mL ZrO_2 milling jar with the given milling balls (ϕ = 8 mm, m_{tot} = 6.5 g) of the same material for 100 minutes. [b] Determined by GC-MS.

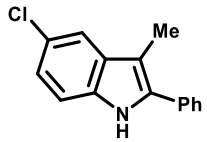
SPECTRAL DATA FOR INDOLE 3a-3z



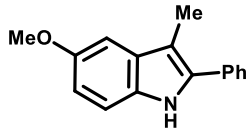
3,5-Dimethyl-2-phenyl-1*H*-indole (3a). The compound was obtained from the reaction of phenylhydrazine **1a** and ketone **2a** as an orange solid, 168 mg, 76% yield. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.87 (br s, 1H), 7.63 – 7.60 (m, 2H), 7.55 – 7.50 (m, 2H), 7.48 (m, 1H), 7.44 – 7.40 (tt, *J* = 8.2, 1.7 Hz, 1H), 7.29 (d, *J* = 8.2 Hz, 1H), 7.12 (dd, *J* = 8.2, 1.7 Hz, 1H), 2.58 (s, 3H), 2.52 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 134.30, 134.29, 133.6, 130.4, 128.85 (2C), 128.80, 127.8 (2C), 127.3, 124.0, 118.8, 110.5, 108.3, 21.7, 9.8. All spectral data are consistent with previously published findings.[1,2]



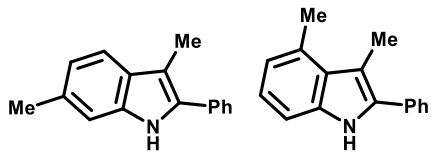
3-Methyl-2-phenyl-1*H*-indole (3b). The compound was obtained from the reaction of phenylhydrazine **1b** and ketone **2a** as a yellow oil, 140 mg, 68% yield. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.03 (br s, 1H), 7.59 – 7.55 (m, 3H), 7.49 (m, 2H), 7.38 (tt, *J* = 8.2, 1.6 Hz, 1H), 7.28 (dd, *J* = 8.5, 0.5 Hz, 1H), 7.15 (dd, *J* = 8.5, 2.0 Hz, 1H), 2.42 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 135.6, 134.3, 133.0, 131.3, 129.0 (2C), 127.9 (2C), 127.8, 125.4, 122.6, 118.7, 111.8, 108.6, 9.7. All spectral data are consistent with previously published findings.[3]



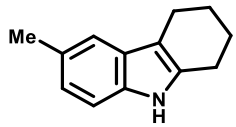
5-Chloro-3-methyl-2-phenyl-1*H*-indole (3c). The compound was obtained from the reaction of phenylhydrazine **1c** and ketone **2a** as a yellow solid, 94 mg, 39% yield. Purified on a column chromatography. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.04 (br s, 1H), 7.60-7.55 (m, 3H), 7.51-7.46 (m, 2H), 7.38 (tt, *J* = 8.2, 1.6 Hz, 1H), 7.28 (d, *J* = 8.2 Hz, 1H), 7.14 (dd, *J* = 8.2, 1.6 Hz, 1H), 2.42 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 135.6, 134.3, 133.0, 131.3, 129.0 (2C), 127.9 (2C), 127.8, 125.4, 122.6, 118.7, 111.8, 108.6, 9.7. HRMS (ESI): 242.0731m/z calcd for $C_{15}H_{13}ClN$: $[M+H]^+$. Found:242.0735.



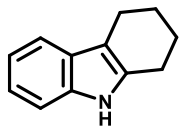
5-Methoxy-3-methyl-2-phenyl-1H-indole (3d). The compound was obtained from the reaction of phenylhydrazine **1d** and ketone **2a** as a white solid, 187 mg, 79% yield. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.92 (br s, 1H), 7.62 – 7.55 (m, 2H), 7.49-7.47 (m, 2H), 7.38 (tt, *J* = 8.2, 1.6 Hz, 1H), 7.26 (d, *J* = 8.7 Hz, 1H), 7.09 (d, *J* = 2.5 Hz, 1H), 6.92 (dd, *J* = 8.7, 2.5 Hz, 1H), 3.93 (s, 3H), 2.48 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 154.2, 135.1, 133.5, 131.2, 130.5, 128.9 (2C), 127.8, 127.4 (2C), 112.5, 111.6, 108.6, 101.0, 56.1, 9.9. All spectral data are consistent with previously published findings.[4]



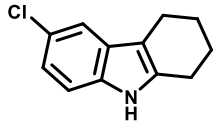
3,6-Dimethyl-2-phenyl-1*H*-indole + 3,4-dimethyl-2-phenyl-1*H*-indole ($3e_a$ + $3e_b$). Non-separable regioisomers (58:42). The compounds were obtained from the reaction of phenylhydrazine **1e** and ketone **2a** as white solid, 148 mg, 67% overall yield (**$3e_a$ + $3e_b$**). Purified on a column chromatography. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.94 (br s, 1H), 7.88 (s, 1H), 7.59 – 7.55 (m, 2H), 7.55 – 7.52 (m, 2H), 7.47 (td, *J* = 7.8, 3.8 Hz, 5H), 7.39 – 7.32 (m, 2H), 7.20 (d, *J* = 8.1 Hz, 1H), 7.16 (dt, *J* = 1.7, 0.9 Hz, 1H), 7.06 (dd, *J* = 8.1, 7.1 Hz, 1H), 6.98 (dd, *J* = 8.1, 1.4 Hz, 1H), 6.85 (dt, *J* = 7.2, 1.0 Hz, 1H), 2.78 (s, 3H), 2.62 (s, 3H), 2.48 (s, 3H), 2.45 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 136.4, 136.3, 134.5, 133.7, 133.6, 133.5, 132.3, 131.6, 128.9, 128.8, 128.6, 128.3, 128.1, 127.7, 127.5, 127.2, 122.4, 121.4, 121.4, 118.8, 110.8, 109.6, 108.8, 108.7, 21.9, 20.6, 12.5, 9.9. All spectral data are consistent with previously published findings.[1]



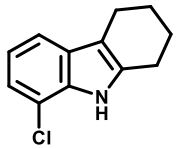
6-Methyl-2,3,4,9-tetrahydro-1*H*-carbazole (3g). The compound was obtained from the reaction of phenylhydrazine **1a** and ketone **2b** as a pale yellow solid**,** 144 mg, 78 % yield. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.49 (br s, 1H), 7.29 (s, 1H), 7.16 (d, *J* = 8.2 Hz, 1H), 6.97 (dd, *J* = 8.2, 1.7 Hz, 1H), 2.72 (t, *J* = 6.0 Hz, 4H), 2.48 (s, 3H), 1.97 – 1.85 (m, 4H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 134.4, 134.1, 128.3, 128.2, 122.5, 117.7, 110.1, 109.8, 23.5, 23.4 (2C), 21.6, 21.1 All spectral data are consistent with previously published findings.[2,5]



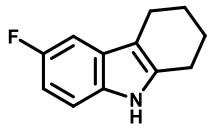
2,3,4,9-Tetrahydro-1*H*-carbazole (3h). The compound was obtained from the reaction of phenylhydrazine **1b** and ketone **2b** as a yellow solid, 200 mg, 81 % yield**. ^{1}H NMR** (600 MHz, DMSO-d_6) δ 10.59 (br s, 1H), 7.32 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.23 (dd, *J* = 8.0, 1.0 Hz, 1H), 6.97 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 6.91 (td, *J* = 7.7, 7.0, 1.2 Hz, 1H), 2.72 – 2.67 (m, 2H), 2.63 – 2.59 (m, 2H), 1.86 – 1.77 (m, 4H).**^{13}C NMR** (151 MHz, DMSO-d_6) δ 135.6, 134.3, 127.3, 120.0, 117.9, 117.0, 110.5, 108.0, 23.0, 22.9, 22.8, 20.6. All spectral data are consistent with previously published findings.[6]



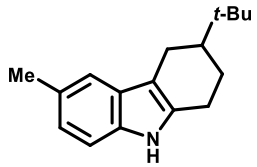
6-Chloro-2,3,4,9-tetrahydro-1*H*-carbazole (3i). The compound was obtained from the reaction of phenylhydrazine **1c** and ketone **2b** as a brown solid, 174 mg, 85 % yield. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 10.82 (br s, 1H), 7.33 (d, *J* = 2.1 Hz, 1H), 7.23 (d, *J* = 8.5 Hz, 1H), 6.96 (dd, *J* = 8.5, 2.1 Hz, 1H), 2.69 (m, 2H), 2.60 – 2.56 (m, 2H), 1.84 – 1.74 (m, 4H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 135.9, 134.1, 129.1, 124.9, 121.2, 117.5, 111.3, 110.2, 23.4, 23.3, 23.2, 20.9. All spectral data are consistent with previously published findings.[7]



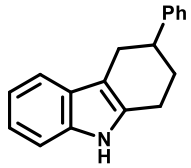
8-Chloro-2,3,4,9-tetrahydro-1*H*-carbazole (3j). The compound was obtained from the reaction of phenylhydrazine **1g** and ketone **2b** as a brown solid, 172 mg, 84 % yield. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.92 (br s, 1H), 7.42 (d, *J* = 7.6 Hz, 1H), 7.18 (d, *J* = 7.6 Hz, 1H), 7.07 (t, *J* = 7.6 Hz, 1H), 2.85 – 2.72 (m, 4H), 2.01 – 1.89 (m, 4H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 135.0, 132.9, 129.5, 120.4, 119.9, 116.5, 115.9, 111.4, 23.3, 23.23, 23.16, 21.1. All spectral data are consistent with previously published findings.[7]



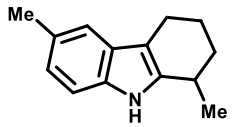
6-Fluoro-2,3,4,9-tetrahydro-1*H*-carbazole (3k). The compound was obtained from the reaction of phenylhydrazine **1h** and ketone **2b** as a yellow solid, 143 mg, 76%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.59 (br s, 1H), 7.18-7.13 (m, 2H), 6.89 (dt, *J* = 9.1, 2.6 Hz, 1H), 2.74 – 2.67 (m, 4H), 1.96 – 1.88 (m, 4H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 157.8 (d, *J* = 233.4 Hz), 136.4, 132.2, 128.3 (d, = 9.8 Hz), 110.8 (d, *J* = 9.8 Hz), 110.5 (d, *J* = 4.3 Hz), 108.8 (d, *J* = 26.0 Hz), 102.9 (d, *J* = 23.3 Hz), 23.4, 23.3, 23.2, 20.9. **^{19}F NMR** (565 MHz, $CDCl_3$) δ -126.32. All spectral data are consistent with previously published findings.[8]



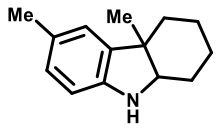
3-(*tert*-Butyl)-6-methyl-2,3,4,9-tetrahydro-1*H*-carbazole (3l). The compound was obtained from the reaction of phenylhydrazine **1a** and ketone **2c** as a white solid, 163 mg, 68% yield. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.52 (br s, 1H), 7.28 (m, 1H), 7.15 (d, *J* = 8.2 Hz, 1H), 6.95 (dd, *J* = 8.2, 1.7 Hz, 1H), 2.85 – 2.80 (m, 1H), 2.76 – 2.71 (m, 2H), 2.46 (s, 3H), 2.43 – 2.36 (m, 1H), 2.13 – 2.08 (m, 1H), 1.59 – 1.49 (m, 2H), 1.02 (s, 9H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 134.5, 134.4, 128.4, 128.3, 122.5, 117.6, 110.2, 110.1, 45.6, 32.8, 27.7 (3C), 24.9, 24.3, 22.4, 21.6. All spectral data are consistent with previously published findings.[9]



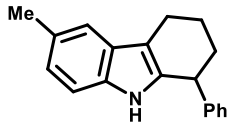
3-Phenyl-2,3,4,9-tetrahydro-1*H*-carbazole (3m). The compound was obtained from the reaction of phenylhydrazine **1b** and ketone **2d** as a white solid, 185 mg, 75% yield. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.41 (br s, 1H), 7.40 (d, *J* = 7.6 Hz, 1H), 7.30 – 7.23 (m, 4H), 7.20 – 7.15 (m, 2H), 7.08 (ddd, *J* = 8.1, 7.0, 1.3 Hz, 1H), 7.04 (ddd, *J* = 8.1, 7.0, 1.3 Hz, 1H), 3.04-2.95 (m, 2H), 2.80 – 2.71 (m, 2H), 2.70 – 2.61 (m, 1H), 2.16 – 2.08 (m, 1H), 2.08 – 1.98 (m, 1H).**^{13}C NMR** (151 MHz, $CDCl_3$) δ 146.8, 136.1, 133.7, 128.6 (2C), 127.6, 127.1 (2C), 126.3, 121.2, 119.3, 117.8, 110.6, 110.1, 41.2, 30.4, 29.4, 23.4. All spectral data are consistent with previously published findings.[9]



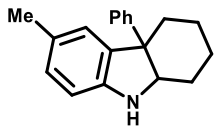
1,6-Dimethyl-2,3,4,9-tetrahydro-1*H*-carbazole ($3n_a$). The compound was obtained from the reaction of phenylhydrazine **1a** and ketone **2e** as a pale brown solid, 134 mg, 67 % overall yield (**$3n_a$+$3n_b$**). Purified on a column chromatography. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.62 (br s, 1H), 7.29 (s, 1H), 7.20 (d, *J* = 8.2 Hz, 1H), 6.99 (dd, *J* = 8.2, 1.7 Hz, 1H), 3.00 – 2.95 (m, 1H), 2.76 – 2.66 (m, 2H), 2. 49 (s, 3H), 2.10 – 1.99 (m, 2H), 1.83-1.76 (m, 1H), 1.59 – 1.52 (m, 1H), 1.31 (d, *J* = 7.0 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 138.9, 134.1, 128.4, 128.1, 122.6, 117.9, 110.2, 109.4, 32.5, 28.9, 22.1, 21.6, 21.3, 20.4. HRMS (ESI): 200,1434 m/z calcd for: $C_{14}H_{18}N$ $[M+H]^+$. Found 200.1436.



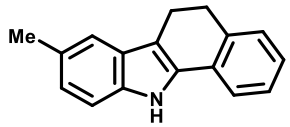
6-dimethyl-2,3,4,4a,9,9a-hexahydro-1*H*-carbazole ($10n_b$). The compound was obtained from the reaction of phenylhydrazine **1a** and ketone **2e** as a yellow oil, 134 mg, **$3n_a$+$3n_b$** 67 % overall yield. Purified on a column chromatography. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.89 – 6.85 (m, 2H), 6.65 – 6.61 (m, 1H), 3.48 (br s, 1H), 3.42 (t, *J* = 4.5 Hz, 1H), 2.32 (s, 3H), 1.75 – 1.60 (m, 4H), 1.51 – 1.39 (m, 4H), 1.33 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 147.2, 139.8, 128.1, 127.4, 122.4, 110.2, 66.2, 42.9, 35.1, 27.7, 23.7, 21.6, 21.3, 21.1. HRMS (ESI): 202.1590 m/z calcd for $C_{14}H_{20}N$: $[M+H]^+$. Found: 202.1588.



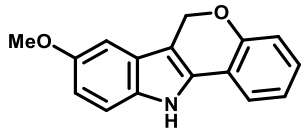
6-Methyl-1-phenyl-2,3,4,9-tetrahydro-1*H*-carbazole ($3o_a$).The compound was obtained from the reaction of phenylhydrazine **1a** and ketone **2f** as a pale brown solid, 186 mg, 71 % overall yield (**$3o_a$+$3o_b$**). Purified on a column chromatography. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.23 (s, 1H), 7.20 (t, *J* = 7.5 Hz, 2H), 7.17 – 7.12 (m, 2H), 7.07 – 7.03 (m, 2H), 6.91 (d, *J* = 8.2 Hz, 1H), 6.84 (dd, *J* = 8.2, 1.7 Hz, 1H), 4.00 (t, *J* = 6.5 Hz, 1H), 2.75 – 2.68 (m, 2H), 2.37 (s, 3H), 2.21 – 2.13 (m, 1H), 1.95 – 1.86 (m, 1H), 1.84 – 1.68 (m, 2H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 144.5, 135.7, 134.3, 128.7 (2C), 128.4 (2C), 128.4, 127. 9, 126.8, 122.9, 118.0, 111.4, 110.4, 41.6, 34.2, 22.0, 21.6, 21.2. HRMS (ESI): 262.1590 m/z calcd for: $C_{19}H_{20}N$ $[M+H]^+$. Found 262.1594



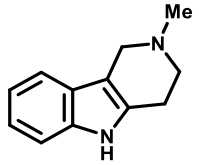
6-Methyl-4a-phenyl-2,3,4,4a,9,9a-hexahydro-1*H*-carbazole ($10o_b$). The compound was obtained from the reaction of phenylhydrazine **1a** and ketone **2f** as a pale brown solid**,** 186 mg, 71 % overall yield (**$3o_a$+$3o_b$**). **^{1}H NMR** (600 MHz, $CDCl_3$) ^{1}H NMR (600 MHz, CDCl3) δ 7.40 – 7.36 (m, 2H), 7.32 (dd, *J* = 8.5, 7.0 Hz, 2H), 7.24 – 7.20 (m, 1H), 6.92 – 6.89 (m, 1H), 6.71 (d, *J* = 1.8 Hz, 1H), 6.66 (d, J = 7.8 Hz, 1H), 4.10 (t, *J* = 5.1 Hz, 1H), 2.26 (s, 3H), 2.23 – 2.17 (m, 1H), 2.03 – 1.95 (m, 1H), 1.77 – 1.68 (m, 2H), 1.65 – 1.42 (m, 4H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 147.4, 146.4, 137.8, 128.5, 128.1, 127.9, 127.8, 126.1, 124.5, 110.6, 67.0, 52.1, 33.7, 28.4, 22.5, 21.2, 21.1. HRMS (ESI): 264.1747 m/z calcd for $C_{19}H_{22}N$: $[M+H]^+$. Found 264.1753.



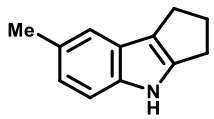
8-Methyl-6,11-dihydro-5*H*-benzo[a]carbazole (3p). The compound was obtained from the reaction of phenylhydrazine **1h** and ketone **2g** as a white solid, 175 mg, 80% yield. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.05 (br s, 1H), 7.34 (s, 1H), 7.29 (dd, *J* = 7.5, 1.3 Hz, 1H), 7.26 – 7.22 (m, 3H), 7.15 (td, *J* = 7.5, 1.4 Hz, 1H), 7.00 (dd, *J* = 8.2, 1.7 Hz, 1H), 3.07-3.02 (m, 2H), 2.97 – 2.92 (m, 2H), 2.46 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 136.6, 135.5, 133.3, 129.3, 129.2, 128.6, 127.8, 126.73, 126.72, 124.1, 119.8, 118.6, 112.4, 110.9, 29.7, 21.6, 19.8. All spectral data are consistent with previously published findings.[2]



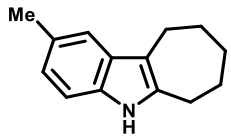
8-Methoxy-6,11-dihydrochromeno[4,3-*b*]indole (3q). The compound was obtained from the reaction of phenylhydrazine **1e** and ketone **2h** as a white solid**,** 203 mg, 81% yield. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 11.47 (br s, 1H), 7.56 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.29 (d, *J* = 8.7 Hz, 1H), 7.14 (dt, *J* = 7.6, 1.6 Hz, 1H), 7.01 – 6.96 (m, 2H), 6.90 (dd, *J* = 8.1, 1.1 Hz, 1H), 6.76 (dd, *J* = 8.7, 2.4 Hz, 1H), 5.55 (s, 2H), 3.76 (s, 3H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 153.7, 153.3, 132.4, 128.4, 125.5, 124.6, 121.3, 121.2, 117.9, 116.3, 112.1, 112.0, 104.8, 100.0, 65.0, 55.3. HRMS (ESI): 252.1019 m/z calcd for: $C_{16}H_{14}NO_2$ $[M+H]^+$. Found 252.1018.



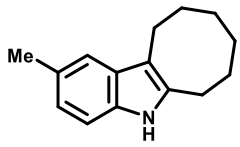
2-methyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (3r). The compound was obtained from the reaction of phenylhydrazine **1a** and ketone **2i** as a yellow solid, 70.7 mg, 38% yield. Purified on a column chromatography after basic treatment. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 10.74 (br s, 1H), 7.30 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.25 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.01 – 6.97 (m, 1H), 6.94 – 6.90 (m, 1H), 3.51 (s, 2H), 2.80 – 2.77 (m, 2H), 2.71 (t, *J* = 5.7 Hz, 2H), 2.42 (s, 3H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 135.9, 132.4, 125.5, 120.1, 118.2, 116.9, 110.7, 107.1, 52.1, 51.4, 45.6, 23.5. All spectral data are consistent with previously published findings.[10]



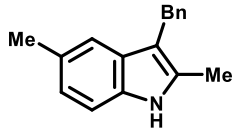
7-Methyl-1,2,3,4-tetrahydrocyclopenta[b]indole (3s). The compound was obtained from the reaction of phenylhydrazine **1a** and ketone **2j** as a yellow oil, 149 mg, 87% yield. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.69 (br s, 1H), 7.24 (s, 1H), 7.18 (d, *J* = 8.2 Hz, 1H), 6.92 (dd, *J* = 8.2, 1.7 Hz, 1H), 2.87 – 2.79 (m, 4H), 2.57 – 2.50 (m, 2H), 2.44 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 144.0, 139.4, 128.8, 125.1, 122.0, 119.5, 118.5, 111.0, 28.8, 26.0, 24.5, 21.6. HRMS (ESI): 172.1121 m/z calcd for $C_{12}H_{14}N$: $[M+H]^+$. Found 172.1121



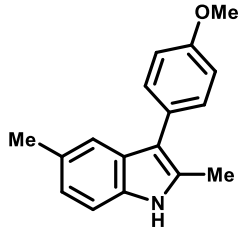
2-Methyl-5,6,7,8,9,10-Hexahydrocyclohepta[b]indole (3t). The compound was obtained from the reaction of phenylhydrazine **1b** and ketone **2k** as a yellow solid, 167 mg, 84% yield. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.60 (br s, 1H), 7.26 (s, 1H), 7.14 (d, *J* = 8.1 Hz, 1H), 6.92 (dd, *J* = 8.1, 1.6 Hz, 1H), 2.78-2.62 (m, 4H), 2.45 (s, 3H), 1.91-1.88 (m, 2H), 1.80 – 1.75 (m, 4H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 137.7, 132.7, 129.6, 128.3, 122.2, 117.5, 113.4, 110.0, 32.0, 29.7, 28.9, 27.7, 24.8, 21.7. HRMS (ESI): 200.1434 m/z calcd for: $C_{14}H_{18}N$ $[M+H]^+$. Found: 200.1431.



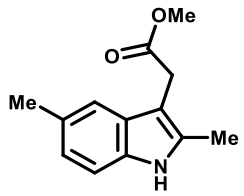
2-Methyl-6,7,8,9,10,11-hexahydro-5*H*-cycloocta[b]indole (3u). The compound was obtained from the reaction of phenylhydrazine **1a** and ketone **2l** as a colourless oil, 183 mg, 86%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.59 (br s, 1H), 7.32 – 7.29 (m, 1H), 7.17 (d, *J* = 8.2 Hz, 1H), 6.95 (dd, *J* = 8.1, 1.6 Hz, 1H), 2.89 – 2.80 (m, 4H), 2.48 (s, 3H), 1.75 (dt, *J* = 12.5, 6.2 Hz, 4H), 1.52 – 1.42 (m, 4H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 135.9, 133.5, 129.9, 128.1, 122.2, 117.6, 111.3, 110.1, 29.8, 29.7, 26.2, 26.05, 26.00, 22.3, 21.7. HRMS (ESI): 214.1590 m/z calcd for: $C_{15}H_{20}N$ $[M+H]^+$. Found 214.1592.



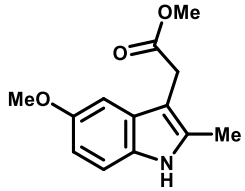
The compound was obtained from the reaction of phenylhydrazine **1a** and ketone **2n** as a white solid**,** 174 mg**,** 74% yield. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.67 (br s, 1H), 7.26 – 7.13 (m, 7H), 6.93 (dd, *J* = 8.2, 1.6 Hz, 1H), 4.05 (s, 2H), 2.39 (s, 3H), 2.36 (s, 3H).**^{13}C NMR** (151 MHz, $CDCl_3$) δ 141.9, 133.7, 131.9, 129.3, 128.5 (2C), 128.4 (2C), 128.3, 125.7, 122.6, 118.2, 110.2, 109.9, 30.1, 21.6, 12.0. HRMS (ESI): 236.1434 m/z calcd for: $C_{17}H_{18}N$ $[M+H]^+$. Found 236.1435.



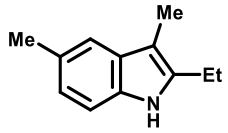
3-(4-Methoxyphenyl)-2,5-dimethyl-1*H*-indole (3x). The compound was obtained from the reaction of phenylhydrazine **1a** and ketone **2o** as a white solid, 249 mg, 99% yield**. ^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.74 (br s, 1H), 7.53 – 7.49 (m, 3H), 7.21 (d, *J* = 8.2 Hz, 1H), 7.13 – 7.09 (m, 2H), 7.07 (dd, *J* = 8.1, 1.6 Hz, 1H), 3.94 (s, 3H), 2.53 (s, 3H), 2.46 (s, 3H).**^{13}C NMR** (151 MHz, $CDCl_3$) δ 157.8, 133.6, 131.3 (2C), 130.6, 129.1, 128.3, 128.1, 122.9, 118.5, 114.1 (2C), 113.6, 110.1, 55.4, 21.6, 12.4. HRMS (ESI): 252.1383 m/z calcd for $C_{17}H_{18}NO$: $[M+H]^+$. Found: 252.1385.



Methyl 2-(2,5-dimethyl-1*H*-indol-3-yl)acetate (3y). The compound was obtained from the reaction of phenylhydrazine **1a** and ketone **2p**, 93 mg, 43% yield. Purified on a column chromatography. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.78 (br s, 1H), 7.31 (s, 1H), 7.13 (d, *J* = 8.2 Hz, 1H), 6.95 (dd, *J* = 8.2, 1.6 Hz, 1H), 3.69-3.65 (m, 5H), 2.45 (s, 3H), 2.37 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 172.8, 133.5, 132.9, 128.9, 128.8, 122.8, 117.9, 110.1, 104.1, 52.0, 30.3, 21.7, 11.8. HRMS (ESI): 218,1176 m/z calcd for $C_{13}H_{16}NO_2$ $[M+H]^+$. Found 218.1178.

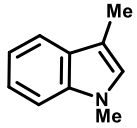


Methyl 2-(5-methoxy-2-methyl-1*H*-indol-3-yl)acetate (3z). The compound was obtained from the reaction of phenylhydrazine **1d** and ketone **2p**, 156 mg, 67% yield. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.95 (br s, 1H), 7.06 (d, *J* = 8.7 Hz, 1H), 7.01 (d, *J* = 2.5 Hz, 1H), 6.78 (dd, *J* = 8.7, 2.5 Hz, 1H), 3.87 (s, 3H), 3.69-3.65 (m, 5H), 2.31 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 172.8, 154.1, 133.8, 130.3, 128.9, 111.1, 110.9, 104.2, 100.5, 56.0, 51.9, 30.3, 11.7. All spectral data are consistent with previously published findings.[11,12]

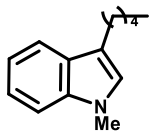


2-Ethyl-3,5-dimethyl-1*H*-indole (3za). The compound was obtained from the reaction of phenylhydrazine **1a** and ketone **2q** as a white solid 171 mg, 99 % yield. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.59 (br s, 1H), 7.30 (s, 1H), 7.17 (d, *J* = 8.1 Hz, 1H), 6.97 (dd, *J* = 8.2, 1.6 Hz, 1H), 2.75 (q, *J* = 7.6 Hz, 2H), 2.49 (s, 3H), 2.24 (s, 3H), 1.28 (t, *J* = 7.6 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 136.8, 133.5, 129.8, 128.3, 122.5, 118.0, 110.0, 105.8, 21.6, 19.5, 14.1, 8.4. HRMS (ESI): 174.1277 m/z calcd for: $C_{12}H_{16}N$ $[M+H]^+$. Found 174.1273.

Spectral data for indole 7a-7g

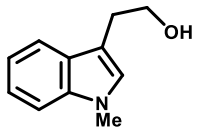


1,3-Dimethyl-1*H*-indole (7a). The compound was obtained from the reaction of phenylhydrazine **5a** and aldehyde **6a** as a colourless oil, 109 mg, 75%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.56 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.25 (dd, *J* = 8.2, 1.0 Hz, 1H), 7.20 (ddd, *J* =7.4, 6.9, 1.1 Hz, 1H), 7.10 (td, *J* = 7.4, 6.9, 1.1 Hz, 1H), 6.78 (s, 1H), 3.69 (s, 3H), 2.31 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 137.1, 128.8, 126.6, 121.5, 119.0, 118.6, 110.2, 109.1, 32.6, 9.6. All spectral data are consistent with previously published findings.[13,14]

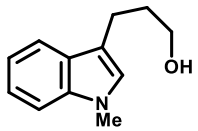


1-Methyl-3-pentyl-1*H*-indole (7b) The compound was obtained from the reaction of phenylhydrazine **5a** and aldehyde **6b** as a colourless oil, 177 mg, 88 %. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.59 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.27 (dt, *J* = 8.2, 0.9 Hz, 1H), 7.23 – 7.18 (m, 1H), 7.09 (ddd, *J* = 7.9, 6.9, 1.1 Hz, 1H), 6.81 (s, 1H), 3.72 (s, 3H), 2.73 (t, *J* = 7.0 Hz, 2H), 1.70 (quint, *J* = 7.0 Hz, 2H), 1.41 – 1.33 (m, 4H), 0.91 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 137.2, 128.2, 126.1, 121.5, 119.2, 118.5, 115.8, 109.2, 32.6, 32.0, 30.3, 25.2, 22.7, 14.2. HRMS (ESI): 202.1590 m/z calcd for: $C_{14}H_{20}N$ $[M+H]^+$. Found Chemical Formula: $C_{14}H_{21}N$ Exact Mass: 202.1588.

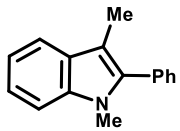
3-Benzyl-1-methyl-1*H*-indole (7c) The compound was obtained from the reaction of phenylhydrazine **5a** and aldehyde **6c**, 157 mg, 71 % yield. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.49 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.26 – 7.20 (m, 5H), 7.19 – 7.13 (m, 2H), 7.04 (ddt, *J* = 8.1, 6.9, 1.2 Hz, 1H), 6.66 (s, 1H), 4.06 (s, 2H), 3.59 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 141.5, 137.3, 128.8, 128.4, 128.0, 127.2, 125.9, 121.7, 119.9, 119.3, 118.9, 114.9, 114.3, 109.2, 32.6, 31.6. All spectral data are consistent with previously published findings.[15]



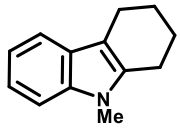
2-(1-Methyl-1*H*-indol-3-yl)ethan-1-ol (7d). The compound was obtained from the reaction of phenylhydrazine **5a** and aldehyde **6d** as a colourless oil, 138 mg, 78% yield. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.57 (td, *J* = 7.9, 1.1 Hz, 1H), 7.27 (dt, *J* = 8.2, 1.1 Hz, 1H), 7.20 (dt *J* = 8.2, 1.1 Hz, 1H), 7.08 (td, *J* = 8.0, 6.9, 1.1 Hz, 1H), 6.89 (s, 1H), 3.85 (t, *J* = 6.4Hz, 2H), 3.71 (s, 3H), 2.98 (t, *J* = 6.4 Hz, 2H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 137.3, 128.0, 127.4, 121.8, 119.03, 119.00, 110.8, 109.4, 62.9, 32.7, 28.8. All spectral data are consistent with previously published findings.[16]



3-(1-Methyl-1*H*-indol-3-yl)propan-1-ol (7e). The compound was obtained from the reaction of phenylhydrazine **5a** and aldehyde **6e** as a colourless oil, 149 mg, 79% yield. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.59 (td, *J* = 7.9, 1.0 Hz, 1H), 7.27 (td, *J* = 8.2, 0.9 Hz, 1H), 7.21 (dt, *J* = 8.1, 6.9, 1.2 Hz, 1H), 7.09 (dt, *J* = 7.9, 6.9, 1.1 Hz, 1H), 6.82 (s, 1H), 3.71 (s, 3H), 3.69 (t, *J* = 6.4 Hz, 2H), 2.83 (t, *J* = 6.4 Hz, 2H), 1.95 (quint, *J* = 6.4 Hz, 2H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 137.2, 128.0, 126.3, 121.6, 119.1, 118.7, 114.5, 109.3, 62.7, 33.3, 32.6, 21.4. All spectral data are consistent with previously published findings.[17]

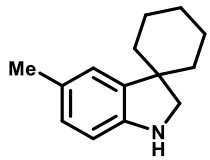


1,3-Dimethyl-2-phenyl-1*H*-indole (7f). The compound was obtained from the reaction of phenylhydrazine **5a** and ketone **2a** as a yellow oil, 142 mg, 64 % yield. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.48 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.36 – 7.34 (m, 2H), 7.29-7.26 (m, 3H), 7.19 (dt, *J* = 8.1, 0.9 Hz, 1H), 7.13 (dt, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.03 (dt, *J* = 7.9, 6.9, 1.0 Hz, 1H), 3.47 (s, 3H), 2.17 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 137.8, 137.4, 132.3, 130.8 (2C), 128.6, 128.4 (2C), 127.9, 121.9, 119.2, 118.9, 109.4, 108.7, 31.0, 9.5. All spectral data are consistent with previously published findings.[18]

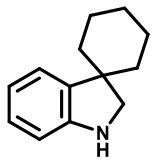


9-Methyl-2,3,4,9-tetrahydro-1*H*-carbazole (7g). The compound was obtained from the reaction of phenylhydrazine **5a** and ketone **2b** as yellow oil**,** 170 mg, 92 % yield. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.51 (d, *J* = 7.8 Hz, 1H), 7.27 (d, *J* = 7.8 Hz, 1H), 7.18 (t, 1H), 7.11 (t, 1H), 3.60 (s, 3H), 2.78– 2.71 (m, 4H), 2.00 – 1.87 (m, 4H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 136.8, 135.8, 127.3, 120.6, 118.7, 117.8, 109.3, 108.5, 29.0, 23.36, 23.38 , 22.2, 21.2. All spectral data are consistent with previously published findings.[19]

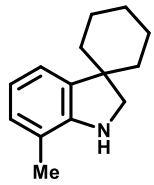
Spectral data for indoline 10a-10k



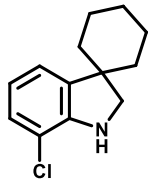
5'-Methylspiro[cyclohexane-1,3'-indoline] (10a). The compound was obtained from the reaction of phenylhydrazine **1a** and aldehyde **7a** as a pale yellow solid, 151 mg, 75 % yield. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.89 (s, 1H), 6.86 (d, *J* = 7.8 Hz, 1H), 6.62 (d, *J* = 7.8 Hz, 1H), 3.64 (br s, 1H), 3.43 (s, 2H), 2.28 (s, 3H), 1.71-1.66 (m, 5H), 1.61-1.56 (m, 2H), 1.45 – 1.29 (m, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 147.2, 139.3, 128.9, 128.0, 123.5, 110.5, 57.0, 46.3, 36.5, 25.9, 23.4, 21.1. All spectral data are consistent with previously published findings.[20]



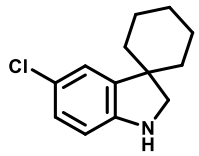
Spiro[cyclohexane-1,3'-indoline] (**10b).** The compound was obtained from the reaction of phenylhydrazine **1b** and aldehyde **7a** as a yellow oil, 129 mg, 69% yield. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.12 – 7.02 (m, 2H), 6.82 (t, *J* = 7.4 Hz, 1H), 6.76 (d, *J* = 7.7 Hz, 1H), 3.47 (s, 2H), 1.79 – 1.69 (m, 5H), 1.65 – 1.57 (m, 2H), 1.43 – 1.28 (m, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 148.7, 139.2, 127.7, 122.8, 120.1, 111.0, 56.6, 46.3, 36.6 (2C), 25.9, 23.3 (2C). All spectral data are consistent with previously published findings.[20]



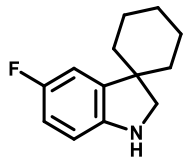
7'-Methylspiro[cyclohexane-1,3'-indoline] (10c) The compound was obtained from the reaction of phenylhydrazine **1i** and aldehyde **7a** as a yellow solid**,** 123 mg, 61% yield. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.94 (d, *J* = 7.4 Hz, 1H), 6.90 (d, *J* = 7.4 Hz, 1H), 6.73 (t, *J* = 7.4 Hz, 1H), 3.47 (s, 2H), 2.17 (s, 3H), 1.77-1.71 (m, 6H), 1.62 – 1.57 (m, 2H), 1.42 – 1.31 (m, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 148.3, 138.3, 128.6, 120.2, 119.8, 119.5, 56.8, 46.6, 36.7 (2C), 25.9, 23.3 (2C), 16.9. HRMS (ESI): 202,1590 m/z calcd for $C_{14}H_{20}N$: $[M+H]^+$. Found: 202.1593.



7'-Chlorospiro[cyclohexane-1,3'-indoline] (10d). The compound was obtained from the reaction of phenylhydrazine **1g** and aldehyde **7a** as an orange solid**,** 78 mg, 35% yield. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.03 (dd, *J* = 7.6, 1.0 Hz, 1H), 6.94 (dd, *J* = 7.6, 1.0 Hz, 1H), 6.67 (t, *J* = 7.6 Hz, 1H), 3.50 (s, 2H), 1.79 – 1.76 (m, 2H), 1.74 – 1.71 (m, 3H), 1.58 (dt, *J* = 12.7, 3.1 Hz, 2H), 1.43 – 1.35 (m, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 147.3, 140.0, 127.2, 120.9, 119.4, 115.0, 56.7, 47.5, 36.6 (2C), 25.8, 23.1 (2C). HRMS (ESI): 222.1044 m/z calcd for: $C_{13}H_{17}ClN$ $[M+H]^+$. Found 222.1045.

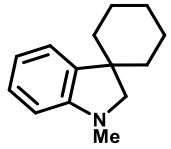


5'-Chlorospiro[cyclohexane-1,3'-indoline] (10e). The compound was obtained from the reaction of phenylhydrazine **1c** and aldehyde **7a** as a yellow solid, 93 mg, 42% yield. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.99-6.95 (m, 2H), 6.56 (d, *J* = 8.2 Hz, 1H), 3.69 (br s, 1H), 3.44 (s, 2H), 1.74– 1.70 (m, 5H), 1.57 – 1.52 (m, 2H), 1.41 – 1.31 (m, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 148.6, 140.7, 127.3, 123.7, 123.1, 110.8, 57.1, 46.6, 36.5 (2C), 25.8, 23.2 (2C). HRMS (ESI): 222.1044 10 m/z calcd for: $C_{13}H_{17}ClN$ $[M+H]^+$. Found 222.1044.

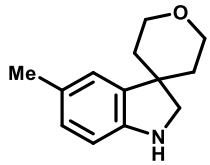


5'-Fluorospiro[cyclohexane-1,3'-indoline] (10f). The compound was obtained from the reaction of phenylhydrazine **1h** and aldehyde **6f** as a yellow oil, 111 mg, 54% yield. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.77 (dd, *J* = 8.7, 2.6 Hz, 1H), 6.72 (dt, *J* = 8.7, 2.7 Hz, 1H), 6.56 (dd, *J* = 8.7, 4.3 Hz, 1H), 3.75 (br s, 1H), 3.44 (s, 2H), 1.76 – 1.69 (m, 5H), 1.57 – 1.51 (m, 2H), 1.43-1.29 (m, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 157.5 (d, *J* = 235 Hz, 1C), 145.9, 140.7 (d, *J* = 7.1 Hz, 1C), 113.5 (d, *J* = 23.5, 1C), 110.4 (d, *J* = 8.2 Hz, 1C), 110.2 (d, *J* = 23.7 Hz, 1C), 57.4,

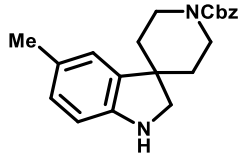
46.7, 36.4 (2C), 25.8, 23.2 (2C). **^{19}F NMR** (565 MHz, $CDCl_3$) δ -125.71. HRMS (ESI): 206.1340 m/z calcd for: $C_{13}H_{17}FN$ $[M+H]^+$. Found 206,1340.



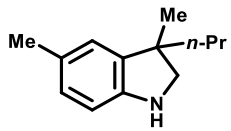
1'-Methylspiro[cyclohexane-1,3'-indoline] (10g). The compound was obtained from the reaction of phenylhydrazine **1b** and aldehyde **7a** as a colourless oil, 159 mg, 79% yield. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.12 (dt, *J* = 7.6, 1.3 Hz, 1H), 7.06 (dd, *J* = 7.3, 1.3 Hz, 1H), 6.73 (dt, *J* = 7.4, 1.0 Hz, 1H), 6.51 (d, *J* = 7.8 Hz, 1H), 3.22 (s, 2H), 2.80 (s, 3H),1.80- 1.72 (m, 5H), 1.65-1.58 (m, 2H), 1.50 – 1.36 (m, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 152.3, 139.3, 127.7, 122.2, 117.8, 107.3, 65.7, 44.8, 36.4 (2C), 36.1, 26.0, 23.4 (2C). All spectral data are consistent with previously published findings.[21]



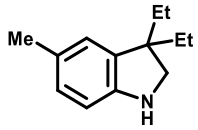
5-Methyl-2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran] (**10h).** The compound was obtained from the reaction of phenylhydrazine **1a** and aldehyde **7b** as a white solid, 156 mg, 77% yield. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.93 (d, *J* = 1.7 Hz, 1H), 6.89 (dd, *J* = 7.8, 1.8 Hz, 1H), 6.59 (d, *J* = 7.8 Hz, 1H), 4.01-3.97 (m, 2H), 3.58 (dt, *J* = 12.0, 2.2 Hz, 2H), 3.53 (s, 2H), 2.30 (s, 3H), 2.02-1.96 (m, 2H), 1.69-1.63 (m, 2H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 148.2, 136.9, 128.3, 128.3, 123.4, 109.9, 65.2 (2C) , 56.8, 43.8, 36.4 (2C), 21.0. HRMS (ESI): 204.1383 m/z calcd for: $C_{13}H_{18}NO$ $[M+H]^+$. Found 204.1381.



Benzyl 5-methylspiro[indoline-3,4'-piperidine]-1'-carboxylate (10i). The compound was obtained from the reaction of phenylhydrazine **1a** and aldehyde **7c** as a white solid, 272 mg, 81% yield. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.42 – 7.38 (m, 4H), 7.35 (dd, *J* = 6.2, 2.7 Hz, 1H), 6.92 – 6.85 (m, 2H), 6.59 (d, *J* = 7.8 Hz, 1H), 5.19 (s, 2H), 4.19-4.09 (m, 2H), 3.51 (br s, 1H), 3.43 (s, 2H) , 3.05-2.93 (m, 2H), 2.29 (s, 3H), 1.89 – 1.69 (m, 4H).**^{13}C NMR** (151 MHz, $CDCl_3$) δ 155.4, 148.1, 136.9, 136.5, 128.6, 128.4 (2C), 128.3, 128.1, 128.0 (2C), 123.4, 109.9, 67.2, 56.2, 44.5 (2C), 41.4 (2C), 35.4, 21.0. HRMS (ESI): 337.1911 m/z calcd for: $C_{21}H_{25}N_2O_2$ $[M+H]^+$. Found 337.1914.



3-Ethyl-3,5-dimethylindoline (10j) The compound was obtained from the reaction of phenylhydrazine **1a** and aldehyde **7d** as a yellow oil, 83 mg, 44% yield. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.88 – 6.82 (m, 2H), 6.62 (d, *J* = 7.7 Hz, 1H), 3.41 (d, *J* = 9.0 Hz, 1H), 3.25 (d, *J* = 9.0 Hz, 1H), 2.28 (s, 3H), 1.65 – 1.52 (m, 2H), 1.43 – 1.32 (m, 2H), 1.29 (s, 3H), 0.90 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 147.4, 138.4, 128.8, 127.8, 123.5, 110.4, 59.6, 45.4, 25.7, 21.1, 18.1, 14.8. HRMS (ESI): 190.1590 m/z calcd for: $C_{13}H_{20}N$ $[M+H]^+$. Found: 190.1587.

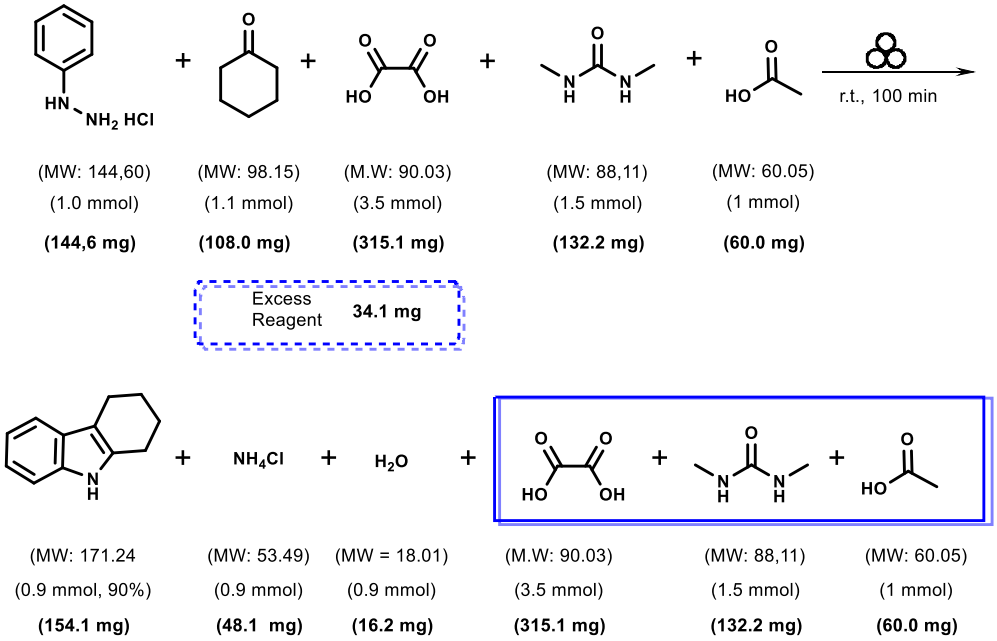


3,3-Diethyl-5-methylindoline (10k). The compound was obtained from the reaction of phenylhydrazine **1a** and aldehyde **7e** as a yellow oil, 123 mg, 65 % yield. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.88 (dd, *J* = 7.9, 1.8 Hz, 1H), 6.80 (br s, 1H), 6.68 (d, *J* = 7.8 Hz, 1H), 3.38 (s, 2H), 2.28 (s, 3H), 1.76 – 1.58 (m, 4H), 0.83 (t, *J* = 7.5 Hz, 6H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 146.8, 136.8, 129.6, 128.0, 124.5, 111.1, 56.8, 49.6, 30.6 (2C), 21.2, 8.9 (2C). HRMS (ESI): 190.1590 m/z calcd for: $C_{13}H_{20}N$ $[M+H]^+$. Found 190.1587.

GREEN CHEMISTRY METRICS CALCULATIONS

Calculation of the Green Chemistry Metrics for the Mechanochemical Preparation of Indole 3h

Environmental Factor (E) for the mechanochemical preparation of indole (Scheme S1)



Scheme S1. Mechanochemical Preparation of Indole **3h**

$$\text{Enviromental factor } (E) = \frac{\textit{mass of total waste}}{\textit{mass of desired product}} = \frac{(34.1 + 48.1 + 16.2 + 315.1 + 132.2 + 60.0)\ \text{mg}}{154.1\ \text{mg}} = \frac{605.7\ \text{mg}}{154.1\ \text{mg}} = \mathbf{3.9}$$

Work-up: 6000 mg of H_2O **or** 5400 mg EtOAc and 1500 mg silica

$$\textbf{\textit{E}} \text{ (after purification, aqueous work-up)} = \frac{(6000 + 606)\ \text{mg}}{154.1\ \text{mg}} = \frac{6606\ \text{mg}}{154.1\ \text{mg}} = \mathbf{42.9}$$

$$\textbf{\textit{E}} \text{ (after purification, silica filtration work-up)} = \frac{(6900 + 606)\ \text{mg}}{154.1\ \text{mg}} = \frac{7506\ \text{mg}}{154.1\ \text{mg}} = \mathbf{48.7}$$

The Eco-scale Score for the Mechanochemical Preparation of Indole ***3h***

EcoScale: 100 – sum of penalty points

Table S3. Calculation of Ecoscale score[a]

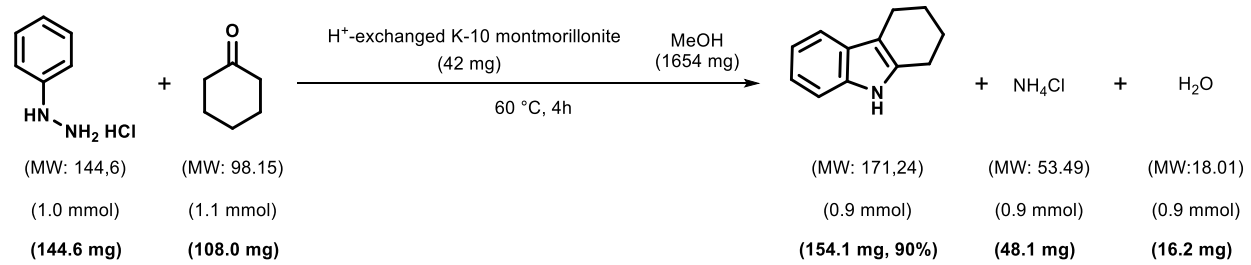
Reagents	**MF**	**MW**	**g**	**mmol**	**Equiv.**
Phenylhydrazine hydrochloride	$C_6H_8N_2$. HCl	144.60	0.1446	1.0	1.0
Cyclohexanone	$C_6H_{10}O$	98.15	0.1080	1.1	1.1
Dimethyl urea	$C_3H_8N_2O$	88.11	0.1322	1.5	1.5
Oxalic acid	$C_2H_2O_4$	90.03	0.3150	3.5	3.5
Acetic acid	$C_2H_4O_2$	60.05	0.0600	1.0	1.0
Product	**MF**	**MW**	**g**	**mmol**	**Yield**
1,2,3,4-Tetrahydrocarbazole (**3h**)	$C_{12}H_{13}N$	171.24	0.1545	0.9	90%

Entry	**Parameters**	**Penalty Points**
1	Yield (90%)	-5
2	Price/availability	-8
3	Safety	-10
4	Technical set-up (Unconventional activation technique)	-2
5	Room temperature (< 24h)	-1
6	Work-up and purification	0
	EcoScale Score	**74**

[a]Values calculated using the eco scale calculator software available at the link: http://ecoscale.cheminfo.org/calculator

Calculation of Green Chemistry Metrices for the Preparation of Indole 3h based on Solution Synthesis[22]

Environmental Factor (E_1) for the preparation of indole based on solution synthesis (Scheme S2)



Scheme S2. Solvent based preparation of Indole **3h**

Work-up: DCM (5532 mg), brine (5000 mg).

$$\textbf{E}\text{nviromental factor } (E) = \frac{\textit{mass of total waste}}{\textit{mass of desired product}} = \frac{(34.1 + 48.1 + 16.2 + 1654)\ \text{mg}}{154.1\ \text{mg}} = \frac{1784.5\ \text{mg}}{154.1\ \text{mg}} = \mathbf{11.4}$$

$$\textbf{\textit{E}}\ \text{(after purification, solvent work-up)} = \frac{(10532 + 1784)\ \text{mg}}{154.1\ \text{mg}} = \frac{12316\ \text{mg}}{154.1\ \text{mg}} = \mathbf{79.9}$$

*The eco-scale calculator for the Preparation of Indole **3h** based on Solution Synthesis*

EcoScale: 100 – sum of penalty points

Table S4. Calculation of EcoScale score[a]

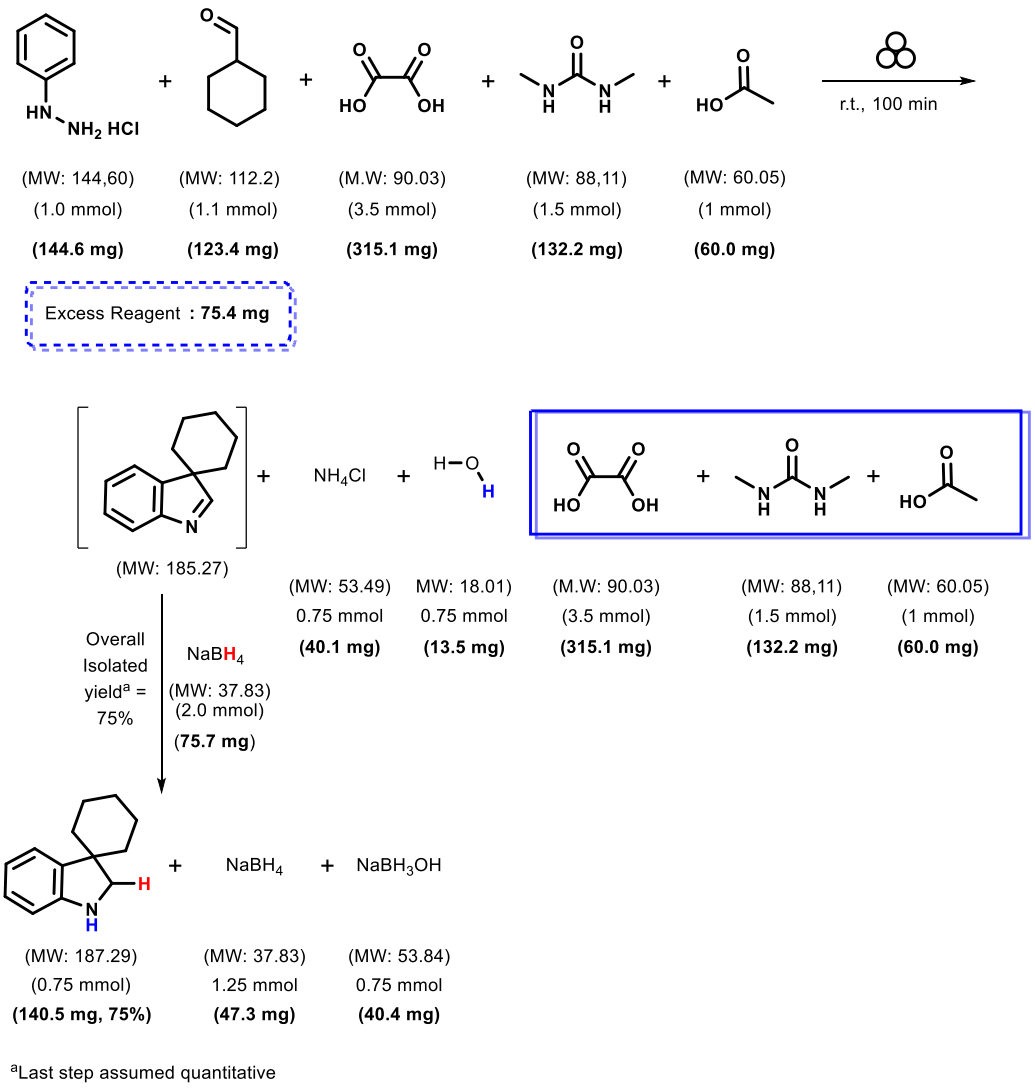
Reagents	MF	MW	g	mmol	Equiv.
Phenylhydrazine hydrochloride	$C_6H_8N_2 \cdot HCl$	144.60	0.1446	1.0	1.0
Cyclohexanone	$C_6H_{10}O$	98.15	0.1079	1.1	1.1
Montmorillonite KSF			0.0420		
Methanol	CH_4O	32.04	1.6400	51.3	51.3
Product	**MF**	**MW**	**g**	**mmol**	**Yield**
1,2,3,4-Tetrahydrocarbazole (**3h**)	$C_{12}H_{13}N$	171.24	0.1545	0.9	90%

Entry	Parameters	Penalty Points
1	Yield (90%)	-5
2	Price/availability	-5
3	Safety	-20
4	Technical set-up (Common set-up)	0
5	Temperature/time (Heating, > 1h)	-3
6	Work-up and purification (liquid -liquid extraction or washing)	-3
	EcoScale Score	**64**

[a]Values calculated using the eco scale calculator software available at the link: http://ecoscale.cheminfo.org/calculator

Calculation of the Green Chemistry Metrics for the Mechanochemical Preparation of Indoline 10b

Environmental Factor (E) for the mechanochemical preparation of Indoline (Scheme S3) using acetic acid as solvent for liquid assisted grinding



[a]Last step assumed quantitative

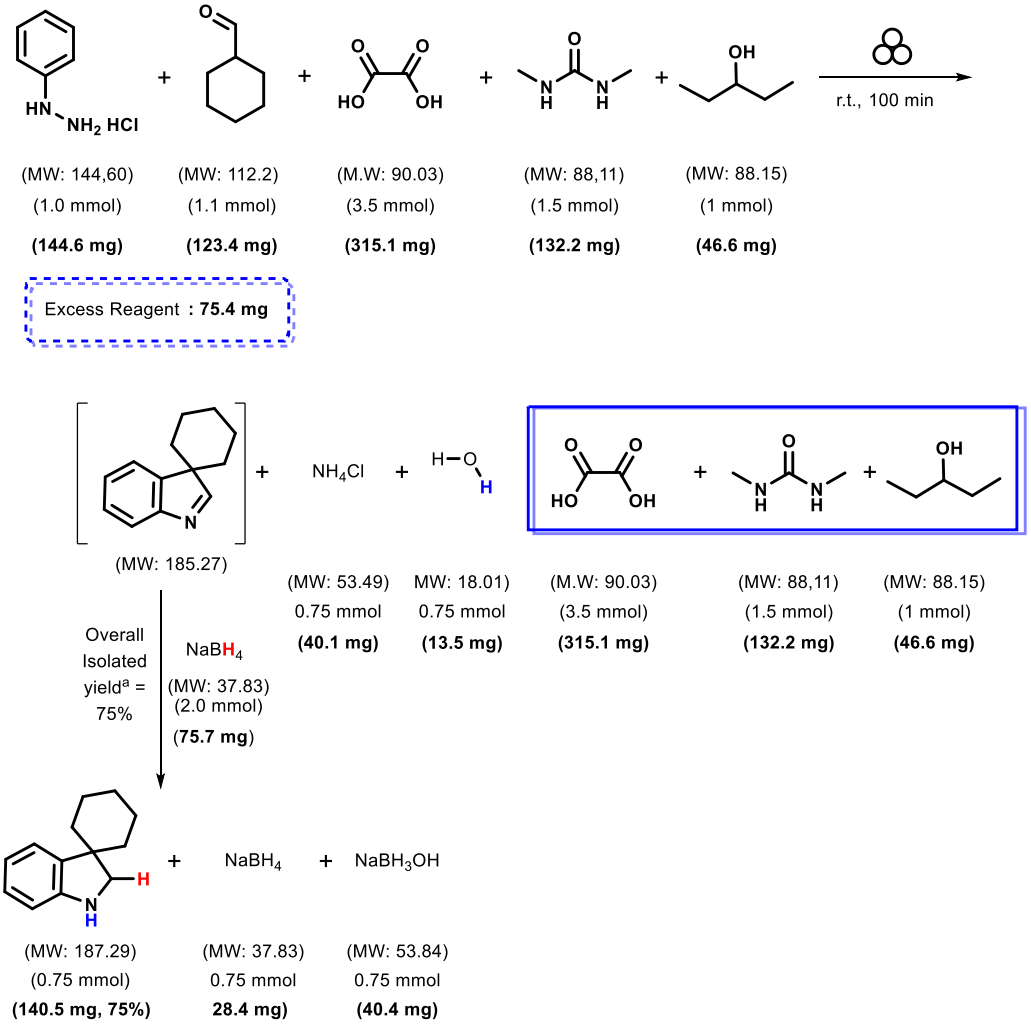
Scheme S3. Mechanochemical Preparation of Indoline **10b**

$$\text{Enviromental factor } (\boldsymbol{E}) = \frac{\textit{mass of total waste}}{\textit{mass of desired product}} = \frac{(75.4 + 40.1 + 13.5 + 315.1 + 132.2 + 60.0 + 47.3 + 26.9)\ \text{mg}}{140.5\ \text{mg}} = \frac{710.5\ \text{mg}}{140.5\ \text{mg}} = \mathbf{5.0}$$

Work-up: H_2O (6000 mg), EtOAc (5400 mg), silica (4000 mg), hexane (10400 mg), EtOAc (3600 mg)

$$\boldsymbol{E}\text{ (after purification: liquid-liquid extraction, filtration on silica plug)} = \frac{(6000\ \text{mg} + 5400 + 4000 + 10400 + 3600 + 710)\ \text{mg}}{140.5\ \text{mg}} = \frac{30110\ \text{mg}}{140.5\ \text{mg}} = \mathbf{214.3}$$

Environmental Factor (E) for the mechanochemical preparation of Indoline (Scheme S4) using 3-pentanol as solvent for liquid assisted grinding



[a]Last step assumed quantitative

Scheme S4. Mechanochemical Preparation of Indoline **10b**

$$\text{Enviromental factor } (\boldsymbol{E}) = \frac{\textit{mass of total waste}}{\textit{mass of desired product}} = \frac{(75.4 + 40.1 + 13.5 + 315.1 + 132.2 + 46.6 + 28.4 + 26.9)\ \text{mg}}{140.5\ \text{mg}} = \frac{678.2\ \text{mg}}{140.5\ \text{mg}} = \mathbf{4.8}$$

Work-up: H_2O (6000 mg), EtOAc (5400 mg), silica (4000 mg), hexane (10400 mg), EtOAc (3600 mg)

$$\boldsymbol{E}\ \text{(after purification: liquid-liquid extraction, filtration on silica plug)} = \frac{(6000\ \text{mg} + 5400 + 4000 + 10400 + 3600 + 678.2)\ \text{mg}}{140.5\ \text{mg}} = \frac{30078\ \text{mg}}{140.5\ \text{mg}} = \mathbf{214.0}$$

*The Eco-scale Score for the Mechanochemical Preparation of Indoline **10b***

EcoScale: 100 – sum of penalty points

Table S5. Calculation of EcoScale score using acetic acid as solvent for liquid assisted grinding

Reagents	**MF**	**MW**	**g**	**mmol**	**Equiv.**
Phenylhydrazine hydrochloride	$C_6H_8N_2$. HCl	144.60	0.1446	1.0	1.0
Cyclohexanecarboxaldehyde	$C_7H_{12}O$	112.17	0.1122	1.1	1.1
Dimethyl urea	$C_3H_8N_2O$	88.11	0.1322	1.5	1.5
Oxalic acid	$C_2H_2O_4$	90.03	0.3150	3.5	3.5
Acetic acid	$C_2H_4O_2$	60.05	0.0600	1.0	1.0
Sodium borohydride	H_4BNa	37.83	0.0756	2	2
Product	**MF**	**MW**	**g**	**mmol**	**Yield**
Spiro[cyclohexane-1,3'-indoline] (**10b**)	$C_{13}H_{17}N$	187,14	0.140	0.75	75%

Entry	**Parameters**	**Penalty Points**
1	Yield (75%)	-12
2	Price/availability	0
3	Safety	-20
4	Technical set-up (Unconventional activation technique)	-2
5	Temperature/time (r.t, > 1h)	0
6	Work-up and purification (liquid-liquid extraction, classical chromatography	-13
	EcoScale Score	**52.5**

[a]Values calculated using the eco scale calculator software available at the link: http://ecoscale.cheminfo.org/calculator

*The Eco-scale Score for the Mechanochemical Preparation of Indoline **10b***

EcoScale: 100 – sum of penalty points

Table S6. Calculation of EcoScale score using 3-pentanol as solvent for liquid assisted grinding

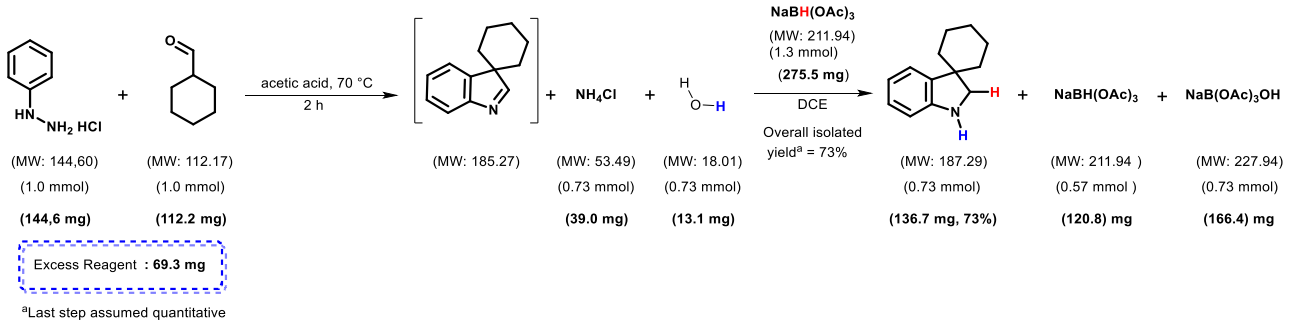
Reagents	**MF**	**MW**	**g**	**mmol**	**Equiv.**
Phenylhydrazine hydrochloride	$C_6H_8N_2$. HCl	144.60	0.1446	1.0	1.0
Cyclohexanecarboxaldehyde	$C_7H_{12}O$	112.17	0.1122	1.1	1.1
Dimethyl urea	$C_3H_8N_2O$	88.11	0.1322	1.5	1.5
Oxalic acid	$C_2H_2O_4$	90.03	0.3150	3.5	3.5
3-pentanol	$C_2H_4O_2$	60.05	0.0464	0.52	0.5
Sodium borohydride	H_4BNa	37.83	0.0378	1	1
Product	**MF**	**MW**	**g**	**mmol**	**Yield**
Spiro[cyclohexane-1,3'-indoline] (**10b**)	$C_{13}H_{17}N$	187,14	0.140	0.75	75%

Entry	**Parameters**	**Penalty Points**
1	Yield (75%)	-12
2	Price/availability	0
3	Safety	-20
4	Technical set-up (Unconventional activation technique)	-2
5	Temperature/time (r.t, > 1h)	0
6	Work-up and purification (liquid-liquid extraction, classical chromatography	-13
	EcoScale Score	**52.5**

[a]Values calculated using the eco scale calculator software available at the link: http://ecoscale.cheminfo.org/calculator

Calculation of the Green Chemistry Metrics for the preparation of indoline based on solution synthesis the Mechanochemical Preparation of Indoline[20]

*Environmental Factor (E) for the preparation of indoline **10b** based on solution synthesis (Scheme S5)*



Scheme S5. Solvent based preparation of Indoline **10b**

Solvent 1st step: acetic acid = 3.33 mL (3.500 mg)

Solvent 2nd step: 1,2-dichloroethane = 3.33 mL (4.162 mg)

$$\text{Enviromental factor } (E) = \frac{\textit{mass of total waste}}{\textit{mass of desired product}} = \frac{(69.3 + 39.0 + 120.8 + 166.4 + 3500 + 4162)\ \text{mg}}{136.7\ \text{mg}} = \frac{8057.5\ \text{mg}}{136.7\ \text{mg}} = \mathbf{58.9}$$

Work-up: H_2O (6000 mg), Na_2CO_3 (600 mg), EtOAc (5400 mg), silica (4000 mg), hexane (10400 mg), EtOAc (3600 mg)

$$\textbf{\textit{E}}\ \text{(after purification, aqueous work-up)} = \frac{(6000 + 600 + 5400 + 4000 + 10400 + 3600 + 8057)\ \text{mg}}{136.7\ \text{mg}} = \frac{38057\ \text{mg}}{136.7\ \text{mg}} = \mathbf{278.4}$$

The eco-scale calculator the Preparation of Indoline 9b based on Solution Synthesis

EcoScale: 100 – sum of penalty points

Table S7. Calculation of EcoScale score[a]

Reagents	MF	MW	g	mmol	Equiv.
Phenylhydrazine hydrochloride	$C_6H_8N_2$ .HCl	144.60	0.1446	1	1
Cyclohexanecarboxaldehyde	$C_7H_{12}O$	112.17	0.112172	1.1	1.1
Acetic acid	$C_2H_4O_2$	60.05	0.0600	1	1
1,2-Dichloroethane	$C_2H_4Cl_2$	98.96	4.162	42	42
Sodium triacetoxyborohydride	$C_6H_{10}BNaO_6$	211.94	0.275	1.3	1.3
Product	**MF**	**MW**	**g**	**mmol**	**Yield**
spiro[cyclohexane-1,3'-indoline]	$C_{13}H_{17}N$	187,14	0.138	0.74	74%

Entry	Parameters	Penalty Points
1	Yield (75%)	-13
2	Price/availability	0
3	Safety	-20
4	Technical set-up (Unconventional activation technique)	0
5	Temperature/time (heating, > 1h, cooling to 0 °C)	-7
6	Work-up and purification (liquid-liquid extraction, classical chromatography	-13
	EcoScale Score	**45**

[a]Values calculated using the eco scale calculator software available at the link: http://ecoscale.cheminfo.org/calculator

Reference

1 M. P. Kumar and R. S. Liu, *J. Org. Chem.*, 2006, **71**, 4951–4955.

2 E. Cuevas Creencia, M. Tsukamoto and T. Horaguchi, *J. Heterocycl. Chem*, 2011, **48**, 1095.

3 Z. He, H. Li and Z. Li, *J. Org. Chem.*, 2010, **75**, 4636–4639.

4 C. A. Simoneau and B. Ganem, *Tetrahedron*, 2005, **61**, 11374–11379.

5 P. Schrögel, A. Tomkevičiene, P. Strohriegl, S. T. Hoffmann, A. Köhler and C. Lennartz, *J. Mater. Chem.*, 2011, **21**, 2266–2273.

6 O. Leogane and H. Lebel, *Angew. Chem. Int. Ed.*, 2008, **47**, 350–352.

7 D. Q. Xu, J. Wu, S. P. Luo, J. X. Zhang, J. Y. Wu, X. H. Du and Z. Y. Xu, *Green Chem.*, 2009, **11**, 1239–1246.

8 P. P. Varma, B. S. Sherigara, K. M. Mahadevan and V. Hulikal, *Synth. Commun.*, 2008, **39**, 158–165.

9 J. Chen and Y. Hu, *Synth. Commun.*, 2006, **36**, 1485–1494.

10 H. Dong, R. T. Latka and T. G. Driver, *Org. Lett.*, 2011, **13**, 2726–2729.

11 M. A. Chowdhury, Z. Huang, K. R. A. Abdellatif, Y. Dong, G. Yu, C. A. Velázquez and E. E. Knaus, *Bioorganic Med. Chem. Lett.*, 2010, **20**, 5776–5780.

12 A. S. Kalgutkar, B. C. Crews, S. Saleh, D. Prudhomme and L. J. Marnett, *Bioorganic Med. Chem.*, 2005, **13**, 6810–6822.

13 R. B. Bedford, N. Fey, M. F. Haddow and R. F. Sankey, *Chem. Commun*, 2011, **47**, 3649–3651.

14 X. H. Xu, G. K. Liu, A. Azuma, E. Tokunaga and N. Shibata, *Org. Lett.*, 2011, **13**, 4854–4857.

15 Y. Jia and J. Zhu, *J. Org. Chem.*, 2006, **71**, 7826–7834.

16 S. J. Garden, R. B. Da Silva and A. C. Pinto, *Tetrahedron*, 2002, **58**, 8399–8412.

17 J. A. Schiffner, T. H. Wöste and M. Oestreich, *Eur. J. Org. Chem.*, 2010, **2010**, 174–182.

18 Z. Liang, B. Yao and Y. Zhang, *Org. Lett.*, 2010, **12**, 3185–3187.

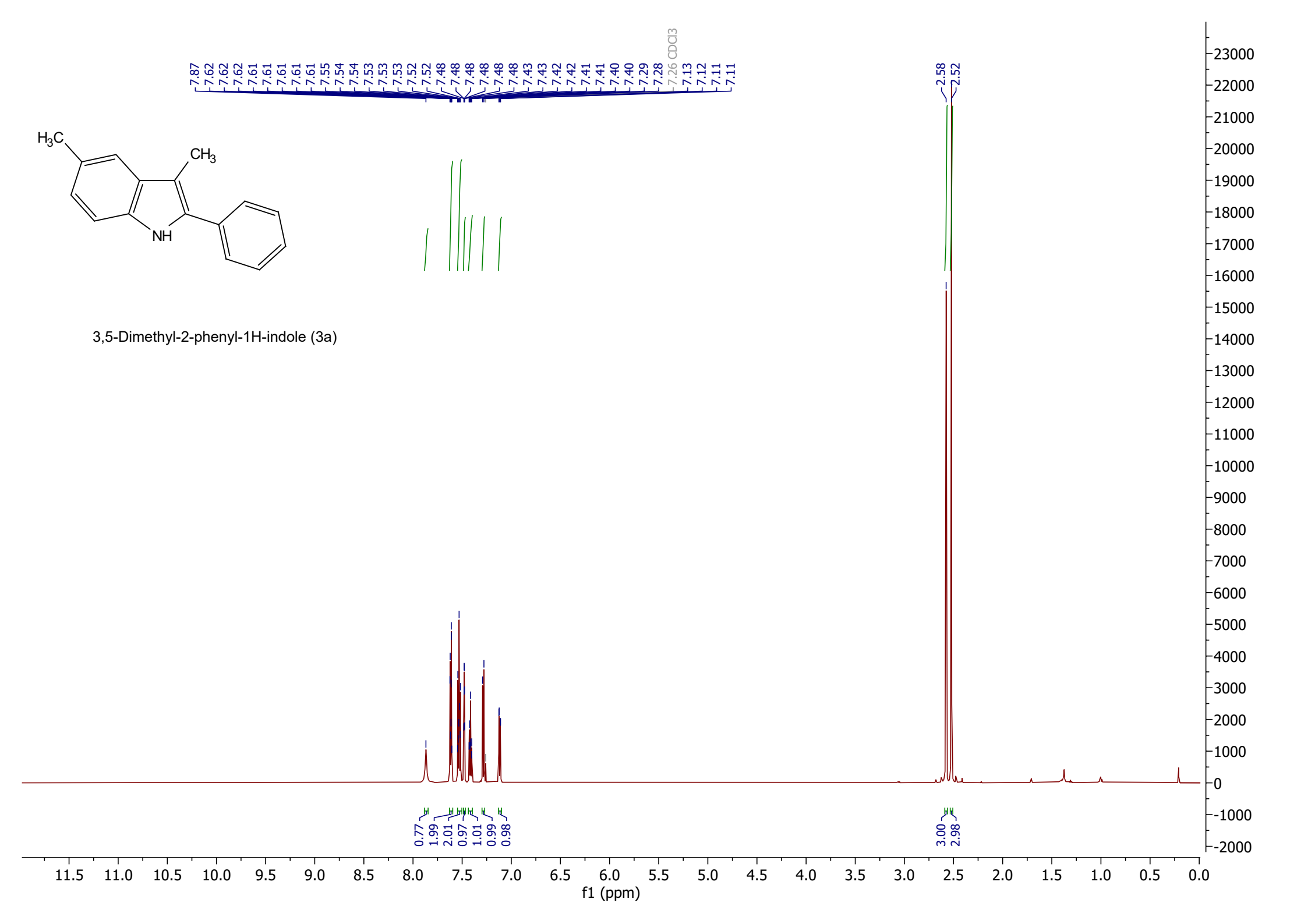
19 M. Yagoubi, A. C. F. Cruz, P. L. Nichols, R. L. Elliott and M. C. Willis, *Angew. Chem. Int. Ed.*, 2010, **49**, 7958–7962.

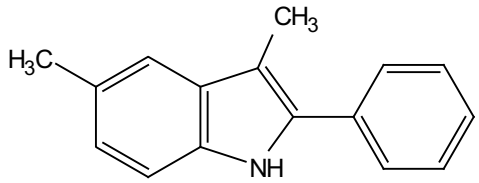
20 K. G. Liu, J. R. Lo and A. J. Robichaud, *Tetrahedron*, 2010, **66**, 573–577.

21 W.-L. Jia, N. Westerveld, K. M. Wong, T. Morsch, M. Hakkennes, K. Naksomboon and M. Á. Fernández-Ibáñez, *Org. Lett.*, 2019, **21**, 9339–9342.

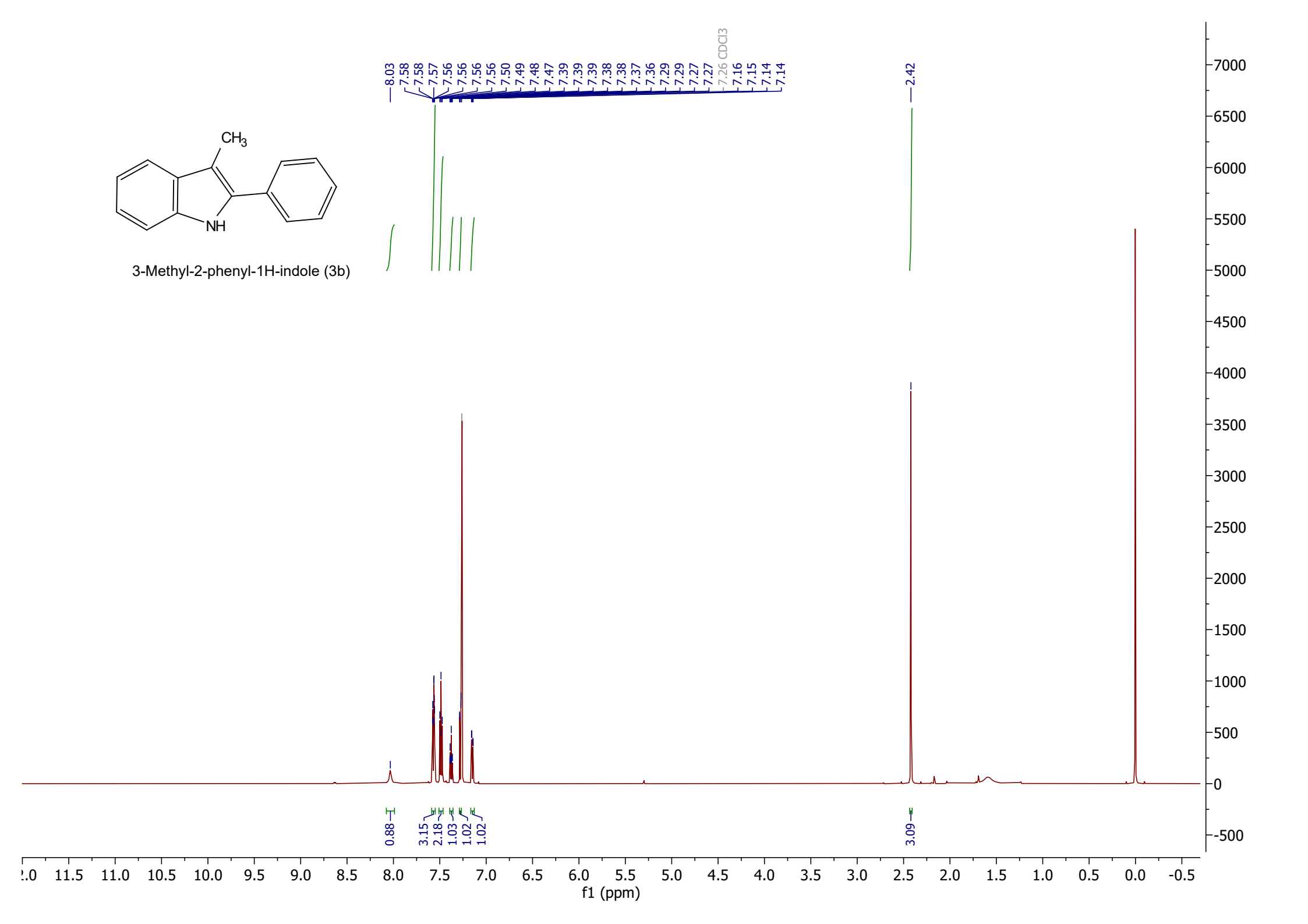
22 A. Dhakshinamoorthy and K. Pitchumani, *Appl. Catal. A Gen.*, 2005, **292**, 305–311.

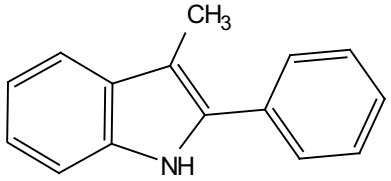
^{1}H and ^{13}C NMR Spectra for Compounds 3a-3za, 7a-7f, and 1a-10k


7.87
7.62
7.62
7.62
7.61
7.61
7.61
7.61
7.55
7.54
7.54
7.53
7.53
7.53
7.52
7.52
7.48
7.48
7.48
7.48
7.48
7.43
7.43
7.42
7.42
7.41
7.41
7.40
7.40
7.29
7.28
7.26 CDCl3
7.13
7.12
7.11
7.11
2.58
2.52
H3C
CH3
NH
3,5-Dimethyl-2-phenyl-1H-indole (3a)
0.77
1.99
2.01
0.97
1.01
0.99
0.98
3.00
2.98
f1 (ppm)

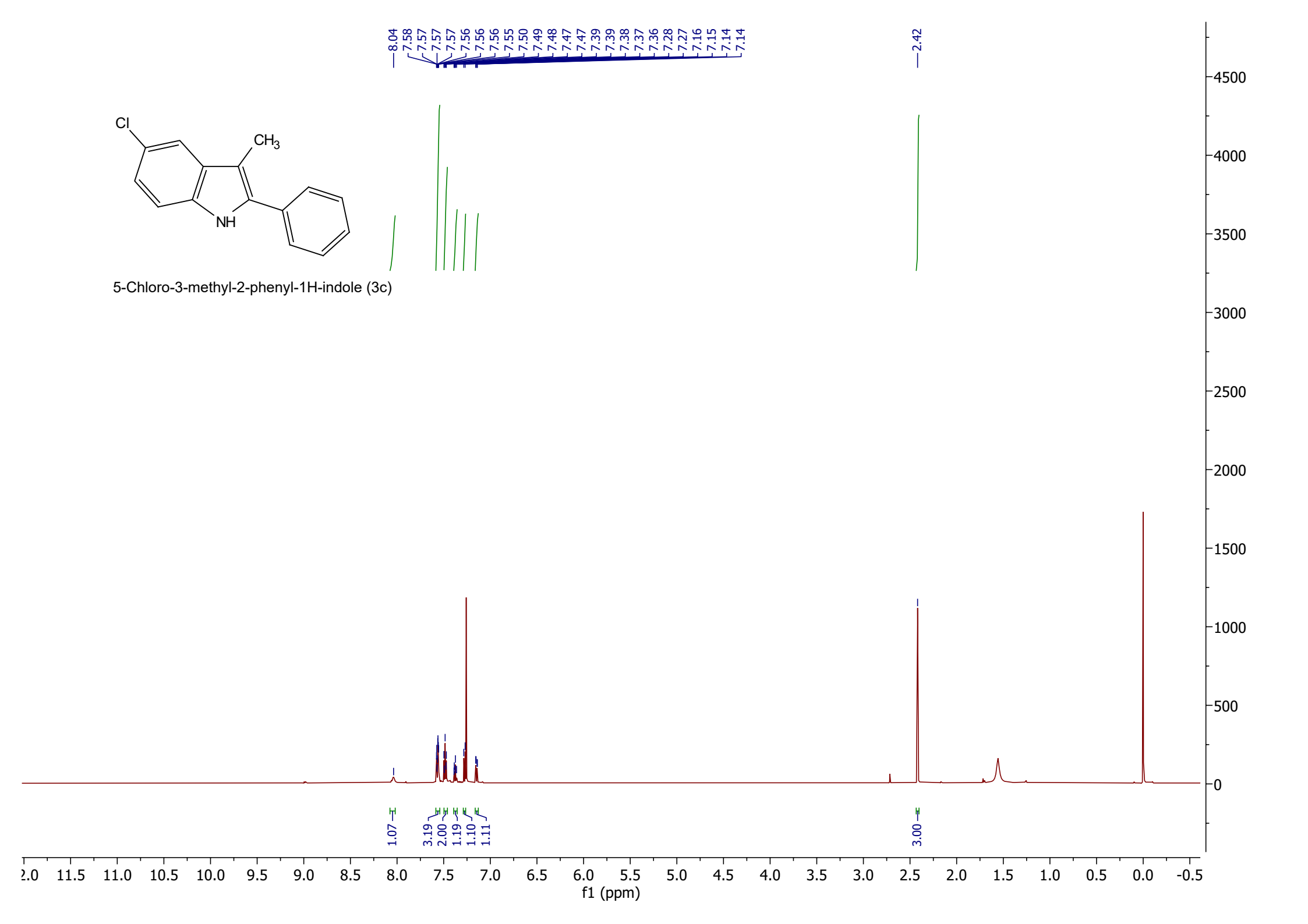


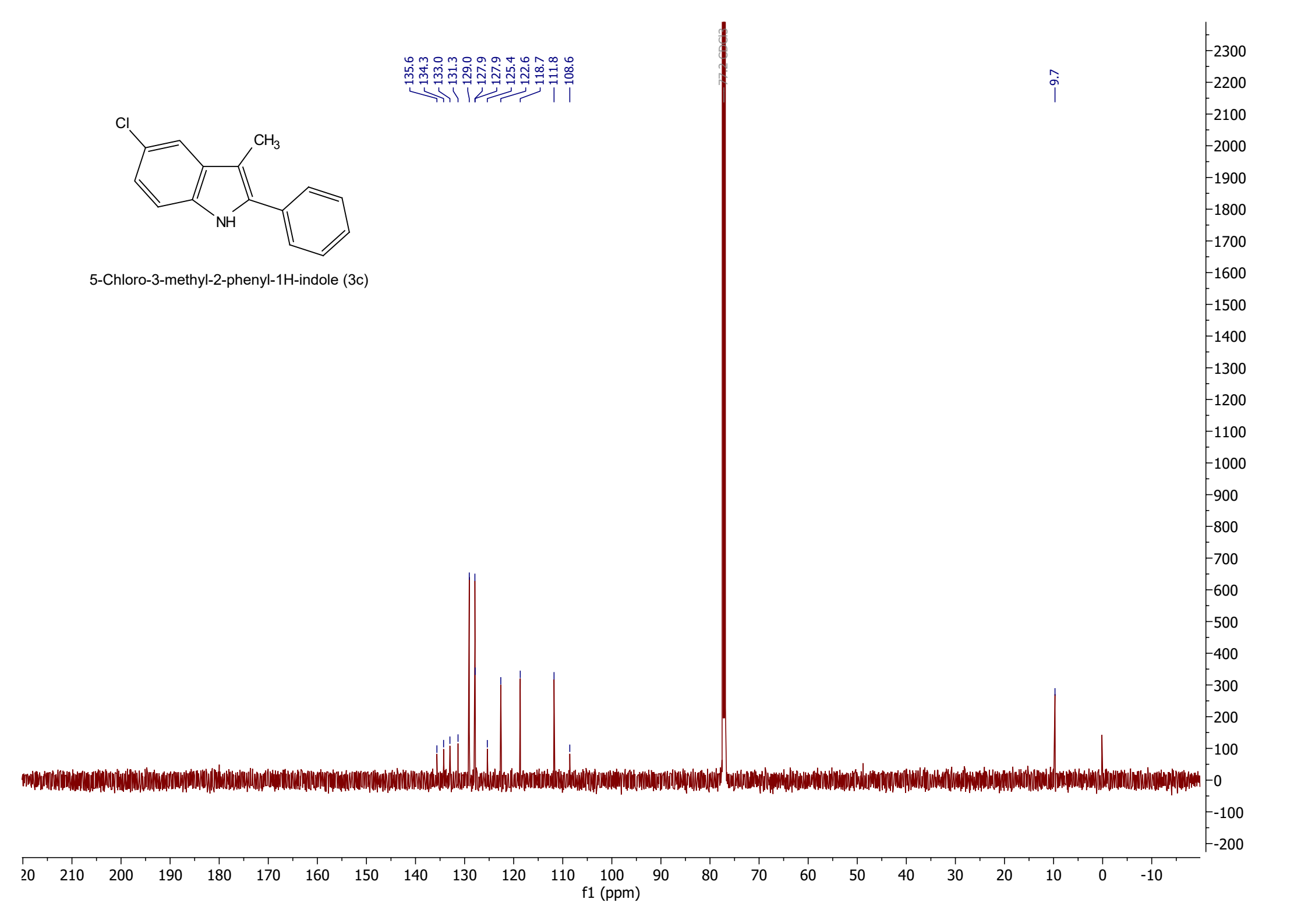
3,5-Dimethyl-2-phenyl-1H-indole (3a)

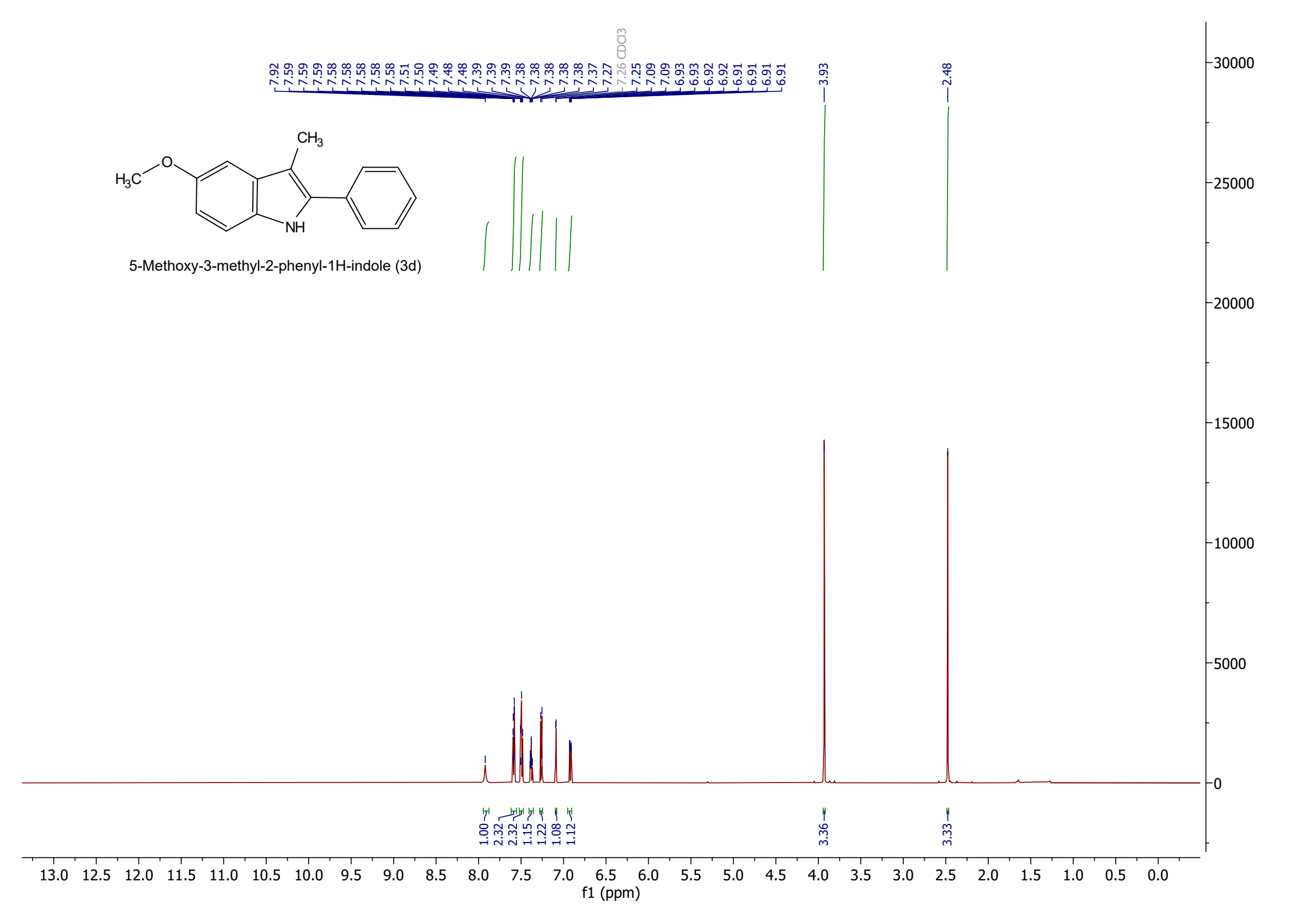

CH3
NH
3-Methyl-2-phenyl-1H-indole (3b)
8.03
7.58
7.58
7.57
7.56
7.56
7.56
7.50
7.49
7.48
7.47
7.39
7.39
7.39
7.38
7.38
7.37
7.36
7.29
7.29
7.27
7.27
7.26 CDCl3
7.16
7.15
7.14
7.14
2.42
0.88
3.15
2.18
1.03
1.02
1.02
3.09
f1 (ppm)

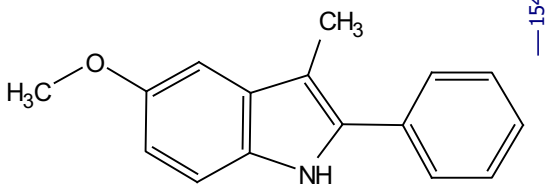


3-Methyl-2-phenyl-1H-indole (3b)

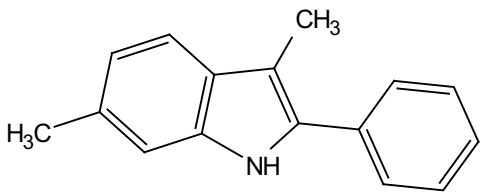

8.04
7.58
7.57
7.57
7.57
7.56
7.56
7.56
7.55
7.50
7.49
7.48
7.47
7.47
7.39
7.39
7.38
7.37
7.36
7.28
7.27
7.16
7.15
7.14
7.14
2.42
Cl
CH3
NH
5-Chloro-3-methyl-2-phenyl-1H-indole (3c)
1.07
3.19
2.00
1.19
1.10
1.11
3.00
f1 (ppm)


Cl
CH3
NH
5-Chloro-3-methyl-2-phenyl-1H-indole (3c)
135.6
134.3
133.0
131.3
129.0
127.9
127.9
125.4
122.6
118.7
111.8
108.6
77.2 CDCl3
9.7
f1 (ppm)

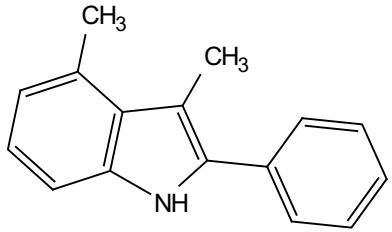

7.92
7.59
7.59
7.59
7.58
7.58
7.58
7.58
7.58
7.51
7.50
7.49
7.48
7.48
7.39
7.39
7.39
7.38
7.38
7.38
7.38
7.38
7.37
7.27
7.26 CDCl3
7.25
7.09
7.09
6.93
6.93
6.92
6.92
6.91
6.91
6.91
6.91
3.93
2.48
CH3
O
H3C
NH
5-Methoxy-3-methyl-2-phenyl-1H-indole (3d)
30000
25000
20000
15000
10000
5000
0
1.00
2.32
2.32
1.15
1.22
1.08
1.12
3.36
3.33
13.0
12.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)



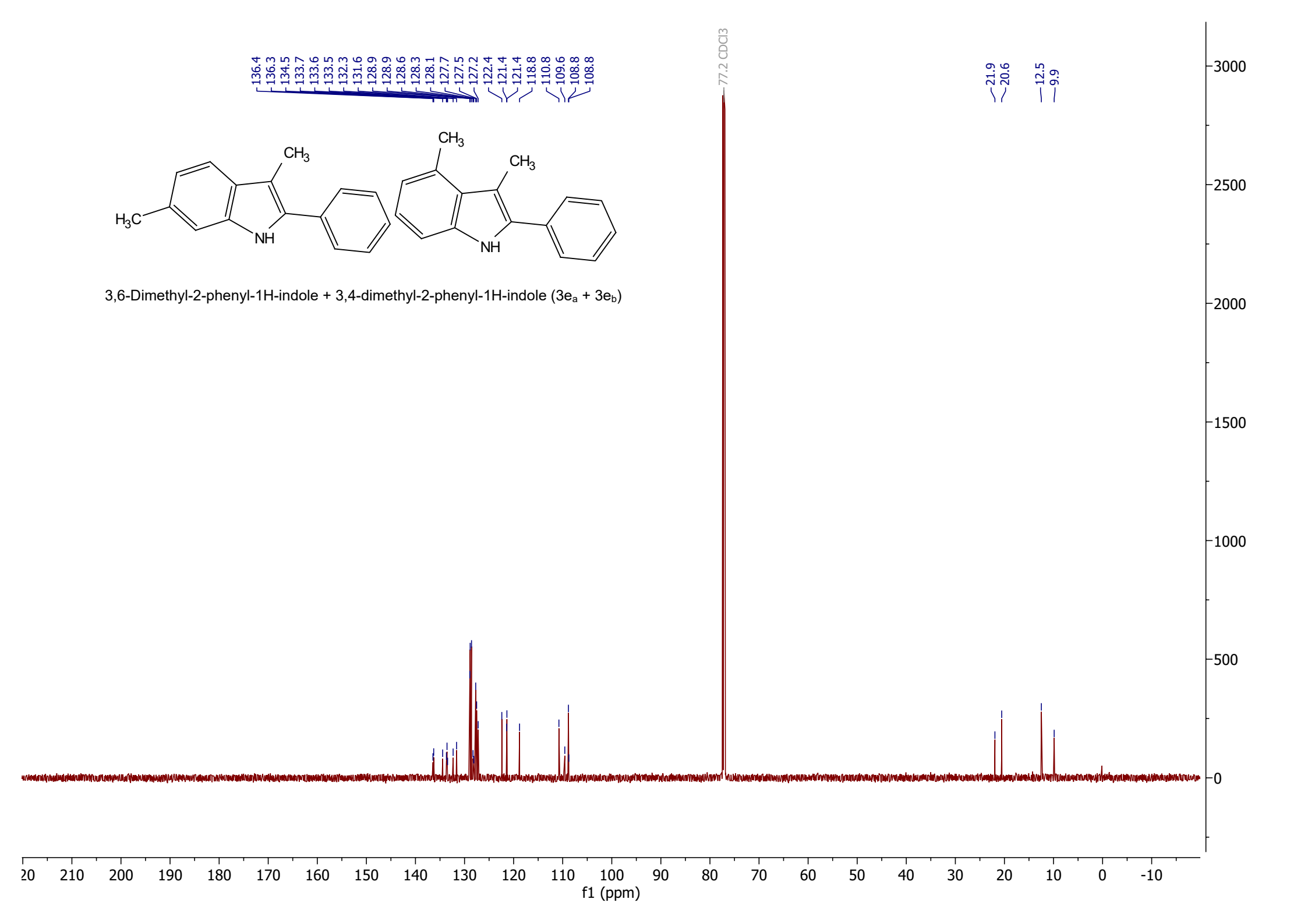
5-Methoxy-3-methyl-2-phenyl-1H-indole (3d)



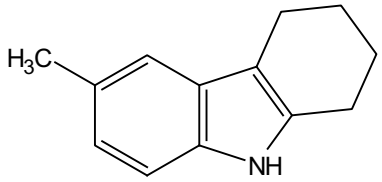
3,6-Dimethyl-2-phenyl-1H-indole ($3e_a$)



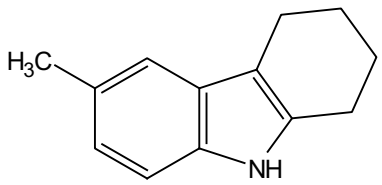
3,4-dimethyl-2-phenyl-1H-indole ($3e_b$)



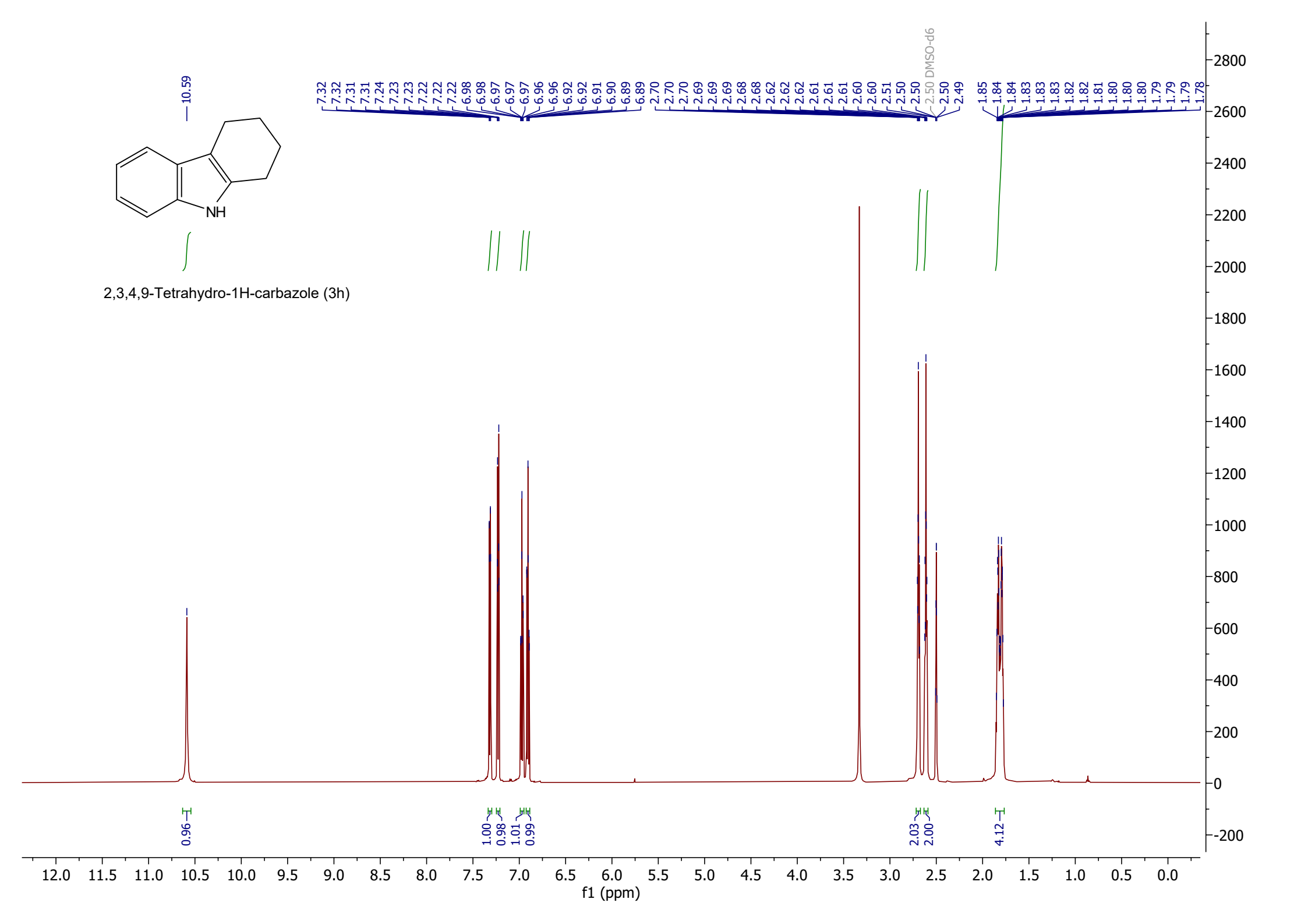
3,6-Dimethyl-2-phenyl-1H-indole + 3,4-dimethyl-2-phenyl-1H-indole ($3e_a$ + $3e_b$)

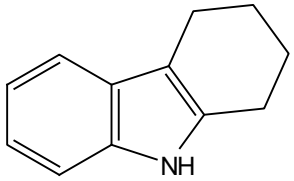


6-Methyl-2,3,4,9-tetrahydro-1H-carbazole (3g)

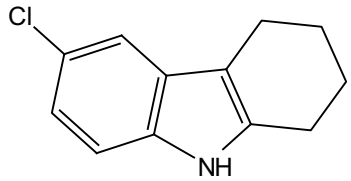


6-Methyl-2,3,4,9-tetrahydro-1H-carbazole (3g)

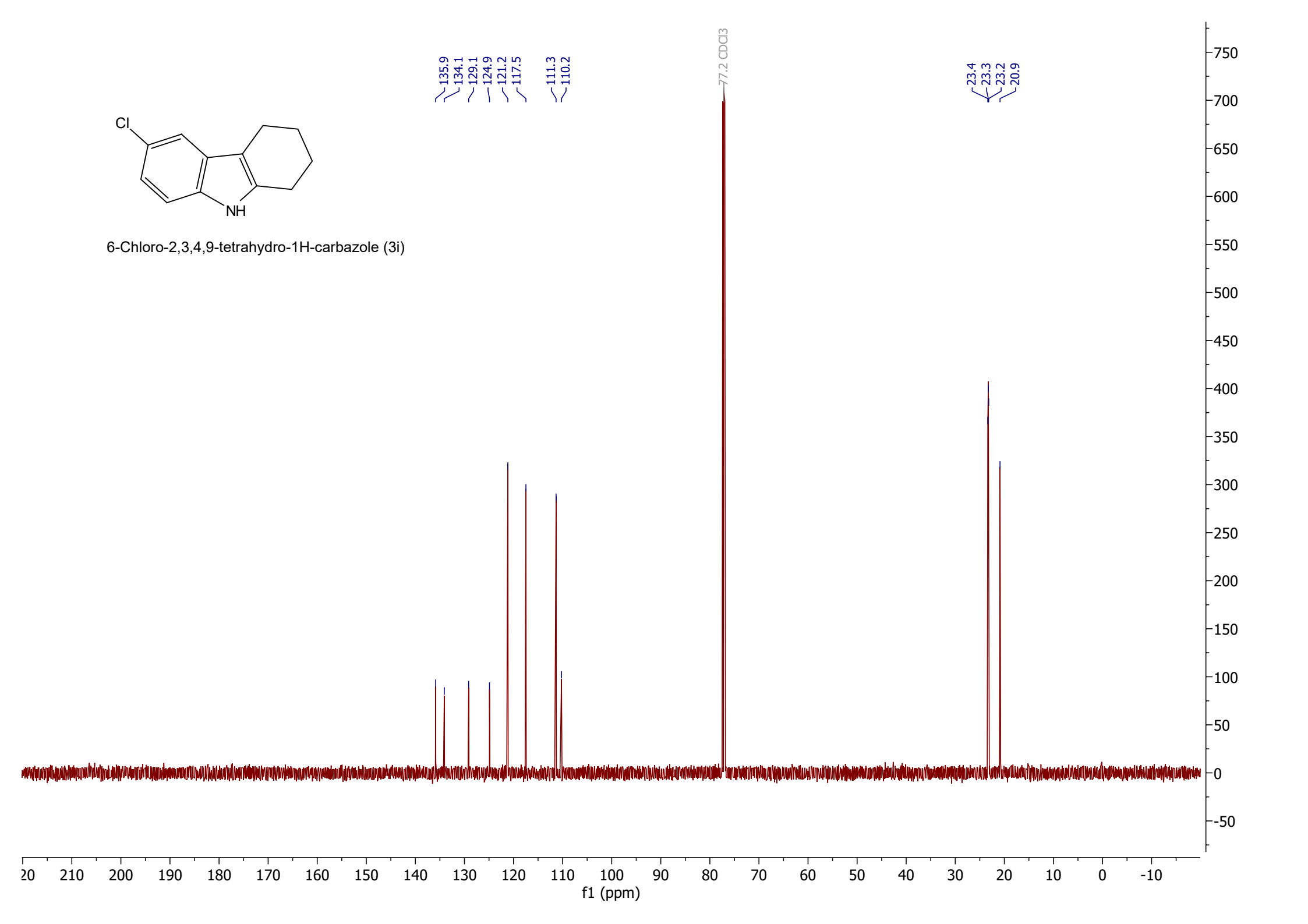

10.59
NH
2,3,4,9-Tetrahydro-1H-carbazole (3h)
DMSO-d6
f1 (ppm)

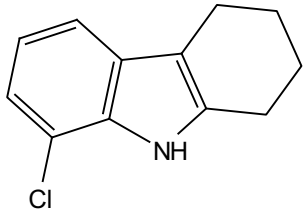


2,3,4,9-Tetrahydro-1H-carbazole (3h)

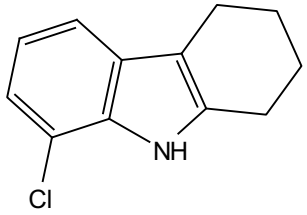


6-Chloro-2,3,4,9-tetrahydro-1H-carbazole (**3i**)

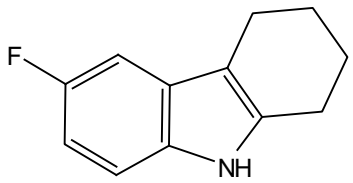

Cl
NH
6-Chloro-2,3,4,9-tetrahydro-1H-carbazole (3i)
135.9
134.1
129.1
124.9
121.2
117.5
111.3
110.2
77.2 CDCl3
23.4
23.3
23.2
20.9
f1 (ppm)



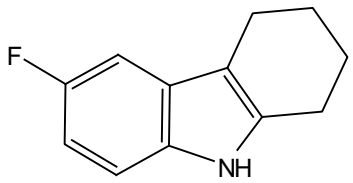
8-Chloro-2,3,4,9-tetrahydro-1H-carbazole (3j)



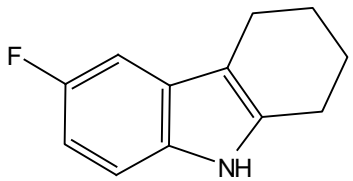
8-Chloro-2,3,4,9-tetrahydro-1H-carbazole (3j)



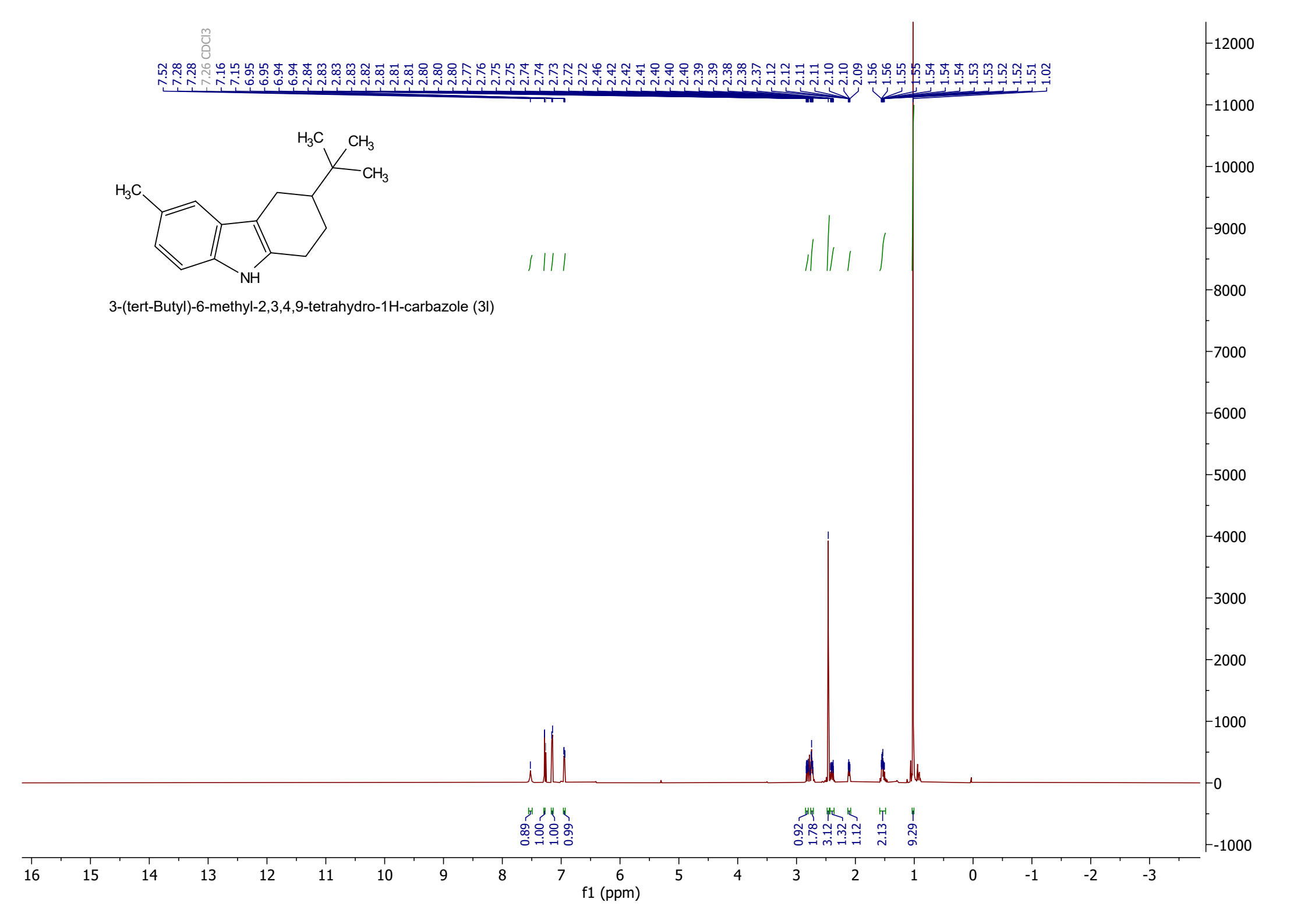
6-Fluoro-2,3,4,9-tetrahydro-1H-carbazole (3k)

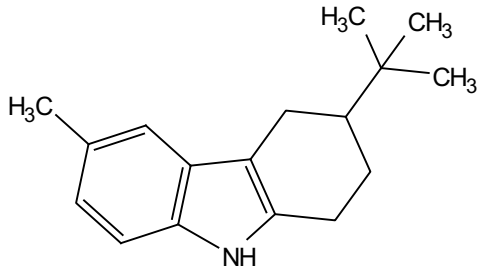


6-Fluoro-2,3,4,9-tetrahydro-1H-carbazole (3k)

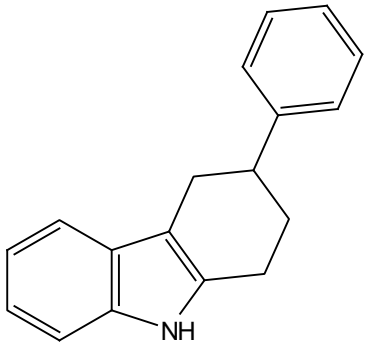


6-Fluoro-2,3,4,9-tetrahydro-1H-carbazole (3k)

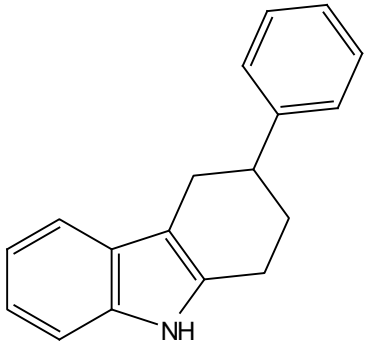

7.52 7.28 7.28 7.26 CDCl3 7.16 7.15 6.95 6.95 6.94 6.94 2.84 2.83 2.83 2.83 2.82 2.81 2.81 2.81 2.80 2.80 2.80 2.77 2.76 2.75 2.75 2.74 2.74 2.73 2.72 2.72 2.46 2.42 2.42 2.41 2.40 2.40 2.40 2.39 2.39 2.38 2.38 2.37 2.12 2.12 2.11 2.11 2.10 2.10 2.09 1.56 1.56 1.55 1.55 1.54 1.54 1.54 1.53 1.53 1.52 1.52 1.51 1.02
H3C
CH3
CH3
H3C
NH
3-(tert-Butyl)-6-methyl-2,3,4,9-tetrahydro-1H-carbazole (3l)
0.89 1.00 1.00 0.99 0.92 1.78 3.12 1.32 1.12 2.13 9.29
f1 (ppm)



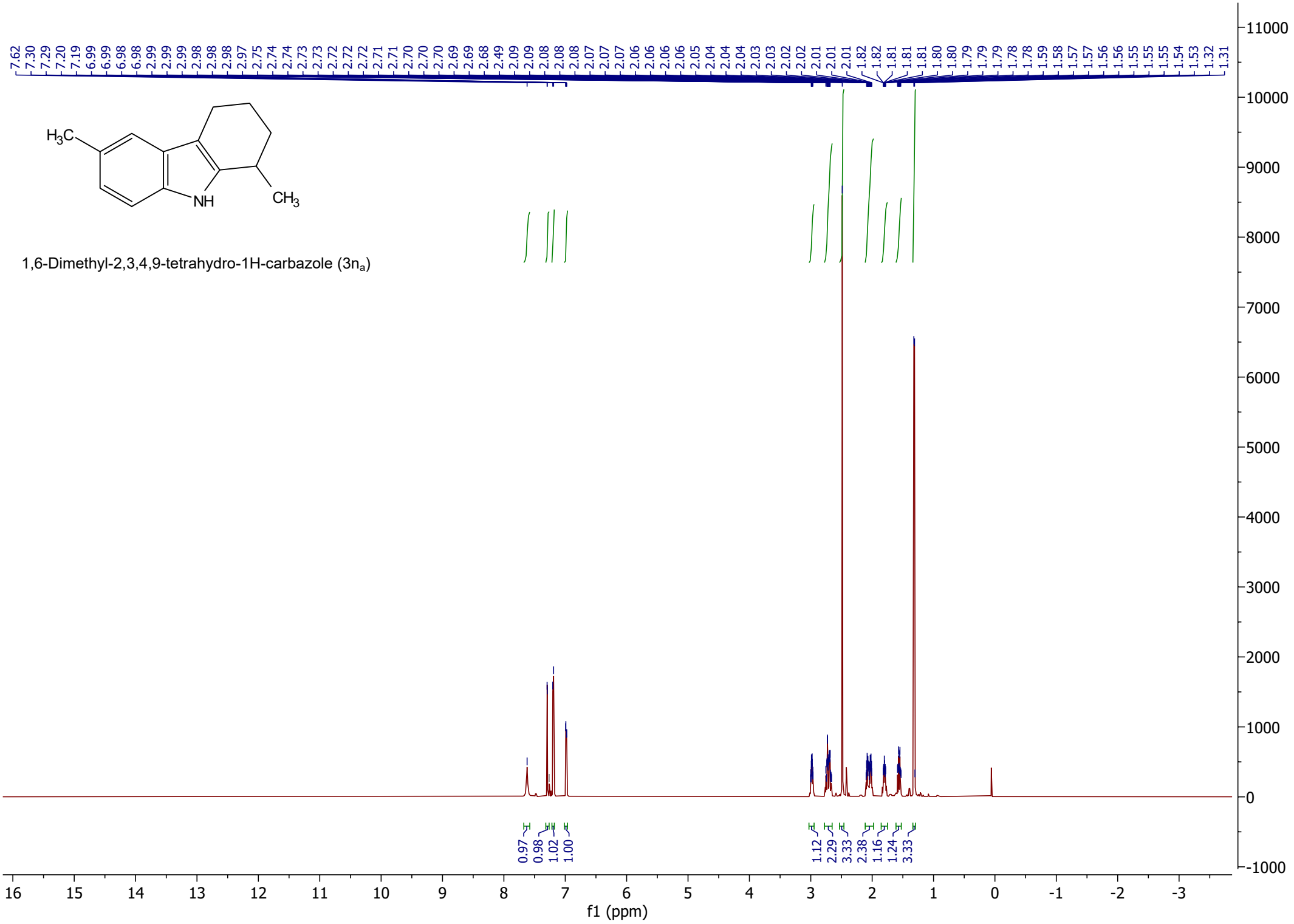
3-(tert-Butyl)-6-methyl-2,3,4,9-tetrahydro-1H-carbazole (3l)

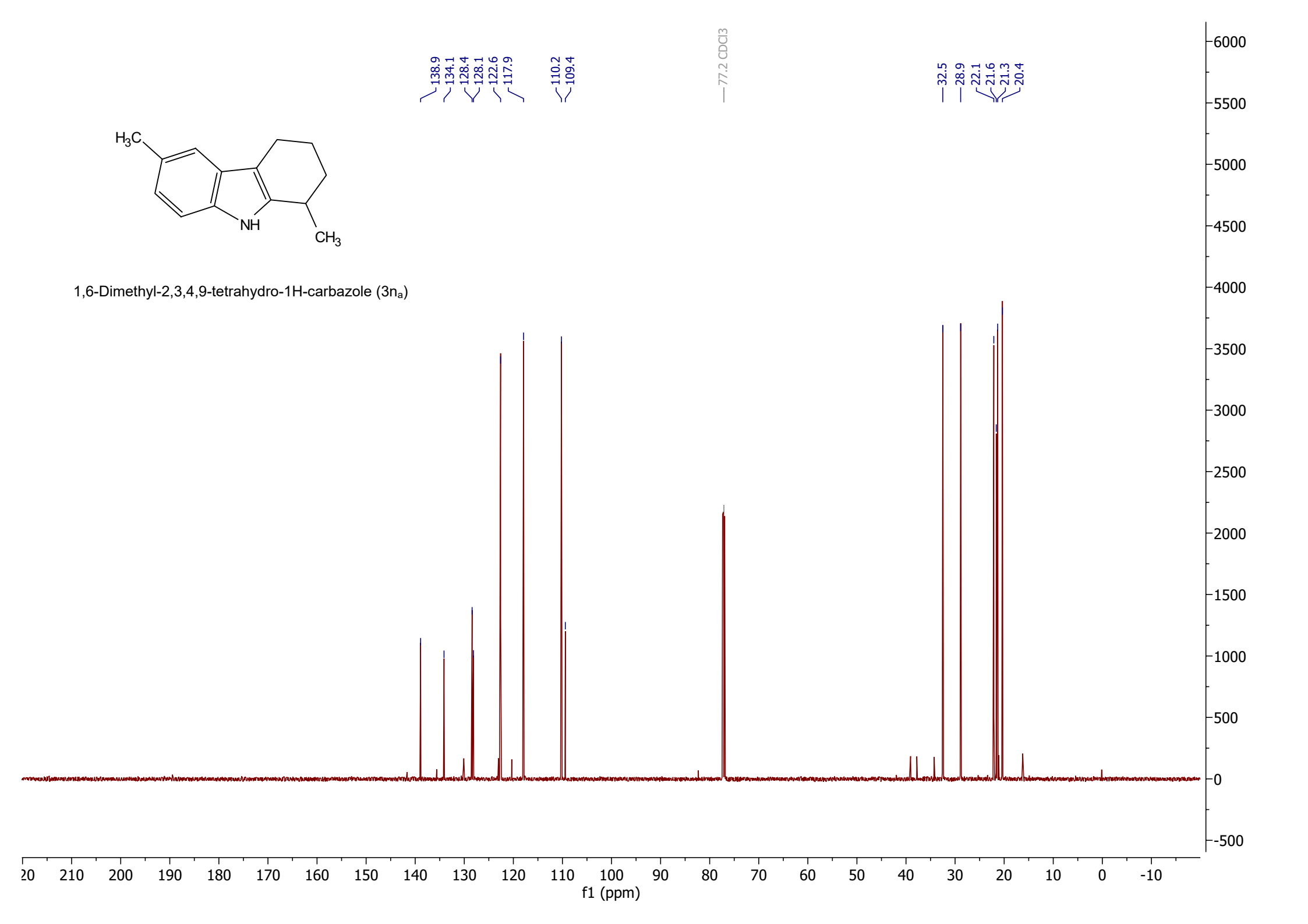


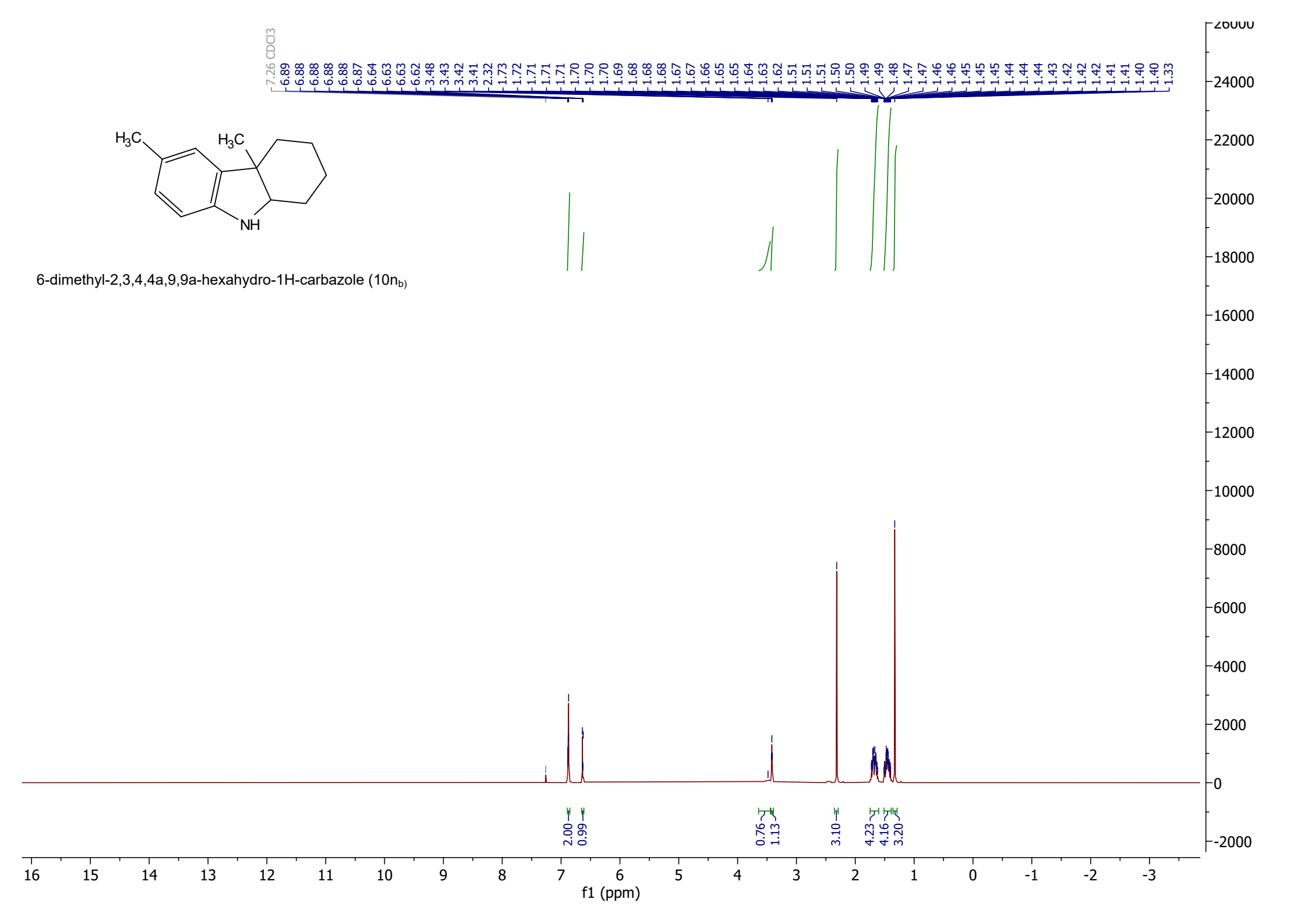
3-Phenyl-2,3,4,9-tetrahydro-1H-carbazole (3m)

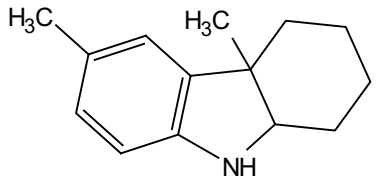


3-Phenyl-2,3,4,9-tetrahydro-1H-carbazole (3m)

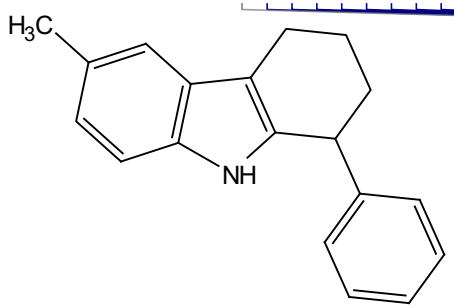

7.62 7.30 7.29 7.20 7.19 6.99 6.99 6.98 6.98 2.99 2.99 2.99 2.98 2.98 2.98 2.97 2.75 2.74 2.74 2.73 2.73 2.72 2.72 2.72 2.71 2.71 2.70 2.70 2.70 2.69 2.69 2.68 2.49 2.09 2.09 2.08 2.08 2.08 2.07 2.07 2.07 2.06 2.06 2.06 2.05 2.04 2.04 2.04 2.03 2.03 2.02 2.02 2.01 2.01 2.01 1.82 1.82 1.81 1.81 1.81 1.80 1.80 1.79 1.79 1.79 1.78 1.78 1.59 1.58 1.57 1.57 1.56 1.56 1.55 1.55 1.55 1.54 1.53 1.32 1.31
H3C
NH
CH3
1,6-Dimethyl-2,3,4,9-tetrahydro-1H-carbazole (3na)
0.97 0.98 1.02 1.00
1.12 2.29 3.33 2.38 1.16 1.24 3.33
11000 10000 9000 8000 7000 6000 5000 4000 3000 2000 1000 0 -1000
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3
f1 (ppm)


138.9
134.1
128.4
128.1
122.6
117.9
110.2
109.4
77.2 CDCl3
32.5
28.9
22.1
21.6
21.3
20.4
H3C
NH
CH3
1,6-Dimethyl-2,3,4,9-tetrahydro-1H-carbazole (3na)
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

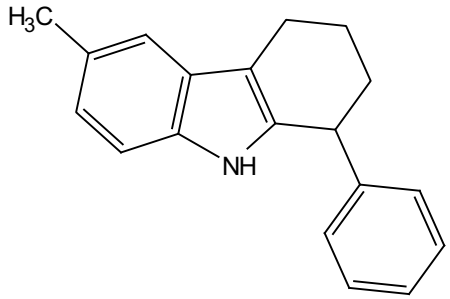

7.26 CDCl3
6.89 6.88 6.88 6.88 6.88 6.87 6.64 6.63 6.63 6.62 3.48 3.43 3.42 3.41 2.32 1.73 1.72 1.71 1.71 1.71 1.70 1.70 1.70 1.69 1.68 1.68 1.68 1.67 1.67 1.66 1.65 1.65 1.64 1.63 1.62 1.51 1.51 1.51 1.50 1.50 1.49 1.49 1.48 1.47 1.47 1.46 1.46 1.45 1.45 1.45 1.44 1.44 1.44 1.43 1.42 1.42 1.42 1.41 1.41 1.40 1.40 1.33
H3C
H3C
NH
6-dimethyl-2,3,4,4a,9,9a-hexahydro-1H-carbazole (10nb)
2.00
0.99
0.76
1.13
3.10
4.23
4.16
3.20
f1 (ppm)



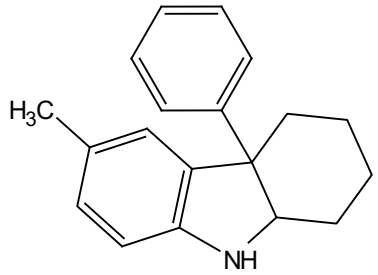
6-dimethyl-2,3,4,4a,9,9a-hexahydro-1H-carbazole (10n_b)



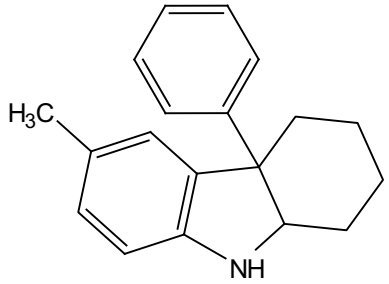
6-Methyl-1-phenyl-2,3,4,9-tetrahydro-1H-carbazole ($3o_{a)}$.



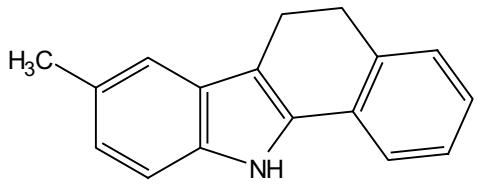
6-Methyl-1-phenyl-2,3,4,9-tetrahydro-1H-carbazole ($3o_a$).



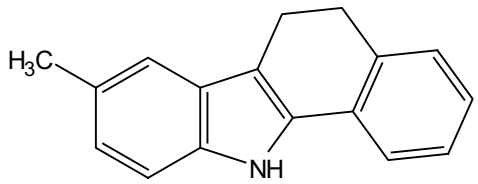
6-Methyl-4a-phenyl-2,3,4,4a,9,9a-hexahydro-1H-carbazole ($10o_b$)



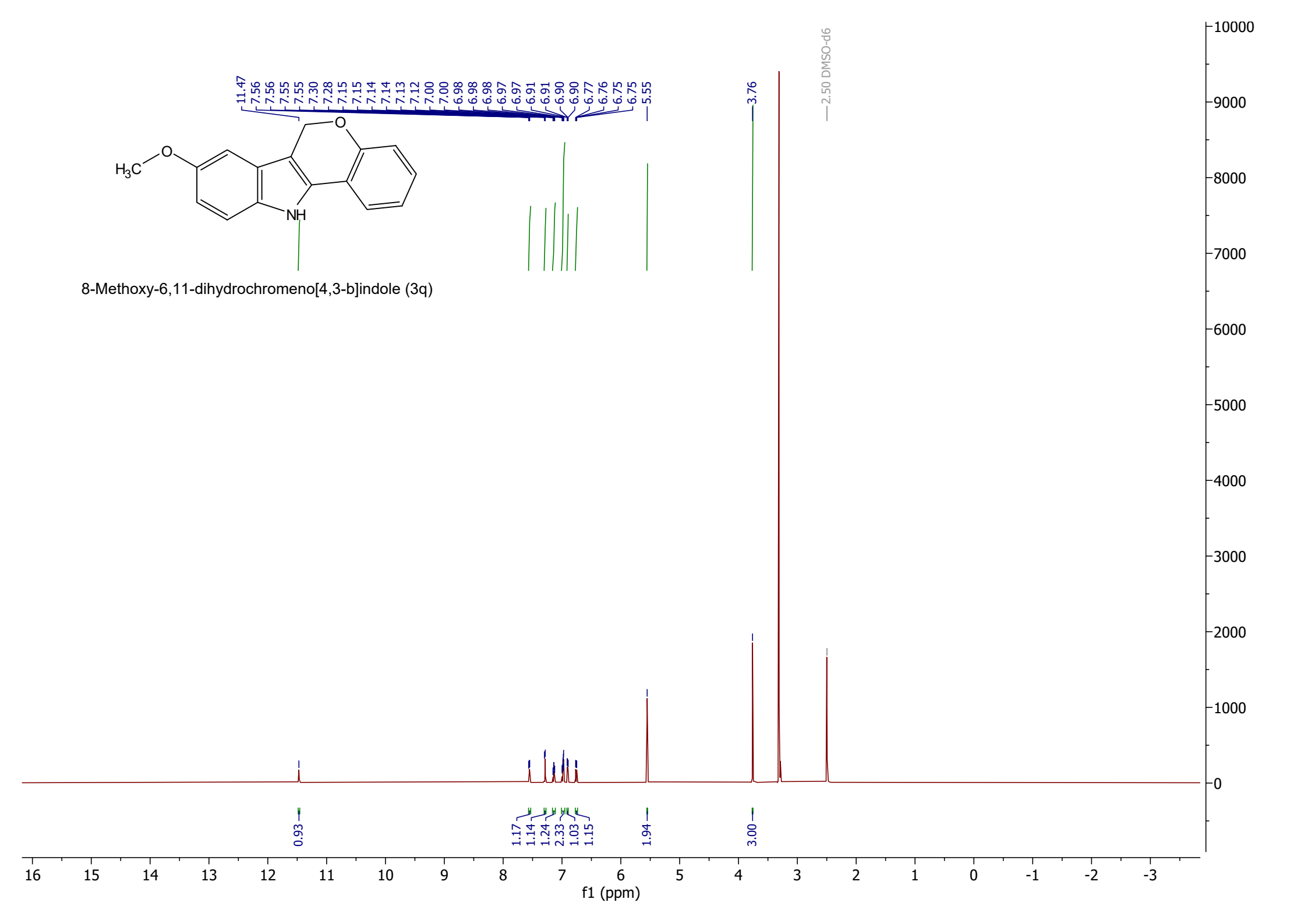
6-Methyl-4a-phenyl-2,3,4,4a,9,9a-hexahydro-1H-carbazole (10o$_b$)

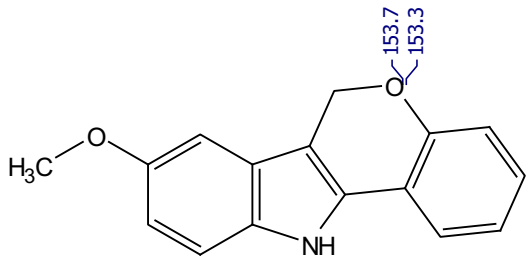


8-Methyl-6,11-dihydro-5H-benzo[a]carbazole (3p)

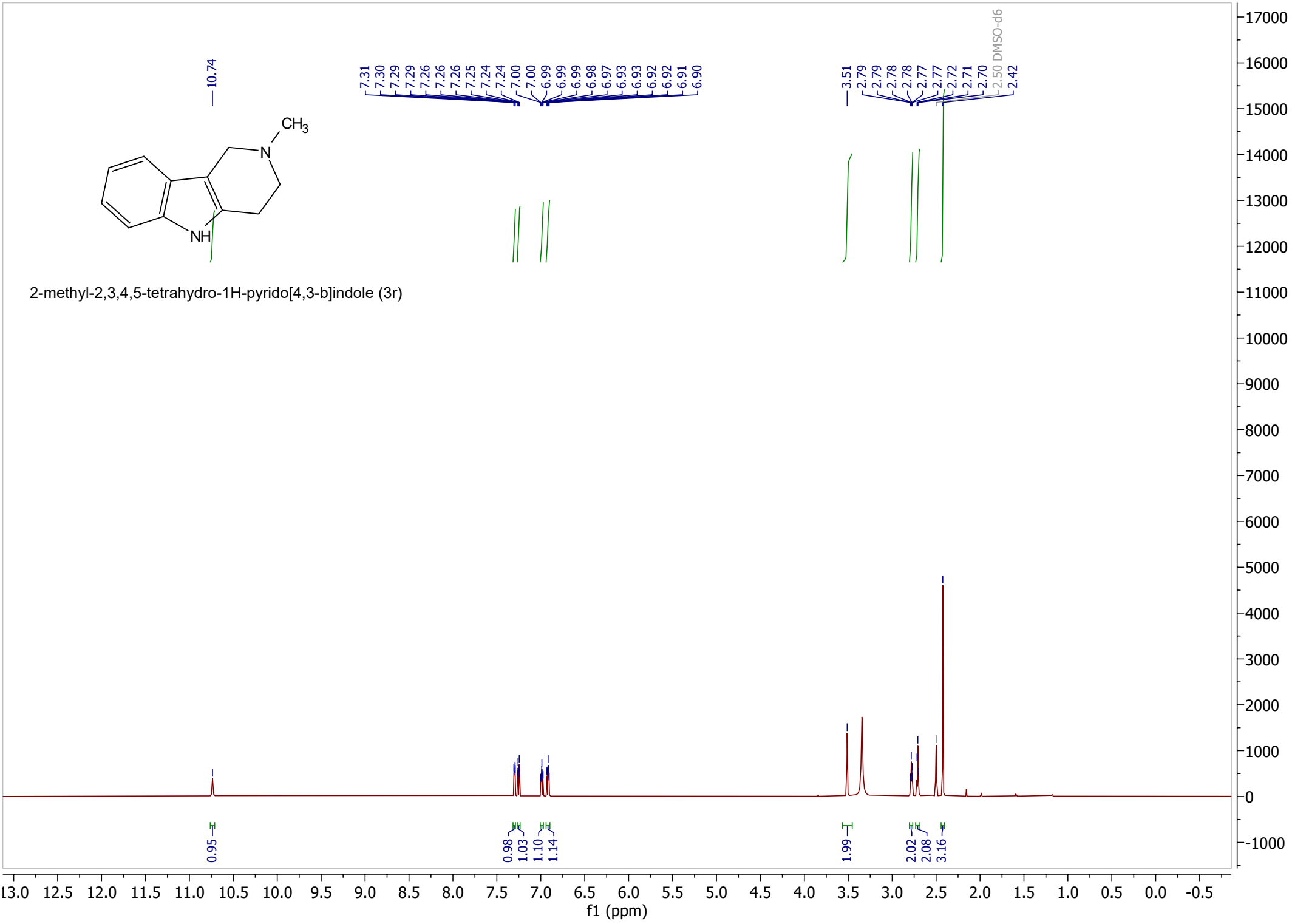


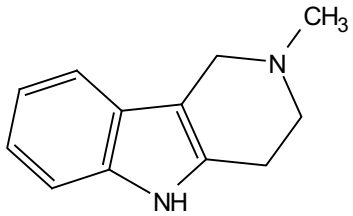
8-Methyl-6,11-dihydro-5H-benzo[a]carbazole (3p)


11.47
7.56
7.56
7.55
7.55
7.30
7.28
7.15
7.15
7.14
7.14
7.13
7.12
7.00
7.00
6.98
6.98
6.98
6.97
6.97
6.91
6.91
6.90
6.90
6.77
6.76
6.75
6.75
5.55
3.76
2.50 DMSO-d6
O
O
H3C
NH
8-Methoxy-6,11-dihydrochromeno[4,3-b]indole (3q)
0.93
1.17
1.14
1.24
2.33
1.03
1.15
1.94
3.00
f1 (ppm)

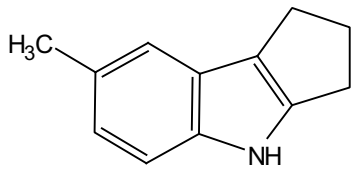


8-Methoxy-6,11-dihydrochromeno[4,3-b]indole (3q)

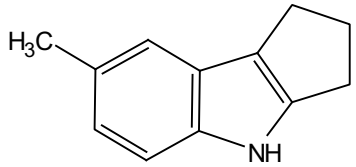

10.74
7.31
7.30
7.29
7.29
7.26
7.26
7.26
7.25
7.24
7.24
7.00
7.00
6.99
6.99
6.99
6.98
6.97
6.93
6.93
6.92
6.92
6.91
6.90
3.51
2.79
2.79
2.78
2.78
2.77
2.77
2.72
2.71
2.70
2.50 DMSO-d6
2.42
CH3
N
NH
2-methyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (3r)
0.95
0.98
1.03
1.10
1.14
1.99
2.02
2.08
3.16
f1 (ppm)



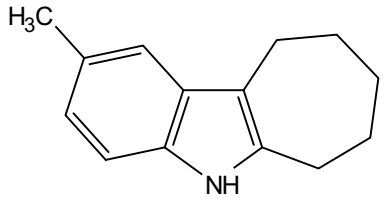
2-methyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (3r)



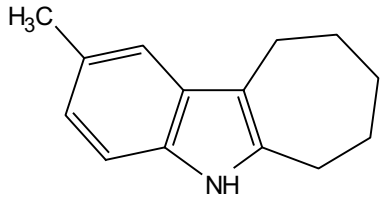
7-Methyl-1,2,3,4-tetrahydrocyclopenta[b]indole (3s)



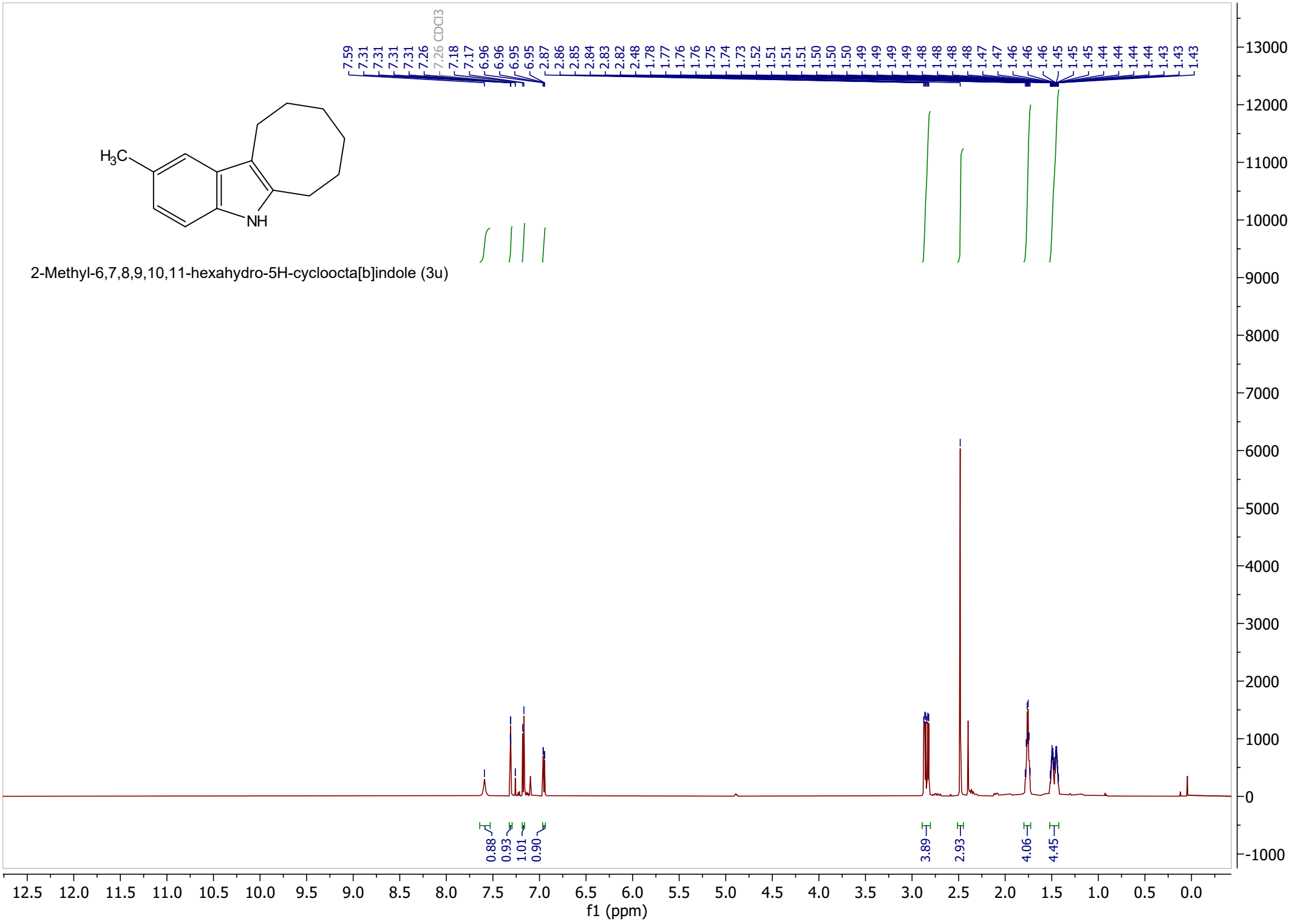
7-Methyl-1,2,3,4-tetrahydrocyclopenta[b]indole (3s).

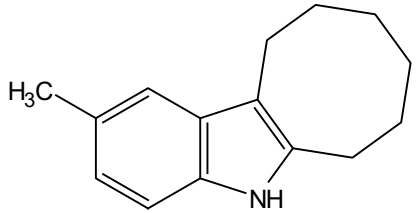


2-Methyl-5,6,7,8,9,10-Hexahydrocyclohepta[b]indole (3t)

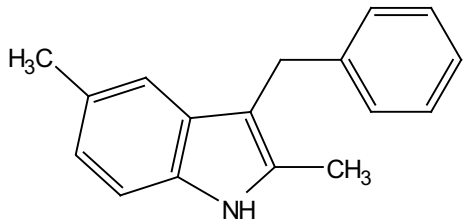


2-Methyl-5,6,7,8,9,10-Hexahydrocyclohepta[b]indole (3t)

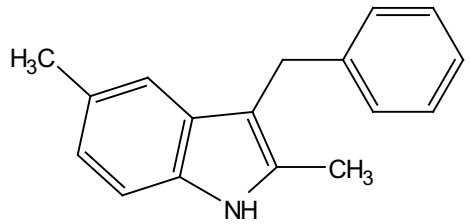

7.59 7.31 7.31 7.31 7.31 7.26 7.26 CDCl3 7.18 7.17 6.96 6.96 6.95 6.95 2.87 2.86 2.85 2.84 2.83 2.82 2.48 1.78 1.77 1.76 1.76 1.75 1.74 1.73 1.52 1.51 1.51 1.51 1.50 1.50 1.49 1.49 1.49 1.49 1.48 1.48 1.48 1.48 1.47 1.47 1.46 1.46 1.46 1.45 1.45 1.45 1.44 1.44 1.44 1.44 1.43 1.43 1.43
H3C
NH
2-Methyl-6,7,8,9,10,11-hexahydro-5H-cycloocta[b]indole (3u)
0.88 0.93 1.01 0.90 3.89 2.93 4.06 4.45
f1 (ppm)



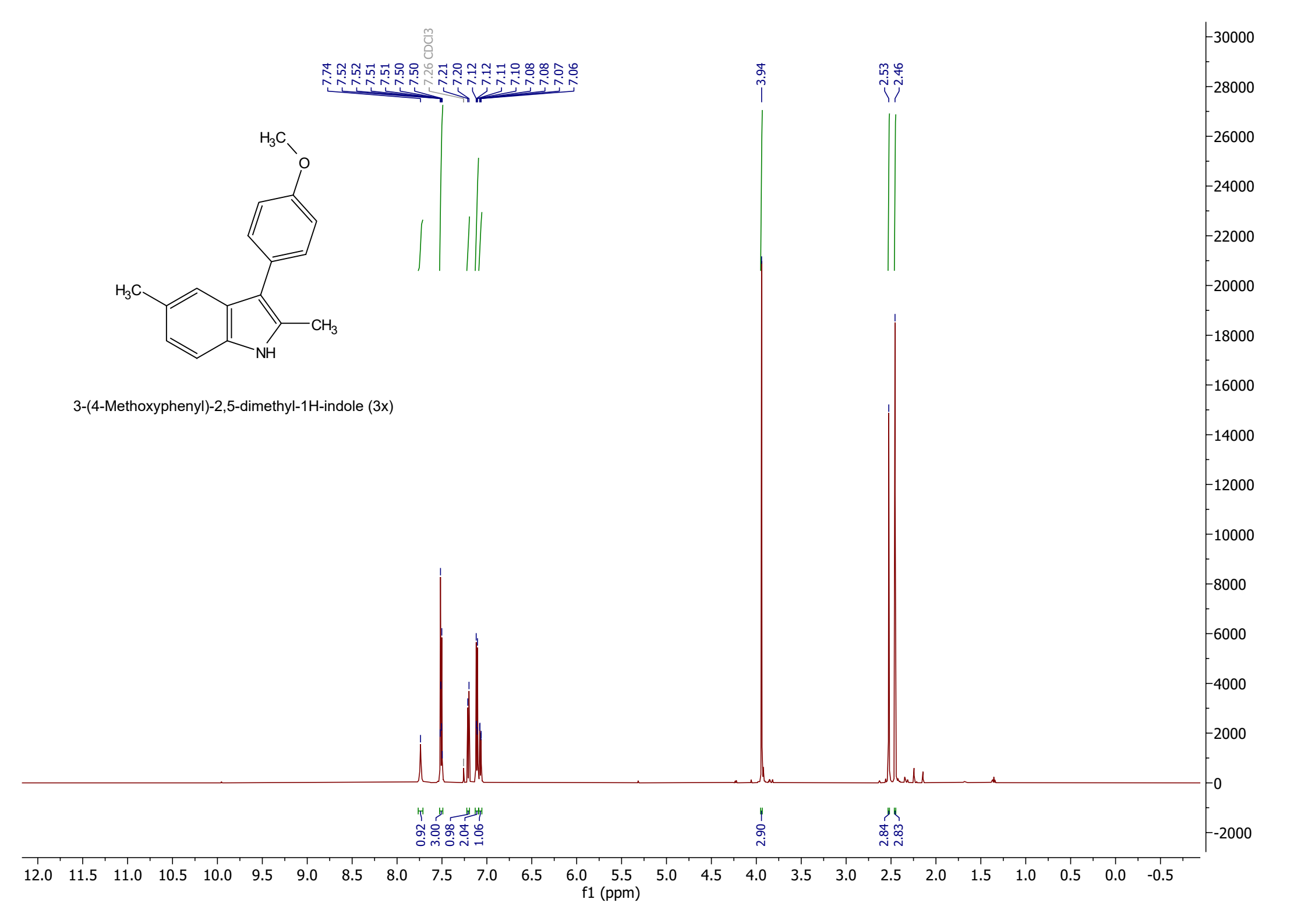
2-Methyl-6,7,8,9,10,11-hexahydro-5H-cycloocta[b]indole (3u)

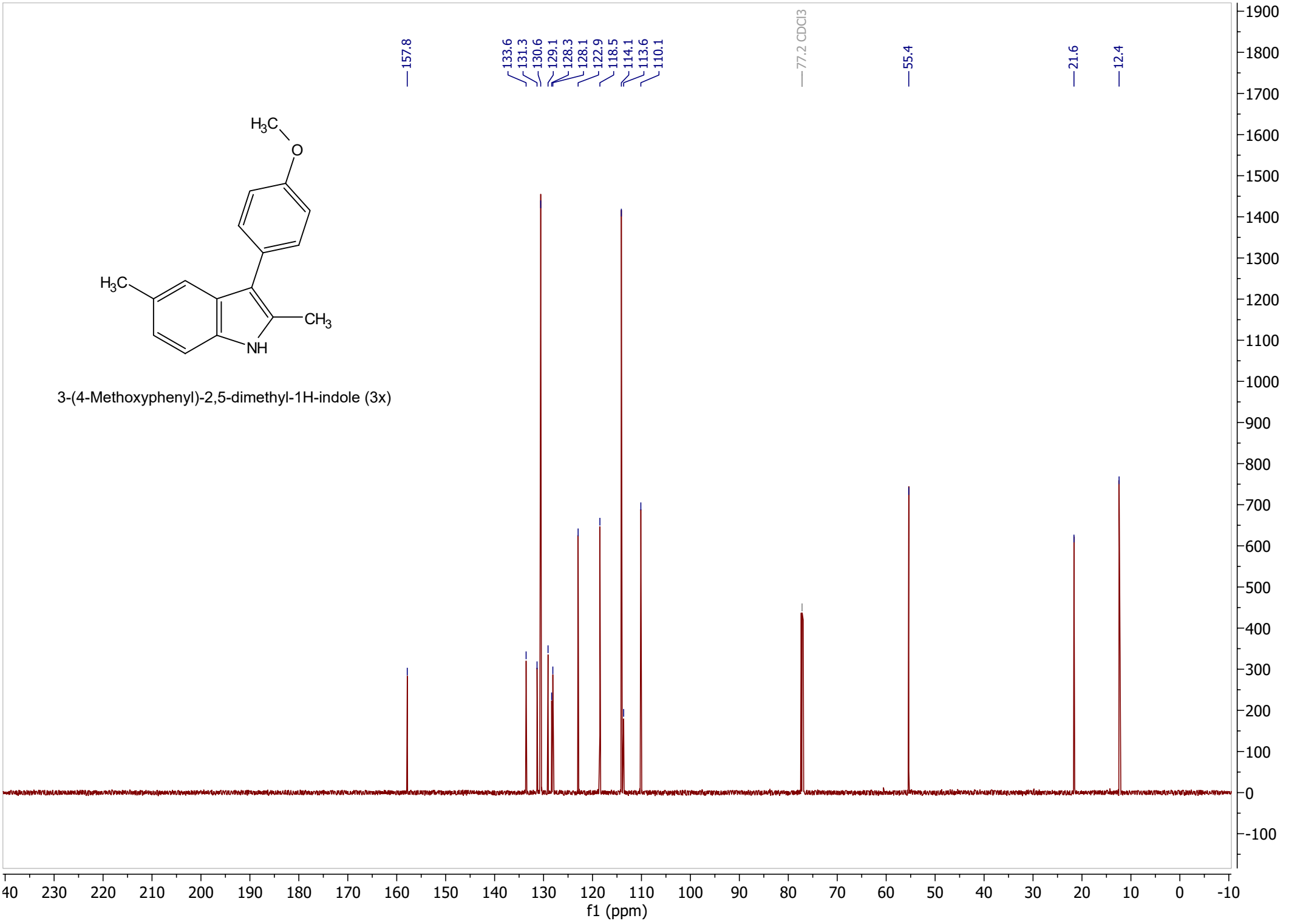


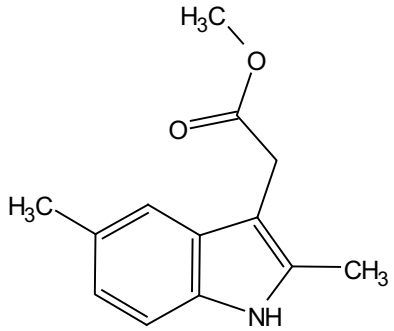
3-Benzyl-2,5-dimethyl-1H-indole (3w).



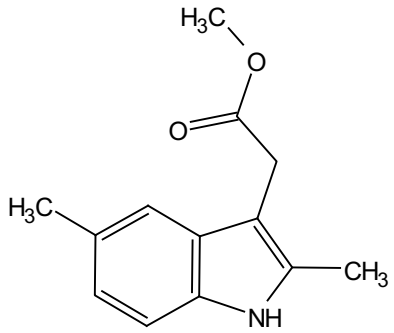
3-Benzyl-2,5-dimethyl-1H-indole (3w)


7.74
7.52
7.52
7.51
7.51
7.50
7.50
7.26 CDCl3
7.21
7.20
7.12
7.12
7.11
7.10
7.08
7.08
7.07
7.06
3.94
2.53
2.46
H3C
O
H3C
CH3
NH
3-(4-Methoxyphenyl)-2,5-dimethyl-1H-indole (3x)
0.92
3.00
0.98
2.04
1.06
2.90
2.84
2.83
f1 (ppm)

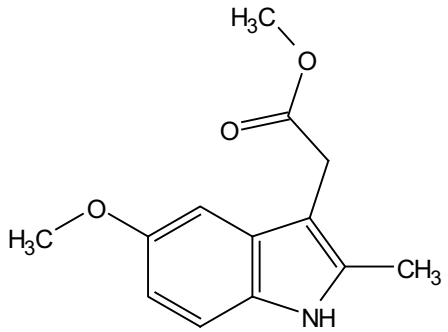

157.8
133.6
131.3
130.6
129.1
128.3
128.1
122.9
118.5
114.1
113.6
110.1
77.2 CDCl3
55.4
21.6
12.4
H3C
O
H3C
CH3
NH
3-(4-Methoxyphenyl)-2,5-dimethyl-1H-indole (3x)
f1 (ppm)



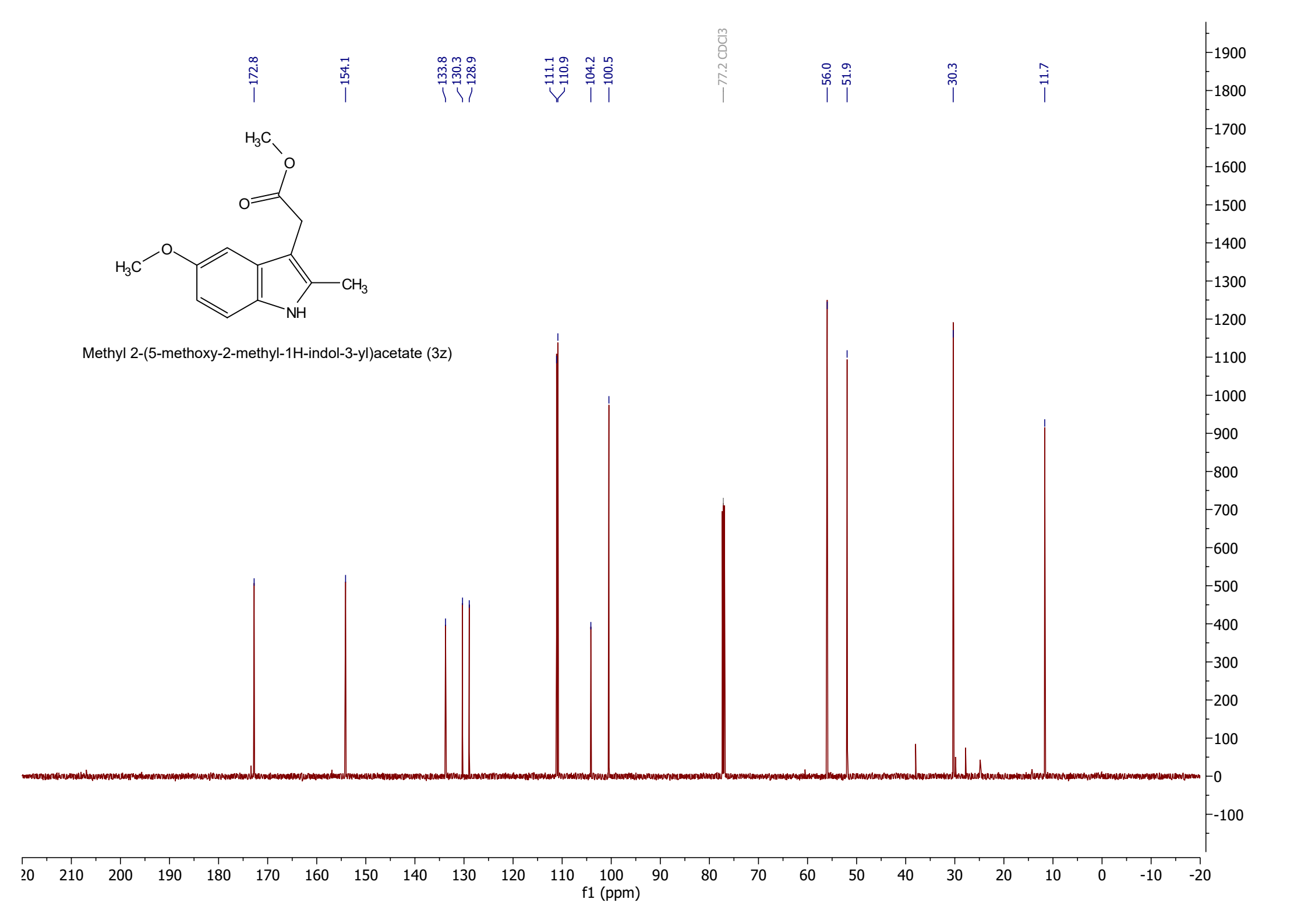
Methyl 2-(2,5-dimethyl-1H-indol-3-yl)acetate (3y)

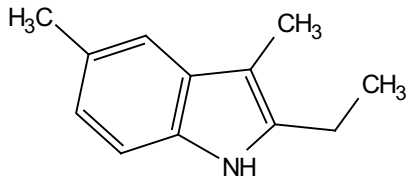


Methyl 2-(2,5-dimethyl-1H-indol-3-yl)acetate (3y)

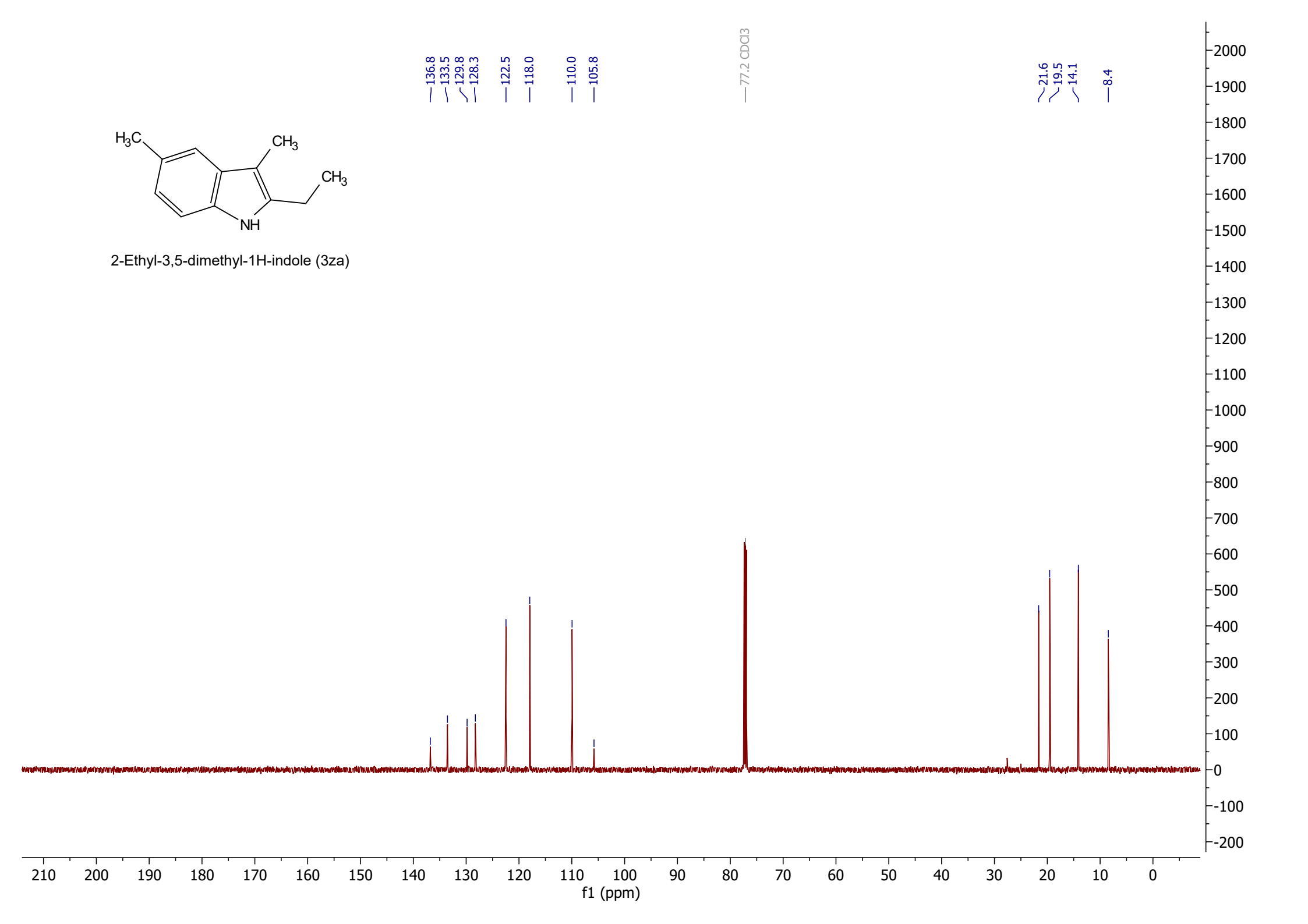


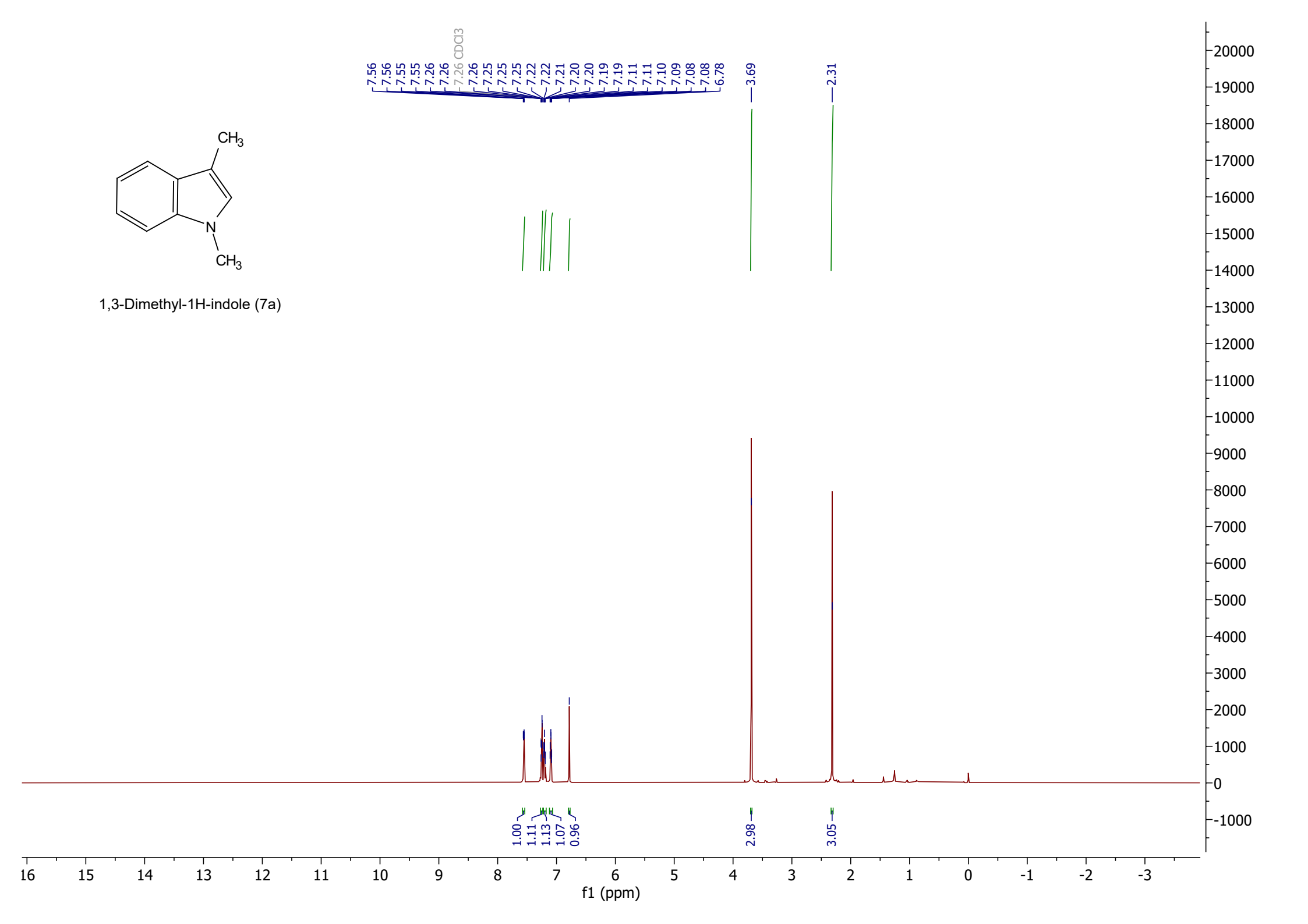
Methyl 2-(5-methoxy-2-methyl-1H-indol-3-yl)acetate (3z)

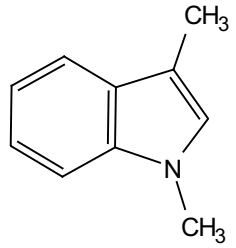

172.8
154.1
133.8
130.3
128.9
111.1
110.9
104.2
100.5
77.2 CDCl3
56.0
51.9
30.3
11.7
H3C
O
O
H3C
O
CH3
NH
Methyl 2-(5-methoxy-2-methyl-1H-indol-3-yl)acetate (3z)
f1 (ppm)



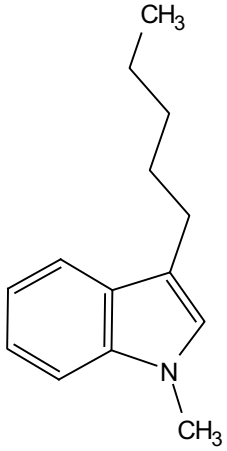
2-Ethyl-3,5-dimethyl-1H-indole (3za)


136.8
133.5
129.8
128.3
122.5
118.0
110.0
105.8
77.2 CDCl3
21.6
19.5
14.1
8.4
H3C
CH3
CH3
NH
2-Ethyl-3,5-dimethyl-1H-indole (3za)
f1 (ppm)

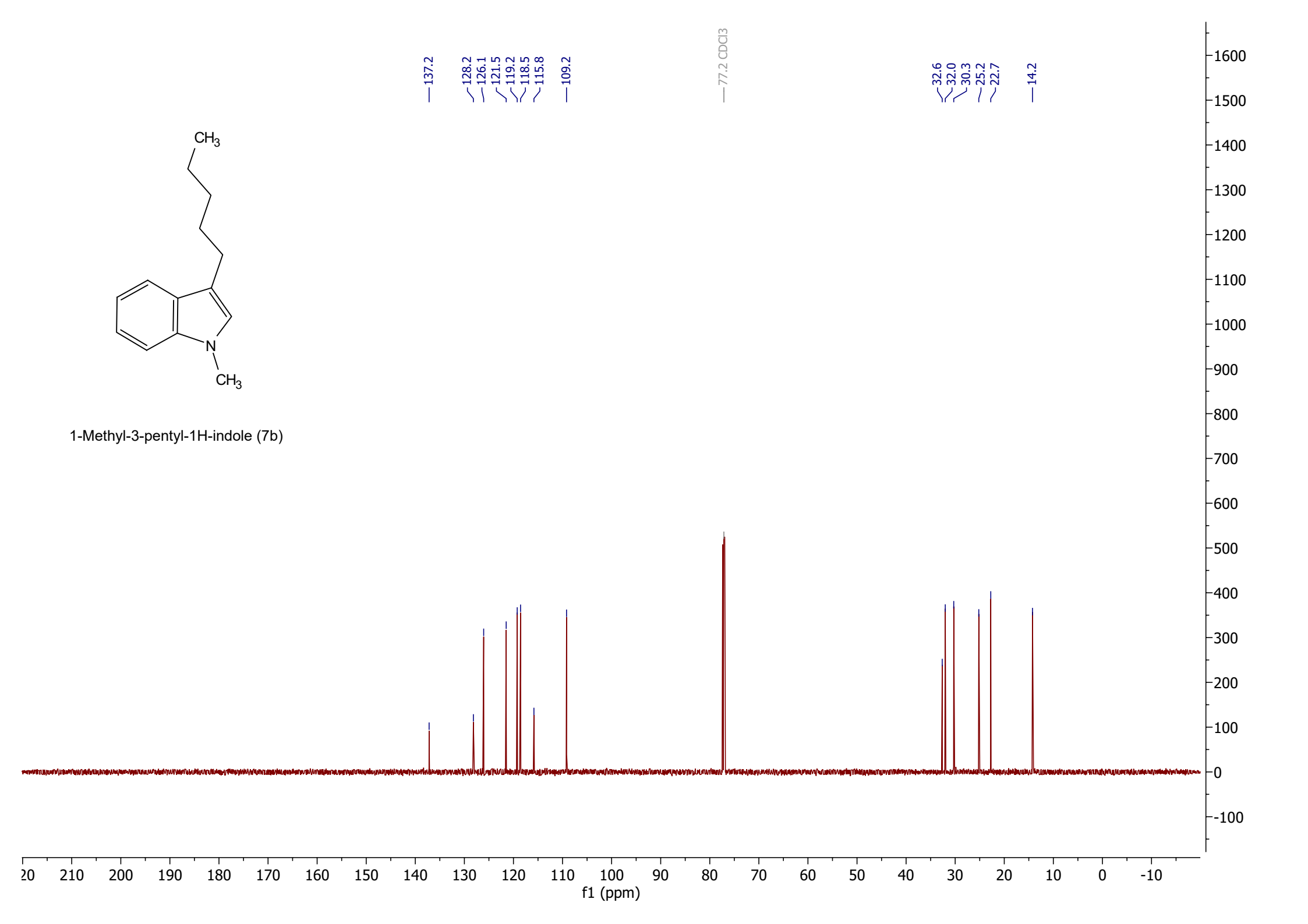

CH3
N
CH3
1,3-Dimethyl-1H-indole (7a)
7.56
7.56
7.55
7.55
7.26
7.26
7.26 CDCl3
7.26
7.25
7.25
7.25
7.22
7.22
7.21
7.20
7.20
7.19
7.19
7.11
7.11
7.10
7.09
7.08
7.08
6.78
3.69
2.31
1.00
1.11
1.13
1.07
0.96
2.98
3.05
f1 (ppm)

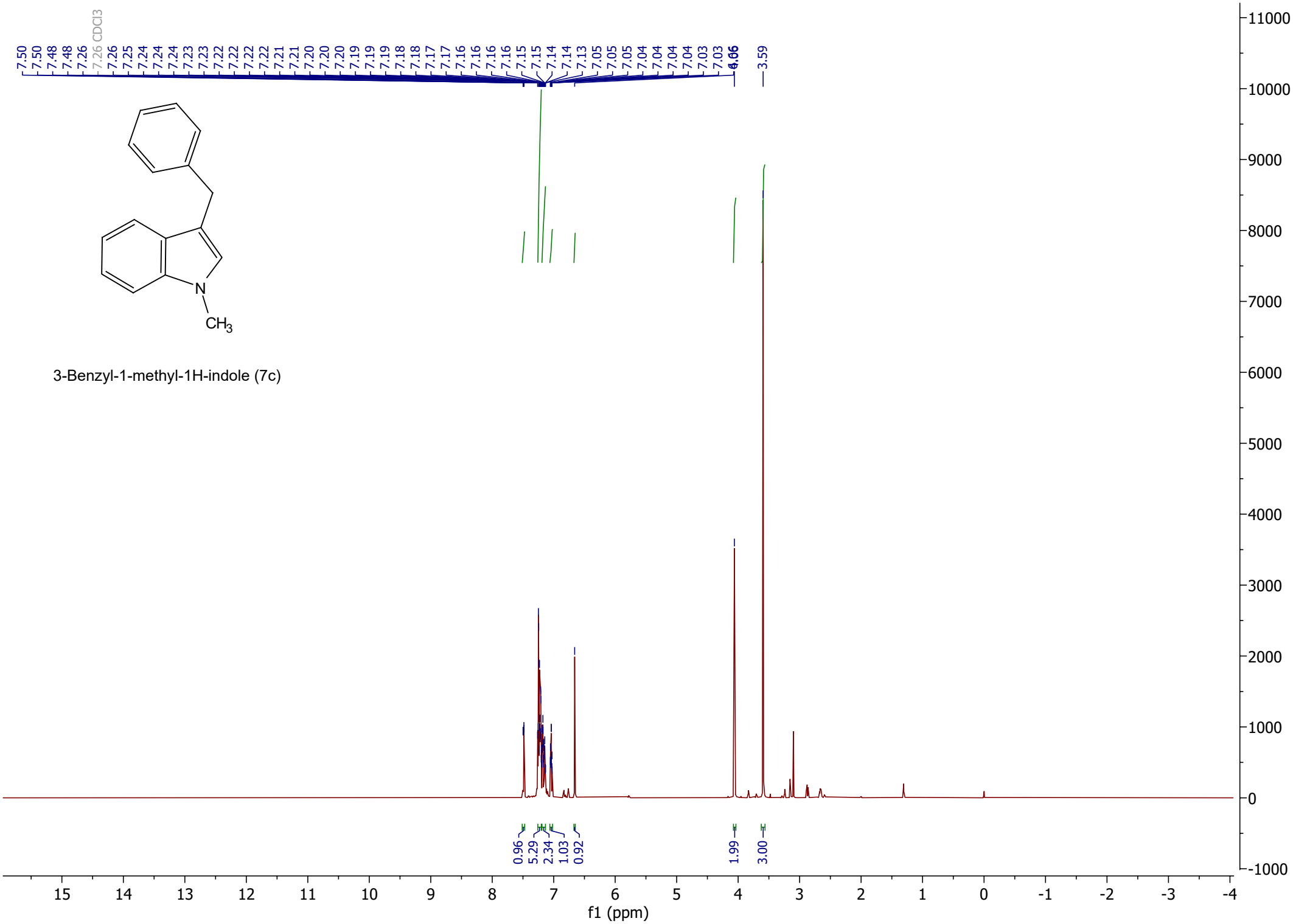


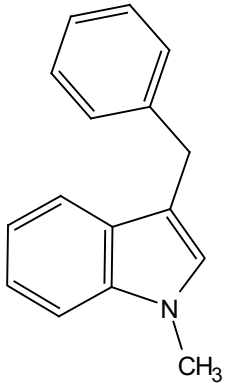
1,3-Dimethyl-1H-indole (7a)



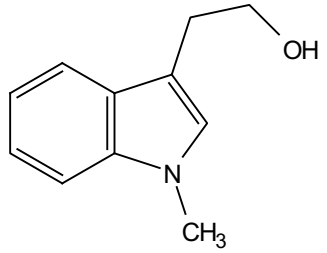
1-Methyl-3-pentyl-1H-indole (7b)


137.2
128.2
126.1
121.5
119.2
118.5
115.8
109.2
77.2 CDCl3
32.6
32.0
30.3
25.2
22.7
14.2
CH3
N
CH3
1-Methyl-3-pentyl-1H-indole (7b)
f1 (ppm)

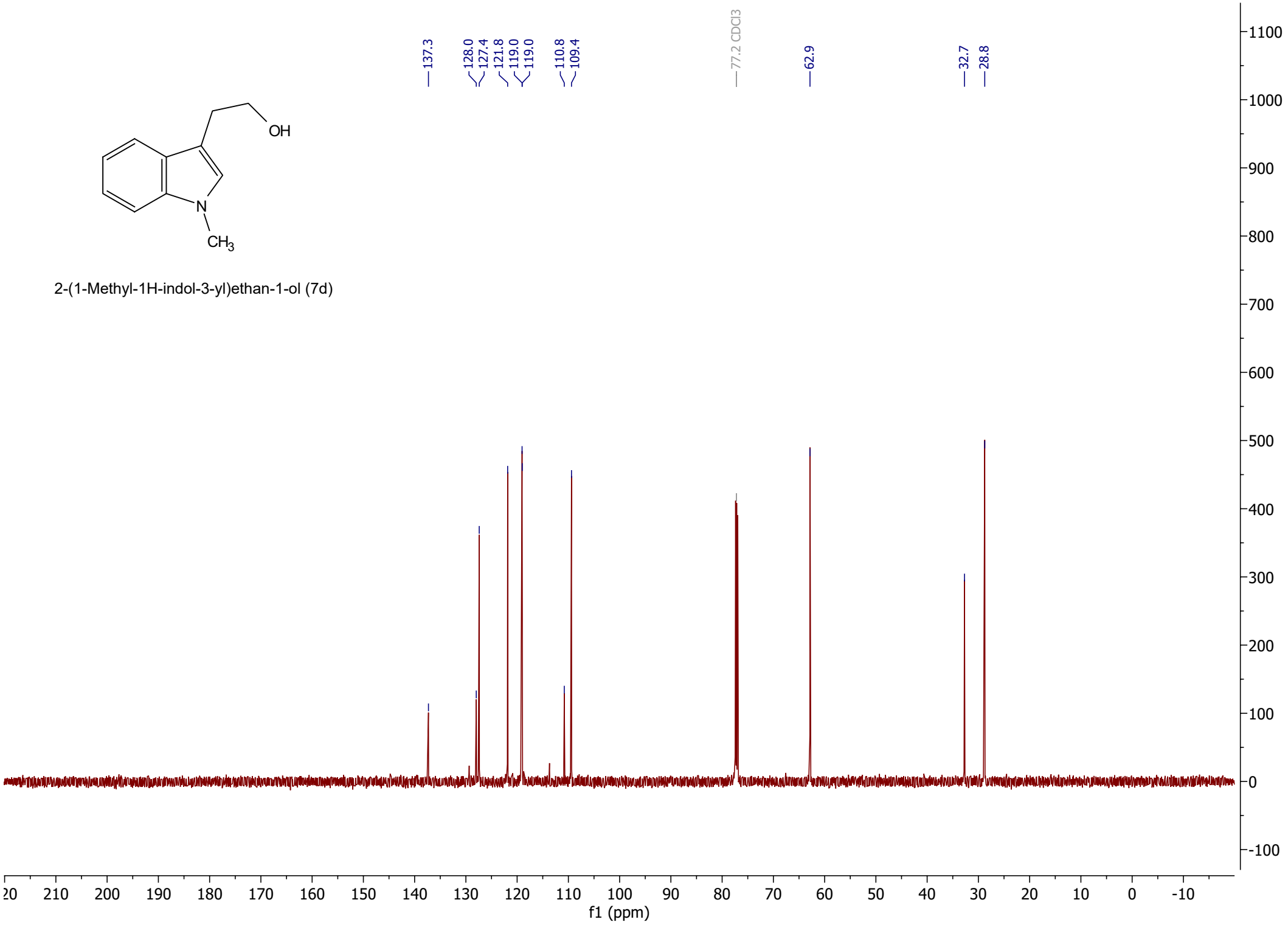

7.50 7.50 7.48 7.48 7.26 7.26 CDCl3 7.26 7.25 7.24 7.24 7.24 7.23 7.23 7.22 7.22 7.22 7.22 7.21 7.21 7.20 7.20 7.20 7.19 7.19 7.19 7.18 7.18 7.17 7.17 7.16 7.16 7.16 7.16 7.15 7.15 7.14 7.14 7.13 7.05 7.05 7.04 7.04 7.04 7.04 7.03 7.03 4.06 4.06 3.59
N
CH3
3-Benzyl-1-methyl-1H-indole (7c)
0.96 5.29 2.34 1.03 0.92 1.99 3.00
11000 10000 9000 8000 7000 6000 5000 4000 3000 2000 1000 0 -1000
15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3 -4
f1 (ppm)

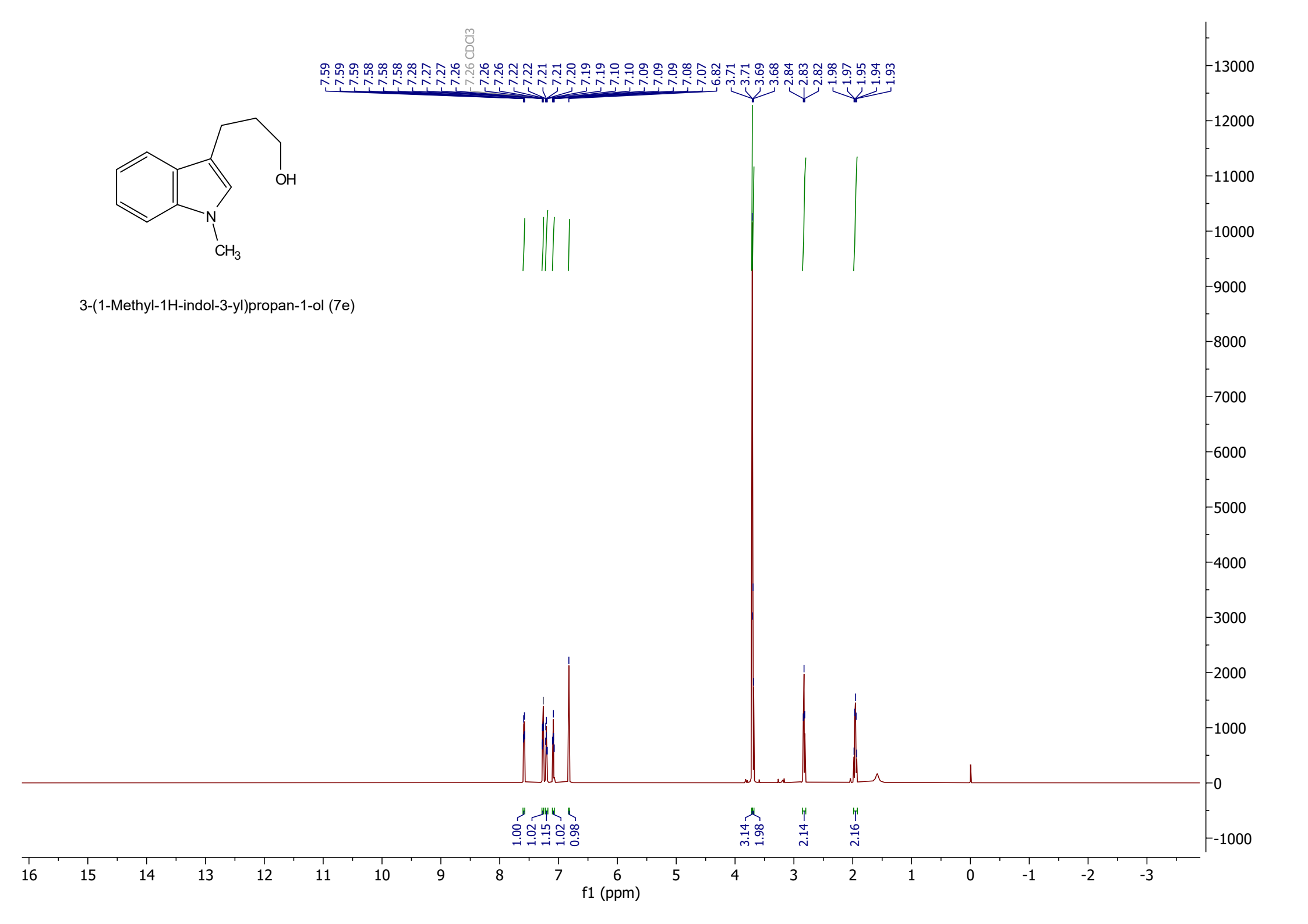


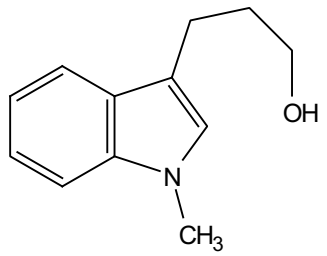
3-Benzyl-1-methyl-1H-indole (7c)



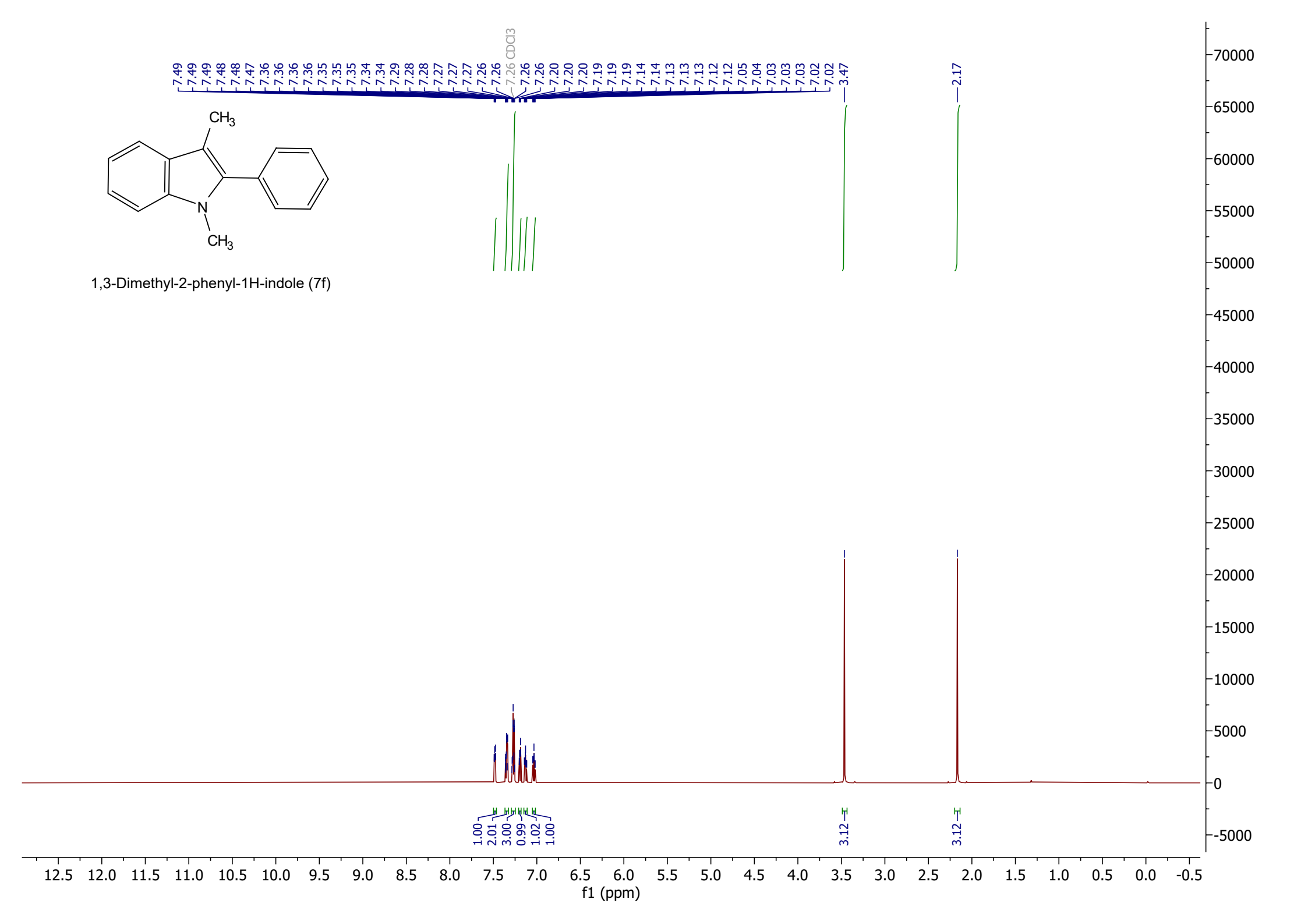
2-(1-Methyl-1H-indol-3-yl)ethan-1-ol (7d)

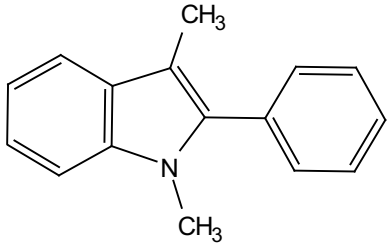

137.3
128.0
127.4
121.8
119.0
119.0
110.8
109.4
77.2 CDCl3
62.9
32.7
28.8
OH
N
CH3
2-(1-Methyl-1H-indol-3-yl)ethan-1-ol (7d)
f1 (ppm)


7.59 7.59 7.59 7.58 7.58 7.58 7.28 7.27 7.27 7.26 7.26 CDCl3 7.26 7.26 7.22 7.22 7.21 7.21 7.20 7.19 7.19 7.10 7.10 7.09 7.09 7.09 7.08 7.07 6.82 3.71 3.71 3.69 3.68 2.84 2.83 2.82 1.98 1.97 1.95 1.94 1.93
OH
N
CH3
3-(1-Methyl-1H-indol-3-yl)propan-1-ol (7e)
1.00 1.02 1.15 1.02 0.98 3.14 1.98 2.14 2.16
f1 (ppm)

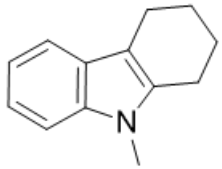


3-(1-Methyl-1H-indol-3-yl)propan-1-ol (7e)

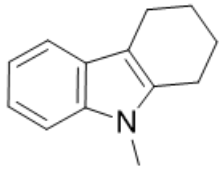

CH3
N
CH3
1,3-Dimethyl-2-phenyl-1H-indole (7f)
7.49 7.49 7.49 7.48 7.48 7.47 7.36 7.36 7.36 7.36 7.35 7.35 7.35 7.34 7.34 7.29 7.28 7.28 7.27 7.27 7.27 7.26 7.26 7.26 CDCl3 7.26 7.20 7.20 7.20 7.19 7.19 7.19 7.14 7.14 7.13 7.13 7.13 7.12 7.12 7.05 7.04 7.03 7.03 7.03 7.02 7.02
3.47
2.17
1.00 2.01 3.00 0.99 1.02 1.00
3.12
3.12
f1 (ppm)



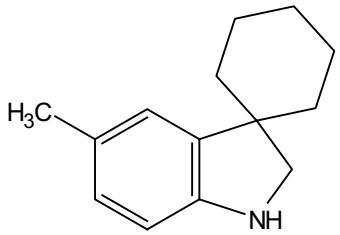
1,3-Dimethyl-2-phenyl-1H-indole (7f)



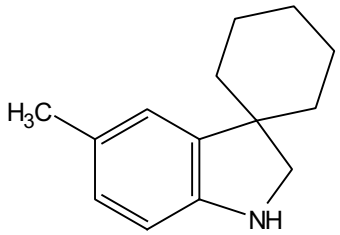
9-Methyl-2,3,4,9-tetrahydro-1H-carbazole (7g)



9-Methyl-2,3,4,9-tetrahydro-1H-carbazole (7g)

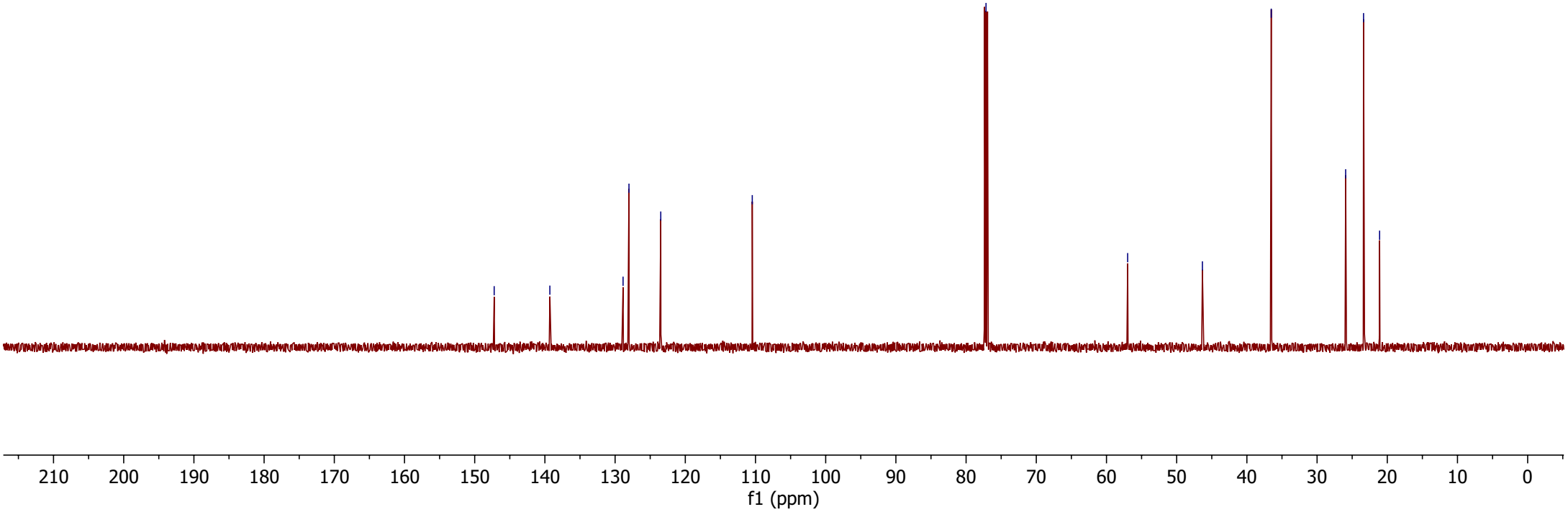


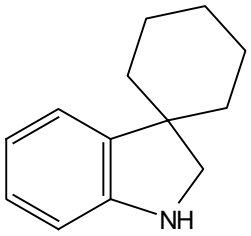
5'-Methylspiro[cyclohexane-1,3'-indoline] (10a)



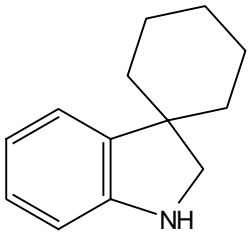
147.2
139.3
128.9
128.0
123.5
110.5
77.2 Chloroform-d
57.0
46.3
36.5
25.9
23.4
21.1

5'-Methylspiro[cyclohexane-1,3'-indoline] (10a)

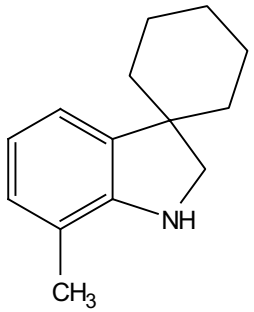




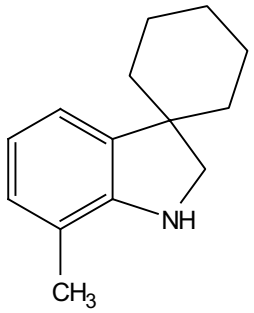
Spiro[cyclohexane-1,3'-indoline] (10b)



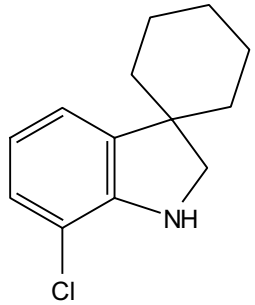
Spiro[cyclohexane-1,3’-indoline] (10b)



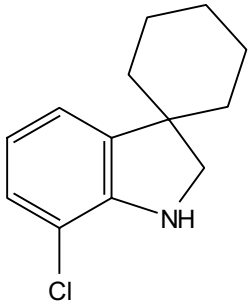
7'-Methylspiro[cyclohexane-1,3'-indoline] (10c)



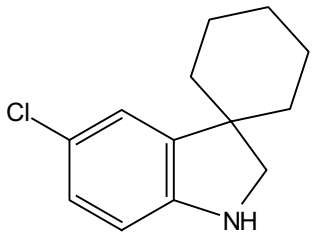
7'-Methylspiro[cyclohexane-1,3'-indoline] (10c)



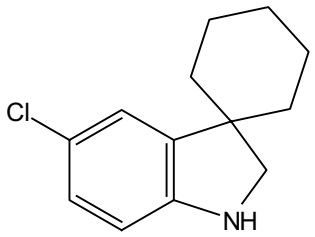
7'-Chlorospiro[cyclohexane-1,3'-indoline] (10d)



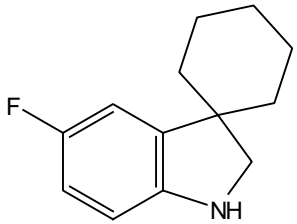
7'-Chlorospiro[cyclohexane-1,3'-indoline] (10d)



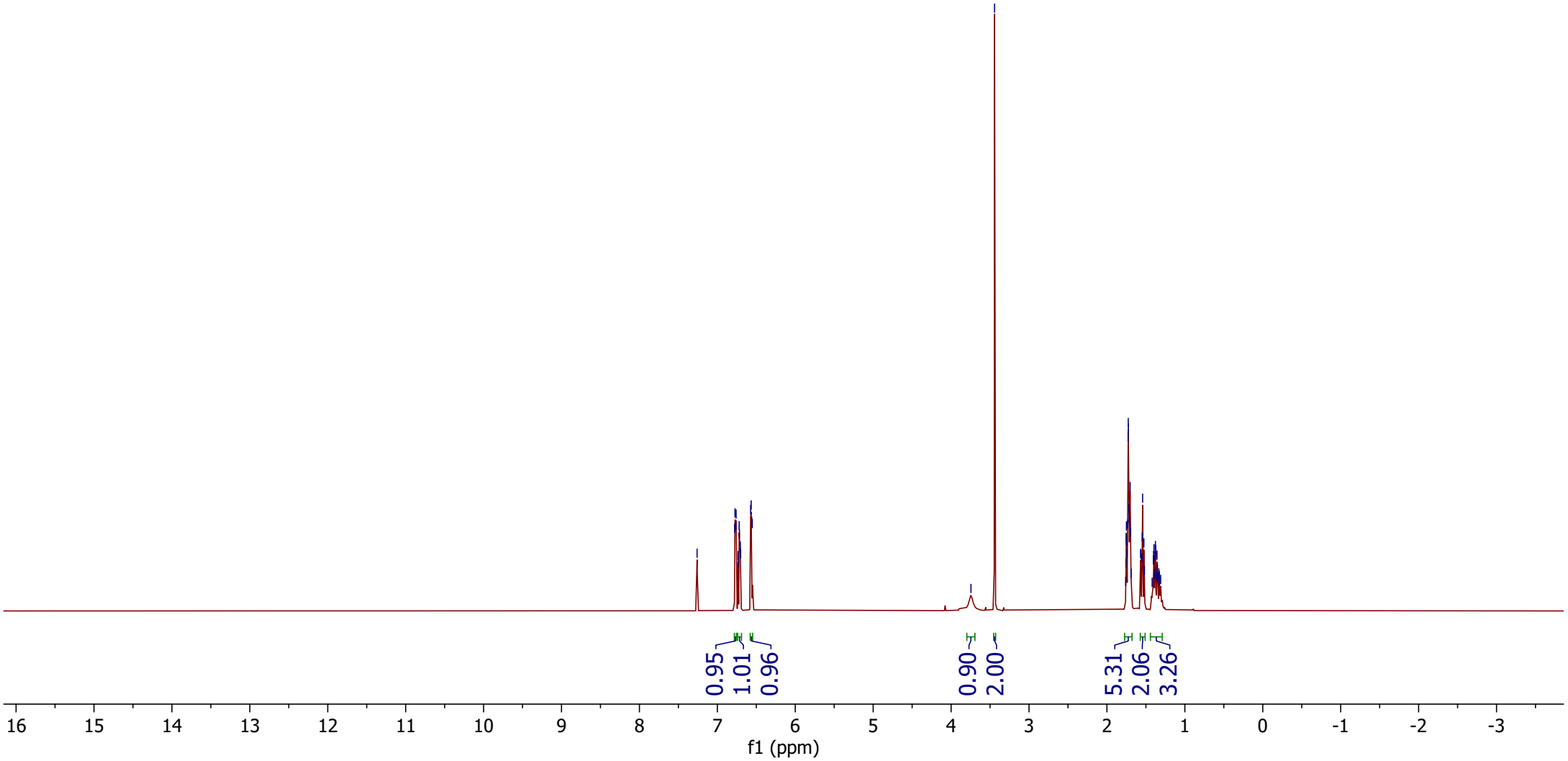
5'-Chlorospiro[cyclohexane-1,3'-indoline] (10e)

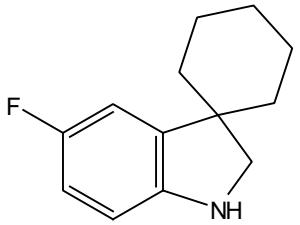


5'-Chlorospiro[cyclohexane-1,3'-indoline] (10e)

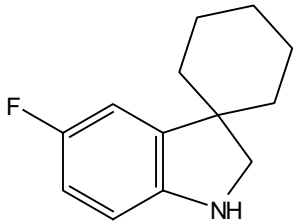


5'-Fluorospiro[cyclohexane-1,3'-indoline] (10f).

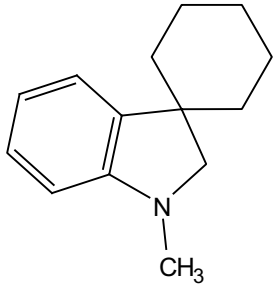




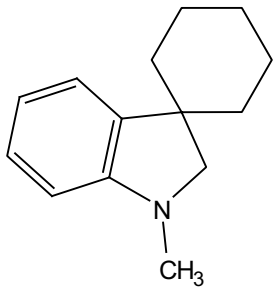
5'-Fluorospiro[cyclohexane-1,3'-indoline] (10f).



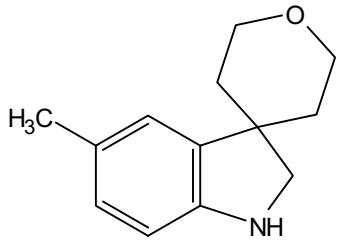
5'-Fluorospiro[cyclohexane-1,3'-indoline] (10f).



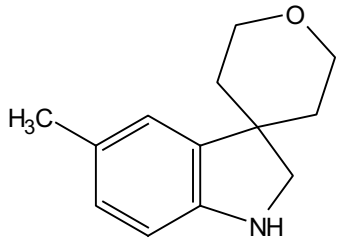
1'-Methylspiro[cyclohexane-1,3'-indoline] (10g)



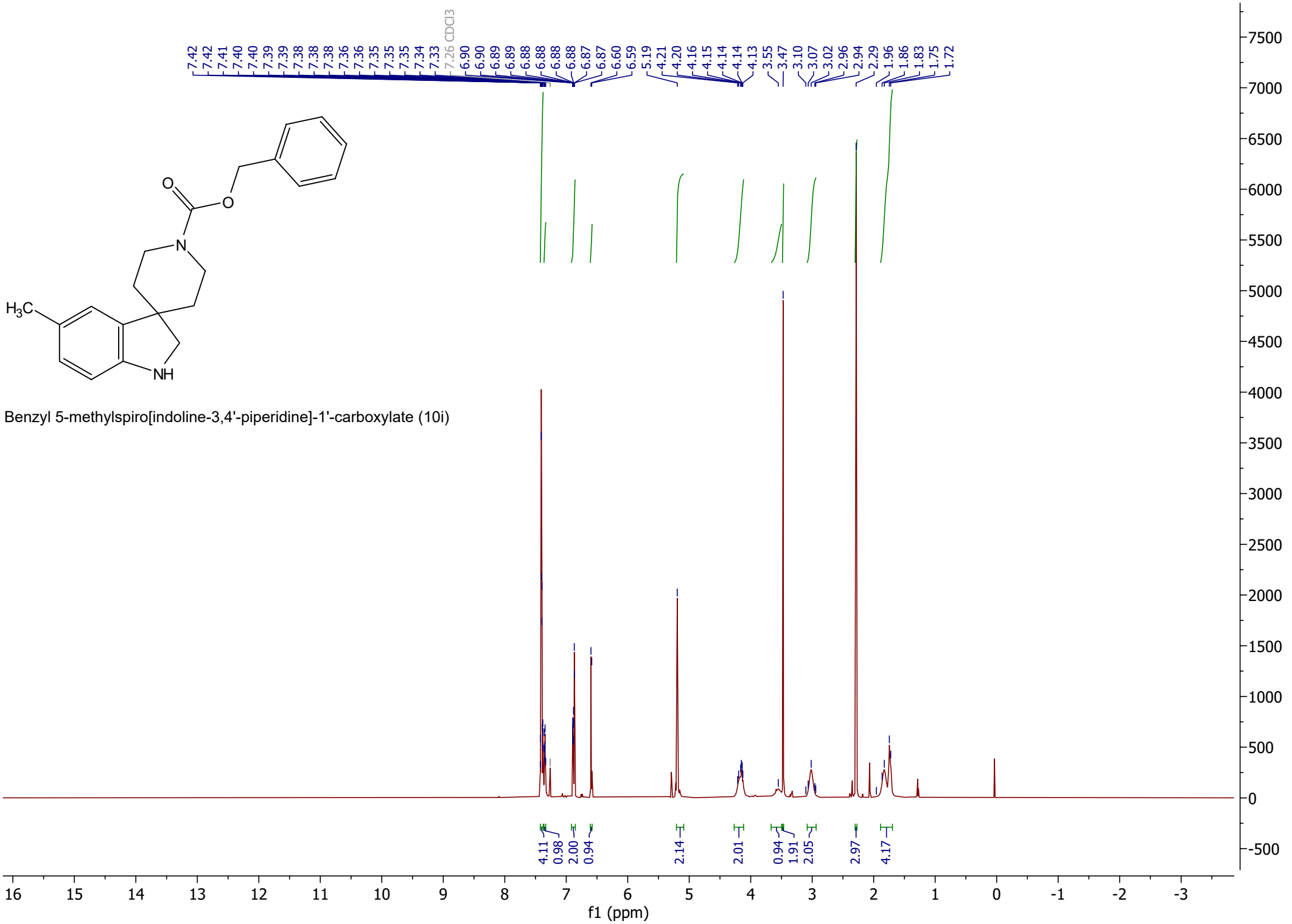
1'-Methylspiro[cyclohexane-1,3'-indoline] (10g)

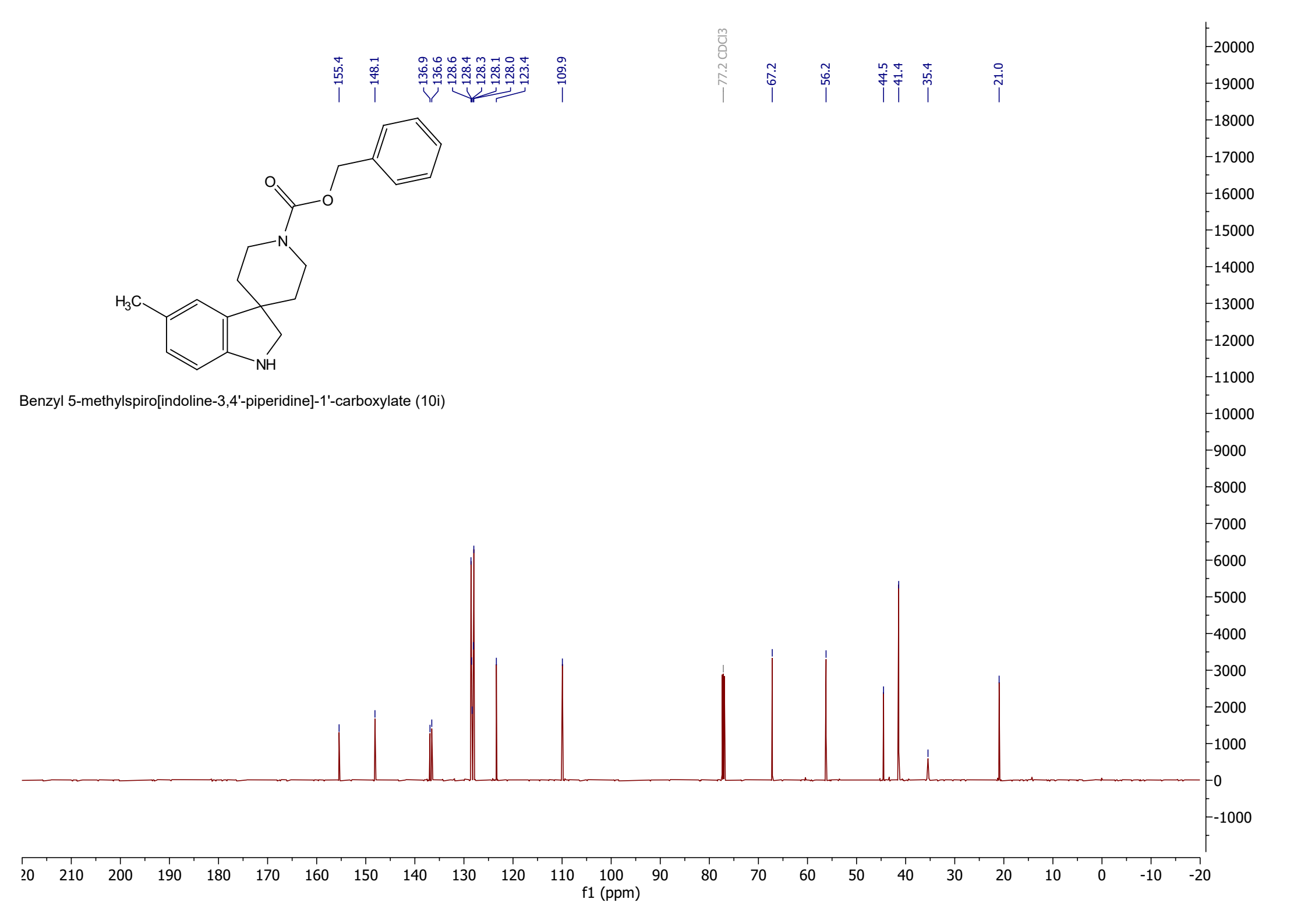


5-Methyl-2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran] (10h).

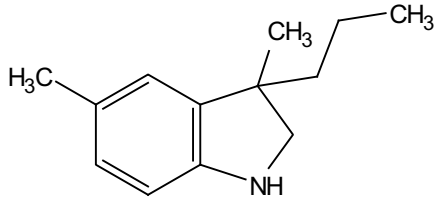


5-Methyl-2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran] (10h).

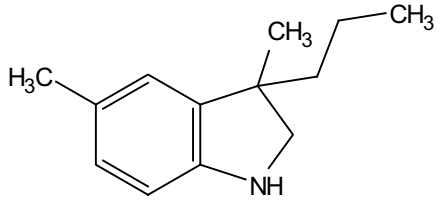

7.42 7.42 7.41 7.40 7.40 7.39 7.39 7.38 7.38 7.38 7.36 7.36 7.35 7.35 7.35 7.34 7.33 7.26 CDCl3 6.90 6.90 6.89 6.89 6.88 6.88 6.88 6.88 6.87 6.87 6.60 6.59 5.19 4.21 4.20 4.16 4.15 4.14 4.14 4.13 3.55 3.47 3.10 3.07 3.02 2.96 2.94 2.29 1.96 1.86 1.83 1.75 1.72
O
O
N
H3C
NH
Benzyl 5-methylspiro[indoline-3,4'-piperidine]-1'-carboxylate (10i)
4.11 0.98 2.00 0.94 2.14 2.01 0.94 1.91 2.05 2.97 4.17
f1 (ppm)



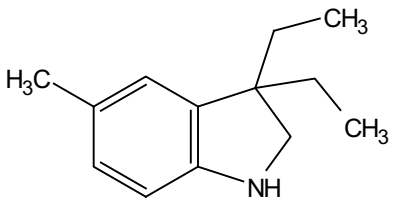
Benzyl 5-methylspiro[indoline-3,4'-piperidine]-1'-carboxylate (10i)



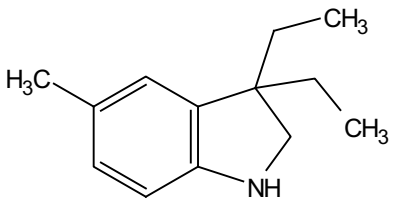
3-Ethyl-3,5-dimethylindoline (10j)



3-Ethyl-3,5-dimethylindoline (10j)



3,3-Diethyl-5-methylindoline (10k)



3,3-Diethyl-5-methylindoline (10k)