Supplementary Materials for

A Condition-Tuned Unorthodox Approach to Indole-3-Carboxylic Acids and Anthranilic Acids via Carbon Atom Translocation

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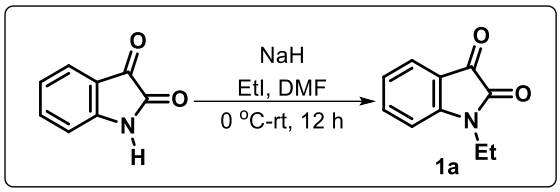
General Information

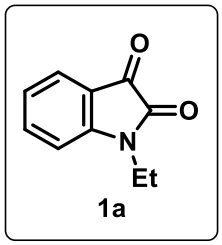
All reactions were carried out in an oven-dried reaction vessel under N_2 atmosphere unless otherwise stated. Commercial reagents were purchased from Sigma-Aldrich, Alfa Aesar, Acros, and other commercial suppliers and used as received without further purification. Anhydrous DCE was purchased from Sigma-Aldrich and used as received. TLC analysis was performed on Merck 60 F_{254} silica gel TLC plates. Column chromatography was done using 230-400 mesh silica gel by applying pressure through an air pump. ^{1}H and ^{13}C NMR spectra were recorded in Bruker 300, 600 MHz and JEOL 400 MHz spectrometer, and are reported as chemical shifts (δ) in parts per million (ppm). Internal standards or residual solvent were used as a reference. HRMS (m/z) were recorded in the Q-TofMicromass spectrometer (LC-MS, ESI mode) and JOEL-JMS 700 (EI mode). Melting points were determined in a capillary melting point apparatus and are uncorrected. Single crystal X-ray data was recorded in a Bruker Kappa APEX2 CCD diffractometer with CuKα/MoKα radiation. The structures were solved by SHELXT and refined with SHELXL using the Olex2 program. The CIF files were submitted to CCDC (2213915-2213920) and can be obtained at https://summary.ccdc.cam.ac.uk/structure-summaryform.

General procedure for the preparation of 1-ethylindoline-2,3-dione (1a):



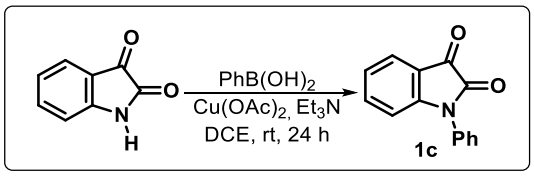
To a suspension of isatin (3.5 mmol) in anhydrous DMF (30 mL), NaH (1.1 equiv.) was added in ice-cold condition under an argon atmosphere. The reaction was stirred at 0 °C for 30 minutes. Then ethyl iodide (1.1 equiv.) was transferred to the reaction mixture and stirred at room temperature (33 °C) and kept overnight (12 h). After the full conversion was monitored by TLC, it was quenched with cold 1N HCl solution (200 mL). The organic part was extracted by EtOAc (3x100 mL) with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Finally, it was purified by column chromatography on silica gel (230-400 mesh) using petroleum ether/ethyl acetate (6:1) as eluent to obtain the desired 1-ethylindoline-2,3-dione (**1a**) in 85% yield (520 mg).The compounds were eluted in 15% of ethyl acetate–petroleum ether. Several *N*-alkyl isatins were prepared following this protocol.

Characterization of 1-ethylindoline-2,3-dione (1a):



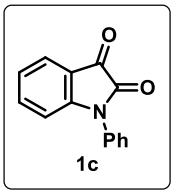
Red solid (520 mg, 85% yield); **column chromatography eluent** petroleumether/EtOAc = 5:1; mp 88-90 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.57 (app t, *J* = 7.4 Hz, 2H), 7.09 (app t, *J* = 7.5 Hz, 1H), 6.90 (app d, *J* = 8.5 Hz, 1H), 3.76 (q, *J* = 7.2 Hz, 2H), 1.29 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 183.6, 157.8, 150.6, 138.3, 125.4, 123.6, 117.5, 110.0, 34.9, 12.4; **HRMS** (ESI, m/z) calcd for $C_{10}H_{10}NO_2$ $[M+H]^+$175.0633, found 175.0630.

General procedure for the preparation of 1-phenylindoline-2,3-dione (1c):



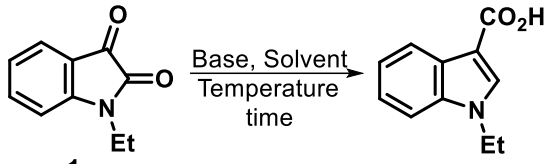
To a suspension of isatin (3 mmol) in anhydrous DCE (30 mL), anhydrous $Cu(OAc)_2$ (4.5 mmol), triethylamine (6 mmol) and the arylboronic acid (4.5 mmol) were added under an argon atmosphere. The reaction was stirred at room temperature for 16 h. After completion of reaction, the mixture was filtered through a pad of celite and washed with dichloromethane. The filtrate was concentrated in vacuo to yield the crude compound, which was subjected to flash chromatography on silica. The compounds were eluted in 15% of ethyl acetate–petroleum ether. Several *N*-aryl isatins were prepared following this procedure.

Characterization of 1-phenylindoline-2,3-dione (1c):



Red solid (555 mg, 83% yield); **column chromatography eluent** petroleumether/EtOAc = 4:1; mp 138-140 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.71 – 7.66 (m, 1H), 7.59 – 7.50 (m, 3H), 7.48 – 7.39 (m, 3H), 7.17 (td, *J* = 7.5, 0.6 Hz, 1H), 6.89 (d, *J* = 8.0 Hz, 1H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 182.9, 157.3, 151.6, 138.3, 132.9, 129.9, 128.8, 126.0, 125.6, 124.3, 117.5, 111.3; **HRMS** (ESI, m/z) calcd for $C_{14}H_{10}NO_2$ $[M+H]^+$ 224.0712, found 224.0709.

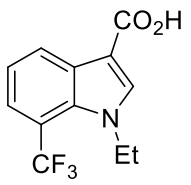
Table S1: Screening of the reaction conditions[a]



Entry	base (x equiv.)	solvent (x mL)	temperature (°C)	time (h)	yield[b] (%)
1	NaH (4)	DMSO (2)	60	6	38
2	NaH (4)	DMSO (2)	80	2	66
3	**NaH (6)**	**DMSO (2)**	**80**	**2**	**82**
4	NaH (6)	DMSO (2)	90	2	66
5	NaH (6)	DMSO (1)	80	2	78
6	LiH (6)	DMSO (2)	80	12	nr
7	CaH_2 (3)	DMSO (1)	80	5	nr
8	KO^{t}Bu (6)	DMSO (1)	80	8	trace
9	NaOMe (6)	DMSO (2)	80	12	trace
10	NaOH (6)	DMSO (2)	80	12	trace
11	NaH (6)	DMSO (0.5) + DMF (1)	80	1	trace
12	NaH (6)	DMSO (0.2) + THF (0.8)	80	1	47
13	NaH (6)	DMSO (0.2) + toluene (0.8)	80	1	48
14	NaH (6)	DMSO (2)	rt (33)	24	33[c]
15	NaH (6)	DMF (2)	88	24	nr

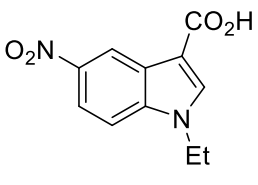
[a]All reactions were set up on a 0.2 mmol scale in presence of base in anhydrous DMSO solvent degassed by applying freeze-pump-thaw method. [b]Isolated yield. [c]Yield of anthranilic acid and without removing dissolved oxygen by the freeze-pump-thaw method.

Table S2: Unsuccessful substrate scope



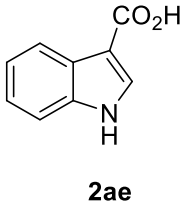
2ac

0%



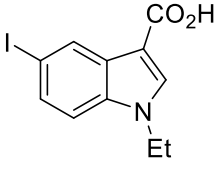
2ad

0%



2ae

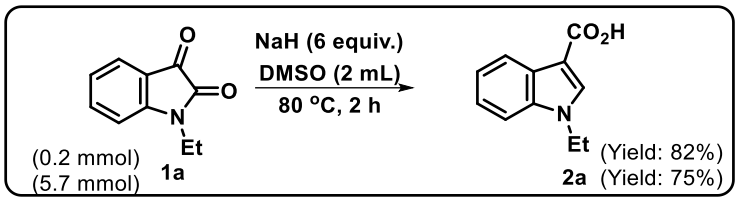
0%



0%

General procedure for the preparation of 1-ethyl-1*H*-indole-3-carboxylic acid (2a):

(**Milligram scale**):



Into a 10 mL two neck round bottom flask equipped with an electromagnetic stirrer *N*-ethyl isatin (**1a**) (1 equiv., 0.2 mmol, 35 mg) and DMSO solvent (2 mL, 0.1 M) were transferred under an inert atmosphere. Then, the whole reaction mixture was subjected to degas by the Freeze-Pump-Thaw method. After degassing, NaH (6 equiv., 1.2 mmol) was added portion-wise using a solid-additional funnel and stirred at room temperature (30°C) for 10 minutes. After that, the reaction mixture was warmed slowly to 80 °C and kept for 2 hours. After the full conversion was monitored by TLC, it was cooled to room temperature and quenched with cold aqueous 1N HCl solution (20 mL). The organic part was extracted by EtOAc (3x20 mL), washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Finally, it was purified by column chromatography on silica gel (230-400 mesh) using petroleum ether/ethyl acetate (4:1) as eluent to obtain the desired 1-ethyl-1*H*-indole-3-carboxylic acid (**2a**) in 82% yield (31 mg). To avoid column purification, we also carried out a re-crystallization technique dissolving crude reaction mixture in hot ethanol and obtained the same yield.

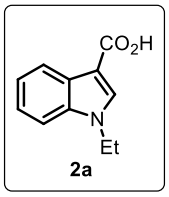
(**Gram scale**)

Into a 100 mL two neck round bottom flask equipped with an electromagnetic stirrer *N*-ethyl isatin (1 equiv., 5.7 mmol, 1g) and DMSO solvent (57 mL, 0.1 M) were transferred under an inert atmosphere. Then, the whole reaction mixture was subjected to degas by the Freeze-Pump-Thaw method. After degassing, NaH (6 equiv., 34.2 mmol) was added portion-wise using a solid-additional funnel and stirred at room temperature (30 °C) for 10 minutes. After that, the reaction mixture was warmed slowly to 80 °C and kept for 2 hours. After the full conversion was monitored by TLC, it was cooled to room temperature and quenched with cold aqueous 1N HCl solution (200 mL). The organic part was extracted by EtOAc (3x100 mL), washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Finally, it was purified by column chromatography on silica gel (230-400 mesh) using petroleum ether/ethyl acetate (4:1) as eluent to obtain the desired 1-ethyl-1*H*-indole-3-carboxylic acid (**2a**) in 75% yield (808 mg). To avoid column purification, we also carried out the re-crystallization method dissolving crude reaction mixture in hot ethanol and obtained the same yield.

We have followed the above procedure for the synthesis of **2b-2ab**. In cases of **1e**, **1e′**, and **1e′′** in-situ deprotection of the *N*-substitution took place and we obtained indole-3-carboxylic acid (**2ac**).

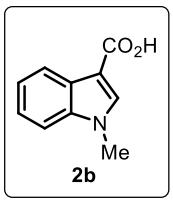
Characterization of the compounds 2a-2ab:

1-ethyl-1*H*-indole-3-carboxylic acid (2a):



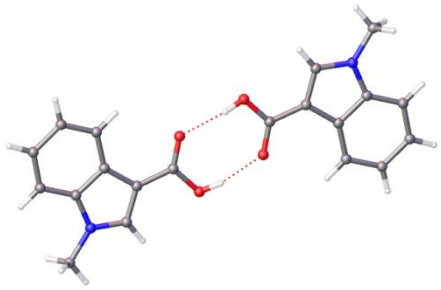
White solid (31 mg, 82% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 138-139 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.29 – 8.24 (m, 1H), 7.97 (s, 1H), 7.41 – 7.38 (m, 1H), 7.34 – 7.30 (comp, 2H), 4.23 (q, *J* = 7.3 Hz, 2H), 1.54 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 170.7, 136.5, 134.7, 127.0, 122.8, 122.1, 121.9, 109.9, 106.3, 41.7, 15.1; **HRMS** (ESI, m/z) calcd for $C_{11}H_{12}NO_2$ $[M+H]^+$ 190.0868, found 190.0866.

1-methyl-1*H*-indole-3-carboxylic acid (2b):



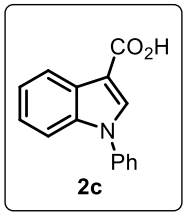
White solid (18.2mg, 52% yield); column chromatography eluent, petroleumether/EtOAc = 4:1; mp 182-184 °C; (Due to solubility problem, a few drops of CD_3OD was added with $CDCl_3$) **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.14 – 8.12 (m, 1H), 7.78 (s, 1H), 7.32–7.29 (m, 1H), 7.27 – 7.21 (comp, 2H), 3.78 (s, 3H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 167.6, 137.2, 135.8, 126.7, 122.6, 121.8, 121.4, 109.7, 106.5, 33.2; **HRMS** (ESI, m/z) calcd for $C_{10}H_{10}NO_2$ $[M+H]^+$ 176.0712, found 176.0719.

Table S3: Crystal Data and Structure of 2b (CCDC No. 2213915)



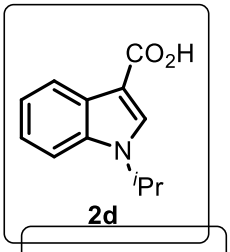
Identification code	AB_03_435_0m_a
Empirical formula	$C_{20}H_{18}N_2O_4$
Formula weight	350.377
Temperature/K	100.00
Crystal system	monoclinic
Space group	$P2_1$
a/Å	5.0202(4)
b/Å	29.187(2)
c/Å	5.9119(5)
α/°	90
β/°	100.468(3)
γ/°	90
Volume/Å^3	851.83(12)
Z	2
ρ_{calc}g/cm^3	1.366
μ/mm^{-1}	0.792
F(000)	369.3
Crystal size/mm^3	0.25 × 0.2 × 0.1
Radiation	Cu Kα (λ = 1.54178)
2Θ range for data collection/°	15.24 to 133.2
Index ranges	-5 ≤ h ≤ 5, -34 ≤ k ≤ 34, -7 ≤ l ≤ 7
Reflections collected	25396
Independent reflections	2910 [R_{int} = 0.0503, R_{sigma} = 0.0289]
Data/restraints/parameters	2910/1/240
Goodness-of-fit on F^2	1.043
Final R indexes [I>=2σ (I)]	R_1 = 0.0587, wR_2 = 0.1568
Final R indexes [all data]	R_1 = 0.0587, wR_2 = 0.1568
Largest diff. peak/hole / e Å^{-3}	0.35/-0.24
Flack parameter	0.3(3)

1-phenyl-1*H*-indole-3-carboxylic acid (2c):

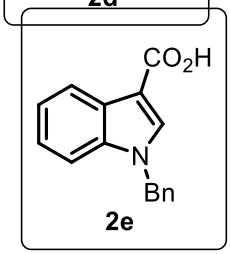


White solid (30.8 mg, 65% yield); column chromatography eluent, petroleumether/EtOAc = 4:1; mp 160-162 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 10.00 (br s, 1H), 8.33 (d, *J* = 7.6 Hz, 1H), 8.14 (s, 1H), 7.59–7.50 (comp, 5H), 7.48 – 7.44 (m, 1H), 7.38 – 7.34 (m, 1H), 7.33 – 7.29 (m, 1H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 170.7, 138.3, 136.9, 135.4, 129.9, 128.0, 127.1, 124.9, 123.6, 122.8, 122.0, 111.1, 108.5; **HRMS** (ESI, m/z) calcd for $C_{15}H_{12}NO_2$ $[M+H]^+$238.0868, found 238.0870.

1-isopropyl-1*H*-indole-3-carboxylic acid (2d):



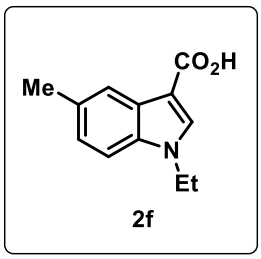
Off-white solid (18.3 mg, 45% yield); column chromatography eluent, petroleumether/EtOAc = 4:1; mp 183-184 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.26-8.22 (m,1H), 8.05 (s, 1H), 7.43-7.40 (m, 1H), 7.32-7.27 (comp, 2H), 4.72 (hept, *J* = 6.7 Hz, 1H), 1.59 (d, *J* = 6.7 Hz, 6H).**^{13}C NMR** (101 MHz, Chloroform-*d*) δ 170.7, 136.3, 131.9, 127.0, 122.7, 122.2, 121.9, 110.1, 106.4, 47.9, 22.6; **HRMS** (ESI, m/z) calcd for $C_{12}H_{14}NO_2$ $[M+H]^+$204.1025, found 204.1022.



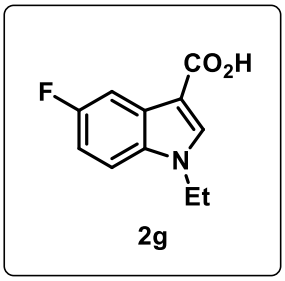
1-benzyl-1*H*-indole-3-carboxylic acid (2e):

Off-white solid (22.6 mg, 45% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 168-169 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.27 – 8.25 (m, 1H), 7.95 (s, 1H), 7.37 – 7.27 (m, 6H), 7.20 – 7.17 (m, 2H), 5.36 (s, 2H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 170.1, 136.9, 135.8, 135.7, 129.0, 128.2, 127.1, 127.0, 123.1, 122.3, 121.9, 110.4, 106.8, 50.9; **HRMS** (ESI, m/z) calcd for $C_{16}H_{14}NO_2$ $[M+H]^+$252.1025, found 252.1017.

1-ethyl-5-methyl-1*H*-indole-3-carboxylic acid (2f):

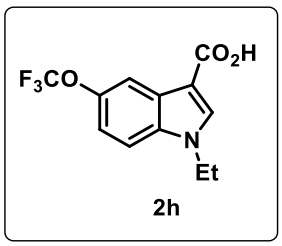


Off-white solid (33.7 mg, 83% yield); column chromatography eluent, petroleumether/EtOAc = 4:1; mp 212-214 °C; (Due to solubility problem, a few drops of CD_3OD was added with $CDCl_3$) **^{1}H NMR** (400 MHz, Chloroform-*d*)δ 7.95 – 7.94 (m, 1H), 7.82 (s, 1H), 7.22 (d, *J* = 8.4 Hz, 1H), 7.08 – 7.04 (m, 1H), 4.13 (q, *J* = 7.3 Hz, 2H), 2.44 (s, 3H), 1.46 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 168.2, 134.7, 134.2, 131.4, 127.2, 124.1, 121.3, 109.5, 105.9, 41.5, 21.3, 15.0; **HRMS** (ESI, m/z) calcd for $C_{12}H_{14}NO_2$ $[M+H]^+$ 204.1025, found 204.1023.



1-ethyl-5-fluoro-1*H*-indole-3-carboxylic acid (2g):

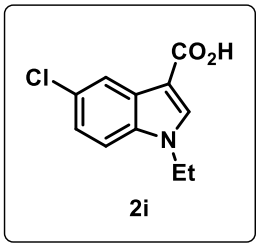
Off-white solid (27.3 mg, 66% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 182-184 °C; (Due to solubility problem, a few drops of CD_3OD was added with $CDCl_3$) **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.89 (s, 1H), 7.82 (dd, *J* = 9.7, 2.5 Hz, 1H), 7.28-7.25 (m, 1H), 6.99 (td, *J* = 9.0, 2.6 Hz, 1H), 4.16 (q, *J* = 7.3 Hz, 2H), 1.49 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 167.7, 159.2 (d, $^1J_{F\text{-}C}$ = 237.4 Hz), 135.3, 132.9, 127.7 (d, $^3J_{F\text{-}C}$ = 11.4 Hz), 111.1 (d, $^2J_{F\text{-}C}$ = 26.5 Hz), 110.6 (d, $^3J_{F\text{-}C}$ = 9.9 Hz), 107.0 (d, $^2J_{F\text{-}C}$= 24.2 Hz), 106.6 (d, $^4J_{F\text{-}C}$ = 5.0 Hz), 41.8, 15.0; **HRMS** (ESI, m/z) calcd for $C_{11}H_{11}FNO_2$ $[M+H]^+$208.0774, found 208.0772.



1-ethyl-5-(trifluoromethoxy)-1*H*-indole-3-carboxylic acid (2h):

Off-white solid (30 mg, 55% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 186-189 °C; (Due to solubility

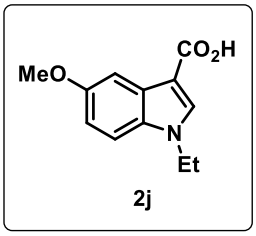
problem, a few drops of CD_3OD was added with $CDCl_3$) **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.97 (apps, 1H), 7.87 (s, 1H), 7.28 (d, *J* = 8.9 Hz, 1H), 7.07 (d, *J* = 8.8 Hz, 1H), 4.13 (q, *J* = 7.3 Hz, 2H), 1.44 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 167.3, 144.5, 135.5, 134.5, 127.3, 120.6 (q, *J* = 256.7 Hz), 116.5, 114.2, 110.6, 107.1, 41.8, 14.9; **HRMS** (ESI, m/z) calcd for $C_{12}H_{11}F_3NO_3$ $[M+H]^+$ 274.0691, found 274.0688.



2i

5-chloro-1-ethyl-1*H*-indole-3-carboxylic acid (2i):

Off-white solid (23.7 mg, 53% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 168-170 °C; (Due to solubility problem, a few drops of CD_3OD was added with $CDCl_3$) **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.14 (d, *J* = 2.0 Hz, 1H), 7.86 (s, 1H), 7.24 (d, *J* = 2.3 Hz, 1H), 7.19 (dd, *J* = 8.7, 2.0 Hz, 1H), 4.15 (q, *J* = 7.3 Hz, 2H), 1.47 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 167.6, 135.1, 134.7, 128.0, 127.9, 123.0, 121.3, 110.9, 106.4, 41.8, 15.0; **HRMS** (ESI, m/z) calcd for $C_{11}H_{11}ClNO_2$ $[M+H]^+$ 224.0478, found 224.0477.

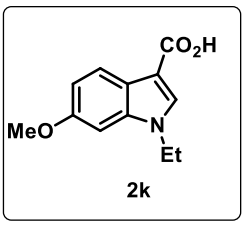


2j

1-ethyl-5-methoxy-1*H*-indole-3-carboxylic acid (2j):

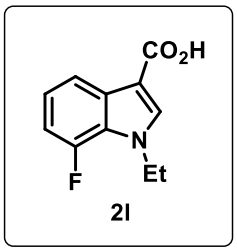
Off-white solid (23 mg, 53% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 168-170 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.89 (s, 1H), 7.70 (d, *J* = 2.4 Hz, 1H), 7.26 (d, *J* = 9.3 Hz, 1H), 6.93 (dd, *J* = 8.9, 2.5 Hz, 1H), 4.17 (q, *J* = 7.3 Hz, 2H), 3.91 (s, 3H), 1.52 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 170.7, 156.0, 134.6, 131.5, 127.9, 113.4, 110.8, 105.8, 103.1, 55.8, 41.9, 15.1; **HRMS** (ESI, m/z) calcd for $C_{12}H_{14}NO_3$$[M+H]^+$ 220.0974 found 220.0978.

1-ethyl-6-methoxy-1*H*-indole-3-carboxylic acid (2k):



2k

Off-white solid (31 mg, 71% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 168-170 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.11 (d, *J* = 8.7 Hz, 1H), 7.86 (s, 1H), 6.96 (dd, *J* = 8.8, 2.2 Hz, 1H), 6.83 (d, *J* = 2.1 Hz, 1H), 4.16 (q, *J* = 7.3 Hz, 2H), 3.89 (s, 3H), 1.53 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 170.6, 156.9, 137.2, 133.8, 122.6, 121.1, 111.5, 106.4, 93.7, 55.7, 41.6, 14.9; **HRMS** (ESI, m/z) calcd for $C_{12}H_{14}NO_3$ $[M+H]^+$ 220.0974, found 220.0976.

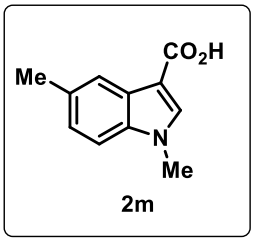


2l

1-ethyl-7-fluoro-1*H*-indole-3-carboxylic acid (2l):

Colourless solid (24 mg, 58% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 172-174 °C; (Due to solubility problem, a few drops of CD_3OD was added with $CDCl_3$) **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.91 (d, *J* = 8.0 Hz, 1H), 7.80 (s, 1H), 7.11 (td, *J* = 8.0, 4.6 Hz, 1H), 6.93 – 6.88 (m, 1H), 4.32 (q, *J* = 7.2 Hz, 2H), 1.47 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (101 MHz, Chloroform-*d*)δ 167.7, 149.9 (d, $^1J_{F-C}$ = 245.8 Hz), 135.7, 130.7 (d, $^3J_{F-C}$ = 4.7 Hz), 124.2 (d, $^2J_{F-C}$ = 9.9 Hz), 122.2 (d, $^3J_{F-C}$ = 6.6 Hz), 117.4 (d, $^4J_{F-C}$ = 3.4 Hz), 108.3 (d, $^2J_{F-C}$ = 17.9 Hz), 107.3, 44.6 (d, *J* = 5.3 Hz), 16.3; **HRMS** (ESI, m/z) calcd for $C_{11}H_{11}FNO_2$ $[M+H]^+$ 208.0774, found 208.0772.

1,5-dimethyl-1*H*-indole-3-carboxylic acid (2m):

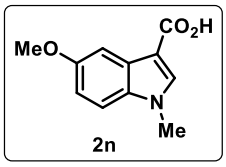


2m

Brown solid (22 mg, 58% yield); column chromatography eluent, petroleumether/EtOAc = 4:1; mp 214-216 °C; (Due to solubility problem, a few drops of CD_3OD was added with $CDCl_3$) **^{1}H NMR**

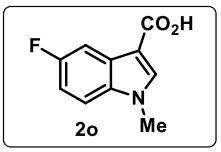
(400 MHz, Chloroform-*d*)δ 7.80 – 7.75 (m, 1H), 7.62 (s, 1H), 7.09 (d, *J* = 8.4 Hz, 1H), 6.97 – 6.94 (m, 1H), 3.66 (s, 3H), 2.31 (s, 3H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 167.4, 135.6, 135.5, 131.1, 126.8, 124.0, 120.8, 109.2, 105.8, 33.0, 21.0; **HRMS** (ESI, m/z) calcd for $C_{11}H_{12}NO_2$ $[M+H]^+$ 190.0868, found 190.0867.

5-methoxy-1-methyl-1*H*-indole-3-carboxylic acid (2n)



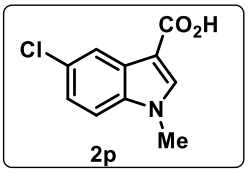
Brown solid (21 mg, 52% yield); column chromatography eluent, petroleumether/EtOAc = 4:1; mp 212-214 °C; **^{1}H NMR** (400 MHz, DMSO-*d*$_6$) δ 7.95 (s, 1H), 7.48 (d, *J* = 2.4 Hz, 1H), 7.42 (d, *J* = 8.9 Hz, 1H), 6.87 (dd, *J* = 8.9, 2.5 Hz, 1H), 3.81 (s, 3H), 3.78 (s, 3H); **^{13}C NMR** (101 MHz, DMSO-*d*$_6$) δ 165.6, 155.1, 136.1, 132.1, 127.2, 112.2, 111.5, 105.7, 102.3, 55.3, 33.1; **HRMS** (ESI, m/z) calcd for $C_{11}H_{12}NO_3$ $[M+H]^+$ 206.0817, found 206.0809.

5-fluoro-1-methyl-1*H*-indole-3-carboxylic acid (2o)



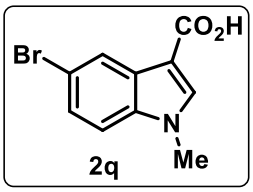
Brown solid (25 mg, 64% yield); column chromatography eluent, petroleumether/EtOAc = 4:1; mp 214-216 °C; **^{1}H NMR** (400 MHz, Methanol-*d*$_4$) δ 7.95 (s, 1H), 7.72 (dd, *J* = 9.8, 2.5 Hz, 1H), 7.44 (dd, *J* = 8.9, 4.3 Hz, 1H), 7.04 (td, *J* = 9.1, 2.6 Hz, 1H), 3.87 (s, 3H); **^{13}C NMR** (101 MHz, Methanol-*d*$_4$) δ 168.4, 159.2 (d, $^1J_{F-C}$ = 237.4 Hz), 138.6, 135.5, 128.9 (d, $^3J_{F-C}$ = 11.0 Hz), 112.3 (d, $^3J_{F-C}$ = 10.1 Hz), 111.8 (d, $^2J_{F-C}$ = 27.3 Hz), 107.8 (d, $^4J_{F-C}$ = 4.0 Hz), 107.2 (d, $^2J_{F-C}$ = 25.1 Hz), 33.8; **HRMS**(ESI, m/z) calcd for $C_{10}H_9FNO_2$ $[M+H]^+$194.0617, found 194.0616.

5-chloro-1-methyl-1*H*-indole-3-carboxylic acid (2p)



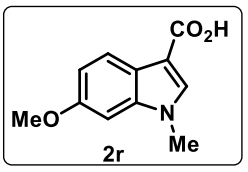
Yellow solid (25.2 mg, 60% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 217-218 °C; **^{1}H NMR** (400 MHz, Methanol-*d*$_4$) δ 8.06 (d, *J* = 1.9 Hz, 1H), 7.95 (s, 1H), 7.45 (d, *J* = 8.7 Hz, 1H), 7.24 (dd, *J* = 8.7, 2.0 Hz, 1H), 3.87 (s, 3H); **^{13}C NMR** (101 MHz, Methanol-*d*$_4$)δ 168.4, 138.3, 137.3, 129.3, 128.7, 127.8, 123.8, 121.7, 112.5, 33.7; **HRMS** (ESI, m/z) calcd for $C_{10}H_9ClNO_2$ $[M+H]^+$210.0322, found 210.0325.

5-bromo-1-methyl-1*H*-indole-3-carboxylic acid (2q)



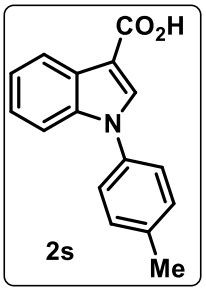
Off-white solid (19.3 mg, 38% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 193-196°C; **^{1}H NMR** (400 MHz, DMSO-*d*$_6$) δ 8.12 (d, *J* = 1.9 Hz, 1H), 8.08 (s, 1H), 7.53 (d, *J* = 8.7 Hz, 1H), 7.38 (dd, *J* = 8.7, 2.0 Hz, 1H), 3.85 (s, 3H); **^{13}C NMR** (101 MHz, DMSO-*d*$_6$) δ 165.2, 137.3, 135.8, 128.1, 124.7, 122.8, 114.3, 112.9, 105.8, 33.2; **HRMS** (ESI, m/z) calcd for $C_{10}H_9BrNO_2$ $[M+H]^+$ 253.9817, found 253.9806.

6-chloro-1-methyl-1*H*-indole-3-carboxylic acid (2r)



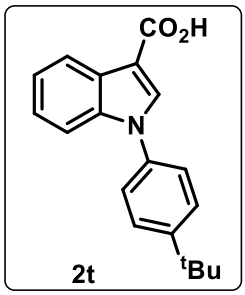
Off-white solid (21 mg, 51% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 155-157 °C; (Due to solubility problem, a few drops of CD_3OD was added with $CDCl_3$) **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.08 (d, *J* = 8.7 Hz, 1H), 7.78 (s, 1H), 6.96 (dd, *J* = 8.7, 2.0 Hz, 1H), 6.81 (d, *J* = 1.8 Hz, 1H), 3.90 (s, 3H), 3.81 (s, 3H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 172.7, 156.9, 138.0, 135.1, 122.3, 120.9, 111.46, 106.5, 93.4, 55.7, 33.4; **HRMS** (ESI, m/z) calcd for $C_{11}H_{12}NO_3$ $[M+H]^+$ 206.0817, found 206.0816.

1-(p-tolyl)-1*H*-indole-3-carboxylic acid (2s)



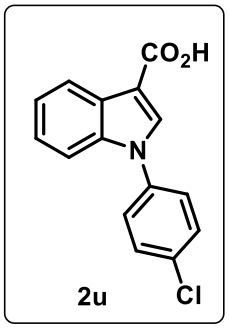
Off-white solid (38.2 mg, 76% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 162-163 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.32 (d, *J* = 7.8 Hz, 1H), 8.11 (s, 1H), 7.49 (d, *J* = 8.1 Hz, 1H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.38 – 7.28 (complex, 4H), 2.47 (s, 3H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 170.5, 138.0, 137.0, 135.8, 135.5, 130.4, 127.0, 124.7, 123.5, 122.7, 121.9, 111.1, 108.1, 21.1; **HRMS** (ESI, m/z) calcd for $C_{16}H_{14}NO_2$ $[M+H]^+$252.1025, found 252.1032.

1-(4-(tert-butyl)phenyl)-1*H*-indole-3-carboxylic acid (2t)



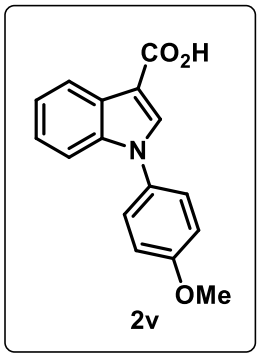
Off-white solid (45.6 mg, 76% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 194-196 °C; (Due to solubility problem, a few drops of CD_3OD was added with $CDCl_3$) **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.25 – 8.20 (m, 1H), 8.02 (s, 1H), 7.55 – 7.49 (m, 2H), 7.47 (d, *J* = 7.8 Hz, 1H), 7.41 – 7.37 (complex, 2H), 7.31 – 7.20 (complex, 2H), 1.35 (s, 9H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 167.9, 151.0, 136.8, 135.7 , 134.9, 127.0, 126.6, 124.3, 123.2, 122.3, 121.6, 111.1, 108.5, 31.2; **HRMS** (ESI, m/z) calcd for $C_{19}H_{20}NO_2$ $[M+H]^+$ 294.1494, found 294.1485.

1-(4-chlorophenyl)-1*H*-indole-3-carboxylic acid (2u)



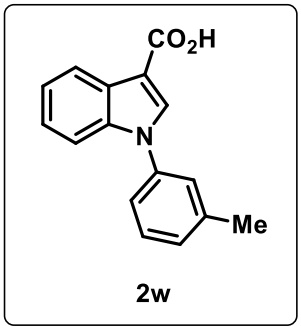
Off-white solid(58 mg, 51% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 193-194 °C; inseparable ICA and AA; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.32 (d, *J* = 7.5 Hz, 1H), 8.09 (s, 1H), 7.58 – 7.53 (m, 2H), 7.51 – 7.45 (m, 2H), 7.40 – 7.30 (m, 2H), 7.23 – 7.15 (m, 1H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 170.2, 136.8, 136.8, 135.1, 133.8, 130.1, 129.5, 126.1, 124.1, 123.9, 123.0, 122.1, 110.9; **HRMS**(ESI, m/z) calcd for $C_{15}H_{11}ClNO_2$ $[M+H]^+$272.0478, found 272.0466.

1-(4-methoxyphenyl)-1*H*-indole-3-carboxylic acid (2v)



Off-white solid (26.7 mg, 50% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 164-165 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.35 – 8.28 (m, 1H), 8.08 (s, 1H), 7.47 – 7.40 (m, 3H), 7.32 (comp, 2H), 7.11 – 7.03 (m, 2H), 3.90 (s, 3H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 170.4, 159.3, 137.4, 135.7, 131.2, 126.9, 126.4, 123.4, 122.6, 121.9, 114.9, 111.0, 107.9, 55.6; **HRMS**(ESI, m/z) calcd for $C_{16}H_{14}NO_3$ $[M+H]^+$268.0974, found 268.0974.

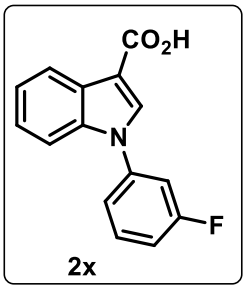
1-(m-tolyl)-1*H*-indole-3-carboxylic acid (2w)



Off-white solid (40.2 mg, 80% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 162-163 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.25 (d, *J* = 7.7 Hz, 1H), 8.05 (s, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.37 (t, *J* = 7.9 Hz, 1H), 7.23 (comp, 5H), 2.39 (s, 3H); **^{13}C NMR** (101 MHz, Chloroform-*d*)δ 170.7, 140.0, 138.3, 136.9, 135.5, 129.6, 128.7, 127.1, 125.4, 123.5, 122.7,

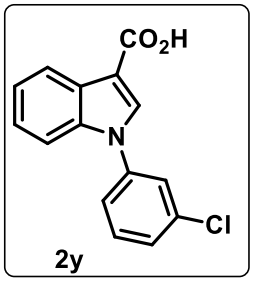
121.9, 121.9, 111.2, 108.2, 21.4; **HRMS** (ESI, m/z) calcd for $C_{16}H_{14}NO_2$ $[M+H]^+$252.1025, found 252.1032.

1-(3-fluorophenyl)-1*H*-indole-3-carboxylic acid (2x)



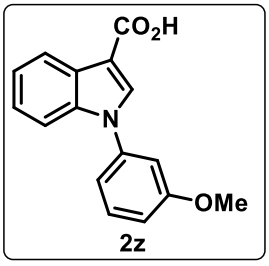
White solid (39.3 mg, 77% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 162-164 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.35 – 8.30 (m, 1H), 8.12 (s, 1H), 7.59 – 7.51 (m, 2H), 7.41 – 7.32 (m, 3H), 7.29 (app dt, *J* = 9.3, 2.2 Hz, 1H), 7.22 – 7.16 (m, 1H); **^{13}C NMR** (101 MHz, Chloroform-*d*)δ 170.2, 163.3 (d, $^1J_{F-C}$ = 250.5 Hz), 139.7 (d, $^3J_{F-C}$ = 9.8 Hz), 136.6, 135.0, 131.2 (d, $^3J_{F-C}$ = 9.3 Hz), 127.1, 123.9, 123.1, 122.1, 120.4 (d, $^4J_{F-C}$ = 3.0 Hz), 115.0 (d, $^2J_{F-C}$ = 21.0 Hz), 112.3 (d, $^2J_{F-C}$ = 24.0 Hz), 110.9, 109.0; **HRMS** (ESI, m/z) calcd for $C_{15}H_{11}NO_2$ $[M+H]^+$ 256.0774, found 256.0771.

1-(3-chlorophenyl)-1*H*-indole-3-carboxylic acid (2y)



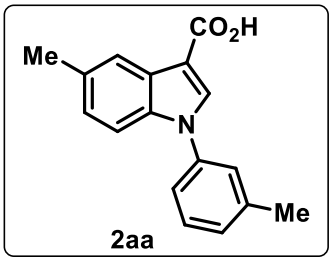
White solid (20.1 mg, 37% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 207-209 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.22 – 8.13 (m, 1H), 7.96 (s, 1H), 7.51 – 7.38 (m, 3H), 7.37 – 7.31 (m, 2H), 7.24 (comp, 2H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 167.1, 139.4, 136.4, 135.3, 134.2, 130.8, 127.8, 127.0, 124.8, 123.6, 122.7, 122.6, 121.8, 110.6, 109.6; **HRMS** (ESI, m/z) calcd for $C_{15}H_{11}ClNO_2$ $[M+H]^+$ 272.0478, found 272.0468.

1-(3-methoxyphenyl)-1*H*-indole-3-carboxylic acid (2z)

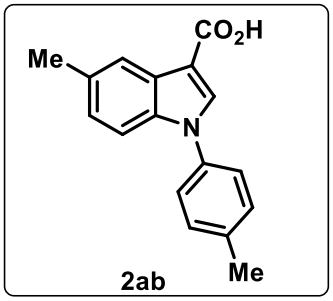


White solid (35.3 mg, 66% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 190 °C; (Due to solubility problem, a few drops of CD_3OD was added with $CDCl_3$) **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.14 (app dd, *J* = 6.7, 1.8 Hz, 1H), 7.96 (s, 1H), 7.44 (app dd, *J* = 6.9, 1.5 Hz, 1H), 7.35 (t, *J* = 8.1 Hz, 1H), 7.20 (comp, 2H), 7.03 – 6.98 (m, 1H), 6.95 (app t, *J* = 2.2 Hz, 1H), 6.89 (app dd, *J* = 8.1, 2.2 Hz, 1H), 3.77 (s, 3H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 167.3, 160.4, 139.3, 136.5, 134.5, 130.4, 126.9, 123.2, 122.3, 121.5, 116.7, 113.2, 110.9, 110.4, 108.8, 55.3; **HRMS** (ESI, m/z) calcd for $C_{10}H_{10}NO_2$ $[M+H]^+$ 268.0974, found 268.0966.

5-methyl-1-(m-tolyl)-1*H*-indole-3-carboxylic acid (2aa)



Colourless solid (28.1 mg, 53% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 202-203 °C; (Due to solubility problem, a few drops of $CDCl_3$ was added with CD_3OD) **^{1}H NMR** (400 MHz, Methanol-d_4) δ 8.01 – 7.99 (m, 1H), 7.97 (s, 1H), 7.80 (d, *J* = 1.0 Hz, 1H), 7.43 (t, *J* = 7.7 Hz, 1H), 7.36 – 7.30 (comp, 2H), 7.29 – 7.24 (m, 1H), 7.07 (d, *J* = 8.5 Hz, 1H), 2.46 (s, 3H), 2.43 (s, 3H); **^{13}C NMR** (101 MHz, Methanol-d_4) δ 168.6, 141.2, 139.7, 136.4, 135.6, 132.8, 130.6, 129.4, 128.6, 126.1, 125.8, 122.6, 122.2, 111.7, 109.5, 21.7, 21.4; **HRMS** (ESI, m/z) calcd for $C_{17}H_{16}NO_2$ $[M+H]^+$ 266.1181, found 266.1183.



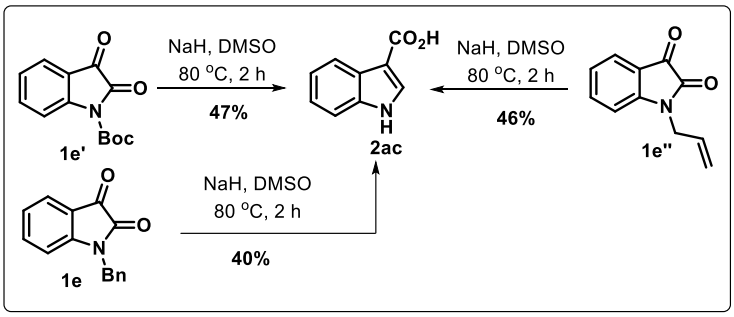
5-methyl-1-(*p*-tolyl)-1*H*-indole-3-carboxylic acid (2ab)

Off-white solid (40.3 mg, 76% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 210-212 °C; (Due to solubility problem, a few drops of $CDCl_3$ was added with CD_3OD) **^{1}H NMR** (400 MHz, Methanol-d_4) δ 7.97 (d, *J* = 3.7 Hz, 2H), 7.67

(s, 1H), 7.38-7.35 (comp, 3H), 7.32 (d, *J* = 8.4 Hz, 1H), 7.06 (d, *J* = 8.3 Hz, 1H), 2.46 (s, 3H), 2.42 (s, 3H); **^{13}C NMR** (101 MHz, Methanol-d_4) δ 168.4, 138.6, 136.9, 136.2, 135.4, 132.6, 131.1, 128.2, 125.6, 125.3, 122.0, 111.5, 109.1, 21.7, 21.2; **HRMS** (ESI, m/z) calcd for $C_{17}H_{16}NO_2$ $[M+H]^+$ 266.1181, found 266.1183.

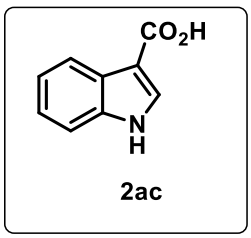
General procedure for the preparation of 1*H*-indole-3-carboxylic acid (2ac)

Into a 10 mL two neck round bottom flask equipped with an electromagnetic stirrer N-alkyl isatins (1 equiv., 0.2 mmol) and DMSO solvent (2 mL, 0.1 M) were taken in an inert atmosphere. Then the whole reaction mixture was degassed by Freeze-Pump-Thaw method. After degassing, NaH (6 equiv., 1.2 mmol) was added portionwise using a solid additional funnel and stirred at room temperature (30 °C) for 10 minutes. After that, the reaction mixture was warmed slowly to 80 °C and kept for 2 hours. After the full conversion was monitored by TLC, it was cooled to room temperature and quenched with cold 1N HCl solution (20 mL). The organic part was extracted by EtOAc (3x20 mL) with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Finally, it was purified by column chromatography on silica gel (230-400 mesh) using petroleum ether/ethyl acetate (4:1) as eluent to obtain the desired 1*H*-indole-3-carboxylic acid (**2ac**) in 40-47% yield.



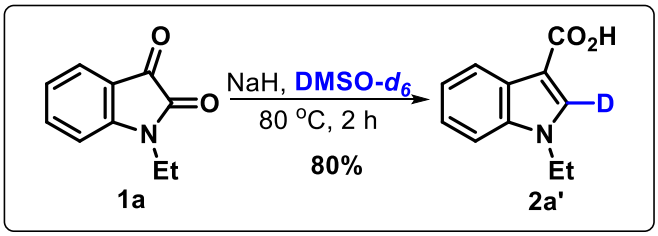
Characterization of the substrate 2ac

1*H*-indole-3-carboxylic acid (2ac)



White solid (40-47% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 232-234 °C; **^{1}H NMR** (400 MHz, Methanol-d^4) δ 8.11 – 8.03 (m, 1H), 7.94 (s, 1H), 7.46 – 7.39 (m, 1H), 7.24 – 7.12 (m, 2H); **^{13}C NMR** (101 MHz, Methanol-d^4) δ 169.2, 138.2, 133.4, 127.6, 123.6, 122.4, 122.0, 112.9, 108.7; **HRMS** (ESI, m/z) calcd for $C_9H_8NO_2$ $[M+H]^+$ 162.0555, found 162.0556.

General procedure for the preparation of (2a′)

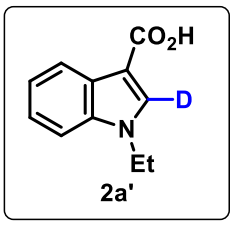


Into a 10 mL two neck round bottom flask equipped with an electromagnetic stirrer, N-ethyl isatin (1 equiv., 0.2 mmol, 35 mg) and anhydrous DMSO-d_6 solvent (1 mL, 0.2 M) were taken under in an inert atmosphere. Then the whole reaction mixture was subjected to degas by the Freeze-Pump-Thaw method. After degassing, NaH (6 equiv., 1.2 mmol) was added portionwise through an additional funnel and stirred at room temperature (30 °C) for 5 minutes. After that, the reaction mixture was warmed slowly to 80 °C and kept for 2 hours. After the full conversion was monitored by TLC, it was cooled to room temperature and quenched with cold 1N HCl solution (20 mL). The organic part was extracted by EtOAc

(3x20 mL) with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Finally, it was purified by column chromatography on silica gel (230-400 mesh) using petroleum ether/ethyl acetate (4:1) as eluent to obtain the desired 2-deuterio-1-ethyl indole-3-carboxylic acid **(2a′)** in 80% yield (30.4 mg). The rest all 2-deuterio indole-3-carboxylic acid derivatives were prepared following this procedure.

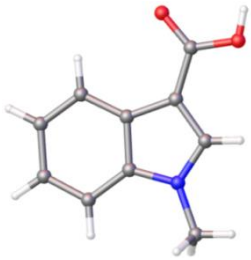
Characterization of the compounds 2a′-2s′

1-ethyl-1*H*-indole-3-carboxylic-2-d acid (2a′)



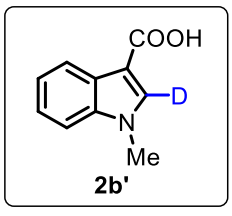
Colourless solid (30.4 mg, 80% yield); column chromatography eluent: petroleum ether/EtOAc = 4:1; mp 168-170 °C; **^{1}H NMR** (**400 MHz**, **$CDCl_3$**) δ 8.28-8.24 (m, 1H), 7.41-7.38 (m, 1H), 7.34-7.29 (comp, 2H), 4.23 (q, *J* = 7.2 Hz, 2H), 1.55 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (**101MHz**, **$CDCl_3$**) δ 170.6, 136.4, 134.5 (t, *J* = 2.8 Hz), 127.0, 122.8, 122.1, 121.9, 109.9, 106.2, 41.7, 15.1; **HRMS** (ESI, m/z) calcd for $C_{11}H_{11}DNO_2$ $[M+H]^+$ 191.0931, found 191.0932.

Table S4: Crystal Data and Structure of 2a′ (CCDC No. 2213917)



Empirical formula	$C_{10}H_8DNO_2$
Formula weight	176.19
Temperature/K	150.0
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	5.0244(4)
b/Å	29.261(2)
c/Å	5.9187(5)
α/°	90
β/°	100.326(5)
γ/°	90
Volume/Å^3	856.08(12)
Z	4
ρ_{calc}g/cm^3	1.367
μ/mm^{-1}	0.788
F(000)	368.0
Crystal size/mm^3	0.15 × 0.12 × 0.06
Radiation	Cu Kα (λ = 1.54178)
2Θ range for data collection/°	6.04 to 133.4
Index ranges	-5 ≤ h ≤ 5, -34 ≤ k ≤ 34, -7 ≤ l ≤ 7
Reflections collected	12421
Independent reflections	1498 [R_{int} = 0.0777, R_{sigma} = 0.0446]
Data/restraints/parameters	1498/0/121
Goodness-of-fit on F^2	1.244
Final R indexes [I>=2σ (I)]	R_1 = 0.0913, wR_2 = 0.1625
Final R indexes [all data]	R_1 = 0.0962, wR_2 = 0.1647

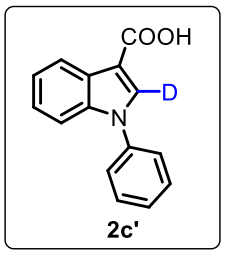
1-methyl-1*H*-indole-3-carboxylic-2-*d* acid (2b′):



Off white solid (21.7 mg, 62% yield); column chromatography eluent:petroleum ether/EtOAc = 4:1; mp 179-181 °C; **^{1}H NMR (400 MHz, $CDCl_3$+0.1 mL CD_3OD)** δ 8.15-8.11 (m, 1H), 7.33-7.30 (m, 1H), 7.28-7.21 (comp, 2H), 3.80 (s, 3H); **^{13}C NMR (101 MHz,**

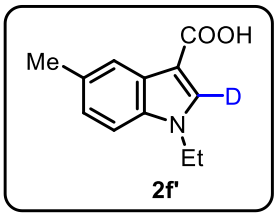
$CDCl_3$+0.1 mL CD_3OD) δ 167.6, 137.2, 126.7, 122.6, 121.8, 121.5, 109.7, 106.3, 33.2; **HRMS** (ESI, m/z) calcd for $C_{10}H_9DNO_2$ $[M+H]^+$ 177.0774, found 177.0777.

1-phenyl-1*H*-indole-3-carboxylic-2-*d* acid (2c′):



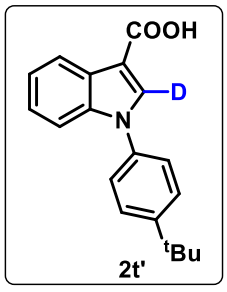
Colourless solid (25.6mg, 54% yield); column chromatography eluent:petroleum ether/EtOAc = 4:1; mp 156-159 °C; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.34 (dd, *J* = 7.2 Hz, 0.8 Hz, 1H), 7.60 – 7.52 (comp, 5H), 7.48 (tt, *J* = 7.2 Hz, 2.0 Hz, 1H), 7.40 – 7.36 (m, 1H), 7.34 – 7.30 (m, 1H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 170.6, 138.3, 136.9, 129.9, 128.0, 127.1, 124.8, 123.6, 122.8, 122.0, 111.1, 108.3; **HRMS** (ESI, m/z) calcd for $C_{15}H_{11}DNO_2$ $[M+H]^+$ 239.0931, found 239.0932.

1-ethyl-5-methyl-1*H*-indole-3-carboxylic-2-*d* acid (2f′):



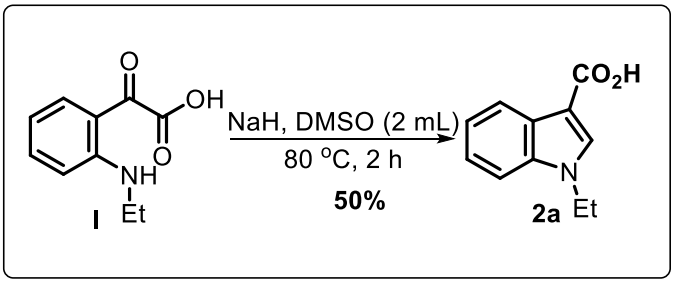
Colourless solid (26.5 mg, 65% yield); column chromatography eluent: petroleum ether/EtOAc = 4:1; mp 191-194 °C; **^{1}H NMR (400 MHz, $CDCl_3$+0.1 mL CD_3OD)** δ 7.99 (app s, 1H), 7.25 (app d, *J* = 7.6 Hz,1H), 7.10 (d, *J* = 8.0 Hz,1H),4.16 (q, *J* = 7.2 Hz, 2H), 2.48 (s, 1H), 1.49 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$+0.1 mL CD_3OD)** δ 168.5, 134.7, 131.5, 127.2, 124.2, 121.4, 109.5, 105.7, 41.6, 21.4, 15.0; **HRMS**(EI, m/z) calcd for $C_{12}H_{12}DNO_2$ $[M]^+$ 204.1009, found 204.1007.

1-(4-(tert-butyl)phenyl)-1*H*-indole-3-carboxylic-2-*d* acid (2t′):



Off white solid (33.8 mg, 57% yield); column chromatography eluent:petroleum ether/EtOAc = 4:1; mp 190-192 °C; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.33 (dd, *J* = 7.2 Hz, 0.8 Hz, 1H), 7.60 – 7.56 (comp, 2H), 7.53 (app d, *J* = 8.0 Hz, 1H), 7.48 – 7.44 (comp, 2H), 7.38 – 7.34 (m, 1H), 7.33 – 7.29 (m, 1H), 1.41 (s, 9H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 170.6, 151.2, 137.0, 135.7, 135.6, 127.0, 126.7, 124.4, 123.4, 122.7, 121.9, 111.2, 108.0, 34.8, 31.3; **HRMS** (ESI, m/z) calcd for $C_{19}H_{19}DNO_2$ $[M+H]^+$ 295.1557, found 295.1556.

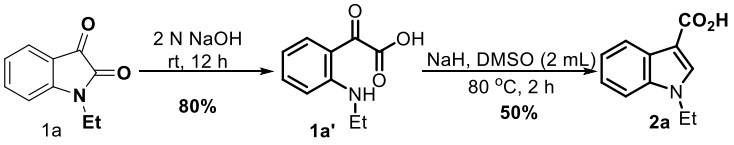
General procedure for the preparation of (2a) from compound I

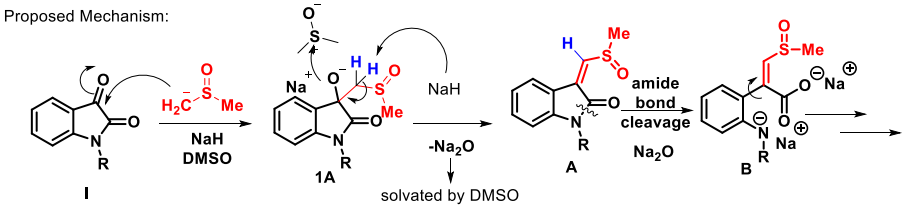


Into a 10 mL two neck round bottom flask equipped with an electromagnetic stirrer, 2-(2-(ethylamino)phenyl)-2-oxoacetic acid (**4**) (1 equiv., 0.2 mmol, 39 mg) and DMSO solvent (2 mL, 0.1 M) were taken in an inert atmosphere. Then the whole reaction mixture was subjected to degas by the Freeze-Pump-Thaw method. After degassing, NaH (6 equiv., 1.2 mmol) was added portionwise through an additional funnel and stirred at room temperature

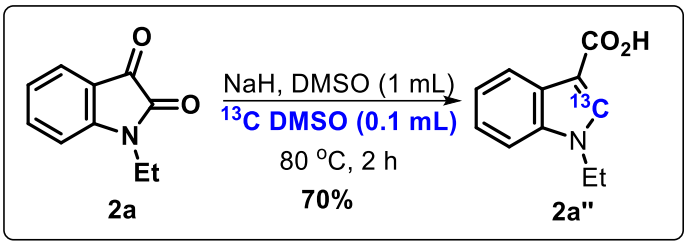
(30 °C) for 5 minutes. After that, the reaction mixture was warmed slowly to 80 °C and kept for 2 hours. After the full conversion was monitored by TLC, it was cooled to room temperature and quenched with cold 1N HCl solution (20 mL). The organic part was extracted by EtOAc (3x20 mL) with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Finally, it was purified by column chromatography on silica gel (230-400 mesh) using petroleum ether/ethyl acetate (4:1) as eluent to obtain the desired 1-ethyl-1H-indole-3-carboxylic acid **(2a)** in 50% yield (19 mg).

Indirect experiment of amide bond cleavage:

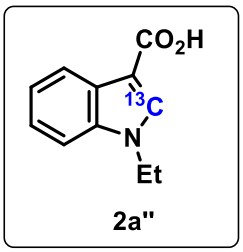




General procedure for the preparation of (2a′′)



Into a 10 mL two neck round bottom flask equipped with an electromagnetic stirrer, N-ethyl isatin (1 equiv., 0.2 mmol, 35 mg), DMSO (1 mL, 0.2 M) and ^{13}C DMSO (0.1 mL) solvent were taken under in an inert atmosphere. Then the whole reaction mixture was subjected to degas by the Freeze-Pump-Thaw method. After degassing, NaH (6 equiv., 1.2 mmol) was added pinch-wise through an additional funnel and stirred at room temperature (30 °C) for 5 minutes. After that, the reaction mixture was warmed slowly to 80 °C and kept for 2 hours. After the full conversion was monitored by TLC, it was cooled to room temperature and quenched with cold 1N HCl solution (20 mL). The organic part was extracted by EtOAc (3x20 mL) with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Finally, it was purified by column chromatography on silica gel (230-400 mesh) using petroleum ether/ethyl acetate (4:1) as eluent to obtain the desired 2-deuterio-1-ethyl-1H-indole-3-carboxylic acid (**2a′′**) in 70% yield (26.6 mg).



Characterization data of 2a′′

1-ethyl-1*H*-indole-3-carboxylic acid (C_2-^{13}C) (2a′′)

White solid (26.6 mg, 70% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 168-170 °C; **^{1}H NMR** (**400 MHz**, **Chloroform-*d***) δ 8.27 – 8.22 (m, 1H), 7.96 (s, 1H), 7.40 (app dt, *J* = 7.3, 3.2 Hz, 1H), 7.34 – 7.28 (m, 2H), 4.23 (q, *J* = 7.3 Hz, 2H), 1.55 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (**101MHz**, **Chloroform-*d***) δ 170.2, 136.5, 134.7(sharp), 127.0, 122.8, 122.1, 121.9, 109.9, 106.3, 41.7, 15.1; **HRMS**(ESI, m/z) calcd for $C_{11}H_{12}NO_2$ $[M+H]^+$191.0902, found 191.0898.

Detection of the intermediate B by ESIMS

The reaction was quenched after 30 minute and crude sample was submitted for ESIMS.

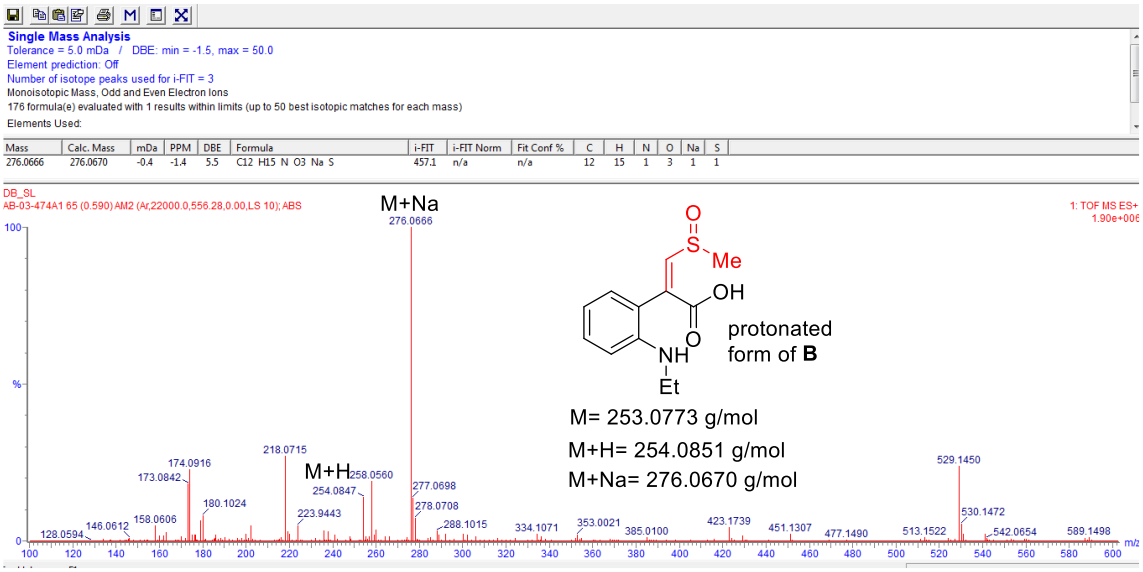
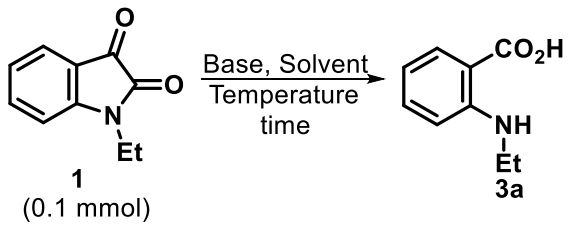


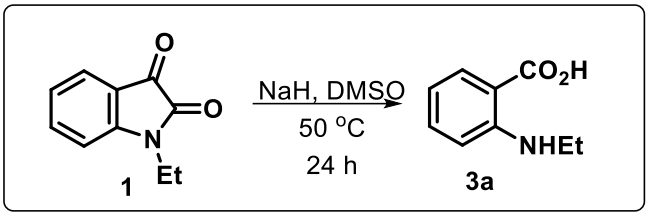
Table S5: Screening of the reaction conditions[a]



entry	base (x equiv.)	solvent (x mL)	temperature (°C)	reaction atmosphere	time (h)	yield[b] (%)
1[c]	NaH (4)	DMSO (1)	rt (33)	air	48	12
2[c]	NaH (4)	DMSO (1)	rt (33)	O_2 balloon	48	18
3[c]	NaH (6)	DMSO (1)	rt (33)	air	48	12
4[c]	NaH (6)	DMSO (1)	40	O_2 balloon	24	30
5[d]	NaH (6)	DMSO (1)	50	O_2 balloon	24	73
6[d]	**NaH (6)**	**DMSO (1)**	**50**	**air**	**24**	**85**
7[d]	NaH (6)	DMSO (1)	60	O_2 balloon	24	61
8[d]	NaH (6)	DMSO (1)	60	air	24	61
9[d]	NaH (4)	DMSO (1)	50	air	24	61
10[d,e]	NaH (6)	DMSO (1)	50	N_2 balloon	24	12
11[f]	NaH (6)	DMF (1)	50	air	24	67
12	NaH (6)	dioxane	50	air	24	37
13	NaH (6)	toluene	50	air	24	40

[a]All reactions were set up on a 0.1 mmol scale in presence of NaH in DMSO solvent [b]Isolated yield. [c]Conditions: **1** (1 equiv.), NaH (4-6 equiv.) in an a bottle grade DMSO solvent (1 mL) at rt to 50 °C. [d]Conditions: **1** (1 equiv.), NaH (4-6 equiv.) in an anhydrous DMSO solvent (1 mL) at 50-60 °C. [e]Applying the Freeze-Pump-Thaw method. [f]Reaction happened in anhydrous DMF solvent.

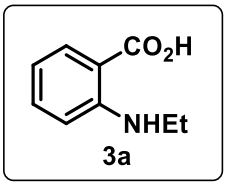
General procedure for the preparation of 2-(ethylamino)benzoic acid (3a)



Into a 10 mL two neck round bottom flask equipped with an electromagnetic stirrer, N-ethyl isatin (1 equiv., 0.2 mmol, 35 mg) and DMSO solvent (2 mL, 0.1 M) were taken in an inert atmosphere. Sodium hydride (6 equiv., 1.2 mmol) was added pinch-wise through an additional funnel and stirred at room temperature (30 °C) for 10 minutes. After that, the reaction mixture was warmed slowly to 50 °C and kept for 24 hours. After the full conversion was monitored by TLC, it was cooled to room temperature and quenched with cold 1N HCl solution (20 mL). The organic part was extracted by EtOAc (3x20 mL) with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Finally, it was purified by column chromatography on silica gel (230-400 mesh) using petroleum ether/ethyl acetate (4:1) as eluent to obtain the desired 2-(ethylamino)benzoic acid (**3a**) in 85% yield (30 mg). The rest all anthranilic acid derivatives were prepared following this procedure.

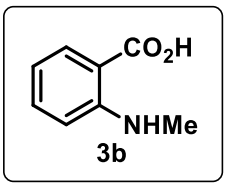
Characterization of the substrate 3a-3aa:

2-(ethylamino)benzoic acid (3a)



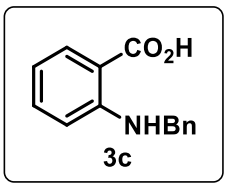
Colourless solid (28 mg, 85% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 148-152 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.98 (app dd, *J* = 8.1, 1.6 Hz, 1H), 7.40 (comp, 1H), 6.71 (app d, *J* = 8.5 Hz, 1H), 6.64 – 6.60 (m, 1H), 3.27 (q, *J* = 7.2 Hz, 2H), 1.33 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (101MHz, Chloroform-*d*) δ 173.8, 151.6, 135.6, 132.7, 114.6, 111.5, 108.6, 37.5, 14.5; **HRMS** (ESI, m/z) calcd for $C_9H_{12}NO_2$ $[M+H]^+$166.0868, found 166.0869.

2-(methylamino)benzoic acid (3b)



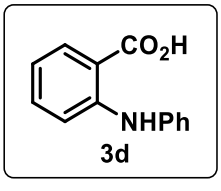
Yellowish solid (27.5 mg, 91% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 176-178 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.99 (app dd, *J* = 8.0, 1.6 Hz, 1H), 7.44 (comp, 1H), 6.71 (d, *J*= 8.4 Hz, 1H),6.66-6.62 (m, 1H), 2.94 (s, 3H); **^{13}C NMR** (101MHz, Chloroform-*d*) δ 173.9, 152.4, 135.7, 132.6, 114.8, 111.1, 108.8, 29.7; **HRMS** (ESI, m/z) calcd for $C_8H_{10}NO_2$ $[M+H]^+$ 152.0712, found 152.0718.

2-(benzylamino)benzoic acid (3c)



Off-white solid (42.6 mg, 94% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 166-168 °C; (Due to solubility problem, a few drops of CD_3OD was added with $CDCl_3$) **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.88 (app d, *J* = 8.0 Hz, 1H), 7.34 – 7.07 (comp, 6H), 6.54 (comp, 2H), 4.35 (d, *J* = 10.1 Hz, 2H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 170.9, 150.8, 138.6, 134.5, 132.1, 128.4, 126.9, 126.9, 114.9, 111.6, 110.2, 46.8; **HRMS** (ESI, m/z) calcd for $C_{14}H_{14}NO_2$ $[M+H]^+$ 228.1025, found 228.1031.

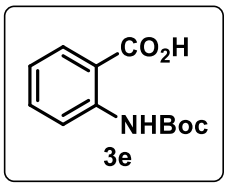
2-(phenylamino)benzoic acid (3d)



Colourless solid (34.1 mg, 80% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 184-186 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 9.32 (br s, 1H), 8.05 (app dd, *J* = 8.1, 1.5 Hz, 1H), 7.40 –

7.33 (comp, 3H), 7.30 – 7.25 (comp, 2H), 7.25 – 7.21 (m, 1H), 7.16 – 7.11 (m, 1H), 6.76 (app td, *J* = 7.6, 7.1, 1.0 Hz, 1H); **^{13}C NMR** (101MHz, Chloroform-*d*) δ 173.3, 148.9, 140.3, 135.2, 132.6, 129.4, 124.1, 123.2, 117.2, 114.0, 110.4; **HRMS**(ESI, m/z) calcd for $C_{13}H_{12}NO_2$ $[M+H]^+$ 214.0868, found 214.0871.

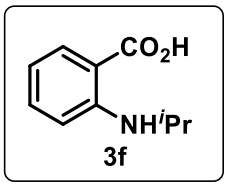
2-((tert-butoxycarbonyl)amino)benzoic acid (3e)



3e

Colourless solid (25.1 mg, 53% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 165-166 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 10.02 (s, 1H), 8.47 (d, *J* = 8.5 Hz, 1H), 8.11 (app dd, *J* = 8.0, 1.6 Hz, 1H), 7.59 – 7.55 (m, 1H), 7.06 – 7.02 (m, 1H), 1.55 (s, 9H); **^{13}C NMR** (101MHz, Chloroform-*d*) δ 172.4, 152.8, 142.9, 135.6, 131.9, 121.3, 119.0, 113.2, 80.9, 28.3; **HRMS** (ESI, m/z) calcd for $C_{12}H_{16}NO_4$ $[M+H]^+$ 238.1079, found 238.1078.

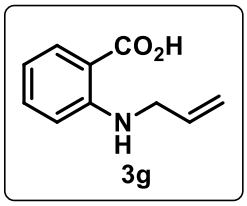
2-(isopropylamino)benzoic acid (3f)



3f

Colourless solid (29.7 mg, 83% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 148-150 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.97 (app dd, *J* = 8.1, 1.7 Hz, 1H), 7.38 (comp, 1H), 6.71 (d, *J* = 8.6 Hz, 1H), 6.57 (comp, 1H), 3.74 (hept, *J* = 6.2 Hz, 1H), 1.29 (d, *J* = 6.3 Hz, 6H); **^{13}C NMR** (101MHz, Chloroform-*d*) δ 173.4, 151.0, 135.5, 132.8, 114.2, 111.8, 108.3, 43.4, 22.8; **HRMS** (ESI, m/z) calcd for $C_{10}H_{14}NO_2$ $[M+H]^+$ 180.1025, found 180.1028.

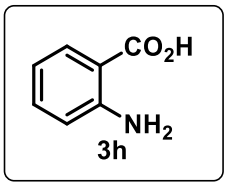
2-(allylamino)benzoic acid (3g)



3g

Colourless solid (26.9 mg, 76% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 150-151 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.00 (app dd, *J* = 8.1, 1.7 Hz, 1H), 7.40 (comp, 1H), 6.69 (d, *J* = 8.5 Hz, 1H), 6.64 (comp, 1H), 5.97 (ddt, *J* = 17.2, 10.2, 5.0 Hz, 1H), 5.31 (dq, *J* = 17.2, 1.7 Hz, 1H), 5.21 (dq, *J* = 10.3, 1.5 Hz, 1H), 3.91 (dt, *J* = 4.9, 1.7 Hz, 2H); **^{13}C NMR** (101MHz, Chloroform-*d*) δ 174.0, 151.5, 135.6, 134.3, 132.6, 116.2, 115.0, 111.8, 108.9, 45.3; **HRMS** (ESI, m/z) calcd for $C_{10}H_{12}NO_2$ $[M+H]^+$ 178.0868, found 178.08721.

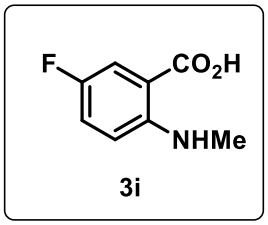
2-aminobenzoic acid (3h)



3h

Off-white solid (20 mg, 73% yield); column chromatography eluent, petroleum ether/EtOAc= 4:1; mp 146-148 °C; (Due to solubility problem, a few drops of CD_3OD was added with $CDCl_3$) **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.86 (d, *J* = 8.0 Hz, 1H), 7.32 – 7.14 (m, 1H), 6.75 – 6.51 (m, 2H), 4.84 (s, 2H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 171.3, 150.5, 134.3, 131.8, 116.7, 116.4, 110.5; **HRMS** (ESI, m/z) calcd for $C_7H_8NO_2$ $[M+H]^+$ 138.0555, found 138.0570.

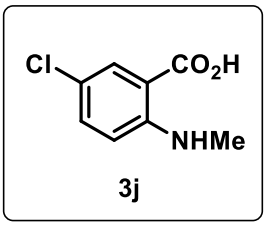
5-fluoro-2-(methylamino)benzoic acid (3i)



3i

Off-white solid (20 mg, 59% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 193-195 °C; (Due to solubility problem, a few drops of CD_3OD was added with $CDCl_3$) **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.57-7.52 (m, 1H),7.10-7.03 (m, 1H), 6.55 (dd, *J* = 9.2, 4.4 Hz, 1H), 2.82 (s, 3H); **^{13}C NMR** (101MHz, Chloroform-*d*) δ 169.9, 153.0(d, $^1J_{F-C}$ = 233.3 Hz), 148.7, 121.6 (d, $^2J_{F-C}$ = 23.2 Hz), 117.2 (d, $^2J_{F-C}$ = 23.2 Hz), 111.8 (d, $^3J_{F-C}$ = 7.1 Hz), 109.9 (d, $^3J_{F-C}$ = 3.8 Hz), 29.7; **HRMS** (ESI, m/z) calcd for $C_8H_9FNO_2$ $[M+H]^+$ 170.0617, found 170.0621.

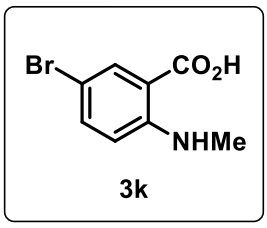
5-chloro-2-(methylamino)benzoic acid (3j)



3j

Colourless solid (24.8 mg, 67% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 178-180 °C; (Due to solubility problem, a few drops of CD_3OD was added with $CDCl_3$) **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.81 (app dd, *J* = 2.6, 1.3 Hz, 1H), 7.23 (comp, 1H), 6.53 (d, *J* = 9.0 Hz, 1H), 2.81 (s, 3H); **^{13}C NMR** (101MHz, Chloroform-*d*) δ 170.0, 150.6, 134.4, 131.3, 118.8, 112.0, 110.6, 29.4; **HRMS** (ESI, m/z) calcd for $C_8H_9ClNO_2$ $[M+H]^+$ 186.0322, found 186.0330.

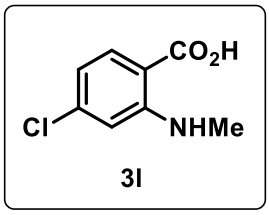
5-bromo-2-(methylamino)benzoic acid (3k)



3k

Off-white solid (24.8 mg, 54% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 172-174 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.06 (d, *J* = 2.4 Hz, 1H), 7.47 (app dd, *J* = 9.0, 2.4 Hz, 1H), 6.59 (d, *J* = 9.1 Hz, 1H), 2.92 (s, 3H); **^{13}C NMR** (101MHz, Chloroform-*d*) δ 172.5, 151.3, 138.3, 134.5, 113.0, 110.0, 106.0, 29.8; **HRMS** (ESI, m/z) calcd for $C_8H_9BrNO_2$ $[M+2+H]^+$ 231.9817, found 231.9796.

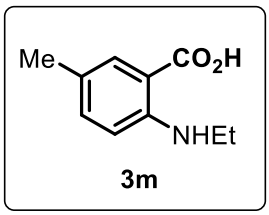
4-chloro-2-(methylamino)benzoic acid (3l)



3l

Off-white solid (30 mg, 81% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 186-188 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.88 (d, *J* = 8.6 Hz, 1H), 6.67 (d, *J* = 1.9 Hz, 1H), 6.59 (app dd, *J* = 8.6, 1.9 Hz, 1H), 2.92 (s, 3H); **^{13}C NMR** (101MHz, Chloroform-*d*) δ 173.0, 153.1, 142.1, 133.9, 115.1, 110.8, 107.2, 29.6; **HRMS** (ESI, m/z) calcd for $C_8H_9ClNO_2$ $[M+H]^+$ 186.0322, found 186.0320.

2-(ethylamino)-5-methylbenzoic acid (3m)

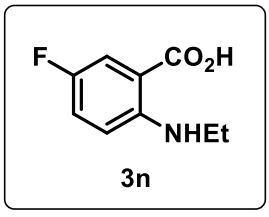


3m

Off-white solid (20 mg, 56% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 155-156 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.82 – 7.75 (m, 1H), 7.24 (app dd, *J* = 8.6, 2.0 Hz, 1H), 6.66 (d, *J* = 8.6 Hz, 1H), 3.25 (q, *J* = 7.2 Hz, 2H), 2.25 (s, 3H), 1.32 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (101MHz, Chloroform-*d*) δ 173.7, 149.5, 136.7, 132.2, 123.9, 111.9, 108.6, 37.8, 20.1, 14.5; **HRMS** (ESI, m/z) calcd for $C_{10}H_{14}NO_2$ $[M+H]^+$180.1025, found 180.1025.

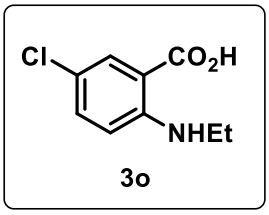
2-(ethylamino)-5-fluorobenzoic acid (3n)

Yellow solid (33 mg, 90% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 143-145 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.66 (app dd, *J* = 9.6, 3.1 Hz, 1H), 7.20-7.15 (m, 1H), 6.66 (app dd, *J* = 9.3, 4.4 Hz, 1H), 3.24 (q, *J* = 7.2 Hz, 2H), 1.33 (t, J = 7.2 Hz, 3H); **^{13}C NMR** (101MHz, Chloroform-*d*) δ 172.6, 152.9 (d, $^1J_{F\text{-}C}$= 232.3 Hz), 148.4, 123.5 (d, $^2J_{F\text{-}C}$ = 23.2 Hz), 117.4 (d, $^2J_{F\text{-}C}$ = 23.1 Hz), 112.8 (d, $^3J_{F\text{-}C}$ = 6.8 Hz), 108.3 (d, $^3J_{F\text{-}C}$ = 6.0 Hz), 38.0, 14.5; **HRMS** (ESI, m/z) calcd for $C_9H_{11}FNO_2$ $[M+H]^+$ 184.0774, found 184.0780.



3n

5-chloro-2-(ethylamino)benzoic acid (3o)

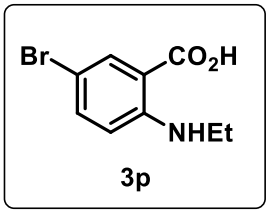


3o

Yellow solid (35 mg, 88% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 168-170 °C; (Due to solubility problem, a few drops of CD_3OD was added with $CDCl_3$) **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.82 (d, *J* = 2.8 Hz, 1H), 7.21 (app dd, *J* =

9.0, 2.5 Hz, 1H), 6.55 (d, *J* = 9.0 Hz, 1H), 3.14 (q, *J* = 7.2 Hz, 2H), 1.23 (t, J = 7.2 Hz, 3H); **^{13}C NMR** (101MHz, Chloroform-*d*) δ 170.0, 149.6, 134.4, 131.3, 118.7, 112.5, 110.5, 37.3, 14.1; **HRMS** (ESI, m/z) calcd for $C_9H_{11}ClNO_2$ $[M+H]^+$ 200.0478, found 200.0481.

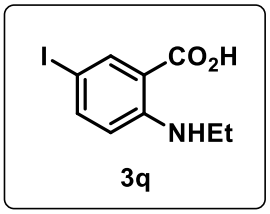
5-bromo-2-(ethylamino)benzoic acid (3p)



3p

Off-white solid (41 mg, 84% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 178-180 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.07 (d, *J* = 2.5 Hz, 1H), 7.44 (app dd, *J* = 9.1, 2.5 Hz, 1H), 6.60 (d, *J* = 9.1 Hz, 1H), 3.24 (q, *J* = 7.2 Hz, 2H), 1.32 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (101MHz, Chloroform-*d*) δ 172.3, 150.5, 138.2, 134.6, 113.3, 109.7, 105.8, 37.6, 14.4; **HRMS** (ESI, m/z) calcd for $C_9H_{11}BrNO_2$ $[M+H]^+$ 245.9953, found 245.9964.

2-(ethylamino)-5-iodobenzoic acid (3q)

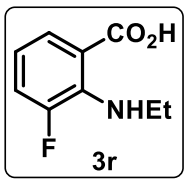


3q

Off-white solid (44.8 mg, 77% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 174-176 °C; (Due to solubility problem, a few drops of CD_3OD was added with $CDCl_3$) **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.09 (d, *J* = 2.2 Hz, 1H), 7.44 (app dd, *J* = 8.9, 2.2 Hz, 1H), 6.37 (d, *J* = 8.9 Hz, 1H), 3.09 (q, *J* = 7.2 Hz, 2H), 1.18 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (101MHz, Chloroform-*d*) δ 169.7, 150.4, 142.7, 140.3, 113.7, 112.0, 73.9, 37.2, 14.0; **HRMS** (ESI, m/z) calcd for $C_9H_{11}INO_2$ $[M+H]^+$ 291.9834, found 291.9842.

2-(ethylamino)-3-fluorobenzoic acid (3r)

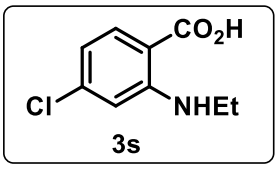
Colourless solid (29.6 mg, 81% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 188-190 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.46 (s, 1H), 7.81 (app dt, *J* = 8.1, 1.1 Hz, 1H), 7.16 (comp, 1H), 6.66 (app td, *J* = 8.0, 4.5 Hz, 1H), 3.50 (qd, *J* = 7.2, 3.7 Hz, 2H), 1.30 – 1.25 (dt, 3H) ; **^{13}C NMR** (101MHz, Chloroform-*d*) δ 172.3(d, $^4J_{F\text{-}COOH}$ = 3.5 Hz), 152.9(d, $^1J_{F\text{-}C}$ = 243.7 Hz), 140.5 (d, $^2J_{F\text{-}C}$ = 10.5 Hz), 128.1(d, $^4J_{F\text{-}C}$ = 2.7 Hz), 121.5(d, $^2J_{F\text{-}C}$ = 20.6 Hz), 116.5(d, $^3J_{F\text{-}C}$ = 7.4 Hz), 114.4(d, $^3J_{F\text{-}C}$ = 4.5 Hz), 41.45 (d, $^4J_{F\text{-}CH2}$ = 10.9 Hz), 15.9(d, $^5J_{F\text{-}CH3}$ = 2.4 Hz); **HRMS**(ESI, m/z) calcd for $C_9H_{11}FNO_2$ $[M+H]^+$ 184.0774, found 184.0779.



3r

4-chloro-2-(ethylamino)benzoic acid (3s)

Off-white solid (35 mg, 88% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 200-204 °C; (Due to solubility problem, a few drops of CD_3OD was added with $CDCl_3$) **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.77 (app d, *J* = 8.5 Hz, 1H), 6.57 (app s, 1H), 6.46 (app dd, *J* = 8.5, 2.0 Hz, 1H), 3.12 (q, *J* = 7.2 Hz, 2H), 1.23 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (101MHz, Chloroform-*d*) δ 170.3, 151.7, 140.7, 133.5, 114.5, 110.7, 108.3, 37.3, 14.0; **HRMS** (ESI, m/z) calcd for $C_9H_{11}ClNO_2$ $[M+H]^+$ 200.0478, found 200.0483.

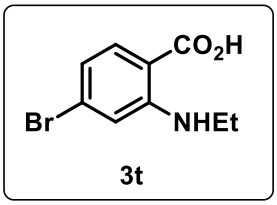


3s

Table S6: Crystal Data and Structure of 3s (CCDC No. 2213916)

Empirical formula	$C_9H_{10}ClNO_2$
Formula weight	199.63
Temperature/K	113.00
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	7.8685(6)
b/Å	7.0616(5)
c/Å	16.2493(12)
α/°	90
β/°	91.433(2)
γ/°	90
Volume/Å^3	902.60(12)
Z	4
ρ_{calc}g/cm^3	1.469
μ/mm^{-1}	3.473
F(000)	416.0
Crystal size/mm^3	0.5 × 0.45 × 0.4
Radiation	Cu Kα (λ = 1.54178)
2Θ range for data collection/°	16.634 to 130.178
Index ranges	$-9 \le h \le 9$, $-8 \le k \le 8$, $-18 \le l \le 19$
Reflections collected	9965
Independent reflections	1481 [R_{int} = 0.0541, R_{sigma} = 0.0394]
Data/restraints/parameters	1481/0/120
Goodness-of-fit on F^2	1.520
Final R indexes [I>=2σ (I)]	R_1 = 0.0522, wR_2 = 0.1272
Final R indexes [all data]	R_1 = 0.0523, wR_2 = 0.1273
Largest diff. peak/hole / e Å^{-3}	0.44/-0.99

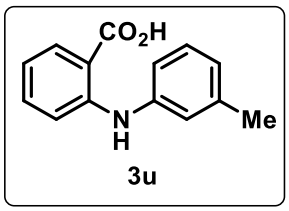
4-bromo-2-(ethylamino)benzoic acid (3t)



3t

Off-white solid (38.5 mg, 79% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 190-192 °C; (Due to solubility problem, a few drops of CD_3OD was added with $CDCl_3$) **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.67 (d, *J* = 8.5 Hz, 1H), 6.72 (d, *J* = 1.7 Hz, 1H), 6.59 (dd, *J* = 8.5, 1.8 Hz, 1H), 3.10 (q, *J* = 7.2 Hz, 2H), 1.21 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (101MHz, Chloroform-*d*) δ 170.4, 151.7, 133.5, 129.6, 117.3, 113.6, 108.5, 37.2, 14.0; **HRMS** (ESI, m/z) calcd for $C_9H_{11}BrNO_2[M+H+2]^+$ 245.9953, found 245.9961.

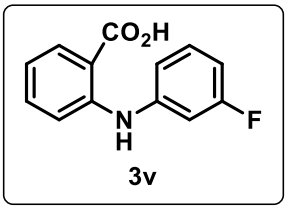
2-(m-tolylamino)benzoic acid (3u)



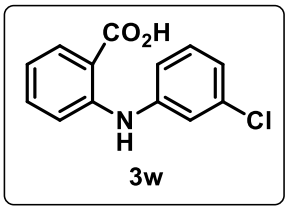
3u

Off-white solid (20 mg, 44% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 142-144 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 9.27 (br s, 1H), 8.04 (app dd, *J* = 8.1, 1.5 Hz, 1H), 7.37-7.33 (m, 1H), 7.27 – 7.22 (comp, 2H), 7.09 (app d, *J* = 5.6 Hz, 2H), 6.95 (app d, *J* = 7.5 Hz, 1H), 6.77 – 6.73 (m, 1H), 2.36 (s, 3H); **^{13}C NMR** (101MHz, Chloroform-*d*) δ 173.0, 149.0, 140.2, 139.4, 135.1, 132.5, 129.2, 124.9, 123.8, 120.1, 117.0, 114.1, 110.2, 21.4; **HRMS**(ESI, m/z) calcd for $C_{14}H_{14}NO_2$ $[M+H]^+$ 228.1025, found 228.1023.

2-((3-fluorophenyl)amino)benzoic acid (3v)



Off-white solid (21.3 mg, 46% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 154-156 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 9.34 (br s, 1H), 8.07 (app dd, *J* = 8.1, 1.5 Hz, 1H), 7.41 (comp, 1H), 7.34 – 7.23 (comp, 2H), 7.08 – 6.94 (comp, 2H), 6.91 – 6.72 (comp, 2H); **^{13}C NMR** (101MHz, Chloroform-*d*) δ 173.3, 163.5 (d, $^1J_{F\text{-}C}$ = 245.7 Hz), 147.8, 142.3 (d, $^3J_{F\text{-}C}$ = 10.2 Hz), 135.3, 132.7, 130.5 (d, $^3J_{F\text{-}C}$ = 9.6 Hz), 118.1, 117.8 (d, $^4J_{F\text{-}C}$ = 2.5 Hz), 114.5, 111.2, 110.4 (d, $^2J_{F\text{-}C}$ = 21.2 Hz), 109.1 (d, $^2J_{F\text{-}C}$ = 23.6 Hz); **HRMS** (ESI, m/z) calcd for $C_{13}H_{11}FNO_2$ $[M+H]^+$ 232.0774, found 232.0771.

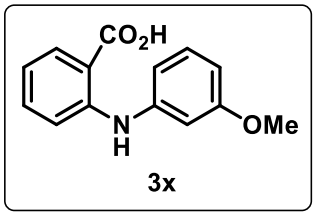


2-((3-chlorophenyl)amino)benzoic acid (3w)

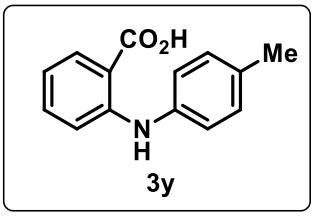
Colourless solid (25.3 mg, 51% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 170-171 °C; **^{1}H NMR (**400 MHz, Chloroform-*d***)** δ 9.30 (s, 1H), 8.06 (app dd, *J* = 8.1, 1.5 Hz, 1H), 7.40 (comp, 1H), 7.27 (app t, *J* = 7.8 Hz, 3H), 7.19 – 7.11 (m, 1H), 7.11 – 7.04 (m, 1H), 6.86 – 6.75 (m, 1H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 173.3, 147.9, 141.9, 135.3, 135.0, 132.7, 130.4, 123.7, 122.3, 120.4, 118.1, 114.4, 111.2; **HRMS**(ESI, m/z) calcd for $C_{13}H_{11}ClNO_2$ $[M+H]^+$ 248.0478, found 248.0482.

2-((3-methoxyphenyl)amino)benzoic acid (3x)

White solid (27.2 mg, 56% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 148-149 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 9.29 (br s, 1H), 8.05 (app dd, *J* = 8.1, 1.5 Hz, 1H), 7.38-7.34 (m, 1H), 7.29-7.24 (comp, 2H), 6.88 – 6.85 (m, 1H), 6.82 (app t, *J* = 2.2 Hz, 1H), 6.79 – 6.74 (m, 1H), 6.68 (app dd, *J* = 8.2, 2.4 Hz, 1H), 3.81 (s, 3H); **^{13}C NMR** (101MHz, Chloroform-*d*) δ 173.5, 160.6, 148.7, 141.6, 135.2, 132.6, 130.1, 117.3, 115.2, 114.5, 110.6, 109.6, 108.6, 55.3; **HRMS**(ESI, m/z) calcd for $C_{14}H_{14}NO_3$ $[M+H]^+$ 244.0974, found 244.0977.

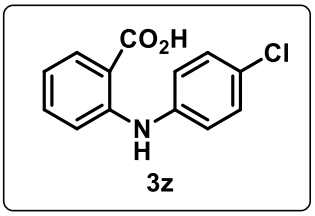


2-(p-tolylamino)benzoic acid (3y)



White solid (18.2 mg, 40% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 186-188 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 9.23 (br s, 1H), 8.03 (app dd, *J* = 8.1, 1.5 Hz, 1H), 7.34-7.30 (m, 1H), 7.20 – 7.11 (comp, 5H), 6.74 – 6.70 (m, 1H), 2.36 (s, 3H); **^{13}C NMR** (101MHz, Chloroform-*d*) δ 173.0, 149.6, 137.6, 135.1, 134.1, 132.5, 130.0, 123.8, 116.7, 113.8, 109.8, 20.9; **HRMS**(ESI, m/z) calcd for $C_{14}H_{14}NO_2$ $[M+H]^+$ 228.1025, found 228.1024.

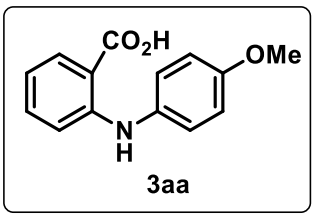
2-((4-chlorophenyl)amino)benzoic acid (3z)



White solid (27.2 mg, 55% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 150-152 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 9.26 (br s, 1H), 8.04 (app dd, *J* = 8.1, 1.6 Hz, 1H), 7.36 (comp, 1H), 7.33 – 7.29 (comp, 2H), 7.21 – 7.14 (comp, 3H), 6.81 – 6.74 (m, 1H); **^{13}C NMR** (101MHz, Chloroform-*d*) δ 173.2, 148.5, 139.0, 135.3, 132.7, 129.5, 129.0,

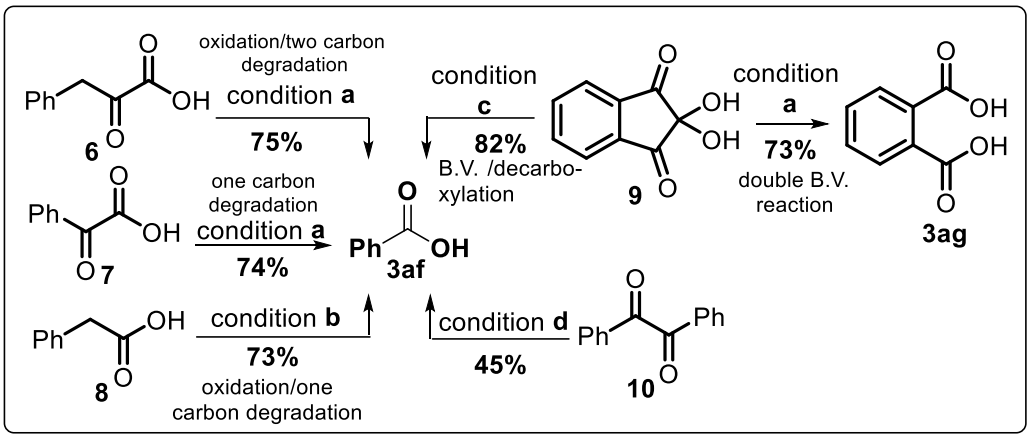
124.2, 117.6, 114.0, 110.7; **HRMS** (ESI, m/z) calcd for $C_{13}H_{11}ClNO_2$ $[M+H]^+$ 248.0478, found 248.0482.

2-((4-methoxyphenyl)amino)benzoic acid (3aa)



Off-white solid (30.1 mg, 62% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 170-172 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 9.13 (s, 1H), 8.02 (app dd, *J* = 8.0, 1.3 Hz, 1H), 7.32 – 7.28 (m, 1H), 7.19 (app d, *J* = 8.8 Hz, 2H), 6.96-6.92 (comp, 3H), 6.69 (app t, *J* = 7.5 Hz, 1H), 3.84 (s, 3H); **^{13}C NMR** (101MHz, Chloroform-*d*) δ 173.4, 157.0, 150.5, 135.2, 133.0, 132.5, 126.4, 116.3, 114.7, 113.5, 109.4, 55.5; **HRMS** (ESI, m/z) calcd for $C_{14}H_{14}NO_3$ $[M+H]^+$244.0974, found 244.0977.

General procedure (dehomologation process) for the preparation of benzoic acid (3af) and phthalic acid (3ag)



Reaction condition a:

Into a 10 mL two neck round bottom flask equipped with an electromagnetic stirrer, compound **6** or **7** or **9** (1 equiv., 0.2 mmol) and DMF solvent (2 mL, 0.1 M) were taken under an inert atmosphere at ice cold condition. NaH (6 equiv., 1.2 mmol) was added portionwise through an additional funnel and stirred at room temperature (33 °C) for 10 h. After the full conversion was monitored by TLC, it was quenched with cold 1N HCl solution (20 mL). The organic part was extracted by EtOAc (3x20 mL) with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Finally, it was purified by column chromatography on silica gel (230-400 mesh) using petroleum ether/ethyl acetate (4:1) as eluent to obtain the desired benzoic acid (**3af**) or phthalic acid (**3ag**) in 73-75% yield.

Condition b: Into a 10 mL two neck round bottom flask equipped with an electromagnetic stirrer, compound **8** (1 equiv., 0.2 mmol) and DMF solvent (2 mL, 0.1 M) were taken under in an inert atmosphere at ice cold condition. NaH (6 equiv., 1.2 mmol) was added portionwise through an additional funnel and initially stirred at room temperature (33 °C). Then the whole reaction mixture was warmed to 80 °C and stirred for 24 h. After the full conversion was monitored by TLC, it was quenched with cold 1N HCl solution (20 mL). The organic part was extracted by EtOAc (3x20 mL) with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Finally, it was purified by column chromatography on silica gel (230-400 mesh) using petroleum ether/ethyl acetate (4:1) as eluent to obtain the desired benzoic acid (**3af**) in 73% yield.

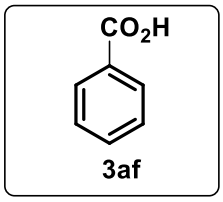
Condition c: Into a 10 mL two neck round bottom flask equipped with an electromagnetic stirrer, compound **8** (1 equiv., 0.2 mmol) and DMF solvent (2 mL, 0.1 M) were taken under in an inert atmosphere at ice cold condition. NaH (6 equiv., 1.2 mmol) was added portionwise

through an additional funnel and initially stirred at room temperature (33 °C). Then the whole reaction mixture was warmed to 80 °C and stirred for 2 h. After the full conversion was monitored by TLC, it was quenched with cold 1N HCl solution (20 mL). The organic part was extracted by EtOAc (3x20 mL) with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Finally, it was purified by column chromatography on silica gel (230-400 mesh) using petroleum ether/ethyl acetate (4:1) as eluent to obtain the desired benzoic acid (**3af**) in 82% yield.

Condition d: Into a 10 mL two neck round bottom flask equipped with an electromagnetic stirrer, compound **6** or **7** or **9** (1 equiv., 0.2 mmol) and DMF solvent (2 mL, 0.1 M) were taken under in an inert atmosphere at ice cold condition. NaH (4 equiv., 0.8 mmol) was added portionwise through an additional funnel and stirred at room temperature (33 °C) for 6 hour. After the full conversion was monitored by TLC, it was quenched with cold 1N HCl solution (20 mL). The organic part was extracted by EtOAc (3x20 mL) with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Finally, it was purified by column chromatography on silica gel (230-400 mesh) using petroleum ether/ethyl acetate (4:1) as eluent to obtain the desired benzoic acid (**3af**) in 45% yield.

Characterization data of 3af

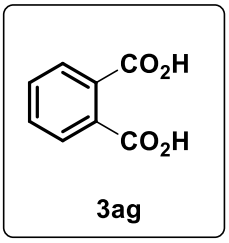
benzoic acid (3af)



White solid (45-82% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 168-170 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 11.84 (s, 1H), 8.15 – 8.13 (comp, 2H), 7.63 (app t, *J* = 7.6, 1H), 7.51 – 7.47 (comp, 2H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 172.5, 133.8, 130.2, 129.3, 128.5; **HRMS** (ESI, m/z) calcd for $C_7H_7O_2$ $[M+H]^+$ 123.0446, found 123.0444.

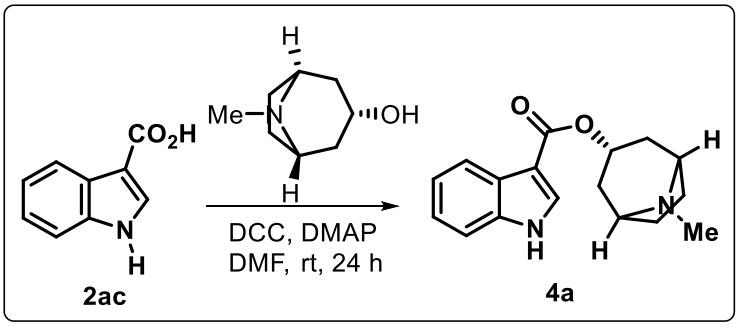
Characterization data of 3ag

phthalic acid (3ag)



White solid (24.2 mg, 73% yield); column chromatography eluent, petroleum ether/EtOAc = 4:1; mp 168-170 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.86-7.82 (comp, 2H), 7.64-7.60 (comp, 2H); **^{13}C NMR** (101MHz, Chloroform-*d*) δ 171.8, 134.6, 132.3, 130.6; **HRMS** (ESI, m/z) calcd for $C_8H_7O_4$ $[M+H]^+$ 167.0344, found 167.0346.

General procedure for the preparation of 4a:



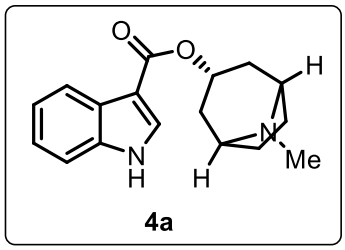
500 mg (3.1 mmol, 1 equiv.) indole-3-carboxylic acid **2ac** was charged in an oven-dried clean 25 mL two neck round bottom flask containing magnetic stir bar in N_2 atmosphere. 4 mL DCM and 0.2 mL (0.4 equiv.) trifluoroacetic acid (TFA) was added respectively at rt (33 °C). After stirring for 5 minutes 1 mL $(CF_3CO)_2O$ (7.2 mmol, 2.3 equiv.) was added dropwise in the reaction mixture at 0 °C. Then it was warmed at rt and stirred for 2h for activating the

acid group. After that, it was transferred to -5 °C and 4 mL tropine solution (450 mg, 1 equiv.) (making previously by 4 mL DCM at the inert condition) added dropwise for 30 minutes, and kept for 4h. After full conversion checking by TLC, the whole reaction mixture was quenched by 100 mL ice-cooled 1N NaOH solution followed by worked up with EtOAc and brine. Then the organic layer was passed through Na_2SO_4, keeping for some time, and concentrated in the rotary evaporator. Then it was dissolved in EtOAc for crystallization, 710 mg (81%) desired tropisetron **4a** was obtained.

Characterization data of 4a

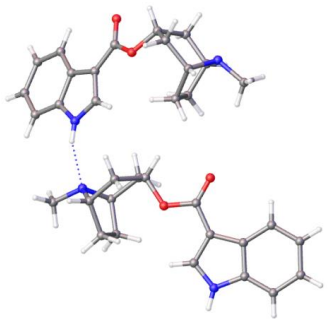
8-methyl-8-azabicyclo[3.2.1]octan-3-yl *1H*-indole-3-carboxylate (4a)

White solid (710 mg, 81% yield); column chromatography eluent: petroleum ether/EtOAc = 5:1; mp 202-204 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.88 (s, 1H), 8.26-8.22 (m, 1H), 7.84 (s, 1H), 7.43 – 7.38 (m, 1H), 7.29 – 7.23 (comp, 2H), 5.28 (app t, *J* = 5.2 Hz, 1H), 3.22 – 3.20 (m, 2H), 2.35 (s, 3H), 2.31-2.25 (m, 2H), 2.15-2.07 (comp, 4H), 1.93 (app d, *J* = 14.8 Hz, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.6, 136.3, 131.0, 126.0, 123.1, 121.9, 121.1, 111.6, 108.9, 66.4, 59.8, 40.1, 36.4, 25.9; **HRMS** (ESI, m/z) calcd for $C_{17}H_{21}N_2O_2$ $[M+H]^+$ 285.1603, found 285.1595.



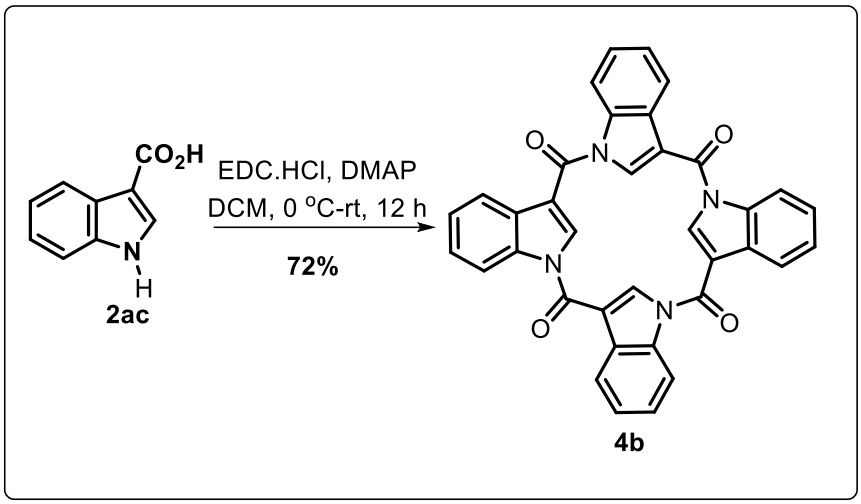
4a

Table S7: Crystal Data and Structure of 4a (CCDC No. 2213920)



Empirical formula	$C_{34}H_{40}N_4O_4$
Formula weight	568.70
Temperature/K	100.0
Crystal system	triclinic
Space group	P-1
a/Å	10.1881(4)
b/Å	11.1979(4)
c/Å	13.8192(5)
α/°	81.9570(10)
β/°	78.9680(10)
γ/°	70.0130(10)
Volume/Å^3	1449.48(9)
Z	2
ρ_{calc}g/cm^3	1.303
μ/mm^{-1}	0.689
F(000)	608.0
Crystal size/mm^3	0.65 × 0.405 × 0.25
Radiation	Cu Kα (λ = 1.54178)
2Θ range for data collection/°	12.218 to 130.018
Index ranges	$-11 \le h \le 11$, $-13 \le k \le 13$, $-16 \le l \le 16$
Reflections collected	49799
Independent reflections	4716 [R_{int} = 0.0616, R_{sigma} = 0.0351]
Data/restraints/parameters	4716/0/382
Goodness-of-fit on F^2	1.101
Final R indexes [I>=2σ (I)]	R_1 = 0.0490, wR_2 = 0.1308
Final R indexes [all data]	R_1 = 0.0493, wR_2 = 0.1312
Largest diff. peak/hole / e Å^{-3}	0.27/-0.25

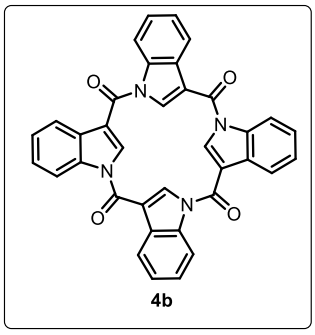
General procedure for the preparation of (4b)



Into a 10 mL two neck round bottom flask equipped with an electromagnetic stirrer, transferred indole-3-carboxylic acid (**2**) (1 equiv., 0.4 mmol, 64.5 mg) and DCM solvent (4 mL, 0.1 M) in an inert atmosphere. The whole reaction mixture was subjected to cool down at 0 °C using crushed ice. After that EDC.HCl (2.5 equiv.) and DMAP (0.1 equiv.) was added slowly to the reaction mixture. Then it was warmed at room temperature (33 °C) and stirred for 12 h. After the full conversion was monitored by TLC, it was quenched with aqueous $NaHCO_3$. The organic part was extracted by EtOAc (3x20 mL) with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Finally, it was purified by column chromatography on silica gel (230-400 mesh) using petroleum ether/ethyl acetate (4:1) as eluent to obtain the desired N-confused porphyrin ring **4b** in 72% yield (40 mg).

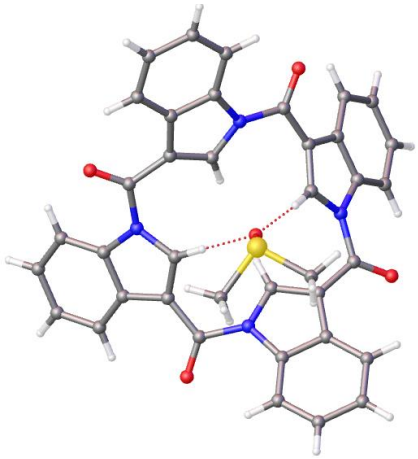
Characterization data of 4b

N-confused porphyrin ring: (1^{2}E,3^{2}E,5^{2}E,7^{2}E)-1^{1}H,3^{1}H,5^{1}H,7^{1}H-1(1,3),3,5,7(3,1)-tetraindolacyclooctaphane-2,4,6,8-tetraone (4b)



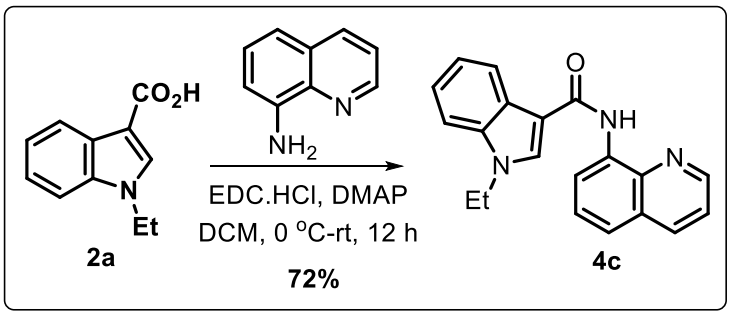
White solid (40 mg, 72% yield); column chromatography eluent: petroleum ether/EtOAc = 5:1; mp above 260 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.46 (s, 4H), 8.42-8.30 (comp, 4H), 8.19-8.17 (comp, 4H), 7.58-7.50 (comp, 8H); **^{13}C NMR** (101 MHz, DMSO-d_6) δ 163.1, 137.7, 135.8, 128.2, 125.9, 125.0, 120.9, 115.5, 112.6; **HRMS** (ESI, m/z) calcd for $C_{36}H_{21}N_4O_4$ $[M+H]^+$ 573.1563, found 573.1553.

Table S8: Crystal Data and Structure of 4b (CCDC No. 2213919)



Empirical formula	$C_{38}H_{26}N_4O_5S$
Formula weight	650.69
Temperature/K	100.0
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	15.3315(10)
b/Å	7.6770(5)
c/Å	25.9418(17)
α/°	90
β/°	96.515(3)
γ/°	90
Volume/$Å^3$	3033.6(3)
Z	4
$\rho_{calc}g/cm^3$	1.425
μ/mm^{-1}	1.400
F(000)	1352.0
Crystal size/mm^3	0.35 × 0.2 × 0.18
Radiation	Cu Kα (λ = 1.54178)
2Θ range for data collection/°	11.618 to 130.352
Index ranges	$-18 \le h \le 17$, $-8 \le k \le 9$, $-27 \le l \le 30$
Reflections collected	44102
Independent reflections	5057 [R_{int} = 0.0520, R_{sigma} = 0.0301]
Data/restraints/parameters	5057/0/435
Goodness-of-fit on F^2	1.077
Final R indexes [I>=2σ (I)]	R_1 = 0.0491, wR_2 = 0.1390
Final R indexes [all data]	R_1 = 0.0498, wR_2 = 0.1397
Largest diff. peak/hole / e $Å^{-3}$	0.44/-0.38

General procedure for the preparation of (4c)

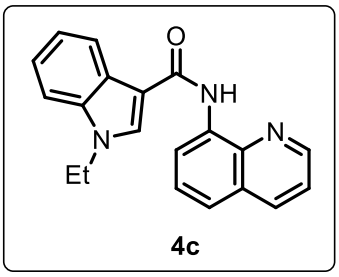


Into a 10 mL two neck round bottom flask equipped with an electromagnetic stirrer, transferred N-ethyl indole-3-carboxylic acid (**2a**) (1 equiv., 0.4 mmol, 76 mg) and DCM solvent (4 mL, 0.1 M) followed by 8-aminoquinoline (1.1 equiv., 64 mg) in an inert atmosphere. The whole reaction mixture was subjected to cool down at 0 °C using crushed ice. After that EDC.HCl (2.5 equiv.) and DMAP (2 equiv.) was added slowly to the reaction mixture. Then it was warmed at room temperature (33 °C) and stirred for 12 h. After the full conversion was monitored by TLC, it was quenched with aqueous $NaHCO_3$. The organic part

was extracted by EtOAc (3x20 mL) with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Finally, it was purified by column chromatography on silica gel (230-400 mesh) using petroleum ether/ethyl acetate (2.3:1) as eluent to obtain the desired amide compound **4c** in 72% yield (91 mg).

Characterization data of 4c

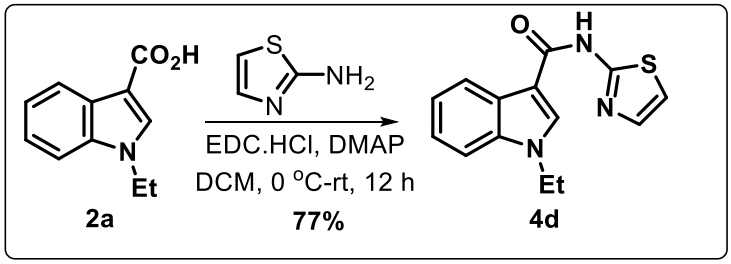
1-ethyl-N-(quinolin-8-yl)-1H-indole-3-carboxamide (4c)



4c

White solid (91 mg, 72% yield); column chromatography eluent: petroleum ether/EtOAc = 5:1; mp 120-122 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.57 (s, 1H), 8.98 (d, *J* = 8.0 Hz, 1H), 8.91-8.89 (m, 1H), 8.50 – 8.48 (m, 1H), 8.21-8.17 (m, 1H), 8.01-8.00 (m, 1H), 7.60 (td, *J* = 8.0 Hz, 2.0 Hz, 1H), 7.52-7.43 (comp, 3H), 7.41-7.33 (comp, 2H), 4.26 (q, *J* = 7.2 Hz, 2H), 1.56 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.4, 148.1, 138.6, 136.5, 136.4, 135.3, 131.6, 128.1, 127.6, 125.6, 122.5, 121.8, 121.5, 120.8, 120.8, 116.3, 111.9, 110.2, 41.6, 15.2; **HRMS** (ESI, m/z) calcd for $C_{20}H_{18}N_3O$ $[M+H]^+$ 316.1450, found 316.1440.

General procedure for the preparation of (4d)

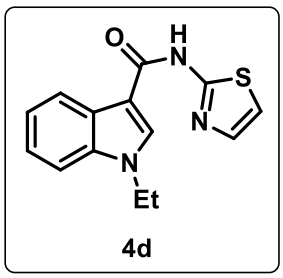


2a **4d**

Into a 10 mL two neck round bottom flask equipped with an electromagnetic stirrer, transferred N-ethyl indole-3-carboxylic acid (**2a**) (1 equiv., 0.4 mmol, 76 mg) and DCM solvent (4 mL, 0.1 M) followed by thiazol-2-amine (1.1 equiv., 44 mg) in an inert atmosphere. The whole reaction mixture was subjected to cool down at 0 °C using crushed ice. After that EDC.HCl (2.5 equiv.) and DMAP (2 equiv.) was added slowly to the reaction mixture. Then it was warmed at room temperature (33 °C) and stirred for 12 h. After the full conversion was monitored by TLC, it was quenched with aqueous $NaHCO_3$. The organic part was extracted by EtOAc (3x20 mL) with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Finally, it was purified by column chromatography on silica gel (230-400 mesh) using petroleum ether/ethyl acetate (2.3:1) as eluent to obtain the desired amide compound **4d** in 77% yield (83 mg).

Characterization data of 4d

1-ethyl-N-(thiazol-2-yl)-1H-indole-3-carboxamide (4d)



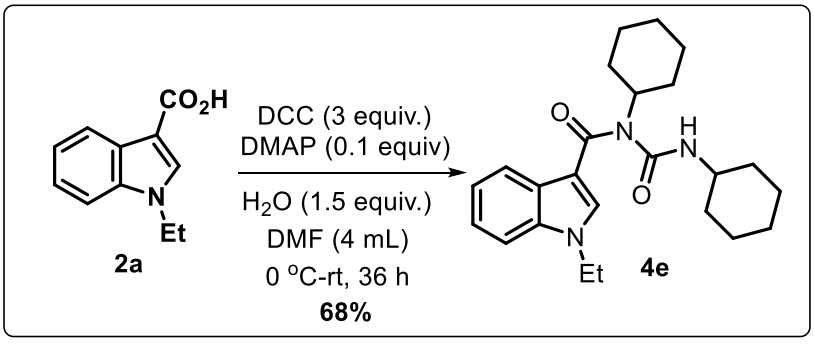
4d

White solid (83 mg, 77% yield); column chromatography eluent: petroleum ether/EtOAc = 5:1; mp 210-212 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.38 – 8.34 (m, 1H), 7.89 (s, 1H), 7.42 (dd, *J* = 6.4 Hz, 2.4 Hz, 1H), 7.36 – 7.30 (comp, 2H), 7.26 (d, *J* = 3.6 Hz, 1H), 6.95 (d, *J* = 3.6 Hz, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 1.50 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.4, 160.6, 136.4, 136.3, 131.0, 126.7, 123.2, 122.2, 121.7, 113.0, 110.0, 108.7, 41.7, 15.1; **HRMS** (ESI, m/z) calcd for $C_{14}H_{14}N_3OS$ $[M+H]^+$ 272.0858, found 272.0860.

Table S9: Crystal Data and Structure of 4d (CCDC No. 2213918)

Empirical formula	$C_{14}H_{13}N_3OS$
Formula weight	271.33
Temperature/K	100.00
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	11.6575(11)
b/Å	7.8732(7)
c/Å	13.6308(13)
α/°	90
β/°	92.216(3)
γ/°	90
Volume/Å^3	1250.1(2)
Z	4
ρ_{calc}g/cm^3	1.442
μ/mm^{-1}	2.259
F(000)	568.0
Crystal size/mm^3	0.28 × 0.25 × 0.2
Radiation	CuKα (λ = 1.54178)
2Θ range for data collection/°	10.18 to 136.308
Index ranges	$-13 \le h \le 13$, $-9 \le k \le 9$, $-16 \le l \le 16$
Reflections collected	25825
Independent reflections	2258 [R_{int} = 0.0607, R_{sigma} = 0.0280]
Data/restraints/parameters	2258/0/173
Goodness-of-fit on F^2	1.085
Final R indexes [I>=2σ (I)]	R_1 = 0.0435, wR_2 = 0.1136
Final R indexes [all data]	R_1 = 0.0442, wR_2 = 0.1143
Largest diff. peak/hole / e Å^{-3}	0.36/-0.47

General procedure for the preparation of 4e:

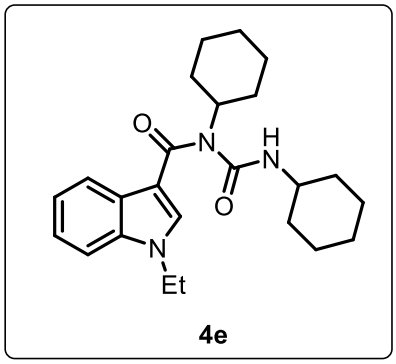


Into a 10 mL two neck round bottom flask equipped with an electromagnetic stirrer, transferred N-ethyl indole-3-carboxylic acid (**2a**) (1 equiv., 0.3 mmol, 57 mg) and DMF solvent (4 mL, 0.075 M) in an inert atmosphere. The whole reaction mixture was subjected to cool down at 0 °C using crushed ice. After that DCC (3.0 equiv.), DMAP (0.1 equiv.), and

H_2O (1.5 equiv.) was added slowly to the reaction mixture. Then it was warmed at room temperature (33 ^oC) and stirred for 36 h. After the full conversion was monitored by TLC, it was quenched with H_2O. The organic part was extracted by EtOAc (3x20 mL) with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Finally, it was purified by column chromatography on silica gel (230-400 mesh) using petroleum ether/ethyl acetate (4:1) as eluent to obtain the desired imide compound **4e** in 68% yield (81 mg).

Characterization data of 4e

N-cyclohexyl-N-(cyclohexylcarbamoyl)-1-ethyl-*1H*-indole-3-carboxamide (4e)

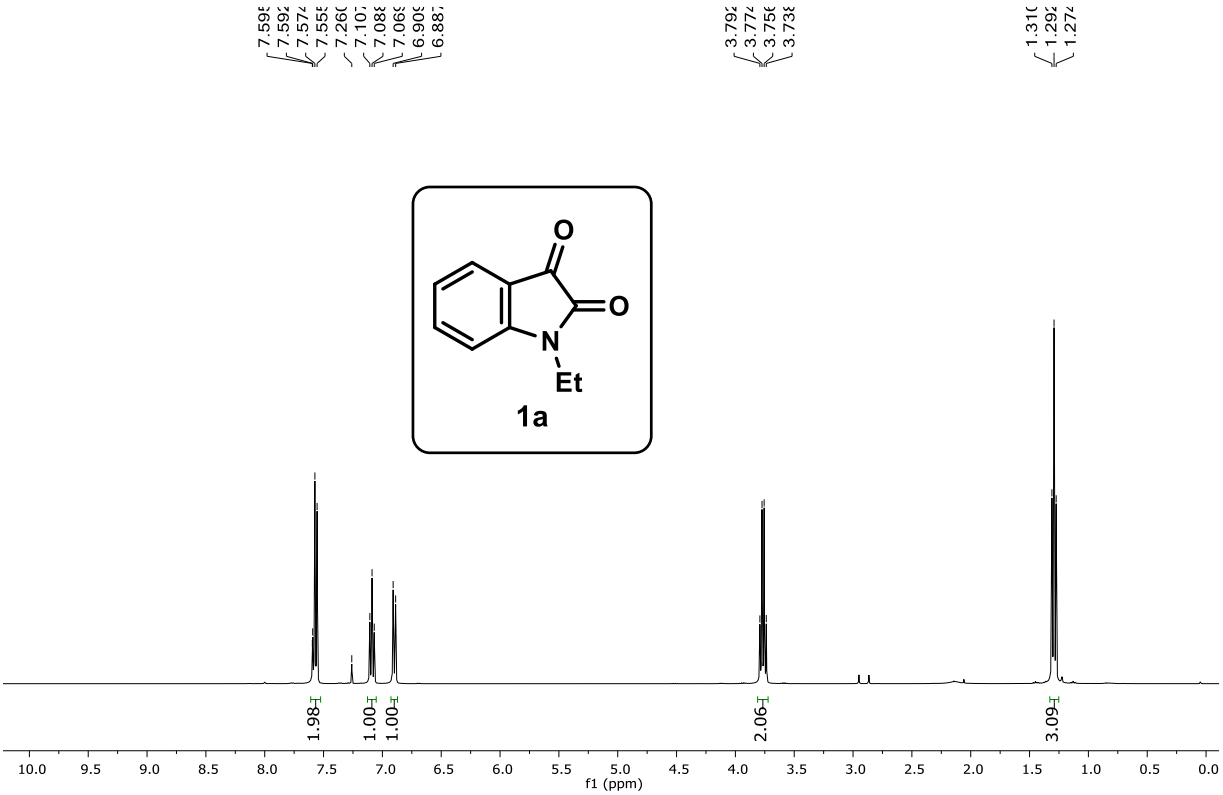


4e

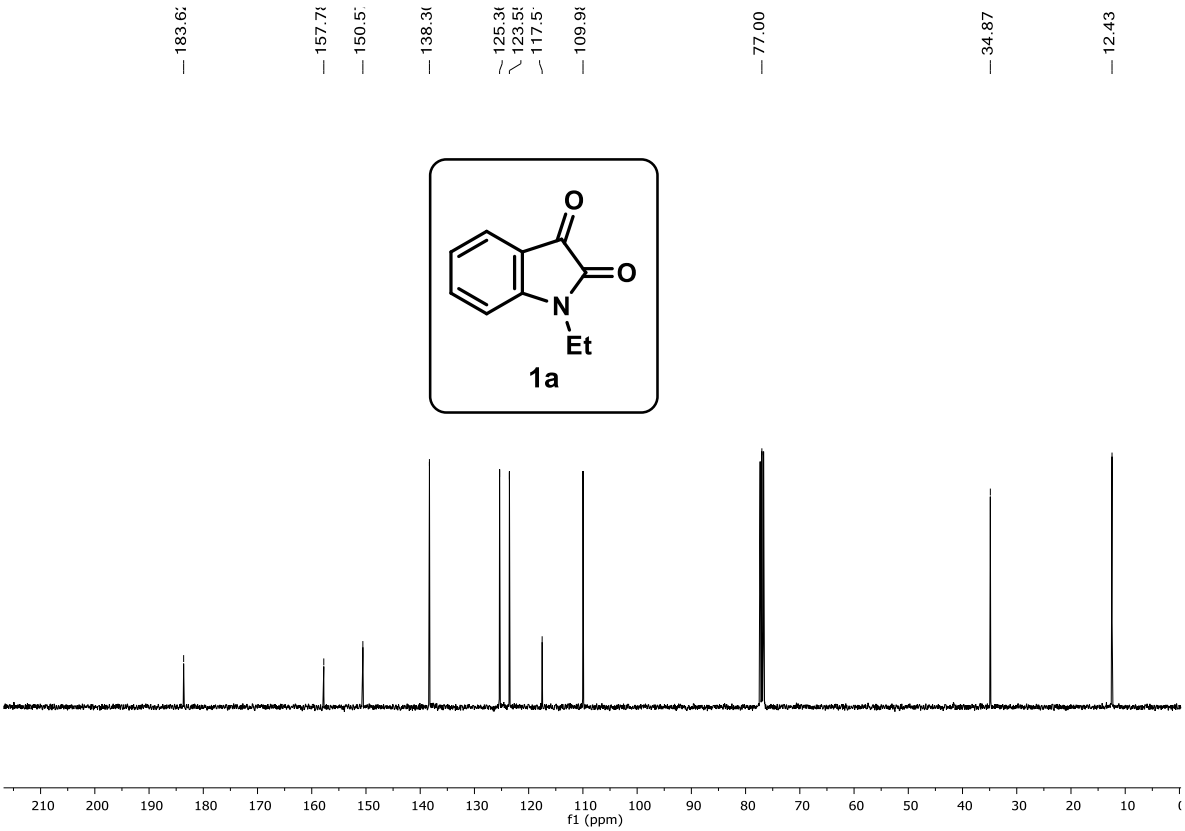
White solid (81 mg, 68% yield); column chromatography eluent: petroleum ether/EtOAc = 5:1; mp 148-150 ^oC; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.06 – 8.04 (m, 1H), 7.59 (s, 1H), 7.35 (dd, *J* = 7.0, 1.4 Hz, 1H), 7.30 – 7.22 (comp, 2H), 5.90 (d, *J* = 8.0 Hz, 1H), 4.40-4.33 (m, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 3.58 – 3.49 (m, 1H), 2.10-2.00 (m, 2H), 1.93-1.86 (comp, 3H), 1.83-1.79 (m, 2H), 1.63 – 1.59 (comp, 3H), 1.47 (t, *J* = 7.2 Hz, 3H), 1.36 – 1.17 (comp, 6H), 1.12 – 1.00 (m, 2H), 0.89 – 0.89 (m, 2H); **^{13}C NMR** (101MHz,$CDCl_3$) δ 166.7, 155.5, 135.9, 130.4, 127.3, 122.9, 121.7, 121.6, 111.2, 109.7, 56.8, 49.7, 49.2, 41.5, 33.8, 32.4, 31.2, 26.3, 25.6, 25.4, 25.3, 24.9, 24.5, 15.3; **HRMS** (ESI, m/z) calcd for $C_{24}H_{34}N_3O_2$ $[M+H]^+$ 396.2651, found 396.2659.

^{1}H and ^{13}C NMR Spectra of Compounds

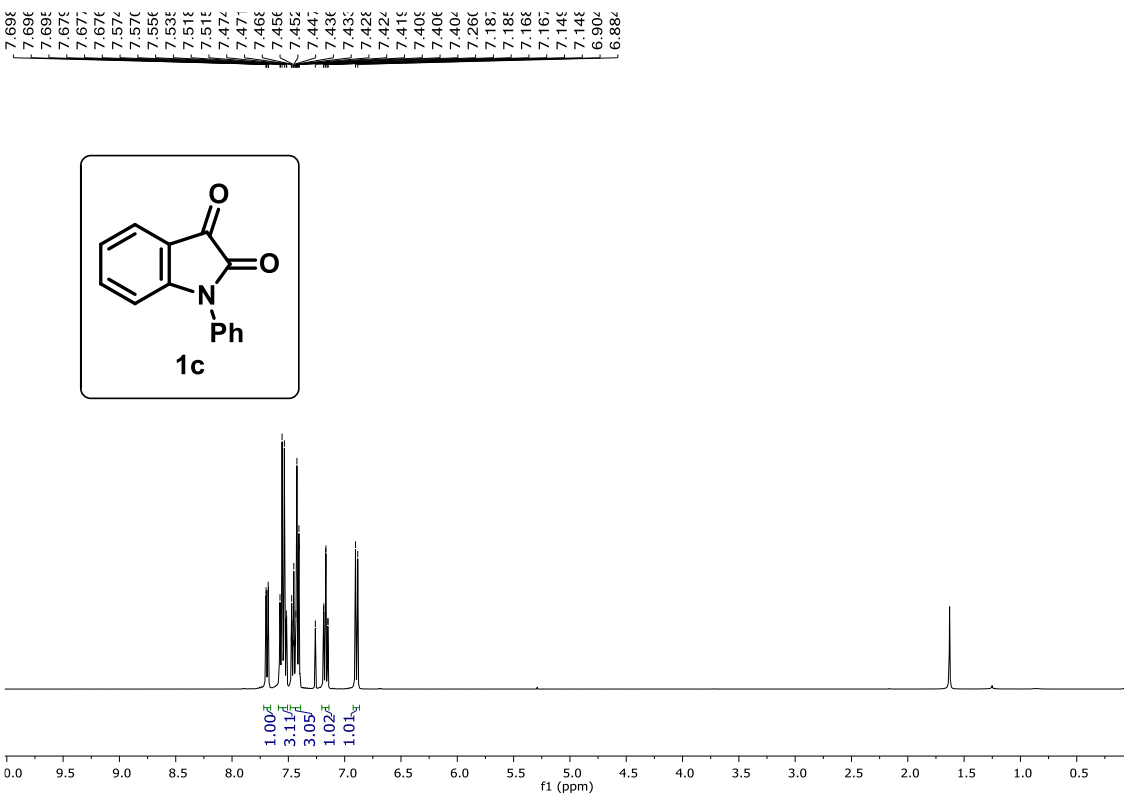
^{1}H NMR of **1a** (400 MHz, Chloroform-*d*)



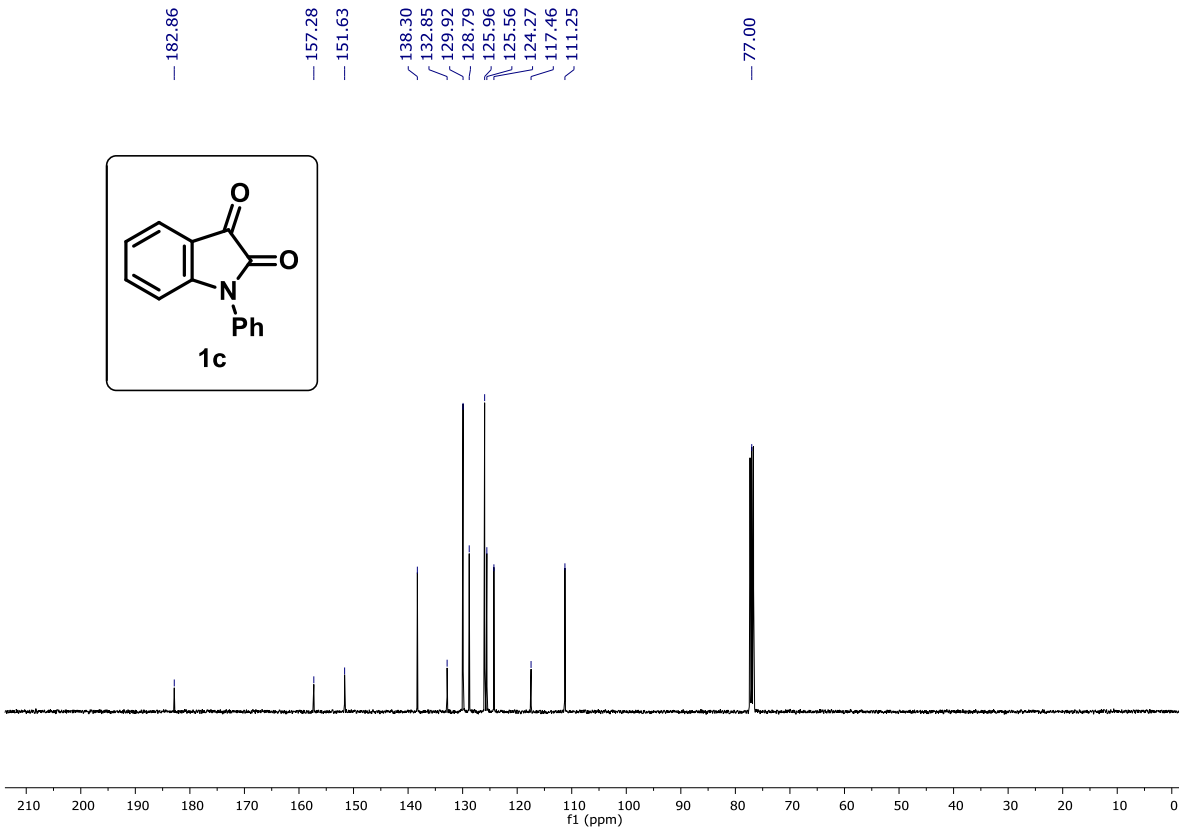
^{13}C NMR of **1a** (101 MHz, $CDCl_3$)



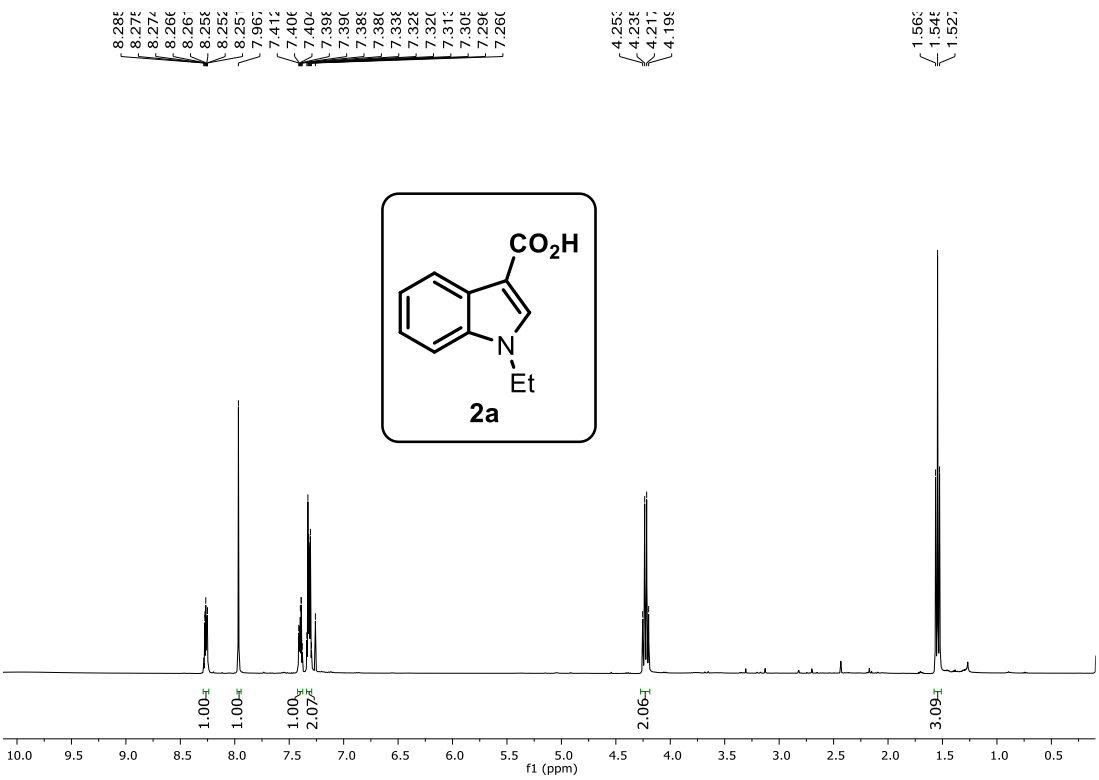
^{1}H NMR of **1c** (400 MHz, Chloroform-*d*)



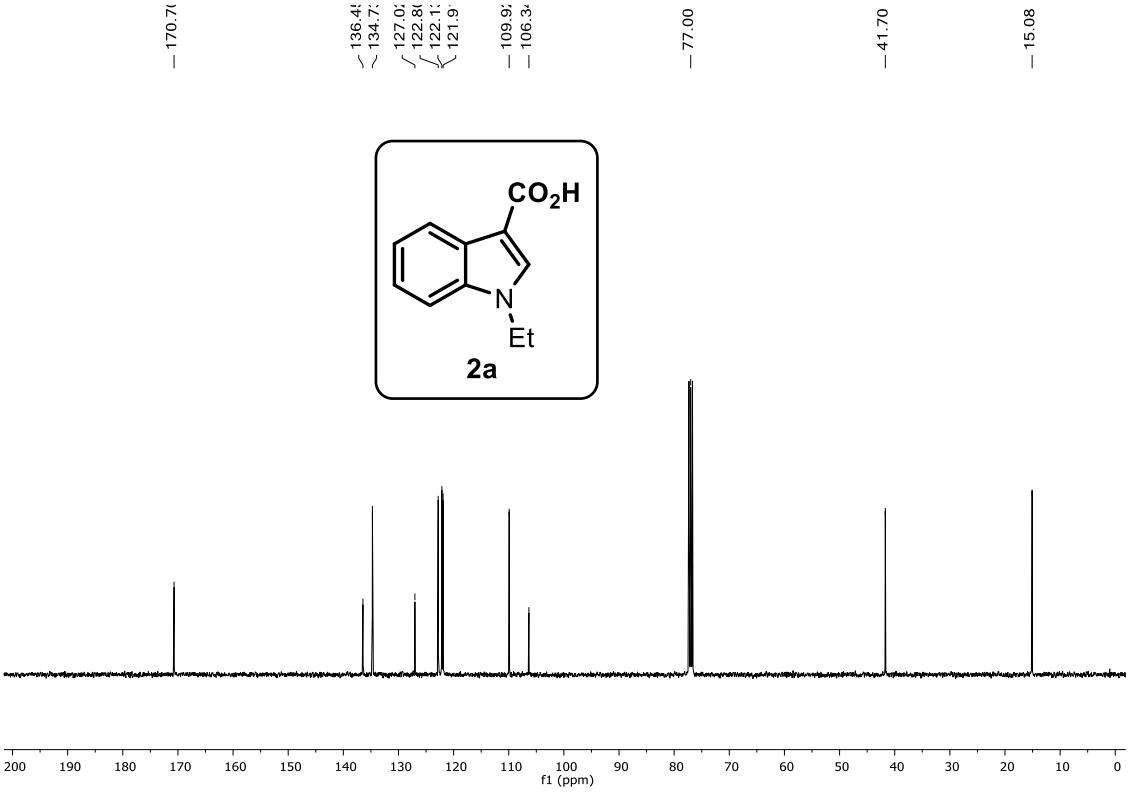
^{13}C NMR of **1c** (100 MHz, $CDCl_3$)



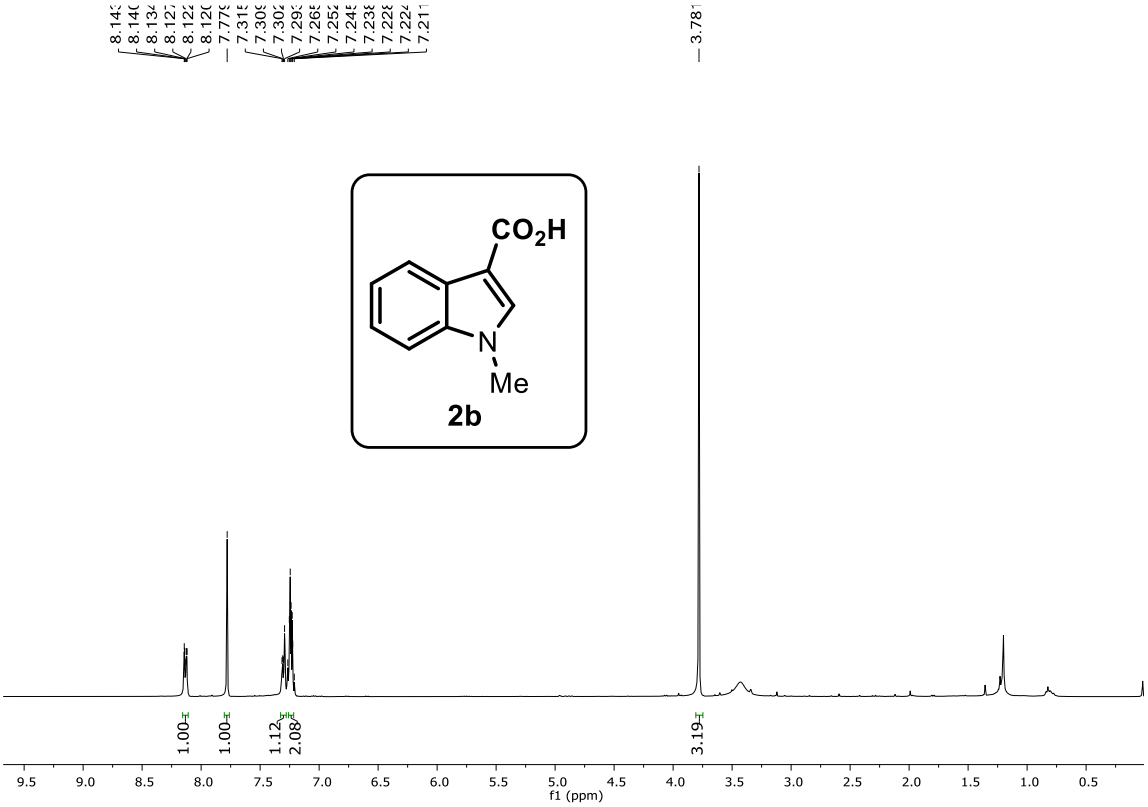
^{1}H NMR of **2a** (400 MHz, Chloroform-*d*)



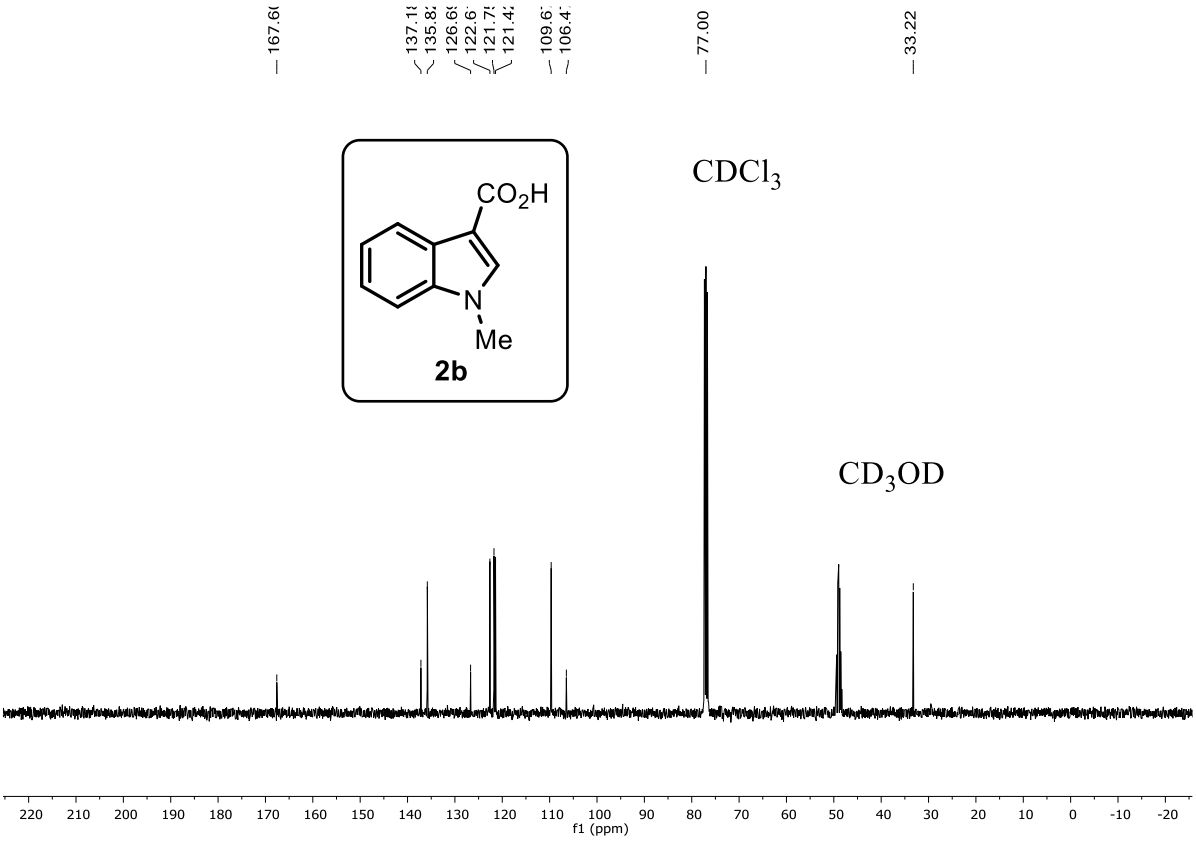
^{13}C NMR of **2a** (101 MHz, $CDCl_3$)



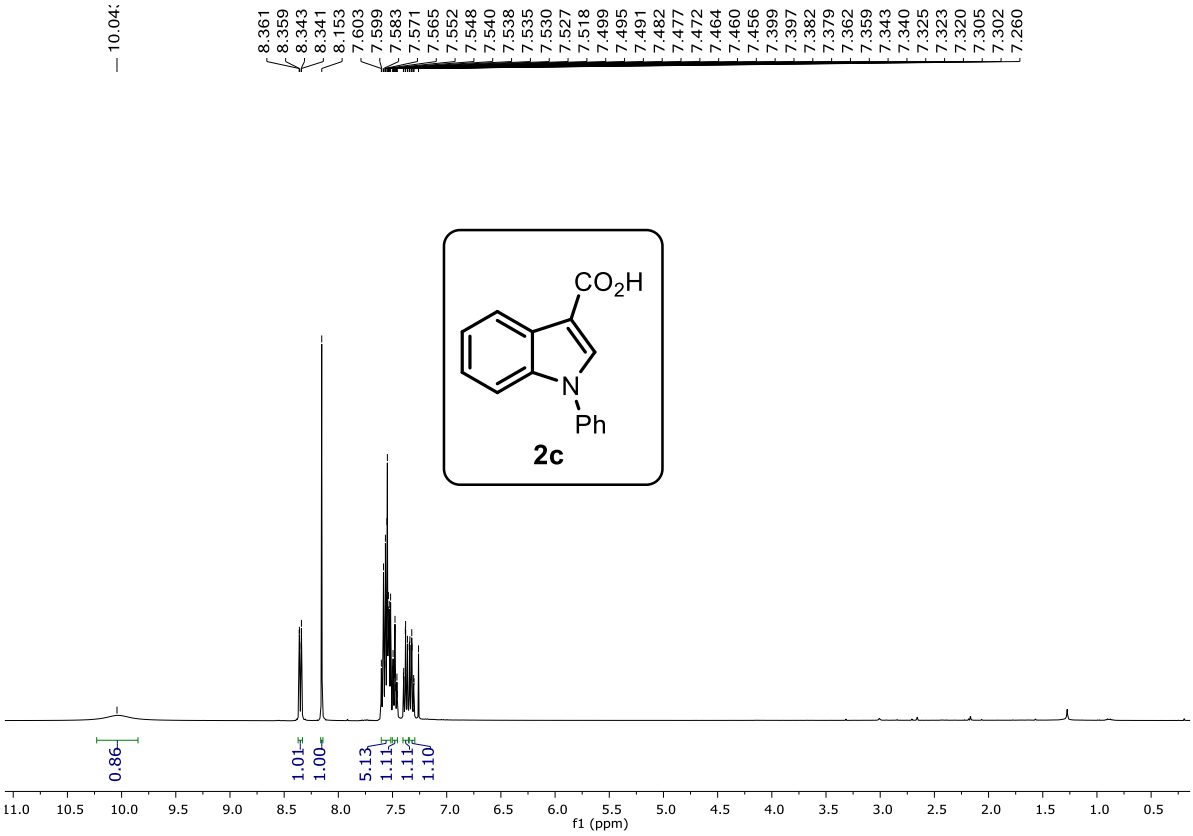
^{1}H NMR of **2b** (400 MHz, Chloroform-*d*)



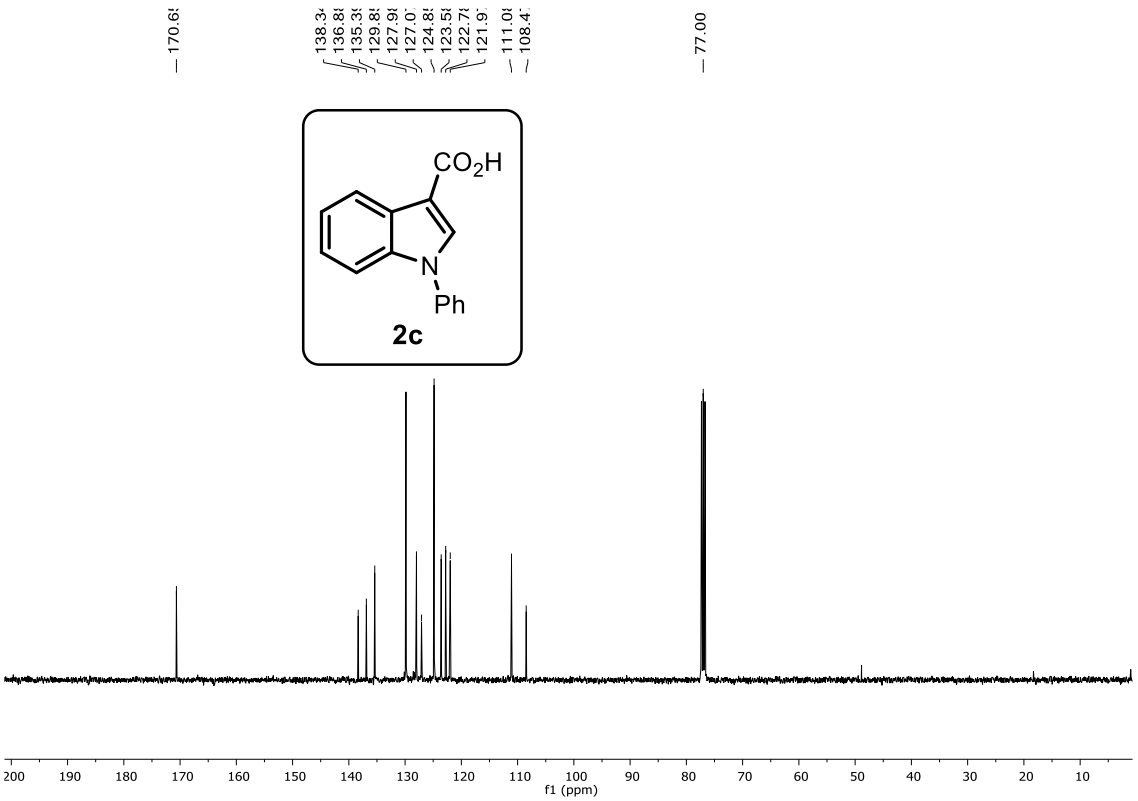
^{13}C NMR of **2b** (100 MHz, $CDCl_3$)



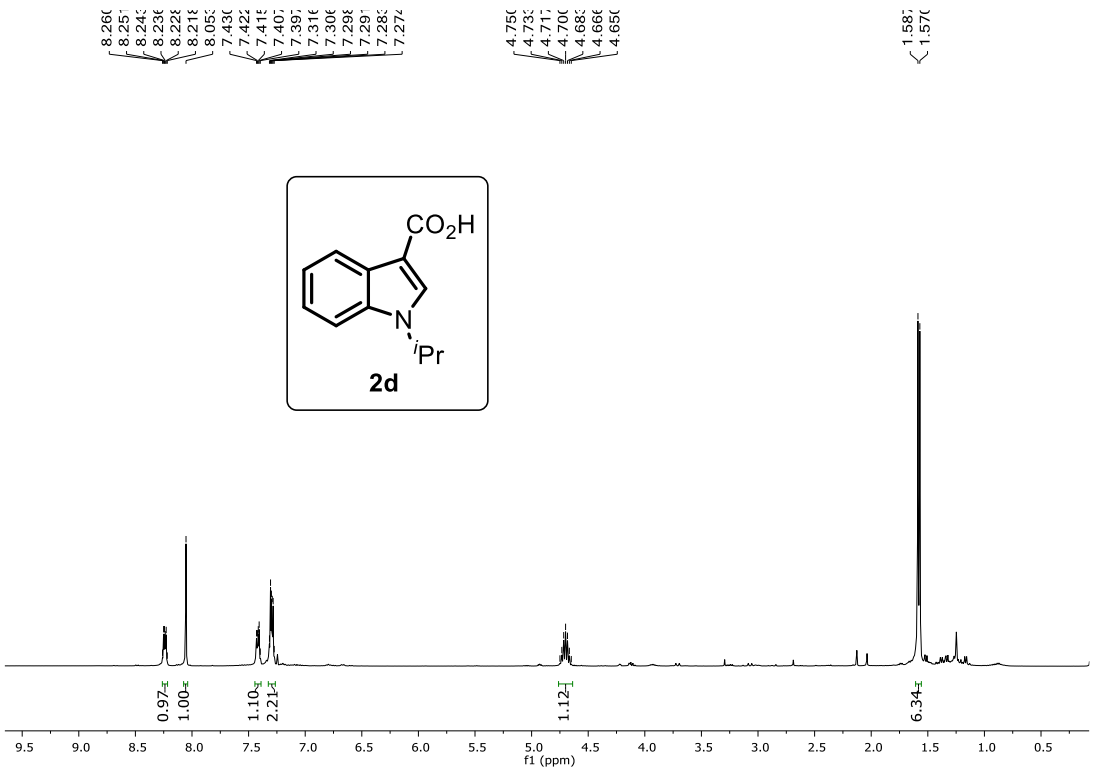
^{1}H NMR of **2c** (400 MHz, Chloroform-*d*)



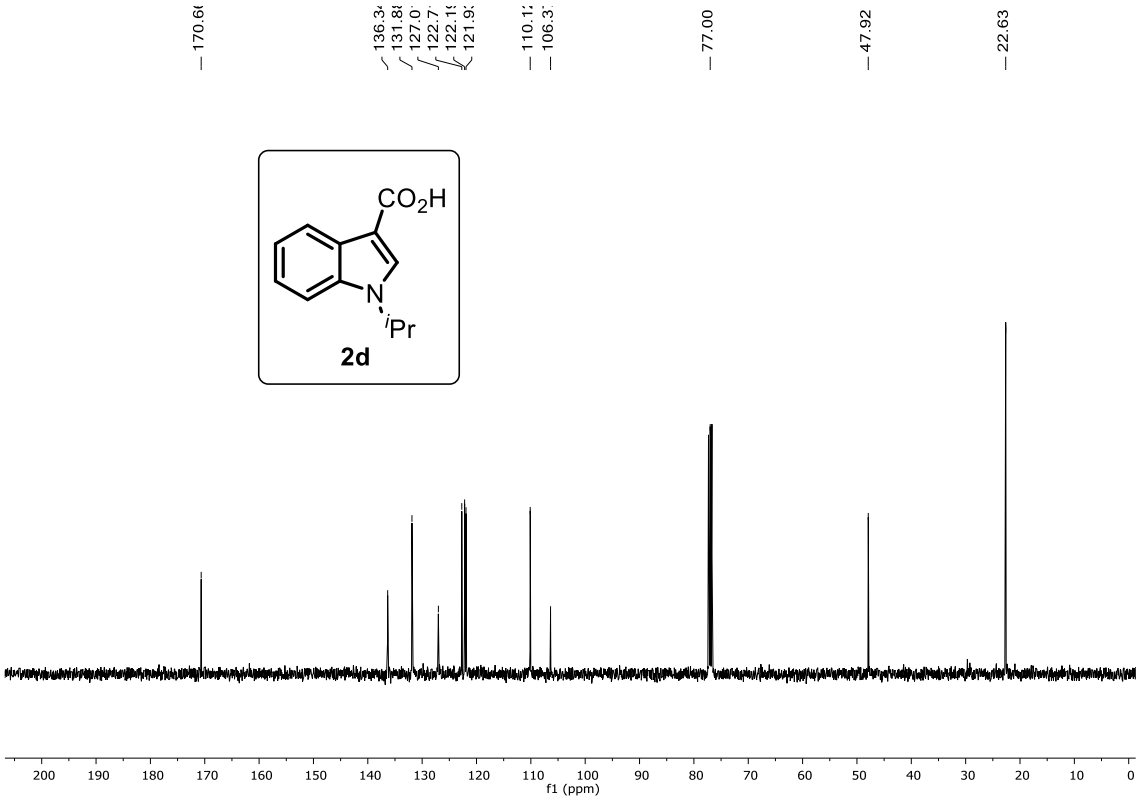
^{13}C NMR of **2c** (100 MHz, $CDCl_3$)



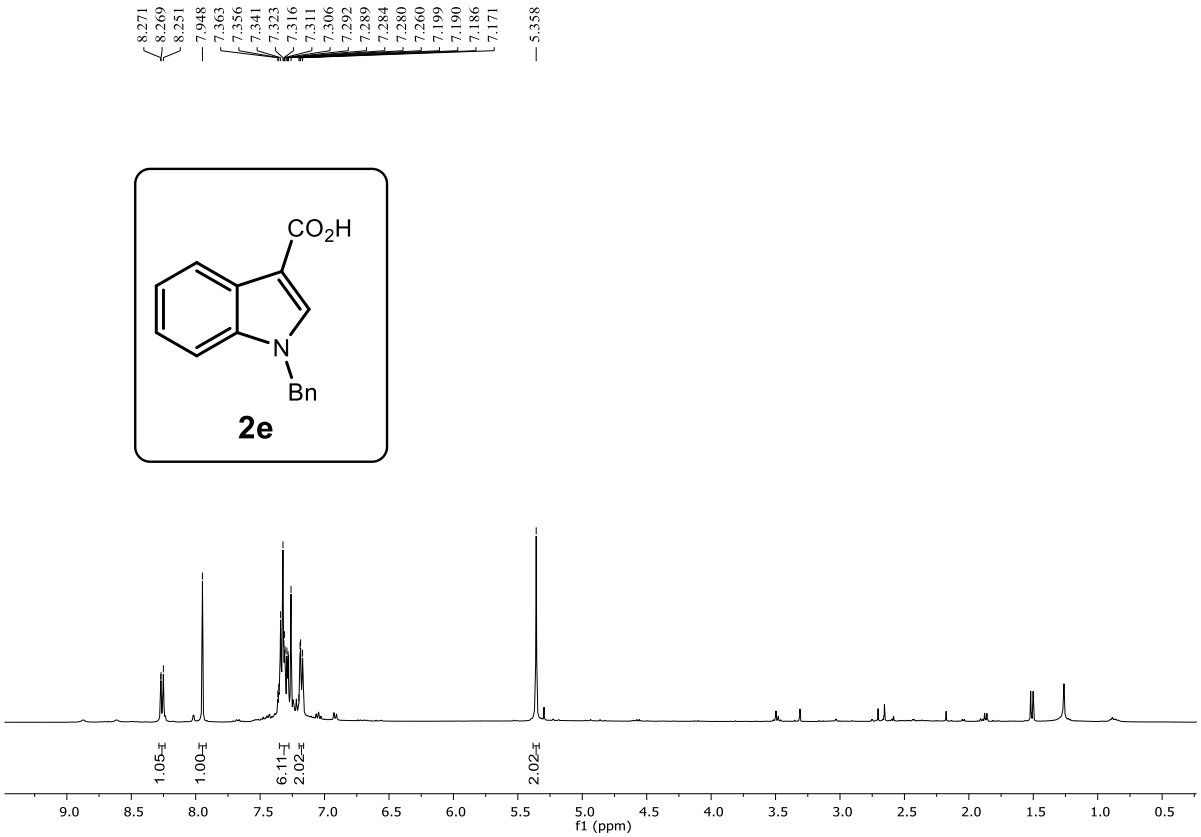
^{1}H NMR of **2d** (400 MHz, Chloroform-*d*)



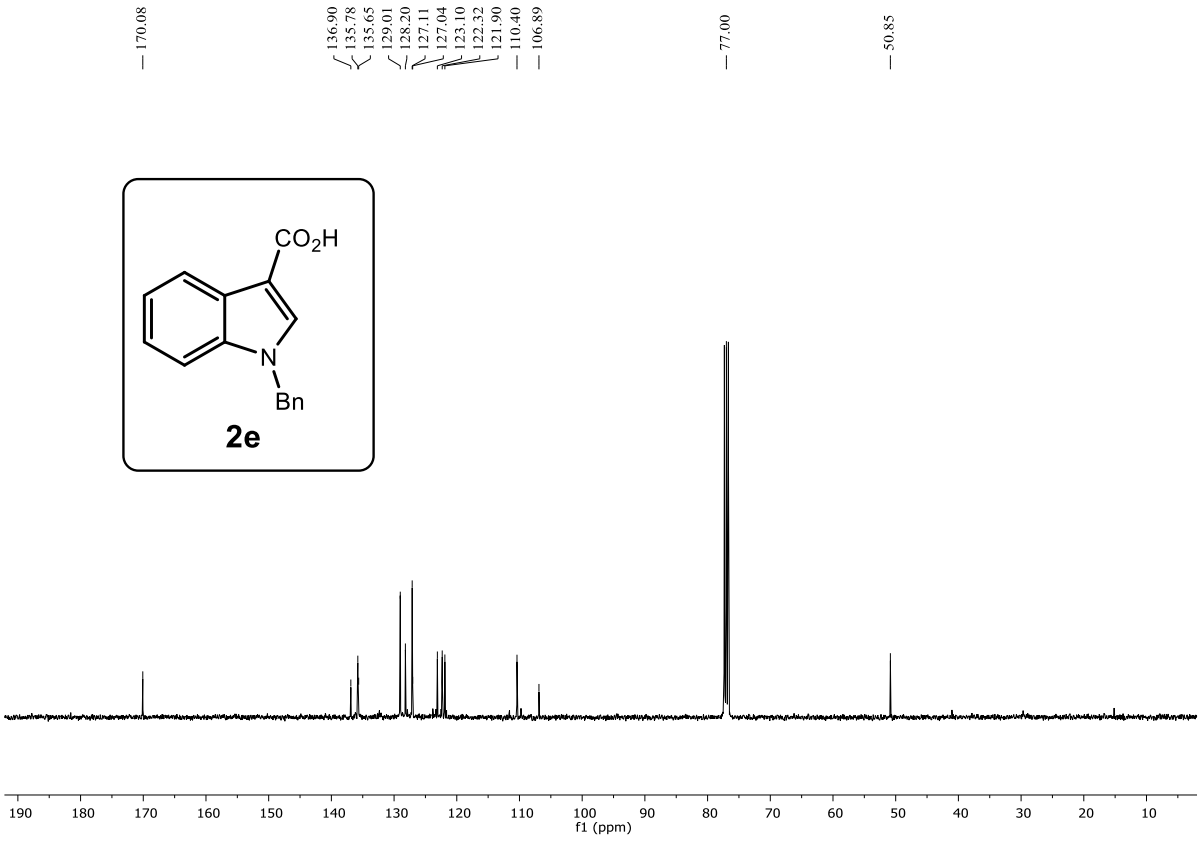
^{13}C NMR of **2d** (100 MHz, $CDCl_3$)



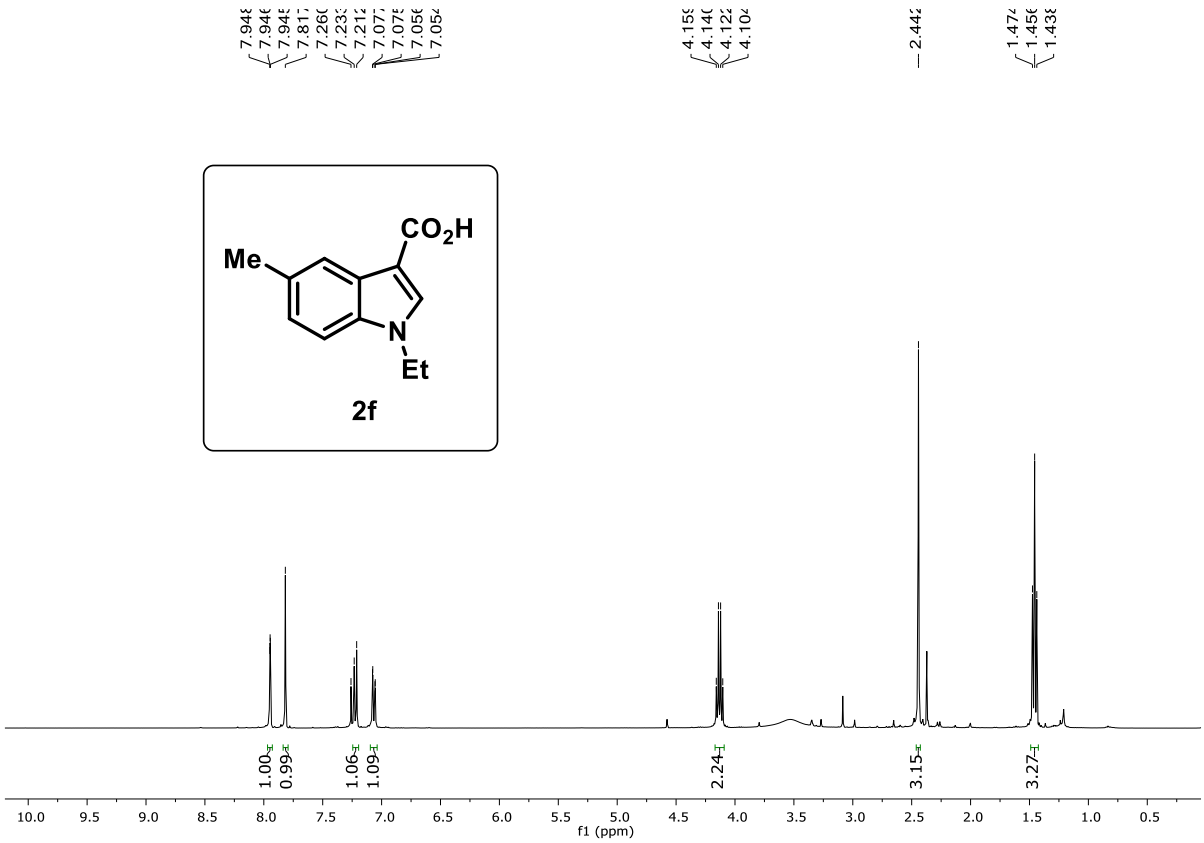
^{1}H NMR of **2e** (400 MHz, Chloroform-*d*)



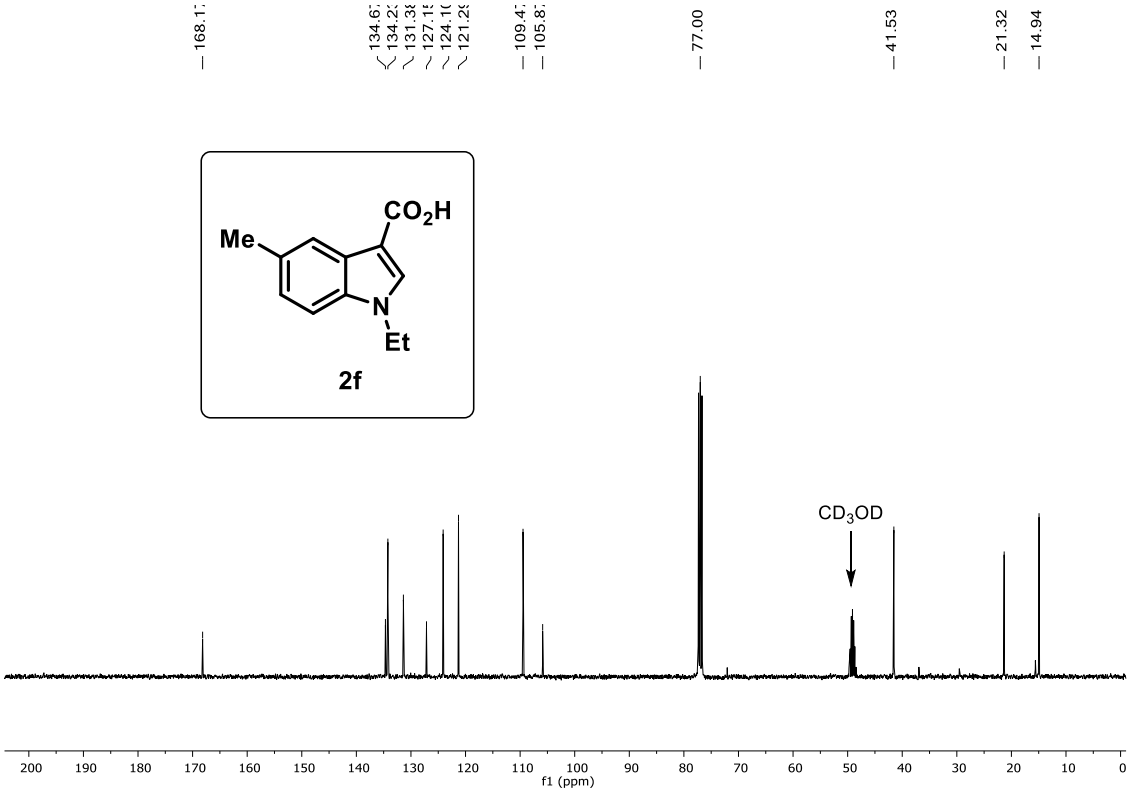
^{13}C NMR of **2e** (100 MHz, $CDCl_3$)



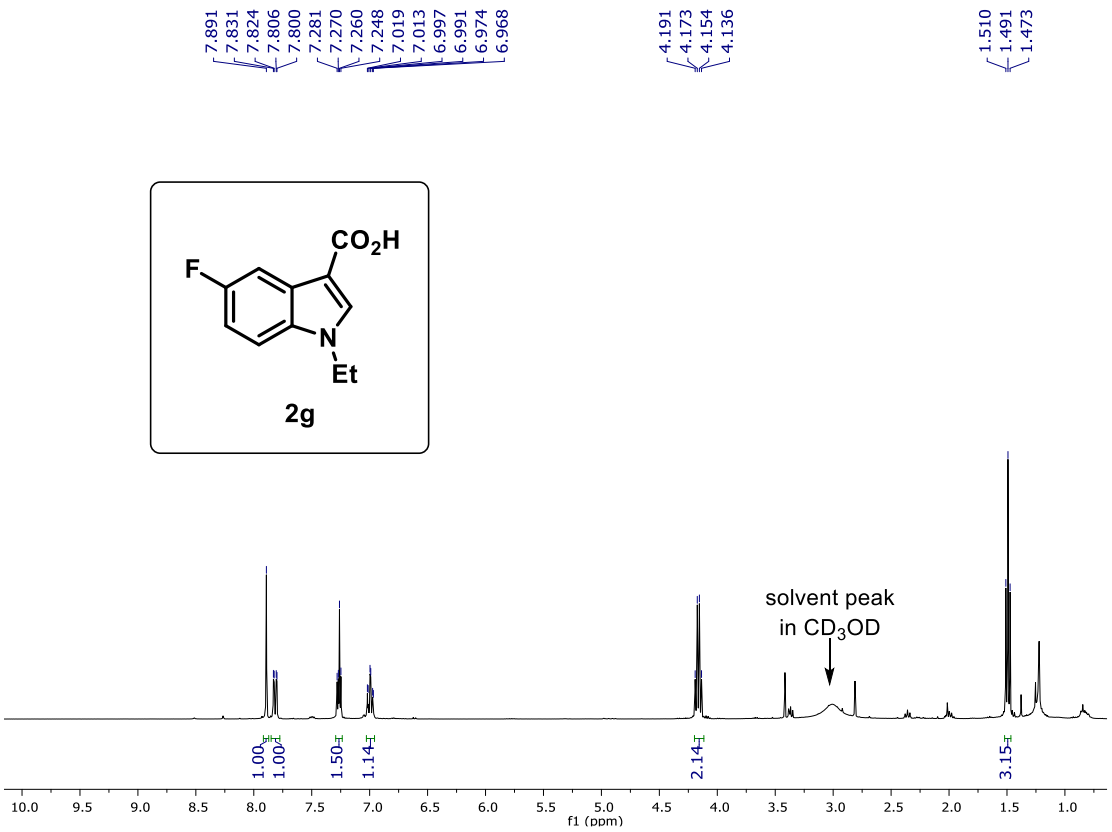
^{1}H NMR of **2f** (400 MHz, Chloroform-*d*)



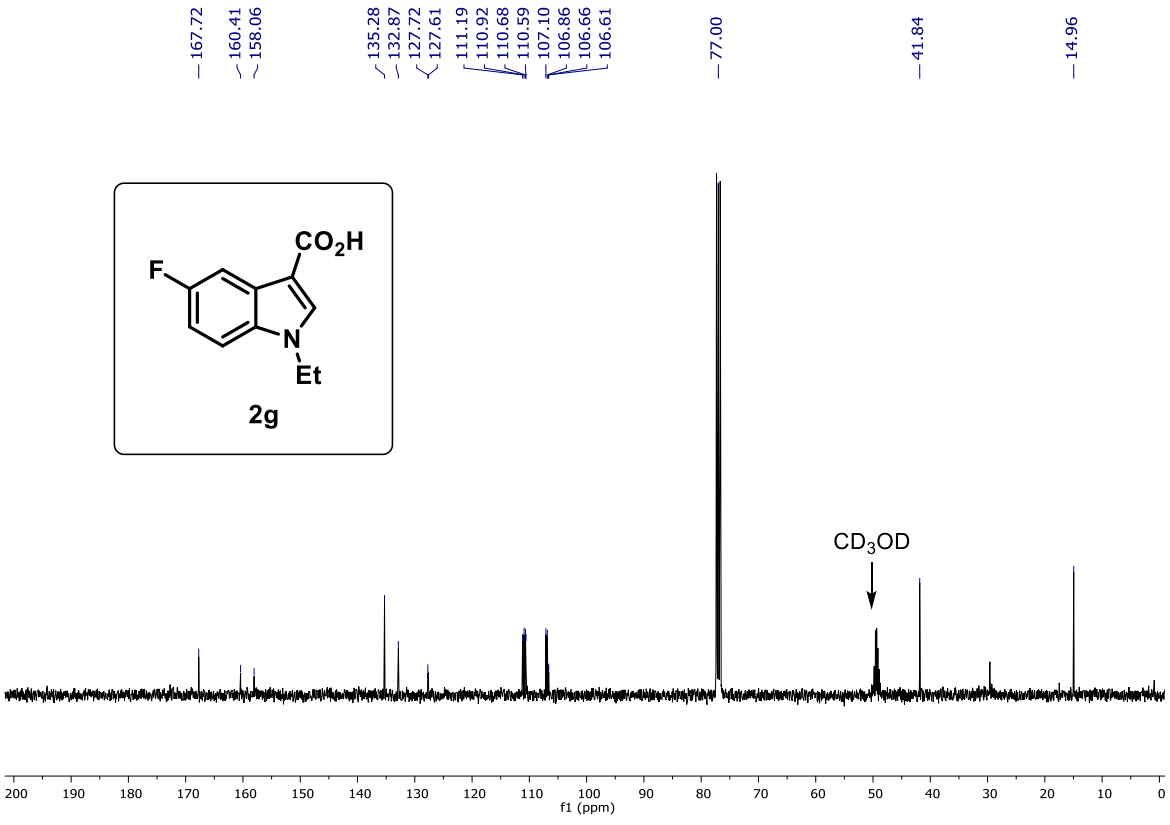
^{13}C NMR of **2f** (100 MHz, $CDCl_3$)



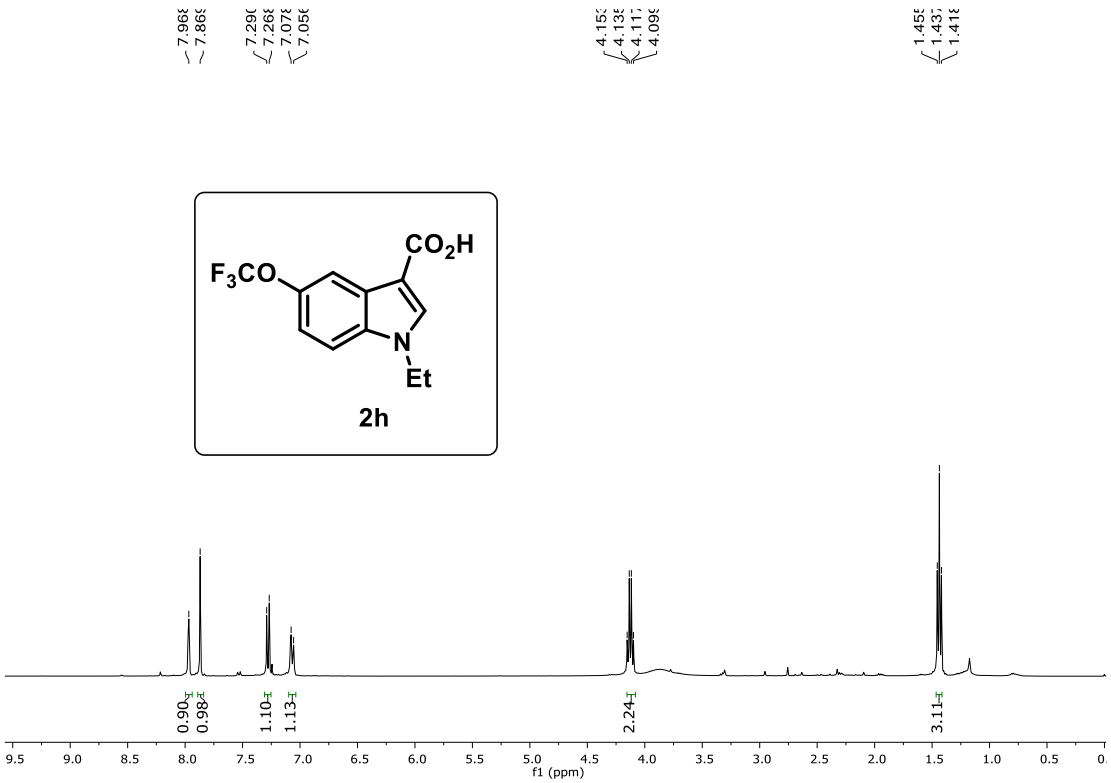
^{1}H NMR of **2g** (400 MHz, Chloroform-*d*)



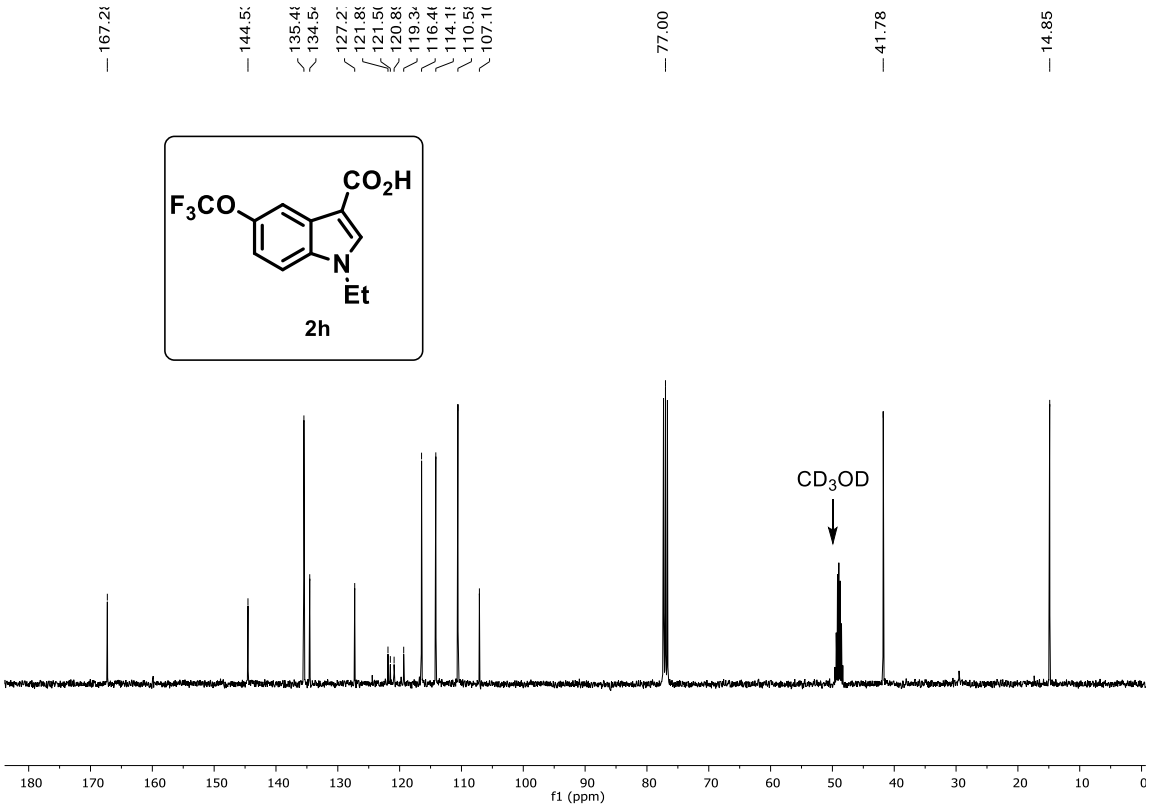
^{13}C NMR of **2g** (100 MHz, $CDCl_3$)



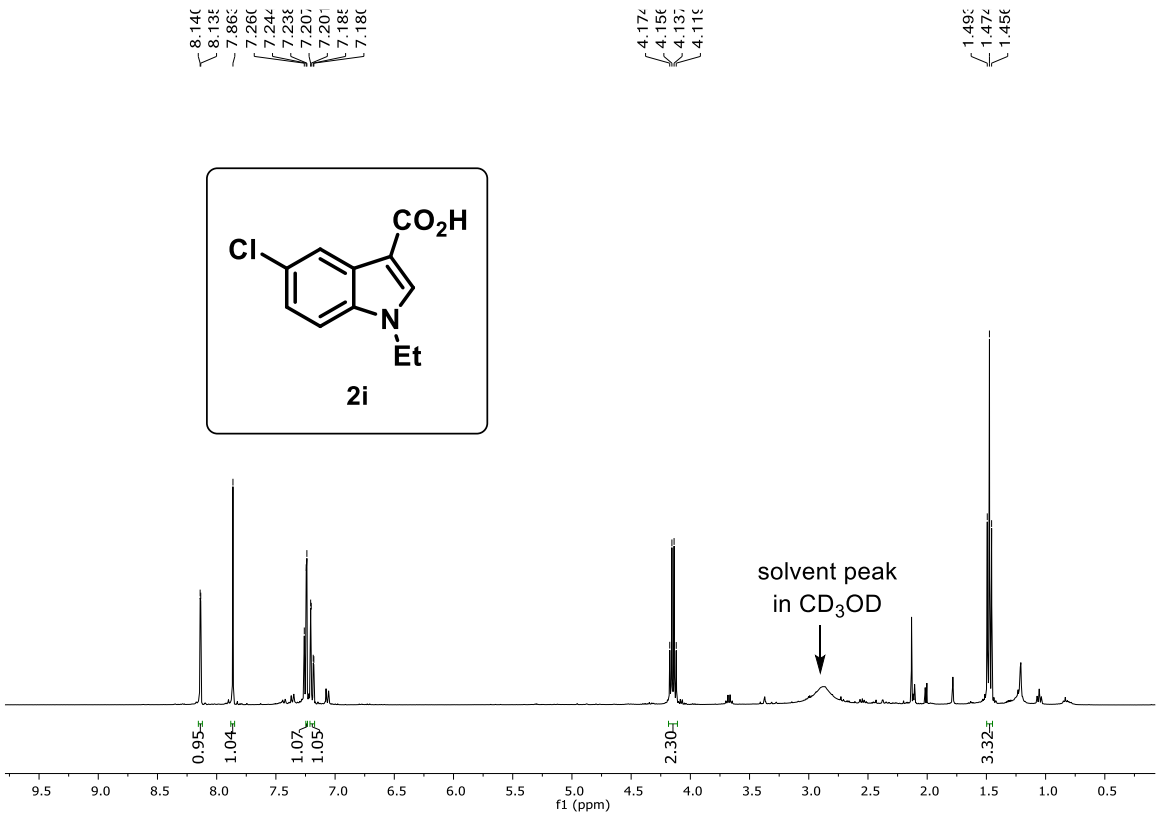
^{1}H NMR of **2h** (400 MHz, Chloroform-*d*)



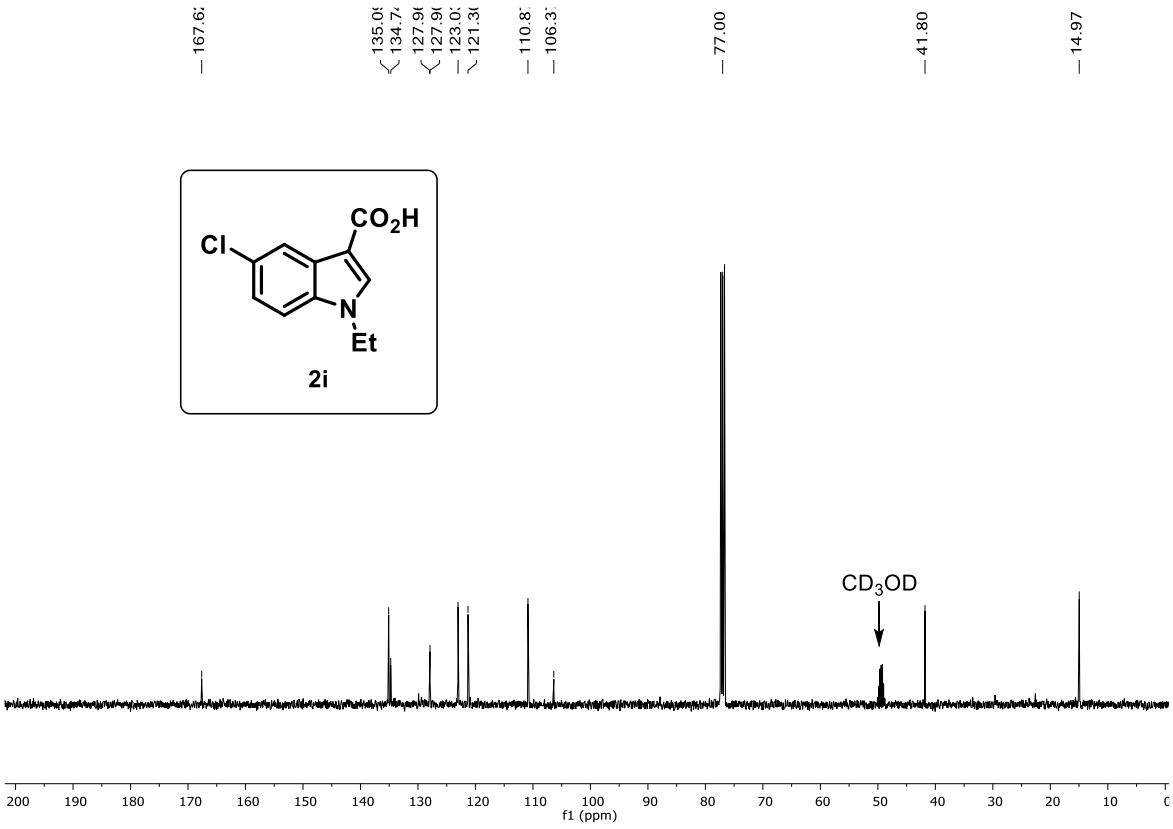
^{13}C NMR of **2h** (100 MHz, $CDCl_3$)



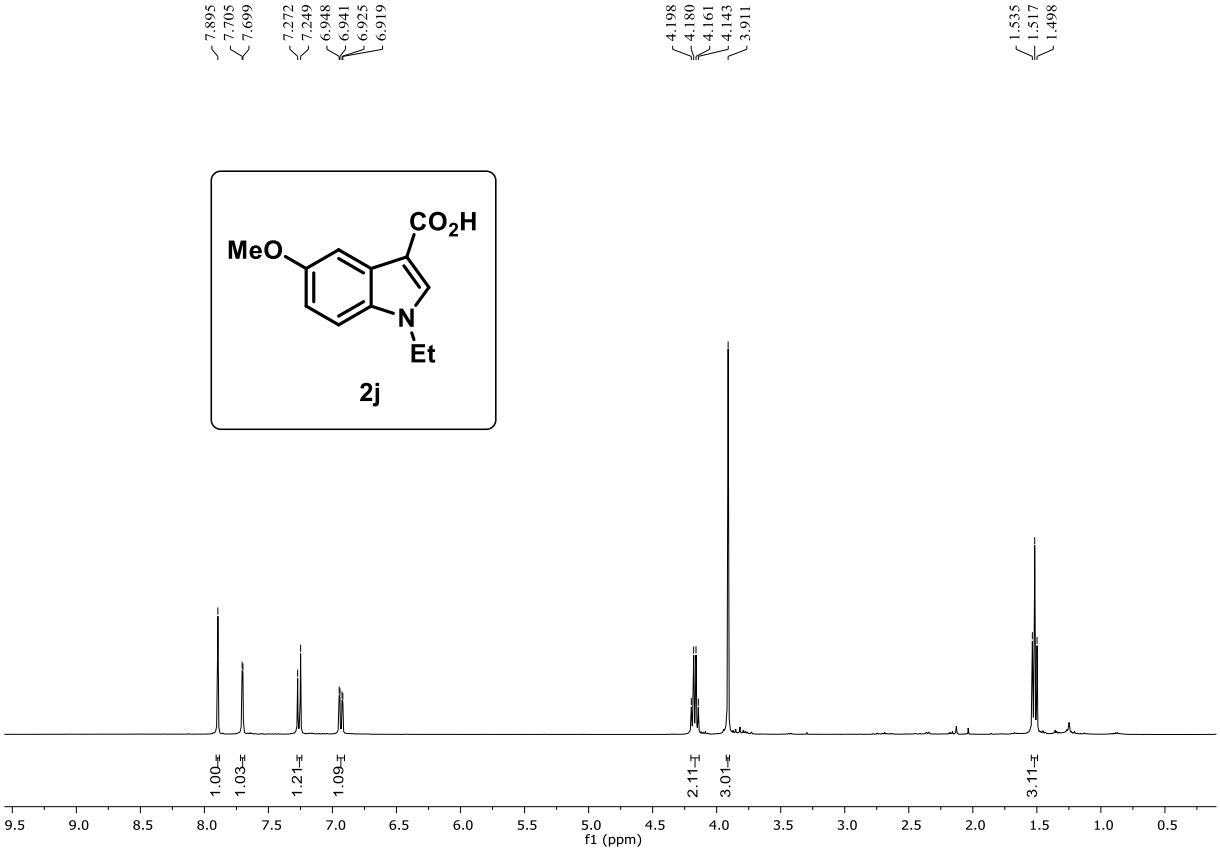
^{1}H NMR of **2i** (400 MHz, Chloroform-*d*)



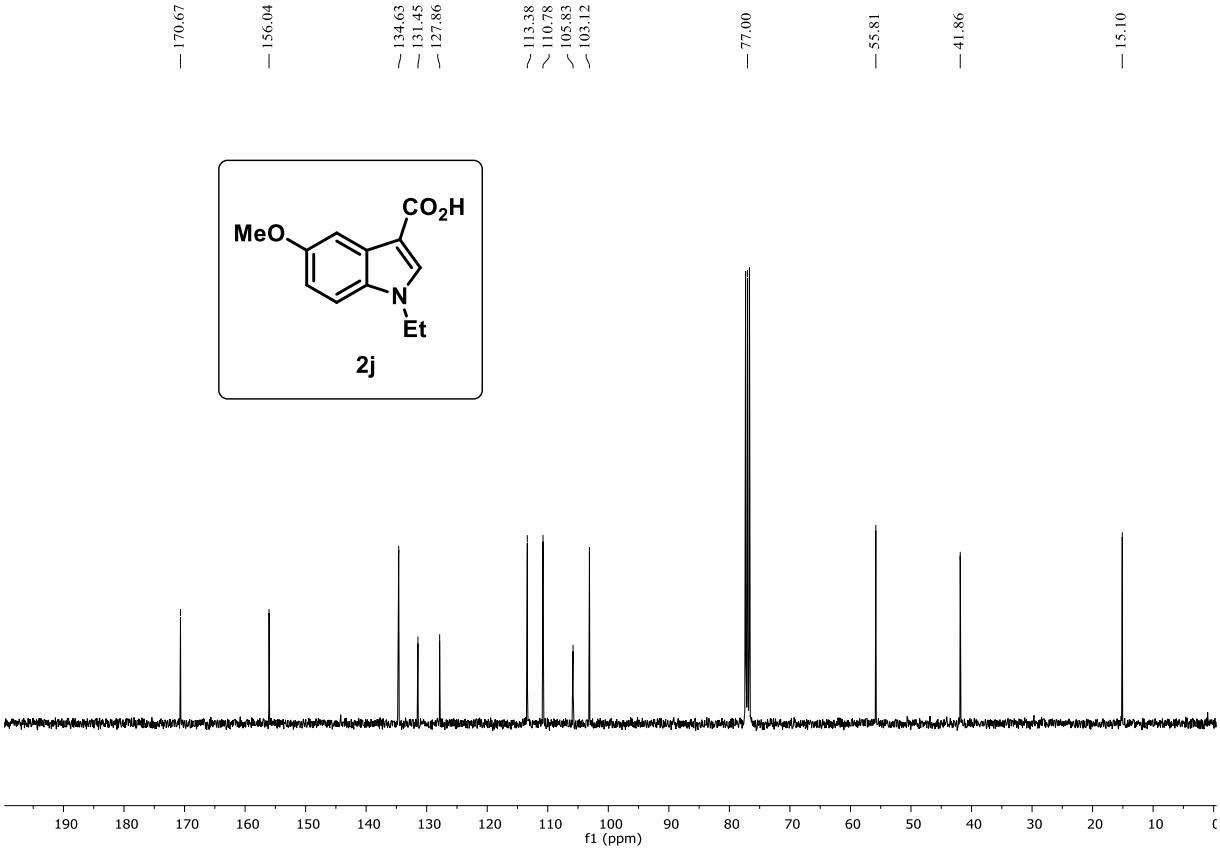
^{13}C NMR of **2i** (100 MHz, $CDCl_3$)



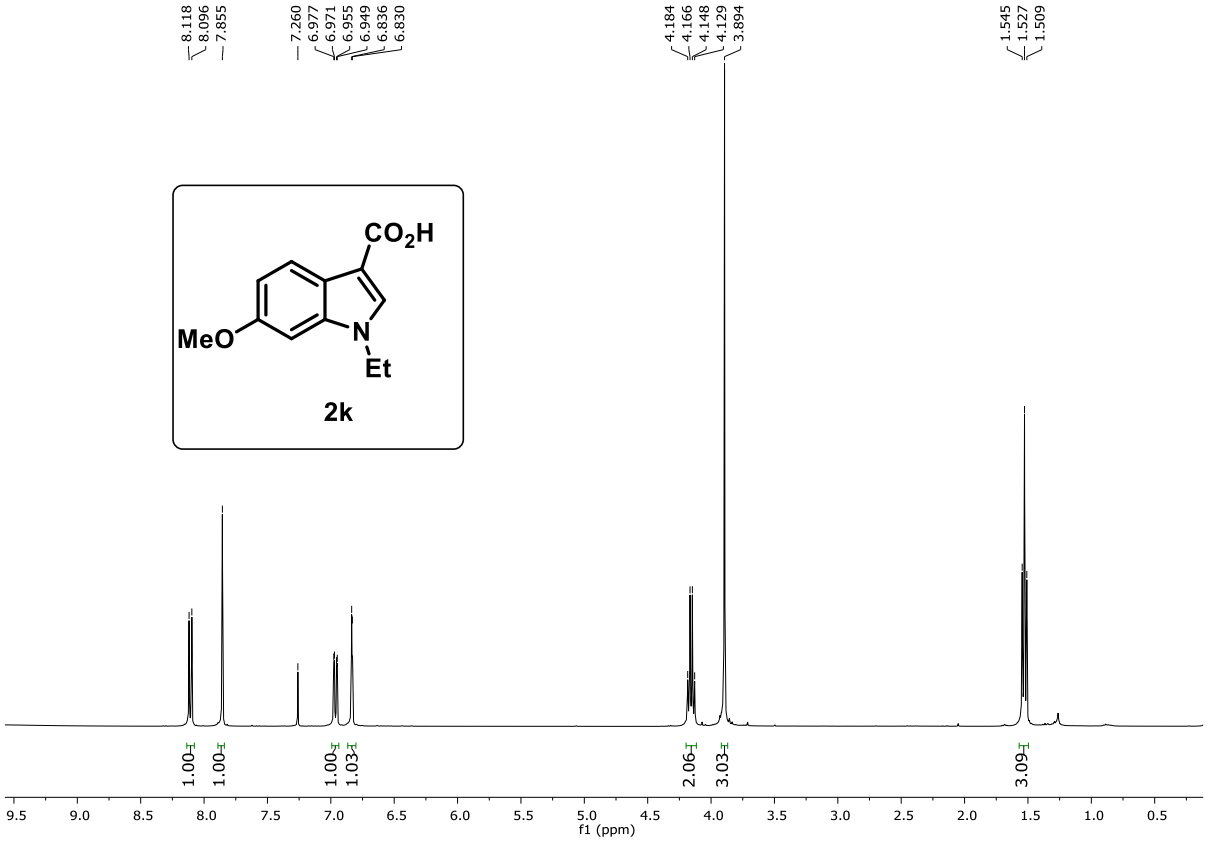
^{1}H NMR of **2j** (400 MHz, Chloroform-*d*)



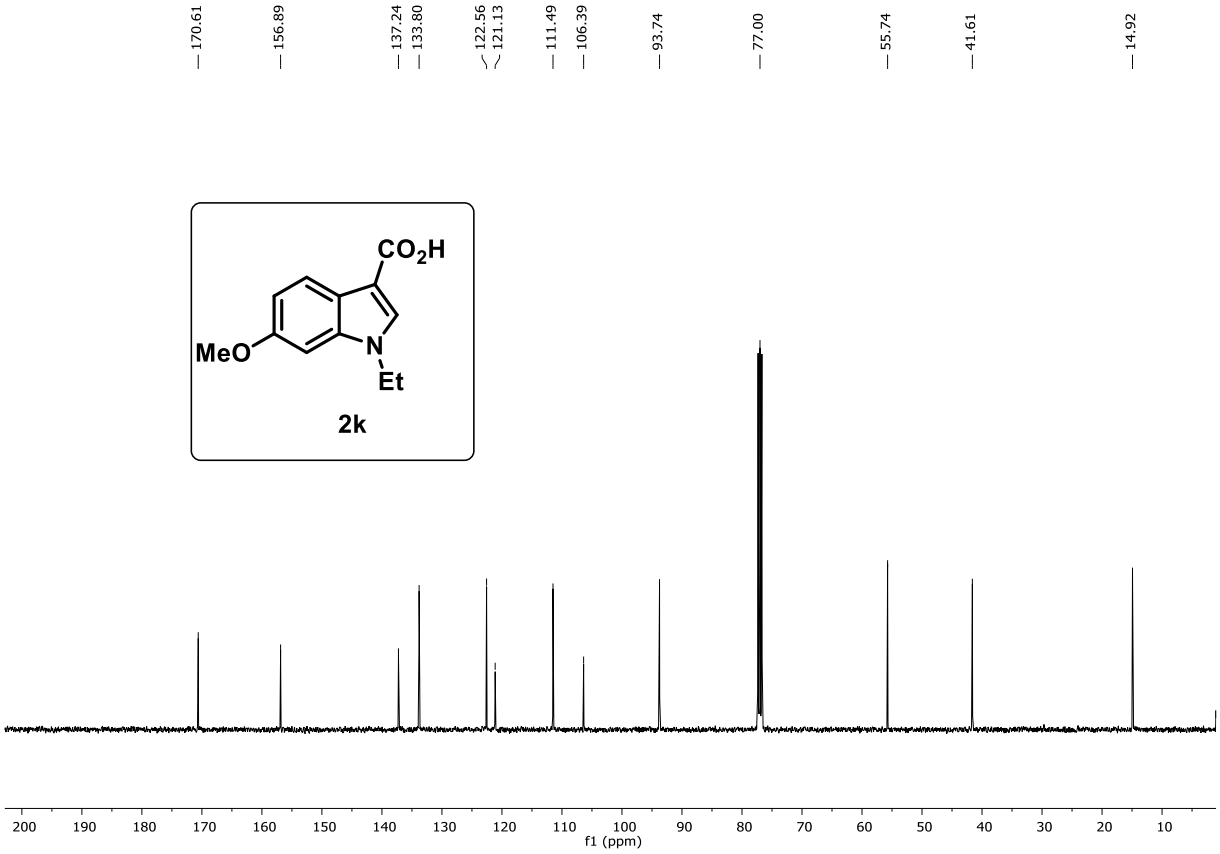
^{13}C NMR of **2j** (100 MHz, $CDCl_3$)



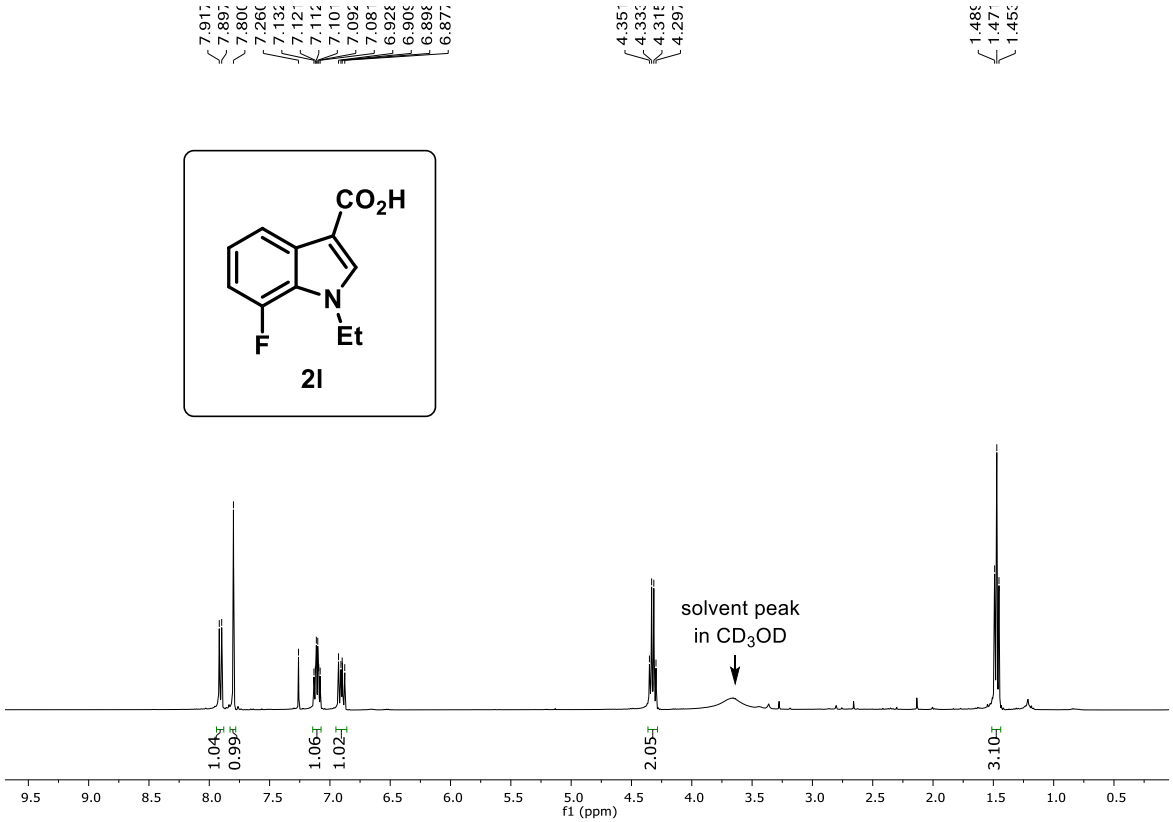
^{1}H NMR of **2k** (400 MHz, Chloroform-*d*)



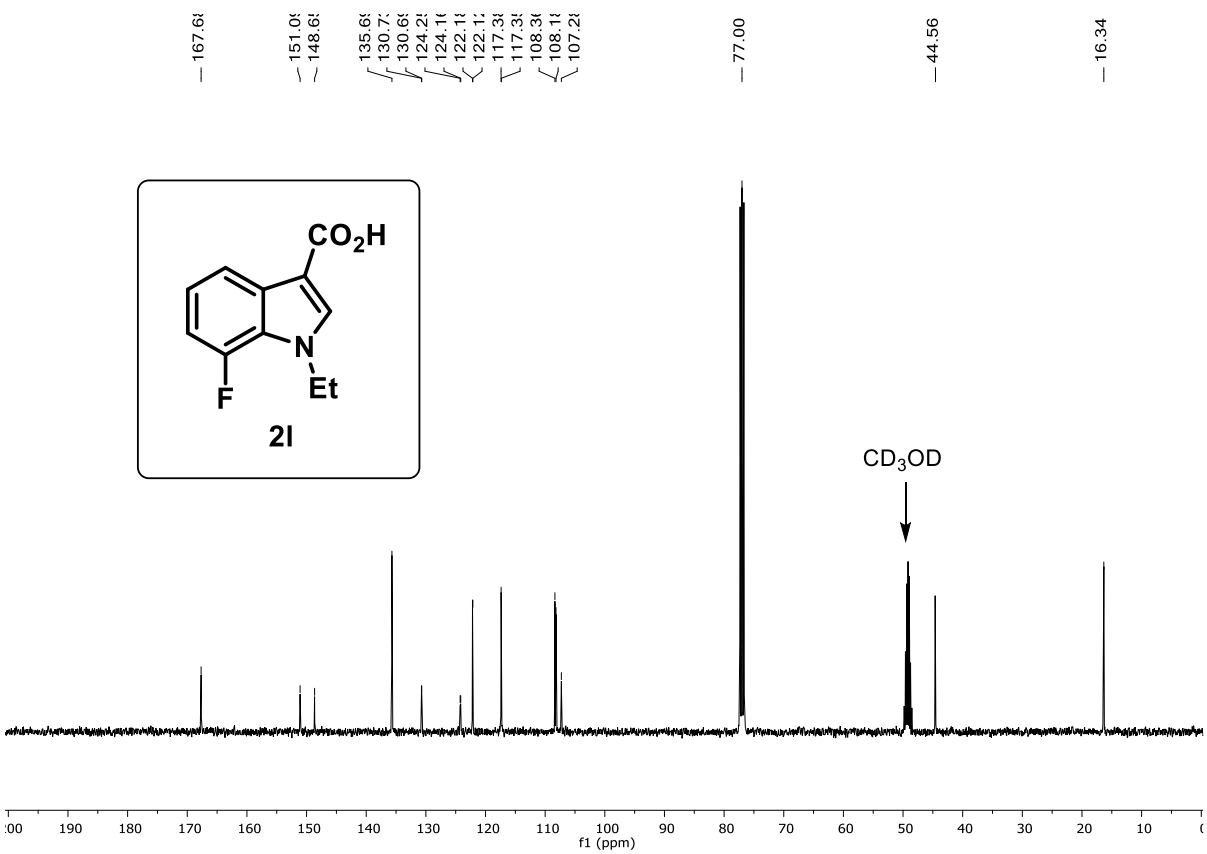
^{13}C NMR of **2k** (100 MHz, $CDCl_3$)



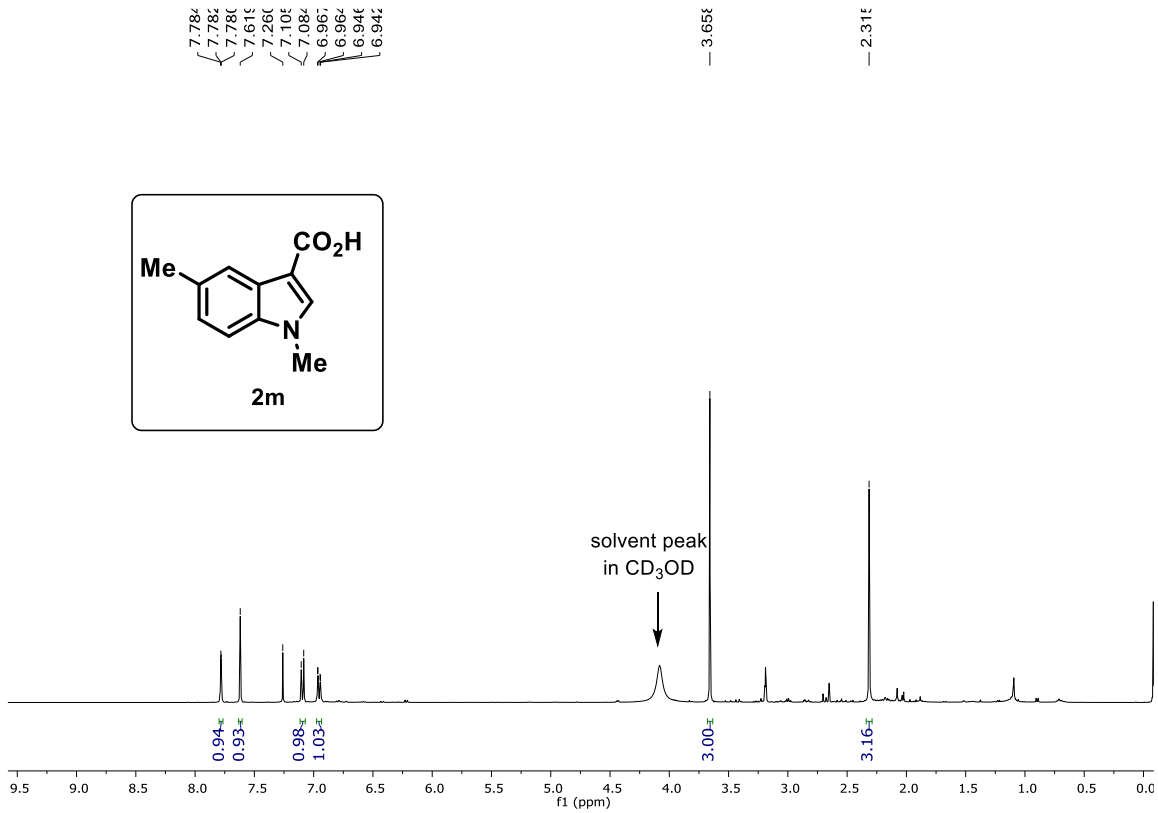
^{1}H NMR of **2l** (400 MHz, Chloroform-*d*)



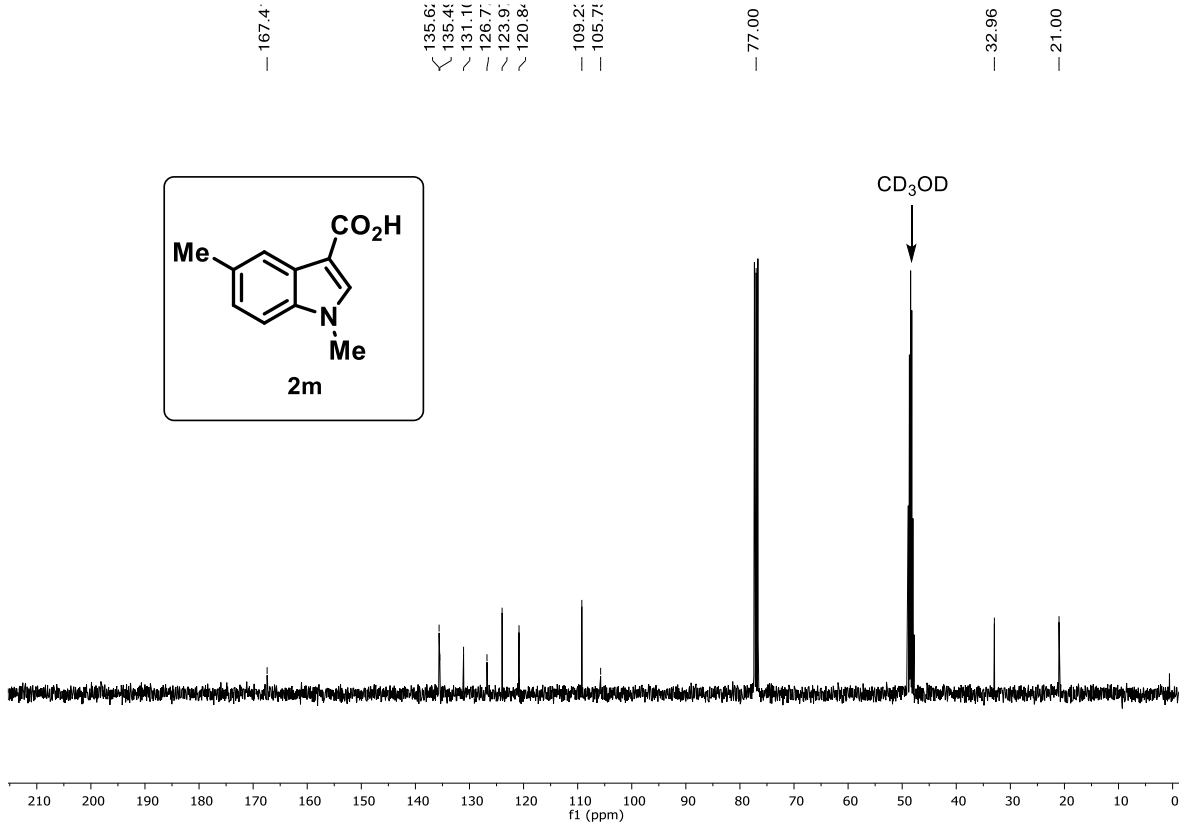
^{13}C NMR of **2l** (100 MHz, $CDCl_3$)



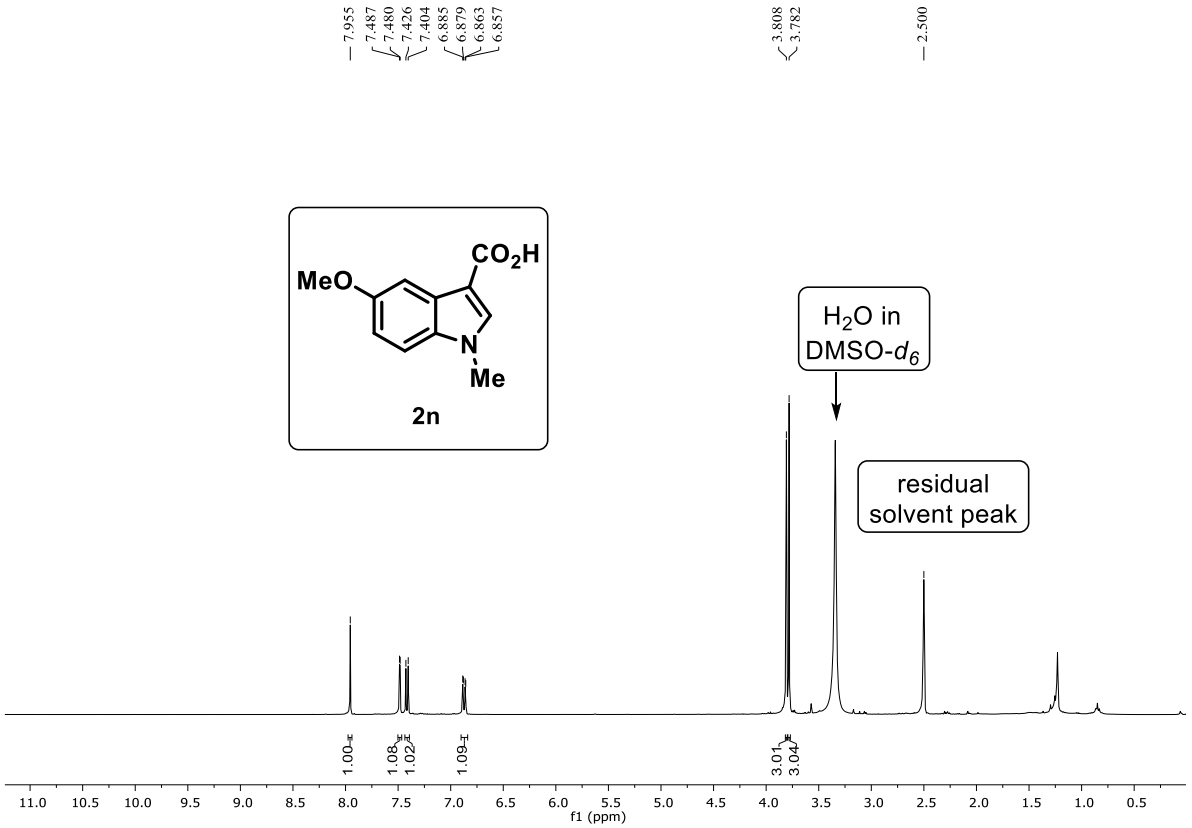
^{1}H NMR of **2m** (400 MHz, Chloroform-*d*)



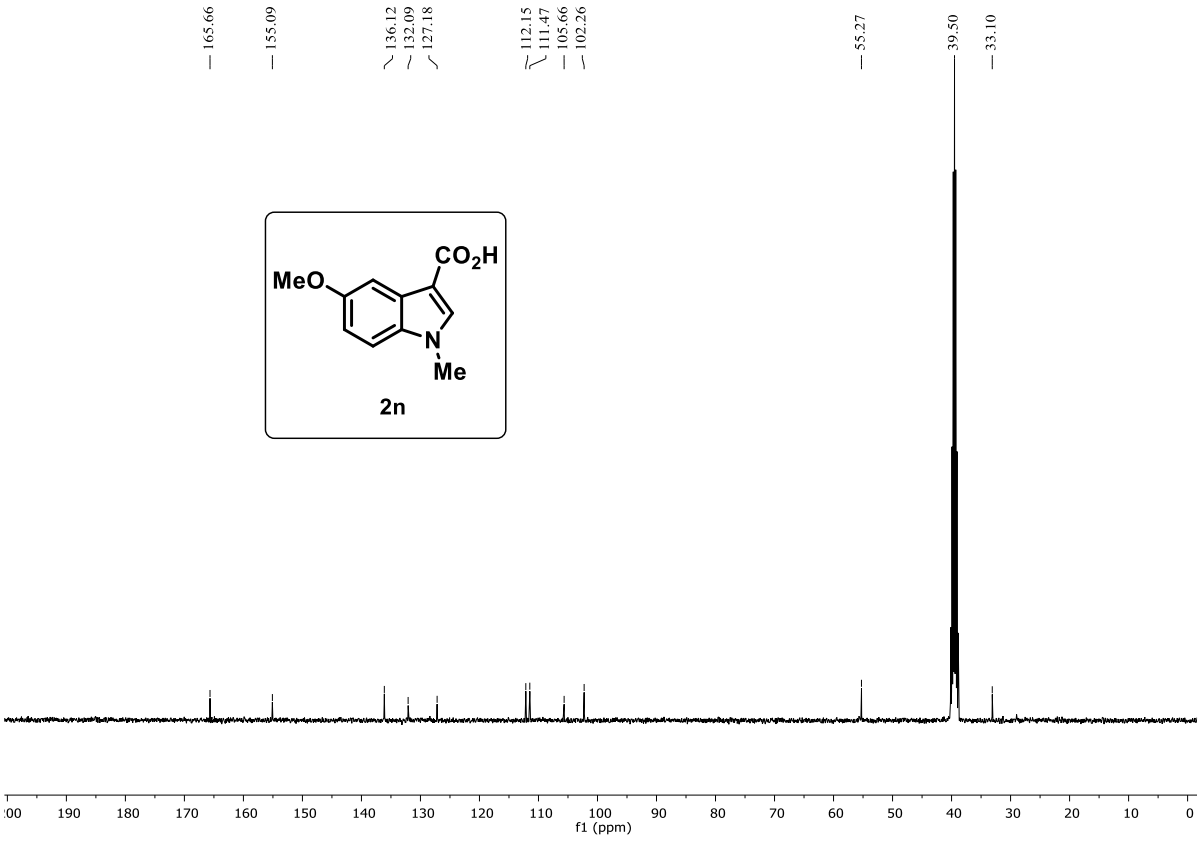
^{13}C NMR of **2m** (100 MHz, $CDCl_3$)



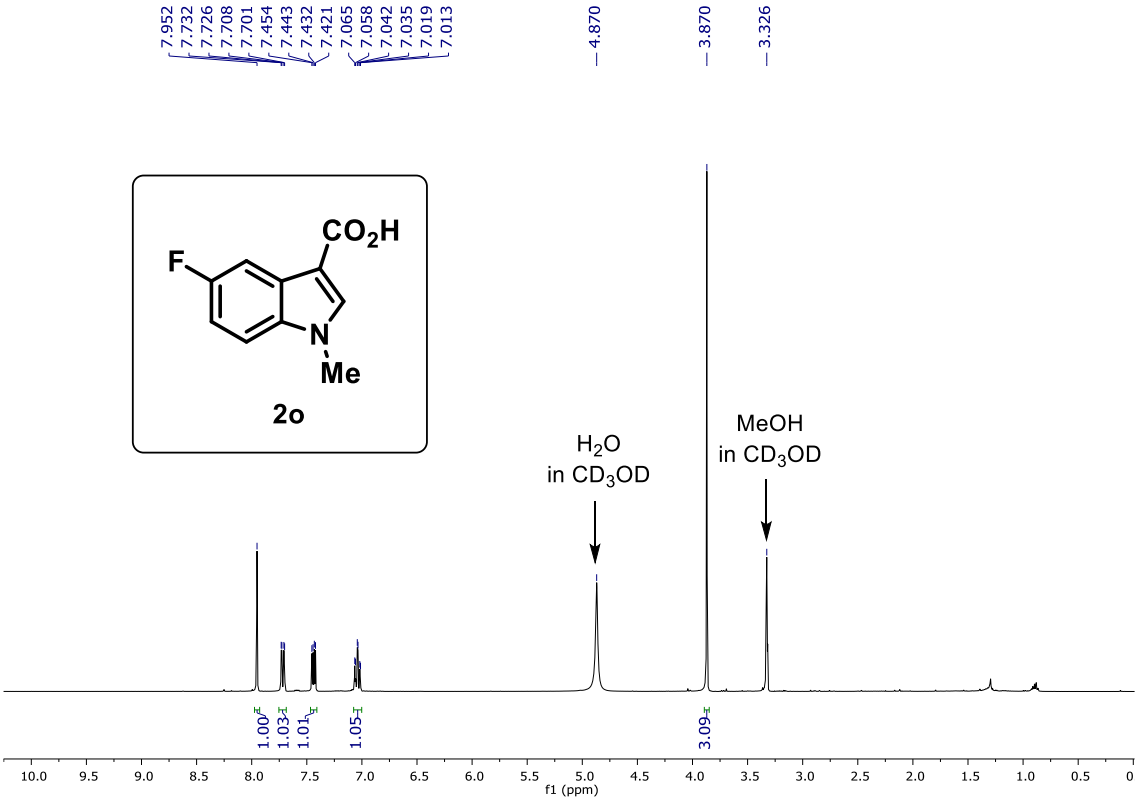
^{1}H NMR of **2n (**400 MHz, DMSO-d_6)



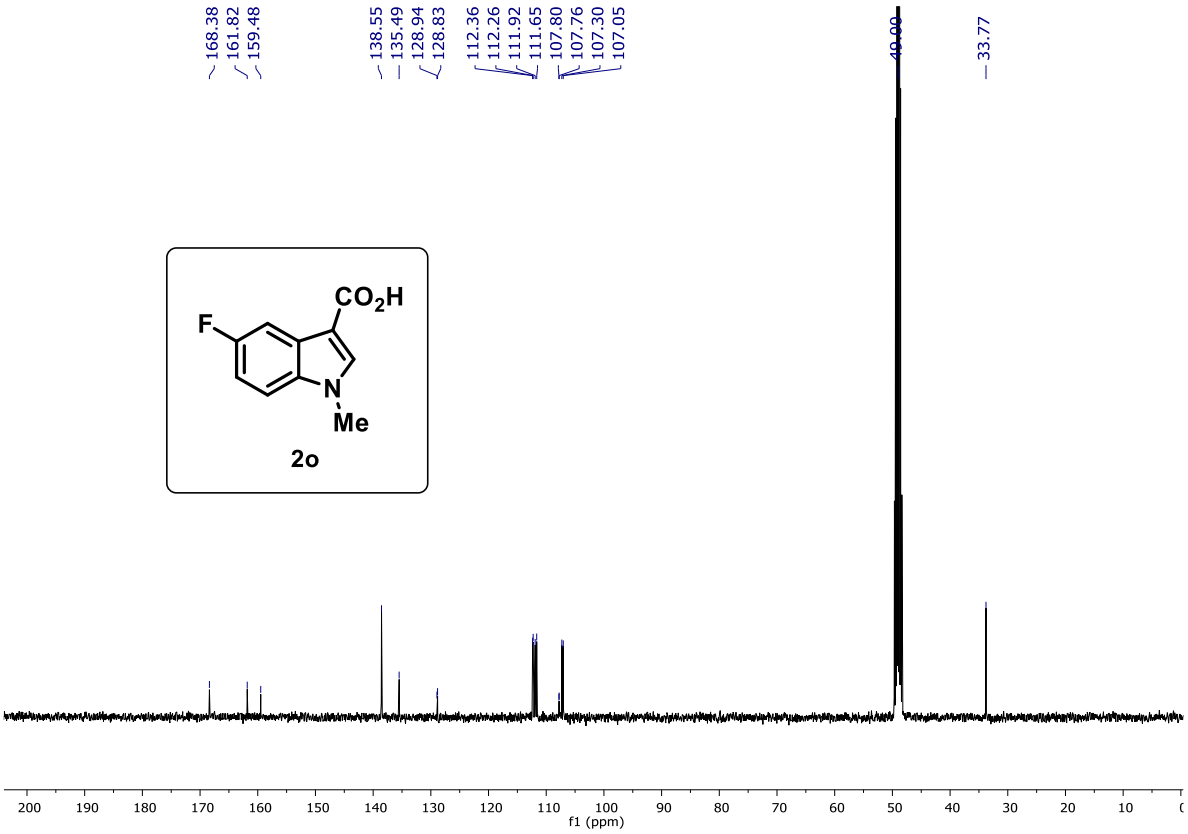
^{13}C NMR of **2n** (100 MHz, DMSO-d_6)



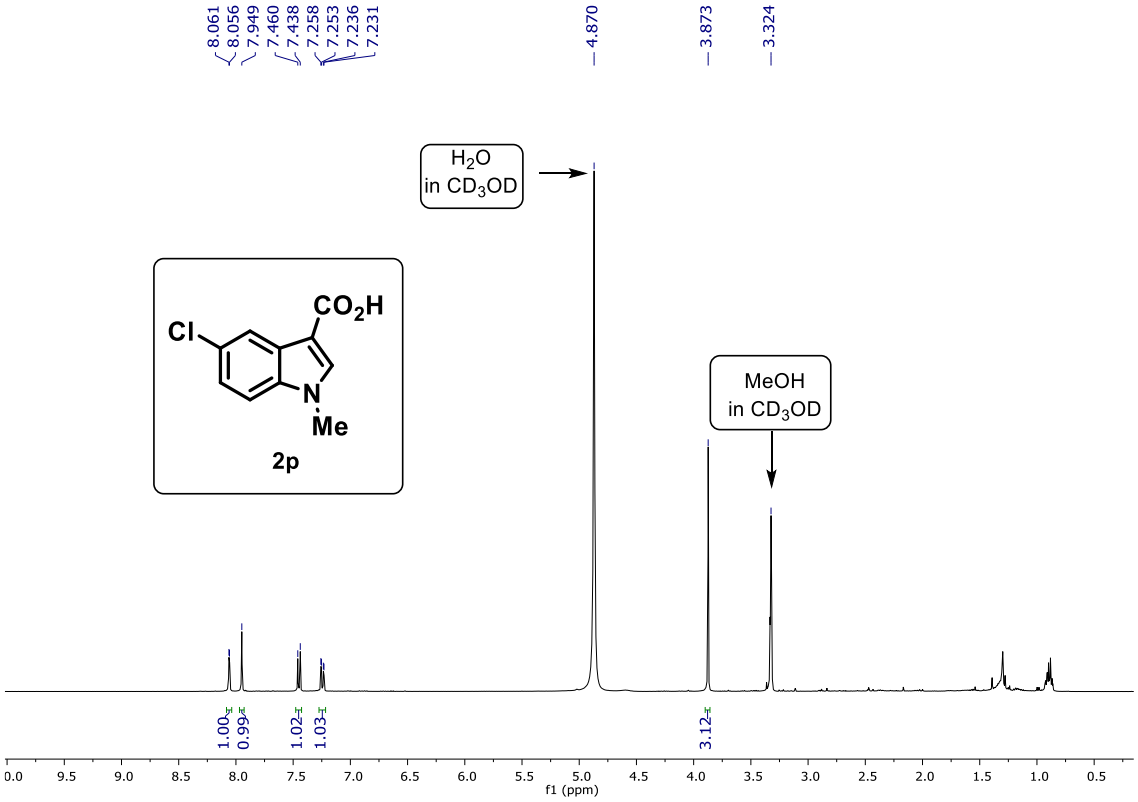
^{1}H NMR of **2o (**400 MHz, Methanol-d^4)



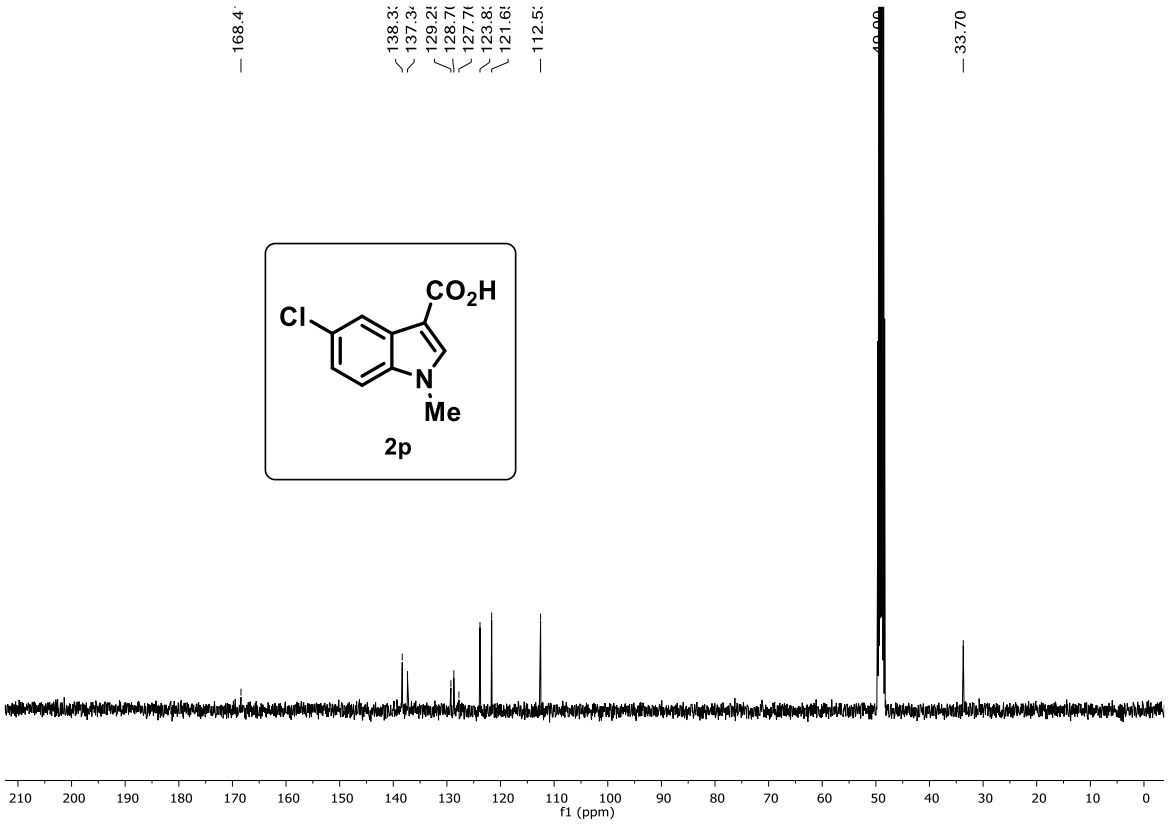
^{13}C NMR of **2o** (100 MHz, Methanol-d^4)



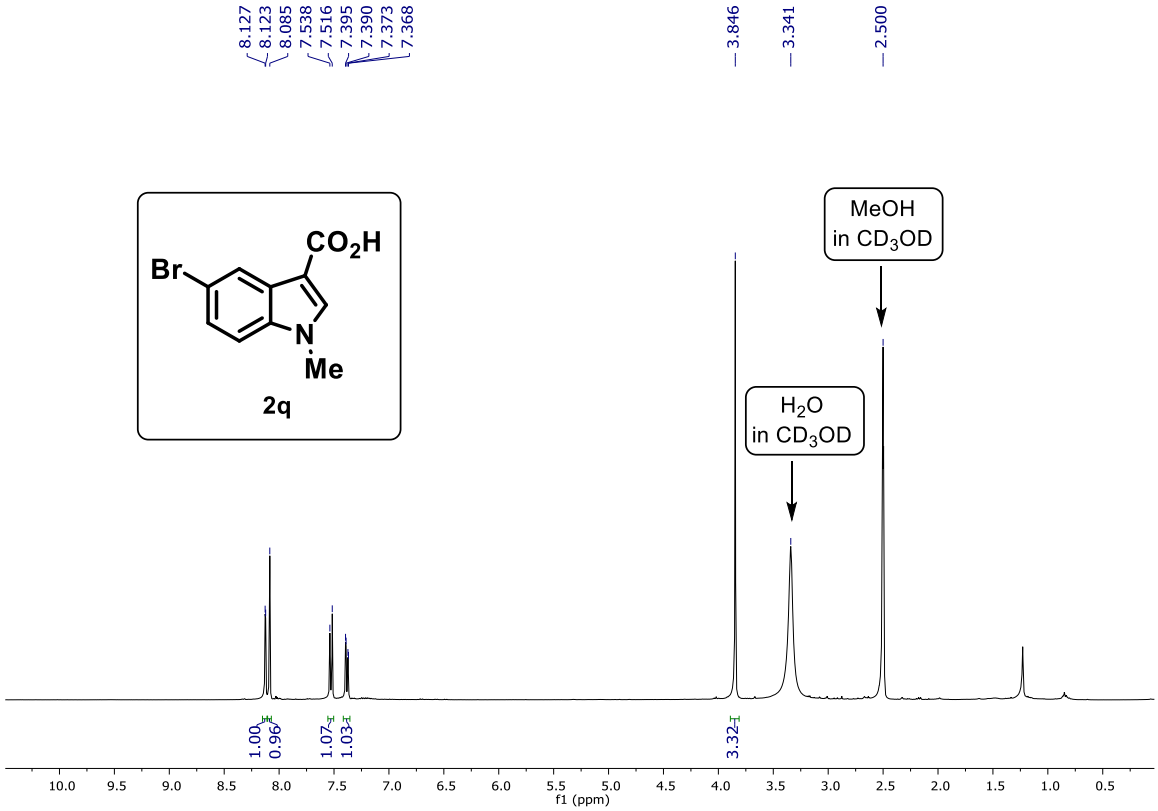
^{1}H NMR of **2p** (400 MHz, Methanol-d^4)



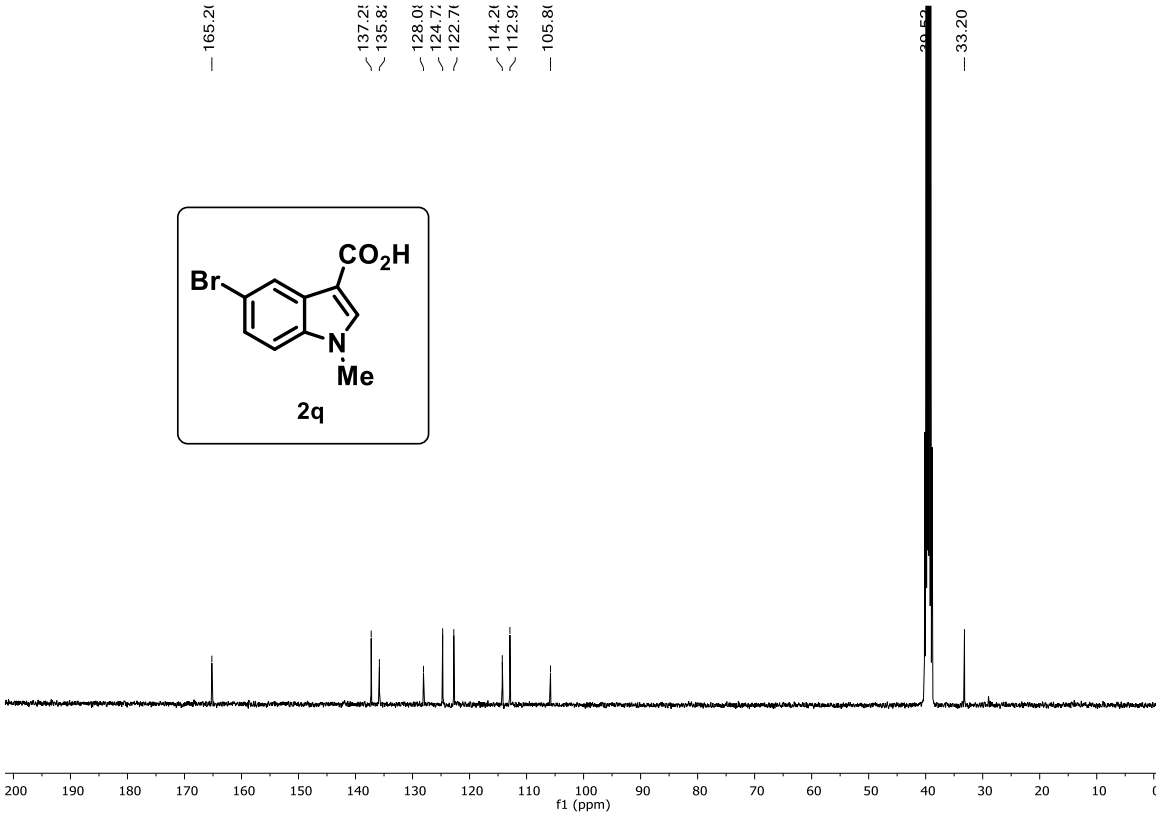
^{13}C NMR of **2p** (100 MHz, Methanol-d^4)



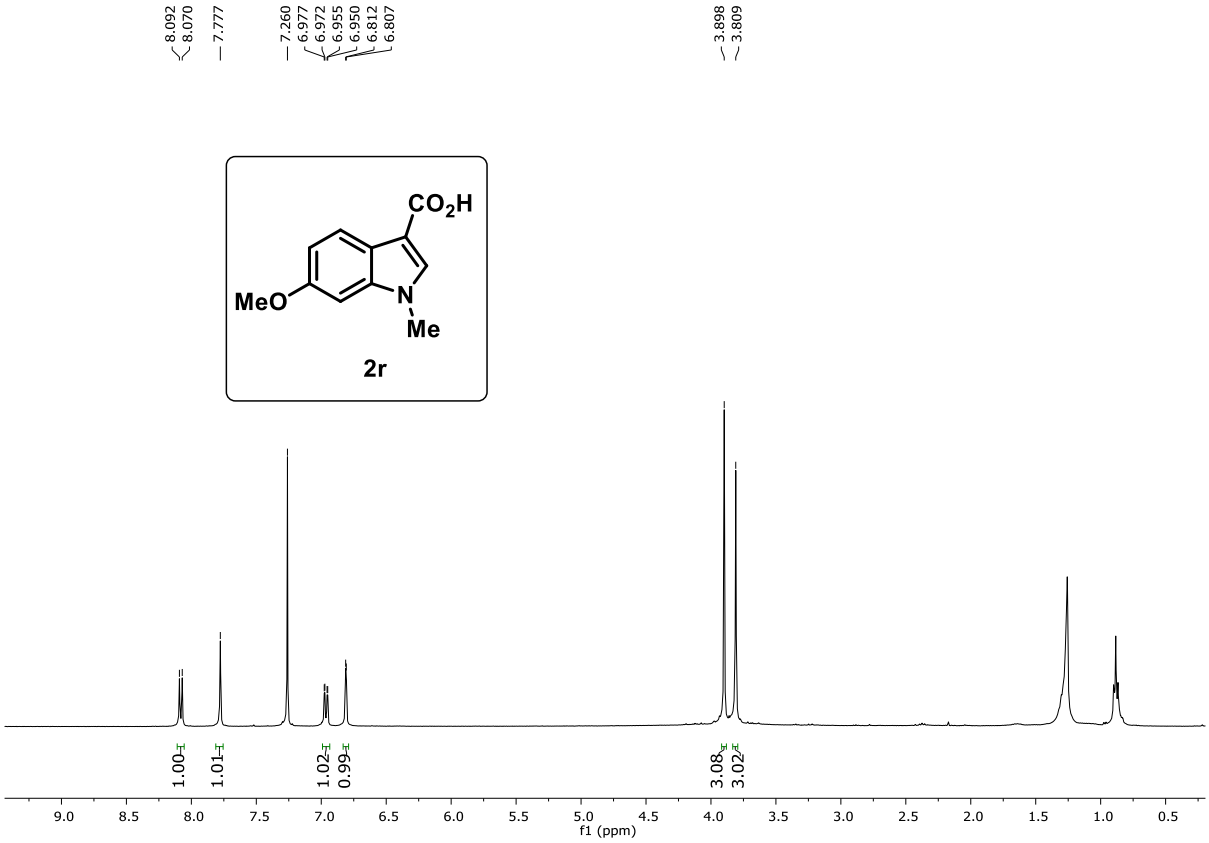
^{1}H NMR of **2q** (400 MHz, Methanol-d^4)



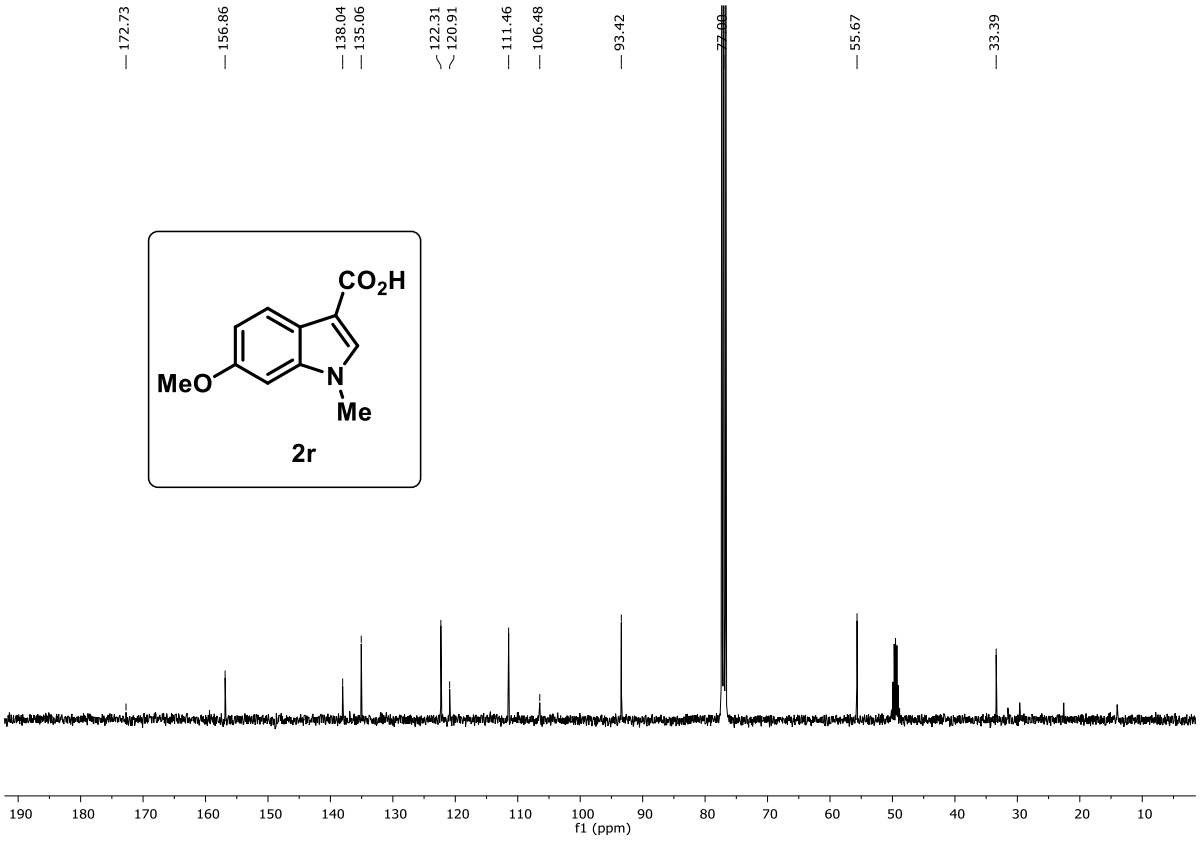
^{13}C NMR of **2q** (100 MHz, Methanol-d^4)



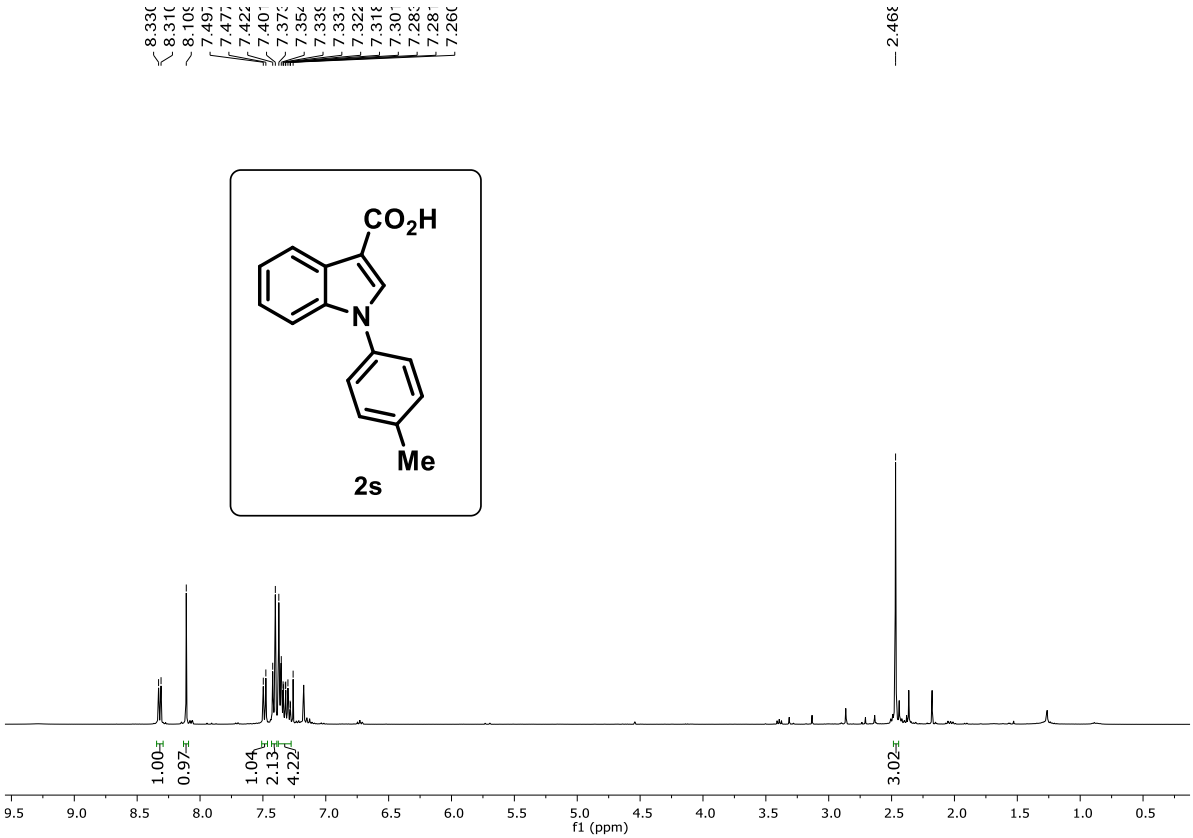
^{1}H NMR of **2r** (400 MHz, Chloroform-*d*)



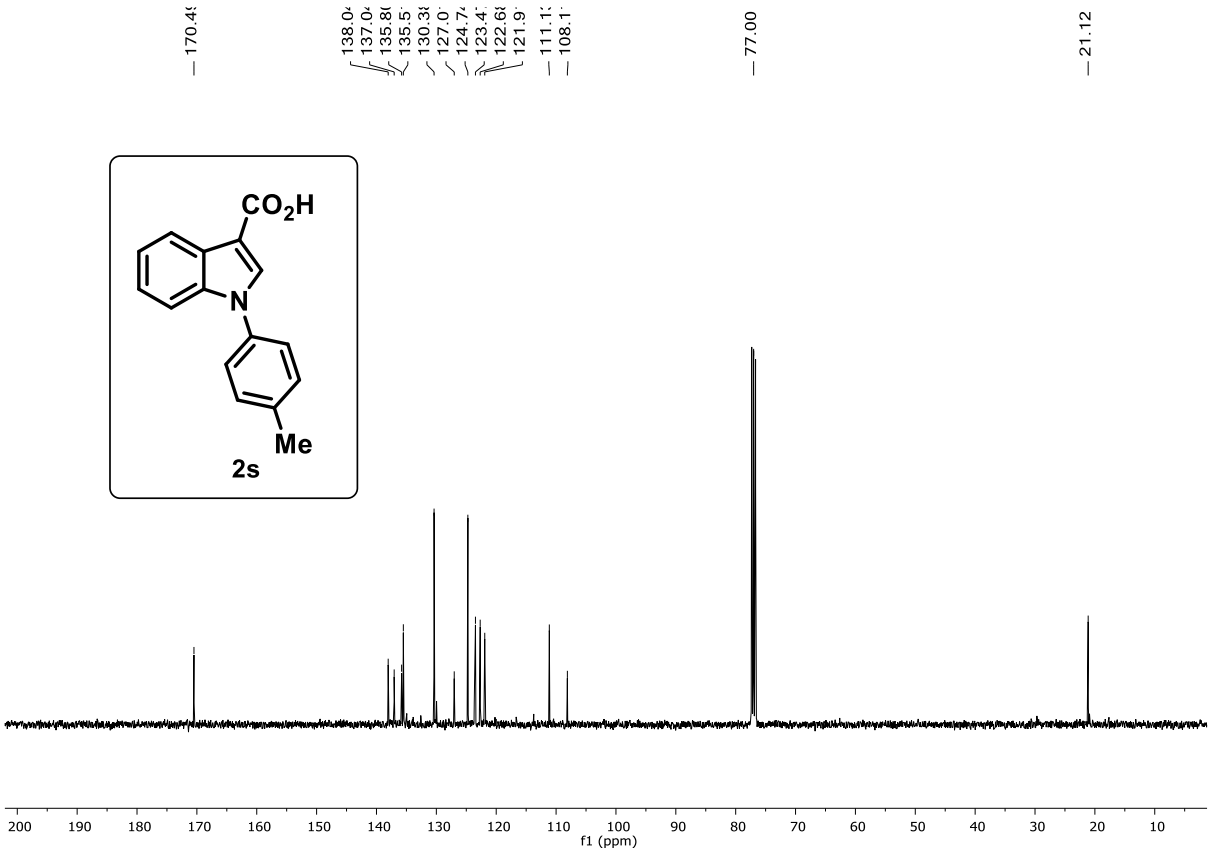
^{13}C NMR of **2r** (100 MHz, $CDCl_3$)



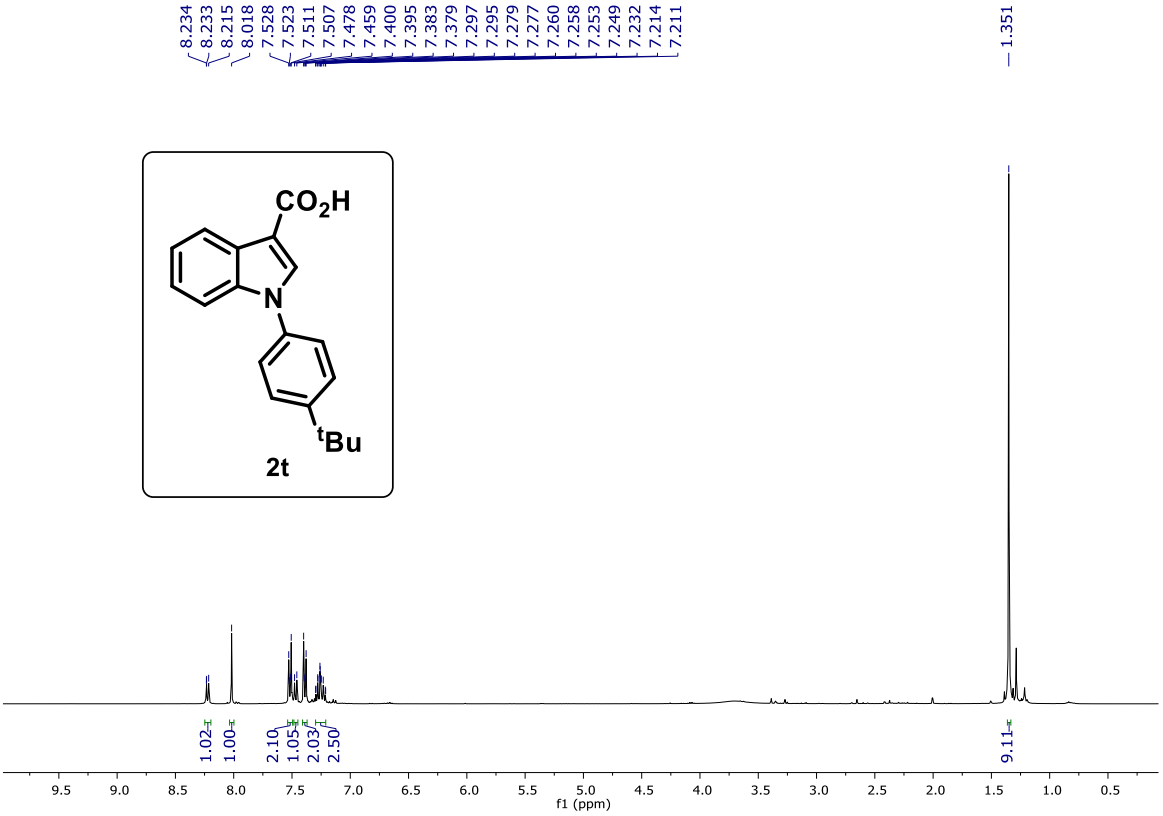
^{1}H NMR of **2s** (400 MHz, Chloroform-*d*)



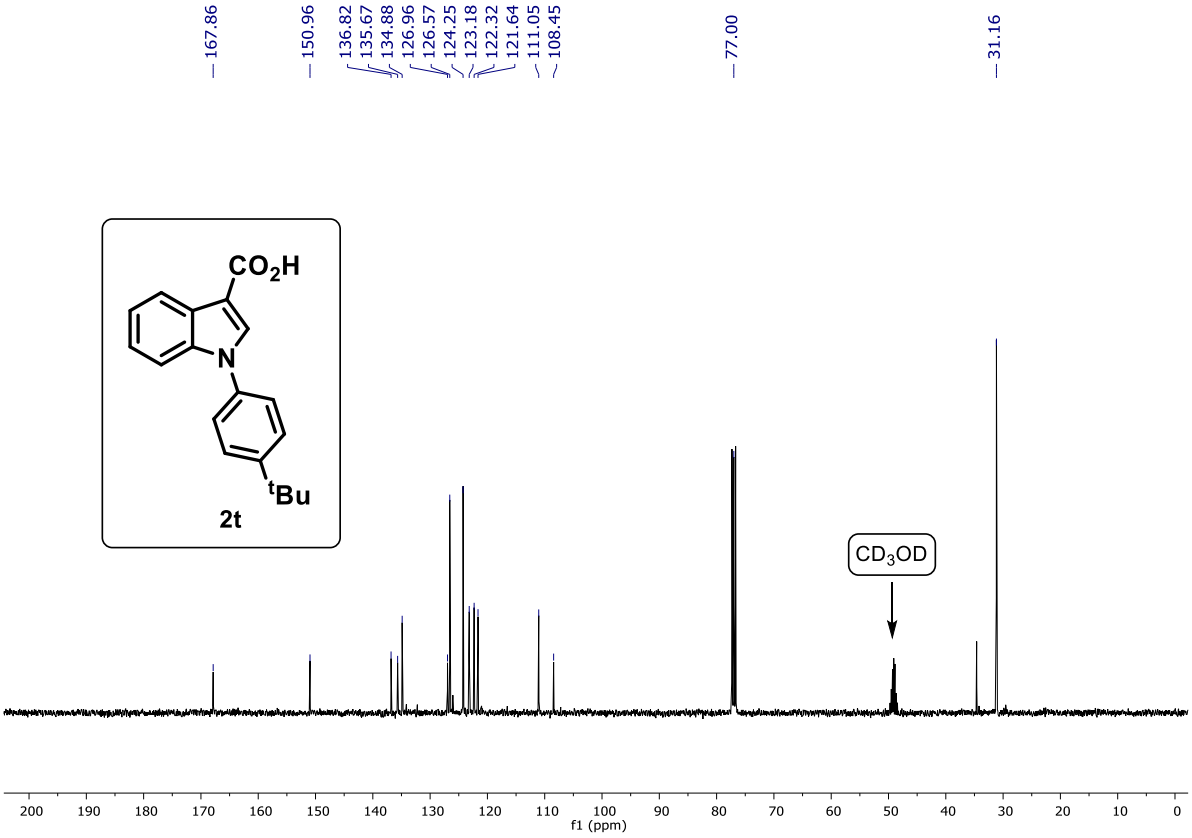
^{13}C NMR of **2s** (100 MHz, $CDCl_3$)



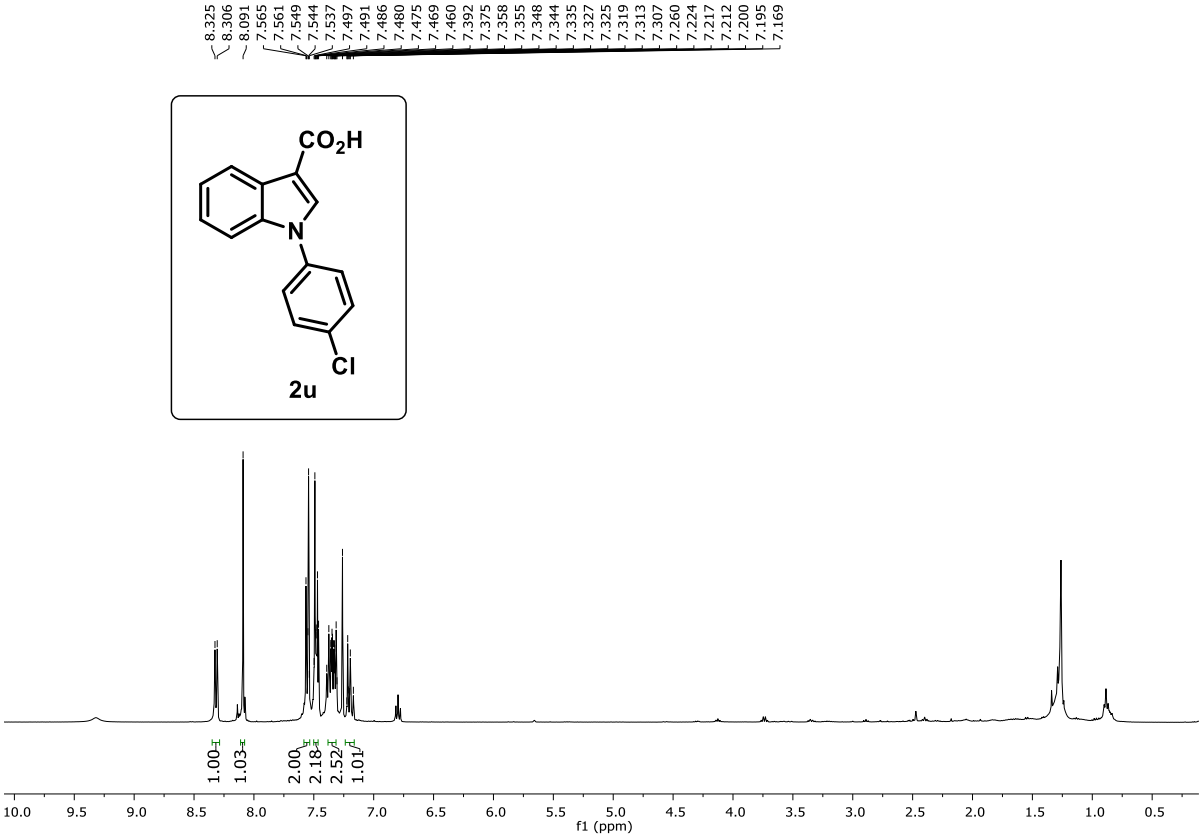
^{1}H NMR of **2t** (400 MHz, Chloroform-*d*)



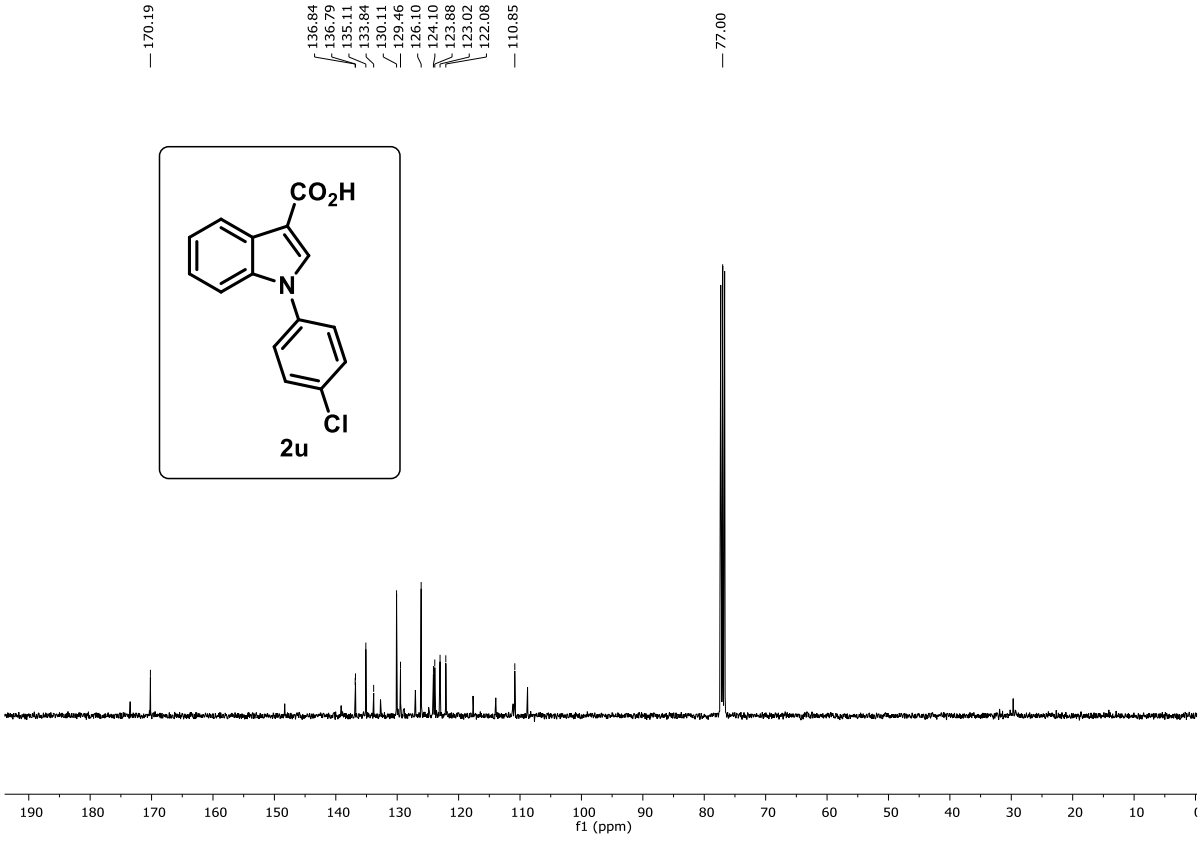
^{13}C NMR of **2t** (100 MHz, $CDCl_3$)



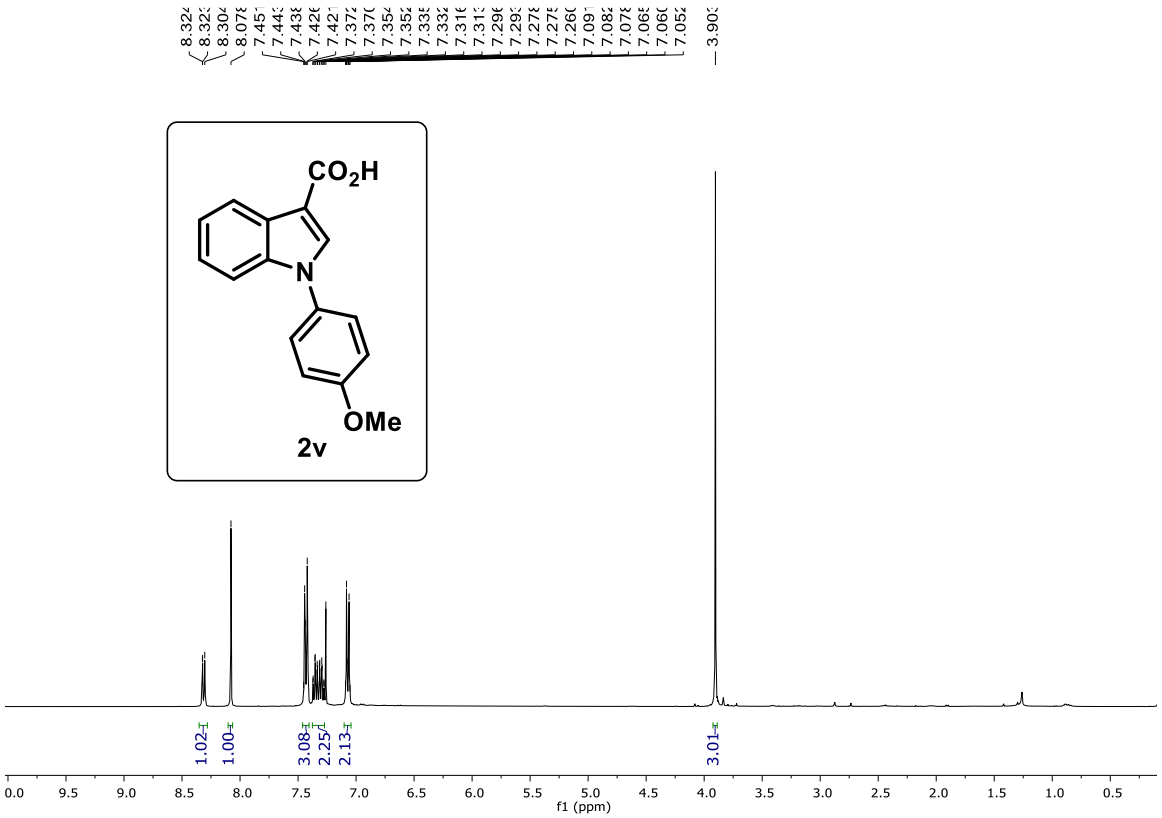
^{1}H NMR of **2u** (400 MHz, Chloroform-*d*)



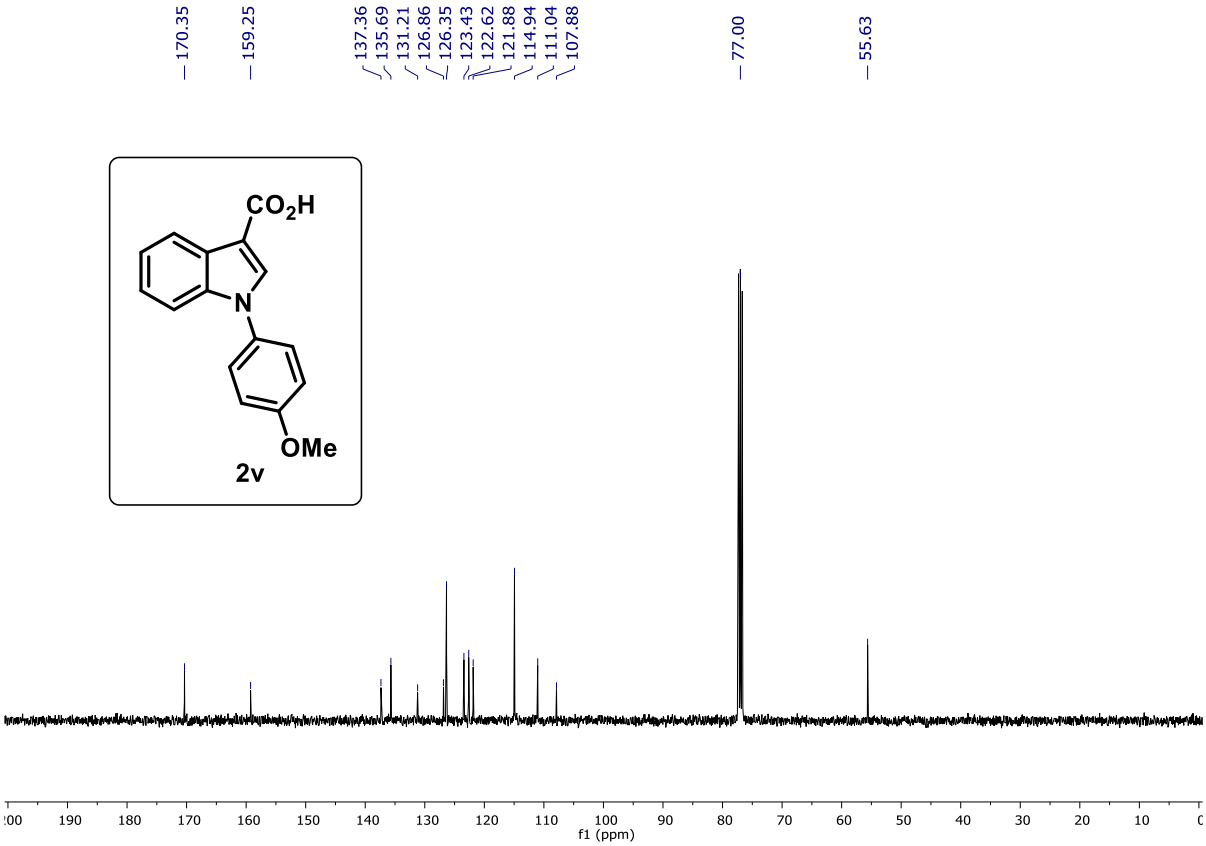
^{13}C NMR of **2u** (100 MHz, $CDCl_3$)



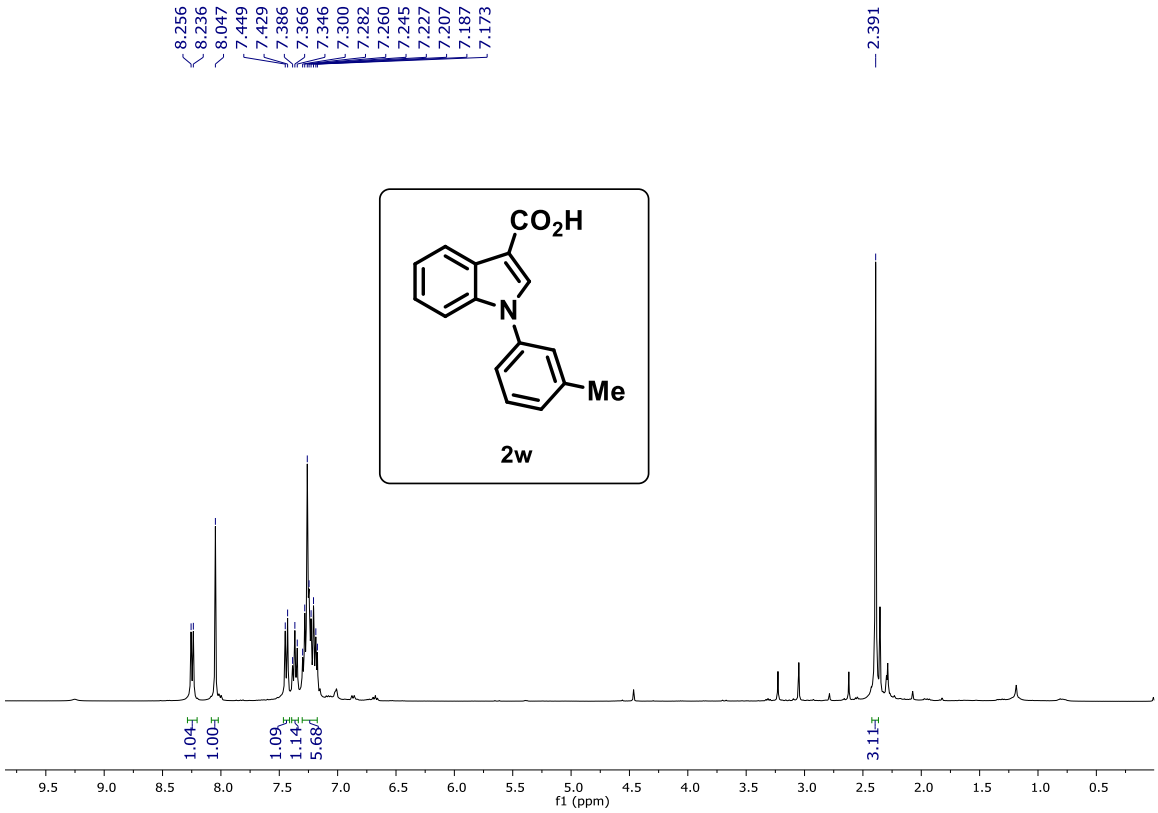
^{1}H NMR of **2v** (400 MHz, Chloroform-*d*)



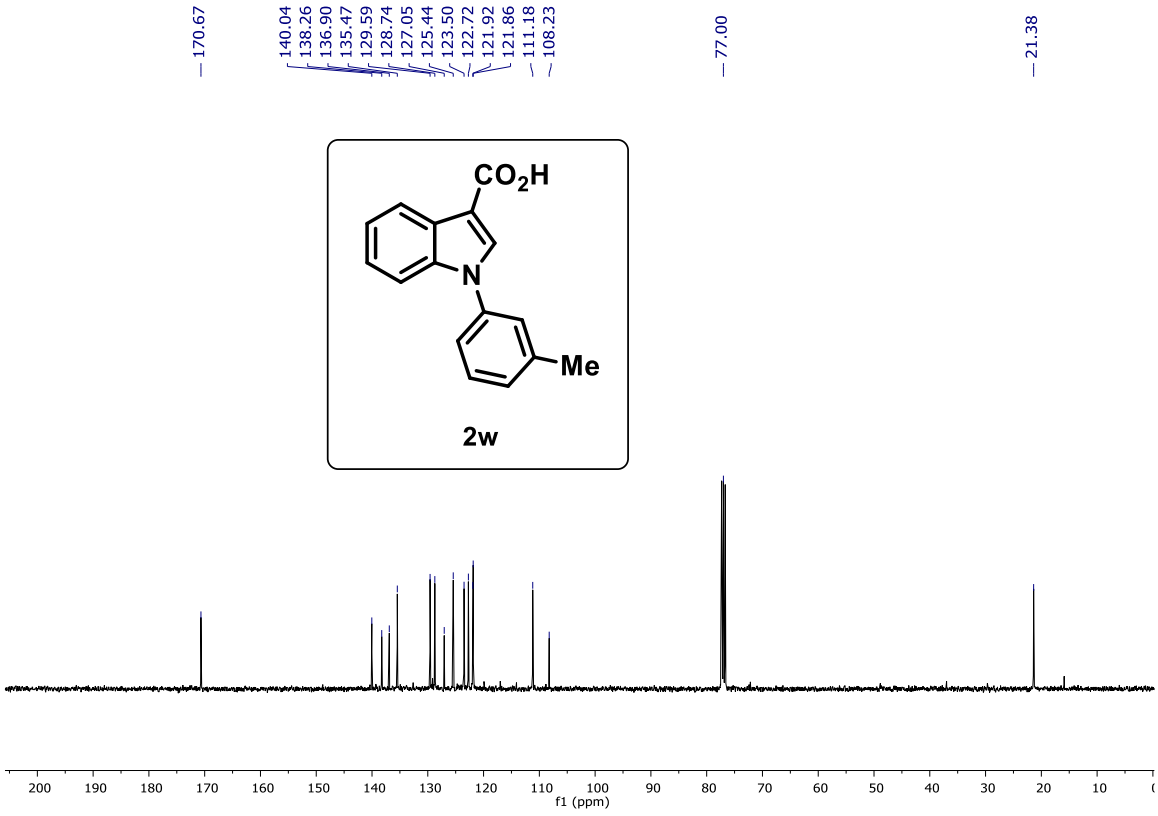
^{13}C NMR of **2v** (100 MHz, $CDCl_3$)



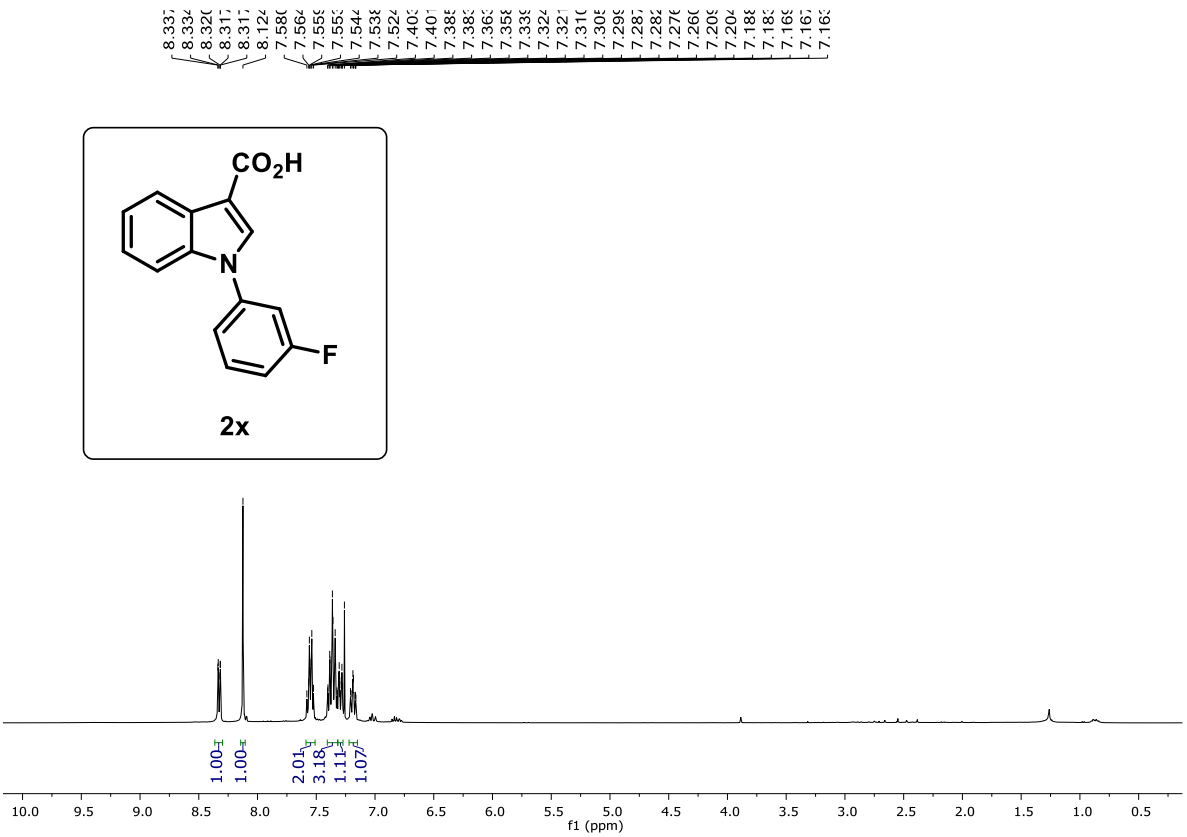
^{1}H NMR of **2w** (400 MHz, Chloroform-*d*)



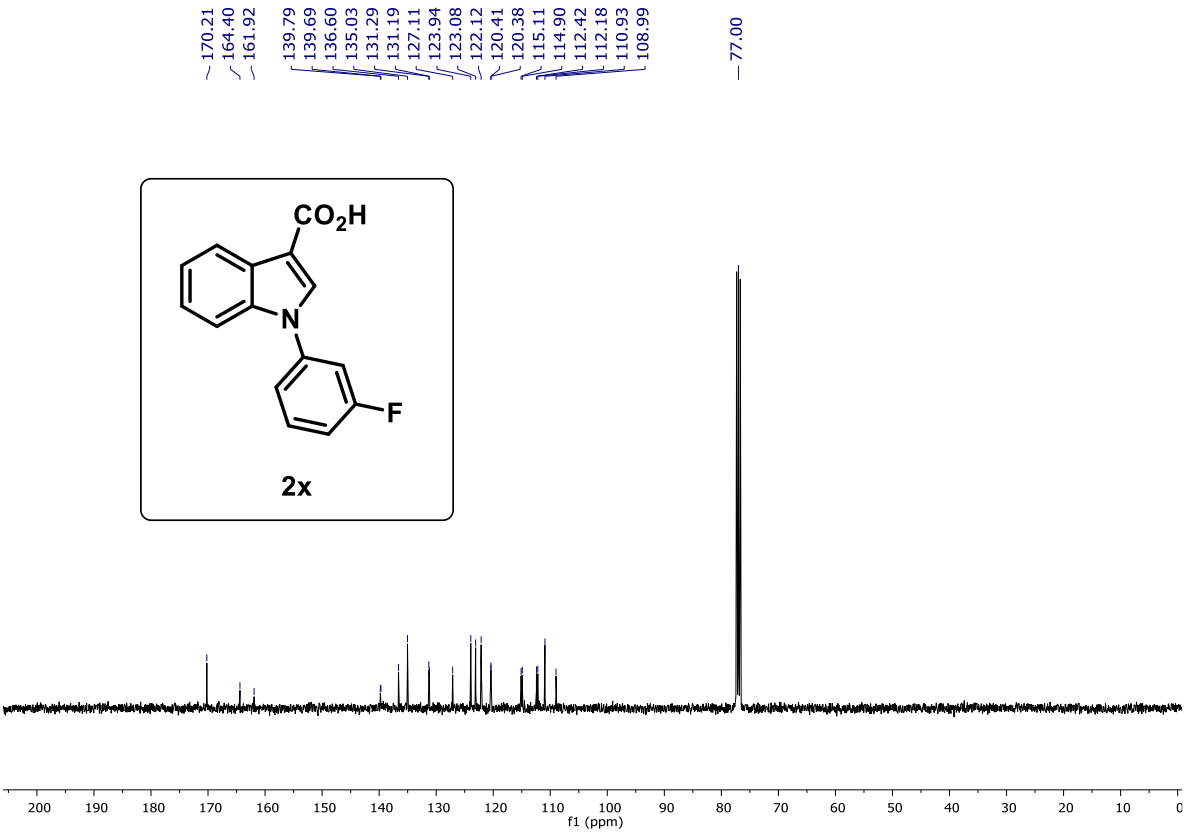
^{13}C NMR of **2w** (100 MHz, $CDCl_3$)



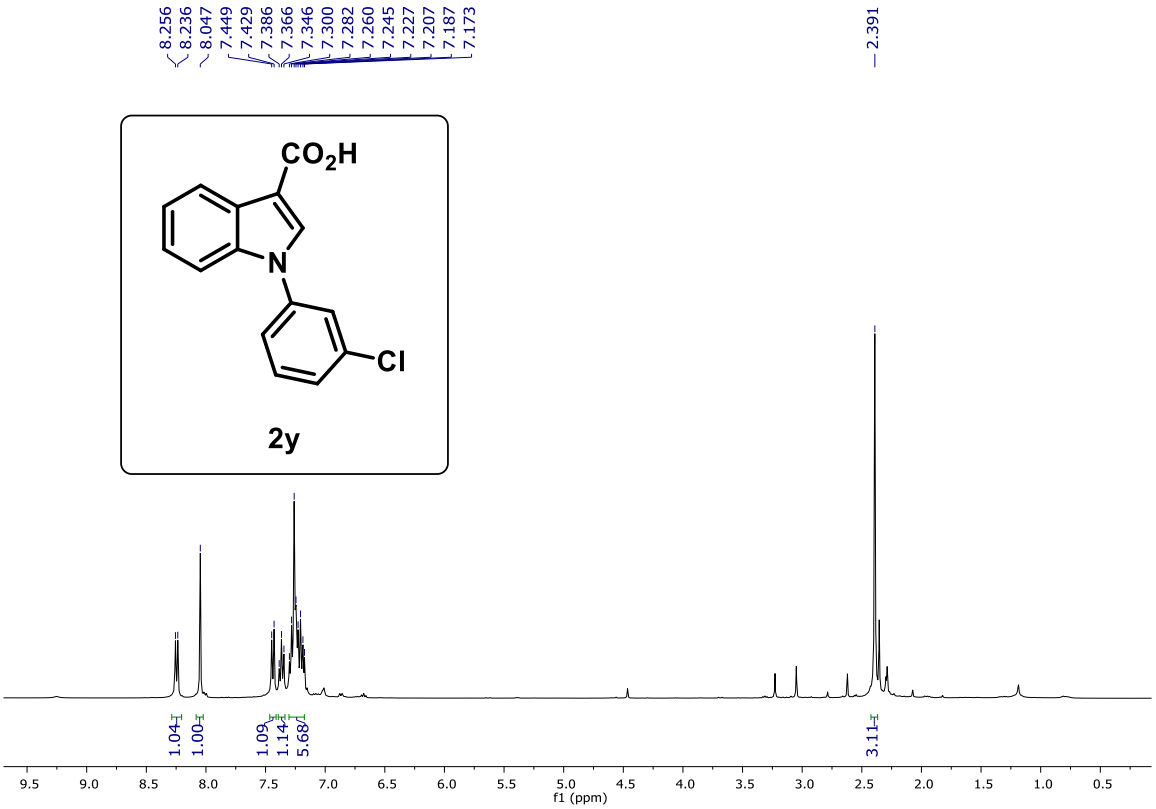
^{1}H NMR of **2x** (400 MHz, Chloroform-*d*)



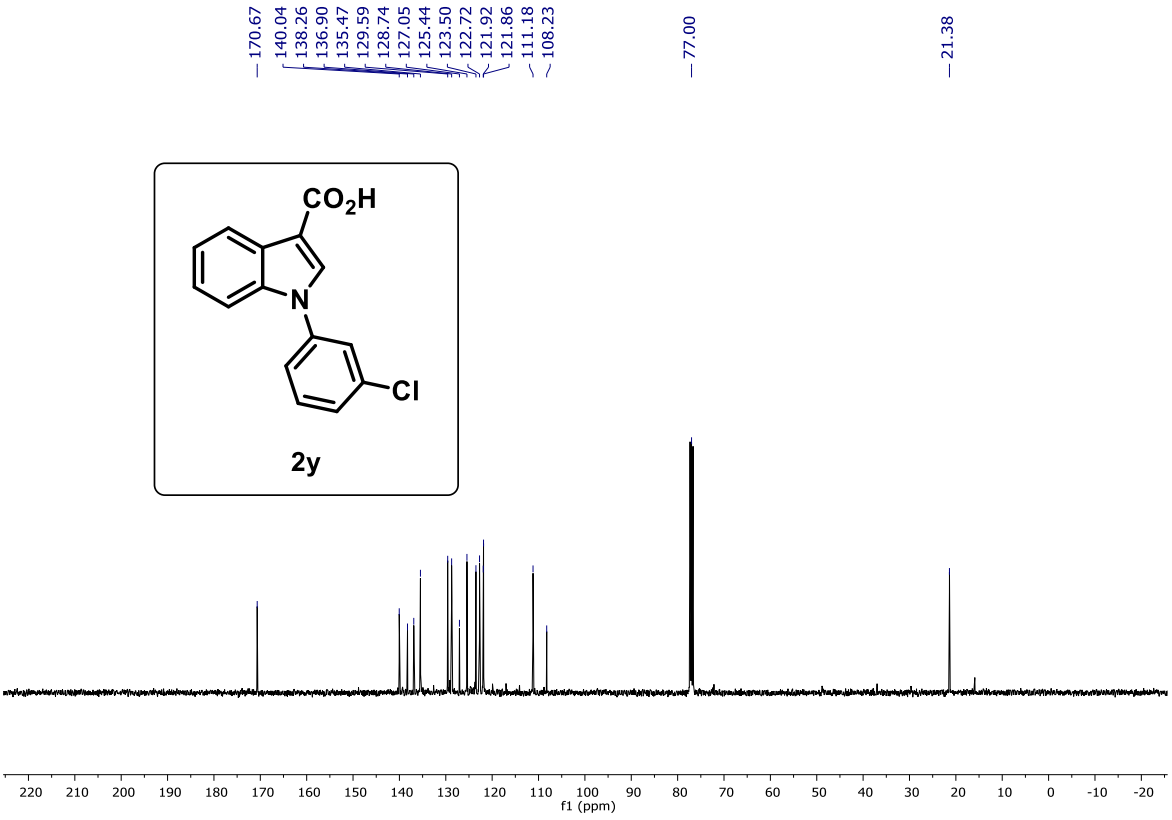
^{13}C NMR of **2x** (100 MHz, $CDCl_3$)



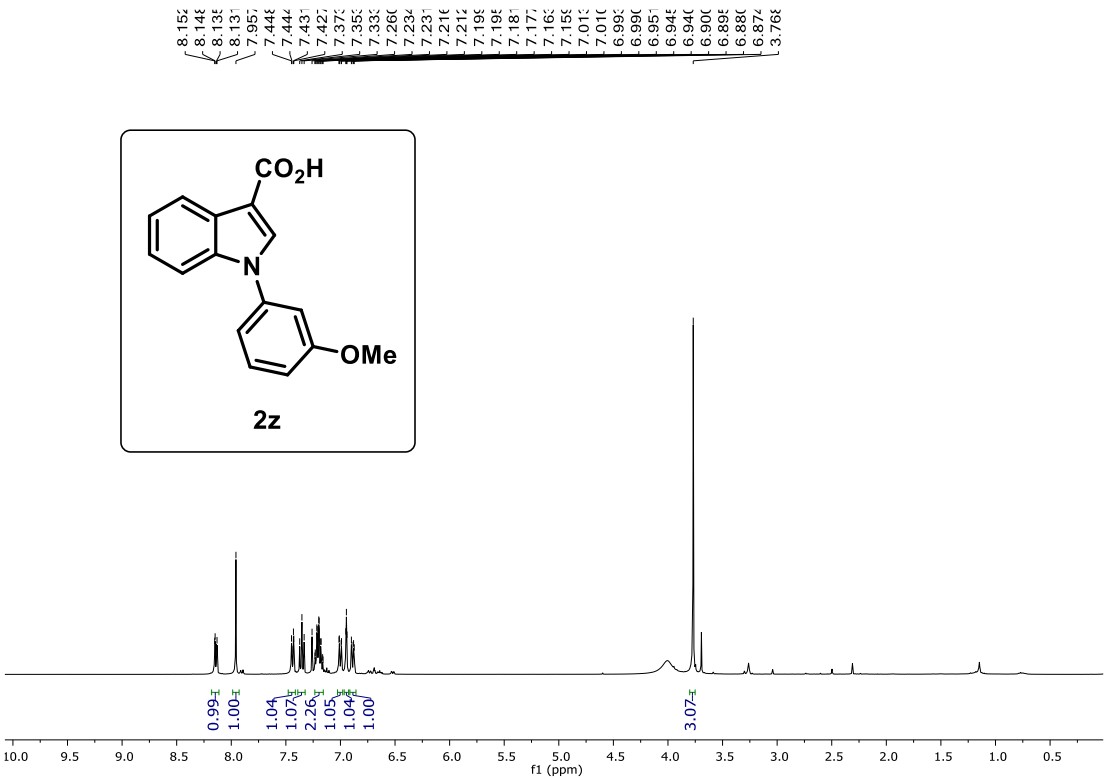
^{1}H NMR of **2y** (400 MHz, Chloroform-*d*)



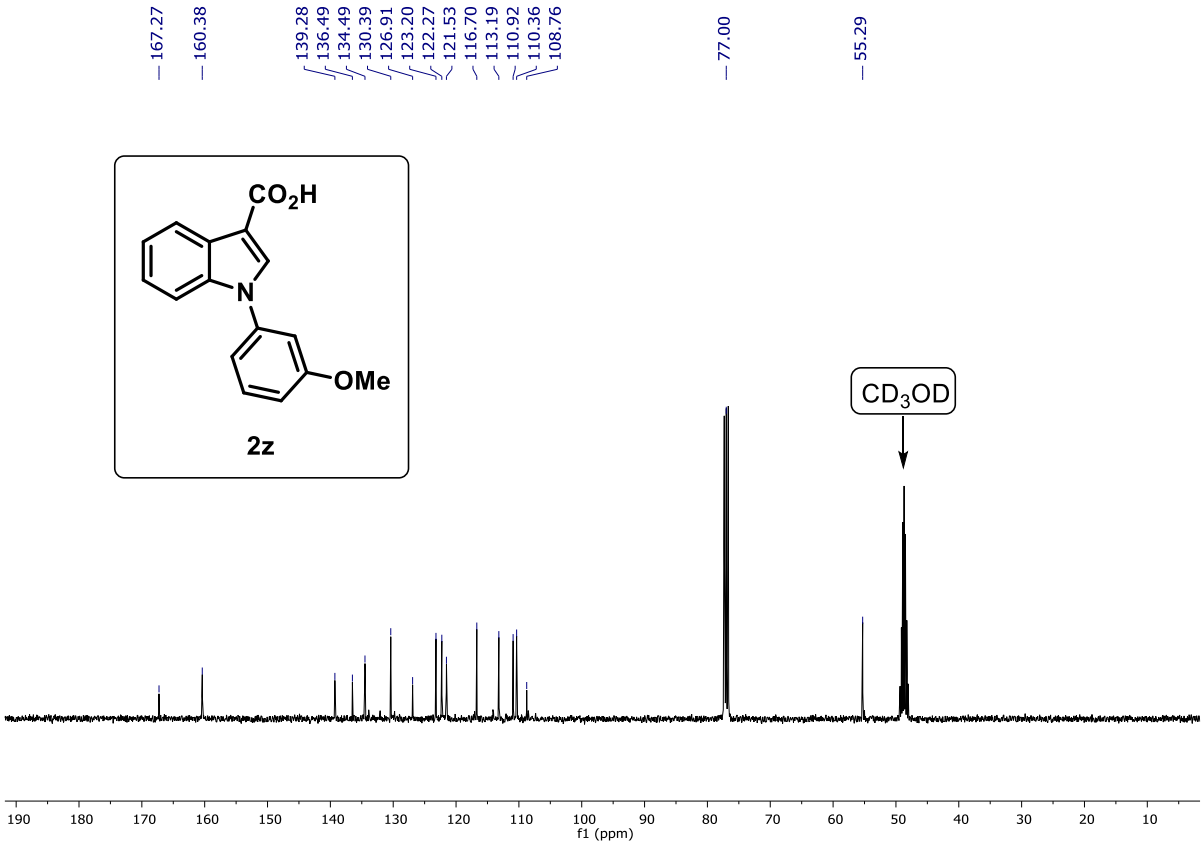
^{13}C NMR of **2y** (100 MHz, $CDCl_3$)



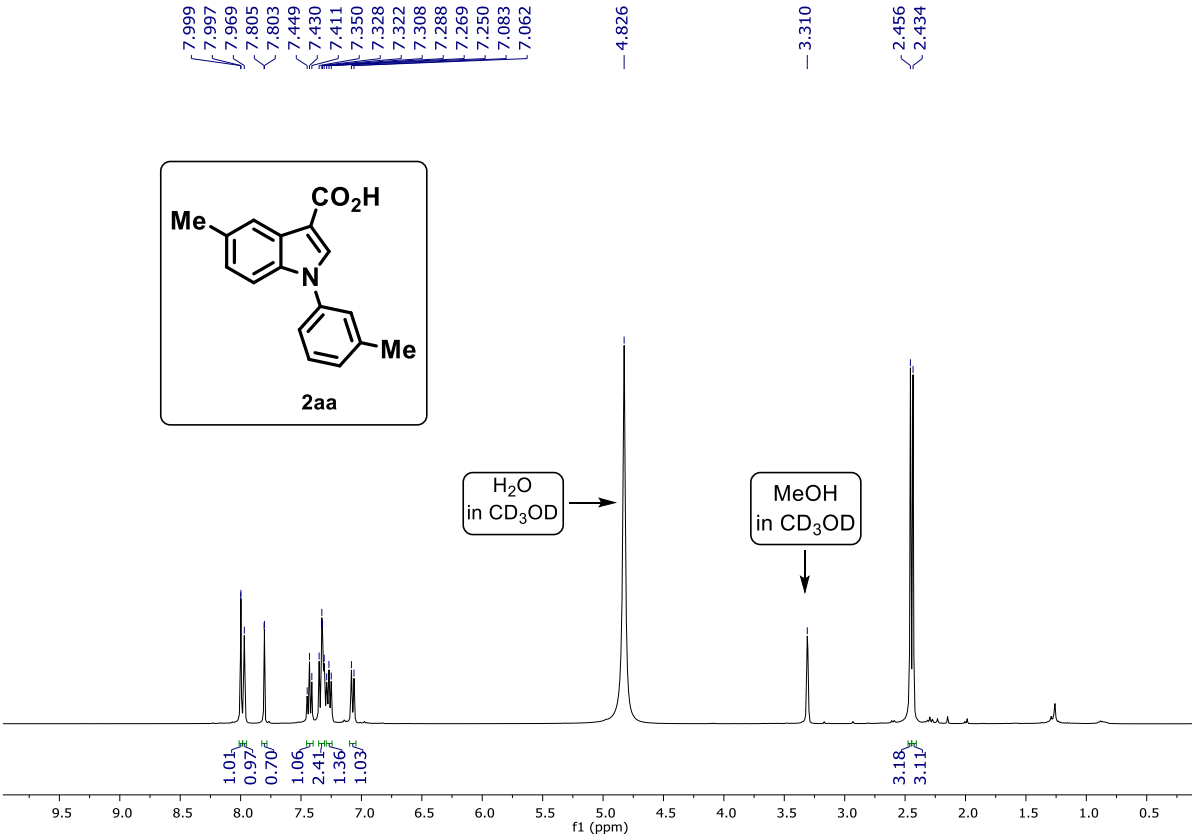
^{1}H NMR of **2z** (400 MHz, Chloroform-*d*)



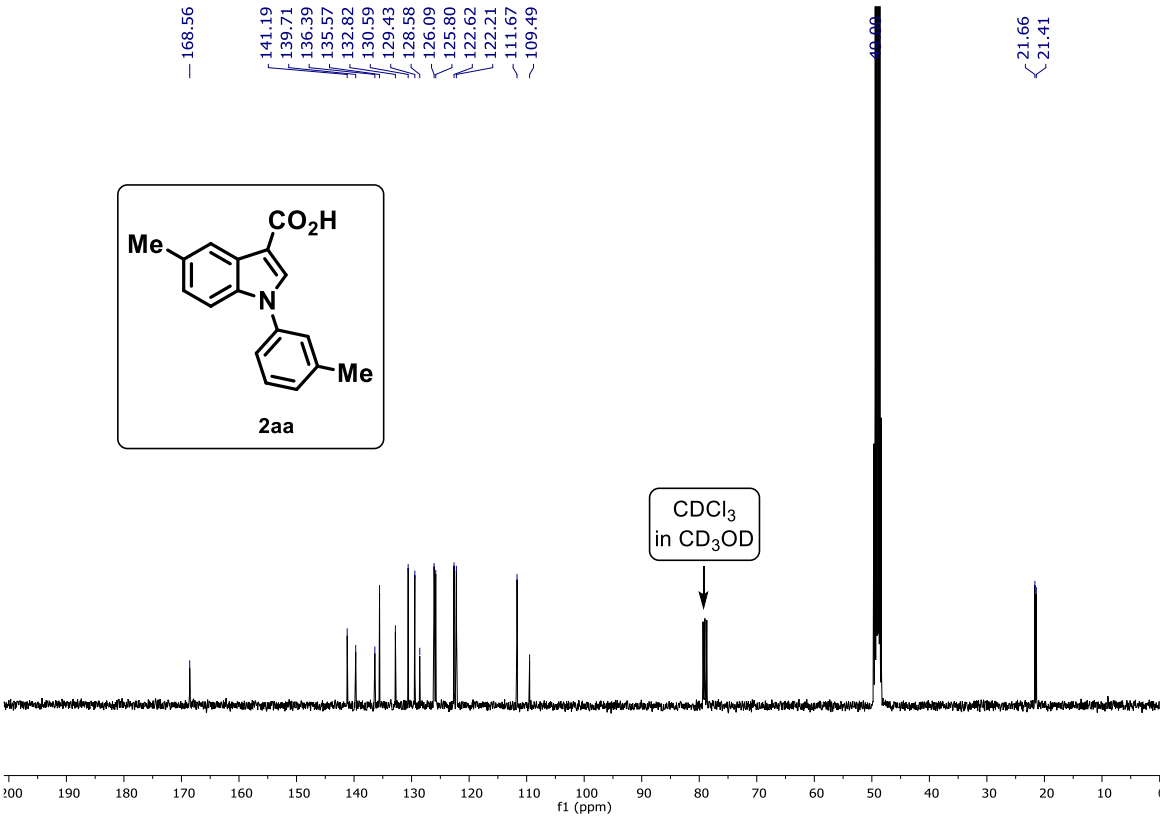
^{13}C NMR of **2z** (100 MHz, $CDCl_3$)



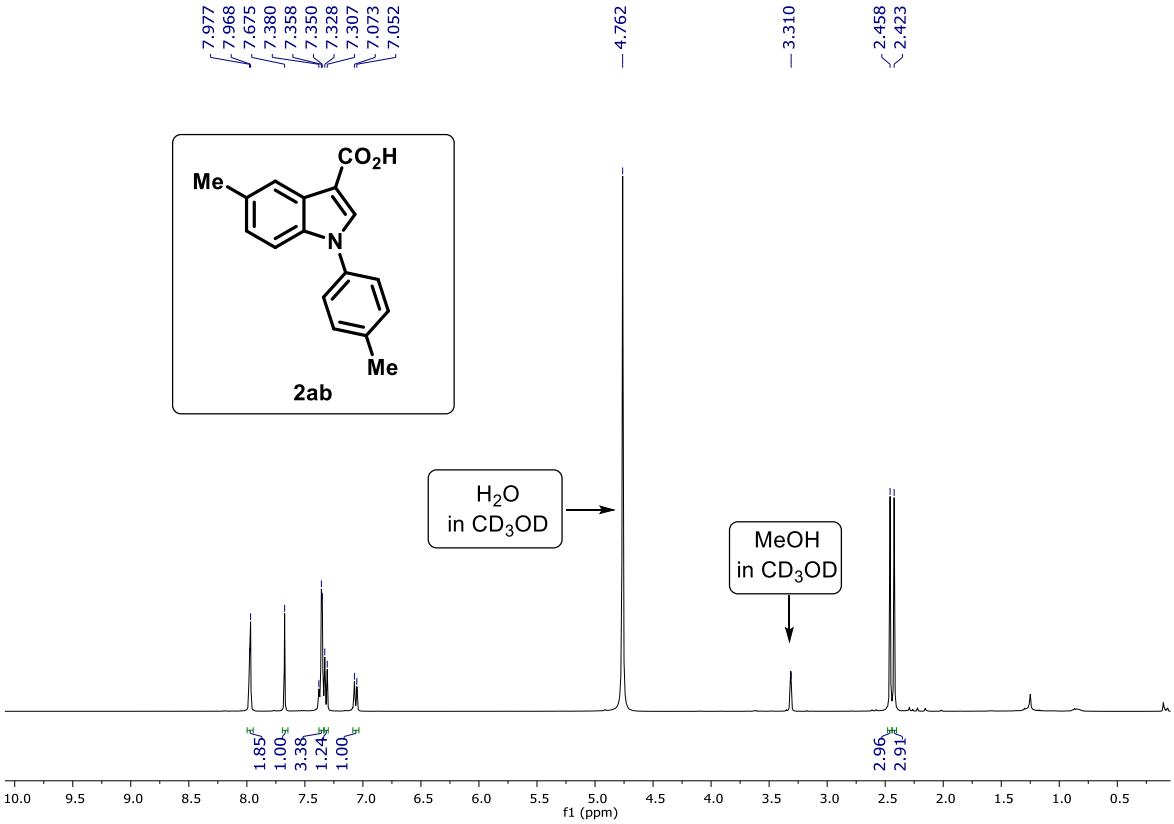
^{1}H NMR of **2aa** (400 MHz, Methanol-d^4)



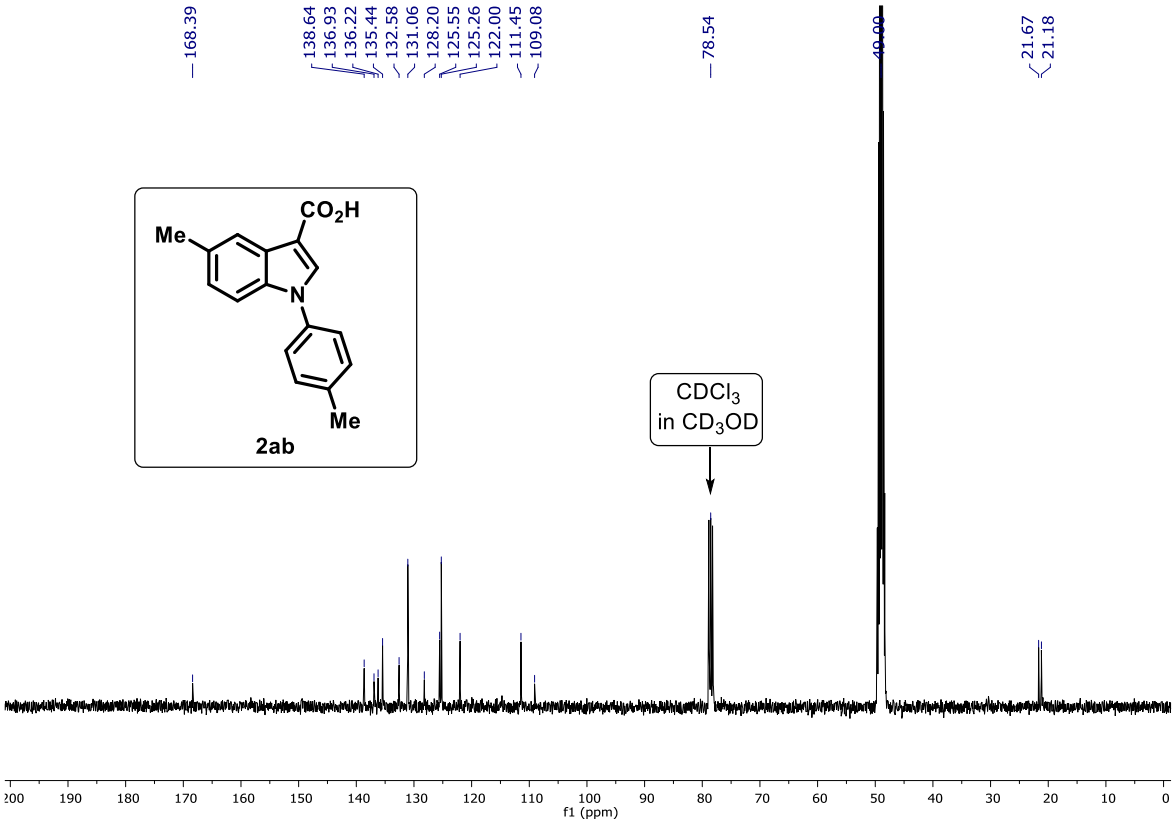
^{13}C NMR of **2aa** (100 MHz, Methanol-d^4)



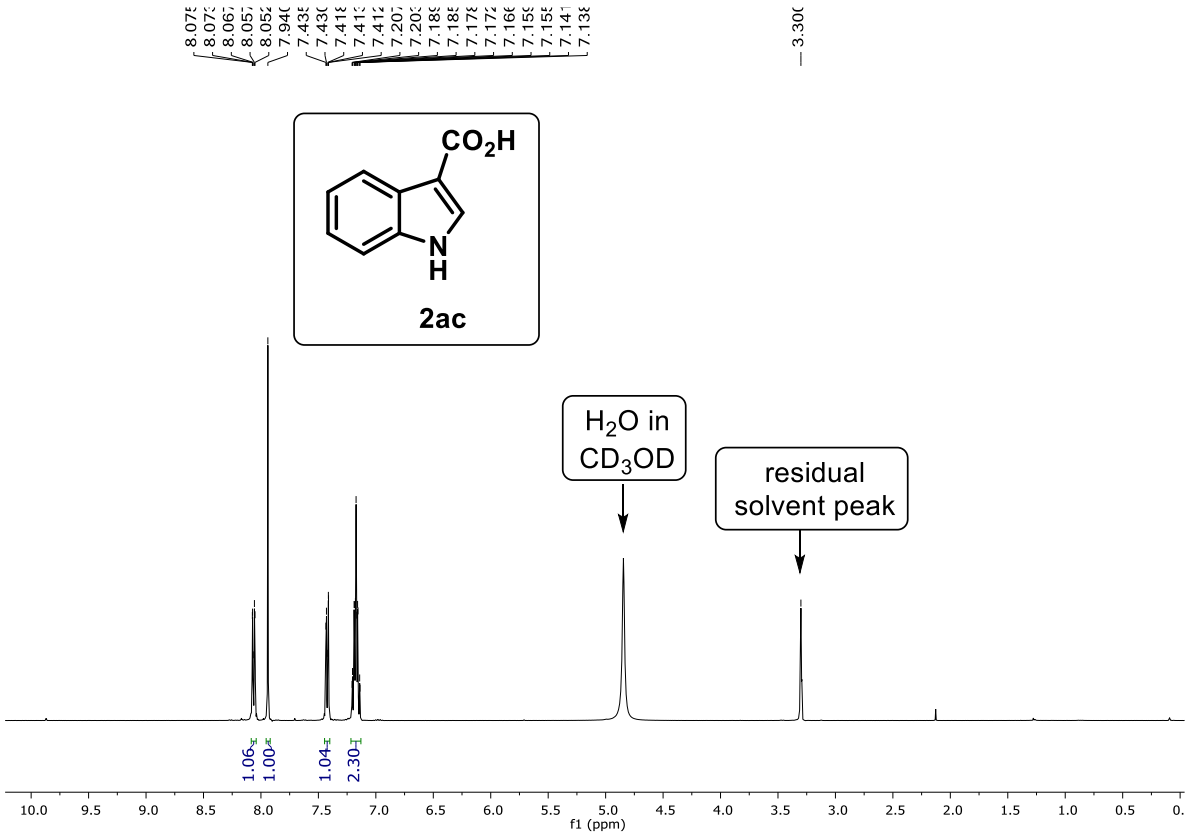
^{1}H NMR of **2ab** (400 MHz, Methanol-d^4)



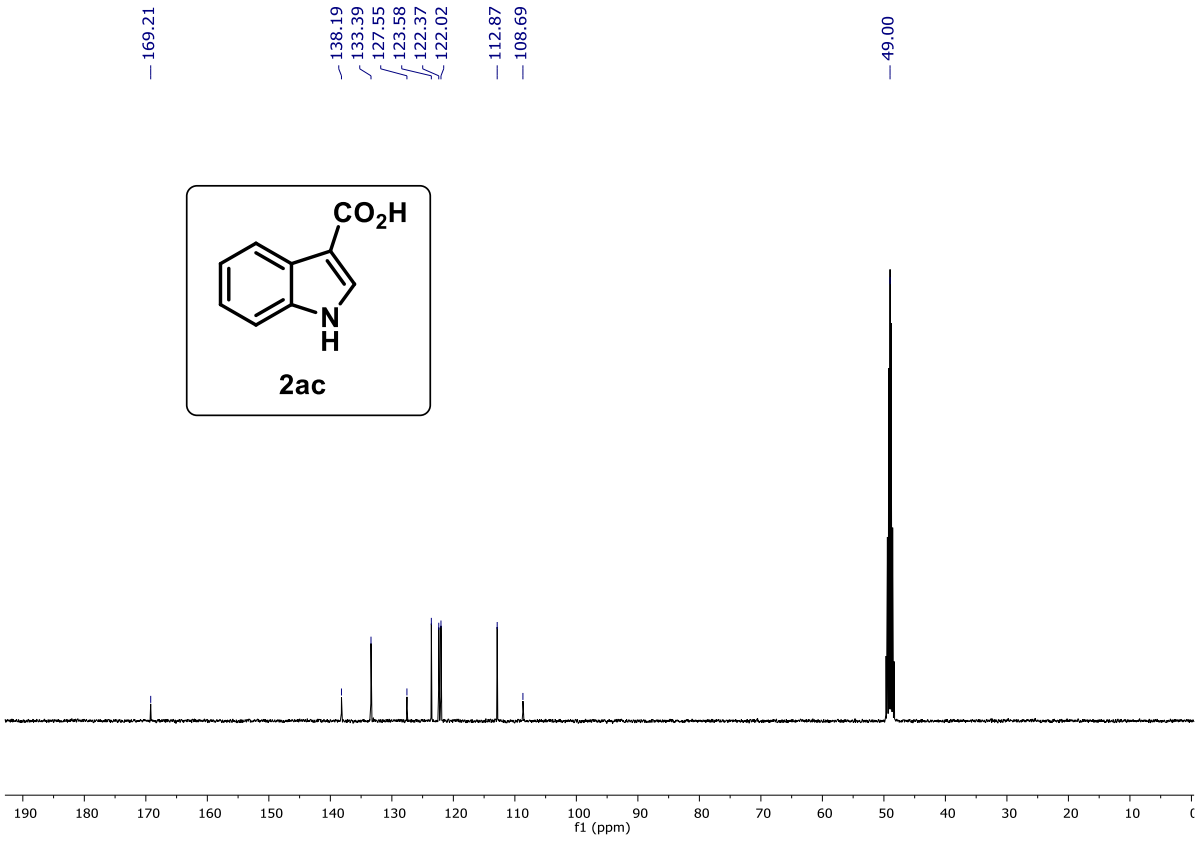
^{13}C NMR of **2ab** (100 MHz, Methanol-d^4)



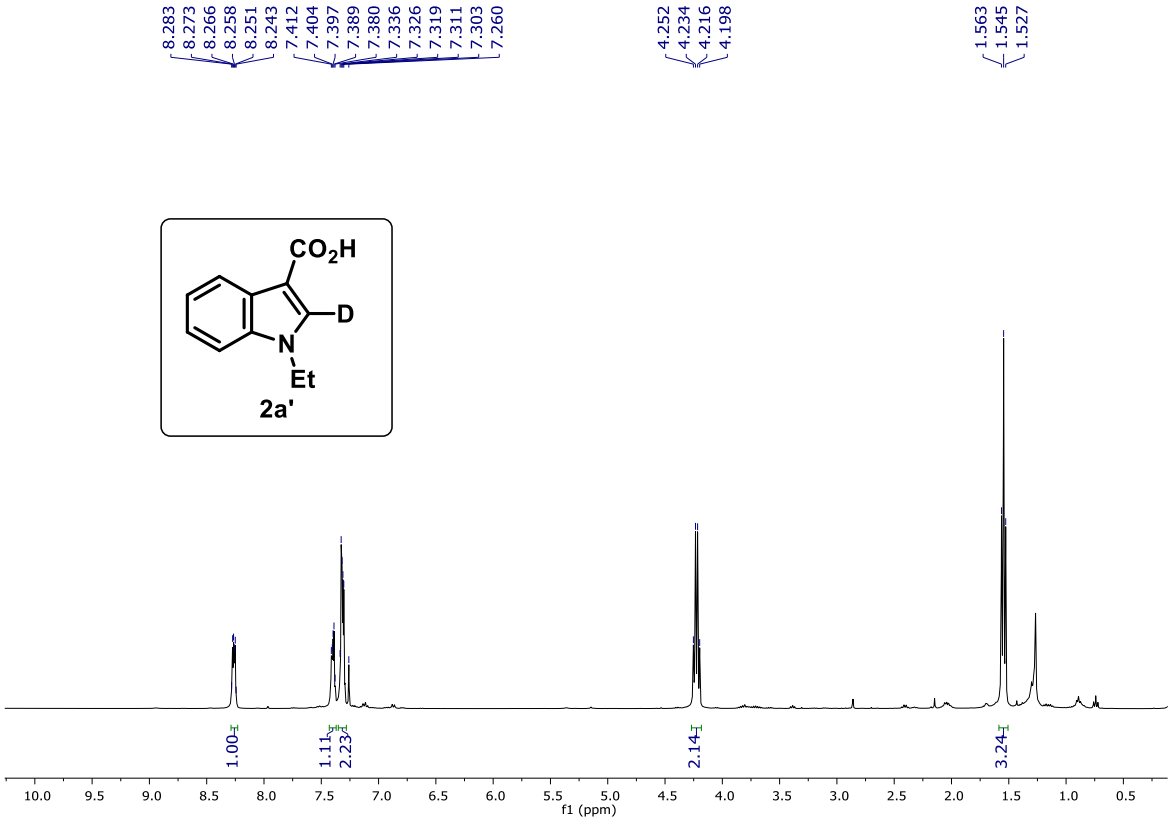
^{1}H NMR of **2ac** (400 MHz, Methanol-d^4)



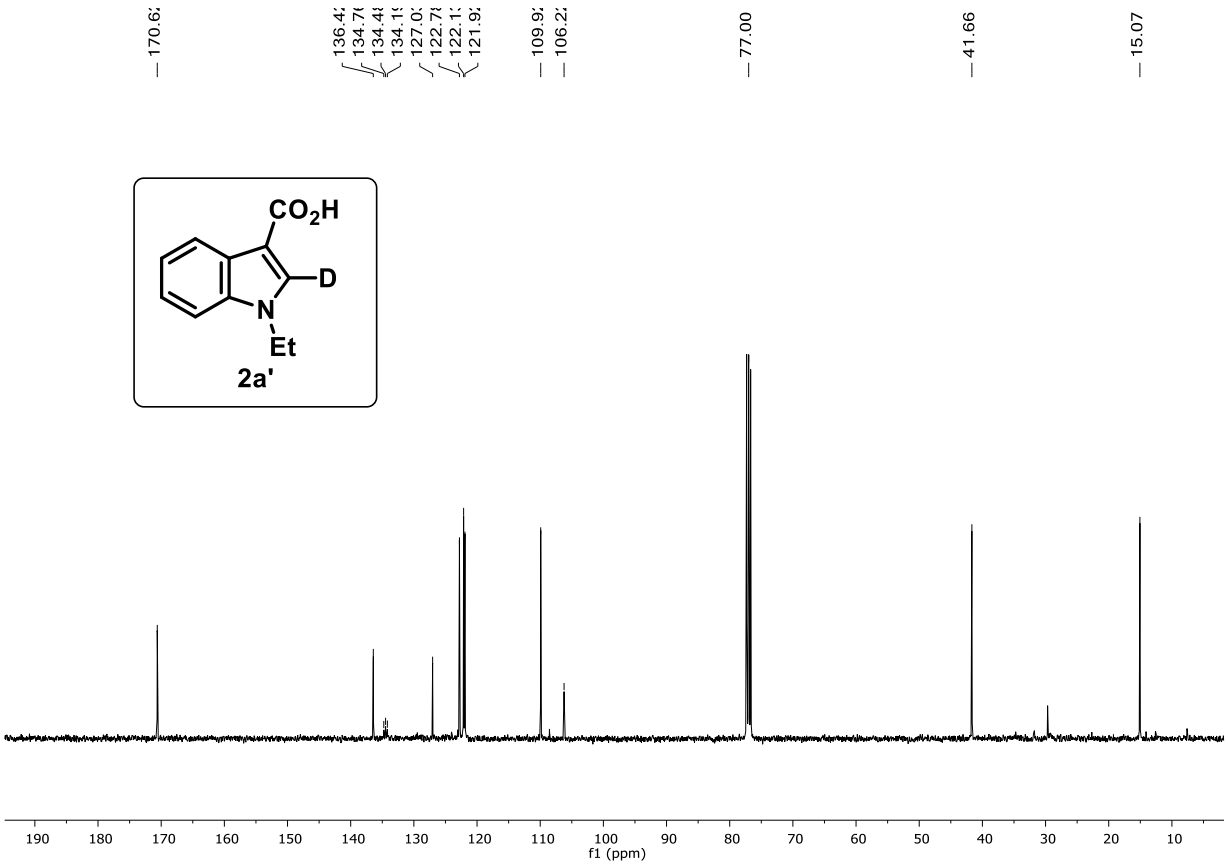
^{13}C NMR of **2ac** (100 MHz, CD_3OD)



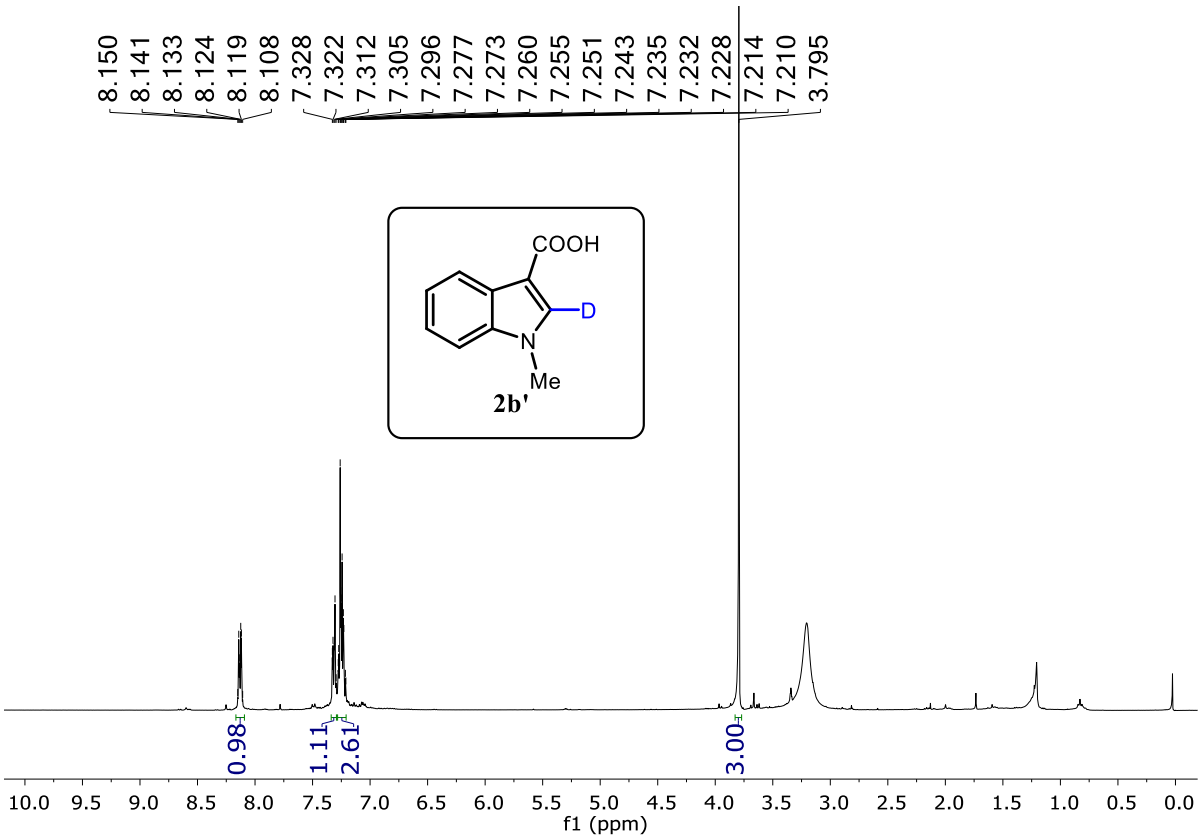
^{1}H NMR of **2a′** (400 MHz, Chloroform-*d*)



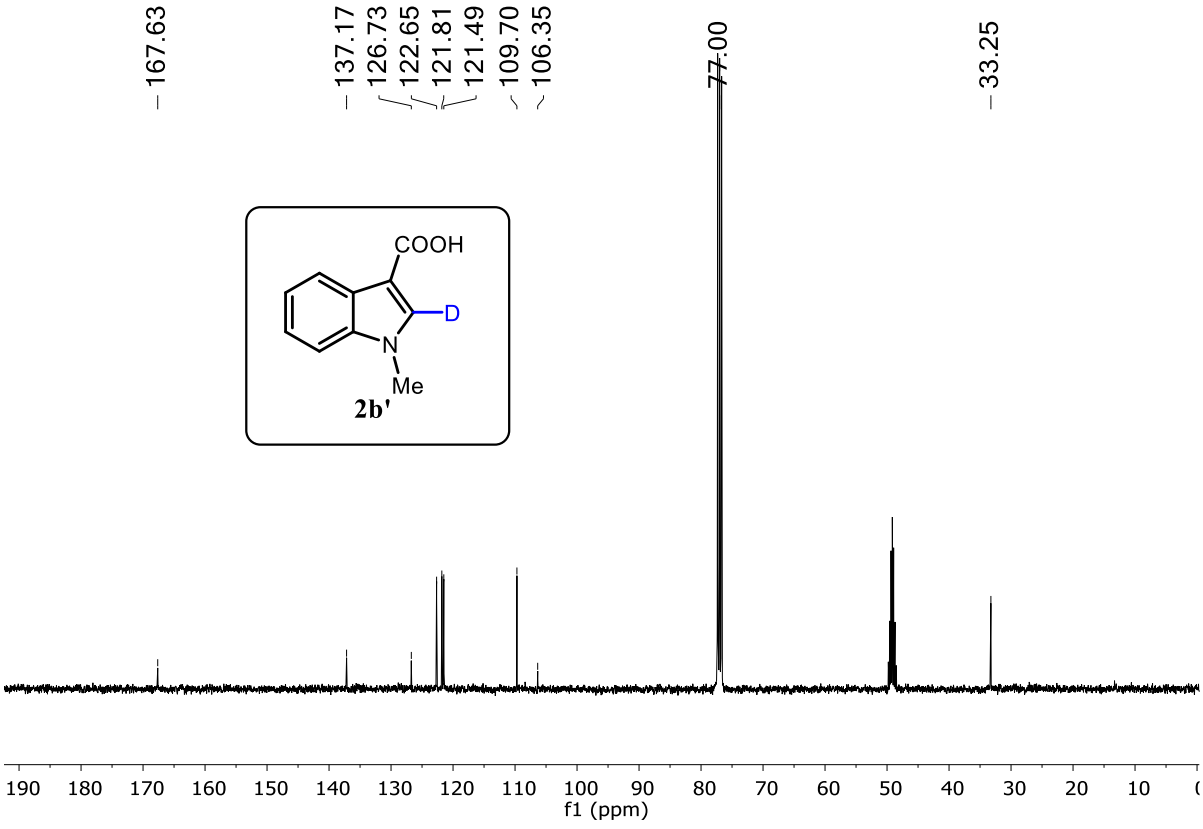
^{13}C NMR of **2a'** (100 MHz, $CDCl_3$)



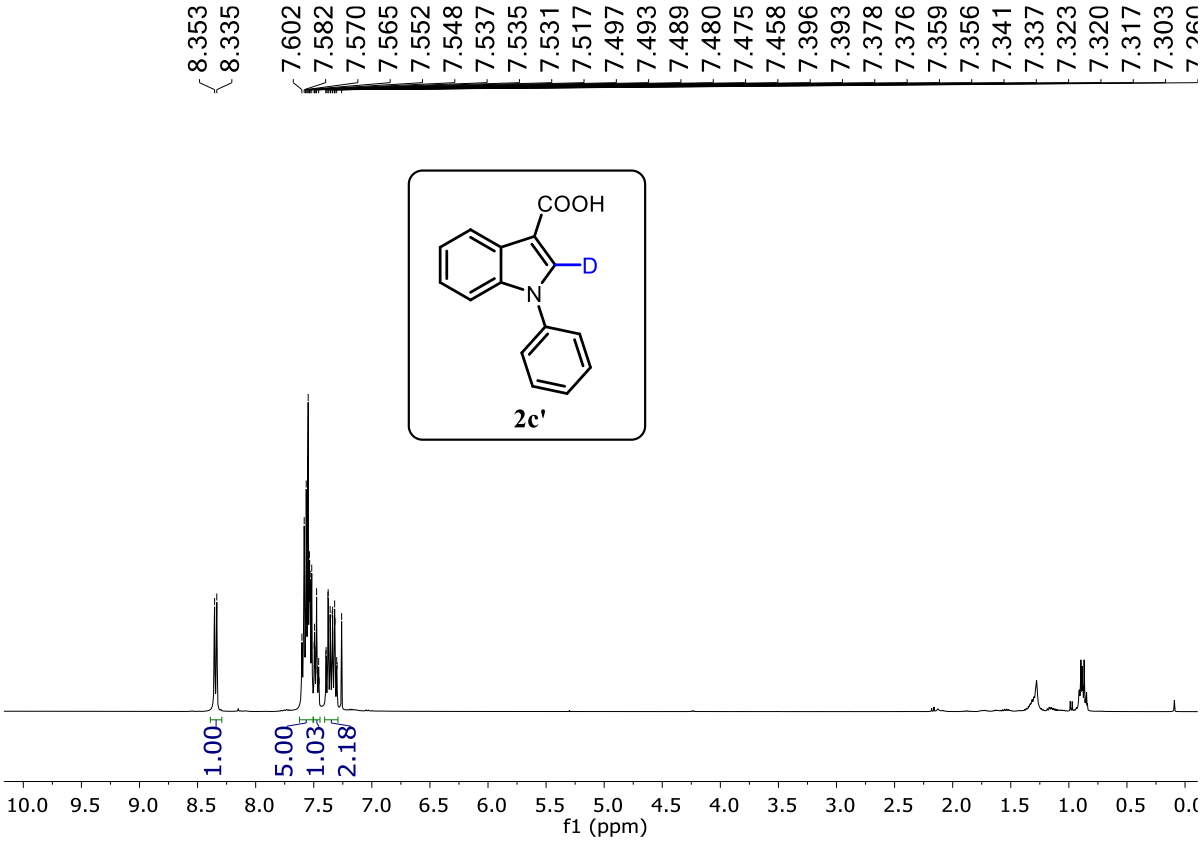
^{1}H NMR of **2b′** (400 MHz, Chloroform-*d*)



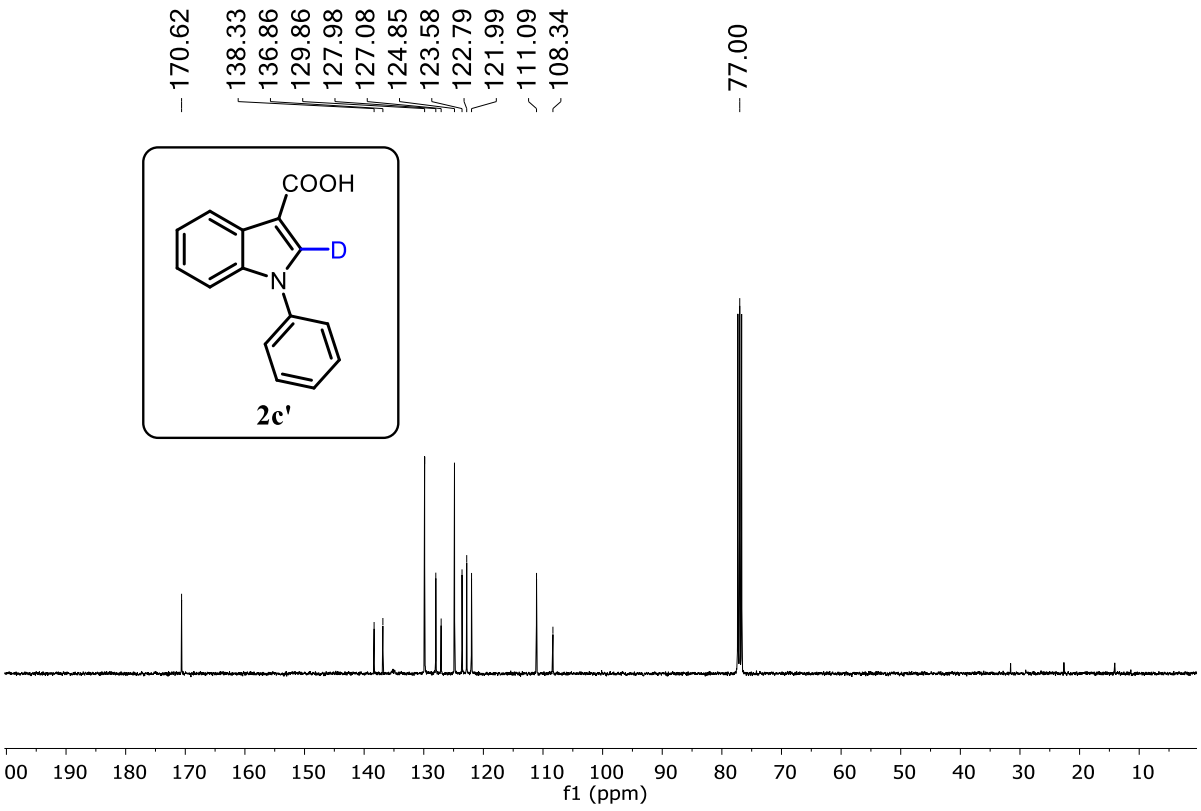
^{13}C NMR of **2b′** (100 MHz, $CDCl_3$)



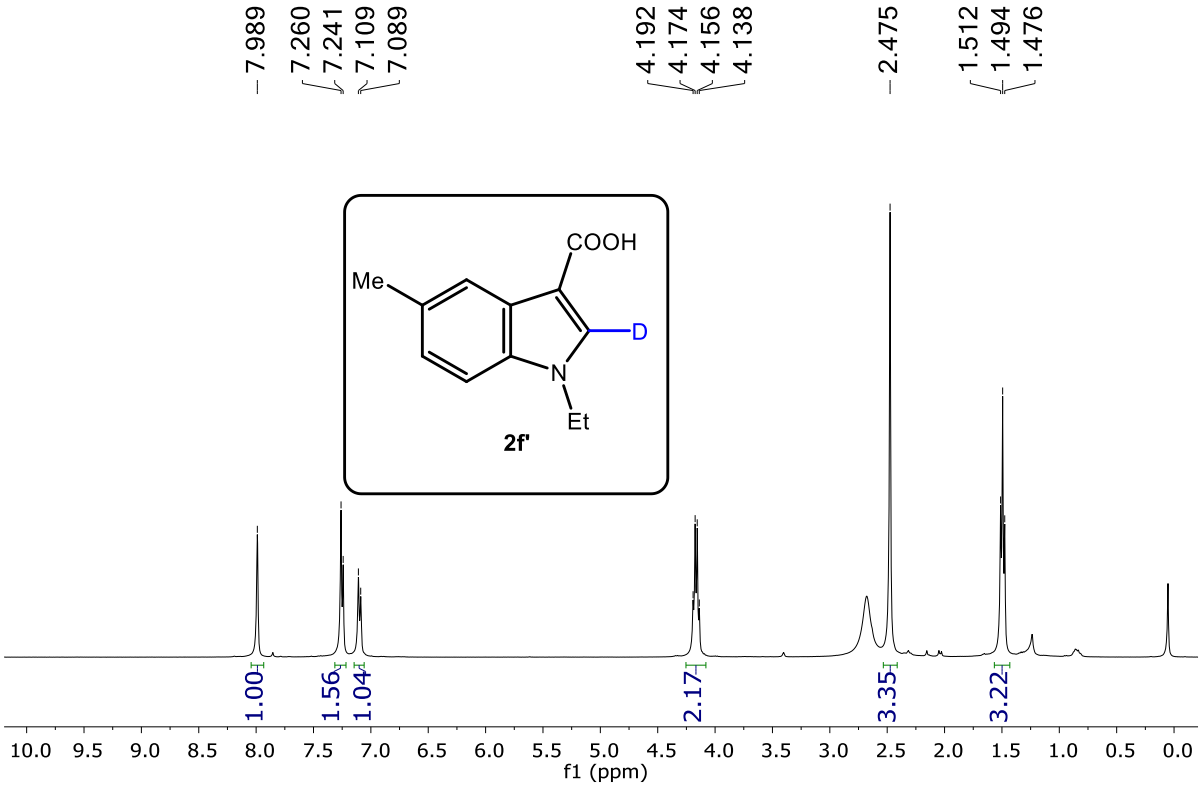
^{1}H NMR of **2c′** (400 MHz, Chloroform-*d*)



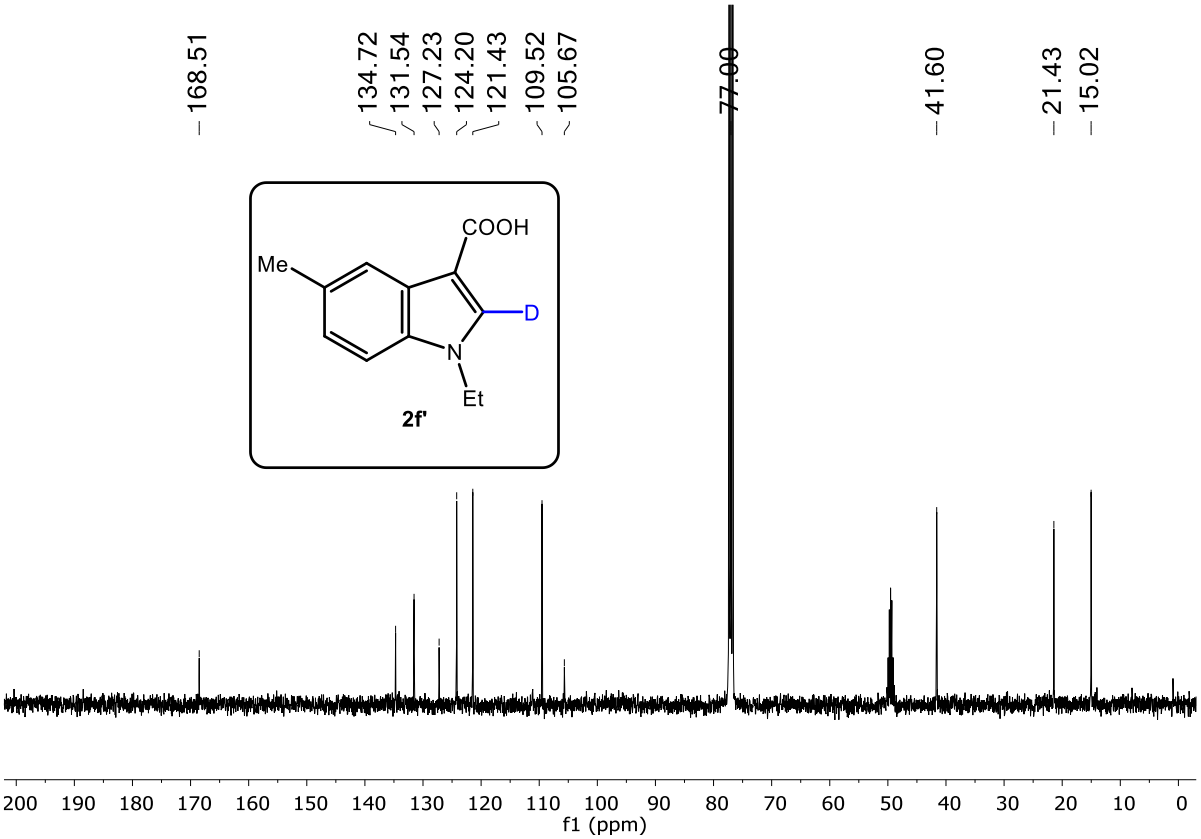
^{13}C NMR of **2c′** (100 MHz, $CDCl_3$)



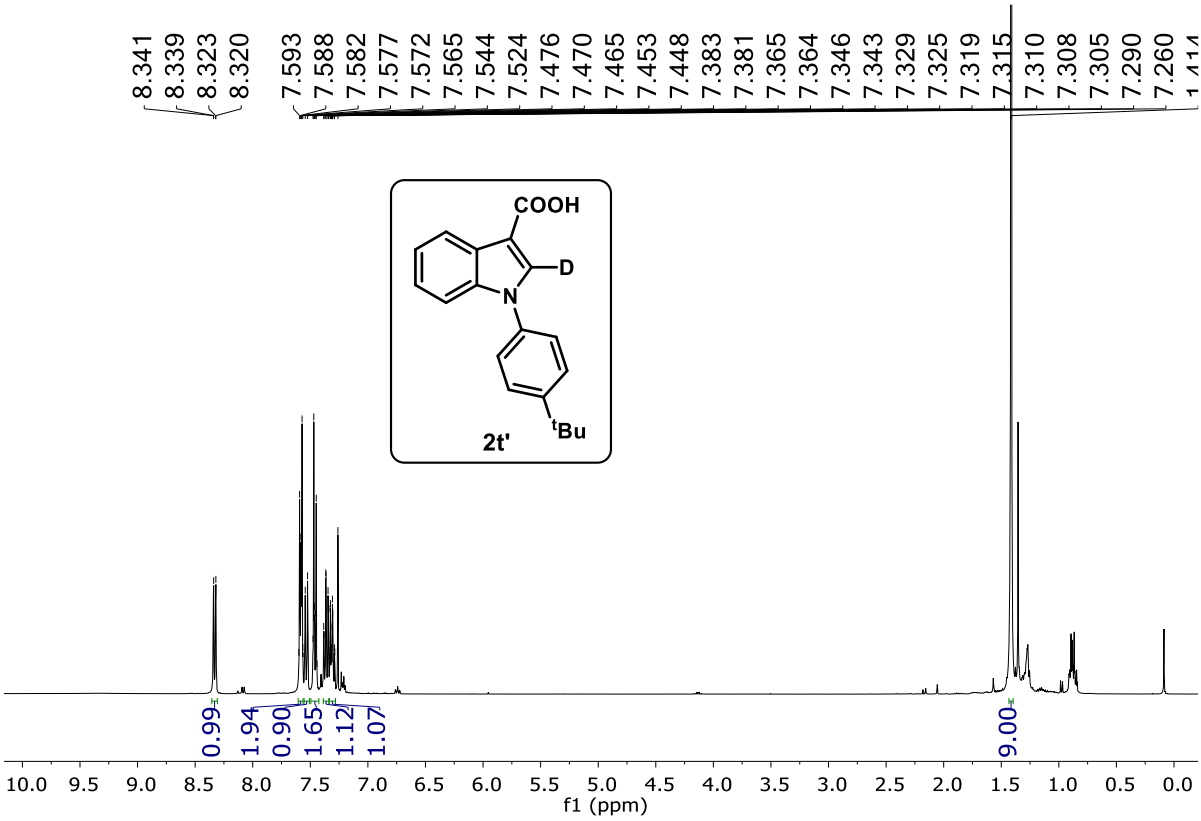
^{1}H NMR of **2f′** (400 MHz, Chloroform-*d*)



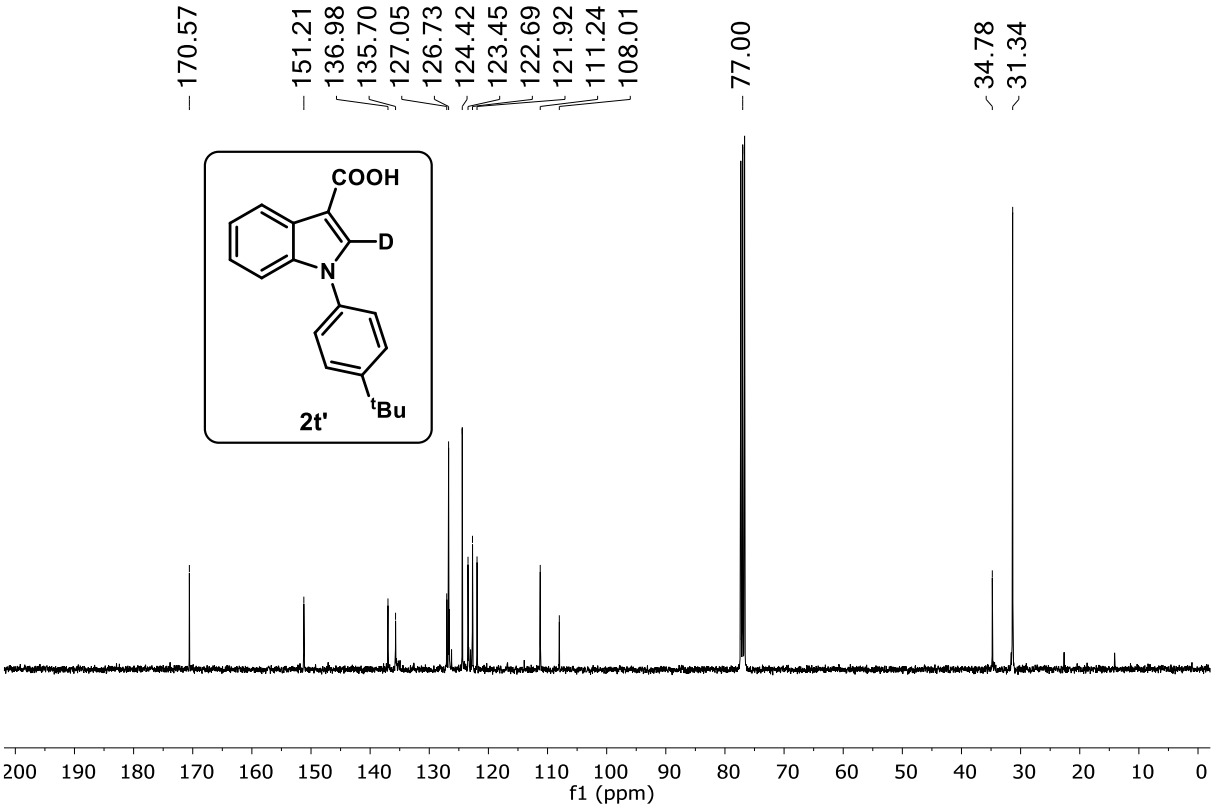
^{13}C NMR of **2f′** (100 MHz, $CDCl_3$)



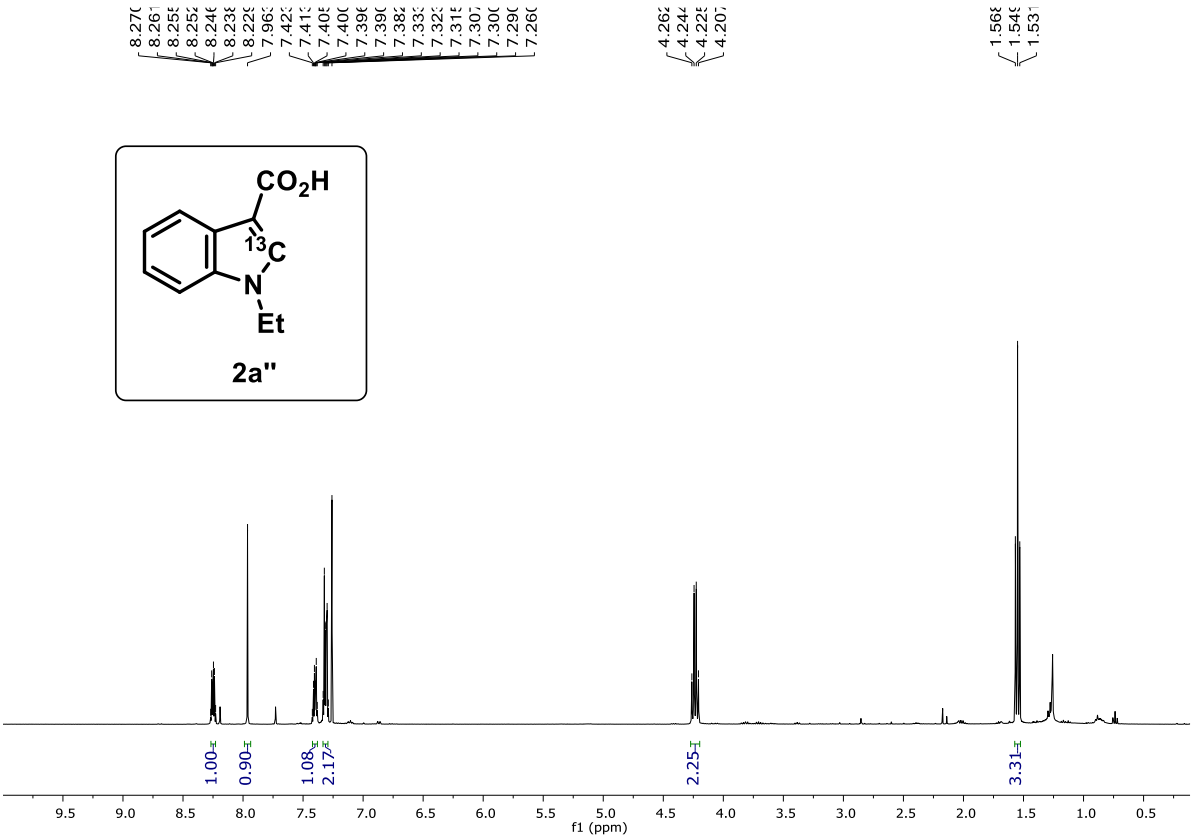
^{1}H NMR of **2t′** (400 MHz, Chloroform-*d*)



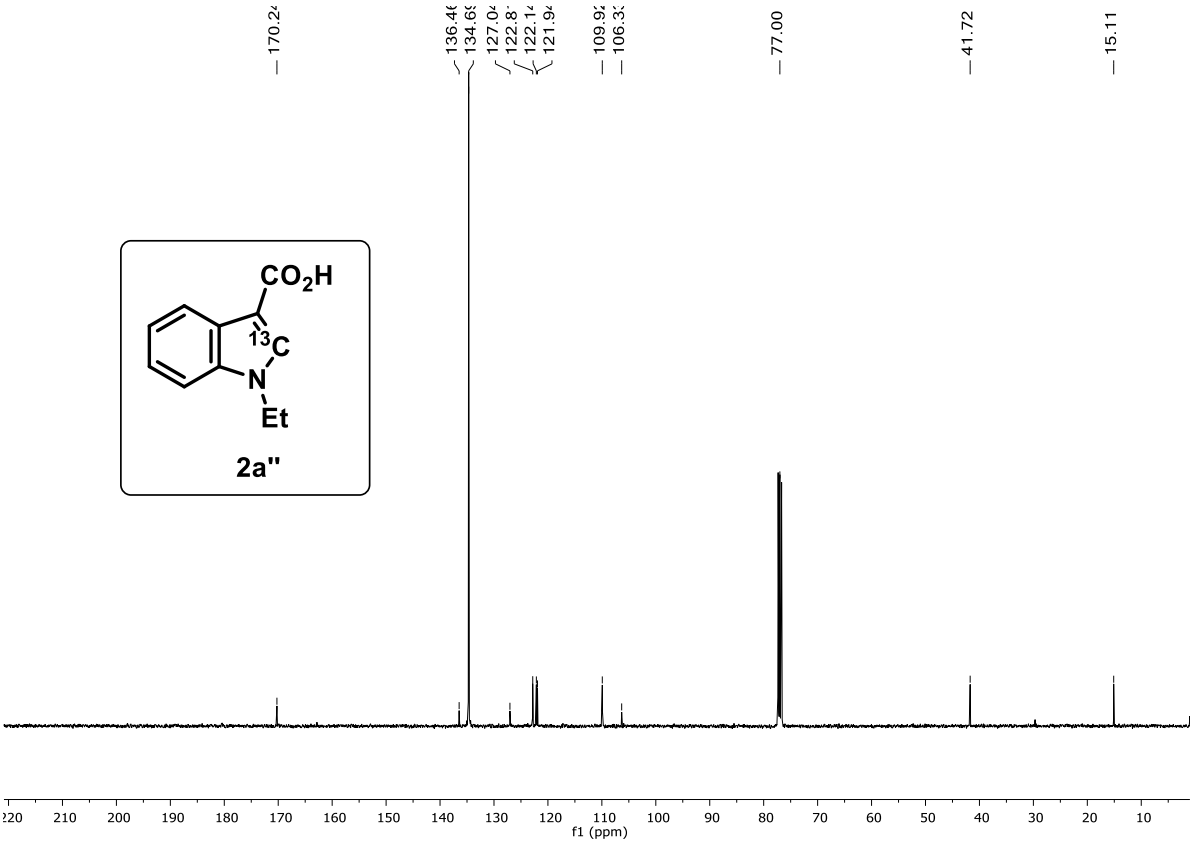
^{13}C NMR of **2t′** (100 MHz, $CDCl_3$)



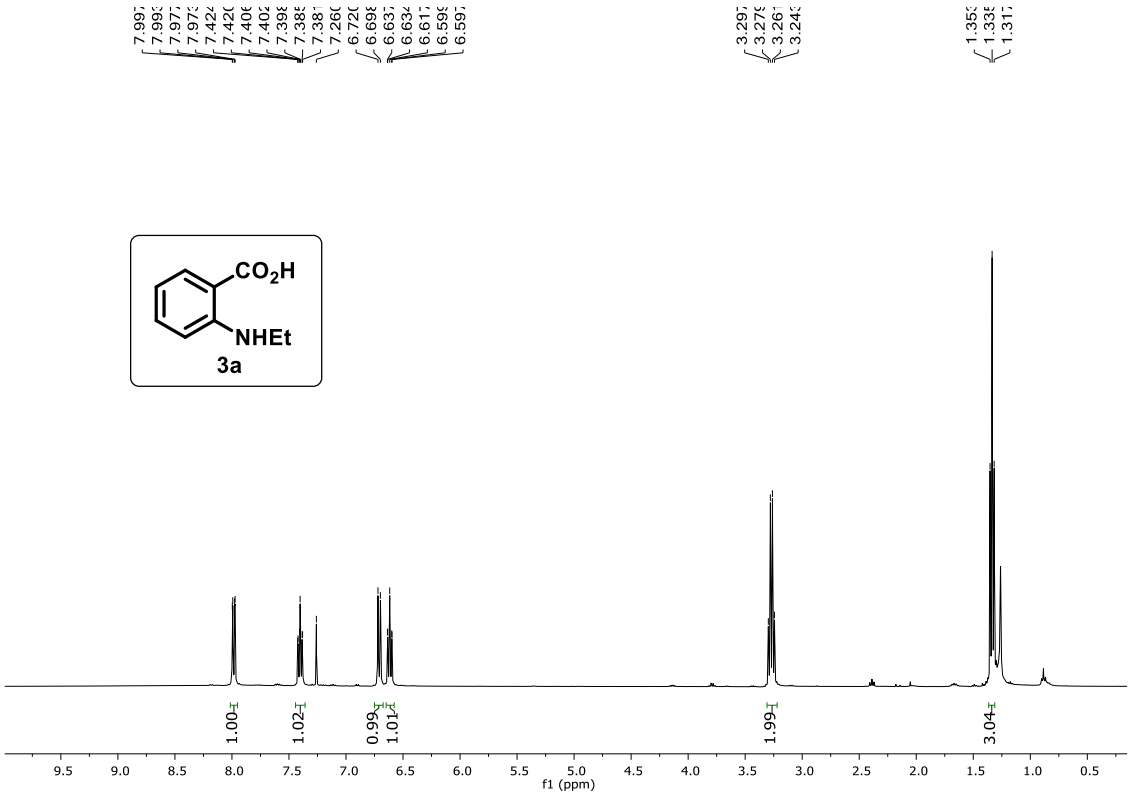
^{1}H NMR of **2a''** (400 MHz, Chloroform-*d*)



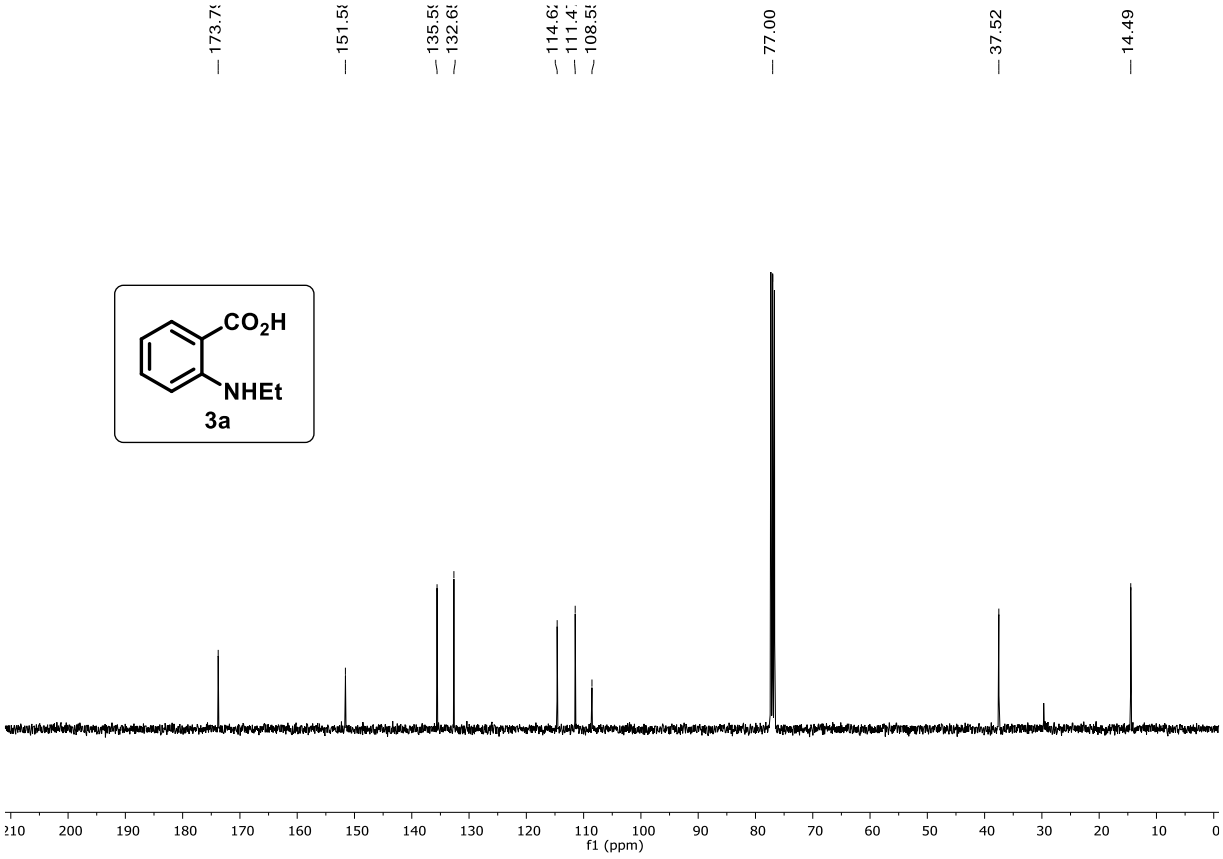
^{13}C NMR of **2a''** (100 MHz, $CDCl_3$)



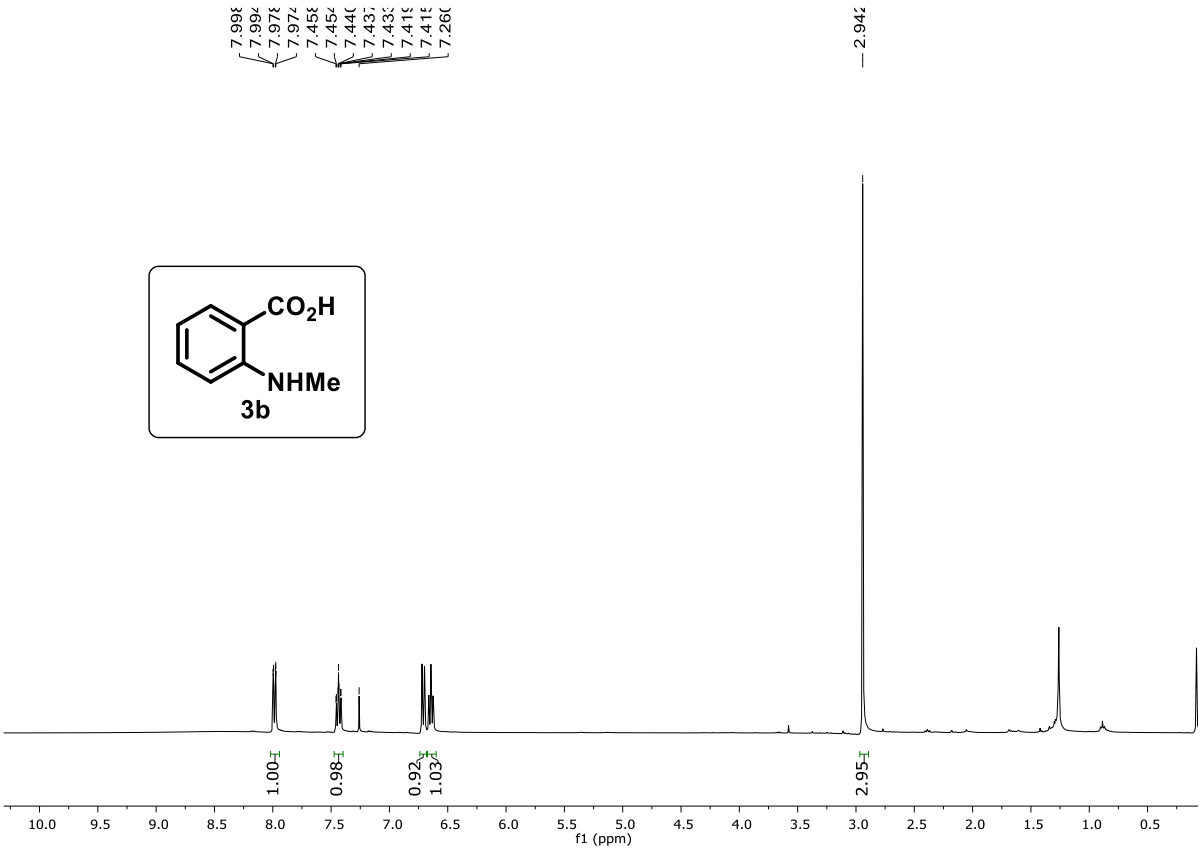
^{1}H NMR of **3a** (400 MHz, Chloroform-*d*)



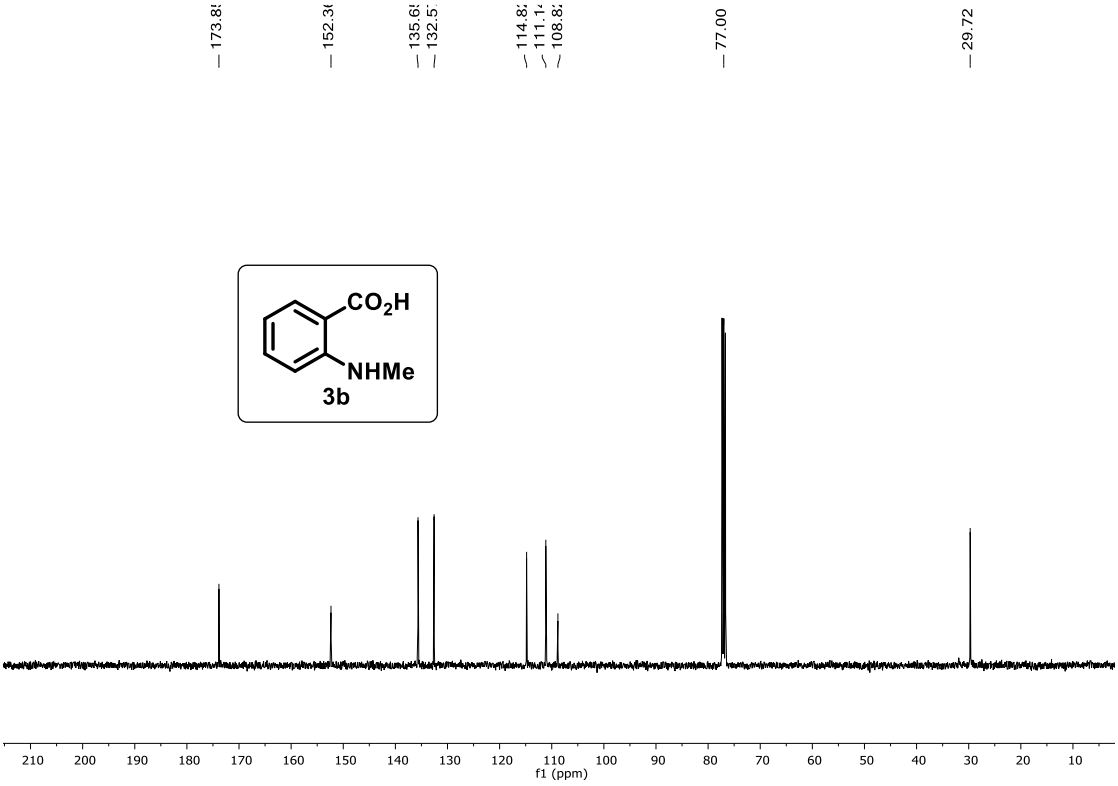
^{13}C NMR of **3a** (100 MHz, $CDCl_3$)



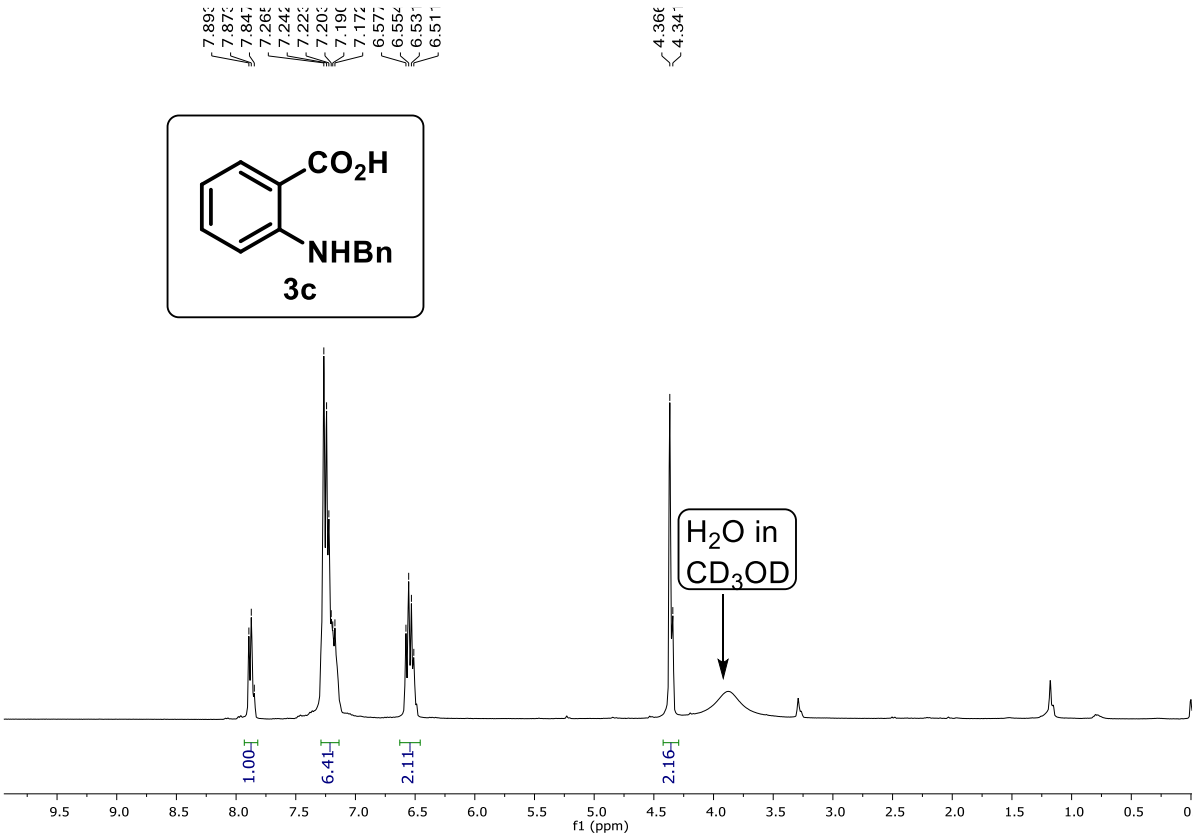
^{1}H NMR of **3b** (400 MHz, Chloroform-*d*)



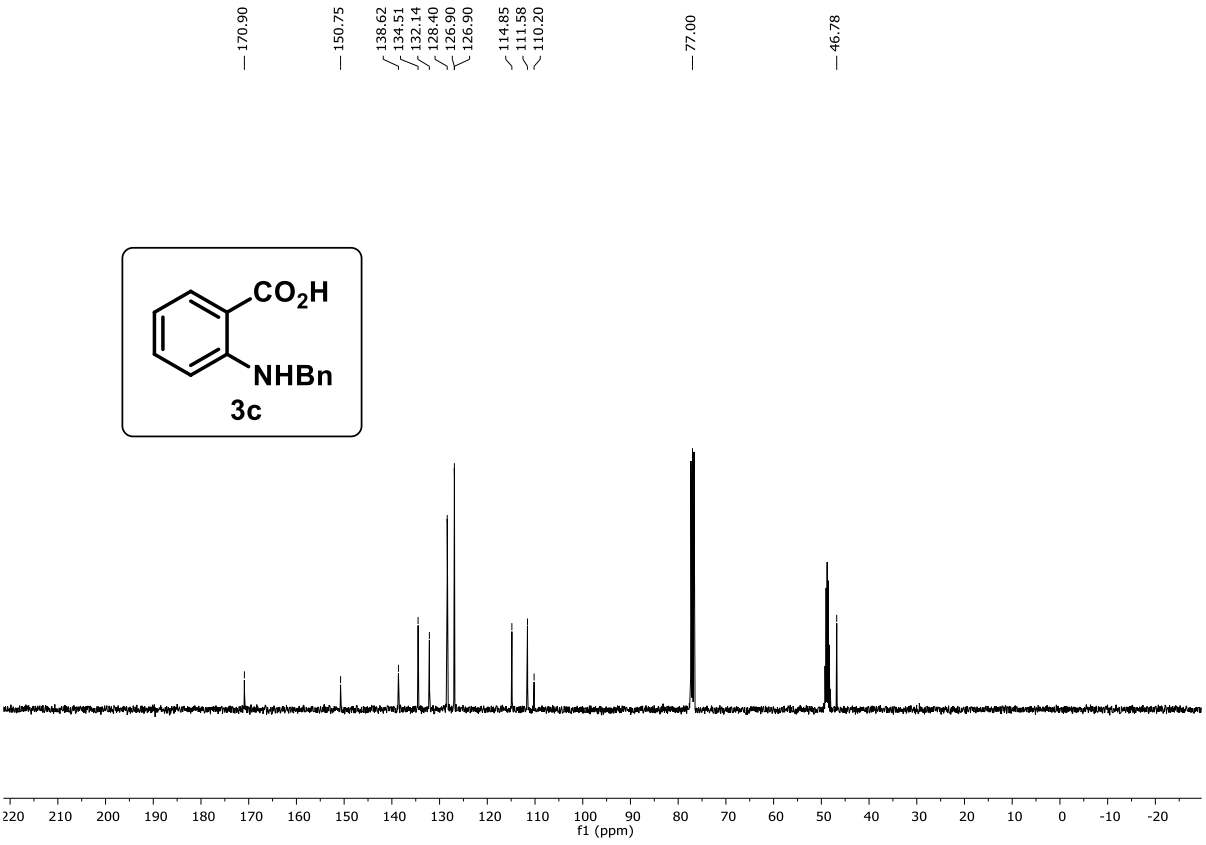
^{13}C NMR of **3b** (100 MHz, $CDCl_3$)



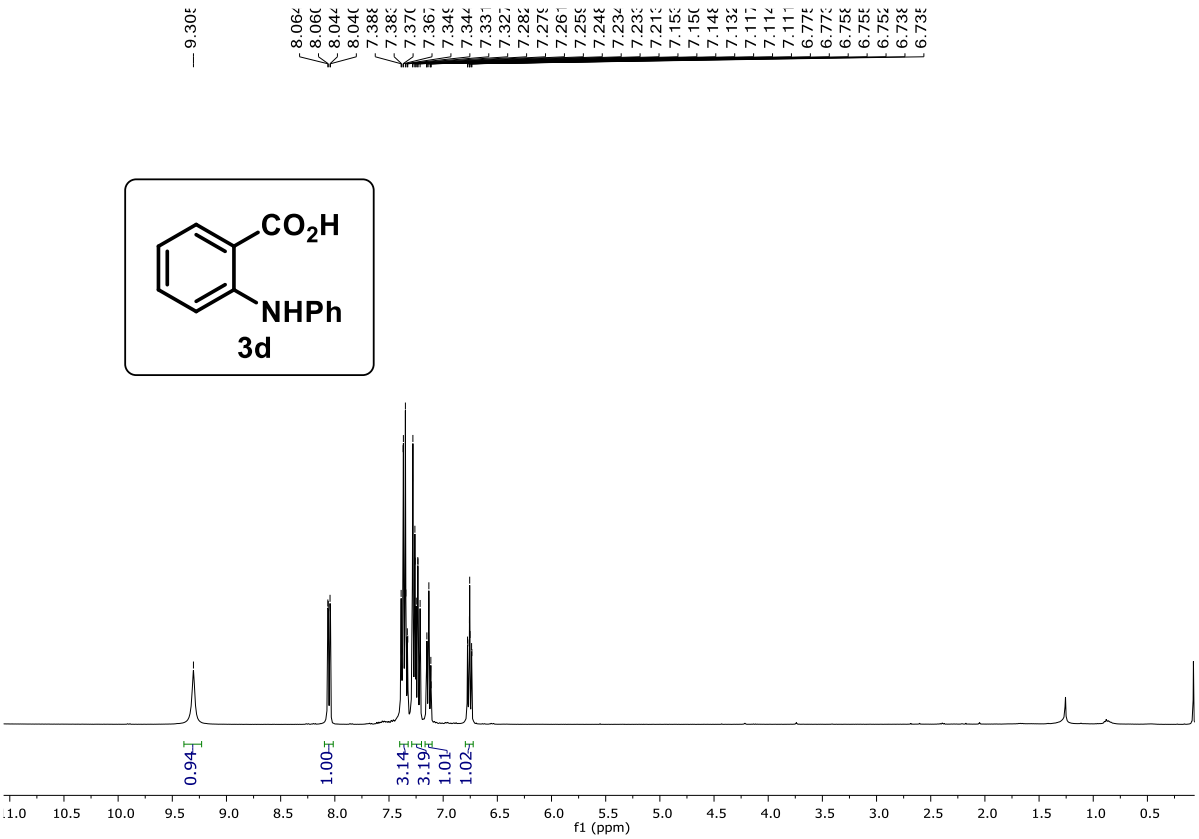
^{1}H NMR of **3c** (400 MHz, Chloroform-*d*)



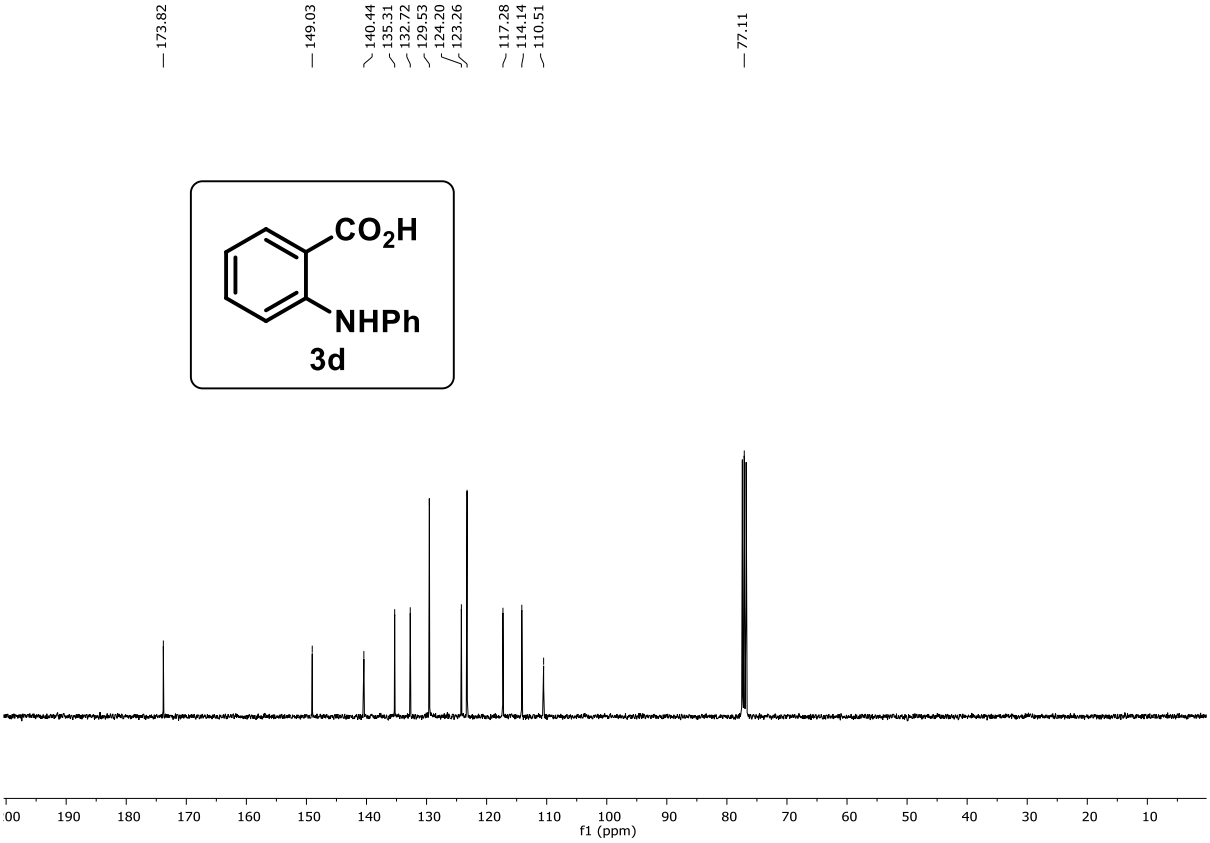
^{13}C NMR of **3c** (100 MHz, $CDCl_3$)



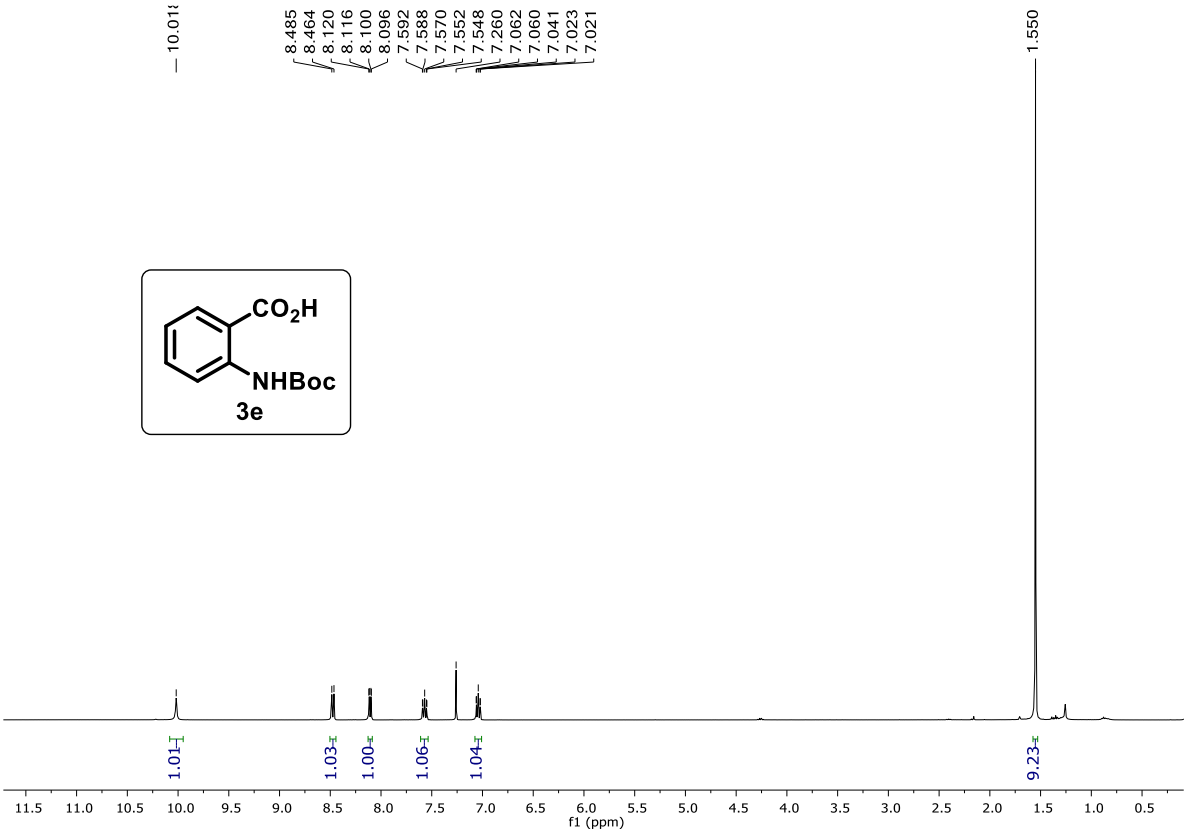
^{1}H NMR of **3d** (400 MHz, Chloroform-*d*)



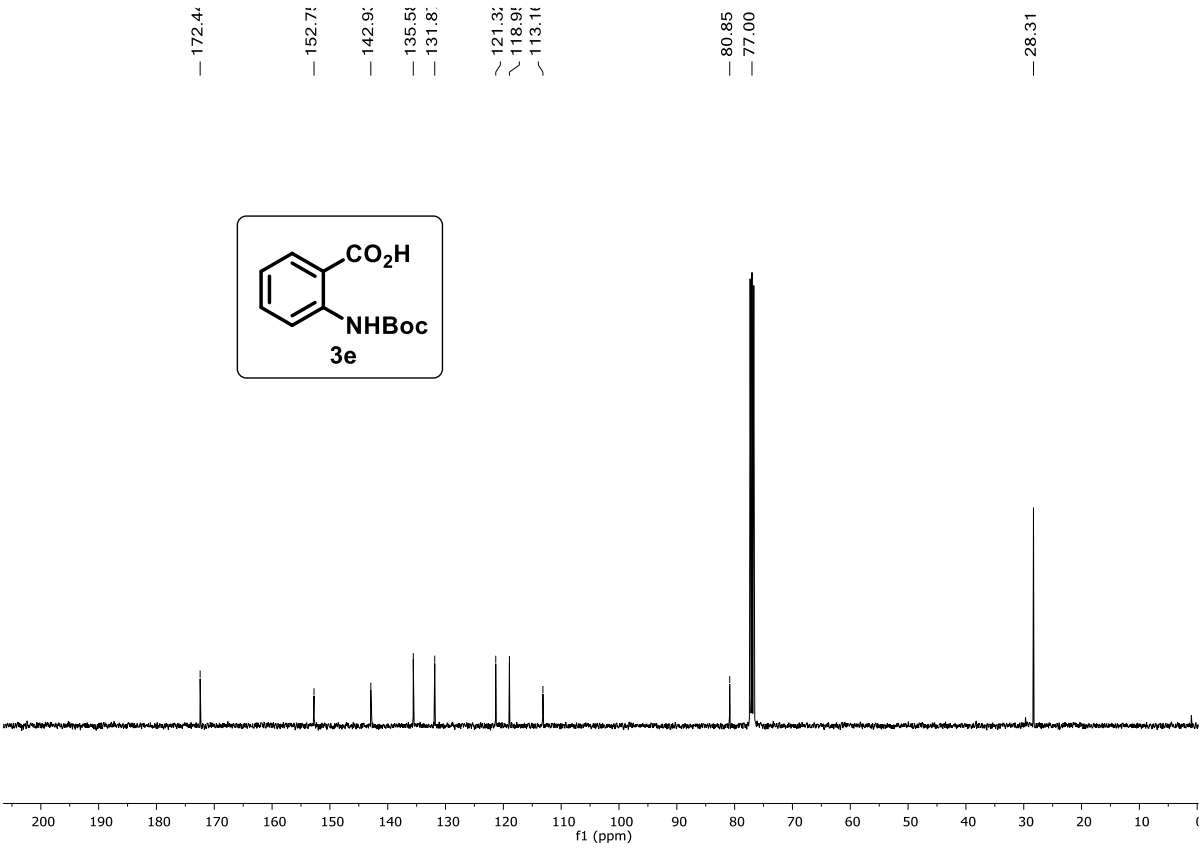
^{13}C NMR of **3d** (100 MHz, $CDCl_3$)



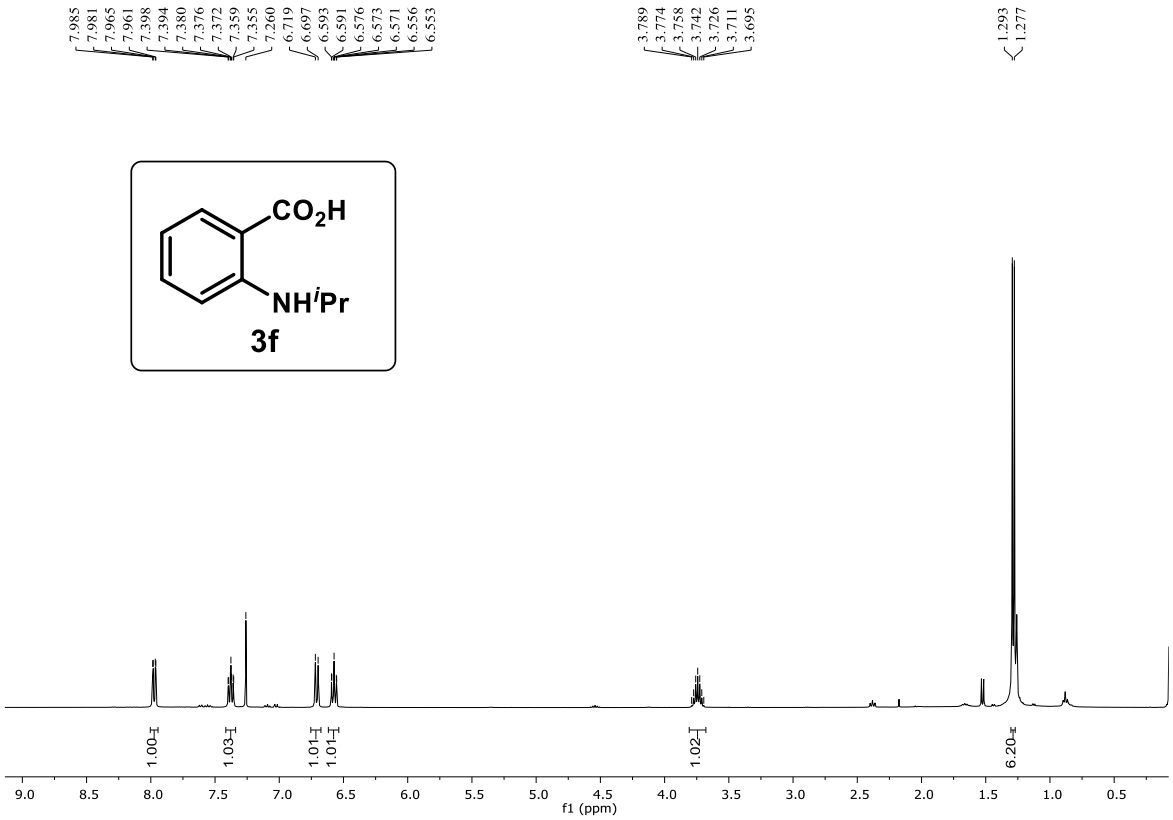
^{1}H NMR of **3e** (400 MHz, Chloroform-*d*)



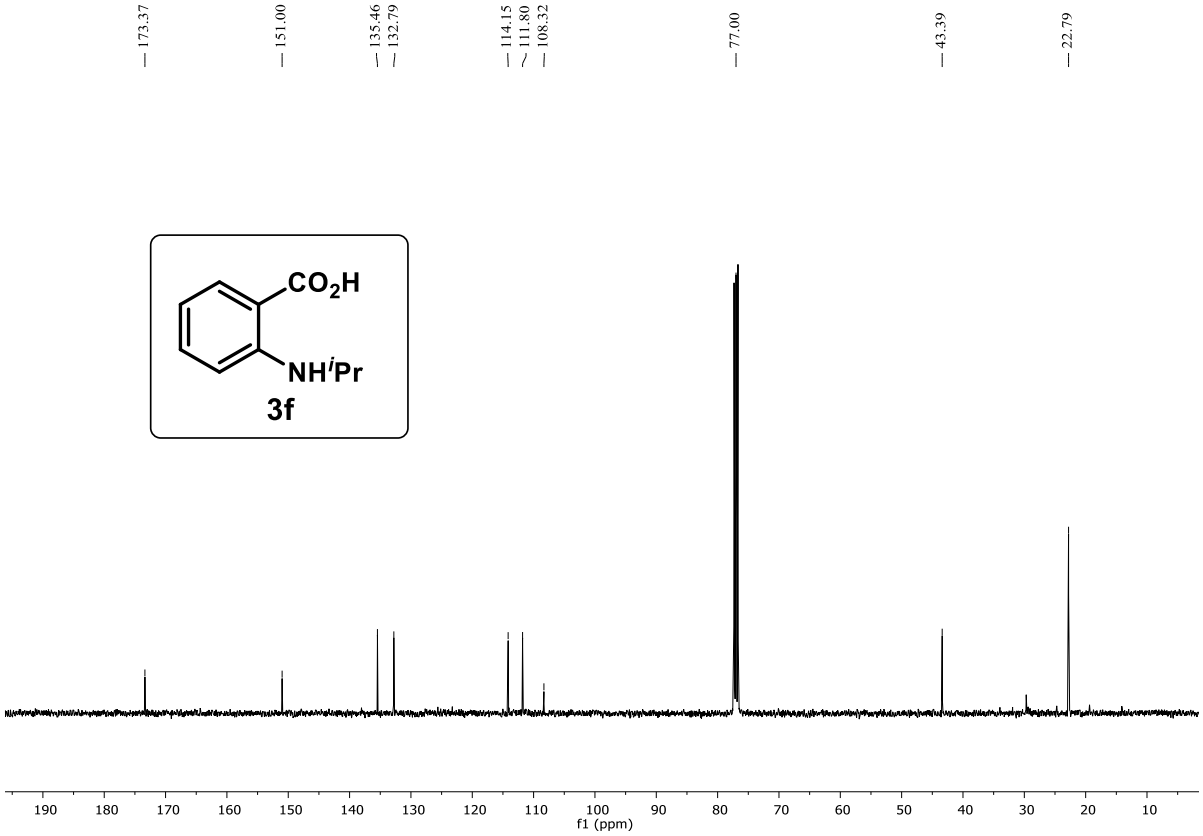
^{13}C NMR of **3e** (100 MHz, $CDCl_3$)



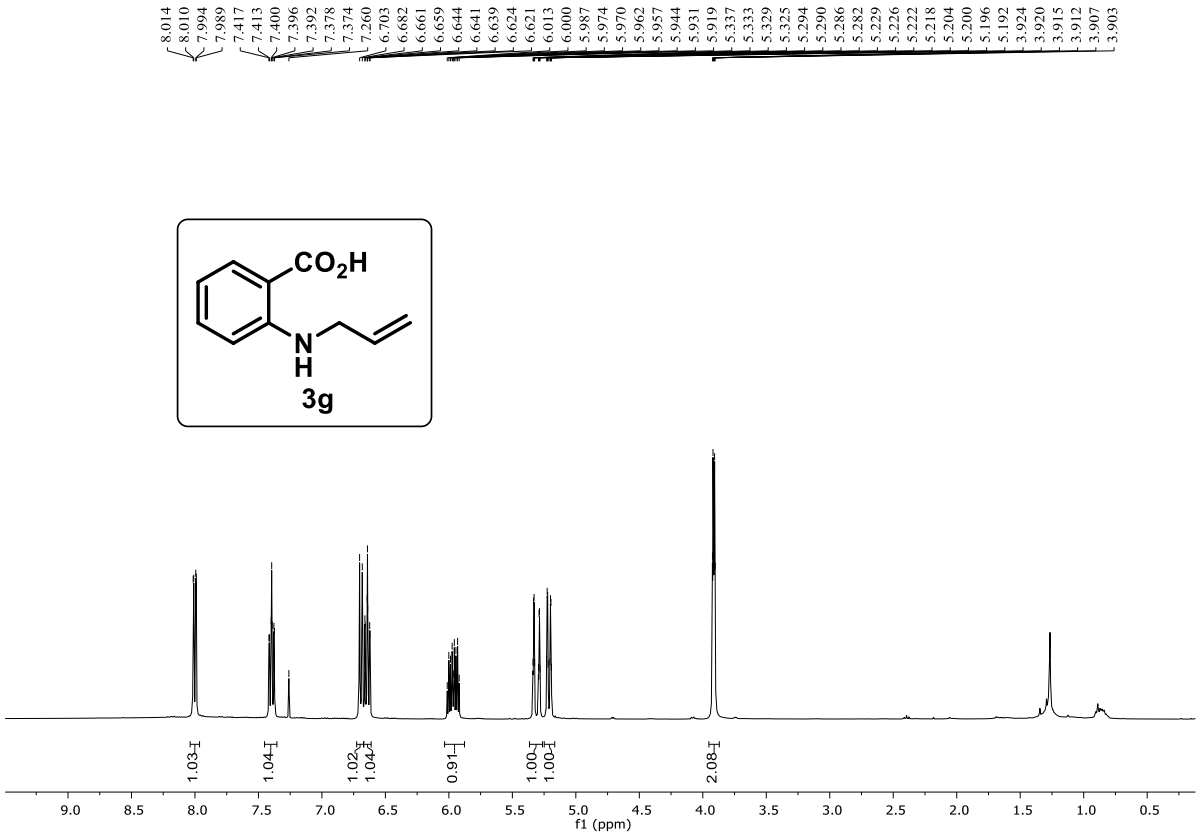
^{1}H NMR of **3f** (400 MHz, Chloroform-*d*)



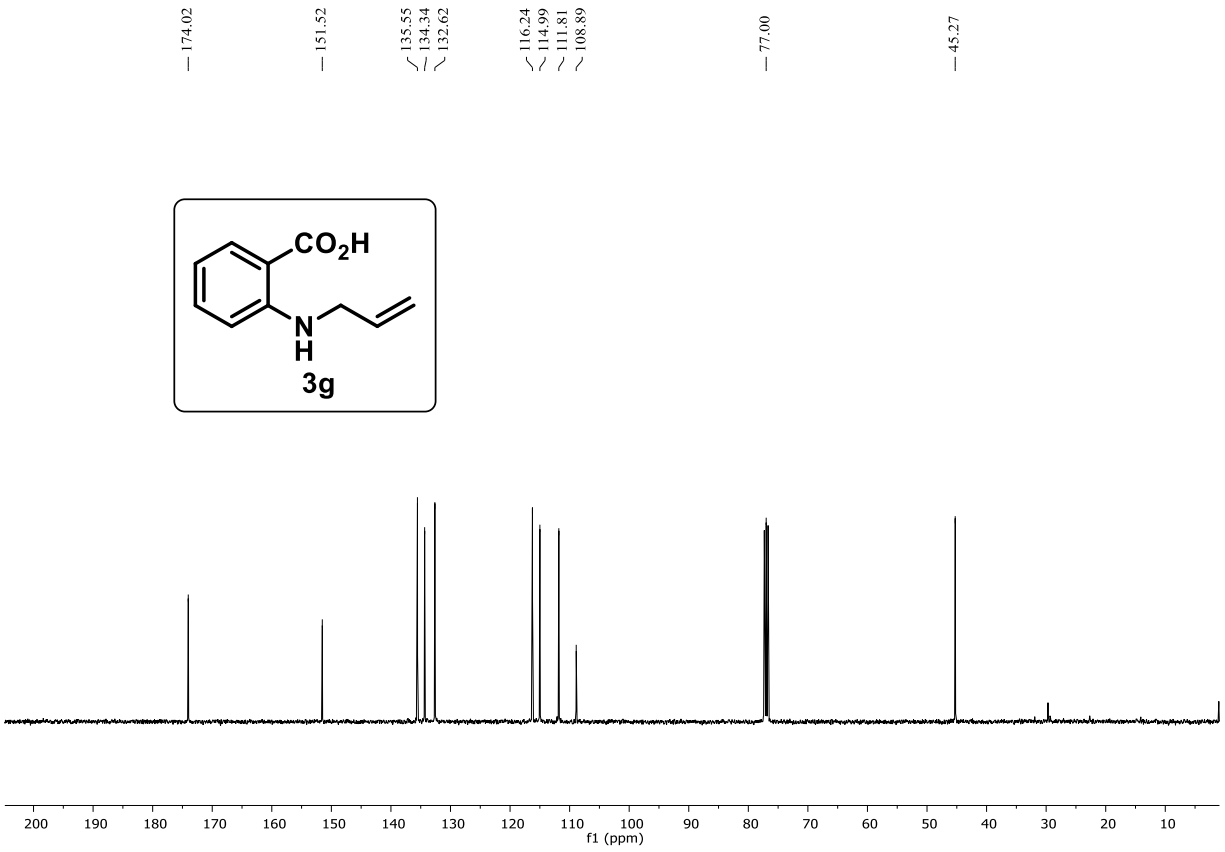
^{13}C NMR of **3f** (100 MHz, $CDCl_3$)



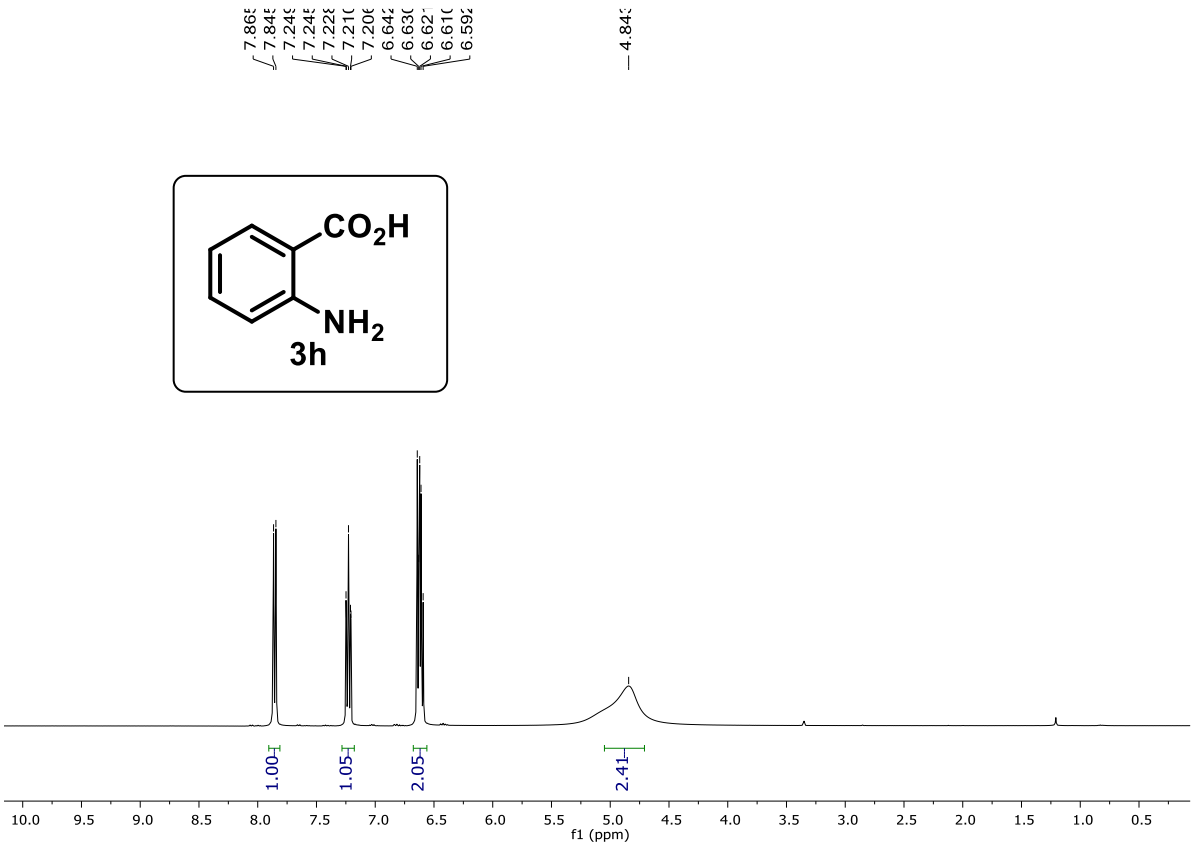
^{1}H NMR of **3g** (400 MHz, Chloroform-*d*)



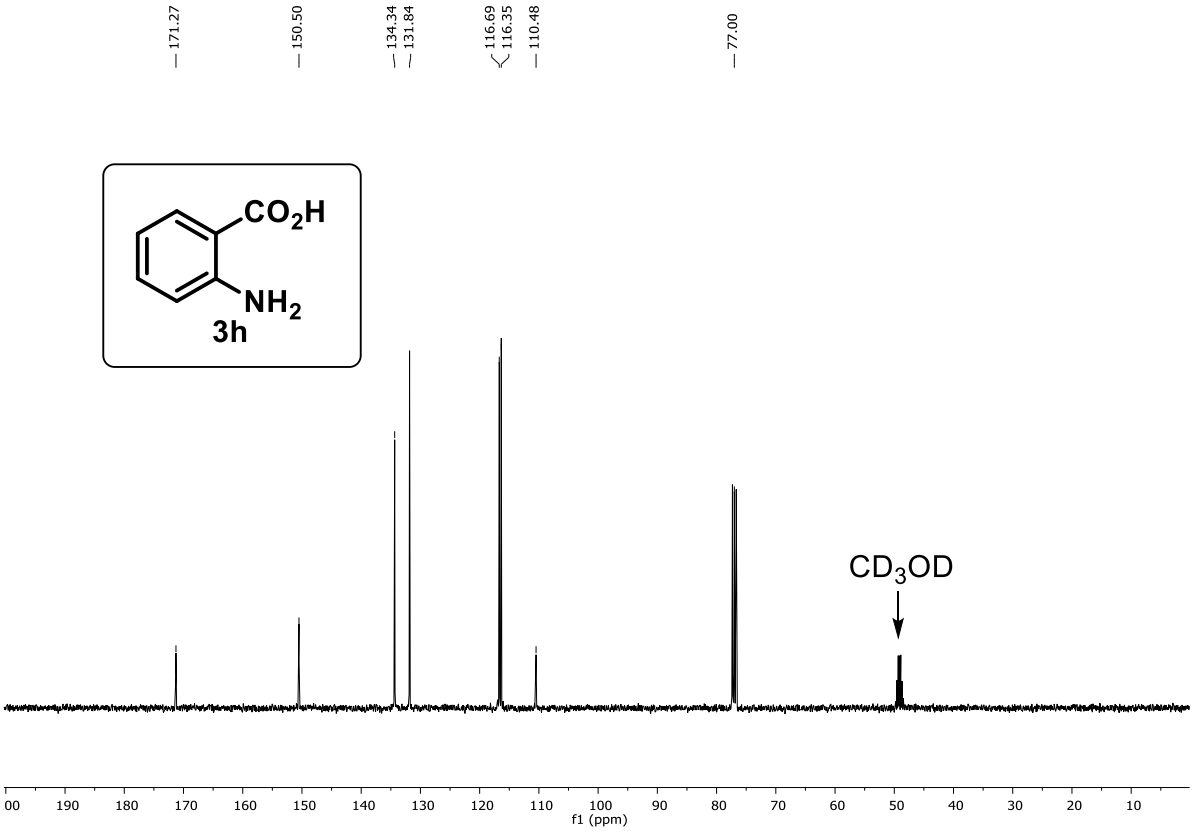
^{13}C NMR of **3g** (100 MHz, $CDCl_3$)



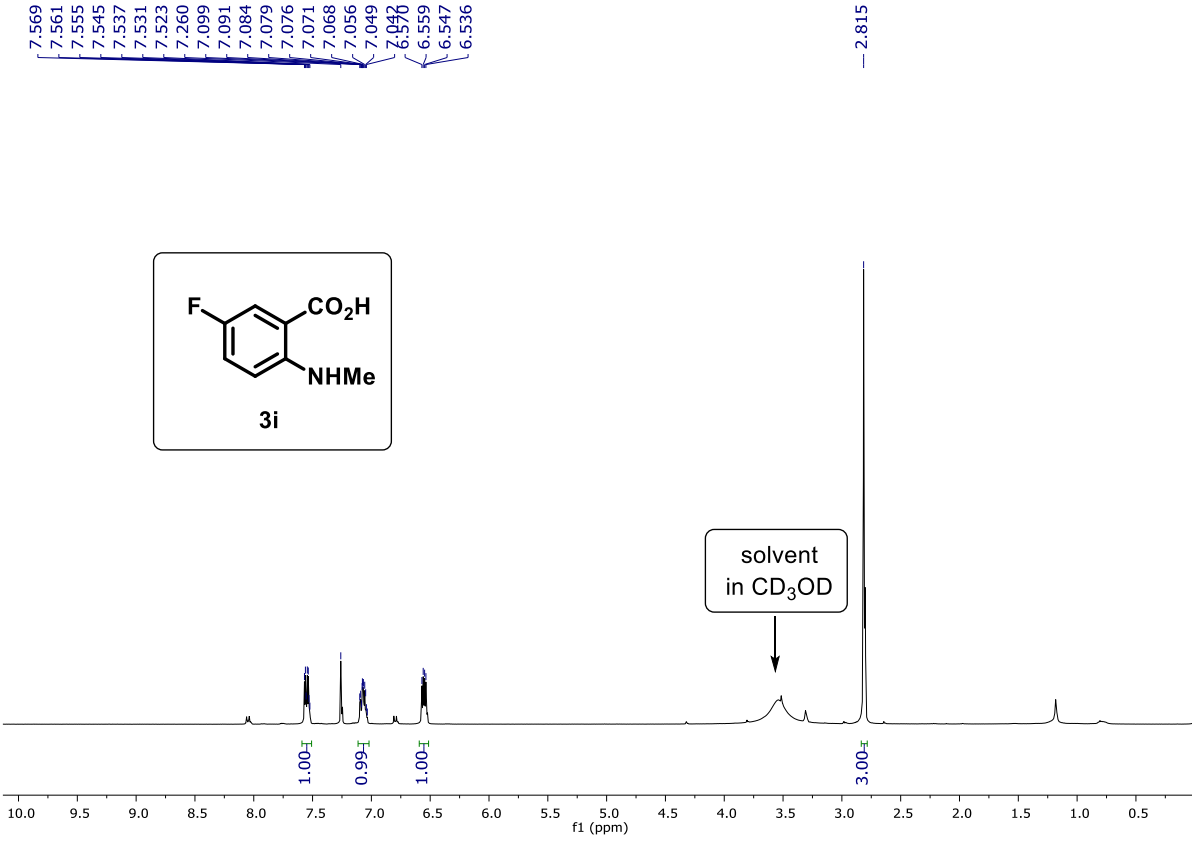
^{1}H NMR of **3h** (400 MHz, Chloroform-*d*)



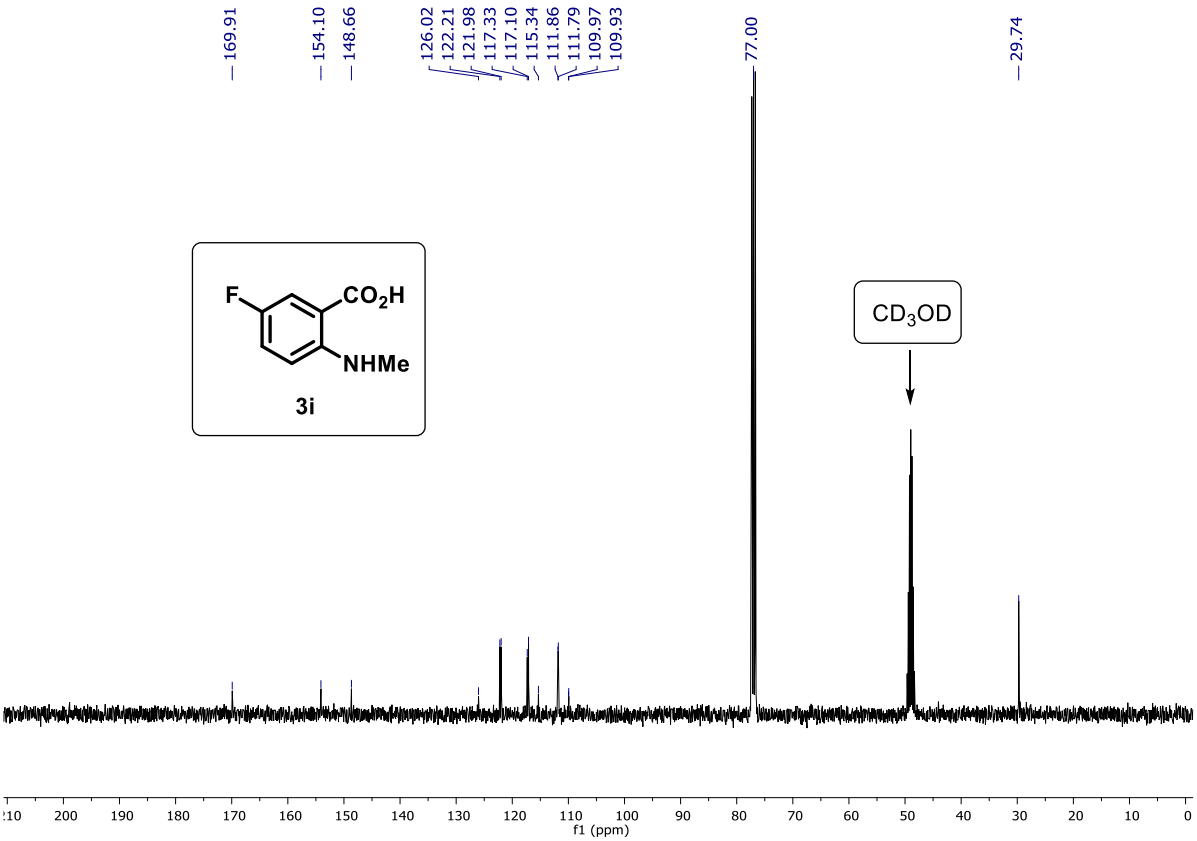
^{13}C NMR of **3h** (100 MHz, $CDCl_3$)



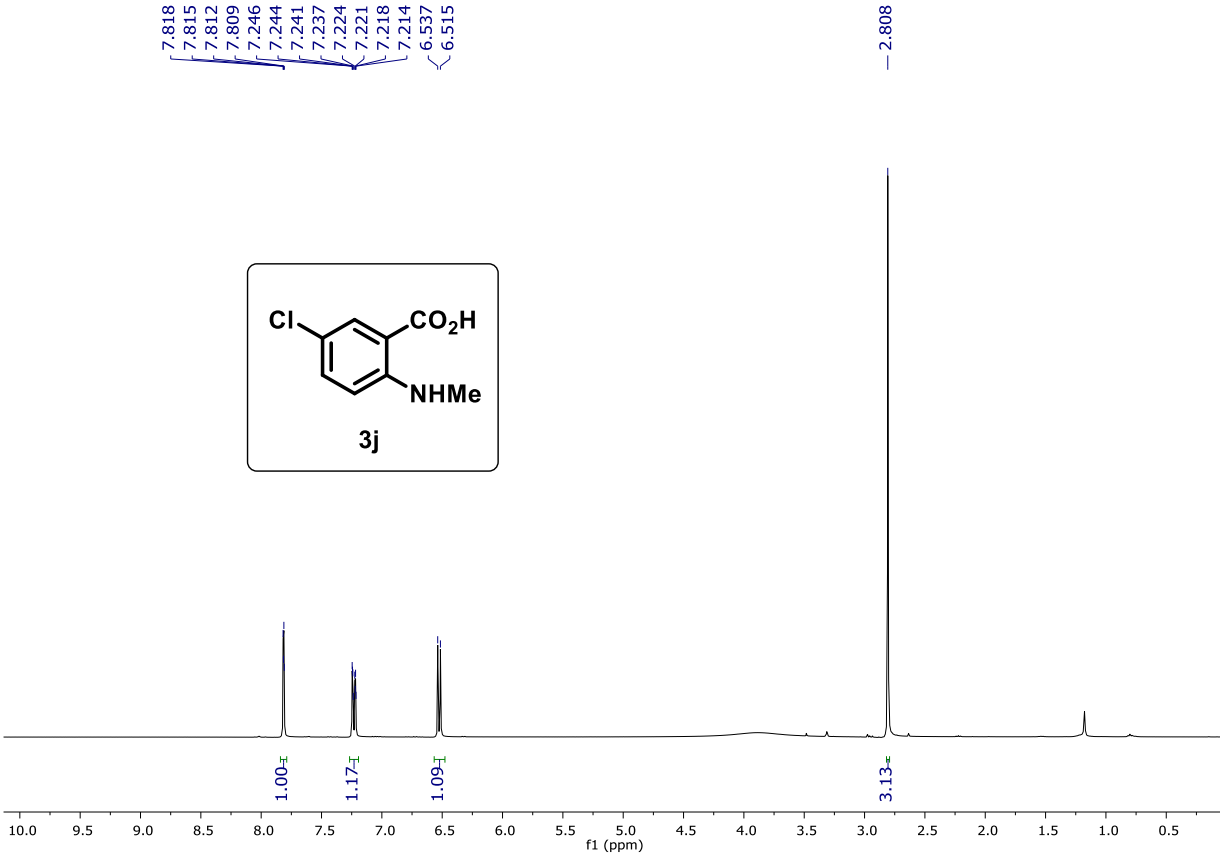
^{1}H NMR of **3i** (400 MHz, Chloroform-*d*)



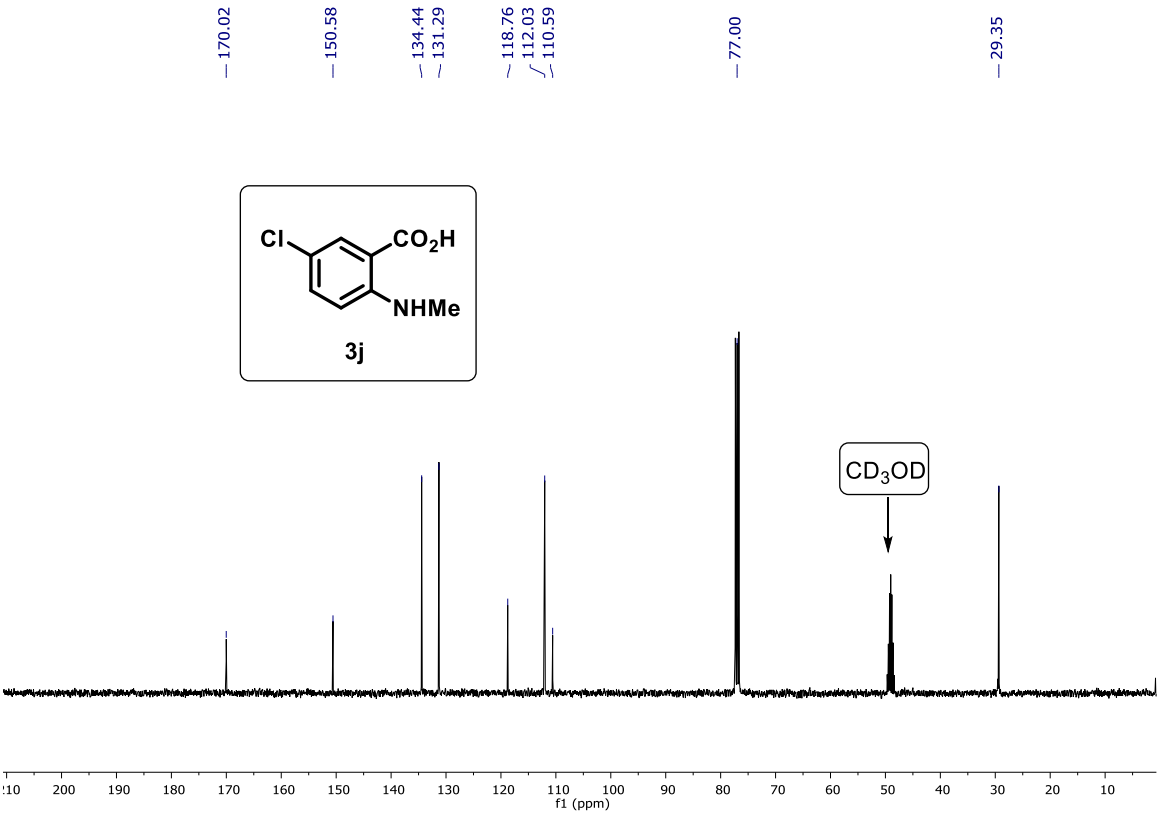
^{13}C NMR of **3i** (100 MHz, $CDCl_3$)



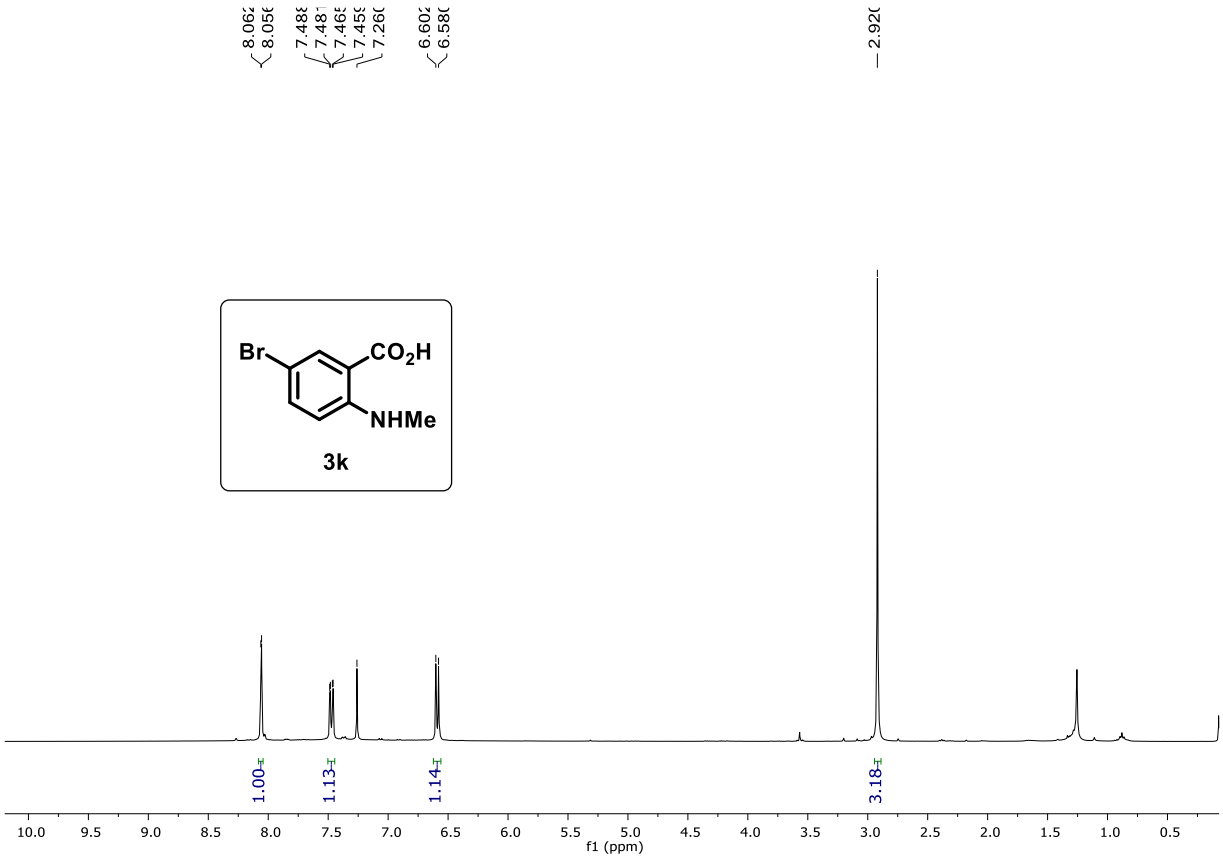
^{1}H NMR of **3j** (400 MHz, Chloroform-*d*)



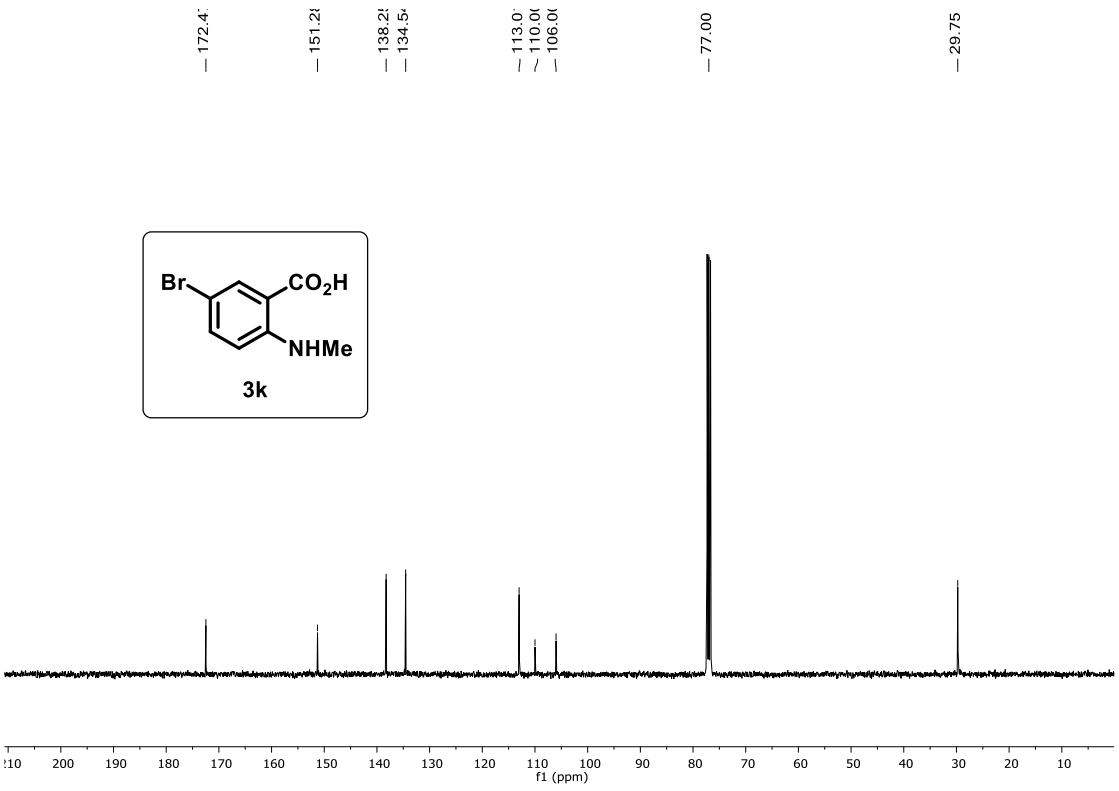
^{13}C NMR of **3j** (100 MHz, $CDCl_3$)



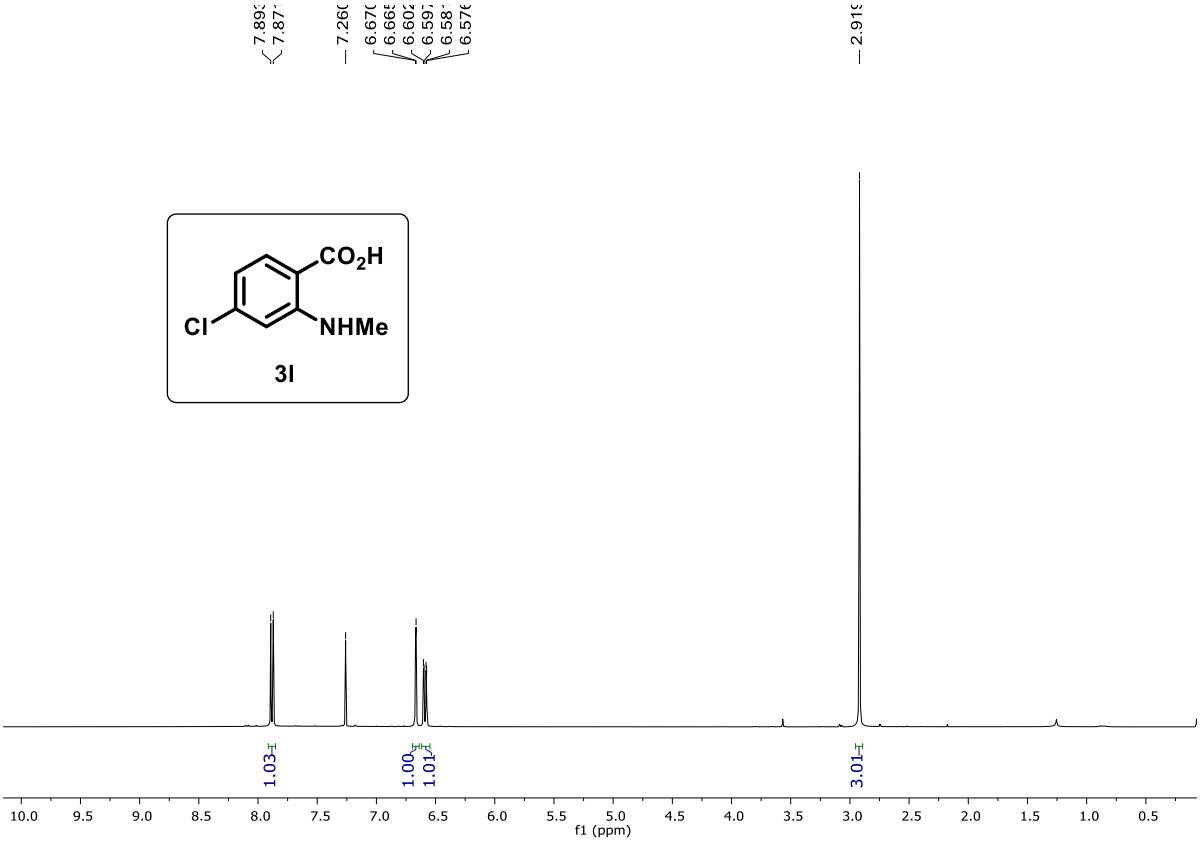
^{1}H NMR of **3k** (400 MHz, Chloroform-*d*)



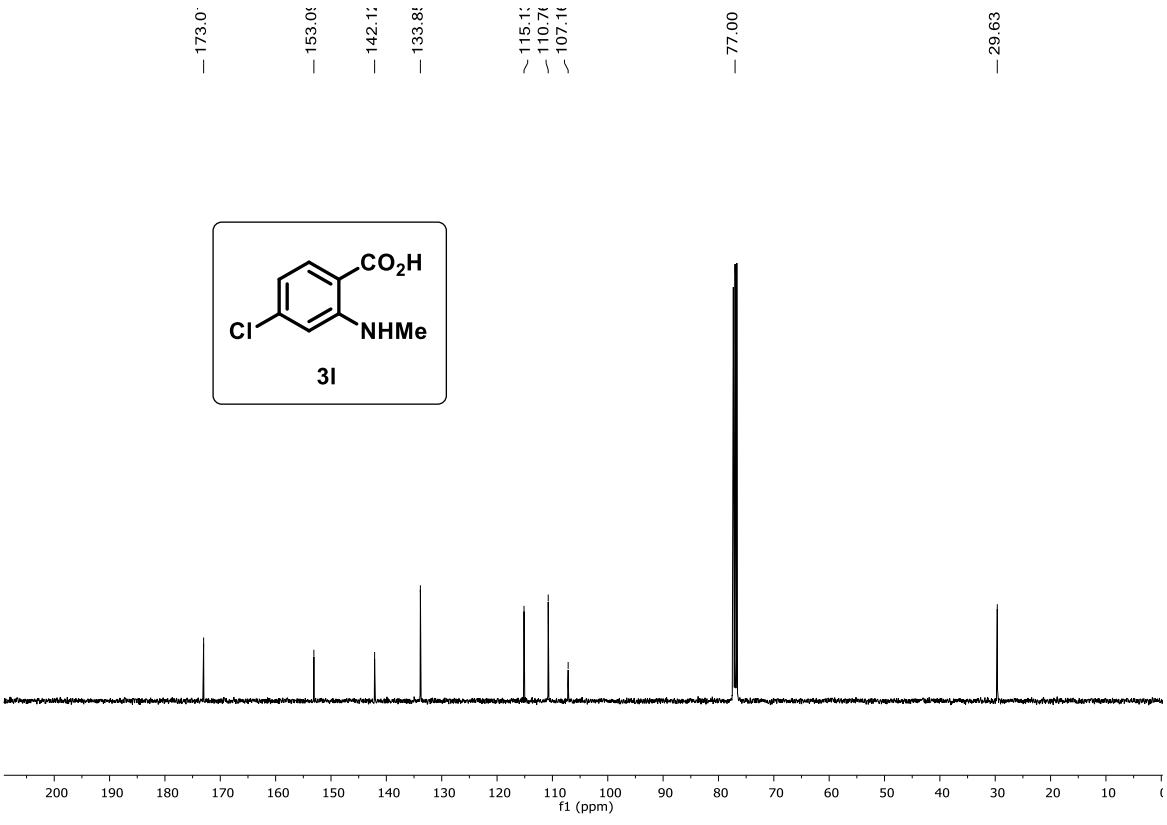
^{13}C NMR of **3k** (100 MHz, $CDCl_3$)



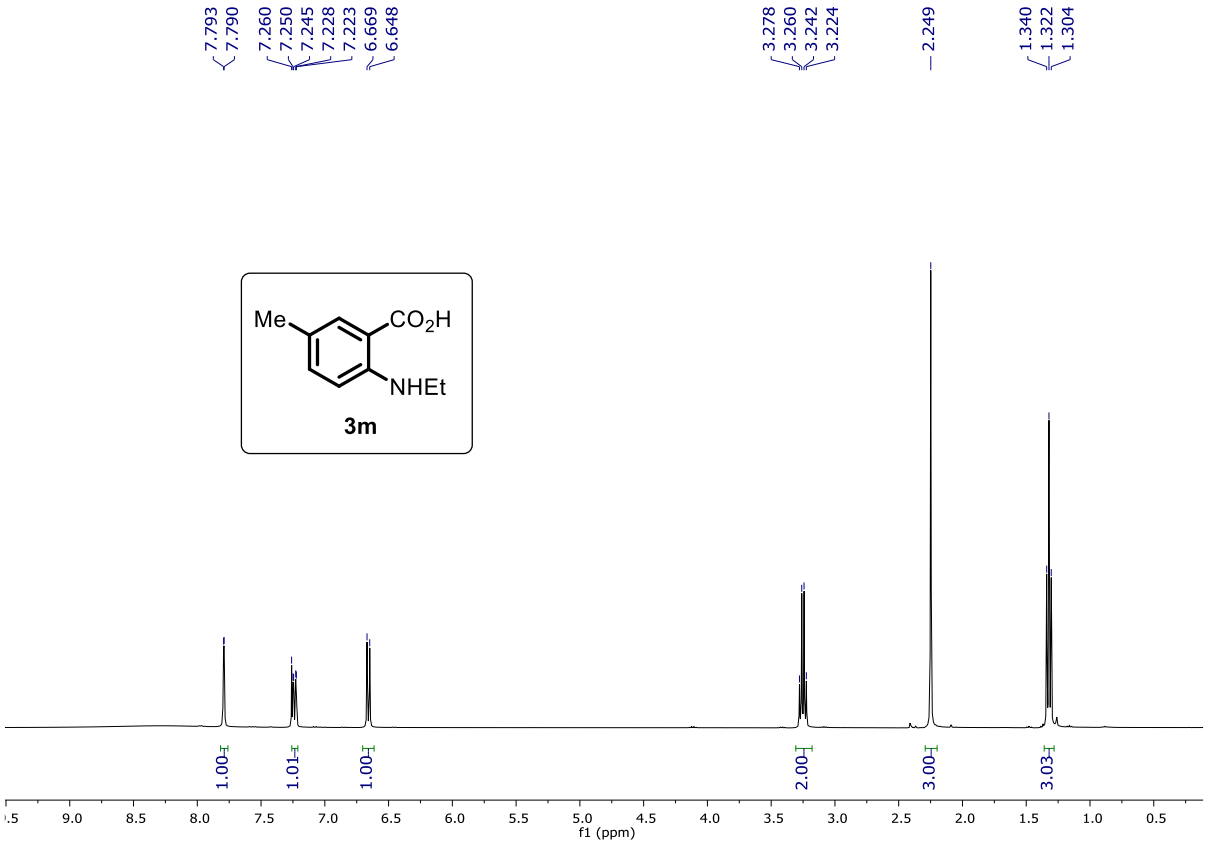
^{1}H NMR of **3l** (400 MHz, Chloroform-*d*)



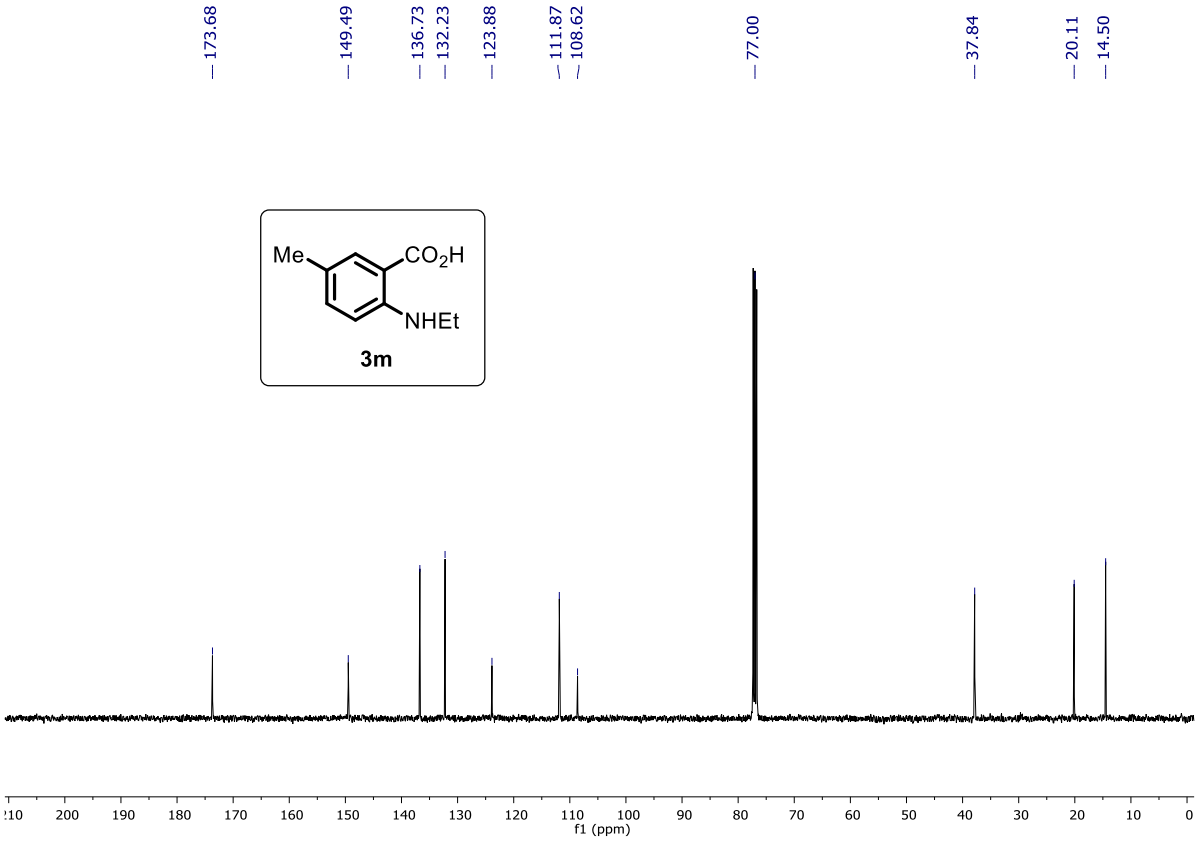
^{13}C NMR of **3l** (100 MHz, $CDCl_3$)



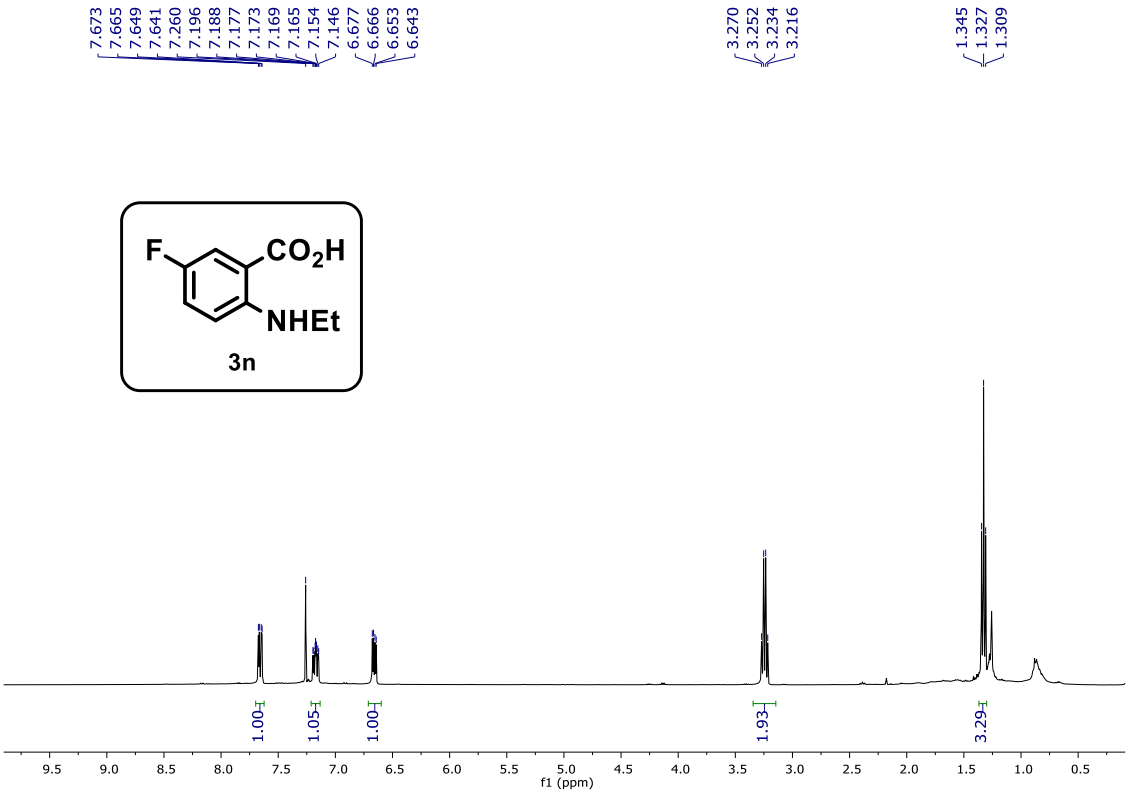
^{1}H NMR of **3m** (400 MHz, Chloroform-*d*)



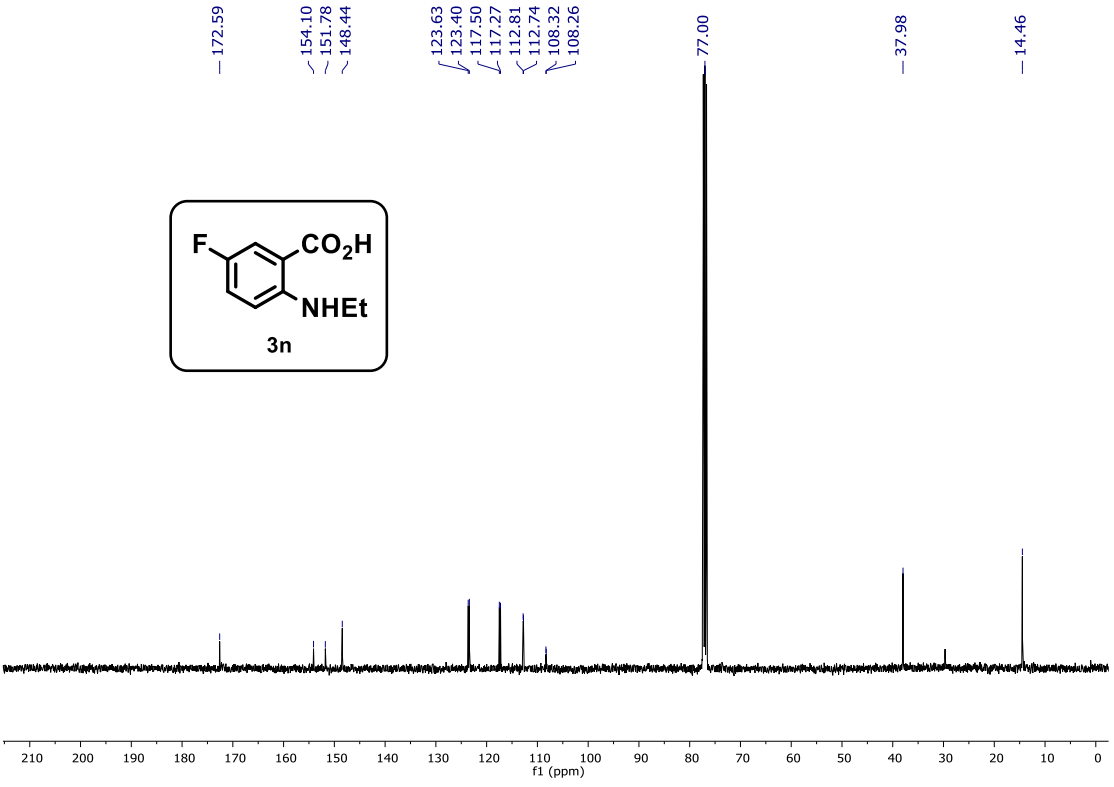
^{13}C NMR of **3m** (100 MHz, $CDCl_3$)



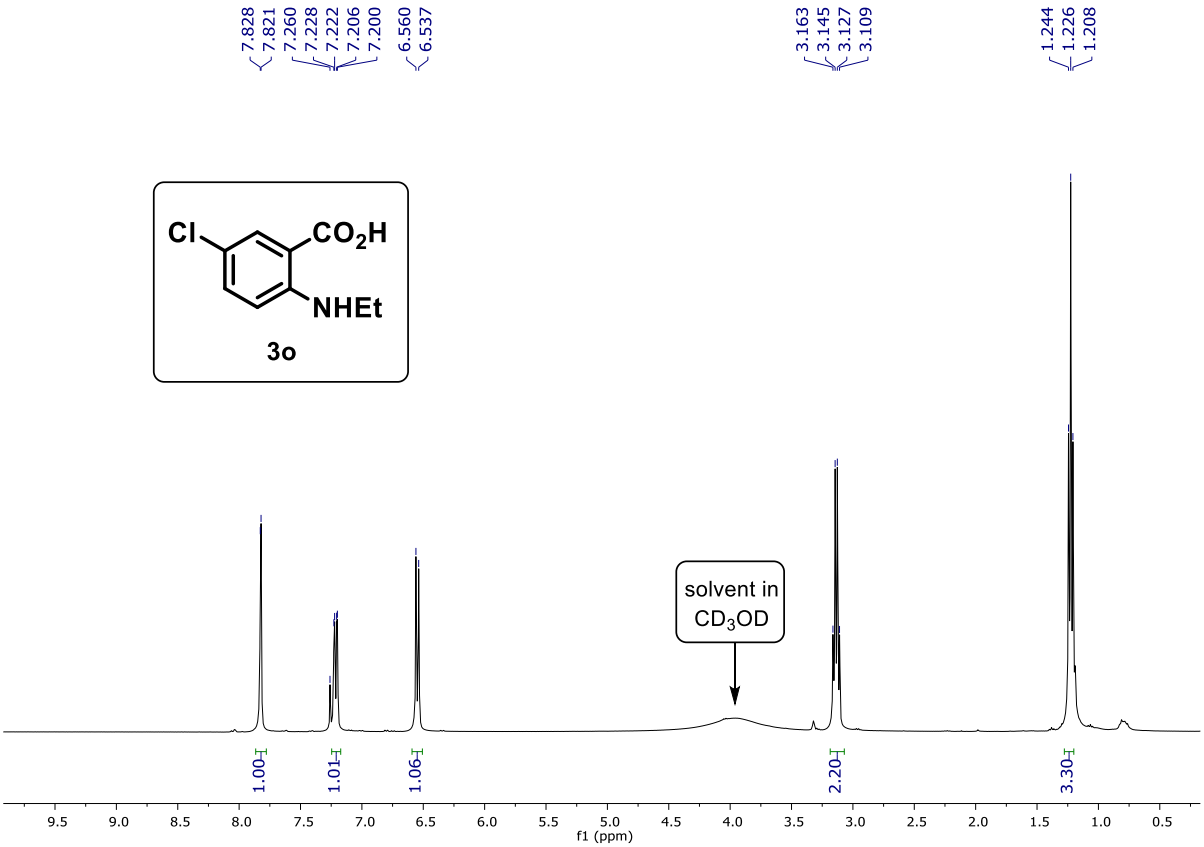
^{1}H NMR of **3n** (400 MHz, Chloroform-*d*)



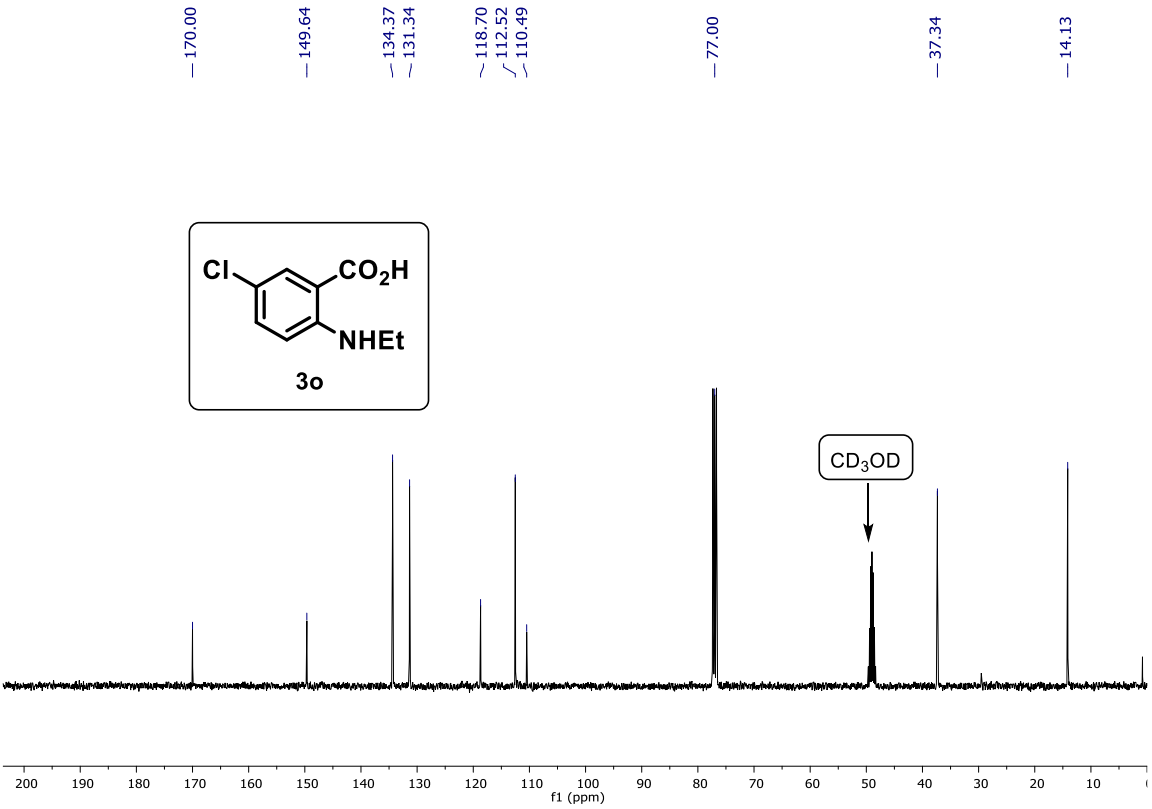
^{13}C NMR of **3n** (100 MHz, $CDCl_3$)



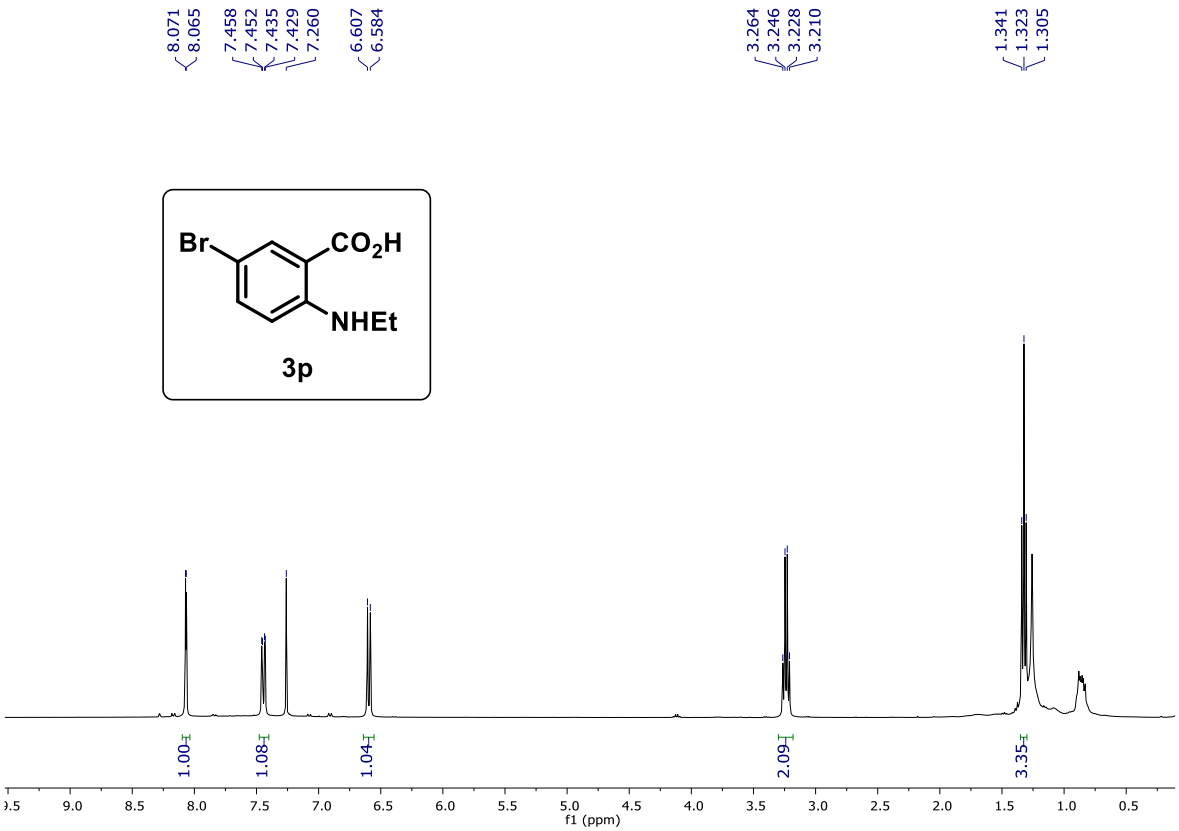
^{1}H NMR of **3o** (400 MHz, Chloroform-*d*)



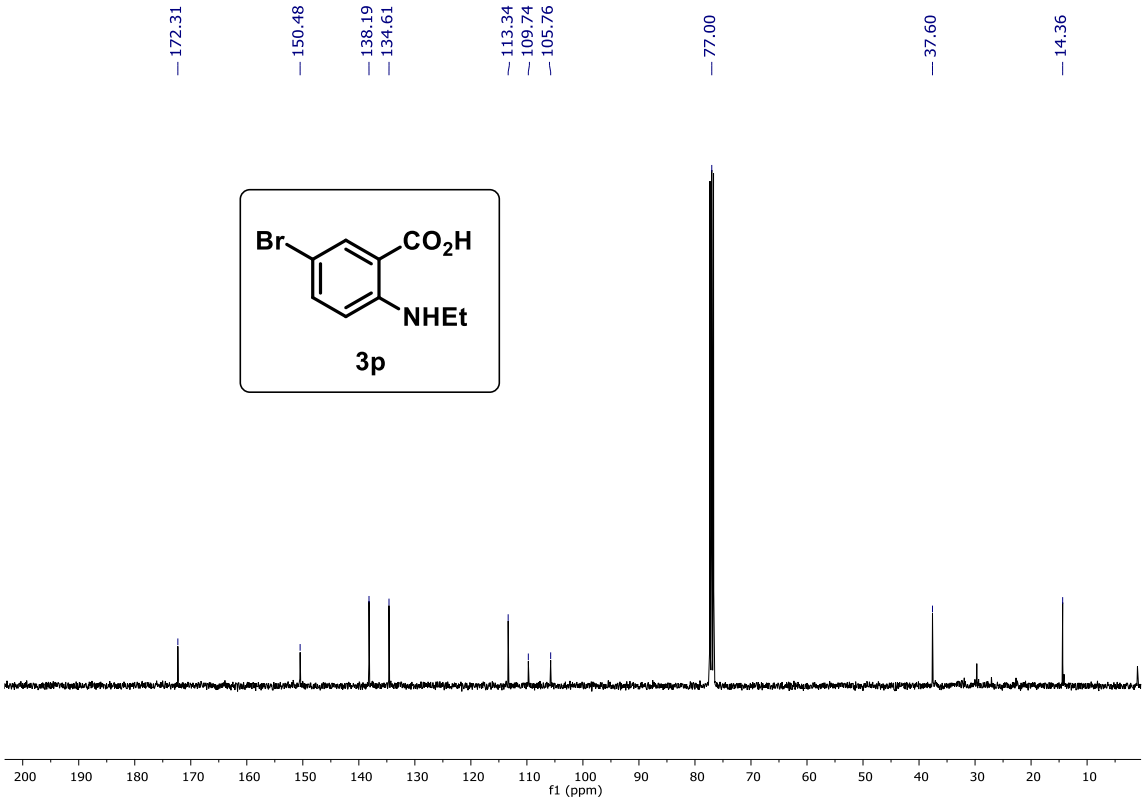
^{13}C NMR of **3o** (100 MHz, $CDCl_3$)



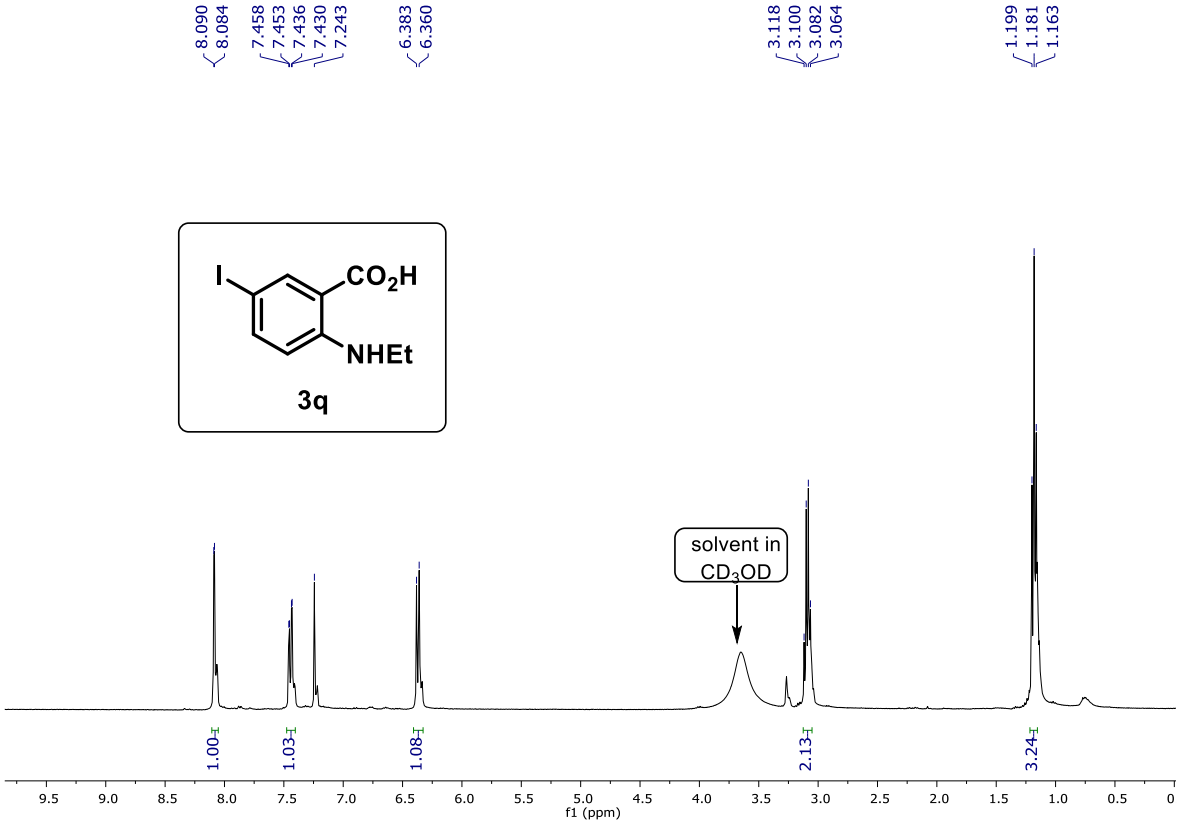
^{1}H NMR of **3p** (400 MHz, Chloroform-*d*)



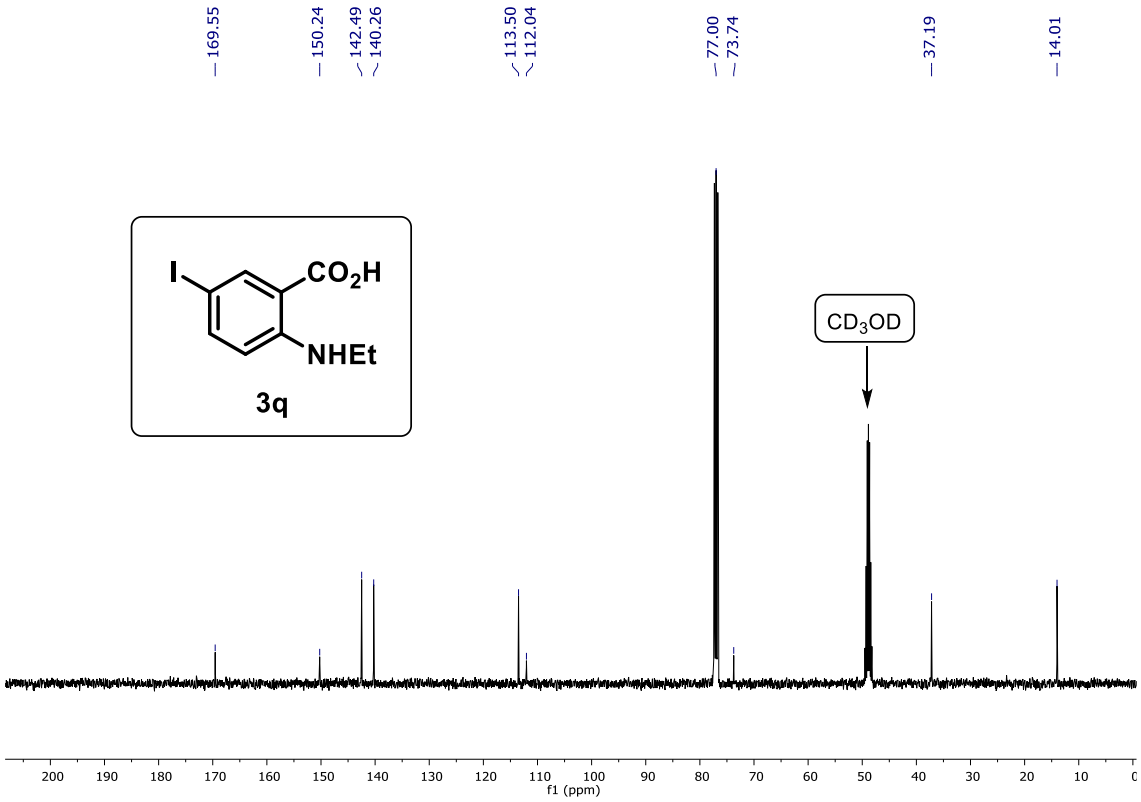
^{13}C NMR of **3p** (100 MHz, $CDCl_3$)



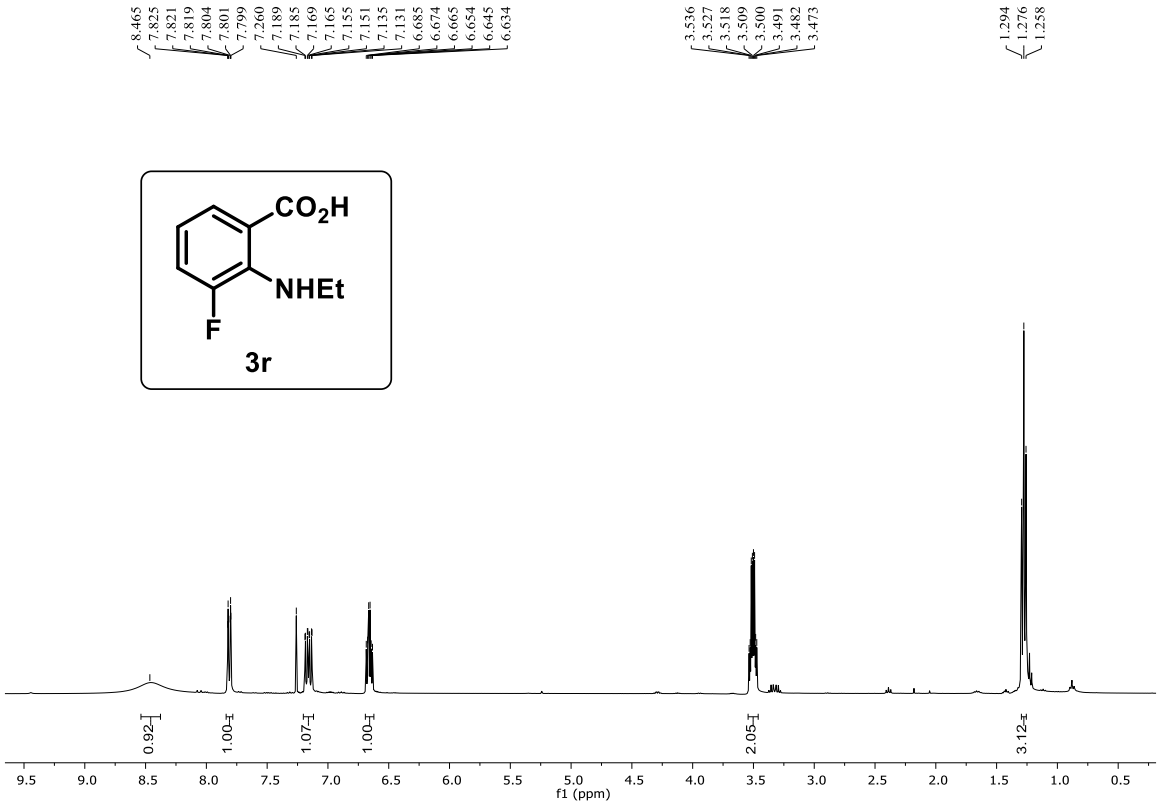
^{1}H NMR of **3q** (400 MHz, Chloroform-*d*)



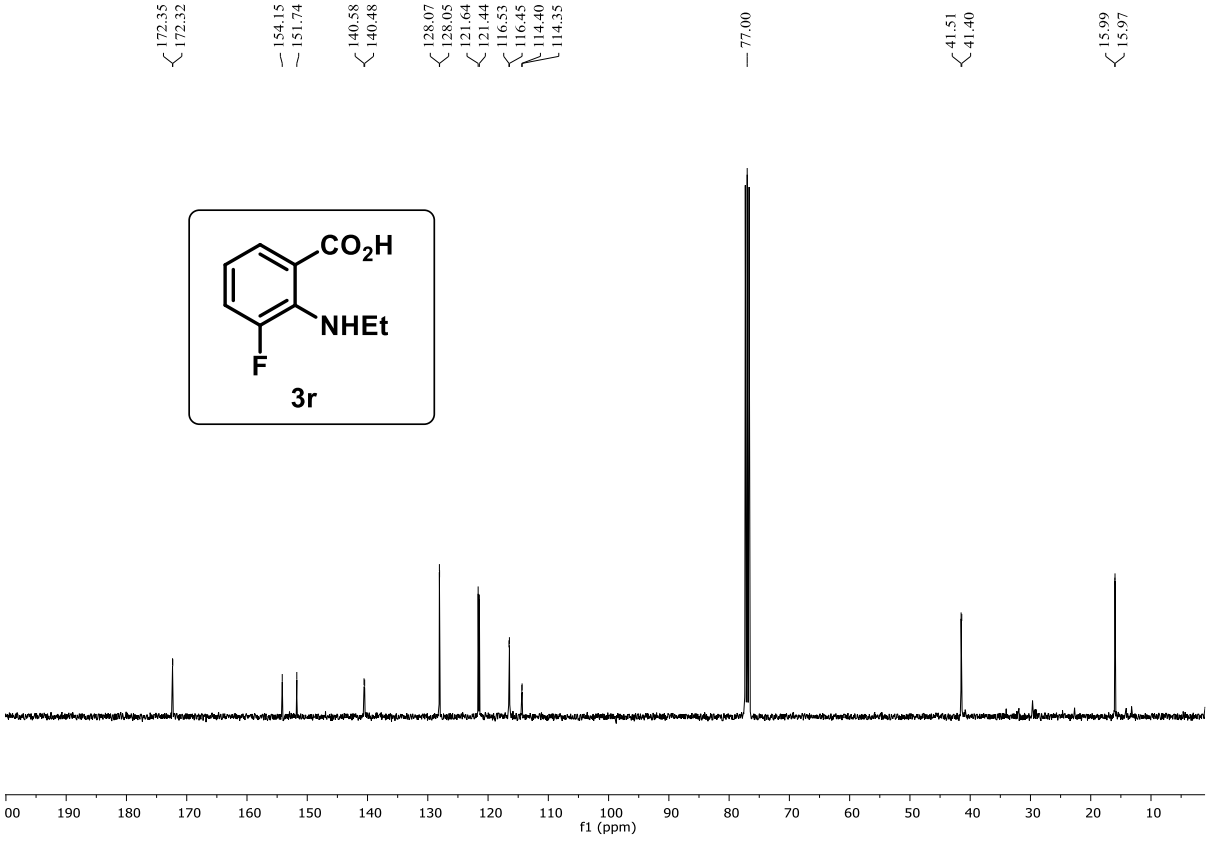
^{13}C NMR of **3q** (100 MHz, $CDCl_3$)



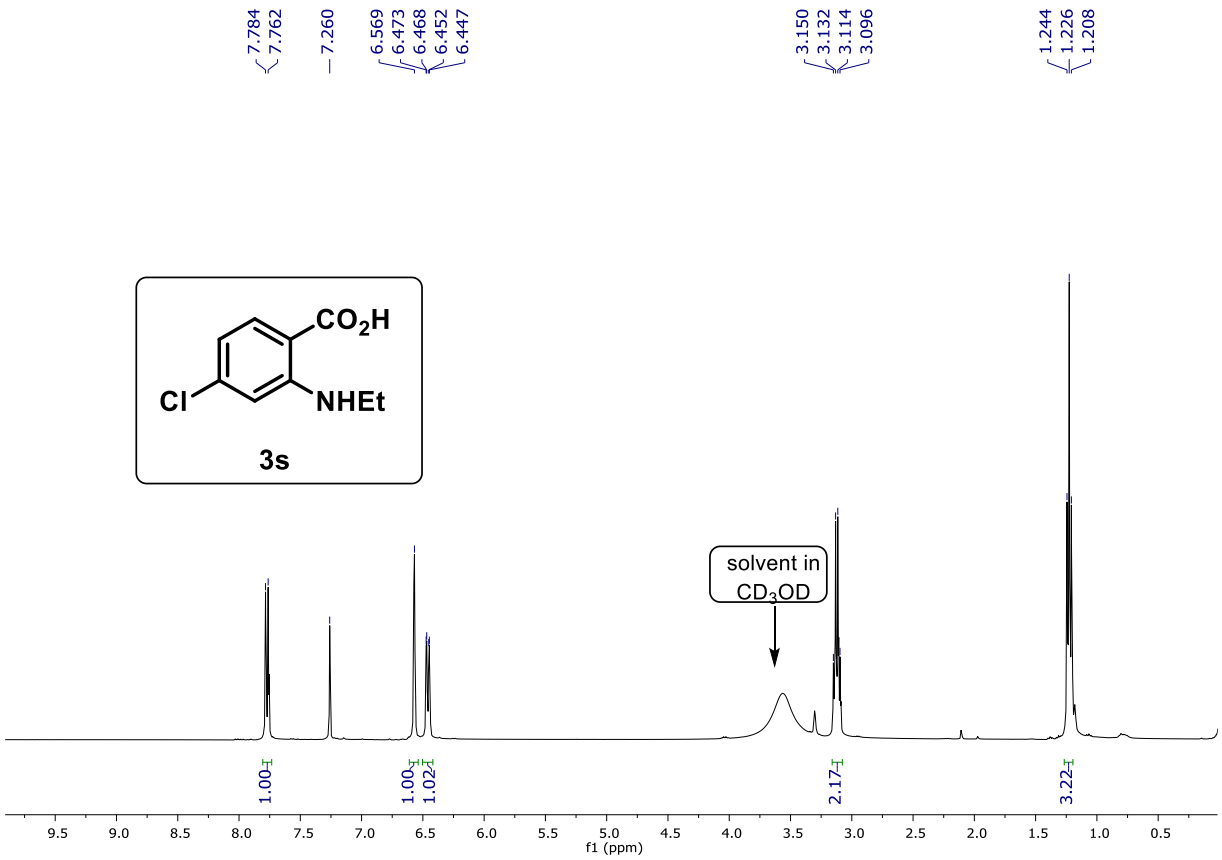
^{1}H NMR of **3r** (400 MHz, Chloroform-*d*)



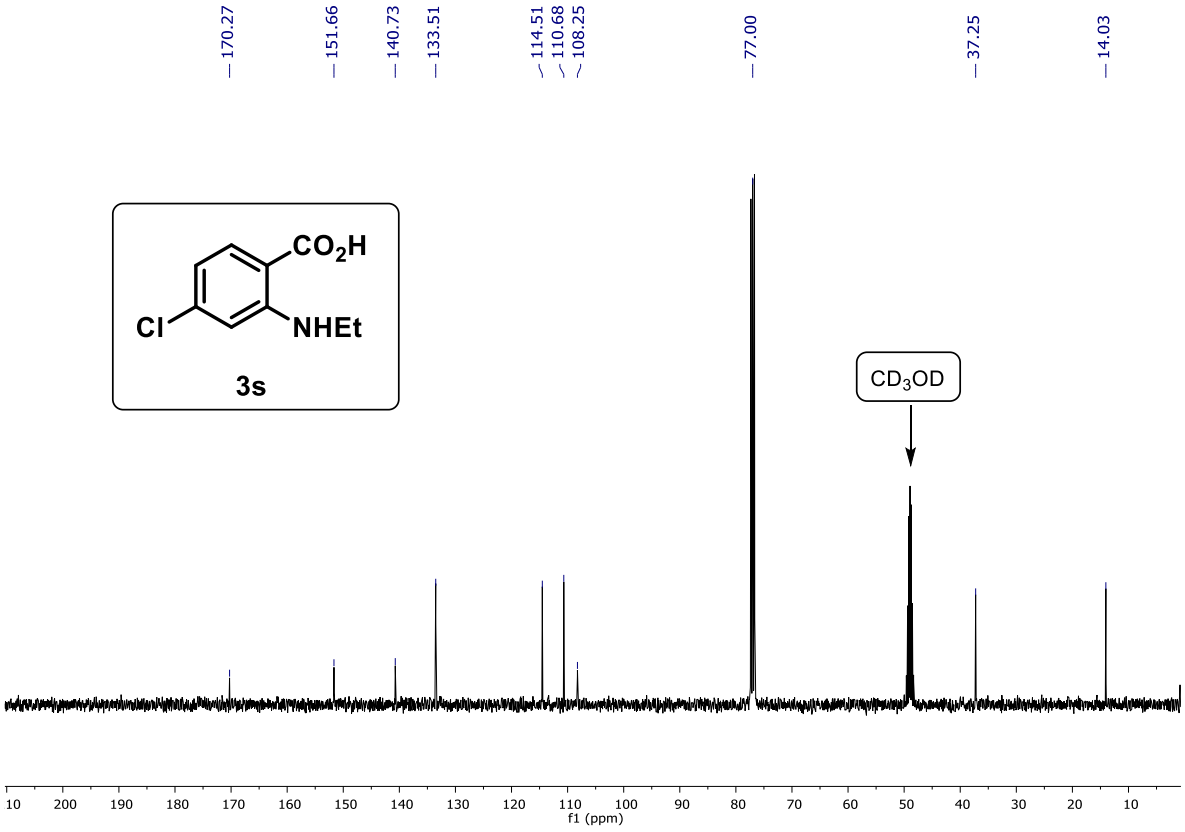
^{13}C NMR of **3r** (100 MHz, $CDCl_3$)



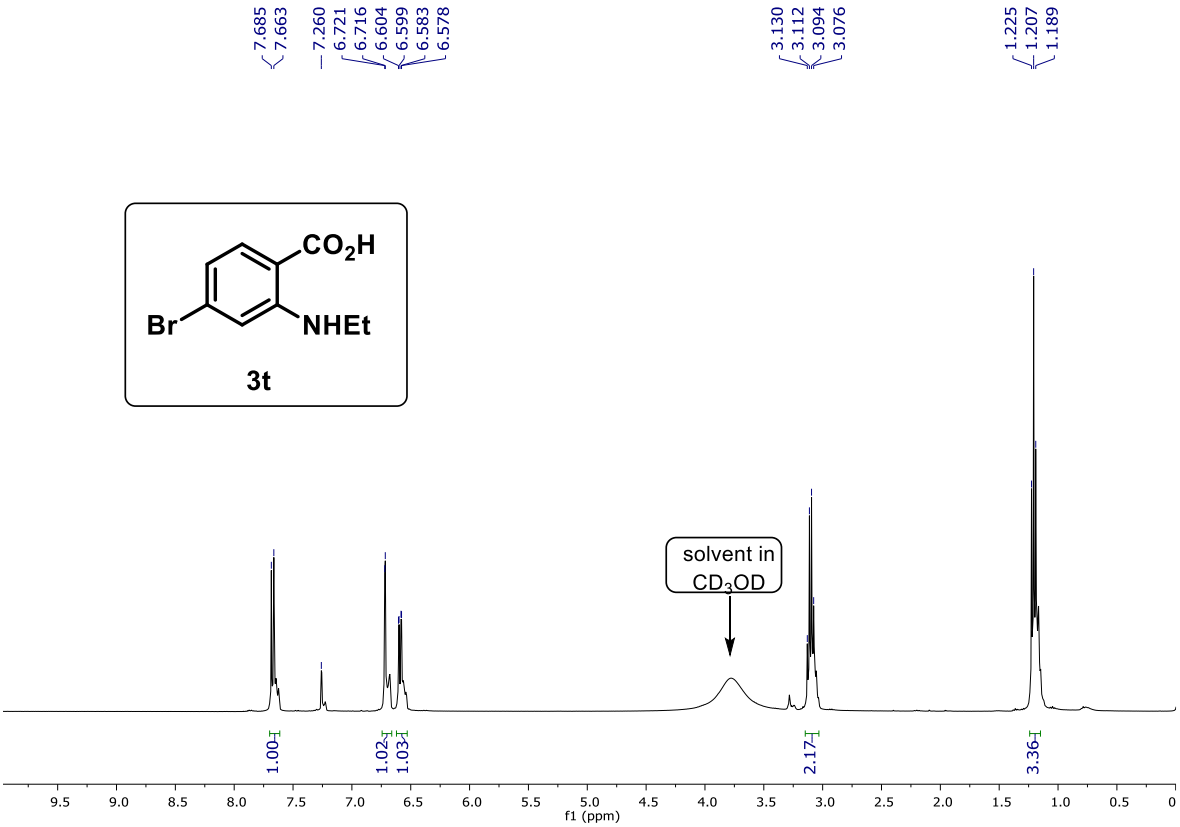
^{1}H NMR of **3s** (400 MHz, Chloroform-*d*)



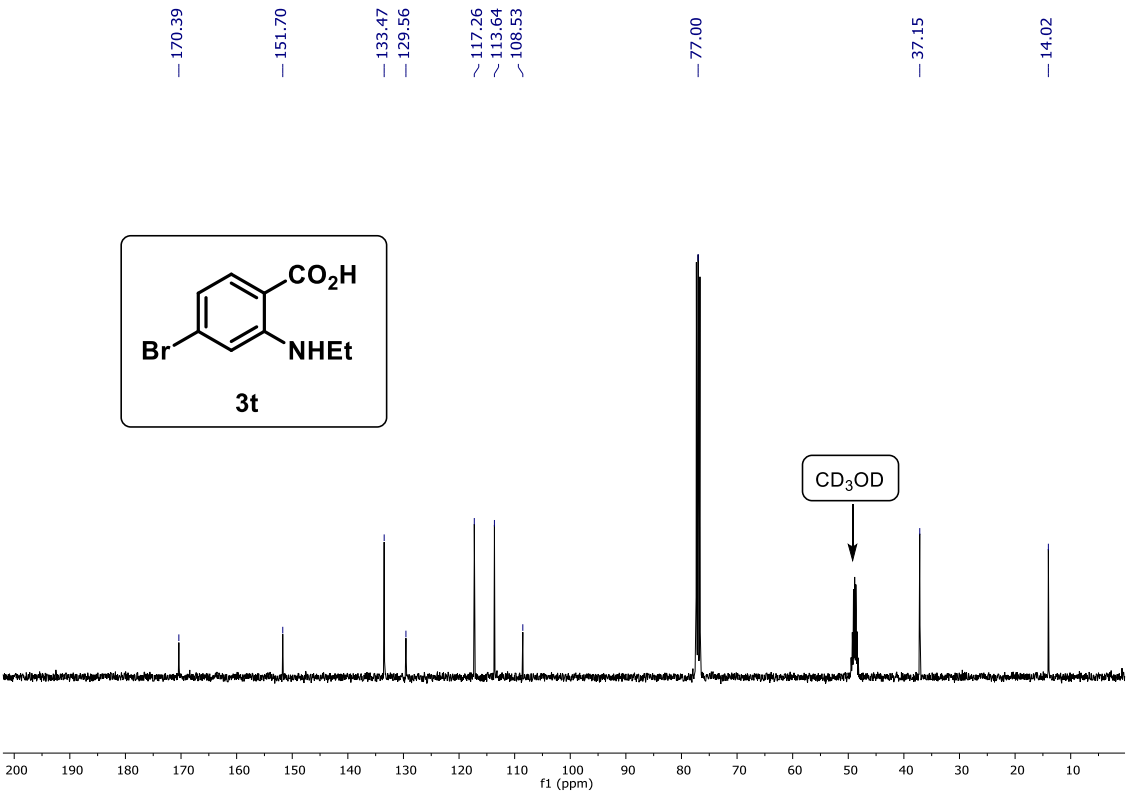
^{13}C NMR of **3s** (100 MHz, $CDCl_3$)



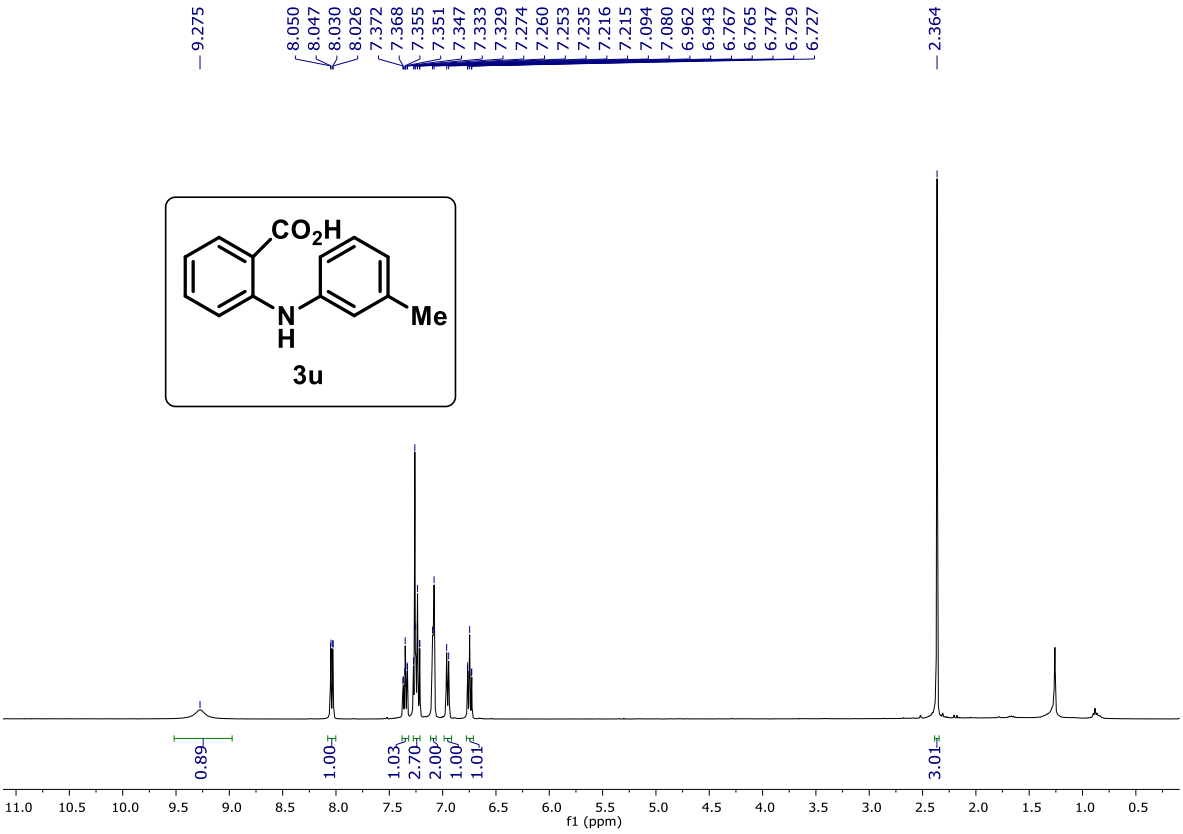
^{1}H NMR of **3t** (400 MHz, Chloroform-*d*)



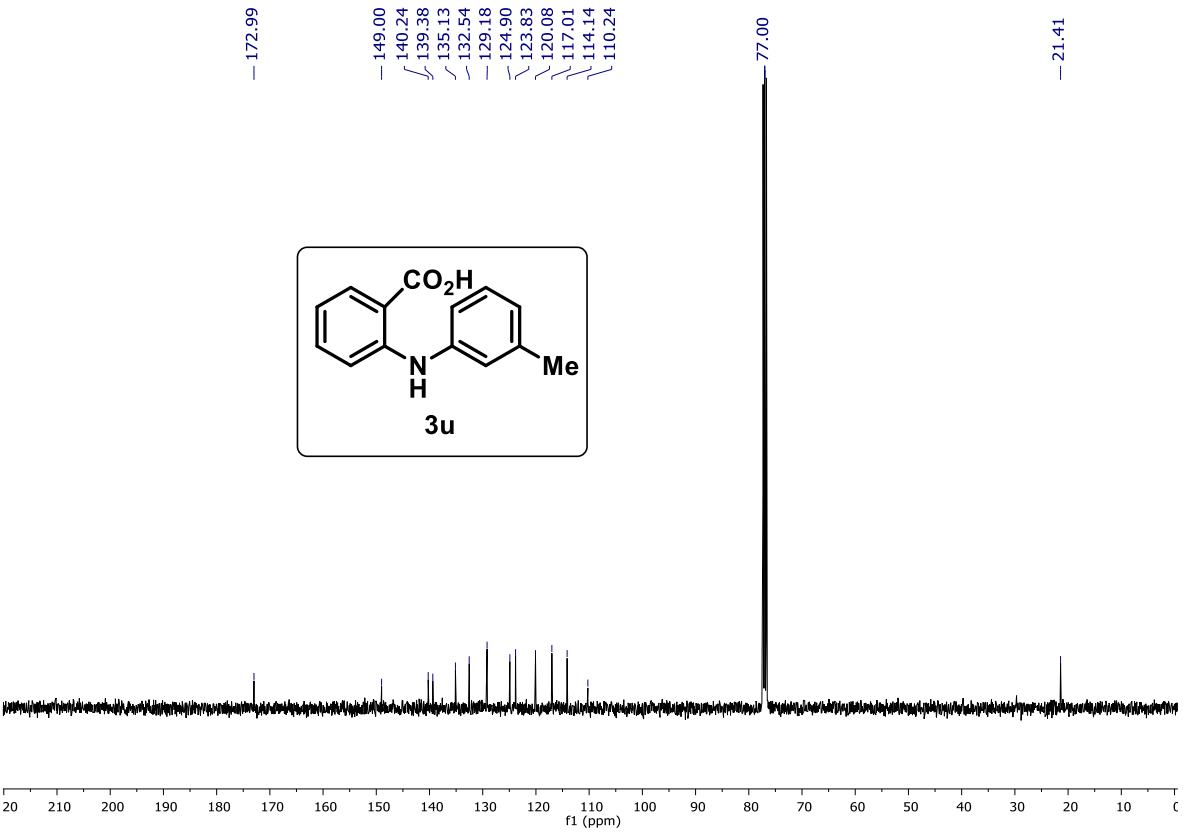
^{13}C NMR of **3t** (100 MHz, $CDCl_3$)



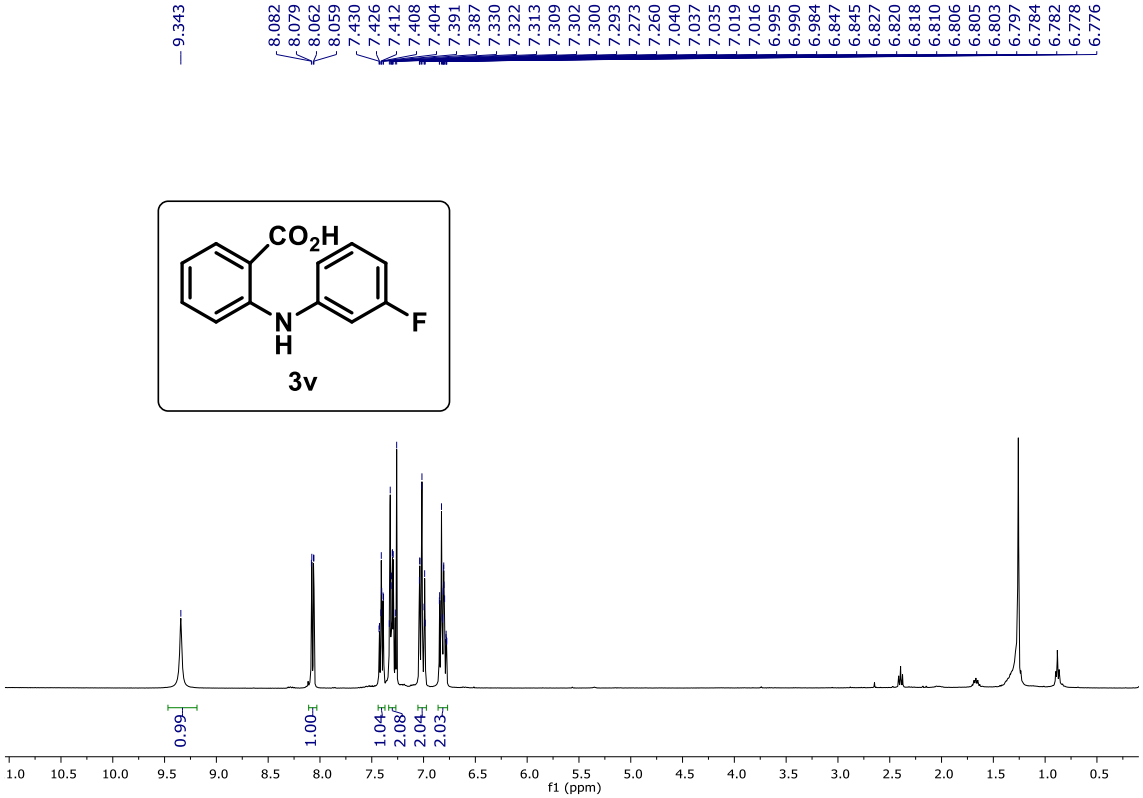
^{1}H NMR of **3u** (400 MHz, Chloroform-*d*)



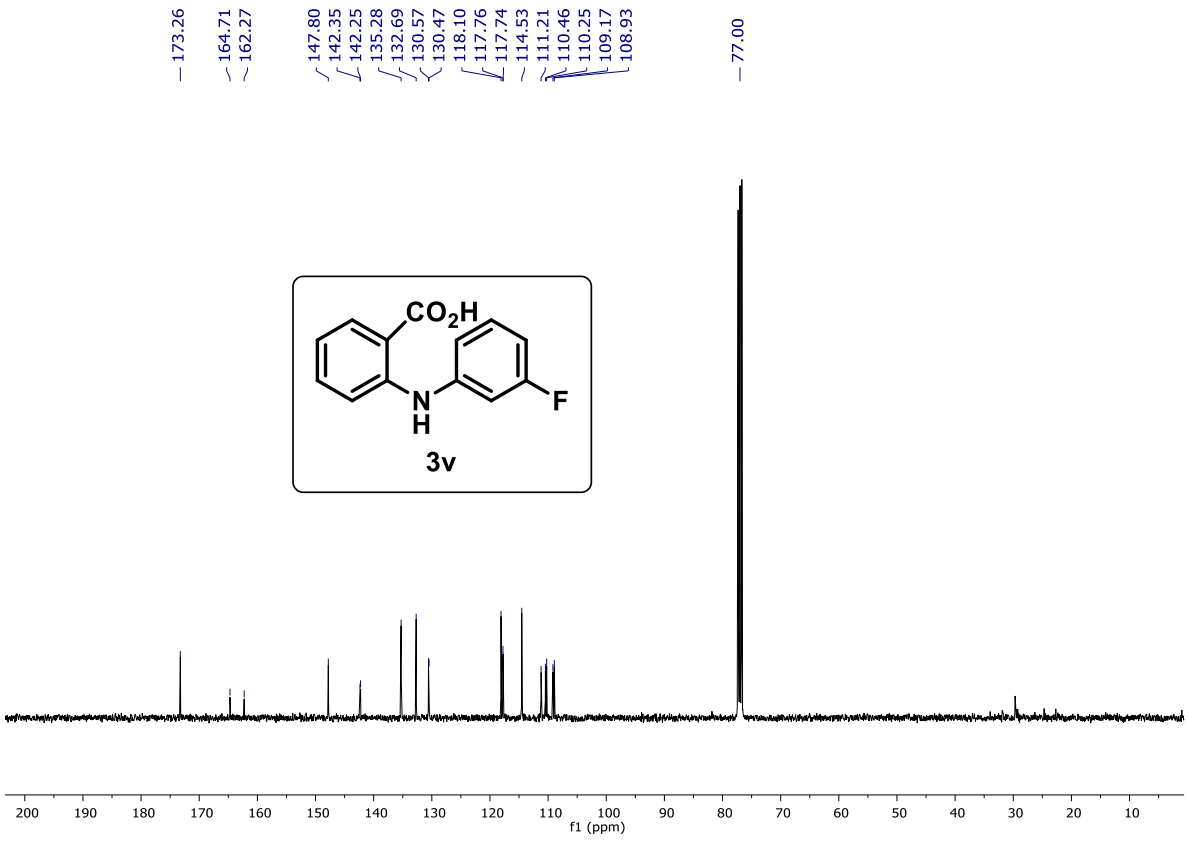
^{13}C NMR of **3u** (100 MHz, $CDCl_3$)



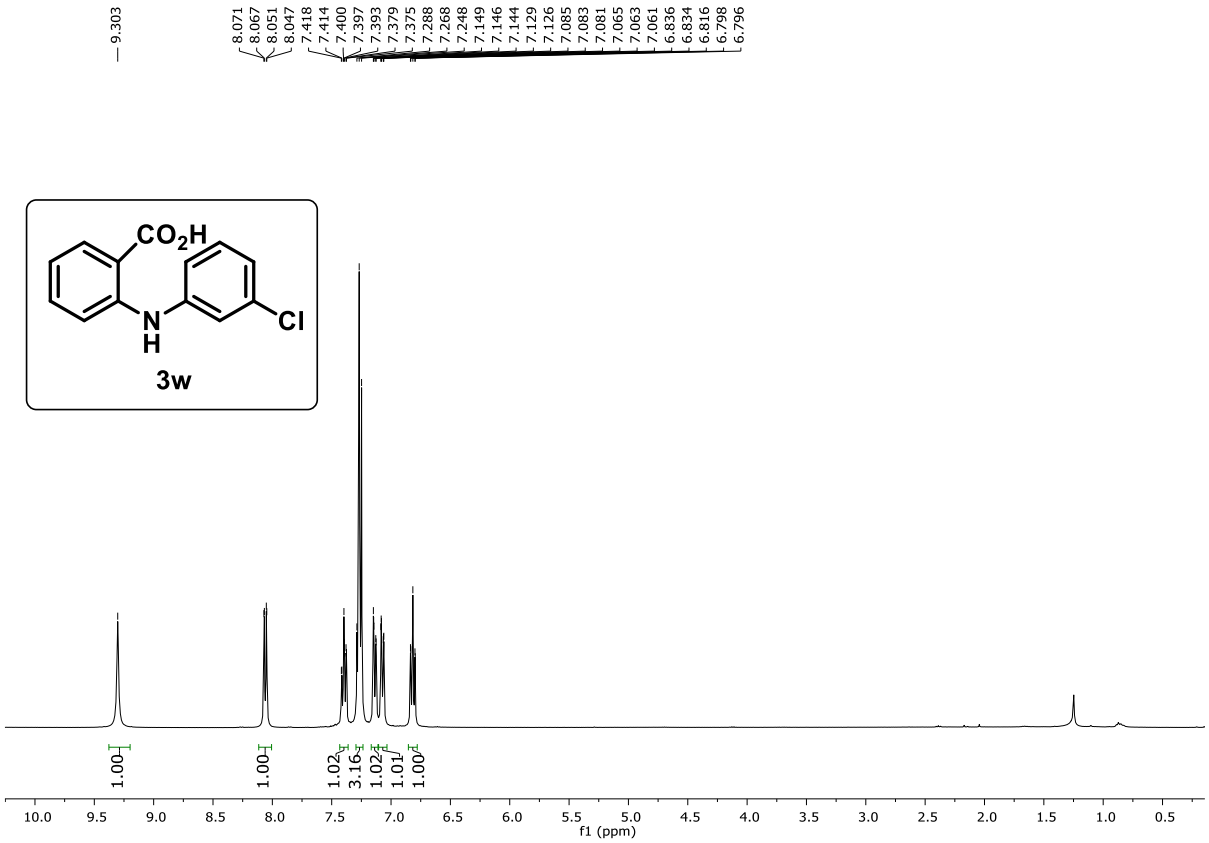
^{1}H NMR of **3v** (400 MHz, Chloroform-*d*)



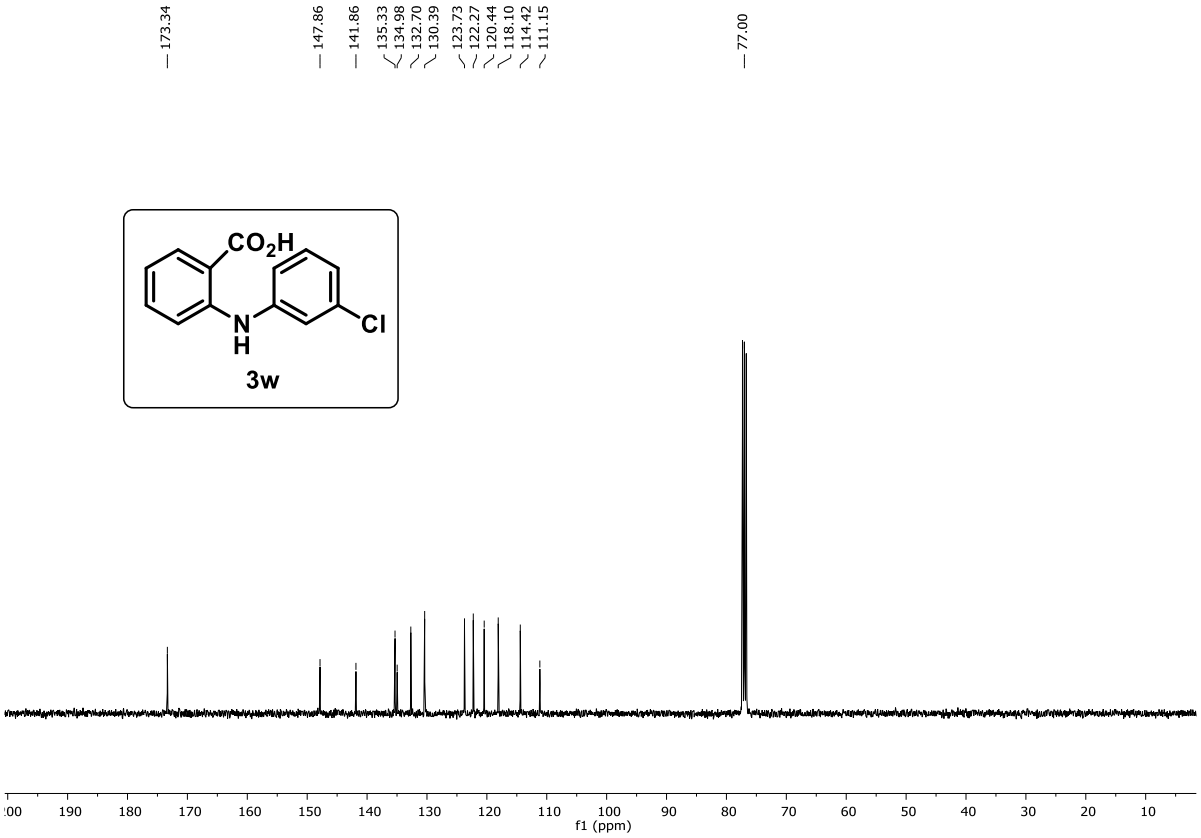
^{13}C NMR of **3v** (100 MHz, $CDCl_3$)



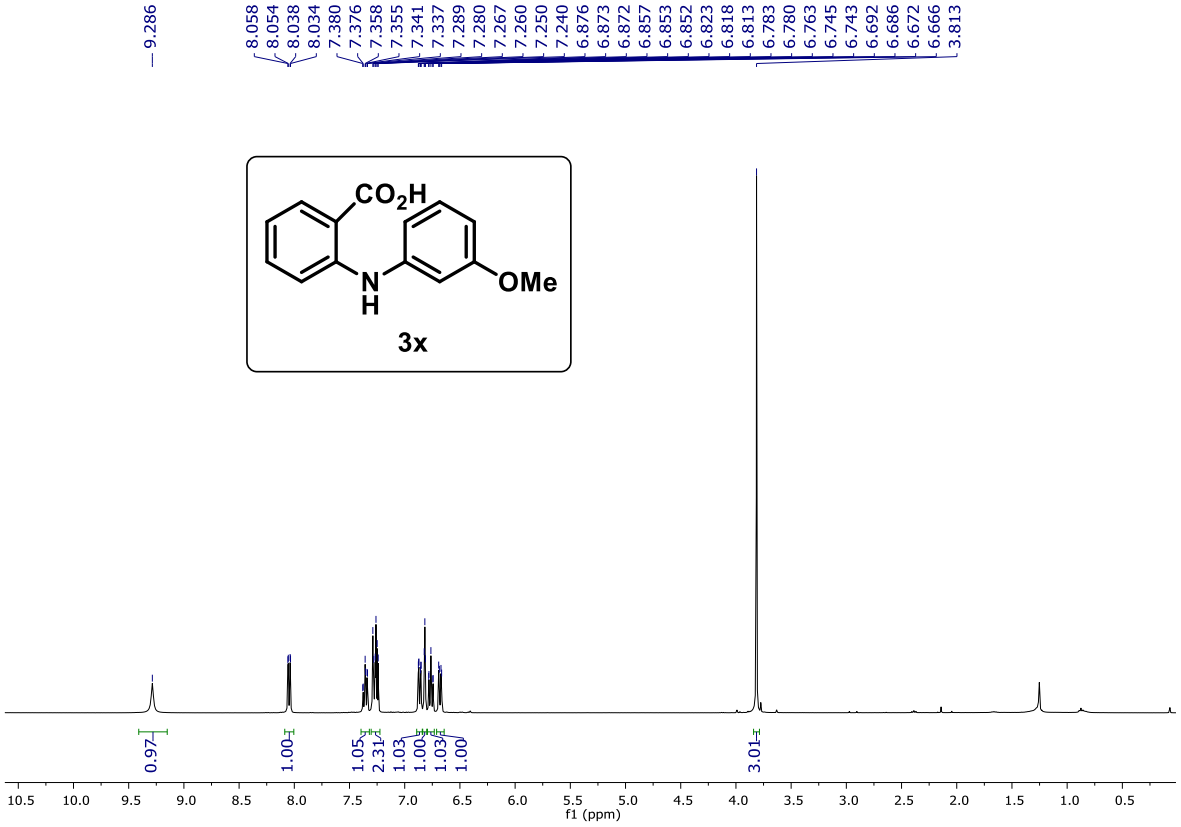
^{1}H NMR of **3w** (400 MHz, Chloroform-*d*)



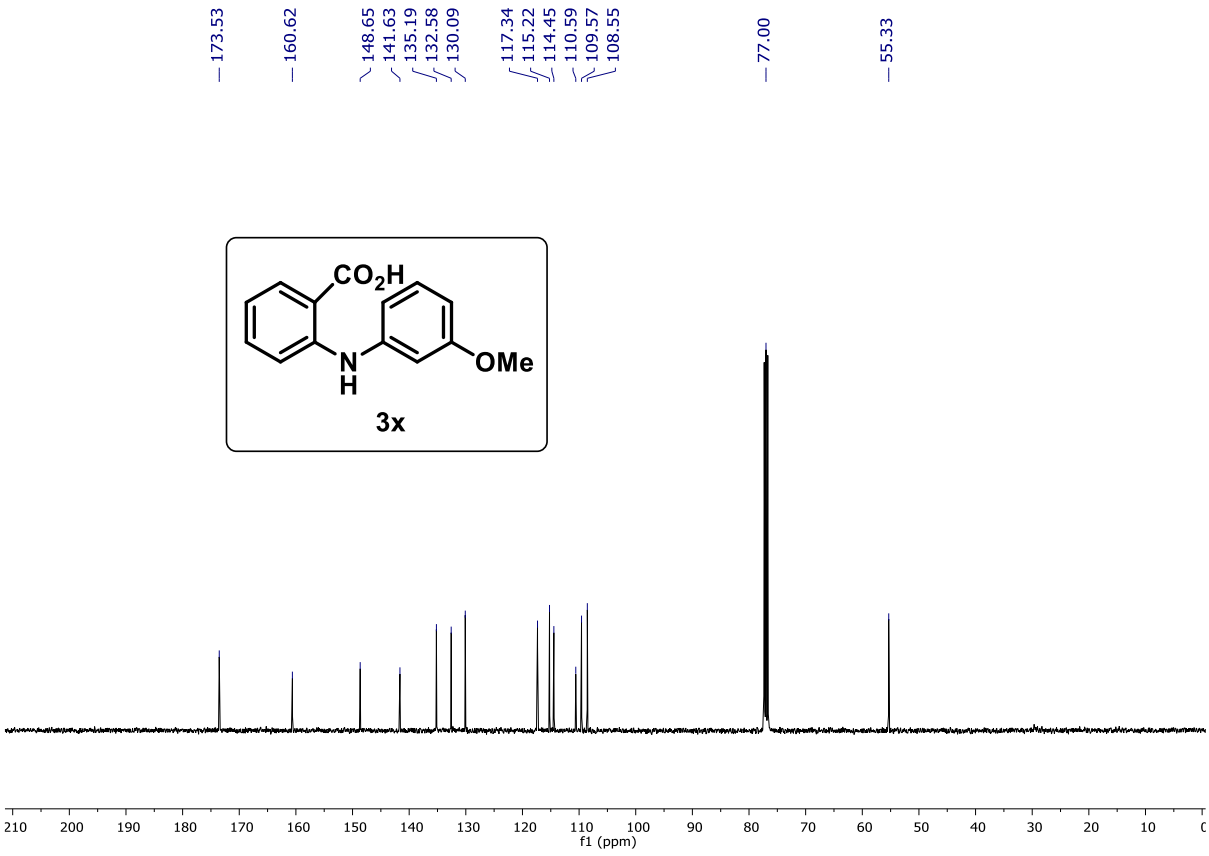
^{13}C NMR of **3w** (100 MHz, $CDCl_3$)



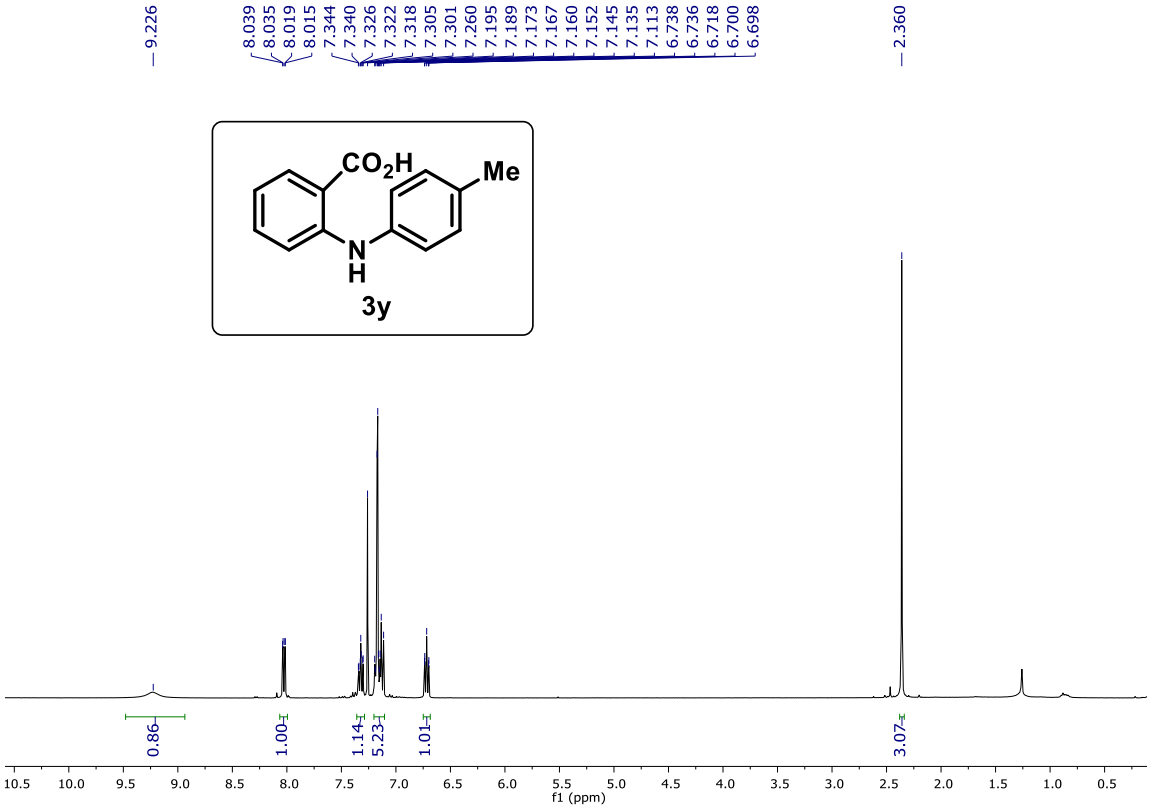
^{1}H NMR of **3x** (400 MHz, Chloroform-*d*)



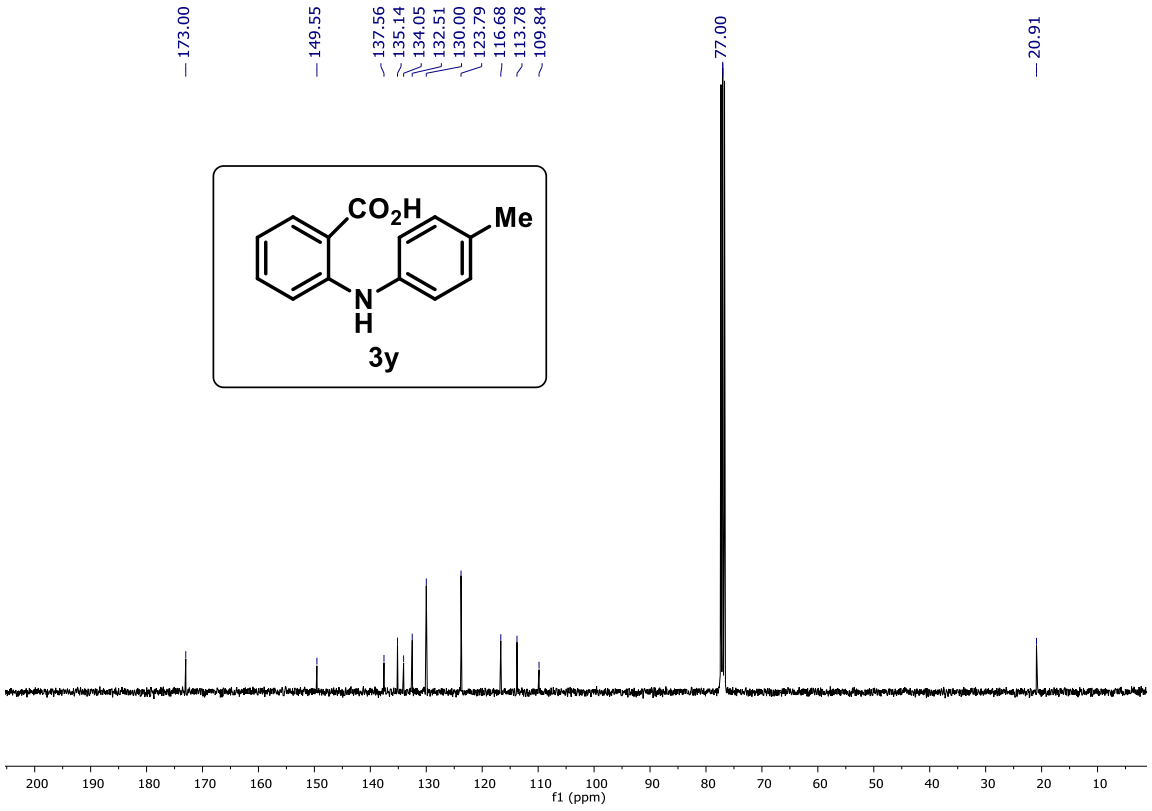
^{13}C NMR of **3x** (100 MHz, $CDCl_3$)



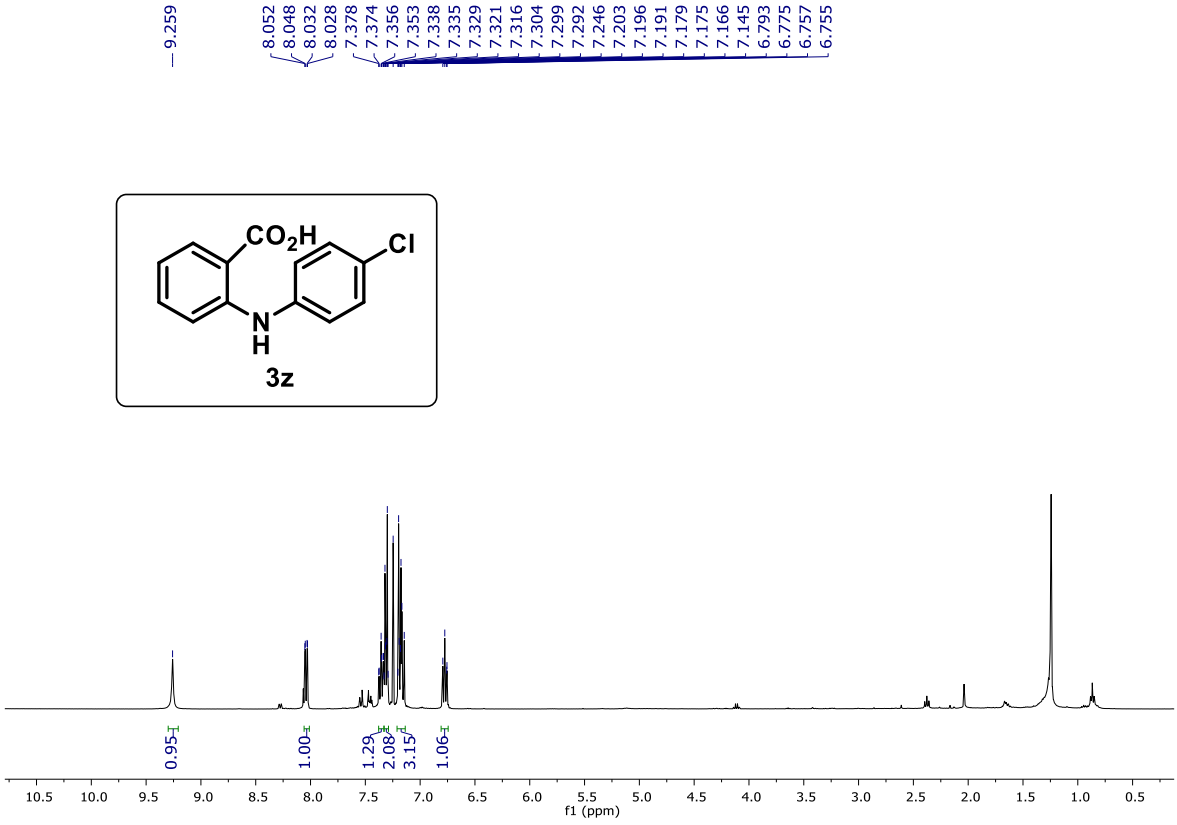
^{1}H NMR of **3y** (400 MHz, Chloroform-*d*)



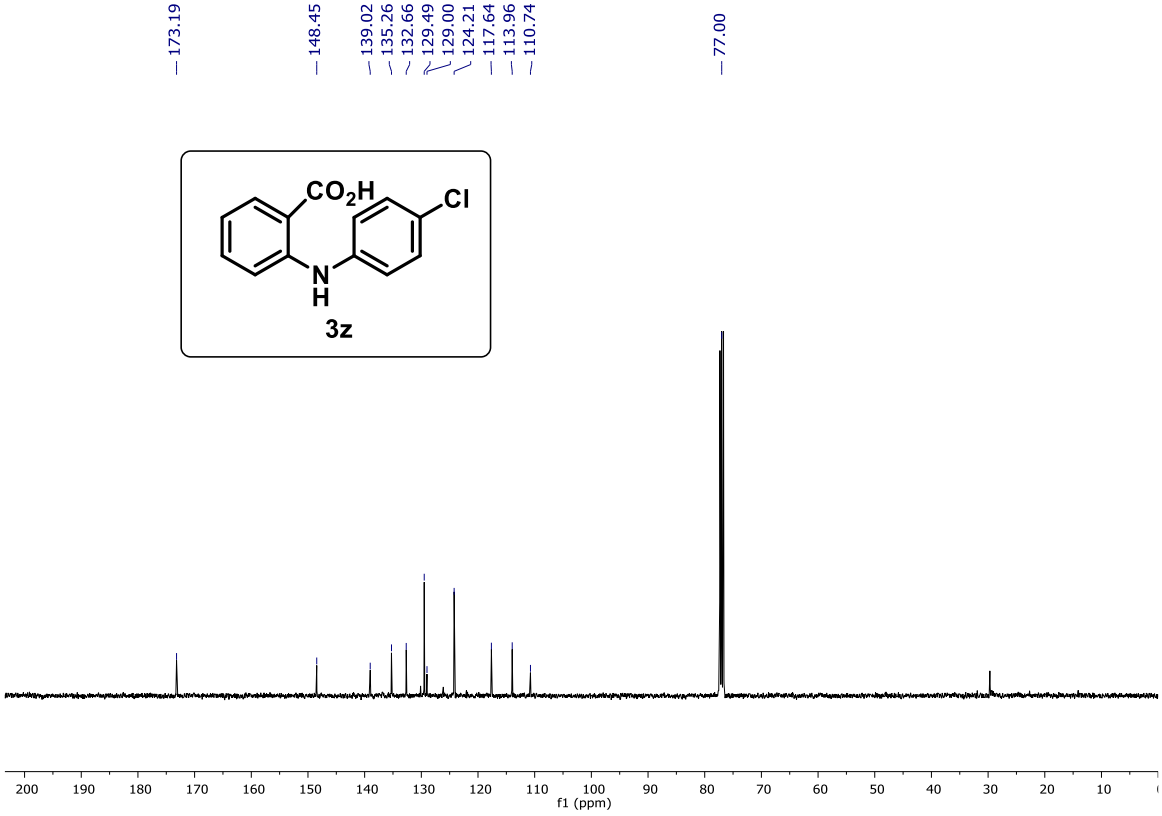
^{13}C NMR of **3y** (100 MHz, $CDCl_3$)



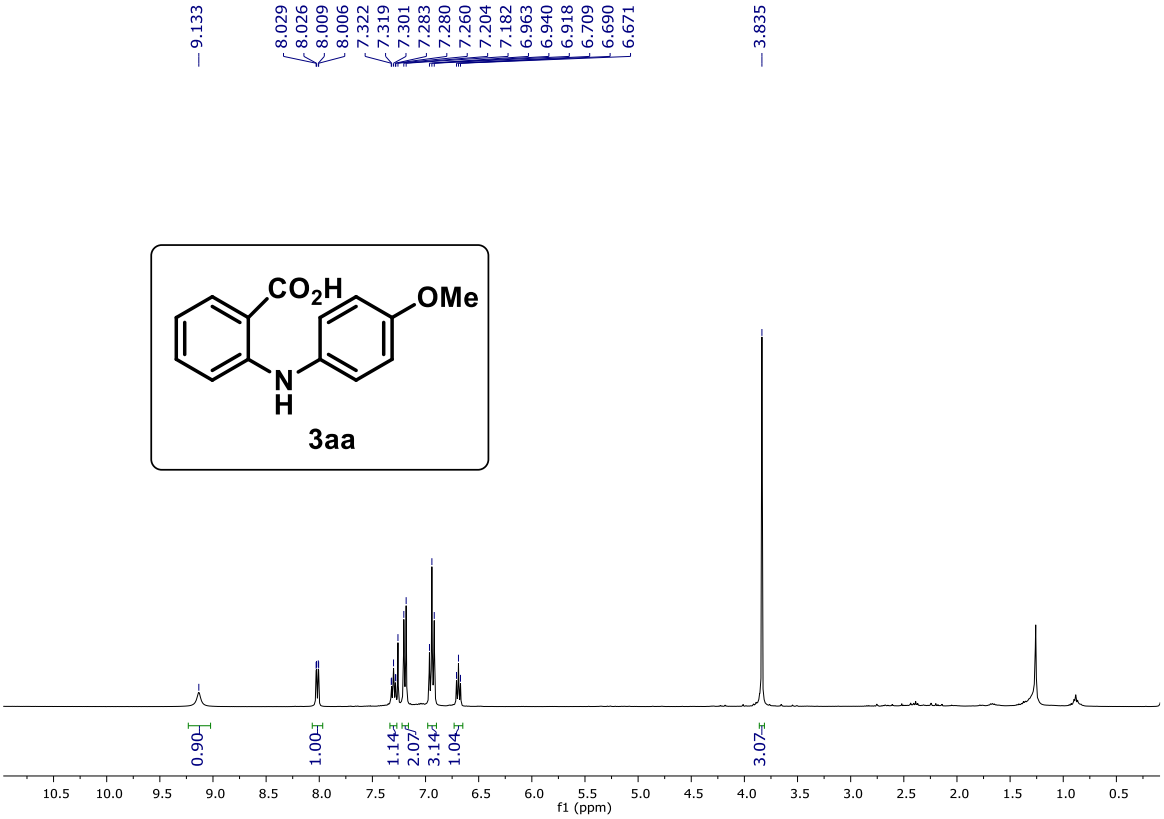
^{1}H NMR of **3z** (400 MHz, Chloroform-*d*)



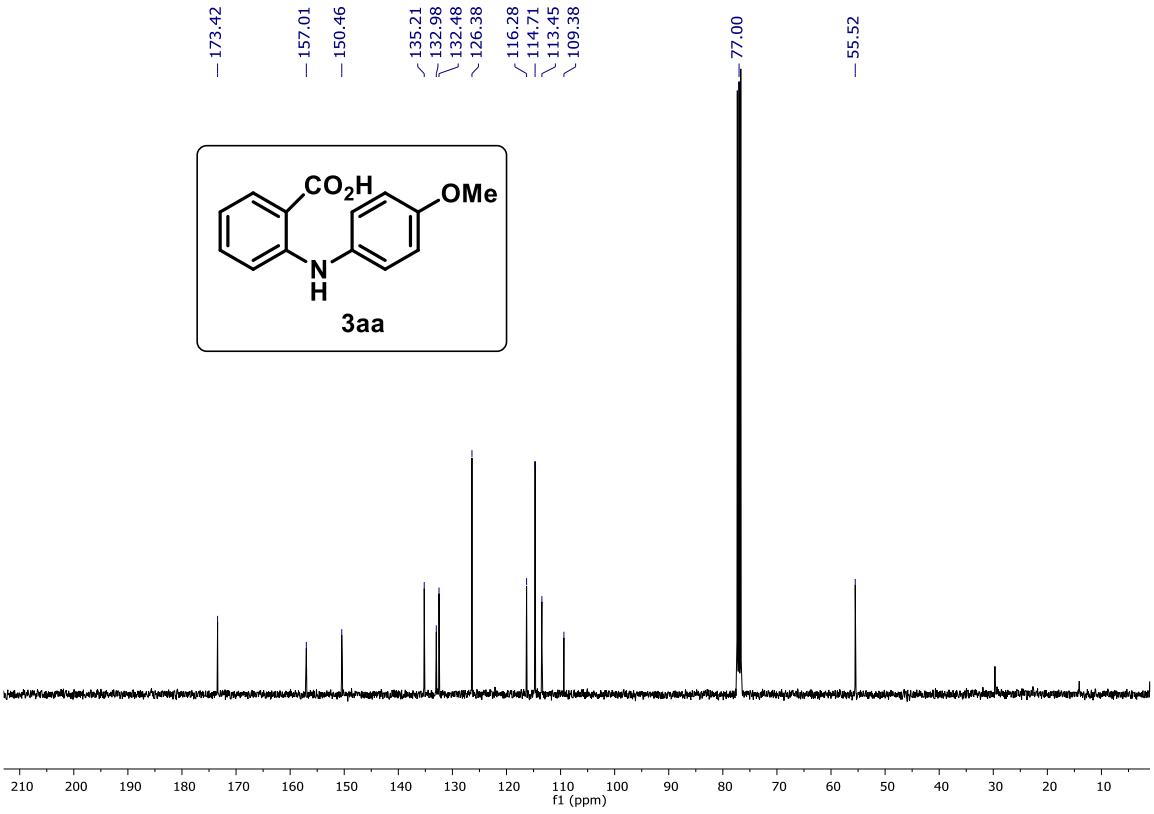
^{13}C NMR of **3z** (100 MHz, $CDCl_3$)



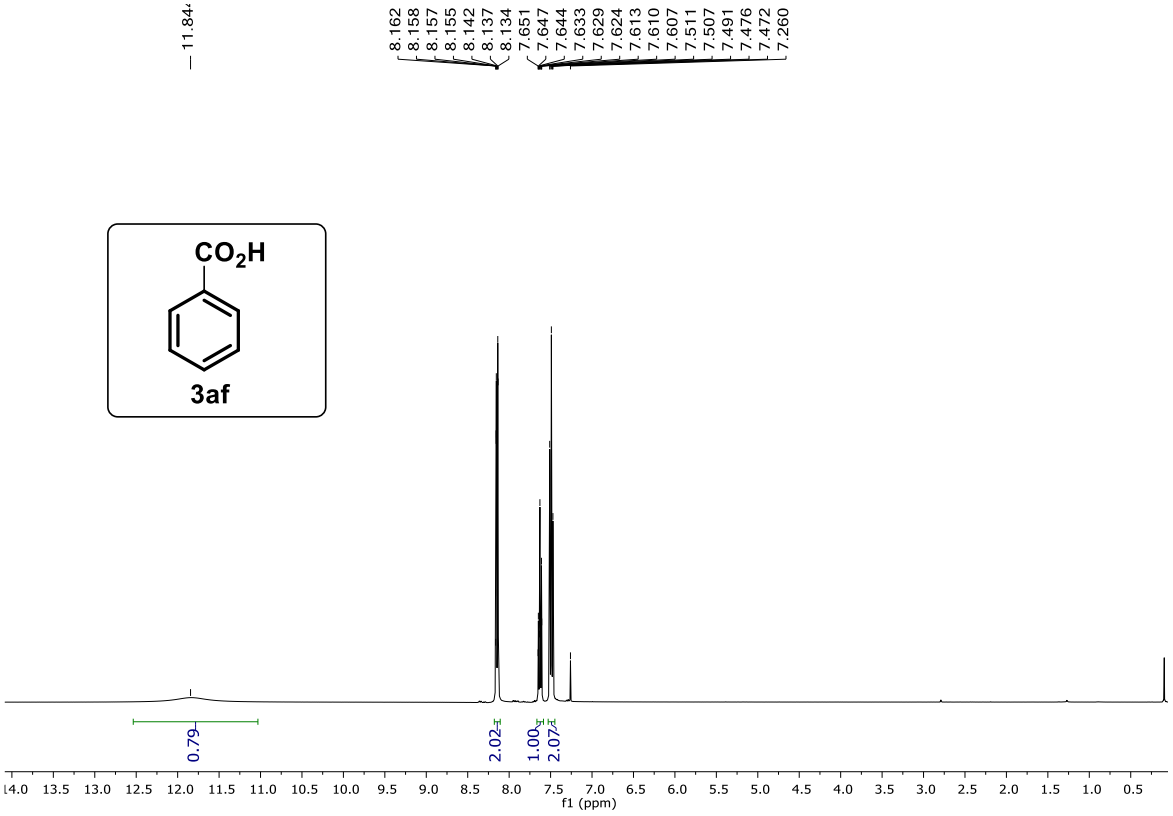
^{1}H NMR of **3aa** (400 MHz, Chloroform-*d*)



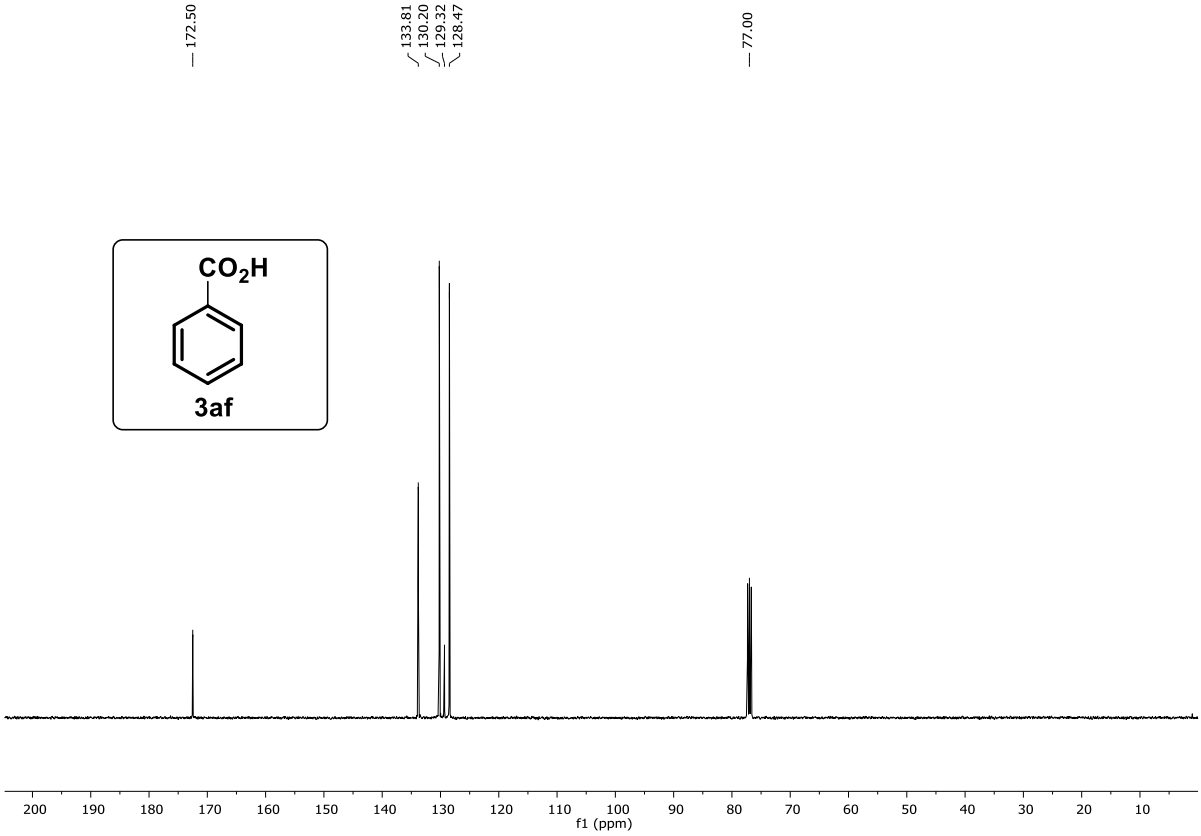
^{13}C NMR of **3aa** (100 MHz, $CDCl_3$)



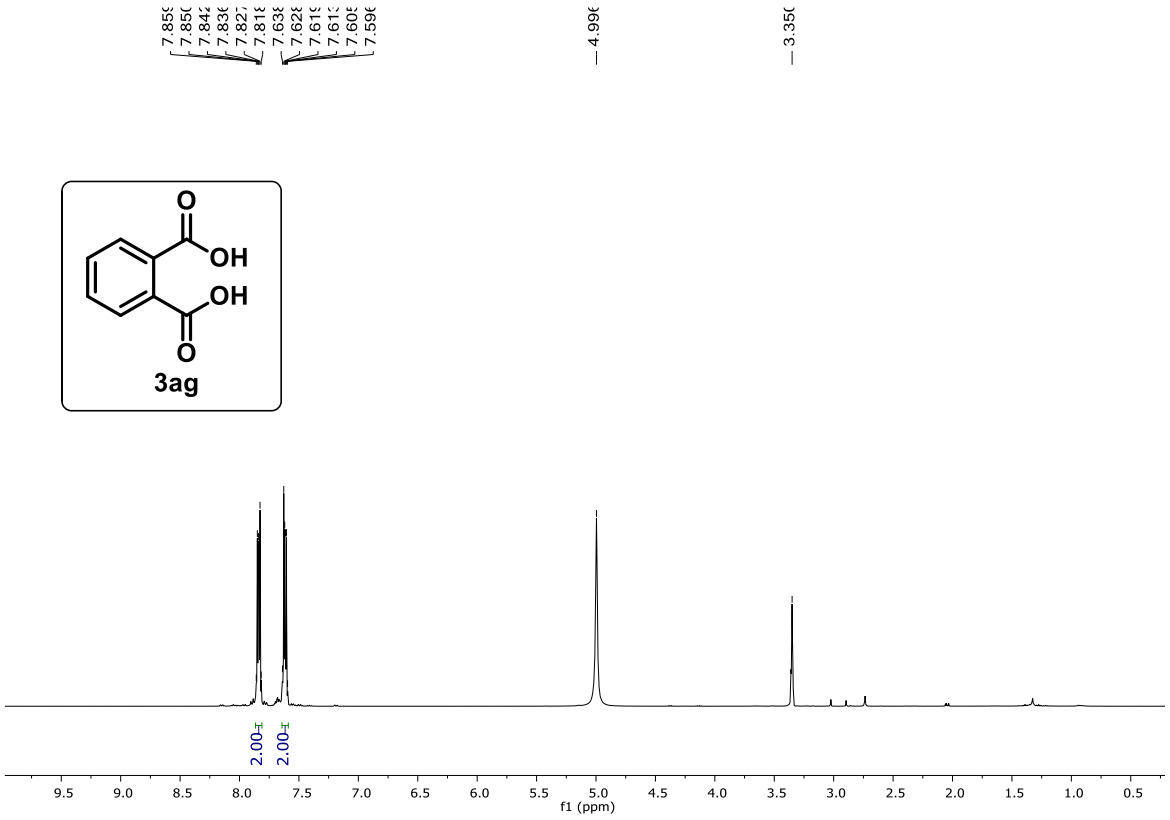
^{1}H NMR of **3af** (400 MHz, Chloroform-*d*)



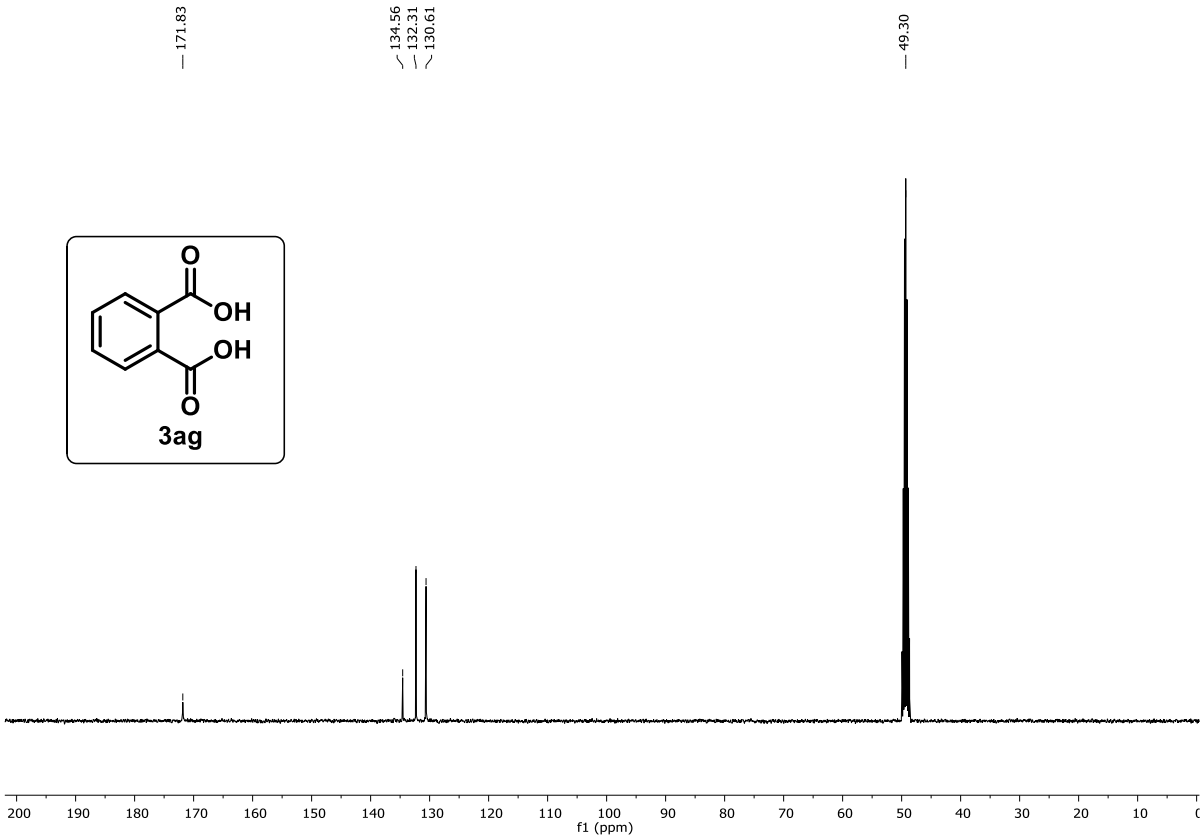
^{13}C NMR of **3af** (100 MHz, $CDCl_3$)



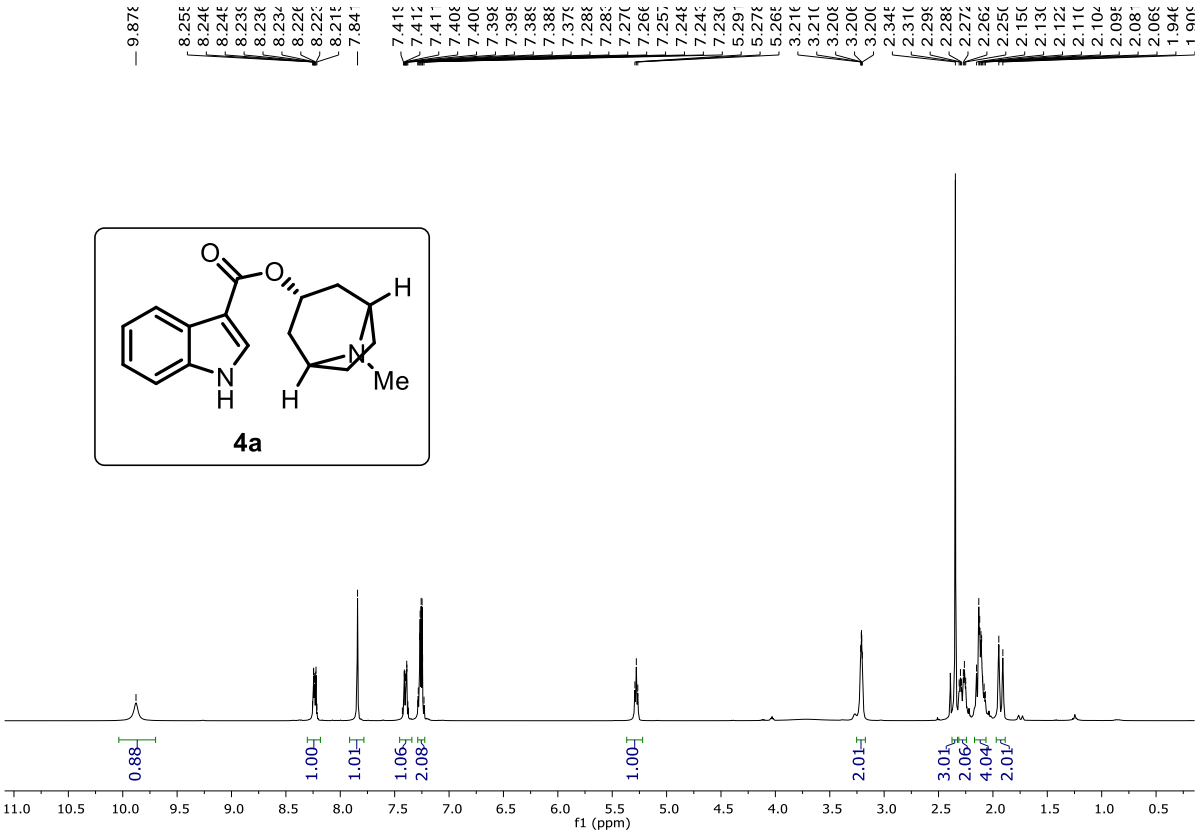
^{1}H NMR of **3ag** (400 MHz, Chloroform-*d*)



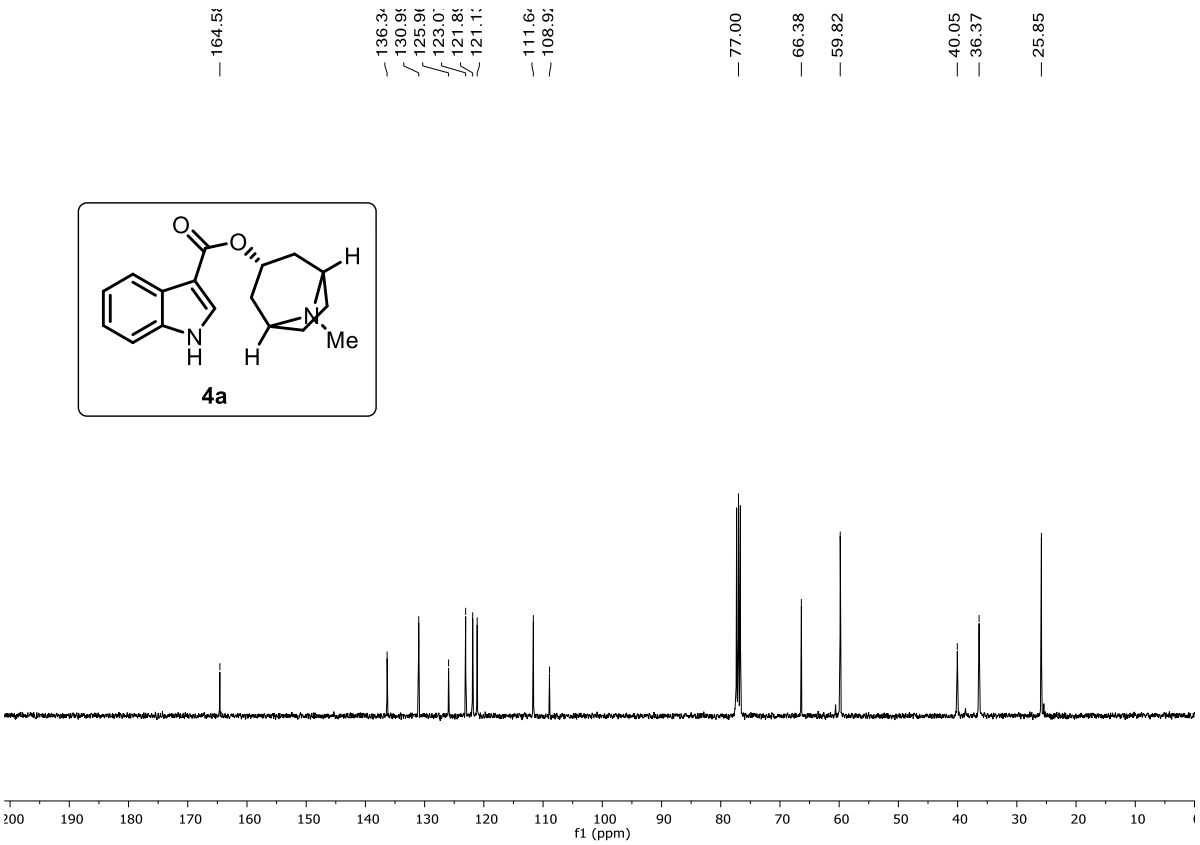
^{13}C NMR of **3ag** (100 MHz, $CDCl_3$)



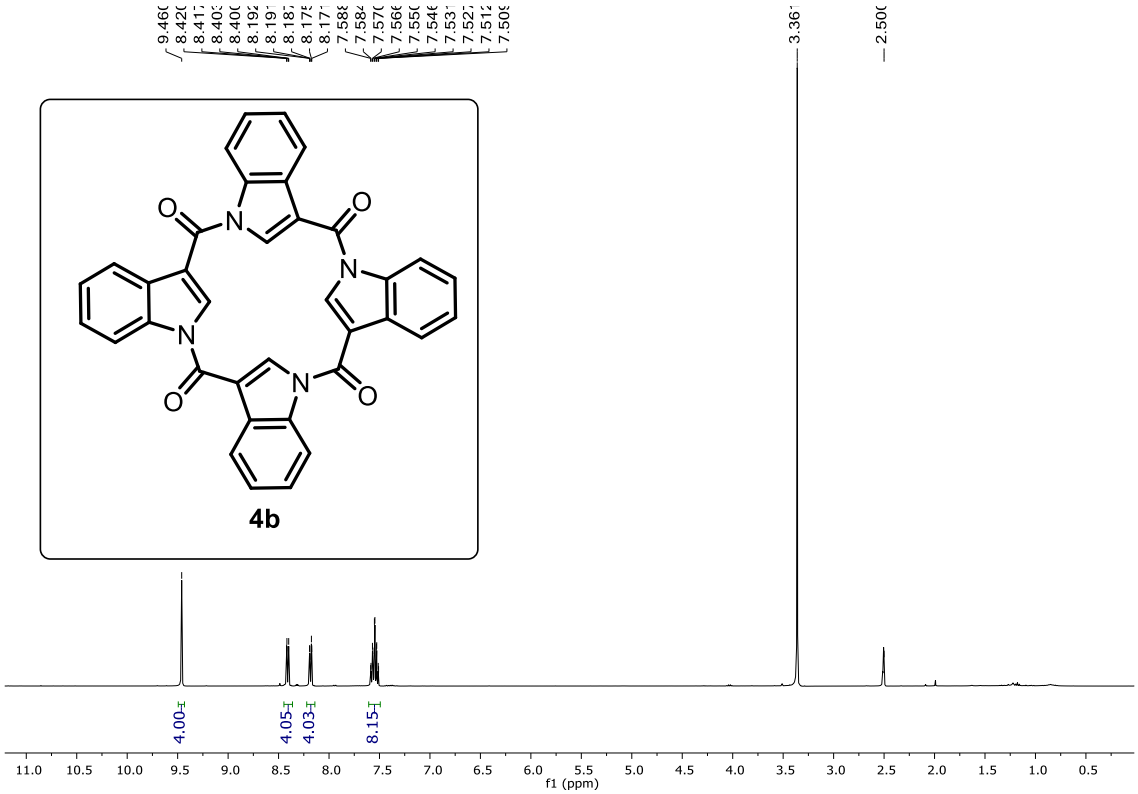
^{1}H NMR of **4a** (400 MHz, Chloroform-*d*)



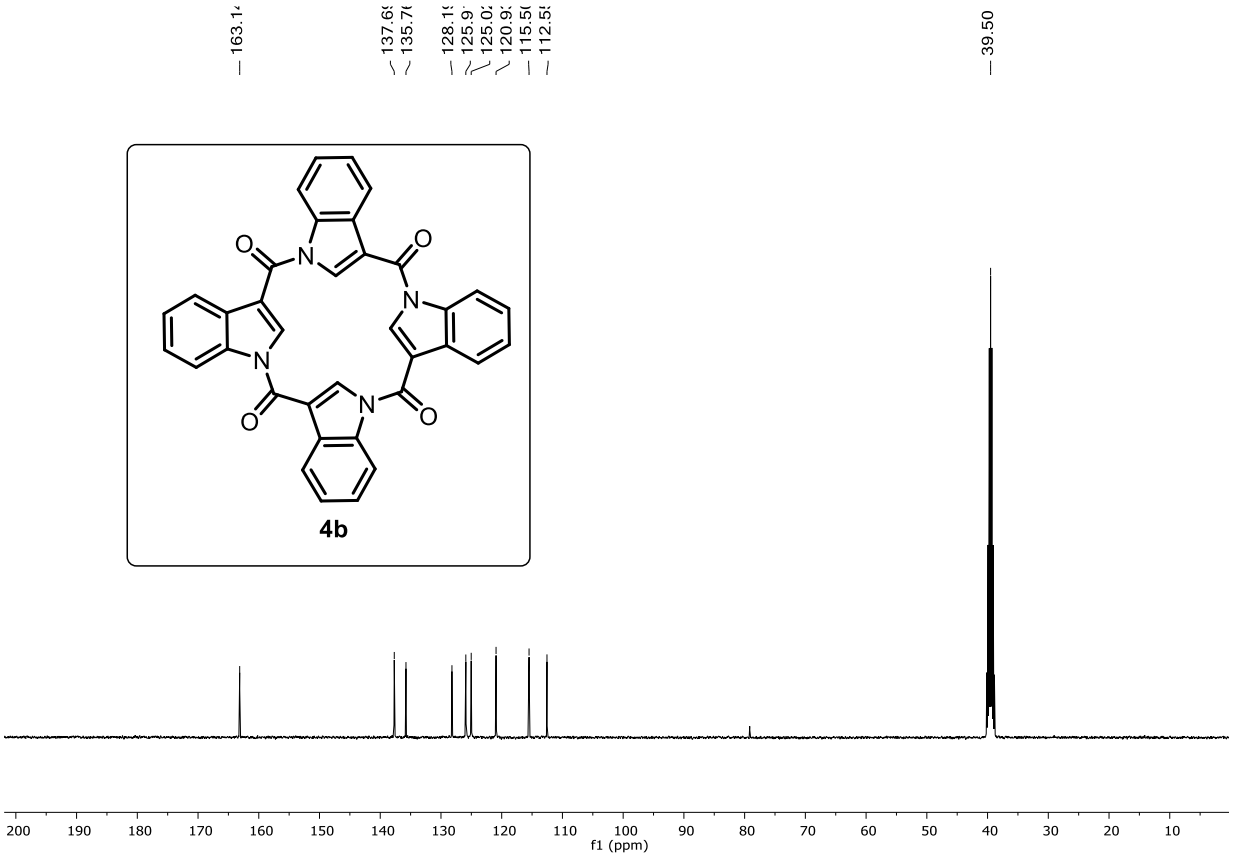
^{13}C NMR of **4a** (100 MHz, $CDCl_3$)



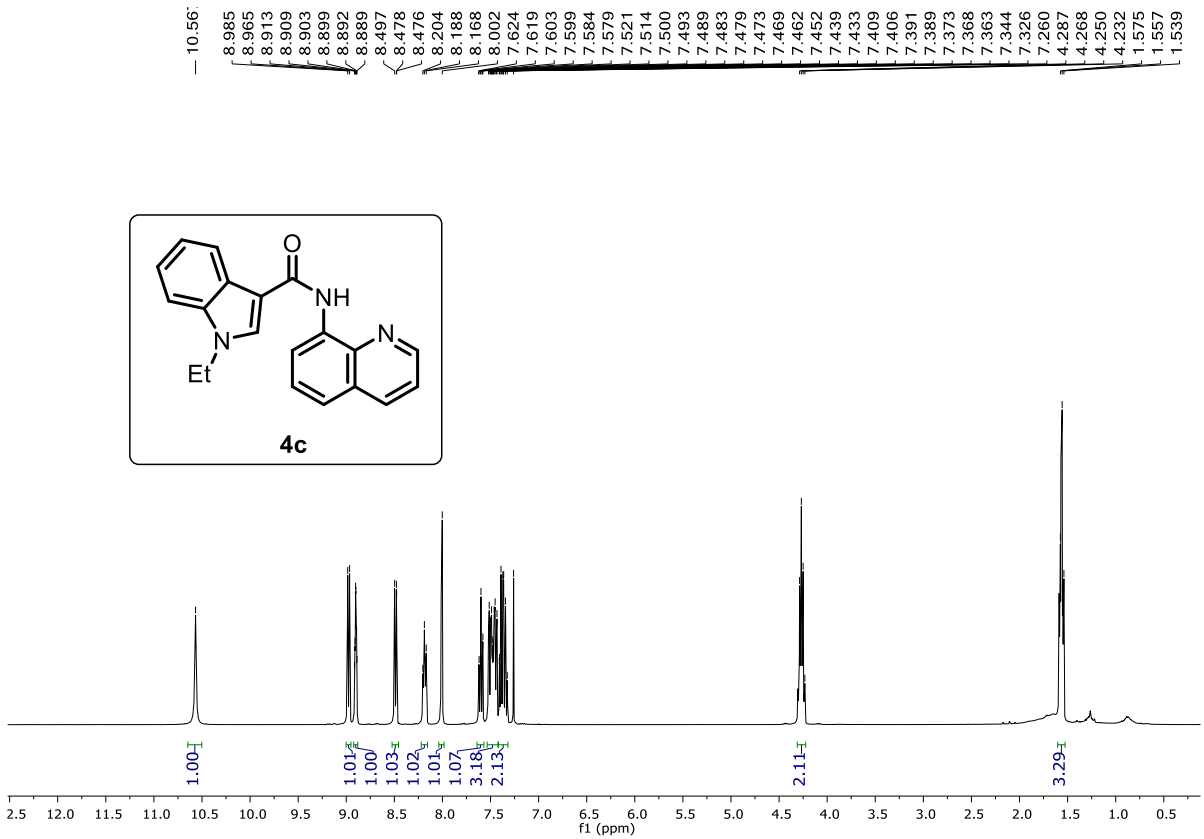
^{1}H NMR of **4b** (400 MHz, DMSO-d_6)



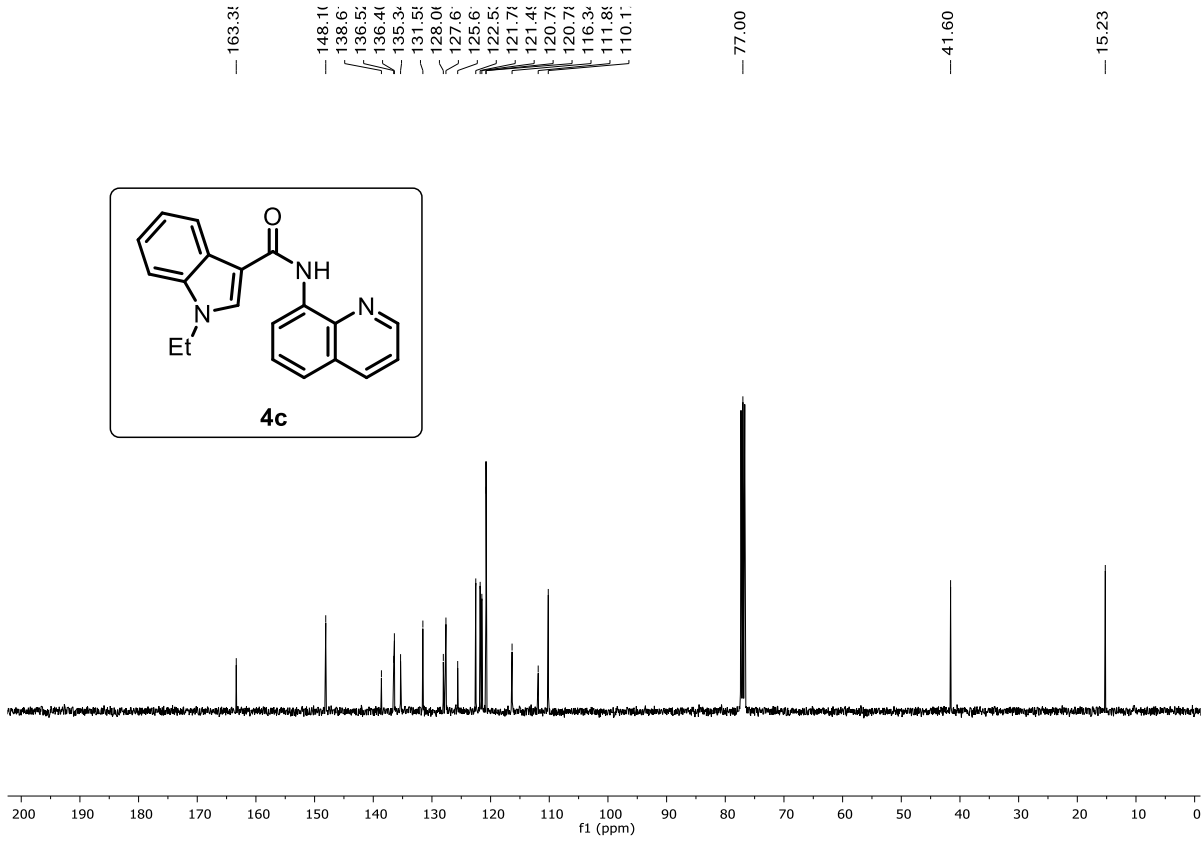
^{13}C NMR of **4b** (100 MHz, DMSO-d_6)



^{1}H NMR of **4c** (400 MHz, Chloroform-*d*)

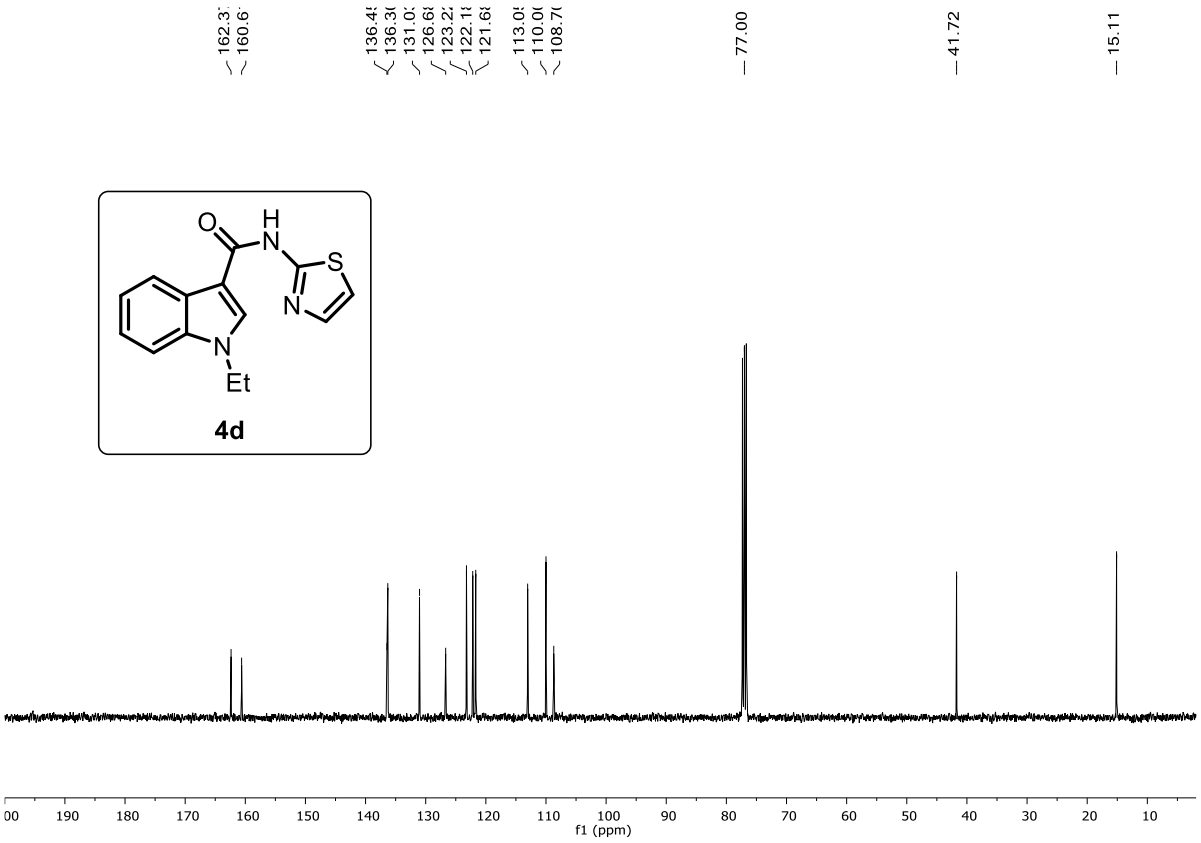


^{13}C NMR of **4c** (100 MHz, $CDCl_3$)

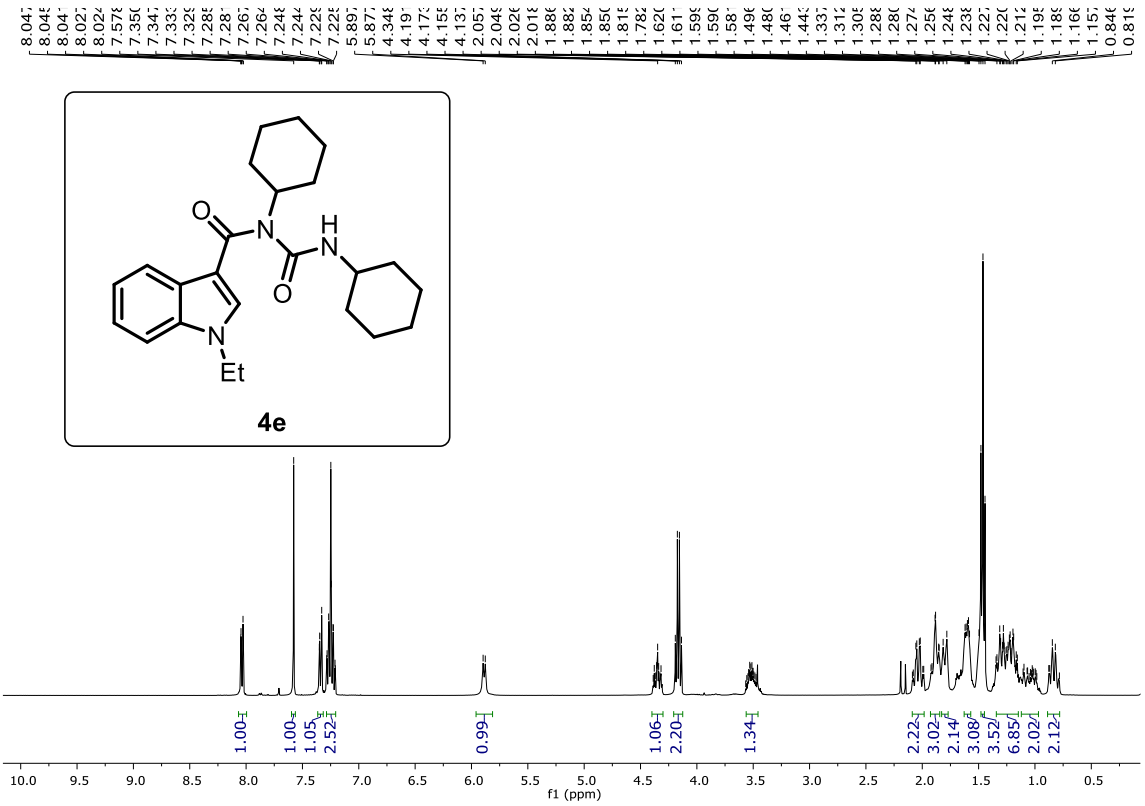


^{1}H NMR of **4d** (400 MHz, Chloroform-*d*)

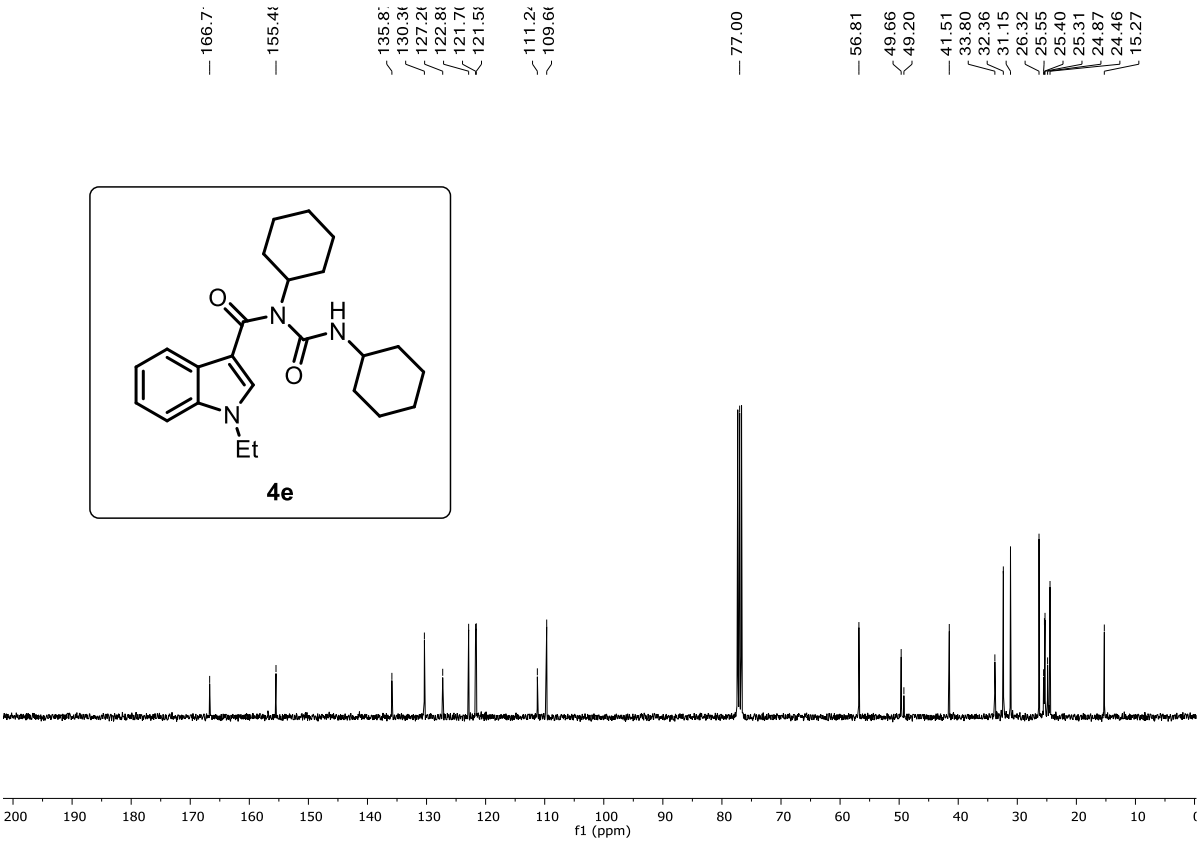
^{13}C NMR of **4d** (100 MHz, $CDCl_3$)



^{1}H NMR of **4e** (400 MHz, Chloroform-*d*)



^{13}C NMR of **4e** (100 MHz, $CDCl_3$)



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