Supplementary Information (SI) for Reaction Chemistry & Engineering.

Supporting Information for

Fast Metal-free CO_2-Mediated *N*-Aryl Amide Synthesis from Nitroarenes and Carboxylic Acids under Continuous Flow Conditions

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1. General Information

All reagents and solvents were purchased from Sigma Aldrich and used as received unless otherwise stated.

The crude products were purified by flash column chromatography on silica gel (60 Å, 220-440 mesh, 35-75 µM). TLC analysis was performed using silica on TLC aluminium sheets (F254, Sigma Aldrich) with visualization under ultraviolet light (254 nm). Impervious graphite electrodes for electrochemical experiments were purchased from Mersen. For electrochemical experiments a Hikari DC HF-3203S power supply was used. Teflon AF 2400 tubing for the tube-in-tube reactor was purchased from Biogeneral. Other tubing and flow chemistry parts were purchased from IDEX Health & Science. A Vapourtec R-Series instrument was used for all additional experiments.

NMR ^{1}H (500 MHz or 600 MHz), ^{13}C{1H} (150 MHz or 125 MHz), ^{19}F (470 MHz) spectra were recorded at ambient temperature using a Bruker Avance III 500 MHz (5 mm BBO S2 probe) or a Bruker Avance NEO 600 MHz (5 mm CryoProbe Prodigy TCI). ^{1}H NMR spectra are reported in parts per million (ppm) downfield relative to $CDCl_3$ (7.26 ppm) and DMSO-d6 (2.5 ppm) and all ^{13}C{^{1}H} NMR spectra are reported in ppm relative to $CDCl_3$ (77.16 ppm) and DMSO-d6 (39.52 ppm). The multiplicities of signals are designated by the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), m (multiplet), dd (doublet of doublets), dt (doublet of triplets), dq (doublet of quartets), ddd (doublet of doublet of doublets), td (triplet of doublets), tt (triplet of triplets). Coupling constants (*J*) are reported in hertz (Hz). NMR data was processed using Bruker TopSpin 3.7.0 and MestReNova 14 software package. Known products were characterized by comparing to the corresponding ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR with those available in the literature.

High resolution mass spectra (HRMS) were collected on an Orbitrap Thermo QExactive Mass Spectrometer.

Melting points were measured using a Mettler Toledo MP50 Melting Point System and are uncorrected. We adopted the following convention: when the compound melts without decomposition we used “m.p. x-y °C”; when the compound decomposes (turns black) before melting we used “decomposition > x °C”. When the compound melts and decomposes at the same time, we used “ m.p. x-y °C, dec”.

Infrared Spectroscopy spectra were obtained on a Thermo Nicolet iS5 FT-IR with an iD3 ATR accessory containing a ZnSe crystal. Spectra were processed using OMNIC Spectroscopy Software. FT-IR spectra are reported in cm-1. Peaks are recorded as s (strong), m (medium), w (weak), and sh (shoulder).

2. Instrument Setup and Reaction Design

For the initial step of the optimization and scope evaluation, the electrochemical microflow cell developed by the Noël Research Group was employed. It contains two impervious graphite electrodes (120x55x2 mm), separated by a PTFE gasket of 250 µm thickness divided in 8 channels (106x3 mm per channels), which equates to 750 µL of active internal reactor volume. The electrodes are housed by PTFE plates containing the electrical connection. The plates are then screwed shut using steel plates. The cell is then connected to the power source.

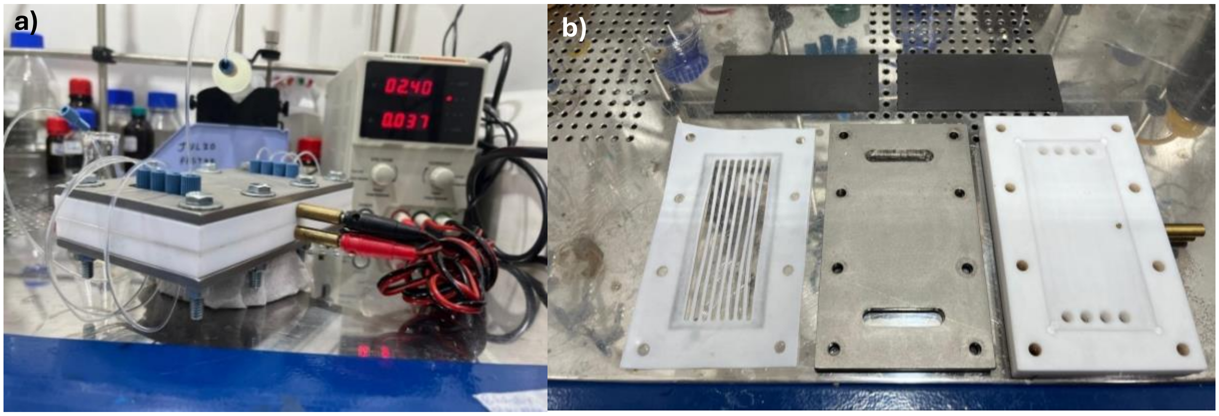


Fig. S1. a) Assembled electrochemical microflow cell; b) Deconstructed cell.

Noël e De Oliveira's groups[1] demonstrated a paired electrochemical process in a microflow cell for the quantitative synthesis of iminophosphorane **3a** from 4-nitrobenzonitrile (**1a**) and triphenylphosphine in the presence of catalytic trifluoroacetic acid (TFA). In this protocol, the crude mixture containing residual TFA was subsequently treated with CO_2 in a tube-in-tube reactor, affording *N*-(4-cyanophenyl)-2,2,2-trifluoroacetamide in 65% yield. To broaden the scope of this method to include a wider range of carboxylic acid derivatives, we investigated amide synthesis using alternative carboxylic acids. However, when electronically neutral phenylacetic acid (**4a**) was employed as the substrate, the expected amide was not obtained. Instead, the reaction yielded exclusively the TFA-derived amide. To circumvent competitive reactions associated with TFA, we evaluated alternative acid catalysts capable of efficiently driving the electrochemical transformation without interfering with the subsequent amidation step. Methanesulfonic acid emerged as a suitable substitute, preserving the efficiency of the electrochemical process. However, when the crude mixture was exposed to CO_2 in the presence of phenylacetic acid (**4a**), no further conversion of **3a** was observed, indicating the necessity of neutralizing the crude prior to amidation. Consequently, the electrochemical product was extracted with a saturated sodium bicarbonate solution to remove the catalytic acid ($MeSO_3H$) from the reaction medium. Later, triethylamine (Et_3N) was employed for the amidation step to neutralize the catalytic acid *in-situ*, without the need for a work-up step. Allowing for utilization of the crude electrolyzed product as is.

For the amidation step of the optimization and scope evaluation, a Vapourtec R-Series System was employed. A 1.4 bar (20 psi) back pressure regulator (BPR) was placed in line before a Teflon AF 2400 (i.d.: 0.8 mm) housed by PTFE tubing (i.d.: 1.59 mm) tube in tube reactor (V=1 mL), followed by a heated 10 mL PFA reactor (i.d.: 0.79 mm), then pressurized with an 8.4 bar (120 psi) BPR before the collection flask.

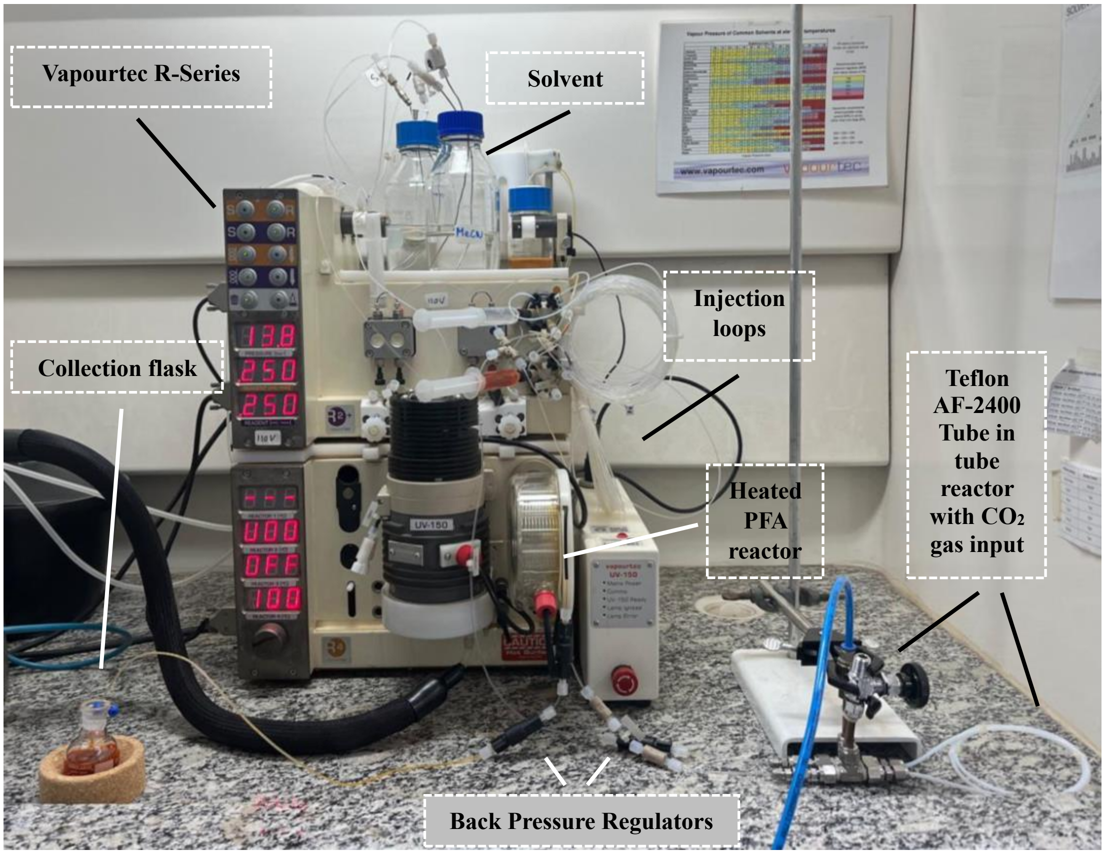
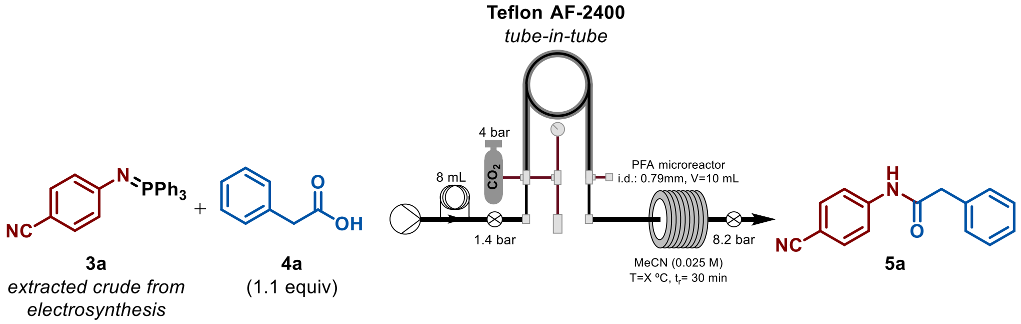


Fig. S2. a) Instrument setup for amidation reaction.

3. Reaction Optimization

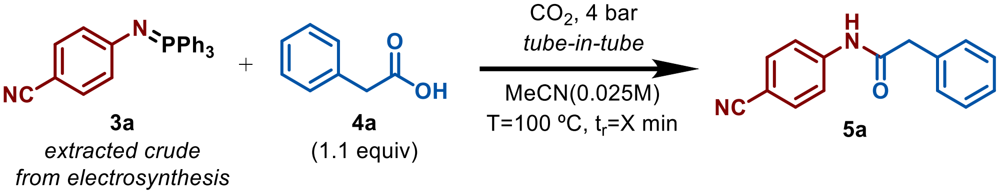
Table S1. Temperature Screening



Entry	Temperature (ºC)	Yield 5a (%)[a]
1	R.T.	23
2	50	44
3	65	56
4	80	65
5	**100**	**79**

A solution of extracted crude electrolyzed product **3a** (0.2 mmol), and **4a** (1.1 equiv.), in acetonitrile (0.025 M) was loaded into an injection loop (8 mL) and pumped at 0.333 mL•min^{-1} through a Teflon AF 2400 tube-in-tube reactor loaded with 4 bar of CO_2, followed by a PFA reactor (i.d.: 0.79 mm) heated to the temperatures above. [a] Yields determined by ^{1}H NMR analysis using dibromomethane as an internal standard.

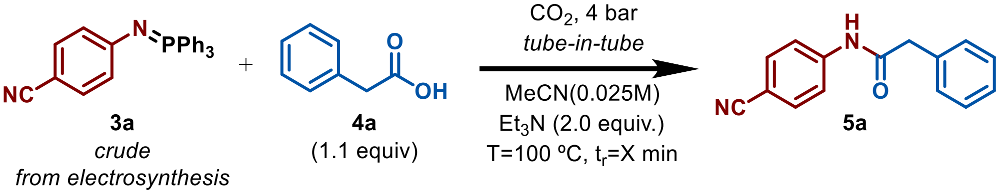
Table S2. Residence time screening



Entry	Residence Time / Flow Rate	Yield 5a (%)^{a}
1	60 min / 0.166 mL•min^{-1}	64
2	45 min / 0.222 mL•min^{-1}	73
3	30 min / 0.333 mL•min^{-1}	79
4	15 min / 0.666 mL•min^{-1}	78
5	**10 min / 1 mL•min^{-1}**	**81**
6	5 min / 0.5 mL•min^{-1}	31

A solution of extracted crude electrolyzed product **3a** (0.2 mmol), and **4a** (1.1 equiv.), in acetonitrile (0.025 M) was loaded into an injection loop (8 mL) and pumped at various flow rates through a Teflon AF 2400 tube-in-tube reactor loaded with 4 bar of CO_2, followed by a PFA reactor (i.d.: 0.79 mm) heated to 100 ºC. ^{a} Yields determined by ^{1}H NMR analysis using dibromomethane as an internal standard.

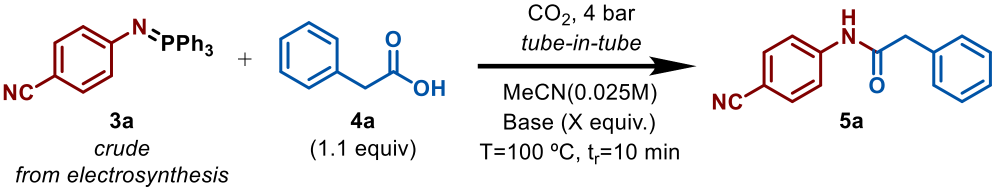
Table S3. Integrated setup residence time screening



Entry	Base (2.0 equiv.)	Residence Time	Yield 5a (%)^{a}
1	Et_3N	5 min.	50
2	**Et_3N**	**10 min.**	**80**
3	Et_3N	15 min.	72
4	-	10 min	16

A solution of crude electrolyzed product **3a** (0.2 mmol), **4a** (1.1 equiv.), and Et_3N (200 mol%), in acetonitrile (0.025 M) was loaded into an injection loop (8 mL) and pumped at various flow rates through a Teflon AF 2400 tube-in-tube reactor loaded with 4 bar of CO_2, followed by a PFA reactor (i.d.: 0.79 mm) heated to 100 ºC. ^{a} Yields determined by ^{1}H NMR analysis using dibromomethane as an internal standard.

Table S4. Base Screening



Entry	Base	Equivalents	Yield 5a (%)[a]
1	Et_3N	2.0	80
2	DBU	2.0	12
3	DABCO	2.0	39
4	DIPEA	2.0	58
5	2,6-Lutidine	2.0	54
6	Pyridine	2.0	32
7	Imidazole	2.0	32
8	TMG	2.0	21
9	Et_3N	1.0	81
10	**Et_3N**	**0.5**	**81 (75)**[b]
11	Et_3N	0.25	29
12	DMAP	0.5	33
13	Piperidine	0.5	traces

A solution of crude electrolyzed product **3a** (0.2 mmol), **4a** (1.1 equiv.), and various bases in acetonitrile (0.025 M) was loaded into an injection loop (8 mL) and pumped at 1.0 mL•min^{-1} through a Teflon AF 2400 tube-in-tube reactor loaded with 4 bar of CO_2, followed by a PFA reactor (i.d.: 0.79 mm) heated to 100 ºC. [a] Yields determined by ^1H NMR analysis using dibromomethane as an internal standard. [b] Refers to isolated yield.

4. Table of Starting Materials

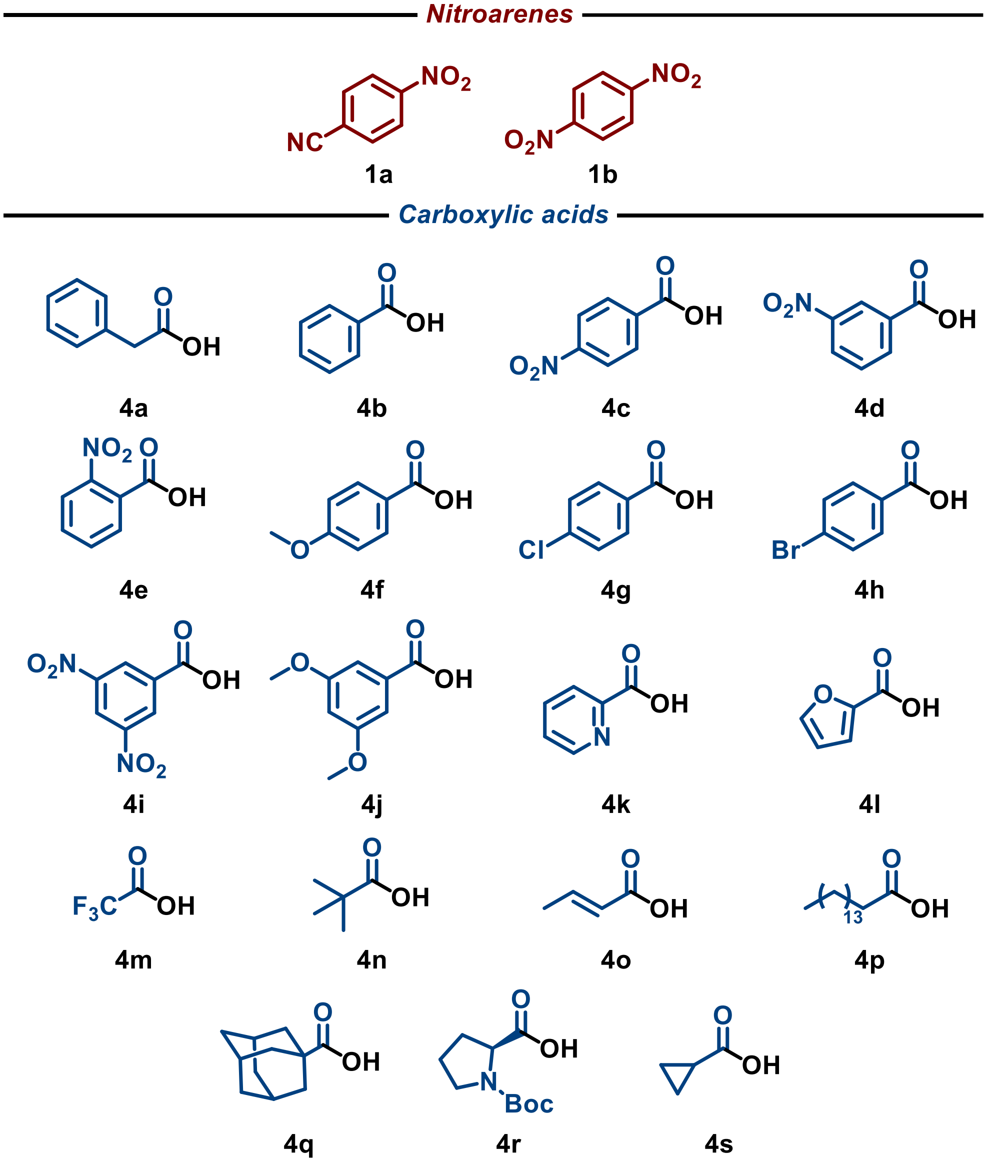


Fig. S3. Nitroarene and carboxylic acid starting materials.

5. Experimental Procedures

Synthesis of starting material

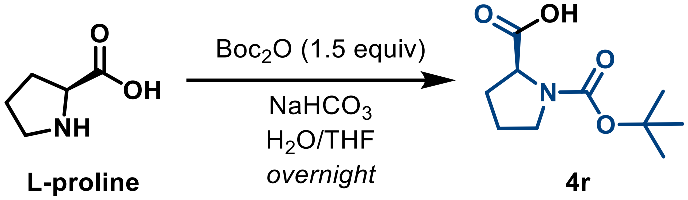
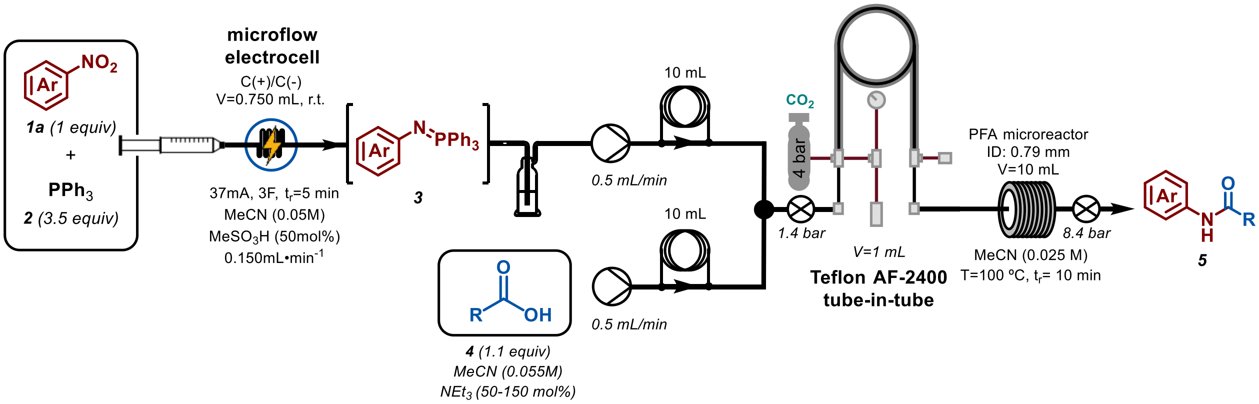


Fig S4. Synthesis of (tert-butoxycarbonyl)-L-proline.

Carboxylic acid **4r** (tert-butoxycarbonyl)-L-proline) was prepared by protecting **L-proline** with Boc₂O as according to the literature.[2] (tert-butoxycarbonyl)-L-proline is obtained as a mixture of rotamers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.66 (s, 1H), 4.28 (ddd, *J* = 57.3, 8.6, 3.8 Hz, 1H), 3.62 – 3.26 (m, 2H), 2.32 – 2.17 (m, 1H), 2.17 – 2.00 (m, 1H), 1.99 – 1.80 (m, 2H), 1.43 (d, *J* = 28.6 Hz, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.9, 175.9, 156.2, 154.0, 81.3, 80.5, 59.1, 59.0, 47.0, 46.4, 30.9, 29.0, 28.5, 28.4, 24.4, 23.8. Spectroscopic data are in accordance with the literature.[3]

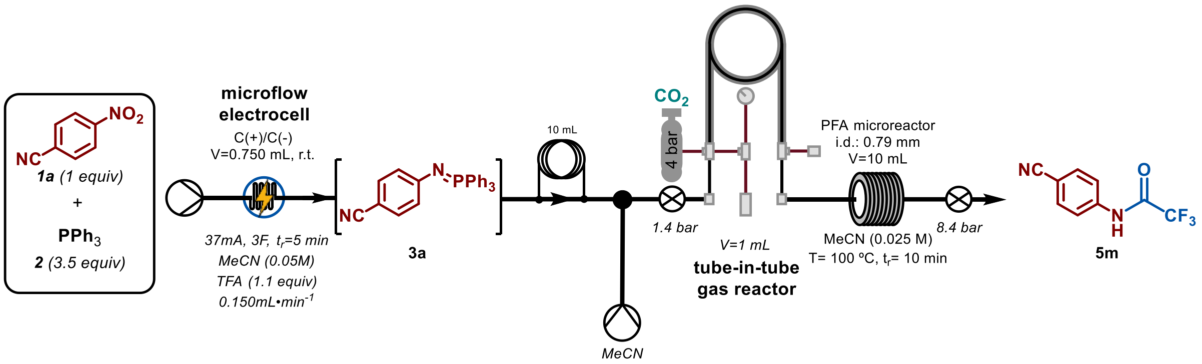
General procedure for amide synthesis



Adapted from Noël and De Oliveira, *et. al.*[30] A mixture of **1** (1.0 equiv., 1 mmol), triphenylphosphine (918 mg, 3.50 mmol, 3.5 equiv.), and methane sulfonic acid ($MeSO_3H$) (32.4 µL, 0.50 mmol, 50 mol%) in acetonitrile (0.05 M) was prepared in a 20 mL volumetric flask. The solution was aspirated with a syringe and mounted onto a syringe pump. It was pumped through the electrochemical microflow cell at 0.150 mL•min^{-1} (t_r= 5 min), operating in galvanostatic mode. The cell was equipped with impervious graphite electrodes and operated at 37 mA (3 F). Following electrolysis of 3 mL (corresponding to four residence times), the system reached steady state, allowing for product collection. The crude electrolyzed **3** is then aspirated with a syringe and loaded into a 10 mL (0.5 mmol) loop on a Vapourtec R-Series instrument. A mixture of **4** (0.6 mmol, 1.1 equiv.) and triethylamine (0.3-0.9 mmol, 50-150 mol%) in 12 mL of acetonitrile (0.055 M) was prepared then aspirated with a syringe and loaded into another 10 mL loop (0.5 mmol); excess solution was injected to ensure loops were completely filled. Each loop was connected to a 6-way valve with independent pumps and injected into a stream of acetonitrile at 0.5 mL•min^{-1}, where they met in a PEEK T-mixer. The mixed diluted solution (0.025 M) then continued at a flow rate of 1.0 mL•min^{-1} through a tube-in-tube reactor (V=1 mL) pressurized with 4 bar of CO_2, followed by a PFA coil reactor (V= 10 mL, t_r = 10 min, i.d.: 0.79 mm) heated to 100 ºC. The crude solution was collected in flask. The mixture was neutralized with a saturated solution of sodium bicarbonate (3 x 10 mL) to remove residual acids. The aqueous phase was back-extracted with ethyl acetate, organic phases combined and washed with brine, dried over sodium sulfate, filtered, and the solvent evaporated under reduced pressure. The product was isolated via column chromatography using silica gel to afford title compounds **5a-5t.**

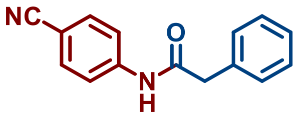
For the gram-scale application, the solutions of **3** and **4** were pumped continuously into each respective stream without the use of injection loops.

Procedure for N-(4-cyanophenyl)-2,2,2-trifluoroacetamide (5m) synthesis

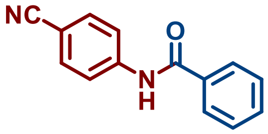


A mixture of **1a** (1.0 equiv., 1 mmol), triphenylphosphine (918 mg, 3.50 mmol, 3.5 equiv.), and trifluoroacetic acid (32.4 µL, 1.1 mmol, 1.1 equiv) in acetonitrile (0.05 M) was prepared in a 20 mL volumetric flask. The solution was aspirated with a syringe and mounted onto a syringe pump. It was pumped through the electrochemical microflow cell at 0.150 mL•min^{-1} (t_r= 5 min), operating in galvanostatic mode. The cell was equipped with impervious graphite electrodes and operated at 37 mA (3 F). Following electrolysis of 3 mL (corresponding to four residence times), the system reached steady state, allowing for product collection. Trifluoroacetic acid is used both as an electrochemical mediator and as the nucleophile in the amidation step. The crude **3a** in acetonitrile is aspirated with a syringe and loaded into a 10 mL (0.5 mmol) loop on a Vapourtec R-Series instrument. The loop is then injected into a stream of acetonitrile at 0.5 mL•min^{-1}, where it was then diluted at a PEEK T-mixer with a stream of acetonitrile delivered by the second pump. The diluted solution (0.025 M) then continued at 1.0 mL•min^{-1} through a tube-in-tube reactor (V=1 mL) pressurized with 4 bar of CO_2, followed by a PFA coil reactor (V= 10 mL, t_r = 10 min, i.d.: 0.79 mm) heated to 100 ºC. The crude solution was collected in flask. The mixture was neutralized with a saturated solution of sodium bicarbonate (3 x 10 mL) to remove residual acid. The aqueous phase was back-extracted with ethyl acetate, organic phases combined and washed with brine, dried over sodium sulfate, filtered, and the solvent evaporated under reduced pressure. The product was isolated via flash column chromatography to afford title compound **5m**.

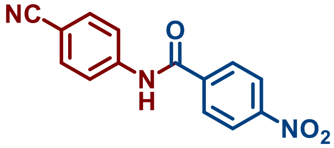
6. Characterization Data



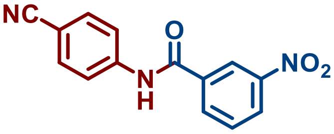
N-(4-cyanophenyl)-2-phenylacetamide (5a). Prepared according to general amide synthesis procedure, from **1a** and **4a.** The crude product was purified by column chromatography on silica gel (Toluene:Acetonitrile 9.5:0.5) to afford the title compound (**5a**) as a light rose solid (89 mg, 0.38 mmol, 75%); m.p. 165-167 ºC.[4] ^{1}H NMR (500 MHz, DMSO-d6) δ 10.60 (s, 1H), δ 7.79 (d, *J* = 8.9 Hz, 2H), δ 7.75 (d, *J* = 8.9 Hz, 2H)., δ 7.35-7.30 (m, 4H), δ 7.28-7.22 (m, 1H), δ 3.70 (s, 2H). ^{13}C NMR (125 MHz, DMSO-d6) δ 170.4, 143.8, 135.9, 133.7, 129.7, 128.8, 127.1, 119.6, 119.5, 105.4, 43.8. Spectroscopic data are in accordance with the literature.[5] FT-IR : 3320 (w), 2925 (m), 2226 (m), 1692 (s).



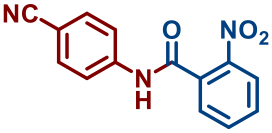
N-(4-cyanophenyl)benzamide (5b). Prepared according to general amide synthesis procedure, from **1a** and **4b.** The crude product was purified by column chromatography on silica gel (Hexane:Ethyl Acetate 7:3) to afford the title compound (**5b**) as a white solid (69 mg, 0.31 mmol, 62%); m.p. 167-170 ºC.[6] ^{1}H NMR (500 MHz, DMSO-d6) δ 10.64 (s, 1H), δ 8.00 (d, *J*= 9.0 Hz, 2H), δ 7.98-7.94 (m, 2H), δ 7.82 (d, *J*= 9.0 Hz, 2H), δ 7.62 (tt, *J*= 6.5, 1.5 Hz, 1H), δ 7.55 (t, *J*= 7.5 Hz, 2H). ^{13}C NMR (125 MHz, DMSO-d6) δ 166.2, 143.5, 134.4, 133.1, 132.0, 128.5, 127.8, 120.2, 119.1, 105.3. Spectroscopic data are in accordance with the literature.[7] I FT-IR: 3349 (m), 2228 (m), 1661 (s).



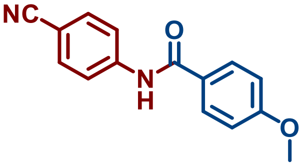
N-(4-cyanophenyl)-4-nitrobenzamide (5c). Prepared according to general amide synthesis procedure, from **1a** and **4c**; except 1.5 equiv. of Et_3N was used. The crude product was purified by column chromatography on silica gel (Toluene:Acetonitrile 9.5:0.5) to afford the title compound (**5c**) as a light brown solid (119 mg, 0.44 mmol, 89%); decomposition >253 ºC. ^{1}H NMR (600 MHz, DMSO-d6) δ 10.96 (s, 1H), δ 8.37 (d, *J*= 9.0 Hz, 2H), δ 8.19 (d, *J*= 9.0 Hz, 2H), δ 8.00 (d, *J*= 9.0 Hz, 2H), δ 7.84 (d, *J*= 9.0 Hz, 2H). ^{13}C NMR (150 MHz, DMSO-d6) δ 164.5, 149.4, 143.0, 139.9, 133.2, 129.4, 123.6, 120.40, 119.0, 105.9. Spectroscopic data are in accordance with the literature.[8] FT-IR: 3420 (m), 2928 (w), 2225 (s), 1692 (s).



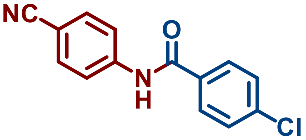
N-(4-cyanophenyl)-3-nitrobenzamide (5d). Prepared according to general amide synthesis procedure, from **1a** and **4d.** The crude product was purified by column chromatography on silica gel (Toluene:Acetonitrile 9.5:0.5) to afford the title compound (**5d**) as an off-white solid (98 mg, 0.37 mmol, 73%); decomposition >248 ºC. ^{1}H NMR (500 MHz, DMSO-d6) δ 10.92 (s, 1H), δ 8.78 (t, *J*= 2.0 Hz, 1H), δ 8.45 (ddd, *J*= 8.0, 2.0, 0.5 Hz, 1H), δ 8.34 (dt, *J*= 8.0, 1.0 Hz, 1H), δ 7.99 (d, *J*= 8.5 Hz, 2H), δ 7.87-7.82 (m, 3H). ^{13}C NMR (125 MHz, DMSO-d6) δ 164.0, 147.7, 143.0, 135.7, 134.3, 133.2, 130.3, 126.6, 122.6, 120.4, 119.0, 105.9. Spectroscopic data are in accordance with the literature.[9] FT-IR: 3352 (w), 2963 (w), 2231 (m), 1678 (s).



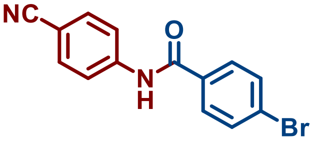
N-(4-cyanophenyl)-2-nitrobenzamide (5e). Prepared according to general amide synthesis procedure, from **1a** and **4e.** The crude product was purified by column chromatography on silica gel (Toluene:Acetonitrile 9.5:0.5) to afford the title compound (**5e**) as an off-white solid (89 mg, 0.33 mmol, 66%); m.p. 221-223 ºC. ^{1}H NMR (500 MHz, DMSO-d6) δ 11.11 (s, 1H), δ 8.19 (dd, *J*= 8.0, 0.5 Hz, 1H), δ 7.91 (td, *J*= 7.5, 1.0 Hz, 1H), δ 7.88-7.77 (m, 6H). ^{13}C NMR (125 MHz, DMSO-d6) δ 164.8, 146.2, 143.0, 134.3, 133.4, 132.1, 131.3, 129.3, 124.4, 119.7, 119.0, 105.8. HRMS (ESI+): m/z calculated for $C_{14}H_9N_3O_3$ [M+H]$^+$: 268.07167; found 268.0713; mass error -1.4 ppm. FT-IR: 3508 (w), 3238 (w), 2928 (w), 2222 (m), 1665 (s).



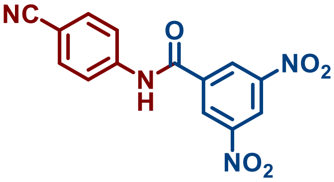
N-(4-cyanophenyl)-4-methoxybenzamide (5f). Prepared according to general amide synthesis procedure, from **1a** and **4f**; except 1.5 equiv. of Et_3N was used. The crude product was purified by column chromatography on silica gel (Toluene:Acetonitrile 9.5:0.5) to afford the title compound (**5f**) as a very light pink solid (115 mg, 0.46 mmol, 89%); m.p. 151-154 ºC.[8] ^{1}H NMR (500 MHz, DMSO-d6) δ 10.47 (s, 1H), δ 7.97 (t, *J*= 8.5 Hz, 4H) δ 7.80 (d, *J*= 8.5 Hz, 2H), δ 7.08 (d, *J*= 9.0 Hz, 2H), δ 3.84, (s, 3H). ^{13}C NMR (125 MHz, DMSO-d6) δ 165.5, 162.3, 143.7, 133.1, 129.9, 126.3 ,120.1, 119.1, 113.7, 105.0, 55.5. Spectroscopic data are in accordance with the literature.[10] FT-IR: 3320 (m), 2961 (w), 2225 (m), 1654 (s).



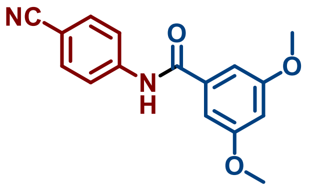
4-chloro-N-(4-cyanophenyl)benzamide (5g). Prepared according to general amide synthesis procedure, from **1a** and **4g**; except 1.5 equiv. of Et_3N was used. The crude product was purified by column chromatography on silica gel (Hexane:Ethyl Acetate 7:3) to afford the title compound (**5g**) as an off-white solid (92 mg, 0.36 mmol 72%); m.p. 208-209 ºC. ^{1}H NMR (500 MHz, DMSO-d6) δ 10.68 (s, 1H), δ 8.00-7.96 (m, 4H), δ 7.82 (d, *J*= 8.5 Hz, 2H), δ 7.62 (d, *J*= 8.5 Hz, 2H). ^{13}C NMR (125 MHz, DMSO-d6) δ 165.0, 143.3, 136.9, 133.1, 133.0, 129.8, 128.6, 120.2, 119.0, 105.5. Spectroscopic data are in accordance with the literature.[5] FT-IR: 3267 (w), 2928 (w), 2222 (w), 1652 (s).



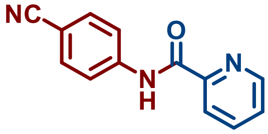
4-bromo-N-(4-cyanophenyl)benzamide (5h). Prepared according to general amide synthesis procedure, from **1a** and **4h**. The crude product was purified by column chromatography on silica gel (Hexane:Ethyl Acetate 7:3) to afford the title compound (**5h**) as an off-white solid (89 mg, 0.29 mmol, 59%); m.p. 225-228 ºC. ^{1}H NMR (500 MHz, DMSO-d6) δ 10.68 (s, 1H), δ 7.97 (d, *J*= 9.0 Hz, 2H), δ 7.91 (d, *J*= 8.5 Hz, 2H), δ 7.82 (d, *J*= 8.5 Hz, 2H), δ 7.76 (d, *J*= 9.0 Hz, 2H). ^{13}C NMR (125 MHz, DMSO-d6) δ 165.2, 143.3, 133.4, 133.1, 131.5, 130.0, 125.9, 120.2, 119.0, 105.5. HRMS (ESI+): m/z calculated for $C_{14}H_9BrN_2O$ $[M+H]^+$: 302.99506; found 302.9944; mass error -2.2 ppm. FT-IR: 3278 (w), 2928 (w), 2219 (m), 1654 (s).



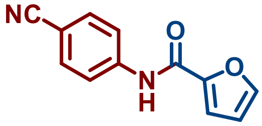
N-(4-cyanophenyl)-3,5-dinitrobenzamide (5i). Prepared according to general amide synthesis procedure, from **1a** and **4i.** The crude product was purified by column chromatography on silica gel (Hexane:Ethyl Acetate 8:2) to afford the title compound (**5i**) as a yellow solid (103 mg, 0.33 mmol, 65%); m.p. >215 ºC. ^{1}H NMR (500 MHz, DMSO-d6) δ 11.16 (s, 1H), δ 9.15 (d, *J*= 2.5 Hz, 2H), δ 9.01 (t, *J*= 2.5 Hz, 1H), δ 7.98 (d, *J*= 8.5 Hz), δ 7.87 (d, *J*= 8.5 Hz, 2H). ^{13}C NMR (125 MHz, DMSO-d6) δ 162.0, 148.1, 142.6, 136.9, 133.3, 128.2, 121.5, 120.7, 118.9, 106.4. HRMS (ESI-): m/z calculated for $C_{14}H_8N_4O_5$ $[M-H]^-$: 311.04219; found 311.0422; mass error 0.03 ppm. FT-IR: 3320 (m), 2966 (w), 2230 (m), 1677 (s).



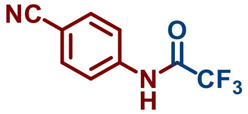
N-(4-cyanophenyl)-3,5-dimethoxybenzamide (5j). Prepared according to general amide synthesis procedure, from **1a** and **4j**; except 1.5 equiv. of Et_3N was used. The crude product was purified by column chromatography on silica gel (Toluene:Acetonitrile 9.5:0.5) to afford the title compound (**5j**) as an off-white solid (101 mg, 0.36 mmol, 71%); m.p. 170-173 ºC. ^1H NMR (500 MHz, DMSO-d6) δ 10.55 (s, 1H), δ 7.98 (d, *J*= 7.5 Hz, 2H), δ 7.82 (d, *J*= 7.5 Hz, 2H), δ 7.10 (d, *J*= 2.0 Hz, 2H), δ 6.74 (t, *J*= 2.0 Hz, 1H), δ 3.82 (s, 6H). ^{13}C NMR (125 MHz, DMSO-d6) δ 165.7, 160.4, 143.3, 136.4, 133.1, 120.3, 119.0, 105.8, 105.4, 103.7, 55.5. Spectroscopic data are in accordance with the literature.[5] FT-IR: 3311 (m), 2937 (w), 2225 (m), 1650 (s).



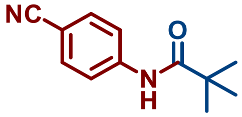
N-(4-cyanophenyl)picolinamide (5k). Prepared according to general amide synthesis procedure, from **1a** and **4k.** The crude product was purified by column chromatography on silica gel (Toluene:Acetonitrile 9.5:0.5) to afford the title compound (**5k**) as a white solid (89 mg, 0.40 mmol, 80%); m.p. 164-166 ºC.[11] ^1H NMR (500 MHz, $CDCl_3$) δ 10.26 (s, 1H), δ 8.61 (d, *J*= 4.5 Hz, 1H), δ 8.28 (d, *J*= 8.0 Hz, 1H), δ 7.93 (dt, *J*= 7.5, 1.2 Hz, 1H), δ 7.90 (d, *J*= 8.5 Hz, 2H), δ 7.65 (d, *J*= 8.5 Hz, 2H), δ 7.52 (ddd, *J*= 7.5, 4.5, 1.2 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.4, 149.0, 148.1, 141.8, 138.1, 133.4, 127.1, 122.8, 119.7, 119.0, 107.2. Spectroscopic data are in accordance with the literature.[11] FT-IR: 3660 (w), 3341 (m), 2971 (m), 2228 (m), 1680 (s).



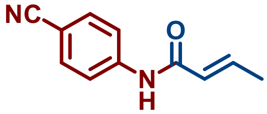
N-(4-cyanophenyl)furan-2-carboxamide (5l). Prepared according to general amide synthesis procedure, from **1a** and **4l.** The crude product was purified by column chromatography on silica gel (Toluene:Acetonitrile 9.5:0.5) to afford the title compound (**5l**) as a yellow solid (59 mg, 0.28 mmol, 56%); m.p. 192-194 ºC.[11] ^1H NMR (500 MHz, DMSO-d6) δ 10.59 (s, 1H), δ 8.07 – 7.90 (m, 3H), δ 7.80 (d, *J* = 8.8 Hz, 2H), δ 7.41 (dd, *J* = 3.5, 0.8 Hz, 1H), δ 6.73 (dd, *J* = 3.5, 1.7 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d6) δ 156.5, 146.9, 146.3, 143.0, 133.1, 120.2, 119.1, 115.9, 112.4, 105.4. HRMS (ESI+): m/z calculated for $C_{12}H_8N_2O_2$ $[M+H]^+$: 213.06585; found 213.0655; mass error -1.6 ppm. FT-IR: 3729 (w), 3626 (w), 3311 (w), 2916 (w), 2360 (s), 2340 (s), 2225 (sh), 1668 (m).



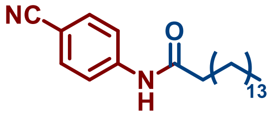
N-(4-cyanophenyl)-2,2,2-trifluoroacetamide (5m). Prepared according to specific **5m** amide synthesis procedure, from **1a** and **4m**. The crude product was purified by column chromatography on silica gel (Hexane:Ethyl Acetate 7:3) to afford the title compound (**5m**) as an white solid (60 mg, 0.28 mmol 66%); m.p. 165-167 ºC.[30] ^{1}H NMR (500 MHz, DMSO-d6) δ 11.62 (s, 1H), 8.20 – 7.50 (m, 4H). ^{13}C NMR (125 MHz, DMSO-d6) δ 154.9 (q, *J* = 38 Hz), 140.6, 133.4, 121.1, 118.9, 115.5 (q, *J*= 289 Hz), 107.7. ^{19}F (470 MHz, DMSO-d6) δ-74.0. Spectroscopic data are in accordance with the literature.[12] FT-IR: 3270 (w), 3122 (w), 2235 (m), 1742 (m), 1607 (m).



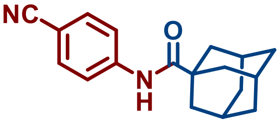
N-(4-cyanophenyl)pivalamide (5n). Prepared according to general amide synthesis procedure, from **1a** and **4n**; except 1.5 equiv. of Et$_3$N was used. The crude product was purified by column chromatography on silica gel (Hexane:Ethyl Acetate 8:2) to afford the title compound (**5n**) as an off-white solid (71 mg, 0.35 mmol, 70%); m.p. 119-121 ºC. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.69 (d, *J* = 8.8 Hz, 2H), δ 7.64 (s, 1H), δ 7.57 (d, *J* = 8.7 Hz, 2H), δ 1.31 (s, 9H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 177.2, 142.4, 133.2, 119.9, 119.0, 106.9, 40.0, 27.6. Spectroscopic data are in accordance with the literature.[13] FT-IR: 3349 (m), 2972 (w), 2230 (m), 1681 (s).



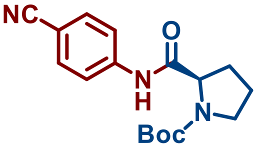
(E)-N-(4-cyanophenyl)but-2-enamide (5o). Prepared according to general amide synthesis procedure, from **1a** and **4o.** The crude product was purified by column chromatography on silica gel (Toluene:Acetonitrile 9.5:0.5) to afford the title compound (**5o**) as a light-yellow solid (54 mg, 0.29 mmol, 58%); m.p. 177-179 ºC. ^{1}H NMR (500 MHz, DMSO-d6) δ 10.35 (s, 1H), δ 7.82 (d, *J* = 8.9 Hz, 2H), δ 7.75 (d, *J* = 8.9 Hz, 2H), δ 6.86 (dq, *J* = 15.4, 6.9 Hz, 1H), δ 6.13 (dd, *J* = 15.4, 1.7 Hz, 1H), δ 1.87 (dd, *J* = 6.9, 1.7 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d6) δ 164.0, 143.5, 141.5, 133.2, 125.5, 119.2, 119.1, 104.8, 17.6. HRMS (ESI+): m/z calculated for $C_{11}H_{10}N_2O$ $[M+H]^+$: 187.08659; found 187.0864; mass error -1.0 ppm. FT-IR: 3299 (w), 2919 (s), 2850 (m), 2357 (m), 2225 (m), 1730 (sh), 1680 (m).



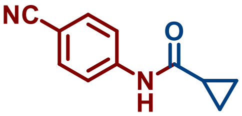
N-(4-cyanophenyl)palmitamide (5p). Prepared according to general amide synthesis procedure, from **1a** and **4p**; except 1.5 equiv. of Et$_3$N was used. The crude product was purified by column chromatography on silica gel (Hexane:Ethyl Acetate 7:3) to afford the title compound (**5p**) as a white solid (158 mg, 0.44 mmol, 89%), gram-scale (1.1 g, 3.1 mmol, 78%); m.p. 94-96 ºC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 – 7.61 (m, 3H), δ 7.59 (d, *J* = 8.6 Hz, 2H), δ 2.38 (t, *J* = 7.6 Hz, 2H), δ 1.71 (p, *J* = 7.5 Hz, 2H), δ 1.42-1.12 (m, 26H), δ 0.87 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.1, 142.3, 133.4, 119.6, 119.0, 106.9, 68.1, 37.9, 32.0, 29.8, 29.8, 29.8, 29.8, 29.7, 29.6, 29.5, 29.5, 29.3, 25.5, 22.8, 14.2. HRMS (ESI+): m/z calculated for $C_{23}H_{36}N_2O$ $[M+H]^+$: 357.29004; found 357.28930; mass error -2.1 ppm. FT-IR: 3340 (m), 2916 (s), 2849 (s), 2240 (m), 2225 (m), 1701 (s), 1687 (s), 1675 (s).



N-(4-cyanophenyl)adamantane-1-carboxamide (5q). Prepared according to general amide synthesis procedure, from **1a** and **4q.** The crude product was purified by column chromatography on silica gel (Hexane:Ethyl Acetate 8:2) to afford the title compound (**5q**) as a white solid (109 mg, 0.39 mmol, 78%); m.p. 169-171 ºC.[14] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.8 Hz, 2H), δ 7.62 – 7.53 (m, 3H), δ 2.13 – 2.06 (m, 3H), δ 1.95 (d, *J* = 2.9 Hz, 6H), δ 1.81 – 1.68 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.6, 142.3, 133.3, 119.9, 119.0, 106.9, 41.9, 39.2, 38.7, 36.5, 36.4, 28.1, 27.9. Spectroscopic data are in accordance with the literature.[14] FT-IR: 3296 (w), 2913 (m), 2849 (sh) 2227 (m), 1695 (sh), 1663 (s).

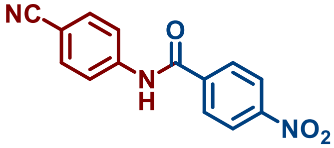


tert-butyl (S)-2-((4-cyanophenyl)carbamoyl)pyrrolidine-1-carboxylate (5r). Prepared according to general amide synthesis procedure, from **1a** and **4r.** The crude product was purified by column chromatography on silica gel (Hexane:Ethyl Acetate 7:3) to afford the title compound (**5r**) as a very light orange solid (97 mg, 0.31 mmol, 61%); m.p. 149-152 ºC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.02 (s, 1H), δ 7.89 – 7.29 (m, 4H), δ 4.50 (s, 1H), δ 3.66 – 3.22 (m, 2H), δ 2.17 (s, 1H), δ 2.15 – 1.79 (m, 3H), δ 1.65 – 1.24 (m, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 156.3, 142.6, 132.9, 119.4, 119.0, 106.2, 81.2, 77.4, 60.7, 47.4, 28.5, 24.6. Spectroscopic data are in accordance with the literature.[15] FT-IR: 3281 (w), 2972 (w), 2225 (m), 1706 (sh), 1665 (s).



N-(4-cyanophenyl)cyclopropanecarboxamide (5s). Prepared according to general amide synthesis procedure, from **1a** and **4s.** The crude product was purified by column chromatography on silica gel (Toluene:Acetonitrile 9.5:0.5) to afford the title compound (**5s**) as a light-yellow solid (26 mg, 0.14 mmol, 25%); m.p. 128-130 ºC. ^{1}H NMR (600 MHz, DMSO-d6) δ 10.63 (s, 1H), δ

7.76 (d, *J* = 8.8 Hz, 2H), δ 7.74 (d, *J* = 8.8 Hz, 2H), δ 1.80 (quint, *J* = 6.3 Hz, 1H), δ 0.84 (d, *J* = 6.3 Hz, 4H). ^{13}C NMR (150 MHz, DMSO-d6) δ 172.56, 143.45, 133.30, 119.14, 118.98, 104.64, 14.82, 7.81. HRMS (ESI+): m/z calculated for $C_{11}H_{10}N_2O$ $[M+H]^+$: 187.08659; found 187.0865; mass error -0.5 ppm. FT-IR: 3293 (w), 2920 (m), 2849 (m), 2222 (m), 1704 (sh), 1662 (m).



4-nitro-N-(4-nitrophenyl)benzamide (5t). Prepared according to general amide synthesis procedure, from **1b** and **4c**; except 1.5 equiv. of Et_3N was used. The crude product was purified by column chromatography on silica gel (Toluene:Acetonitrile 9.5:0.5) to afford the title compound (**5t**) as a light orange solid (62 mg, 0.22 mmol, 43%); m.p. 268-271 ºC. ^{1}H NMR (600 MHz, DMSO-d6) δ 11.10 (s, 1H), δ 8.40 (d, *J* = 8.6 Hz, 2H), δ 8.29 (d, *J*= 8.7 Hz, 2H), δ 8.21 (d, *J* = 8.6 Hz, 2H), δ 8.06 (d, *J*= 9.0 Hz 2H). ^{13}C NMR (150 MHz, DMSO-d6) δ 164.7, 149.5, 145.0, 142.9, 139.8, 129.5, 124.9, 123.7, 120.1. Spectroscopic data are in accordance with the literature.[16] FT-IR: 3368 (m), 3112 (w), 2924 (w), 1684 (s).

7. References

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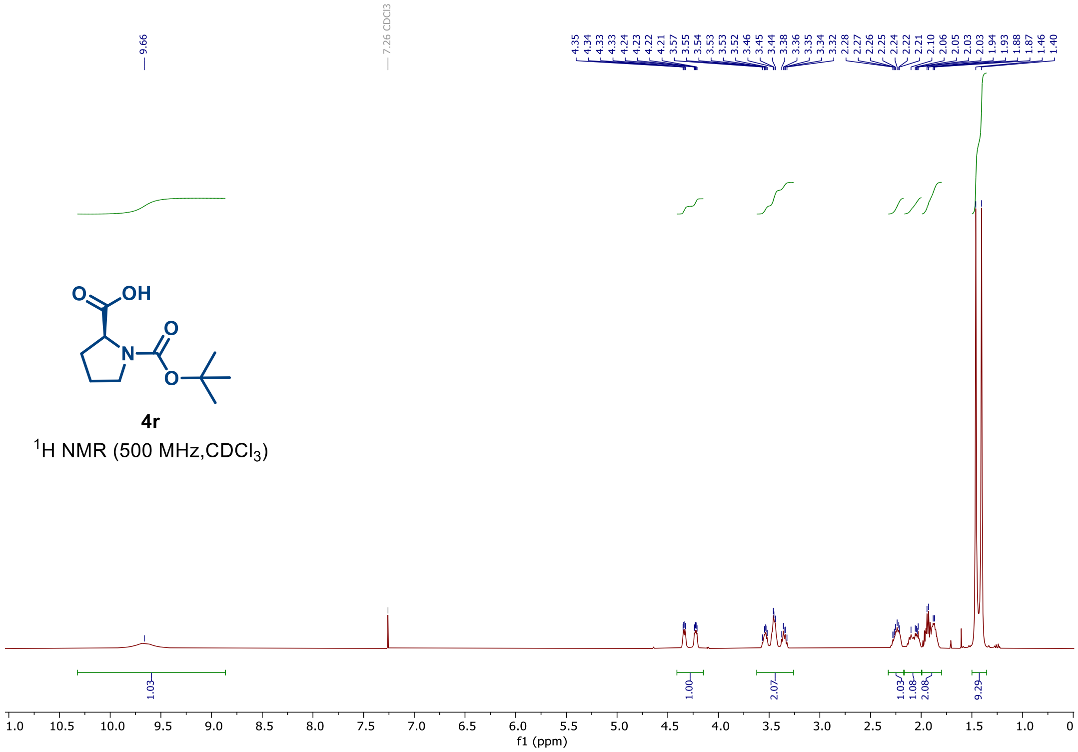
8. NMR Spectra

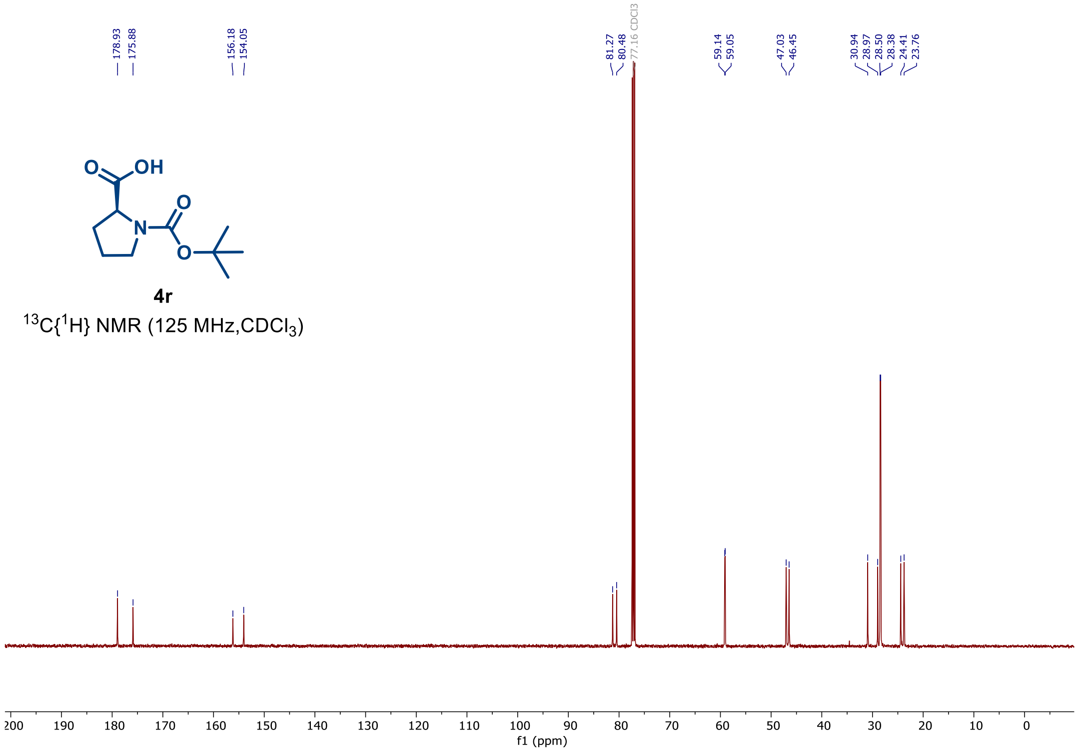
Starting material

^{1}H and ^{13}C{^{1}H} NMR of tert-butoxycarbonyl)-L-proline



4r

^{1}H NMR (500 MHz,CDCl$_3$)

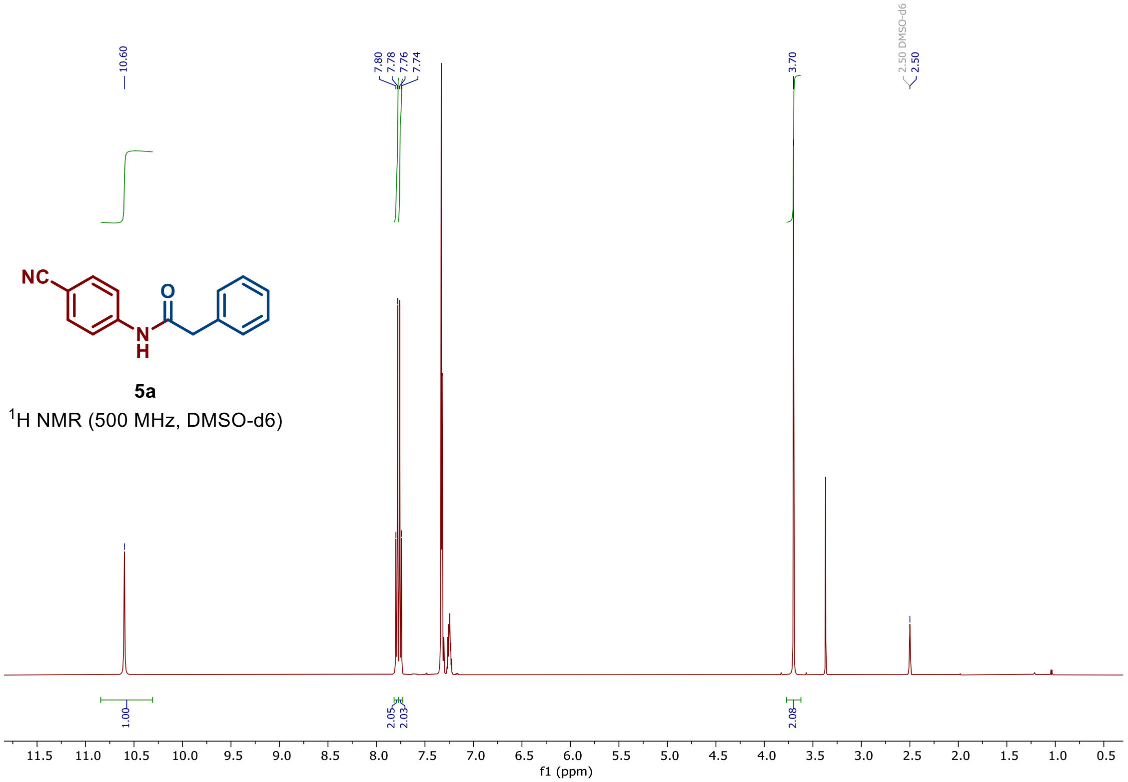


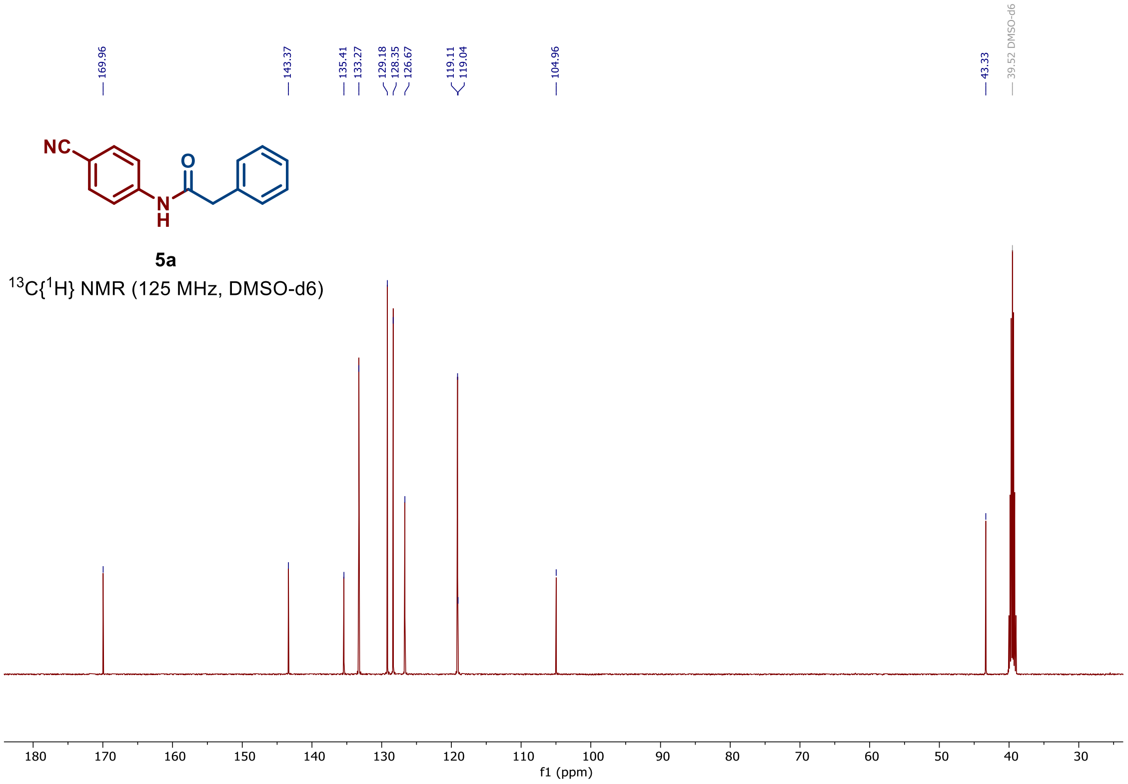
4r

^{13}C{^{1}H} NMR (125 MHz,CDCl$_3$)

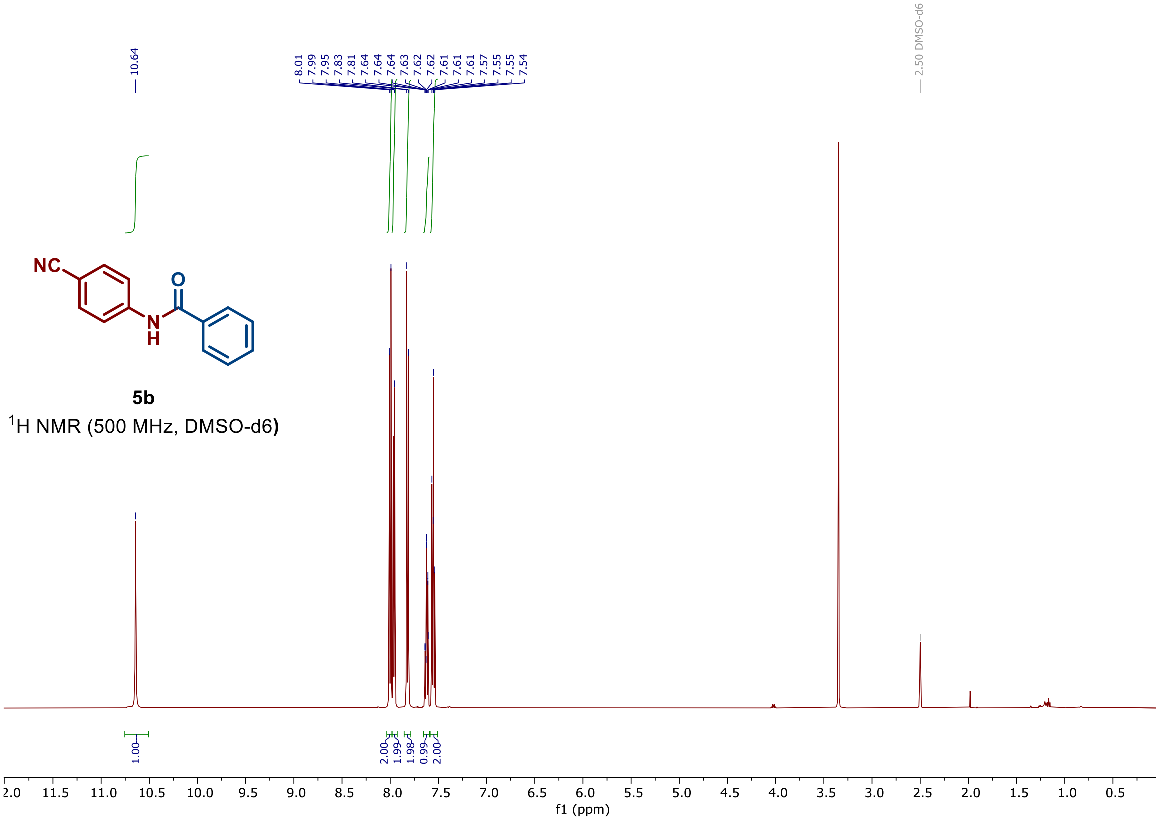
Amides

^{1}H and ^{13}C{^{1}H} NMR of N-(4-cyanophenyl)-2-phenylacetamide (5a).



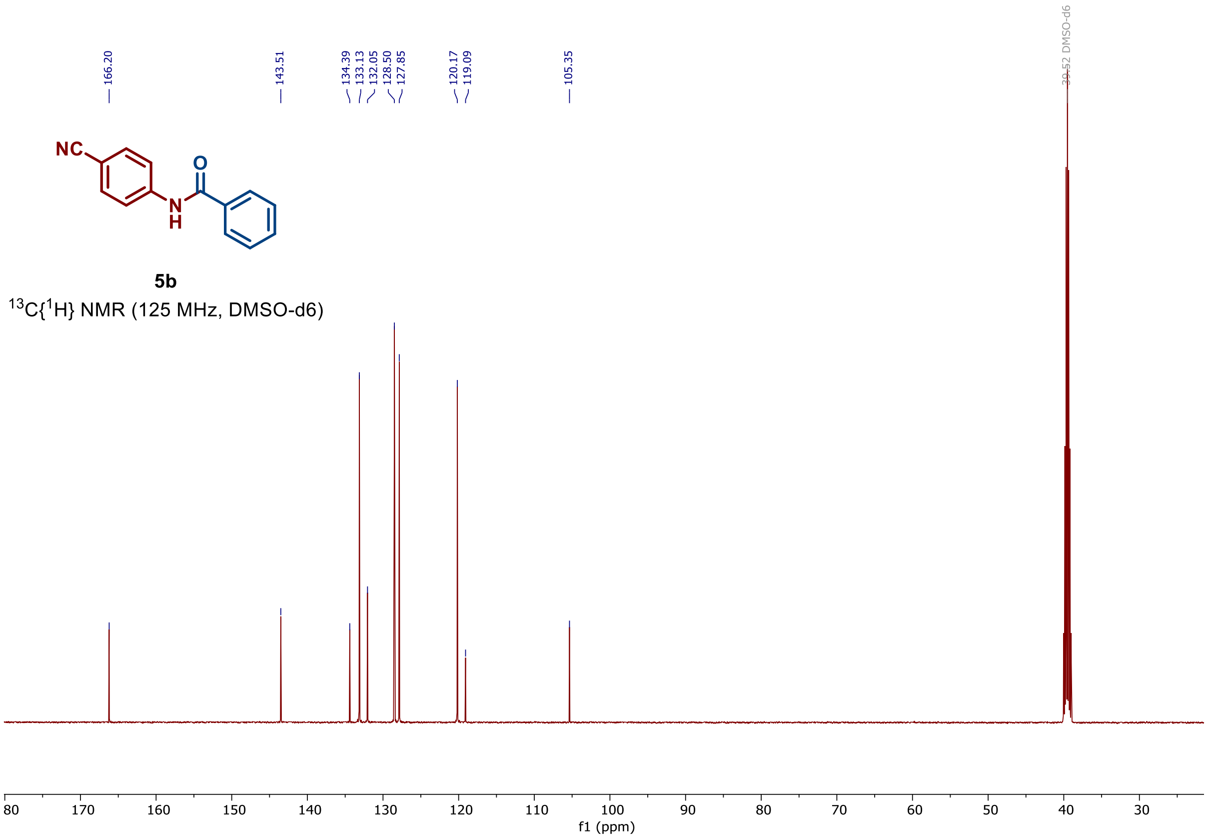


^{1}H and $^{13}C\{^{1}H\}$ NMR of N-(4-cyanophenyl)benzamide (5b).



5b

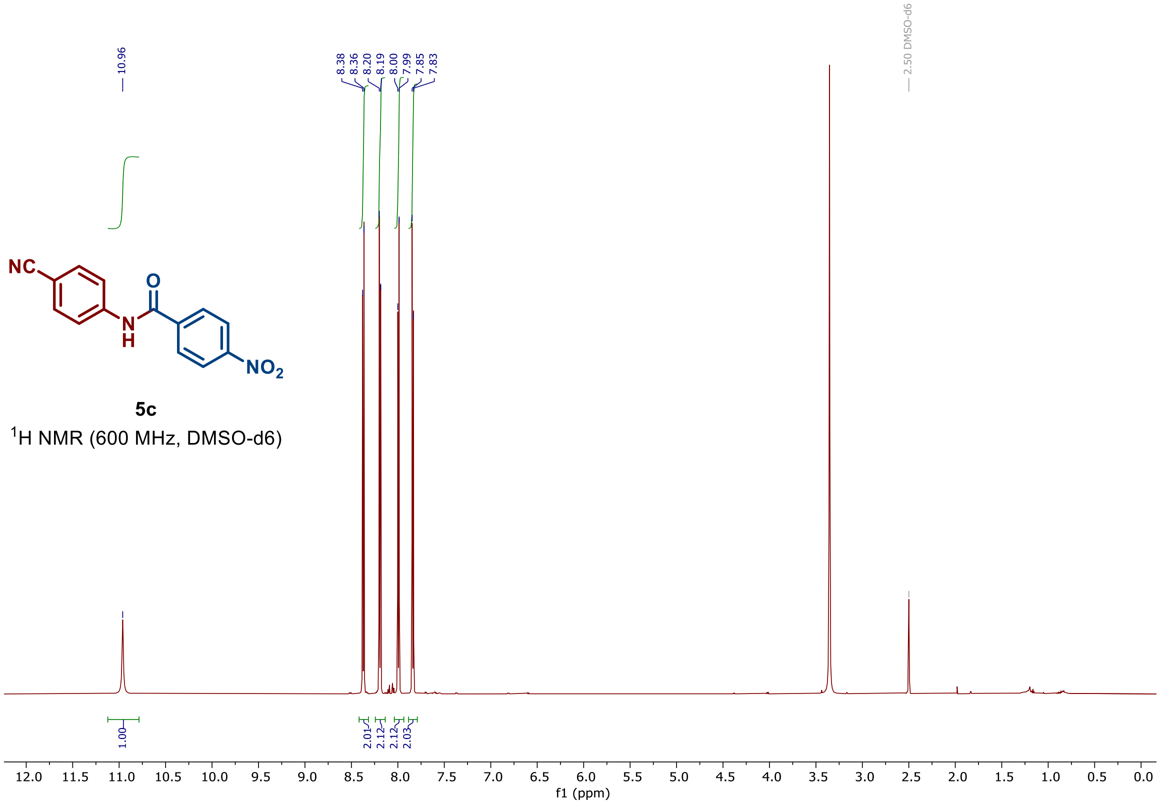
^{1}H NMR (500 MHz, DMSO-d6)

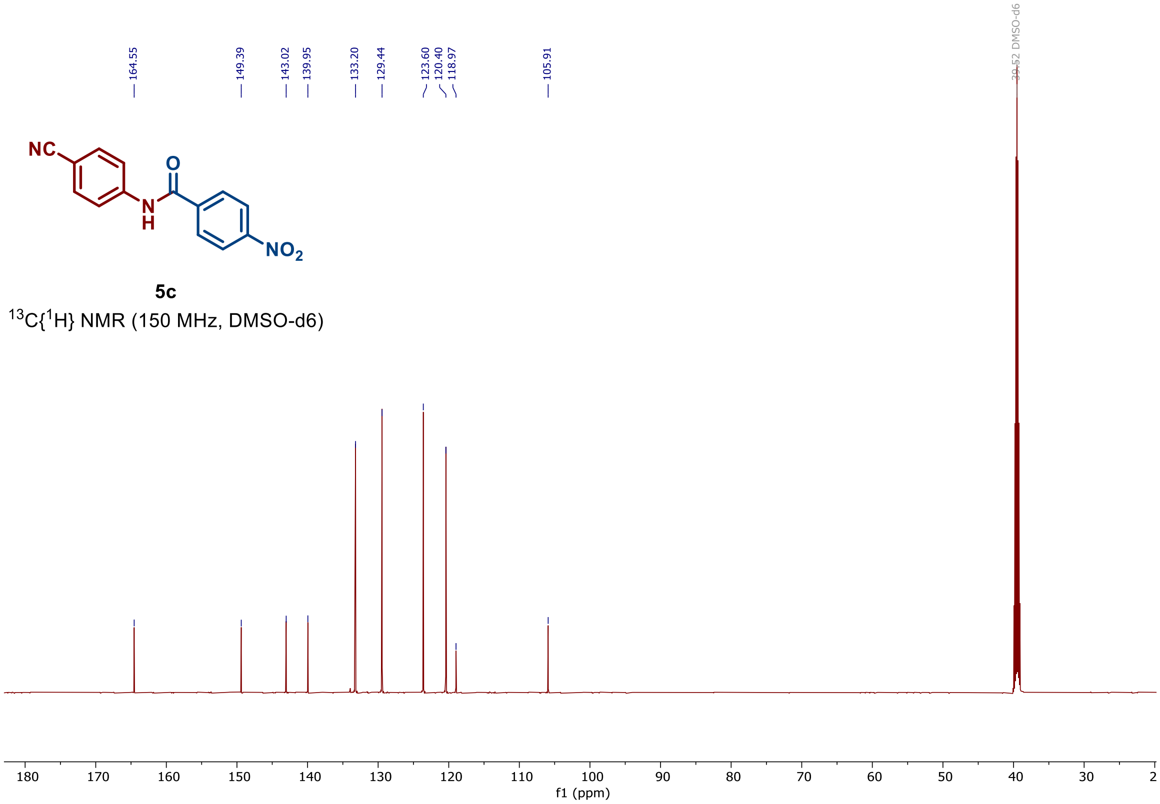


5b

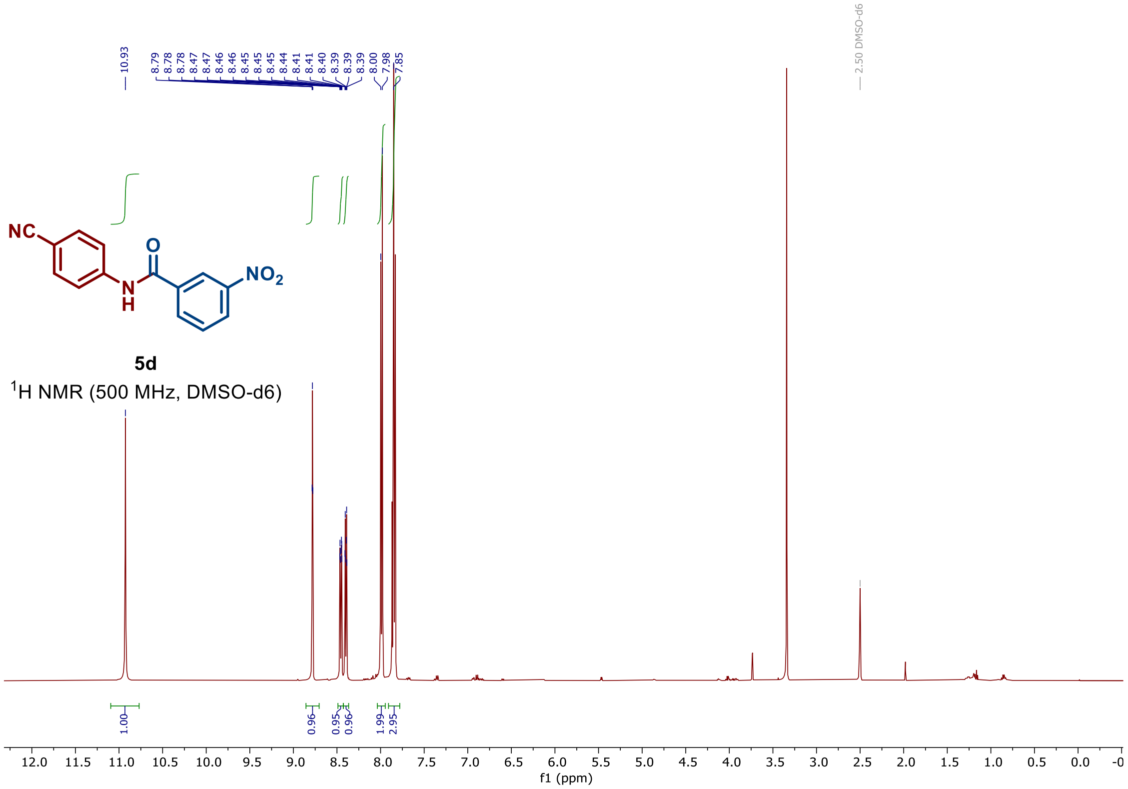
$^{13}C\{^{1}H\}$ NMR (125 MHz, DMSO-d6)

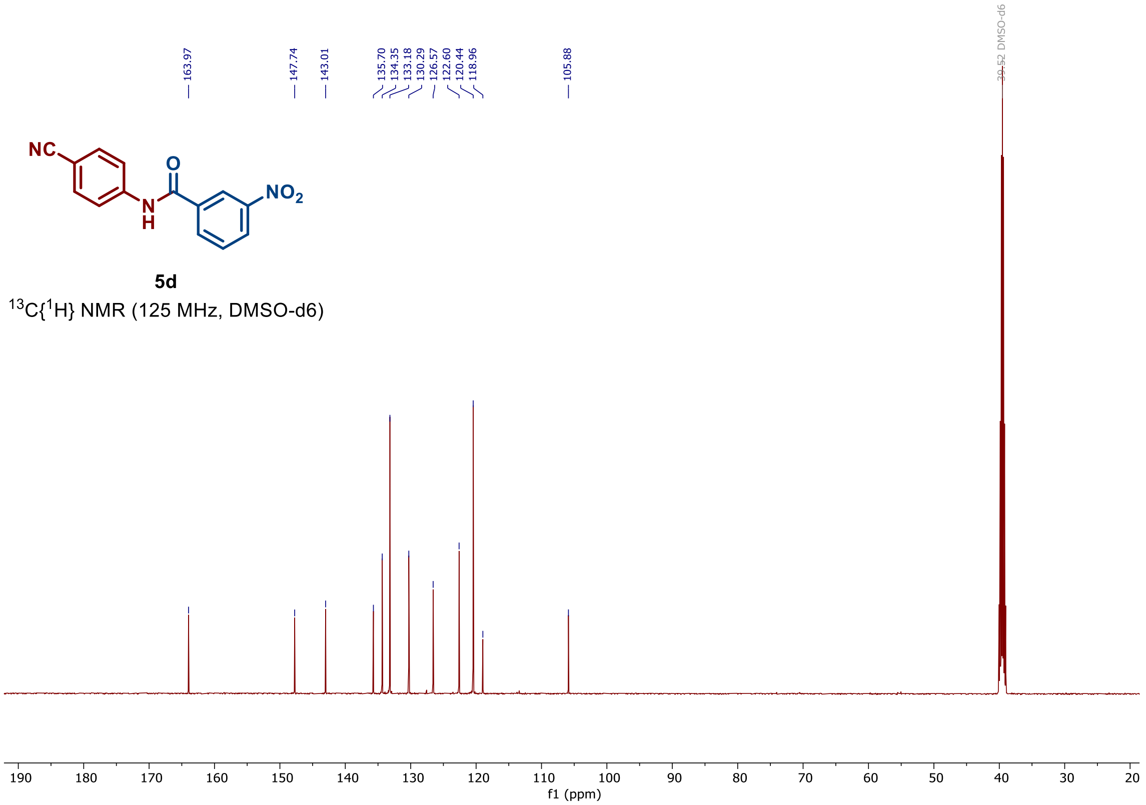
^{1}H and ^{13}C{^{1}H} NMR of N-(4-cyanophenyl)-4-nitrobenzamide (5c).



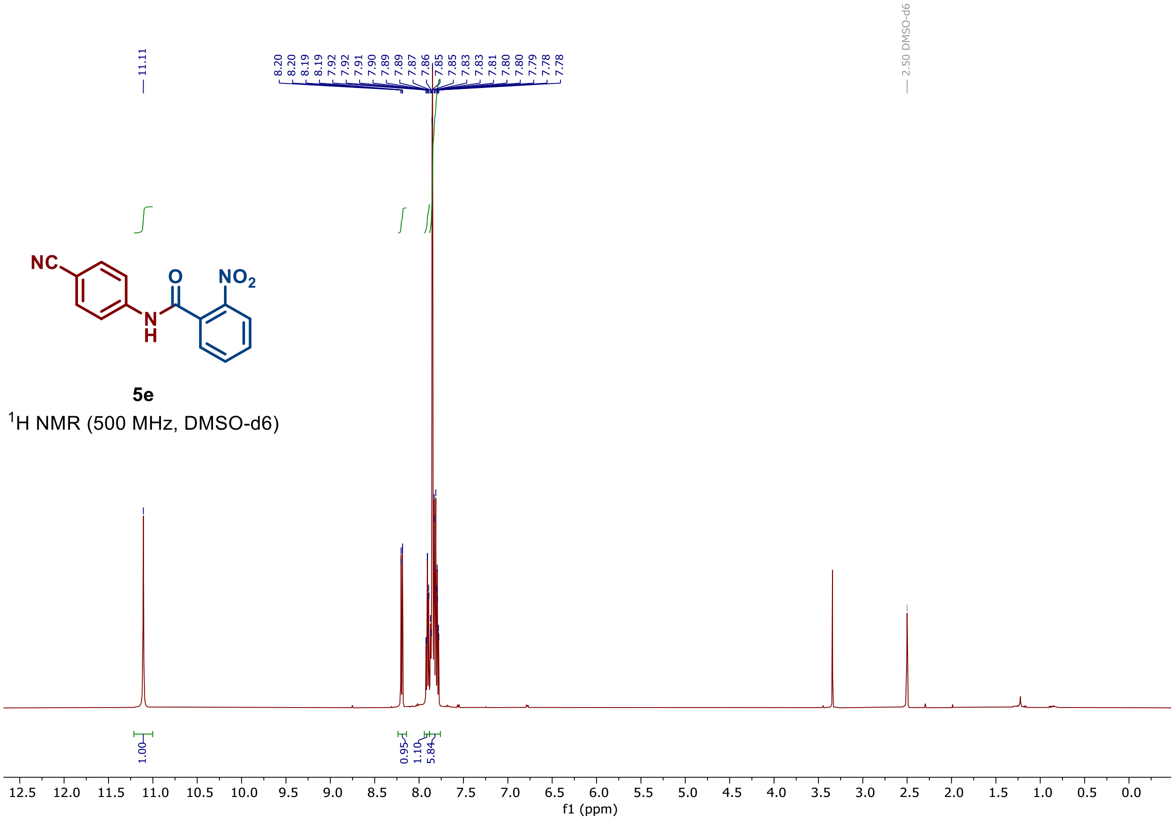


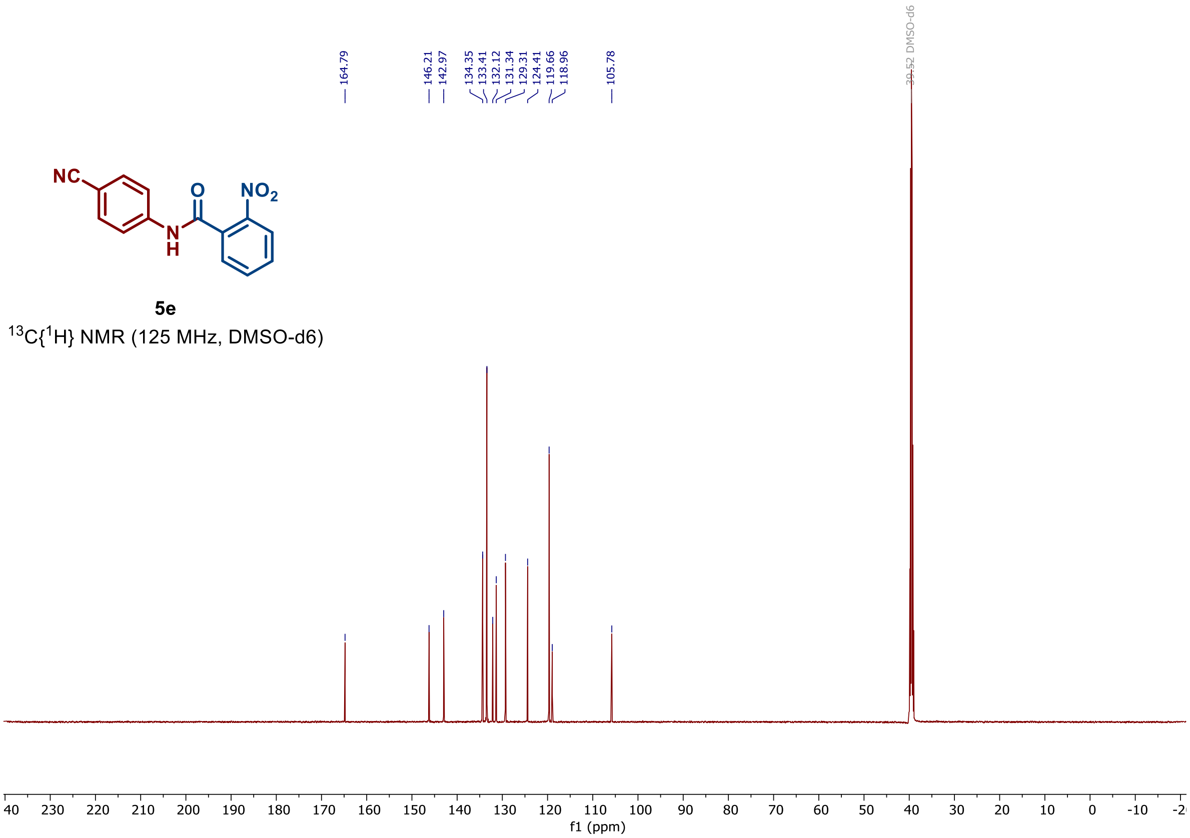
^{1}H and ^{13}C{^{1}H} NMR of N-(4-cyanophenyl)-3-nitrobenzamide (5d).



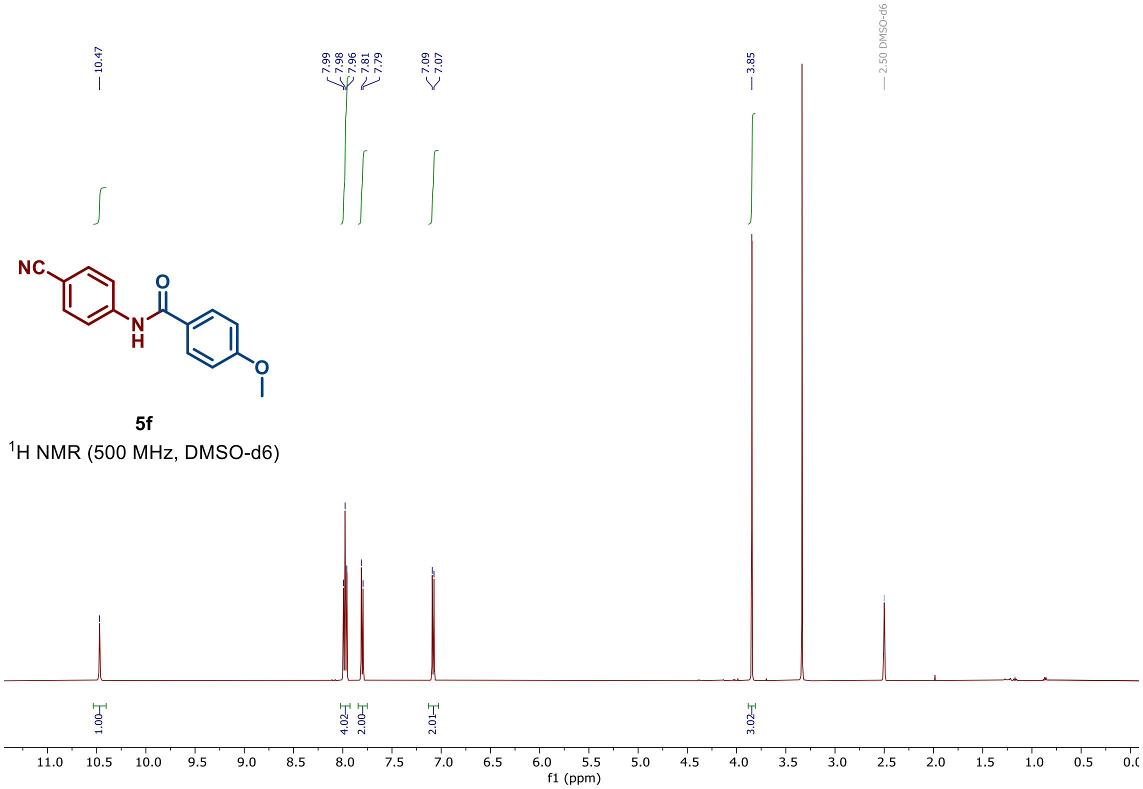


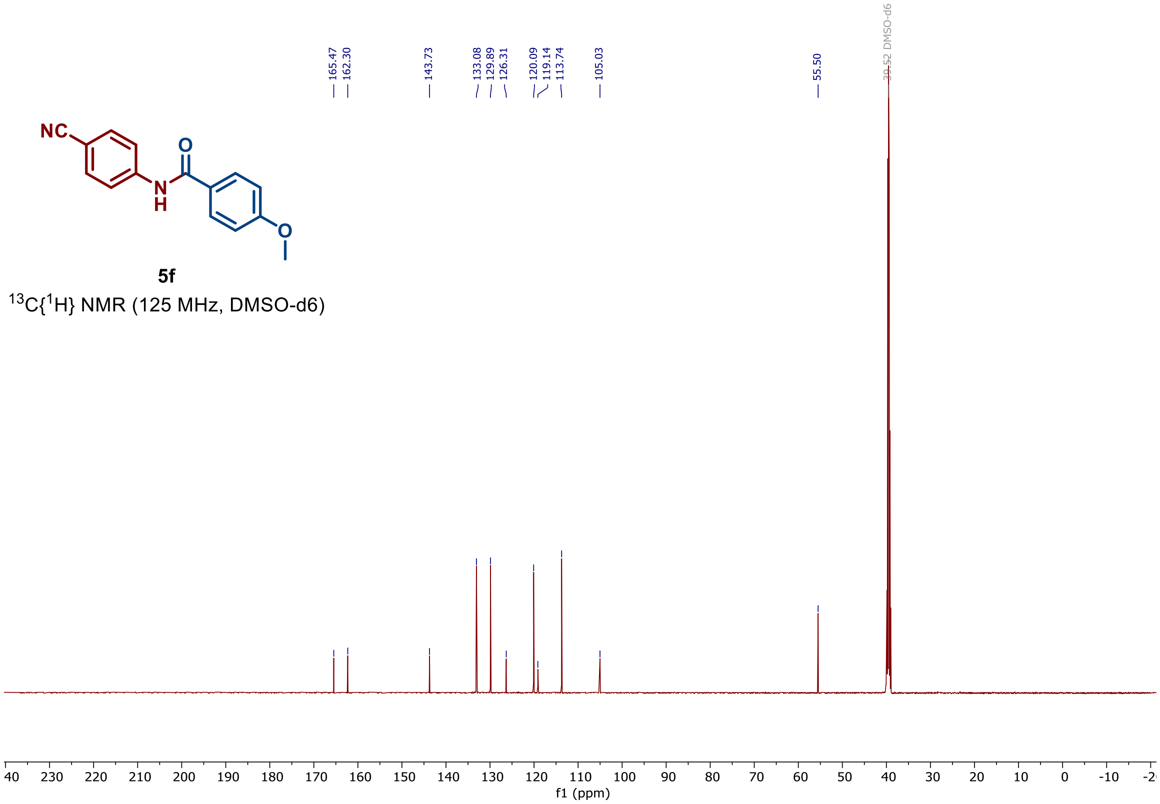
^{1}H and ^{13}C{^{1}H} NMR of N-(4-cyanophenyl)-2-nitrobenzamide (5e).



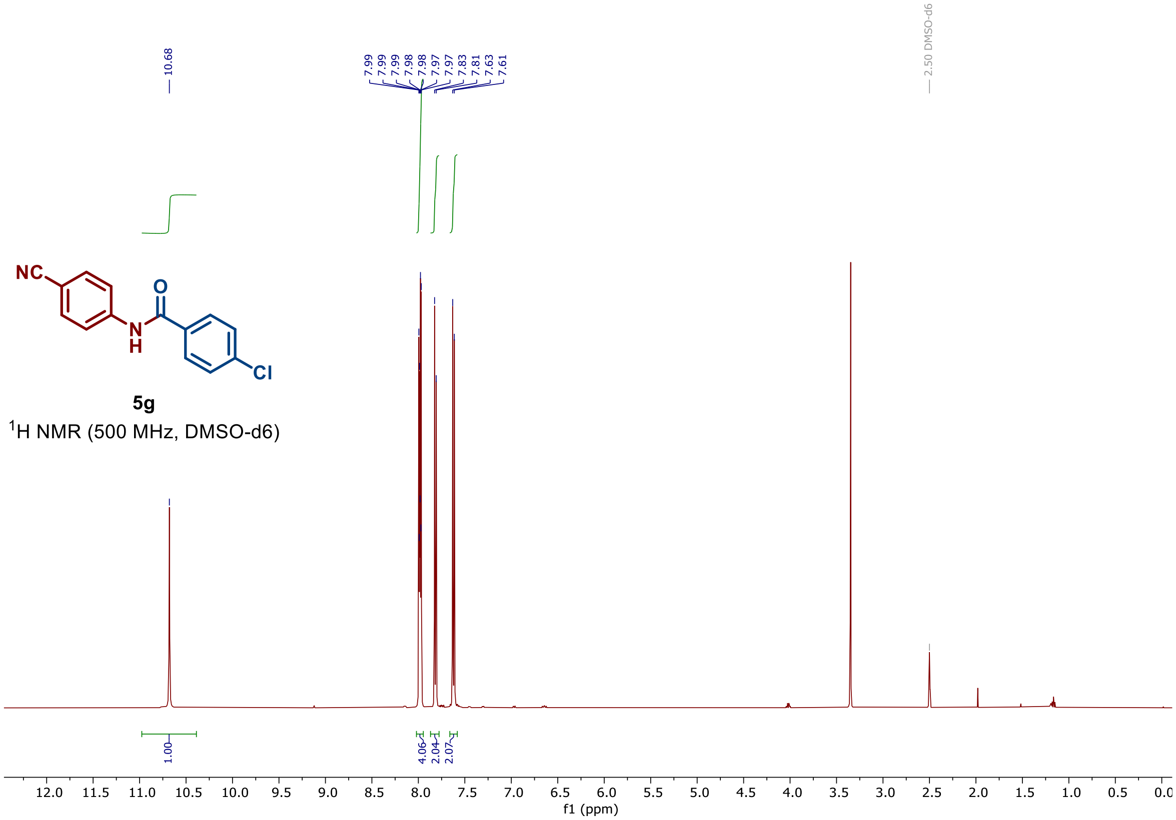


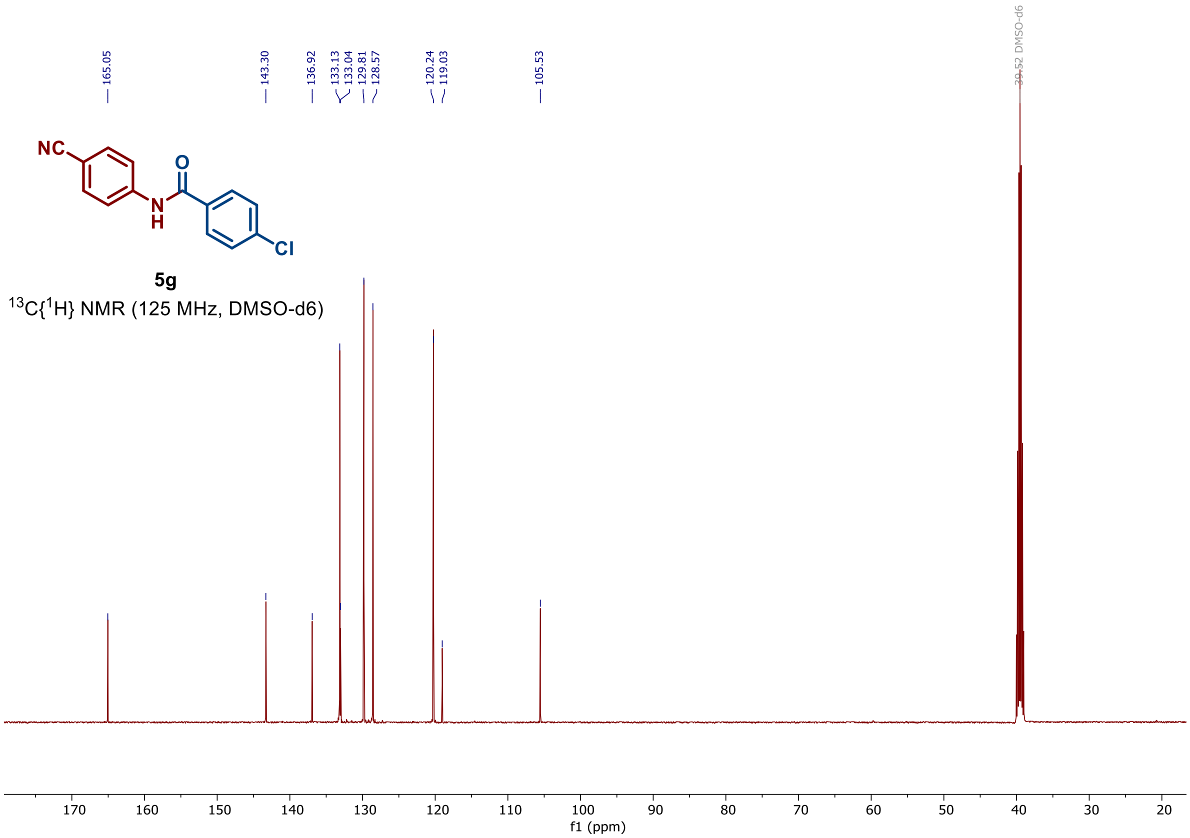
^{1}H and ^{13}C{^{1}H} NMR of N-(4-cyanophenyl)-4-methoxybenzamide (5f).



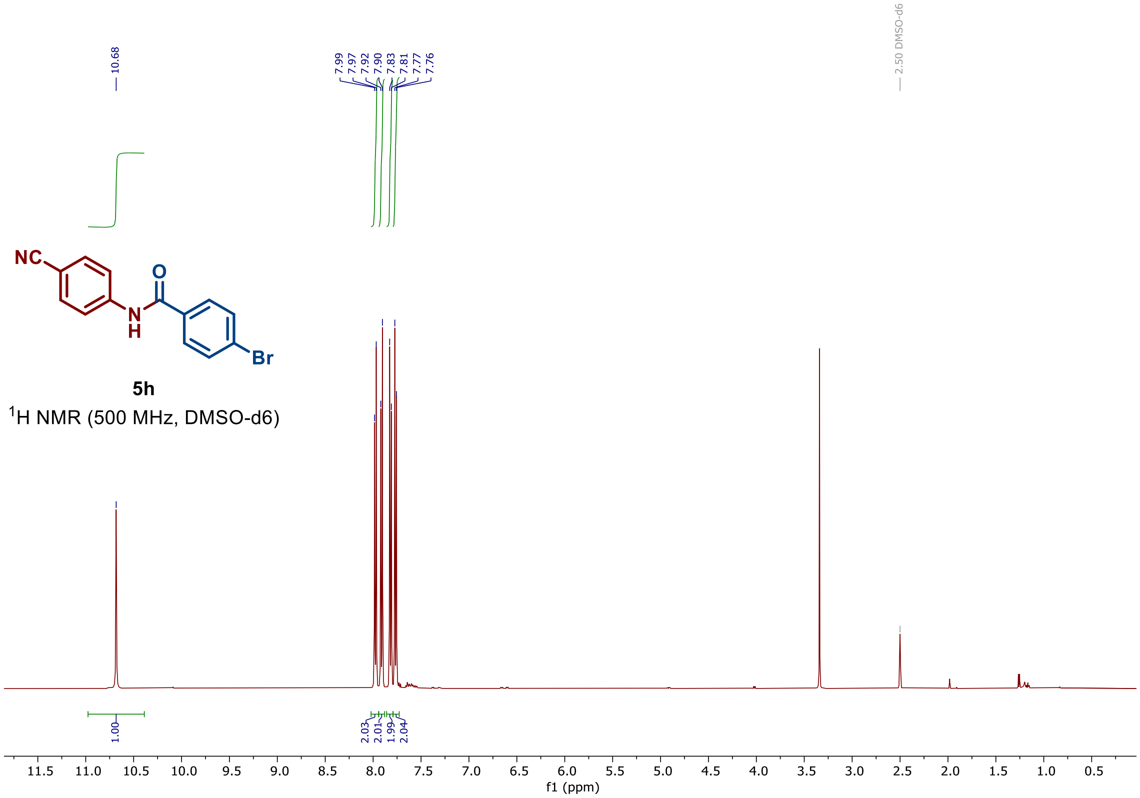


^{1}H and ^{13}C{^{1}H} NMR of 4-chloro-N-(4-cyanophenyl)benzamide (5g).



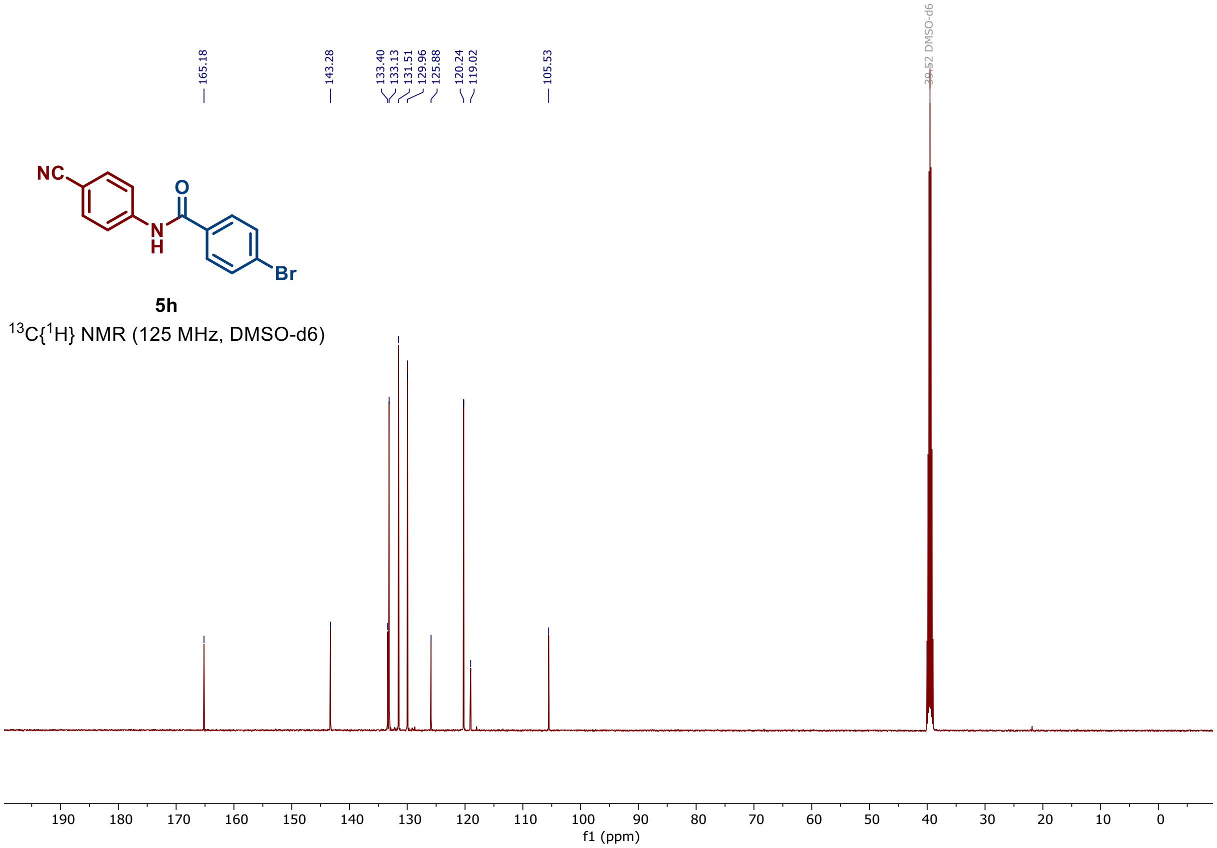


^{1}H and ^{13}C{^{1}H} NMR of 4-bromo-N-(4-cyanophenyl)benzamide (5h).



5h

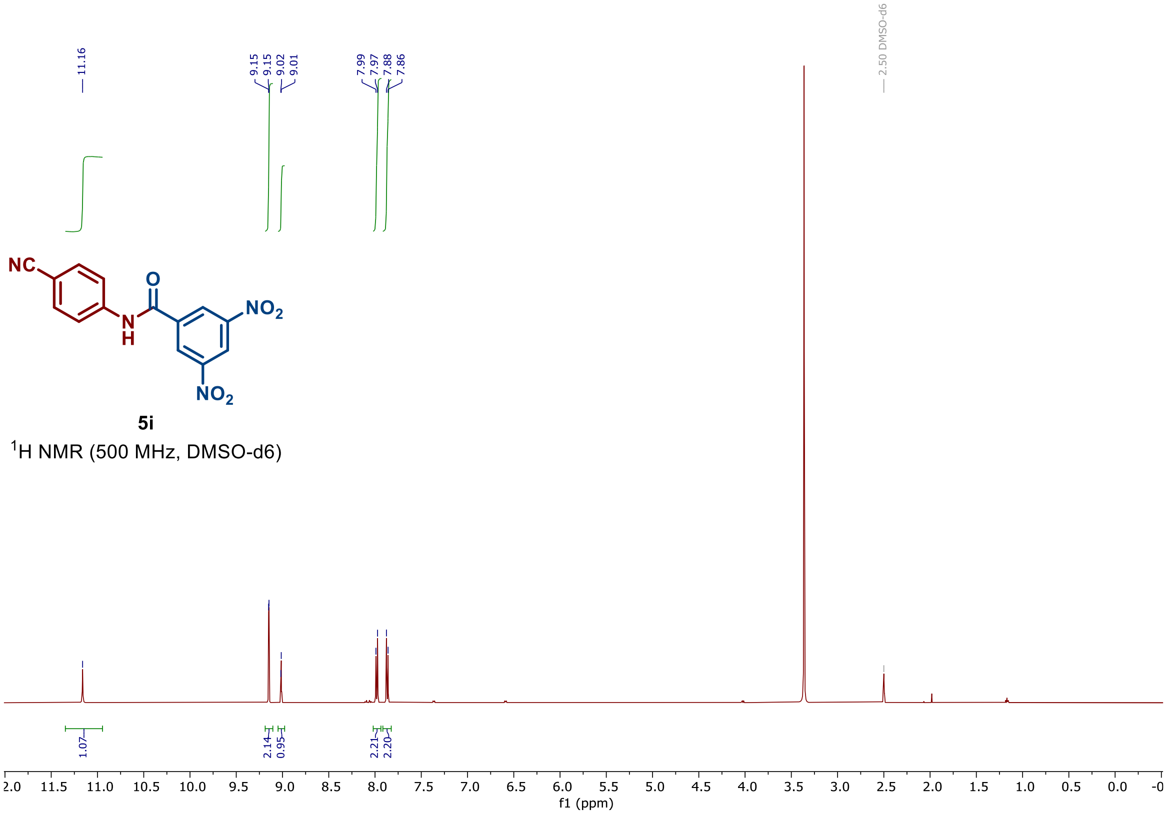
^{1}H NMR (500 MHz, DMSO-d6)



5h

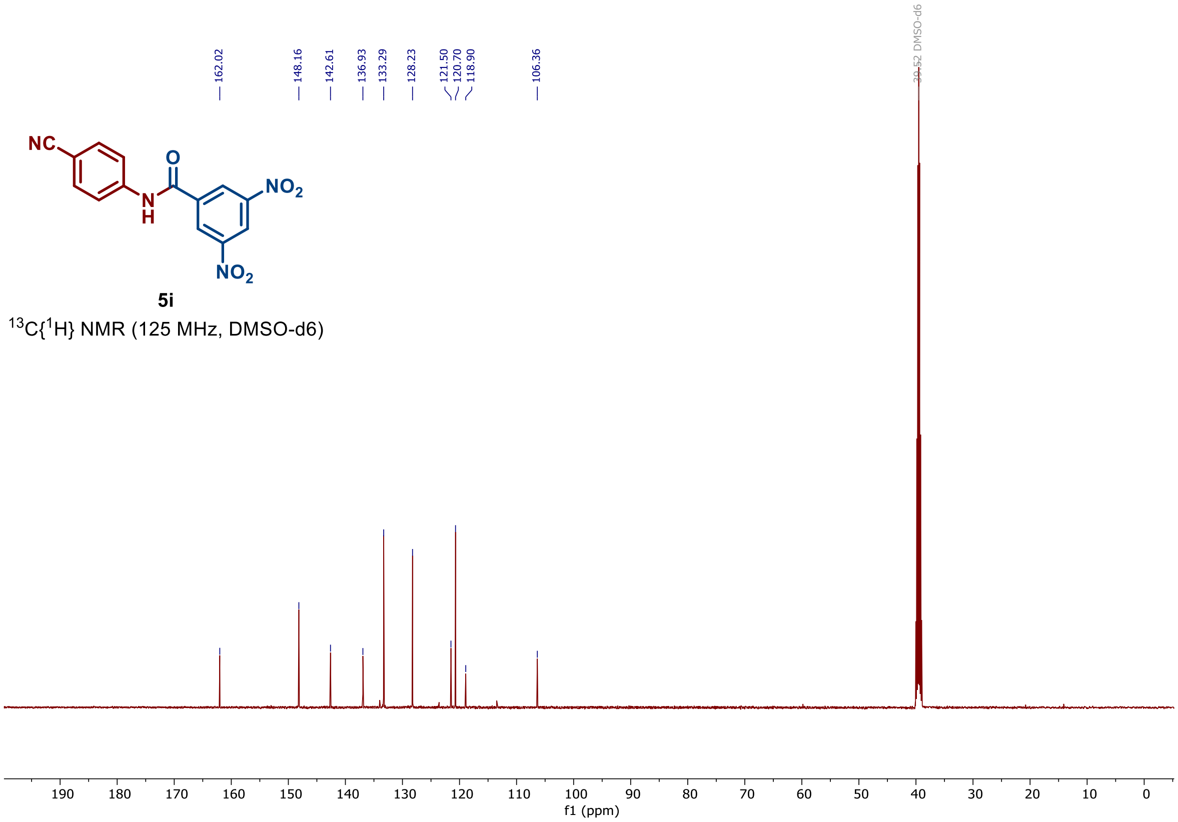
^{13}C{^{1}H} NMR (125 MHz, DMSO-d6)

^{1}H and ^{13}C{^{1}H} NMR of N-(4-cyanophenyl)-3,5-dinitrobenzamide (5i).



5i

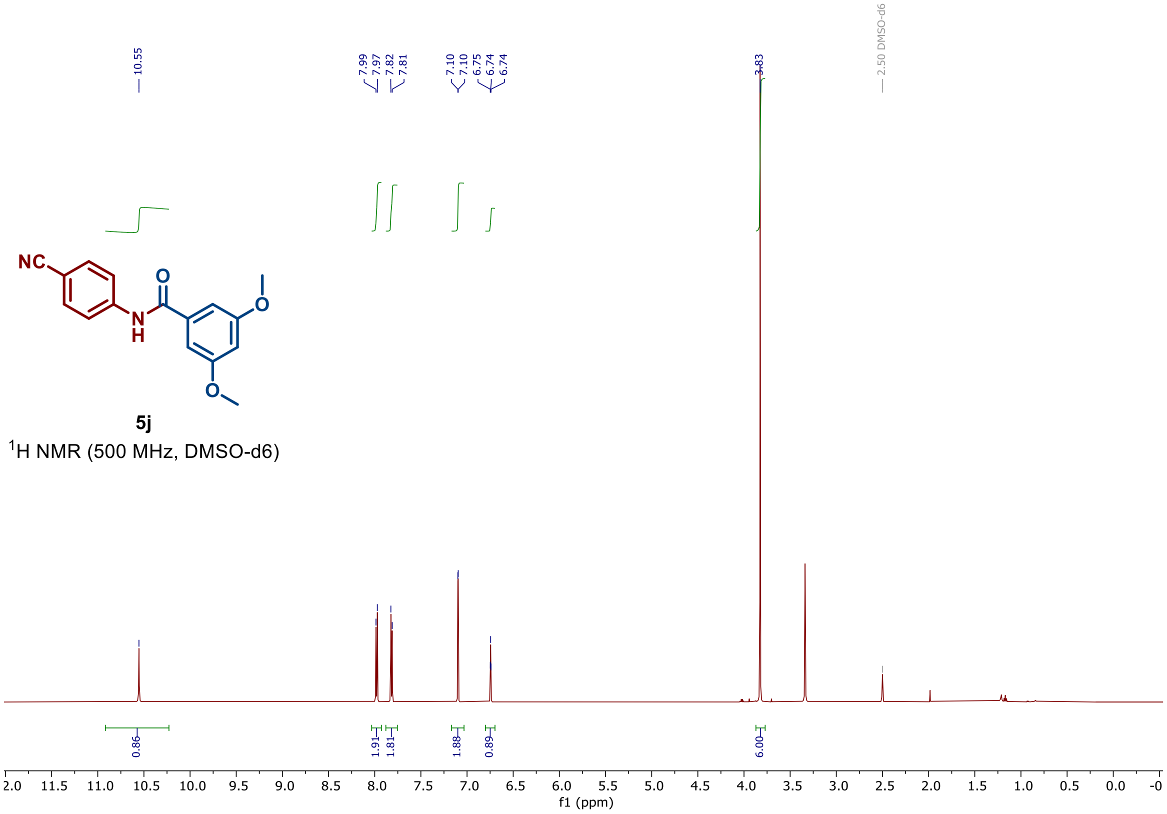
^{1}H NMR (500 MHz, DMSO-d6)

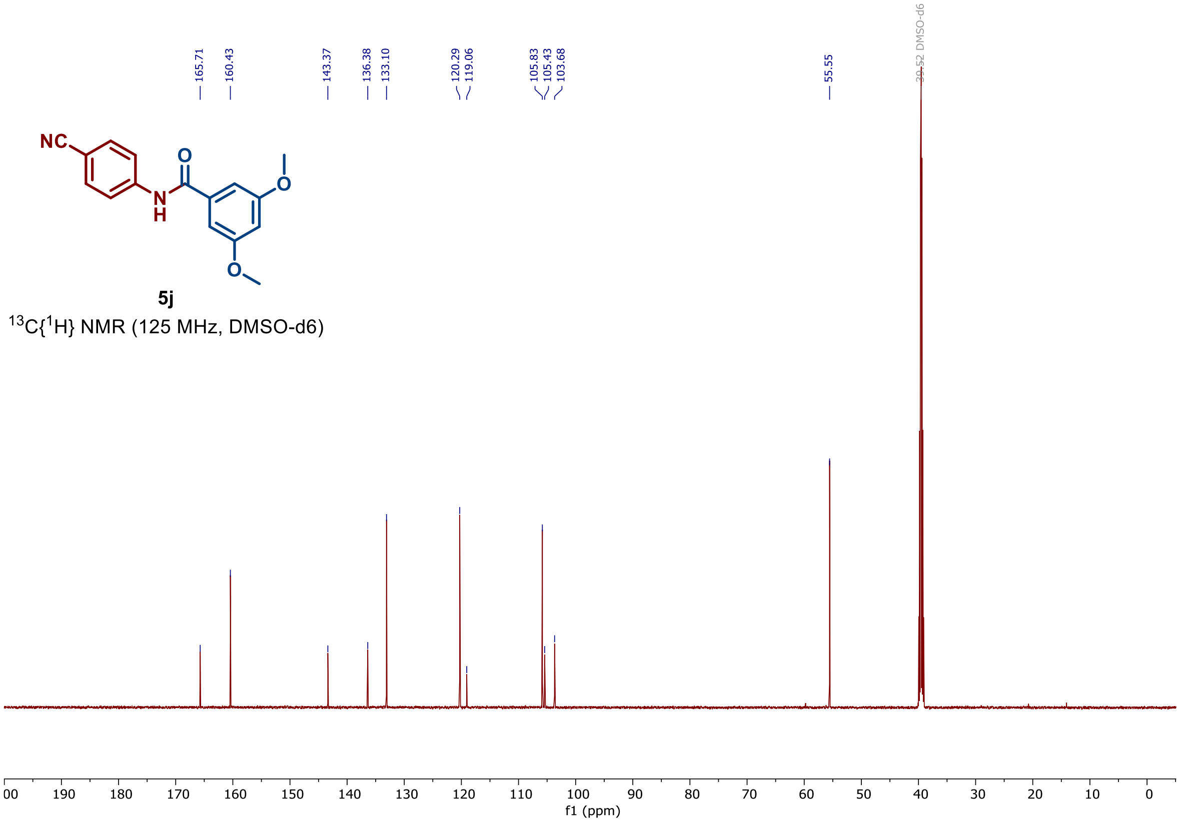


5i

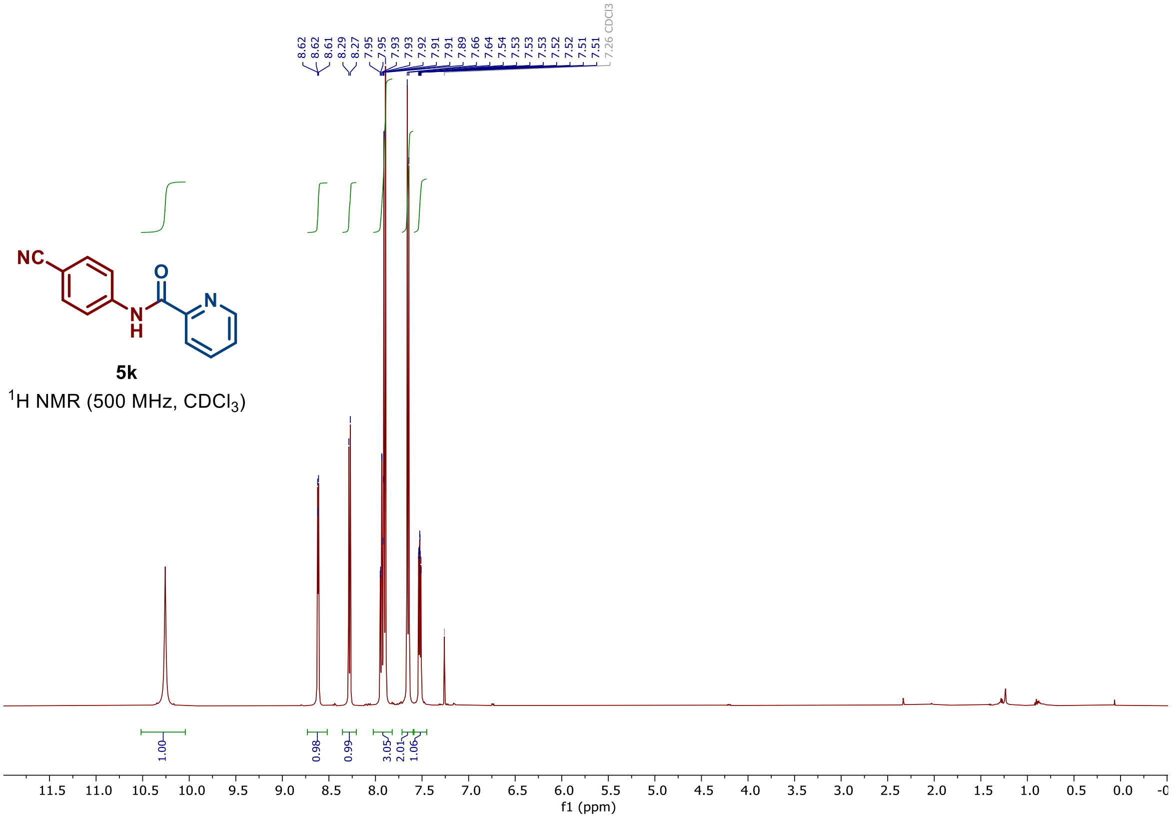
^{13}C{^{1}H} NMR (125 MHz, DMSO-d6)

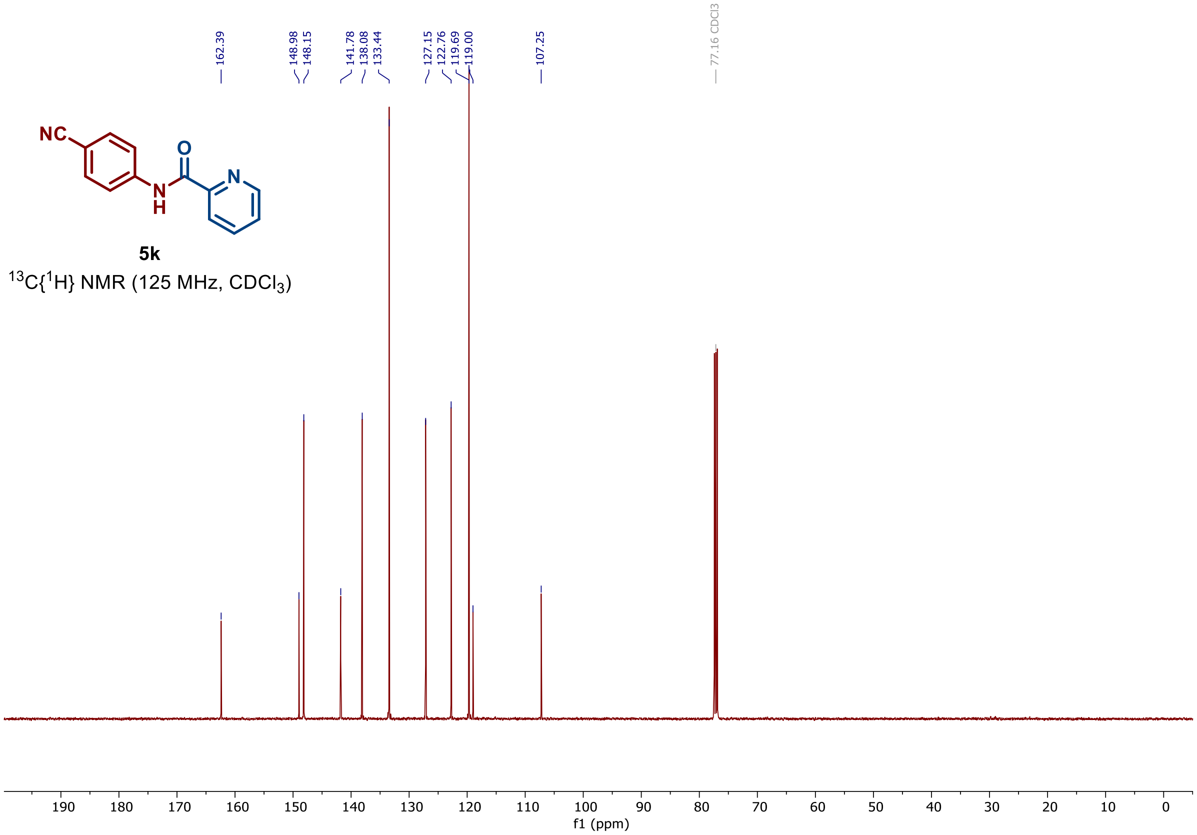
^{1}H and ^{13}C{^{1}H} NMR of N-(4-cyanophenyl)-3,5-dimethoxybenzamide (5j).



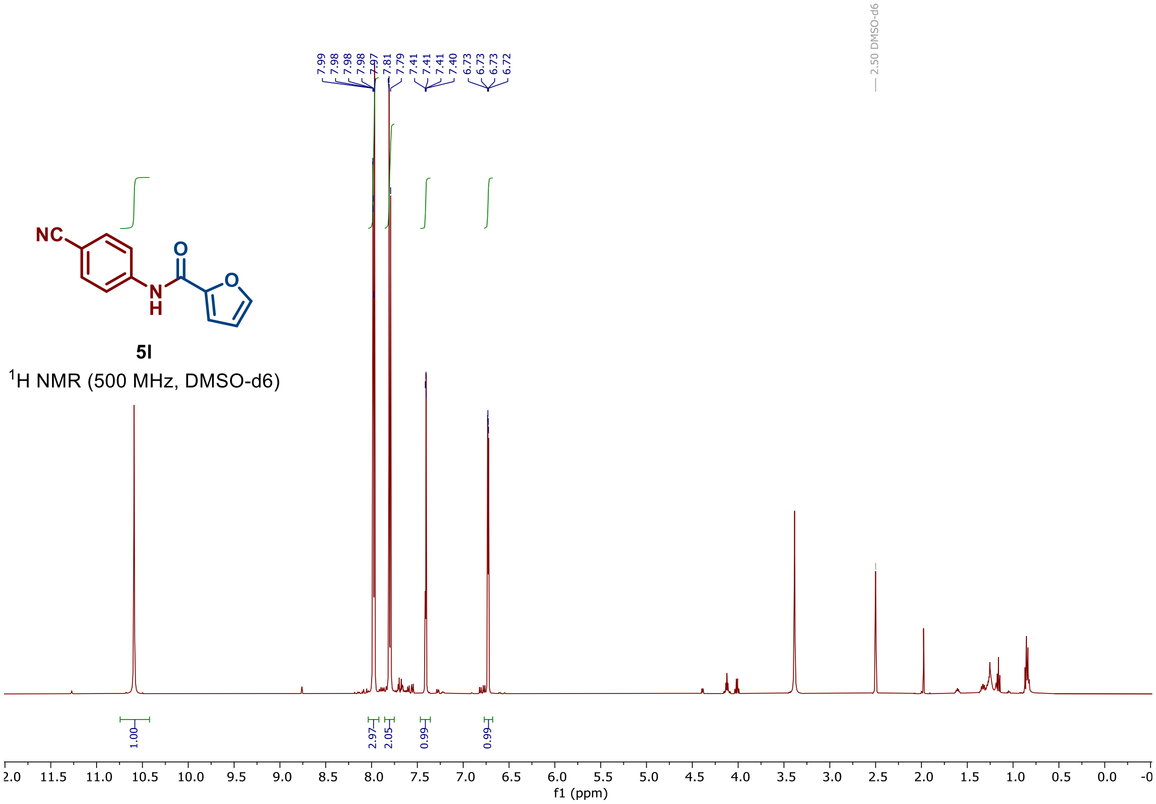


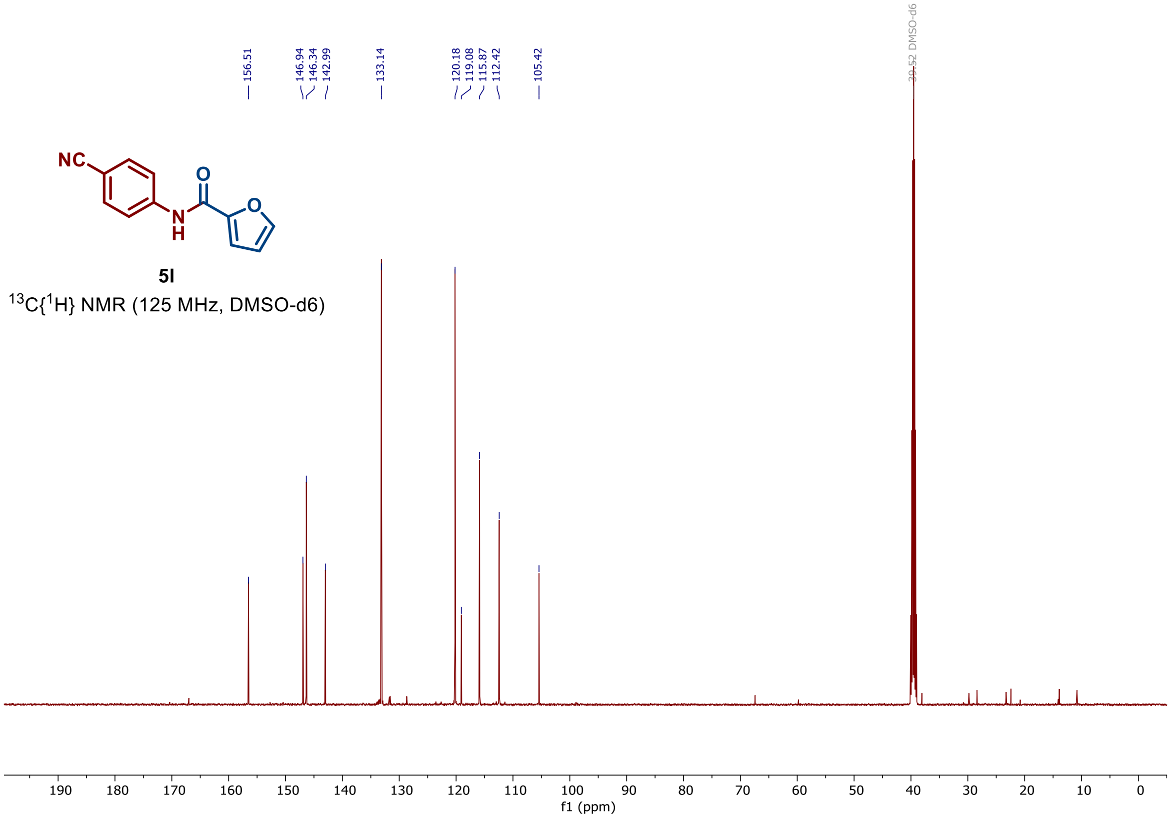
^{1}H and ^{13}C{^{1}H} NMR of N-(4-cyanophenyl)picolinamide (5k).



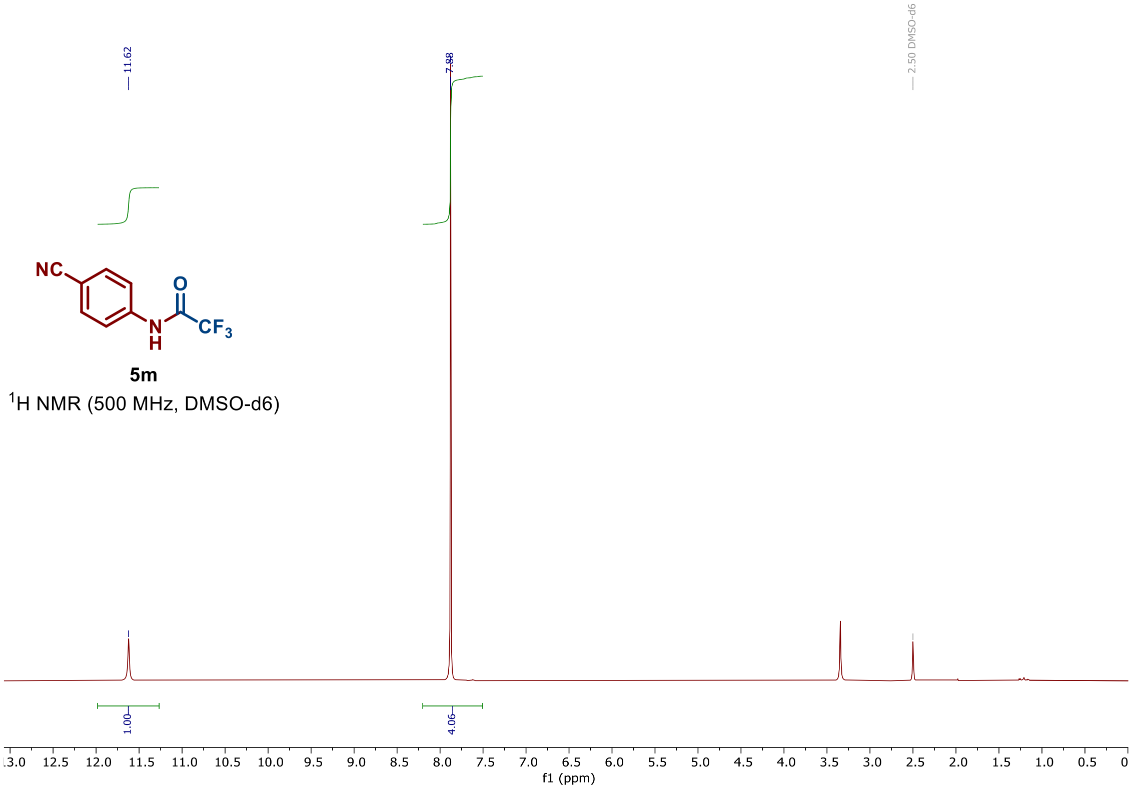


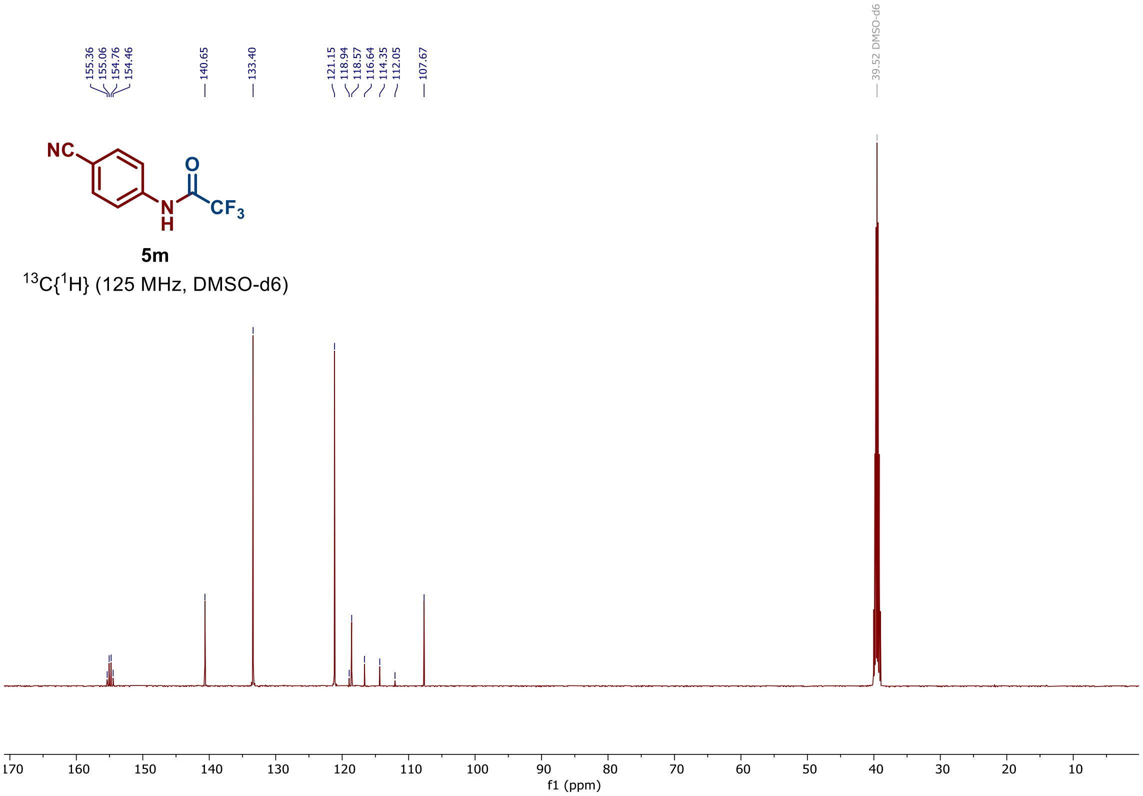
^{1}H and ^{13}C{^{1}H} NMR of N-(4-cyanophenyl)furan-2-carboxamide (5l).

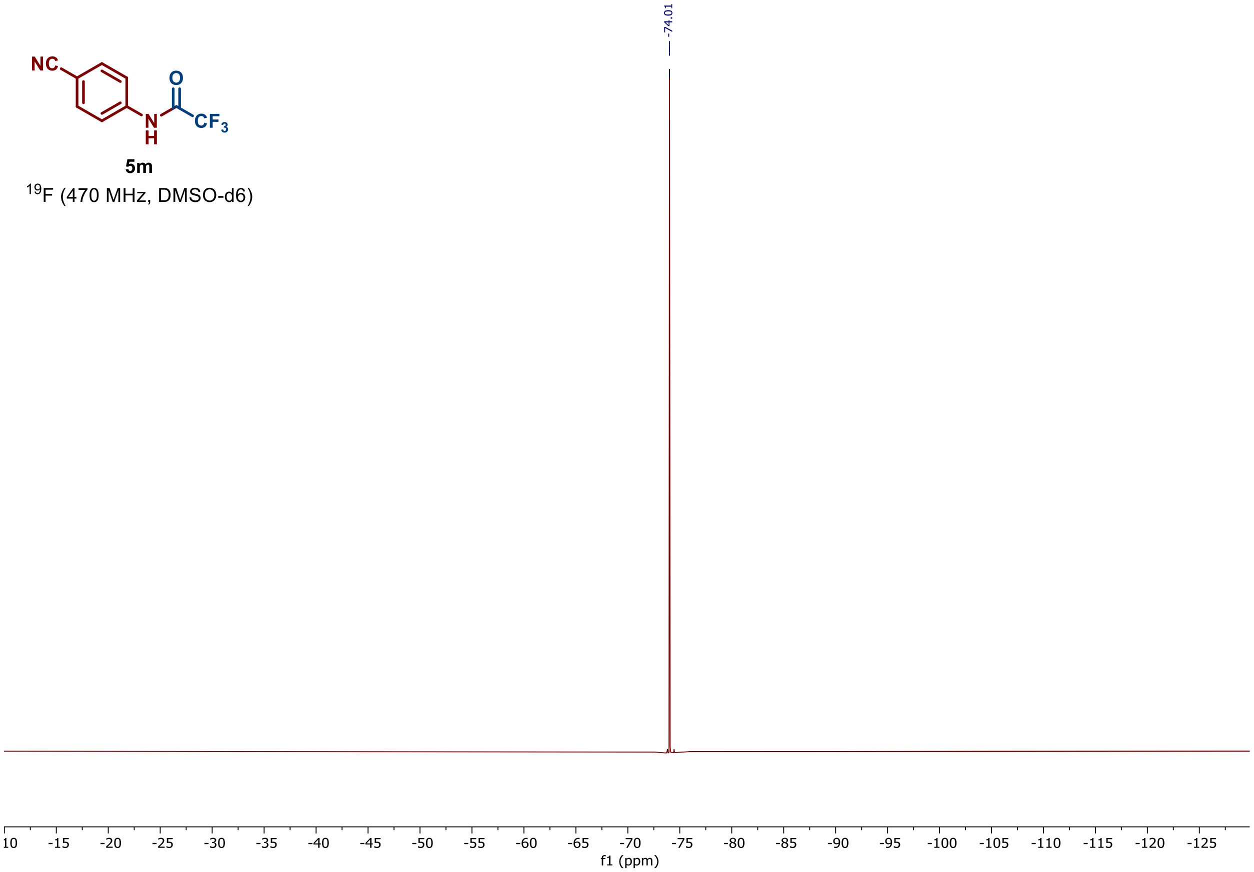




^{1}H, ^{13}C{^{1}H}, and ^{19}F NMR of N-(4-cyanophenyl)-2,2,2-trifluoroacetamide (5m).



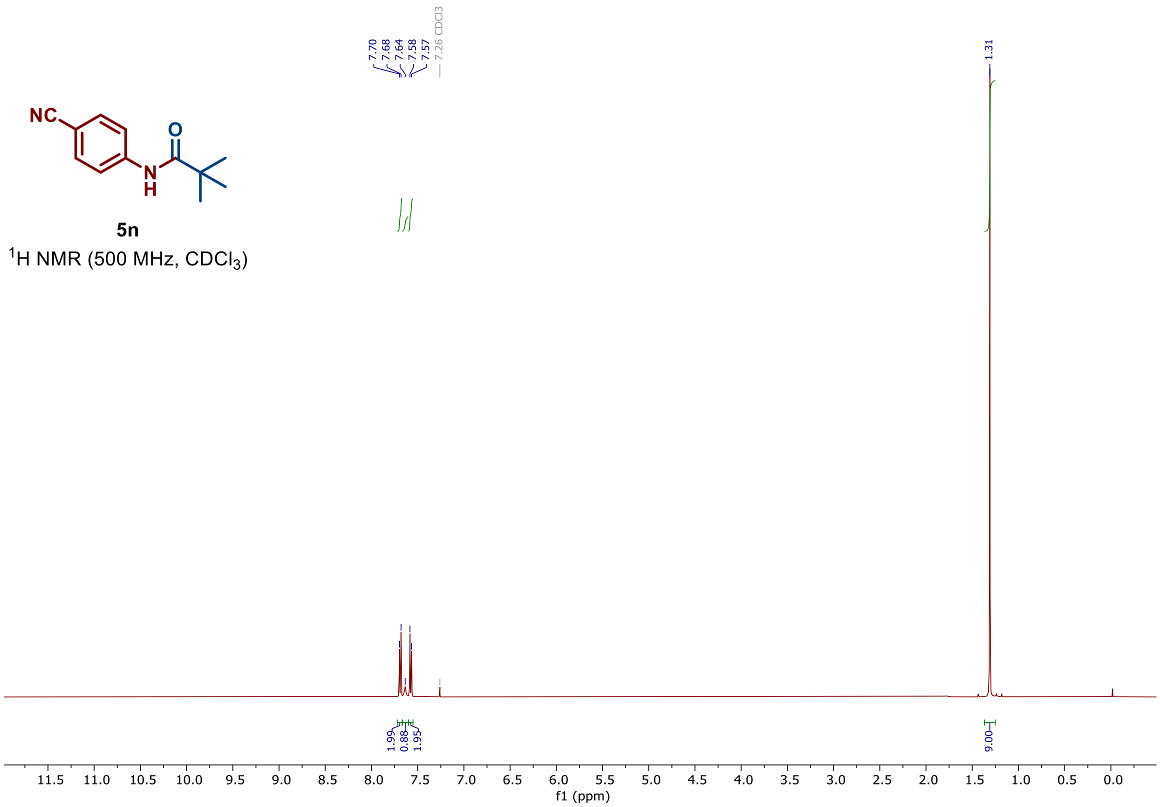




5m

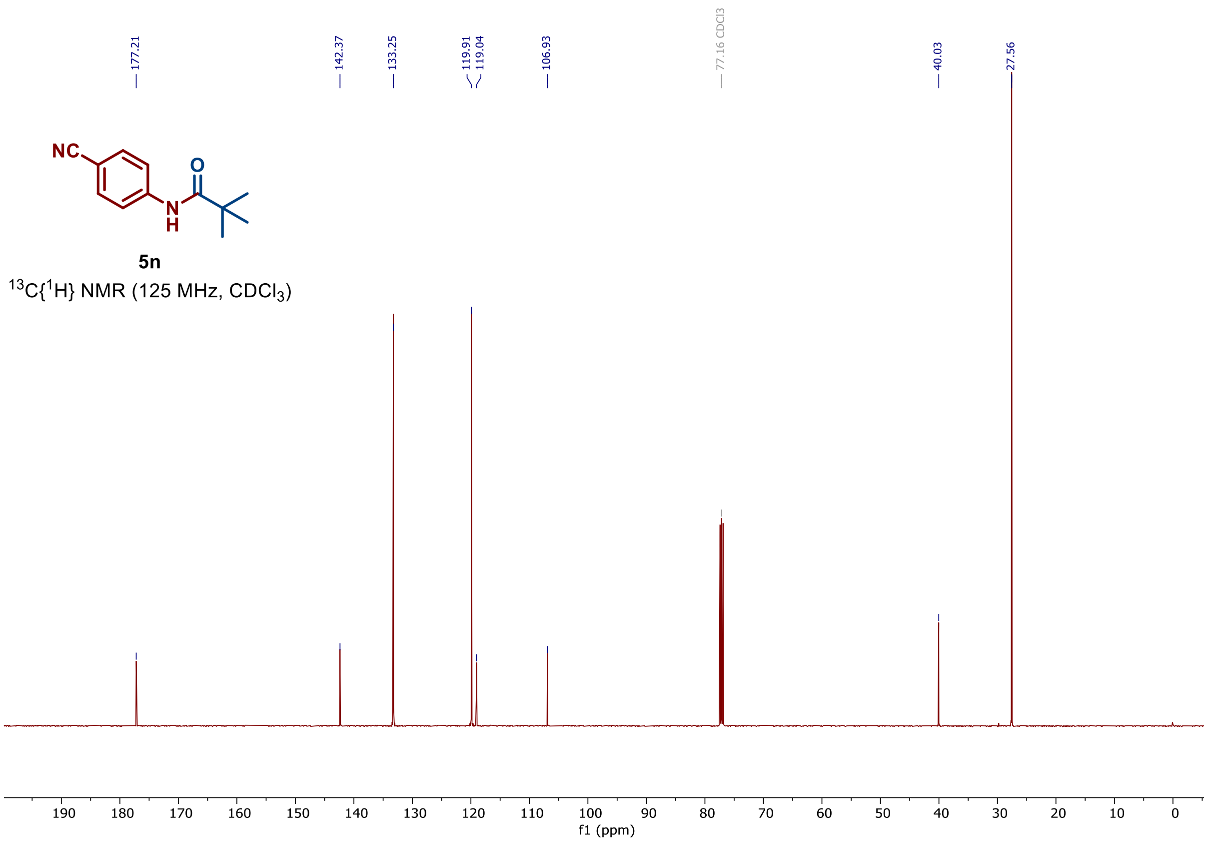
^{19}F (470 MHz, DMSO-d6)

^{1}H and ^{13}C{^{1}H} NMR of N-(4-cyanophenyl)pivalamide (5n).



5n

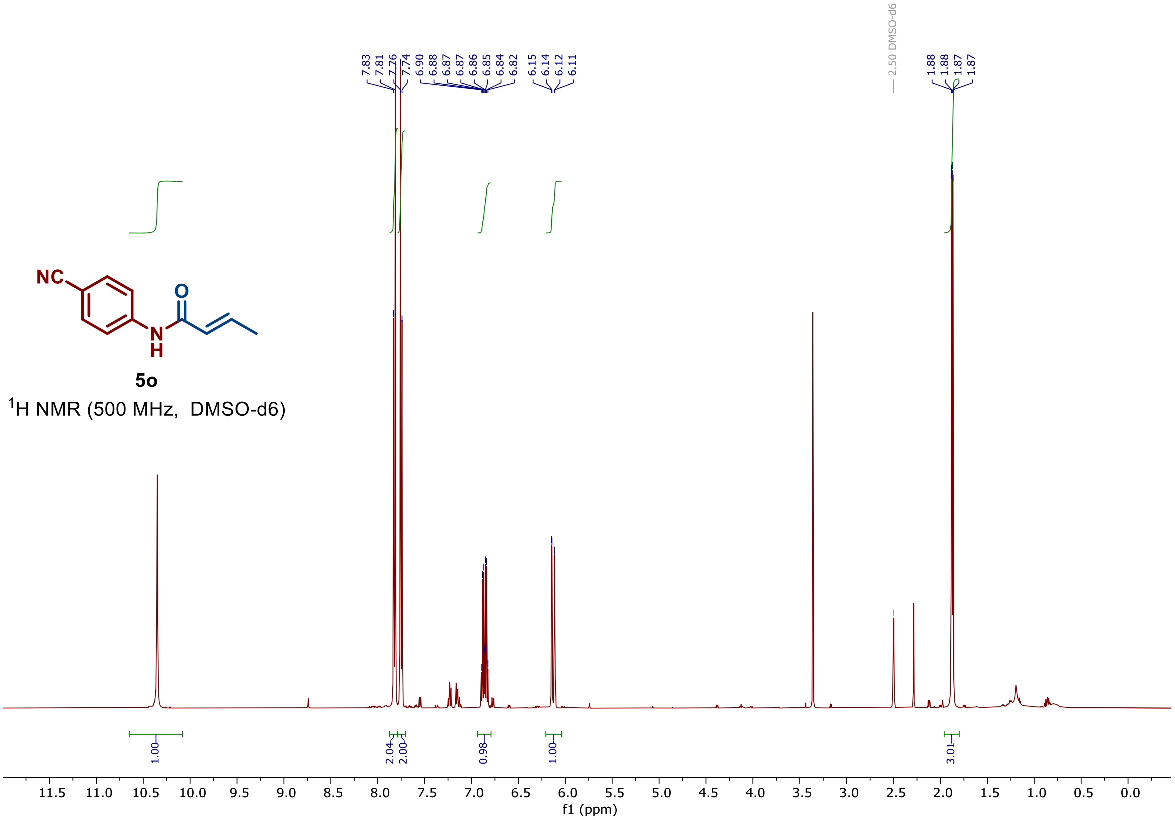
^{1}H NMR (500 MHz, CDCl$_3$)

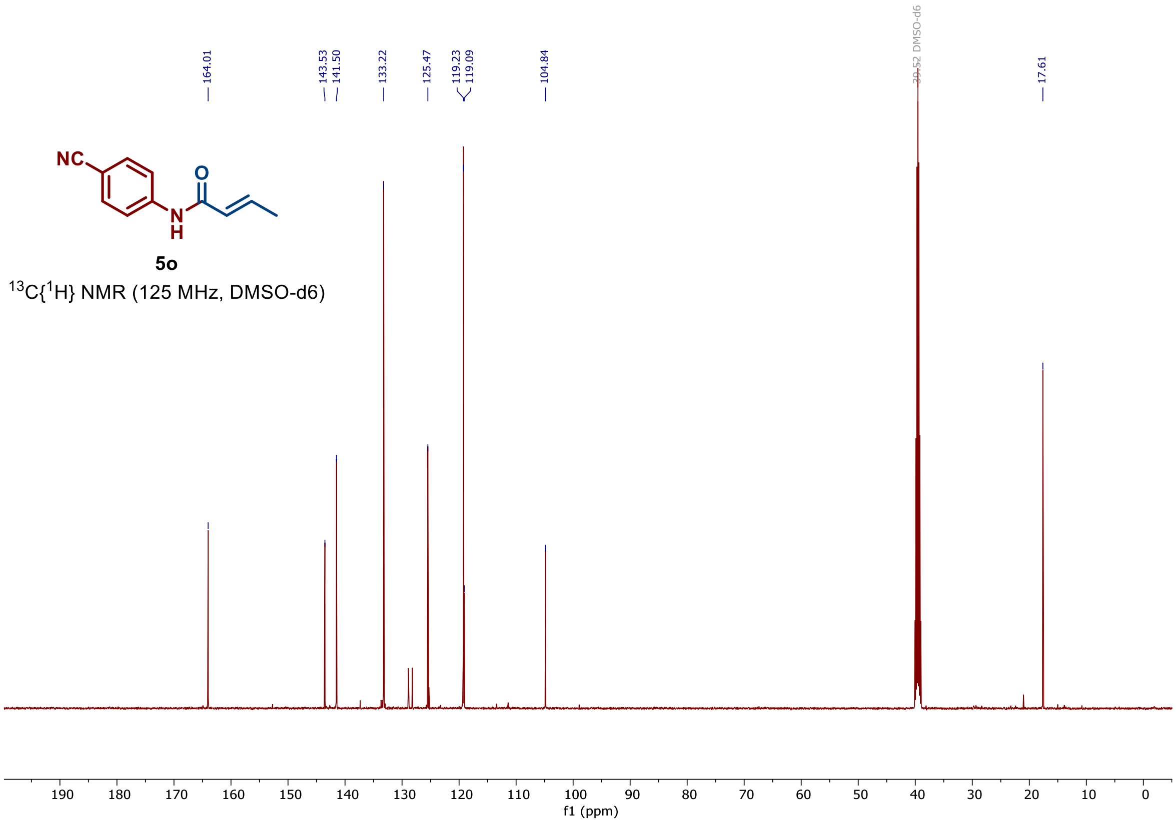


5n

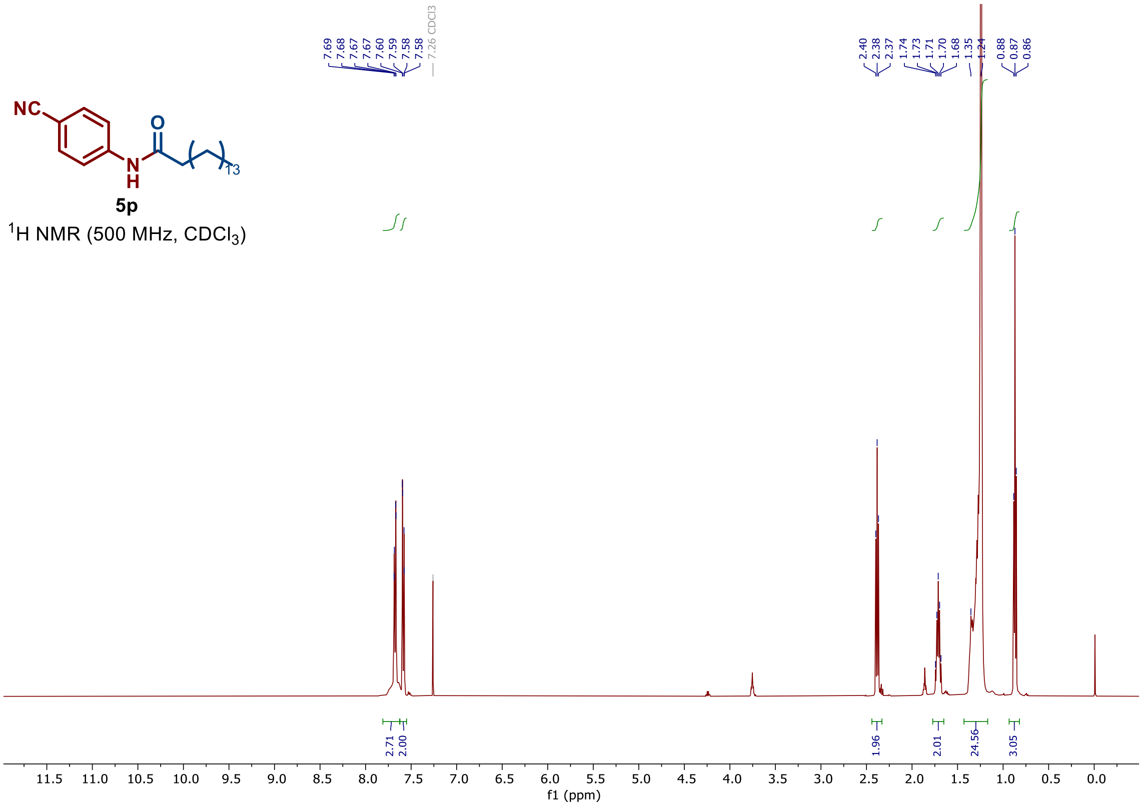
^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$)

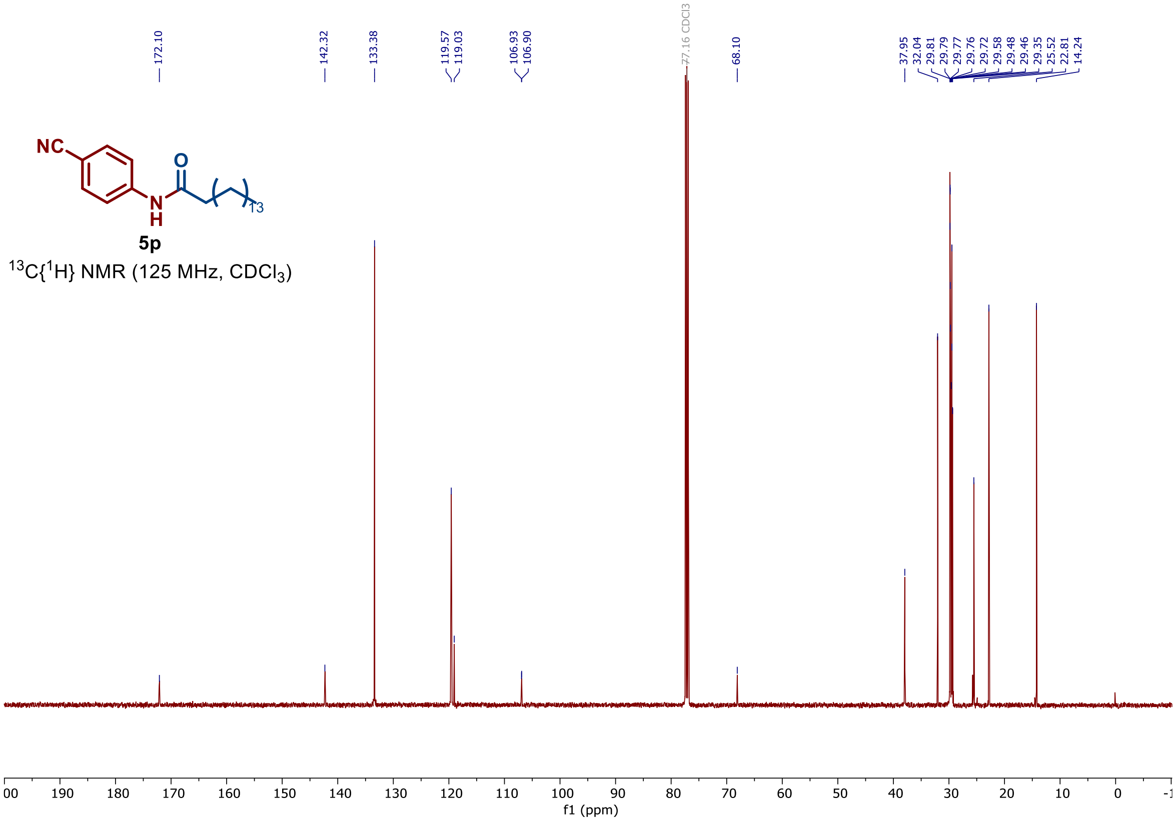
^{1}H and ^{13}C{^{1}H} NMR of (E)-N-(4-cyanophenyl)but-2-enamide (5o).



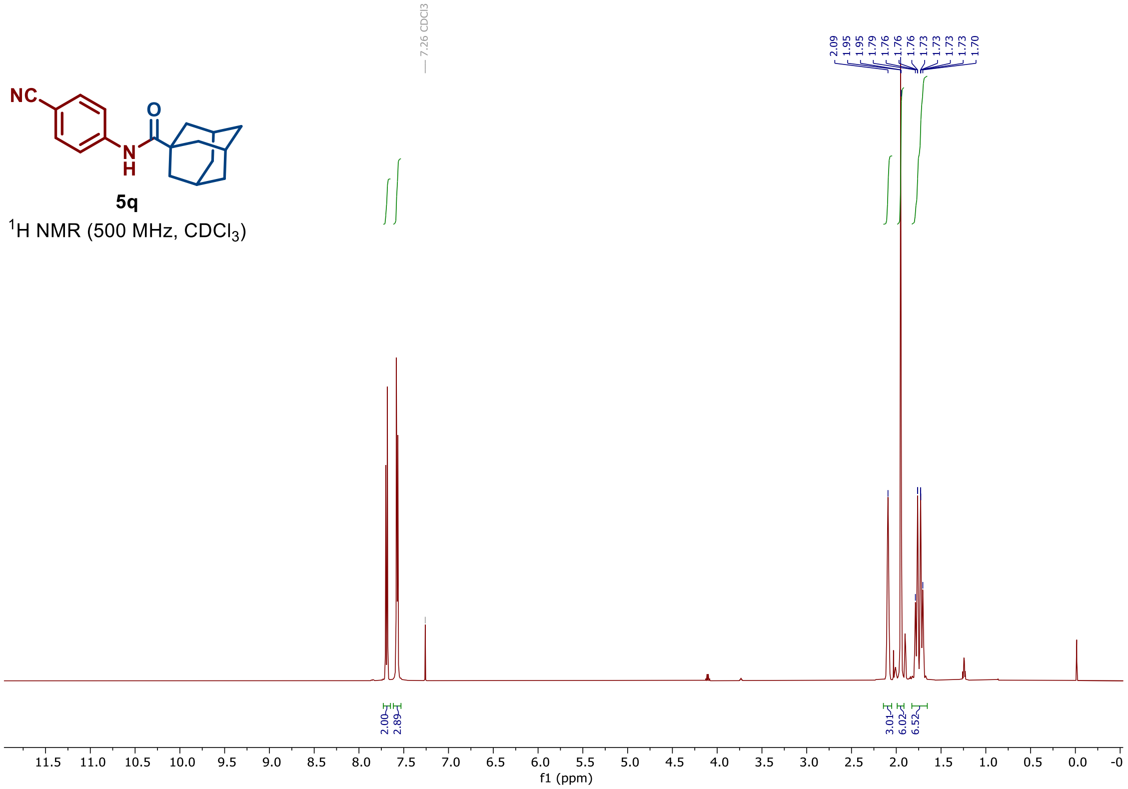


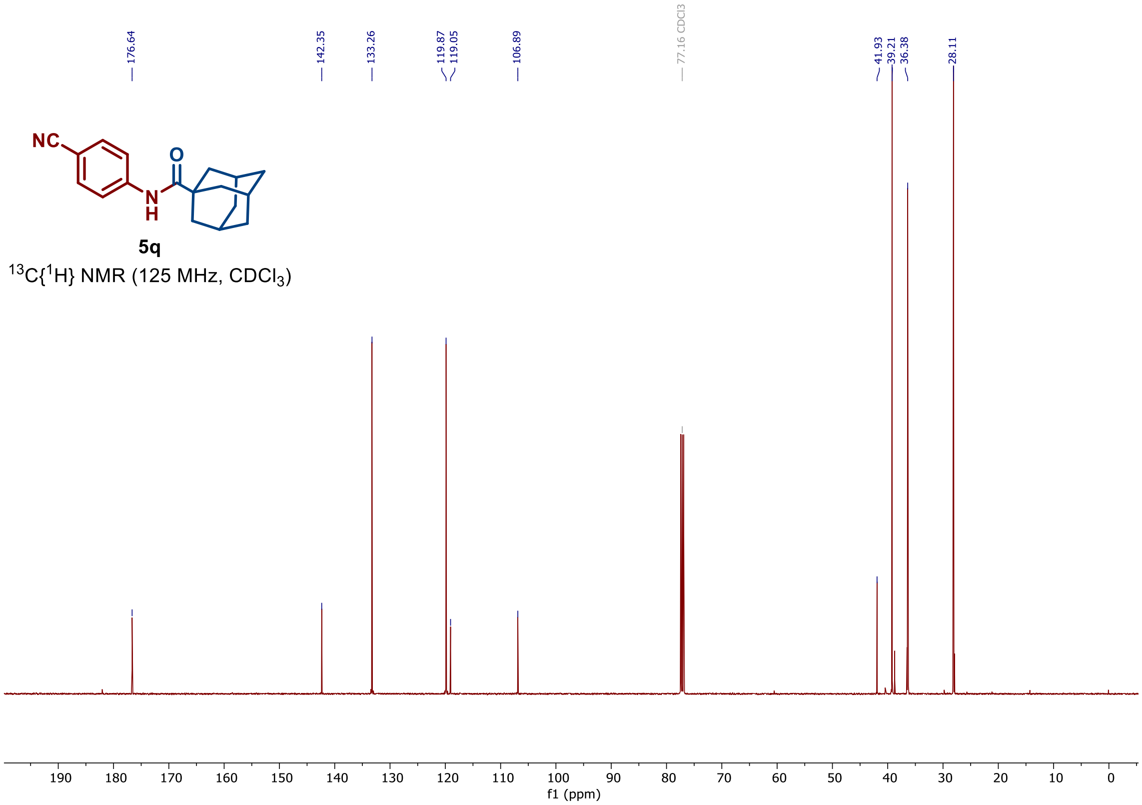
^{1}H and ^{13}C{^{1}H} NMR of N-(4-cyanophenyl)palmitamide (5p).



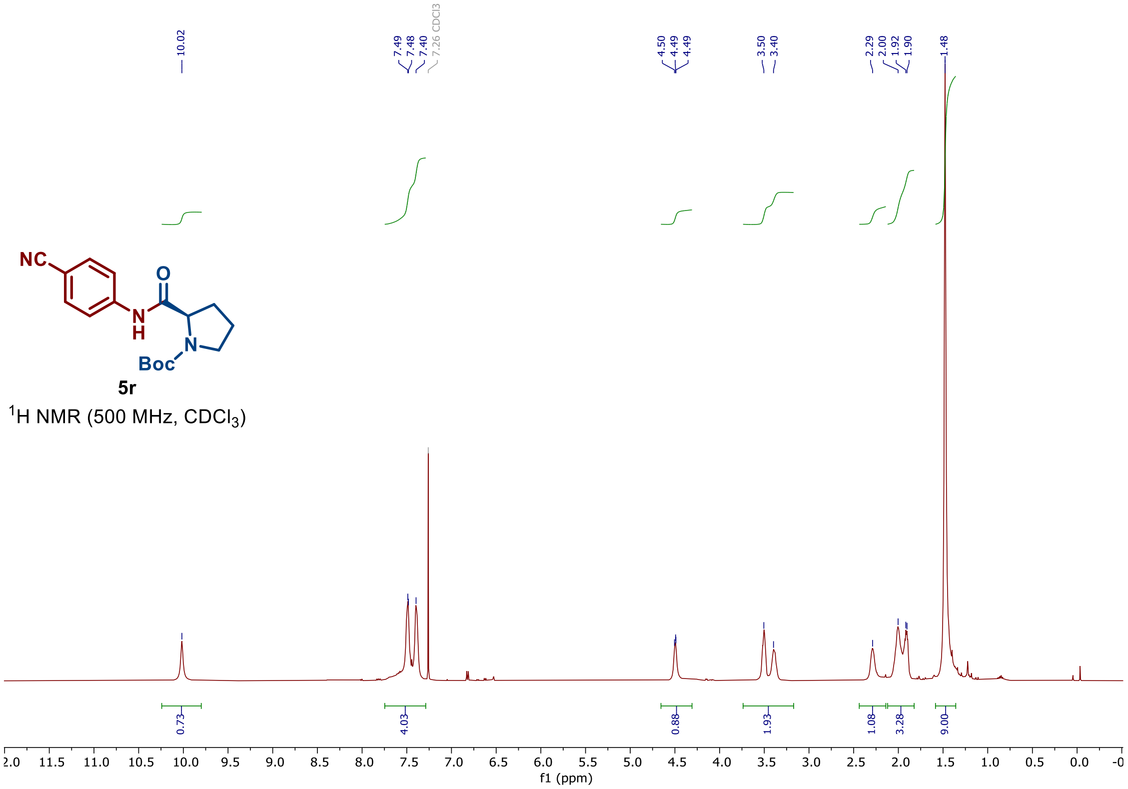


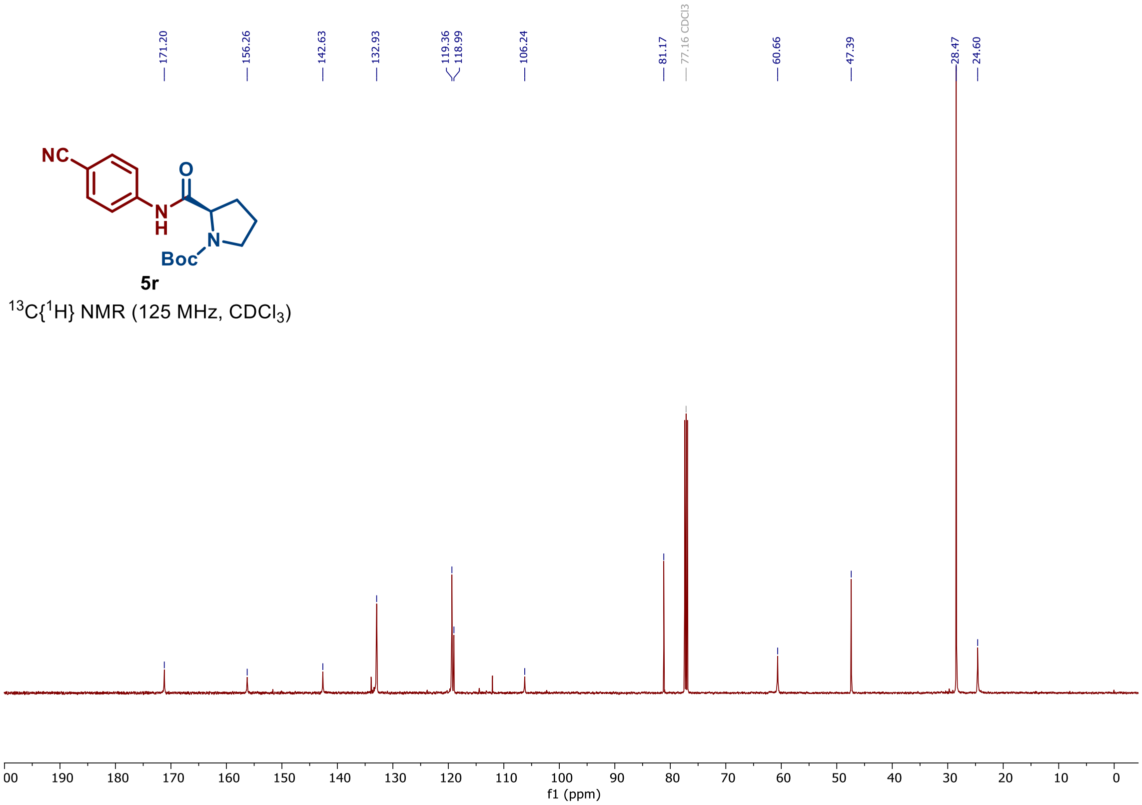
^{1}H and ^{13}C{^{1}H} NMR of N-(4-cyanophenyl)adamantane-1-carboxamide (5q).



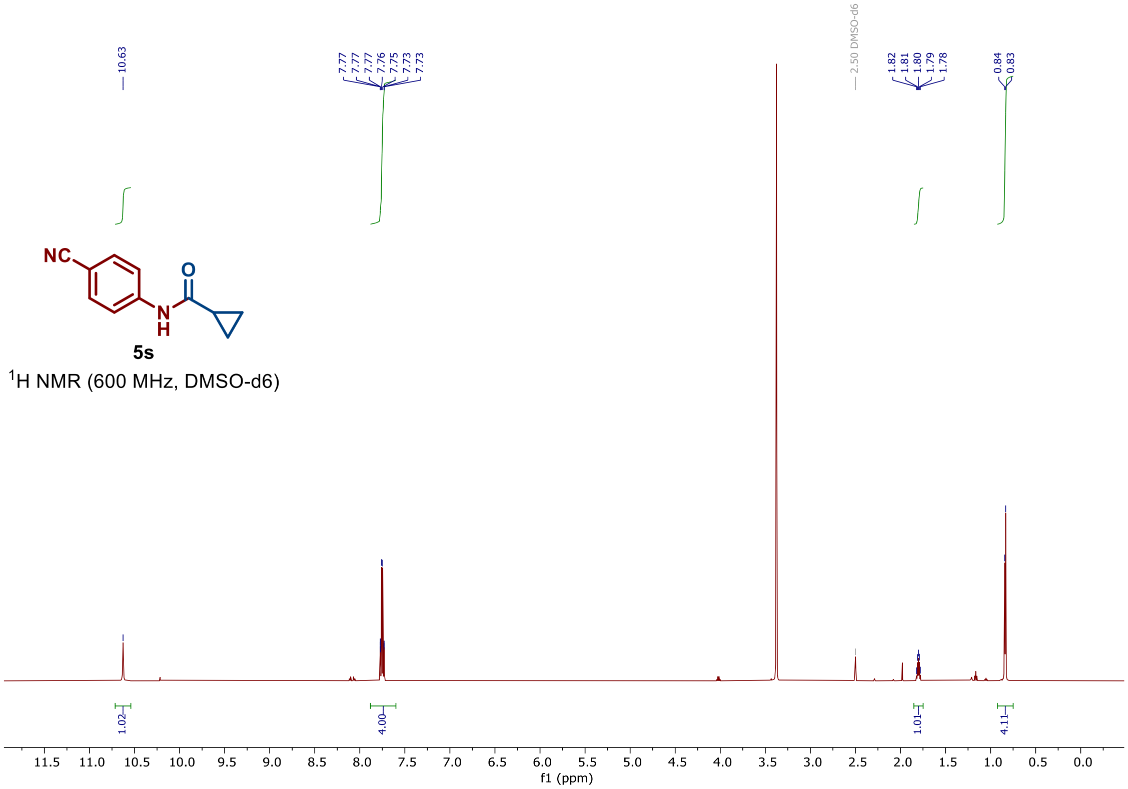


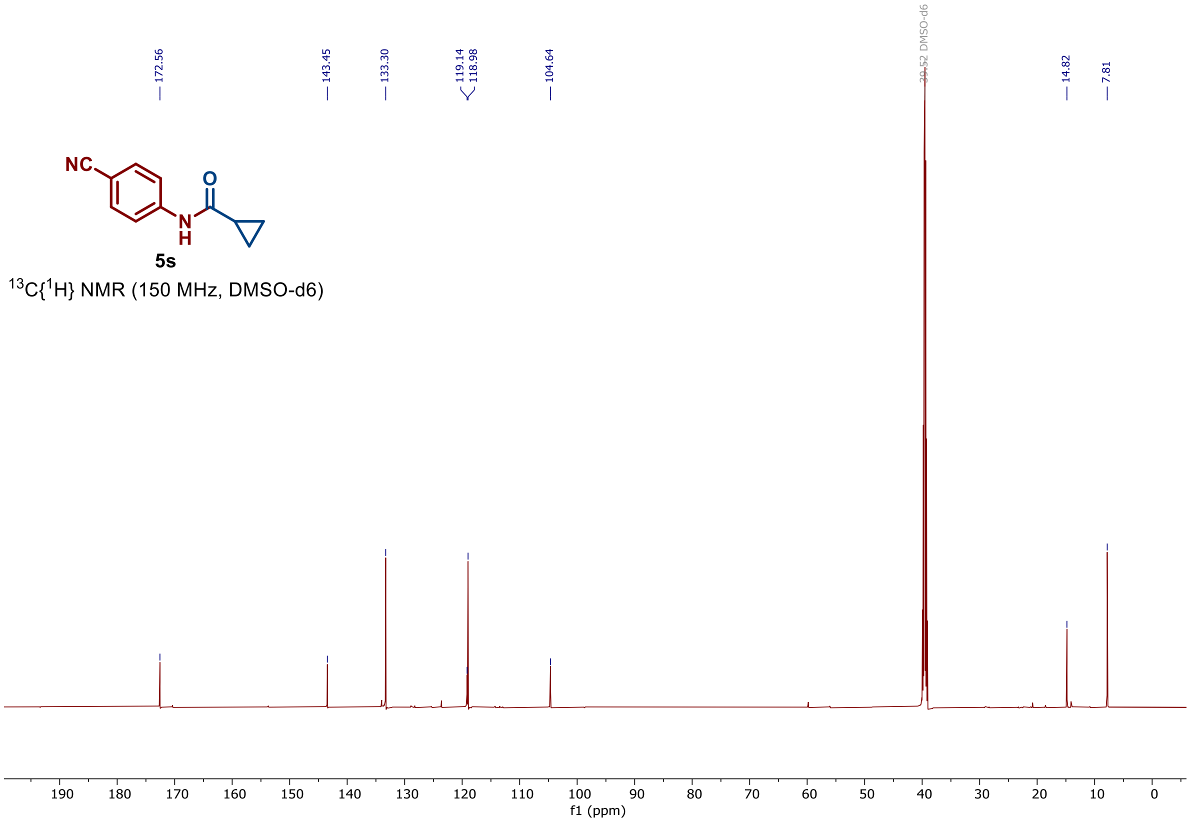
^{1}H and ^{13}C{^{1}H} NMR of tert-butyl (S)-2-((4-cyanophenyl)carbamoyl)pyrrolidine-1-carboxylate (5r).



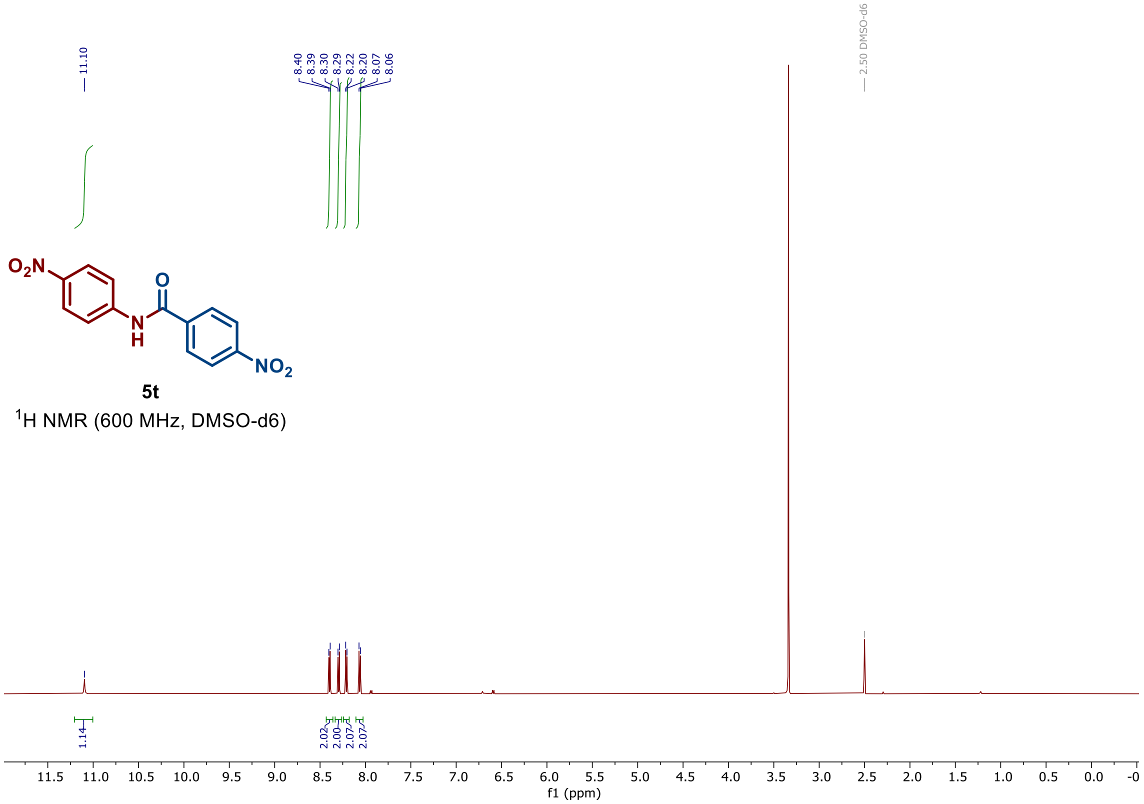


^{1}H and ^{13}C{^{1}H} NMR of N-(4-cyanophenyl)cyclopropanecarboxamide (5s).

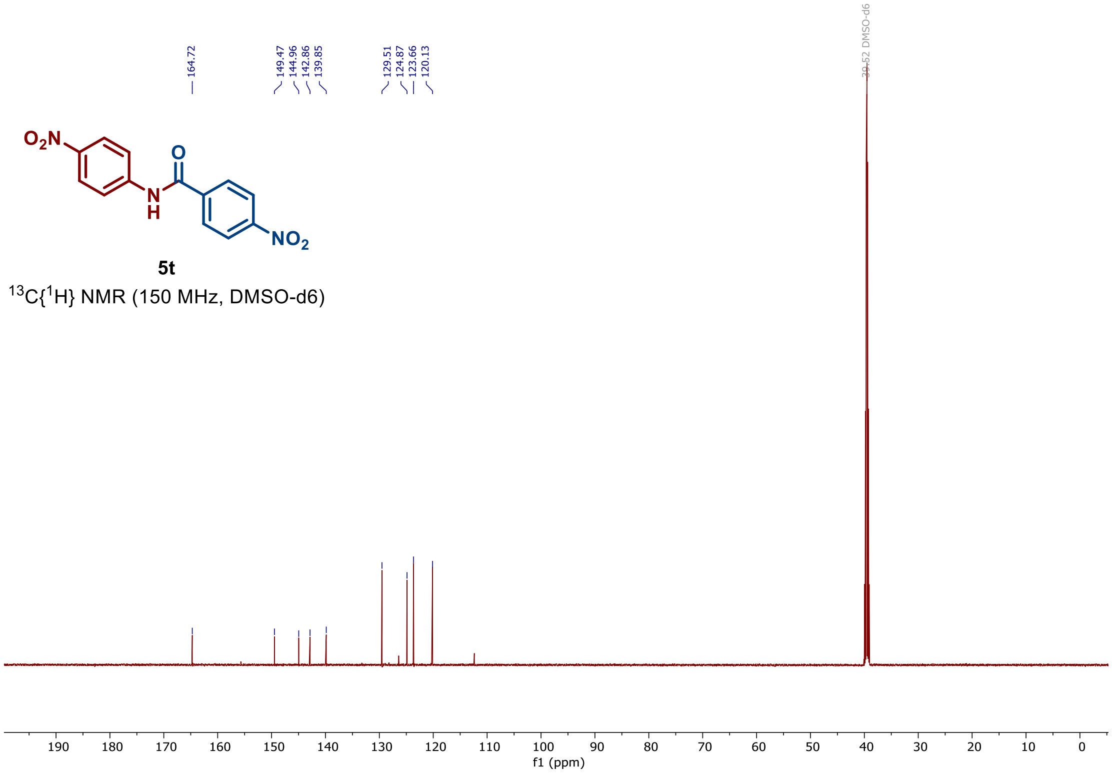




^{1}H and ^{13}C{^{1}H} NMR of 4-nitro-N-(4-nitrophenyl)benzamide (5t).


5t

^{1}H NMR (600 MHz, DMSO-d6)


5t

^{13}C{^{1}H} NMR (150 MHz, DMSO-d6)