Electronic Supplementary Material (ESI) for ChemComm.

Supporting Information

Modular Synthesis of Congested $\beta^{2,2}$-Amino Acids via the Merger of Photocatalysis and Oxidative Functionalisations

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Table of Contents

General information

Commercial reagents and solvents were used as purchased. Unless otherwise noted, all reactions were carried out under an atmosphere of N_2 in flame-dried glassware.
TLC were conducted with precoated glass-backed plates (silica gel 60 F254) and visualized by exposure to UV light (254 nm) or stained with basic potassium permanganate (KMnO4), Ninhydrin or *p*-anisaldehyde solutions, and subsequent heating.
Flash column chromatography was performed on silica gel (40-60 µm) or on neutral aluminumoxide (Brockmann Grade I, 58 Å), the eluent used is reported in the respective experiments.
^{1}H NMR spectra were recorded at 400 MHz or 600 MHz, ^{13}C NMR spectra at 101 MHz or 151 MHz, using Bruker Avance III 600 and Bruker Avance 400 Chemical shifts are reported in ppm relative to the solvent signal, coupling constants *J* in Hz. Multiplicities were defined by standard abbreviations. High-resolution mass spectra (HRMS) were obtained using ESI ionization (positive) on a Bruker micrOTOF.
As far as the flow setup is concerned, liquids and O_2 gas were pumped by means of a HPLC pump (Shimadzu LC-20AD) and a Mass Flow Controller (Bronkhorst EL-FLOW), respectively. Fittings and other components were purchased from IDEX (Switch Valve: IDEX P-783; Check Valve: IDEX CV-3000; PEEK T-mixer: IDEX P-712). Perfluoroalkoxy (PFA) tubing was used (ID: 0.75mm, unless otherwise specified).

LED’s emission spectra & standard reaction set up

Blue LEDs (32 W, λ_{max} = 440 nm, Figure S1A) were used for irradiation, in combination with an EvoluChem™ PhotoRedOx Box (Figure S1B). The reaction temperature was kept at 27 °C thanks to the fans incorporated in the reactor. With the fans switched off, reactions could be conducted at a constant temperature of 42 °C. For reactions carried out at 60 °C, two 32 W LED lamps were placed at 3.0 cm from the reaction vessel (Figure S1C). The heat produced by the LEDs was sufficient to maintain a constant temperature.

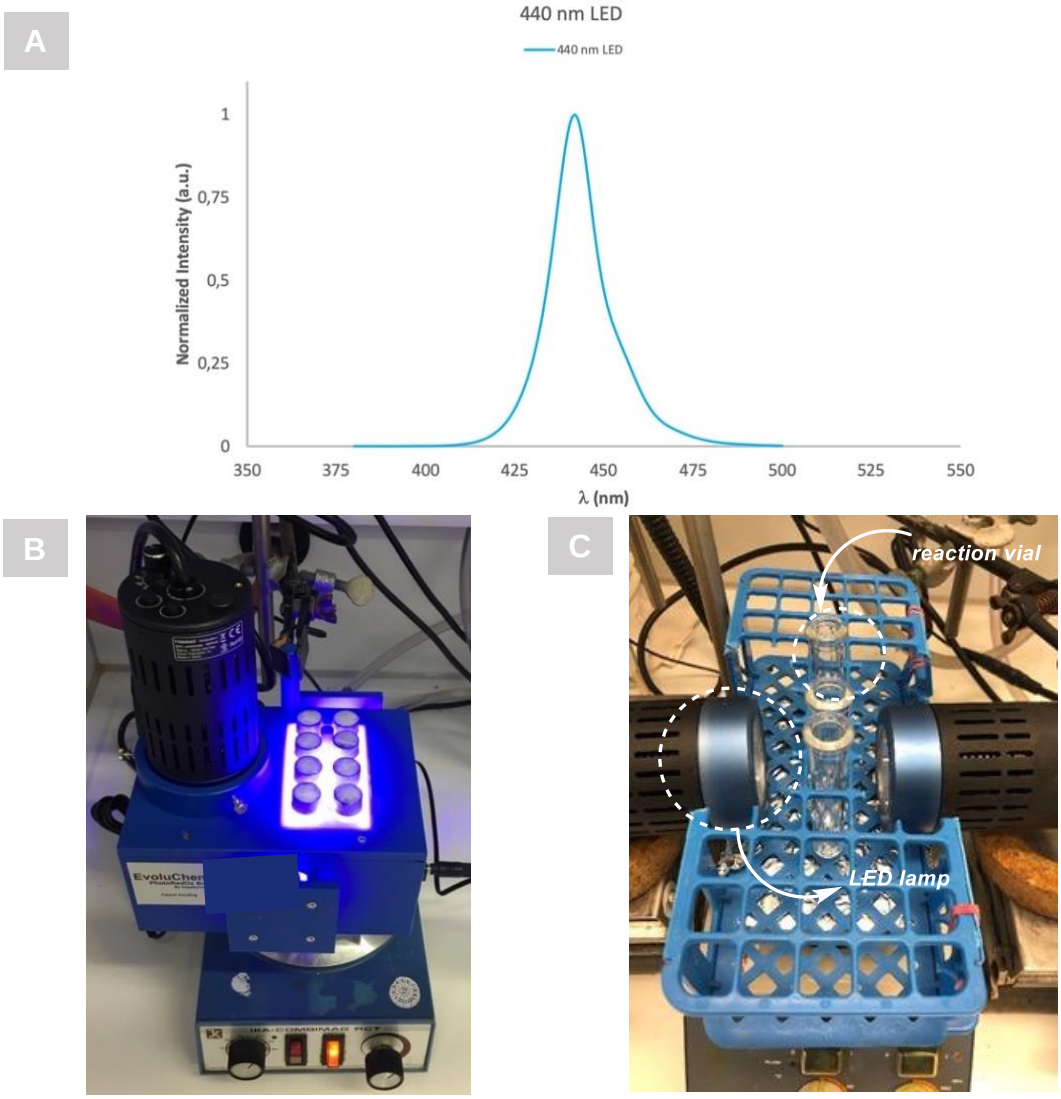


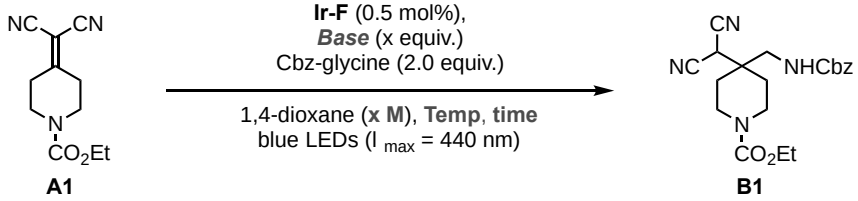
Figure S1. A) LED lamp emission spectrum. **B)** Reaction set-up for reactions at 27 °C or 42 °C. **C)** Reaction set-up for reactions at 60 °C

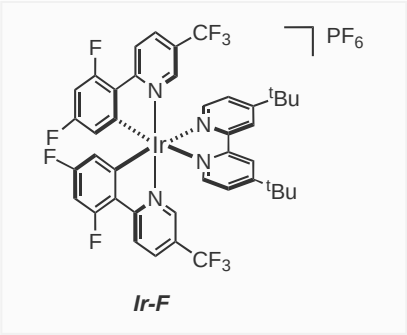
Optimization of the reaction conditions

Giese-type reaction

General protocol: A1 (21.9 mg, 1.0 equiv. 0.1 mmol), **Ir-F** (0.5-1.0 mol%,), base (1.0 – 2.0 equiv.) and Cbz-glycine (41.8 mg, 0.2 mmol, 2.0 equiv.) were added to an 8 mL microwave vial and purged with N_2 (10 minutes under vacuum then open to N_2, repeated three times). 1,4-dioxane was added and the reaction bubbled with N_2 for 15 minutes. Bubbling was stopped and the vial was sealed and wrapped with parafilm, then irradiated at 440 nm, 60 °C for 16 hours. After removal of the solvent, the yields of the product and remaining starting material were calculated by ^{1}H NMR using trichloroethylene (9.0 µl, 0.1 mmol, 1.0 equiv.) as internal standard.

Table S1. Optimization studies Gise-type reaction



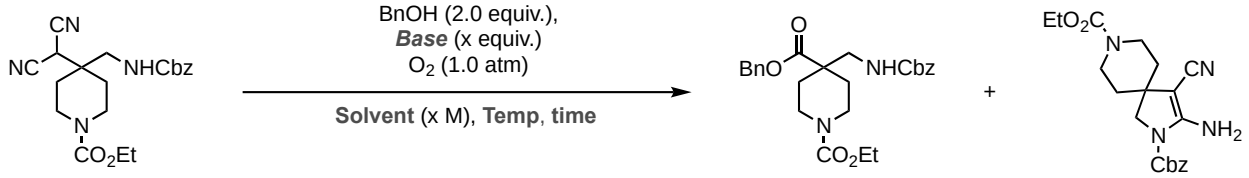


Entry	Base (equiv.)	Concentration (M)	Photocatalyst (mol%)	Temp. (°C)	Time (h)	B1 (%)	A1 left (%)
1	K_2HPO_4 (2.4)	0.1	**Ir-F** (1)	42	16	<5	84
2	2,6-Lutidine (2.4)	0.1	**Ir-F** (1)	42	16	43	58
3	Collidine (2.4)	0.1	**Ir-F** (1)	42	16	59	44
4	Collidine (2.4)	0.1	**Ir-F** (1)	24	16	24	76
5	Collidine (2.4)	0.1	**Ir-F** (1)	42	24	73	39
6	Collidine (2)	0.1	**Ir-F** (1)	60	16	>99	-
7	Collidine (2)	0.2	**Ir-F** (1)	60	16	>99	-
8	Collidine (2)	0.2	**Ir-F** (0.5)	60	16	>99	-
9	Collidine (2.4)	0.2	**Ir-F** (1)	42	16	46	21
10	Collidine (2.4)	0.4	**Ir-F** (1)	42	16	59	41

Oxidative esterification

General protocol: The following procedure was adapted from Hayashi and co-workers.[1] **B1** (39 mg, 0.1 mmol, 1.0 equiv.) and Cs_2CO_3 (65 mg, 0.2 mmol, 2.0 equiv.) were purged with O_2. The solvent (0.1 M, pre-bubbled with O_2 for at least 4 h) was added. Then, benzyl alcohol (22 mg, 0.2 mmol, 2.0 equiv.) was added, and the reaction was bubbled for 2 min. The reaction was stirred with an O_2 balloon inserted. After removal of the solvent and solids, the yields of the product, spirocyclic by-product (**D1**),[2] and remaining starting material were calculated by ^1H NMR using trichloroethylene (9.0 µl, 0.1 mmol, 1.0 equiv.) as internal standard.

Table S2. Optimization studies oxidative esterification.



B1 **14** **D1**

Entry	Base (equiv.)	Nucleophile (equiv.)	Solvent (M)	Temp. (°C)	Time (h)	B1 (%)	14 (%)	D1 (%)
1	Cs_2CO_3 (2)	BnOH (2)	MeCN (0.1)	RT	16	30	26	34
2	Cs_2CO_3 (2)	BnOH (2)	MeCN (0.1)	RT	24	0	72	3
3	Cs_2CO_3 (2)	BnOH (2)	MeCN (0.1)	RT	72	0	74	22
4	Cs_2CO_3 (2)	BnOH (2)	MeCN (0.1)	0	16	0	24	35
5	Cs_2CO_3 (2)	BnOH (2)	MeCN (0.1)	50	24	0	52	19
6	Cs_2CO_3 (2)	BnOH (2)	MeCN/Pentafluorobenzene (9:1)	RT	16	0	42	55
7	Cs_2CO_3 (1)	BnOH (2)	MeCN (0.1)	RT	24	0	50	45
8	DIPEA (2)	BnOH (2)	MeCN (0.1)	RT	24	0	32	37
9	Collidine (2)	BnOH (2)	MeCN (0.1)	RT	24	99	0	0
10	Et_3N (2)	BnOH (2)	MeCN (0.1)	RT	24	0	13	16
11*	DBU (2)	BnOH (2)	MeCN (0.1)	RT	24	0	82	0
12**	Cs_2CO_3 (2)	EtOH (10)	MeCN (0.1)	RT	24	0	60	10

***Although DBU provided slightly higher NMR yields than C_2CO_3, work-up and isolation of the targeted product in small scale was easier with the latter. Therefore, C_2CO_3 was selected as the optimal base for the reaction.

****While results using BnOH as the nucleophile performed slightly better, it was decided to use EtOH for the scope, due to practicality in purification, as well as the utility of the EtO-protected amino esters. Additionally, to avoid evaporation of the volatile substrate, a large excess of 10 equiv. of the nucleophile was used.

Synthesis & Characterization of Starting materials

Alkylidenemalononitriles A

General procedure 1 (GP1): Adapted from a procedure reported by Grenning and co-workers.[3] The corresponding cyclic ketone (1.0 equiv.) was dissolved in toluene (1.0 M). Malononitrile (1.0 equiv.), ammonium acetate (0.1 equiv.), and toluene/glacial acetic acid (3:1 v/v, 1.0 M total) were added. The reaction was heated at reflux (110-120 °C) with a Dean-Stark apparatus until completion (monitored by TLC). The reaction was then concentrated and quenched with 2N aq. HCl. The aqueous layer was extracted with ethyl acetate and the combined organic phases were washed with $NaHCO_3$, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography to afford the targeted product. Alkylidenemalononitriles **A12** (CAS 13166-10-4) , and **A14** (CAS 2972-73-8) are commercially available and were purchased from Fluorochem.

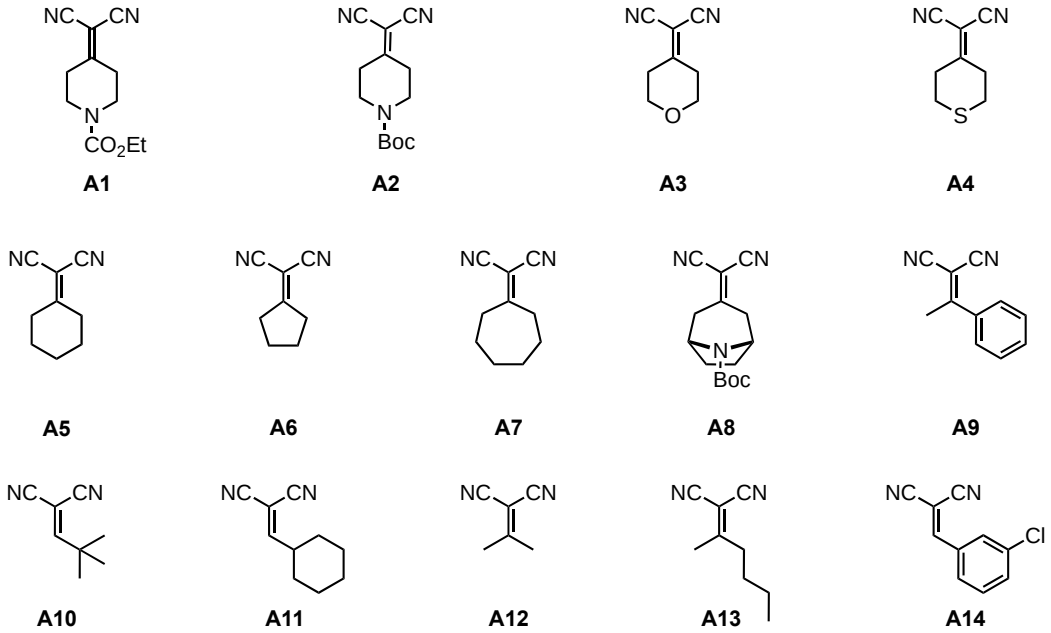
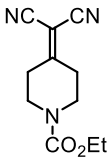


Figure S2. Synthesised alkylidenemalononitriles.

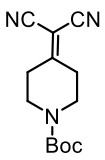
A1



Synthesized following **GP1** using ethyl 4-oxopiperidine-1-carboxylate (5.0 g, 29.2 mmol, 1.0 equiv.). Purification via flash chromatography using silica gel (cyclohexane/EtOAc 3:1) afforded **A1** as an off-white solid in 76% yield (4.85 g, 22.2 mmol). Characterization data matches the literature.[4]

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.19 (q, *J* = 7.1 Hz, 2H), 3.66 (t, *J* = 5.9 Hz, 4H), 2.75 (t, *J* = 5.9 Hz, 4H), 1.29 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (151 MHz, CDCl3) δ 179.0, 155.0, 111.2, 85.1, 62.4, 43.8, 34.1, 14.7.

A2

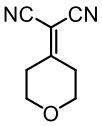


Synthesized following **GP1** using tert-butyl 4-oxopiperidine-1-carboxylate (1.0 g, 5.0 mmol, 1.0 equiv.). Purification via flash chromatography using silica gel (cyclohexane/EtOAc 3:1) afforded **A2** as a white solid in 76% yield (0.94 g, 3.8 mmol).[2]

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.60 (t, *J* = 5.8 Hz, 4H), 2.72 (t, *J* = 5.8 Hz, 4H), 1.47 (s, 9H).
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 179.5, 154.1, 111.2, 84.8, 81.2, 43.8, 34.1, 28.4.

HRMS (ESI): [m/z] calculated for $C_{13}H_{16}N_3O_2$ ([M-H]$^-$): 246.1249; Found: 246.1248.
R_f (cyHex/EtOAc, 4:1) = 0.4 [Ninhydrin]

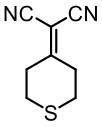
A3



Synthesized following **GP1** using tetrahydro-4H-pyran-4-one (0.6 mL g, 6.6 mmol, 1.0 equiv.). During the extraction a white precipitate formed which was filtered and washed to afford **A3** as a white solid in 43% yield (417 g, 2.8 mmol). Characterization data matches the literature.[5]

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.86 (t, *J* = 5.56, 4H), 2.80 (t, *J* = 5.56, 8 4H) ppm.
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 178.5, 111.1, 84.2, 67.8, 35.1 ppm.

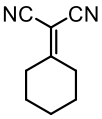
A4



Synthesized following **GP1** using tetrahydro-4H-thiopyran-4-one (0.582 g, 5.0 mmol, 1.0 equiv.). **A4** was isolated as a white solid in 48% yield (393 mg , 2.4 mmol). Characterization data matches the literature.[5]

^{1}H NMR (400 MHz, $CDCl_3$): 3.04-2.99 (m, 4H), 2.91-2.86 (m, 4H) ppm.
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 180.8, 111.2, 85.2, 36.4, 30.8 ppm.

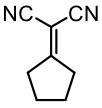
A5



Synthesized following **GP1** using cyclohexanone (0.68 mL, 6.6 mmol, 1.0 equiv.). Purification via flash chromatography using silica gel (cyclohexane/EtOAc 4:1) afforded **A5** as a colorless oil in 63% yield (4.85 g, 4.2 mmol). Characterization data matches the literature.[5]

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.67-2.64 (m, 4H), 1.83-1.77 (m, 4H), 1.71-1.66 (m, 2H)
^{13}C{^{1}H} NMR (101 MHz, CDCl3) δ 185.0, 111.7, 82.6, 34.7, 28.0, 25.0.

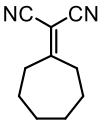
A6



Synthesized following **GP1** using cyclopentanone (750 mg, 8.9 mmol, 1.0 equiv.). Purification via flash chromatography using silica gel (cyclohexane/EtOAc 7:1 → 5:1) afforded **A6** as a yellow oil in 81% yield (952 mg, 7.2 mmol). Characterization data matches the literature.[5]

^{1}H NMR (600 MHz, $CDCl_3$) δ 2.82 – 2.72 (m, 4H), 1.94 – 1.86 (m, 4H).
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 192.6, 111.8, 81.3, 36.2, 26.0.

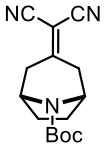
A7



Synthesized following **GP1** using cycloheptanone 2.5 g, 22.3 mmol, 1.0 equiv.). Purification via flash chromatography using silica gel (cyclohexane/EtOAc 1:1) afforded **A7** as a yellow solid in 87% yield (3.1 g, 19.4 mmol). Characterization data matches the literature.[3]

^{1}H NMR (600 MHz, $CDCl_3$) δ 2.79 (t, 4H), 1.76 (dt, *J* = 9.47, 4.52 Hz, 4H), 1.58 (dt, *J* = 6.15, 2.83 Hz, 4H).
^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 188.6, 111.9, 85.0, 36.3, 29.1, 26.2.

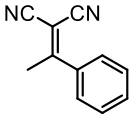
A8



Synthesized following **GP1** using tert-butyl 3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (500 mg, 2.22 mmol, 1.0 equiv.). Purification via flash chromatography using silica gel (cyclohexane/EtOAc 4:1 → 2:1) afforded **A8** as a pink solid in 87% yield (428 mg, 1.93 mmol). Characterization data matches the literature.[6]

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.45 (s, 2H), 2.91 (d, *J* = 15.62 Hz, 2H), 2.72 (d, *J* = 58.40 Hz, 2H), 2.16 – 1.97 (m, 2H), 1.55 (d, *J* = 8.19 Hz, 2H), 1.48 (s, 9H).
^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 178.9, 153.2, 111.3, 87.9, 81.0, 53.8, 40.1, 28.5.

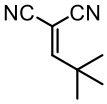
A9



Synthesized following **GP1** using cycloheptanone 2.5 g, 22.3 mmol, 1.0 equiv.). Purification via flash chromatography using silica gel (cyclohexane/EtOAc 1:1) afforded **A9** as a yellow solid in 87% yield (3.1 g, 19.4 mmol). Characterization data matches the literature.[7]

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.55 (dt, *J* = 7.68, 2.84 Hz, 3H), 7.53 – 7.49 (m, 2H), 2.64 (s, 3H).
^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 175.6, 136.0, 132.4, 129.2, 127.5, 112.9, 112.8, 84.9, 24.4.

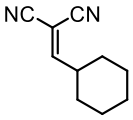
A10



Synthesized following **GP1** using cycloheptanone 2.5 g, 22.3 mmol, 1.0 equiv.). Purification via flash chromatography using silica gel (cyclohexane/EtOAc 1:1) afforded **A10** as a yellow solid in 87% yield (3.1 g, 19.4 mmol). Characterization data matches the literature.[8]

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.21 (s, 1H), 1.31 (s, 9H).
^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 177.6, 113.2, 111.2, 87.0, 37.1, 28.7.

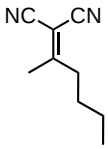
A11



Synthesized following **GP1** using cycloheptanone 2.5 g, 22.3 mmol, 1.0 equiv.). Purification via flash chromatography using silica gel (cyclohexane/EtOAc 1:1) afforded **A11** as a yellow solid in 87% yield (3.1 g, 19.4 mmol). Characterization data matches the literature.[9]

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.15 (d, *J* = 10.49 Hz, 1H), 2.82 – 2.62 (m, 1H), 1.83 – 1.70 (m, 5H), 1.42 – 1.31 (m, 2H), 1.25 (qd, *J* = 12.59, 11.93, 3.21 Hz, 3H).
^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 173.8, 112.4, 110.7, 88.0, 42.3, 31.0, 25.2, 24.7.

A13



Synthesized following **GP1** using 2-hexanone (0.45 g, 4.5 mmol, 1.0 equiv.). Purification via flash chromatography using silica gel (cyclohexane/EtOAc 1:1) afforded **A13** as an orange oil in 66% yield (0.36 g, 2.9 mmol). Characterization data matches the literature.[10]

^{1}H NMR (600 MHz, $CDCl_3$) δ 2.58 (m, 2H), 2.27 (s, 3H), 1.55 (p, *J* = 7.6 Hz, 2H), 1.43 – 1.35 (m, 2H), 0.95 (t, *J* = 7.4 Hz, 3H).

Synthesis & Characterization of Substituted Malononitrile Derivatives

General procedure 2 (GP2): The malononitrile derivative (1.0 mmol, 1.0 equiv.), **Ir-F** (5.5 mg, 0.5 mol%) and Cbz-glycine (209.2 mg, 1.0 mmol, 2.0 equiv.,) were added to an 8 mL microwave vial and purged with N_2 (5 minutes under vacuum then open to N_2, repeating three times). 1,4-dioxane (5 mL, 0.2 M) was added and the reaction was bubbled with N_2 for 10 minutes. Bubbling was stopped and *sym*-collidine (264 µL, 2.0 mmol, 2.0 equiv.) was added, and the solution was bubbled for an additional 30 seconds. The vial was sealed and wrapped with parafilm, then irradiated at 440 nm, 60 °C (fan off) for 16 hours. Afterwards, the solvent was removed in vacuo and EtOAc was added. Citric acid (10 wt%) was added and the aqueous phase was washed with EtOAc. The organic phases were then washed with sat. $NaHCO_3$ (aq.), dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified to afford the desired product.

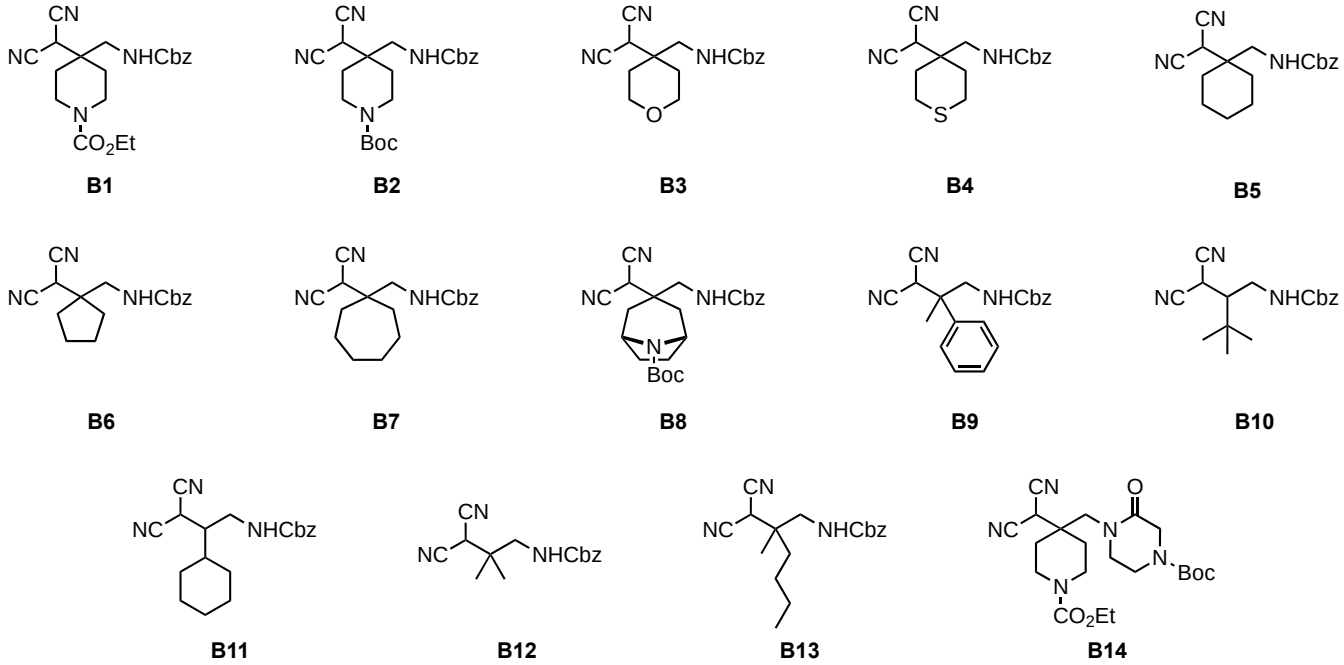
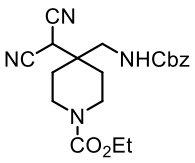


Figure S3. Synthesised substituted malononitrile derivatives.

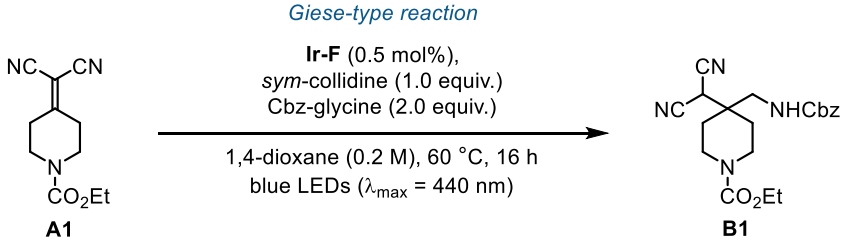
B1



Synthesized following **GP2** using **A1** (0.22 g, 1.0 mmol, 1.0 equiv.) and *Z*-glycine (418.4 mg, 2.0 mmol, 2.0 equiv.). **B1** was isolated as a yellowish solid in 95% yield (0.37 g, 0.95 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.28 (m, 5H), 5.37 (s, 1H), 5.11 (s, 2H), 4.13 (q, *J* = 7.13 Hz, 2H), 3.96 (s, 2H), 3.87 (s, 1H), 3.51 (s, 2H), 3.16 (s, 2H), 1.69 (dt, *J* = 17.43, 8.61 Hz, 4H), 1.25 (t, *J* = 7.12 Hz, 3H).
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 157.3, 155.4, 135.9, 128.8, 128.6, 128.4, 111.3, 67.7, 61.9, 42.5, 41.4, 39.1, 32.2, 29.9, 14.7.
HRMS (ESI): [m/z] calculated for $C_{20}H_{24}N_4NaO_4$ ([M+Na]$^+$): 407.1693; Found: 407.1690.

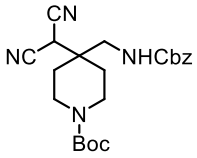
Scale-up synthesis of B1 – 2 x 5.0 mmol



The following reaction was performed in duplicate and combined for purification. **A1** (1.1 g, 5.0 mmol, 1.0 equiv.), Ir-F (27.5 mg, 0.5 mol%) and Cbz-glycine (2.09 g, 10.0 mmol, 2.0 equiv.,) were added to a 50 mL Schlenk flask (external ø = 3.0 cm, internal ø = 2.2 cm)

and purged with N_2 (10 minutes under vacuum then open to N_2, repeated three times). Dry and degassed 1,4-dioxane (25 mL, 0.2 M) was added and the reaction was bubbled with N_2 for 5 minutes. Bubbling was stopped and *sym*-collidine (264 µL, 2.0 mmol, 2.0 equiv.) was added, and the solution was bubbled for an additional 30 seconds. The vial was sealed and wrapped with parafilm, then irradiated at 440 nm, 60 °C (fan off) for 16 hours. Afterwards, the solvent was removed in vacuo and EtOAc was added. Citric acid (10 wt%) was added and the aqueous phase was washed with EtOAc. The organic phases were then washed with sat. $NaHCO_3$ (aq.), dried over anhydrous Na_2SO_4, filtered, and concentrated. No further purification was necessary, and **B1** was isolated in a combined yield of 88% (3.38 g).

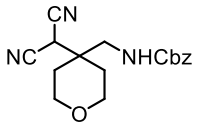
B2



Synthesized following **GP2** using **A2** (247.3 mg, 1.0 mmol, 1.0 equiv.) and *Z*-glycine (418.4 mg, 2.0 mmol, 2.0 equiv.). Purification via flash chromatography using silica gel (cyclohexane/EtOAc, 4:1) afforded **B2** as a yellowish solid in 60% yield (247.5 mg, 0.60 mmol).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35 (dp, *J* = 12.96, 6.62, 5.90 Hz, 5H), 5.25 (s, 1H), 5.11 (s, 2H), 4.00 – 3.73 (m, 3H), 3.50 (s, 2H), 3.12 (s, 2H), 1.83 – 1.58 (m, 4H), 1.45 (s, 9H).
^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 157.3, 154.6, 135.9, 128.8, 128.6, 128.4, 111.3, 80.5, 67.7, 42.7, 41.4, 32.2, 30.0, 28.5.
HRMS (ESI): [m/z] calculated for $C_{22}H_{28}N_4NaO_4$ ([M+Na]$^+$): 435.2007; Found: 435.2003.
R_f (cyHex/EtOAc, 1:1) = 0.50 [Ninhydrin].

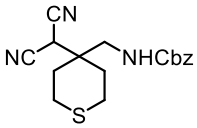
B3



Synthesized following **GP2** using **A3** (148.2 mg, 1.0 mmol, 1.0 equiv.) and *Z*-glycine (418.4 mg, 2.0 mmol, 2.0 equiv.). Purification via flash chromatography using silica gel (cyclohexane/EtOAc, 4:1) afforded **B3** as a white solid in 95% yield (266.4 mg, 0.95 mmol).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35 (q, *J* = 6.59 Hz, 5H), 5.22 (t, *J* = 7.61 Hz, 1H), 5.12 (s, 2H), 3.84 (d, *J* = 11.46 Hz, 3H), 3.69 (q, *J* = 9.28, 8.38 Hz, 2H), 3.57 (d, *J* = 6.83 Hz, 2H), 1.84 (d, *J* = 10.26 Hz, 2H), 1.64 (d, *J* = 13.84 Hz, 2H).
^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 157.3, 135.9, 128.8, 128.6, 128.3, 111.3, 67.7, 63.0, 42.9, 40.6, 32.6, 30.6.
HRMS (ESI): [m/z] calculated for $C_{17}H_{19}N_3NaO_3$ ([M+Na]$^+$): 336.1320; Found: 336.1319.
R_f (cyHex/EtOAc, 1:1) = 0.55 [Ninhydrin].

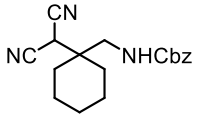
B4



Synthesized following **GP2** using **A4** (164.04 mg, 1.0 mmol, 1.0 equiv.) and *Z*-glycine (418.4 mg, 2.0 mmol, 2.0 equiv.). Purification via flash chromatography using silica gel (CyHex/EtOAc, 4:1) afforded **B4** as a yellow solid in 95% yield (312.9 mg, 0.95 mmol).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40 – 7.31 (m, 5H), 5.22 – 4.99 (m, 3H), 3.81 (s, 1H), 3.48 (d, *J* = 6.88 Hz, 2H), 2.89 (d, *J* = 12.45 Hz, 2H), 2.54 (d, *J* = 14.05 Hz, 2H), 2.04 – 1.91 (m, 4H).
^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 157.2, 135.9, 128.8, 128.7, 128.4, 111.2, 67.8, 43.4, 41.8, 32.5, 32.0, 23.1.
HRMS (ESI): [m/z] calculated for $C_{17}H_{19}N_3NaO_2S$ ([M+Na]$^+$): 352.1088; Found: 352.1090.
R_f (cyHex/EtOAc, 1:1) = 0.46 [Ninhydrin].

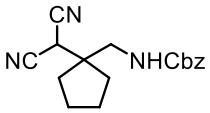
B5



Synthesized following **GP2** using **A5** (146.2 mg, 1.0 mmol, 1.0 equiv.) and *Z*-glycine (418.4 mg, 2.0 mmol, 2.0 equiv.). Purification via flash chromatography using silica gel (CyHex/EtOAc, 4:1) afforded **B5** as a yellowish solid in 86% yield (267.8 mg, 0.86 mmol).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35 (q, *J* = 8.46, 7.27 Hz, 5H), 5.12 (s, 2H), 5.06 (s, 1H), 3.83 (s, 1H), 3.46 (d, *J* = 6.97 Hz, 2H), 1.77 – 1.47 (m, 9H), 1.37 – 1.27 (m, 1H).
^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 157.2, 136.1, 128.7, 128.5, 128.3, 111.8, 67.5, 43.9, 42.3, 32.3, 30.8, 24.9, 21.3.
HRMS (ESI): [m/z] calculated for $C_{18}H_{21}N_3NaO_2$ ([M+Na]$^+$): 334.1523; Found: 334.1526.
R_f (cyHex/EtOAc, 1:1) = 0.35 [Ninhydrin].

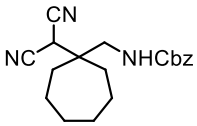
B6



Synthesized following **GP2** using **A6** (132.2 mg, 1.0 mmol, 1.0 equiv.) and *Z*-glycine (418.4 mg, 2.0 mmol, 2.0 equiv.). Purification via flash chromatography using silica gel (CyHex/EtOAc, 4:1) afforded **B6** as a yellowish oil in 95% yield (282.5 mg, 0.95 mmol).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34 (q, *J* = 7.83, 7.24 Hz, 6H), 5.36 – 5.24 (m, 1H), 5.12 (s, 2H), 3.89 (s, 1H), 3.33 (d, *J* = 6.84 Hz, 2H), 1.81 (s, 2H), 1.73 (s, 6H).
^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 157.3, 136.1, 128.7, 128.5, 128.3, 112.5, 67.5, 50.5, 46.7, 33.9, 31.3, 25.1.
HRMS (ESI): [m/z] calculated for $C_{17}H_{19}N_3NaO_2$ ([M+Na]$^+$): 320.1369; Found: 320.1369.
R_f (cyHex/EtOAc, 1:1) = 0.30 [Ninhydrin].

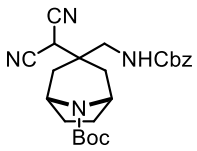
B7



Synthesized following **GP2** using **A7** (160.2 mg, 1.0 mmol, 1.0 equiv.) and *Z*-glycine (418.4 mg, 2.0 mmol, 2.0 equiv.). Purification via flash chromatography using silica gel (CyHex/EtOAc, 4:1) afforded **B7** as a yellow oil in 88% yield (286.4 mg, 0.88 mmol).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.44 – 7.28 (m, 5H), 5.11 (d, *J* = 17.05 Hz, 3H), 3.71 (s, 1H), 3.35 (d, *J* = 6.94 Hz, 2H), 1.74 – 1.61 (m, 6H), 1.57 (s, 6H).
^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 157.2, 136.1, 128.7, 128.5, 128.3, 112.3, 67.5, 47.0, 45.3, 36.4, 34.4, 32.4, 30.2, 29.2, 26.3, 22.8.
HRMS (ESI): [m/z] calculated for $C_{19}H_{23}N_3NaO_2$ ([M+Na]$^+$): 348.1682; Found: 348.1682.
R_f (cyHex/EtOAc, 1:1) = 0.34 [Ninhydrin].

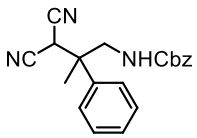
B8



Synthesized following **GP2** using **A8** (273.3 mg, 1.0 mmol, 1.0 equiv.) and *Z*-glycine (418.4 mg, 2.0 mmol, 2.0 equiv.). Purification via flash chromatography using silica gel (CyHex/EtOAc, 4:1) afforded **B8** as a yellowish solid in 88% yield (385.9 mg, 0.88 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.33 (m, 5H), 5.37 (t, *J* = 6.95 Hz, 1H), 5.15 – 5.07 (m, 2H), 4.28 (s, 2H), 4.19 (s, 1H), 3.30 (d, *J* = 6.69 Hz, 2H), 2.08 (s, 4H), 1.72 (s, 2H), 1.56 (s, 2H), 1.44 (s, 9H).
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 157.2, 153.3, 136.0, 128.7, 128.5, 128.2, 111.8, 80.4, 67.6, 51.8 & 51.1 (rotamer, 1C), 50.0, 39.4, 34.9 & 34.1 (rotamer, 1C), 32.6, 28.5 (4C).
HRMS (ESI): [m/z] calculated for $C_{24}H_{30}N_4NaO_4$ ([M+Na]$^+$): 461.2157; Found: 461.2159.
R_f (cyHex/EtOAc, 1:1) = 0.28 [Ninhydrin].

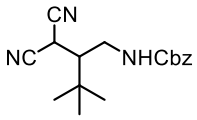
B9



Synthesized following **GP2** using **A9** (168.2 mg, 1.0 mmol, 1.0 equiv.) and *Z*-glycine (418.4 mg, 2.0 mmol, 2.0 equiv.). Purification via flash chromatography using silica gel (CyHex/EtOAc, 4:1) afforded **B9** as a yellow oil in 85% yield (283.4 mg, 0.85 mmol).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.44 Hz, 2H), 7.41 – 7.30 (m, 8H), 5.13 – 5.05 (m, 2H), 4.79 (t, *J* = 6.73 Hz, 1H), 4.15 (s, 1H), 3.77 (dd, *J* = 14.62, 7.21 Hz, 1H), 3.70 (dd, *J* = 14.20, 6.01 Hz, 1H), 1.71 (s, 3H).
^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 156.8, 137.9, 136.0, 129.6, 128.9, 128.7, 128.5, 128.4, 126.3, 111.7, 111.6, 67.6, 48.9, 46.0, 33.4, 20.9.
HRMS (ESI): [m/z] calculated for $C_{20}H_{19}N_3NaO_2$ ([M+Na]$^+$): 356.1376; Found: 356.1369.
R_f (cyHex/EtOAc, 1:1) = 0.35 [Ninhydrin].

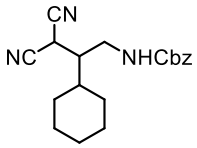
B10



Synthesized following **GP2** using **A10** (134.2 mg, 1.0 mmol, 1.0 equiv.) and *Z*-glycine (418.4 mg, 2.0 mmol, 2.0 equiv.). Purification via flash chromatography using silica gel (CyHex/EtOAc, 4:1) afforded **B10** as a pale oil in 56% yield (167.7 mg, 0.56 mmol).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39 – 7.30 (m, 5H), 5.24 (s, 1H), 5.19 – 5.09 (m, 2H), 3.98 (d, *J* = 1.90 Hz, 1H), 3.84 – 3.73 (m, 1H), 3.21 (ddd, *J* = 14.55, 10.92, 6.58 Hz, 1H), 2.47 – 2.36 (m, 1H), 1.08 (s, 9H).
^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 156.7, 136.2, 128.7, 128.4, 128.3, 113.3, 112.8, 67.5, 50.0, 40.4, 33.5, 27.8, 21.7.
HRMS (ESI): [m/z] calculated for $C_{17}H_{21}N_3NaO_2$ ([M+Na]$^+$): 322.1527; Found: 322.1526.
R_f (cyHex/EtOAc, 1:1) = 0.44 [Ninhydrin].

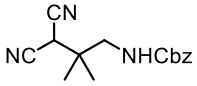
B11



Synthesized following **GP2** using **A11** (160.2 mg, 1.0 mmol, 1.0 equiv.) and *Z*-glycine (418.4 mg, 2.0 mmol, 2.0 equiv.). Purification via flash chromatography using silica gel (CyHex/EtOAc, 4:1) afforded **B11** as a yellow oil in 91% yield (296.1 mg, 0.91 mmol).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38 – 7.31 (m, 5H), 5.13 (d, *J* = 5.73 Hz, 3H), 4.01 (d, *J* = 3.99 Hz, 1H), 3.68 – 3.57 (m, 1H), 3.24 (dt, *J* = 15.27, 7.62 Hz, 1H), 2.19 (s, 1H), 1.87 – 1.59 (m, 6H), 1.32 – 1.07 (m, 5H).
^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 156.8, 136.1, 128.7, 128.5, 128.4, 112.7, 112.5, 67.5, 46.2, 41.0, 38.5, 30.9, 29.7, 26.3, 26.1, 26.0, 23.7.
HRMS (ESI): [m/z] calculated for $C_{19}H_{23}N_3NaO_2$ ([M+Na]$^+$): 348.1682; Found: 348.1682.
R_f (cyHex/EtOAc, 1:1) = 0.30 [Ninhydrin].

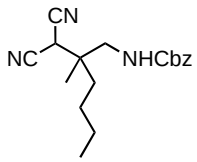
B12



Synthesized following **GP2** using **A12** (106.1 mg, 1.0 mmol, 1.0 equiv.) and *Z*-glycine (418.4 mg, 2.0 mmol, 2.0 equiv.). Purification via flash chromatography using silica gel (CyHex/EtOAc, 4:1) afforded **B12** as a yellowish oil in 89% yield (241.5 mg, 0.89 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 2.58 Hz, 6H), 5.12 (s, 2H), 5.05 (s, 1H), 3.71 (s, 1H), 3.30 (d, *J* = 6.90 Hz, 2H), 1.23 (s, 5H).
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 157.1, 136.0, 128.8, 128.6, 128.5, 111.8, 67.7, 48.9, 40.1, 32.5, 23.0.
HRMS (ESI): [m/z] calculated for $C_{15}H_{17}N_3NaO_2$ ([M+Na]$^+$): 294.1210; Found: 294.1213.
R_f (cyHex/EtOAc, 1:1) = 0.40 [Ninhydrin].

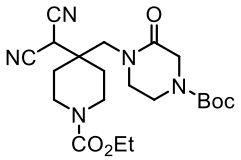
B13



Synthesized following **GP2** using **A13** (148.2 mg, 1.0 mmol, 1.0 equiv.) and *Z*-glycine (418.4 mg, 2.0 mmol, 2.0 equiv.). Purification via flash chromatography using silica gel (CyHex/EtOAc, 4:1) afforded **B13** as a yellowish oil in 71% yield 222.5 mg, 0.71 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.28 (m, 5H), 5.12 (s, 2H), 5.01 (s, 1H), 3.74 (s, 1H), 3.31 (q, *J* = 7.85 Hz, 2H), 1.63 – 1.42 (m, 2H), 1.39 – 1.26 (m, 4H), 1.18 (s, 3H), 0.93 (t, *J* = 6.90 Hz, 3H).
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 157.1, 136.0, 128.8, 128.6, 128.4, 112.0, 111.9, 67.6, 46.7, 42.4, 35.4, 31.9, 25.7, 23.2, 20.4, 14.0.
HRMS (ESI): [m/z] calculated for $C_{18}H_{23}N_3NaO_2$ ([M+Na]$^+$): 336.1681; Found: 336.1682.
R_f (cyHex/EtOAc, 1:1) = 0.41 [Ninhydrin].

B14

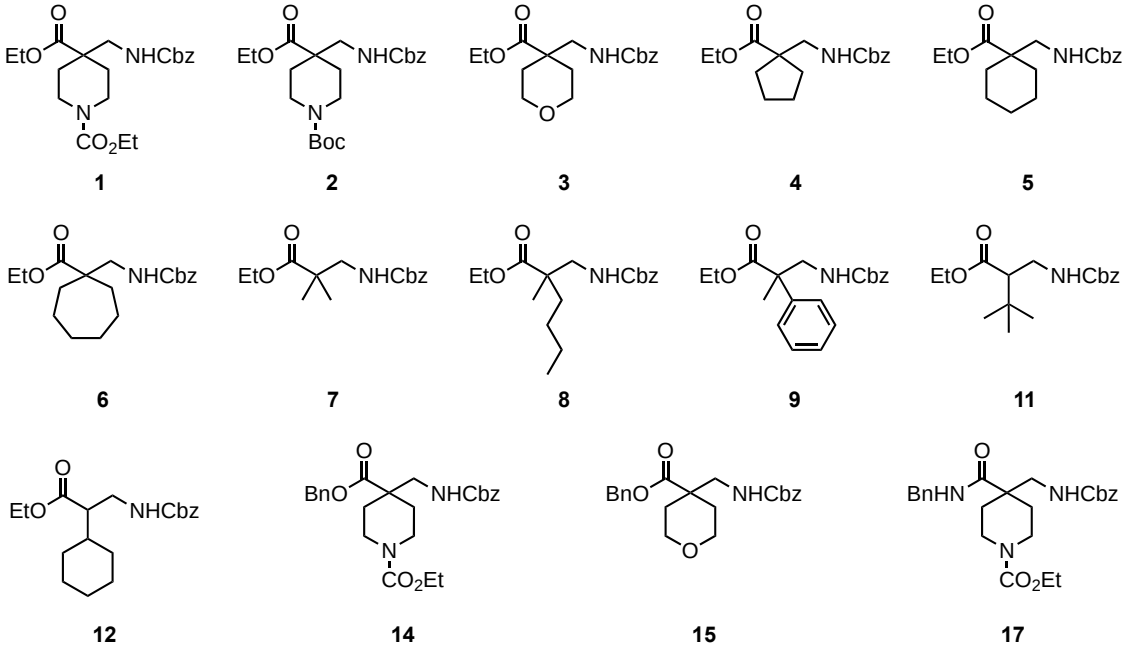


Synthesized following **GP2** using **A1** (219 .2 mg, 1.0 mmol, 1.0 equiv.)and 2-(4-(tert-butoxycarbonyl)-2-oxopiperazin-1-yl)acetic acid (387.5 mg, 1.5 mmol, 1.5 equiv.). Purification via flash chromatography using silica gel (CyHex/EtOAc, 4:1) afforded **B14** as a white solid in 80% yield (346.8 mg, 0.80 mmol).

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.16 (q, *J* = 7.07 Hz, 4H), 4.13 (d, *J* = 4.09 Hz, 3H), 3.87 (dt, *J* = 14.19, 4.76 Hz, 2H), 3.69 (dd, *J* = 9.48, 3.99 Hz, 4H), 3.50 (t, *J* = 5.35 Hz, 2H), 3.33 (ddd, *J* = 13.89, 8.07, 5.36 Hz, 2H), 1.87 – 1.75 (m, 4H), 1.47 (s, 9H), 1.27 (t, *J* = 7.11 Hz, 3H).
^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 169.1, 155.4, 153.9, 111.6, 81.3, 61.9, 51.7, 50.7, 48.2, 41.7, 39.5, 32.4, 31.6, 28.5, 28.5, 14.7.
HRMS (ESI): [m/z] calculated for $C_{21}H_{31}N_5NaO_5$ ([M+Na]$^+$): 456.2217; Found: 456.2217.
R_f (cyHex/EtOAc, 1:1) = 0.25 [Ninhydrin].

Synthesis & Characterization of *β*-Amino Esters/Amides

General procedure for oxidative esterification/amidation (GP3): In an 8 mL glass vial, the desired malononitrile derivative **B** (0.2 mmol, 2.0 equiv.) and Cs_2CO_3 (130.4 mg, 0.4 mmol, 2.0 equiv.) were purged with O_2. MeCN (0.1 M, pre-bubbled with O_2 for at least 4h) was added. The nucleophile (2.0–10.0 equiv.) was added, and the reaction was bubbled for 2 min. The reaction was stirred for 18 hours with an O_2 balloon inserted. Then, the solvent was removed, and the resulting residue was purified to afford the desired product.



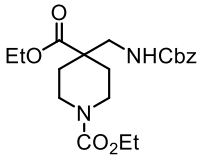
1 **2** **3** **4** **5**

6 **7** **8** **9** **11**

12 **14** **15** **17**

Figure S4. Synthesised substituted β-amino esters.

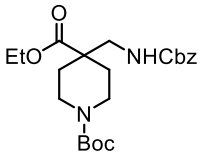
Product 1



Synthesized following **GP3** using **B1** (76.9 mg, 0.2 mmol, 1.0 equiv.) and EtOH (113 µL, 2.0 mmol, 10.0 equiv.). Purification via flash chromatography using silica gel (CyHex/EtOAc, 4:1) afforded **1** as a yellow oil in 50% yield (39.2 mg, 0.10 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.26 (m, 5H), 5.13 (t, *J* = 6.57 Hz, 1H), 5.06 (s, 2H), 4.12 (dq, *J* = 19.46, 7.10 Hz, 4H), 3.84 – 3.70 (m, 2H), 3.35 (d, *J* = 6.52 Hz, 2H), 3.20 – 3.05 (m, 2H), 2.02 (dt, *J* = 13.61, 4.33 Hz, 2H), 1.41 (ddd, *J* = 13.83, 9.82, 4.11 Hz, 2H), 1.23 (td, *J* = 7.09, 3.92 Hz, 6H).
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 174.6, 156.6, 155.5, 136.4, 128.6, 128.2, 128.2, 66.9, 61.4, 61.2, 47.5, 46.6, 40.7, 30.6, 14.7, 14.2.
HRMS (ESI): [m/z] calculated for $C_{20}H_{28}N_2O_6$ ([M-H]$^-$): 393.2025; Found: 393.2026.
R_f (cyHex/EtOAc, 1:1) = 0.33 [Ninhydrin].

Product 2

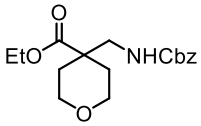


Synthesized following **GP3** using **B2** (82.5 mg, 0.2 mmol, 1.0 equiv.) and EtOH (113 µL, 2.0 mmol, 10.0 equiv.). Purification via flash chromatography using silica gel (CyHex/EtOAc, 4:1) afforded **2** as a yellow oil in 95% yield (79.9 mg, 0.19 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.26 (m, 5H), 5.08 (s, 2H), 5.02 (d, *J* = 6.46 Hz, 1H), 4.16 (q, *J* = 7.10 Hz, 2H), 3.72 (dt, *J* = 13.77, 4.87 Hz, 2H), 3.37 (d, *J* = 6.48 Hz, 2H), 3.11 (ddd, *J* = 13.52, 9.69, 3.28 Hz, 2H), 2.08 – 1.98 (m, 2H), 1.44 (s, 11H), 1.25 (t, *J* = 7.11 Hz, 3H).

$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 174.8, 156.6, 154.9, 136.5, 128.7, 128.3, 128.3, 79.7, 67.0, 61.3, 47.4, 46.6, 40.6, 30.8, 28.5, 14.3.
HRMS (ESI): [m/z] calculated for $C_{22}H_{32}N_2NaO_6$ ($[M+Na]^+$): 443.2153; Found: 443.2153.
R_f (cyHex/EtOAc, 1:1) = 0.25 [Ninhydrin].

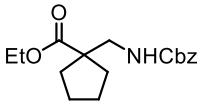
Product 3



Synthesized following **GP3** using **B3** (62.7 mg, 0.2 mmol, 1.0 equiv.) and EtOH (113 µL, 2.0 mmol, 10.0 equiv.). Purification via flash chromatography using silica gel (CyHex/EtOAc, 4:1) afforded **5** as a yellow oil in 50% yield (32.1 mg, 0.10 mmol).

^1H NMR (600 MHz, $CDCl_3$) δ 7.38 – 7.29 (m, 5H), 5.08 (s, 2H), 5.01 (s, 1H), 4.18 (q, *J* = 7.13 Hz, 2H), 3.82 (dt, *J* = 12.13, 4.50 Hz, 2H), 3.52 (ddd, *J* = 12.21, 9.51, 2.86 Hz, 2H), 3.40 (d, *J* = 6.48 Hz, 2H), 2.09 – 2.02 (m, 2H), 1.54 (ddd, *J* = 13.88, 9.58, 4.16 Hz, 2H), 1.27 – 1.24 (m, 4H).
$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 174.9, 156.6, 136.5, 128.7, 128.3, 128.3, 67.0, 64.8, 61.3, 47.9, 45.8, 31.5, 14.3.
HRMS (ESI): [m/z] calculated for $C_{17}H_{23}NNaO_5$ ($[M+Na]^+$): 344.1469; Found: 344.1468.
R_f (cyHex/EtOAc, 1:1) = 0.30 [Ninhydrin].

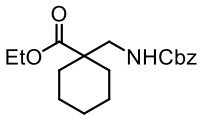
Product 4



Synthesized following **GP3** using **B6** (59.5 mg, 0.2 mmol, 1.0 equiv.) and EtOH (113 µL, 2.0 mmol, 10.0 equiv.). Purification via flash chromatography using silica gel (CyHex/EtOAc, 4:1) afforded **4** as a yellow oil in 33% yield (20.2 mg, 0.07 mmol).

^1H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.27 (m, 5H), 5.32 (t, *J* = 6.46 Hz, 1H), 5.09 (s, 2H), 4.13 (q, *J* = 7.11 Hz, 2H), 3.34 (d, *J* = 6.41 Hz, 2H), 2.03 – 1.90 (m, 2H), 1.73 (qd, *J* = 7.43, 6.77, 3.43 Hz, 5H), 1.62 (dt, *J* = 10.80, 3.40 Hz, 3H), 1.25 (t, *J* = 7.12 Hz, 4H).
$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 177.8, 157.0, 136.7, 128.7, 128.2, 128.2, 66.8, 60.9, 54.3, 46.7, 34.6, 25.7, 14.3.
HRMS (ESI): [m/z] calculated for $C_{17}H_{23}NNaO_4$ ($[M+Na]^+$): 328.1518; Found: 328.1519.
R_f (cyHex/EtOAc, 1:1) = 0.22 [Ninhydrin].

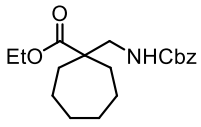
Product 5



Synthesized following **GP3** using **B5** (62.3 mg, 0.2 mmol, 1.0 equiv.) and EtOH (113 µL, 2.0 mmol, 10.0 equiv.). Purification via flash chromatography using silica gel (CyHex/EtOAc, 4:1) afforded **5** as a yellow oil in 40% yield (25.6 mg, 0.08 mmol).

^1H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.27 (m, 5H), 5.08 (s, 2H), 5.03 (s, 1H), 4.14 (q, *J* = 7.10 Hz, 2H), 3.35 (d, *J* = 6.36 Hz, 2H), 2.04 – 1.90 (m, 2H), 1.65 – 1.46 (m, 3H), 1.36 (tdd, *J* = 21.86, 10.67, 3.41 Hz, 5H), 1.25 (t, *J* = 7.11 Hz, 4H).
$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 176.1, 156.6, 136.7, 128.6, 128.2, 66.8, 60.8, 47.7, 47.6, 31.5, 25.7, 22.5, 14.3.
HRMS (ESI): [m/z] calculated for $C_{18}H_{25}NNaO_4$ ($[M+Na]^+$): 342.1675; Found: 342.1676.
R_f (cyHex/EtOAc, 1:1) = 0.34 [Ninhydrin].

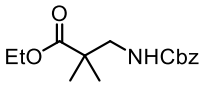
Product 6



Synthesized following **GP3** using **B7** (65.1 mg, 0.2 mmol, 1.0 equiv.) and EtOH (113 µL, 2.0 mmol, 10.0 equiv.). Purification via flash chromatography using silica gel (CyHex/EtOAc, 4:1) afforded **6** as a yellow oil in 47% yield (31.3 mg, 0.09 mmol).

^1H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 5H), 5.19 – 5.11 (m, 1H), 5.08 (s, 2H), 4.13 (q, *J* = 7.12 Hz, 2H), 3.31 (d, *J* = 6.45 Hz, 2H), 2.02 – 1.88 (m, 2H), 1.62 – 1.45 (m, 10H), 1.25 (t, *J* = 7.14 Hz, 4H).
$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 177.4, 156.8, 136.7, 128.6, 128.4, 128.2, 66.8, 60.9, 50.4, 47.9, 33.9, 30.7, 23.6, 14.3.
HRMS (ESI): [m/z] calculated for $C_{19}H_{27}NNaO_4$ ($[M+Na]^+$): 356.1829; Found: 356.1832.
R_f (cyHex/EtOAc, 1:1) = 0.25 [Ninhydrin].

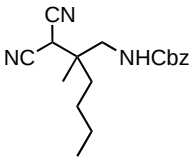
Product 7



Synthesized following **GP3** using **B12** (54.3 mg, 0.2 mmol, 1.0 equiv.) and EtOH (113 µL, 2.0 mmol, 10.0 equiv.). Purification via flash chromatography using silica gel (CyHex/EtOAc, 4:1) afforded **7** as a yellow oil in 59% yield (33.0 mg, 0.12 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.28 (m, 5H), 5.25 (s, 1H), 5.09 (s, 2H), 4.12 (q, *J* = 7.16 Hz, 2H), 3.31 (d, *J* = 6.57 Hz, 2H), 1.24 (t, *J* = 7.13 Hz, 4H), 1.19 (s, 6H).
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 177.2, 156.8, 136.7, 128.6, 128.2, 128.2, 66.8, 60.9, 48.9, 43.6, 23.1, 14.2.
HRMS (ESI): [m/z] calculated for $C_{15}H_{21}NNaO_4$ ([M+Na]$^+$): 302.1471; Found: 302.1394.
R_f (cyHex/EtOAc, 1:1) = 0.33 [Ninhydrin].

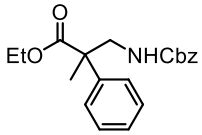
Product 8



Synthesized following **GP3** using **B13** (62.7 mg, 0.2 mmol, 1.0 equiv.) and EtOH (113 µL, 2.0 mmol, 10.0 equiv.). Purification via flash chromatography using silica gel (CyHex/EtOAc, 4:1) afforded **8** as a yellow oil in 33% yield (21.2 mg, 0.07 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 4.59 Hz, 5H), 5.19 – 5.11 (m, 1H), 5.09 (d, *J* = 3.77 Hz, 2H), 4.13 (q, *J* = 7.13 Hz, 2H), 3.45 – 3.20 (m, 2H), 1.62 – 1.43 (m, 2H), 1.29 – 1.18 (m, 7H), 1.16 (s, 3H), 0.87 (t, *J* = 7.03 Hz, 3H).
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 176.8, 156.8, 136.8, 128.6, 128.5, 128.2, 66.8, 60.8, 47.5, 47.1, 36.9, 26.5, 23.2, 20.5, 14.3, 14.0.
HRMS (ESI): [m/z] calculated for $C_{18}H_{27}NNaO_4$ ([M+Na]$^+$): 344.1940; Found: 344.1928.
R_f (cyHex/EtOAc, 1:1) = 0.28 [Ninhydrin].

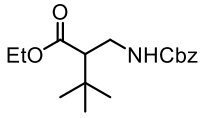
Product 10



Synthesized following **GP3** using **B9** (66.7 mg, 0.2 mmol, 1.0 equiv.) and EtOH (113 µL, 2.0 mmol, 10.0 equiv.). Purification via flash chromatography using silica gel (CyHex/EtOAc, 4:1) afforded **9** as a yellow oil in 49% yield (33.5 mg, 0.10 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.25 (m, 10H), 5.23 (t, *J* = 6.58 Hz, 1H), 5.07 (s, 2H), 4.17 (qd, *J* = 7.11, 4.48 Hz, 2H), 3.75 – 3.51 (m, 2H), 1.63 (s, 3H), 1.21 (t, *J* = 7.12 Hz, 3H).
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 175.7, 156.7, 140.9, 136.7, 128.8, 128.6, 128.2, 128.2, 127.4, 126.1, 66.8, 61.3, 52.0, 49.3, 20.6, 14.1.
HRMS (ESI): [m/z] calculated for $C_{20}H_{23}NNaO_4$ ([M+Na]$^+$): 364.1519; Found: 364.1519.
R_f (cyHex/EtOAc, 1:1) = 0.45 [Ninhydrin].

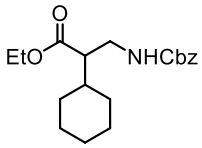
Product 11



Synthesized following **GP3** using **B10** (59.9 mg, 0.2 mmol, 1.0 equiv.) and EtOH (113 µL, 2.0 mmol, 10.0 equiv.). Purification via flash chromatography using silica gel (CyHex/EtOAc, 4:1) afforded **11** as a yellow oil in 67% yield (41.2 mg, 0.13 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.26 (m, 5H), 5.08 (d, *J* = 5.80 Hz, 2H), 4.94 (t, *J* = 6.22 Hz, 1H), 4.20 – 4.07 (m, 2H), 3.56 (ddd, *J* = 13.39, 7.05, 3.73 Hz, 1H), 3.30 (ddd, *J* = 13.46, 11.27, 5.43 Hz, 1H), 2.51 (dd, *J* = 11.23, 3.75 Hz, 1H), 1.24 (t, *J* = 7.15 Hz, 3H), 1.00 (s, 9H).
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 174.1, 156.4, 136.6, 128.6, 128.2, 128.2, 66.8, 60.4, 56.0, 39.9, 32.6, 28.1, 14.4.
HRMS (ESI): [m/z] calculated for $C_{17}H_{25}NNaO_4$ ([M+Na]$^+$): 330.1672; Found: 330.1676.
R_f (cyHex/EtOAc, 1:1) = 0.22 [Ninhydrin].

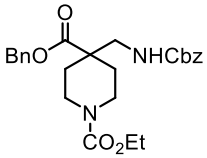
Product 12



Synthesized following **GP3** using **B11** (65.0 mg, 0.2 mmol, 1.0 equiv.) and EtOH (113 µL, 2.0 mmol, 10.0 equiv.). Purification via flash chromatography using silica gel (CyHex/EtOAc, 4:1) afforded **12** as a yellow oil in 95% yield (63.3 mg, 0.19 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.28 (m, 5H), 5.18 – 5.04 (m, 3H), 4.25 – 4.01 (m, 2H), 3.48 (ddd, *J* = 13.64, 6.60, 3.98 Hz, 1H), 3.34 (ddd, *J* = 13.67, 9.31, 5.73 Hz, 1H), 2.51 – 2.37 (m, 1H), 1.78 – 1.57 (m, 6H), 1.25 (t, *J* = 7.13 Hz, 3H), 1.22 – 0.92 (m, 5H).
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 174.7, 156.4, 136.7, 128.6, 128.2, 128.2, 66.8, 60.6, 51.5, 40.2, 38.4, 30.8, 30.4, 26.3, 14.4.
HRMS (ESI): [m/z] calculated for $C_{19}H_{27}NNaO_4$ ($[M+Na]^+$): 356.1840; Found: 356.1832.
R_f (cyHex/EtOAc, 1:1) = 0.20 [Ninhydrin].

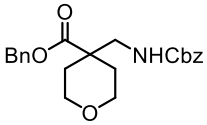
Product 14



Synthesized following **GP3** using **B1** (76.9 mg, 0.2 mmol, 1.0 equiv.) and benzyl alcohol (41.3 µL, 0.4 mmol, 2.0 equiv.). Purification via flash chromatography using silica gel (CyHex/EtOAc, 4:1) afforded **14** as a yellowish oil in 82% yield (74.5 mg, 0.16 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.28 (m, 10H), 5.14 (s, 2H), 5.06 (s, 2H), 4.98 (t, *J* = 6.59 Hz, 1H), 4.10 (q, *J* = 7.12 Hz, 2H), 3.78 (d, *J* = 13.73 Hz, 2H), 3.38 (d, *J* = 6.31 Hz, 2H), 3.12 (t, *J* = 11.08 Hz, 2H), 2.07 (dd, *J* = 10.53, 6.49 Hz, 2H), 1.45 (ddd, *J* = 13.88, 9.82, 4.14 Hz, 2H), 1.23 (t, *J* = 7.16 Hz, 4H).
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 174.5, 156.6, 155.5, 136.4, 135.7, 128.8, 128.6, 128.6, 128.3, 128.3, 128.2, 67.1, 67.0, 61.4, 47.6, 46.9, 40.7, 30.7, 14.8.
HRMS (ESI): [m/z] calculated for $C_{25}H_{30}N_2NaO_6$ ($[M+Na]^+$): 477.1997; Found: 477.1996.
R_f (cyHex/EtOAc, 1:1) = 0.30 [Ninhydrin].

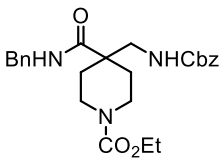
Product 15



Synthesized following **GP3** using **B3** (62.7 mg, 0.2 mmol, 1.0 equiv.) and benzyl alcohol (41.3 µL, 0.4 mmol, 2.0 equiv.). Purification via flash chromatography using silica gel (CyHex/EtOAc, 4:1) afforded **15** as a yellow oil in 75% yield (57.5 mg, 0.15 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.28 (m, 10H), 5.15 (s, 2H), 5.07 (s, 2H), 5.04 – 4.92 (m, 1H), 3.81 (dt, *J* = 12.00, 4.45 Hz, 2H), 3.49 (ddd, *J* = 12.14, 9.55, 2.79 Hz, 2H), 3.41 (d, *J* = 6.60 Hz, 2H), 2.08 (dt, *J* = 13.80, 3.53 Hz, 2H), 1.55 (ddd, *J* = 13.75, 9.60, 4.11 Hz, 2H).
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 174.6, 156.6, 136.4, 135.7, 128.8, 128.6, 128.5, 128.3, 128.3, 128.2, 67.0, 66.9, 64.7, 48.0, 46.0, 31.4.
HRMS (ESI): [m/z] calculated for $C_{22}H_{25}NO_5$ ($[M-H]^-$): 384.1805; Found: 384.1811.
R_f (cyHex/EtOAc, 1:1) = 0.40 [Ninhydrin].

Product 17



Synthesized following **GP3** using **B1** (76.9 mg, 0.2 mmol, 1.0 equiv.) and benzyl amine (43.7 µL, 0.4 mmol, 2.0 equiv.). Purification via flash chromatography using silica gel (CyHex/EtOAc, 4:1) afforded **17** as a yellow oil in 77% yield (69.8 mg, 0.15 mmol).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 – 7.12 (m, 11H), 6.49 (t, *J* = 5.66 Hz, 1H), 5.06 (s, 2H), 4.40 (d, *J* = 5.64 Hz, 2H), 4.10 (q, *J* = 7.10 Hz, 2H), 3.76 – 3.49 (m, 2H), 3.39 (d, *J* = 5.88 Hz, 4H), 1.92 (ddd, *J* = 13.66, 6.94, 3.69 Hz, 2H), 1.54 (ddd, *J* = 13.14, 8.53, 3.73 Hz, 2H), 1.24 (t, *J* = 7.09 Hz, 4H).

$^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 174.2, 156.8, 155.5, 138.2, 136.4, 128.8, 128.6, 128.2, 128.1, 127.6, 127.6, 66.9, 61.4, 46.8, 46.0, 43.8, 40.4, 30.9, 14.7.
HRMS (ESI): [m/z] calculated for $C_{25}H_{31}N_3O_5$ ($[M-H]^-$): 454.2354; Found: 454.2342.
R_f (cyHex/EtOAc, 1:1) = 0.40 [Ninhydrin].

Synthesis & Characterization of *β*-Amino acids

General procedure 4 (GP4): This procedure was adapted from the one reported by Sun and co-workers.[11] Cs_2CO_3 (130.4 mg, 0.4 mmol, 2.0 equiv.) was added to a solution of the desired malononitrile (0.2 mmol, 1.0 equiv.) in MeCN (2.0 mL, 0.1 M), and H_2O_2 (35 wt%, 10.0 equiv.) was added dropwise. The solution was stirred for 16 h at room temperature, then concentrated in vacuo. The reaction was then diluted with CH_2Cl_2 and washed with aqueous sat. $NaHCO_3$ solution three times. The combined aqueous phases were acidified with 1.0 M HCl until a pH of 2 was reached, and then extracted with EtOAc five times. The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated to give the desired product.

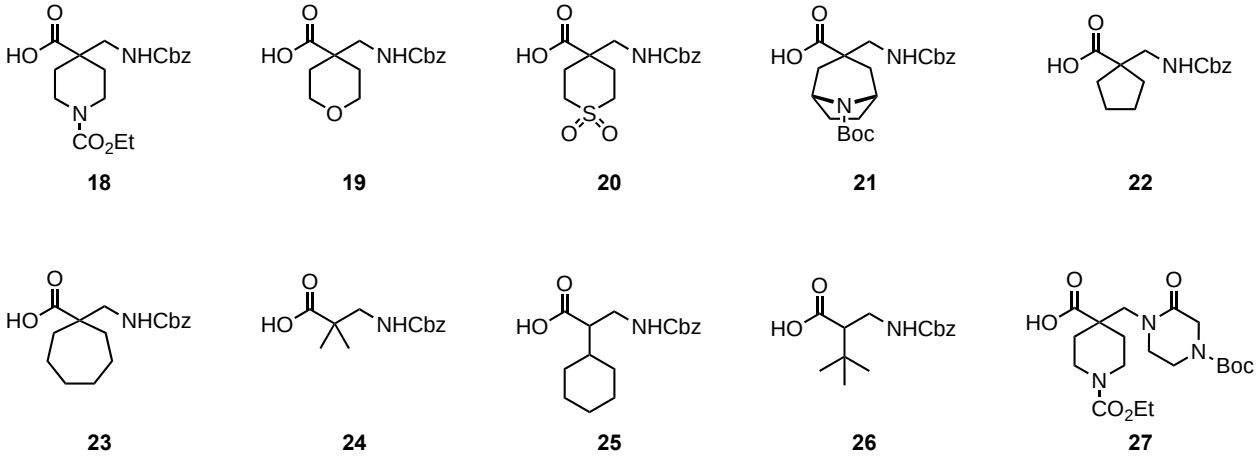
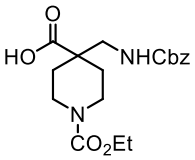


Figure S5. Synthesised β-amino acids.

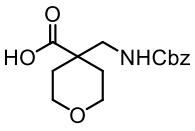
Product 18



Synthesized following **GP4** using **B1** (76.9 mg, 0.2 mmol, 1.0 equiv.). **18** was isolated as a yellowish solid in 60% yield (43.7 mg, 0.12 mmol).

^1H NMR (600 MHz, CD_3CN) δ 7.66 – 7.34 (m, 5H), 5.98 (d, *J* = 7.07 Hz, 1H), 5.21 (s, 2H), 4.22 (q, *J* = 7.09 Hz, 2H), 3.98 – 3.91 (m, 2H), 3.45 (d, *J* = 6.41 Hz, 2H), 1.57 – 1.48 (m, 2H), 1.37 (t, *J* = 7.10 Hz, 3H).
$^{13}C\{^1H\}$ NMR (101 MHz, CD_3CN) δ 176.9, 157.7, 156.2, 138.2, 129.4, 128.8, 128.6, 66.9, 61.9, 48.7, 47.5, 41.7, 31.4, 14.9.
HRMS (ESI): [m/z] calculated for $C_{18}H_{24}N_2NaO_6$ ($[M+Na]^+$): 387.1527; Found: 387.1527.

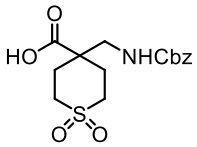
Product 19



Synthesized following **GP4** using **B3** (62.7 mg, 0.2 mmol, 1.0 equiv.). **19** was isolated as a yellowish solid in 73% yield (42.8 mg, 0.15 mmol).

^1H NMR (400 MHz, CD_3CN) δ 7.58 – 7.16 (m, 5H), 5.84 (s, 1H), 5.07 (s, 2H), 3.79 (dt, *J* = 12.00, 4.19 Hz, 2H), 3.46 (d, *J* = 9.78 Hz, 2H), 3.34 (d, *J* = 6.70 Hz, 2H), 2.00 – 1.89 (m, 2H), 1.50 (ddd, *J* = 14.19, 10.31, 4.26 Hz, 2H).
$^{13}C\{^1H\}$ NMR (101 MHz, CD_3CN) δ 176.7, 157.8, 138.3, 129.5, 128.9, 128.6, 67.0, 65.4, 49.0, 46.7, 32.3.
HRMS (ESI): [m/z] calculated for $C_{15}H_{18}NO_5$ ($[M-H]^-$): 292.1182; Found: 292.1190.

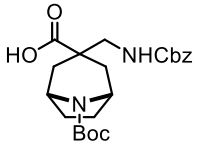
Product 20



Synthesized following **GP4** using **B4** (65.9 mg, 0.2 mmol, 1.0 equiv.). **20** was isolated as a yellowish solid in 55% yield (37.6 mg, 0.11 mmol).

^{1}H NMR (400 MHz, CD_3CN) δ 7.45 – 7.26 (m, 3H), 5.93 (s, 0H), 5.06 (s, 1H), 3.35 (d, *J* = 6.72 Hz, 1H), 3.13 – 2.84 (m, 2H), 2.37 (d, *J* = 13.61 Hz, 1H), 1.98 (s, 2H).
^{13}C{^{1}H} NMR (101 MHz, CD_3CN) δ 175.2, 157.8, 138.1, 129.4, 128.8, 128.6, 67.1, 48.7, 48.1, 47.1, 30.2.
HRMS (ESI): [m/z] calculated for $C_{15}H_{18}NO_6S$ ($[M-H]^-$): 340.0860; Found: 340.0860.

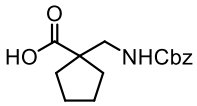
Product 21



Synthesized following **GP4** using **B8** (87.7 mg, 0.2 mmol, 1.0 equiv.). **21** was isolated as an orange oil in 40% yield (33.5 mg, 0.08 mmol).

^{1}H NMR (600 MHz, CD_3CN) δ 7.35 (dq, *J* = 14.32, 7.37 Hz, 5H), 5.75 (d, *J* = 6.88 Hz, 1H), 5.03 (s, 2H), 4.07 (s, 2H), 3.12 (d, *J* = 6.78 Hz, 2H), 2.26 (d, *J* = 14.12 Hz, 2H), 1.80 (s, 2H), 1.67 (d, *J* = 26.14 Hz, 4H), 1.42 (s, 9H).
^{13}C{^{1}H} NMR (101 MHz, CD_3CN) δ 178.0, 157.7, 154.2, 138.1, 129.4, 128.8, 128.6, 79.7, 66.9, 54.0, 53.2, 52.4, 45.0, 35.8, 35.2, 28.6, 27.7, 26.9.
HRMS (ESI): [m/z] calculated for $C_{22}H_{29}N_2O_6$ ($[M-H]^-$): 417.2029; Found: 417.2031.

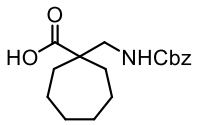
Product 22



Synthesized following **GP4** using **B6** (59.5 mg, 0.2 mmol, 1.0 equiv.). **22** was isolated as a yellowish oil in 43% yield (23.8 mg, 0.09 mmol).

^{1}H NMR (400 MHz, CD_3CN) δ 7.50 – 7.18 (m, 5H), 5.71 (s, 1H), 5.05 (s, 2H), 3.30 (d, *J* = 6.48 Hz, 2H), 2.00 – 1.93 (m, 2H), 1.70 – 1.55 (m, 6H).
^{13}C{^{1}H} NMR (101 MHz, CD_3CN) δ 178.8, 157.8, 138.4, 129.4, 128.8, 128.6, 66.8, 55.1, 47.4, 34.7, 26.0.
HRMS (ESI): [m/z] calculated for $C_{15}H_{18}NO_4$ ($[M-H]^-$): 276.1236; Found: 276.1241.

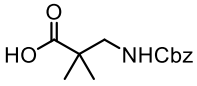
Product 23



Synthesized following **GP4** using **B7** (65.1 mg, 0.2 mmol, 1.0 equiv.). **23** was isolated as a yellow oil in 45% yield (27.5 mg, 0.09 mmol).

^{1}H NMR (400 MHz, CD_3CN) δ 7.43 – 7.24 (m, 5H), 5.64 (s, 1H), 5.04 (s, 2H), 3.24 (d, *J* = 6.58 Hz, 2H), 2.00 – 1.91 (m, 2H), 1.51 (s, 10H).
^{13}C{^{1}H} NMR (101 MHz, CD_3CN) δ 178.4, 157.7, 138.4, 129.4, 128.8, 128.6, 66.8, 51.2, 49.0, 34.3, 31.0, 24.1.
HRMS (ESI): [m/z] calculated for $C_{17}H_{22}NO_4$ ($[M-H]^-$): 304.1557; Found: 304.1554.

Product 24

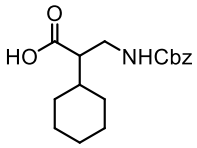


Synthesized following **GP4** using **B12** (54.3 mg, 0.2 mmol, 1.0 equiv.). **24** was isolated as a yellow oil in 88% yield (44.2 mg, 0.18 mmol).

^{1}H NMR (400 MHz, CD_3CN) δ 7.44 – 7.25 (m, 5H), 5.74 (s, 1H), 5.05 (s, 2H), 3.24 (d, *J* = 6.59 Hz, 3H), 1.12 (s, 6H).

$^{13}C\{^1H\}$ NMR (101 MHz, CD_3CN) δ 179.0, 157.7, 138.4, 129.4, 128.8, 128.6, 66.9, 49.5, 44.0, 23.3.
HRMS (ESI): [m/z] calculated for $C_{13}H_{16}NO_4$ ([M-H]$^-$): 250.1081; Found: 250.1085.

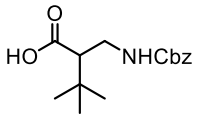
Product 25



Synthesized following **GP4** using **B11** (65.0 mg, 0.2 mmol, 1.0 equiv.). **25** was isolated as a yellowish oil in 30% yield (18.3 mg, 0.06 mmol).

^1H NMR (400 MHz, CD_3CN) δ 7.52 – 7.17 (m, 5H), 5.70 (s, 1H), 5.04 (s, 2H), 3.43 – 3.16 (m, 2H), 1.79 – 1.49 (m, 7H), 1.27 – 1.01 (m, 5H).
$^{13}C\{^1H\}$ NMR (101 MHz, CD_3CN) δ 175.7, 157.3, 138.4, 129.4, 128.8, 128.6, 66.8, 52.2, 41.2, 38.9, 31.2, 31.2, 30.3, 27.0, 26.9.
HRMS (ESI): [m/z] calculated for $C_{17}H_{22}NO_4$ ([M-H]$^-$): 304.1555; Found: 304.1554.

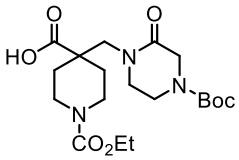
Product 26



Synthesized following **GP4** using **B10** (59.9 mg, 0.2 mmol, 1.0 equiv.). **26** was isolated as a yellow oil in 54% yield (30.2 mg, 0.11 mmol).

^1H NMR (400 MHz, CD_3CN) δ 7.53 – 7.13 (m, 5H), 5.68 (s, 1H), 5.04 (s, 2H), 3.47 – 3.19 (m, 2H), 2.41 (dd, *J* = 11.01, 3.65 Hz, 1H), 0.98 (s, 9H).
$^{13}C\{^1H\}$ NMR (101 MHz, CD_3CN) δ 175.5, 157.2, 138.4, 129.4, 128.8, 128.6, 66.8, 56.5, 40.7, 32.6, 28.0.
HRMS (ESI): [m/z] calculated for $C_{15}H_{20}NO_4$ ([M-H]$^-$): 278.1396; Found: 278.1398.

Product 27

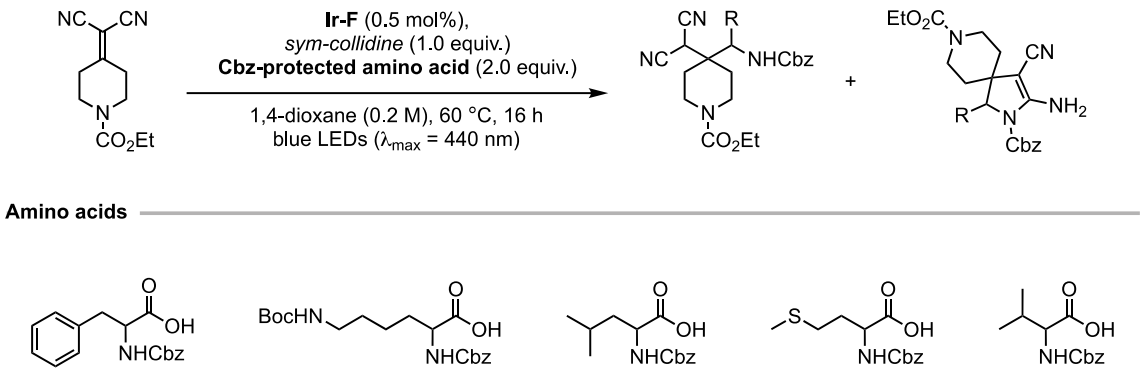


Synthesized following **GP4** using **B14** (86.7 mg, 0.2 mmol, 1.0 equiv.). **27** was isolated as a yellowish oil in 48% yield (39.7 mg, 0.10 mmol).

^1H NMR (400 MHz, $CDCl_3$) δ 4.12 (t, *J* = 7.11 Hz, 2H), 4.08 (d, *J* = 2.62 Hz, 2H), 4.02 (s, 2H), 3.60 (t, *J* = 5.24 Hz, 4H), 3.41 (dd, *J* = 6.40, 4.10 Hz, 2H), 2.91 (s, 2H), 2.12 (d, *J* = 13.28 Hz, 2H), 1.46 (s, 11H), 1.23 (d, *J* = 7.08 Hz, 3H).
$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 177.4, 167.6, 155.7, 154.0, 81.4, 61.6, 56.0, 48.9, 47.8, 46.9, 41.2, 40.7 & 40.3 (rotamers, 1C), 31.8, 28.4, 14.8.
HRMS (ESI): [m/z] calculated for $C_{19}H_{30}N_3O_7$ ([M-H]$^-$): 412.2085; Found: 412.2089.

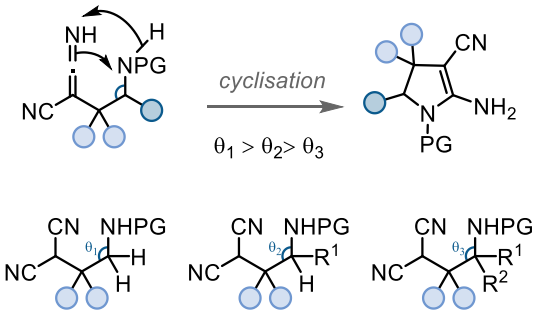
Limitations of the current methodology

Giese-type reaction



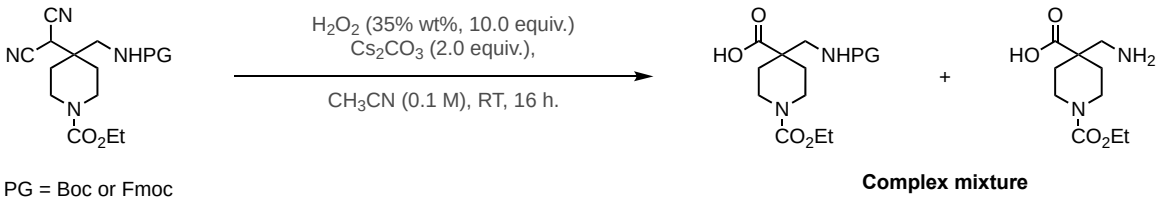
Scheme S1. Limitations of the Giese-type reaction

α-substituted amino acids can be used in the Giese-type reaction, however, they afford a mixture of spirocyclic derivatives and the targeted malononitrile. We believe that when using amino acids with greater α-substitution compared to Cbz-glycine, the increased steric hinderance drives the reaction towards the intramolecular, 5-exo-dig cyclisation, forming the spirocyclic species. This can be rationalised via the Thorpe-Ingold effect, substitution of methylene hydrogens with more sterically demanding alkyl groups compresses the bond angle θ between the two reacting groups to be narrower than the typical tetrahedral angle of 109.5°, bringing them closer together (J. Chem. Soc., Trans. 1915, 107, 1080). Coupled with the decreased conformational freedom caused by steric repulsion of the substituents, the probability of entering a conformation favouring intramolecular cyclisation significantly increases.



Scheme S2. Possible explanation for the observed reactivity with α-substituted amino acids.

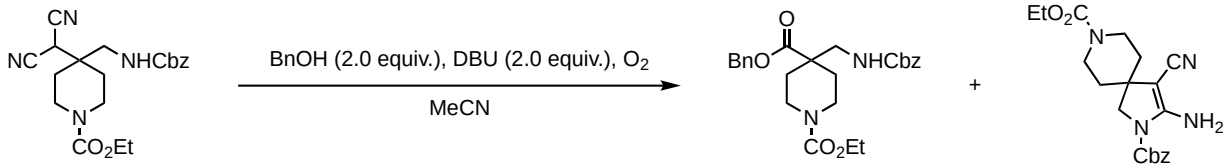
Oxidative functionalisation



Scheme S3. Limitations of the oxidative functionalisation.

The use of other protecting groups on the glycine (e.g. Fmoc or Boc) for the formation of the corresponding free acids resulted in *N*-deprotections, incomplete reactions, or decompositions, resulting in complex mixtures.

Synthesis of β-amino esters in continuous-flow



B1 **14** **D1**

Approach

The conversion of compound **B1** to **14** was chosen as our model reaction to translate this reaction from batch to flow on a 0.08 mmol scale. To avoid clogging, we replaced the inorganic base used in the batch setup (Cs_2CO_3) with DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), which showed comparable results (see Table S2, entry 11) and has the advantage of being completely soluble in organic solvents. O_2 availability in the organic solvent is key to drive the reaction towards the targeted product **14**: indeed, a scarce concentration of O_2 would not only slow down the conversion of **B1**, but also promote the formation of the undesired spiro compound **D1**.
In view of the above, we set as our priority to increase O_2 pressure in the reactor and we opted for a stop-flow approach, which allowed us to reach 33 bar in our reactor.[12] Once full conversion was reached, we aimed at reducing operating pressures, by counterbalancing reactivity drops with temperature increase, to eventually establish a continuous-flow protocol to make this oxidative benzylation scalable. Optimized conditions were adopted for scale-up on 0.5 mmol and 5 mmol scale.

Stop-flow: optimization

A 4 mL glass vial was charged with 1 mL of a mother solution of **B1** (0.08 M in CH_3CN), DBU (24 μL, 0.16 mmol, 2 equiv.) and benzyl alcohol (17 μL, 0.16 mmol, 2 equiv.). The mixture was taken up with a 5 mL disposable syringe and injected into a 1.5 mL pre-loop. The pre-loop was then connected to a HPLC pump. In the meantime, the flow of oxygen was regulated by means of a mass flow controller (MFC). The two feeds (liquid and gas) were combined by means of a PEEK T-mixer and flowed into a 54 mL coil (PFA, ID: 2 mm), which was pressurized with a HPLC pump at the desired pressure by means of a back-pressure regulator (cartridge). Once the pressure was reached, the reactor was sealed by shutting switch valves and the crude was held at the desired pressure and temperature (water bath used in this work) for the desired amount of time. Finally, the crude was flushed out, quenched, and worked up as described for batch experiments.

Table S3. Optimisation of stop-flow conditions.

Entry	f_1 (mL/min)	f_2 (mL/min)	t (min)	T (°C)	BPR	14 (%)[a]	D1 (%)[a]	B1 (%)[a]
1	1.74	0.05	0	20	1	n.d.	n.d.	>95
2	1.74	0.05	0	20	33	46	n.d.	54
3	1.74	0.05	60	20	33	86	n.d.	Traces
4	1.74	0.05	90	20	33	89	n.d.	n.d.
5	1.74	0.05	90	20	7	43	n.d.	43
6	1.74	0.05	90	30	7	58	6	27
7	1.74	0.05	90	50	7	71	11	7

[a] Yields calculated via NMR using trichloroethylene (1 equiv.) as external standard. f_1: flow rate of O_2 feed. f_2: flow rate of the solution.

As shown in Table S3, Entry 1, when the reaction was performed at ambient pressure, the rection did not proceed. However, increasing the pressure at 33 bar, the formation of **14** was observed (Entry 2). Using longer reaction times proved beneficial (Entries 3 and 4), however comparable results could be obtained at much lower pressure (7 bar) with slightly increased temperature (Entries 5-7). The conditions reported in Table S3, entry 7 allowed us to move to continuous flow, which is a more suitable technique for scale up.

Continuous-flow: optimization

A 4 mL glass vial was charged with 1 mL of a mother solution of **B1** (0.08 M in CH_3CN), DBU (24 μL, 0.16 mmol, 2 equiv.) and benzyl alcohol (17 μL, 0.16 mmol, 2 equiv.). The mixture was taken up with a 5 mL disposable syringe and injected into a 1.5 mL pre-loop. The pre-loop was then connected to a HPLC pump. In the meantime, the flow of oxygen was regulated with a mass flow controller (MFC) to obtain the desired stoichiometry. The two feeds (liquid and gas) were combined by means of a PEEK T-mixer and flowed through a 25 mL coil (PFA, ID: 2 mm) at the desired pressure by means of an adjustable back-pressure regulator (IDEX) thermostatted with a water bath at 50 °C. Finally, the crude was quenched and worked up as described for batch experiments.

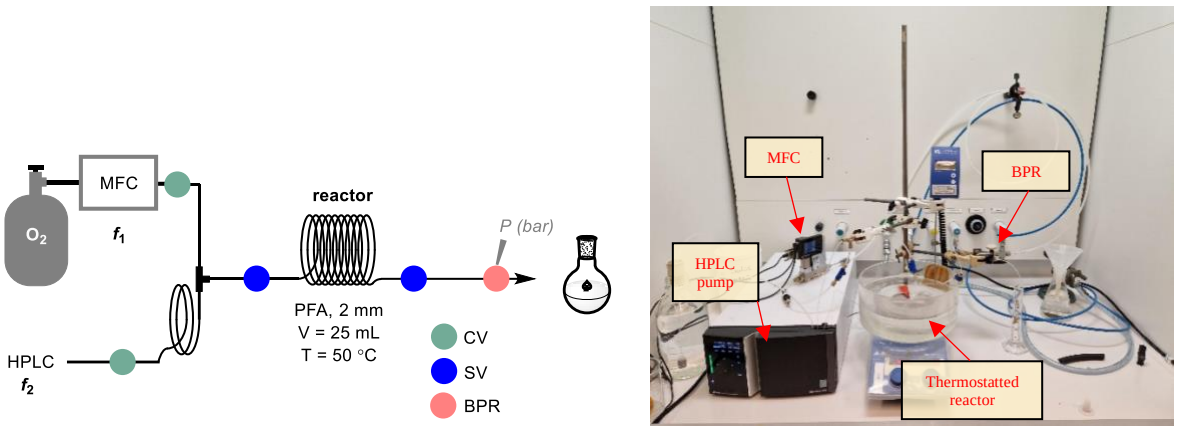


Figure S6. Continuous-flow setup. MFC: Mass Flow Controller; SV: Switch Valve; CV: Check Valve; BPR: Back-Pressure Regulator.

Table S4. Optimisation of continuous-flow conditions.

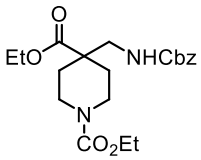
Entry	f_1 (mL/min)	f_2 (mL/min)	Press. (bar)	Experimental t_R (min)	14 (%)[a]	D1 (%)[a]	B1 (%)[a]
1	1.9	0.05	7	88	56%	14%	29%
2	1.9	0.05	12	142	78%	6%	0
3	3.8	0.1	12	70	83%	9%	0

[a] Yields calculated via NMR using trichloroethylene (1 equiv.) as external standard. Isolated yields in parentheses.

As shown in Table S4, the transition from stop-flow to continuous-flow was accompanied by the formation of by-product **D1** (Entry 1); however, by simply increasing the pressure in the system to 12 bar, the selectivity was restored (Entry 2). Remarkably, the reaction remained efficient when we doubled the flow rates of both the liquid and gas feeds, thus enhancing the overall productivity (Entry 3). We assessed the validity of these conditions (Table S4, Entry 3) across several entries of the scope by performing an intermediate scale-up on 0.5 mmol scale.

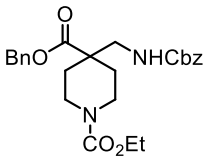
Generality assessment of continuous-flow conditions

Product 1



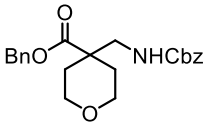
Synthesized following the general procedure using **B1** (192 mg, 0.5 mmol, 1.0 equiv.) and EtOH (58 µL, 1.0 mmol, 2.0 equiv.). Purification via flash chromatography using silica gel (pentane/EtOAc 7:3) afforded **1** as a yellow oil in 72% yield (141 mg, 0.36 mmol).

Product 14



Synthesized following the general procedure using **B1** (192 mg, 0.5 mmol, 1.0 equiv.) and benzyl alcohol (104 µL, 1.0 mmol, 2.0 equiv.). Purification via flash chromatography using silica gel (pentane/EtOAc 7:3) afforded **14** as a yellowish oil in 70% yield (159 mg, 0.35 mmol).

Product 15



Synthesized following the general procedure using **B3** (157 mg, 0.5 mmol, 1.0 equiv.) and benzyl alcohol (104 µL, 1.0 mmol, 2.0 equiv.). Purification via flash chromatography using silica gel (pentane/EtOAc 7:3) afforded **15** as a yellow oil in 84% yield (161 mg,0.42 mmol).

Scale-up in continuous-flow (5 mmol)

In a 50 mL volumetric flask, **B1** (1.92 g, 5 mmol) was dissolved in some CH_3CN, next benzyl alcohol (1.04 mL, 10 mmol, 2 equiv.), DBU (1.49 mL, 10 mmol, 2 equiv.) were added; finally, the total volume was taken up to the mark with more CH_3CN. The obtained solution worked as a reservoir for a HPLC pump set at 0.1 mL/min. Next, the flow of oxygen was regulated with a mass flow controller (MFC) at 3.8 mL/min. The two feeds (liquid and gas) were combined by means of a PEEK T-mixer and flowed through a 25 mL coil (PFA, ID: 2 mm) pressurized at 12 bar by means of an adjustable back-pressure regulator (residence time: 65 min) thermostatted with a water bath at 50 °C. Finally, the crude was quenched and worked up as described for batch experiments. After column chromatography (pentane/EtOAc 7:3 → 6:4) **14** was obtained as a chewy, orange liquid (1.62 g, 71%).

Quantum yield determination

Determination of the light intensity at 440 nm

Following the procedure of Yoon,[13] the photon flux of the LED (λ_{max} = 440 nm) was determined by standard ferrioxalate actinometry.[14] A 0.15 M solution of ferrioxalate was prepared by dissolving potassium ferrioxalate trihydrate (0.73 g) in H_2SO_4 (10 mL of a 0.05 M solution). A buffered solution of 1,10-phenanthroline was prepared by dissolving 1,10-phenanthroline (25 mg) and sodium acetate (5.6 g) in H_2SO_4 (25 mL of a 0.50 M solution). Both solutions were stored in the dark. To determine the photon flux of the LED, the ferrioxalate solution (1.0 mL) was placed in a cuvette and irradiated for 120 seconds at λ_{max} = 440 nm. After irradiation, the phenanthroline solution (175 µL) was added to the cuvette and the mixture was allowed to stir in the dark for 1 h to allow the ferrous ions to fully coordinate to the phenanthroline. The absorbance of the solution was measured at 510 nm. A non-irradiated sample was also prepared, and the absorbance was measured at 510 nm. Conversion was calculated using eq. S1.

$$\text{mol Fe}^{2+} = \frac{V\Delta A(510\text{ nm})}{l\varepsilon} \quad \text{(eq. S1)}$$

where V is the total volume (0.001175 L) of the solution after addition of phenanthroline, ∆A is the difference in absorbance at 510 nm between the irradiated and non-irradiated solutions, l is the path length (1.00 cm), and ε is the molar absorptivity of the ferrioxalate actinometer at 510 nm (11,100 $Lmol^{-1}cm^{-1}$).[15] With this data, the photon flux was calculated using eq. S2.

$$\text{Photon flux} = \frac{\text{mol } Fe^{2+}}{\Phi t f} \quad \text{(eq. S2)}$$

where Φ is the quantum yield for the ferrioxalate actinometer (1.01 at λ_{ex} = 437 nm),[16] t is the irradiation time (120 s), and f is the fraction of light absorbed at λ_{ex} = 437 nm by the ferrioxalate actinometer. This value was calculated using eq. S3 where A (440 nm) is the absorbance of the ferrioxalate solution at 440 nm. An absorption spectrum gave an A (440 nm) value of > 3, indicating that the fraction of absorbed light (f) is > 0.999.

$$\text{f} = 1 - 10^{-A(440\,nm)} \quad \text{(eq. S3)}$$

The **photon flux** was thus calculated (as an average of three experiments) to be **8.84367 x 10^{-11} einsteins s^{-1}**

Determination of the reaction quantum yield

A reaction under the standard conditions using **A1** (21.9 mg, 0.1 mmol, 1.0 equiv.) and *Z*-glycine in MeCN (0.1 mL, 0.1 M) was irradiated at 440 nm for 3600 sec. Afterwards, the solvent was removed and CD_3Cl added, followed by the addition of trichloroethylene (8.89 µL, 0.1 mmol, 1.0 equiv.) was added as an internal standard, and an aliquot of the reaction mixture was then analysed by ^{1}H NMR. The desired product **B1** was formed (as an average of three experiments) in 82% yield (8.2 x 10^{-5} mol). The reaction quantum yield (Φ) was determined using eq. S4, where the photon flux is 8.84367 x 10^{-11} einsteins s^{-1} (determined by actinometry as described above), *t* is the reaction time (3600 s) and *f* is the fraction of incident light absorbed by the reaction mixture, determined using eq. S3. An absorption spectrum of the reaction mixture gave an absorbance value of 3.37148 at 437 nm, thus *f* was determined to be a value of 0.9996.

$$\Phi = \frac{\text{mol of product formed}}{\text{Photon flux}tf} \quad \text{(eq. S4)}$$

Hence, the **reaction quantum yield (Φ)** was thus determined to be **275.67**.

Proposed Mechanism for the Giese-type reaction

A plausible mechanism for the key step, the formation of the α-quaternary centre, is proposed (Figure 2). Based on the measured quantum yield (Φ = 276),[17] the Giese-type reaction should proceed via a light-initiated radical-chain mechanism. The process starts with the reductive quenching of the excited photocatalyst (***Ir-F**^{III}, $^*E_{1/2}$ = +1.21 V vs SCE in CH_3CN)[18] by the corresponding α-amino carboxylate species **I** ($E_{1/2}$ = +0.95 V versus SCE in CH_3CN);[19] this generates an acyloxy radical (**II**) that undergoes rapid decarboxylation, affording a nucleophilic α-amino radical (**III**). Subsequent addition of **III** to a highly electrophilic alkylidenemalononitrile (**A**) affords stabilised tertiary radical intermediate **IV**. The latter can react via two pathways: *pathway a*) **IV** can undergo a single electron transfer with α-amino carboxylate **I**, generating species **II** and anion **V**, thus propagating the radical chain, or *pathway b*) **IV** can undergo facile single-electron transfer (SET) with the reduced photocatalyst (**Ir-F**^{II}, $E_{1/2}$ = −1.37 V vs SCE in CH_3CN),[18] closing the photocatalytic cycle and generating anion **V**. Finally, protonation of the latter affords the targeted β-quaternary malononitrile species **B**.

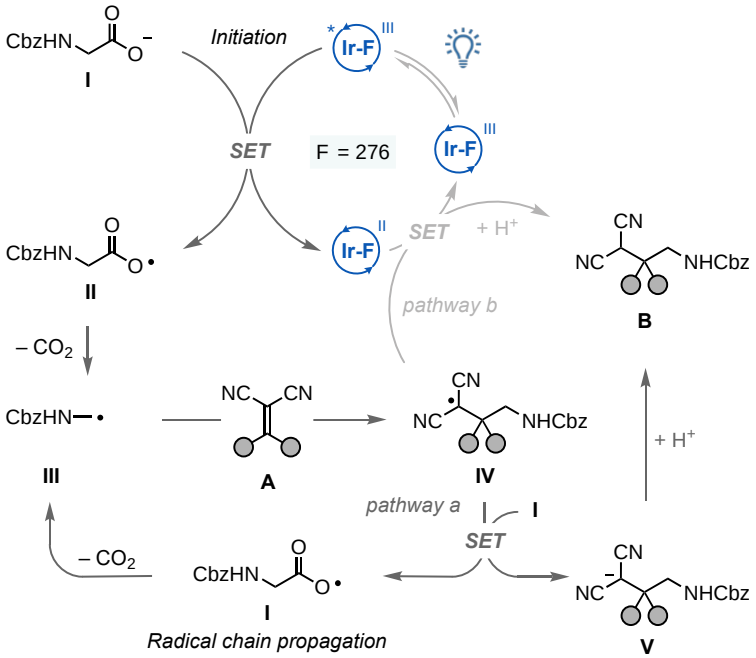


Figure S7. Plausible reaction mechanism for the light-mediated Giese-type reaction.

Proposed Mechanism for Oxidative Esterification/Amidation

Based on Hayashi's work,[1] a plausible mechanism for the oxidative esterification reaction is proposed. First, deprotonation of **B** with either Cs_2CO_3 (pKa = 10.3 in H_2O)[20] or DBU (pKa = 13.5 ± 1.5 in H_2O)[21] affords anionic intermediate **I**. At this point, if the concentration of oxygen in solution is low, formation of spirocycle **D** is favoured. However, at high O_2 concentrations, **I** undergoes single electron transfer (SET) and addition with molecular oxygen, resulting in the formation of peroxide intermediate **II**. The latter can undergo an intramolecular cyclisation to afford dioxirane **III**, which, in turn, can react with another molecule of carbanion **I** to produce anionic adduct **IV**. Finally, fragmentation of the later, and release of a cyanide anion, produces two molecules of acyl cyanide species **V**, which reacts with an alcohol, delivering targeted $\beta^{2,2}$-amino ester **C**.

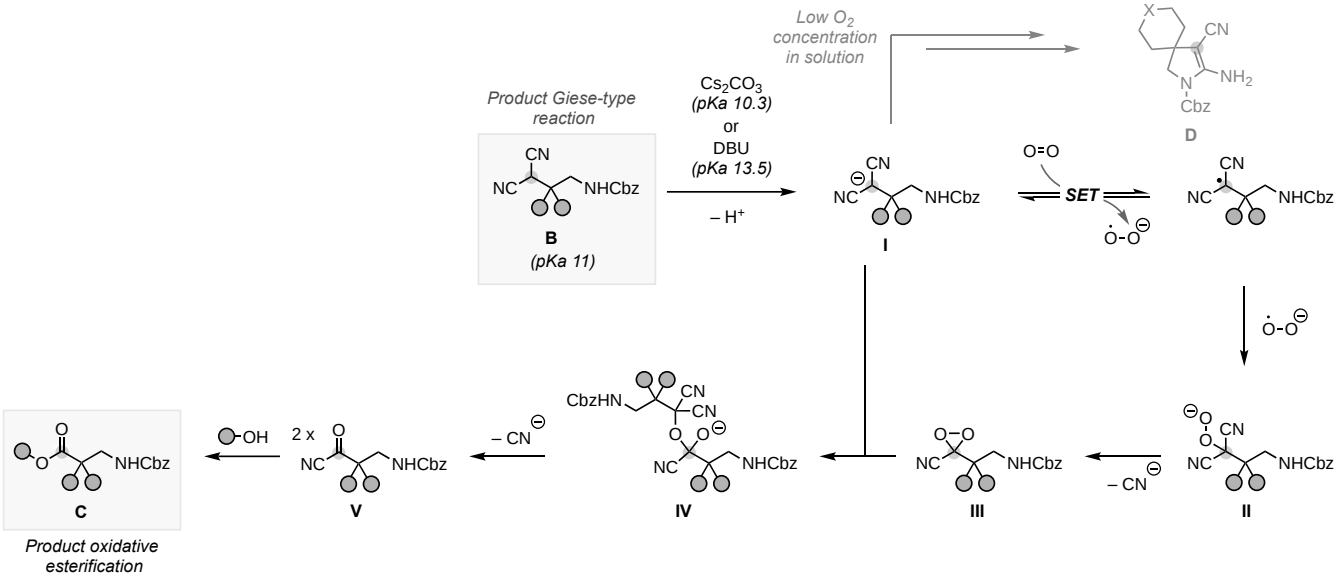


Figure S8. Proposed mechanism for the oxidative esterification/amidation process.

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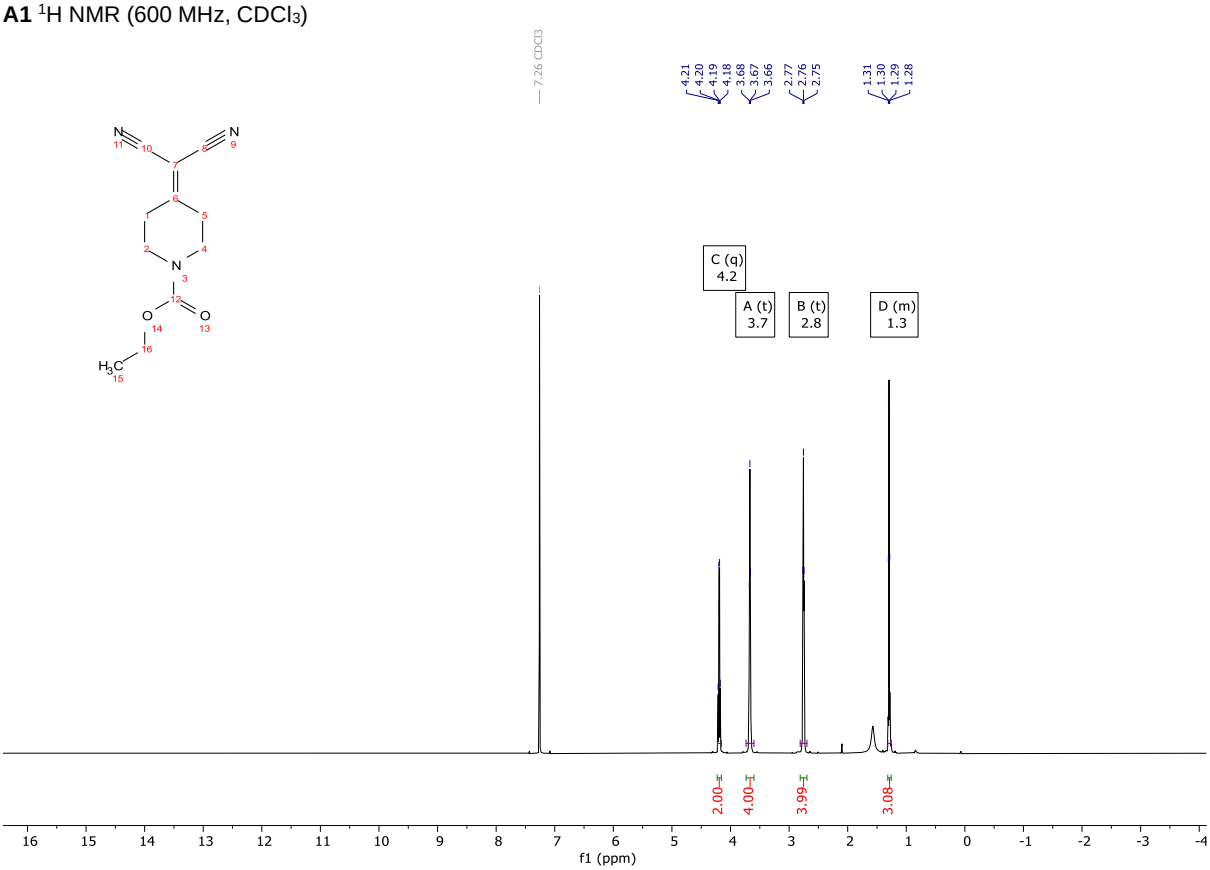
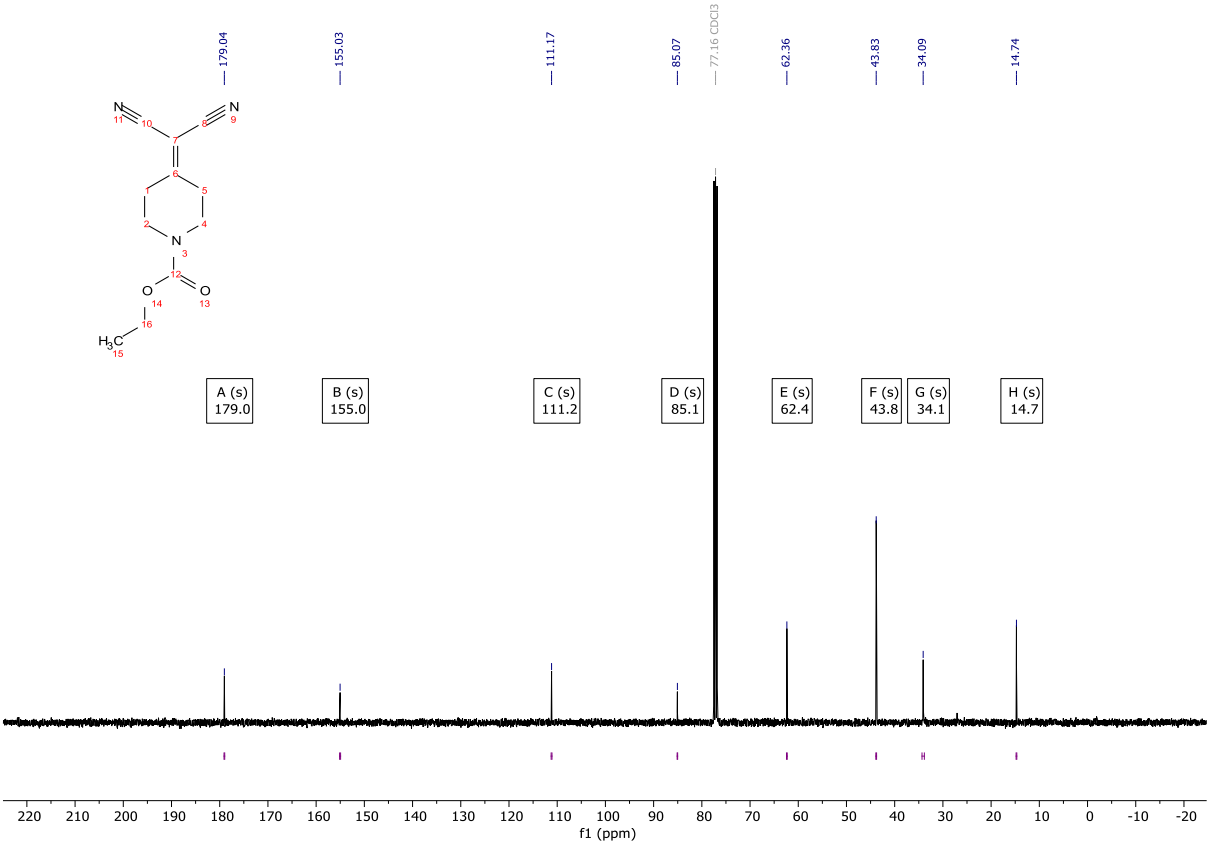
^{1}H, ^{13}C NMR Spectra

Alkylidenemalononitriles

A1 ^{1}H NMR (600 MHz, $CDCl_3$)



A1 ^{13}C NMR (151 MHz, $CDCl_3$)



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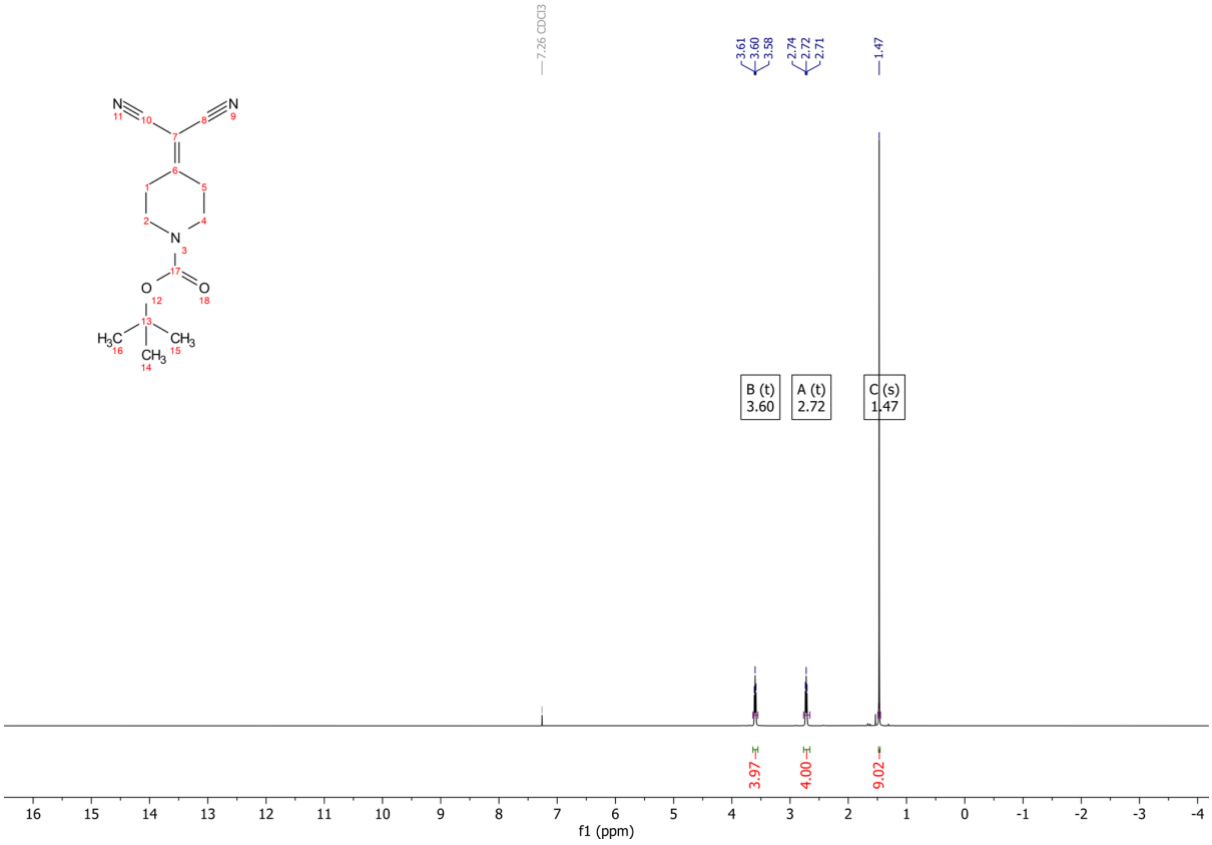
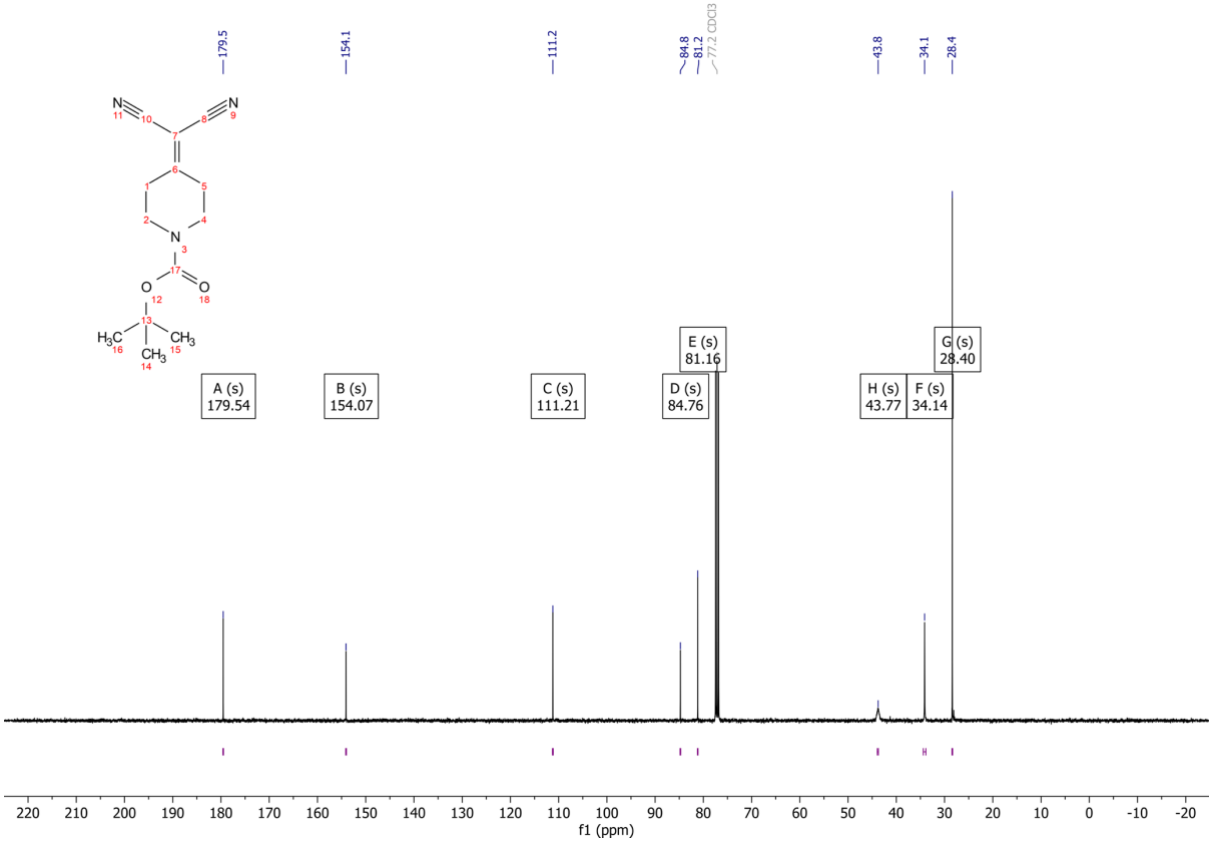
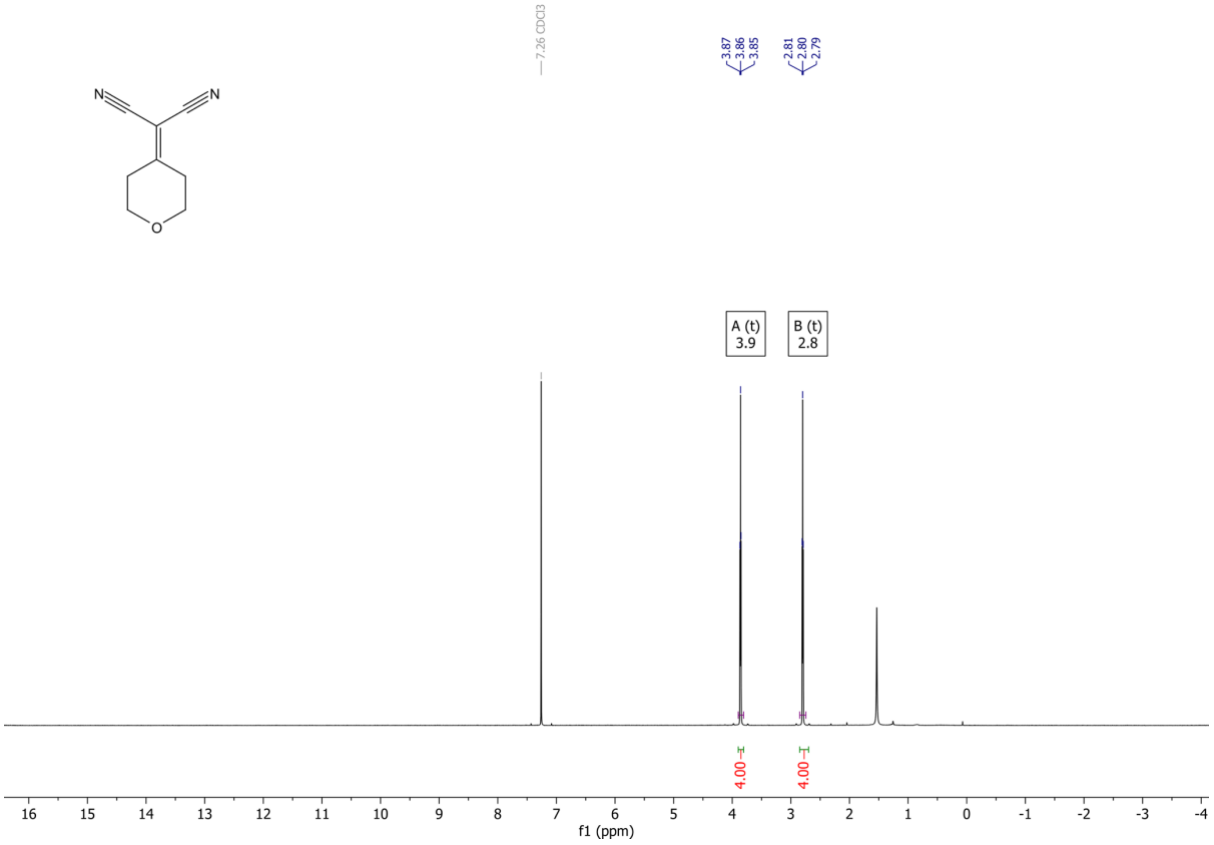


A2 ^{13}C NMR (101 MHz, $CDCl_3$)



A3 ^{1}H NMR (400 MHz, $CDCl_3$)



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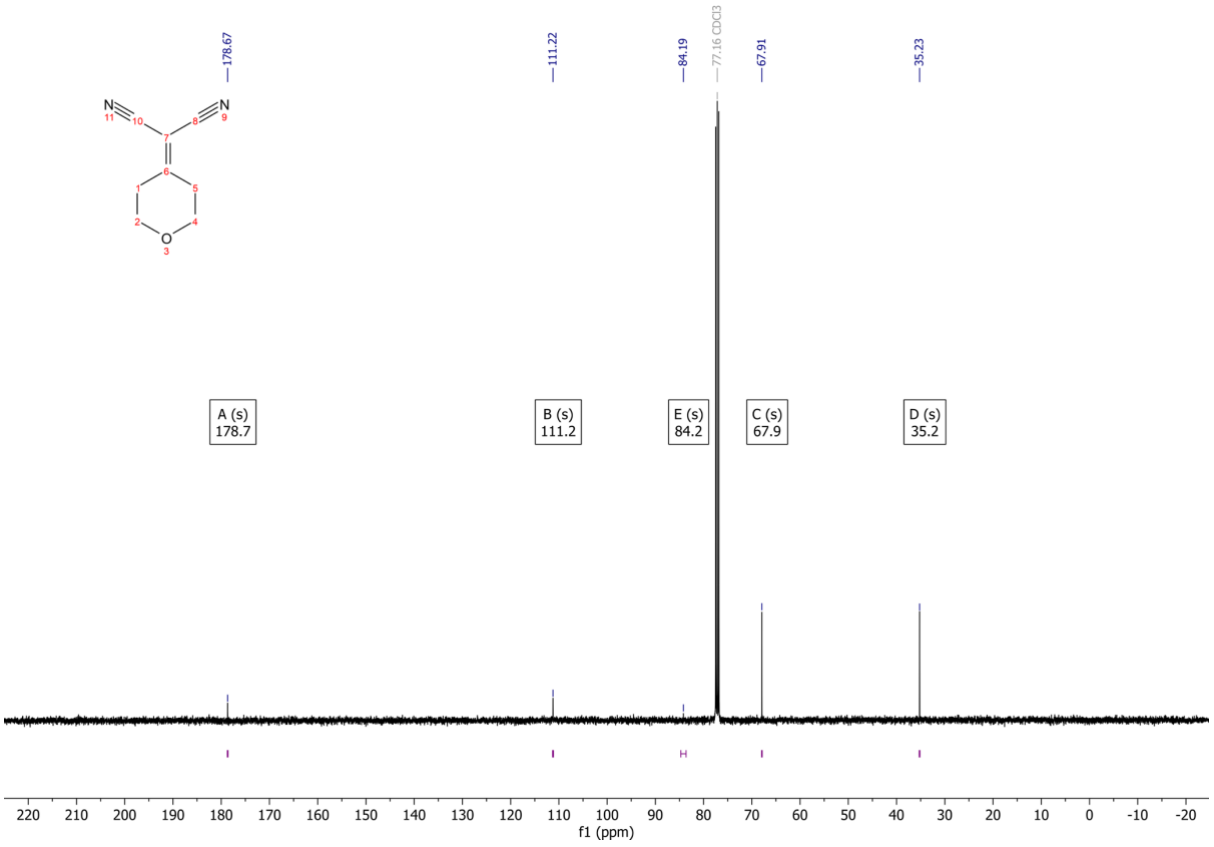

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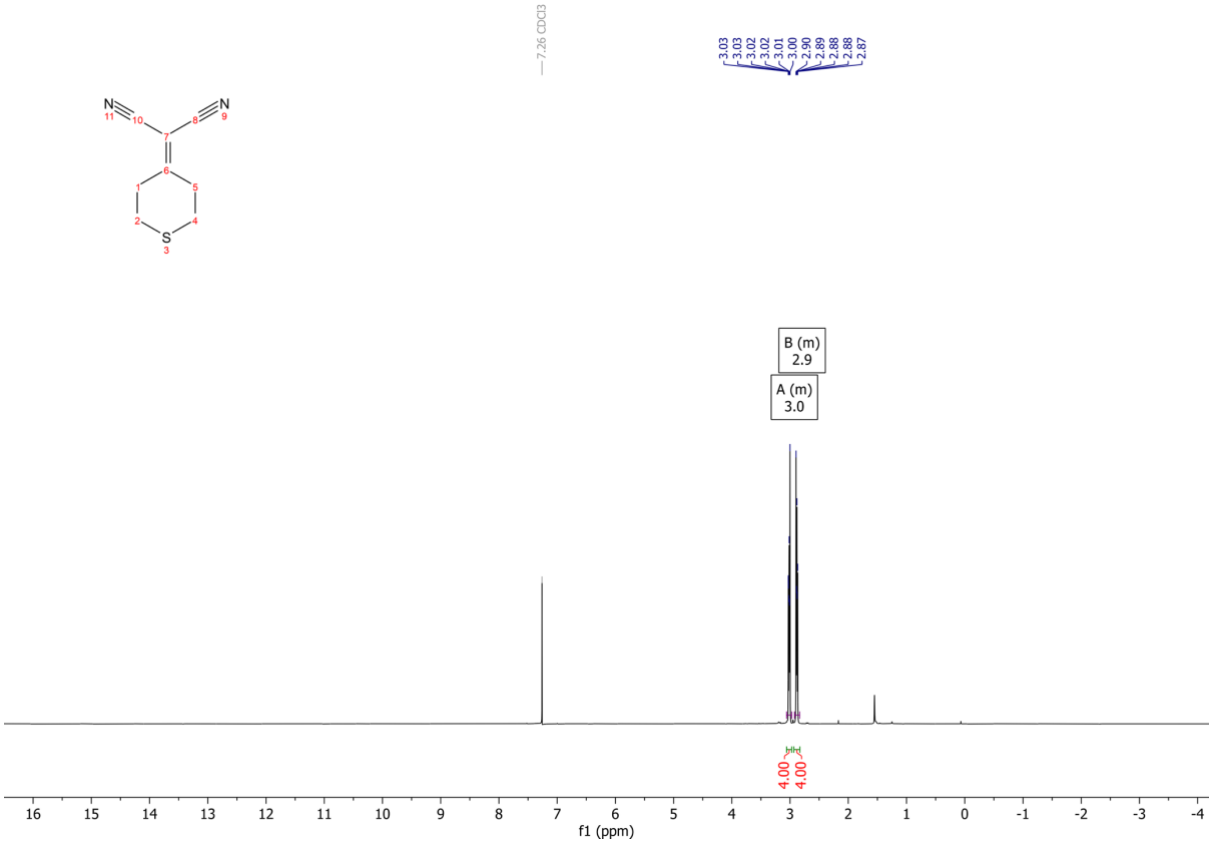
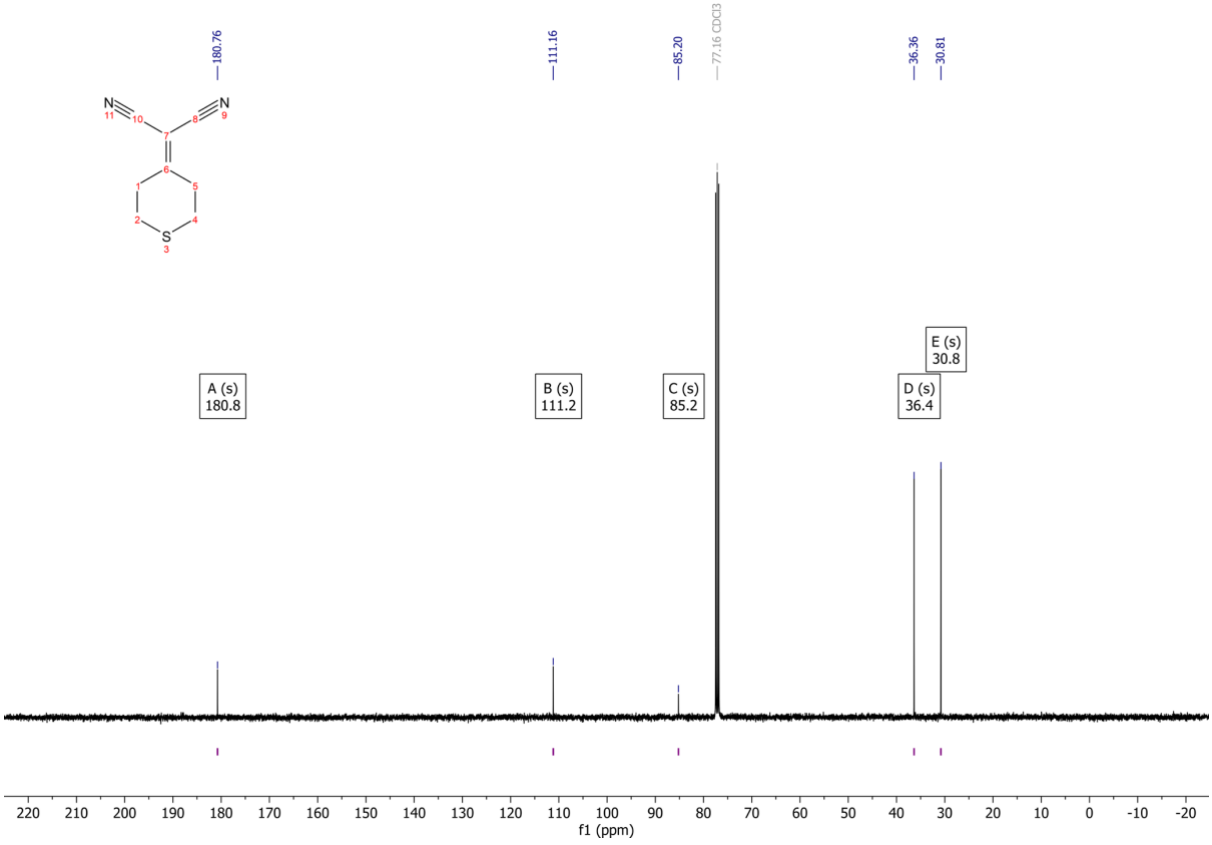
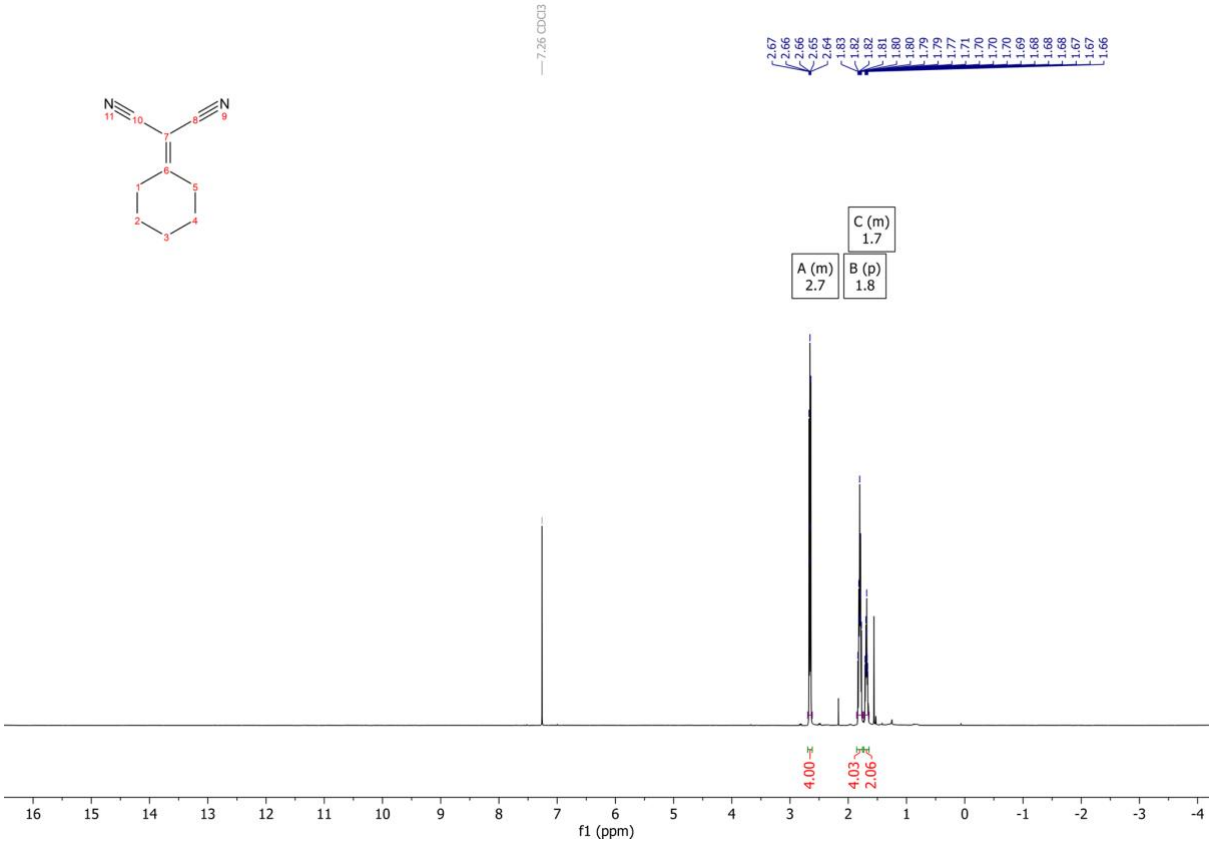


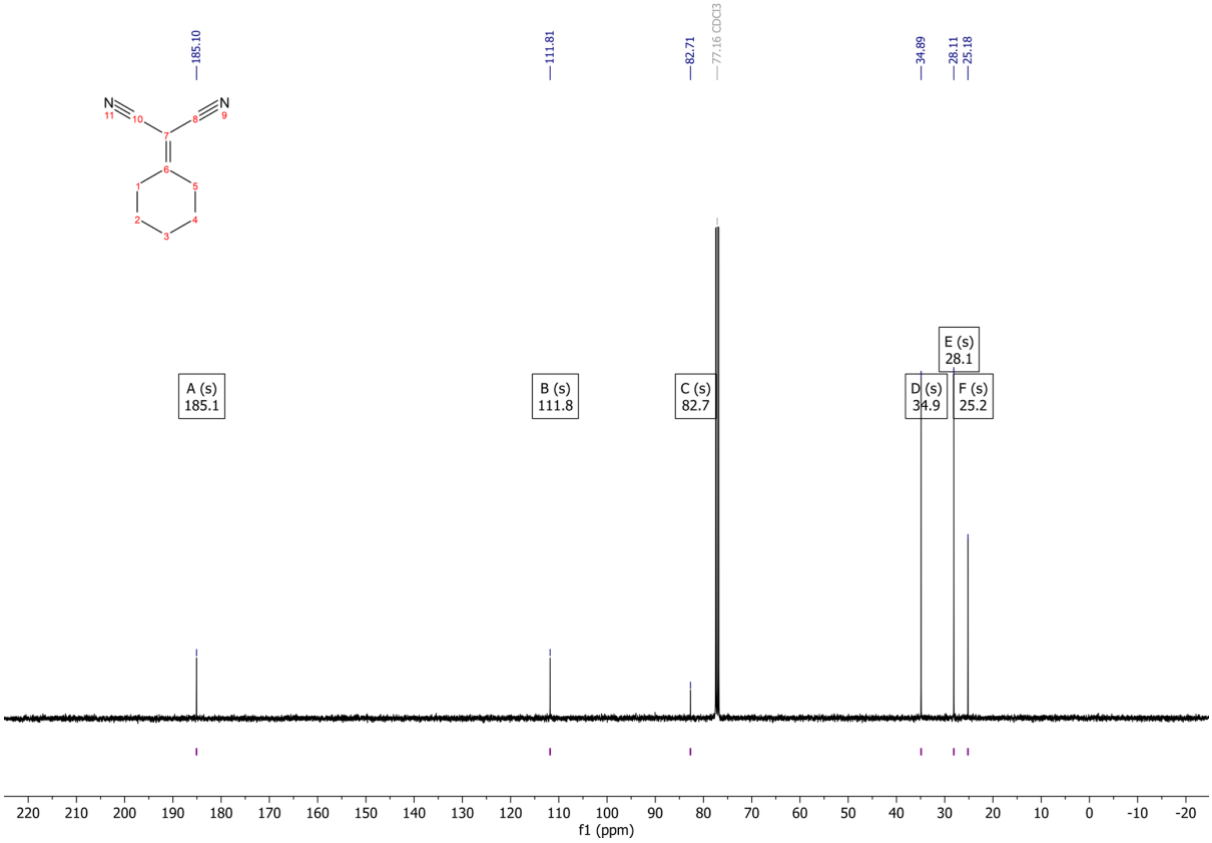
A4 ^{13}C NMR (101 MHz, $CDCl_3$)



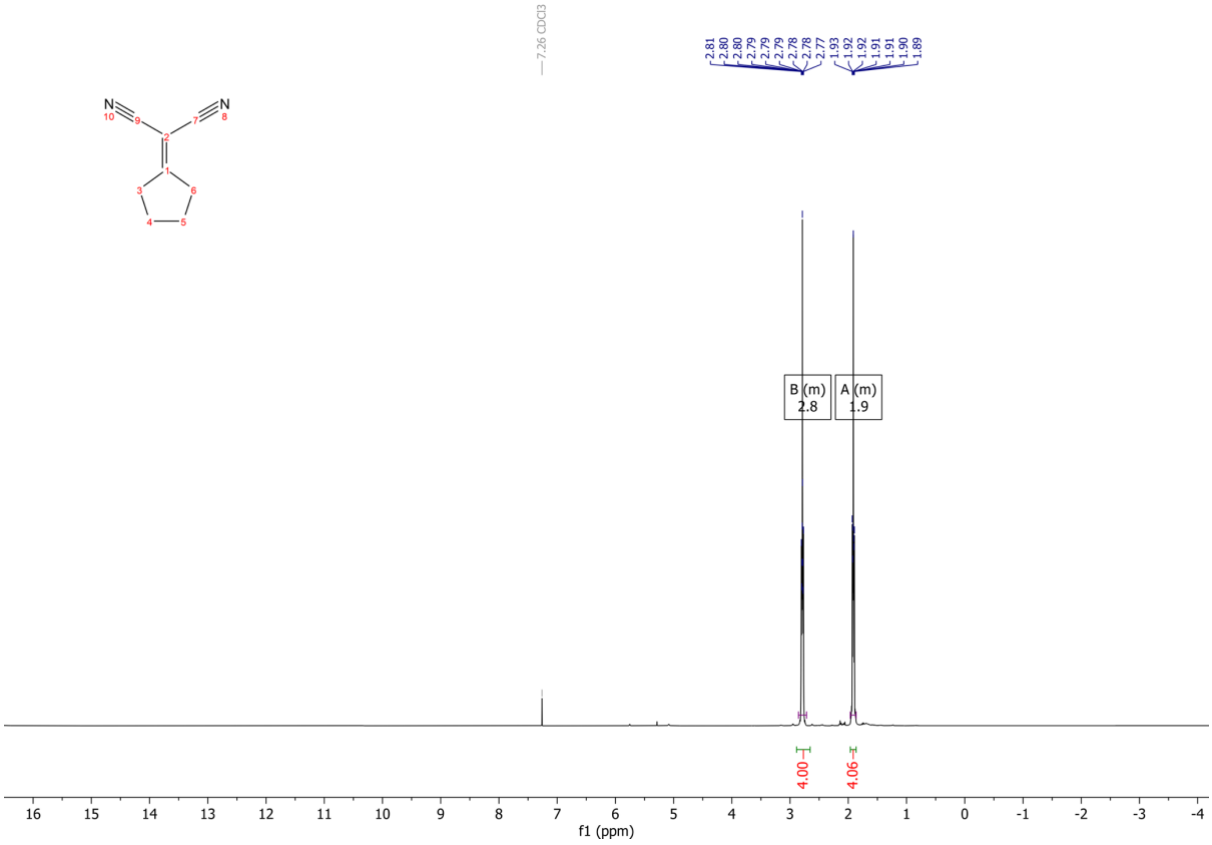
A5 ^{1}H NMR (400 MHz, $CDCl_3$)



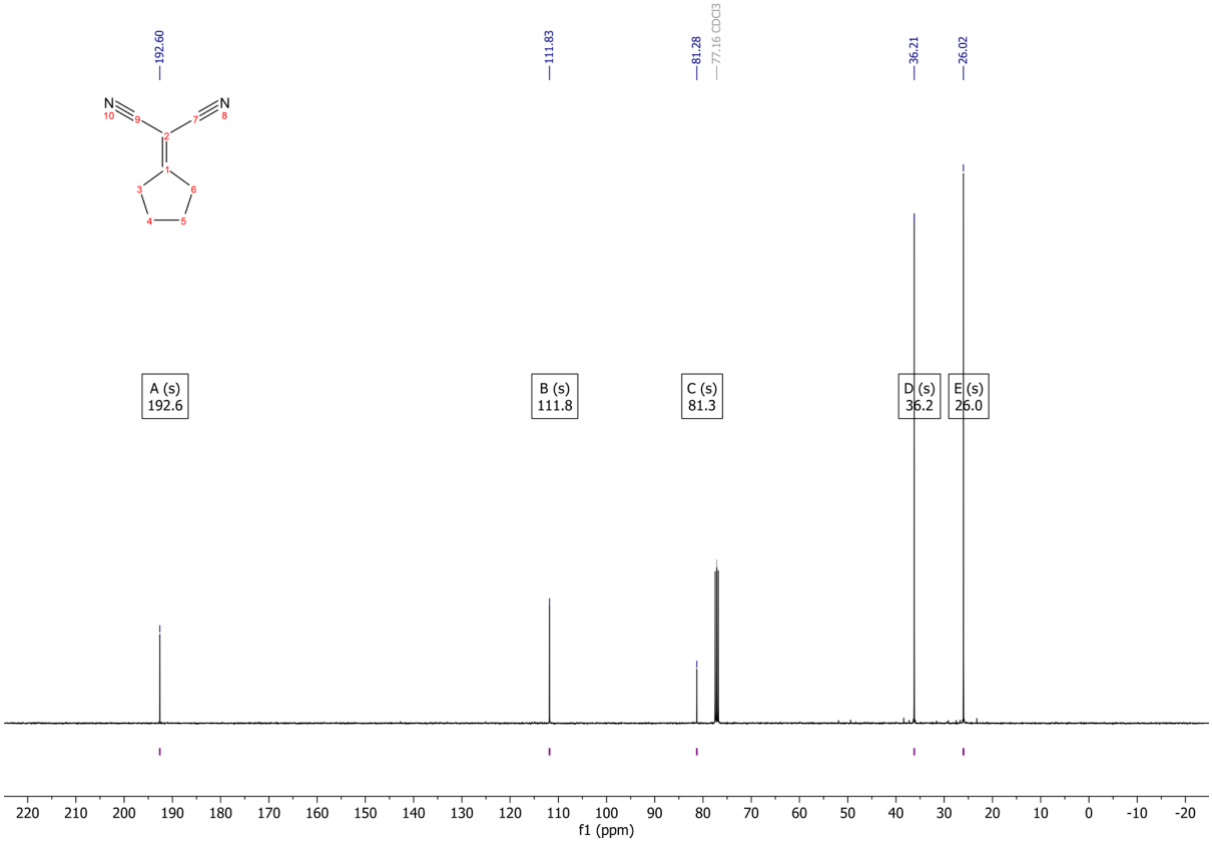
A5 ^{13}C NMR (101 MHz, $CDCl_3$)



A6 ^{1}H NMR (600 MHz, $CDCl_3$)



A6 ^{13}C NMR (101 MHz, $CDCl_3$)



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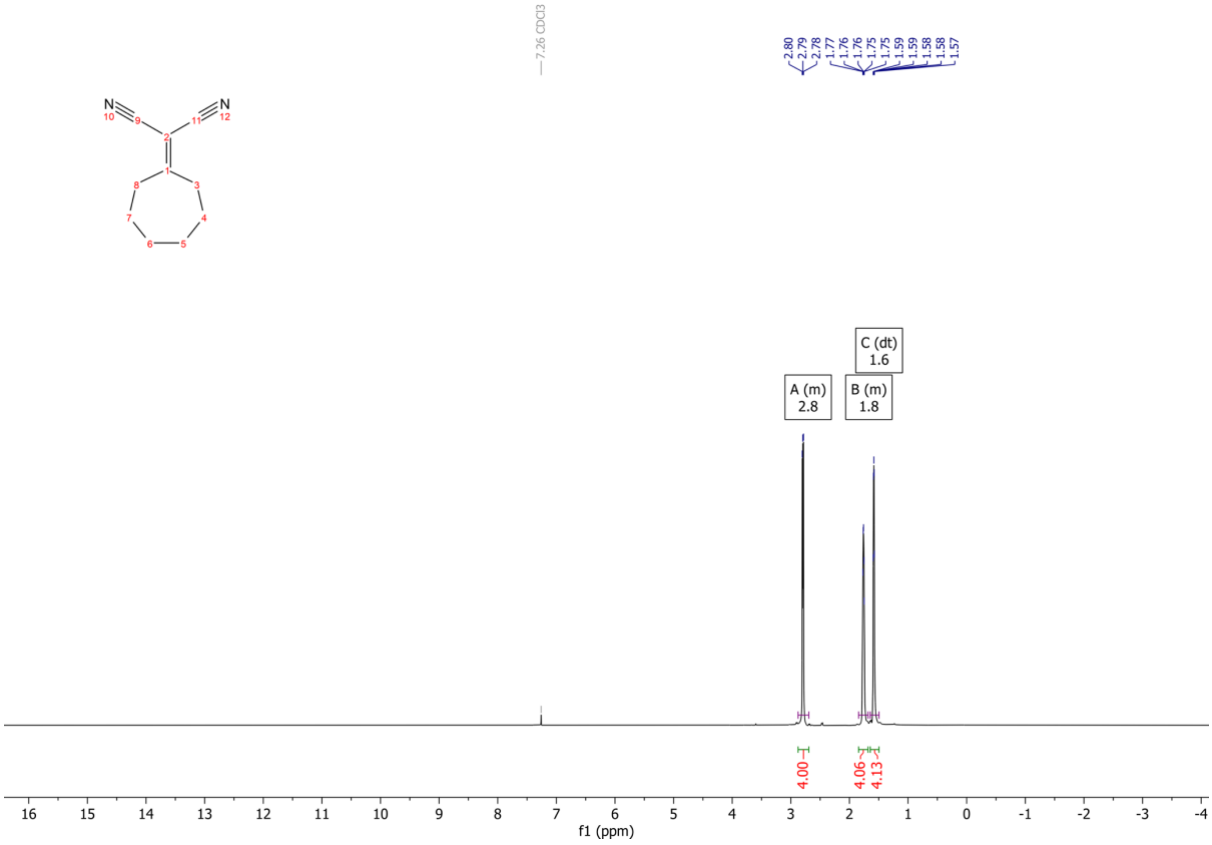

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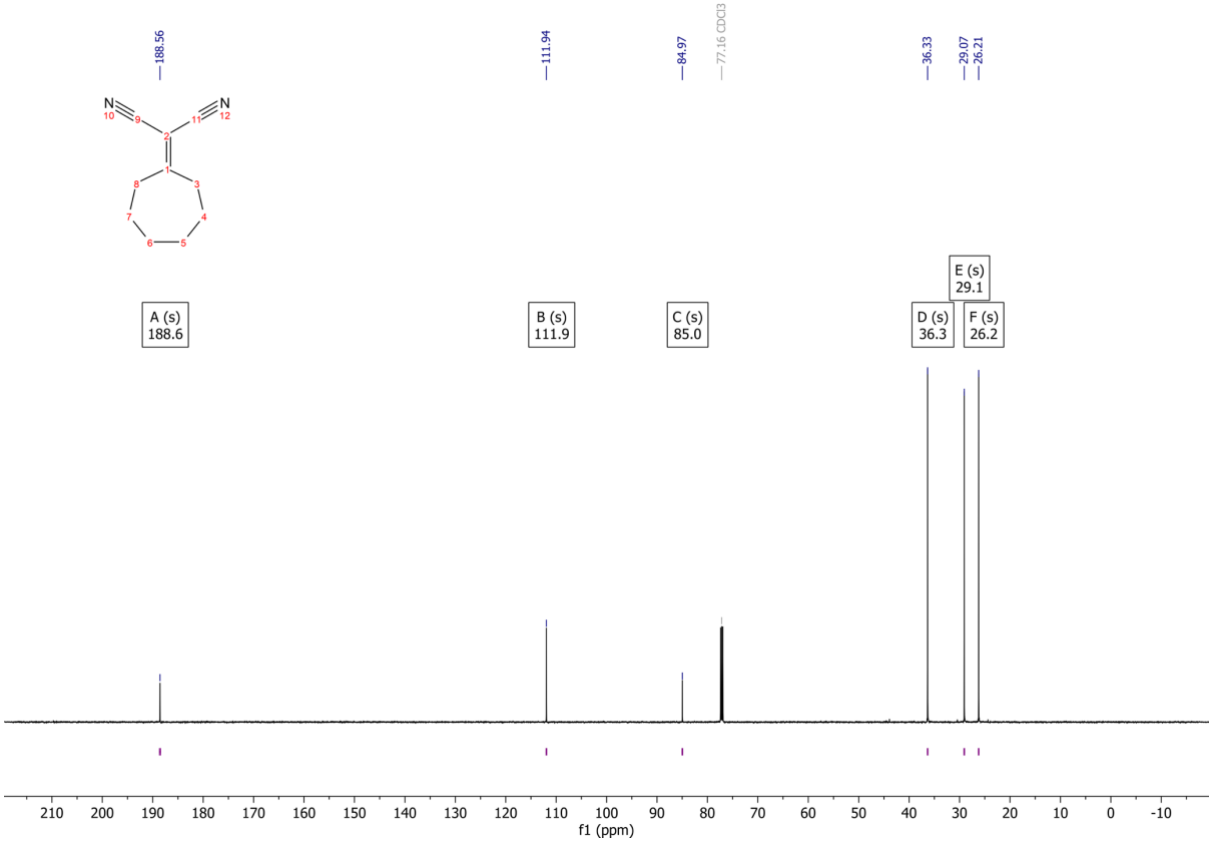
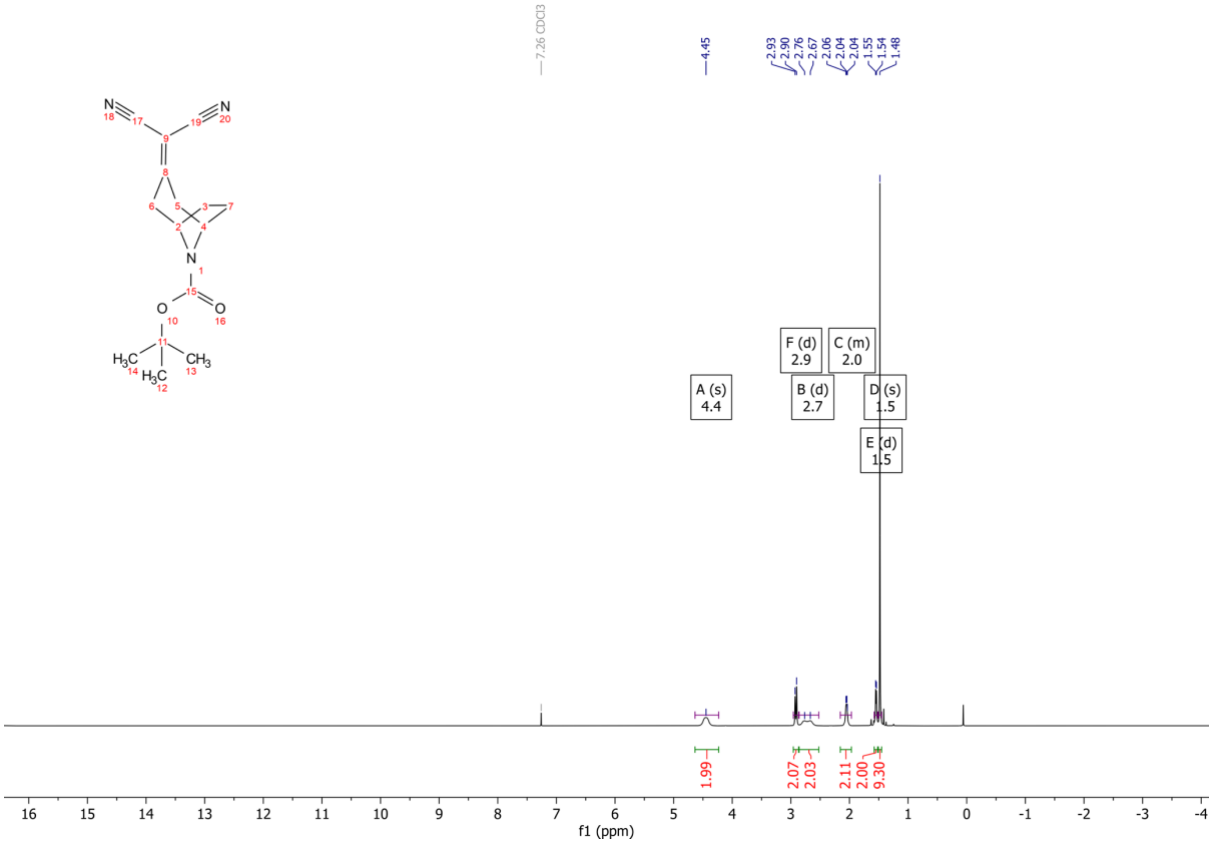
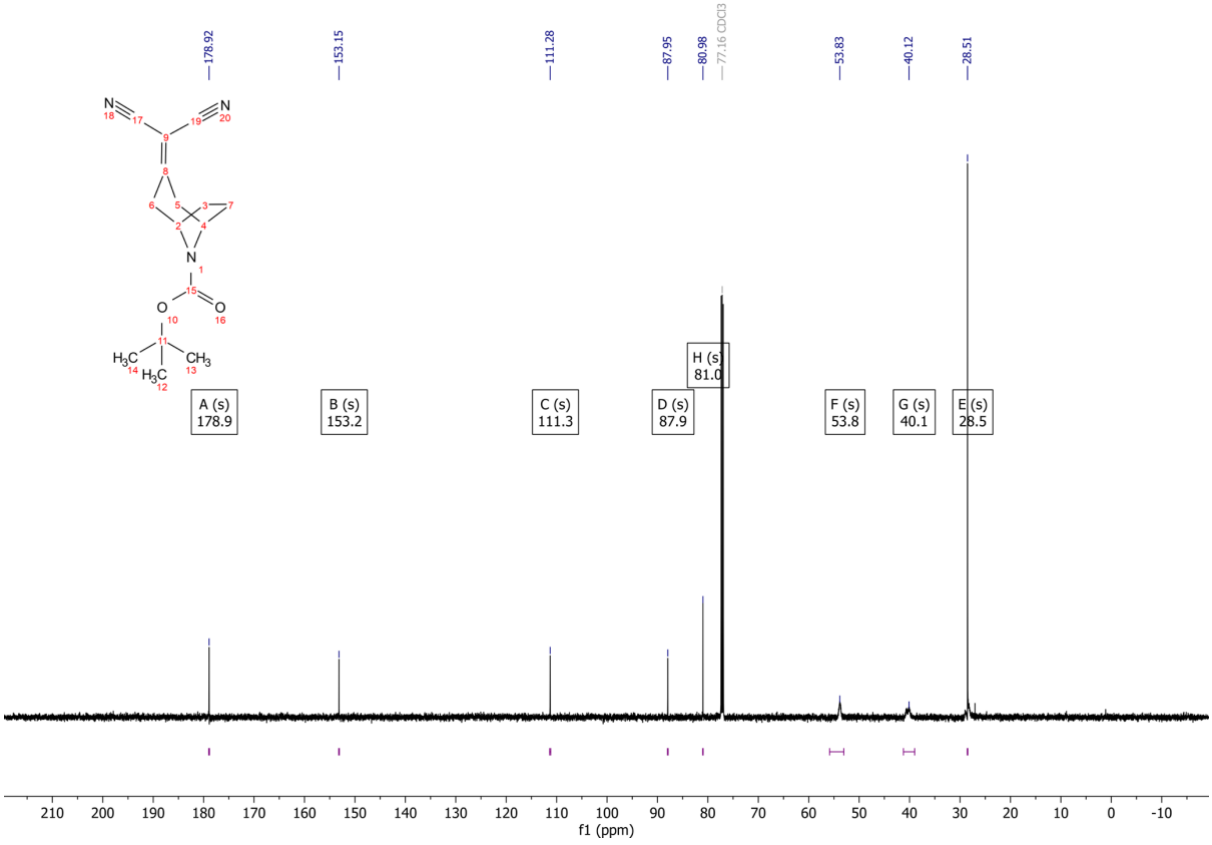


A8 ^{1}H NMR (600 MHz, $CDCl_3$)



A8 ^{13}C NMR (151 MHz, $CDCl_3$)



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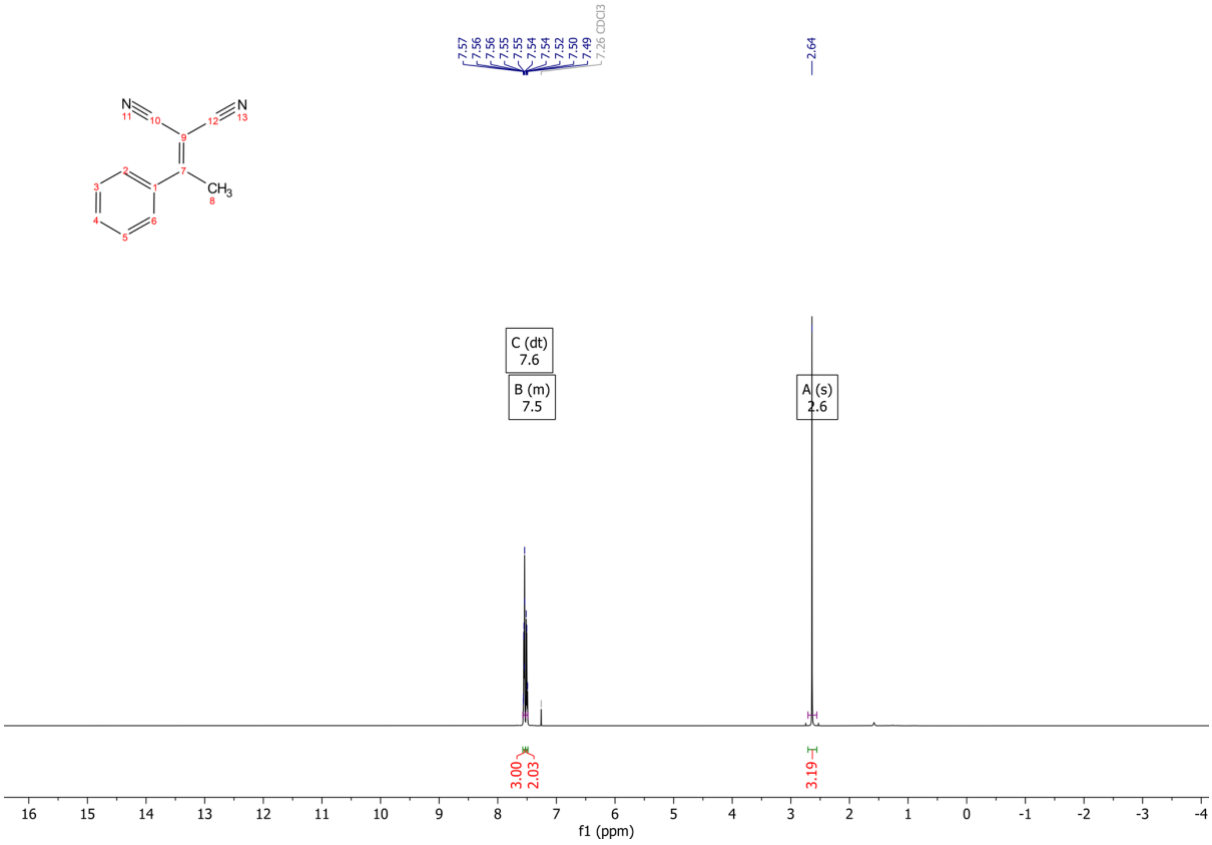

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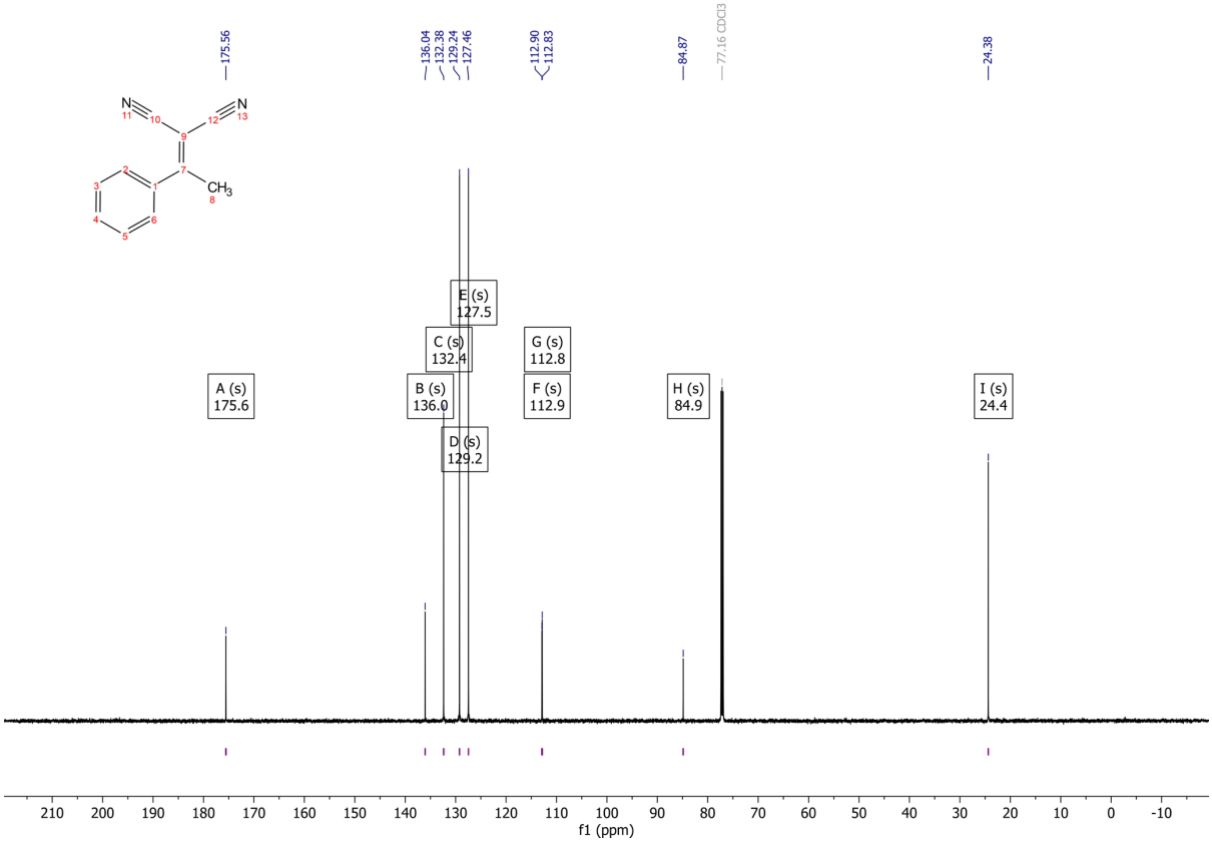

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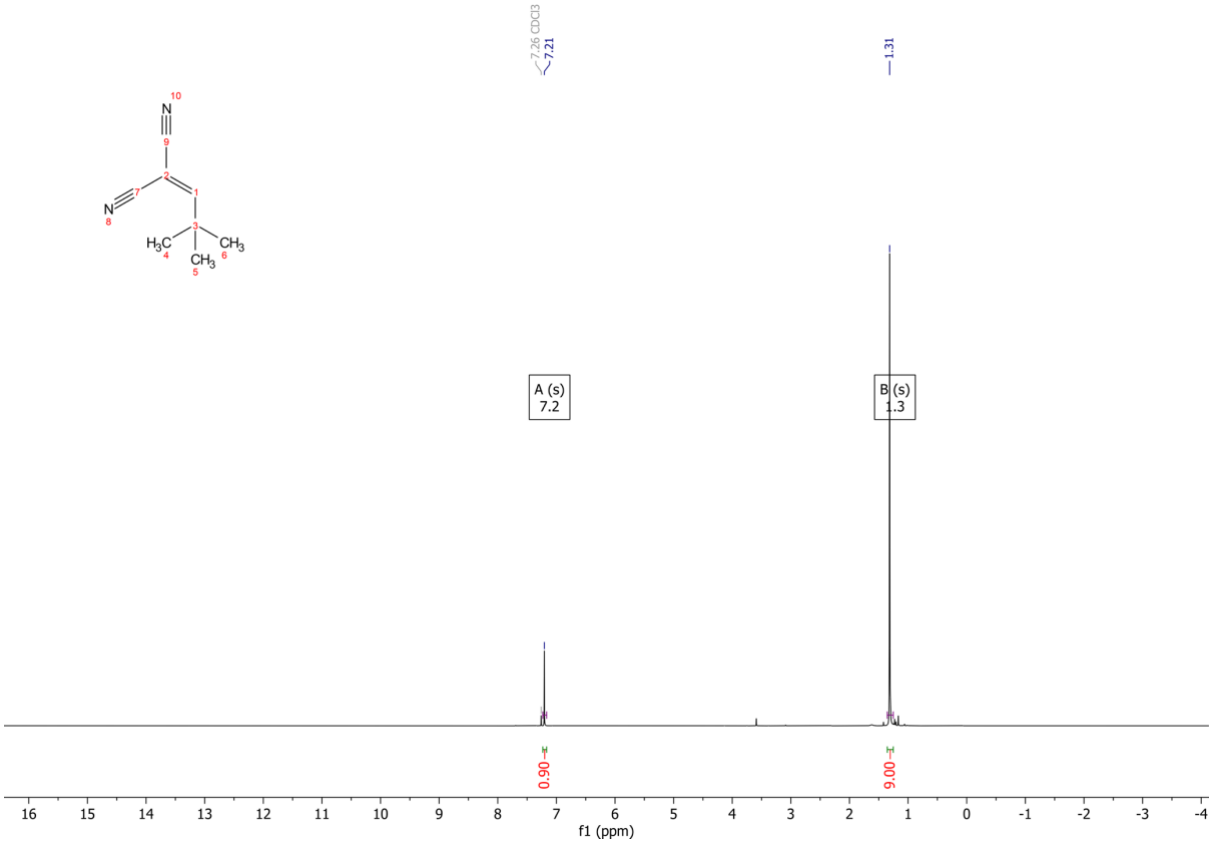

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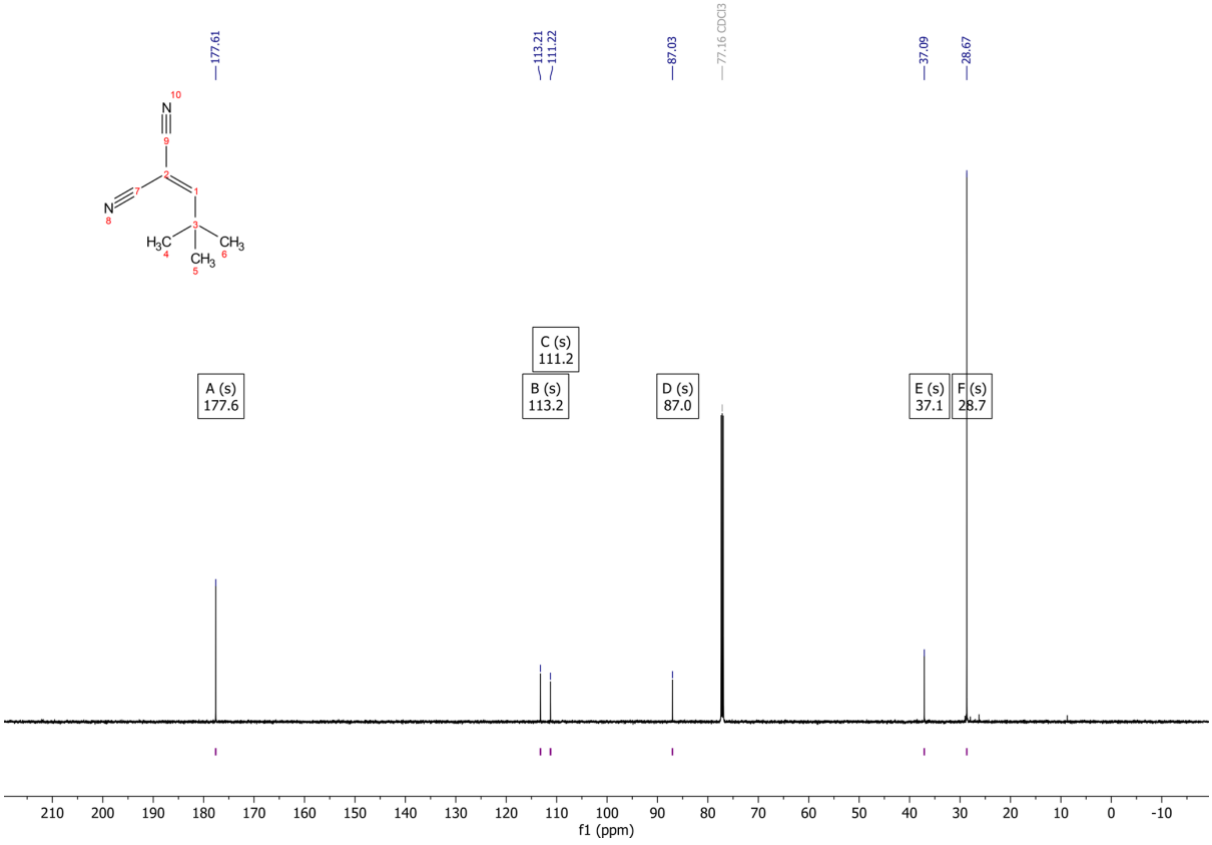

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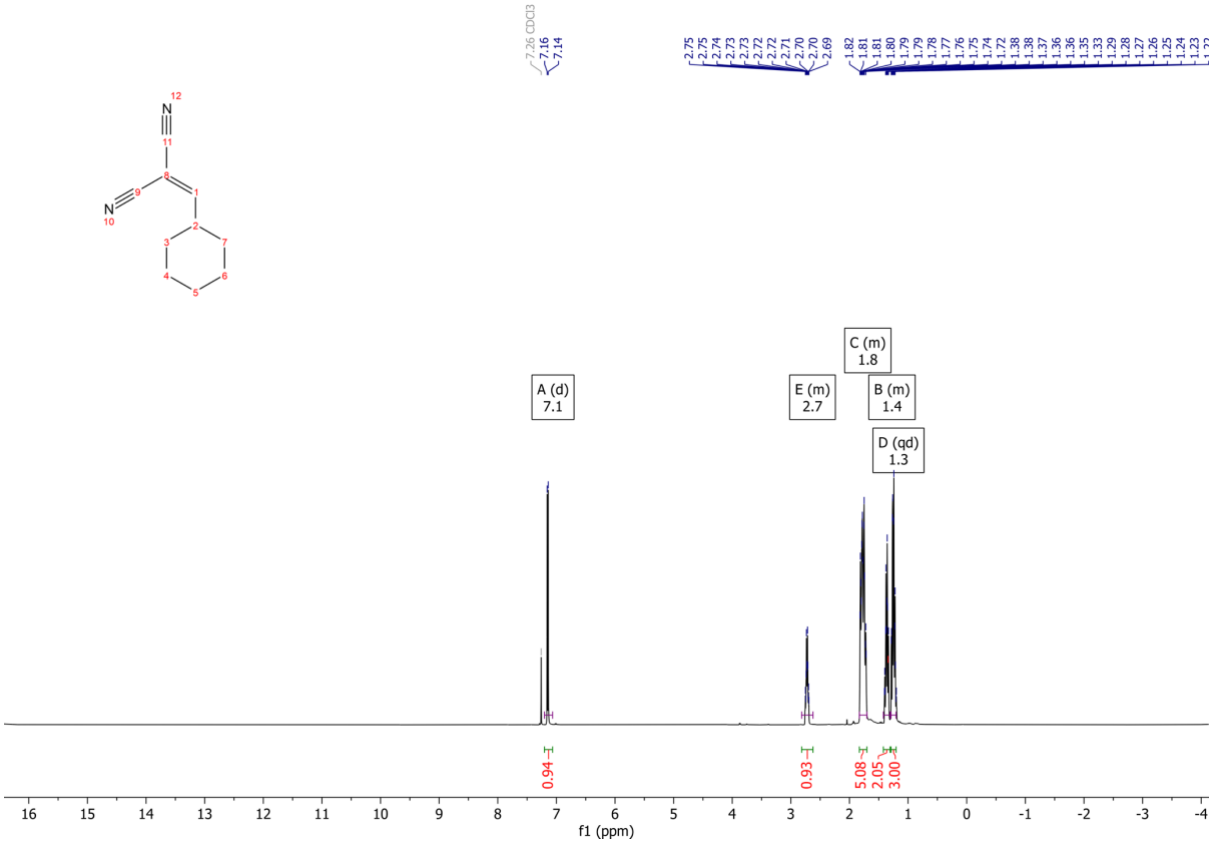
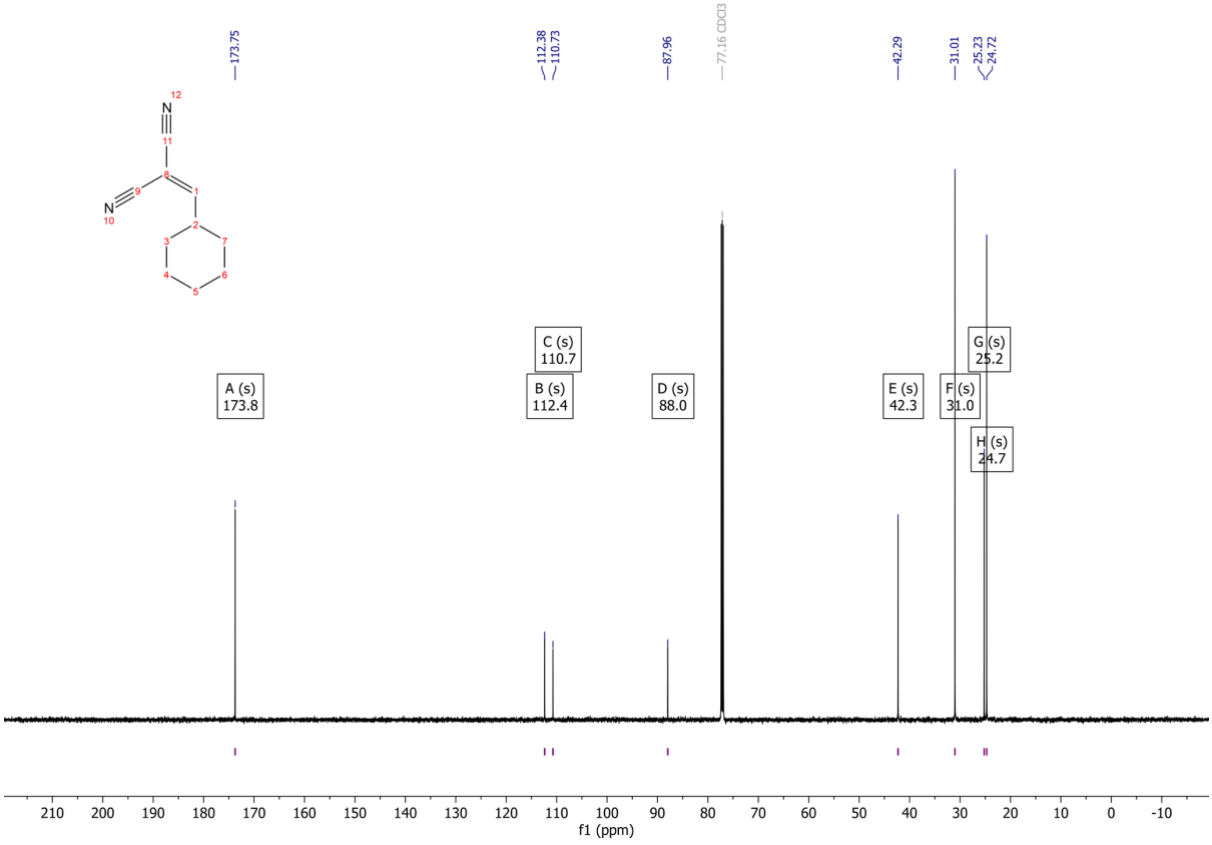
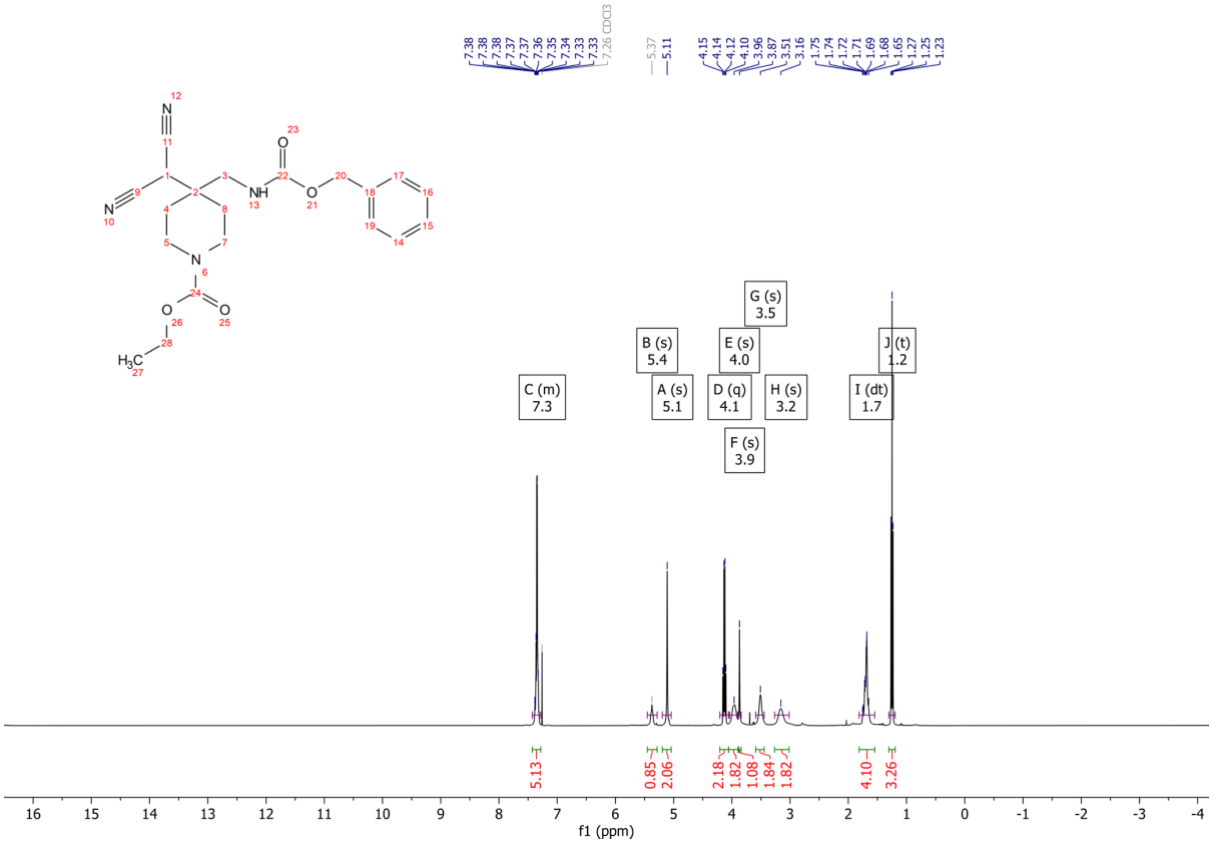


A11 ^{13}C NMR (151 MHz, $CDCl_3$)

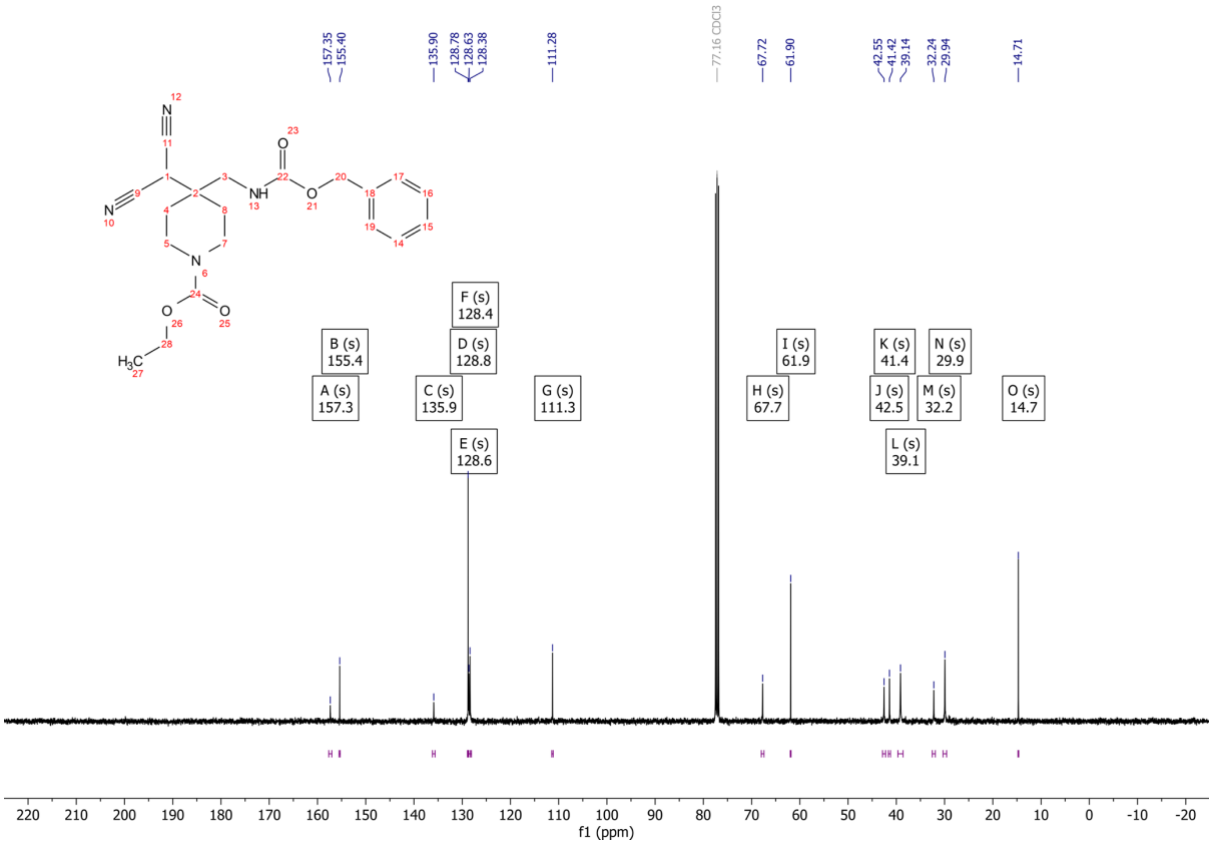


Substituted Malononitrile Derivatives

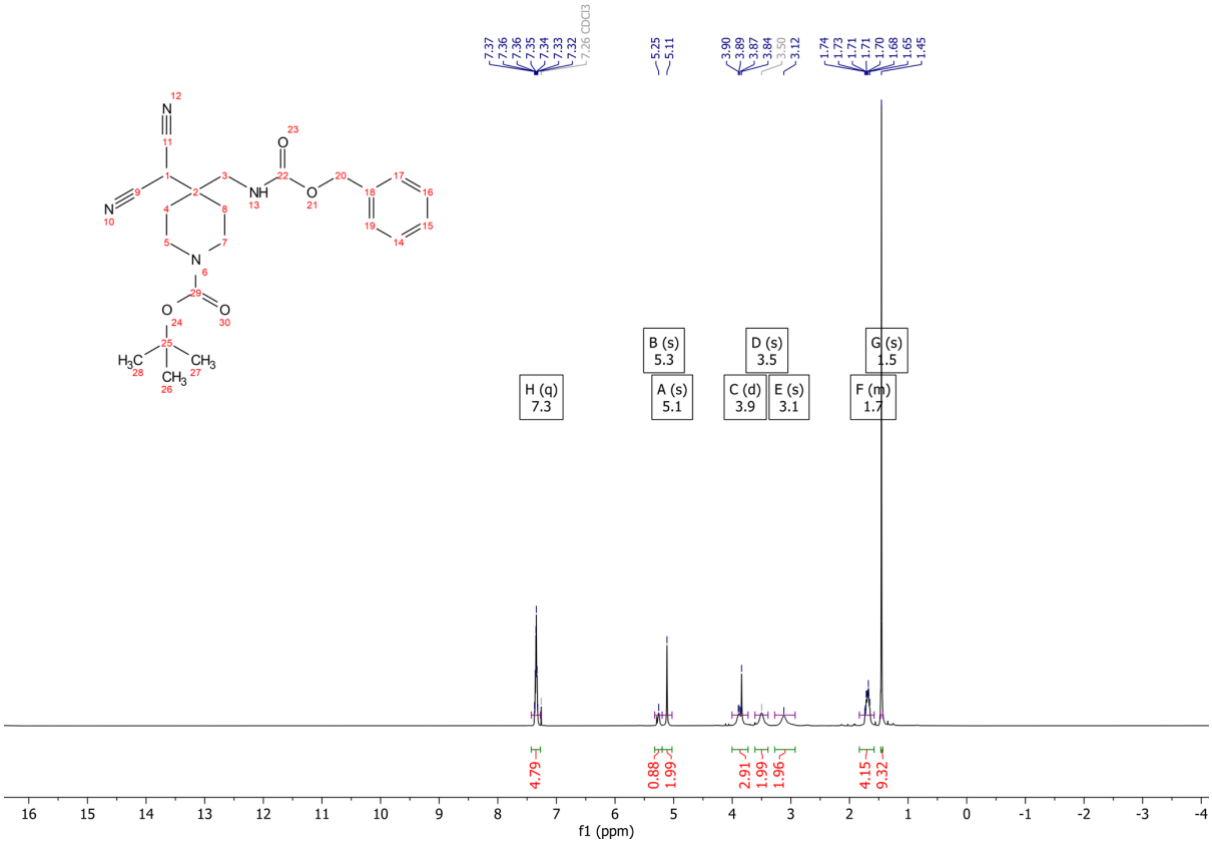
B1 ^{1}H NMR (400 MHz, $CDCl_3$)



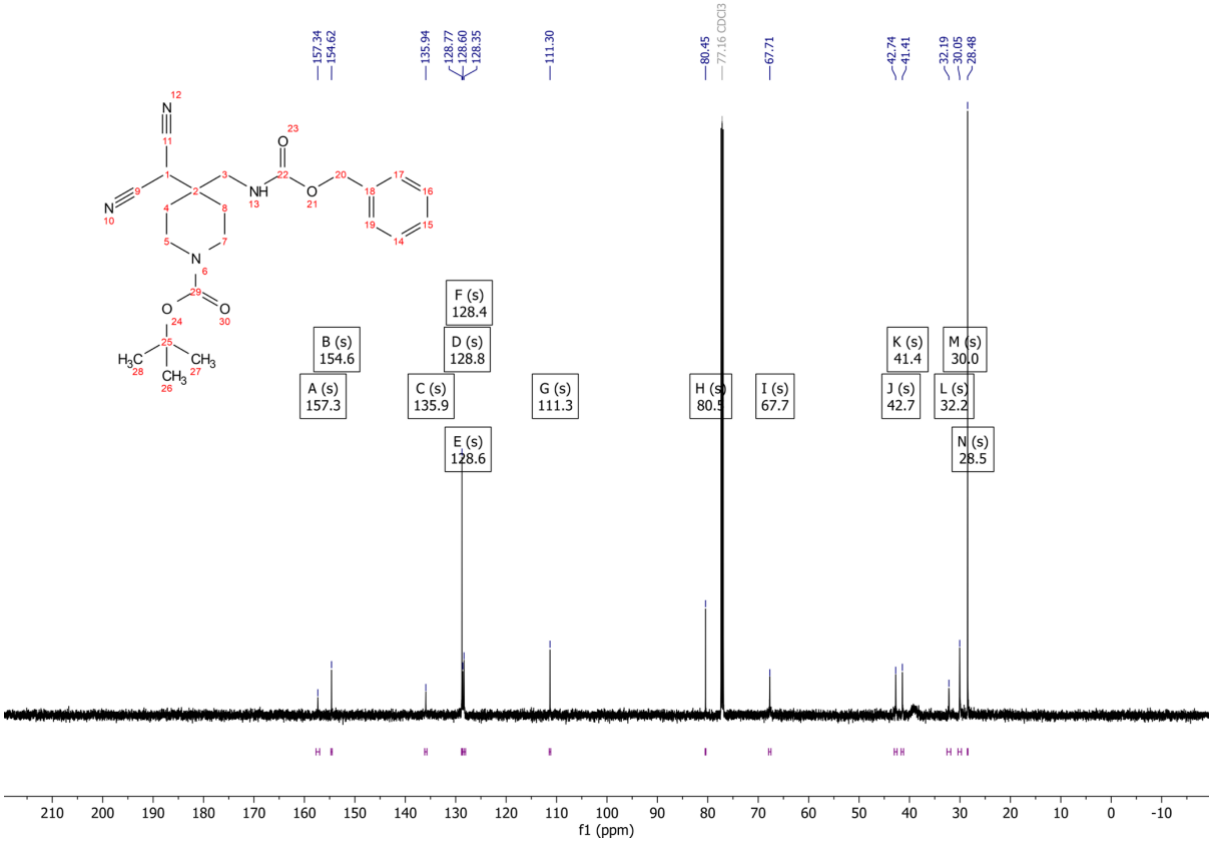
B1 ^{13}C NMR (101 MHz, $CDCl_3$)



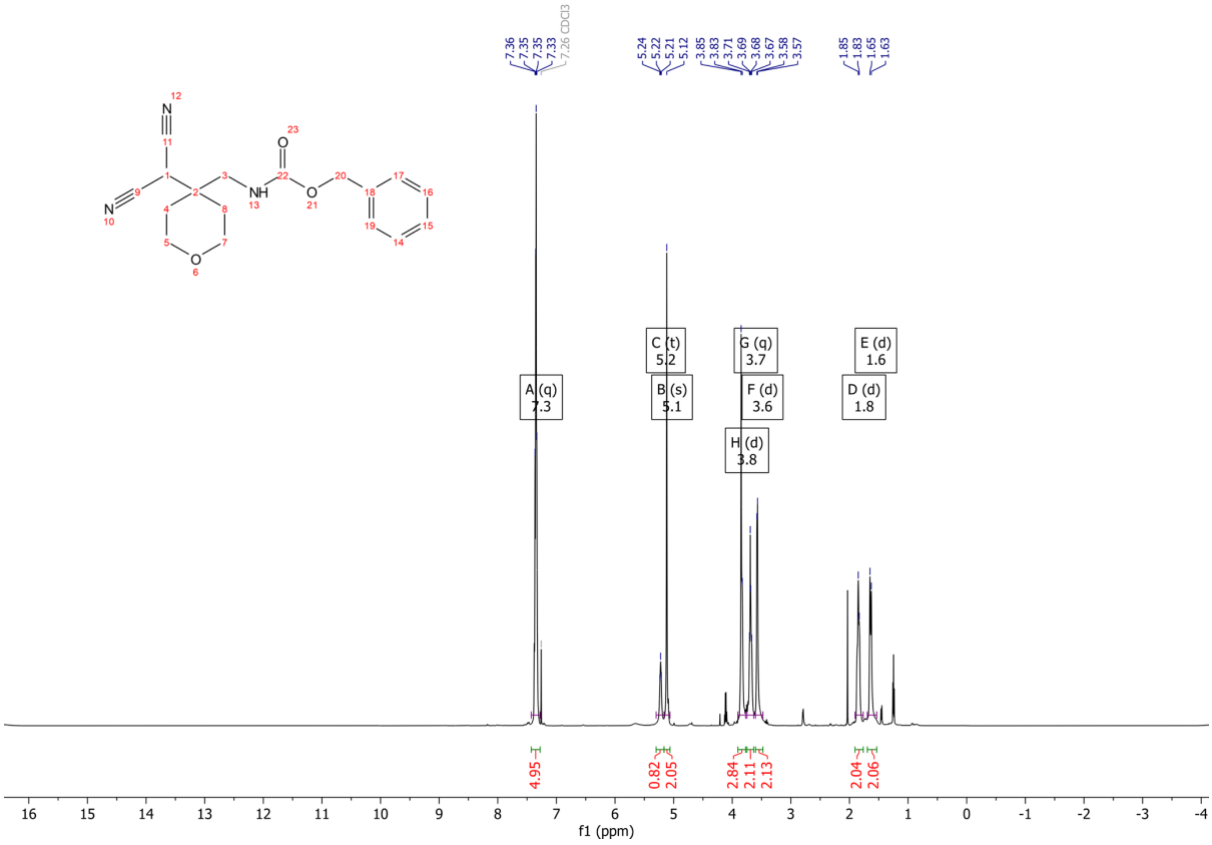
B2 ^{1}H NMR (600 MHz, $CDCl_3$)



B2 ^{13}C NMR (151 MHz, $CDCl_3$)



B3 ^{1}H NMR (600 MHz, $CDCl_3$)



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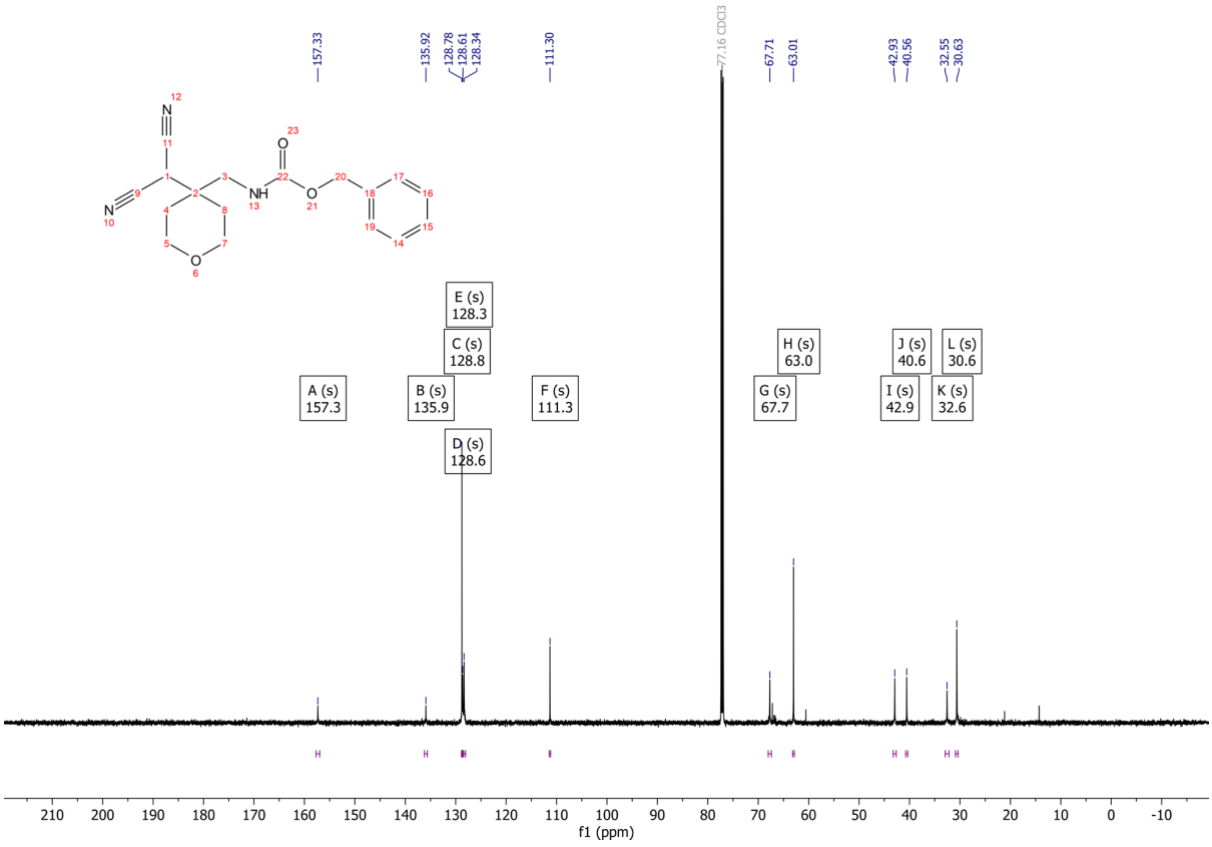

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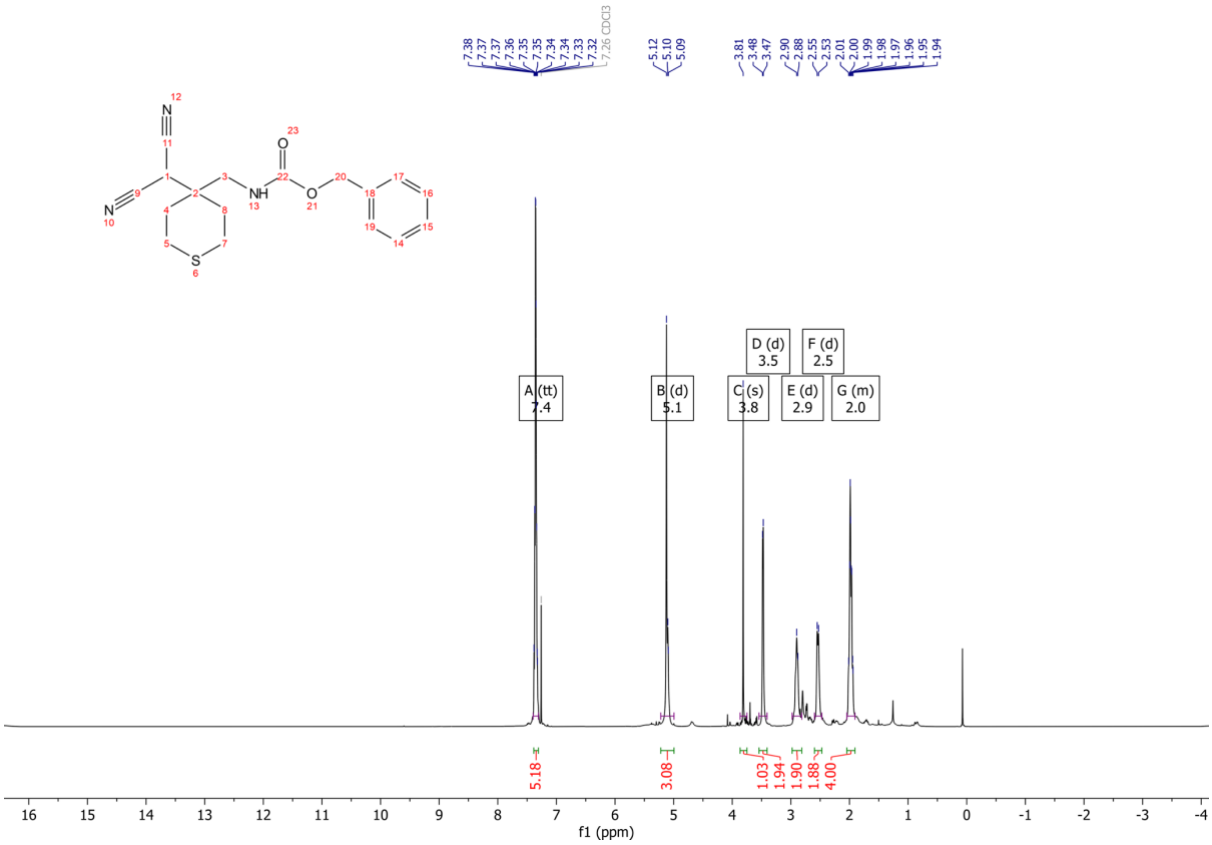
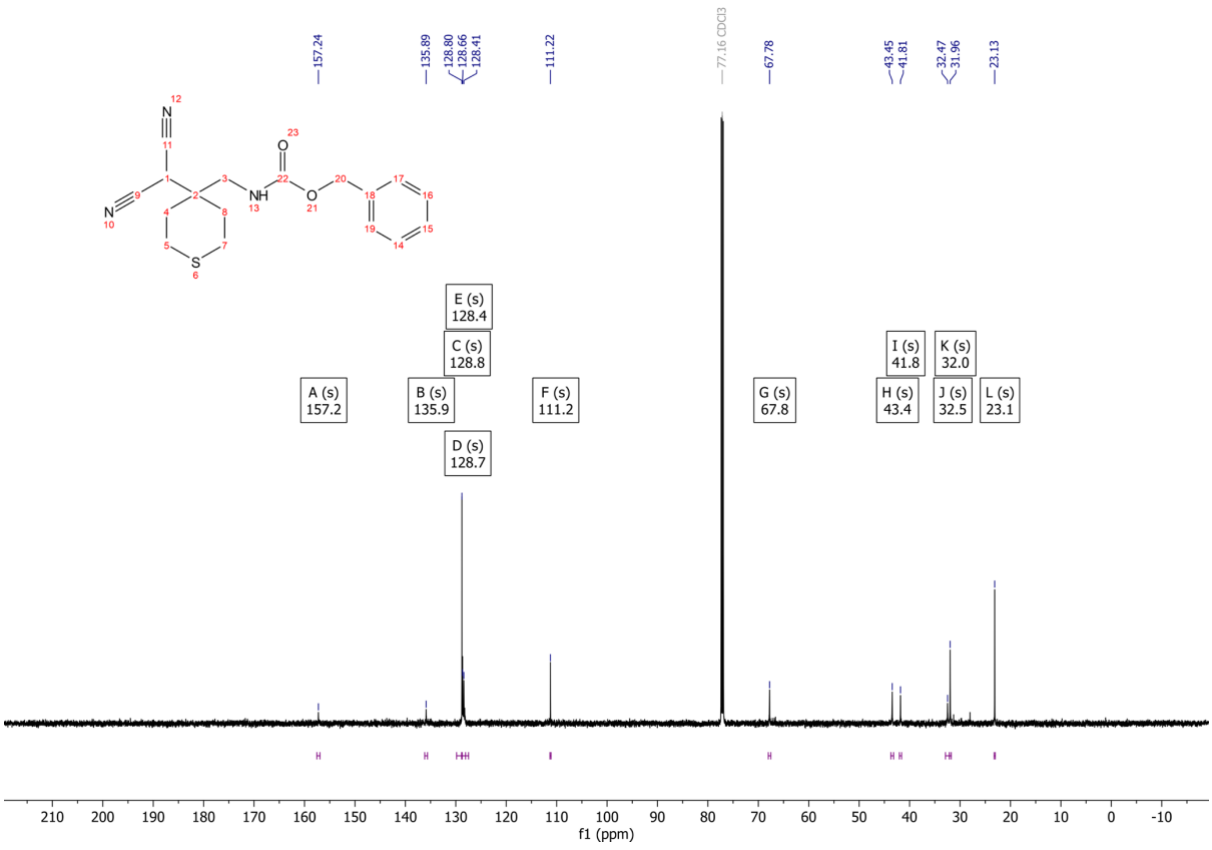
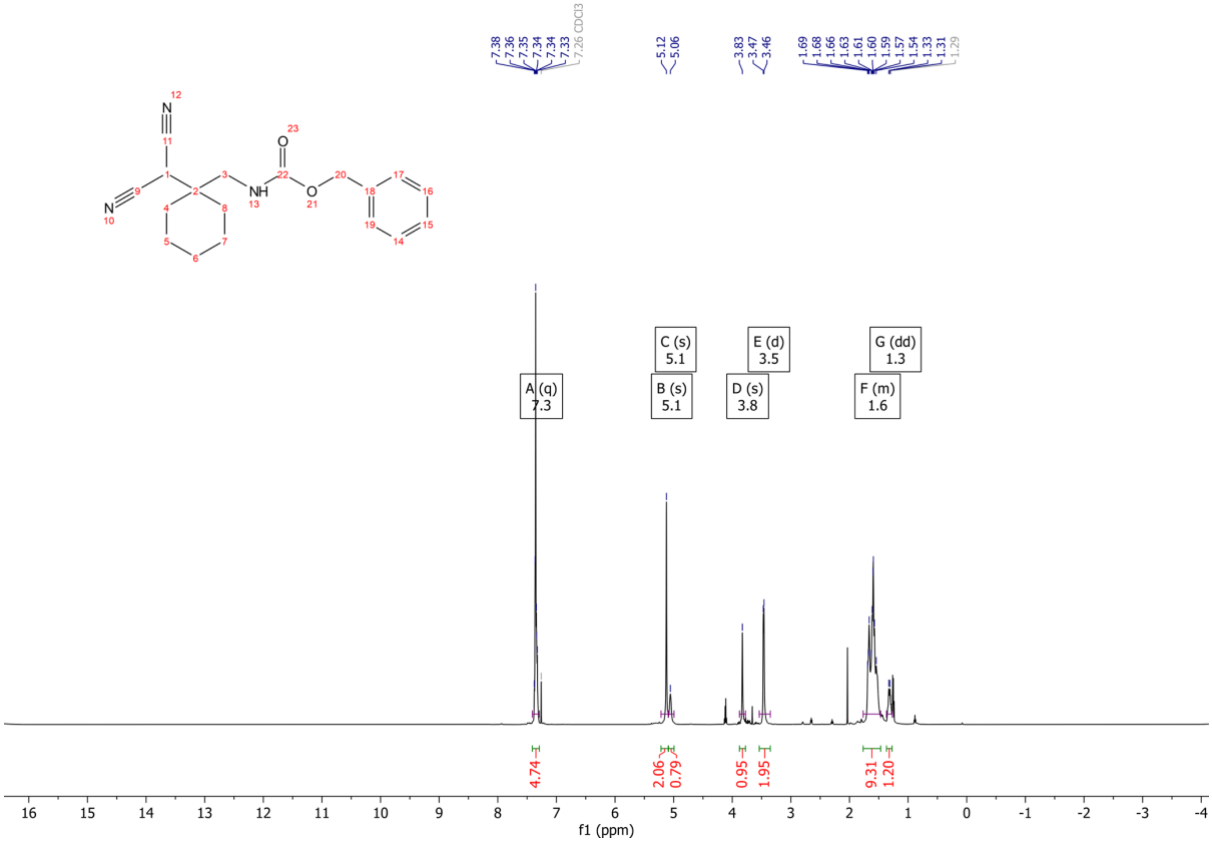


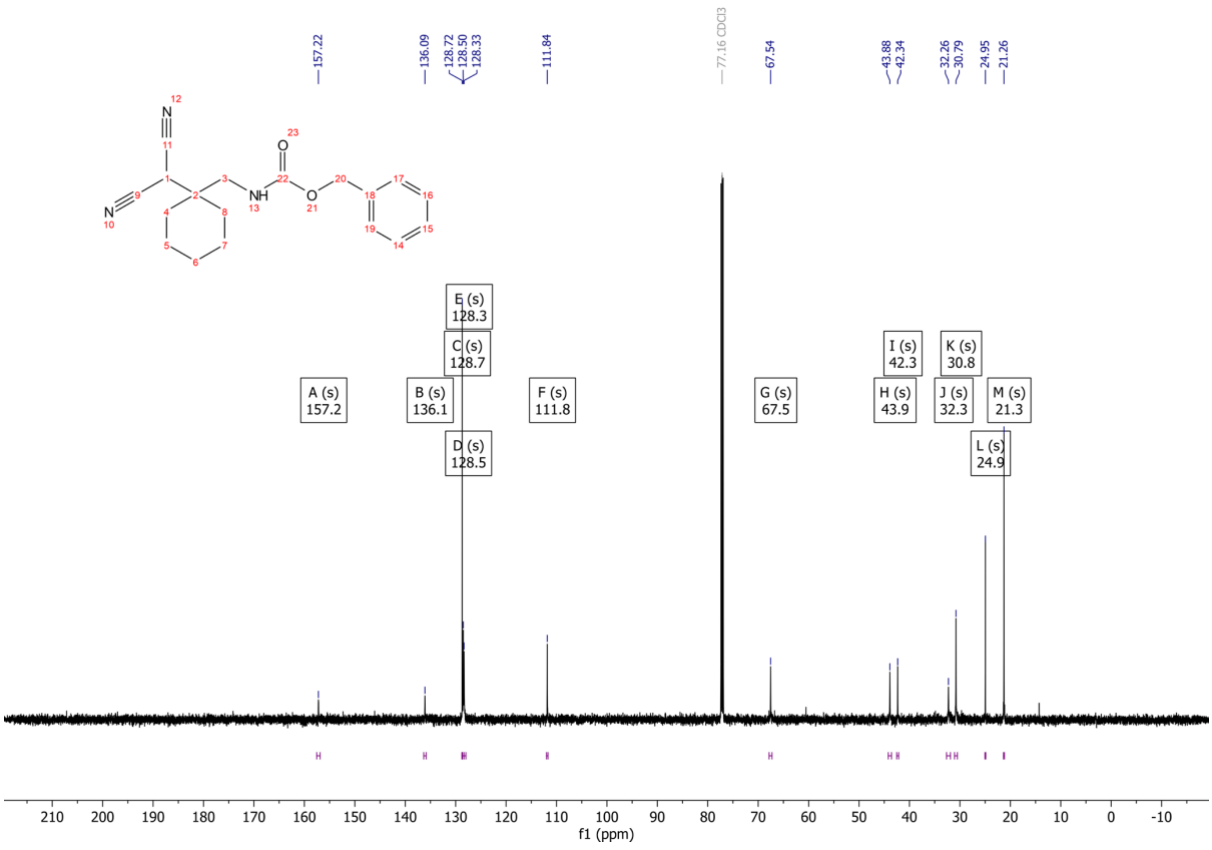
B4 ^{13}C NMR (151 MHz, $CDCl_3$)



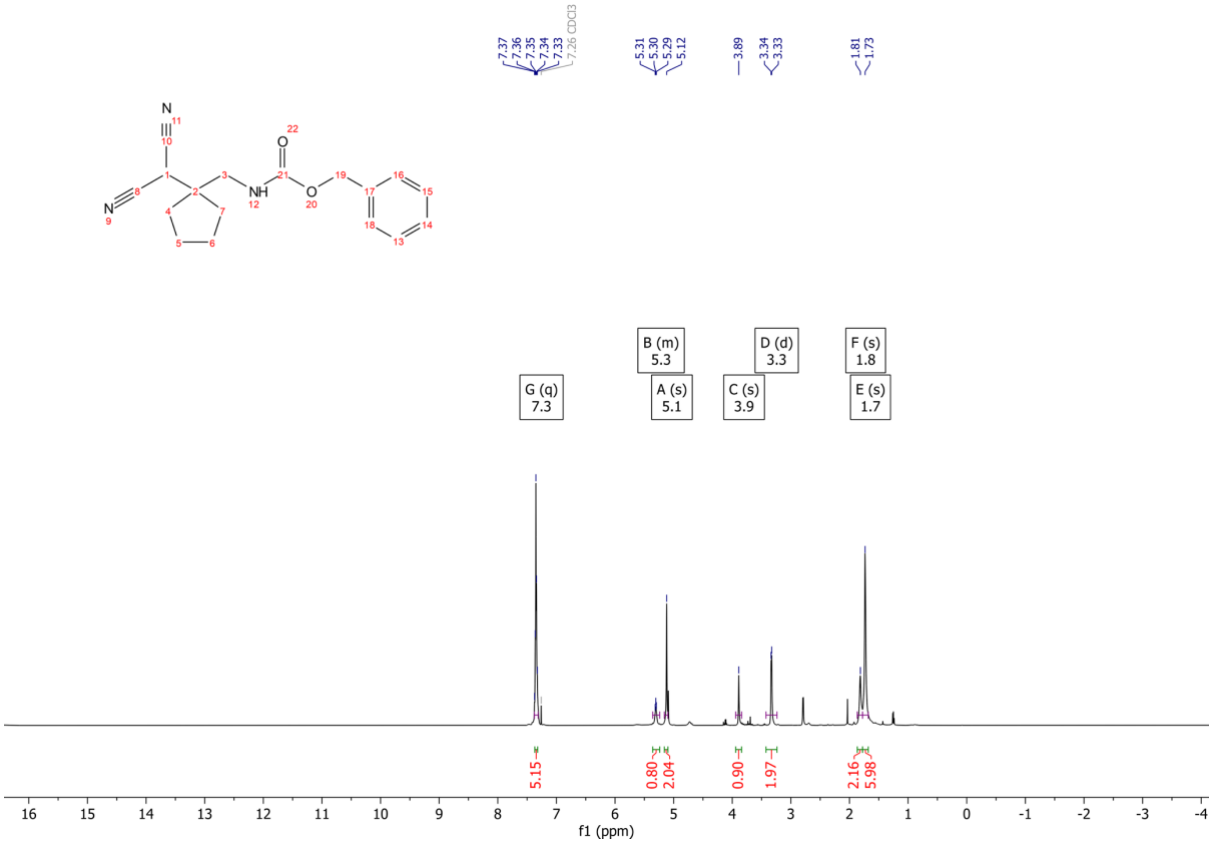
B5 ^{1}H NMR (600 MHz, $CDCl_3$)



B5 ^{13}C NMR (151 MHz, $CDCl_3$)



B6 ^{1}H NMR (600 MHz, $CDCl_3$)



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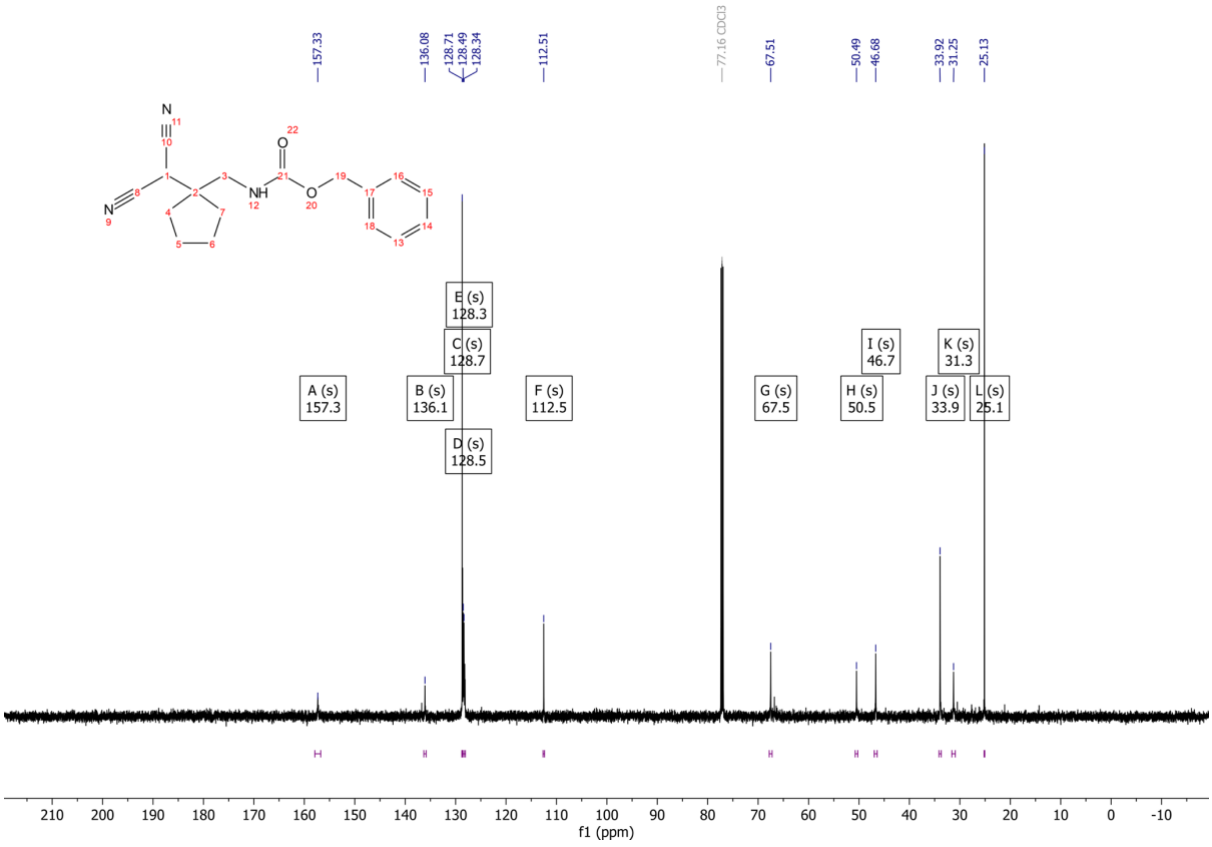

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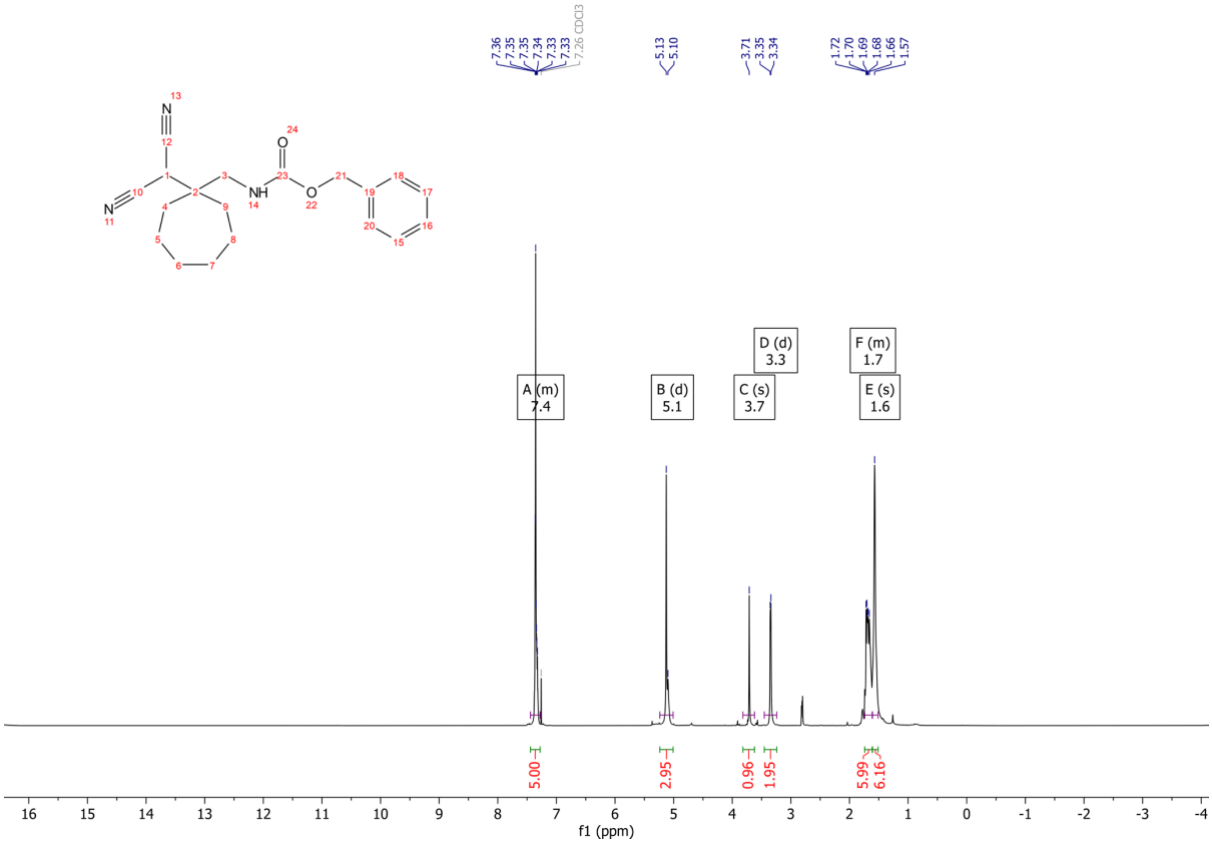
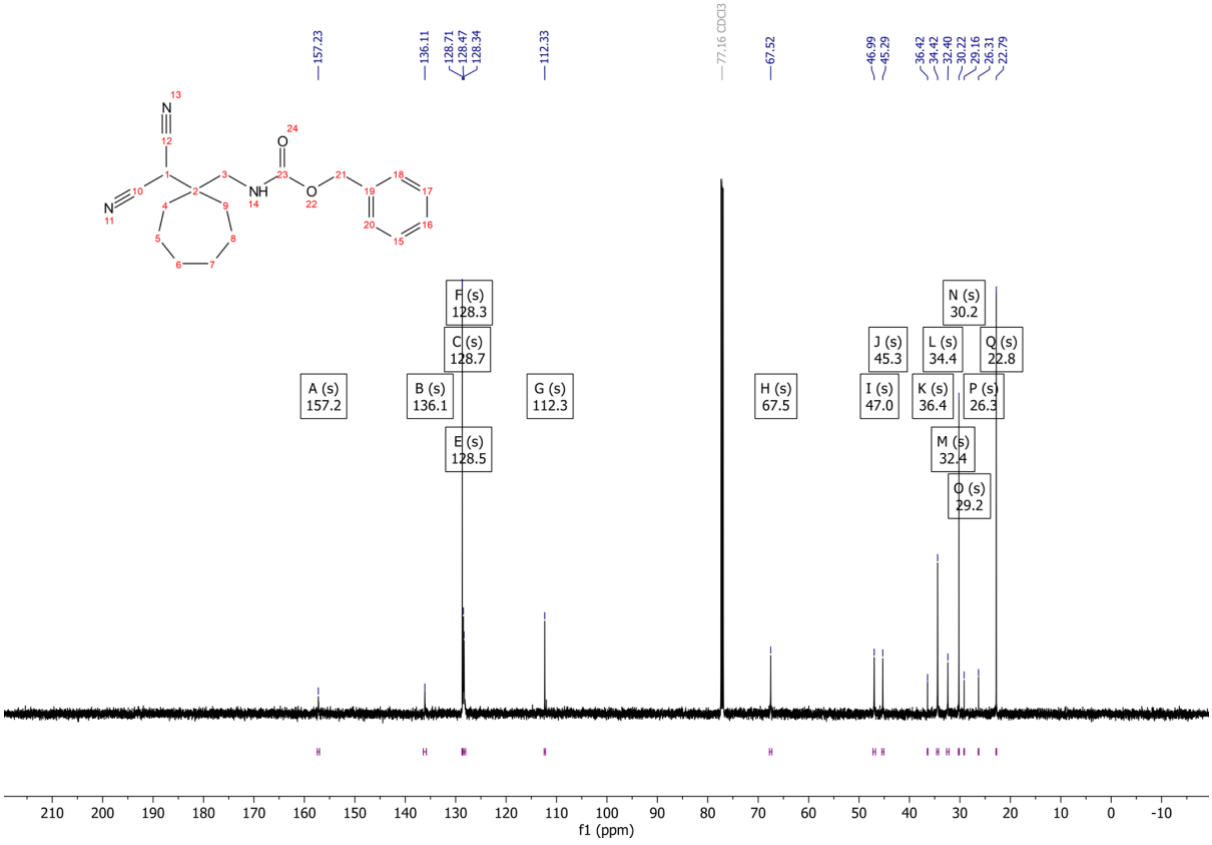
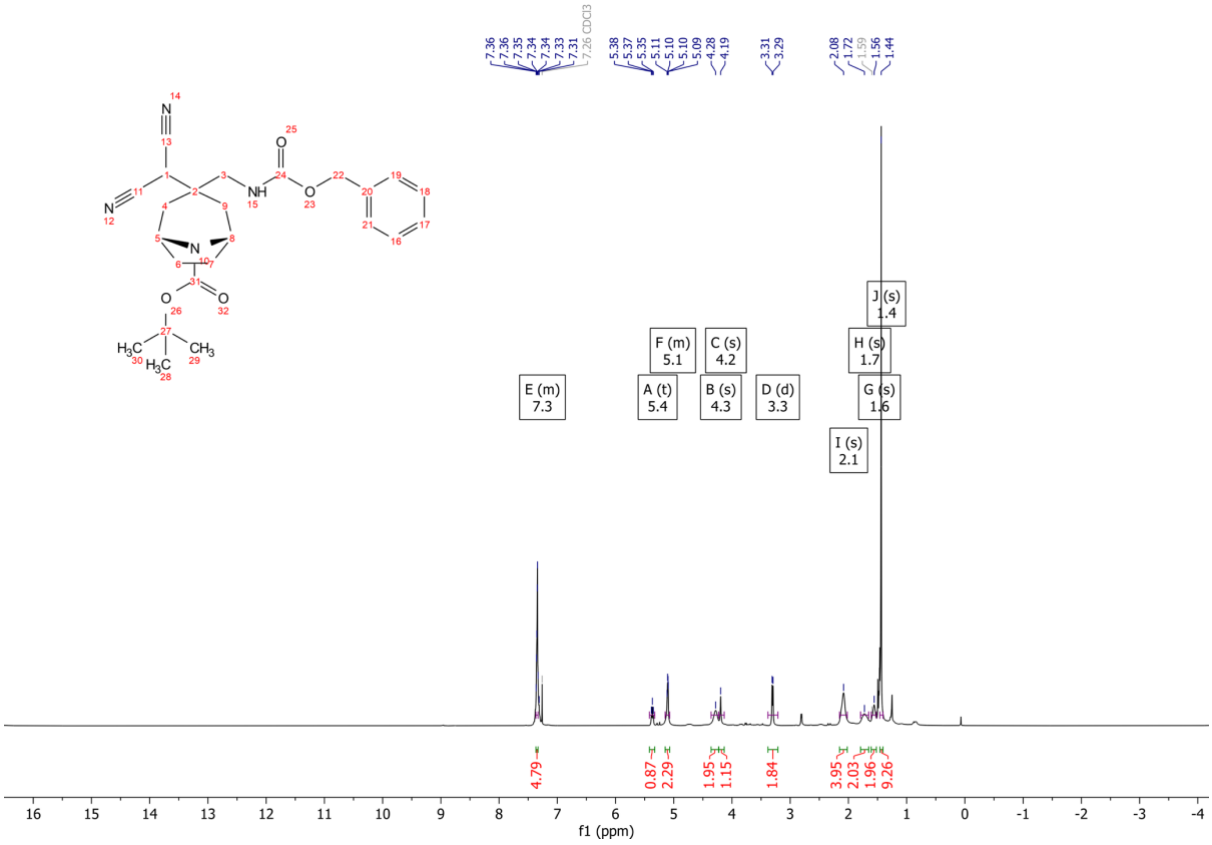


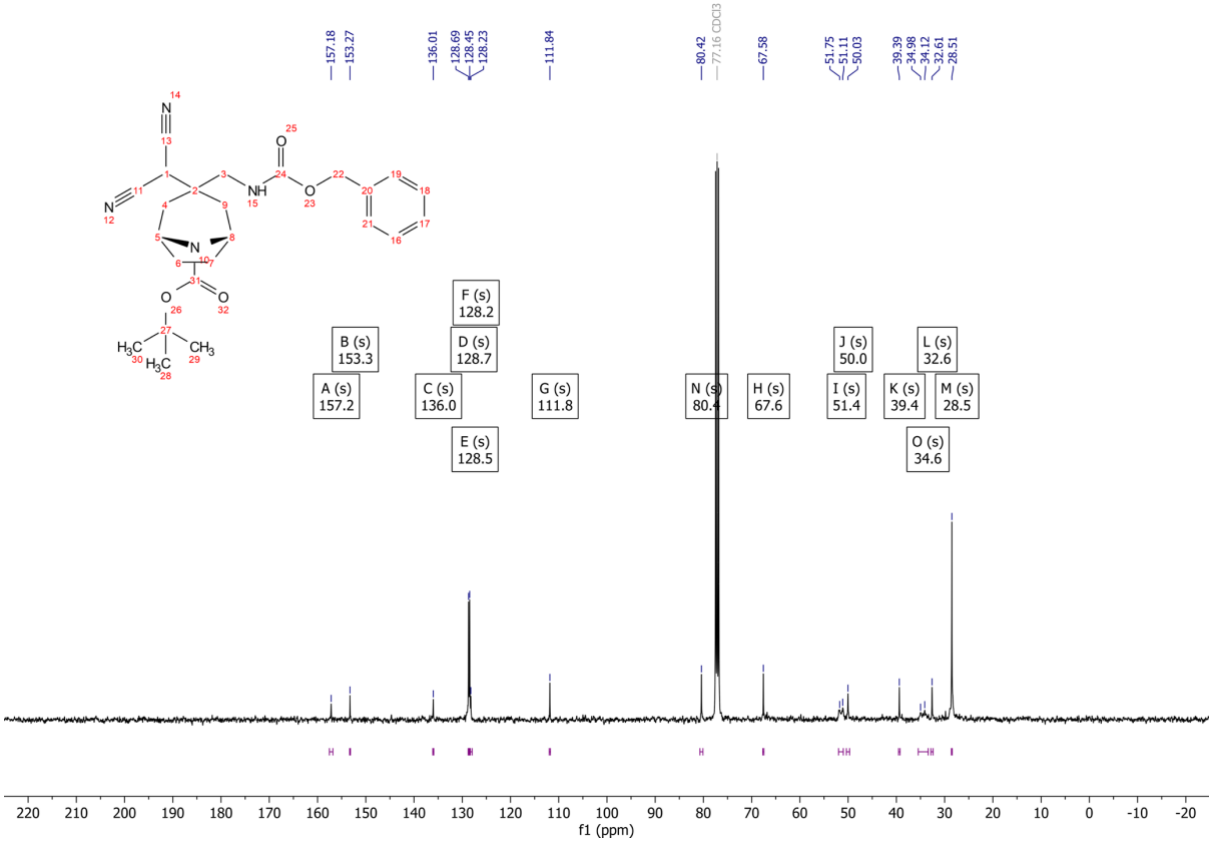
B7 ^{13}C NMR (151 MHz, $CDCl_3$)



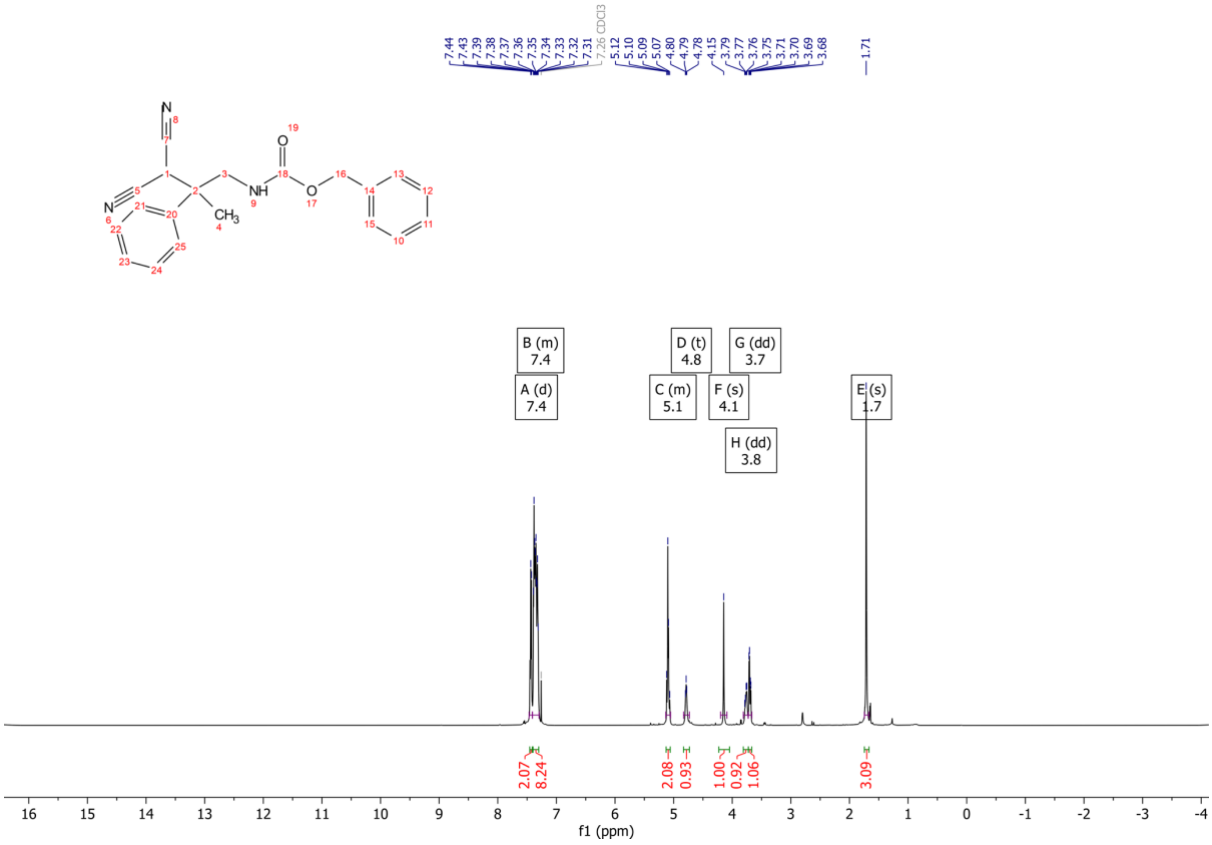
B8 ^{1}H NMR (400 MHz, $CDCl_3$)



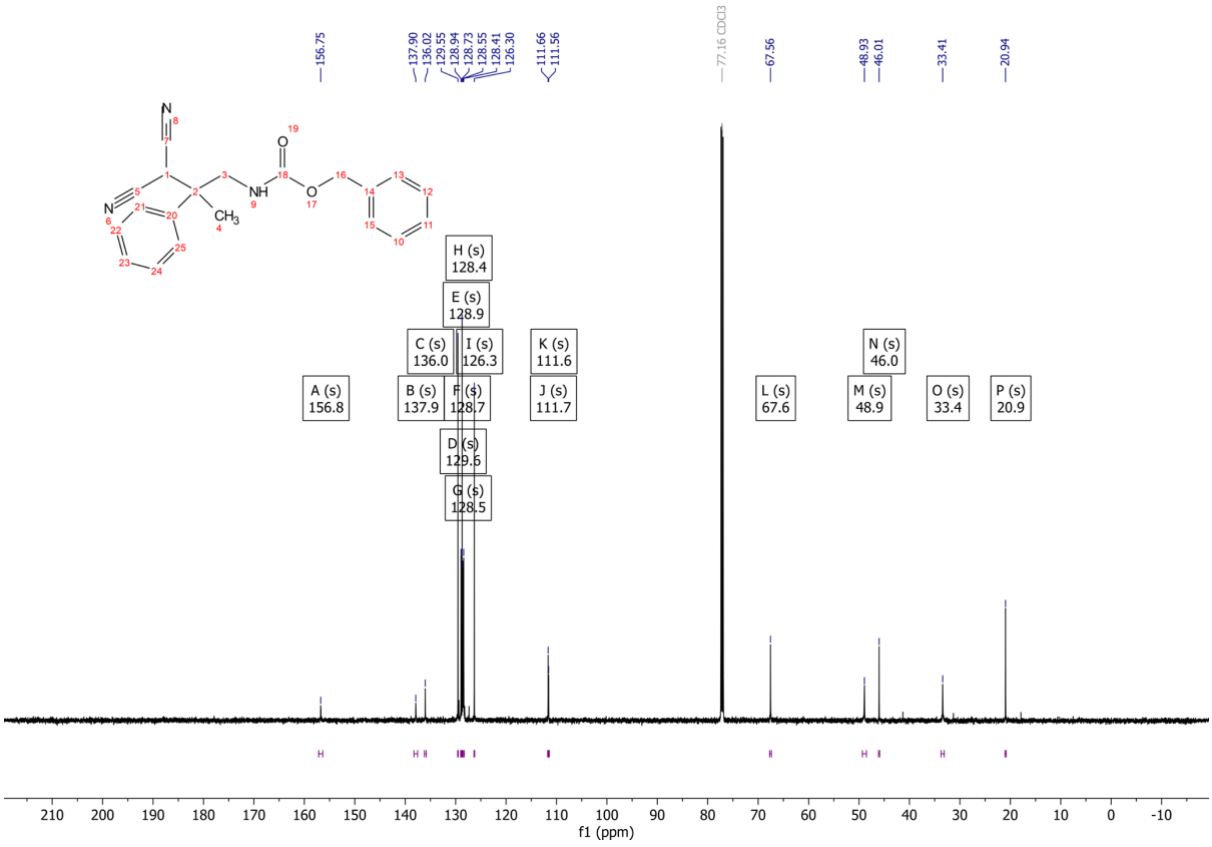
B8 ^{13}C NMR (101 MHz, $CDCl_3$)



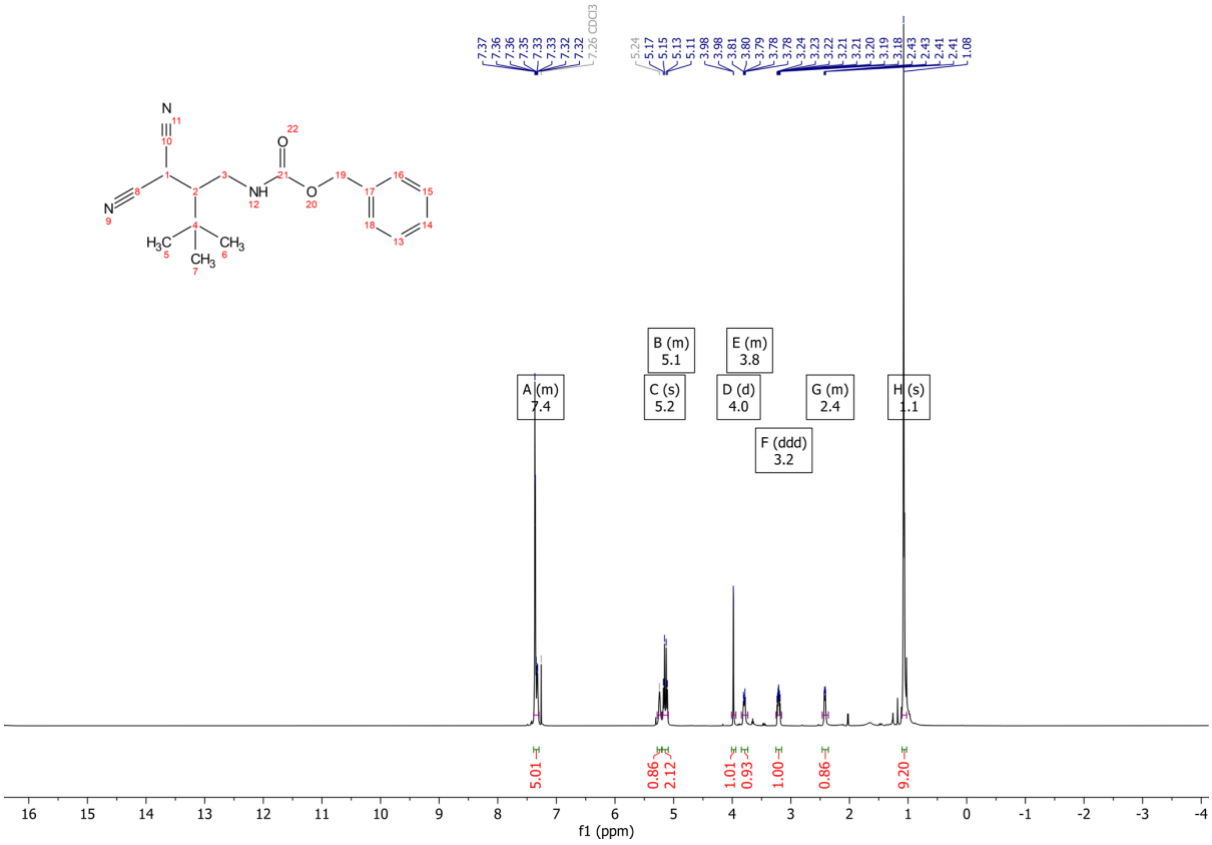
B9 ^{1}H NMR (600 MHz, $CDCl_3$)



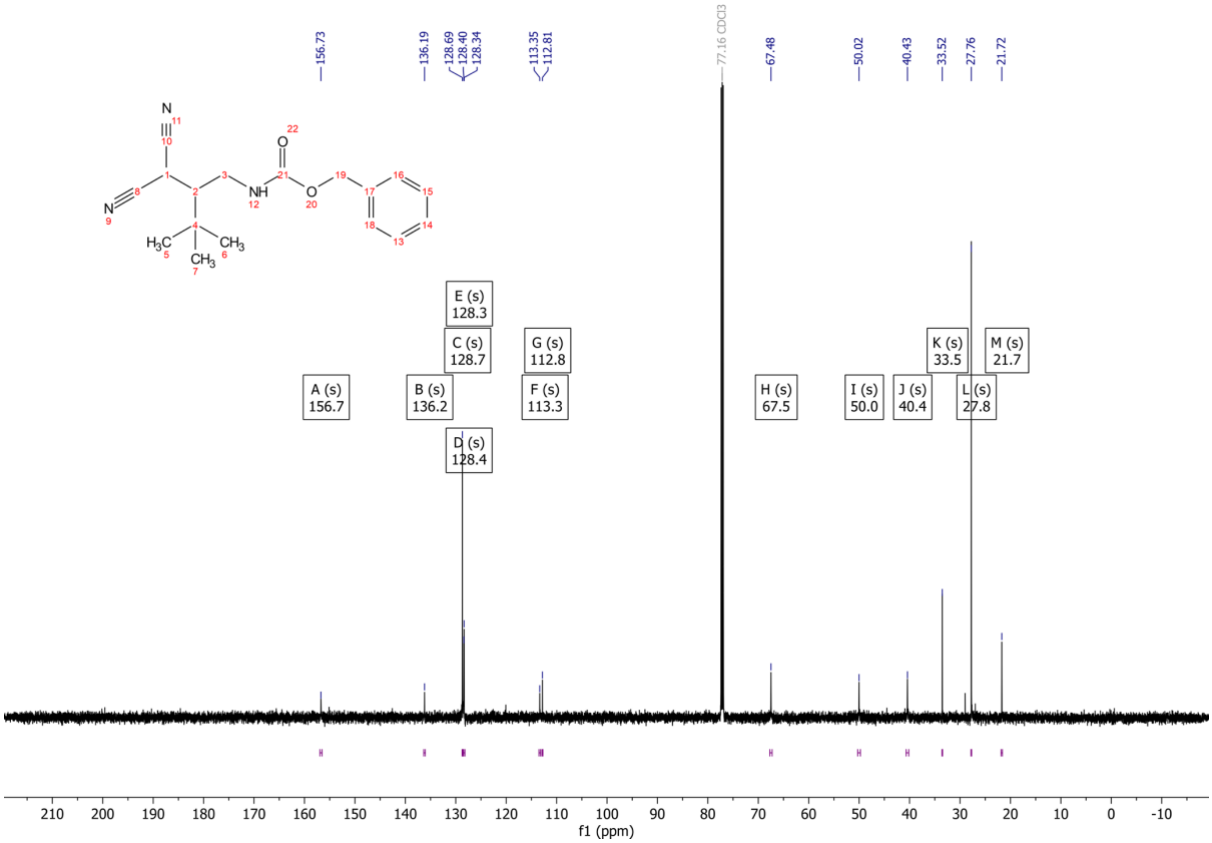
B9 ^{13}C NMR (151 MHz, $CDCl_3$)



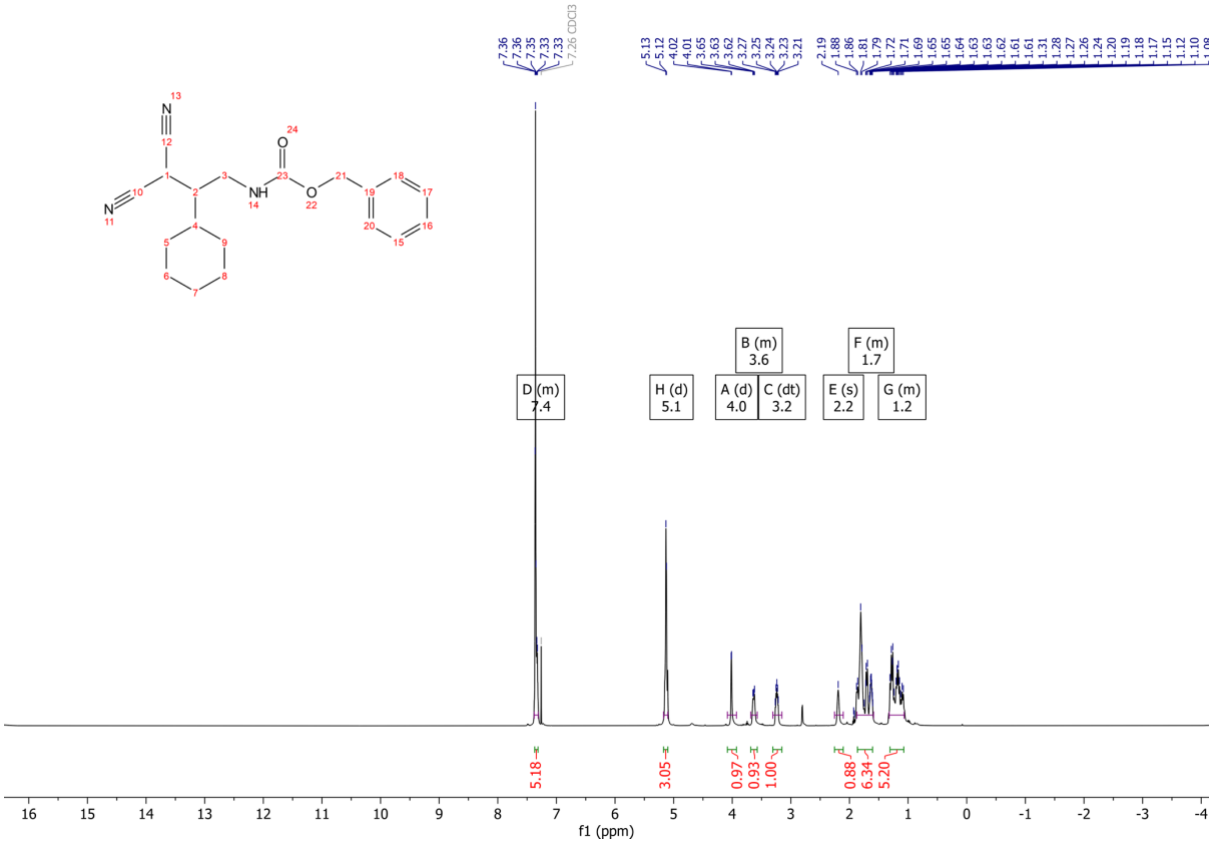
B10 ^{1}H NMR (600 MHz, $CDCl_3$)



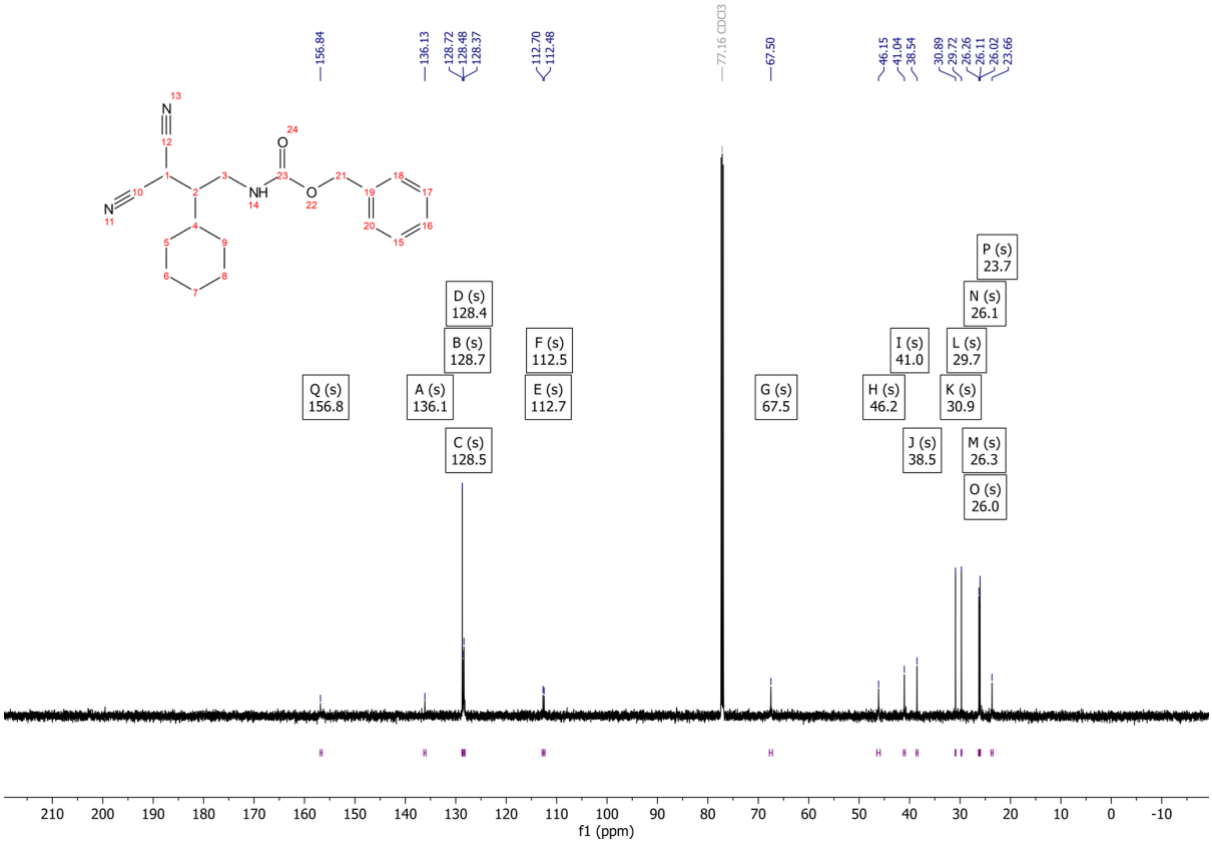
B10 ^{13}C NMR (151 MHz, $CDCl_3$)



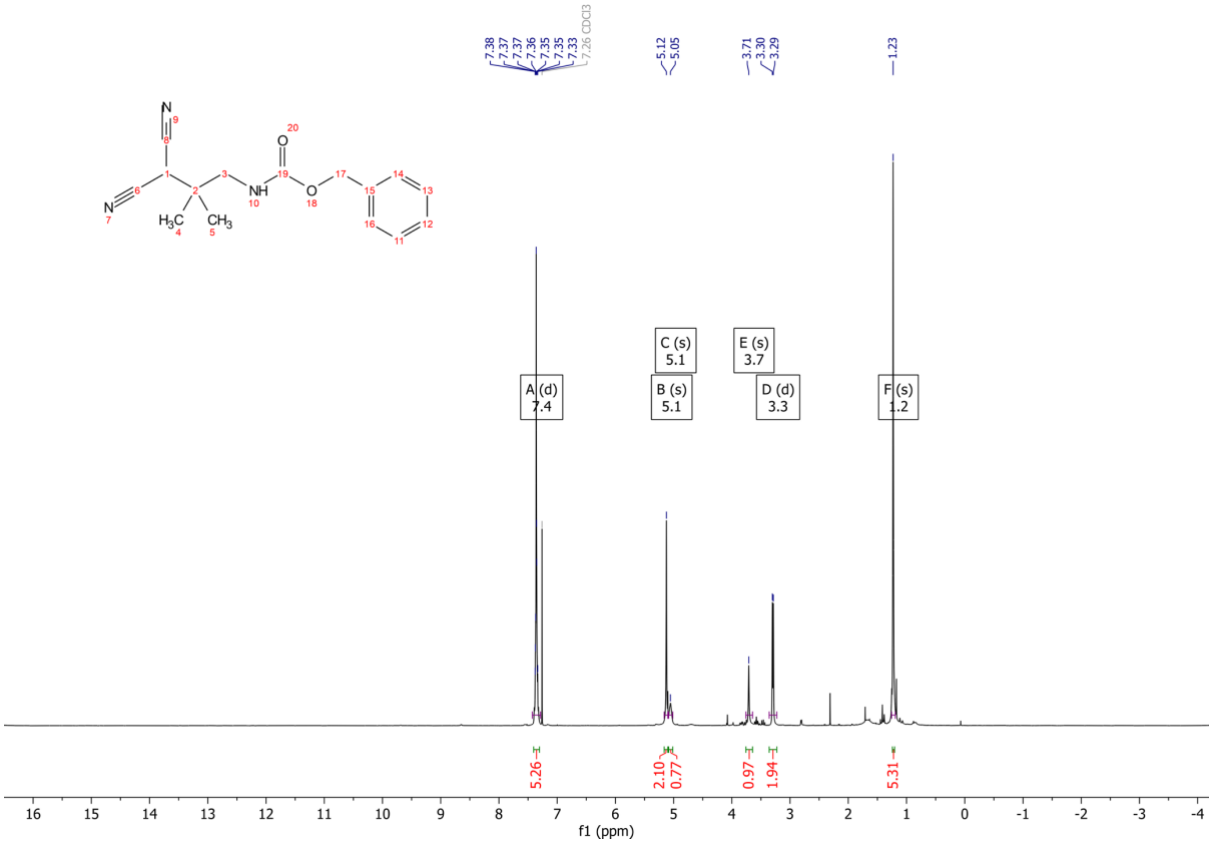
B11 ^{1}H NMR (600 MHz, $CDCl_3$)



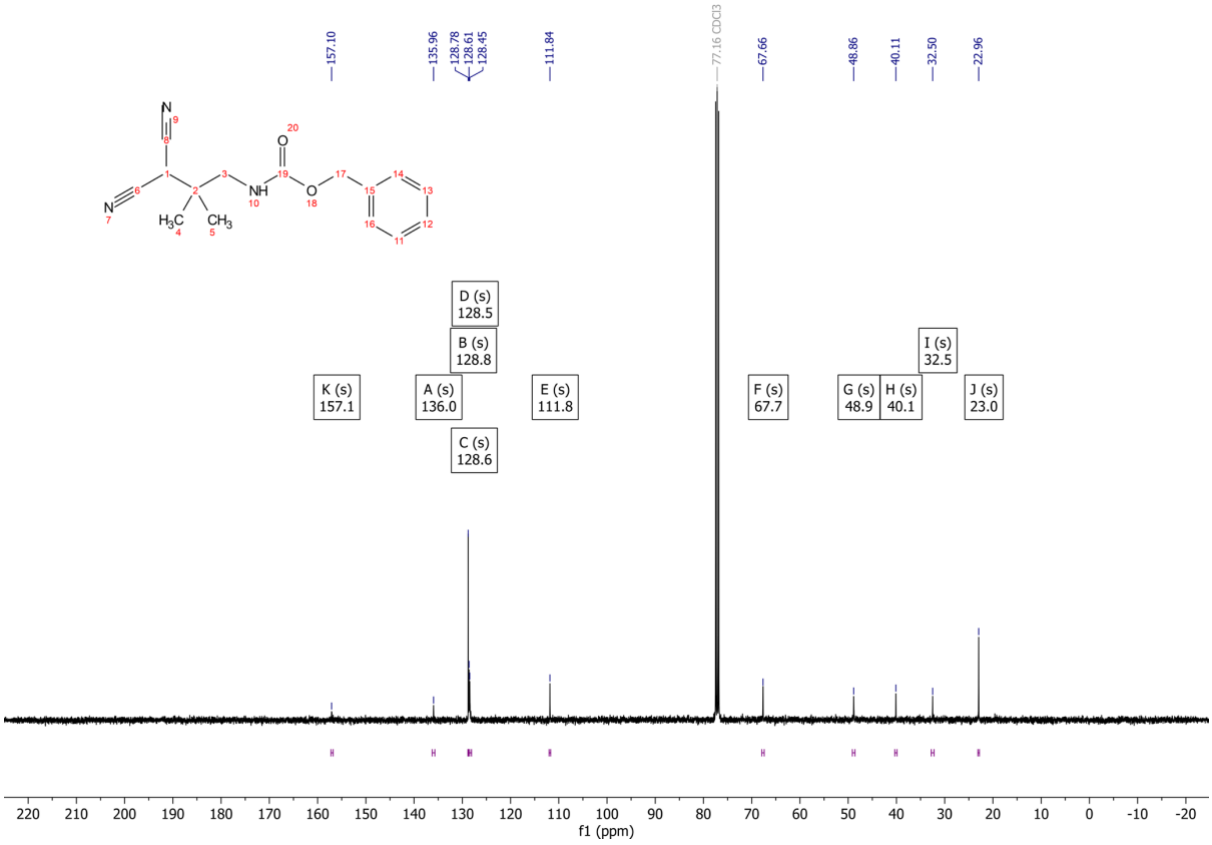
B11 ^{13}C NMR (151 MHz, $CDCl_3$)



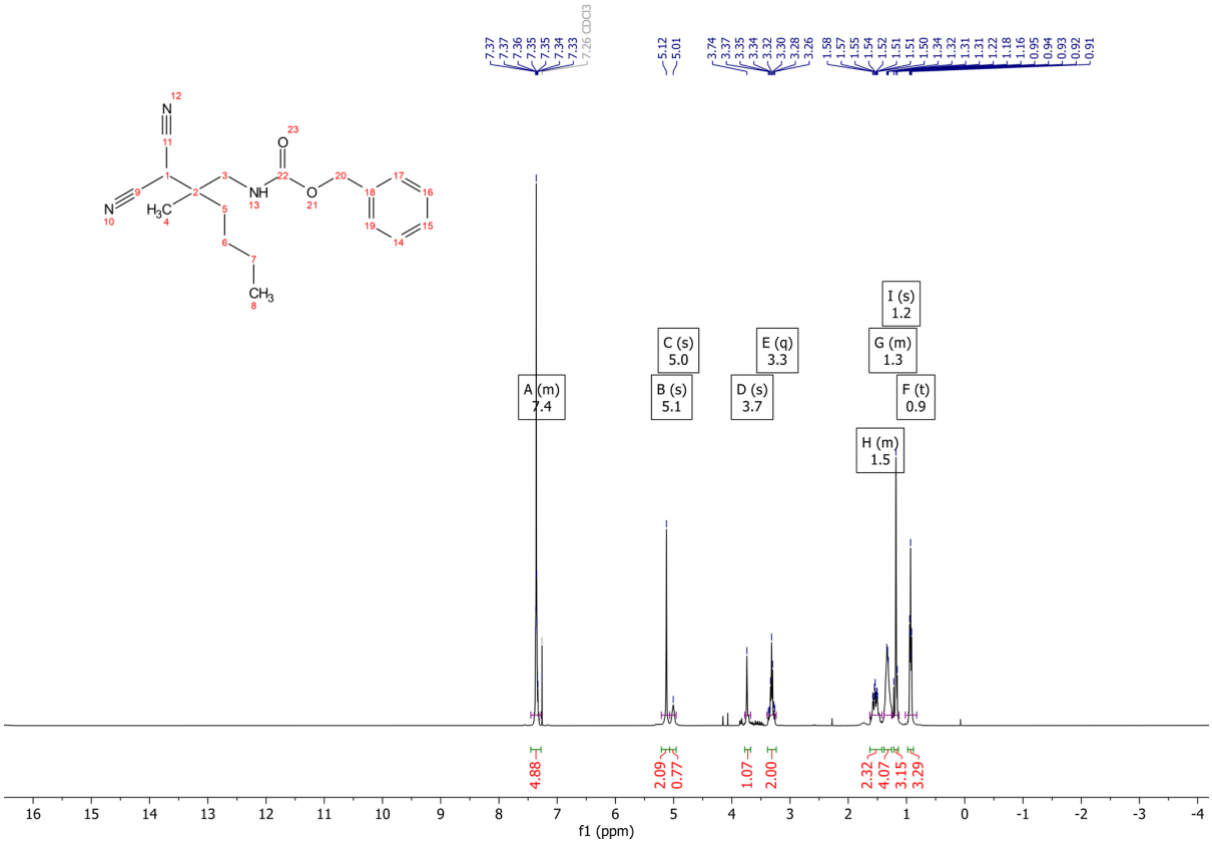
B12 ^{1}H NMR (400 MHz, $CDCl_3$)



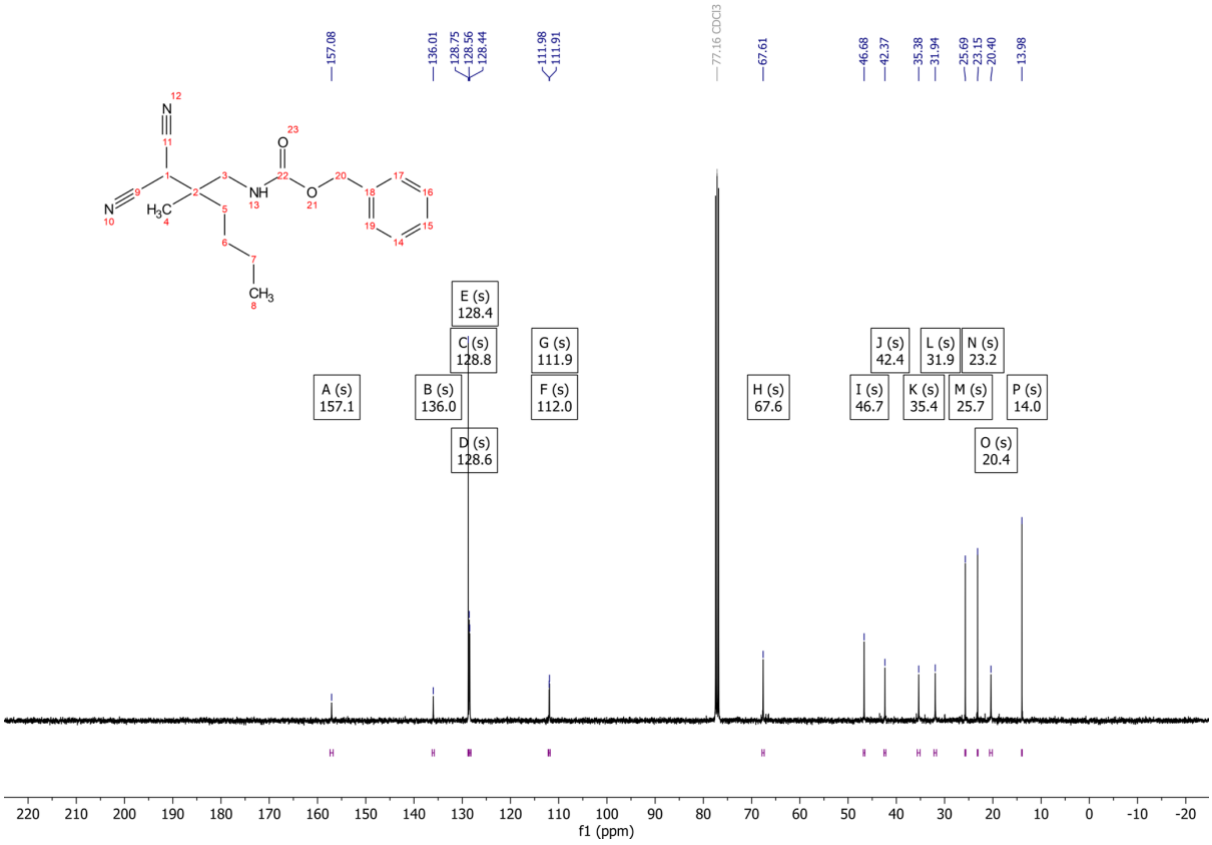
B12 ^{13}C NMR (101 MHz, $CDCl_3$)



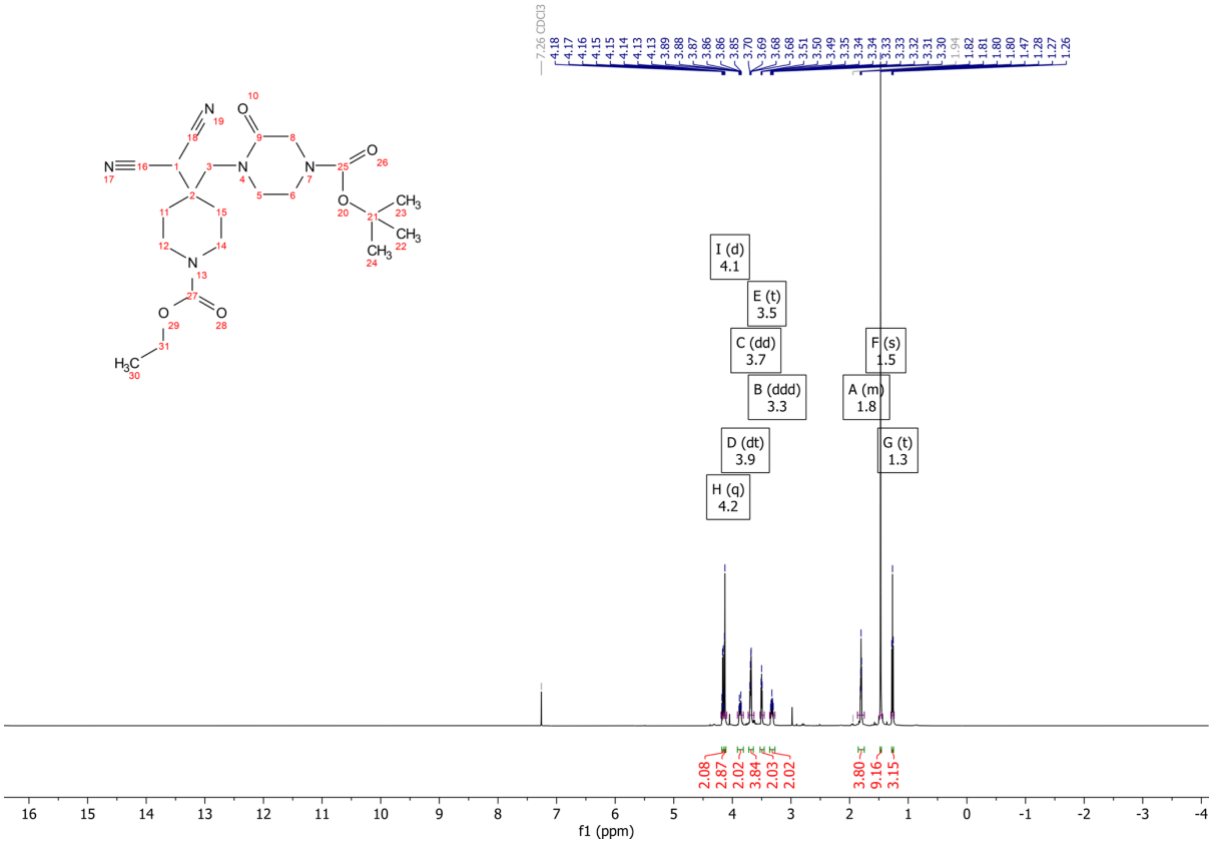
B13 ^{1}H NMR (400 MHz, $CDCl_3$)



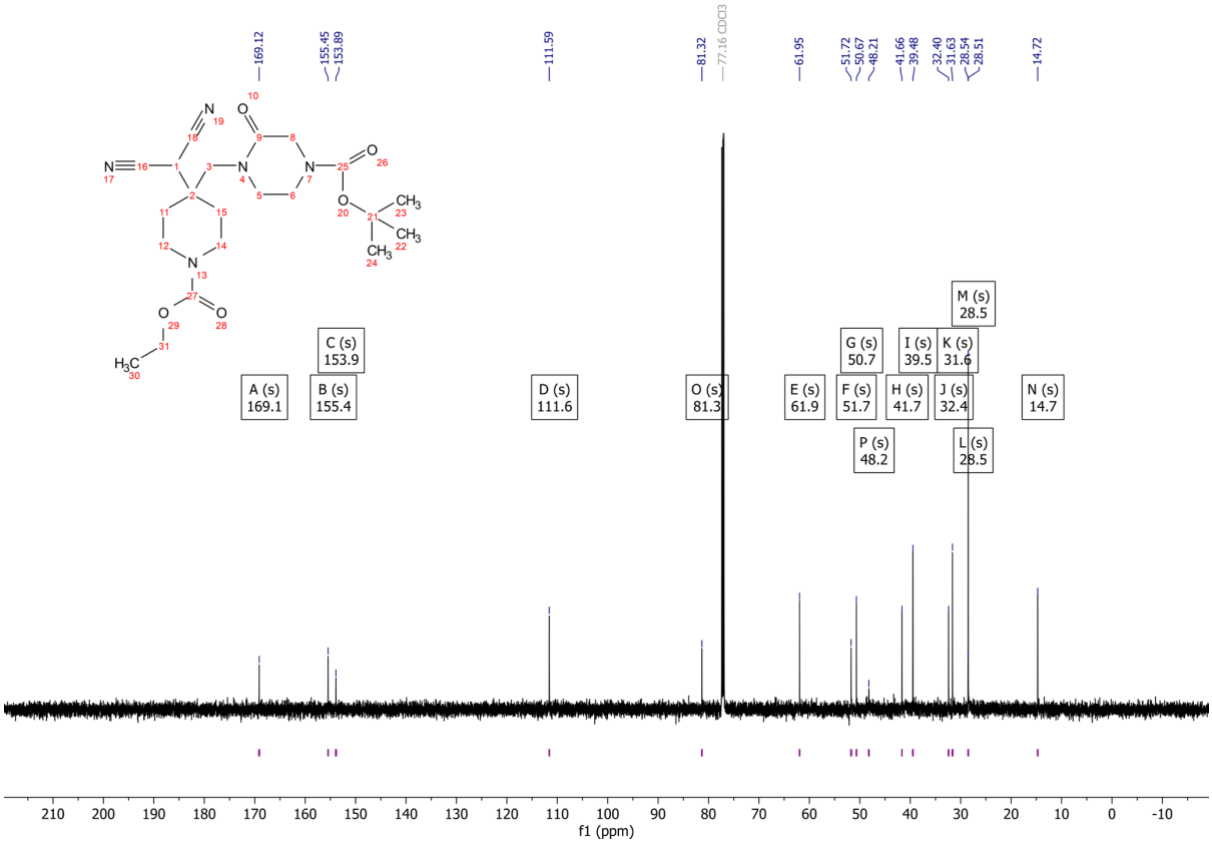
B13 ^{13}C NMR (101 MHz, $CDCl_3$)



B14 ^{1}H NMR (600 MHz, $CDCl_3$)

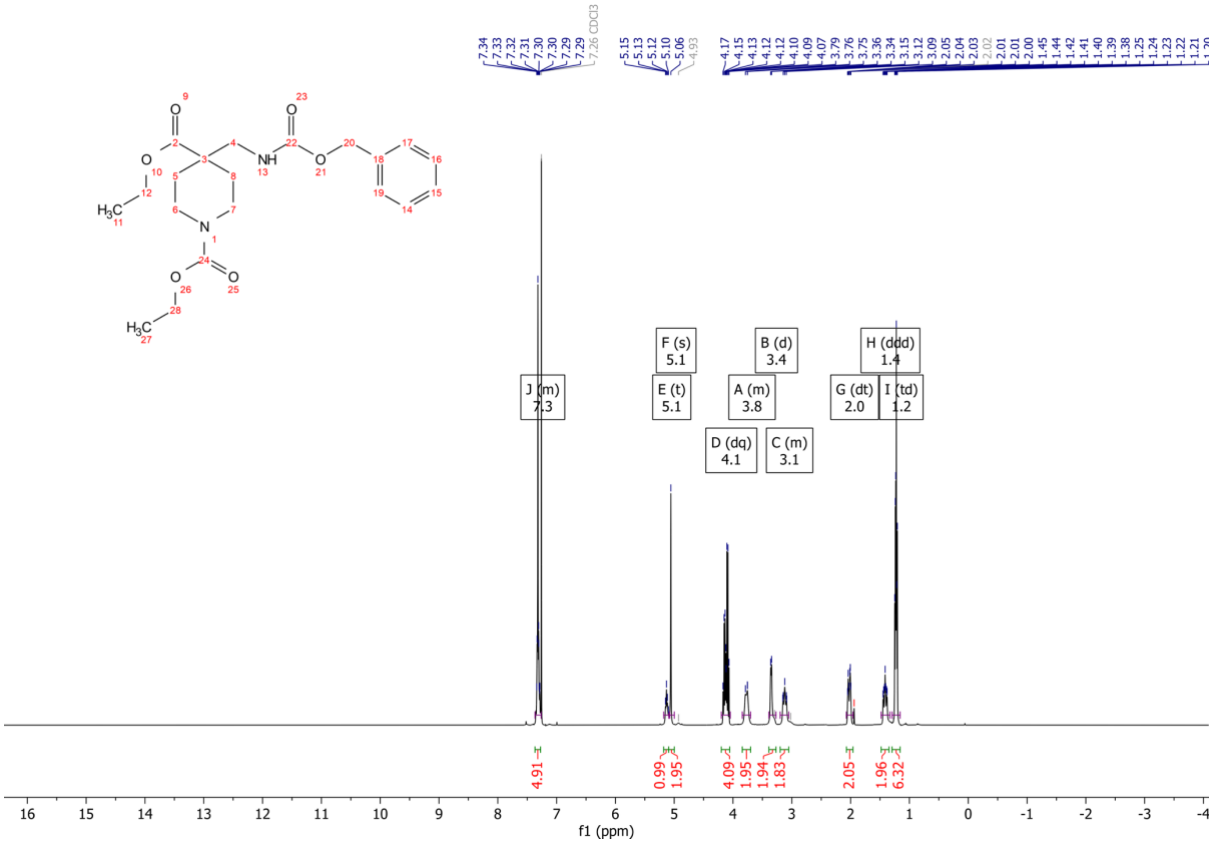


B14 ^{13}C NMR (151 MHz, $CDCl_3$)

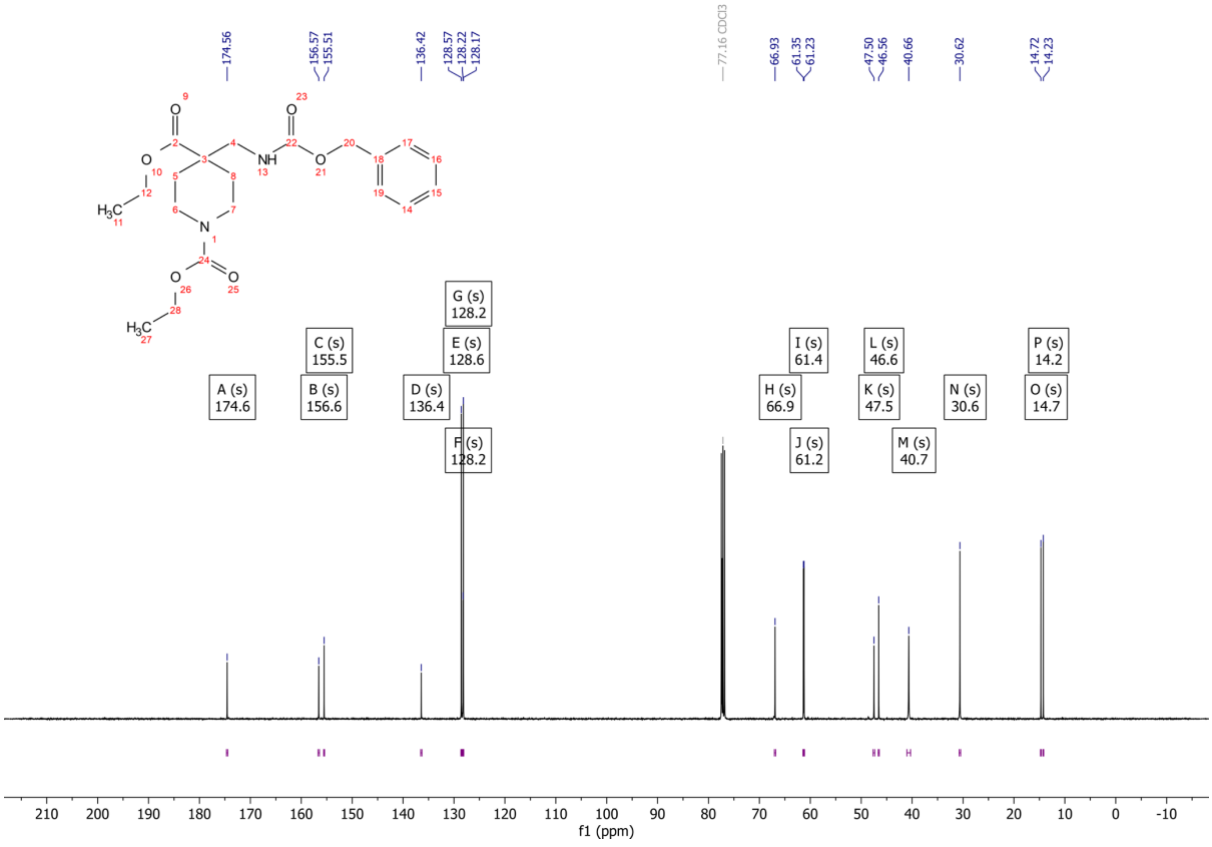


β-Amino Esters/Amides

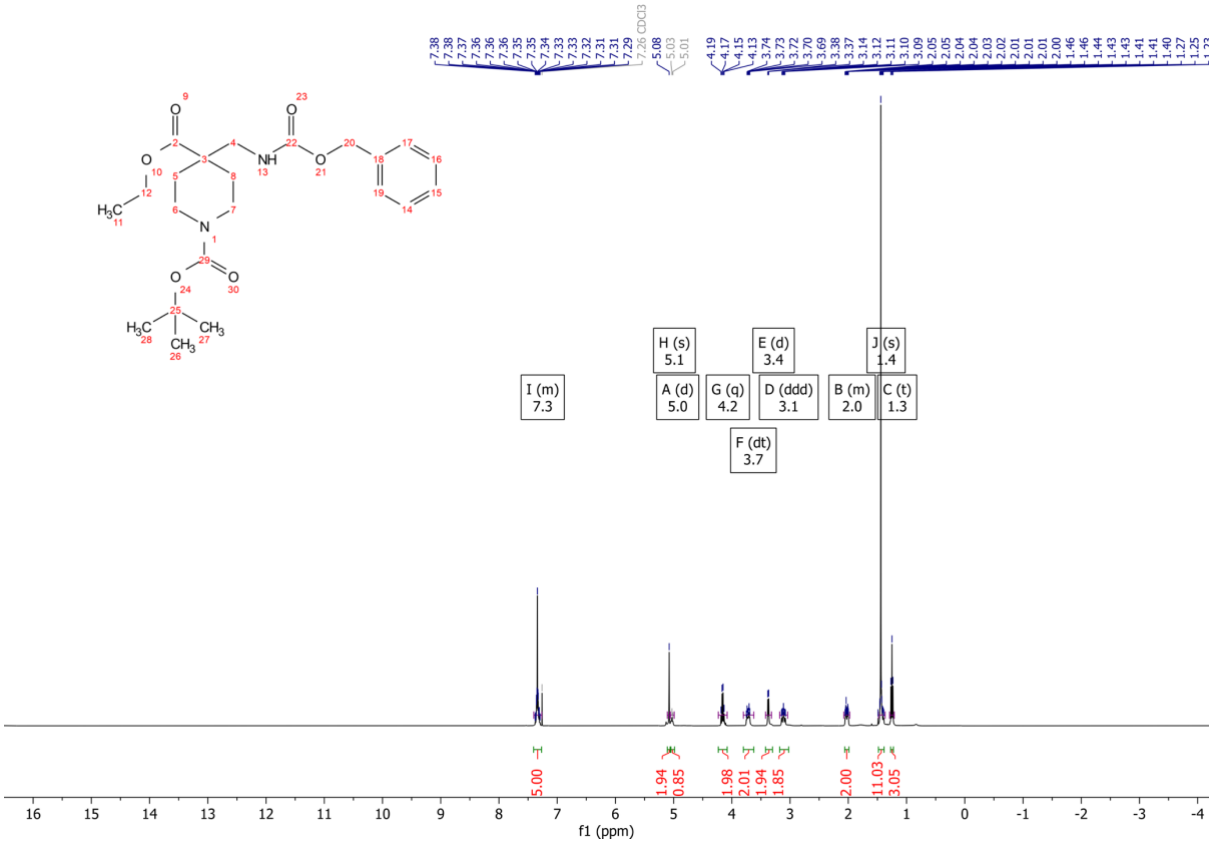
1 ^{1}H NMR (400 MHz, $CDCl_3$)



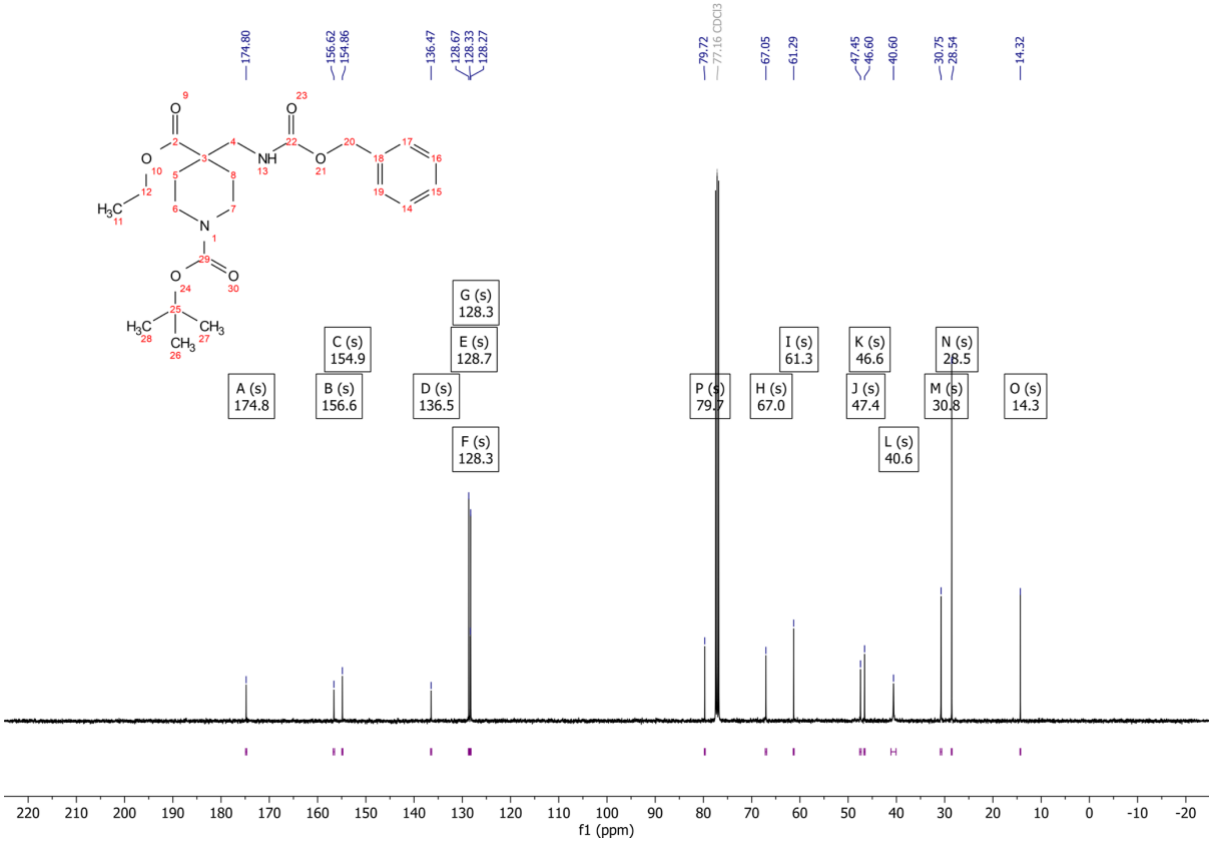
1 ^{13}C NMR (101 MHz, $CDCl_3$)



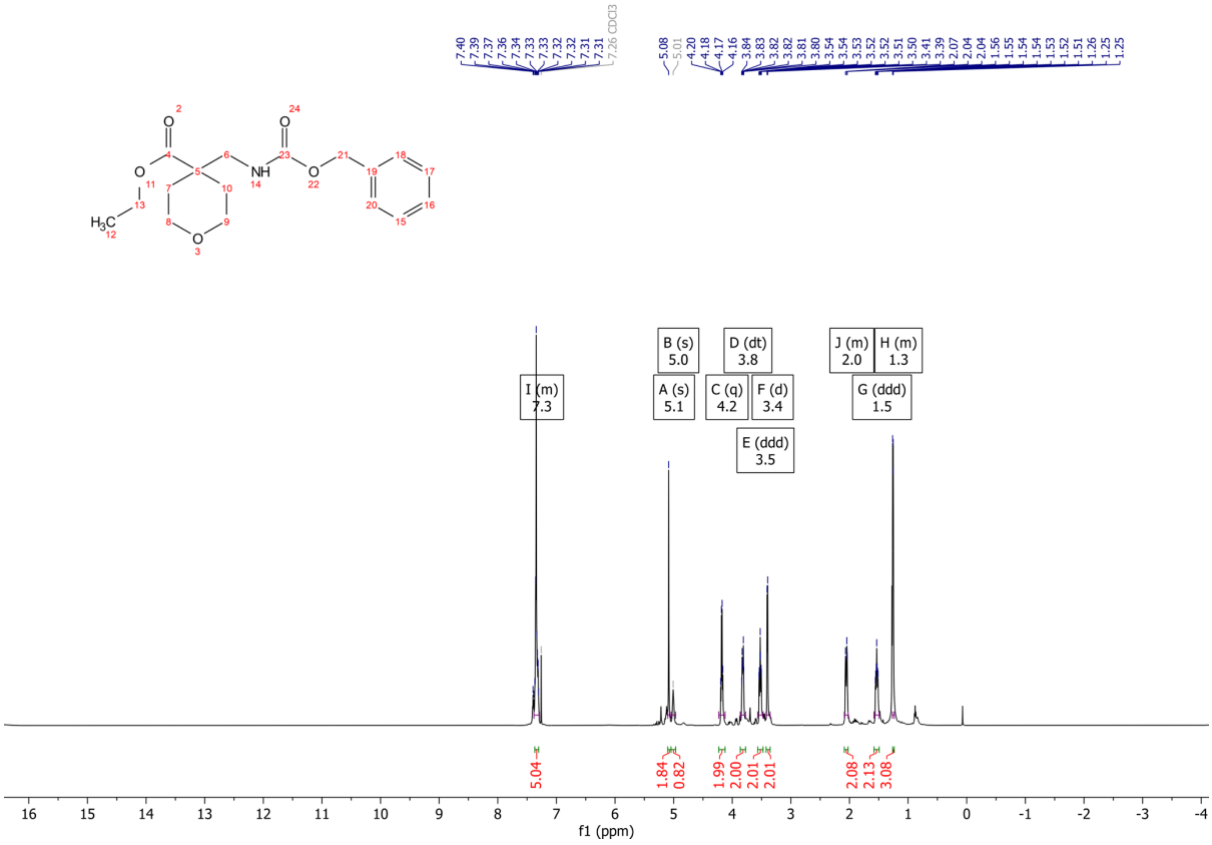
2 ^{1}H NMR (400 MHz, $CDCl_3$)



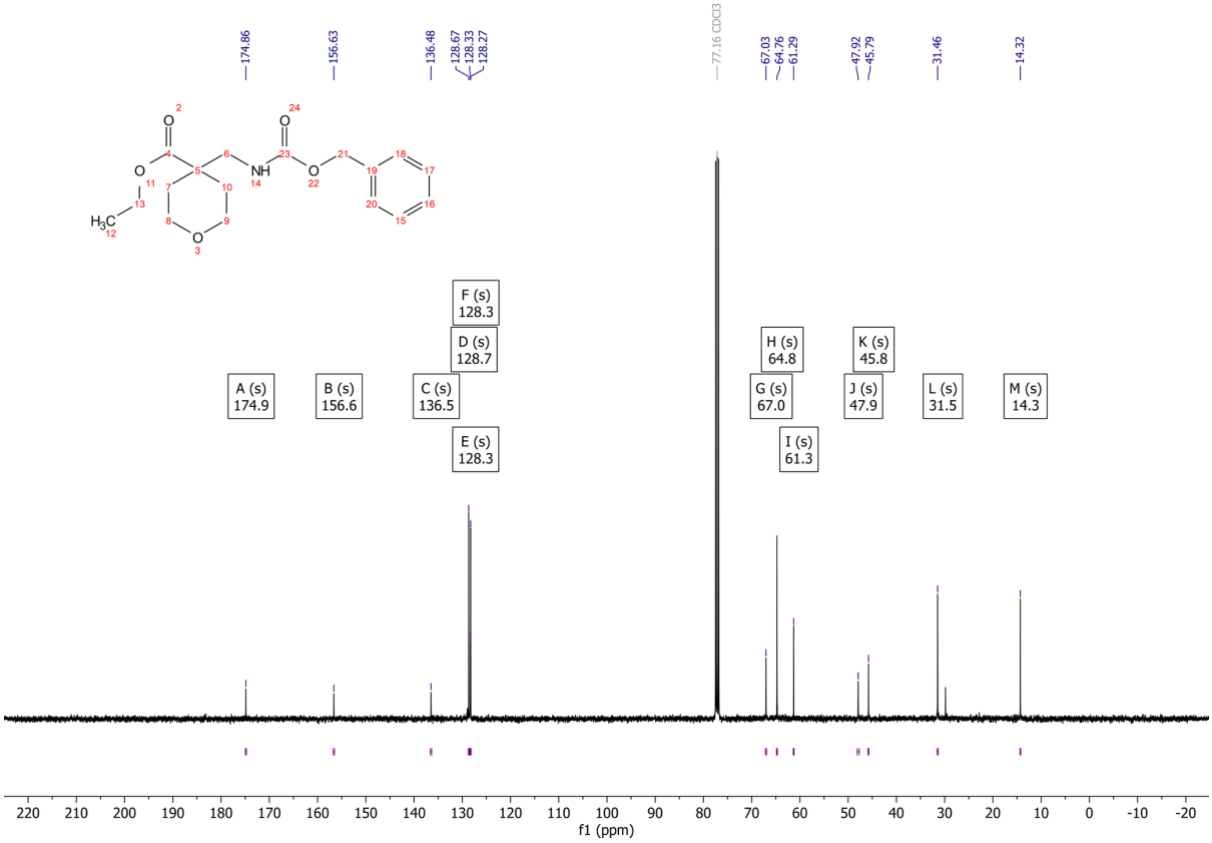
2 ^{13}C NMR (101 MHz, $CDCl_3$)



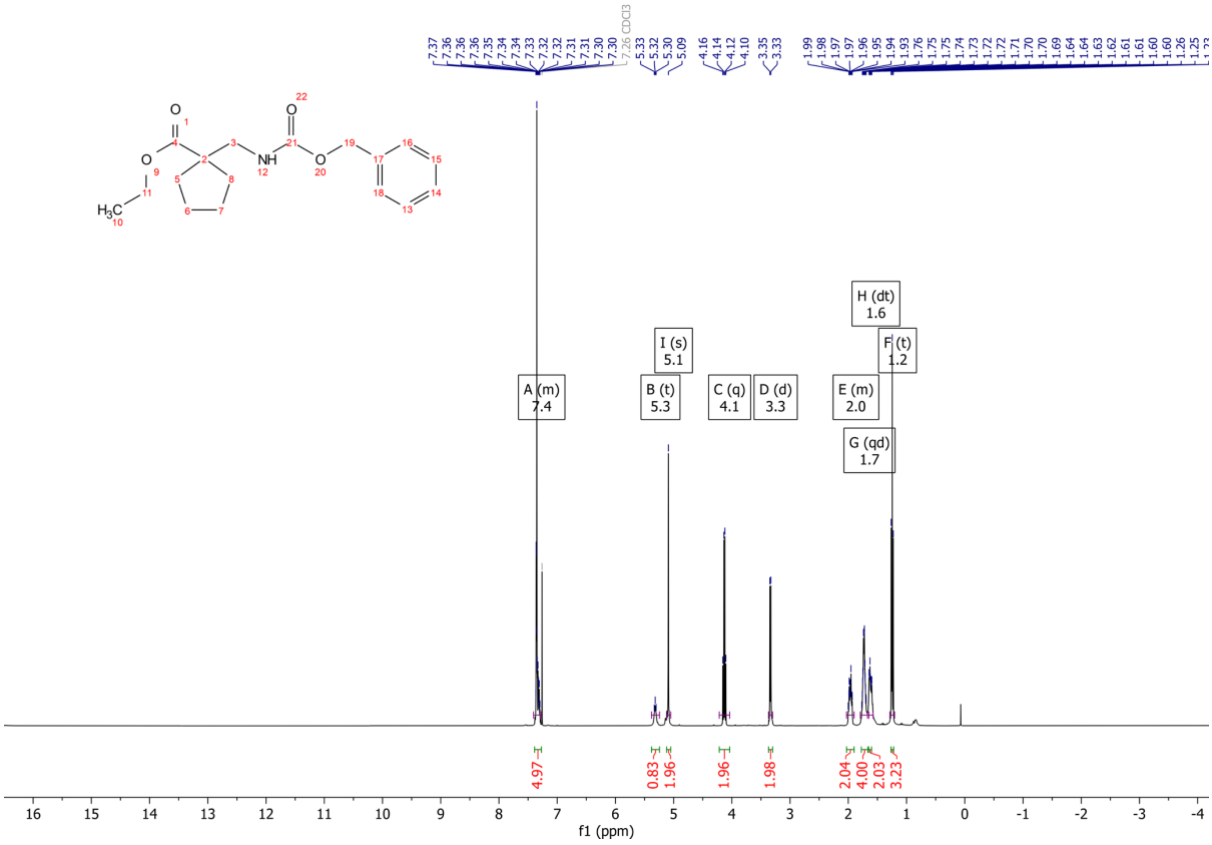
3 ^{1}H NMR (600 MHz, $CDCl_3$)



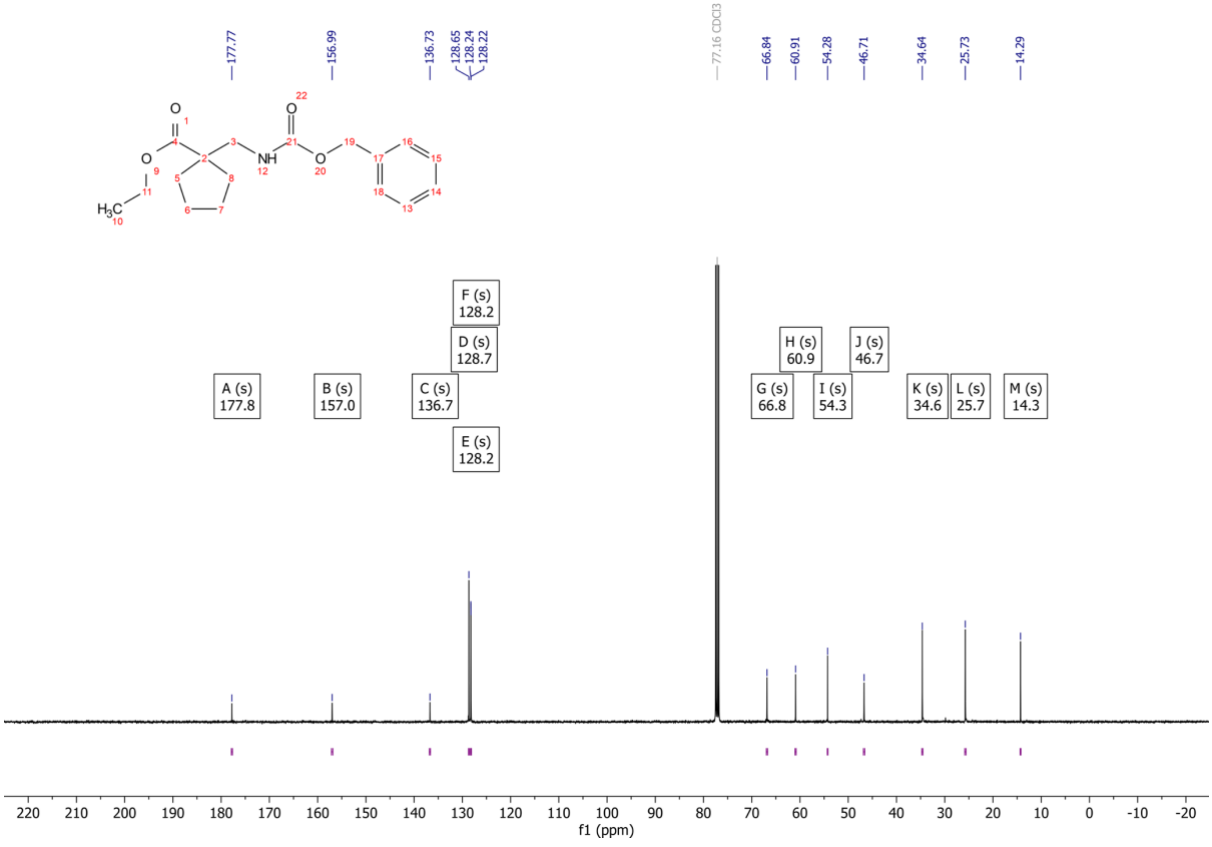
3 ^{13}C NMR (101 MHz, $CDCl_3$)



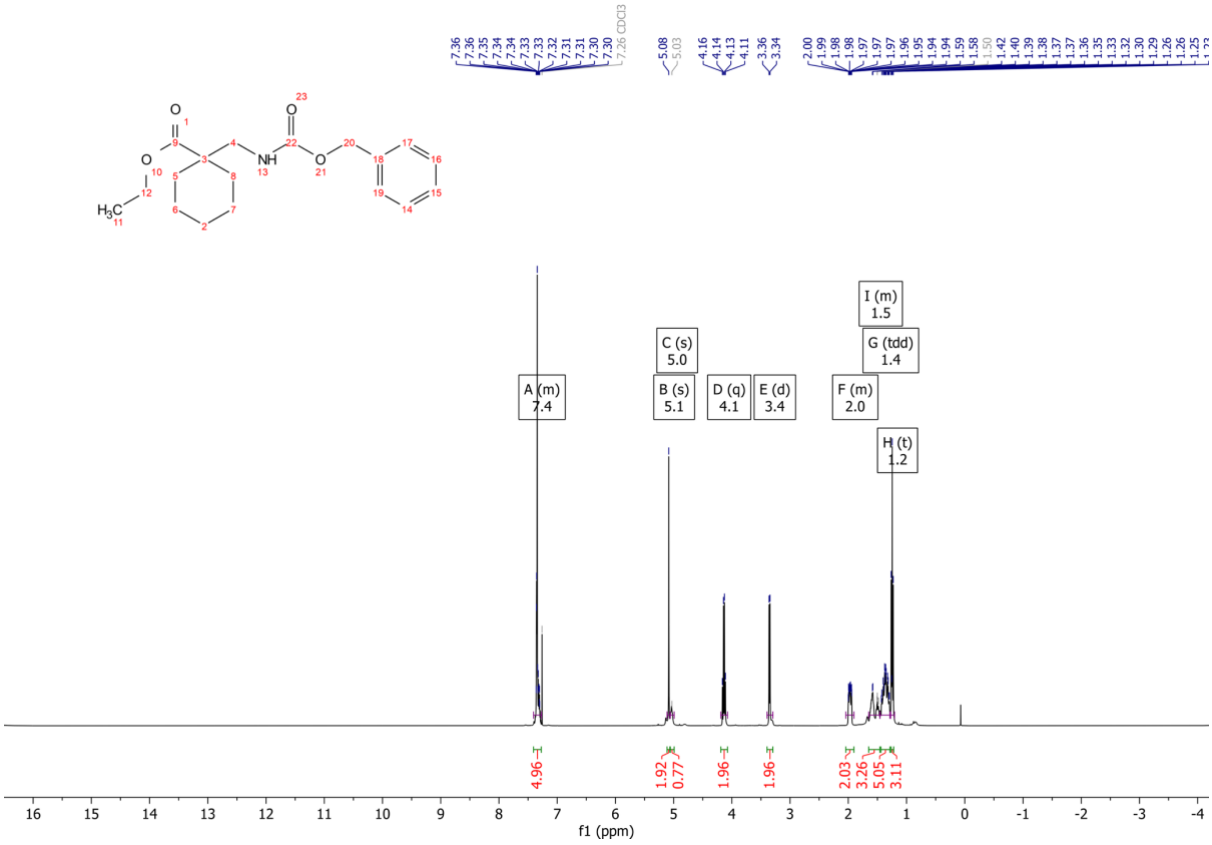
4 ^{1}H NMR (400 MHz, $CDCl_3$)



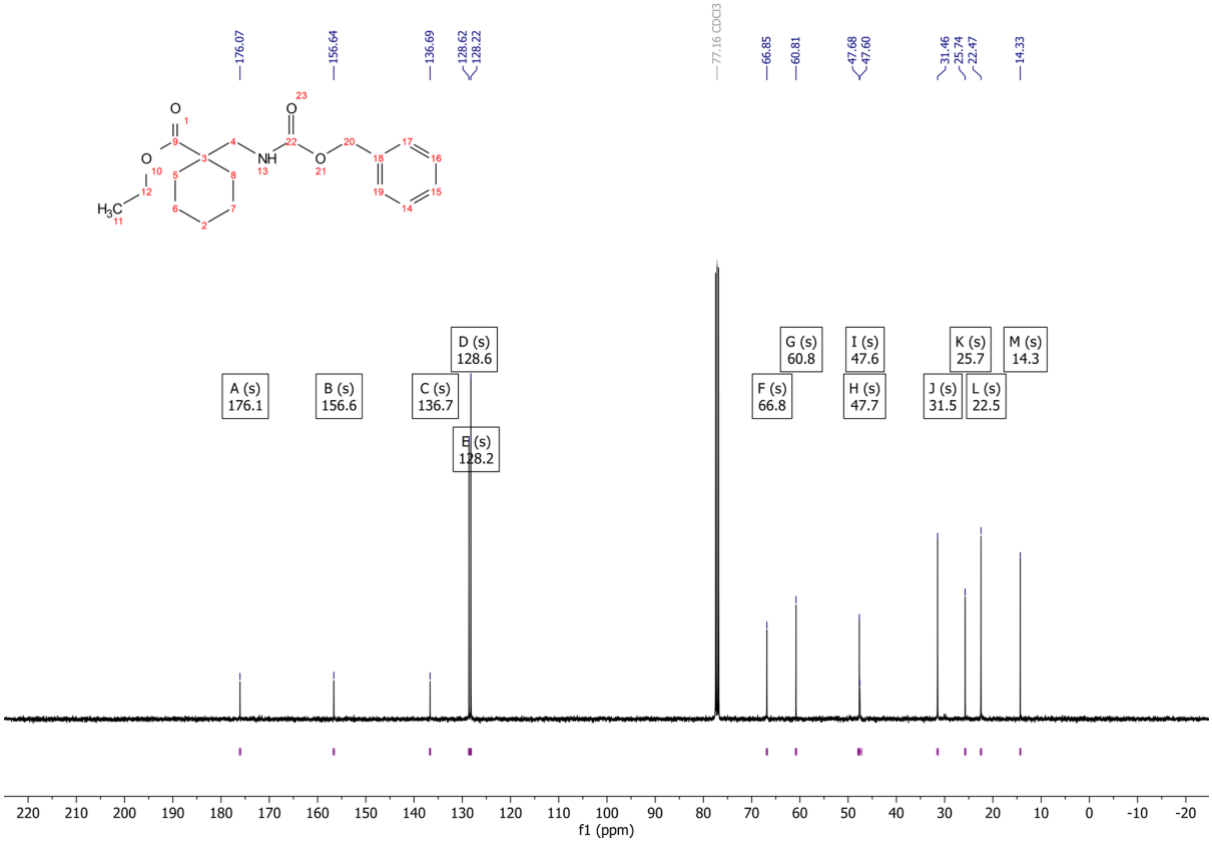
4 ^{13}C NMR (101 MHz, $CDCl_3$)



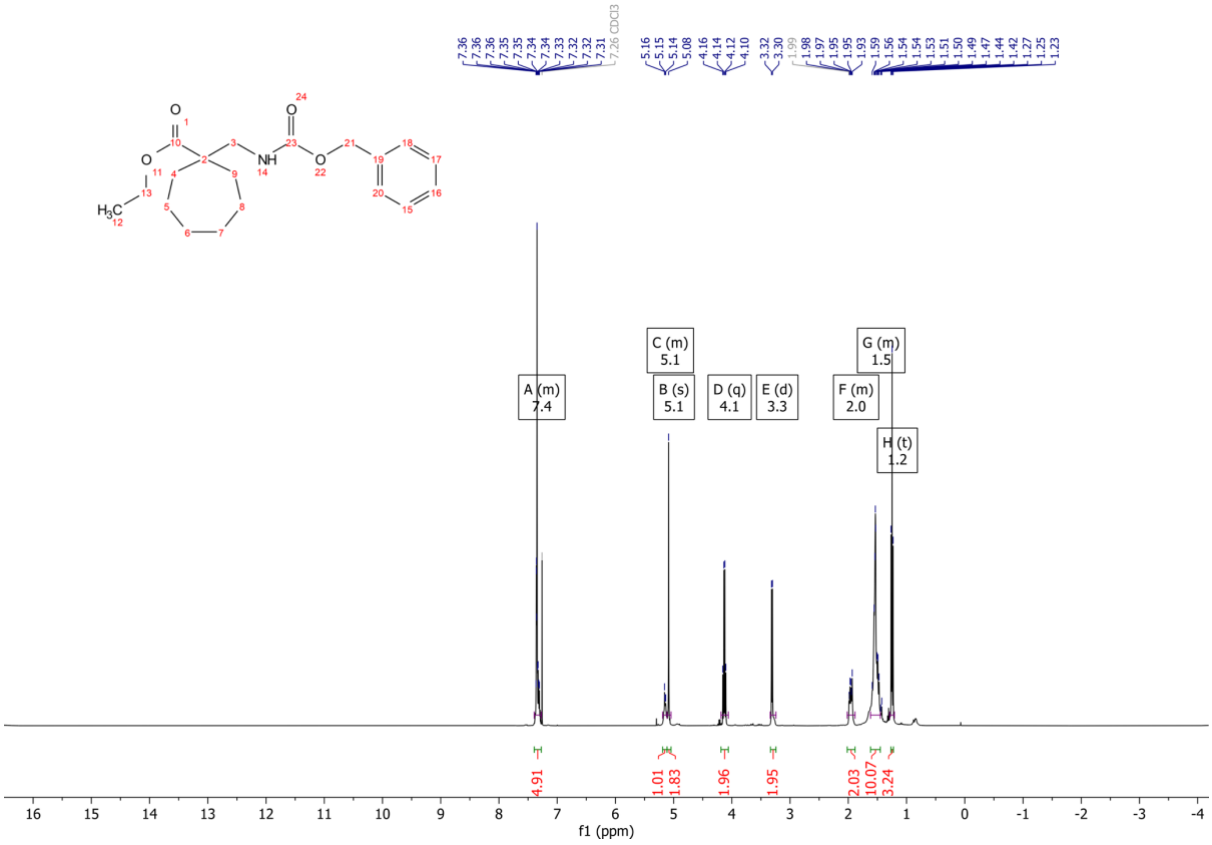
5 ^{1}H NMR (400 MHz, $CDCl_3$)



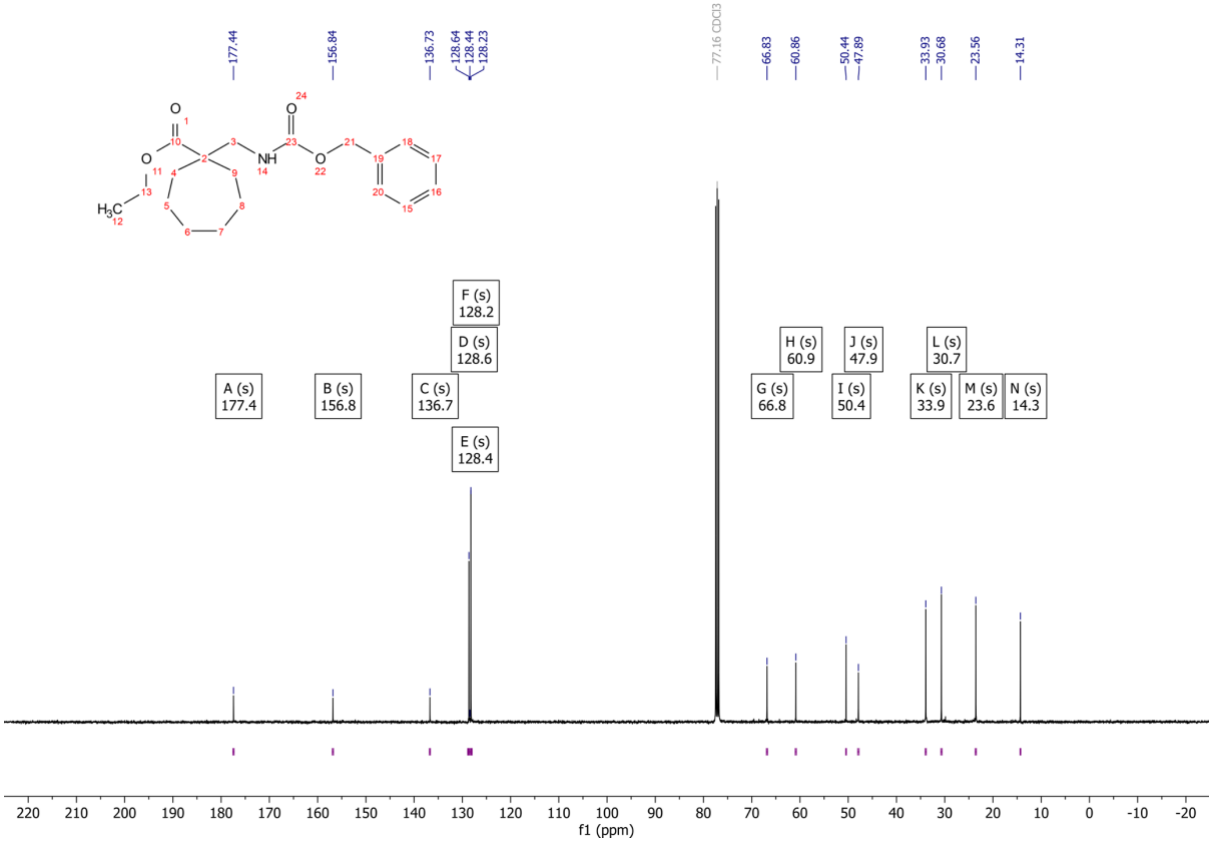
5 ^{13}C NMR (101 MHz, $CDCl_3$)



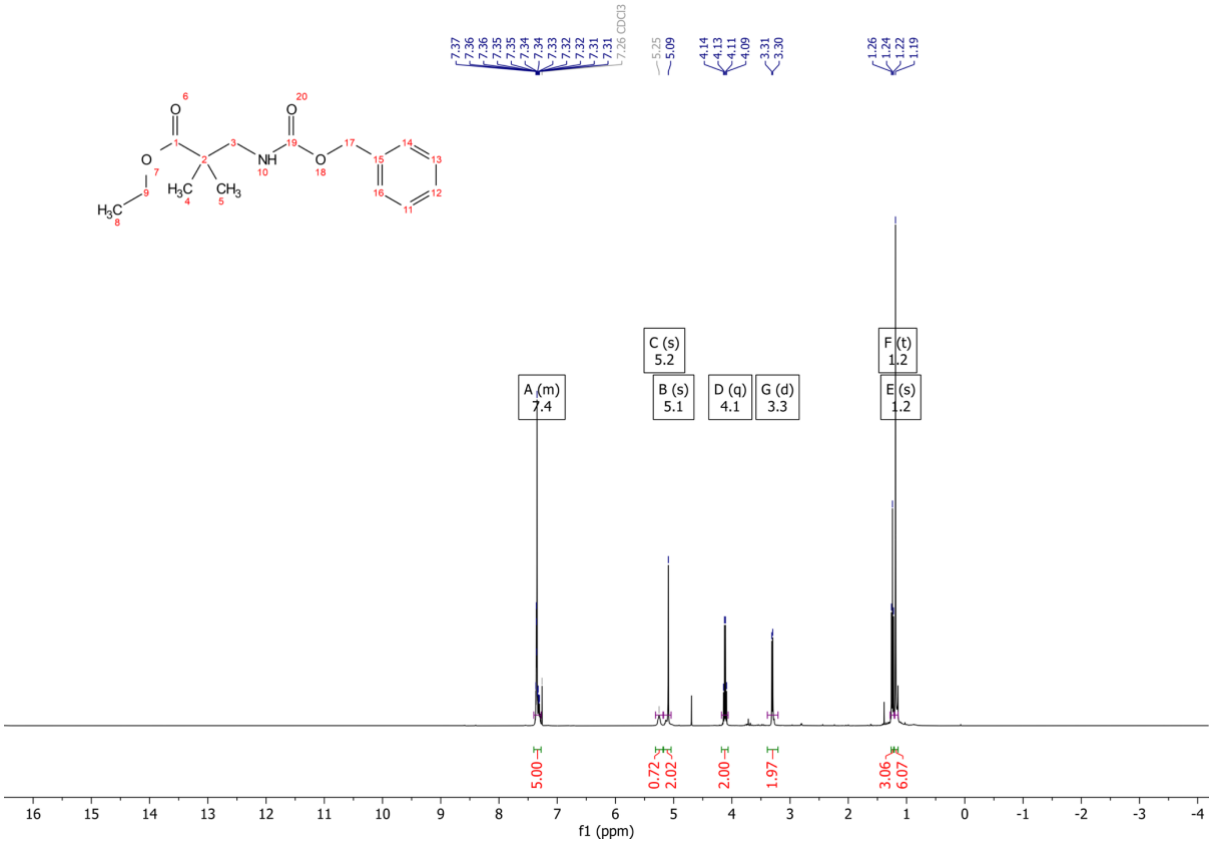
6 ^{1}H NMR (400 MHz, $CDCl_3$)



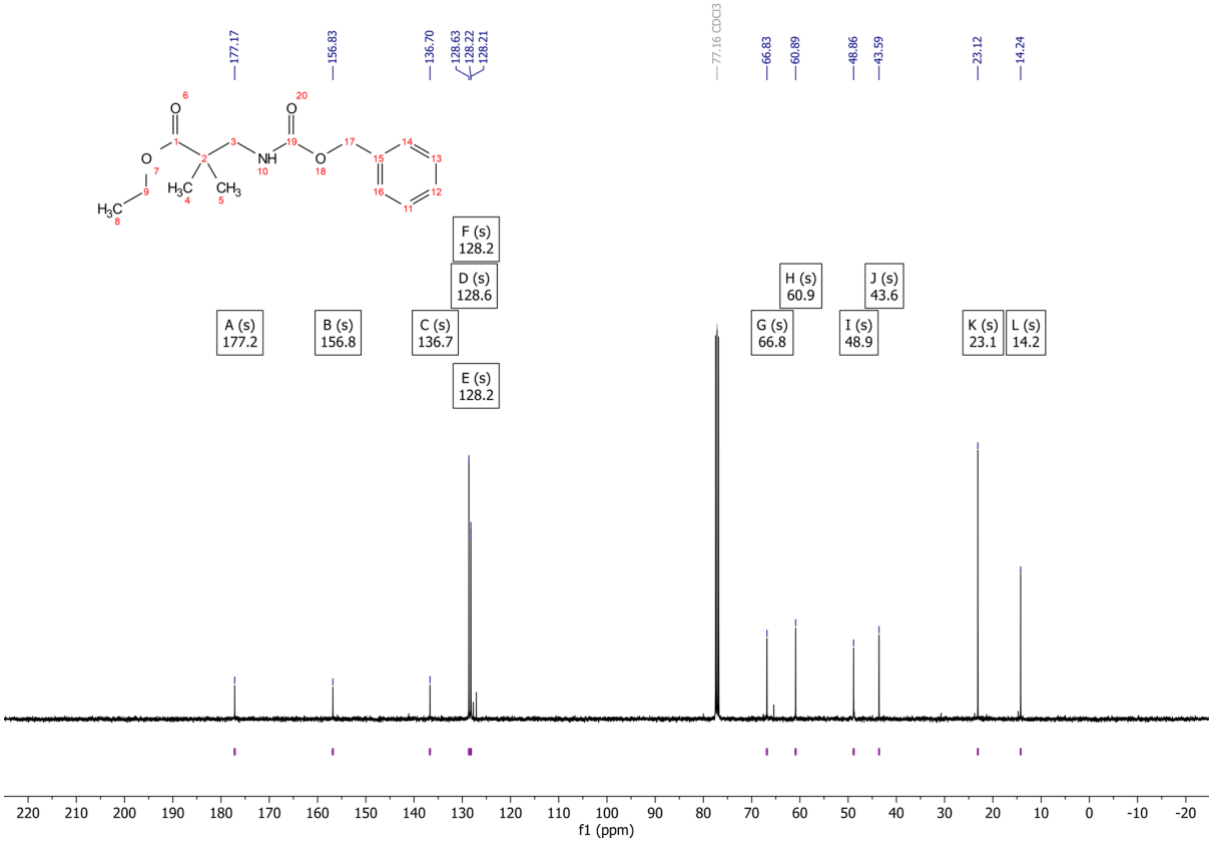
6 ^{13}C NMR (101 MHz, $CDCl_3$)



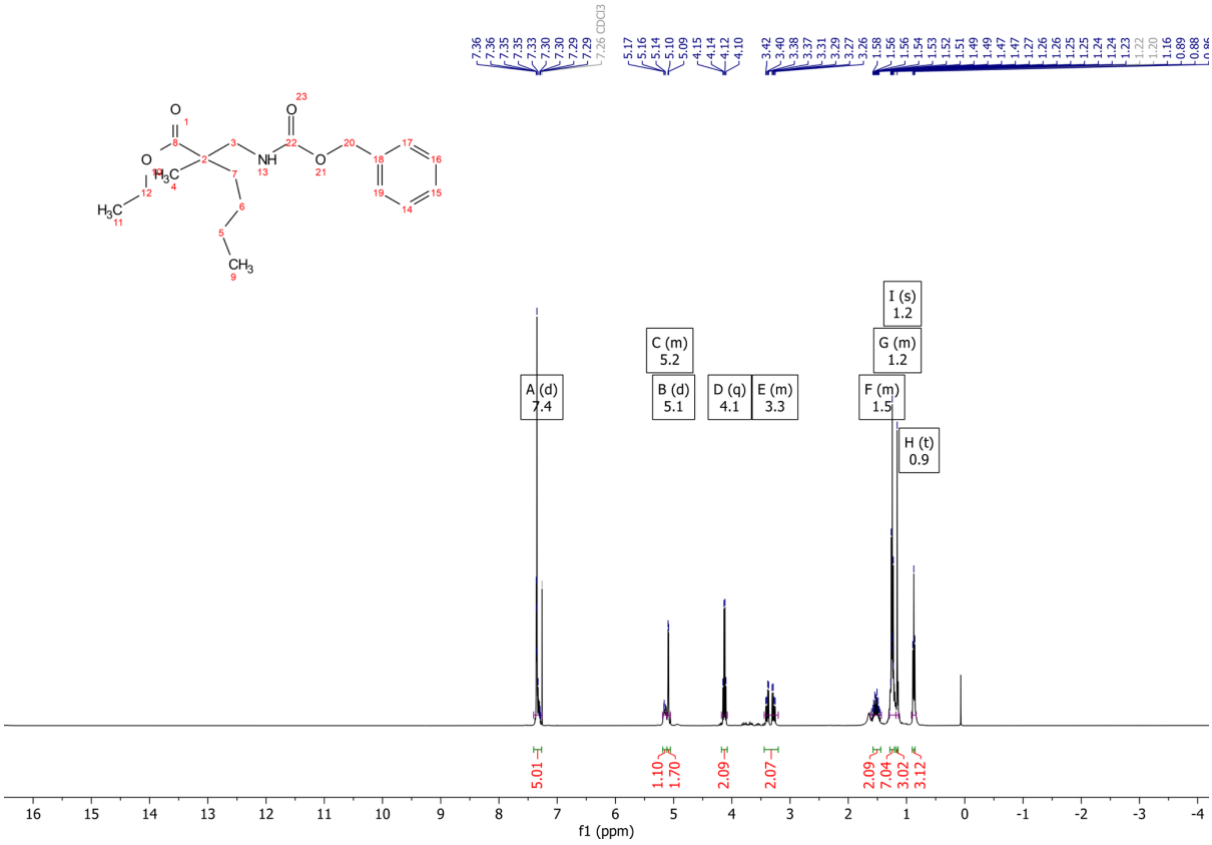
7 ^{1}H NMR (400 MHz, $CDCl_3$)



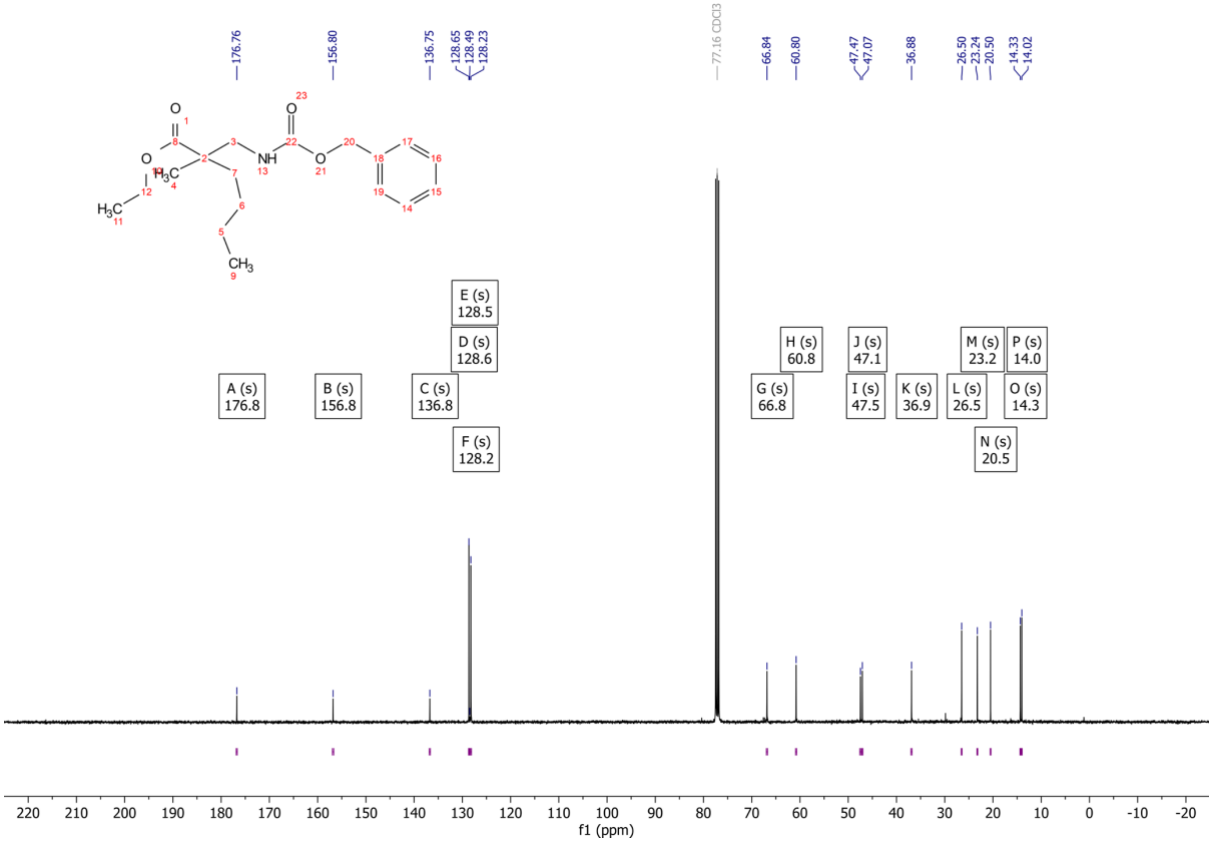
7 ^{13}C NMR (101 MHz, $CDCl_3$)



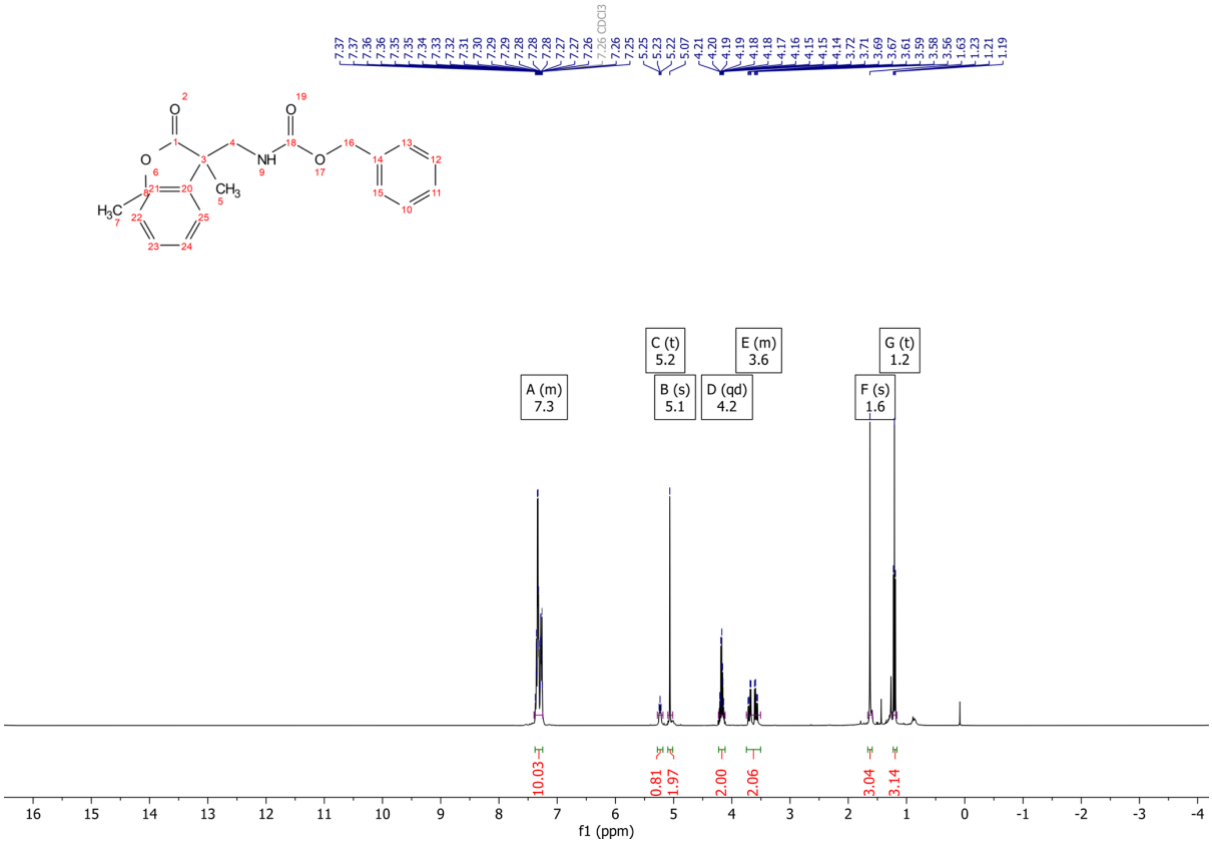
8 ^{1}H NMR (400 MHz, $CDCl_3$)



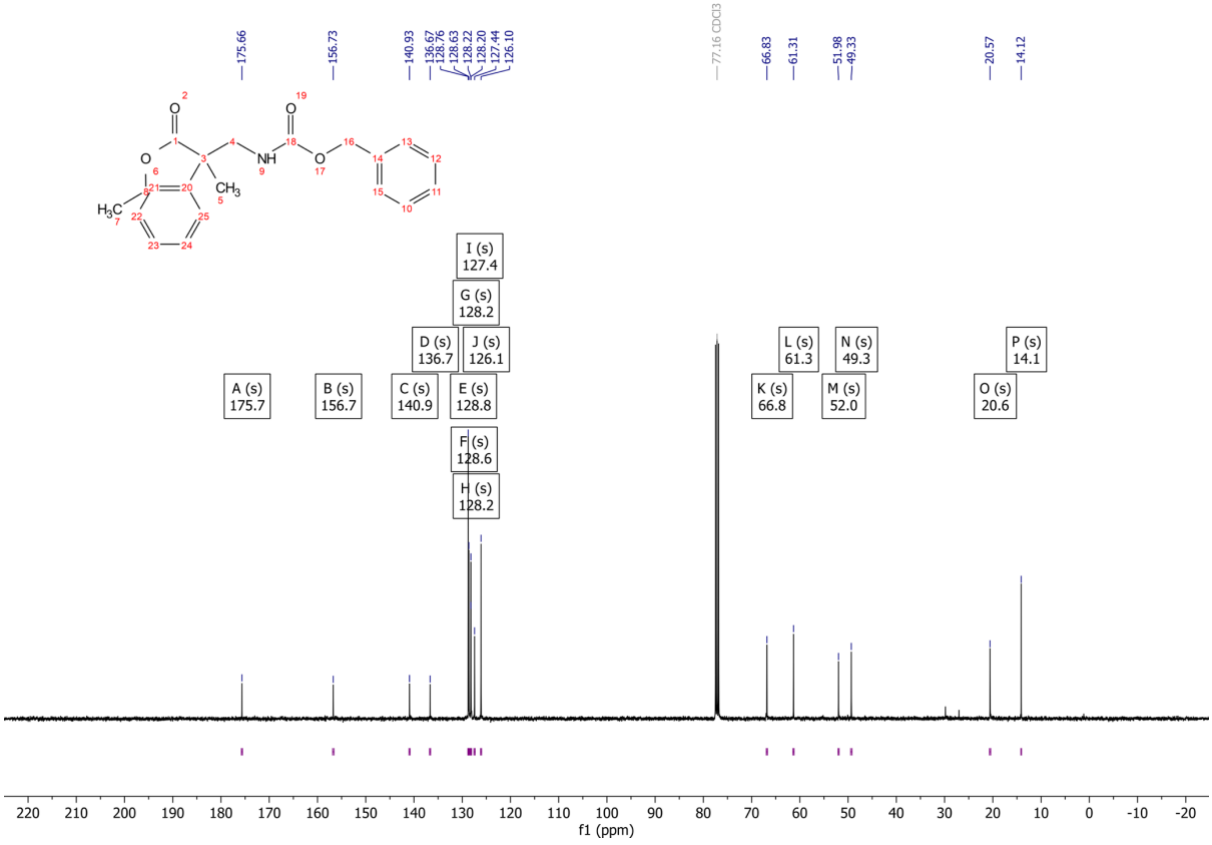
8 ^{13}C NMR (101 MHz, $CDCl_3$)



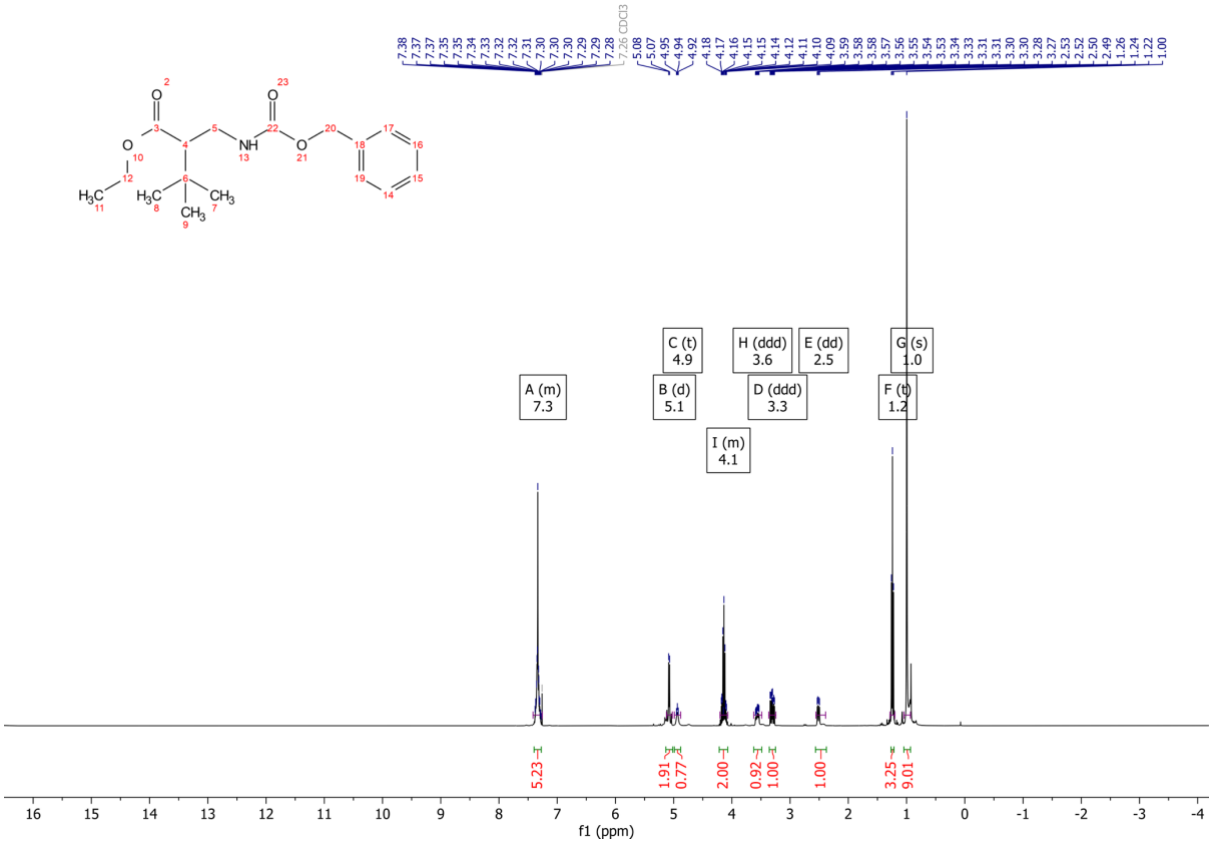
9 ^{1}H NMR (400 MHz, $CDCl_3$)



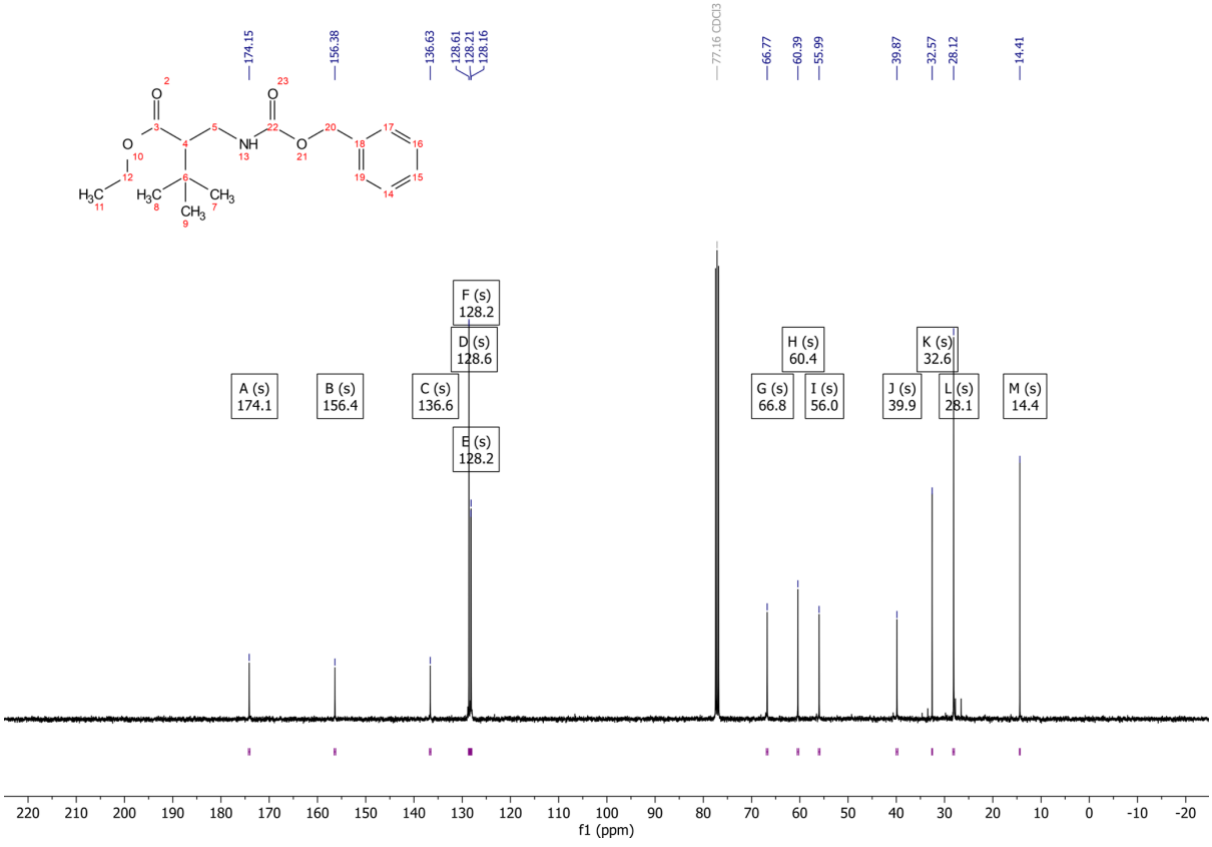
9 ^{13}C NMR (101 MHz, $CDCl_3$)



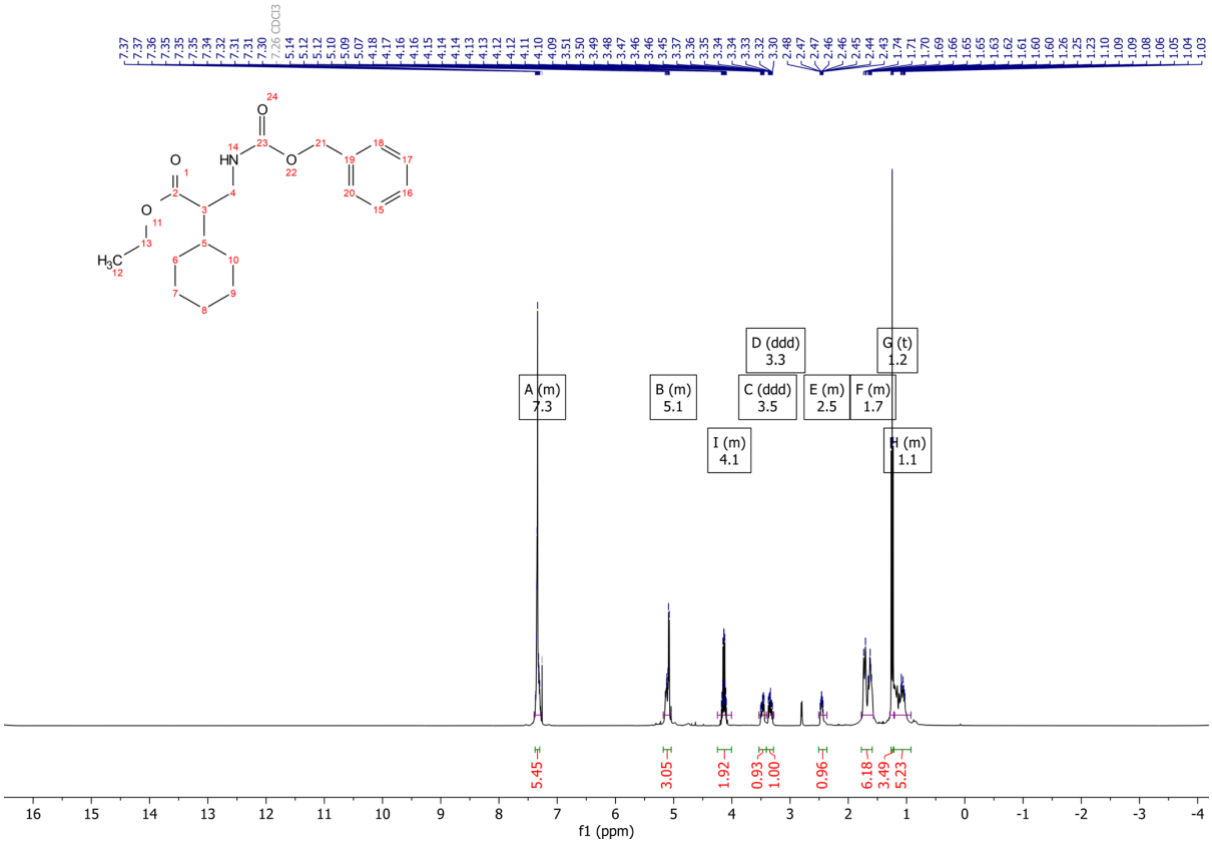
11 ^{1}H NMR (400 MHz, $CDCl_3$)



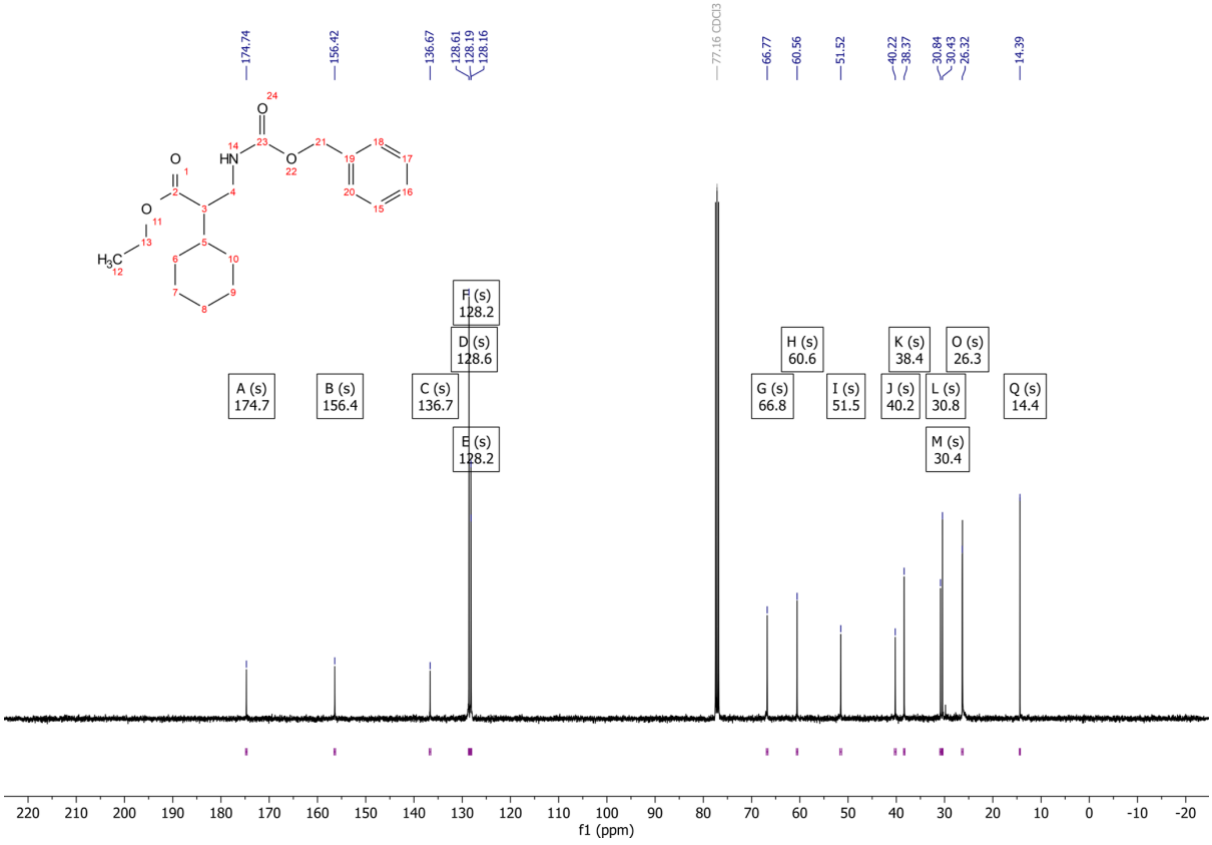
11 ^{13}C NMR (101 MHz, $CDCl_3$)



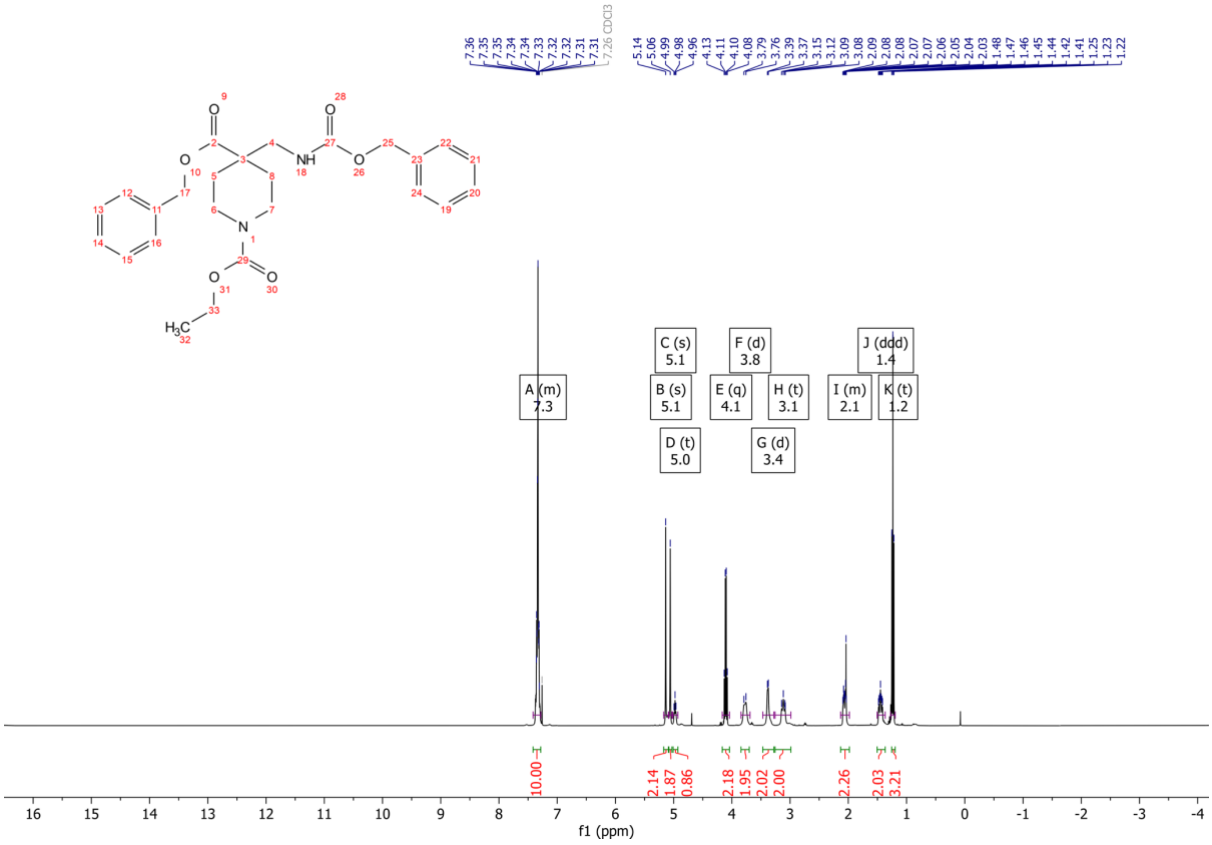
12 ^{1}H NMR (400 MHz, $CDCl_3$)



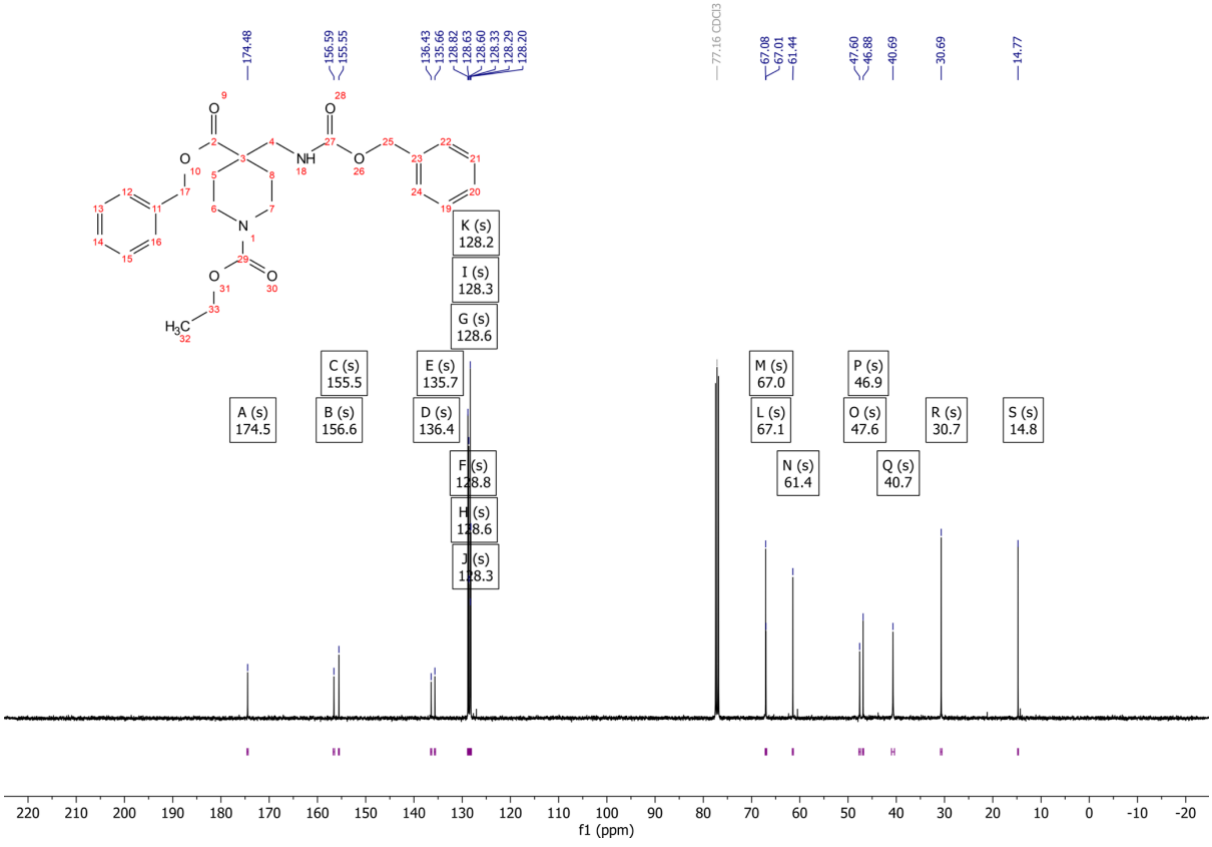
12 ^{13}C NMR (101 MHz, $CDCl_3$)



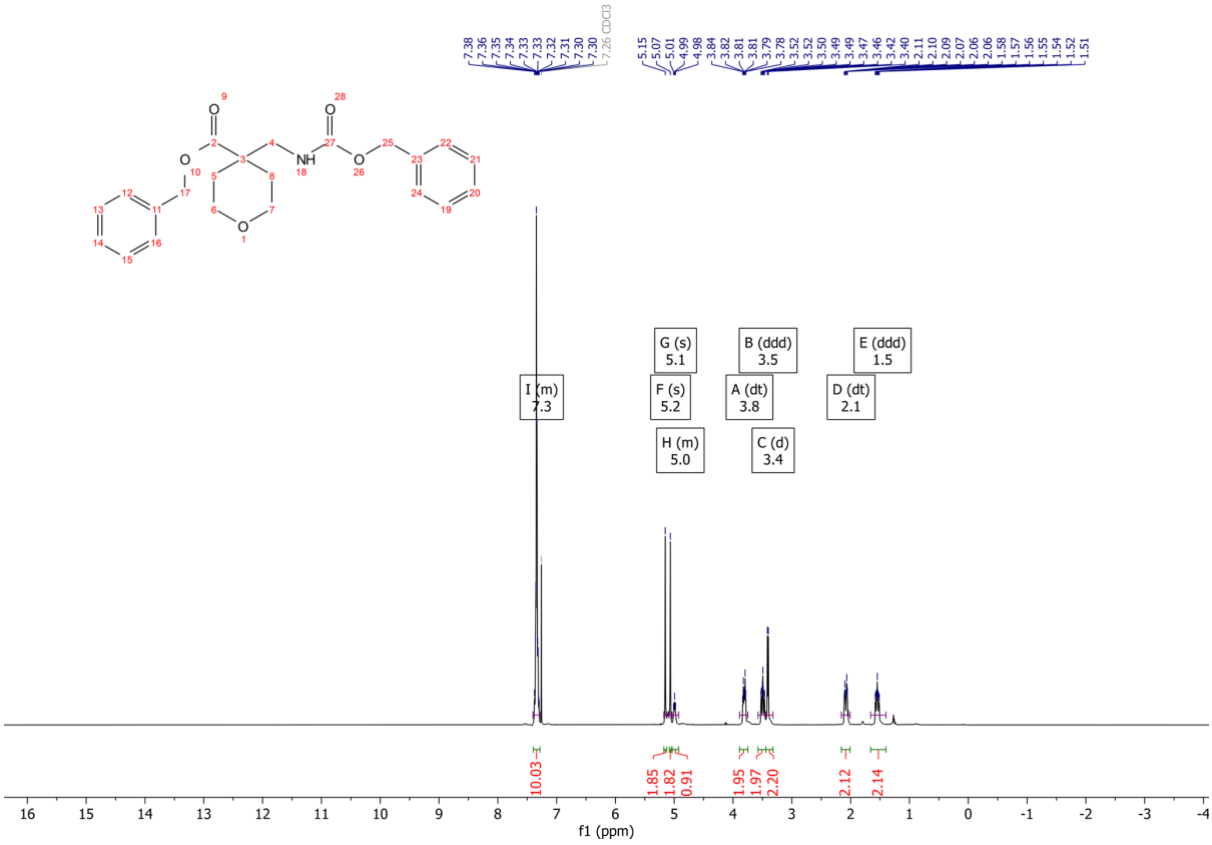
14 ^{1}H NMR (400 MHz, $CDCl_3$)



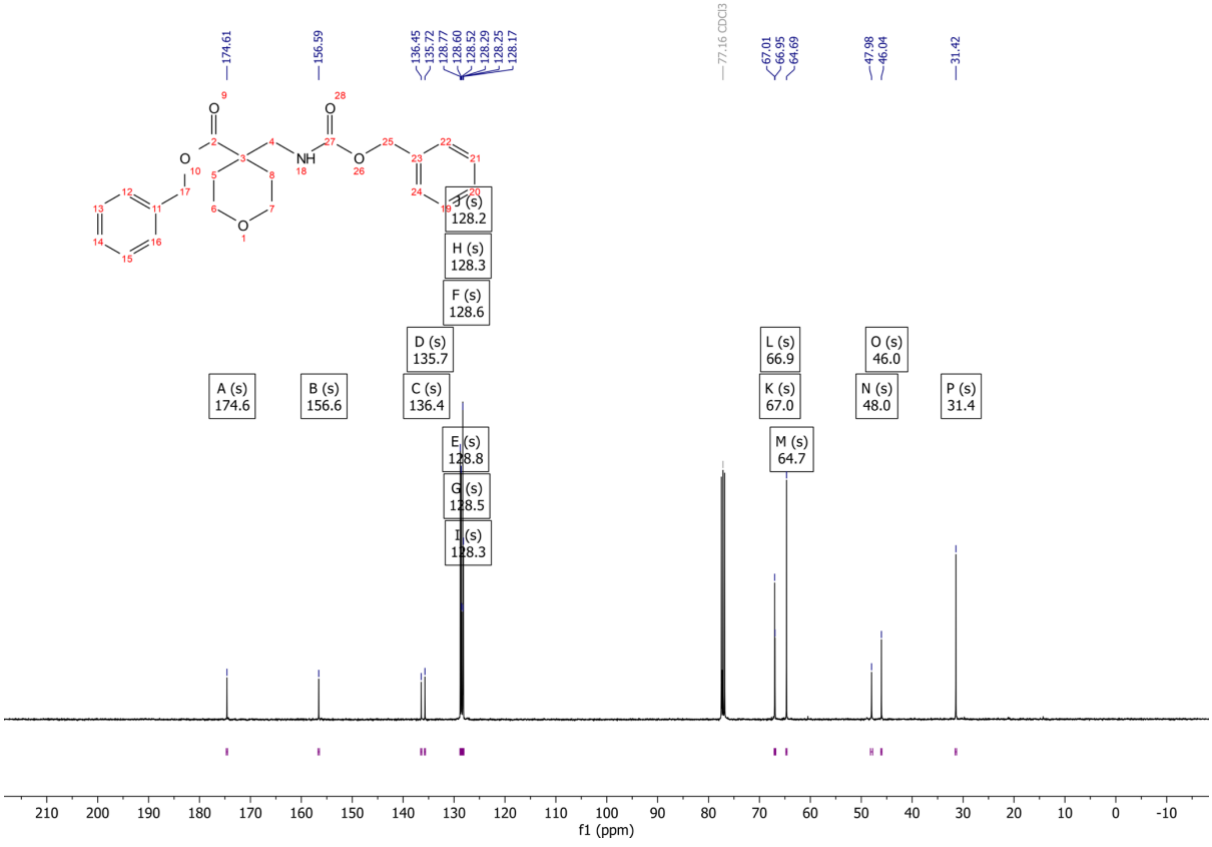
14 ^{13}C NMR (101 MHz, $CDCl_3$)



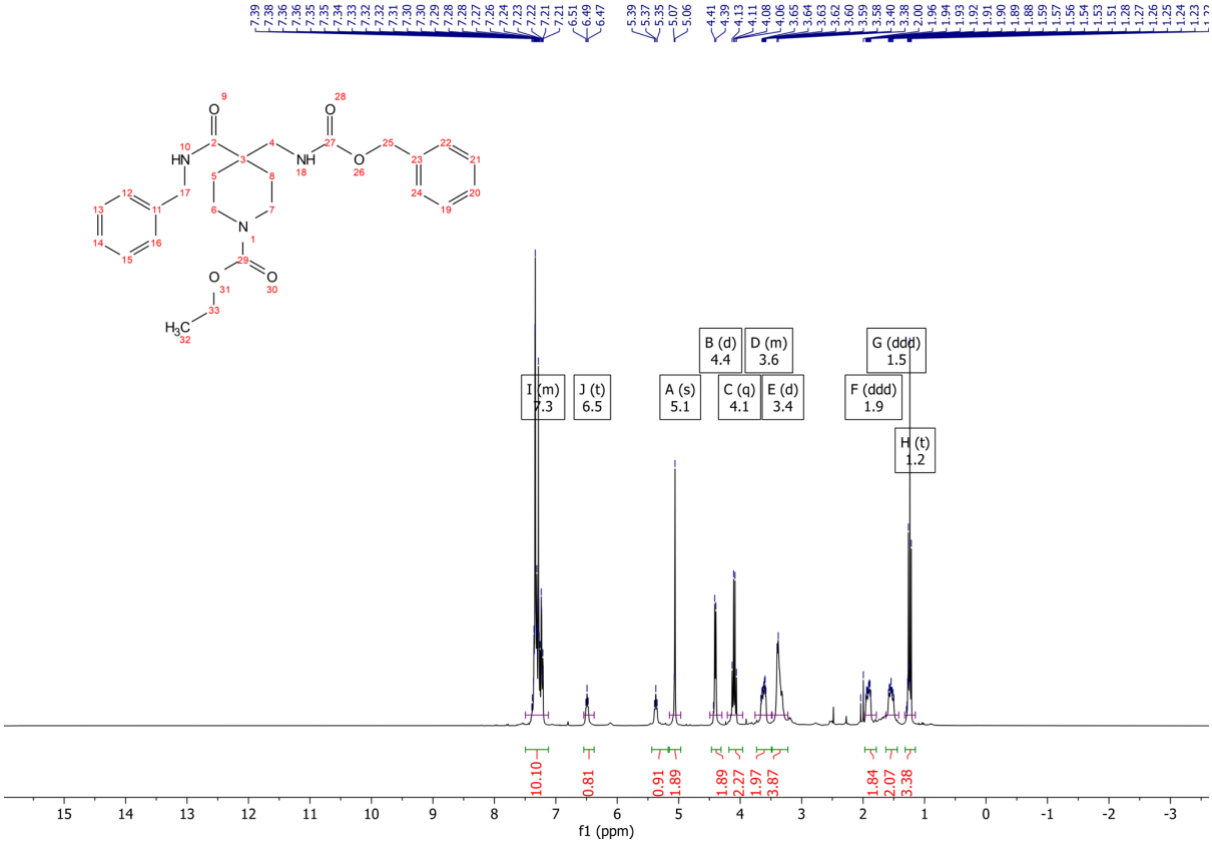
15 ^{1}H NMR (400 MHz, $CDCl_3$)



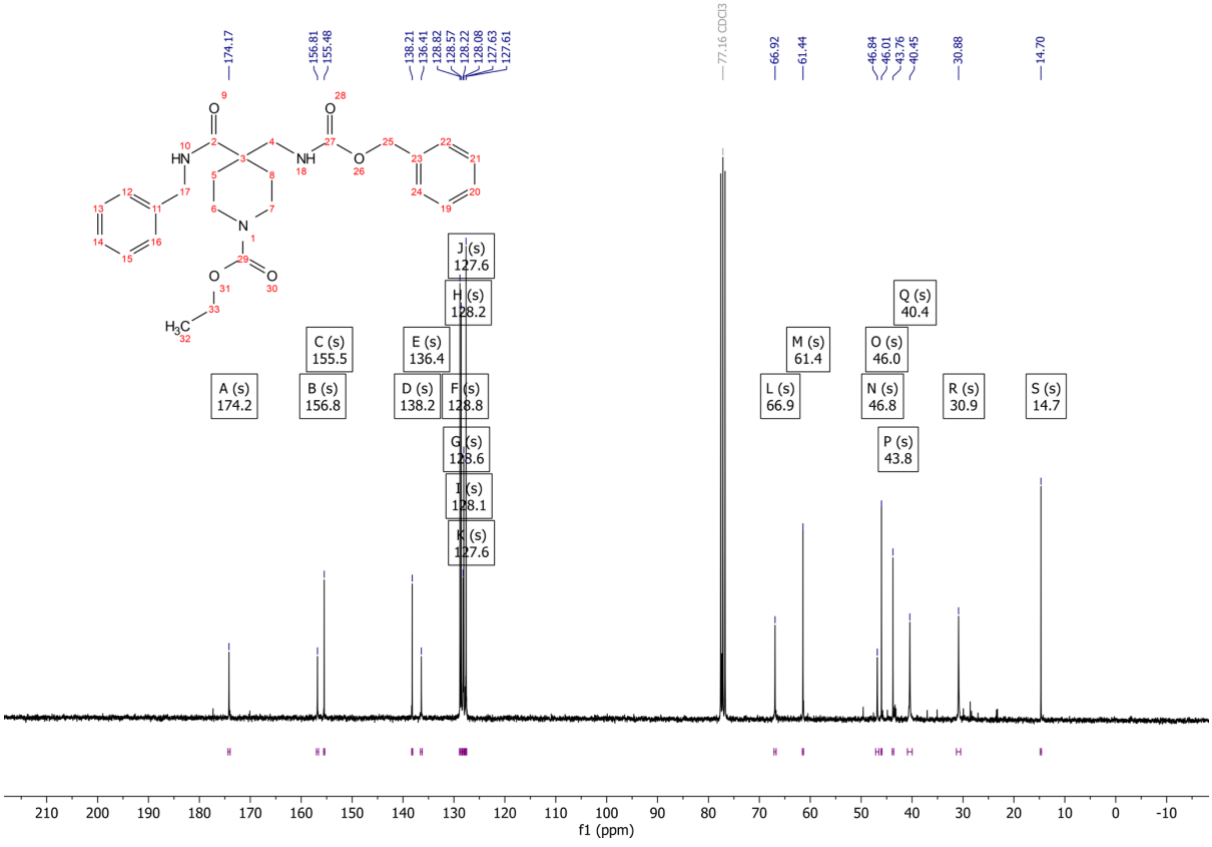
15 ^{13}C NMR (101 MHz, $CDCl_3$)



17 ^{1}H NMR (300 MHz, $CDCl_3$)

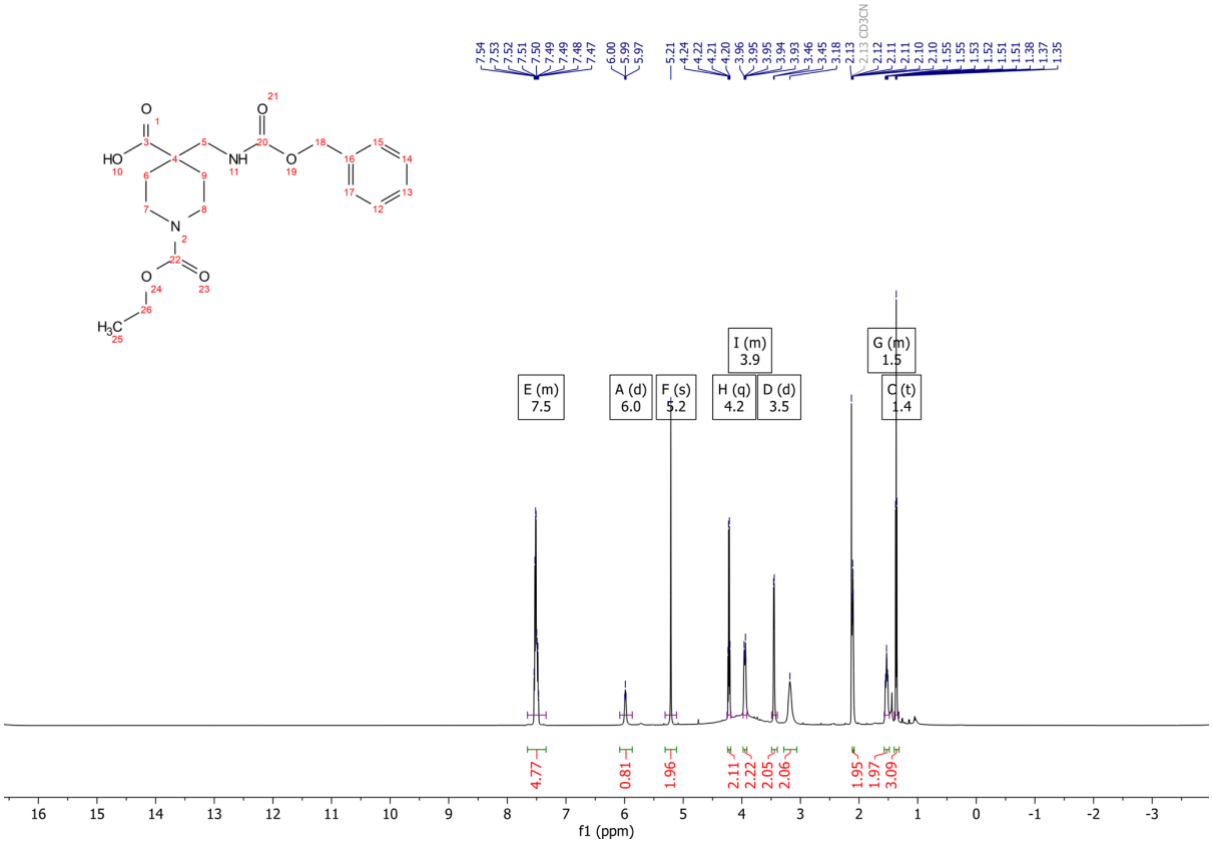


17 ^{13}C NMR (75 MHz, $CDCl_3$)

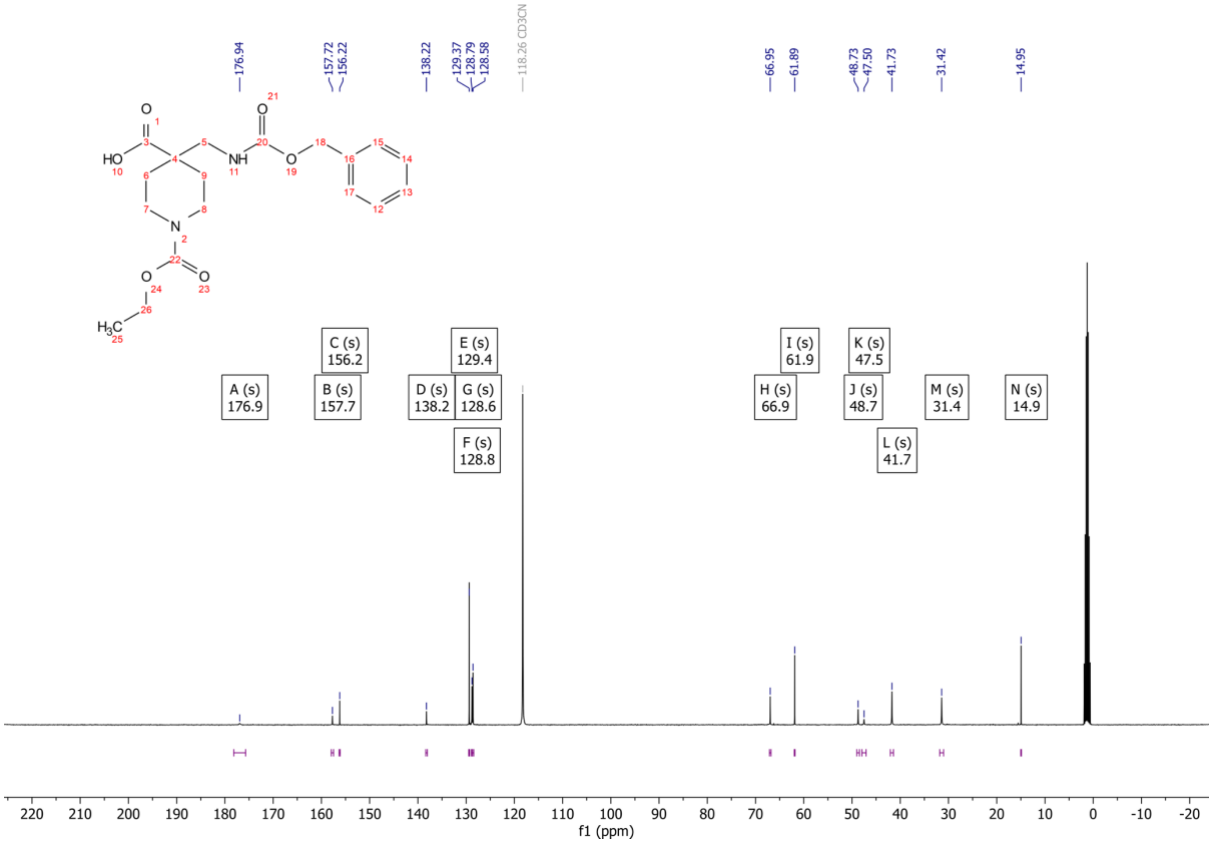


β-Amino Acids

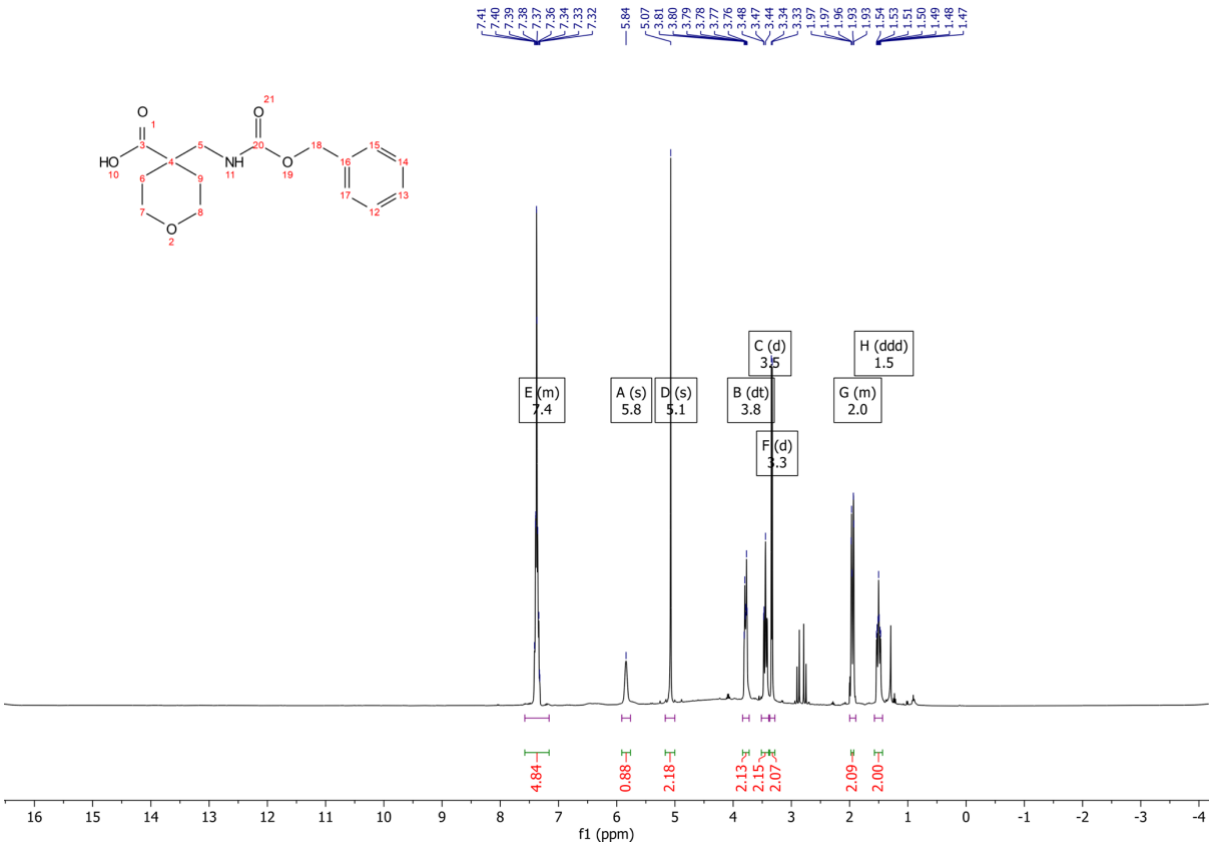
18 ^{1}H NMR (600 MHz, CD_3CN)



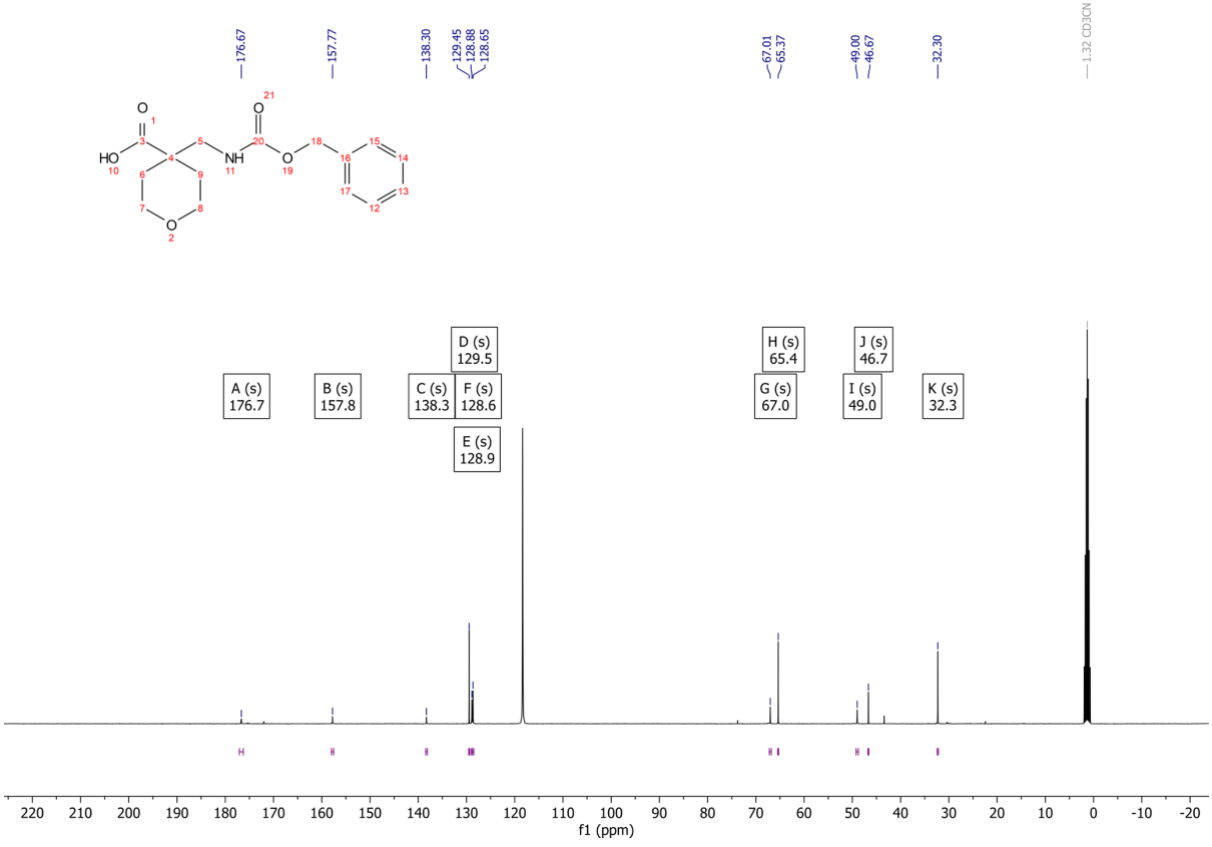
18 ^{13}C NMR (101 MHz, CD_3CN)



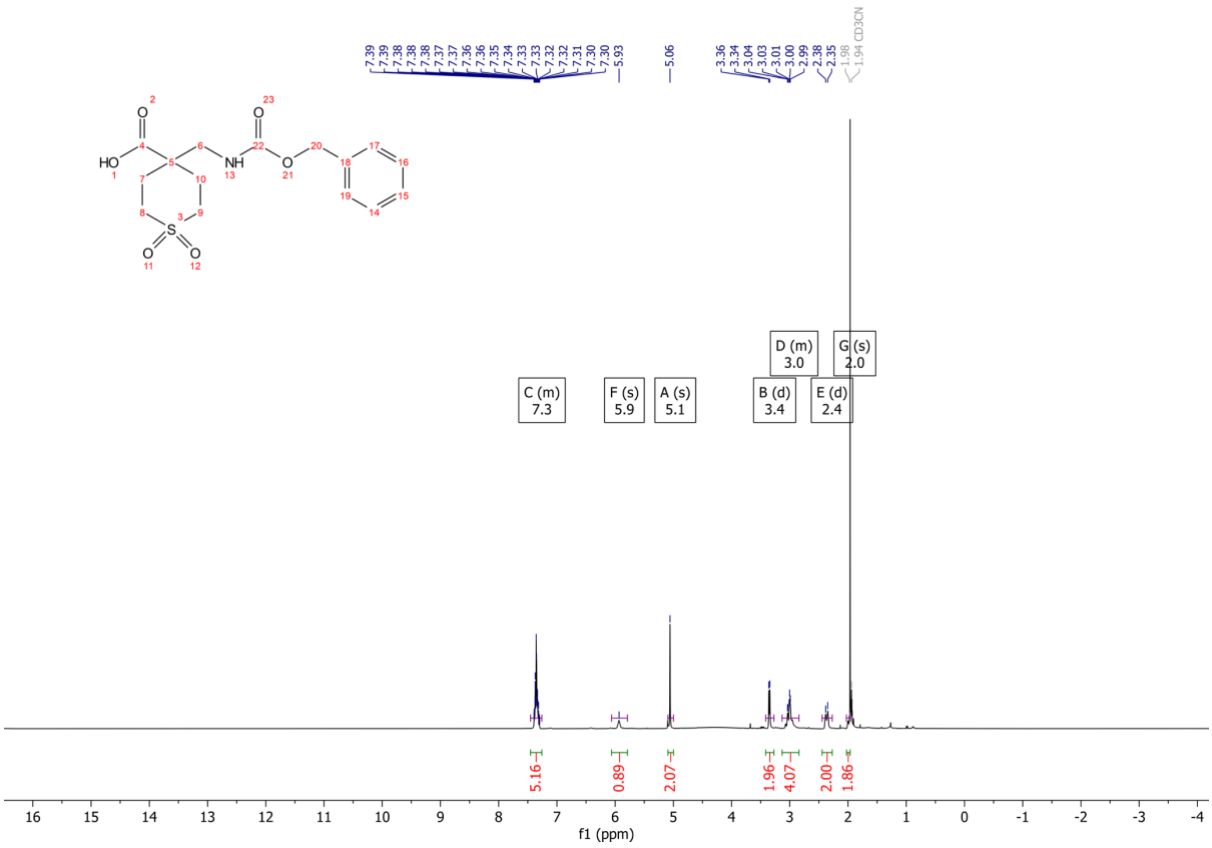
19 ^{1}H NMR (400 MHz, CD_3CN)



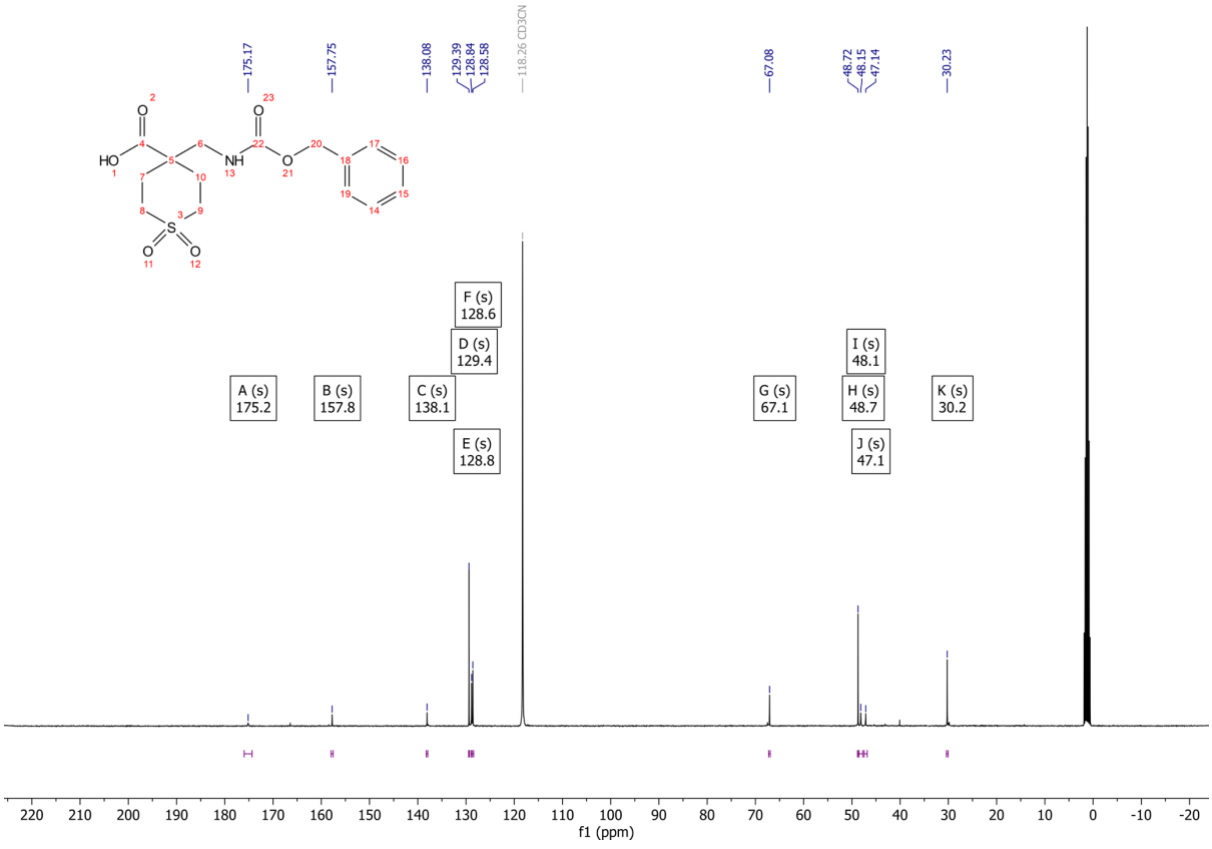
19 ^{13}C NMR (101 MHz, CD_3CN)



20 ^{1}H NMR (400 MHz, CD_3CN)

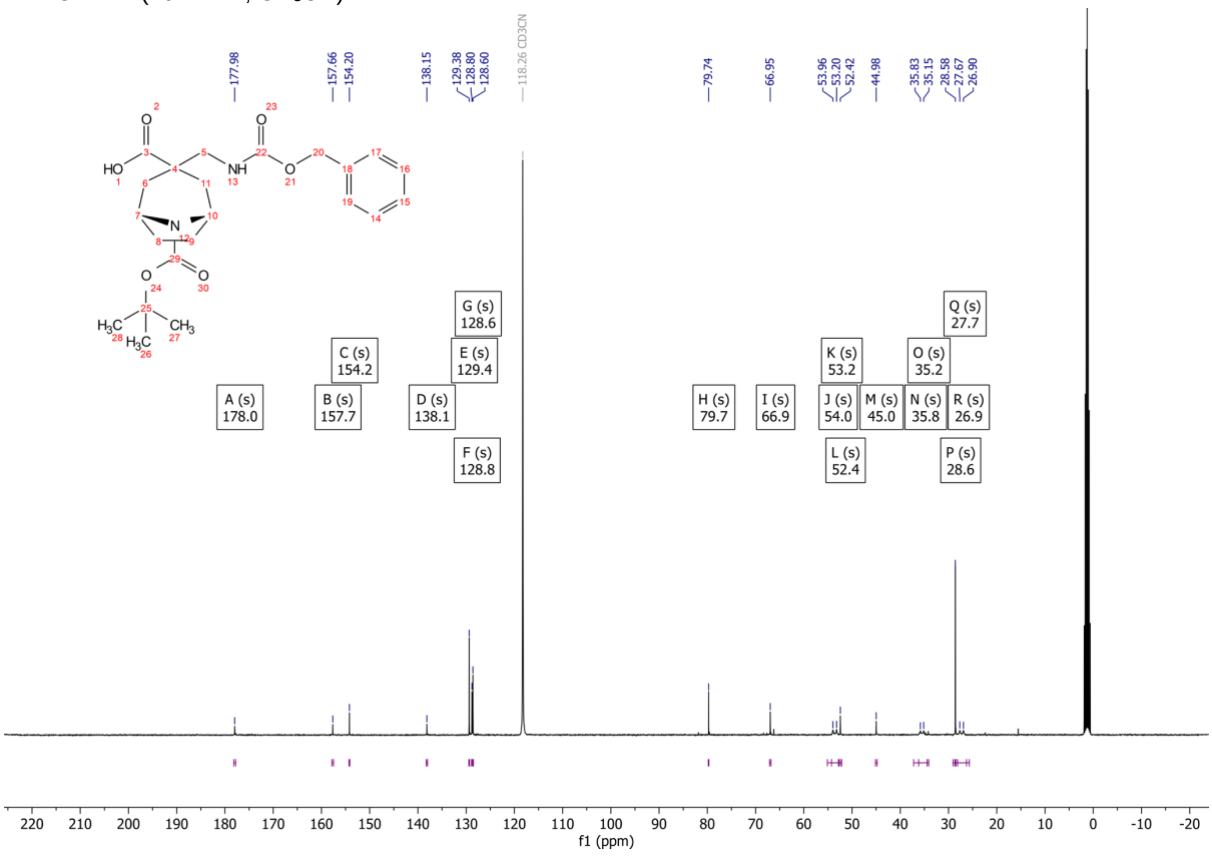


20 ^{13}C NMR (101 MHz, CD_3CN)

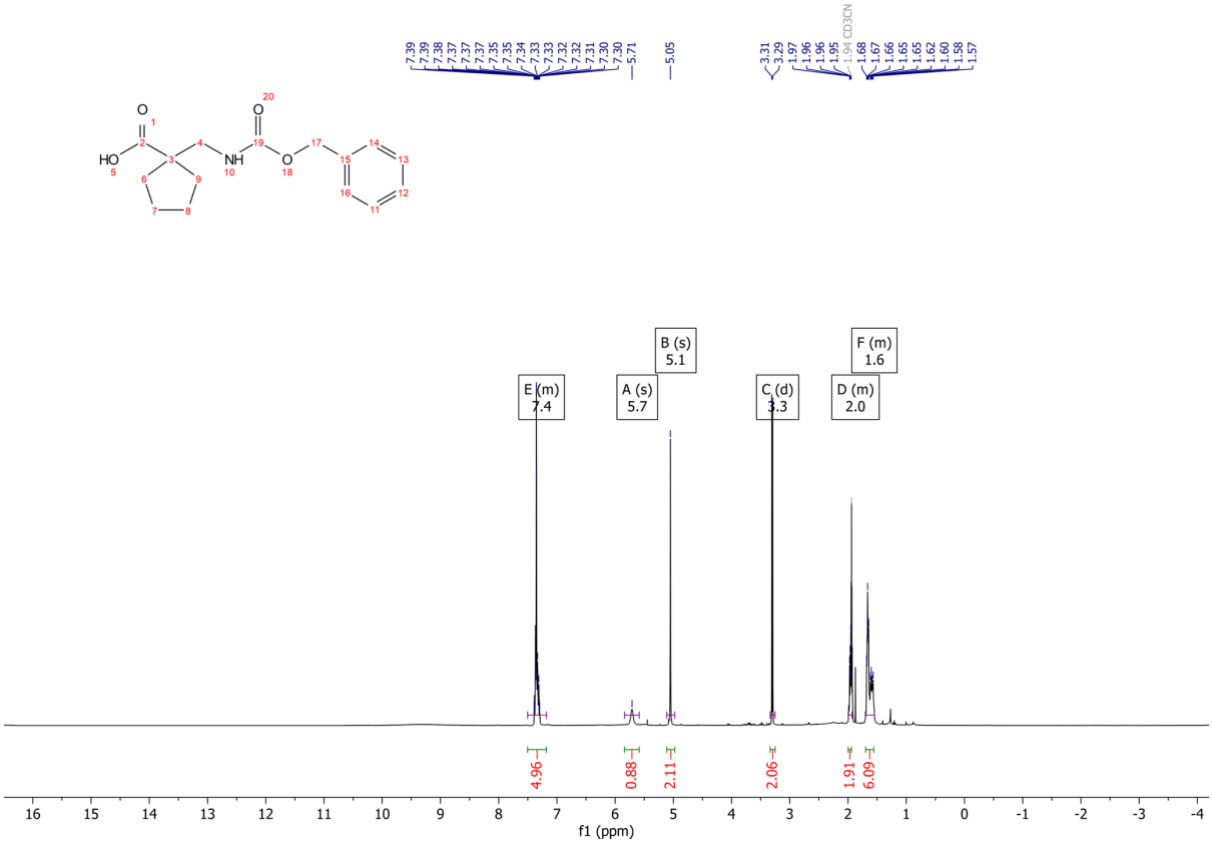


21 ^{1}H NMR (600 MHz, CD_3CN)

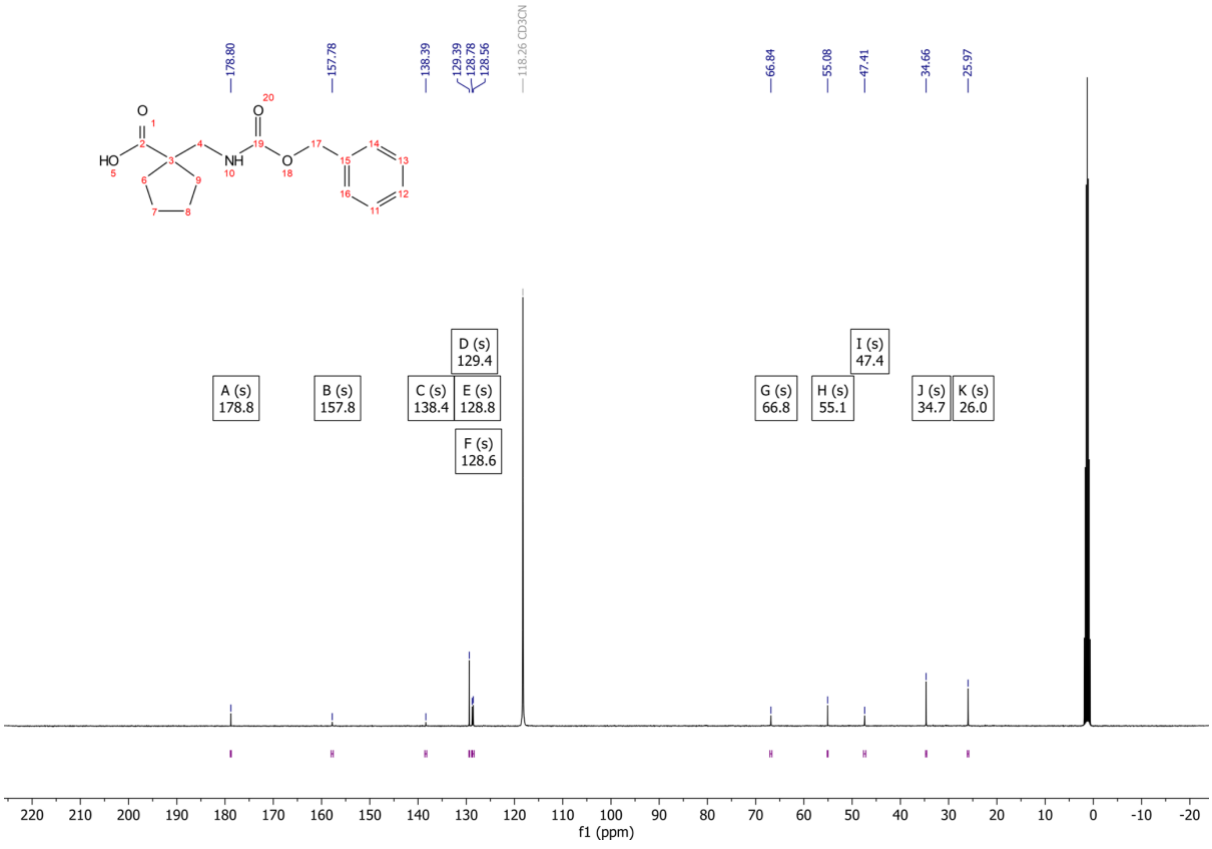
21 ^{13}C NMR (101 MHz, CD_3CN)



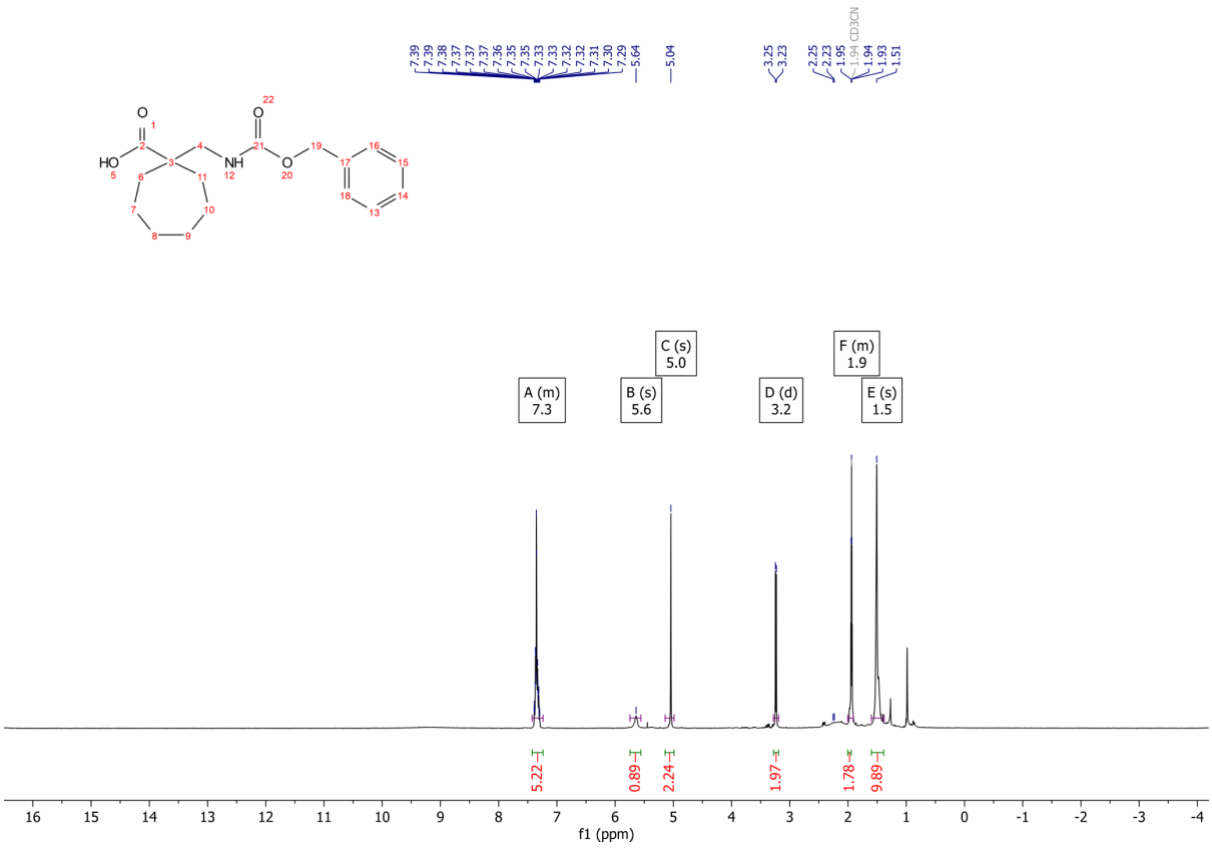
22 ^{1}H NMR (400 MHz, CD_3CN)



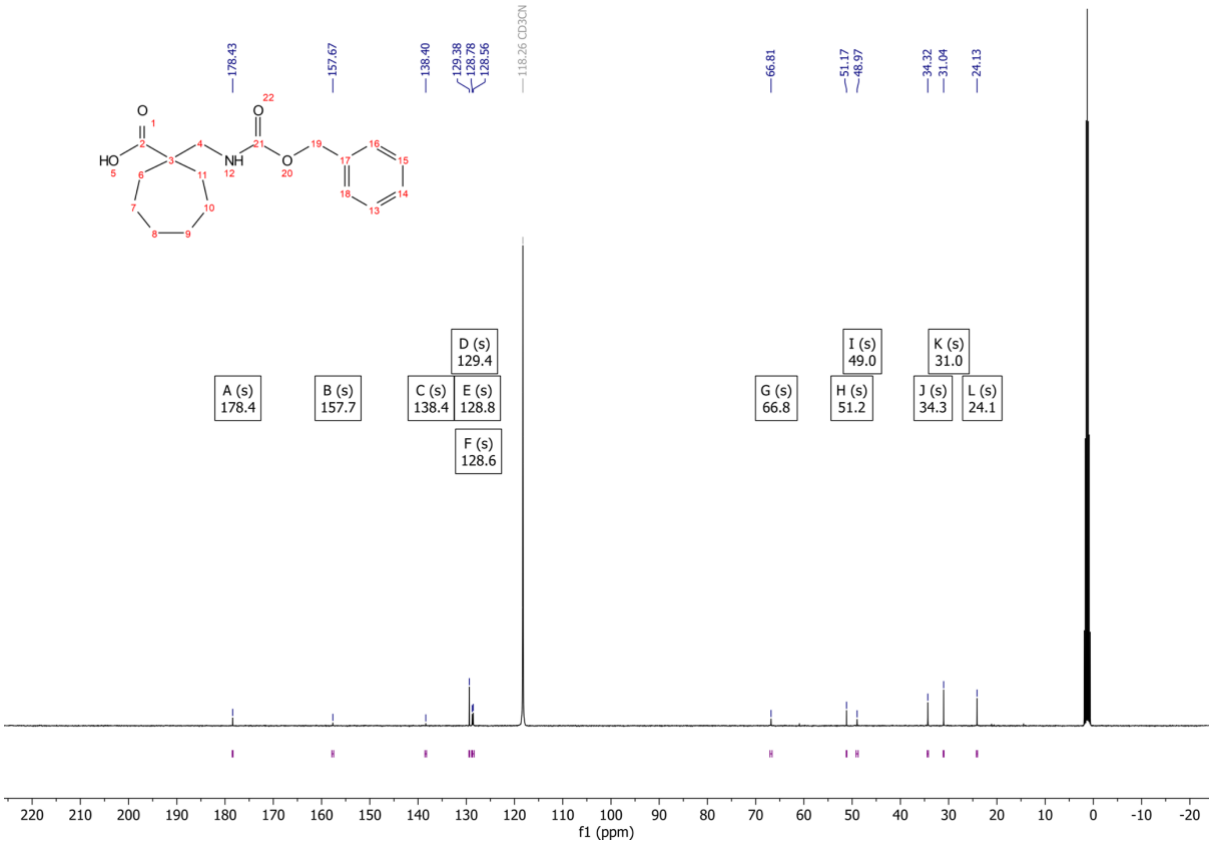
22 ^{13}C NMR (101 MHz, CD_3CN)



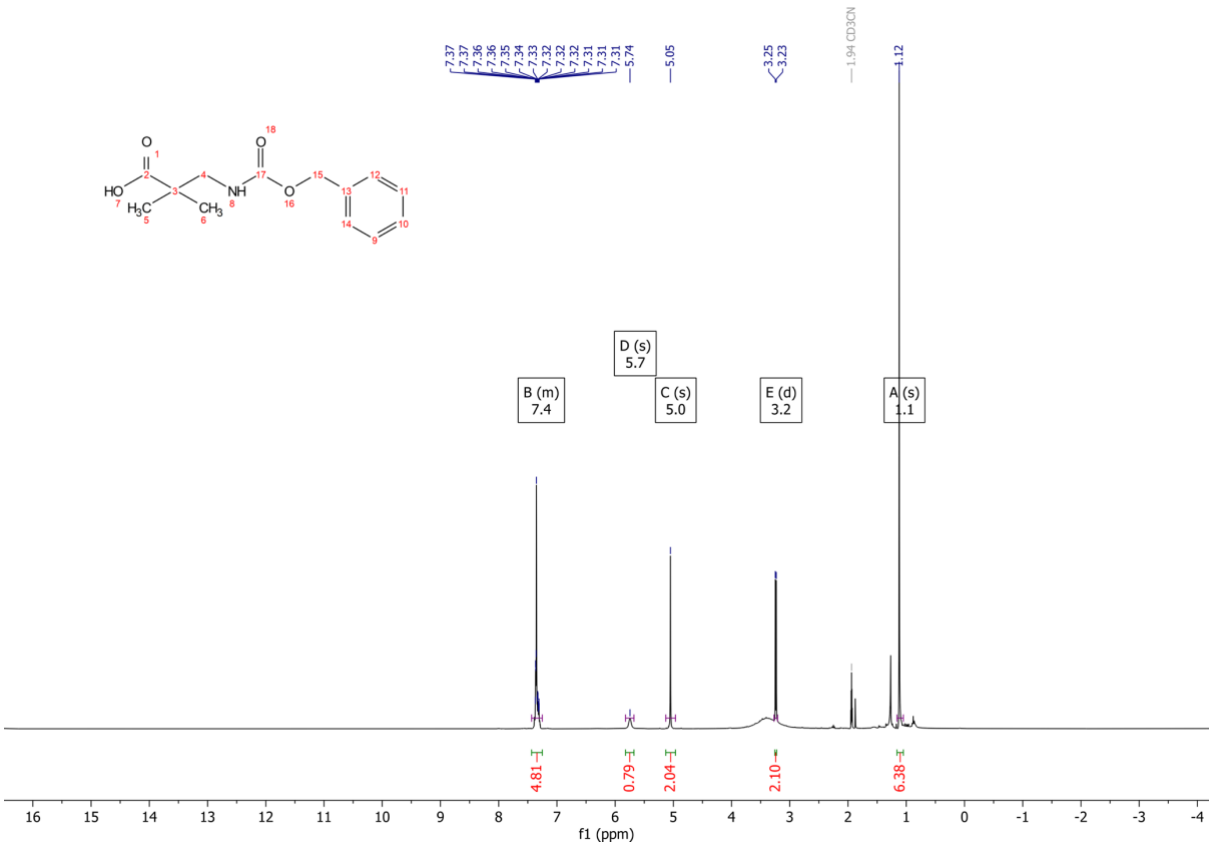
23 ^{1}H NMR (400 MHz, CD_3CN)



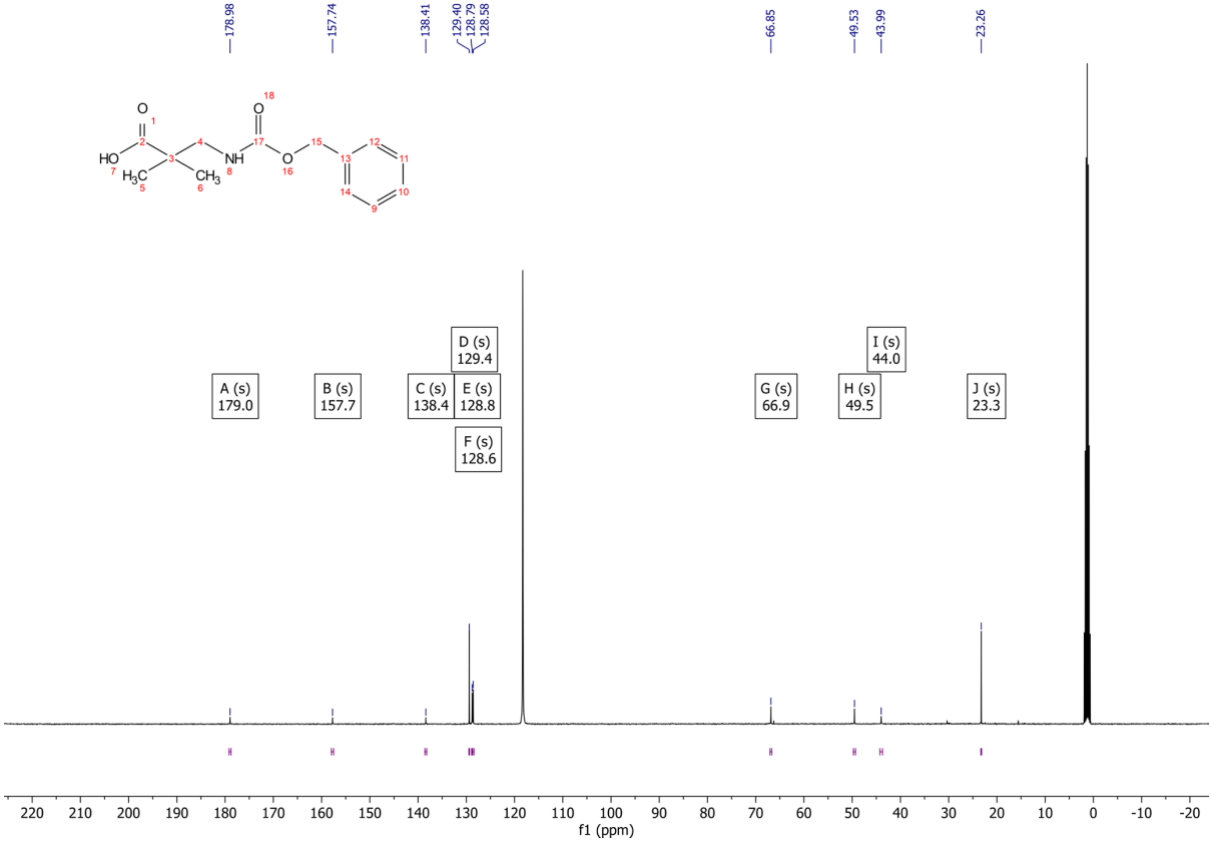
23 ^{13}C NMR (101 MHz, CD_3CN)



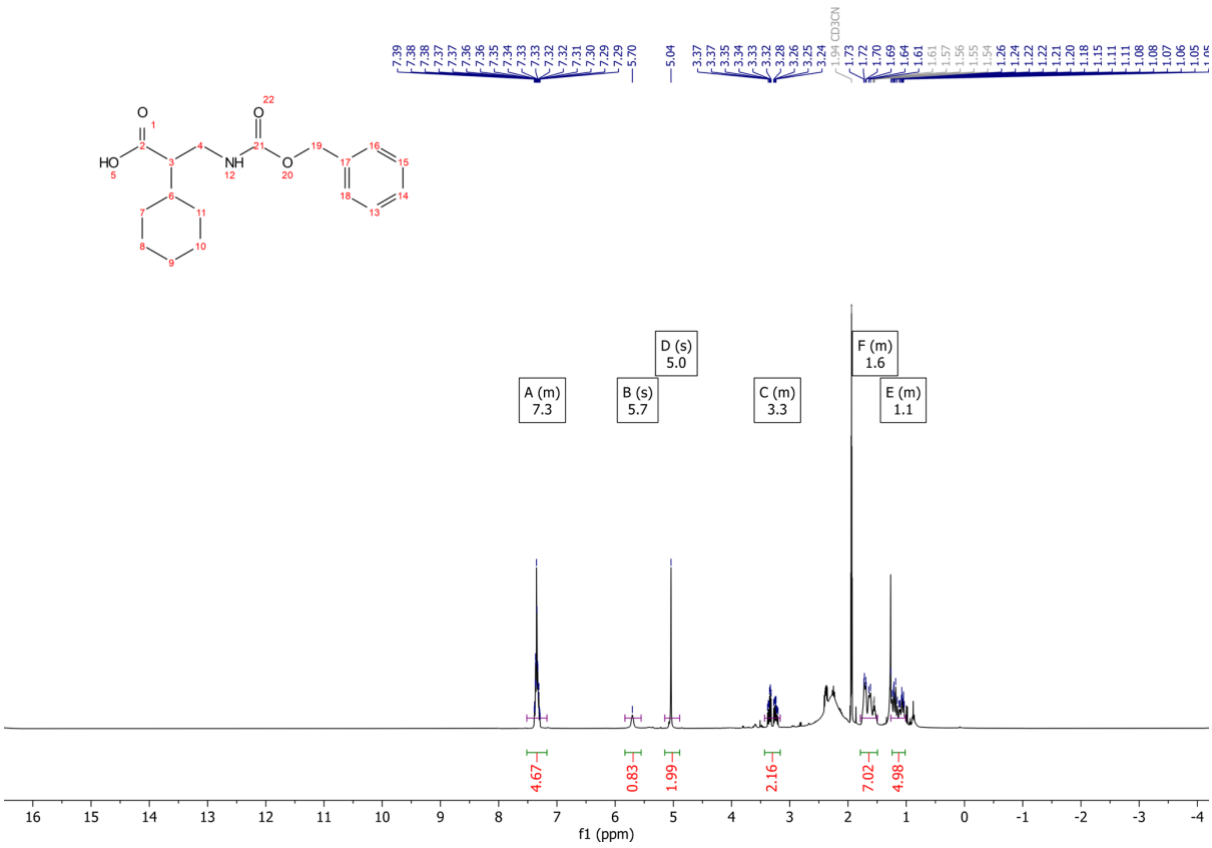
24 ^{1}H NMR (400 MHz, CD_3CN)



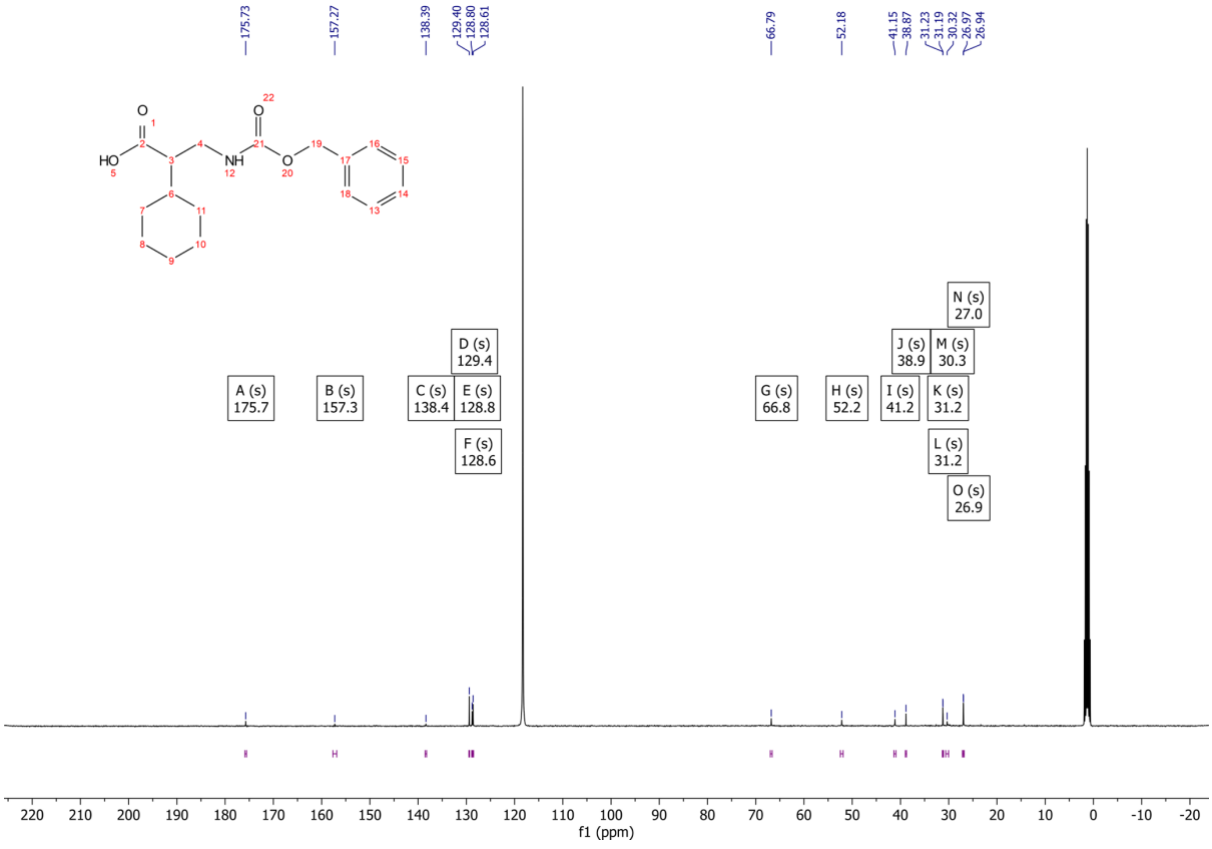
24 ^{13}C NMR (101 MHz, CD_3CN)



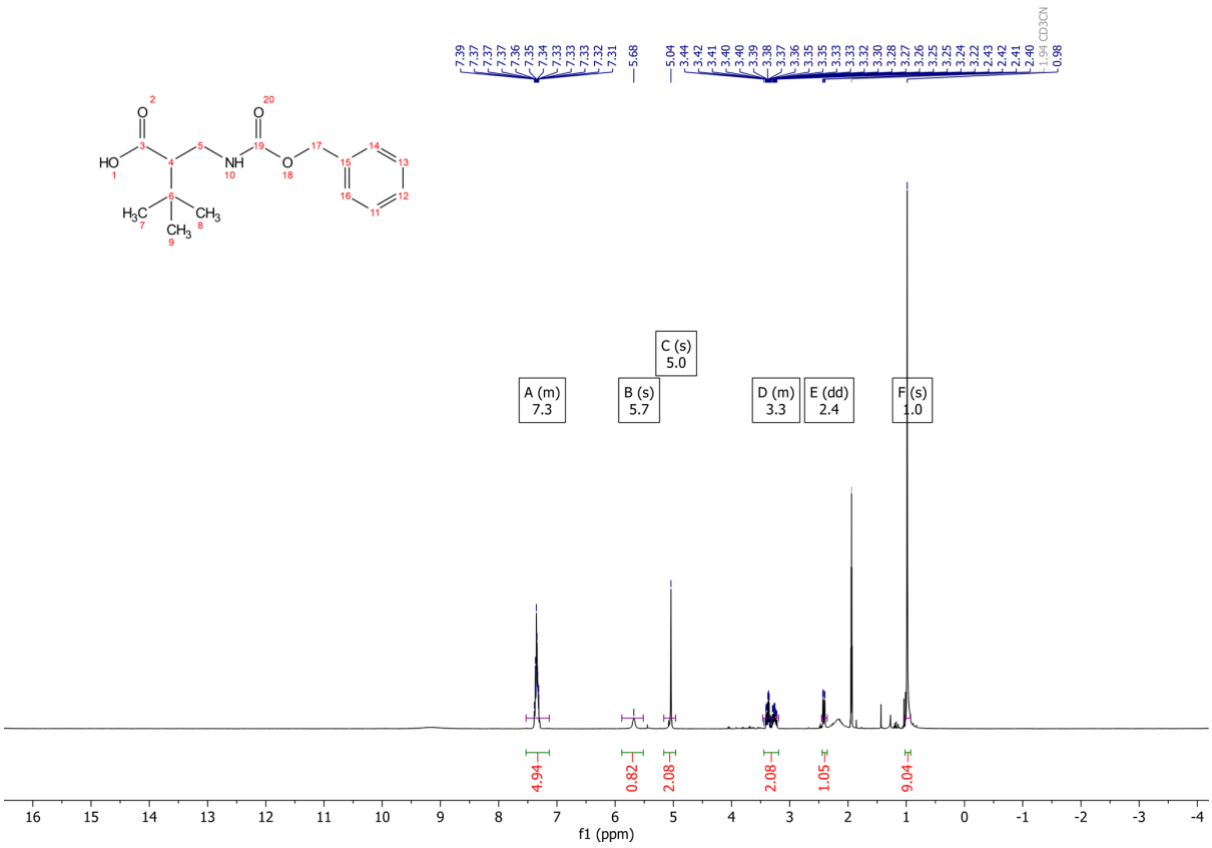
25 ^{1}H NMR (400 MHz, CD_3CN)



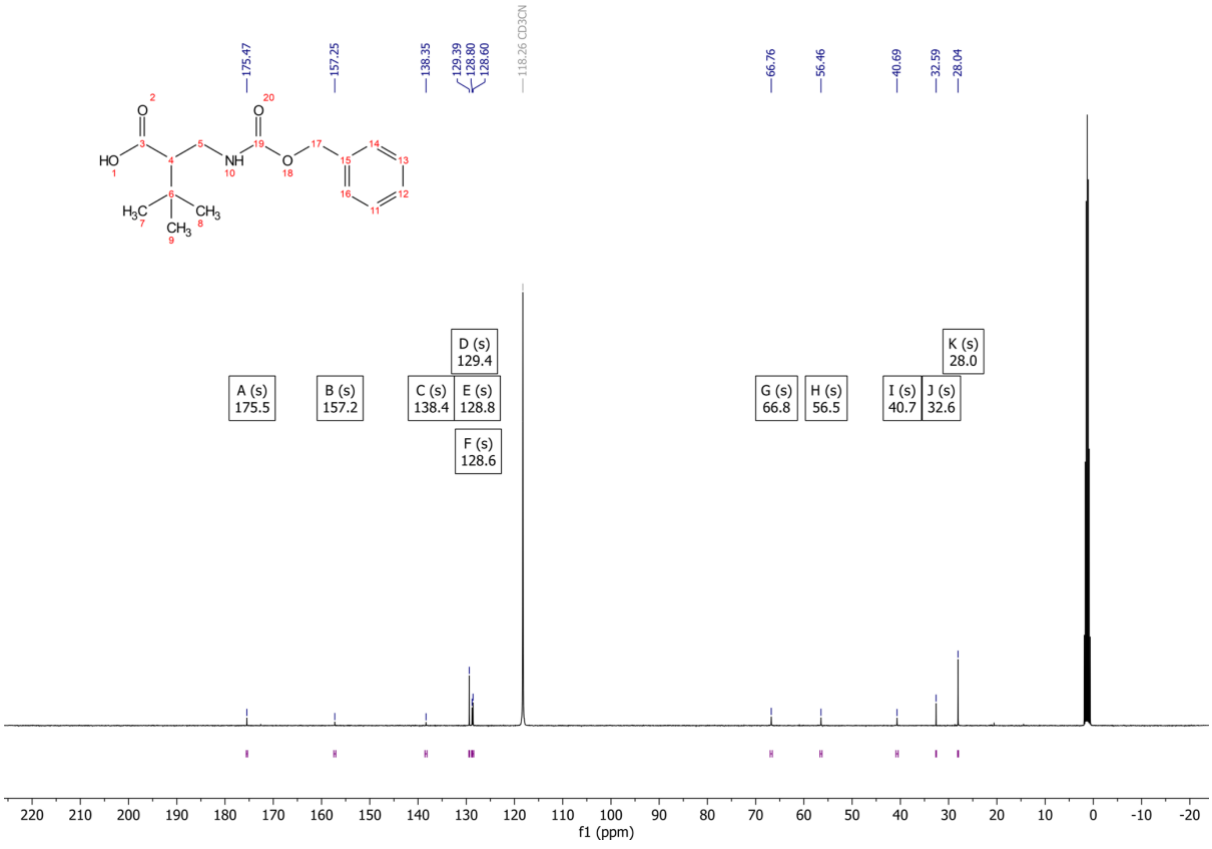
25 ^{13}C NMR (101 MHz, CD_3CN)



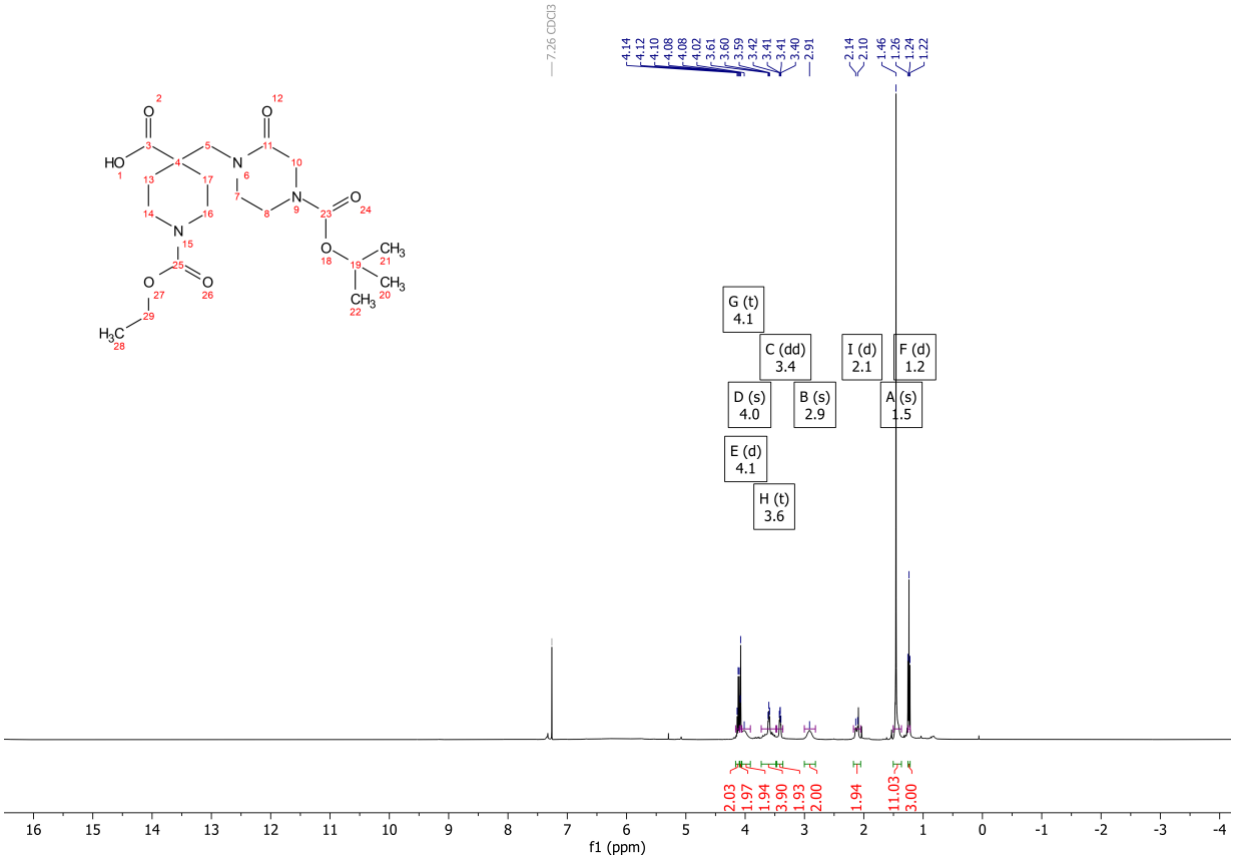
26 ^{1}H NMR (400 MHz, CD_3CN)



26 ^{13}C NMR (101 MHz, CD_3CN)



27 ^{1}H NMR (400 MHz, $CDCl_3$)



27 ^{13}C NMR (101 MHz, $CDCl_3$)