

The Efficacy of Sodium Hexafluoroaluminate (Cryolite) for Direct Amidation of Carboxylic Acids

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Experimental Section:

General Information:

Unless otherwise noted, all additions were carried out under open air conditions. ^{11}B , ^{13}C and ^1H NMR spectra were recorded at room temperature, on a Bruker 300 MHz or Bruker 400 MHz NMR spectrophotometer as stated. Data are reported as: δ value, multiplicity (*s*=singlet, *d*=doublet, *t*=triplet, *q*=quartet, *p*=pentet, *h*=hextet, *m*=multiplet, *br*=broad) and integration. All solvents for routine isolation of products were reagent-grade. Amines, carboxylic acids, and catalysts were purchased from Sigma-Aldrich and/or Oakwood Chemicals and used without further purification. All reactions requiring heat were brought to temperature using an oil bath and heated stir plate. The cryolite powder prior to the reaction, and the cryolite isolated post-reaction were measured using a XRDynamic 500 diffractometer from Anton Paar using Cu K α ($\lambda = 1.5406 \text{ \AA}$). The samples for XRD measurements were mounted on the fixed sample stage and scanned from 5° to 70° with a step size of 0.01° and a time per step of 20 s.

General procedure for the preparation of amides:

A 100 ml round bottom flask containing a magnetic stir-bar was charged with carboxylic acid (6 mmol, 1.2 eq) and xylenes (5 mL, 1 M with respect to amine). To this stirring mixture, cryolite ((0.5 mmol, 0.1 eq.) or (2.5 mmol, 0.5 eq.)) was introduced followed by addition of the respective amine (5 mmol, 1 eq.). A reflux condenser was attached to the flask and the reaction mixture was brought to reflux, using an oil bath. After completion (24 hours) the reaction mixture was cooled down, diluted with methanol and condensed via rotary evaporation. The crude mixture was diluted with dichloromethane (15mL) and transferred to a separatory funnel. The mixture was first washed with 3M HCl (2 x 10 mL) and then the separated organic layer was further washed with 3M sodium hydroxide solution (2 x 10 mL). The resultant organic layer was dried with sodium sulfate, filtered through cotton, and condensed via rotary evaporation following by drying *in vacuo* for 12 h.

Procedure for the preparation of esters using toluene as solvent:

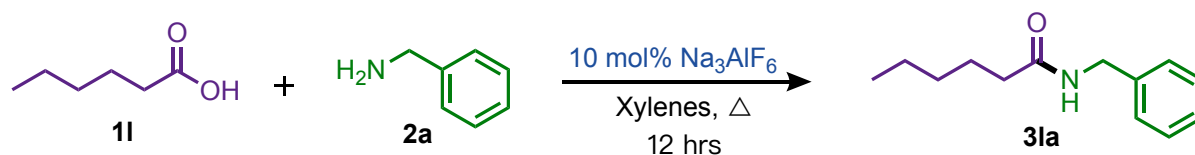
A 100 ml round bottom flask containing a magnetic stir-bar was charged with carboxylic acid (6 mmol, 1.2 eq), toluene (5 mL, 1 M with respect to alcohol) and cryolite (5 mmol, 1 equiv.). To this stirring mixture, alcohol (5 mmol, 1 eq.) was introduced, and the heterogeneous mixture was then brought to reflux, using an oil bath. After completion (24 hours) the reaction mixture was cooled down, diluted with methanol and condensed via rotary evaporation. The crude mixture was diluted with dichloromethane (15mL) and transferred to a separatory funnel. The mixture was first washed with 3M HCl (2 x 10 mL) and then the separated organic layer was further washed with 3M sodium

hydroxide solution (2 x 10 mL). The resultant organic layer was dried with sodium sulfate, filtered through cotton, and condensed via rotary evaporation following by drying *in vacuo* for 12 h.

Procedure for the preparation of esters using alcohol as solvent:

A 100 ml round bottom flask containing a magnetic stir-bar was charged with carboxylic acid (5 mmol, 1 eq), alcohol (5 mL, 1 M with respect to carboxylic acid) and cryolite (5 mmol, 1 equiv.). This heterogeneous mixture was then brought to reflux, using an oil bath. After completion (24 hours) the reaction mixture was cooled down, diluted with hexanes and condensed via rotary evaporation. The crude mixture was diluted with dichloromethane (15mL) and transferred to a separatory funnel. The mixture was first washed with 3M HCl (2 x 10 mL) and then the separated organic layer was further washed with 3M sodium hydroxide solution (2 x 10 mL) (*Note: if the organic layer appears to not be clear after the base wash, another acid wash is recommended!*). The resultant organic layer was dried with sodium sulfate, filtered through cotton, and condensed via rotary evaporation following by drying *in vacuo* for 12 h.

Catalyst Recyclability Experiment: SI Table 1



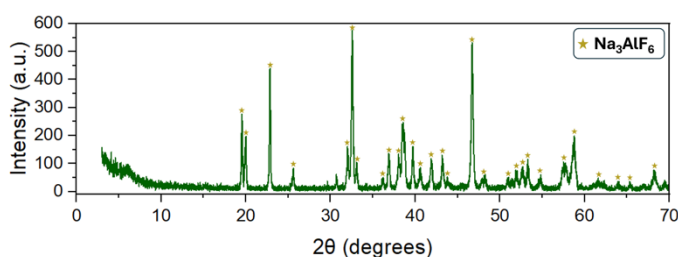
Number of Cycles:	Overall Yield (Isolated)
1 st Cycle (Fresh)	97%
2 nd Cycle	94%
3 rd Cycle	86%
4 th Cycle	85%
5 th Cycle	80%

Note:

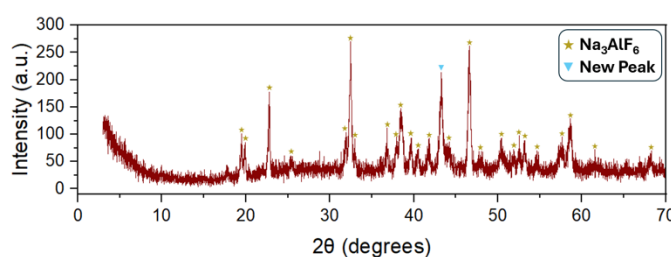
All recycling experiments were carried in one pot, i.e.: once the reaction time was completed, fresh equivalents of carboxylic acid and amine were added to the same reaction flask without altering the amount of cryolite.

XRD Data:

Pre-Reaction Cryolite:



Post-Reaction Cryolite:

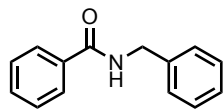


Note: The new observed peak at 43° may have risen due to the product mass from the reaction.

Pre-reaction cryolite XRD is in agreement with the previous report.¹

Characterization of Amide Products:

N-benzylbenzamide (1)



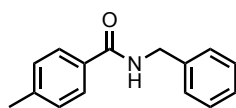
Yield 77%, Mass 0.81g, White Solid.

^1H NMR (300 MHz, CDCl_3): δ 7.85 – 7.75 (m, 2H), 7.55 – 7.28 (m, 8H), 6.42 (s, 1H), 4.66 (d, J = 5.7 Hz, 2H).

^{13}C { ^1H } NMR (75 MHz, CDCl_3) δ 167.4, 138.2, 134.4, 131.6, 128.8, 128.6, 127.9, 127.6, 127.0, 44.1

Characterisation is in agreement with previous reports of this compound. ²

N-benzyl-4-methylbenzamide (2)



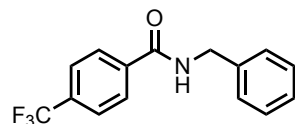
Yield 76%, Mass 0.86g, Pale Orange Solid

^1H NMR (300 MHz, CDCl_3) δ 7.75 – 7.63 (m, 2H), 7.41 – 7.16 (m, 7H), 6.41 (s, 1H), 4.63 (d, J = 5.7 Hz, 2H), 2.39 (s, 3H).

^{13}C { ^1H } NMR (75 MHz, CDCl_3) δ 167.3, 142.0, 138.3, 131.5, 129.3, 128.8, 127.9, 127.6, 127.0, 44.1, 21.4.

Characterisation is in agreement with previous reports of this compound. ²

N-benzyl-4-(trifluoromethyl)benzamide (3)



Yield 61%, Mass 0.85g, White Solid

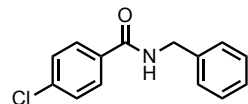
^1H NMR (300 MHz, CDCl_3) δ 7.90 (dt, J = 8.0, 0.8 Hz, 2H), 7.73 – 7.65 (m, 2H), 7.39 – 7.28 (m, 5H), 6.48 (s, 1H), 4.66 (d, J = 5.6 Hz, 2H).

^{13}C { ^1H } NMR (75 MHz, CDCl_3) δ 166.1, 137.7, 128.9, 128.0, 127.9, 127.5, 125.7 (d, J = 3.4 Hz), 44.4

^{19}F NMR (282 MHz, CDCl_3) δ -62.97.

Characterisation is in agreement with previous reports of this compound. ²

N-benzyl-4-chlorobenzamide (4)



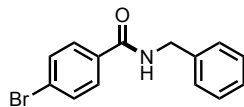
Yield 74%, Mass 0.91g, White Solid

^1H NMR (300 MHz, CDCl_3) δ 7.72 (d, J = 8.7 Hz, 2H), 7.45 – 7.23 (m, 7H), 6.50 (s, 1H), 4.62 (d, J = 5.7 Hz, 2H).

^{13}C { ^1H } NMR (75 MHz, CDCl_3) δ 166.3, 138.0, 137.8, 132.7, 128.8, 128.4, 127.9, 127.7, 44.2

Characterisation is in agreement with previous reports of this compound. ²

N-benzyl-4-bromobenzamide (5)



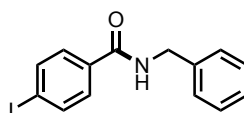
Yield 70%, Mass 1.01g, Off-white Solid.

¹H NMR (300 MHz, CDCl₃) δ 7.65 (*d*, *J* = 8.6 Hz, 2H), 7.55 (*d*, *J* = 8.5 Hz, 2H), 7.41 – 7.29 (*m*, 5H), 6.49 (*s*, 1H), 4.61 (*d*, *J* = 5.6 Hz, 2H).

¹³C {¹H} NMR (75 MHz, CDCl₃) δ 166.4, 137.9, 133.2, 131.8, 128.9, 128.6, 128.0, 127.8, 126.3, 44.2

*Characterisation is in agreement with previous reports of this compound.*²

N-benzyl-4-iodobenzamide (6)



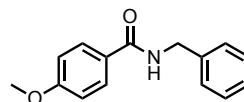
Yield 70%, Mass 1.17g, Off-white Solid.

¹H NMR (300 MHz, DMSO) δ 9.22 (*t*, *J* = 6.0 Hz, 1H), 7.98 (*d*, *J* = 8.4 Hz, 2H), 7.80 (*d*, *J* = 8.5 Hz, 2H), 7.51 – 7.29 (*m*, 5H), 4.59 (*d*, *J* = 6.0 Hz, 2H).

¹³C {¹H} NMR (75 MHz, DMSO) δ 166.0, 140.0, 137.7, 134.2, 129.7, 128.8, 127.7, 127.2, 99.3, 43.1

*Characterisation is in agreement with previous reports of this compound.*²

N-benzyl-4-methoxybenzamide (7)



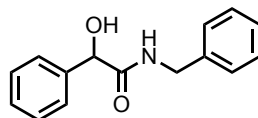
Yield 64%, Mass 0.76g, White Solid.

¹H NMR (300 MHz, CDCl₃): δ 7.76 (*d*, *J* = 8.8 Hz, 2H), 7.39 – 7.23 (*m*, 5H), 6.96 – 6.86 (*m*, 2H), 6.38 (*s*, 1H), 4.63 (*d*, *J* = 5.6 Hz, 2H), 3.84 (*s*, 3H)

¹³C {¹H} NMR (75 MHz, CDCl₃): δ 166.9, 162.2, 138.4, 128.8, 127.9, 127.6, 126.7, 113.8, 55.4, 44.1

*Characterisation is in agreement with previous reports of this compound.*³

N-benzyl-2-hydroxy-2-phenylacetamide (8)



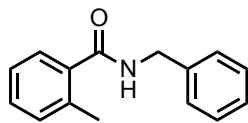
Yield 93%, Mass 1.12g, Yellow Solid.

¹H NMR (300 MHz, CDCl₃) δ 7.45 – 7.24 (*m*, 8H), 7.18 (*dd*, *J* = 7.7, 1.9 Hz, 2H), 6.53 (*s*, 1H), 5.05 (*d*, *J* = 2.5 Hz, 1H), 4.43 (*dd*, *J* = 5.9, 4.2 Hz, 2H), 3.69 (*d*, *J* = 3.4 Hz, 1H).

¹³C {¹H} NMR (75 MHz, CDCl₃) δ 172.1, 139.4, 137.7, 128.9, 128.7, 127.6, 126.9, 74.3, 43.5

*Characterisation is in agreement with previous reports of this compound.*⁴

N-benzyl-2-methylbenzamide (9)



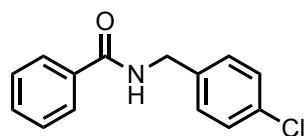
Yield 62%, Mass 0.70g, Brown Solid.

$^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.44 – 7.11 (*m*, 9H), 6.06 (*s*, 1H), 4.62 (*d*, $J = 5.7$ Hz, 2H), 2.46 (*s*, 3H).

^{13}C $\{^1\text{H}\}$ NMR (75 MHz, CDCl_3) δ 169.9, 138.2, 131.0, 130.0, 128.8, 127.9, 127.6, 126.7, 125.7, 43.9, 19.9.

Characterisation is in agreement with previous reports of this compound. ⁴

N-(4-chlorobenzyl)benzamide (10)



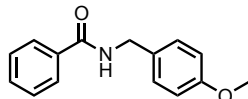
Yield 78%, Mass 0.96g, White Solid.

$^1\text{H NMR}$ (300 MHz, CDCl_3): δ 7.84 – 7.74 (*m*, 2H), 7.57 – 7.38 (*m*, 3H), 7.35 – 7.24 (*m*, 4H), 6.52 (*s*, 1H), 4.60 (*d*, $J = 5.8$ Hz, 2H).

^{13}C $\{^1\text{H}\}$ NMR (75 MHz, CDCl_3) δ 167.4, 136.8, 134.2, 133.4, 131.7, 129.2, 128.9, 128.7, 127.0, 43.4

Characterisation is in agreement with previous reports of this compound. ⁵

N-(4-methoxybenzyl)benzamide (11)



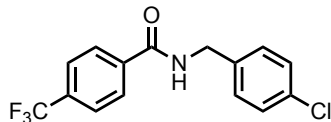
Yield 73%, Mass 0.88g, Brown Solid.

$^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.81 – 7.74 (*m*, 2H), 7.54 – 7.35 (*m*, 3H), 7.31 – 7.23 (*m*, 2H), 6.92 – 6.84 (*m*, 2H), 6.46 (*s*, 1H), 4.56 (*d*, $J = 5.6$ Hz, 2H), 3.79 (*s*, 3H).

^{13}C $\{^1\text{H}\}$ NMR (75 MHz, CDCl_3) δ 167.3, 159.1, 134.5, 131.5, 130.3, 129.3, 128.6, 127.0, 114.2, 55.3, 43.6.

Characterisation is in agreement with previous reports of this compound. ⁶

N-(4-chlorobenzyl)-4-(trifluoromethyl)benzamide (12)



Yield 78%, Mass 1.23g, White Solid.

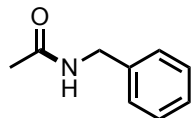
$^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.89 (ddt, $J = 7.8, 1.6, 0.9$ Hz, 2H), 7.77 – 7.64 (*m*, 2H), 7.39 – 7.23 (*m*, 4H), 6.48 (*s*, 1H), 4.62 (*d*, $J = 5.8$ Hz, 2H).

^{13}C $\{^1\text{H}\}$ NMR (75 MHz, CDCl_3) δ 166.1, 136.3, 133.7, 129.3, 129.0, 127.5, 125.7, 43.6

$^{19}\text{F NMR}$ (282 MHz, CDCl_3) δ -62.99.

Characterisation is in agreement with previous reports of this compound. ⁷

N-benzylacetamide (13)



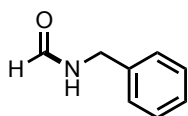
Yield 48%, Mass 0.36g, Brown Solid.

¹H NMR (300 MHz, CDCl₃) δ 7.32 – 7.11 (*m*, 5H), 6.08 (*s*, 1H), 4.31 (*d*, *J* = 5.7 Hz, 2H), 1.90 (*s*, 3H).

¹³C {¹H} NMR (75 MHz, CDCl₃) δ 170.1, 138.3, 128.7, 127.8, 127.5, 43.7, 23.2

Characterisation is in agreement with previous reports of this compound.⁴

N-benzylformamide (14)



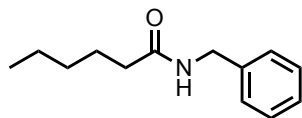
Yield 51%, Mass 0.39g, Off-White Solid.

¹H NMR (300 MHz, CDCl₃) δ 8.16 – 8.08 (*m*, 1H), 7.34 – 7.13 (*m*, 5H), 6.30 – 6.14 (*m*, 1H), 4.36 (*d*, *J* = 5.9 Hz, 2H).

¹³C {¹H} NMR (75 MHz, CDCl₃) δ 161.2, 137.7, 128.8, 127.8, 127.0, 42.1

Characterisation is in agreement with previous reports of this compound.⁴

N-benzylhexanamide (15)



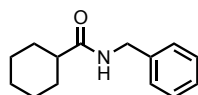
Yield 97%, Mass 1.00g, Yellow Solid.

¹H NMR (300 MHz, CDCl₃): δ 7.28 – 7.12 (*m*, 5H), 6.08 (*s*, 1H), 4.31 (*d*, *J* = 5.7 Hz, 2H), 2.10 (*t*, *J* = 7.6 Hz, 2H), 1.55 (*dq*, *J* = 9.1, 7.3 Hz, 2H), 1.35 – 1.08 (*m*, 4H), 0.88 – 0.76 (*m*, 3H).

¹³C {¹H} NMR (75 MHz, CDCl₃) δ 173.0, 138.4, 128.7, 127.8, 127.5, 44.6, 36.8, 31.5, 25.5, 22.4, 13.9.

Characterisation is in agreement with previous reports of this compound.⁸

N-benzylcyclohexanecarboxamide (16)



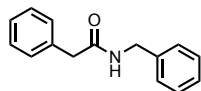
Yield 86%, Mass 0.93g, Brown Solid.

¹H NMR (300 MHz, CDCl₃): δ 7.32 – 7.13 (*m*, 5H), 5.68 (*s*, 1H), 4.35 (*d*, *J* = 5.6 Hz, 2H), 2.03 (*tt*, *J* = 11.7, 3.5 Hz, 1H), 1.88 – 1.54 (*m*, 5H), 1.39 (*qd*, *J* = 11.9, 3.1 Hz, 2H), 1.29 – 1.06 (*m*, 3H).

¹³C {¹H} NMR (75 MHz, CDCl₃): δ 175.9, 138.6, 128.7, 127.7, 127.5, 45.6, 43.4, 29.7, 25.8

Characterisation is in agreement with previous reports of this compound.⁹

N-benzyl-2-phenylacetamide (17)



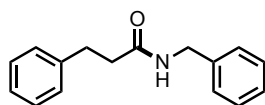
Yield 81%, Mass 0.92g, White Solid.

^1H NMR (300 MHz, CDCl_3): δ 7.38 – 7.15 (m, 8H), 7.15 – 7.06 (m, 2H), 5.63 (s, 1H), 4.34 (d, J = 5.8 Hz, 2H), 3.55 (s, 2H).

^{13}C { ^1H } NMR (75 MHz, CDCl_3): δ 170.9, 138.1, 134.9, 129.5, 129.1, 128.7, 127.5, 127.4, 43.9, 43.6

Characterisation is in agreement with previous reports of this compound.²

N-benzyl-3-phenylpropanamide (18)



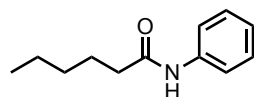
Yield 68%, Mass 0.82g, Brown Solid.

^1H NMR (300 MHz, CDCl_3) δ 7.29 – 7.01 (m, 10H), 5.52 (s, 1H), 4.33 (d, J = 5.7 Hz, 2H), 2.93 (t, J = 7.6 Hz, 2H), 2.45 (dd, J = 8.3, 7.0 Hz, 2H).

^{13}C { ^1H } NMR (75 MHz, CDCl_3) δ 171.99, 140.81, 138.22, 128.66, 128.57, 128.43, 127.73, 127.44, 126.27, 43.56, 38.45, 31.75.

Characterisation is in agreement with previous reports of this compound.²

N-phenylhexanamide (19)



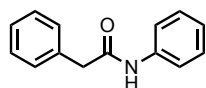
Yield 79%, Mass 0.76g, Dark Brown Solid.

^1H NMR (300 MHz, CDCl_3) δ 7.52 (d, J = 7.9 Hz, 2H), 7.37 – 7.28 (m, 2H), 7.23 (s, 1H), 7.10 (t, J = 7.4 Hz, 1H), 2.35 (t, J = 7.6 Hz, 2H), 1.74 (t, J = 7.5 Hz, 2H), 1.36 (dp, J = 7.6, 3.9 Hz, 4H), 0.97 – 0.85 (m, 3H).

^{13}C { ^1H } NMR (75 MHz, CDCl_3) δ 171.4, 138.0, 129.0, 124.2, 119.8, 37.8, 31.4, 25.3, 22.4, 13.9.

Characterisation is in agreement with previous reports of this compound.⁴

N,2-diphenylacetamide (20)



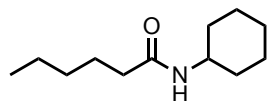
Yield 82%, Mass 0.87g, Light Brown Solid.

^1H NMR (300 MHz, CDCl_3) δ 7.47 – 7.21 (m, 9H), 7.17 – 7.01 (m, 2H), 3.73 (s, 2H).

^{13}C { ^1H } NMR (75 MHz, CDCl_3) δ 169.1, 137.6, 134.4, 129.5, 129.3, 128.9, 127.7, 124.5, 119.8, 44.9.

Characterisation is in agreement with previous reports of this compound.⁴

N-cyclohexylhexanamide (21)



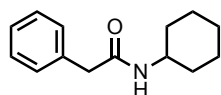
Yield 90%, Mass 0.88g, Dark Brown Solid.

^1H NMR (300 MHz, CDCl_3) δ 5.30 (s, 1H), 3.77 (tdt, J = 10.6, 8.0, 4.0 Hz, 1H), 2.19 – 2.07 (m, 2H), 1.98 – 1.85 (m, 2H), 1.77 – 1.55 (m, 5H), 1.46 – 1.25 (m, 6H), 1.24 – 1.01 (m, 3H), 0.95 – 0.84 (m, 3H).

^{13}C $\{^1\text{H}\}$ NMR (75 MHz, CDCl_3) δ 172.2, 48.0, 37.1, 33.3, 31.5, 25.6, 24.9, 22.4, 14.0.

Characterisation is in agreement with previous reports of this compound. ¹⁰

N-cyclohexyl-2-phenylacetamide (22)



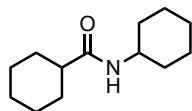
Yield 83%, Mass 0.90g, Brown Solid.

^1H NMR (300 MHz, CDCl_3) δ 7.45 – 7.19 (m, 5H), 5.25 (s, 1H), 3.87 – 3.68 (m, 1H), 3.54 (s, 2H), 1.93 – 1.75 (m, 2H), 1.59 (tt, J = 13.1, 4.3 Hz, 3H), 1.45 – 1.22 (m, 2H), 1.05 (tdt, J = 23.5, 10.2, 4.6 Hz, 3H).

^{13}C $\{^1\text{H}\}$ NMR (75 MHz, CDCl_3) δ 170.0, 135.2, 129.4, 129.0, 127.3, 48.2, 44.0, 32.9, 25.5, 24.7.

Characterisation is in agreement with previous reports of this compound. ¹¹

N-cyclohexylcyclohexanecarboxamide (23)



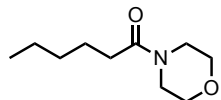
Yield 74%, Mass 0.77g, Brown Solid.

^1H NMR (300 MHz, CDCl_3) δ 3.76 (tdt, J = 10.6, 8.1, 3.9 Hz, 1H), 2.02 (tt, J = 11.8, 3.4 Hz, 1H), 1.95 – 1.53 (m, 10H), 1.51 – 1.01 (m, 10H).

^{13}C $\{^1\text{H}\}$ NMR (75 MHz, CDCl_3) δ 175.1, 47.7, 45.7, 33.3, 29.8, 25.8, 25.6, 24.9.

Characterisation is in agreement with previous reports of this compound. ⁵

1-morpholinohexan-1-one (24)



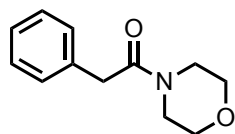
Yield 78%, Mass 0.72g, Orange Liquid.

^1H NMR (300 MHz, CDCl_3) δ 3.73 – 3.38 (m, 8H), 2.37 – 2.26 (m, 2H), 1.71 – 1.55 (m, 2H), 1.33 (dt, J = 7.3, 3.8 Hz, 4H), 0.99 – 0.84 (m, 3H).

^{13}C $\{^1\text{H}\}$ NMR (75 MHz, CDCl_3) δ 171.9, 66.8, 46.1, 33.1, 31.6, 25.0, 22.5, 14.0.

Characterisation is in agreement with previous reports of this compound. ⁵

1-morpholino-2-phenylethan-1-one (25)



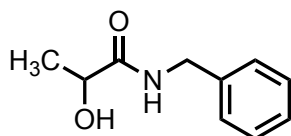
Yield 81%, Mass 0.83g, Dark Brown Solid.

^1H NMR (300 MHz, CDCl_3) δ 7.38 – 7.30 (*m*, 2H), 7.30 – 7.22 (*m*, 3H), 3.74 (*s*, 2H), 3.65 (*s*, 4H), 3.53 – 3.41 (*m*, 4H).

^{13}C { ^1H } NMR (75 MHz, CDCl_3) δ 169.6, 134.8, 128.8, 128.5, 126.9, 66.8, 66.5, 46.5, 42.1, 40.8

Characterisation is in agreement with previous reports of this compound.¹²

N-benzyl-2-hydroxypropanamide (26)



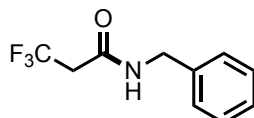
Yield 68%, Mass 0.61g, White Solid.

^1H NMR (300 MHz, CDCl_3) δ 7.39 – 7.23 (*m*, 5H), 6.81 (*s*, 1H), 4.46 (*d*, $J = 5.9$ Hz, 2H), 4.29 (*dd*, $J = 6.9$, 3.1 Hz, 1H), 2.63 (*s*, 1H), 1.47 (*d*, $J = 6.8$ Hz, 3H).

^{13}C { ^1H } NMR (75 MHz, CDCl_3) δ 174.1, 138.0, 128.8, 127.8, 127.6, 68.5, 43.2, 21.4.

Characterisation is in agreement with previous reports of this compound¹³

N-benzyl-3,3,3-trifluoropropanamide (27)



Yield 69%, Mass 0.75g, Brown Solid.

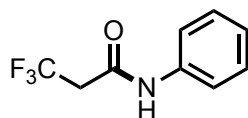
^1H NMR (300 MHz, CDCl_3) δ 7.34 – 7.13 (*m*, 5H), 6.09 (*s*, 1H), 4.38 (*dd*, $J = 13.2$, 5.7 Hz, 2H), 3.03 (*q*, $J = 10.6$ Hz, 2H).

^{13}C { ^1H } NMR (75 MHz, CDCl_3) δ 162.6, 137.3, 128.8, 127.8, 125.9, 44.0, 41.4.

^{19}F NMR (282 MHz, CDCl_3) δ -62.91 (*t*, $J = 10.6$ Hz).

Characterisation is in agreement with previous reports of this compound¹⁴

N-phenyl-3,3,3-trifluoropropanamide (28)



Yield 59%, Mass 0.60g, Brown Solid.

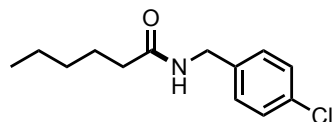
^1H NMR (300 MHz, CDCl_3) δ 7.81 (*s*, 1H), 7.54 – 7.44 (*m*, 2H), 7.32 (*dd*, $J = 8.7$, 7.1 Hz, 2H), 7.21 – 7.10 (*m*, 1H), 3.22 (*q*, $J = 10.4$ Hz, 2H).

^{13}C $\{^1\text{H}\}$ NMR (75 MHz, CDCl_3) δ 161.0, 136.9, 129.1, 125.3, 120.5, 42.5 (*q*, J = 29.2 Hz).

^{19}F NMR (282 MHz, CDCl_3) δ -62.84 (*t*, J = 10.4 Hz).

Characterisation is in agreement with previous reports of this compound ¹⁴

***N*-(4-chlorobenzyl)hexanamide (29)**



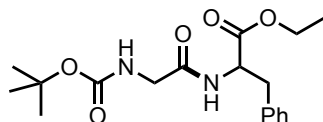
Yield 93%, Mass 1.11g, Yellow Solid.

^1H NMR (300 MHz, CDCl_3) δ 7.25 – 7.18 (*m*, 2H), 7.12 (*d*, J = 8.5 Hz, 2H), 5.92 (*s*, 1H), 4.31 (*d*, J = 5.8 Hz, 2H), 2.12 (*t*, J = 7.6 Hz, 2H), 1.64 – 1.50 (*m*, 2H), 1.32 – 1.17 (*m*, 4H), 0.89 – 0.74 (*m*, 3H).

^{13}C $\{^1\text{H}\}$ NMR (75 MHz, CDCl_3) δ 173.2, 137.1, 133.2, 129.1, 128.8, 42.8, 36.7, 31.5, 25.4, 22.4, 14.0

Characterisation is in agreement with previous reports of this compound ¹⁵

ethyl (tert-butoxycarbonyl)glycylphenylalaninate (30)



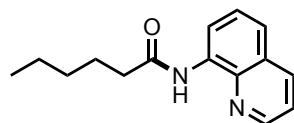
Yield 57%, Mass 0.99g, Yellow Solid.

^1H NMR (300 MHz, CDCl_3) δ 7.25 – 7.12 (*m*, 3H), 7.07 – 7.01 (*m*, 2H), 6.55 (*d*, J = 7.9 Hz, 1H), 5.11 (*s*, 1H), 4.78 (*dt*, J = 7.9, 5.9 Hz, 1H), 4.08 (*q*, J = 7.1 Hz, 2H), 3.71 (*dd*, J = 10.7, 5.5 Hz, 2H), 3.04 (*dd*, J = 5.9, 1.4 Hz, 2H), 1.37 (*s*, 9H), 1.15 (*t*, J = 7.2 Hz, 3H).

^{13}C $\{^1\text{H}\}$ NMR (75 MHz, CDCl_3) δ 171.4, 169.2, 156.0, 135.9, 129.4, 128.7, 127.2, 80.3, 61.7, 53.2, 44.3, 38.1, 28.4, 14.2

Characterisation is in agreement with previous reports of this compound ⁴

***N*-(quinolin-8-yl)hexanamide (31)**



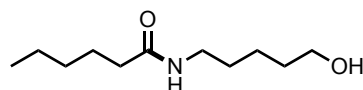
Yield 8%, Mass 0.05g, Dark Brown Liquid.

^1H NMR (400 MHz, CDCl_3) δ 9.81 (*s*, 1H), 8.90 – 8.71 (*m*, 2H), 8.21 – 8.08 (*m*, 1H), 7.60 – 7.40 (*m*, 3H), 2.56 (*t*, J = 7.6 Hz, 2H), 1.83 (*t*, J = 7.4 Hz, 2H), 1.40 (*dt*, J = 8.9, 5.0 Hz, 4H), 1.03 – 0.87 (*m*, 3H).

^{13}C $\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 172.1, 148.2, 138.5, 136.5, 134.7, 128.1, 127.6, 121.7, 121.4, 116.5, 38.3, 31.6, 25.5, 22.6, 14.1.

Characterisation is in agreement with previous reports of this compound ¹⁶

***N*-(5-hydroxypentyl)hexanamide (32)**



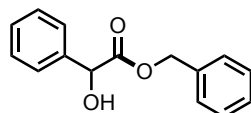
Yield 46%, Mass 0.46g, White Solid.

^1H NMR (300 MHz, CDCl_3) δ 3.58 (t, J = 6.3 Hz, 2H), 3.19 (td, J = 6.9, 5.8 Hz, 2H), 2.16 – 2.02 (m, 3H), 1.70 (s, 1H), 1.63 – 1.10 (m, 12H), 0.91 – 0.74 (m, 3H).

^{13}C { ^1H } NMR (75 MHz, CDCl_3) δ 173.5, 62.3, 39.3, 36.8, 32.2, 31.5, 29.4, 25.5, 23.1, 22.4, 13.9

No reported characterisation is available for this compound.

Benzyl 2-hydroxy-2-phenylacetate (33)



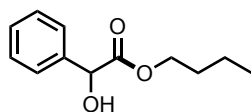
Yield 92%, Mass 1.11g, White Solid.

^1H NMR (300 MHz, CDCl_3) δ 7.39 – 7.07 (m, 10H), 5.16 (d, J = 12.2 Hz, 2H), 5.06 (d, J = 12.3 Hz, 1H).

^{13}C { ^1H } NMR (75 MHz, CDCl_3) δ 173.5, 138.2, 135.0, 128.6, 128.6, 128.5, 128.5, 128.0, 126.6, 73.0, 67.7

Characterisation is in agreement with previous reports of this compound.¹⁷

Butyl 2-hydroxy-2-phenylacetate (34)



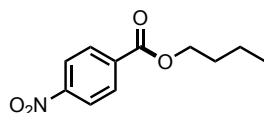
Yield 83%, Mass 0.87g, Colorless Liquid.

^1H NMR (300 MHz, CDCl_3) δ 7.43 – 7.22 (m, 5H), 5.09 (d, J = 5.5 Hz, 1H), 4.20 – 4.01 (m, 2H), 3.40 (d, J = 5.8 Hz, 1H), 1.59 – 1.42 (m, 2H), 1.18 (dq, J = 14.5, 7.3 Hz, 2H), 0.78 (t, J = 7.4 Hz, 3H).

^{13}C { ^1H } NMR (75 MHz, CDCl_3) δ 173.8, 138.5, 128.5, 128.4, 126.5, 72.9, 66.1, 30.4, 18.9, 13.5

Characterisation is in agreement with previous reports of this compound.¹⁸

Butyl 4-nitrobenzoate (35)

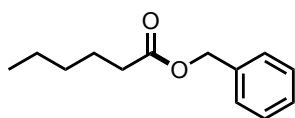


Yield 41%, Mass 0.45g, Yellow Solid

^1H NMR (300 MHz, CDCl_3) δ 8.32 – 8.26 (m, 2H), 8.24 – 8.18 (m, 2H), 4.38 (t, J = 6.6 Hz, 2H), 1.85 – 1.72 (m, 2H), 1.57 – 1.41 (m, 2H), 0.99 (t, J = 7.4 Hz, 3H).

^{13}C { ^1H } NMR (75 MHz, CDCl_3) δ 164.8, 150.5, 135.9, 130.7, 123.5, 65.8, 30.6, 19.2, 13.8

No reported characterisation is available for this compound.

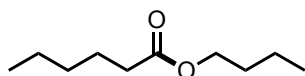
Benzyl hexanoate (36)

Yield 78%, Mass 0.80g, Dark Brown Liquid.

$^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.46 – 7.29 (*m*, 5H), 5.12 (*s*, 2H), 2.36 (*t*, $J = 7.5$ Hz, 2H), 1.75 – 1.58 (*m*, 2H), 1.31 (*tt*, $J = 7.6, 3.1$ Hz, 4H), 0.89 (*h*, $J = 2.8$ Hz, 3H).

$^{13}\text{C } \{^1\text{H}\}$ NMR (75 MHz, CDCl_3) δ 173.7, 136.2, 128.6, 128.2, 66.1, 34.3, 31.3, 24.7, 22.3, 13.9

Characterisation is in agreement with previous reports of this compound.¹⁹

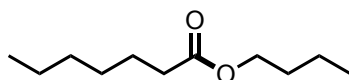
Butyl hexanoate (37)

Yield 53%, Mass 0.46g, Colorless Liquid.

$^1\text{H NMR}$ (300 MHz, CDCl_3) δ 4.00 (*t*, $J = 6.7$ Hz, 2H), 2.22 (*t*, $J = 7.5$ Hz, 2H), 1.65 – 1.48 (*m*, 4H), 1.38 – 1.18 (*m*, 6H), 0.84 (*dt*, $J = 11.0, 7.1$ Hz, 6H).

$^{13}\text{C } \{^1\text{H}\}$ NMR (75 MHz, CDCl_3) δ 174.0, 64.1, 34.4, 31.3, 30.7, 24.7, 22.3, 19.2, 13.9, 13.7

Characterisation is in agreement with previous reports of this compound.²⁰

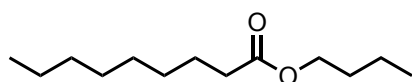
Butyl heptanoate (38)

Yield 59%, Mass 0.54g, Colorless Liquid.

$^1\text{H NMR}$ (300 MHz, CDCl_3) δ 4.07 (*t*, $J = 6.7$ Hz, 2H), 2.29 (*t*, $J = 7.5$ Hz, 2H), 1.70 – 1.53 (*m*, 4H), 1.47 – 1.23 (*m*, 8H), 0.91 (*dt*, $J = 14.4, 7.1$ Hz, 6H).

$^{13}\text{C } \{^1\text{H}\}$ NMR (75 MHz, CDCl_3) δ 174.0, 64.1, 34.4, 31.5, 30.7, 28.8, 25.0, 22.5, 19.2, 14.0, 13.7

Characterisation is in agreement with previous reports of this compound.²¹

Butyl nonanoate (39)

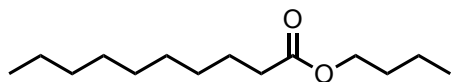
Yield 78%, Mass 0.84g, Colorless Liquid.

$^1\text{H NMR}$ (300 MHz, CDCl_3) δ 4.00 (*t*, $J = 6.6$ Hz, 2H), 2.22 (*t*, $J = 7.5$ Hz, 2H), 1.62 – 1.47 (*m*, 4H), 1.39 – 1.14 (*m*, 12H), 0.94 – 0.75 (*m*, 6H).

$^{13}\text{C } \{^1\text{H}\}$ NMR (75 MHz, CDCl_3) δ 174.0, 64.1, 34.4, 31.8, 30.7, 29.2, 29.2, 29.1, 25.0, 22.6, 19.2, 14.1, 13.7

Characterisation is in agreement with previous reports of this compound.²²

Butyl decanoate (40)



Yield 65%, Mass 0.74g, Colorless Liquid.

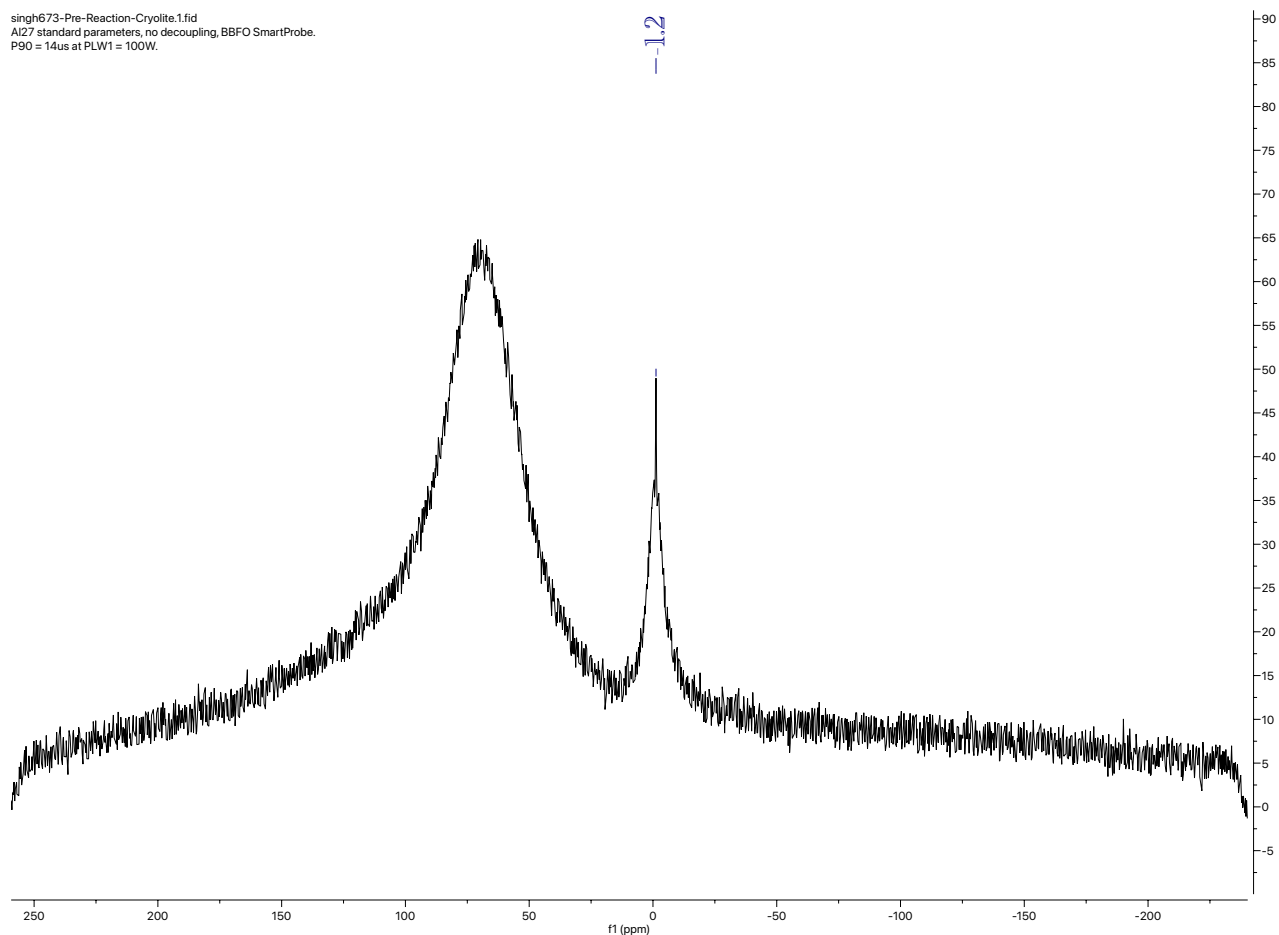
^1H NMR (300 MHz, CDCl_3) δ 4.07 (t, J = 6.7 Hz, 2H), 2.29 (t, J = 7.5 Hz, 2H), 1.61 (tt, J = 8.7, 5.3 Hz, 4H), 1.46 – 1.20 (m, 14H), 0.90 (dt, J = 16.2, 7.1 Hz, 6H).

^{13}C { ^1H } NMR (75 MHz, CDCl_3) δ 174.0, 64.1, 34.4, 31.9, 30.7, 29.4, 29.3, 29.2, 25.0, 22.7, 19.2, 14.1, 13.7
Characterisation is in agreement with previous reports of this compound.²³

References:

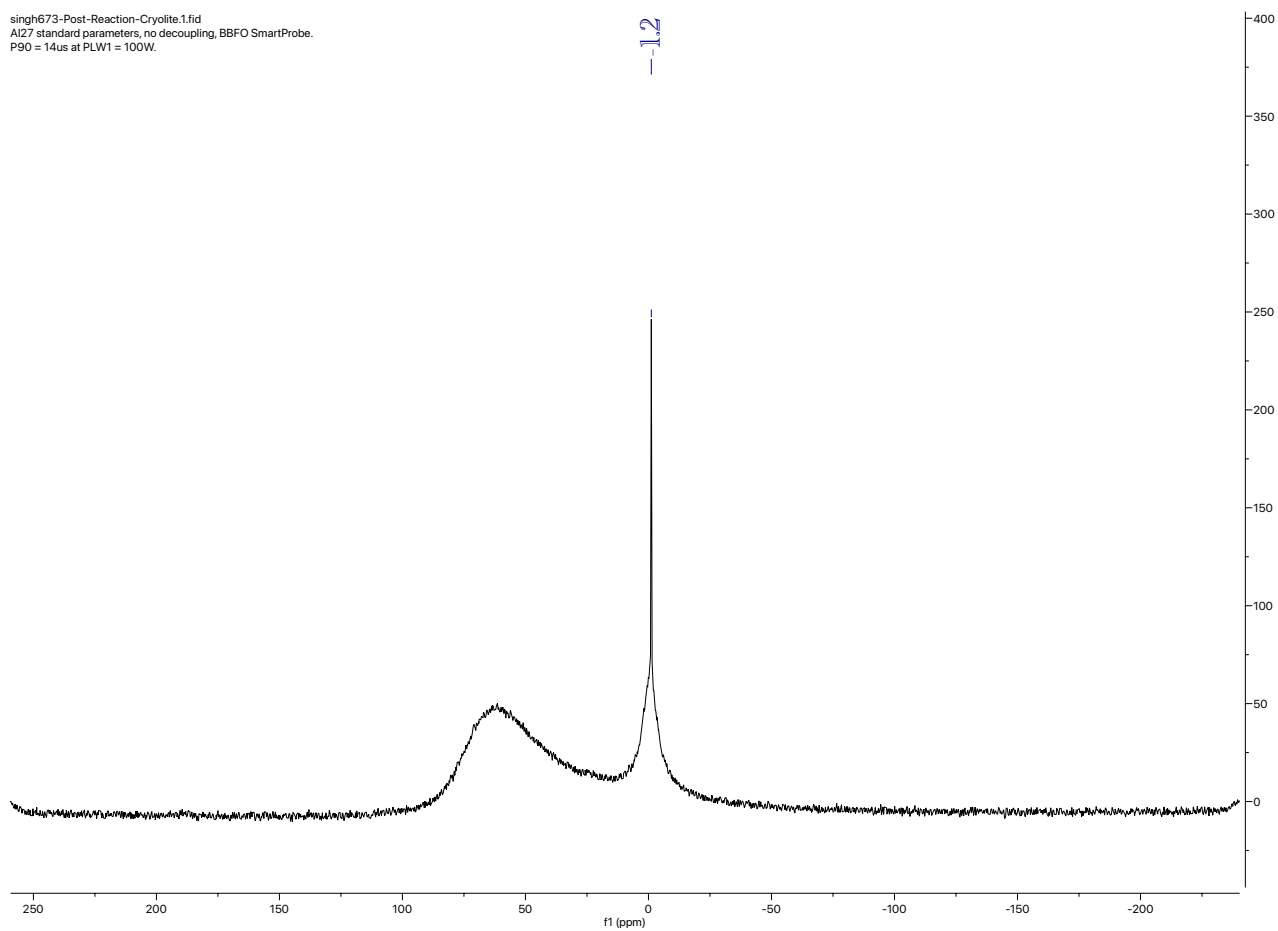
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singh673-Pre-Reaction-Cryolite.1.fid
AI27 standard parameters, no decoupling, BBFO SmartProbe.
P90 = 14us at PLW1 = 100W.

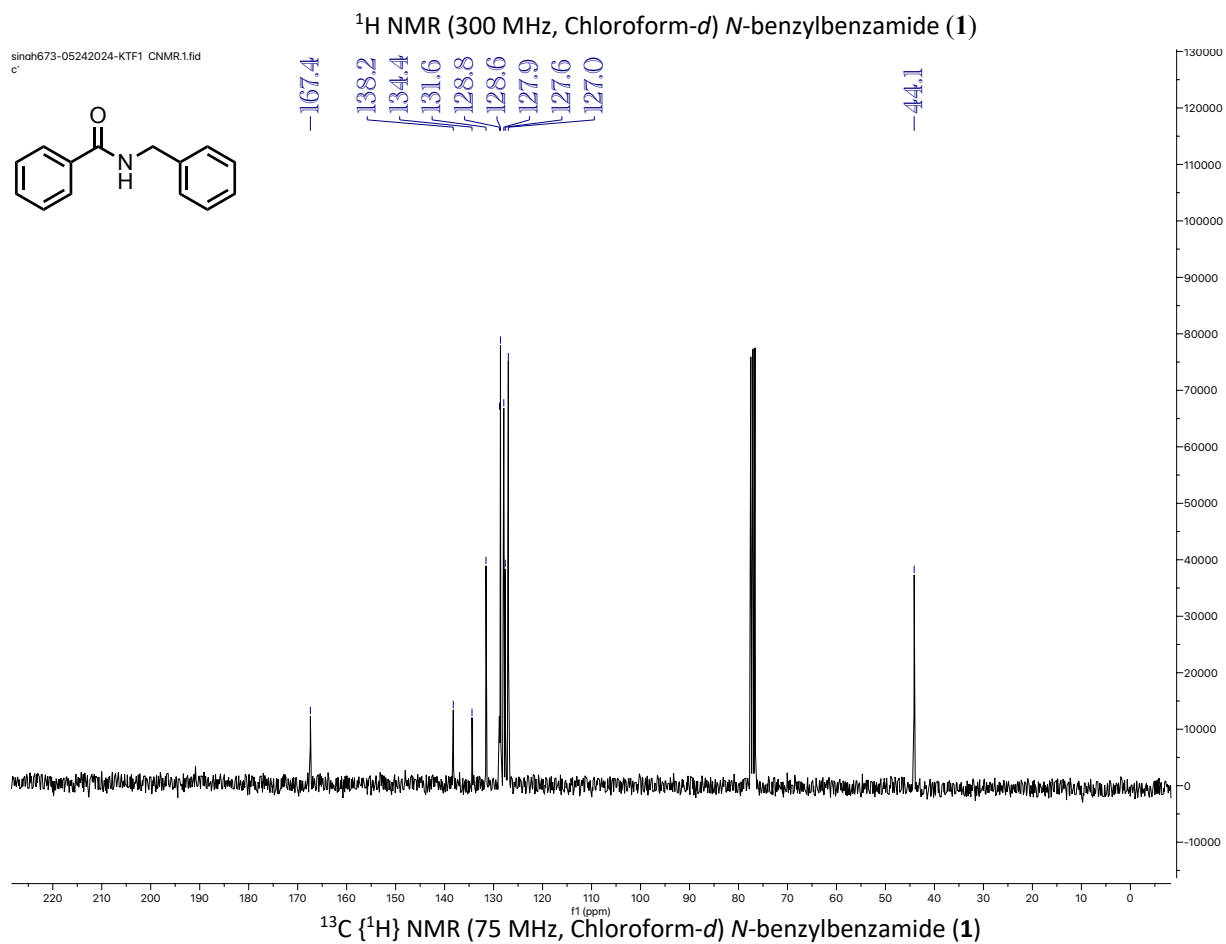
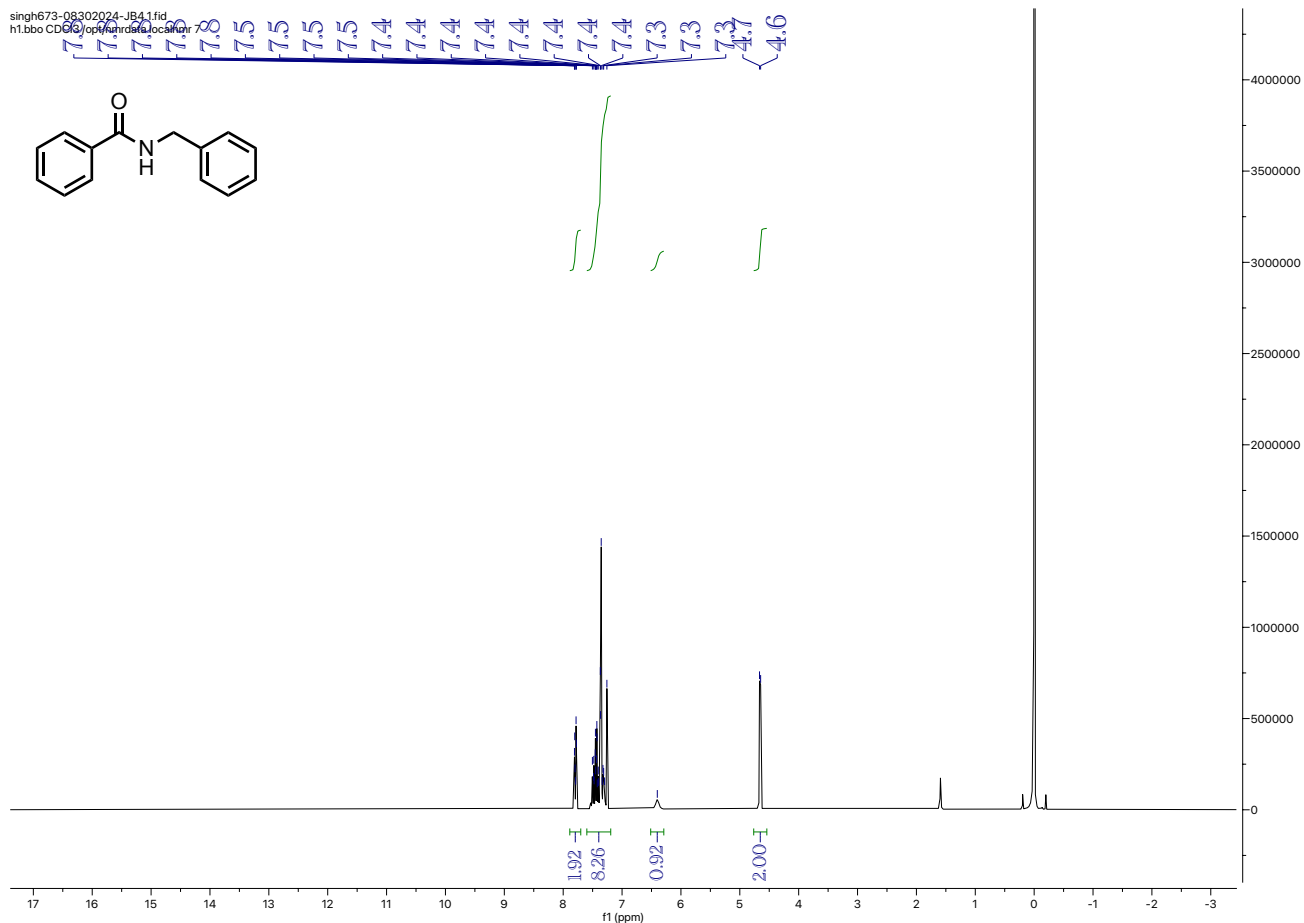


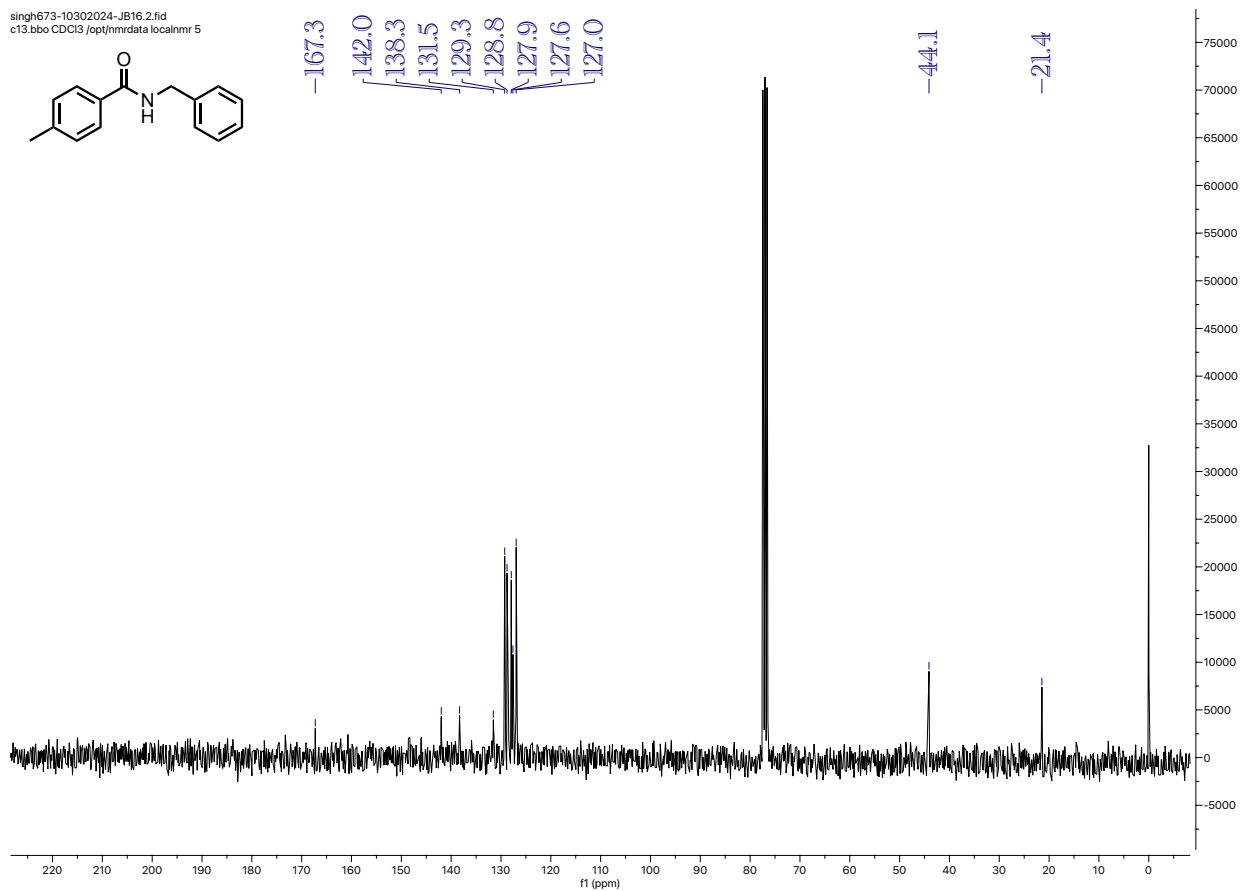
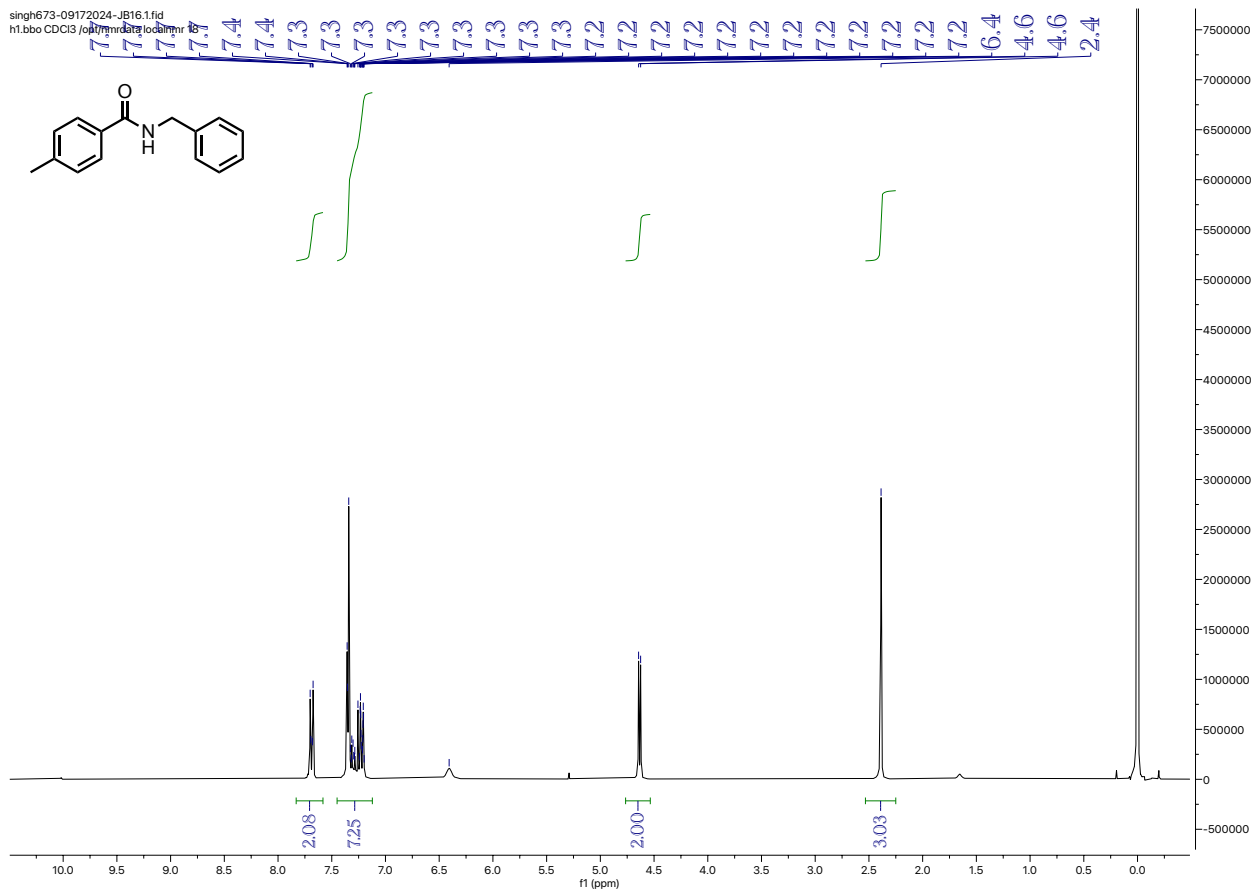
^{27}Al NMR (104 MHz, D_2O) Pre-Reaction Cryolite

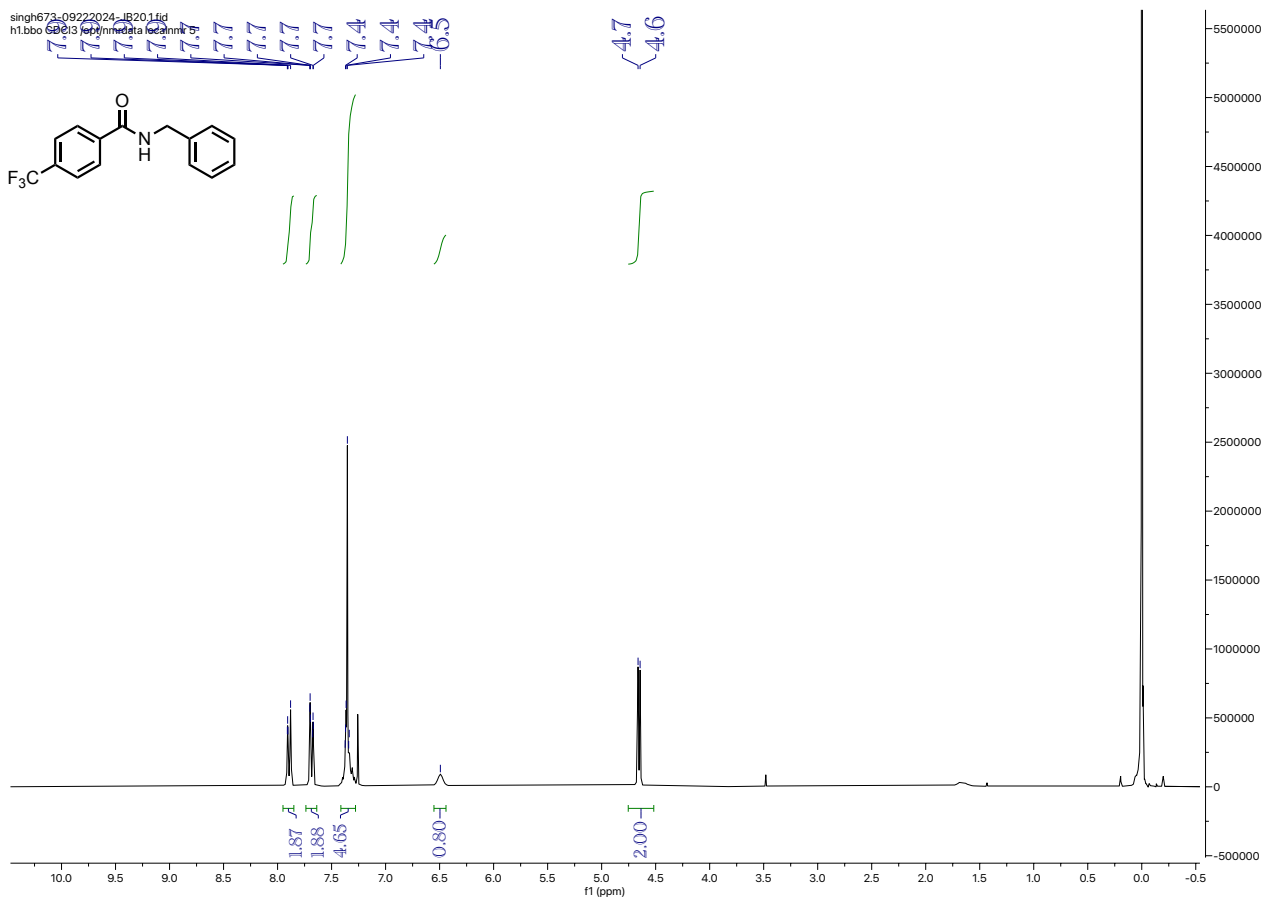
singh673-Post-Reaction-Cryolite.1.fid
AI27 standard parameters, no decoupling, BBFO SmartProbe.
P90 = 14us at PLW1 = 100W.

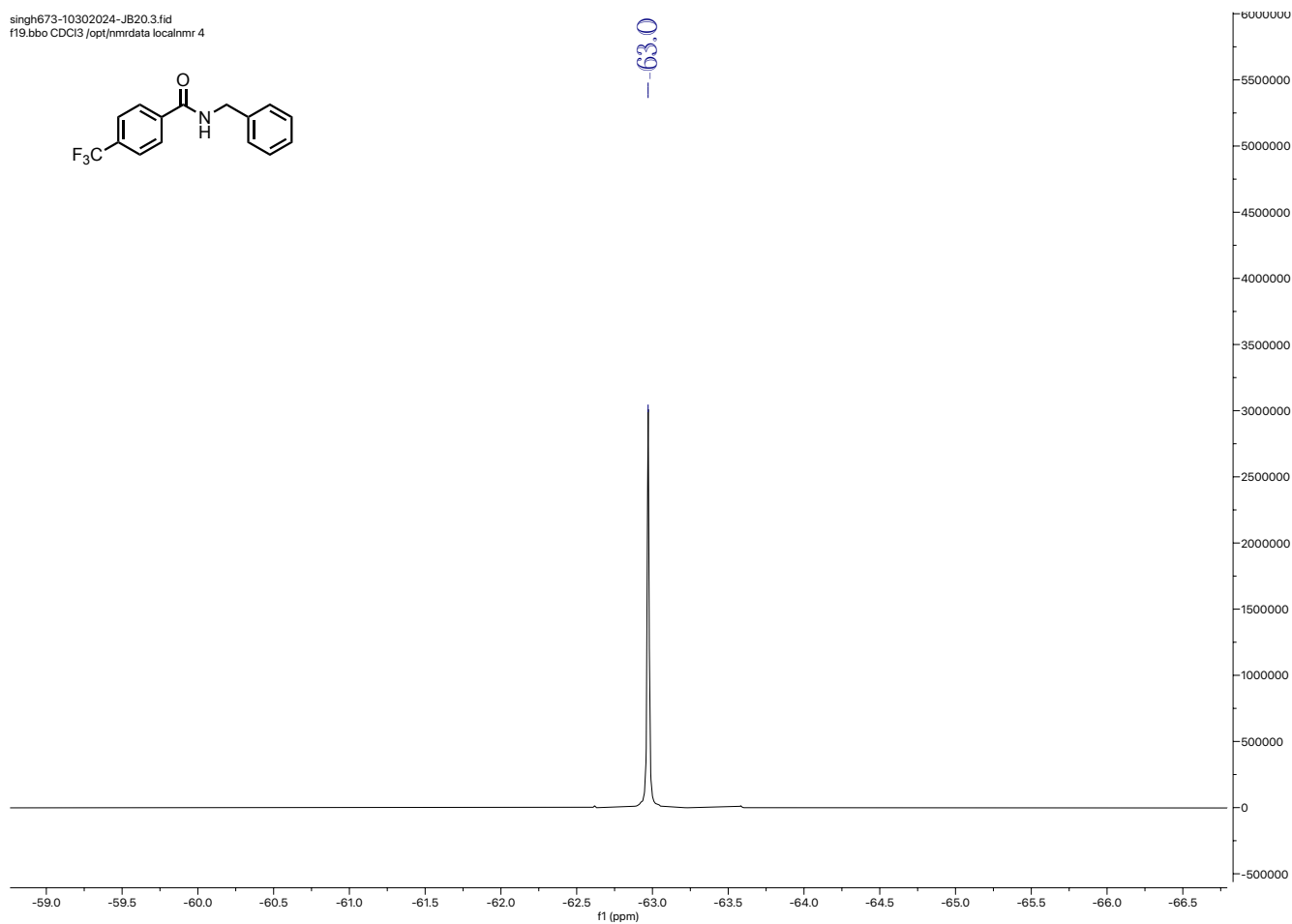
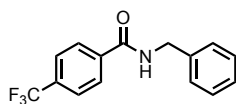


^{27}Al NMR (104 MHz, D_2O) Post-Reaction Cryolite

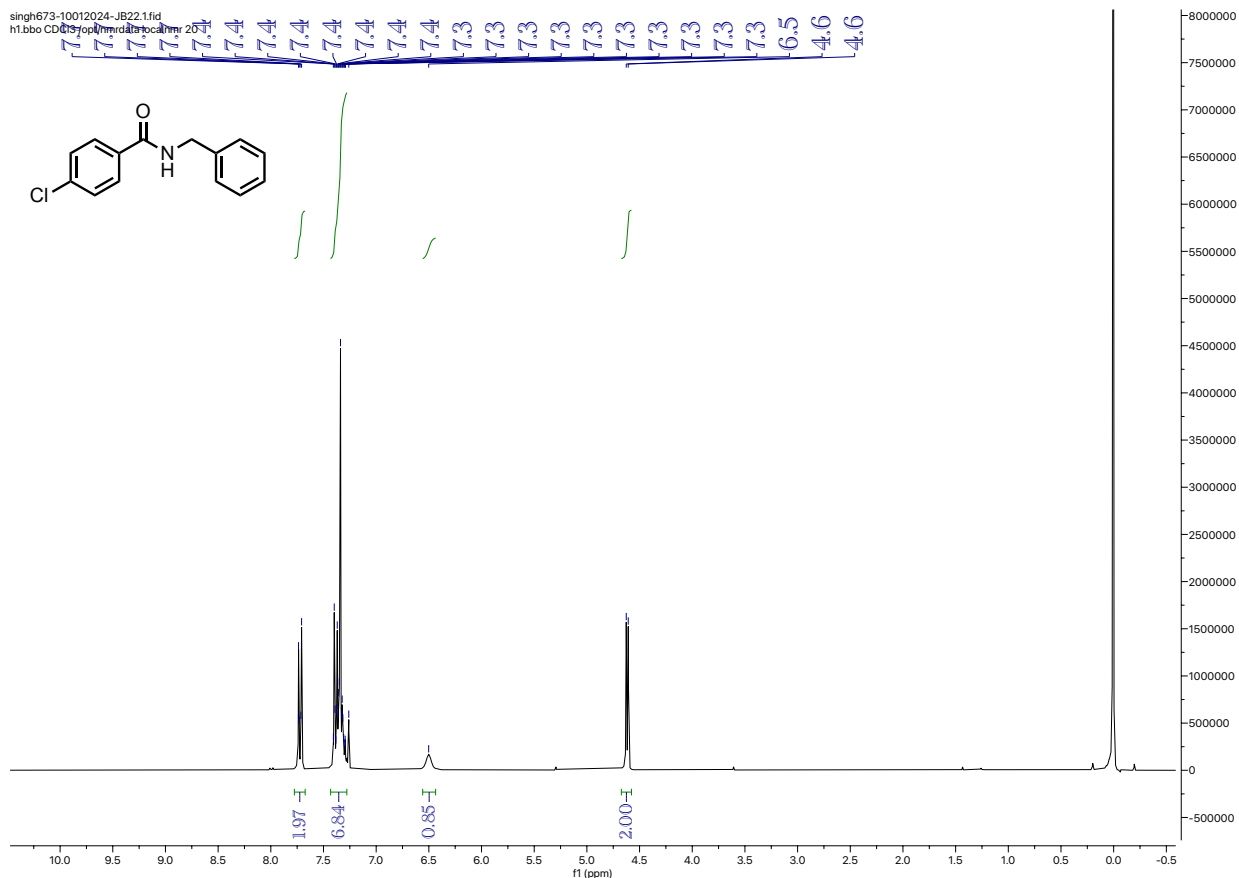




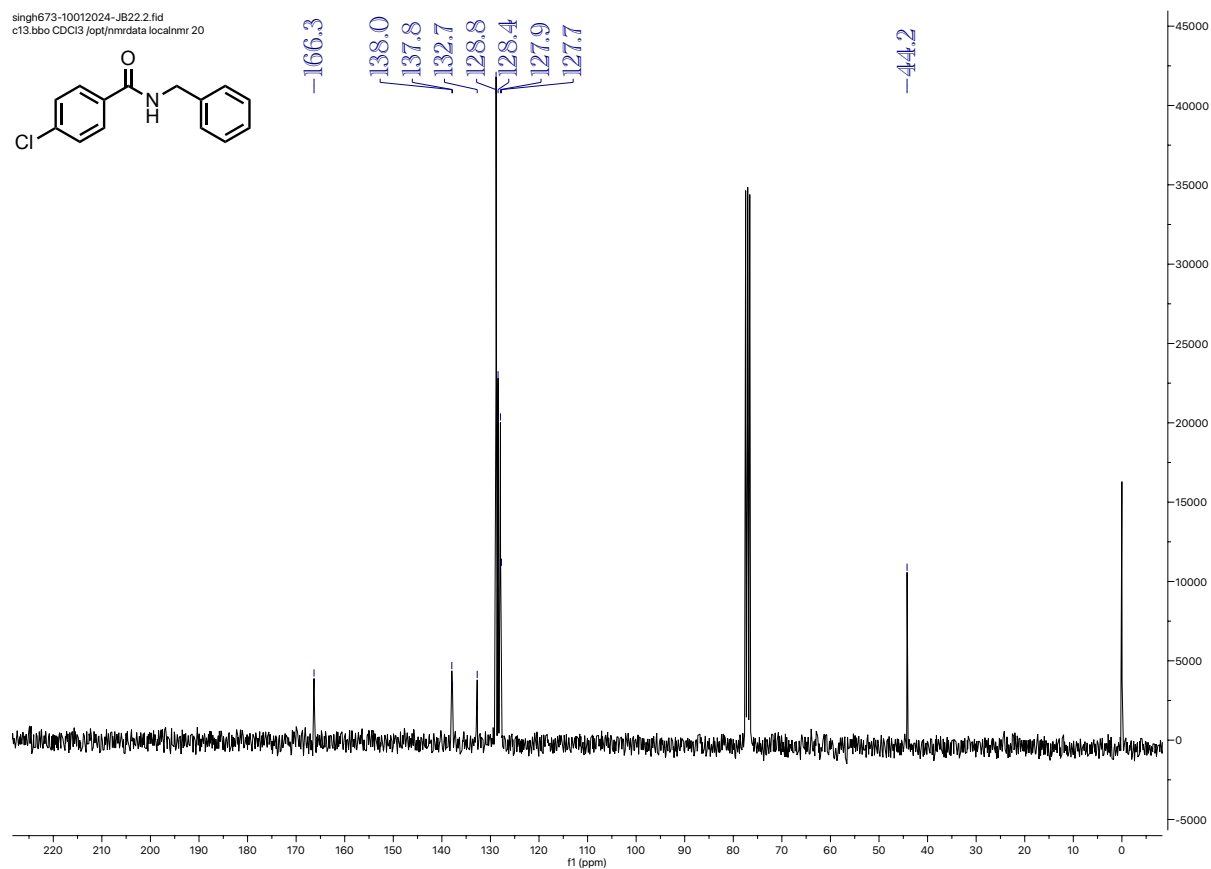




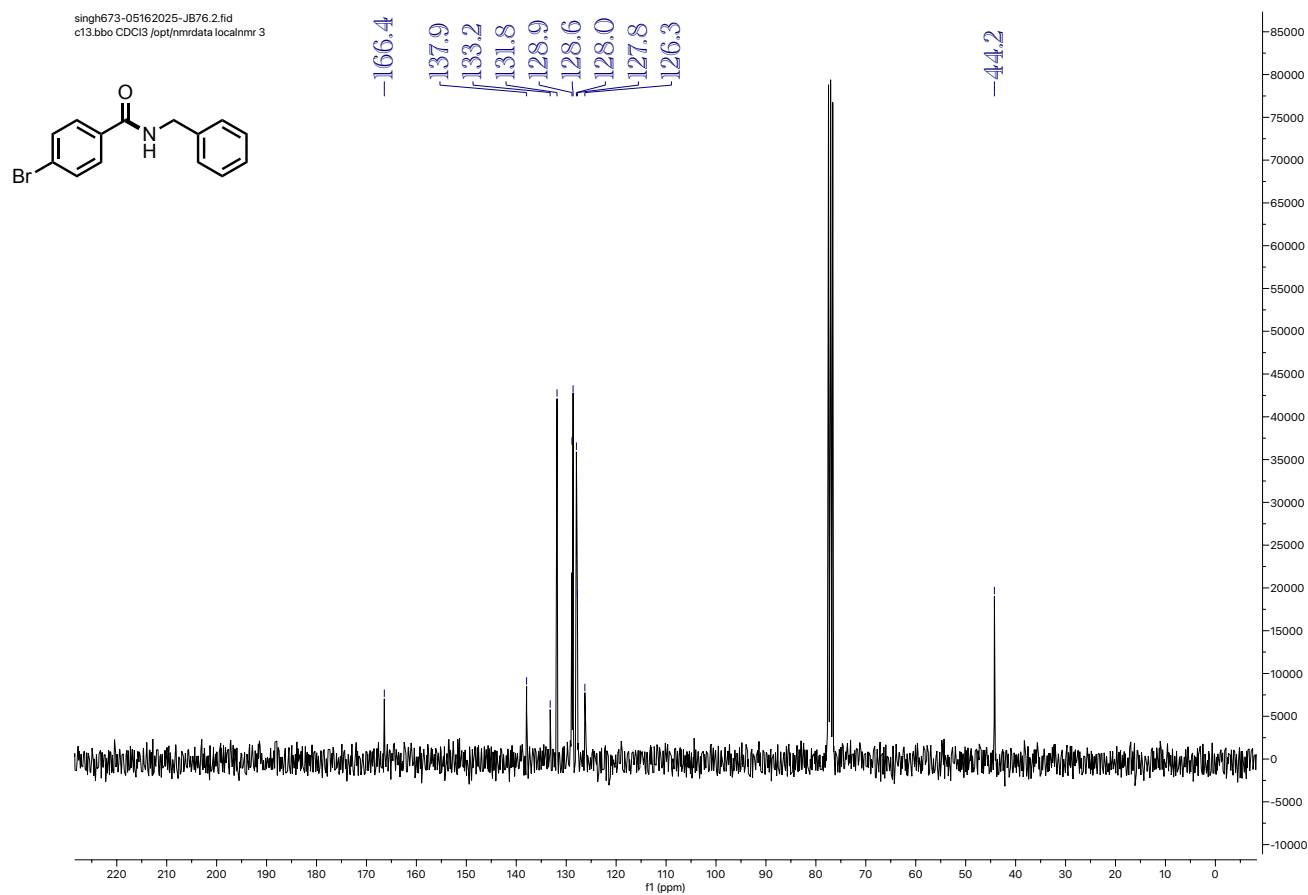
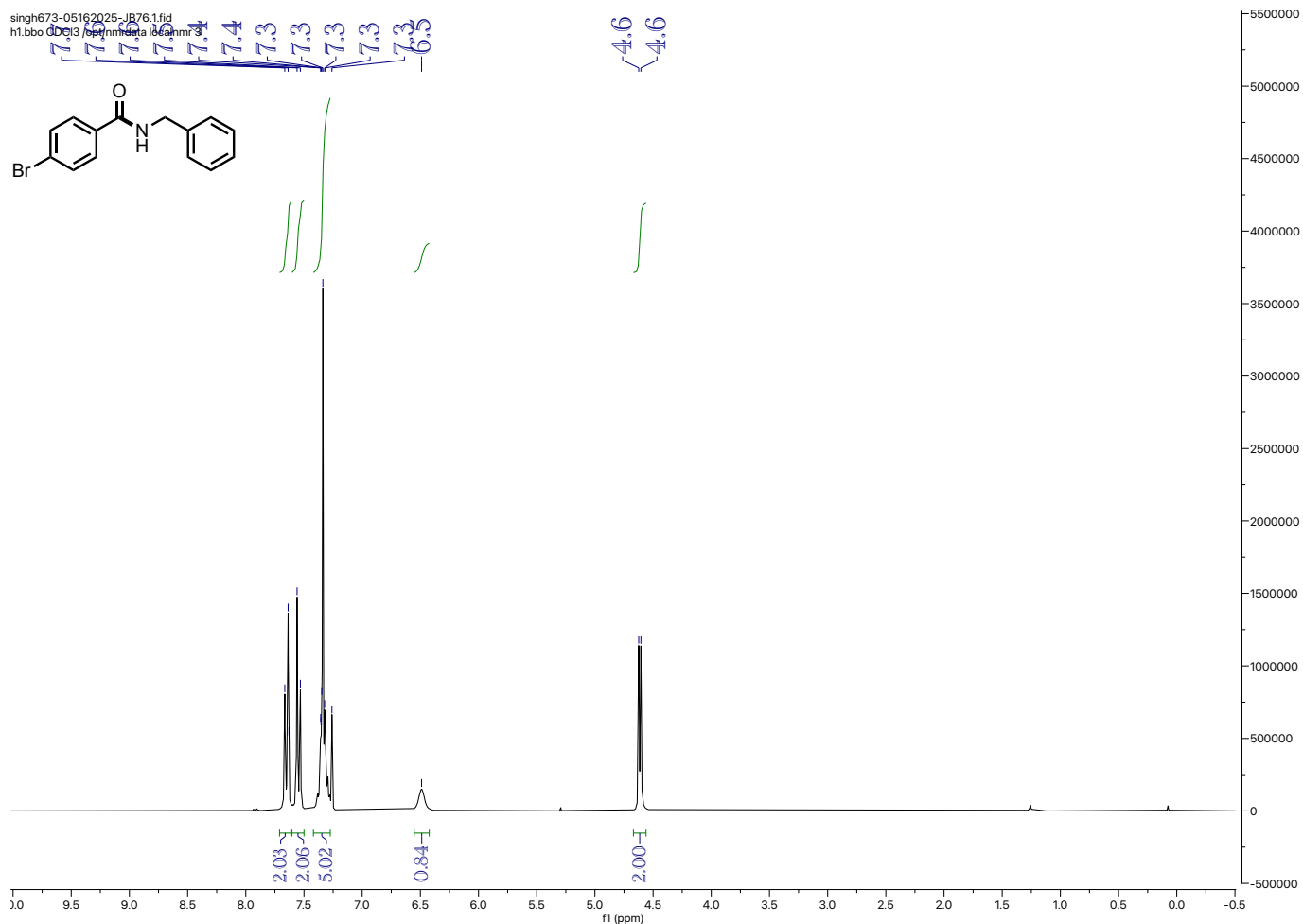
^{19}F NMR (282 MHz, Chloroform-*d*) *N*-benzyl-4-(trifluoromethyl)benzamide (**3**)

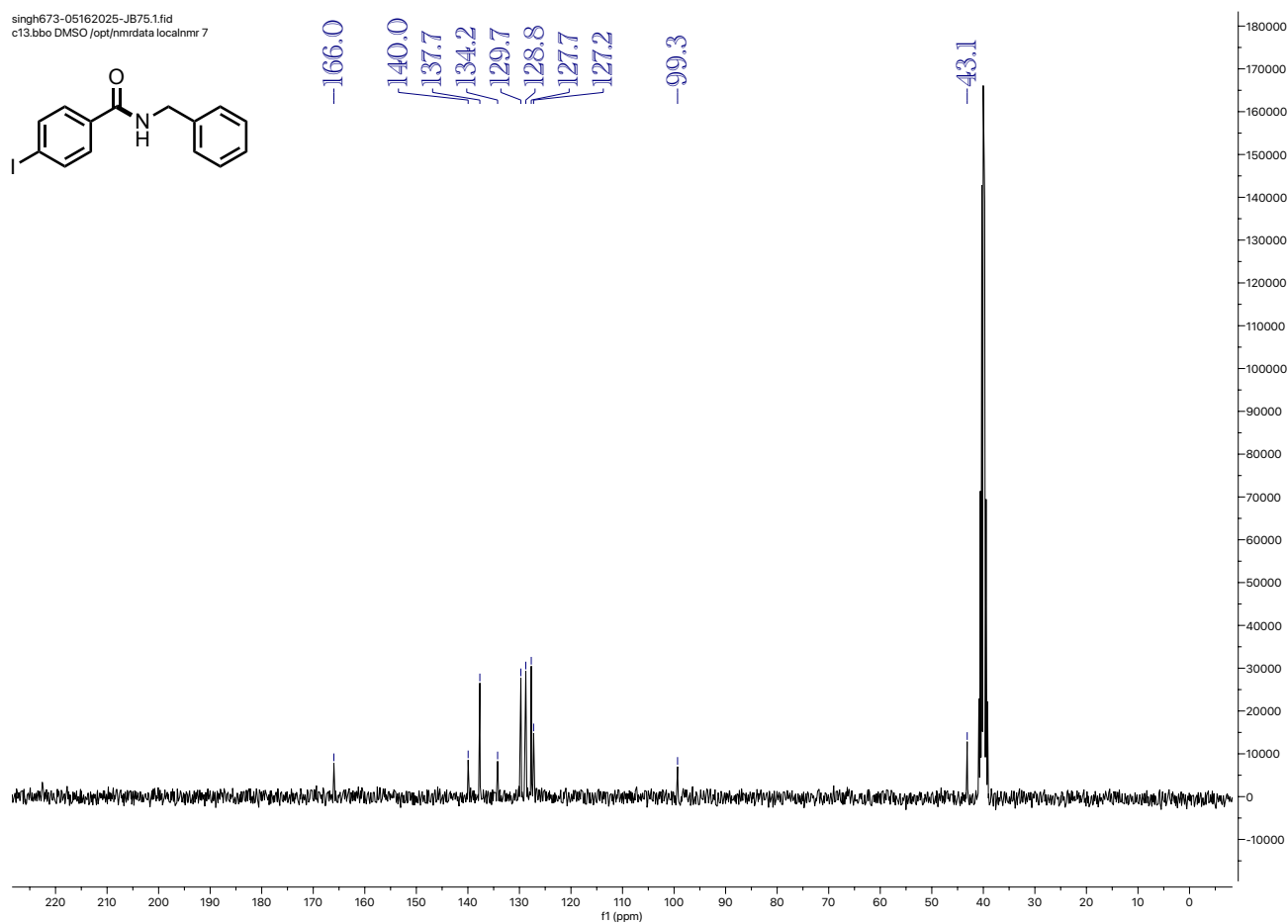
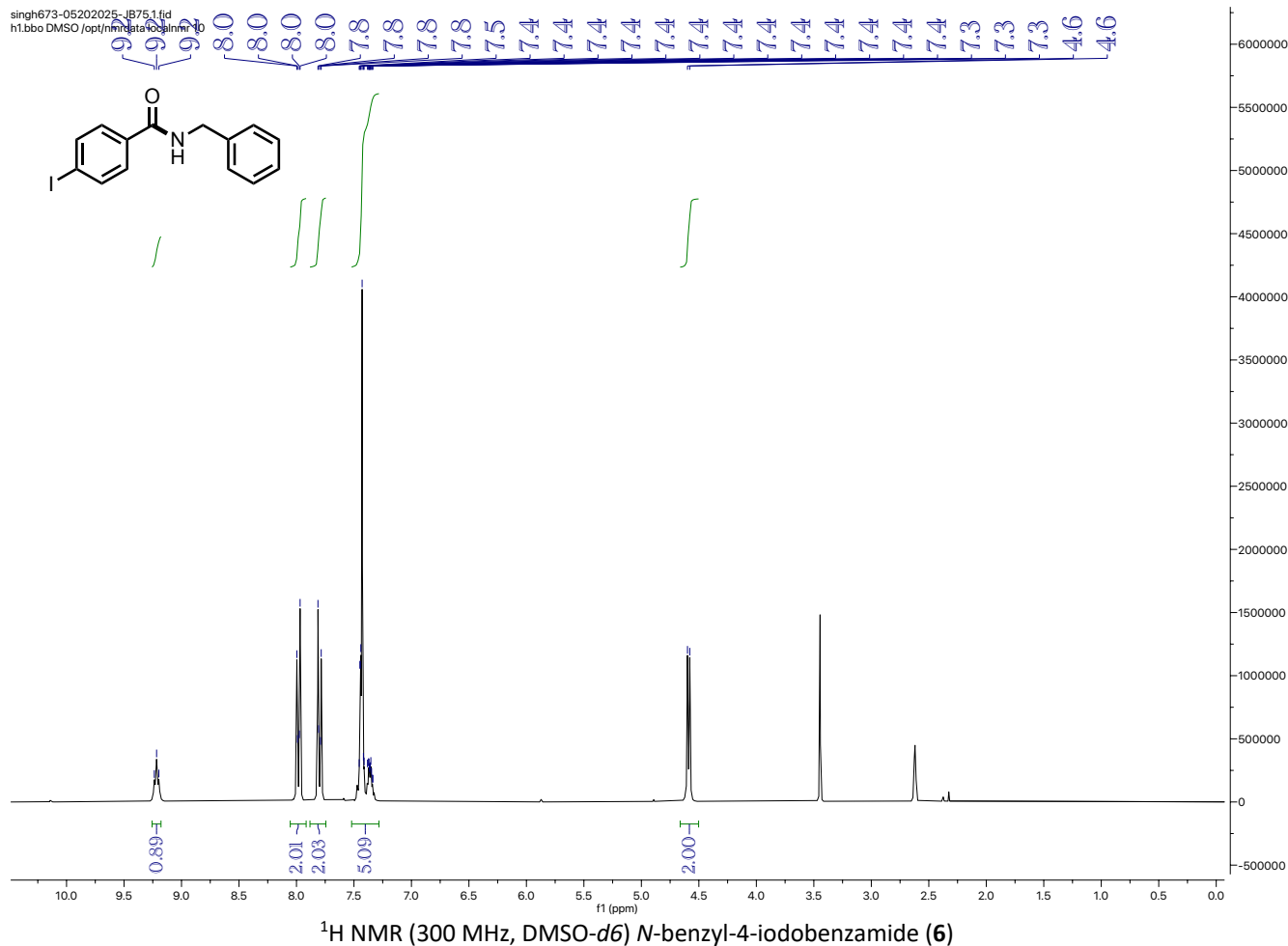


^1H NMR (300 MHz, Chloroform-*d*) *N*-benzyl-4-chlorobenzamide (**4**)

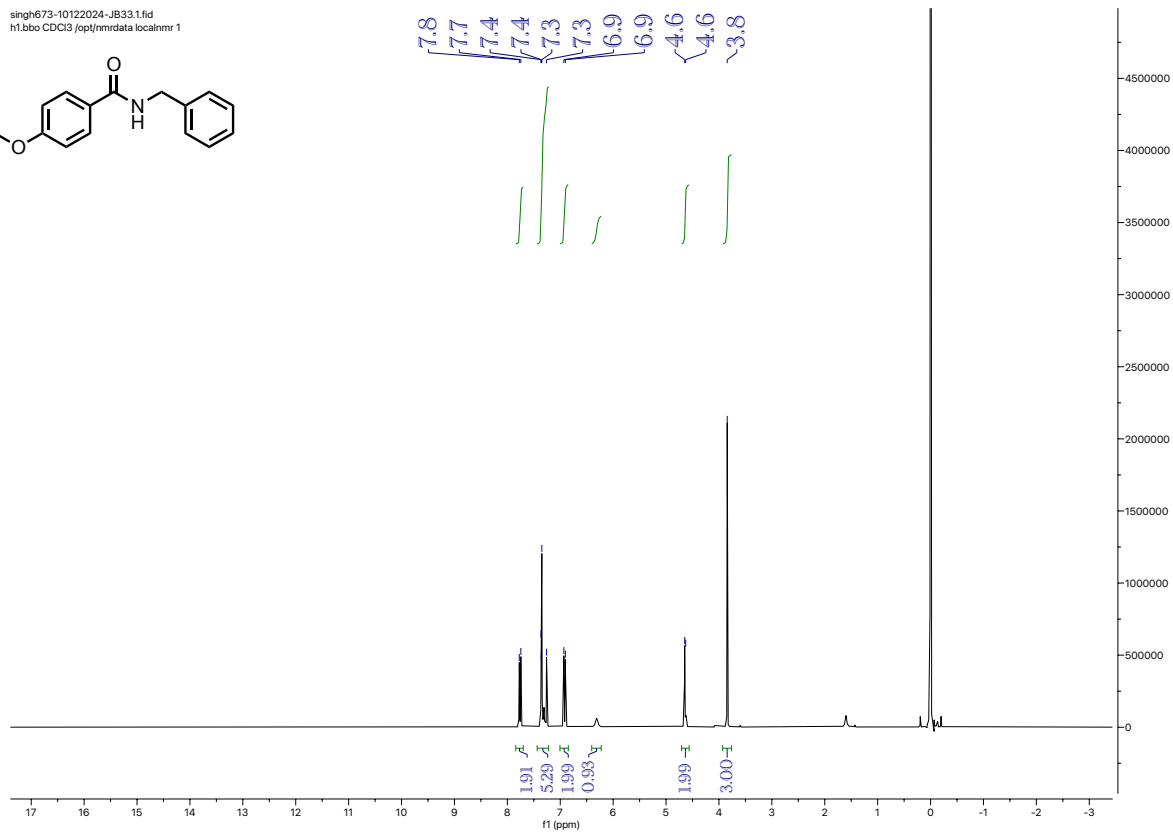
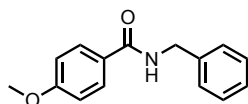


^{13}C $\{^1\text{H}\}$ NMR (75 MHz, Chloroform-*d*) *N*-benzyl-4-chlorobenzamide (**4**)



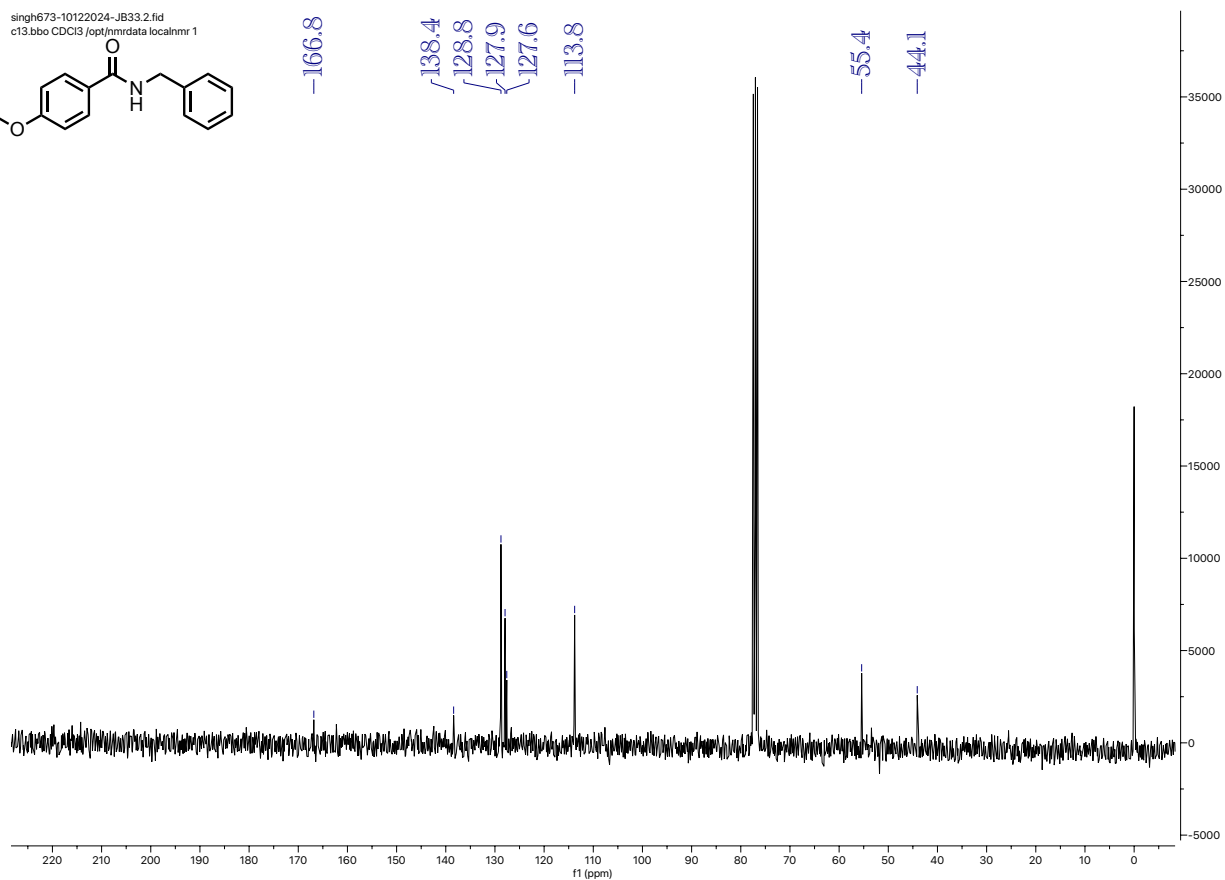
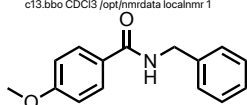


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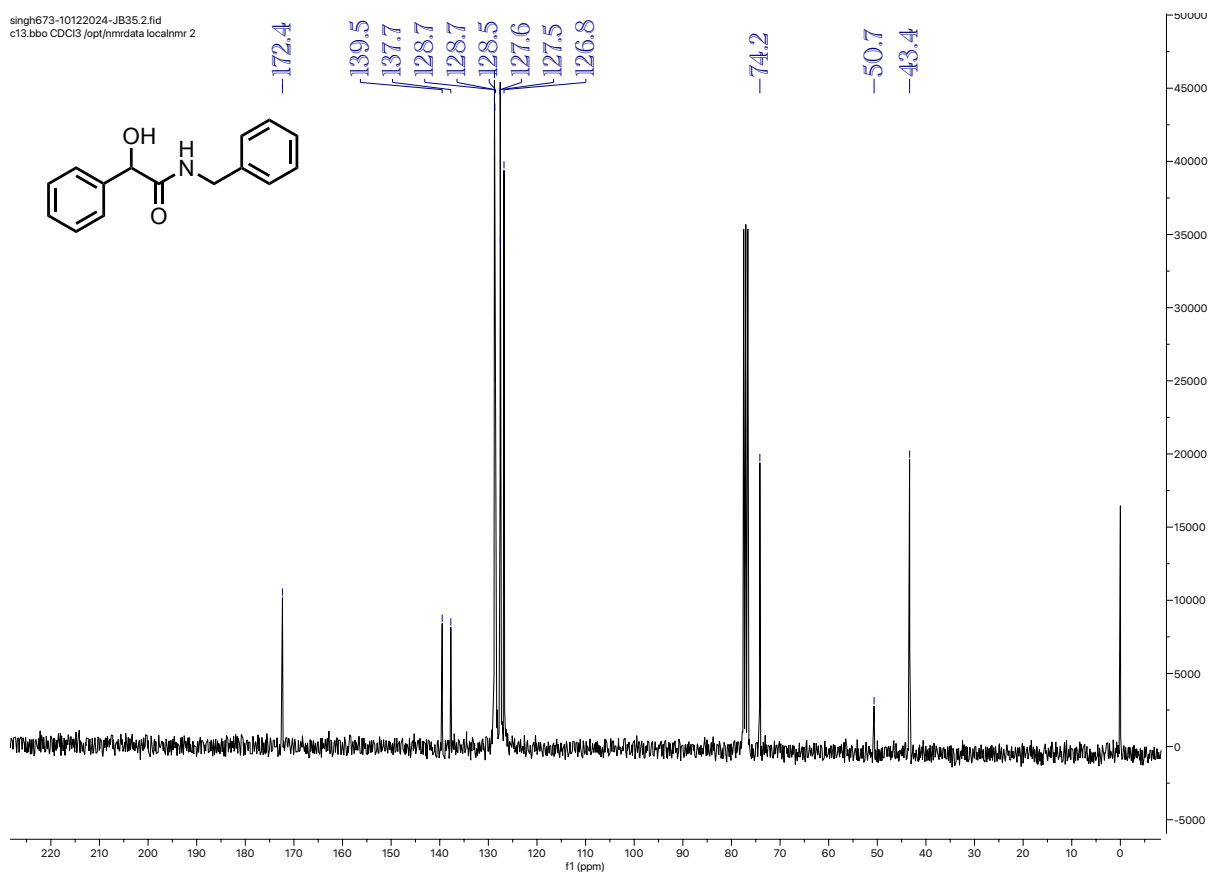
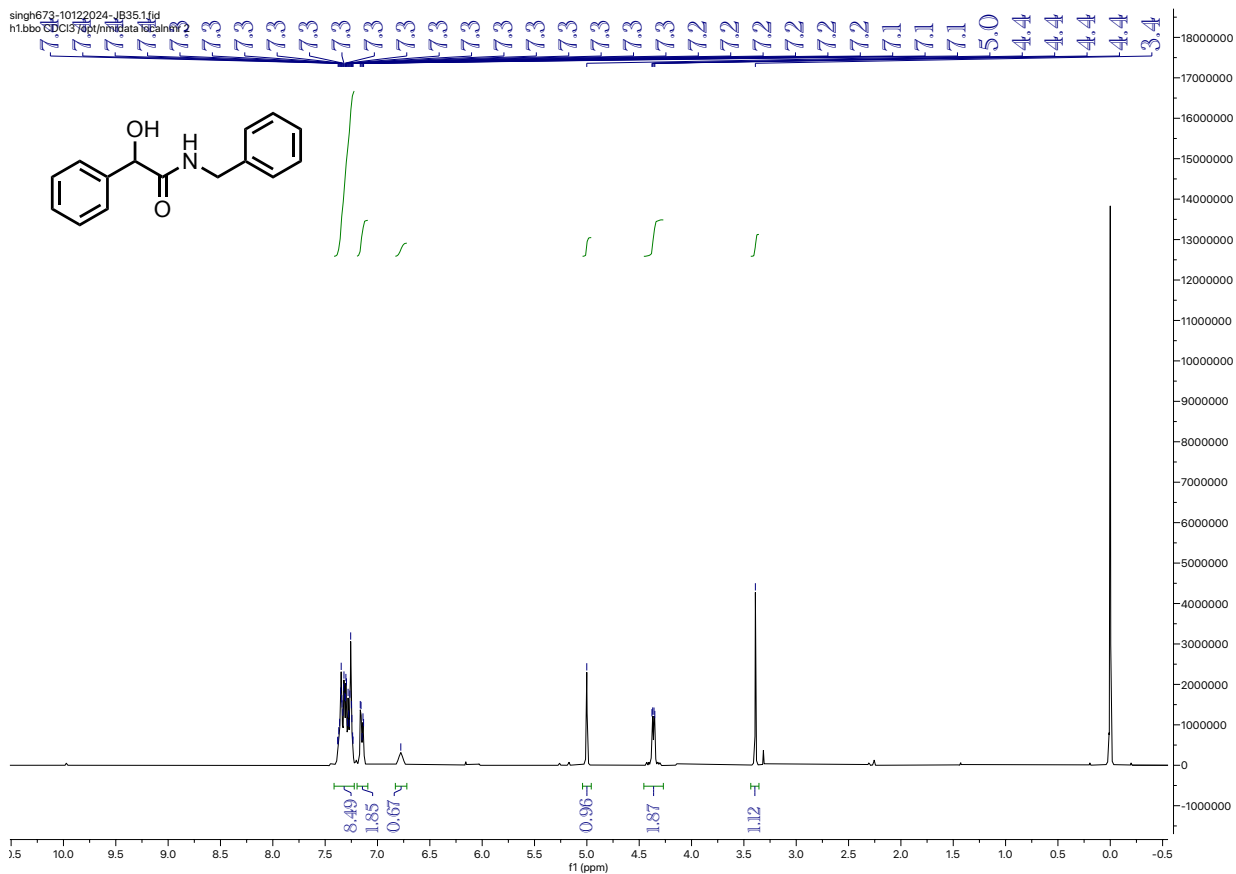


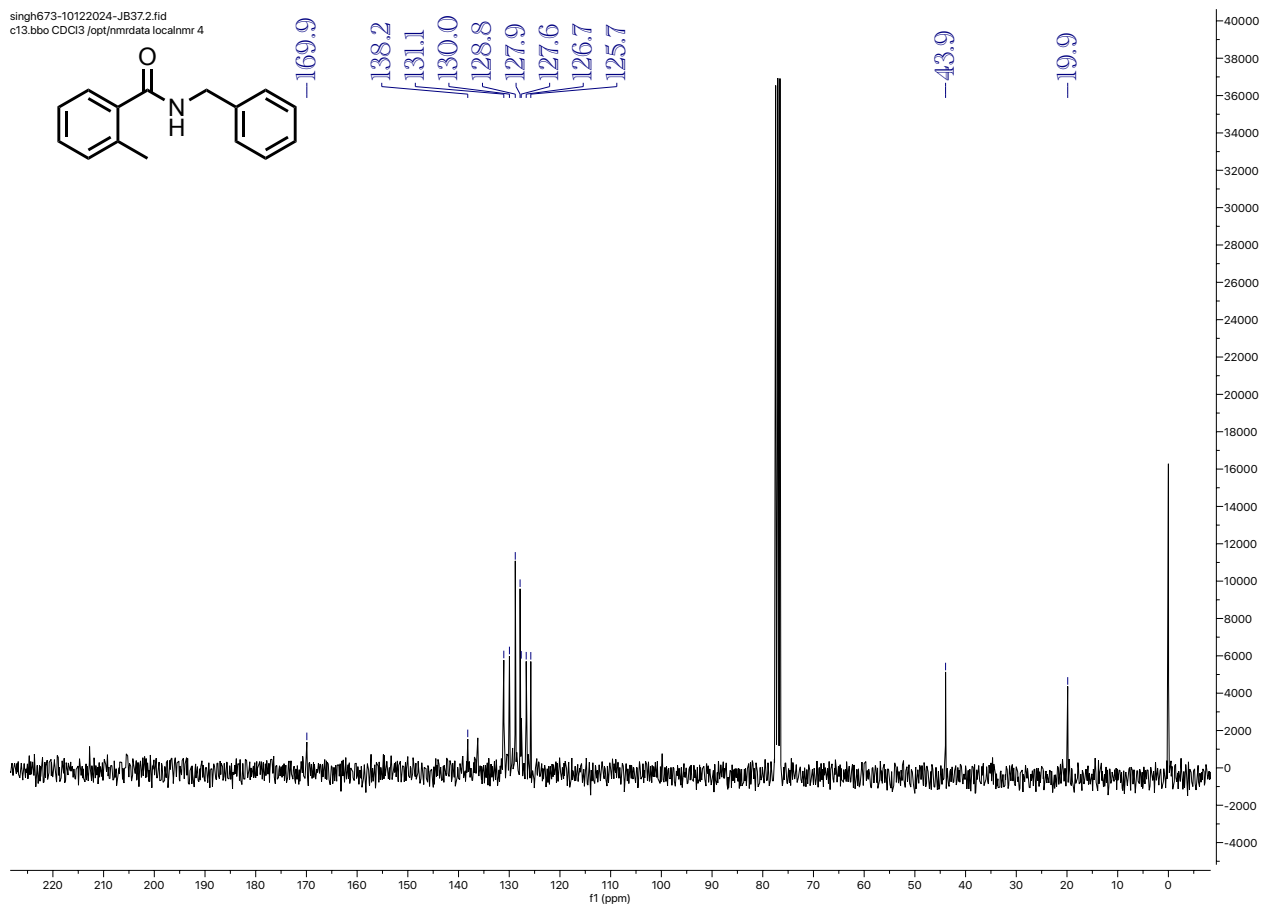
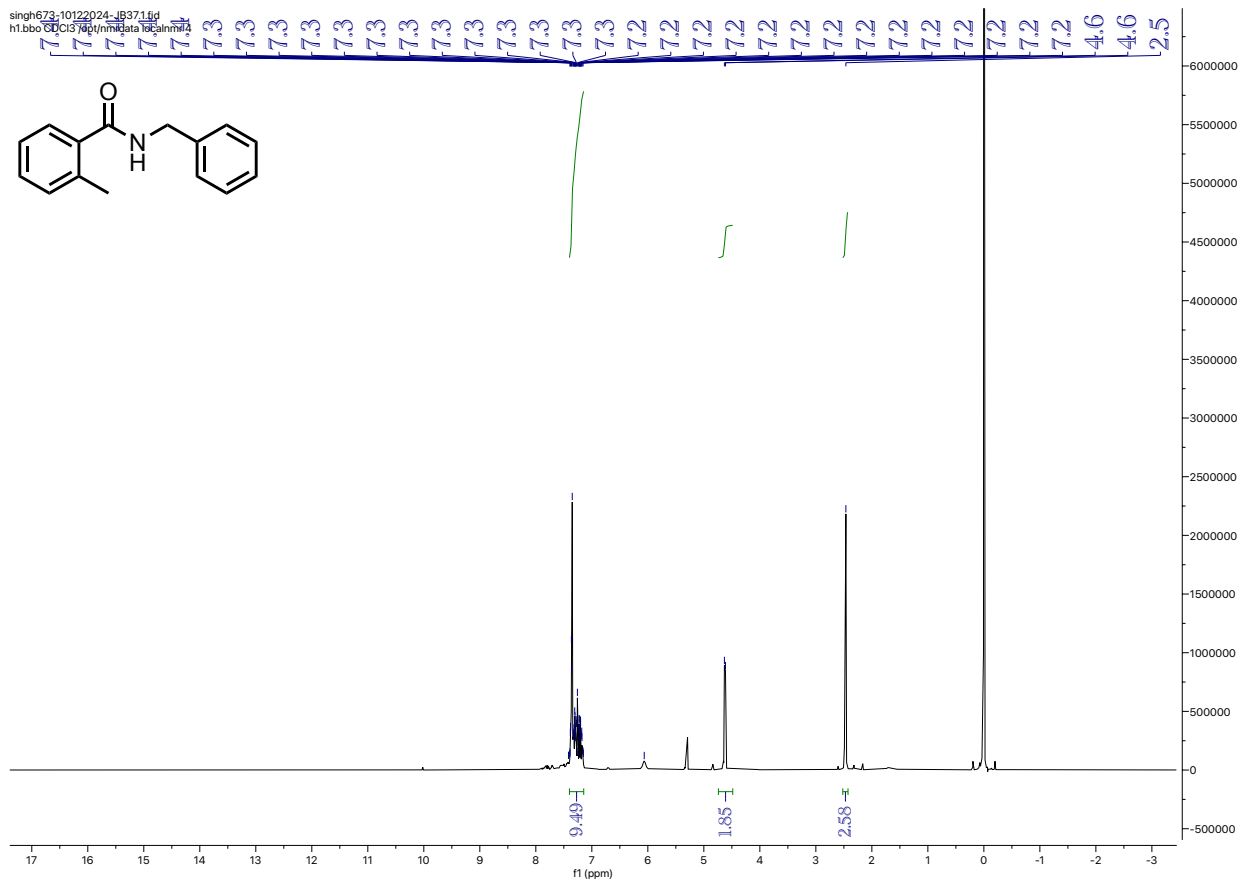
¹H NMR (300 MHz, Chloroform-*d*) *N*-benzyl-4-methoxybenzamide (**7**)

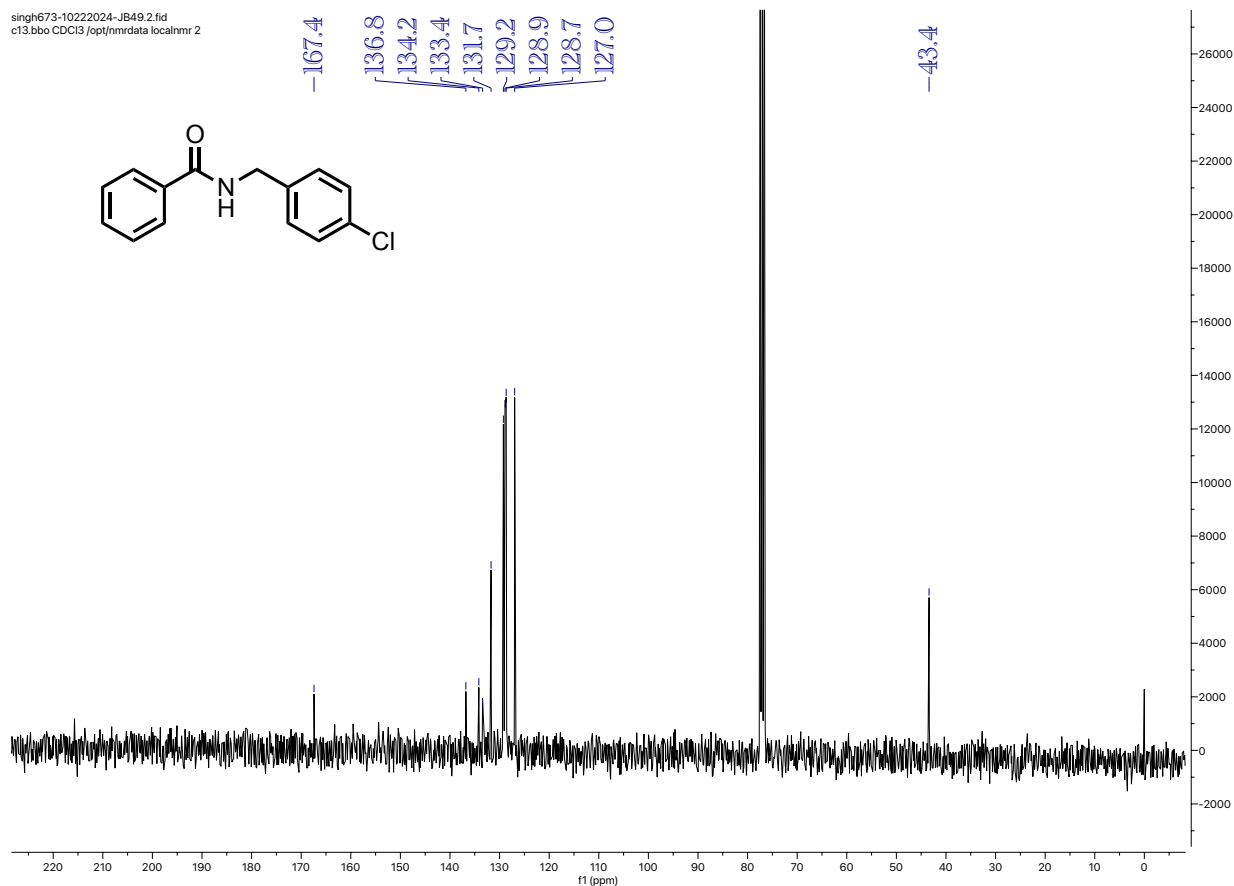
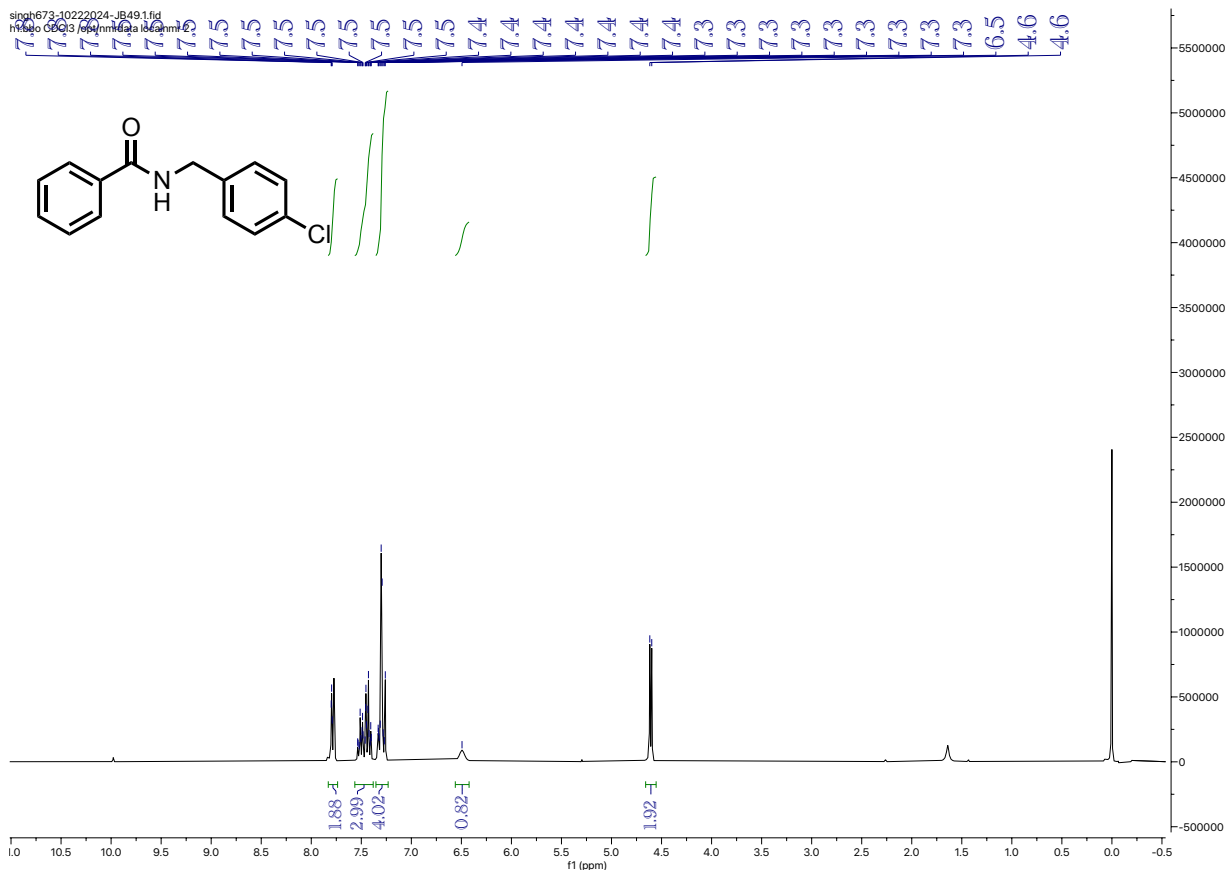
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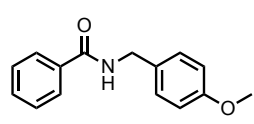
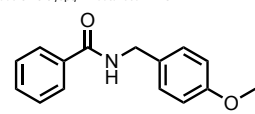


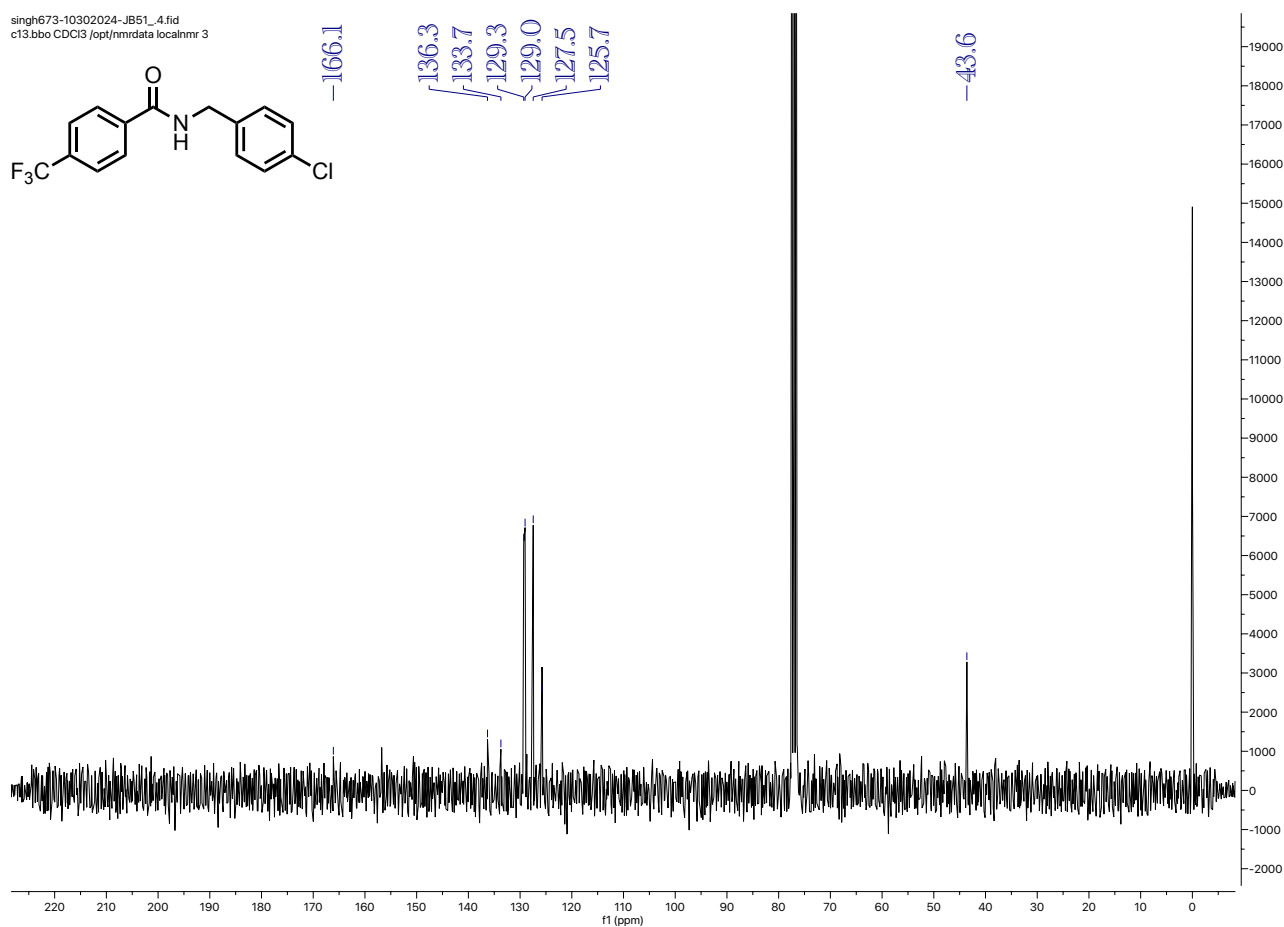
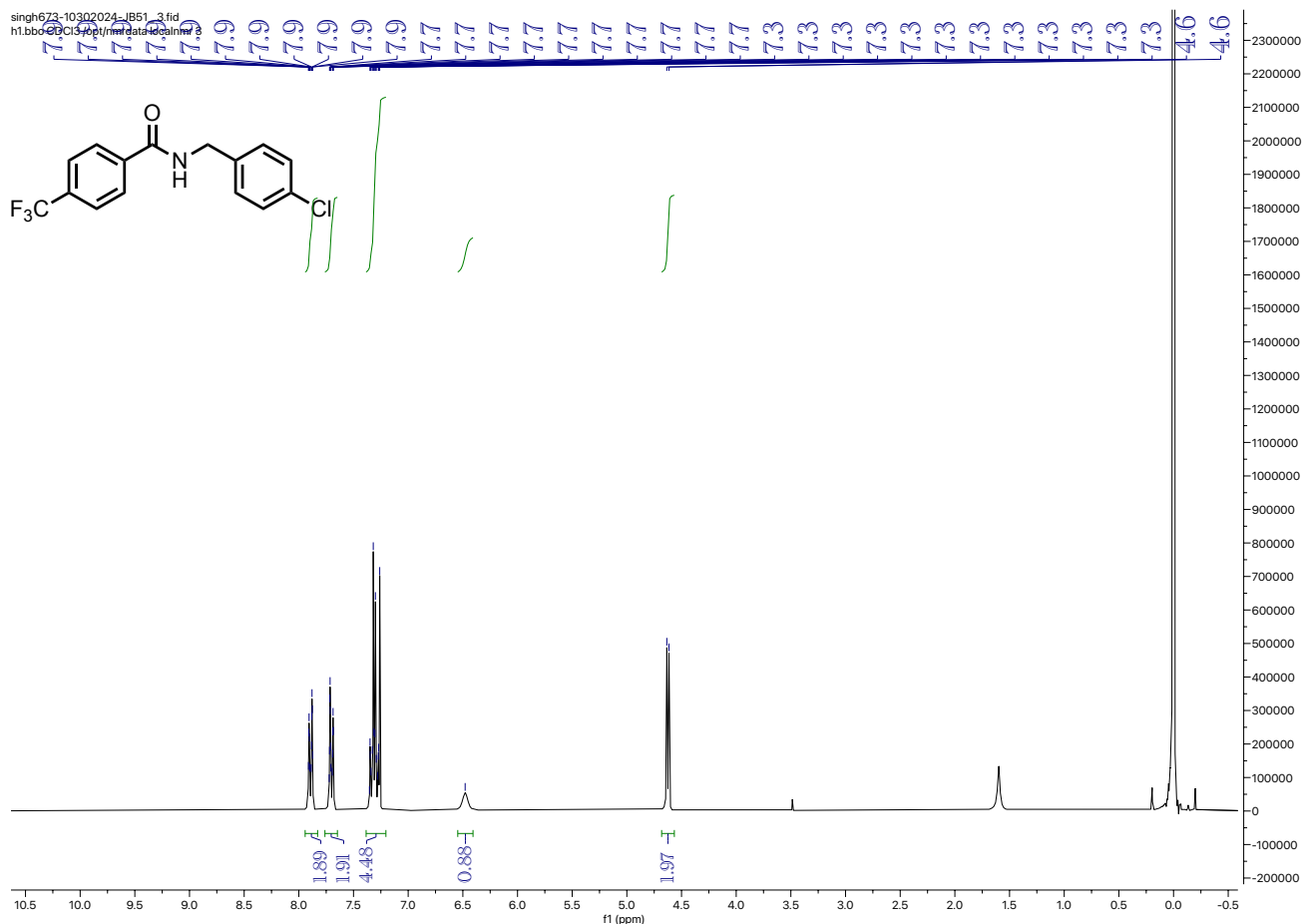
¹³C {¹H} NMR (75 MHz, Chloroform-*d*) *N*-benzyl-4-methoxybenzamide (**7**)

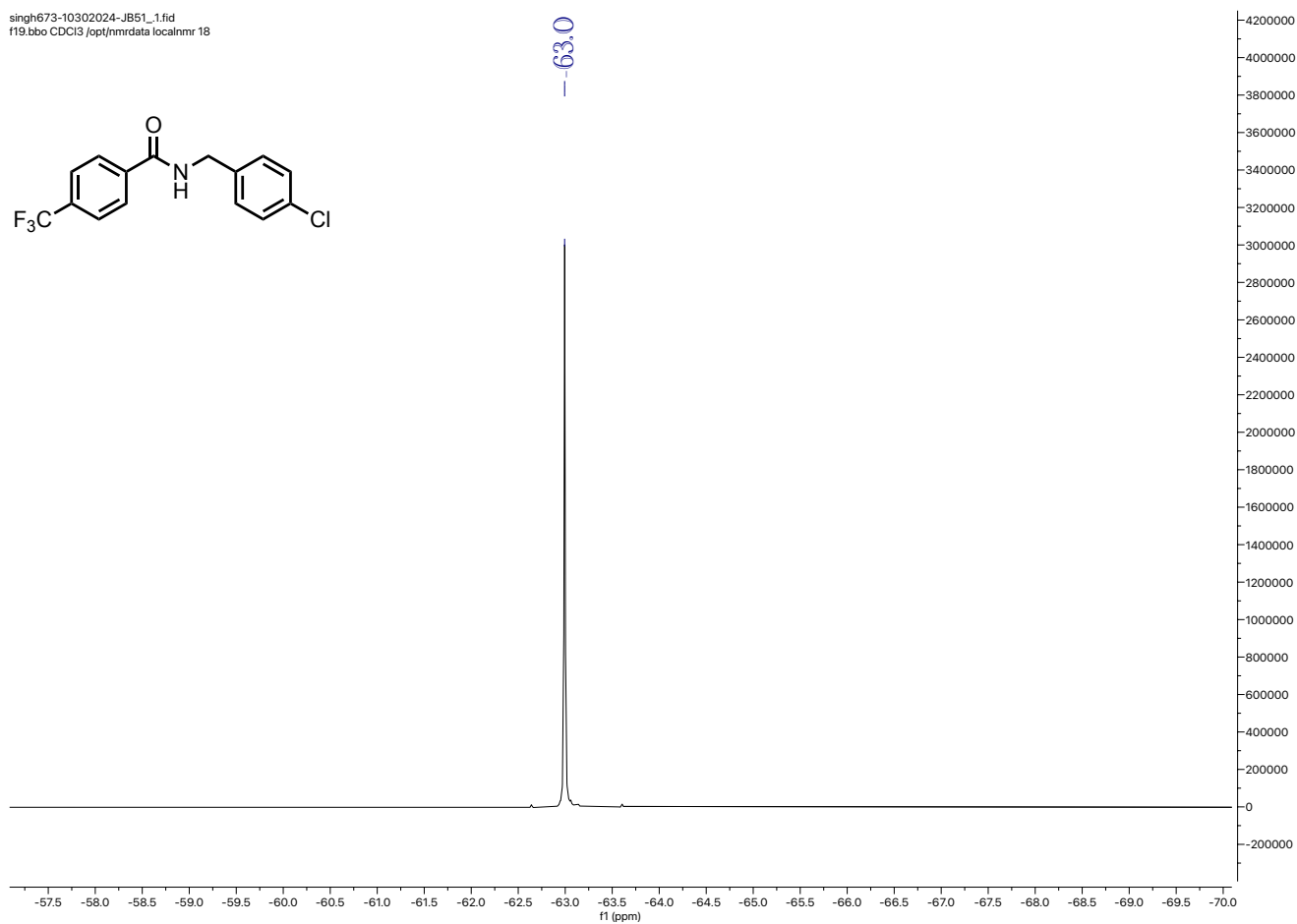


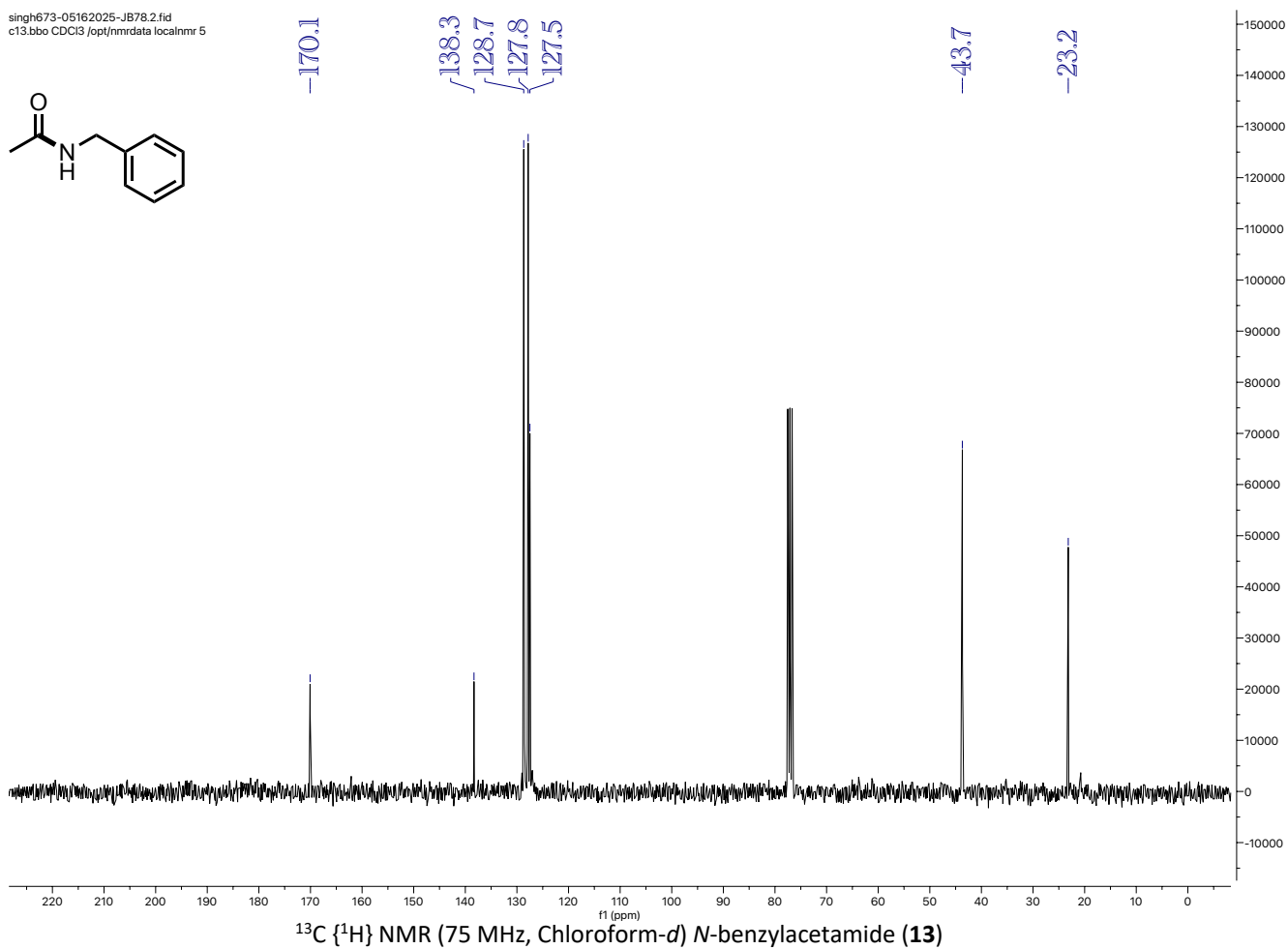
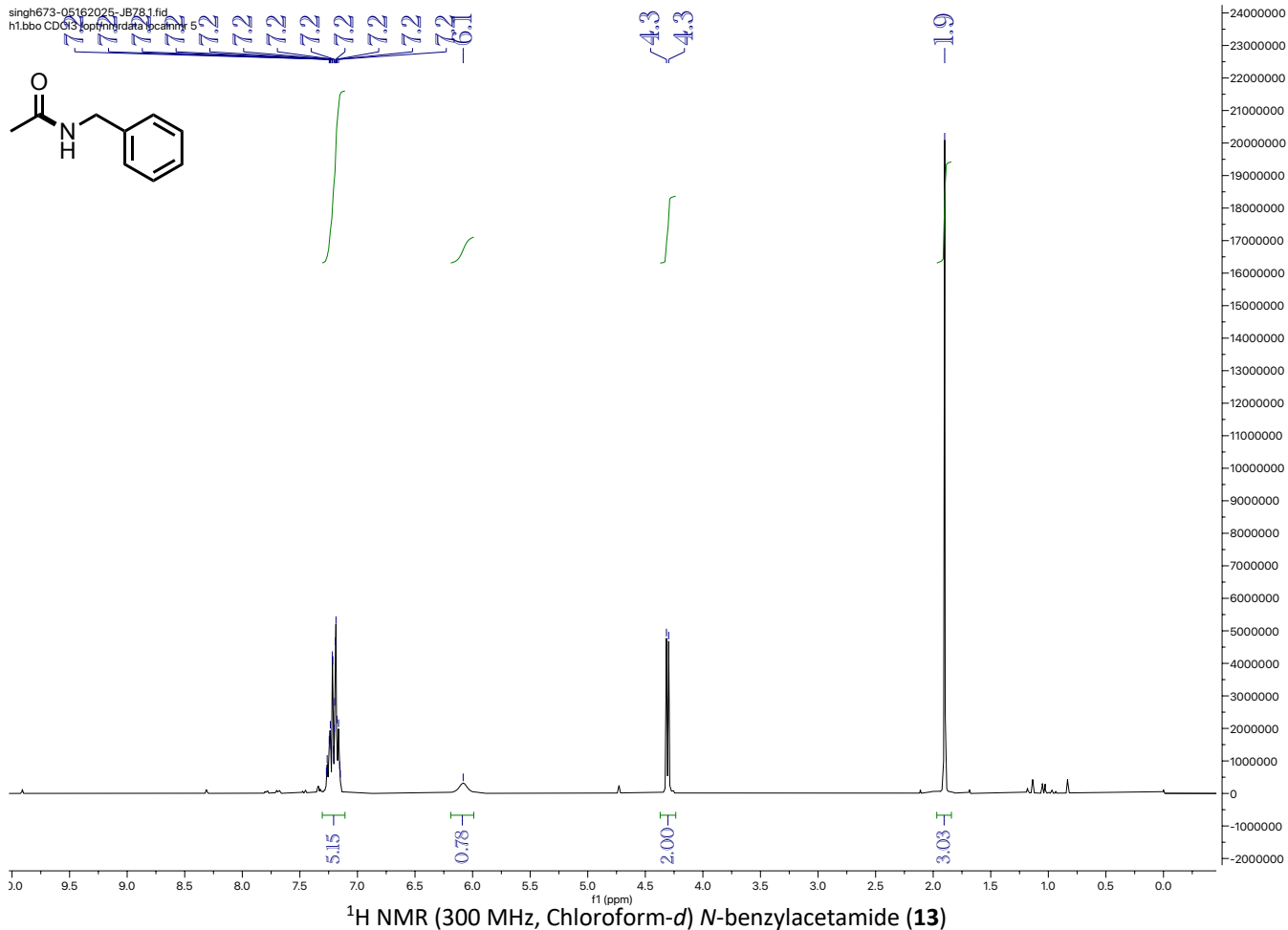


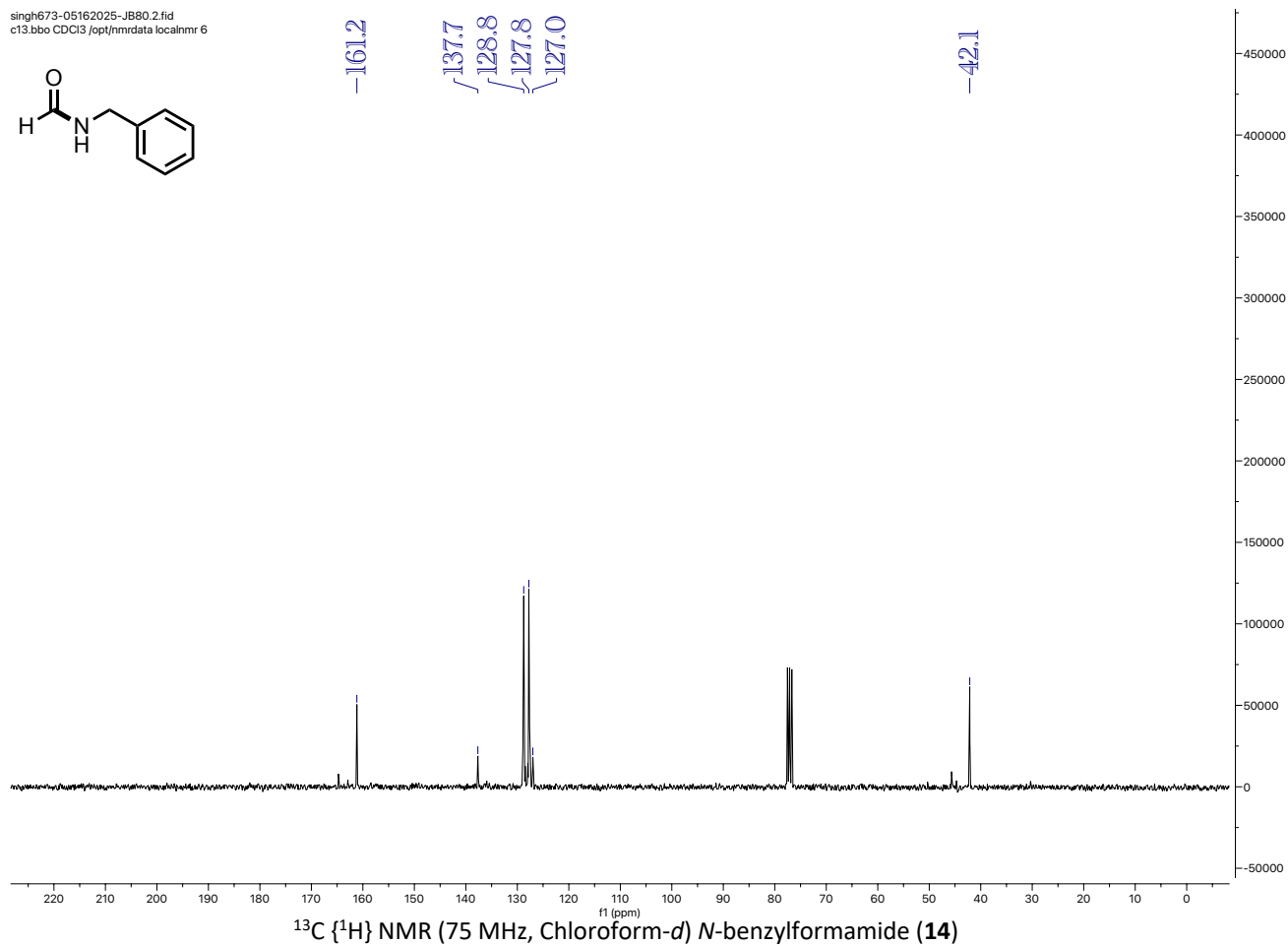
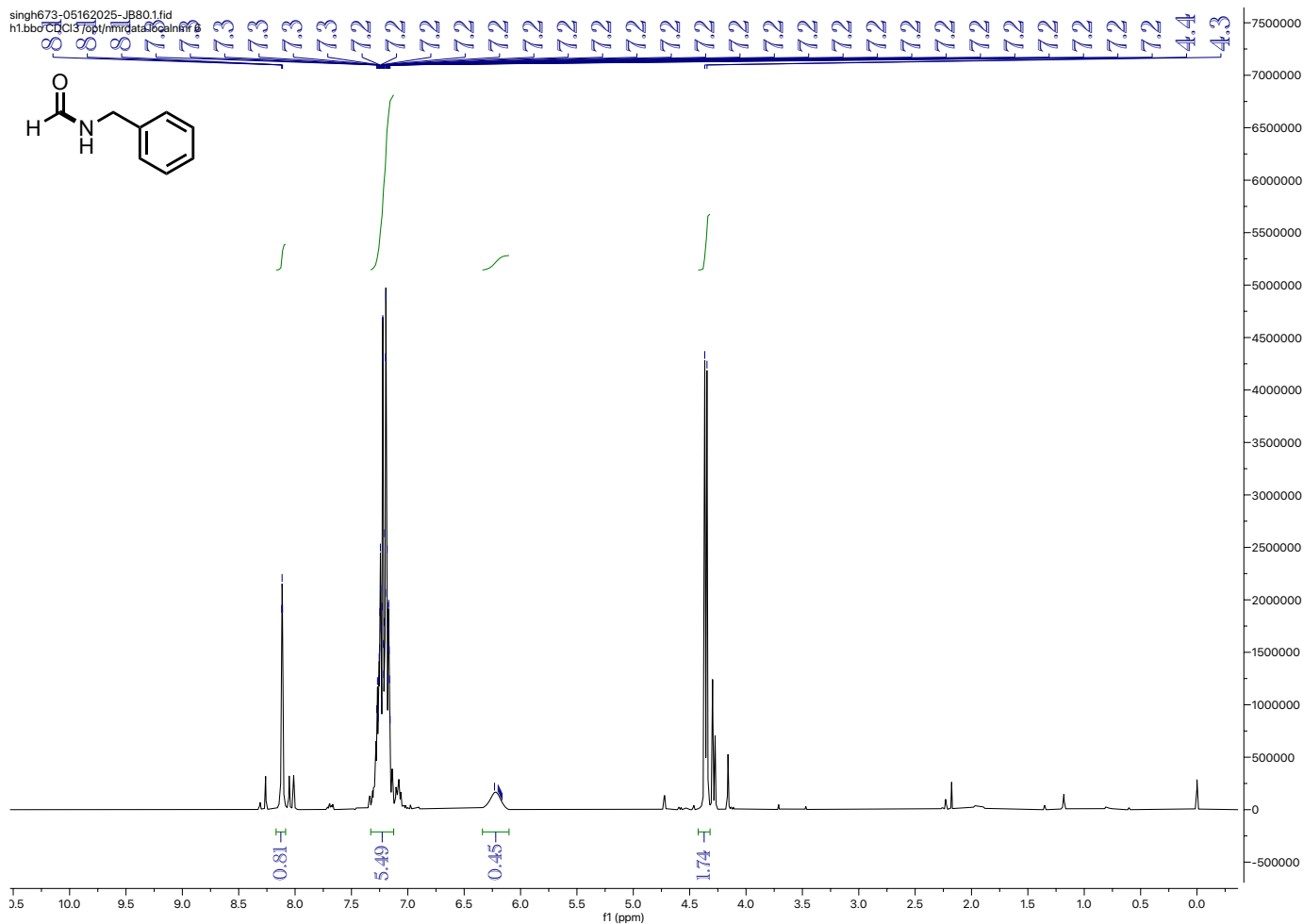


¹H NMR (300 MHz, Chloroform-*d*) *N*-(4-methoxybenzyl)benzamide (**11**)¹³C {¹H} NMR (75 MHz, Chloroform-*d*) *N*-(4-methoxybenzyl)benzamide (**11**)

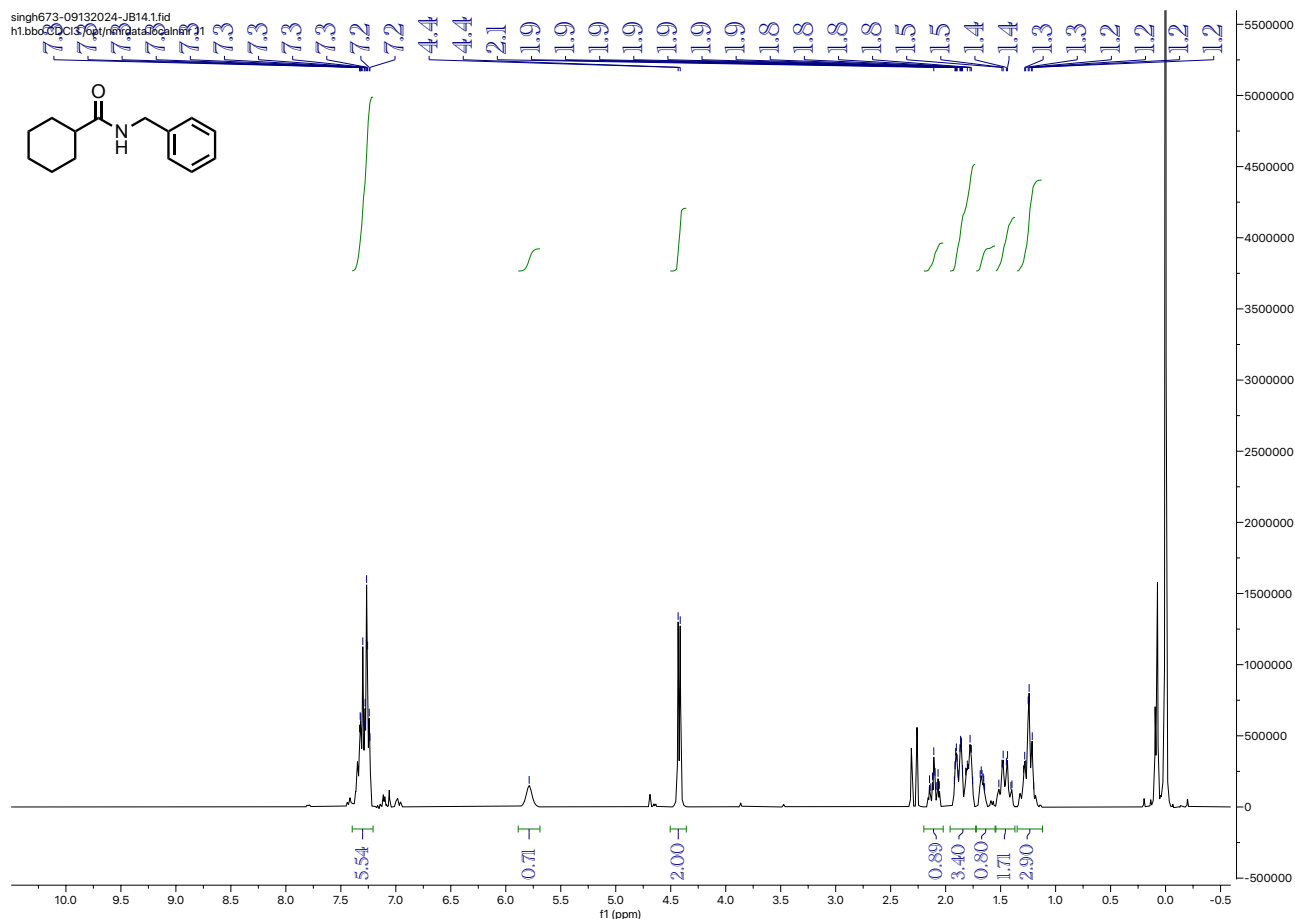




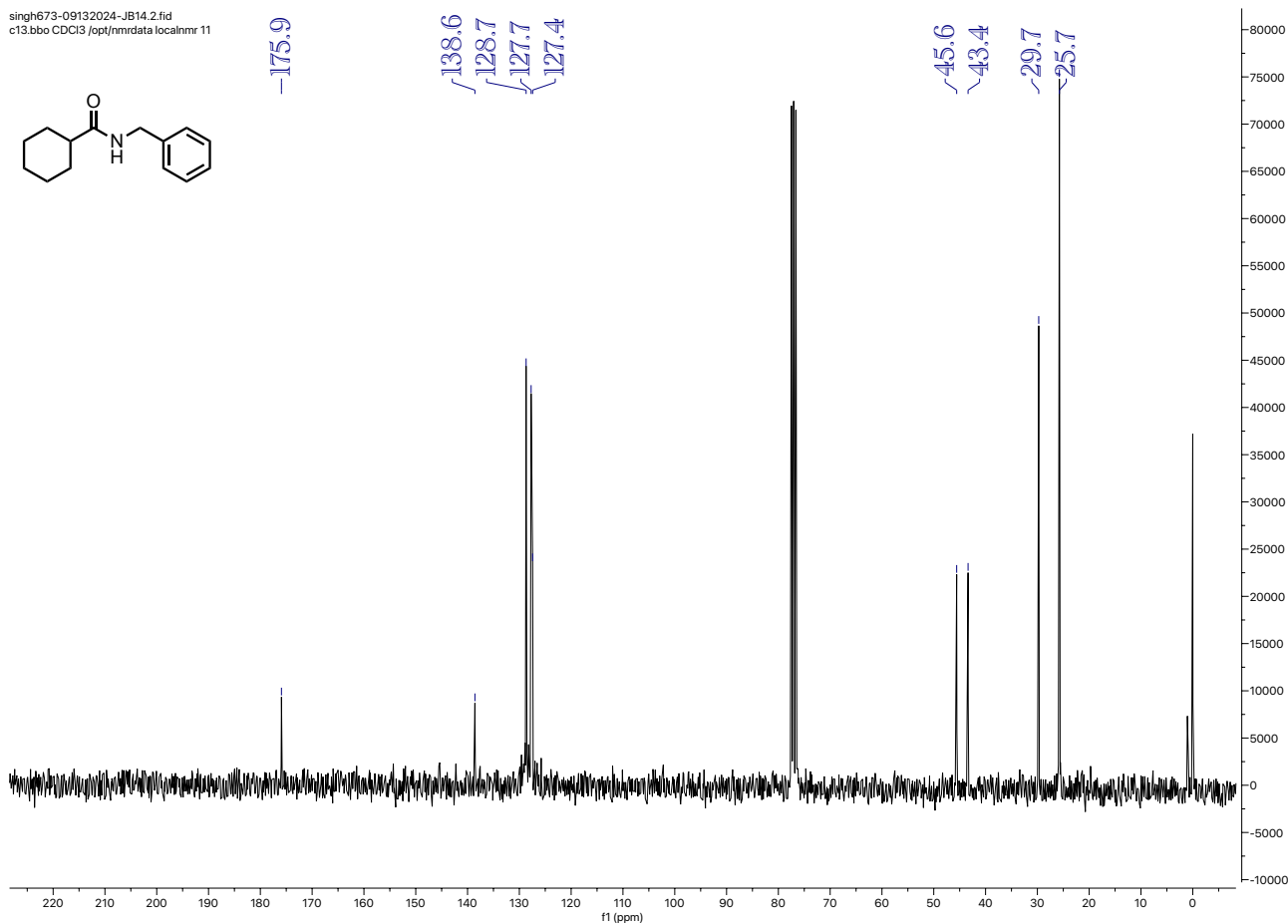




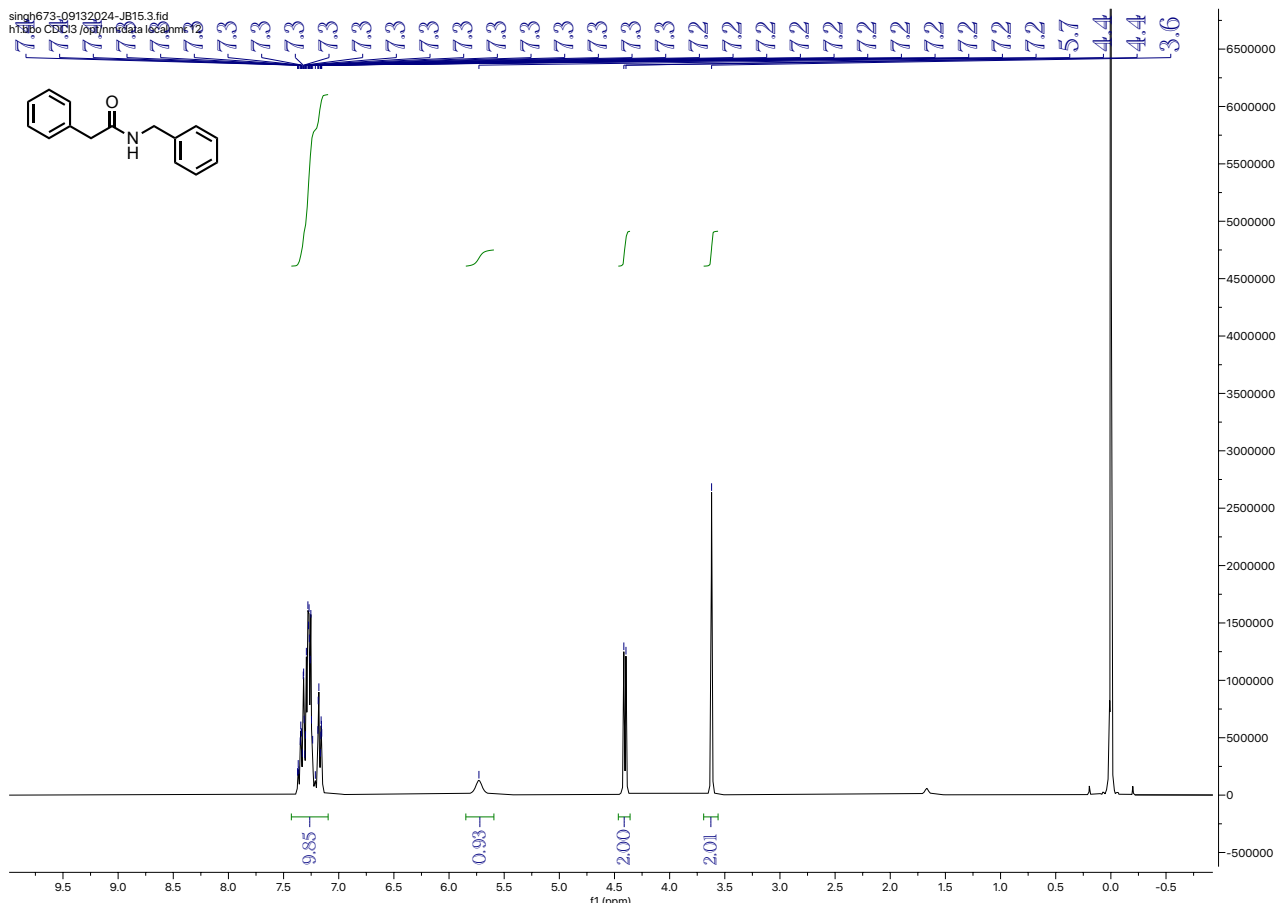
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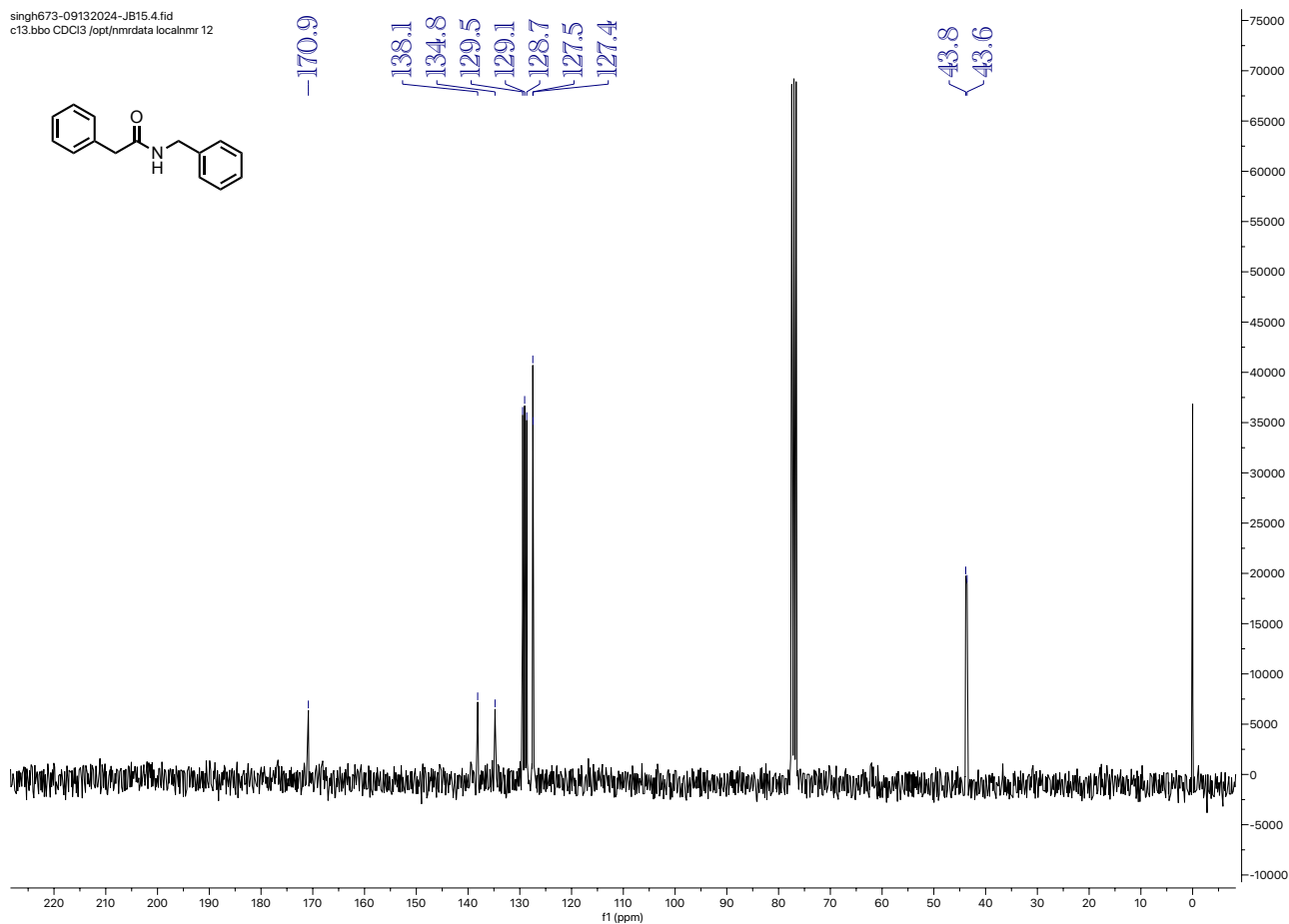
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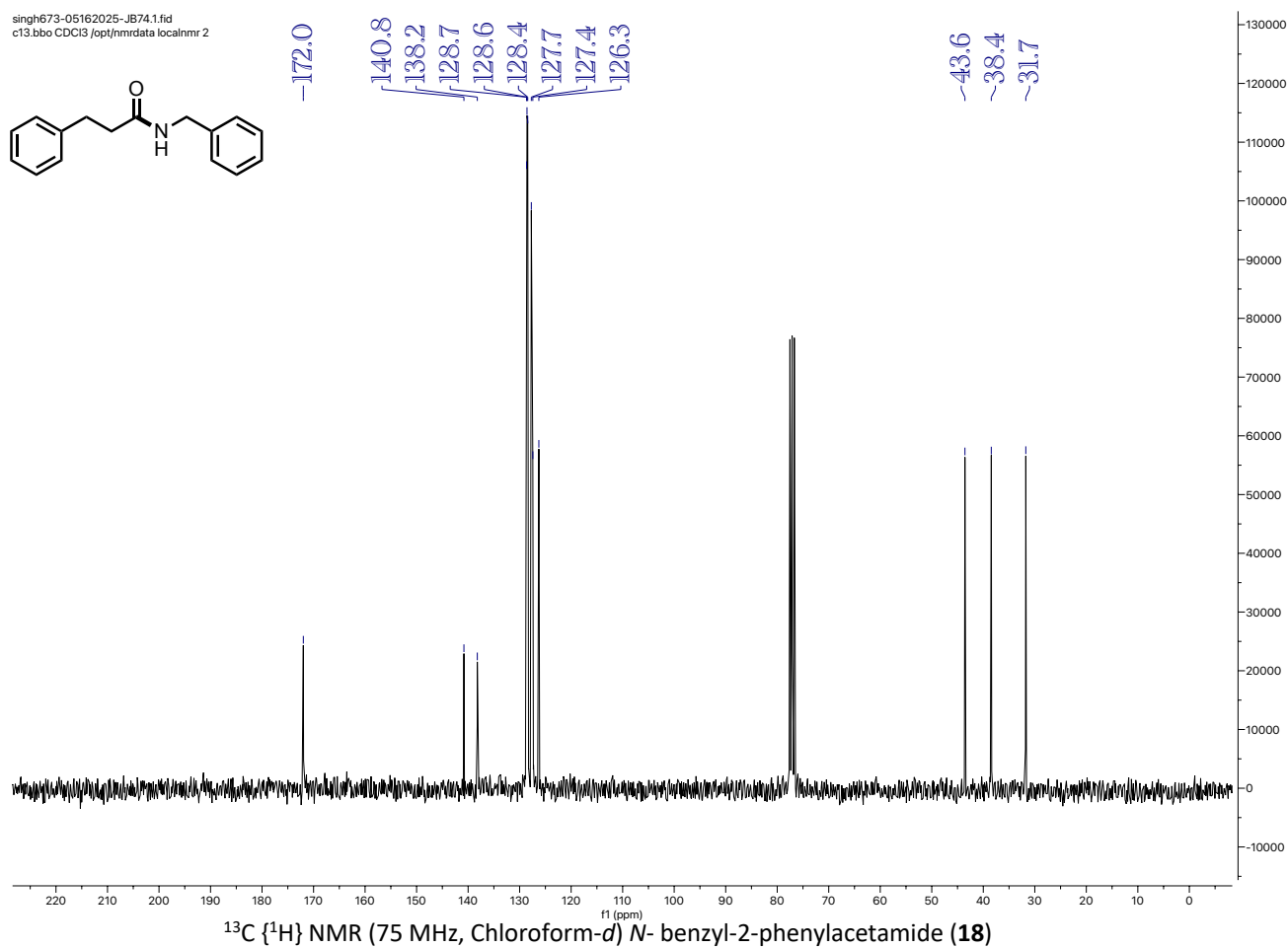
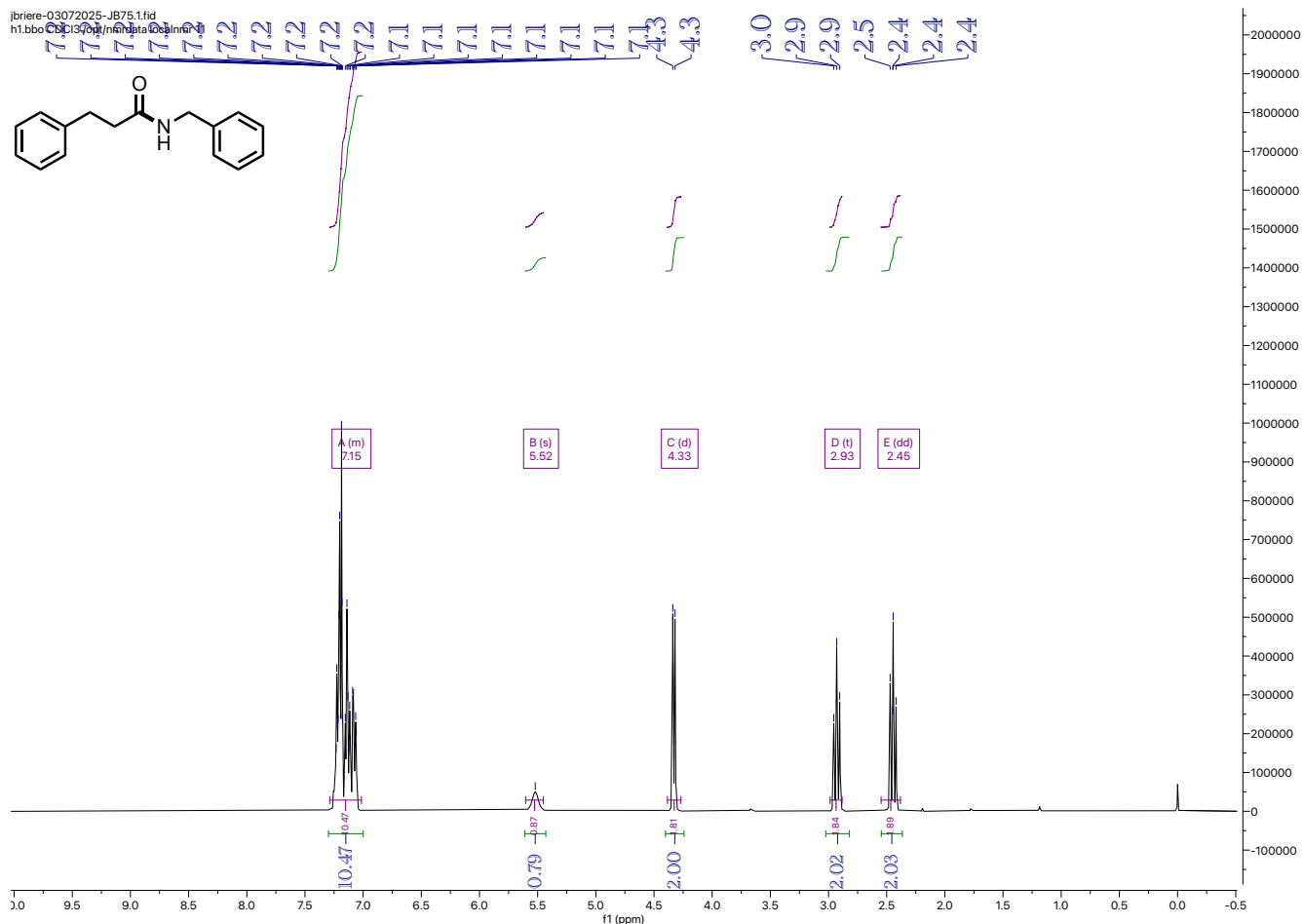


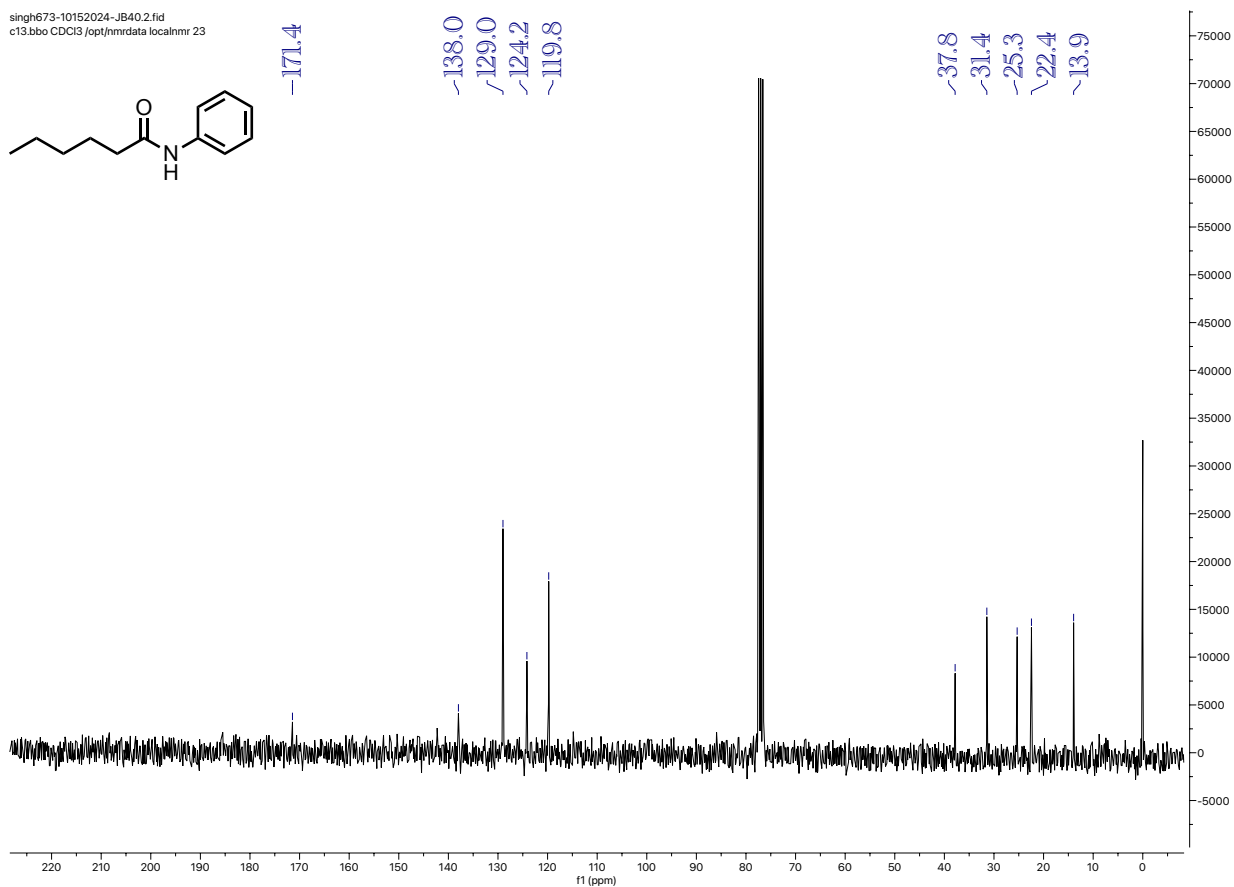
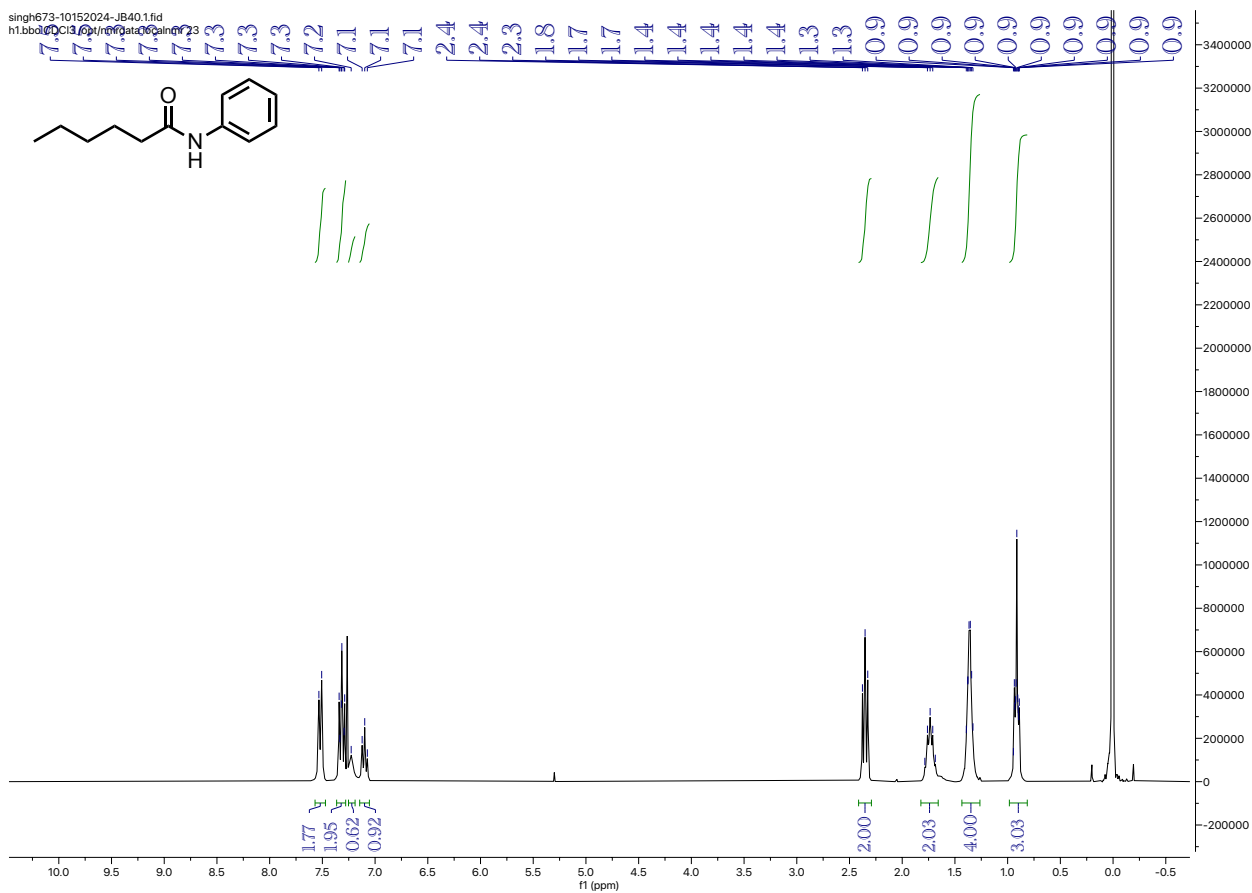
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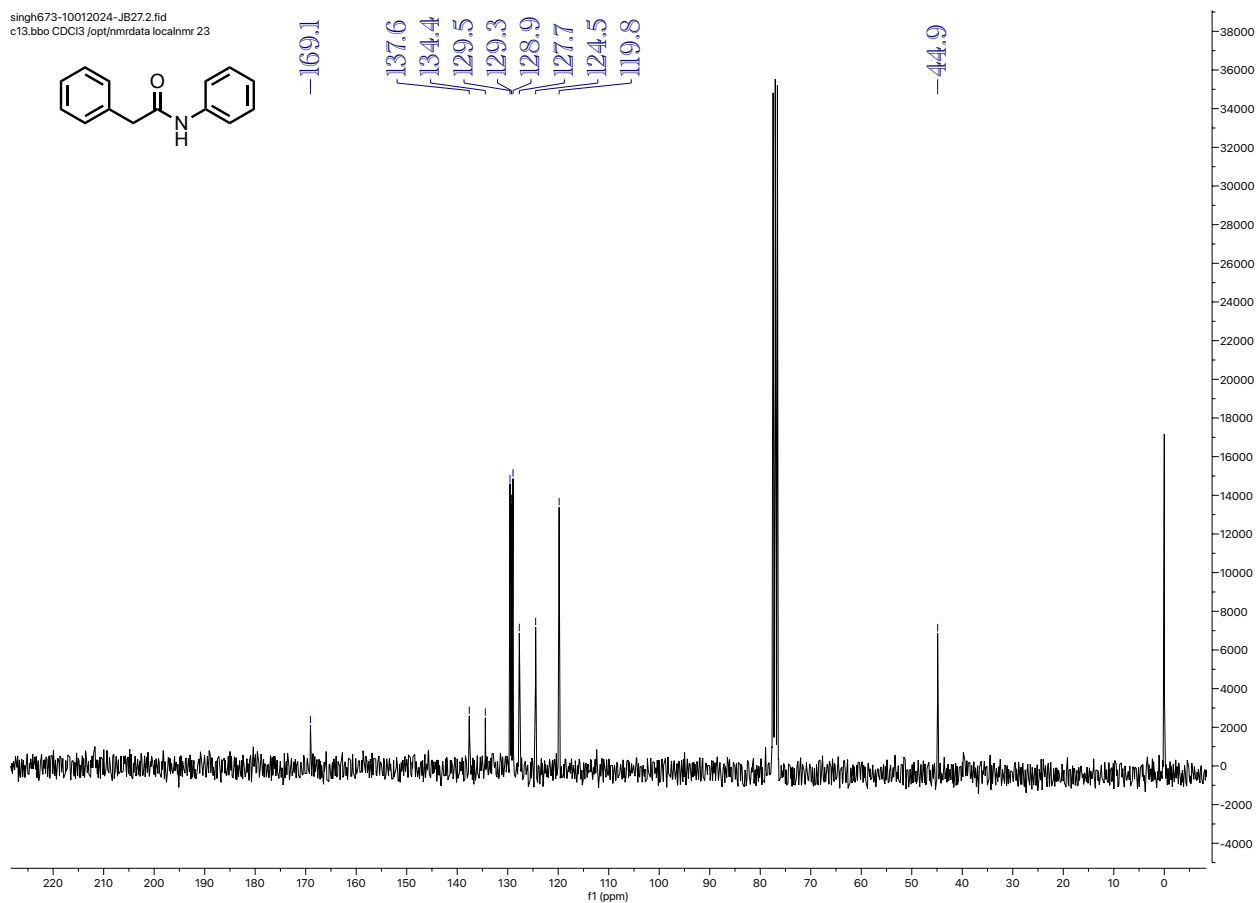
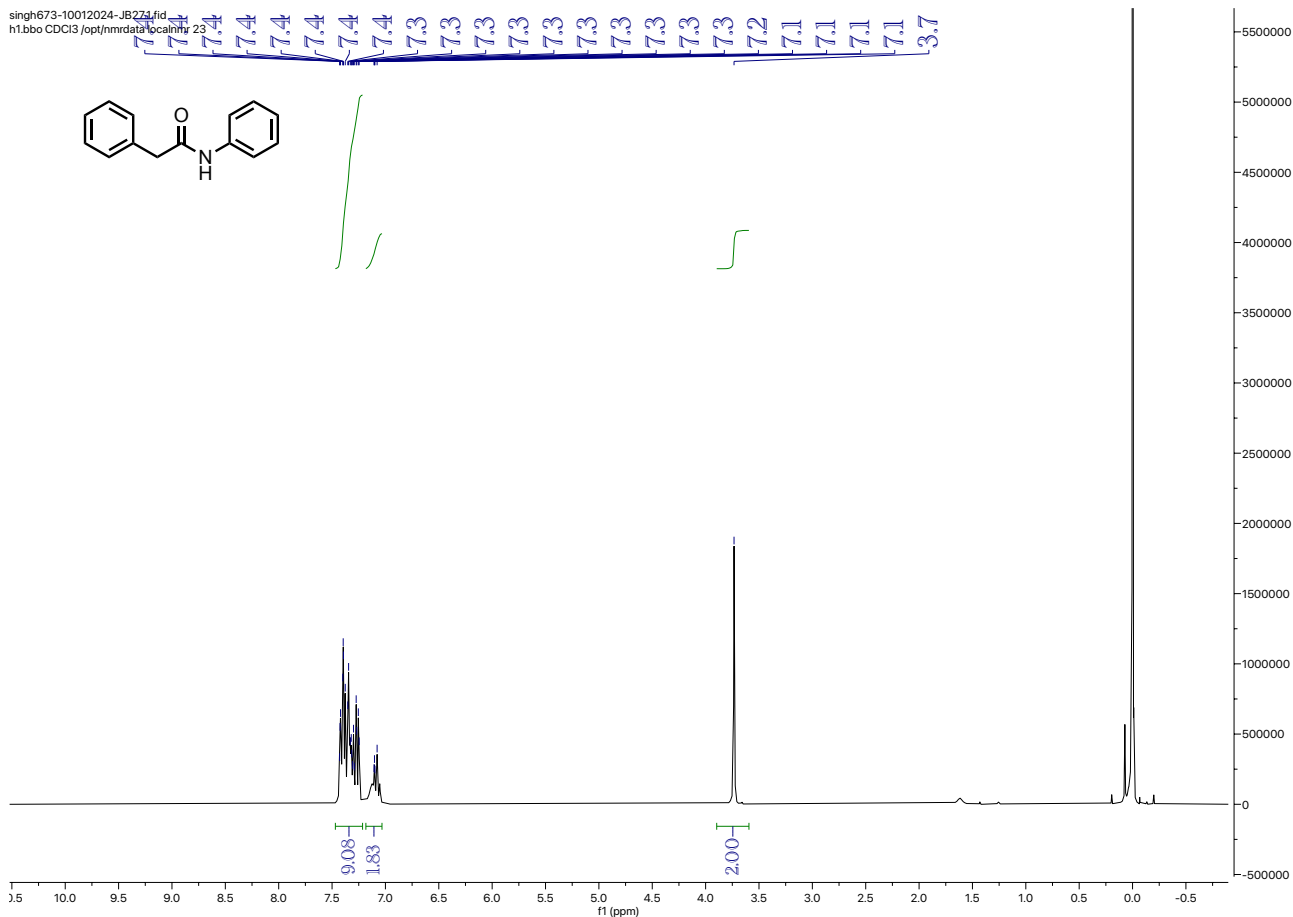


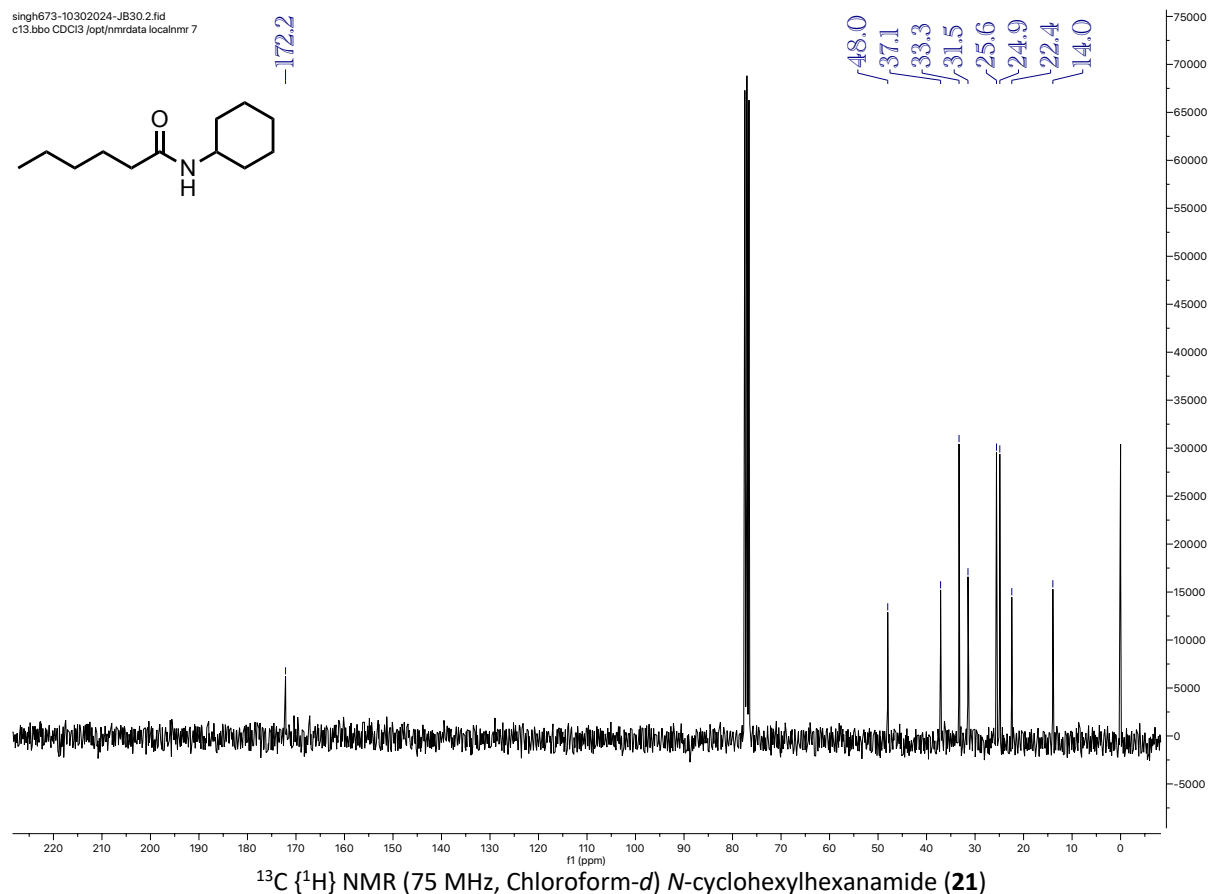
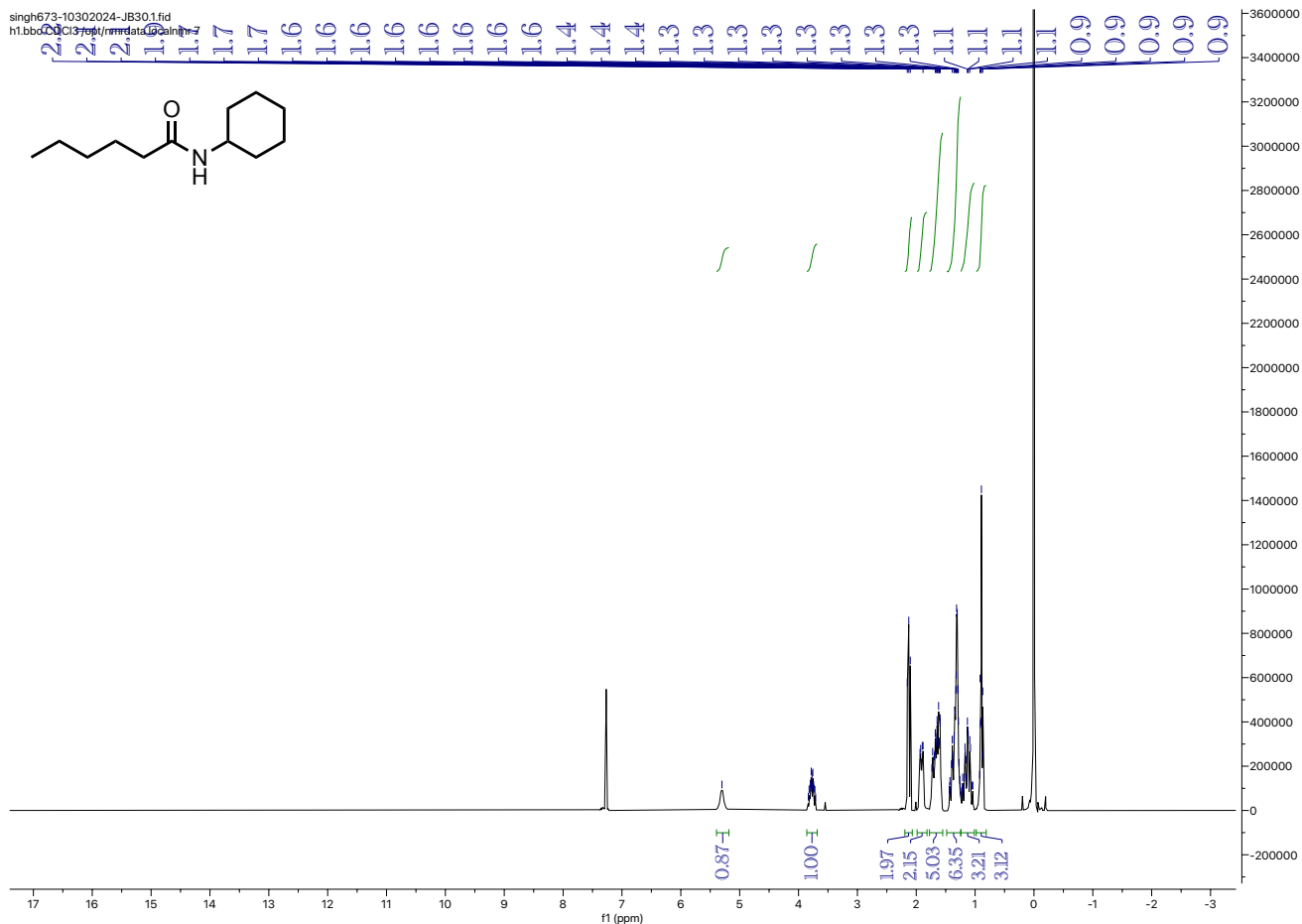
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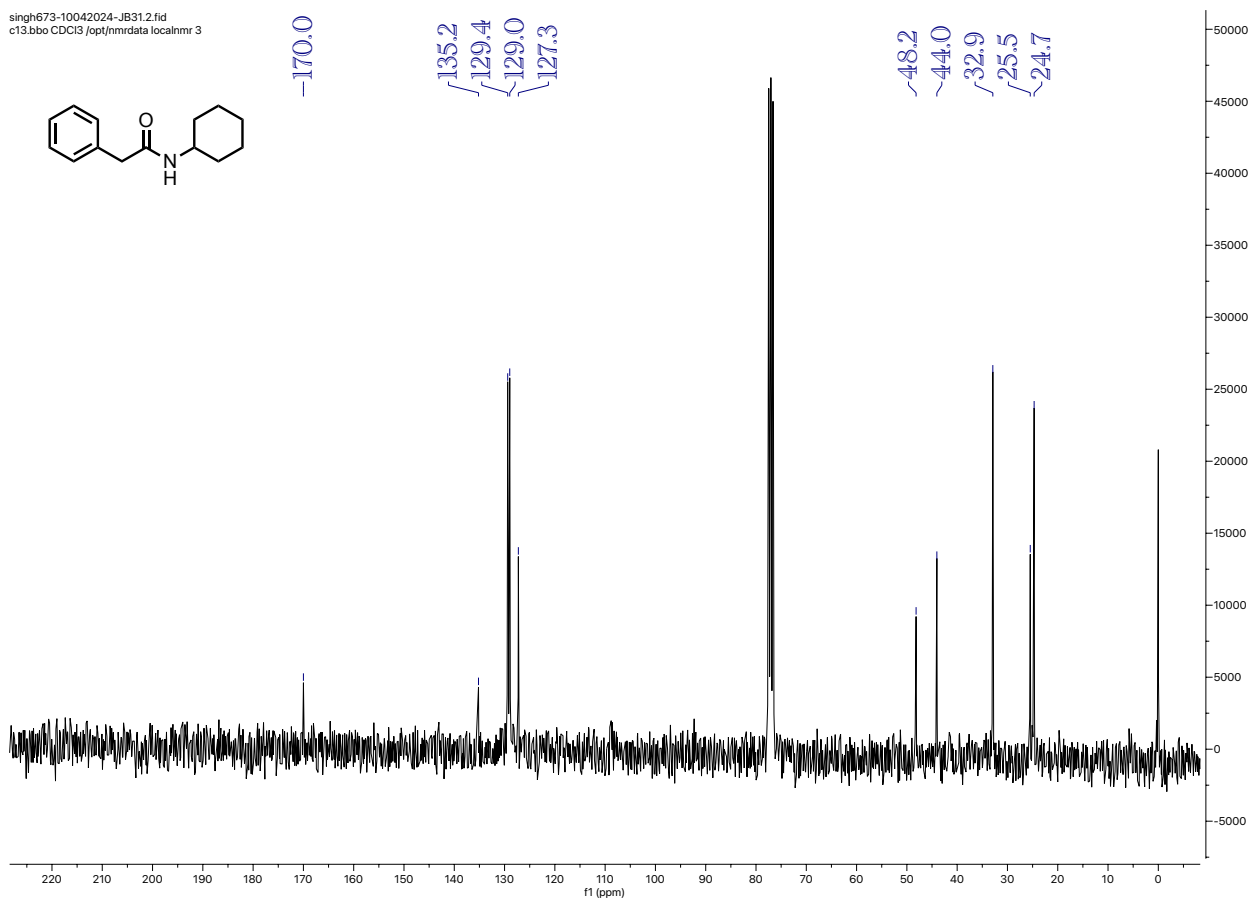
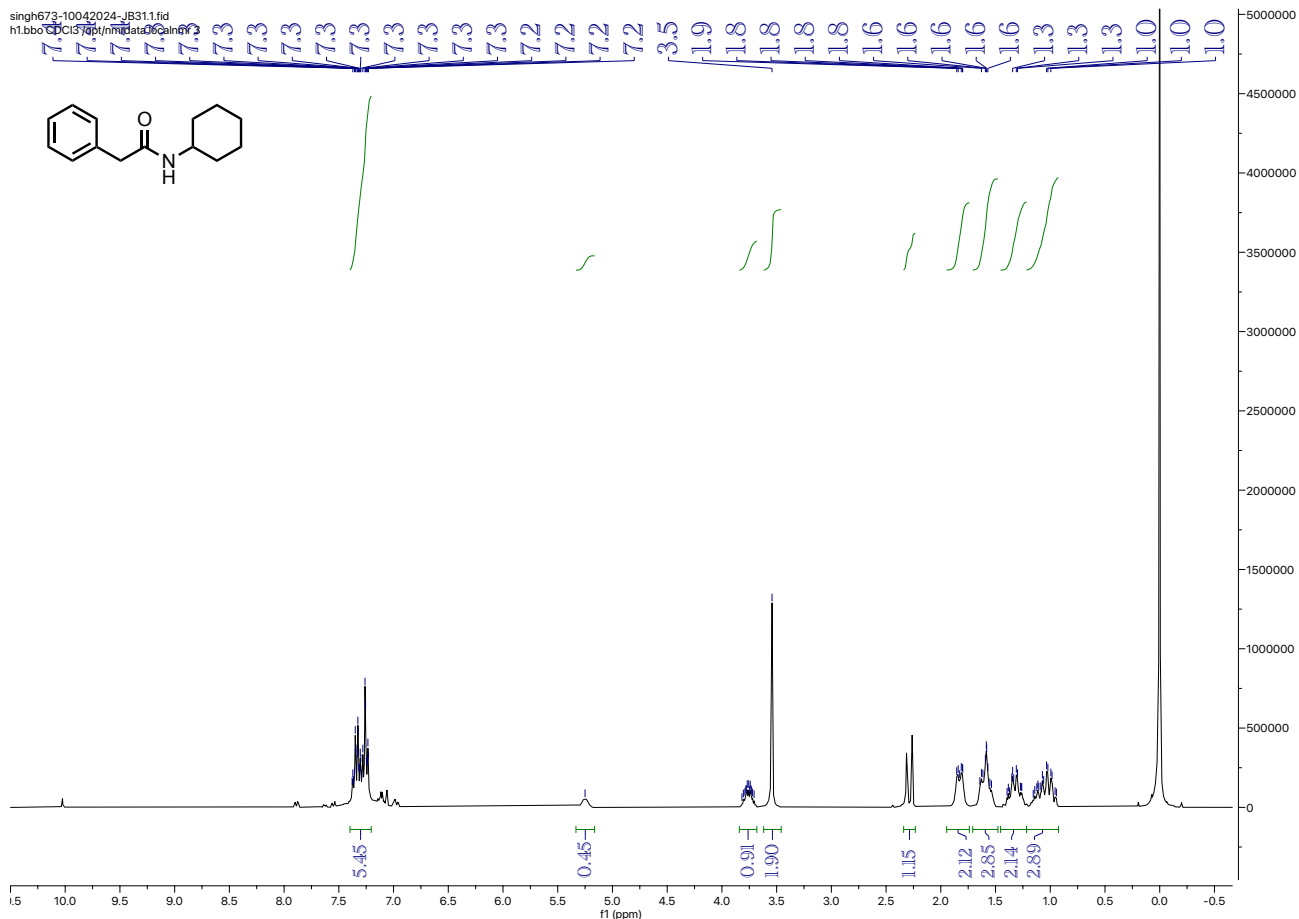




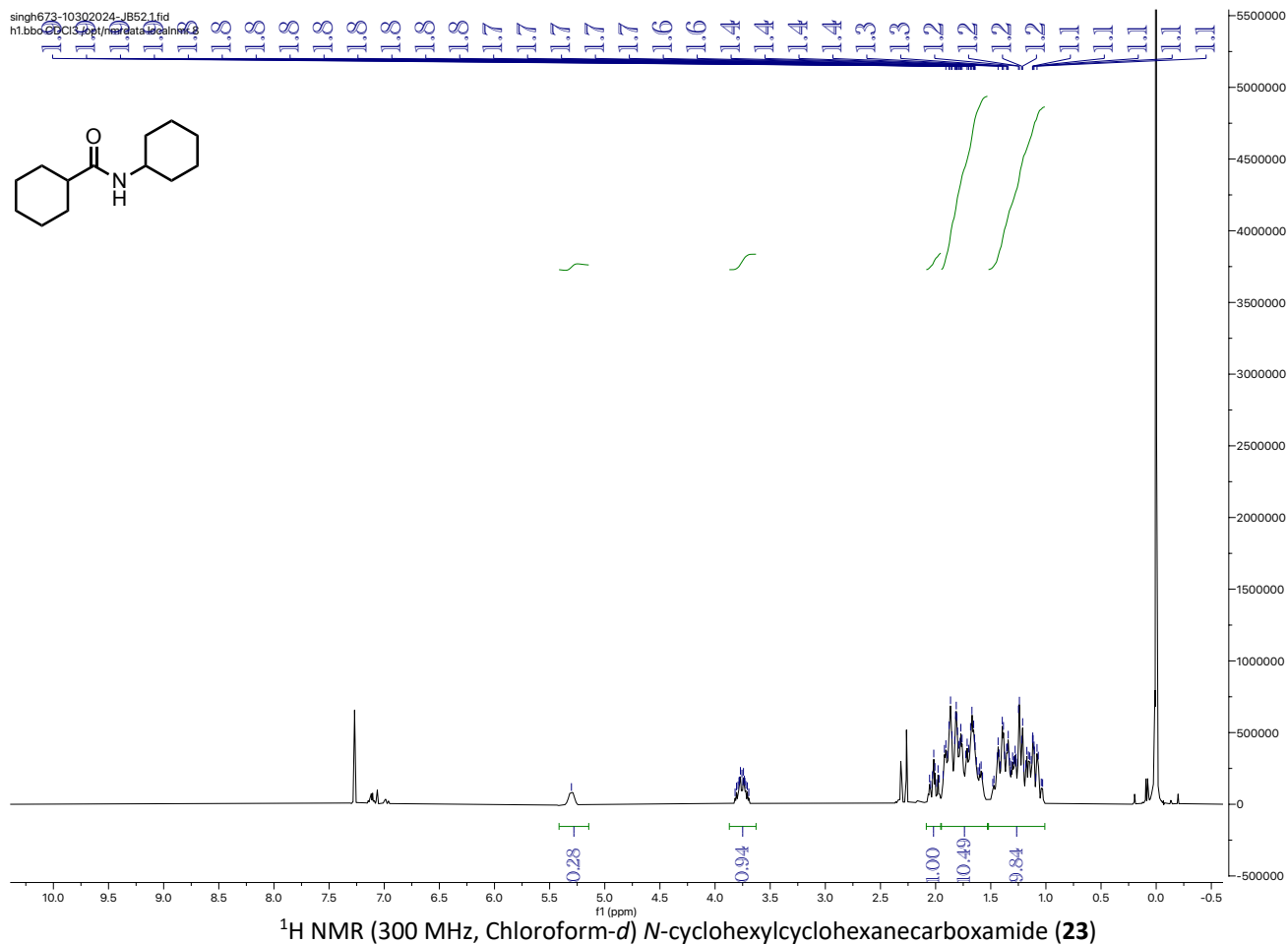
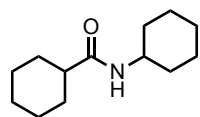




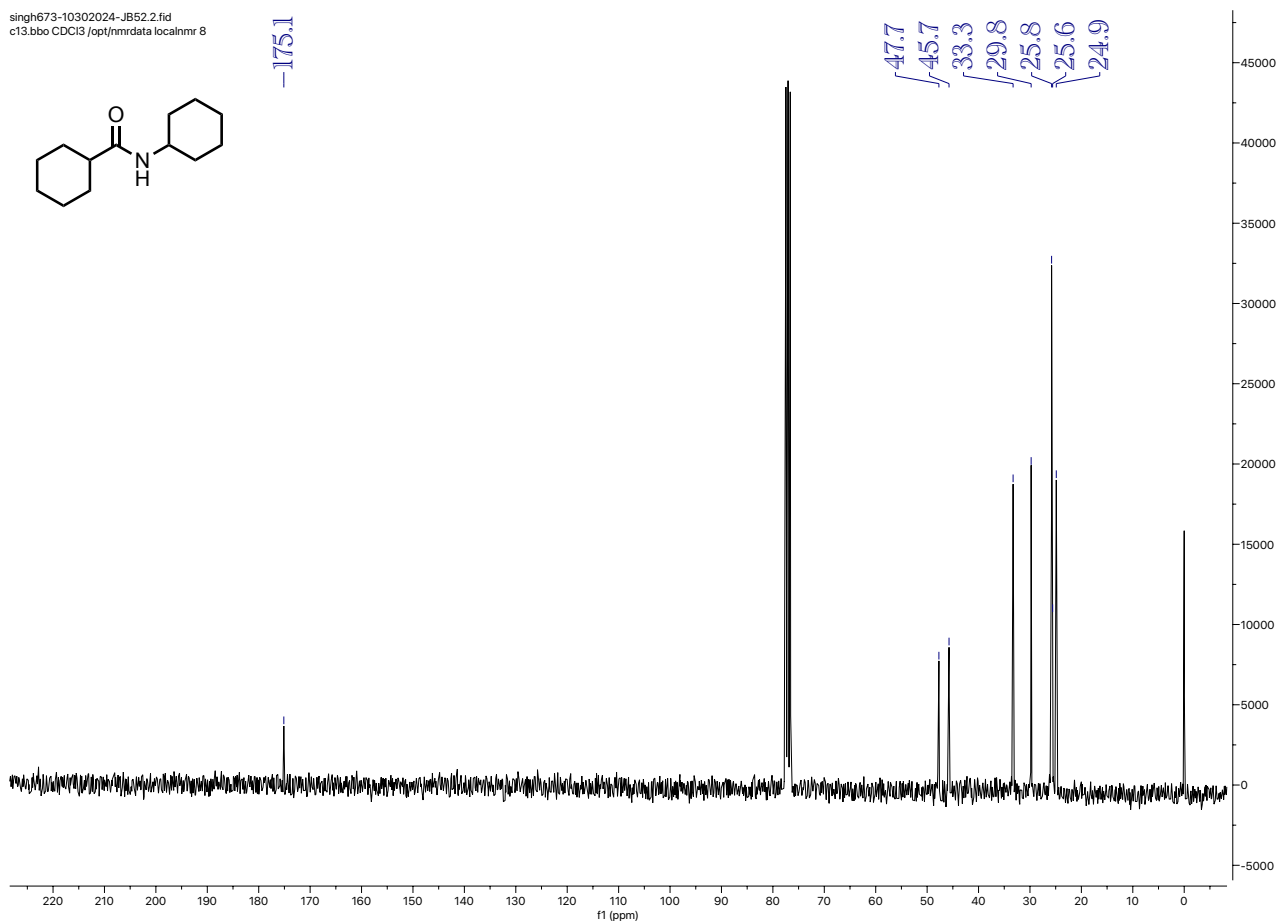
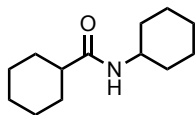


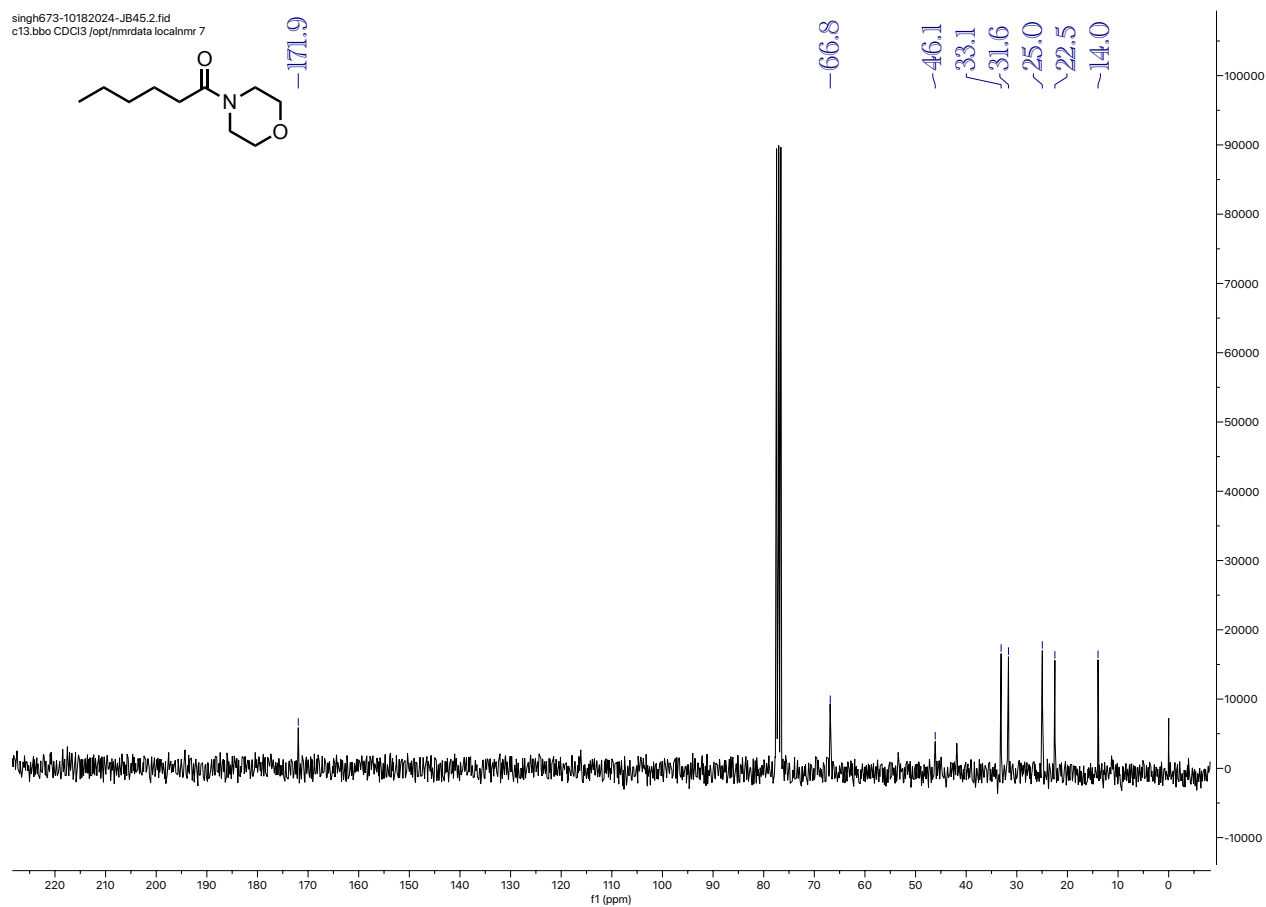
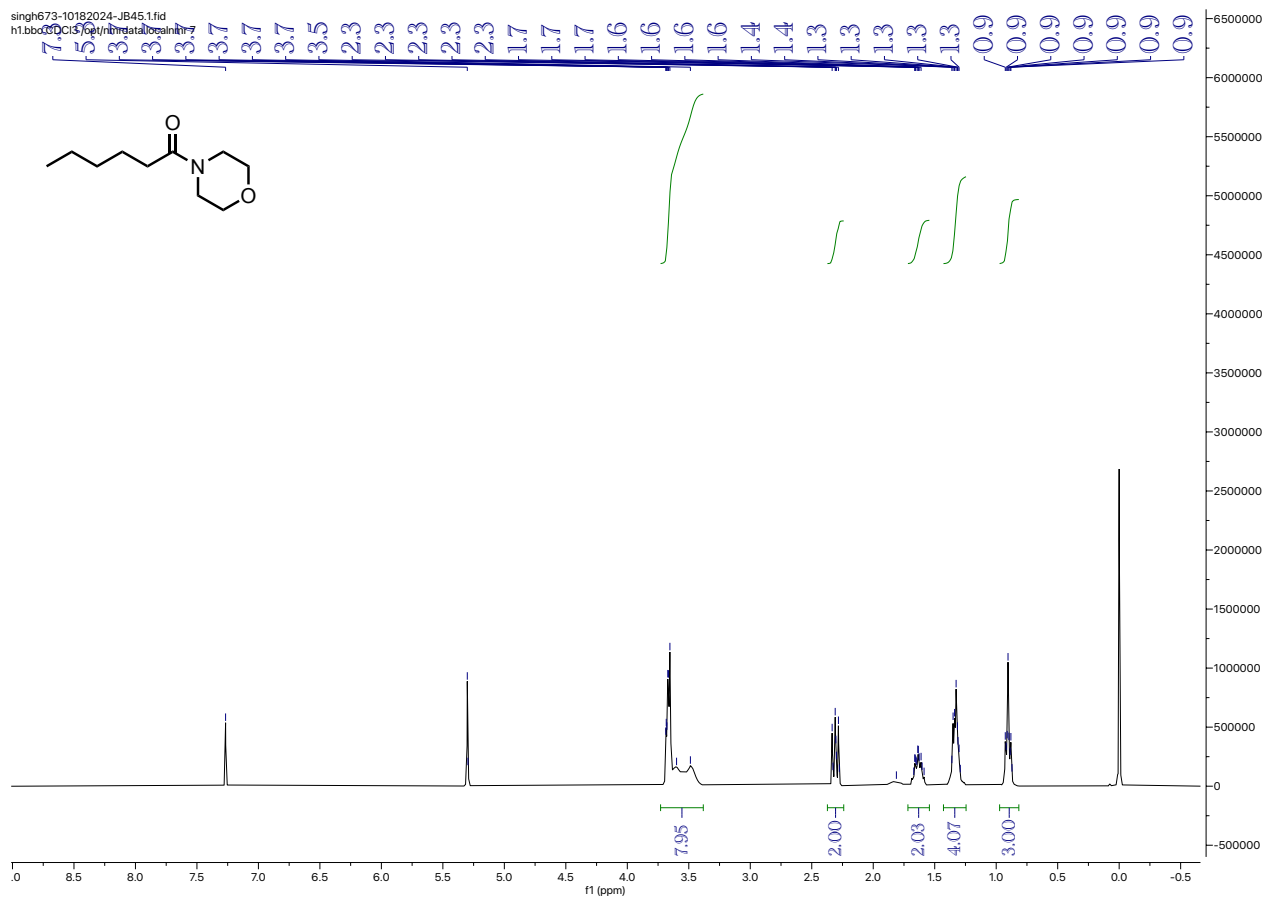


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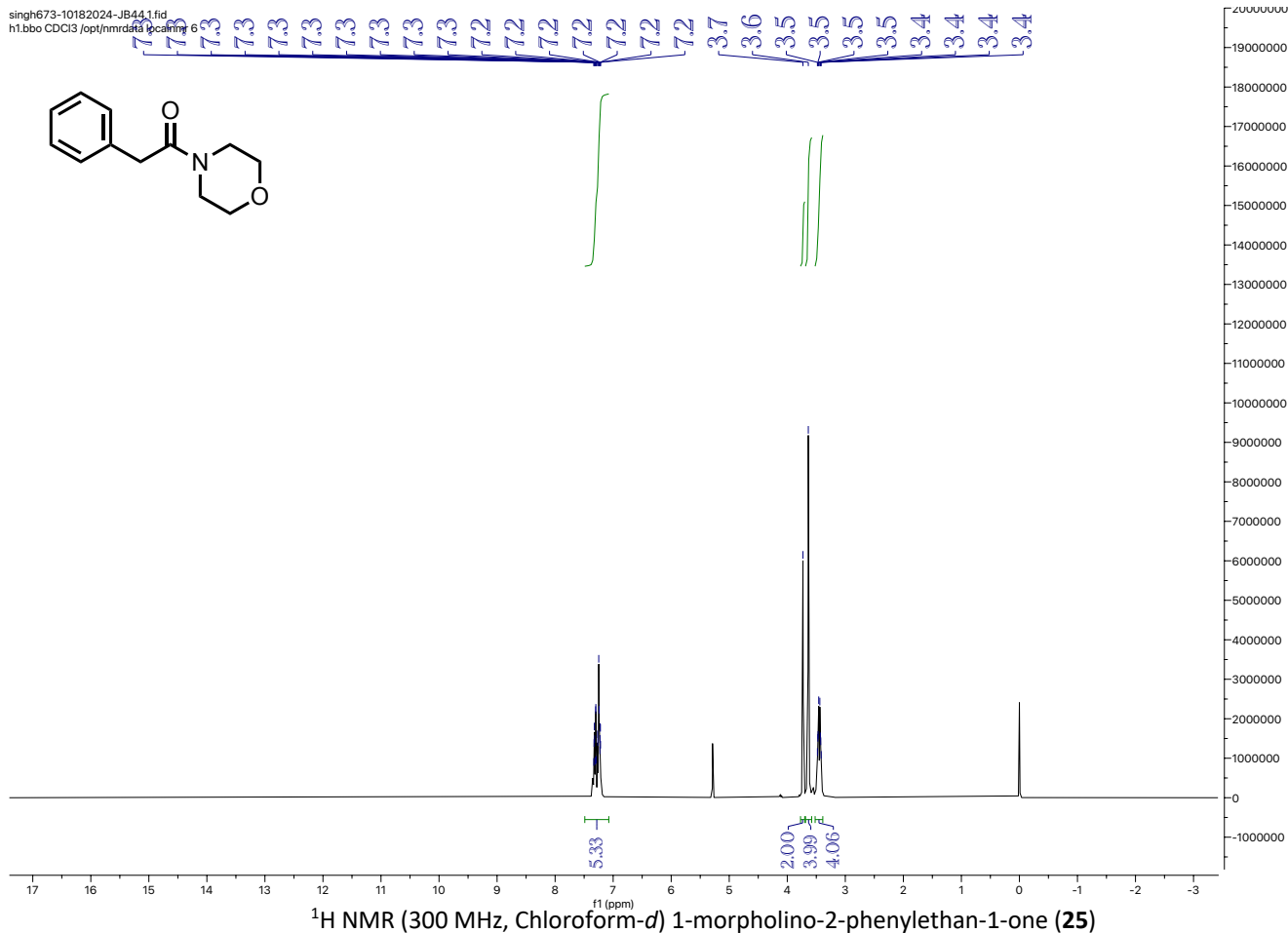


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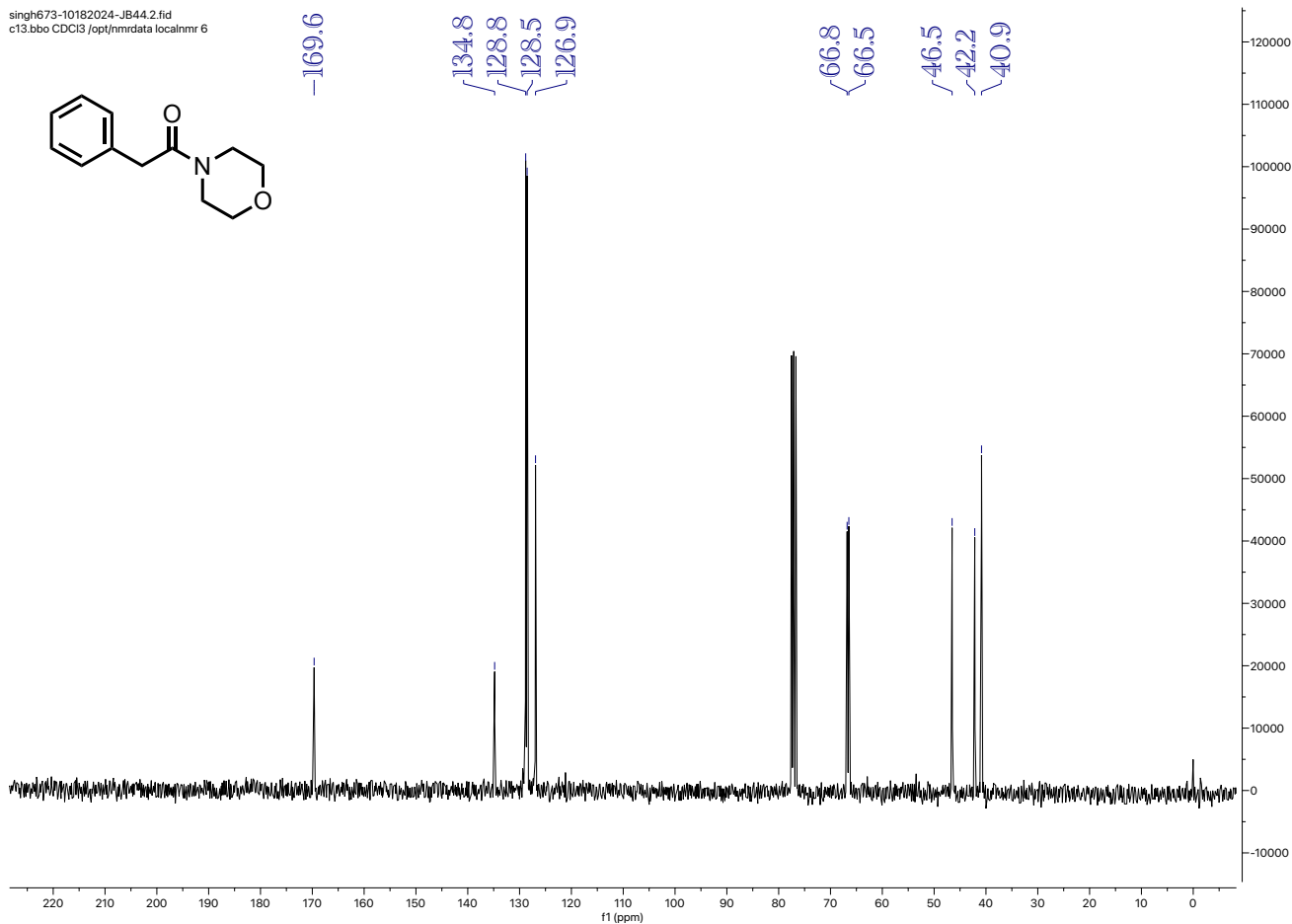


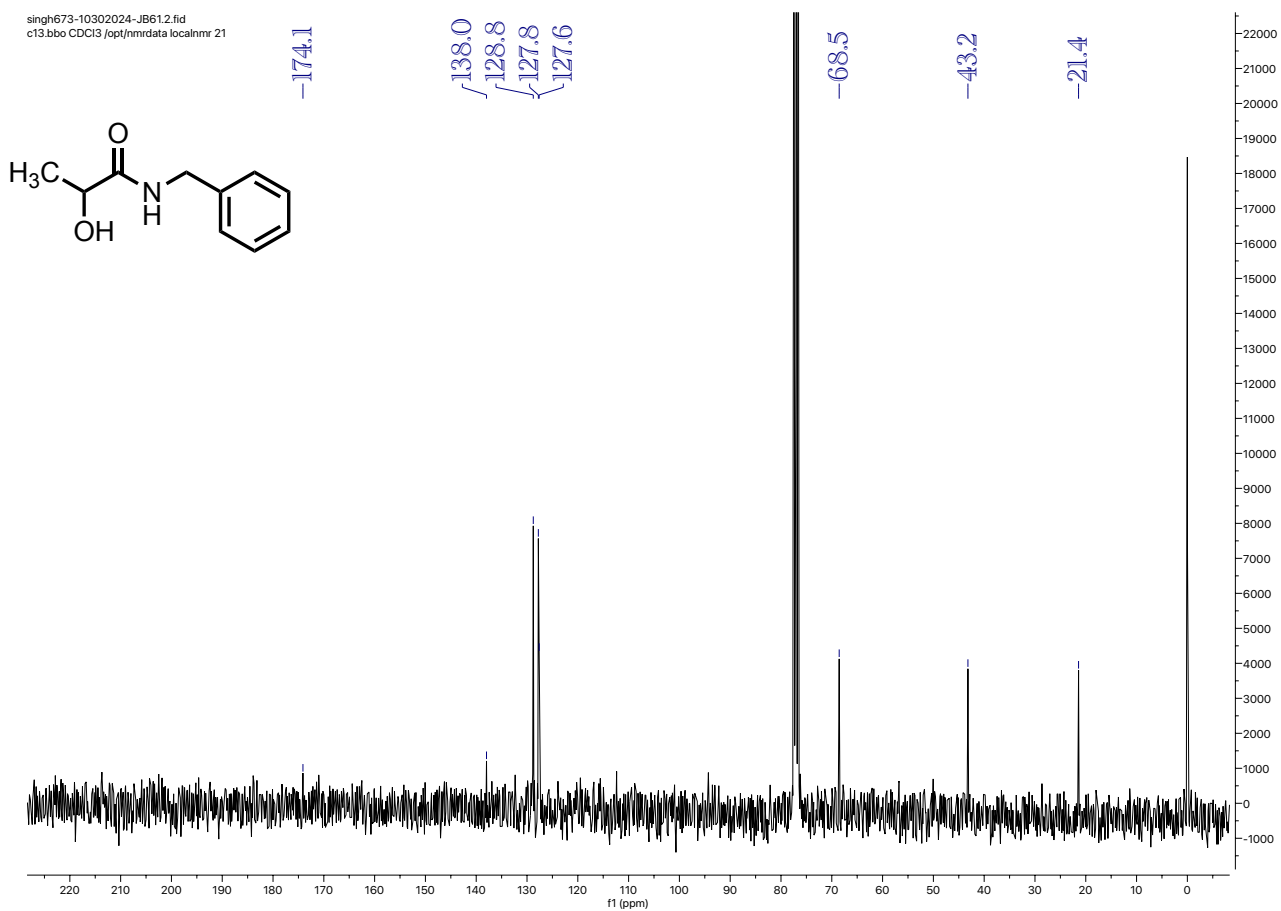
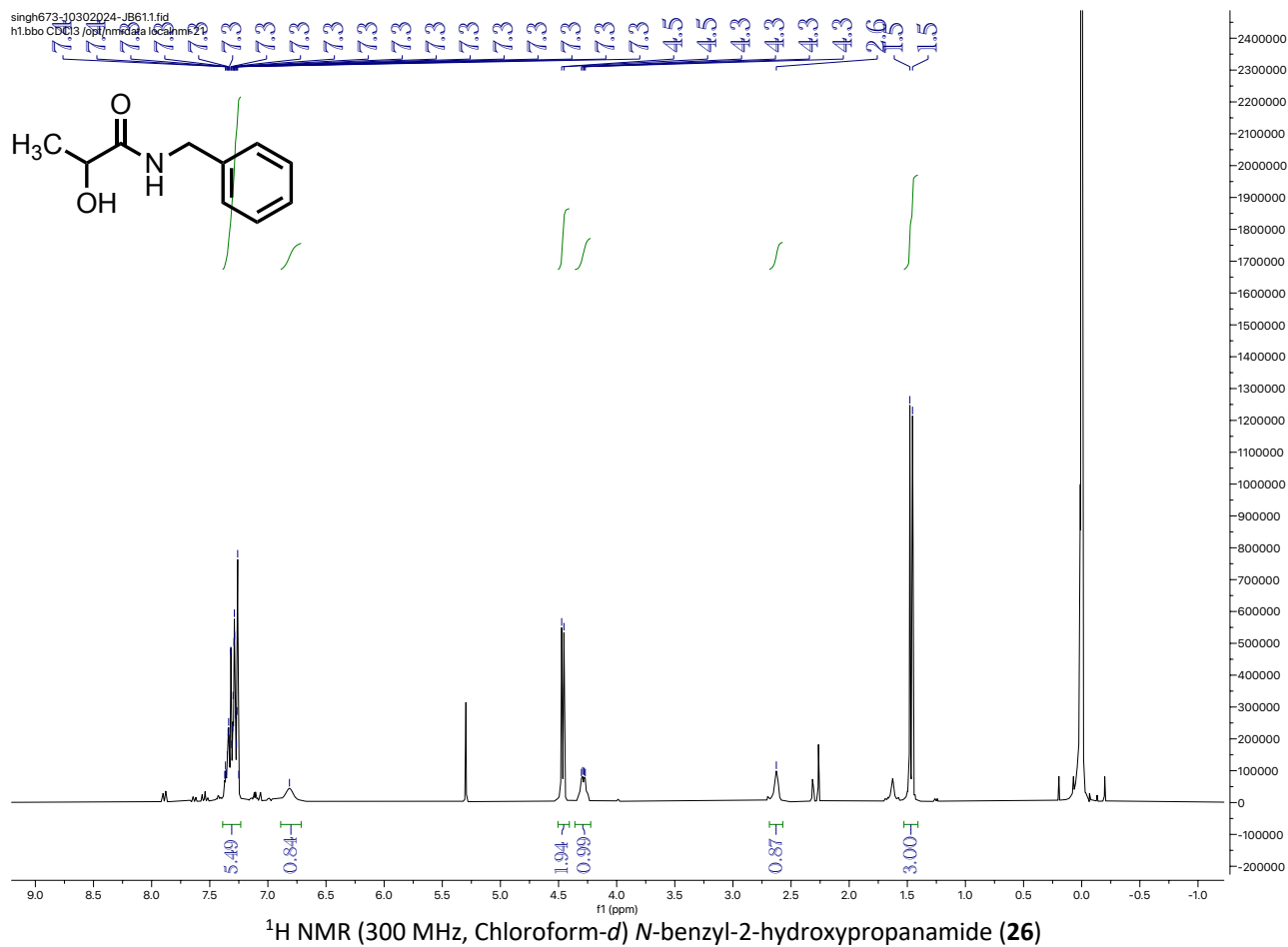


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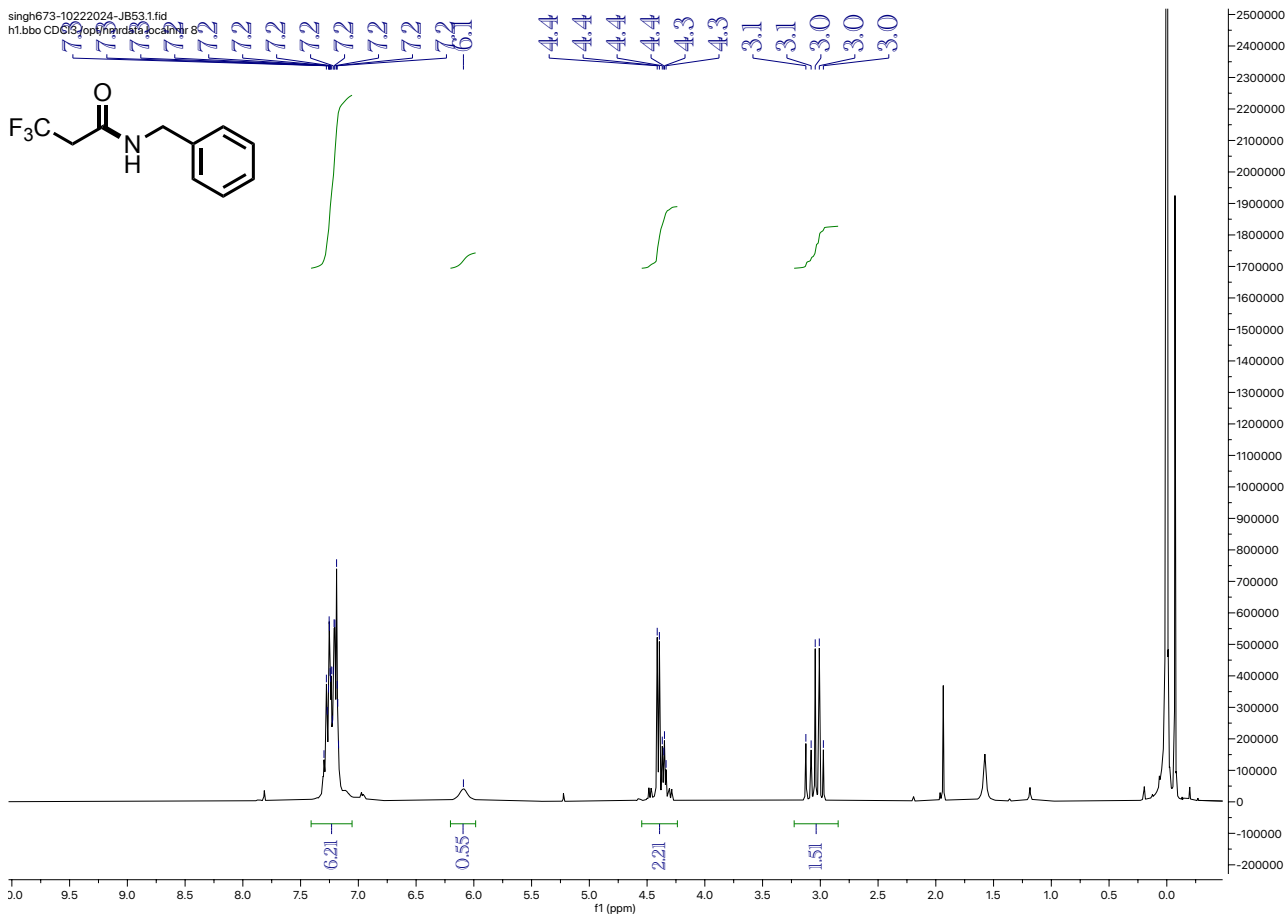
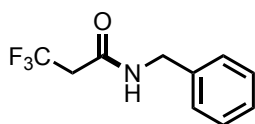


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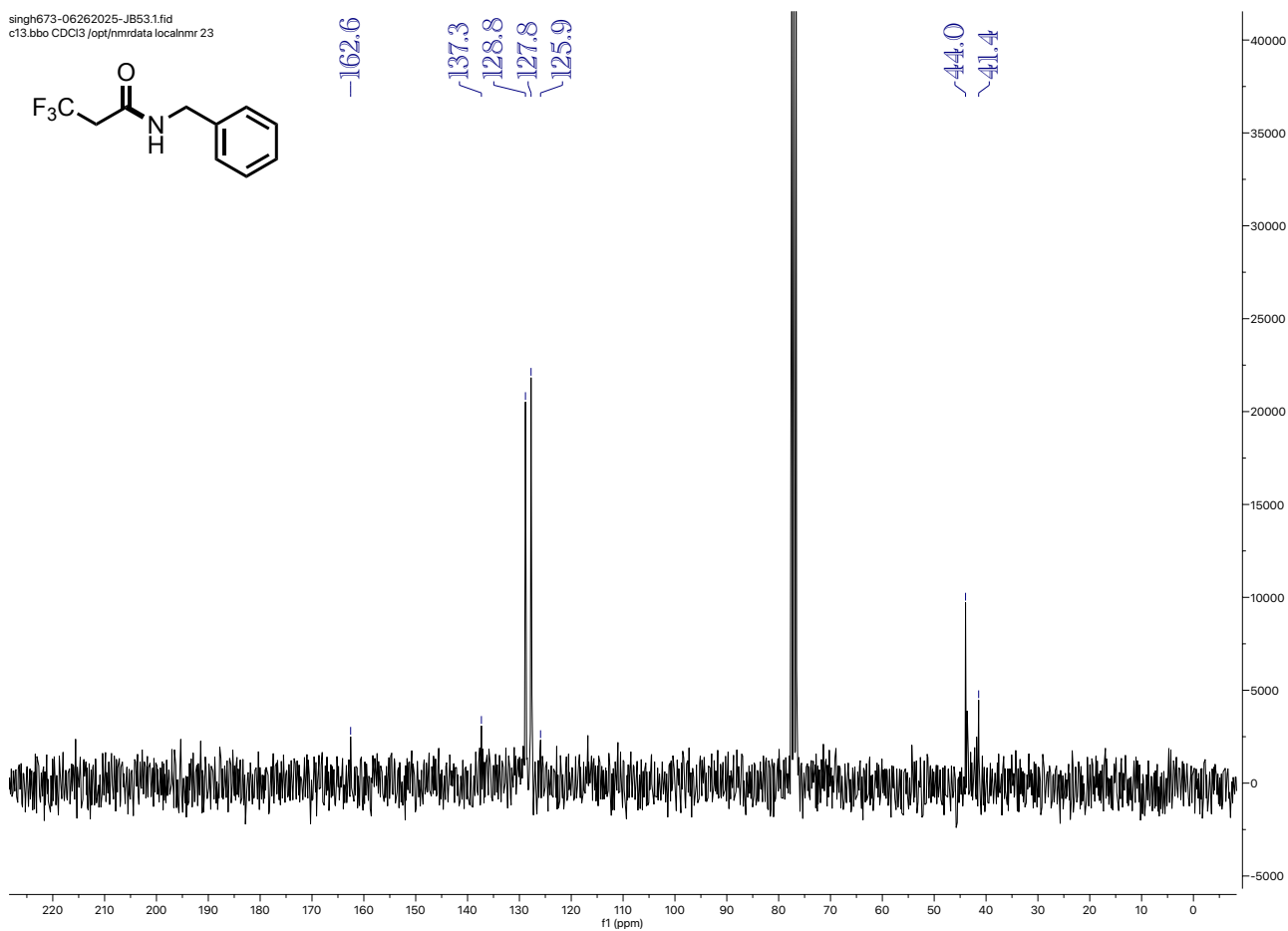
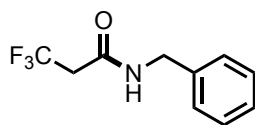


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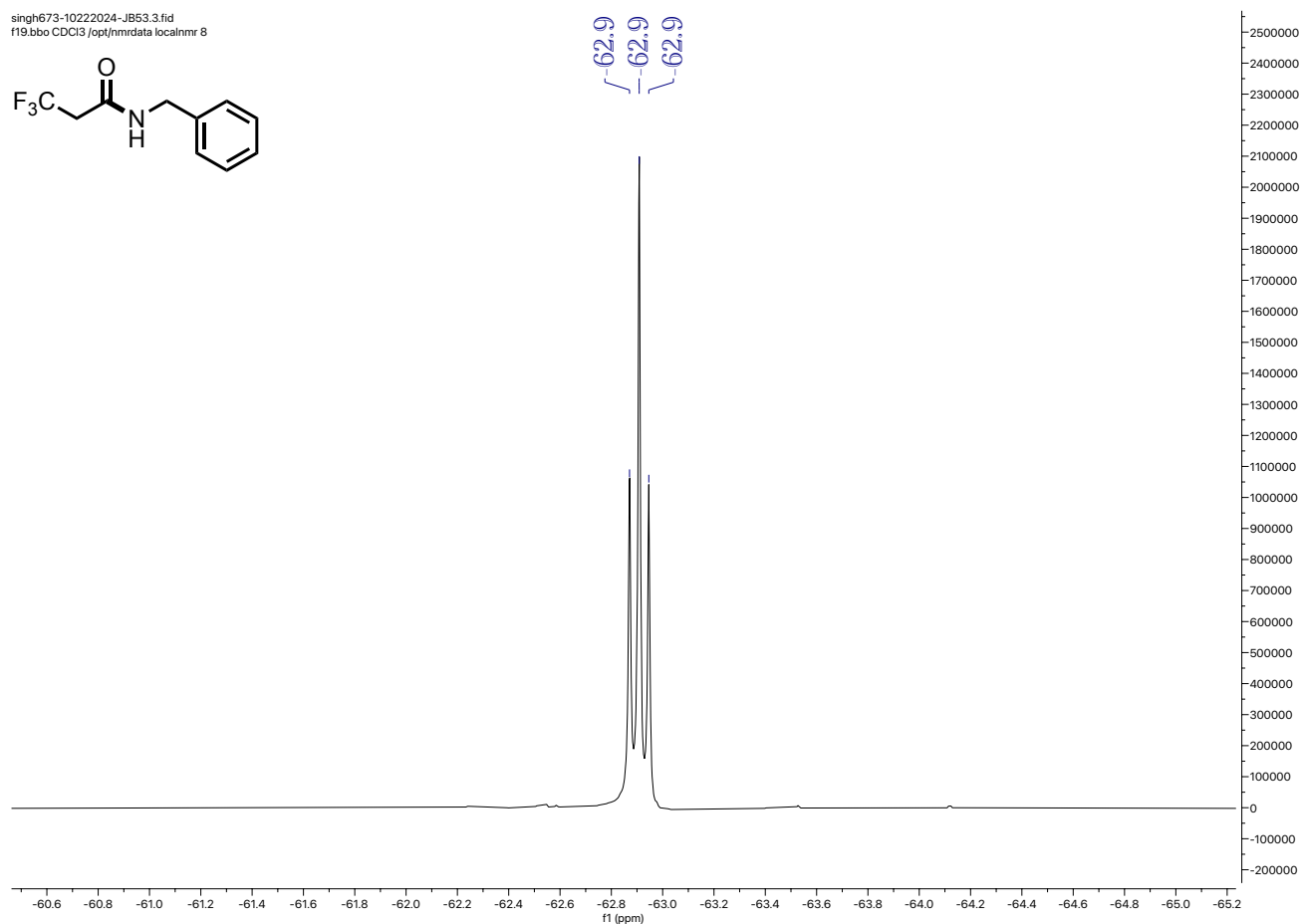
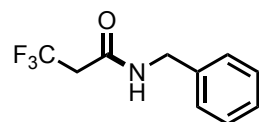


¹H NMR (300 MHz, Chloroform-*d*) *N*-benzyl-3,3,3-trifluoropropanamide (**27**)

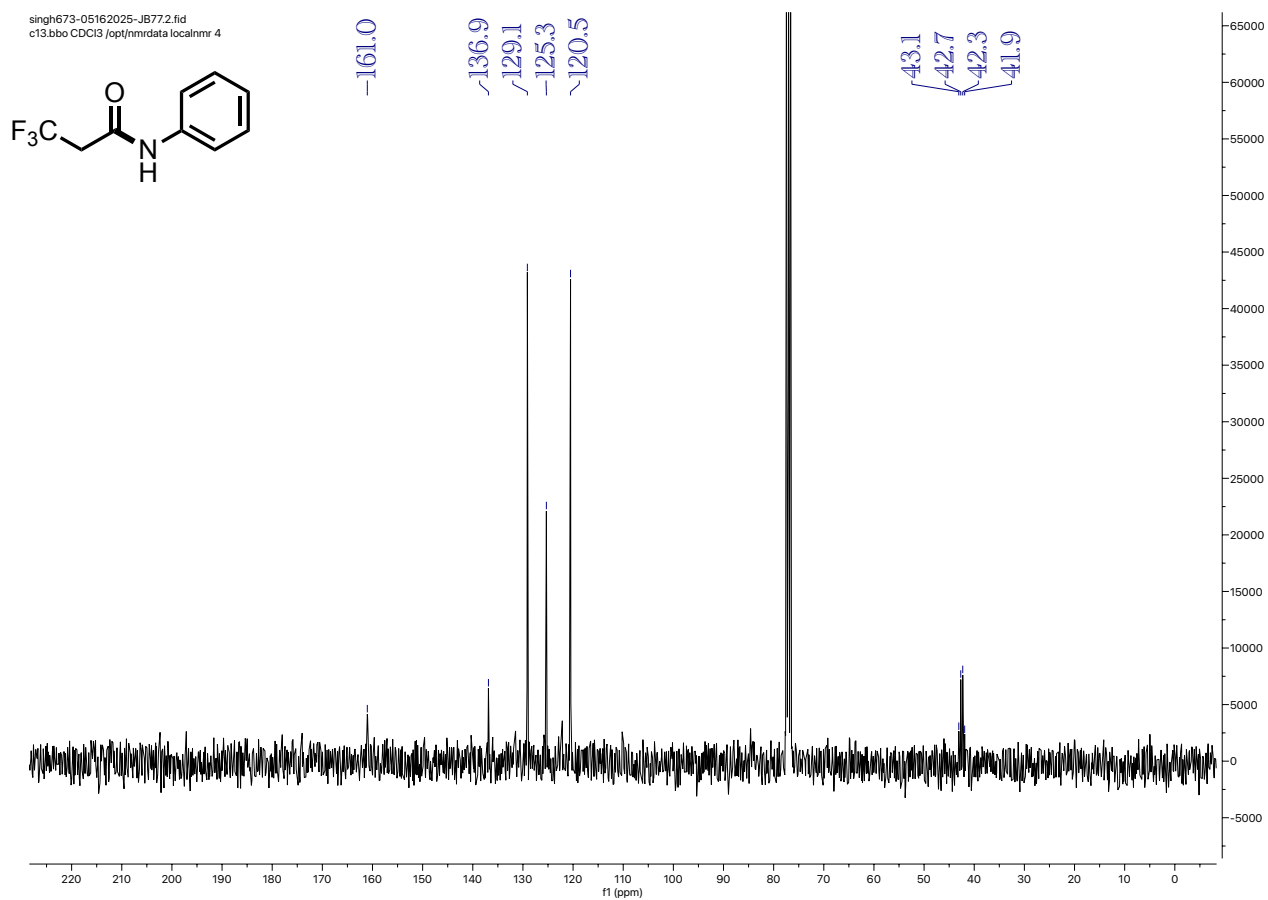
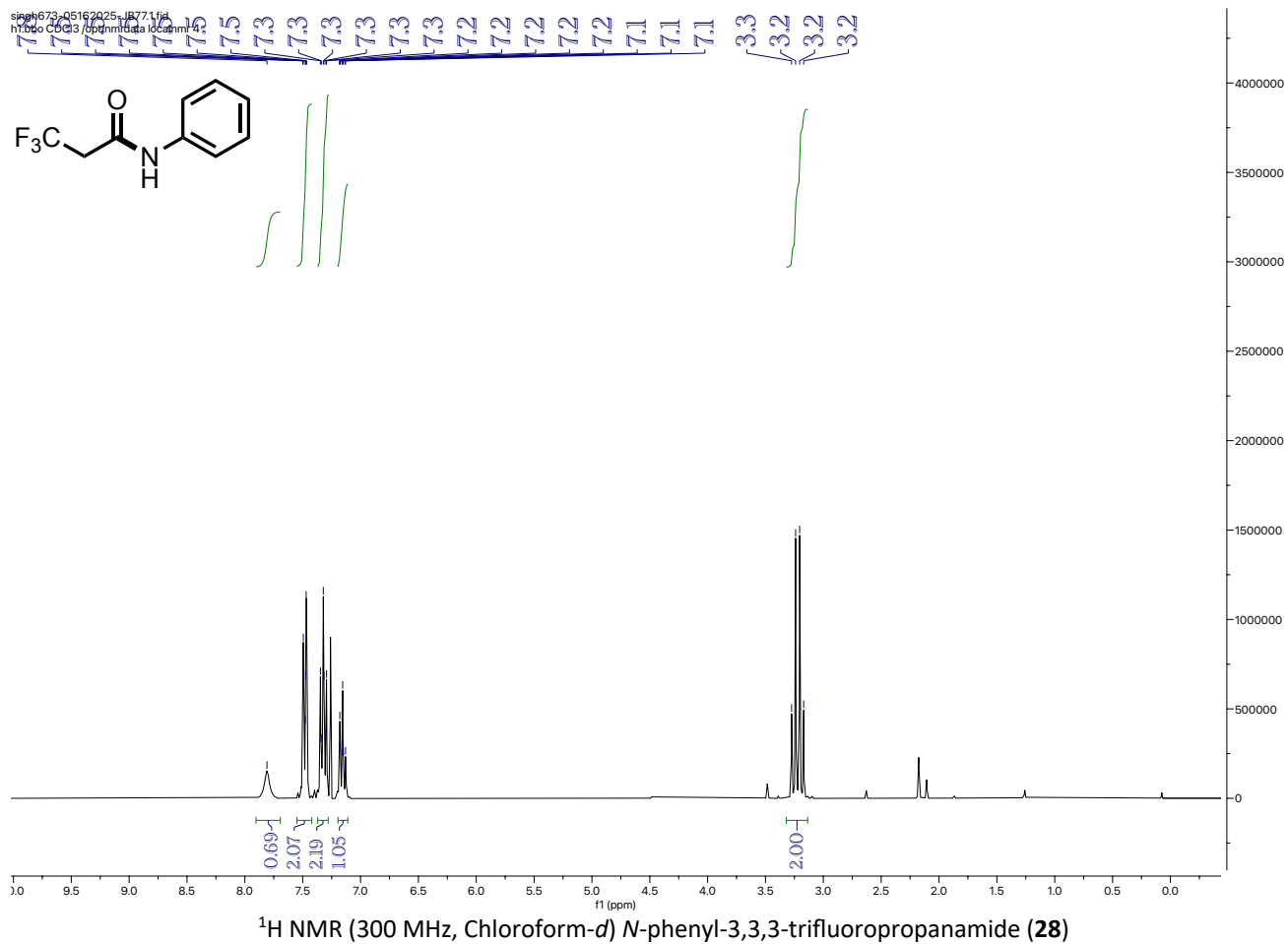
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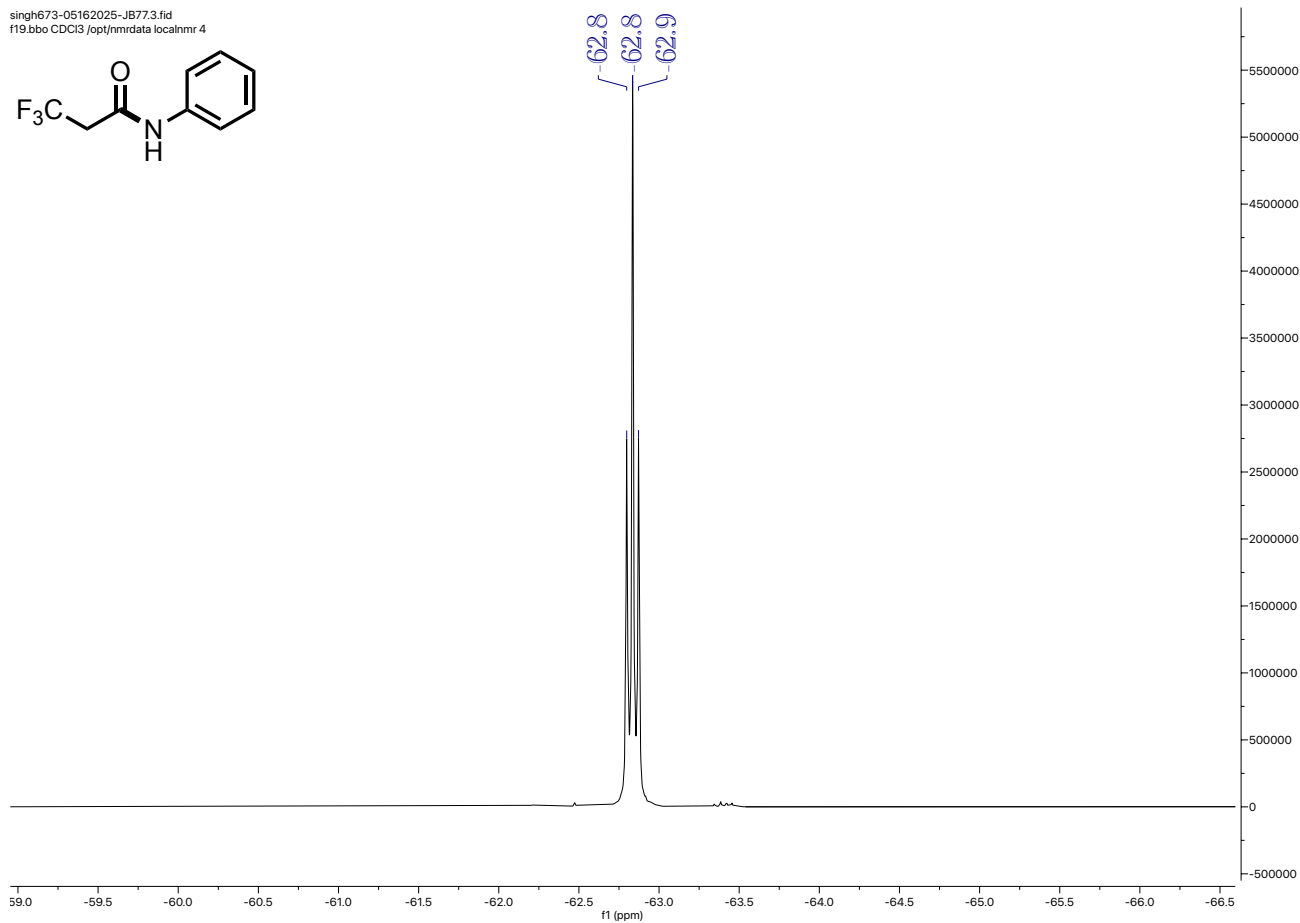
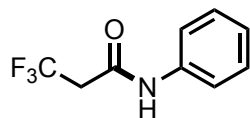
¹³C NMR (75 MHz, Chloroform-*d*) *N*-benzyl-3,3,3-trifluoropropanamide (**27**)



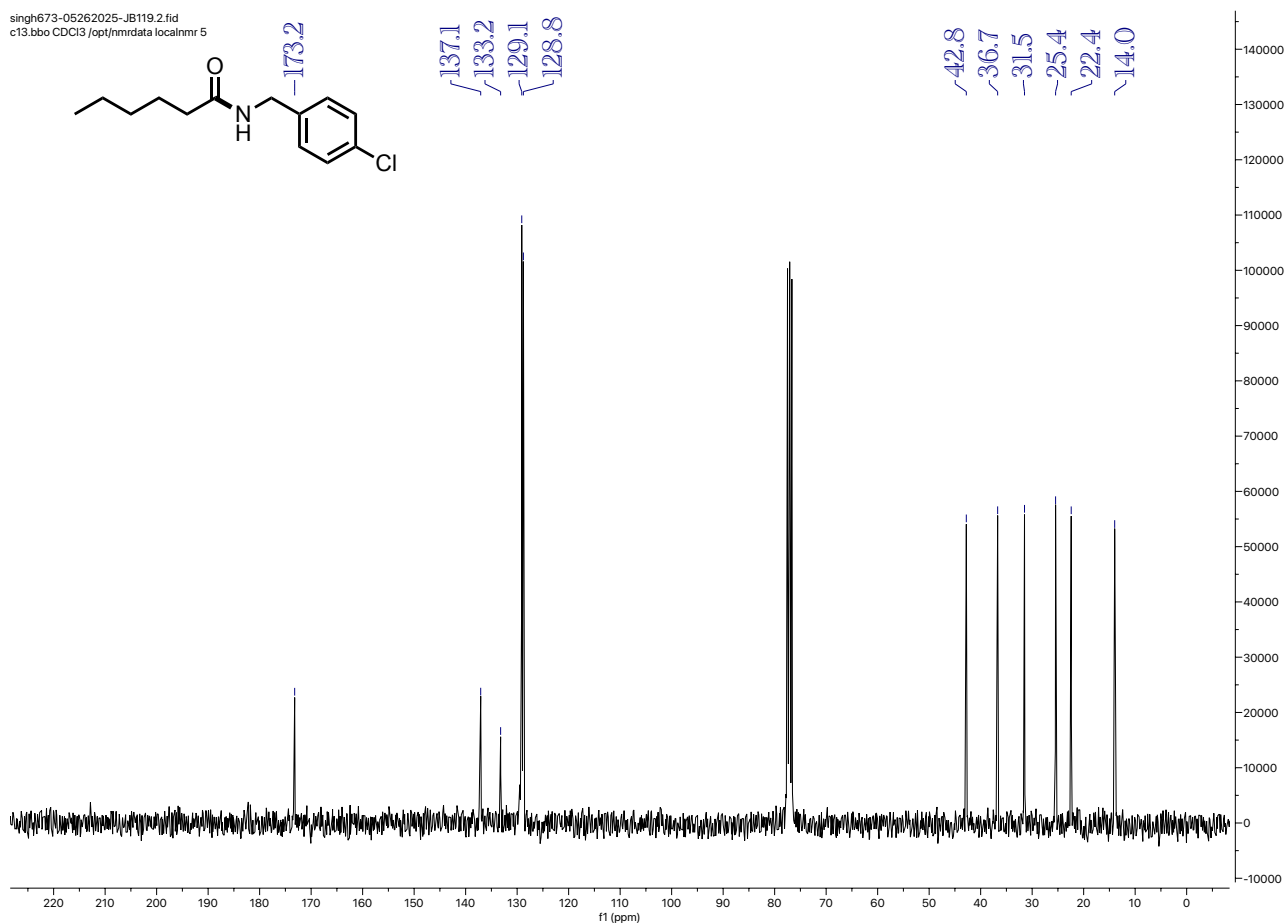
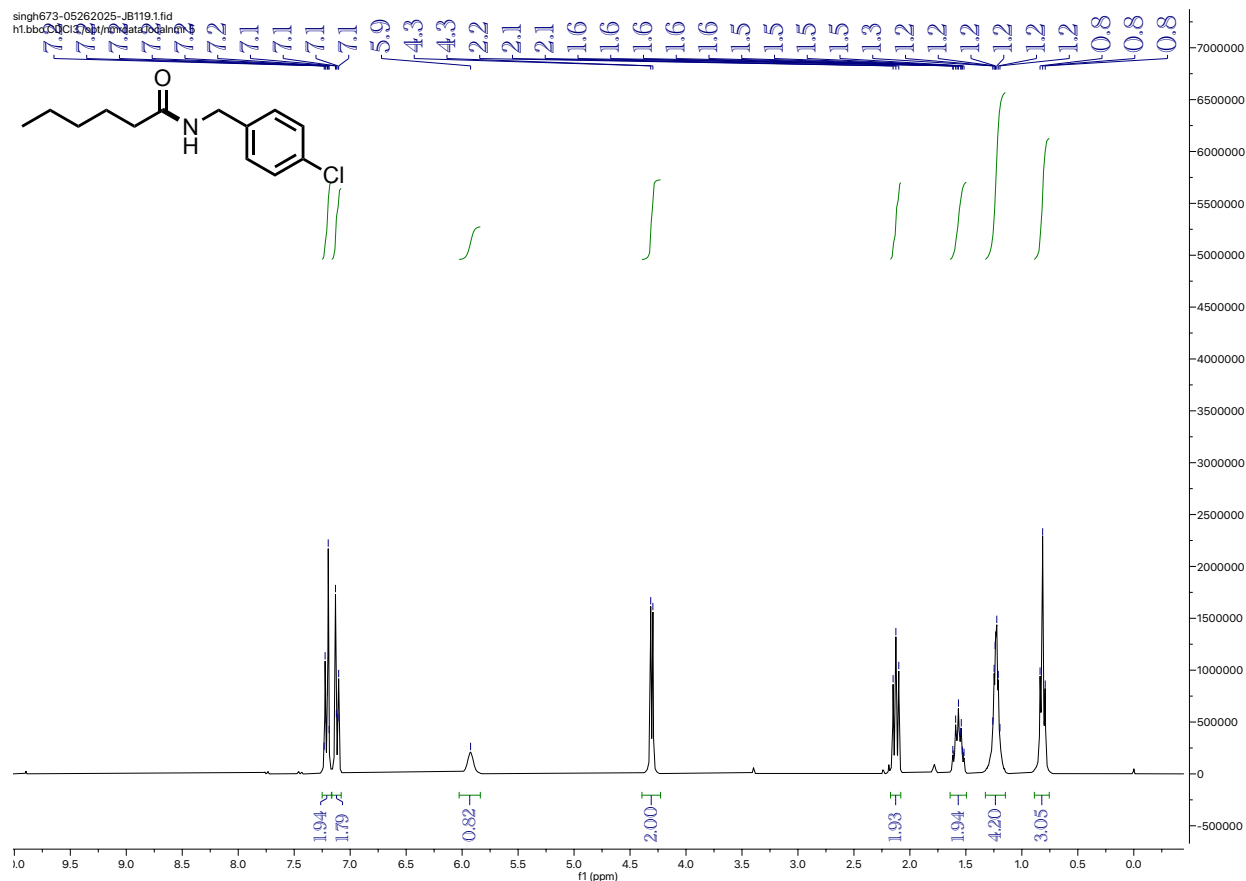
^{19}F NMR (282 MHz, Chloroform-*d*) *N*-benzyl-3,3,3-trifluoropropanamide (**27**)

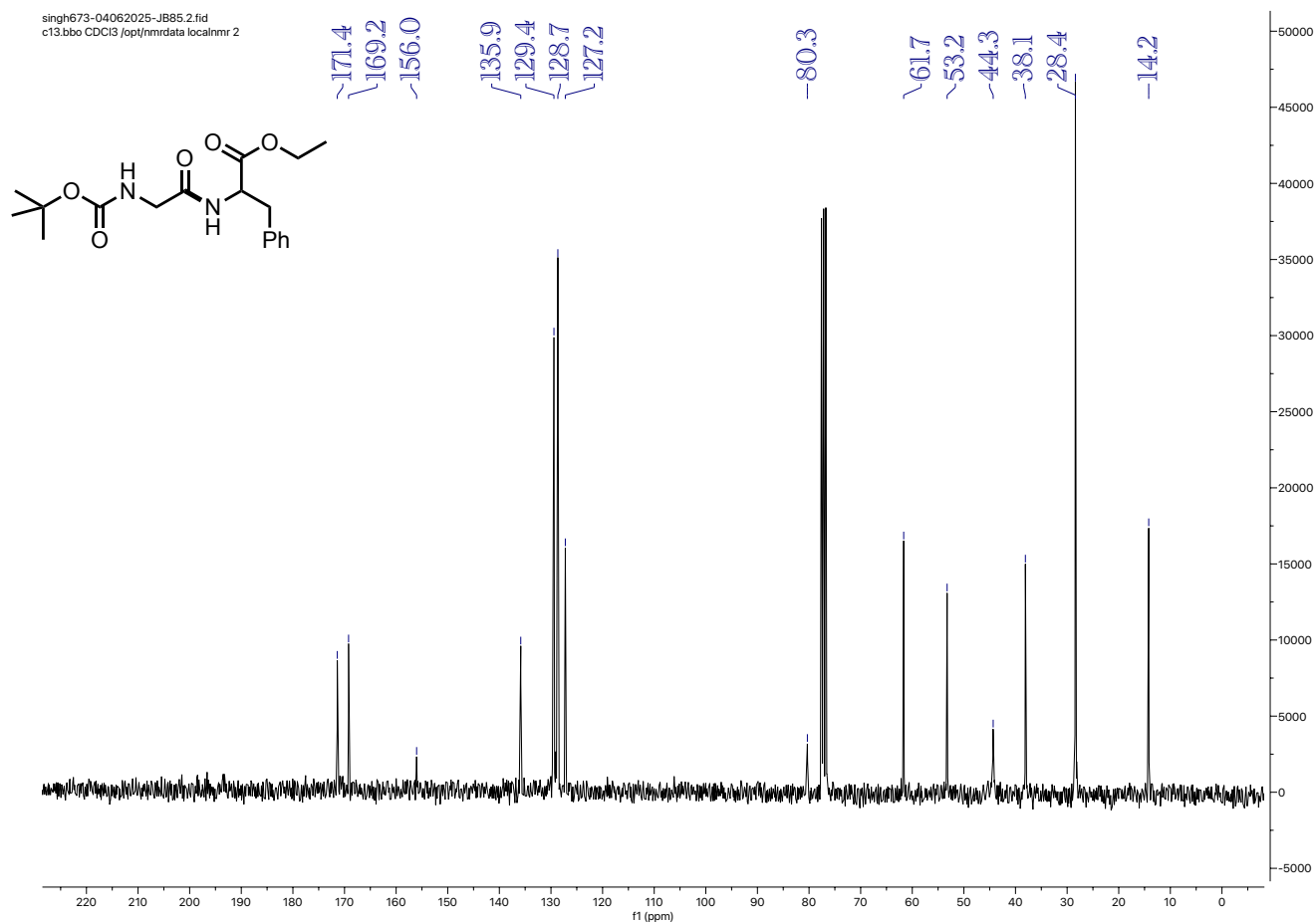
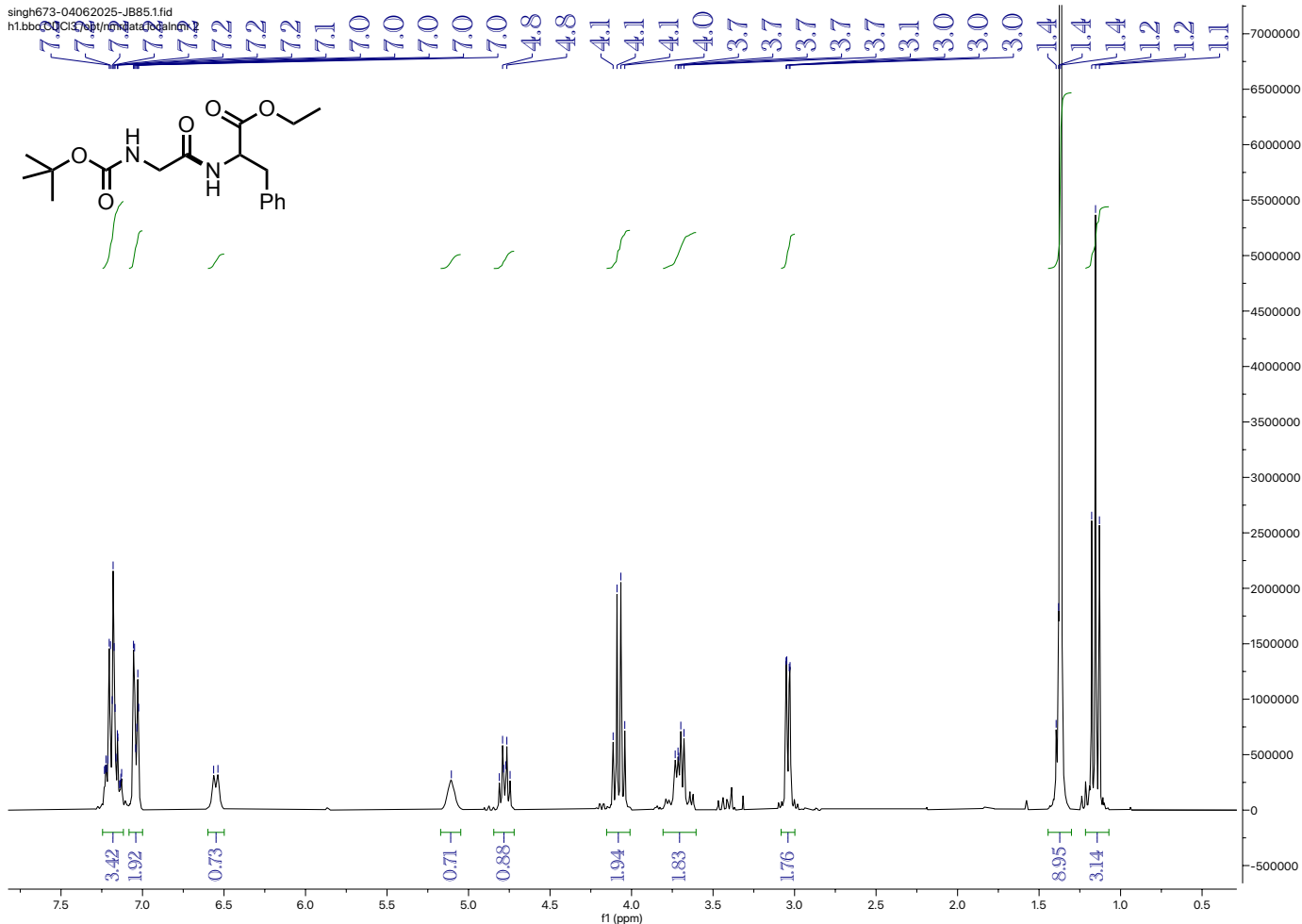


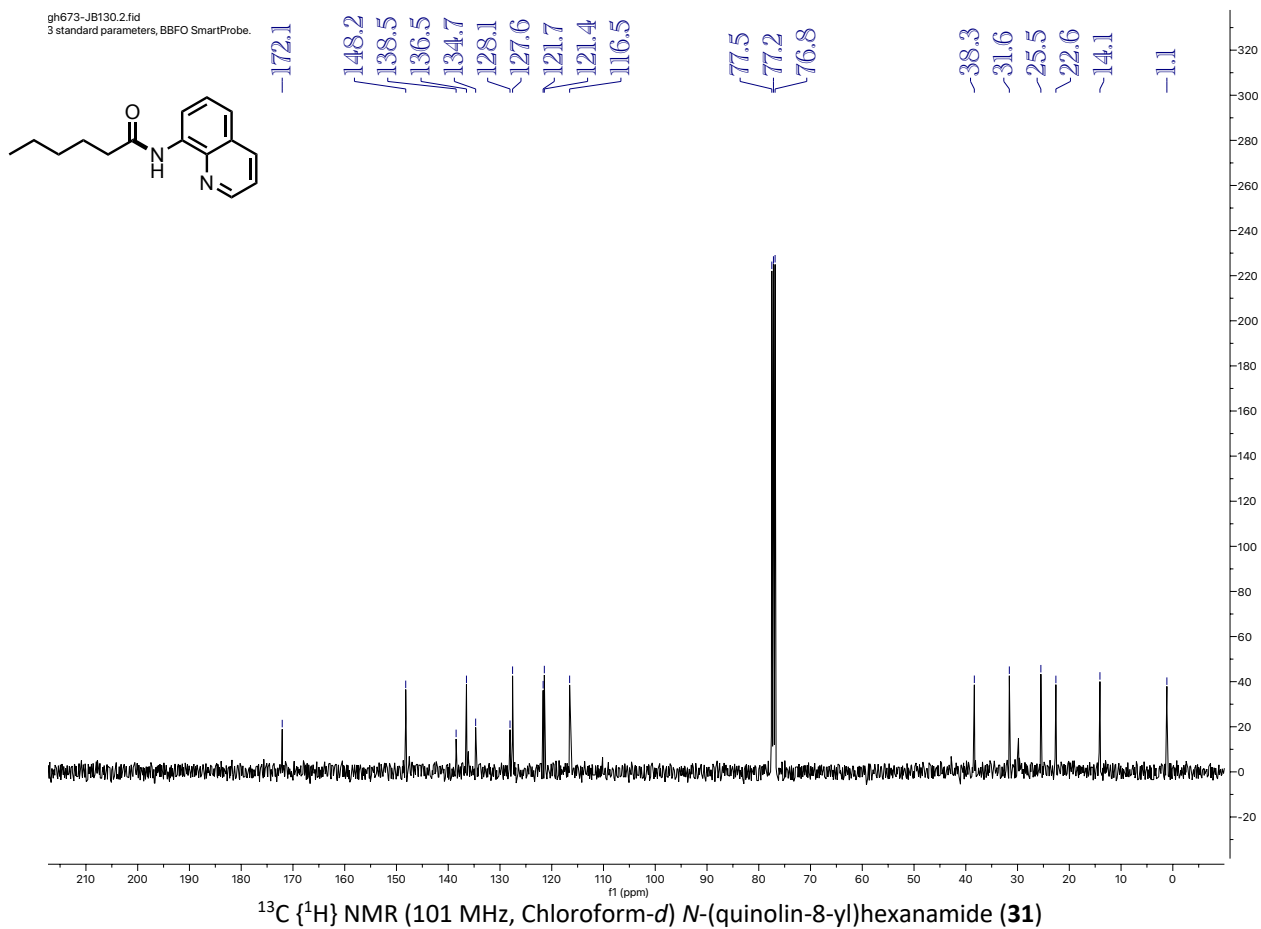
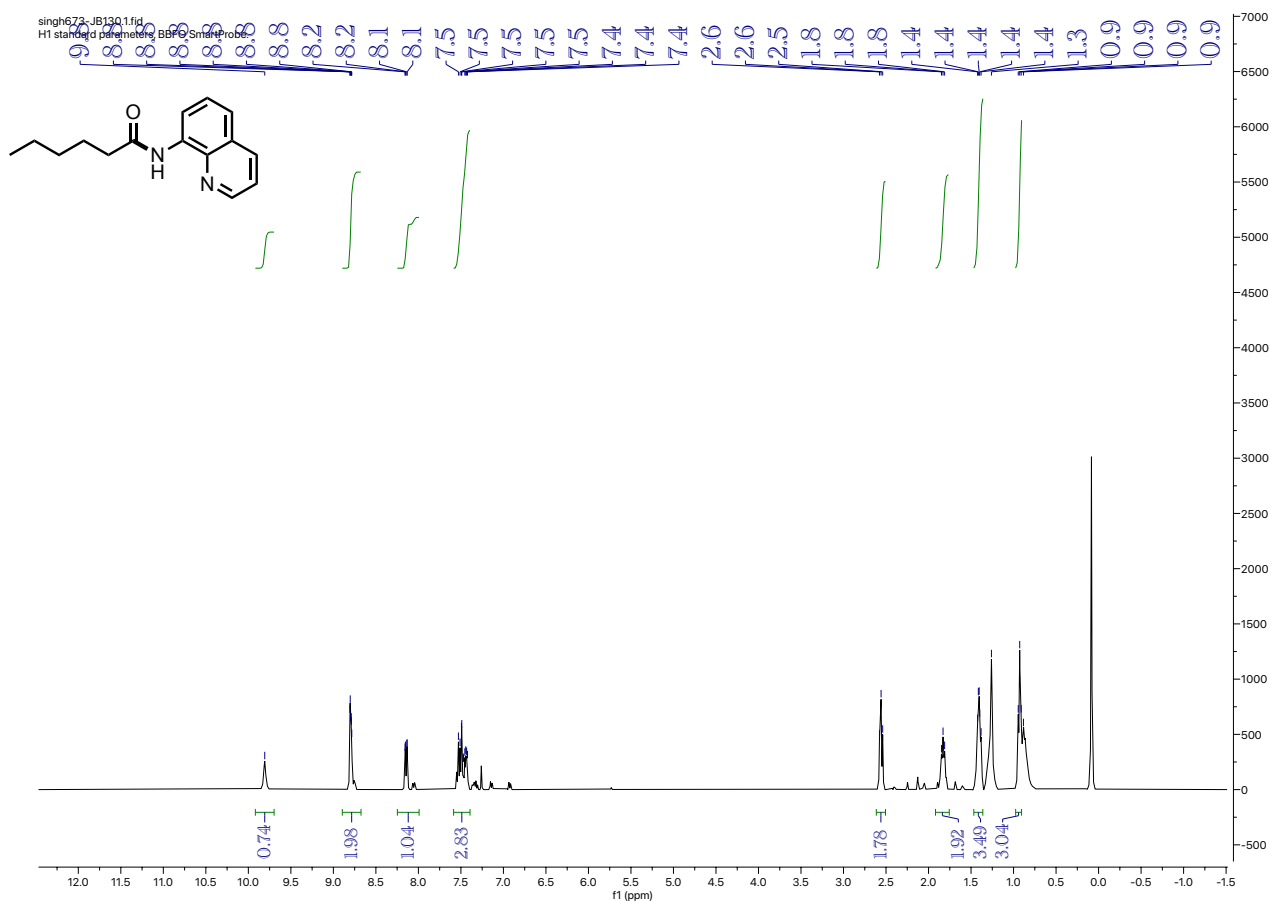
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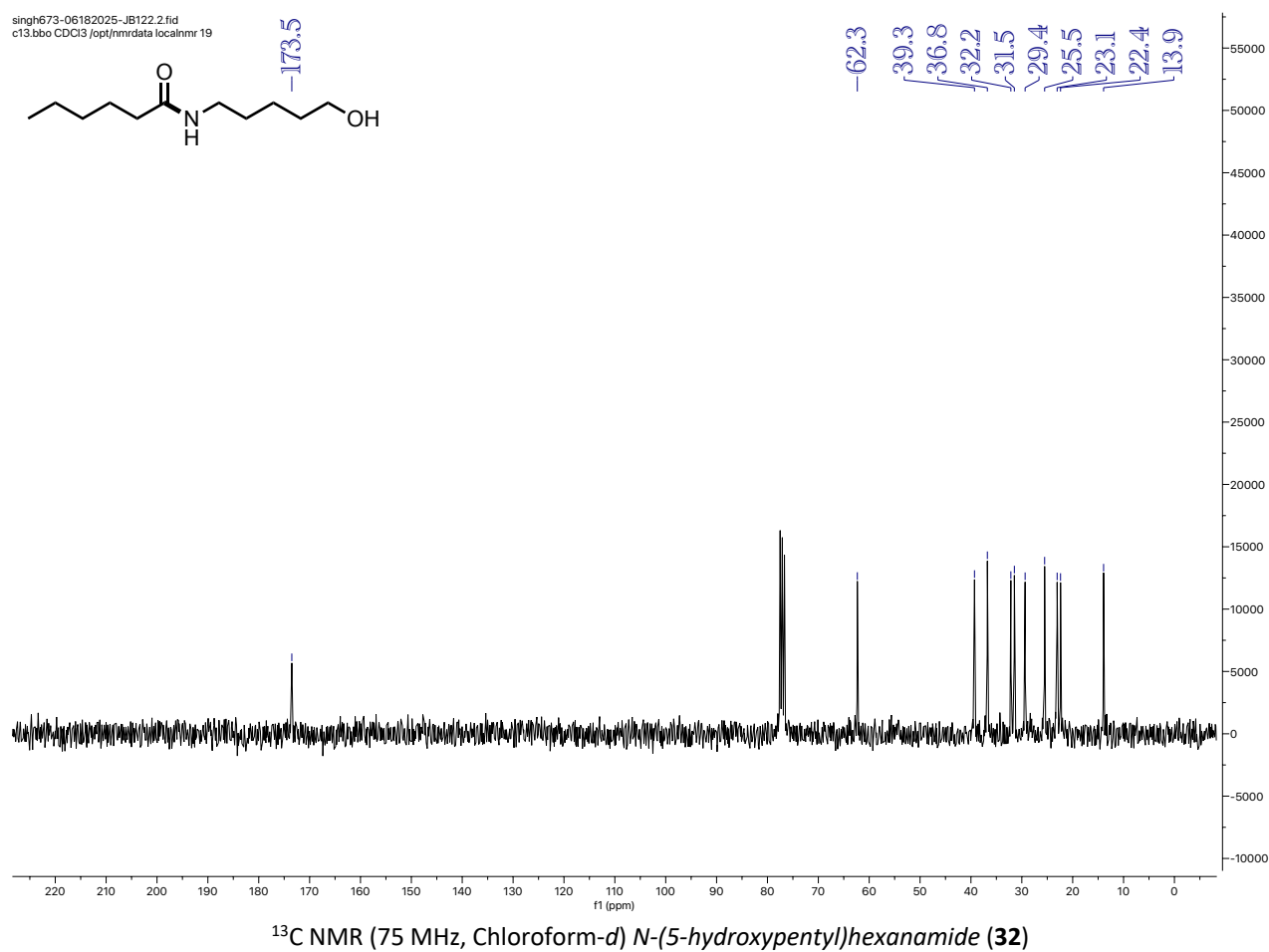
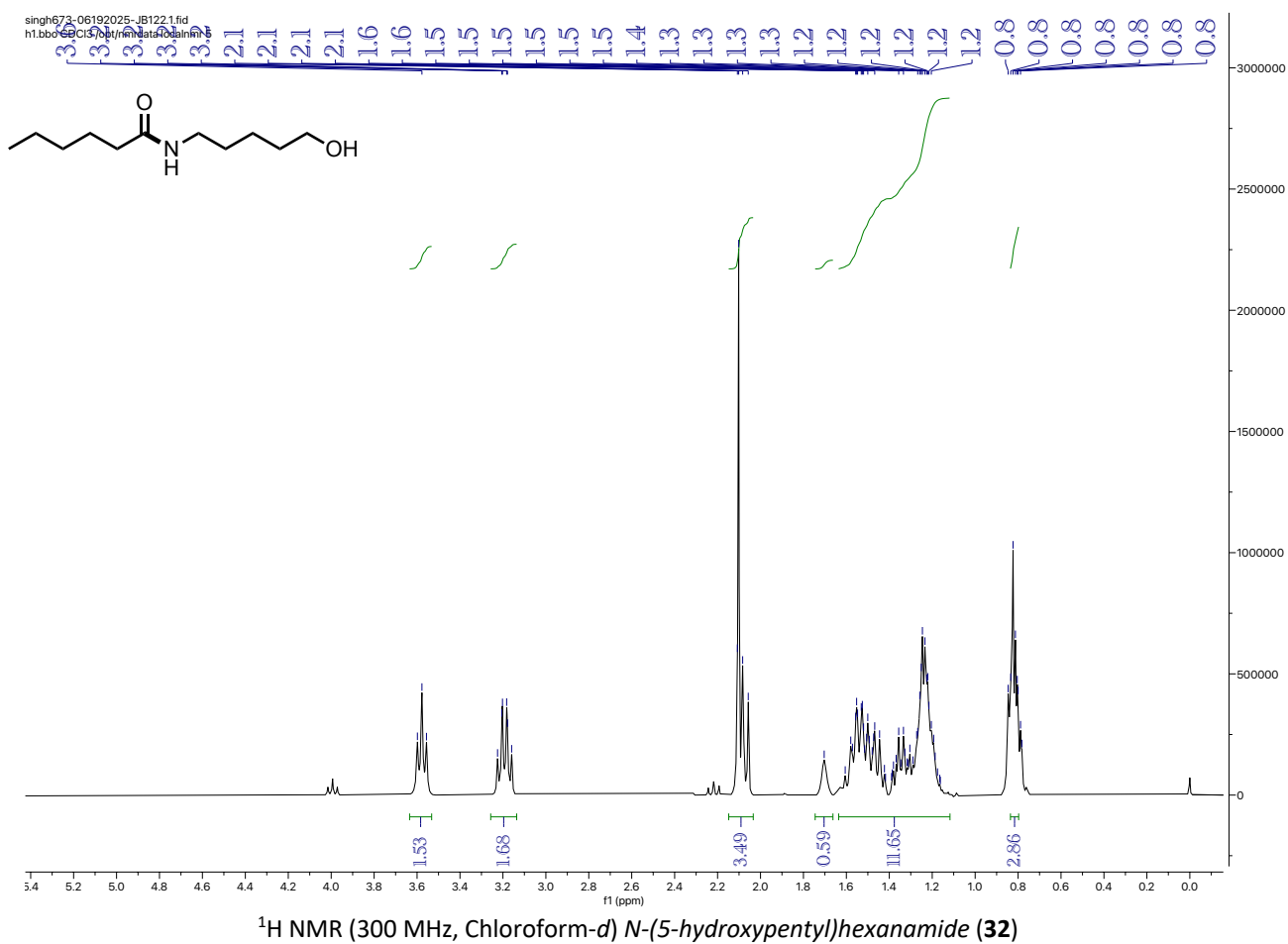


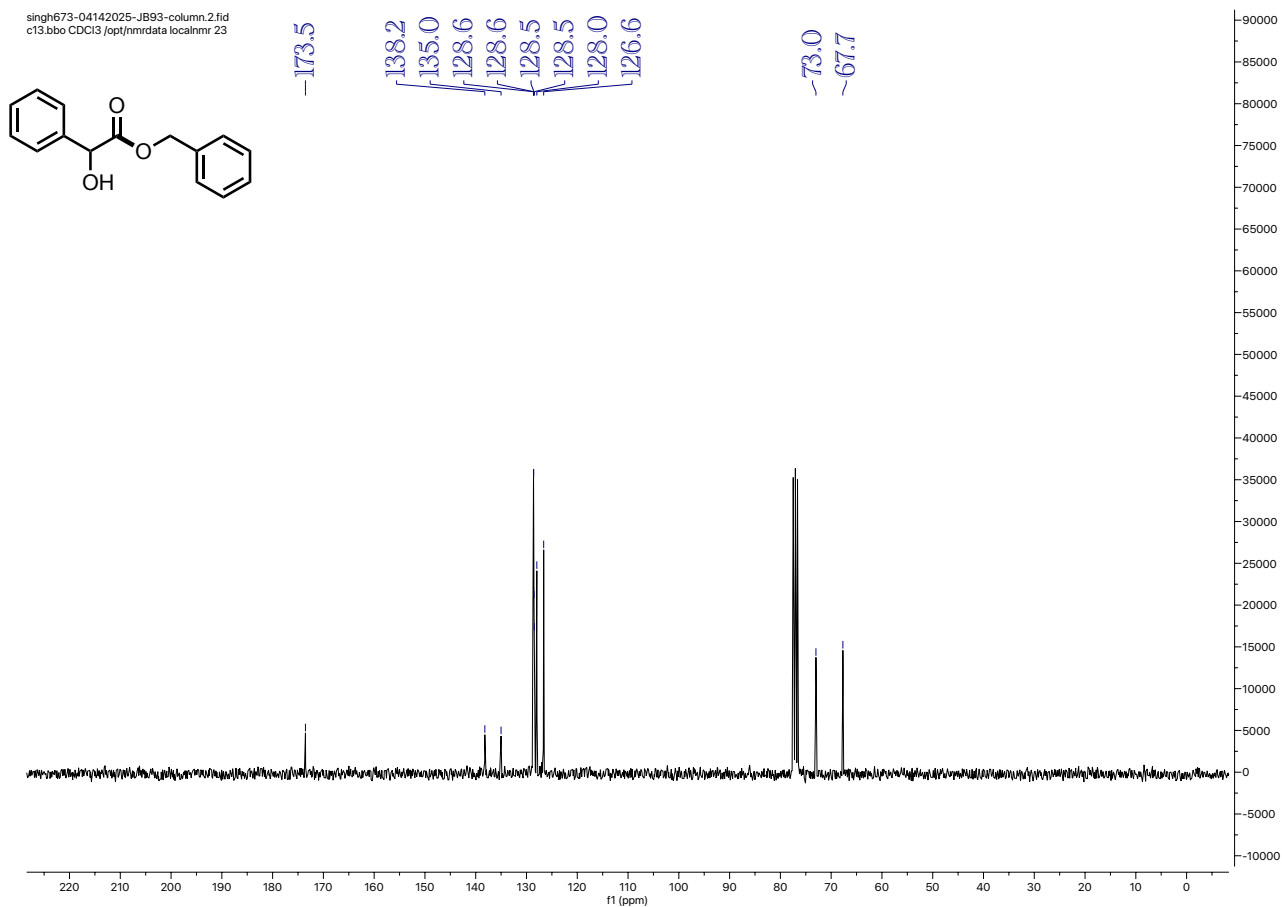
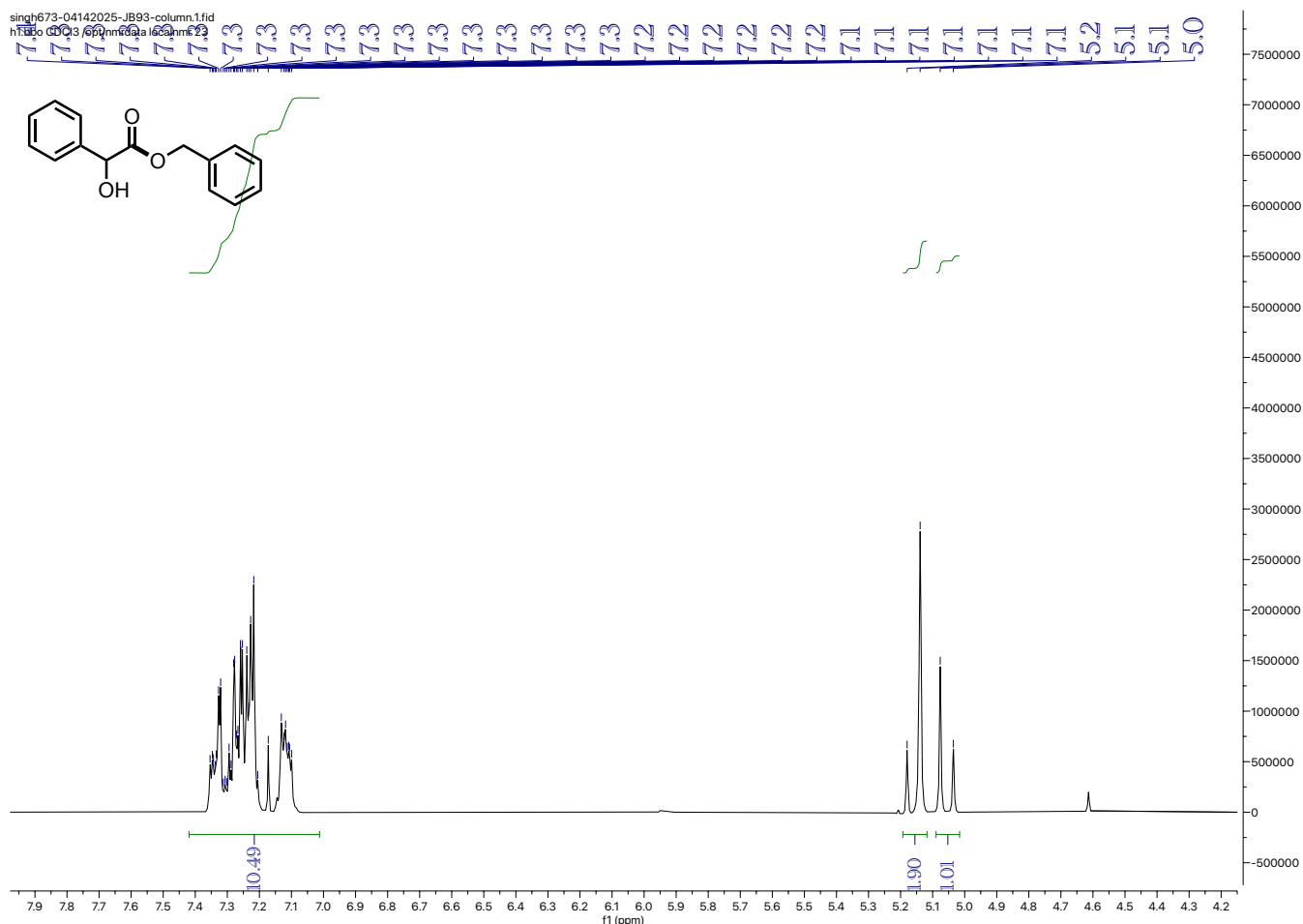
^{19}F NMR (282 MHz, Chloroform-*d*) *N*-benzyl-3,3,3-trifluoropropanamide (**28**)

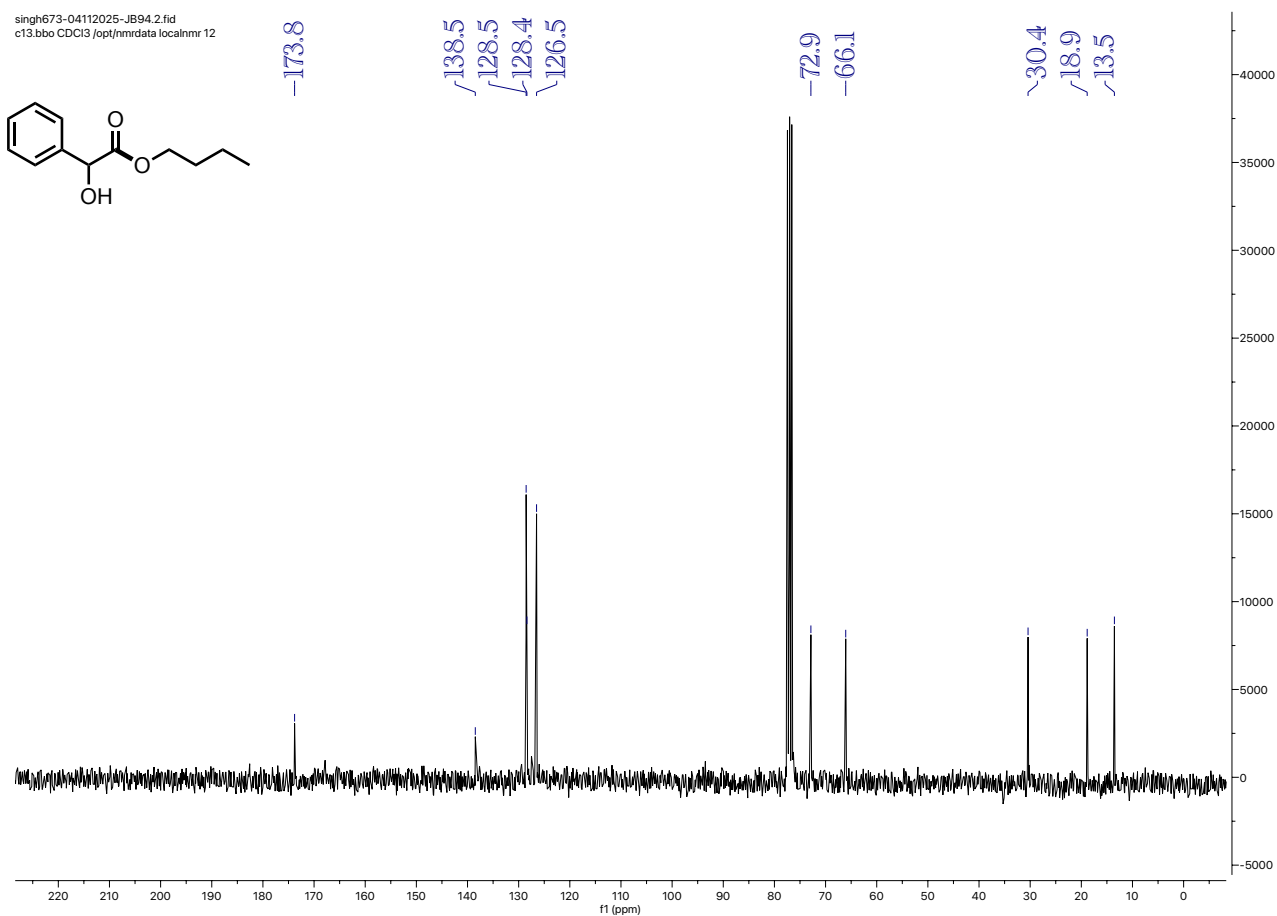
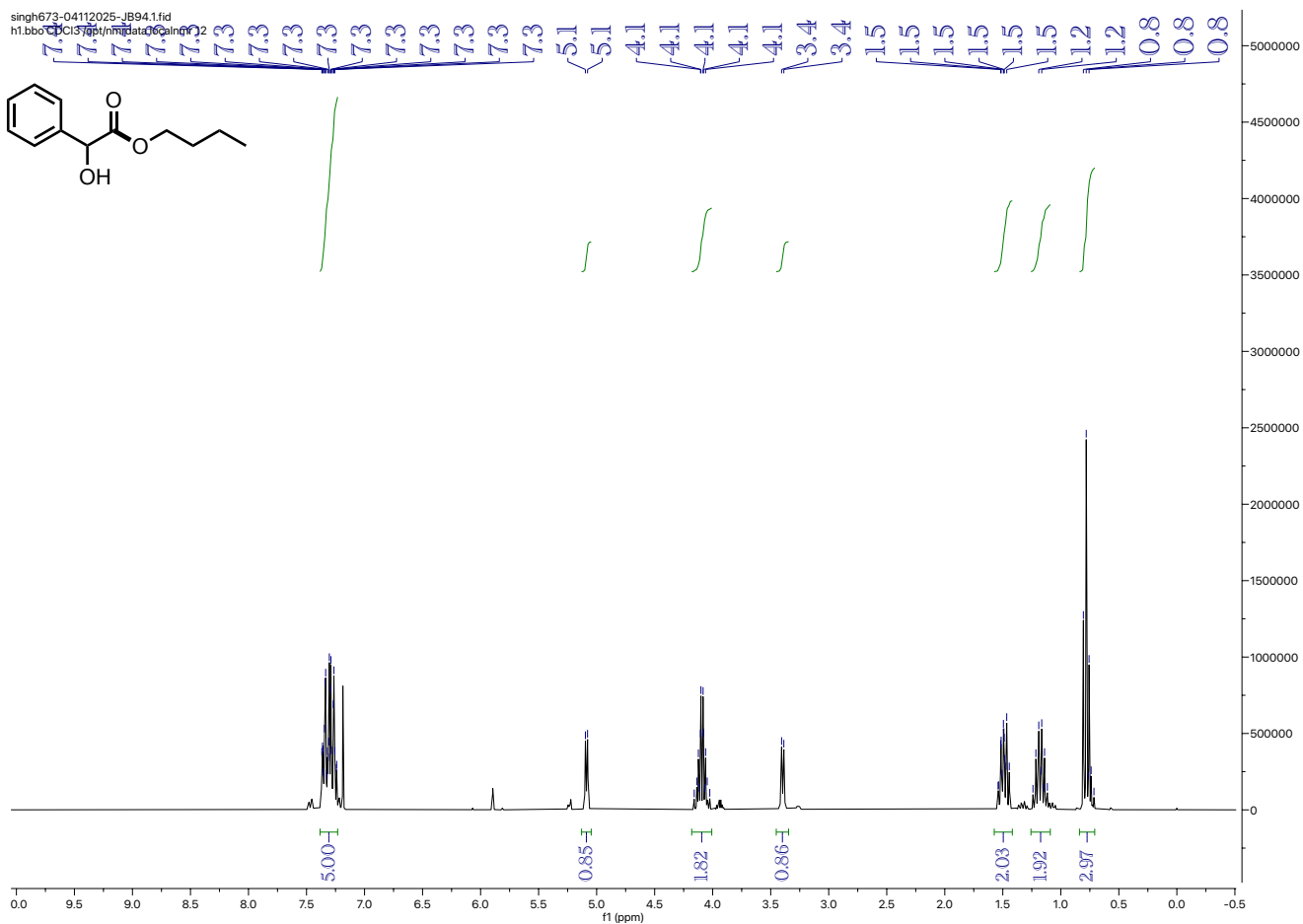


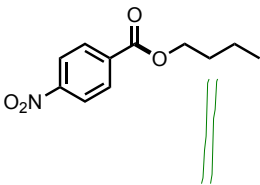
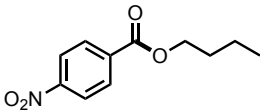


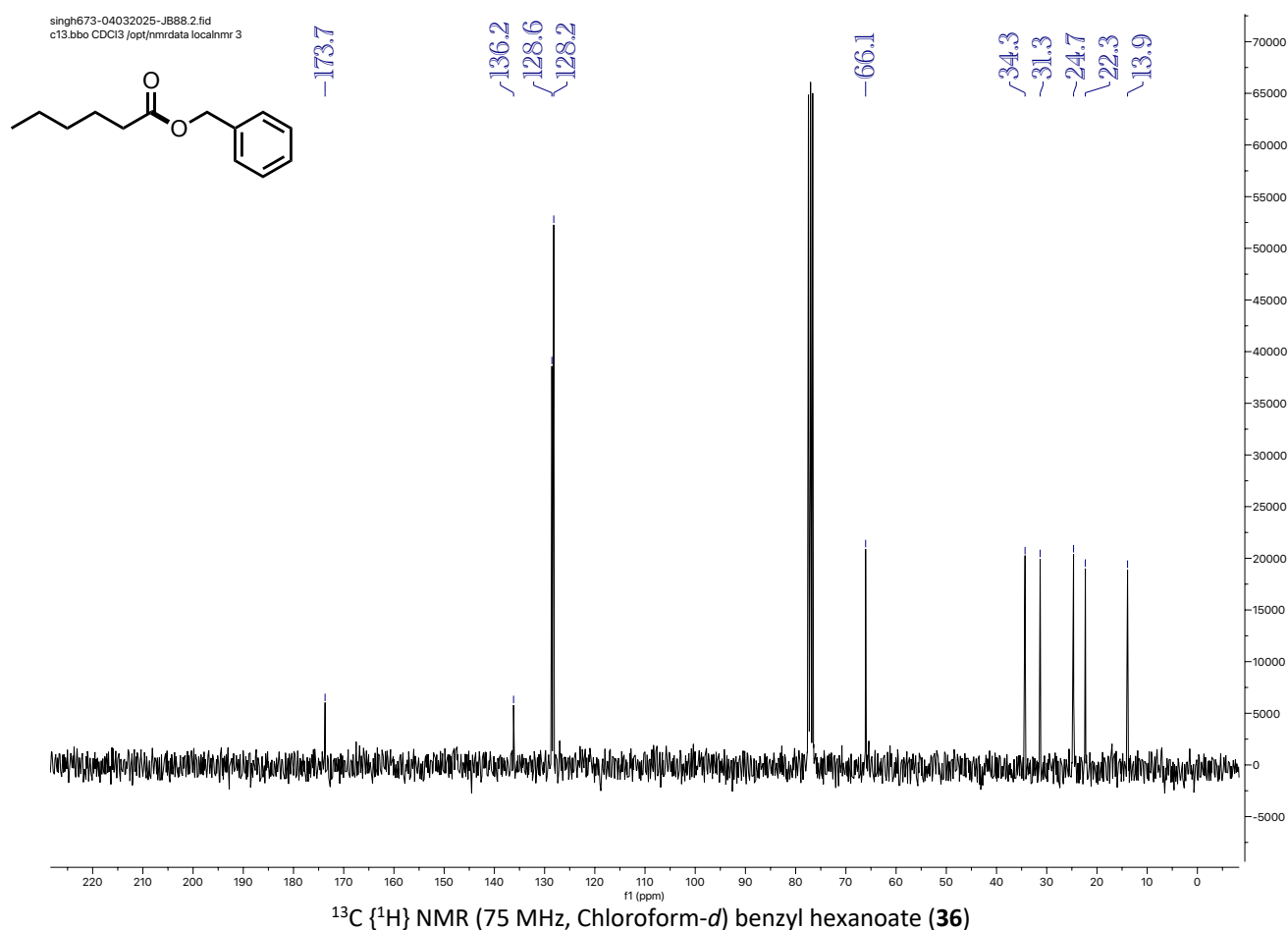
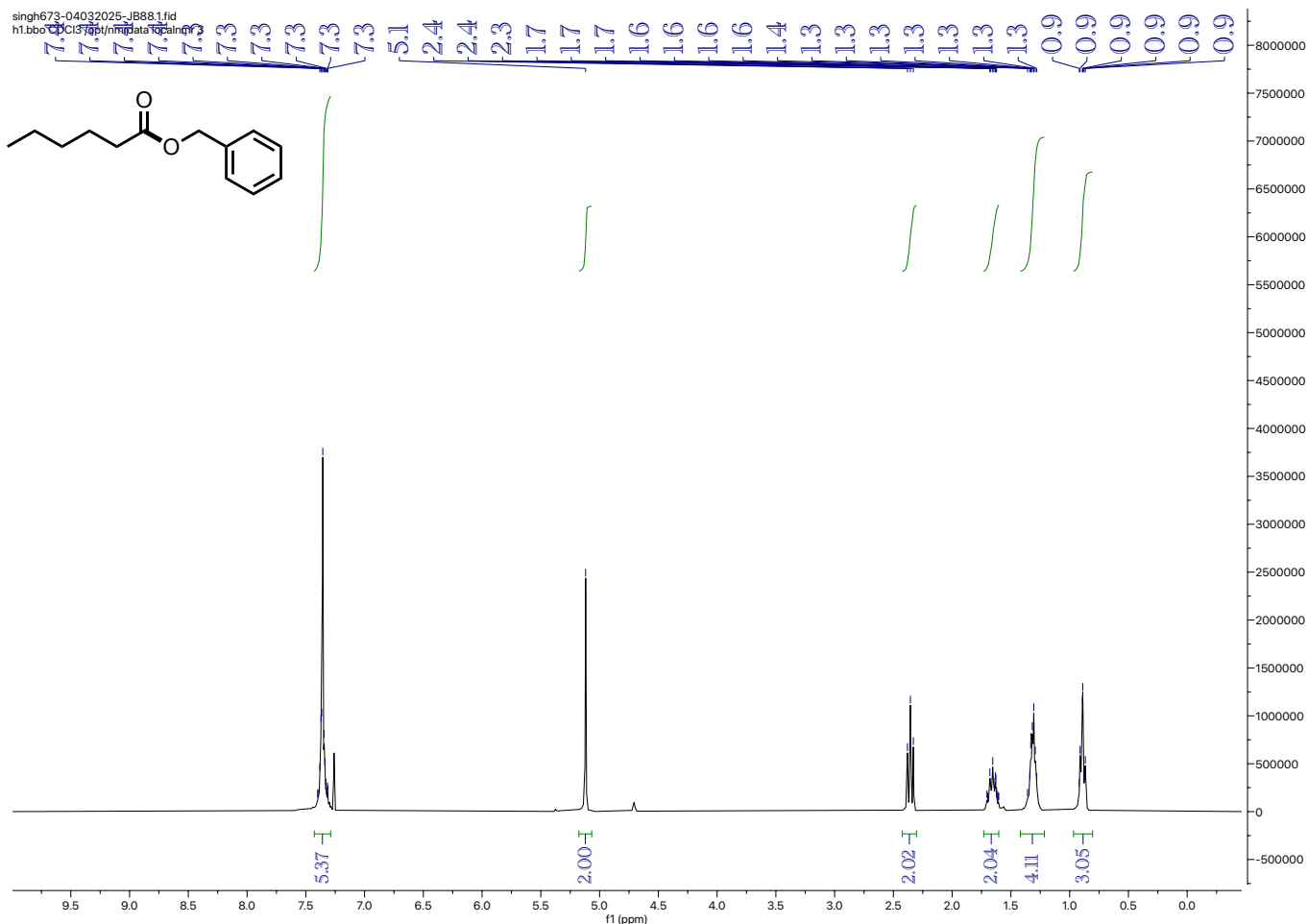


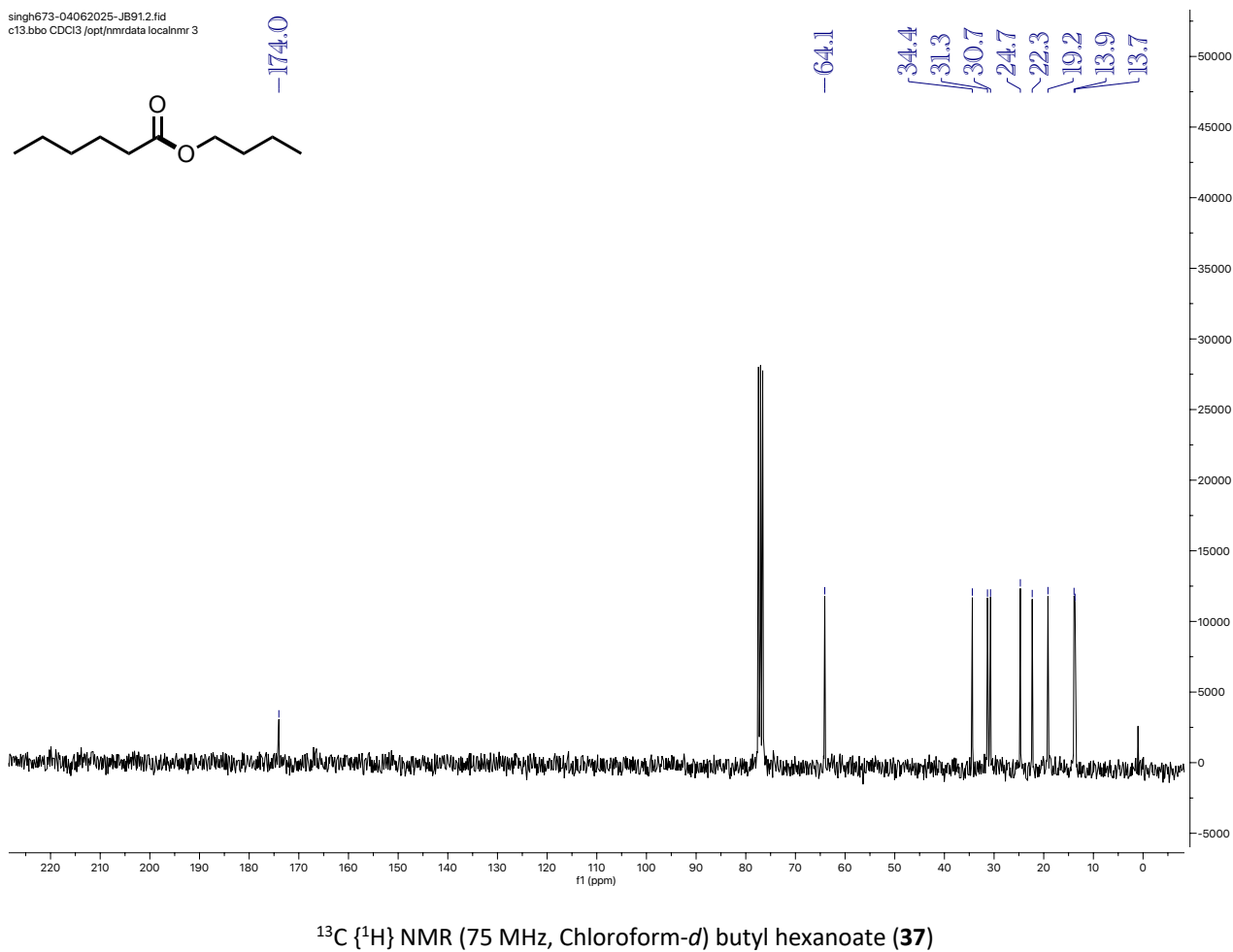
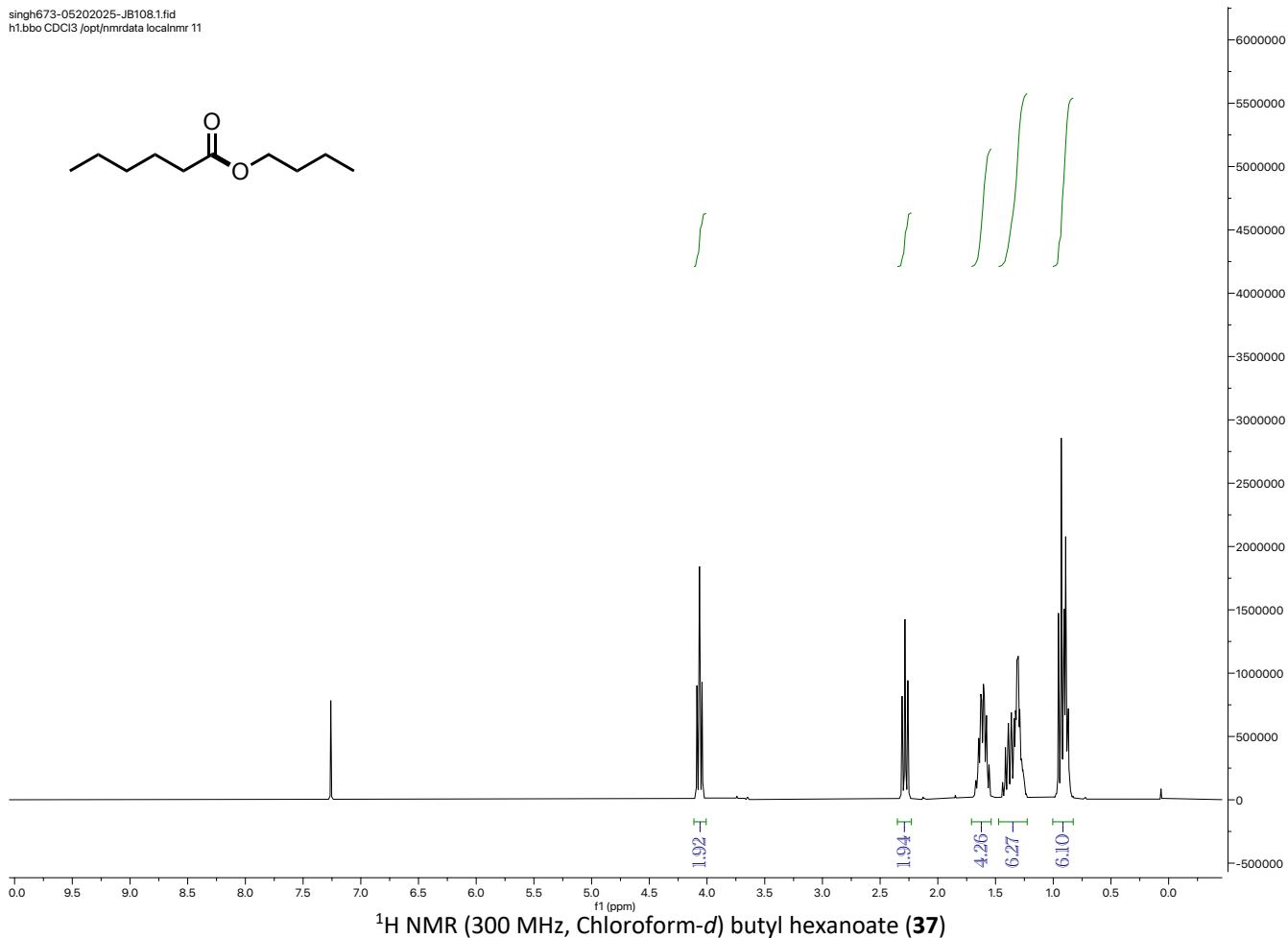


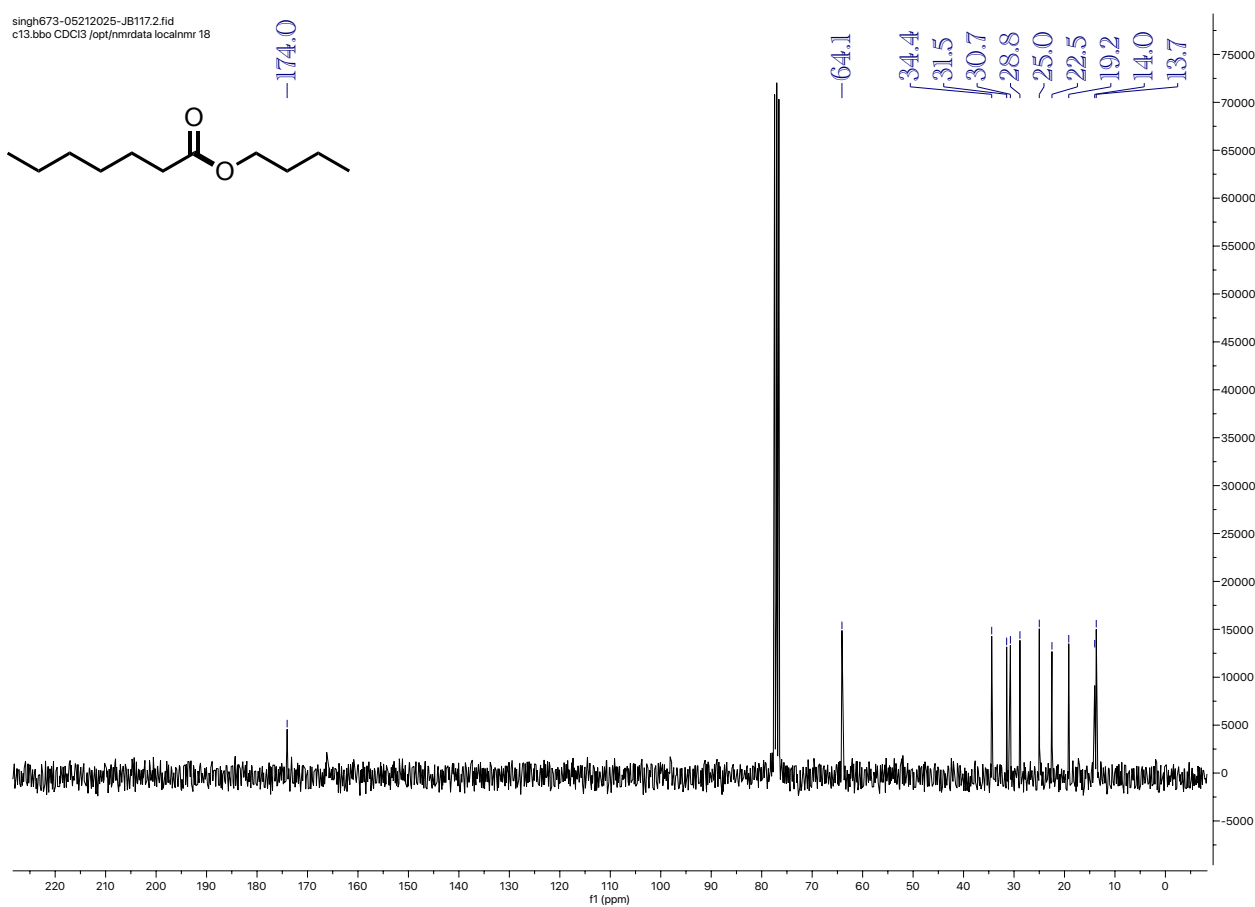
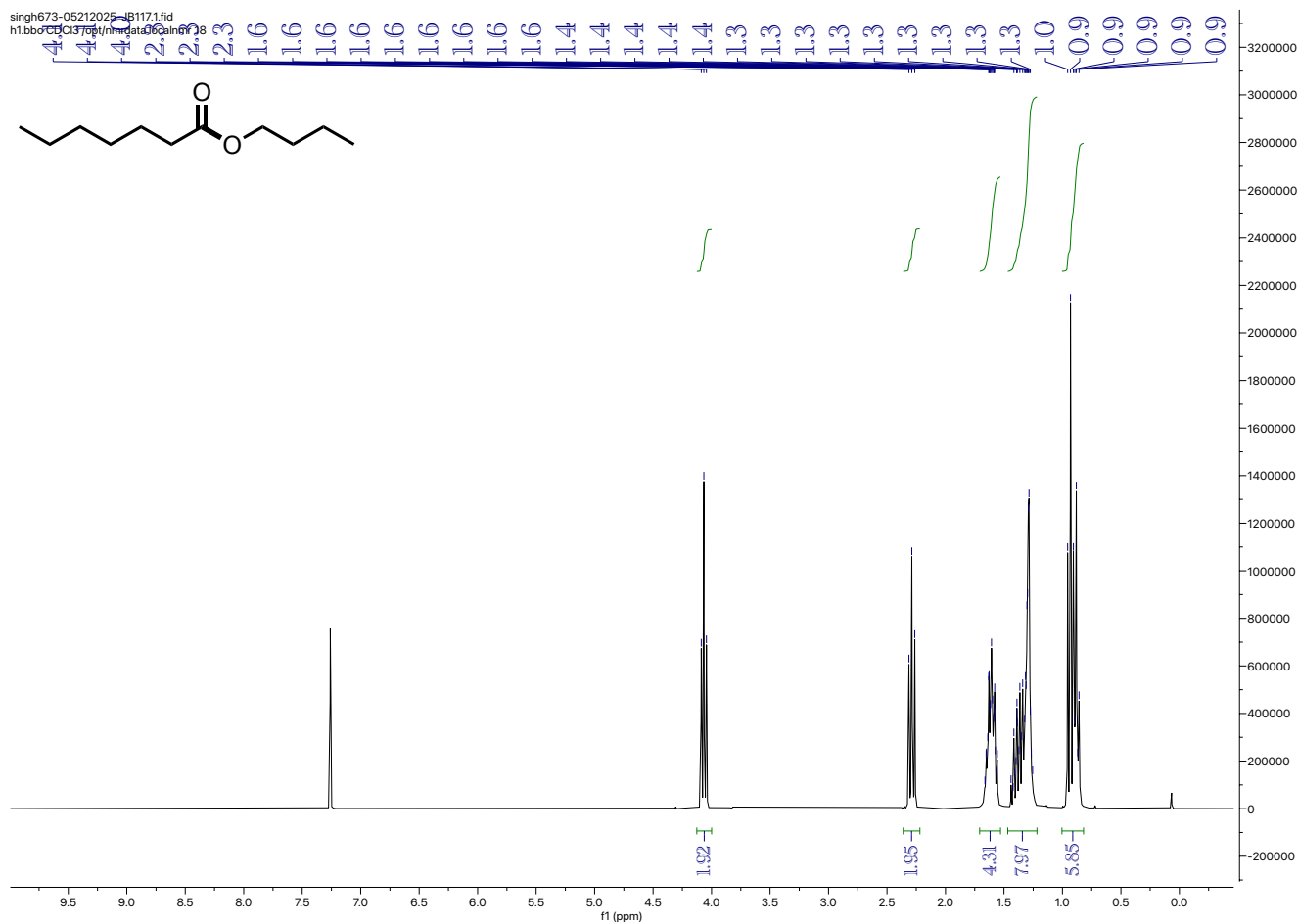


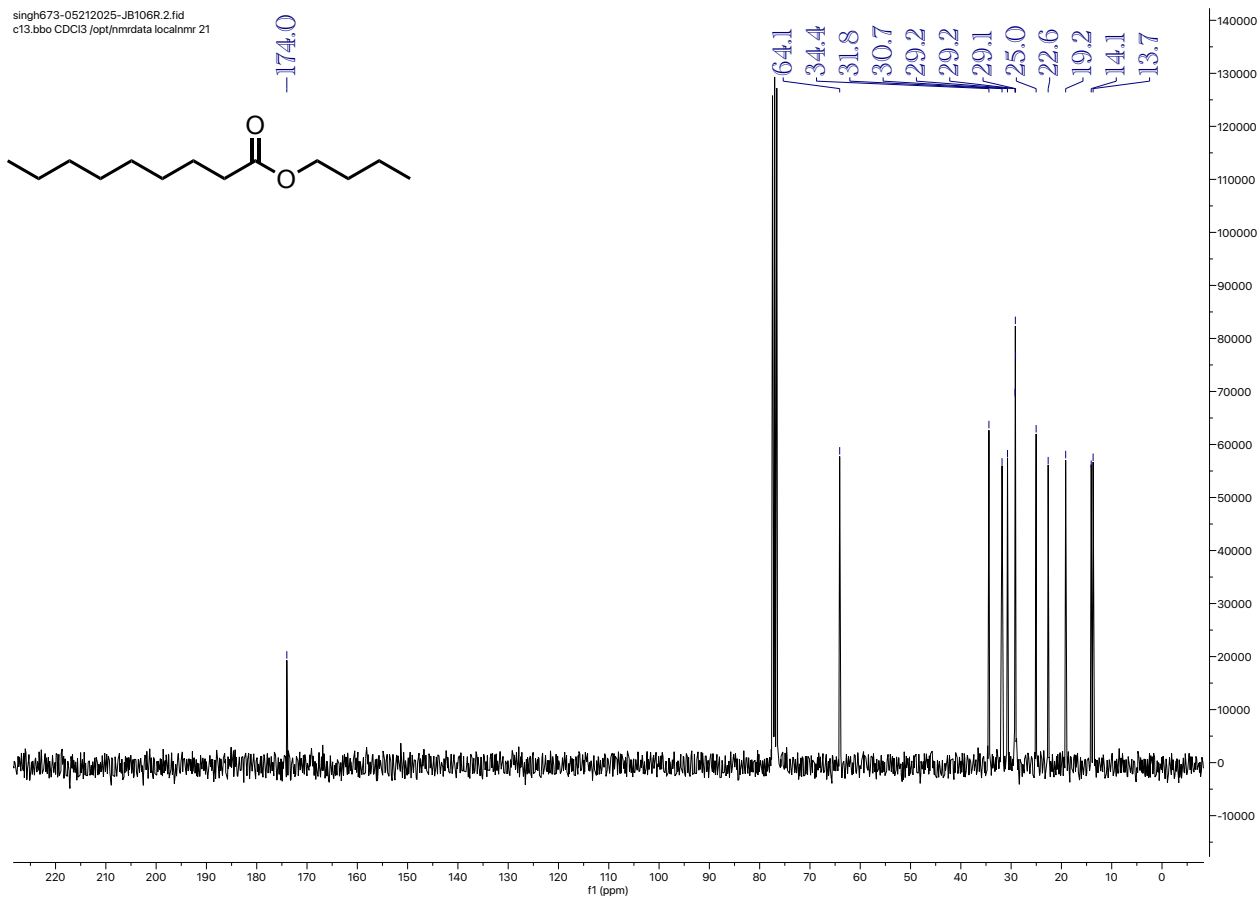
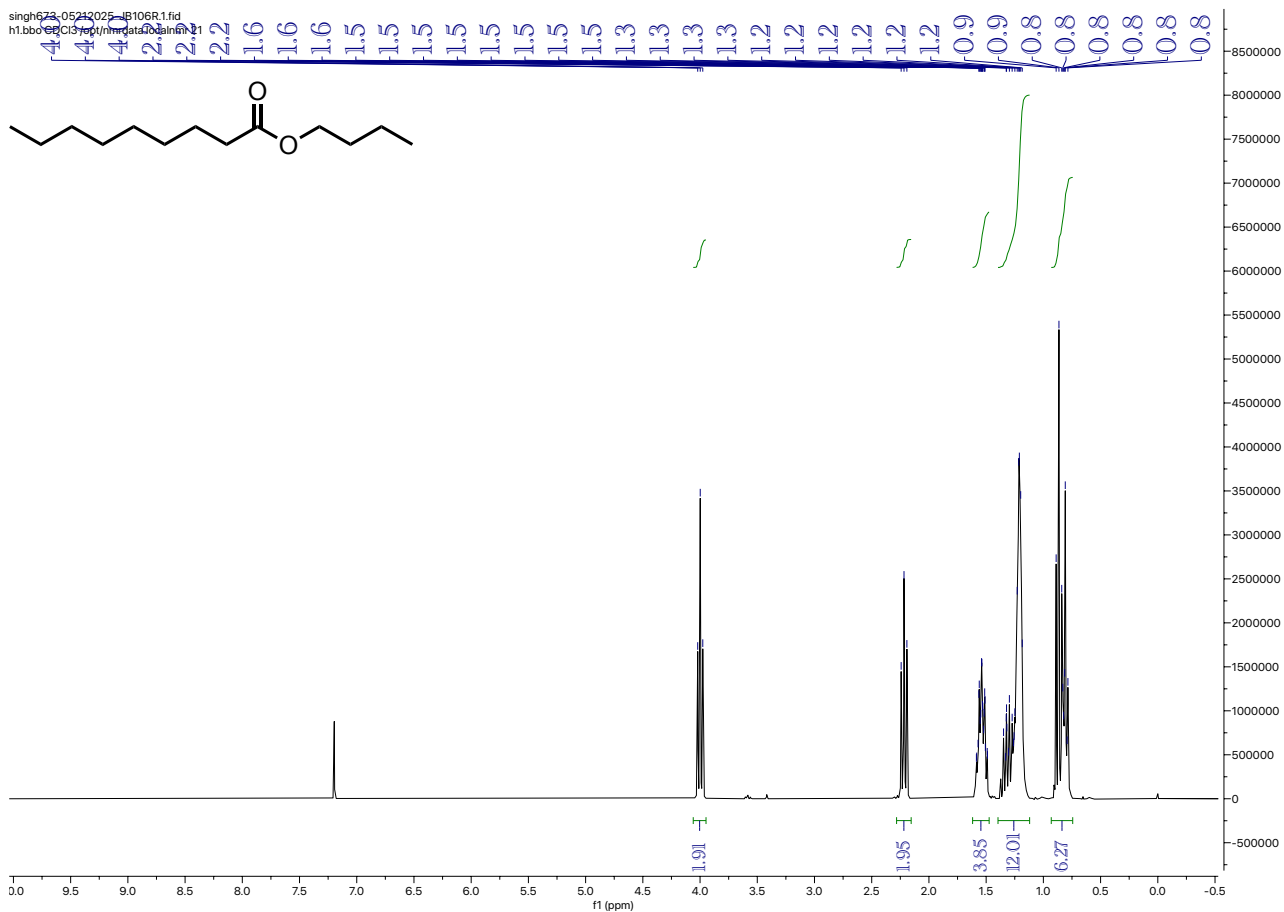


¹H NMR (300 MHz, Chloroform-*d*) butyl 4-nitrobenzoate (**35**)¹³C NMR (75 MHz, Chloroform-*d*) butyl 4-nitrobenzoate (**35**)

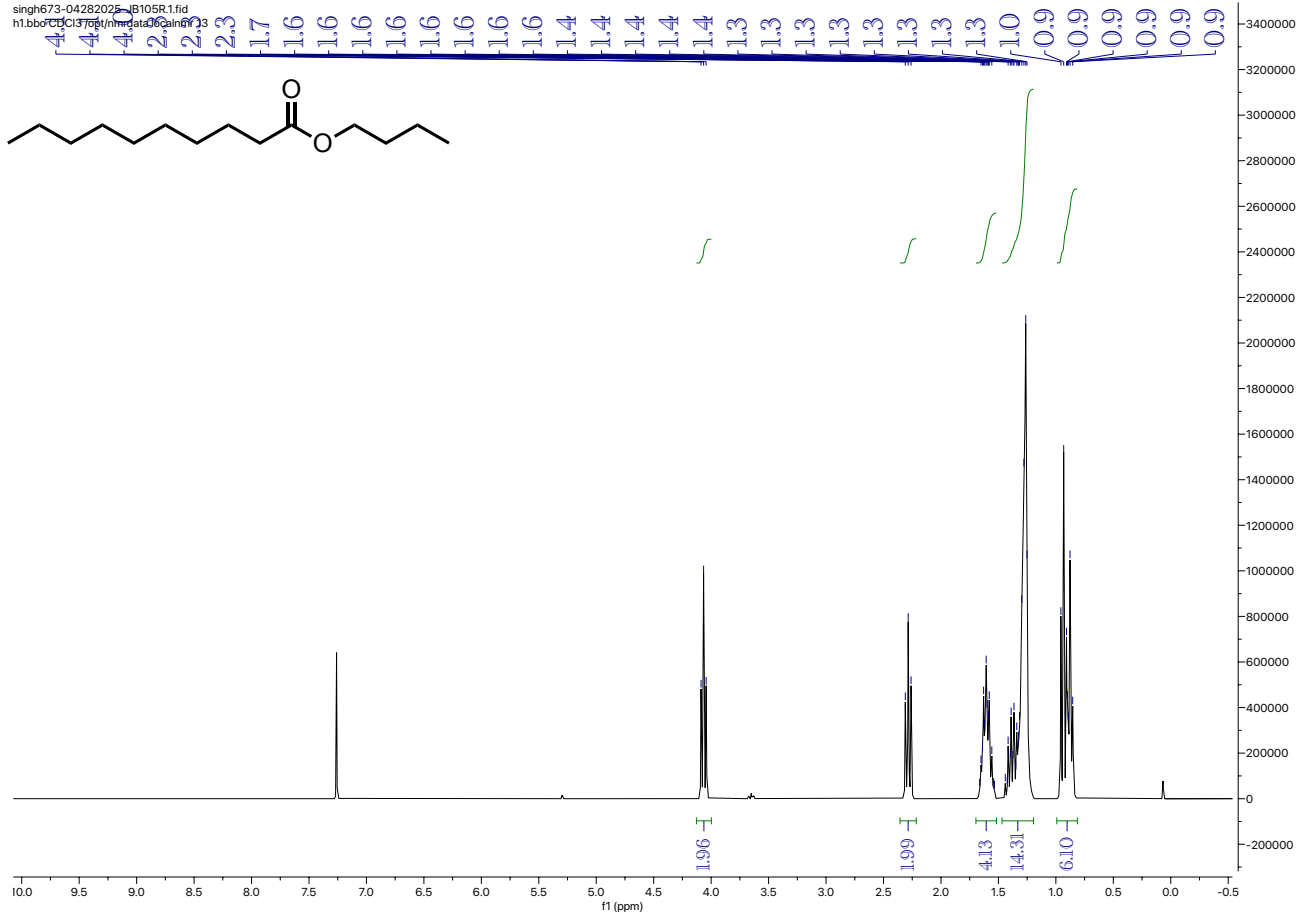




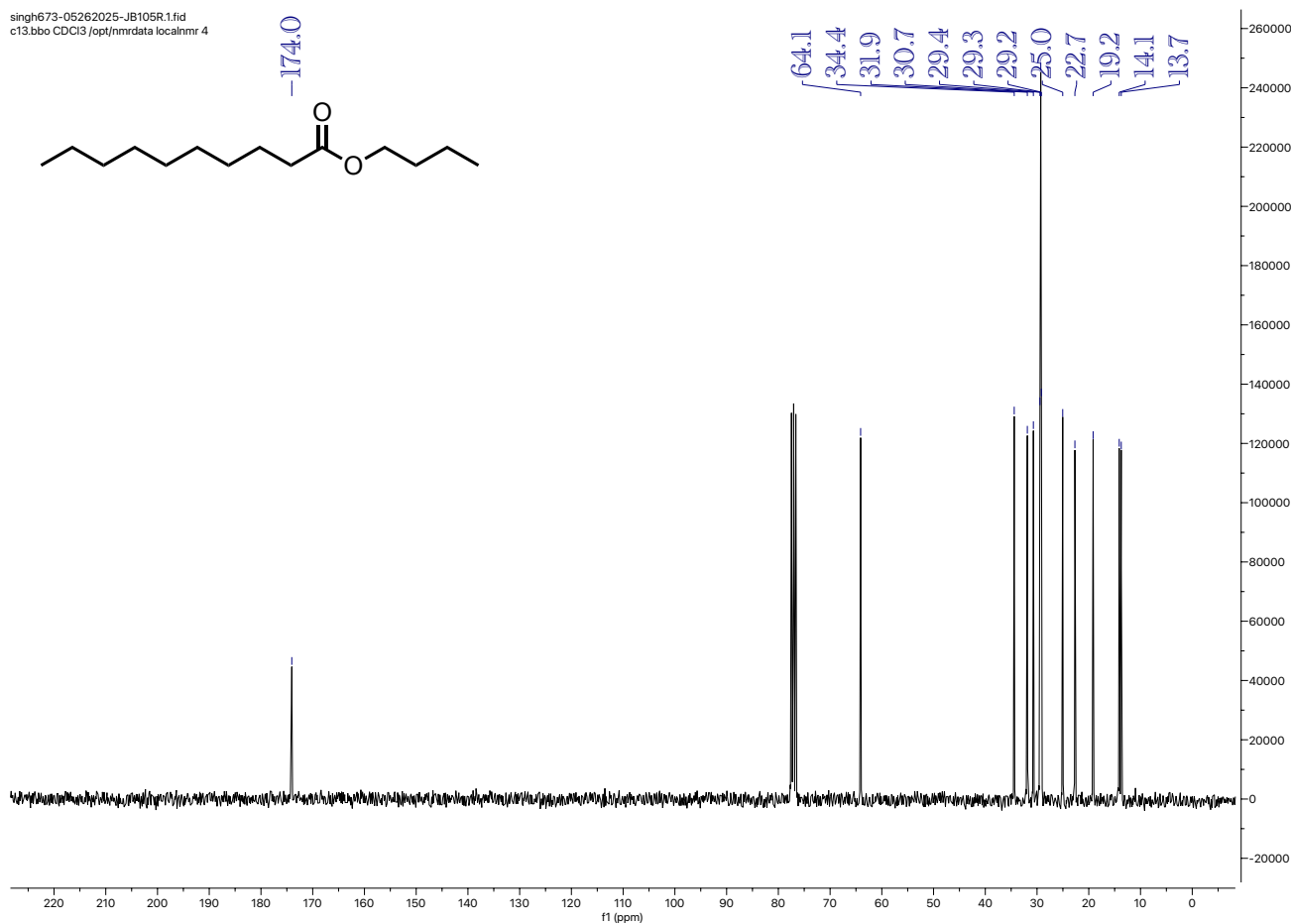




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Green Chemistry Metrics:

Entry	Reagent 1	Reagent 2	Catalyst	Additive	Solvent	Product
1	Hexanoic Acid MW: 116.2 g/mol Mass: 0.697g	Benzylamine MW: 107.2 g/mol Mass: 0.535g	Cryolite	-	Xylenes	<i>N</i> -Benzylhexanamide MW: 205.3 g/mol Mass: 1.001g Yield: 97%
2	Hexanoic Acid MW: 116.2 g/mol Mass: 0.116g	Benzylamine MW: 107.2 g/mol Mass: 0.107g	<i>Candida antarctica lipase B</i>	-	CPME	<i>N</i> -Benzylhexanamide MW: 205.3 g/mol Mass: 0.201g Yield: 98%
3	Hexanoic Acid MW: 116.2 g/mol Mass: 0.116g	Benzylamine MW: 107.2 g/mol Mass: 0.107g	POM-Fe	Phenyl Silane MW: 108.22g/mol Mass: 0.032g (0.3 equiv.)	Toluene	<i>N</i> -Benzylhexanamide MW: 205.3 g/mol Mass: 0.133g Yield: 65%

Atom Economy:

$$= \frac{\text{Molecular Mass of desired product}}{\text{Molecular Mass of all reactants}} \times 100$$

$$= \frac{205.3}{139.4+107.2} \times 100\% = 83.2\% \text{ (Entry 1)}$$

$$= \frac{205.3}{116.2+107.2} \times 100\% = 92\% \text{ (Entry 2)}$$

$$= \frac{205.3}{116.2+107.2+32.4} \times 100\% = 80.2\% \text{ (Entry 3)}$$

Atom Efficiency:

$$= \% \text{Yield} \times \text{Atom Economy}$$

$$= 97 \times 0.83 = 80.5\% \text{ (Entry 1)}$$

$$= 98 \times 0.92 = 90.2\% \text{ (Entry 2)}$$

$$= 65 \times 0.80 = 52\% \text{ (Entry 3)}$$

Reaction Mass Efficiency:

$$= \frac{\text{Mass of desired product}}{\text{Mass of all reactants}} \times 100$$

$$= \frac{1.001}{0.697+0.535} = 81.3\% \text{ (Entry 1)}$$

$$= \frac{0.201}{0.116+0.106} = 90.1\% \text{ (Entry 2)}$$

$$= \frac{0.133}{0.116+0.107+0.032} = 52\% \text{ (Entry 3)}$$