Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Amidation of Unactivated Ester Derivatives Mediated by Trifluoroethanol

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Contents

1. General

All reagents and solvents were obtained from commercial suppliers and were used without further purification unless otherwise stated. Purification was carried out according to standard laboratory methods.[1]

1.1 Purification of Solvents

i) Anhydrous THF and toluene were obtained from a PureSolv SPS-400-5 solvent purification system.

ii) Acetonitrile, 1,2-Dichloroethane, isopropanol and 2-MeTHF were purified by fractional distillation under vacuum from CaH_2; n-butanol was purified by stirring over 4 Å molecular sieves; CPME was purified by vacuum distillation from sodium metal; 1,4-Dioxane was purified by vacuum distillation from $LiAlH_4$; Dimethyl carbonate was purified by fractional distillation under vacuum from 4 Å molecular sieves; DMF was purified by fractional distillation under vacuum from $MgSO_4$.

iii) Purified solvents were transferred to and stored in septum-sealed oven-dried flasks over previously activated 4 Å molecular sieves and purged with and stored under nitrogen.

1.2 Purification of Starting Materials

i) Methyl benzoate, benzylamine and *N*-methylbenzylamine used for optimisation reactions, were purified by vacuum distillation from KOH; trifluoroethanol, used as an additive, was purified by fractional distillation from Na_2SO_4.

ii) BEMP was purified by vacuum distillation from CaH_2; $Ca_3(PO_4)_2$, Cs_2CO_3, Cs_3PO_4, K_2CO_3, KH_2PO_4, K_2HPO_4, K_3PO_4, Li_3PO_4, $Mg_3(PO_4)_2$ and Na_3PO_4 were stored in a vacuum oven at 60 °C; DABCO was recrystallised from MeOH/diethyl ether (1:1); DBU was purified by fractional distillation under vacuum; Et_3N was purified by fractional distillation under vacuum over CaH_2, Potassium acetate was stored in a desiccator over P_2O_5; KOAc, KOH and KTFA were stored in a desiccator over P_2O_5; KOtBu was purified by sublimation.

iii) Dichloromethane, ethyl acetate, methanol, and petroleum ether 40–60 °C for purification purposes were used as obtained from suppliers without further purification.

1.3 Experimental Details

i) All reactions were carried out using oven-dried glassware, which was evacuated and purged with N_2 before use.

ii) Amidation reactions were performed using 25 mL Schlenk reaction vessels.

iii) Purging refers to a vacuum/nitrogen-refilling procedure.

iv) Room temperature was generally ca. 20 °C.

v) Reactions were carried out at elevated temperatures using a temperature-regulated hotplate/stirrer.

vi) Amidation reactions at elevated temperatures were carried out using a STEM heating block.

vii) Reactions requiring the use of Radleys tubes with elevated temperatures were performed in a carousel resting on a temperature-regulated hotplate/stirrer.

1.4 Purification of Products

i) Thin layer chromatography was carried out using Merck silica plates coated with fluorescent indicator UV254. These were analysed under 254 nm UV light or developed using potassium permanganate solution.

ii) Flash chromatography was carried out using ZEOprep 60 HYD 40-63 μm silica gel.

1.5 Analysis of Products

i) Fourier Transformed Infra-Red (FTIR) spectra were obtained using an A2 Technologies ATR 32 machine.

ii) 1H and 13C NMR spectra were obtained on a Bruker DRX 500 spectrometer at 500 and 126MHz, respectively or on a Bruker AV3 400 at 400 and 101 MHz, respectively, or on a Bruker AVANCE 400 spectrometer at 400 and 101 MHz respectively. Chemical shifts are reported in ppm and coupling constants are reported in Hz with $CDCl_3$ referenced at 7.26 (^{1}H) and 77.16 ppm (^{13}C), and DMSO referenced at 2.50 (^{1}H) and 39.52 ppm (^{13}C).

iii) Variable temperature NMR experiments were obtained using a Bruker AVANCE 400 spectrometer at 400 and 100 MHz respectively, or a Bruker DRX 500 spectrometer at 500 and 126MHz, respectively at 333 K.

iv) High-resolution mass spectra were obtained on a Thermofisher LTQ Orbitrap XL instrument at the EPSRC National Mass Spectrometry Service Centre (NMSSC), Swansea.

v) Reverse phase HPLC data was obtained on an Agilent 1200 series HPLC using a Machery-Nagel Nucleodur C18 column.

vi) Chiral HPLC data was obtained on an Agilent 1260 Infinity HPLC using a Chiralpak IA column.

vii) Optical rotations were measured at 589 nm using a Perkin Elmer 341 Polarimeter

1.6 HPLC Methods

i) For *N*-Benzylbenzylamide **2**: Reversed phase HPLC analysis was performed using a gradient method, eluting with 5 – 80% MeCN/H_2O over 5 minutes at a flow rate of 2 mL/min, with methyl benzoate, 2,2,2-trifluoroethyl benzoate intermediate, *N*-benzylbenzamide product **2**, and iodobenzene internal standard eluting at 2.0, 2.5, 1.9 and 2.9 minutes, respectively

Time (min)	Concentration of MeCN (%)
0	5
1	55
3.9	60
4.1	80
4.3	5
5	5

For *N*-benzyl-*N*-methylbenzamide **23**: Reversed phase HPLC analysis was performed using a gradient method, eluting with 5 – 60% MeCN/H_2O over 8 minutes at a flow rate of 2 mL/min, with methyl benzoate, *N*-methylbenzylamine, *N*-benzyl-*N*-methylbenzamide product **23**, and caffeine internal standard eluting at 4.7, 1.0, 5.1 and 2.0, respectively.

Time (min)	Concentration of MeCN (%)
0	5
5.5	60
5.8	5
8	5

ii) For *N*-Benzylbenzylamide **2**: For reactions using an internal standard, prior HPLC calibration was carried out using samples containing varying molarities of product and iodobenzene, allowing calculation of the response factor by substituting values into the following equation:

$$Response\ Factor = \frac{(\frac{Area}{Molarity})Product}{(\frac{Area}{Molarity})Standard}$$

Screening reactions were carried out using a known molarity of iodobenzene internal standard as indicated in the relevant general experimental procedures.
Unknown molarities of product were calculated by rearranging the above equation, using the average value for the response factor as determined during calibration.
Conversion to product was calculated as a percentage of the theoretical molarity for the reaction.

For *N*-benzyl-*N*-methylbenzamide **23**: Conversion factor established by running 3 samples with a ratio of 0.25:1 caffeine:analyte, with the average conversion factor calculated by substituting values for each sample into the following equation:

$$Conversion\ factor = \frac{Peak\ Area\ Analyte}{Peak\ Area\ Caffeine}$$

For standard sampling of reaction mixtures, the ratio of Caffeine:Analyte is 0.25:1. Therefore, when calculating the % conversion:

$$\frac{Peak\ Area\ Analyte}{Peak\ Area\ Caffeine\ \times 4} = X$$

$$\frac{X}{Average\ Conversion\ Factor} = \%\ Conversion$$

iii) For *N*-Benzylbenzylamide **2**: Samples for HPLC analysis were prepared by diluting a 10 µL aliquot from the reaction mixture to 1 mL with MeCN.

For *N*-benzyl-*N*-methylbenzamide **23**: Samples for HPLC analysis were prepared through the addition of 7 mL of a 0.05 M caffeine standard to the completed reaction mixture. The resulting solution was then stirred before the removal of a 200 µL aliquot. The

aliquot was diluted to 1 mL with MeOH, a 200 µL aliquot of the diluted solution was then further diluted with 800 µL MeOH and then filtered for HPLC analysis against established conversion factors.

iv) For compounds **11**, **63**, **64**, **65**, **66** and **72:** Chiral HPLC was performed using an isocratic method, using a Chiralpak IA column, eluting with 10% IPA/hexanes over 20 minutes with a flow rate of 1 mL/min.
For compound **59**: Chiral HPLC was performed using an isocratic method, using a Chiralpak IA column, eluting with 5% IPA/hexanes over 1 hour with a flow rate of 1 mL/min.
For compounds **60** and **61**: Chiral HPLC was performed using an isocratic method, using a Chiralpak IA column, eluting with 10% IPA/hexanes over 1 hour with a flow rate of 1 mL/min.
For compound **62**: Chiral HPLC was performed using an isocratic method, using a Chiralpak IA column, eluting with 10% IPA/hexanes over 40 min with a flow rate of 1 mL/min.
For compounds **69**, **70** and **71**: Chiral HPLC was performed using an isocratic method, using a ChiralpakIA column, eluting with 5% IPA/hexanes over 40 min with a flow rate of 1 mL/min.
The major and minor enantiomers were found to elute as follows:

Product	Major enantiomer retention time (min)	Minor enantiomer retention time (min)
11	8.44	11.78
59	38.34	N/A
60	11.16	17.24
61	24.78	51.32
62	15.34	24.06
63	11.91	10.12
64	9.38	8.87
65	8.79	10.31
66	9.13	16.91
69	34.01	N/A
70	18.17	N/A
71	50.66	N/A
72	9.37	N/A

2. General Experimental Procedures

2.1 General Procedure A for Investigating the Nature of the Base Species

To an oven-dried, purged and sealed Schlenk tube containing trifluoroethanol (20 µL, 0.28 mmol, 0.2 equiv.), base (1.42 mmol, 1 equiv.) and THF (700 µL) was added methyl benzoate (178 µL, 1.42 mmol, 1 equiv.) and benzylamine (155 µL, 1.42 mmol, 1 equiv.). The reaction mixture was heated at 90 °C for 22 h. The reaction mixture was sampled at the end of the required reaction time and the conversion was determined by HPLC with reference to iodobenzene (1.4 M), which was used as an internal standard.

Entry	Base	pKa	Conversion (%)
1	KTFA	0	1
2	KH_2PO_4	2	1
3	KOAc	6	1
4	K_2HPO_4	7	1
5	K_2CO_3	10	2
6	K_3PO_4	12	78
7	KOH	16	5
8	KOtBu	18	47
9	Ca_3PO_4	13	1
10	Cs_3PO_4	13	1
11	Li_3PO_4	13	0
12	Mg_3PO_4	13	16
13	Na_3PO_4	13	1
14	Cs_2CO_3	10	11
15	NMO	7	13
16	DABCO	9	4
17	Et_3N	11	1
18	DBU	12	61
19	BEMP	19	8

2.2 General Procedure B for Optimisation of the TFE Mediated Tertiary Amide Formation: Additive Screen

To an oven-dried, purged and sealed Schlenk tube containing additive (0.28 mmol, 0.2 equiv.), K_3PO_4 (301 mg, 1.42 mmol, 1 equiv.) and THF (700 µL) was added methyl benzoate (178 µL, 1.42 mmol, 1 equiv.) and *N*-methylbenzylamine (183 µL, 1.42 mmol, 1 equiv.) was added and the reaction mixture was heated at 90 °C for 22 h. The reaction mixture was sampled at the end of the required reaction time and the conversion was determined by HPLC with reference to a 0.05M caffeine solution.

Entry	Additive	Conversion (%)
1	4-$CF_3C_6H_4OH$	1
2	HFIP	0

3	HOAt	0
4	HOBt	0
5	HOCt	0
6	N-hydroxysuccinimide	0
7	Oxyma	0
8	2-Picoline *N*-oxide	0
9	TFE	1

2.3 General Procedure C for Optimisation of the TFE Mediated Tertiary Amide Formation: Base and Solvent Screen

To an oven-dried, purged and sealed Schlenk tube containing trifluoroethanol (20 µL, 0.28 mmol, 0.2 equiv.), base (1.42 mmol, 1 equiv.) and solvent (700 µL) was added methyl benzoate (178 µL, 1.42 mmol, 1 equiv.) and *N*-methylbenzylamine (183 µL, 1.42 mmol, 1 equiv.) was added and the reaction mixture was heated at 90 °C for 22 h. The reaction mixture was sampled at the end of the required reaction time and the conversion was determined by HPLC with reference to a 0.05M caffeine solution.

Entry	Base	Solvent	Conversion (%)
1	DABCO	n-butanol	0
2	K_3PO_4	n-butanol	3
3	DBU	n-butanol	2
4	KOtBu	n-butanol	22
5	DABCO	CPME	0
6	K_3PO_4	CPME	37
7	DBU	CPME	4
8	KOtBu	CPME	96
9	DABCO	DCE	0
10	K_3PO_4	DCE	0
11	DBU	DCE	0
12	KOtBu	DCE	0
13	DABCO	1,4-Dioxane	0
14	K_3PO_4	1,4-Dioxane	12
15	DBU	1,4-Dioxane	3
16	KOtBu	1,4-Dioxane	37
17	DABCO	DMC	0
18	K_3PO_4	DMC	0
19	DBU	DMC	0
20	KOtBu	DMC	0
21	DABCO	DMF	0
22	K_3PO_4	DMF	8
23	DBU	DMF	3
24	KOtBu	DMF	21
25	DABCO	IPA	0
26	K_3PO_4	IPA	9
27	DBU	IPA	2
28	KOtBu	IPA	0
29	DABCO	2-MeTHF	1

30	K_3PO_4	2-MeTHF	43
31	DBU	2-MeTHF	5
32	KOtBu	2-MeTHF	2
33	DABCO	MeCN	0
34	K_3PO_4	MeCN	0
35	DBU	MeCN	4
36	KOtBu	MeCN	32
37	DABCO	THF	2
38	K_3PO_4	THF	1
39	DBU	THF	8
40	KOtBu	THF	56

2.4 General Procedure D for Optimisation of the TFE Mediated Tertiary Amide Formation: Elevated Temperature Screen

To an oven-dried, purged and sealed Schlenk tube containing trifluoroethanol (20 µL, 0.28 mmol, 0.2 equiv.), K_3PO_4 (301 mg, 1.42 mmol, 1 equiv.) and solvent (700 µL) was added methyl 4-(trifluoromethyl)benzoate (229 µL, 1.42 mmol, 1 equiv.) and the reaction heated at the desired temperature for 30 min. *N*-methylbenzylamine (183 µL, 1.42 mmol, 1 equiv.) was then added and the reaction mixture was heated at the desired temperature for a further 22 h. The reaction mixture was sampled at the end of the required reaction time and the conversion was determined by HPLC with reference to a 0.05M caffeine solution.

Entry	Solvent	Temperature (°C)	Conversion (%)
1	THF	90	0
2[a]	THF	90	70
3[a,b]	THF	90	62
4[a]	CPME	125	77[c]
5[a]	1,4-dioxane	125	93[c]
6[a]	2-MeTHF	100	72[c]
7[a,d]	1,4-dioxane	125	0[c]
8[a,e]	1,4-dioxane	125	0[c]
9[a,f]	1,4-dioxane	125	0[c]

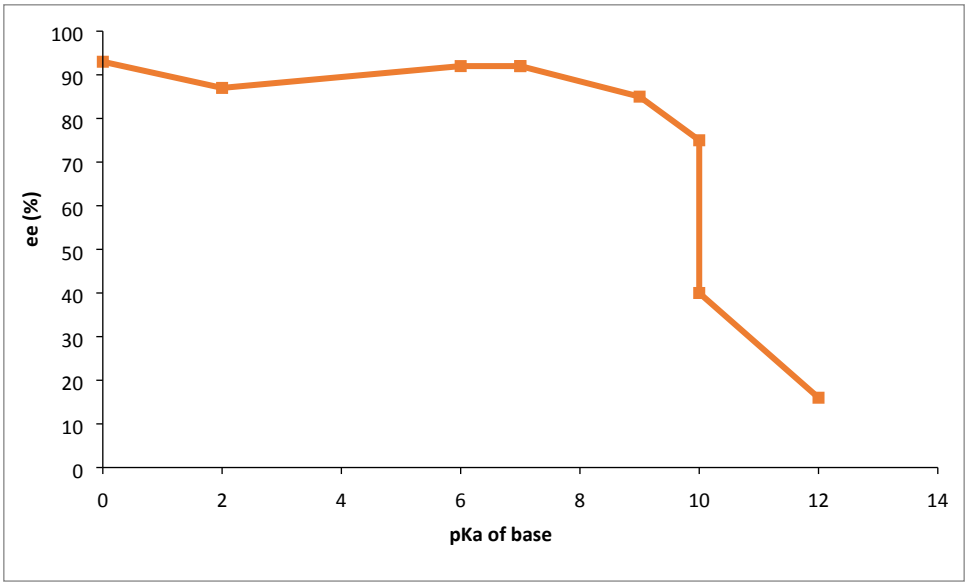
[a]Preformation of the active ester intermediate for 30 min at reaction temperature. [b]Methyl benzoate used as ester substrate. [c]Isolated Yield. [d]Performed in the absence of K_3PO_4. [e]Performed in the absence of TFE. [f]Performed in the absence of both K_3PO_4 and TFE.

2.5 General Procedure E for Chiral Secondary Amide Base Screen

To an oven-dried, purged and sealed Schlenk tube containing 4-(trifluoromethyl)phenol (46 mg, 0.28 mmol, 0.2 equiv.), base (1.42 mmol, 1 equiv.), Boc-L-phenylalanine methyl ester (397 mg, 1.42 mmol, 1 equiv.) and THF (700 µL) was added benzylamine (155 µL, 1.42 mmol, 1 equiv.). The reaction mixture was heated at 90 °C for 22 h then diluted with EtOAc (10 mL), washed with brine (3 x 10 mL), dried over Na_2SO_4, and concentrated to a residue *in vacuo* which was purified by silica gel chromatography (1% MeOH/CH_2Cl_2).

Entry	Base	Base pKa	Yield (%)	ee (%)

1	KTFA	0	46	93
2	KH_2PO_4	2	62	87
3	KOAc	6	55	92
4	NMO	7	36	92
5	K_2HPO_4	7	48	92
6	DABCO	9	40	85
7	K_2CO_3	10	46	75
8	Cs_2CO_3	10	34	40
9	DBU	12	69	16



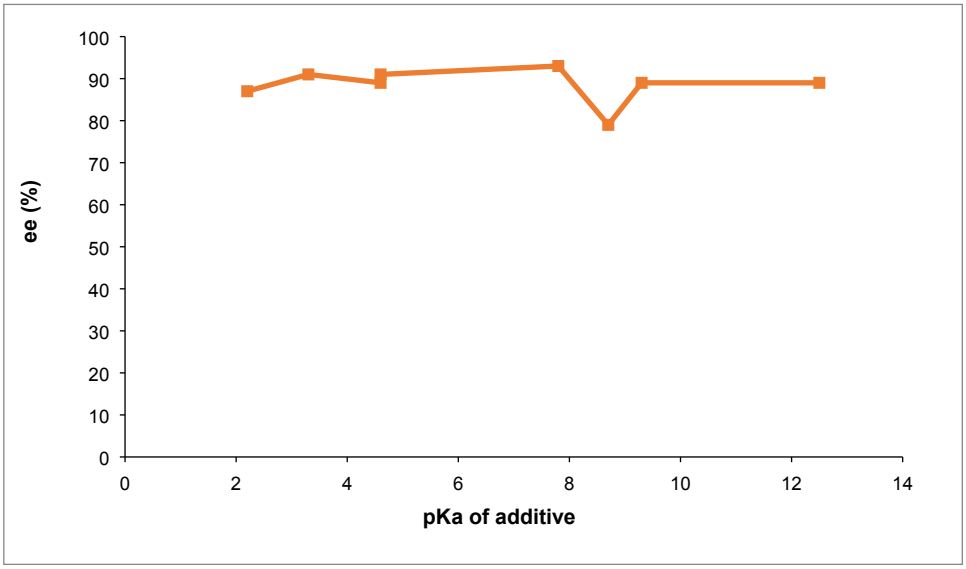
2.6 General Procedure F for Chiral Secondary Amide Additive Screen

To an oven-dried, purged and sealed Schlenk tube containing additive (0.28 mmol, 0.2 equiv.), KOAc (139 mg, 1.42 mmol, 1 equiv.), Boc-L-phenylalanine methyl ester (397 mg, 1.42 mmol, 1 equiv.) and THF (700 µL) was added benzylamine (155 µL, 1.42 mmol, 1 equiv.). The reaction mixture was heated at 90 °C for 22 h then diluted with EtOAc (10 mL), washed with brine (3 x 10 mL), dried over Na_2SO_4, and concentrated to a residue *in vacuo* which was purified by silica gel chromatography (1% MeOH/CH_2Cl_2).

Entry	Additive	Additive pKa	Yield (%)	ee (%)
1	Picoline n-oxide	-	28	87
2	HOCt	2.2	54	91
3	HOAt	3.3	32	89
4	HOBt	4.6	47	91
5	Oxyma	4.6	50	93
6	NHS	7.8	58	79
7	4-$CF_3C_6H_4OH$	8.7	55	92
8	HFIP	9.3	35	89
9	TFE	12.5	31	89

10[a]	4-$CF_3C_6H_4OH$	8.7	44	92
11	No additive	-	17	89
12[a]	No additive	-	28	88

[a]Performed in the absence of KOAc



2.8 General Procedure G for Investigating the Point of Racemisation in the Chiral Secondary Amide Methodology.

To an oven-dried, purged and sealed Schlenk tube containing KOAc (1 equiv.), Boc-L-phenylalanine methyl ester (397 mg, 1.42 mmol, 1 equiv.) **or** amide **11** (150 mg, 0.43 mmol, 1 equiv.) was added THF (700/210 µL respectively). The reaction mixture was heated at 90 °C for 22 h then diluted with EtOAc (10 mL), washed with brine (3 x 10 mL), dried over Na_2SO_4, and concentrated to a residue *in vacuo*. The ee of the resulting products was then determined by HPLC.

Entry	Substrate	Initial ee (%)	ee upon reaction completion (%)
1	Boc-Phe-OMe	100	100
2	**11**	92	92

2.7 General Procedure H for Synthesis of Secondary Amine Starting Materials

To a round-bottomed flask containing a solution of amine (1 equiv.) in DCM (10 mL) at 0 °C was added Et_3N (2 equiv.) and a solution of di-*tert*-butyl dicarbonate (1.2 equiv.) in DCM (5 mL). Reaction warmed to room temperature and stirred for 16 h, at which point it was washed sequentially with 2M HCl (10 mL), 5% $NaHCO_3$ (aq) (10 mL) and water (10 mL). Organics dried over Na_2SO_4 and

concentrated to a residue *in vacuo*, to which was added THF (10 mL) and NaH (1.1 equiv.) reaction stirred until effervescence had ceased, at which point methyl iodide (1.2 equiv.) was added and the reaction heated at 45 °C for 72 hours. THF removed *in vacuo*, the resulting crude product dissolved in EtOAc (10 mL), washed with water (3 x 10 mL), dried over Na_2SO_4 and concentrated to a residue *in vacuo* which was purified by silica gel chromatography (5% EtOAc/Pet. ether 40–60 °C).

To a solution of the resulting *N*-methylated Boc-protected amine in DCM (10 mL) was added TFA (10 mL). Reaction stirred at room temperature for 16 h, at which point the reaction mixture was concentrated to a residue *in vacuo*. Resulting crude product dissolved in EtOAc (10 mL) and washed with 2M NaOH (aq) until pH ≥ 9. Organics extracted with EtOAc (3 x 20 mL), dried over Na_2SO_4 and concentrated *in vacuo* to afford the desired *N*-methyl amine.

2.8 General Procedure I for Synthesis of Chiral Ester Starting Materials *via* Esterification

To an oven-dried, purged Radleys tube containing carboxylic acid (1 equiv.) was added MeOH (20 mL), and the solution cooled to 0 °C. $SOCl_2$ (1.2 equiv.) added dropwise and the reaction refluxed for 16 h. Reaction mixture washed with saturated $NaHCO_3$ (aq) until pH ≥ 8, extracted with DCM (3 x 20 mL), dried over Na_2SO_4 and concentrated to a residue *in vacuo*. Resulting crude product was purified by silica gel chromatography (EtOAc/Pet. ether 40–60 °C).

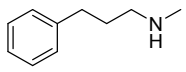
2.9 General Procedure J for Synthesis of Chiral Ester Starting Materials *via* Cbz Protection

To a round-bottomed flask was added ester hydrochloride salt (1 equiv.), *N*-(benzyloxycarbonyloxy)succinimide (1.1 equiv.), $NaHCO_3$ (2.5 equiv.), THF (7 mL) and water (7 mL). Reaction stirred for 16 h at room temperature, at which point the reaction mixture was diluted with water (20 mL) and extracted with EtOAc (2 x 20 mL). Organics dried over Na_2SO_4 and concentrated to a residue *in vacuo* which was purified by silica gel chromatography (EtOAc/pet. ether 40–60 °C).

3. Characterisation Data

3.1 Characterisation Data for Synthesised Starting Materials

_N_-methyl-3-phenylpropan-1-amine (67).[2]



Synthesised according to General Experimental Procedure H using 3.7 mmol of 3-phenylpropan-1-amine, affording the title compound as a pale yellow liquid (372 mg, 67%).

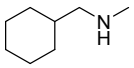
υ_{max} (neat): 3027, 2932, 2857, 2794, 1673, 1455, 1033, 748, 700 cm^{-1}

^{1}H NMR (500 MHz, DMSO-d_6): δ 7.27, (t, J = 7.5 Hz, 2H), 7.17 (dd, J = 16.9, 7.5 Hz, 3H), 2.59 (t, J = 7.6 Hz, 2H), 2.45 (t, J = 7.0 Hz), 1.68 (p, J = 7.8 Hz, 5H)

^{13}C NMR (126 MHz, DMSO-d_6): δ 142.2, 128.2, 128.2, 125.6, 50.9, 36.1, 32.9, 31.0

HRMS *m/z*: $[M+H]^+$ Calcd for $C_{10}H_{16}N$ 150.1277, Found 150.1275

1-cyclohexyl-*N*-methylmethanamine (68).[3]



Synthesised according to General Experimental Procedure H using 8.8 mmol of cyclohexylmethanamine, affording the title compound as a pale yellow liquid (404 mg, 36%).

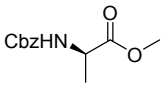
υ_{max} (neat): 2919, 2850, 2788, 1448, 1126, 1150, 742 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$): δ 2.41 (d, *J* = 9.2 Hz, 4H), 1.74 – 1.64 (m, 5H), 1.49 – 1.42 (m, 2H), 1.28 - 1.10 (m, 3H), 0.95 – 0.87 (m, 2H)

^{13}C NMR (126 MHz,$CDCl_3$): δ 54.3, 44.4, 35.5, 34.4, 33.2, 29.7, 29.7, 25.6, 25.6, 25.0, 25.0

HRMS *m/z*: $[M+H]^+$ Calcd for $C_8H_{18}N$ 128.1434, Found 128.1429

Methyl ((benzyloxy)carbonyl)-*D*-alaninate (69).[4]



Synthesised according to General Experimental Procedure J, using 3.58 mmol of methyl *D*-alaninate hydrochloride, and purified by flash column chromatography (20% EtOAc/Pet. ether 40 – 60 °C) to afford the title compound as a pale yellow oil (581 mg, 68%).

υ_{max} (neat): 3336, 3036, 2993, 2958, 1753, 1684, 1526, 1215, 1174, 1076, 754, 702 cm^{-1}

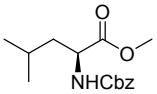
^1H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.29 (m, 5H), 5.31 (s, 1H), 5.11 (m, 2H), 4.40 (p, *J* = 7.2 Hz, 1H), 3.75 (s, 3H), 1.42 (d, *J* = 7.2 Hz, 3H)

^{13}C NMR (101 MHz,$CDCl_3$): δ 173.6, 155.7, 136.4, 128.6, 128.3, 128.2, 67.0, 52.5, 49.7, 18.8

HRMS *m/z*: $[M+H]^+$ Calcd for $C_{12}H_{16}NO_4$ 238.1074, Found 238.1076

ee = 100%

Methyl ((benzyloxy)carbonyl)-*L*-leucinate (70).[5]



Synthesised according to General Experimental Procedure J, using 2.75 mmol of methyl *L*-leucinate hydrochloride, and purified by flash column chromatography (20% EtOAc/Pet. ether 40 – 60 °C) to afford the title compound as a colourless oil (683 mg, 89%).

υ_{max} (neat): 3339, 2956, 1699, 1526, 1262, 1208, 1171, 1046, 739, 700 cm^{-1}

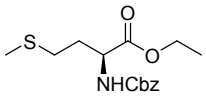
^1H NMR (500 MHz, $CDCl_3$): δ 7.36 – 7.30 (m, 5H), 5.12 (m, 3H), 4.4 (dd, *J* = 13.8, 8.8 Hz, 1H), 3.74 (s, 3H), 1.74 – 1.61 (m, 2H), 1.55 – 1.49 (m, 1H), 0.94 (m, 6H)

^{13}C NMR (126 MHz,$CDCl_3$): δ 173.8, 156.1, 136.4, 128.7, 128.3, 128.3, 67.1, 52.6, 52.4, 24.9, 23.0, 22.0

HRMS *m/z*: $[M+H]^+$ Calcd for $C_{15}H_{22}NO_4$ 280.1543, Found 280.1541

ee = 100%

ethyl ((benzyloxy)carbonyl)-*L*-methioninate (71).[6]



Synthesised according to General Experimental Procedure J, using 2.81 mmol of methyl *L*-methioninate hydrochloride, and purified by flash column chromatography (20% EtOAc/Pet. ether 40 – 60 °C) to afford the title compound as a pale yellow oil (629 mg, 72%).

υ_{max} (neat): 3326, 2980, 2917, 1705, 1521, 1210, 1046, 1029, 700 cm^{-1}

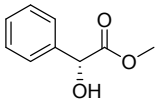
^1H NMR (500 MHz, $CDCl_3$): δ 7.36 – 7.29 (m, 5H), 5.42 (s, 1H), 5.11 (s, 2H), 4.48 (dd, *J* = 12.7, 7.6 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 2.58 - 2.47 (m, 2H), 2.20 – 2.09 (m, 4H), 1.96 (td, *J* = 14.4, 7.5 Hz, 1H), 1.28 (t, *J* = 7.1Hz, 3H)

^{13}C NMR (126 MHz,$CDCl_3$): δ 172.1, 156.0, 136.3, 128.7, 128.3, 128.3, 67.2, 61.8, 53.4, 32.2, 30.0, 15.6, 14.3

HRMS *m/z*: $[M+H]^+$ Calcd for $C_{15}H_{22}NO_4S$ 312.1264, Found 312.1261

ee = 100%

Methyl (*R*)-2-hydroxy-2-phenylacetate (72).[7]



Synthesised according to General Experimental Procedure I, using 4.93 (mmol) of (*R*)-2-hydroxy-2-phenylacetic acid, and purified by flash column chromatography (20% EtOAc/Pet. ether 40 – 60 °C) to afford the title compound as a colourless oil (643 mg, 80%).

υ_{max} (neat): 3434, 1738, 1206, 1191, 1068, 977, 739, 696 cm^{-1}

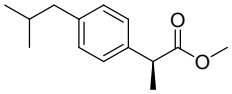
^1H NMR (400 MHz, $CDCl_3$): δ 7.43 -7.31 (m, 5H), 5.18 (d, *J* = 5.3 Hz, 1H), 3.76 (d, *J* = 1.7 Hz, 3H), 3.49 – 3.43 (m, 1H)

^{13}C NMR (101 MHz,$CDCl_3$): δ 174.3, 138.4, 128.8, 128.7, 126.7, 73.0, 53.2

HRMS *m/z*: $[M+H]^+$ Calcd for $C_9H_{11}O_3$ 167.0703, Found 167.0701

ee = 100%

Methyl (*S*)-2-(4-isobutylphenyl)propanoate (73).[8]



Synthesised according to General Experimental Procedure I, using 3.64 mmol of (*S*)-2-(4-isobutylphenyl)propanoic acid, and purified by flash column chromatography (10% EtOAc/Pet. ether 40 – 60 °C) to afford the title compound as a pale yellow oil (583 mg, 73%).

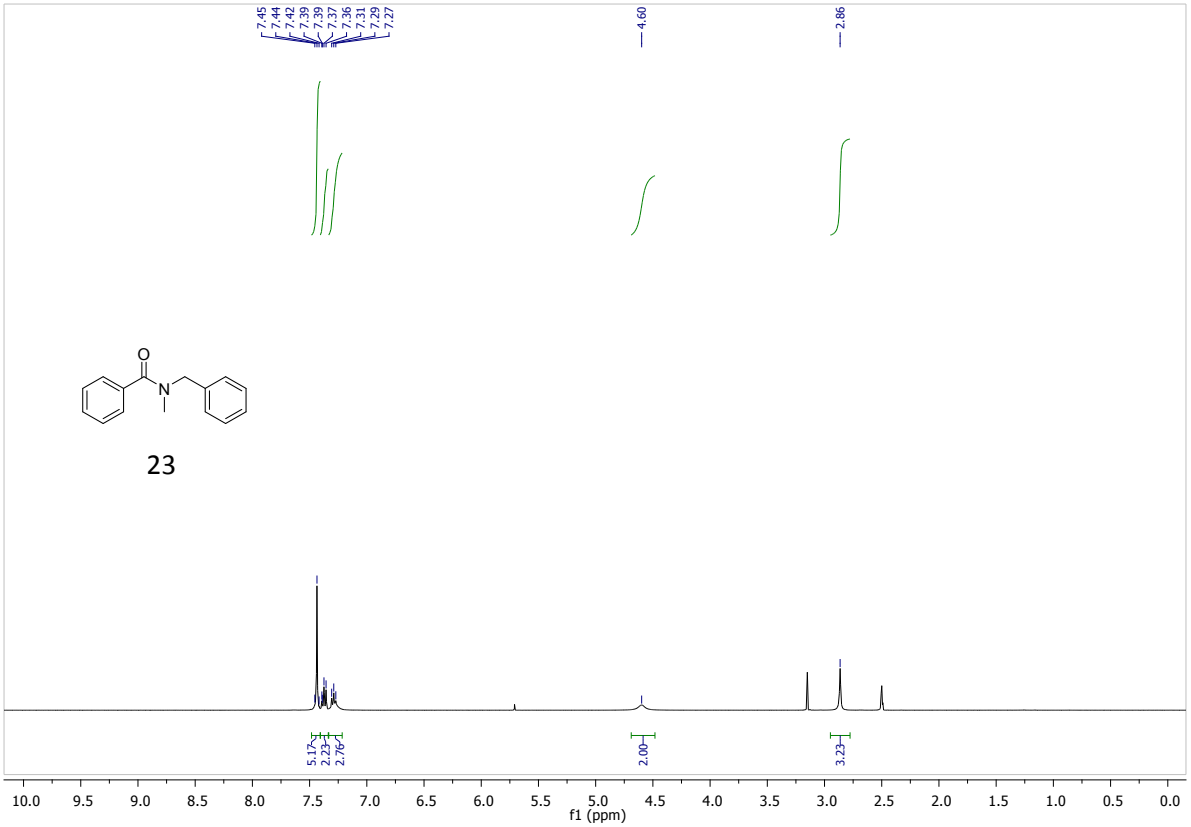
υ_{max} (neat): 2954, 2870, 1738, 1206, 1163, 1066 cm^{-1}
^1H NMR (400 MHz, $CDCl_3$): δ 7.21 – 7.18 (m, 2H), 7.11 – 7.09 (m, 2H), 3.70 (q, *J* = 7.2 Hz, 1H), 3.66 (s, 3H), 2.45 (d, *J* = 7.2 Hz, 2H), 1.92 – 1.76 (m, 1H), 1.49 (d, *J* = 7.2 Hz, 3H), 0.90 (d, *J* = 6.6 Hz, 6H)

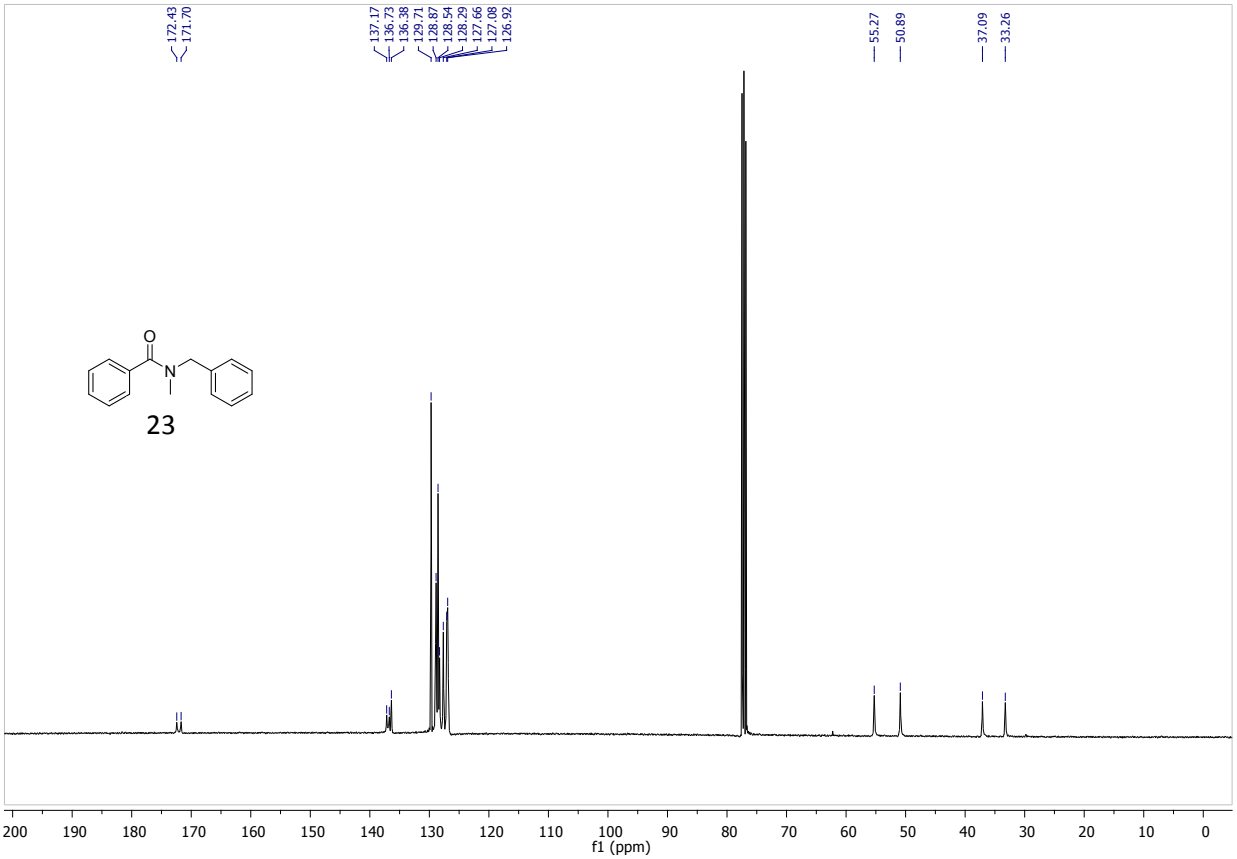
^{13}C NMR (101 MHz,$CDCl_3$): δ 175.4, 140.7, 137.9, 129.5, 127.3, 52.1, 45.2, 30.3, 22.5, 18.8

HRMS *m/z*: $[M+H]^+$ Calcd for $C_{14}H_{21}O_2$ 221.1536, Found 221.15

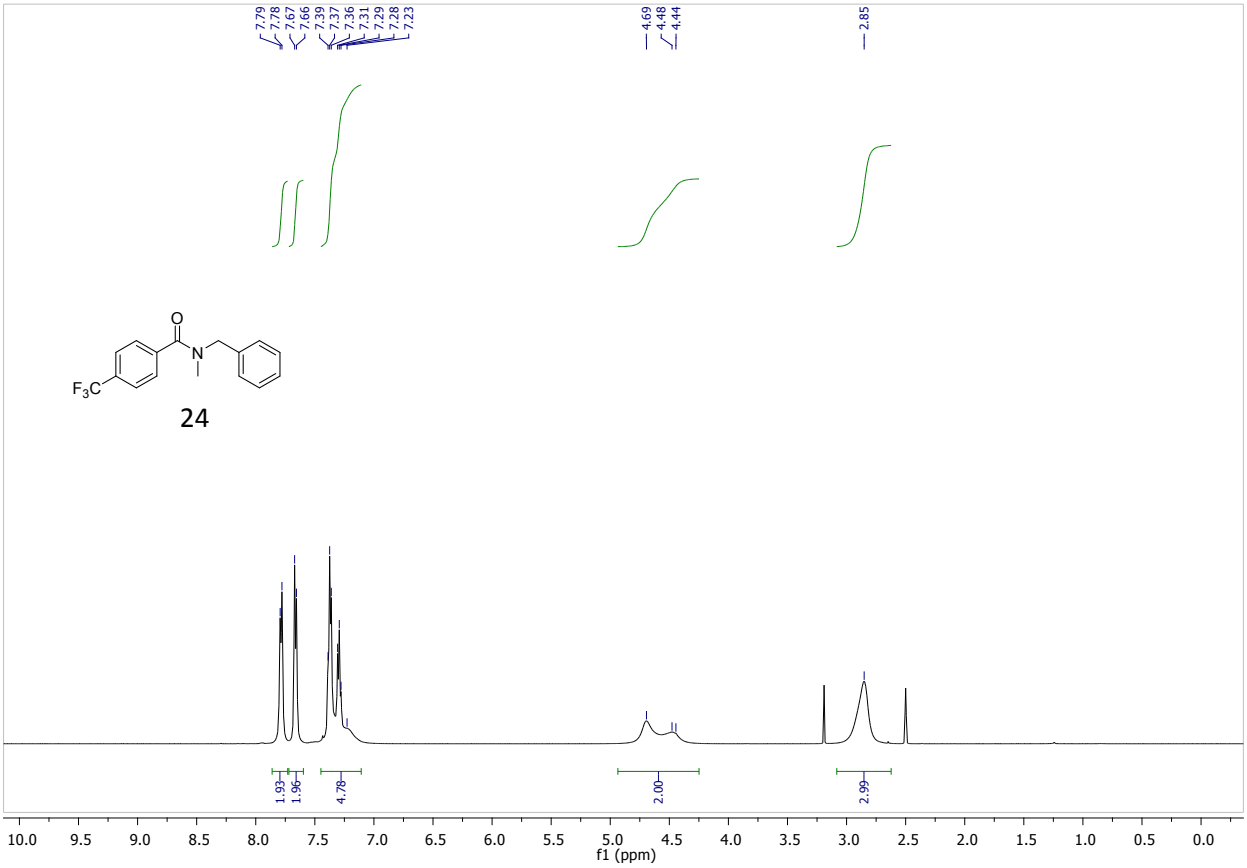
4. ^1H and ^{13}C Spectra for Exemplified Compounds

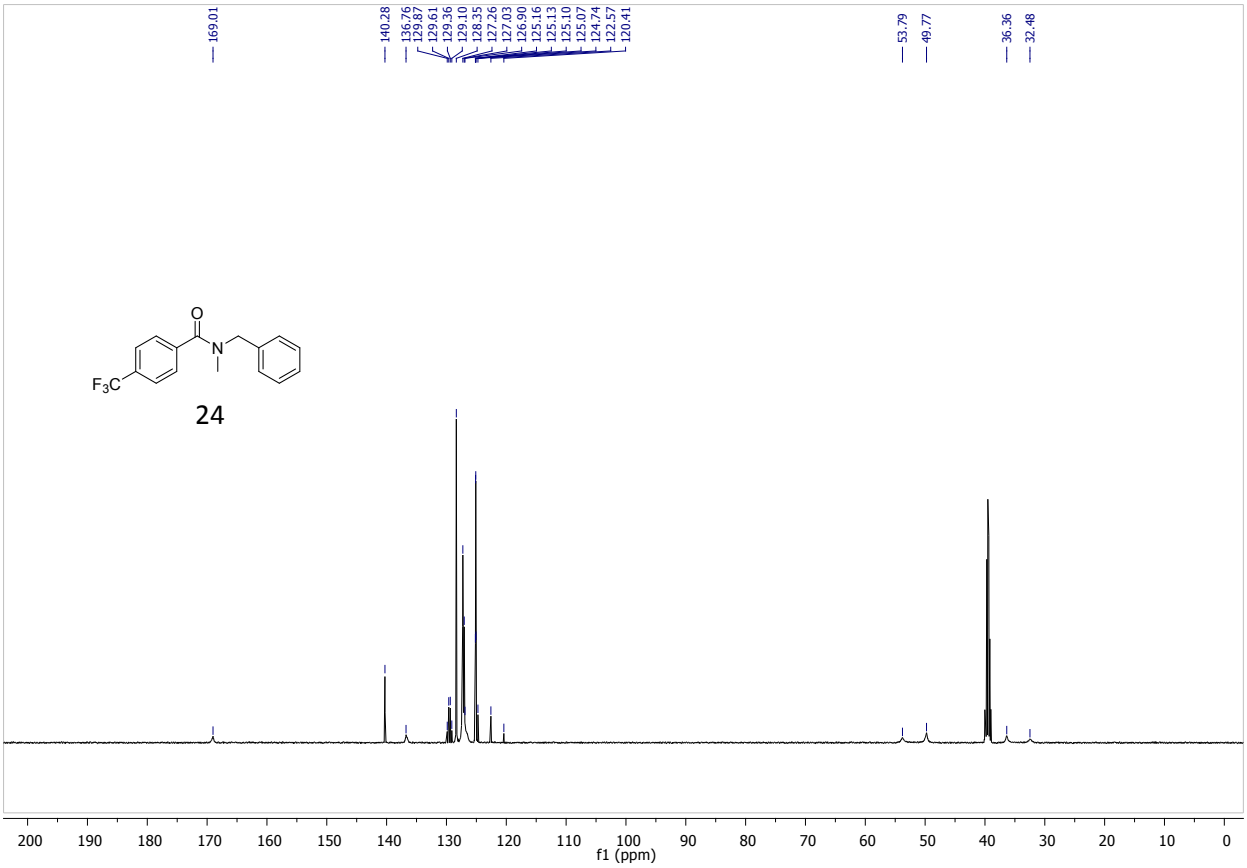
***N*-benzyl-*N*-methylbenzamide (23)**.



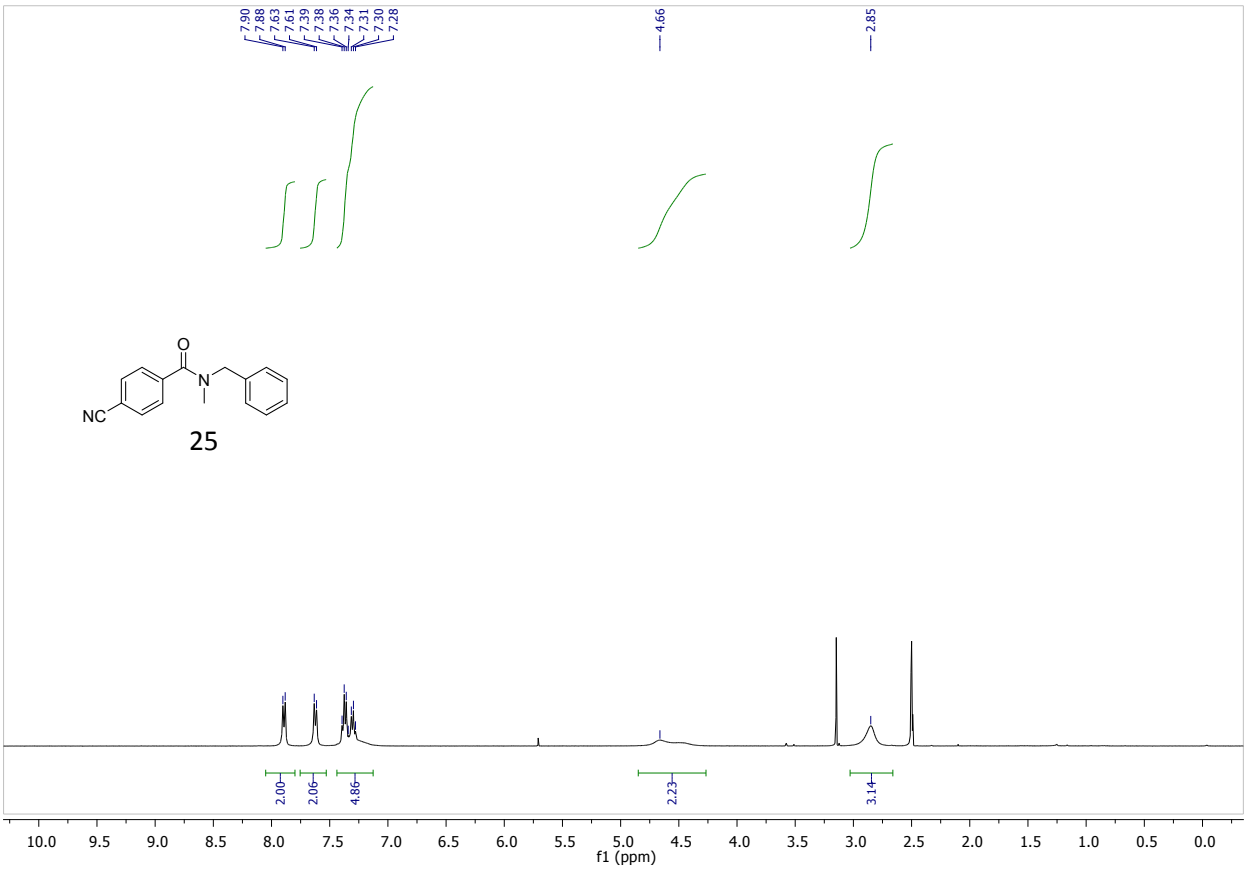


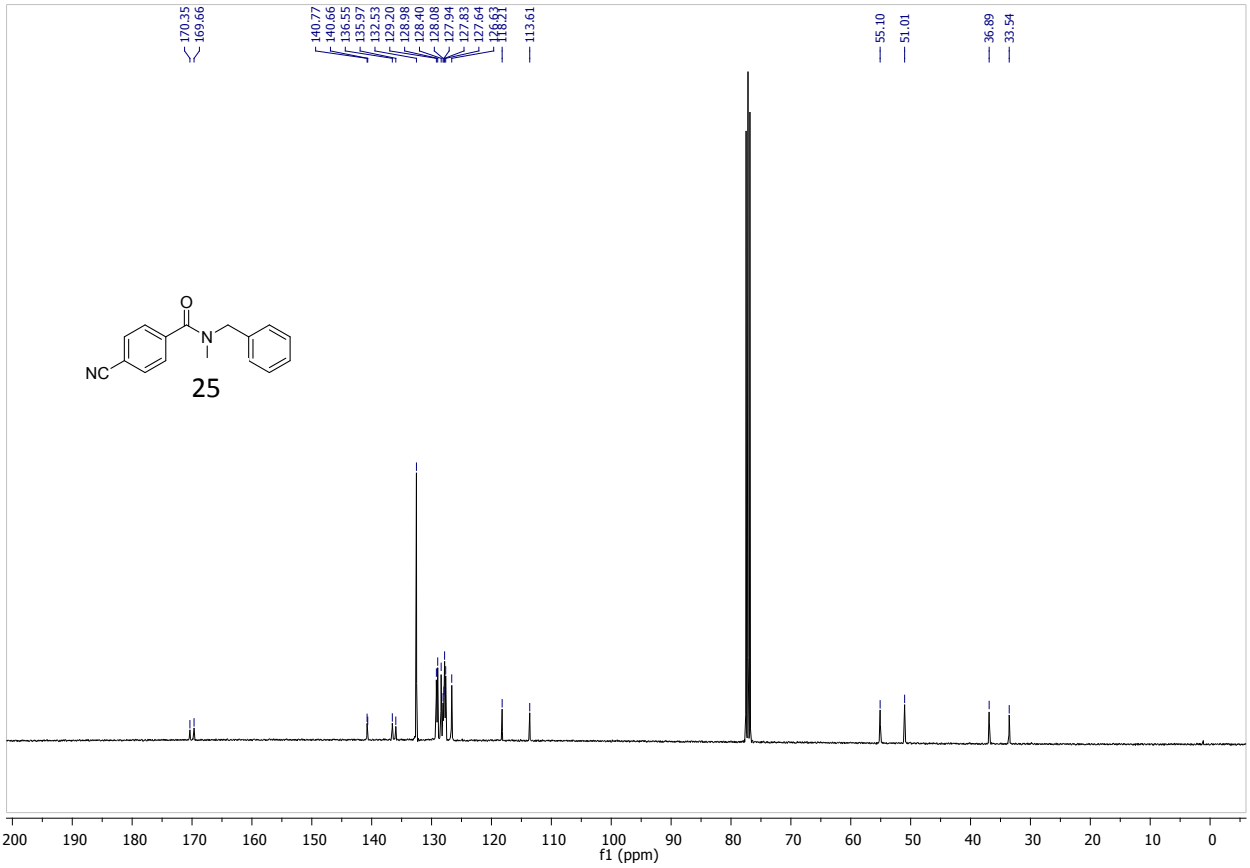
***N*-benzyl-*N*-methyl-4-(trifluoromethyl)benzamide (24)**



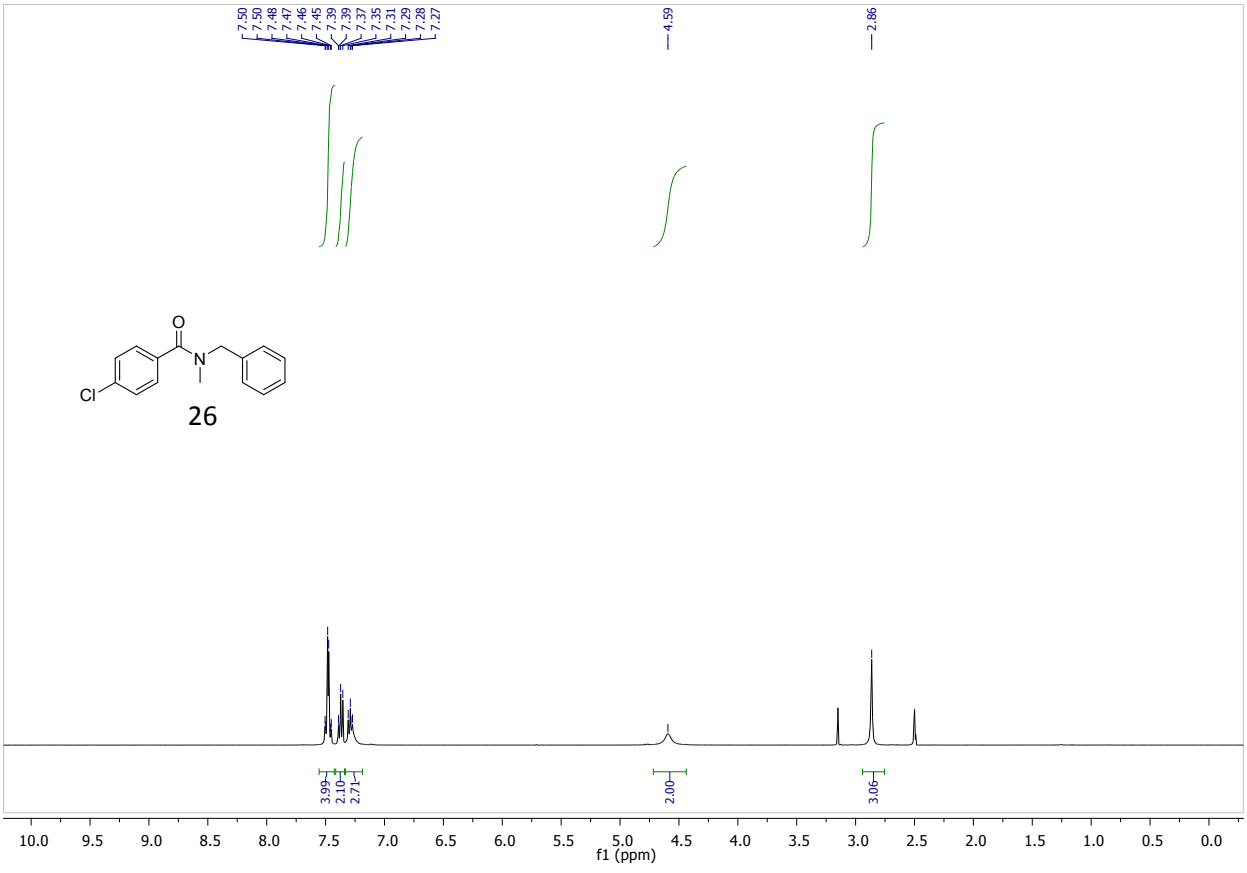


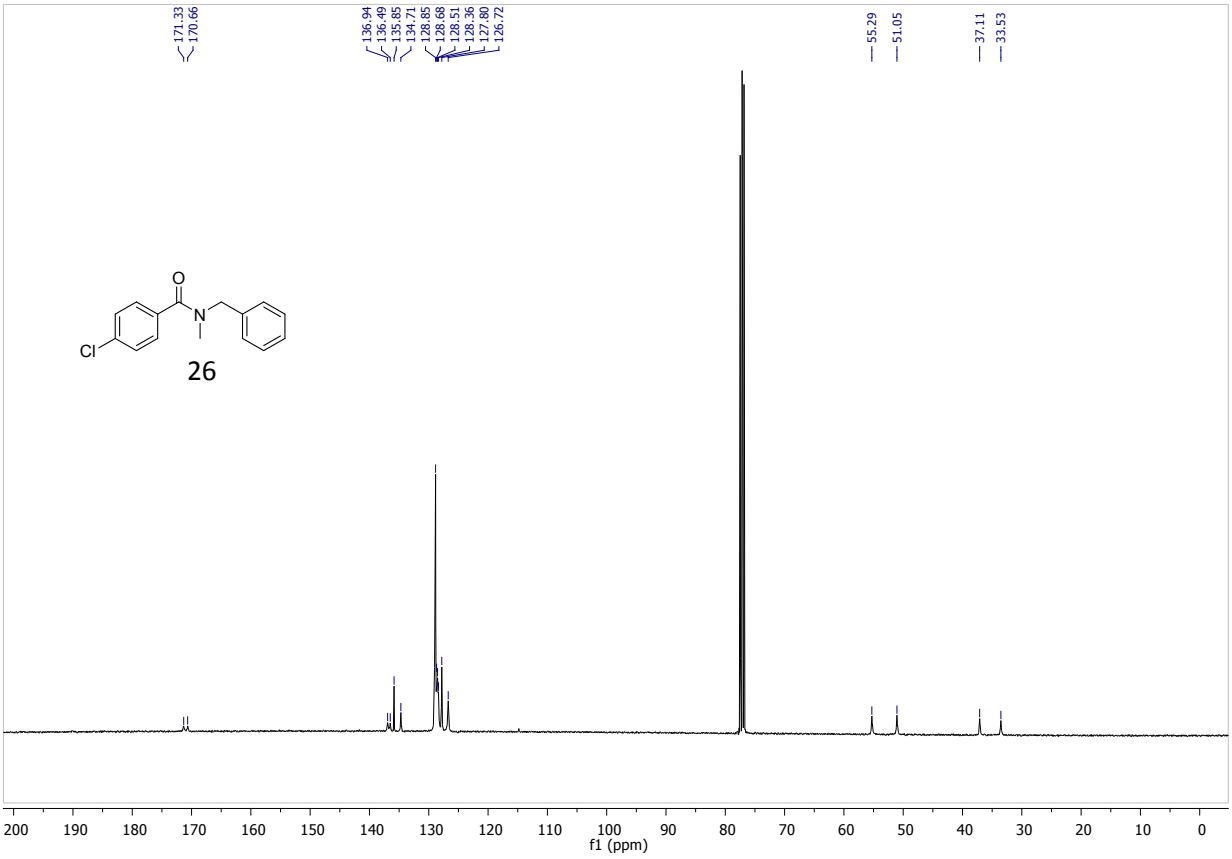
***N*-benzyl-4-cyano-*N*-methylbenzamide (25)**



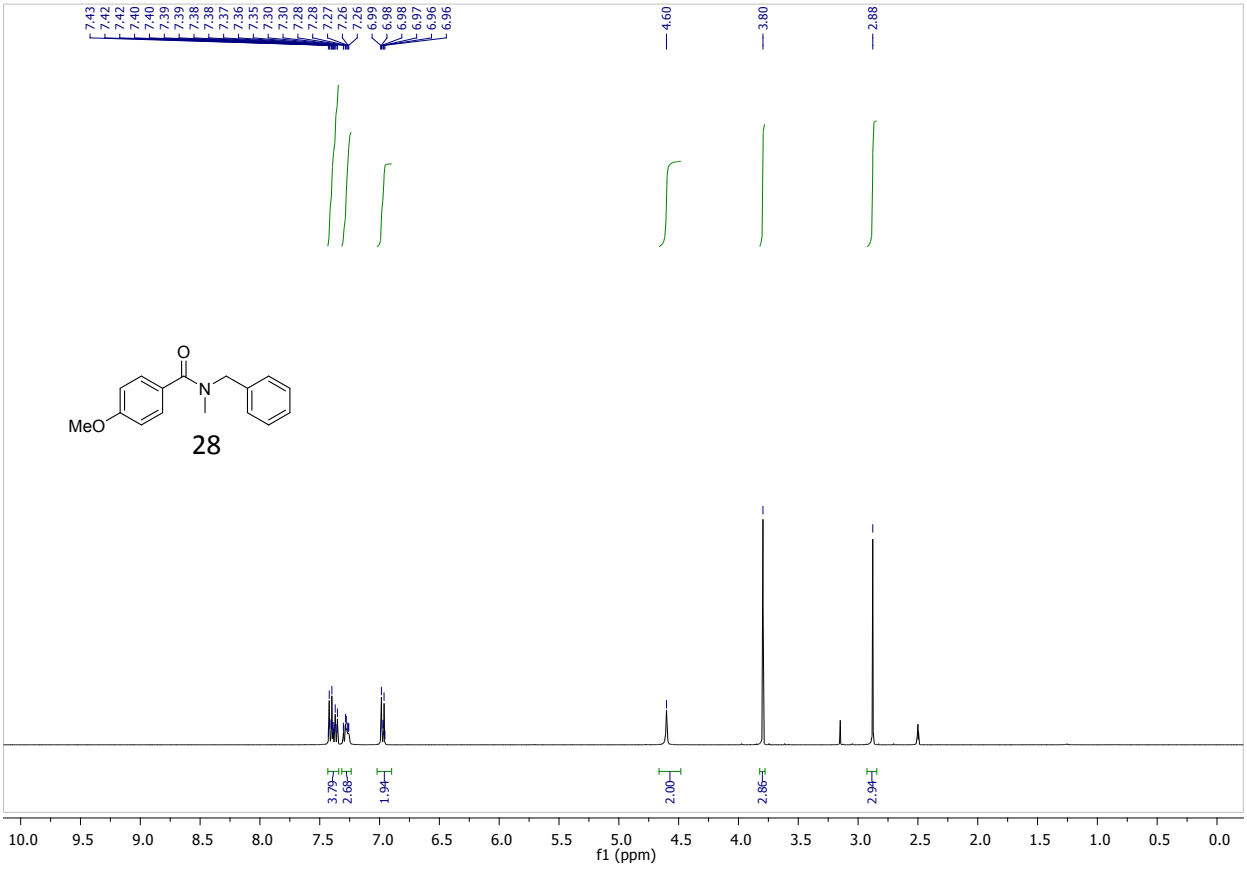


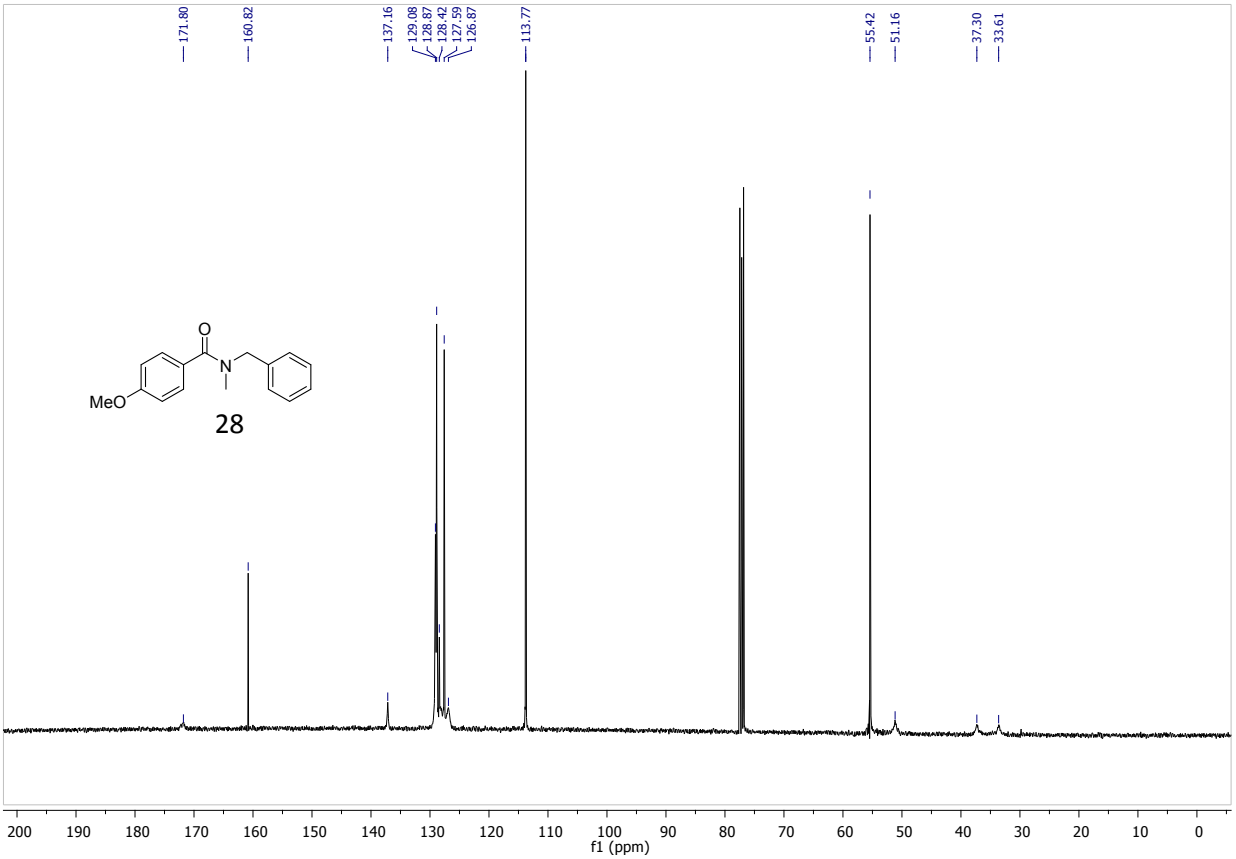
***N*-benzyl-4-chloro-*N*-methylbenzamide (26)**



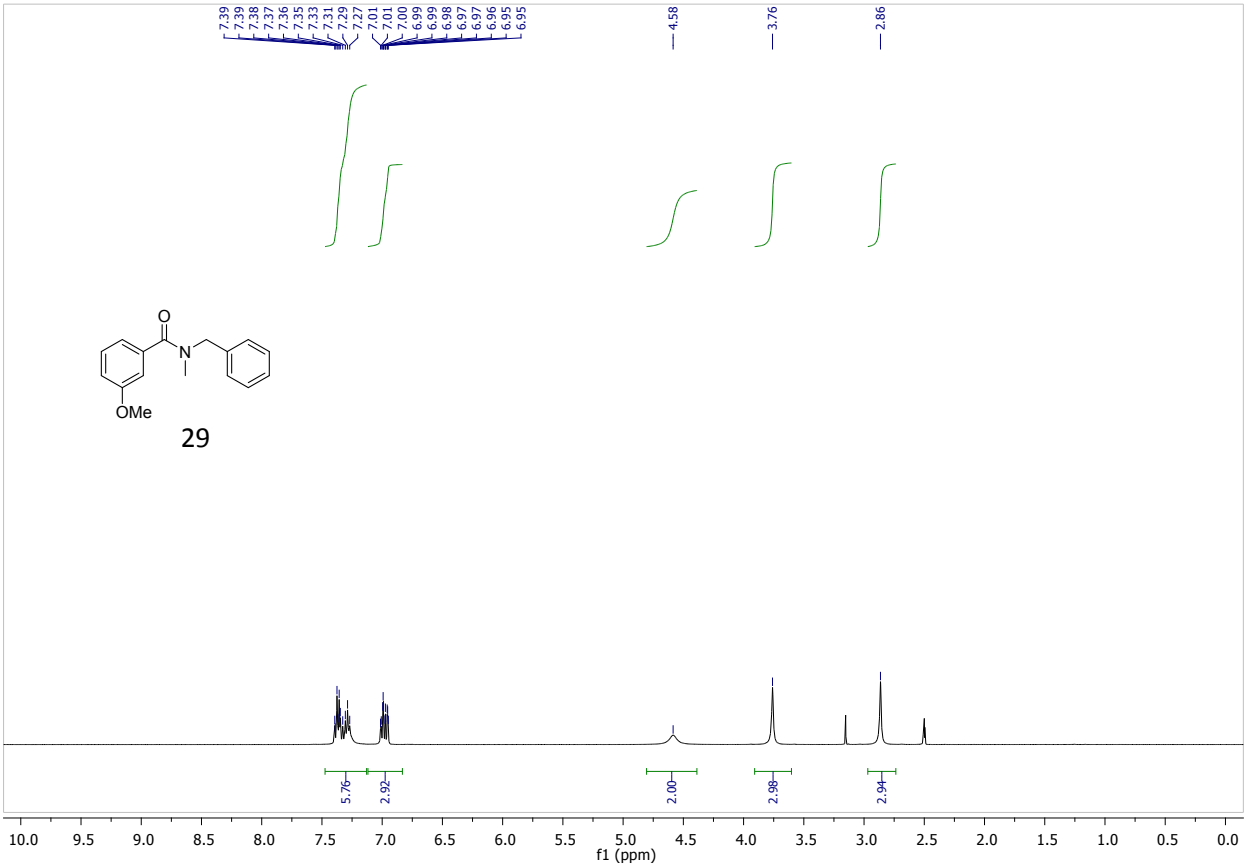


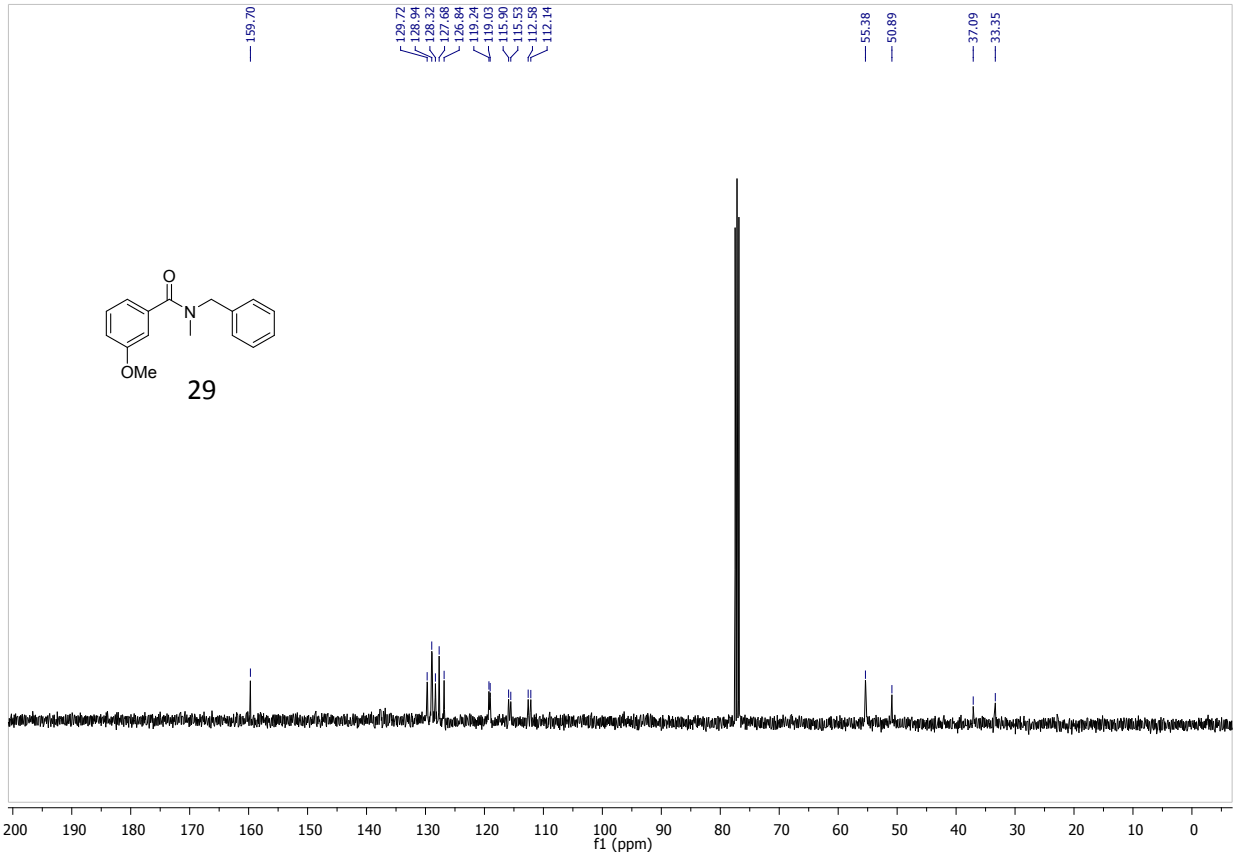
***N*-benzyl-4-methoxy-*N*-methylbenzamide (28)**



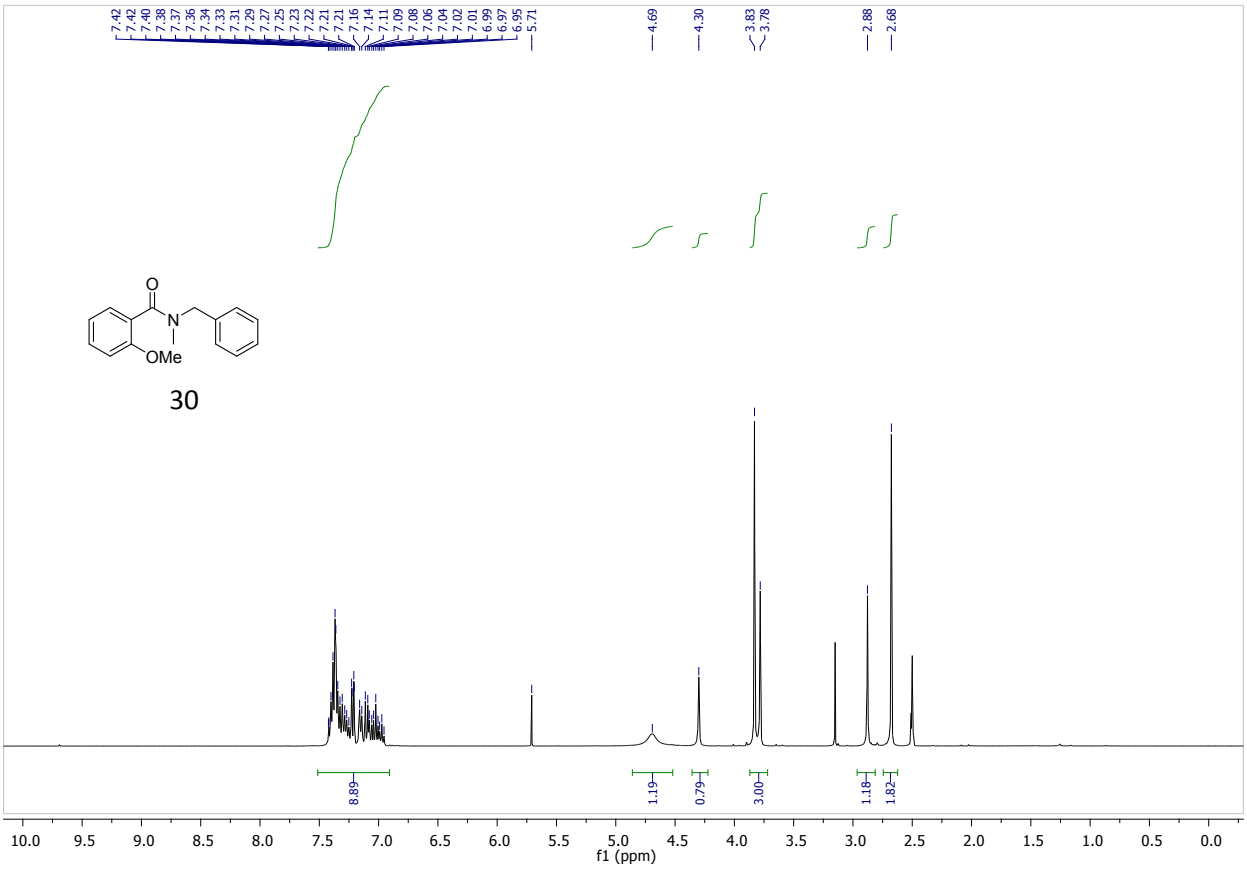


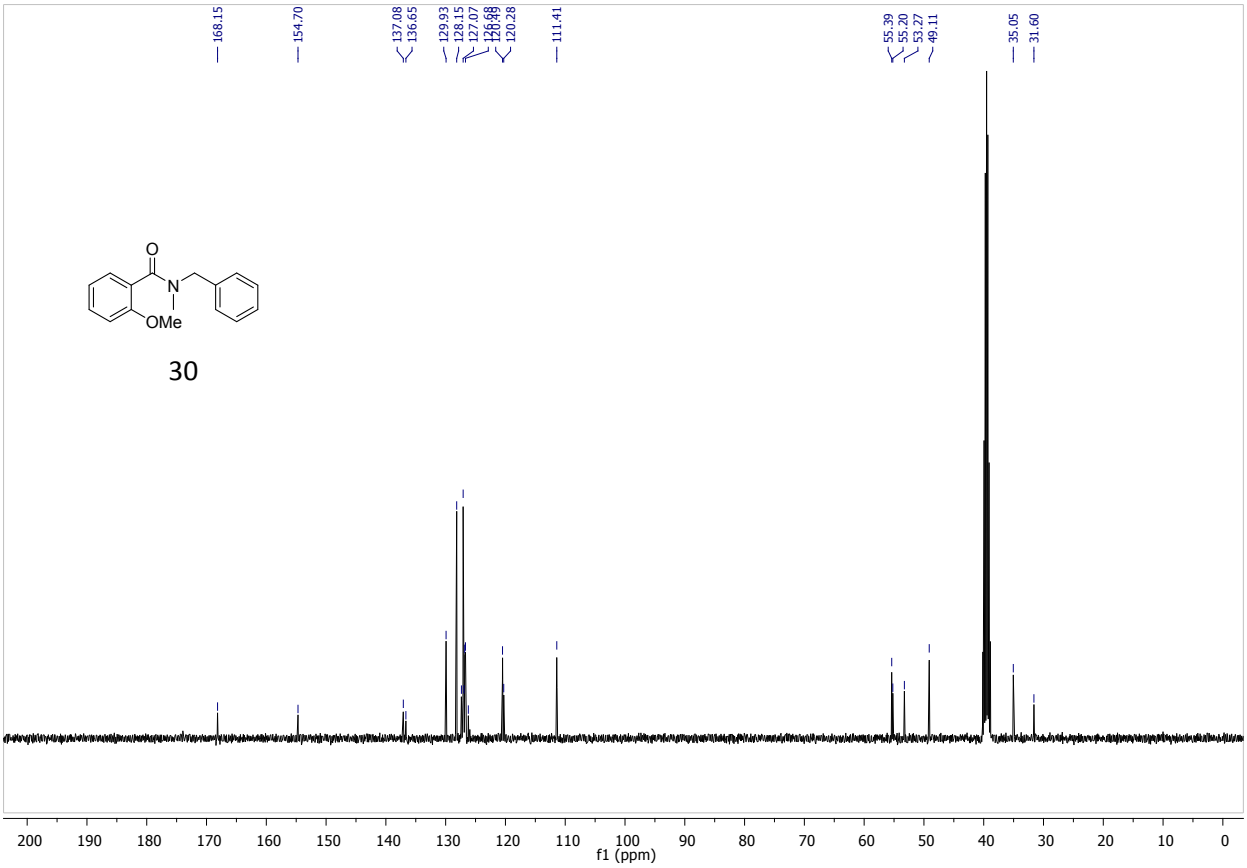
***N*-benzyl-3-methoxy-*N*-methylbenzamide (29)**



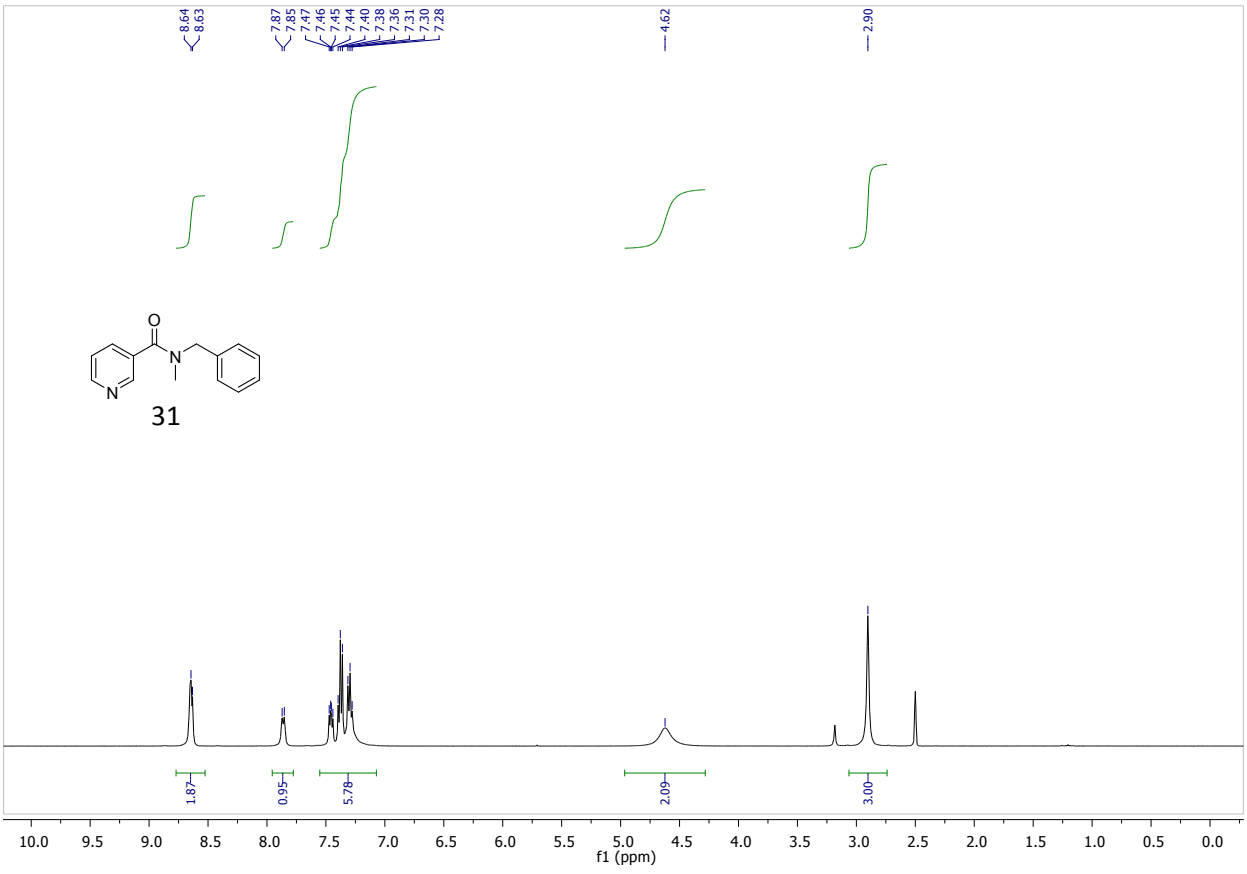


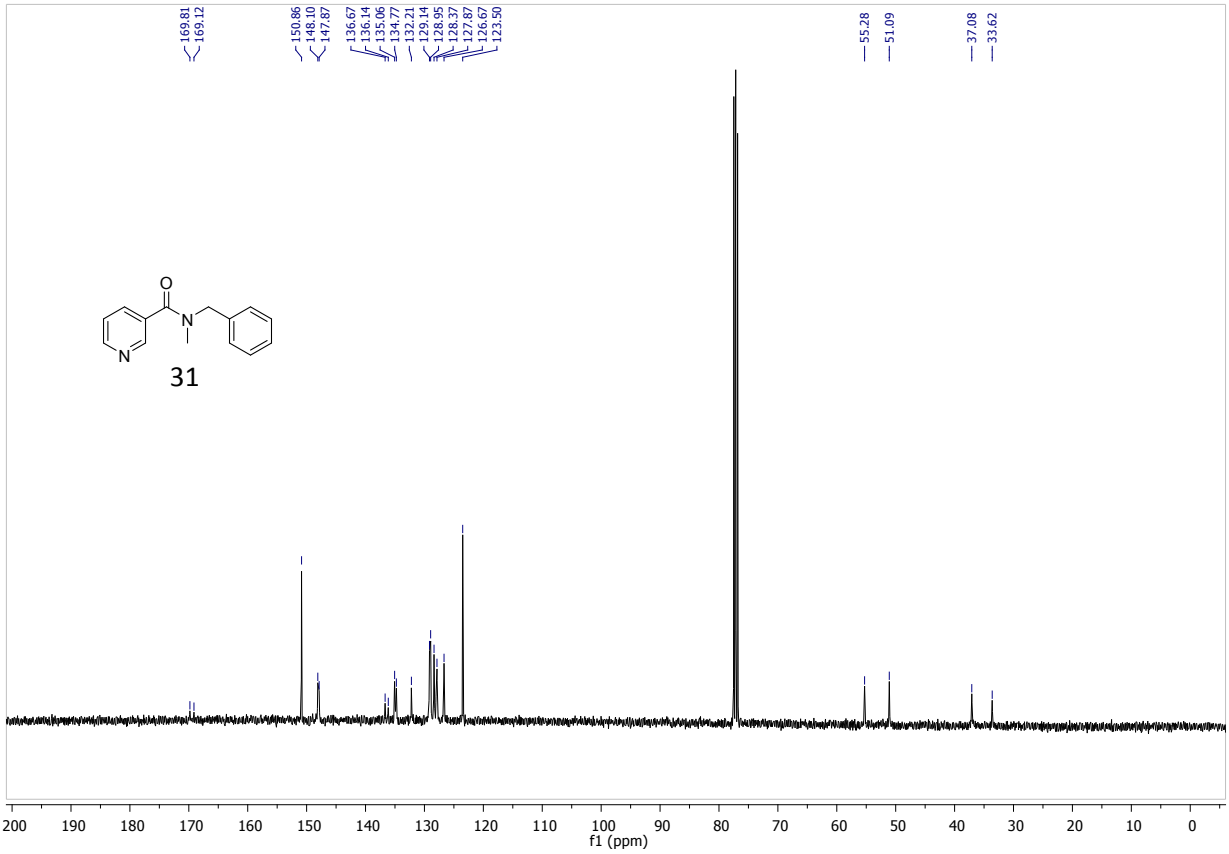
***N*-benzyl-2-methoxy-*N*-methylbenzamide (30)**



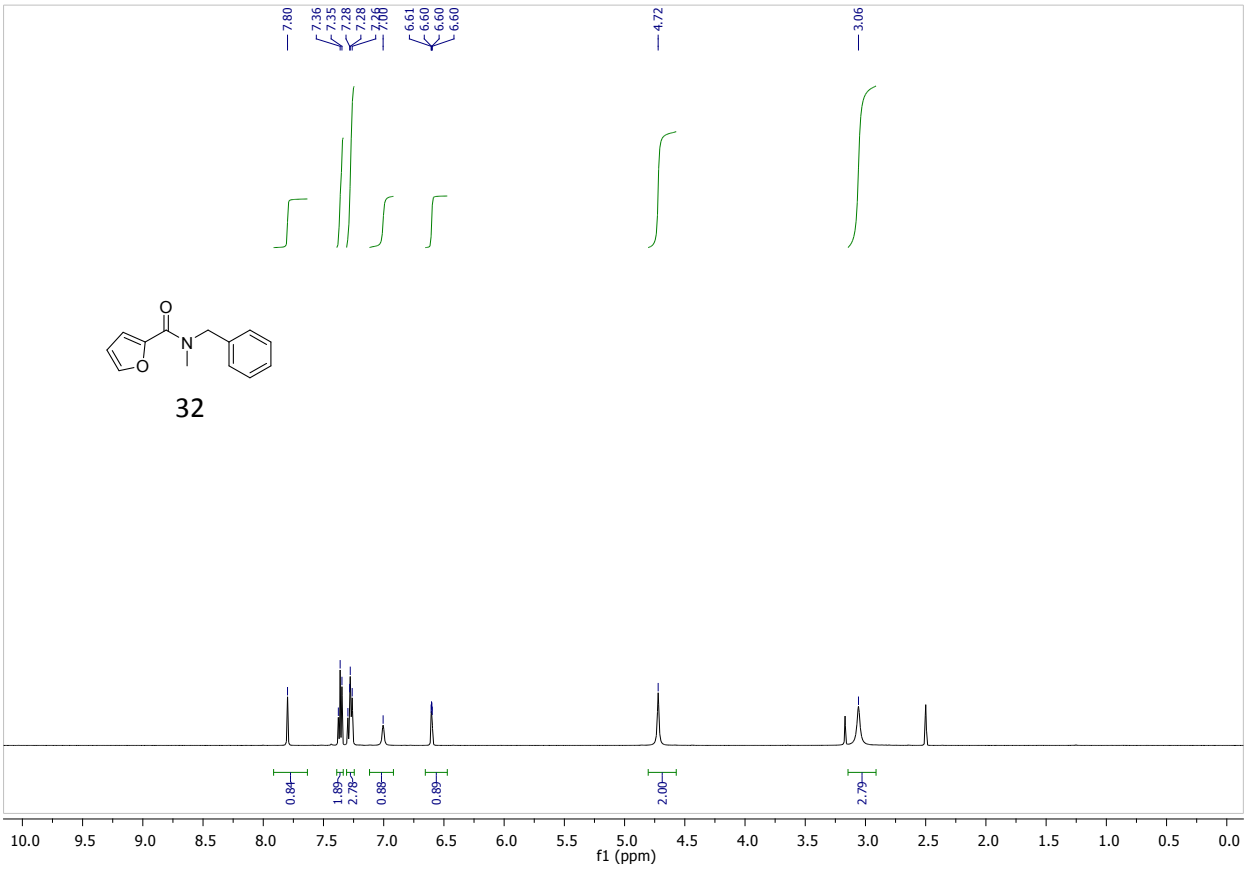


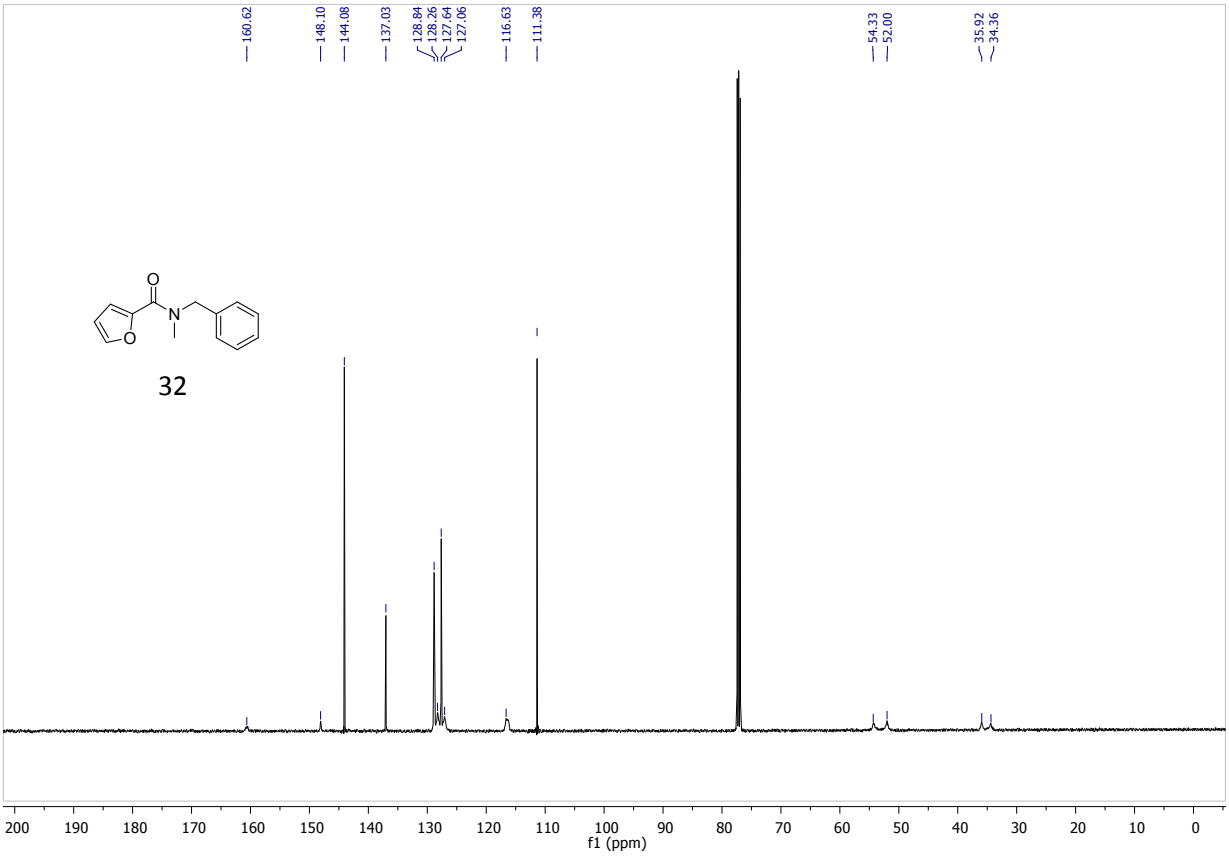
***N*-benzyl-*N*-methylnicotinamide (31)**





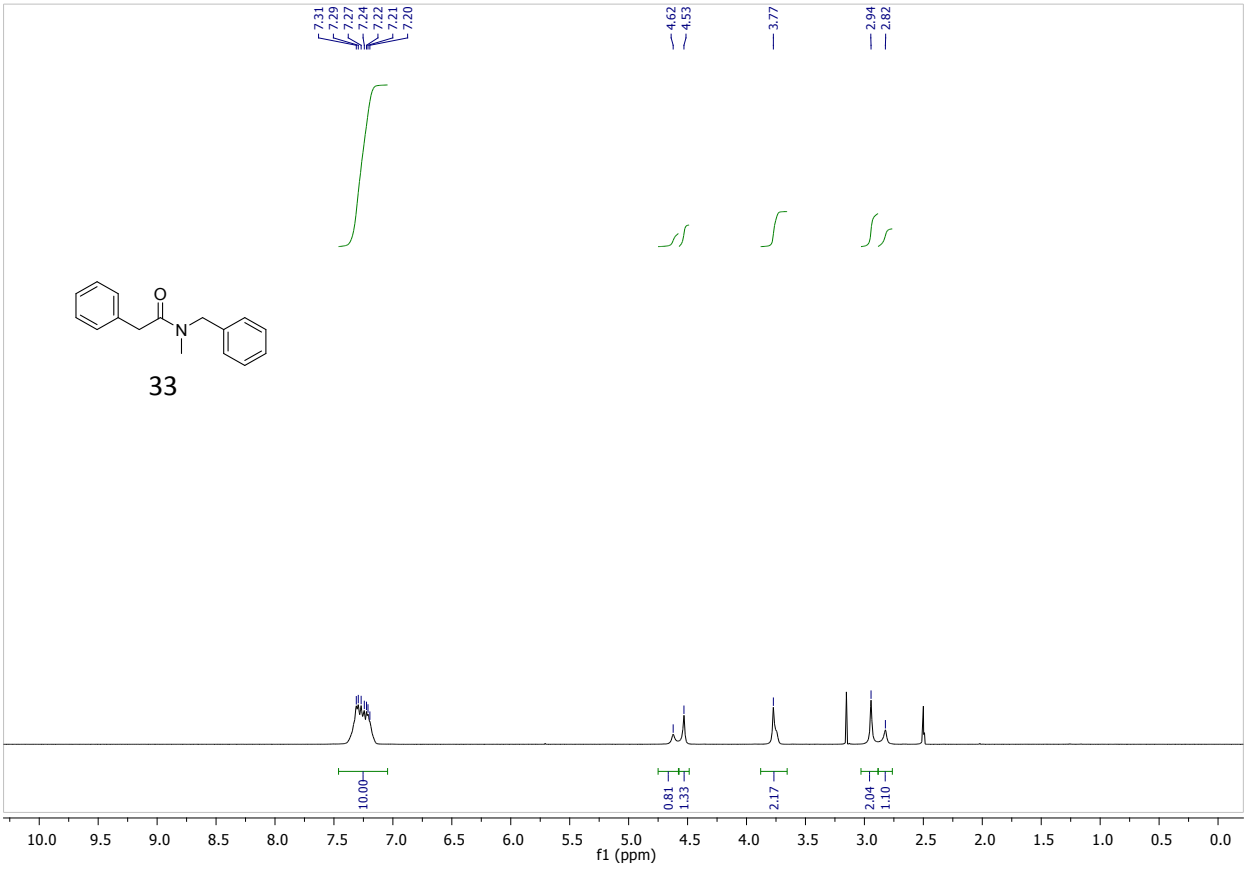
***N*-benzyl-*N*-methylfuran-2-carboxamide (32)**



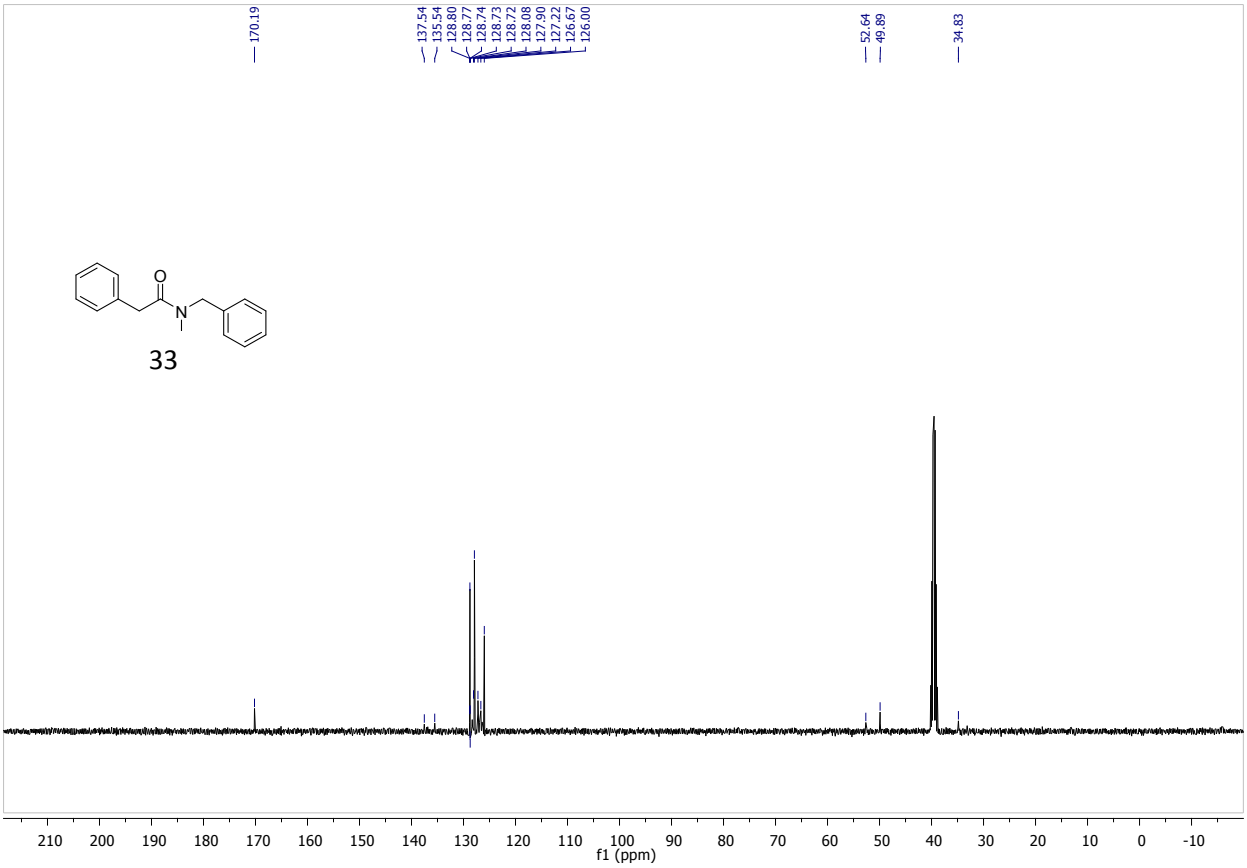


32

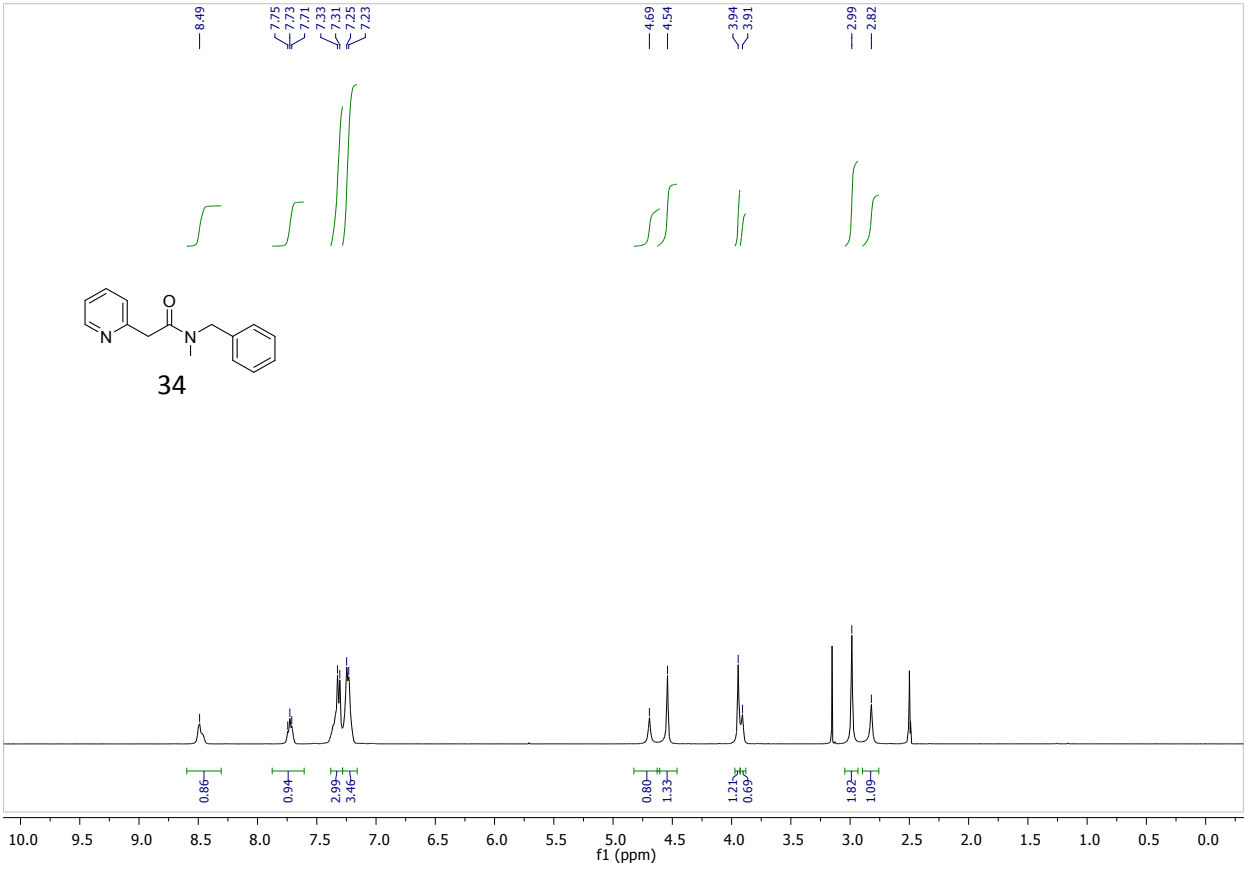
***N*-benzyl-*N*-methyl-2-phenylacetamide (33)**

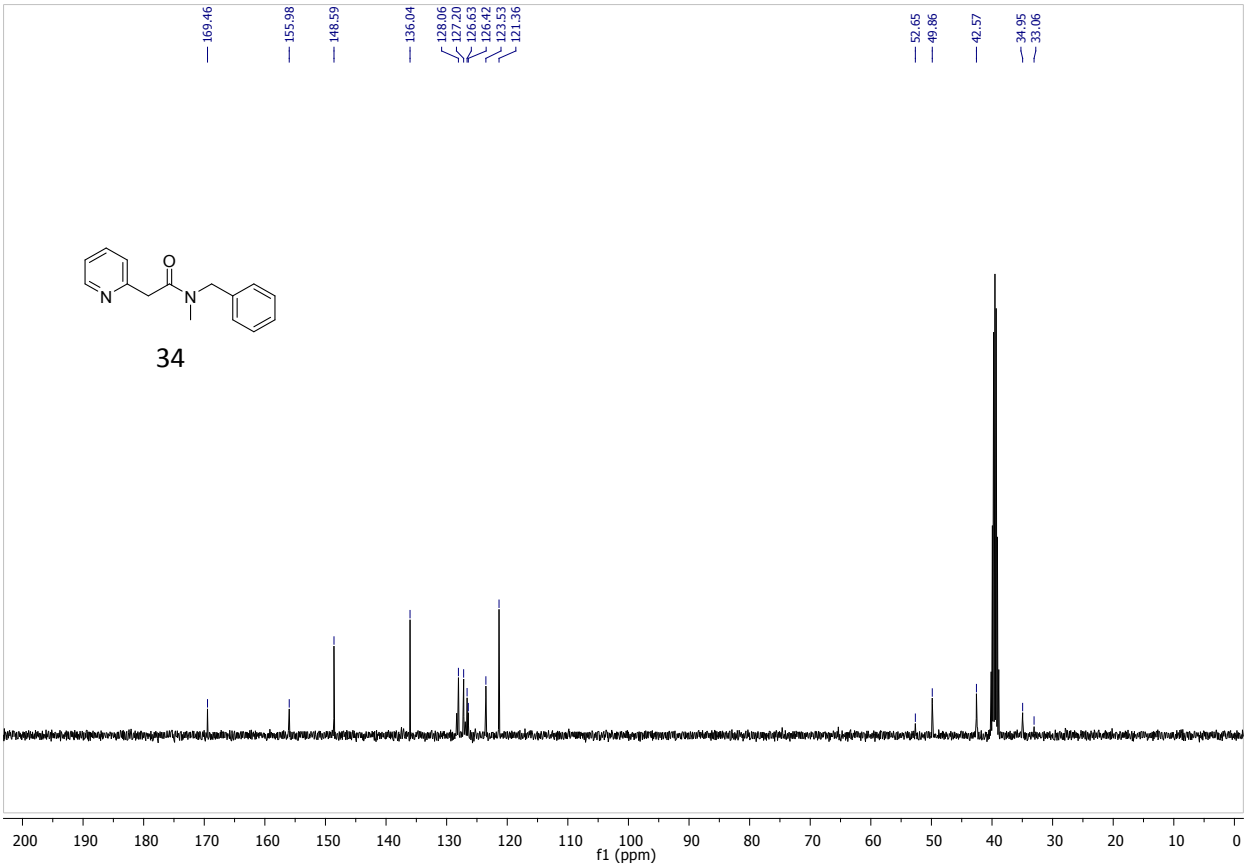


33



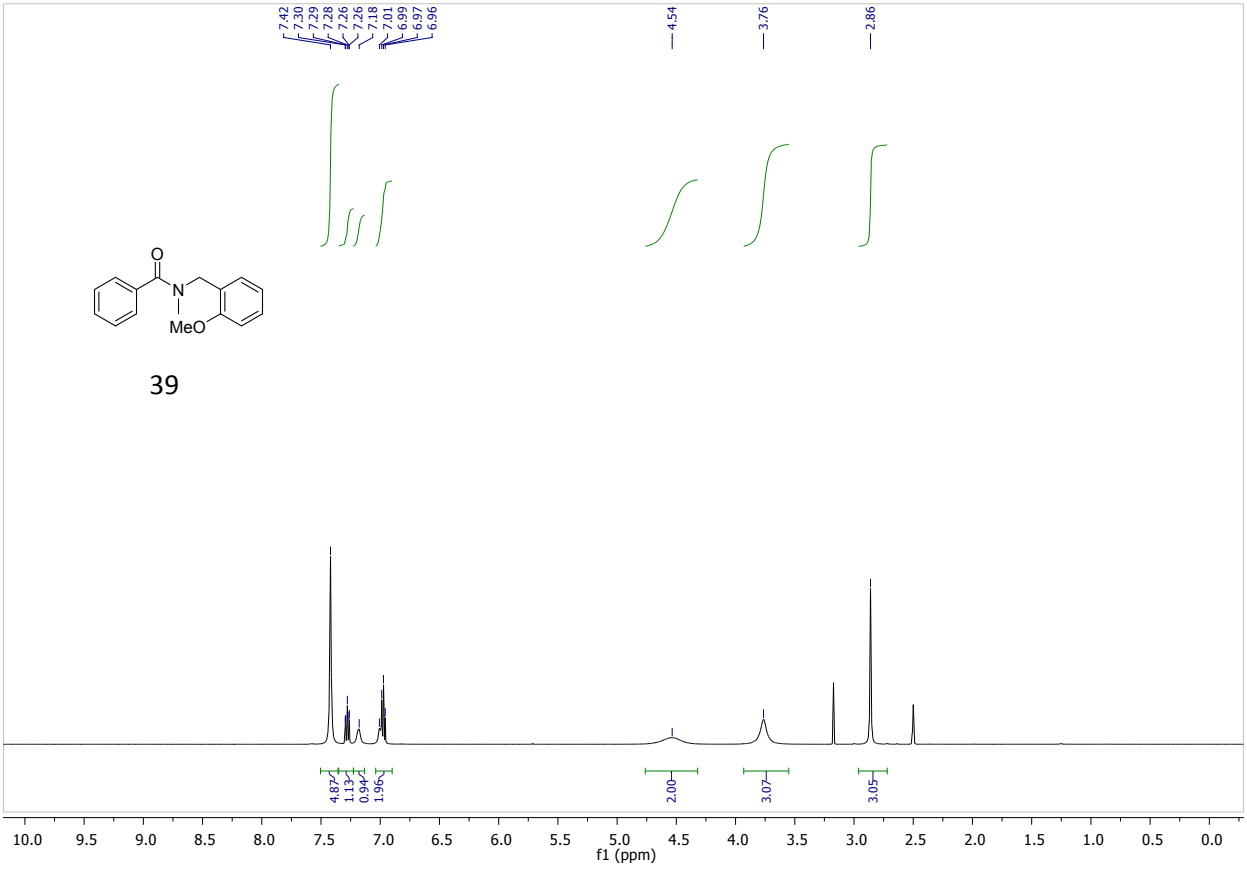
***N*-benzyl-*N*-methyl-2-(pyridin-2-yl)acetamide (34)**



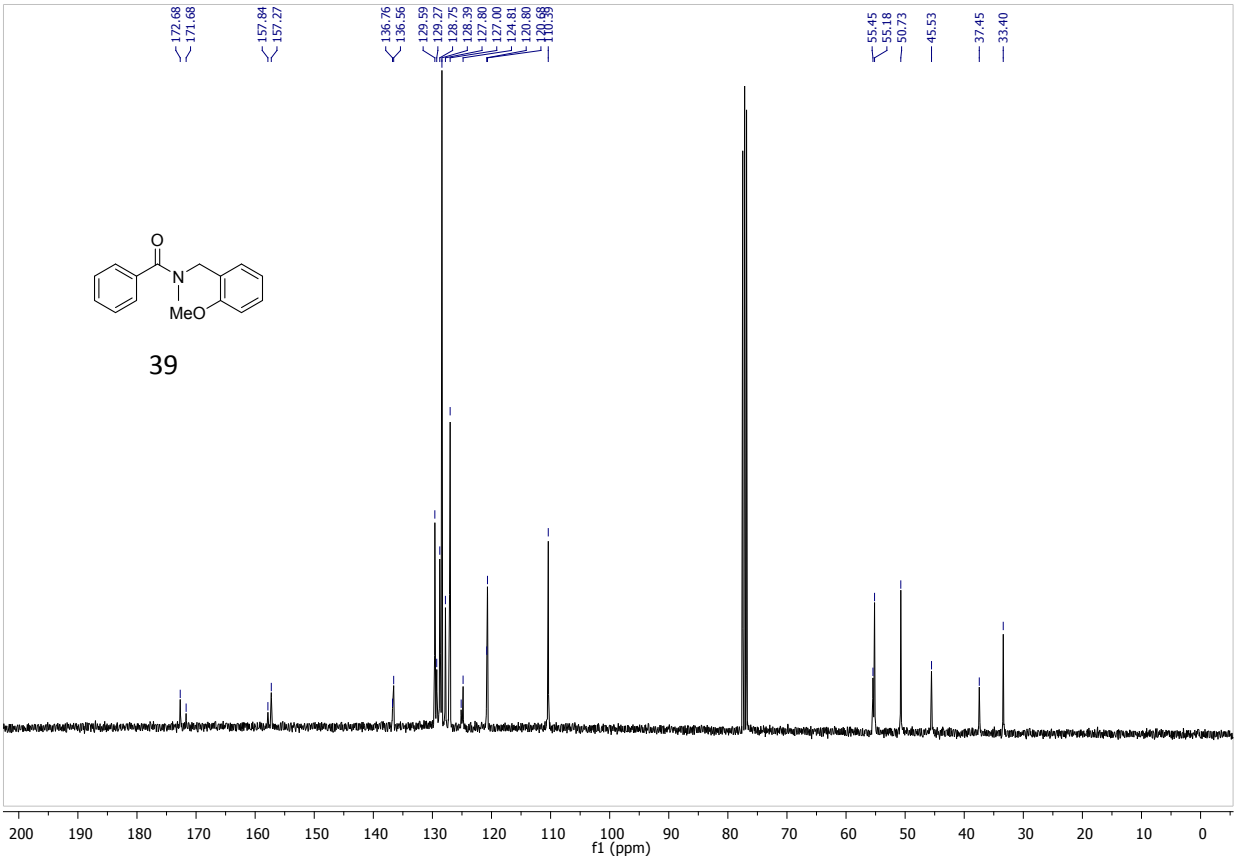


34

_N_-(2-methoxybenzyl)-_N_-methylbenzamide (39)

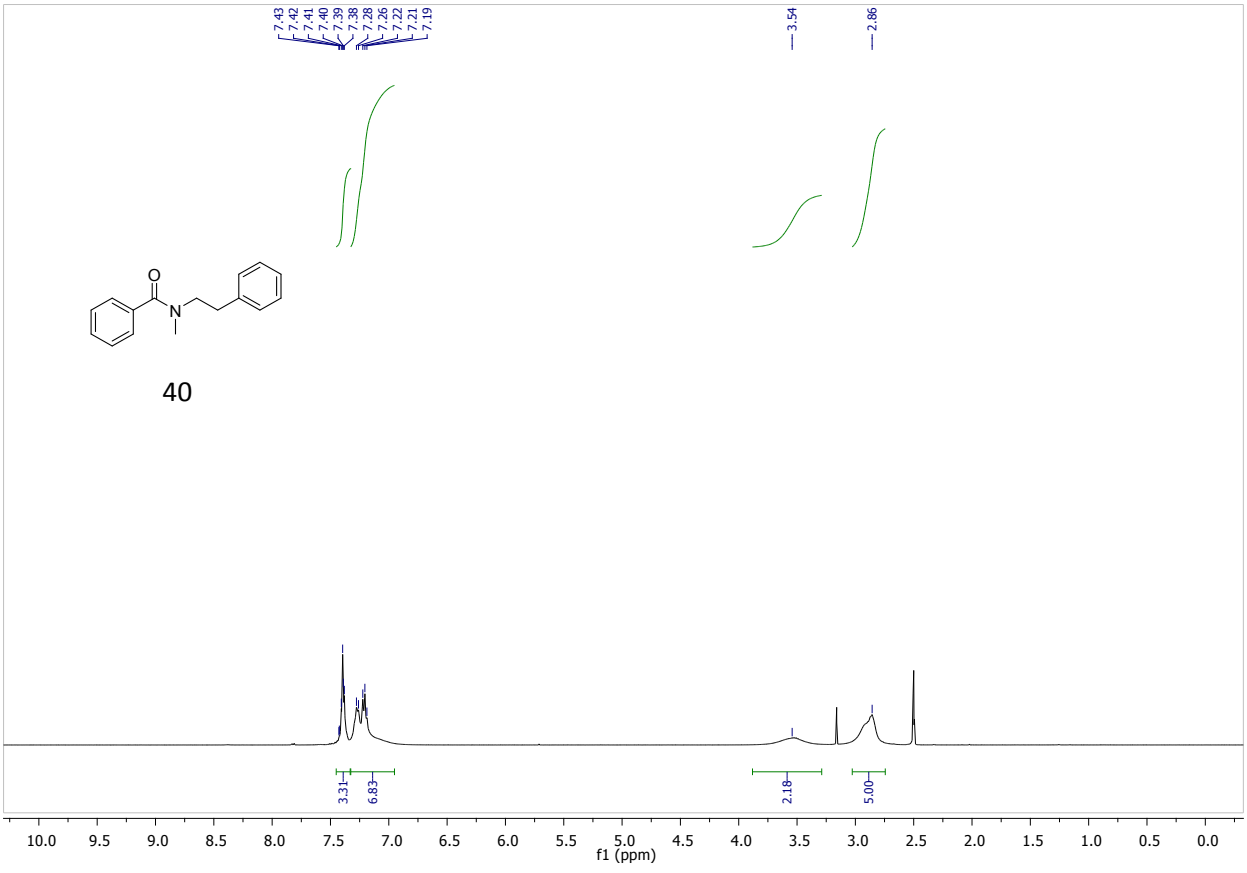


39

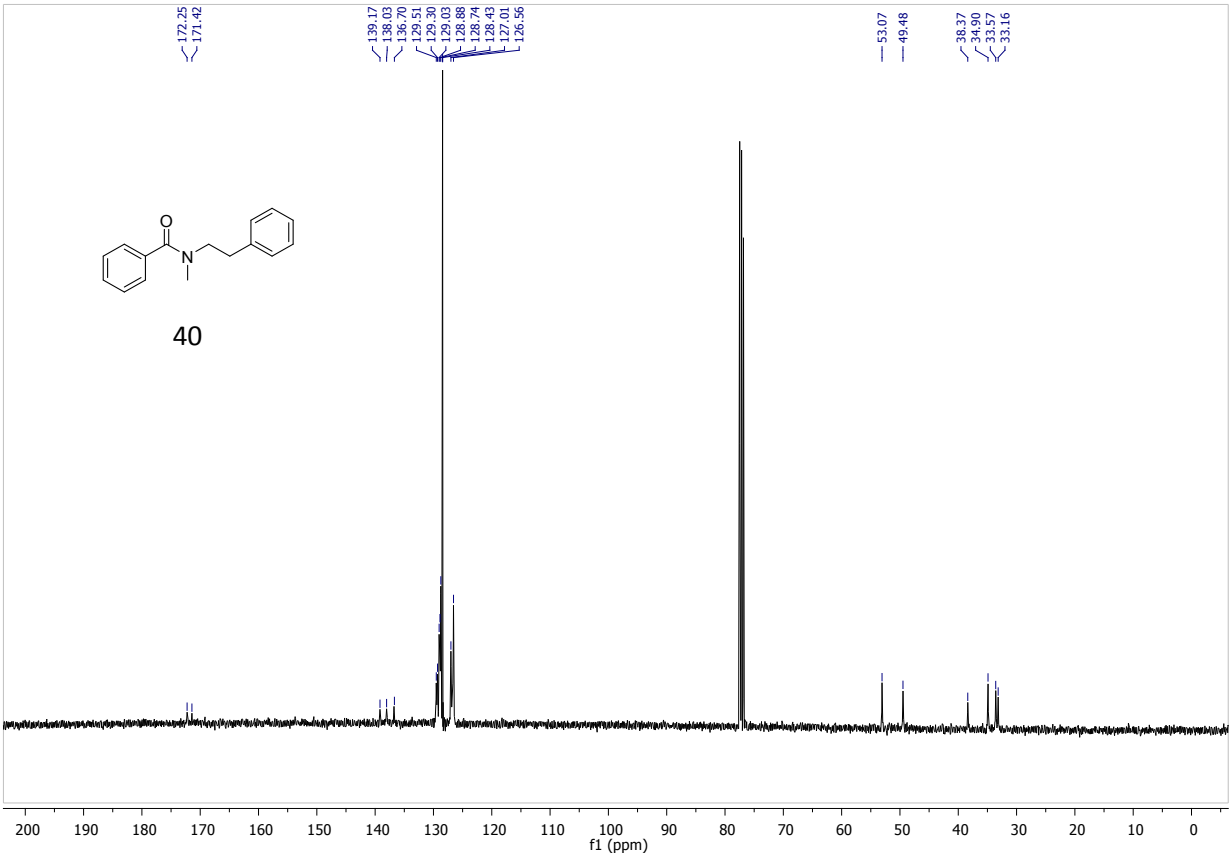


39

_N_-methyl-_N_-phenethylbenzamide (40)

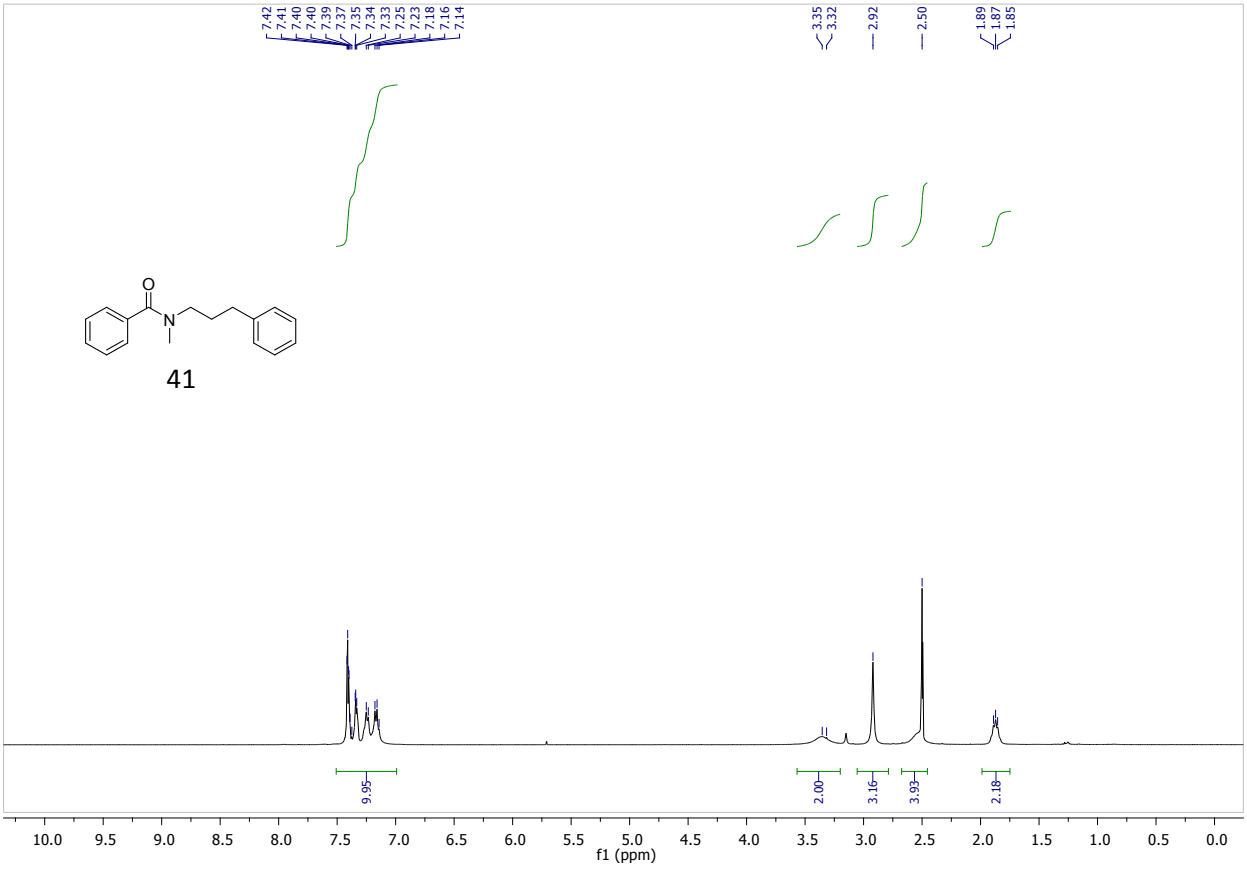


40

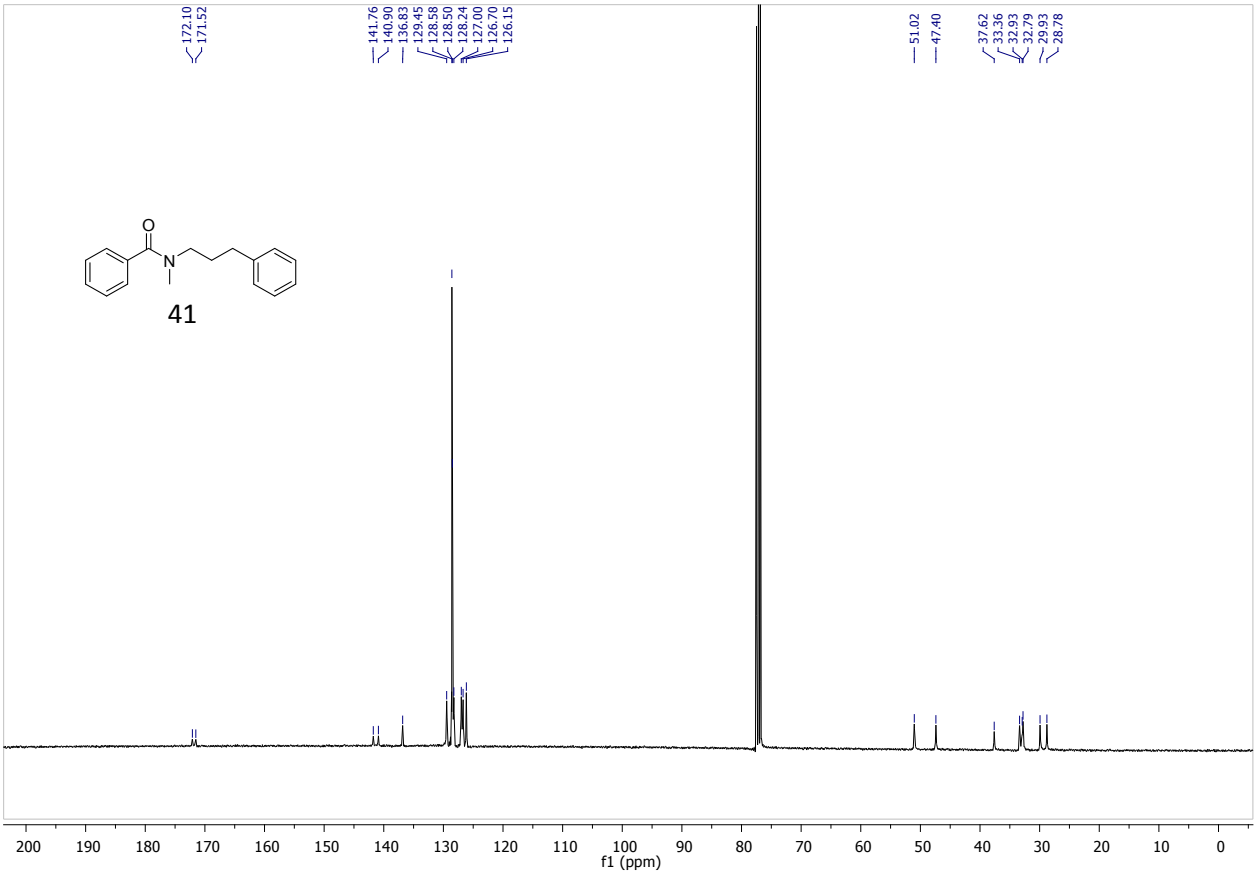


40

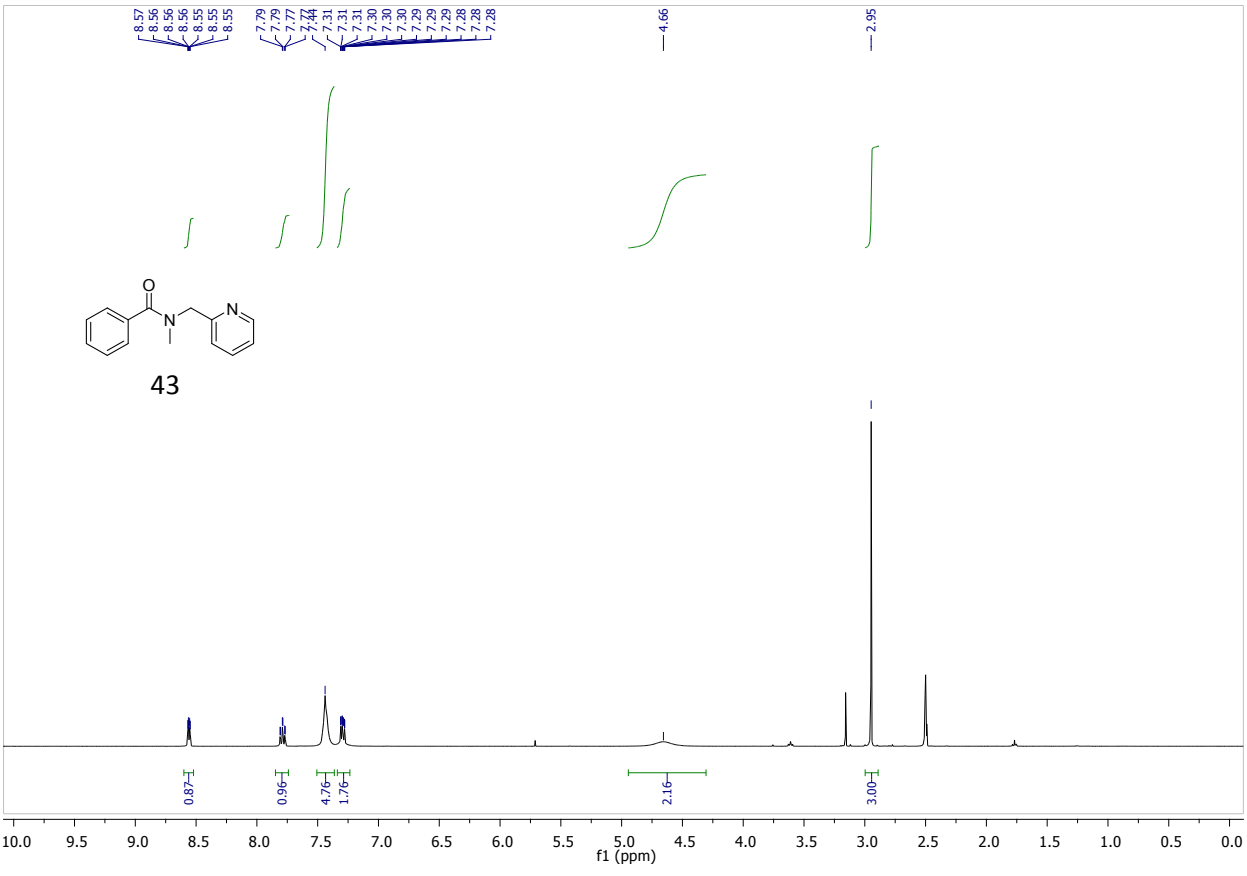
***N*-methyl-*N*-(3-phenylpropyl)benzamide (41)**

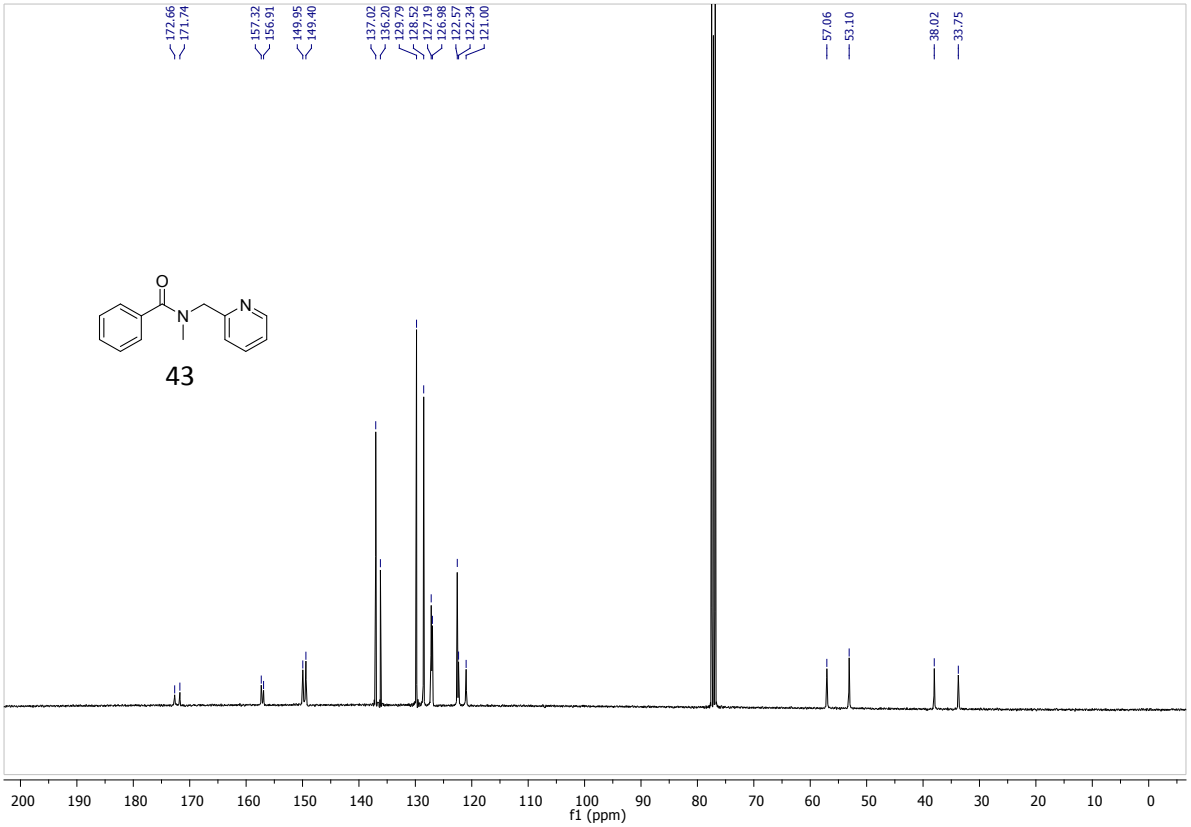


41

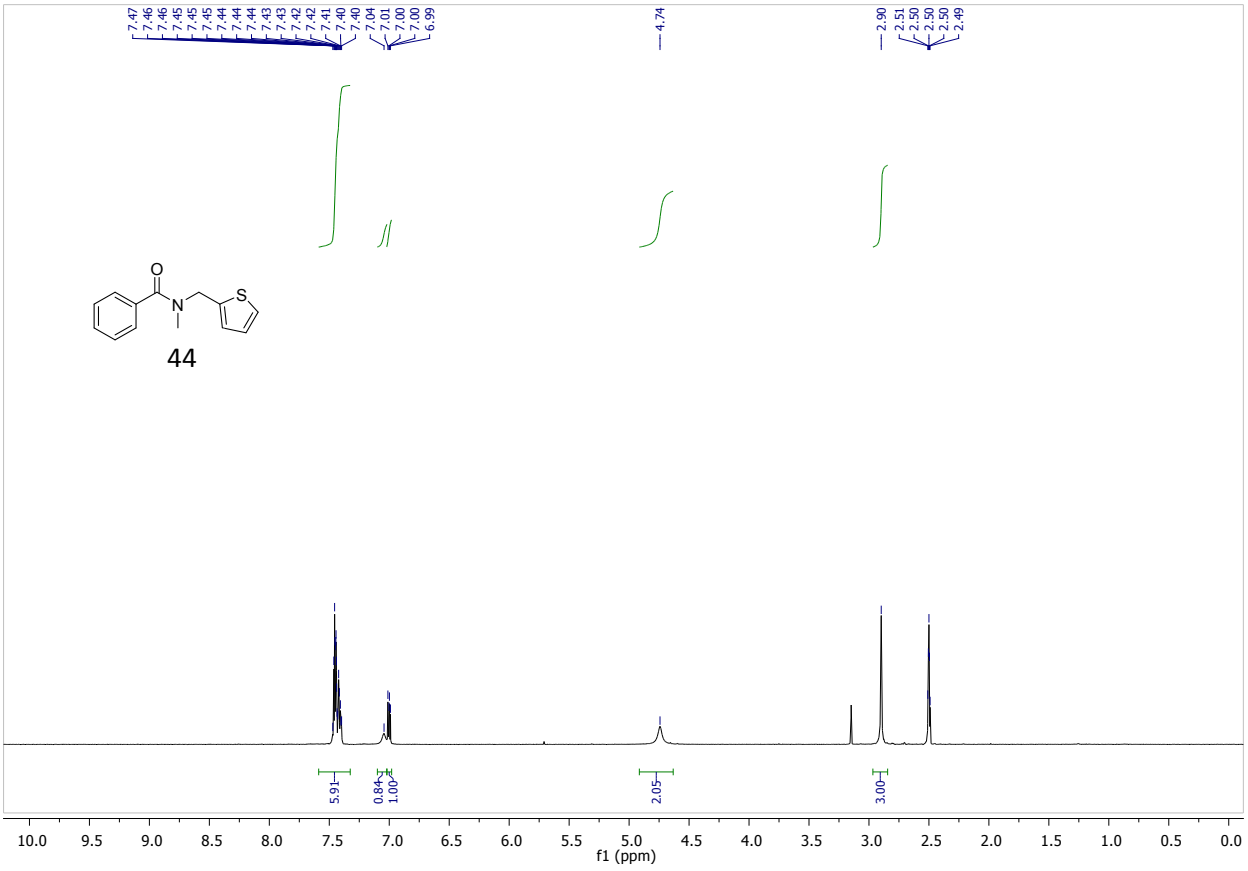


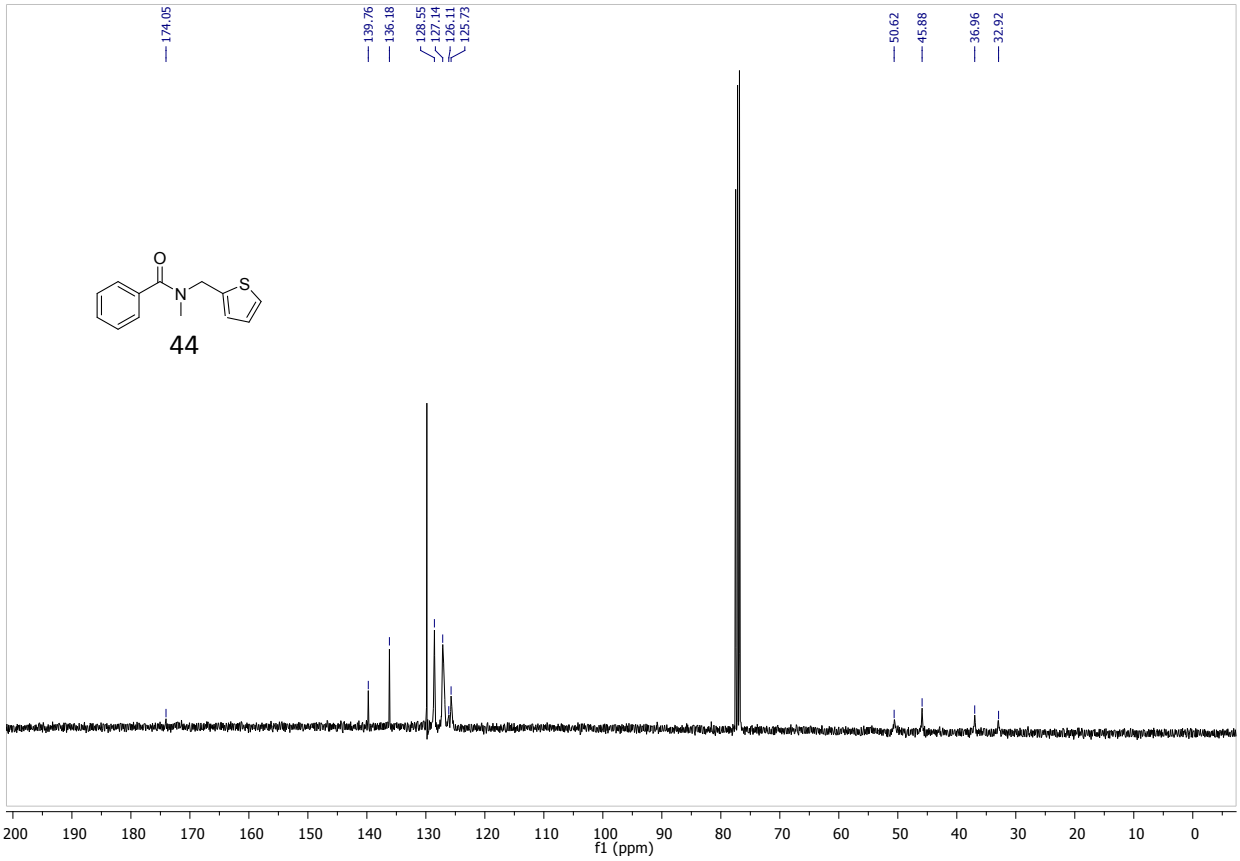
***N*-methyl-*N*-(pyridin-2-ylmethyl)benzamide (43)**



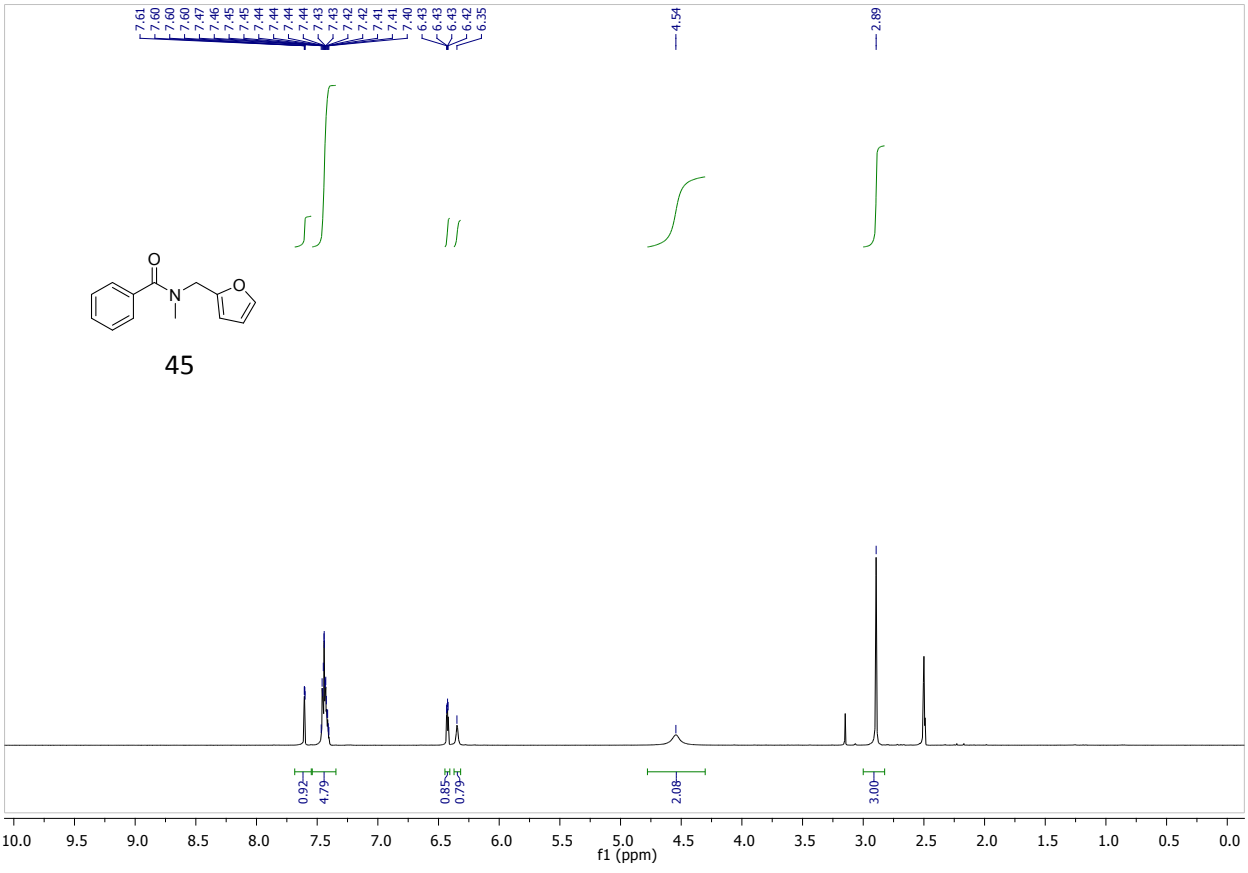


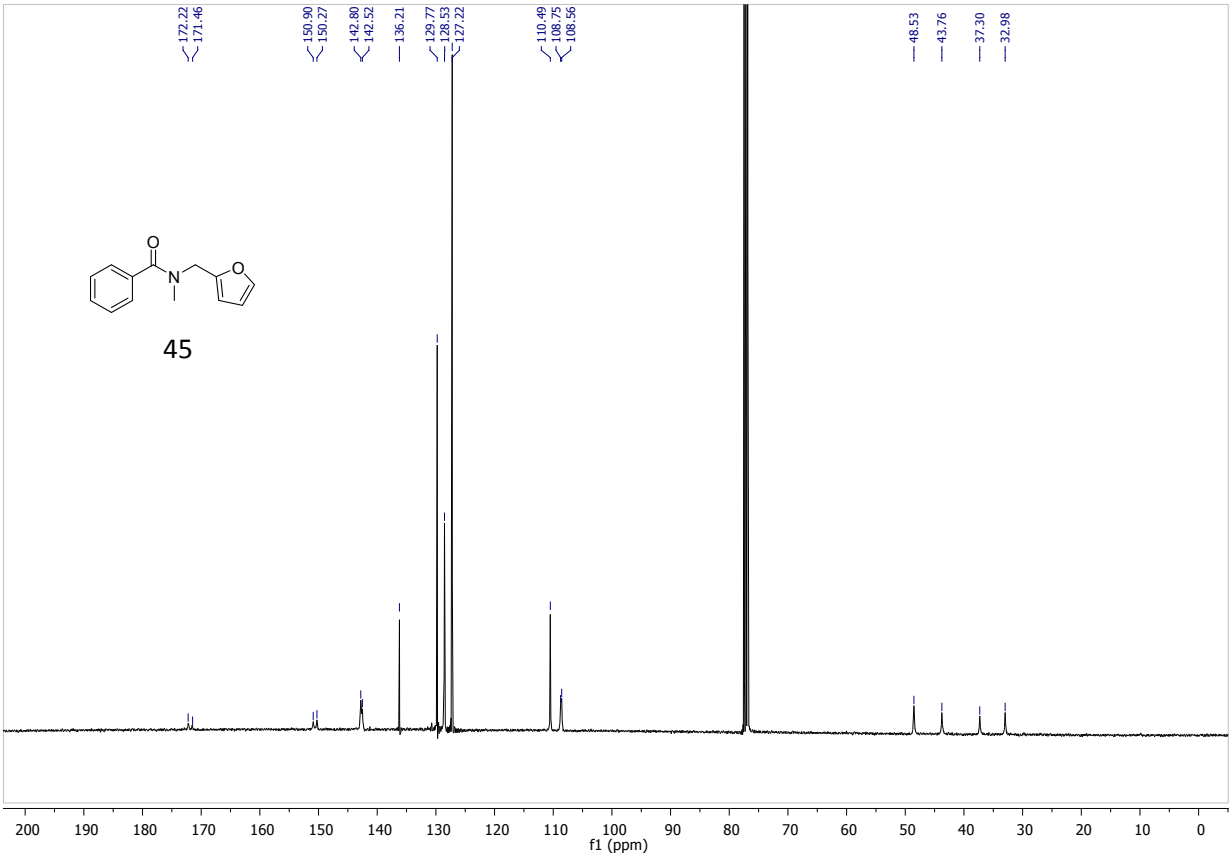
***N*-methyl-*N*-(thiophen-2-ylmethyl)benzamide (44)**



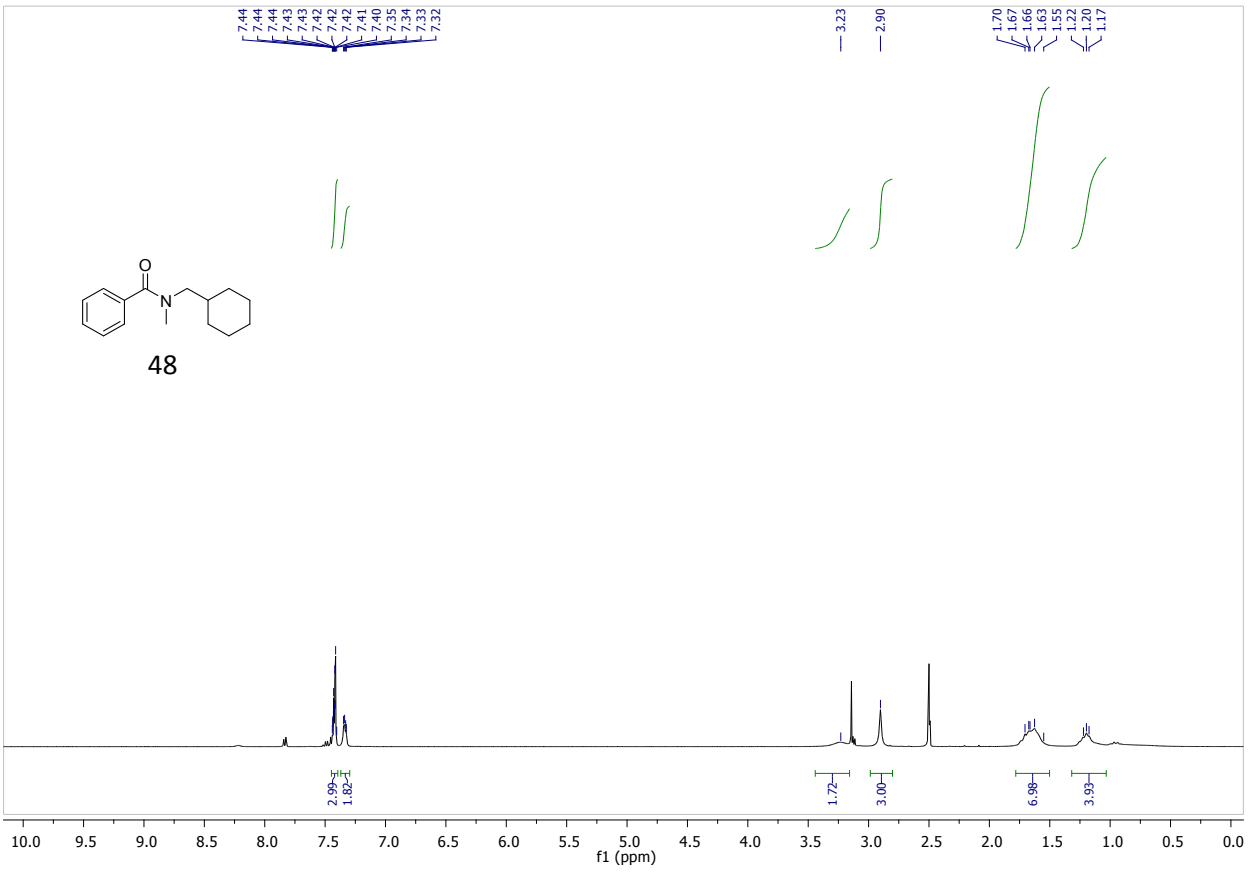


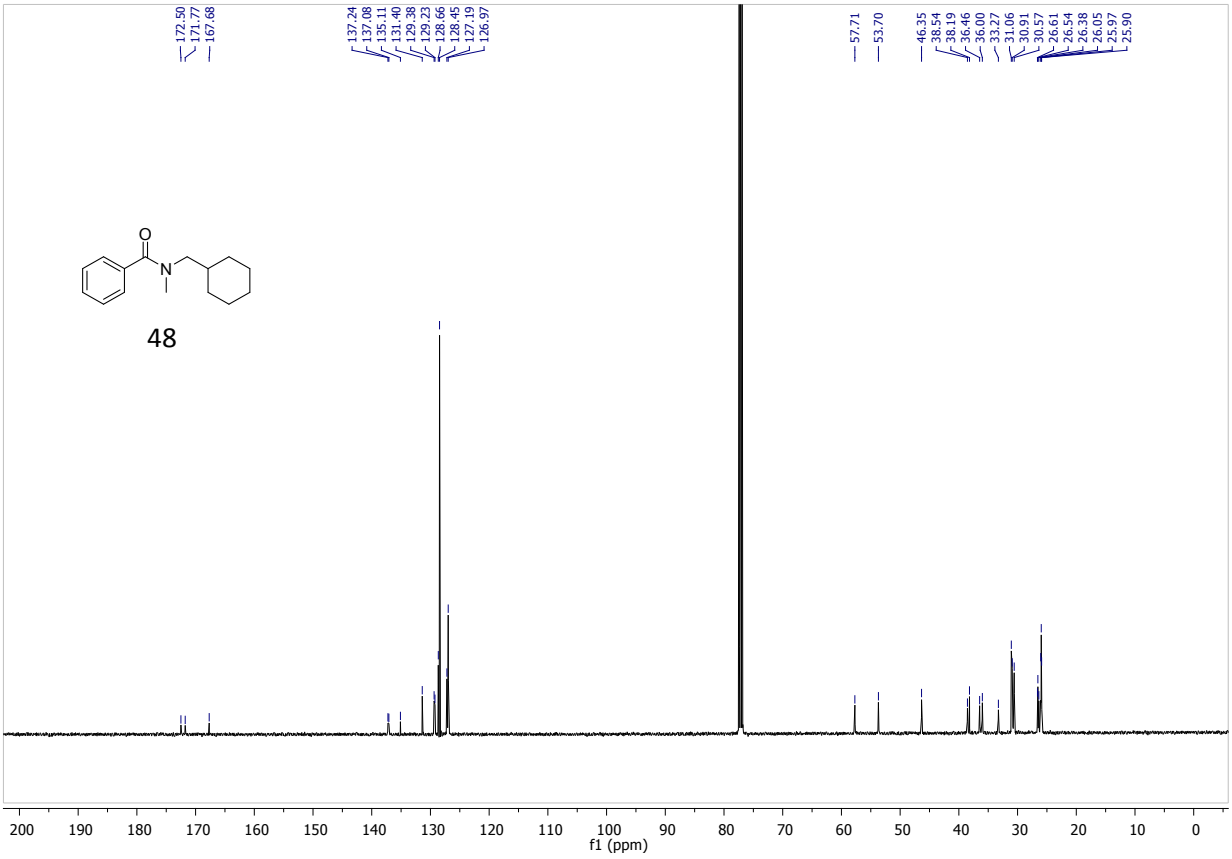
***N*-(furan-2-ylmethyl)-*N*-methylbenzamide (45)**



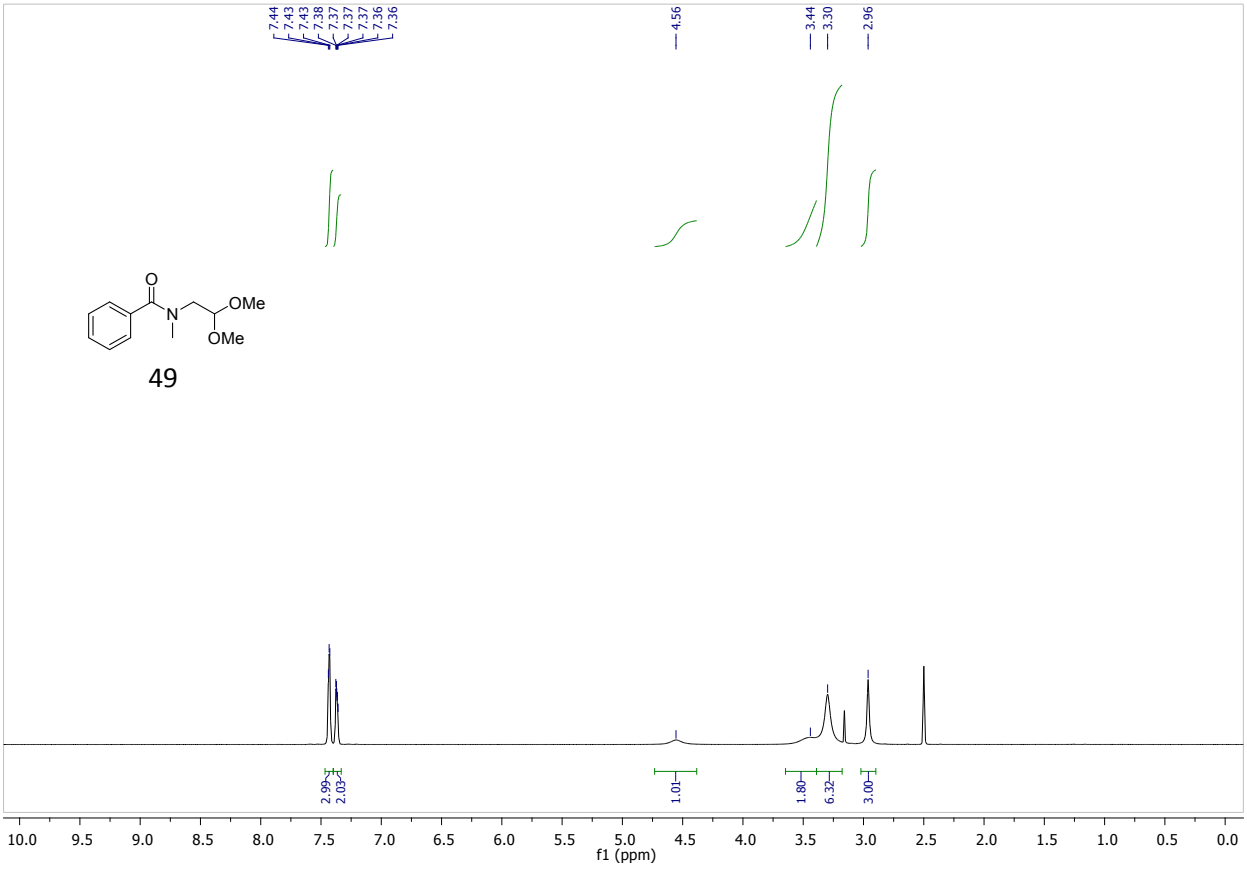


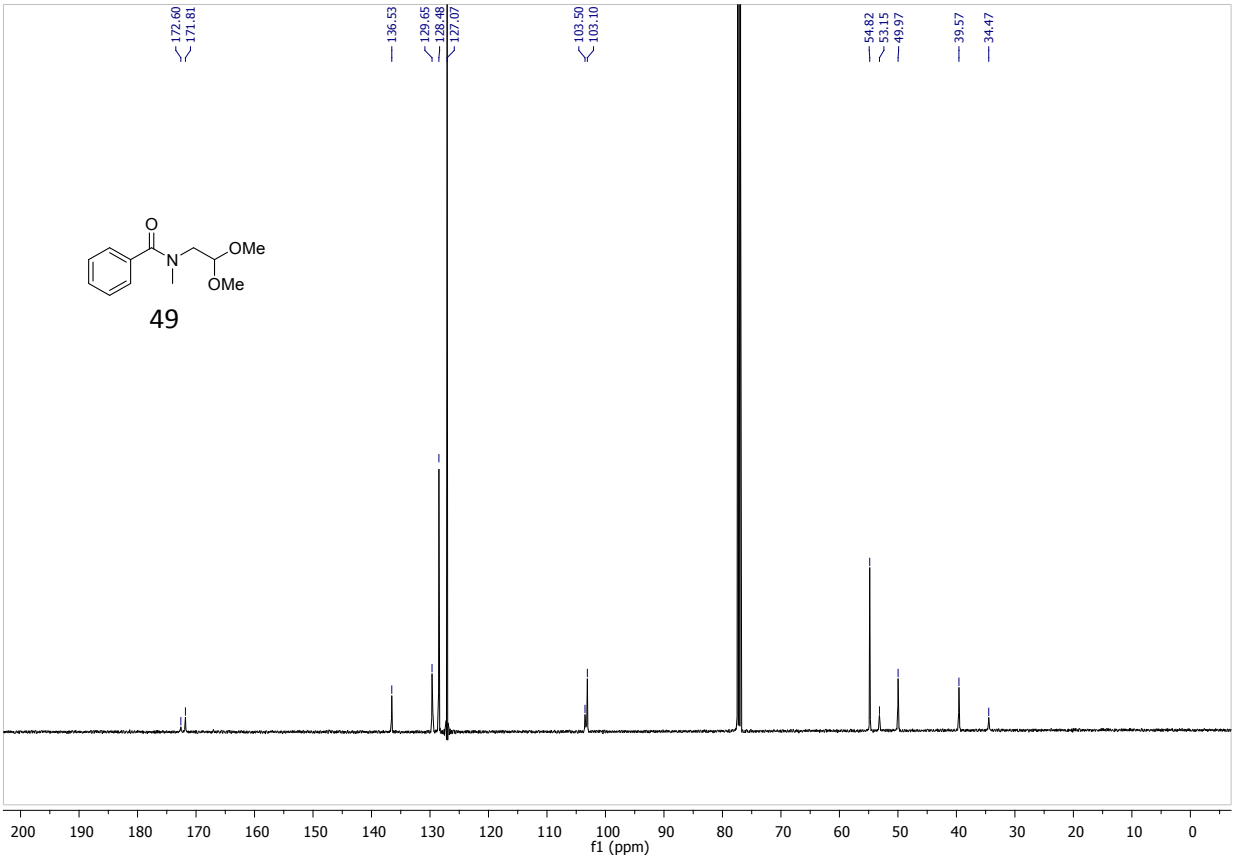
***N*-(cyclohexylmethyl)-*N*-methylbenzamide (48)**





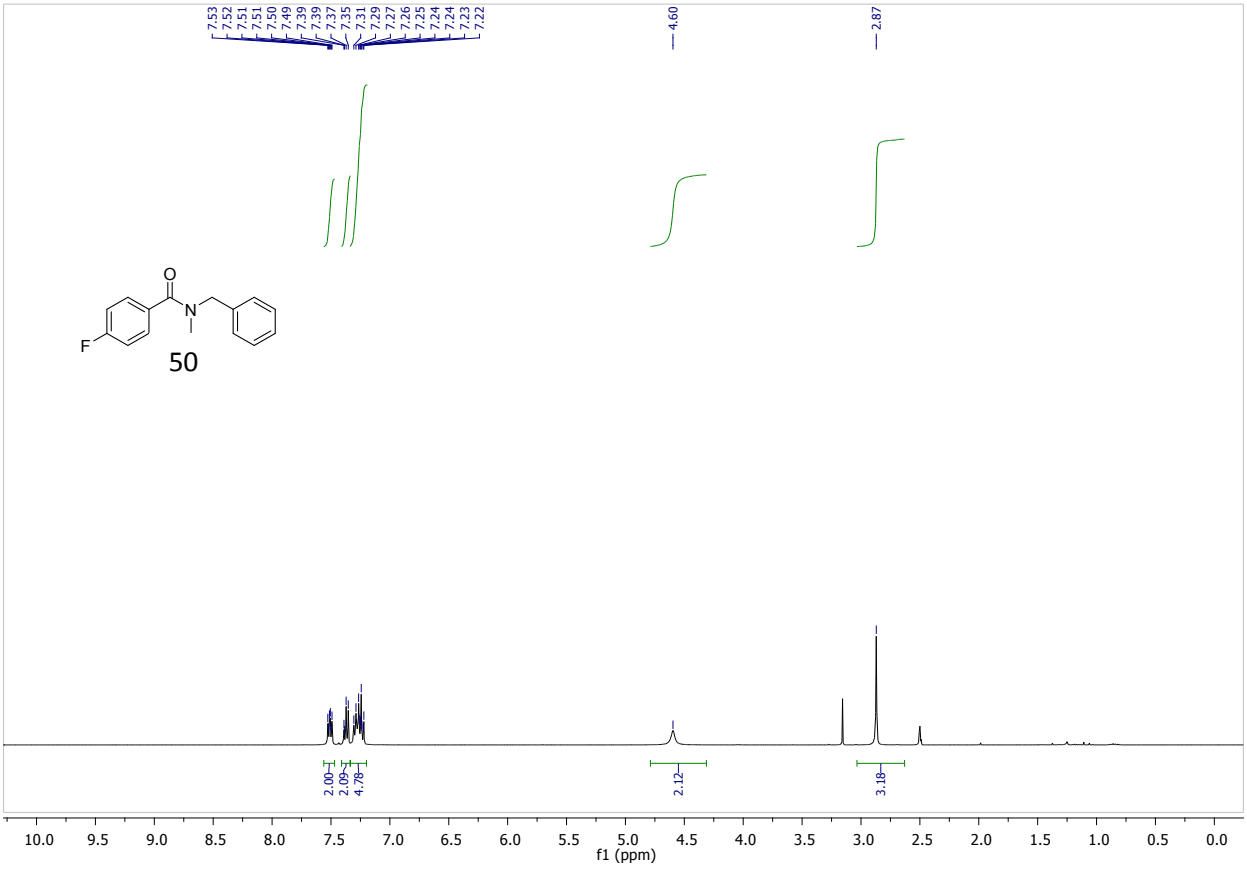
_N_-(2,2-dimethoxyethyl)-_N_-methylbenzamide (49)



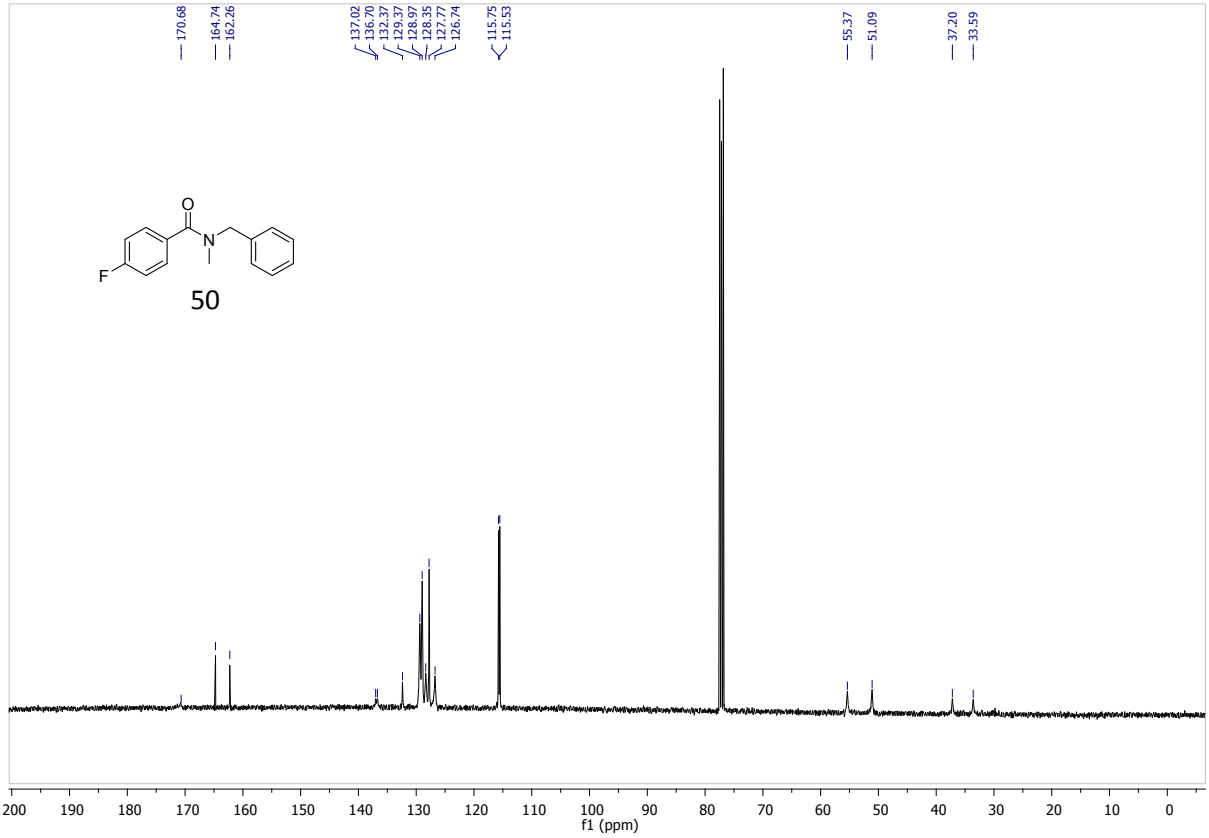


49

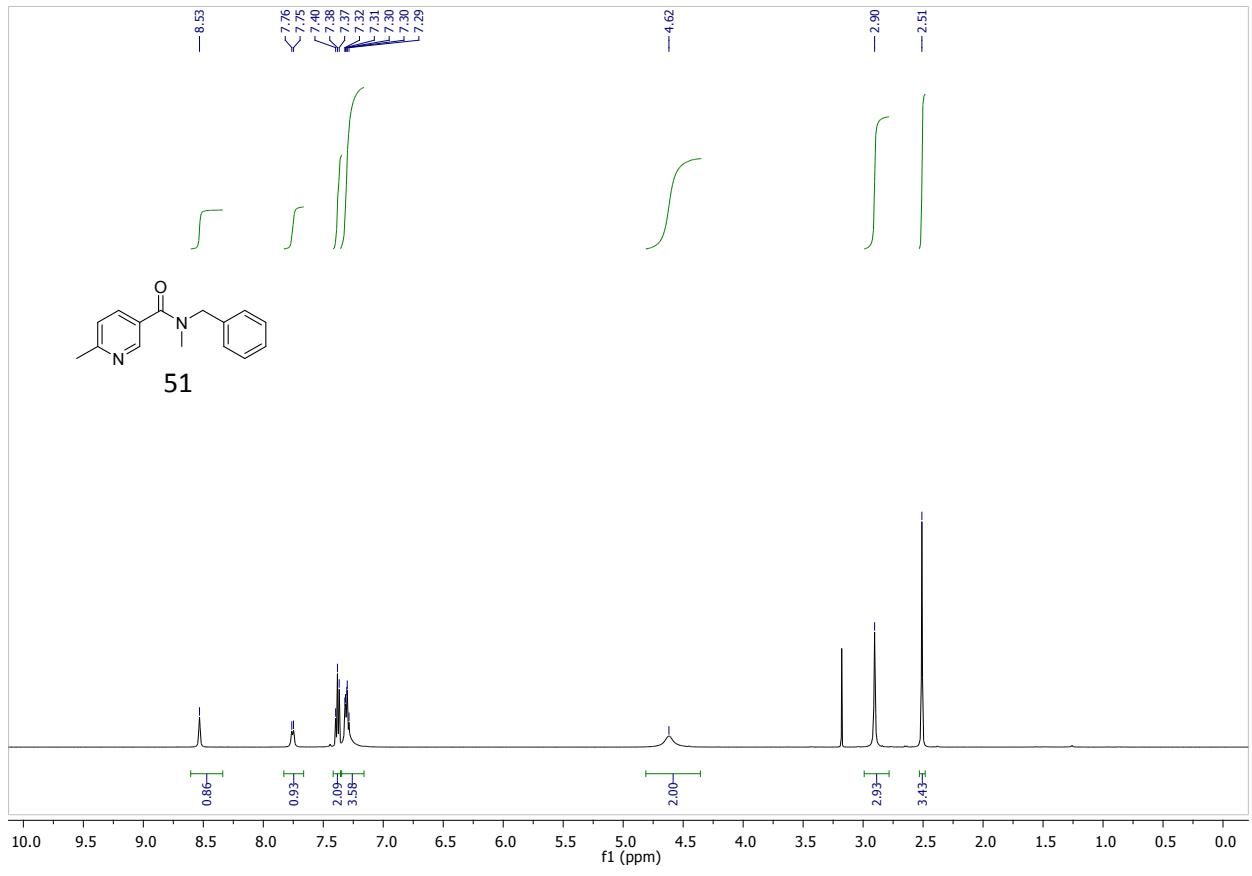
_N_-benzyl-4-fluoro-_N_-methylbenzamide (50)

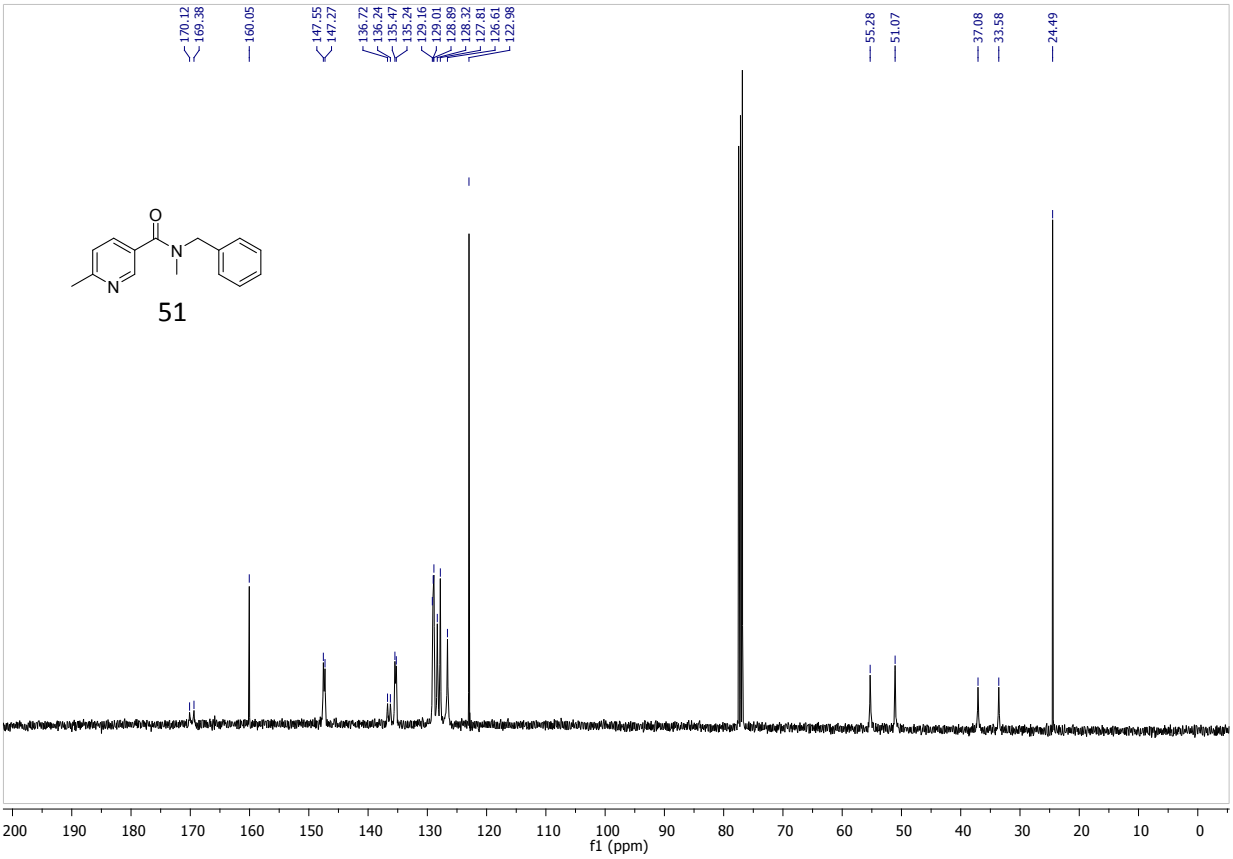


50

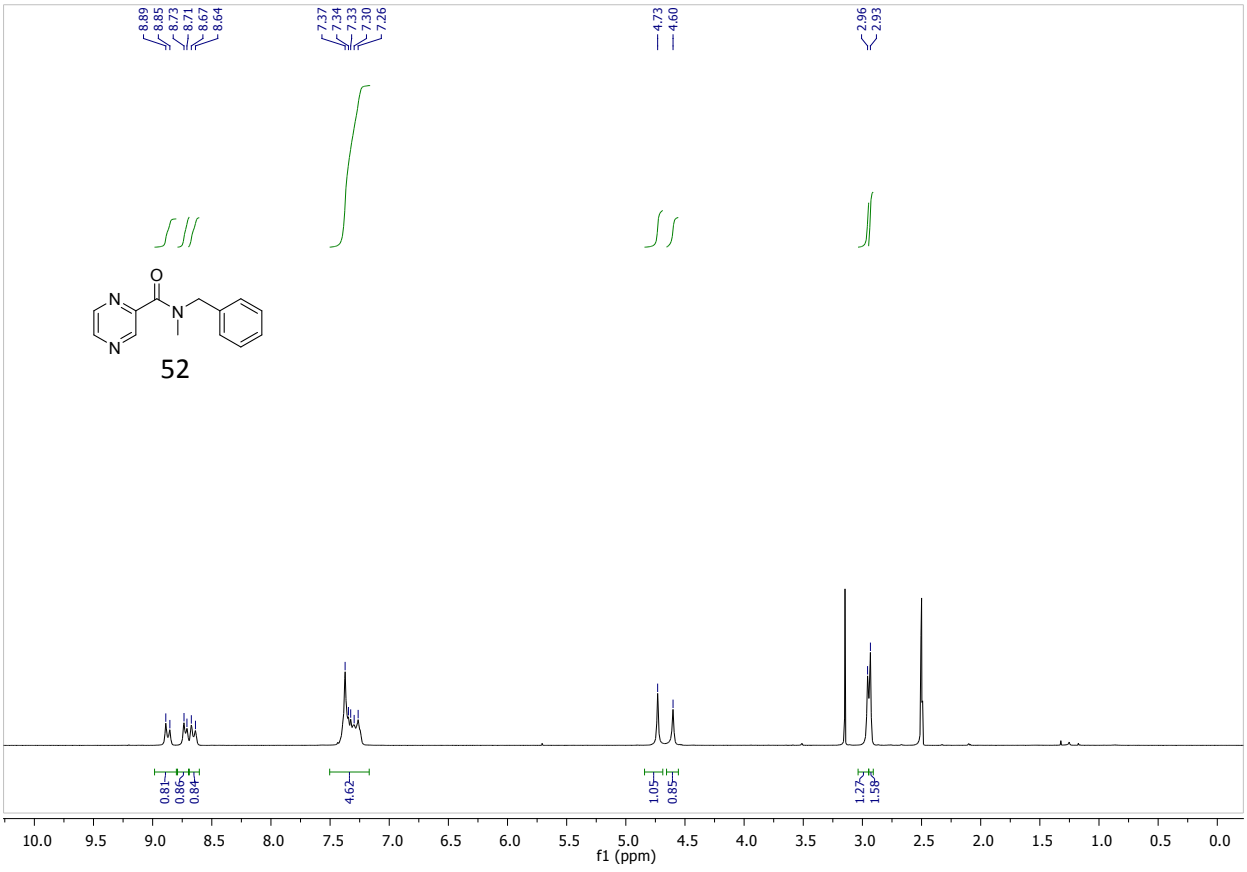


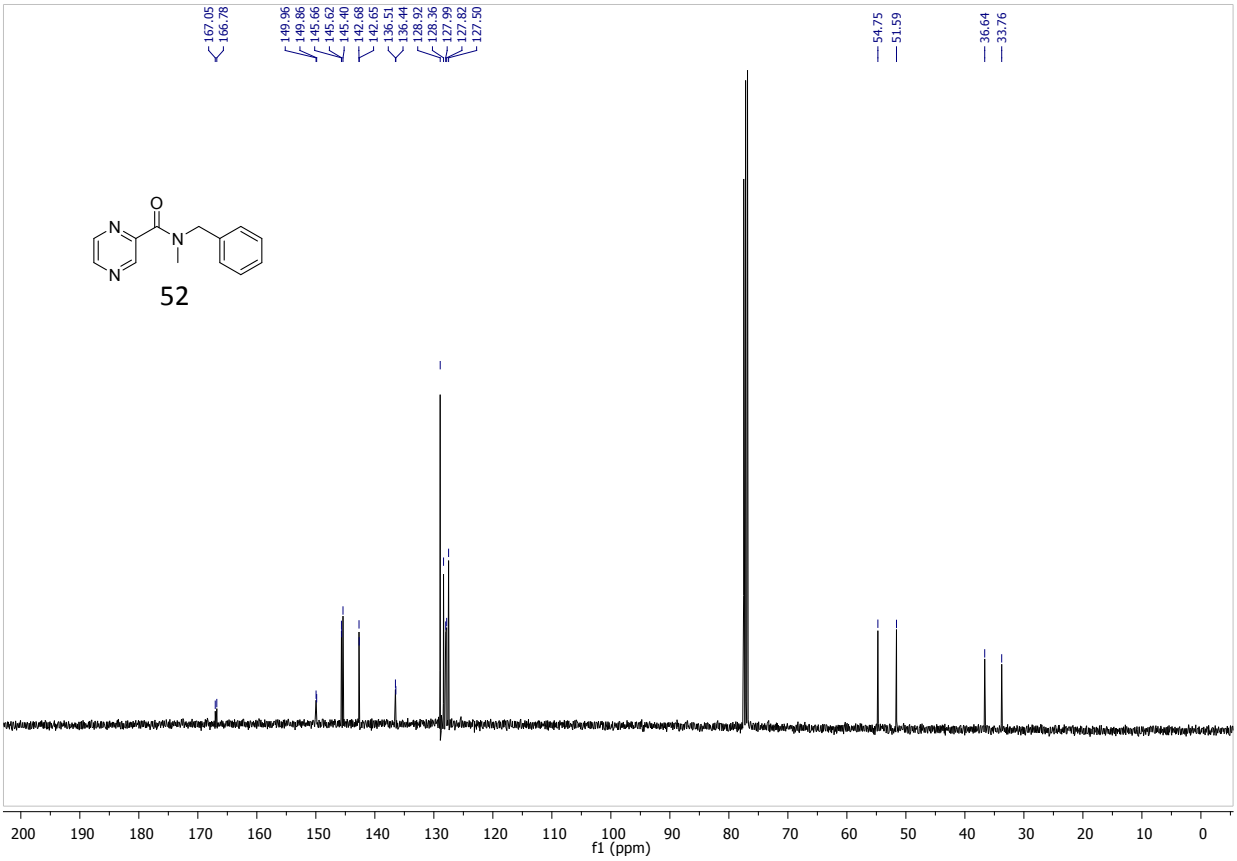
_N_-benzyl-_N_,6-dimethylnicotinamide (51)



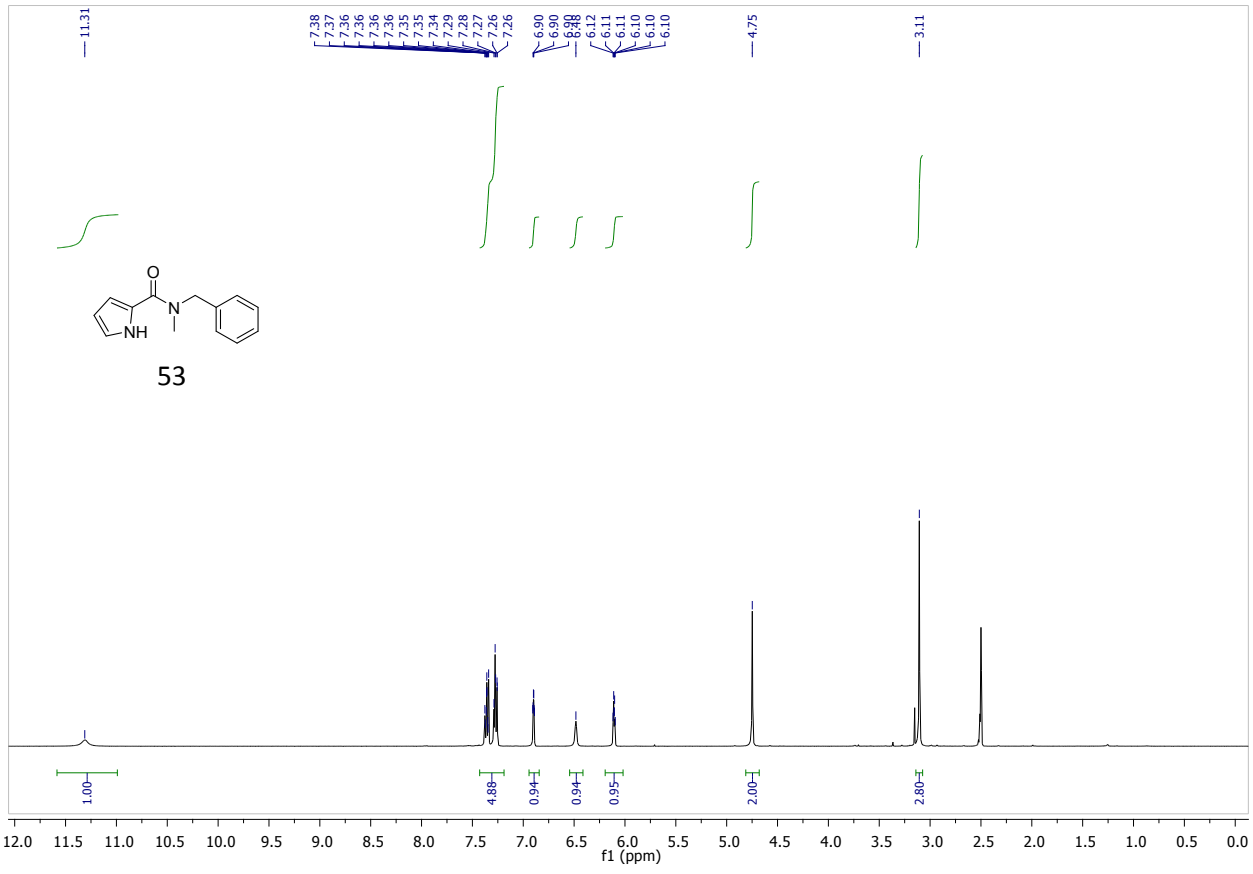


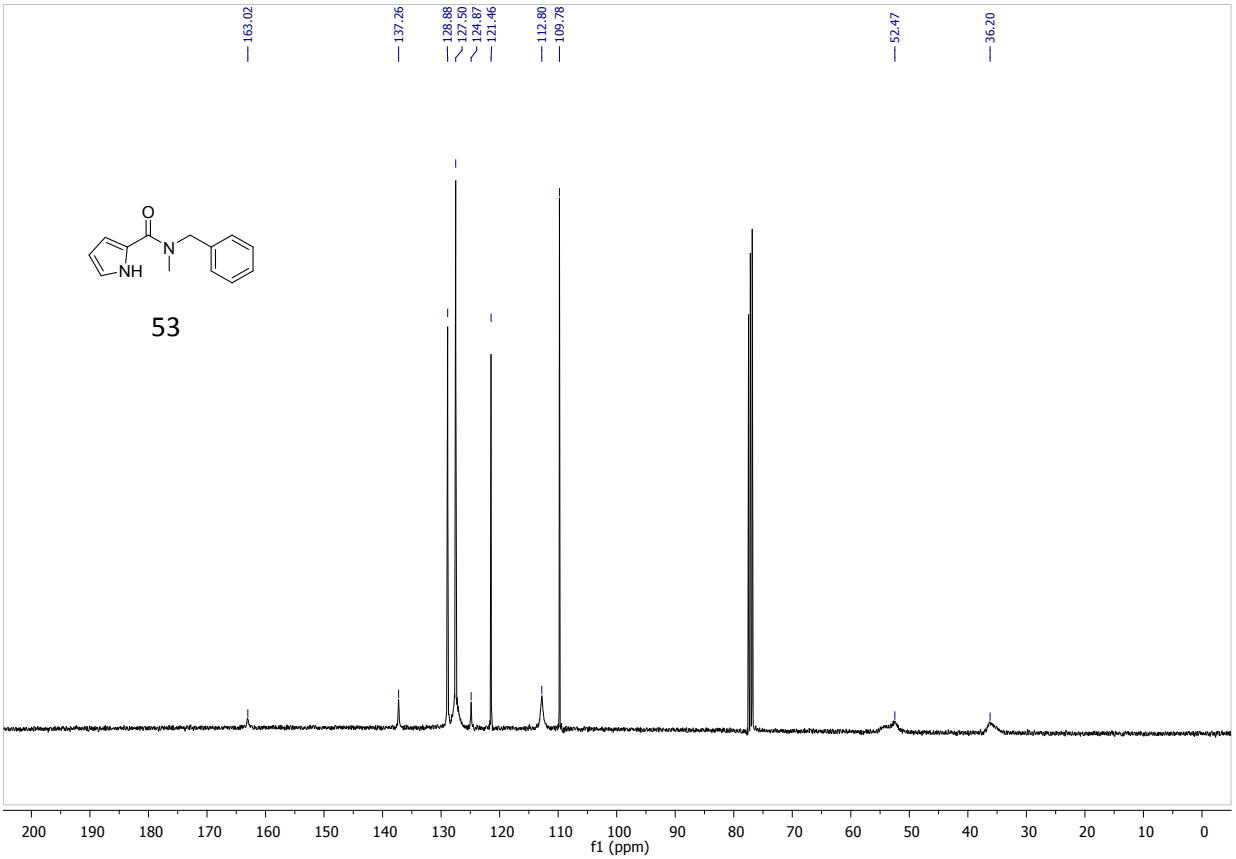
***N*-benzyl-*N*-methylpyrazine-2-carboxamide (52)**





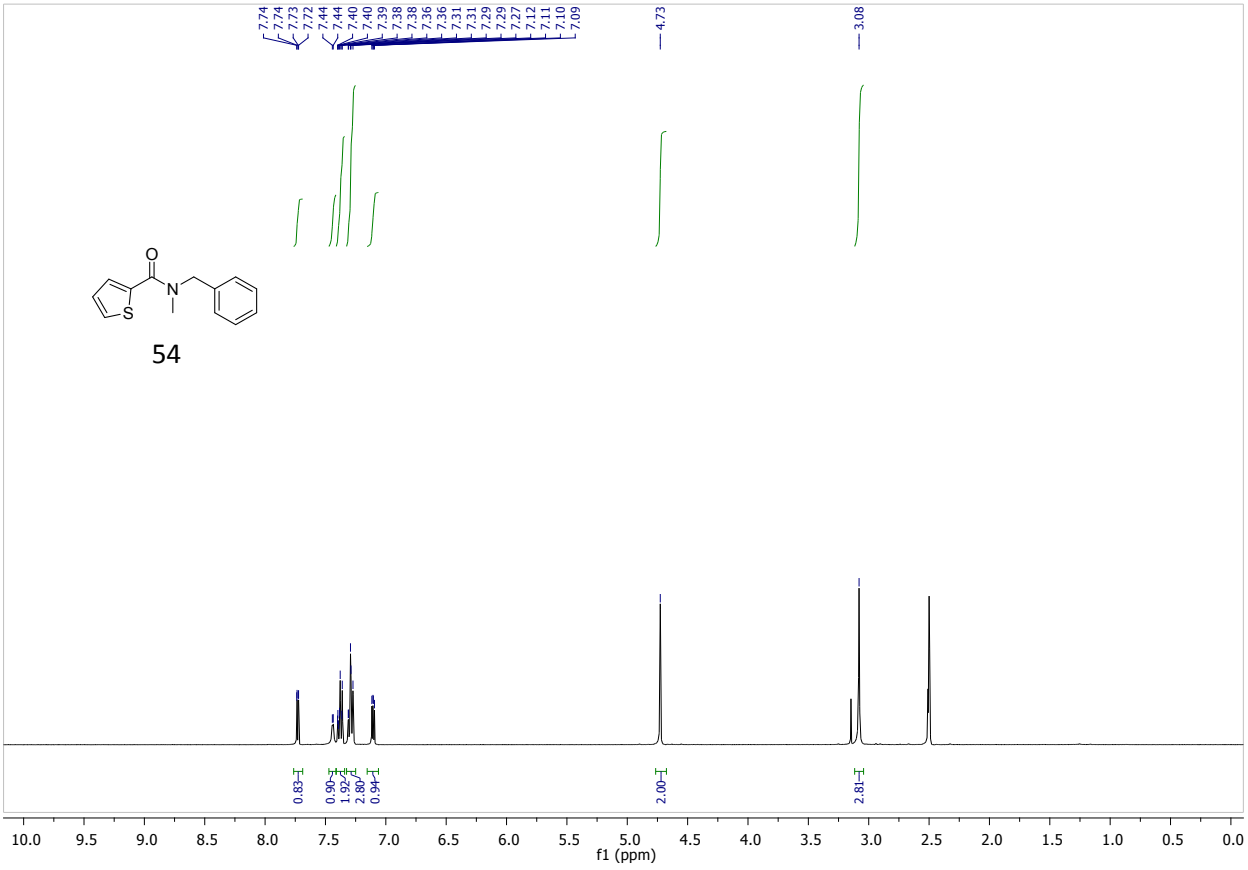
***N*-benzyl-*N*-methyl-1H-pyrrole-2-carboxamide (53)**



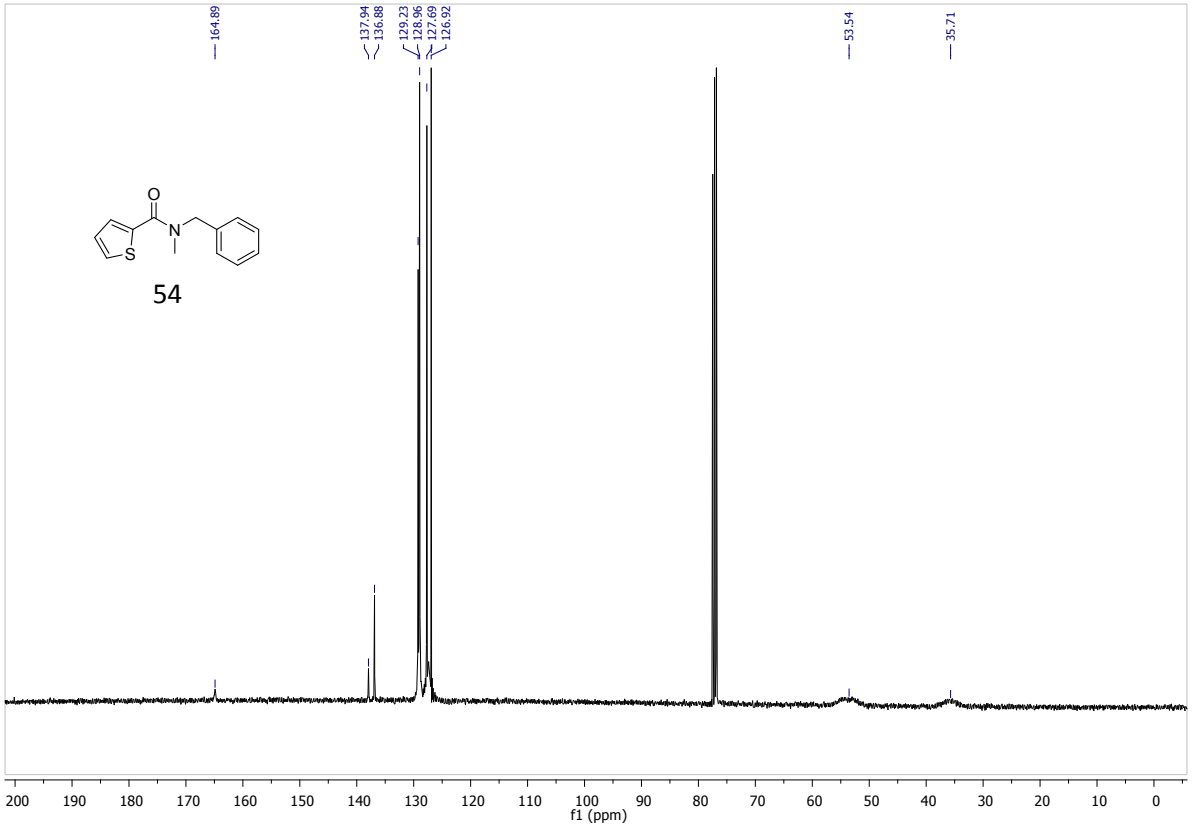


53

***N*-benzyl-*N*-methylthiophene-2-carboxamide (54)**

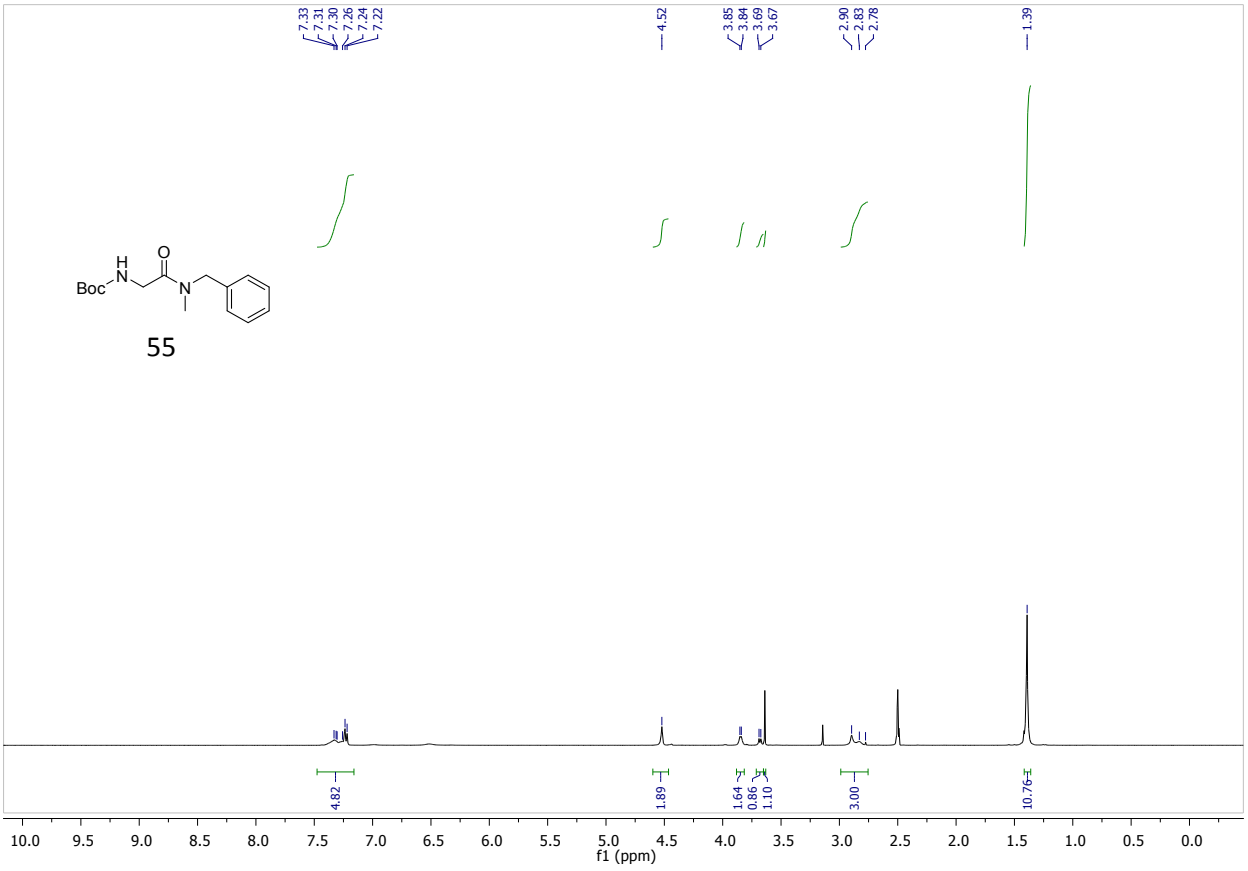


54

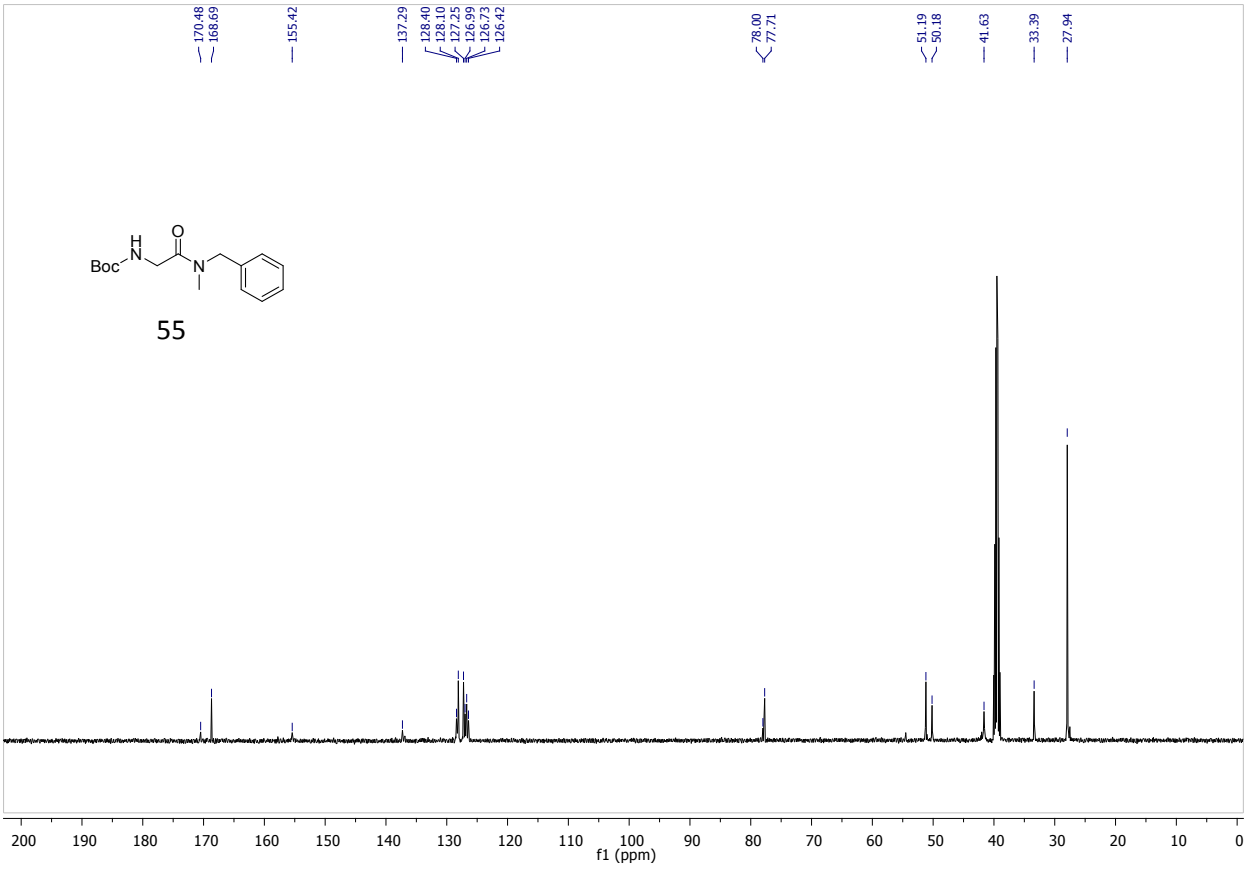


54

***tert*-butyl (2-(benzyl(methyl)amino)-2-oxoethyl)carbamate (55)**

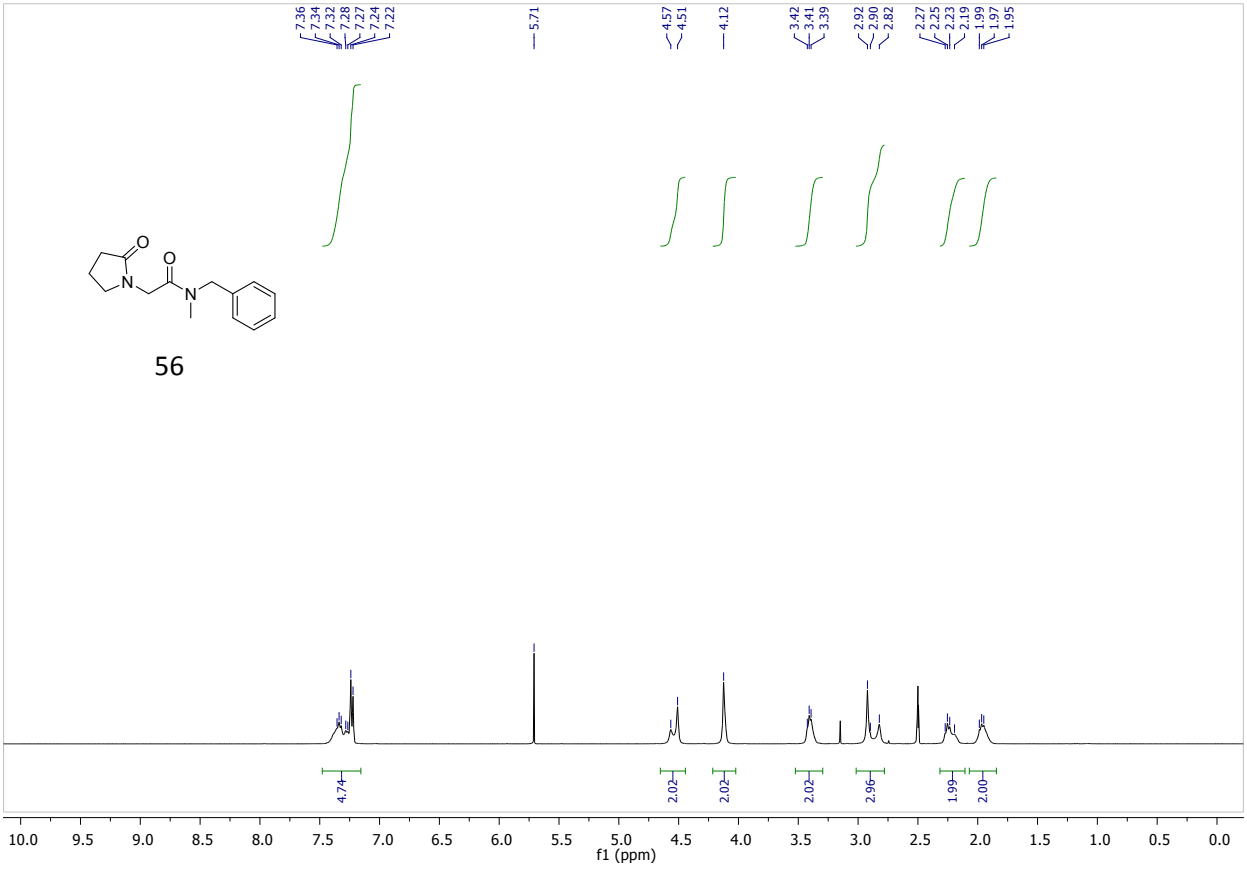


55

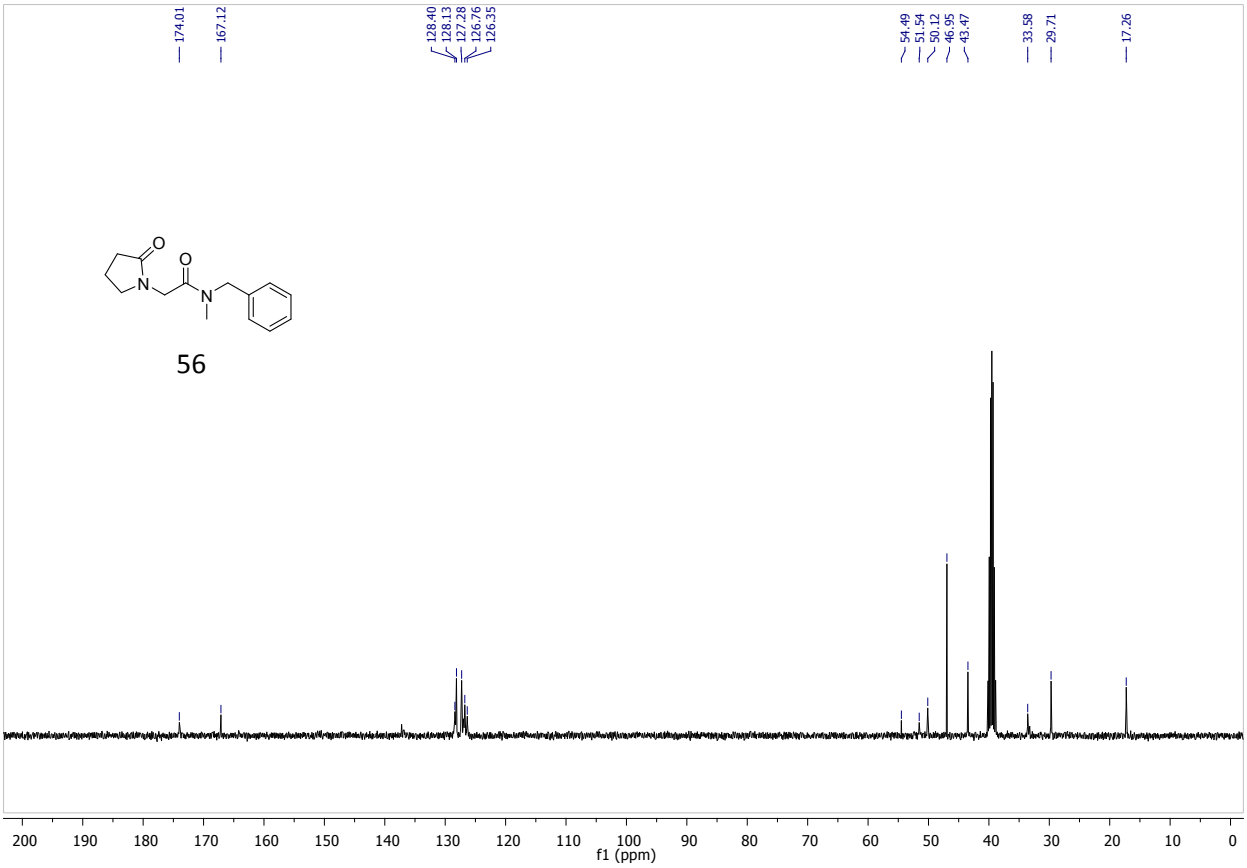


55

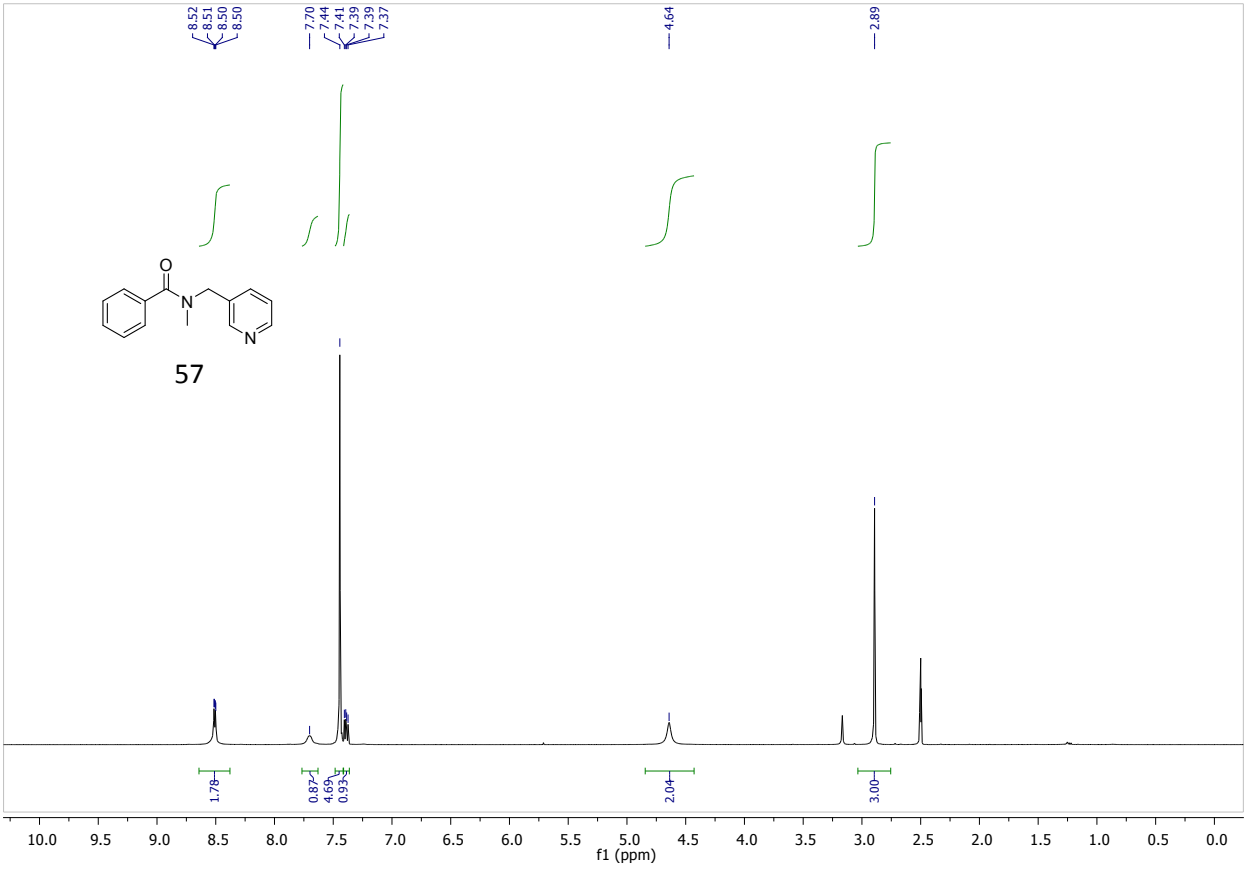
***N*-benzyl-*N*-methyl-2-(2-oxopyrrolidin-1-yl)acetamide (56)**

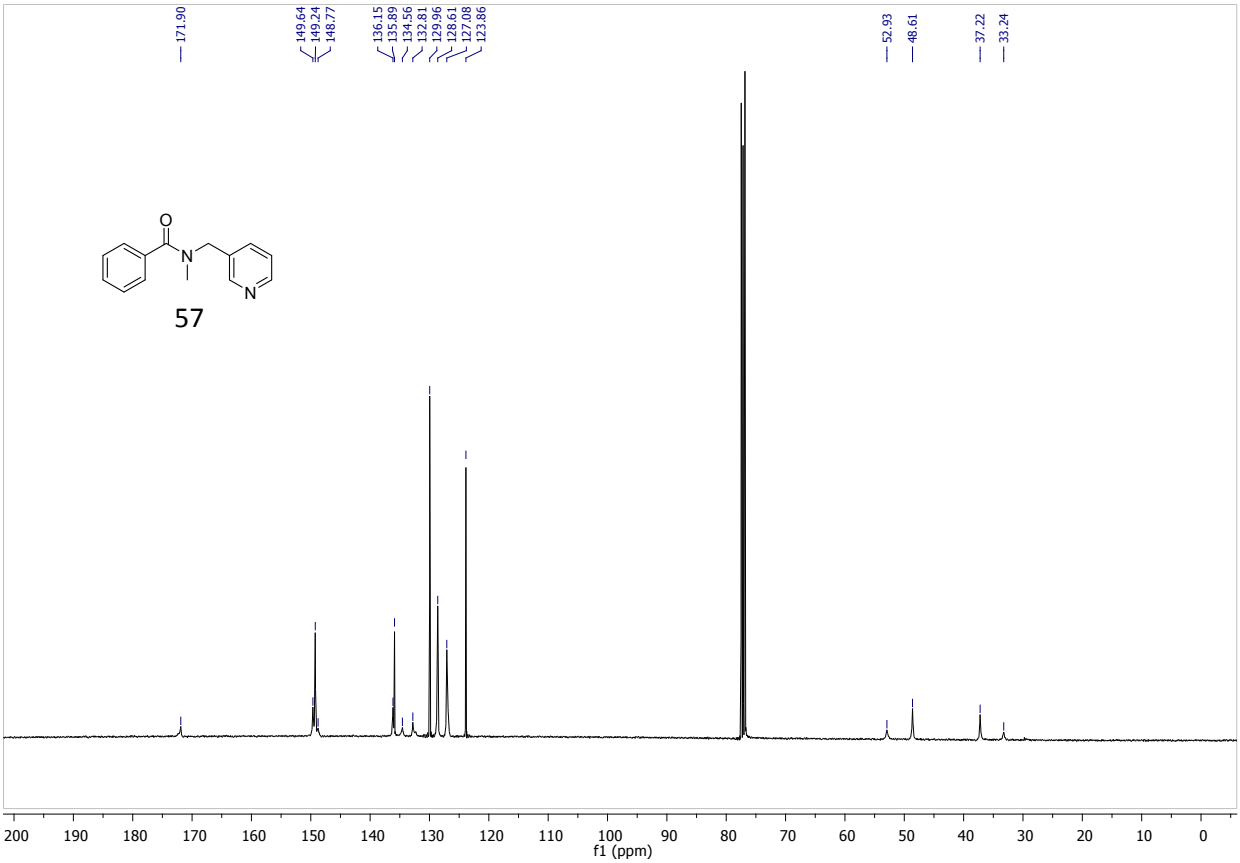


56

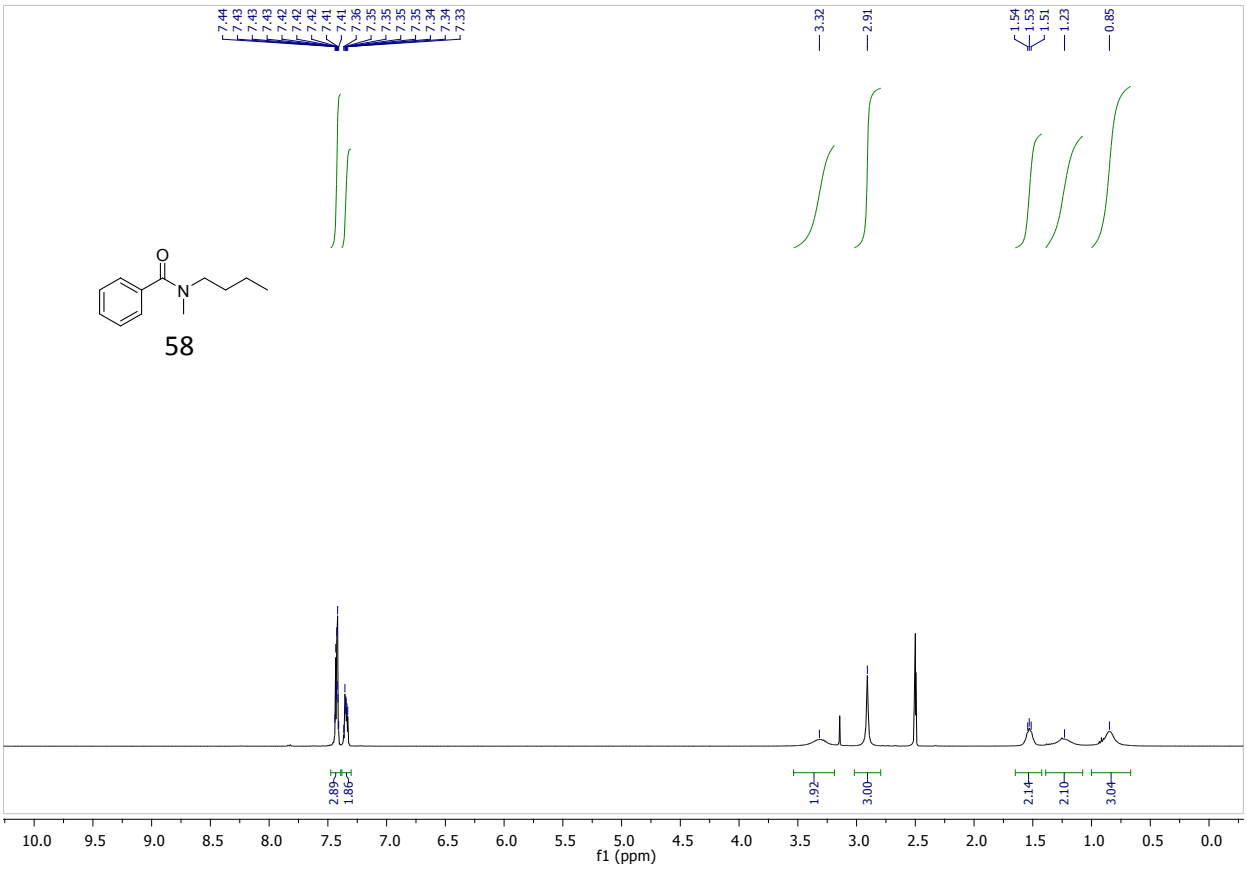


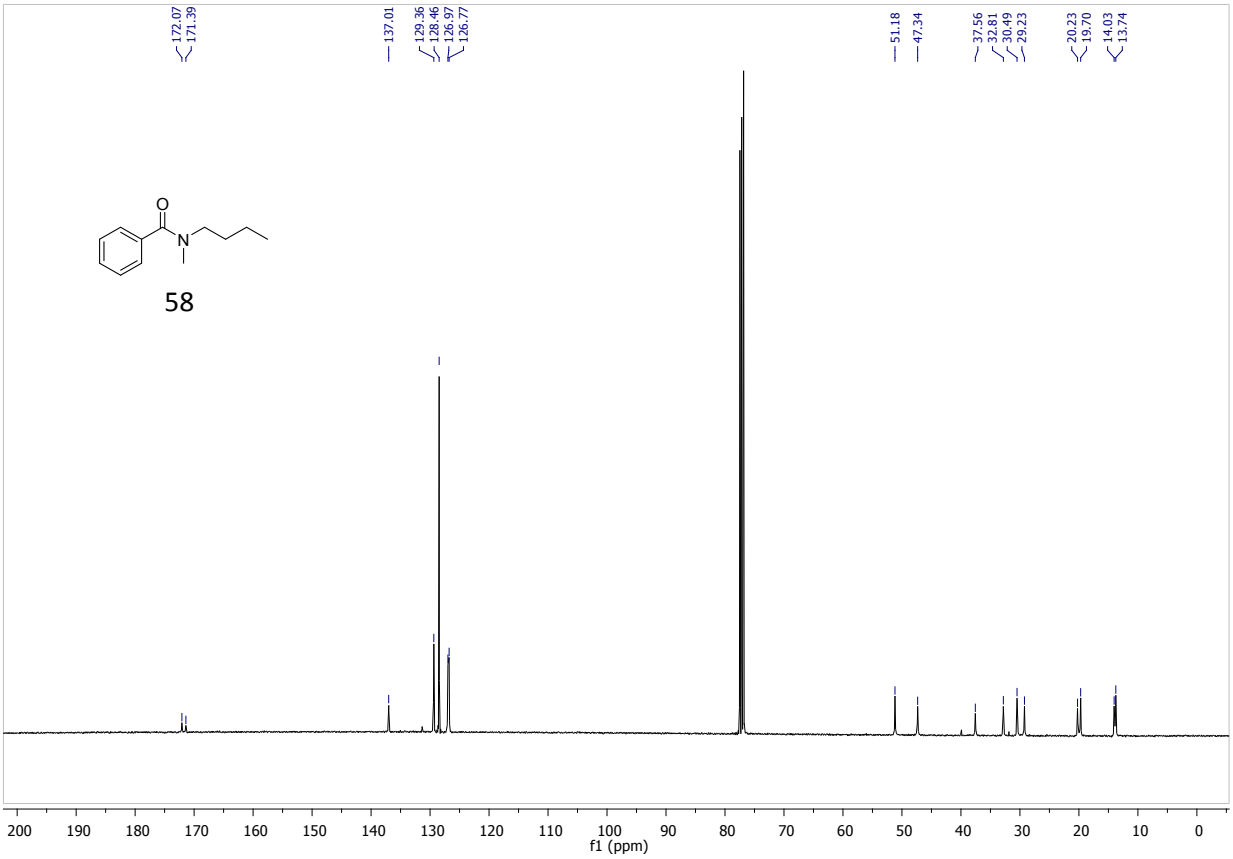
***N*-methyl-*N*-(pyridin-3-ylmethyl)benzamide (57)**



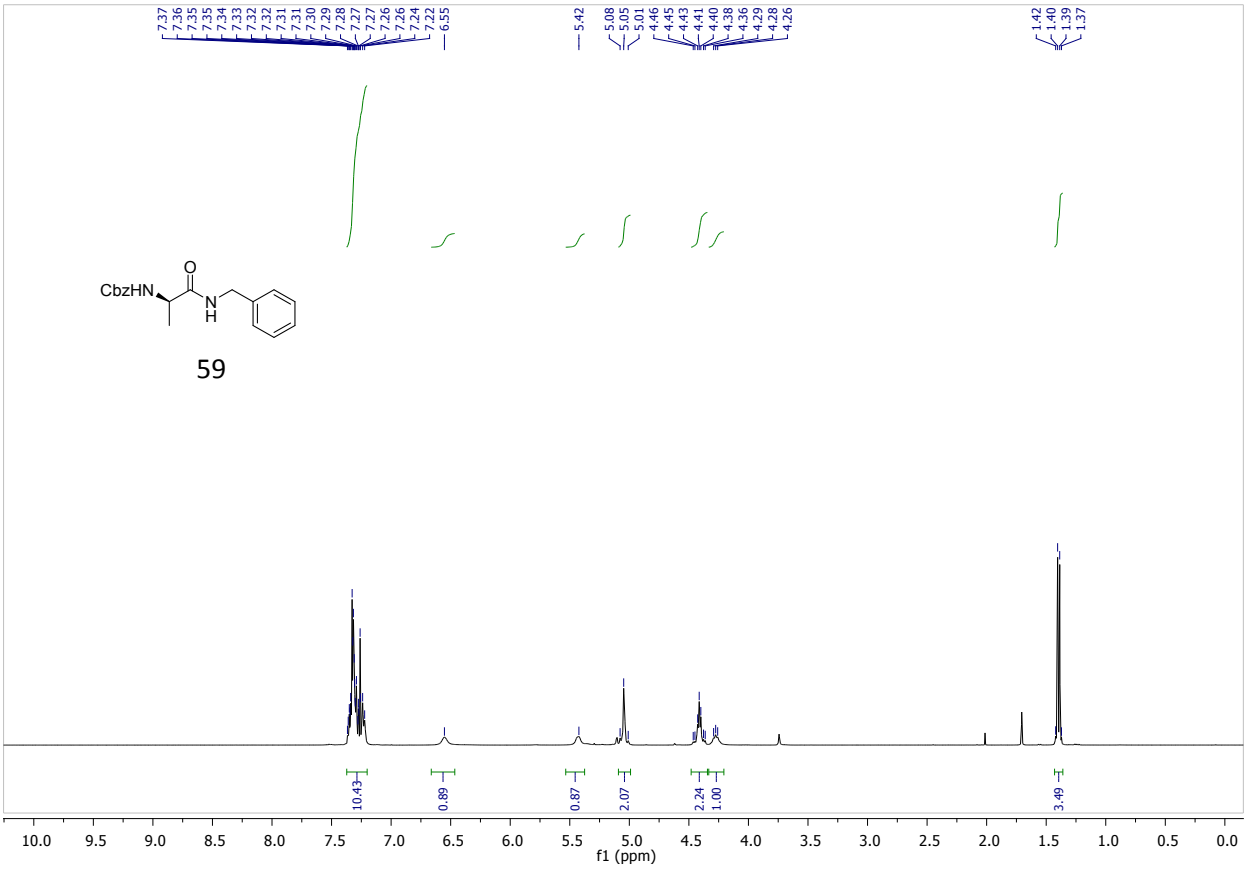


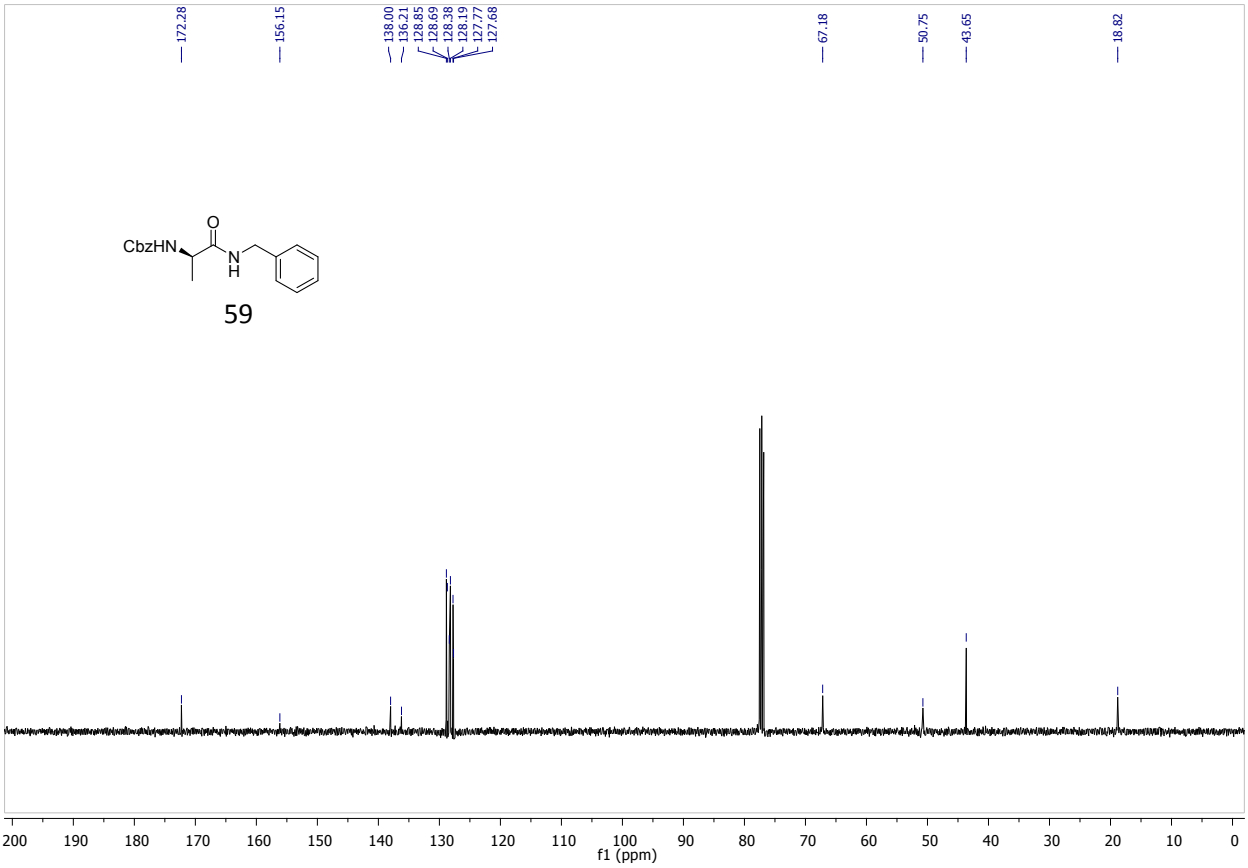
***N*-butyl-*N*-methylbenzamide (58)**



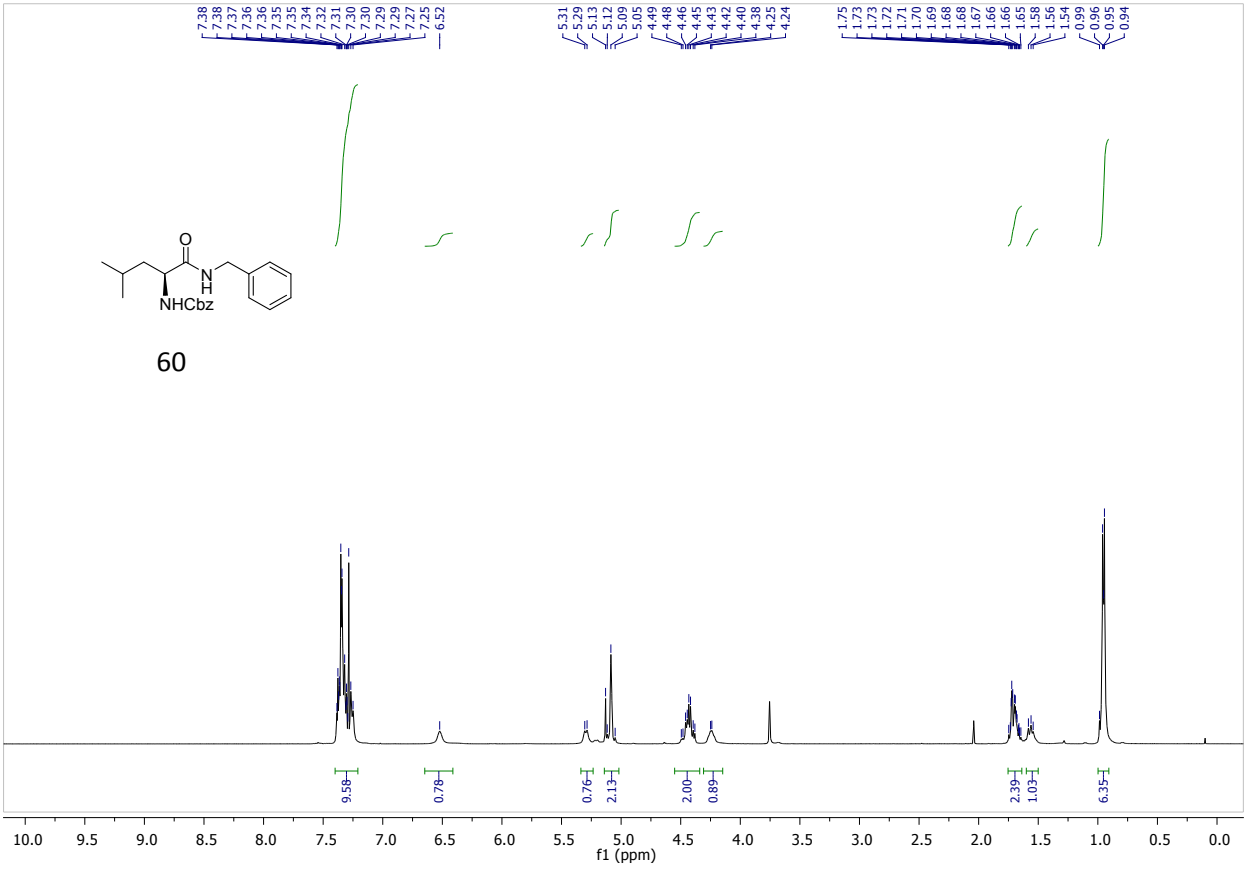


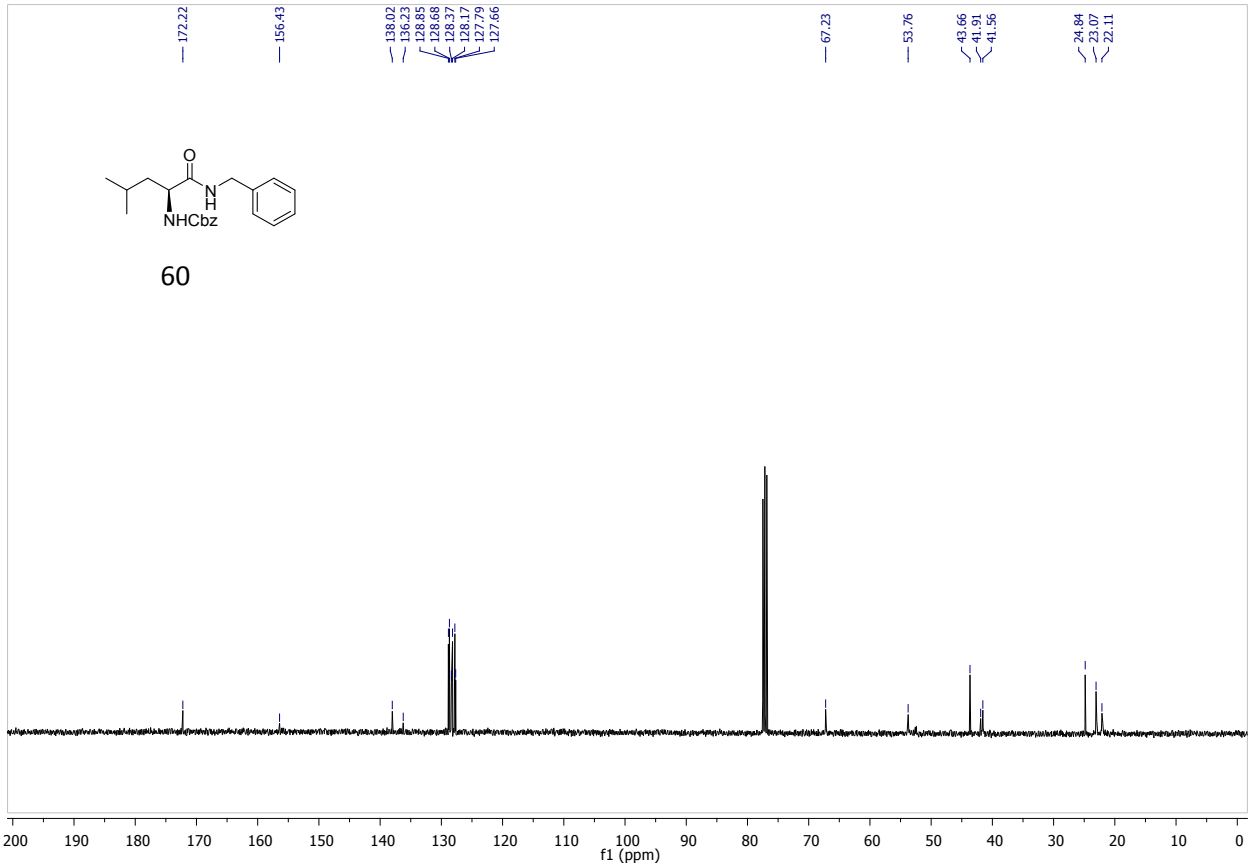
benzyl (*R*)-(1-(benzylamino)-1-oxopropan-2-yl)carbamate (59)





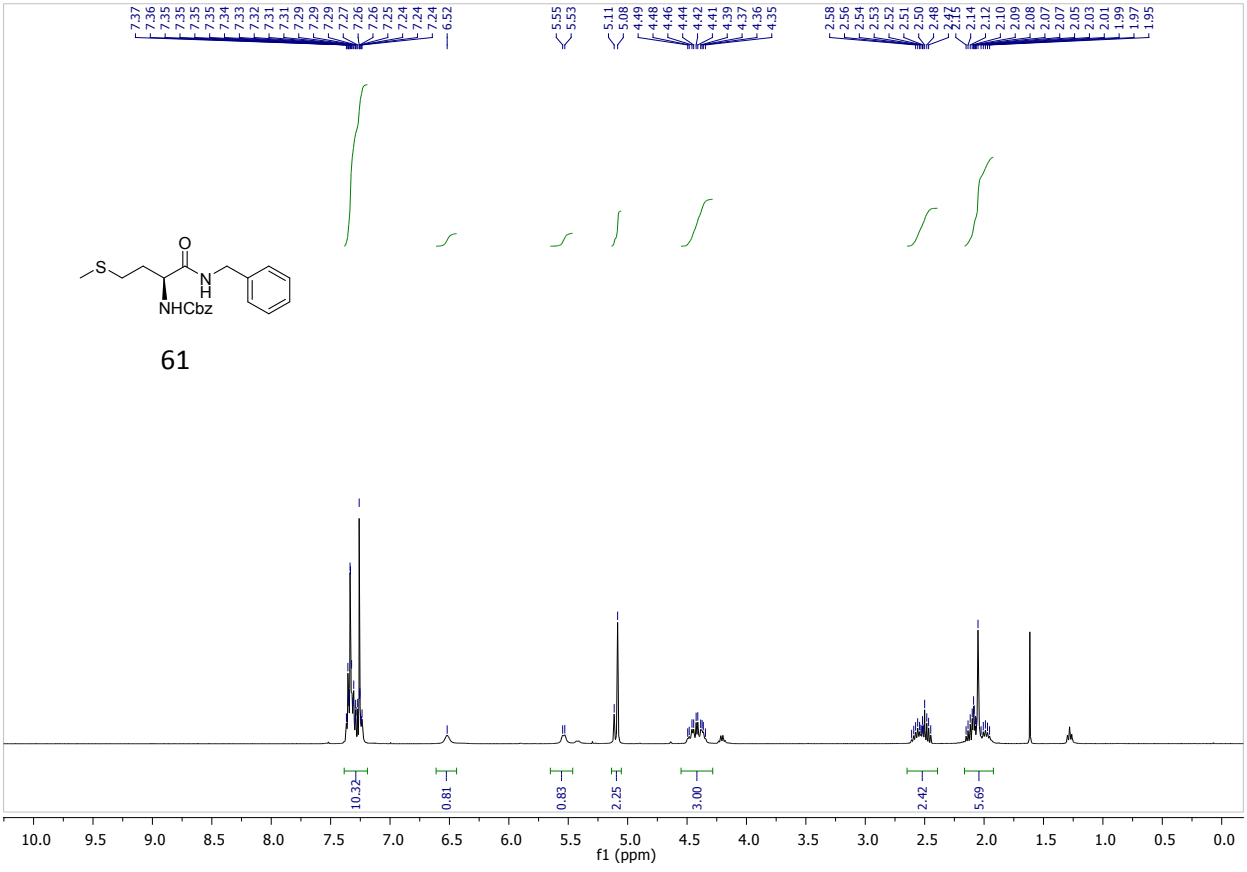
benzyl (*S*)-(1-(benzylamino)-4-methyl-1-oxopentan-2-yl)carbamate (60)



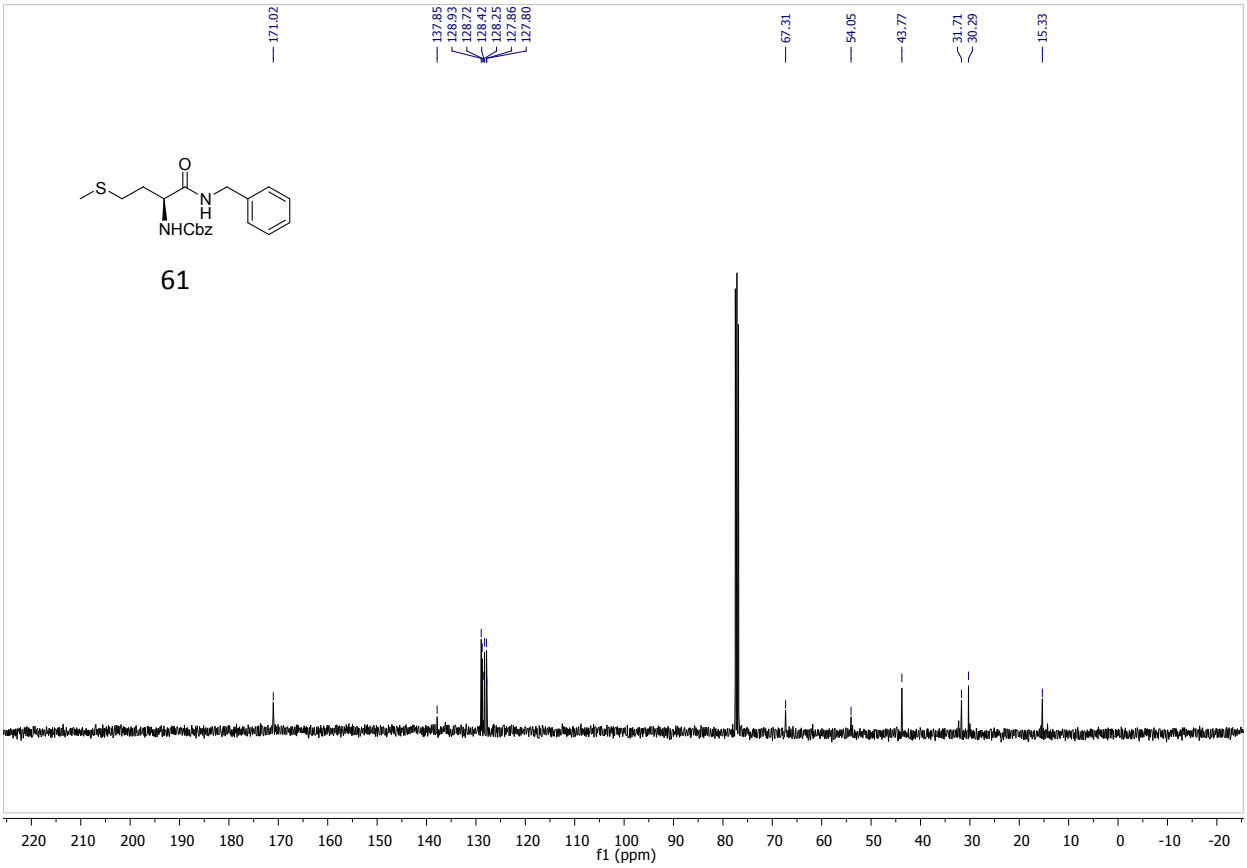


60

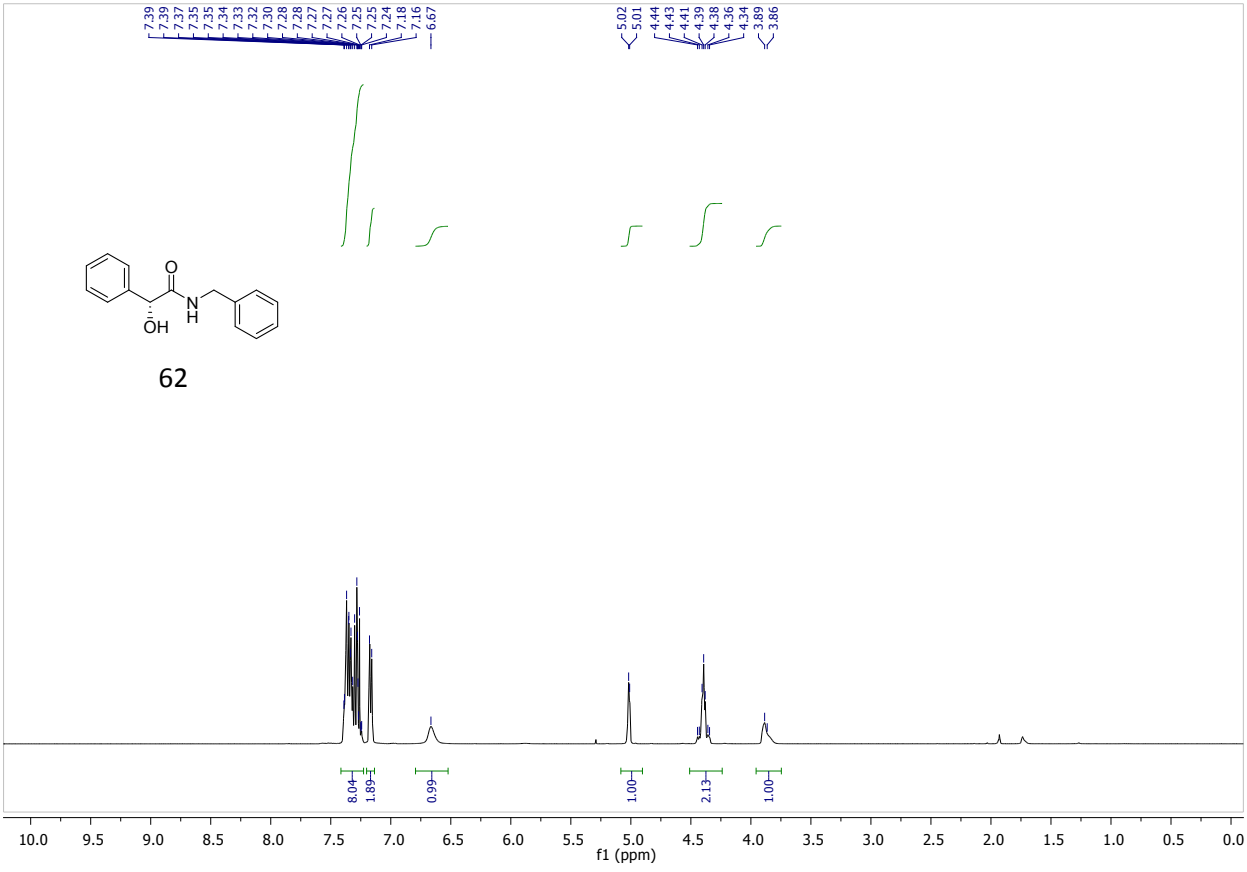
benzyl (*S*)-(1-(benzylamino)-4-(methylthio)-1-oxobutan-2-yl)carbamate (61)

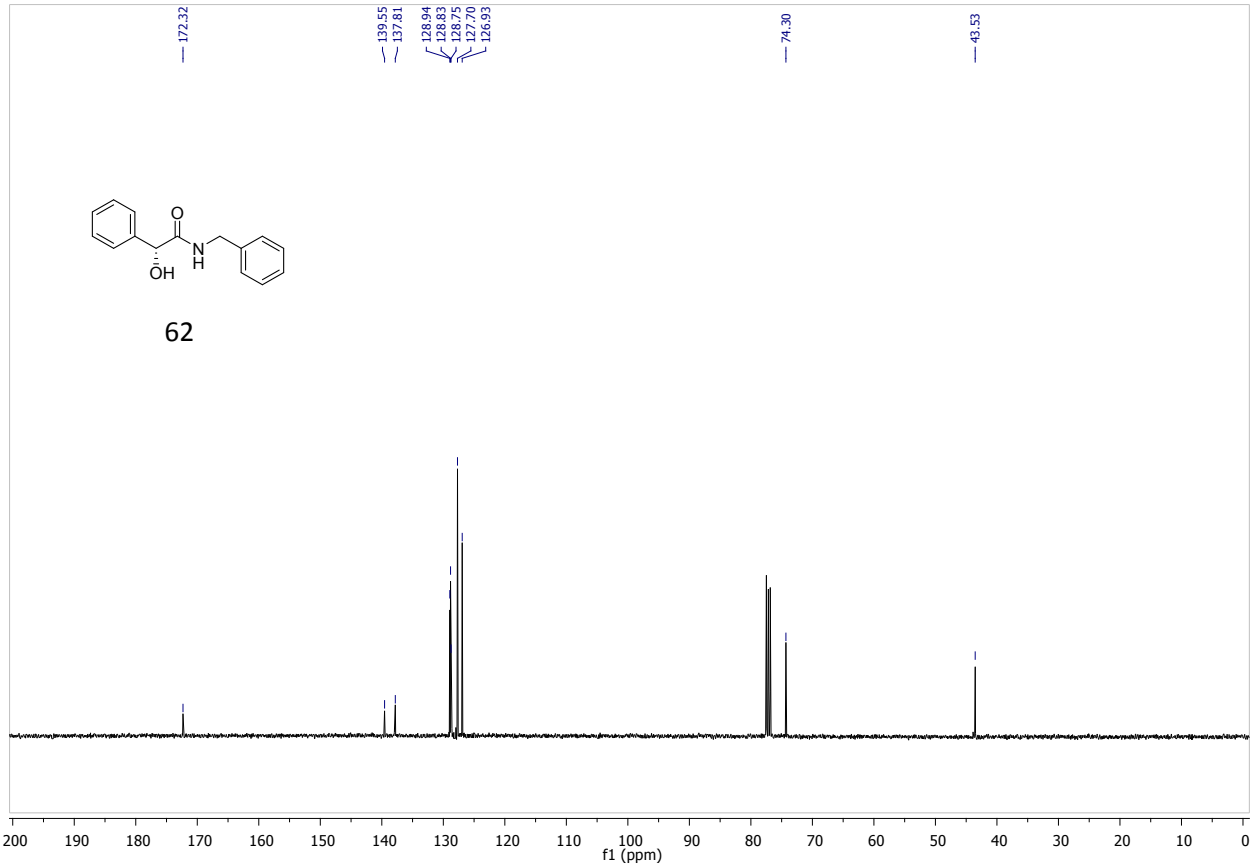


61

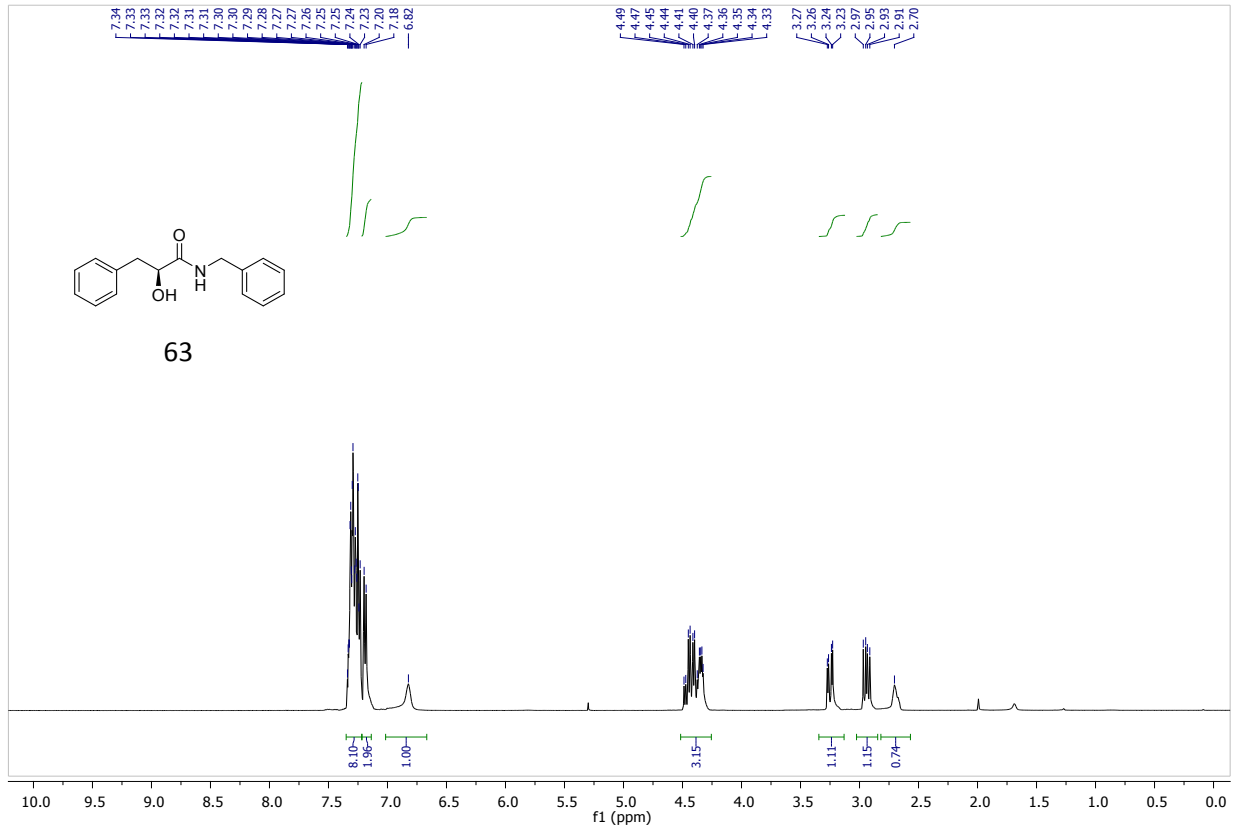


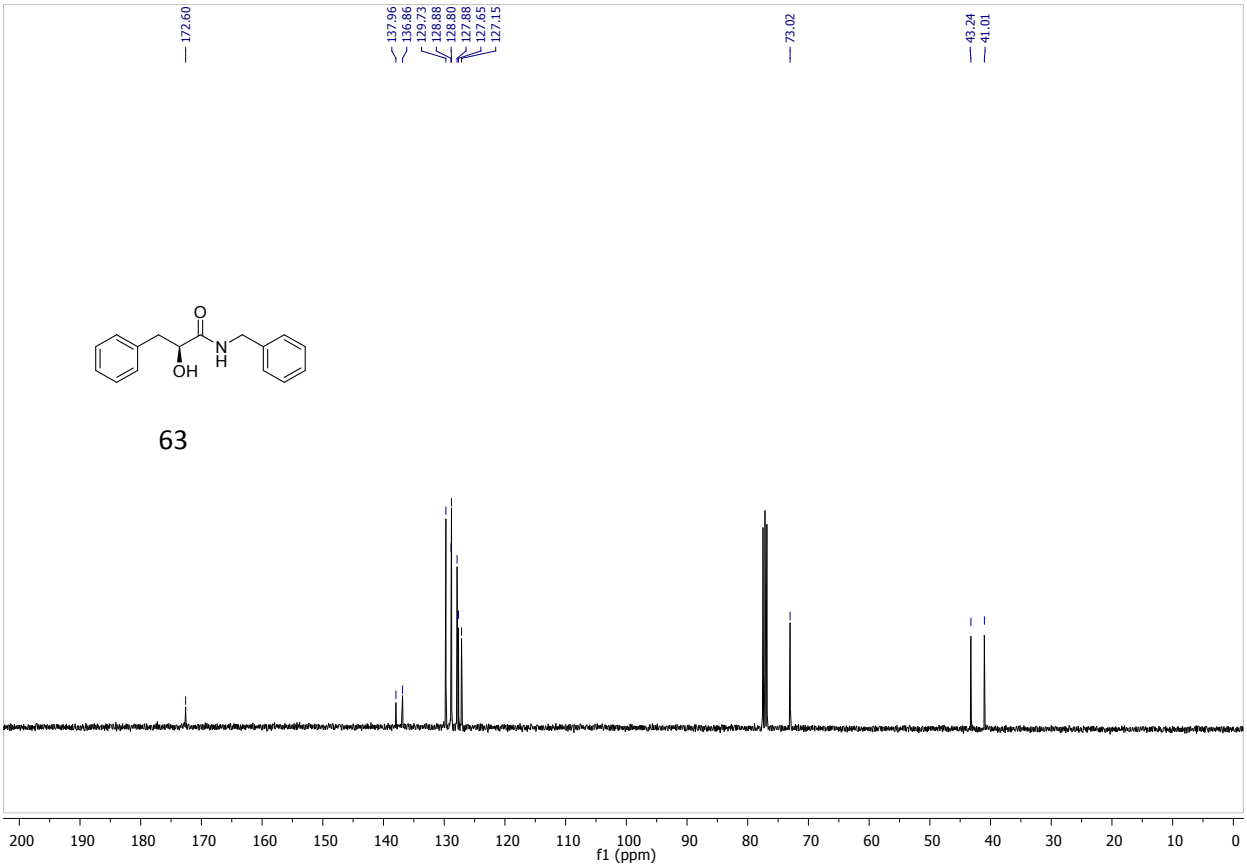
(*R*)-*N*-benzyl-2-hydroxy-2-phenylacetamide (62)



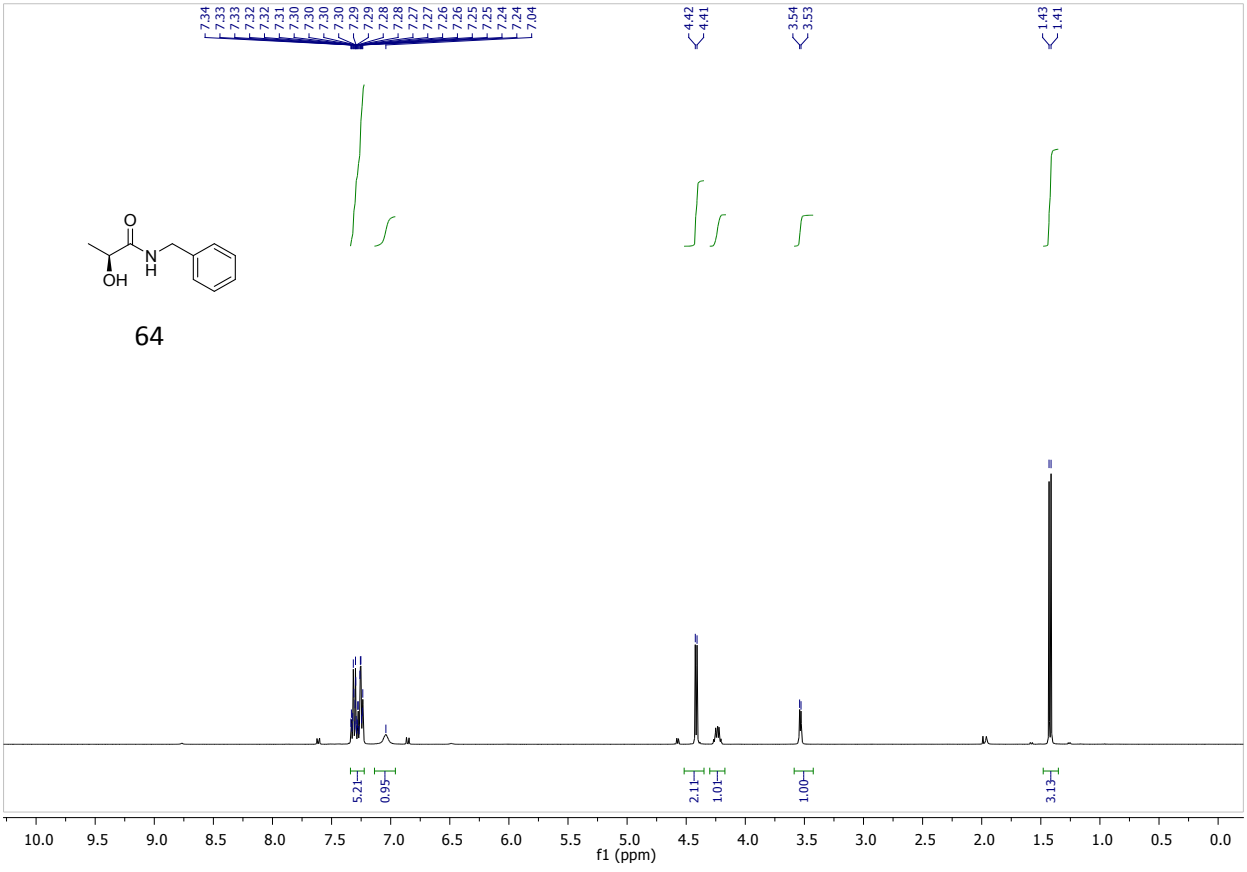


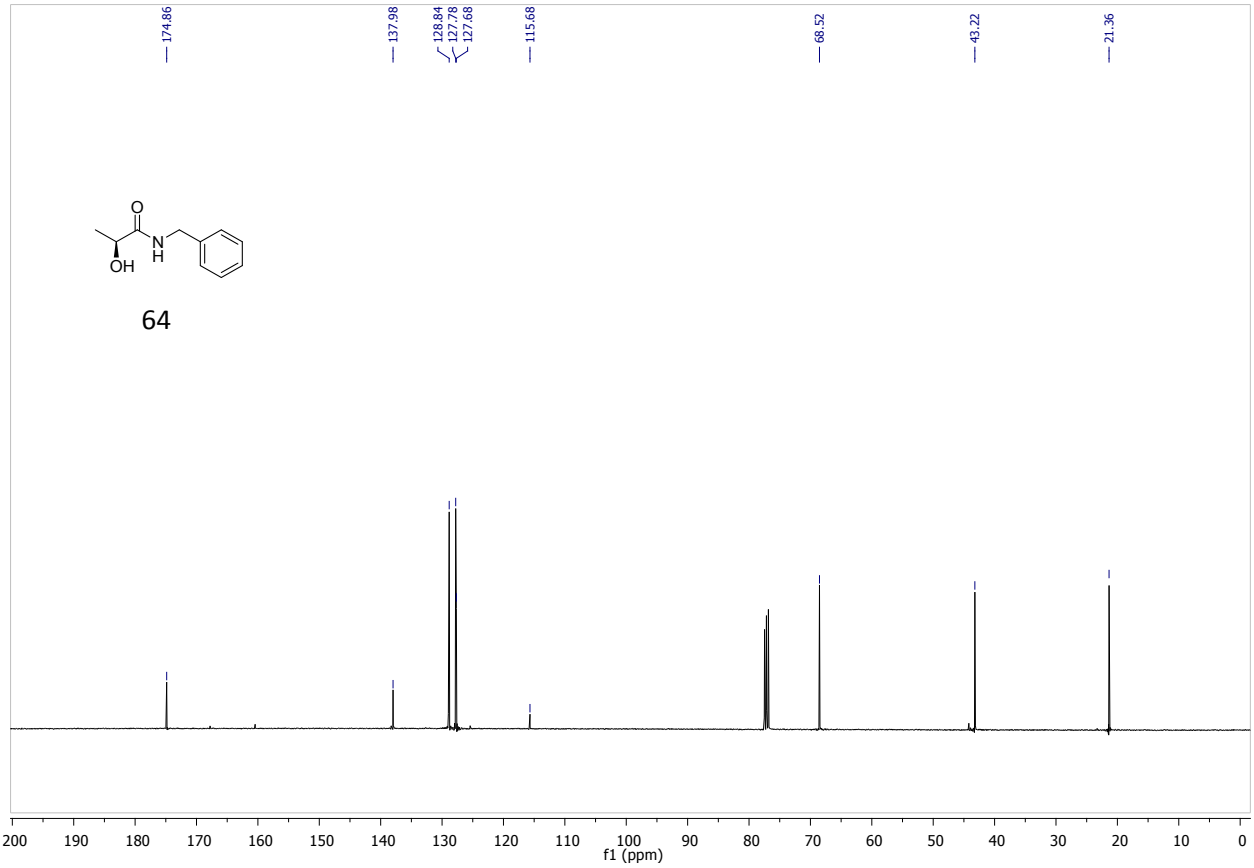
(*S*)-*N*-benzyl-2-hydroxy-3-phenylpropanamide (63)



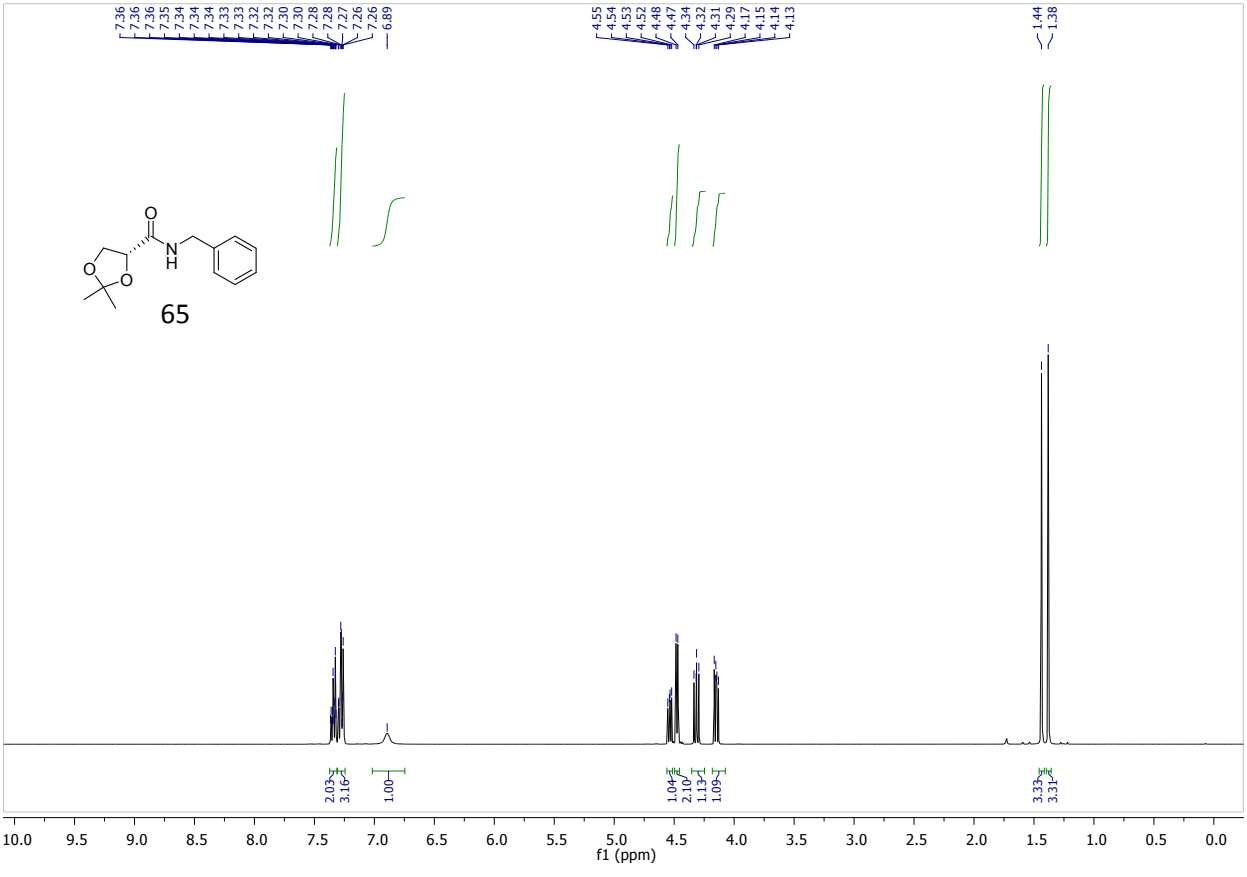


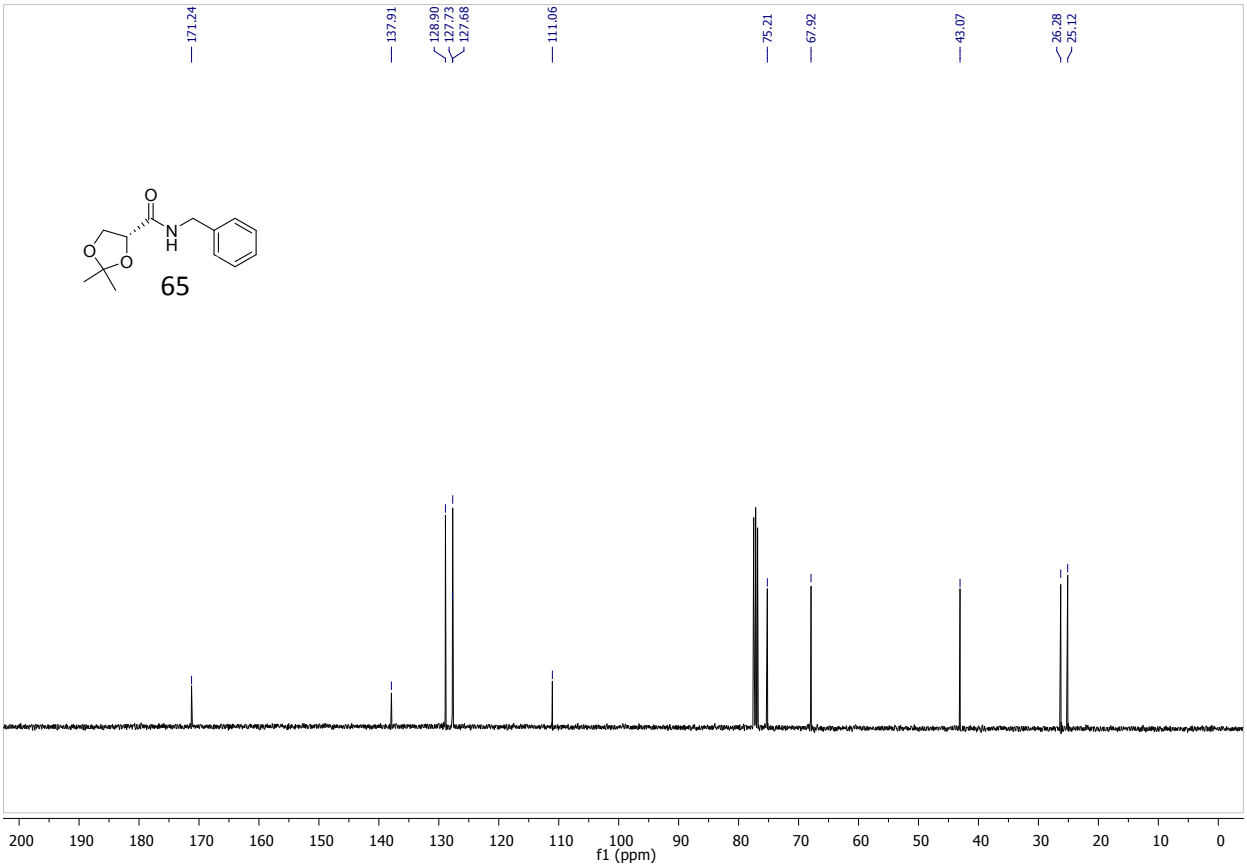
(*S*)-*N*-benzyl-2-hydroxypropanamide (64)



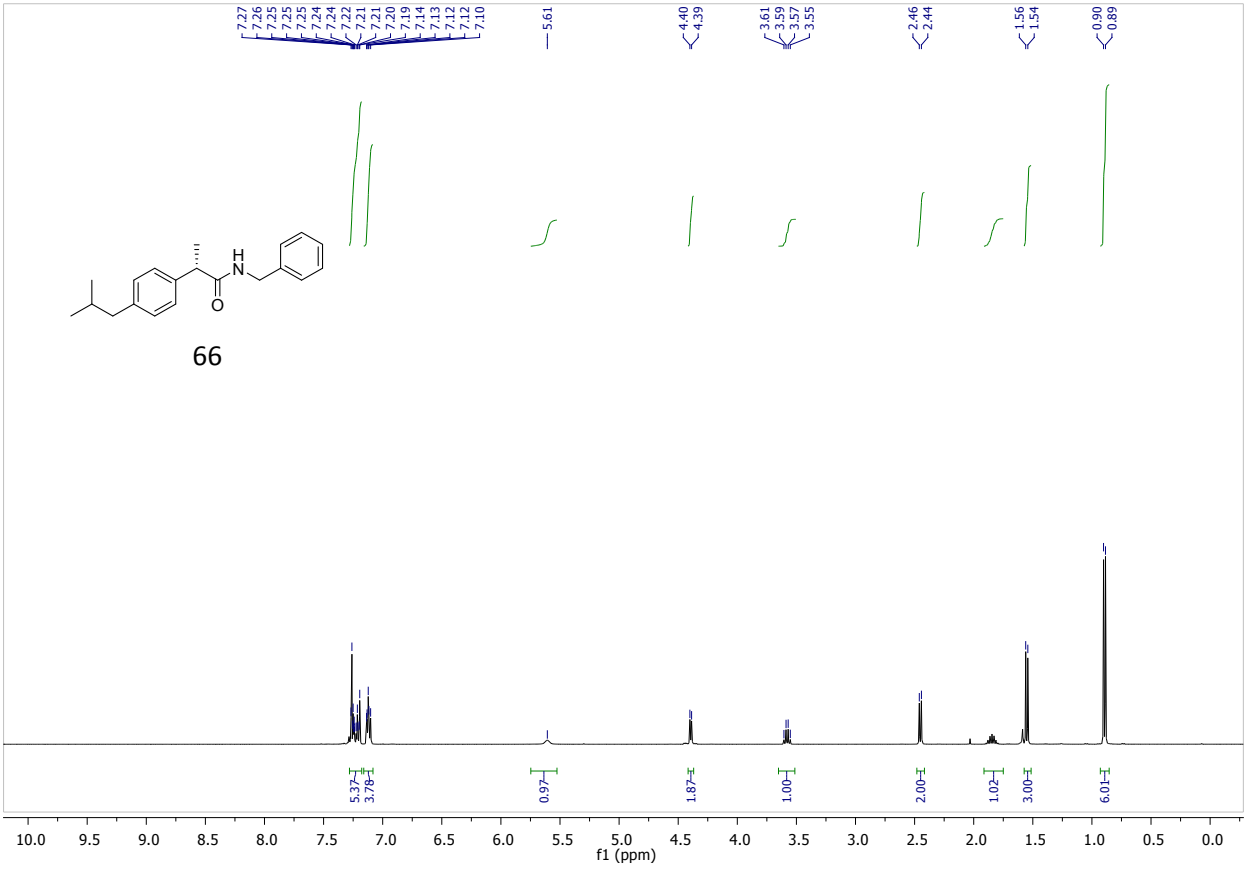


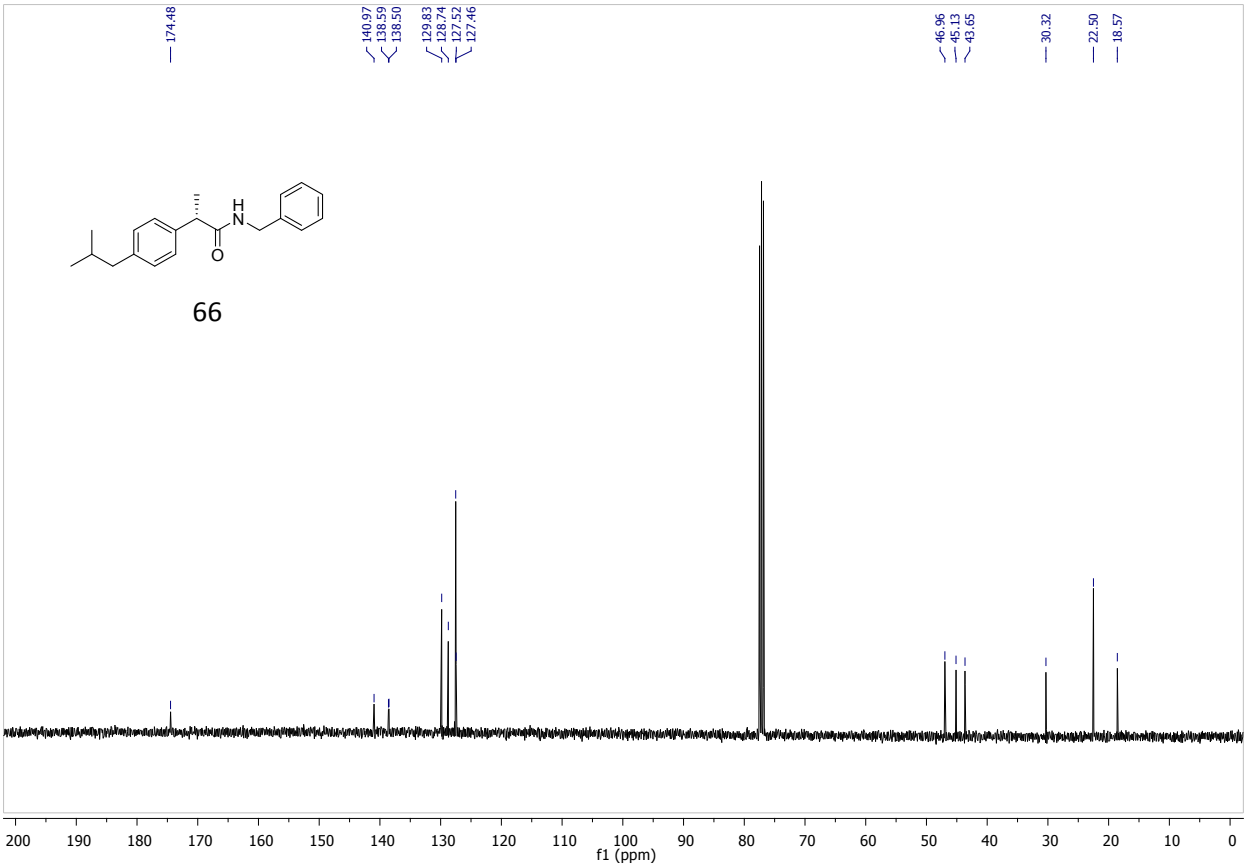
(*R*)-*N*-benzyl-2,2-dimethyl-1,3-dioxolane-4-carboxamide (65)



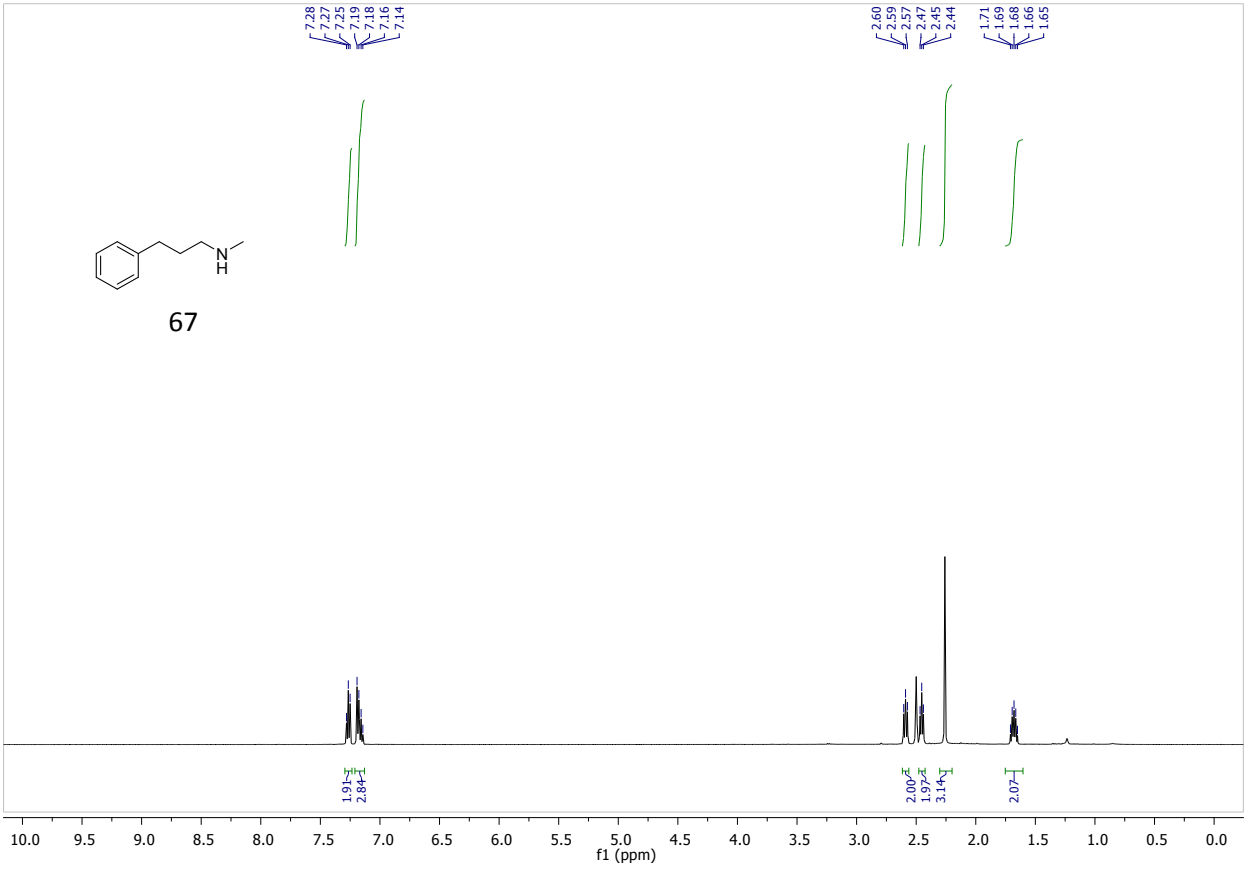


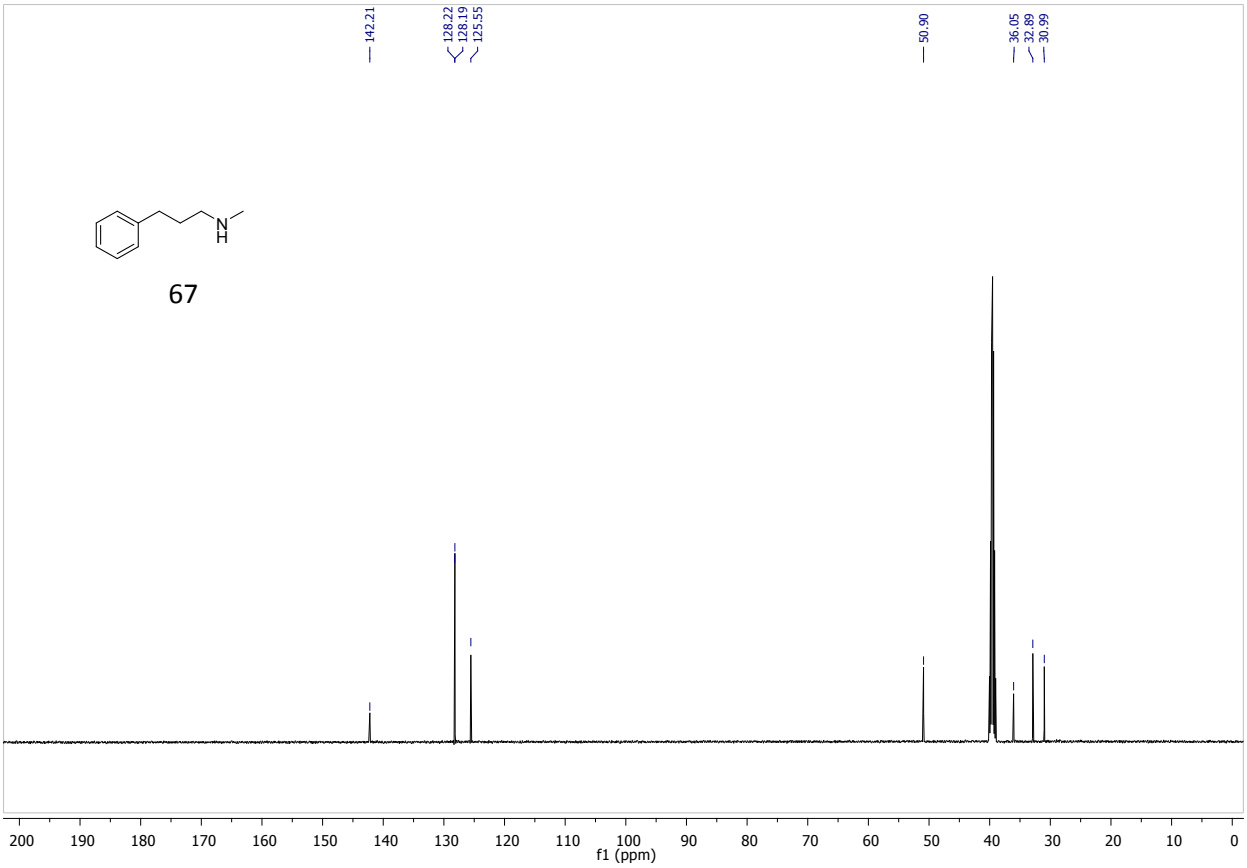
(*S*)-*N*-benzyl-2-(4-isobutylphenyl)propanamide (66)



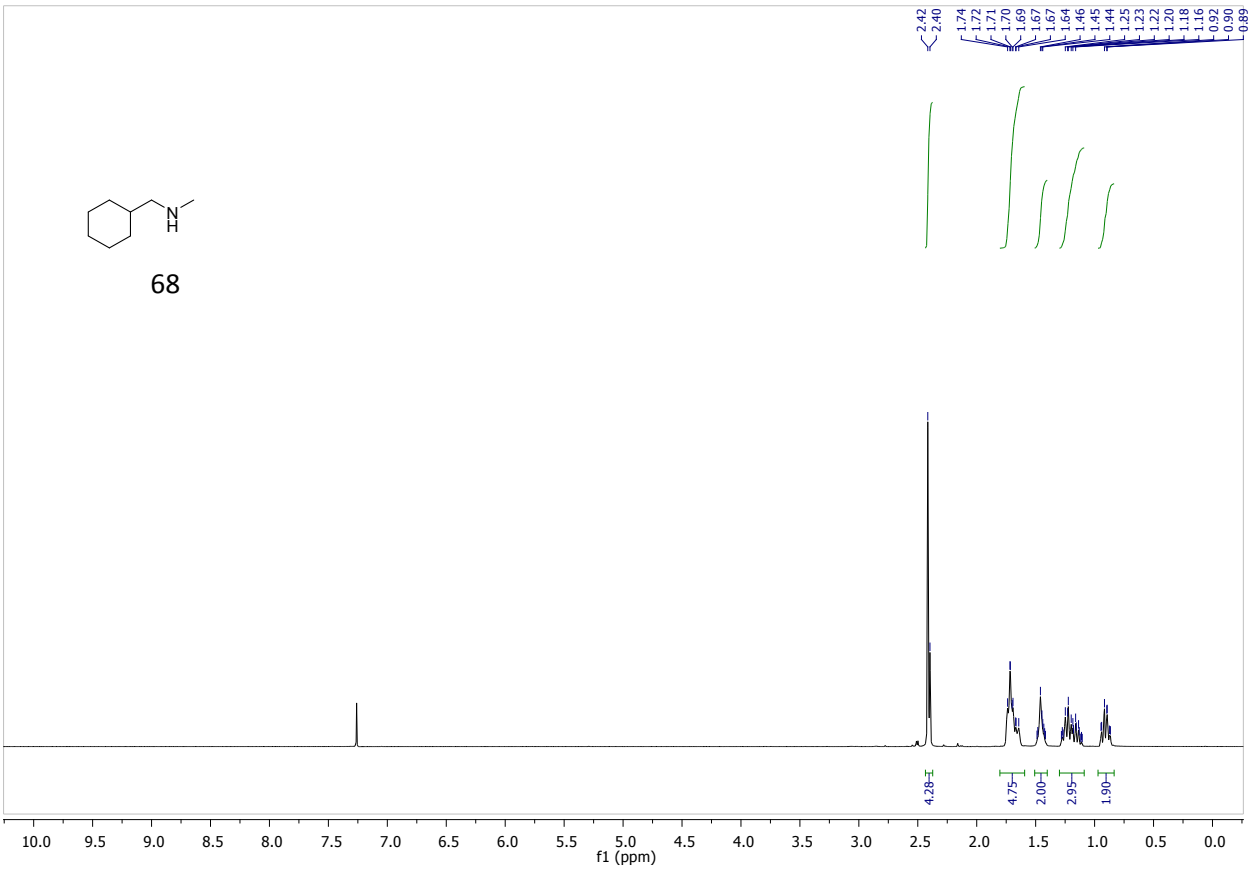


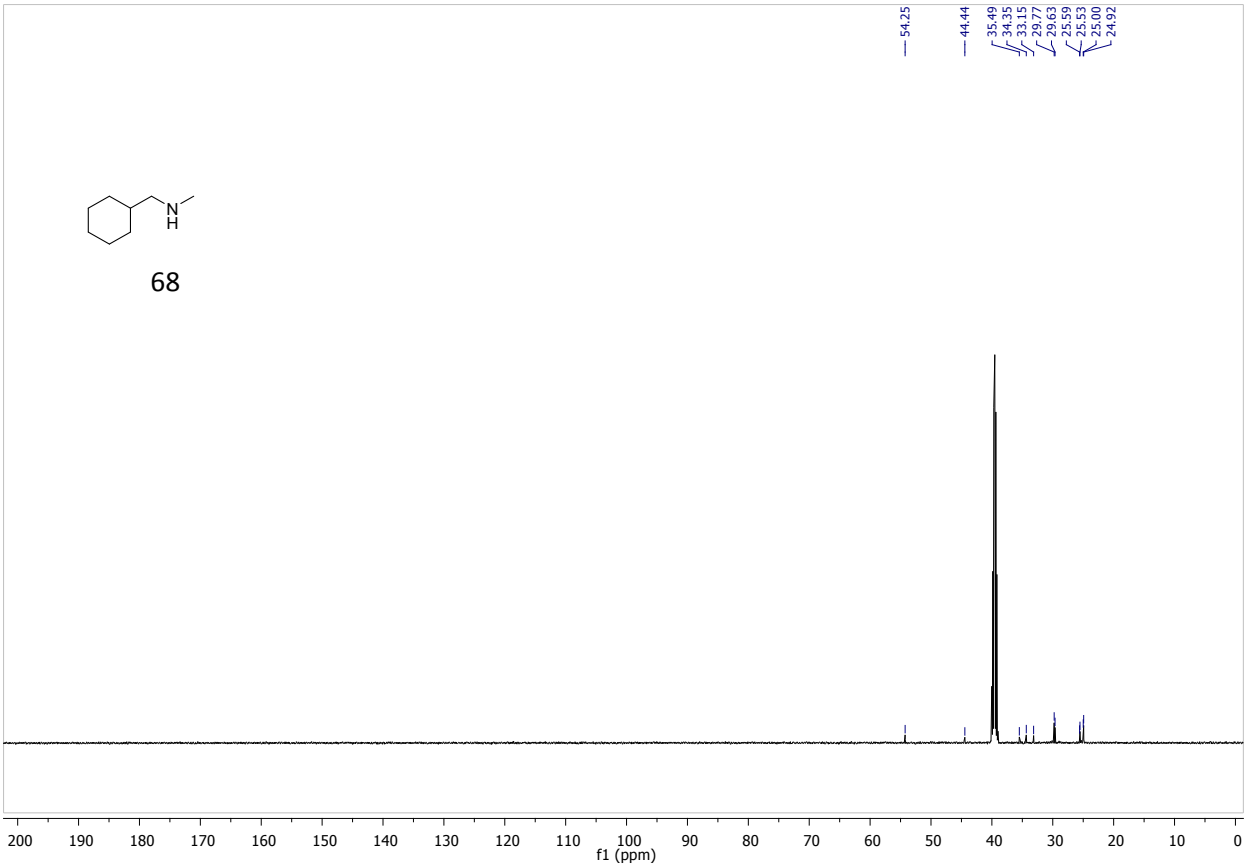
***N*-methyl-3-phenylpropan-1-amine (67)**



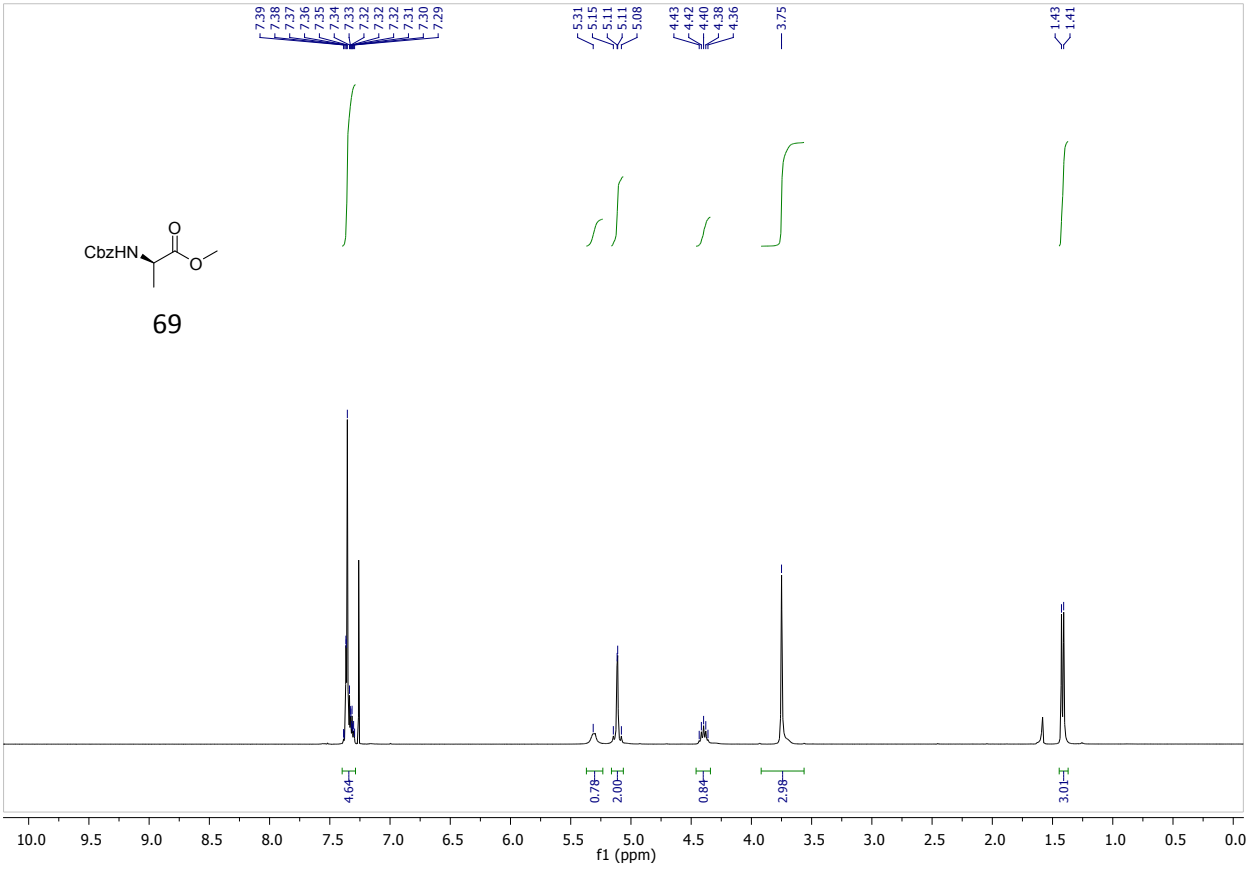


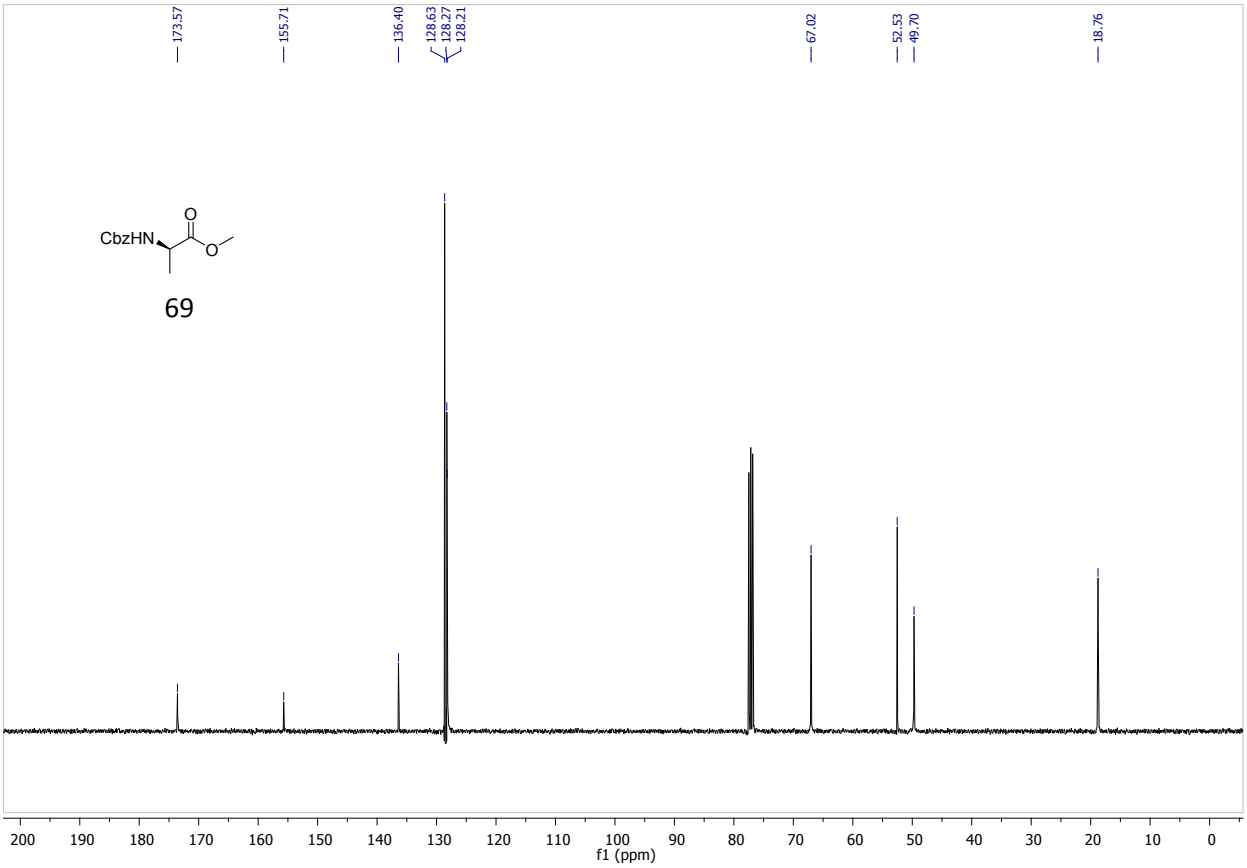
1-cyclohexyl-*N*-methylmethanamine (68)





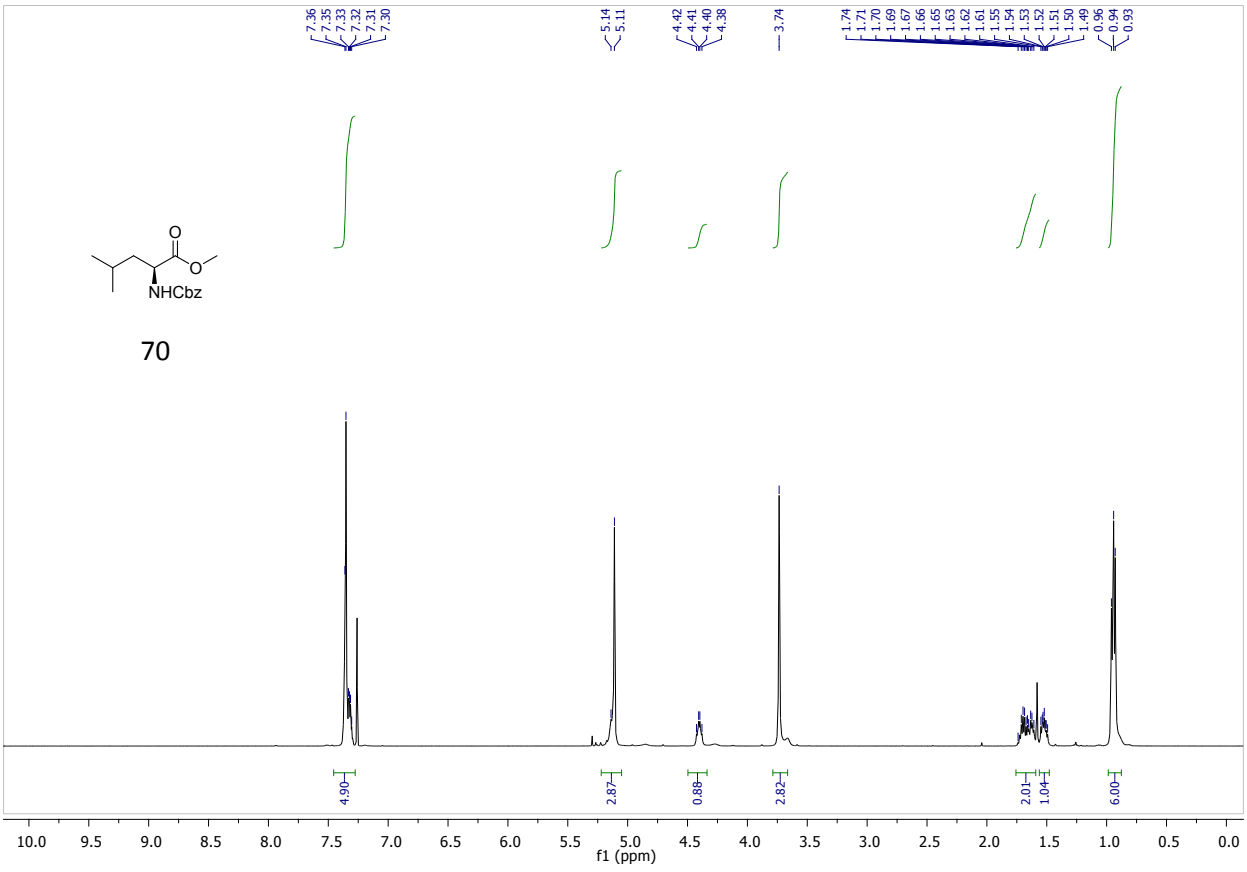
Methyl ((benzyloxy)carbonyl)-*D*-alaninate (69)



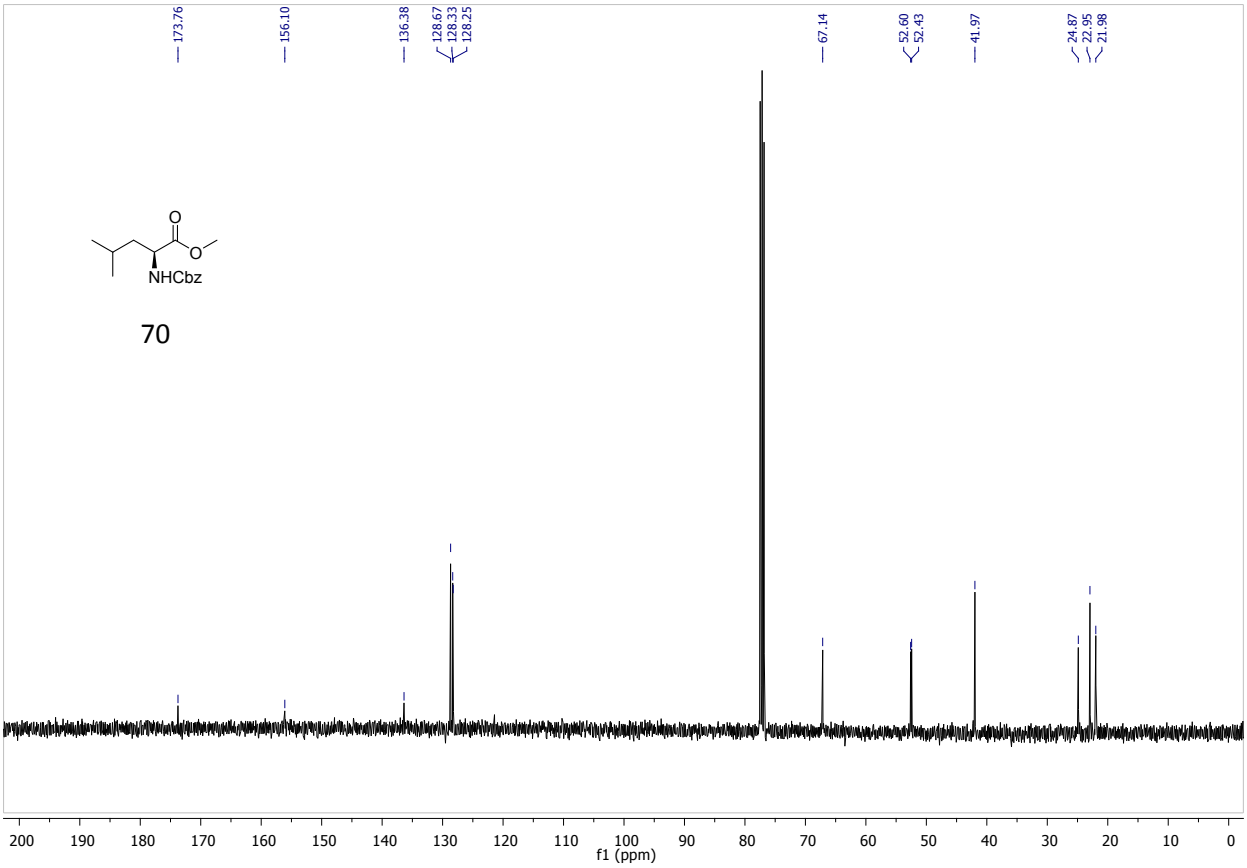


69

Methyl ((benzyloxy)carbonyl)-*L*-leucinate (70)

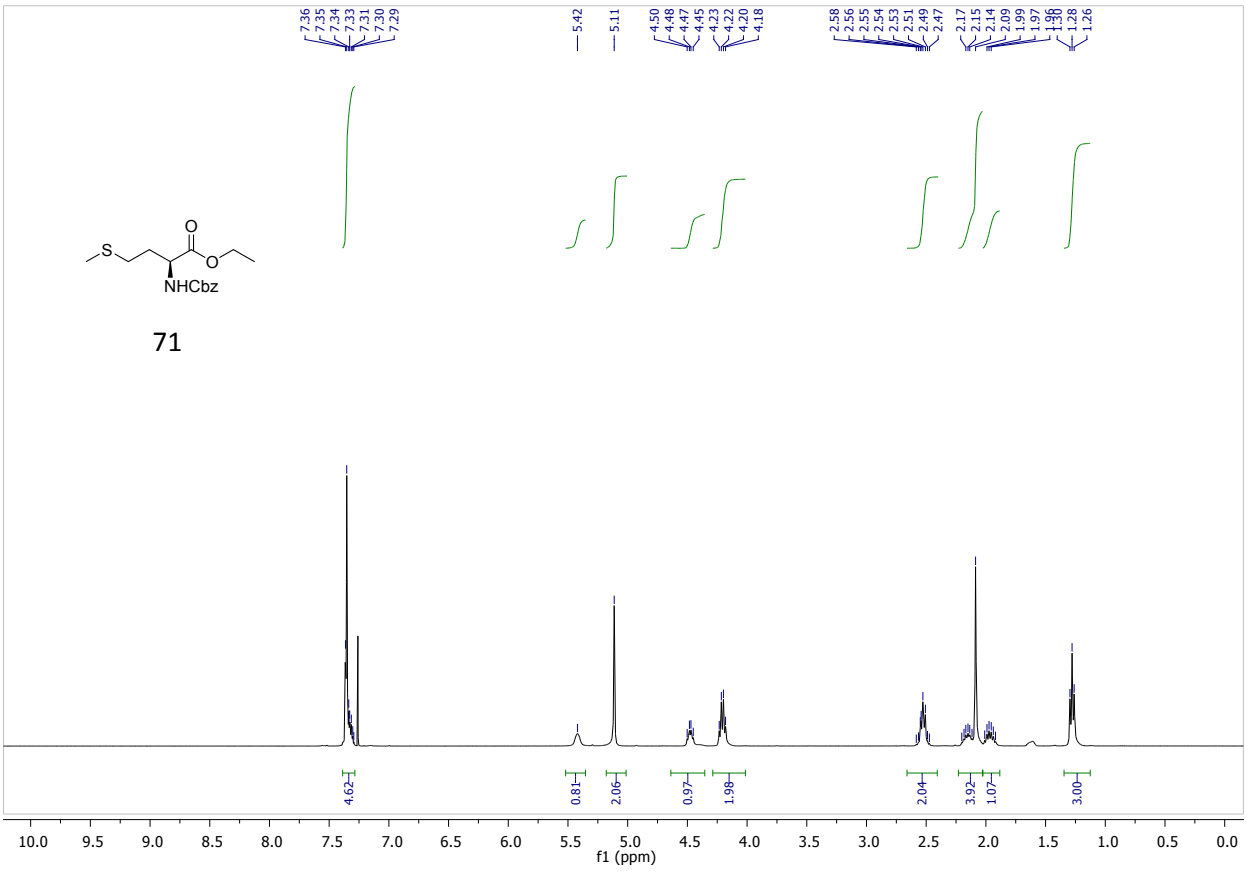


70

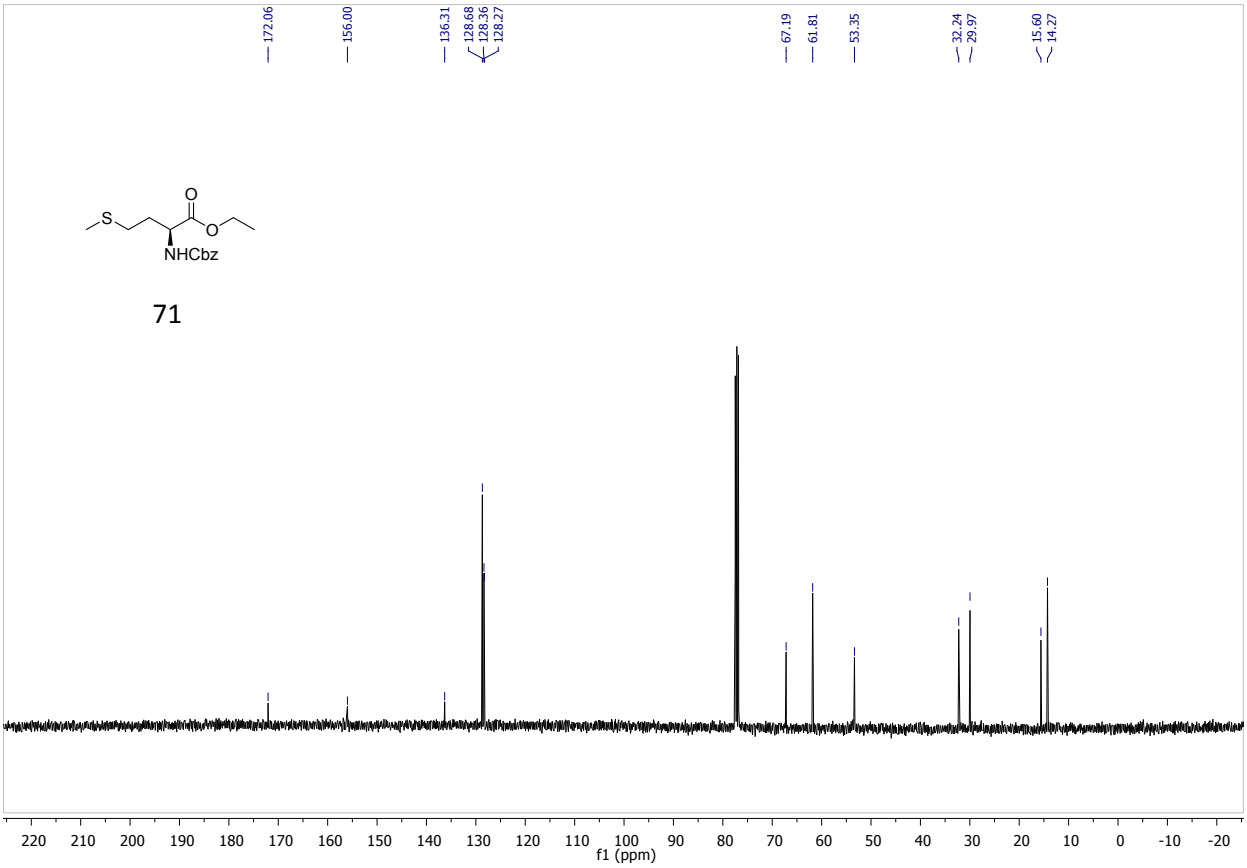


70

ethyl ((benzyloxy)carbonyl)-*L*-methioninate (71)

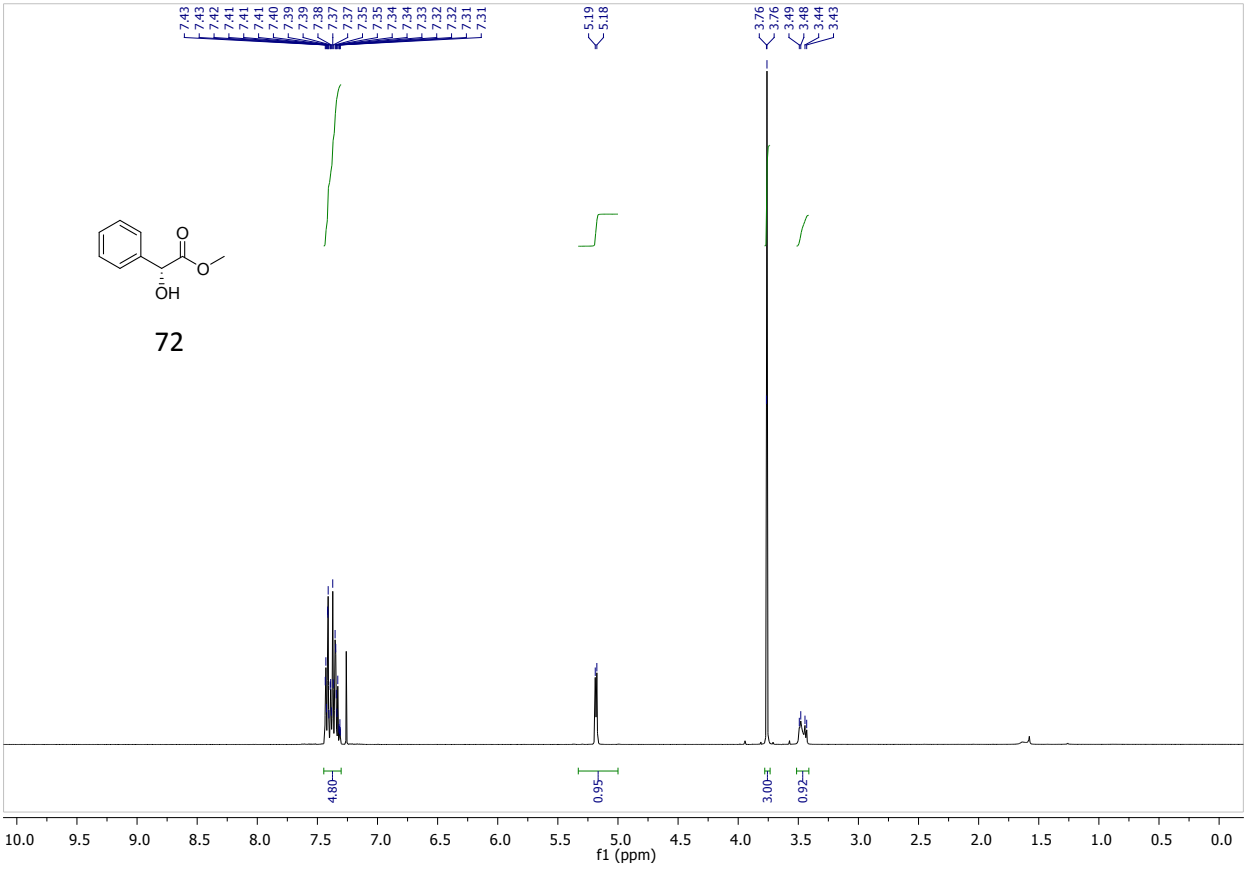


71

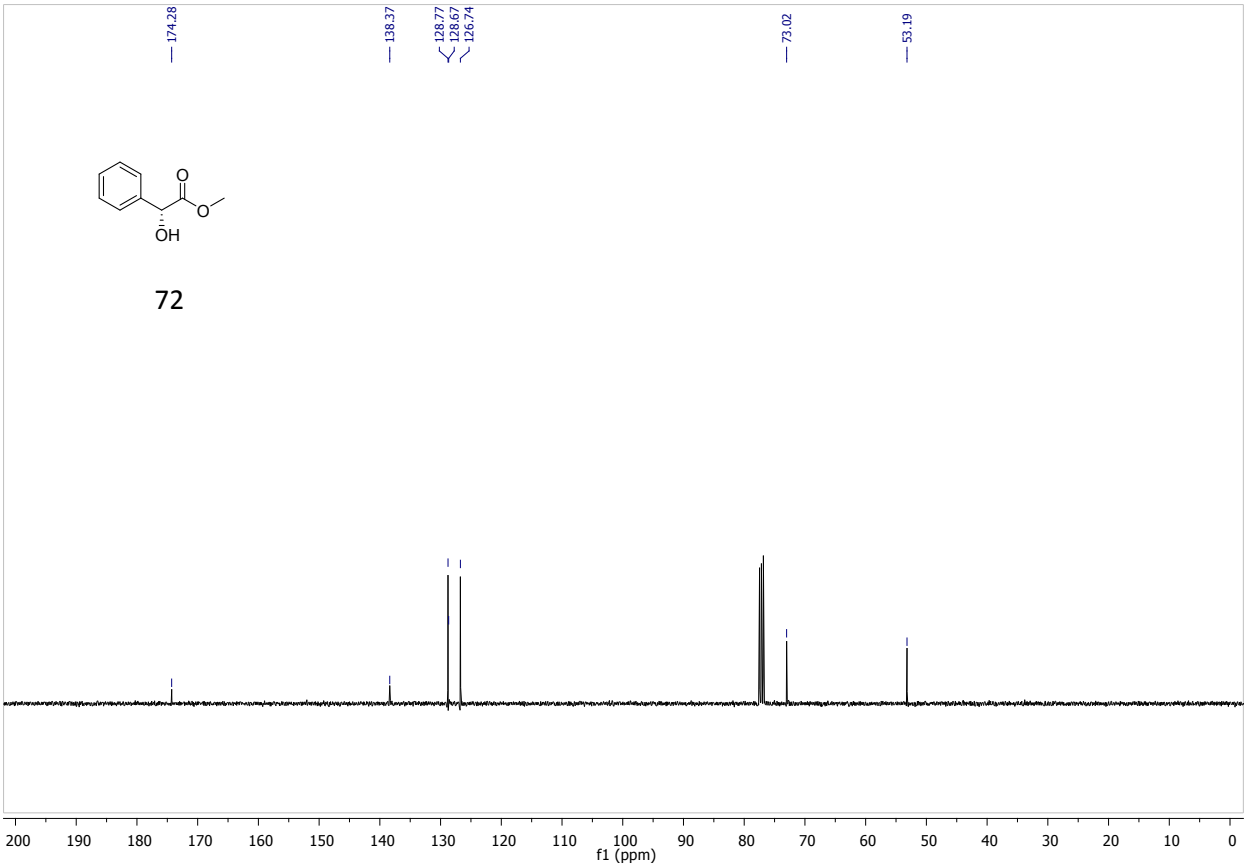


71

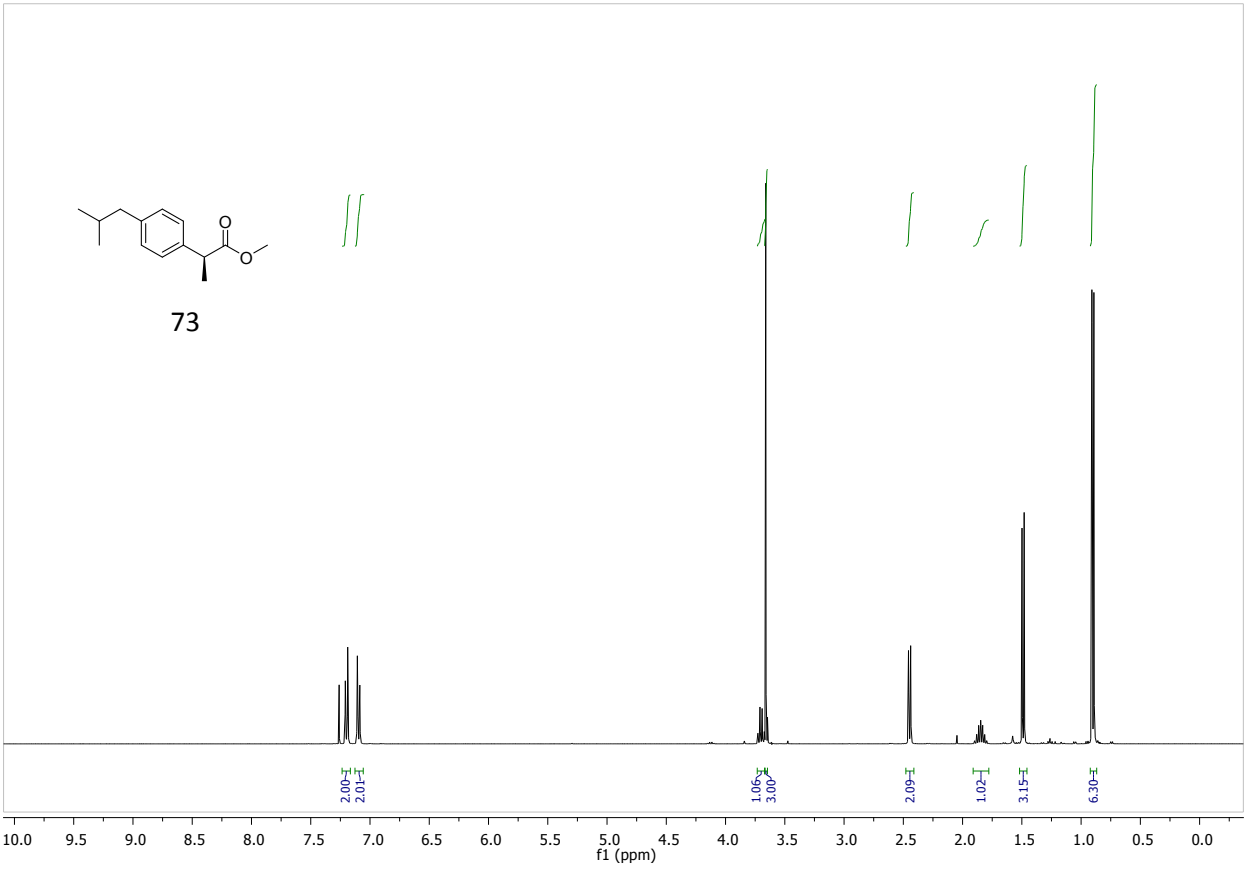
Methyl (*R*)-2-hydroxy-2-phenylacetate (72)

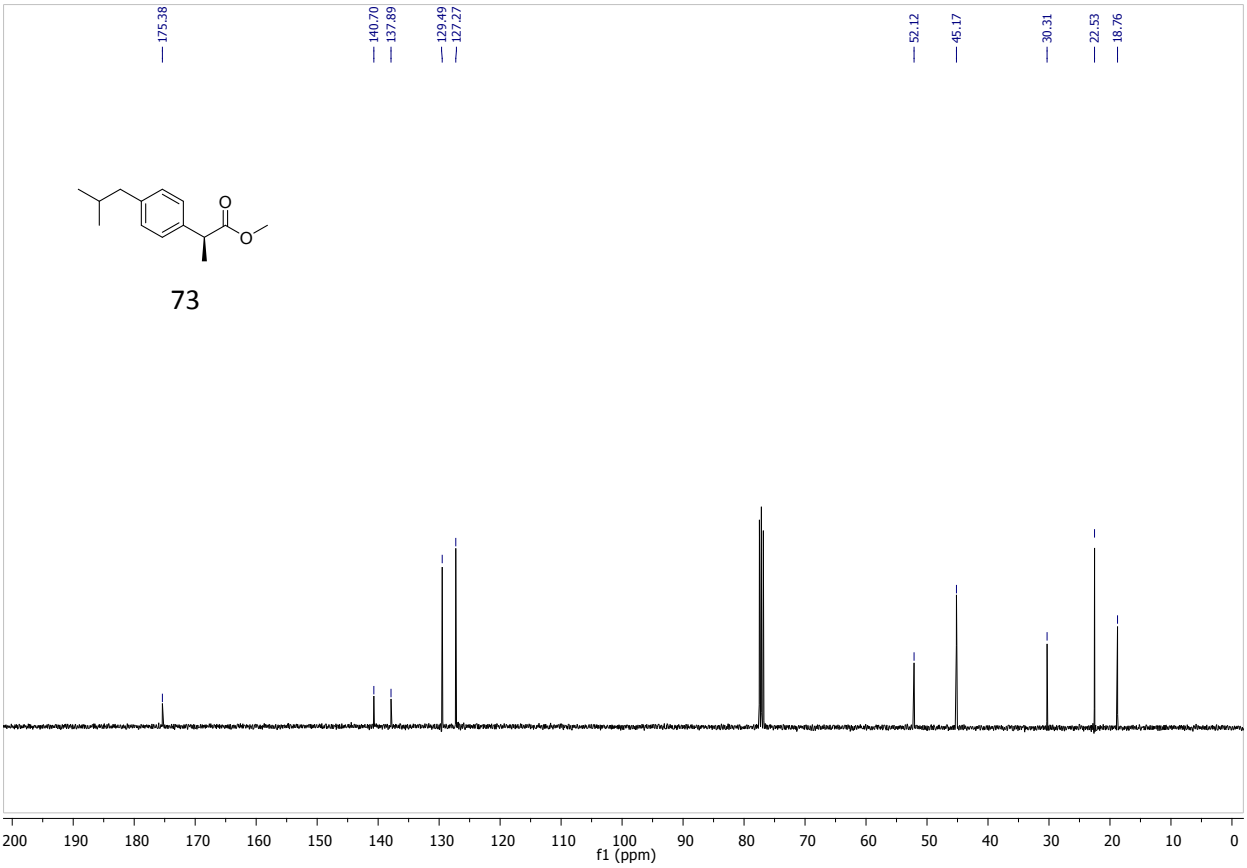


72



Methyl (*S*)-2-(4-isobutylphenyl)propanoate (73).

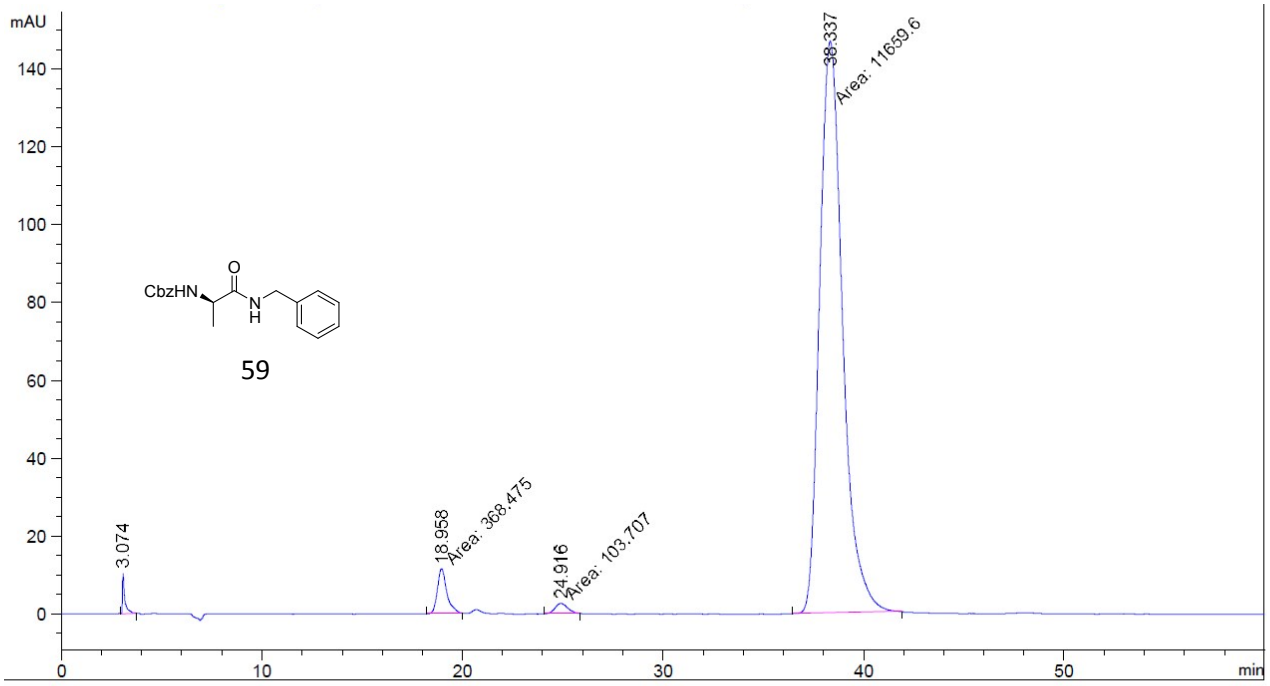


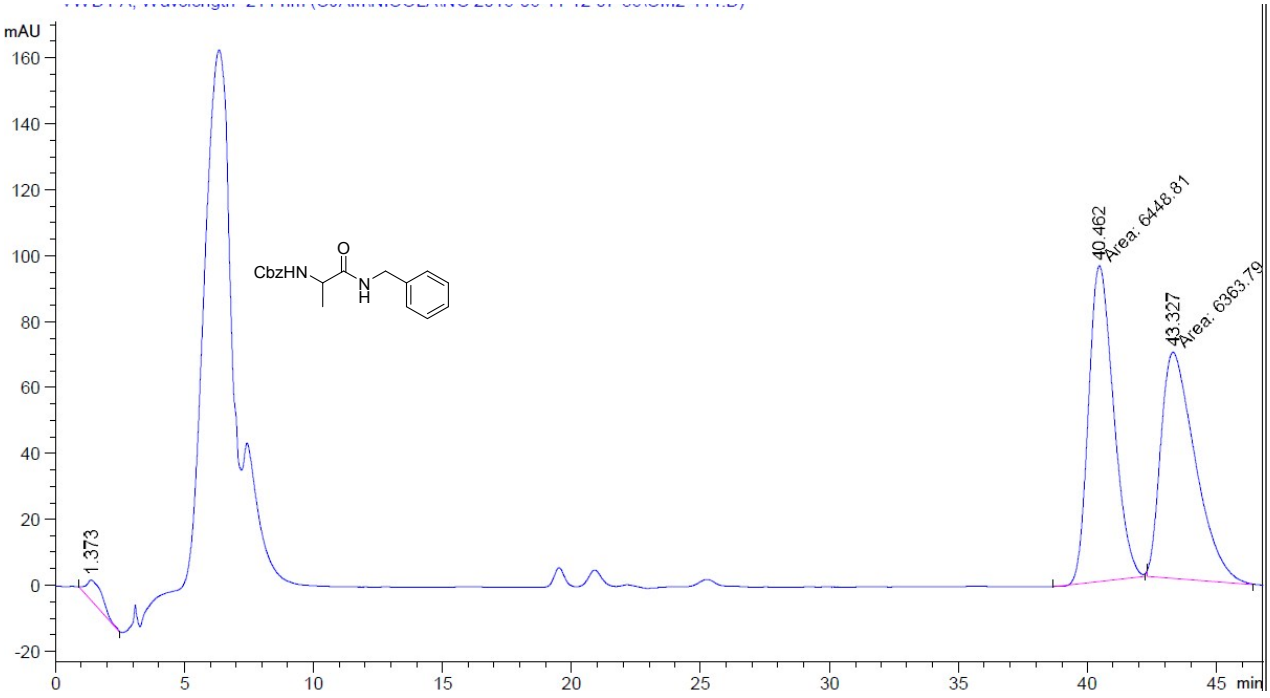

175.38
140.70
137.89
129.49
127.27
52.12
45.17
30.31
22.53
18.76
O
O
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

73

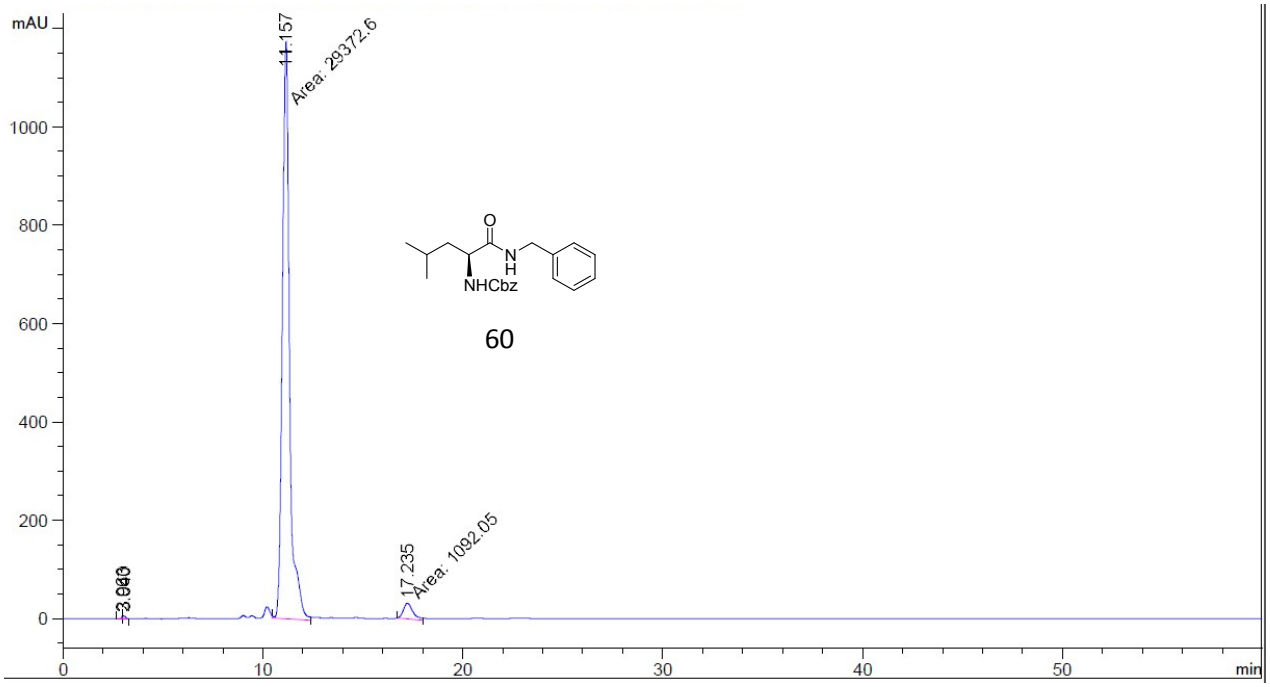
5. Chiral HPLC Spectra

benzyl (*R*)-(1-(benzylamino)-1-oxopropan-2-yl)carbamate (59).

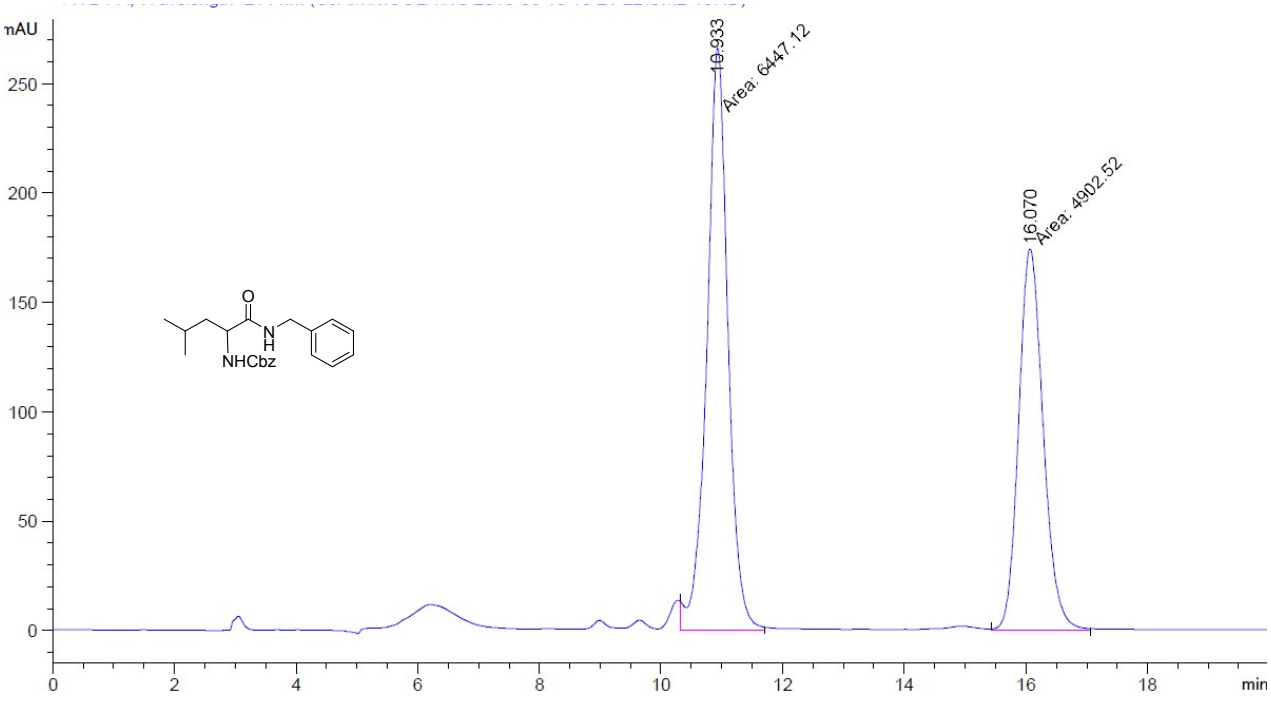




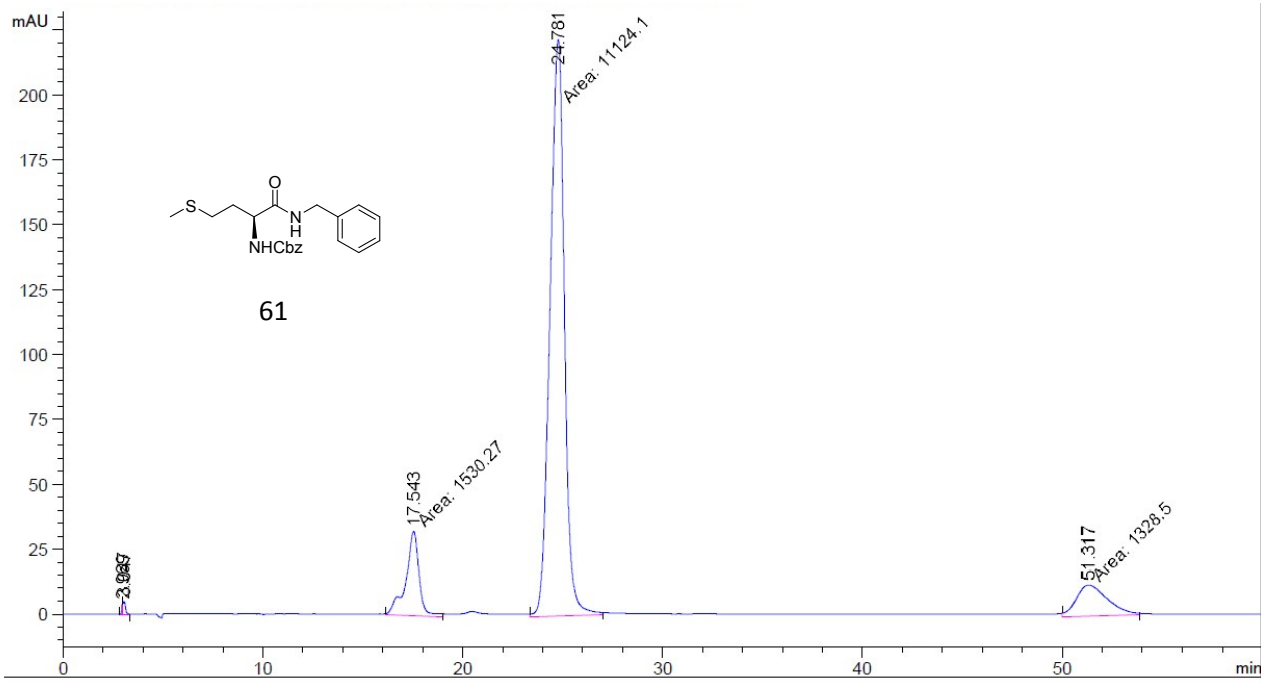
benzyl (*S*)-(1-(benzylamino)-4-methyl-1-oxopentan-2-yl)carbamate (60).

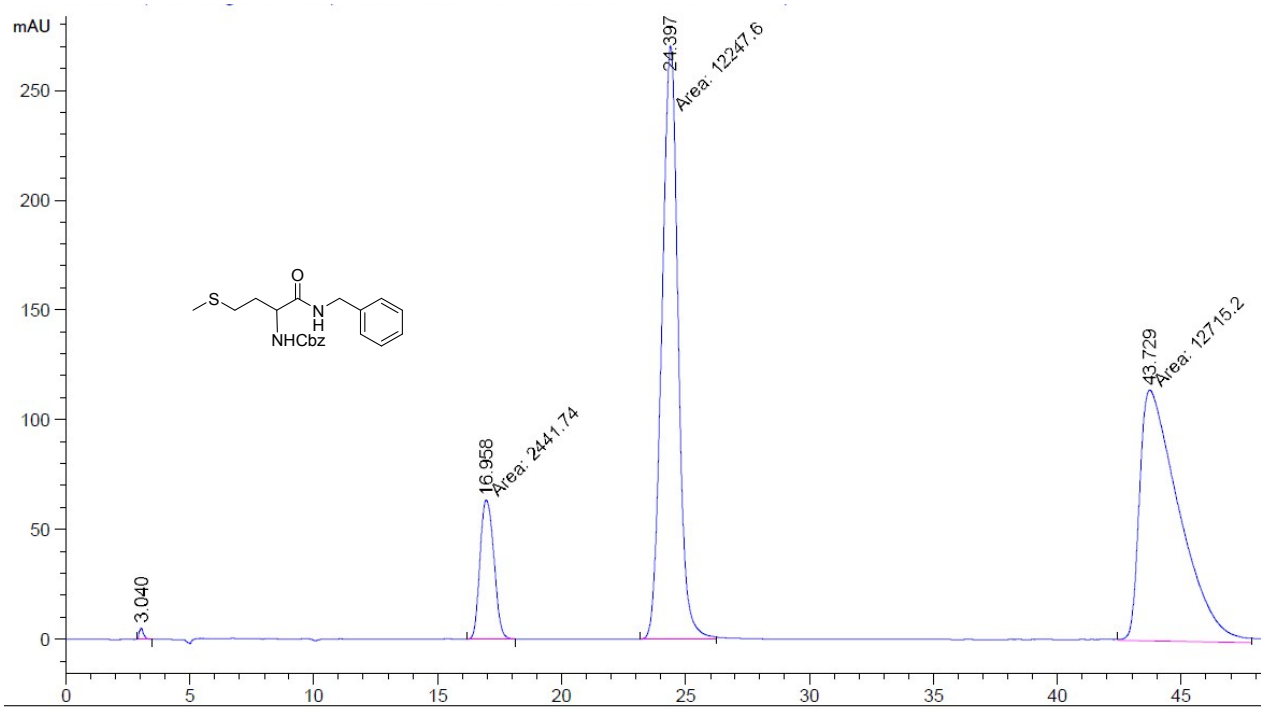


60

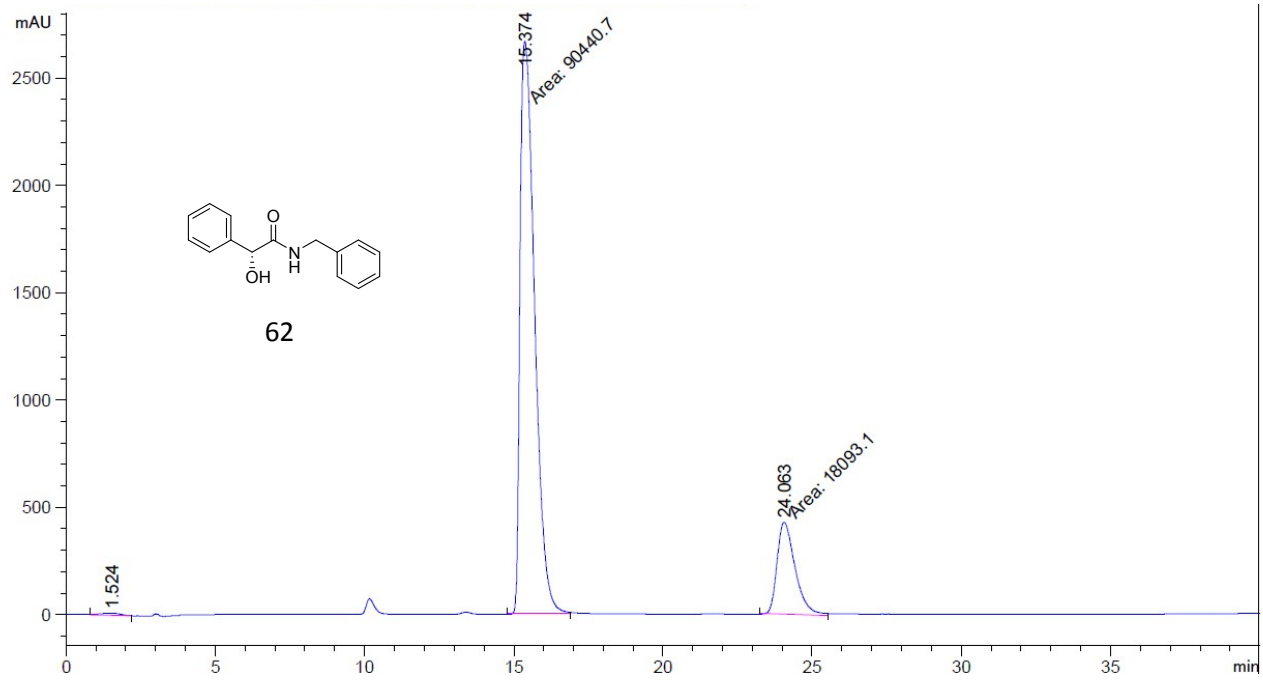


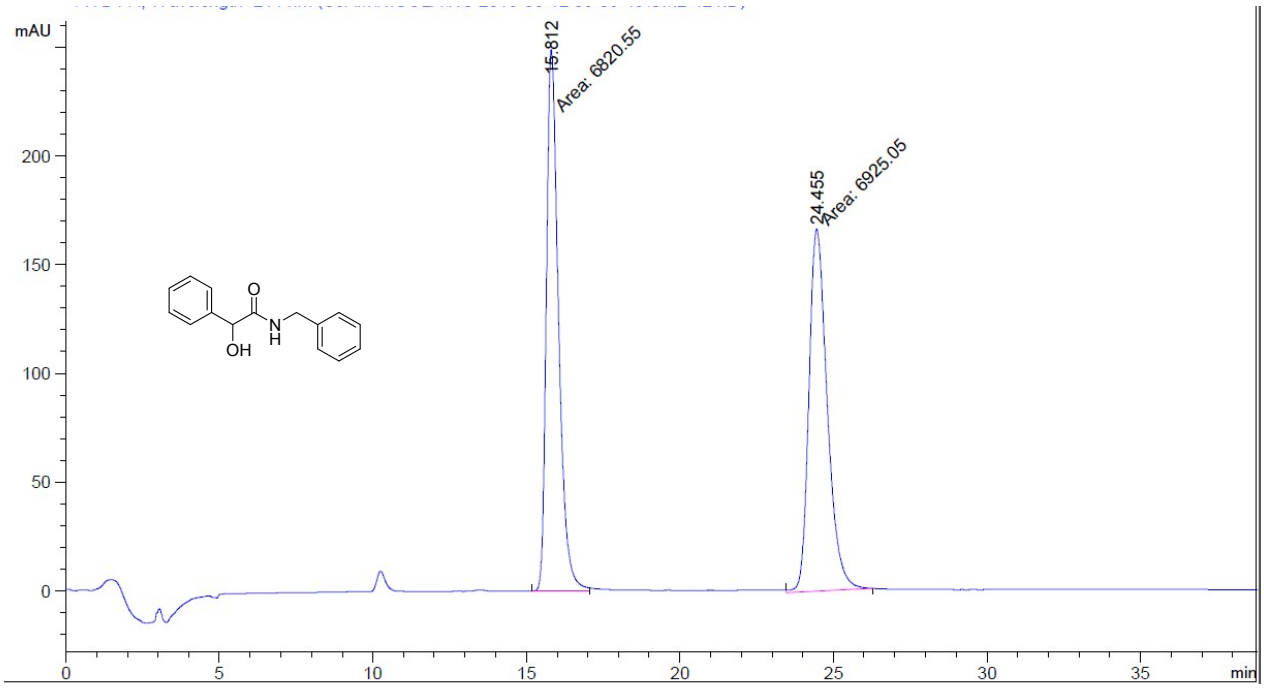
benzyl (*S*)-(1-(benzylamino)-4-(methylthio)-1-oxobutan-2-yl)carbamate (61).



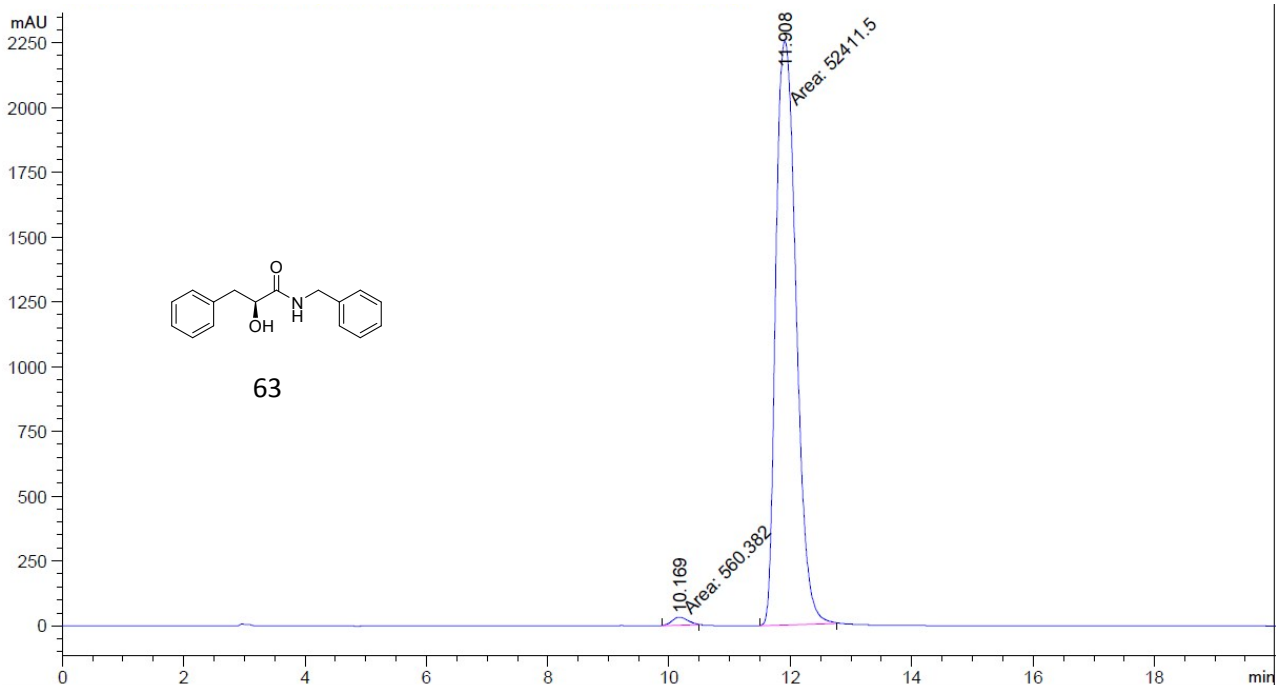


(*R*)-*N*-benzyl-2-hydroxy-2-phenylacetamide (62).

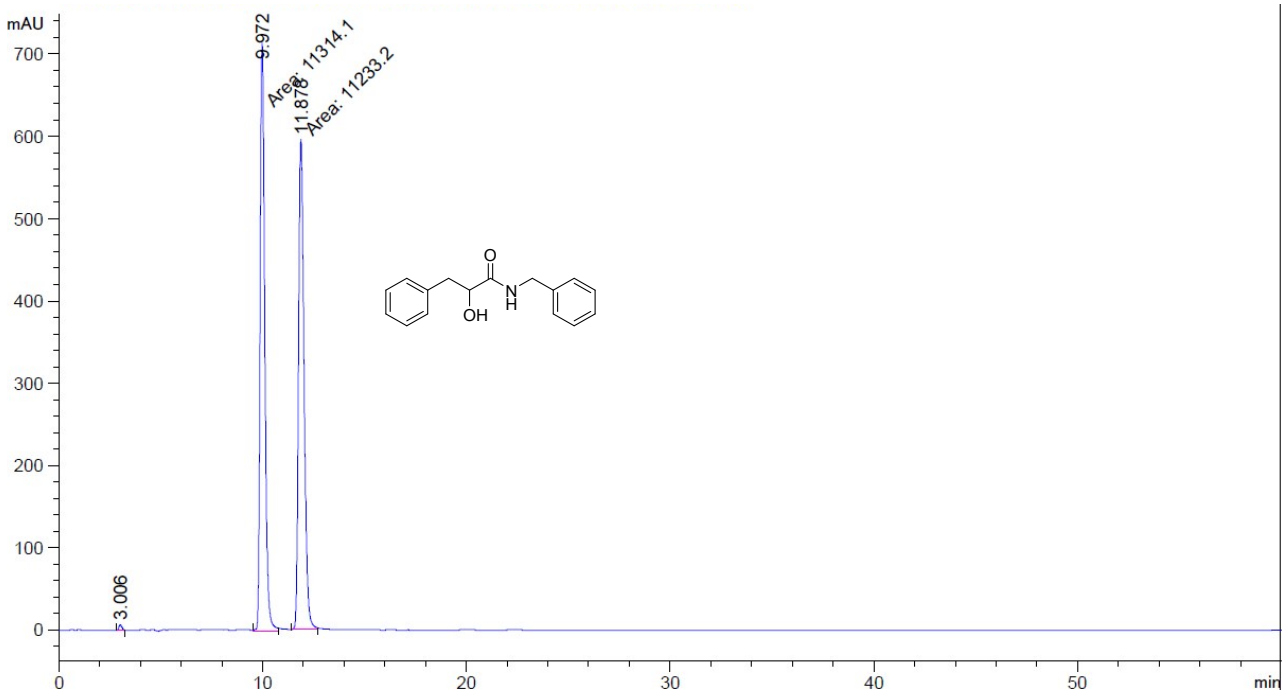




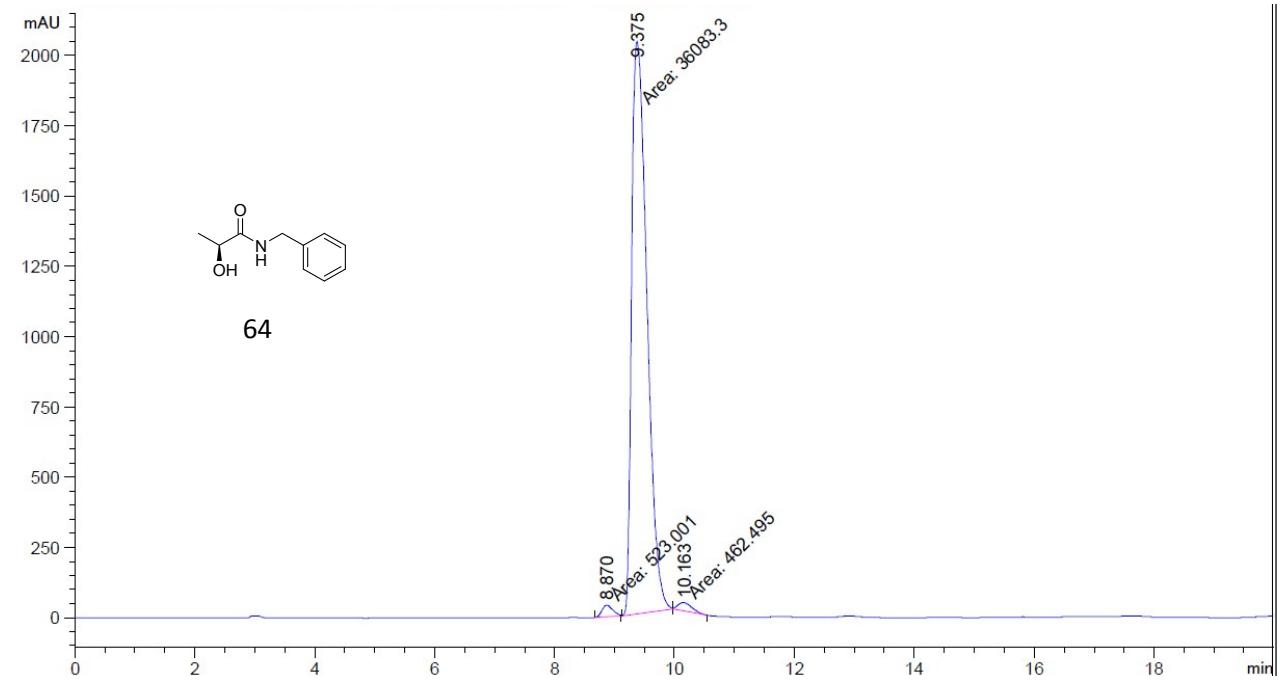
(*S*)-*N*-benzyl-2-hydroxy-3-phenylpropanamide (63).



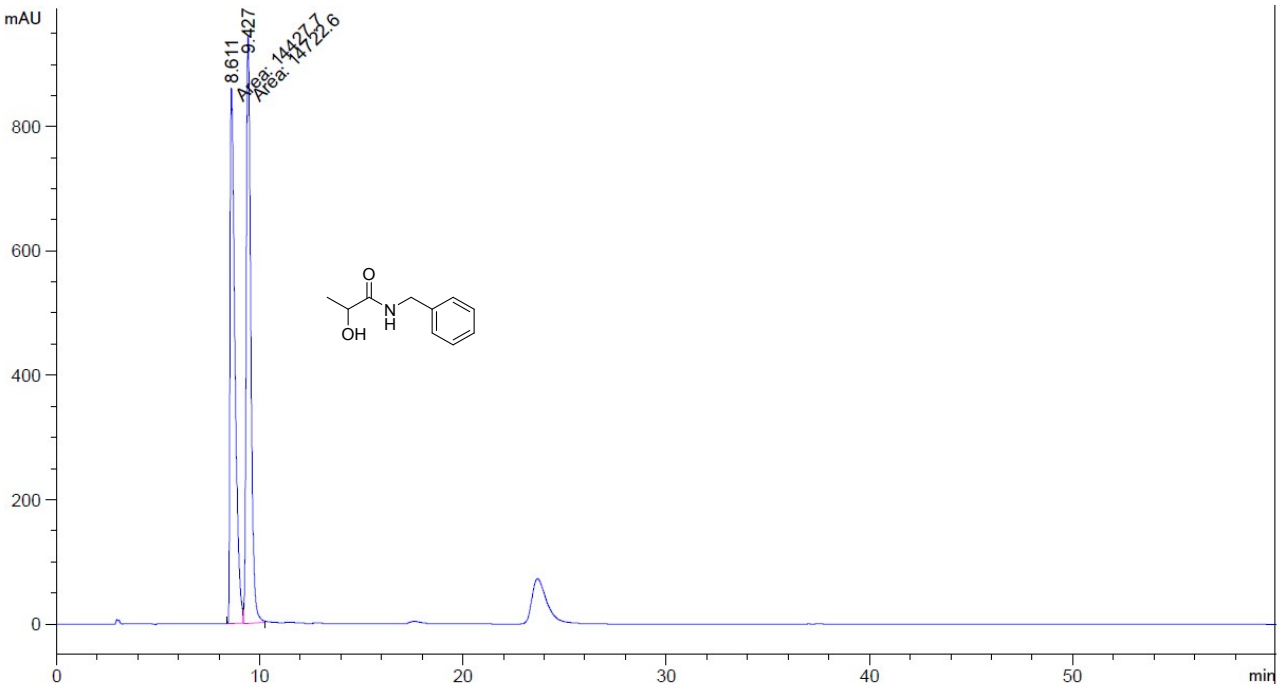
63



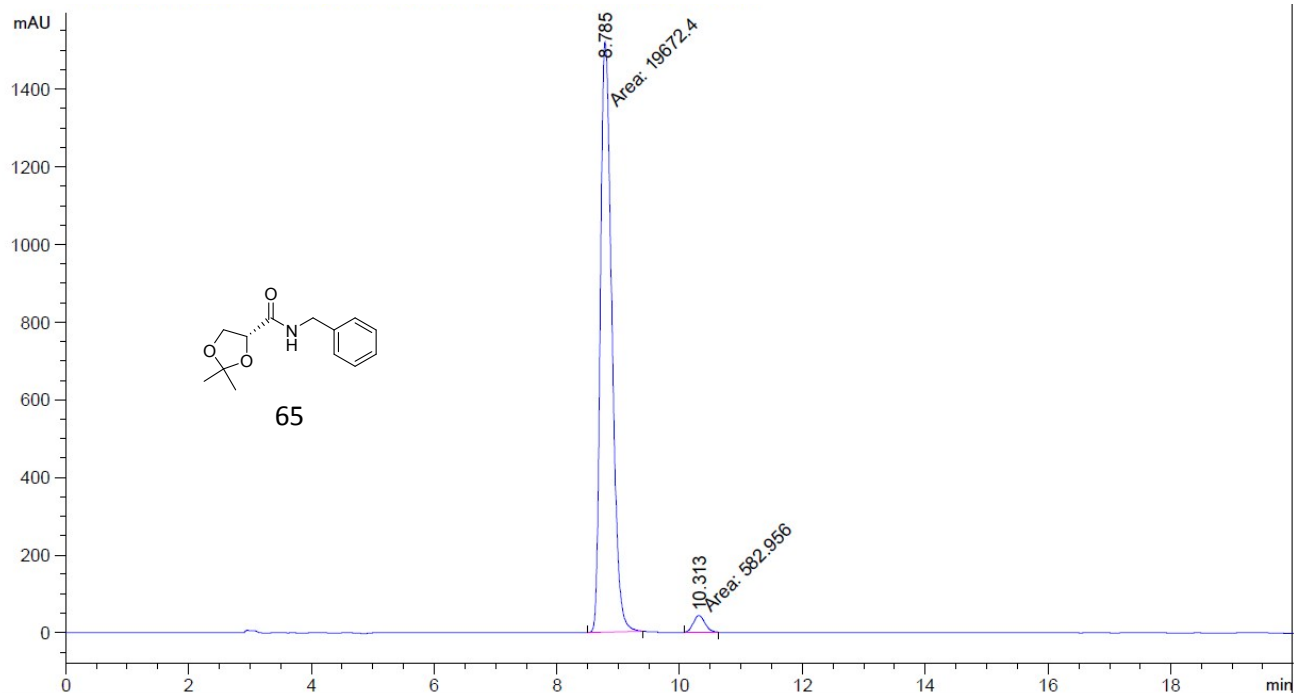
(*S*)-*N*-benzyl-2-hydroxypropanamide (64).



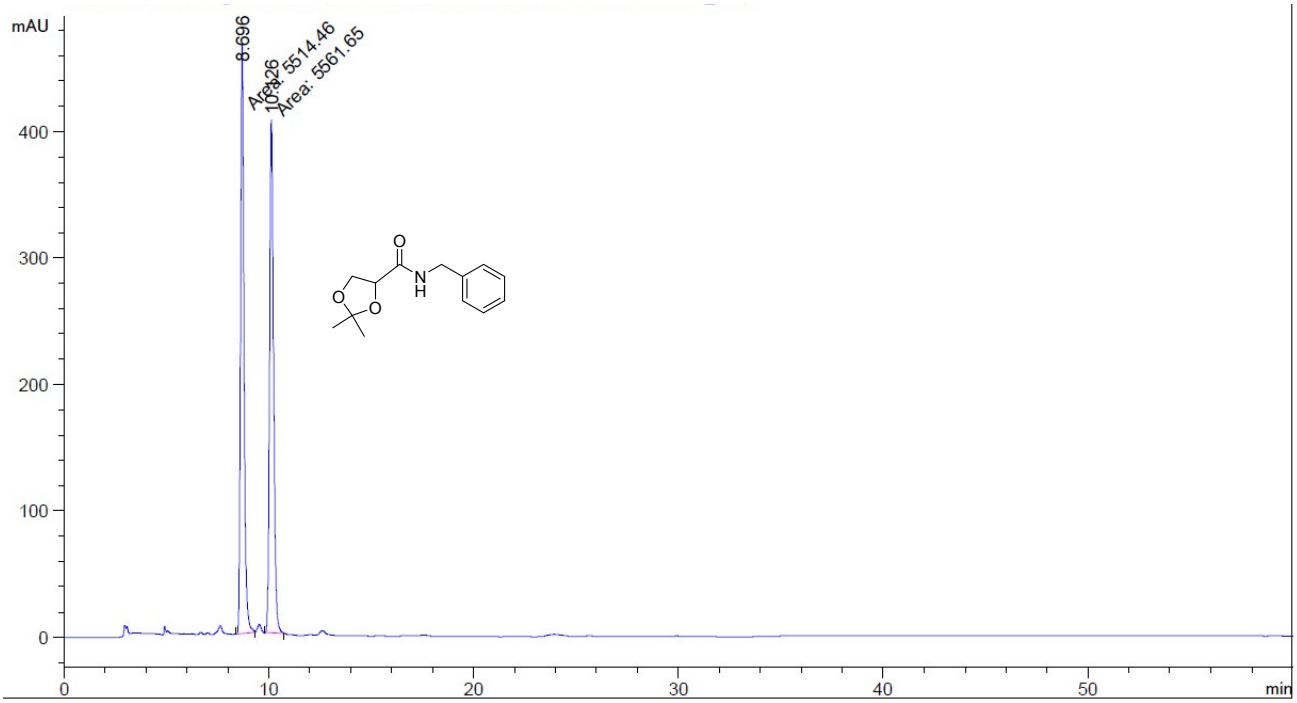
64



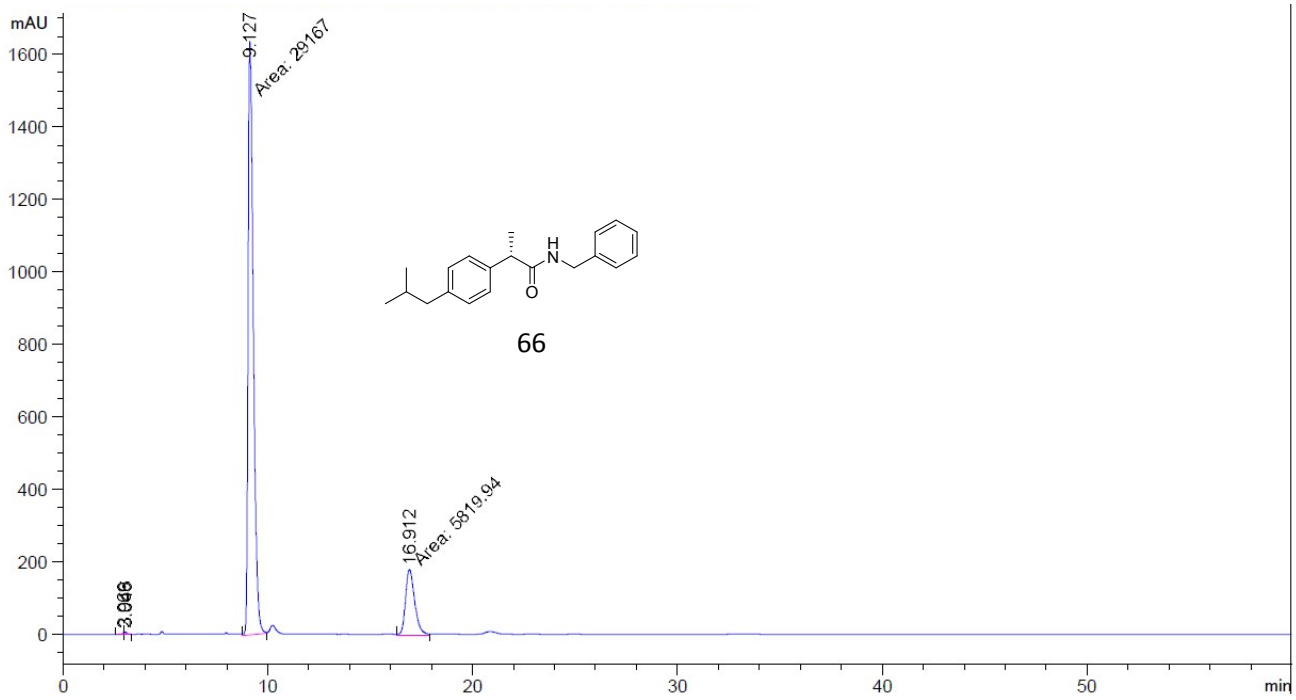
(*R*)-*N*-benzyl-2,2-dimethyl-1,3-dioxolane-4-carboxamide (65).



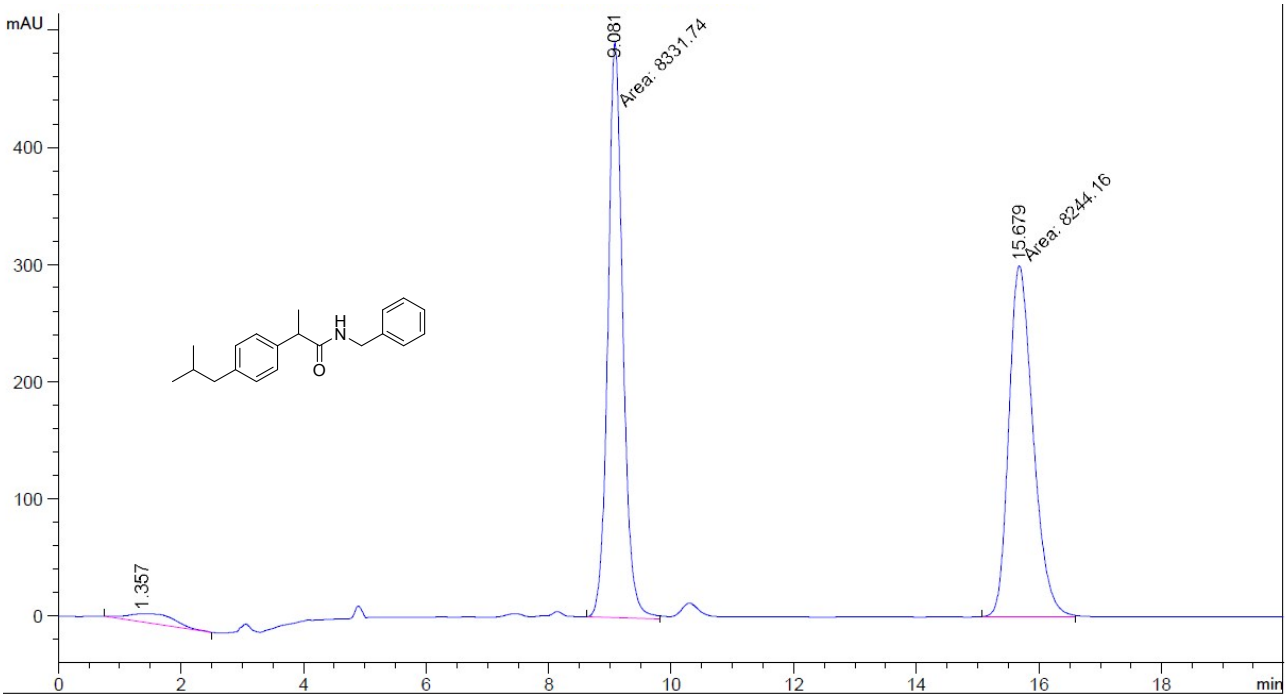
65



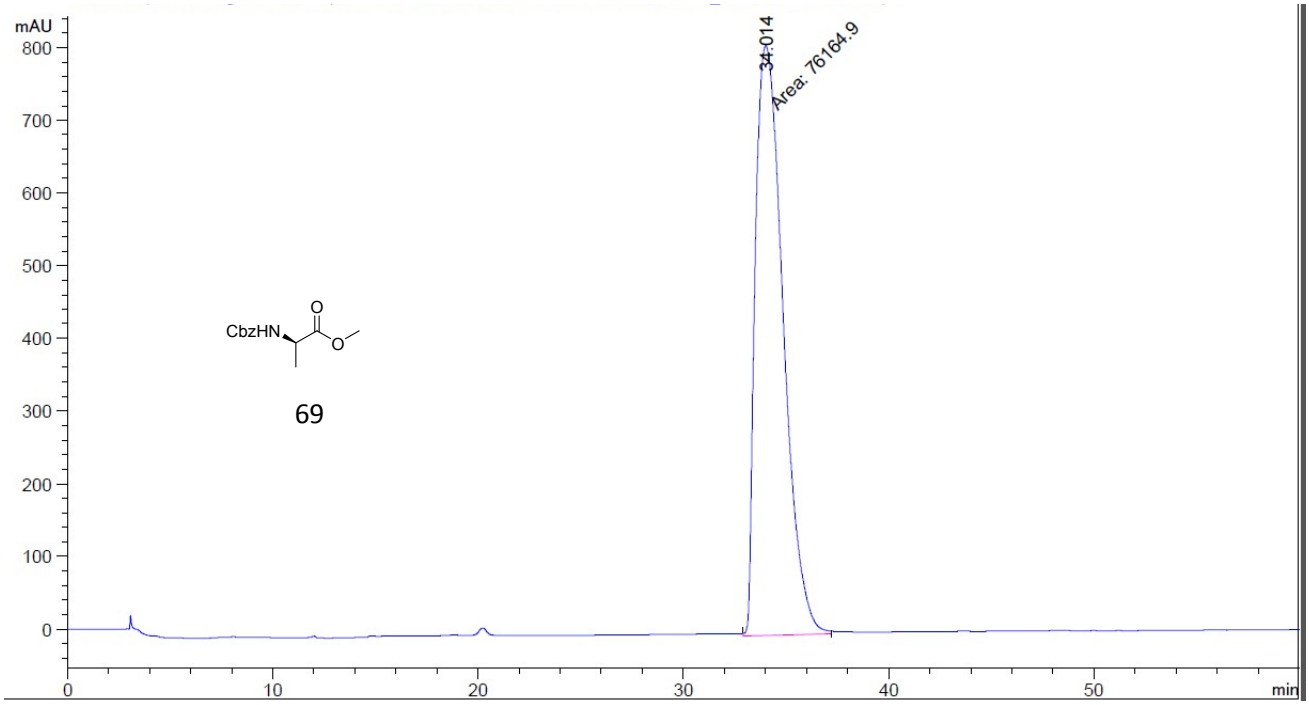
(*S*)-*N*-benzyl-2-(4-isobutylphenyl)propanamide (66).



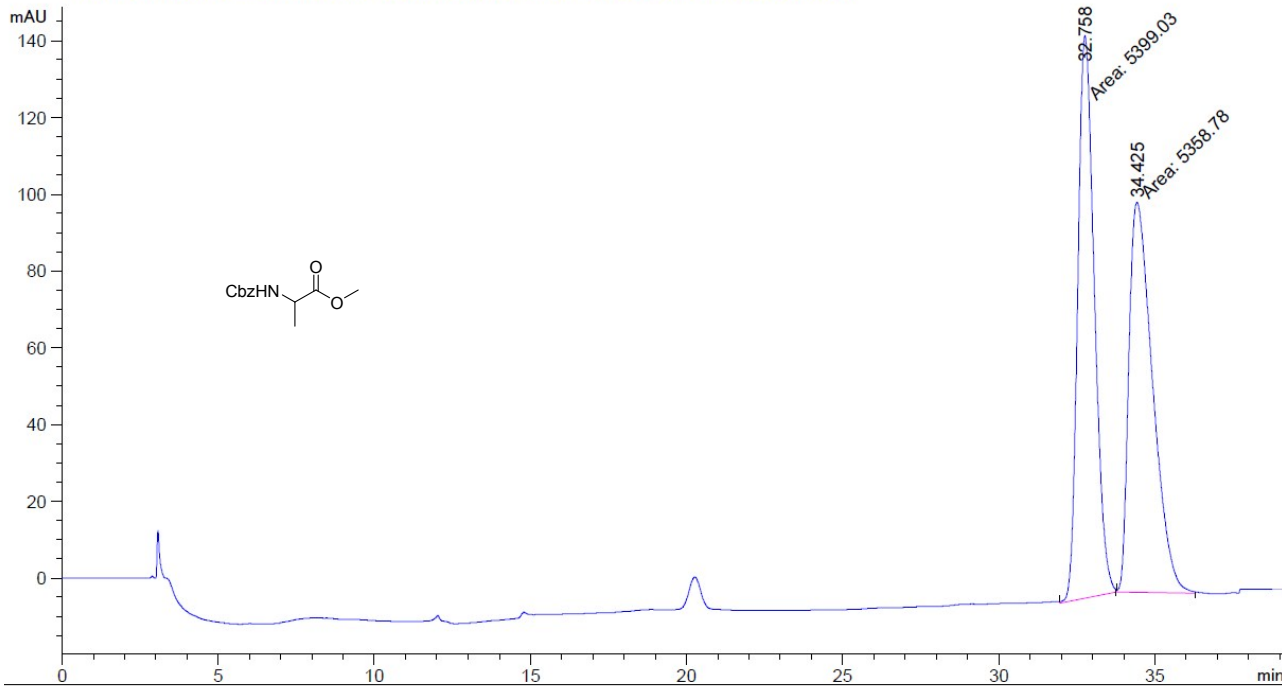
66



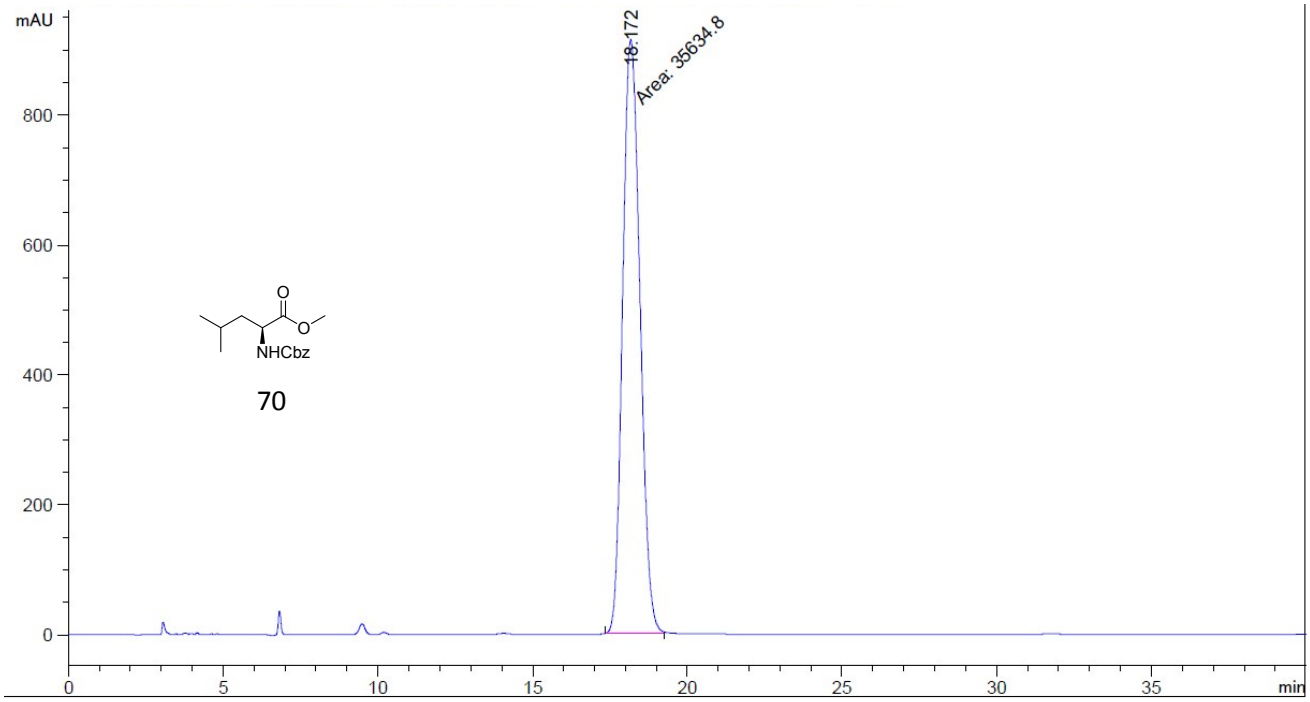
Methyl ((benzyloxy)carbonyl)-*D*-alaninate (69).

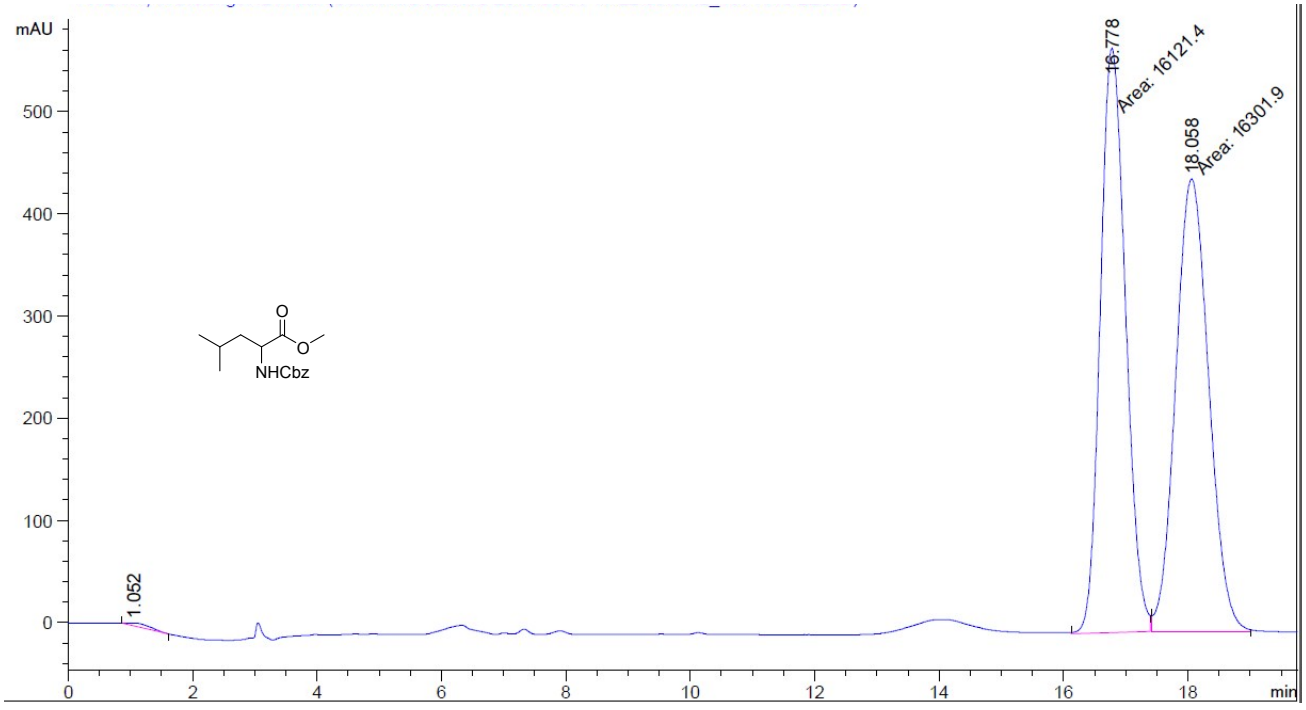


69

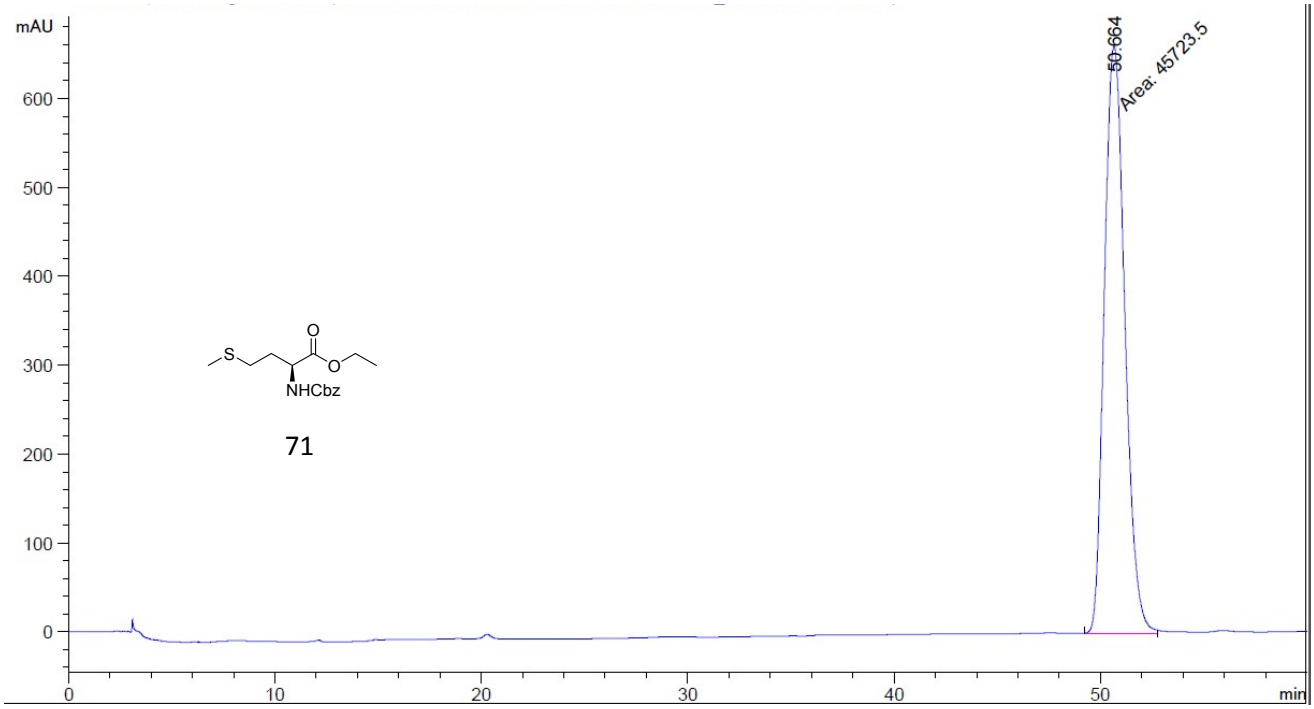


Methyl ((benzyloxy)carbonyl)-*L*-leucinate (70).

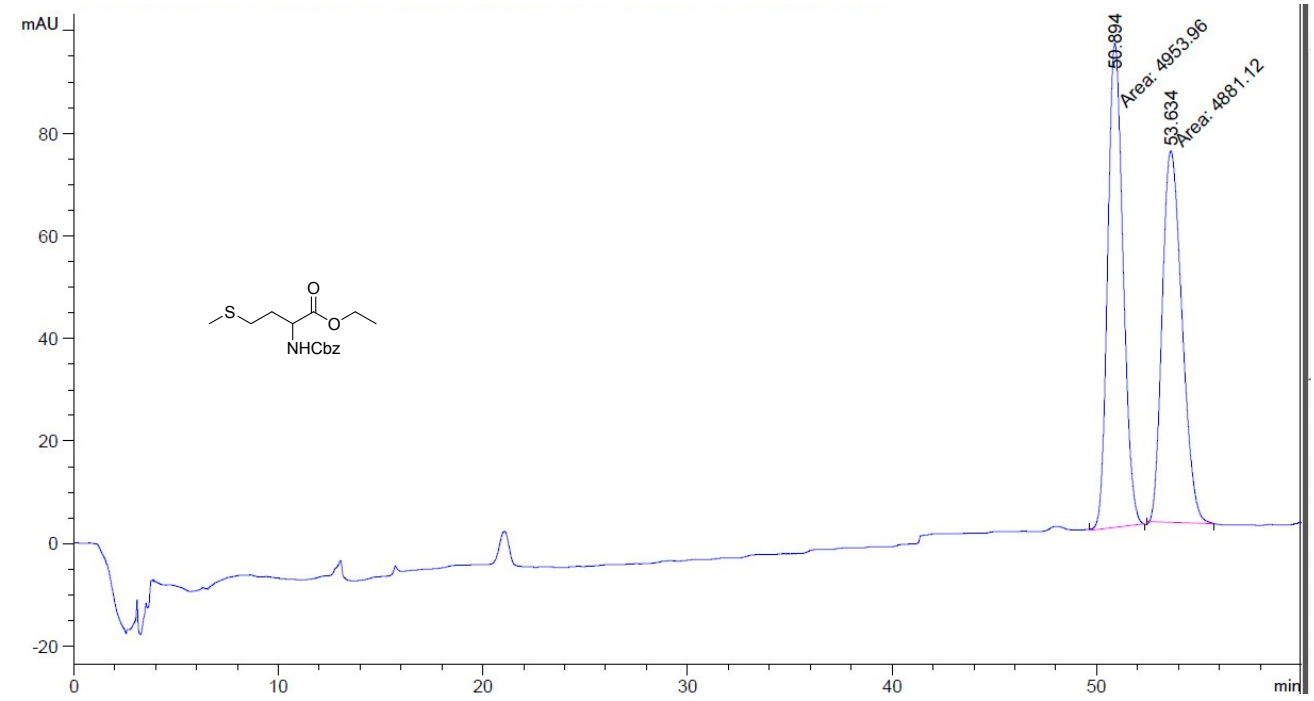




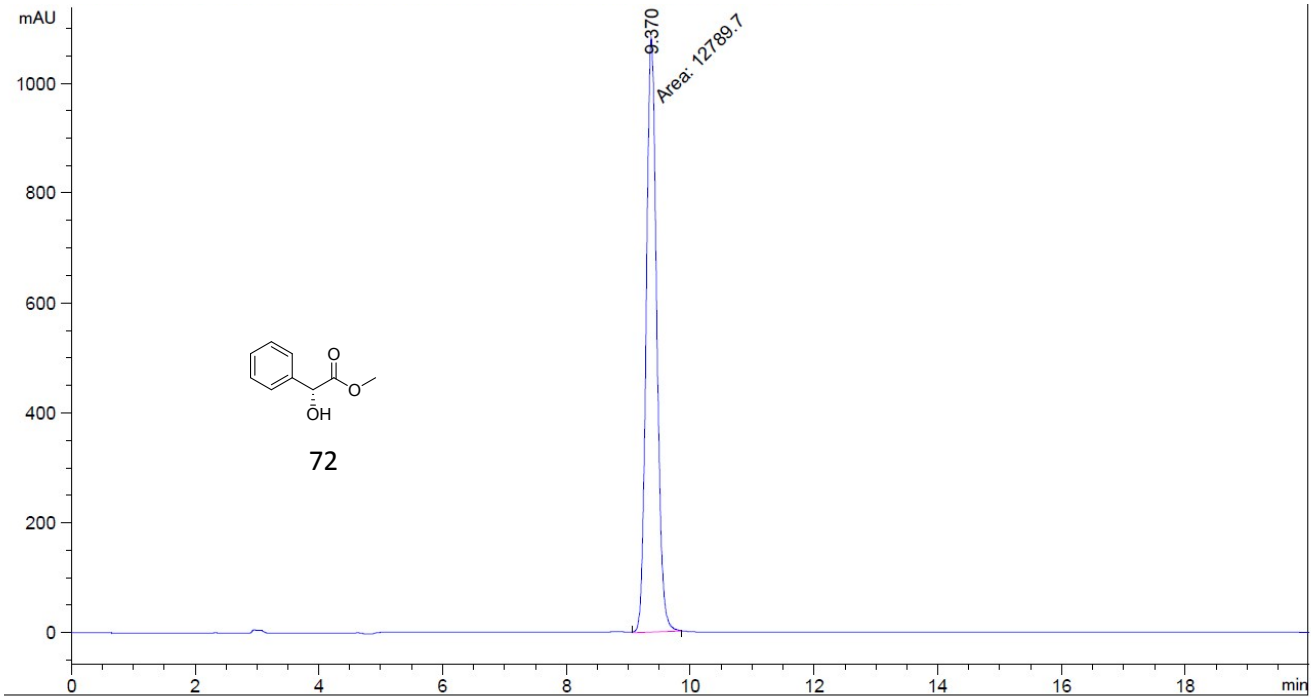
ethyl ((benzyloxy)carbonyl)-*L*-methioninate (71).



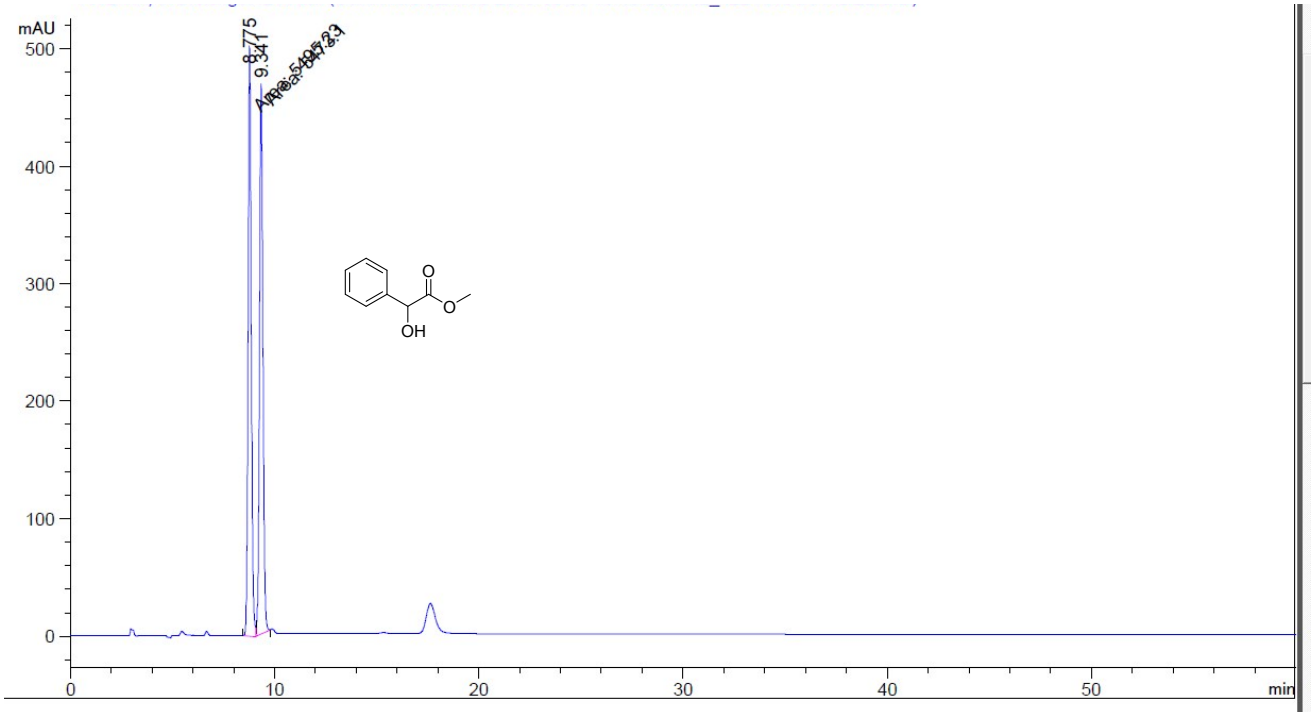
71



Methyl (*R*)-2-hydroxy-2-phenylacetate (72).



72



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