Electronic Supplementary Material (ESI) for ChemComm.

Organocatalytic Amidation of Unactivated Ester Derivatives

Supporting Information

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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 and NMP were purified by fractional distillation from CaH_2; DMF was purified by fractional distillation 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 and benzylamine, used for optimisation reactions, were purified by vacuum distillation from KOH; iodobenzene, used as an internal standard for calculating HPLC conversions, was purified by vacuum distillation from CaH_2; trifluoroethanol, used as an additive, was purified by fractional distillation from Na_2SO_4.

ii) BEMP was purified by vacuum distillation from CaH_2; DBU was purified by vacuum distillation; *t*-BuOK was purified by sublimation; NaH was purified by washing with petroleum ether 40-60°; K_3PO_4 was oven-dried at 230 °C prior to use.

iii) Dichloromethane, ethyl acetate, methanol, and petroleum ether 40–60° 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) Purging refers to a vacuum/nitrogen-refilling procedure.

iii) Room temperature was generally *ca*. 20 °C.

iv) Reactions were carried out at elevated temperatures using 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 IST Isolute Flash Silica SPE cartridges.

1.5 Analysis of Products

i) Fourier Transformed Infra-Red (FTIR) spectra were obtained on a Shimadzu IRAffinity-1 machine.

ii) ^{1}H and ^{13}C NMR spectra were obtained on a Bruker DRX 500 spectrometer at 500 and 126 MHz, respectively or on a Bruker AV3 400 at 400 and 101 MHz, respectively. Chemical shifts are reported in ppm and coupling constants are reported in Hz with $CDCl_3$ referenced at 7.27 (^{1}H) and 77.23 ppm (^{13}C), and DMSO referenced at 2.50 (^{1}H) and 39.51 ppm (^{13}C).

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

iv) Reversed phase HPLC data was obtained on an Agilent 1200 series HPLC using a Machery-Nagel Nucleodur C18 column, which was maintained at a constant temperature of 40 °C.

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

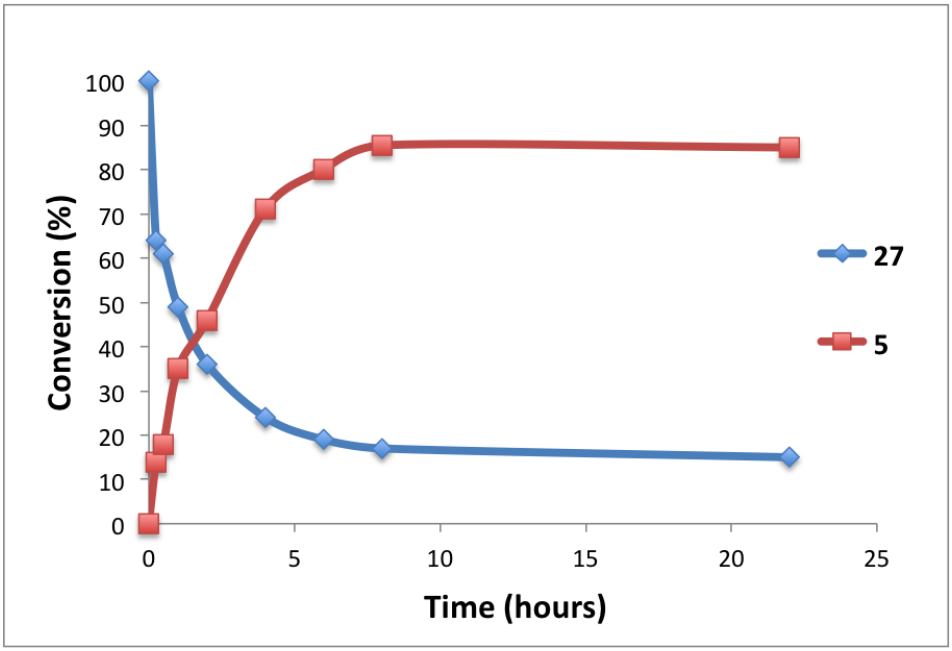
1.6 HPLC Method

i) 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 starting material **3**, 2,2,2-trifluoroethyl benzoate intermediate **26**, *N*-benzylbenzamide product **5**, 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

ii) Samples for HPLC analysis were prepared by diluting a 10 µL aliquot from the reaction mixture to 1 mL with MeCN.

iii) HPLC time study examining the conversion of **27** to **5**:



Time (hours)	Conversion of Intermediate (%)	Conversion to Product (%)
0	100	0
0.25	64	14
0.5	61	18
1	49	35
2	36	46
4	24	71
6	19	80
8	17	85
22	15	85

iv) For compound **14**, 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. The major and minor enantiomers were found to elute at 7.6 and 11.5 minutes, respectively.

2 General Procedures

2.1 General Procedure A for Initial Additive Screening

To an oven-dried sealed tube containing additive (1.42 mmol, 1 equiv), BEMP (41 μL, 0.14 mmol, 0.1 equiv) and acetonitrile (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 40 °C for 15 h. Conversion to product was determined by HPLC with reference to iodobenzene (1.4 M), which was used as an internal standard.

Additive (Amount)	Conversion (%)
HOAt (331μL, 0.6 M in DMF)	0
HOBt (191 mg)	0
HOCt (223 mg)	0
Oxyma (201 mg)	0
N-Hydroxysuccinimide (163 mg)	1
$(CF_3)_2CHOH$ (150 μL)	0
CF_3CH_2OH (102 μL)	6

2.2 General Procedure B for Initial Base and Solvent Screening

To an oven-dried sealed tube containing trifluoroethanol (102 μL, 1.42 mmol, 1 equiv), base (0.14 mmol, 0.1 equiv) and solvent (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 40 °C for 15 h. Conversion to product was determined by HPLC with reference to iodobenzene (1.4 M), which was used as an internal standard.

Base (Amount)	Solvent (Conversion, %)				
	MeCN	DMF	NMP	THF	PhMe
BEMP (41 μL)	6	7	6	7	5
DBU (21 μL)	3	4	3	9	8
K_3PO_4 (30 mg)	5	8	6	14	13
NaH (3 mg)	4	8	7	19	14
*t*BuOK (16 mg)	5	5	6	13	13
No Base	0	0	0	1	0
No Base, No CF_3CH_2OH	0	0	0	1	0

2.3 General Procedure C for DoE Optimisation of Trifluoroethanol-Catalysed Reaction

To an oven-dried sealed tube containing trifluoroethanol (0.2 – 1 equiv), K_3PO_4 (0.2 – 1 equiv) and THF (0.5 – 2 M) was added methyl benzoate, (178 μL, 1.42 mmol, 1 equiv) and benzylamine (155 μL, 1.42 mmol, 1 equiv). The reaction mixture was stirred at the required temperature (40 – 80 °C) for 8 – 22 hours. 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	Time (h)	Temp (°C)	Conc (M)	Amount of THF (mL)	Cat. Loading (eq)	Amount of TFE (μL)	Base Loading (eq)	Amount of K_3PO_4 (mg)	Conv (%)
1	15	60	1.25	1.1	0.6	61	0.6	181	42
2	8	80	0.5	2.8	1	102	1	301	38
3	8	80	2	0.7	0.2	20	1	301	54
4	15	60	0.13	10.8	0.6	61	0.6	181	3
5	8	40	0.5	2.8	0.2	20	1	301	2
6	25	60	1.25	1.1	0.6	61	0.6	181	38
7	15	60	1.25	1.1	0.6	61	1.2	362	41
8	22	80	2	0.7	0.2	20	0.2	60	53
9	22	80	0.5	2.8	0.2	20	1	301	58
10	22	80	0.5	2.8	1	102	0.2	69	55
11	15	60	1.25	1.1	0.6	61	0.6	181	44
12	8	40	0.5	2.8	1	102	0.2	60	3
13	15	60	1.25	1.1	0.6	61	0.002	0.6	4
14	22	40	0.5	2.8	1	102	1	301	13
15	22	40	2	0.7	1	102	0.2	60	32
16	15	60	1.25	1.1	0.6	61	0.6	181	45
17	15	60	1.25	1.1	1.2	123	0.6	181	44
18	8	40	2	0.7	1	102	1	301	20
19	15	90	1.25	1.1	0.6	61	0.6	181	88
20	15	60	1.25	1.1	0.002	0.2	0.6	181	1
21	15	60	1.25	1.1	0.6	61	0.6	181	43
22	22	40	0.5	2.8	0.2	20	0.2	60	2
23	15	30	1.25	1.1	0.6	61	0.6	181	7
24	15	60	2.37	0.6	0.6	61	0.6	181	63
25	22	40	2	0.7	0.2	20	1	301	31
26	8	80	0.5	2.8	0.2	20	0.2	60	6
27	4.5	60	1.25	1.1	0.6	61	0.6	181	9
28	22	80	2	0.7	1	102	1	301	67
29	8	40	2	0.7	0.2	20	0.2	60	5
30	8	80	2	0.7	1	102	0.2	60	61
31	22	90	2	0.7	0.2	20	1	301	86

The data from entries 1–30 was processed using Design Expert™ software v8.0 (Stat-Ease Inc., Minneapolis, MN). Entries 4, 6, 7, 13, 17, 19, 20, 23, 24, and 27 represent axial points of the central composite design. Analysis of the data using a quadratic model enabled generation of response surfaces and a half-normal plot. From this, it could be inferred that that most significant parameter was temperature (A), with an optimum balance existing for base (E) and TFE equivalents (D).

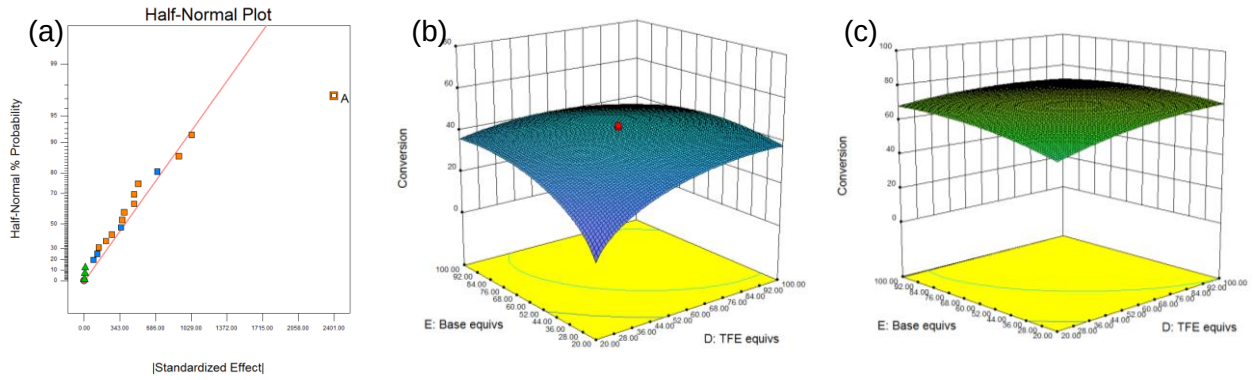


Figure 1: (a) Half-normal plot; (b) 3D response surface modelled at 60 °C; (c) 3D response surface modelled at 90 °C

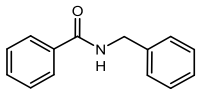
Utilising the optimisation module, conditions were sought in order to maximise conversion to the amide product. This analysis revealed the conditions shown in entry 31 in the table above as a possible solution. Repeating the screen using General Experimental Procedure C with the quantities of reagents indicated above gave 86% isolated yield.

2.4 General Procedure D for the Synthesis of Amides *via* Trifluoroethanol-Catalysed Amide Bond Formation

To an oven-dried sealed tube containing trifluoroethanol (20 μL, 0.28 mmol, 0.2 equiv), K_3PO_4 (301 mg, 1.42 mmol, 1 equiv) and THF (700 μL) was added ester (1.42 mmol, 1 equiv) and amine (1.42 mmol, 1 equiv). The reaction mixture was heated at 90 °C for 22 h then diluted with EtOAc (10 mL), washed with water (3 x 10 mL), passed through a hydrophobic frit, and concentrated to a residue that was purified by flash column chromatography (MeOH/CH_2Cl_2 or EtOAc/pet. ether 40–60°).

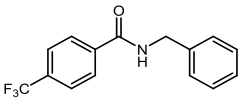
3 Characterisation Data for Substrate Scope

***N*-Benzylbenzamide (5)**.[2]



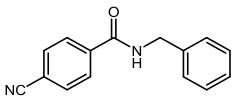
Synthesised according to General Experimental Procedure D and purified by flash column chromatography (1% MeOH/CH_2Cl_2) to afford the title compound as a white solid (258 mg, 86%): υ_{max} (neat) 3356, 3092, 3036, 2932, 1636, 1560, 1261 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 9.06 (t, J = 5.9 Hz, 1H), 7.91 – 7.88 (m, 2H), 7.54 (dt, J = 7.2, 1.9 Hz, 1H), 7.50 – 7.45 (m, 2H), 7.36 – 7.30 (m, 4H), 7.27 – 7.22 (m, 1H), 4.48 (d, J = 6.0 Hz, 2H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 166.2, 139.7, 134.3, 131.2, 128.3, 128.2, 127.2, 127.1, 126.7, 42.6; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{14}H_{14}NO$ 212.1070, Found 212.1069.

***N*-Benzyl-4-(trifluoromethyl)benzamide (6)**.[3]



Synthesised according to General Experimental Procedure D and purified by flash column chromatography (1% MeOH/CH_2Cl_2) to afford the title compound as a white solid (377 mg, 95%): υ_{max} (neat): 3356, 3092, 3036, 2932, 1641, 1549, 1310, 1155 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 9.29 (t, J = 6.0 Hz, 1H), 8.09, (d, J = 8.0 Hz, 2H), 7.87 (d, J = 8.0 Hz, 2H), 7.35 – 7.32 (m, 4H), 7.28 – 7.23 (m, 1H), 4.50 (d, J = 6.0 Hz, 2H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 165.0, 139.2, 138.0, 131.1 (q, $^2J_{CF}$ = 32.1 Hz), 128.2, 128.1, 127.2, 126.7, 125.3 (q, $^3J_{CF}$ = 3.6 Hz), 124.0 (q, $^1J_{CF}$ = 273.3 Hz), 42.7; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{15}H_{13}F_3NO$ 280.0944, Found 280.0943.

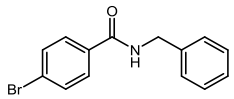
***N*-Benzyl-4-cyanobenzamide (7)**.[4]



Synthesised according to General Experimental Procedure D and purified by flash column chromatography (100% CH_2Cl_2) to afford the title compound as a white solid (201 mg, 60%): υ_{max} (neat): 3310, 3092, 3036, 2932, 2837, 2210, 1643, 1560 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 9.28 (t, J = 5.8 Hz, 1H), 8.05 – 8.03

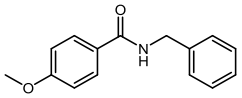
(m, 2H), 7.98 – 7.96 (m, 2H), 7.34 – 7.31 (m, 4H), 7.28 – 7.23 (m, 1H), 4.50 (d, J = 6.0 Hz, 2H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 164.8, 139.1, 138.3, 132.4, 128.3, 128.1, 127.2, 126.8, 118.3, 113.6, 42.8; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{15}H_{13}N_2O$ 237.1022, Found 237.1023.

***N*-Benzyl-4-bromobenzamide (8)**.[4]



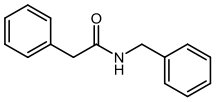
Synthesised according to General Experimental Procedure D and purified by flash column chromatography (1% MeOH/CH_2Cl_2) to afford the title compound as a white solid (358 mg, 87%): υ_{max} (neat): 3298, 3092, 3063, 2932, 2837, 1641, 1560 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.10 (t, J = 5.8 Hz, 1H), 7.84 (dt, J = 8.8, 2.2 Hz, 2H), 7.69 (dt, J = 8.8, 2.2 Hz, 2H), 7.35 – 7.30 (m, 4H), 7.28 – 7.22 (m, 1H), 4.47 (d, J = 6.0 Hz, 2H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 165.2, 139.4, 133.4, 131.3, 129.4, 128.3, 127.2, 126.8, 124.9, 42.6; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{14}H_{13}{}^{79}BrNO$ 290.0175, Found 290.0177.

***N*-Benzyl-4-methoxybenzamide (9)**.[3]



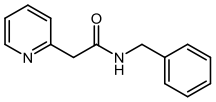
Synthesised according to General Experimental Procedure D and purified by flash column chromatography (1% MeOH/CH_2Cl_2) to afford the title compound as a white solid (140 mg, 41%): υ_{max} (neat): 3254, 3092, 3036, 2932, 2837, 1630, 1028 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.88 (t, J = 6.1 Hz, 1H), 7.88 (dt, J = 9.0, 2.4 Hz, 2H), 7.34 – 7.30 (m, 4H), 7.25 – 7.21 (m, 1H), 7.00 (dt, J = 8.5, 2.5 Hz, 2H), 4.47 (d, J = 6.0 Hz, 2H), 3.81 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 165.6, 161.6, 139.9, 129.0, 128.2, 127.1, 126.6, 126.5, 113.5, 55.3, 42.5; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{15}H_{16}NO_2$ 242.1176, Found 242.1173.

***N*-Benzyl-2-phenylacetamide (10)**.[2]



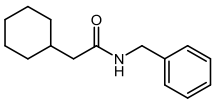
Synthesised according to General Experimental Procedure D and purified by flash column chromatography (40% EtOAc/pet. ether 40–60°) to afford the title compound as a white solid (288 mg, 90%): υ_{max} (neat): 3283, 3092, 3036, 2932, 1636, 1547, 1431 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 8.53 (t, *J* = 4.8 Hz, 1H), 7.32 – 7.27 (m, 6H), 7.24 – 7.20 (m, 4H), 4.27 (d, *J* = 6.0 Hz, 2H), 3.48 (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 170.0, 139.4, 136.4, 129.0, 128.2, 128.1, 127.2, 126.7, 126.3, 42.3, 42.1; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{15}H_{16}NO$ 226.1226, Found 226.1224.

***N*-Benzyl-2-(pyridin-2-yl)acetamide (11)**.



Synthesised according to General Experimental Procedure D and purified by flash column chromatography (2% MeOH/CH_2Cl_2) to afford the title compound as a white solid (276 mg, 86%): υ_{max} (neat): 3265, 3061, 3028, 2924, 2874, 1633, 1539, 1454 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.58 (t, *J* = 5.2 Hz, 1H), 8.48 (ddd, *J* = 4.8, 1.8, 1.0 Hz, 1H), 7.73 (td, *J* = 7.6, 2.0 Hz, 1H), 7.36 – 7.29 (m, 3H), 7.27 – 7.21 (m, 4H), 4.29 (d, *J* = 6.0 Hz, 2H), 3.68 (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 169.1, 156.3, 148.8, 139.4, 136.4, 128.2, 127.2, 126.7, 123.7, 121.7, 44.9, 42.2; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{14}H_{15}N_2O$ 227.1179, Found 229.1175.

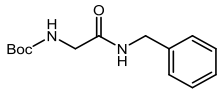
***N*-Benzyl-2-cyclohexylacetamide (12)**.[5]



Synthesised according to General Experimental Procedure D and purified by flash column chromatography (1% MeOH/CH_2Cl_2) to afford the title compound as a white solid (263 mg, 80%): υ_{max} (neat): 3067, 3030, 2920, 2849, 1636, 1553 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.26 (t, *J* = 5.4 Hz, 1H), 7.33 – 7.29 (m, 2H), 7.24 – 7.20 (m, 3H), 4.25 (d, *J* = 6.0 Hz, 2H), 2.01 (d, *J* = 7.0 Hz, 2H), 1.71 – 1.58 (m, 6H), 1.25 –

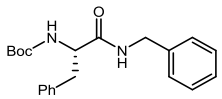
1.08 (m, 3H), 0.95 – 0.86 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 173.7, 137.9, 129.0, 128.1, 128.0, 44.9, 44.2, 35.7, 33.3, 26.3, 26.2; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd $C_{15}H_{22}NO$ for 232.1696, Found 232.1695.

***tert*-Butyl (2-(benzylamino)-2-oxoethyl)carbamate (13)**.[6]



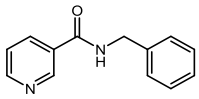
Synthesised according to General Experimental Procedure D and purified by flash column chromatography (2% MeOH/CH_2Cl_2) to afford the title compound as a white solid (285 mg, 76%): υ_{max} (neat): 3314, 3092, 2932, 2926, 1703, 1655 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 – 7.30 (m, 2H), 7.28 – 7.25 (m, 3H), 6.95 (br. s, 1H), 5.53 (t, *J* = 5.4 Hz, 1H), 4.43 (d, *J* = 5.6 Hz, 2H), 3.81 (d, *J* = 5.2 Hz, 2H), 1.43 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.6, 156.3, 138.1, 128.9, 127.9, 127.7, 44.7, 43.6, 28.5, 1C missing (coincident); HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{14}H_{21}N_2O_3$ 265.1547, Found 265.1551.

(*S*)-*tert*-Butyl (1-(benzylamino)-1-oxo-3-phenylpropan-2-yl)carbamate (14).[3]



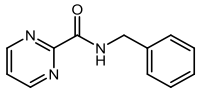
Synthesised according to General Experimental Procedure D and purified by flash column chromatography (1% MeOH/CH_2Cl_2) to afford the title compound as a white solid (211 mg, 42%): υ_{max} (neat): 3067, 3030, 2926, 1714, 1661, 1528, 1161 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.38 (t, *J* = 5.8 Hz, 1H), 7.30 – 7.18 (m, 9H), 6.94 (d, *J* = 8.4 Hz, 1H), 4.28 (d, *J* = 6.0 Hz, 2H), 4.23 – 4.17 (m, 1H), 3.17 (d, *J* = 5.2 Hz, 1H), 2.96 (dd, *J* = 13.6, 5.2 Hz, 1H), 2.78 (dd, *J* = 13.6, 10.0 Hz, 1H), 1.31 (s, 9H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 171.6, 155.2, 139.3, 138.1, 129.2, 128.1, 128.0, 127.0, 126.6, 126.1, 78.0, 55.9, 42.0, 37.5, 28.1; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{21}H_{27}N_2O_3$ 355.2016, Found 355.2017; ee = 8%.

***N*-Benzylnicotinamide (15)**.[7]



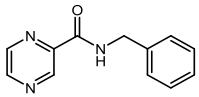
Synthesised according to General Experimental Procedure D and purified by flash column chromatography (2% MeOH/CH_2Cl_2) to afford the title compound as a white solid (202 mg, 67%): υ_{max} (neat): 3281, 3092, 2932, 2837, 1632, 1541 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 9.23 (t, *J* = 5.6 Hz, 1H), 9.06 (dd, *J* = 2.4, 0.8 Hz, 1H), 8.71 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.25 – 8.22 (m, 1H), 7.51 (ddd, *J* = 8.0, 4.8, 0.8 Hz, 1H), 7.36 – 7.31 (m, 4H), 7.28 – 7.23 (m, 1H), 4.51 (d, *J* = 6.0 Hz, 2H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 164.8, 151.9, 148.4, 139.3, 135.0, 129.8, 128.3, 127.3, 126.9, 123.5, 42.6; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{13}H_{13}N_2O$ 213.1022, Found 213.1019.

***N*-Benzylpyrimidine-2-carboxamide (16)**.



Synthesised according to General Experimental Procedure D and purified by flash column chromatography (100% CH_2Cl_2) to afford the title compound as a yellow solid (200 mg, 66%): υ_{max} (neat): 3356, 3092, 3063, 2932, 2837, 1680, 1537, 1408 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 9.41 (t, *J* = 5.2 Hz, 1H), 8.97 (d, *J* = 4.8 Hz, 2H), 7.68 (t, *J* = 4.8 Hz, 1H), 7.36 – 7.30 (m, 4H), 7.26 – 7.22 (m, 1H), 4.50 (d, *J* = 6.4 Hz, 2H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 162.6, 158.2, 157.7, 139.3, 128.3, 127.3, 126.8, 123.0, 42.6; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{12}H_{12}N_3O$ 214.0975, Found 214.0975.

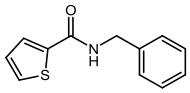
***N*-Benzylpyrazine-2-carboxamide (17)**.[8]



Synthesised according to General Experimental Procedure D and purified by flash column chromatography (1% MeOH/CH_2Cl_2) to afford the title compound as a white solid (194 mg, 64%): υ_{max} (neat): 3356, 3092, 3036, 2926, 1668, 1514 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 9.47 (t, *J* = 6.0 Hz, 1H), 9.20 (d, *J* = 1.5 Hz, 1H), 8.88 (d, *J* = 2.5 Hz, 1H), 8.74 (dd, *J* = 2.5, 1.5 Hz, 1H), 7.35 – 7.30 (m, 4H), 7.25 – 7.22 (m, 1H),

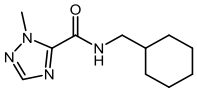
4.51 (d, J = 6.5 Hz, 2H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 163.0, 147.5, 144.8, 143.6, 143.4, 139.2, 128.2, 127.3, 126.8, 42.3; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{12}H_{12}N_3O$ 214.0975, Found 214.0974.

***N*-Benzylthiophene-2-carboxamide (18)**.[9]



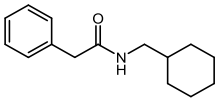
Synthesised according to General Experimental Procedure D and purified by flash column chromatography (100% CH_2Cl_2) to afford the title compound as a white solid (234 mg, 76%): υ_{max} (neat): 3356, 3092, 3036, 2932, 2838, 1620, 1541, 1301 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.03 (t, J = 5.5 Hz, 1H), 7.81 (dd, J = 3.5, 1.0 Hz, 1H), 7.75 (dd, J = 5.0, 1.0 Hz, 1H), 7.35 – 7.30 (m, 4H), 7.26 – 7.23 (m, 1H), 7.16 – 7.14 (m, 1H), 4.45 (d, J = 6.0 Hz, 2H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 161.1, 139.9, 139.5, 130.8, 128.3, 128.1, 127.9, 127.2, 126.8, 42.4; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{12}H_{12}NOS$ 218.0634, Found 218.0634.

***N*-(Cyclohexylmethyl)-1-methyl-1*H*-1,2,4-triazole-5-carboxamide (19)**.



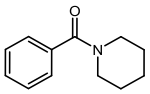
Synthesised according to General Experimental Procedure D and purified by flash column chromatography (1% MeOH/CH_2Cl_2) to afford the title compound as a colourless oil (253 mg, 80%): υ_{max} (neat): 3356, 2932, 2851, 1674, 1543, 1481 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.78 (t, J = 5.8 Hz, 1H), 8.03 (s, 1H), 4.12 (s, 3H), 3.08 (t, J = 6.5 Hz, 2H), 1.67 – 1.65 (m, 4H), 1.61 – 1.52 (m, 2H), 1.20 – 1.11 (m, 3H), 0.93 – 0.87 (m, 2H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 157.0, 149.4, 146.4, 44.7, 37.6, 37.2, 30.3, 26.0, 25.3; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{11}H_{19}N_4O$ 223.1553, Found 223.1555.

***N*-(Cyclohexylmethyl)-2-phenylacetamide (20)**.[10]



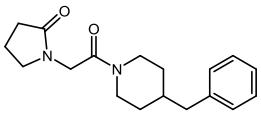
Synthesised according to General Experimental Procedure D and purified by flash column chromatography (100% CH_2Cl_2) to afford the title compound as a white solid (210 mg, 64%): υ_{max} (neat): 3356, 3084, 3063, 2932, 2926, 1641, 1560 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 7.95 (t, J = 4.8 Hz, 1H), 7.31 – 7.18 (m, 5H), 3.39 (s, 2H), 2.89 (t, J = 6.4 Hz, 2H), 1.65 – 1.59 (m, 5H), 1.41 – 1.32 (m, 1H), 1.21 – 1.07 (m, 3H), 0.88 – 0.79 (m, 2H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 169.9, 136.6, 128.9, 128.1, 126.2, 44.9, 42.4, 37.4, 30.3, 26.0, 25.3; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{15}H_{22}NO$ 232.1696, Found 232.1695.

Phenyl(piperidin-1-yl)methanone (21).[11]



Synthesised according to General Experimental Procedure D and purified by flash column chromatography (1% MeOH/CH_2Cl_2) to afford the title compound as a yellow oil (207 mg, 77%): υ_{max} (neat): 2936, 2926, 2837, 1626, 1427 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 7.44 – 7.42 (m, 3H), 7.37 – 7.34 (m, 2H), 3.57 (br. s, 2H), 3.26 (br. s, 2H), 1.61 – 1.60 (m, 2H), 1.48 (br. s, 4H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.4, 136.6, 129.5, 128.5, 126.9, 48.9, 43.2, 26.6, 25.7, 24.7; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{12}H_{16}NO$ 190.1226, Found 190.1225.

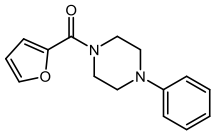
1-(2-(4-Benzylpiperidin-1-yl)-2-oxoethyl)pyrrolidin-2-one (22).



Synthesised according to General Experimental Procedure D and purified by flash column chromatography (1% MeOH/CH_2Cl_2) to afford the title compound as a colourless oil (269 mg, 63%): υ_{max} (neat): 3306, 3036, 2932, 2918, 1682, 1645, 1452, 1287 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 7.30 – 7.27 (m, 2H), 7.20 – 7.16 (m, 3H), 4.28 (d, J = 13.0 Hz, 1H), 4.10 – 4.05 (m, 1H), 3.99 – 3.95 (m, 1H), 3.77 (d, J = 13.5 Hz, 1H), 3.46 – 3.32 (m, 2H), 3.17 (d, J = 5.5 Hz, 1H), 2.94 – 2.89 (m, 1H), 2.52 (s, 2H), 2.22 (t, J = 8.0

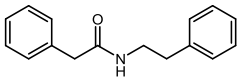
Hz, 2H), 1.96 – 1.90 (m, 2H), 1.79 – 1.70 (m, 1H), 1.58 (d, *J* = 13.0 Hz, 2H), 1.10 (qd, *J* = 12.4, 3.9 Hz, 1H), 0.99 (qd, *J* = 12.3, 4.1 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 175.7, 165.7, 139.9, 129.2, 128.5, 126.2, 48.1, 45.3, 44.4, 43.0, 42.5, 38.2, 32.5, 31.7, 30.6, 18.1; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{18}H_{25}N_2O_2$ 301.1911, Found 301.1909.

Furan-2-yl(4-phenylpiperazin-1-yl)methanone (23).[12]



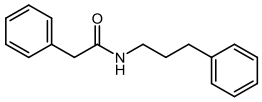
Synthesised according to General Experimental Procedure D and purified by flash column chromatography (2% MeOH/CH_2Cl_2) to afford the title compound as an orange oil (233 mg, 64%): υ_{max} (neat): 3092, 3036, 2932, 2837, 1620, 1485, 1229 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.86 (d, *J* = 1.5 Hz, 1H), 7.25 – 7.22 (m, 2H), 7.03 (d, *J* = 3.5 Hz, 1H), 6.97 – 6.96 (m, 2H), 6.81 (t, *J* = 7.3 Hz, 1H), 6.64 (dd, *J* = 3.5, 2.0 Hz, 1H), 3.81 (br. s, 4H), 3.20 (t, *J* = 5.3 Hz, 4H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 158.3, 150.7, 147.0, 144.8, 129.0, 119.3, 115.8, 115.7, 111.3, 48.5, 40.1; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{15}H_{17}N_2O_2$ 257.1285, Found 257.1286.

***N*-Phenethyl-2-phenylacetamide (24)**.



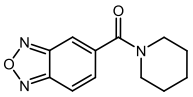
Synthesised according to General Experimental Procedure D and purified by flash column chromatography (2% MeOH/CH_2Cl_2) to afford the title compound as a white solid (228 mg, 67%): υ_{max} (neat): 3298, 3084, 3063, 2932, 2837, 1668, 1537 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.10 (t, *J* = 5.0 Hz, 1H), 7.30 – 7.25 (m, 4H), 7.22 – 7.15 (m, 6H), 3.37 (s, 2H), 3.27 (q, *J* = 7.2 Hz, 2H), 2.70 (t, *J* = 7.3 Hz, 2H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 169.9, 139.4, 136.4, 128.9, 128.6, 128.2, 128.1, 126.2, 126.0, 42.4, 40.2, 35.0; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{18}NO$ 240.1383, Found 240.1382.

2-Phenyl-*N*-(3-phenylpropyl)acetamide (25).



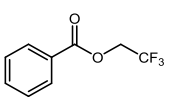
Synthesised according to General Experimental Procedure D and purified by flash column chromatography (2% MeOH/CH_2Cl_2) to afford the title compound as a white solid (252 mg, 70%): υ_{max} (neat): 3356, 3092, 2932, 2837, 1632, 1560, 1452 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 8.05 (t, J = 5.0 Hz, 1H), 7.31 – 7.19 (m, 7H), 7.18 – 7.14 (m, 3H), 3.40 (s, 2H), 3.05 (q, J = 6.5 Hz, 2H), 2.54 (t, J = 7.8 Hz, 2H), 1.72 – 1.65 (m, 2H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 170.0, 141.7, 136.6, 128.9, 128.3, 128.2, 126.3, 125.7, 42.5, 38.2, 32.5, 30.9, 1C missing (coincident); HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{20}NO$ 254.1539, Found 254.1539.

benzo[*c*][1,2,5]oxadiazol-5-yl(piperidin-1-yl)methanone (26)



Synthesised according to General Experimental Procedure D and purified by flash column chromatography (1% MeOH/CH_2Cl_2) to afford the title compound as an orange solid (196 mg, 60%): υ_{max} (neat): 3103, 3073, 3047, 2921, 2857, 1629, 1619, 1446, 1258 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 7.91 (dd, J = 9.0, 1.0 Hz, 1H), 7.85 (t, J = 1.0 Hz, 1H), 7.44 (dd, J = 9.2, 1.2 Hz, 1H), 3.75 (s, 2H), 3.40 (s, 2H), 1.73 (s, 4H), 1.60 (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 167.6, 148.9, 148.8, 139.7, 131.0, 117.5, 114.6, 48.9, 43.5, 26.8, 25.7, 24.6; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{12}H_{14}N_3O_2$ 232.1081, Found 232.1080.

2,2,2-Trifluoroethyl benzoate (27).[13]

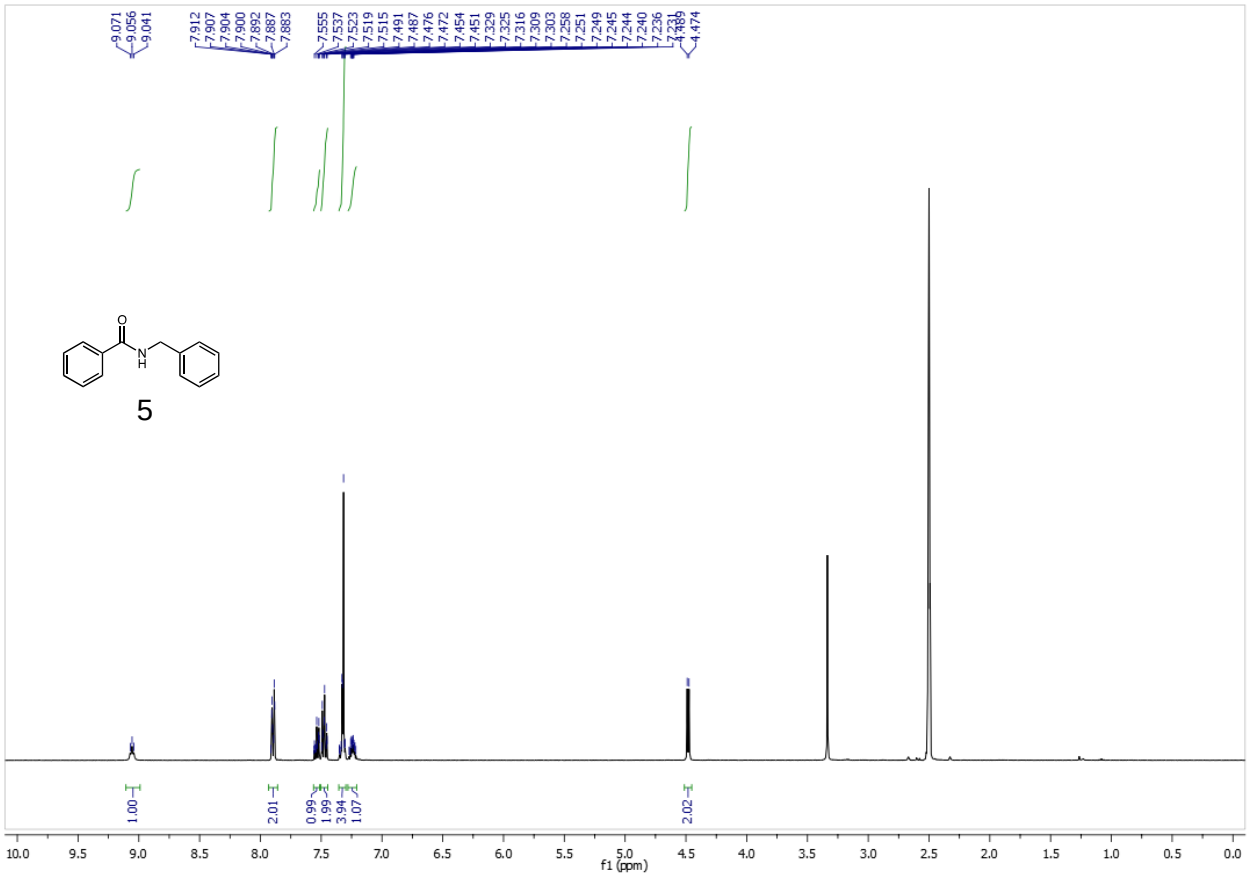


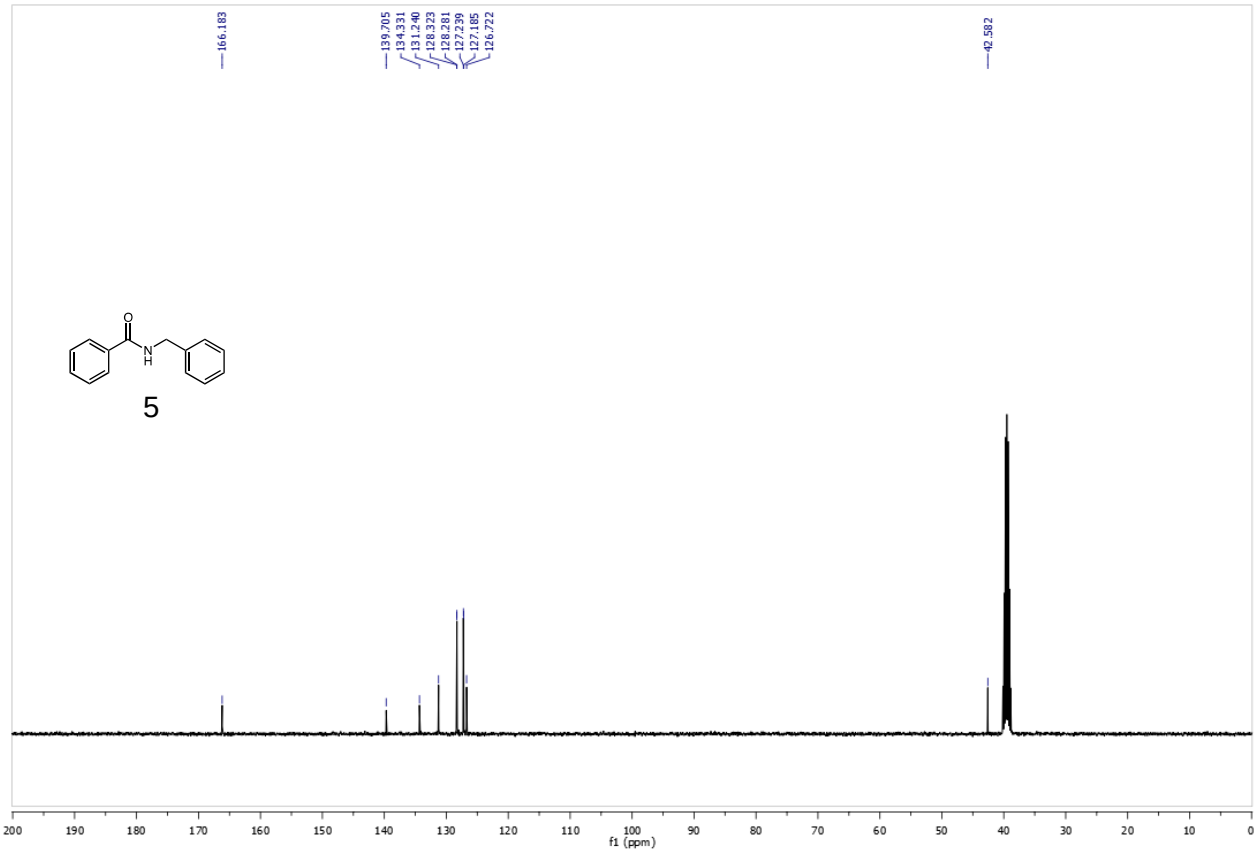
To a round-bottomed flask containing 2,2,2-trifluoroethanol (0.7 mL, 10 mmol, 1 equiv) and triethylamine (1.7 mL, 12 mmol, 1.2 equiv) in DCM (15 mL) was added benzoyl chloride (1.7 mL, 15 mmol, 1.5 equiv). The reaction mixture was heated at 60 °C for 15 h then concentrated under vacuum. The resulting residue was dissolved in EtOAc (20 mL), washed with saturated $NaHCO_3$ (20 mL) and brine (20 mL), dried over

Na_2SO_4, and concentrated to a residue that was purified by flash column chromatography (10% ethyl acetate/pet. ether 40−60°) to afford the title compound as a colourless liquid (2.00 g, 98%): υ_{max} (neat): 3061, 3028, 2924, 2874, 1736, 1254, 1163 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.11 – 8.09 (m, 2H), 7.63 (tt, J = 7.4, 1.5 Hz, 1H), 7.51 – 7.47 (m, 2H), 4.72 (q, J = 8.4 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 165.2, 134.1, 130.2, 128.8, 128.7, 123.4 (q, $^1J_{CF}$ = 278.3 Hz), 61.0 (q, $^2J_{CF}$ = 36.9 Hz).

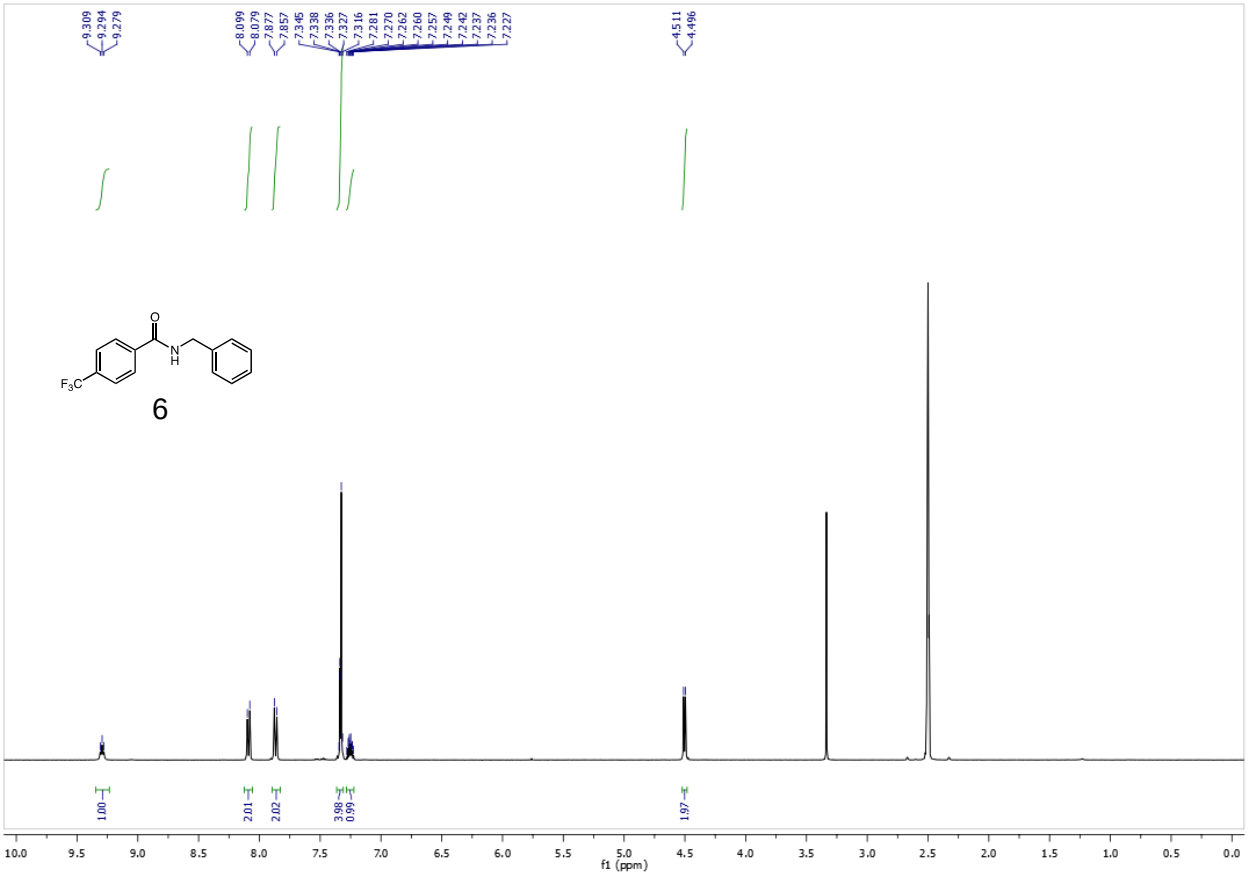
4 ^{1}H and ^{13}C Spectra for Exemplified Compounds

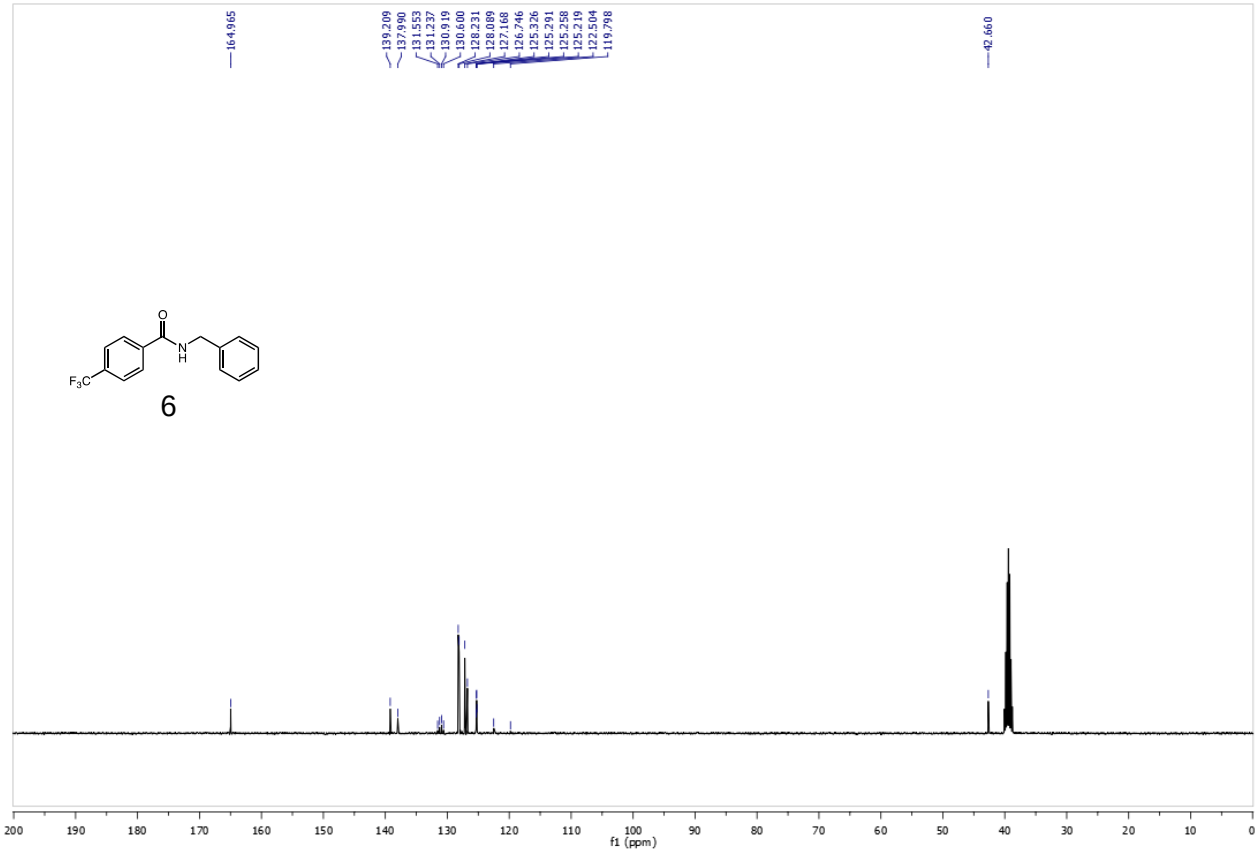
N-benzylbenzamide (5)



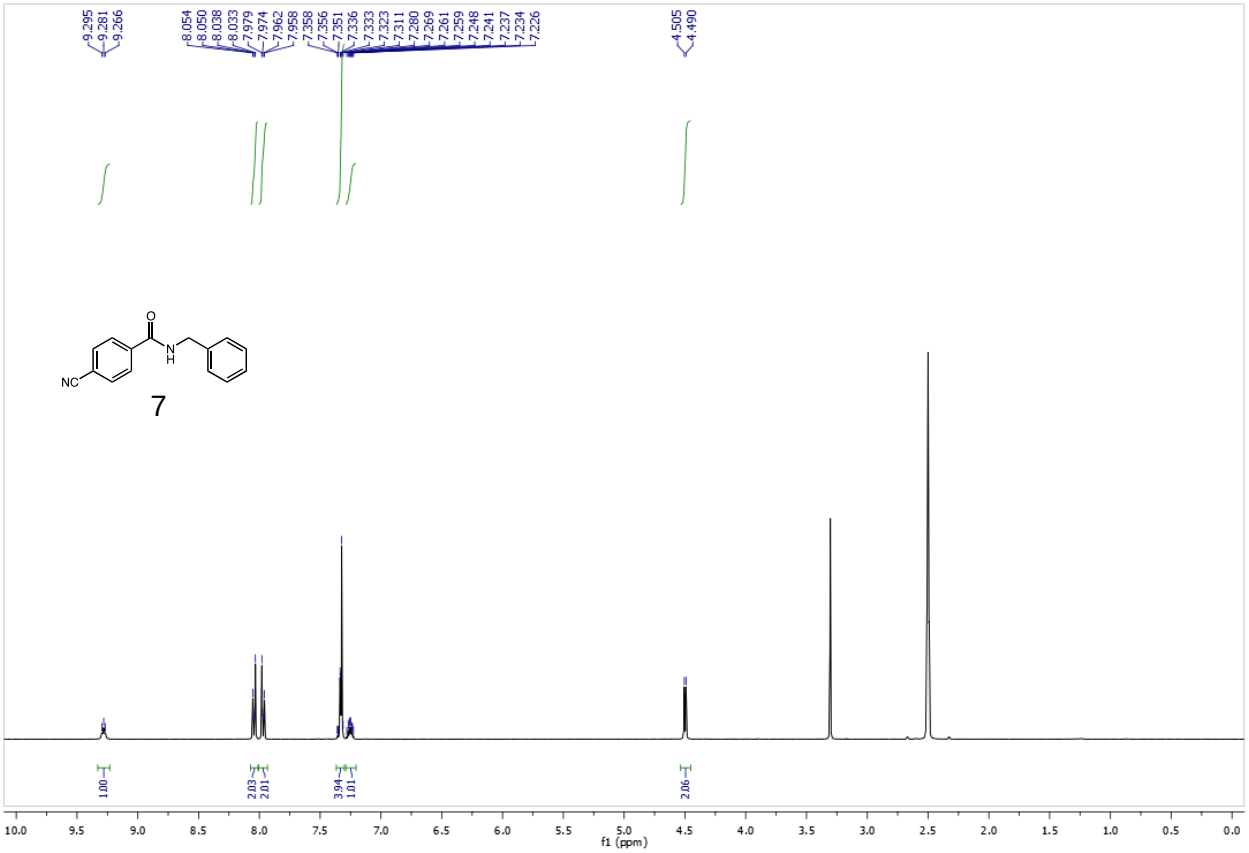


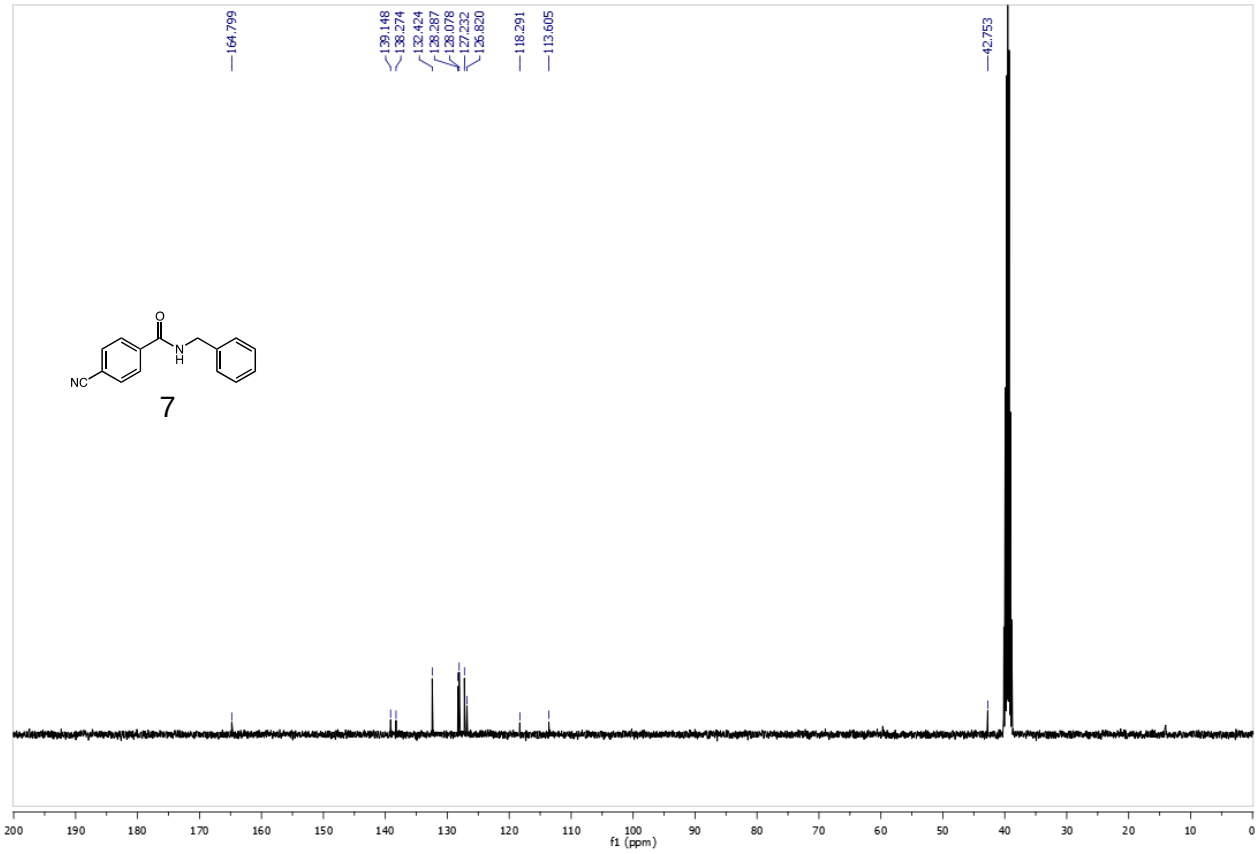
_N_-benzyl-4-(trifluoromethyl)benzamide (6)



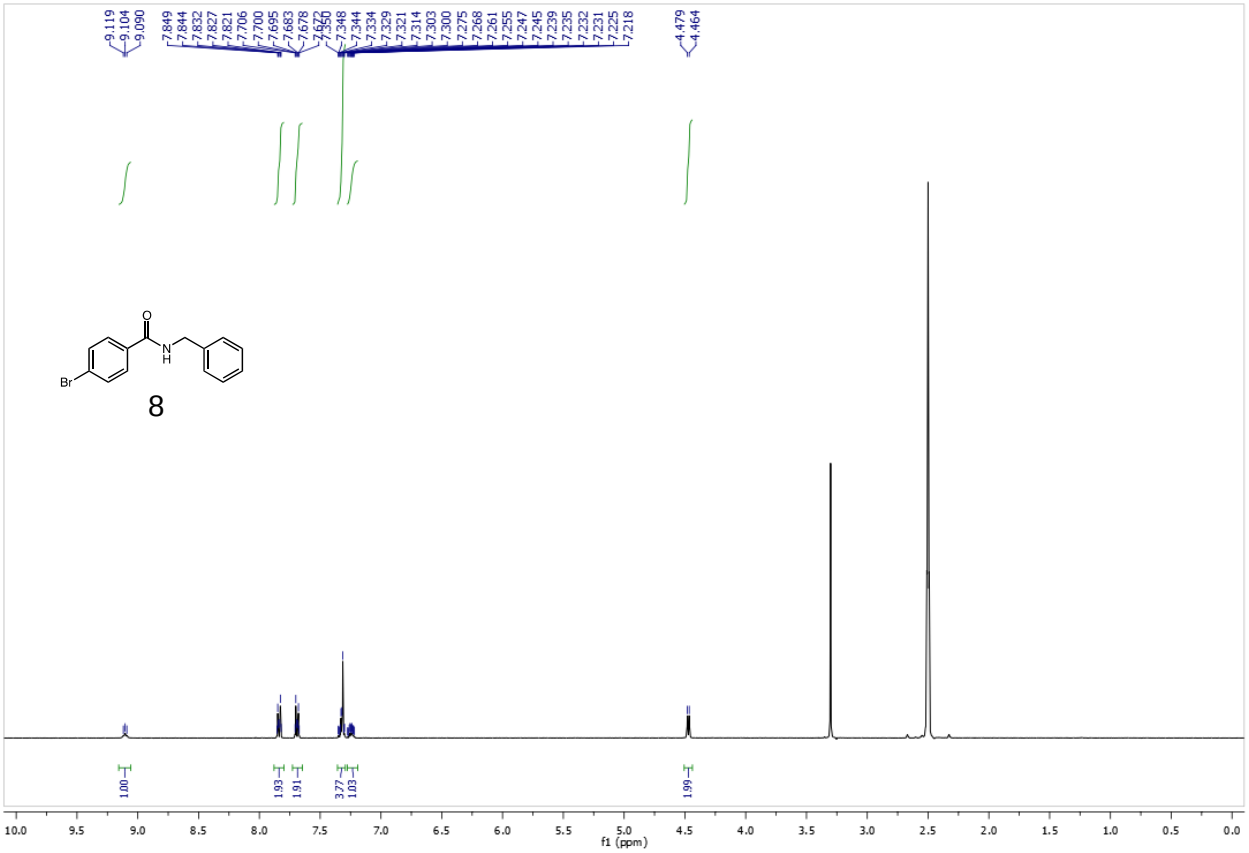


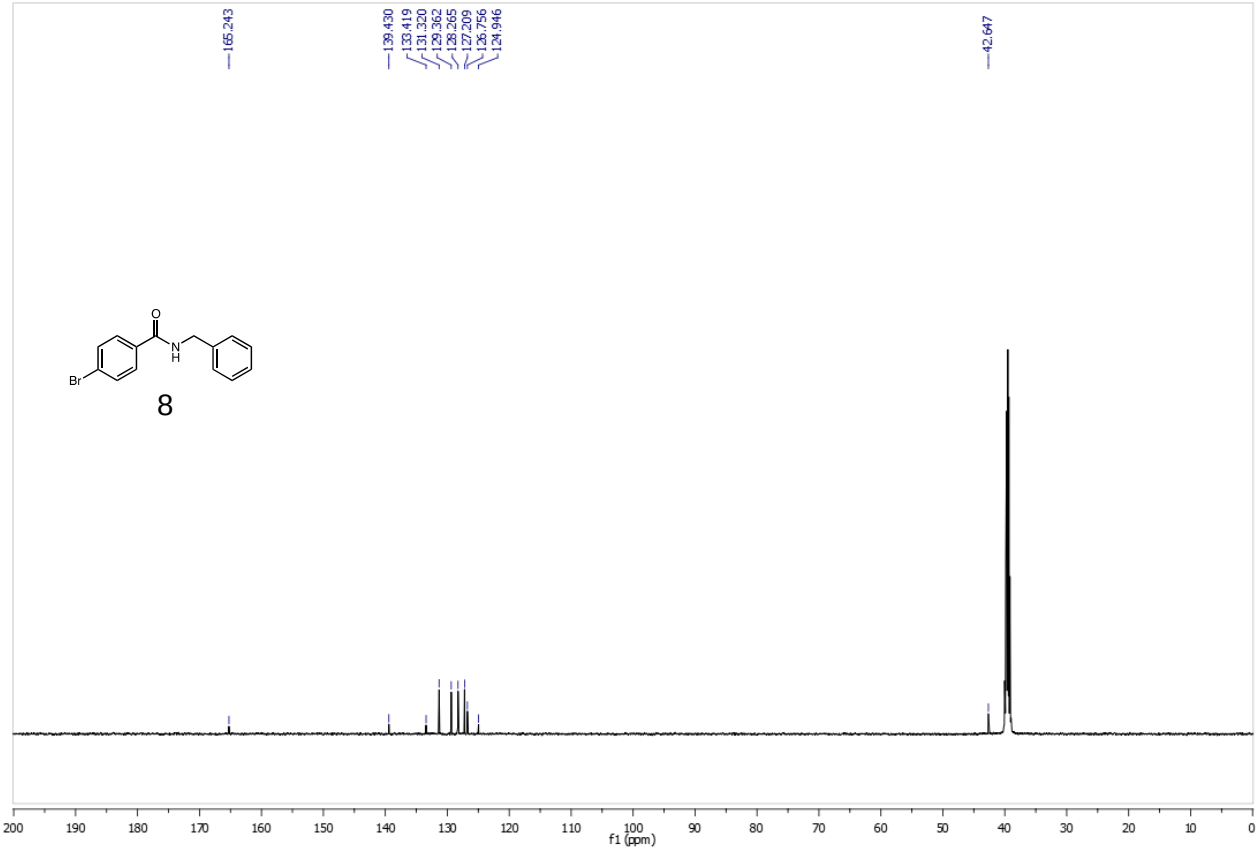
_N_-benzyl-4-cyanobenzamide (7)



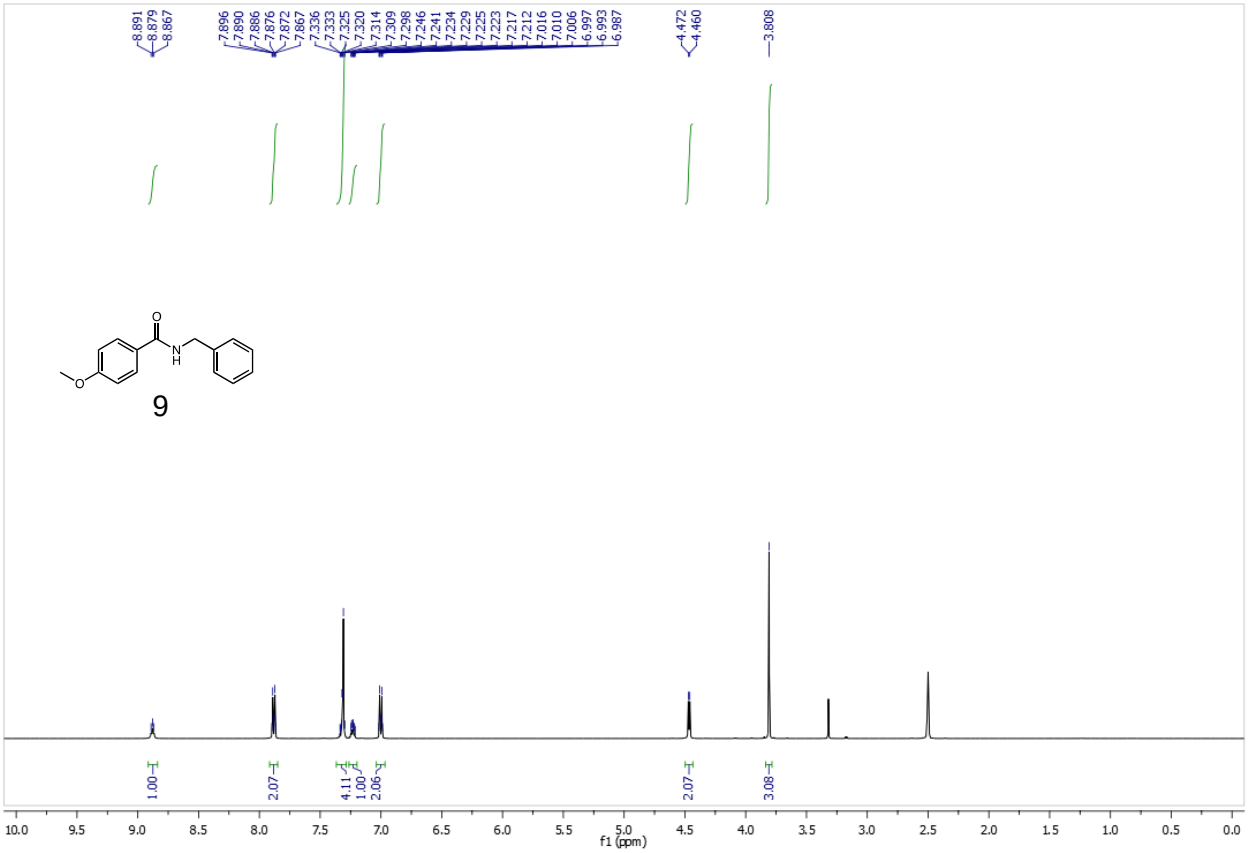


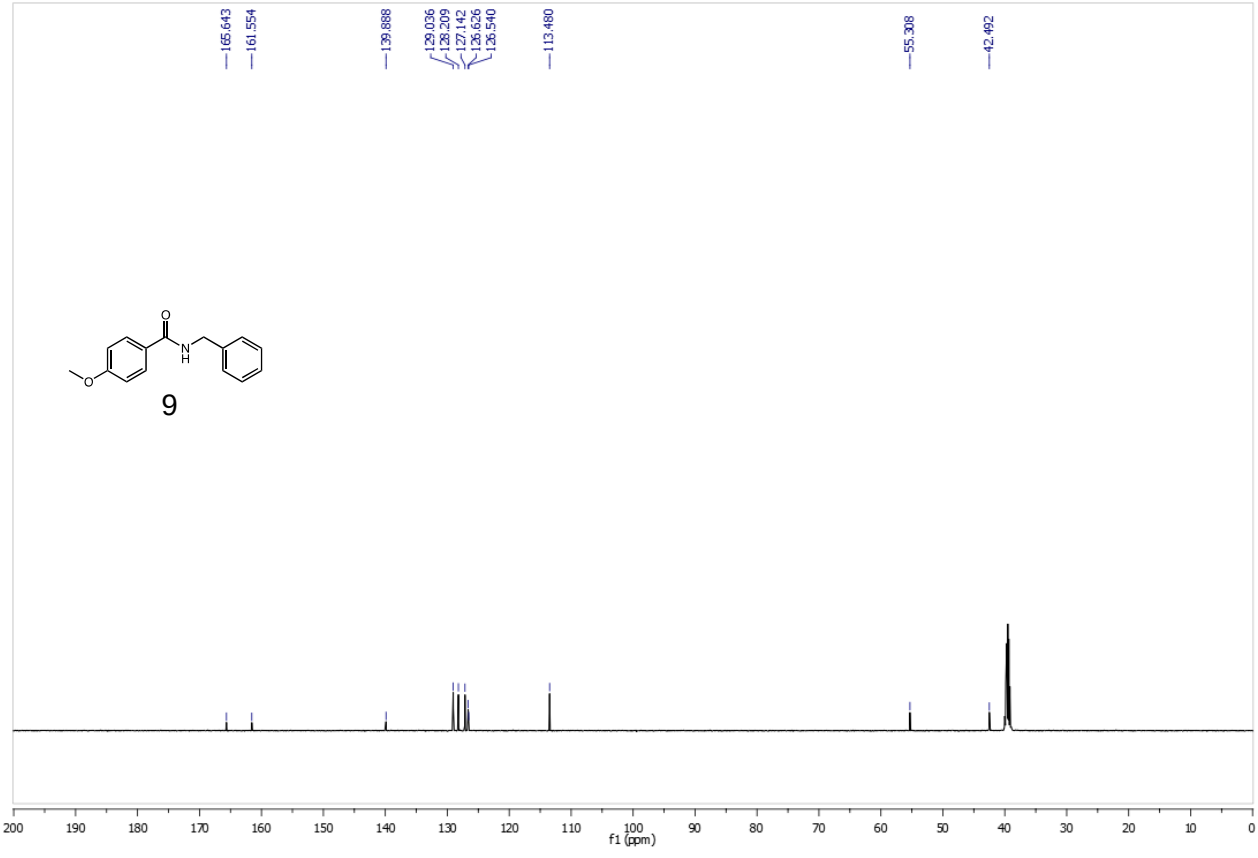
***N*-benzyl-4-bromobenzamide (8)**



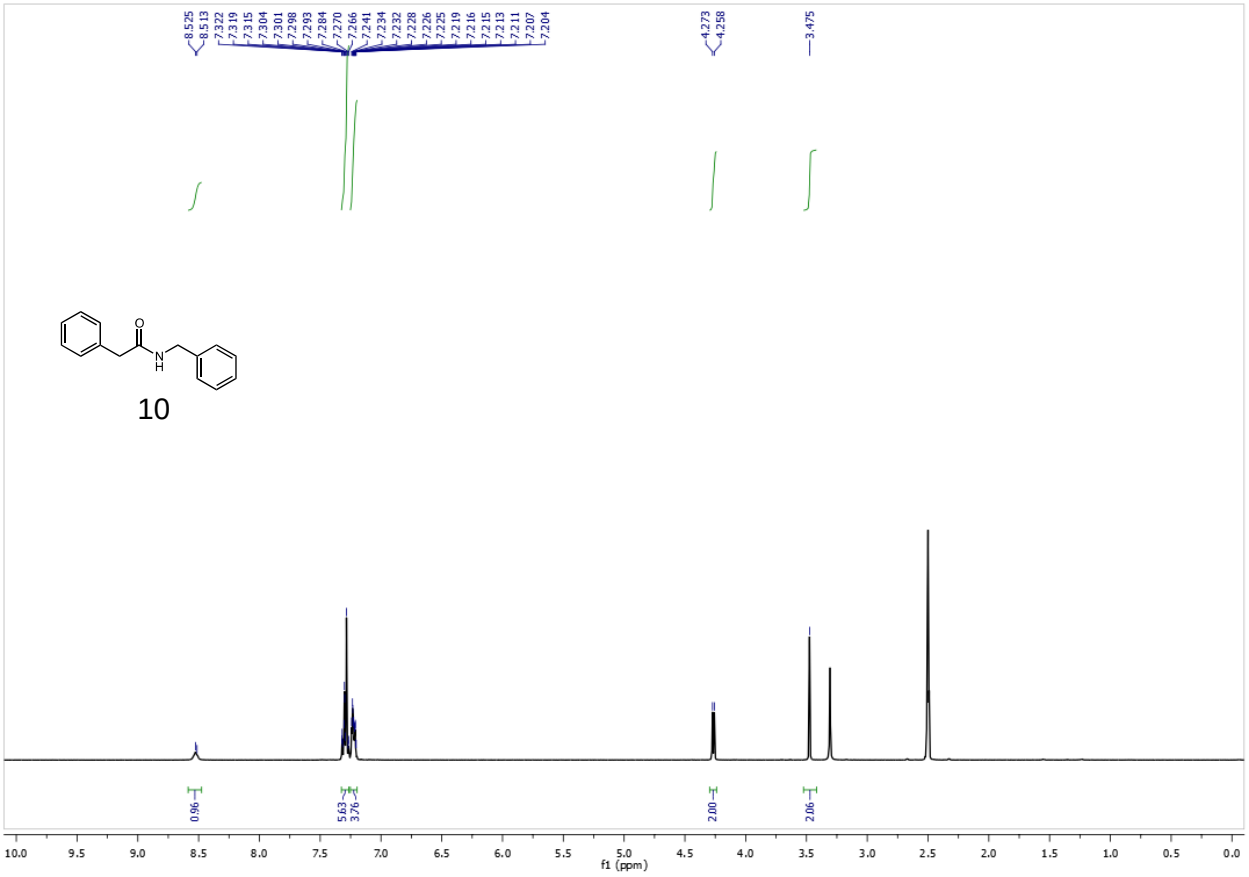


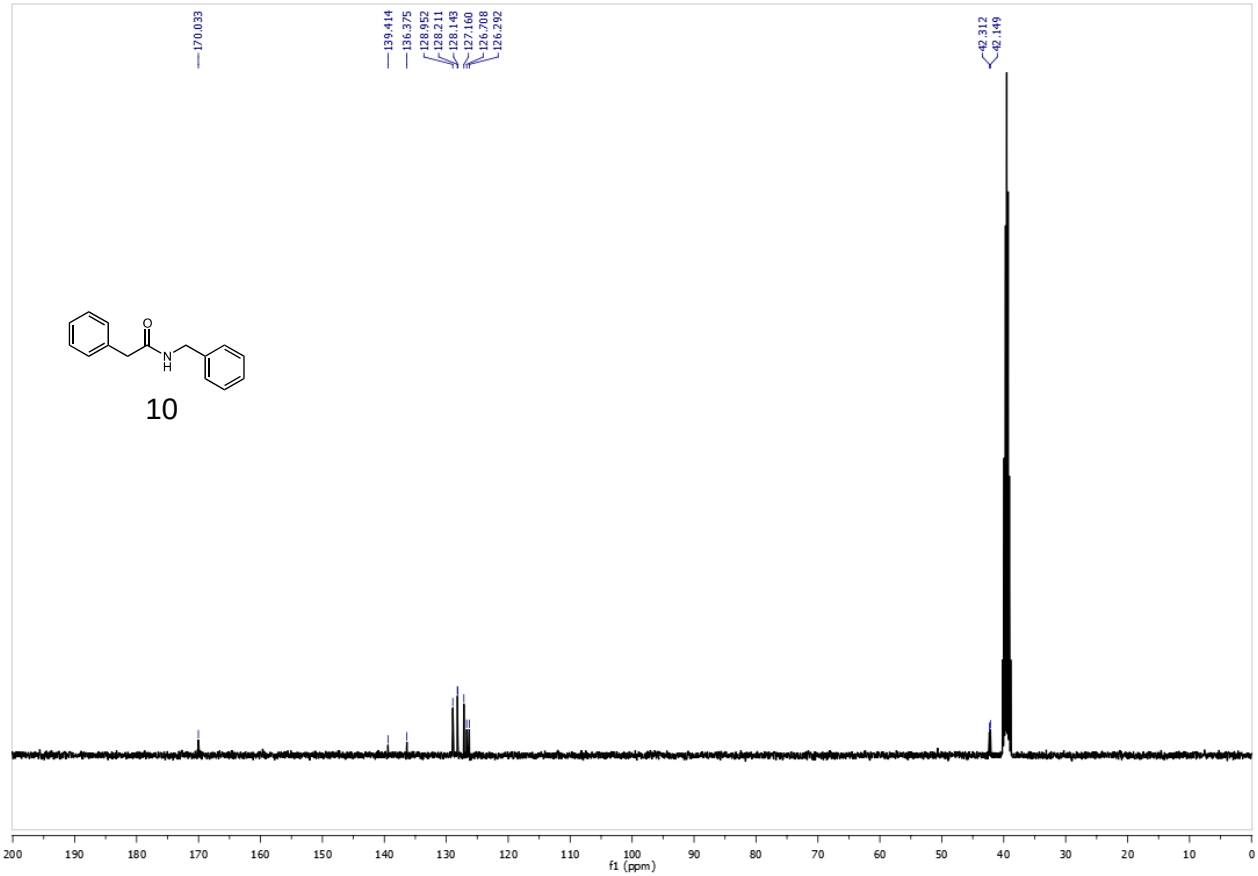
_N_-benzyl-4-methoxybenzamide (9)



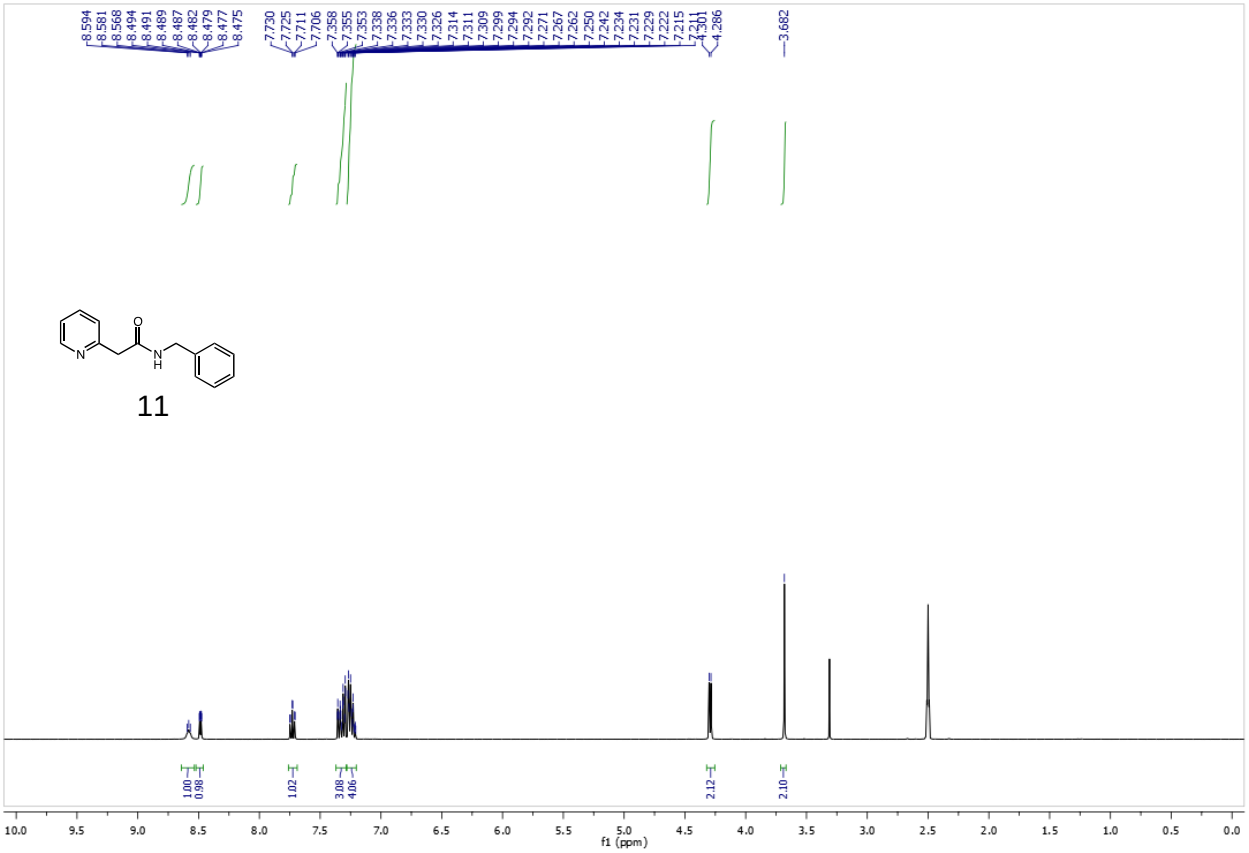


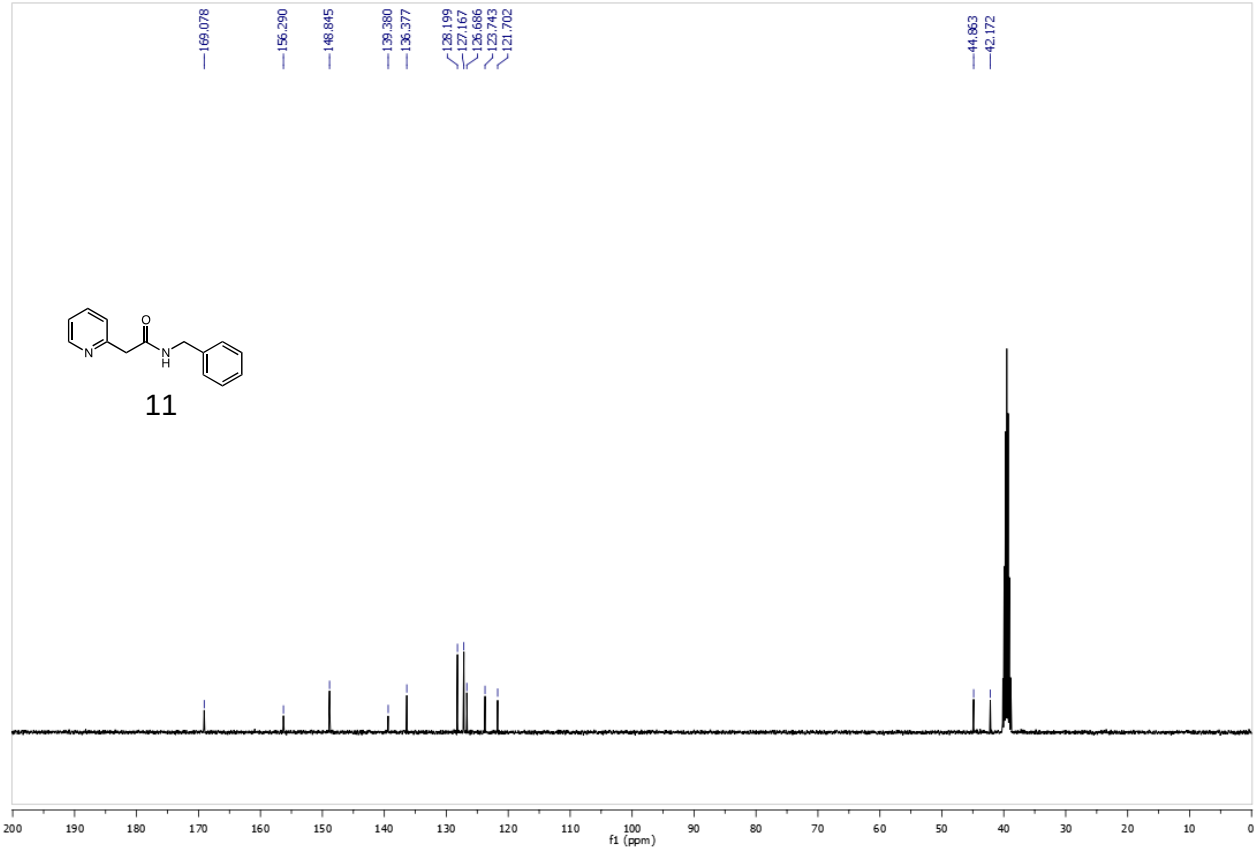
_N_-benzyl-2-phenylacetamide (10)



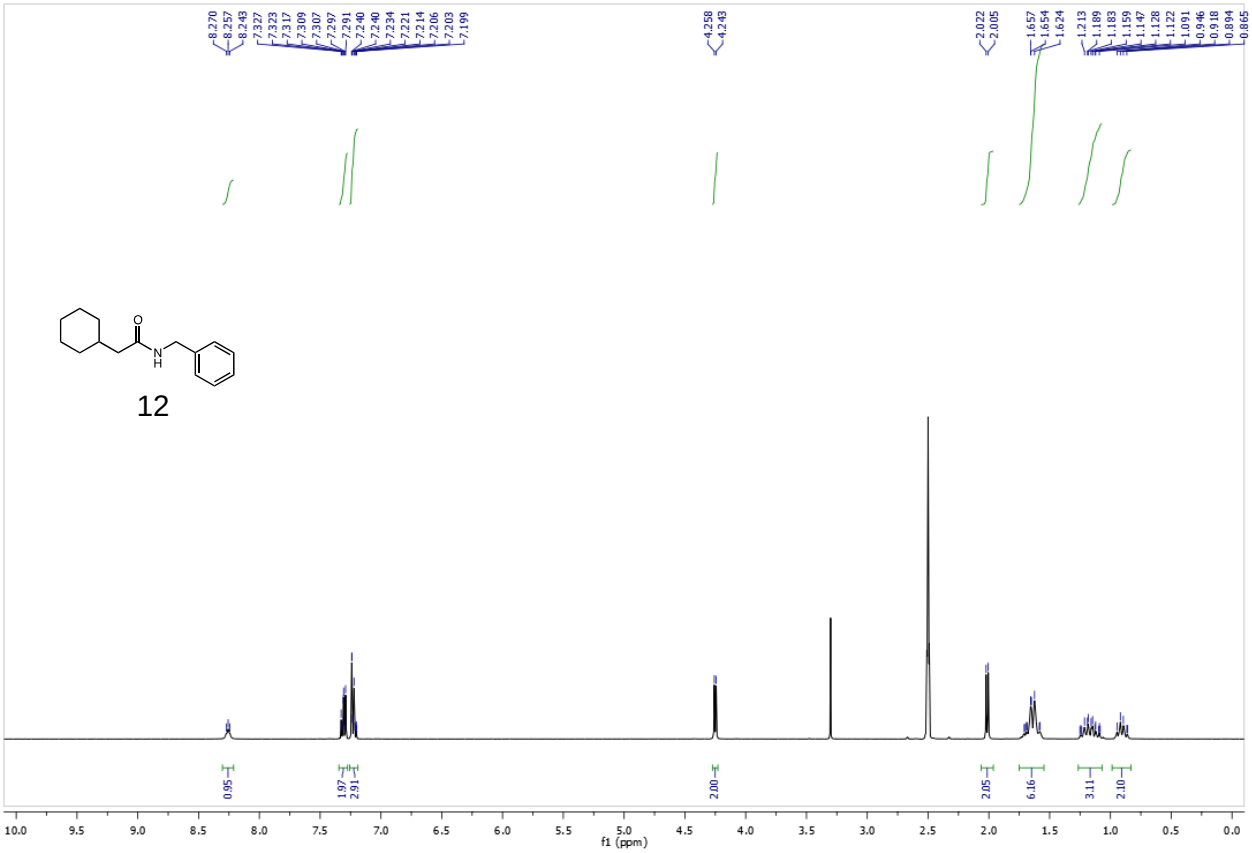


***N*-benzyl-2-(pyridin-2-yl)acetamide (11)**





***N*-benzyl-2-cyclohexylacetamide (12)**



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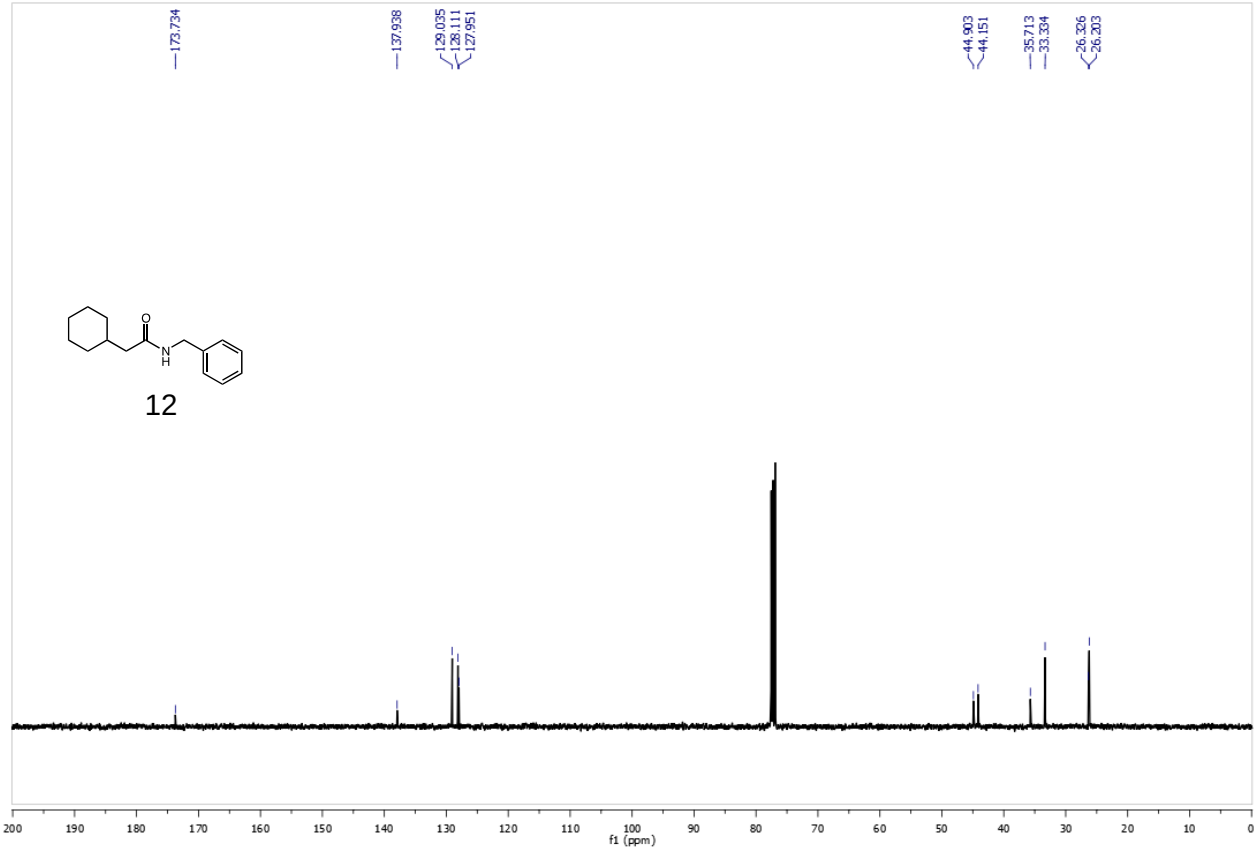
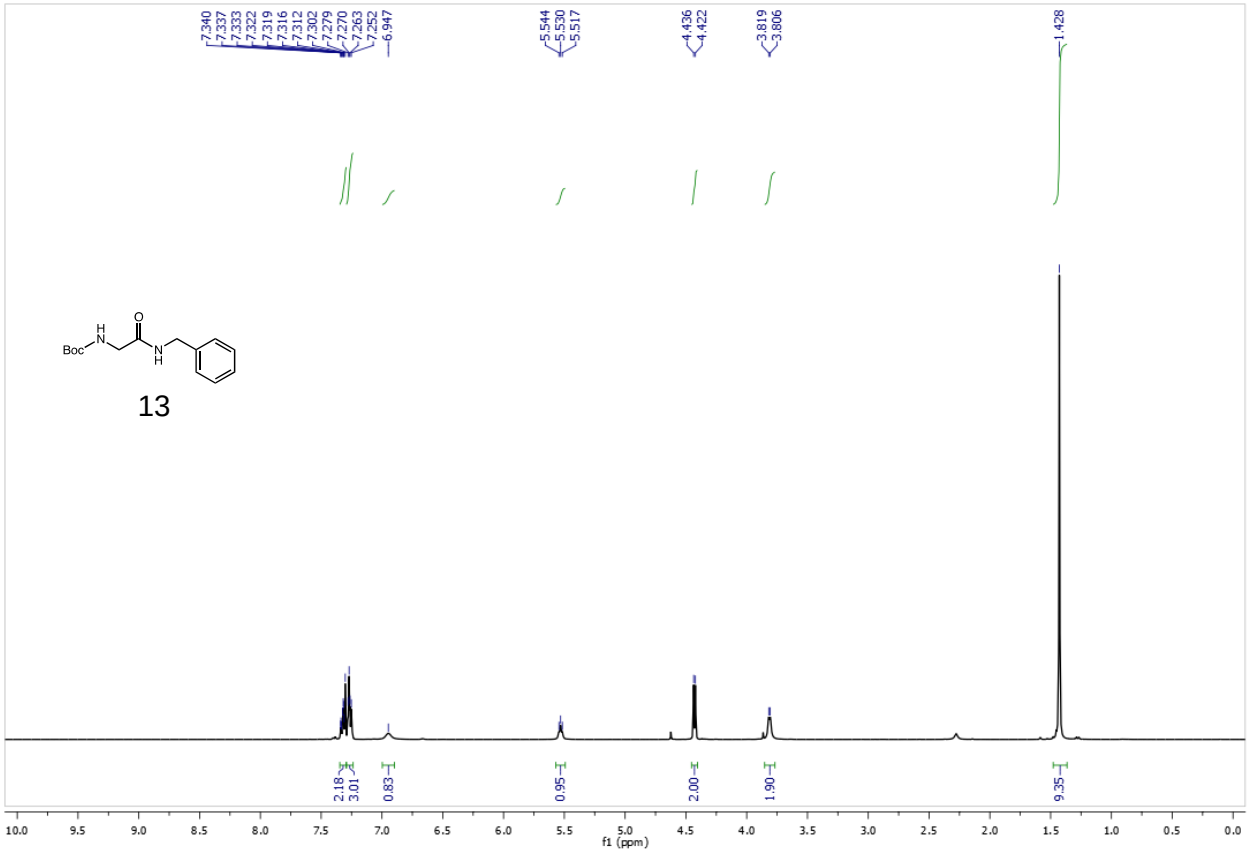
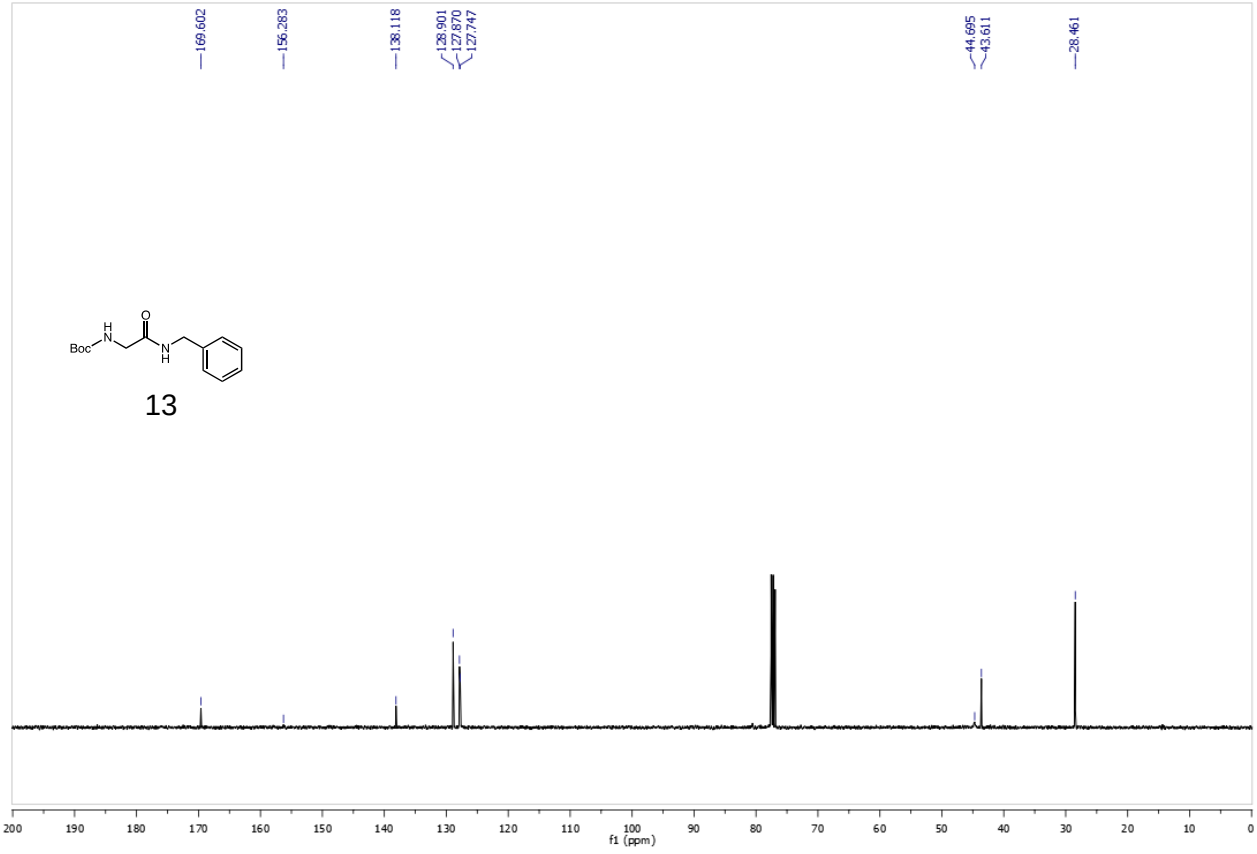


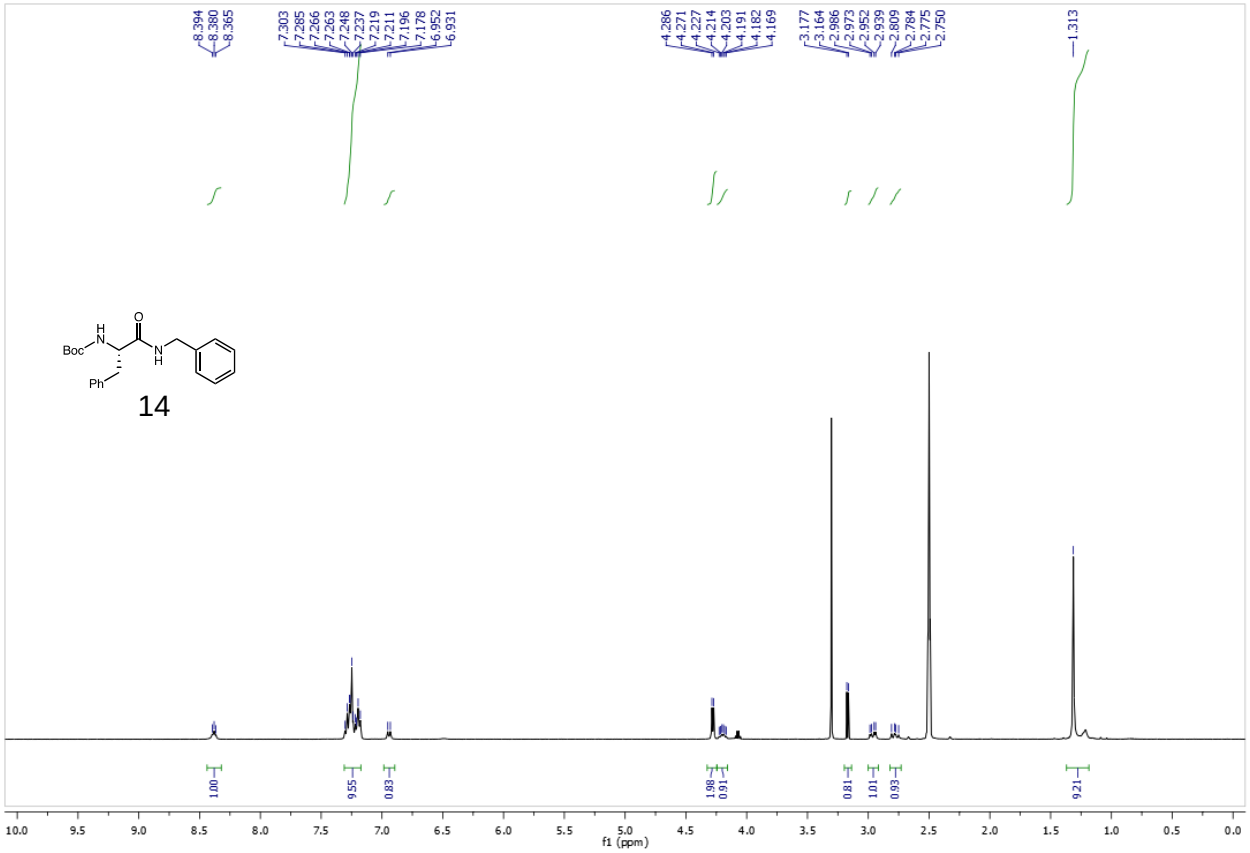
12

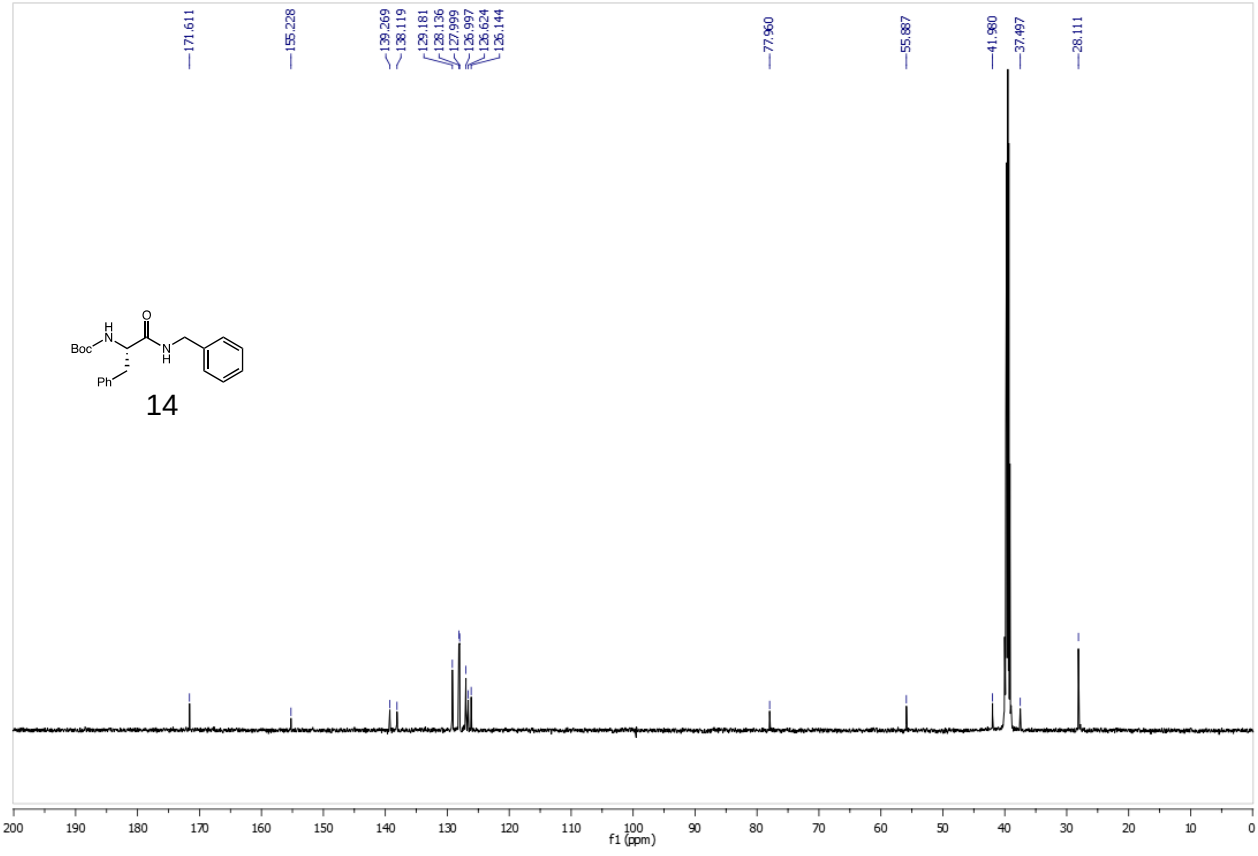
***tert*-butyl (2-(benzylamino)-2-oxoethyl)carbamate (13)**



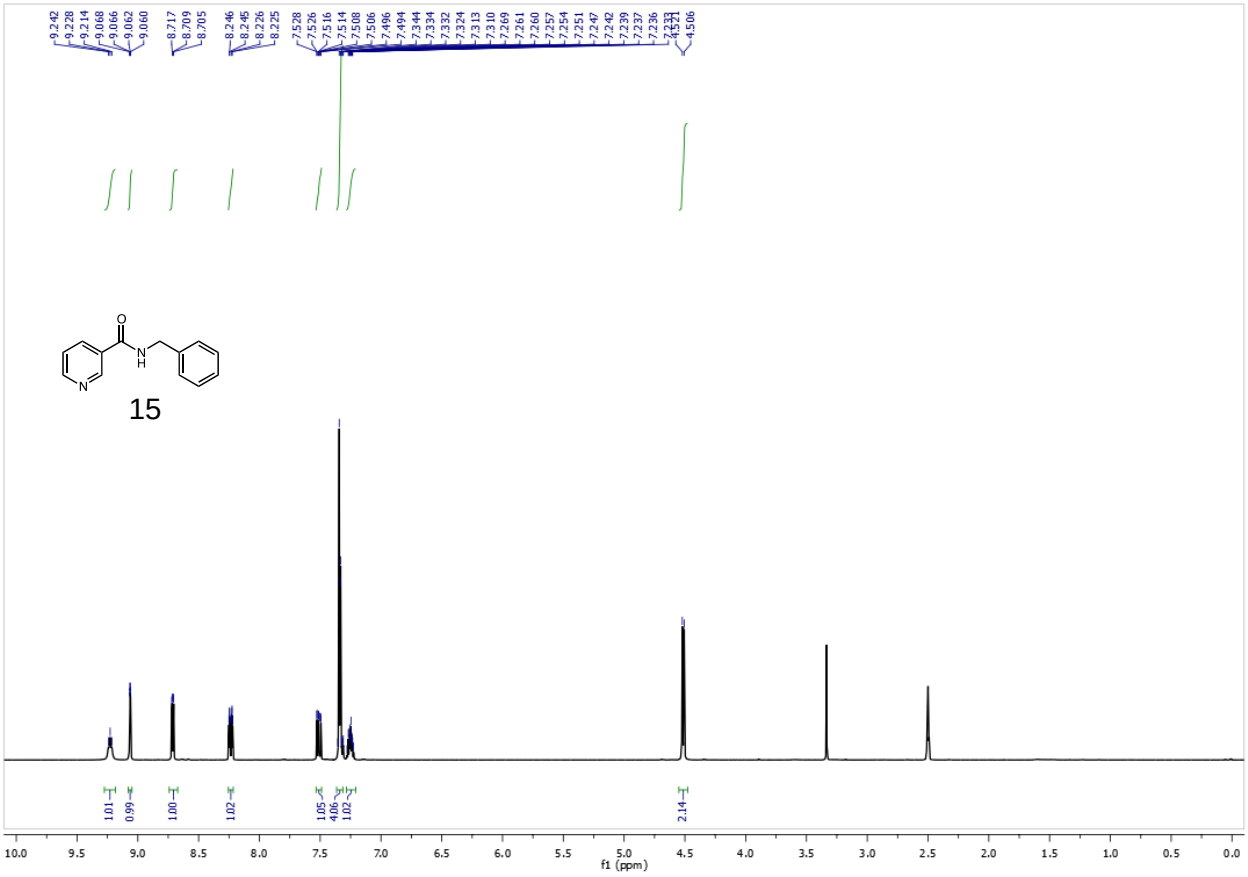


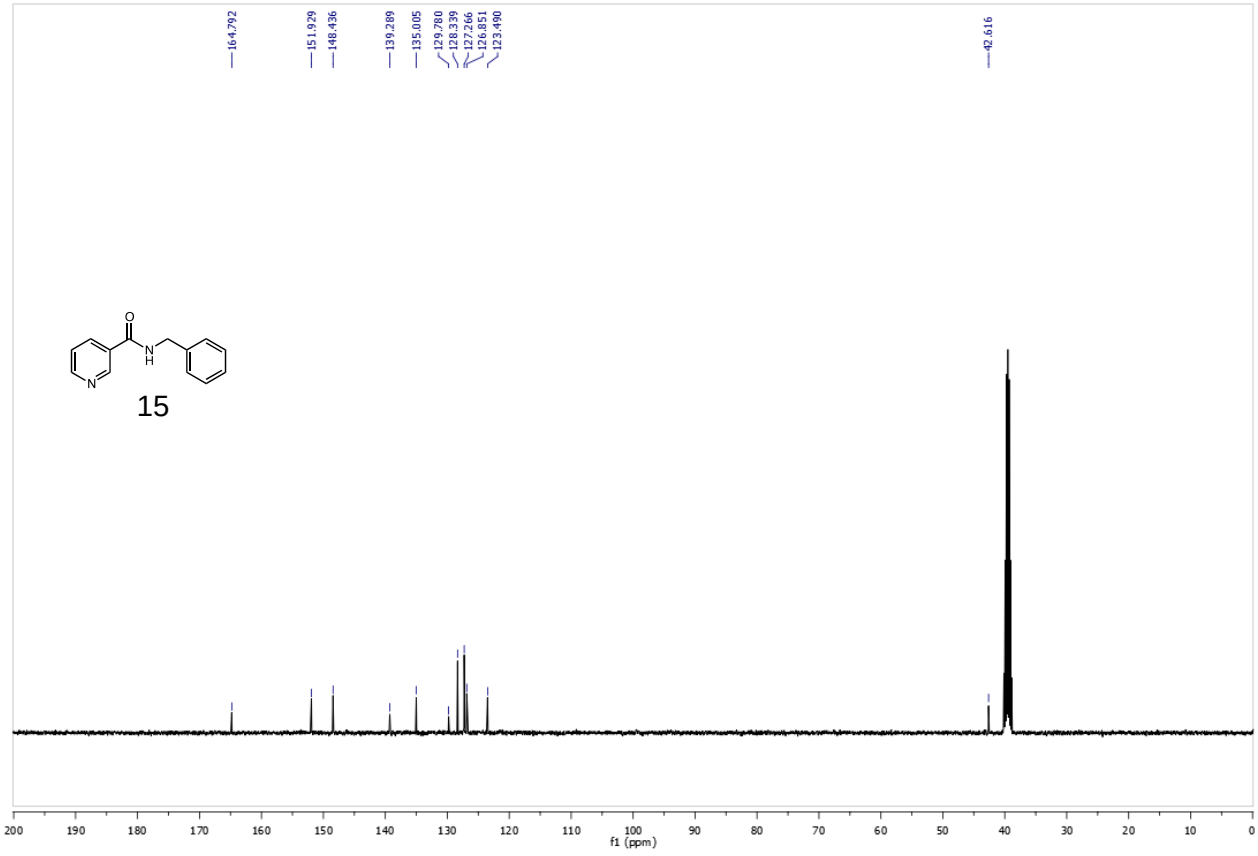
(*S*)-*tert*-butyl (1-(benzylamino)-1-oxo-3-phenylpropan-2-yl)carbamate (14)



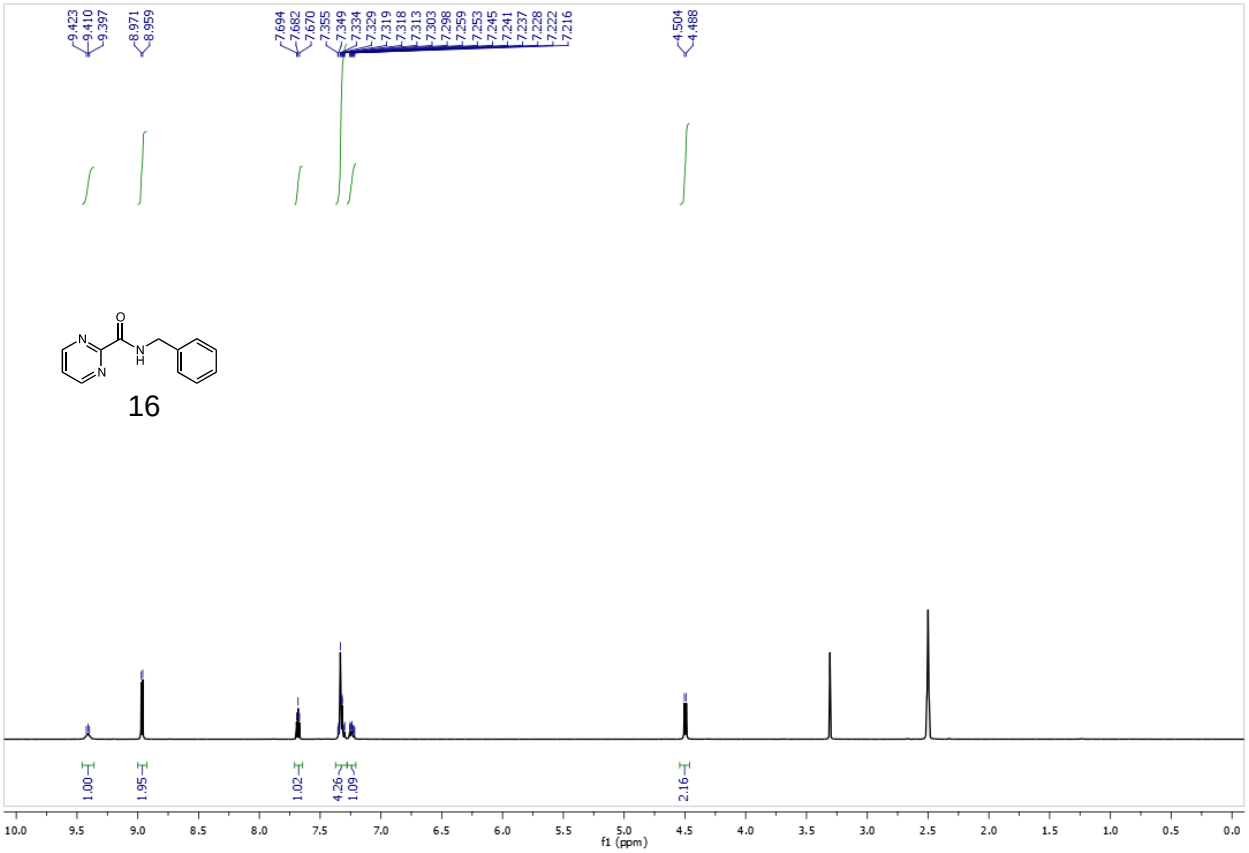


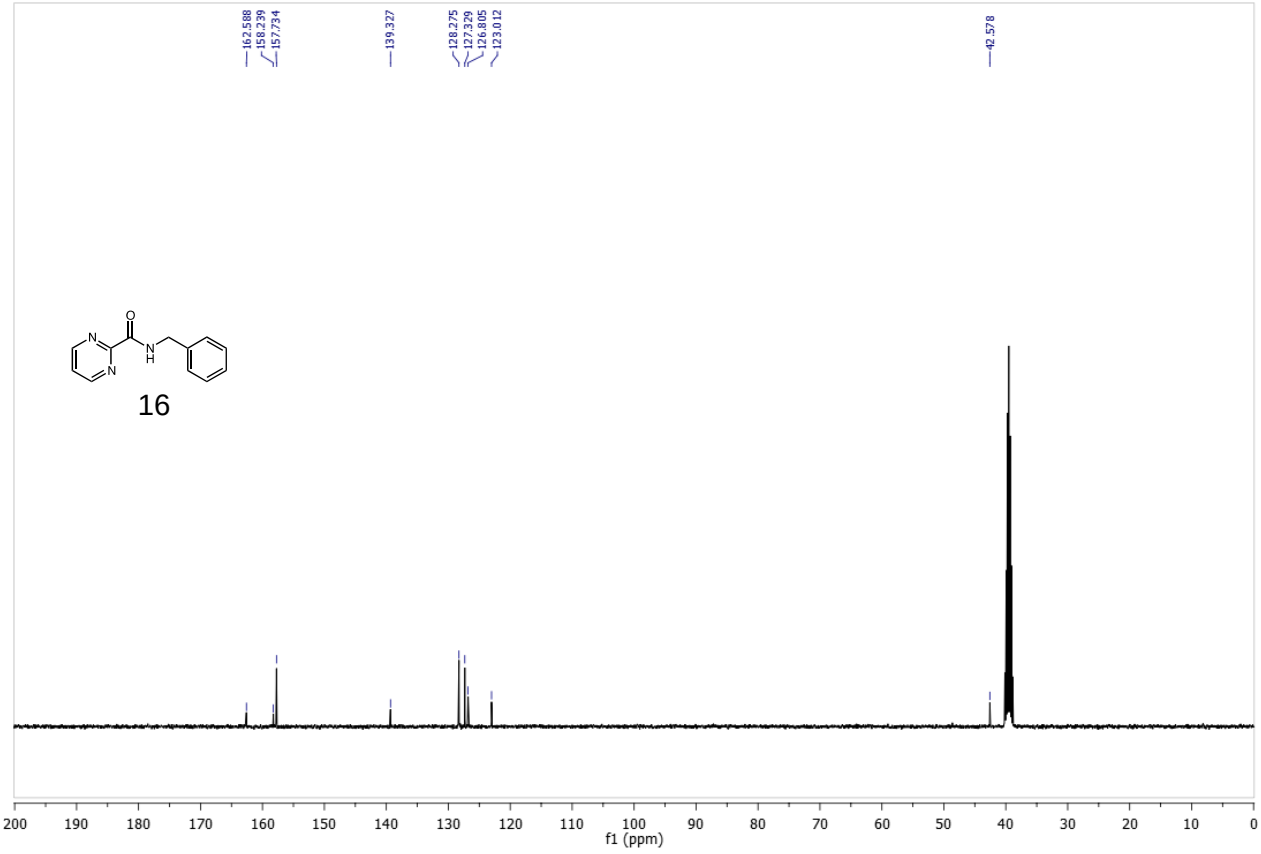
_N_-benzylnicotinamide (15)



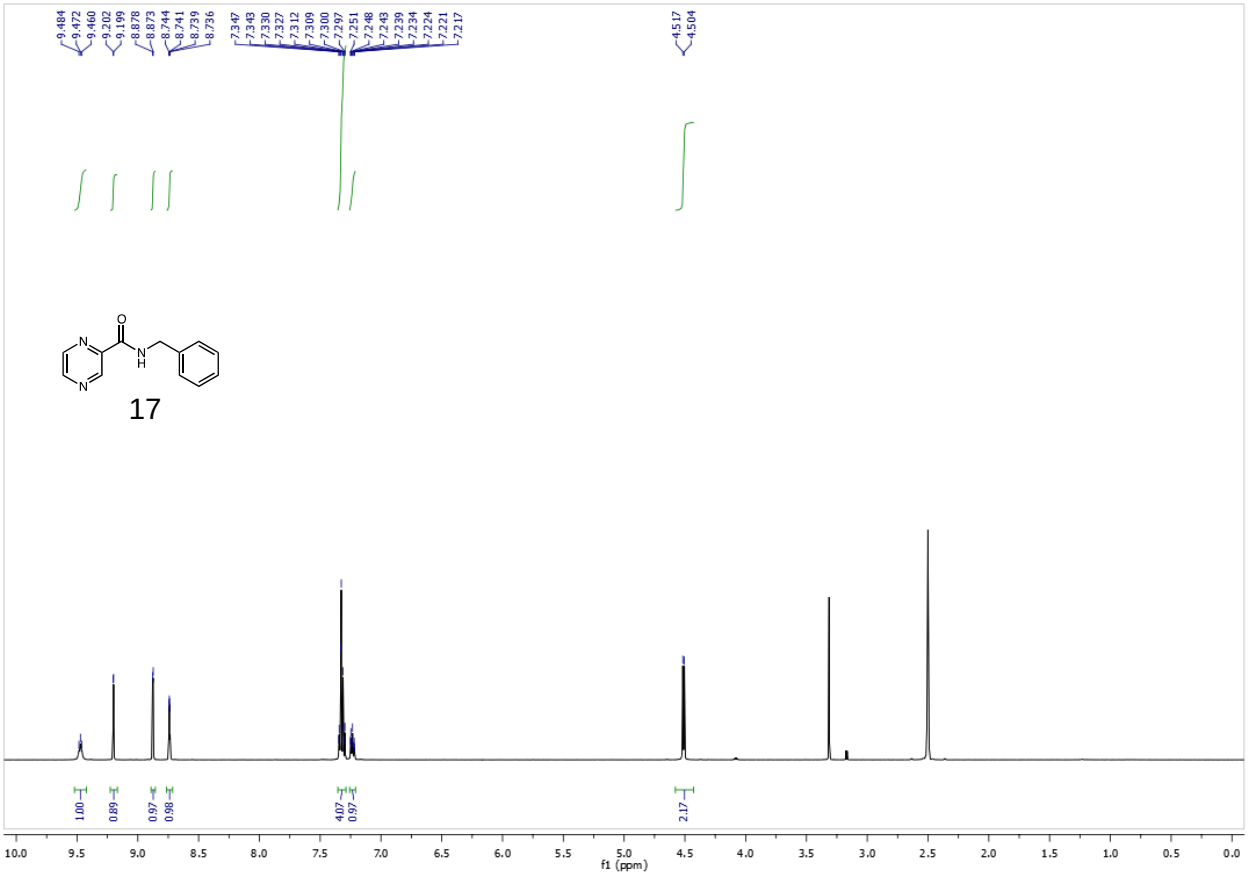


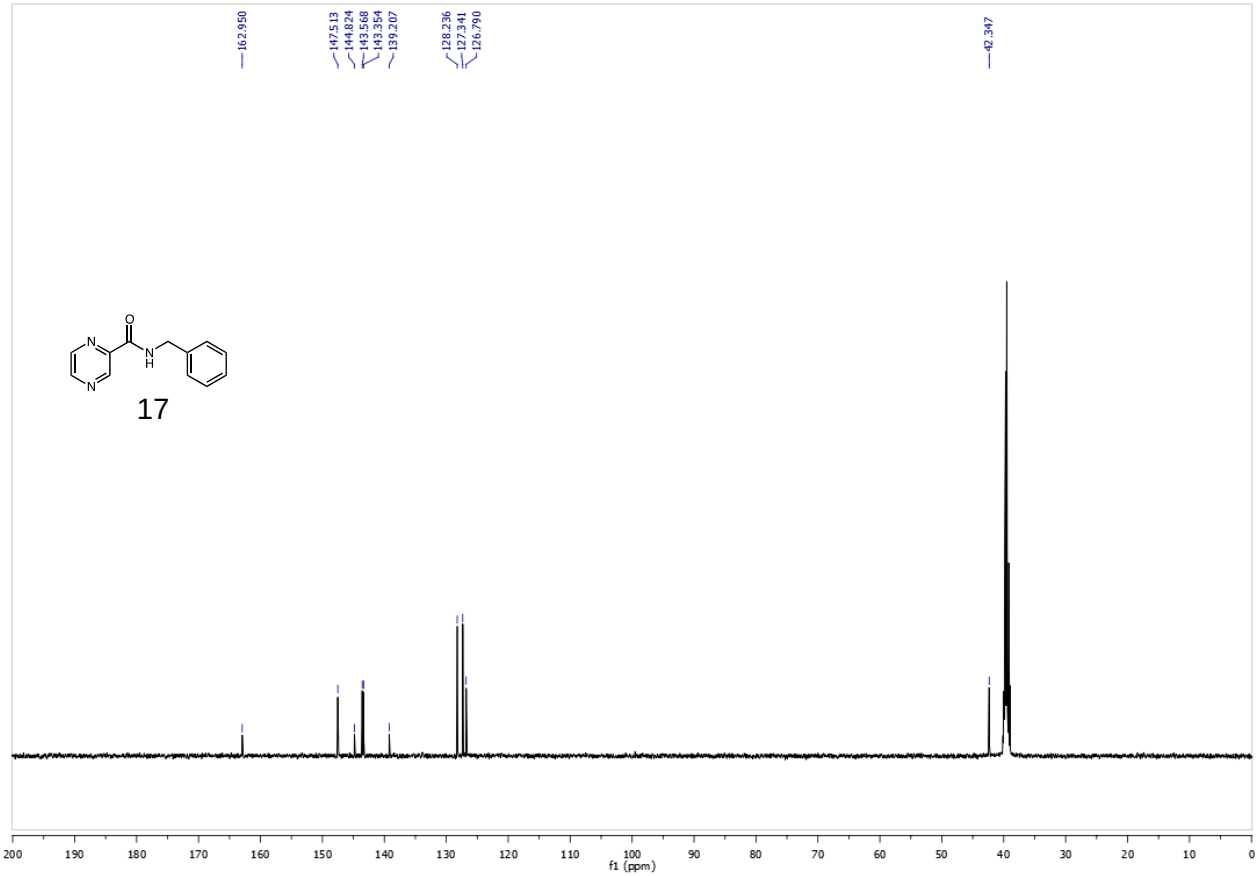
***N*-benzylpyrimidine-2-carboxamide (16)**



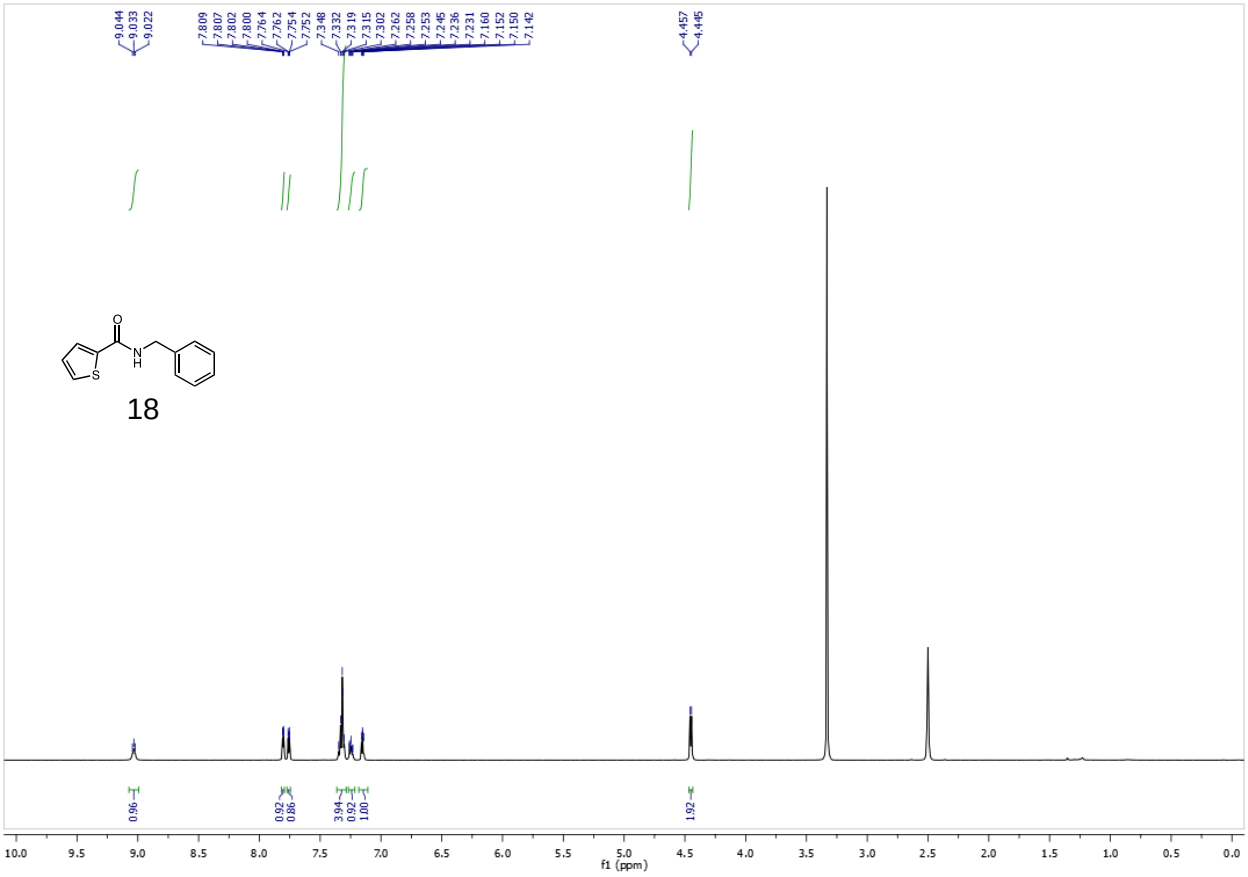


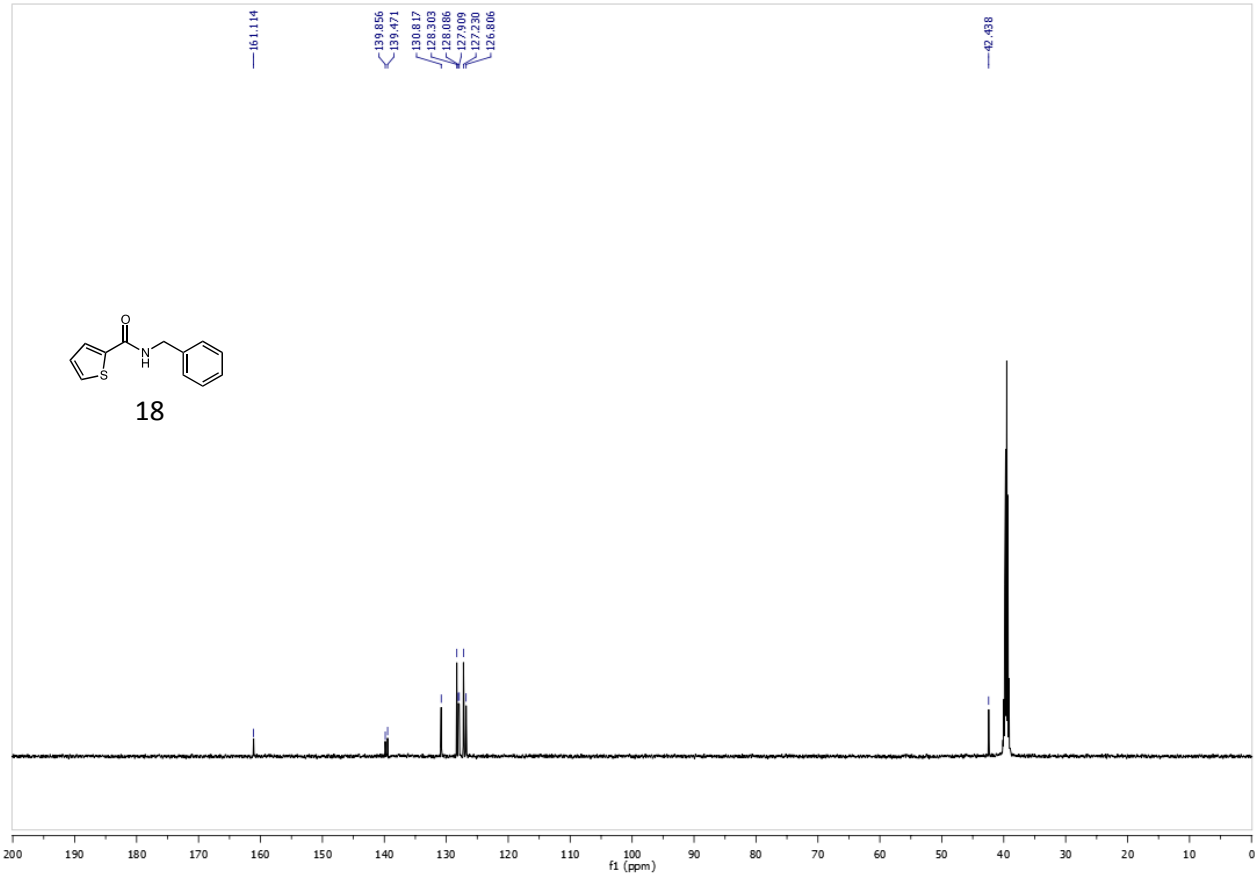
_N_-benzylpyrazine-2-carboxamide (17)



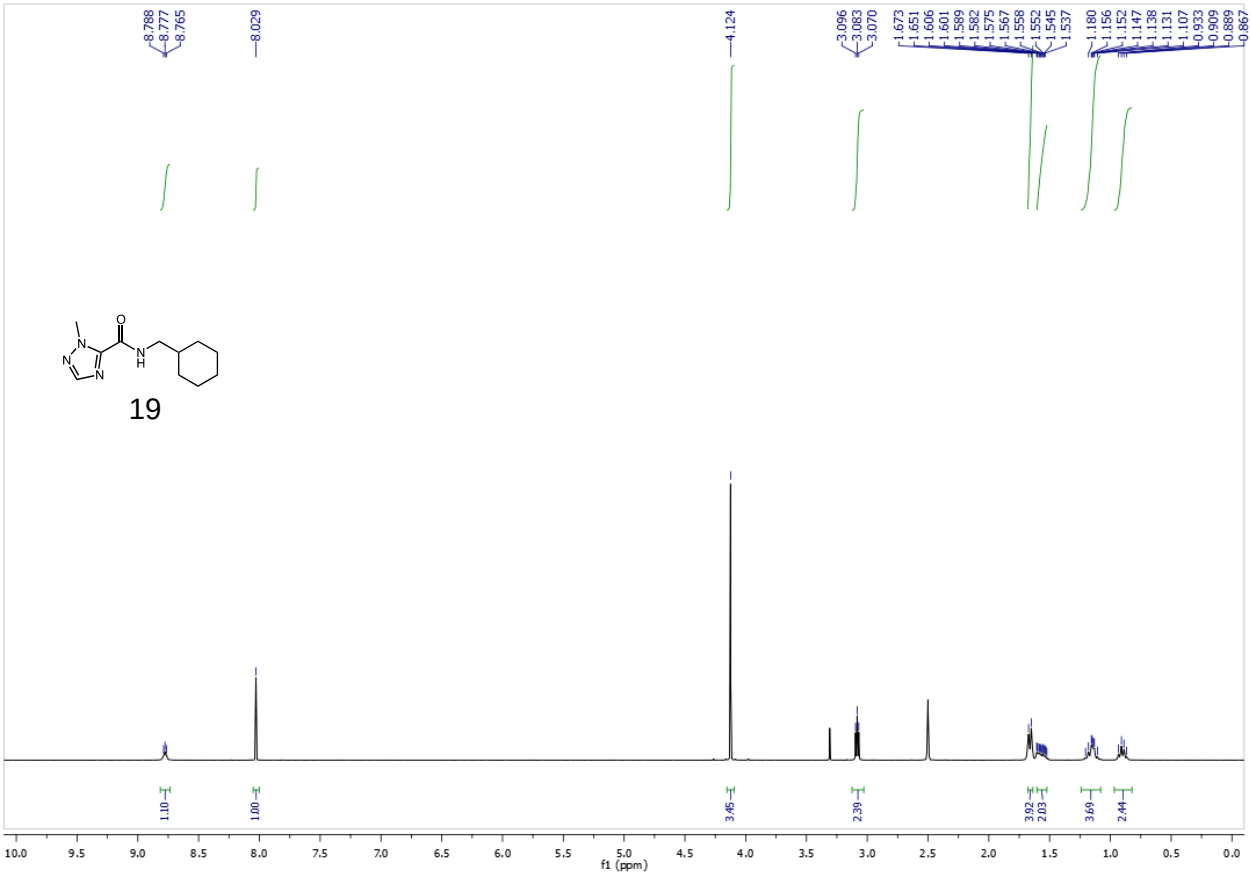


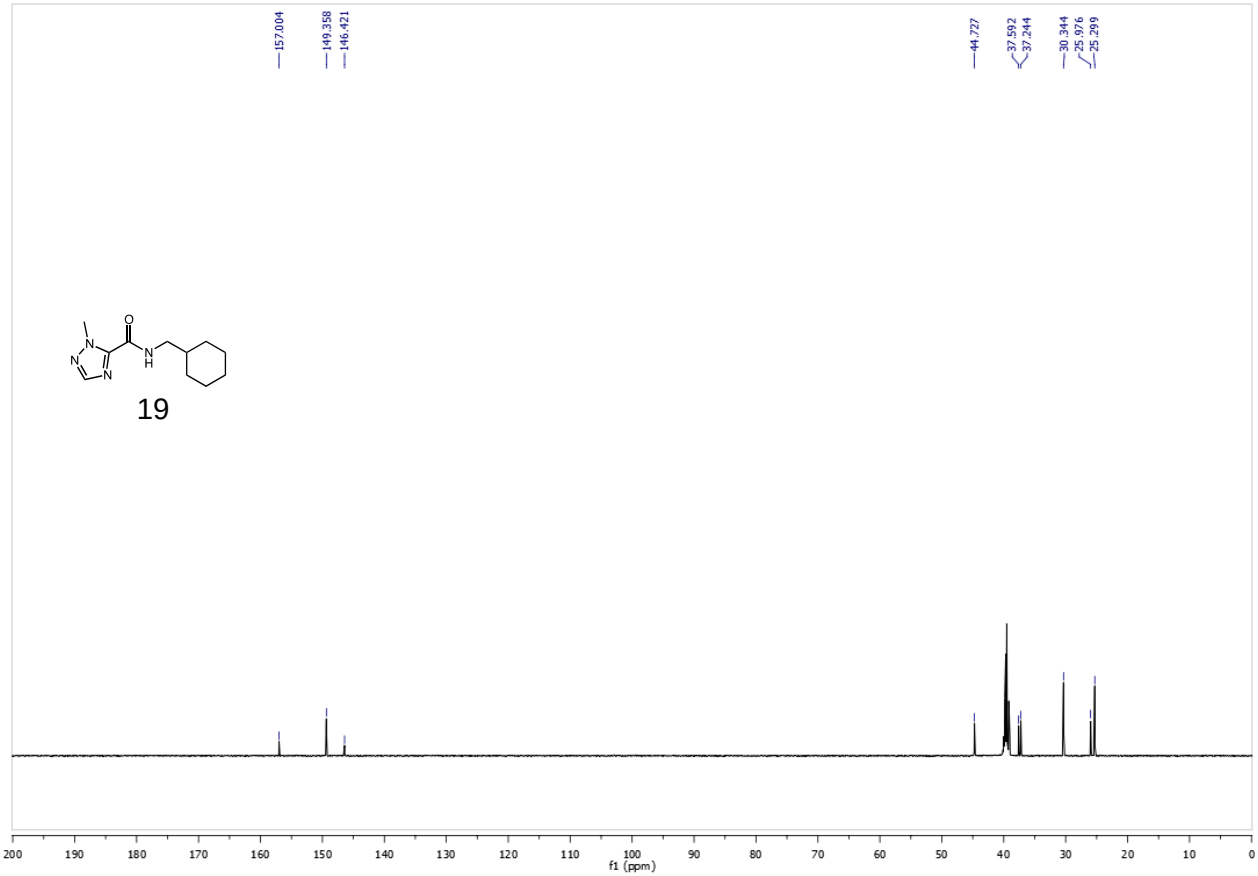
_N_-benzylthiophene-2-carboxamide (18)



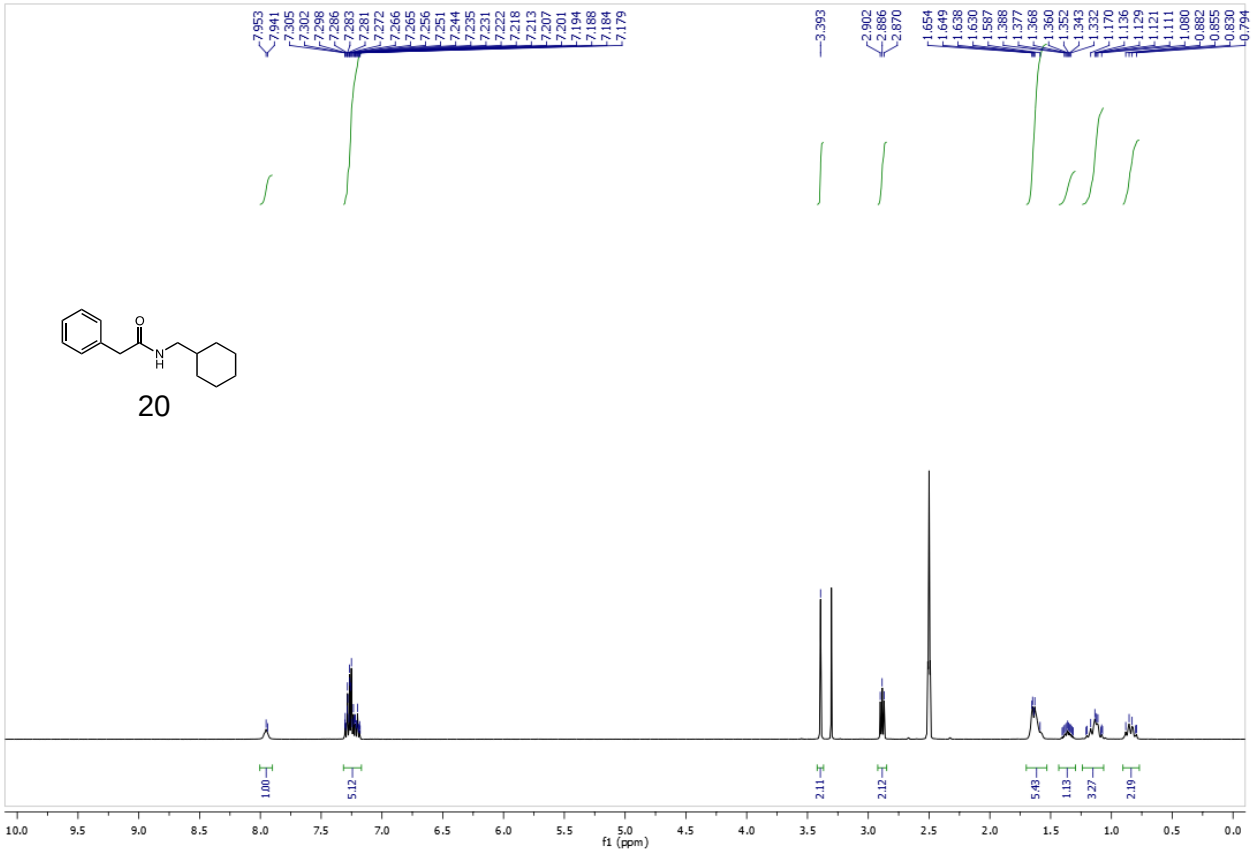


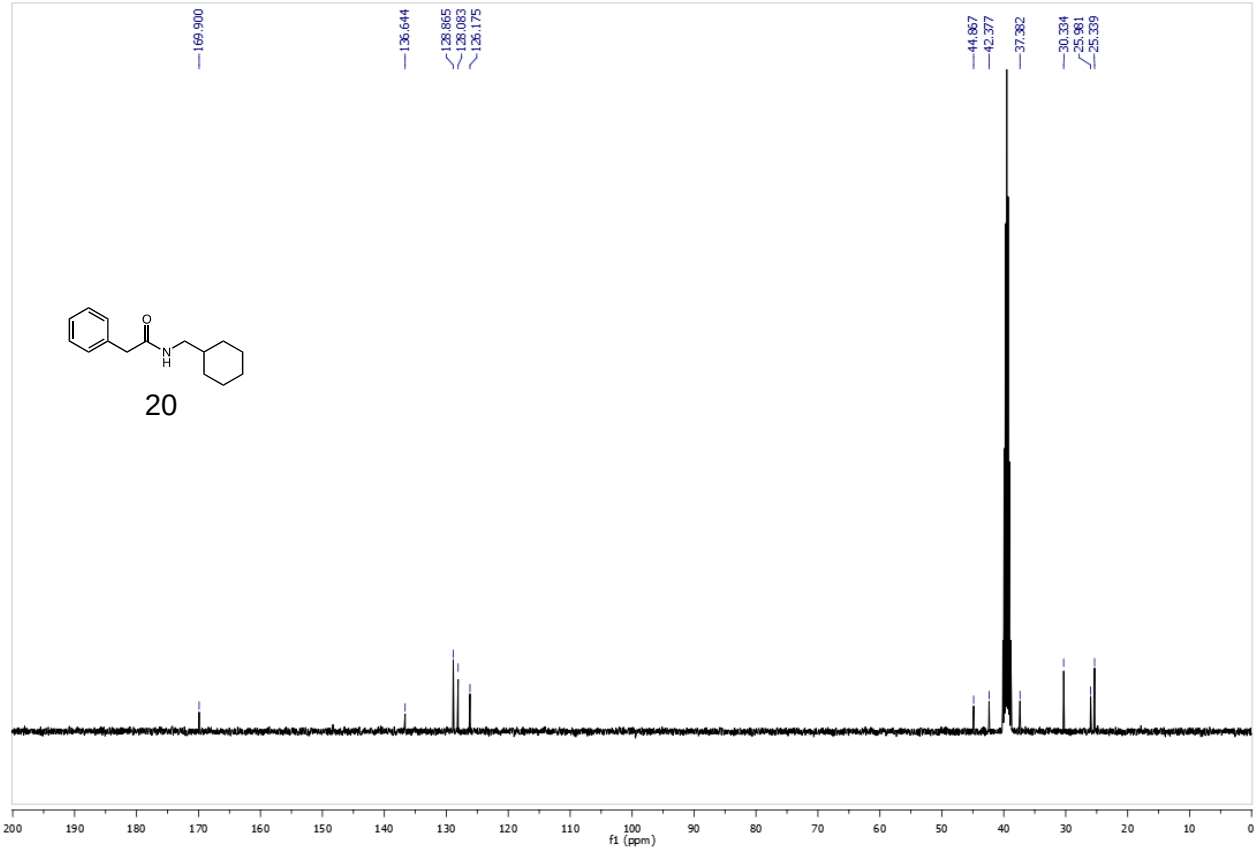
_N_-(cyclohexylmethyl)-1-methyl-1_H_-1,2,4-triazole-5-carboxamide (19)



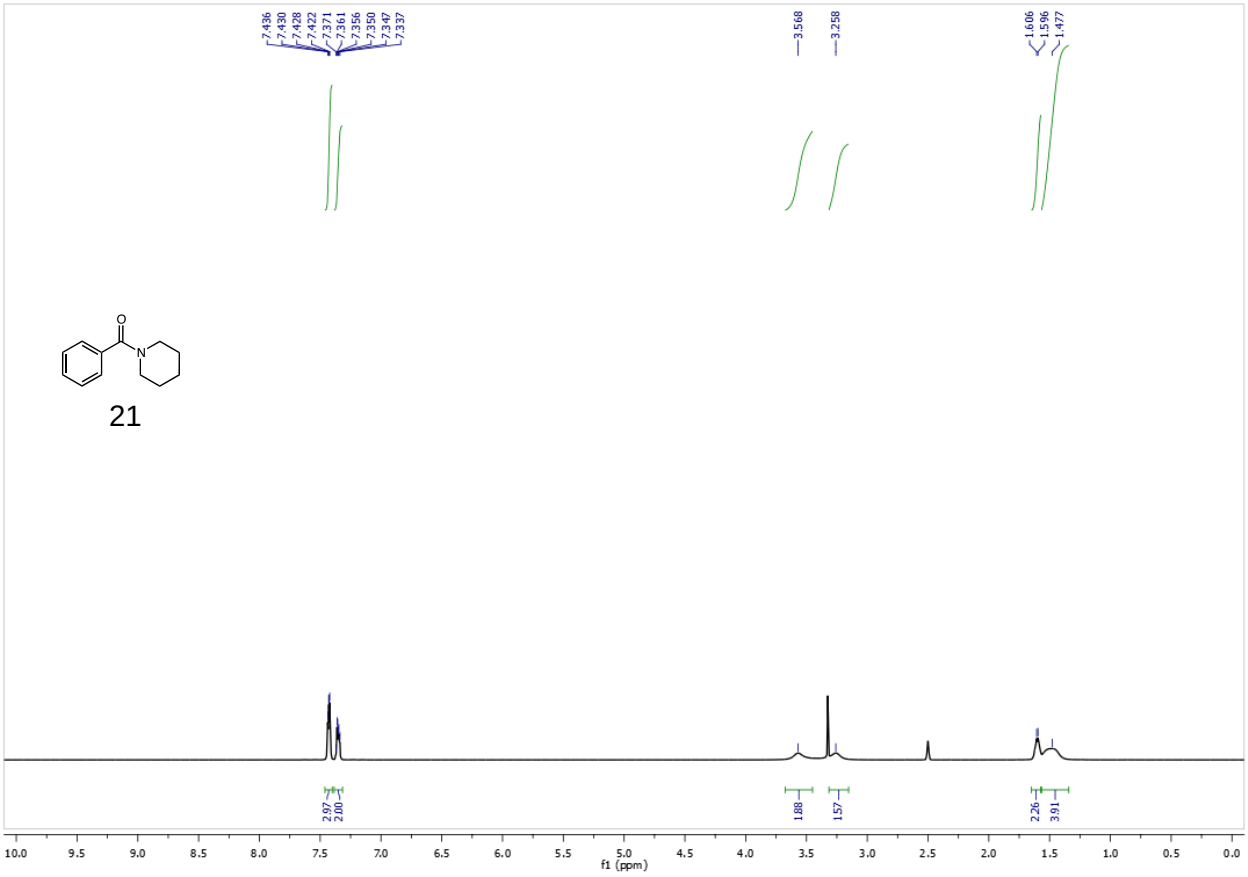


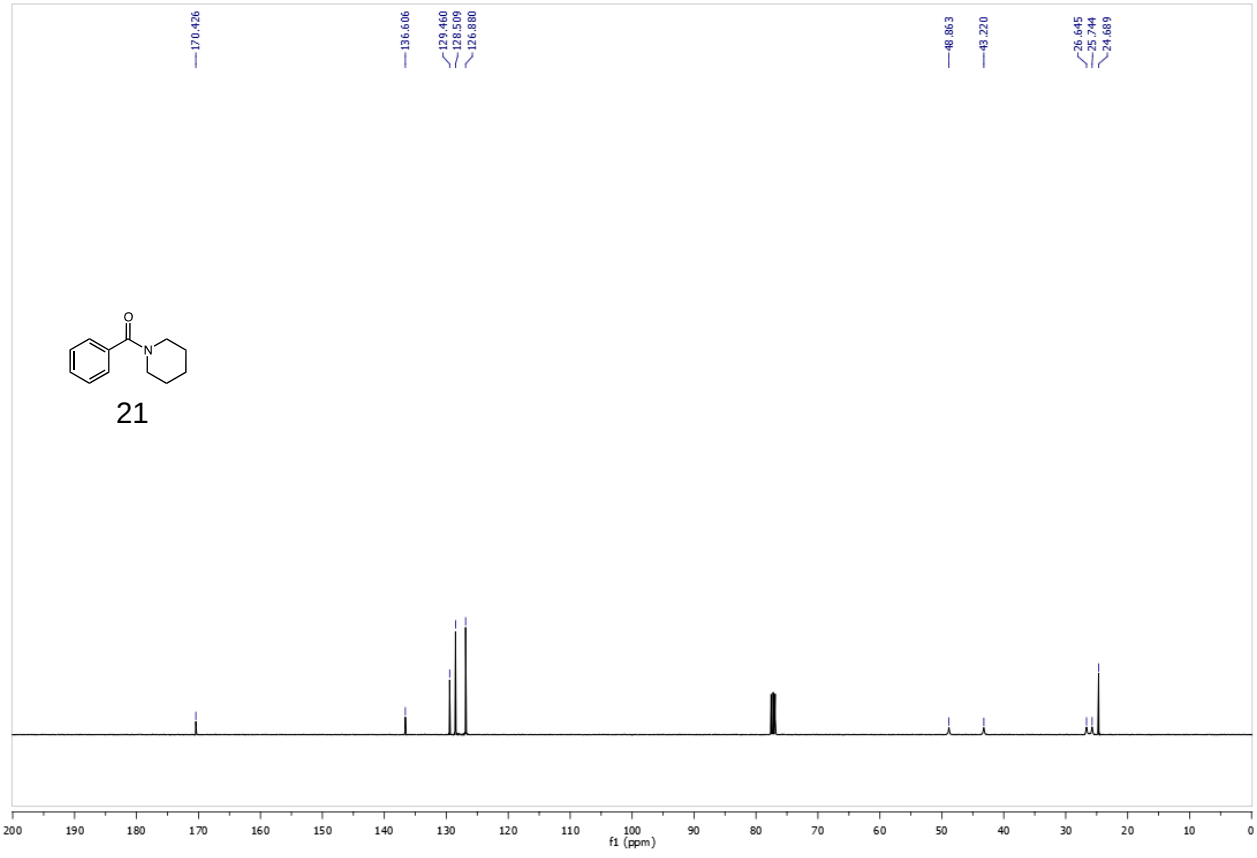
_N_-(cyclohexylmethyl)-2-phenylacetamide (20)



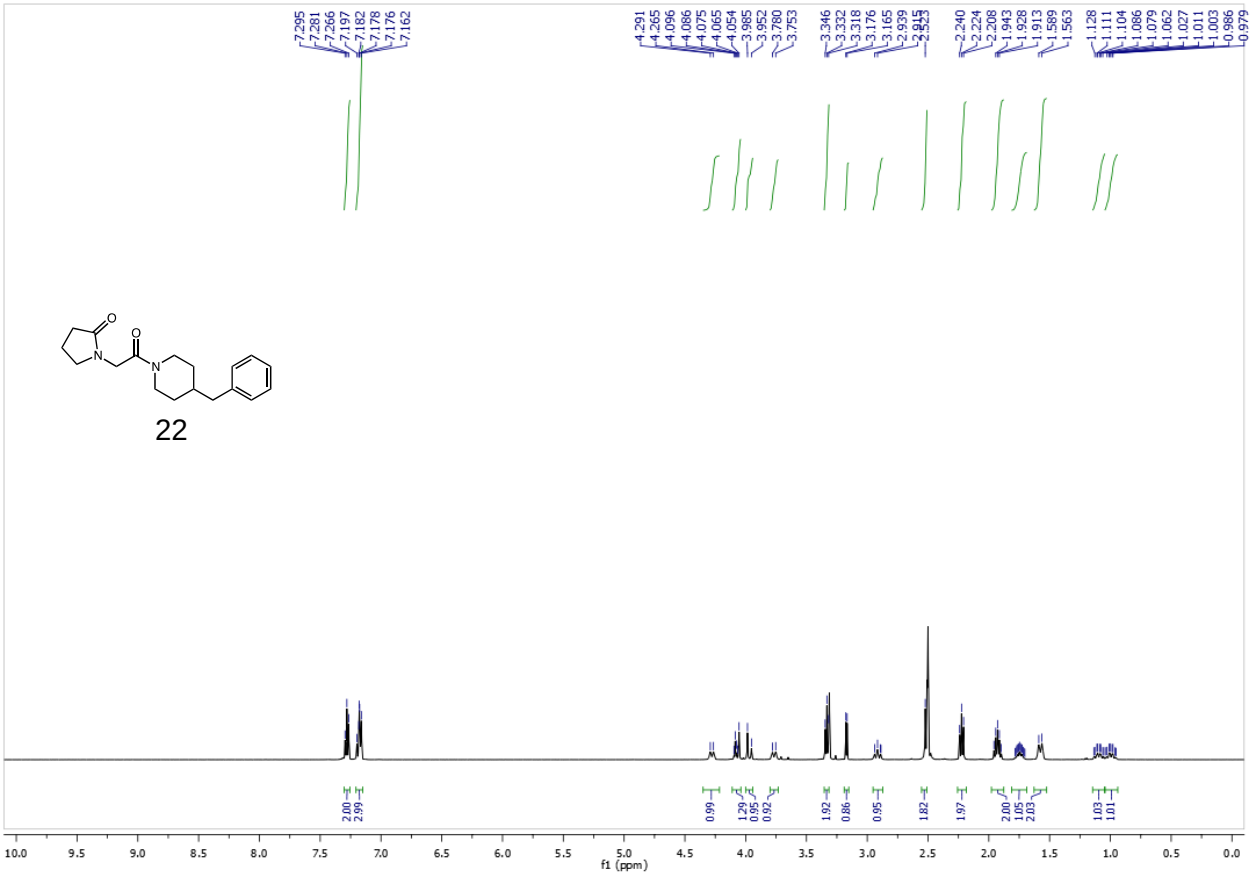


phenyl(piperidin-1-yl)methanone (21)





1-(2-(4-benzylpiperidin-1-yl)-2-oxoethyl)pyrrolidin-2-one (22)



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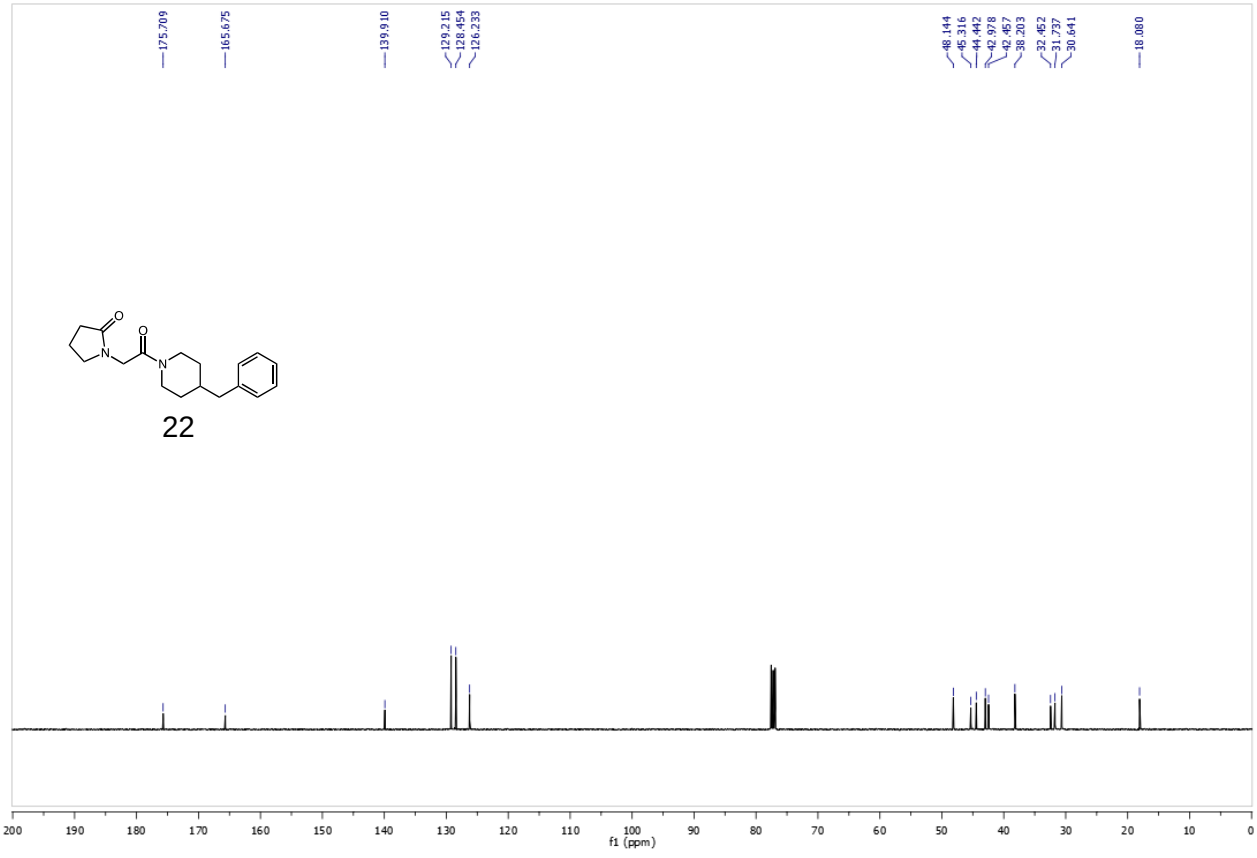
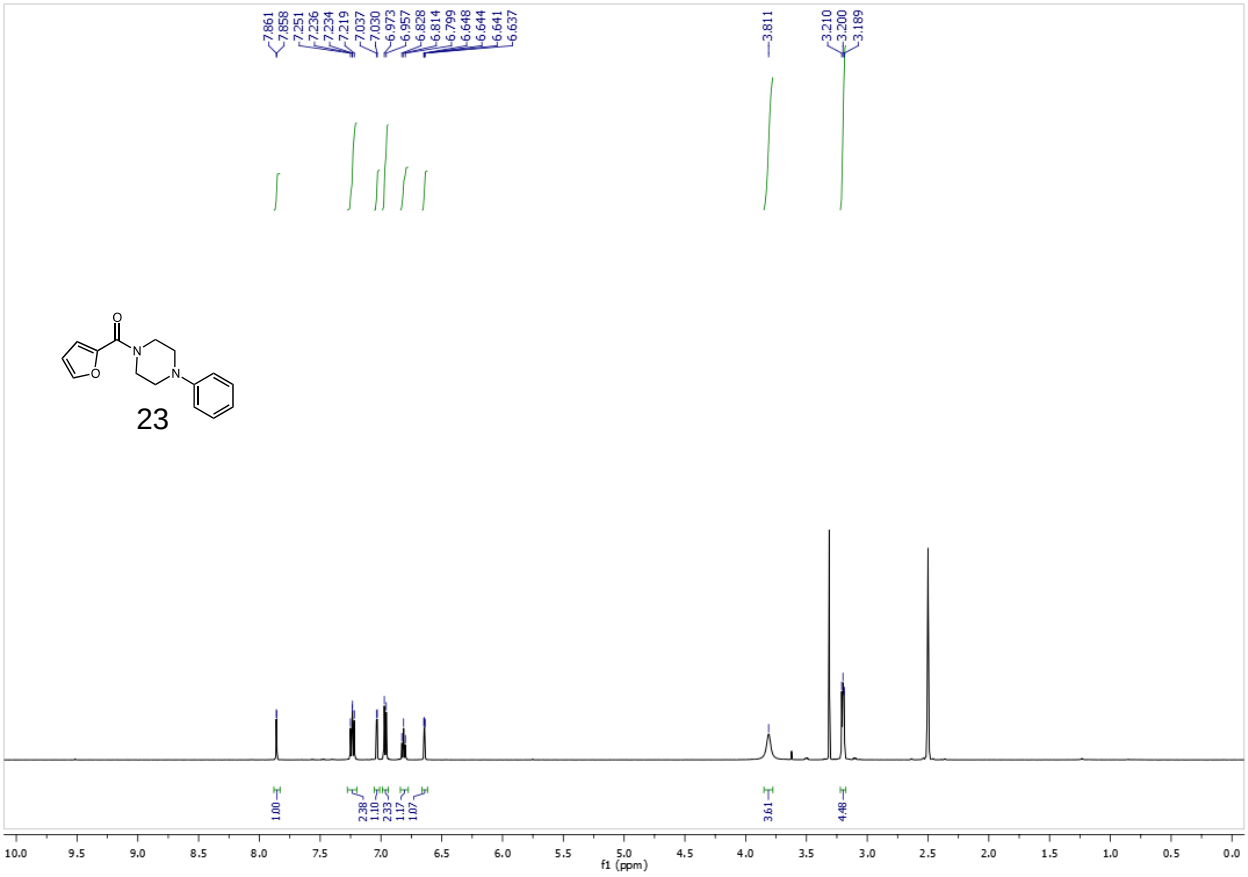
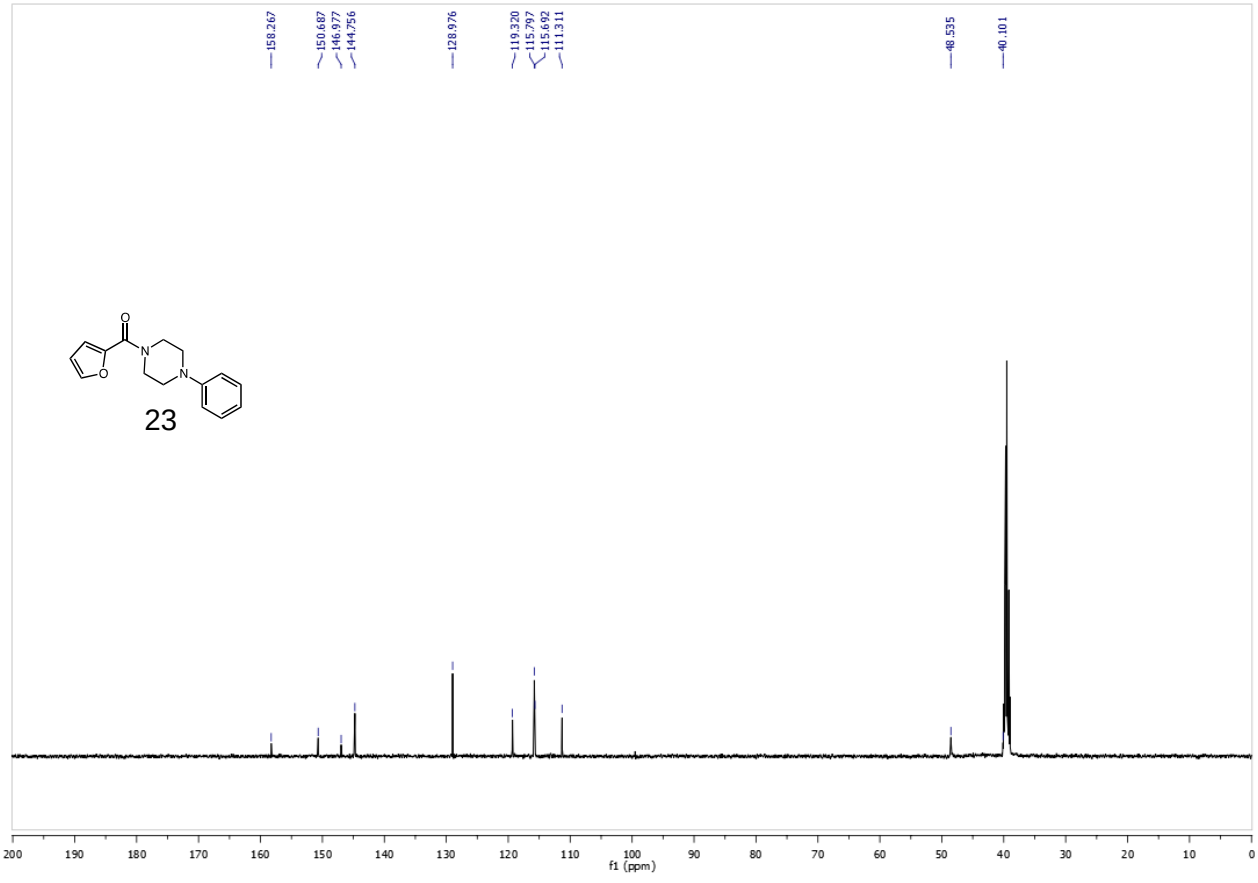


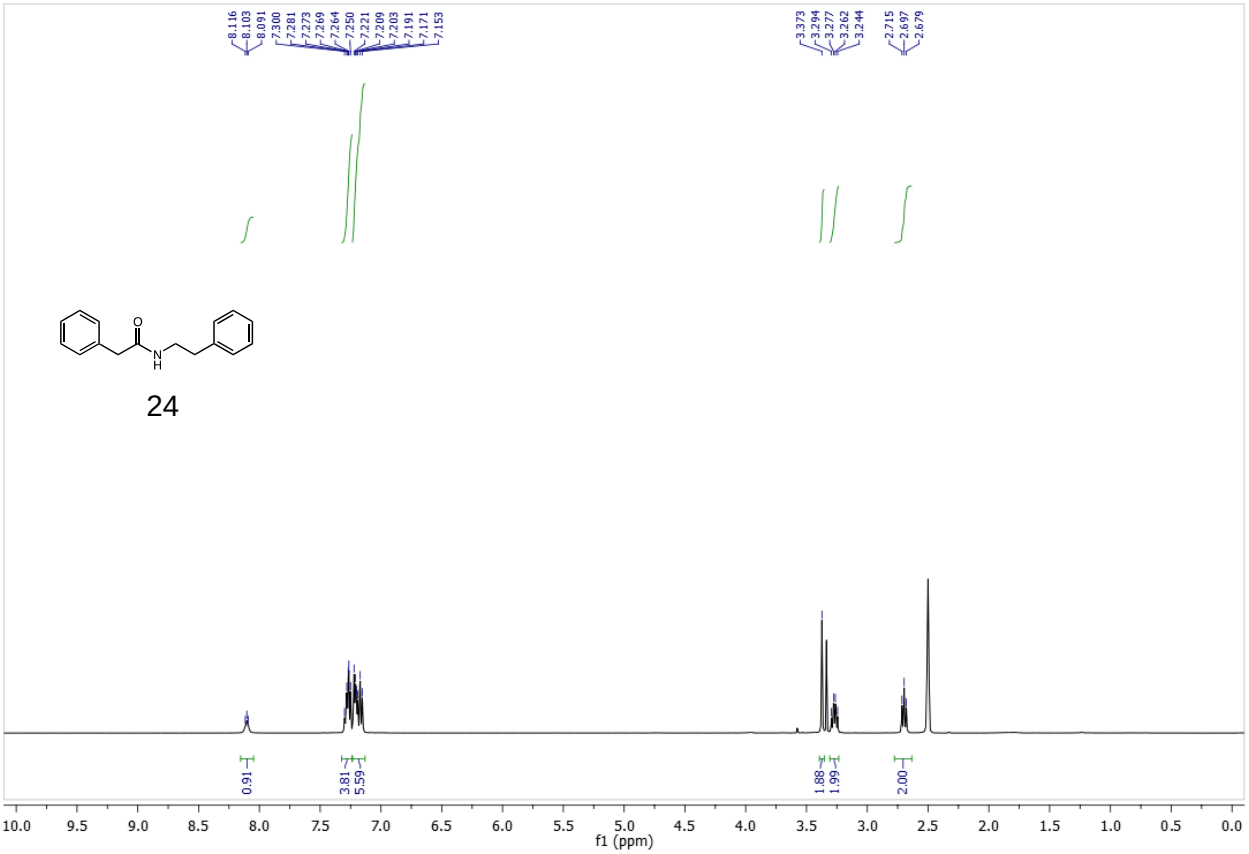
22

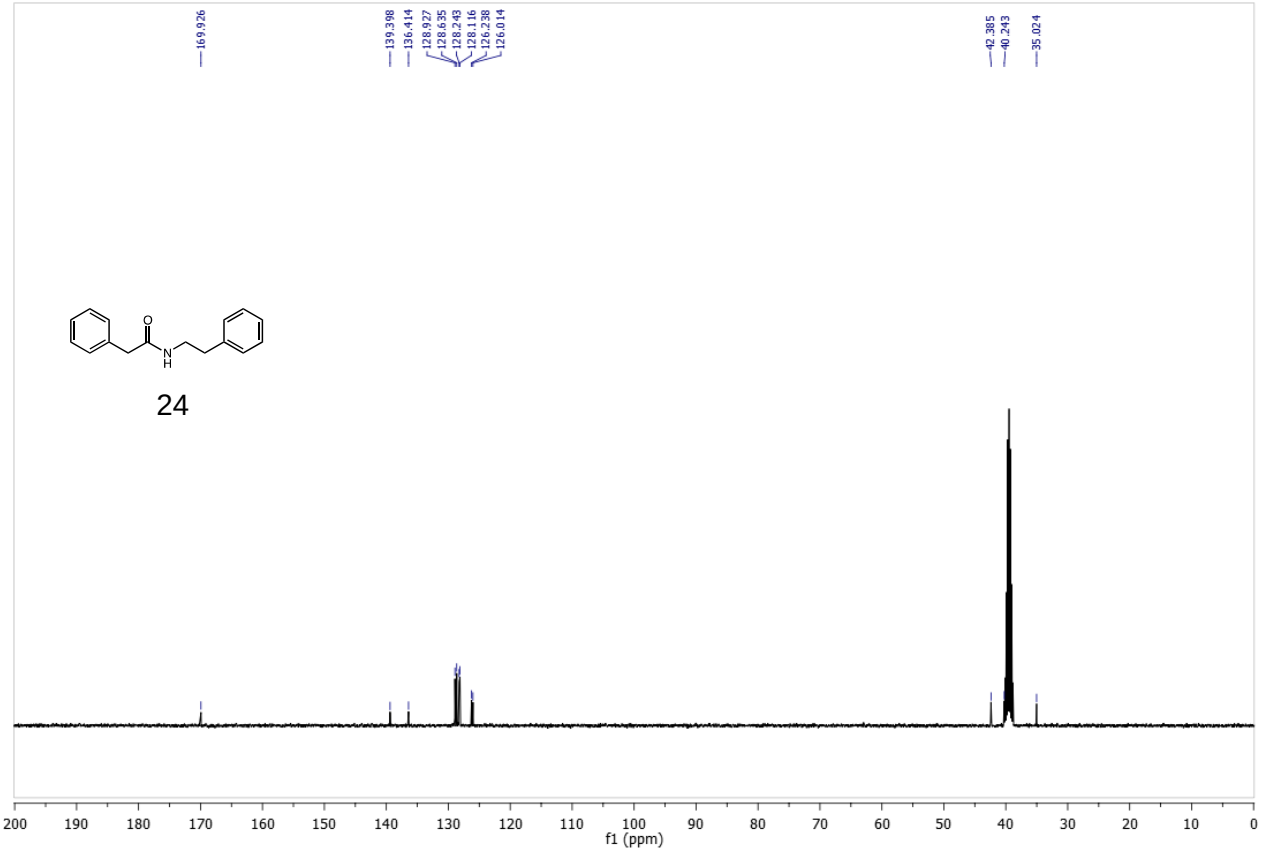
furan-2-yl(4-phenylpiperazin-1-yl)methanone (23)



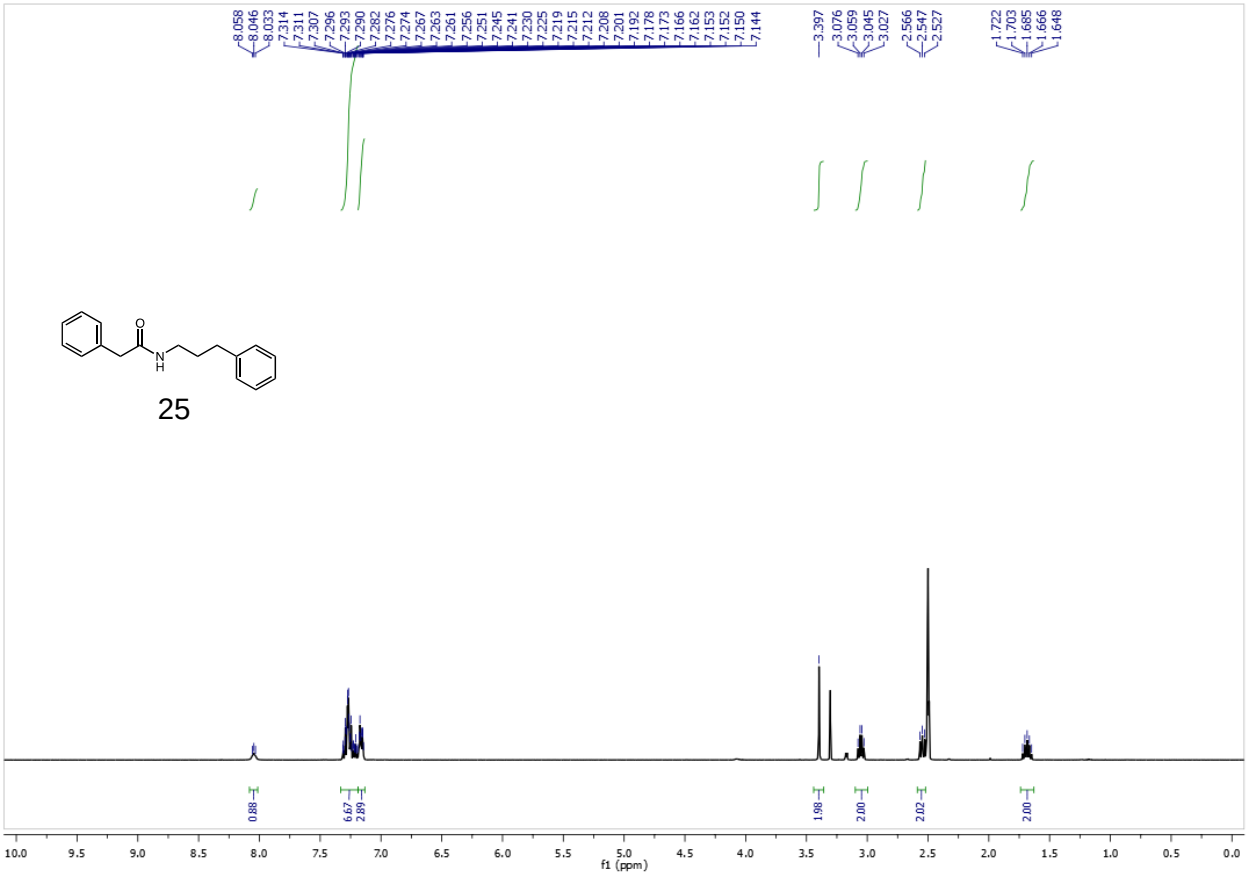


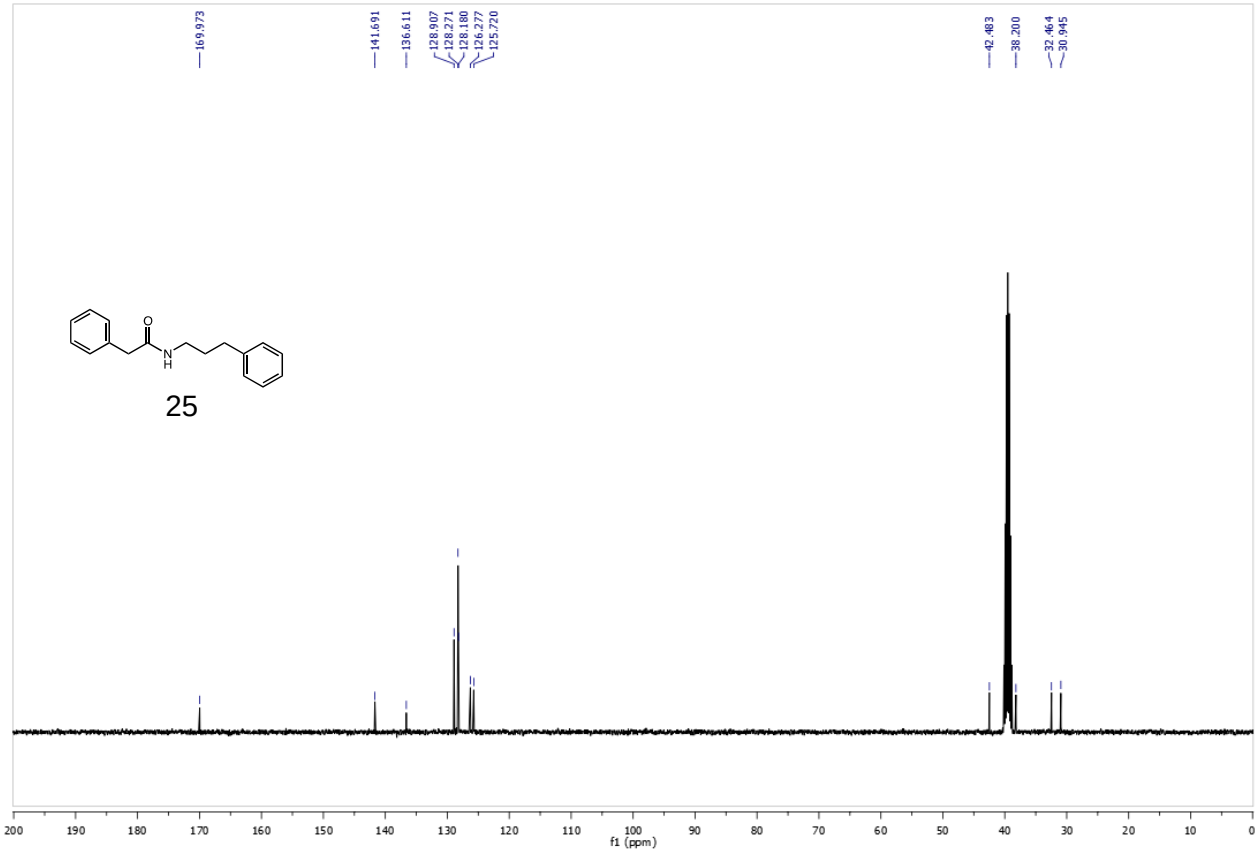
_N_-phenethyl-2-phenylacetamide (24)



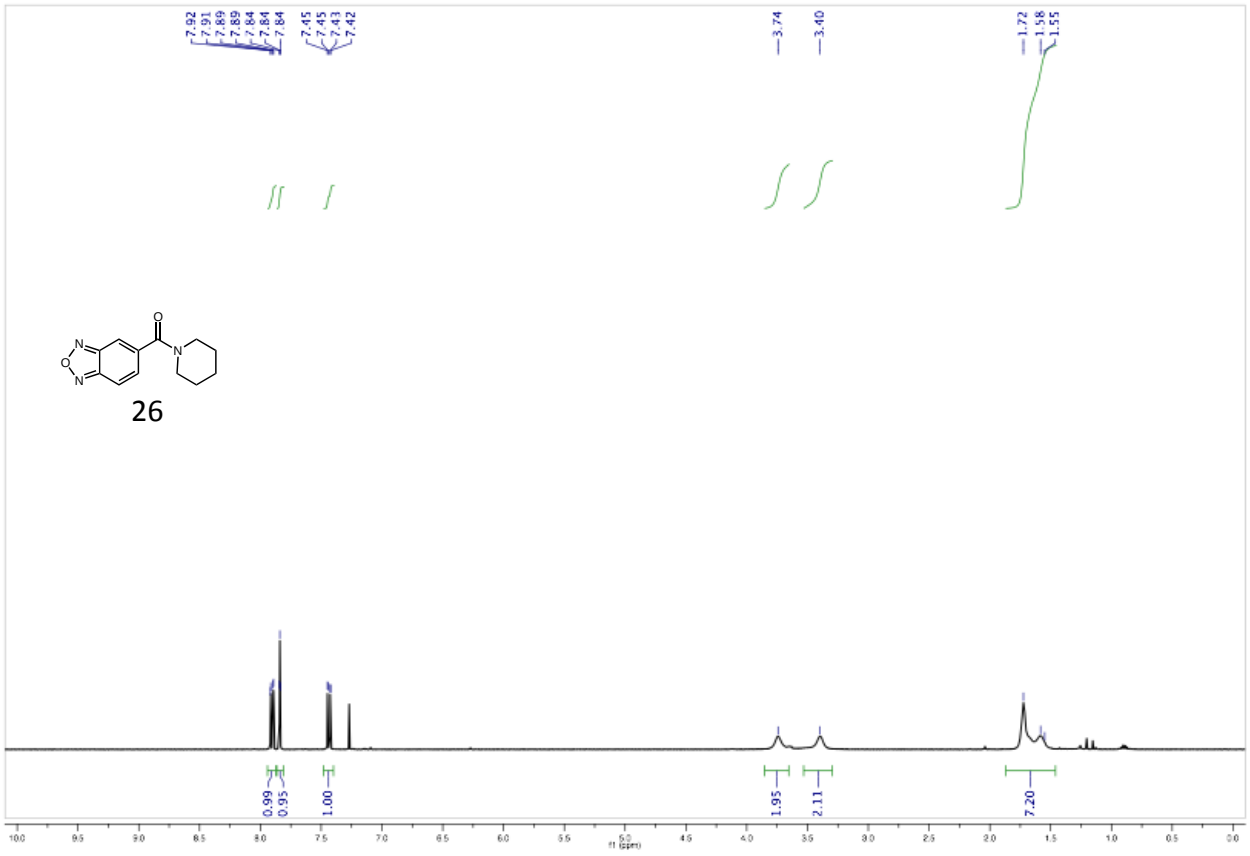


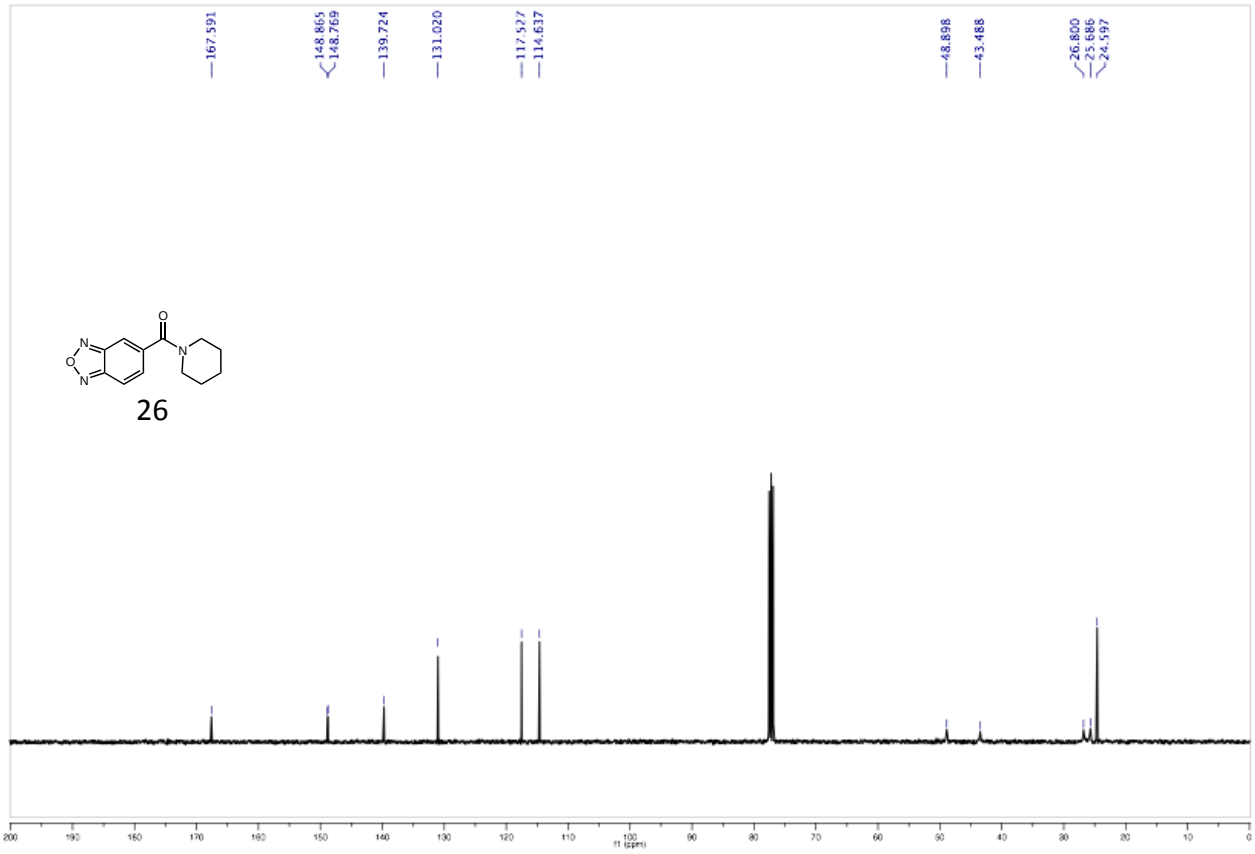
2-phenyl-*N*-(3-phenylpropyl)acetamide (25)



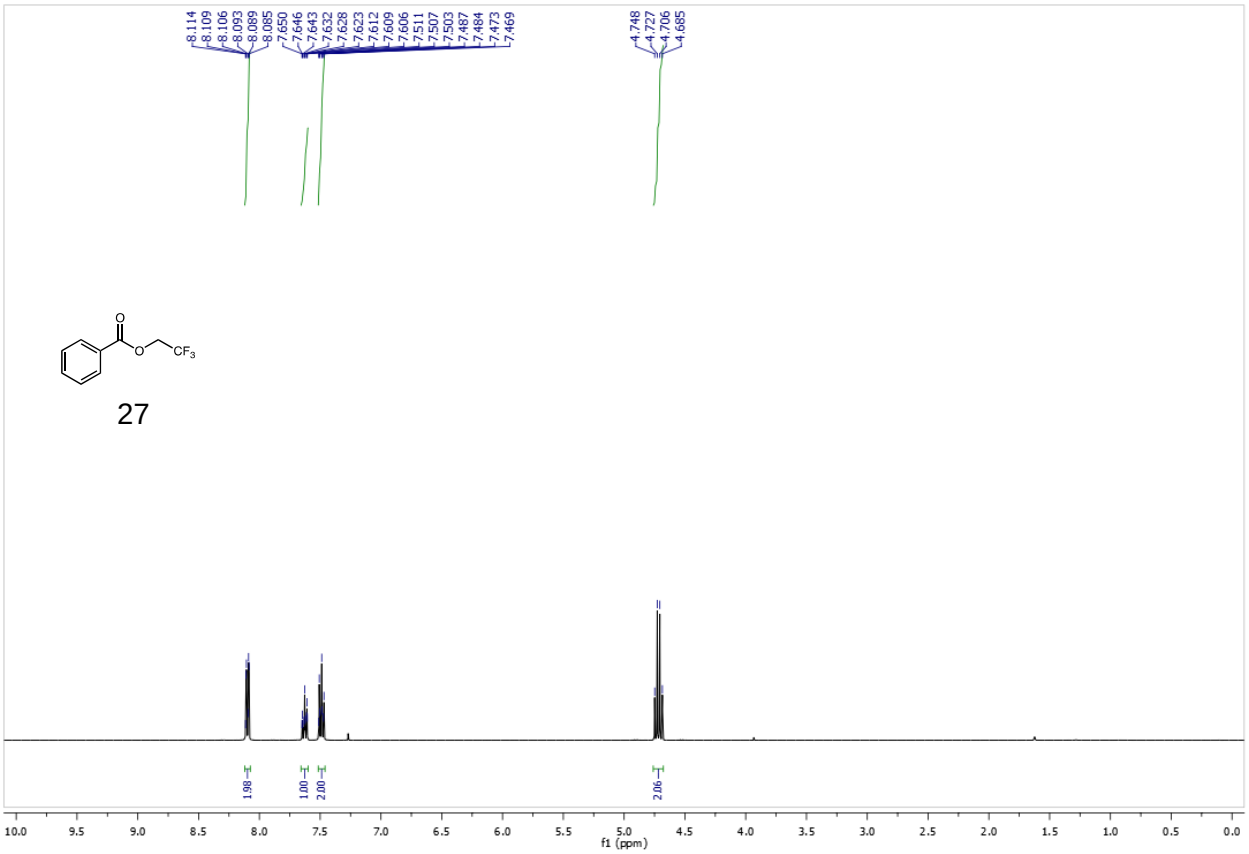


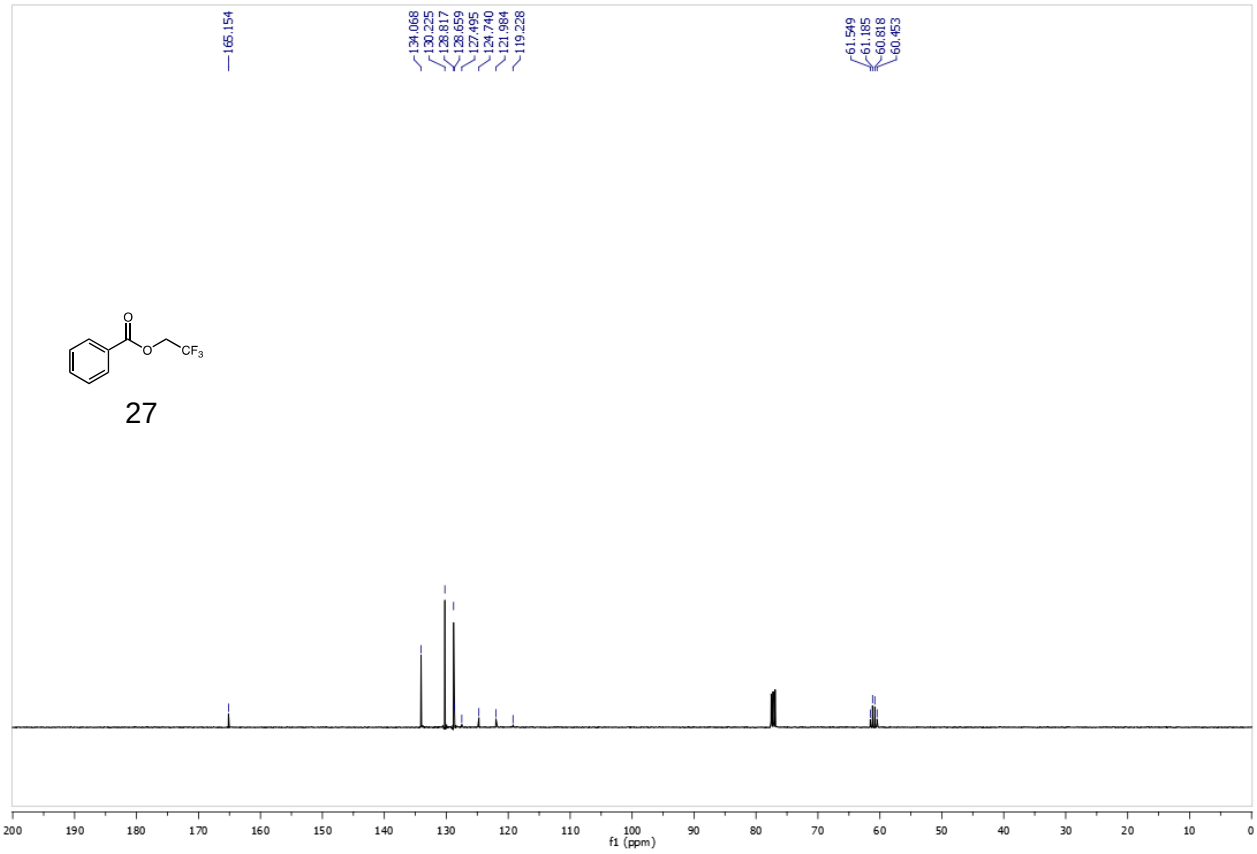
benzo[c][1,2,5]oxadiazol-5-yl(piperidin-1-yl)methanone (26)





2,2,2-trifluoroethyl benzoate (27)





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