Electronic Supplementary Material (ESI) for RSC Advances.

Supplementary Information

Chemoselective calcium-catalysed direct amidation of carboxylic esters

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1. Materials and Methods

Solvents were purchased from commercial suppliers and dried over activated alumina prior to use on a MBraun MB SPS800 and stored under a protected atmosphere of nitrogen. Dry solvents were handled using standard syringe techniques. Chemicals, which were obtained from commercial suppliers, were used without further purification.

Reactions were carried out in reaction tubes purchased from Radleys designed for a Radley Carousel Plus 12. Analysis by gas chromatography was carried out using a Shimadzu GC2010+, containing an Agilent DB-1 column (30 m, 0.32 mm ID, 0.25 Am DF). Signals were detected by FID. Chiral HPLC measurements were recorded on a Shimadzu LC2010C Analytical HPLC system using a Diacel Chiralpak AD-H column (250 x 4.6 ID), *n*-heptane/isopropanol (90:10 v/v). Nuclear Magnetic Resonance (NMR) data were recorded on a Varian 400 (400 MHz) or Bruker DMX 300 (300 MHz) spectrometer. ^{1}H NMR chemical shifts are reported as δ in units of parts per million (ppm) relative to tetramethylsilane (TMS, δ 0.00 ppm) as the internal standard. ^{13}C NMR shift are reported as δ in units of parts per million (ppm) relative to $CHCl_3$ (δ 77.0 ppm). Multiplicities are given as: s (singlet), bs (broad singlet), d (doublet), t (triplet), q (quartet), quin (quintet), m (multiplet), app (apparent). Coupling constants are reported as *J*-values in Hertz (Hz). A Thermo Finnigan LCQ Advantage Max electrospray-ion trap mass spectrometer was used to record low resolution mass spectrometry data. High resolution mass spectra were recorded on a JEOL JMS-T10m=0CS AccuTOF, 2005, TOF, LCMS, ESI, Agilent 1100 series HPLC. Melting points were determined using a Buchi Melting Point B-545.

2. General Procedures

2.1 Catalytic reaction

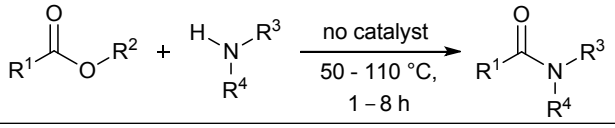
Amine (3.25 mmol) and carboxylic ester (2.5 mmol) were suspended in anhydrous toluene giving a 2M solution. The catalyst (10 – 20 mol%) was then added and the reaction was stirred at 110 °C for 1 - 8 hours. After cooling to room temperature, the crude mixture was concentrated under reduced pressure. Subsequently, ethyl acetate (10 mL) was used to redissolve the crude product and next 1M HCl (10 mL) was added. The product was extracted using ethyl acetate (4 x 12mL). The combined organic fractions were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The desired products were isolated on a Biotage Isolera™ One. Prepacked Biotage SNAP Ultra cartridges were used (12 or 25 g, 10 –40% EtOAc in *n*-heptane).

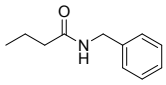
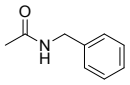
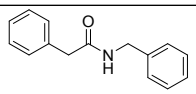
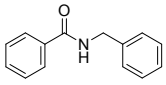
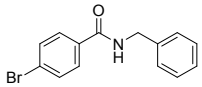
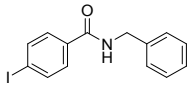
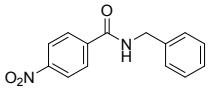
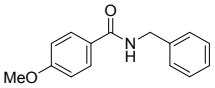
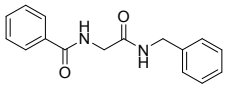
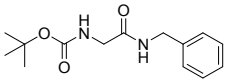
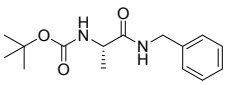
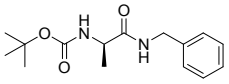
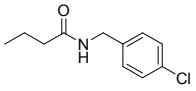
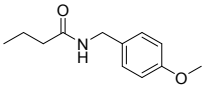
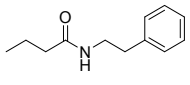
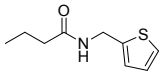
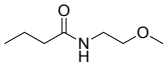
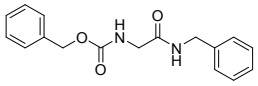
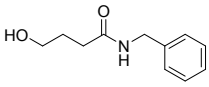
2.2 Uncatalytic reaction

Amine (3.25 mmol) and ester (2.5 mmol) were suspended in anhydrous toluene giving a 2M solution. The reaction was stirred at 110 °C for 1 - 8 hours. After cooling to room temperature, the crude mixture was concentrated under reduced pressure. The uncatalytic conversions were determined by GC and are summarized in table S0.

3. Background reaction conversions

Table S0 Background reactions: conversions[b] of uncatalytic amidation of carboxylic esters with amines[a]



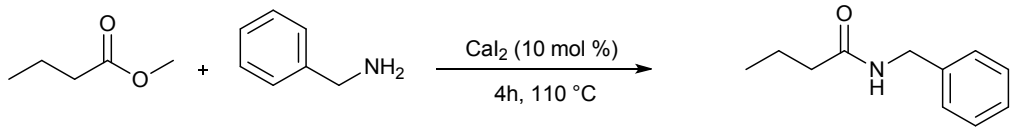
 7%	 0%	 18%
 7%	 7%	 4%
 19%	 0%	 15%
 15%	 8%	 10%
 18%	 2%	 4%
 0%	 2%	 19%
 20%[c]		

[a] Conditions: Carboxylic ester (2.5 mmol), amine (3.25 mmol), toluene (2M), 110 °C, 1 - 4 h for aliphatic esters, 8 h for aromatic esters; [b] Conversions determined by GC; [c] 50 °C, 2 h.

4. Optimization of Reaction Conditions

4.1 Optimisation of Reaction Conditions for Aliphatic Esters (Table S1 - S4)

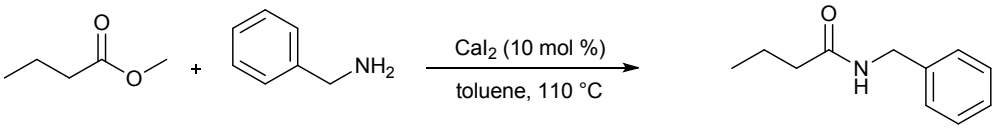
Table S1: Solvent effect on the amide bond formation of aliphatic esters[a]



Entry	Solvent (2M)	Catalytic conversion (%)
1	toluene[b]	91
2	*o*-xylene	90
3	toluene[c]	87
4	*n*-heptane	87
5	-	96
6	THF	82
7	dioxane	79
8	*tert*-amyl alcohol	77
9	toluene[d]	75
10	DMF	63
11	Water	60

[a] Conditions: Carboxylic ester (2.5 mmol), amine (3.25 mmol), CaI_2 (10 mol%), solvent, 110 °C, 4 h; [b] anhydrous; [c] stock; [d] 1M.

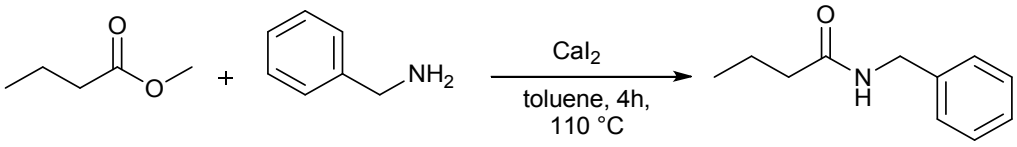
Table S2: Effect of reaction time[a]



Entry	t (h)	Catalytic conversion (%)
1	0.5	61
2	1	72
3	2	80
4	4	91
5	6	92

[a] Conditions: Carboxylic ester (2.5 mmol), amine (3.25 mmol), CaI_2 (10 mol%), toluene (2M), 110 °C.

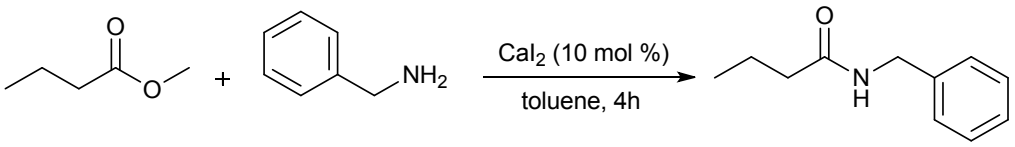
Table S3: Effect of catalyst load[a]



Entry	Catalyst load (mol%)	Catalytic Conversion (%)
1	1	53
2	2	76
3	5	84
4	10	91
5	15	94
6	20	94

[a] Conditions: Carboxylic ester (2.5 mmol), amine (3.25 mmol), CaI_2 , toluene (2M), 110 °C, 4 h.

Table S4: Effect of reaction temperature[a]

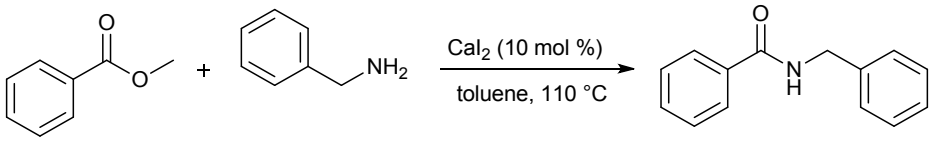


Entry	Reaction temperature (°C)	Catalytic Conversion (%)
1	21	12
2	50	59
3	70	76
4	90	80
5	100	84
6	110	91

[a] Conditions: Carboxylic ester (2.5 mmol), amine (3.25 mmol), CaI_2 (10 mol%), toluene (2M), 4 h.

4.2 Optimisation of Reaction Conditions for Aromatic Esters (Table S5 – S7)

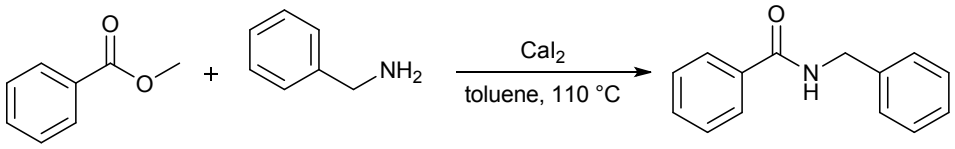
Table S5: Effect of reaction time[a]



Entry	t (h)	Catalytic conversion (%)
1	1	54
2	4	60
3	8	84
4	16	83
5	20	83

[a] Conditions: Carboxylic ester (2.5 mmol), amine (3.25 mmol), CaI_2 (10 mol%), toluene (2M), 110 °C.

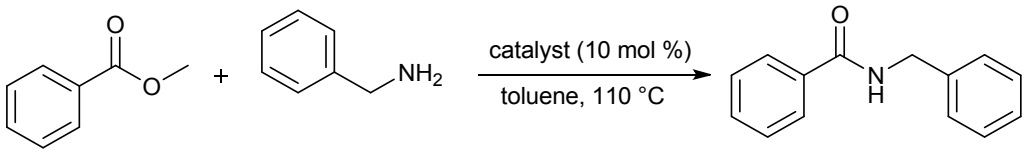
Table S6: Effect of catalyst load[a]



Entry	Catalyst load (mol%)	Catalytic Conversion (%)
1	0	7
2	5	64
3	10	84
4	20	84

[a] Conditions: Carboxylic ester (2.5 mmol), amine (3.25 mmol), CaI_2, toluene (2M), 110 °C, 4 h.

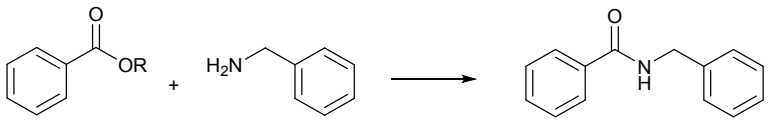
Table S7: Catalyst Screening[a]



Entry	Catalyst	Catalytic conversion (%)[b]
1	CaI_2 pure 99.999%	75
2	$CaI_2 \cdot 5H_2O$	84
3	SrI_2	78
4	CaI_2	83
5	$CaBr_2$	78
6	MgI_2	70
7	$Ca(OTf)_2$	84
8	-	7
9	$CaCO_3$	34

[a] Conditions: Carboxylic ester (2.5 mmol), amine (3.25 mmol), catalyst (10 mol%), toluene (2M), 110 °C, 4 h; [b] Conversion determined by GC.

Table S8: The effect of the side-chain of the ester on Ca-catalyzed amidation of carboxylic esters and amines[a]

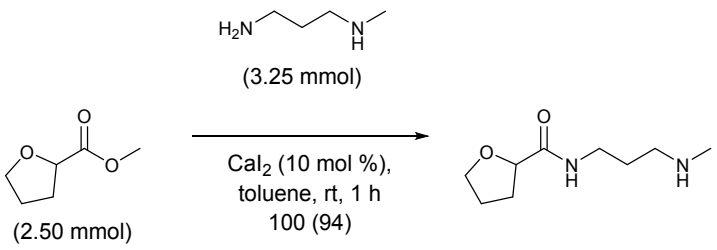


Entry	R	Catalytic Conversion (%)
1	Me	84
2	Et	73
3	Bn	81
4	Allyl	83

[a]Alkyl benzoate (2.5 mmol), benzylamine (3.25 mmol), CaI_2 (10 mol%), toluene (2M), 110 °C, 8 h; [b] Conversion determined by GC.

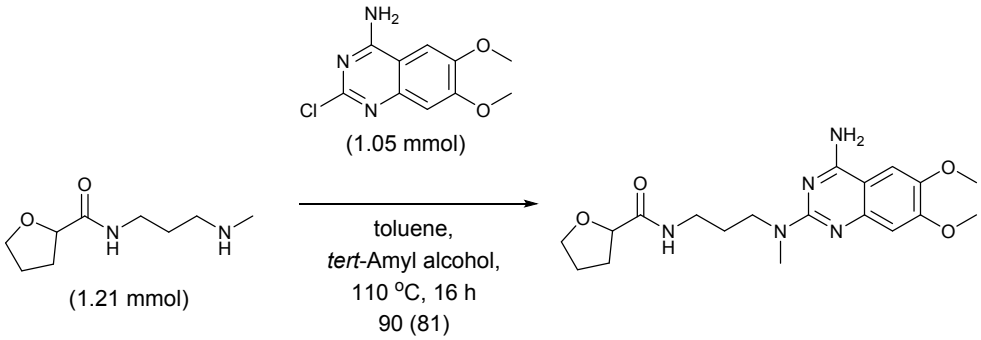
5. Synthesis of N-(3-(methylamino)propyl)tetrahydrofuran-2-carboxamide

Methyl tetrahydrofuran-2-carboxylate (2.50 mmol) and N^1-methylpropane-1,3-diamine (3.25 mmol) were suspended in toluene to give a 2M solution. CaI_2 (10 mol%) was then added and the mixture was stirred at room temperature for 1h. Subsequently, the solvent was removed under reduced pressure. Purification was performed on a Biotage Isolera™ One employing a Biotage SNAP Ultra cartridge (12 g, EtOAc/MeOH/Et_3N, 7:3:1) to isolate the desired amide as a yellow oil (0.437 g, 94%).



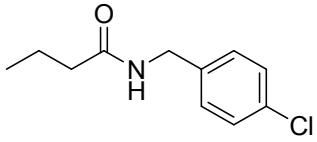
6. Synthesis of N-(3-((4-amino-6,7-dimethoxyquinazolin-2-yl)(methyl)amino)propyl)tetrahydrofuran-2-carboxamide

2-chloro-6,7-dimethoxyquinazolin-4-amine (1.05 mmol) was dissolved in *tert*-amyl alcohol (5 mL) while stirring. N-(3-(methylamino)propyl)tetrahydrofuran-2-carboxamide was first dissolved in toluene (4 mL) and then added to the reaction mixture. The resulting mixture was heated under reflux at 110 °C for 16 h. After completion, the mixture was allowed to cool to rt, which was then concentrated under reduced pressure. Subsequently, the pH was increased to pH 10 - 11 using a 20% aqueous $NaHCO_3$ solution, while it was cooled in an ice bath. The product was extracted with ethyl acetate (3 × 20 mL). The separated organic phases were combined, washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure. Recrystallization from *n*-heptane gave the desired product as a brown solid (330 mg, 81%).


NH2
N
Cl
N
O
O
(1.05 mmol)
O
O
N
H
N
H
(1.21 mmol)
toluene,
tert-Amyl alcohol,
110 °C, 16 h
90 (81)
NH2
N
N
O
O
O
O
N
H
N

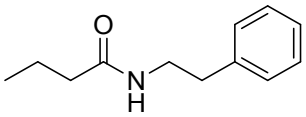
7. Characterisation of products

_N_-(4-chlorobenzyl)butyramide



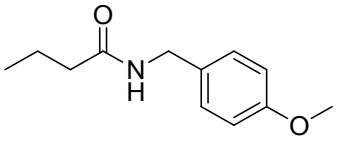
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38 - 7.14 (m, 4H), 6.02 (bs, 1H), 4.39 (d, *J* = 5.9 Hz, 2H), 2.19 (t, *J* = 5.9 Hz, 2H), 1.85 - 1.49 (m, 2H), 0.95 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.1, 137.3, 133.4, 129.2, 128.9, 42.9, 38.8, 19.3, 14.9; MS (ESI): *m/z* 212.1 (M + H^+). Data are in accordance to that previously reported.[1]

_N_-phenethylbutyramide



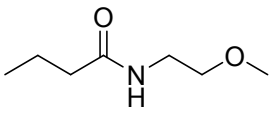
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 - 7.17 (m, 5H), 5.62 (bs, 1H), 3.51 (td, *J* = 7.0, 5.9 Hz, 2H), 2.81 (t, *J* = 7.0 Hz, 2H), 2.10 (t, *J* = 7.0 Hz, 2H), 1.62 (m, 2H), 0.91 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.0, 138.9, 128.7, 128.6, 126.4, 40.5, 38.7, 35.7, 19.1, 13.7; MS (ESI): *m/z* 191.0 (M + H^+). Data are in accordance to that previously reported.[2]

N-(4-methoxybenzyl)butyramide



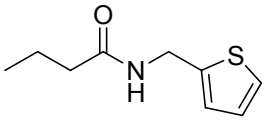
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.18 (d, *J* = 8.8 Hz, 2H); 6.84 (d, *J* = 8.8 Hz, 2H), 5.89 (bs, 1H), 4.36 (d, *J* = 5.6 Hz, 2H), 3.79 (s, 3H), 2.27 - 2.03 (t, *J* = 7.6 Hz, 2H), 1.68 (m, 2H), 0.95 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.3, 158.5, 130.1, 128.6, 113.6, 54.8, 42.5, 38.2, 18.7, 13.3; MS (ESI): *m/z* 207.9 (M + H^+). Data are in accordance to that previously reported.[2]

_N_-(2-methoxyethyl)butyramide



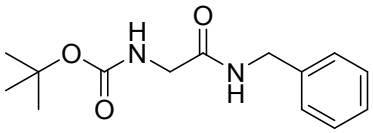
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.86 (bs, 1H), 3.48 - 3.42 (m, 4H), 3.36 (s, 3H), 2.17 (t, *J* = 7.3 Hz, 2H), 1.67 (m, 2H), 0.95 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.0, 77.3, 77.0, 76.7, 71.2, 58.6, 39.0, 38.5, 19.1, 13.6; MS (ESI): *m/z* 146.1 (M + H^+); HRMS (ESI): (M + Na^+), found 168.0983. $[C_7H_{15}NO_2Na]^+$ requires 168.1001; brown oil.

_N_-(thiophen-2-ylmethyl)butyramide



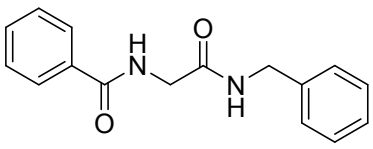
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.21 (dd, *J* = 4.7, 1.7 Hz, 1 H), 6.97 - 6.93 (m, 2H), 6.03 (bs, 1H), 4.61 (d, *J*= 5.6 Hz, 2H), 2.18 (t, *J* = 7.5 Hz, 2H), 1.82 - 1.52 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.9, 141.4, 127.0, 126.0, 125.3, 38.7, 38.4, 19.3, 13.9; MS (ESI): *m/z* 183.9 (M + H^+); HRMS (ESI): (M + Na^+), found 206.0611 $[C_9H_{13}NOSNa]^+$ requires 206.0616; grey solid, mp (*n*-heptane/EtOAc): 59 - 60 °C.

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



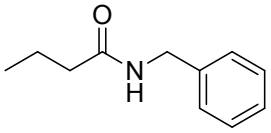
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33 - 7.25 (m, 5H), 6.77 (bs, 1H), 5.38 (bs, 1H), 4.44 (d, *J* = 5.8 Hz, 2H), 3.81 (d, *J* = 5.5 Hz, 2H), 1.41 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.7, 156.3, 138.1, 128.8, 127.8, 127.7, 80.5, 44.6, 43.5, 28.4; MS (ESI): *m/z* 264.9 (M + H^+). Data are in accordance to that previously reported.[3]

_N_-(2-(benzylamino)-2-oxoethyl)benzamide



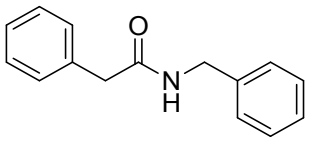
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 - 7.68 (m, 2H), 7.61 - 7.55 (m, 1H), 7.52 - 7.41 (m, 2H), 7.40 - 7.34 (m, 2H), 7.31 - 7.18 (m, 5H), 4.41 (d, *J* = 5.8 Hz, 2H), 4.14 (d, *J* = 5.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.1, 167.9, 137.8, 133.2, 131.9, 128.6, 128.5, 127.7, 127.4, 127.2, 43.9, 43.6; MS (ESI): *m/z* 269.0 (M + H^+). Data are in accordance to that previously reported.[4]

***N*-benzylbutyramide**



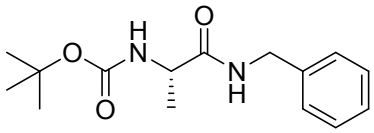
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.48 - 7.11 (m, 5H), 5.99 (bs, 1H), 4.43 (d, *J* = 5.7 Hz, 2H), 2.22 (t, *J* = 7.2 2H), 1.69 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.1, 138.6, 128.8, 127.9, 127.6, 43.7, 38.8, 19.3, 14.0; MS (ESI): *m/z* 178.1 (M + H^+). Data are in accordance to that previously reported.[5]

***N*-benzyl-2-phenylacetamide**



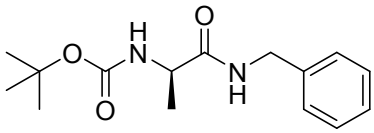
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.56 - 7.01 (m, 10H), 5.88 (bs, 1H), 4.42 (d, *J* = 5.8 Hz, 2H), 3.63 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.1, 108.4, 105.0, 99.6, 99.2, 98.2, 97.7, 97.6, 97.6, 14.0, 13.7; MS (ESI): *m/z* 226.1 (M + H^+). Data are in accordance to that previously reported.[6]

(*S*)-tert-butyl (1-(benzylamino)-1-oxopropan-2-yl)carbamate



^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 - 7.10 (m, 5H), 6.68 (bs, 1H), 5.10 (bs, 1H), 4.43 (d, *J* = 5.8 Hz, 2H), 4.20 (bs, 1H), 1.40 (s, 9H), 1.37 (d, *J* = 6.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.5, 155.1, 138.0, 128.6, 127.5, 127.4, 79.9, 50.1, 43.3, 28.2, 18.3; *m/z* 301.1 (M + Na^+). Data are in accordance to that previously reported.[7]

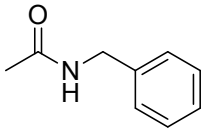
(*R*)-tert-butyl (1-(benzylamino)-1-oxopropan-2-yl)carbamate



^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 - 7.06 (m, 5H), 6.69 (s, 1H), 5.10 (bs, 1H), 4.43 (d, *J* = 5.8 Hz, 2H), 4.21 (bs, 1H), 1.40 (s, 9H), 1.37 (d, *J* = 6.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.5, 155.1, 138.0,

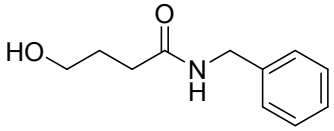
128.6, 127.5, 127.4, 79.9, 50.1, 43.3, 28.3, 18.6; MS (ESI): *m/z* 301.0 (M + Na^+). Data are in accordance to that previously reported.[7]

_N_-benzylacetamide



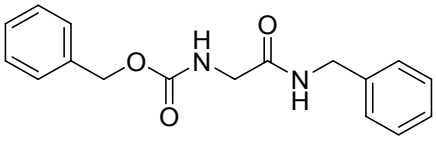
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 - 7.10 (m, 5H), 6.01 (bs, 1H), 4.41 (d, *J* = 5.7 Hz, 2H), 2.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1, 138.1, 128.7, 127.8, 127.5, 43.7, 23.2; MS (ESI): *m/z* 150.1 (M + H^+). Data are in accordance to that previously reported.[8]

_N_-benzyl-4-hydroxybutanamide



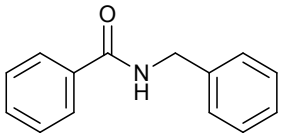
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 - 7.16 (m, 5H), 6.44 (bs, 1H), 4.40 (d, *J* = 5.7 Hz, 2H), 3.66 (t, *J* = 5.7 Hz, 2H), 3.42 (bs, 1H), 2.36 (t, *J* = 6.9 Hz, 2H), 1.92 - 1.78 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.5, 138.1, 128.6, 127.7, 127.5, 62.1, 43.6, 33.7, 28.1; MS (ESI): *m/z* 194.1 (M + H^+). Data are in accordance to that previously reported.[9]

benzyl (2-(benzylamino)-2-oxoethyl)carbamate



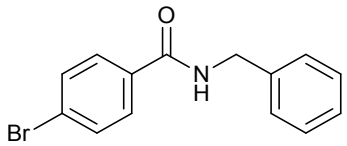
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 - 7.03 (m, 10H), 6.55 (bs, 1H), 5.58 (bs, 1H), 5.06 (s, 2H), 4.41 (d, *J* = 5.7 Hz, 2H), 3.87 (d, *J* = 5.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.9, 168.6, 137.6, 137.6, 128.7, 128.5, 128.3, 128.1, 127.7, 127.6, 67.2, 44.6, 43.5; MS (ESI): *m/z* 321.1 (M + Na^+). Data are in accordance to that previously reported.[10]

***N*-benzylbenzamide**



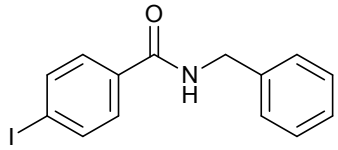
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 - 7.22 (m, 10H), 6.53 (bs, 1H), 4.65 (d, *J* = 5.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.3, 138.2, 134.3, 131.5, 128.8, 128.6, 127.9, 127.6, 126.9, 44.1; MS (ESI): *m/z* 212.1 ($M + H^+$). Data are in accordance to that previously reported.[11]

***N*-benzyl-4-bromobenzamide**



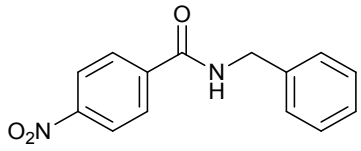
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (d, *J* = 8.7 Hz, 2H), 7.54 (d, *J* = 8.7 Hz, 2H), 7.38 - 7.27 (m, 5H), 6.52 (bs, 1H), 4.61 (d, *J* = 5.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.4, 137.9, 133.1, 131.8, 128.8, 128.6, 127.9, 127.7, 126.2, 44.2; MS (ESI): *m/z* 290.0 ($M + H^+$). Data are in accordance to that previously reported.[12]

***N*-benzyl-4-iodobenzamide**



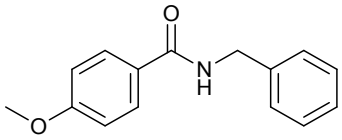
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, *J* = 8.6 Hz, 2H), 7.50 (d, *J* = 8.6 Hz, 2H), 7.38 - 7.27 (m, 5H), , 6.45 (bs, 1H), 4.62 (d, *J* = 5.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.5, 137.8, 137.8, 133.7, 128.8, 128.5, 127.9, 127.7, 98.5, 44.2; MS (ESI): *m/z* 360.0 ($M + Na^+$). Data are in accordance to that previously reported.[13]

N-benzyl-4-nitrobenzamide



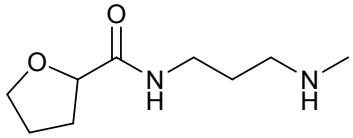
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (d, *J* = 8.4 Hz, 2H), 7.93 (d, *J* = 8.4 Hz, 2H), 7.38 - 7.26 (m, 5H), 6.86 (bs, 1H), 4.63 (d, *J* = 5.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.4, 149.6, 139.8, 137.4, 128.9, 128.2, 127.9, 127.9, 123.8, 44.4; MS (ESI): *m/z* 256.5 ($M + H^+$). Data are in accordance to that previously reported.[14]

***N*-benzyl-4-methoxybenzamide**



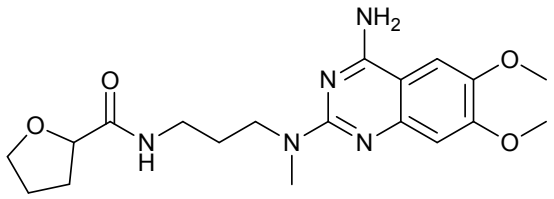
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, *J* = 10.0 Hz, 2H), 7.34 - 7.25 (m, 5H), 6.89 (d, *J* = 10.0 Hz, 2H), 6.50 (bs, 1H), 4.61 (d, *J* = 5.7 Hz, 2H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.9, 162.2, 138.4, 128.8, 128.7, 127.8,127.5, 126.6, 113.7, 55.4, 44.0; MS (ESI): *m/z* 242.2 ($M + H^+$). Data are in accordance to that previously reported.[14]

***N*-(3-(methylamino)propyl)tetrahydrofuran-2-carboxamide**



^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 - 7.28 (m, 1H), 4.39 (dd, *J* = 8.4, 5.7 Hz, 1H), 4.01 (dt, *J* = 6.7, 6.1 Hz, 1H), 3.91 (dt, *J* = 8.2, 6.6 Hz, 1H), 3.58 - 3.38 (m, 2H), 3.19 (q, *J* = 7.4 Hz, 1H), 3.06 - 2.91 (m, 2H), 2.70 (s, 3H), 2.40 - 2.26 (m, 2H), 2.21 - 2.08 (m, 1H), 2.05 - 1.87 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.4, 78.2, 69.5, 48.5, 36.7, 35.1, 30.3, 28.0, 25.5; MS (ESI): *m/z* 187.1 ($M + H^+$). Data are in accordance to that previously reported.[15]

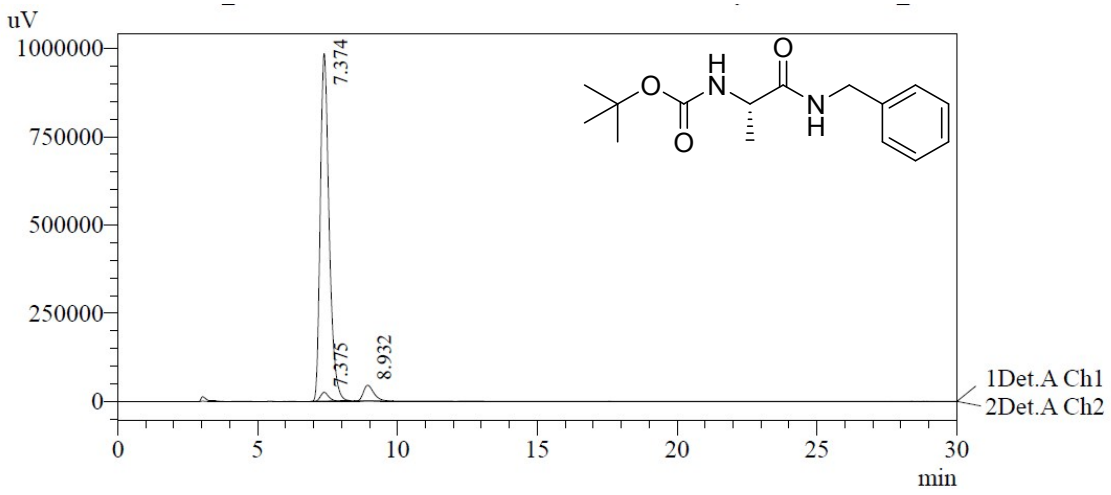
***N*-(3-((4-amino-6,7-dimethoxyquinazolin-2-yl)(methyl)amino)propyl)tetrahydrofuran-2-carboxamide**



^{1}H NMR (400 MHz, $CDCl_3$): δ 8.59 (bs, 1H), 7.02 (s, 1H), 6.83 (s, 1H), 5.92 (bs, 2H), 4.49 (dd, *J* = 8.1, 5.3 Hz, 1H), 4.16 - 4.08 (m, 1H), 4.06 - 3.88 (m, 9H), 3.58 (dq, *J* = 8.9, 4.7 Hz, 1H), 3.38 (dt, *J* = 14.5, 4.7 Hz, 1H), 3.17 (s, 3H), 3.00 - 2.86 (m, 1H), 2.39 - 2.19 (m, 2H), 2.03 - 1.89 (m, 2H), 1.88 - 1.55 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.6, 172.5, 160.9, 155.1, 145.4, 105.4, 102.4, 101.6, 78.9, 69.2, 56.1, 56.1, 50.7, 45.2, 34.7, 34.3, 30.2, 27.6, 25.2; MS (ESI): *m/z* 390.3 ($M + H^+$). Data are in accordance to that previously reported.[16]

8. Chiral HPLC Data

(*S*)-tert-butyl (1-(benzylamino)-1-oxopropan-2-yl)carbamate

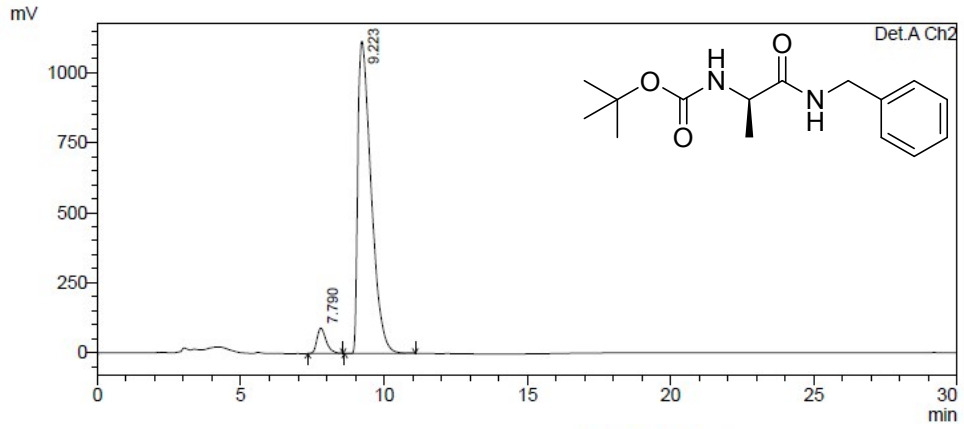


PeakTable

Detector A Ch2 215nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	7.374	21693817	984491	95.018	95.682
2	8.932	1137372	44425	4.982	4.318
Total		22831189	1028917	100.000	100.000

(*R*)-tert-butyl (1-(benzylamino)-1-oxopropan-2-yl)carbamate



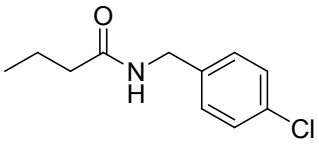
PeakTable

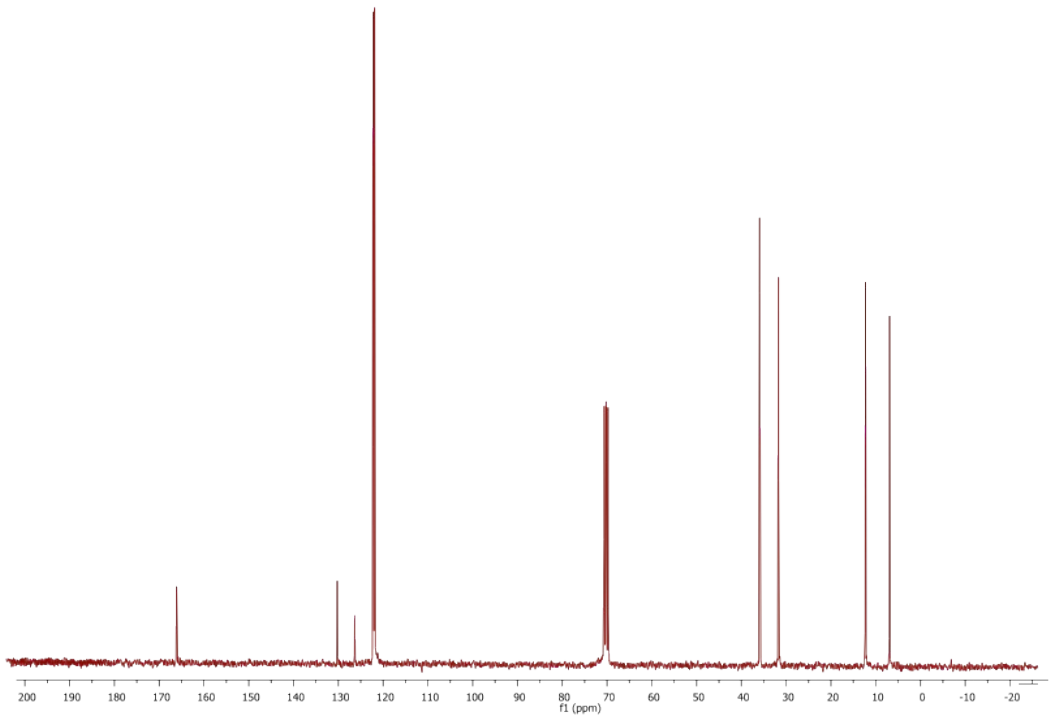
Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	7.782	56508	2545	5.819	7.827
2	9.224	914550	29971	94.181	92.173
Total		971058	32516	100.000	100.000

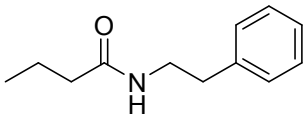
9. ^{1}H and ^{13}C NMR Spectra

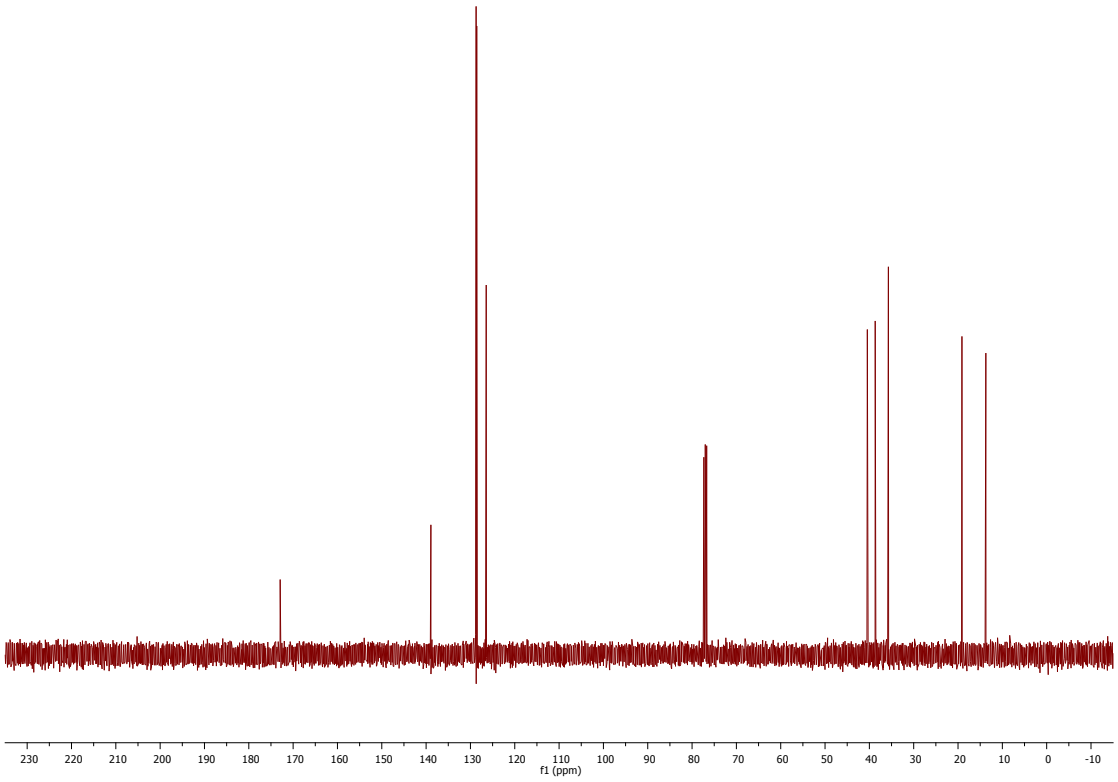
_N_-(4-chlorobenzyl)butyramide



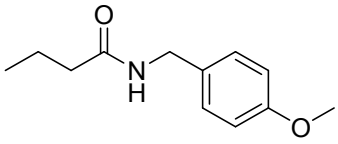


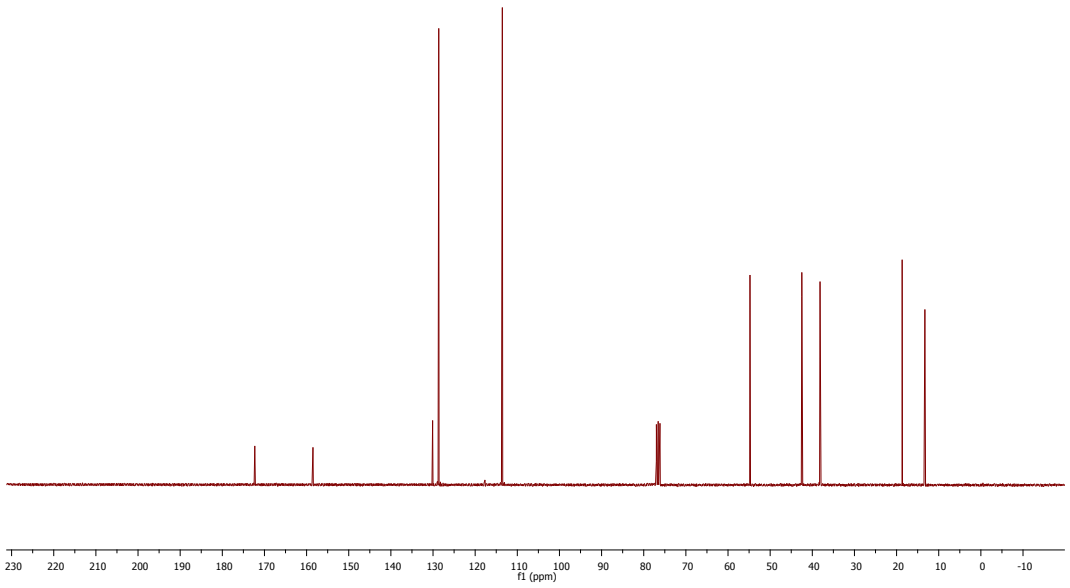
***N*-phenethylbutyramide**



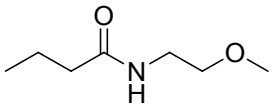


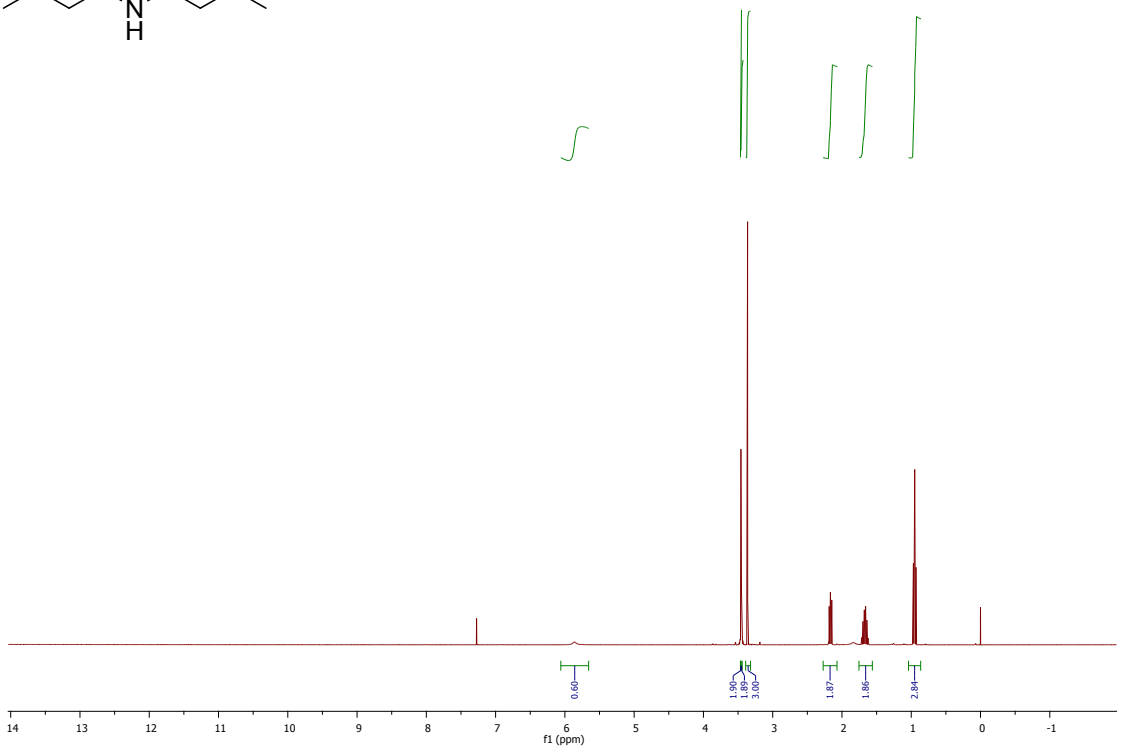
***N*-(4-methoxybenzyl)butyramide**

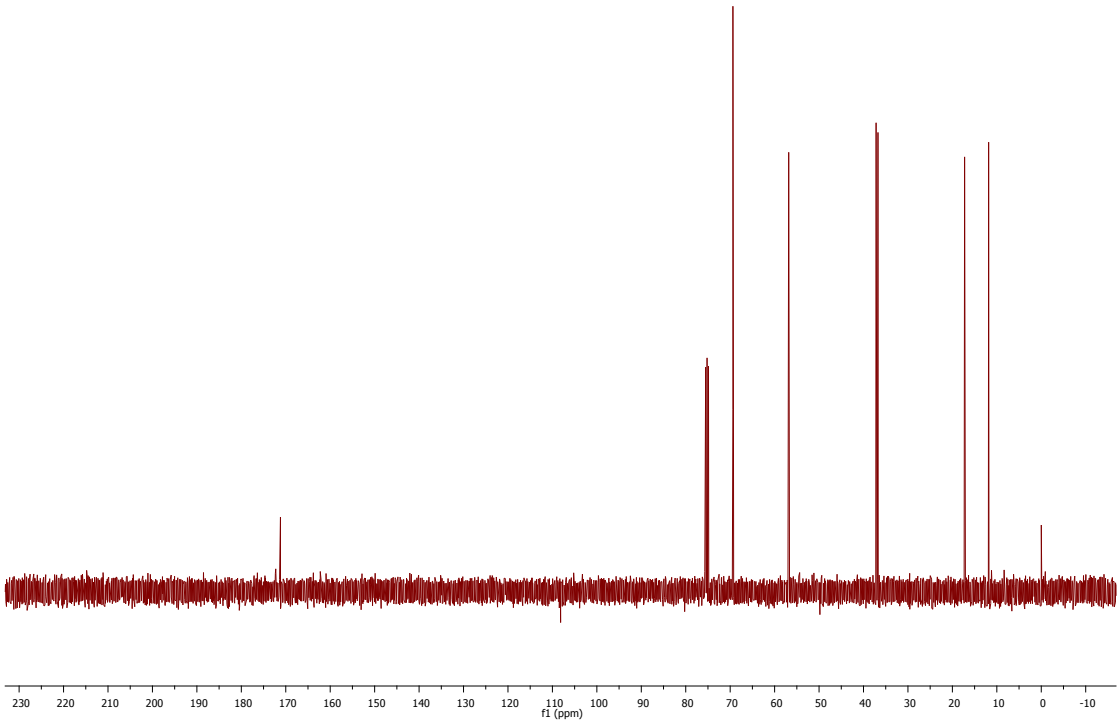




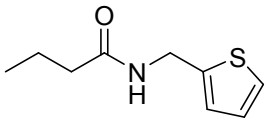
***N*-(2-methoxyethyl)butyramide**

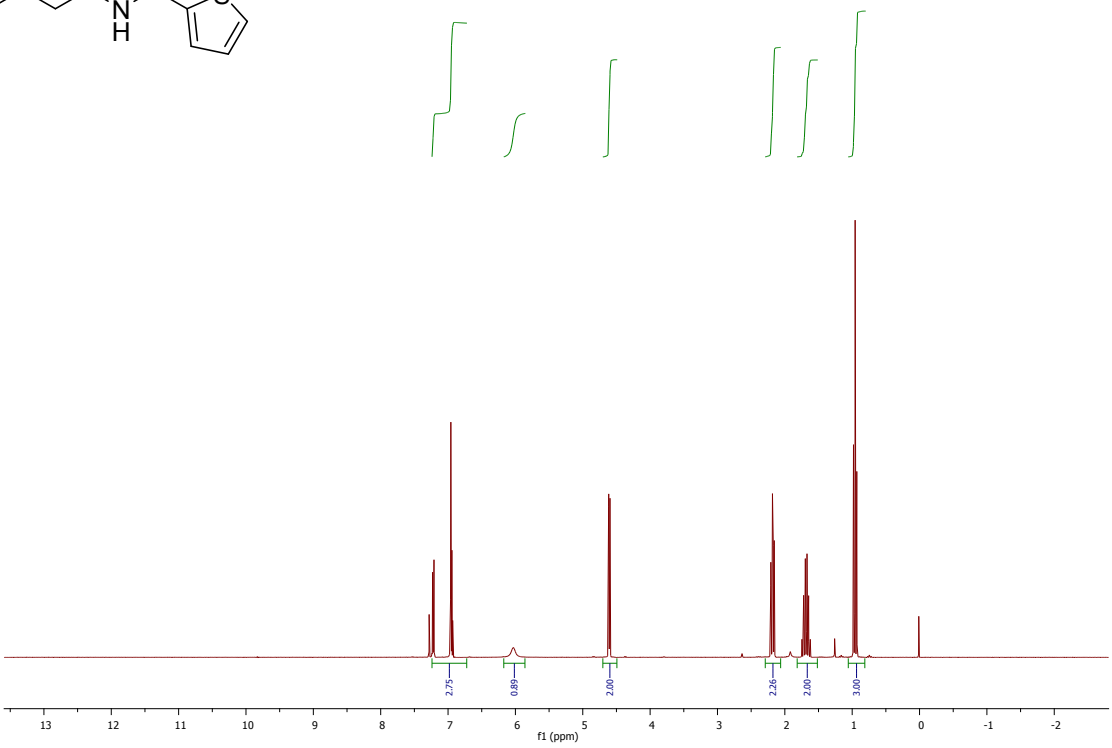


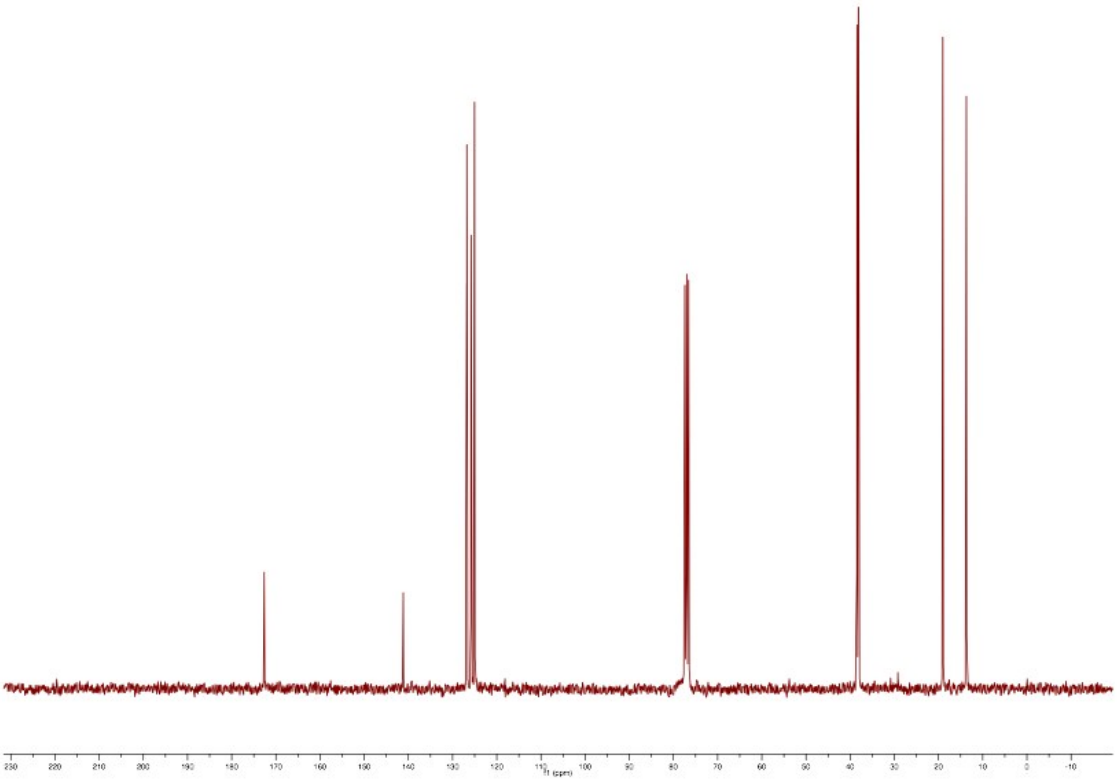




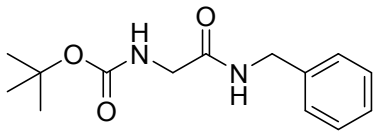
***N*-(thiophen-2-ylmethyl)butyramide**

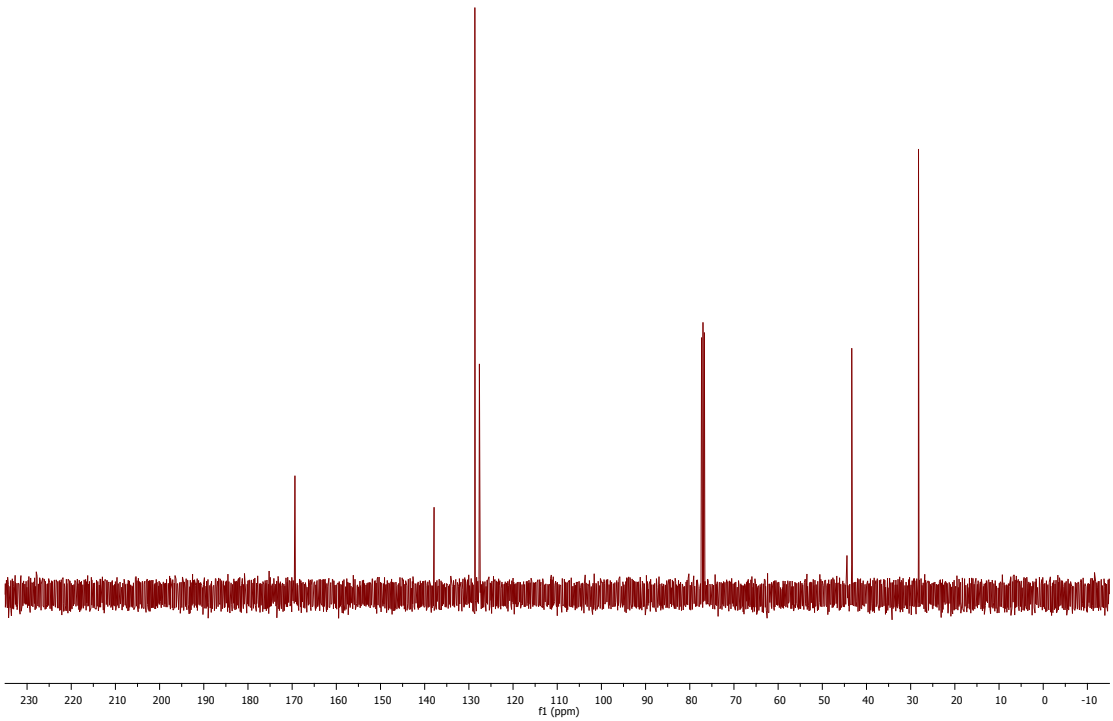




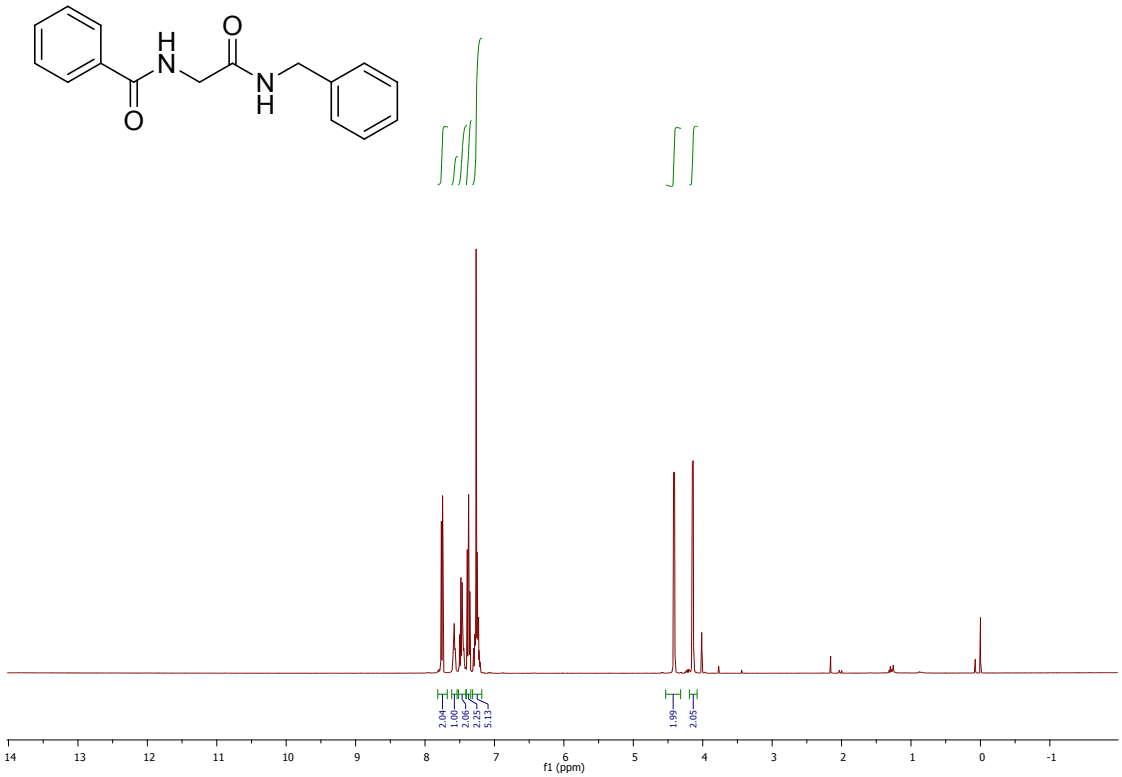


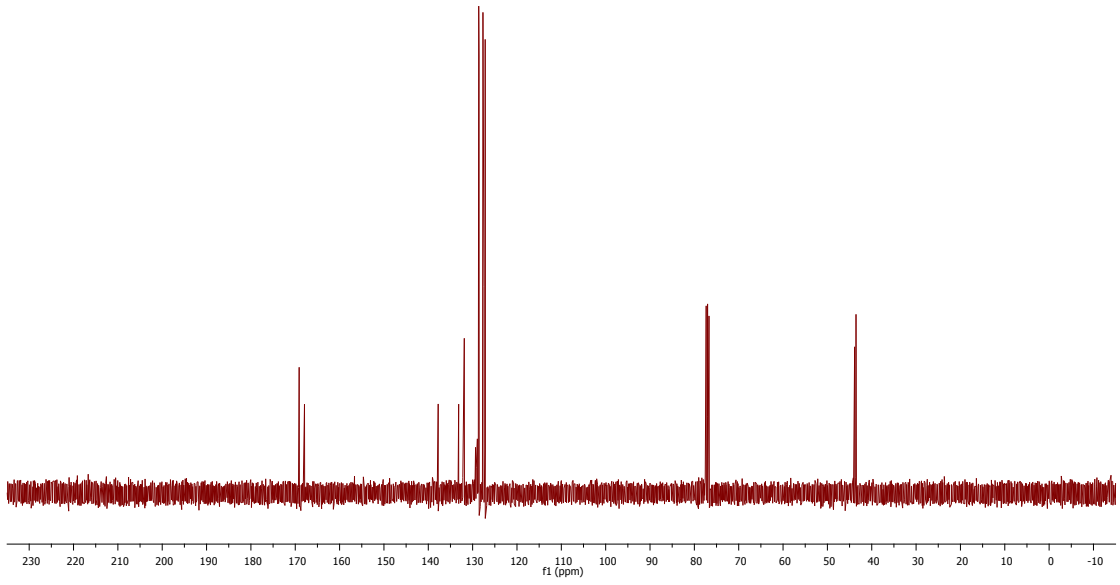
tert-butyl (2-(benzylamino)-2-oxoethyl)carbamate



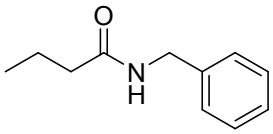


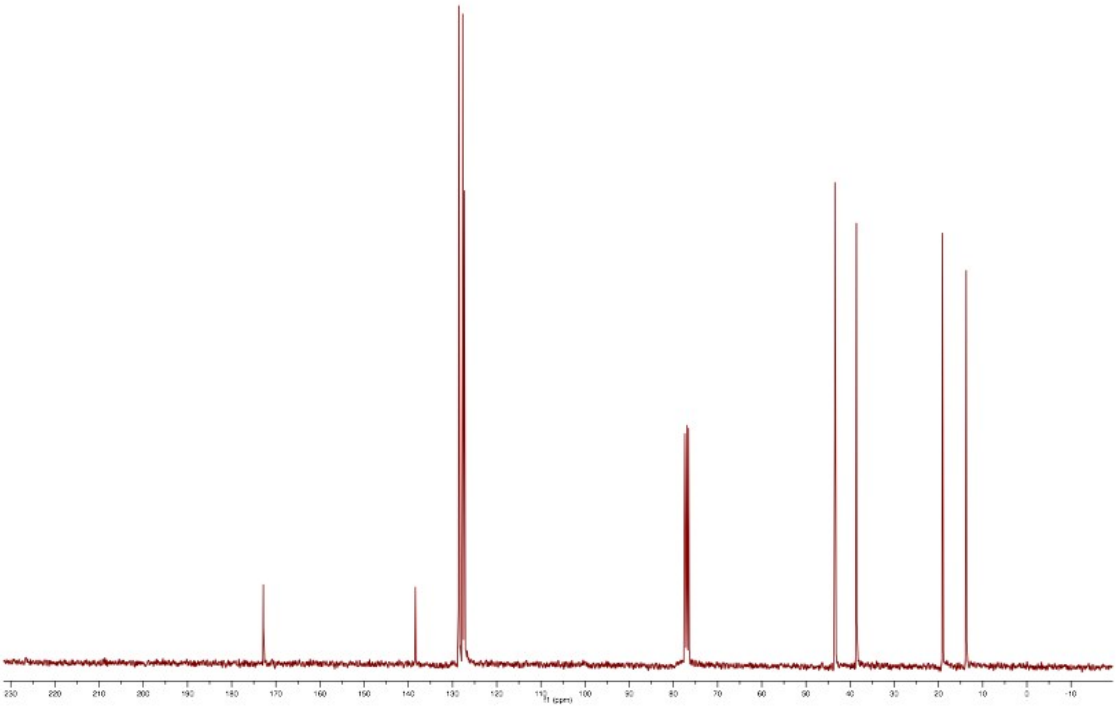
***N*-(2-(benzylamino)-2-oxoethyl)benzamide**





***N*-benzylbutyramide**





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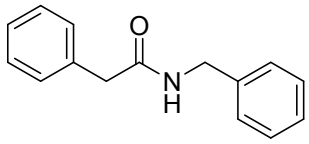

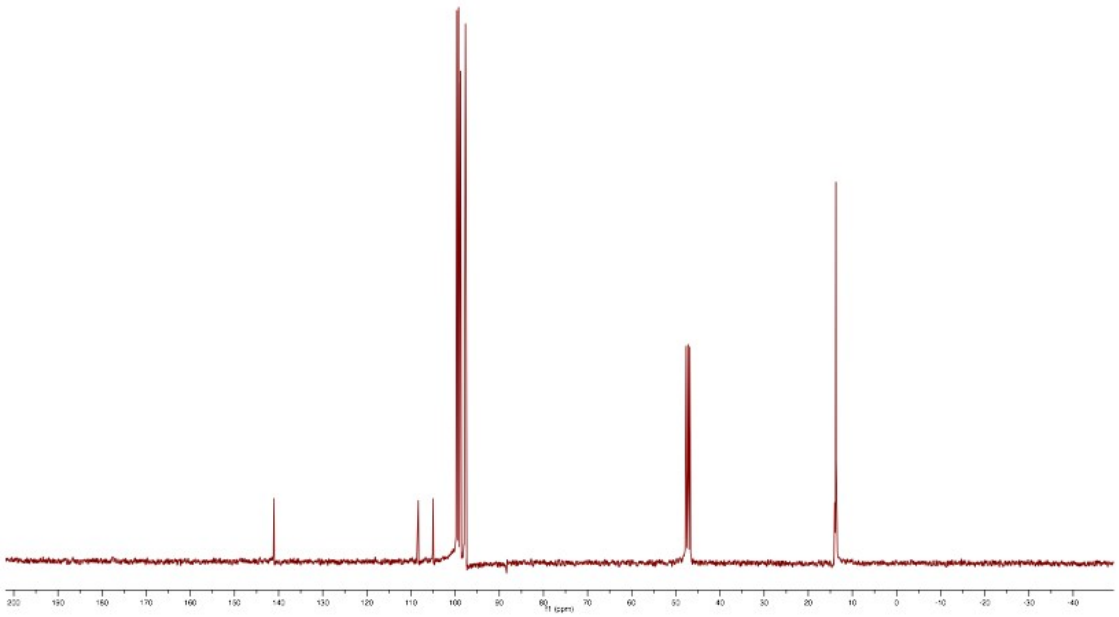

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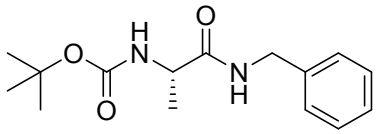

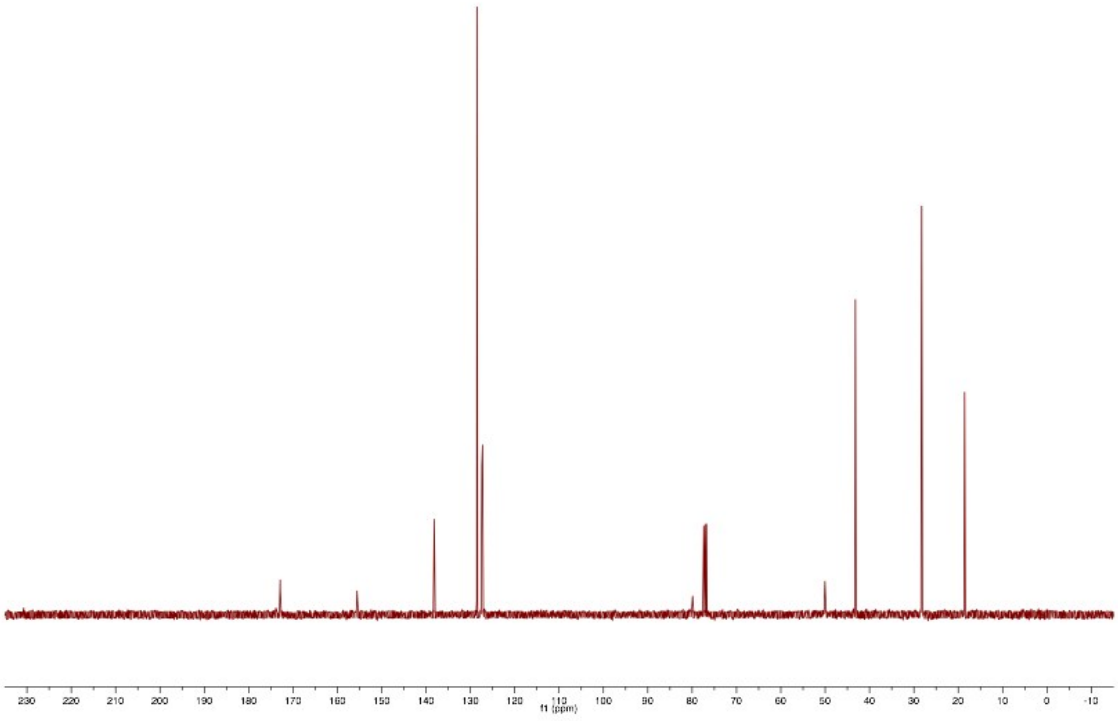

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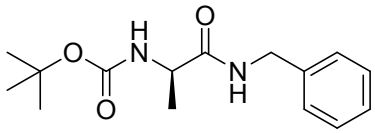

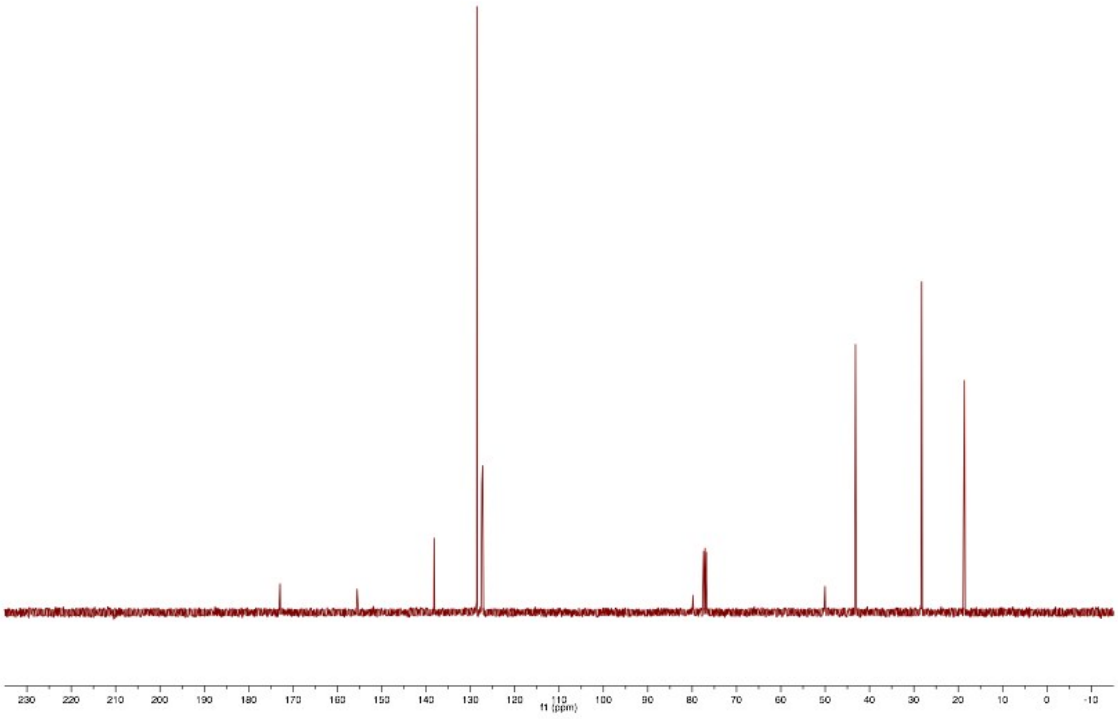

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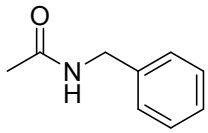
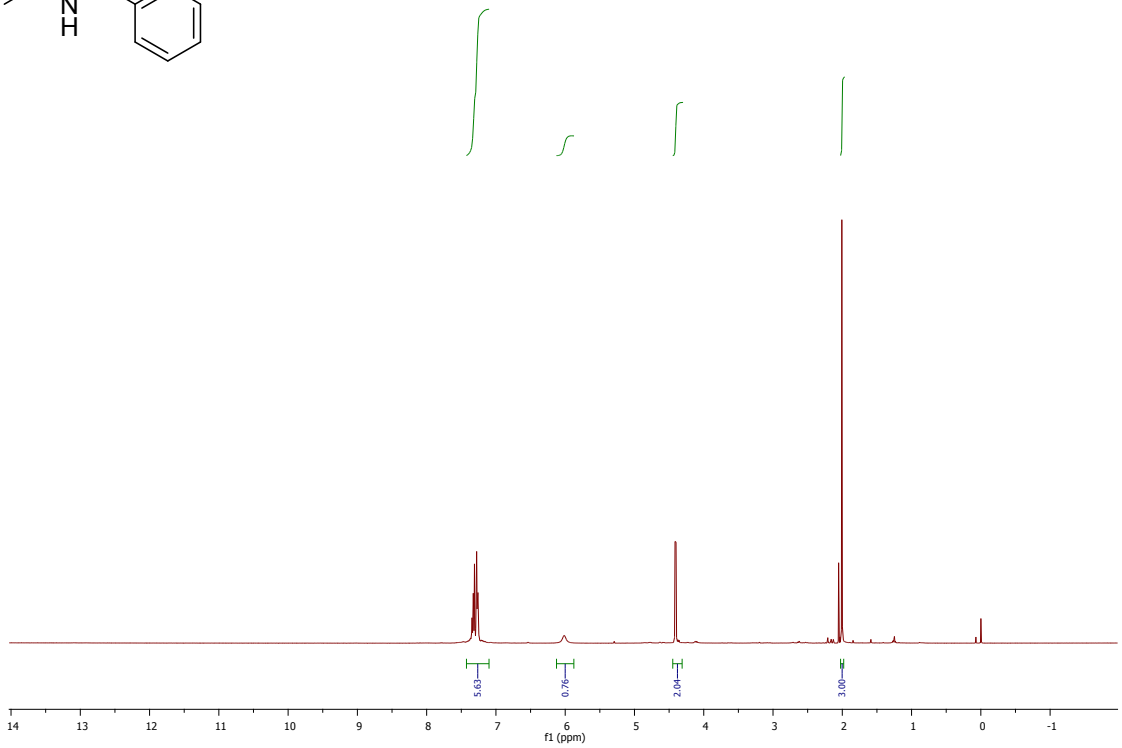
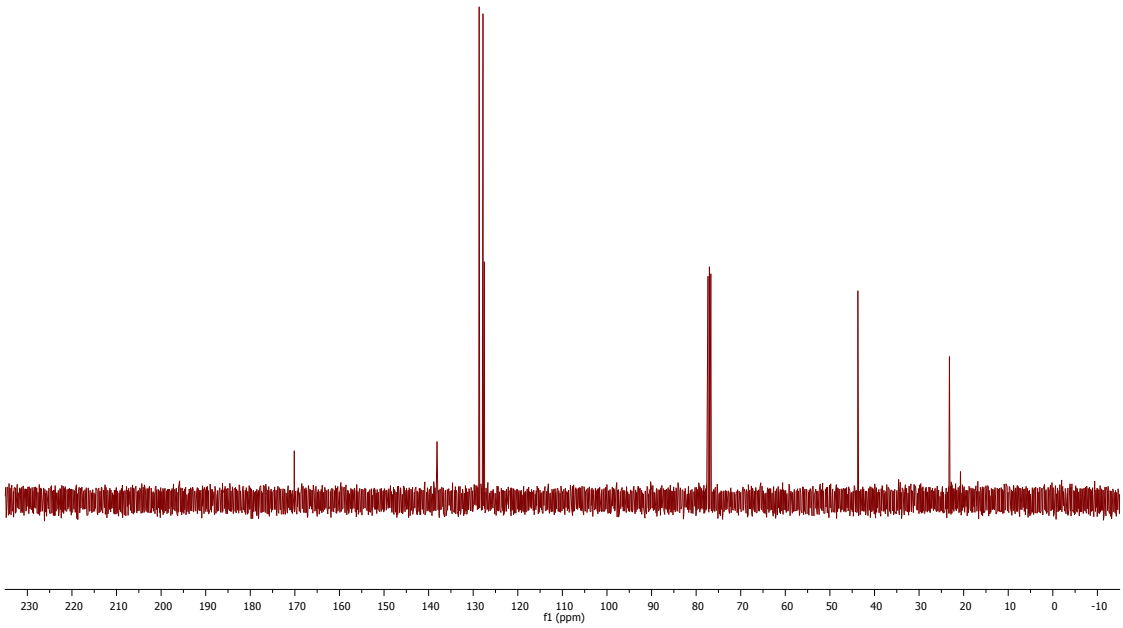
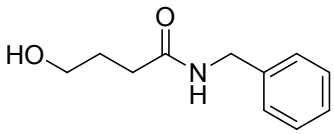
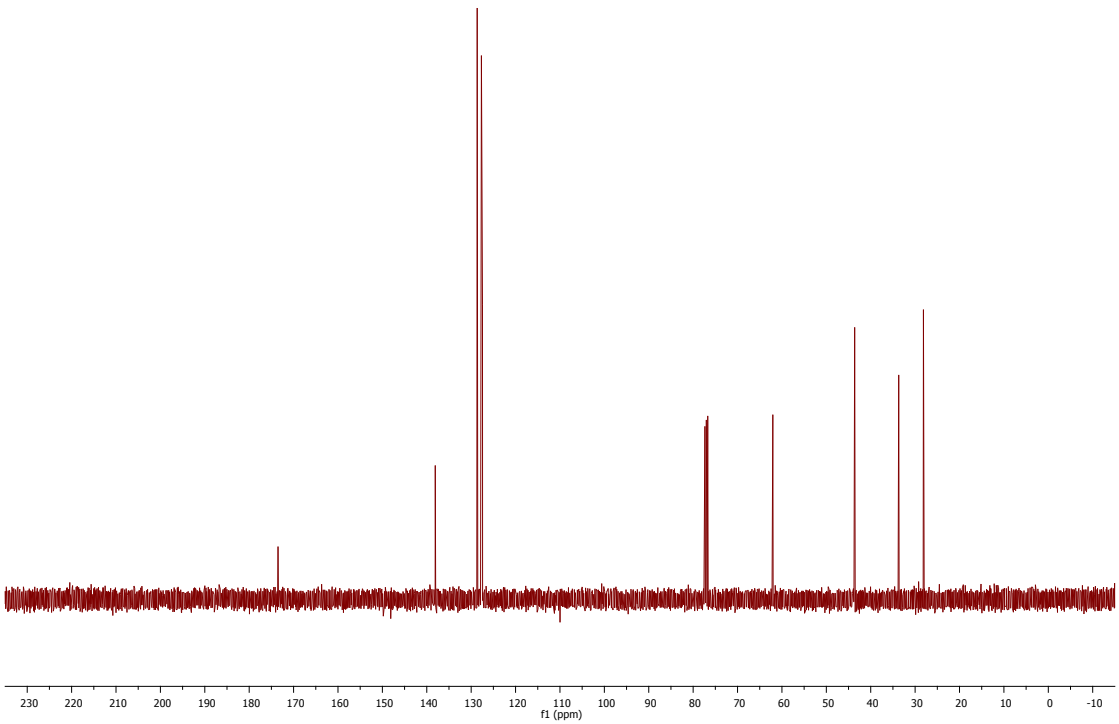




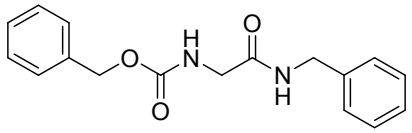


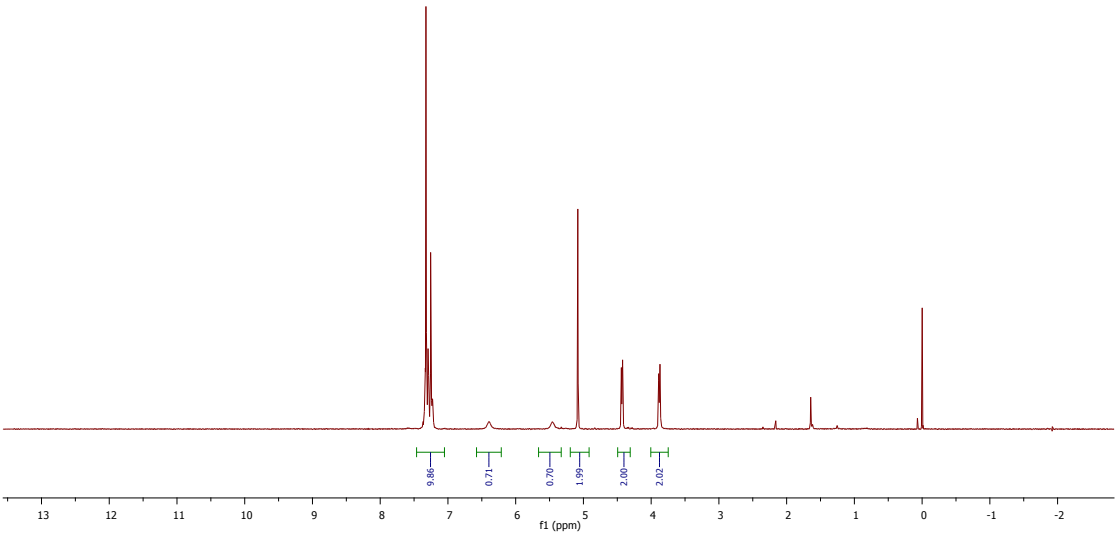
***N*-benzyl-4-hydroxybutanamide**

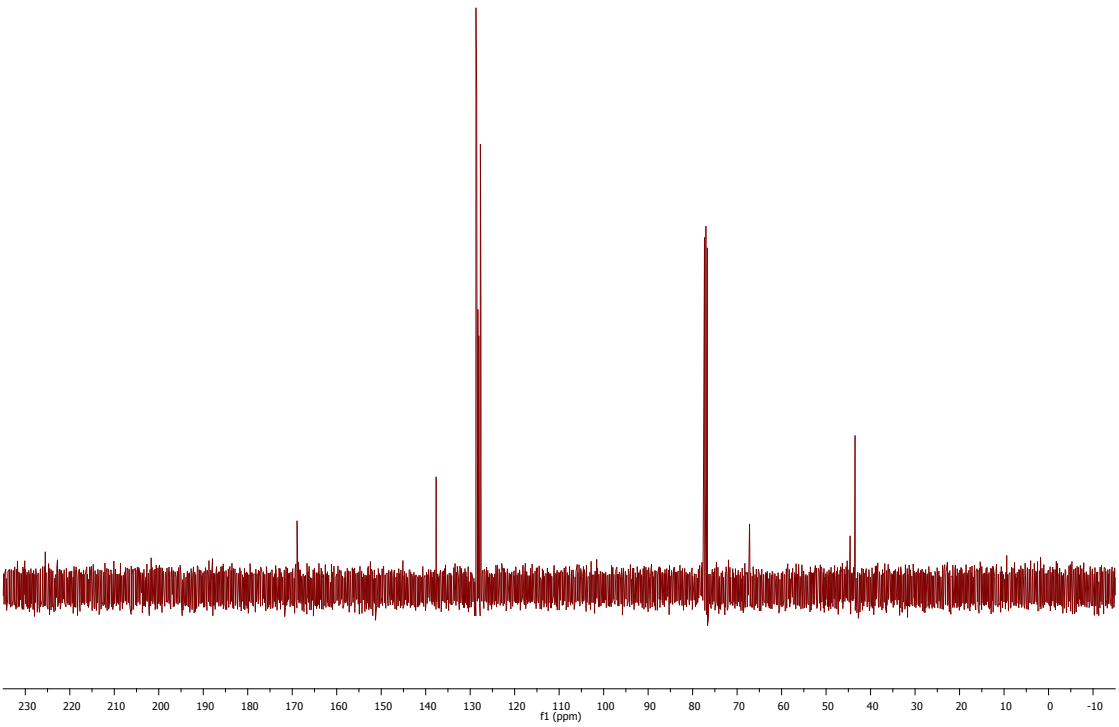




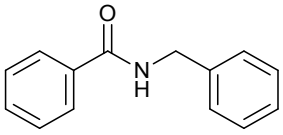
benzyl (2-(benzylamino)-2-oxoethyl)carbamate

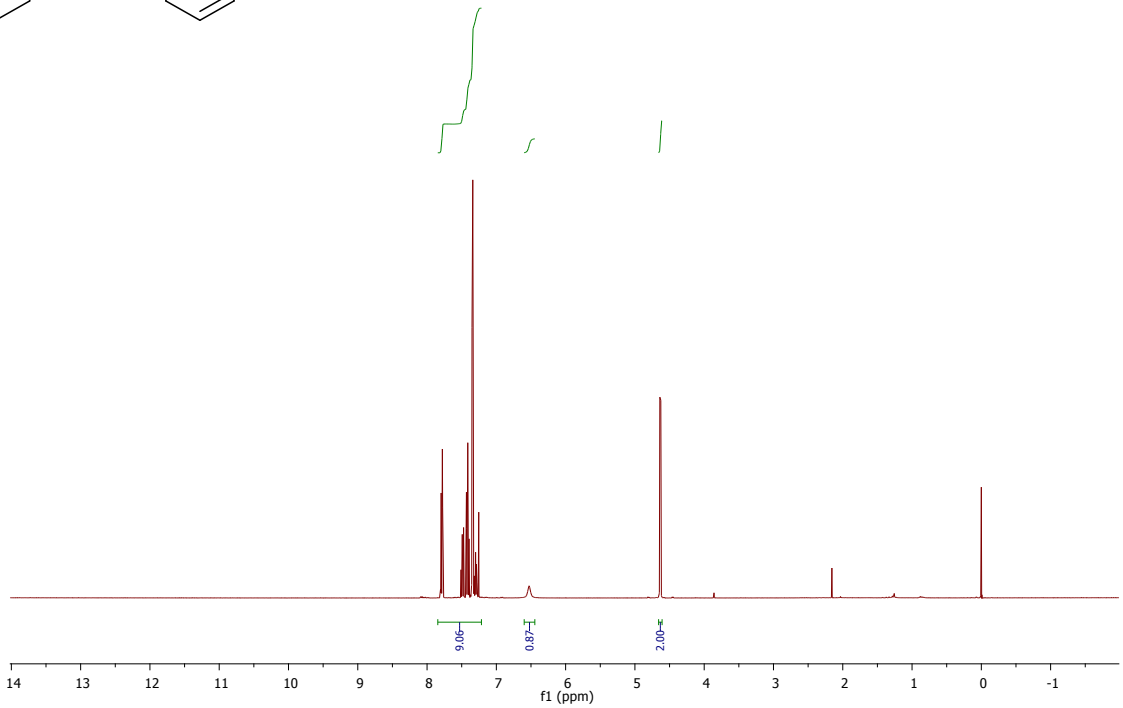


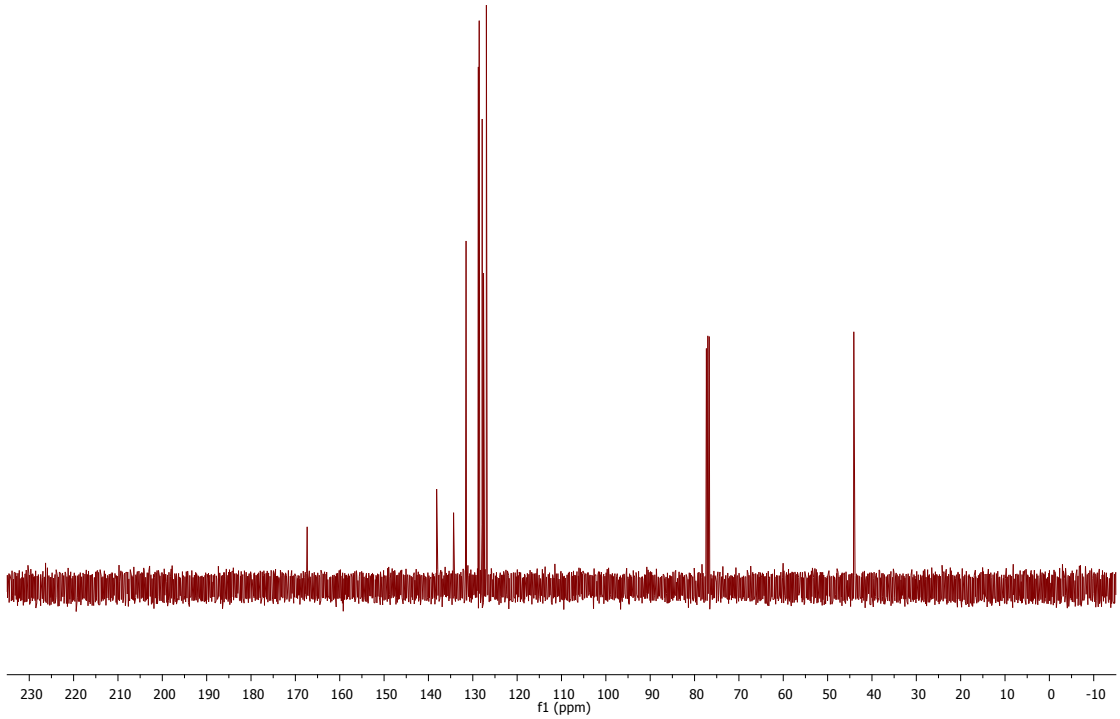




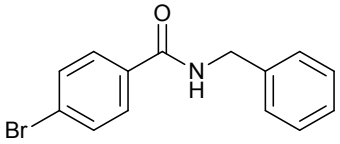
***N*-benzylbenzamide**

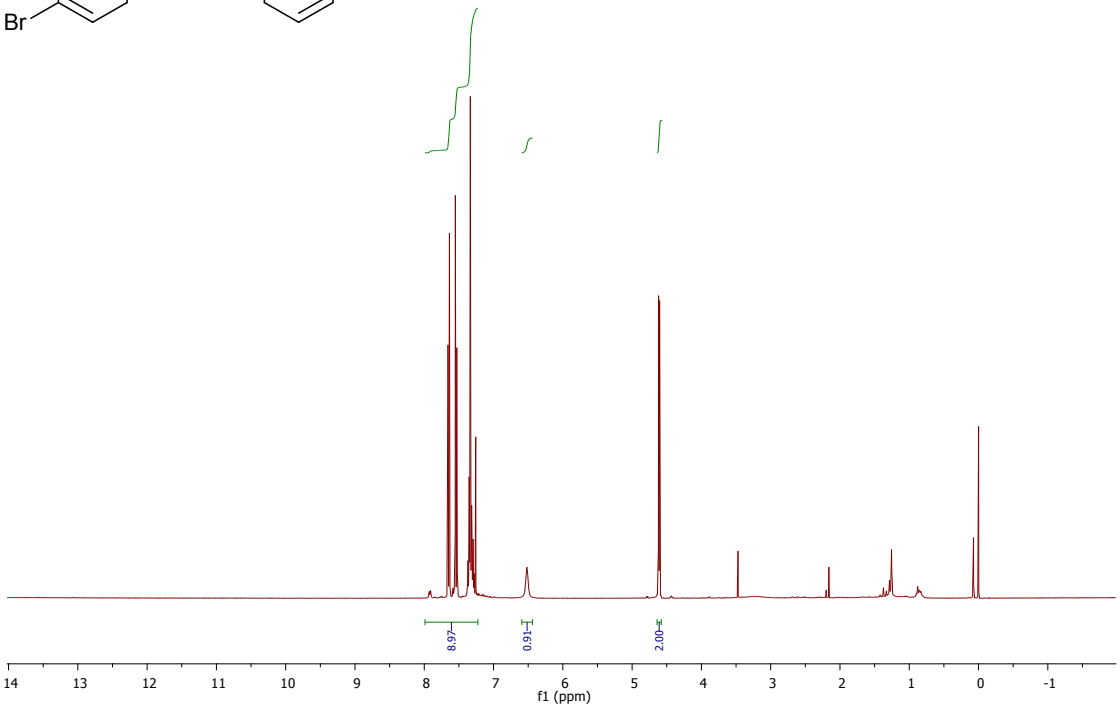


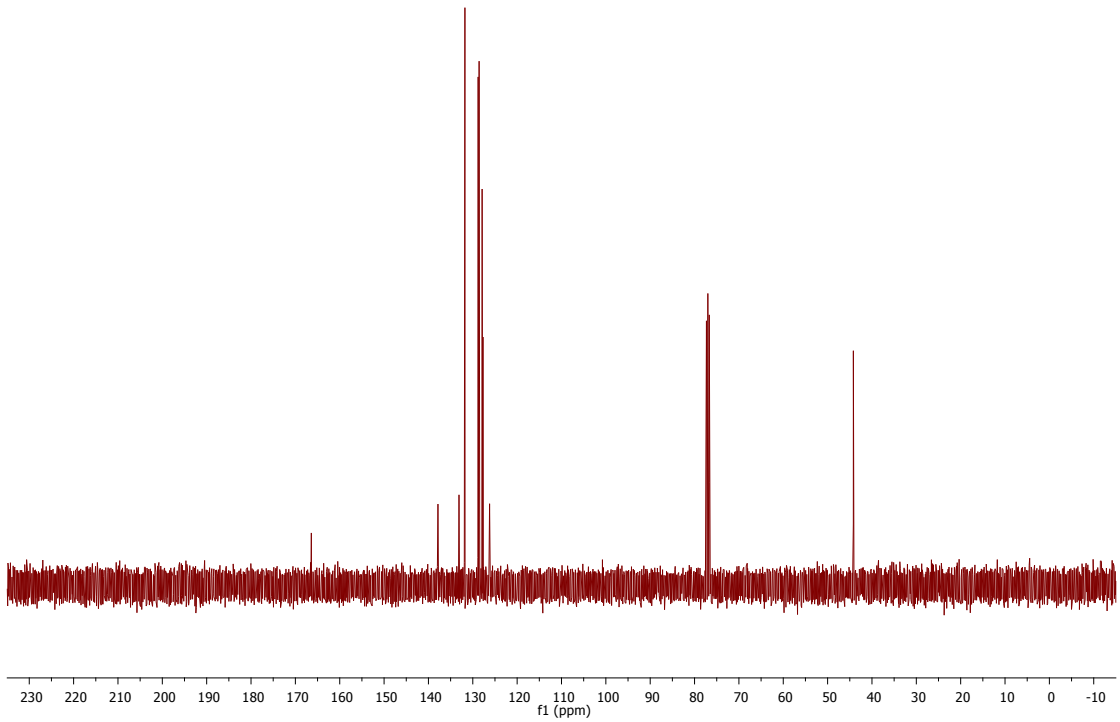




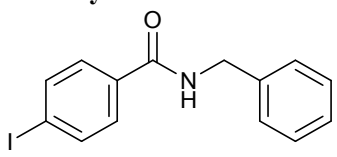
***N*-benzyl-4-bromobenzamide**

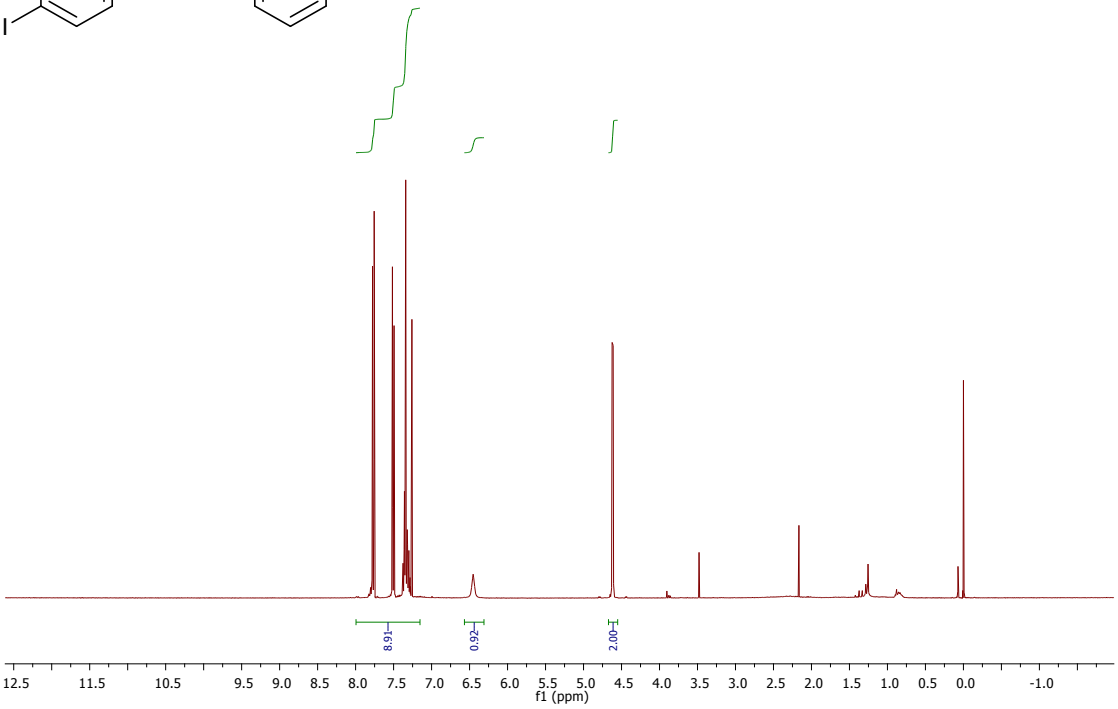


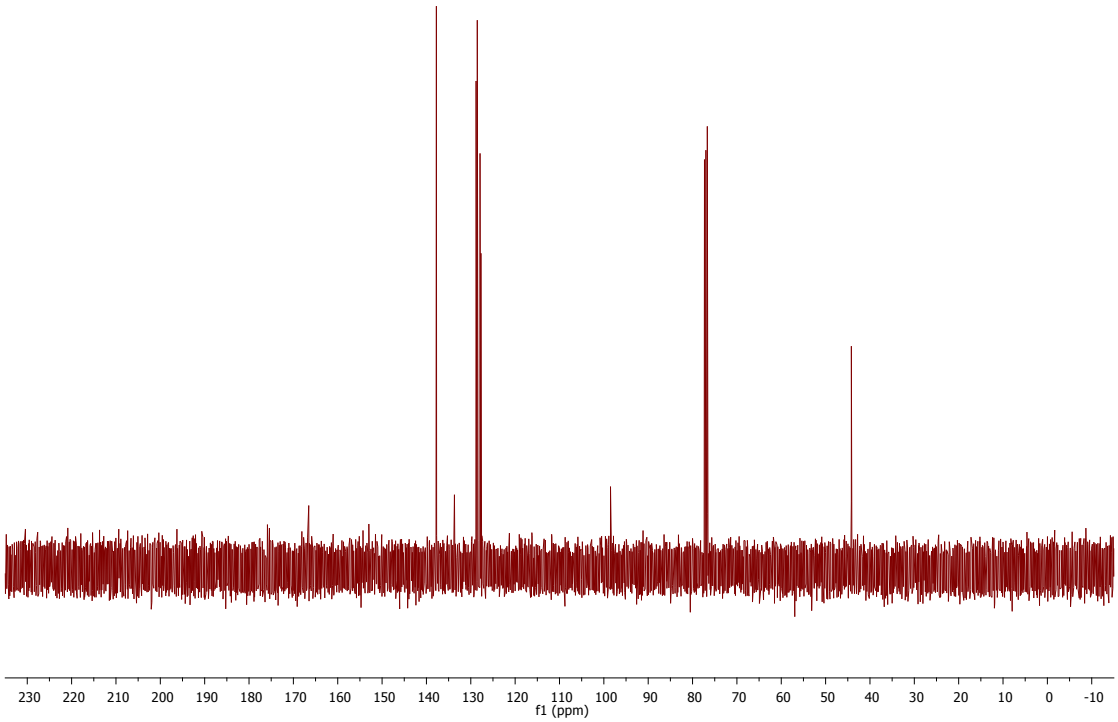




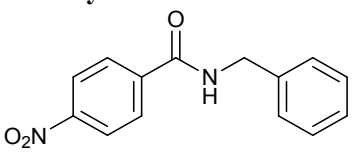
***N*-benzyl-4-iodobenzamide**

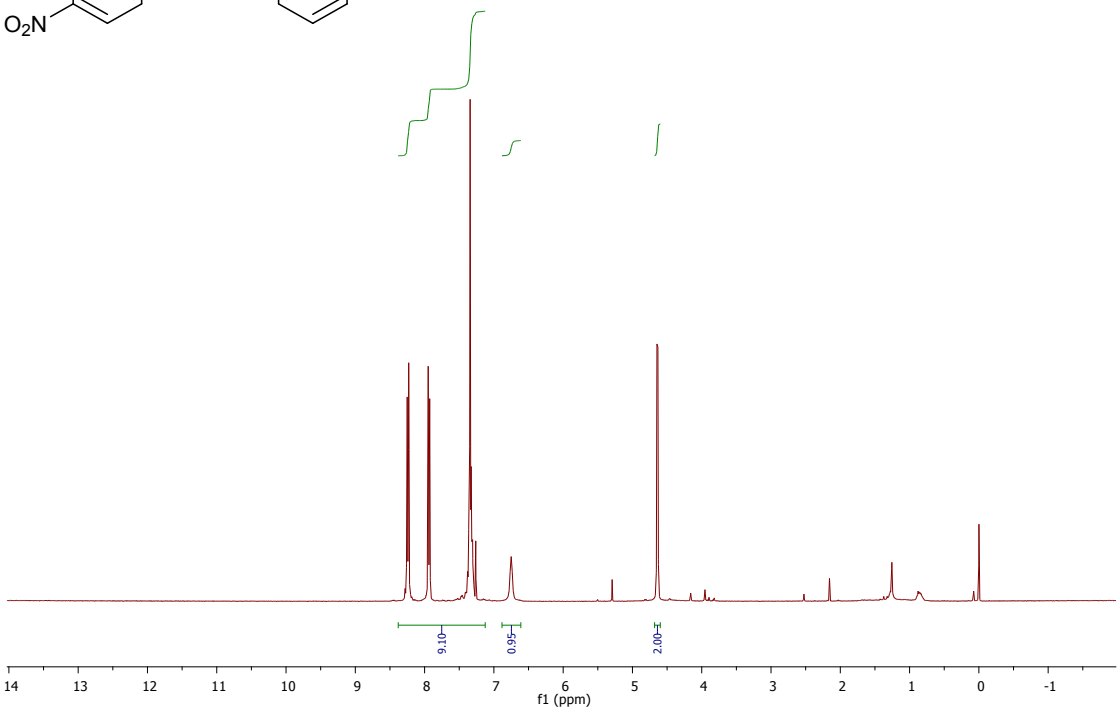


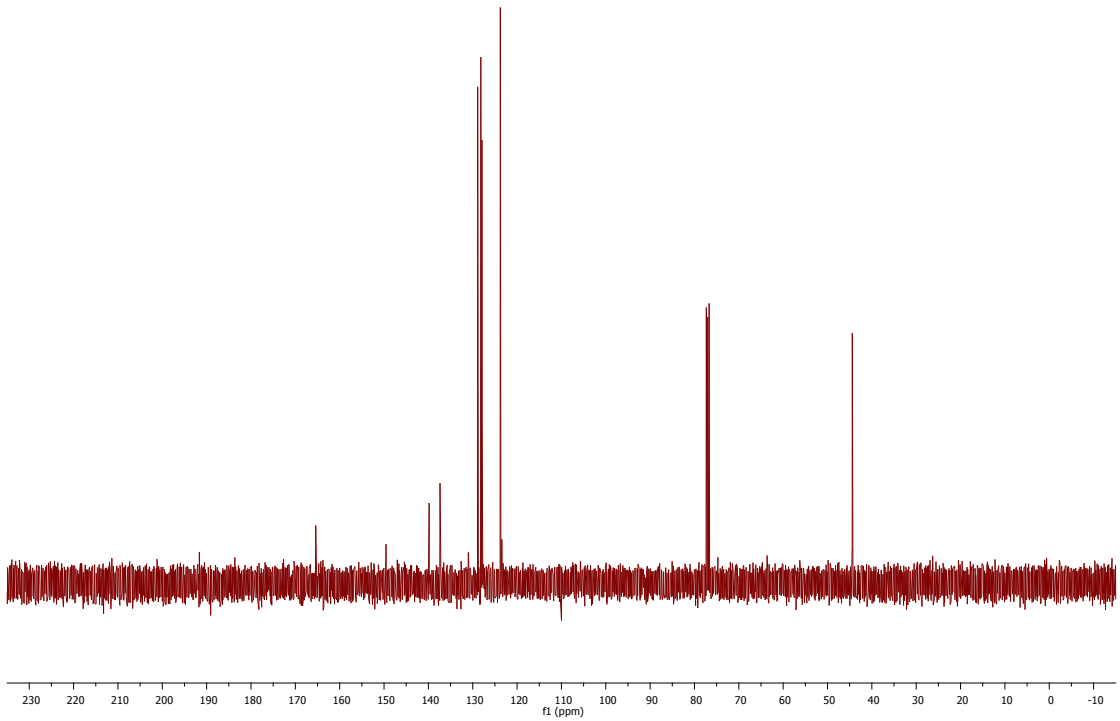




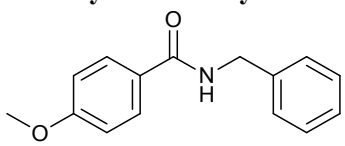
N-benzyl-4-nitrobenzamide

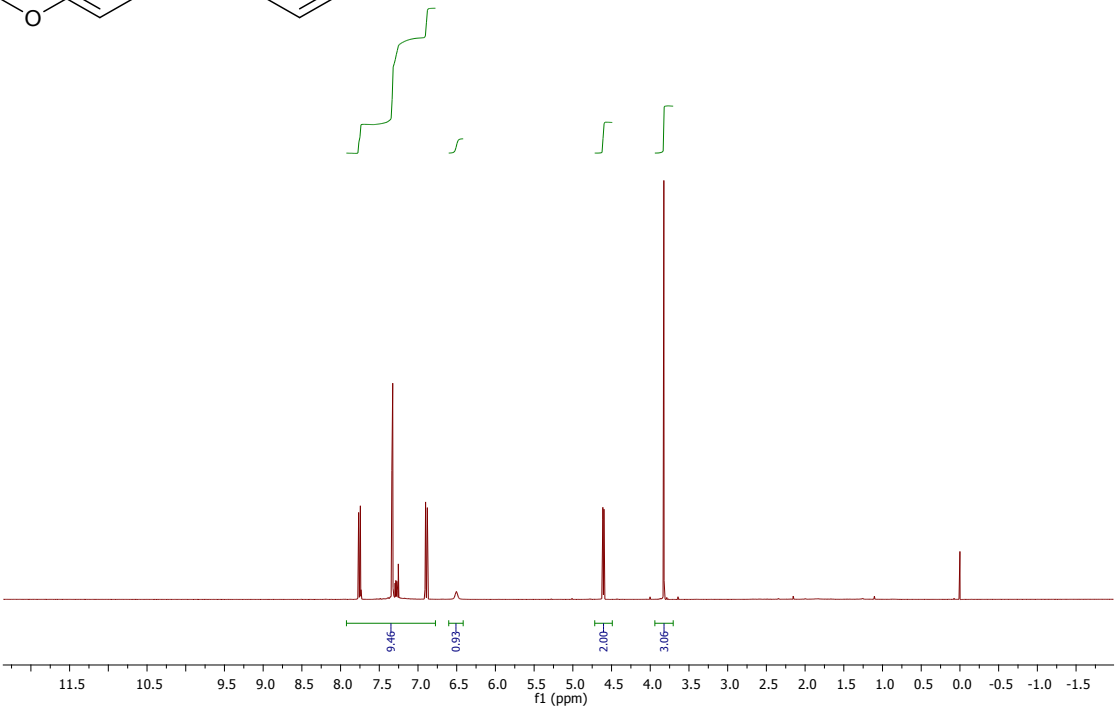


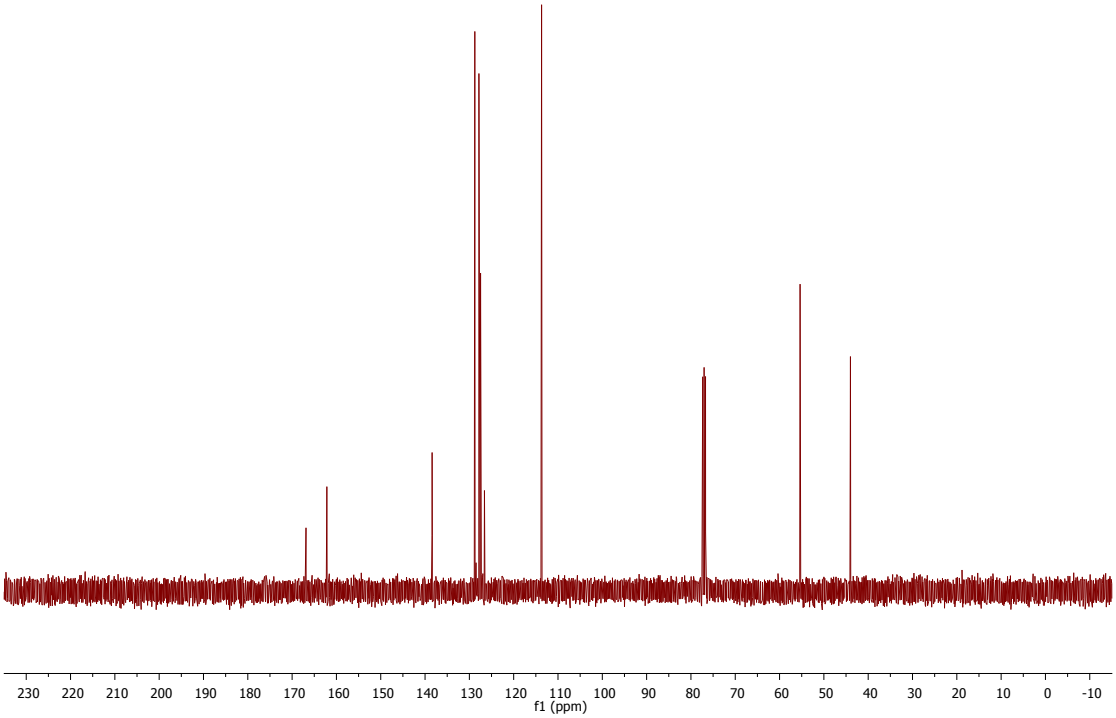




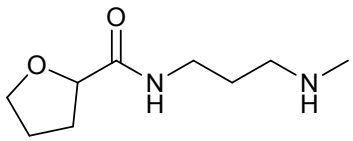
***N*-benzyl-4-methoxybenzamide**

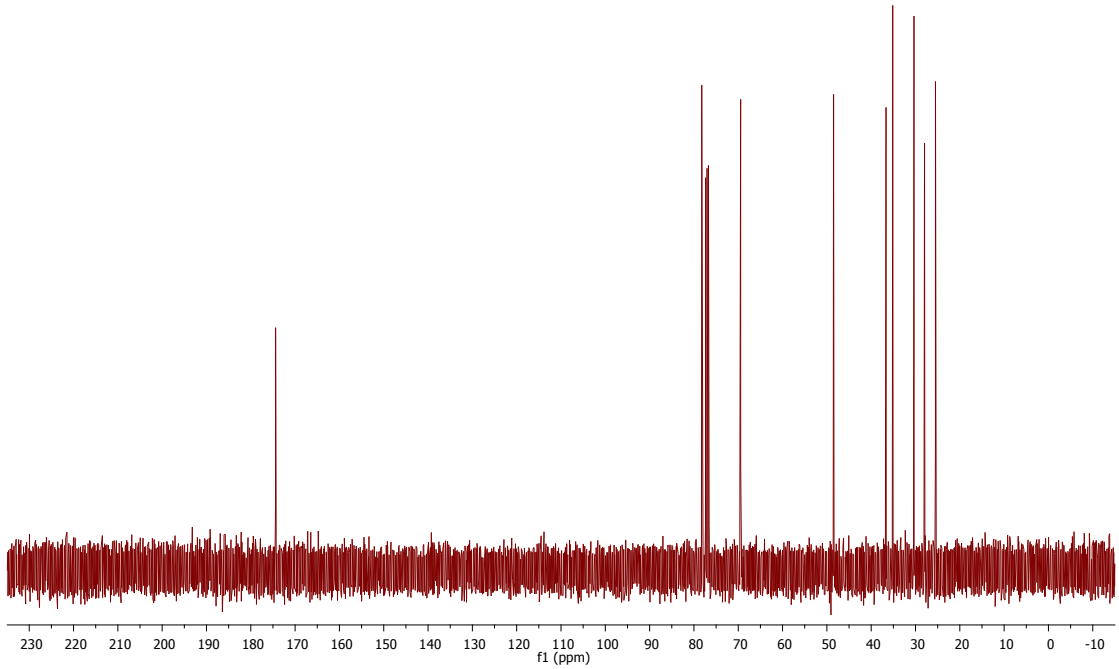




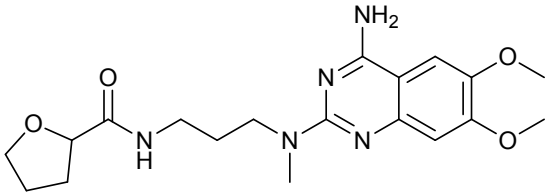


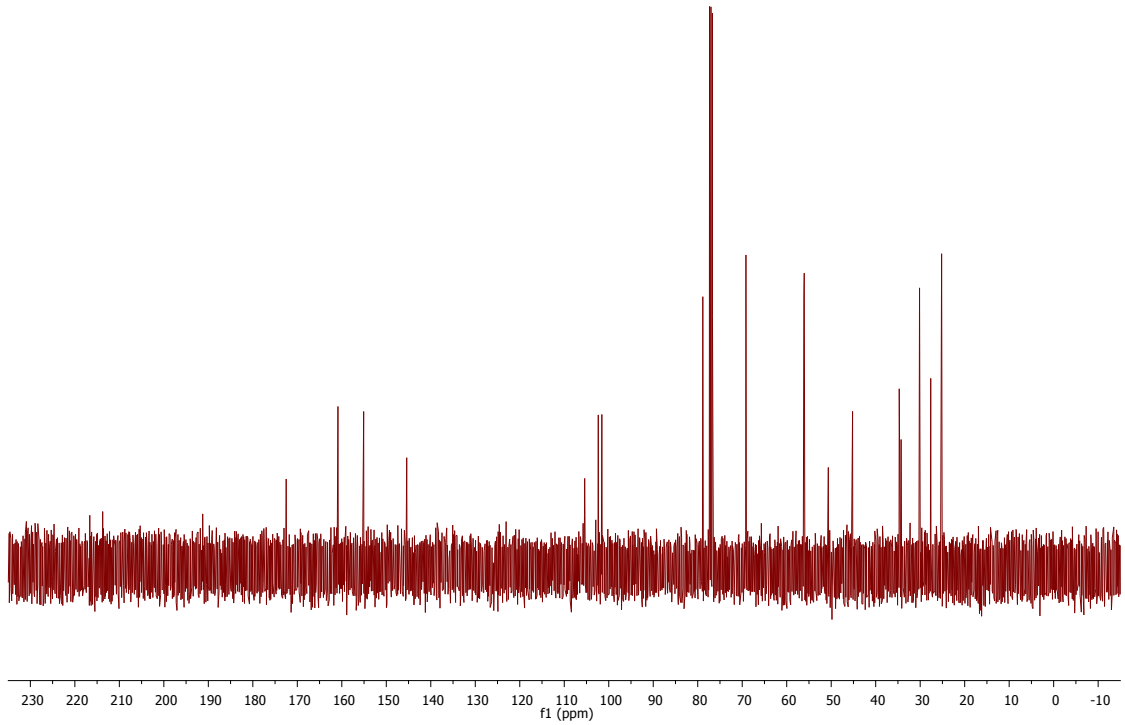
***N*-(3-(methylamino)propyl)tetrahydrofuran-2-carboxamide**





***N*-(3-((4-amino-6,7-dimethoxyquinazolin-2-yl)(methyl)amino)propyl)tetrahydrofuran-2-carboxamide**





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