

Direct amide formation from unactivated carboxylic acids and amines

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Materials and Methods

All reactions requiring an anhydrous, inert atmosphere were carried out under a nitrogen atmosphere using evacuated carousel or ampules. Unless preparative details are provided, all reagents were purchased from commercial suppliers Aldrich, Fluka, Lancaster, TCI and Acros Organics and used without further purification. All solvents were distilled and degassed and stored in the presence of 3 Å molecular sieves prior to use. Thin layer chromatography was carried out on aluminium or glass backed silica plates, purchased from Aldrich. The plates were visualised under UV (254 nm) light, sometimes followed by staining with potassium permanganate or ninhydrin dip and gentle heating. During compound separations, column chromatography was carried out using 60 micron dry silica purchased from Aldrich. Organic layers were routinely dried with anhydrous MgSO₄ and concentrated using a Büchi rotary evaporator.

¹H NMR / ¹³C NMR spectra were run in CDCl₃, unless stated otherwise, on either a Bruker Avance 250 (250 MHz) or a Bruker Avance 300 (300 MHz). Any chemical shifts (δ) are reported as parts per million (ppm) with reference to tetramethylsilane (TMS) (δ_H = 0.00 ppm) unless otherwise stated. The coupling constants (*J*) are reported in Hz and signal multiplicities are reported as singlet (s), doublet (d), triplet (t), quartet (q), quintet (qu), doublet of doublets (dd), doublet of triplets (dt), triplet of triplets (tt), multiplet (m), or broad (br. s).

For mass spectrometry data acquisition a micrOTOF electrospray time-of-flight (ESI-TOF) mass spectrometer (Bruker Daltonik GmbH, Bremen, Germany) was used; this was coupled to an Agilent 1200 LC system (Agilent Technologies, Waldbronn, Germany). The LC system was used as an autosampler only. 10 µL of sample was injected into a 30:70 flow of water:acetonitrile at 0.3 mL/min to the mass spectrometer. For each acquisition 10 µL of a calibrant of 5 mM sodium formate was injected after the sample. The observed mass and isotope pattern matched the corresponding theoretical values as calculated from the expected elemental formula.

Infra-red spectra were recorded on a Perkin Elmer Spectrum 100 FT-IR spectrometer, using a Universal ATR accessory for sampling, with relevant absorbances quoted as ν in cm^{-1} .

Enantiomeric excess was measured using a Perkin Elmer 200 Series HPLC machine fitted with a Chiralcel OD-H column (25 cm), eluting with HPLC grade hexane and isopropylalcohol.

All characterization data was consistent with that reported in the literature.

General Procedures

I. Solvent screening: 3-Phenylpropionamide (0.150 g, 1 mmol) was added to an oven dried Radleys carousel tube. 4-Methylbenzylamine (0.13 mL, 1 mmol) and the appropriate solvent (1 mL, see Table S1) was added then the tube was sealed and heated at reflux for 20 hours. The reaction mixture was allowed to cool to room temperature before the solvent was removed *in vacuo* on a rotary evaporator and the crude reaction mixtures were analysed by their ^1H NMR and ^{13}C NMR spectra.

II. Catalyst screening: 3-Phenylpropionamide (0.150 g, 1 mmol) was added to an oven dried Radleys carousel tube. Benzylamine (0.11 mL, 1 mmol), the appropriate catalyst (10 mol %, see Table 3) and toluene (1 mL) was added then the tube was sealed and heated at reflux for 4 hours. The reaction mixture was allowed to cool to room temperature before the solvent was removed *in vacuo* on a rotary evaporator and the crude reaction mixtures were analysed by their ^1H NMR and ^{13}C NMR spectra.

III. Catalyst free direct coupling of carboxylic acids and amines: The appropriate carboxylic acid (1.0 mmol) was added to an oven dried Radleys carousel tube, followed by the appropriate amine (1.0 mmol) and 0.5 mL toluene (unless otherwise stated). The tube was then sealed and the reaction mixture heated at reflux for 22 hours before being allowed to cool to room temperature. The solvent was then removed on a rotary evaporator and the products were isolated by column chromatography and recrystallized where appropriate. The resulting amides were

characterised by their IR, ^1H NMR and ^{13}C NMR spectroscopy and mass spectrometry data.

IV. Zirconium catalyzed coupling of carboxylic acids and amines: The carboxylic acid species (2 mmol) was added to an oven dried Radleys carousel tube, followed by the zirconium catalyst (ZrCl_4 : 0.023 g, 5 mol% unless otherwise stated; ZrCp_2Cl_2 : 0.029 g, 5 mol%; see Table 2), toluene (2 mL) and the amine species (2 mmol). The carousel tube was then sealed before the reaction mixture was heated at reflux for the appropriate time (see Table 2). After being allowed to cool to room temperature, the solvent was removed *in vacuo* on a rotary evaporator and the resulting crude reaction mixtures were analysed by their ^1H NMR and ^{13}C NMR spectroscopy and mass spectrometry data. Where the reaction had gone to 100% conversion, the reaction mixture was passed through a short plug of silica to remove the catalyst; otherwise the amides were purified by column chromatography where appropriate.

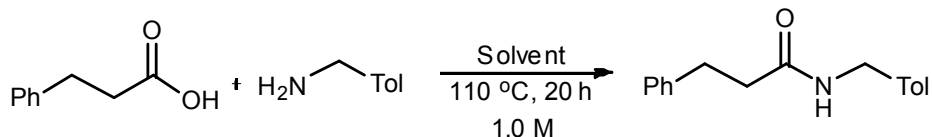
V. Scale up reaction: 3-Phenylpropionamide (62.74 g, 418 mmol) was added to an oven dried single neck 500 mL round bottom flask. Benzylamine (45.6 mL, 418 mmol) and toluene (210 mL) were added and the flask was fitted with a reflux condenser (and left open to the air) before being heated at reflux for 28 hours. The reaction mixture was allowed to cool to room temperature before the solvent was removed *in vacuo* on a rotary evaporator and the resulting amide was recrystallized from dichloromethane.

VI. Rate study: 3-Phenylpropionamide (0.150 g, 1 mmol) was added to an oven dried Radleys carousel tube. Benzylamine (0.11 mL, 1 mmol), ZrCl_4 (0.012 g, 5 mol%) and toluene (1 mL) was added then the tube was sealed and heated at reflux for the appropriate number of hours. The reaction mixture was allowed to cool to room temperature before the solvent was removed *in vacuo* on a rotary evaporator and the crude reaction mixtures were analysed by their ^1H NMR and ^{13}C NMR spectra.

VII. Reversibility study: The appropriate secondary amide (0.15 mmol) and water (0.004 mL, 0.2 mmol) were added to an oven dried Radleys carousel tube. Toluene (0.2 mL) and, if required, ZrCl_4 (0.0012 g, 5 mol%) were added and the tube was sealed and heated at reflux for 22 hours. The reaction mixture was allowed to cool to

room temperature before the solvent was removed on a rotary evaporator and the products analysed by their ^1H NMR and ^{13}C NMR spectra.

Table S1 Direct amide bond formation in a range of solvents after 20 hours

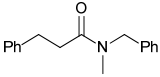
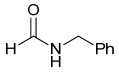
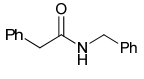
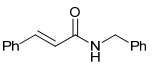
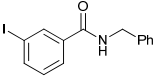


Entry	Solvent	Conversion (%) ^a
1	Toluene	92
2	Cyclohexane	4
3	Isopropanol	3
4	Dimethylsulfoxide	0
5	Water	0
6	1,2-Dichloroethane	12
7	1,4-Dioxane	66
8	Acetonitrile	50
9	No solvent	58
10	Toluene	100 ^b

^aDetermined by analysis of the ^1H NMR spectra.

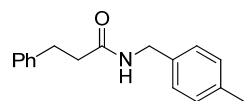
^bRun at 2.0M for 22 h

Table S2 Additional examples of substrates

Entry	Amide	Conversion	Conversion	Catalyst	Time (h)	Conversion
		(%) ^a neat	(%) ^a in toluene			(%) ^a
1		18	100 (95)	ZrCl ₄	18	96 (81)
2		100	100 (89)	ZrCl ₄	5	100 (93)
3		48	100 (91)	ZrCl ₄	5	100 (88)
4		<1 56 (150 °C) ^b	32 100 (91) (150 °C) ^b	ZrCl ₄	18	57
5		0 45 (150 °C) ^b	0 53 (150 °C) ^b	ZrCl ₄	24	27

^a Determined by ¹H NMR spectroscopy, isolated yields shown in parentheses where appropriate; ^b Reaction at 150 °C were run on xylenes.

Characterisations of Products

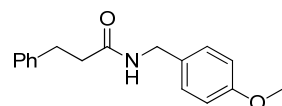


***N*-(4-Methylbenzyl)-3-phenylpropionamide (Table 2, Entry 1)**

Following general procedure III, 3-phenylpropionic acid (0.150 g, 1.0 mmol) was used as the acid species and 4-methylbenzylamine (0.13 mL, 1.0 mmol) was used as the amine species. *N*-(4-Methylbenzyl)-3-phenylpropionamide was recovered as an off-white solid (0.205 g, 81 %) after removal of toluene and recrystallisation (dichloromethane/hexane).

^1H NMR (250 MHz, CDCl_3): δ = 2.36 (3H, s, CH_3), 2.50 – 2.56 (2H, t, J = 7.5 Hz, PhCH_2CH_2), 2.99 – 3.06 (2H, t, J = 7.5 Hz, PhCH_2CH_2), 4.38 – 4.40 (2H, d, J = 5.75 Hz, $\text{NHCH}_2(4\text{-Me})\text{Ph}$), 7.06 – 7.32 (9H, m, 2xPh); ^{13}C NMR (75 MHz, CDCl_3): δ = 21.1, 31.7, 38.6, 43.4, 126.3, 127.8, 128.4, 128.6, 129.3, 135.1, 137.2, 140.8, 171.8; ESI-MS of $[\text{C}_{17}\text{H}_{20}\text{NO}]^+$; theoretical m/z of $[\text{M}+\text{H}]^+$ = 254.15, measured m/z of $[\text{M}+\text{H}]^+$ = 254.14; IR: ν (cm^{-1}) = 1636.58 cm^{-1} (C=O stretch); Elemental analysis: predicted C:80.60, H:7.56, N:5.53; Found C:80.58, H:7.55, N:5.54.

Following general procedure IV, 3-phenylpropionic acid (0.300 g, 2.0 mmol) was used as the acid species and 4-methylbenzylamine (0.26 mL, 2.0 mmol) was used as the amine species. *N*-(4-Methylbenzyl)-3-phenylpropionamide was recovered as an off-white solid (0.476 g, 94 %, ZrCp_2Cl_2 ; 0.466 g, 92 %, ZrCl_4) after filtration through a pad of silica (eluting with dichloromethane) and recrystallisation (dichloromethane/hexane).

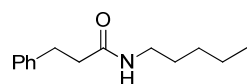


***N*-(4-Methoxybenzyl)-3-phenylpropionamide (Table 2, Entry 2)¹**

Following general procedure III, 3-phenylpropionic acid (0.150 g, 1.0 mmol) was used as the acid species and 4-methoxybenzylamine (0.14 mL, 1.0 mmol) was used as the amine species. *N*-(4-Methoxybenzyl)-3-phenylpropionamide was recovered as a yellow solid (0.194 g, 72 %) after column chromatography (eluting with dichloromethane/methanol 95:5).

^1H NMR (250 MHz, CDCl_3): 2.50 - 2.56 (2H, t, $J = 7.75$ Hz, PhCH_2CH_2), 2.99 - 3.05 (2H, t, $J = 7.75$ Hz, PhCH_2CH_2), 3.82 (3H, s, OCH_3), 4.34 - 4.37 (2H, d, $J = 5.75$ Hz, NHCH_2Ph), 5.67 (1H, br. s., NH), 6.84 - 6.87 (2H, d, $J = 8.75$ Hz, (4-OMe)Ph), 7.09 - 7.12 (2H, d, $J = 8.75$ Hz, (4-OMe)Ph), 7.21 - 7.33 (m, 5H, Ph); ^{13}C NMR (75 MHz, CDCl_3): $\delta = 31.8, 38.5, 43.1, 55.3, 114.1, 126.3, 128.3, 128.4, 128.6, 129.1, 130.2, 140.8, 159.0, 172.0$; ESI-MS of $[\text{C}_{17}\text{H}_{20}\text{NO}_2]^+$; theoretical m/z of $[\text{M}+\text{H}]^+ = 270.157$, measured m/z of $[\text{M}+\text{H}]^+ = 270.157$; IR: ν (cm^{-1}) = 1637.37 cm^{-1} (C=O stretch).

Following general procedure IV, 3-phenylpropionic acid (0.300 g, 2.0 mmol) was used as the acid species and 4-methoxybenzylamine (0.27 mL, 2.0 mmol) was used as the amine species. *N*-(4-Methoxybenzyl)-3-phenylpropionamide was recovered as a pale yellow solid (0.323 g, 60 % ZrCp_2Cl_2 ; 0.479 g, 89 % ZrCl_4) after filtration through a pad of silica, eluting with dichloromethane. Analytical data was consistent with that above.

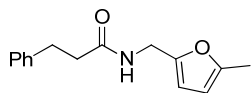


***N*-(Pentyl)-3-phenylpropionamide (Table 2, Entry 3)²**

Following general procedure III, 3-phenylpropionic acid (0.150 g, 1.0 mmol) was used as the acid species and pentylamine (0.13 mL, 1.0 mmol) was used as the amine species. *N*-(Pentyl)-3-phenylpropionamide was recovered as a dark brown oil (0.199 g, 94 %) after removal of toluene.

^1H NMR (250 MHz, CDCl_3): $\delta = 0.87 - 0.93$ (3H, t, $J = 6.75$ Hz, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.22 - 1.47 (6H, m, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 2.46 - 2.52 (2H, t, $J = 8.0$ Hz, PhCH_2CH_2), 2.96 - 3.02 (2H, t, $J = 8.0$ Hz, PhCH_2CH_2), 3.18 - 3.26 (2H, q, $J = 7.0$ Hz, NHCH_2CH_2), 5.35 (1H, br. s., NH), 7.23 - 7.31 (5H, m, Ph); ^{13}C NMR (75 MHz, CDCl_3): $\delta = 14.0, 22.3, 29.0, 29.2, 31.8, 38.6, 39.5, 126.2, 128.3, 128.4, 128.5, 140.9, 172.0$; ESI-MS of $[\text{C}_{14}\text{H}_{22}\text{NO}]^+$; theoretical m/z of $[\text{M}+\text{H}]^+ = 220.128$, measured m/z of $[\text{M}+\text{H}]^+ = 220.127$.

Following general procedure IV, 3-phenylpropionic acid (0.300 g, 2.0 mmol) was used as the acid species and pentylamine (0.26 mL, 2.0 mmol) was used as the amine species. *N*-(Pentyl)-3-phenylpropionamide was isolated as a brown oil (0.301g, 71%) after column chromatography (eluting with 95:5 dichloromethane:methanol). Analytical data was consistent with that above.

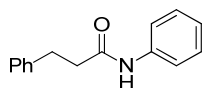


***N*-(5-Methylfurfuryl)-3-phenylpropionamide (Table 2, Entry 4)**

Following general procedure III, 3-phenylpropionic acid (0.150 g, 1.0 mmol) was used as the acid species and 5-methylfurfurylamine (0.18 mL, 1.0 mmol) was used as the amine species. *N*-(5-Methylfurfuryl)-3-phenylpropionamide was recovered as a brown oil (0.454 g, 92 %) after removal of the solvent.

¹H NMR (250 MHz, CDCl₃): δ = 2.17 (3H, s, CH₃), 2.38 - 2.44 (2H, t, *J* = 8.25 Hz, PhCH₂CH₂), 2.86 - 2.92 (2H, t, *J* = 8.25 Hz, PhCH₂CH₂), 4.25 - 4.27 (2H, d, *J* = 5.25 Hz, NHCH₂Furyl), 5.67 (1H, br. s., NH), 5.79 - 5.80 (1H, d, Furyl), 5.95 - 5.96 (1H, d, Furyl), 7.09 - 7.18 (5H, m, Ph); ¹³C NMR (75 MHz, CDCl₃): δ = 13.5, 31.6, 36.6, 38.4, 106.3, 108.3, 126.2, 128.4, 128.5, 140.8, 149.3, 151.9, 171.8; ESI-MS of [C₁₅H₁₈NO₂]⁺; theoretical *m/z* of [M+H]⁺ = 244.130, measured *m/z* of [M+H]⁺ = 244.130; IR: ν (cm⁻¹) = 1647.39 cm⁻¹ (C=O stretch); Elemental analysis: predicted C:74.05, H:7.04, N:5.76; Found C:74.05, H:7.05, N:5.74.

Following general procedure IV, 3-phenylpropionic acid (0.300 g, 2.0 mmol) was used as the acid species and 5-methylfurfurylamine (0.36 mL, 2.0 mmol) was used as the amine species. *N*-(5-Methylfurfuryl)-3-phenylpropionamide was recovered as a brown oil (0.442 g, 91 %) after filtration through a pad of silica, eluting with dichloromethane. Analytical data was consistent with that above.

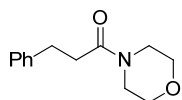


***N*-(Phenyl)-3-phenylpropionamide (Table 2, Entry 5)³**

Following general procedure III, 3-phenylpropionic acid (0.150 g, 1.0 mmol) was used as the acid species and aniline (0.09 mL, 1.0 mmol) was used as the amine species. The reaction mixture was heated at reflux in 0.5 mL *p*-xylene. An ¹H NMR of the crude reaction mixture showed a 73 % conversion into *N*-(phenyl)-3-phenylpropionamide.

¹H NMR (250 MHz, CDCl₃): δ = 2.66 - 2.72 (2H, t, *J* = 7.25 Hz, PhCH₂CH₂), 3.06 - 3.12 (2H, t, *J* = 7.25 Hz, PhCH₂CH₂), 5.60 (1H, br. S., NH), 7.30 - 7.37 (8H, m, 2xPh), 7.45 - 7.48 (2H, d, *J* = 7.5 Hz, Ph); ESI-MS of [C₁₅H₁₆NO]⁺; theoretical *m/z* of [M+H]⁺ = 226.135, measured *m/z* of [M+H]⁺ = 226.135; IR: ν (cm⁻¹) = 1649.38 cm⁻¹ (C=O stretch).

Following general procedure IV, 3-phenylpropionic acid (0.300 g, 2.0 mmol) was used as the acid species and aniline (0.17 mL, 2.0 mmol) was used as the amine species. 10 mol% ZrCl₄ (0.046g) was used. An ¹H NMR of the crude reaction mixture showed a 45 % conversion into *N*-(phenyl)-3-phenylpropionamide when ZrCp₂Cl₂ was used as catalyst and a 41 % conversion when ZrCl₂ was used as catalyst. Analytical data was consistent with that above.

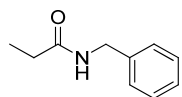


***N*-(Morpholino)-3-phenylpropionamide (Table 2, Entry 6)¹**

Following general procedure III, 3-phenylpropionic acid (0.150 g, 1.0 mmol) was used as the acid species and morpholine (0.08 mL, 1.0 mmol) was used as the amine species. The reaction mixture was heated at reflux in 0.5 mL *p*-xylene. *N*-(Morpholino)-3-phenylpropionamide was recovered as a colourless oil (0.206 g, 94 %) after removal of *p*-xylene.

¹H NMR (250 MHz, CDCl₃): δ = 2.51 - 2.57 (t, 2H, *J* = 8.3 Hz, PhCH₂CH₂), 2.88 - 2.94 (t, 2H, *J* = 8.3 Hz, PhCH₂CH₂), 3.26 - 3.30 (t, 2H, *J* = 6.3 Hz), 3.42 - 3.46 (t, 2H, *J* = 6.3 Hz), 3.55 (s, 4H), 7.13 - 7.22 (m, 5H, Ph); ¹³C NMR (75 MHz, CDCl₃): δ = 31.49, 34.76, 41.94, 45.95, 66.44, 66.80, 126.29, 128.49, 128.56, 141.06, 170.89; ESI-MS of [C₁₃H₁₇NO₂]⁺; theoretical m/z of [M+H]⁺ = 220.134, measured m/z of [M+H]⁺ = 220.132; IR: ν (cm⁻¹) = 1635.83 (C=O stretch).

Following general procedure IV, 3-phenylpropionic acid (0.300 g, 2.0 mmol) was used as the acid species and morpholine (0.17 mL, 2.0 mmol) was used as the amine species. *N*-(Morpholino)-3-phenylpropionamide was recovered as a colourless oil (0.386 g, 88 %) after filtration through a pad of silica, eluting with dichloromethane. Analytical data was consistent with that above.



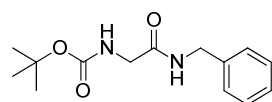
***N*-(Benzyl)-propionamide (Table 2, Entry 7)⁴**

Following general procedure III, propionic acid (0.15 mL, 2.0 mmol) was used as the acid species and benzylamine (0.22 mL, 2.0 mmol) was used as the amine species. *N*-

(Benzyl)-propionamide was recovered as a white solid (0.293 g, 90 %) removal of toluene and recrystallisation (dichloromethane/hexane).

^1H NMR (250 MHz, CDCl_3 , 25 °C): δ = 1.02 – 1.07 (3H, t, J = 6.0, CH_3CH_2), 2.08 – 2.14 (2H, q, J = 6.0 Hz, $\text{CH}_3\text{CH}_2\text{C}(\text{O})$), 4.31 (2H, d, J = 9.0 Hz, PhCH_2NH), 7.08 – 7.22 (5H, m, aromatic); ^{13}C NMR (75.5 MHz, CDCl_3 , 25 °C): δ = 10.2, 30.1, 40.0, 127.9, 128.2, 129.1, 138.8, 173.9; ESI-MS of $[\text{C}_{10}\text{H}_{13}\text{NO}]^+$; theoretical m/z of $[\text{M}+\text{H}]^+$ = 164.11, measured m/z of $[\text{M}+\text{H}]^+$ = 164.11; IR : ν (cm^{-1}) = 1642.09 cm^{-1} (C=O stretch).

Following general procedure IV, propionic acid (0.15 mL, 2.0 mmol) was used as the acid species and benzylamine (0.22 mL, 2.0 mmol) was used as the amine species. *N*-(Benzyl)-propionamide was recovered as a white solid (0.264 g, 81%) after filtration through a pad of silica, eluting with dichloromethane. Analytical data was consistent with that above.



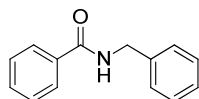
***N*-(Benzyl)*N'*-Boc]-glycinamide (Table 2, Entry 8)⁵**

Following general procedure III, *N*-Boc-glycine (0.350 g, 2.0 mmol) was used as the acid species and benzylamine (0.22 mL, 2.0 mmol) was used as the amine species. An ^1H NMR of the crude reaction mixture showed a 71% conversion into [*N*-(Benzyl)*N'*-Boc]-glycinamide.

^1H NMR (250 MHz, DMSO-d_6): δ = 1.41 (9H, s, 3x CH_3), 3.59 - 3.61 (2H, d, J = 6.25 Hz, $\text{NHCH}_2\text{C}(\text{O})\text{NH}$), 4.29 - 4.31 (2H, d, J = 5.75 Hz, $\text{C}(\text{O})\text{NHCH}_2\text{Ph}$), 7.02 (1H, br. s., NH), 7.24 - 7.32 (5H, m, Ph), 8.32 (1H, br. s., NH).

Following general procedure IV, *N*-Boc-glycine (0.350 g, 2.0 mmol) was used as the acid species and benzylamine (0.22 mL, 2.0 mmol) was used as the amine species. [*N*-(Benzyl)*N'*-Boc]-glycinamide was recovered as a pale yellow viscous oil (0.423 g, 80 %) after column chromatography (eluting with 97:3 dichloromethane: methanol) and washing with hexanes.

^{13}C NMR (75 MHz, DMSO-d_6): δ = 28.2, 42.0, 43.4, 78.0, 126.7, 127.1, 128.1, 139.4, 155.8, 169.4; ESI-MS of $[\text{C}_{14}\text{H}_{21}\text{N}_2\text{O}_3]^+$; theoretical m/z of $[\text{M}+\text{H}]^+$ = 265.153, measured m/z of $[\text{M}+\text{H}]^+$ = 265.153.



***N*-(Benzyl)-benzamide (Table 2, Entry 9)⁵**

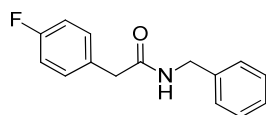
Following general procedure III, benzoic acid (0.246 g, 2.0 mmol) was used as the acid species and benzylamine (0.22 mL, 2.0 mmol) was used as the amine species. The reaction mixture was heated at reflux in 0.5 mL *p*-xylene. An ¹H NMR of the crude reaction mixture showed a 44% conversion into *N*-(benzyl)-benzamide.

¹H NMR (300 MHz, CDCl₃): δ = 4.57 - 4.59 (d, 2H, *J* = 5.7 Hz, PhCH₂NH), 6.36 (br. s, 1H, NH), 7.18 - 7.43 (m, 8H, 2Ph), 7.70 - 7.73 (m, 2H, Ph).

Following general procedure IV, benzoic acid (0.241 g, 2.0 mmol) was used as the acid species and benzylamine (0.22 mL, 2.0 mmol) was used as the amine species. 10 mol% ZrCl₄ (0.046g) was used. An ¹H NMR of the crude reaction mixture showed 55 % conversion into *N*-(benzyl)-benzamide when ZrCl₄ was used as catalyst.

N-(Benzyl)-benzamide was recovered as a white solid (0.304 g, 72 %, ZrCp₂Cl₂) after column chromatography (eluting with 92:8 dichloromethane:methanol).

¹³C NMR (75 MHz, CDCl₃): δ = 44.17, 126.97, 127.66, 127.95, 128.62, 128.82, 131.56, 134.43, 138.21, 167.35; ESI-MS of [C₁₄H₁₃NO]⁺; theoretical *m/z* of [M+H]⁺ = 212.107, measured *m/z* of [M+H]⁺ = 212.106.



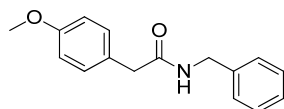
***N*-(Benzyl)-4-fluorophenylacetamide (Table 2, Entry 10)**

Following general procedure III, 4-fluorophenylacetic acid (0.308 g, 2.0 mmol) was used as the acid species and benzylamine (0.22 mL, 2.0 mmol) was used as the amine species. *N*-(Benzyl)-4-fluorophenylacetamide was recovered as an off white solid (0.435 g, 90 %) after removal of toluene.

¹H NMR (300 MHz, DMSO-*d*₆): δ = 3.46 (2H, s, CH₂C(O)), 4.24 - 4.26 (2H, d, *J* = 6.0 Hz, NHCH₂Ph), 7.08 - 7.32 (9H, m, 2xPh), 8.54 (1H, br. s., NH); ¹³C NMR (75

MHz, DMSO-d₆): δ = 41.7, 42.5, 114.9, 115.1, 115.2, 115.4, 127.1, 127.6, 127.9, 128.6, 128.7, 131.1, 131.2, 131.5, 131.6, 132.9, 132.9, 139.8, 159.8, 162.9, 170.4; ESI-MS of [C₁₅H₁₅NOF]⁺; theoretical m/z of [M+H]⁺ = 244.109, measured m/z of [M+H]⁺ = 244.109; IR: ν (cm⁻¹) = 1640.13 cm⁻¹ (C=O stretch); Elemental analysis: predicted C:74.06, H:5.80, N:5.76; Found C:74.08, H:5.85, N:5.74.

Following general procedure IV, 4-fluorophenylacetic acid (0.308 g, 2.0 mmol) was used as the acid species and benzylamine (0.22 mL, 2.0 mmol) was used as the amine species. *N*-(Benzyl)-4-fluorophenylacetamide was recovered as an off white solid (0.442 g, 91 %) after filtration through a pad of silica, eluting with dichloromethane and methanol. Analytical data was consistent with that above.

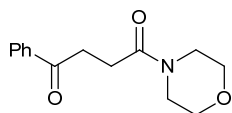


***N*-(Benzyl)-4-methoxyphenylacetamide (Table 2, Entry 11)⁶**

Following general procedure III, 4-methoxyphenylacetic acid (0.333 g, 2.0 mmol) was used as the acid species and benzylamine (0.22 mL, 2.0 mmol) was used as the amine species. *N*-(Benzyl)-4-methoxyphenylacetamide was recovered as a yellow solid (0.469 g, 92 %) after removal of toluene and recrystallization (dichloromethane/hexane).

¹H NMR (300 MHz, DMSO-d₆): δ = 3.38 (2H, s, (4-OMe)PhCH₂C(O)), 3.70 (3H, s, OCH₃), 4.22 – 4.24 (2H, d, *J* = 5.7 Hz, NHCH₂Ph), 6.83 – 6.86 (2H, d, *J* = 8.4 Hz, (4-OMe)Ph), 7.12 – 7.37 (7H, m, 2xPh), 8.47 (1H, br. s., NH); ¹³C NMR (75 MHz, DMSO-d₆): δ = 41.8, 42.5, 55.4, 114.0, 127.1, 127.5, 128.3, 128.6, 130.3, 130.6, 139.9, 158.3, 170.8; ESI-MS of [C₁₆H₁₈NO₂]⁺; theoretical m/z of [M+H]⁺ = 256.135, measured m/z of [M+H]⁺ = 256.137; IR: ν (cm⁻¹) = 1634.93 cm⁻¹ (C=O stretch).

Following general procedure IV, 4-methoxyphenylacetic acid (0.333 g, 2.0 mmol) was used as the acid species and benzylamine (0.22 mL, 2.0 mmol) was used as the amine species. *N*-(Benzyl)-4-methoxyphenylacetamide was recovered as a yellow solid (0.455 g, 91 %) after filtration through a pad of silica, eluting with dichloromethane. Analytical data was consistent with that above.

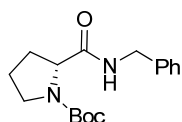


3-Benzoyl-*N*-morpholinopropionic acid (Table 2, Entry 12)⁷

Following general procedure III, 3-benzoylpropionic acid (0.178 g, 1.0 mmol) was used as the acid species and morpholine (0.08 mL, 1.0 mmol) was used as the amine species. 3-Benzoyl-*N*-morpholinopropionamide was recovered as a dark yellow oil (0.193 g, 78 %) after removal of toluene and recrystallization (dichloromethane/hexane).

¹H NMR (300 MHz, CDCl₃): δ = 2.74 – 2.78 (2H, t, *J* = 6.6 Hz, PhC(O)CH₂), 3.33 – 3.38 (2H, t, *J* = 6.6 Hz, PhC(O)CH₂CH₂), 3.55 – 3.73 (8H, m, morpholine ring), 7.42 – 7.57 (3H, m, PhC(O)), 7.99 – 8.01 (2H, d, *J* = 6.9 Hz, PhC(O)); ¹³C NMR (75 MHz, CDCl₃): δ = 26.9, 33.5, 42.1, 45.9, 128.0, 128.1, 128.5, 128.6, 133.2, 136.7, 170.5, 199.1; ESI-MS of [C₁₆H₁₈NO₂]⁺; theoretical *m/z* of [M+H]⁺ = 248.124, measured *m/z* of [M+H]⁺ = 248.122; IR: ν (cm⁻¹) = 1682.76 cm⁻¹ (C=O stretch, amide).

Following general procedure IV, 3-benzoylpropionic acid (0.356 g, 2.0 mmol) was used as the acid species and morpholine (0.16 mL, 2.0 mmol) was used as the amine species. 3-Benzoyl-*N*-morpholinopropionamide was recovered as a dark yellow oil (0.386 g, 78 %) after filtration through a pad of silica, eluting with dichloromethane. Analytical data was consistent with that above.



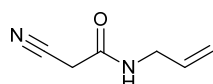
[*N*-(Benzyl)*N'*-Boc]-D-prolinamide (Table 2, Entry 13)⁵

Following general procedure IV, *N*-Boc-D-proline (0.431 g, 2.0 mmol) was used as the acid species and benzylamine (0.22 mL, 2.0 mmol) was used as the amine species. The reaction was heated at reflux in 0.5 mL *p*-xylene. An ¹H NMR of the crude reaction mixture showed 79 % conversion into [*N*-(Benzyl)*N'*-Boc]-D-prolinamide.

Following general procedure IV, *N*-Boc-D-proline (0.323 g, 1.5 mmol) was used as the acid species and benzylamine (0.22 mL, 2.0 mmol) was used as the amine species. [*N*-(Benzyl)*N'*-Boc]-D-prolinamide was recovered as a white solid (0.256 g, 56 %) after column chromatography eluting with 1:1 hexane : ethyl acetate.

¹H NMR (250 MHz, DMSO-d₆): δ = 1.30 (5.5H, s, ^tBu), 1.42 (3.5H, s, ^tBu), 1.79 – 1.82 (3H, m, pyrrolidine ring), 2.07 – 2.18 (1H, m, pyrrolidine ring), 3.25 – 3.43 (2H,

m, pyrrolidine ring), 4.07 - 4.39 (3H, m, NHCH_2Ph and $(\text{Boc})\text{NCHC}(\text{O})$), 7.24 - 7.32 (5H, m, Ph), 8.36 - 8.43 (1H, m, NH); ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 23.5, 28.3, 31.4, 31.5, 42.4, 46.8, 60.1, 60.3, 78.8, 127.1, 127.6, 128.5, 139.9, 161.7, 172.8$; ESI-MS of $[\text{C}_{17}\text{H}_{23}\text{N}_2\text{O}_3]^+$; theoretical m/z of $[\text{M}+\text{H}]^+ = 305.154$, measured m/z of $[\text{M}+\text{H}]^+ = 305.148$; IR: ν (cm^{-1}) = 1675.75 cm^{-1} ($\text{C}=\text{O}$ stretch, amide); $[\alpha]_{\text{D}}^{25} = 80.3^\circ$ (CHCl_3 , $c = 0.09$); HPLC: Chiralcel AD column (25 cm), 90:10 hexane : isopropylalcohol, 0.5 mL min^{-1} flow rate, 16.39 min (D-enantiomer). No peak observed for L-enantiomer @ 22.94 min.

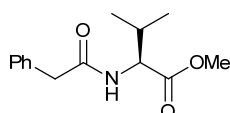


***N*-(Allyl)-cyanoacetamide (Table 2, Entry 14)⁸**

Following general procedure III, cyanoacetic acid (0.085 g, 1.0 mmol) was used as the acid species and allylamine (0.08 mL, 1.0 mmol) was used as the amine species. *N*-(Allyl)-cyanoacetamide was recovered as a light brown solid (0.095 g, 76 %) after removal of toluene.

^1H NMR (300 MHz, CDCl_3): $\delta = 3.34$ (2H, s, $\text{NCCCH}_2\text{C}(\text{O})$), 3.84 – 3.88 (2H, m, NHCH_2CH), 5.09 – 5.21 (2H, m, $\text{NHCH}_2\text{CHCH}_2$), 5.71 – 5.84 (1H, m, $\text{NHCH}_2\text{CHCH}_2$), 6.29 (1H, br. s., NH); ^{13}C NMR (75 MHz, CDCl_3): $\delta = 25.8, 42.7, 117.6, 132.8, 133.5, 160.8$; ESI-MS of $[\text{C}_6\text{H}_9\text{N}_2\text{O}]^+$; theoretical m/z of $[\text{M}+\text{H}]^+ = 125.069$ measured m/z of $[\text{M}+\text{H}]^+ = 125.068$; IR: ν (cm^{-1}) = 1657.64 cm^{-1} ($\text{C}=\text{O}$ stretch).

Following general procedure VI, cyanoacetic acid (0.085 g, 1.0 mmol) was used as the acid species and allylamine (0.08 mL, 1.0 mmol) was used as the amine species. *N*-(Allyl)-cyanoacetamide was recovered as a light brown solid (0.104 g, 84 %) after filtration through a short pad of silica (eluting with 97:3 dichloromethane : methanol). Analytical data was consistent with that above.



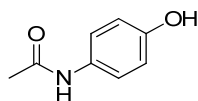
***N*-(Phenylacetyl)-valine methyl ester (Table 2, Entry 15)⁹**

Following general procedure III, phenylacetic acid (0.135 g, 1.0 mmol) was used as the acid species and valine methyl ester hydrochloride (0.167 g, 1.0 mmol) was used as the amine species. One equivalent of *N,N*-diisopropylethylamine (0.17 mL, 1 mmol)

was included in the reaction. *N*-(Phenylacetyl)-valine methyl ester was recovered as a yellow oil (0.218 g, 88 %) after removal of toluene and washing with water to remove the base.

^1H NMR (300 MHz, CDCl_3): δ = 0.67 – 0.69 (3H, d, J = 6.0 Hz, $(\text{CH}_3)\text{CH}(\text{CH}_3)\text{CH}$), 0.77 – 0.79 (3H, d, J = 6.0 Hz, $(\text{CH}_3)\text{CH}(\text{CH}_3)\text{CH}$), 1.97 – 2.08 (1H, m, $(\text{CH}_3)\text{CH}(\text{CH}_3)\text{CH}$), 3.55 – 3.56 (2H, d, J = 3.0 Hz, $\text{PhCH}_2\text{C}(\text{O})$), 3.63 (3H, s, OCH_3), 4.45 – 4.49 (1H, dd, J = 4.8 Hz, 8.7 Hz, $(\text{CH}_3)\text{CH}(\text{CH}_3)\text{CHNH}$), 5.83 (1H, br. s, NH), 7.19 – 7.28 (5H, m, Ph); ^{13}C NMR (75 MHz, CDCl_3): δ = 17.6, 18.9, 31.2, 43.7, 52.2, 57.0, 127.5, 128.6, 129.0, 129.4, 134.6, 171.0, 172.4; ESI-MS of $[\text{C}_{14}\text{H}_{20}\text{NO}_3]^+$; theoretical m/z of $[\text{M}+\text{H}]^+ = 249.136$, measured m/z of $[\text{M}+\text{H}]^+ = 249.136$.

Following general procedure VI, phenylacetic acid (0.135 g, 1.0 mmol) was used as the acid species and valine methyl ester hydrochloride (0.167 g, 1.0 mmol) was used as the amine species. One equivalent of *N,N*-diisopropylethylamine (0.17 mL, 1 mmol) was included in the reaction. *N*-(Phenylacetyl)-valine methyl ester was recovered as a yellow oil (0.202 g, 81 %) after filtration through a short pad of silica and washing with water to remove the base. Analytical data was consistent with that above.

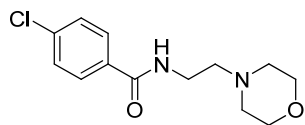


***N*-(Acetyl)-4-hydroxyaniline (Paracetamol) (Table 2, Entry 16)¹⁰**

Following general procedure III, acetic acid (0.12 mL, 2.0 mmol) was used as the acid species and 4-aminophenol (0.218 g, 2.0 mmol) was used as the amine species. The reaction mixture was heated at reflux in 1.0 mL *p*-xylene. An ^1H NMR of the crude reaction mixture showed 69 % conversion into *N*-(acetyl)-4-hydroxyaniline.

Following general procedure IV, acetic acid (0.12 mL, 2.0 mmol) was used as the acid species and 4-aminophenol (0.218 g, 2.0 mmol) was used as the amine species. *N*-(Acetyl)-4-hydroxyaniline was recovered as a dark brown solid (0.266 g, 88 %) after filtration through a pad of celite, eluting with dichloromethane.

^1H NMR (300 MHz, DMSO-d_6): δ = 1.99 (3H, s, $\text{C}(\text{O})\text{CH}_3$), 6.66 - 6.70 (2H, d, J = 8.75 Hz, Ph), 7.33 - 7.36 (2H, d, J = 8.75 Hz, Ph), 9.16 (1H, s, NH), 9.67 (1H, s, OH); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 24.1, 115.3, 121.1, 131.4, 153.5, 167.8; ESI-MS of $[\text{C}_8\text{H}_9\text{NO}_2]^+$; theoretical m/z of $[\text{M}+\text{H}]^+ = 152.071$, measured m/z of $[\text{M}+\text{H}]^+ = 152.072$.

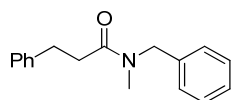


***N*-(2-morpholinoethyl)-4-chlorobenzamide (Moclobemide) (Table 2, Entry 17)¹¹**

Following general procedure III, 4-chlorobenzoic acid (0.312 g, 2.0 mmol) was used as the acid species and benzylamine (0.22 mL, 2.0 mmol) was used as the amine species. The reaction mixture was heated at reflux in 1.0 mL *p*-xylene. An ¹H NMR of the crude reaction mixture showed 66 % conversion into *N*-(2-morpholinoethyl)-4-chlorobenzamide.

Following general procedure IV, 4-chlorobenzoic acid (0.313 g, 2.0 mmol) was used as the acid species and 2-(morpholino)ethylamine (0.26 mL, 2.0 mmol) was used as the amine species. *N*-(2-morpholinoethyl)-4-chlorobenzamide was recovered as an off white solid (0.462 g, 86 %) after filtration through a pad of silica, eluting with dichloromethane.

¹H NMR (300 MHz, CDCl₃, 25 °C): δ = 2.54 – 2.58 (4H, t, *J* = 4.3 Hz, CH₂NCH₂), 2.63 – 2.68 (2H, t, *J* = 6.0 Hz, NCH₂CH₂), 3.56 – 3.62 (2H, q, *J* = 5.6 Hz, NHCH₂CH₂), 3.76 – 3.79 (4H, t, *J* = 4.6 Hz, CH₂OCH₂), 6.83 (1H, br. s, NH), 7.43 – 7.47 (2H, d, *J* = 8.6 Hz, aromatic), 7.73 – 7.77 (2H, d, *J* = 8.6 Hz, aromatic). ¹³C NMR (75.5 MHz, CDCl₃, 25 °C): δ = 36.5, 53.6, 57.5, 67.1, 128.8, 129.2, 129.3, 133.4, 138.2, 166.7. IR: 1117.04, 1486.97, 1540.68, 1594.76, 1634.53, 2968.43, 3285.8 cm⁻¹. ESI-MS of [C₁₃H₁₈N₂O₂Cl]⁺; theoretical *m/z* of [M+H]⁺ = 269.105, measured *m/z* of [M+H]⁺ = 269.104; IR: ν (cm⁻¹) = 1634.53 (C=O stretch).

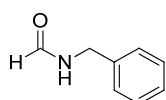


[*N*-(Benzyl)-*N*-methyl]-3-phenylpropionamide (Table S2, Entry 1)¹²

Following general procedure III, 3-phenylpropionic acid (0.150 g, 1.0 mmol) was used as the acid species and *N*-methylbenzylamine (0.13 mL, 1.0 mmol) was used as the amine species. [*N*-(Benzyl)-*N*-methyl]-3-phenylpropionamide was recovered as a yellow oil (0.241 g, 95 %) after removal of toluene. The product was observed as two rotamers in its ¹H and ¹³C NMR spectra.

^1H NMR (250 MHz, CDCl_3): δ = 2.72 - 2.77 (2H, t, J = 8.0 Hz, PhCH_2CH_2), 2.88 (1.8H, s, CH_3 major rotamer), 2.99 (1.2H, s, CH_3 minor rotamer), 3.01 - 3.07 (2H, t, J = 8.0 Hz, PhCH_2CH_2), 4.50 (0.8H, s, $\text{N}(\text{CH}_3)\text{CH}_2\text{Ph}$, minor rotamer), 4.64 (1.2H, s, $\text{N}(\text{CH}_3)\text{CH}_2\text{Ph}$, major rotamer), 7.23 - 7.36 (10H, m, 2xPh); ^{13}C NMR (75 MHz, CDCl_3): δ = 31.4, 31.6, 35.4, 50.9, 126.1, 126.3, 127.3, 128.1, 128.5, 128.6, 128.9, 137.4, 141.3, 172.4; ESI-MS of $[\text{C}_{17}\text{H}_{20}\text{NO}]^+$; theoretical m/z of $[\text{M}+\text{H}]^+$ = 254.154, measured m/z of $[\text{M}+\text{H}]^+$ = 254.155.

Following general procedure IV, 3-phenylpropionic acid (0.150 g, 1.0 mmol) was used as the acid species and *N*-methylbenzylamine (0.13 mL, 1.0 mmol) was used as the amine species. [*N*-(Benzyl)-*N*-methyl]-3-phenylpropionamide was recovered as a yellow oil (0.206 g, 81 %) after column chromatography (eluting with 98:2 dichloromethane:methanol). Analytical data was consistent with that above.



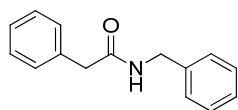
***N*-(Benzyl)-formamide (Table S2, Entry 2)¹³**

Following general procedure III, formic acid (0.06 mL, 1.0 mmol) was used as the acid species and benzylamine (0.11 mL, 1.0 mmol) was used as the amine species. *N*-(Benzyl)-formamide was recovered as a white solid (0.132 g, 89 %) after removal of toluene and recrystallisation (dichloromethane/hexane). The product was observed as 2 rotamers in its NMR spectra.

^1H NMR (300 MHz, CDCl_3): δ = 4.29 - 4.31 (2H (minor rotamer), d, J = 6.3 Hz, NHCH_2Ph), 4.36 - 4.38 (2H (major rotamer), d, J = 6.3 Hz, NHCH_2Ph), 6.11 (1H, br. s., NH), 7.18 - 7.25 (5H, m, Ph), 8.03 (1H (minor rotamer), s, $\text{HC}(\text{O})\text{NH}$), 8.14 (1H (major rotamer), s, $\text{HC}(\text{O})\text{NH}$); ^{13}C NMR (75 MHz, CDCl_3): δ = 42.2 (major rotamer), 45.7 (minor rotamer), 126.9, 127.7, 127.8, 128.8, 128.9, 137.5 (major rotamer), 137.6 (minor rotamer), 161.1 (major rotamer), 164.7 (minor rotamer); ESI-MS of $[\text{C}_8\text{H}_{10}\text{NOCl}]^+$; theoretical m/z of $[\text{M}+\text{H}]^+$ = 136.076, measured m/z of $[\text{M}+\text{H}]^+$ = 136.078; IR: ν (cm^{-1}) = 1649.88 cm^{-1} (C=O stretch).

Following general procedure IV, formic acid (0.11 mL, 2.0 mmol) was used as the acid species and benzylamine (0.22 mL, 2.0 mmol) was used as the amine species. *N*-(Benzyl)-formamide was recovered as a white solid (0.251 g, 93 %) after filtration

through a pad of silica, eluting with dichloromethane. Analytical data was consistent with that above.

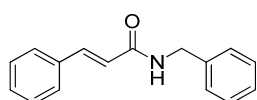


***N*-(Benzyl)-phenylacetamide (Table S2, Entry 3)⁵**

Following general procedure III, phenylacetic acid (0.272 g, 2.0 mmol) was used as the acid species and benzylamine (0.22 mL, 2.0 mmol) was used as the amine species. *N*-(Benzyl)-phenylacetamide was recovered as a white solid (0.410 g, 91 %) after removal of toluene and recrystallization (dichloromethane/hexane).

¹H NMR (300 MHz, CDCl₃): δ = 3.56 (2H, s, PhCH₂C(O)), 4.33 – 4.35 (2H, d, *J* = 5.7 Hz, NHCH₂Ph), 5.63 (1H, br. s., NH), 7.09 – 7.28 (10H, m, 2xPh); ¹³C NMR (75 MHz, CDCl₃): δ = 43.6, 43.9, 127.5, 128.7, 129.1, 129.5, 134.8, 138.1, 170.9; ESI-MS of [C₁₅H₁₆NO]⁺; theoretical *m/z* of [M+H]⁺ = 226.132, measured *m/z* of [M+H]⁺ = 226.133; IR: ν (cm⁻¹) = 1636.35 cm⁻¹ (C=O stretch).

Following general procedure IV, phenylacetic acid (0.272 g, 2.0 mmol) was used as the acid species and benzylamine (0.22 mL, 2.0 mmol) was used as the amine species. *N*-(Benzyl)-phenylacetamide was recovered as a white solid (0.396 g, 88 %) after filtration through a pad of silica, eluting with dichloromethane. Analytical data was consistent with that above.



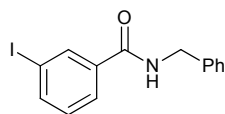
***N*-(Benzyl)-cinnamamide (Table S2, Entry 4)¹⁴**

Following general procedure III, cinnamic acid (0.296 g, 2.0 mmol) was used as the acid species and benzylamine (0.22 mL, 2.0 mmol) was used as the amine species. The reaction was heated at reflux in 0.5 mL *p*-xylene. *N*-(Benzyl)-cinnamamide was recovered as an off-white solid (0.216 g, 91 %) after removal of *p*-xylene and recrystallization (dichloromethane/hexane).

¹H NMR (250 MHz, CDCl₃): δ = 4.47 – 4.49 (2H, d, *J* = 5.75 Hz, NHCH₂Ph), 6.05 (1H, br. s., NH), 6.33 – 6.39 (1H, d, *J* = 15.75 Hz, PhCHCHC(O)), 7.25 – 7.42 (10H, m, 2xPh), 7.56 – 7.62 (1H, d, *J* = 15.75 Hz, PhCHCHC(O)); ¹³C NMR (75 MHz, CDCl₃): δ = 42.3, 120.5, 127.6, 127.8, 127.9, 128.8, 129.7, 134.8, 138.2, 141.4, 165.8;

ESI-MS of $[C_{16}H_{16}NO]^+$; theoretical m/z of $[M+H]^+ = 238.131$, measured m/z of $[M+H]^+ = 238.132$; IR: ν (cm^{-1}) = $1650.39\ cm^{-1}$ (C=O stretch).

Following general procedure IV, cinnamic acid (0.296 g, 2.0 mmol) was used as the acid species and benzylamine (0.22 mL, 2.0 mmol) was used as the amine species. An 1H NMR of the crude reaction mixture showed a 57 % conversion into *N*-(benzyl)-cinnamamide when $ZrCl_4$ was used as catalyst and 72 % conversion when $ZrCp_2Cl_2$ was used as catalyst. Analytical data was consistent with that above.

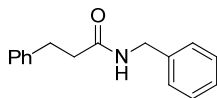


***N*-(Benzyl)-3-iodobenzamide (Table S2, Entry 5)**

Following general procedure III, 3-iodobenzoic acid (0.248 g, 1.0 mmol) was used as the acid species and benzylamine (0.11 mL, 1.0 mmol) was used as the amine species. The reaction mixture was heated at reflux in 0.5 mL *p*-xylene. An 1H NMR of the crude reaction mixture showed a 53% conversion into *N*-(benzyl)-benzamide.

1H NMR (250 MHz, DMSO-*d*₆): δ = 4.47 - 4.50 (2H, d, $J = 5.75$ Hz, $PhCH_2NH$), 7.20 - 7.41 (6H, m, 2Ph), 8.24 - 8.27 (2H, d, $J = 7.25$ Hz, (*m*-I)Ph), 8.52 (1H, s, (*m*-I)Ph), 9.19 (br. s, 1H, NH), ESI-MS of $[C_{14}H_{13}NOI]^+$; theoretical m/z of $[M+H]^+ = 238.131$, measured m/z of $[M+H]^+ = 238.132$.

Following general procedure IV, 3-iodobenzoic acid (0.496 g, 2.0 mmol) was used as the acid species and benzylamine (0.22 mL, 2.0 mmol) was used as the amine species. 10 mol% $ZrCl_4$ (0.046g) was used. An 1H NMR of the crude reaction mixture showed 27 % conversion into *N*-(benzyl)-3-iodobenzamide when $ZrCl_4$ was used as catalyst. Analytical data was consistent with that shown above.



***N*-(Benzyl)-3-phenylpropionamide (Scale up example)¹¹**

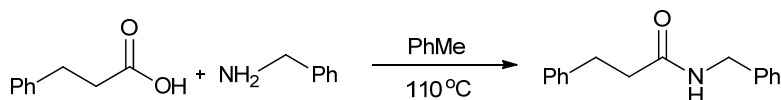
Following general procedure V, *N*-(benzyl)-3-phenylpropionamide was recovered as a pale yellow solid (0.439 g, 92 %) after removal of toluene *in vacuo*.

1H NMR (250 MHz, $CDCl_3$): δ = 2.52 - 2.58 (t, 2H, $J = 7.8$ Hz, CH_2CH_2Ph), 3.00 - 3.06 (t, 2H, $J = 7.8$ Hz, CH_2CH_2Ph), 4.42 - 4.44 (d, 2H, $J = 5.8$ Hz, $PhCH_2NH$), 5.68

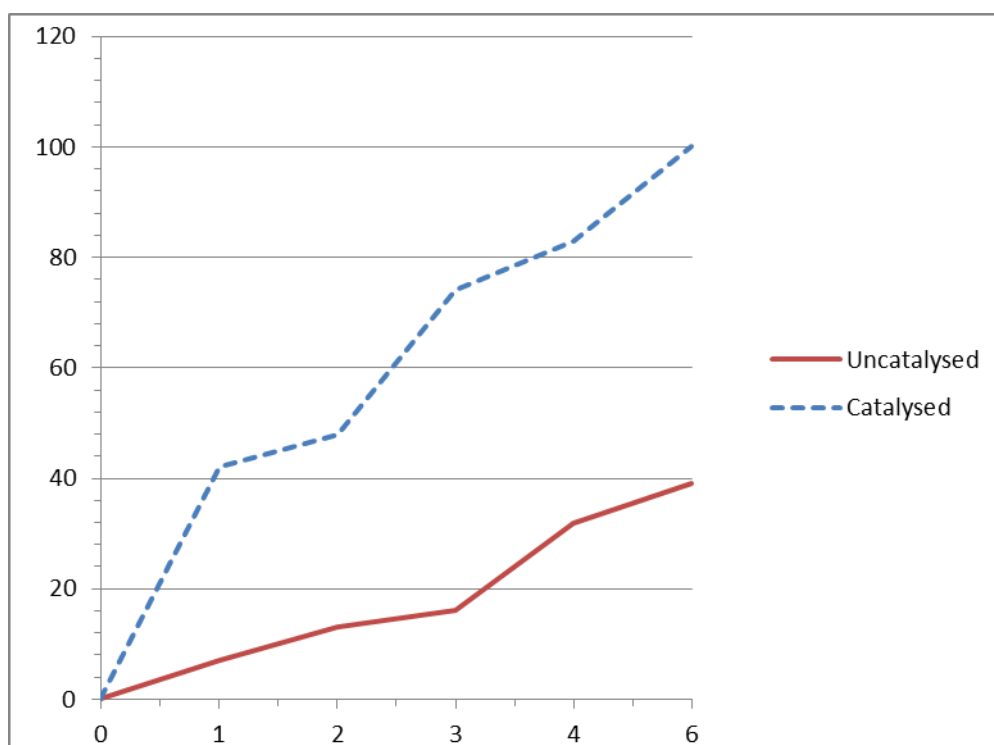
(br. s, 1H, NH), 7.16 - 7.35 (m, 10H, aromatic); ^{13}C NMR (75 MHz, CDCl_3): δ = 31.74, 38.54, 43.61, 126.28, 127.48, 127.77, 128.42, 128.58, 128.68, 138.17, 140.79, 171.89; ESI-MS of $[\text{C}_{16}\text{H}_{17}\text{NO}]^+$; theoretical m/z of $[\text{M}+\text{H}]^+ = 240.139$, measured m/z of $[\text{M}+\text{H}]^+ = 240.139$; IR: ν (cm^{-1}) = 1637.28 (C=O stretch).

Rate Study

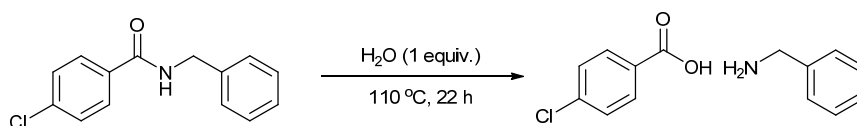
Results were obtained following general procedure VI.



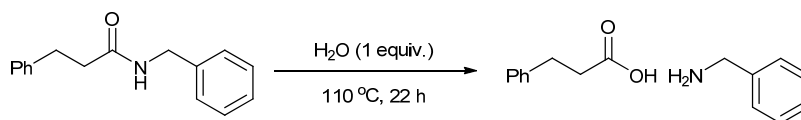
Entry	Time (h)	Conversion (%)	
		Uncatalysed	Catalysed
1	1	7	42
2	2	13	48
3	3	16	74
4	4	32	83
5	6	39	100



Reversibility study:



Following general procedure VII, *N*-benzyl-4-chlorobenzamide (0.035 g, 0.15 mmol) was used as the secondary amide species. With no catalyst, no reaction was observed. With ZrCl_4 (0.0012 g, 5 mol%), 5% hydrolysis into 4-chlorobenzoic acid and benzylamine was observed.

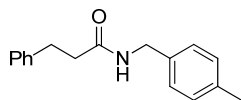


Following general procedure VII, *N*-benzyl-3-phenylpropionamide (0.024 g, 0.15 mmol) was used as the secondary amide species. No reaction was observed with or without the catalyst.

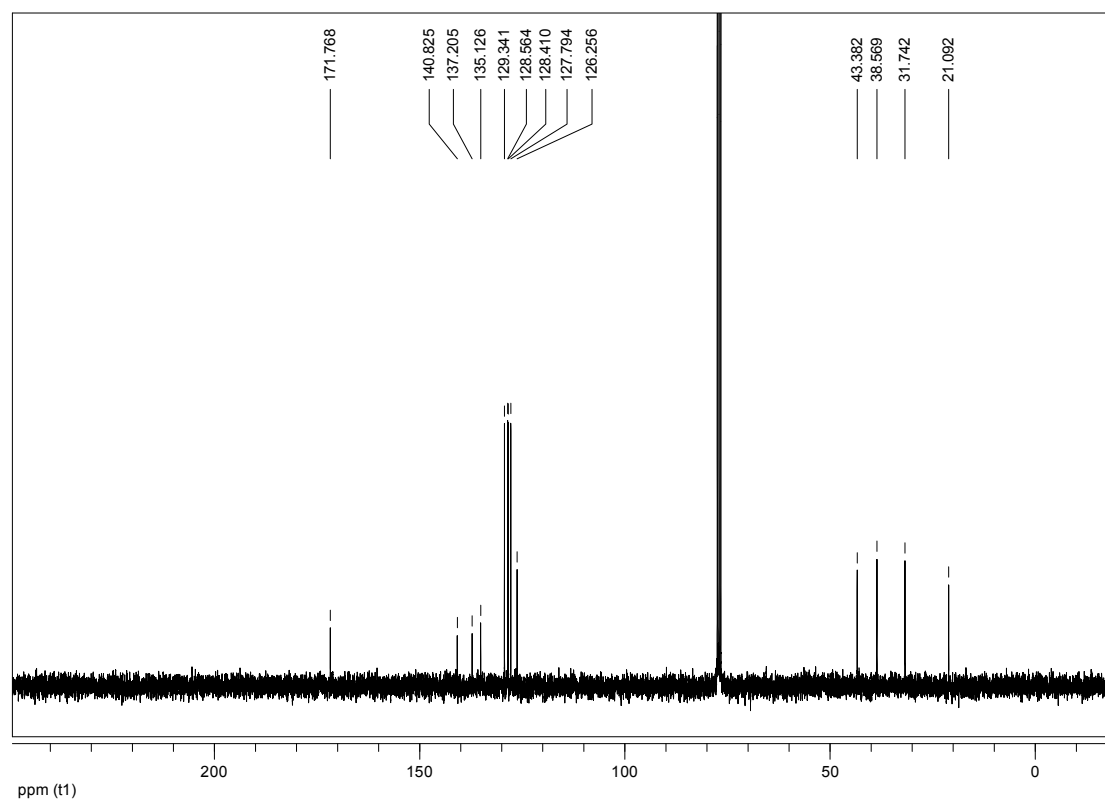
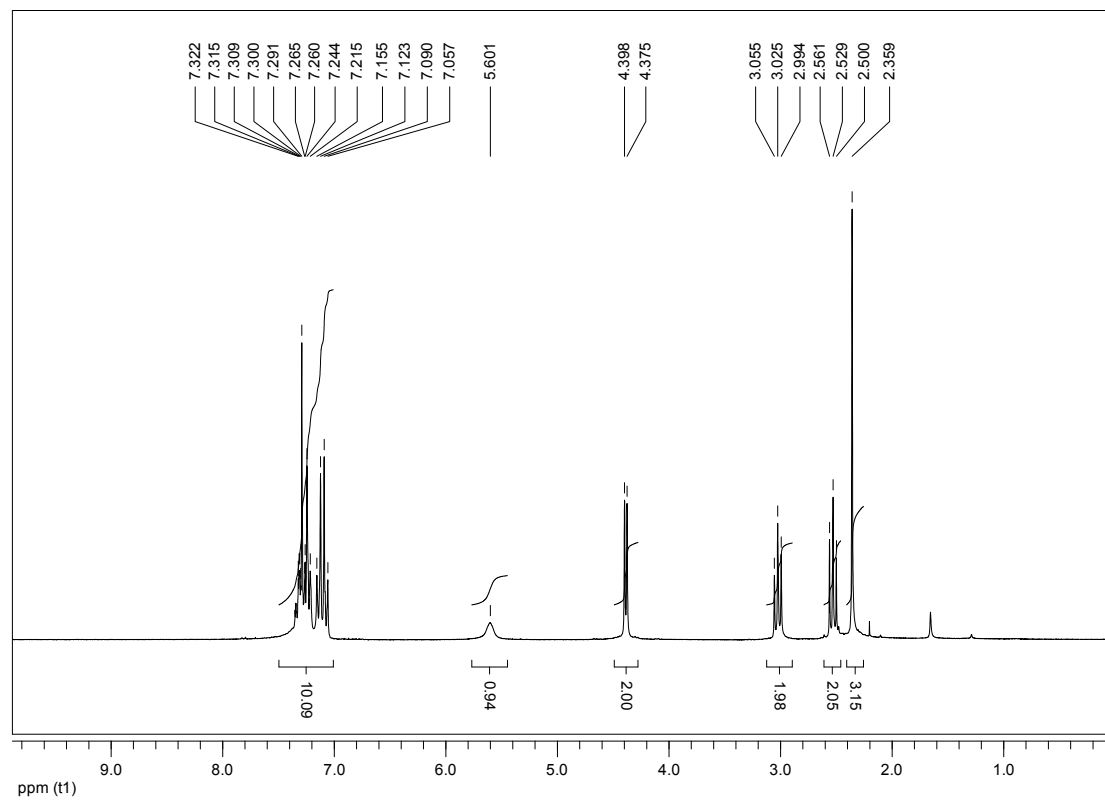
References

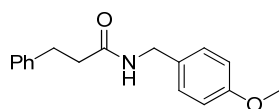
- 1) A. J. A. Watson, A. C. Maxwell and J. M. J. Williams, *Org. Lett.*, 2009, **11**, 2667.
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- 13) Y. Wan, M. Alterman, M. Larhed, A. Hallberg, *J. Org. Chem.*, 2002, **67**, 6232.
- 14) L. J. Goossen, D. M. Ohlmann, P. P. Lange, *Synthesis*, 2009, **1**, 160.

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

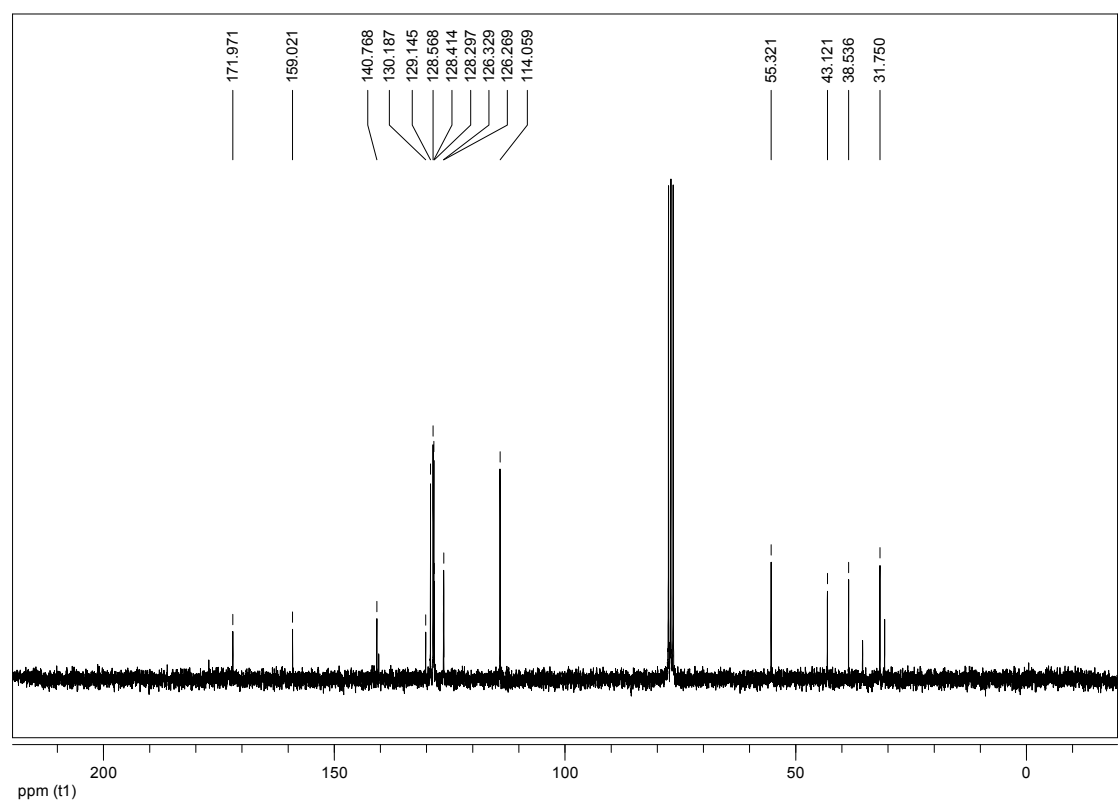
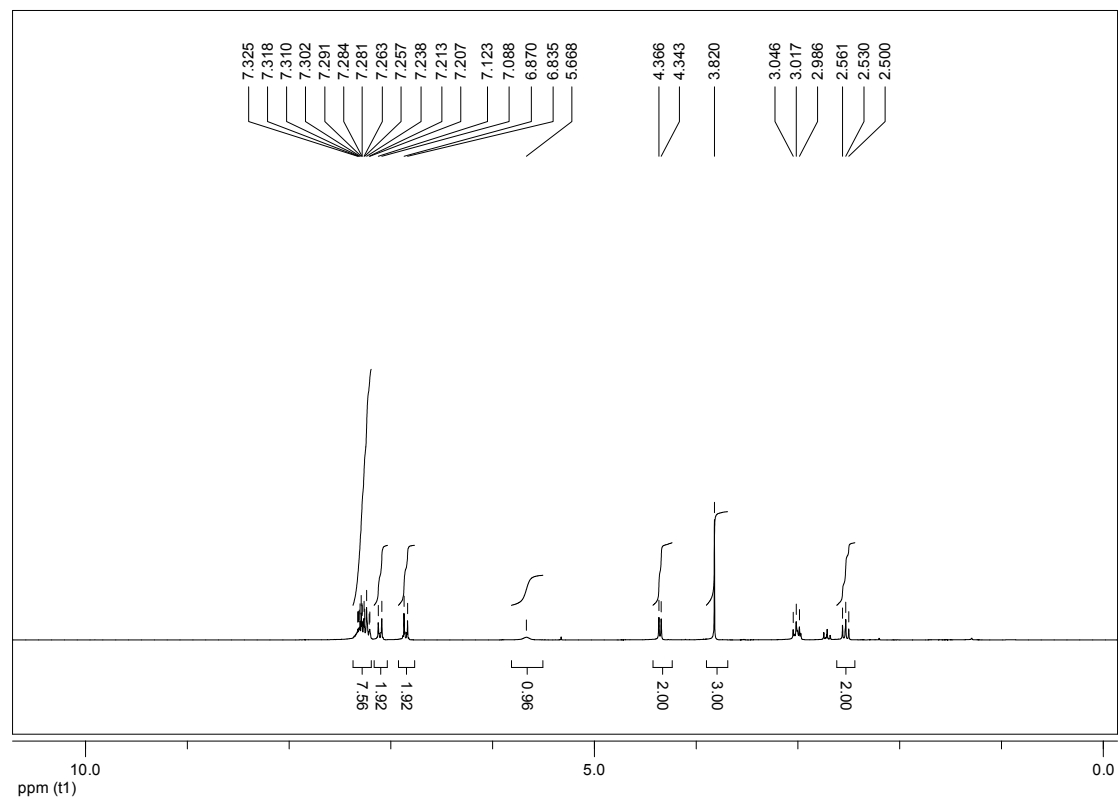


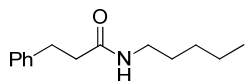
***N*-(4-Methylbenzyl)-3-phenylpropionamide (Table 2, Entry 1)**



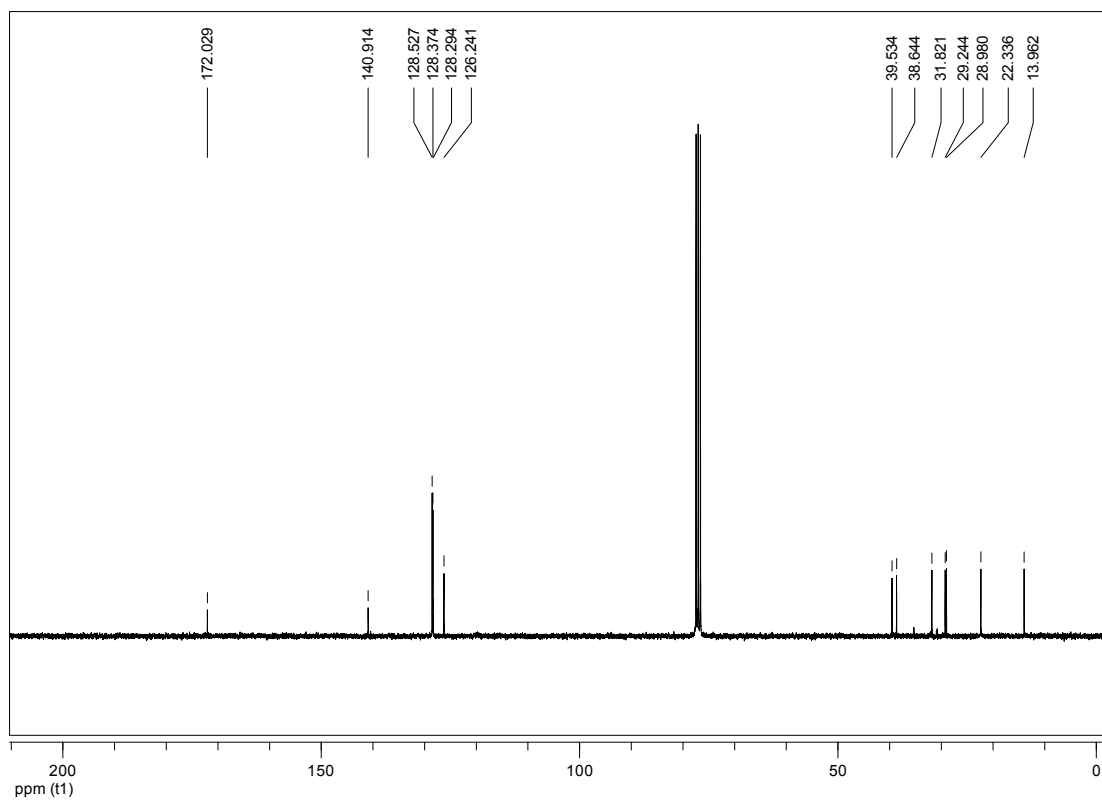
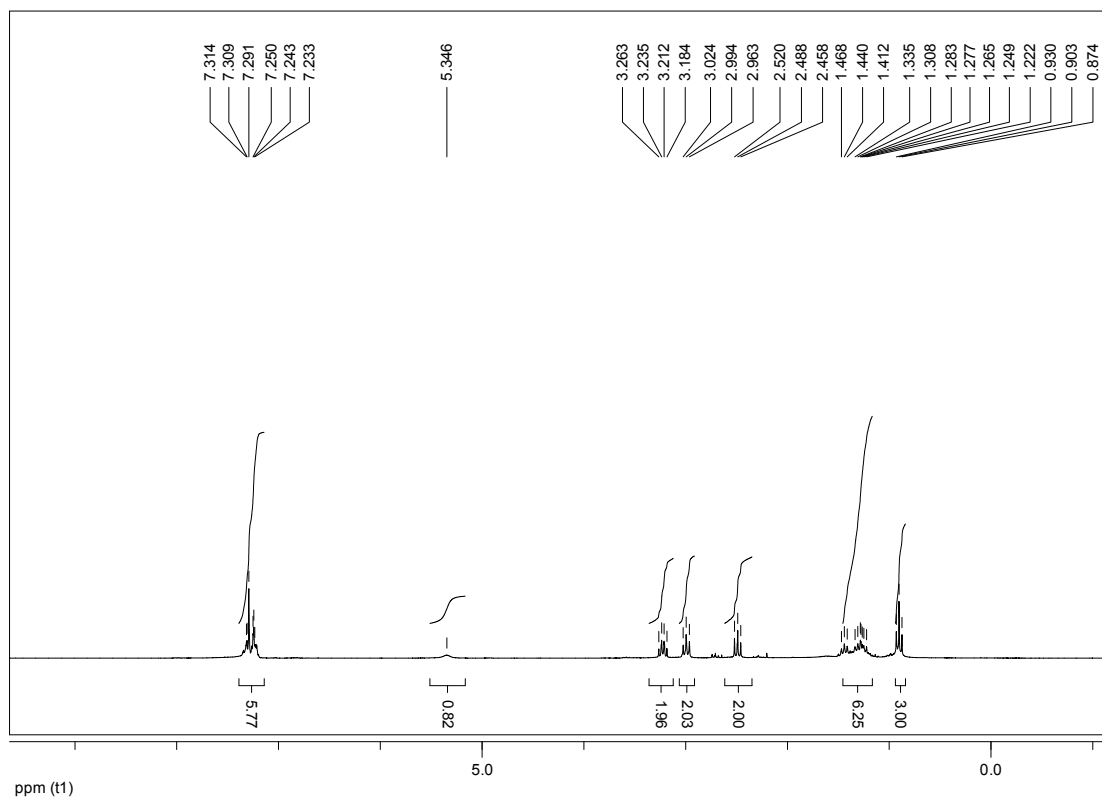


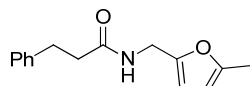
***N*-(4-Methoxybenzyl)-3-phenylpropionamide (Table 2, Entry 2)**



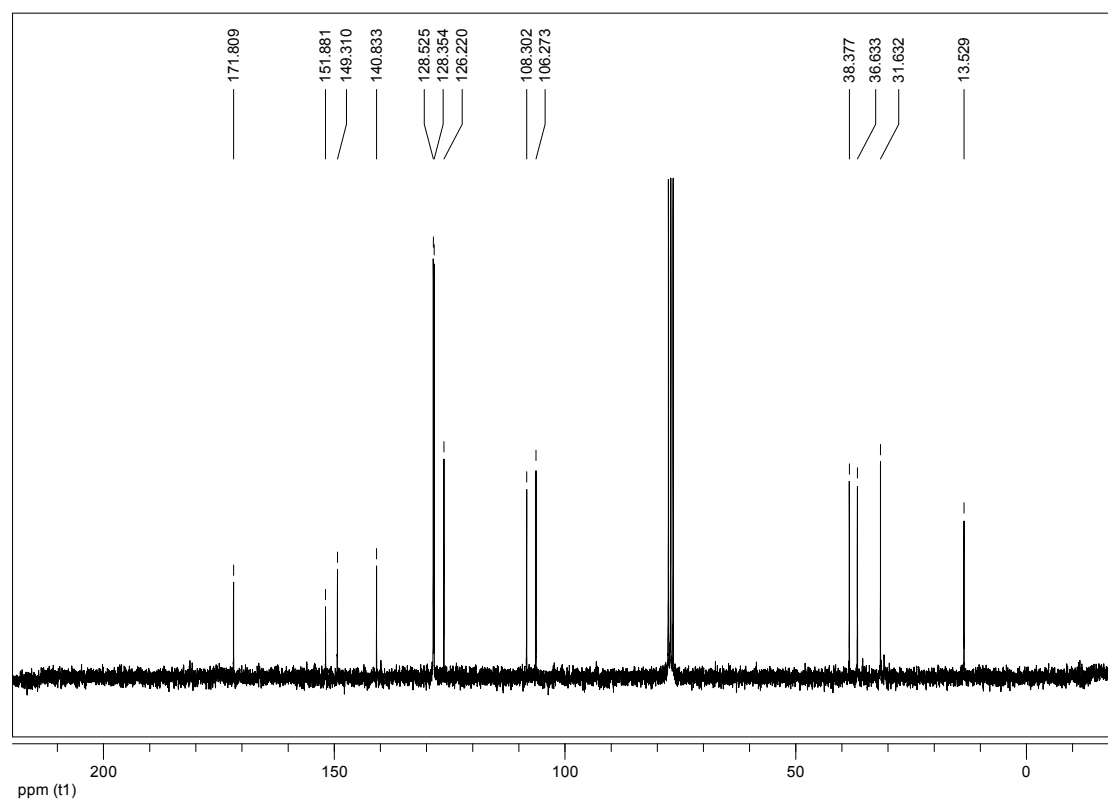
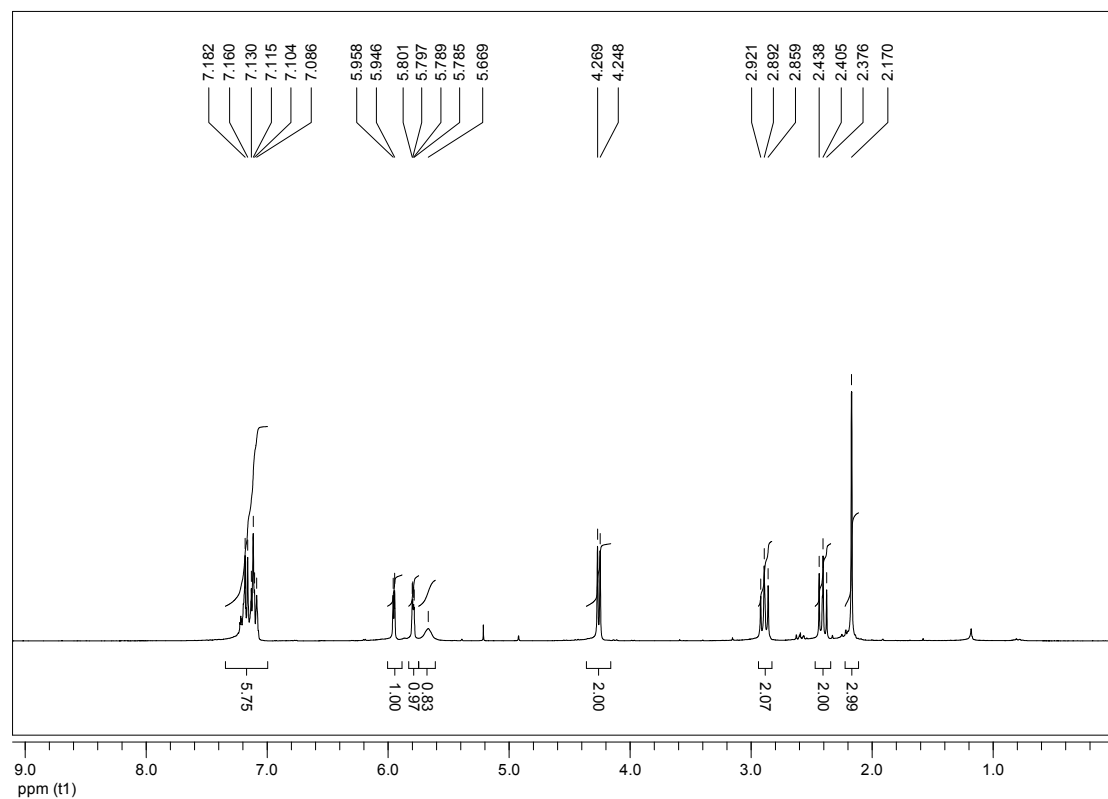


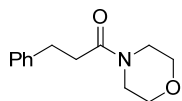
***N*-(Pentyl)-3-phenylpropionamide (Table 1, Entry 3)**



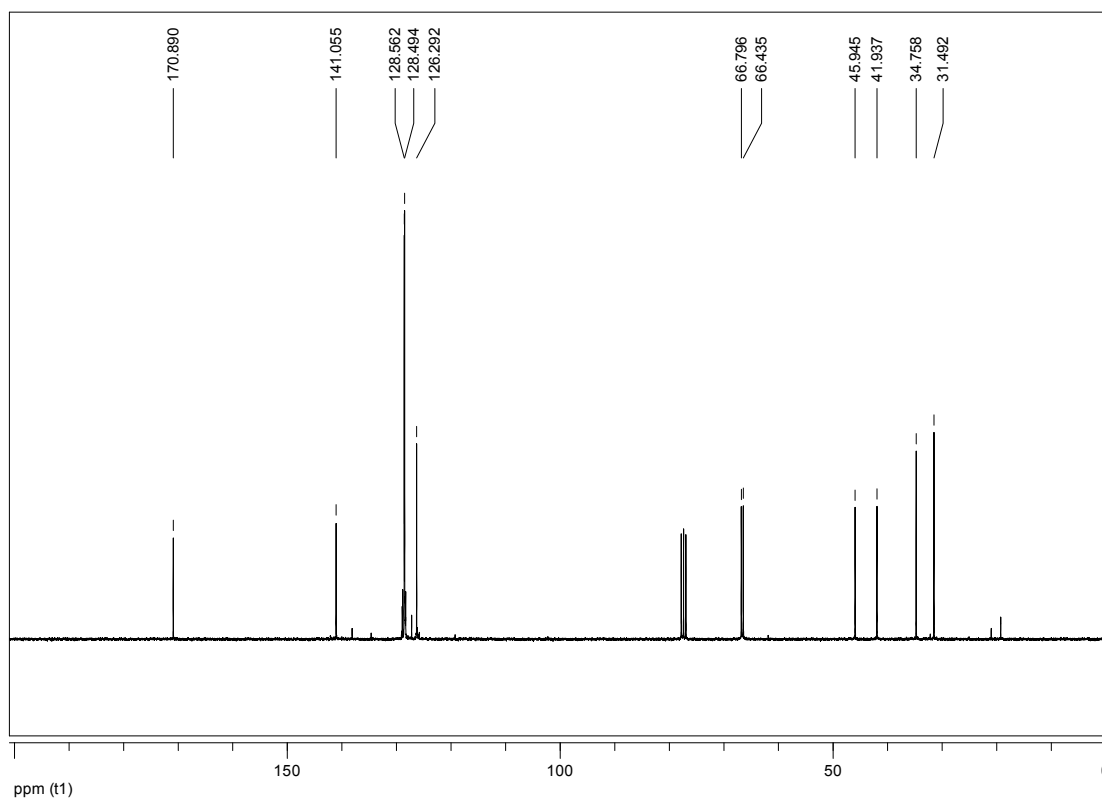
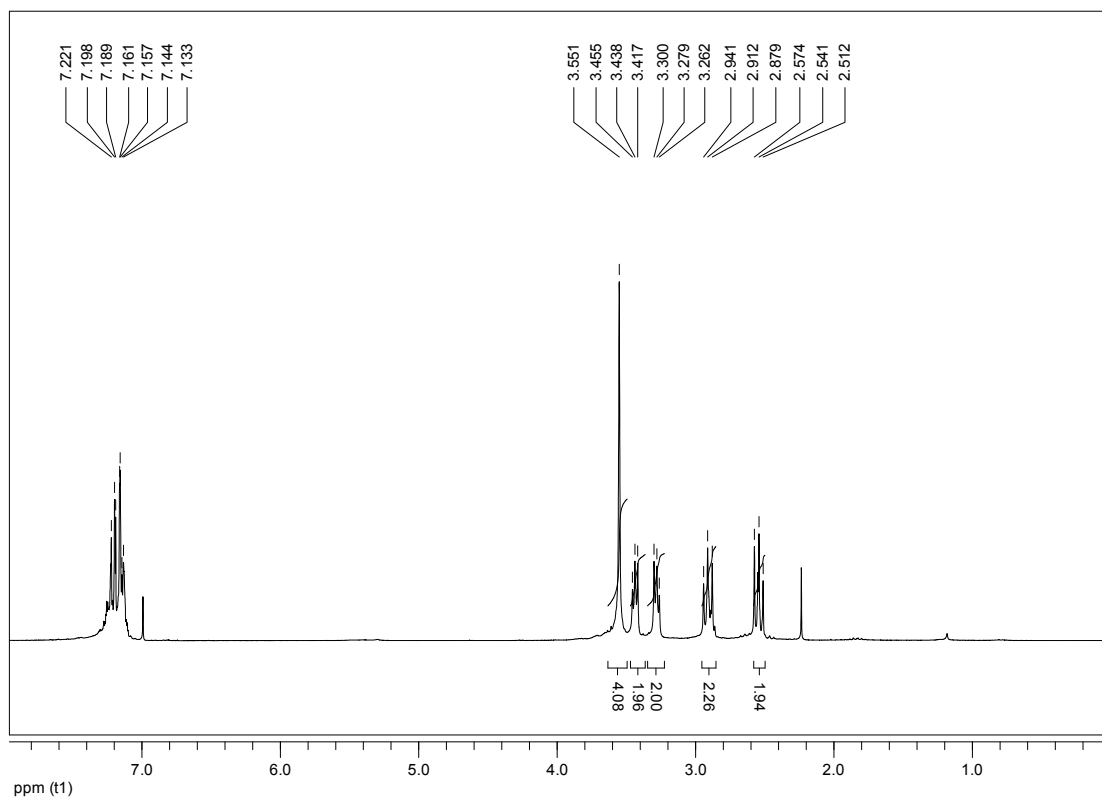


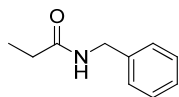
***N*-(5-Methylfurfuryl)-3-phenylpropionamide (Table 2, Entry 4)**



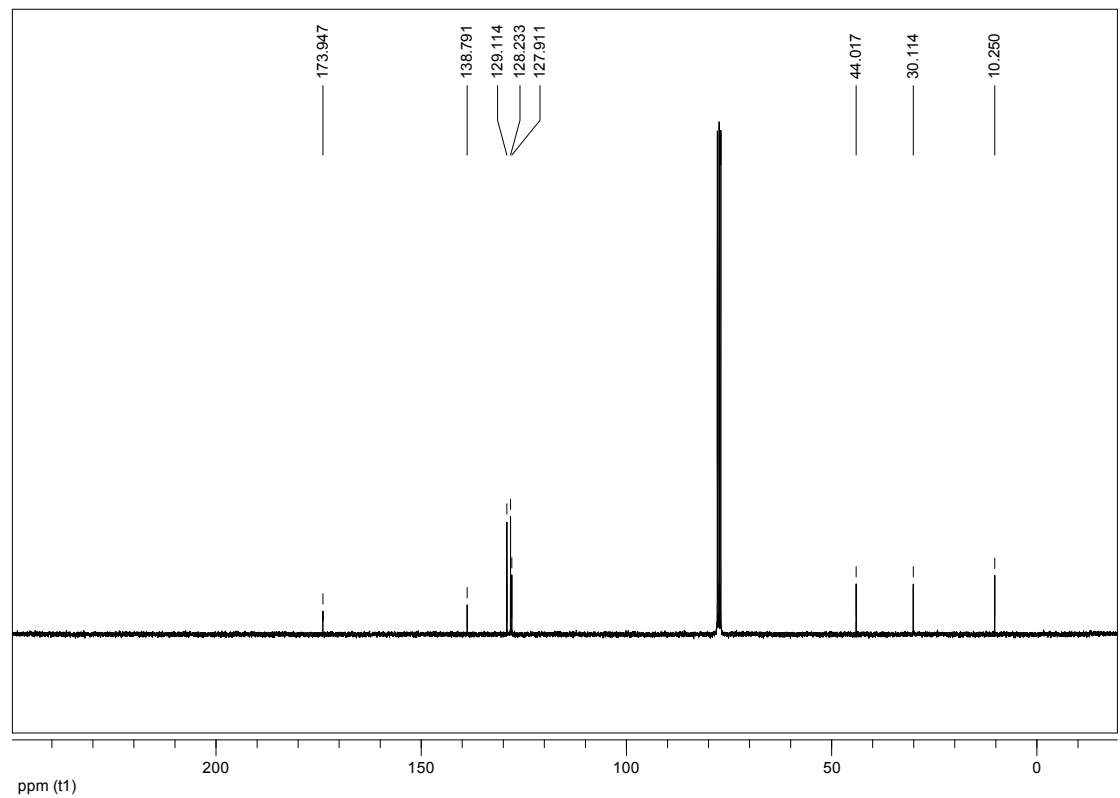
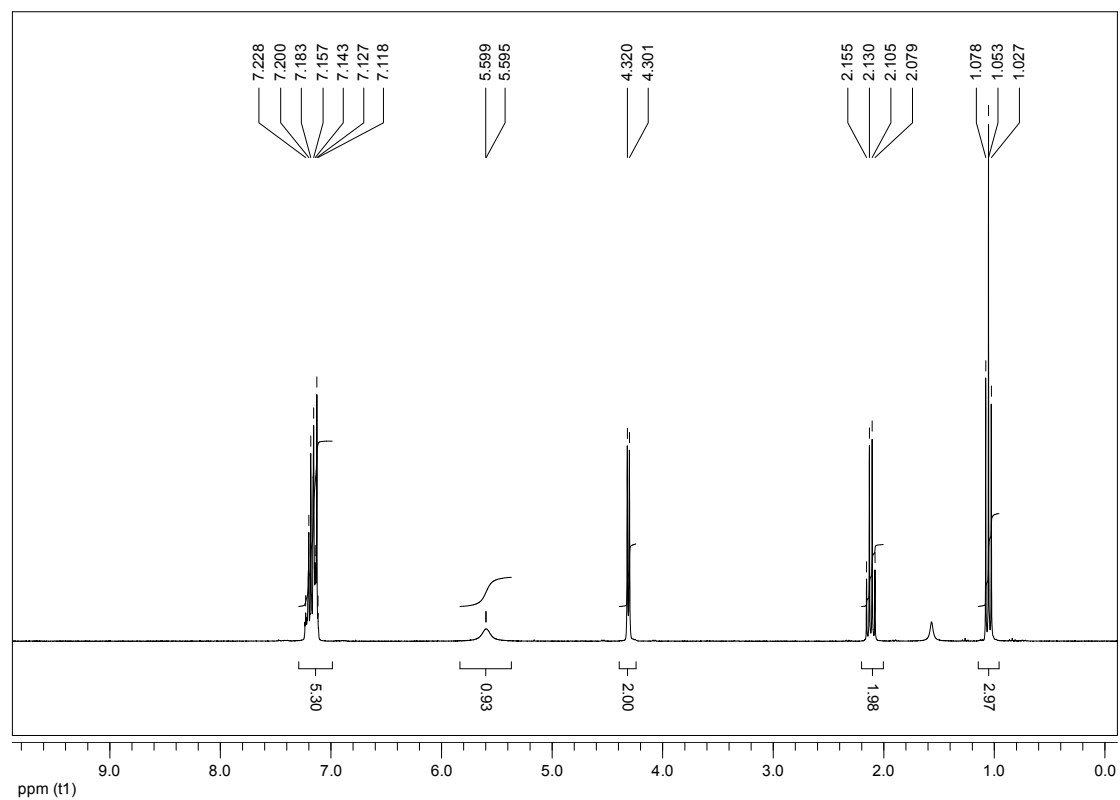


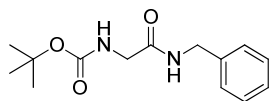
***N*-(Morpholino)-3-phenylpropionamide (Table 2, Entry 6)**



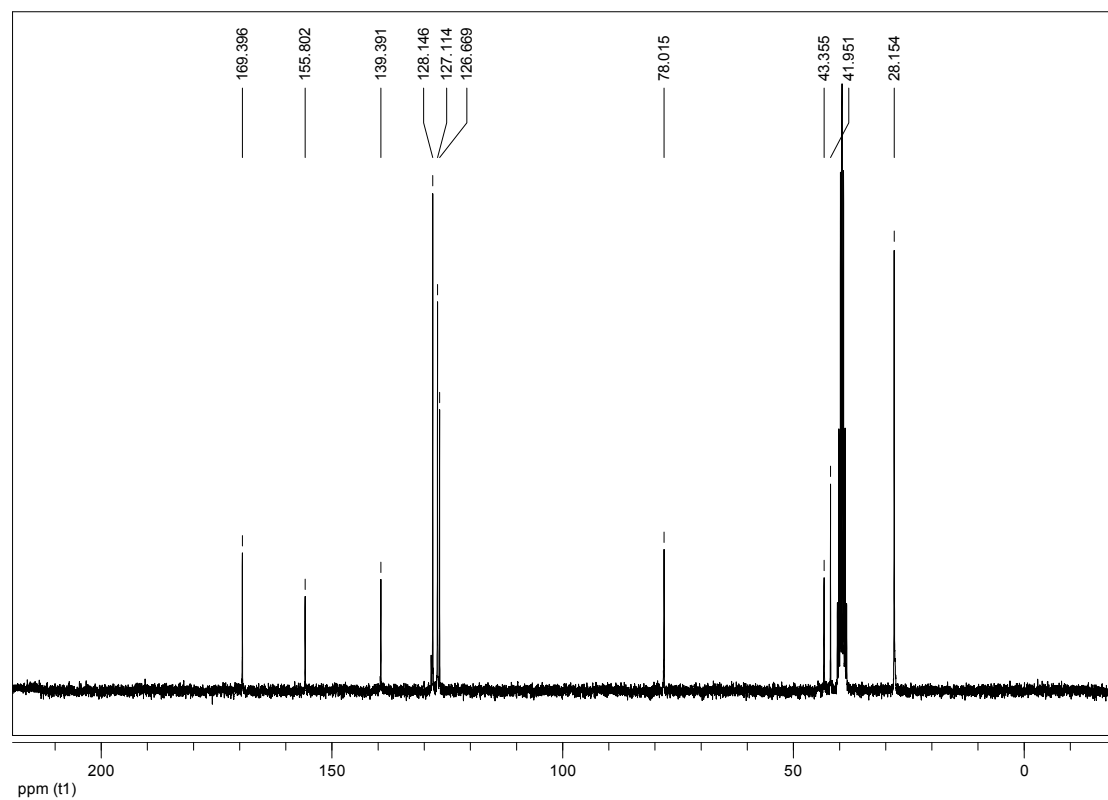
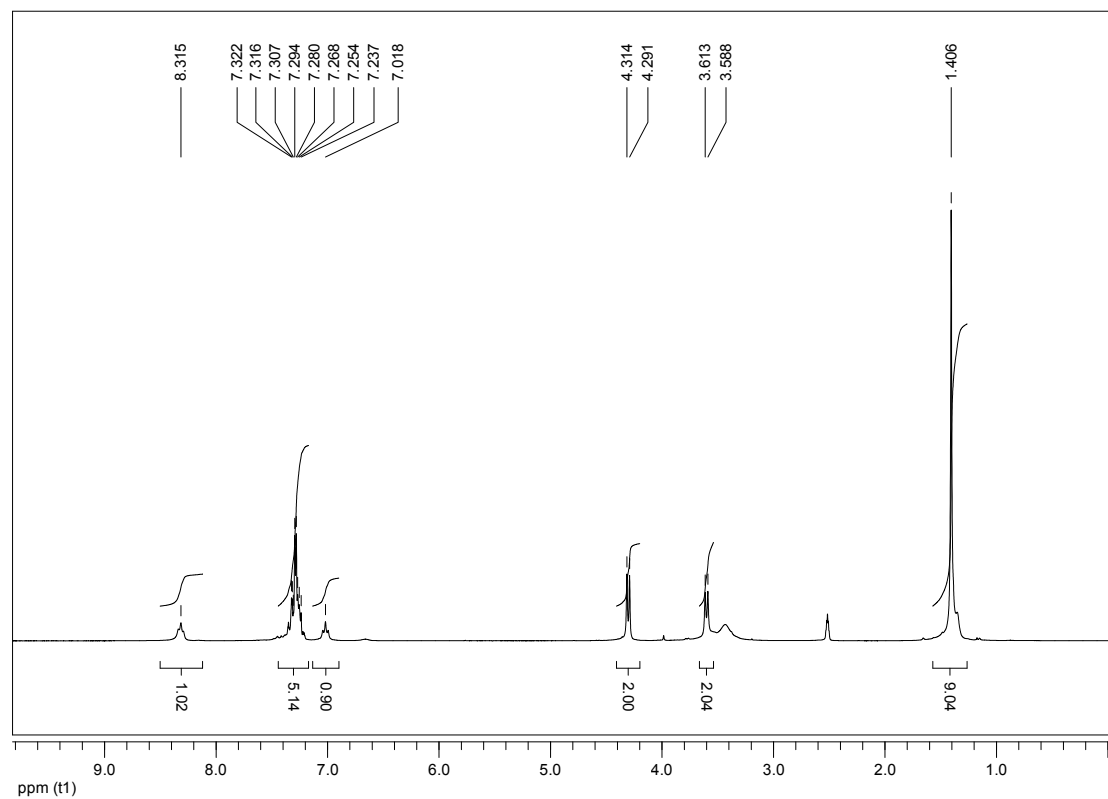


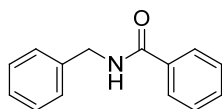
***N*-(Benzyl)-propionamide (Table 2, Entry 7)**



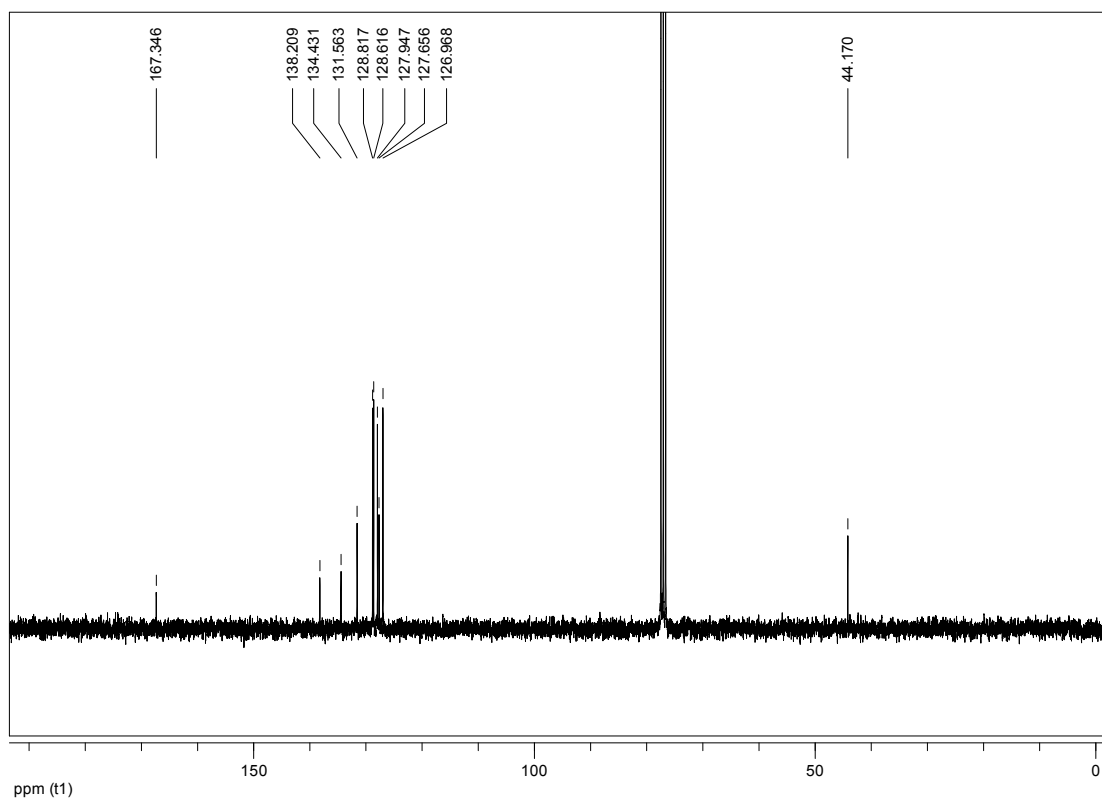
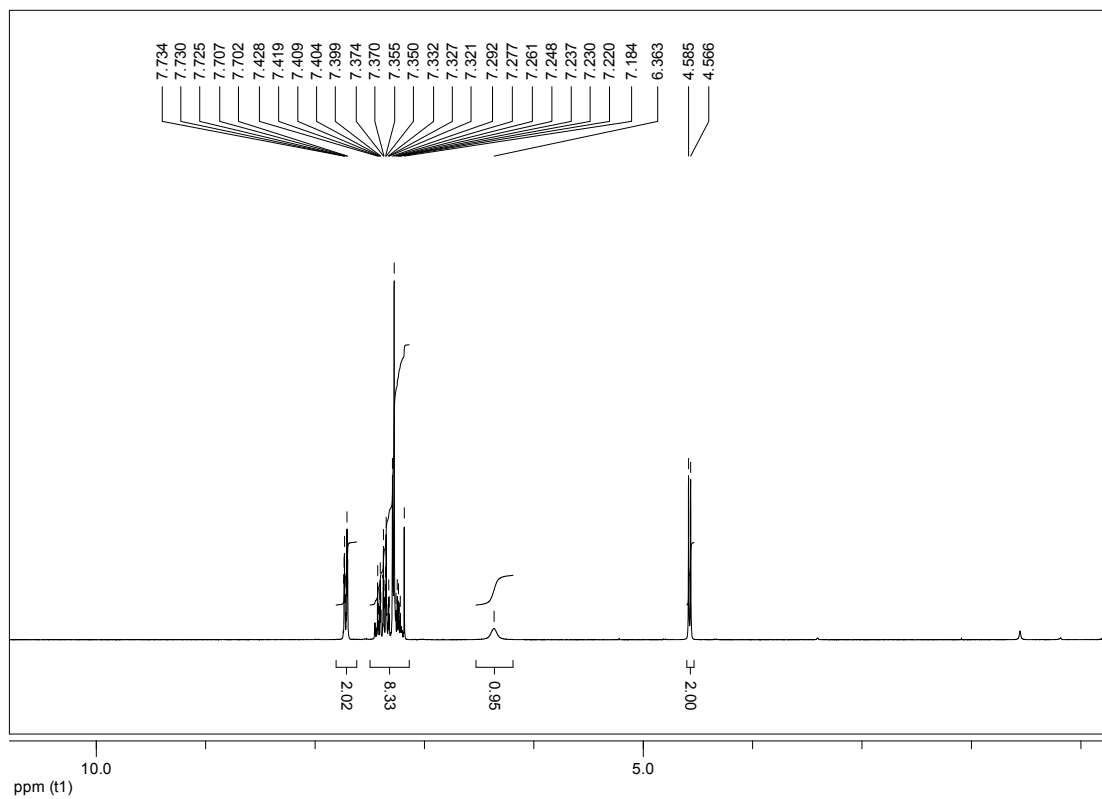


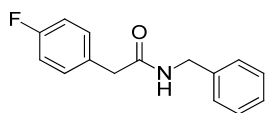
[N-(Benzyl)N'-Boc]-glycinamide (Table 2, Entry 8)



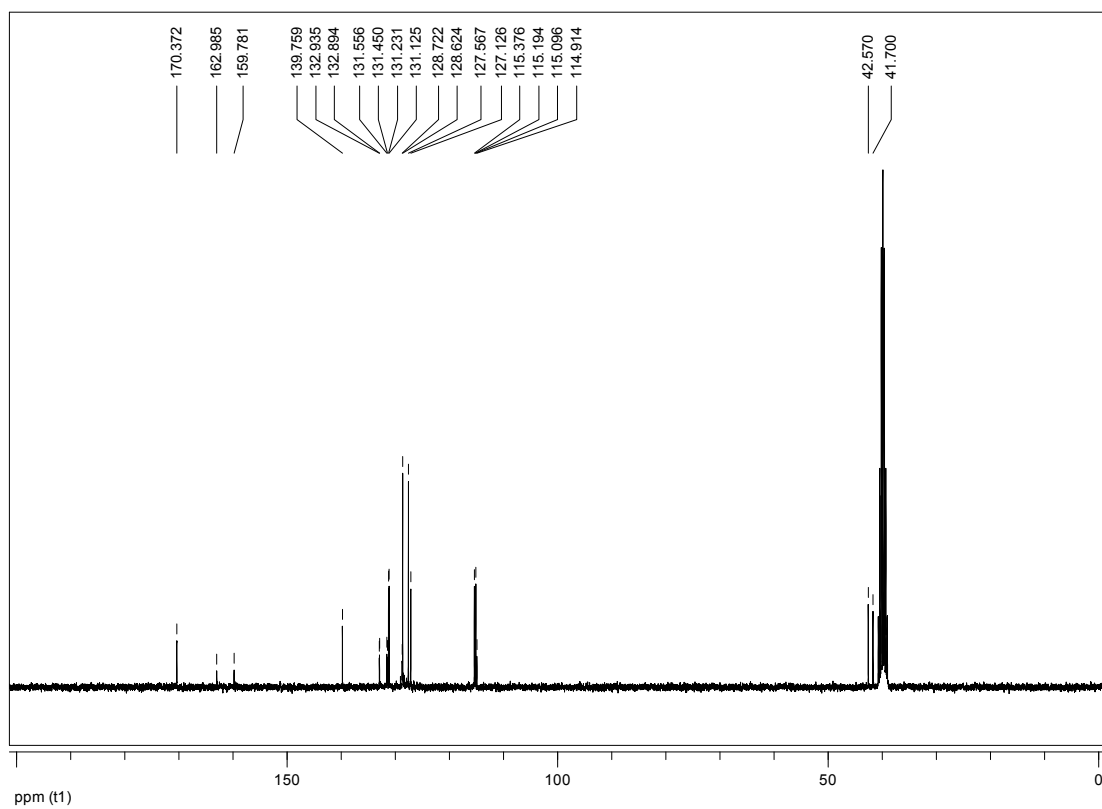
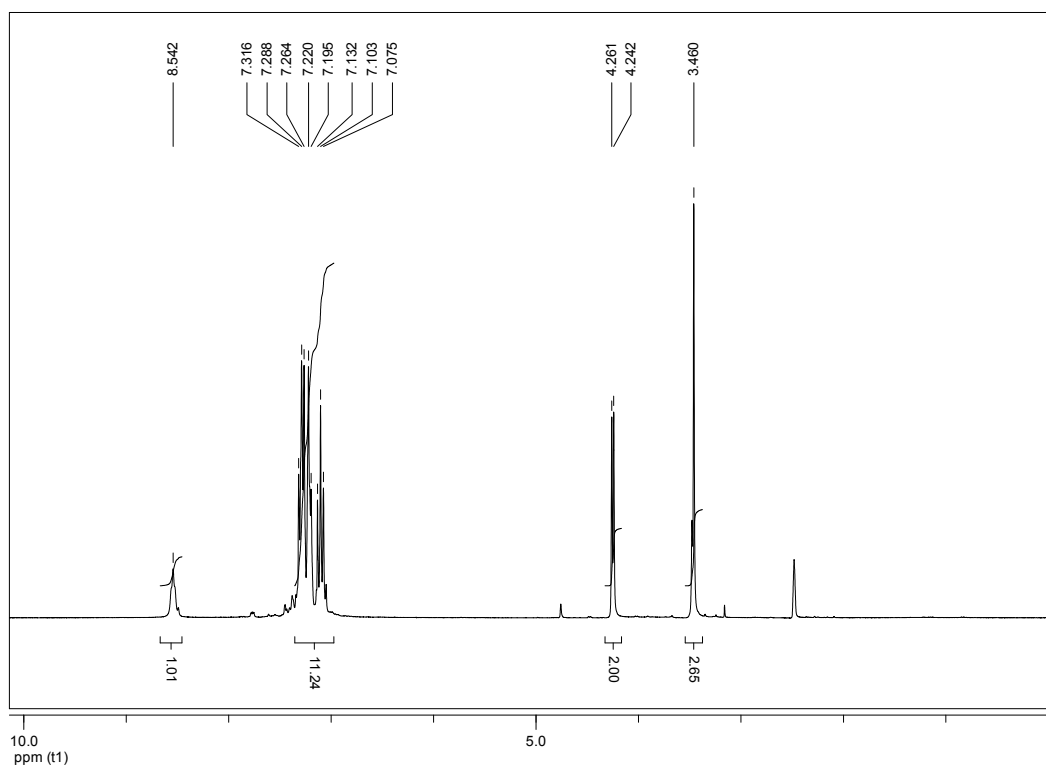


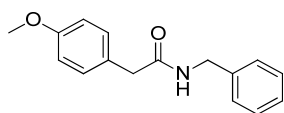
***N*-Benzylbenzamide (Table 2, Entry 9)**



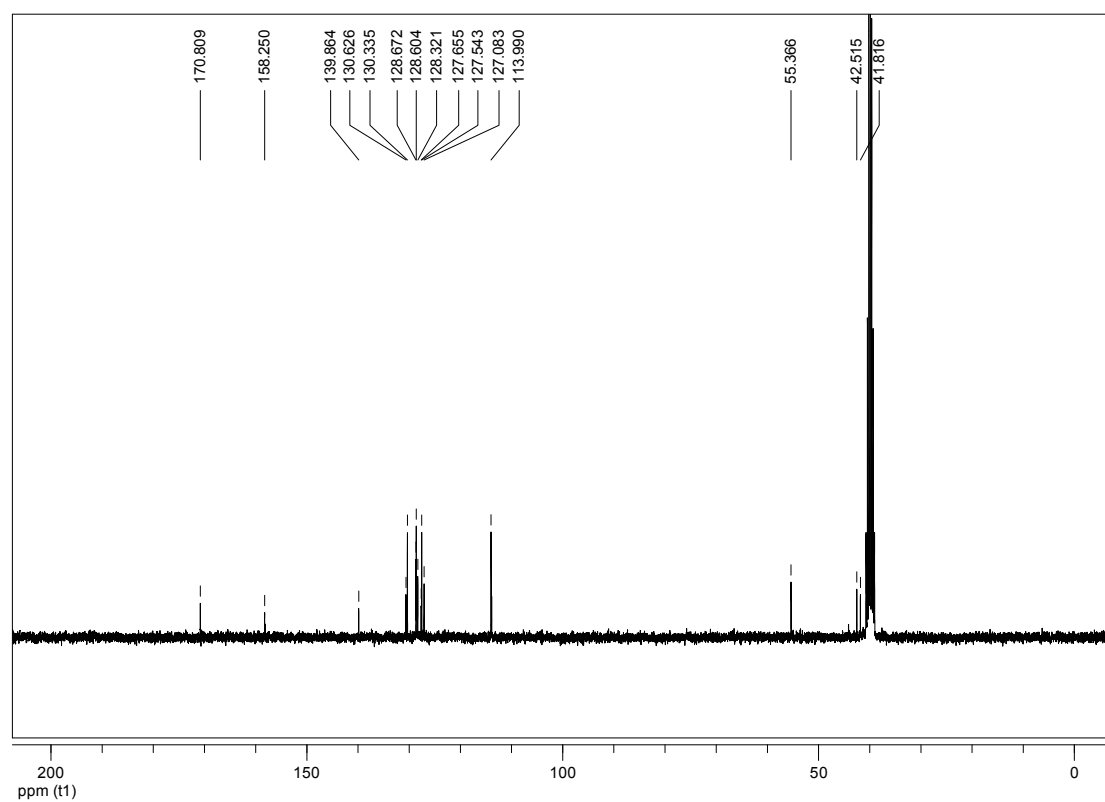
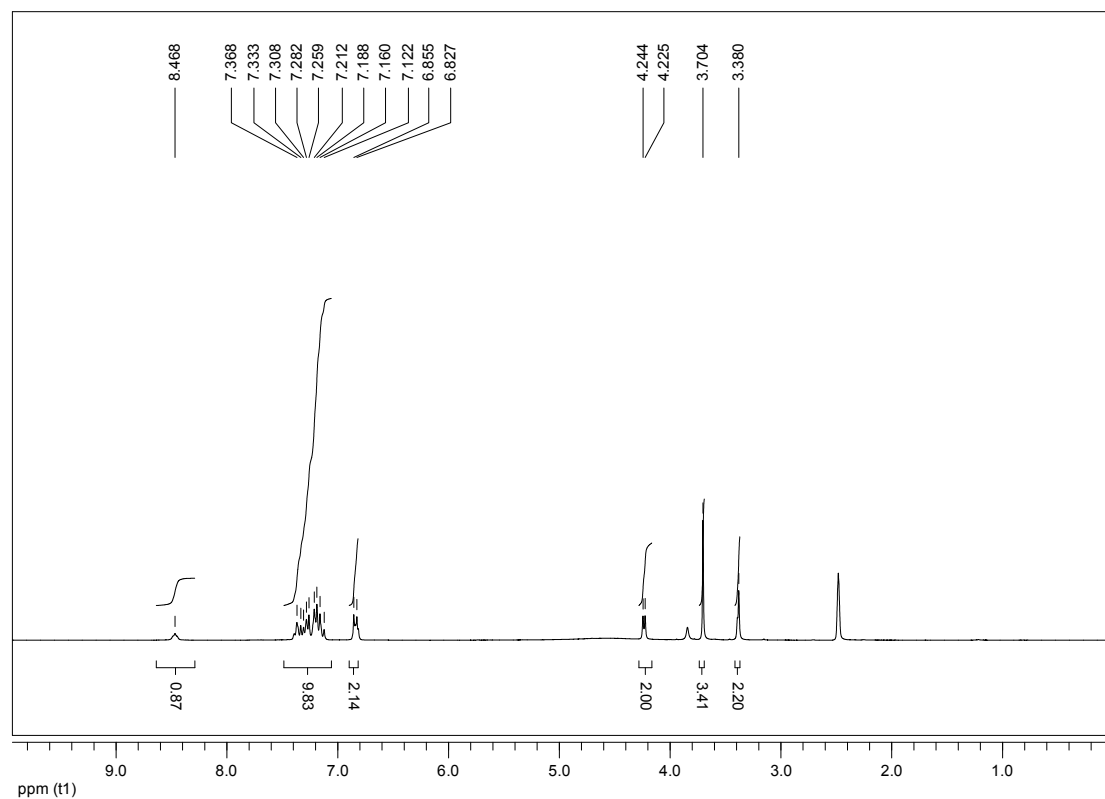


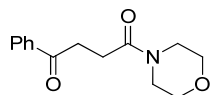
***N*-(Benzyl)-4-fluorophenylacetamide (Table 2, Entry 10)**



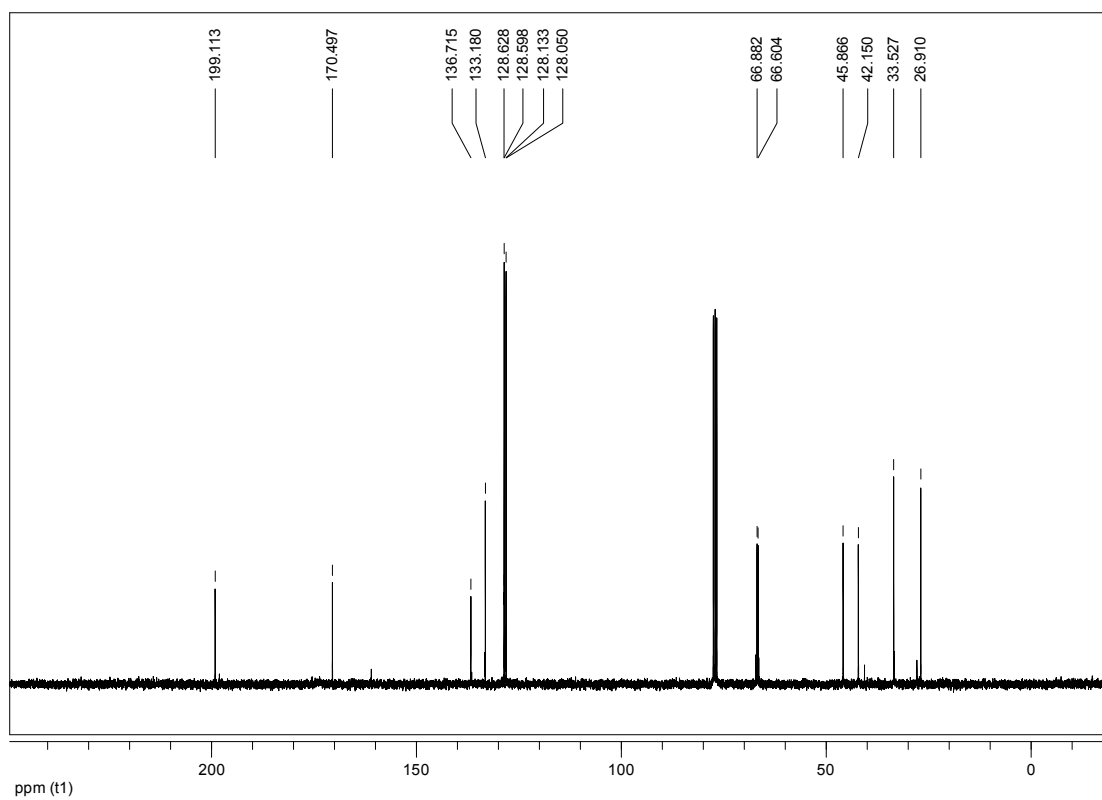
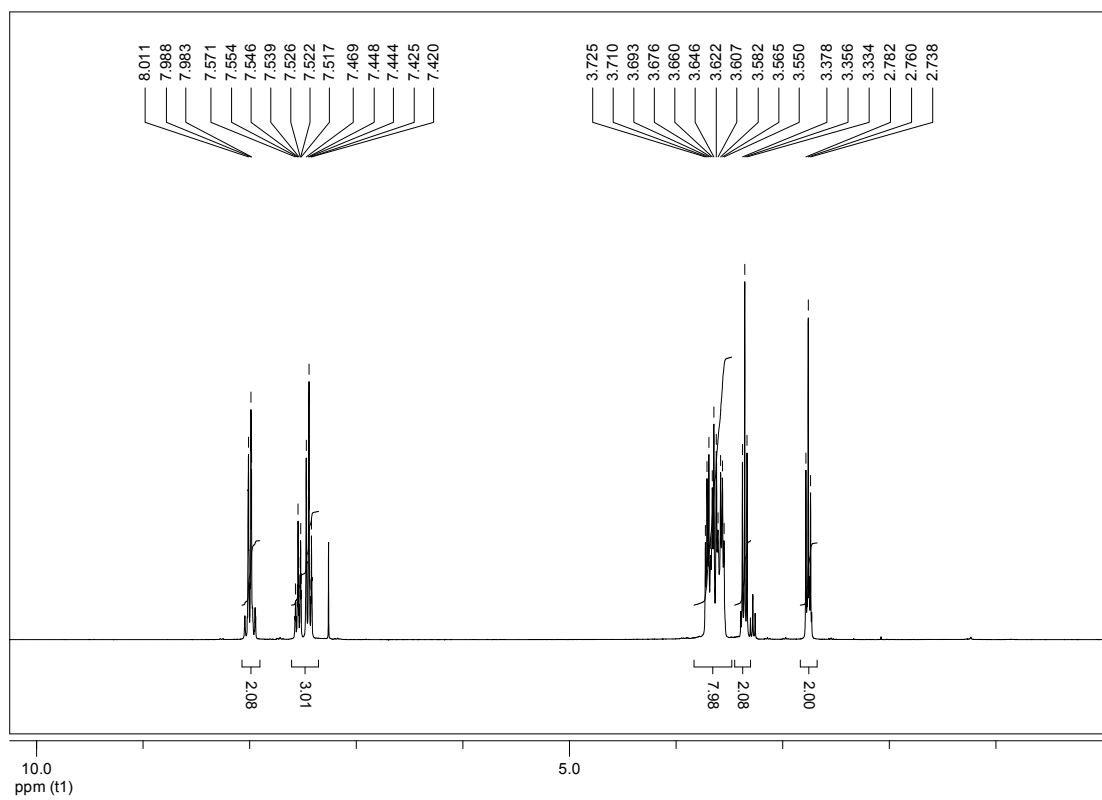


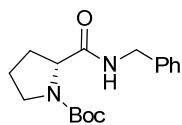
***N*-(Benzyl)-4-methoxyphenylacetamide (Table 2, Entry 11)**



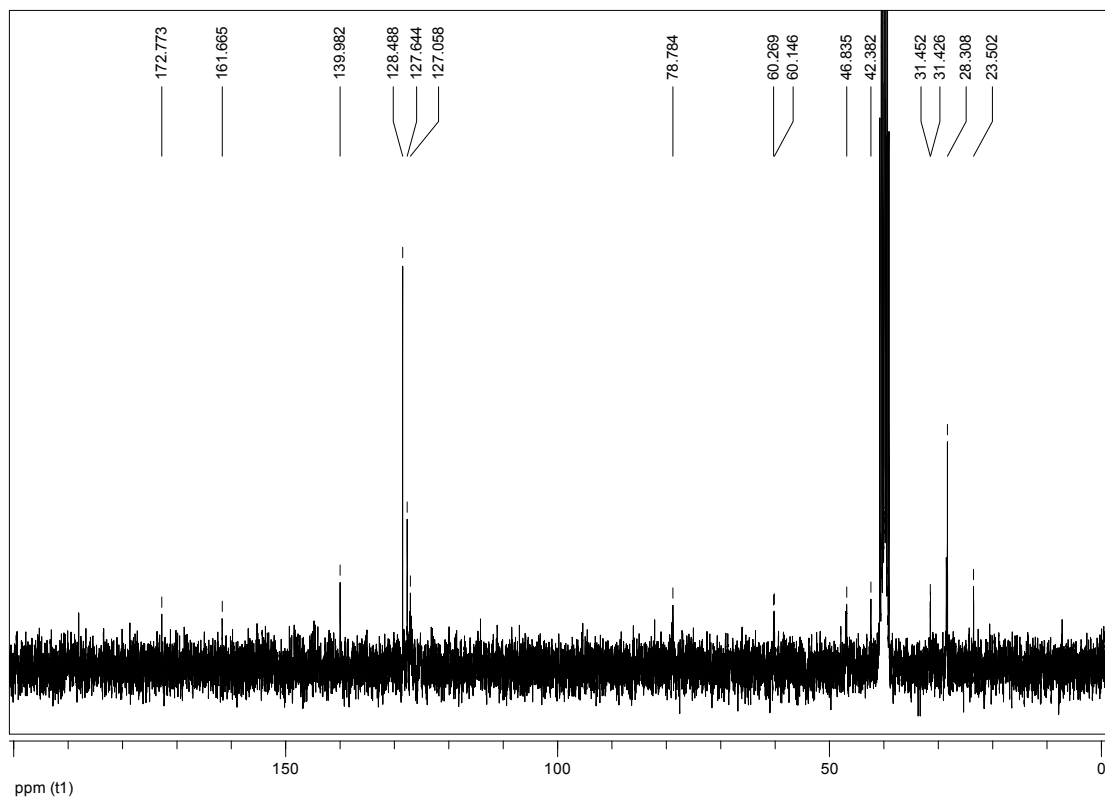
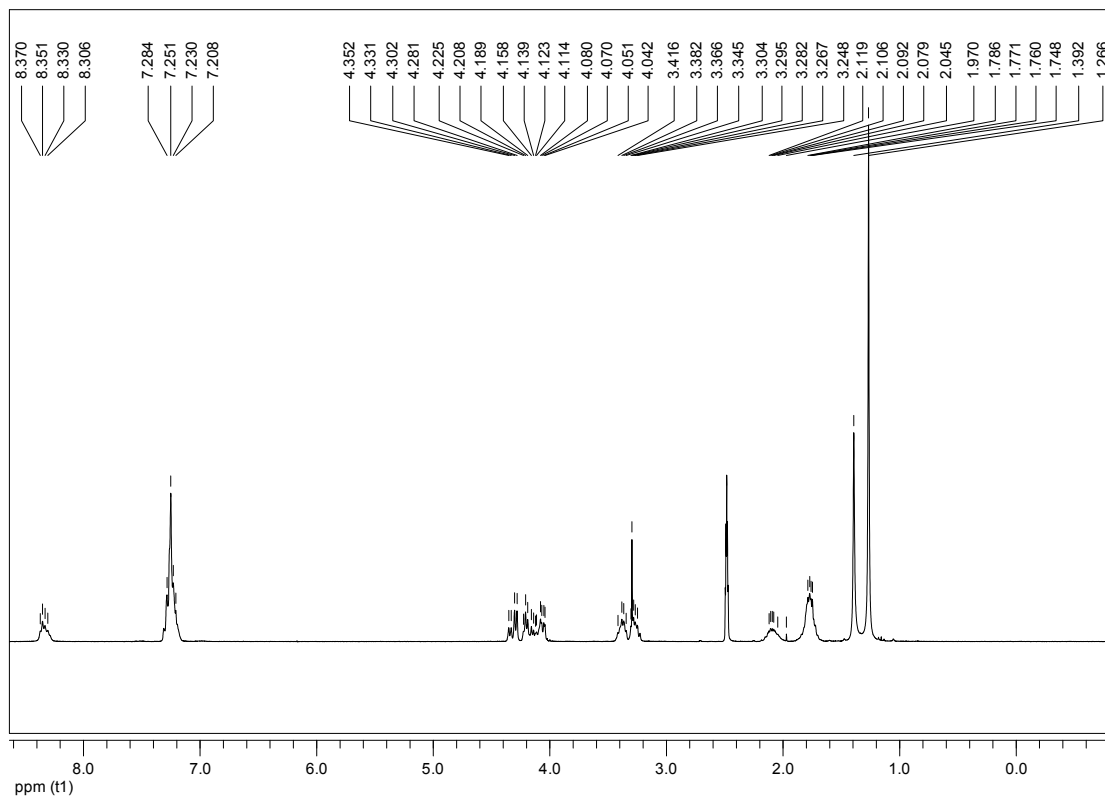


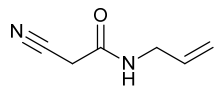
3-Benzoyl-*N*-morpholinopropionamide (Table 2, Entry 12)



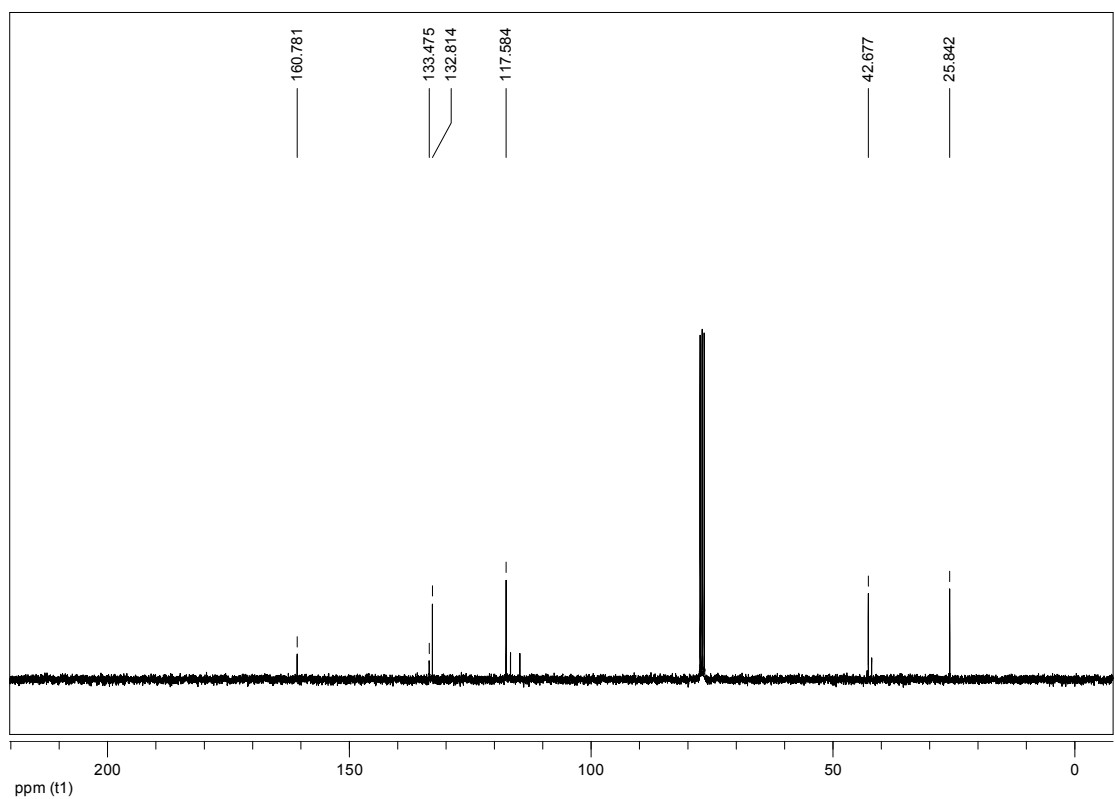
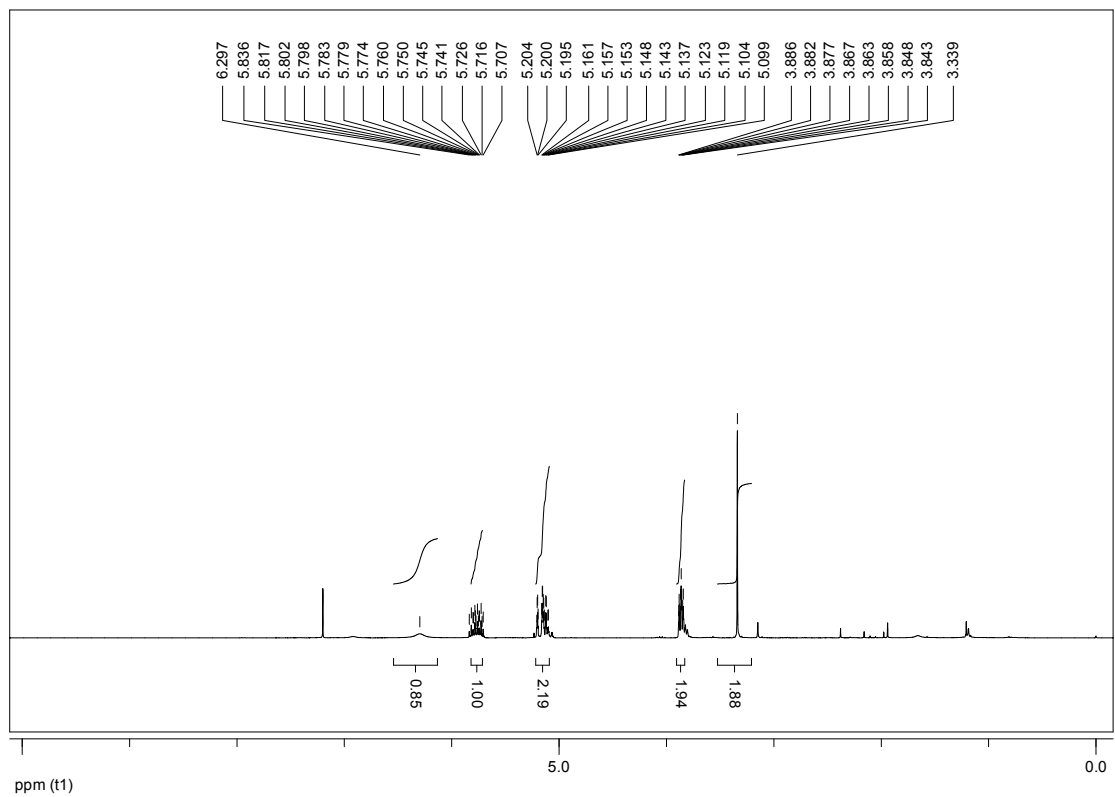


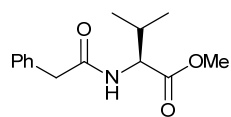
(Table 2, Entry 13)



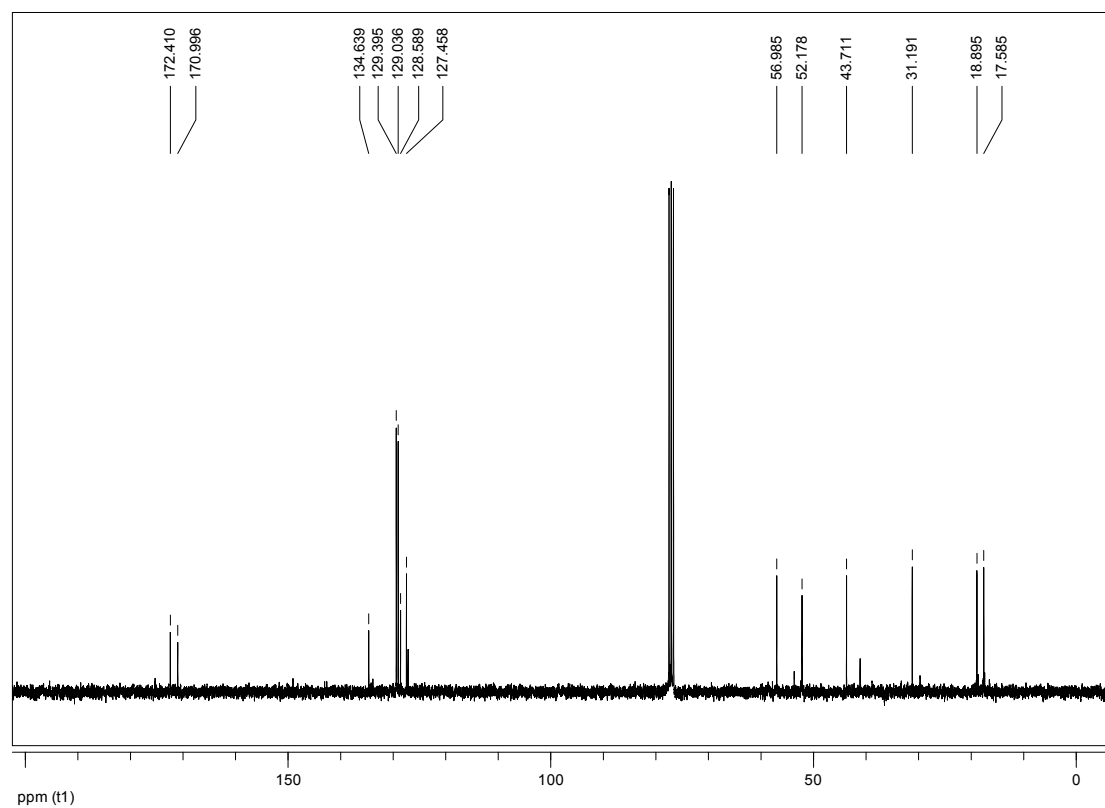
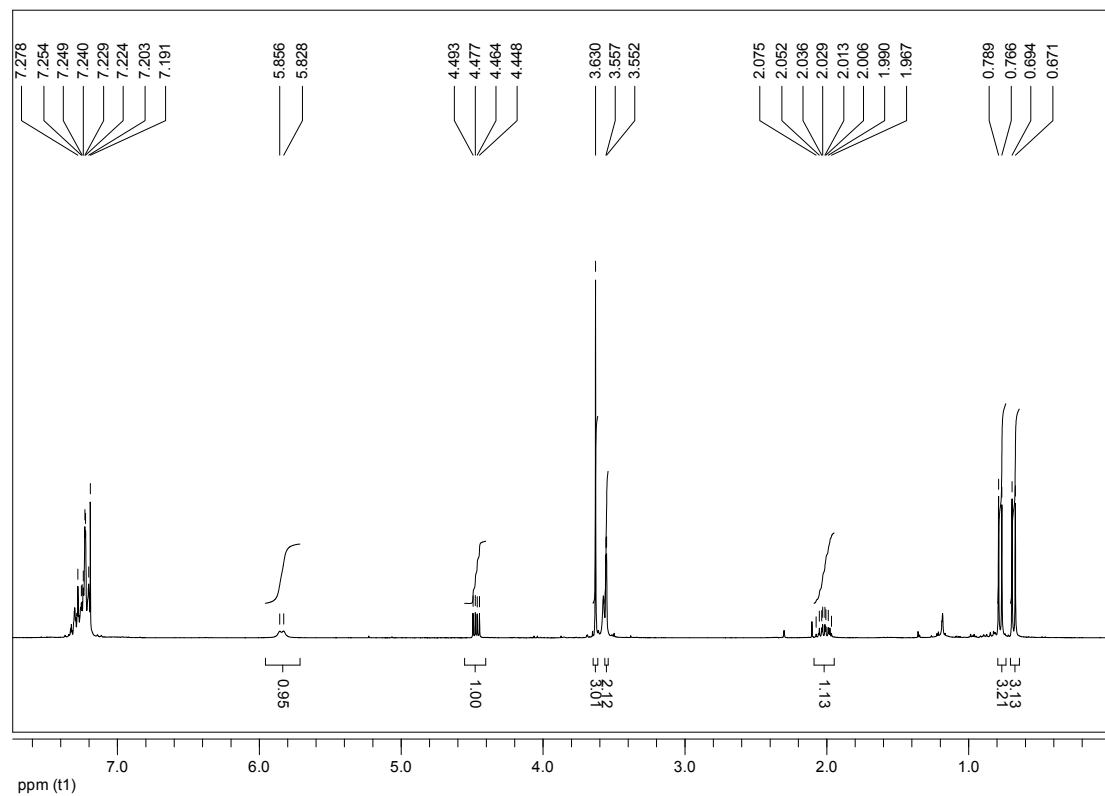


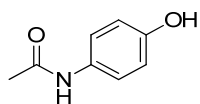
***N*-(Allyl)-cyanoacetamide (Table 2, Entry 14)⁸**



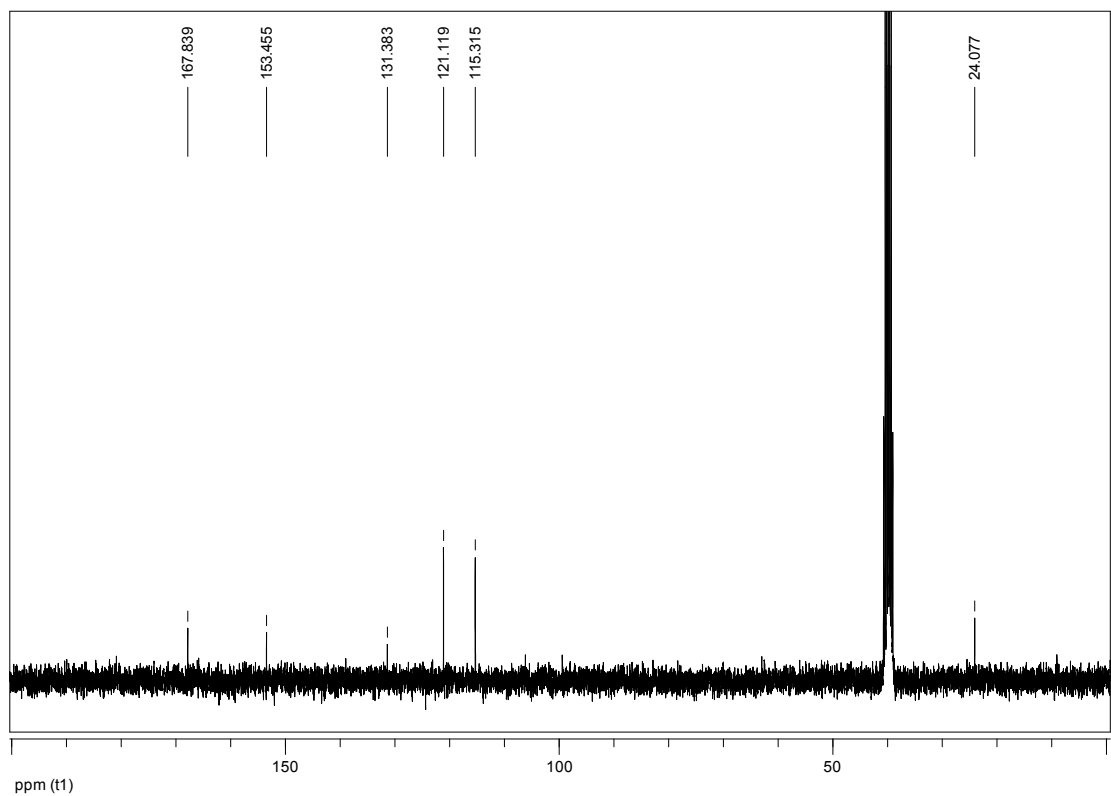
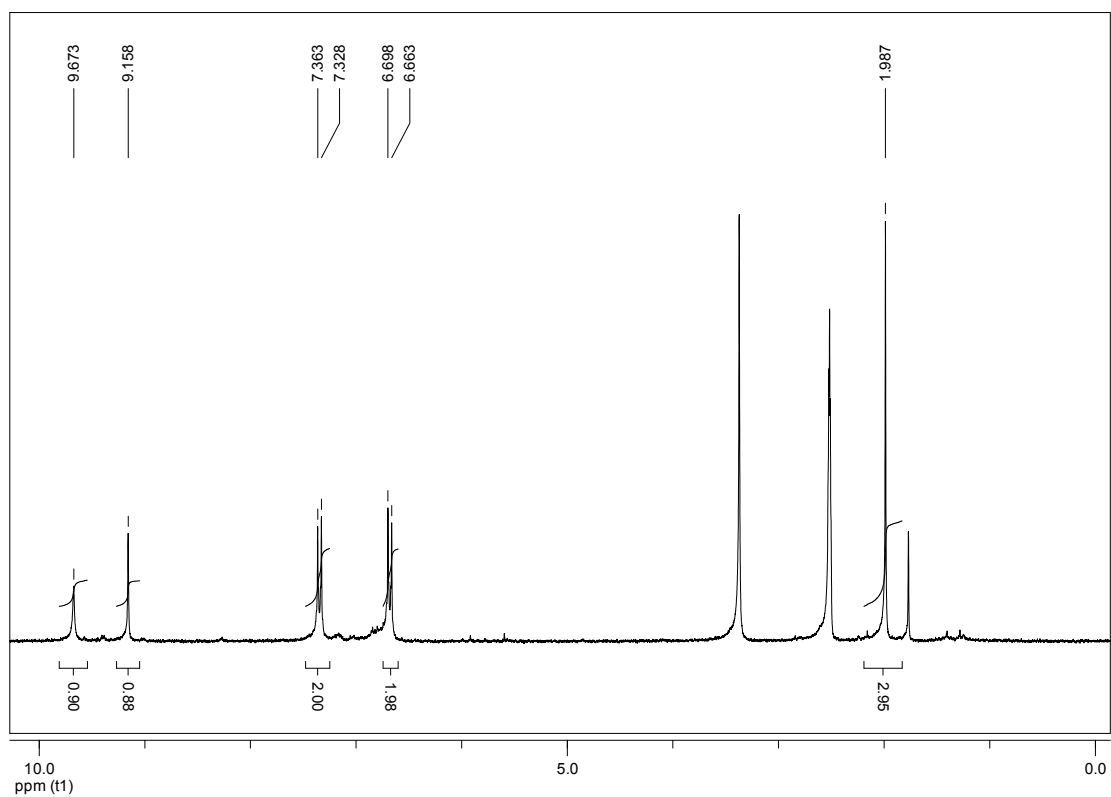


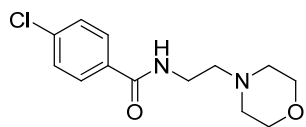
***N*-(Phenylacetyl)-valine methyl ester (Table 2, Entry 15)**



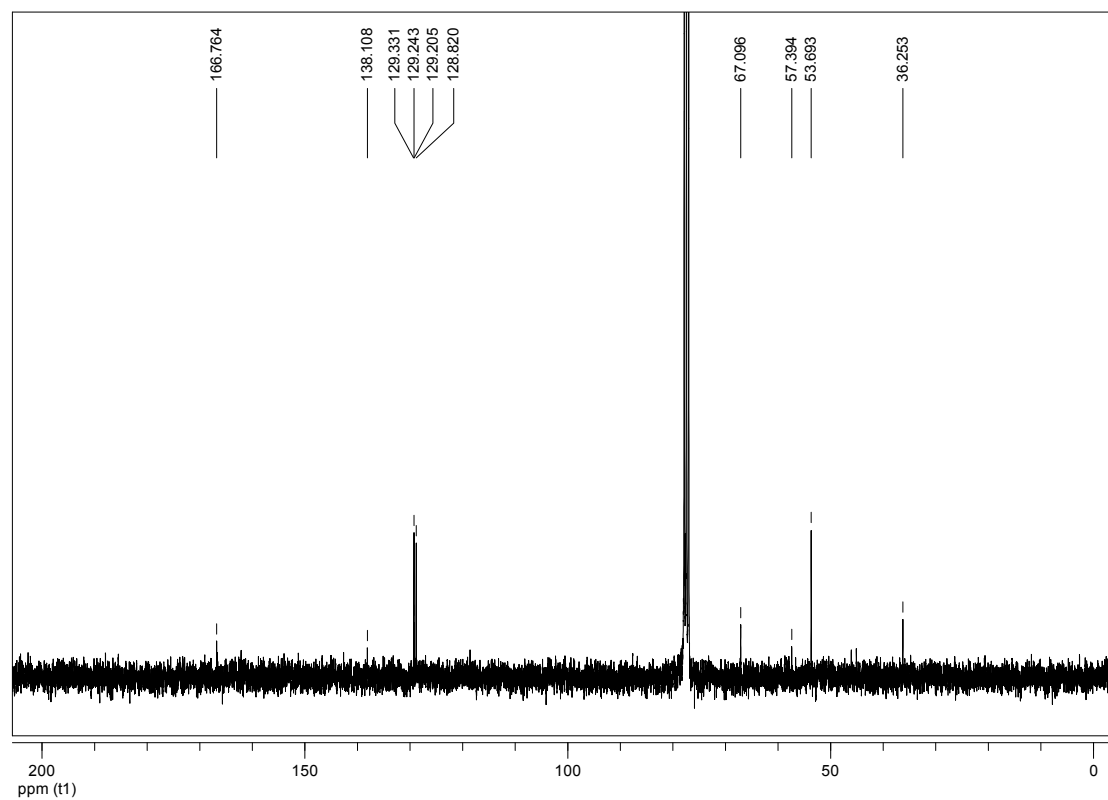
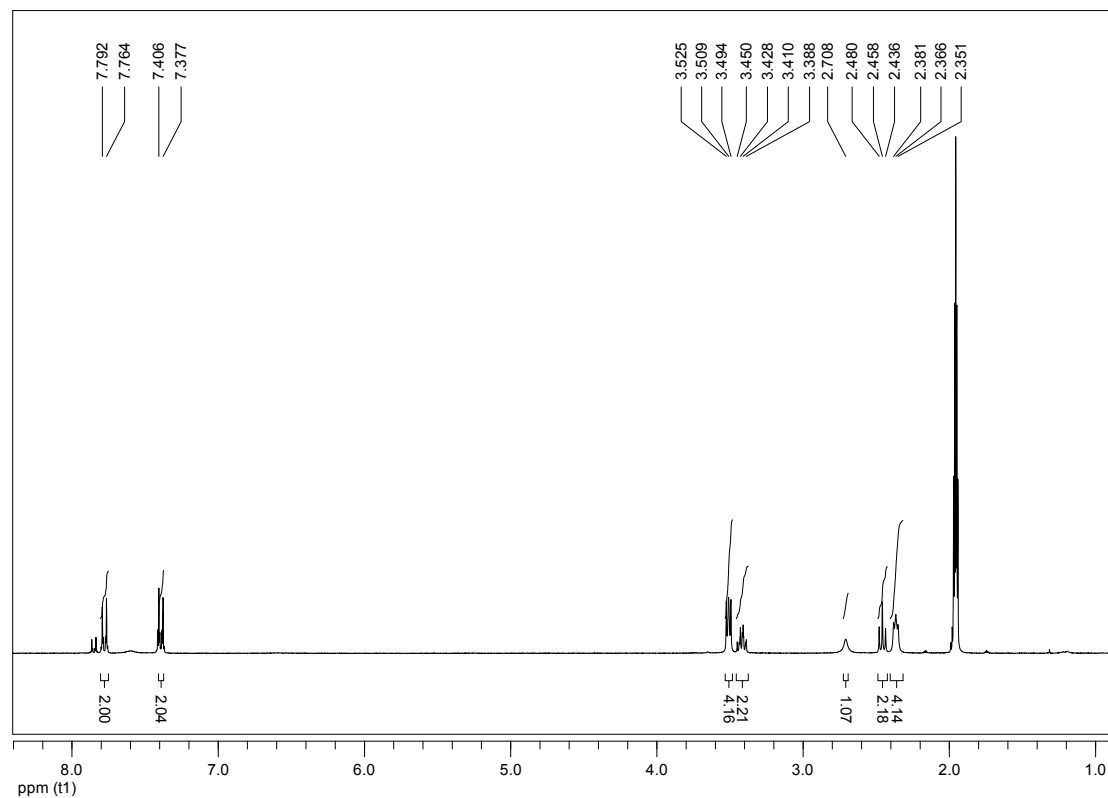


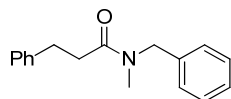
Paracetamol (Table 2, Entry 16)



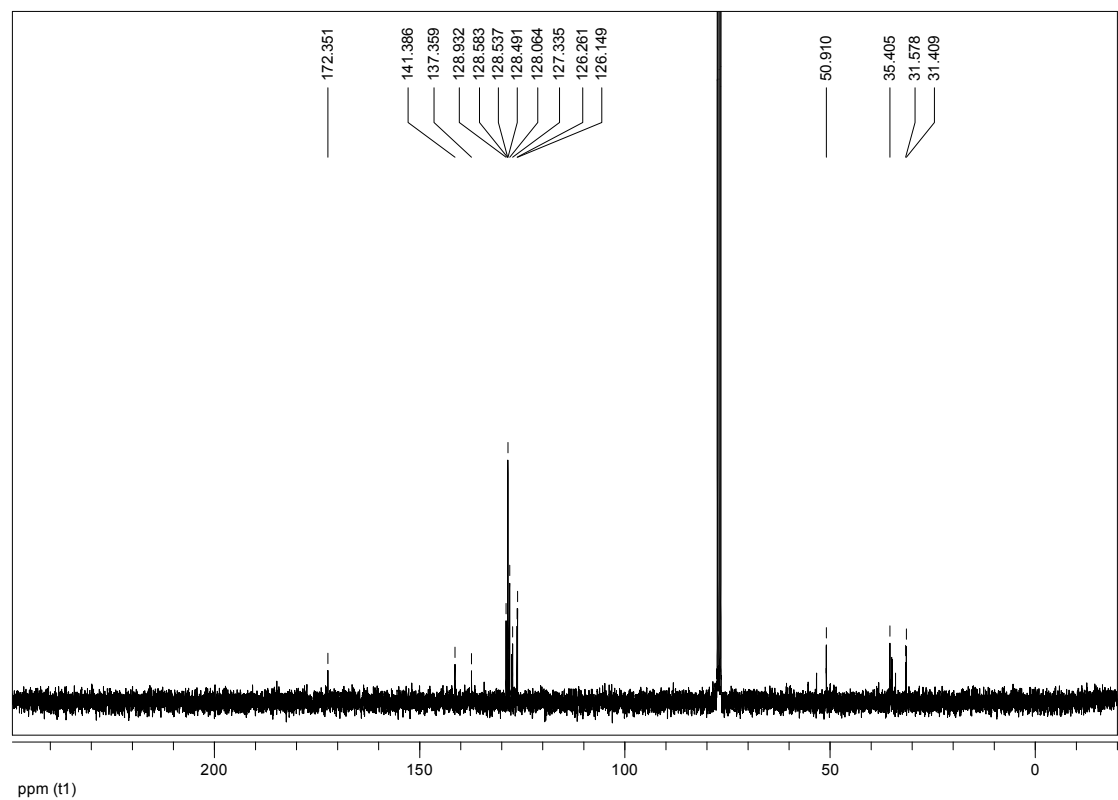
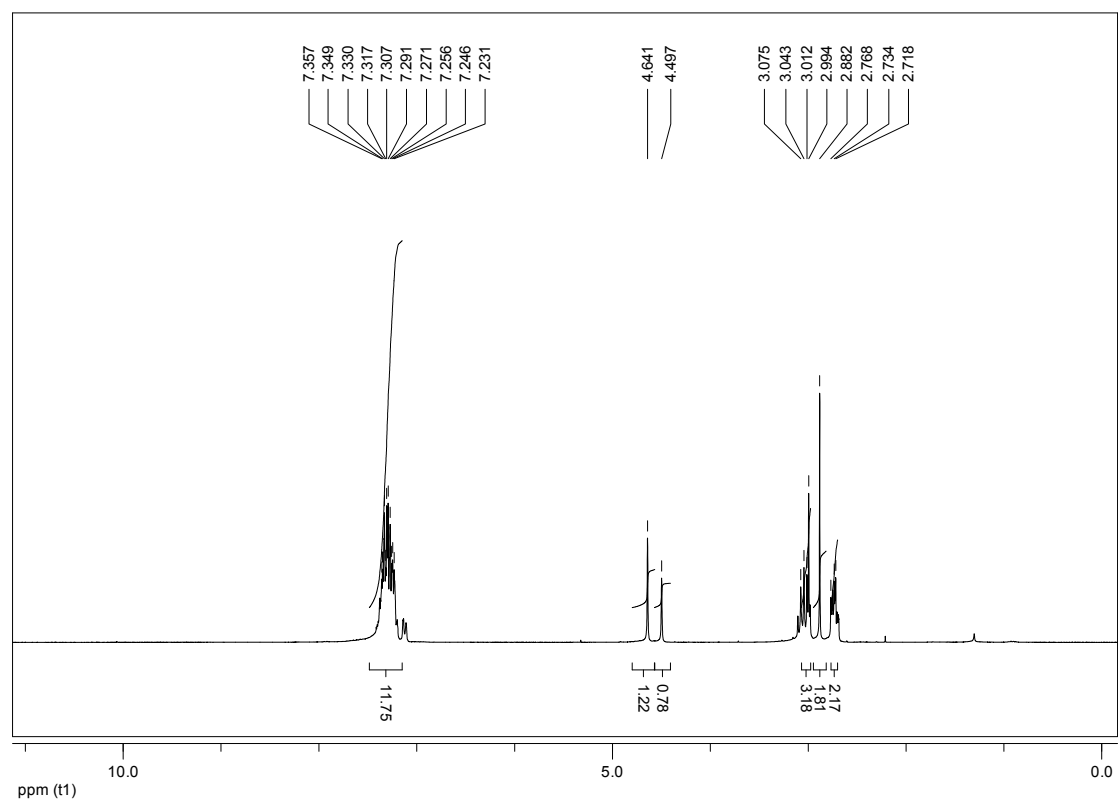


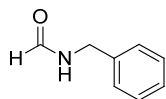
Moclobemide (Table 2, Entry 17)



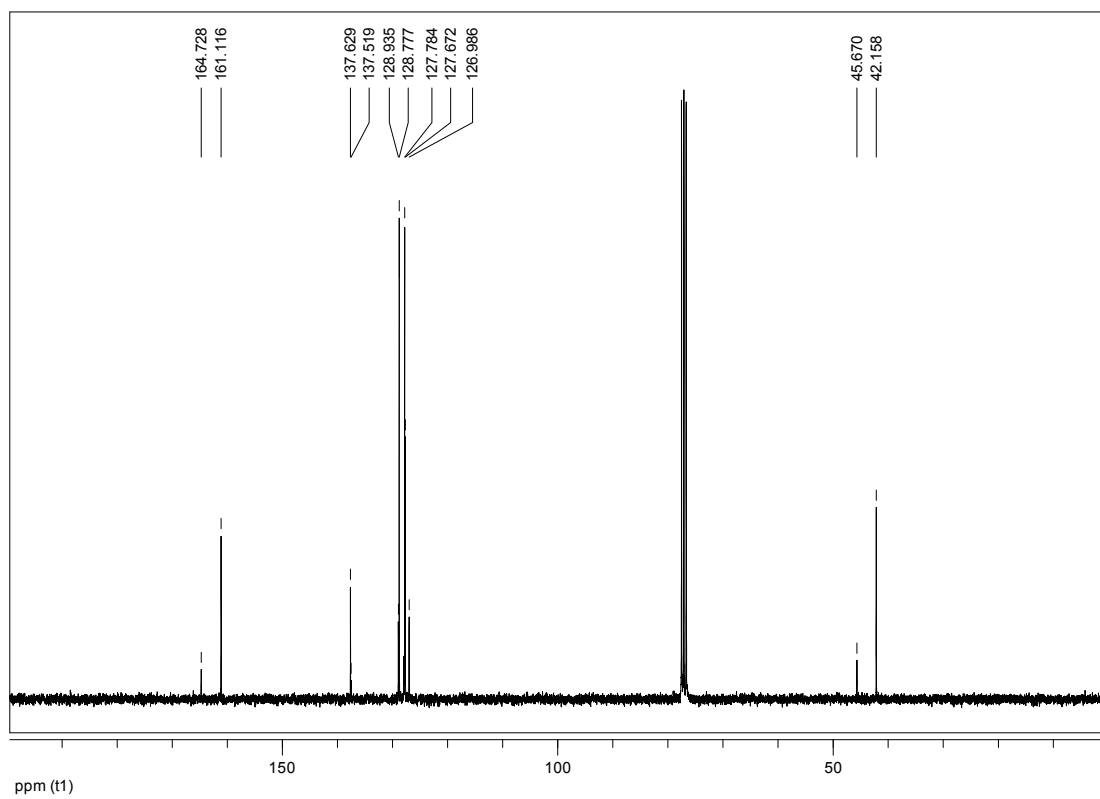
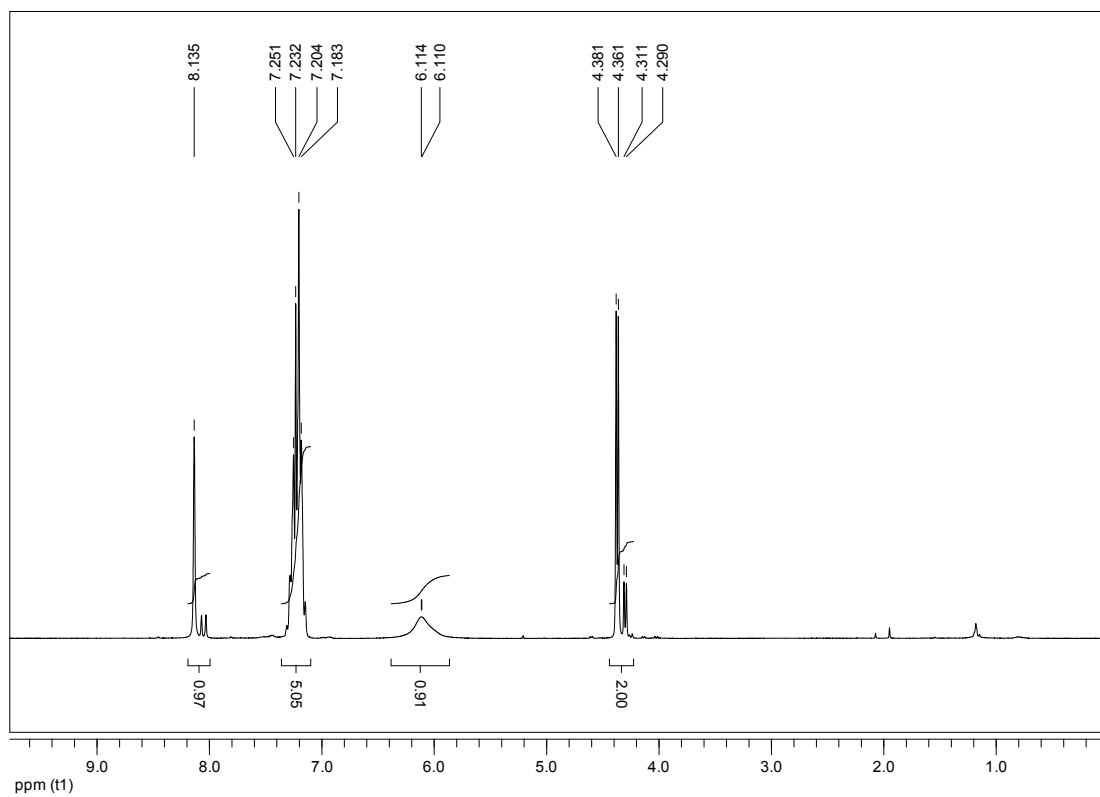


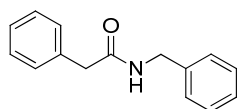
[*N*-(Benzyl)-*N*-methyl]-3-phenylpropionamide (Table S2, Entry 1)



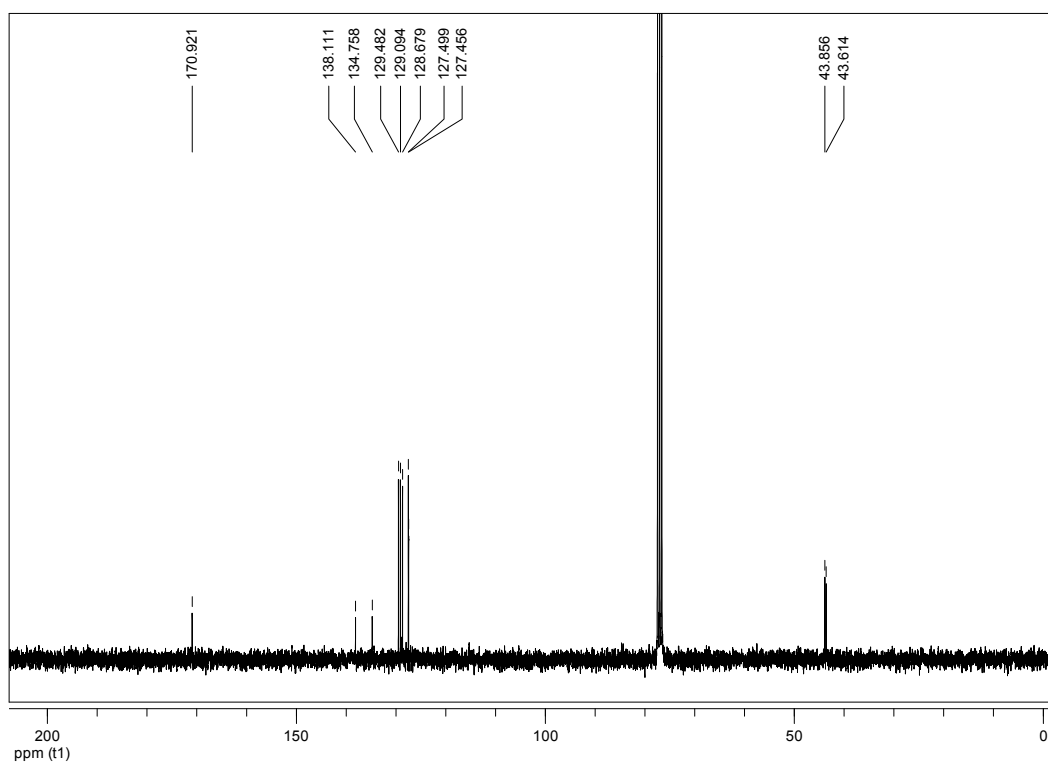
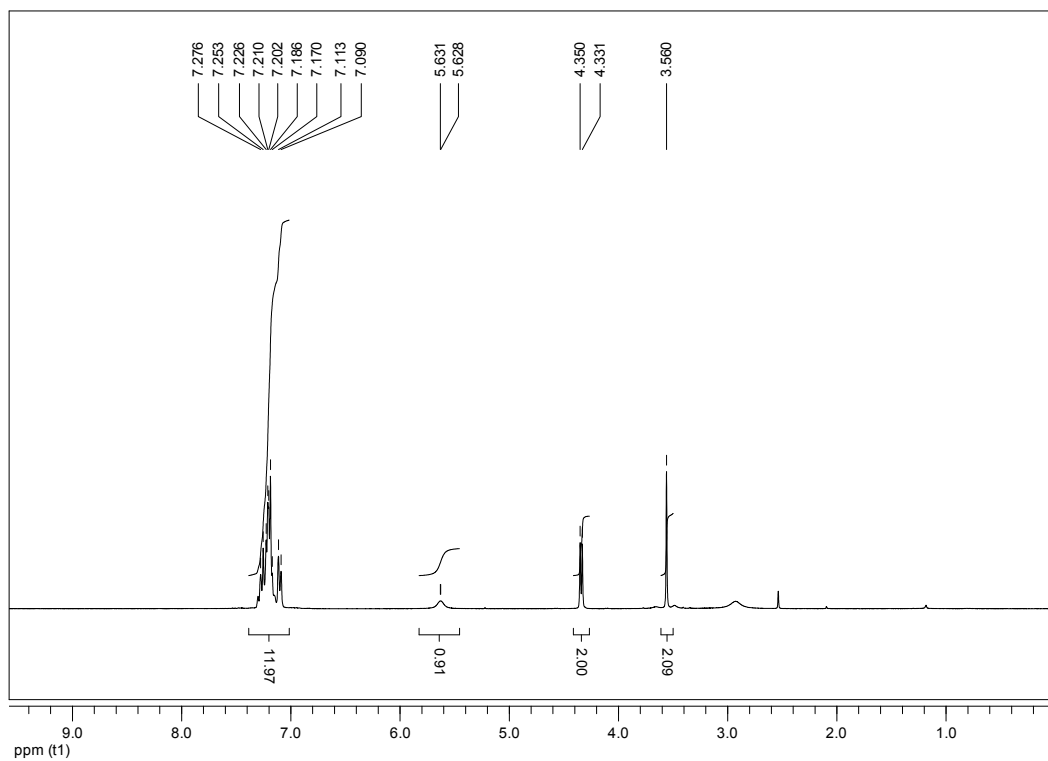


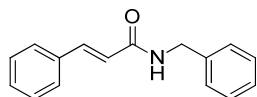
***N*-(Benzyl)-formamide (Table S2, Entry 2)**



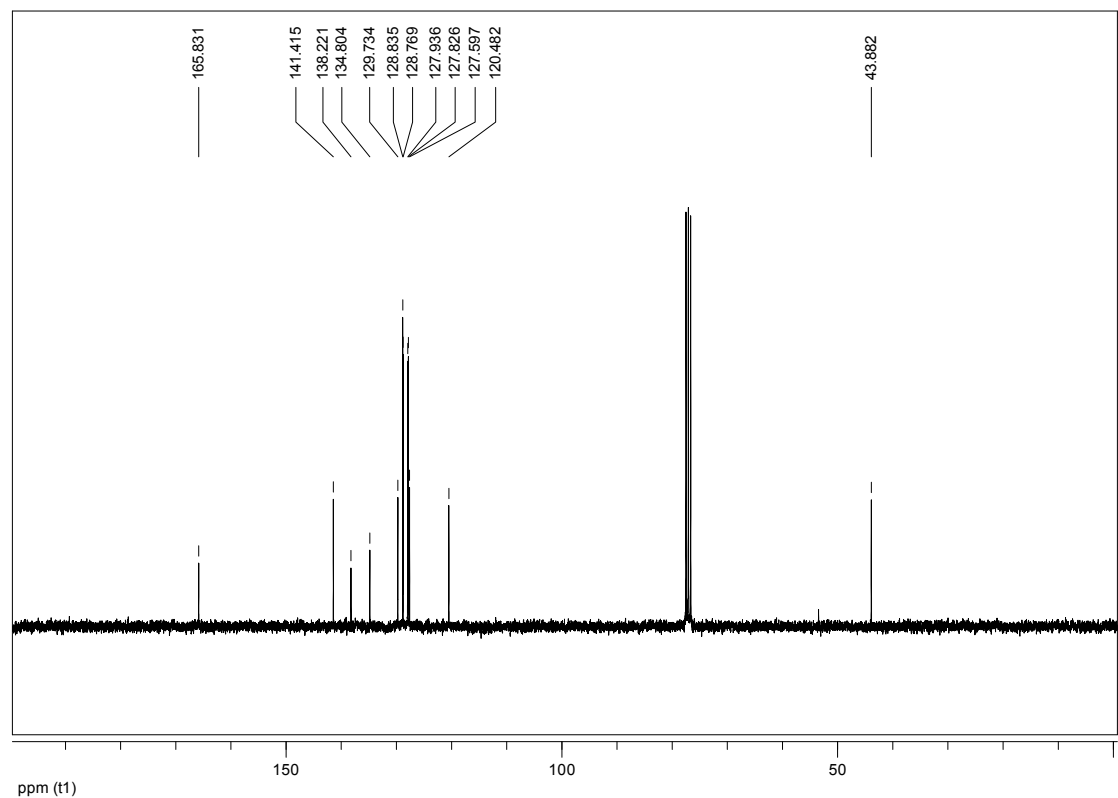
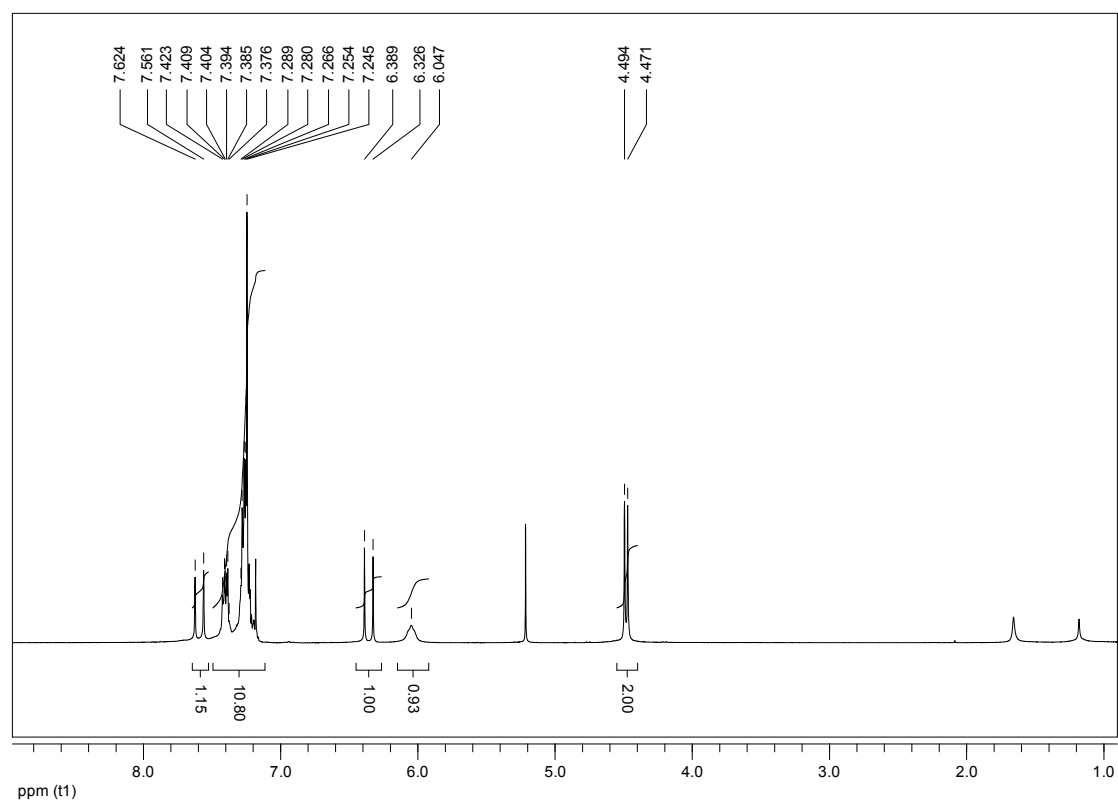


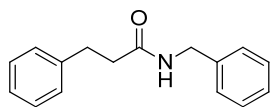
***N*-(Benzyl)-phenylacetamide (Table S2, Entry 3)**





***N*-(Benzyl)-cinnamide (Table S2, Entry 4)**





***N*-(Benzyl)-3-phenylpropanamide (Scale up procedure).**

