Supporting Information for:

C-H Functionalisation of Aldehydes using Light Generated, Non-Stabilised Diazo Compounds in Flow

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1 Experimental

1.1 General Details

All batch reactions were performed under an atmosphere of argon using oven-dried glassware unless otherwise stated. All flow reactions were performed using a Vapourtec E-series and UV-150 system.[1] Solvents were collected from a Grubbs column[2] (CH_2Cl_2). All liquid aldehydes were purified *via* distillation (reduced pressure when required) prior to use.[3] Solid aldehydes were obtained from commercial sources and used without further purification. Flash column chromatography was performed using a Biotage SPX system with single use disposable silica columns of the appropriate size (SiliaSep Flash Cartridges 4 or 12 g 40-60 μm ISO04/012). Analytical thin layer chromatography (TLC) was performed using silica gel 60 F254 pre-coated glass backed plates and visualized by ultraviolet radiation (254 nm) and appropriate dip (typically potassium permanganate or ninhydrin).

^{1}H NMR spectra were recorded on a 600 MHz Avance 600 BBI Spectrometer. Chemical shifts are reported in ppm with the resonance resulting from incomplete deuteration of the solvent as the internal standard ($CDCl_3$: 7.26 ppm). ^{13}C NMR spectra were recorded on the same spectrometer with proton decoupling. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($^{13}CDCl_3$: 77.16 ppm, t). Data are reported as follows: chemical shift δ/ppm, integration (^{1}H only), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sept = septet, oct = octet, br = broad, m = multiplet or combinations thereof; ^{13}C signals are singlets unless otherwise stated), coupling constants *J* in Hz, assignment. Spectra are assigned as fully as possible, using ^{1}H-COSY, DEPT-135, HMQC and HMBC where appropriate to facilitate structural determination. Signals that cannot be unambiguously assigned are reported with all possible assignments separated by a slash (e.g. H1/H2) or descriptions of their environments (e.g. ArH, NH, OH). Multiple signals arising from diastereotopic or (pseudo)axial/equatorial positions are suffixed alphabetically (e.g. H1a, H1b). Overlapping signals that cannot be resolved are reported with their assignments denoted in list format (e.g. H1, H2 and H3). ^{1}H NMR signals are reported to 2 decimal places and ^{13}C signals to 1 decimal place unless rounding would produce a value identical to another signal. In this case, an additional decimal place is reported for both signals concerned.

Infrared spectra were recorded neat as thin films on a Perkin-Elmer Spectrum One FTIR spectrometer with a universal ATR sampling accessory, selected peaks are reported.

High resolution mass spectrometry (HRMS) was performed using positive or negative electrospray ionisation (ESI+) by the Mass Spectrometry Service for the Chemistry Department at the University of Cambridge. All *m/z* values are reported to 4 decimal places and are within ± 5 ppm of theoretical values.

Melting points were recorded on a Stanford Research Systems OptiMelt Automated Melting Point System calibrated against vanillin (m.p. 83 °C), phenacetin (m.p. 136 °C) and caffeine (m.p. 237 °C).

UV-Vis spectra were recorded on a Uniqsys Flow-UV in-line spectrophotometer.

2 Synthetic Procedures

2.1 General Procedures

A general procedure and detailed descriptions of oxadiazoline synthesis has been reported previously by our group as well as others.[4-7] All oxadiazolines used for this work were synthesised by the general procedure outlined below.

General procedure for oxadiazoline synthesis:[4] A solution of the appropriate ketone (1 equiv.) and acetic hydrazide (1.1 equiv.) in toluene was heated under reflux for 2 h. The mixture was then evaporated under reduced pressure and the residue redissolved in MeOH and cooled to 0 °C. (Diacetoxyiodo)benzene (1.1 equiv.) was added portionwise, then the mixture stirred further at this temperature for 1 h. The mixture was evaporated under reduced pressure and the residue purified by silica gel column chromatography.

General procedure for coupling: A solution of the appropriate oxadiazoline (0.4 mmol), aldehyde (0.2 mmol) and NMR internal standard 1,3,5-trimethoxybenzene (0.05 mmol) in CH_2Cl_2 (4 mL) was pumped (0.25 mL min^{-1}, t_R = 40 min) through a Vapourte UV-150 photochemical reactor (10 mL, FEP tubing) while irradiate by a 310 nm UV lamp (low power, 9W) held at 20 °C. The reactor output was monitored using a Mettler Toledo FlowIR instrument (SiComp head, bands of interest: 1750-1700 for diazo formation by-product methyl acetate and 2100-2000 cm^{-1} for unreacted diazo compound). The reaction slug was collected in round-bottom flask under air. If a significant quantity of unreacted diazo observed this was quenched by addition of acetic acid. The reaction mixture was evaporated under reduced pressure and purified by silica gel column chromatography.

2.2 UV Light Source and Setup

All flow reactions were performed using a Vapourtec E-series and UV-150 photochemical reactor. The UV-150 allows a choice of three light sources: a medium pressure mercury lamp, a low pressure mercury lamp, and monochromatic LEDs (which were not investigated during this work as the highest wavelength available in our lab, 420 nm, was still too low to photolyse the oxadiazolines). We found the medium pressure mercury lamp to be problematic in this reaction due to it's broad radiant output and very high intensity; even with the appropriate filter while we found an increased reaction rate over the low pressure bulb (residence time could be reduced to roughly three minutes) although this coincided

with significant product decomposition. The low pressure mercury bulb, at a wavelength of 310 nm, offered a compromise amenable to this work. Bulbs of this type offer specific single wavelengths, although at a significantly lower output power than a medium pressure mercury lamp, requiring only a longer residence time to deliver higher yields and cleaner reactions, they are also very cheap (ca. £20 each). Figure S1 shows the UV-Vis of an oxadiazoline commonly used in this work. The λ_{max} appears at 330 nm, meaning that irradiation at 310 nm is not at an optimum wavelength to initiate oxadiazoline photolysis. Further, it could be assumed that irradiation in the region of 330-350 nm would be preferable as, while this would still initiate photolysis of the oxadiazoline, this is slightly above the λ_{max} of most aromatic aldehydes, so side-stepping the issues of competitive absorption observed. However, these low-pressure bulbs are commercially available in three wavelengths (254 nm, 310 nm, 370 nm). Other wavelengths are available but sourcing and costing of such bulbs would be problematic.[8] We chose the 310 nm low pressure mercury bulb as a compromise we felt best suited to this work.

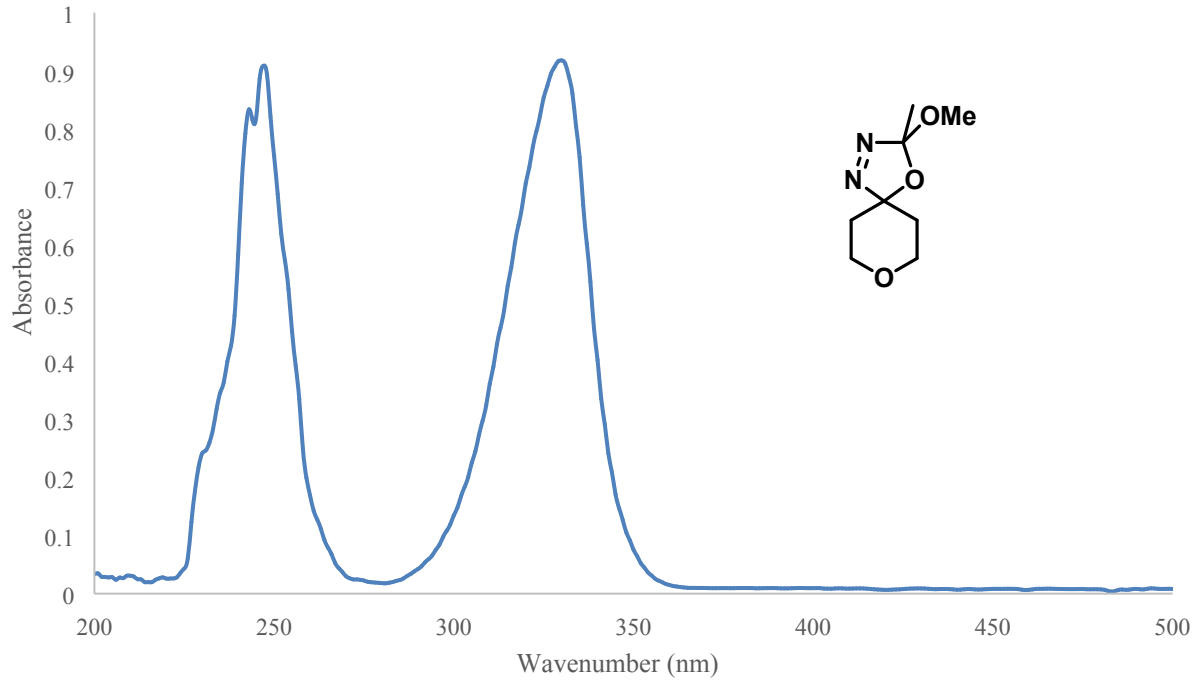


Figure S1: UV-Vis spectra of commonly used oxadiazoline.

3 UV-Vis Data

Table S1: UV-Vis data with associated conversions and yields

Aldehyde	Product Number	Absorption at 310 nm	λ_{Max} (nm)	Oxadiazoline Conversion[a] (%)	Reaction Yield[a] (%)
4-Chloro	**8**	0.1489	291	94	94
3-CO_2Me	**19**	0.2163	297	94	91
4-Bromo	**21**	0.1744	291	97	74
3-Bromo	**22**	1.7971	299	96	45
3-Bpin	**23**	0.2932	297	94	52
4-Methoxy	**24**	1.1271	299	93	26
2-Pyr	**25**	0.3026	287	70	48
6Cl-3Pyr	**26**	0.2419	291	85	76
2-Thiophene	**27**	2.4948	311	39	16 (41)[c]
Isoxazole	**28**	0.0776	274	80	74
Cinnamaldehyde	**32**	2.636	314	0	0
Benzothiazole[b]	**33**	2.5865	312	8	0
2-NH_2[b]	**34**	0.7223	348	0	0
4-NO_2	**35**	2.6273	312	23	0

[a] Determined by NMR spectroscopy with reference to trimethoxybenzene as internal standard, [b] Solution was diluted until absorption was within the limits of the UV-Vis photospectrometer, [c] t_r = 80 minutes, half standard reaction concentrations

Alkyl aldehydes were not included as they typically do not absorb UV irradiation. 0.1M solutions of each aldehyde were made and a UV-Vis was taken from 200-500 nm. Relationship between oxadiazoline conversion and λ_{max}, showing a precipitous drop in conversion once the λ_{max} of the aldehyde reached the wavelength of irradiation (310nm) (Figure S2). However, only a very poor correlation existed between reaction yield and aldehyde λ_{max} (Figure S3).

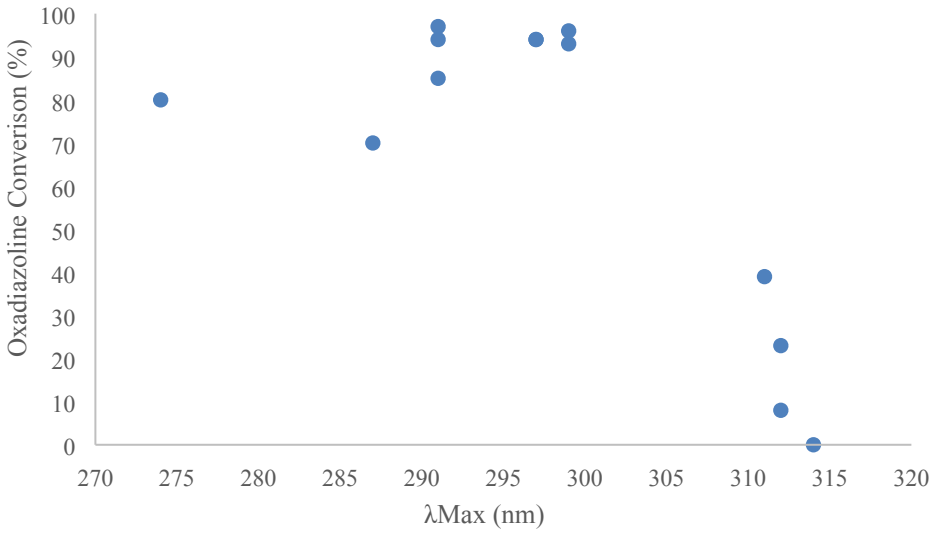


Figure S2: Relationship between aldehyde λ_{max} and oxadiazoline conversion

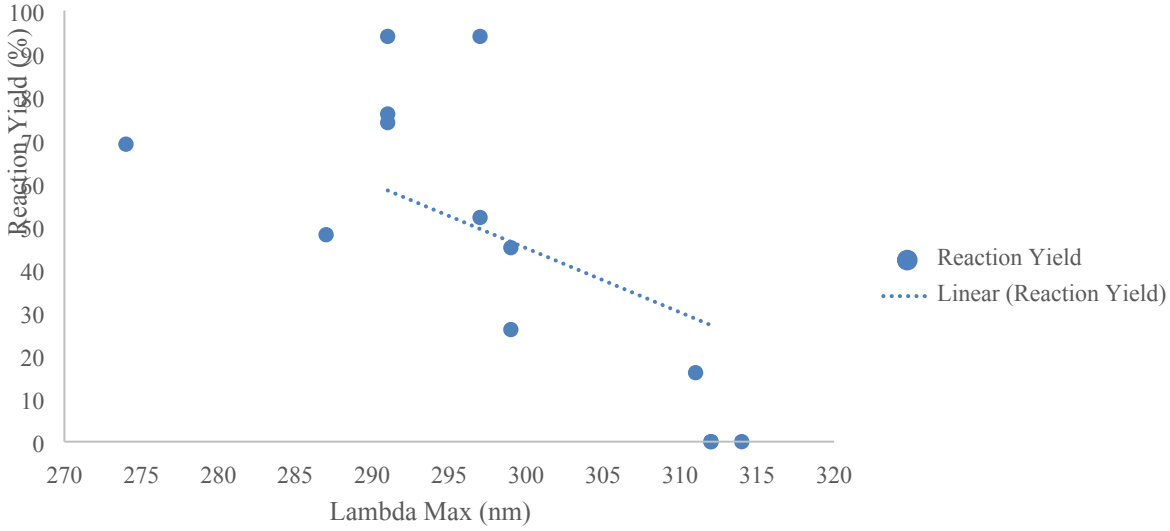
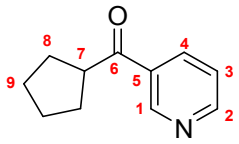


Figure S3: Relationship between aldehyde λ_{max} and reaction yield

cyclopentyl(pyridin-3-yl)methanone (1):



R*f*: 0.44 (3/7 PE/EtOAc).

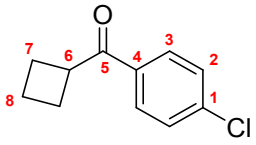
^{1}H NMR (600 MHz, $CDCl_3$) δ 9.17 (s, 1H, H^1), 8.75 (s, 1H, H^2), 8.23 (d, *J* = 8.0 Hz, 1H, H^4), 7.40 (dd, *J* = 8.0, 4.6 Hz, 1H, H^3), 3.67 (p, *J* = 7.8 Hz, 1H, H^7), 1.95-1.89 (m, 4H, H^8), 1.73-1.65 (m, 4H, H^9).

^{13}C NMR (150 MHz, $CDCl_3$) δ 201.4 (C^6), 153.1 (C^2), 150.0 (C^1), 135.8 (C^4), 132.0 (C^5), 123.6 (C^3), 46.7 (C^7), 29.6 (C^8), 26.2 (C^9).

FTIR (ATR, neat): ν_{max}/cm^{-1} 2957, 2869, 1682, 1584, 1417, 1230, 997, 702.

HRMS (ESI+): m/z calcd for $C_{11}H_{14}NO$: 176.1075, found 176.1080 $[M+H]^+$.

(4-chlorophenyl)(cyclobutyl)methanone (2):



R*f*: 0.48 (9/1 hexane/EtOAc).

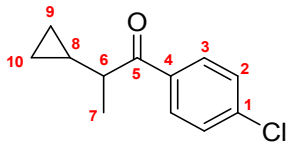
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.6 Hz, 2H, H^3), 7.42 (d, *J* = 8.6 Hz, 2H, H^2), 3.95 (pd, J = 8.4, 1.2 Hz, 1H, H^6), 2.44-2.37 (m, 2H, H^7), 2.32-3.26 (m, 2H, H^7), 2.13-2.05 (m, 1H, H^8), 1.95-1.88 (m, 1H, H^8).

^{13}C NMR (150 MHz, $CDCl_3$) δ 199.7 (C^5), 139.2 (C^1), 133.9 (C^4), 129.7 (C^3), 128.9 (C^2), 42.1 (C^6), 25.0 (C^7), 18.1 (C^8).

FTIR (ATR, neat): ν_{max}/cm^{-1} 2988, 2945, 1678, 1588, 1402, 1344, 1249, 1219, 1089, 1013, 967, 838, 735.

HRMS (ESI+): m/z calcd for $C_{11}H_{20}OCl$: 195.0571, found 195.0566 $[M+H]^+$.

1-(4-chlorophenyl)-2-cyclopropylpropan-1-one (3):



R*f*: 0.41 (9/1 hexane/EtOAc).

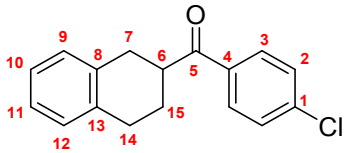
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.6 Hz, 2H, H^3), 7.43 (d, *J* = 8.6 Hz, 2H, H^2), 2.73 (dq, *J* = 9.1, 7.0 Hz, 1H, H^6), 1.26 (d, *J* = 7.0 Hz, 3H, H^7), 1.04 (qt, *J* = 8.4, 5.0 Hz, 1H, H^8), 0.57-0.53 (m, 1H, H^9/H^{10}), 0.50-0.45 (m, 1H, H^9/H^{10}), 0.21-0.13 (m, 2H, H^9/H^{10}).

^{13}C NMR (150 MHz, $CDCl_3$) δ 202.8 (C^5), 139.2 (C^1), 135.2 (C^4), 129.7 (C^3), 128.9 (C^2), 45.1 (C^6), 17.0 (C^7), 14.6 (C^8), 4.4 (C^9/C^{10}), 3.4 (C^9/C^{10}).

FTIR (ATR, neat): ν_{max}/cm^{-1} 3080, 2974, 2932, 1681, 1588, 1400, 1217, 1091, 1014, 973, 909, 843, 766.

HRMS (ESI+): m/z calcd for $C_{12}H_{14}OCl$: 209.0733, found 209.0731 $[M+H]^+$.

(4-chlorophenyl)(1,2,3,4-tetrahydronaphthalen-2-yl)methanone (4):



R*f*: 0.43 (9/1 PE/EtOAc).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.6 Hz, 2H, H^3), 7.47 (d, *J* = 8.6 Hz, 2H, H^2), 7.15-7.10 (m, 4H, H^9, H^{10}, H^{11}, H^{12}), 3.65 (tdd, *J* = 11.2, 4.1, 3.0 Hz, 1H, H^6), 3.09 (dd, *J* = 16.5, 11.2 Hz, 1H, H^7), 2.98-2.94 (m, 3H, H^7, $2H^{14}$), 2.19-2.16 (m, 1H, H^{15}), 1.94-1.87 (m, 1H, H^{15}).

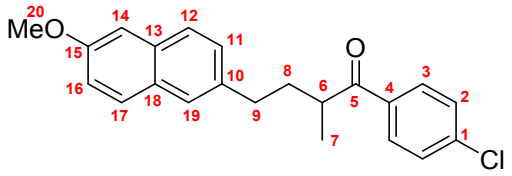
^{13}C NMR (150 MHz, $CDCl_3$) δ 201.6 (C^5), 139.5 (C^1), 135.7 (C^{13}), 135.2 (C^8), 134.4 (C^4), 129.8 (C^3), 129.1 (C^2), 129.0 (C^{12}), 128.8 (C^9), 126.0 (C^{10}), 125.9 (C^{11}), 42.2 (C^6), 32.1 (C^7), 28.8 (C^{14}), 26.4 (C^{15}).

M.p.: 61-63 °C.

FTIR (ATR, neat): ν_{max}/cm^{-1} 3019, 2931, 2868, 2842, 1677, 1584, 1486, 1451, 1399, 1371, 1283, 1262, 1217, 1191, 1085, 1009, 921, 840, 798, 743.

HRMS (ESI+): m/z calcd for $C_{17}H_{16}OCl$: 271.0884, found 271.0874 $[M+H]^+$.

1-(4-chlorophenyl)-4-(6-methoxynaphthalen-2-yl)-2-methylbutan-1-one (5):



R*f*: 0.25 (9/1 PE/EtOAc).

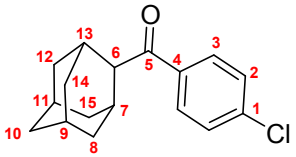
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.6 Hz, 2H, H^{3}), 7.67 (d, *J* = 8.4 Hz, 1H, H^{12}), 7.62 (d, *J* = 8.7 Hz, 1H, H^{17}), 7.47 (s, 1H, H^{19}), 7.36 (d, *J* = 8.5 Hz, 2H, H^{2}), 7.26-7.25 (m, 1H, H^{11}), 7.15-7.12 (m, 2H, H^{14}, H^{16}), 3.92 (m, 3H, H^{20}), 3.41 (h, *J* = 6.8 Hz, 1H, H^{6}), 2.81-2.74 (m, 2H, H^{9}), 2.27-2.21 (m, 1H, H^{8}), 1.85-1.80 (m, 1H, H^{8}), 1.24 (d, *J* = 6.8 Hz, 3H, H^{7}).

^{13}C NMR (150 MHz, $CDCl_3$) δ 202.9 (C^{5}), 157.3 (C^{15}), 139.3 (C^{1}), 136.6 (C^{10}), 134.8 (C^{4}), 133.1 (C^{13}), 129.7 (C^{3}), 129.0 (C^{17}), 128.9 (C^{2}), 128.8 (C^{18}), 127.7 (C^{11}), 126.9 (C^{12}), 126.5 (C^{19}), 118.8 (C^{16}), 105.6 (C^{14}), 55.5 (C^{20}), 39.6 (C^{6}), 35.0 (C^{8}), 33.3 (C^{9}), 17.2 (C^{7}).

FTIR (ATR, neat): ν_{max}/cm^{-1} 2968, 2934, 1676, 1606, 1589, 1484, 1391, 1264, 1229, 1091, 1032, 975, 843, 810, 733.

HRMS (ESI+): m/z calcd for $C_{22}H_{22}OCl$: 353.1303, found 353.1293 $[M+H]^{+}$.

adamantan-2-yl)(4-chlorophenyl)methanone (6):



R*f*: 0.57 (9/1 hexane/EtOAc).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.6 Hz, 2H, H^{3}), 7.41 (d, *J* = 8.6 Hz, 2H, H^{2}), 3.40 (s, 1H, H^{6}), 2.28 (s, 2H, H^{7}, H^{13}), 2.03-1.98 (m, 3H, H^{9}/H^{11}, 2H^{8}/H^{12}/H^{14}/H^{15}), 1.93-1.90 (m, 4H, H^{8}/H^{12}/H^{14}/H^{15}), 1.87-1.84 (m, 1H, H^{9}/H^{11}), 1.74 (m, 2H, H^{10}), 1.58 (d, *J* = 12.3 Hz, 2H, H^{8}/H^{12}/H^{14}/H^{15}).

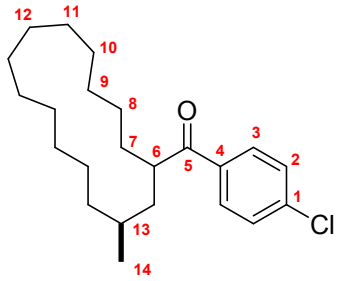
^{13}C NMR (150 MHz, $CDCl_3$) δ 202.7 (C^{5}), 138.4 (C^{1}), 135.4 (C^{4}), 129.5 (C^{3}), 128.7 (C^{2}), 52.2 (C^{6}), 38.8 (C^{8}/C^{12}/C^{14}/C^{15}), 37.4 (C^{10}), 32.7 (C^{8}/C^{12}/C^{14}/C^{15}), 30.3 (C^{7}, C^{13}), 27.9 (C^{9}/C^{11}), 27.5 (C^{9}/C^{11}).

M.p.: 86-88 °C.

FTIR (ATR, neat): ν_{max}/cm^{-1} 2909, 2849, 1681, 1589, 1209, 1191, 1006, 862, 810.

HRMS (ESI+): m/z calcd for $C_{17}H_{20}OCl$: 275.1203, found 275.1194 $[M+H]^{+}$.

(4-chlorophenyl)((3S)-3-methylcyclopentadecyl)methanone (7)



R*f*: 0.24 (98/2 PE/EtOAc).

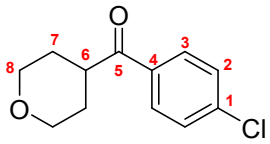
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.6 Hz, 2H, H^3)), 7.45 (dd, *J* = 8.7, 2.2 Hz, 2H, H^2), 3.47 (tt, *J* = 8.8, 4.3 Hz, 1H, H^6), 1.47 – 1.19 (m, 27H), 0.82 (d, *J* = 6.6 Hz, 3H, H^{14}).

^{13}C NMR (150 MHz, $CDCl_3$) δ 203.1 (C^5), 139.1 (C^1), 135.4 (C^4), 129.6 (C^3), 128.9 (C^2), 42.9 (C^6), 40.0 (CH_2), 33.6 (CH_2), 29.4 (C^{13}), 28.9 (CH_2), 27.2 (CH_2), 27.2 (CH_2), 26.8 (CH_2), 26.8 (CH_2), 26.7 (CH_2), 26.6 (CH_2), 26.6 (CH_2), 26.4 (CH_2), 25.9 (CH_2), 25.3 (CH_2), 20.9 (C^{14}).

FTIR (ATR, neat): 2924, 2855, 1718, 1684, 1590, 1458, 1209, 1092, 1013,839, 741

HRMS (ESI+): m/z calcd for $C_{23}H_{36}OCl$: 363.2449, found 363.2445 $[M+H]^+$.

(4-chlorophenyl)(tetrahydro-2H-pyran-4-yl)methanone (8):



R*f*: 0.25 (7/3 hexane/EtOAc).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.6 Hz, 2H, H^3), 7.45 (d, *J* = 8.6 Hz, 2H, H^2), 4.05 (ddd, *J* = 11.6, 4.3, 2.5 Hz, 2H, H^8), 3.55 (td, *J* = 11.6, 2.5 Hz, H^8), 3.44 (tt, *J* = 11.1, 3.9 Hz, 1H, H^6), 1.91-1.84 (m, 2H, H^7), 1.79-1.75 (m, 2H, H^7).

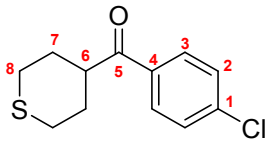
^{13}C NMR (150 MHz, $CDCl_3$) δ 200.5 (C^5), 139.5 (C^1), 134.1 (C^4), 129.7 (C^3), 129.0 (C^2), 67.2 (C^8), 42.6 (C^6), 29.0 (C^7).

M.p.: 117-119 °C.

FTIR (ATR, neat): ν_{max}/cm^{-1} 2961, 2921, 2850, 1678, 1582, 1401, 1266, 1208, 1113, 1084, 984, 849, 809, 734, 660.

HRMS (ESI+): m/z calcd for $C_{12}H_{14}O_2Cl$: 225.0682, found 225.0680 $[M+H]^+$.

(4-chlorophenyl)(tetrahydro-2H-thiopyran-4-yl)methanone (9):



R*f*: 0.50 (100% DCM).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.6 Hz, 2H, H^3), 7.45 (d, *J* = 8.6 Hz, 2H, H^2), 3.27 (tt, *J* = 11.2, 3.1 Hz, 1H, H^6), 2.81 (ddd, *J* = 14.4, 12.0, 2.6 Hz, 2H, H^8), 2.74-2.70 (m, 2H, H^8), 2.19-2.15 (m, 2H, H^7), 1.91 (dtd, *J* = 14.4, 12.0, 3.3 Hz, 2H, H^7).

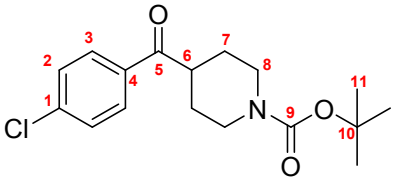
^{13}C NMR (150 MHz, $CDCl_3$) δ 200.9 (C^5), 139.5 (C^1), 134.0 (C^4), 129.7 (C^3), 129.1 (C^2), 44.8 (C^6), 30.1 (C^8), 27.9 (C^7).

M.p.: 120-122 °C.

FTIR (ATR, neat): ν_{max}/cm^{-1} 2905, 2842, 1677, 1586, 1402, 1313, 1273, 1227, 1177, 1095, 1014, 933, 843, 742.

HRMS (ESI+): m/z calcd for $C_{12}H_{14}OSCl$: 241.0454, found 241.0451 $[M+H]^+$.

tert-butyl 4-(4-chlorobenzoyl)piperidine-1-carboxylate (10):



R*f*: 0.19 (4/1 PE/EtOAc).

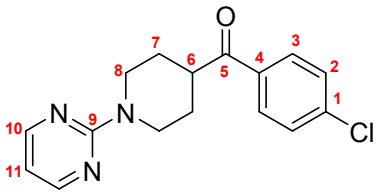
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.6 Hz, 2H, H^3), 7.45 (d, *J* = 8.6 Hz, 2H, H^2), 4.16 (br s, 2H, H^8), 3.35 (tt, *J* = 11.2, 3.7 Hz, 1H, H^6), 2.89 (br s, 2H, H^8), 1.82 (br m, *J* = 13.5 Hz, 2H, H^7), 1.74 – 1.64 (br m, 2H, H^7), 1.46 (s, 9H, H^{11}).

^{13}C NMR (150 MHz, $CDCl_3$) δ 200.8 (C^5), 154.6 (C^9), 139.5 (C^4), 134.1 (C^1), 129.6 (C^3), 129.0 (C^2), 79.7 (C^8), 43.7 (C^6), 42.8 (C^8) 28.4 (C^{11}).

FTIR (ATR, neat): ν_{max}/cm^{-1} 2975, 2858, 1680, 1590, 1421, 1366, 1165, 1091, 970, 847, 740.

HRMS (ESI+): m/z calcd for $C_{17}H_{21}NO_3Cl$: 322.1210, found 322.1203 $[M+H]^+$.

(4-chlorophenyl)(1-(pyrimidin-2-yl)piperidin-4-yl)methanone (11):



R*f*: 0.18 (8/2 PE/EtOAc).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.31 (d, *J* = 4.8 Hz, 2H, H^{10}), 7.91 (d, *J* = 8.6 Hz, 2H, H^{3}), 7.46 (d, *J* = 8.6 Hz, 2H, H^{2}), 6.48 (t, *J* = 4.8 Hz, 1H, H^{11}), 4.82 (dt, *J* = 13.5, 3.0 Hz, 2H, H^{8}), 3.49 (tt, *J* = 11.2, 3.7 Hz, 1H, H^{6}), 3.09 (ddd, *J* = 13.5, 12.0, 3.0 Hz, 2H, H^{8}), 1.94-1.91 (m, 2H, H^{7}), 1.81-1.74 (m, 2H, H^{7}).

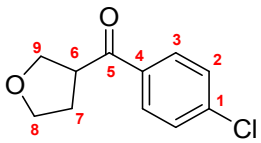
^{13}C NMR (150 MHz, $CDCl_3$) δ 201.0 (C^{5}), 161.5 (C^{9}), 157.7 (C^{10}), 139.5 (C^{1}), 134.2 (C^{4}), 129.7 (C^{3}), 129.1 (C^{2}), 109.7 (C^{11}), 43.9 (C^{6}), 43.3 (C^{8}), 28.2 (C^{7}).

M.p.: 90-92 °C.

FTIR (ATR, neat): ν_{max}/cm^{-1}2951, 2853, 1672, 1583, 1546, 1480, 1453, 1357, 1308, 1278, 1203, 1092, 970, 943, 846, 797, 659.

HRMS (ESI+): m/z calcd for $C_{16}H_{17}N_3OCl$: 302.1055, found 302.1042 $[M+H]^+$.

(4-chlorophenyl)(tetrahydrofuran-3-yl)methanone:



R*f*: 0.31 (7/3 hexane/EtOAc).

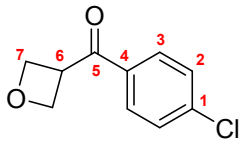
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.6 Hz, 2H, H^{3}), 7.45 (d, *J* = 8.6 Hz, 2H, H^{2}), 4.10-4.06 (m, 1H, H^{9}), 3.98-3.93 (m, 2H, H^{9}, H^{6}), 3.92-3.86 (m, 2H, H^{8}), 2.31-2.26 (m, 1H, H^{7}), 2.22-2.16 (m, 1H, H^{7}).

^{13}C NMR (150 MHz, $CDCl_3$) δ 198.2 (C^{5}), 139.8 (C^{1}), 134.6 (C^{4}), 129.8 (C^{3}), 129.1 (C^{2}), 70.1 (C^{9}), 68.5 (C^{8}), 46.3 (C^{6}), 29.6 (C^{7}).

FTIR (ATR, neat): ν_{max}/cm^{-1} 2974, 2868, 1681, 1587, 1402, 1218, 1089, 1062, 1011, 919, 842, 742.

HRMS (ESI+): m/z calcd for $C_{11}H_{12}O_2Cl$: 211.0526, found 211.0524 $[M+H]^+$.

(4-chlorophenyl)(oxetan-3-yl)methanone (13):



R*f*: 0.28 (7/3 hexane/EtOAc).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.6 Hz, 2H, H^3), 7.45 (d, *J* = 8.6 Hz, 2H, H^2), 4.97-4.93 (m, 4H, H^7), 4.60 (tt, *J* = 8.5, 7.0 Hz, 1H, H^6).

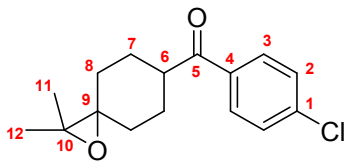
^{13}C NMR (150 MHz, $CDCl_3$) δ 195.8 (C^5), 140.2 (C^1), 133.2 (C^4), 129.5 (C^3), 129.3 (C^2), 72.5 (C^7), 42.0 (C^6).

M.p.: 85-87 °C.

FTIR (ATR, neat): ν_{max}/cm^{-1} 2910, 2849, 1679, 1588, 1210, 1089, 958, 844, 810, 729.

HRMS (ESI+): m/z calcd for $C_{10}H_{10}O_2Cl$: 197.0369, found 197.0369 $[M+H]^+$.

(4-chlorophenyl)(2,2-dimethyl-1-oxaspiro[2.5]octan-6-yl)methanone (14):



R*f*: 0.24 (100% DCM).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.6 Hz, 2H, H^3), 7.46 (d, *J* = 8.6 Hz, 2H, H^2), 3.35 (tt, *J* = 10.9, 3.8 Hz, 1H, H^6), 2.05-2.02 (m, 2H, H^7), 1.82-1.78 (m, 4H, H^8), 1.71-1.64 –m, 2H, H^7), 1.37 (s, 6H, H^{11}/H^{12}).

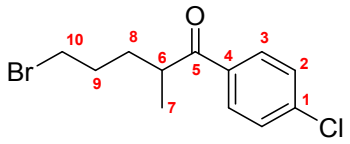
^{13}C NMR (150 MHz, $CDCl_3$) δ 201.8 (C^5), 139.5 (C^1), 134.4 (C^4), 129.7 (C^3), 129.0 (C^2), 65.8 (C^9/C^{10}), 62.5 (C^9/C^{10}), 44.3 (C^6), 30.2 (C^8), 28.4 (C^7), 20.7 (C^{11}/C^{12}).

M.p.: 94-96 °C.

FTIR (ATR, neat): ν_{max}/cm^{-1} 3001, 2978, 2923, 2857, 1669, 1588, 1446, 1401, 1377, 1319, 1261, 1204, 1091, 1002, 976, 883, 838, 748.

HRMS (ESI+): m/z calcd for $C_{16}H_{20}O_2Cl$: 279.1146, found 279.1136 $[M+H]^+$.

5-bromo-1-(4-chlorophenyl)-2-methylpentan-1-one (15)



R*f*: 0.27 (9/1 hexane/EtOAc).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.6 Hz, 2H, H^3), 7.44 (d, *J* = 8.6 Hz, 2H, H^2), 3.4 (h, *J* = 6.7 Hz, 1H, H^6), 3.4 (td, *J* = 6.6, 2.1 Hz, 2H, H^{aa}), 1.97-1.91 (m, 1H, H^9), 1.89-1.83 (m, 2H, H^8), 1.64-1.58 (m, 1H, H^9), 1.21 (d, *J* = 7.0 Hz, 3H, H^7).

^{13}C NMR (150 MHz, $CDCl_3$) δ 202.3 (C^5), 139.5 (C^1), 134.6 (C^4), 129.7 (C^3), 129.0 (C^2), 39.9 (C^6), 33.4 (C^{10}), 31.8 (C^9), 30.4 (C^8), 17.5 (C^7).

FTIR (ATR, neat): ν_{max}/cm^{-1} 2968, 2933, 1681, 1589, 1400, 1252, 1219, 1091, 1013, 974, 842, 745.

HRMS (ESI+): m/z calcd for $C_{12}H_{15}OClBr$: 288.9989, found 288.9977 $[M+H]^+$.

1-(4-chlorophenyl)-5-iodo-2-methylpentan-1-one (16)

x

R*f*: 0.17 (98/2 PE/EtOAc).

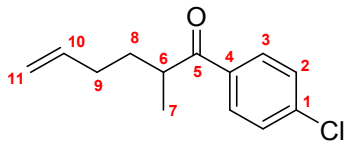
^{1}H xNMR (600 MHz, $CDCl_3$): δ 7.89 (d, *J* = 8.6 Hz, 2H, H^3), 7.45 (d, *J* = 8.6 Hz, 1H, H^2), 3.43 (h, *J* = 6.8 Hz, 1H, H^6), 3.21 – 3.11 (m, 1H, H^{10}), 1.95 – 1.88 (m, 1H, H^9), 1.87 – 1.79 (m, 2H, H^8), 1.64 – 1.52 (m, 1H, H^9), 1.21 (d, *J* = 6.9 Hz, 3H, H^7).

^{13}C NMR (150 MHz, $CDCl_3$) δ 202.3 (C^5), 139.5 (C^1), 134.6 (C^4), 129.7 (C^3), 129.0 (C^2), 39.8 (C^6), 34.1 (C^{10}), 31.1 (C^9), 17.5 (C^8), 6.2 (C^7).

FTIR (ATR, neat): 2925, 1682, 1590, 1459, 1401, 1212, 1173, 1092, 1014, 976, 843, 753

HRMS (ESI+): m/z calcd for $C_{12}H_{15}OClI$: 336.9851, found 336.9844 $[M+H]^+$.

1-(4-chlorophenyl)-2-methylhex-5-en-1-one (17):



R*f*: 0.59 (9/1 hexane/EtOAc).

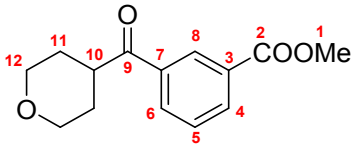
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.6 Hz, 2H, H^3), 7.44 (d, *J* = 8.6 Hz, 2H, H^2), 5.77 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H, H^{10}), 5.00-4.95 (m, 2H, H^{11}), 3.44 (h, J = 6.8 Hz, 1H, H^6), 2.08 (d, *J* = 6.7 Hz, 2H, H^9), 1.92 (h, *J* = 7.8 Hz, 1H, H^8), 1.54-1.50 (m, 1H, H^8), 1.19 (d, *J* = 6.8 Hz, 3H, H^7).

^{13}C NMR (150 MHz, $CDCl_3$) δ 203.0 (C^5), 139.3 (C^1), 137.9 (C^{10}), 134.9 (C^4), 129.7 (C^3), 128.9 (C^2), 115.3 (C^{11}), 39.7 (C^6), 32.5 (C^8), 31.4 (C^9), 17.2 (C^7).

FTIR (ATR, neat): ν_{max}/cm^{-1} 2974, 2933, 1682, 1589, 1400, 1227, 1092, 972, 911, 842, 746.

HRMS (ESI+): m/z calcd for $C_{13}H_{16}OCl$: 223.0890, found 223.0887 $[M+H]^+$.

methyl 3-(tetrahydro-2H-pyran-4-carbonyl)benzoate (19):



R*f*: 0.24 (6/4 hexane/EtOAc).

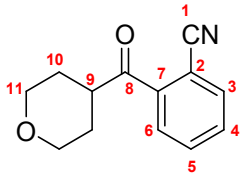
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.56 (t, *J* = 1.8 Hz, 1H, H^8), 8.24 (dt, *J* = 7.7, 1.8 Hz, 1H, H^4), 8.14 (dt, *J* = 7.7, 1.8 Hz, 1H, H^6), 7.57 (t, *J* = 7.7 Hz, 1H, H^5), 4.07-4.04 (m, 2H, H^{12}), 3.96 (s, 3H, H^1), 3.60-3.53 (m, 3H, H^{10}, $2H^{12}$), 1.92-1.85 (m, 2H, H^{11}), 1.81-1.77 (m, 2H, H^{11}).

^{13}C NMR (150 MHz, $CDCl_3$) δ 201.0 (C^9), 166.3 (C^2), 136.1 (C^7), 133.8 (C^4), 132.5 (C^6), 130.9 (C^3), 129.2 (C^8), 129.1 (C^5), 67.2 (C^{12}), 52.4 (C^1), 42.6 (C^{10}), 28.9 (C^{11}).

FTIR (ATR, neat): ν_{max}/cm^{-1} 2954, 2847, 1722, 1682, 1432, 1300, 1257, 1201, 1132, 1086, 1016, 968, 762, 717.

HRMS (ESI+): m/z calcd for $C_{14}H_{17}O_4$: 249.1121, found 249.1112 $[M+H]^+$.

2-(tetrahydro-2H-pyran-4-carbonyl)benzonitrile. (20):



R*f*: 0.09 (6/4 hexane/EtOAc).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.83 (ddd, *J* = 7.6, 6.0, 1.3 Hz, 2H, H^4, H^5), 7.71 (td, *J* = 7.6, 1.3 Hz, 1H, H^6), 7.65 (td, *J* = 7.6, 1.3 Hz, 1H, H^3), 4.05 (dt, J = 11.6, 3.6 Hz, 2H, H^{11}), 3.56-3.48 (m, 3H, H^9, $2H^{11}$), 1.91-1.81 (m, 4H, H^{10}).

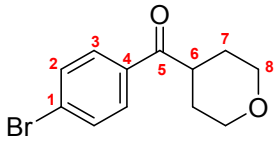
^{13}C NMR (150 MHz, $CDCl_3$) δ 200.8 (C^8), 139.9 (C^7), 135.1 (C^4/C^5), 132.6 (C^6), 132.0 (C^3), 128.9 (C^4/C^5), 117.8 (C^1), 111.2 (C^2), 67.0 (C^{11}), 44.2 (C^9), 28.6 (C^{10}).

M.p.: 110-112 °C.

FTIR (ATR, neat): ν_{max}/cm^{-1} 2966, 2933, 2860, 2221, 1684, 1573, 1442, 1382, 1303, 1276, 1257, 1240, 1215, 1112, 1083, 1018, 982, 790, 761.

HRMS (ESI+): m/z calcd for $C_{13}H_{14}O_2N$: 216.1019, found 216.1012 $[M+H]^+$.

(4-bromophenyl)(tetrahydro-2H-pyran-4-yl)methanone (21):



R*f*: 0.25 (7/3 PE/EtOAc).

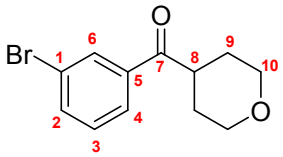
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.6 Hz, 2H, H^3), 7.63 (d, *J* = 8.6 Hz, 2H, H^2), 4.06 (ddd, *J* = 11.5, 4.3, 2.5 Hz, 2H, H^8), 3.56 (td, *J* = 11.7, 2.3 Hz, 2H, H^8), 3.45 (tt, *J* = 11.2, 3.9 Hz, 1H, H^6), 1.88 (dtd, *J* = 13.8, 11.4, 4.3 Hz, 2H, H^7), 1.81 – 1.74 (m, 3H, H^7).

^{13}C NMR (150 MHz, $CDCl_3$) δ 200.7 (C^5), 134.5 (C^4), 132.0 (C^2), 129.8 (C^3), 128.2 (C^4), 67.2 (C^8), 42.6 (C^6), 29.0 (C^7).

FTIR (ATR, neat): ν_{max}/cm^{-1} 2957,1848, 1682, 1586, 1398, 1275, 1209, 1071, 984, 825, 733.

HRMS (ESI+): m/z calcd for $C_{12}H_{14}O_2Br$: 269.0177, found 269.0164 $[M+H]^+$.

(3-bromophenyl)(tetrahydro-2H-pyran-4-yl)methanone (22):



R*f*: 0.16 (4/1 PE/EtOAc).

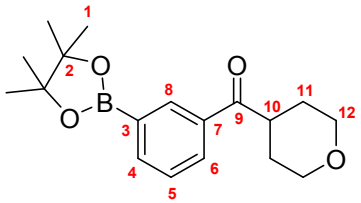
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.06 (t, *J* = 1.8 Hz, 1H, H^6), 7.86 (dt, *J* = 7.8, 1.3 Hz, 1H, H^4), 7.70 (dt, *J* = 7.9, 1.4 Hz, 1H, H^2), 7.36 (t, *J* = 7.8 Hz, 1H, H^3), 4.06 (ddd, *J* = 11.6, 4.3, 2.5 Hz, 2H, H^{10}), 3.56 (td, *J* = 11.6, 2.4 Hz, 2H, H^{10}), 3.44 (tt, *J* = 11.1, 3.9 Hz, 1H, H^8), 1.92 – 1.82 (m, 2H, H^9), 1.78 (ddq, *J* = 13.4, 4.5, 2.4 Hz, 2H, H^9).

^{13}C NMR (150 MHz, $CDCl_3$) δ 200.4 (C^7), 137.6 (C^5), 135.9 (C^2), 131.3 (C^6), 130.3 (C^3), 126.7 (C^4), 123.1 (C^1), 67.2 (C^{10}), 42.7 (C^8), 28.9 (C^9).

FTIR (ATR, neat): ν_{max}/cm^{-1} 2953, 2848, 1683, 1566, 1445, 1420, 1279, 1203, 1132, 986, 728.

HRMS (ESI+): m/z calcd for $C_{12}H_{14}O_2Br$: 269.0177, found 269.0164 $[M+H]^+$.

(tetrahydro-2H-pyran-4-yl)(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanone (23):



R*f*: 0.25 (2/1 PE/EtOAc).

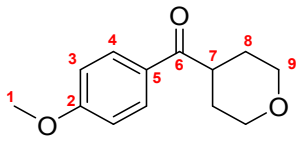
^{1}H NMR (600 MHz, $CDCl_3$) 8.32 (t, *J* = 1.4 Hz, 1H, H^8), 8.03 (dt, *J* = 7.8, 1.6 Hz, 1H, H^6), 7.99 (dt, *J* = 7.4, 1.3 Hz, 1H, H^4), 7.48 (t, *J* = 7.6 Hz, 1H, H^5), 4.05 (ddd, *J* = 11.5, 4.2, 2.5 Hz, 2H, H^{12}), 3.60 (dd, *J* = 11.5, 2.4 Hz, 2H, H^{12}), 3.57 (tt, *J* = 11.1, 3.8 Hz, 1H, H^{10}), 1.88 (dtd, *J* = 13.7, 11.3, 4.3 Hz, 2H, H^{11}), 1.78 (ddd, *J* = 13.4, 4.3, 2.1 Hz, 2H, H^{11}), 1.37 (s, 12H, H^1).

^{13}C NMR (150 MHz, $CDCl_3$) δ 202.2 (C^9), 139.3 (C^4), 135.4 (C^7), 134.3 (C^8), 131.0 (C^6), 128.2 (C^5), 84.2 (C^2), 67.2 (C^{12}), 42.4 (C^{10}), 29.0 (C^{11}), 24.9 (C^1).

FTIR (ATR, neat): ν_{max}/cm^{-1} 2977, 2852, 1680, 1600, 1355, 1322, 1271, 1205, 1141, 963, 848, 700.

HRMS (ESI+): m/z calcd for $C_{18}H_{26}O_4B$: 317.1924, found 3317.1914 $[M+H]^+$.

(4-methoxyphenyl)(tetrahydro-2H-pyran-4-yl)methanone (25):



R*f*: 0.19 (4/1 PE/EtOAc).

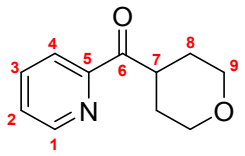
^{1}H NMR (600 MHz, $CDCl_3$)) δ 7.95 (d, *J* = 8.9 Hz, 2H, H^4), 6.96 (d, *J* = 8.9 Hz, 2H, H^3), 4.06 (ddd, *J* = 11.5, 4.2, 2.4 Hz, 2H, H^9), 3.88 (s, 3H, H^1), 3.56 (td, *J* = 11.7, 2.4 Hz, 2H, H^9), 3.46 (tt, *J* = 11.2, 3.8 Hz, 1H, H^7), 1.90 (m, 2H, H^8), 1.77 (m, 2H, H^8).

^{13}C NMR (150 MHz, $CDCl_3$) δ 200.3 (C^6), 163.4 (C^2), 130.5 (C^4), 128.7 (C^5), 113.9 (C^3), 67.3 (C^9), 55.5 (C^1), 42.2 (C^7), 29.2 (C^8).

FTIR (ATR, neat): 2958, 2943, 2854, 1655, 1601, 1574, 1513, 1423, 1317, 1287, 1259, 1185, 1129, 1085, 1014, 992, 848.

HRMS (ESI+): m/z calcd for $C_{13}H_{17}O_3$: 221.1171, found 221.1178 $[M+H]^+$.

pyridin-2-yl(tetrahydro-2H-pyran-4-yl)methanone (PD-061 25):



R*f*: 0.22 (4/1 PE/EtOAc).

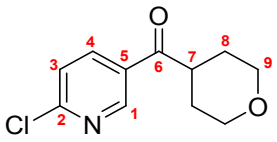
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.7 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 1H, H^1), 8.1 (dt, *J* = 7.9, 1.1 Hz, 1H, H^4), 7.9 (td, *J* = 7.7, 1.7 Hz, 1H, H^3), 7.5 (ddd, *J* = 7.6, 4.7, 1.2 Hz, 1H, H^2), 4.2 – 4.1 (m, 1H, H^7), 4.1 (dt, *J* = 11.4, 3.6 Hz, 2H, H^9), 3.7 – 3.6 (m, 2H, H^9), 1.9 – 1.8 (m, 4H, H^8).

^{13}C NMR (150 MHz, $CDCl_3$) δ 202.9 (C^6), 152.5 (C^5), 148.8 (C^1), 137.0 (C^3), 127.1 (C^2), 122.6 (C^4), 67.4 (C^9), 41.3 (C^7), 28.6 (C^9).

FTIR (ATR, neat): ν_{max}/cm^{-1} 2953, 2848, 1695, 1584, 1444, 1372, 1298, 1239, 1113, 989, 825, 745.

HRMS (ESI+): m/z calcd for $C_{11}H_{14}O_2N$: 192.1019 found 192.1013 $[M+H]^+$.

(6-chloropyridin-3-yl)(tetrahydro-2H-pyran-4-yl)methanone (26):



R*f*: 0.25 (1/1 PE/EtOAc).

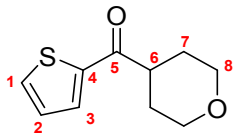
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.9 (d, *J* = 2.4 Hz, 1H, H^1), 8.2 (dd, *J* = 8.3, 2.5 Hz, 1H, H^4), 7.5 (d, *J* = 8.3 Hz, 1H, H^3), 4.1 (ddd, *J* = 11.6, 4.2, 2.5 Hz, 2H, H^9), 3.6 (td, *J* = 11.6, 2.3 Hz, 2H, H^9), 3.4 (tt, *J* = 11.1, 3.9 Hz, 1H, H^7), 1.9 – 1.8 (m, 2H, H^8), 1.8 (ddq, *J* = 13.5, 4.6, 2.4 Hz, 2H, H^8).

^{13}C NMR (150 MHz, $CDCl_3$) δ 199.3 (C^6), 155.6 (C^2), 149.8 (C^1), 138.4 (C^4), 129.9 (, 124.8, 67.0, 43.1, 28.7.

FTIR (ATR, neat): ν_{max}/cm^{-1} 2955, 2851, 1684, 1578, 1447, 1359, 1294, 1216, 1109, 986, 830, 754.

HRMS (ESI+): m/z calcd for $C_{11}H_{13}O_2N^{35}Cl$: 226.0629, found 226.0622 $[M+H]^+$.

(tetrahydro-2H-pyran-4-yl)(thiophen-2-yl)methanone (27):



R*f*: 0.20 (4/1 PE/EtOAc).

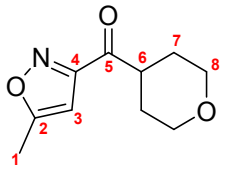
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.75 (dd, *J* = 3.8, 1.1 Hz, 1H, H^3), 7.66 (dd, *J* = 5.0, 1.1 Hz, 1H, H^1), 7.2 (dd, *J* = 5.0, 3.8 Hz, 1H, H^2), 4.1 (ddd, *J* = 11.6, 4.4, 2.3 Hz, 2H, H^8), 3.5 (td, *J* = 11.6, 2.3 Hz, 2H, H^8), 3.4 (tt, *J* = 11.3, 3.9 Hz, 1H, H^6), 2.0 (dtd, *J* = 13.5, 11.5, 4.4 Hz, 2H, H^7), 1.8 (ddq, *J* = 13.5, 4.4, 2.3 Hz, 2H, H^7).

^{13}C NMR (150 MHz, $CDCl_3$) δ 194.6 (C_5), 143.2 (C^4), 133.8 (C^1), 131.6 (C^3), 128.1 (C^2), 67.2 (C^8), 44.3 (C^6), 29.2 (C^7).

FTIR (ATR, neat): ν_{max}/cm^{-1} 2960, 2841, 1647, 1518, 1449, 1413, 1215, 1129, 1087, 729

HRMS (ESI+): m/z calcd for $C_{10}H_{13}O_2S$: 197.0636, found 197.0630 $[M+H]^+$.

(5-methylisoxazol-3-yl)(tetrahydro-2H-pyran-4-yl)methanone (28):



R*f*: 0.19 (4/1 PE/EtOAc).

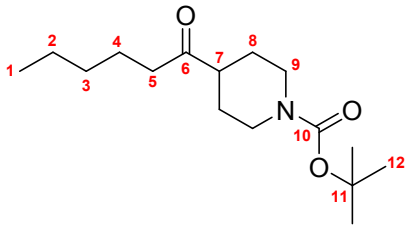
^{1}H NMR (600 MHz, $CDCl_3$) δ 6.37 (d, *J* = 1.0 Hz, 1H, H^3), 4.04 (ddd, *J* = 11.6, 4.2, 2.6 Hz, 2H, H^8), 3.63 – 3.56 (m, 1H, H^6), 3.54 (td, *J* = 11.4, 3.1 Hz, 2H, H^8), 2.49 (d, *J* = 0.9 Hz, 3H, H^1), 1.91 – 1.79 (m, 4H, H^7).

^{13}C NMR (150 MHz, $CDCl_3$) δ 196.0 (C^5), 171.1 (C^2), 160.9 (C^4), 100.6 (C^3), 67.1 (C^8), 44.5 (C^6), 28.3 (C^7), 12.3 (C^1).

FTIR (ATR, neat): ν_{max}/cm^{-1} 2955, 2847, 1697, 1599, 1452, 1276, 1241, 1154, 1125, 1089, 1022, 917, 808, 738.

HRMS (ESI+): m/z calcd for $C_{10}H_{14}O_3N$: 196.0968, found 196.0963 $[M+H]^+$.

tert-butyl 4-hexanoylpiperidine-1-carboxylate (29):



R*f*: 0.16 (98/2 CH_2Cl_2/EtOAc).

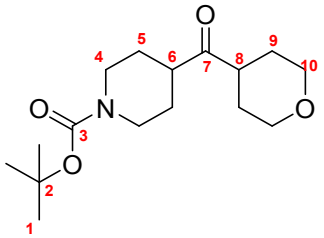
^{1}H NMR (600 MHz, $CDCl_3$) δ 4.09 (br s, 2H, H^9), 2.75 (br s, 2H, H^9), 2.48 – 2.43 (m, 1H, H^7), 2.42 (t, *J* = 7.4 Hz, 2H, H^5), 1.85 – 1.70 (br s, 2H, H^8), 1.53 (m, 2H, H^4), 1.52 – 1.47 (m, 2H, H^8), 1.44 (s, 9H, H^{12}), 1.34 – 1.26 (m, 2H, H^2), 1.26 – 1.20 (m, 2H, H^3), 0.87 (t, *J* = 7.2 Hz, 3H, H^1).

^{13}C NMR (150 MHz, $CDCl_3$) ^{13}C NMR (151 MHz, $CDCl_3$) δ 212.4 (C^6), 154.6 (C^{10}), 79.5 (C^{11}), 48.5 (C^7), 43.4 (br s, C^9) 40.5 (C^5), 31.4 (C^3), 28.4 (C^{12}), 27.5 (C^8), 23.3 (C^2), 22.4 (C^4), 13.9 (C^1).

FTIR (ATR, neat): 2933, 2860, 1691, 1449, 1421, 1366, 1235, 1168, 1136, 1016, 908, 866, 770.

HRMS (ESI+): m/z calcd for $C_{16}H_{29}O_3N^{23}Na$: 306.2040, found 306.2037 $[M+Na]^+$

tert-butyl 4-(tetrahydro-2H-pyran-4-carbonyl)piperidine-1-carboxylate (30):



R*f*: 0.15 (1/2 PE/EtOAc).

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.1 (s, 2H, H^4), 4.0 (dt, *J* = 11.5, 3.4 Hz, 2H, H^{10}), 3.4 (td, *J* = 11.4, 3.4 Hz, 2H, H^{10}), 2.8 (s, 2H, H^4), 2.7 (td, *J* = 10.3, 5.3 Hz, 1H, H^8), 2.6 (tt, *J* = 11.4, 3.7 Hz, 1H, H^6), 1.8 – 1.7 (m, 2H, H^5), 1.7 – 1.7 (m, 4H, H^9), 1.6 – 1.5 (m, 2H, H^5), 1.5 (s, 9H, H^1).

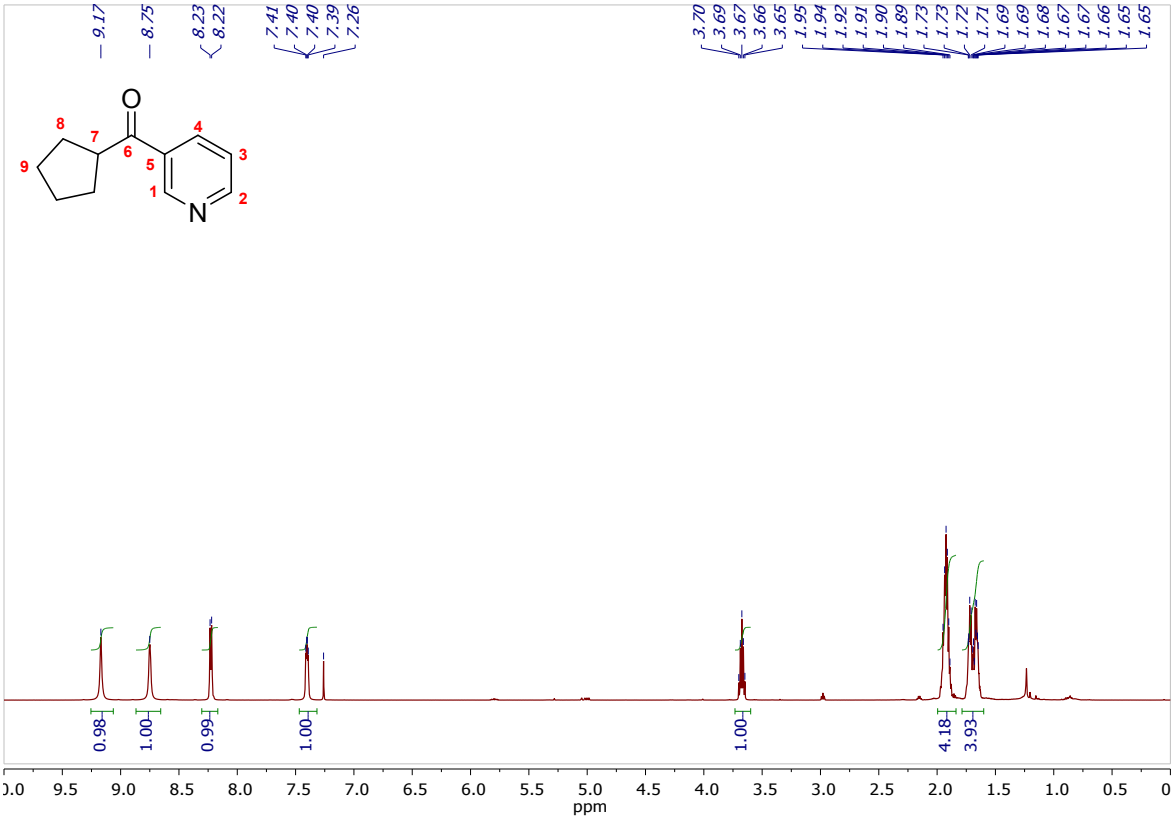
^{13}C NMR (150 MHz, $CDCl_3$) δ 213.1 (C^7), 154.6 (C^3), 79.6 (C^2), 67.2 (C^{10}), 46.5 (C^6), 45.8 (C^8), 43.1 (C^4 observed by HSQC), 28.4 (C^1), 28.2 (C^9), 27.6 (C^5).

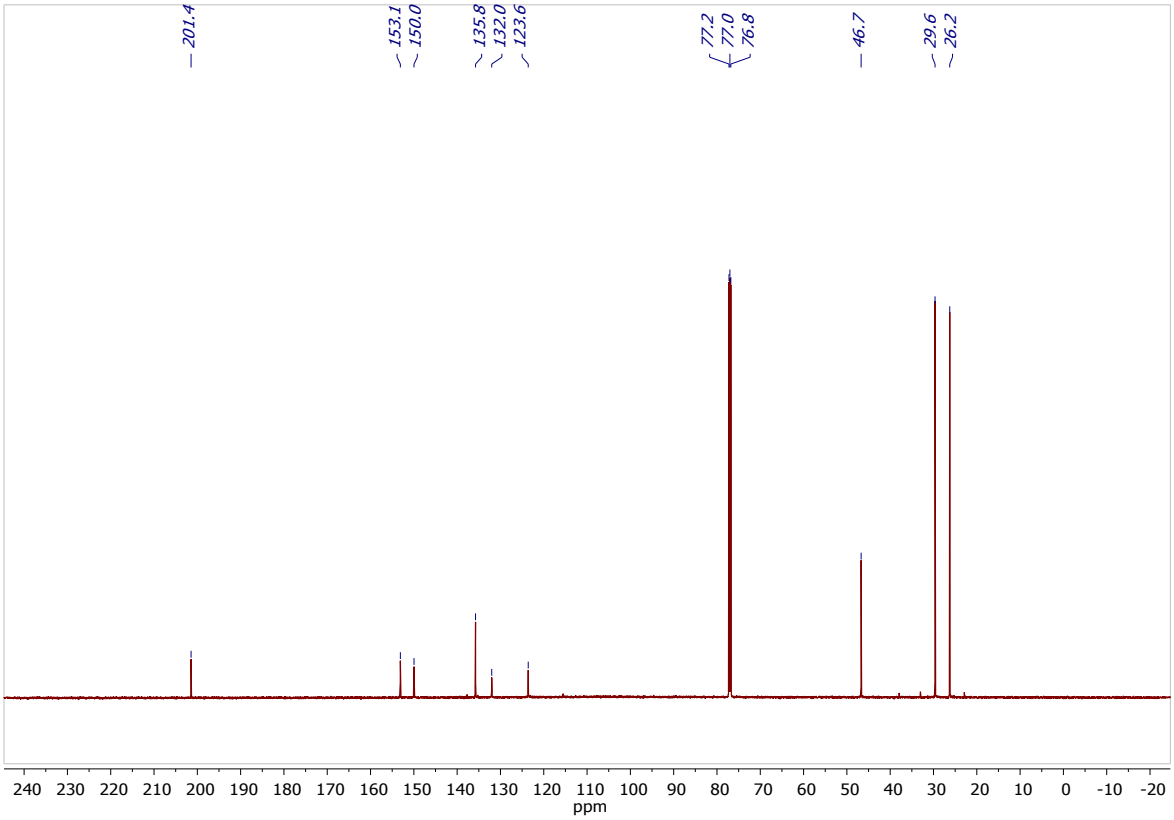
FTIR (ATR, neat): ν_{max}/cm^{-1} 2955, 2852, 1691, 1424, 1366, 1279, 1235, 1171, 1132, 1017, 866, 769.

HRMS (ESI+): m/z calcd for $C_{16}H_{28}O_4N$: 298.2013, found 298.2005 $[M+H]^+$.

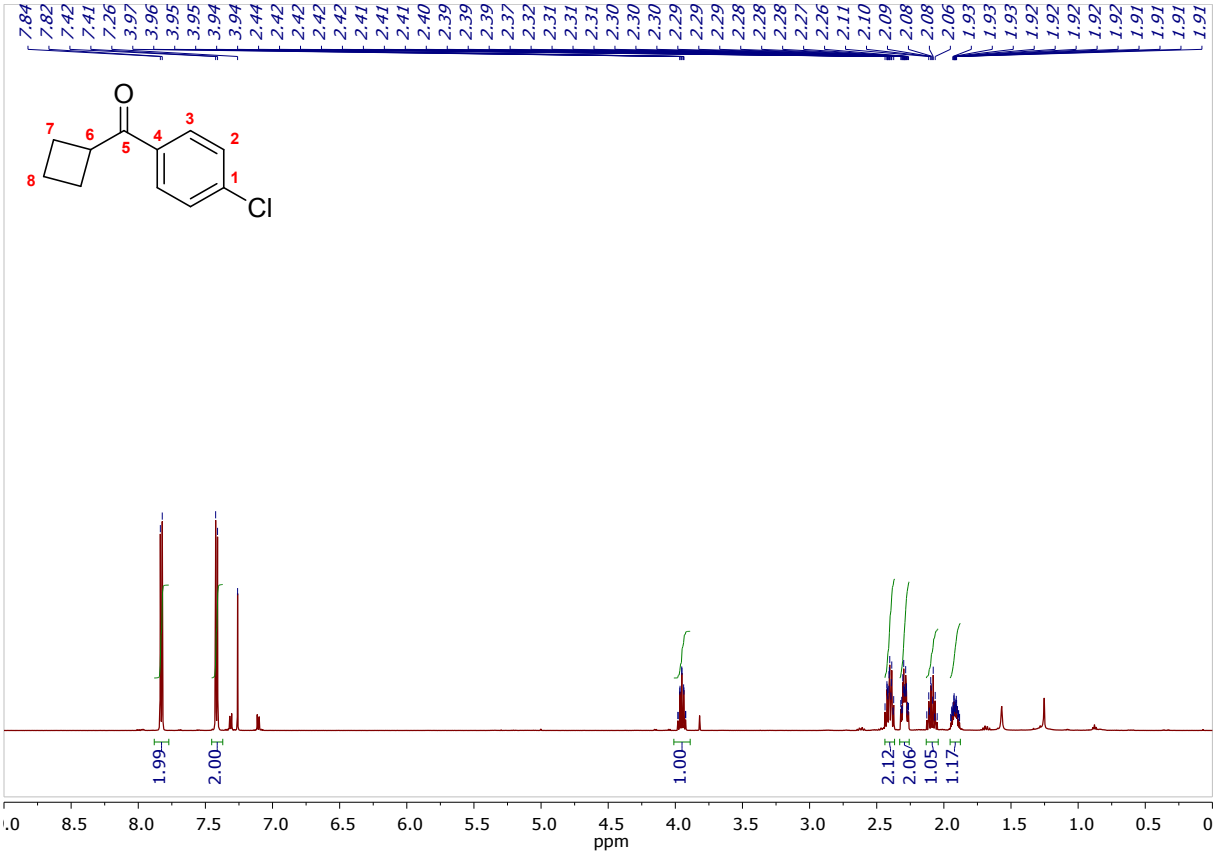
5 NMR Spectra

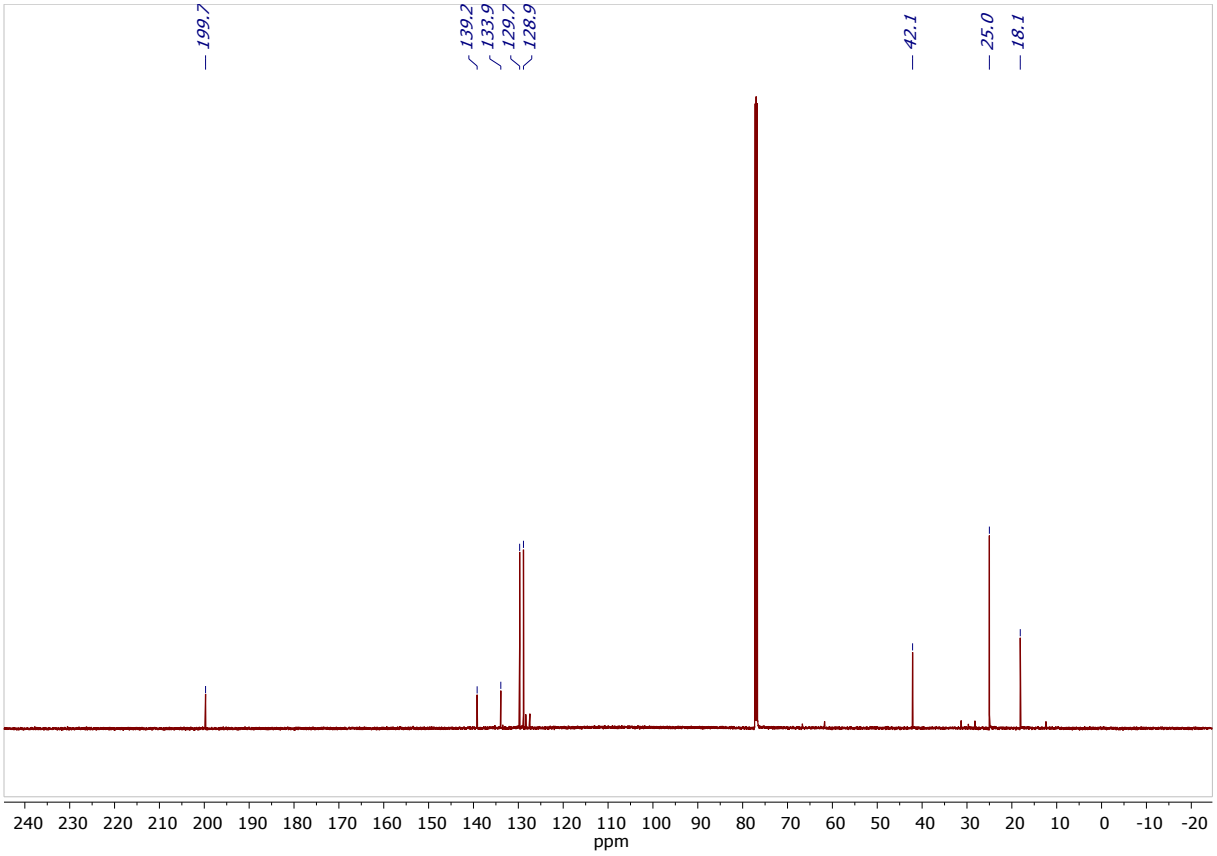
cyclopentyl(pyridin-3-yl)methanone (1):



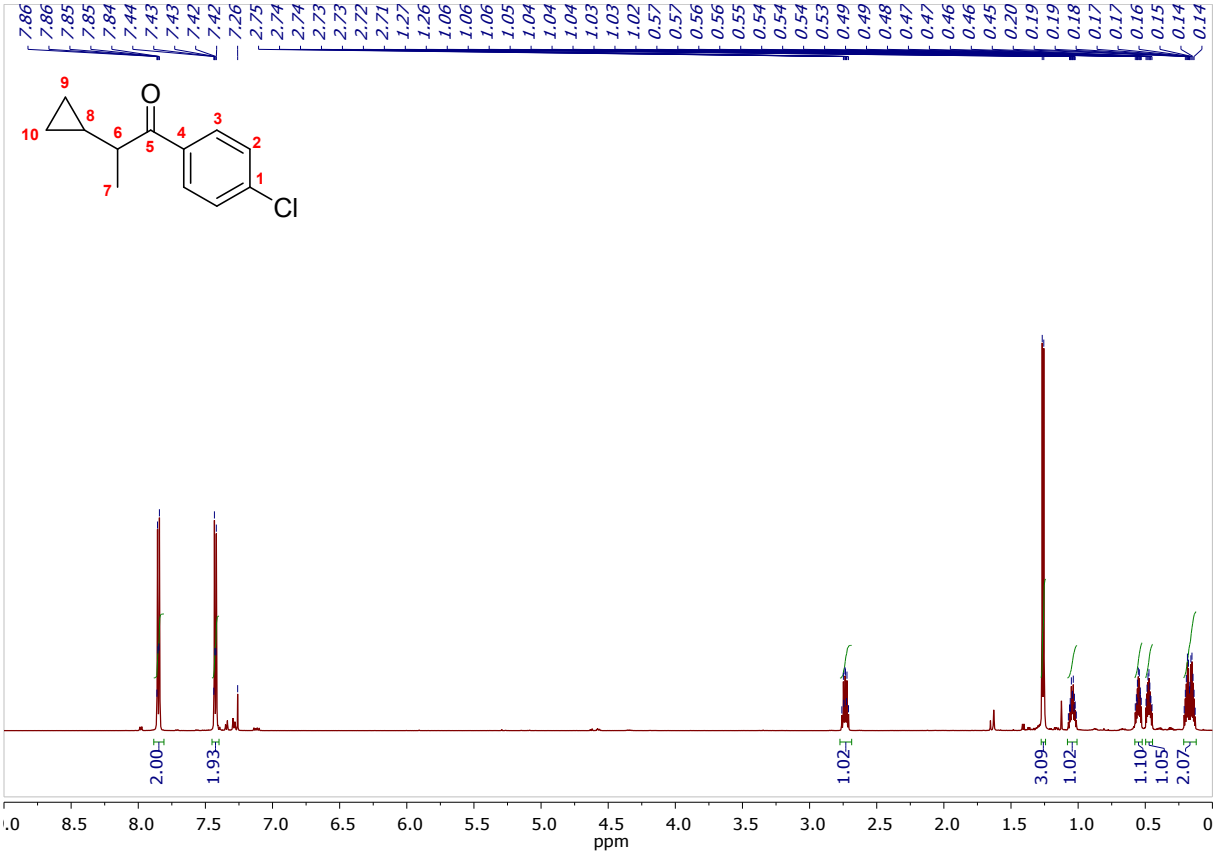


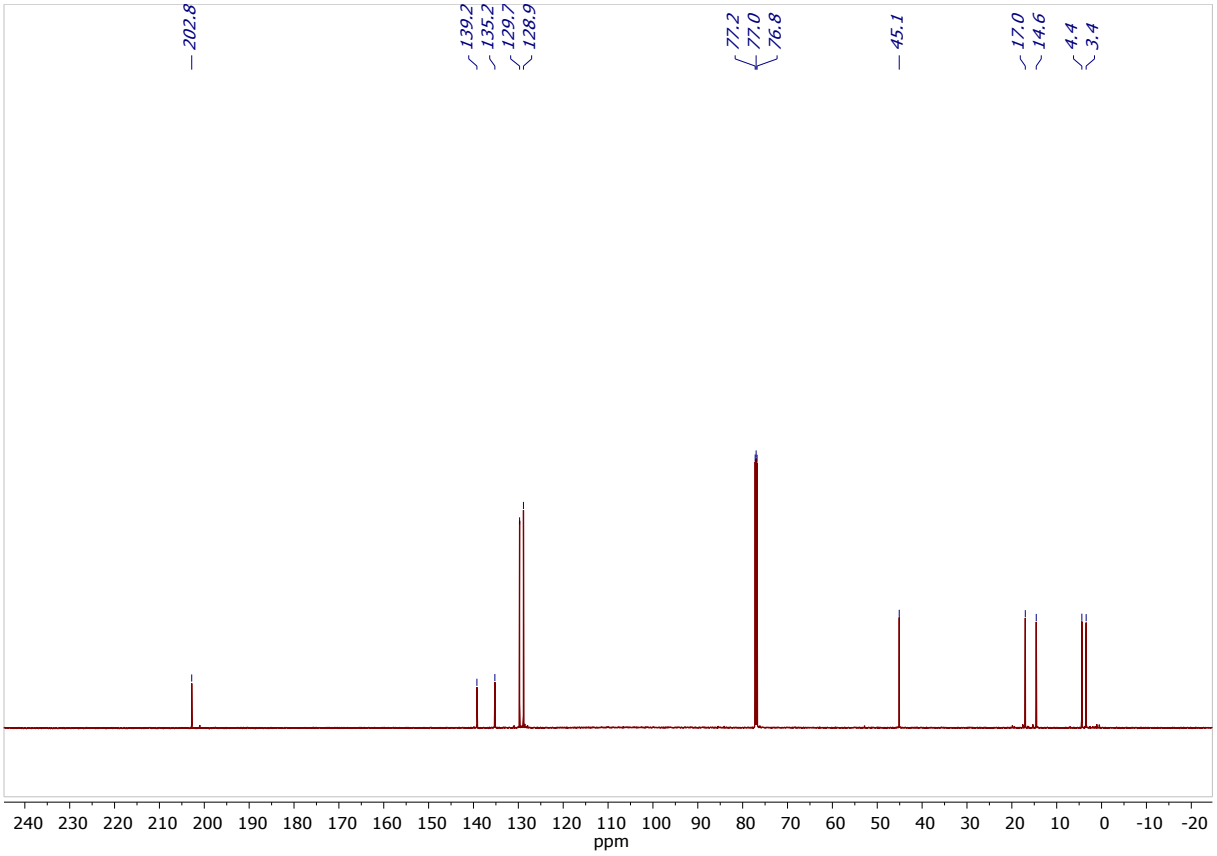
(4-chlorophenyl)(cyclobutyl)methanone (2):



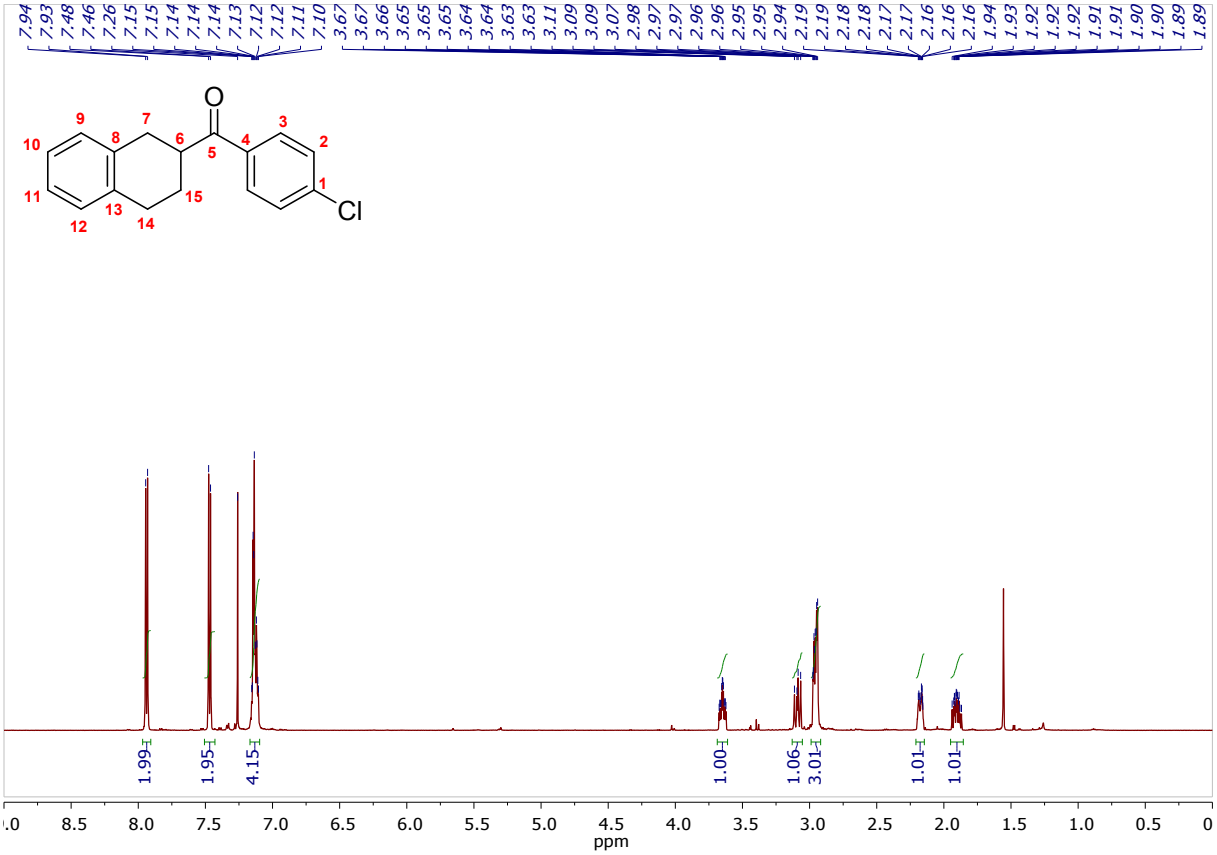


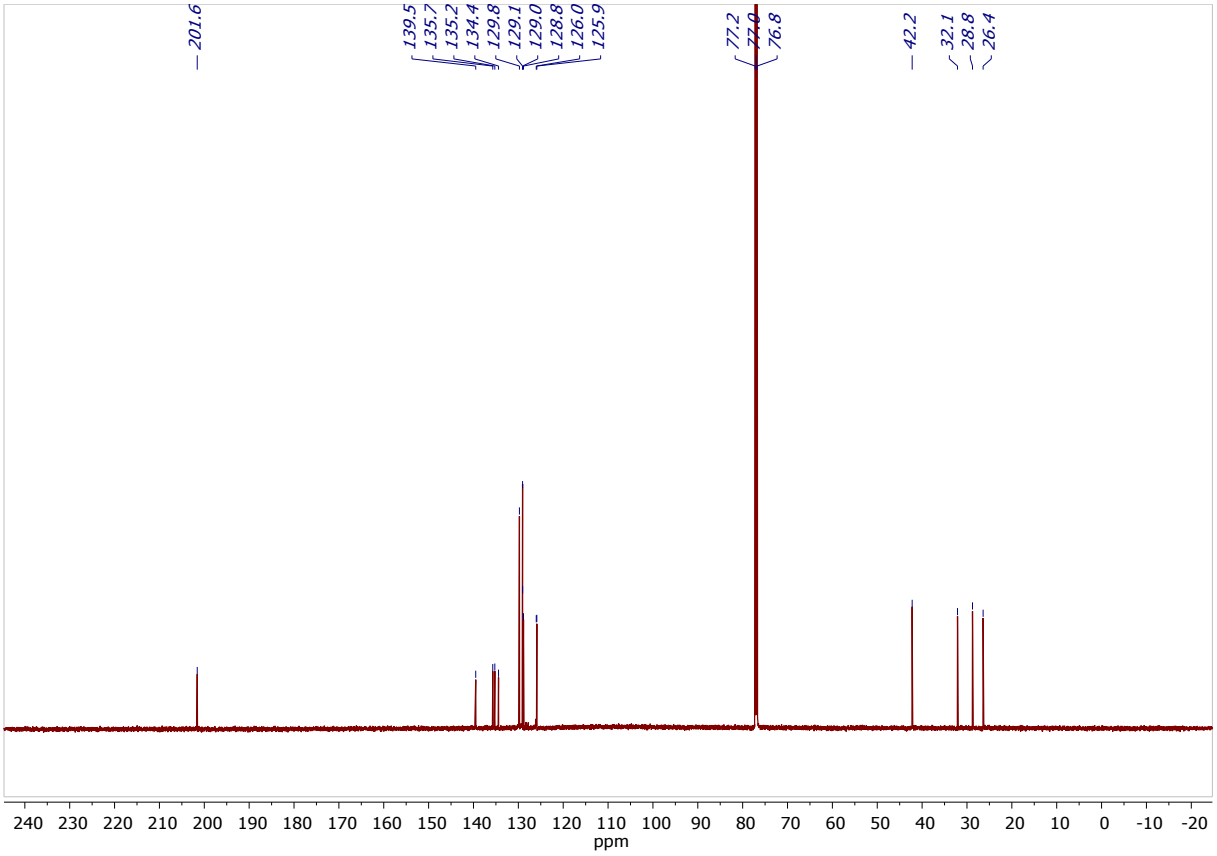
1-(4-chlorophenyl)-2-cyclopropylpropan-1-one (3):



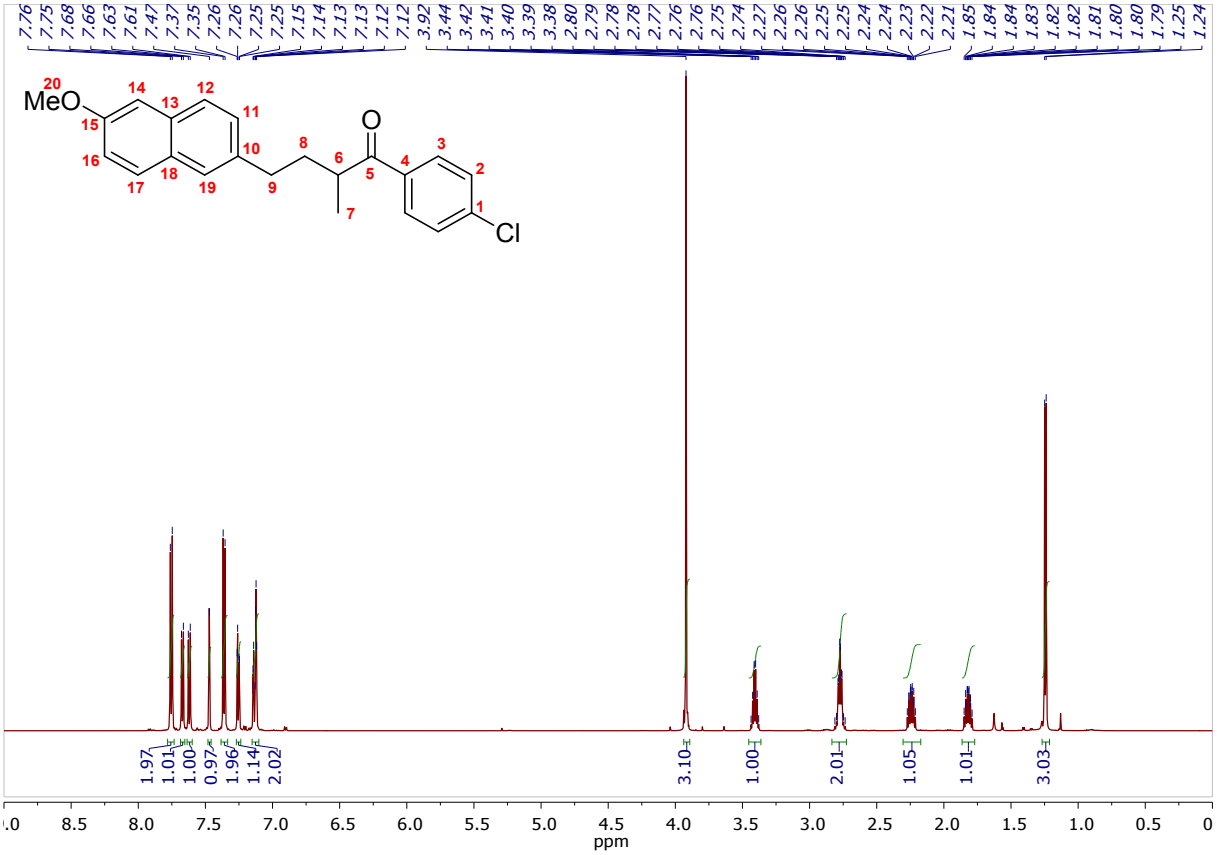


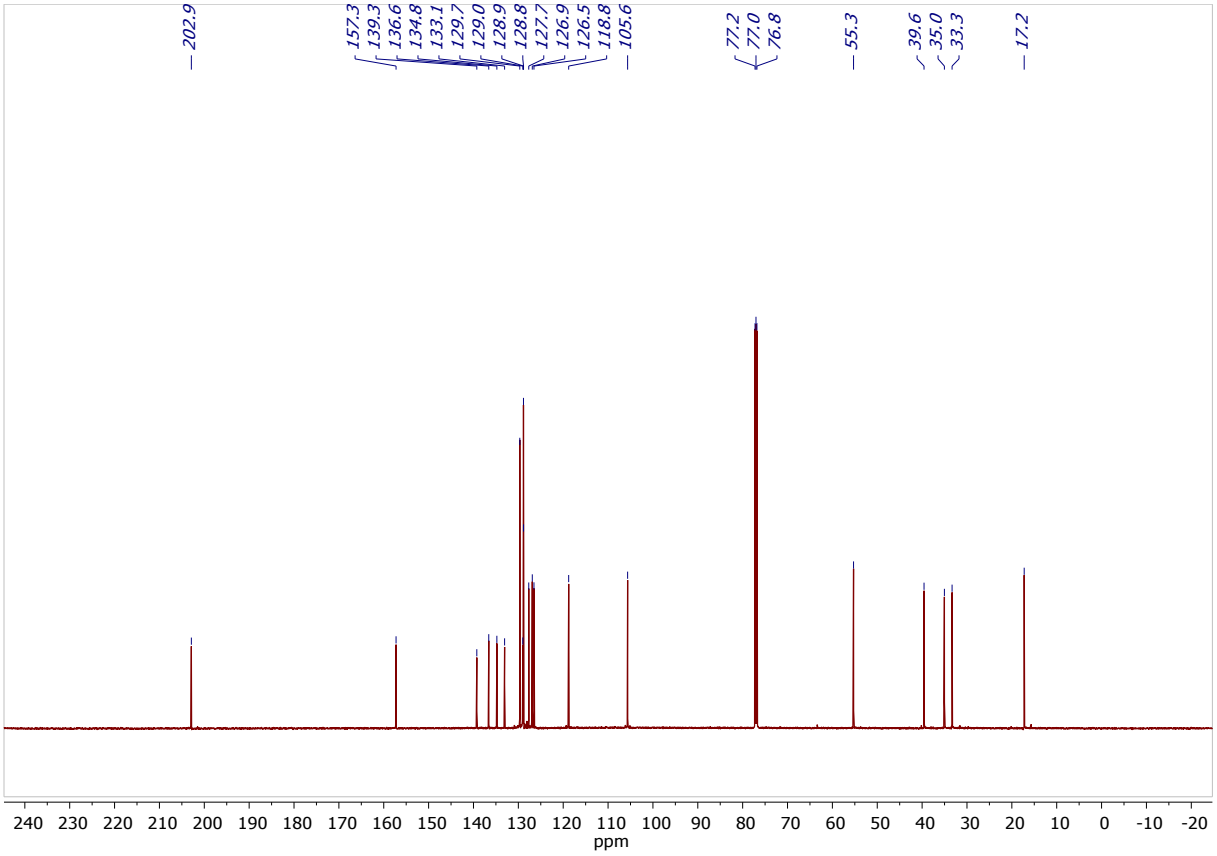
(4-chlorophenyl)(1,2,3,4-tetrahydronaphthalen-2-yl)methanone (4):



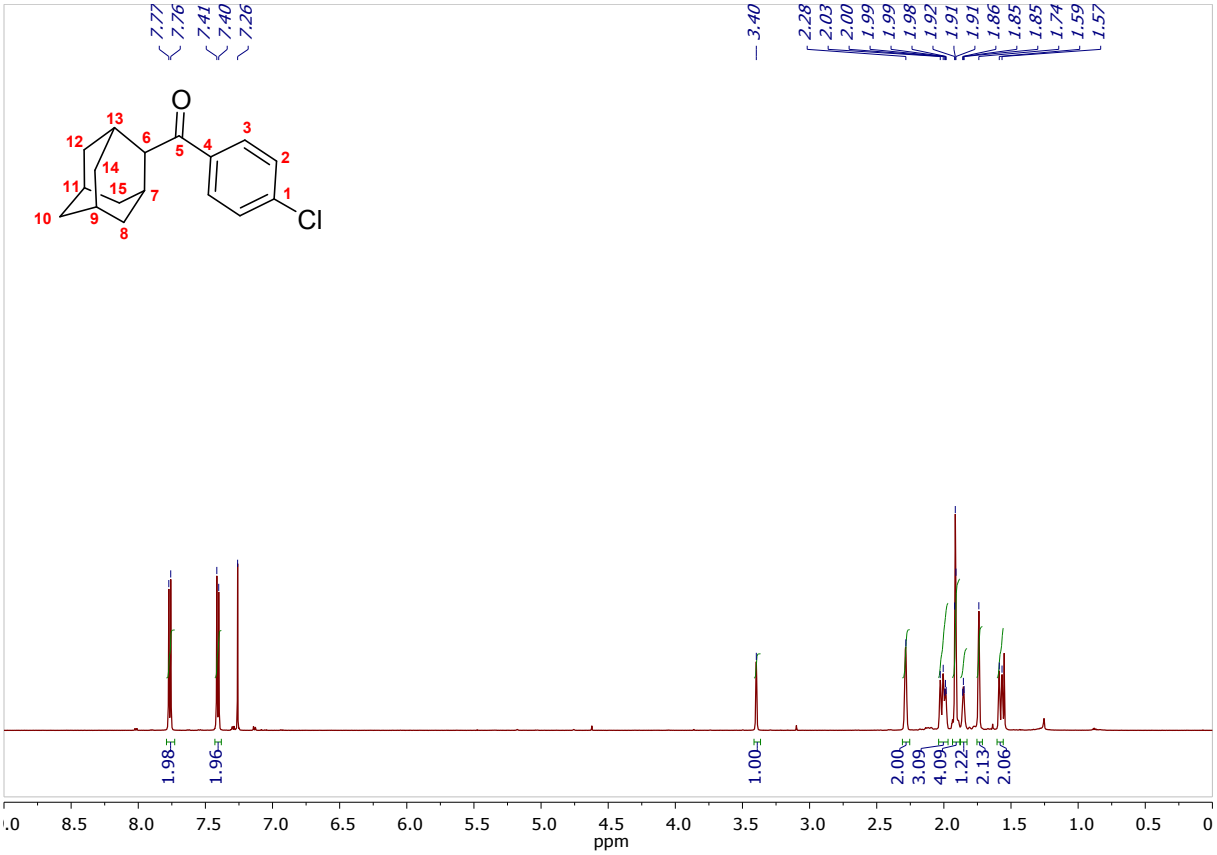


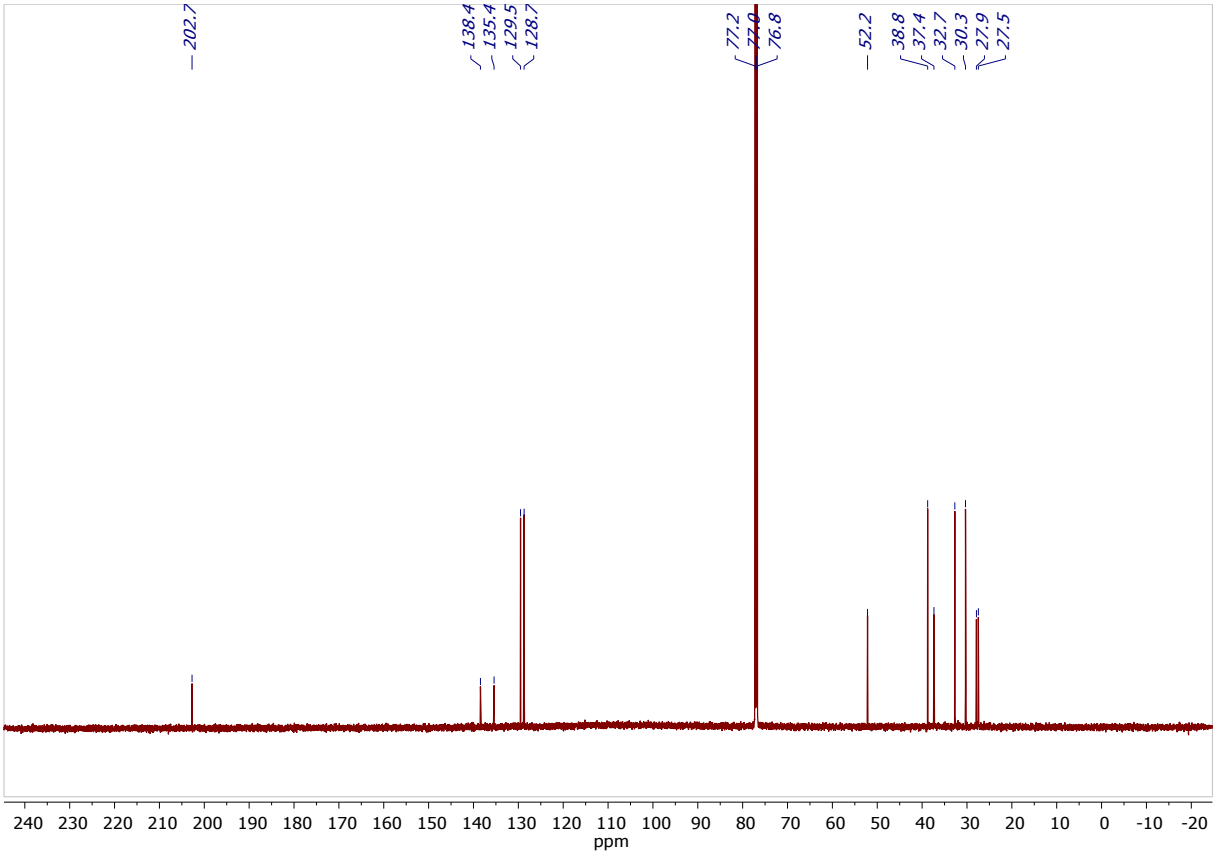
1-(4-chlorophenyl)-4-(6-methoxynaphthalen-2-yl)-2-methylbutan-1-one (5):



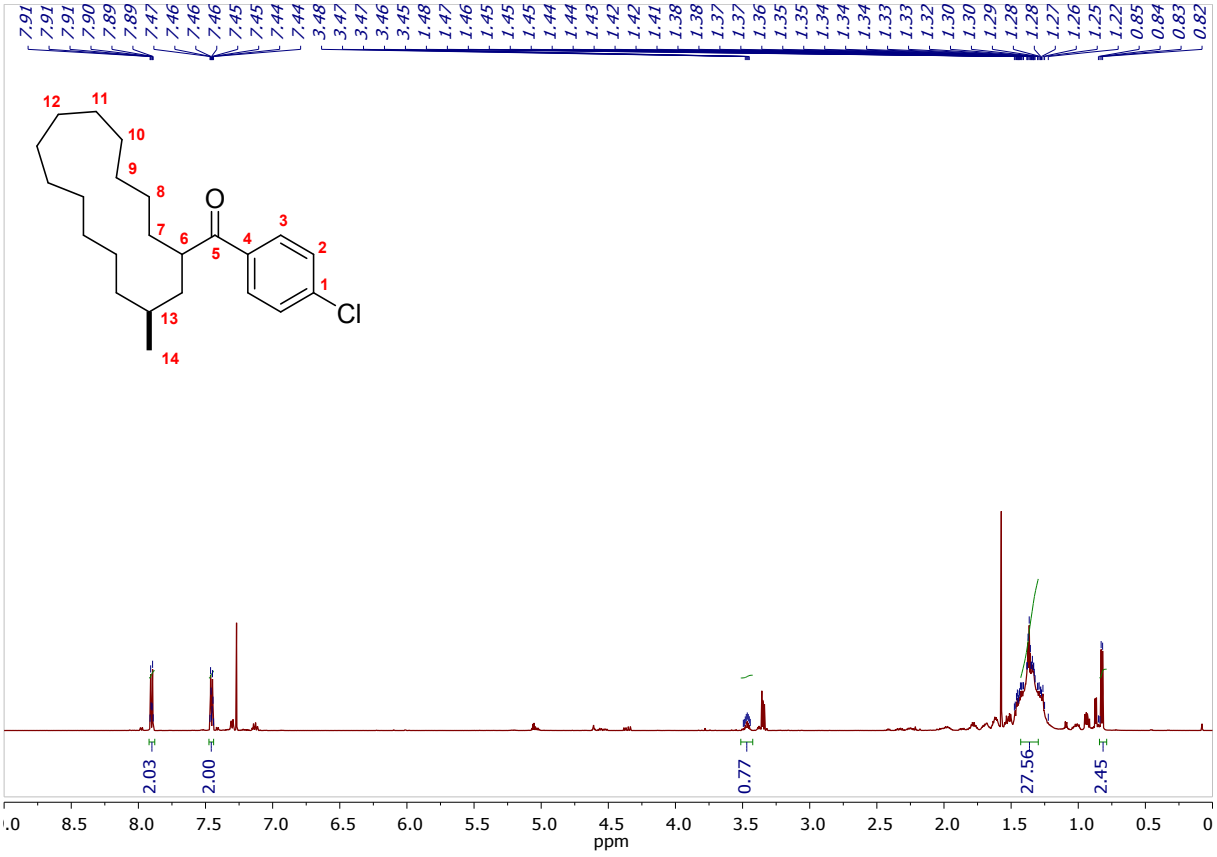


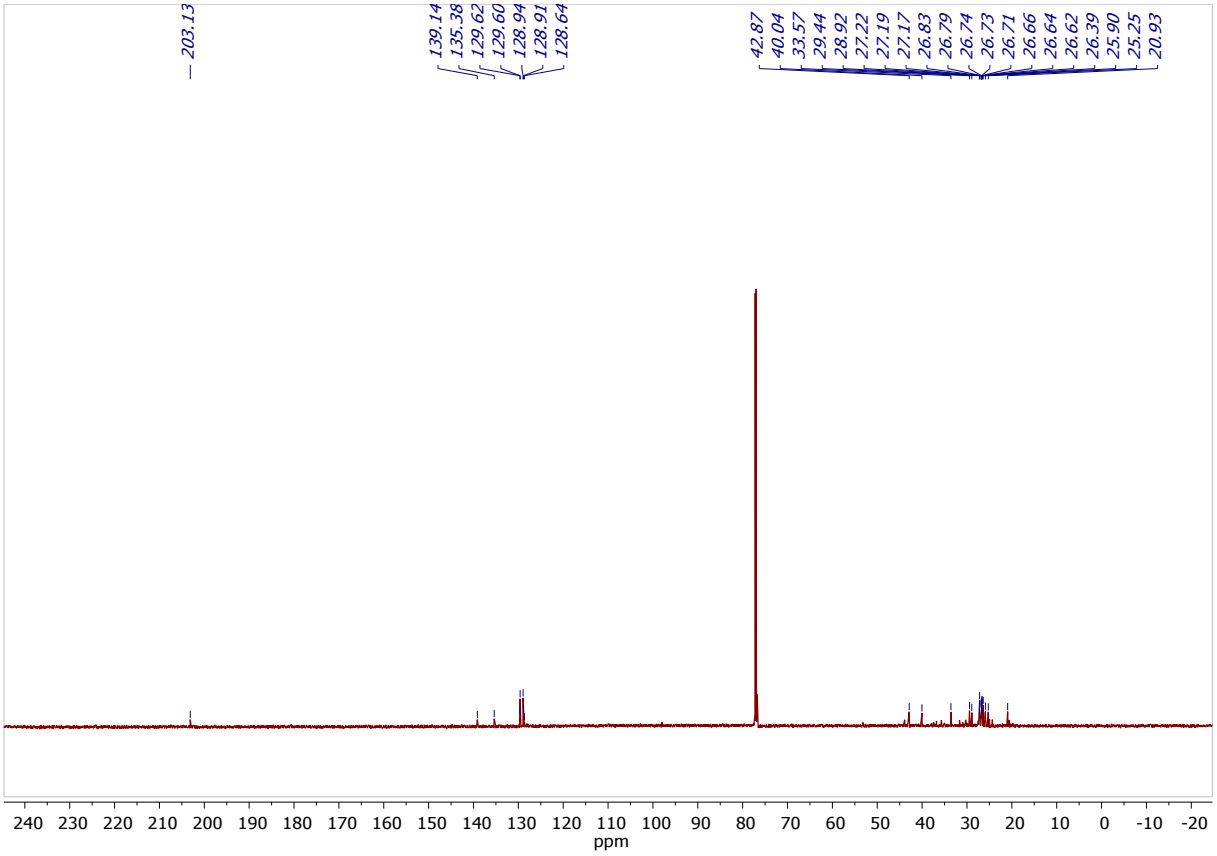
adamantan-2-yl)(4-chlorophenyl)methanone (6):



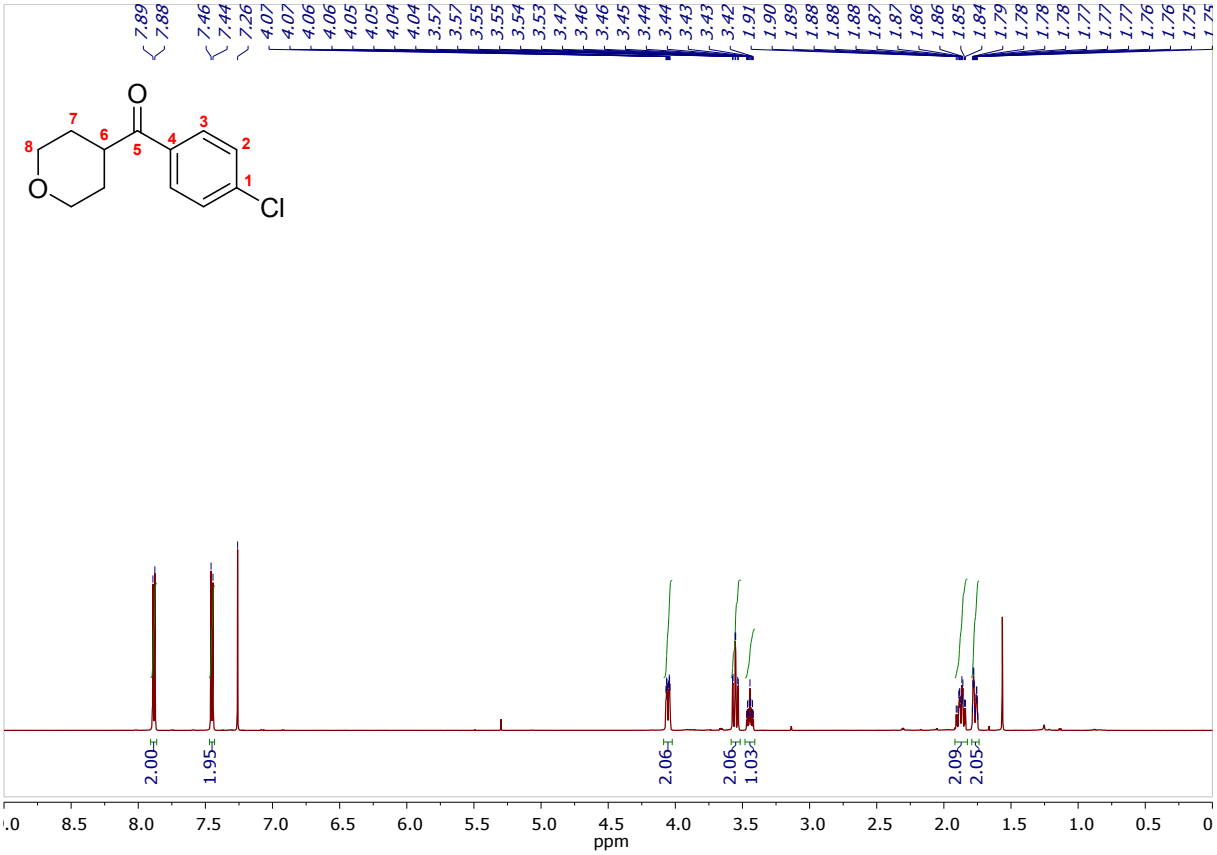


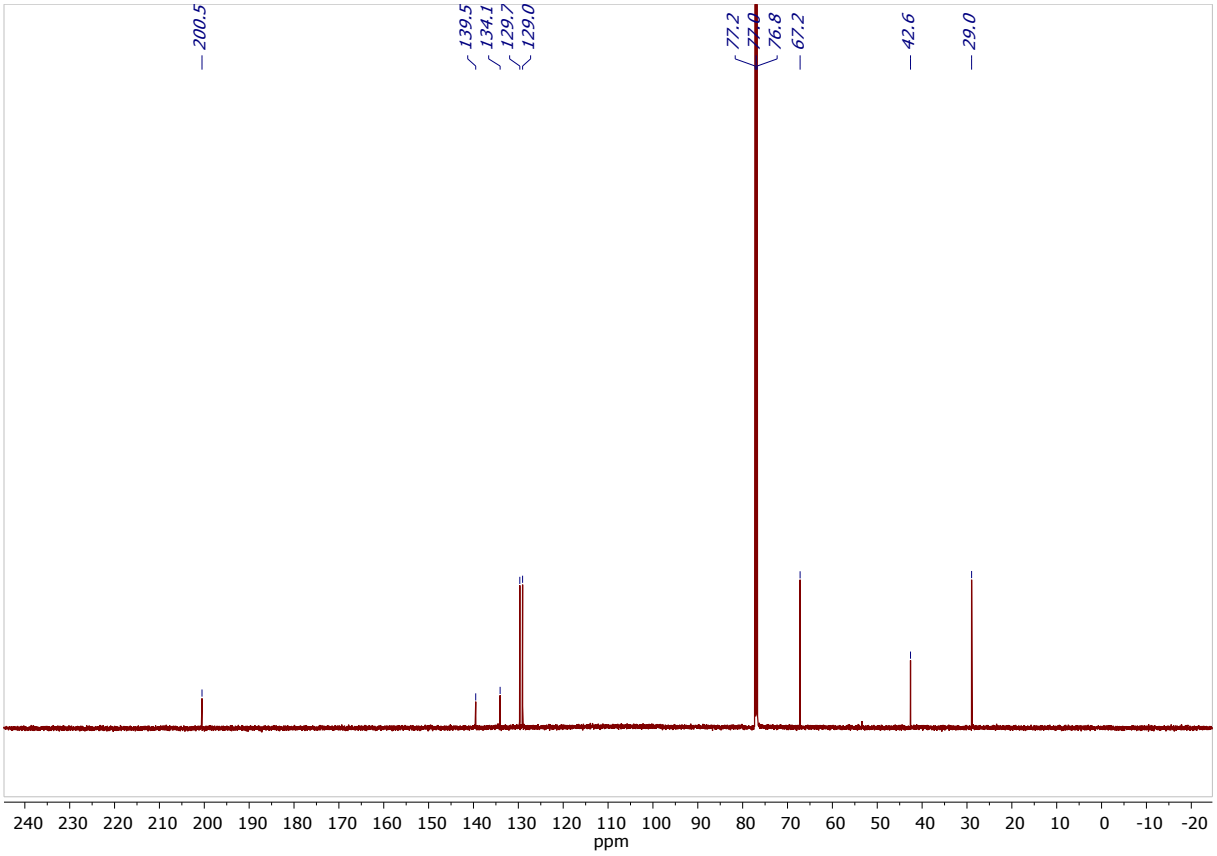
(4-chlorophenyl)((3S)-3-methylcyclopentadecyl)methanone (7)



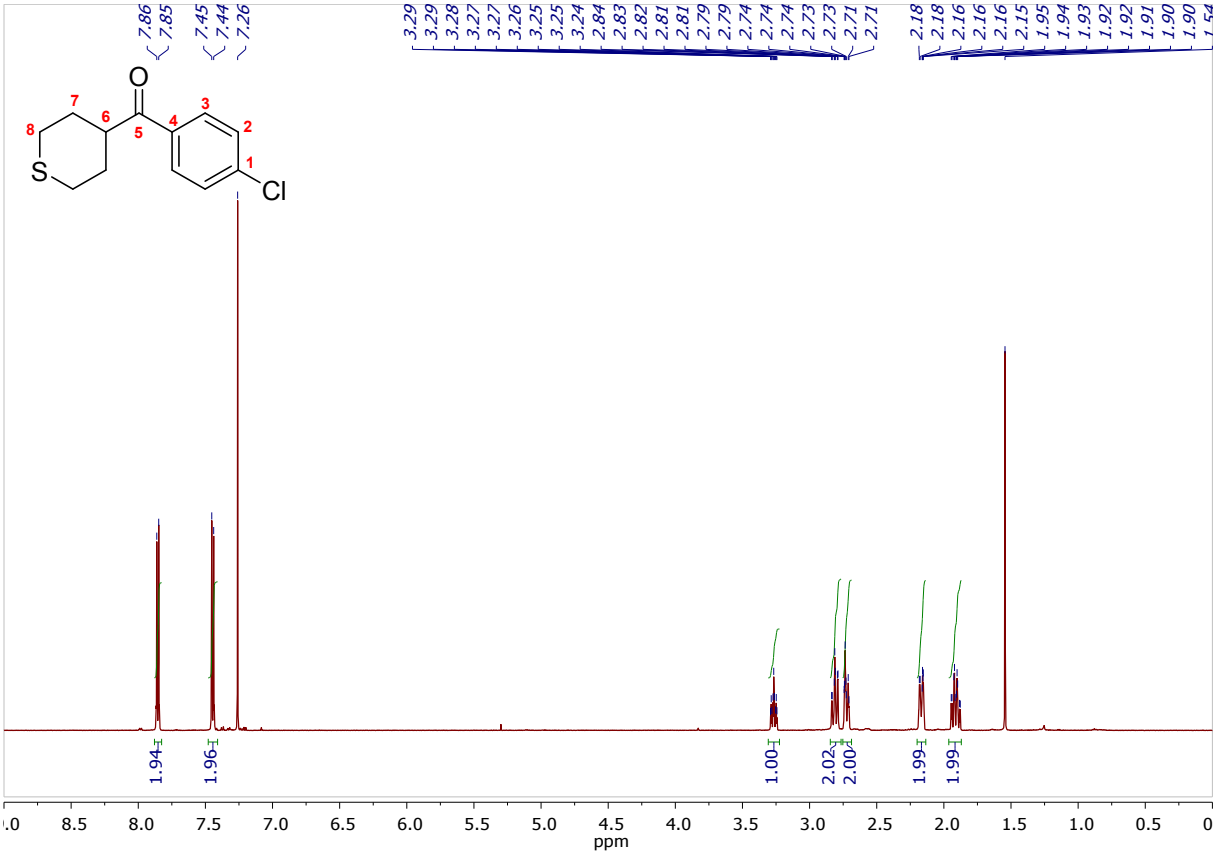


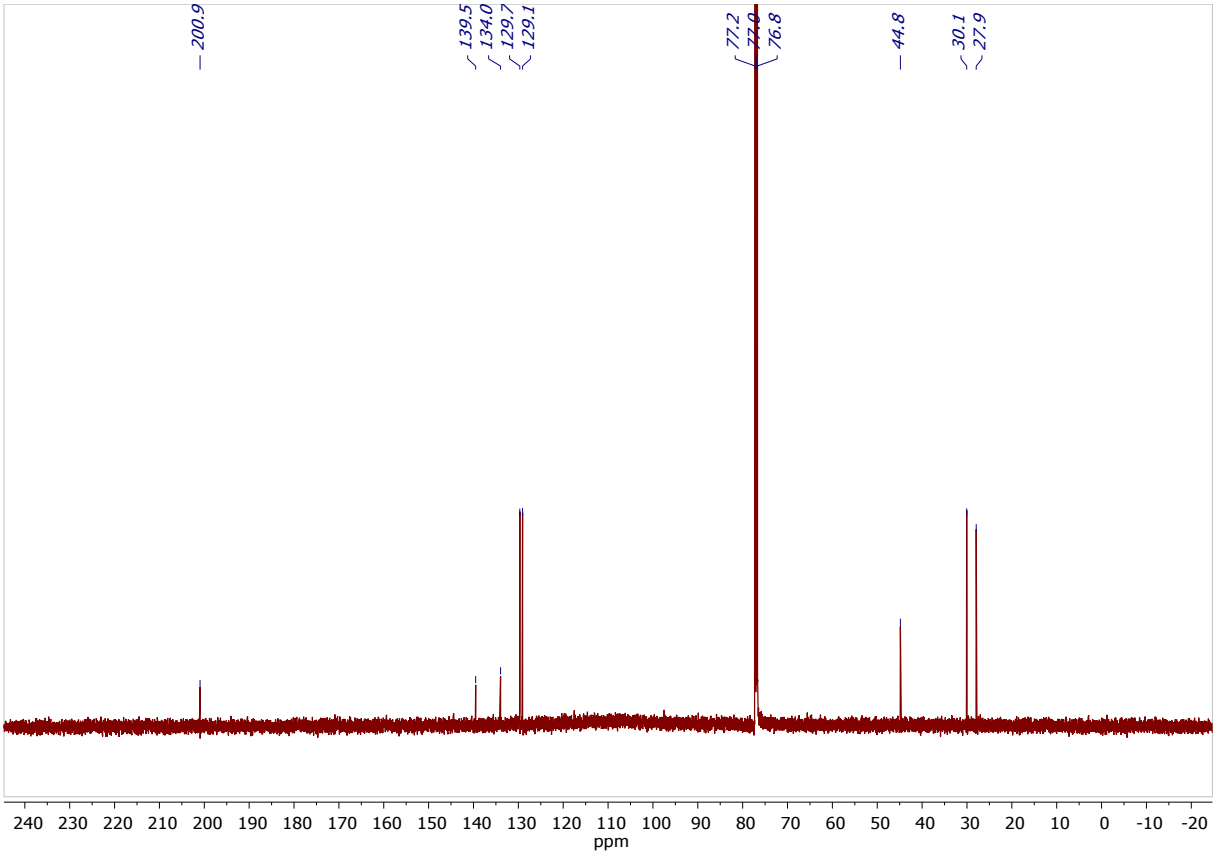
(4-chlorophenyl)(tetrahydro-2H-pyran-4-yl)methanone (8):



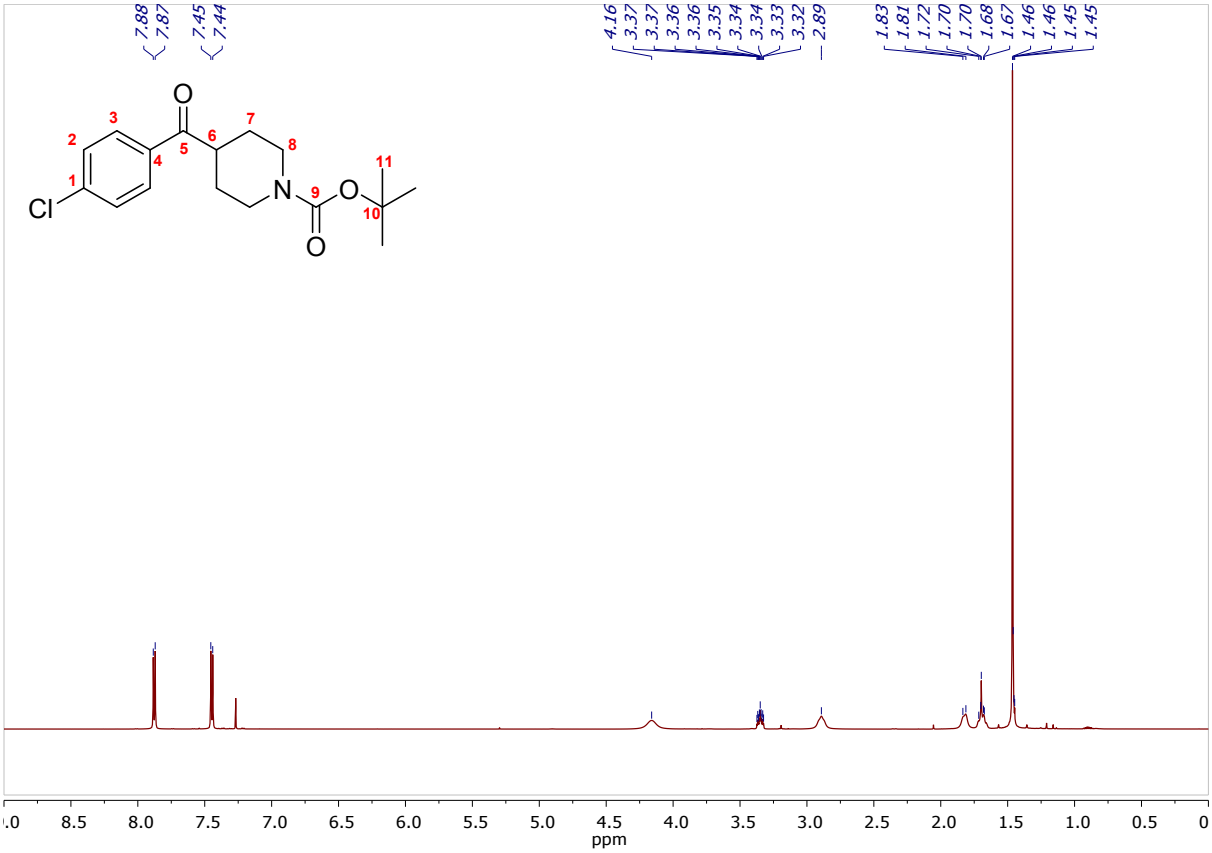


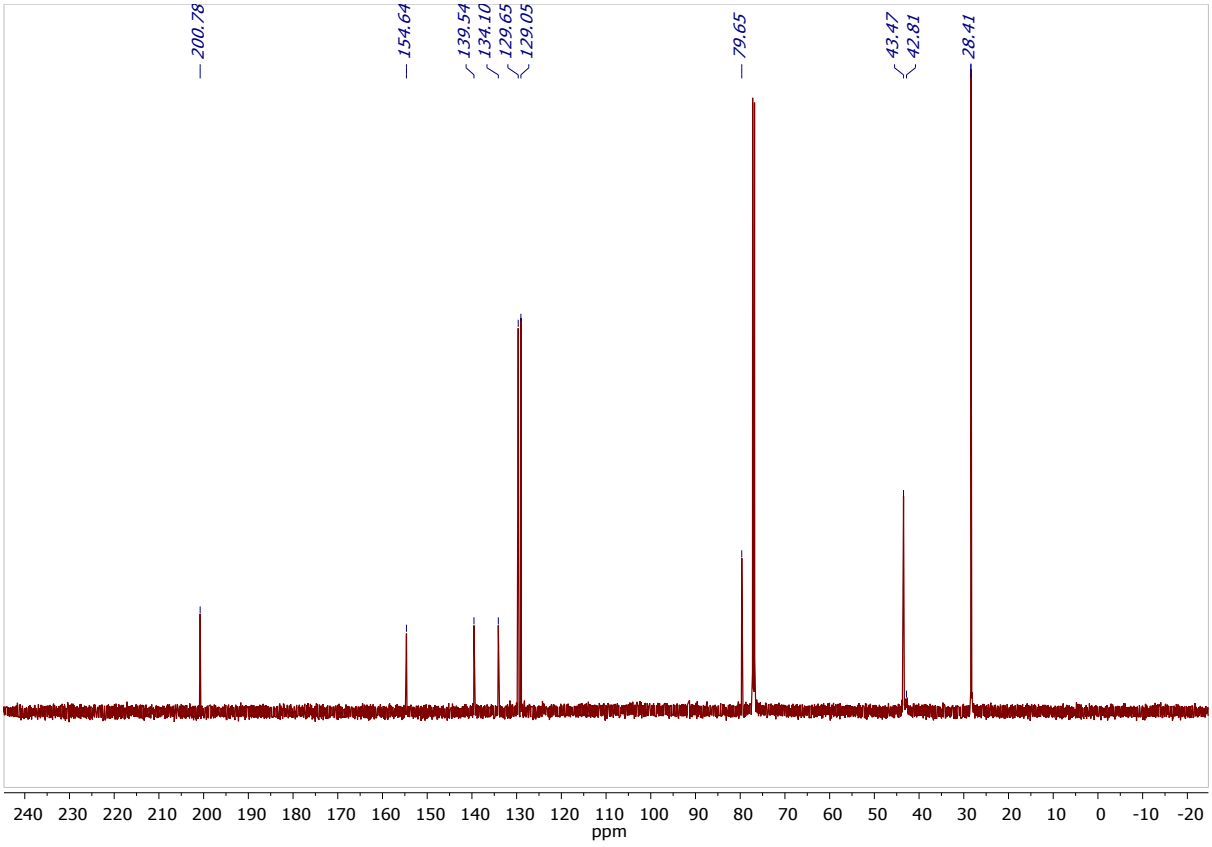
(4-chlorophenyl)(tetrahydro-2H-thiopyran-4-yl)methanone (9):



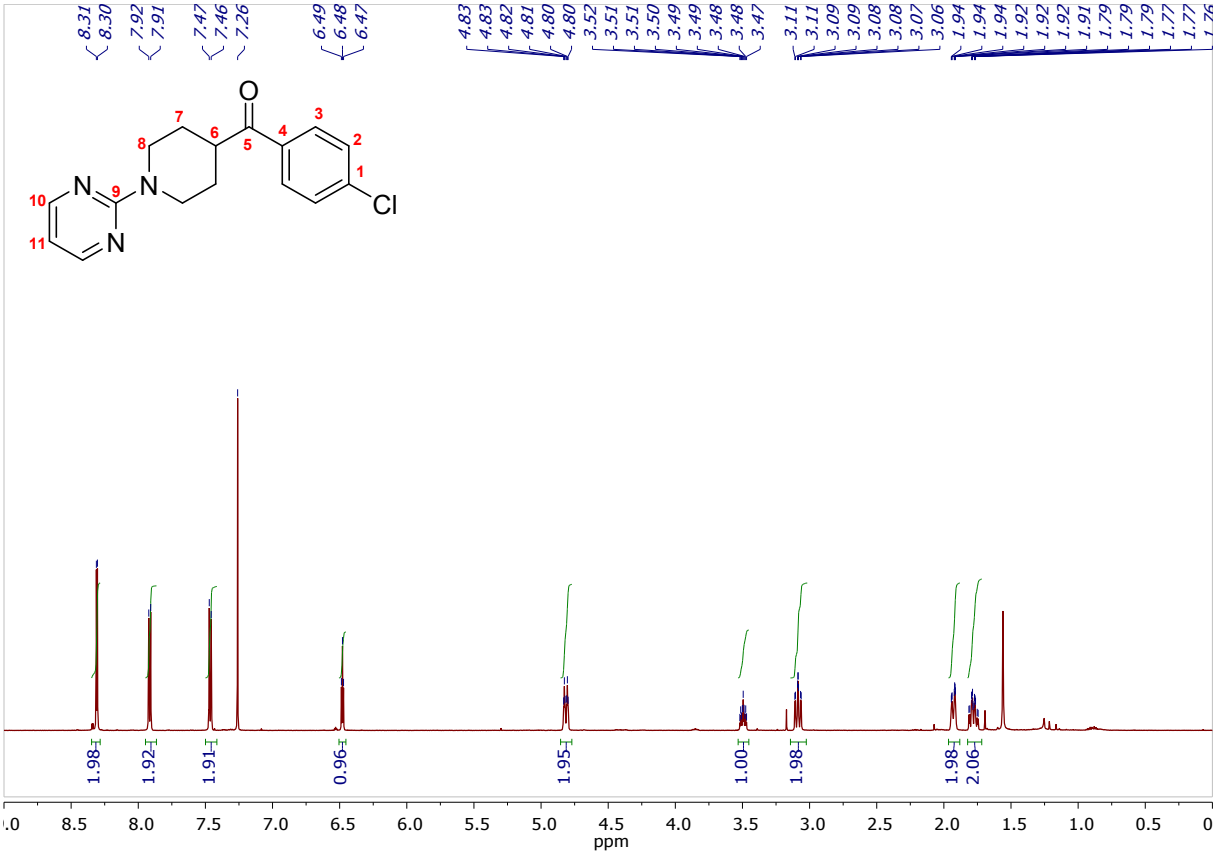


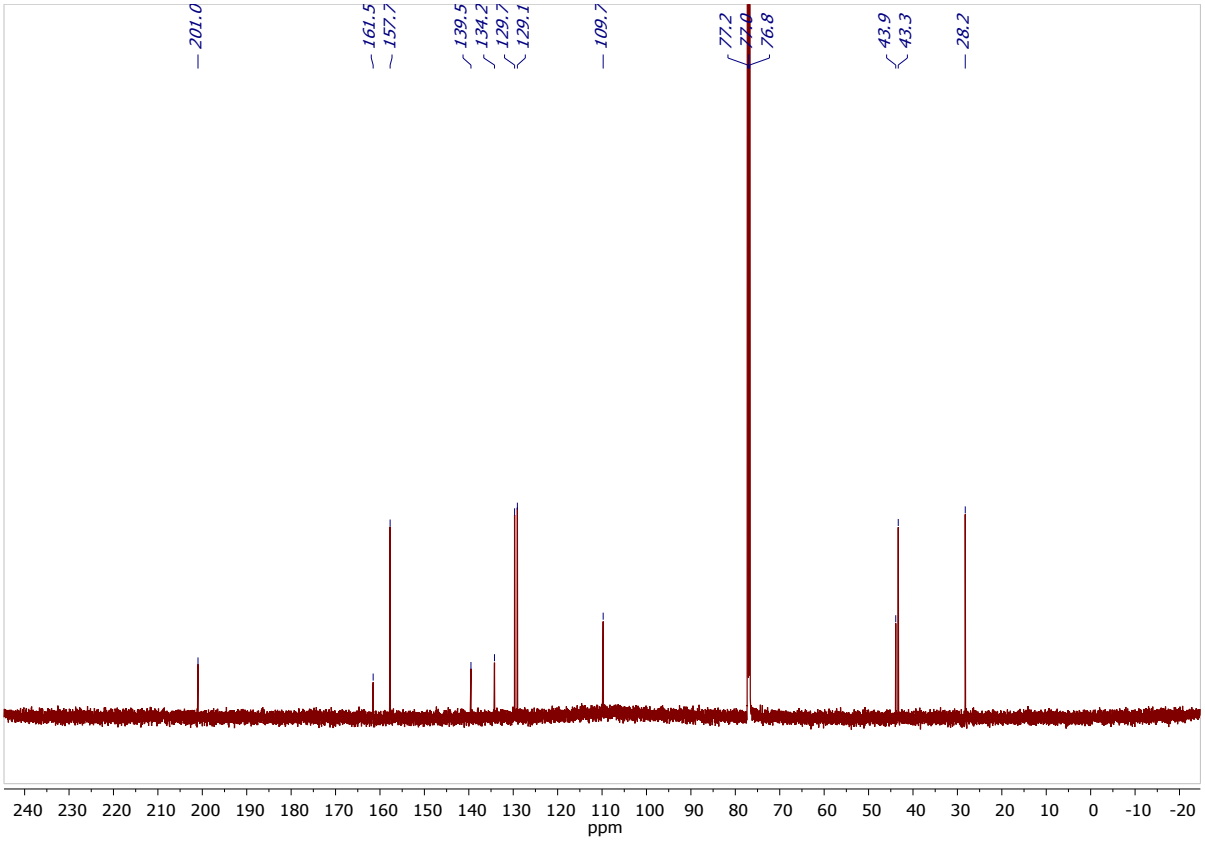
tert-butyl 4-(4-chlorobenzoyl)piperidine-1-carboxylate (PD-054 10):



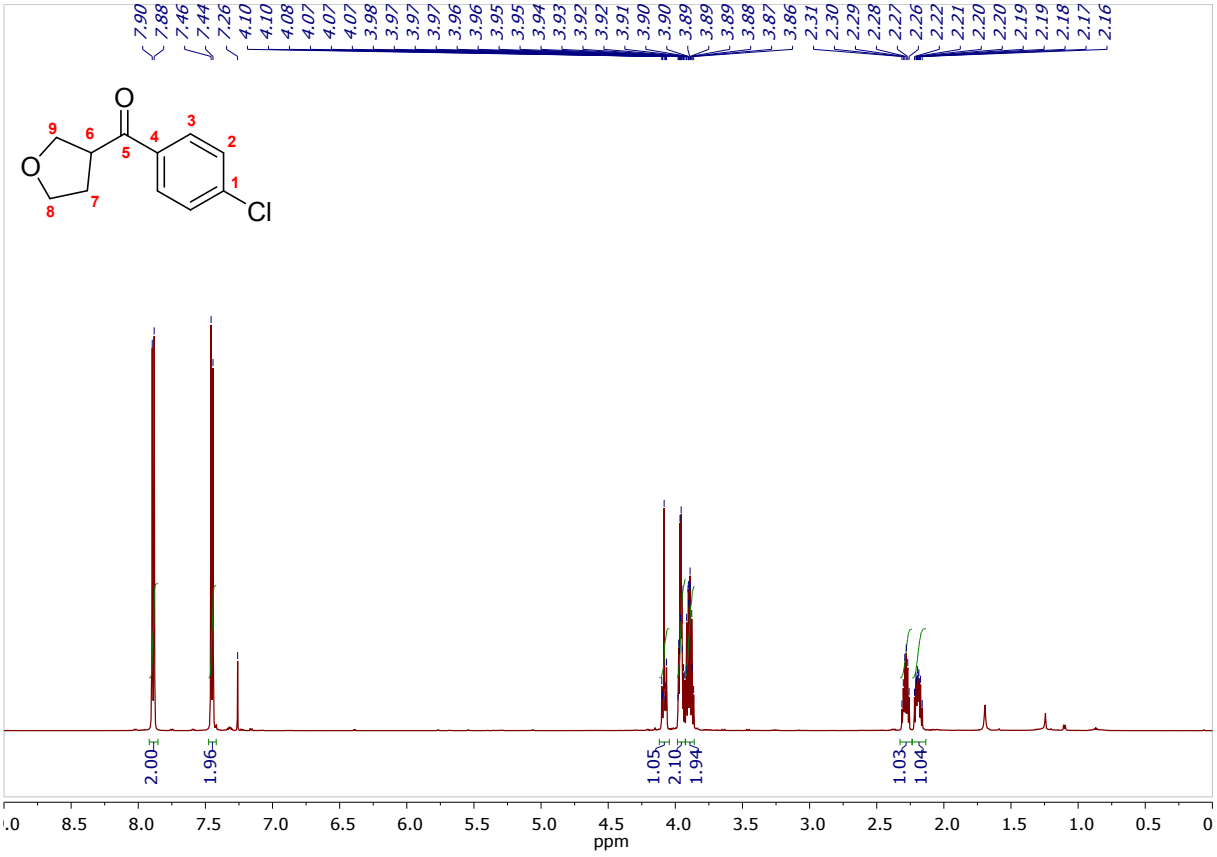


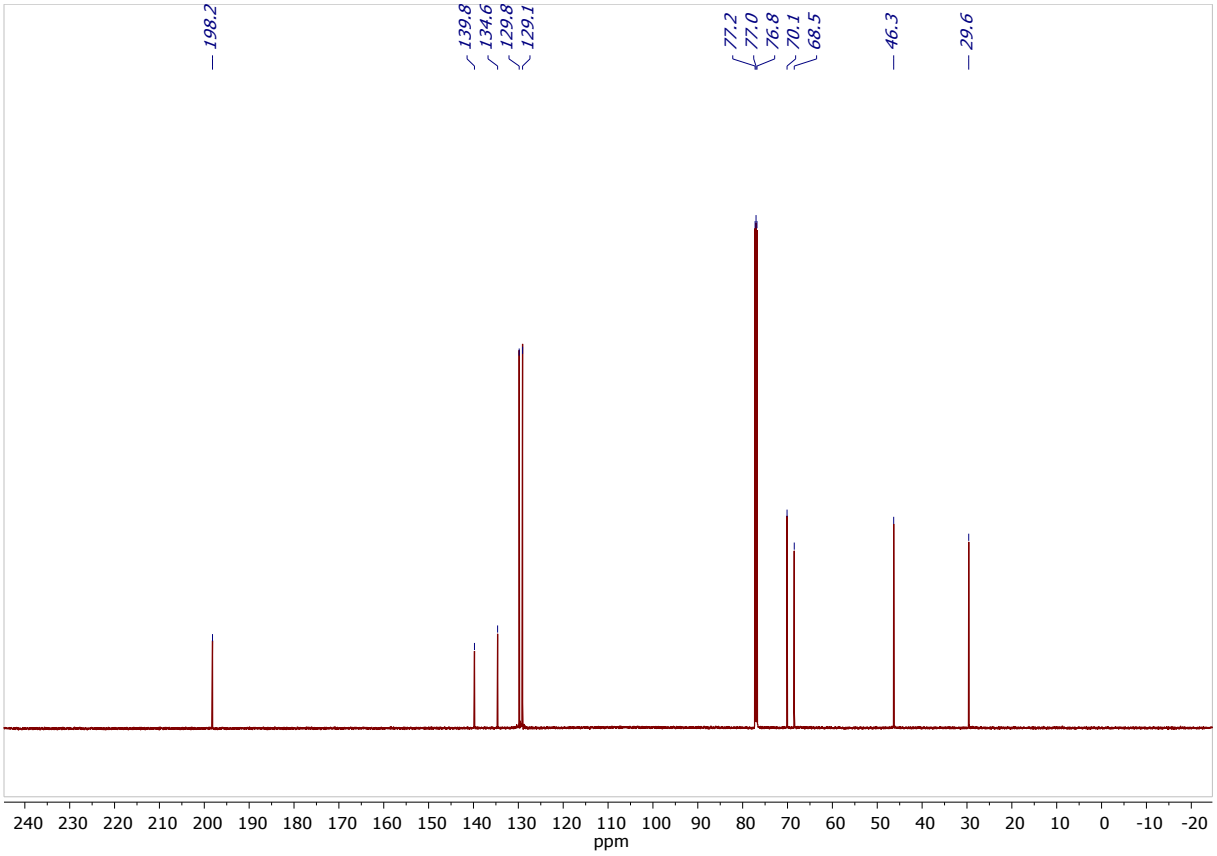
(4-chlorophenyl)(1-(pyrimidin-2-yl)piperidin-4-yl)methanone (11):



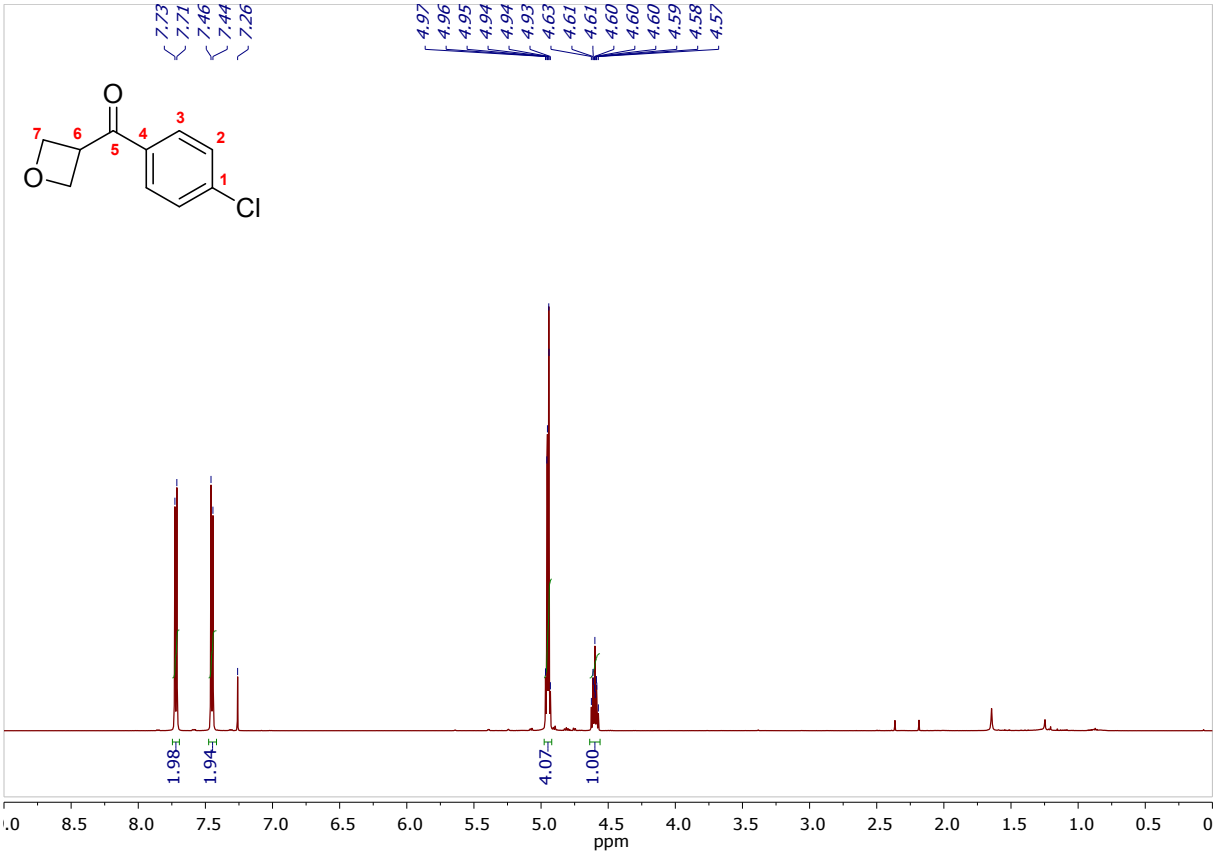


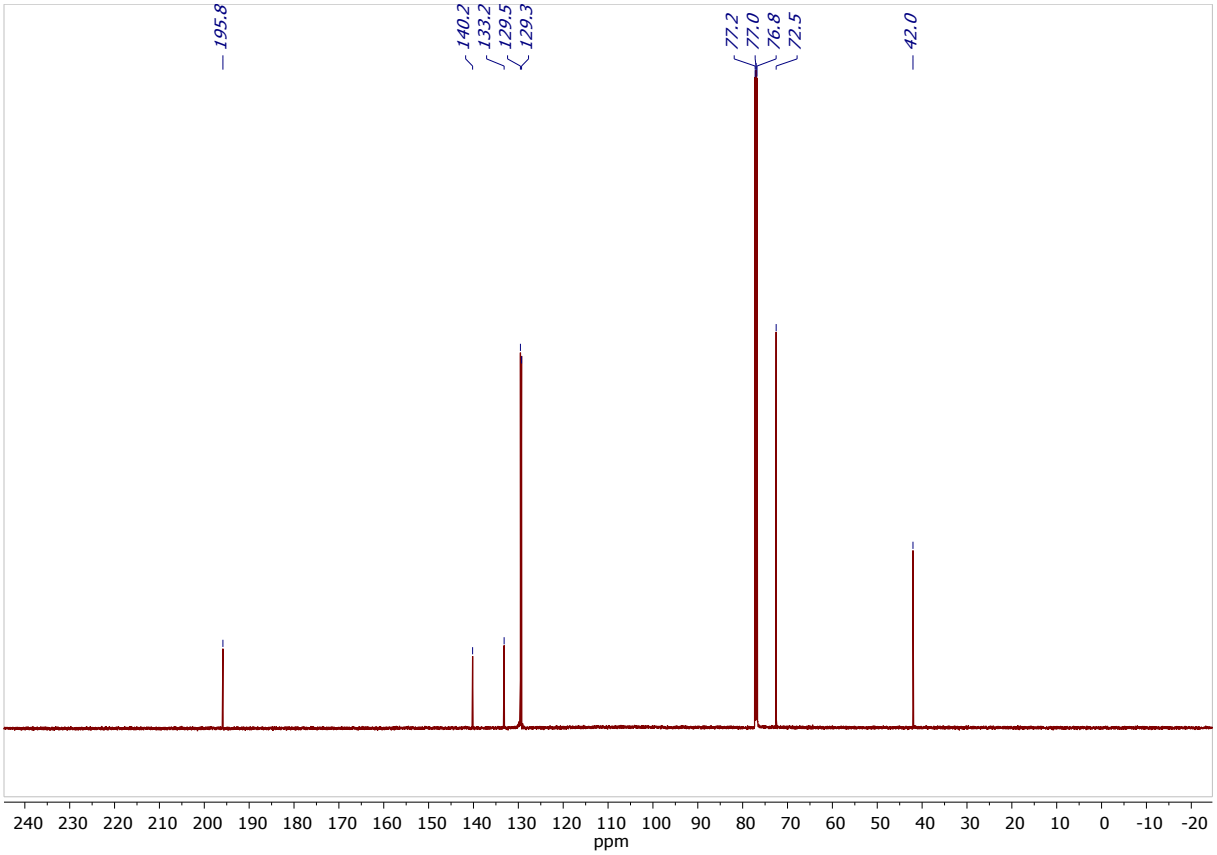
(4-chlorophenyl)(tetrahydrofuran-3-yl)methanone (12):



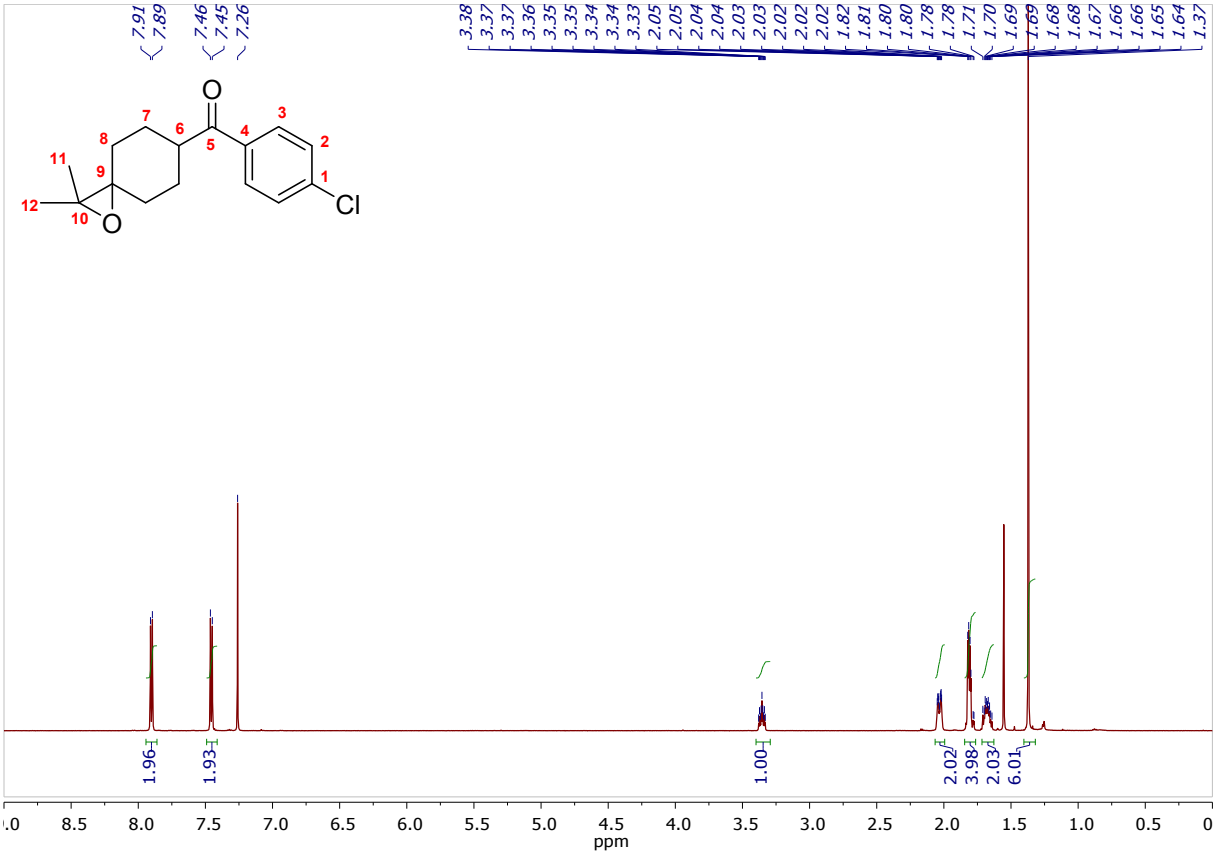


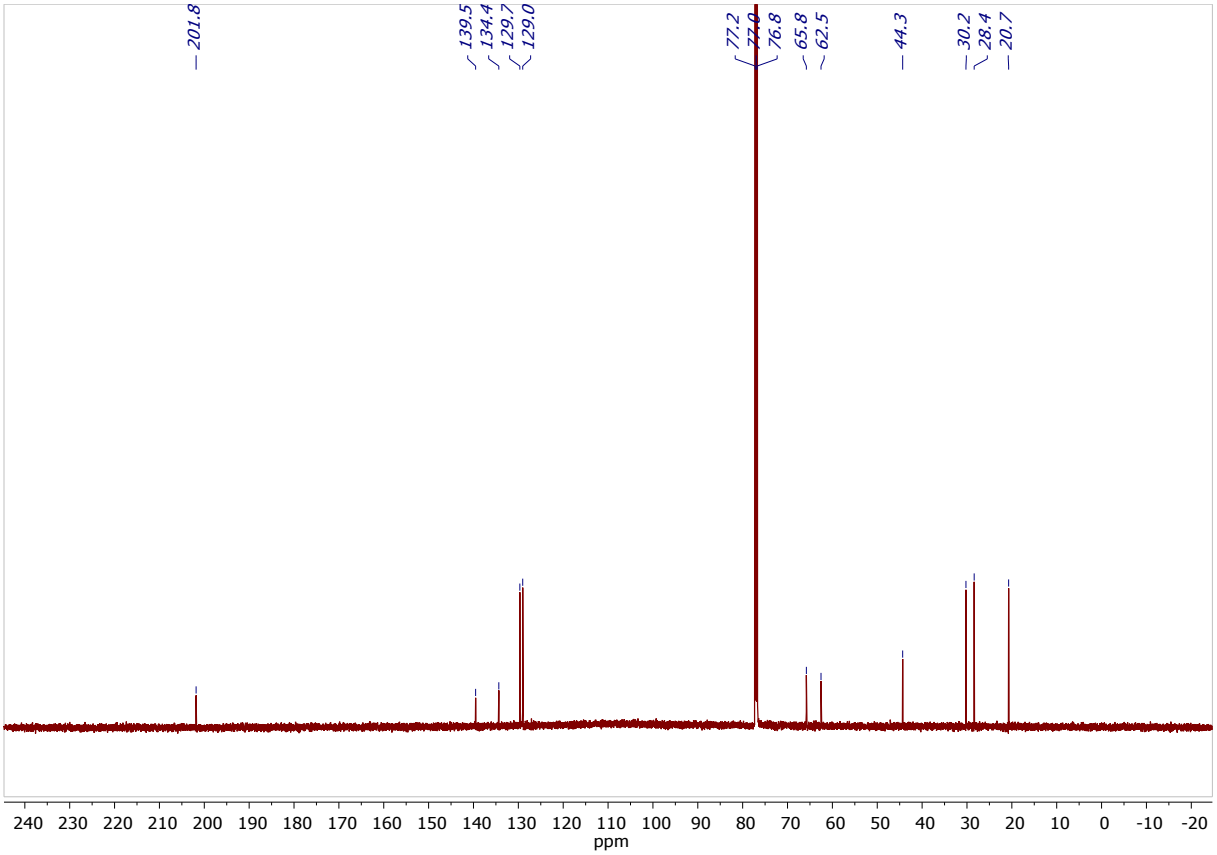
(4-chlorophenyl)(oxetan-3-yl)methanone (13):



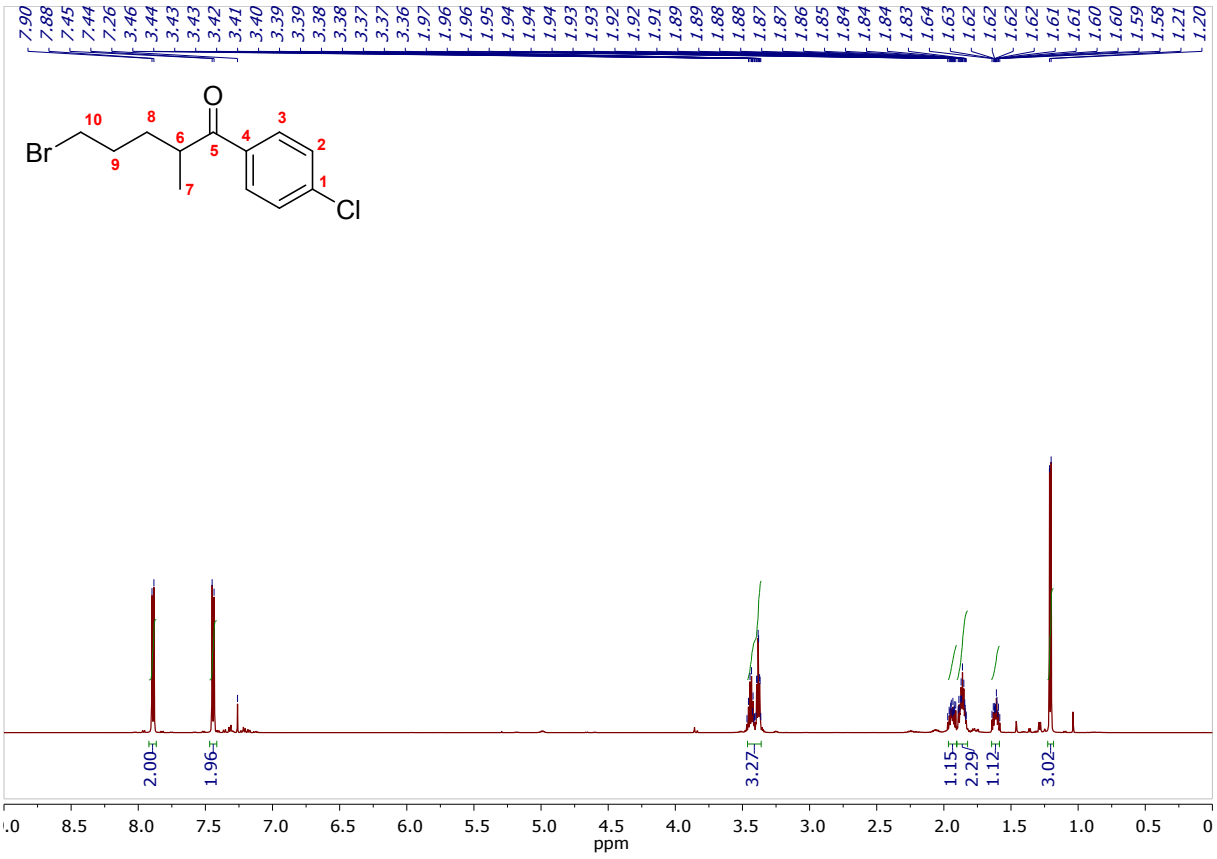


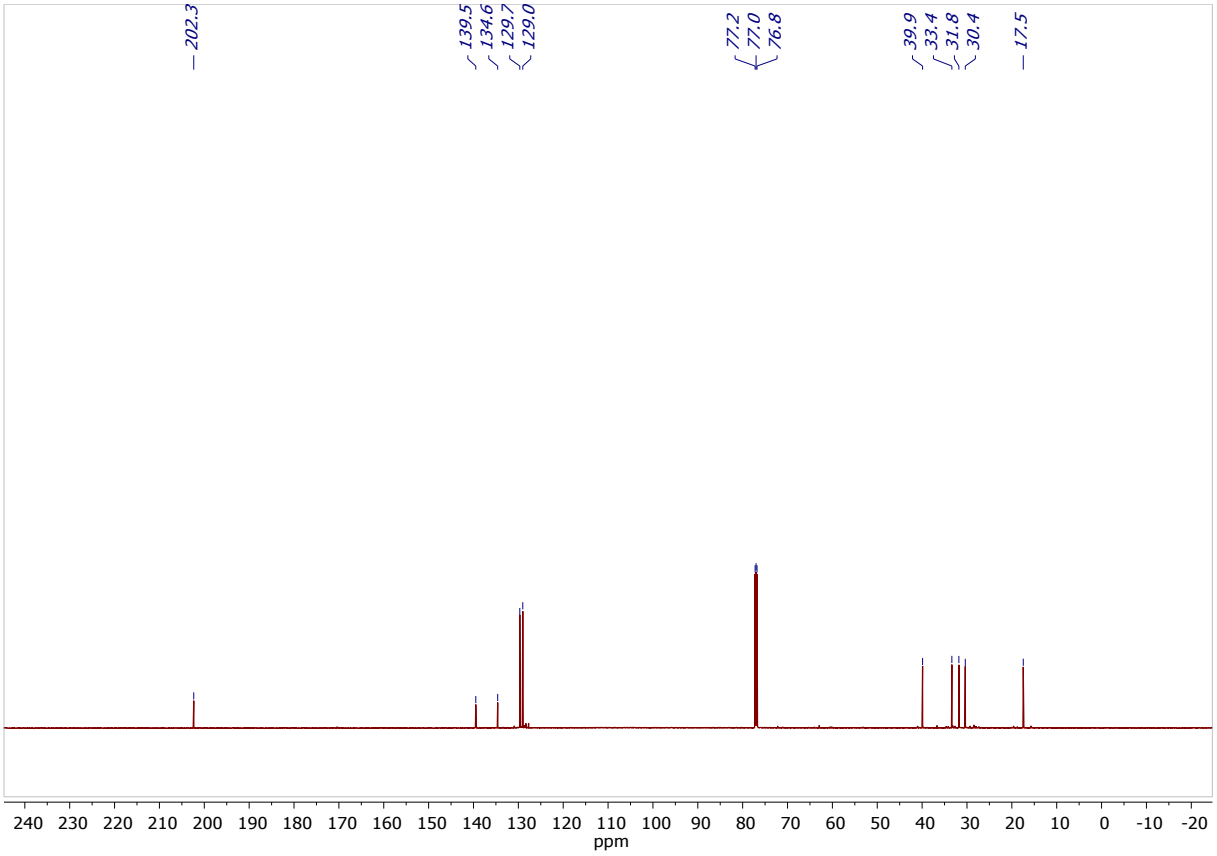
(4-chlorophenyl)(2,2-dimethyl-1-oxaspiro[2.5]octan-6-yl)methanone (14):



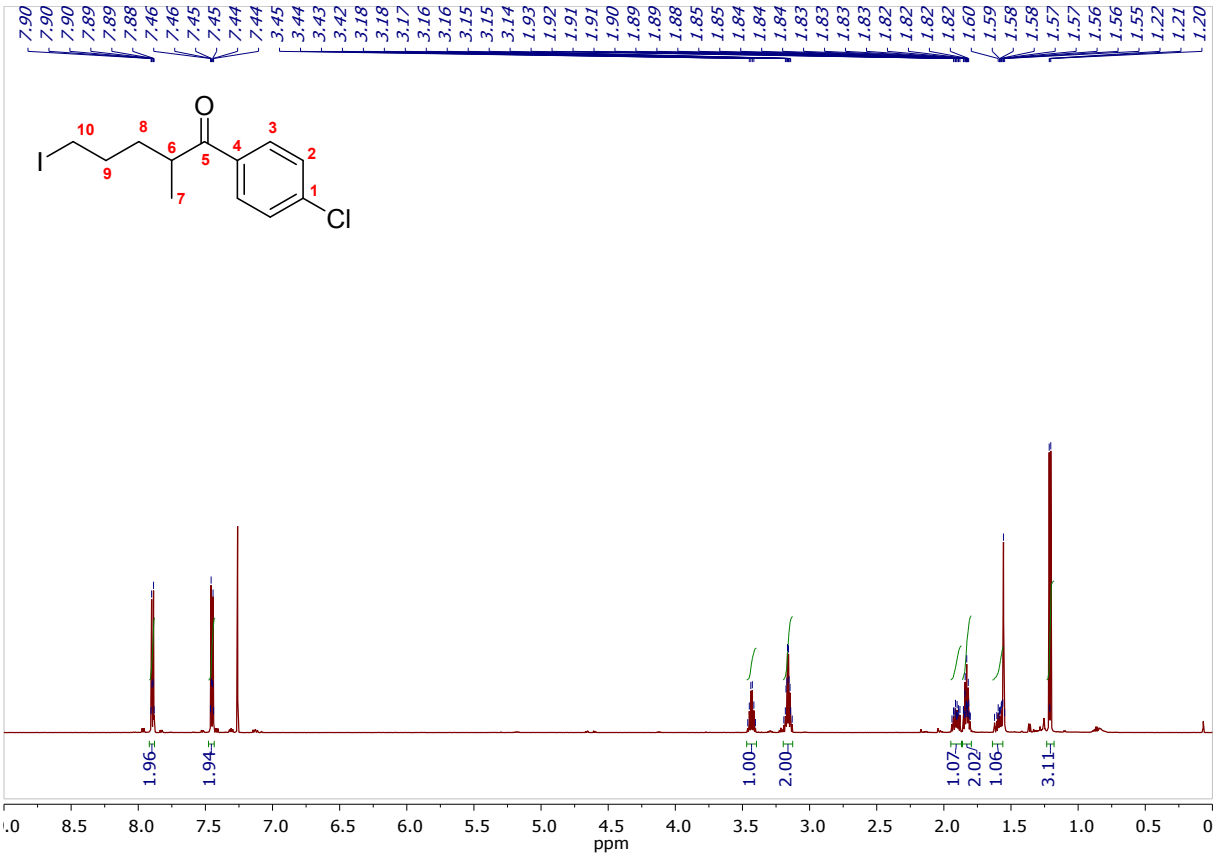


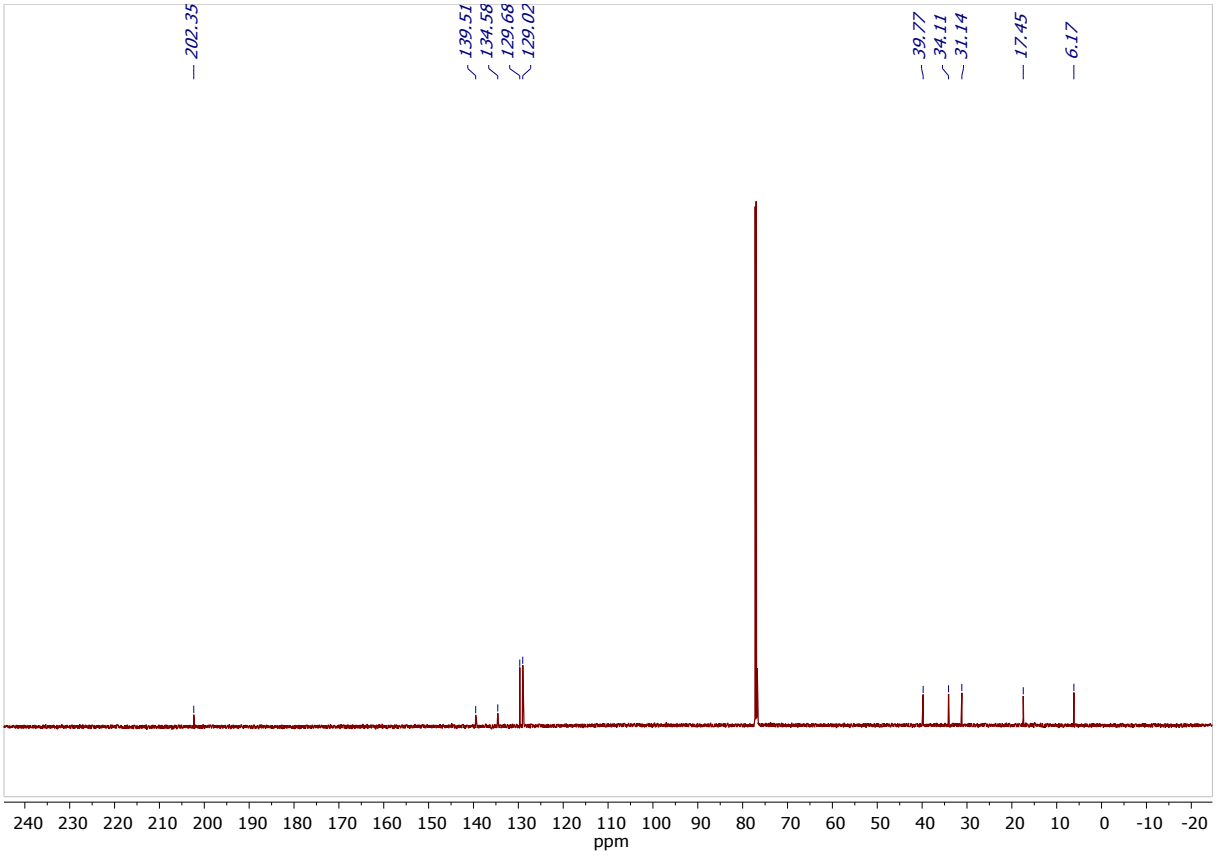
5-bromo-1-(4-chlorophenyl)-2-methylpentan-1-one (15):



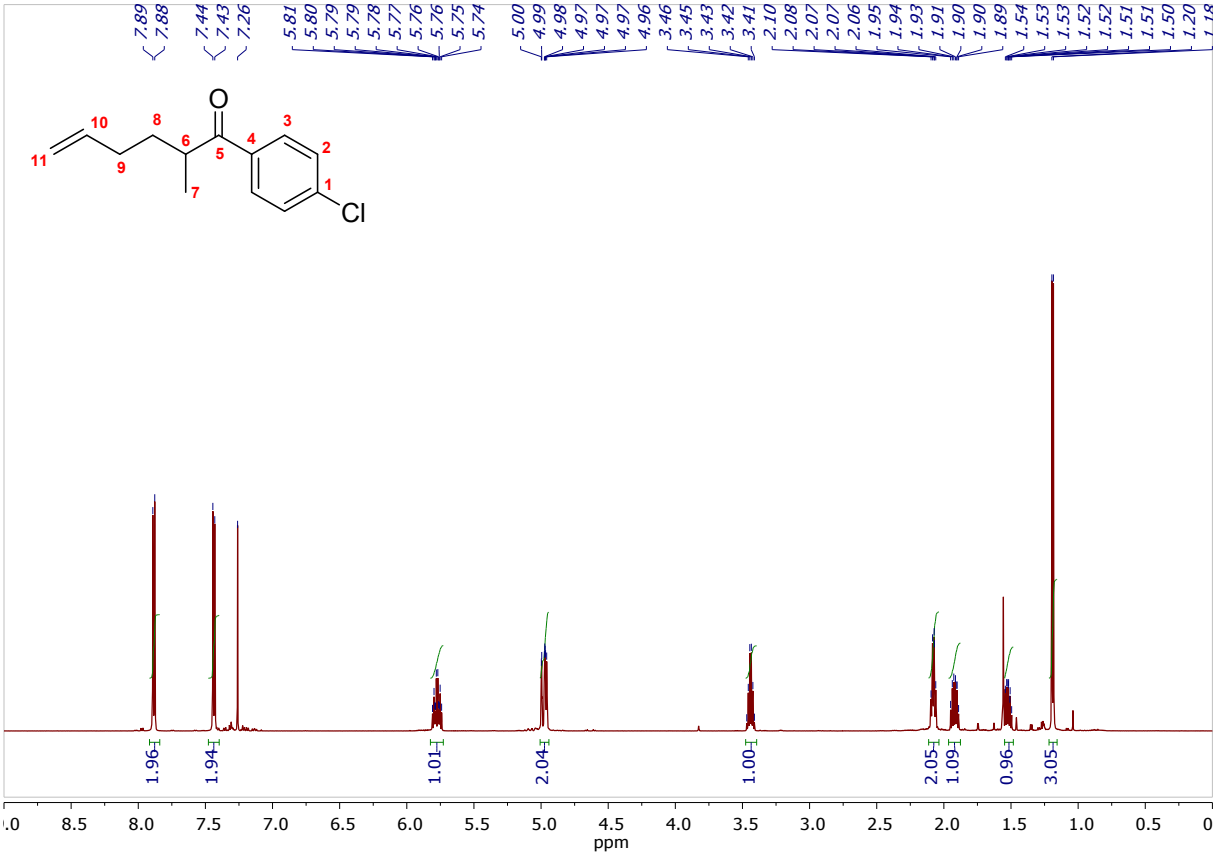


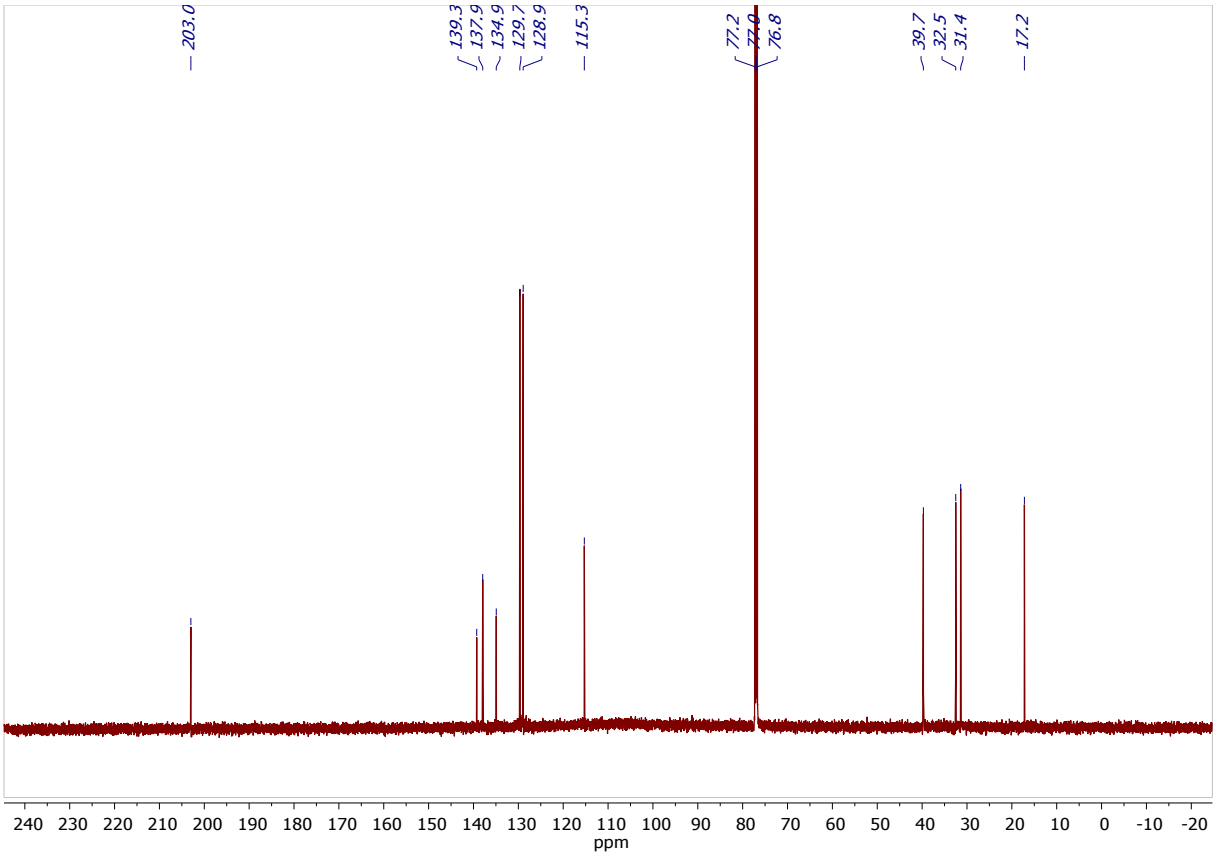
1-(4-chlorophenyl)-5-iodo-2-methylpentan-1-one (16)



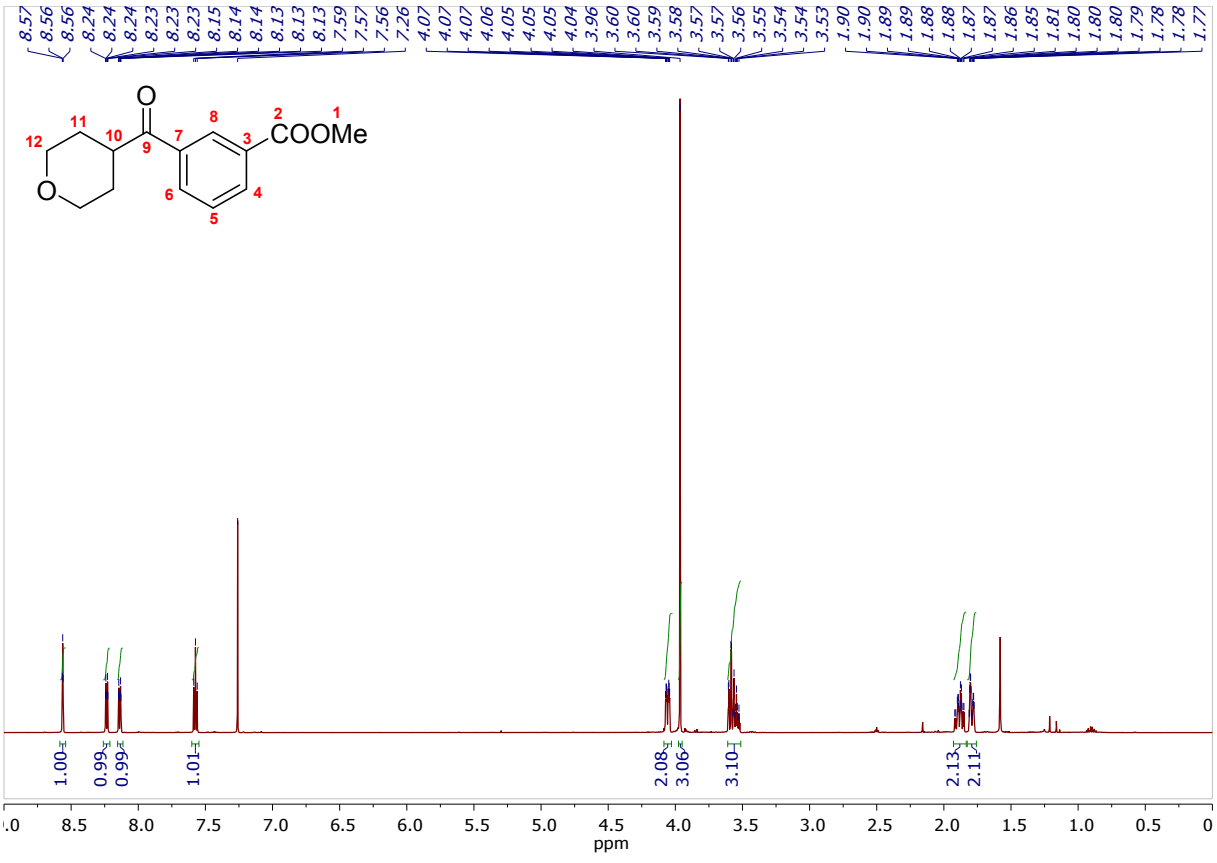


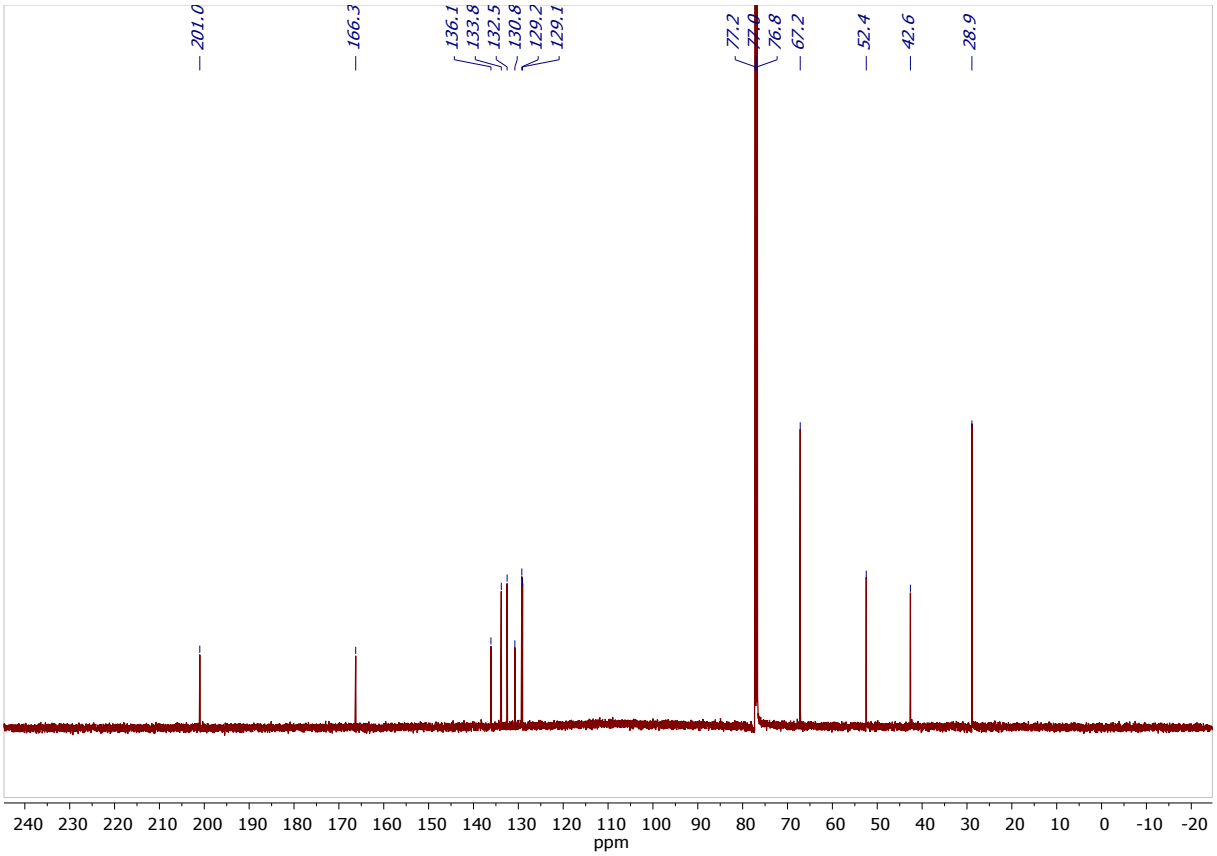
1-(4-chlorophenyl)-2-methylhex-5-en-1-one (17):



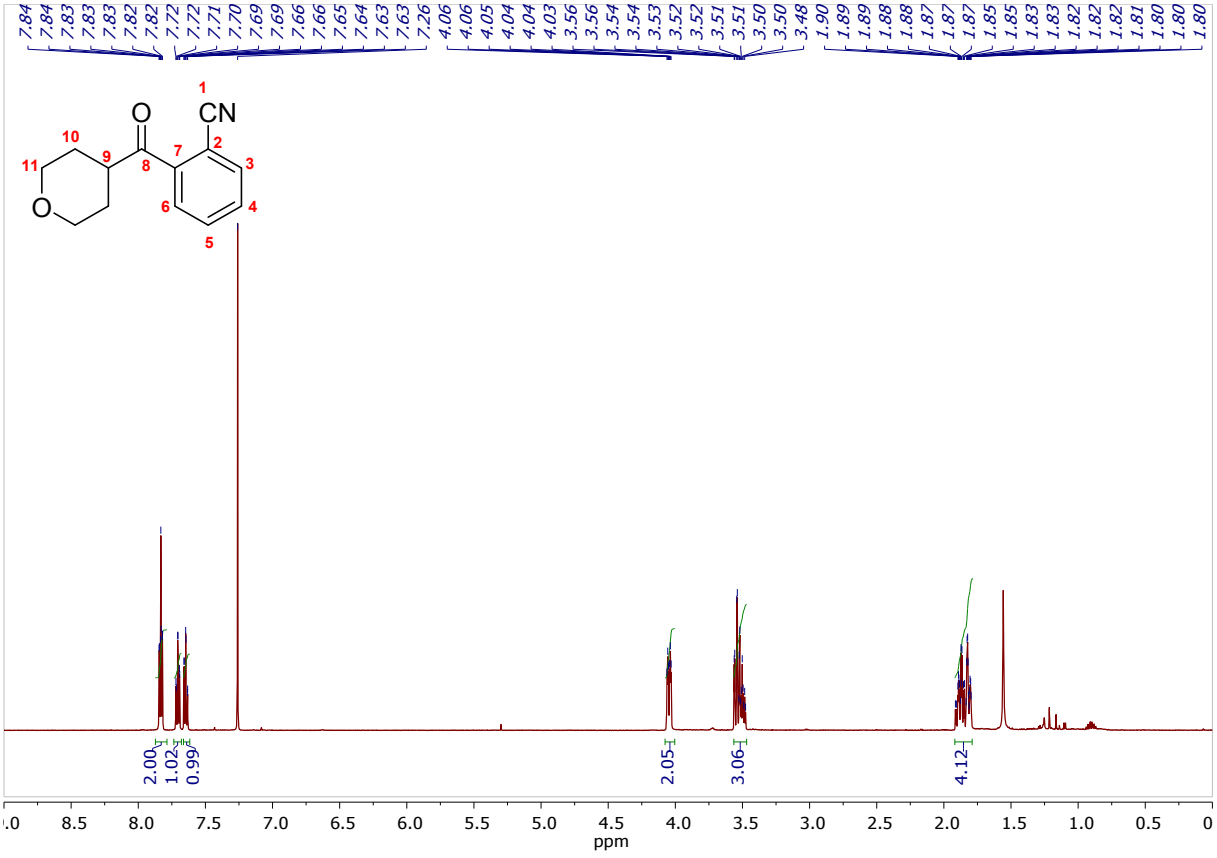


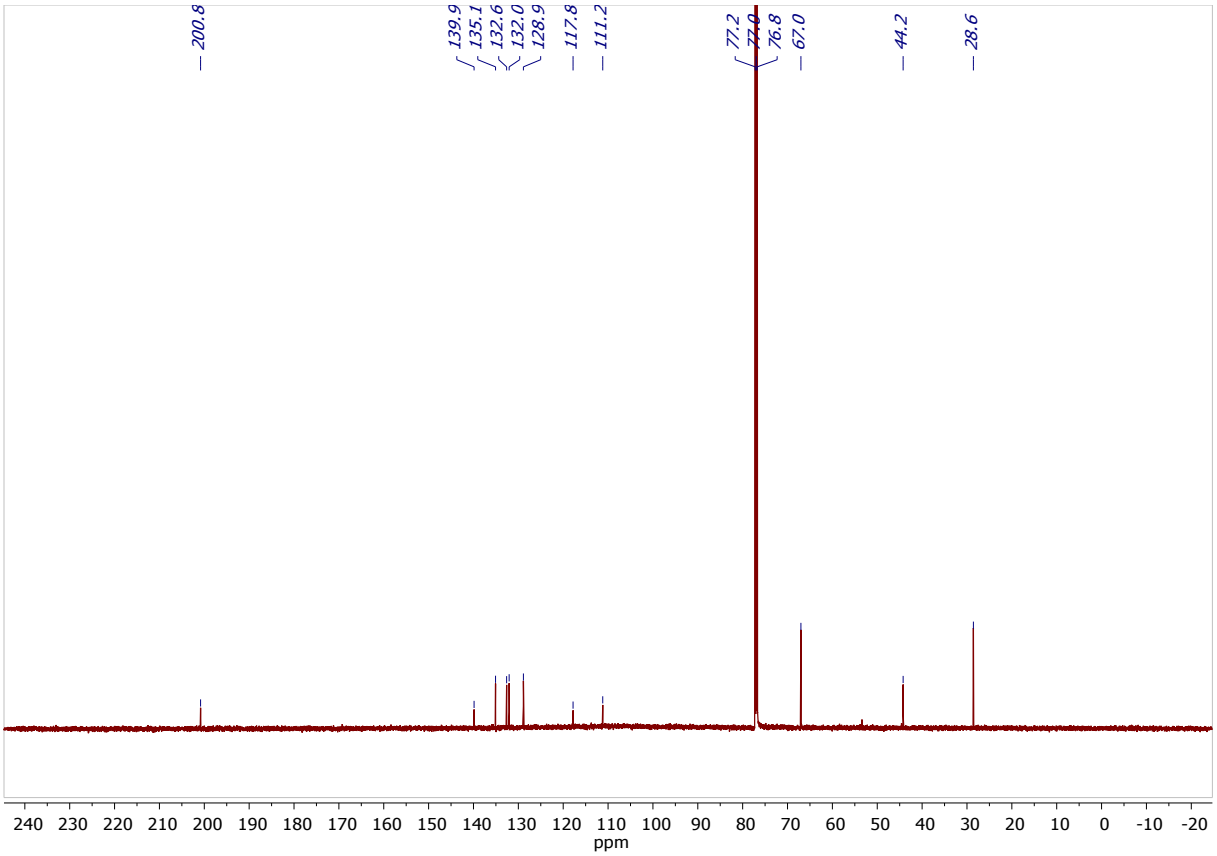
methyl 3-(tetrahydro-2H-pyran-4-carbonyl)benzoate (19):



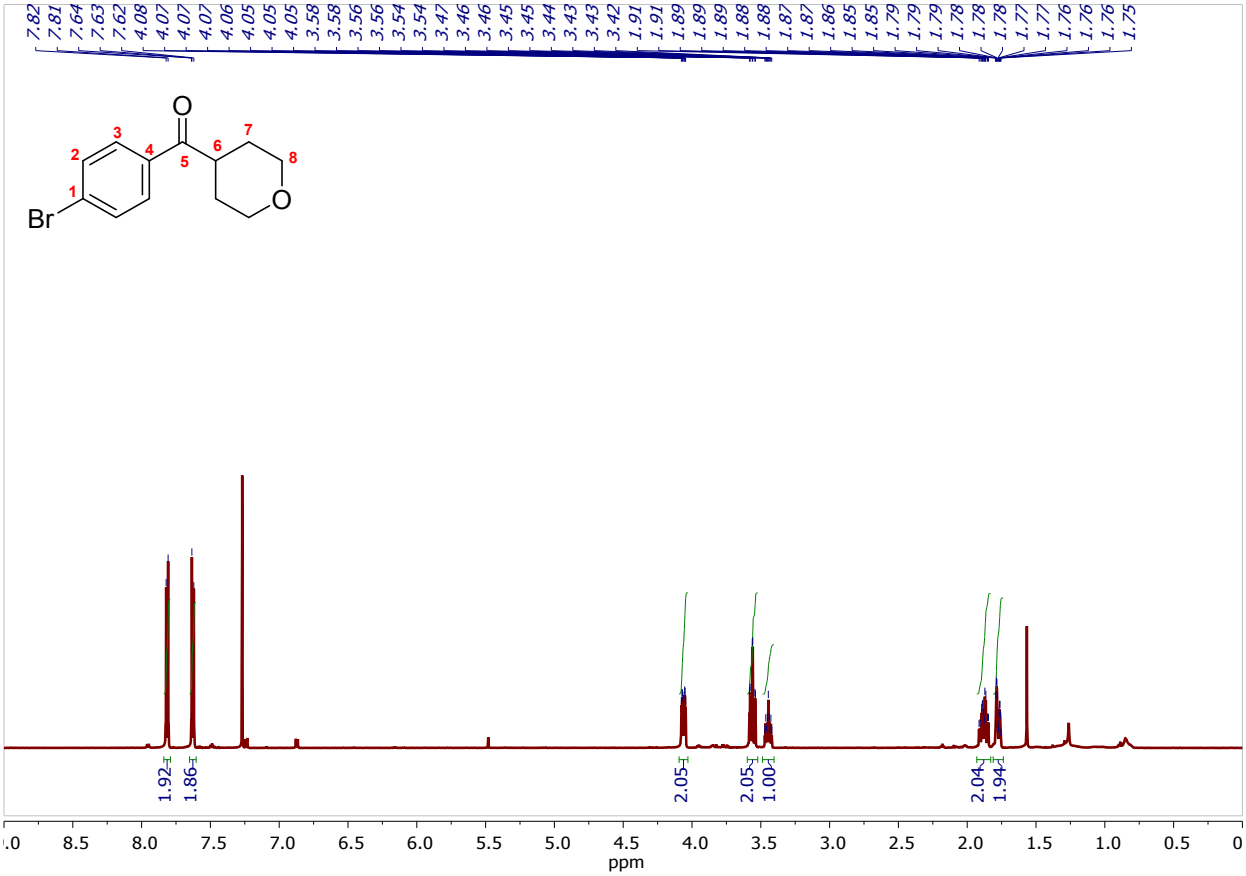


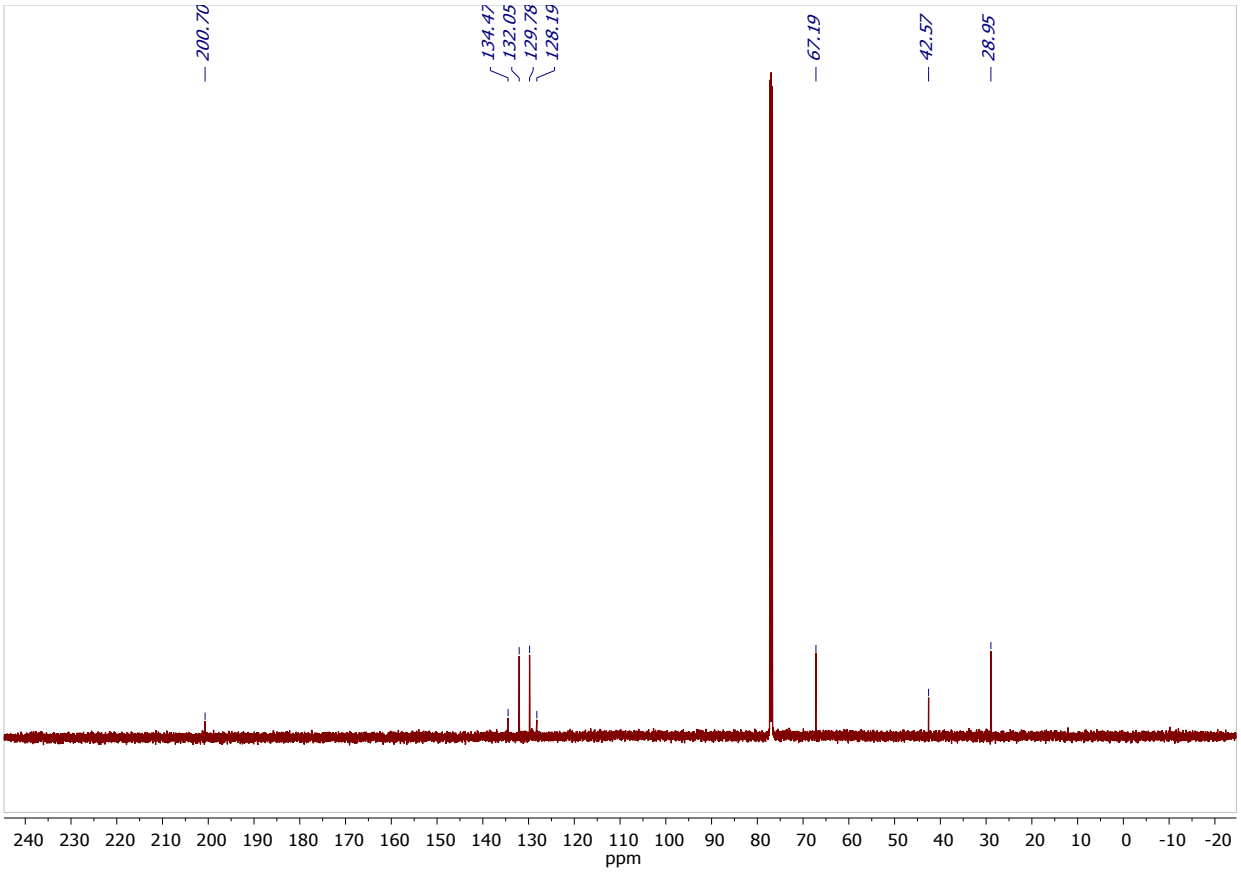
2-(tetrahydro-2H-pyran-4-carbonyl)benzonitrile (20):



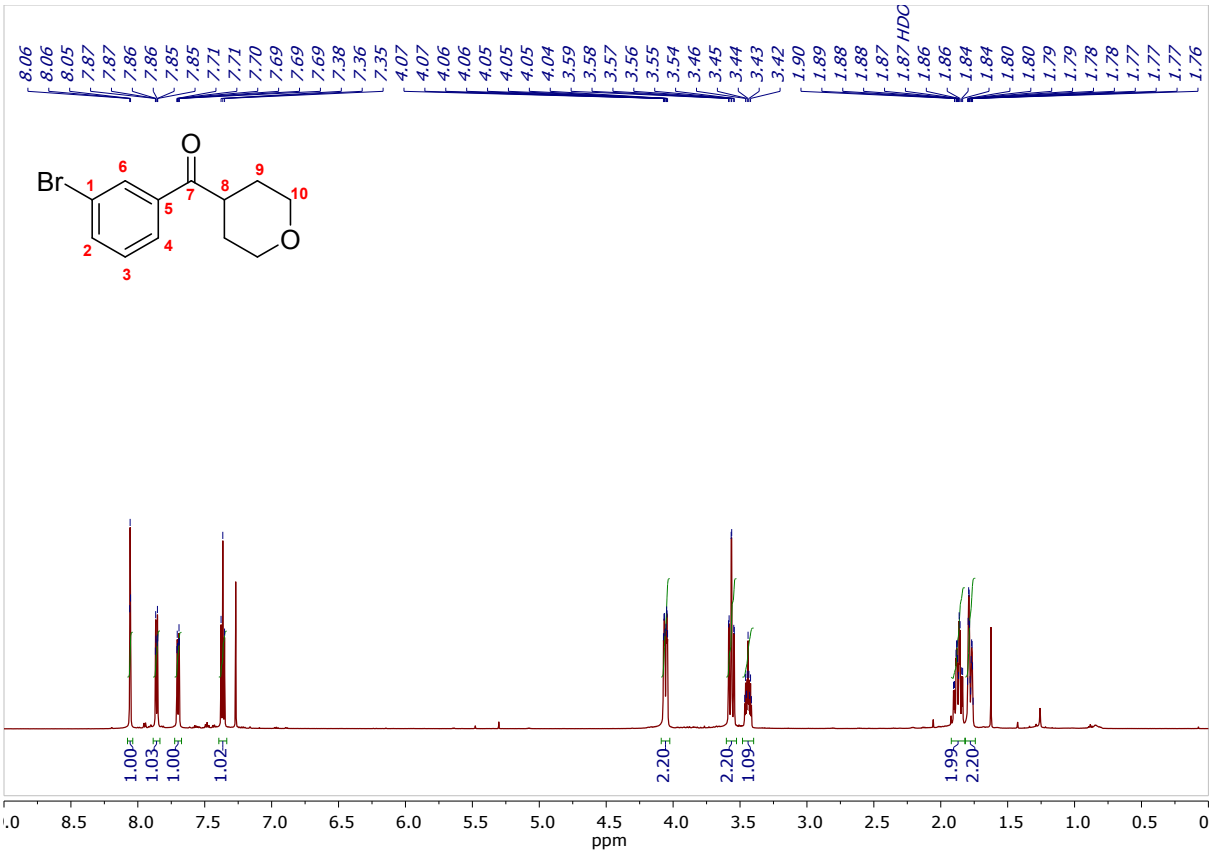


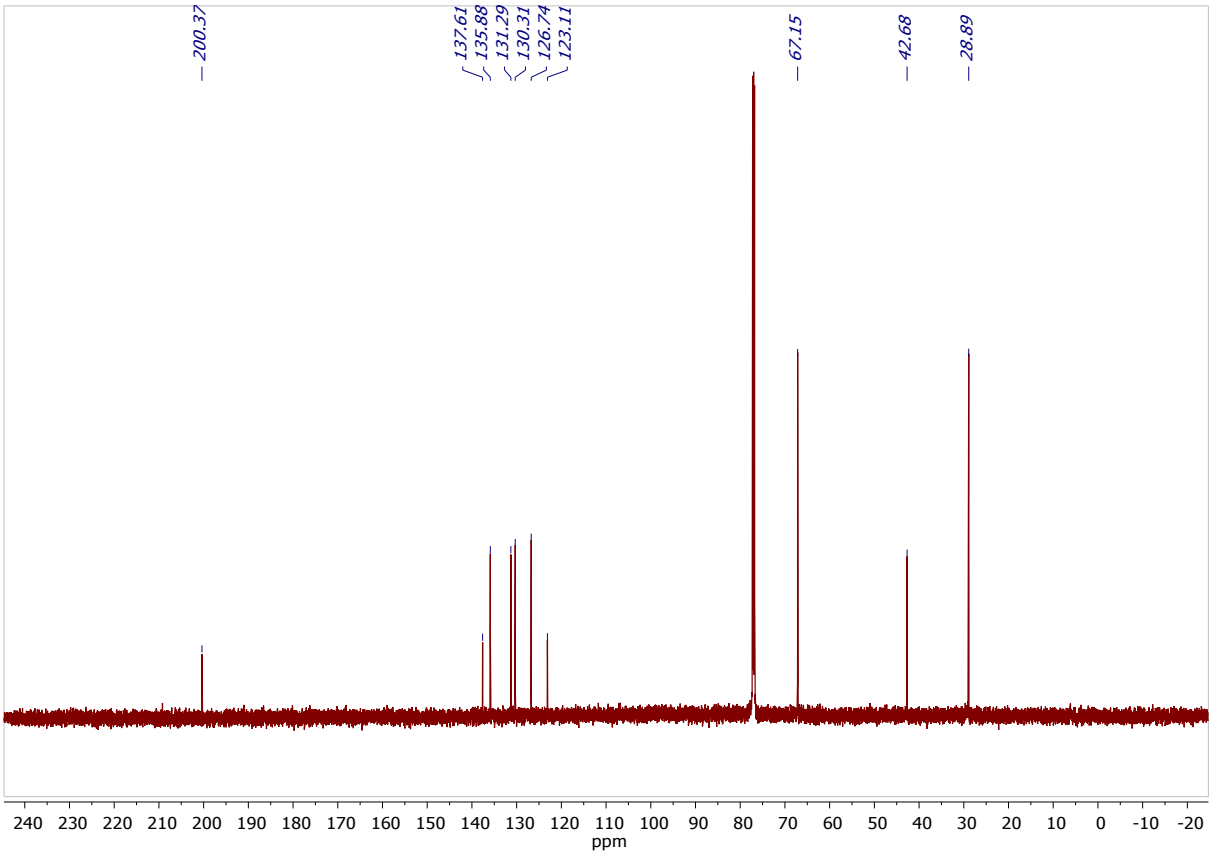
(4-bromophenyl)(tetrahydro-2H-pyran-4-yl)methanone (21)



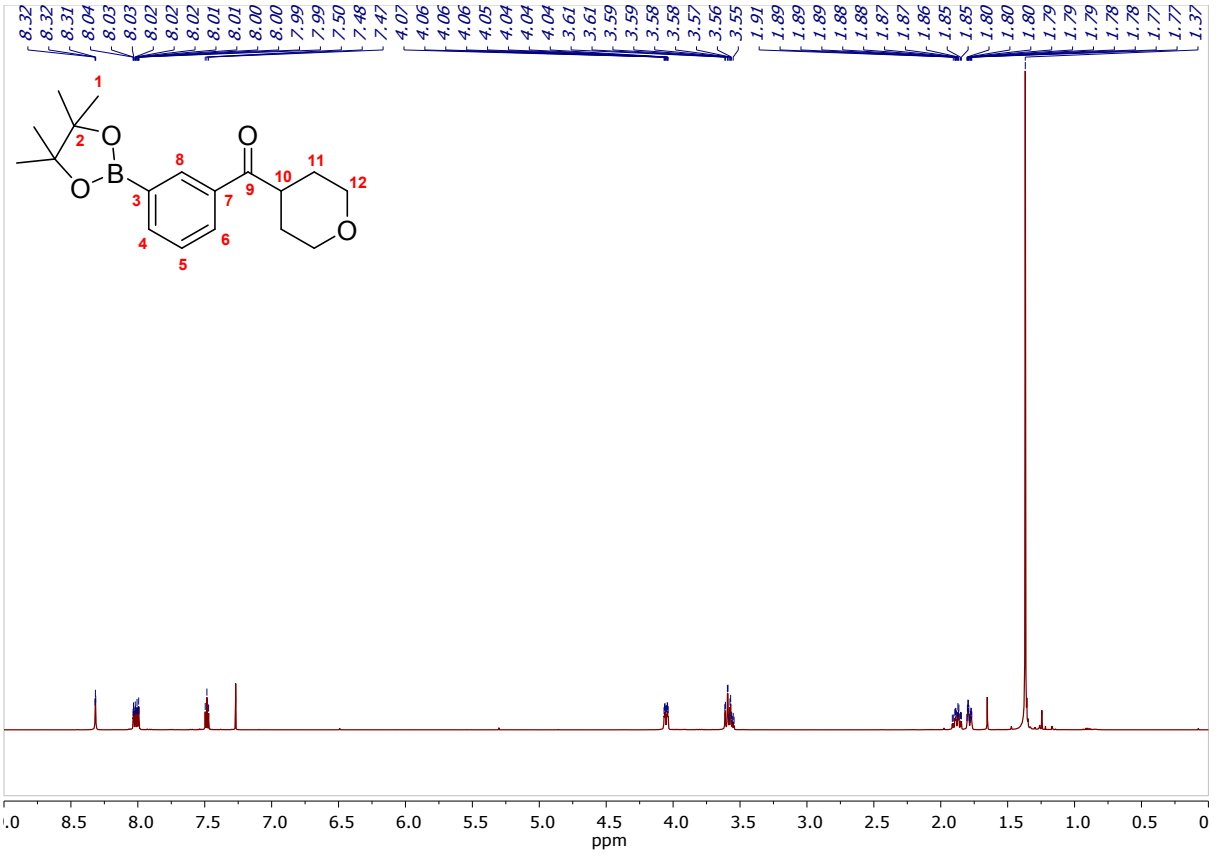


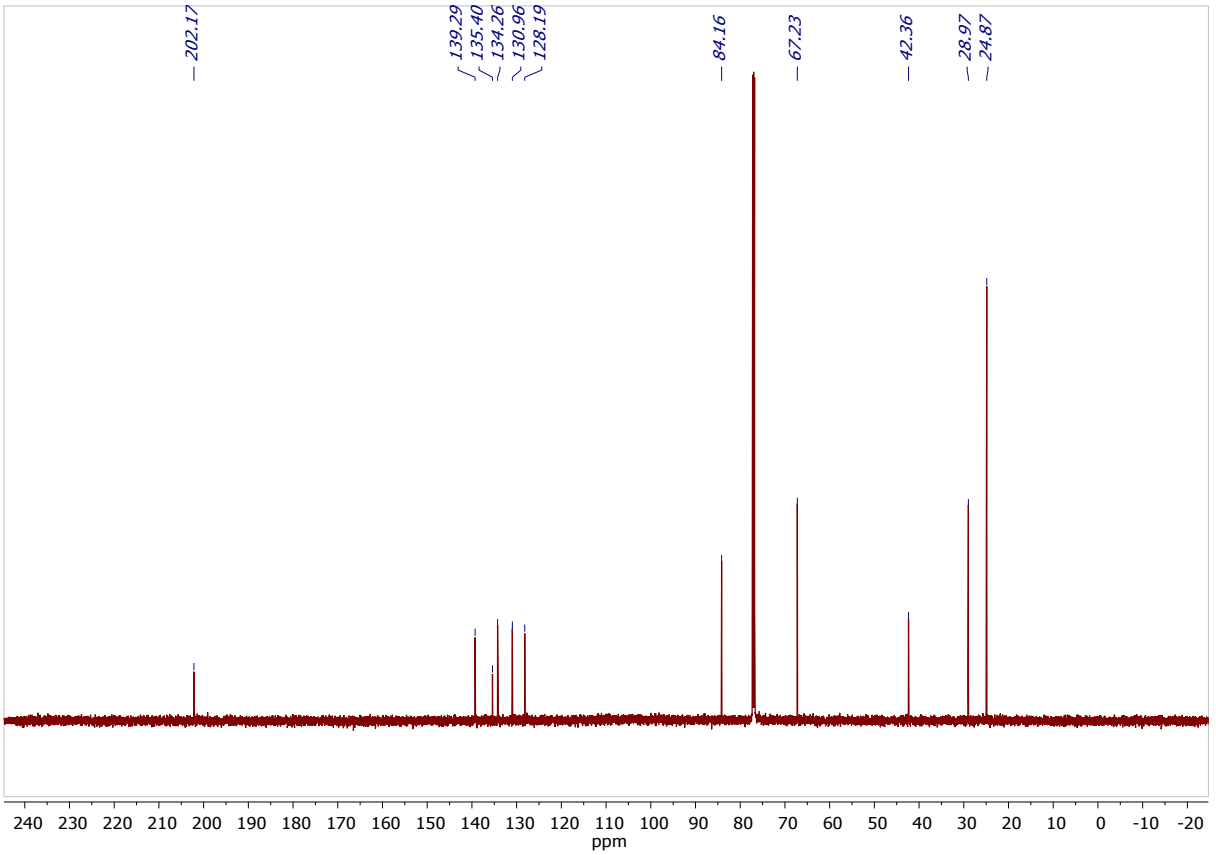
(3-bromophenyl)(tetrahydro-2H-pyran-4-yl)methanone (PD-049, 22):



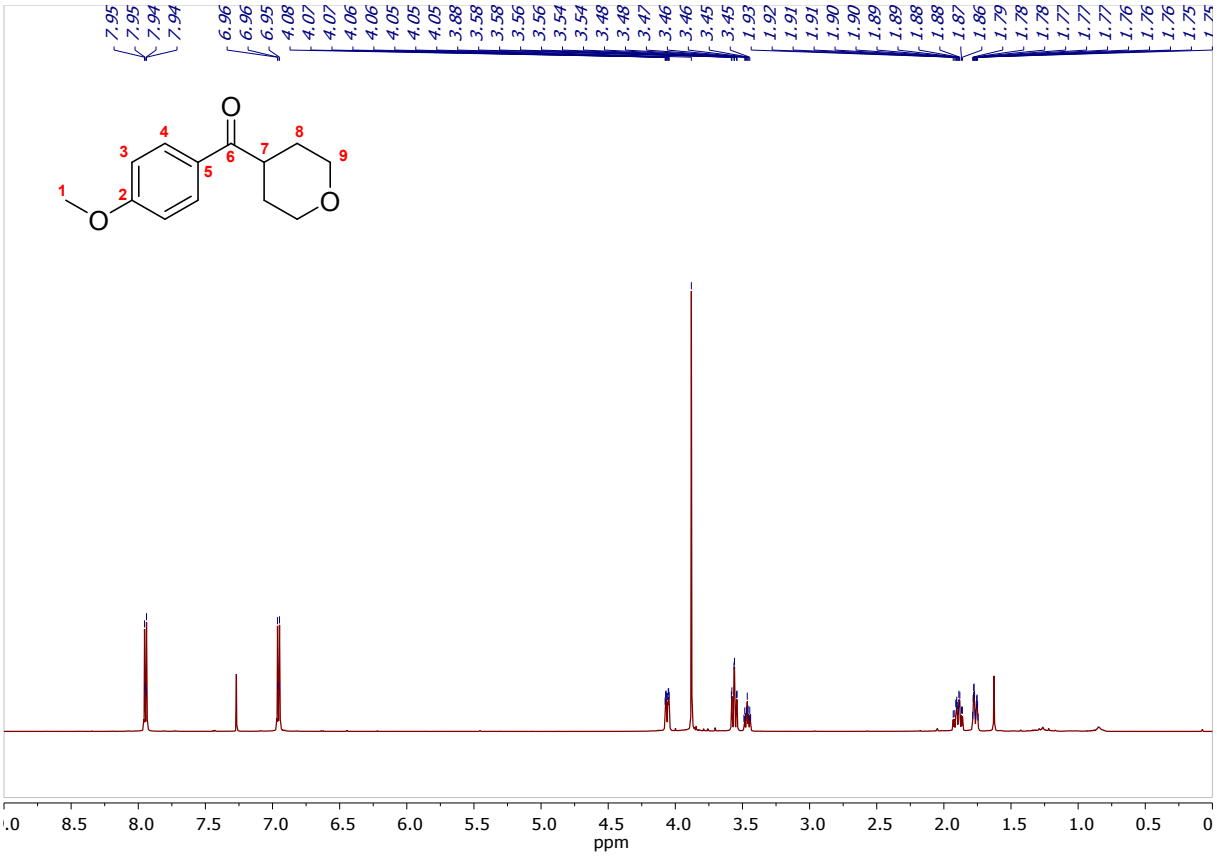


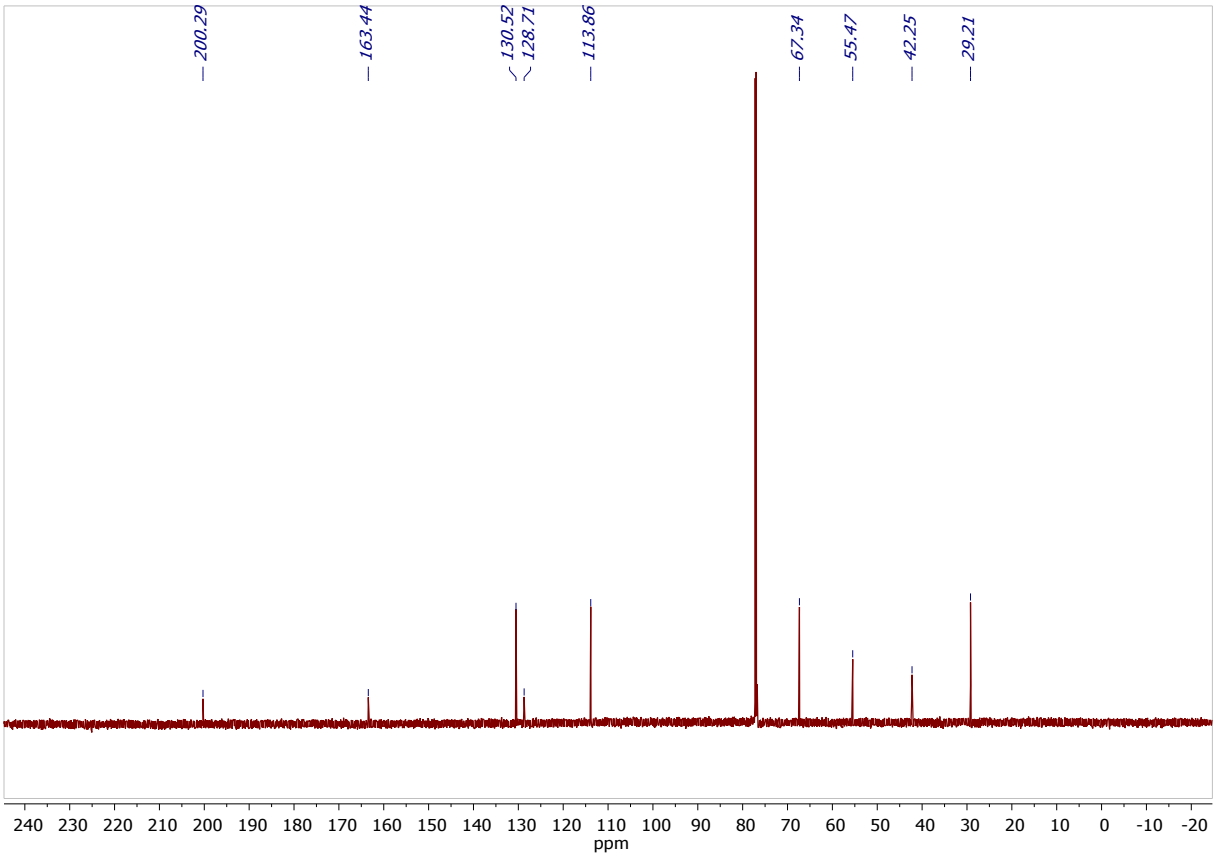
(tetrahydro-2H-pyran-4-yl)(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanone (23)



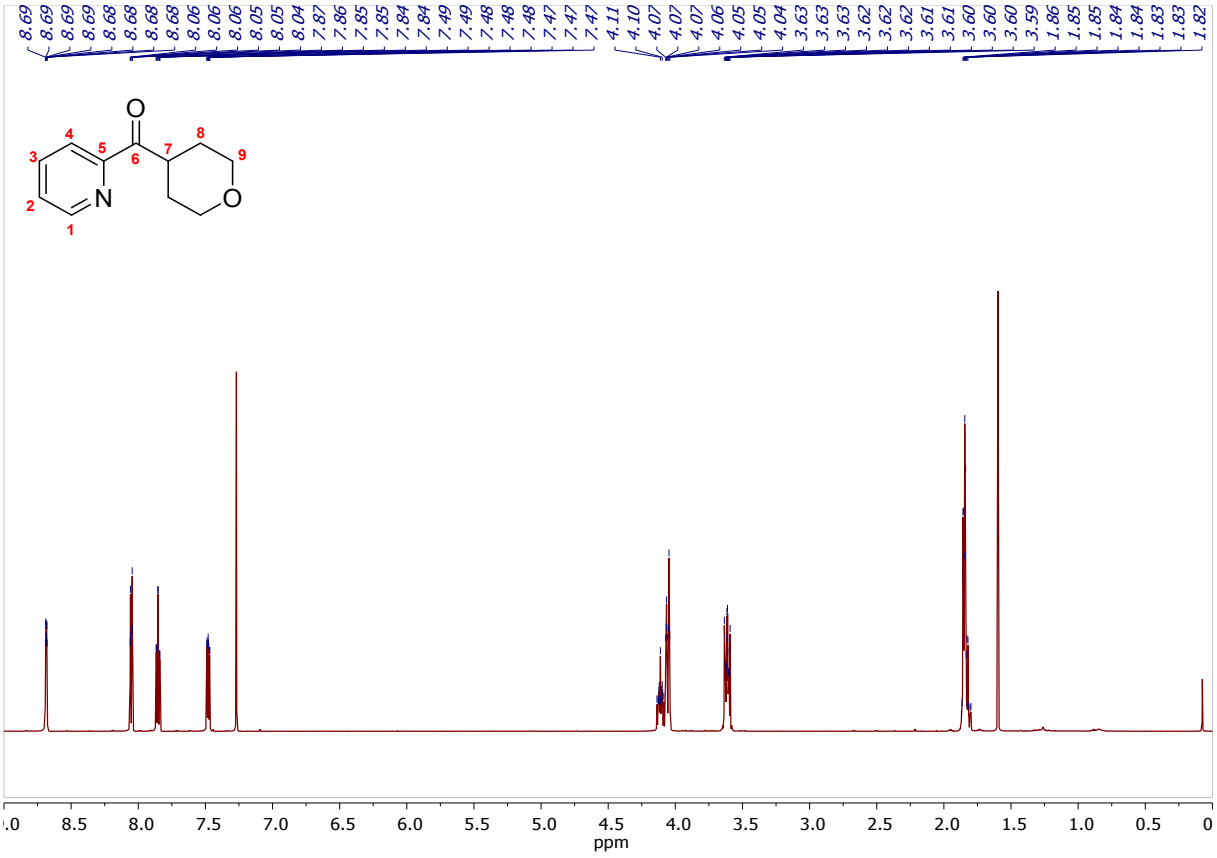


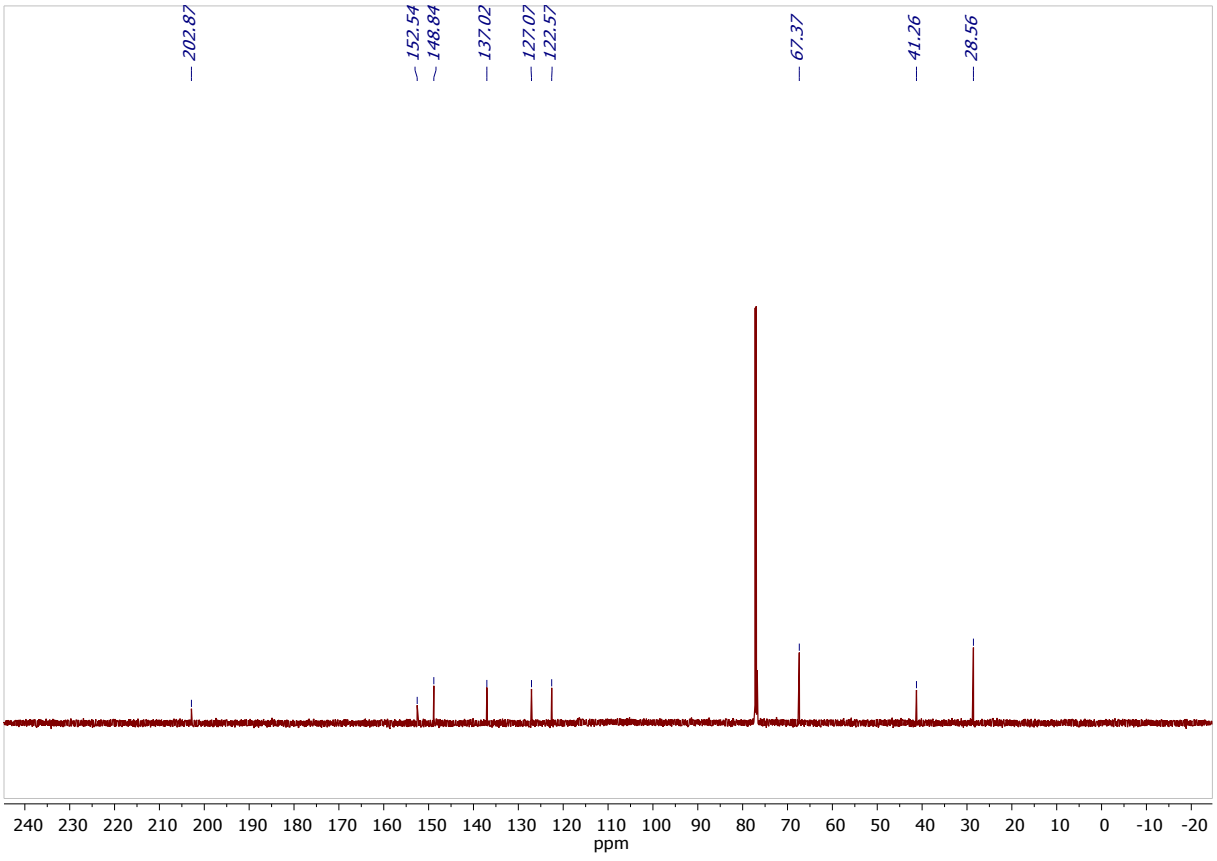
(4-methoxyphenyl)(tetrahydro-2H-pyran-4-yl)methanone (24):



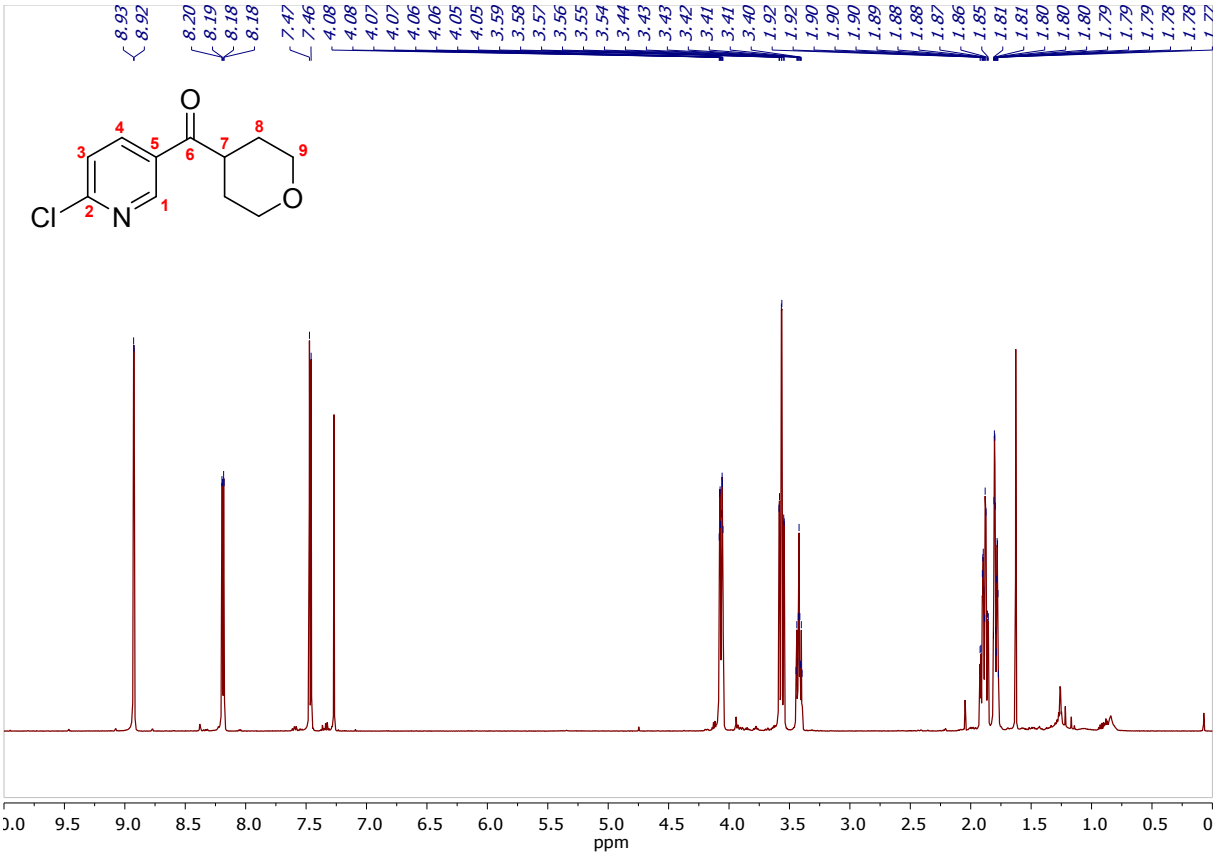


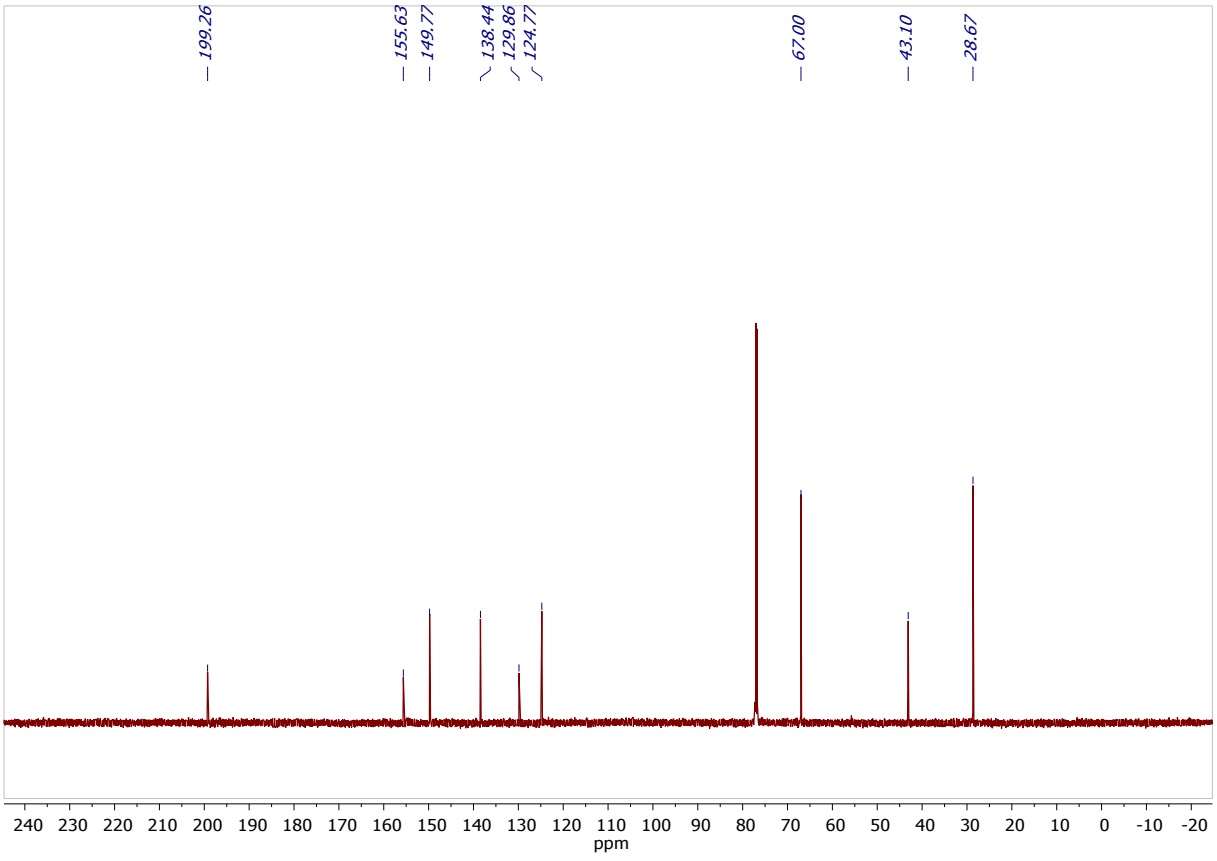
pyridin-2-yl(tetrahydro-2H-pyran-4-yl)methanone (25):



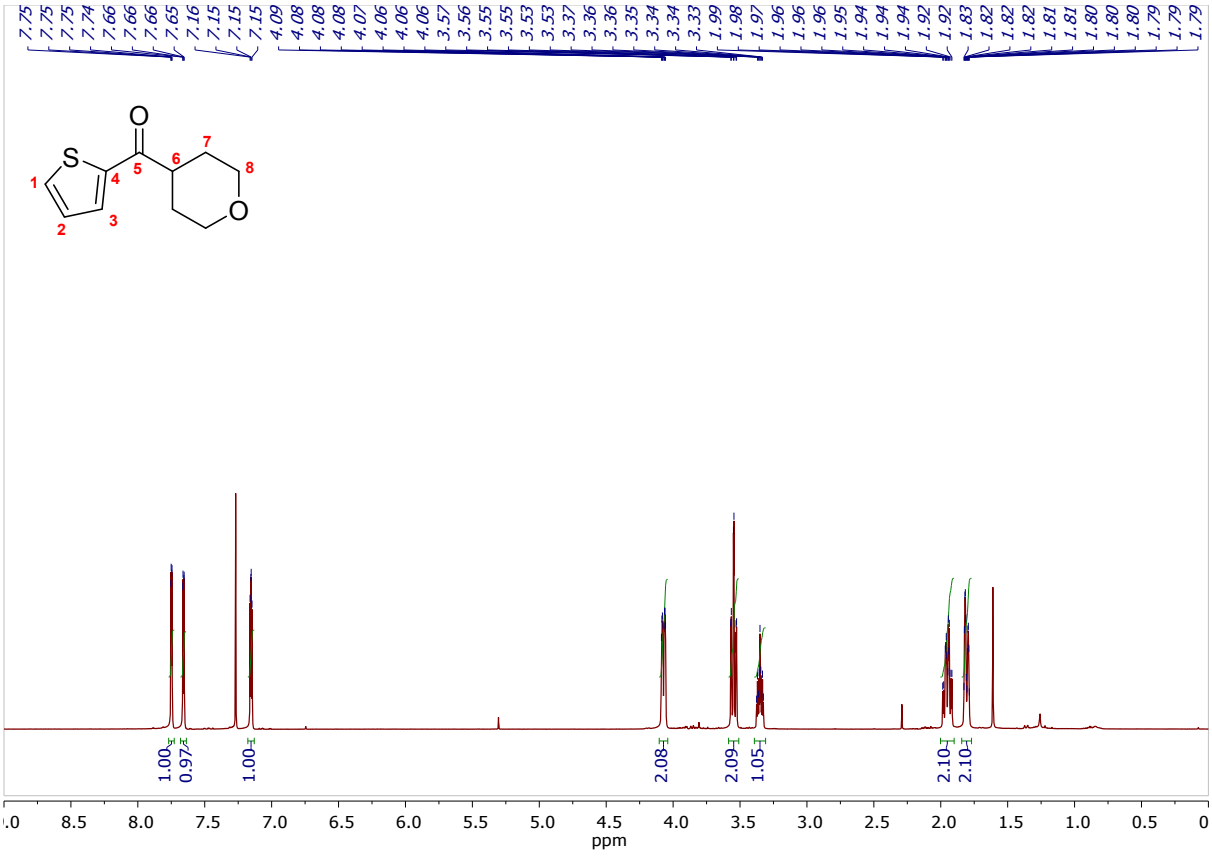


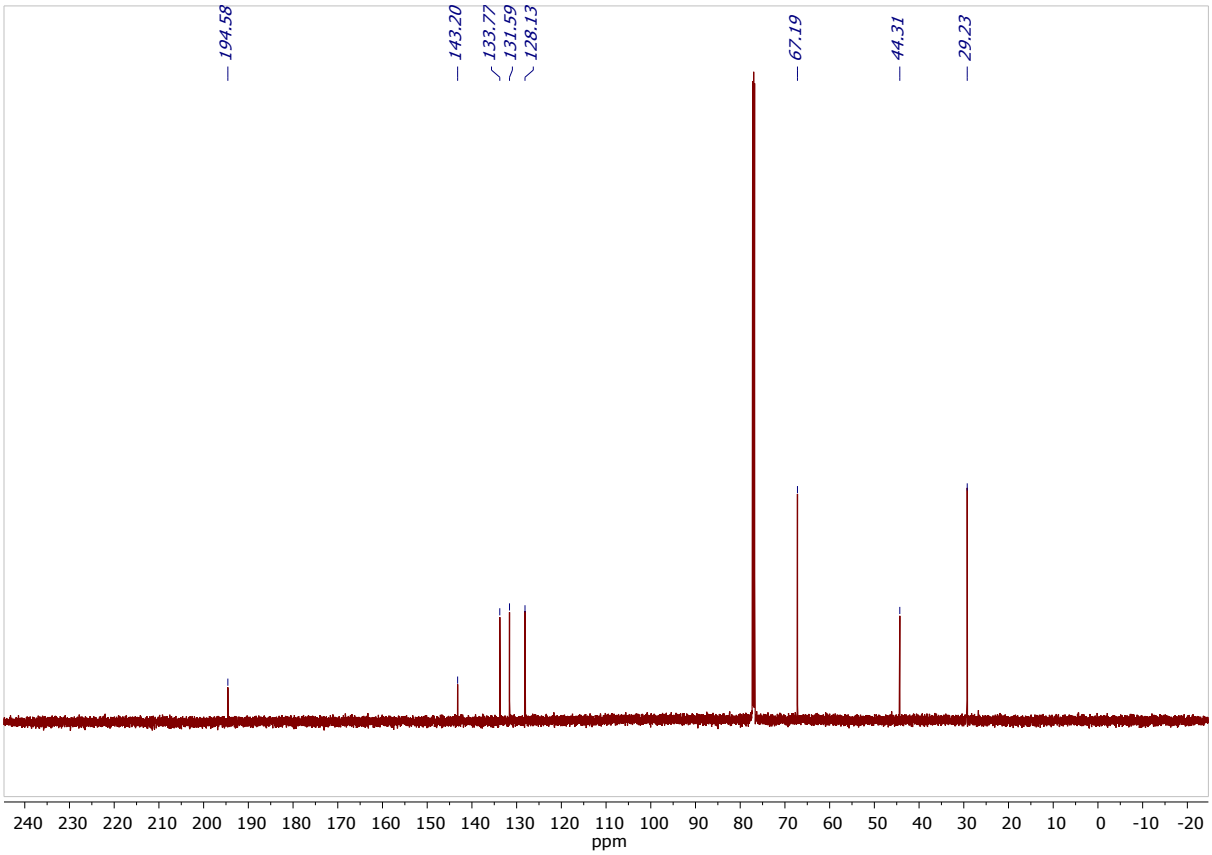
(6-chloropyridin-3-yl)(tetrahydro-2H-pyran-4-yl)methanone (26):



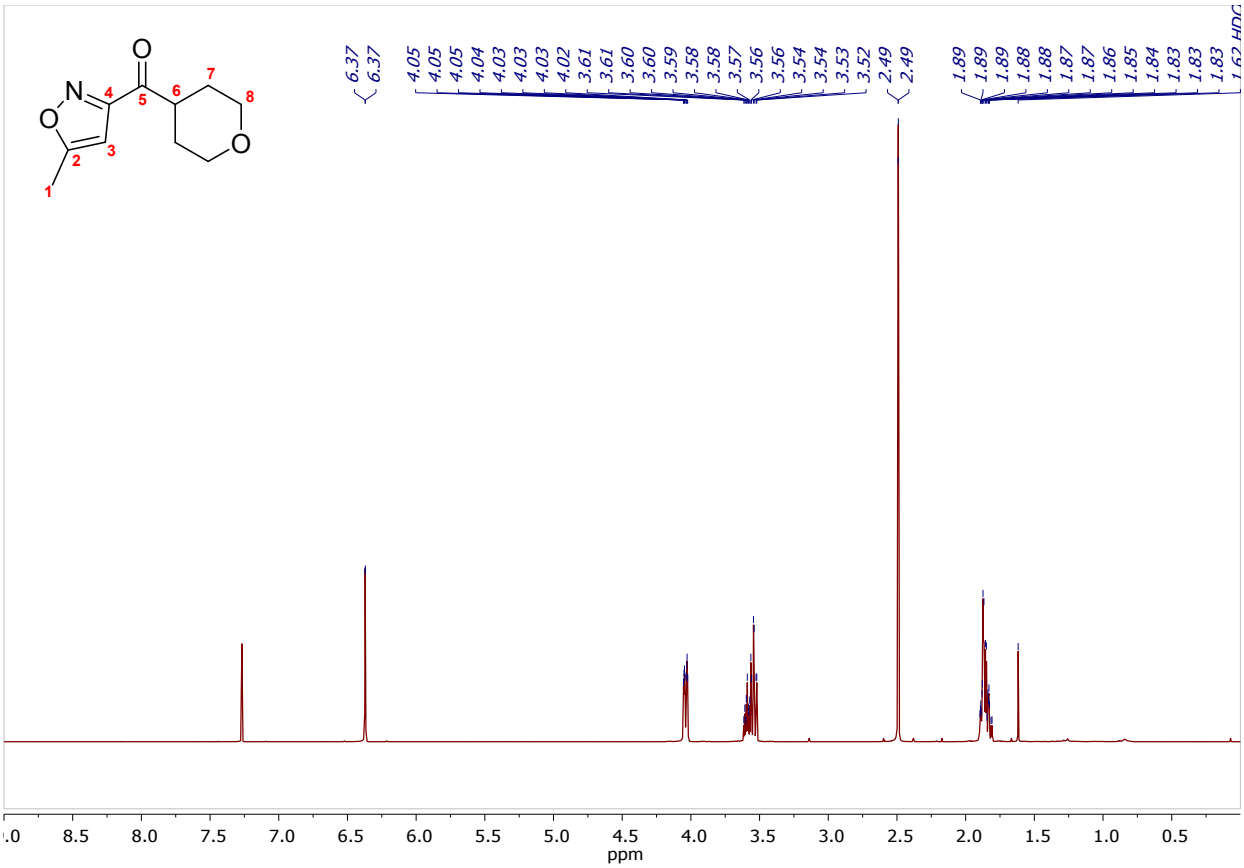


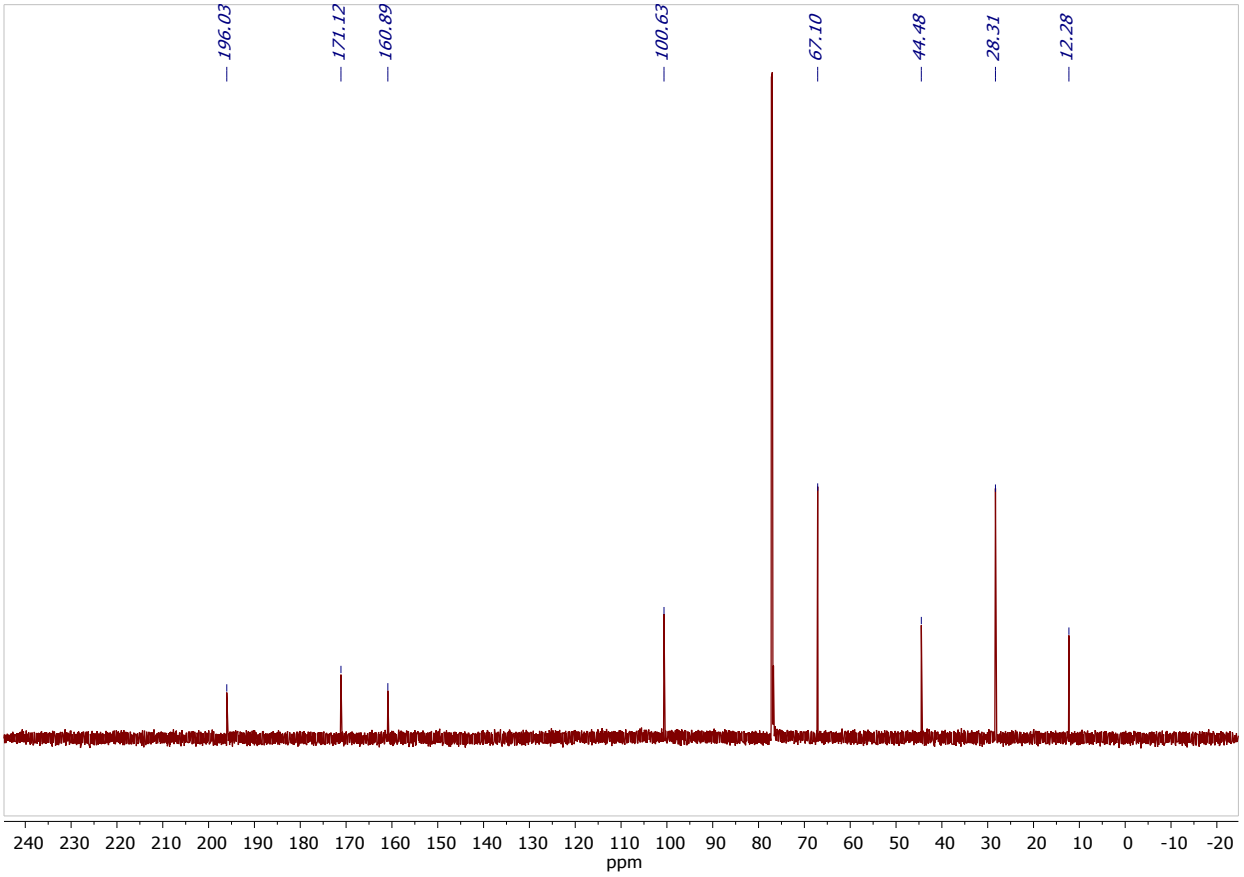
(tetrahydro-2H-pyran-4-yl)(thiophen-2-yl)methanone (27)



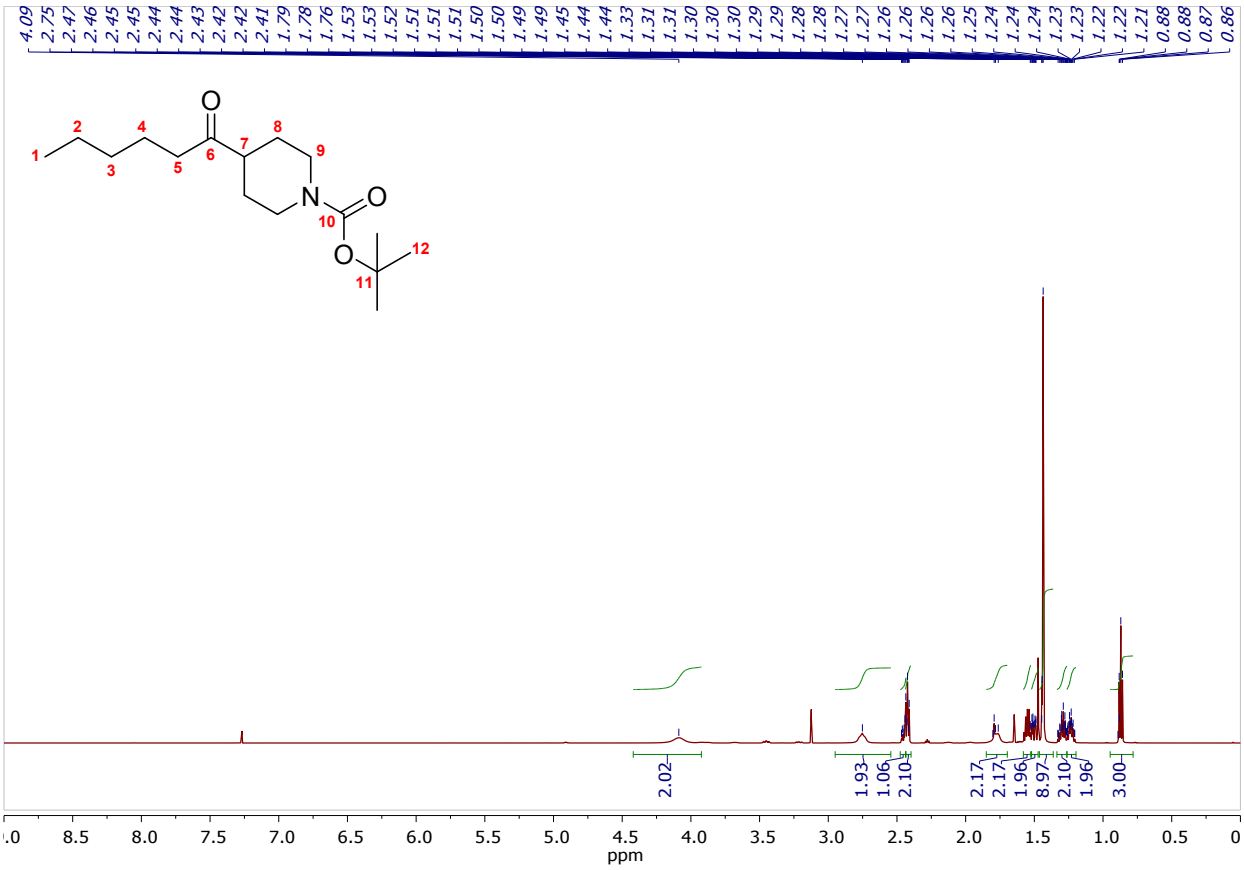


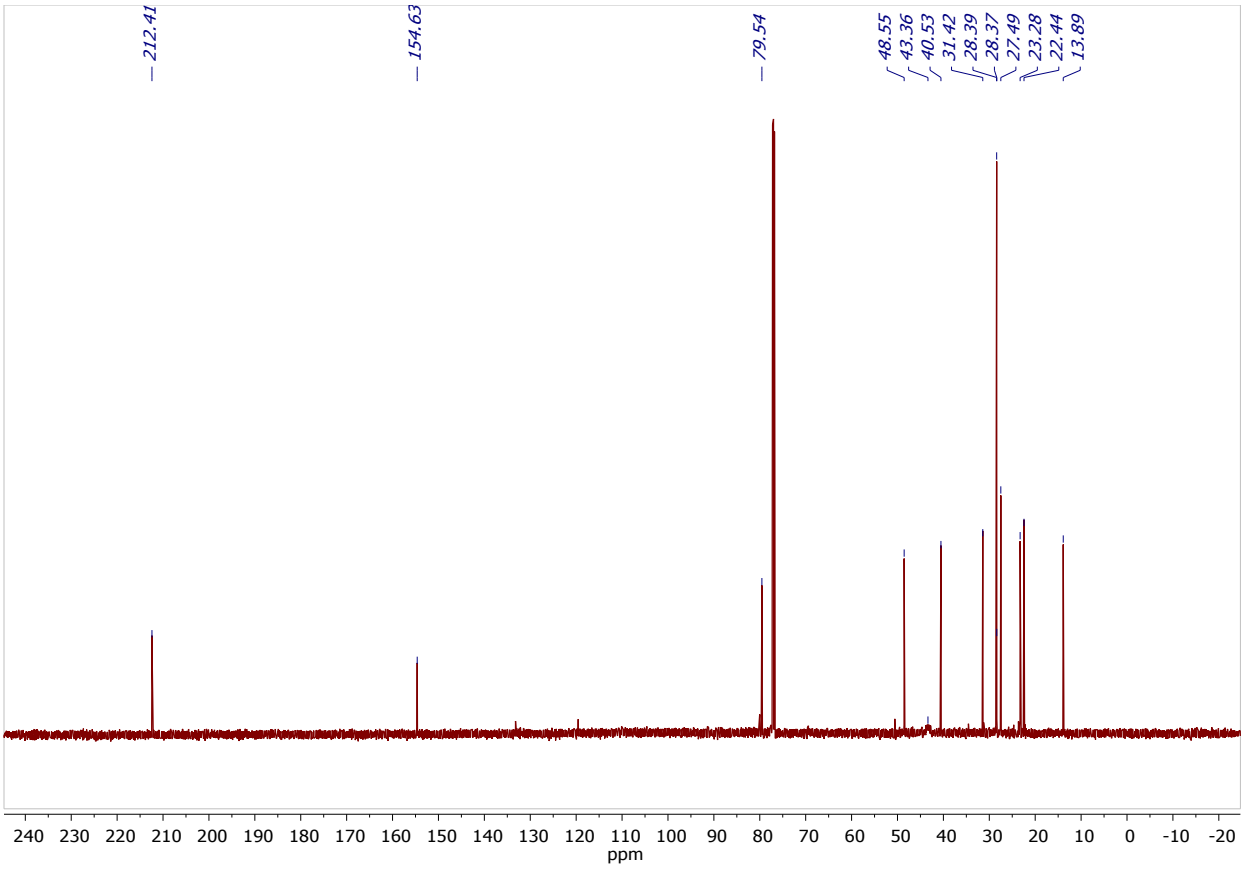
(5-methylisoxazol-3-yl)(tetrahydro-2H-pyran-4-yl)methanone (28):


6.37
6.37
4.05
4.05
4.05
4.04
4.03
4.03
4.02
3.61
3.61
3.60
3.60
3.59
3.58
3.58
3.57
3.56
3.56
3.54
3.54
3.53
3.52
2.49
2.49
1.89
1.89
1.89
1.88
1.88
1.87
1.87
1.86
1.85
1.84
1.83
1.83
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

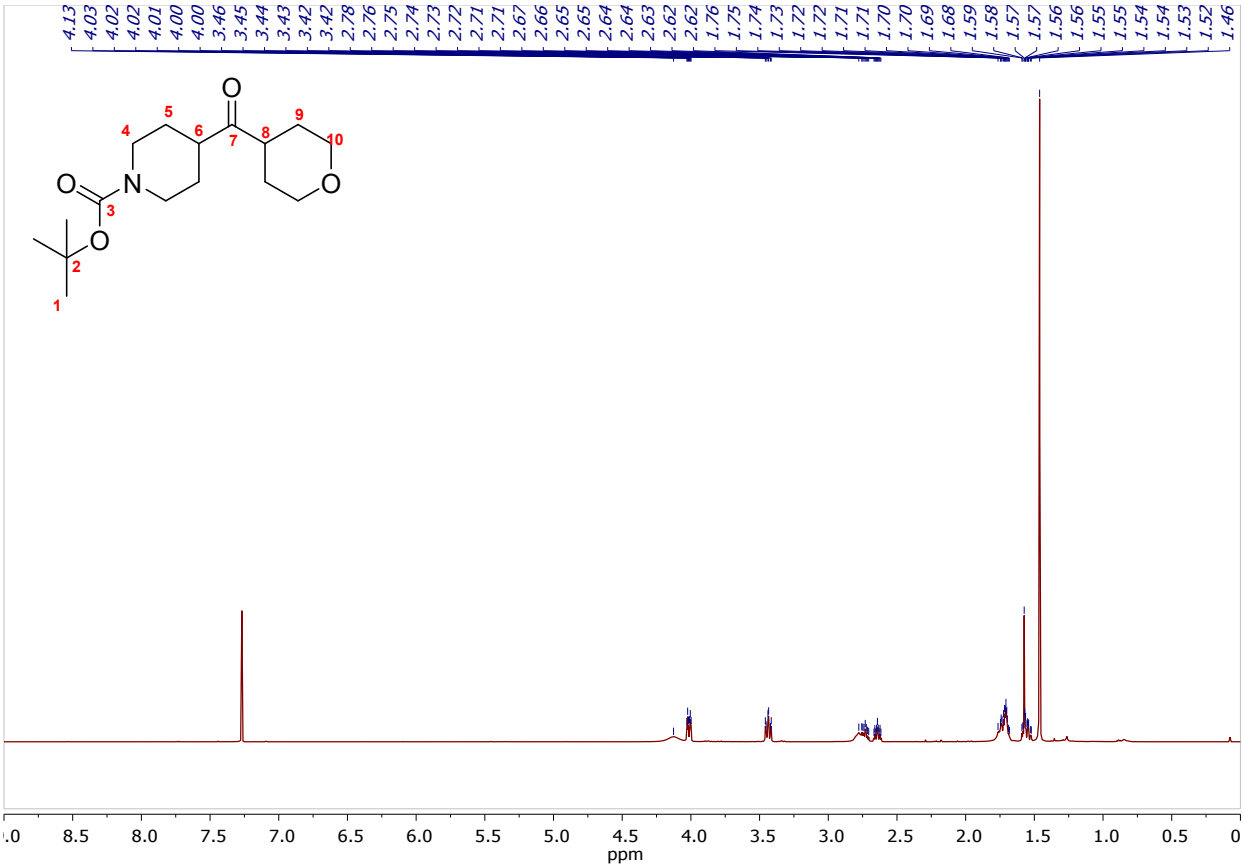

196.03
171.12
160.89
100.63
67.10
44.48
28.31
12.28
240
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
ppm

tert-butyl 4-hexanoylpiperidine-1-carboxylate (29):





tert-butyl 4-(tetrahydro-2H-pyran-4-carbonyl)piperidine-1-carboxylate (30):


4.13 4.03 4.02 4.02 4.01 4.00 4.00 3.46 3.45 3.44 3.43 3.42 2.78 2.76 2.75 2.74 2.73 2.72 2.71 2.71 2.67 2.66 2.65 2.65 2.64 2.64 2.63 2.62 2.62 1.76 1.75 1.74 1.73 1.72 1.72 1.71 1.71 1.70 1.70 1.69 1.68 1.59 1.58 1.57 1.57 1.56 1.56 1.55 1.55 1.54 1.54 1.53 1.52 1.46
O
O
N
O
O
1
2
3
4
5
6
7
8
9
10
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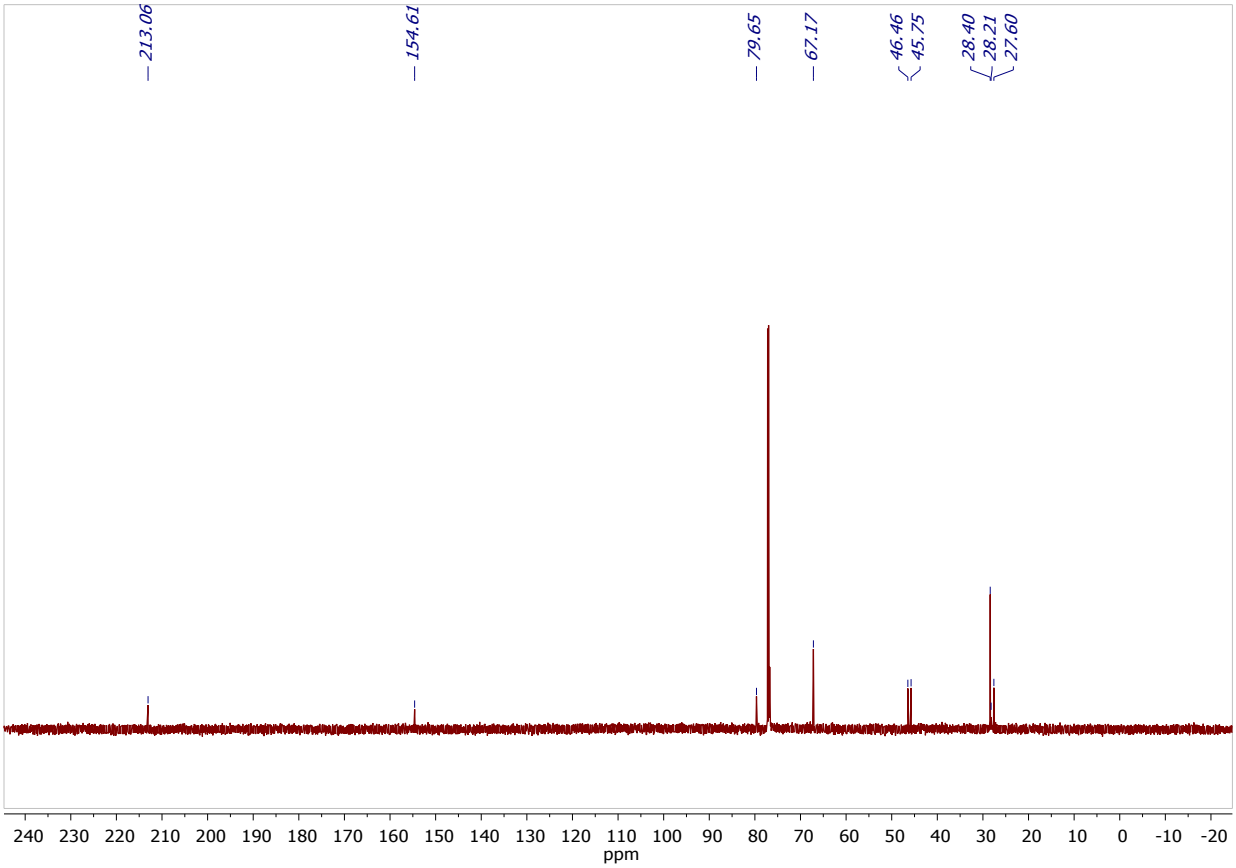
ppm


213.06
154.61
79.65
67.17
46.46
45.75
28.40
28.21
27.60
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
ppm

6 References

1. https://www.vapourtec.com/, (accessed 27/05/2018).

2. A. B. Pangborn, M. A. Giardello, R. H. Grubbs, R. K. Rosen and F. J. Timmers, *Organometallics*, 1996, **15**, 1518-1520.

3. The reaction can tolerate the use of non-distilled aldehydes however they were distilled for the sake of accuracy and to simplify post reaction purification procedures.

4. A. Greb, J. S. Poh, S. Greed, C. Battilocchio, P. Pasau, D. C. Blakemore and S. V. Ley, *Angew. Chem. Int. Ed.*, 2017, **56**, 16602-16605.

5. J. Warkentin, *J. Chem. Soc., Perkin Trans. 1*, 2000, 2161-2169.

6. M. Békhazi, P. J. Smith and J. Warkentin, *Can. J. Chem.*, 1984, **62**, 1646-1652.

7. T. Chiba and M. Okimoto, *J. Org. Chem.*, 1992, **57**, 1375-1379.

8. D. Guthrie, personal communication, 25/04/2018.