Supporting Information for

Simple and convenient access to α,α,α-trisubstituted amides by double addition of Grignard reagents to acyl cyanohydrins

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I. General information

All experiments were carried out under N_2 atmosphere. THF and CH_2Cl_2 were purified by passing through neutral alumina columns under nitrogen. The Grignard reagents for the synthesis of amides **5a-r** were prepared in anhydrous THF using the conventional method from the appropriate bromide precursors and Mg turnings.

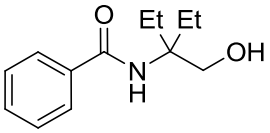
Analytical TLC were performed on Alugram SIL G/UV254 silica gel sheets (Macherey-Nagel) with detection by 5% ethanolic potassium permanganate solution. Column chromatography was carried out using silica gel 60 (0.040-0.063 mm) from Merck. Melting points were determined with a Büchi B-540 melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker DPX-200 or Bruker AC-400 spectrometer. Chemical shifts (δ) are expressed in ppm units, relative to the residual solvent peak. Coupling constants are given in Hz. The multiplicities are reported as follows: singlet (s), doublet (d), triplet (t), quadruplet (q), sextuplet (sext), multiplet (m), and broad signal (bs). IR spectra were obtained on a Perkin Elmer Spectrum One spectrometer on a single-reflection diamond ATR unit. High resolution mass spectra were recorded on a Waters Micromass GCT Premier spectrometer.

II. Synthesis and analytical data of amides 5a-r

General procedure for the synthesis of amides 5a-r

To a solution of cyanoester **2a-j** (1 mmol, unless otherwise mentioned) in THF (5 mL) cooled to 0 °C was added dropwise a solution of the appropriate Grignard reagent in THF (2.2 mmol). The mixture was allowed to warm up to room temperature and stirred at this temperature for 1 h. After addition of water (5 mL) and 1M aqueous HCl solution (1 mL), the aqueous phase was extracted with EtOAc (3 × 10 mL) and the combined organic layers were washed with brine. After drying over $MgSO_4$, the organic fraction was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel or recrystallization to afford the pure amides **5a-r**.

***N*-(3-(Hydroxymethyl)pentan-3-yl)benzamide (5a)**



General procedure applied on 3 mmol of cyanoester **2a**. Purification by flash chromatography (cyclohexane–EtOAc, 5:5) afforded amide **5a** as a yellow oil (432 mg, 65%).

R_f = 0.30 (cyclohexane–EtOAc, 5:5).

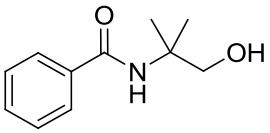
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 – 7.69 (m, 2H, Harom), 7.52 – 7.46 (m, 1H, Harom), 7.44 – 7.38 (m, 2H, Harom), 6.12 (bs, 1H, N*H*), 5.03 (bs, 1H, O*H*), 3.74 (s, 2H, CH_2), 1.84 – 1.68 (m, 4H, CH_2), 0.92 (t, *J* = 7.5 Hz, 6H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.7 (*C*=O), 135.1 (1 Carom), 131.7 (1 Carom), 128.8 (2 Carom), 127.0 (2 Carom), 67.1 (*C*H_2OH), 62.0 (*C*), 26.5 (2 *C*H_2), 7.7 (2 *C*H_3).

IR (neat): 3174, 3067, 2972, 2947, 2865, 1727, 1635, 1549, 1489, 1454, 1319, 1252, 1054 cm^{-1}.

HRMS (CI-NH_3/CH_4): m/z $[M + H]^+$ calcd for $C_{13}H_{20}NO_2$: 222.1494; found: 222.1489.

***N*-(1-Hydroxy-2-methylpropan-2-yl)benzamide (5b)**



Purification by flash chromatography (cyclohexane–EtOAc, 5:5) afforded amide **5b** as a white solid (112 mg, 58%).

Mp 87–89 °C; R_f = 0.35 (cyclohexane–EtOAc, 5:5).

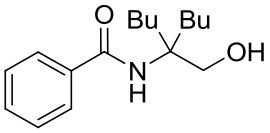
^{1}H NMR (200 MHz, $CDCl_3$): δ 7.74 – 7.67 (m, 2H, Harom), 7.53 – 7.33 (m, 3H, Harom), 6.38 (bs, 1H, N*H*), 5.02 (bs, 1H, O*H*), 3.64 (s, 2H, CH_2), 1.39 (s, 6 H, CH_3).

^{13}C NMR (50 MHz, $CDCl_3$): δ 168.6 (*C*=O), 134.9 (1 Carom), 131.7 (1 Carom), 128.7 (2 Carom), 127.0 (2 Carom), 70.7 (*C*H_2OH), 56.4 (*C*), 24.6 (2 *C*H_3).

IR (neat): 3296, 3181, 2980, 2930, 1700, 1628, 1539, 1490, 1449, 1314, 1263, 1066 cm^{-1}.

HRMS (CI-NH_3/CH_4): m/z $[M + H]^+$ calcd for $C_{11}H_{16}NO_2$: 194.1181; found: 194.1181.

_N_-(5-(Hydroxymethyl)nonan-5-yl)benzamide (5c)



Purification by flash chromatography (cyclohexane–EtOAc, 7:3) afforded amide **5c** as a pale yellow oil (135 mg, 49%).

R_f = 0.40 (cyclohexane–EtOAc, 7:3).

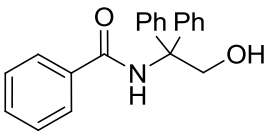
^{1}H NMR (200 MHz, $CDCl_3$): δ 7.74 – 7.66 (m, 2H, Harom), 7.53 – 7.33 (m, 3H, Harom), 6.19 (bs, 1H, N*H*), 5.18 (bs, 1H, O*H*), 3.72 (m, 2H, CH_2), 1.79 – 1.61 (m, 4H, CH_2), 1.41 – 1.19 (m, 8H, CH_2), 0.90 (t, *J* = 6.6 Hz, 6H, CH_3).

^{13}C NMR (50 MHz, $CDCl_3$): δ 168.6 (*C*=O), 135.2 (1 Carom), 131.8 (1 Carom), 128.8 (2 Carom), 127.0 (2 Carom), 68.0 (*C*H_2OH), 61.9 (*C*), 34.4 (2 *C*H_2), 25.6 (2 *C*H_2), 23.3 (2 *C*H_2), 14.2 (2 *C*H_3).

IR (neat): 3309, 2955, 2930, 2862, 1739, 1638, 1525, 1488, 1466, 1365, 1217, 1054 cm^{-1}.

HRMS (CI-NH_3/CH_4): m/z $[M + H]^+$ calcd for $C_{17}H_{28}NO_2$: 277.2120; found: 277.2121.

_N_-(2-Hydroxy-1,1-diphenylethyl)benzamide (5d)



General procedure applied on 12 mmol of cyanoester **2a.** Purification by recrystallization from toluene afforded amide **5d** as white crystals (3.05 g, 80%).

Mp 185–187 °C.

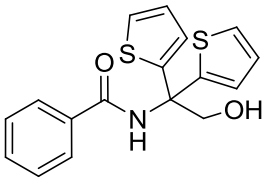
^{1}H NMR (200 MHz, $CDCl_3$): δ 7.86 – 7.80 (m, 2H, Harom), 7.61 – 7.29 (m, 13H, Harom), 6.99 (bs, 1H, N*H*), 5.31 (t, *J* = 6.4 Hz, 1H, O*H*), 4.50 (d, *J* = 6.4 Hz, 2H, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.5 (*C*=O), 142.0 (2 Carom), 134.3 (1 Carom), 132.2 (1 Carom), 128.9 (2 Carom), 128.8 (4 Carom), 128.0 (2 Carom), 127.4 (4 Carom), 127.2 (2 Carom), 70.1 (*C*H_2OH), 69.4 (*C*).

IR (neat): 3271, 3059, 3027, 2920, 2867, 1726, 1638, 1600, 1578, 1525, 1485, 1444, 1312, 1283, 1075 cm^{-1}.

HRMS (CI-NH_3/CH_4): m/z $[M + H]^+$ calcd for $C_{21}H_{20}NO_2$: 318.1494; found: 318.1495.

***N*-(2-Hydroxy-1,1-di(thiophen-2-yl)ethyl)benzamide (5e)**



Purification by flash chromatography (cyclohexane–EtOAc, 7:3) afforded amide **5e** as a dark red solid (197 mg, 60%).

Mp 156.5–158.5 °C; R_f = 0.31 (cyclohexane–EtOAc, 7:3).

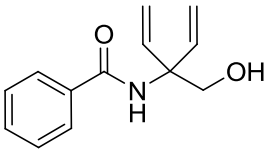
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, *J* = 7.3 Hz, 2H, Harom), 7.56 (t, *J* = 7.4 Hz, 1H, Harom), 7.47 (t, *J* = 7.6 Hz, 2H, Harom), 7.31 (dd, *J* = 5.1 Hz, *J* = 1.0 Hz, 2H, Harom), 7.21 (bs, 1H, N*H*), 7.09 (dd, *J* = 3.6 Hz, *J* = 1.0 Hz, 2H, Harom), 7.02 (dd, *J* = 5.1 Hz, *J* = 3.6 Hz, 2H, Harom), 4.96 (bs, 1H, O*H*), 4.45 (s, 2H, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.9 (*C*=O), 146.3 (2 Carom), 134.2 (1 Carom), 132.2 (1 Carom), 128.9 (2 Carom), 127.3 (2 Carom), 127.0 (2 Carom), 126.1 (2 Carom), 125.5 (2 Carom), 71.1 (*C*H_2OH), 64.9 (*C*).

IR (neat): 3283, 1739, 1650, 1578, 1515, 1483, 1290, 1060 cm^{-1}.

HRMS (CI-NH_3): m/z $[M + H]^+$ calcd for $C_{17}H_{16}NO_2S_2$: 330.0622; found: 330.0616.

***N*-(3-(Hydroxymethyl)penta-1,4-dien-3-yl)benzamide (5f)**



Purification by flash chromatography (cyclohexane–EtOAc, 7:3) afforded amide **5f** as a pale yellow solid (155 mg, 71%).

Mp 82–84 °C; R_f = 0.17 (cyclohexane–EtOAc, 7:3).

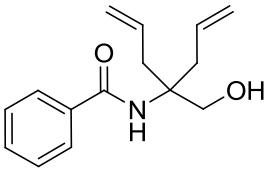
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 – 7.76 (m, 2H, Harom), 7.49 (m, 1H, Harom), 7.45 – 7.40 (m, 2H, Harom), 6.59 (bs, 1H, N*H*), 6.02 (dd, *J* = 17.4 Hz, *J* = 10.7 Hz, 2H, C*H*), 5.33 (d, *J* = 10.7 Hz, 2H, CH_2), 5.26 (d, *J* = 17.4 Hz, 2H, CH_2), 4.47 (bs, 1H, O*H*), 3.77 (s, 2H, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.9 (*C*=O), 137.7 (2 *C*H), 134.6 (1 Carom), 131.9 (1 Carom), 128.8 (2 Carom), 127.1 (2 Carom), 115.9 (2 *C*H_2), 67.9 (*C*H_2), 64.9 (*C*).

IR (neat): 3292, 3151, 3065, 2917, 2857, 1727, 1632, 1601, 1579, 1548, 1489, 1409, 1347, 1315, 1260, 1163, 1091 cm^{-1}.

HRMS (CI-NH_3): m/z $[M + H]^+$ calcd for $C_{13}H_{16}NO_2$: 218.1181; found: 218.1181.

***N*-(4-(Hydroxymethyl)hepta-1,6-dien-4-yl)benzamide (5g)**



Purification by flash chromatography (cyclohexane–EtOAc, 7:3) afforded amide **5g** as a colorless oil (157 mg, 64%).

R_f = 0.20 (cyclohexane–EtOAc, 7:3).

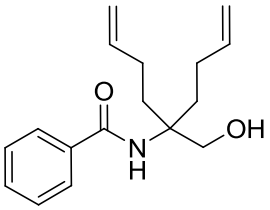
^{1}H NMR (200 MHz, $CDCl_3$): δ 7.75 – 7.67 (m, 2H, Harom), 7.57 – 7.39 (m, 3H, Harom), 6.39 (bs, 1H, N*H*), 5.92 (dddd, *J* = 18.9 Hz, *J* = 9.3 Hz, *J* = 8.5 Hz, *J* = 6.6 Hz, 2H, C*H*), 5.28 – 5.17 (m, 4H, CH_2), 5.08 (t, *J* = 5.6 Hz, 1H, O*H*), 3.78 (d, *J* = 5.6 Hz, 2H, CH_2), 2.66 (dd, *J* = 13.9 Hz, *J* = 6.6 Hz, 2H, CH_2), 2.38 (dd, *J* = 13.9 Hz, *J* = 8.5 Hz, 2H, CH_2).

^{13}C NMR (50 MHz, $CDCl_3$): δ 168.4 (*C*=O), 134.8 (1 Carom), 133.1 (2 *C*H), 131.9 (1 Carom), 128.9 (2 Carom), 127.0 (2 Carom), 120.1 (2 *C*H_2), 68.3 (*C*H_2), 60.4 (*C*), 39.1 (2 *C*H_2).

IR (neat): 3343, 3075, 2978, 2922, 1735, 1638, 1602, 1579, 1520, 1487, 1439, 1326, 1308, 1058 cm^{-1}.

HRMS (CI-NH_3): m/z $[M + H]^+$ calcd for $C_{15}H_{20}NO_2$: 246.1494; found: 246.1499.

***N*-(5-(Hydroxymethyl)nona-1,8-dien-5-yl)benzamide (5h)**



Purification by flash chromatography (cyclohexane–EtOAc, 7:3) afforded amide **5h** as a yellow oil (145 mg, 53%).

R_f = 0.30 (cyclohexane–EtOAc, 7:3).

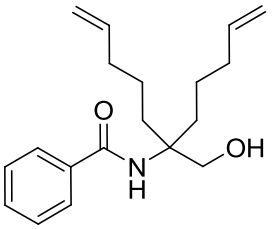
^{1}H NMR (200 MHz, $CDCl_3$): δ 7.75 – 7.67 (m, 2H, Harom), 7.54 – 7.36 (m, 3H, Harom), 6.23 (bs, 1H, N*H*), 5.83 (ddt, *J* = 16.7 Hz, *J* = 10.0 Hz, *J* = 6.4 Hz, 2H, C*H*), 5.16 – 4.92 (m, 4H, CH_2), 3.78 (s, 2H, CH_2), 2.25 – 1.99 (m, 4H, CH_2), 1.85 (t, *J* = 7.9 Hz, 4H, CH_2).

^{13}C NMR (50 MHz, $CDCl_3$): δ 168.5 (*C*=O), 138.1 (2 *C*H), 134.9 (1 Carom), 131.9 (1 Carom), 128.8 (2 Carom), 127.0 (2 Carom), 115.4 (2 *C*H_2), 67.7 (*C*H_2), 61.6 (*C*), 33.9 (2 *C*H_2), 27.8 (2 *C*H_2).

IR (neat): 3315, 3074, 2931, 1727, 1639, 1603, 1578, 1520, 1488, 1450, 1289, 1068 cm^{-1}.

HRMS (CI-NH_3/CH_4): m/z $[M + H]^+$ calcd for $C_{17}H_{24}NO_2$: 274.1807; found: 274.1807.

***N*-(6-(Hydroxymethyl)undeca-1,10-dien-6-yl)benzamide (5i)**



Purification by flash chromatography (cyclohexane–EtOAc, 7:3) afforded amide **5i** as a pale yellow oil (172 mg, 57%).

R_f = 0.50 (cyclohexane–EtOAc, 7:3).

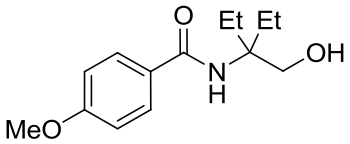
^{1}H NMR (200 MHz, $CDCl_3$): δ 7.76 – 7.67 (m, 2H, Harom), 7.56 – 7.39 (m, 3H, Harom), 6.06 (bs, 1H, N*H*), 5.80 (ddt, *J* = 16.8 Hz, *J* = 10.0 Hz, *J* = 6.6 Hz, 2H, C*H*), 5.08 – 4.95 (m, 5H, CH_2, O*H*), 3.77 (s, 2H, CH_2), 2.09 (q, *J* = 7.1 Hz, 4H, CH_2), 1.81 – 1.68 (m, 4H, CH_2), 1.49 – 1.36 (m, 4H, CH_2).

^{13}C NMR (50 MHz, $CDCl_3$): δ 168.6 (*C*=O), 138.3 (2 *C*H), 135.0 (1 Carom), 131.9 (1 Carom), 128.9 (2 Carom), 127.0 (2 Carom), 115.4 (2 *C*H_2), 67.9 (*C*H_2), 61.8 (*C*), 34.2 (2 *C*H_2), 34.1 (2 *C*H_2), 22.8 (2 *C*H_2).

IR (neat): 3317, 3075, 2971, 2931, 2863, 1739, 1639, 1603, 1578, 1520, 1488, 1365, 1217, 1071 cm^{-1}.

HRMS (CI-NH_3/CH_4): m/z $[M + H]^+$ calcd for $C_{19}H_{28}NO_2$: 302.2120; found: 302.2110.

***N*-(3-(Hydroxymethyl)pentan-3-yl)-4-methoxybenzamide (5j)**



General procedure applied on 2 mmol of cyanoester **2b**. Purification by flash chromatography (cyclohexane–EtOAc, 5:5) afforded amide **5j** as a white solid (367 mg, 73%).

Mp 70.5–72.5 °C; R_f = 0.41 (cyclohexane–EtOAc, 5:5).

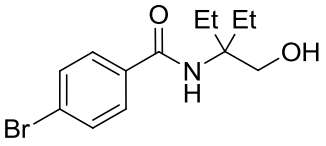
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, *J* = 8.8 Hz, 2H, Harom), 6.92 (d, *J* = 8.8 Hz, 2H, Harom), 5.97 (bs, 1H, N*H*), 5.26 (bs, 1H, O*H*), 3.84 (s, 3H, CH_3O), 3.75 (s, 2H, CH_2), 1.83 – 1.67 (m, 4H, CH_2), 0.93 (t, *J* = 7.5 Hz, 6H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3 (*C*=O), 162.4 (1 Carom), 128.8 (2 Carom), 127.2 (1 Carom), 114.0 (2 Carom), 67.6 (*C*H_2OH), 61.9 (*C*), 55.6 (*C*H_3O), 26.6 (2 *C*H_2), 7.8 (2 *C*H_3).

IR (neat): 3318, 3281, 3004, 2965, 2934, 2878, 1726, 1627, 1605, 1548, 1461, 1254, 1174, 1035 cm^{-1}.

HRMS (CI-NH_3/CH_4): m/z $[M + H]^+$ calcd for $C_{14}H_{22}NO_3$: 252.1600; found: 252.1604.

4-Bromo-*N*-(3-(hydroxymethyl)pentan-3-yl)benzamide (5k)



Purification by flash chromatography (cyclohexane–EtOAc, 5:5) afforded amide **5k** as a white solid (174 mg, 58%).

Mp 95–97 °C; R_f = 0.40 (cyclohexane–EtOAc, 5:5).

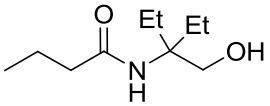
^{1}H NMR (200 MHz, $CDCl_3$): δ 7.61 – 7.49 (m, 4H, Harom), 6.10 (bs, 1H, N*H*), 4.83 (bs, 1H, O*H*), 3.73 (bs, 2H, CH_2), 1.75 (q, *J* = 7.5 Hz, 4H, CH_2), 0.90 (t, *J* = 7.5 Hz, 6H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.7 (*C*=O), 134.0 (1 Carom), 132.0 (2 Carom), 128.6 (2 Carom), 126.4 (1 Carom), 66.9 (*C*H_2OH), 62.1 (*C*), 26.5 (2 *C*H_2), 7.8 (2 *C*H_3).

IR (neat): 3196, 3071, 2970, 2938, 2864, 1737, 1634, 1591, 1548, 1481, 1455, 1443, 1343, 1250, 1053 cm^{-1}.

HRMS (CI-NH_3): m/z $[M + H]^+$ calcd for $C_{13}H_{19}NO_2Br$: 300.0599; found: 300.0602.

***N*-(3-(Hydroxymethyl)pentan-3-yl)butyramide (5l)**



Purification by flash chromatography (cyclohexane–EtOAc, 7:3) afforded amide **5l** as a pale yellow oil (97 mg, 52%).

R_f = 0.33 (cyclohexane–EtOAc, 7:3).

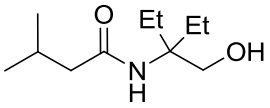
^{1}H NMR (200 MHz, $CDCl_3$): δ 5.38 (bs, 1H, N*H*), 5.16 (bs, 1H, O*H*), 3.65 (s, 2H, CH_2), 2.18 (t, *J* = 7.4 Hz, 2H, CH_2), 1.76 – 1.54 (m, 6H, CH_2), 0.95 (t, *J* = 7.4 Hz, 3H, CH_3), 0.86 (t, *J* = 7.5 Hz, 6H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ 174.5 (*C*=O), 67.5 (*C*H_2OH), 61.6 (*C*), 39.3 (*C*H_2C=O), 26.6 (2 *C*H_2), 19.5 (*C*H_2), 13.7 (*C*H_3), 7.6 (2 *C*H_3).

IR (neat): 3300, 3083, 2966, 2936, 2877, 1740, 1645, 1547, 1459, 1376, 1217, 1062 cm^{-1}.

HRMS (CI-NH_3/CH_4): m/z $[M + H]^+$ calcd for $C_{10}H_{22}NO_2$: 188.1651; found: 188.1647.

_N_-(3-(Hydroxymethyl)pentan-3-yl)-3-methylbutanamide (5m)



Purification by flash chromatography (cyclohexane–EtOAc, 7:3) afforded amide **5m** as a colorless oil (124 mg, 62%).

R_f = 0.35 (cyclohexane–EtOAc, 7:3).

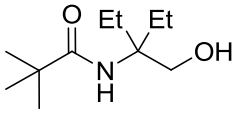
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.53 (bs, 1H, N*H*), 5.27 (bs, 1H, O*H*), 3.62 (s, 2H, CH_2), 2.07 – 2.01 (m, 3H, CH_2. C*H*), 1.69 – 1.54 (m, 4H, CH_2), 0.93 (d, *J* = 5.9 Hz, 6H, CH_3), 0.84 (t, *J* = 7.4 Hz, 6H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ 174.0 (*C*=O), 67.5 (*C*H_2OH), 61.7 (*C*), 46.8 (*C*H_2C=O), 26.7 (2 *C*H_2), 26.5 (*C*H), 22.4 (2 *C*H_3), 7.6 (2 *C*H_3).

IR (neat): 3267, 3183, 3086, 2963, 2933, 2870, 1631, 1558, 1457, 1263, 1051 cm^{-1}.

HRMS (CI-NH_3/CH_4): m/z $[M + H]^+$ calcd for $C_{11}H_{24}NO_2$: 202.1807; found: 202.1809.

_N_-(3-(Hydroxymethyl)pentan-3-yl)pivalamide (5n)



Purification by flash chromatography (cyclohexane–EtOAc, 7:3) afforded amide **5n** as a colorless oil (110 mg, 55%).

R_f = 0.34 (cyclohexane–EtOAc, 7:3).

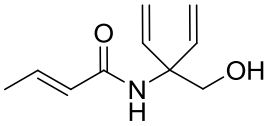
^{1}H NMR (200 MHz, $CDCl_3$): δ 5.55 (bs, 1H, N*H*), 5.21 (bs, 1H, O*H*), 3.60 (s, 2H, CH_2), 1.70 – 1.54 (m, 4H, CH_2), 1.18 (s, 9H, CH_3), 0.84 (t, *J* = 7.5 Hz, 6H, CH_3).

^{13}C NMR (500 MHz, $CDCl_3$): δ 179.8 (*C*=O), 67.8 (*C*H_2OH), 61.1 (*C*), 39.4 (*C*$(CH_3)_3$), 27.9 (3 *C*H_3), 26.5 (2 *C*H_2), 7.7 (2 *C*H_3).

IR (neat): 3438, 2970, 2880, 1739, 1640, 1558, 1515, 1455, 1365, 1217 cm^{-1}.

HRMS (CI-NH_3/CH_4): m/z $[M + H]^+$ calcd for $C_{11}H_{24}NO_2$: 202.1807; found: 202.1812.

***(E)*-*N*-(3-(Hydroxymethyl)penta-1,4-dien-3-yl)but-2-enamide (5o)**



Purification by flash chromatography (cyclohexane–EtOAc, 5:5) afforded amide **5o** as a yellow oil (100 mg, 55%).

R_f = 0.20 (cyclohexane–EtOAc, 5:5).

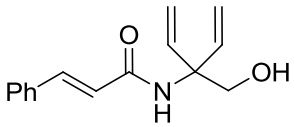
^{1}H NMR (200 MHz, $CDCl_3$): δ 6.90 (dq, *J* = 15.1 Hz, *J* = 6.9 Hz, 1H, C*H*), 5.94 (dd, *J* = 17.3 Hz, *J* = 10.6 Hz, 2H, C*H*), 5.90 (dq, *J* = 15.1 Hz, *J* = 1.7 Hz, 1H, C*H*), 5.69 (bs, 1H, N*H*), 5.29 (dd, *J* = 10.6 Hz, *J* = 0.5 Hz, 2H, CH_2), 5.20 (dd, *J* = 17.3 Hz, *J* = 0.5 Hz, 2H, CH_2), 4.76 (t, *J* = 6.7 Hz, 1H, O*H*), 3.72 (d, *J* = 6.7 Hz, 2H, CH_2), 1.88 (dd, *J* = 6.9 Hz, *J* = 1.7 Hz, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.5 (*C*=O), 141.4 (*C*H), 137.7 (2 *C*H), 124.9 (*C*H), 115.8 (2 *C*H_2), 68.0 (*C*H_2), 65.1 (*C*), 17.8 (*C*H_3).

IR (neat): 3283, 3087, 2916, 2870, 1670, 1628, 1534, 1446, 1409, 1344, 1290, 1230, 1050 cm^{-1}.

HRMS (CI-NH_3): m/z $[M + H]^+$ calcd for $C_{10}H_{16}NO_2$: 182.1181; found: 182.1183.

***N*-(3-(Hydroxymethyl)penta-1,4-dien-3-yl)cinnamamide (5p)**



Purification by flash chromatography (cyclohexane–EtOAc, 5:5) afforded amide **5p** as a yellow solid (153 mg, 63%).

Mp 79–81 °C; R_f = 0.50 (cyclohexane–EtOAc, 5:5).

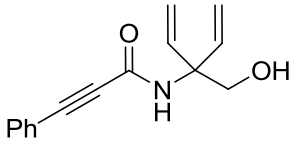
^{1}H NMR (200 MHz, $CDCl_3$): δ 7.67 (d, *J* = 15.6 Hz, 1H, C*H*), 7.55– 7.48 (m, 2H, Harom), 7.42 – 7.35 (m, 3H, Harom), 6.50 (d, *J* = 15.6 Hz, 1H, C*H*), 5.99 (dd, *J* = 17.3 Hz, *J* = 10.6 Hz, 2H, C*H*), 5.94 (bs, 1H, N*H*), 5.32 (d, *J* = 10.6 Hz, 2H, CH_2), 5.27 (d, *J* = 17.3 Hz, 2H, CH_2), 4.67 (t, *J* = 6.8 Hz, 1H, O*H*), 3.77 (d, *J* = 6.8 Hz, 2H, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.5 (*C*=O), 142.4 (*C*H), 137.6 (2 *C*H), 134.6 (1 Carom), 130.1 (1 Carom), 129.0 (2 Carom), 128.1 (2 Carom), 120.4 (*C*H), 116.0 (2 *C*H_2), 68.1 (*C*H_2), 65.4 (*C*).

IR (neat): 3260, 3060, 2920, 2855, 1718, 1654, 1615, 1578, 1549, 1498, 1448, 1416, 1348, 1228, 1057 cm^{-1}.

HRMS (CI-NH_3): m/z $[M + H]^+$ calcd for $C_{15}H_{18}NO_2$: 244.1338; found: 244.1341.

_N_-(3-(Hydroxymethyl)penta-1,4-dien-3-yl)-3-phenylpropiolamide (5q)



Purification by flash chromatography (cyclohexane–EtOAc, 7:3) afforded amide **5q** as a yellow oil (123 mg, 51%).

R_f = 0.15 (cyclohexane–EtOAc, 7:3).

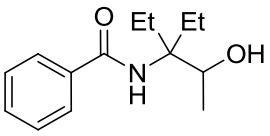
^{1}H NMR (200 MHz, $CDCl_3$): δ 7.59– 7.51 (m, 2H, Harom), 7.47 – 7.31 (m, 3H, Harom), 6.22 (bs, 1H, N*H*), 5.97 (dd, *J* = 17.3 Hz, *J* = 10.7 Hz, 2H, C*H*), 5.36 (d, *J* = 10.7 Hz, 2H, CH_2), 5.31 (d, *J* = 17.3 Hz, 2H, CH_2), 3.74 (d, *J* = 6.6 Hz, 2H, CH_2), 3.57 (t, *J* = 6.6 Hz, 1H, O*H*).

^{13}C NMR (100 MHz, $CDCl_3$): δ 153.5 (*C*=O), 136.9 (2 *C*H), 132.7 (2 Carom), 130.4 (1 Carom), 128.7 (2 Carom), 120.1 (1 Carom), 116.5 (2 *C*H_2), 85.3 (*C*), 83.2 (*C*), 67.5 (*C*H_2), 65.6 (*C*).

IR (neat): 3259, 3022, 2933, 2873, 2213, 1736, 1628, 1491, 1443, 1409, 1365, 1302, 1217, 1050 cm^{-1}.

HRMS (CI-NH_3): m/z $[M + H]^+$ calcd for $C_{15}H_{16}NO_2$: 242.1181; found: 242.1190.

_N_-(3-Ethyl-2-hydroxypentan-3-yl)benzamide (5r)



Purification by flash chromatography (cyclohexane–EtOAc, 7:3) afforded amide **5r** as a pale yellow oil (53 mg, 23%).

R_f = 0.35 (cyclohexane–EtOAc, 7:3).

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.77 – 7.68 (m, 2H, Harom), 7.57 – 7.37 (m, 3H, Harom), 5.93 (bs, 1H, N*H*), 5.74 (d, *J* = 9.5 Hz, 1H, O*H*), 3.80 (dq, *J* = 9.5 Hz, *J* = 6.4 Hz, 1H, C*H*), 2.09 (dt, *J* = 14.6 Hz, *J* = 7.4 Hz, 1H, CH_2), 1.95 (dt, *J* = 14.6 Hz, *J* = 7.4 Hz, 1H, CH_2), 1.66 (m, 1H, CH_2), 1.59 (dt, *J* = 14.2 Hz, *J* = 7.4 Hz, 1H, CH_2), 1.18 (d, *J* = 6.4 Hz, 3H, CH_3), 0.96 (t, *J* = 7.4 Hz, 3H, CH_3), 0.91 (t, *J* = 7.4 Hz, 3H, CH_3).

^{13}C NMR (50 MHz, $CDCl_3$): δ 168.7 (*C*=O), 135.1 (1 Carom), 131.8 (1 Carom), 128.9 (2 Carom), 127.0 (2 Carom), 67.4 (*C*H), 62.1 (*C*), 26.7 (2 *C*H_2), 7.8 (3 *C*H_3).

IR (neat): 3308, 3210, 3061, 2975, 2931, 2882, 1729, 1630, 1600, 1577, 1539, 1489, 1451, 1334, 1315, 1274, 1107, 1028 cm^{-1}.

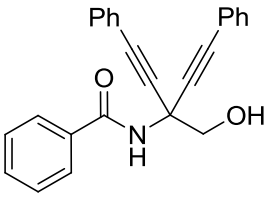
HRMS (CI-NH_3/CH_4): m/z $[M + H]^+$ calcd for $C_{14}H_{22}NO_2$: 236.1651; found: 236.1652.

III. Synthesis and analytical data of amides 5s-t

General procedure for the synthesis of amides 5s-t

To a solution of cyanomethyl benzoate **2a** (161 mg, 1 mmol) in THF (5 mL) cooled to 0 °C was added dropwise a solution of the appropriate Grignard reagent in THF (2.2 mmol) which was previously prepared from TMS-acetylene or phenylacetylene (2.2 mmol) and EtMgBr (2.2 mmol). The mixture was allowed to warm up to room temperature and stirred at 50 °C for 3 h. After addition of water (5 mL) and 1M aqueous HCl solution (1 mL), the aqueous phase was extracted with EtOAc (3 × 10 mL) and the combined organic layers were washed with brine. After drying over $MgSO_4$, the organic fraction was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel to afford the pure amides **5s-t**.

N-(3-(Hydroxymethyl)-1,5-diphenylpenta-1,4-diyn-3-yl)benzamide (5s)



Purification by flash chromatography (cyclohexane–EtOAc, 7:3) afforded amide **5s** as a yellow solid (234 mg, 64%).

Mp 184–186 °C; R_f = 0.23 (cyclohexane–EtOAc, 7:3).

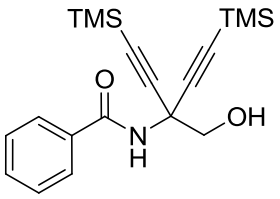
^{1}H NMR (200 MHz, $CDCl_3$): δ 7.89 – 7.83 (m, 2H, Harom), 7.55 – 7.43 (m, 8H, Harom), 7.35 – 7.29 (m, 5H, Harom), 6.91 (bs, 1H, N*H*), 4.27 (s, 2H, CH_2), 3.76 (bs, 1H, O*H*).

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.0 (*C*=O), 134.0 (1 Carom), 132.3 (4 Carom), 132.2 (1 Carom), 129.0 (2 Carom), 128.8 (2 Carom), 128.4 (4 Carom), 127.4 (2 Carom), 122.0 (2 Carom), 85.0 (2 *C*), 84.4 (2 *C*), 70.1 (*C*H_2OH), 51.8 (*C*).

IR (neat): 3438, 3327, 3059, 2962, 2932, 2231, 1727, 1629, 1601, 1577, 1532, 1489, 1451, 1402, 1370, 1312, 1260, 1069 cm^{-1}.

HRMS (CI-NH_3): m/z $[M + H]^+$ calcd for $C_{25}H_{20}NO_2$: 366.1494; found: 366.1487.

_N_-(3-(Hydroxymethyl)-1,5-bis(trimethylsilyl)penta-1,4-diyn-3-yl)benzamide (5t)



Purification by flash chromatography (cyclohexane–EtOAc, 8:2) afforded amide **5t** as a yellow solid (198 mg, 55%).

Mp 173–175 °C; R_f = 0.37 (cyclohexane–EtOAc, 8:2).

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.78 (dd, *J* = 8.2 Hz, *J* = 1.1 Hz, 2H, Harom), 7.54 – 7.41 (m, 3H, Harom), 6.62 (bs, 1H, N*H*), 4.05 (d, *J* = 7.2 Hz, 2H, CH_2), 3.62 (t, *J* = 7.2 Hz, 1H, O*H*), 0.20 (s, 18H, CH_3).

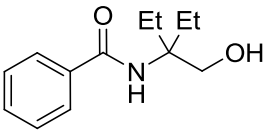
^{13}C NMR (100 MHz, $CDCl_3$): δ 166.8 (*C*=O), 134.1 (1 Carom), 132.1 (1 Carom), 128.8 (2 Carom), 127.3 (2 Carom), 100.5 (2 *C*), 89.5 (2 *C*), 69.8 (*C*H_2OH), 51.7 (*C*), -0.1 (6 *C*H_3).

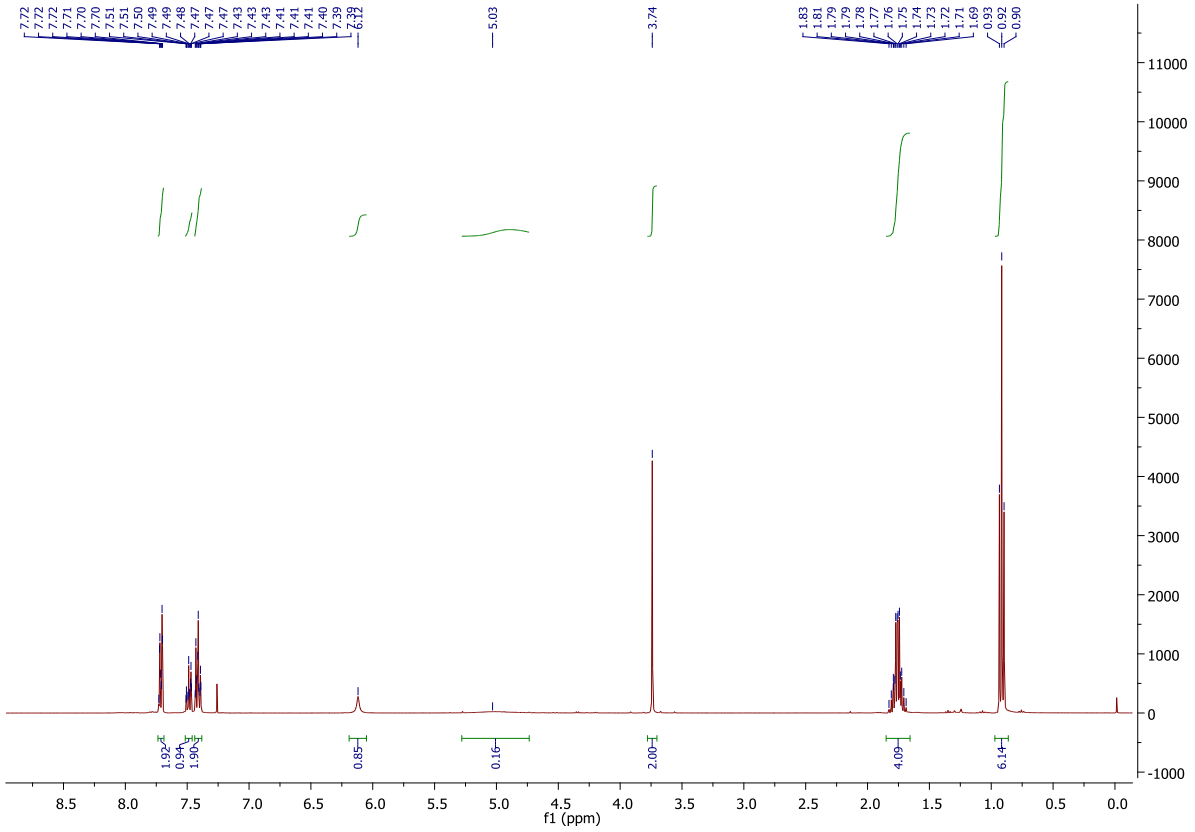
IR (neat): 3410, 3389, 2961, 2929, 2900, 2166, 1726, 1656, 1601, 1581, 1506, 1480, 1459, 1248, 1075 cm^{-1}.

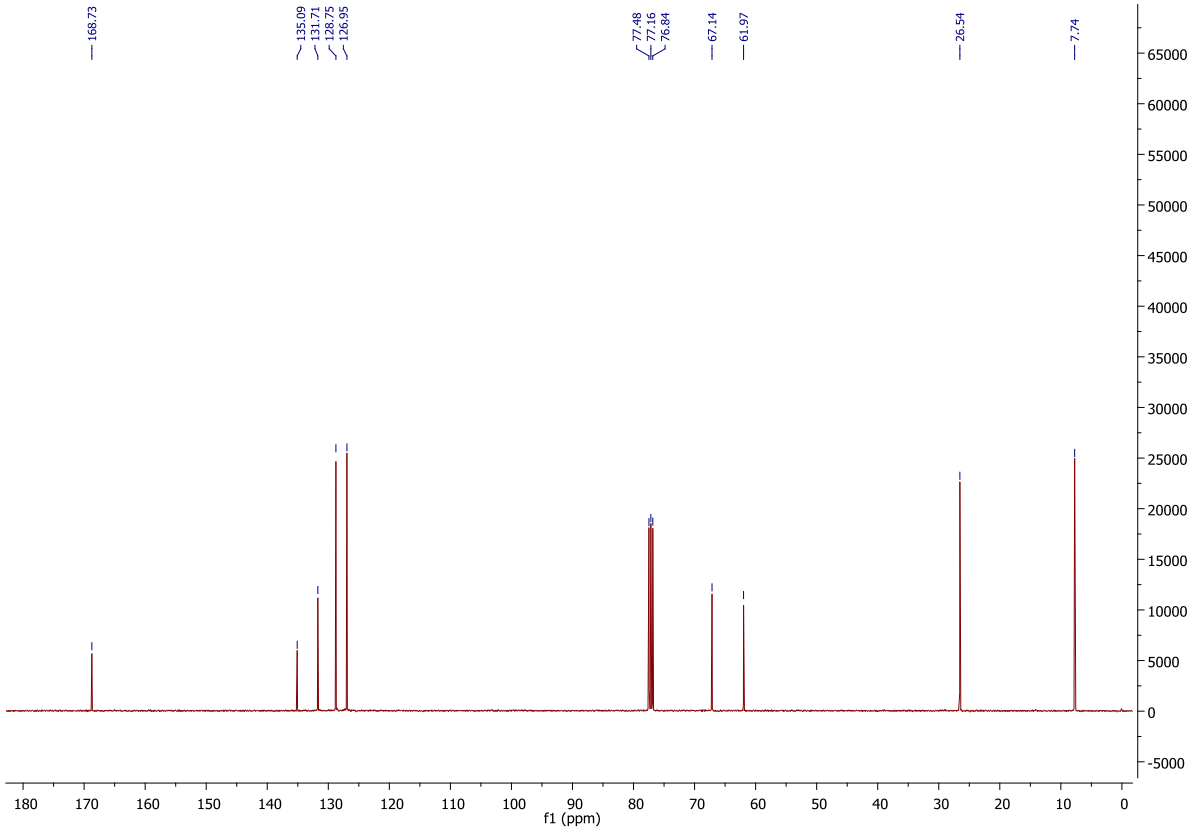
HRMS (CI-NH_3): m/z [$M^{+\bullet}$] calcd for $C_{19}H_{27}NO_2Si_2$: 357.1580; found: 357.1593.

V. Copies of ^{1}H and ^{13}C NMR spectra

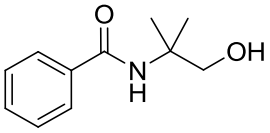
N-(3-(Hydroxymethyl)pentan-3-yl)benzamide **(5a)**

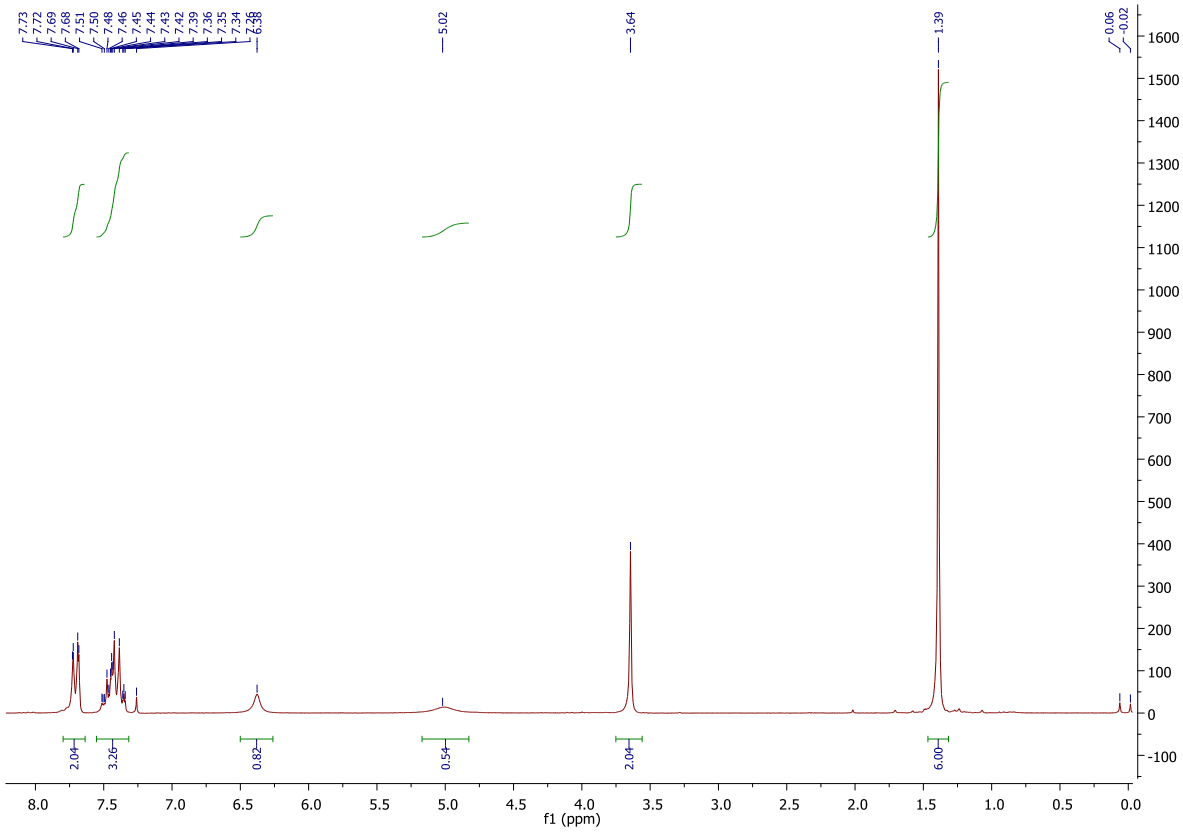


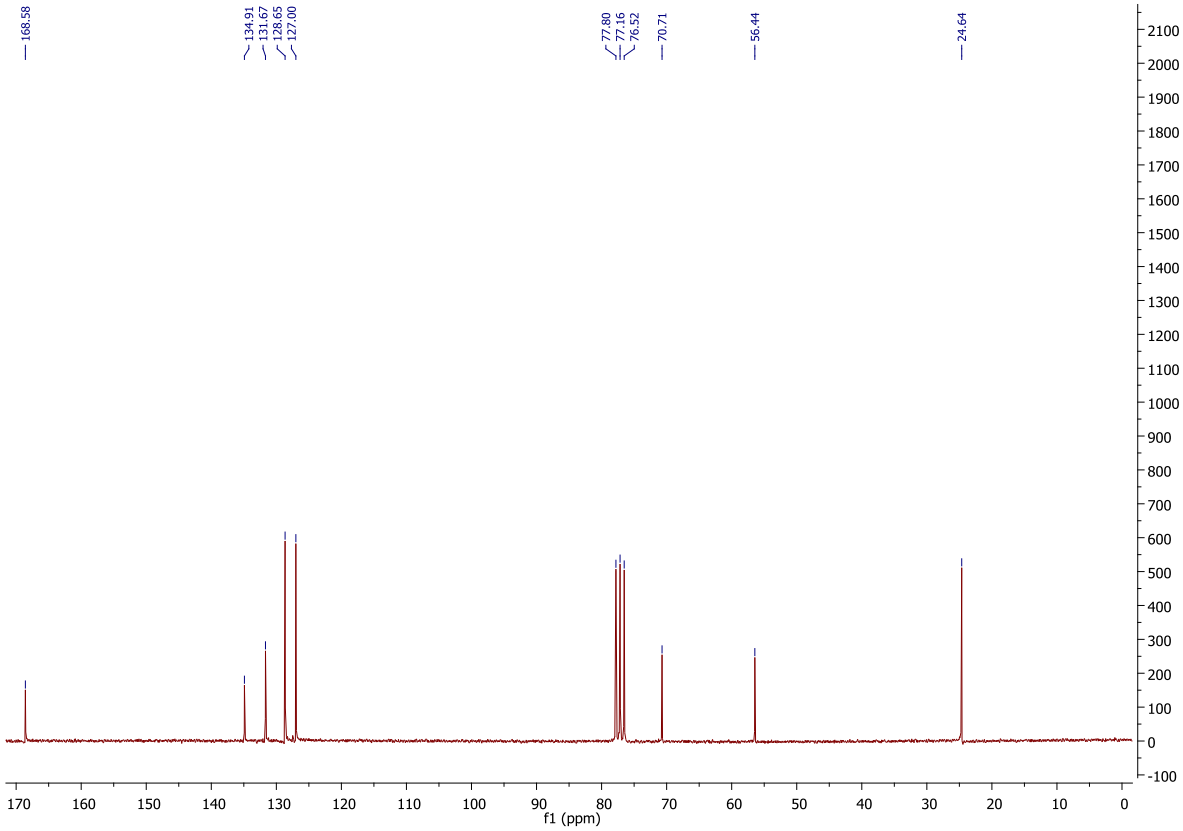




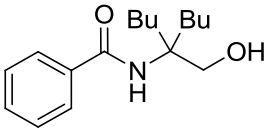
N-(1-Hydroxy-2-methylpropan-2-yl)benzamide **(5b)**

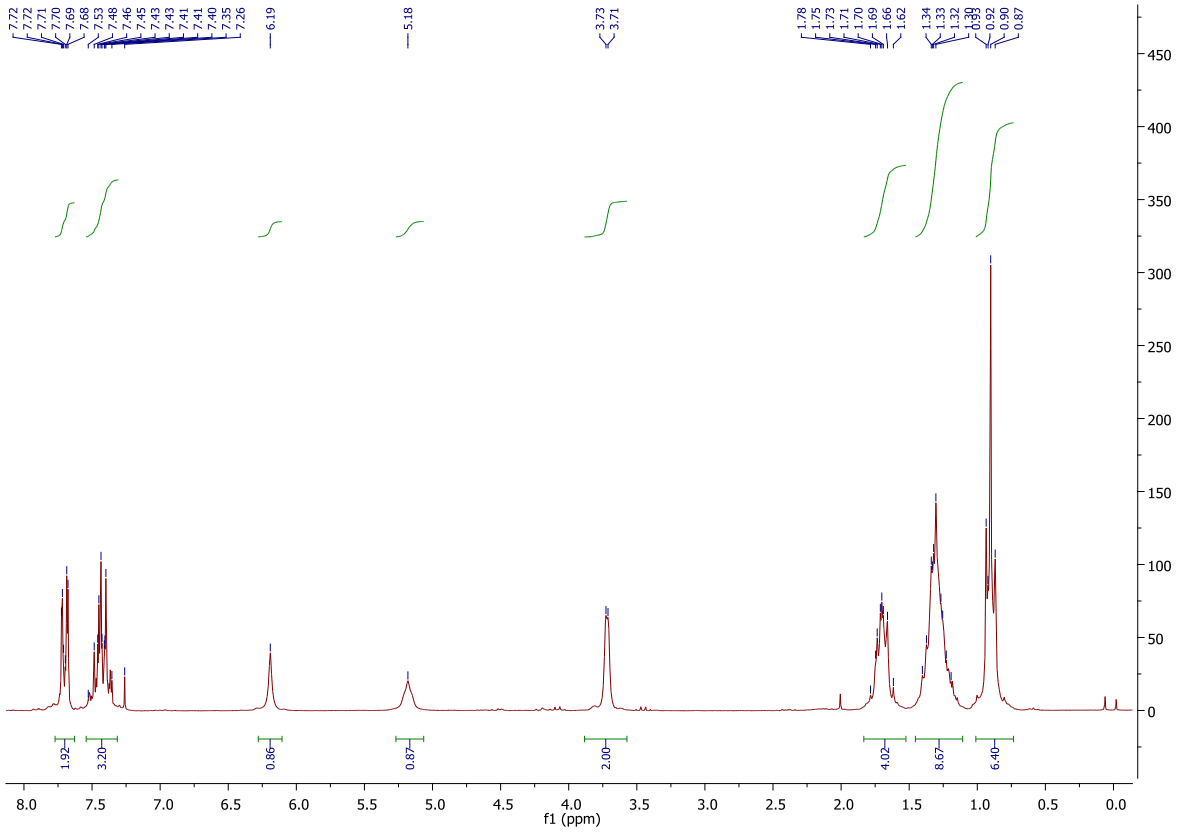


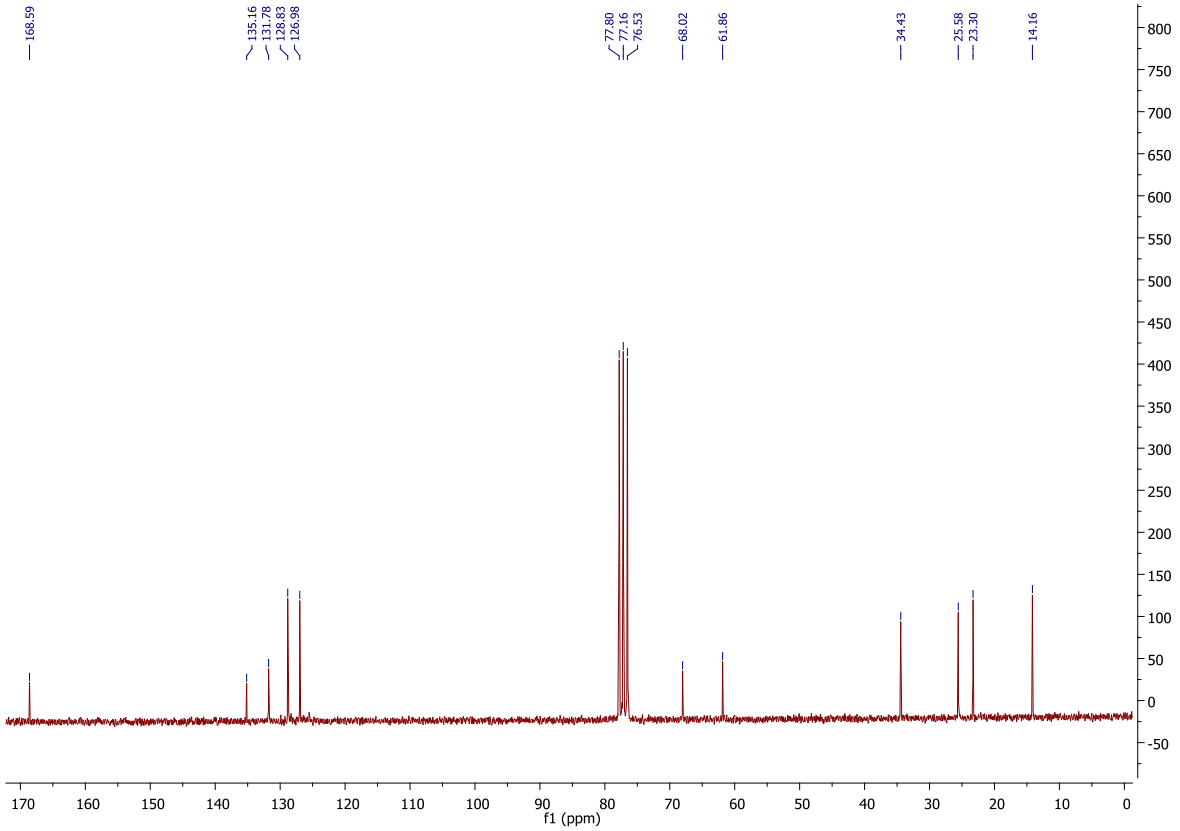




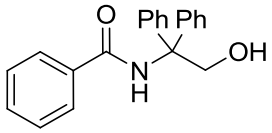
N-(5-(Hydroxymethyl)nonan-5-yl)benzamide **(5c)**

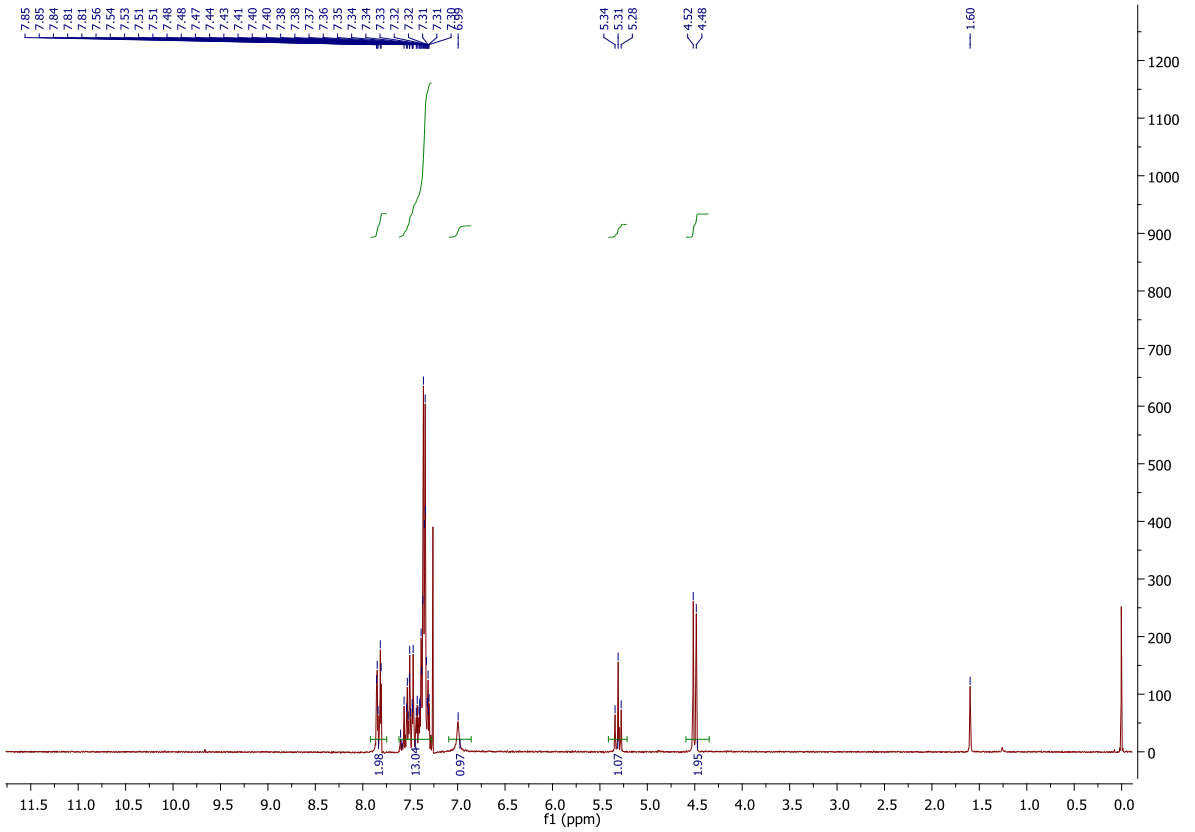


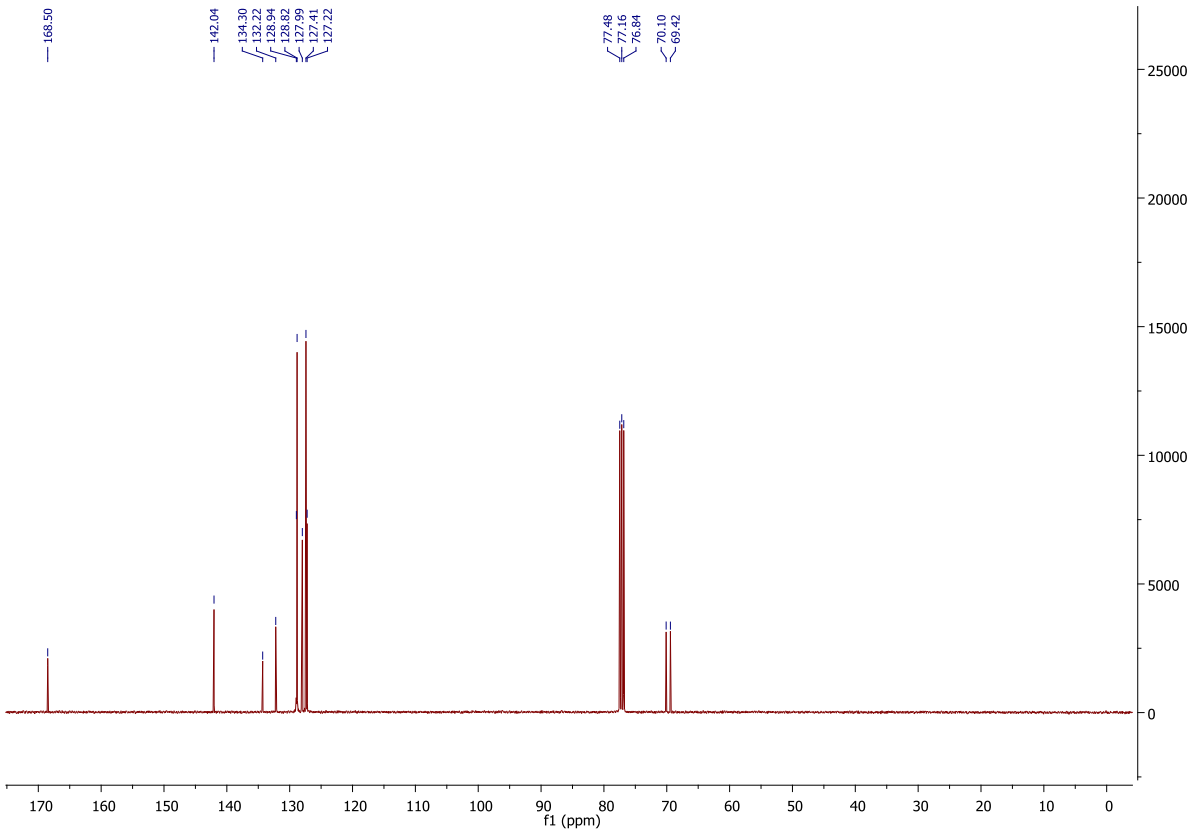




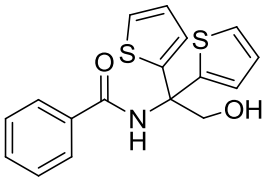
N-(2-Hydroxy-1,1-diphenylethyl)benzamide **(5d)**

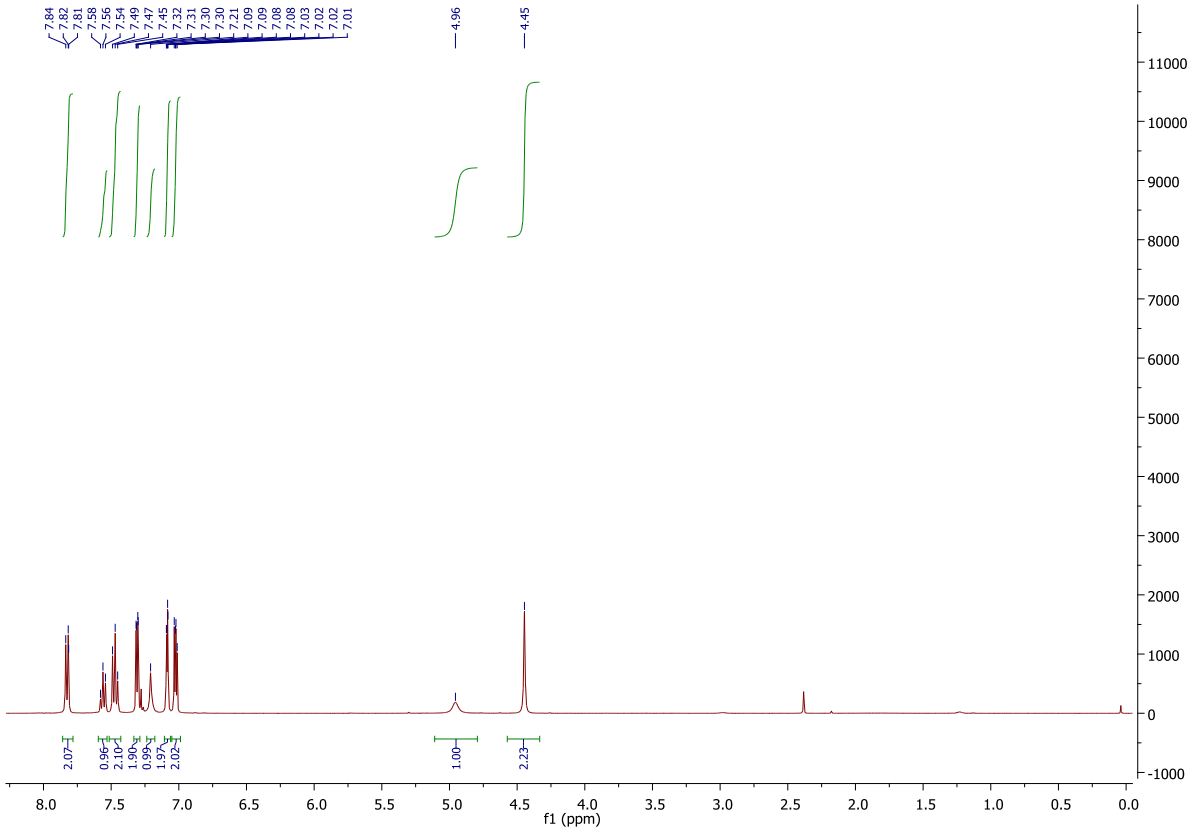


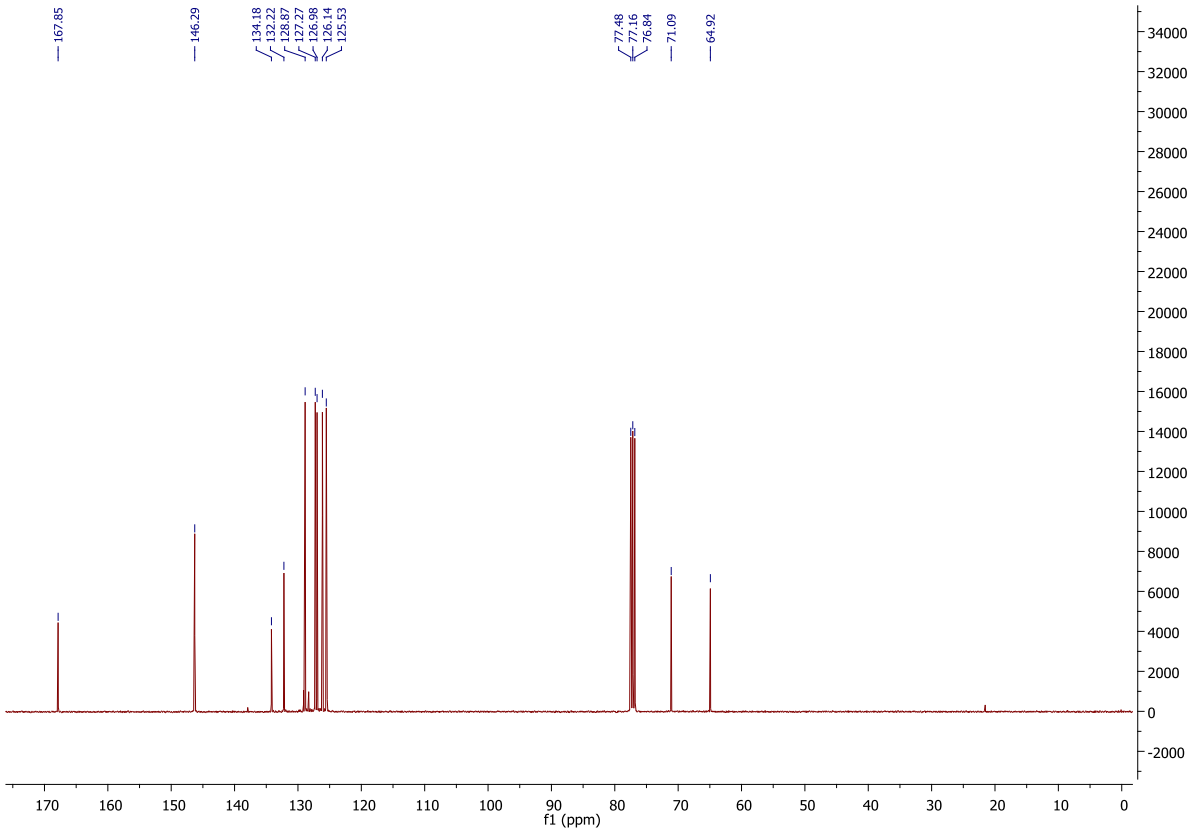




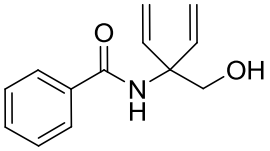
N-(2-Hydroxy-1,1-di(thiophen-2-yl)ethyl)benzamide **(5e)**

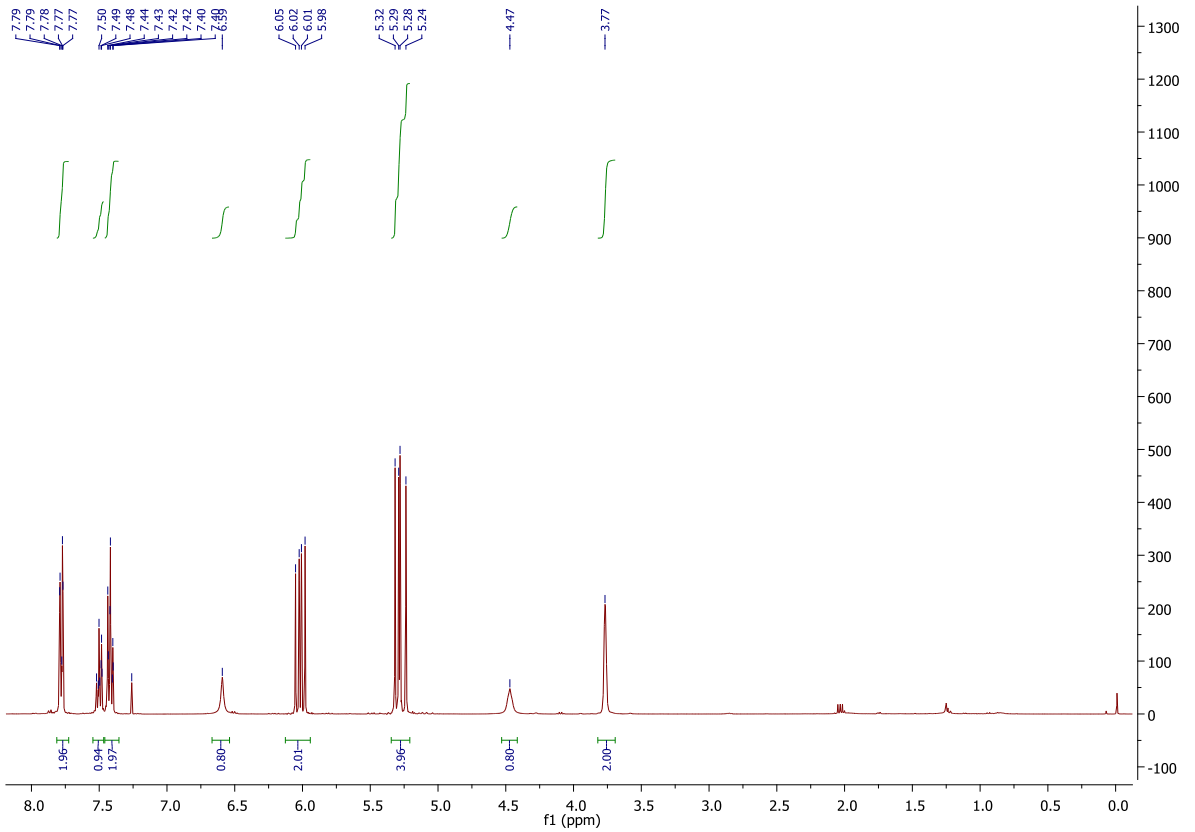


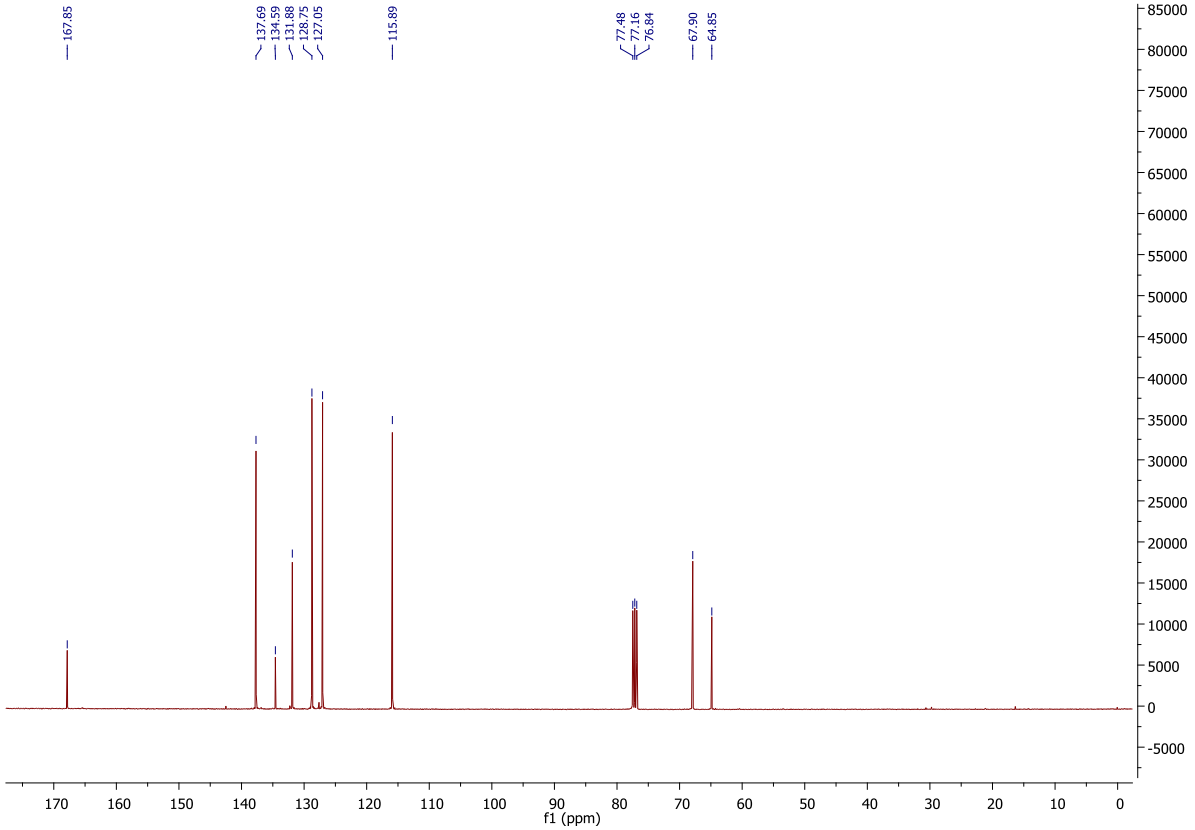




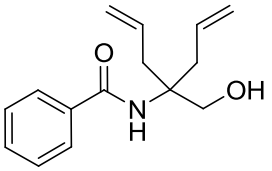
N-(3-(Hydroxymethyl)penta-1,4-dien-3-yl)benzamide **(5f)**

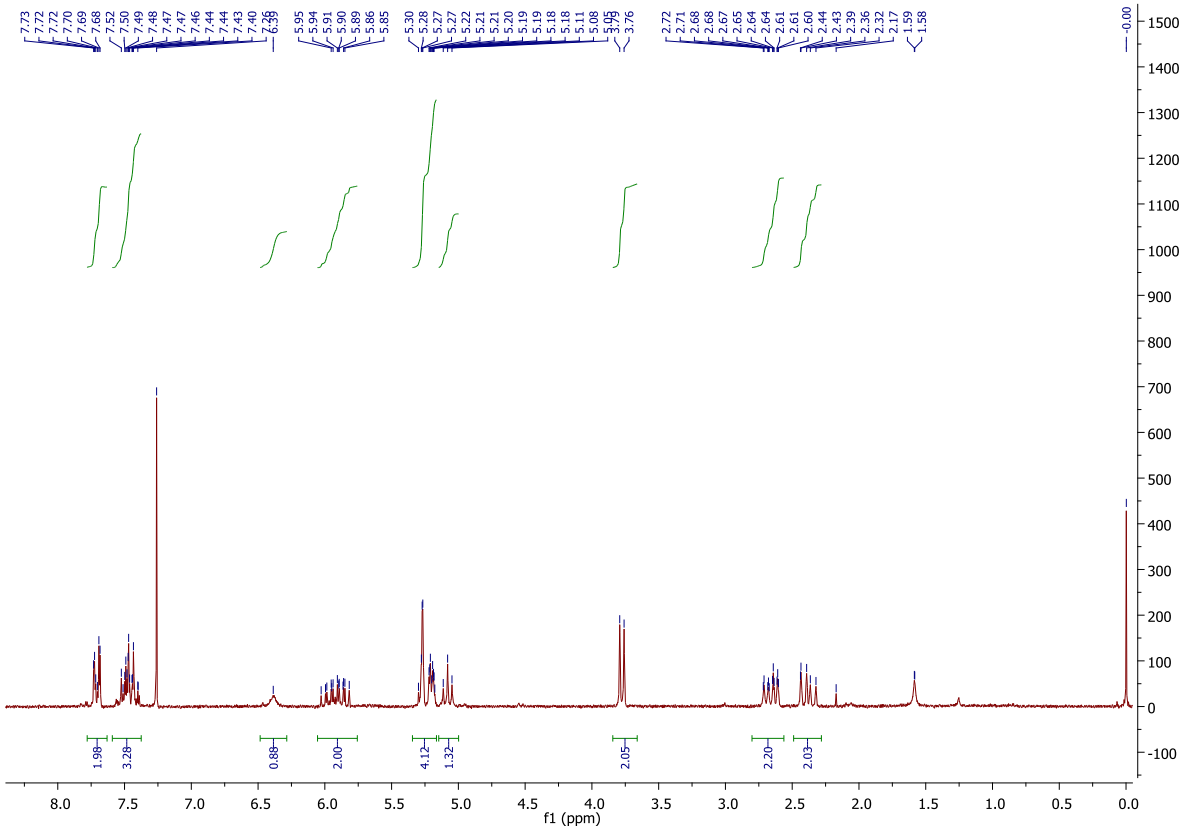


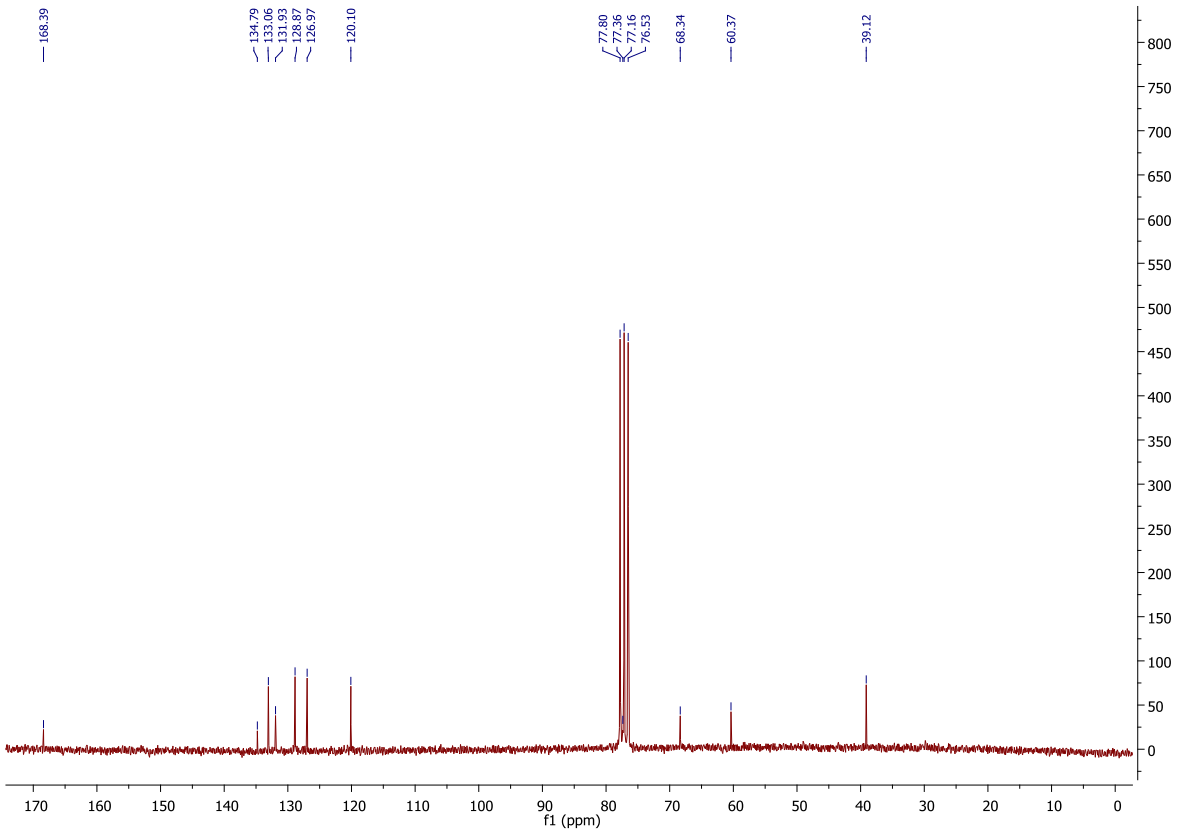




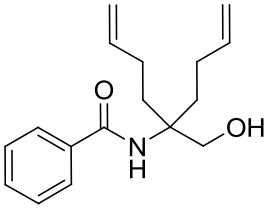
N-(4-(Hydroxymethyl)hepta-1,6-dien-4-yl)benzamide **(5g)**

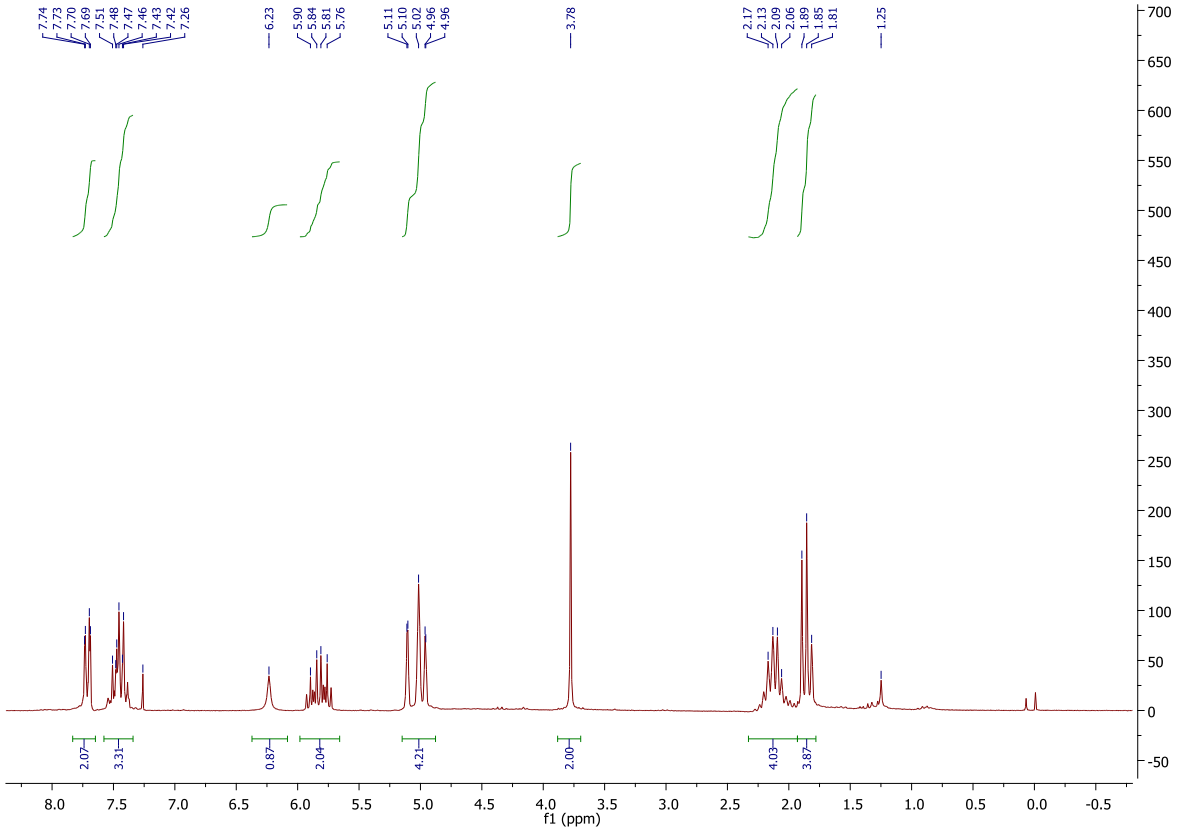


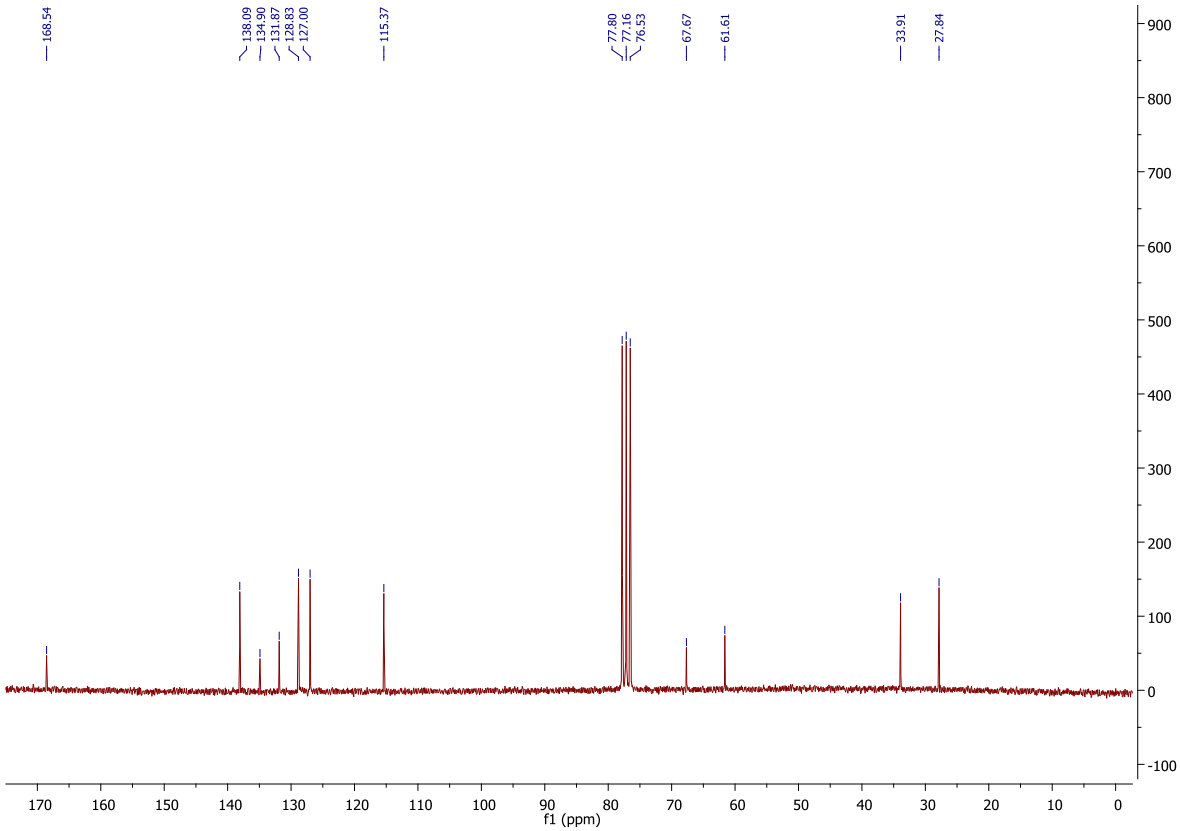




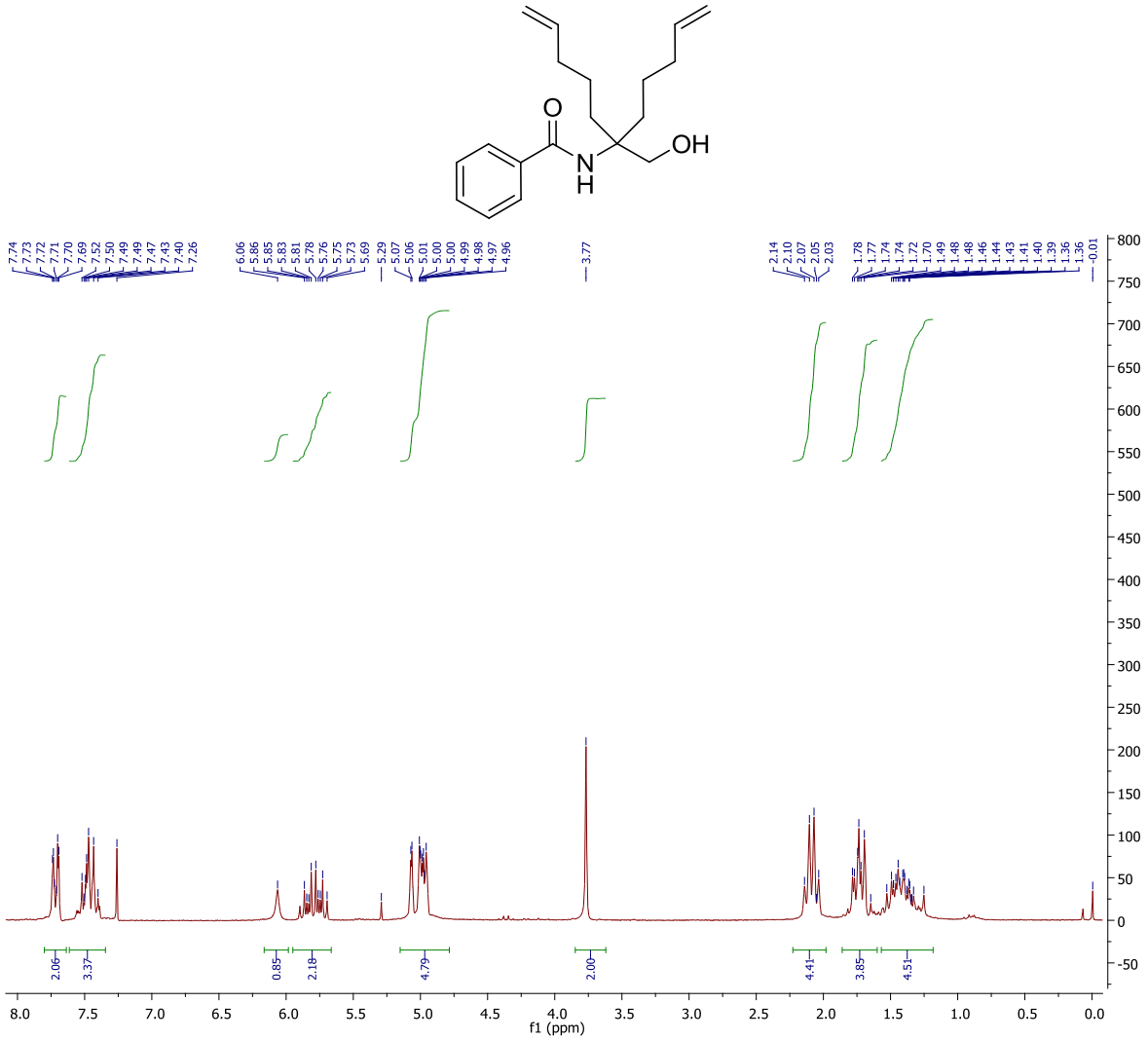
N-(5-(Hydroxymethyl)nona-1,8-dien-5-yl)benzamide **(5h)**

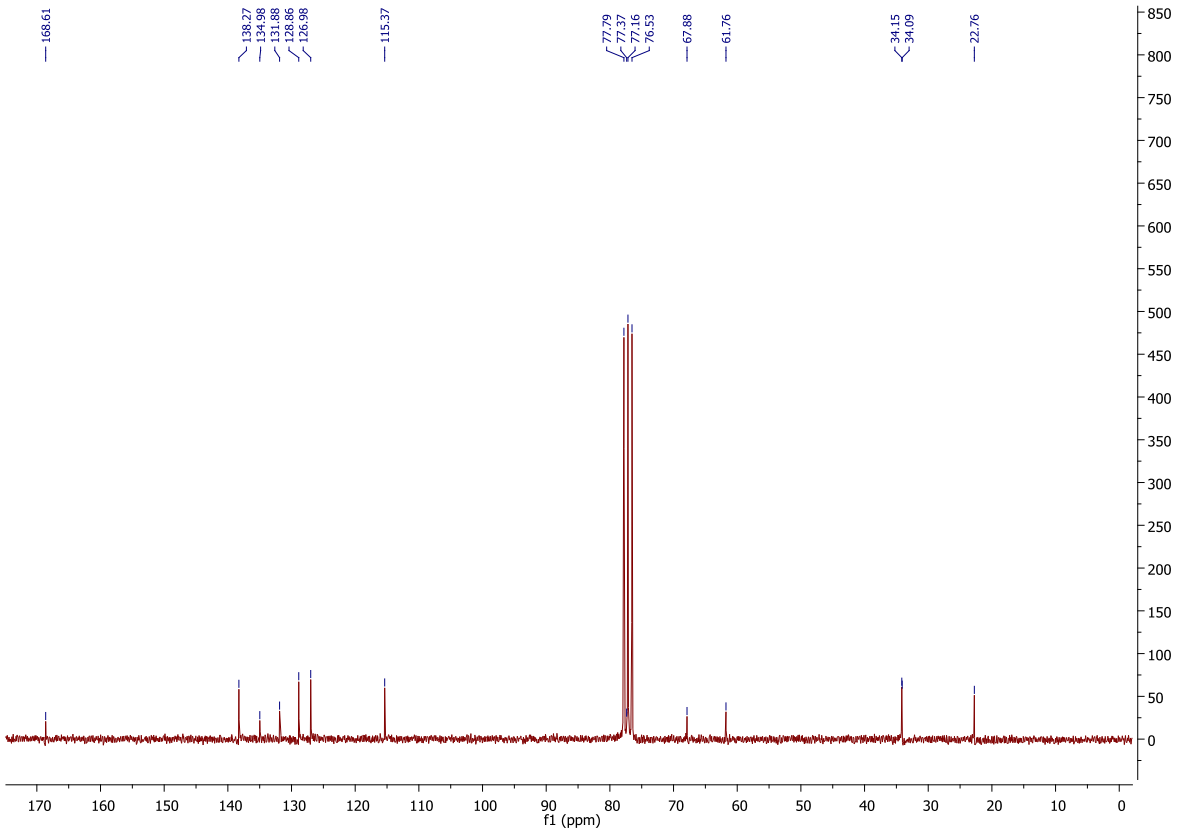




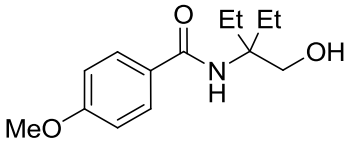


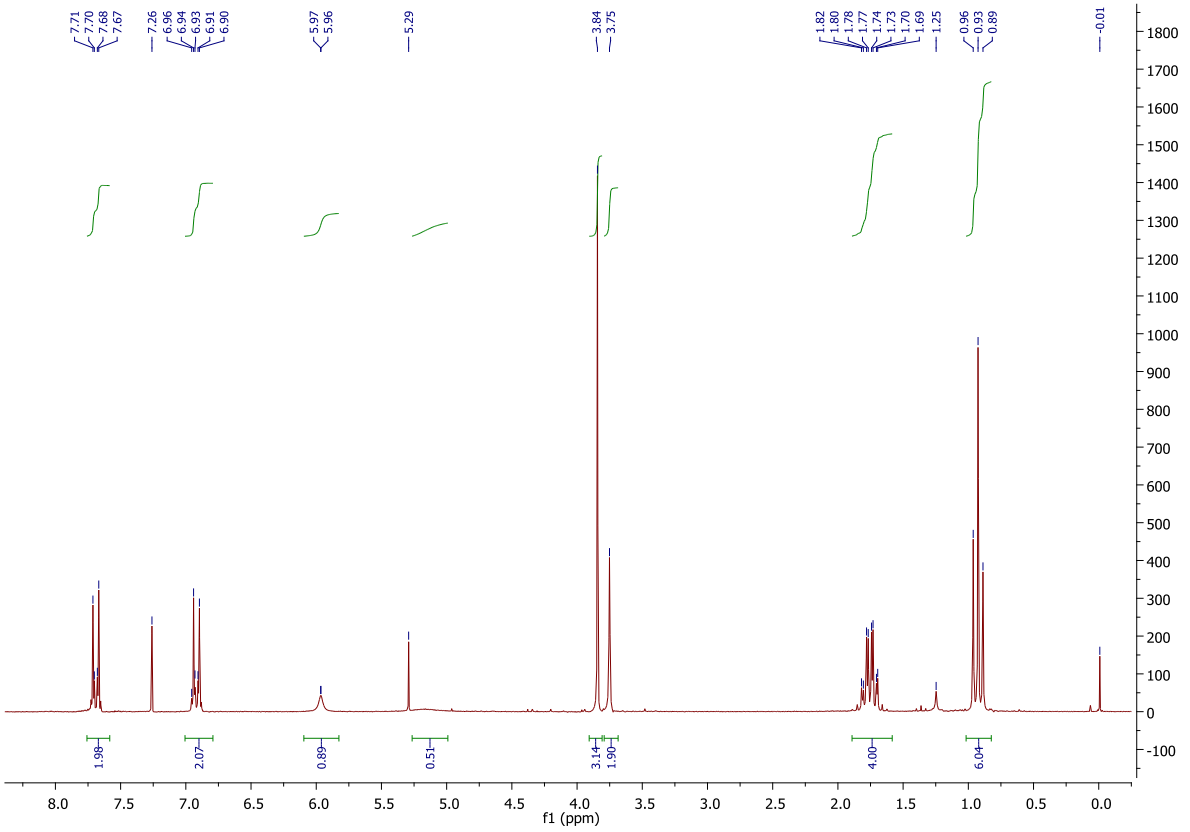
N-(6-(Hydroxymethyl)undeca-1,10-dien-6-yl)benzamide **(5i)**

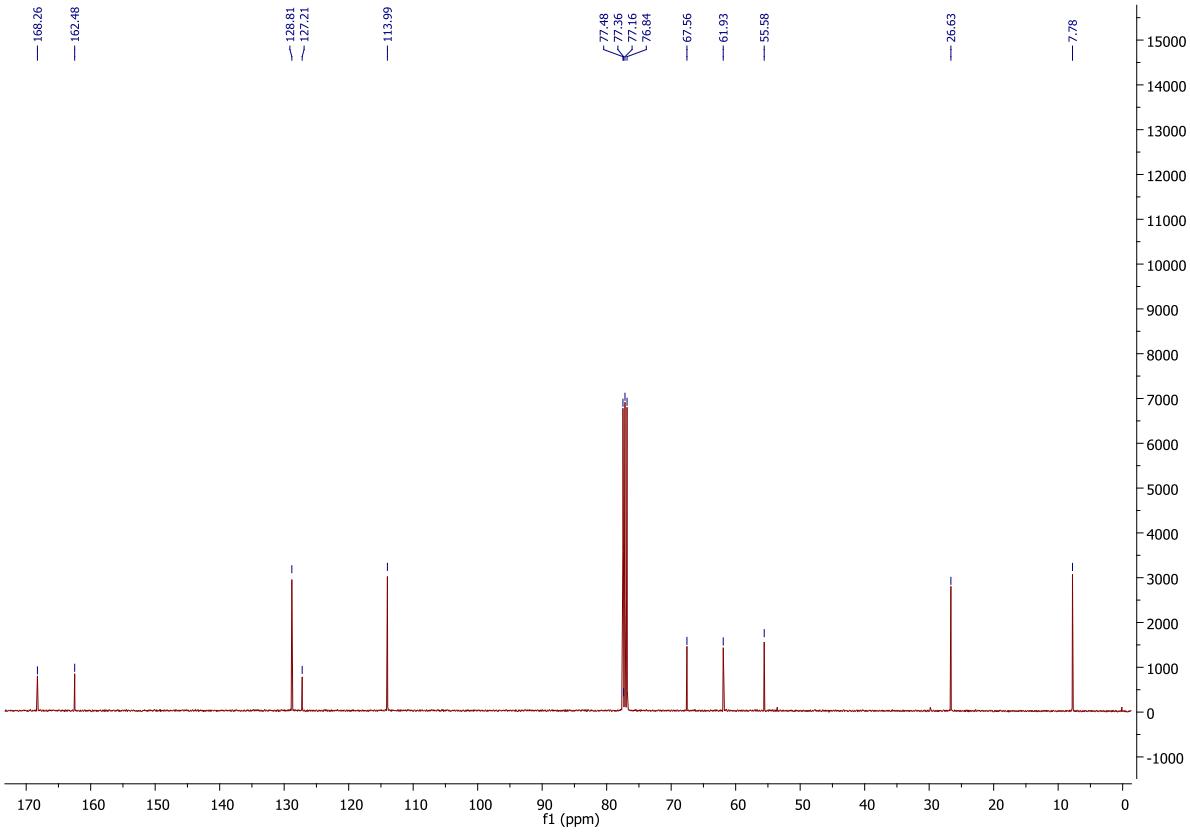




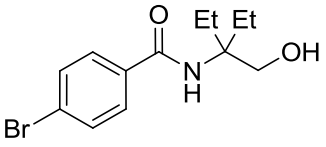
N-(3-(Hydroxymethyl)pentan-3-yl)-4-methoxybenzamide **(5j)**

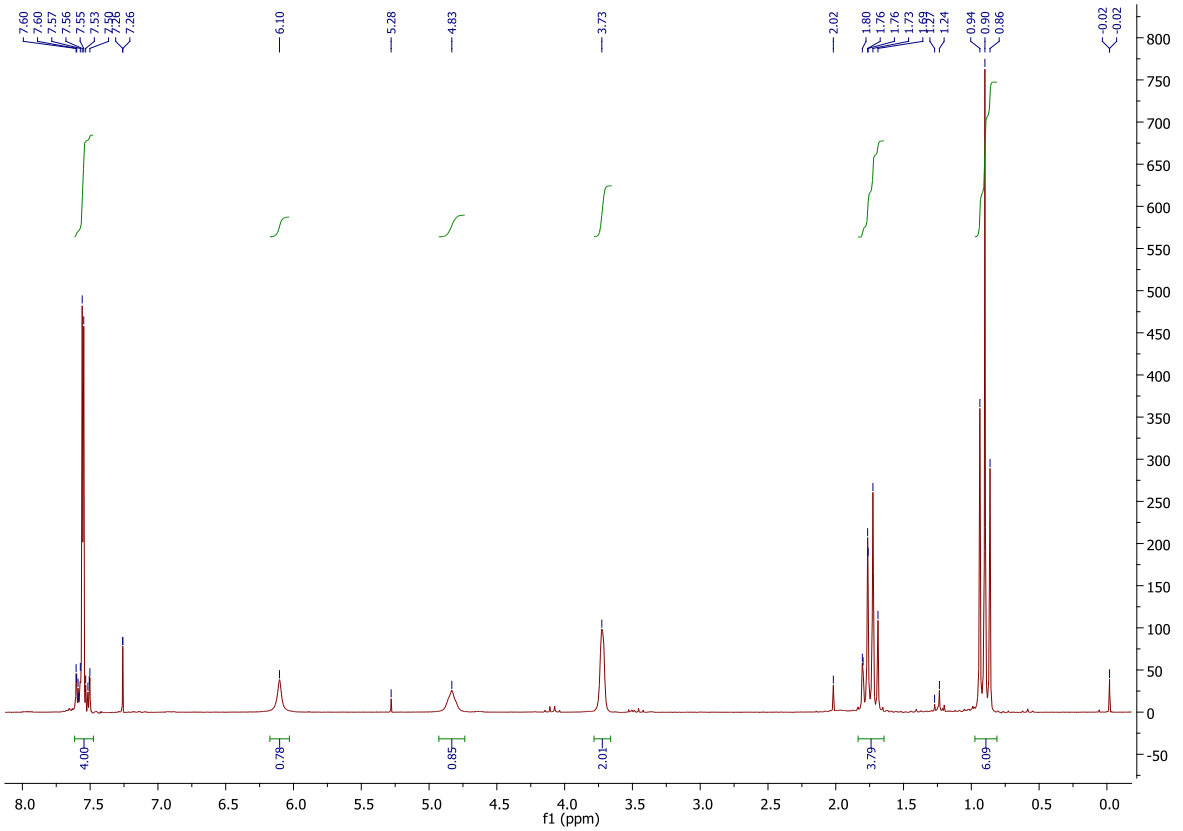


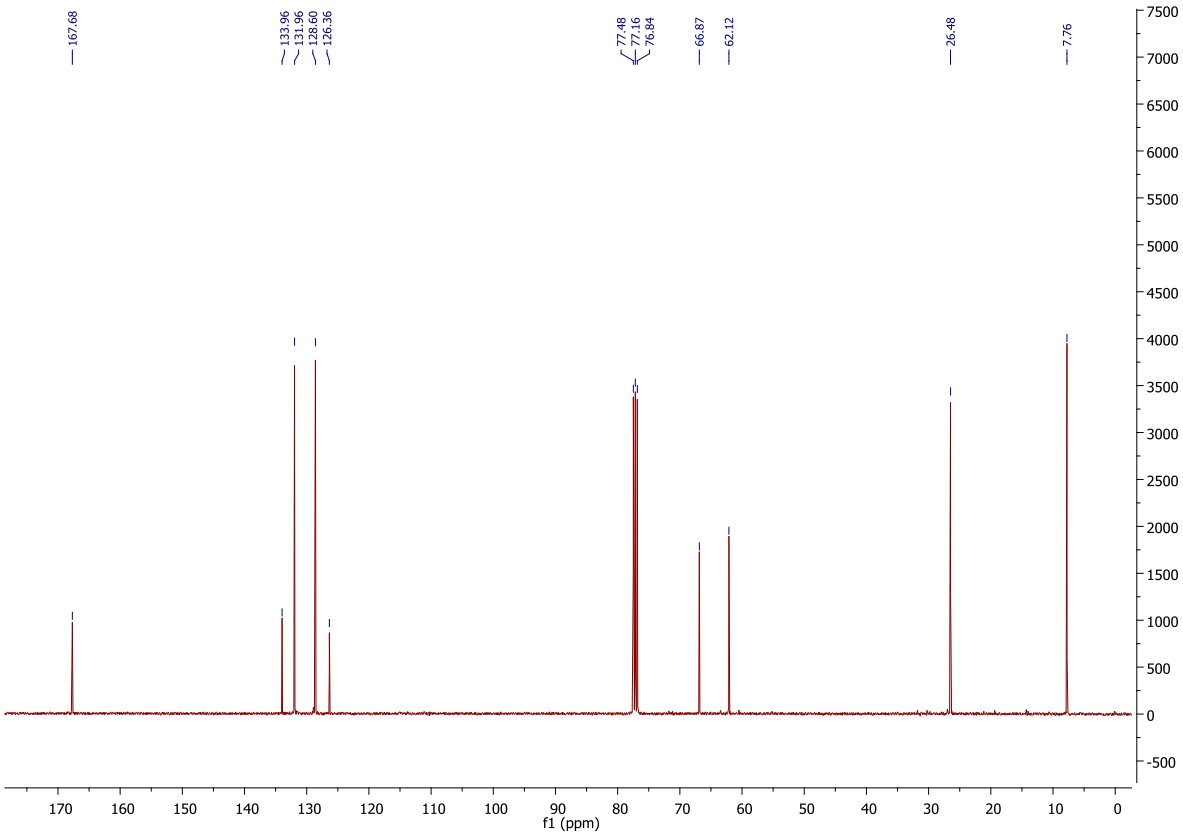




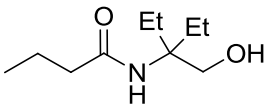
4-Bromo-*N*-(3-(hydroxymethyl)pentan-3-yl)benzamide **(5k)**

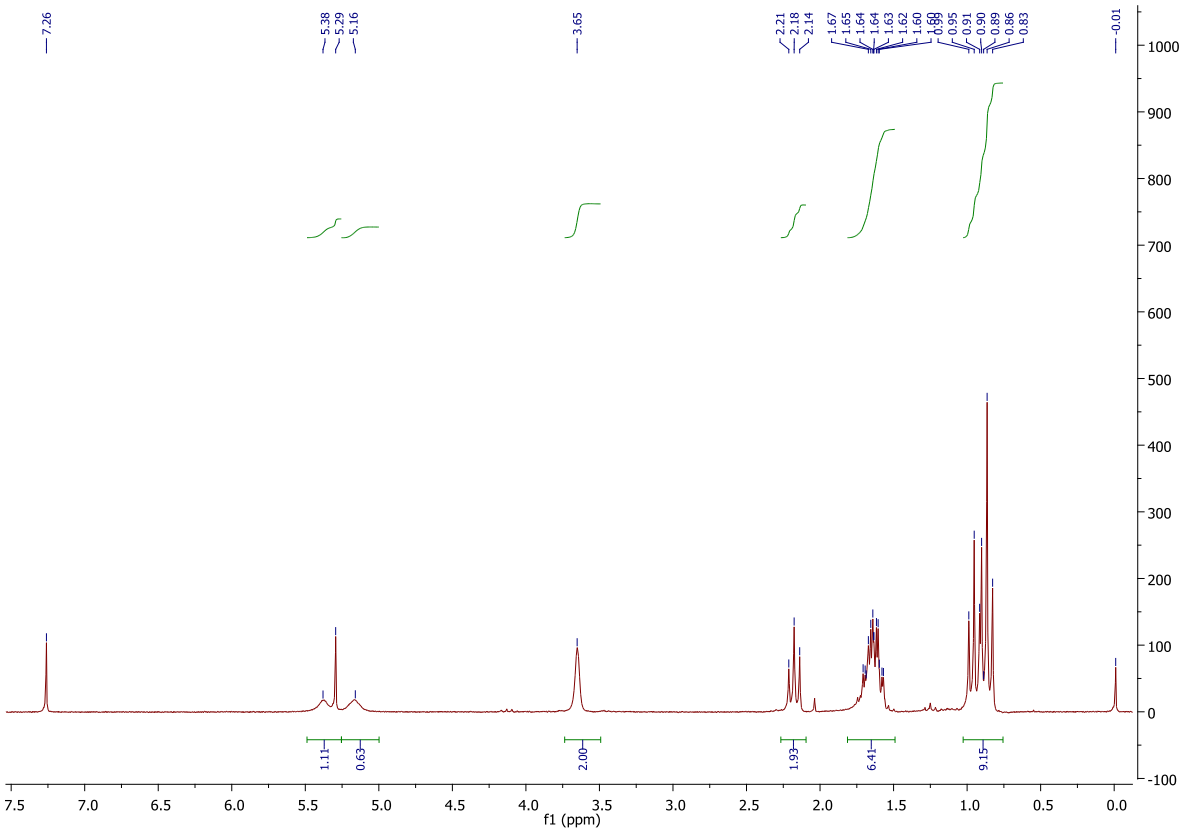


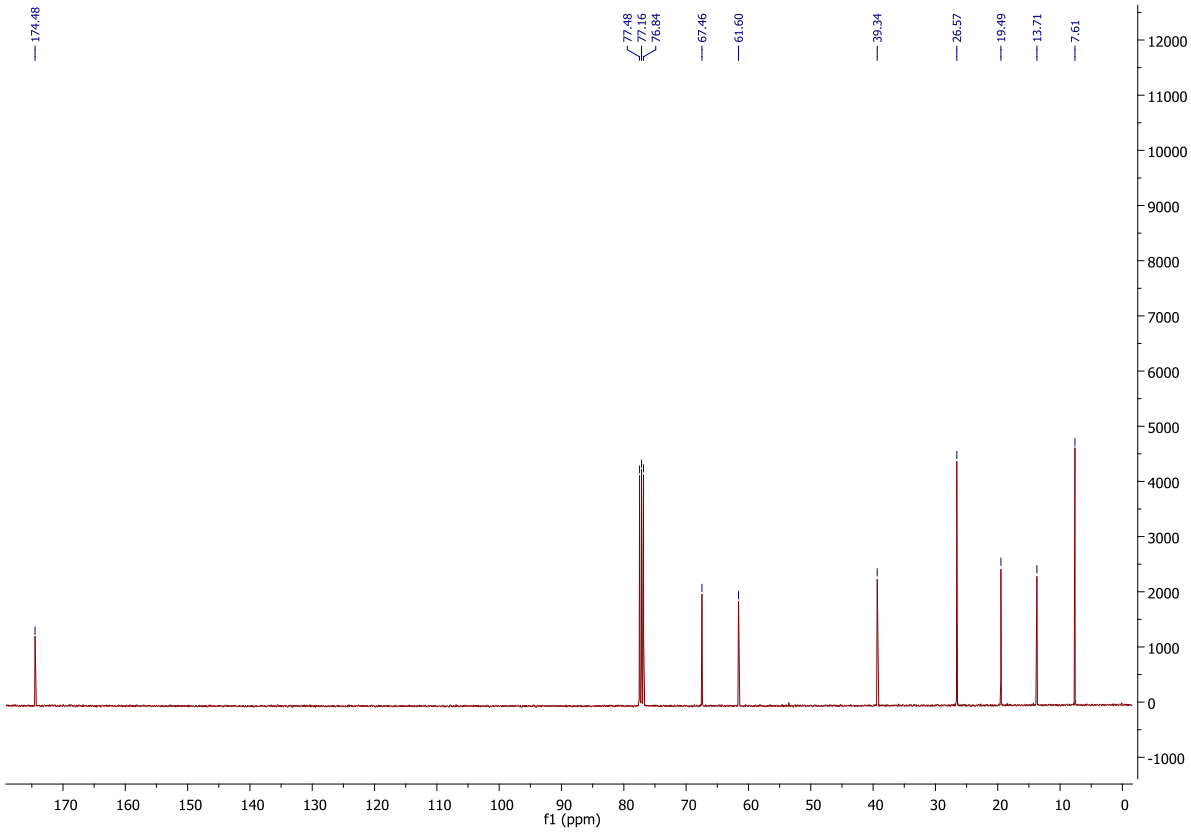




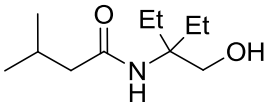
N-(3-(Hydroxymethyl)pentan-3-yl)butyramide **(5l)**

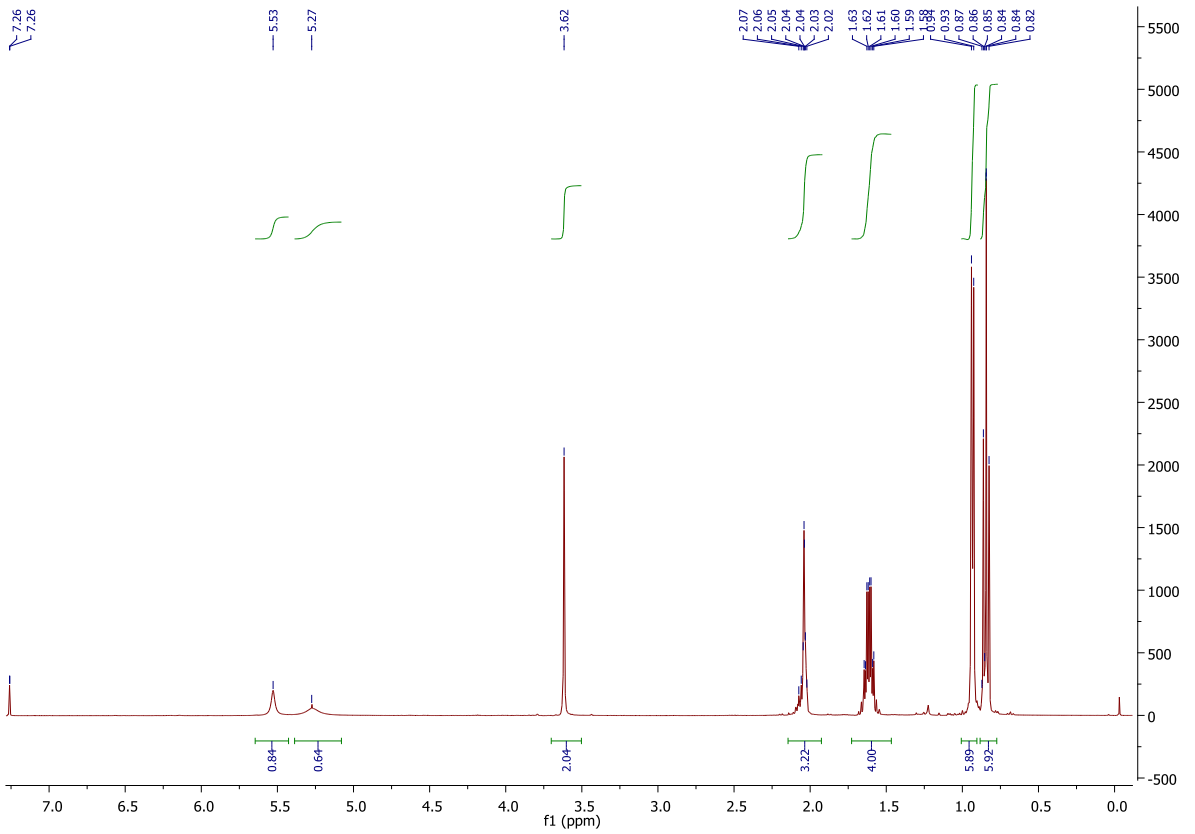


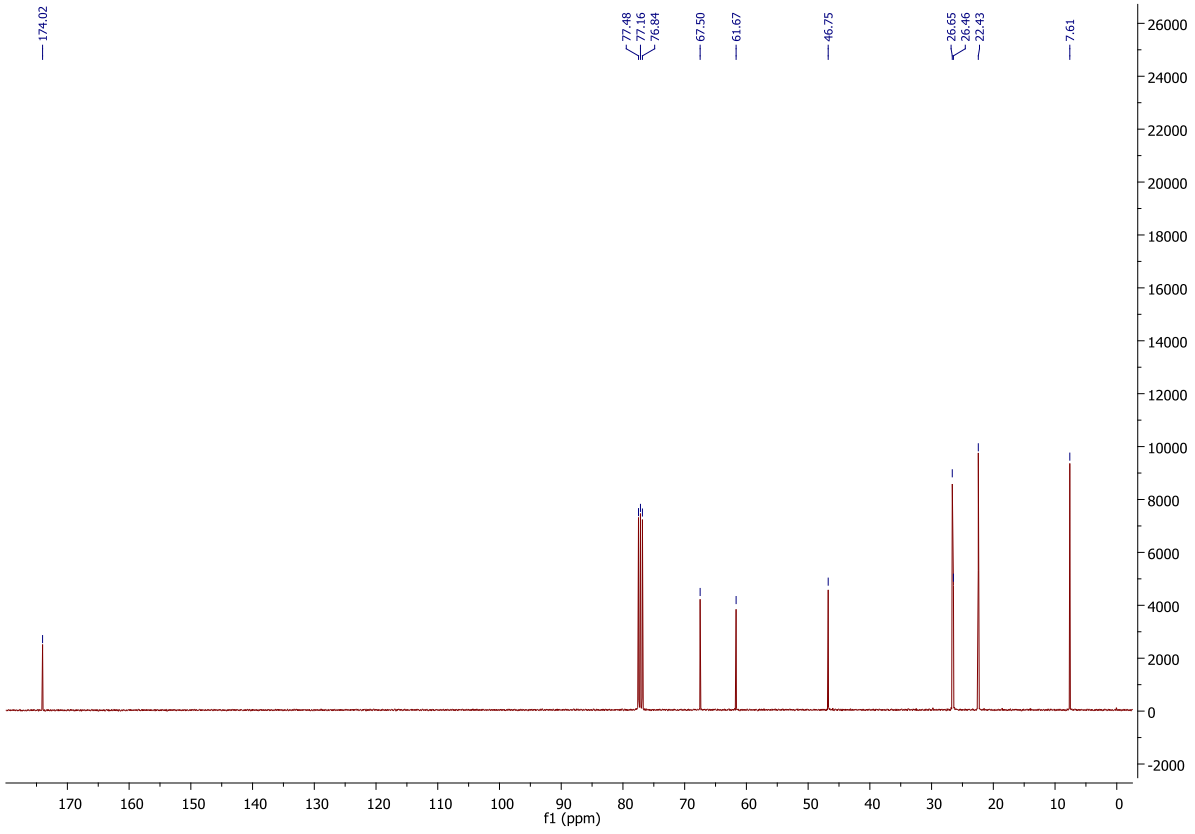




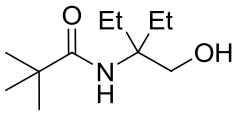
N-(3-(Hydroxymethyl)pentan-3-yl)-3-methylbutanamide **(5m)**

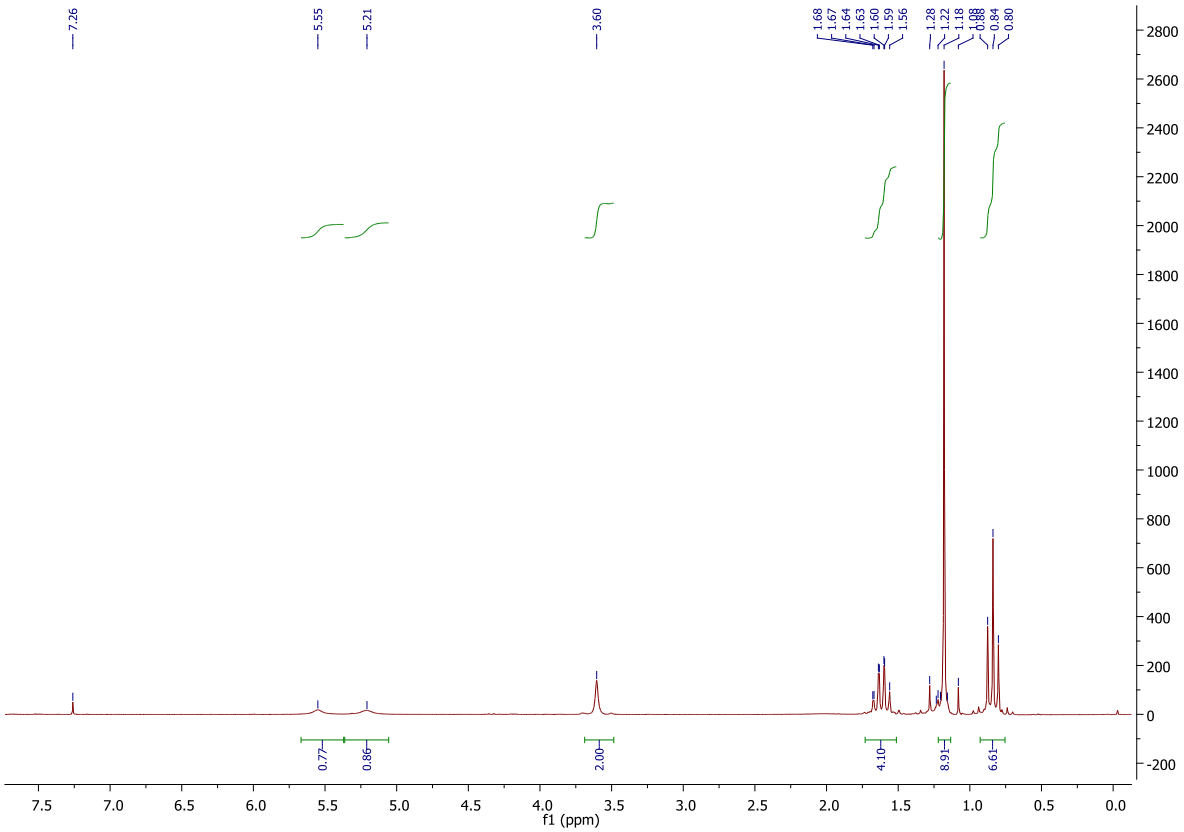


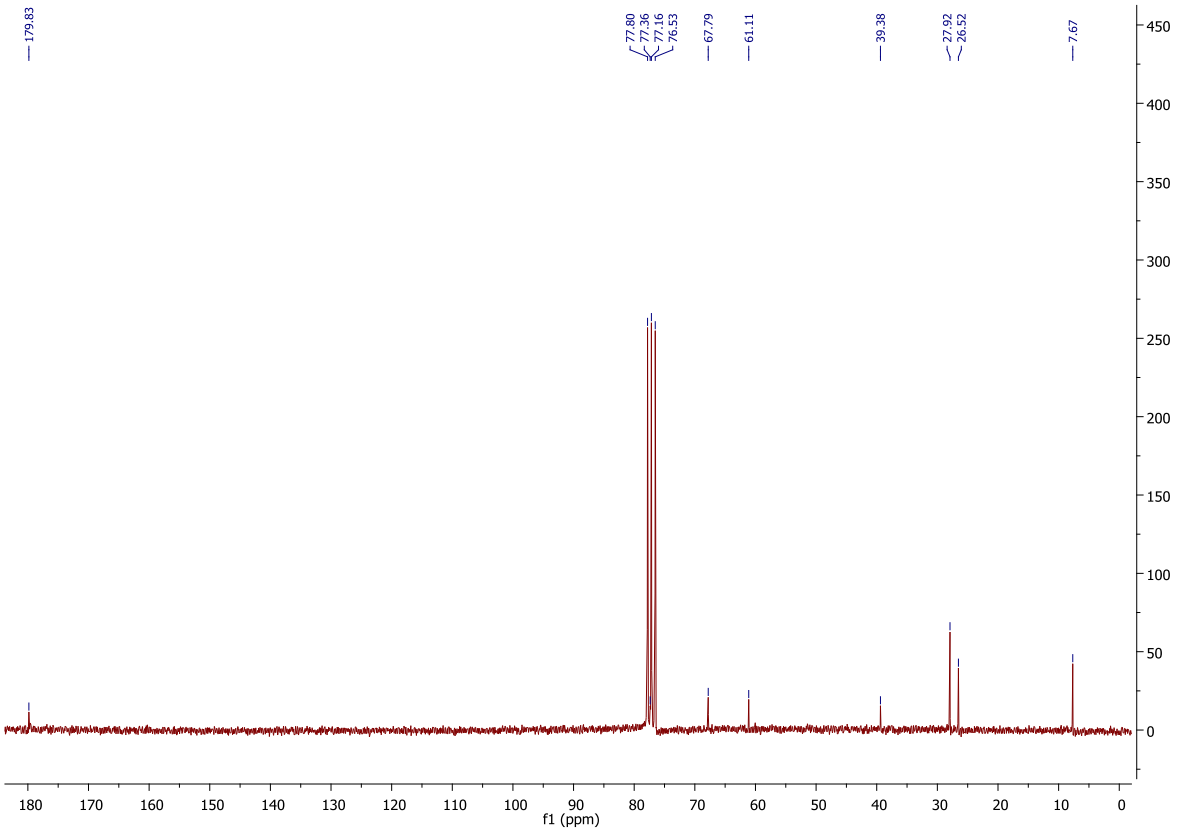




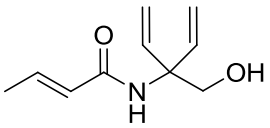
N-(3-(Hydroxymethyl)pentan-3-yl)pivalamide **(5n)**

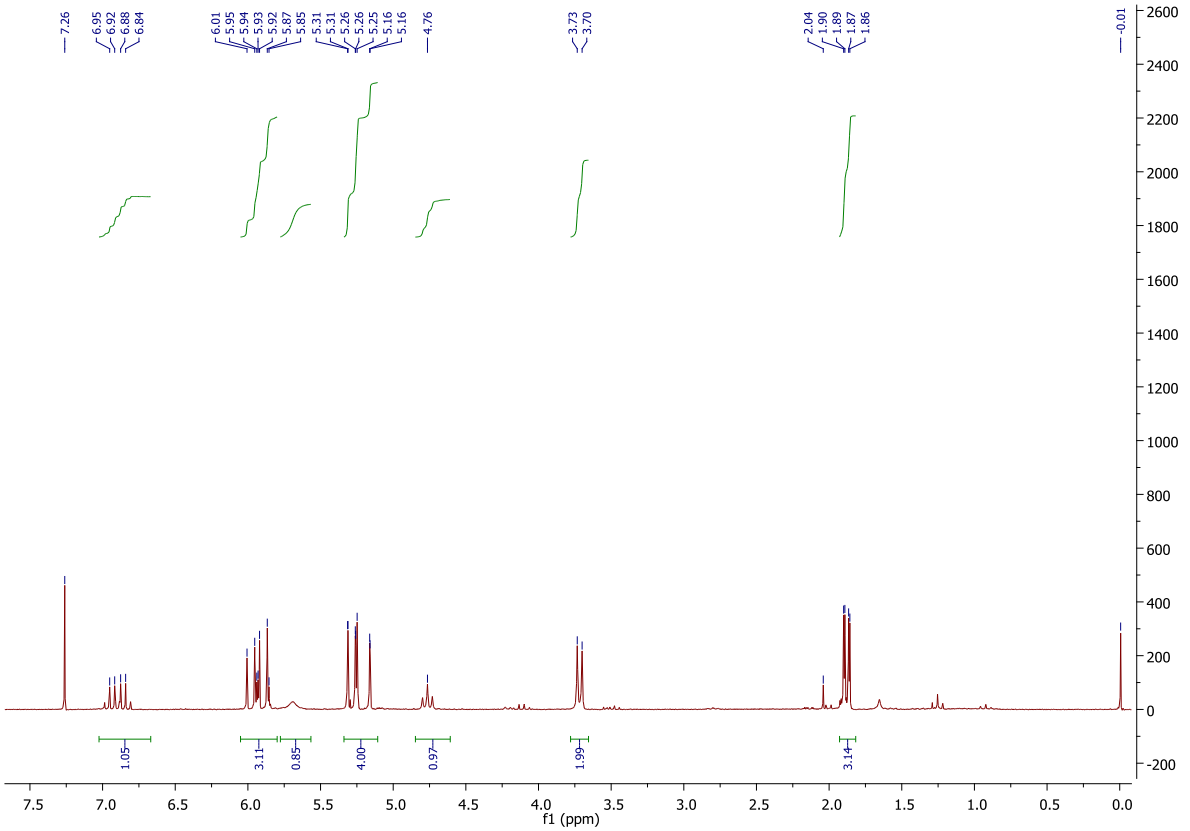


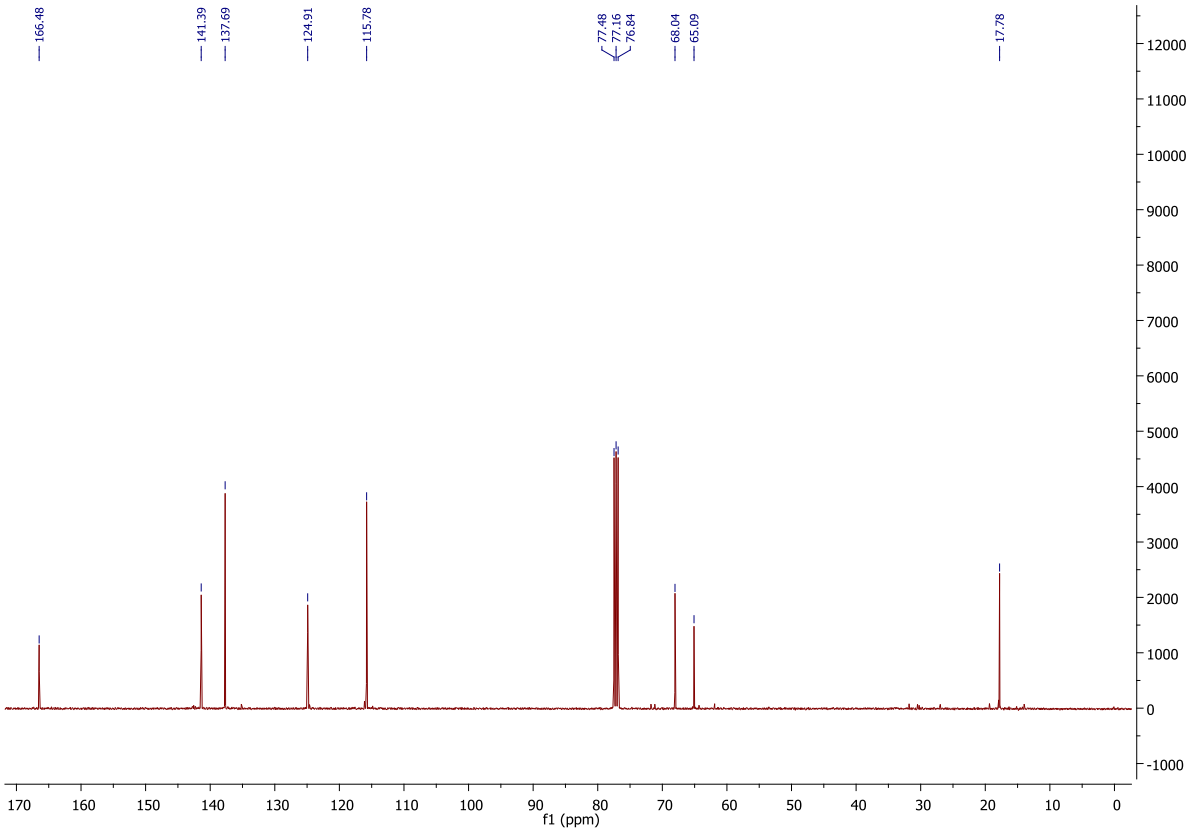




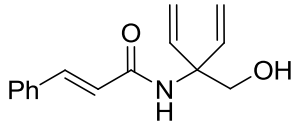
(E)-N-(3-(Hydroxymethyl)penta-1,4-dien-3-yl)but-2-enamide **(5o)**

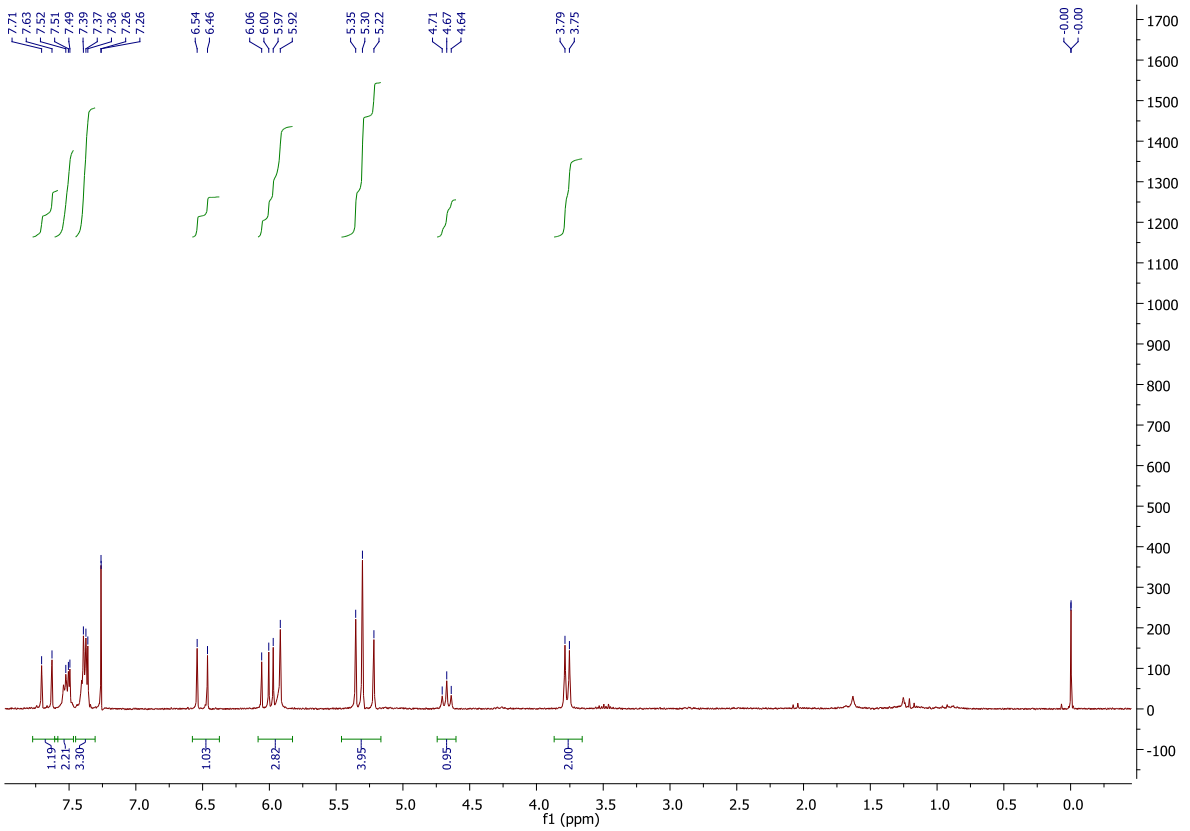


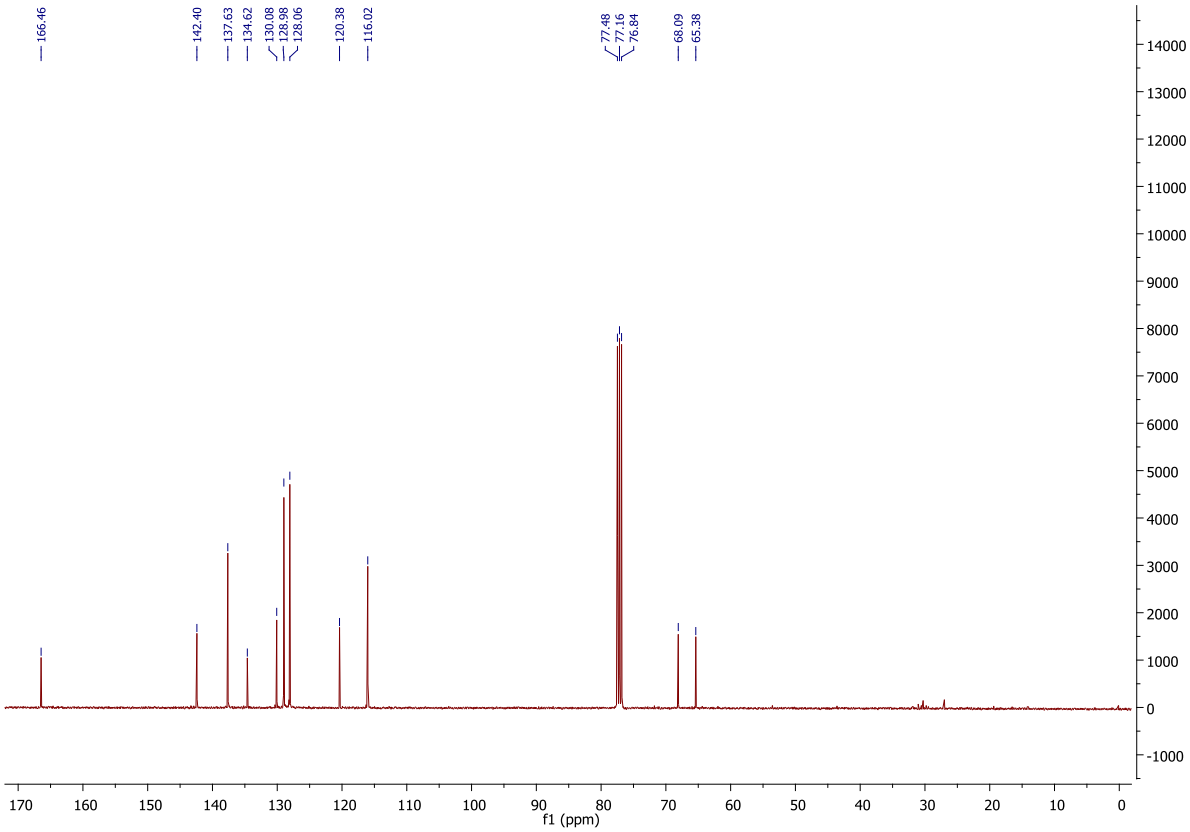




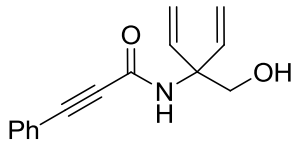
N-(3-(Hydroxymethyl)penta-1,4-dien-3-yl)cinnamamide **(5p)**

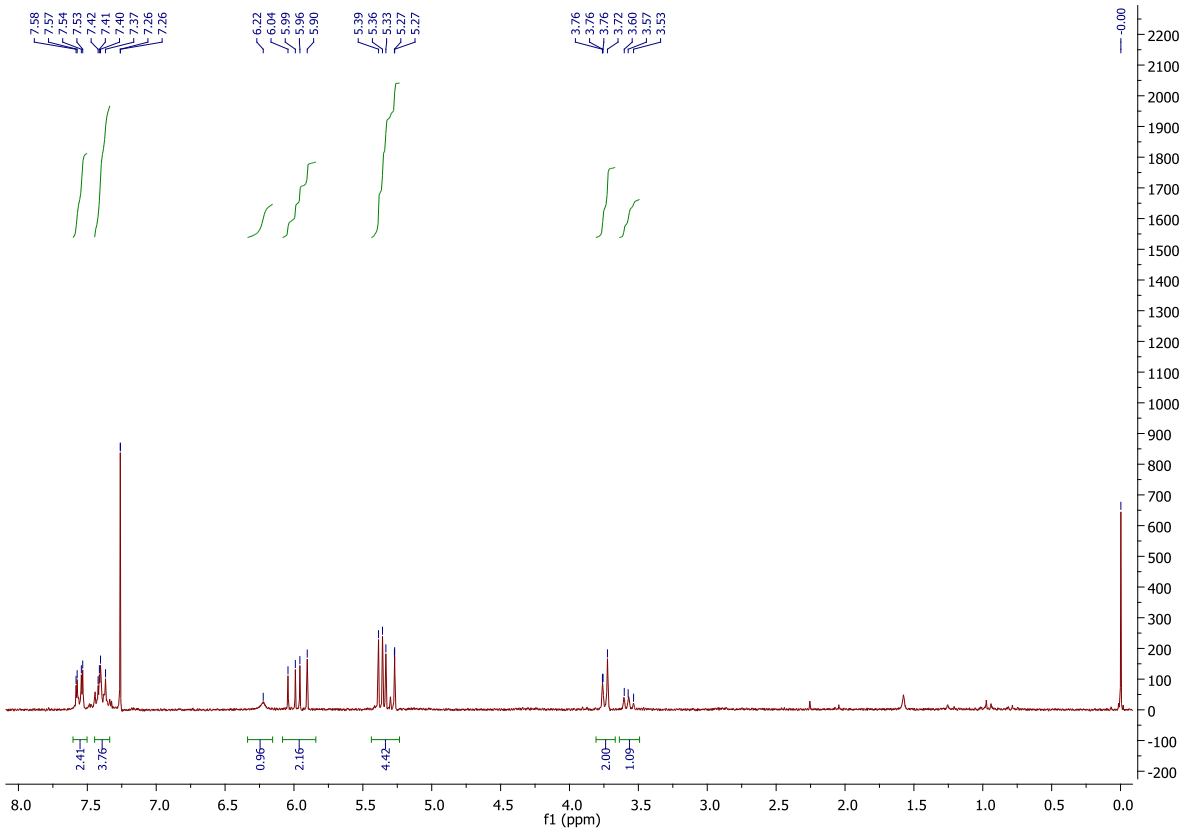


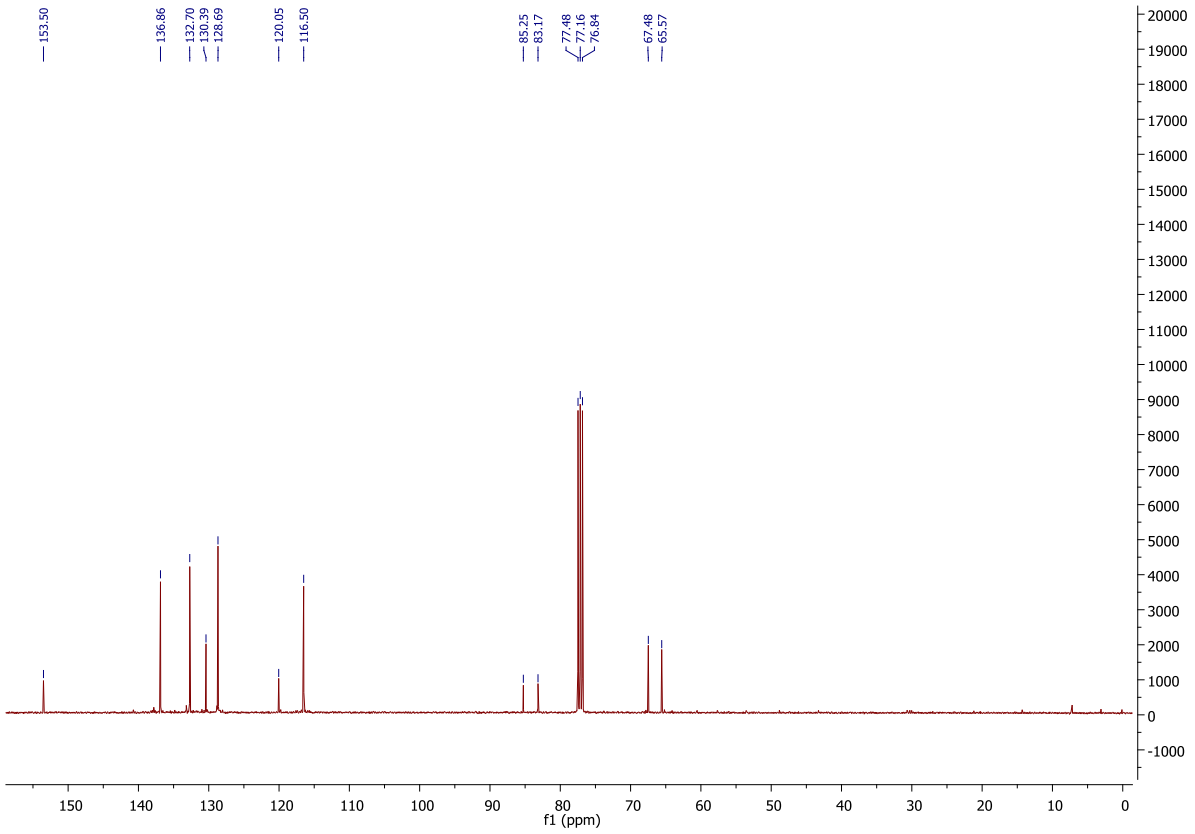




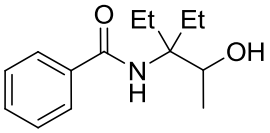
N-(3-(Hydroxymethyl)penta-1,4-dien-3-yl)-3-phenylpropiolamide **(5q)**

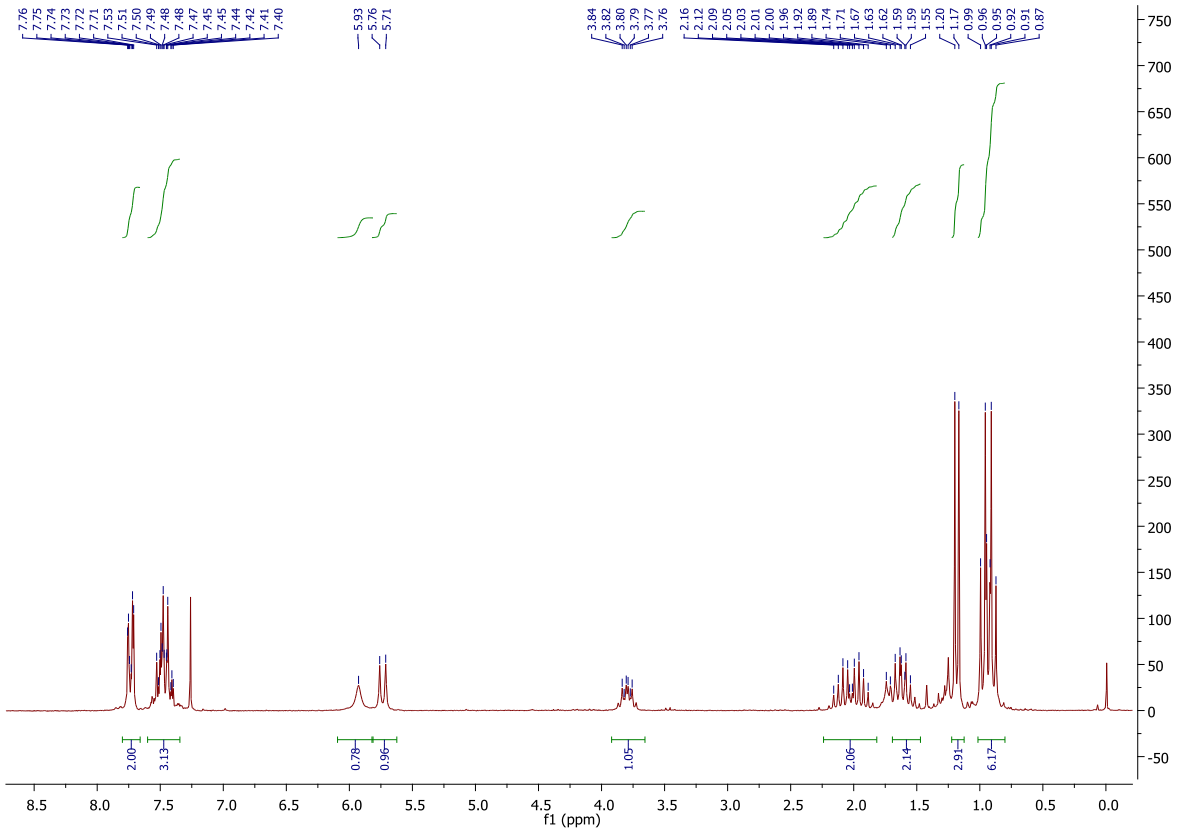


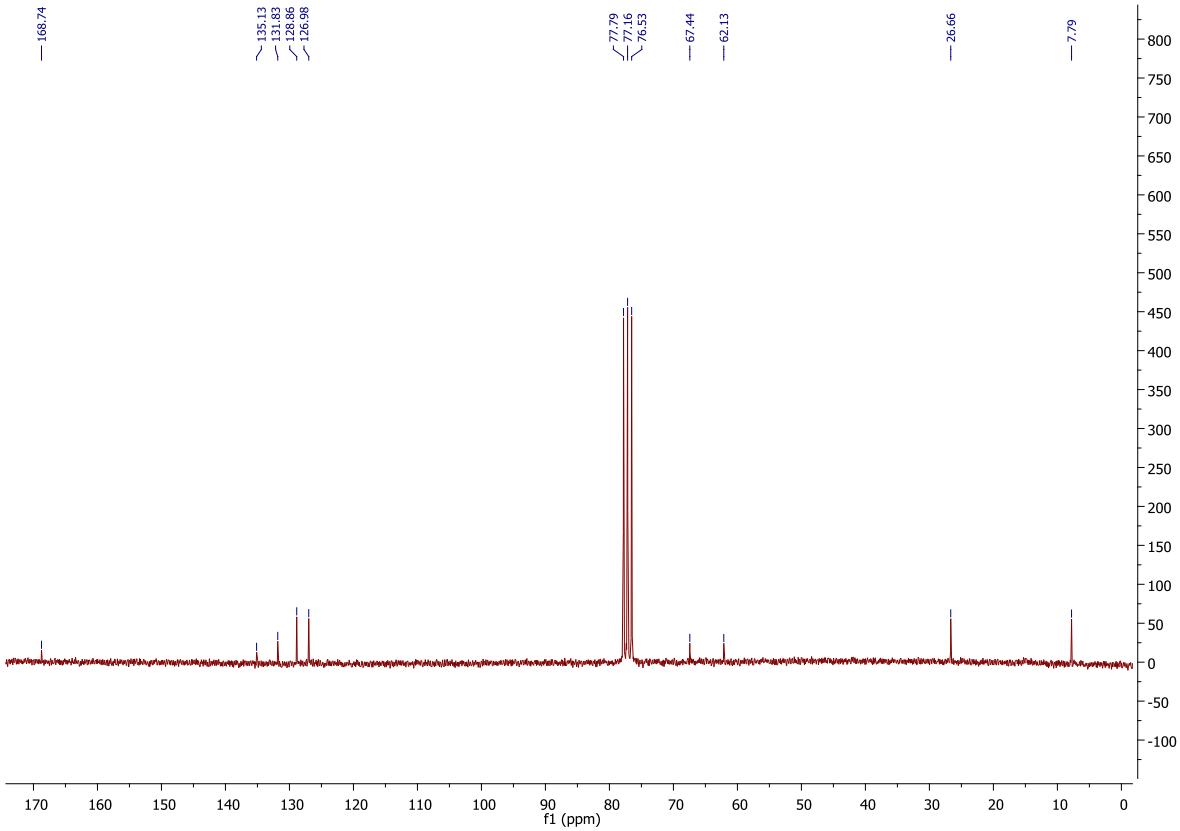




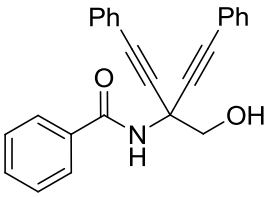
N-(3-Ethyl-2-hydroxypentan-3-yl)benzamide **(5r)**

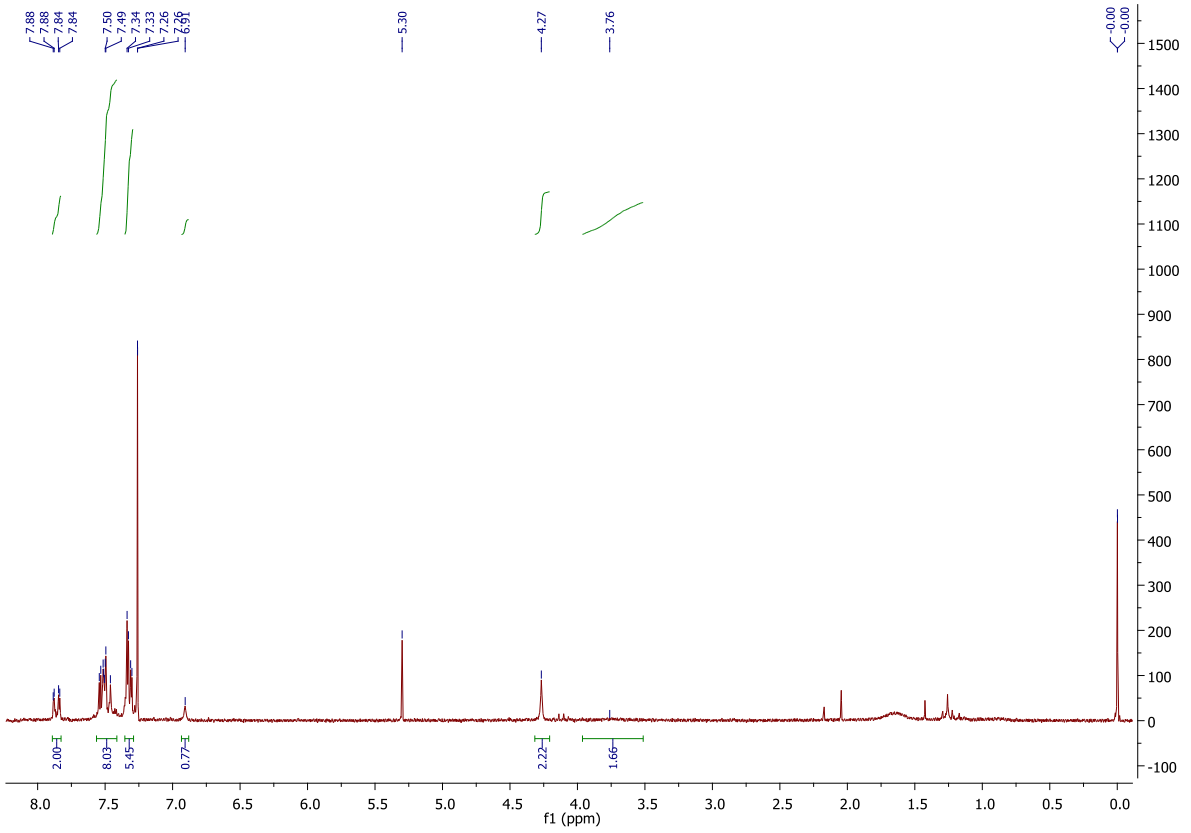


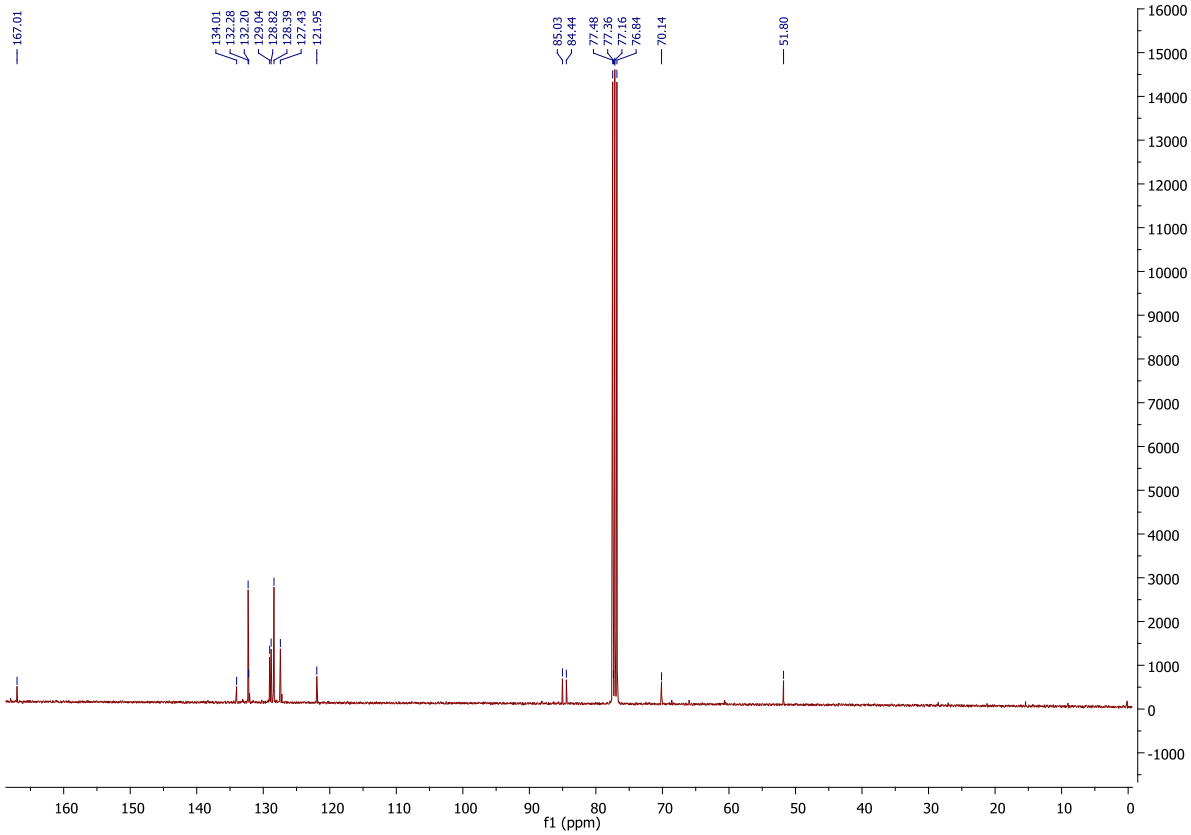




N-(3-(Hydroxymethyl)-1,5-diphenylpenta-1,4-diyn-3-yl)benzamide **(5s)**







N-(3-(Hydroxymethyl)-1,5-bis(trimethylsilyl)penta-1,4-diyn-3-yl)benzamide **(5t)**