Flow Synthesis of Cyclobutanones via [2+2] Cycloaddition of Keteneiminium Salts and Ethylene Gas

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Supporting Information Placeholder

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1. General Information

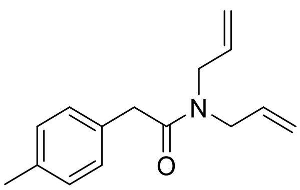
Unless stated otherwise, reagents were obtained from commercial sources and used without purification. New compounds have been fully characterized. NMR characterisation was performed on reported ones. ^{1}H NMR spectra were recorded on Bruker Avance DPX-600 (600 MHz), with the residual solvent peak as the internal reference ($CDCl_3$ = 7.26 ppm). ^{1}H resonances are reported to the nearest 0.01 ppm. ^{13}C-NMR spectra were recorded on the same spectrometer with proton decoupling, with the solvent peak as the internal reference ($CDCl_3$ = 77.00 ppm). All ^{13}C resonances are reported to the nearest 0.01 ppm. The multiplicity of 1H signals are indicated as: s =singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublets of doublets, t = triplet, q = quadruplet, sext = sextet, m = multiplet, br = broad, or combinations of thereof. Coupling constants (*J*) are quoted in Hz and reported to the nearest 0.1 Hz. Where appropriate, measures of the same coupling constant are averaged. The removal of solvent under reduced pressure was carried out on a standard rotary evaporator. Infrared spectra were recorded on a Perkin-Elmer Spectrum RX One FT-IR ATR (Attenuated Total Reflectance) spectrometer. The samples were prepared as thin films deposited on the ATR, unless otherwise specified. Only structurally important absorptions are quoted. Absorption maxima (ν_{max}) are reported in wavenumbers (cm^{-1}). All gas-flow reactions were performed on a Vapourtec R2+/R4 module, a peristaltic Vapourtec SF-10 pump[1] and using a tube-in-tube reactor to introduce gases into a continuous flow stream. For the design of the tube-in-tube reactor see previous publications.[2]

2. General procedure for the preparation of the amides (1a-r)

To a solution of carboxylic acid (1 mmol) in anhydrous CH_2Cl_2 (3 ml) were added bis-allylamine (1.1 mmol), *N*-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide (EDC) (1.5 mmol) and 4-(dimethylamino)pyridine (DMAP) (0.2 mmol).[3] The resulting solution was stirred overnight at room temperature, then diluted with CH_2Cl_2 (5 ml) and washed with 10 % HCl (3 x 10 ml). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the crude residue was purified by silica gel column chromatography using Hex/AcOEt (1:1) as eluent.

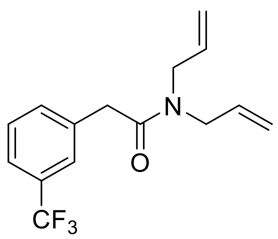
2.1. Characterisation data of the amides (1a-r)

N,N-diallyl-2-(p-tolyl)acetamide (1a)



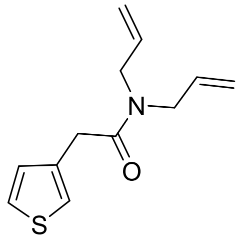
Yellowish oil, 85 % yield. **FT-IR** (ν_{max}, cm^{-1}) 1639. **^{1}H-NMR** (600 MHz, $CDCl_3$) δ 7.14 (dd, *J* = 16.4, 8.1 Hz, 4H), 5.85 – 5.63 (m, 2H), 5.15 (dddd, *J* = 29.8, 18.6, 13.7, 1.2 Hz, 4H), 4.00 (d, *J* = 6.0 Hz, 2H), 3.86 (d, *J* = 5.0 Hz, 2H), 3.67 (s, 2H), 2.33 (s, 3H). **^{13}C-NMR** (151 MHz, $CDCl_3$) δ 171.2, 136.3, 133.2, 132.9, 132.0, 129.3, 128.6, 117.2, 116.8, 49.4, 47.8, 40.4, 21.0.

N,N-diallyl-2-(3-(trifluoromethyl)phenyl)acetamide(1b)



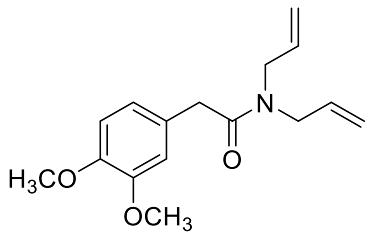
Yellowish oil, 85 % yield. **FT-IR** (ν_{max}, cm^{-1}) 1639. **^{1}H-NMR** (600 MHz, $CDCl_3$) δ 7.51 – 7.37 (m, 4H), 5.74 – 5.70 (m, 2H), 5.15 – 5.09 (m, 4H), 3.99 (d, *J* = 5.9 Hz, 2H), 3.88 (d, *J* = 4.4 Hz, 2H), 3.72 (s, 2H). **^{13}C-NMR** (151 MHz, $CDCl_3$) δ 170.1, 136.1, 132.8, 132.6, 130.6, 128.8, 125.8, 124.9, 123.6, 123.1, 117.4, 116.7, 49.4, 48.1, 39.8.

N,N-diallyl-2-(thiophen-3-yl)acetamide (1c)



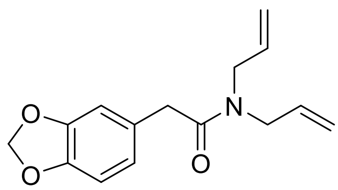
Yellowish oil, 72 % yield. **FT-IR** (ν_{max}, cm^{-1}) 1634. **^{1}H-NMR** (600 MHz, $CDCl_3$) δ 7.16 (dd, *J* = 4.9, 3.0 Hz, 1H), 6.99 (m, 1H), 6.93 (d, *J* = 5.0 Hz, 1H), 5.73 – 5.53 (m, 2H), 5.15 – 4.93 (m, 4H), 3.90 (d, *J* = 6.1 Hz, 2H), 3.78 (d, *J* = 5.0 Hz, 2H), 3.60 (s, 2H). **^{13}C-NMR** (151 MHz, $CDCl_3$) δ 170.5, 134.9, 133.0, 132.8, 128.2, 125.6, 121.9, 117.2, 116.6, 49.4, 47.8, 35.3.

N,N-diallyl-2-(3,4-dimethoxyphenyl)acetamide (1d)



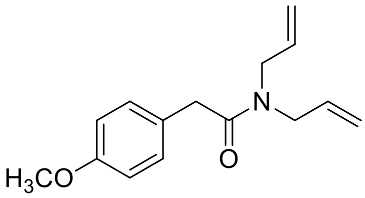
Yellowish oil, 85 % yield. **FT-IR** (ν_{max}, cm^{-1}) 1634. **^{1}H-NMR** (600 MHz, $CDCl_3$) δ 6.81 (m, 2H), 6.76 (m, 1H), 5.81 – 5.63 (m, 2H), 5.23 – 5.04 (m, 4H), 3.99 (d, *J* = 5.8 Hz, 2H), 3.86 (bs, 8H), 3.64 (s, 2H). **^{13}C-NMR** (151 MHz, $CDCl_3$) δ 171.1, 149.0, 147.8, 133.0, 132.9, 127.6, 120.8, 117.1, 116.7, 111.7, 111.2, 55.8, 55.8, 49.4, 47.8, 40.3.

N,N-diallyl-2-(benzo[d][1,3]dioxol-5-yl)acetamide (1e)



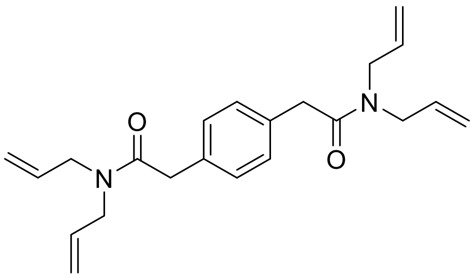
Yellowish oil, 80 % yield. **FT-IR** (ν_{max}, cm^{-1}) 1636.**^{1}H-NMR** (600 MHz, $CDCl_3$) δ 6.80 – 6.68 (m, 2H), 6.66 (d, *J* = 8.0 Hz, 1H), 5.90 (s, 2H), 5.80 – 5.65 (m, 2H), 5.24 – 5.03 (m, 4H), 3.98 (d, *J* = 6.0 Hz, 2H), 3.86 (d, *J* = 4.8 Hz, 2H), 3.59 (s, 2H). **^{13}C-NMR** (151 MHz, $CDCl_3$) δ 171.1, 147.8, 146.4, 133.0, 132.8, 128.7, 121.8, 117.3, 116.8, 109.2, 108.2, 100.9, 49.3, 47.9, 40.1.

N,N-diallyl-2-(p-methoxyphenyl)acetamide (1f)



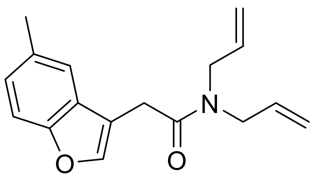
Yellowish oil, 70% yield. **FT-IR** (ν_{max}, cm^{-1}) 1635. **^{1}H-NMR** (600 MHz, $CDCl_3$) δ 7.11 (d, *J* = 8.7 Hz, 2H), 6.78 (d, *J* = 8.8 Hz, 2H), 5.75 – 5.56 (m, 2H), 5.20 – 4.94 (m, 4H), 3.92 (d, *J* = 6.0 Hz, 2H), 3.79 (d, *J* = 5.0 Hz, 2H), 3.69 (s, 3H), 3.57 (s, 2H). **^{13}C-NMR** (151 MHz, $CDCl_3$) δ 171.1, 158.4, 133.1, 132.9, 129.7, 127.1, 117.1, 116.6, 113.9, 55.1, 49.3, 47.7, 39.6.

2,2'-(1,4-phenylene)bis(N,N-diallylacetamide) (1g)



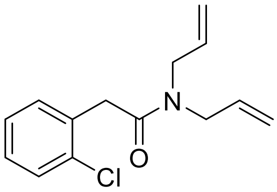
Yellowish solid, 83 %. **FT-IR** (ν_{max}, cm^{-1}) 1652, 1634. **^{1}H-NMR** (600 MHz, $CDCl_3$) δ 7.22 (s, 4H), 5.81 – 5.65 (m, 4H), 5.26 – 5.06 (m, 8H), 4.00 (d, *J* = 5.9 Hz, 4H), 3.88 – 3.84 (m, 4H), 3.69 (s, 4H). **^{13}C-NMR** (151 MHz, $CDCl_3$) δ 170.9, 133.6, 133.1, 132.8, 129.0, 117.3, 116.8, 49.4, 47.9, 40.3.

N,N-diallyl-2-(5-methylbenzofuran-3-yl)acetamide (1h)



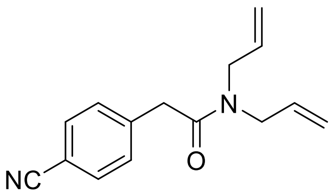
Yellowish oil, 70 % yield. **FT-IR** (ν_{max}, cm^{-1}) 1640. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.56 (s, 1H), 7.37 (d, *J* = 8.7 Hz, 2H), 7.13 (dd, *J* = 8.3, 1.7 Hz, 1H), 5.80 (d, *J* = 6.4 Hz, 2H), 5.34 – 4.97 (m, 4H), 4.06 (d, *J* = 6.0 Hz, 2H), 3.96 (d, *J* = 4.8 Hz, 2H), 2.46 (s, 3H). **^{13}C-NMR** (151 MHz, $CDCl_3$) δ 169.98, 153.67, 142.62, 133.04, 132.82, 127.57, 125.90, 119.30, 117.55, 116.85, 113.94, 112.72, 111.09, 49.60, 48.21, 37.08, 29.29.

N,N-diallyl-2-(2-chlorophenyl)acetamide (1i)



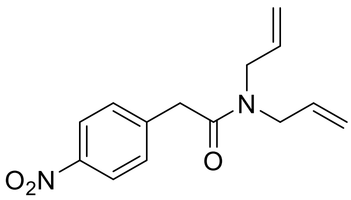
Yellowish oil, 72 % yield. **FT-IR** ($\nu_{max,}$ cm^{-1}) 1639. **^{1}H-NMR** (600 MHz, $CDCl_3$) δ 7.39 (d, *J* = 1.6 Hz, 1H), 7.38 (d, *J* = 1.8 Hz, 1H), 7.27 – 7.20 (m, 2H), 5.85 – 5.73 (m, 2H), 5.29 – 5.11 (m, 4H), 4.05 (d, *J* = 6.0 Hz, 2H), 3.96 – 3.90 (m, 2H), 3.82 (s, 2H). **^{13}C-NMR** (151 MHz, $CDCl_3$) δ 170.0, 134.0, 133.4, 133.0, 132.5, 130.9, 129.4, 128.3, 126.9, 117.5, 116.8, 49.4, 48.1, 37.9.

N,N-diallyl-2-(4-cyanophenyl)acetamide (1j)



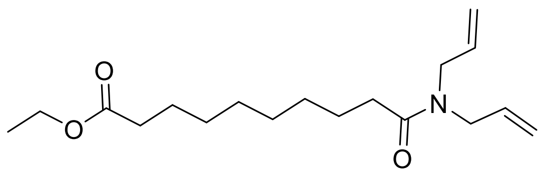
Yellowish oil, 78 % yield. **FT-IR** ($\nu_{max,}$ cm^{-1}) 2227, 1636. **^{1}H-NMR** (600 MHz, $CDCl_3$) δ 7.59 (d, *J* = 7.9 Hz, 2H), 7.36 (d, *J* = 7.8 Hz, 2H), 5.82 – 5.69 (m, 2H), 5.28 – 5.05 (m, 4H), 3.99 (d, *J* = 5.4 Hz, 2H), 3.89 (s, 2H), 3.73 (s, 2H). **^{13}C-NMR** (151 MHz, $CDCl_3$) δ 169.6, 140.7, 132.7, 132.5, 132.2, 130.0, 118.8, 117.7, 116.9, 110.7, 49.4, 48.3, 40.1.

N,N-diallyl-2-(4-nitrophenyl)acetamide (1k)



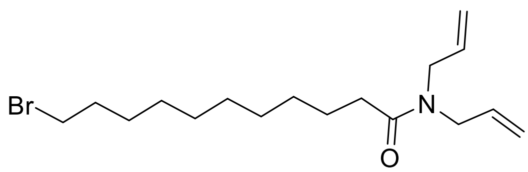
Yellowish oil, 73 % yield. **FT-IR** ($\nu_{max,}$ cm^{-1}) 1637. **^{1}H-NMR** (600 MHz, $CDCl_3$) δ 8.20 – 8.11 (m, 2H), 7.42 (d, *J* = 8.6 Hz, 2H), 5.85 – 5.68 (m, 2H), 5.30 – 5.05 (m, 4H), 4.01 (s, 2H), 3.94 – 3.89 (m, 2H), 3.79 (s, 2H). **^{13}C-NMR** (151 MHz, $CDCl_3$) δ 169.4, 146.9, 142.8, 132.7, 132.5, 130.1, 123.6, 117.7, 116.9, 49.4, 48.3, 39.8.

Ethyl 10-(diallylamino)-10-oxodecanoate (1l)



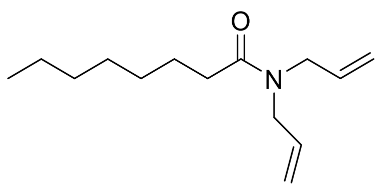
Yellowish oil, 71% yield. **FT-IR** (ν_{max}, cm^{-1}) 1641. **^{1}H-NMR** (600 MHz, $CDCl_3$) δ 5.81 – 5.72 (m, 2H), 5.25 – 5.10 (m, 4H), 4.14 (q, *J* = 7.1 Hz, 2H), 4.00 (d, *J* = 5.9 Hz, 2H), 3.88 (dd, *J* = 2.9, 1.8 Hz, 2H), 2.30 (dt, *J* = 10.9, 7.6 Hz, 4H), 1.66 – 1.58 (m, 5H), 1.28 (dd, *J* = 21.8, 14.7 Hz, 11H). **^{13}C-NMR** (151 MHz, $CDCl_3$) δ 173.7, 173.0, 133.3, 132.9, 116.9, 116.3, 60.0, 49.0, 47.7, 34.2, 32.8, 29.2, 29.1, 29.0, 28.9, 25.2, 24.8, 14.2.

N,N-diallyl-11-bromoundecanamide (1m)



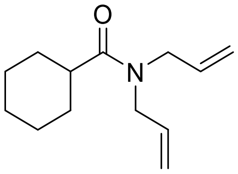
Amorphous white solid, 83% yield. **FT-IR** (ν_{max}, cm^{-1}) 1653. **^{1}H-NMR** (600 MHz, $CDCl_3$) δ 5.83 – 5.73 (m, 2H), 5.26 – 5.09 (m, 4H), 4.00 (d, *J* = 5.9 Hz, 2H), 3.89 (d, *J* = 4.7 Hz, 2H), 3.42 (t, *J* = 6.9 Hz, 2H), 2.35 – 2.30 (m, 2H), 1.91 – 1.82 (m, 2H), 1.65 (dd, *J* = 14.6, 7.2 Hz, 2H), 1.43 (dd, *J* = 14.6, 7.1 Hz, 2H), 1.29 (d, *J* = 13.3 Hz, 10H).**^{13}C-NMR** (151 MHz, $CDCl_3$) δ 173.1, 133.4, 132.9, 117.0, 116.4, 49.0, 47.7, 34.1, 33.0, 32.8, 29.4, 29.4, 29.3, 29.3, 28.7, 28.1, 25.3.

N,N-diallyloctanamide (1n)



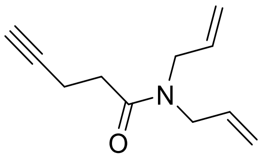
Yellowish oil, 48 % yield. **FT-IR** (ν_{max}, cm^{-1}) 1641. **^{1}H-NMR** (600 MHz, $CDCl_3$) δ 5.75 – 5.63 (m, 2H), 5.16 – 5.01 (m, 4H), 3.91 (d, *J* = 6.0 Hz, 2H), 3.83 – 3.78 (m, 2H), 2.29 – 2.18 (m, 2H), 1.62 – 1.53 (m, 2H), 1.28 – 1.15 (m, 8H), 0.80 (t, *J* = 6.9 Hz, 3H). **^{13}C-NMR** (151 MHz, $CDCl_3$) δ 173.1, 133.3, 132.8, 116.9, 116.3, 49.0, 47.6, 32.9, 31.6, 29.3, 29.0, 25.2, 22.5, 14.0.

N,N-diallylcyclohexanecarboxamide (1o)



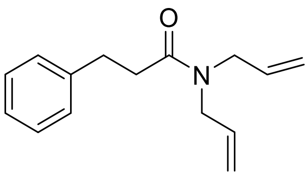
Colorless oil, 40 % yield. **FT-IR** (ν_{max}, cm^{-1}) 1630. **^{1}H-NMR** (600 MHz, $CDCl_3$) δ 5.78 (m, 2H), 5.30 – 5.01 (m, 4H), 3.97 (s, 2H), 3.90 (s, 2H), 2.50 – 2.35 (m, 1H), 1.87 – 1.45 (m, 7H), 1.26 (s, 3H). **^{13}C-NMR** (151 MHz, $CDCl_3$) δ 176.3, 133.5, 116.7, 116.3, 48.9, 47.7, 40.8, 29.6, 25.8, 25.7.

N,N-diallylpent-4-ynamide (1p)



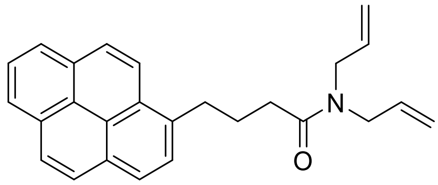
Yellowish oil, 53 % yield. **FT-IR** (ν_{max}, cm^{-1}) 1637. **^{1}H-NMR** (600 MHz, $CDCl_3$) δ 5.81 – 5.63 (m, 2H), 5.35 – 4.95 (m, 4H), 3.96 (d, *J* = 6.4 Hz, 2H), 3.91 – 3.79 (m, 2H), 2.59 – 2.43 (m, 4H), 1.98 – 1.92 (m, 1H). **^{13}C-NMR** (151 MHz, $CDCl_3$) δ 170.8, 133.0, 132.4, 117.3, 116.6, 83.5, 68.7, 48.9, 48.0, 31.9, 14.5.

N,N-diallyl-3-phenylpropanamide (1q)



Yellowish oil, 86 % yield. **FT-IR** (ν_{max}, cm^{-1}) 1637. **^{1}H-NMR** (600 MHz, $CDCl_3$) δ 7.26 (t, *J* = 7.5 Hz, 2H), 7.23 – 7.15 (m, 3H), 5.79 – 5.64 (m, 2H), 5.20 – 5.03 (m, 4H), 3.98 (d, *J* = 6.1 Hz, 2H), 3.81 – 3.75 (m, 2H), 3.01 – 2.94 (m, 2H), 2.65 – 2.57 (m, 2H). **^{13}C-NMR** (151 MHz, $CDCl_3$) δ 172.1, 141.3, 133.2, 132.8, 128.4, 126.0, 117.1, 116.4, 49.0, 48.0, 34.8, 31.4.

N,N-diallyl-4-(pyren-1-yl)butanamide (1r)

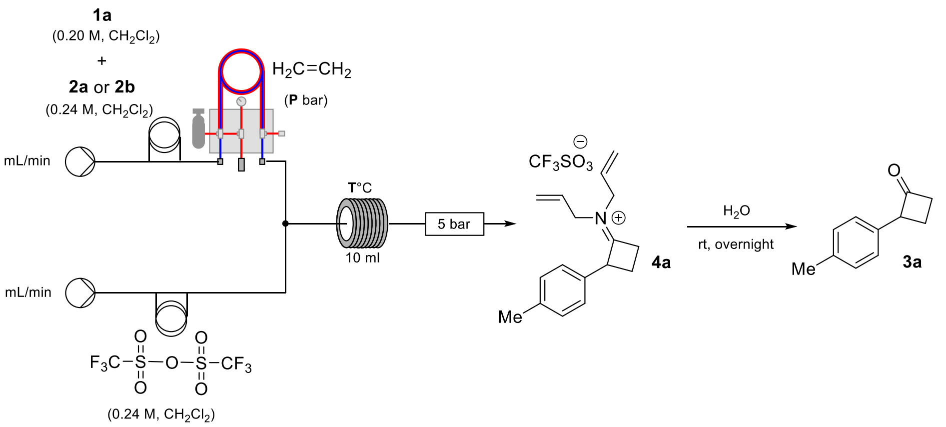


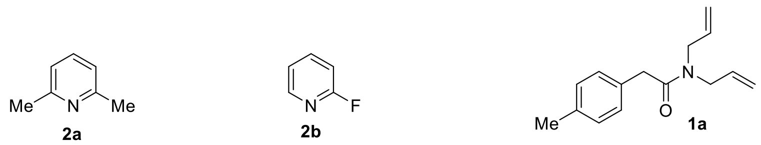
Yellowish oil, 60% yield. **FT-IR** ($\nu_{max,}$ cm^{-1}) 1635. **^{1}H-NMR** (600 MHz, $CDCl_3$) δ 8.37 (d, *J* = 9.2 Hz, 1H), 8.17 (t, *J* = 6.7 Hz, 2H), 8.12 (d, *J* = 3.5 Hz, 1H), 8.11 (d, *J* = 2.0 Hz, 1H), 8.06 – 7.97 (m, 3H), 7.88 (d, *J* = 7.7 Hz, 1H), 5.79 (ddt, *J* = 16.2, 10.2, 6.0 Hz, 1H), 5.67 (ddt, *J* = 17.1, 10.1, 4.9 Hz, 1H), 5.21 – 5.02 (m, 4H), 4.03 (d, *J* = 6.0 Hz, 2H), 3.83 – 3.73 (m, 2H), 3.50 – 3.40 (m, 2H), 2.45 (t, *J* = 7.1 Hz, 2H), 2.28 – 2.20 (m, 2H). **^{13}C-NMR** (151 MHz, $CDCl_3$) δ 172.5, 136.2, 133.4, 132.8, 131.4, 130.9, 129.8, 128.8, 127.4, 127.3, 127.3, 126.6, 125.7, 125.0, 124.9, 124.8, 124.7, 124.7, 123.5, 117.1, 116.5, 49.1, 47.9, 32.8, 32.3, 27.0.

3. Initial screening, optimised flow protocol for the synthesis of cyclobutanones (3a-r) and scale up procedure

Initial screening of flow parameters

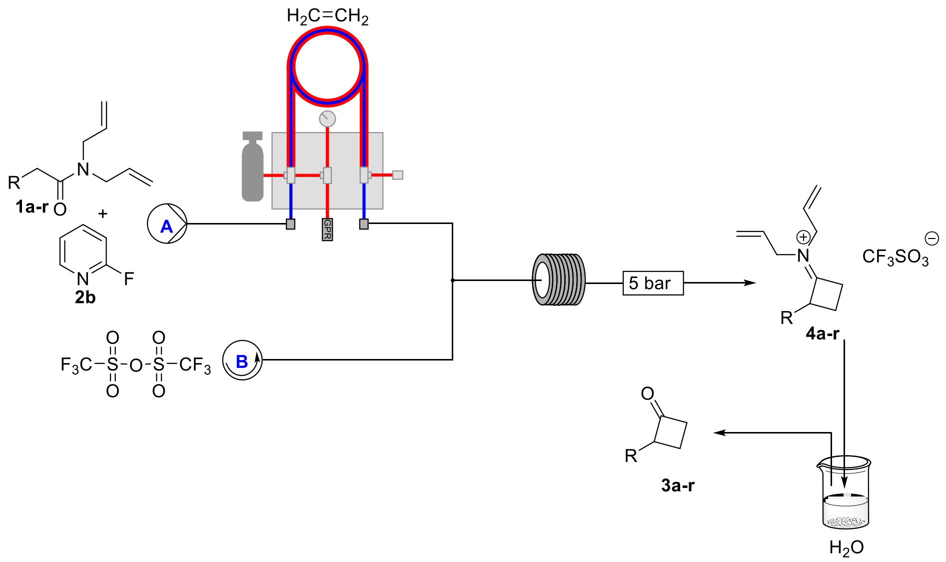
Table S1. Screening of main parameters for the synthesis of cyclobutanone **3a**.





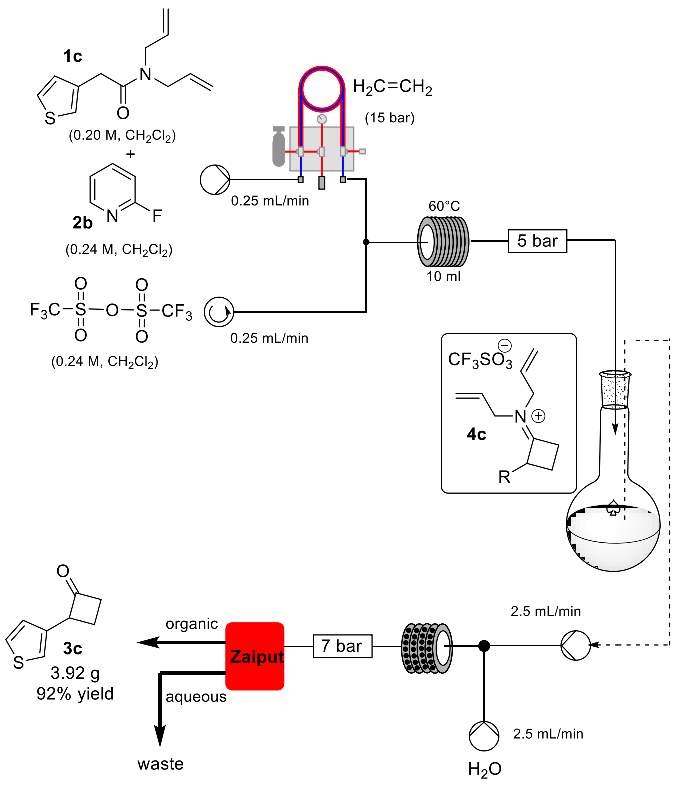
entry	base	τ	T	P	yield
1	**2a**	5	rt	10	20%
2	**2a**	10	rt	15	35%
3	**2a**	20	rt	15	40%
4	**2a**	5	40	10	37%
5	**2a**	20	40	15	51%
6	**2b**	20	40	15	59%
7	**2a**	20	60	15	65%
8	**2b**	20	60	10	74%
9	**2b**	20	60	15	89%
10	**2b**	20	80	15	72%
11	**2b**	20	100	15	69%

Optimised flow protocol



A solution of the amide **1** (2.2 mmol, 0.20 M) and 2-fluoro-pyridine **2b** (2.64 mmol, 0.24 M) in anhydrous CH_2Cl_2 was pumped (flow rate 0.25 mL/min) through a tube-in-tube gas reactor pressurised with ethylene gas (ΔP = 10 bar) and combined at a T-piece with a solution of triflic anhydride (2.64 mmol, 0.24 M) in anhydrous CH_2Cl_2 (pumped at 0.25 mL/min using a Vapourtec SF-10 peristaltic pump[1]) to react in a 10 mL perfluoxoalkoxy (PFA) polymeric coil, heated at 60 °C. The reactor output was directed through a 5 bar back pressure regulator, collected in a flask containing water and stirred overnight. The organic layer was recovered, the solvent was evaporated *in vacuo* and the mixture purified by flash chromatography to give the cyclobutanone product **3a-r**.

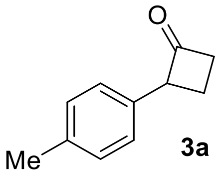
Scale up flow protocol



A solution of the amide **1c** (0.20 M) and 2-fluoro-pyridine **2b** (0.24 M) in anhydrous CH_2Cl_2 (Pump A) was pumped (flow rate 0.25 mL/min) through a tube-in-tube gas reactor pressurised with ethylene gas (ΔP = 10 bar) and combined at a T-piece with a solution of triflic anhydride (0.24 M) in anhydrous CH_2Cl_2 (loaded in a PFA coil 60 mL, Pump B) (flow rate 0.25 mL/min) to react in a 10 mL perfluoxoalkoxy (PFA) polymeric coil, heated at 60 °C. The reactor output was directed through a 5 bar back pressure regulator and collected in a reservoir. The solution was combined at a T-piece with a stream of distilled water (each channel pumped at 2.5 mL/min) and reacted at 80 °C in a static mixer coil (residence time of 7 min). The biphasic system was then directed to a membrane based liquid-liquid separator,[4] whereby the organic layer was recovered and evaporated *in vacuo*. The crude mixture was purified by flash chromatography to give the cyclobutanone product **3c** (3.92 g, 92% yield).

3.1. Characterisation data of cyclobutanones (3a-r)

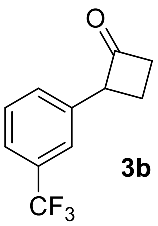
2-(p-tolyl)cyclobutan-1-one (3a)



3a

(SiO_2, CH_2Cl_2/ Hexane = 3:1). Yellowish oil, 89 % yield. **FT-IR** ($\nu_{max,}$ cm^{-1}) 1779. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.17 (s, 4H), 4.56 – 4.48 (m, 1H), 3.28 – 3.19 (m, 1H), 3.09 – 3.00 (m, 1H), 2.60 – 2.50 (m, 1H), 2.36 (s, 3H), 2.27 – 2.19 (m, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 208.2, 136.6, 133.5, 129.3, 126.8, 64.3, 44.8, 21.0, 17.8. **HRMS** for $C_{11}H_{10}ON$, calculated 161.0966, found 161.0962.

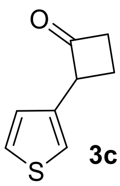
2-(3-(trifluoromethyl)phenyl)cyclobutan-1-one (3b)



3b

(SiO_2, CH_2Cl_2/ Hexane = 3:1). Yellowish oil, 84 % yield. **FT-IR** ($\nu_{max,}$ cm^{-1}) 1781. **^{1}H NMR** (600 MHz, $CDCl_3$) δ: 7.54 – 7.44 (m, 4H), 4.63 – 4.56 (m, 1H), 3.36 – 3.24 (m, 1H), 3.10-3.00 (m, 1H), 2.59 (ddd, *J* = 21.8, 10.7, 4.8 Hz, 1H), 2.31 – 2.23 (m, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 206.4, 137.3, 130.9, 130.4, 130.4, 129.0, 123.8, 123.6, 63.8, 44.9, 17.4. **HRMS** for $C_{11}H_9OF_3$, calculated 214.0605, found 214.0600.

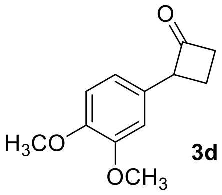
2-(thiophen-3-yl)cyclobutan-1-one (3c)



3c

(SiO_2, CH_2Cl_2/ Hexane = 19:1). Yellow oil, 92 % yield. **FT-IR** ($\nu_{max,}$ cm^{-1}) 1775. **^{1}H-NMR** (600 MHz, $CDCl_3$) δ: 7.33 – 7.29 (m, 1H), 7.14 – 7.11 (m, 1H), 7.01 (dd, *J* = 5.0, 1.2 Hz, 1H), 4.55 (td, *J* = 8.2, 2.1 Hz, 1H), 3.26 – 3.17 (m, 1H), 3.01-3.09 (m, 1H), 2.54 (ddd, *J* = 21.5, 10.7, 5.0 Hz, 1H), 2.20 – 2.11 (m, 1H). **^{13}C-NMR** (151 MHz, $CDCl_3$) δ: 207.4, 136.8, 126.5, 126.0, 120.7, 60.3, 44.9, 18.2. **HRMS** for C_8H_9OS, calculated 153.0374, found 153.0371.

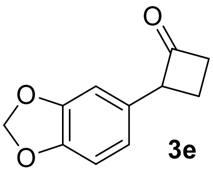
2-(3,4-Dimethoxyphenyl)cyclobutan-1-one (3d)



3d

(SiO_2, CH_2Cl_2/ Hexane = 19:1). Orange amorphous solid, 91% yield. **FT-IR** ($\nu_{max,}$ cm^{-1}) 1774. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.82 – 6.71 (m, 3H), 4.47 – 4.40 (m, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 3.22 – 3.11 (m, 1H), 3.01 – 2.92 (m, 1H), 2.48 (qd, *J* = 10.7, 4.9 Hz, 1H), 2.20 – 2.10 (m, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 208.2 149.0, 148.0, 129.2, 118.9, 111.3, 110.3, 64.0, 55.9, 55.8, 44.64, 17.9. **HRMS** for $C_{12}H_{15}O_3$, calculated 207.1021, found 207.1015.

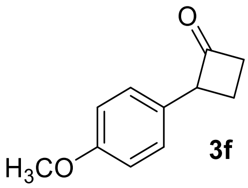
2-(benzo[d][1,3]dioxol-5-yl)cyclobutan-1-one (3e)



3e

(SiO_2, CH_2Cl_2/ Hexane = 19:1). Red oil, 81 % yield. **FT-IR** ($\nu_{max,}$ cm^{-1}) 1775. **^{1}H-NMR** (600 MHz, $CDCl_3$) δ 6.80 – 6.72 (m, 2H), 6.72 – 6.66 (m, 1H), 5.93 (s, 2H), 4.48 – 4.41 (m, 1H), 3.26 – 3.15 (m, 1H), 3.04 – 2.96 (m, 1H), 2.51 (qd, *J* = 10.6, 4.9 Hz, 1H), 2.20 – 2.10 (m, 1H). **^{13}C-NMR** (151 MHz, $CDCl_3$) δ 207.9, 147.8, 146.5, 130.3, 120.0, 108.3, 107.5, 101.0, 64.2, 44.6, 18.1. **HRMS** for $C_{11}H_{11}O_3$, calculated 191.0708, found 191.0704.

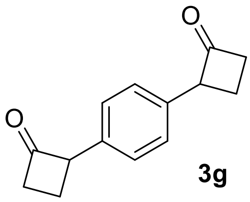
2-(4-Methoxyphenyl)cyclobutan-1-one (3f)



3f

(SiO_2, Hexane/AcOEt = 19:1). Orange amorphous solid, 85 % yield. **FT-IR** ($\nu_{max,}$ cm^{-1}) 1777. **^{1}H-NMR** (600 MHz, $CDCl_3$) δ 7.18 (d, *J*= 8.5 Hz, 2 H), 6.88 (d, *J*= 8.8 Hz, 2 H), 4.51-445 (m, 1 H), 3.80 (s, 3 H), 3.26- 3.17 (m, 1 H), 3.05- 2.98 (m, 1 H), 2.56- 2.48 (m, 1 H), 2.22- 2.14 (m, 1 H). **^{13}C-NMR** (151 MHz, $CDCl_3$) δ 208.4, 158.6, 128.7, 128.1, 114.1, 63.9, 55.3, 44.7, 18.0. **HRMS** for $C_{11}H_{13}O_2$, calculated 177.0916, found 177.0917.

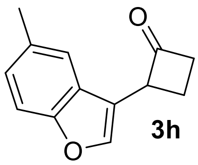
2,2'-(1,4-Phenylene)bis(cyclobutan-1-one) (3g)



3g

(SiO_2, CH_2Cl_2/ Hexane = 70:30). Yellowish solid, 78 % yield. **FT-IR** ($\nu_{max,}$ cm^{-1}) 1765. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.23 (s, 4H), 4.58 – 4.49 (m, 2H), 3.28 – 3.19 (m, 2H), 3.09 – 2.99 (m, 2H), 2.54 (qd, *J* = 10.7, 4.9 Hz, 2H), 2.28 – 2.16 (m, 2H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 207.7, 135.23, 127.2, 64.2, 44.8, 17.7. **HRMS** for $C_{14}H_{15}O_2$, calculated 215.1072, found 215.1067.

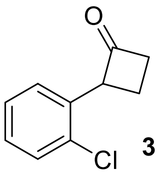
2-(Benzofuran-3-yl)cyclobutan-1-one (3h)



3h

(SiO_2, CH_2Cl_2/ Hexane = 3:1). Yellowish oil, 65 % yield. **FT-IR** ($\nu_{max,}$ cm^{-1}) 1779. **^{1}H-NMR** (600 MHz, $CDCl_3$) δ 7.55 (d, *J* = 1.0 Hz, 1H), 7.36 (d, *J* = 8.4 Hz, 1H), 7.32 (s, 1H), 7.13 (dd, *J* = 8.4, 1.1 Hz, 1H), 4.68 – 4.59 (m, 1H), 3.39 – 3.29 (m, 1H), 3.21 – 3.15 (m, 1H), 2.63 (qd, *J* = 10.7, 5.0 Hz, 1H), 2.45 (s, 3H), 2.22 – 2.18 (m, 1H). **^{13}C-NMR** (151 MHz, $CDCl_3$) δ 206.8, 153.8, 141.2, 132.1, 126.7, 125.9, 119.6, 115.9, 111.1, 55.2, 45.5, 21.3, 17.3.

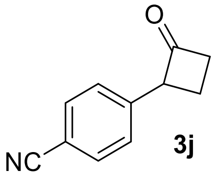
2-(2-Chlorophenyl)cyclobutan-1-one (3i)



3i

(SiO_2, CH_2Cl_2/ Hexane = 19:1). Orange oil, 51 % yield. **FT-IR** ($\nu_{max,}$ cm^{-1}) 1779. **^{1}H-NMR** (600 MHz, $CDCl_3$) δ 7.57 – 7.44 (m, 4H), 4.65 – 4.58 (m, 1H), 3.35 – 3.27 (m, 1H), 3.13- 3.05 (m, 1H), 2.62 (qd, *J* = 10.7, 4.8 Hz, 1H), 2.33 – 2.25 (m, 1H). **^{13}C-NMR** (151 MHz, $CDCl_3$) δ 206.4, 137.2, 130.4, 129.0, 123.8, 123.8, 123.6, 123.6, 63.8, 45.0, 17.5. **HRMS** for $C_{10}H_{10}OCl$, calculated 181.0420, found 181.0416.

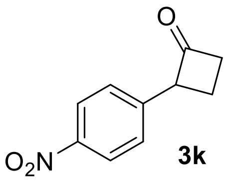
2-(4-Cyanophenyl)cyclobutan-1-one (3j)



3j

(SiO_2, CH_2Cl_2/ Hexane = 19:1). Yellow oil, 60 % yield. **FT-IR** ($\nu_{max,}$ cm^{-1}) 1778. **^{1}H-NMR** (600 MHz, $CDCl_3$) δ 7.62 (d, *J*=8.2 Hz, 2 H), 7.38 (d, *J*=8.0 Hz, 2 H), 4.61 (m, 1 H), 3.34 – 3.25 (m, 1 H), 3.11 – 3.02 (m, 1 H), 2.60 (qd, *J*=10.7, 4.8 Hz, 1 H), 2.31 – 2.22 (m, 1 H). **^{13}C-NMR** (151 MHz, $CDCl_3$) δ 205.7, 141.5, 132.3, 127.7, 118.7, 110.7, 64.0, 45.0, 17.2. **HRMS** for $C_{11}H_{10}ON$, calculated 172.0762, found 172.0757.

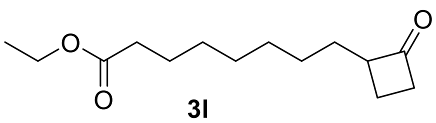
2-(4-Nitrophenyl)cyclobutan-1-one (3k)



3k

(SiO_2, CH_2Cl_2/ Hexane = 3:1). Red amorphous solid, 58 % yield. **FT-IR** ($\nu_{max,}$ cm^{-1}) 1780. **^{1}H-NMR** (600 MHz, $CDCl_3$), δ: 8.15 (d, *J*= 8.2 Hz, 2 H), 7.42 (d, *J*= 8.2 Hz, 2 H), 4.66 (m, 1 H), 3.35-3.27 (m, 1 H), 3.12- 3.03 (m, 1 H), 2.67-2.59 (m, 1 H), 2.34-2.25 (m, 1 H). **^{13}C-NMR** (151 MHz, $CDCl_3$), δ: 205.4, 146.8, 143.6, 127.7, 123.7, 63.8, 45.1, 17.3. **HRMS** for $C_{10}H_9O_3N$, calculated 191.0582, found 191.0579.

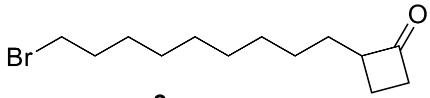
Ethyl 8-(2-oxocyclobutyl)octanoate (l)



3l

(SiO_2, CH_2Cl_2/ Hexane = 3:1). Yellowish oil, 52 % yield. **FT-IR** ($\nu_{max,}$ cm^{-1}) 1777, 1740. **^{1}H-NMR** (600 MHz, $CDCl_3$) δ 4.14 (q, *J* = 7.1 Hz, 2H), 3.29 (m, 1H), 3.03 (m, 1H), 2.93 (m, 1H), 2.30 (t, *J* = 7.5 Hz, 2H), 2.19 (ddd, *J* = 21.0, 10.4, 5.2 Hz, 1H), 1.74 – 1.59 (m, 4H), 1.53 – 1.45 (m, 1H), 1.40 – 1.26 (m, 11H). **^{13}C-NMR** (151 MHz, $CDCl_3$) δ 212.4, 173.6, 60.6, 60.2, 44.4, 34.3, 29.2, 29.1, 29.0, 27.0, 24.9, 16.9, 14.2.

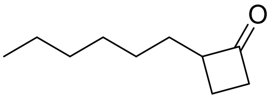
2-(9-Bromononyl)cyclobutan-1-one (3m)



3m

(SiO_2, CH_2Cl_2/ Hexane = 3:1). White amorphous solid, 68 % yield. **FT-IR** ($\nu_{max,}$ cm^{-1}) 1779. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 3.42 (t, *J* = 6.9 Hz, 2H), 3.25 (m, 1H), 3.03 (m, 1H), 2.93 (m, 1H), 2.19 (ddd, *J* = 21.1, 10.4, 5.2 Hz, 1H), 1.90 – 1.84 (m, 2H), 1.73 – 1.62 (m, 2H), 1.53 – 1.26 (m, 13H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 212.4, 60.6, 44.4, 29.5, 29.4, 29.3, 29.3, 28.7, 28.1, 27.0, 16.9.

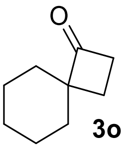
2-Hexylcyclobutan-1-one (3n)



3n

(SiO_2, CH_2Cl_2: Hexane = 19: 1). Yellowish oil, > 95 % yield (with internal standard). **FT-IR** ($\nu_{max,}$ cm^{-1}) 1776. **^{1}H-NMR** (600 MHz, $CDCl_3$) δ 3.29 – 3.22 (m, 1H), 3.04 – 2.95 (m, 1H), 2.93 – 2.85 (m, 1H), 2.15 (ddd, *J* = 21.1, 10.4, 5.2 Hz, 1H), 1.71 – 1.58 (m, 2H), 1.51 – 1.42 (m, 1H), 1.39 – 1.16 (m, 7H), 0.85 (t, *J* = 7.0 Hz, 3H). **^{13}C-NMR** (151 MHz, $CDCl_3$) δ 212.6, 60.5, 44.3, 31.6, 29.5, 29.1, 26.9, 22.5, 16.8, 14.0. **HRMS** for $C_{10}H_{19}O$, calculated 155.1436, found 155.1435.

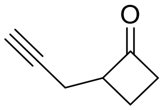
Spiro[3.5]nonan-1-one (3o)



3o

(SiO_2, CH_2Cl_2: Hexane = 9: 1). Colorless oil, 85 % yield (with internal standard). **FT-IR** ($\nu_{max,}$ cm^{-1}) 1764. **^{1}H-NMR** (600 MHz, $CDCl_3$) δ: 2.95 (t, *J* = 8.2 Hz, 2H), 1.81 (t, *J* = 8.4 Hz, 2H), 1.71 – 1.32 (m, 10H). **^{13}C-NMR** (151 MHz, $CDCl_3$) δ 216.0, 65.7, 41.2, 32.0, 25.4, 24.0, 22.4.

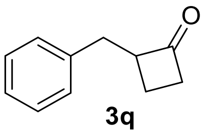
2-(Prop-2-yn-1-yl)cyclobutan-1-one (3p)



3p

(SiO_2, CH_2Cl_2: Hexane = 19:1). Colorless oil, 47% yield (with internal standard). **FT-IR** ($\nu_{max,}$ cm^{-1}) 3300, 1778. **^{1}H-NMR** (600 MHz, $CDCl_3$) δ 3.53 – 3.45 (m, 1H), 3.18 – 3.06 (m, 1H), 3.04 – 2.94 (m, 1H), 2.54 – 2.47 (m, 2H), 2.31 – 2.23 (m, 1H), 2.04 – 1.91 (m, 2H). **^{13}C-NMR** (151 MHz, $CDCl_3$) δ 209.1, 80.4, 69.7, 57.7, 45.1, 18.1, 15.8.

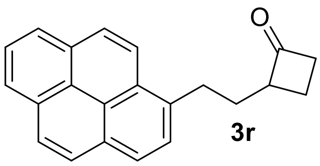
2-Benzylcyclobutan-1-one (3q)



3q

(SiO_2, CH_2Cl_2/ Hexane = 95:5). Yellowish oil, 92 % yield. **IR** ($\nu_{max,}$ cm^{-1}) 1772. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.38 – 7.29 (m, 2H), 7.26 – 7.19 (m, 3H), 3.70 – 3.55 (m, 1H), 3.13 – 2.97 (m, 2H), 2.96 – 2.74 (m, 2H), 2.17 (ddd, *J* = 21.2, 10.5, 5.1 Hz, 1H), 1.85 – 1.69 (m, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 210.8, 138.9, 128.7, 128.5, 126.3, 61.2, 44.5, 35.2, 16.6. **HRMS** for $C_{11}H_{13}O$, calculated 161.0966, found 161.0967.

2-(2-(Pyren-2-yl)ethyl)cyclobutan-1-one (3r)

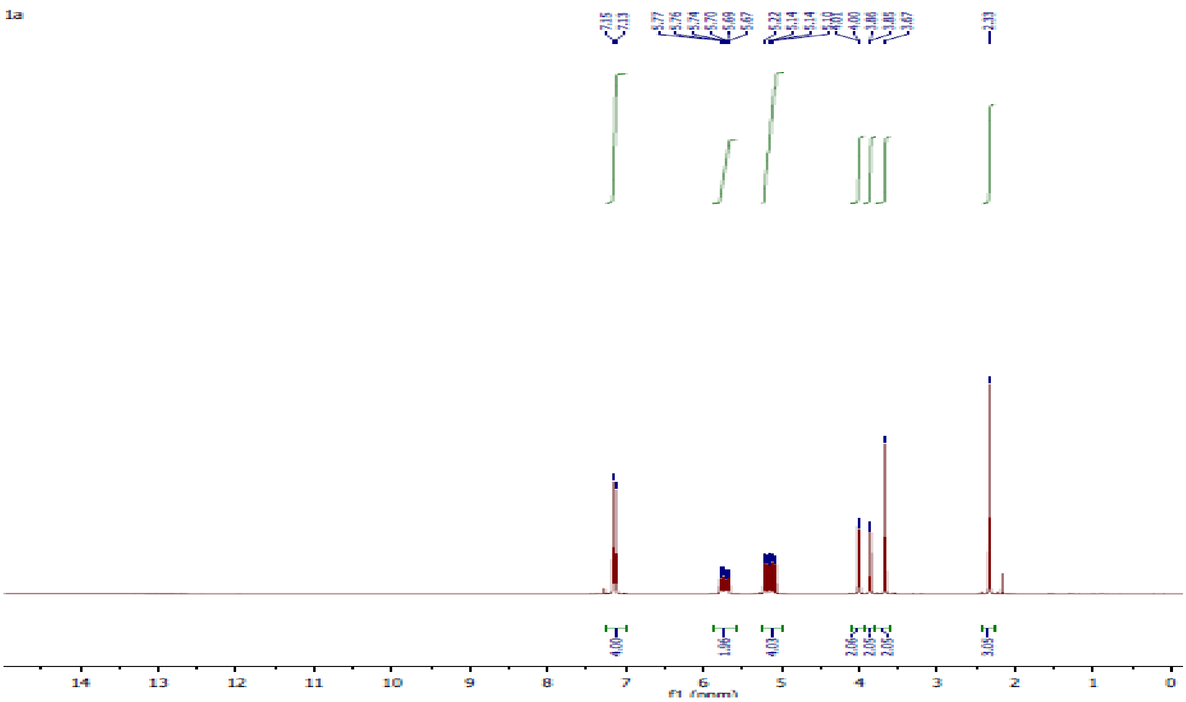


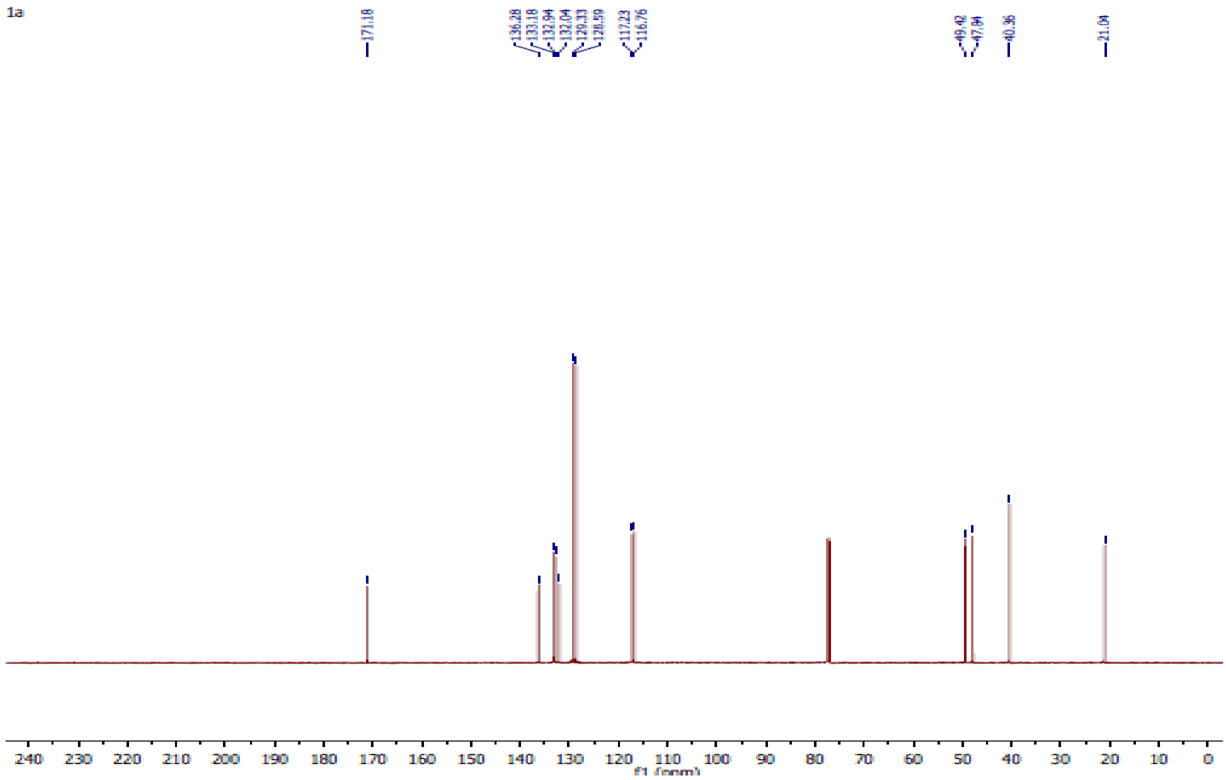
3r

(SiO_2, CH_2Cl_2/ Hexane = 70:30). Yellow oil, 61 % yield. **IR** ($\nu_{max,}$ cm^{-1}) 1770. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.28 (d, *J* = 9.2 Hz, 1H), 8.21 – 8.17 (m, 2H), 8.12 (dd, *J* = 8.5, 5.9 Hz, 2H), 8.02 (t, *J* = 7.6 Hz, 3H), 7.86 (d, *J* = 7.8 Hz, 1H), 3.56 – 3.44 (m, 1H), 3.42 – 3.32 (m, 2H), 3.09-3.0 (m, 1 H), 3.0-2.92 (m, 1 H), 2.31 – 2.23 (m, 1H), 2.14 (ddd, *J* = 21.2, 10.5, 5.2 Hz, 1H), 2.09 – 2.01 (m, 1H), 1.69 – 1.62 (m, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 212.0, 135.7, 131.4, 130.9, 130.0, 128.7, 127.5, 127.4, 127.3, 126.7, 125.9, 125.1, 125.0, 124.9, 124.8, 124.8, 123.2, 59.9, 44.6, 31.7, 30.8, 17.0. **HRMS** for $C_{22}H_{19}O$, calculated 299.1436, found 299.1428.

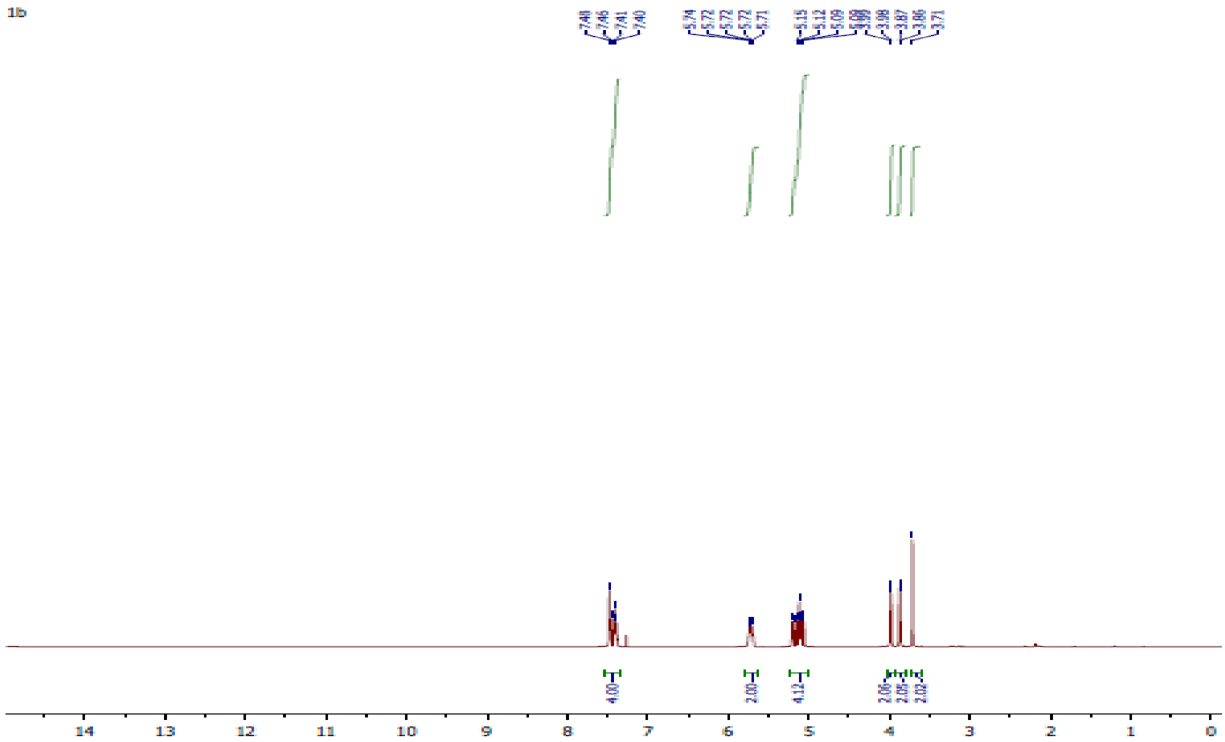
4. ^{1}H- and ^{13}C-NMR spectra

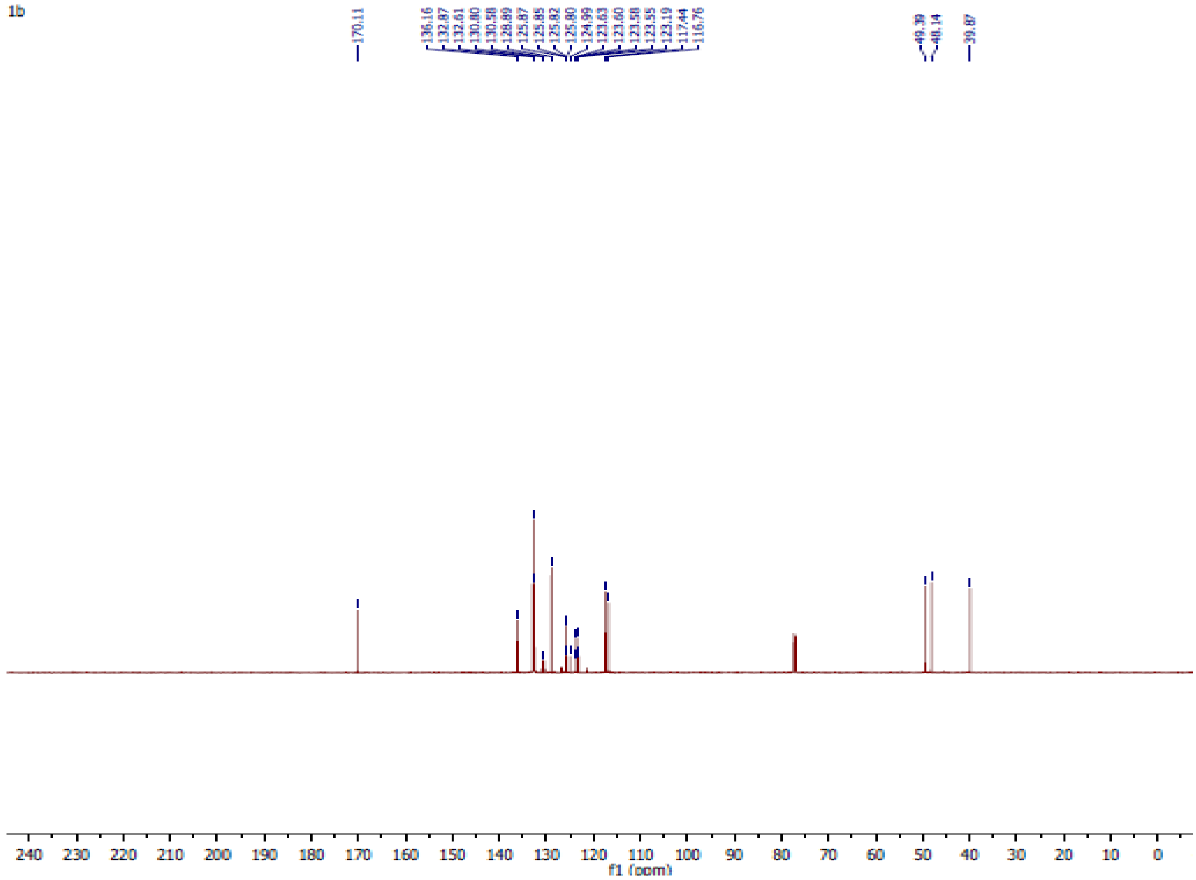
N,N-diallyl-2-(p-tolyl)acetamide (1a)



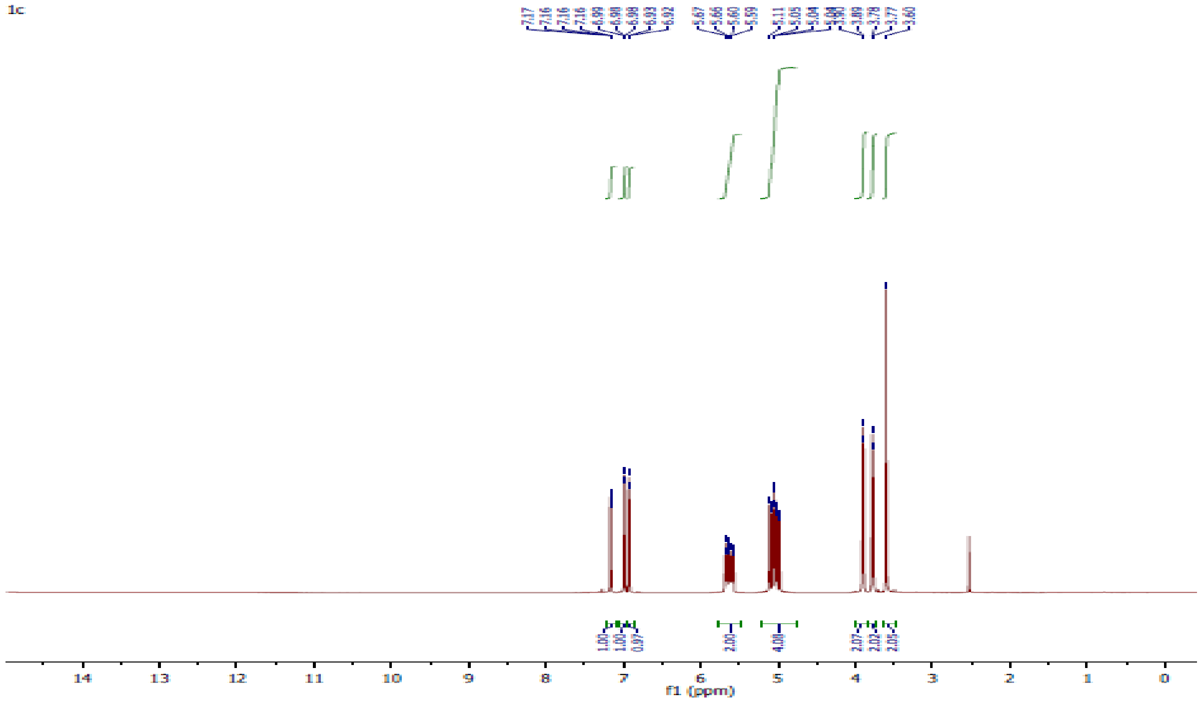


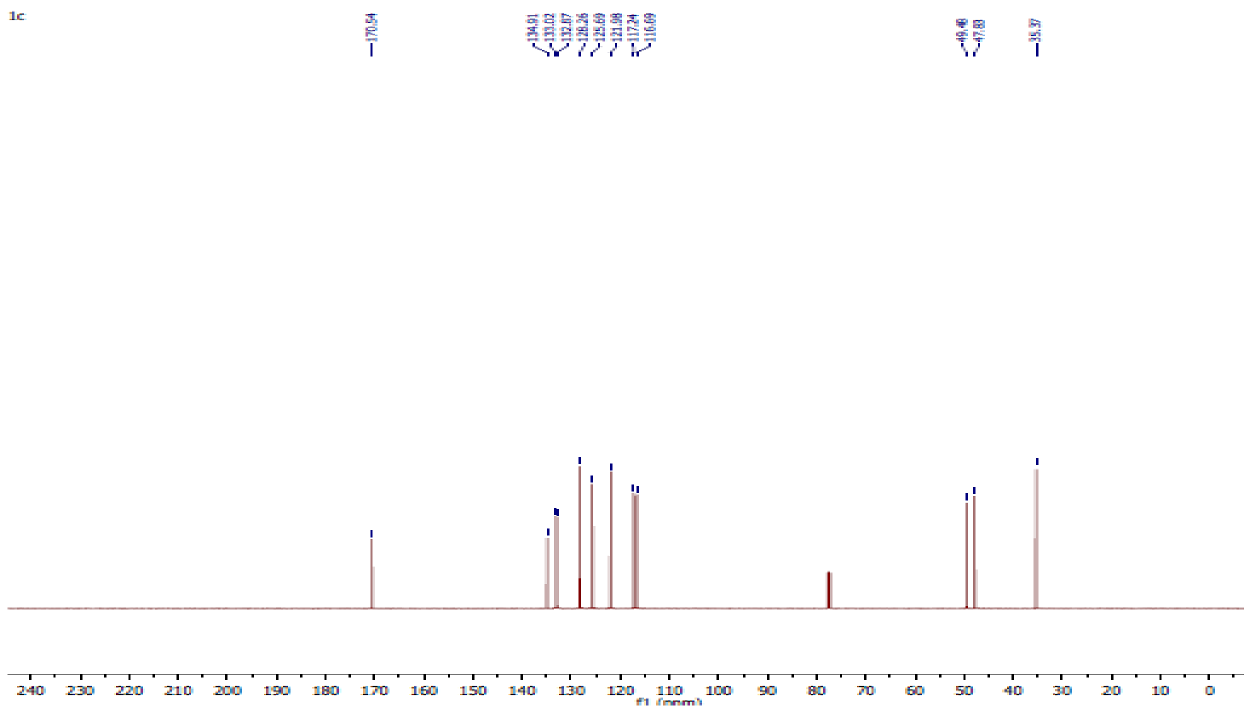
N,N-diallyl-2-(3-(trifluoromethyl)phenyl)acetamide(1b)



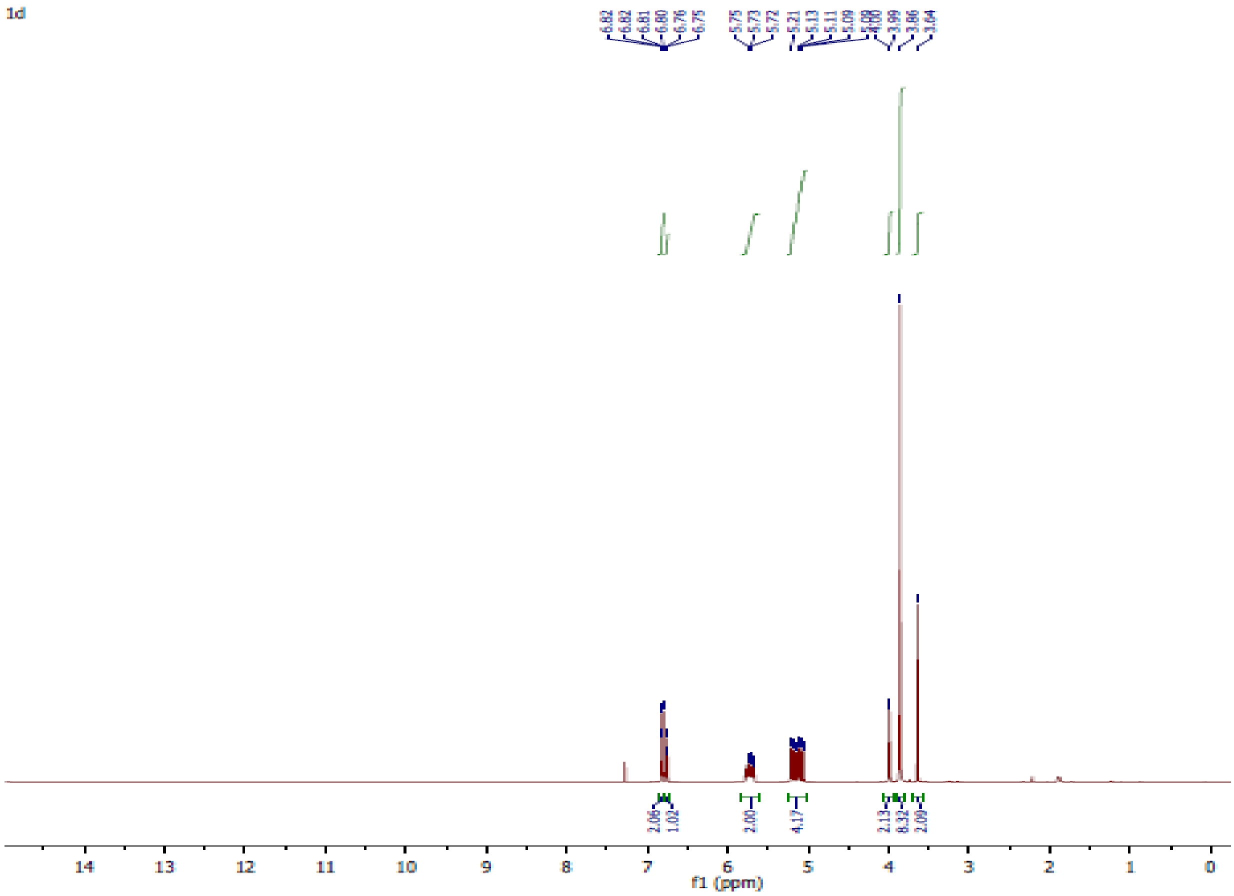


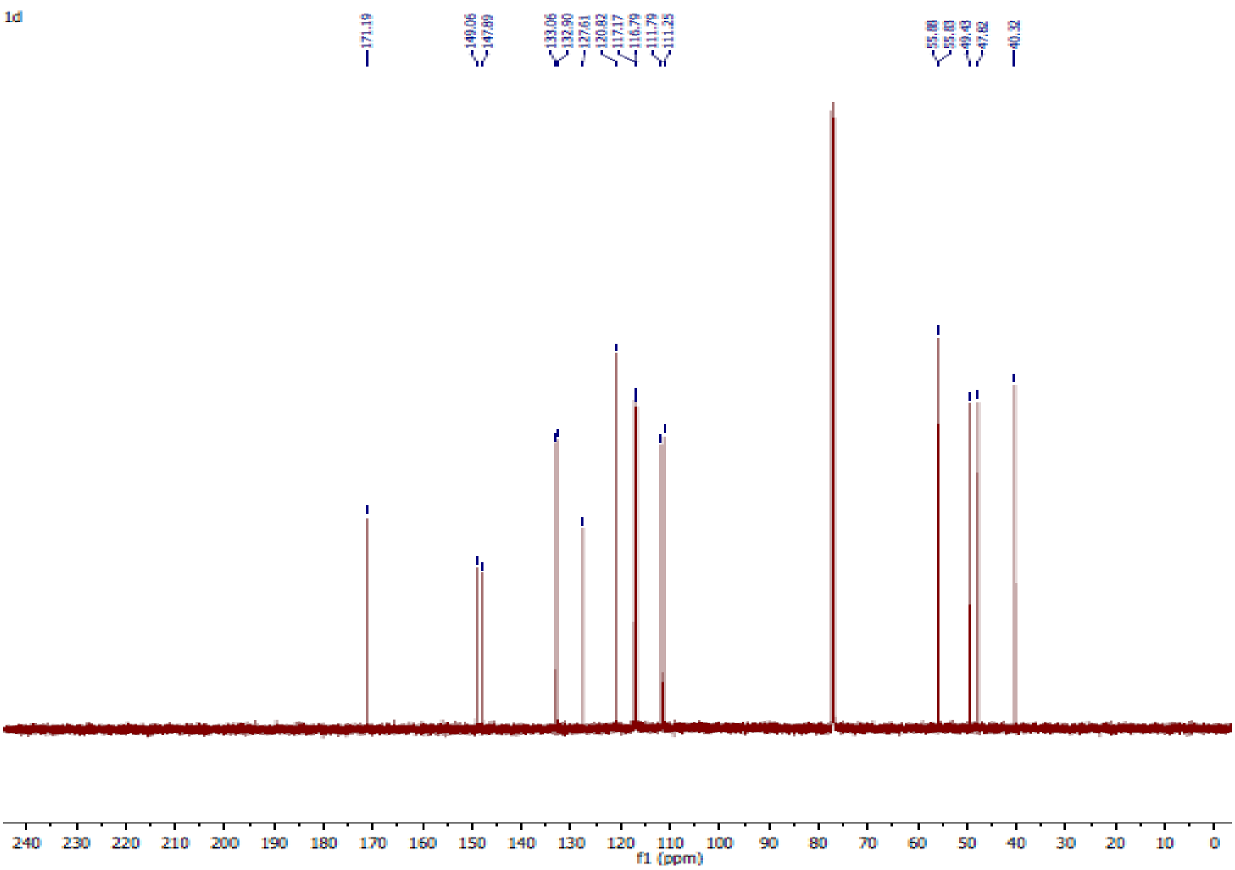
N,N-diallyl-2-(thiophen-3-yl)acetamide (1c)



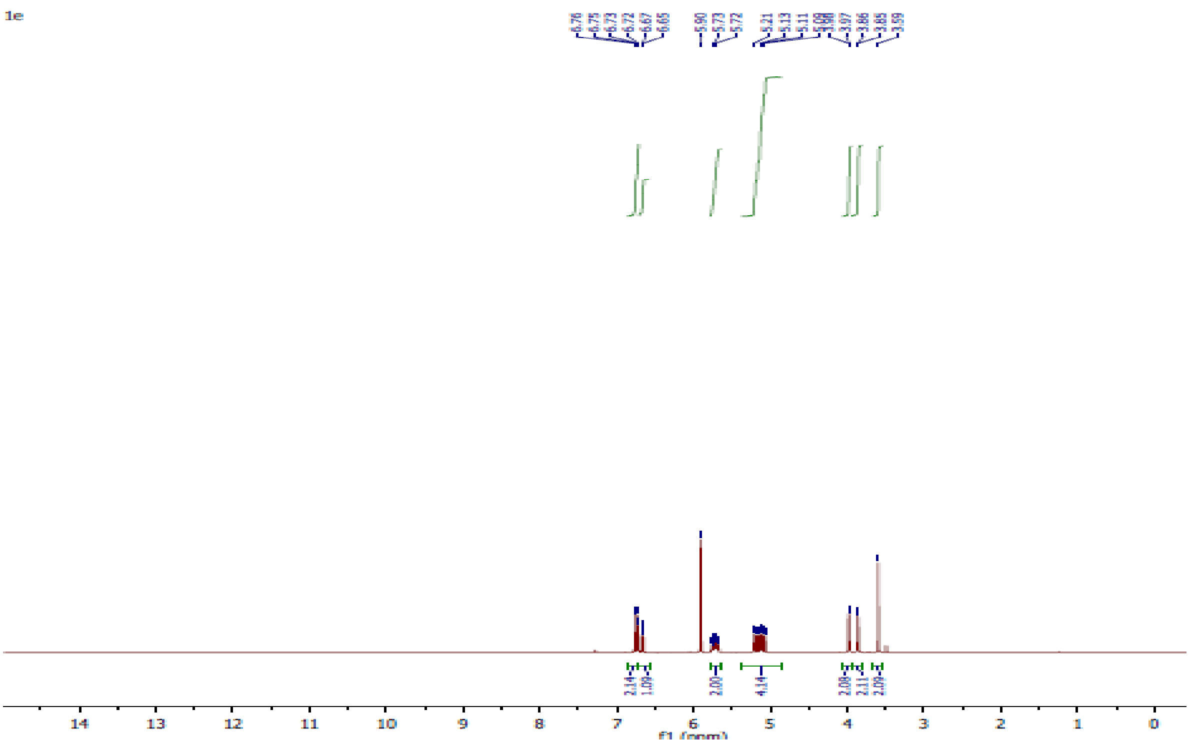


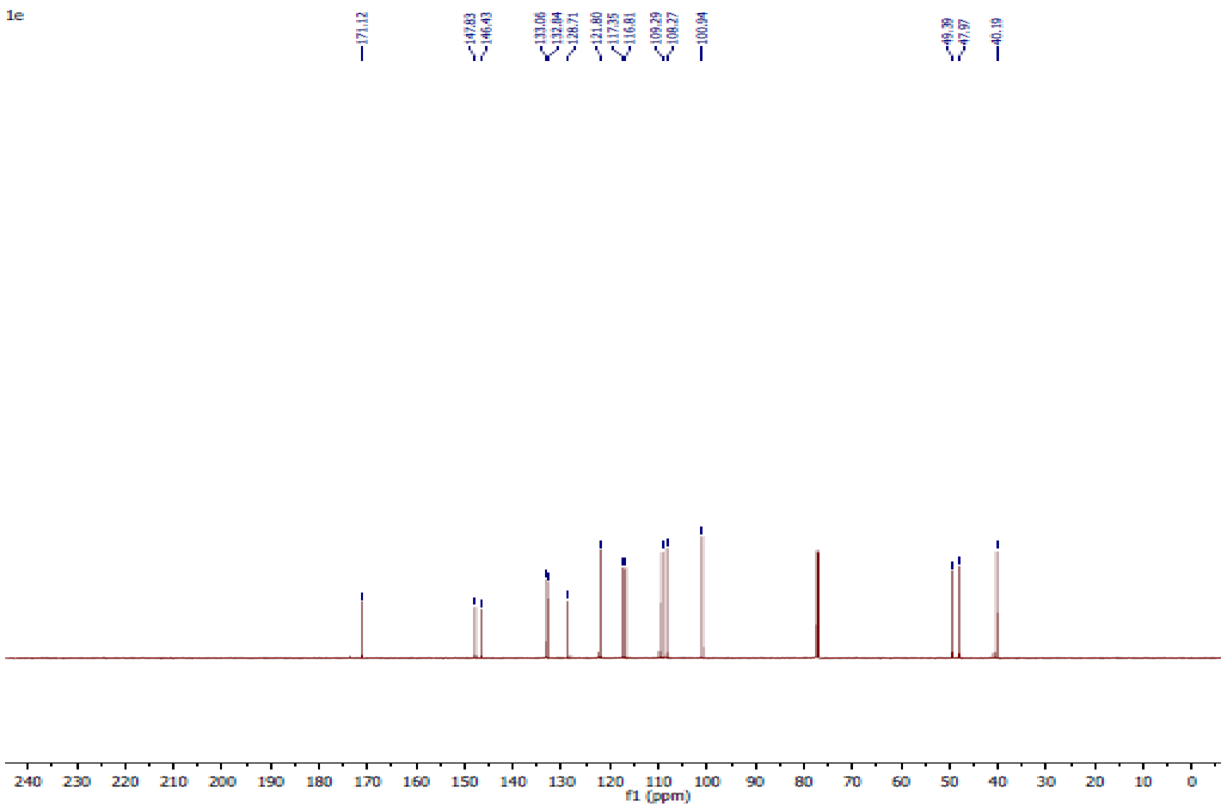
N,N-diallyl-2-(3,4-dimethoxyphenyl)acetamide (1d)



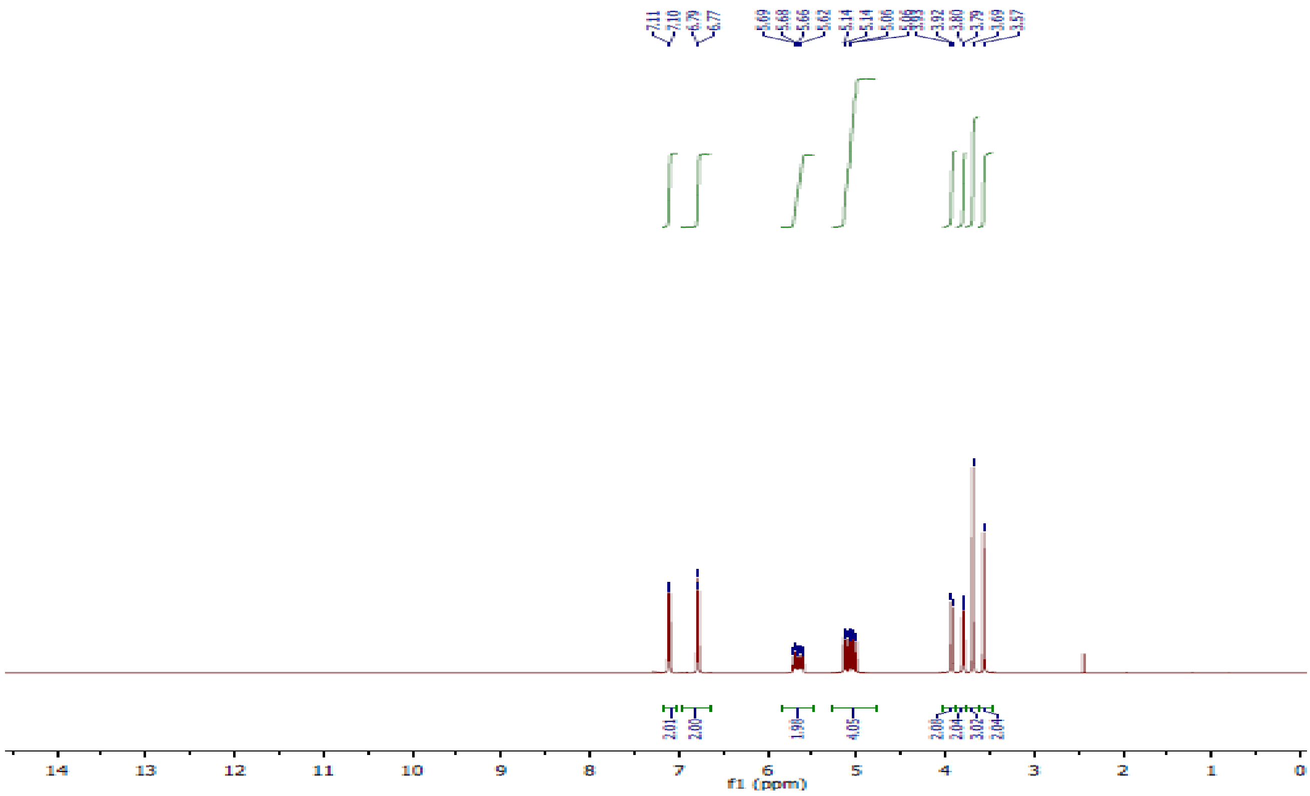


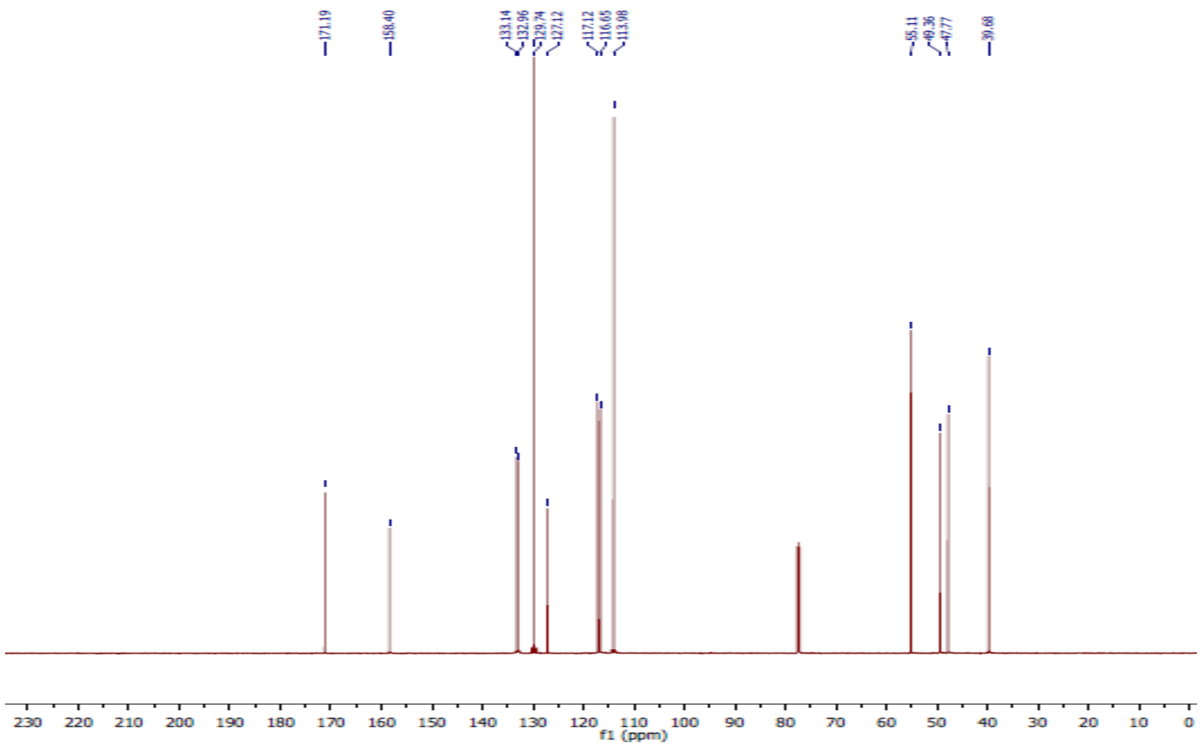
N,N-diallyl-2-(benzo [d] dioxol-5-yl)acetamide (1e)



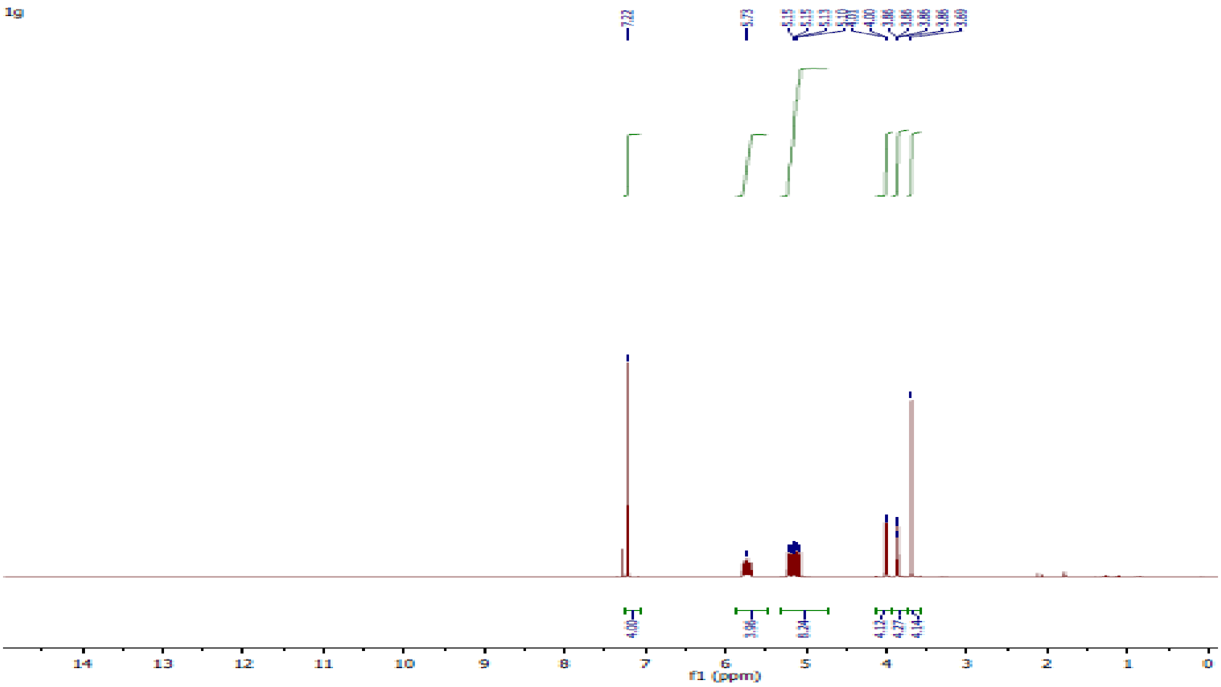


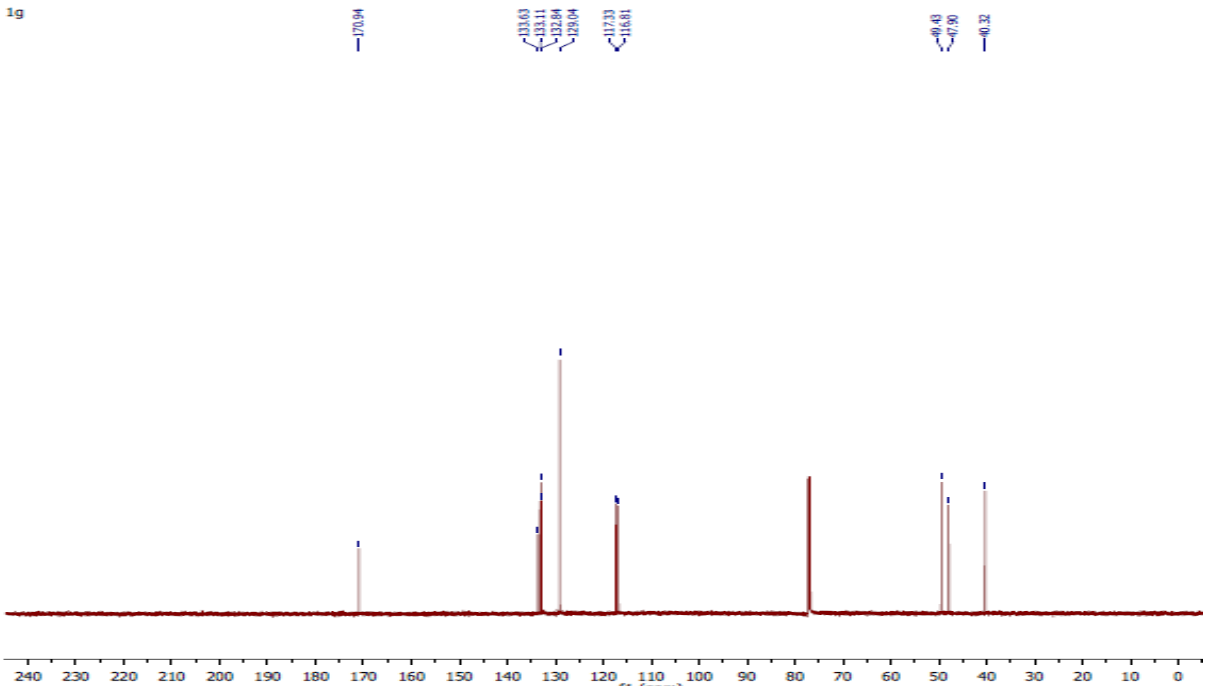
N,N-diallyl-2-(p-methoxyphenyl)acetamide (1f)



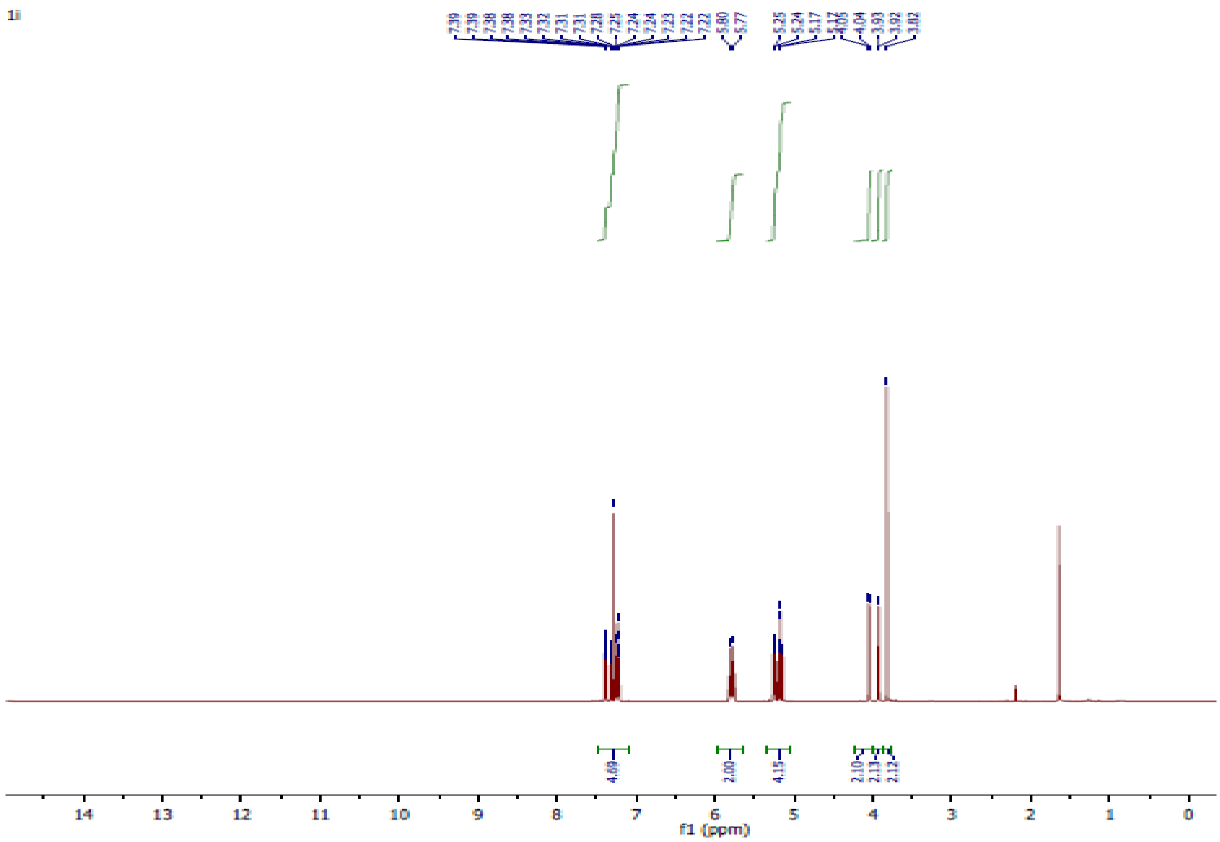


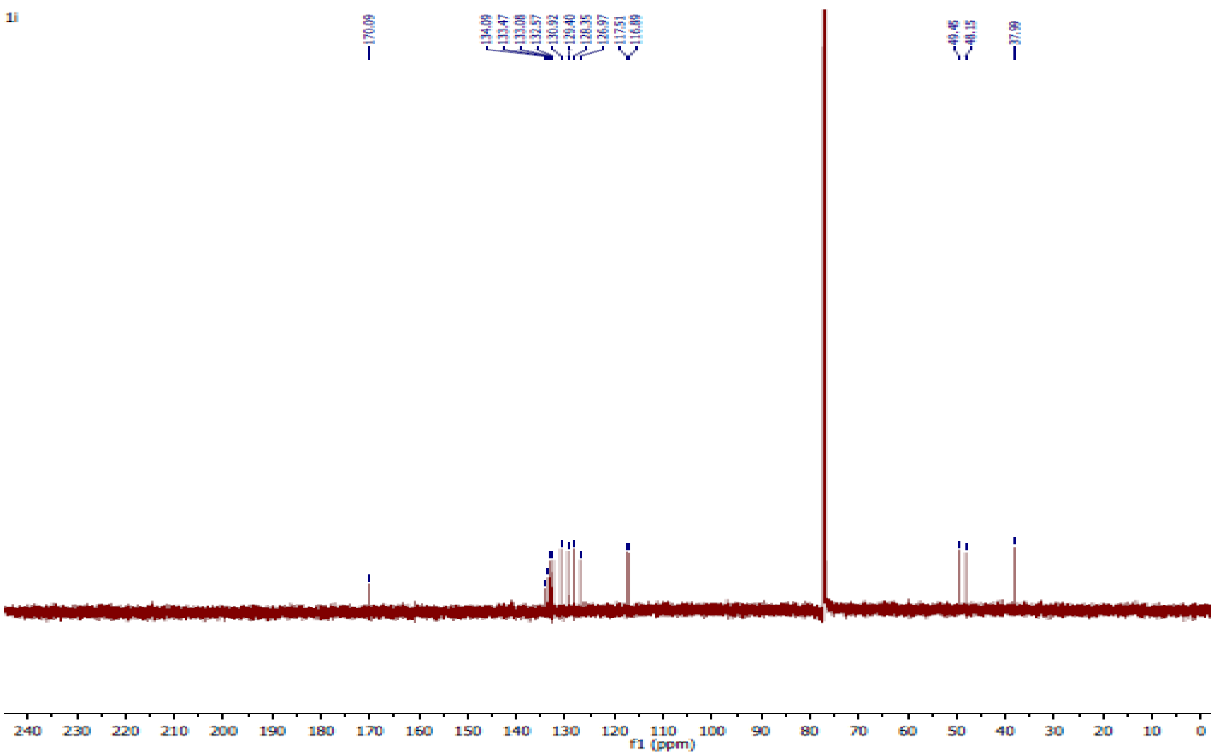
2,2'-(1,4-phenylene)bis(N,N-diallylacetamide) (1g)



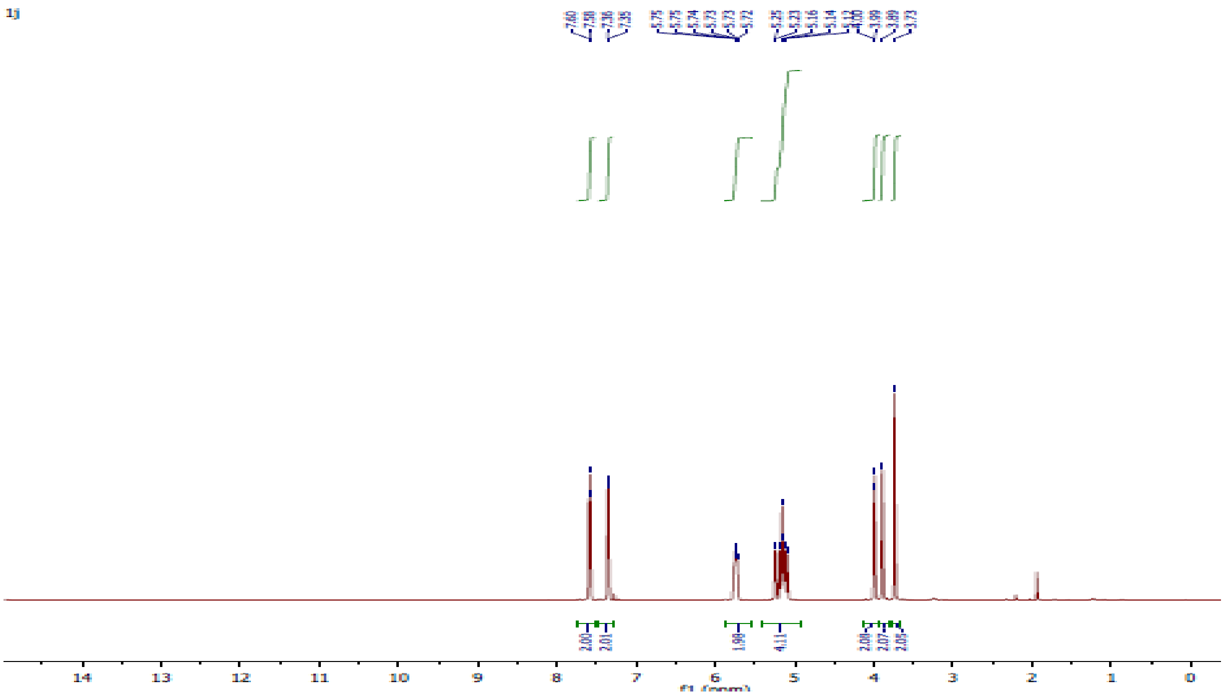


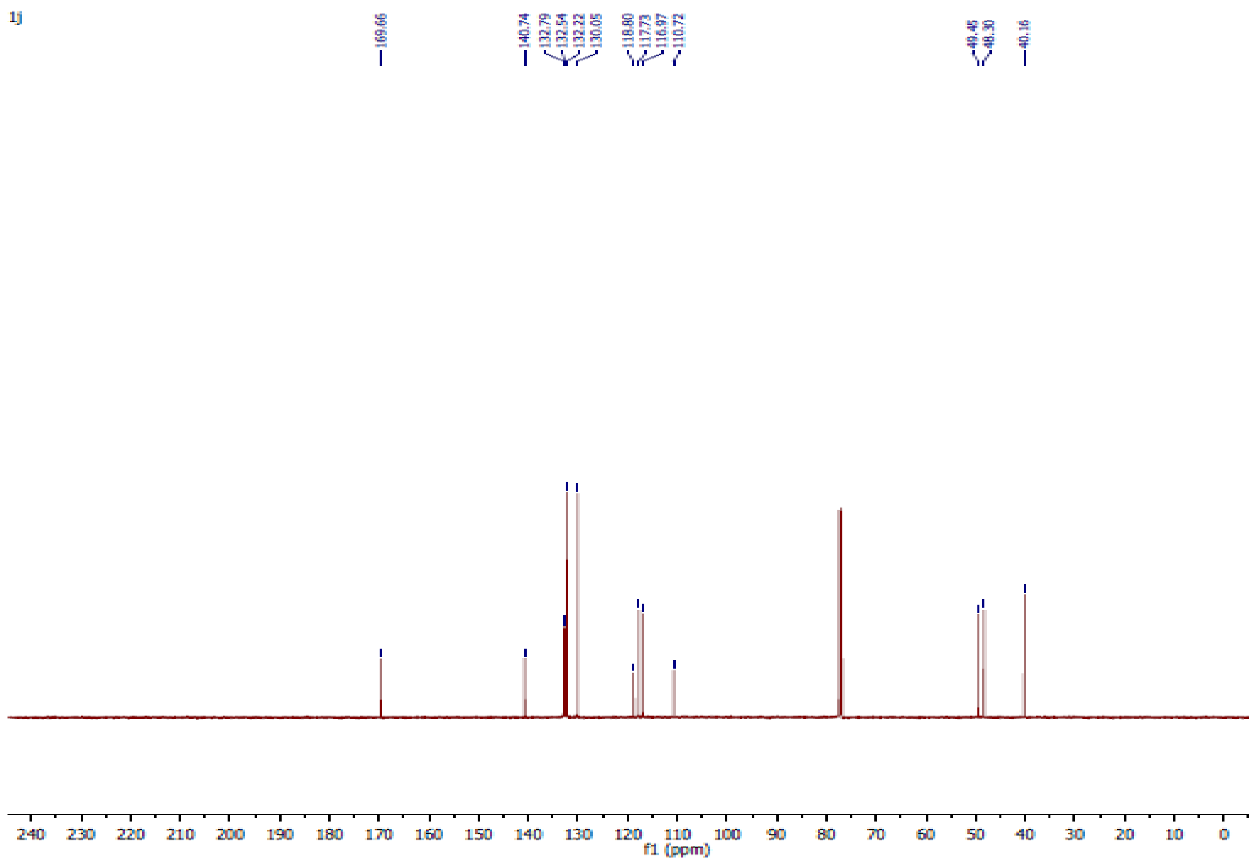
N,N-diallyl-2-(2-chlorophenyl)acetamide (1i)



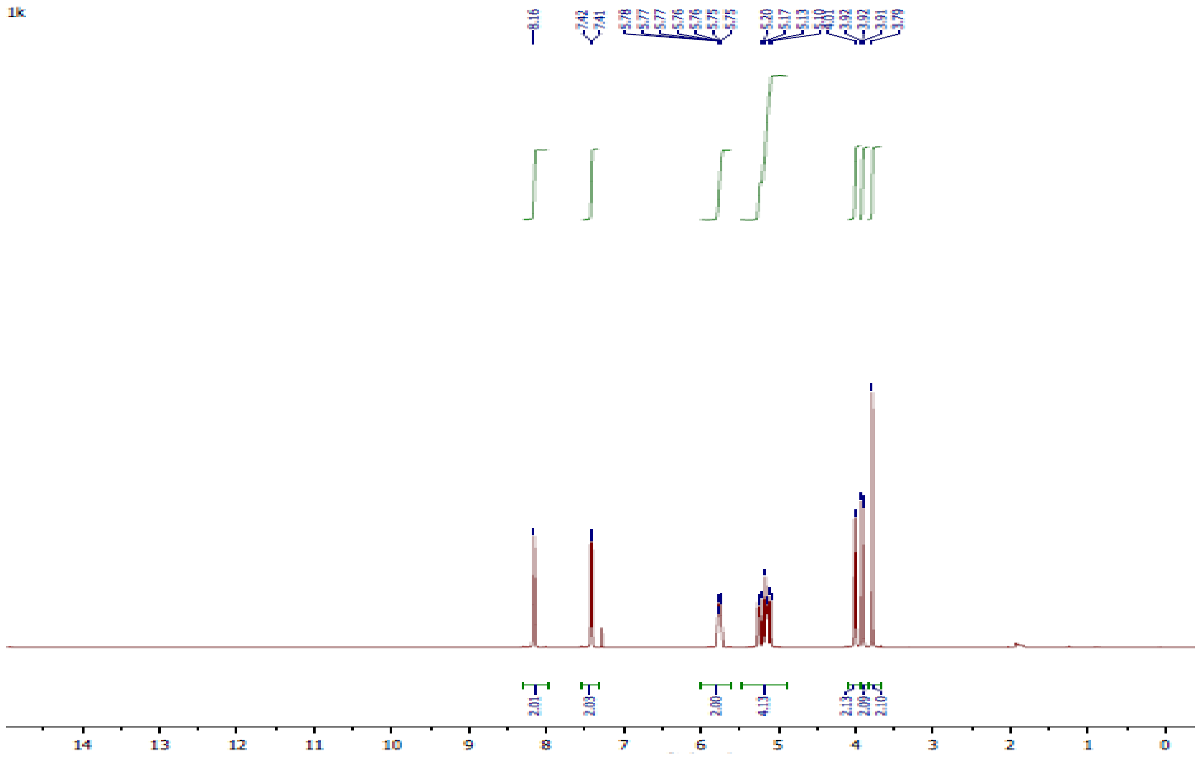


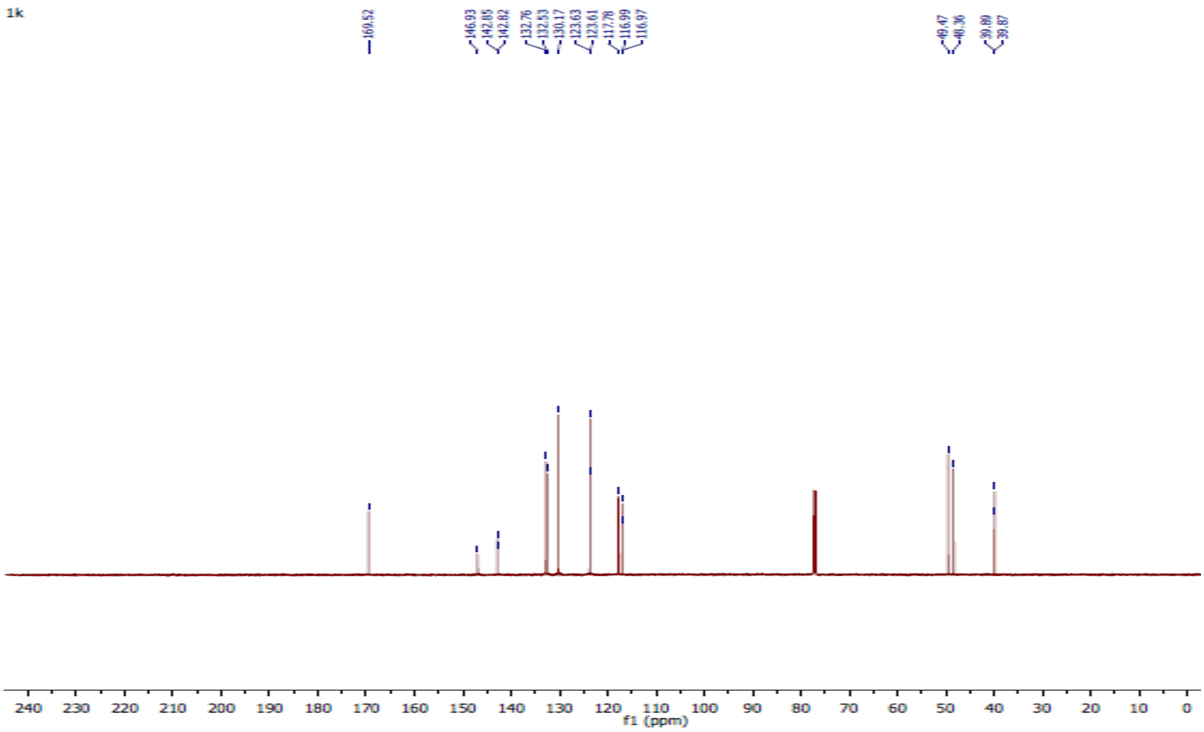
N,N-diallyl-2-(4-cyanophenyl)acetamide (1j)



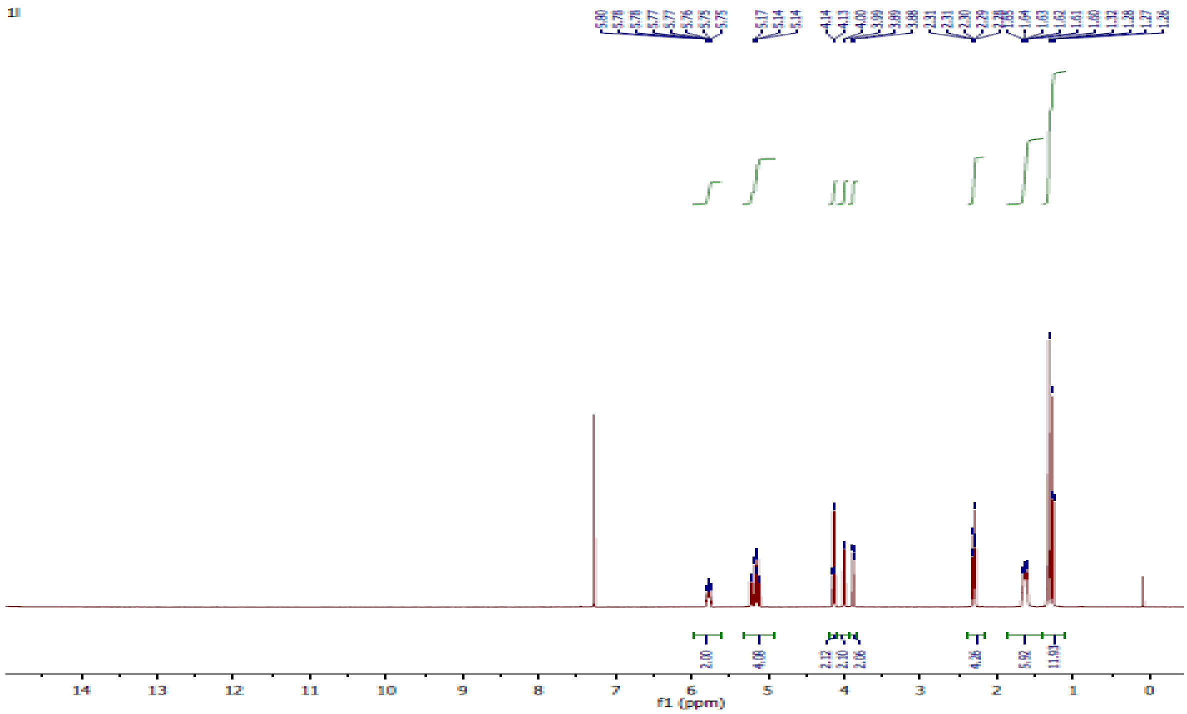


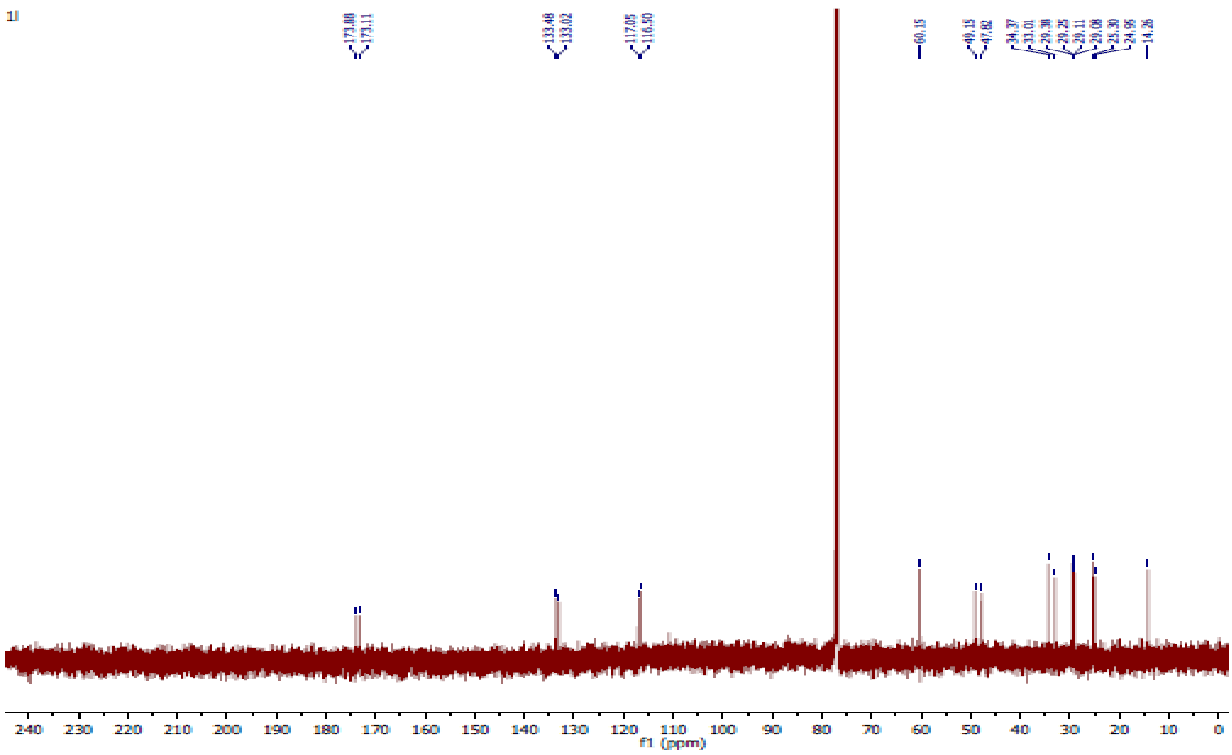
N,N-diallyl-2-(4-nitrophenyl)acetamide (1k)



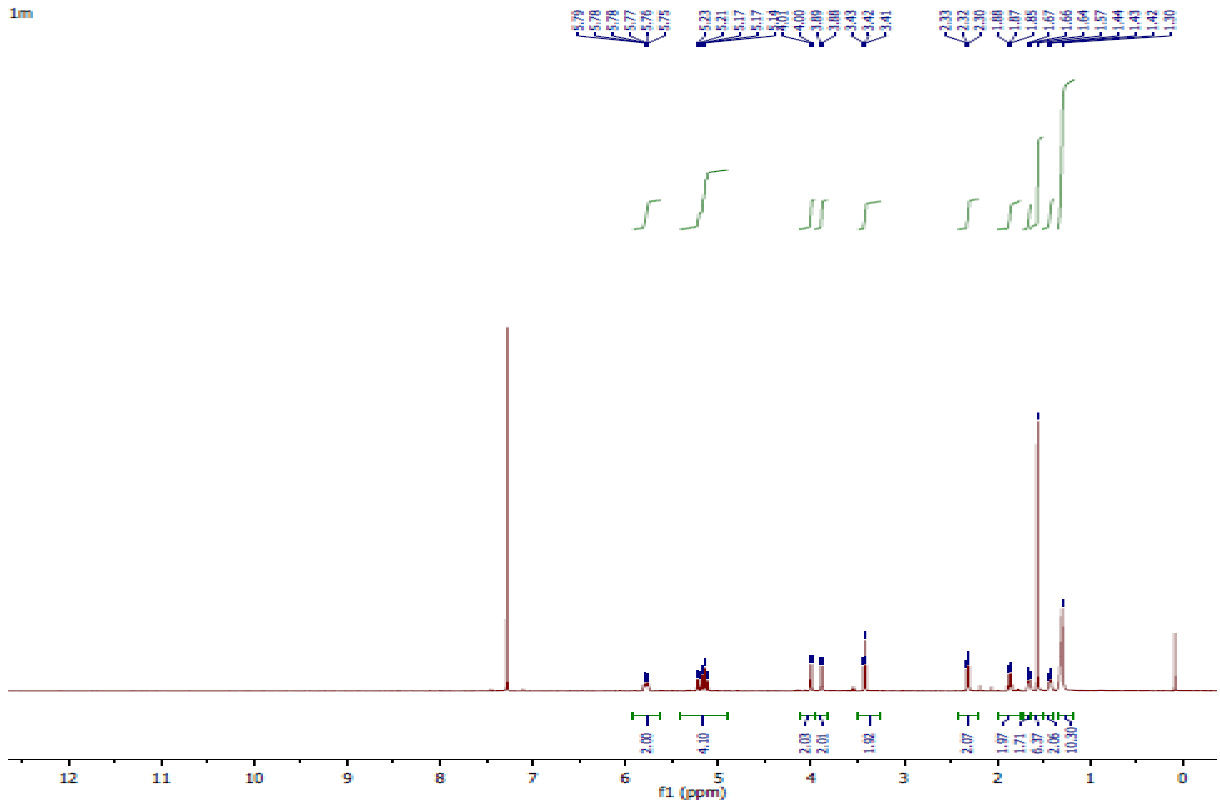


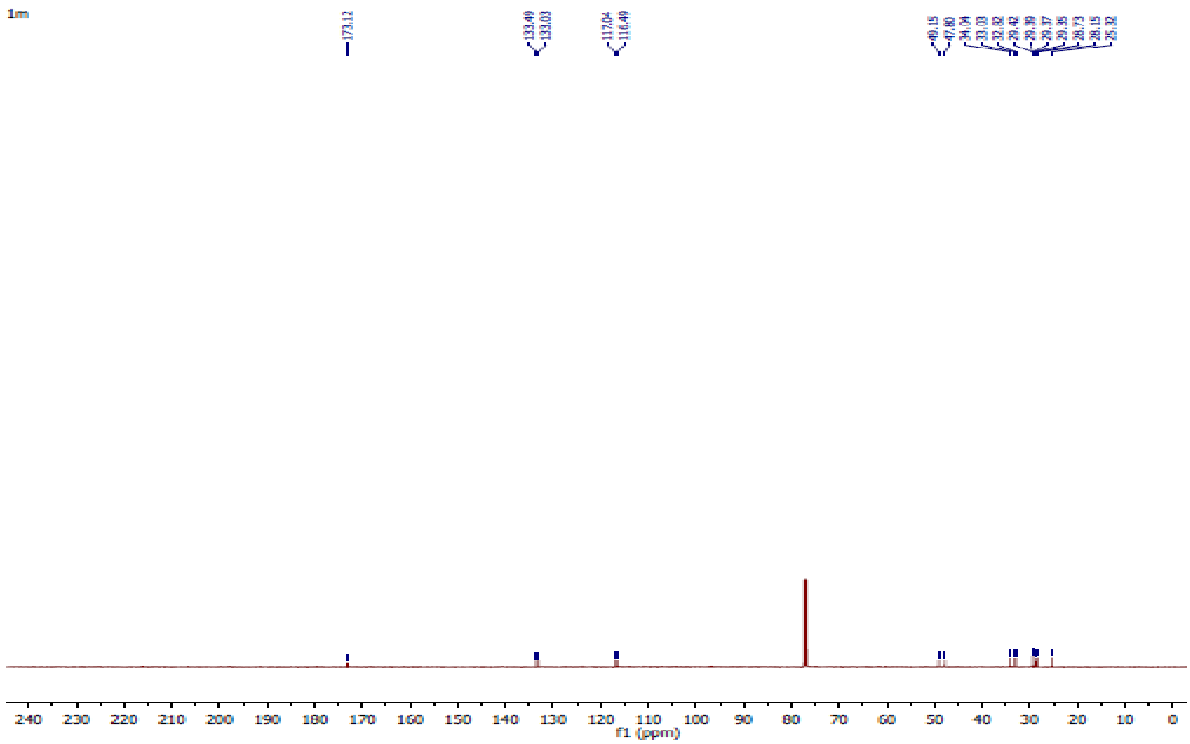
Ethyl 10-(diallylamino)-10-oxodecanoate (1l)



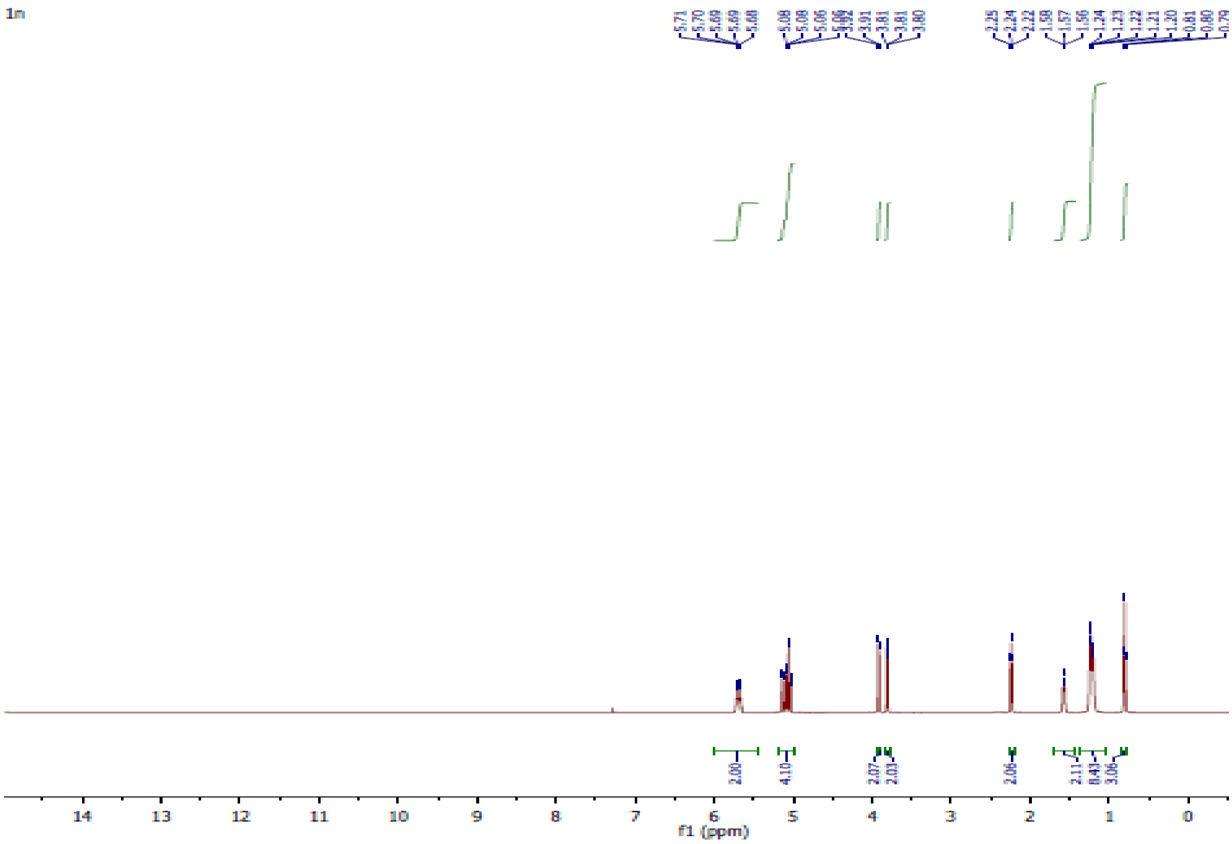


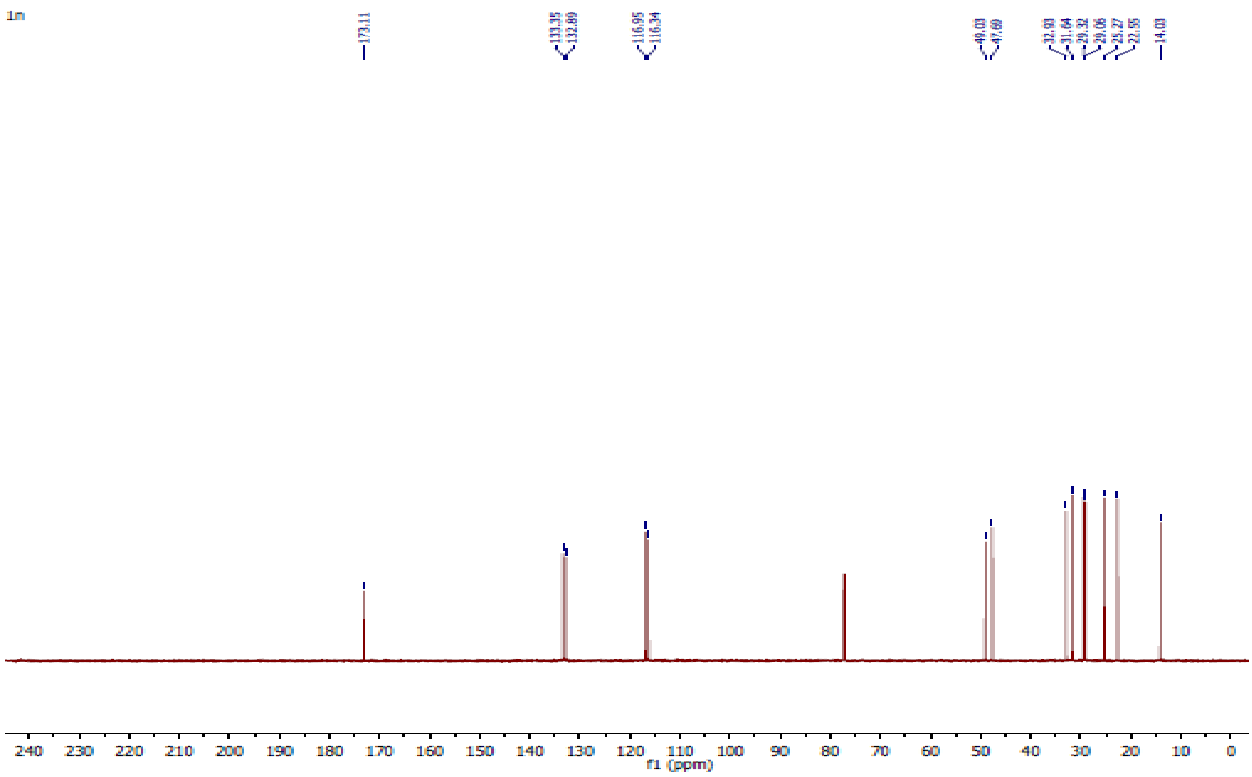
N,N-diallyl-11-bromoundecanamide (1m)



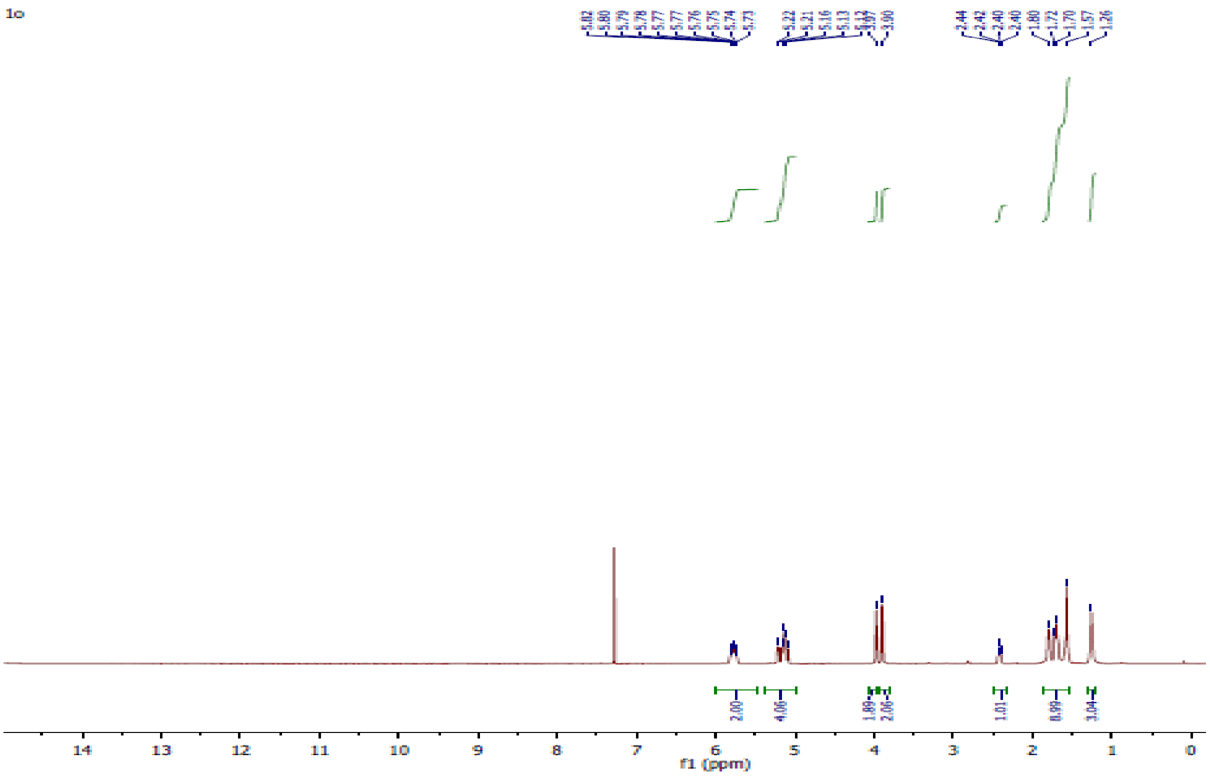


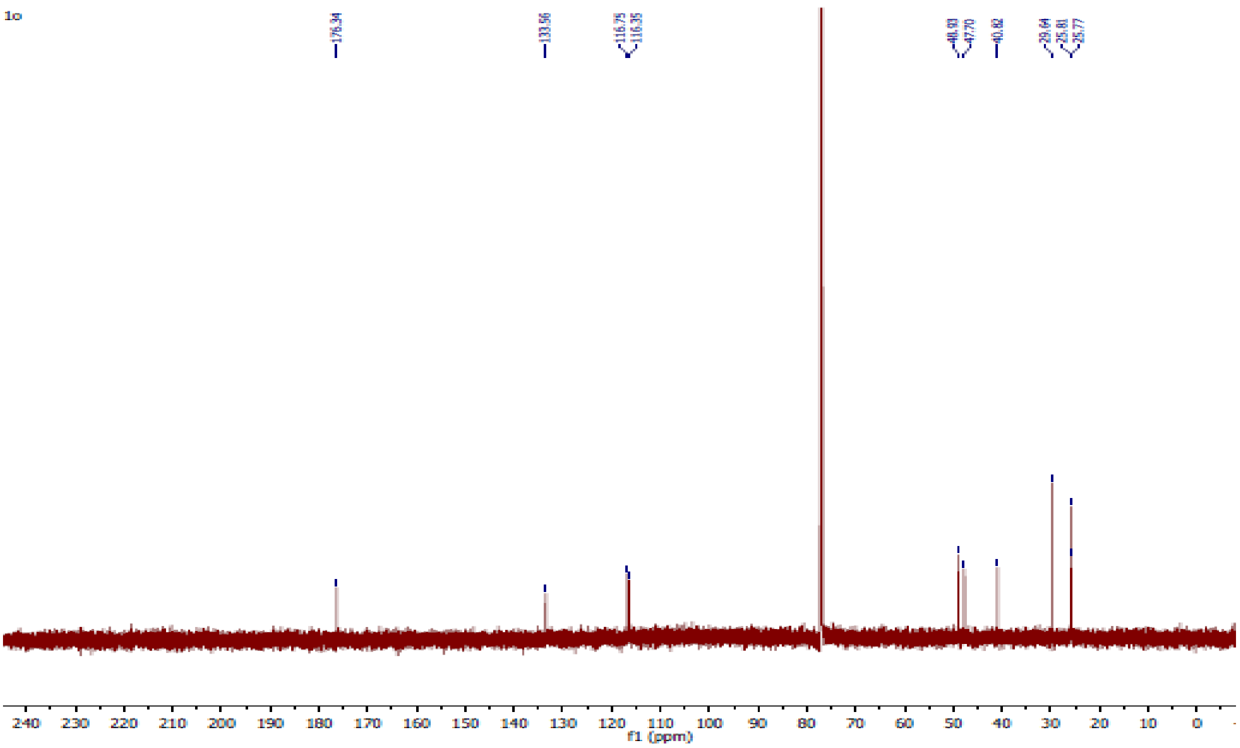
***N,N*-diallyloctanamide (1n)**



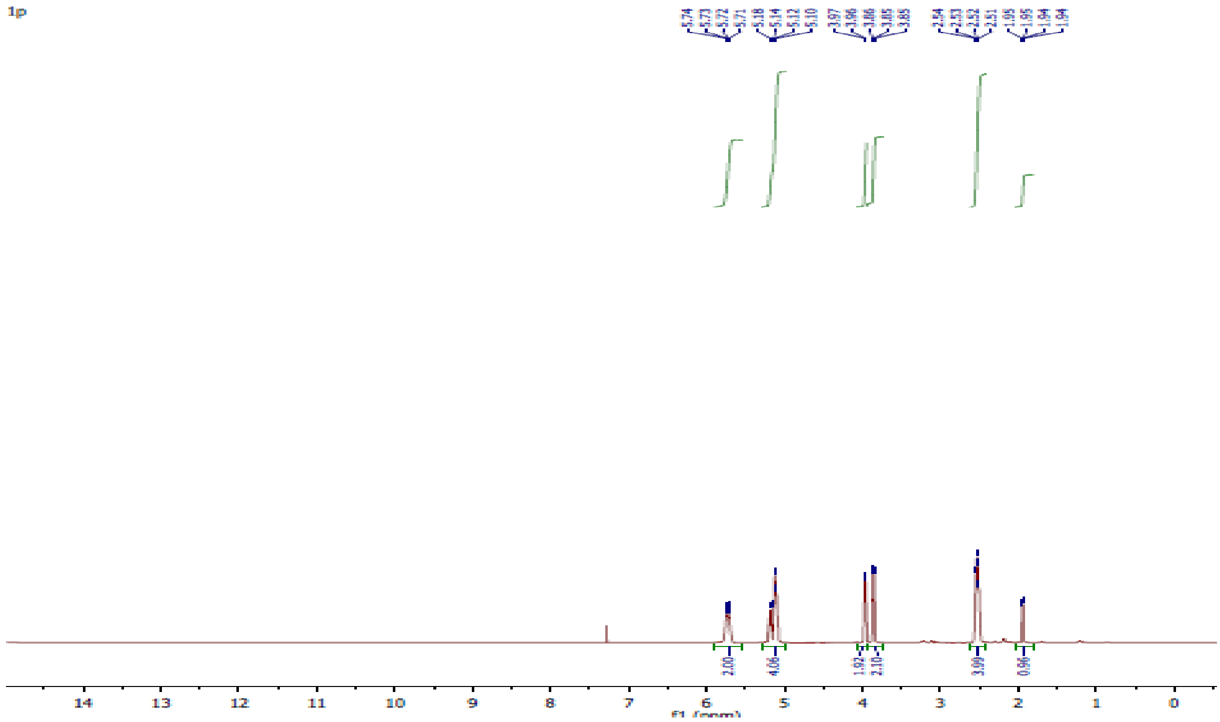


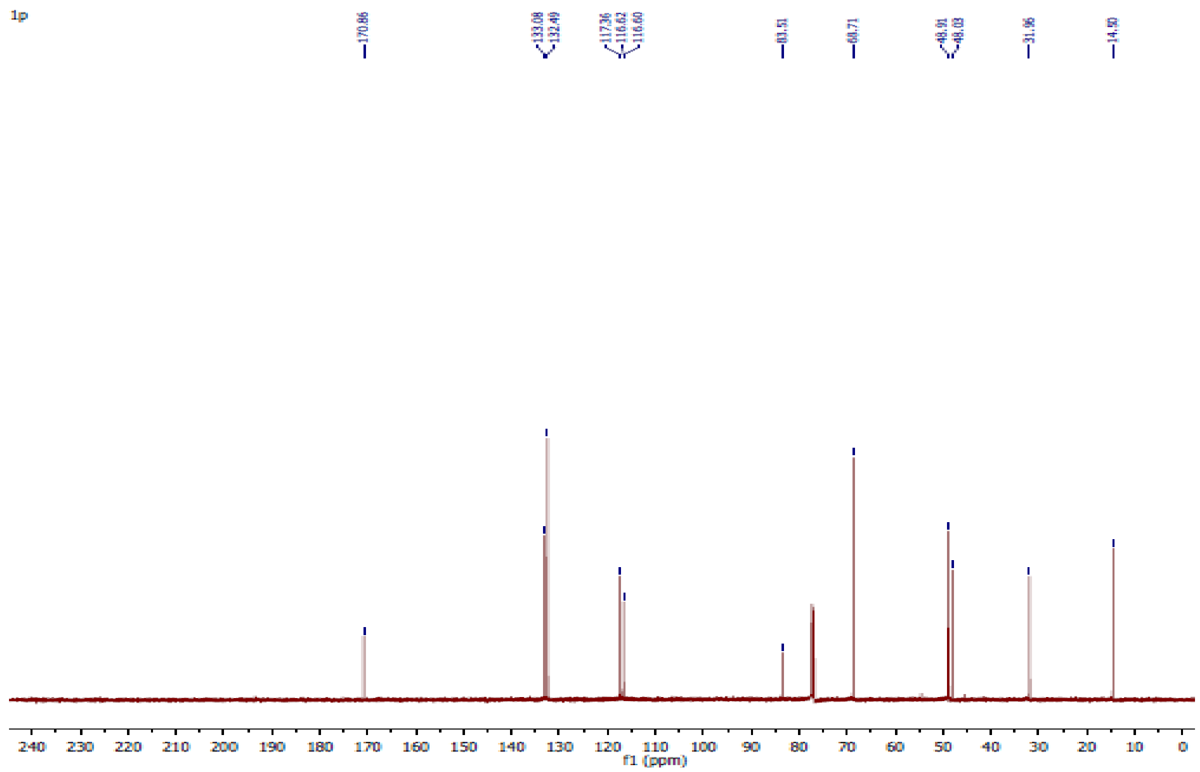
***N,N*-diallylcyclohexanecarboxamide (1o)**



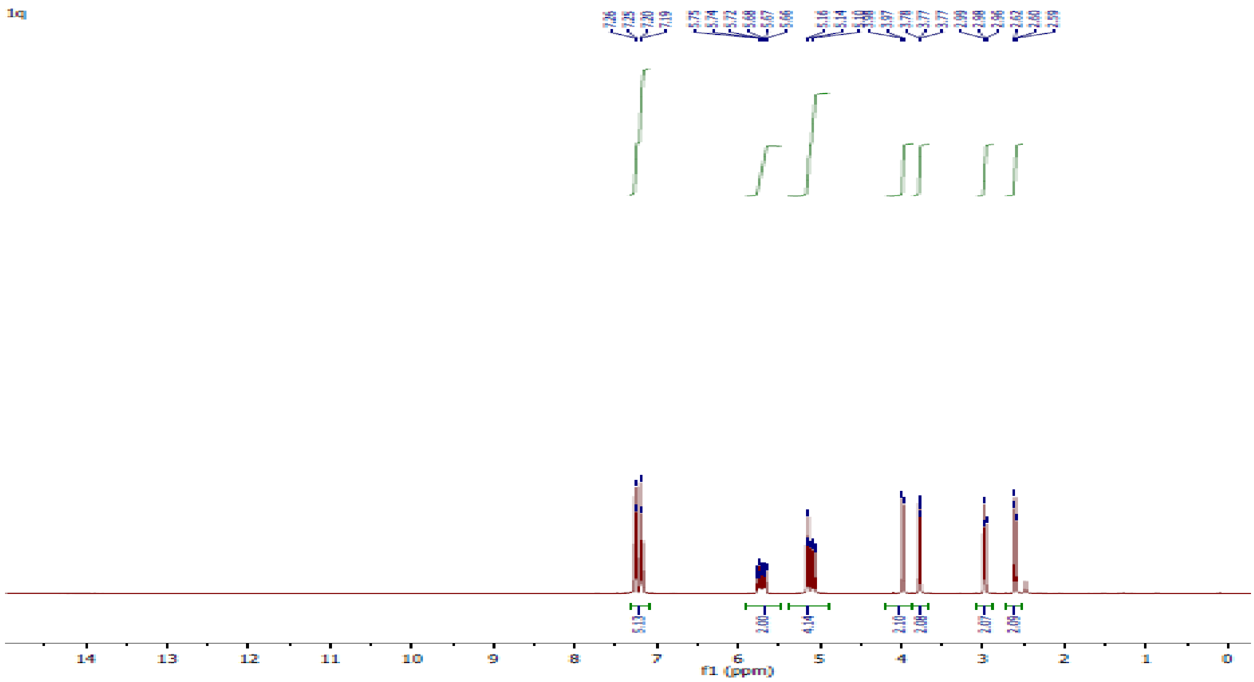


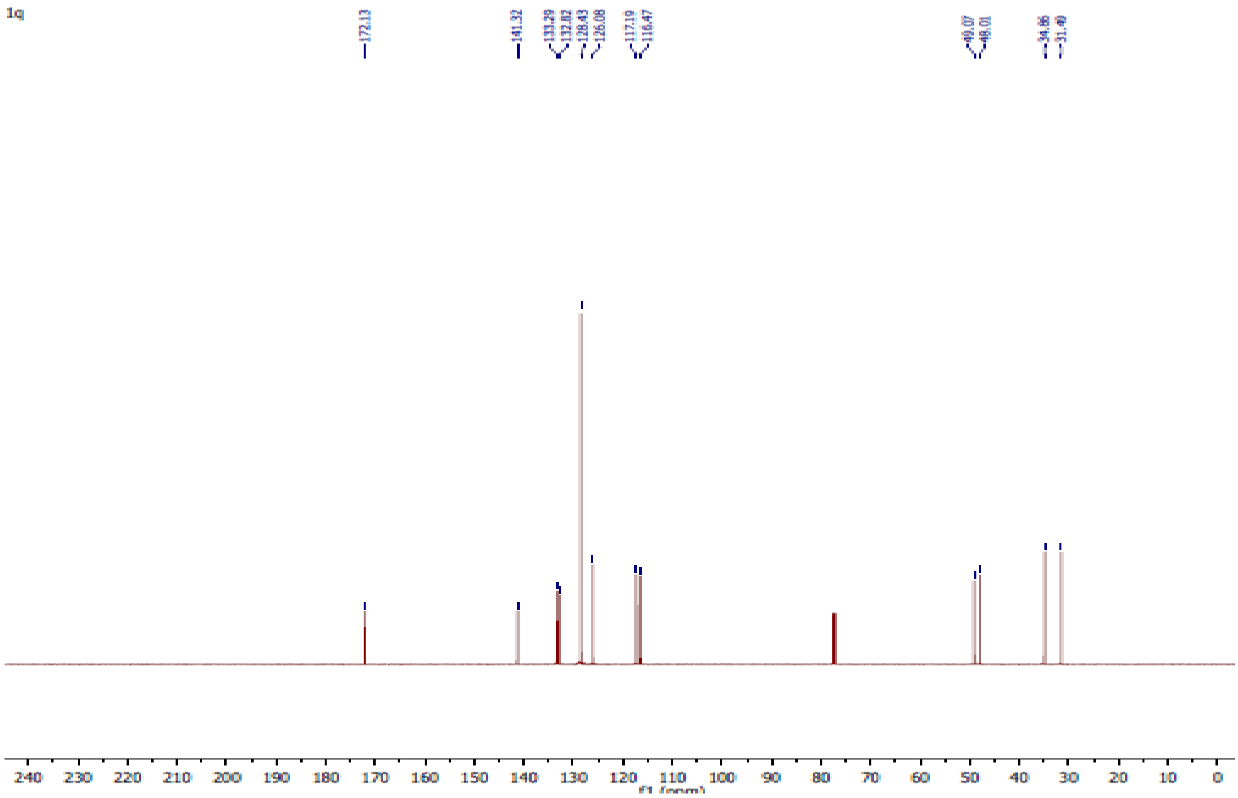
N,N-diallylpent-4-ynamide (1p)



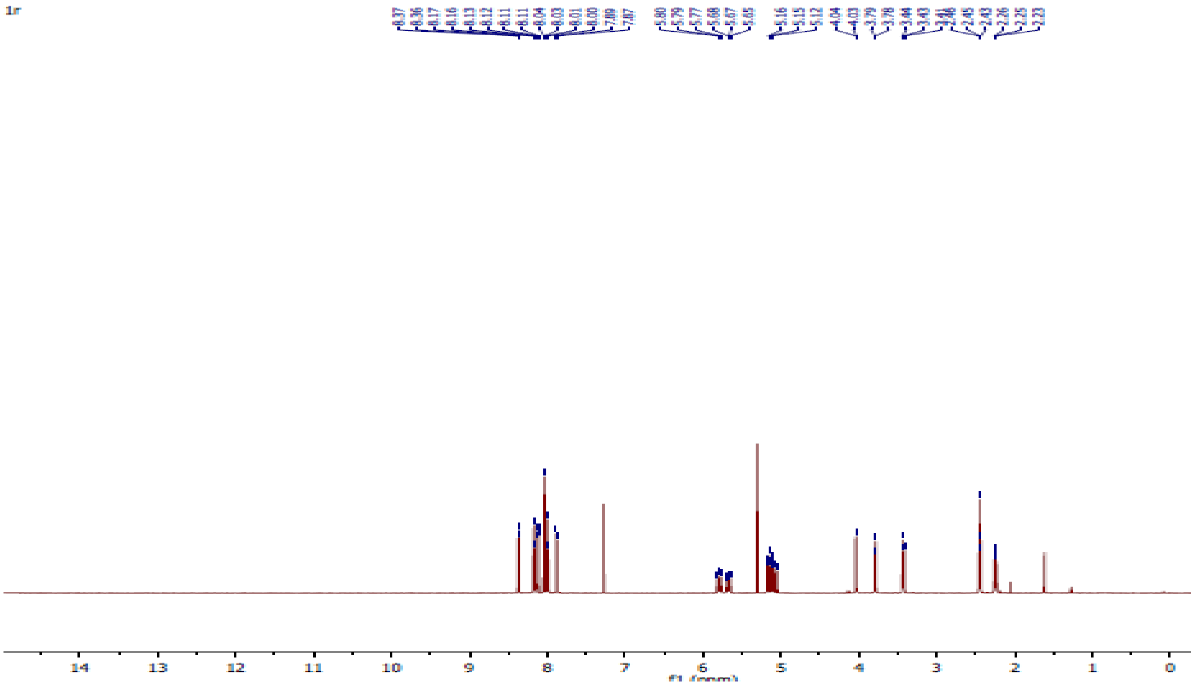


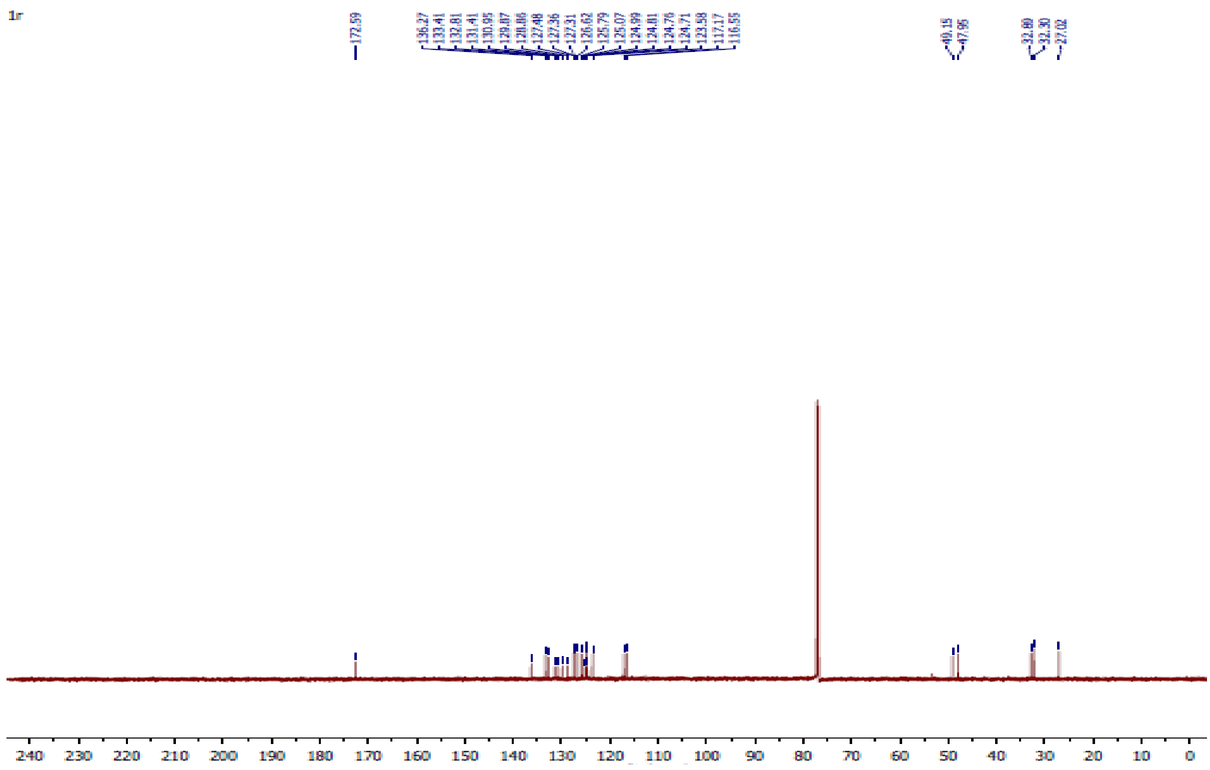
N,N-diallyl-3-phenylpropanamide (1q)



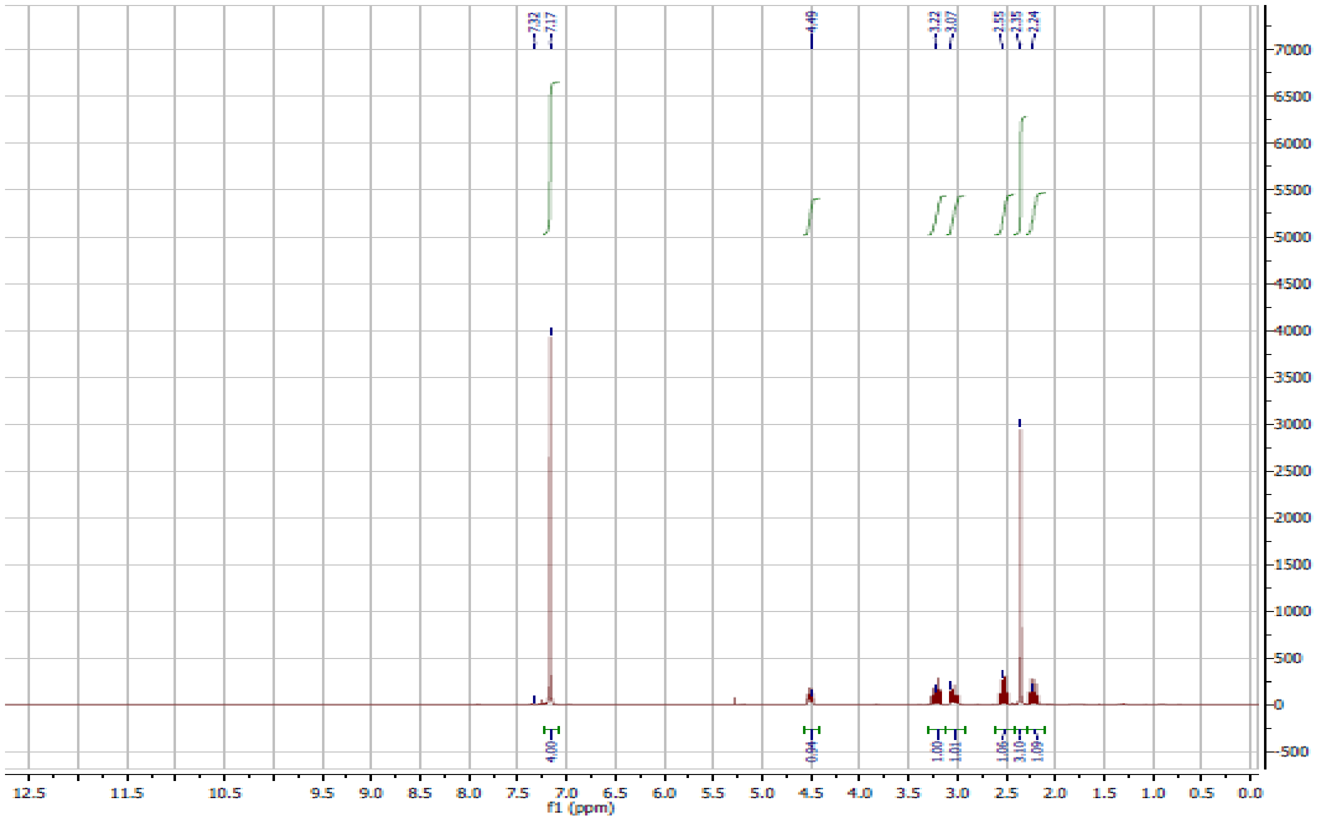


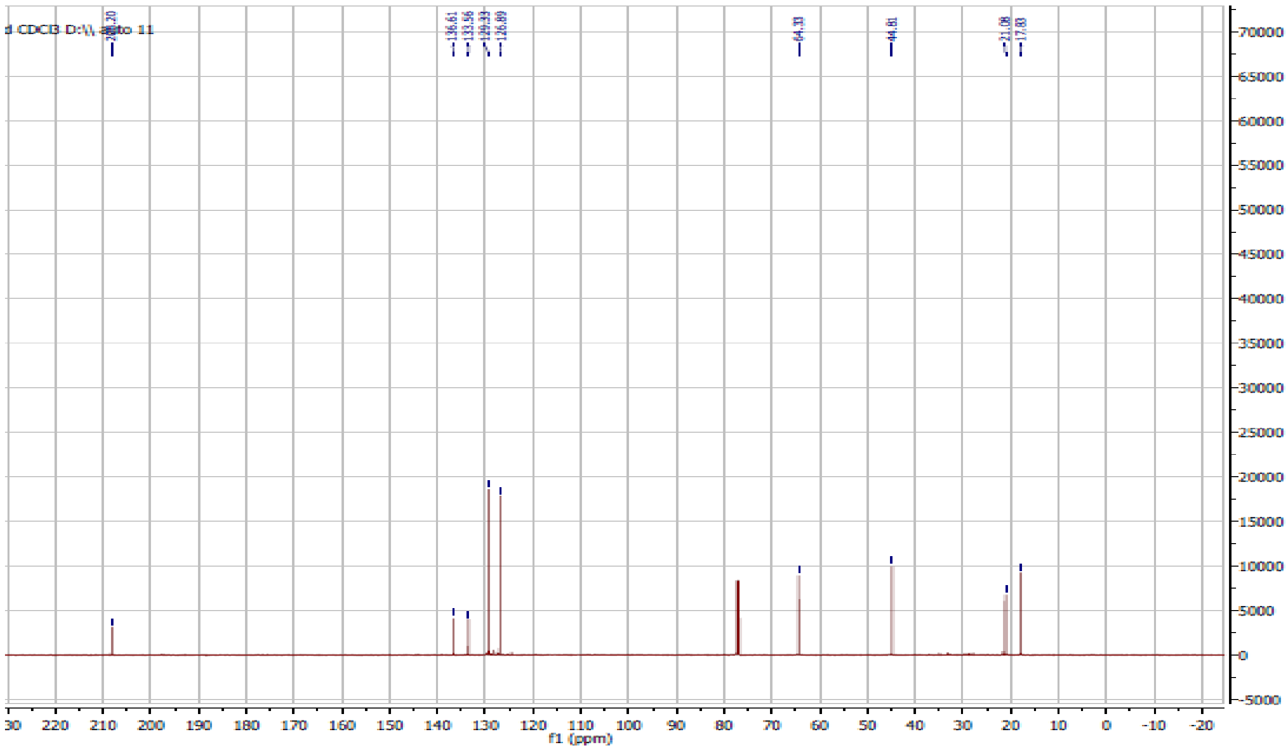
N,N-diallyl-4-(pyren-1-yl)butanamide (1r)



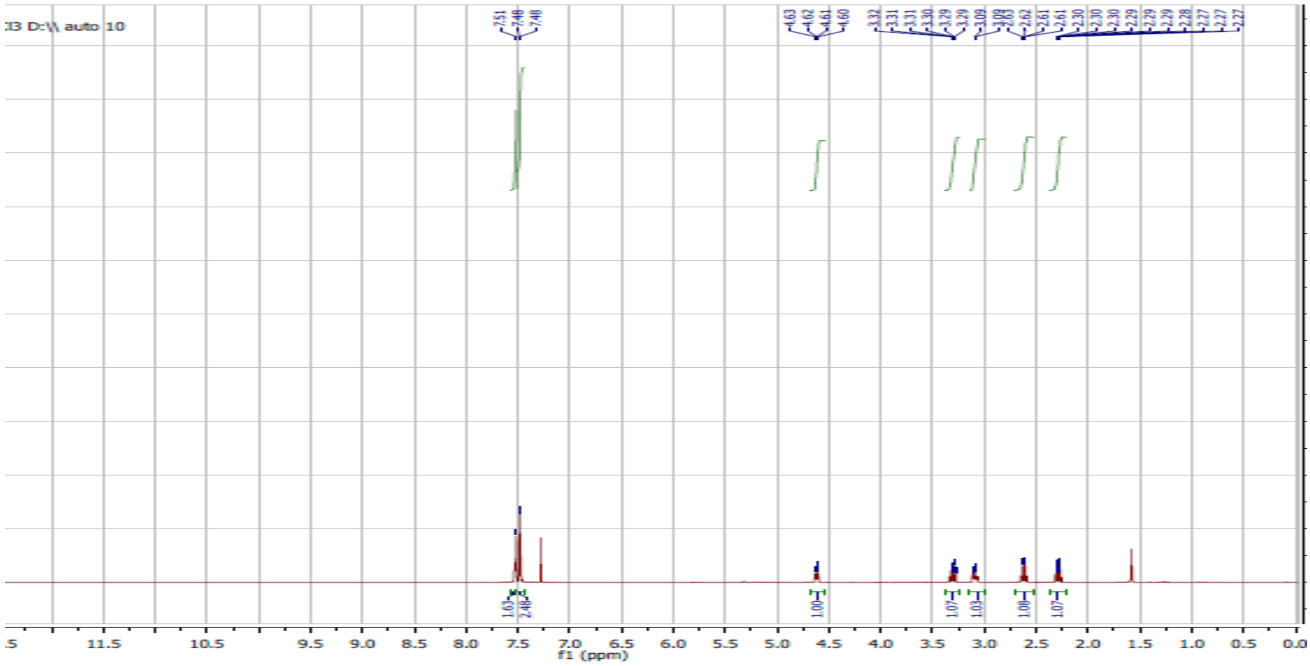


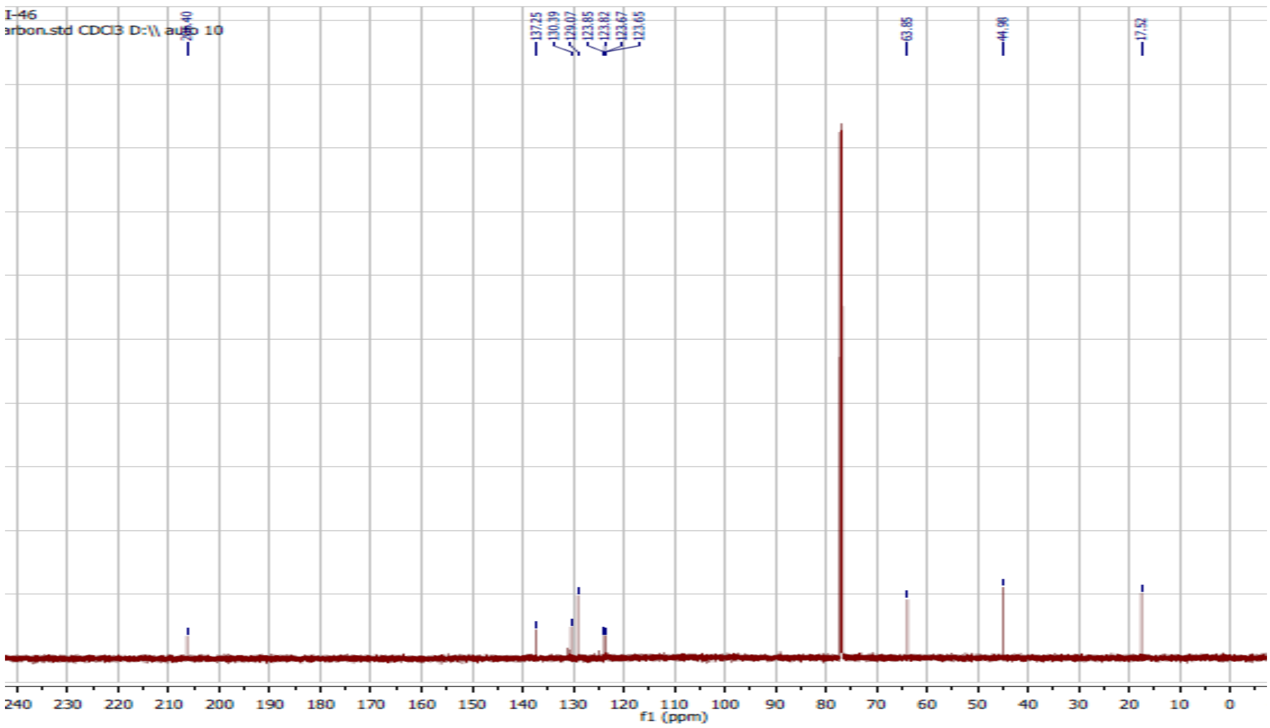
2-(p-Tolyl)cyclobutan-1-one (3a)



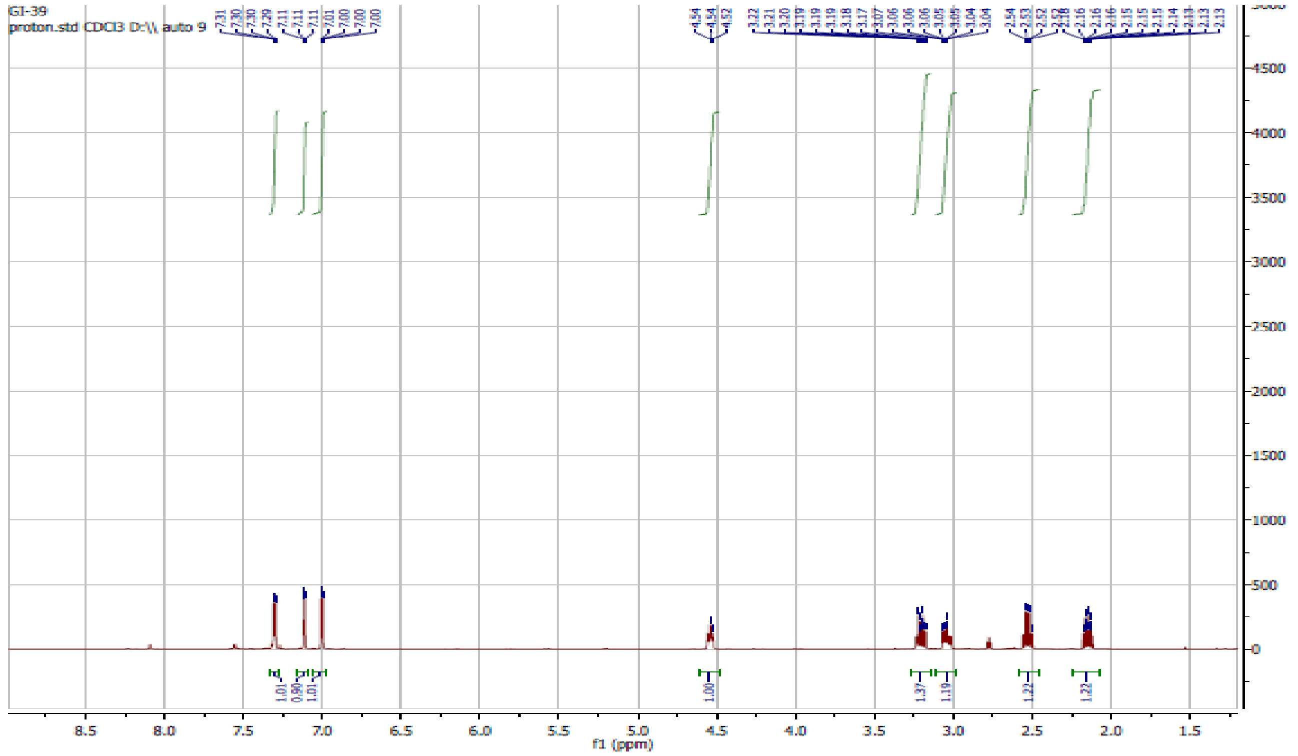


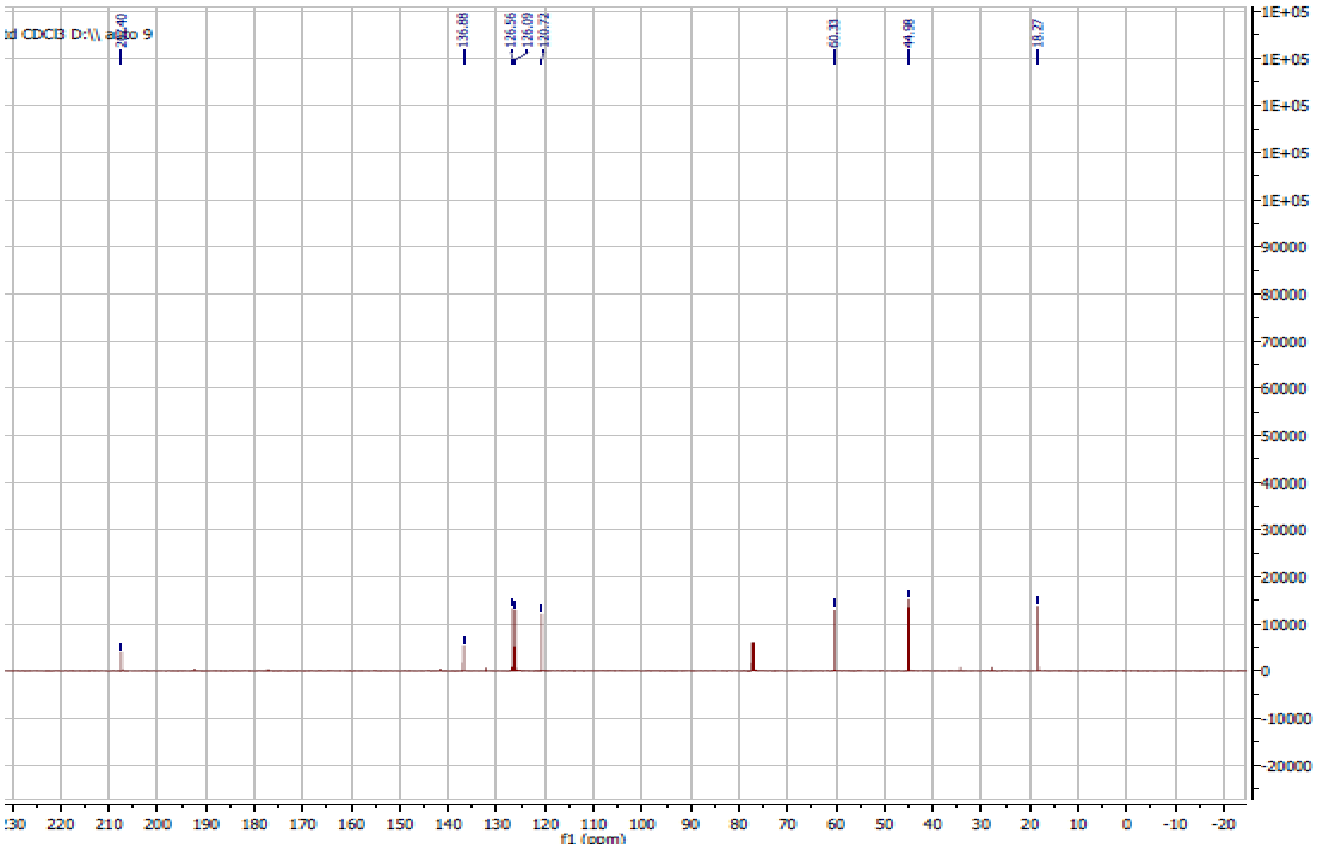
2-(3-(Trifluoromethyl)phenyl)cyclobutan-1-one (3b)



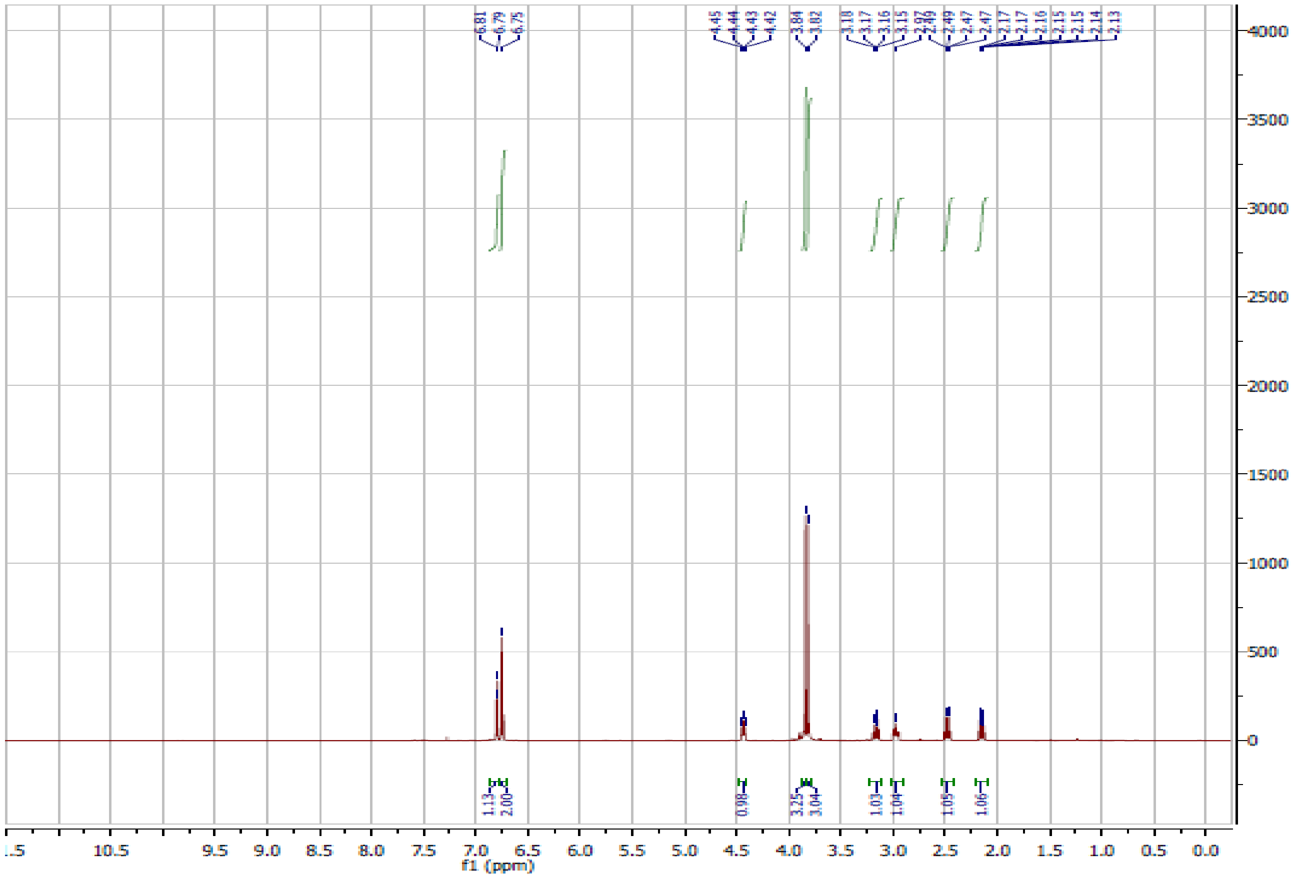


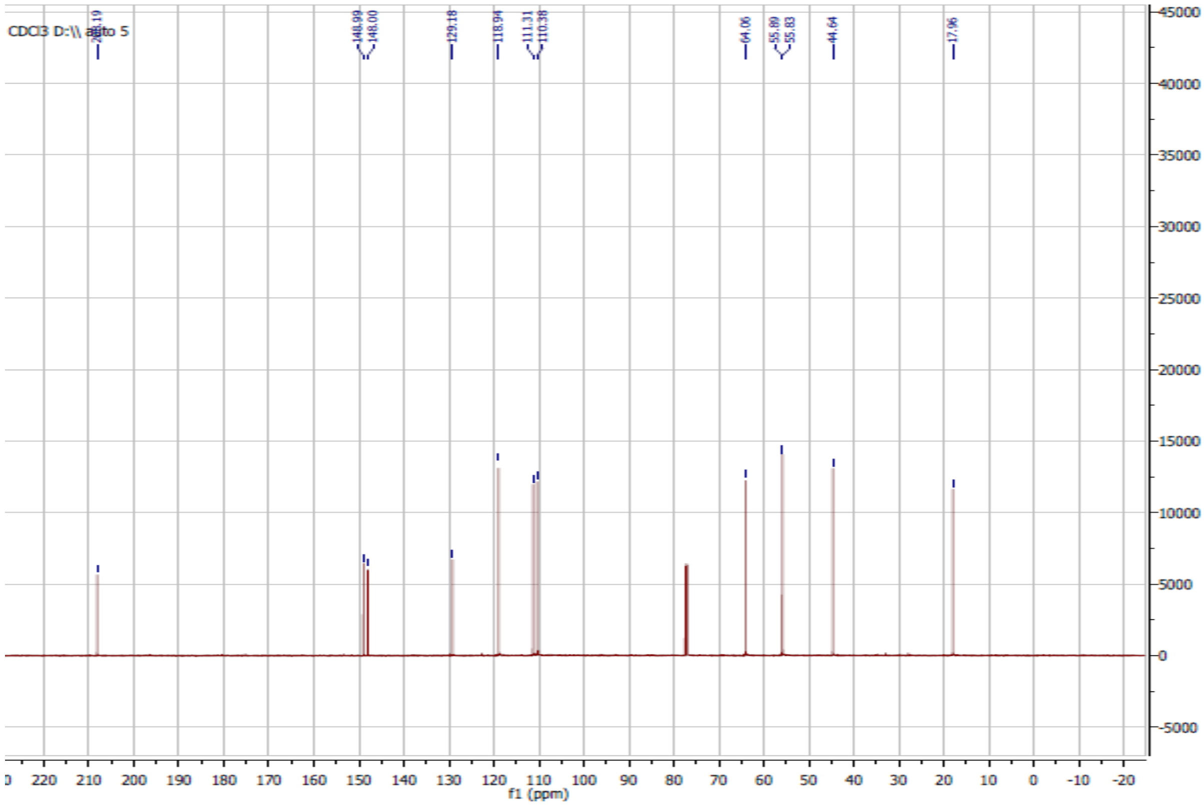
2-(Thiophen-3-yl)cyclobutan-1-one (3c)



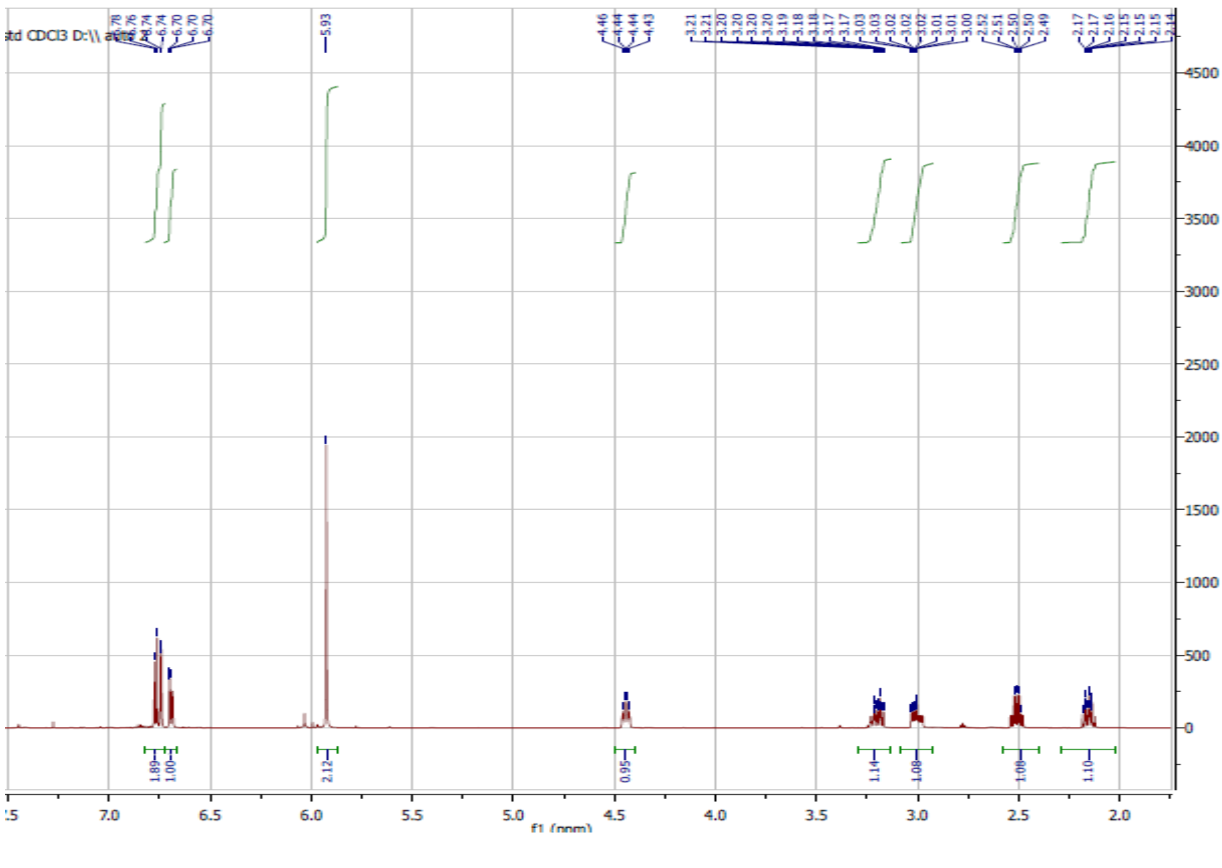


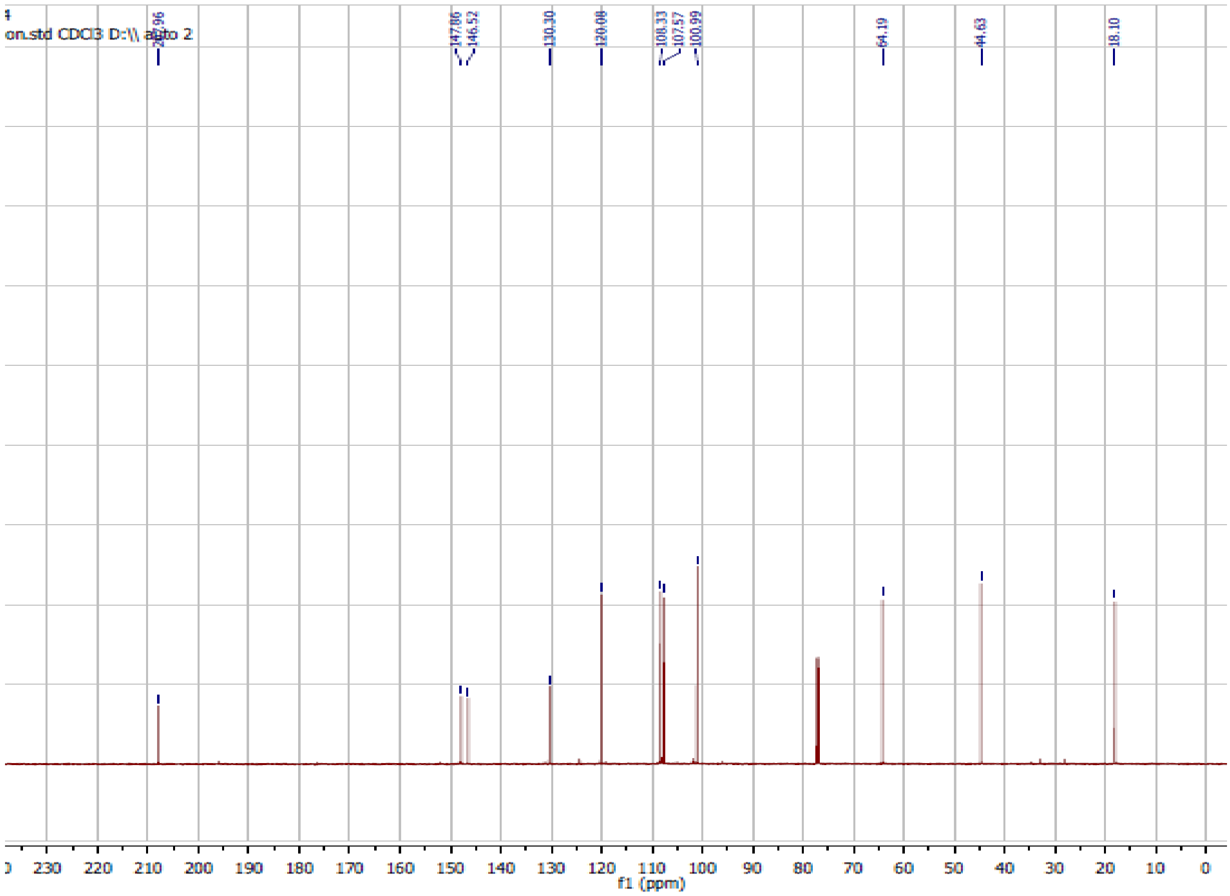
2-(3,4-Dimethoxyphenyl)cyclobutan-1-one (3d)



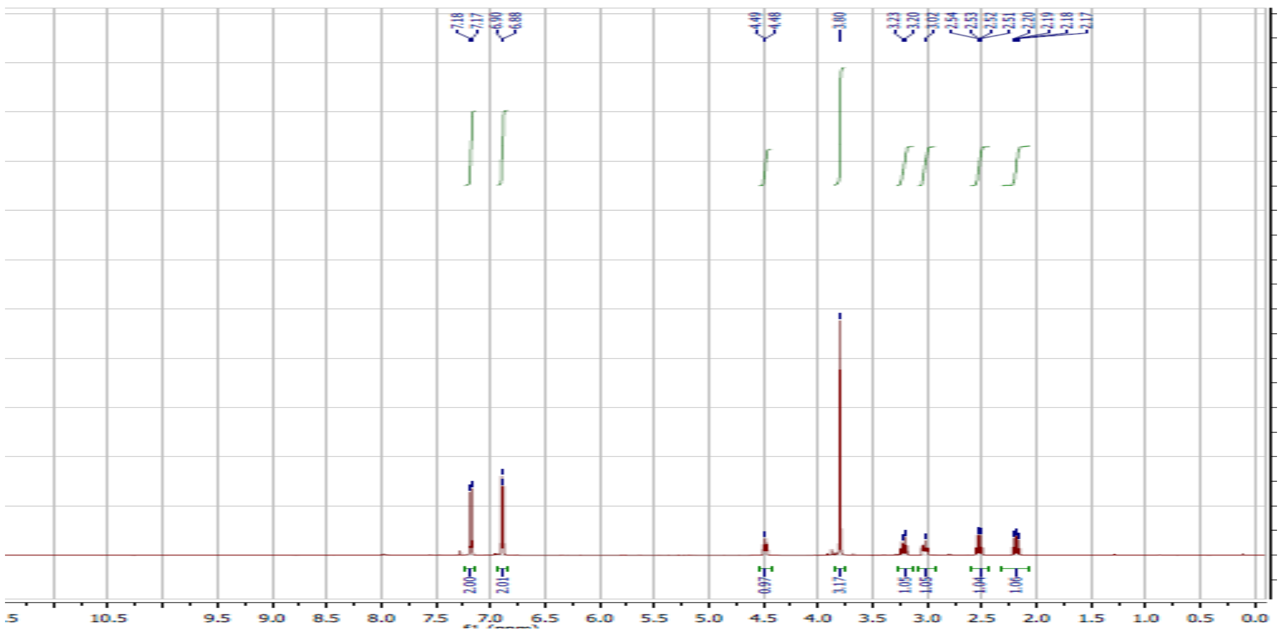


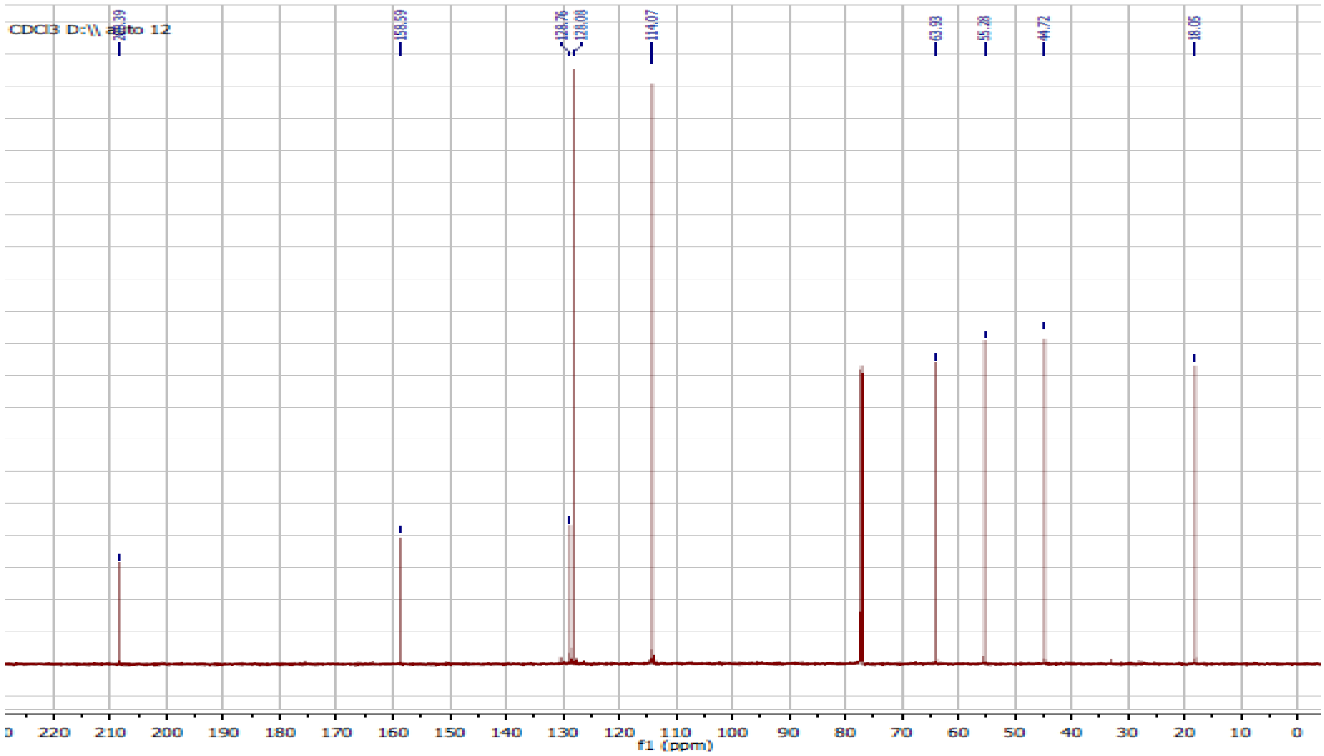
2-(Benzo[d][1,3]dioxol-5-yl)cyclobutan-1-one (3e)



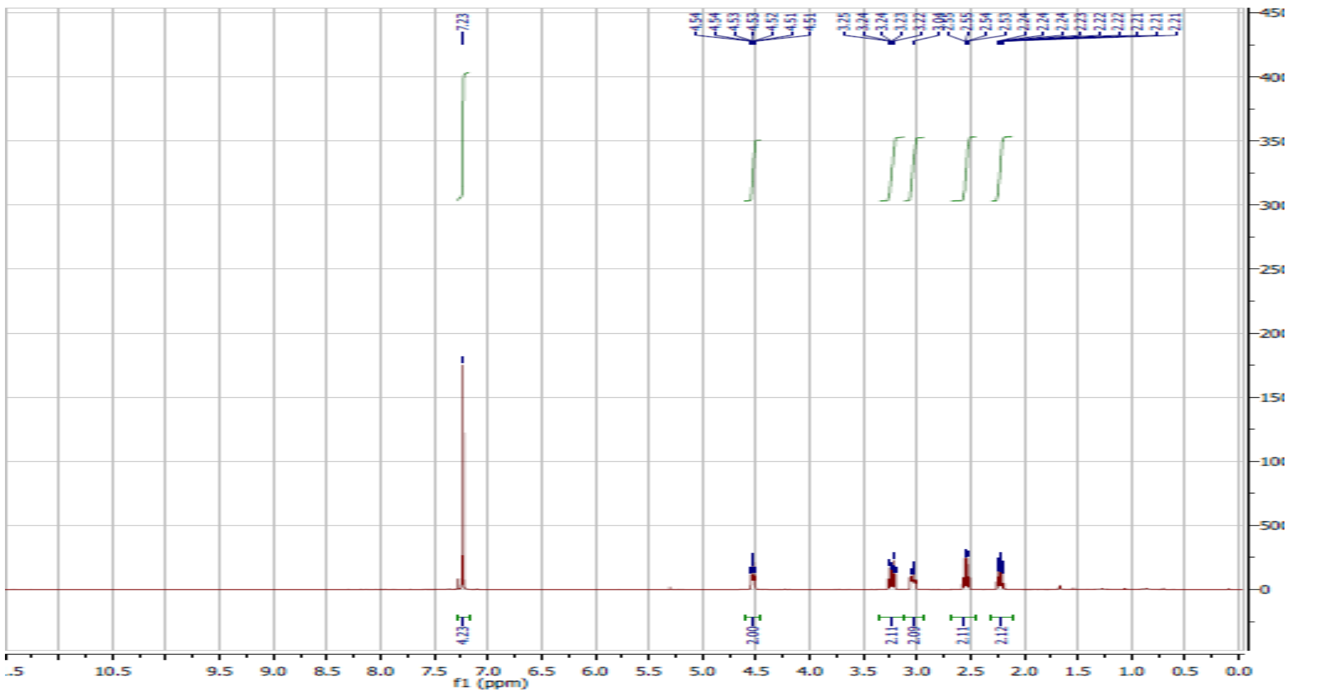


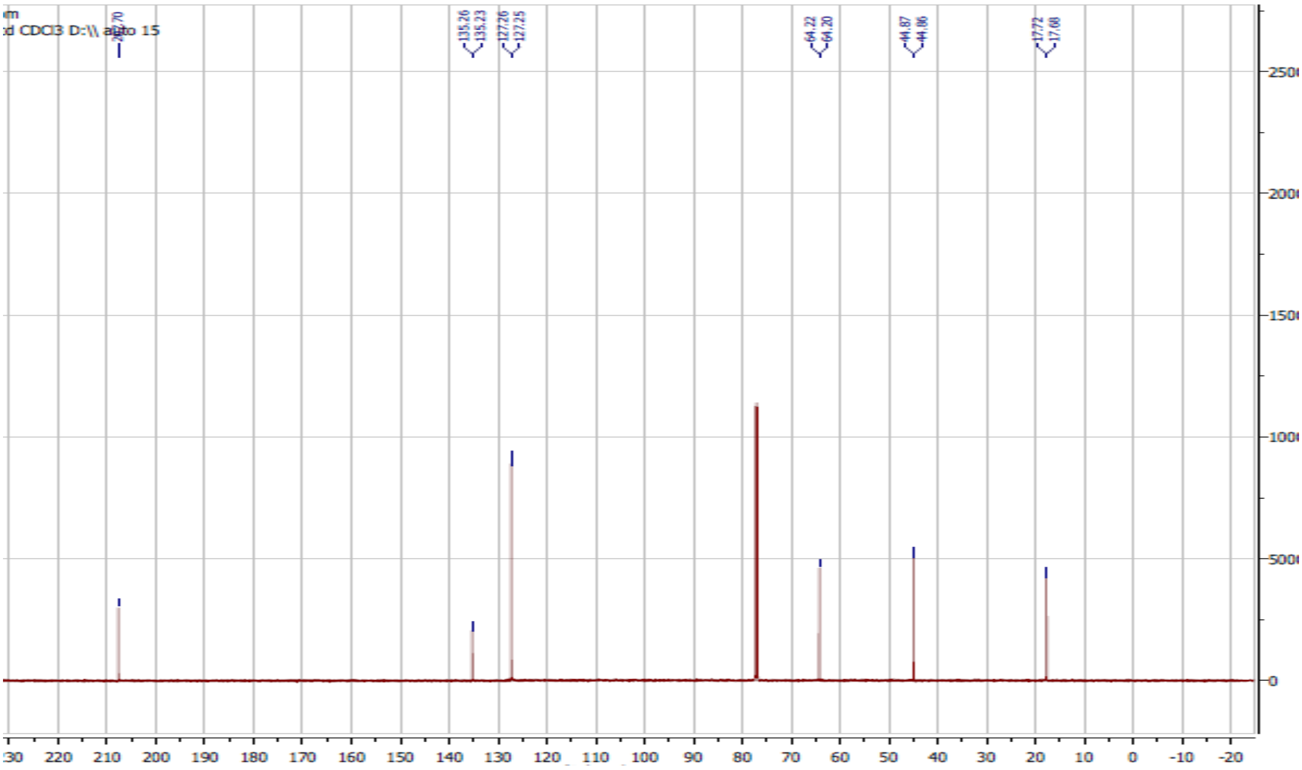
2-(4-Methoxyphenyl)cyclobutan-1-one (3f)



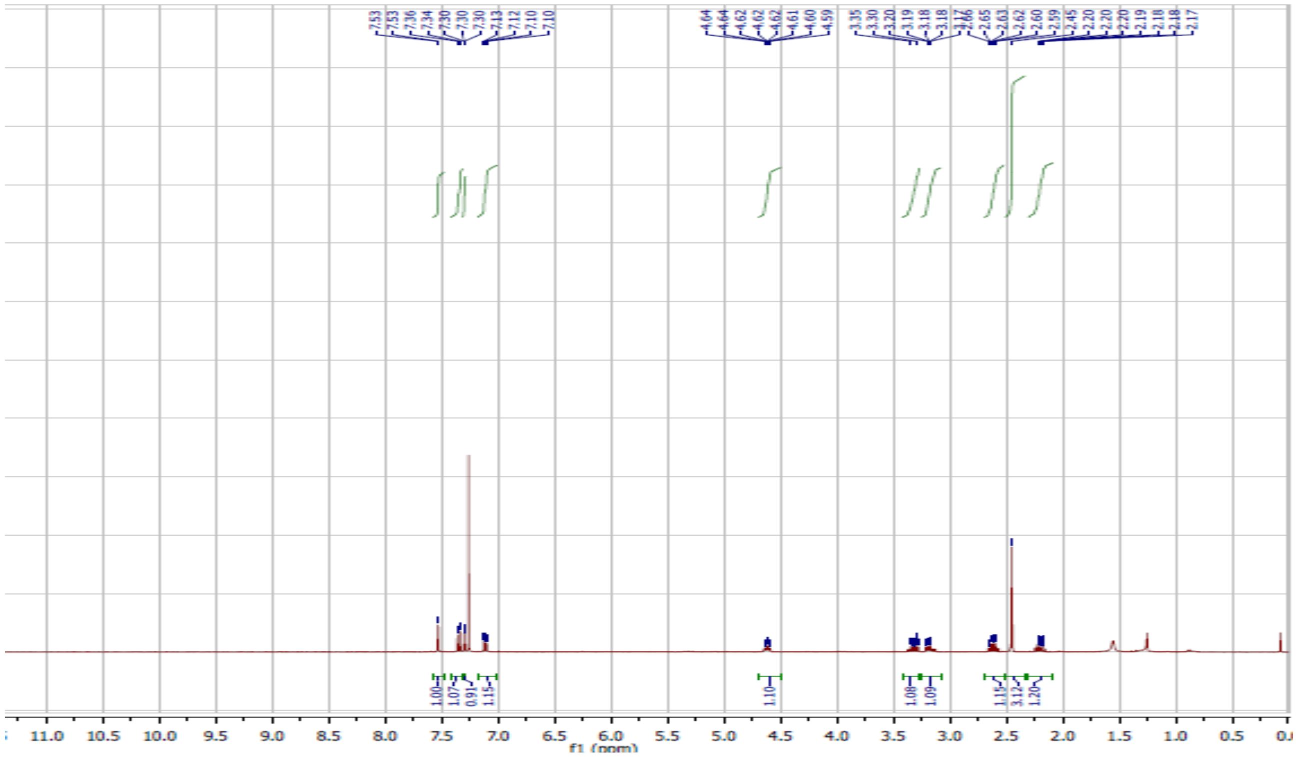


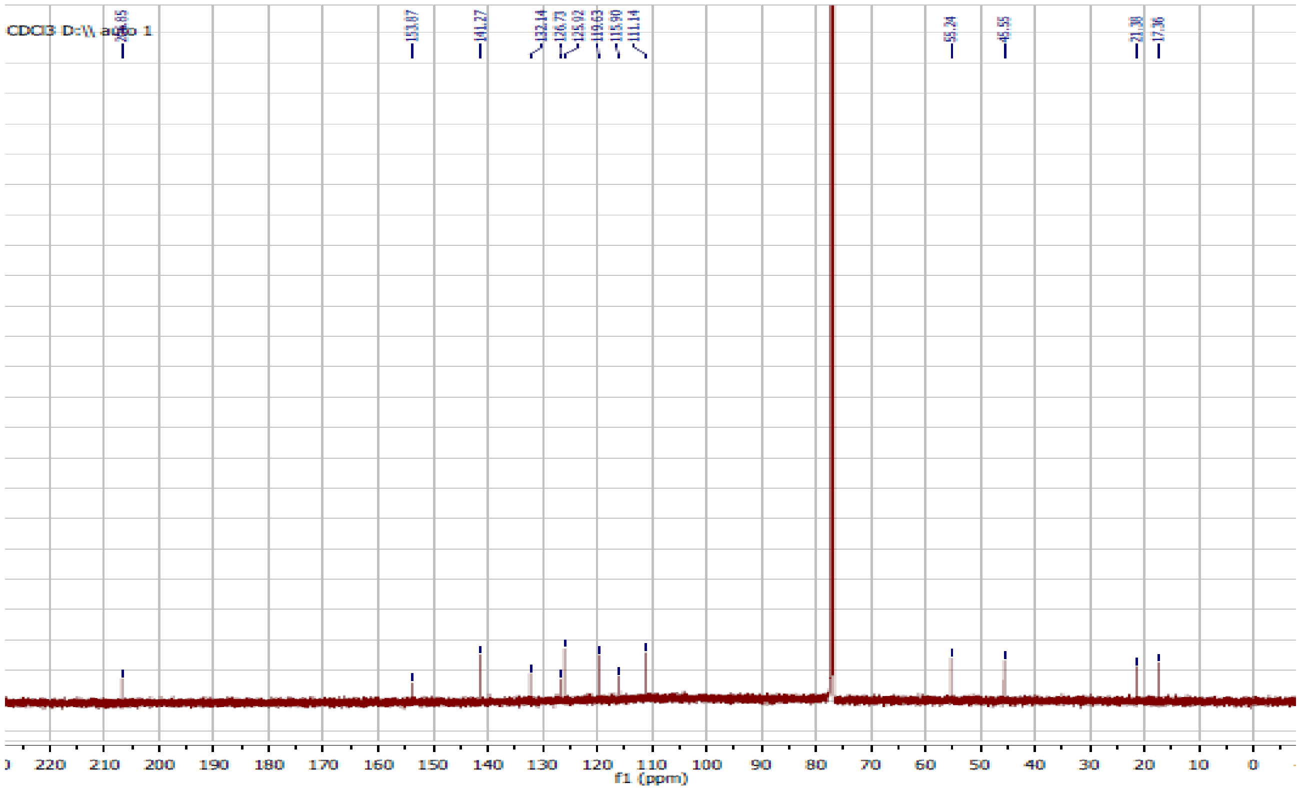
2,2'-(1,4-Phenylene)bis(cyclobutan-1-one) (3g)



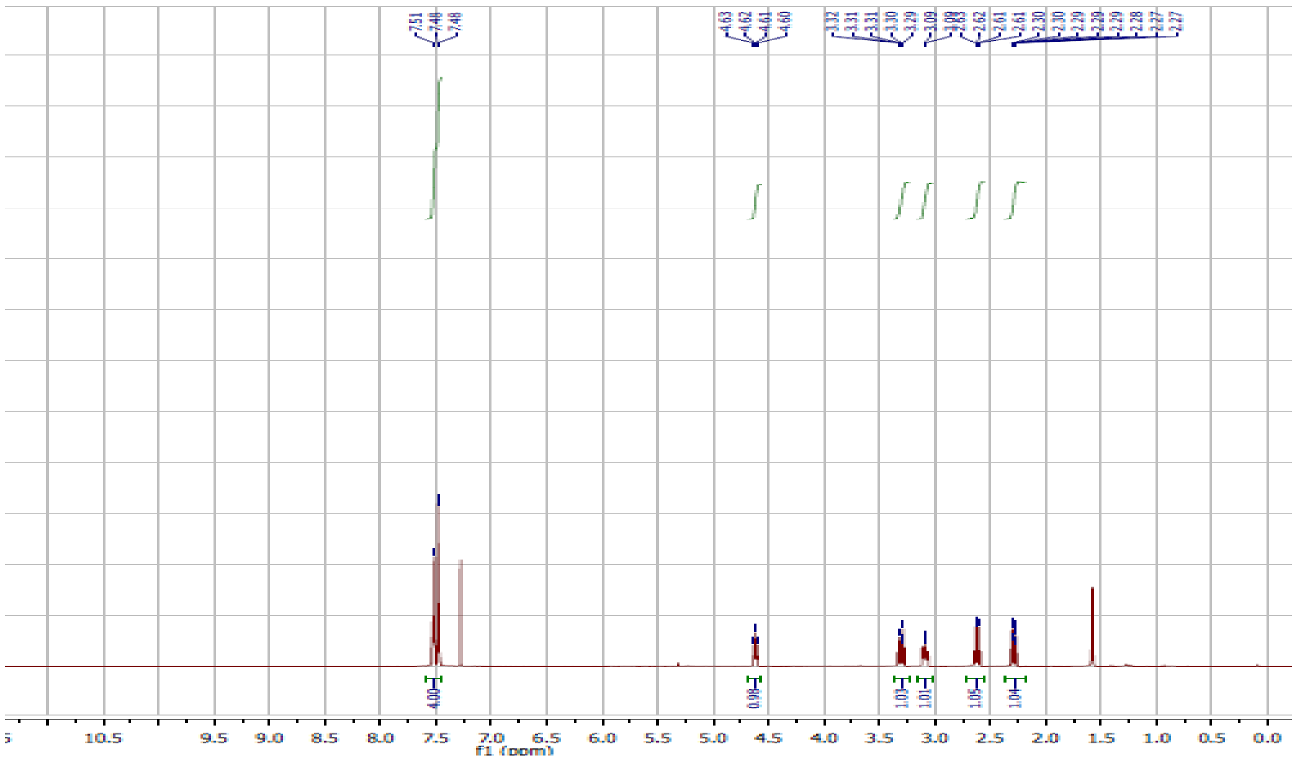


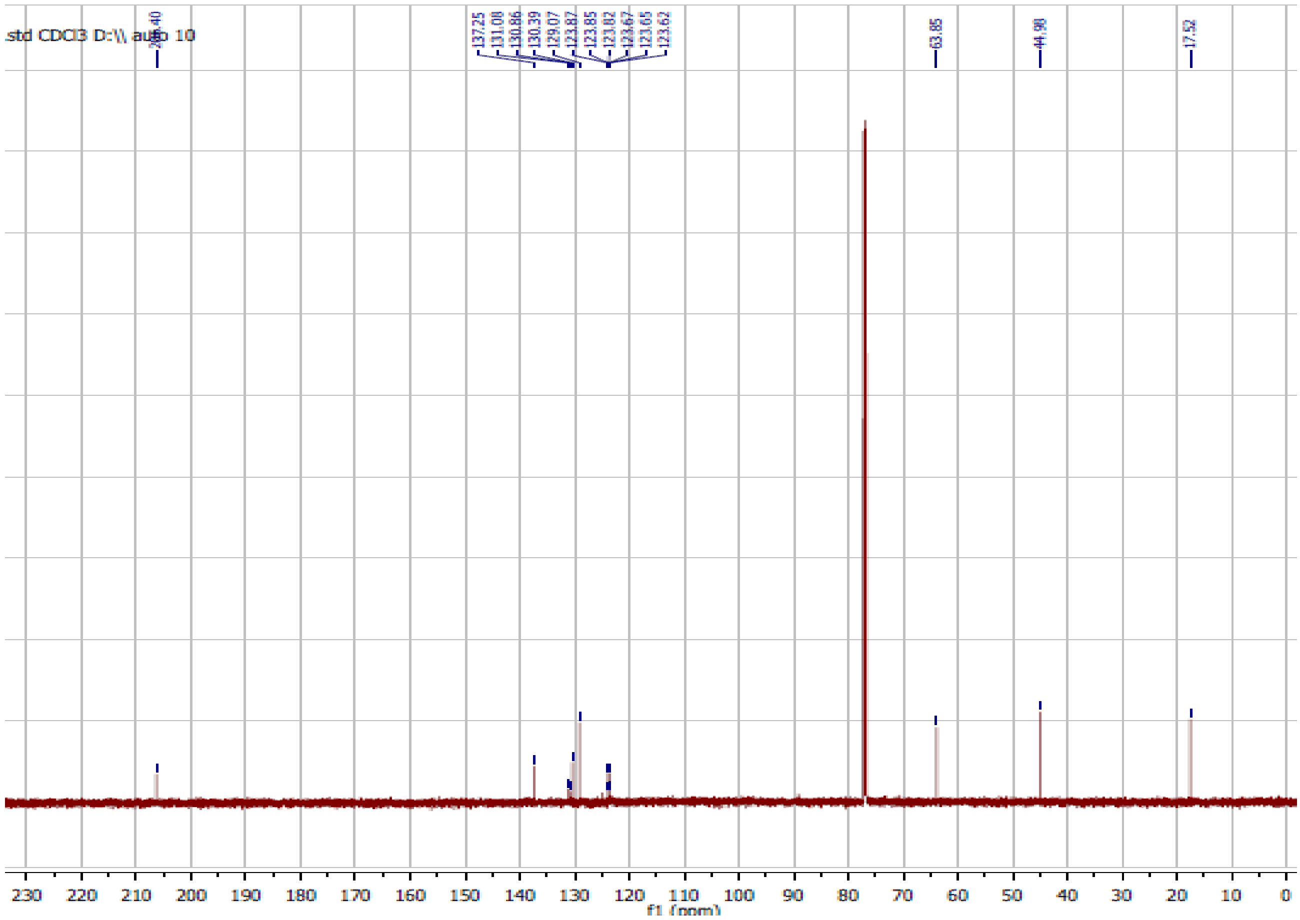
2-(5-Methyl-benzofuran-3-yl)cyclobutan-1-one (3h)



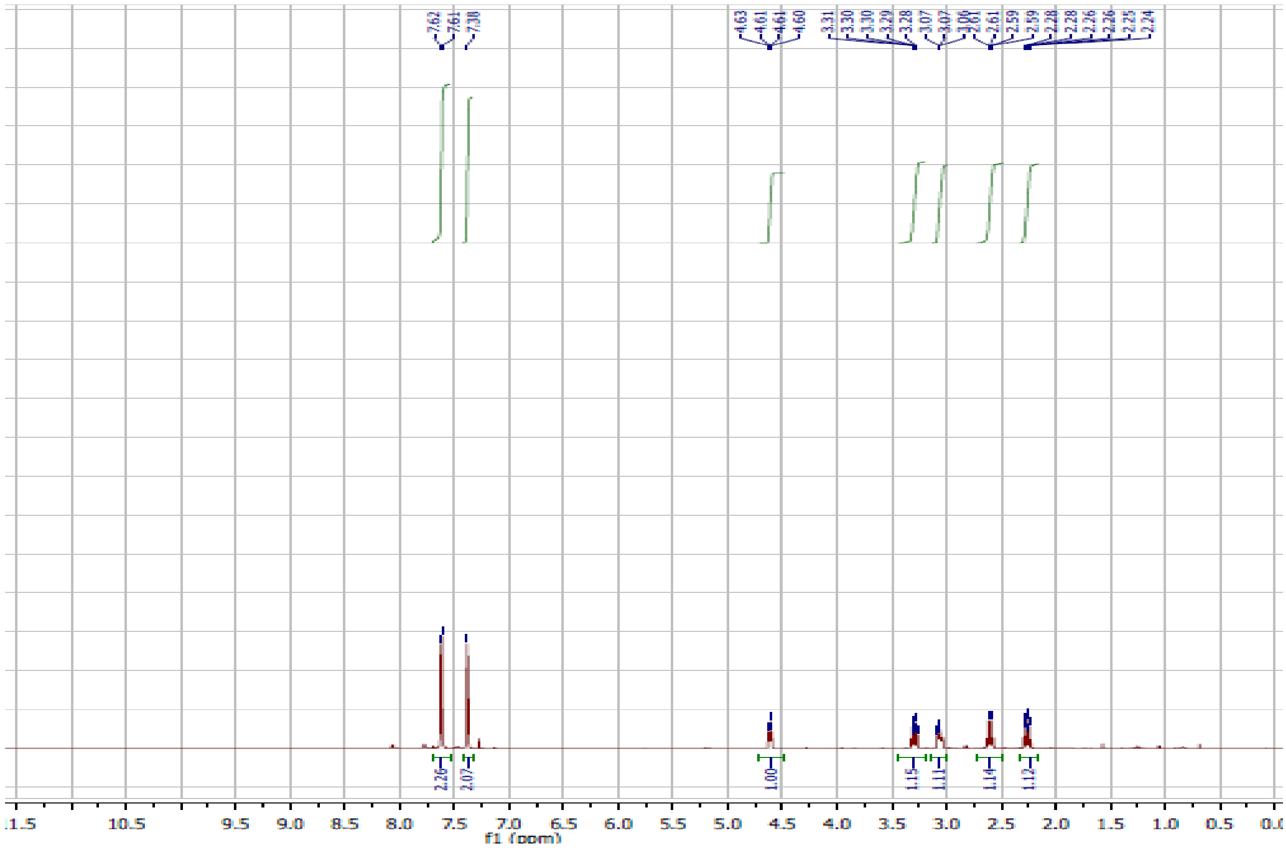


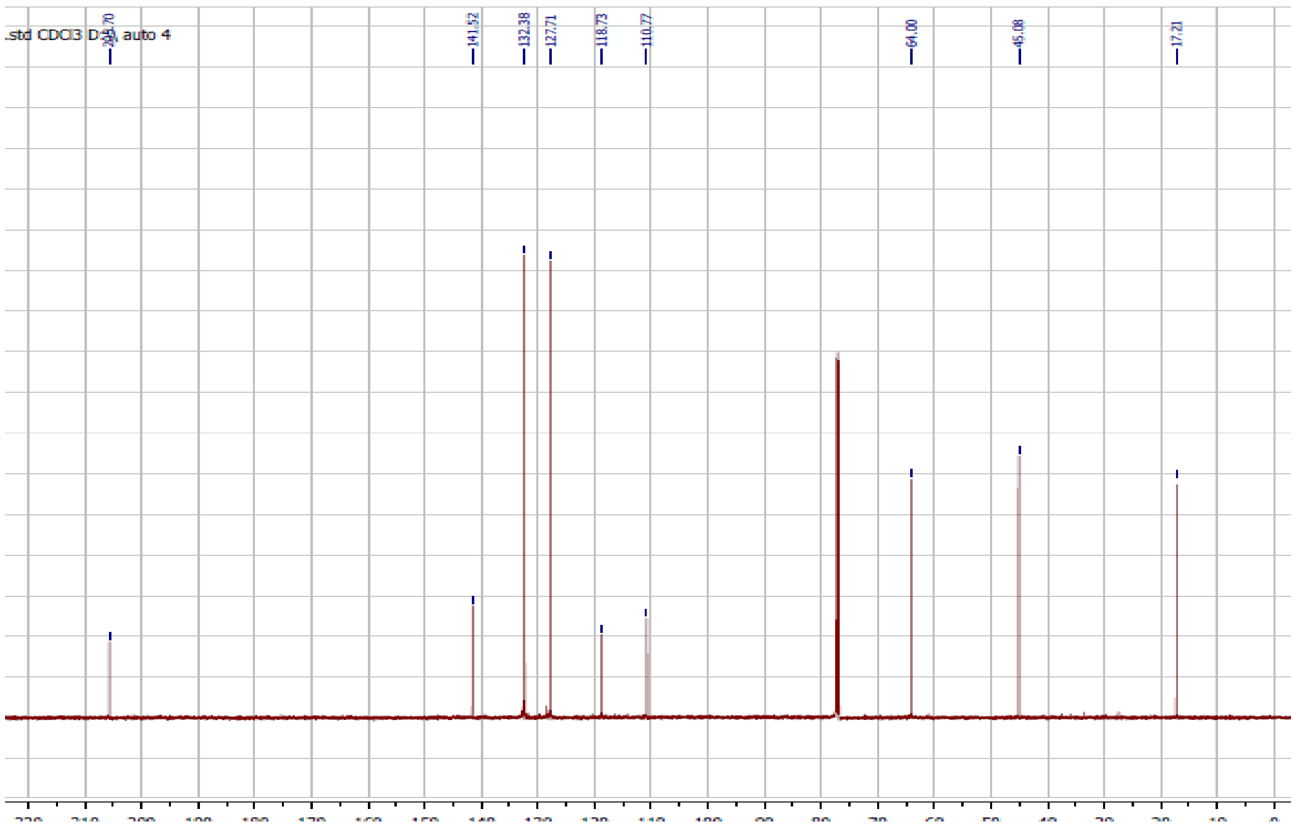
2-(2-Chlorophenyl)cyclobutan-1-one (3i)



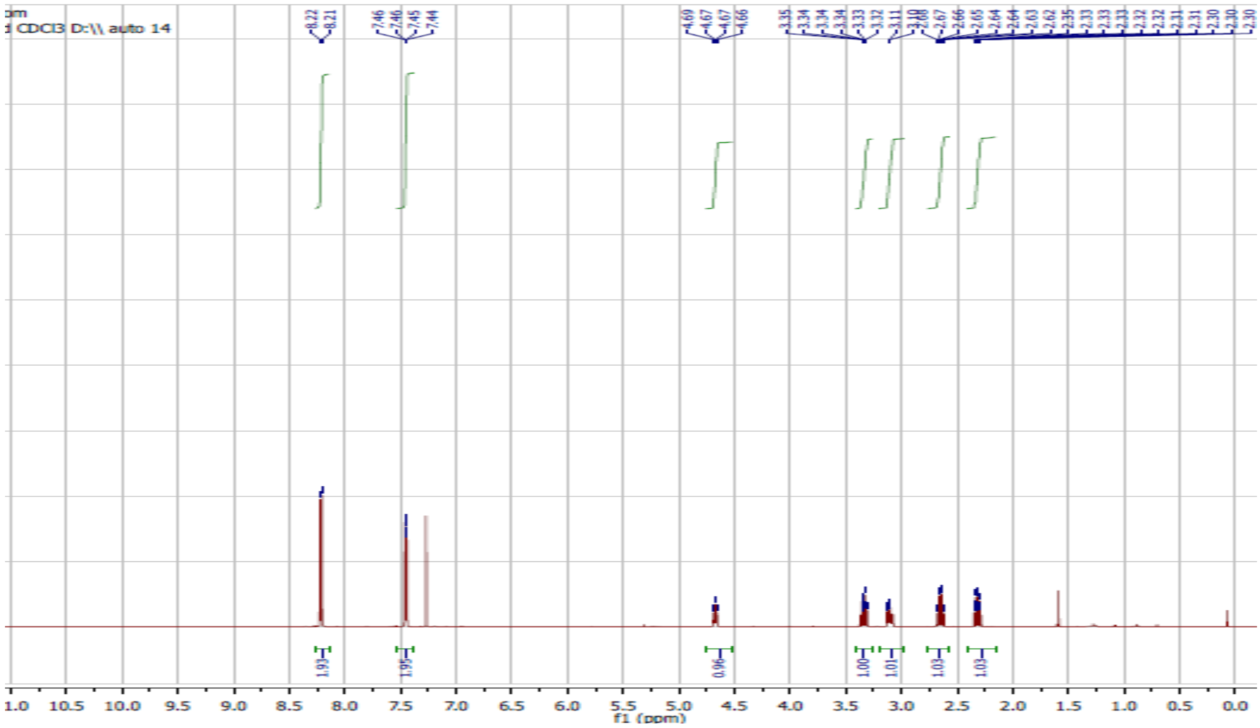


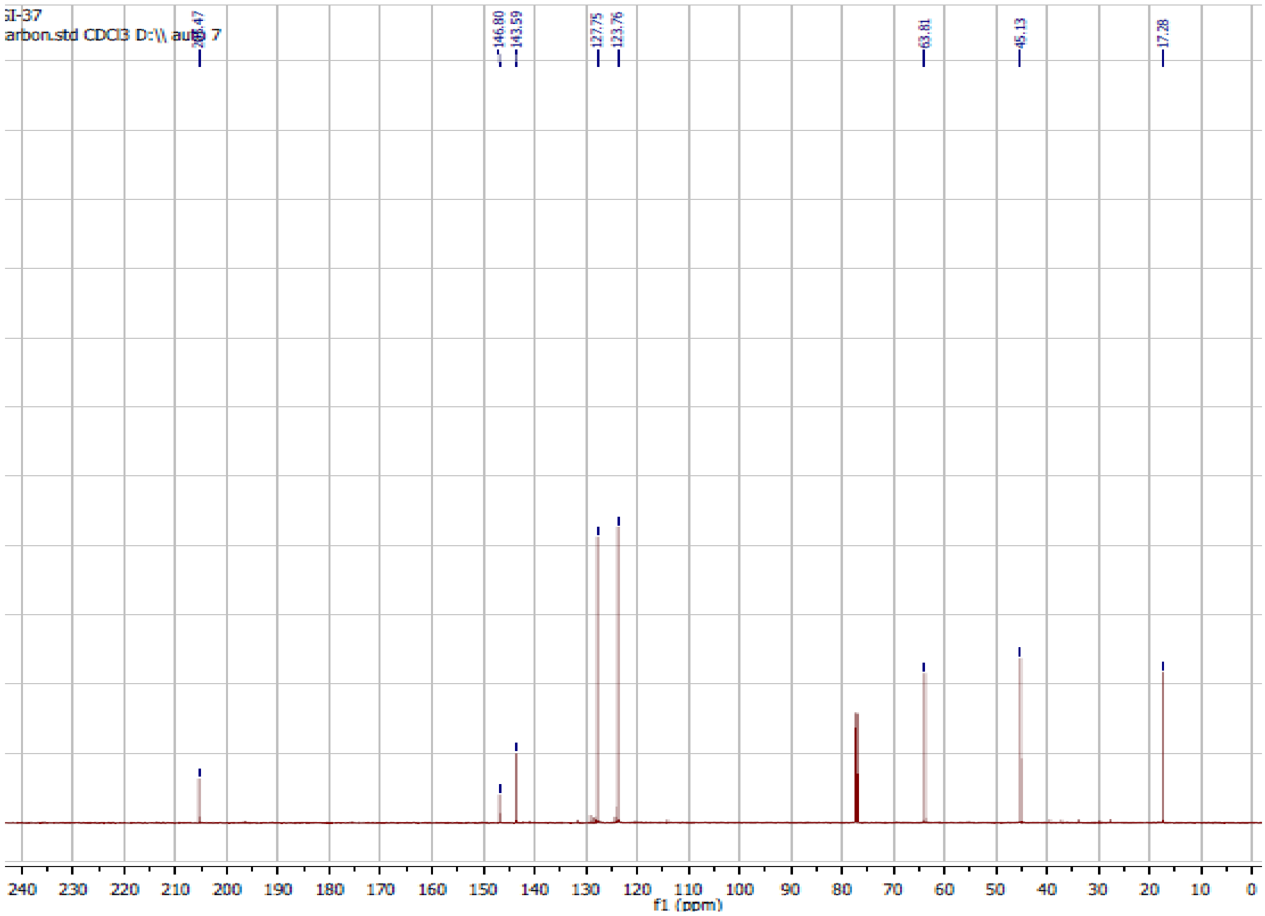
(4-Cyanophenyl)cyclobutan-1-one (3j)



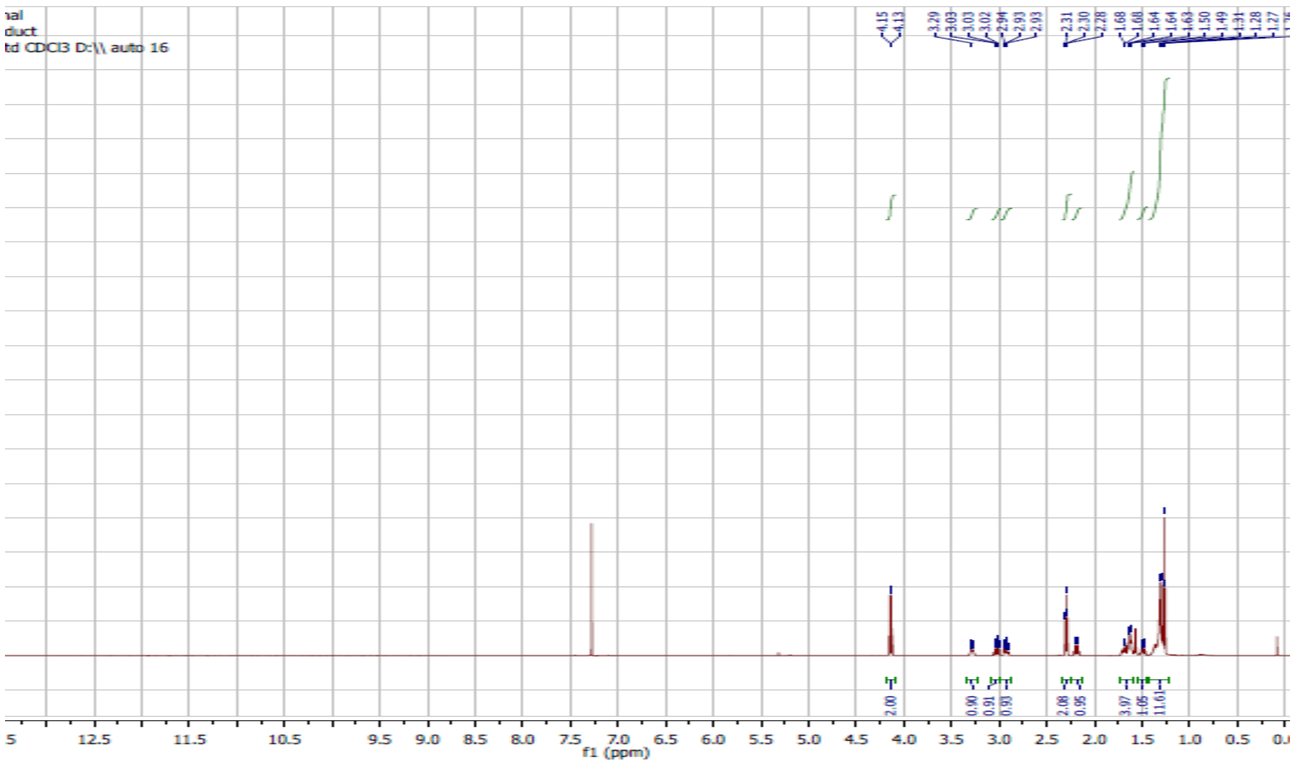


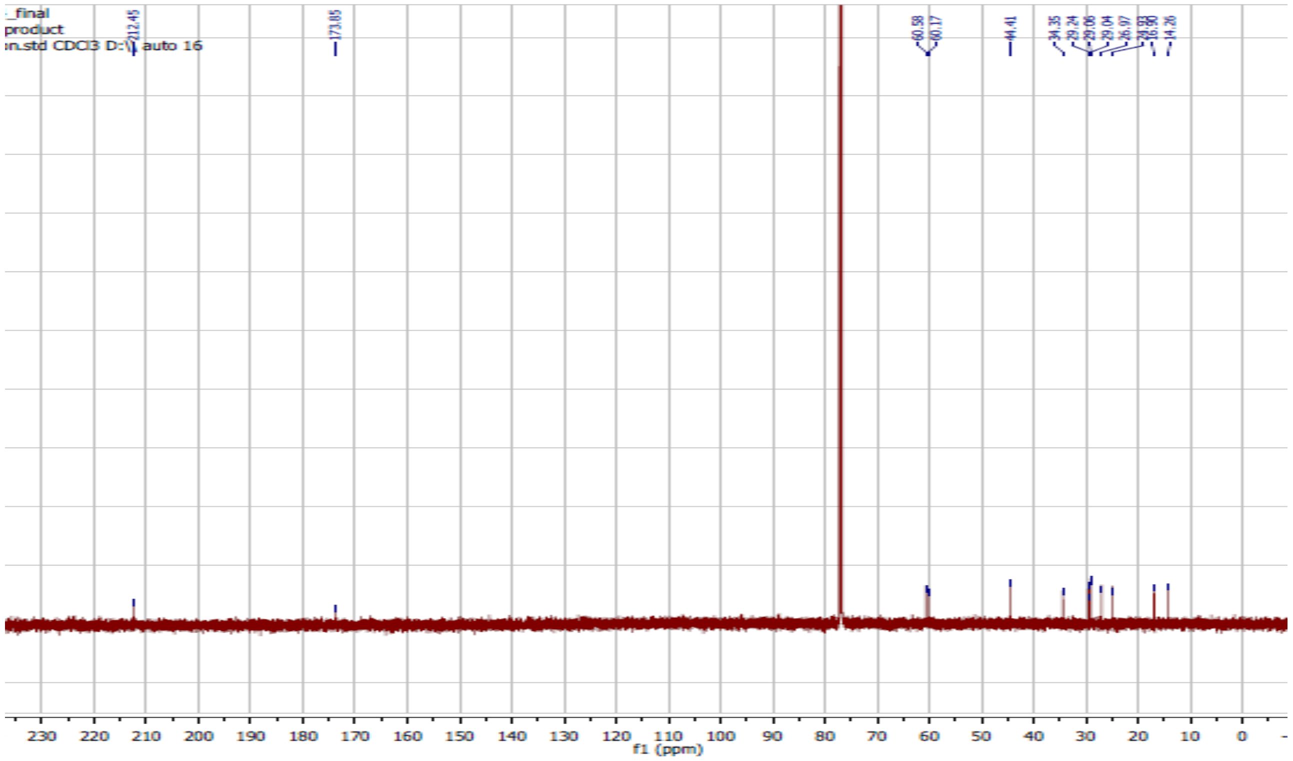
2-(4-Nitrophenyl)cyclobutan-1-one (3k)



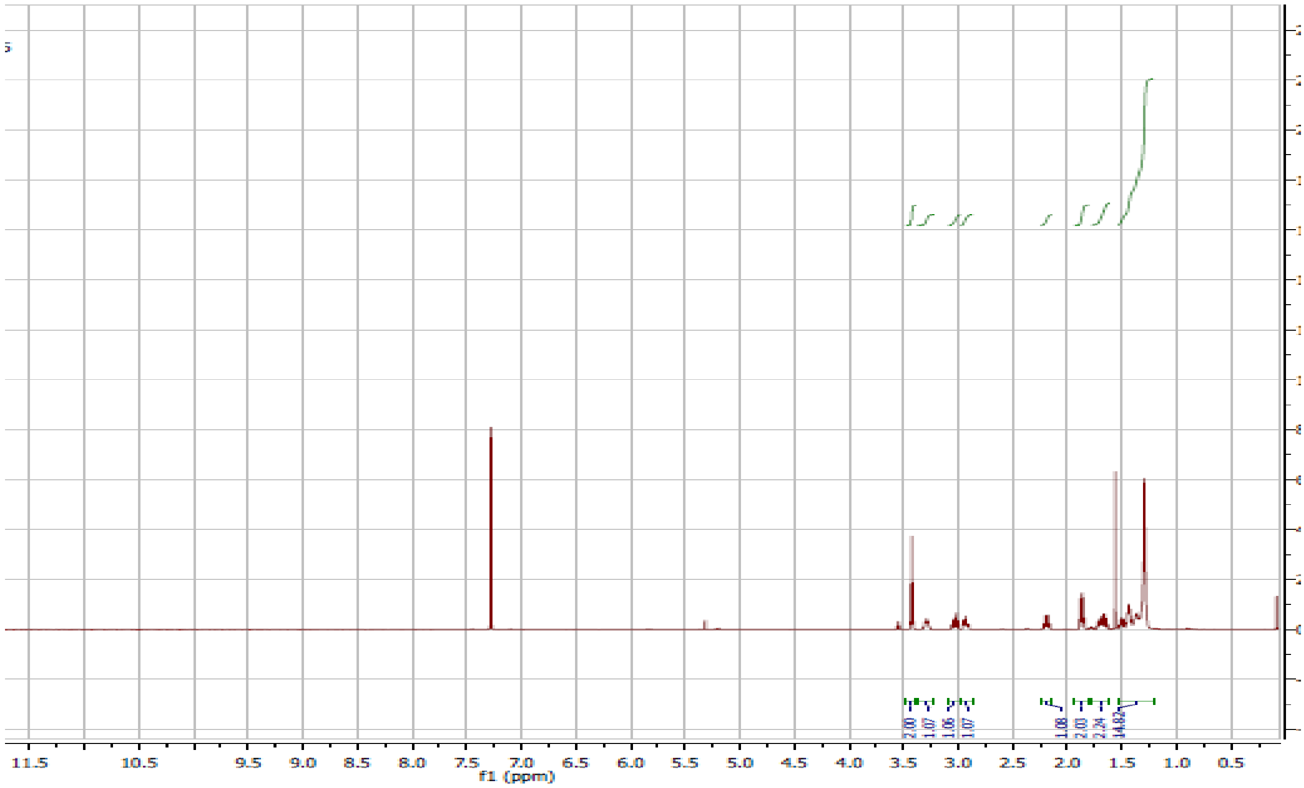


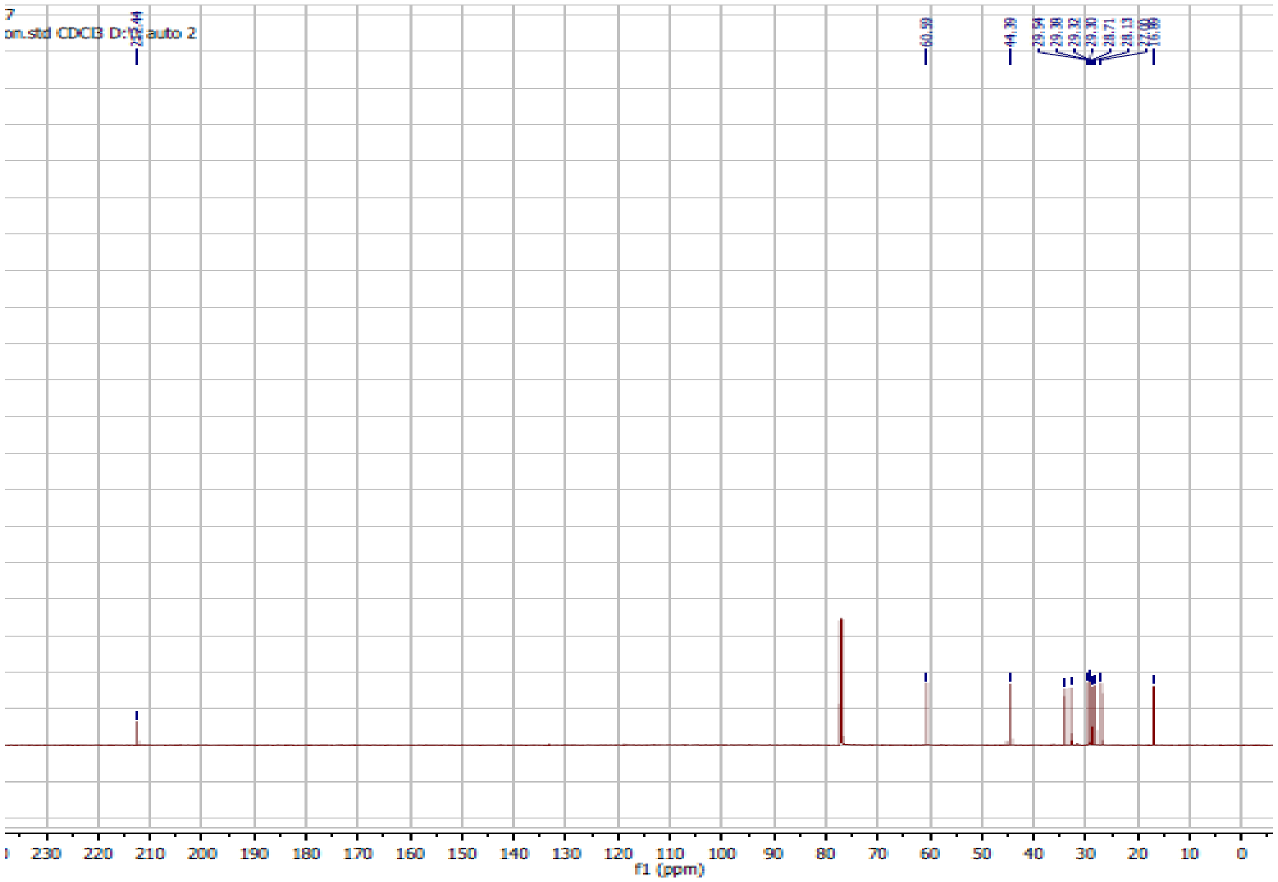
Ethyl 8-(2-oxocyclobutyl)octanoate (3l)



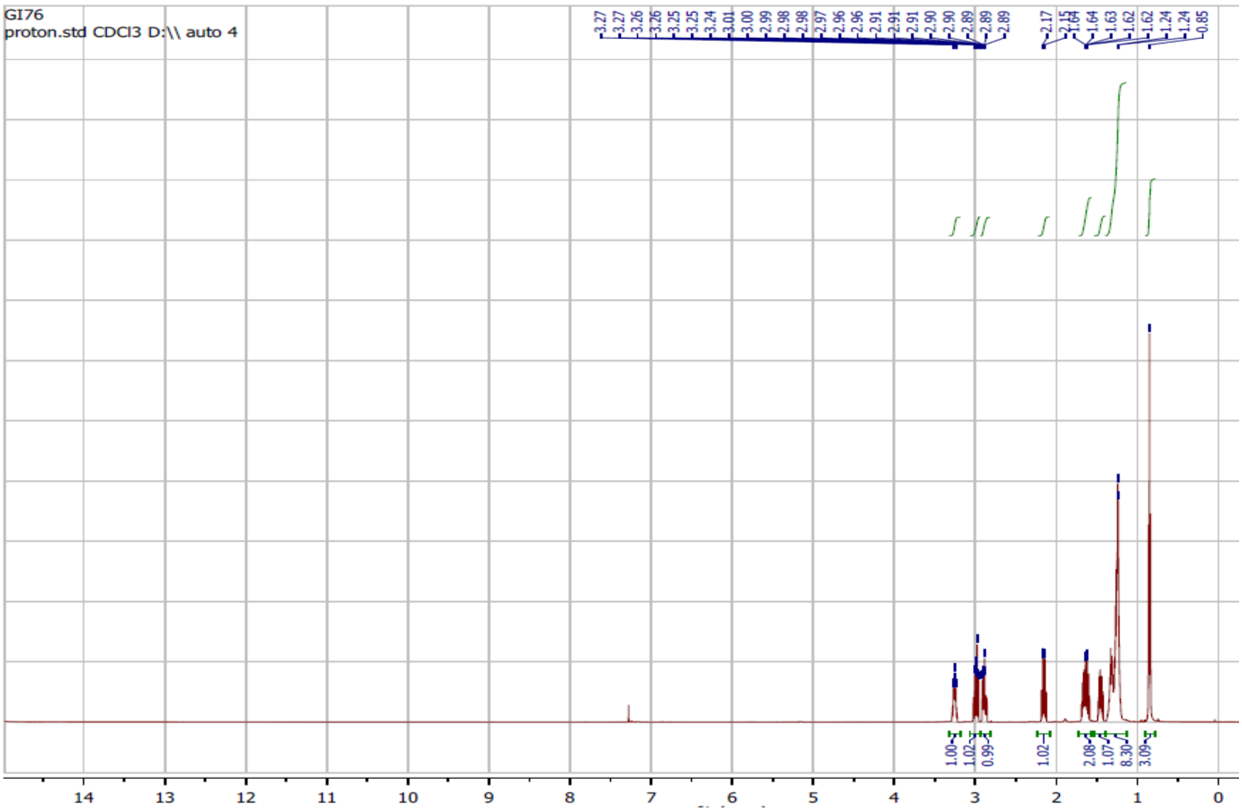


2-(9-Bromononyl)cyclobutan-1-one (3m)





2-Hexylcyclobutan-1-one (3n)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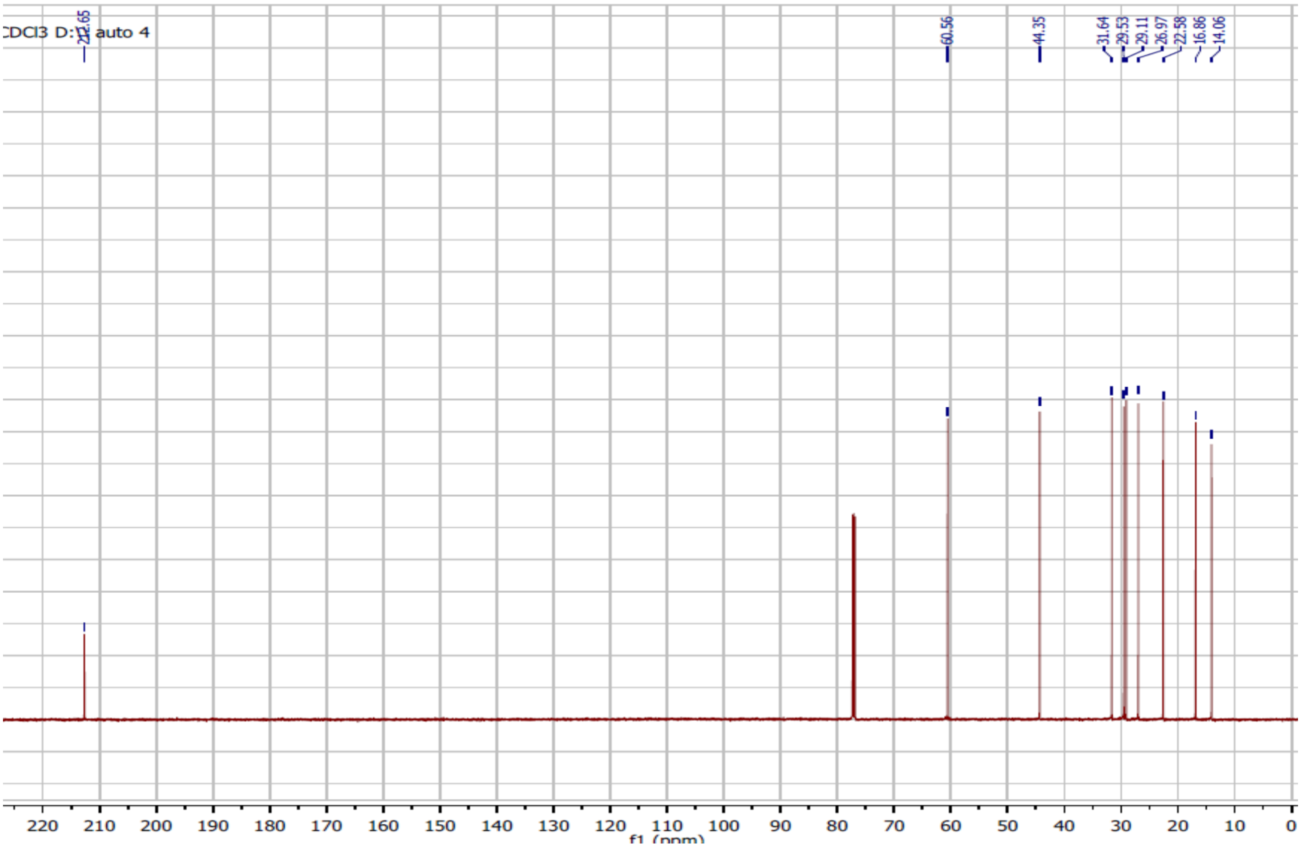
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130
120
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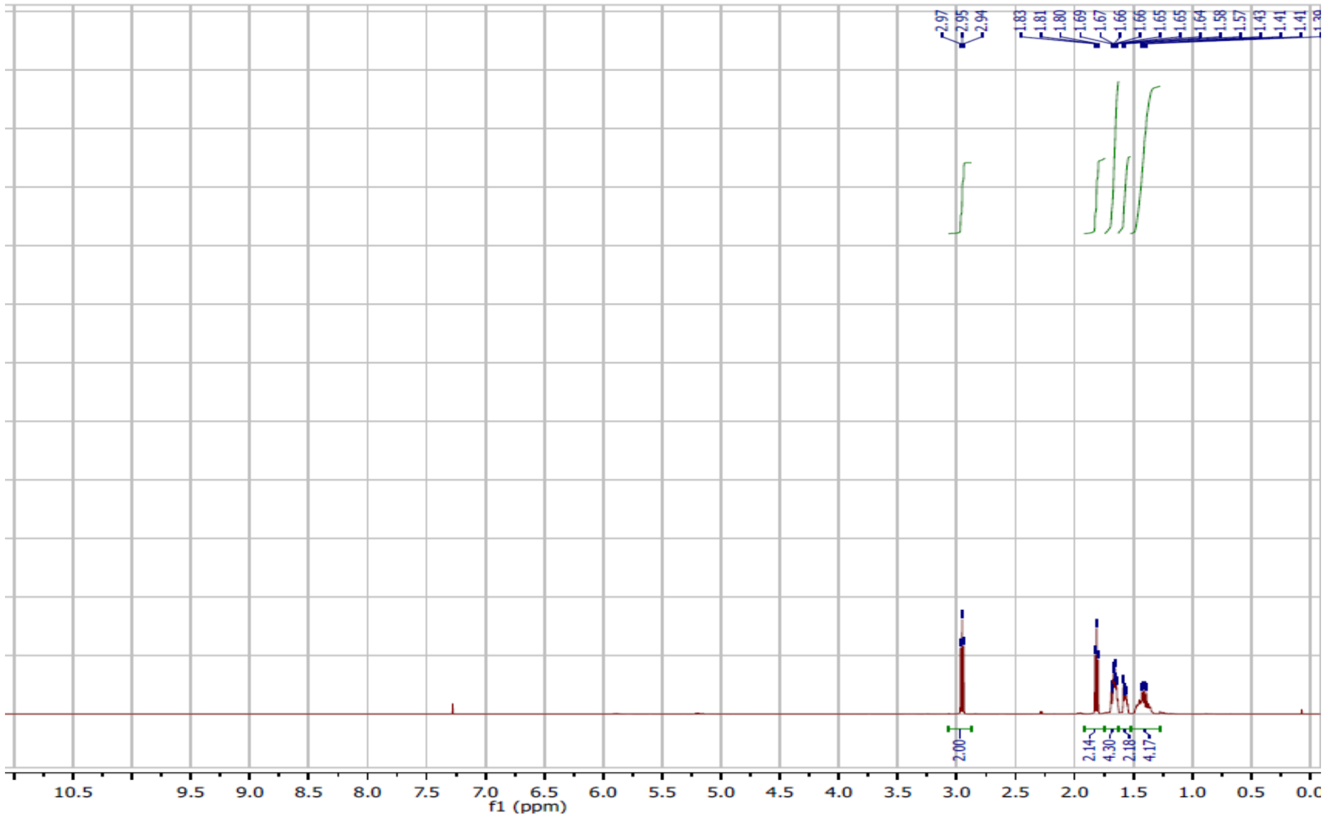
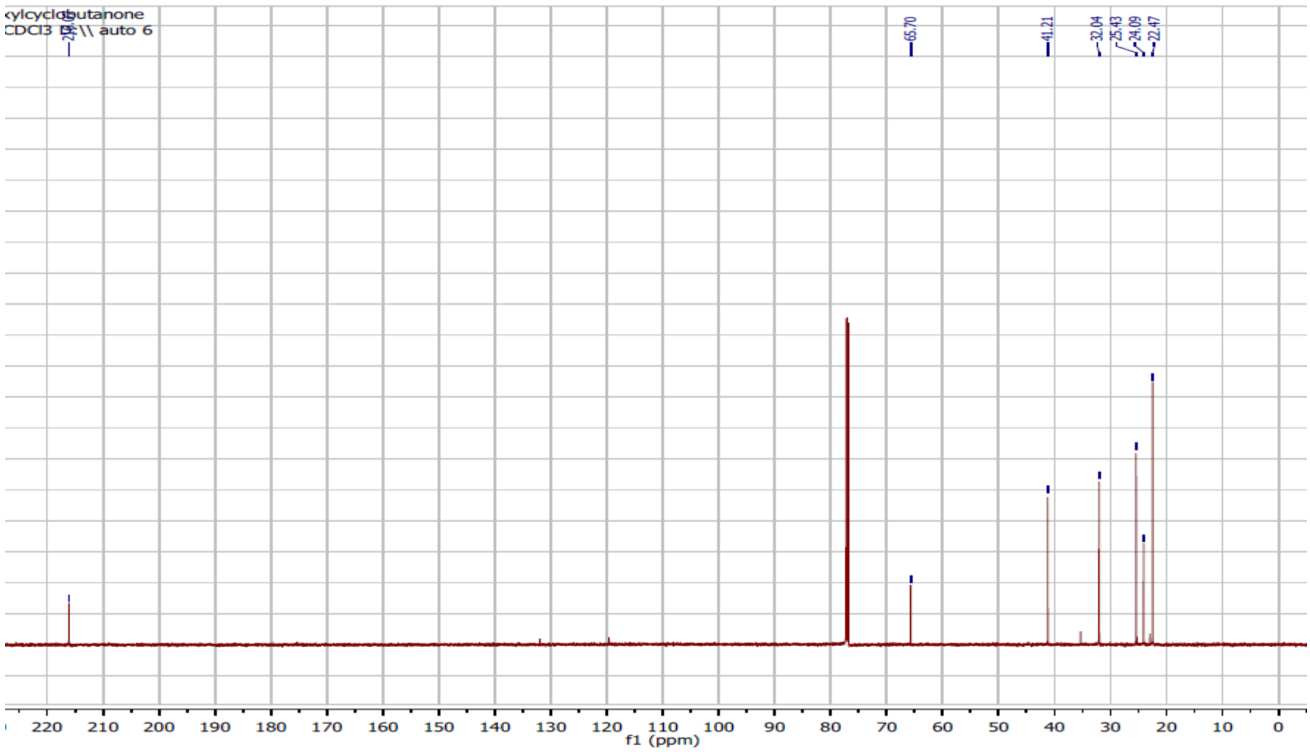
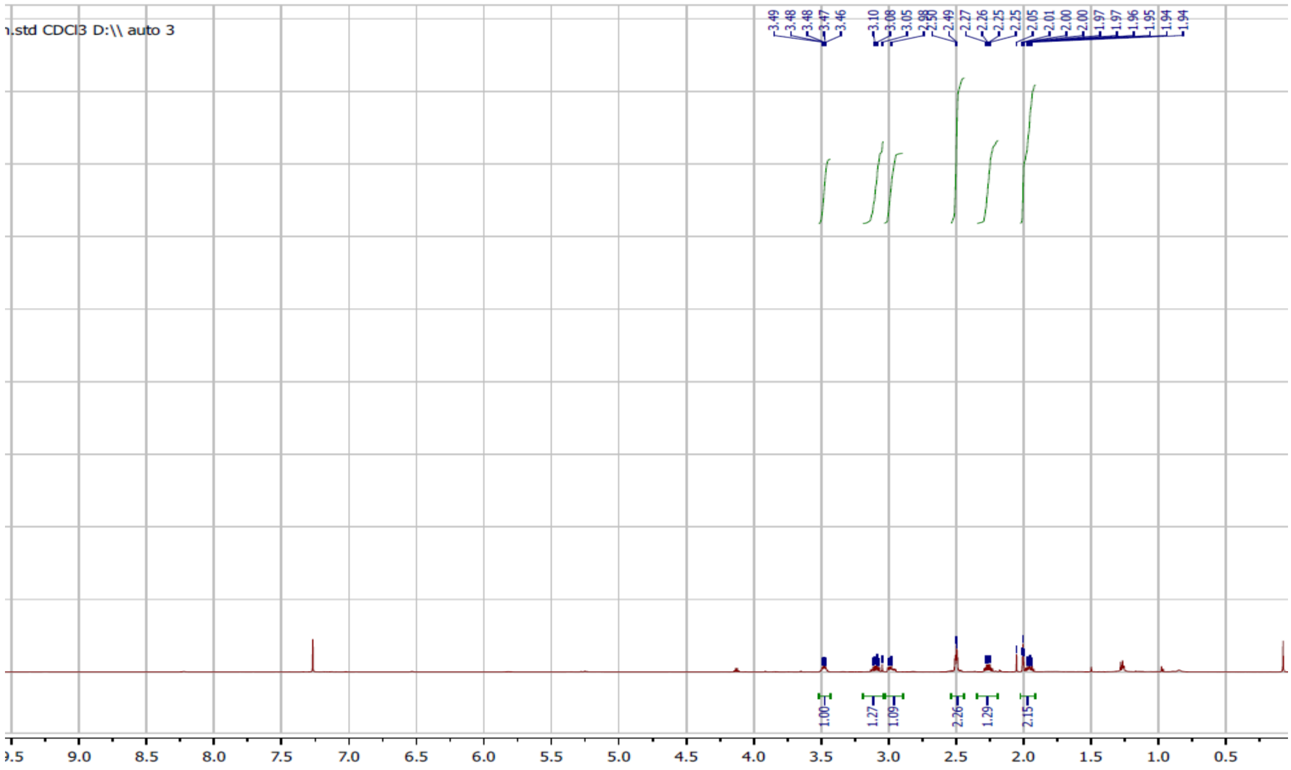
f1 (ppm)

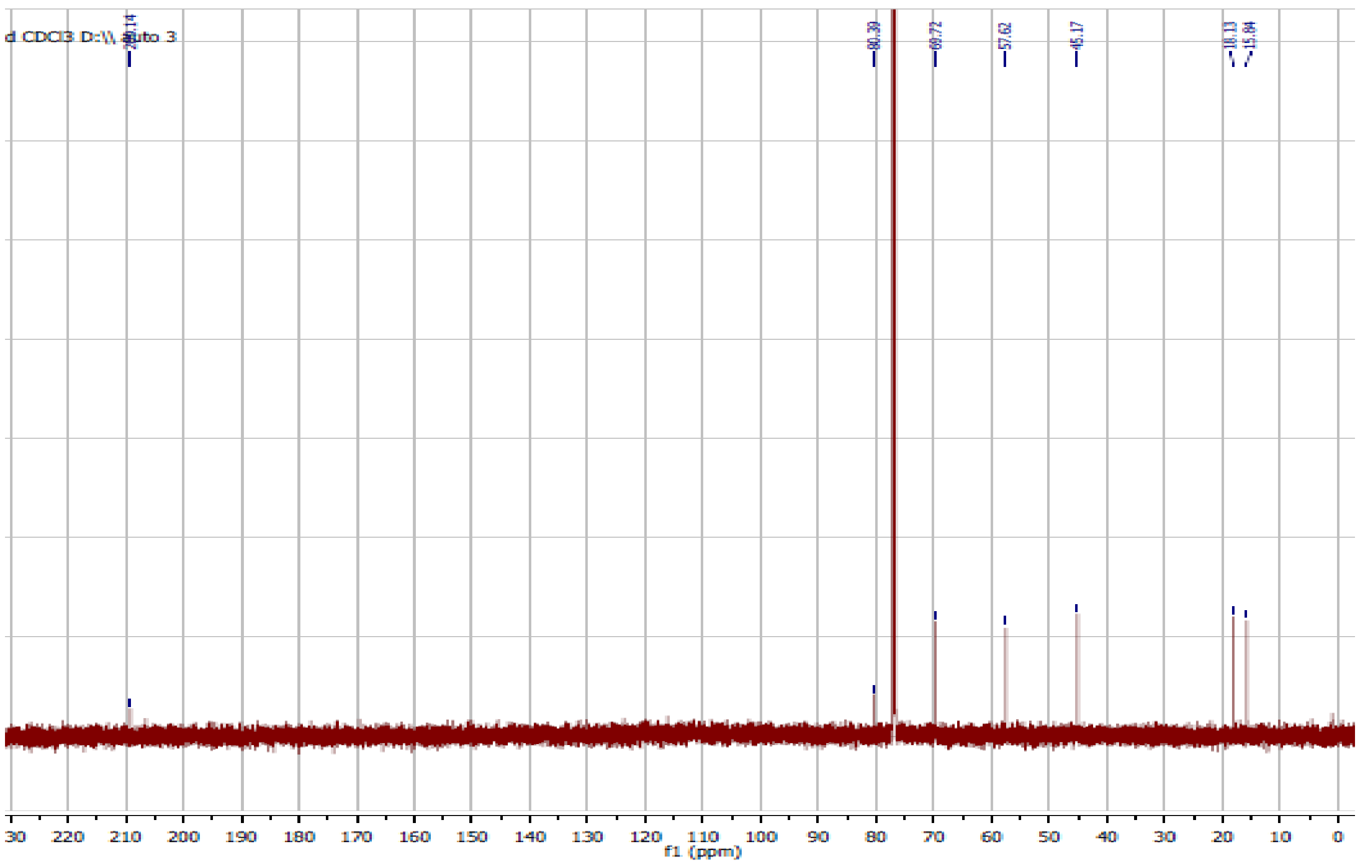
Spiro[3.5]nonan-1-one (3o)



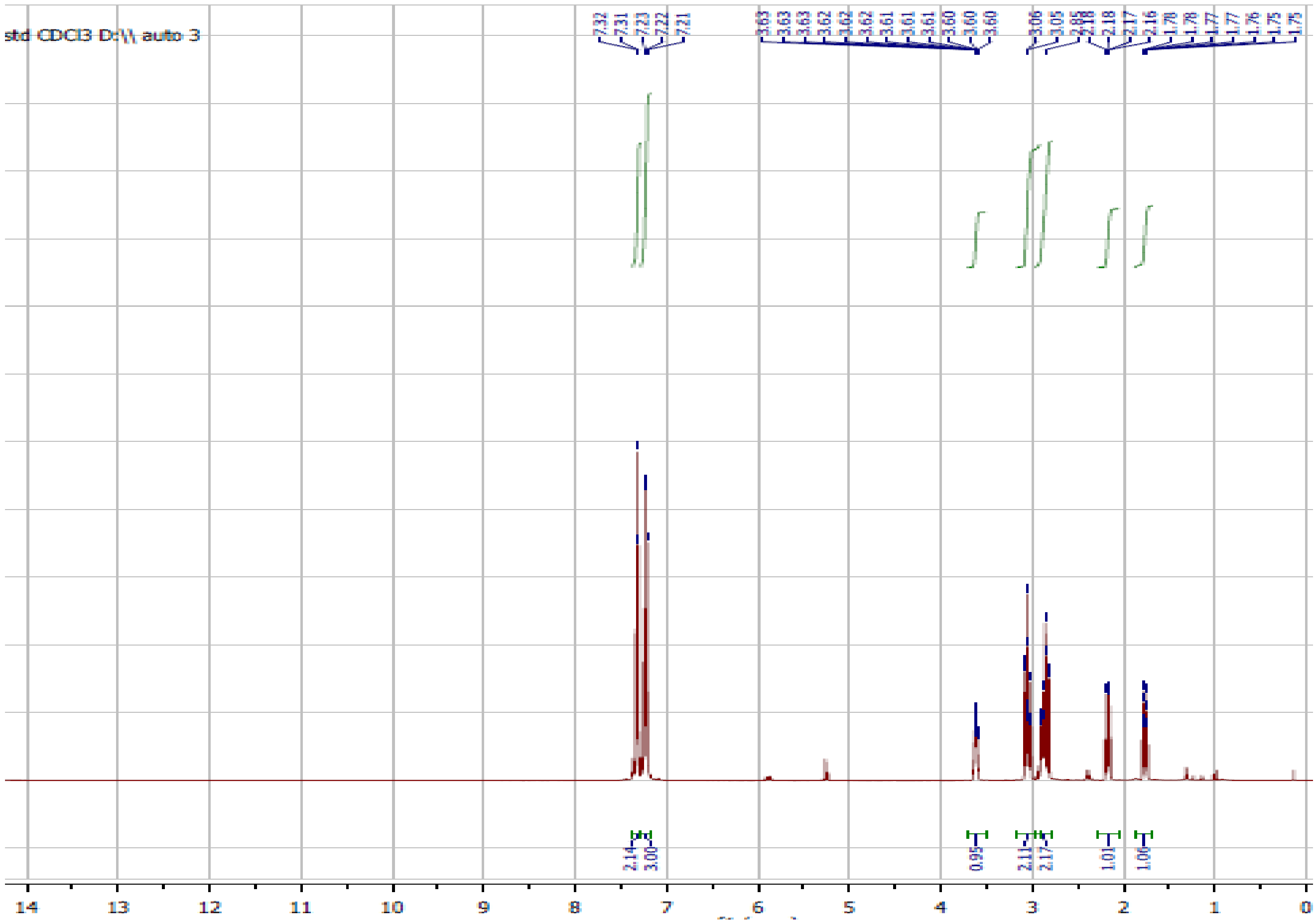


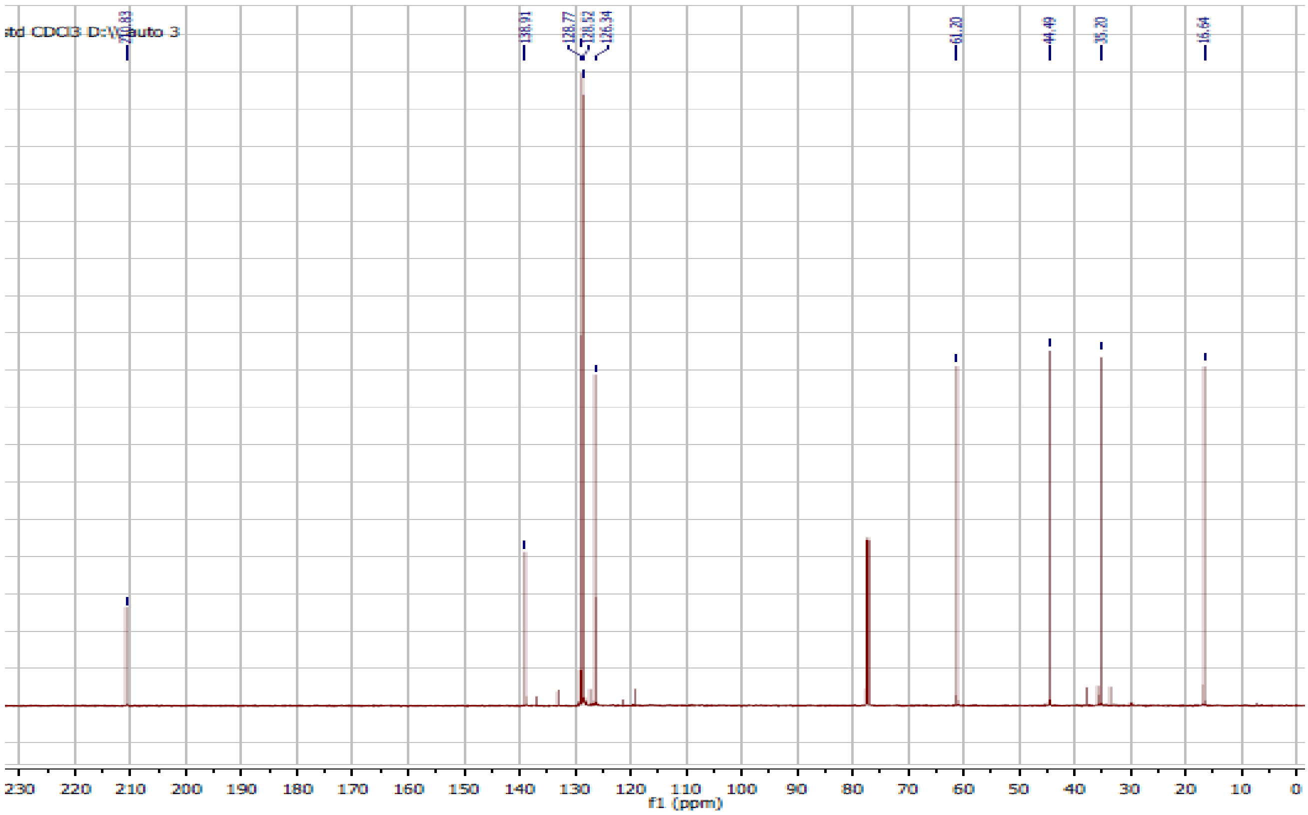
2-(Prop-2-yn-1-yl)cyclobutan-1-one (3p)



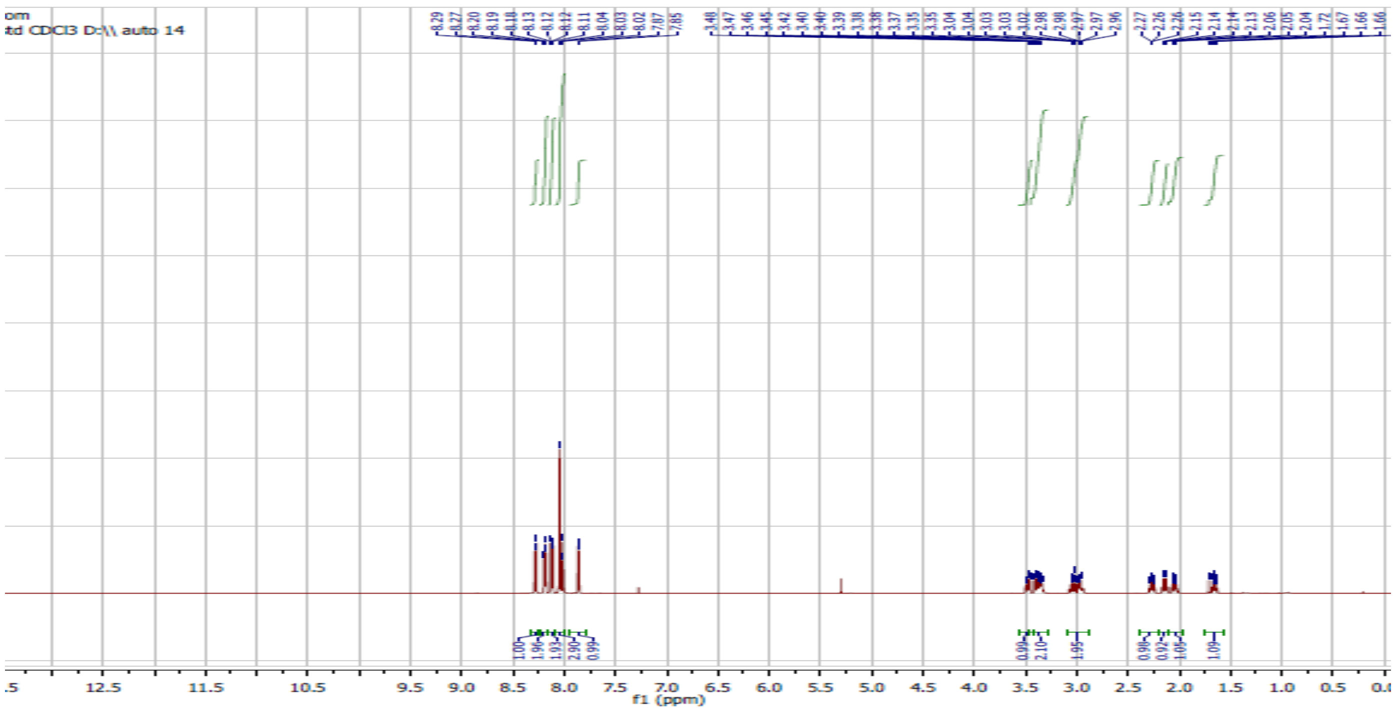


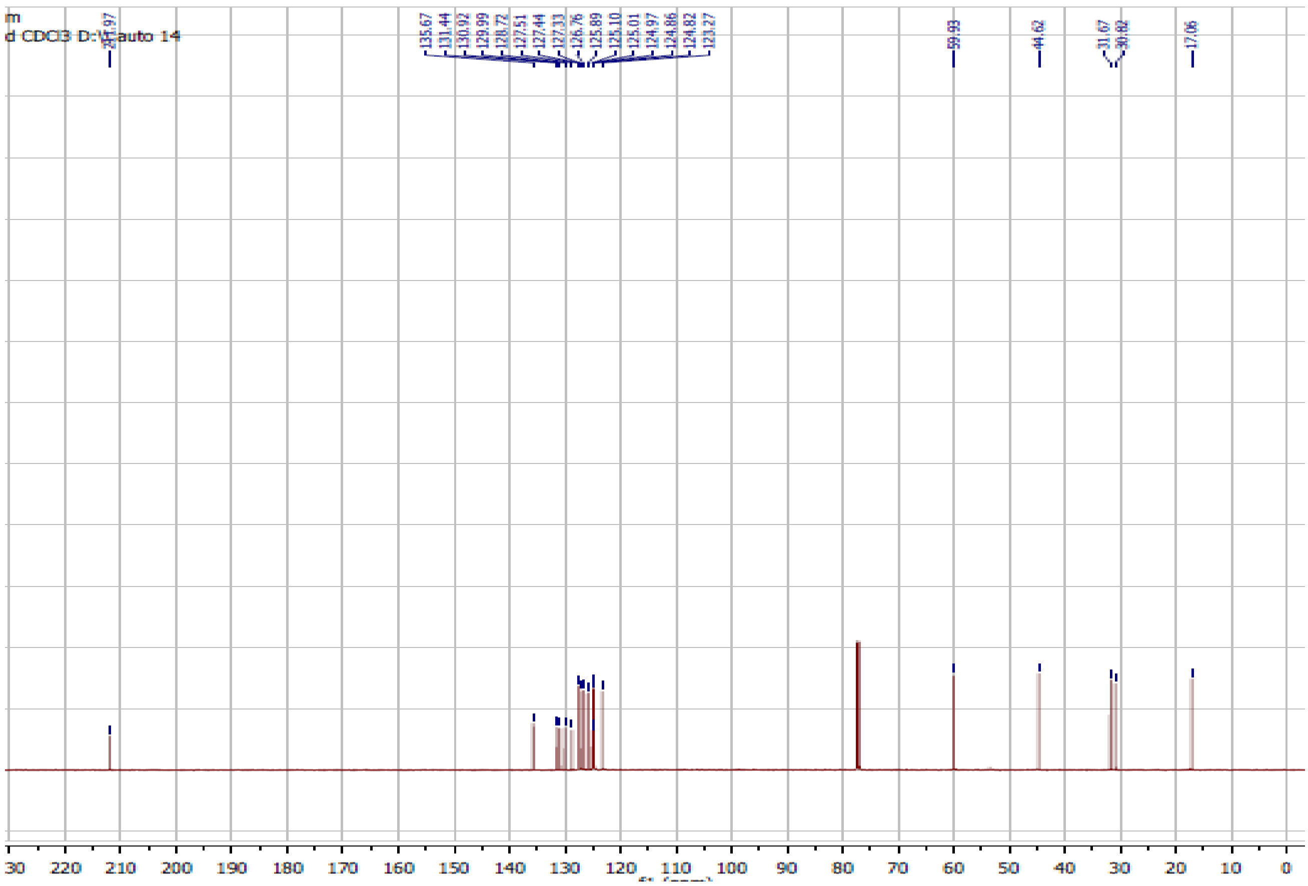
2-Benzylcyclobutan-1-one (3q)





2-(2-(Pyren-2-yl)ethyl)cyclobutan-1-one (3r)


td CDCl3 D:\\ auto 14
f1 (ppm)


d CDCl3 D:\\ auto 14

References

[1] www.vapourtec.co.uk/
[2] Polyzos, A.; O'Brien, M.; Petersen, T. P.; Baxendale, I. R. and Ley, S. V. *Angew. Chem.* **2011**, *123*, 1222-1225; *Angew. Chem. Int. Ed.* **2011**, *50*, 1190-1193.
[3] Superchi S.; Bisaccia R.; Casarini D.; Laurita A.; Rosini C., *J. Am. Chem. Soc.* **2006**, *128*, 6893-6902.
[4] Zaiput technology membrane based liquid-liquid separator, see: http://www.zaiput.com/