Highly Potent, Chemically Stable Quorum Sensing Agonists for *Vibrio Cholerae*

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Supporting Information

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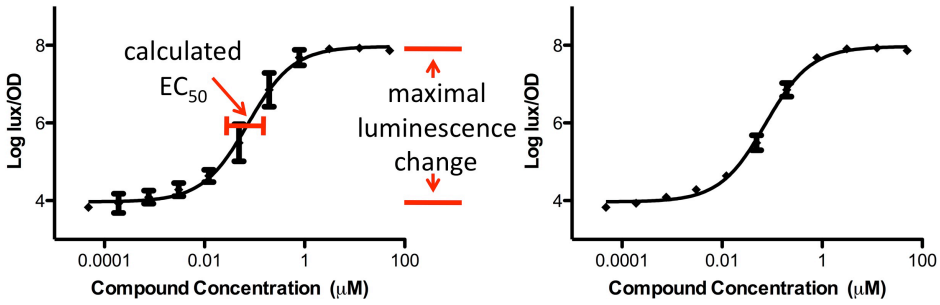
A. Bioassay data for all new compounds.

A.1. *Vibrio cholerae* Agonism Bioassay.

Reporter strain MM920 (*V. cholerae* Δ*cqsA* Δ*luxQ* carrying pBB1 cosmid, which contains the *V. harveyi luxCDABE* luciferase operon) was used to assay agonist activity of each synthetic compound. This strain was grown in LB medium containing 10 μg/mL tetracycline at 30 °C for >16 hours and diluted 20-fold with the same medium. Two μL of each synthetic compound dissolved in DMSO in various concentrations was added to 200 μL of the diluted reporter strain in triplicate in a 96-well plate. Bioluminescence and OD_{600} were measured in a PerkinElmer EnVision Multilabel Reader following 4-hour incubation at 30 °C with shaking. DMSO was used as the negative control.

A.1.1. Example of dose-response curves from bioassay and data extracted.



Above is an example of typical dose response curve highlighting the data that is represented in the Tables presented in the manuscript. Both of the above dose-response curves were generated using GraphPad Prism 5 from the identical primary luminescence measurements.

The dose-response curve on the left displays error bars that represent the 95% confidence intervals for each of the luminescence measurements. The curve on the right displays the standard deviation of the data.

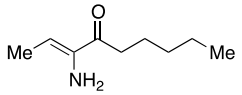
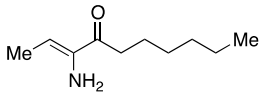
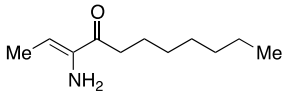
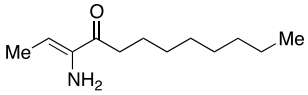
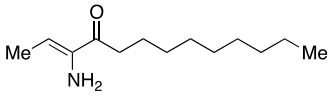
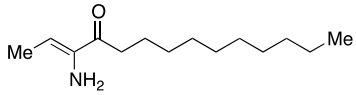
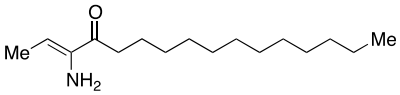
EC_{50} values were calculated by Prism 5 using standard settings and are described in the Tables and text in the manuscript with the error representing the 95% confidence interval for the calculated EC_{50} value.

The values for % response described in the Tables and text in the manuscript describe the maximal luminescence change for each of the analogs as a percent of EaCAI-1 or **18** (set at 100%). One of these molecules was included as a positive standard of activity for each of the assays. The error described within the tables represents the 95% confidence intervals for this data expressed as a percentage. While there is typically little variation in the maximal luminescence at saturation, there is some noise at low concentrations, compare for example the

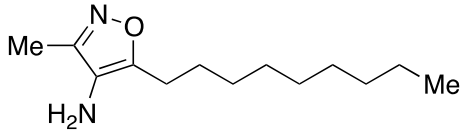
95% confidence intervals for the points of low compound concentration and the points of high concentration on the left.

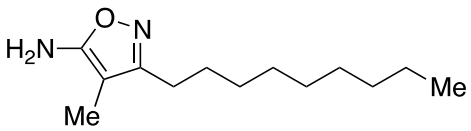
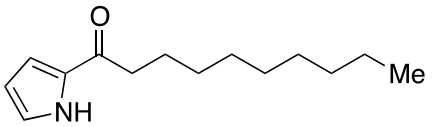
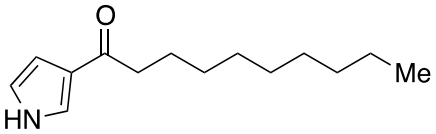
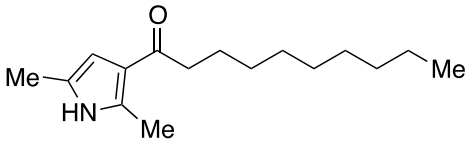
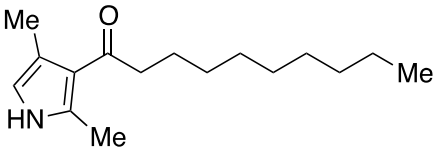
A.2. Complete Bioassay Data and 95% Confidence Intervals for all Compounds.

A.2.1. Tabulated bioassay data for the compounds in Table 1.

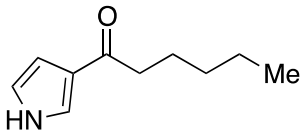
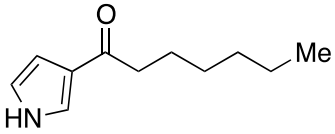
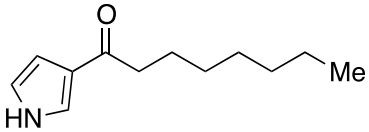
Entry	Compound	*Vibrio cholerae*	
		EC_{50} (nM)[a]	% Response[b]
1	 **6**	594±319	100±57
2	 **7**	286±240	120±117
3	 **8**	40±14.5	109±25
4	 **9**	2.6±0.32	112±7.0
5	 **Ea-CAI1**	4.1±0.45	100±6.6
6	 **10**	169±32	105±11
7	 **11**	>5000	38

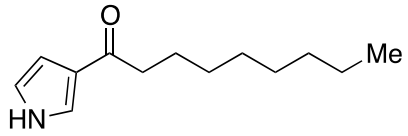
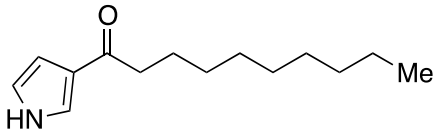
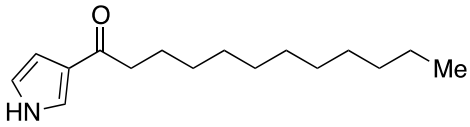
A.2.2. Tabulated bioassay data for the compounds in Scheme 2 and Figure 2.

Entry	Compound	EC_{50} (nM)[a]	% Response[b]
1	 **15**	13,090±5,765	68±52

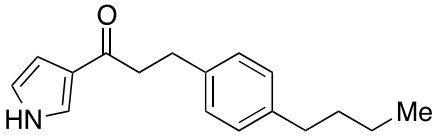
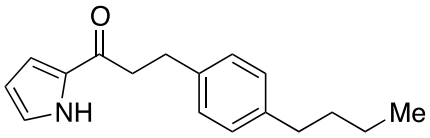
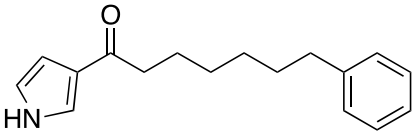
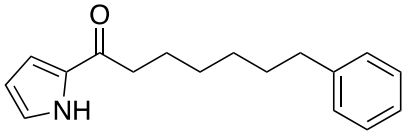
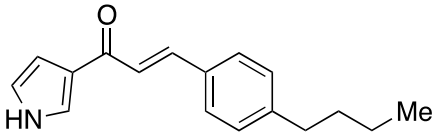
2	 **16**	8,263±4,870	72±56
3	 **17**	5,166±2,174	103±91
4	 **18**	4.2±0.8	107±10
6	 **19**	679±92	66±14
7	 **20**	536±80	65±16

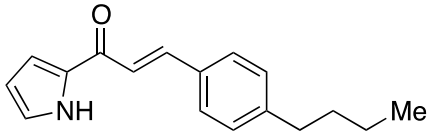
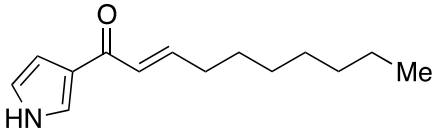
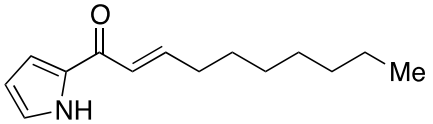
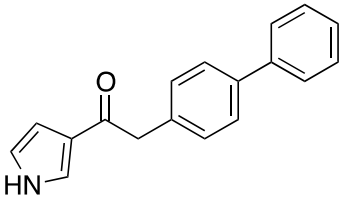
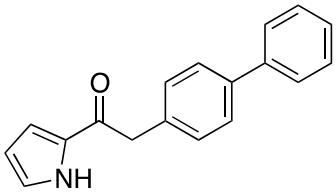
A.2.3. Tabulated bioassay data for the compounds in Table 2.

Entry	Compound	EC_{50} (nM)[a]	% Response[b]
1	 **21**	1152±247	14±50
2	 **22**	737±472	43±42
3	 **23**	51±15	50±15

4	 **24**	8.2±2.0	101±14
5	 **18**	4.2±0.8	107±10
6	 **25**	301±98	29±45

A.2.4. Tabulated bioassay data for the compounds in Figure 3.

Entry	Compound	EC_{50} (nM)[a]	% Response[b]
1	 **26**	10.9±4.8	64±42
2	 **27**	2017±1681	75±45
3	 **28**	35.8±6.1	75±10
4	 **29**	>5000	60
5	 **30**	88.4±24.9	54±29

6	 **31**	731±686	45±62
7	 **32**	3.8±0.4	97±5
8	 **33**	288±92	109±31
9	 **34**	>5000	25
10	 **35**	>5000	26

B. Compound synthesis and tabulated compound data

B.1. General Experimental.

Unless otherwise noted, all reactions were performed in flame-dried glassware under an atmosphere of nitrogen or argon using dried reagents and solvents. All chemicals were purchased from commercial vendors and used without further purification. Anhydrous solvents were purchased from commercial vendors.

Flash chromatography was performed using standard grade silica gel 60 230-400 mesh from SORBENT Technologies. Silica gel was loaded into glass columns as a slurry. Analytical thin-layer chromatography was carried out using Silica G TLC plates, 200 μm with UV_{254} fluorescent indicator (SORBENT Technologies), and visualization was performed by staining and/or by absorbance of UV light.

NMR spectra were recorded using a Bruker Avance II (500 MHz for ^{1}H; 125 MHz for ^{13}C) spectrometer fitted with either a ^{1}H-optimized TCI (H/C/N) cryoprobe or a ^{13}C-optimized dual C/H cryoprobe. Chemical shifts are reported in parts per

million (ppm) and were calibrated according to residual protonated solvent. High-resolution mass spectral analysis was performed using an Agilent 1200-series electrospray ionization – time-of-flight (ESI-TOF) mass spectrometer in the positive ESI mode.

B.2. Compound Synthesis.

(*Z*)-benzyl (1-(methoxy(methyl)amino)-1-oxobut-2-en-2-yl)carbamate, 3a. To a solution of (*Z*)-2-(benzyloxycarbonylamino)but-2-enoic acid[1] (800 mg, 3.4 mmol) in DMF (16.7 mL) at ambient temperature and was treated with HOBt (1.2 g, 9.17 mmol), HNMe(OMe)-HCl (814 mg, 8.3 mmol), EDC (2.4 g, 12.5 mmol), and Et_3N (2.3 mL, 16.7 mmol) sequentially and the mixture was allowed to stir for 10h at ambient temperature. The crude mixture was filtered through a plug of celite and concentrated *in vacuo*. The resulting oil was purified by silica gel chromatography eluting with a gradient from hexanes to 60%EtOAc/hexanes. Fractions containing the desired product were combined and concentrated *in vacuo* to provide (*Z*)-benzyl (1-(methoxy(methyl)amino)-1-oxobut-2-en-2-yl)carbamate (100 mg, 11%). ^{1}H-NMR (500MHz, $CDCl_3$) δ 7.39-7.21 (m, 5H); 6.99 (s, 1H); 5.69 (bs, 1H); 5.05 (s, 2H); 3.62 (s, 3H); 3.22 (s, 3H); 1.66 (d, *J*=7.1Hz, 3H). ^{13}C-NMR (125MHz, $CDCl_3$) δ 167.1, 153.7, 135.9, 128.5, 128.2, 128.2, 128.1, 121.7, 67.1, 60.8, 34.6, 12.5. HRMS (ESI-TOF) 279.1351 $[M+H]^+$ (calculated for $C_{14}H_{19}N_2O_4$ = 279.1345).

(*Z*)-benzyl (4-oxotridec-2-en-3-yl)carbamate, 3. To a solution of (*Z*)-benzyl (1-(methoxy(methyl)amino)-1-oxobut-2-en-2-yl)carbamate (100 mg, 0.359 mmol) in THF (3.6 mL) at 0^{o}C was added nonyl-MgBr (1.0M in Et_2O, 1.8 mL, 1.8 mmol) and the mixture was stirred at 0^{o}C for 5h. The reaction was quenched with sat. NH_4Cl, extracted with Et_2O (3 x 10 mL), the combined organics were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluting with 10% EtOAc/hexanes to 40% EtOAc/hexanes to provide (*Z*)-benzyl (4-oxotridec-2-en-3-yl)carbamate (72 mg, 58%) ^{1}H-NMR (500MHz, $CDCl_3$) δ 7.45-7.29 (m, 5H); 6.66 (s, 1H); 6.57 (q, *J*=7.1Hz, 1H); 5.11 (s, 2H); 2.64 (t, *J*=7.5Hz, 2H); 1.86 (d, *J*=7.1Hz, 3H); 1.56-1.51 (m, 2H); 1.37-1.14 (m, 12H); 0.85 (t, *J*=6.9Hz, 3H). ^{13}C-NMR (125MHz, $CDCl_3$) δ 197.7, 153.9, 136.2, 134.9, 131.4, 128.8, 128.5, 128.4, 67.5, 36.8, 31.9, 29.9, 29.4, 29.3, 25.8, 24.8, 22.8, 15.4, 14.3. HRMS (ESI-TOF) 346.2388 $[M+H]^+$ (calculated for $C_{21}H_{32}NO_3$ = 346.2382).

(*Z*)-2-(trimethylsilyl)ethyl (1-(methoxy(methyl)amino)-1-oxobut-2-en-2-yl)carbamate, 4a. L-Vinylglycine hydrochloride[1] (320 mg, 2.33 mmol) was dissolved in dioxane/H_2O (26 mL, 0.017M, 1:1 dioxane:H_2O) and was treated with $NaHCO_3$ (391 mg, 4.66 mmol) and *N*-[2-(Trimethylsilyl)ethoxycarbonyloxy]succinimide (633 mg, 2.44 mmol) sequentially at room temperature. The resulting mixture was stirred at room temperature for 24h and was then concentrated *in vacuo* to a volume of ca. 10 mL. The resulting solution was acidified with 10% $KHSO_4$ to ~pH6.5, was extracted with DCM (3 x 50 mL), dried over Na_2SO_4 and concentrated to dryness. The resulting oil was

dissolved in THF (23 mL) at ambient temperature and was treated with HOBt (944 mg, 6.99 mmol, 3.0 eq to VGly-HCl), HNMe(OMe)-HCl (341 mg, 3.5 mmol, 1.15 eq to VGly-HCl), EDC (671 mg, 3.5 mmol, 1.15 eq to VGly-HCl), and Et_3N (975 μL, 6.99 mmol, 3.0 eq to VGly-HCl) sequentially and the mixture was allowed to stir for 10h at ambient temperature. The crude mixture was filtered through a plug of celite and concentrated *in vacuo*. The resulting oil was purified by silica gel chromatography eluting with a gradient from hexanes to 60%EtOAc/hexanes. Fractions containing the desired product were combined and concentrated *in vacuo* to provide (*Z*)-2-(trimethylsilyl)ethyl (1-(methoxy(methyl)amino)-1-oxobut-2-en-2-yl)carbamate as a pale yellow oil (280 mg, 42% from VGly-HCl). ^{1}H-NMR (500MHz, $CDCl_3$) δ 6.28 (s, 1H); 5.81-5.68 (m, 1H); 4.19-4.10 (m, 2H); 3.67 (s, 3H); 3.24 (s, 3H); 1.70 (d, *J*=7.0Hz, 3H); 1.03-0.91 (m, 2H); -0.01 (s, 9H). ^{13}C-NMR (125MHz, $CDCl_3$) δ 167.2, 154.2, 130.1, 121.2, 64.1, 61.1, 34.3, 17.8, 12.6, -1.34. HRMS (ESI-TOF) 289.1578 $[M+H]^+$ (calculated for $C_{12}H_{25}N_2O_4Si$ = 289.1584).

(*Z*)-2-(trimethylsilyl)ethyl (4-oxotridec-2-en-3-yl)carbamate, 4. To a solution of (*Z*)-2-(trimethylsilyl)ethyl (1-(methoxy(methyl)amino)-1-oxobut-2-en-2-yl)carbamate (115.3 mg, 0.40 mmol) in THF (4 mL) at 0°C was added nonyl-MgBr (1.0M in Et_2O, 2 mL, 2 mmol) and the mixture was stirred at 0°C for 2 h. The reaction was quenched with 10% $KHSO_4$, extracted with Et_2O (3 x 10 mL), the combined organics were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluting with 10% EtOAc/hexanes to 40% EtOAc/hexanes to provide (*Z*)-2-(trimethylsilyl)ethyl (4-oxotridec-2-en-3-yl)carbamate (132.1 mg, 93%) ^{1}H-NMR (500MHz, $CDCl_3$) δ 6.55 (q, *J*=7.1Hz, 1H); 6.53 (s, 1H); 4.19-4.12 (m, 2H); 2.64 (t, *J*=7.5Hz, 2H); 1.86 (d, *J*=7.1Hz, 3H); 1.64-1.51 (m, 2H); 1.33-1.17 (m, 12H); 0.94-0.86 (m, 2H); 0.85 (t, *J*=7.0Hz, 3H), 0.01 (s, 9H). ^{13}C-NMR (125MHz, $CDCl_3$) δ 197.8, 154.3, 135.1, 131.2, 64.0, 36.8, 32.1, 29.6, 29.6, 29.5, 29.5, 24.8, 22.9, 17.8, 15.3, 14.3, -1.3. HRMS (ESI-TOF) 356.2623 $[M+H]^+$ (calculated for $C_{19}H_{38}NO_3Si$ = 356.2621).

(*Z*)-allyl (1-(methoxy(methyl)amino)-1-oxobut-2-en-2-yl)carbamate, 5a. To a solution of VGly-HCl[1] (284.9 mg, 2.07 mmol) was dissolved in dioxane/H_2O (20 mL, 0.02M, 1:1 dioxane:H_2O) and was treated with $NaHCO_3$ (348 mg, 4.14 mmol) and allyl chloroformate (240 μL, 2.28 mmol) sequentially at room temperature. The resulting mixture was stirred at room temperature for 24 h and was then concentrated *in vacuo* to a volume of ca. 10 mL. The resulting solution was acidified with 10% $KHSO_4$ to ~pH6.5, was extracted with DCM (3 x 50mL), dried over Na_2SO_4 and concentrated to dryness. The resulting oil was dissolved in THF (20.7 mL) at ambient temperature and was treated with HOBt (839 mg, 6.21 mmol), HNMe(OMe)-HCl (232 mg, 2.38 mmol), EDC (456 mg, 2.38 mmol), and Et_3N (1.4 mL, 10.35 mmol) sequentially and the mixture was allowed to stir overnight at ambient temperature. The crude mixture was filtered through a plug of celite and concentrated *in vacuo*. The resulting oil was purified by silica gel chromatography eluting with a gradient from hexanes to 60% EtOAc/hexanes. Fractions containing the desired product were combined and concentrated *in*

vacuo to provide (*Z*)-allyl (1-(methoxy(methyl)amino)-1-oxobut-2-en-2-yl)carbamate as a pale yellow oil (200 mg, 42% from VGly-HCl). ^{1}H-NMR (500MHz, $CDCl_3$) δ 6.29 (s, 1H); 5.97-5.78 (m, 2H); 5.31 (d, *J*=17.3Hz, 1H); 5.22 (d, *J*=10.4Hz, 1H); 4.58 (d, *J*=5.7Hz, 2H); 3.67 (s, 3H); 3.25 (s, 3H); 1.73 (d, *J*=7.1Hz, 3H). ^{13}C-NMR (125MHz, $CDCl_3$) δ 167.1, 153.8, 132.5, 128.1, 118.5, 118.1, 61.2, 60.6, 34.2, 14.4. HRMS (ESI-TOF) 229.1192 $[M+H]^+$ (calculated for $C_{10}H_{17}N_2O_4$ = 229.1188).

(*Z*)-allyl (4-oxotridec-2-en-3-yl)carbamate, 5. To a solution of (*Z*)-allyl (1-(methoxy(methyl)amino)-1-oxobut-2-en-2-yl)carbamate (91.3 mg, 0.40 mmol) in THF (4 mL) at 0^{o}C was added nonyl-MgBr (1.0M in Et_2O, 2 mL, 2 mmol) and the mixture was stirred at 0^{o}C for 2 h. The reaction was quenched with 10% $KHSO_4$, extracted with Et_2O (3 x 10 mL), the combined organics were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluting with 10% EtOAc/hexanes to 40% EtOAc/hexanes to provide (*Z*)-allyl (4-oxotridec-2-en-3-yl)carbamate (98.3 mg, 83%) ^{1}H-NMR (500MHz, $CDCl_3$) δ 6.63 (s, 1H); 6.57 (q, *J*=7.1Hz, 1H); 5.96-5.84 (m, 1H); 5.31 (dd, *J*=17.2, 1.4Hz, 1H); 5.21 (dd, *J*=10.5, 1.3Hz, 1H); 4.57 (d, *J*=5.6Hz, 2H); 2.64 (t, *J*=7.6Hz, 2H); 1.86 (d, *J*=7.1Hz, 3H); 1.65-1.51 (m, 2H); 1.35-1.15 (m, 12H); 0.85 (t, *J*=7.0Hz, 3H). ^{13}C-NMR (125MHz, $CDCl_3$) δ 131.4, 118.2, 66.3, 36.8, 32.1, 29.6, 29.6, 29.5, 29.5, 24.8, 22.9, 15.3, 14.3. HRMS (ESI-TOF) 296.2230 $[M+H]^+$ (calculated for $C_{17}H_{30}NO_3$ = 296.2226).

(*Z*)-allyl (4-oxonon-2-en-3-yl)carbamate, 6a. Prepared in a manner analogous to (*Z*)-allyl (4-oxotridec-2-en-3-yl)carbamate (**5**) from (*Z*)-allyl (1-(methoxy(methyl)amino)-1-oxobut-2-en-2-yl)carbamate and pentyl-MgBr to provide (*Z*)-allyl (4-oxonon-2-en-3-yl)carbamate (21.1 mg, 67%). ^{1}H-NMR (500MHz, $CDCl_3$) δ 6.62 (s, 1H); 6.57 (q, *J*=7.1Hz, 1H); 5.98-5.81 (m, 1H); 5.31 (d, *J*=17.2Hz, 1H); 5.21 (d, *J*=11.6Hz, 1H); 4.57 (d, *J*=5.6Hz, 2H); 2.65 (t, *J*=7.51Hz, 2H); 1.86 (d, *J*=7.1Hz, 3H); 1.68-1.51 (m, 2H); 1.34-1.15 (m, 4H); 0.86 (t, *J*=6.9Hz, 3H). ^{13}C-NMR (125MHz, $CDCl_3$) δ 197.7, 153.8, 134.9, 132.6, 131.5, 118.3, 66.3, 36.7, 31.7, 24.5, 22.7, 15.3, 14.2. HRMS (ESI-TOF) 240.1602 $[M+H]^+$ (calculated for $C_{13}H_{22}NO_3$ = 240.1600).

(*Z*)-allyl (4-oxodec-2-en-3-yl)carbamate, 7a. Prepared in a manner analogous to (*Z*)-allyl (4-oxotridec-2-en-3-yl)carbamate (**5**) from (*Z*)-allyl (1-(methoxy(methyl)amino)-1-oxobut-2-en-2-yl)carbamate and hexyl-MgBr to provide (*Z*)-allyl (4-oxodec-2-en-3-yl)carbamate (27 mg, 81%). ^{1}H-NMR (500MHz, $CDCl_3$) δ 6.63 (s, 1H); 6.56 (q, *J*=7.1Hz, 1H); 5.96-5.83 (m, 1H); 5.30 (d, *J*=17.2Hz, 1H); 5.21 (d, *J*=11.6Hz, 1H); 4.56 (d, *J*=5.6Hz, 2H); 2.64 (t, *J*=7.6Hz, 2H); 1.85 (d, *J*=7.1Hz, 3H); 1.64-1.48 (m, 2H); 1.35-1.16 (m, 6H); 0.85 (t, *J*=6.9Hz, 3H). ^{13}C-NMR (125MHz, $CDCl_3$) δ 197.4, 153.9, 134.8, 132.6, 131.5, 118.3, 66.2, 36.8, 32.0, 29.3, 24.8, 22.8, 15.4, 14.3. HRMS (ESI-TOF) 254.1756 $[M+H]^+$ (calculated for $C_{14}H_{24}NO_3$ = 254.1756).

(*Z*)-allyl (4-oxoundec-2-en-3-yl)carbamate, 8a. Prepared in a manner analogous to (*Z*)-allyl (4-oxotridec-2-en-3-yl)carbamate (**5**) from (*Z*)-allyl (1-(methoxy(methyl)amino)-1-oxobut-2-en-2-yl)carbamate and heptyl-MgBr to provide (*Z*)-allyl (4-oxoundec-2-en-3-yl)carbamate (26.6 mg, 76%). ^{1}H-NMR (500MHz, $CDCl_3$) δ 6.64 (s, 1H); 6.56 (q, *J*=7.1Hz, 1H); 5.96-5.83 (m, 1H); 5.30 (d, *J*=18.2Hz, 1H); 5.20 (d, *J*=10.4Hz, 1H); 4.56 (d, *J*=5.6Hz, 2H); 2.64 (t, *J*=7.5Hz, 2H); 1.85 (d, *J*=7.5Hz, 3H); 1.63-1.48 (m, 2H); 1.36-1.15 (m, 8H); 0.84 (t, *J*=6.8Hz, 3H). ^{13}C-NMR (125MHz, $CDCl_3$) δ 197.1, 153.8, 134.9, 132.6, 131.5, 118.3, 66.3, 36.8, 31.9, 29.5, 29.3, 24.8, 22.8, 15.4, 14.3. HRMS (ESI-TOF) 268.1913 $[M+H]^+$ (calculated for $C_{15}H_{26}NO_3$ = 268.1913).

(*Z*)-allyl (4-oxododec-2-en-3-yl)carbamate, 9a. Prepared in a manner analogous to (*Z*)-allyl (4-oxotridec-2-en-3-yl)carbamate (**5**) from (*Z*)-allyl (1-(methoxy(methyl)amino)-1-oxobut-2-en-2-yl)carbamate and octyl-MgBr to provide (*Z*)-allyl (4-oxododec-2-en-3-yl)carbamate (27.9 mg, 78%). ^{1}H-NMR (500MHz, $CDCl_3$) δ 6.64 (s, 1H); 6.57 (q, *J*=7.1Hz, 1H); 5.96-5.85 (m, 1H); 5.31 (d, *J*=17.2Hz, 1H); 5.21 (d, *J*=10.4Hz, 1H); 4.57 (d, *J*=5.6Hz, 2H); 2.65 (t, *J*=7.5Hz, 2H); 1.86 (d, *J*=7.1Hz, 3H); 1.60-1.48 (m, 2H); 1.38-1.18 (m, 10H); 0.85 (t, *J*=6.8Hz, 3H). ^{13}C-NMR (125MHz, $CDCl_3$) δ 197.7, 153.8, 134.9, 132.6, 131.5, 118.3, 63.3, 32.9, 32.0, 29.6, 29.5, 25.9, 24.8, 22.9, 15.4, 14.3. HRMS (ESI-TOF) 282.2065 $[M+H]^+$ (calculated for $C_{16}H_{28}NO_3$ = 282.2069).

(*Z*)-allyl (4-oxotetradec-2-en-3-yl)carbamate, 10a. Prepared in a manner analogous to (*Z*)-allyl (4-oxotridec-2-en-3-yl)carbamate (**5**) from (*Z*)-allyl (1-(methoxy(methyl)amino)-1-oxobut-2-en-2-yl)carbamate and decyl-MgBr to provide (*Z*)-allyl (4-oxotetradec-2-en-3-yl)carbamate (12.9 mg, 32%). ^{1}H-NMR (500MHz, $CDCl_3$) δ 6.64 (s, 1H); 6.57 (q, *J*=7.1Hz, 1H); 5.97-5.84 (m, 1H); 5.31 (dd, *J*=17.2, 1.4Hz, 1H); 5.21 (dd, *J*=10.4, 1.2Hz, 1H); 4.57 (d, *J*=5.6Hz, 2H); 2.65 (t, *J*=7.5Hz, 2H); 1.86 (d, *J*=7.1Hz, 3H); 1.66-1.50 (m, 2H); 1.37-1.16 (m, 14H); 0.85 (t, *J*=6.9Hz, 3H). ^{13}C-NMR (125MHz, $CDCl_3$) δ 197.7, 153.8, 134.9, 132.6, 131.5, 118.2, 63.3, 37.6, 32.9, 32.1, 29.8, 29.8, 29.6, 29.5, 25.9, 22.9, 15.3, 14.3. HRMS (ESI-TOF) 310.2378 $[M+H]^+$ (calculated for $C_{18}H_{32}NO_3$ = 310.2382).

(*Z*)-allyl (4-oxohexadec-2-en-3-yl)carbamate, 11a. Prepared in a manner analogous to (*Z*)-allyl (4-oxotridec-2-en-3-yl)carbamate (**5**) from (*Z*)-allyl (1-(methoxy(methyl)amino)-1-oxobut-2-en-2-yl)carbamate and dodecyl-MgBr to provide (*Z*)-allyl (4-oxohexadec-2-en-3-yl)carbamate (28.9 mg, 65%). ^{1}H-NMR (500MHz, $CDCl_3$) δ 6.63 (s, 1H); 6.57 (q, *J*=7.1Hz, 1H); 5.97-5.85 (m, 1H); 5.31 (d, *J*=17.2Hz, 1H); 5.21 (d, *J*=10.4Hz, 1H); 4.57 (d, *J*=5.6Hz, 2H); 2.65 (t, *J*=7.5Hz, 2H); 1.86 (d, *J*=7.1Hz, 3H); 1.66-1.51 (m, 2H); 1.36-1.15 (m, 18H); 0.85 (t, *J*=6.9Hz, 3H). ^{13}C-NMR (125MHz, $CDCl_3$) δ 197.7, 153.8, 134.9, 132.6, 131.4, 118.2, 63.3, 36.8, 33.0, 32.1, 29.9, 29.9, 29.8, 29.8, 29.6, 29.6, 24.8, 22.9, 15.4, 14.3. HRMS (ESI-TOF) 338.2696 $[M+H]^+$ (calculated for $C_{20}H_{36}NO_3$ = 338.2695).

(*Z*)-3-aminotridec-2-en-4-one, Ea-CAI1. To a solution of (*Z*)-allyl (4-oxotridec-2-en-3-yl)carbamate (**5**) (8.6 mg, 0.029 mmol) in THF (300 μL) was added Et_2NH

(45 μL, 0.435 mmol) followed by $Pd(PPh_3)_4$ (5.1 mg, 0.0044mmol) and the mixture was allowed to stir at room temperature for 4 h in a flask shielded from light. The mixture was diluted with heptane (~1.5 mL) and concentrated to remove the THF. The remaining solution (~1 mL) was loaded onto a short plug of SiO_2 pre-equilibrated in hexane containing 1% Et_3N. The product was eluted with one column volume of hexane (1% Et_3N), 2 column volumes of 4:1 hexane:CH_2Cl_2 (1% Et_3N), 2 column volumes of 1:1 hexane:CH_2Cl_2 (1% Et_3N), 2 column volumes of 1:4 hexane:CH_2Cl_2 (1% Et_3N) and 1 column volume of CH_2Cl_2 (1% Et_3N). Fractions containing the desired product (R_f~0.4, 20% EtOAc/hexane, CAM stain) were combined to provide (*Z*)-3-aminotridec-2-en-4-one (2.9 mg, 47%) The product was typically immediately dissolved in anhydrous DMSO and was stored frozen. ^{1}H-NMR (500MHz, d6-DMSO) δ 5.53 (q, *J*=7.1 Hz, 1H); 4.31 (s, 2H); 2.60 (t, *J*=7.4 Hz, 2H); 1.65 (d, *J*= 7.1 Hz, 3H); 1.51-1.43 (m, 2H); 1.29-1.16 (m, 12H); 0.85 (t, *J*=6.8 Hz, 3H). ^{13}C-NMR (125MHz, d6-DMSO) δ 197.1, 141.8, 106.7, 35.2, 31.3, 29.0, 28.9, 28.7 (2C), 25.0, 22.2, 14.0, 12.1. HRMS (ESI-TOF) 212.2010 $[M+H]^+$ (calculated for $C_{13}H_{26}NO$ = 212.2014).

(*Z*)-3-aminonon-2-en-4-one, 6. Prepared in an analogous manner to (*Z*)-3-aminotridec-2-en-4-one (**Ea-CAI1**) from (*Z*)-allyl (4-oxonon-2-en-3-yl)carbamate to provide (*Z*)-3-aminonon-2-en-4-one (4.7 mg, 66%). ^{1}H-NMR (500MHz, d6-DMSO) δ 5.53 (q, *J*=7.1 Hz, 1H); 4.31 (s, 2H); 2.61 (t, *J*=7.4 Hz, 2H); 1.65 (d, *J*= 7.1 Hz, 3H); 1.48 (pentet, *J*=7.4 Hz, 2H); 1.33-1.14 (m, 4H); 0.85 (t, *J*=7.1 Hz, 3H). ^{13}C-NMR (125MHz, d6-DMSO) δ 197.1, 141.8, 106.7, 35.1, 30.9, 24.7, 22.0, 13.9, 12.1. HRMS (ESI-TOF) 156.1386 $[M+H]^+$ (calculated for $C_9H_{18}NO$ = 156.1388).

(*Z*)-3-aminodec-2-en-4-one, 7. Prepared in an analogous manner to (*Z*)-3-aminotridec-2-en-4-one (**Ea-CAI1**) from (*Z*)-allyl (4-oxodec-2-en-3-yl)carbamate to provide (*Z*)-3-aminodec-2-en-4-one (5.9 mg, 66%). ^{1}H-NMR (500MHz, d6-DMSO) δ 5.53 (q, *J*=7.1 Hz, 1H); 4.31 (s, 2H); 2.61 (t, *J*=7.4 Hz, 2H); 1.65 (d, *J*= 7.1 Hz, 3H); 1.52-1.44 (m, 2H); 1.31-1.18 (m, 6H); 0.85 (t, *J*=6.8 Hz, 3H). ^{13}C-NMR (125MHz, d6-DMSO) δ 197.1, 141.8, 106.7, 35.1, 31.2, 28.4, 25.0, 22.1, 14.0, 12.1. HRMS (ESI-TOF) 170.1539 $[M+H]^+$ (calculated for $C_{10}H_{20}NO$ = 170.1545).

(*Z*)-3-aminoundec-2-en-4-one, 8. Prepared in an analogous manner to (*Z*)-3-aminotridec-2-en-4-one (**Ea-CAI1**) from (*Z*)-allyl (4-oxoundec-2-en-3-yl)carbamate to provide (*Z*)-3-aminoundec-2-en-4-one (3.9 mg, 34%). ^{1}H-NMR (500MHz, d6-DMSO) δ 5.53 (q, *J*=7.1 Hz, 1H); 4.31 (s, 2H); 2.61 (t, *J*=7.4 Hz, 2H); 1.65 (d, *J*= 7.1 Hz, 3H); 1.51-1.43 (m, 2H); 1.30-1.18 (m, 8H); 0.85 (t, *J*=6.9 Hz, 3H). ^{13}C-NMR (125MHz, d6-DMSO) δ 197.1, 141.8, 106.7, 35.2, 31.2, 28.7, 28.6, 25.0, 22.1, 14.0, 12.1. HRMS (ESI-TOF) 184.1699 $[M+H]^+$ (calculated for $C_{11}H_{22}NO$ = 184.1701).

(*Z*)-3-aminododec-2-en-4-one, 9. Prepared in an analogous manner to (*Z*)-3-aminotridec-2-en-4-one (**Ea-CAI1**) from (*Z*)-allyl (4-oxododec-2-en-3-yl)carbamate to provide (*Z*)-3-aminododec-2-en-4-one (2.8 mg, 59%). ^{1}H-NMR

(500MHz, d6-DMSO) δ 5.53 (q, *J*=7.1 Hz, 1H); 4.31 (s, 2H); 2.61 (t, *J*=7.4 Hz, 2H); 1.65 (d, *J*= 7.1 Hz, 3H); 1.52-1.43 (m, 2H); 1.32-1.16 (m, 10H); 0.85 (t, *J*=6.8 Hz, 3H). ^{13}C-NMR (125MHz, d6-DMSO) δ 197.1, 141.8, 106.7, 35.2, 31.3, 28.9, 28.7, 28.7, 25.0, 22.1, 14.0, 12.1. HRMS (ESI-TOF) 198.1853 $[M+H]^+$ (calculated for $C_{12}H_{24}NO$ = 198.1858).

(*Z*)-3-aminotetradec-2-en-4-one, 10. Prepared in an analogous manner to (*Z*)-3-aminotridec-2-en-4-one (**Ea-CAI1**) from (*Z*)-allyl (4-oxotetradec-2-en-3-yl)carbamate to provide (*Z*)-3-aminotetradec-2-en-4-one (4.4 mg, 51%). ^{1}H-NMR (500MHz, d6-DMSO) δ 5.53 (q, *J*=7.1 Hz, 1H); 4.30 (s, 2H); 2.60 (t, *J*=7.4 Hz, 2H); 1.65 (d, *J*= 7.1 Hz, 3H); 1.53-1.43 (m, 2H); 1.36-1.14 (m, 14H); 0.85 (t, *J*=6.8 Hz, 3H). ^{13}C-NMR (125MHz, d6-DMSO) δ 197.1, 141.8, 106.7, 35.2, 31.3, 29.0, 28.9, 28.8, 28.8, 28.7, 25.0, 22.2, 14.0, 12.1. HRMS (ESI-TOF) 226.2166 $[M+H]^+$ (calculated for $C_{14}H_{28}NO$ = 226.2171).

(*Z*)-3-aminohexadec-2-en-4-one, 11. Prepared in an analogous manner to (*Z*)-3-aminotridec-2-en-4-one (**Ea-CAI1**) from (*Z*)-allyl (4-oxohexadec-2-en-3-yl)carbamate to provide (*Z*)-3-aminohexadec-2-en-4-one (7.5 mg, 67%). ^{1}H-NMR (500MHz, d6-DMSO) δ 5.52 (q, *J*=7.1 Hz, 1H); 4.31 (s, 2H); 2.60 (t, *J*=7.4 Hz, 2H); 1.65 (d, *J*= 7.1 Hz, 3H); 1.53-1.43 (m, 2H); 1.33-1.15 (m, 18H); 0.85 (t, *J*=6.8 Hz, 3H). ^{13}C-NMR (125MHz, d6-DMSO) δ 197.1, 141.8, 106.7, 35.2, 31.4, 29.2, 29.1, 29.0, 29.0, 28.9, 28.8, 28.7, 25.0, 22.2, 14.0, 12.1. HRMS (ESI-TOF) 254.2481 $[M+H]^+$ (calculated for $C_{16}H_{32}NO$ = 254.2484).

***tert*-butyl (2-oxoundecyl)carbonate.** Prepared using a modification of a reported procedure.[2] To a solution of *tert*-Butyl (2-(methoxy(methyl)amino)-2-oxoethyl)carbamate (500 mg, 2.29mmol) in THF (23 mL) at 0°C was added nonyl-MgBr (1.0M in Et_2O, 11.5 mL, 11.5 mmol) and the mixture was allowed to stir at 0°C for 4 h. The mixture was quenched with sat. NH_4Cl (50 mL), extract with Et_2O (2 x 50 mL), dry over Na_2SO_4 and concentrate *in vacuo*. The mixture was purified by silica gel chromatography (20% to 40% EtOAc/hexanes) to provide *tert*-butyl (2-oxoundecyl)carbonate as a clear colorless oil (510 mg, 78%). ^{1}H-NMR (500MHz, $CDCl_3$) δ 5.22 (s, 1H); 4.00 (d, *J*=4.7Hz, 1H); 3.62 (m, 1H); 2.39 (t, *J*=7.5Hz, 2H); 1.63-1.50 (m, 2H); 1.39 (s, 9H); 1.36-1.17 (m, 12H); 0.85 (t, *J*=7.0Hz, 3H). ^{13}C-NMR (125MHz, $CDCl_3$) δ 206.2, 155.8, 79.9, 50.4, 40.3, 32.1, 29.5, 29.5, 29.5, 29.4, 28.5, 23.9, 22.9, 14.3.

3-methyl-5-nonylisoxazol-4-amine, 15. To a solution of acetaldehyde oxime (1 g, 16.9 mmol) in DMF (34 mL) at room temperature was added *N*-chloro succinimide (2.9 g, 21.9 mmol) and the mixture was allowed to stir for 3.5 h. The reaction was quenched with H_2O (40 mL), extracted with EtOAc (3 x 40 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield *N*-hydroxyacetimidoyl chloride as a clear, colorless oil that was used without further purification. To *tert*-butyl (2-oxoundecyl)carbonate (510 mg, 1.78 mmol) in THF (3.6 mL) at –78°C was added *tert*-butyl lithium (1.7M in pentane, 2.1 mL, 3.56 mmol). The resulting mixture was allowed to stir at –78°C for 20 min and was treated with the above prepared *N*-hydroxyacetimidoyl chloride (166.4 mg, 1.78

mmol) as a solution in THF (1.8 mL). The resulting mixture was allowed to warm slowly to room temperature and was stirred at room temperature overnight. The reaction was quenched with sat. NH_4Cl (10 mL), extracted with Et_2O (3 x 10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue (300 mg) was dissolved in CH_2Cl_2 (9.3 mL) and H_2O (140 μL) at room temperature and was treated with TFA (700 μL, 9.25 mmol). The mixture was allowed to stir overnight, was concentrated to dryness and the residue was purified by silica gel chromatography (40% EtOAc/hexanes to 100% EtOAc) to yield 3-methyl-5-nonylisoxazol-4-amine as a yellow solid (48 mg, 12% over two steps). ^{1}H-NMR (500MHz, $CDCl_3$) δ 8.18 (bs, 2H); 2.72 (t, *J*= 7.6 Hz, 2H); 2.25 (s, 3H); 1.69-1.55 (m, 2H); 1.34-1.15 (m,12H); 0.86 (t, *J*= 6.9 Hz, 3H). ^{13}C-NMR (125MHz, $CDCl_3$) δ 165.1, 155.2, 111.0, 32.0, 29.5, 29.4, 29.3, 29.3, 27.2, 25.0, 22.8, 14.2, 9.1. HRMS (ESI-TOF) 225.1961 $[M+H]^+$ (calculated for $C_{13}H_{25}N_2O$ = 225.1967).

4-methyl-3-nonylisoxazol-5-amine, 16. To a solution of decanal oxime[3] (2 g, 11.67 mmol) in CH_2Cl_2 (58 mL) at room temperature was added benzyltrimethylammonium tetrachloroiodate (4.89 g, 11.67 mmol) and the mixture was allowed to stir for 1 h before dilution with Et_2O (280 mL). The resulting precipitate was removed by filtration and the filtrate was concentrated to dryness to provide *N*-hydroxydecanimidoyl chloride which was used without further purification. To propionitrile (1.22 mL, 17.49 mmol) in THF (35 mL) at -78 ^{o}C was added *tert*-butyl lithium (1.7M in pentane, 10.3 mL, 17.5 mmol) and the mixture was allowed to react at -78 ^{o}C for 40 min before the addition of a solution of *N*-hydroxydecanimidoyl chloride (1.0M solution in Et_2O, 5.83 mL). The mixture was allowed to stir at -78 ^{o}C for 4 h. The reaction was quenched with sat. NH_4Cl (70 mL), extracted with Et_2O (3 x 70 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel chromatography (40% EtOAc/hexanes to 100% EtOAc) to yield 4-methyl-3-nonylisoxazol-5-amine as a white solid (116 mg, 9% over two steps). ^{1}H-NMR (500MHz, $CDCl_3$) δ 4.16-4.05 (m, 2H); 2.47 (t, *J*= 7.9 Hz, 2H); 1.76 (s, 3H); 1.66-1.54 (m, 2H); 1.41-1.17 (m, 12H); 0.87 (t, *J*= 6.8 Hz, 3H). ^{13}C-NMR (125MHz, $CDCl_3$) δ 165.1, 164.5, 87.5, 32.0, 29.6, 29.5, 29.5, 27.6, 25.7, 22.8, 21.2, 14.3, 6.2. HRMS (ESI-TOF) 225.1966 $[M+H]^+$ (calculated for $C_{13}H_{25}N_2O$ = 225.1967).

General Proceedure A. Synthesis of Acylated Pyrrole Analogs (Compounds 17, 18 and 21-35). To a solution of the pyrrole (1.0 eq) in Et_2O (1.4M) was added MeMgBr (1.0 eq) and the mixture is stirred at reflux for 30 minutes before cooling to 0 ^{o}C. The cooled solution is treated with the appropriate acid chloride (1.0 eq) as a solution in PhMe (1.0M) and the mixture is allowed to warm slowly to room temperature and stirred overnight. The reaction is quenched with sat. NH_4Cl (double reaction volume), extracted with Et_2O (3 x double reaction volume), dried over Na_2SO_4 and concentrated *in vacuo* before purification by silica gel chromatography. Both regioisomers of the acylated pyrrole are readily accessible in this manner. The 3-acylated pyrrole analogs typically eluted after the 2-acylated analogs.

1-(1*H*-pyrrol-2-yl)decan-1-one, 17. Prepared according to general procedure A to provide 1-(1*H*-pyrrol-2-yl)decan-1-one as an off-white solid (1.8 g, 28%). ^{1}H-NMR (500MHz, $CDCl_3$) δ 10.5 (s, 1H); 7.04 (s, 1H); 6.92 (s, 1H); 6.25 (s, 1H); 2.76 (t, *J*=7.5Hz, 2H); 1.80-1.65 (m, 2H); 1.45-1.14 (m, 12H); 0.86 (t, *J*=6.8Hz, 3H). ^{13}C-NMR (125MHz, $CDCl_3$) δ 191.8, 132.1, 125.3, 116.7, 110.5, 38.2, 32.0, 29.6, 29.5, 25.6, 22.8, 14.3. HRMS (ESI-TOF) 222.1852 $[M+H]^+$ (calculated for $C_{14}H_{24}NO$ = 222.1858).

1-(1*H*-pyrrol-3-yl)decan-1-one, 18. Prepared according to general procedure A to provide 1-(1*H*-pyrrol-2-yl)decan-1-one as an off-white solid (1.3 g, 20%). ^{1}H-NMR (500MHz, $CDCl_3$) δ 9.32 (s, 1H); 7.41 (s, 1H); 6.76 (s, 1H); 6.63 (s, 1H); 2.73 (t, *J*=7.6Hz, 2H); 1.75-1.62 (m, 2H); 1.39-1.12 (m, 12H); 0.85 (t, *J*=6.8Hz, 3H). ^{13}C-NMR (125MHz, $CDCl_3$) δ 197.7, 126.0, 123.6, 119.8, 108.8, 40.0, 32.1, 29.7, 29.7, 29.5, 25.4, 22.9, 14.3. HRMS (ESI-TOF) 222.1854 $[M+H]^+$ (calculated for $C_{14}H_{24}NO$ = 222.1858).

1-(2,5-dimethyl-1*H*-pyrrol-3-yl)decan-1-one, 19. To a solution of 2,5-dimethyl pyrrole (500 μL, 4.91mmol) in CH_2Cl_2 (5 mL) at 0 ^{o}C was added decanoyl chloride (1.0 mL, 4.91mmol). Aluminum (III) chloride (654.7 mg, 4.91 mmol) was added portion wise to the resulting solution and the mixture was allowed to stir at 0 ^{o}C for 1 h. The mixture was quenched by the addition of sat. $NaHCO_3$ (10 mL), extracted with CH_2Cl_2 (3 x 10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel chromatography (hexanes to 40%EtOAc/hexane) to provide 1-(2,5-dimethyl-1*H*-pyrrol-3-yl)decan-1-one (153 mg, 13%). ^{1}H-NMR (500MHz, $CDCl_3$) δ 7.90 (s, 1H); 6.17 (s, 1H); 2.68 (t, *J*= 7.6 Hz, 2H); 2.51 (s, 3H); 2.22 (s, 3H); 1.71-1.59 (m, 2H); 1.39-1.18 (m, 12H); 0.87 (t, *J* = 6.8 Hz, 3H). ^{13}C-NMR (125MHz, $CDCl_3$) δ 198.0, 134.0, 125.4, 120.6, 107.6, 40.6, 31.9, 29.7, 29.7, 29.7, 29.5, 24.9, 22.7, 14.3, 14.1, 12.8. HRMS (ESI-TOF) 250.2161 $[M+H]^+$ (calculated for $C_{16}H_{28}NO$ = 250.2171).

1(2,4-dimethyl-1*H*-pyrrol-3-yl)decan-1-one, 20. To a solution of 2,4-dimethyl pyrrole (500 μL, 4.91 mmol) in CH_2Cl_2 (5 mL) at 0 ^{o}C was added decanoyl chloride (1.0 mL, 4.91 mmol). Aluminum (III) chloride (654.7 mg, 4.91 mmol) was added portion wise to the resulting solution and the mixture was allowed to stir at 0 ^{o}C for 1 h. The mixture was quenched by the addition of sat. $NaHCO_3$ (10 mL), extracted with CH_2Cl_2 (3 x 10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel chromatography (hexanes to 40% EtOAc/hexane) to provide 1-(2,4-dimethyl-1*H*-pyrrol-3-yl)decan-1-one as an off white solid (82 mg, 7%). ^{1}H-NMR (500MHz, $CDCl_3$) δ 7.85 (s, 1H); 6.17 (s, 1H); 2.68 (t, *J*= 7.5 Hz, 2H); 2.51 (s, 3H); 2.22 (s, 3H); 1.72-1.60 (m, 2H); 1.39-1.18 (m, 12H); 0.87 (t, *J*= 6.7 Hz, 3H). ^{13}C-NMR (125MHz, $CDCl_3$) δ 197.9, 134.0, 125.3, 120.6, 107.6, 40.6, 32.0, 29.7, 29.7, 29.7, 29.5, 24.9, 22.7, 14.3, 14.1, 12.8. HRMS (ESI-TOF) 250.2160 $[M+H]^+$ (calculated for $C_{16}H_{28}NO$ = 250.2171).

1-(1*H*-pyrrol-3-yl)hexan-1-one, 21. Prepared according to general procedure A to provide 1-(1*H*-pyrrol-3-yl)hexan-1-one as an off-white solid (387 mg, 16%). ^{1}H-NMR (500MHz, $CDCl_3$) δ 8.55 (s, 1H); 7.41 (s, 1H); 6.76 (s, 1H); 6.65 (s, 1H);

2.73 (t, *J*=7.6Hz, 2H); 1.76-1.64 (m, 2H); 1.38-1.28 (m, 4H); 0.87 (t, *J*=6.7Hz, 3H). ^{13}C-NMR (125MHz, $CDCl_3$) δ 197.0, 126.3, 123.0, 119.4, 109.1, 40.0, 31.9, 24.9, 22.8, 14.2. HRMS (ESI-TOF) 166.1232 $[M+H]^+$ (calculated for $C_{10}H_{16}NO$ = 166.1232).

1-(1*H*-pyrrol-3-yl)heptan-1-one, 22. Prepared according to general procedure A to provide 1-(1*H*-pyrrol-3-yl)heptan-1-one as an off-white solid (121 mg, 5%). ^{1}H-NMR (500MHz, $CDCl_3$) δ 8.71 (s, 1H); 7.41 (s, 1H); 6.96 (s, 1H); 6.65 (s, 1H); 2.73 (t, *J*=7.6Hz, 2H); 1.74-1.56 (m, 2H); 1.39-1.18 (m, 6H); 0.86 (t, *J*=6.9Hz, 3H). ^{13}C-NMR (125MHz, $CDCl_3$) δ 197.1, 126.2, 123.2, 119.5, 109.0, 40.0, 31.9, 29.4, 25.2, 22.8, 14.3. HRMS (ESI-TOF) 180.1384 $[M+H]^+$ (calculated for $C_{11}H_{18}NO$ = 180.1388).

1-(1*H*-pyrrol-3-yl)octan-1-one, 23. Prepared according to general procedure A to provide 1-(1*H*-pyrrol-3-yl)octan-1-one as an off-white solid (92 mg, 33%). ^{1}H-NMR (500MHz, $CDCl_3$) δ 8.47 (s, 1H); 7.41 (s, 1H); 6.76 (s, 1H); 6.65 (s, 1H); 2.72 (t, *J*=7.4Hz, 2H); 1.73-1.57 (m, 2H); 1.38-1.17 (m, 8H); 0.85 (t, *J*=6.8Hz, 3H). ^{13}C-NMR (125MHz, $CDCl_3$) δ 196.7, 126.4, 123.0, 119.4, 109.1, 40.0, 32.0, 29.7, 29.4, 25.3, 22.9, 14.3. HRMS (ESI-TOF) 194.1545 $[M+H]^+$ (calculated for $C_{12}H_{20}NO$ = 194.1545).

1-(1*H*-pyrrol-3-yl)nonan-1-one, 24. Prepared according to general procedure A to provide 1-(1*H*-pyrrol-3-yl)nonan-1-one as an off-white solid (431 mg, 14%). ^{1}H-NMR (500MHz, $CDCl_3$) δ 9.32 (s, 1H); 7.41 (s, 1H); 6.76 (s, 1H); 6.63 (s, 1H); 2.73 (t, *J*=7.4Hz, 2H); 1.75-1.62 (m, 2H); 1.39-1.12 (m, 10H); 0.85 (t, *J*=6.8Hz, 3H). ^{13}C-NMR (125MHz, $CDCl_3$) δ 196.7, 126.0, 123.6, 119.7, 108.8, 40.0, 32.0, 29.7, 29.7, 29.5, 25.4, 22.9, 14.3. HRMS (ESI-TOF) 208.1703 $[M+H]^+$ (calculated for $C_{13}H_{22}NO$ = 208.1701).

1-(1*H*-pyrrol-3-yl)dodecan-1-one, 25. Prepared according to general procedure A to provide 1-(1*H*-pyrrol-3-yl)dodecan-1-one as an off-white solid (108 mg, 3%).^{1}H-NMR (500MHz, $CDCl_3$) δ 8.50 (s, 1H); 7.41 (s, 1H); 6.77 (s, 1H); 6.65 (s, 1H); 2.72 (t, *J*=7.4Hz, 2H); 1.73-1.62 (m, 2H); 1.37-1.16 (m, 16H); 0.85 (t, *J*=6.7Hz, 3H). ^{13}C-NMR (125MHz, $CDCl_3$) δ 196.9, 126.3, 123.0, 119.4, 109.1, 40.0, 32.1, 29.9, 29.8, 29.7, 29.6, 25.2, 22.9, 14.4. HRMS (ESI-TOF) 250.2167 $[M+H]^+$ (calculated for $C_{16}H_{28}NO$ = 250.2171).

3-(4-butylphenyl)-1-(1*H*-pyrrol-3-yl)propan-1-one, 26. Prepared according to general procedure A to provide 3-(4-butylphenyl)-1-(1*H*-pyrrol-3-yl)propan-1-one as an off-white solid (62.7 mg, 4%) ^{1}H-NMR (500MHz, $CDCl_3$) δ 8.55 (s, 1H), 7.42-7.41 (m, 1H), 7.17-7.09 (m, 4H), 6.78-6.77 (m, 1H), 6.68-6.67 (m, 1H), 3.09-3.06 (m, 2H), 3.02-2.99 (m, 2H), 2.57 (t, *J*=7.8 Hz, 2H), 1.61-1.55 (m, 4H), 1.39-1.31 (m, 2H), 0.93-0.91 (t, *J*=7.3 Hz, 3H). ^{13}C-NMR (125MHz, $CDCl_3$) δ 195.4, 140.7, 139.0, 128.5, 128.3, 126.0, 123.0, 119.4, 109.0, 41.8, 35.4, 33.9, 30.3, 22.5, 14.1. HRMS (ESI-TOF) 256.1701 $[M+H]^+$ (calculated for $C_{17}H_{22}NO$ = 256.1701).

3-(4-butylphenyl)-1-(1*H*-pyrrol-2-yl)propan-1-one, 27. Prepared according to general procedure A to provide 3-(4-butylphenyl)-1-(1*H*-pyrrol-2-yl)propan-1-one as an off-white solid (190.3 mg, 11%) ^{1}H-NMR (500MHz, $CDCl_3$) δ 9.60 (s, 1H), 7.17-7.10 (m, 4H), 7.03-7.02 (m, 1H), 6.91-6.90 (m, 1H), 6.28-6.26 (m, 1H), 3.12-3.07 (m, 2H), 3.04-3.00 (m, 2H), 2.58 (t, *J*=7.77, 2H), 1.62-1.56 (m, 2H), 1.39-1.32 (m, 2H), 0.93 (t, *J*=7.35, 3H). ^{13}C-NMR (125MHz, $CDCl_3$) δ 190.0, 140.8, 138.5, 132.0, 128.7, 128.3, 124.7, 116.3, 110.8, 39.9, 35.4, 33.9, 30.5, 22.5, 14.1. HRMS (ESI-TOF) 256.1701 $[M+H]^+$ (calculated for $C_{17}H_{22}NO$ = 256.1701).

7-phenyl-1-(1*H*-pyrrol-3-yl)heptan-1-one, 28. Prepared according to general procedure A to provide 7-phenyl-1-(1*H*-pyrrol-2-yl)heptan-1-one as an off-white solid (69.8 mg, 3%) ^{1}H-NMR (500MHz, $CDCl_3$) δ 8.67 (s,1H), 7.42-7.41 (m, 1H), 7.29-7.25 (m, 2H), 7.19-7.15 (m, 3H), 6.79-6.77 (dd, *J*=2.4 Hz, 1H), 6.67-6.66 (dd, *J*=2.6, 1.5 Hz, 1H), 2.74 (t, *J*=7.5 Hz, 2H), 2.59 (t, *J*=7.8 Hz, 2H), 1.74-1.68 (m, 2H), 1.65-1.59 (m, 2H), 1.42-1.33 (m, 4H). ^{13}C-NMR (125MHz, $CDCl_3$) δ 197.4, 142.9, 128.5, 128.3, 125.8, 125.7, 123.5, 119.7, 108.7, 39.8, 36.0, 31.5, 29.4, 29.2, 25.1. HRMS (ESI-TOF) 256.1700 $[M+H]^+$ (calculated for $C_{17}H_{22}NO$ = 256.1701).

7-phenyl-1-(1*H*-pyrrol-2-yl)heptan-1-one, 29. Prepared according to general procedure A to provide 7-phenyl-1-(1*H*-pyrrol-2-yl)heptan-1-one as an off-white solid (267 mg, 13%) ^{1}H-NMR (500MHz, $CDCl_3$) δ 9.48 (s, 1H), 7.32-7.28 (m, 2H), 7.22-7.19 (m, 3H), 7.05-7.04 (m, 1H), 6.93-6.92 (m, 1H), 6.31-6.29 (m, 1H), 2.78 (t, *J*=7.5 Hz, 2H), 2.63 (t, *J*=7.7 Hz, 2H),1.77-1.70 (m, 2H), 1.68-1.62 (m, 2H), 1.46-1.36 (m, 4H). ^{13}C-NMR (125MHz, $CDCl_3$) δ 191.2, 142.9, 132.2, 128.5, 128.4, 125.7, 124.4, 116.1, 110.7, 38.1, 36.0, 31.5, 29.4, 29.2, 25.3. HRMS (ESI-TOF) 256.1713 $[M+H]^+$ (calculated for $C_{17}H_{22}NO$ = 256.1701).

3-(4-butylphenyl)-1-(1*H*-pyrrol-3-yl)prop-2-en-1-one, 30. Prepared according to general procedure A to provide 3-(4-butylphenyl)-1-(1*H*-pyrrol-3-yl)prop-2-en-1-one as an off-white solid (62.7 mg, 4%) ^{1}H-NMR (500MHz, $CDCl_3$) δ 8.73 (s, 1H), 7.78 (d, *J*=15.6 Hz, 1H), 7.59 (s, 1H), 7.54 (d, *J*=7.8 Hz, 2H), 7.27 (d, *J*=15.6 Hz, 1H), 7.21 (d, *J*=7.7 Hz, 2H), 6.83 (d, *J*=14.2, 2H), 2.63 (t, *J*=7.7 Hz, 2H), 1.64-1.58 (m, 2H), 1.36 (h, *J*=7.4 Hz, 2H), 0.93 (t, *J*=7.3 Hz, 3H). ^{13}C-NMR (125MHz, $CDCl_3$) δ 185.25, 145.60, 142.31, 132.77, 129.09, 128.48, 127.00, 123.69, 122.70, 119.74, 109.40, 35.74, 33.59, 22.50, 14.11. HRMS (ESI-TOF) 254.1554 $[M+H]^+$ (calculated for $C_{17}H_{20}NO$ = 254.1545).

3-(4-butylphenyl)-1-(1*H*-pyrrol-2-yl)prop-2-en-1-one, 31. Prepared according to general procedure A to provide 3-(4-butylphenyl)-1-(1*H*-pyrrol-2-yl)prop-2-en-1-one as an off-white solid (18.6 mg, 5%) ^{1}H-NMR (500MHz, $CDCl_3$) δ 10.86 (s, 1H), 7.94 (d, *J*=15.7 Hz, 1H), 7.63 (d, *J*=8.3 Hz, 2H), 7.44 (d, *J*=15.7 Hz, 1H), 7.29 (d, *J*=8.3 Hz, 2H), 7.24-7.23 (m, 1H), 7.20-7.18 (m, 1H), 6.44-6.41 (m, 1H), 2.70 (t, *J*=7.9 Hz, 2H), 1.70-1.65 (m, 2H), 1.43 (h, *J*=7.3 Hz, 2H), 1.01 (t, *J*=7.5 Hz, 3H). ^{13}C-NMR (125MHz, $CDCl_3$) δ 179.14, 145.84, 142.55, 133.28, 132.53,

129.11, 128.48, 125.75, 121.03, 116.55, 111.03, 35.72, 33.54, 22.46, 14.08. HRMS (ESI-TOF) 254.1564 $[M+H]^+$ (calculated for $C_{17}H_{20}NO$ = 254.1545).

(*E*)-1-(1*H*-pyrrol-3-yl)dec-2-en-1-one, 32. Prepared according to general procedure A to provide (*E*)-1-(1*H*-pyrrol-3-yl)dec-2-en-1-one as an off-white solid (14.6 mg, 1%) ^{1}H-NMR (500MHz, $CDCl_3$) δ 8.64 (s, 1H), 7.49 (m, 1H), 7.05-6.99 (dt, *J*=15.3, 7.0 Hz, 1H), 6.81-6.78 (m, 1H), 6.75-6.73 (m, 1H), 6.68-6.64 (dt, *J*=15.3, 1.5 Hz, 1H), 2.29-2.24 (m, 2H), 1.51-1.46 (m, 2H), 1.29-1.26 (m, 8H), 0.89-0.83 (m, 3H). ^{13}C-NMR (125MHz, $CDCl_3$) δ 185.6, 147.0, 127.0, 126.6, 123.5, 119.6, 109.4, 32.8, 31.9, 29.4, 29.3, 28.5, 22.8, 14.3. HRMS (ESI-TOF) 220.1700 $[M+H]^+$ (calculated for $C_{14}H_{22}NO$ = 220.1701).

(*E*)-1-(1*H*-pyrrol-2-yl)dec-2-en-1-one, 33. Prepared according to general procedure A to provide (*E*)-1-(1*H*-pyrrol-2-yl)dec-2-en-1-one as an off-white solid (42.1 mg, 2%). ^{1}H-NMR (500MHz, $CDCl_3$) δ 10.13 (s, 1H), 7.13-7.07 (m, 2H), 6.98-6.96 (m, 1H), 6.73 (d, *J*=15.6, 1H), 6.31-6.29 (m, 1H), 2.32-2.27 (m, 2H), 1.54-1.48 (m, 2H), 1.38-1.23 (m, 8H), 0.89 (t, *J*=6.7 Hz, 3H). ^{13}C-NMR (125MHz, $CDCl_3$) δ 179.5, 147.5, 132.8, 125.4, 116.5, 110.8, 32.8, 32.0, 29.4, 29.2, 28.4, 22.8, 14.2. HRMS (ESI-TOF) 220.1723 $[M+H]^+$ (calculated for $C_{14}H_{22}NO$ = 220.1701).

2-([1,1'-biphenyl]-4-yl)-1-(1*H*-pyrrol-3-yl)ethanone, 34. Prepared according to general procedure A to provide 2-([1,1'-biphenyl]-4-yl)-1-(1*H*-pyrrol-3-yl)ethanone as an off-white solid (13.4 mg, 2%) ^{1}H-NMR (500MHz, $CDCl_3$) δ 8.60 (s, 1H), 7.59-7.53 (m, 4H), 7.49-7.48 (m, 1H), 7.44-7.40 (m, 2H), 7.38-7.31 (m, 3H), 6.79-6.78 (m, 1H), 6.73-6.72 (m, 1H), 4.10 (s, 2H). ^{13}C-NMR (125MHz, $CDCl_3$) δ 193.4, 141.0, 139.7, 134.7, 129.9, 128.9, 127.4, 127.2, 125.7, 123.8, 119.6, 109.5, 46.6. HRMS (ESI-TOF) 262.1228 $[M+H]^+$ (calculated for $C_{18}H_{16}NO$ = 262.1232).

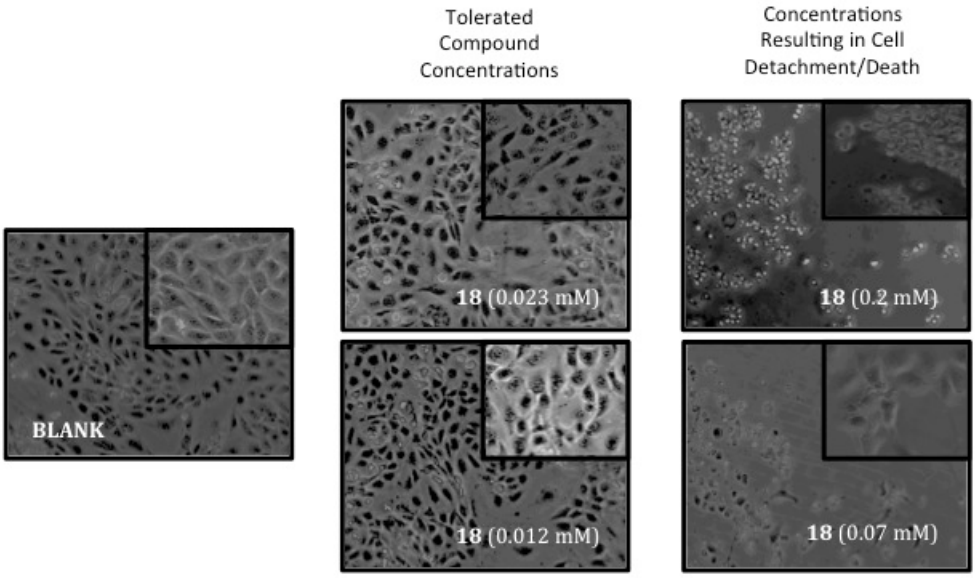
2-([1,1'-biphenyl]-4-yl)-1-(1*H*-pyrrol-2-yl)ethanone, 35. Prepared according to general procedure A to provide 2-([1,1'-biphenyl]-4-yl)-1-(1*H*-pyrrol-2-yl)ethanone as an off-white solid (175 mg, 20%) ^{1}H-NMR (500MHz, $CDCl_3$) δ 9.60 (s, 1H), 7.58-7,54 (m, 4H), 7.45-7.32 (m, 4H), 7.36-7.32 (m, 1H), 7.06-7.04 (dd, *J*=4.5, 2.5 Hz, 2H), 6.32-6.30 (m, 1H), 4.11 (s, 2H). ^{13}C-NMR (125MHz, $CDCl_3$) δ 187.8, 141.0, 139.9, 134.2, 131.7, 129.9, 128.9, 127.5, 127.3, 127.2, 125.1, 117.1, 111.1, 44.6. HRMS (ESI-TOF) 262.1235 $[M+H]^+$ (calculated for $C_{18}H_{16}NO$ = 262.1232).

C. Western Blot Analysis.

Overnight cultures of *V. cholerae* CqsA- LuxQ- were diluted 1000-fold in AKI medium containing the indicated compounds. The cultures were grown under static conditions at 37^{o}C for 4h and then were shaken for 18h at 37^{o}C. Cells were collected by centrifugation, TcpA and HapR from different samples were analyzed by Western Blot as previously described.[4,5]

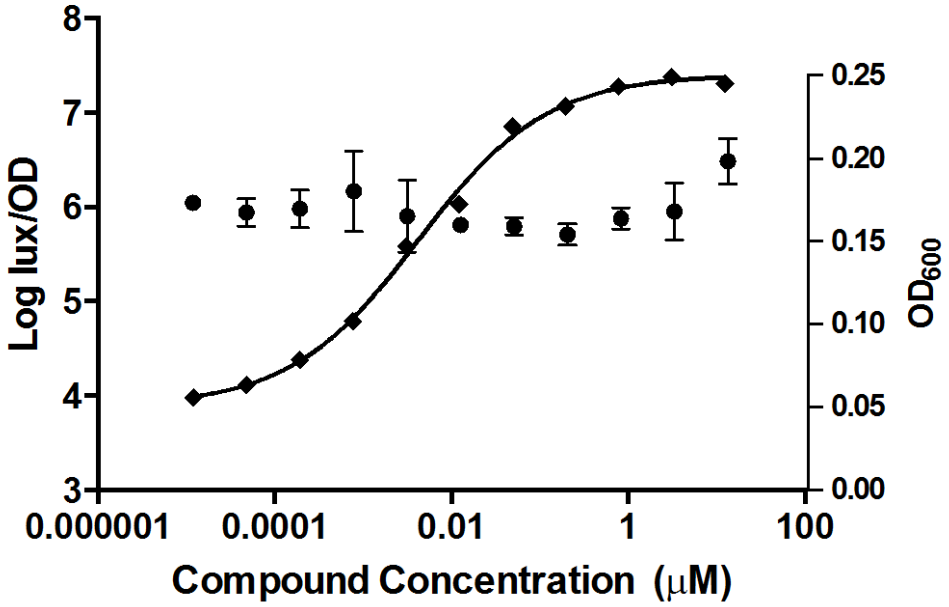
D. Murine 3T3 Fibroblast Cell Toxicity Assay.

3T3 cells were prepared as described previously in a 24-well plate and incubated for 24h at 37 °C. [6] The culture media was replaced by media containing the compound **18** at the indicated concentrations and the plates were visually examined using a microscope for cytotoxicity after incubation in the presence of the compound for 24h. Representative images displaying the effects of different concentrations of **18** on 3T3 cells are provided below.



E. Cytotoxicity of 18 in *V. cholerae* as assessed by OD_{600}.

Plot showing the no effect on growth of *Vibrio cholerae* strain MM920 under the conditions described for biological assay (Section A). Diamonds represent luminescence measurements in the presence of varying concentrations of compound **18**. Circles represent the OD_{600} at each of the concentrations of **18**.



F. References.

[1] A. Afzali-Ardakani, H. Rapoport, *J. Org. Chem.* **1980**, *45*, 4817–4820.

[2] J. Liu, N. Ikemoto, D. Petrillo, J. D. Armstrong III, *Tetrahedron Letters* **2002**, *43*, 8223–8226.

[3] A. C. Biraboneye, S. Madonna, P. Maher, J.-L. Kraus, *ChemMedChem* **2010**, *5*, 79–85.

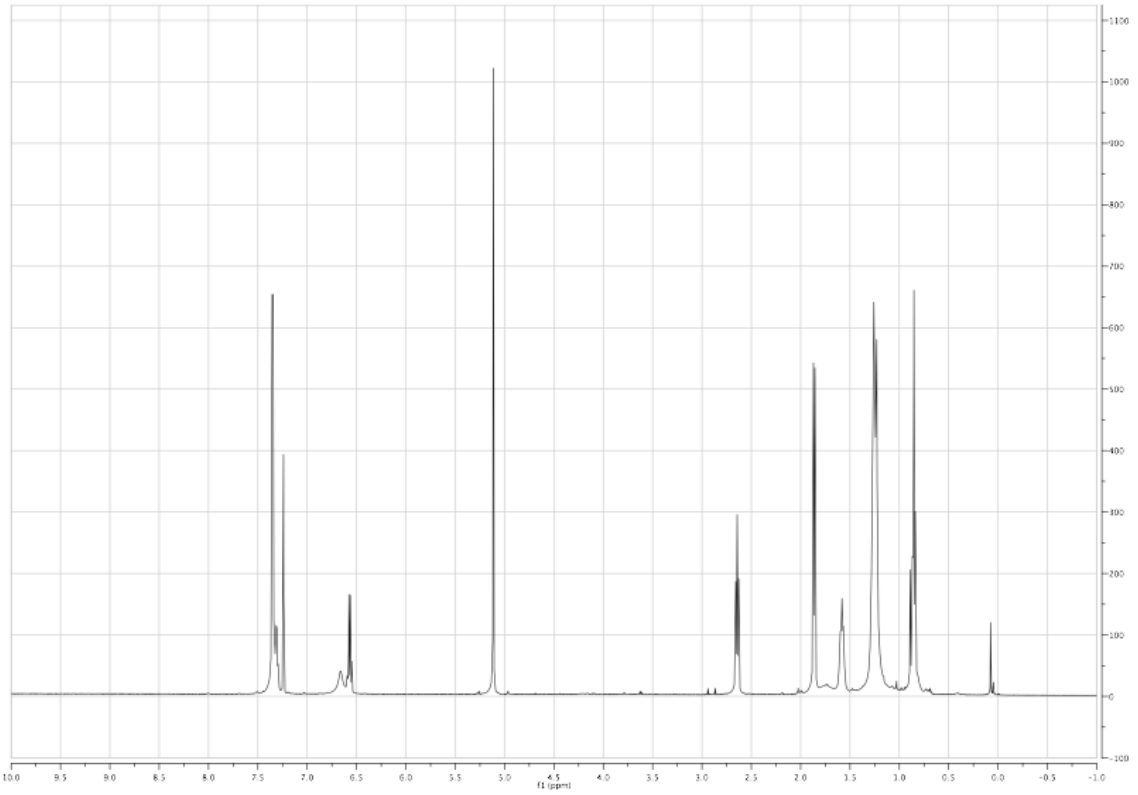
[4] D. H. Lenz, K. C. Mok, B. N. Lilley, R. V. Kulkarni, N. S. Wingreen, B. L. Bassler, *Cell* **2004**, *118*, 69–82.

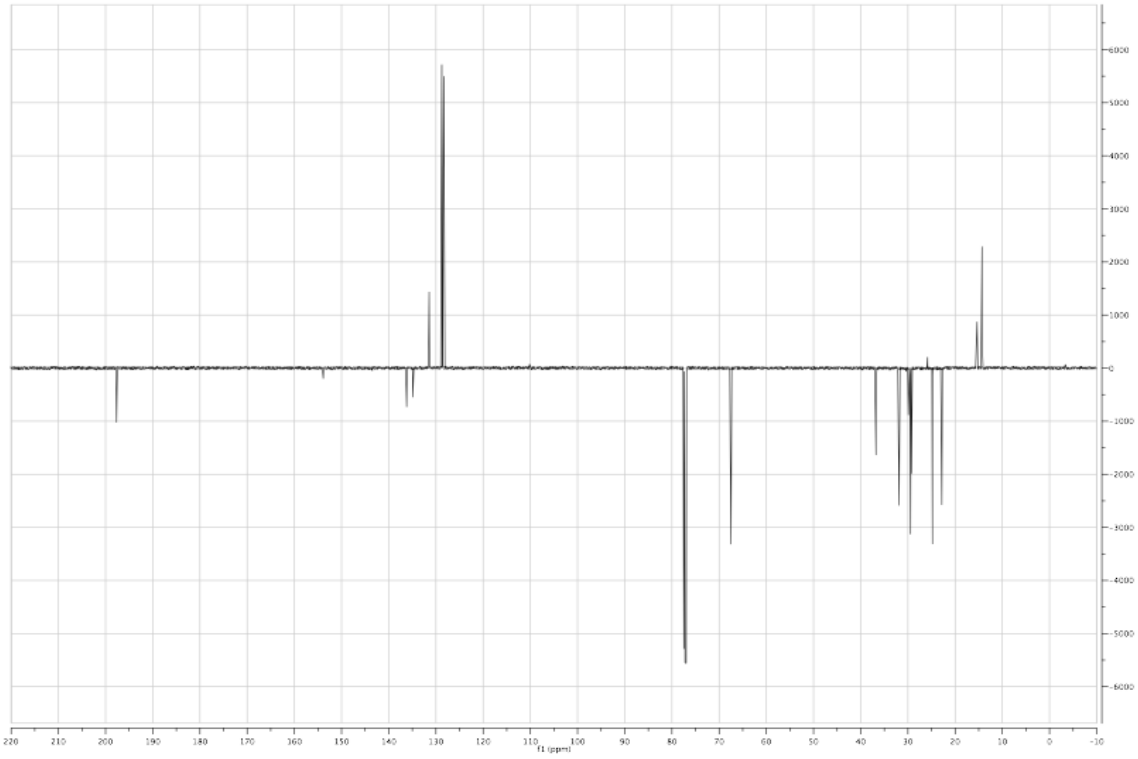
[5] D. A. Higgins, M. E. Pomianek, C. M. Kraml, R. K. Taylor, M. F. Semmelhack, B. L. Bassler, *Nature* **2007**, *450*, 883–886.

[6] ICCVAM. 2006a. Background Review Document: In Vitro Cytotoxicity Test Methods for Estimating Acute Oral Systemic Toxicity. NIH Publication No. 07-4518. Research Triangle Park, NC:National Institute of Environmental Health Sciences. Available 8/13/2013: http://iccvam.niehs.nih.gov/.

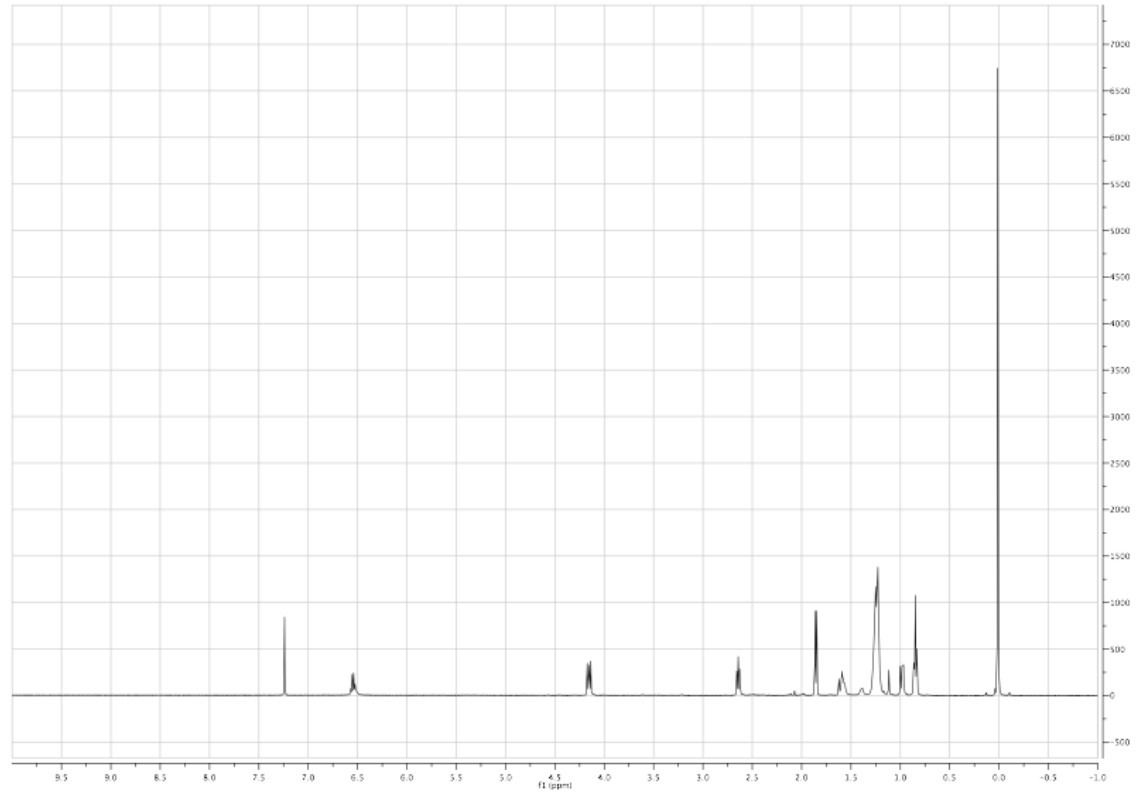
G. 1H-NMR and 13C-NMR Spectra For Compounds 3-11 and 15-35.

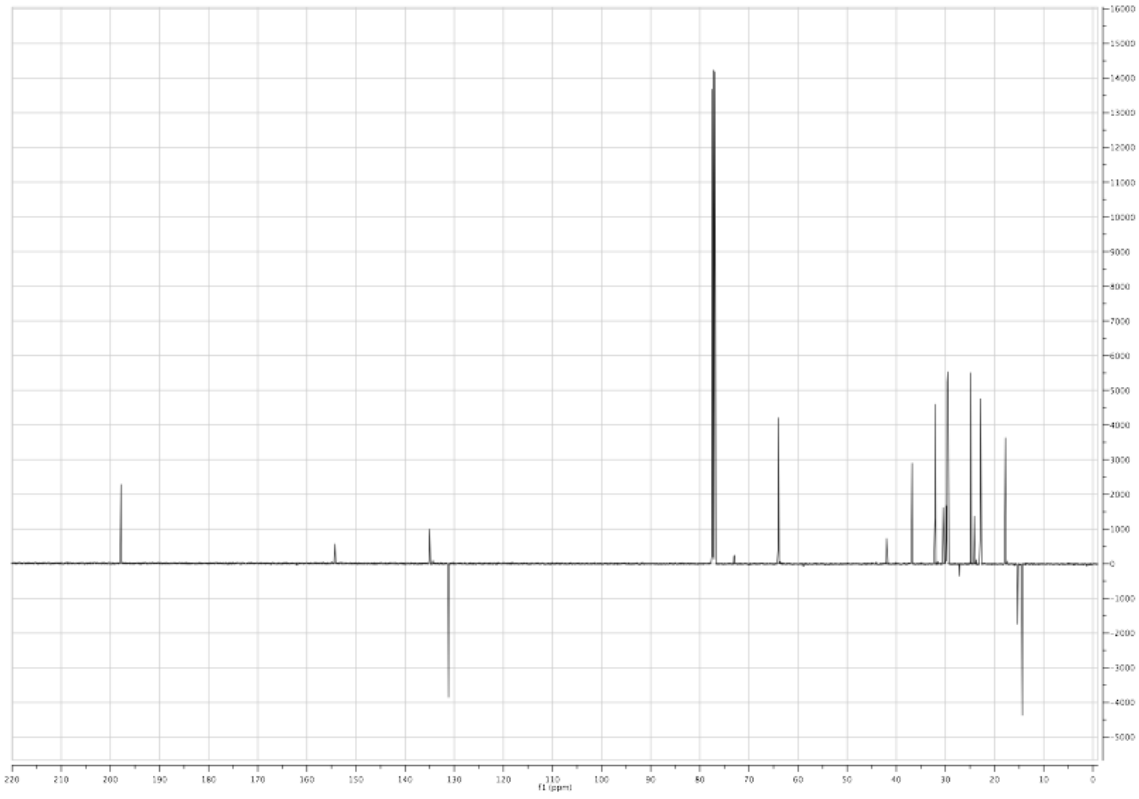
(*Z*)-benzyl (4-oxotridec-2-en-3-yl)carbamate, 3.



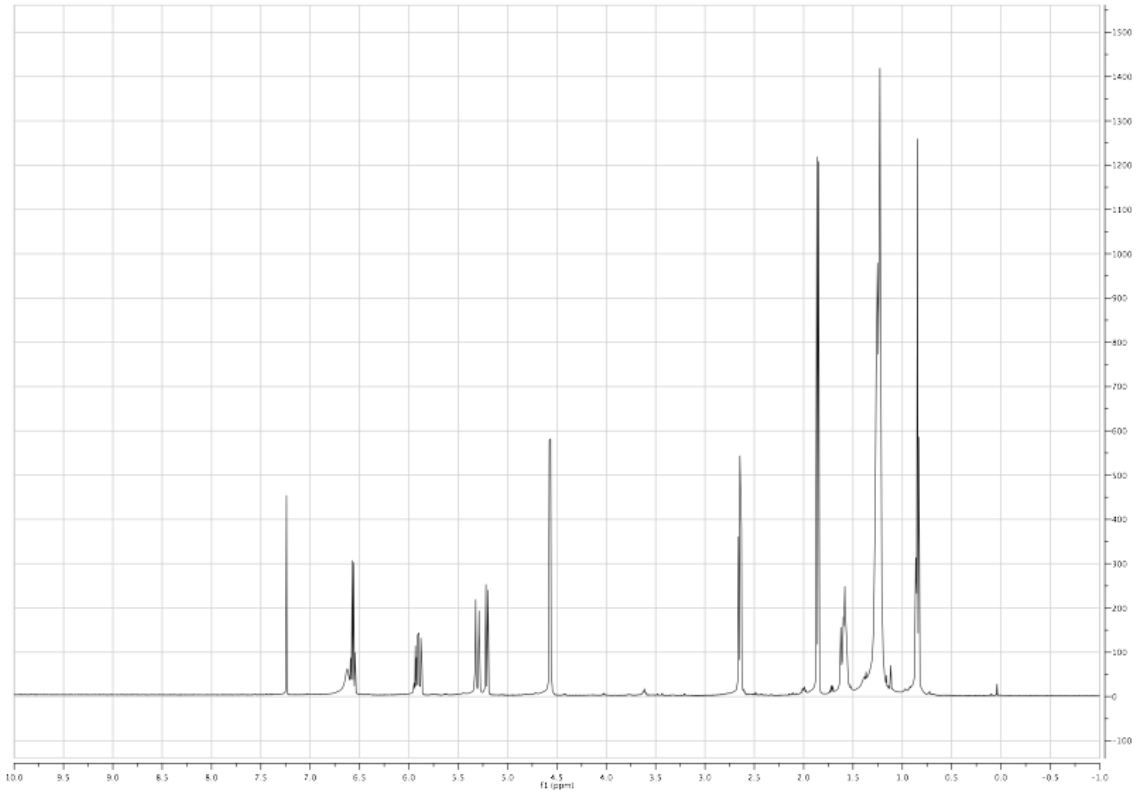


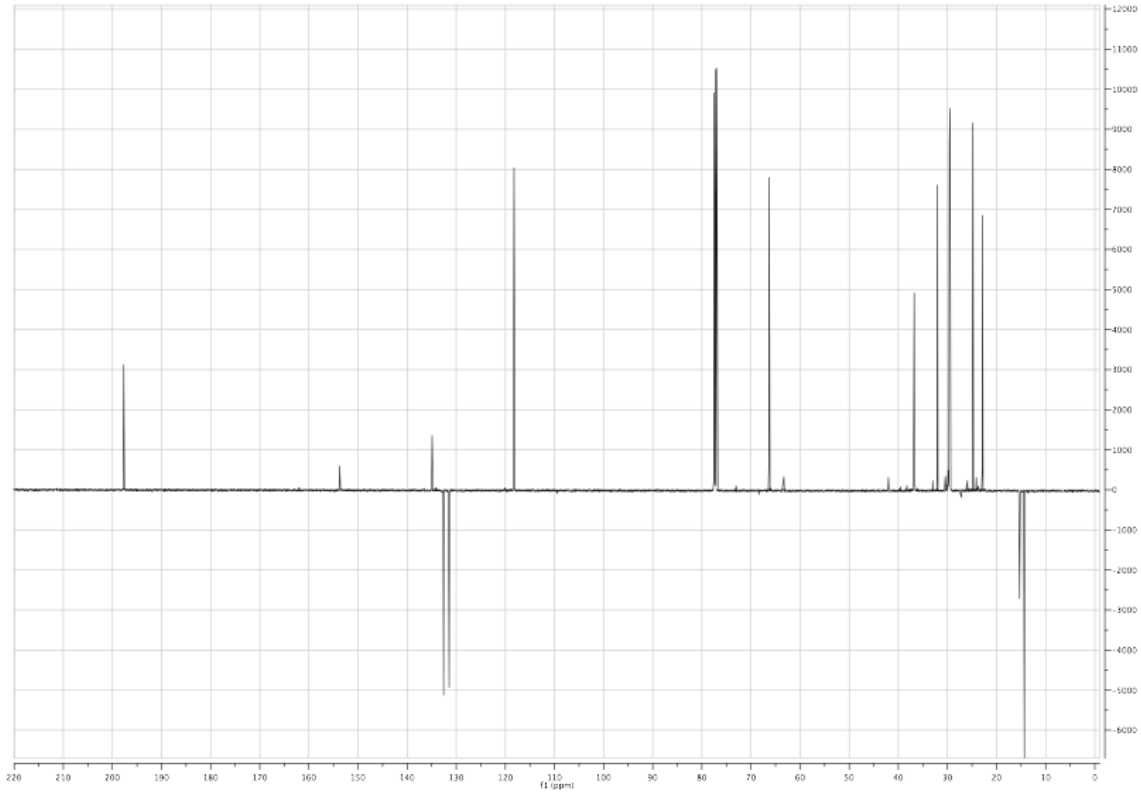
(*Z*)-2-(trimethylsilyl)ethyl (4-oxotridec-2-en-3-yl)carbamate, 4.



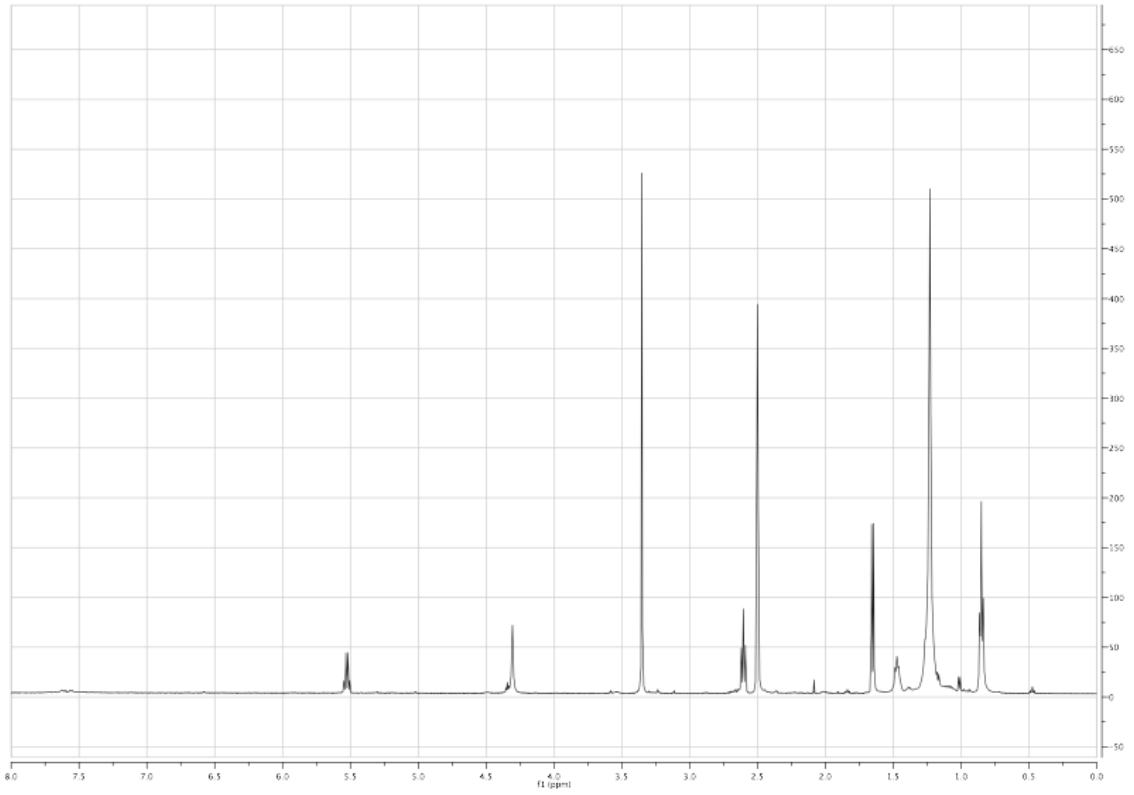


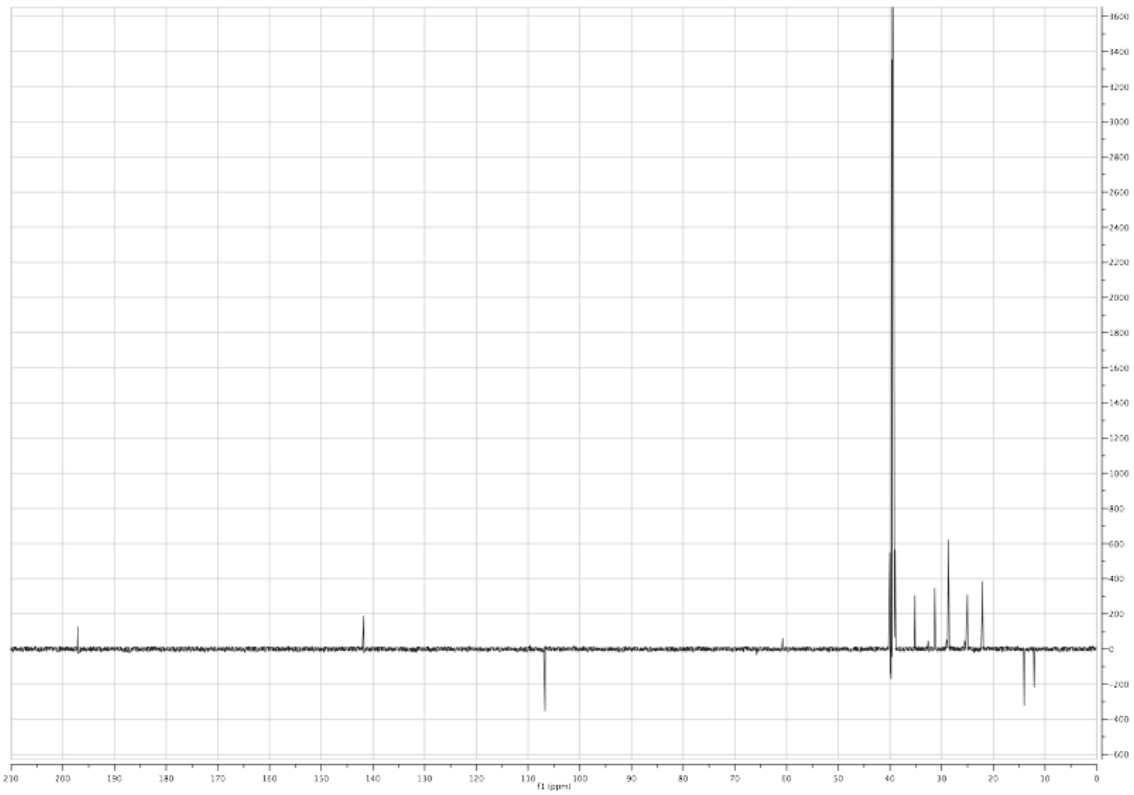
(*Z*)-allyl (4-oxotridec-2-en-3-yl)carbamate, 5.



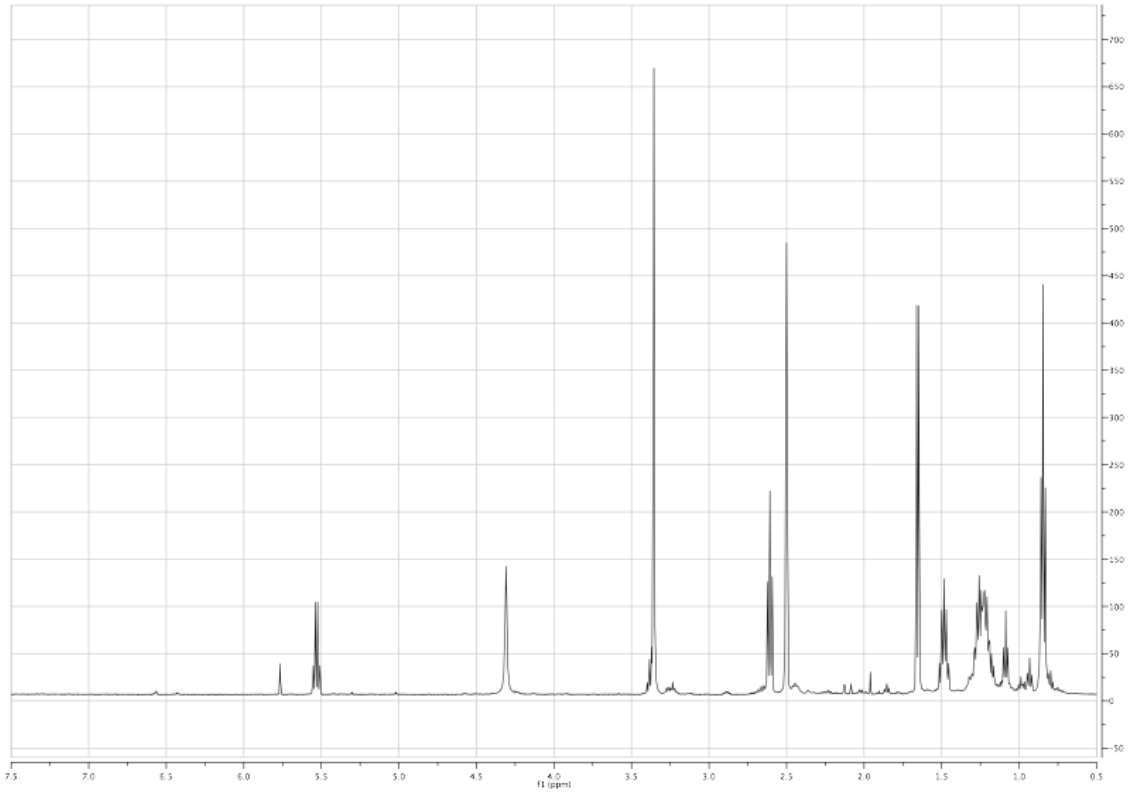


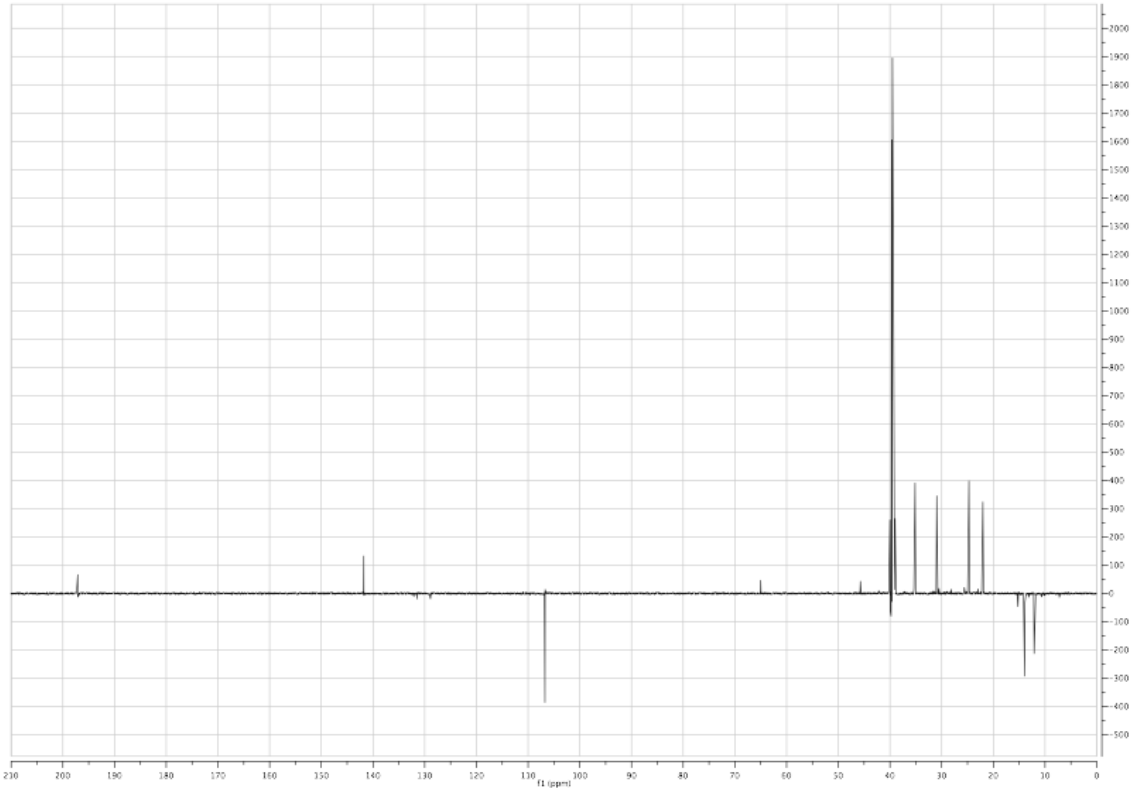
(*Z*)-3-aminotridec-2-en-4-one, Ea-CAI1.



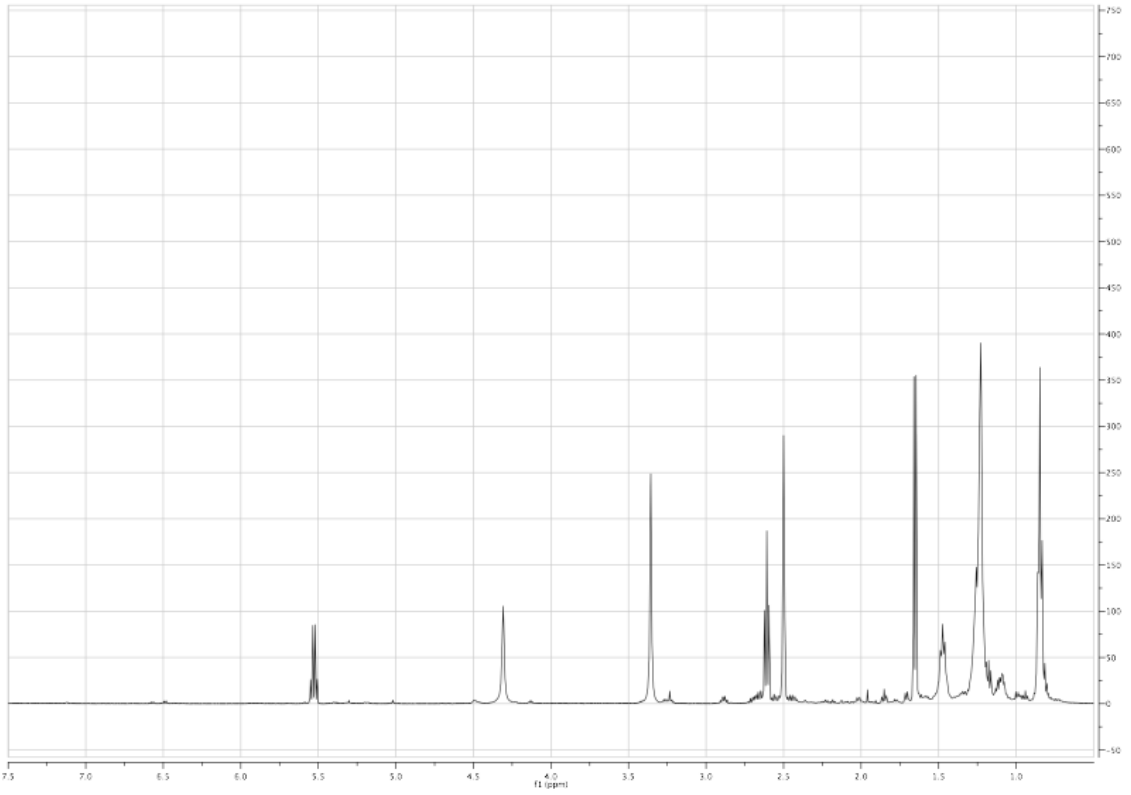


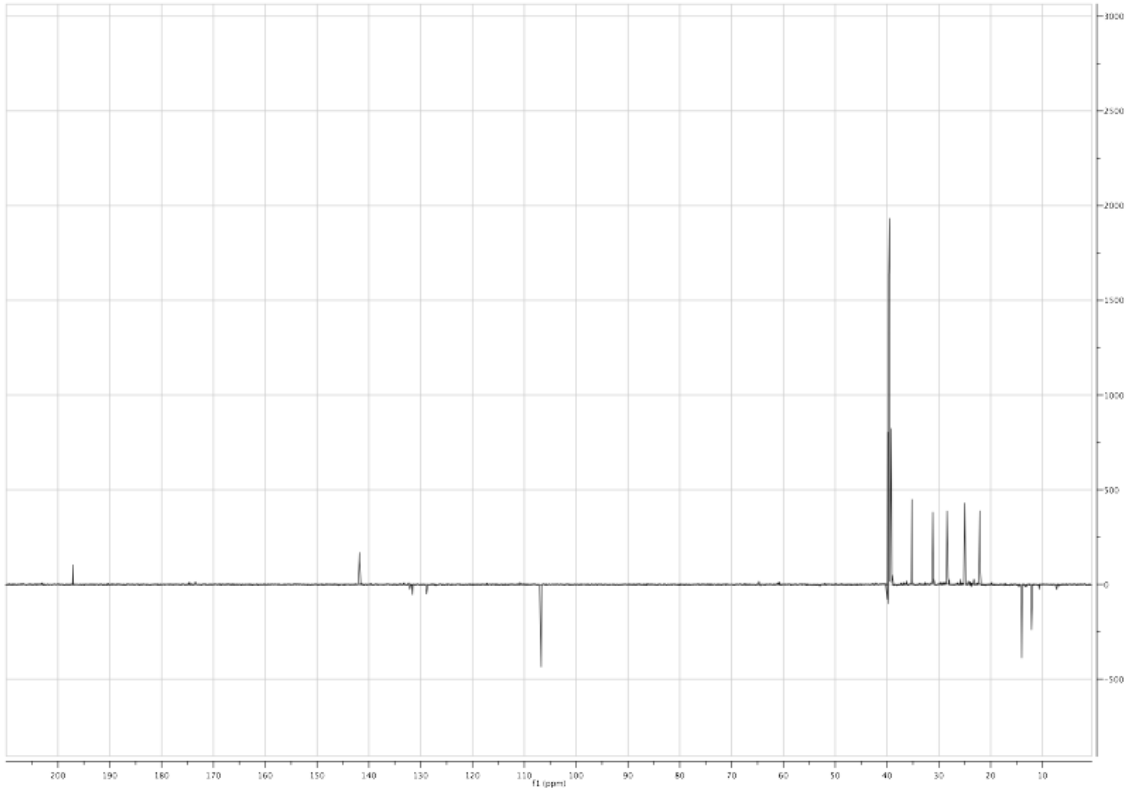
(*Z*)-3-aminonon-2-en-4-one, 6.



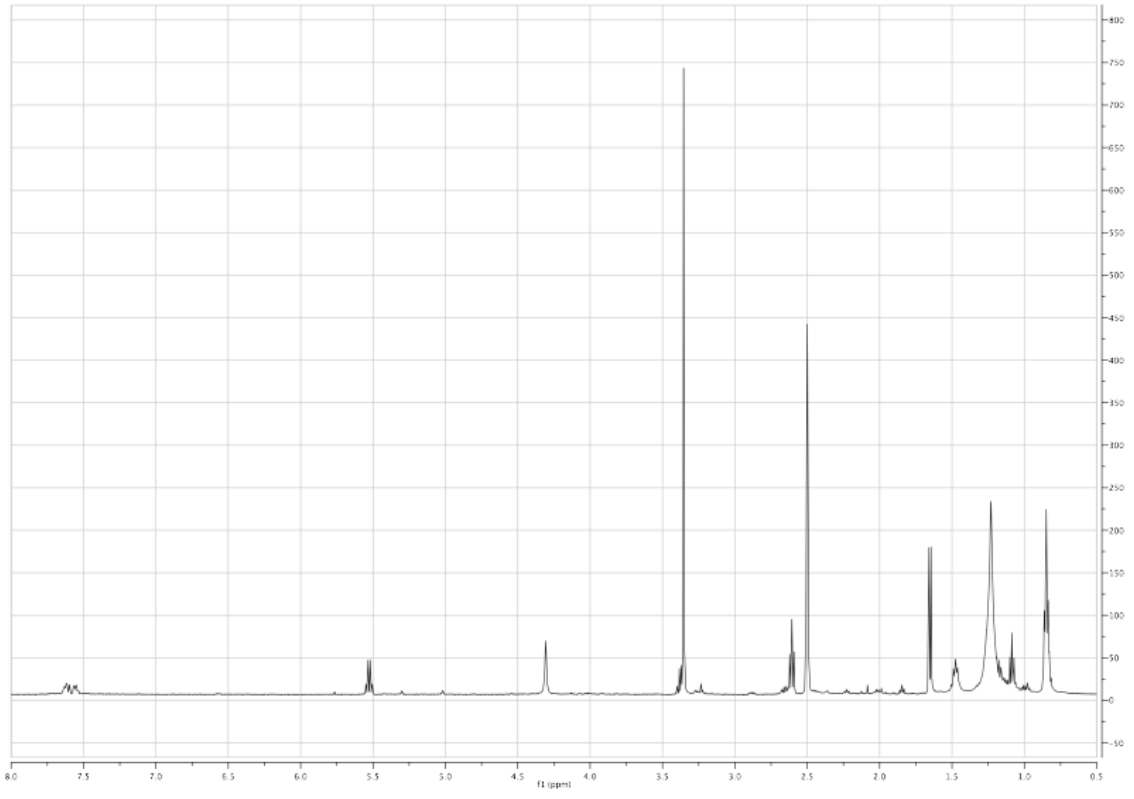


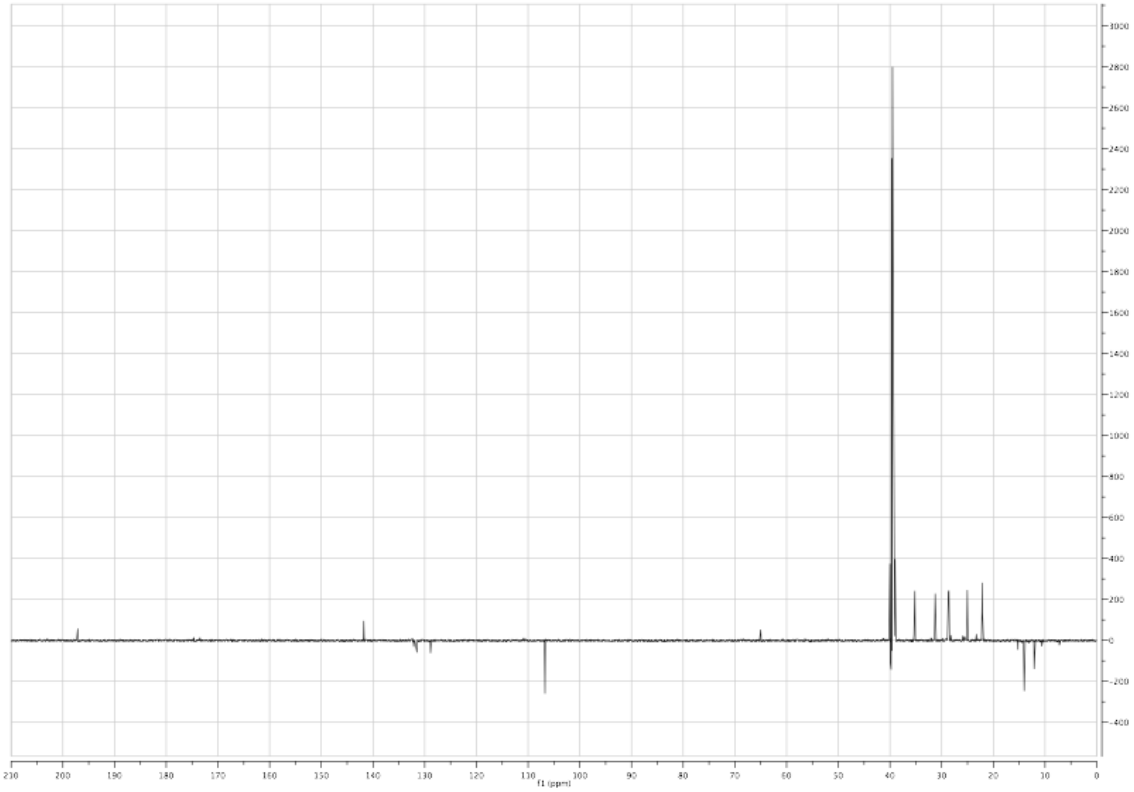
(*Z*)-3-aminodec-2-en-4-one, 7.



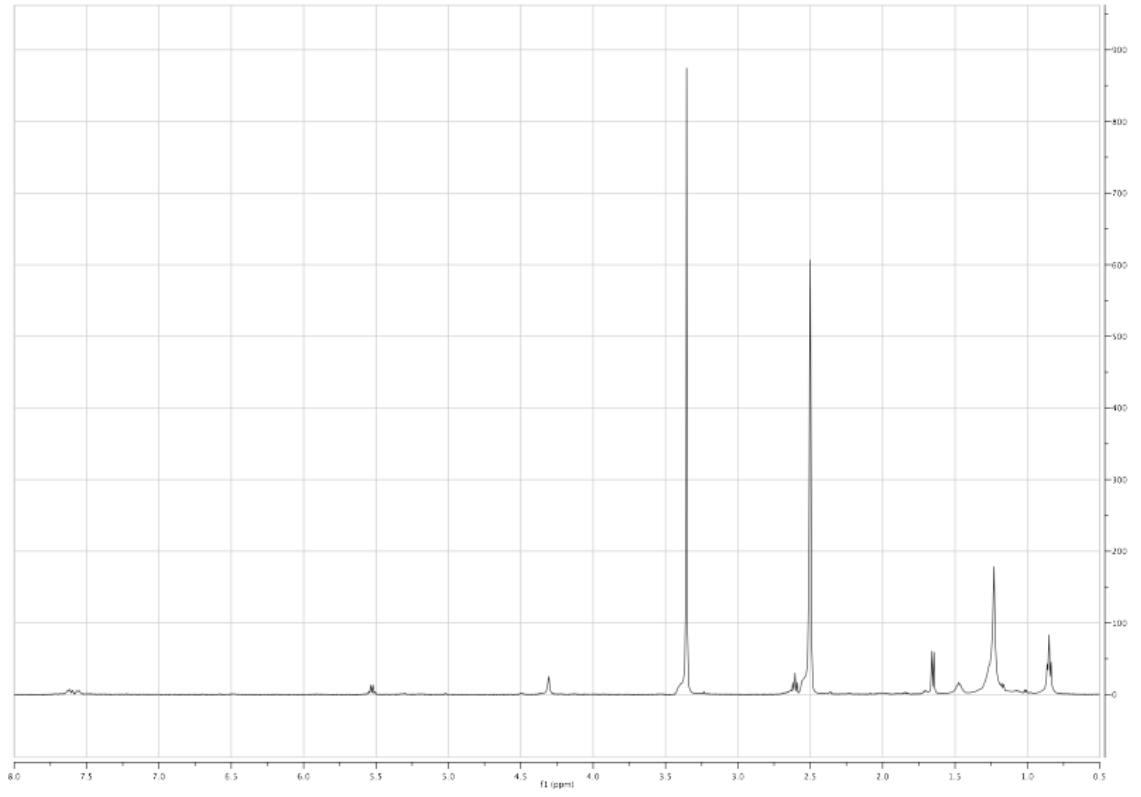


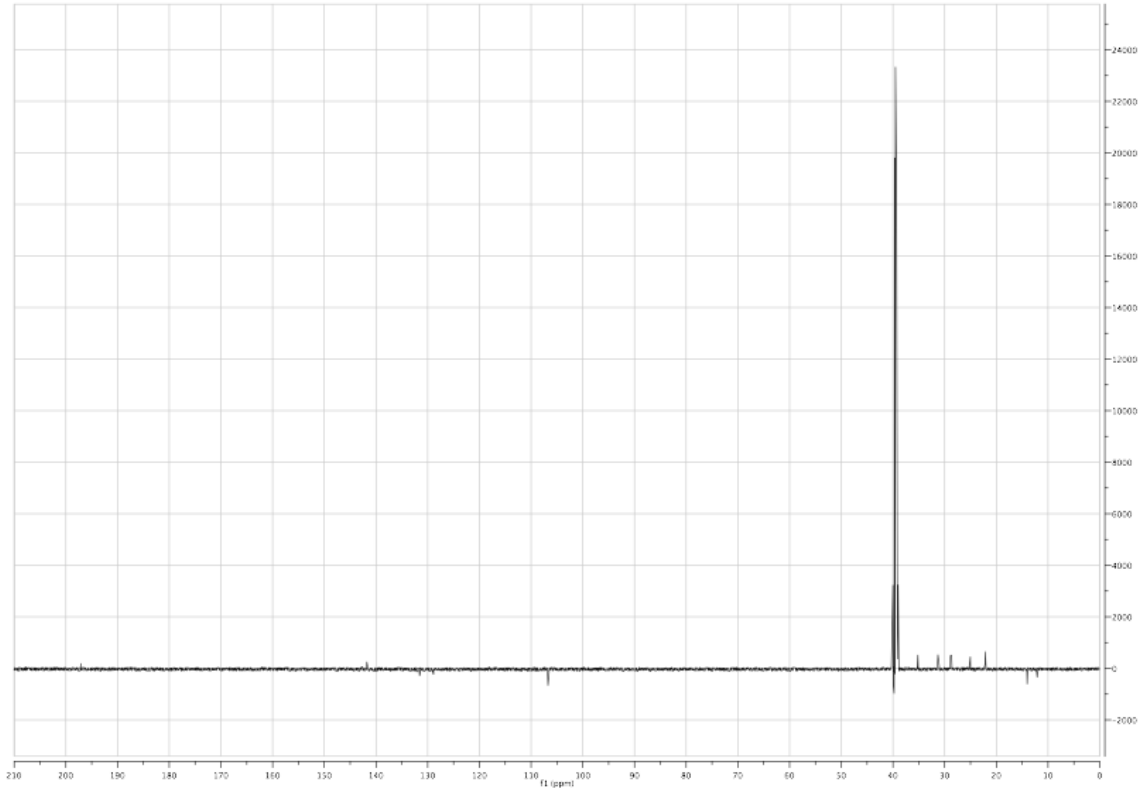
(*Z*)-3-aminoundec-2-en-4-one, 8.



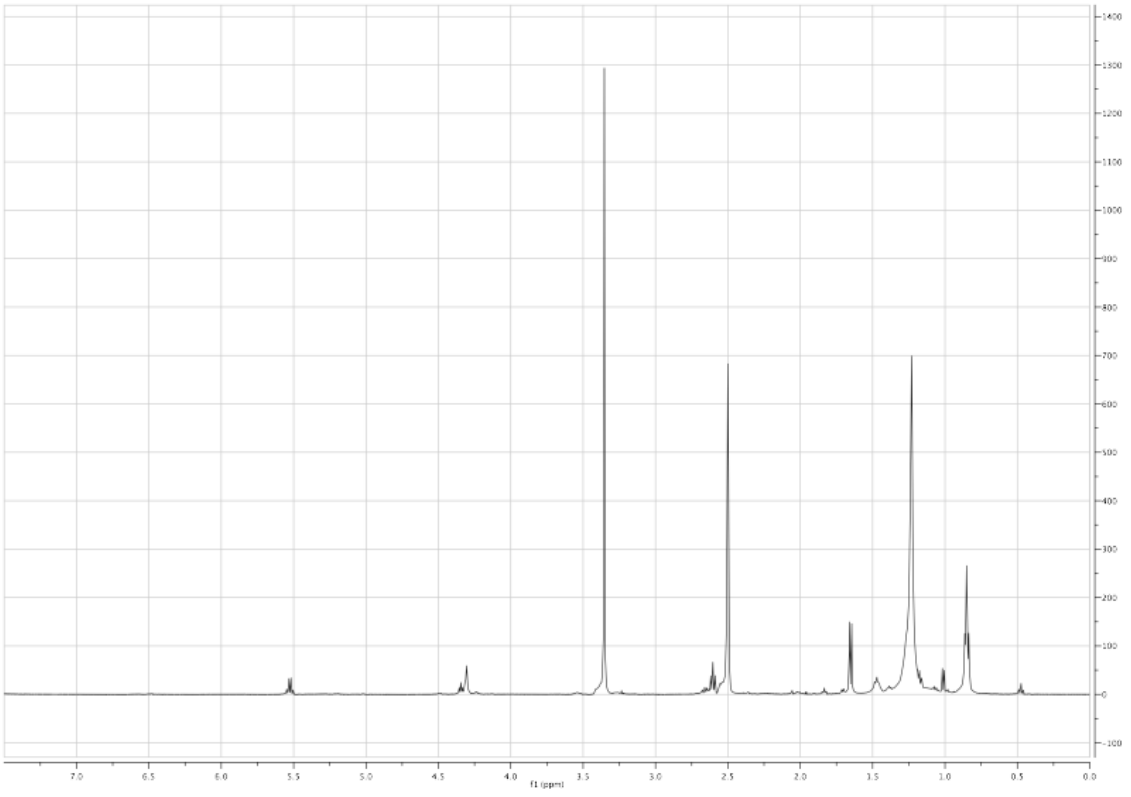


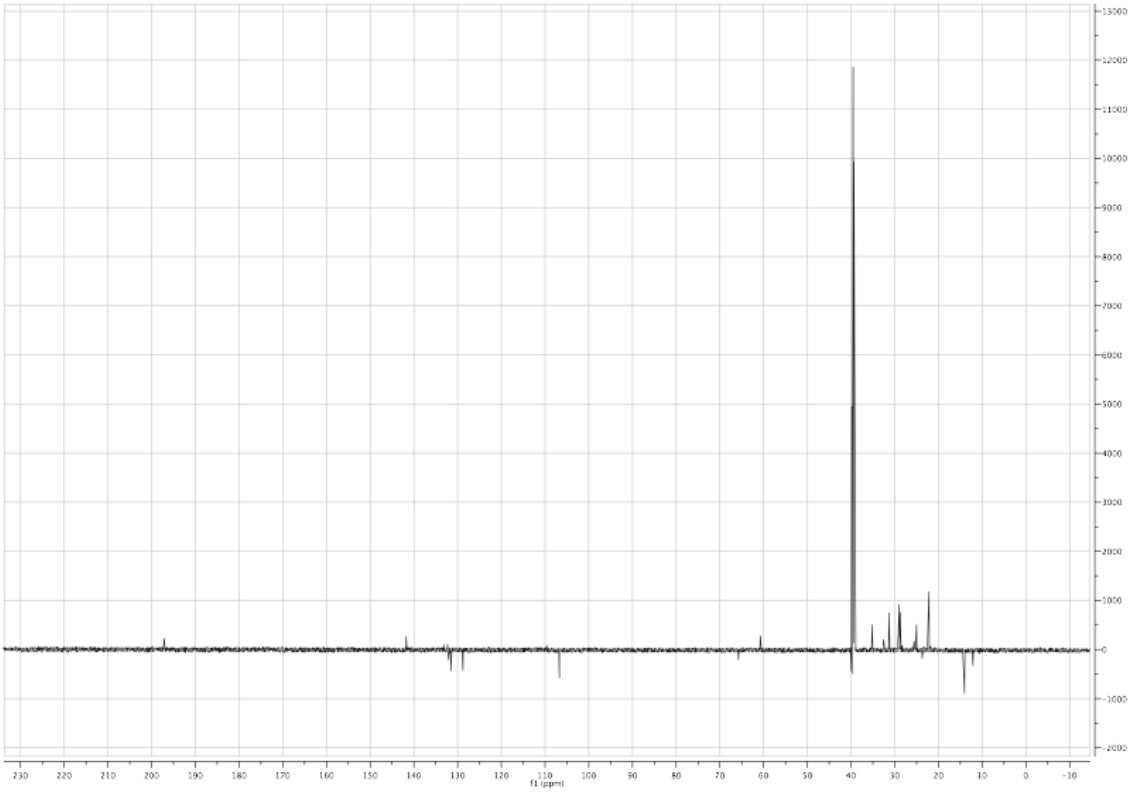
(*Z*)-3-aminododec-2-en-4-one, 9.



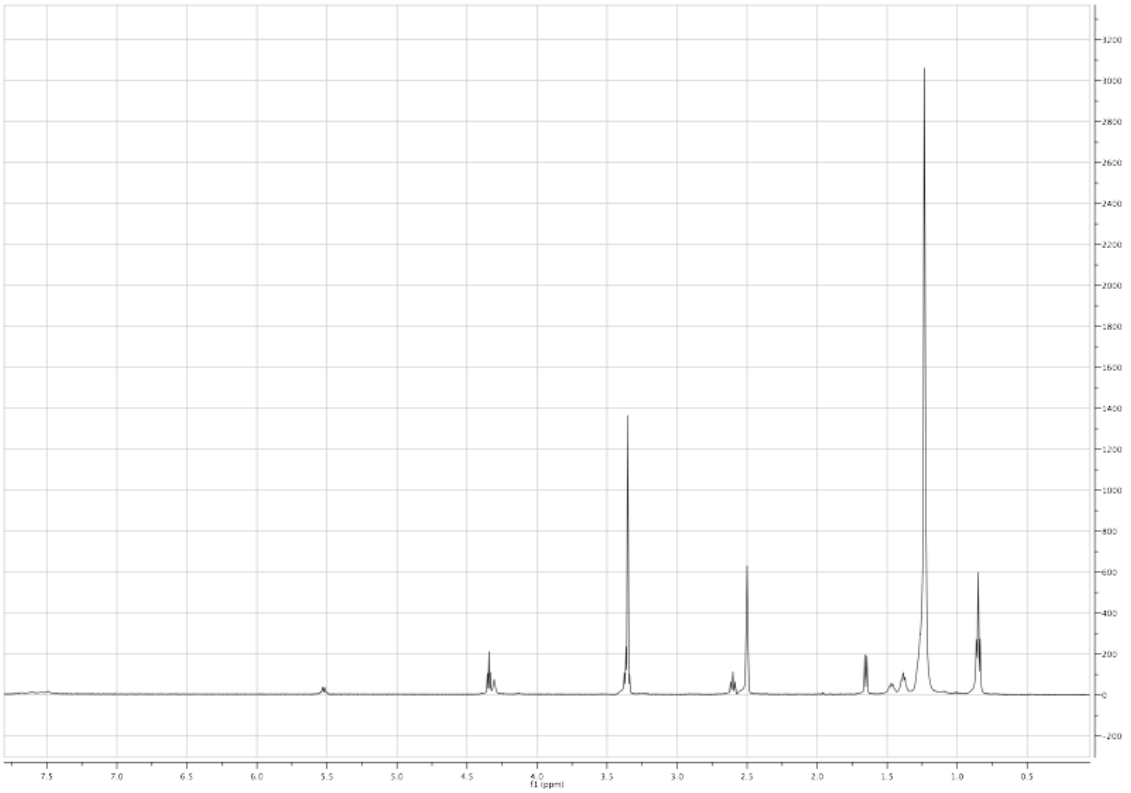


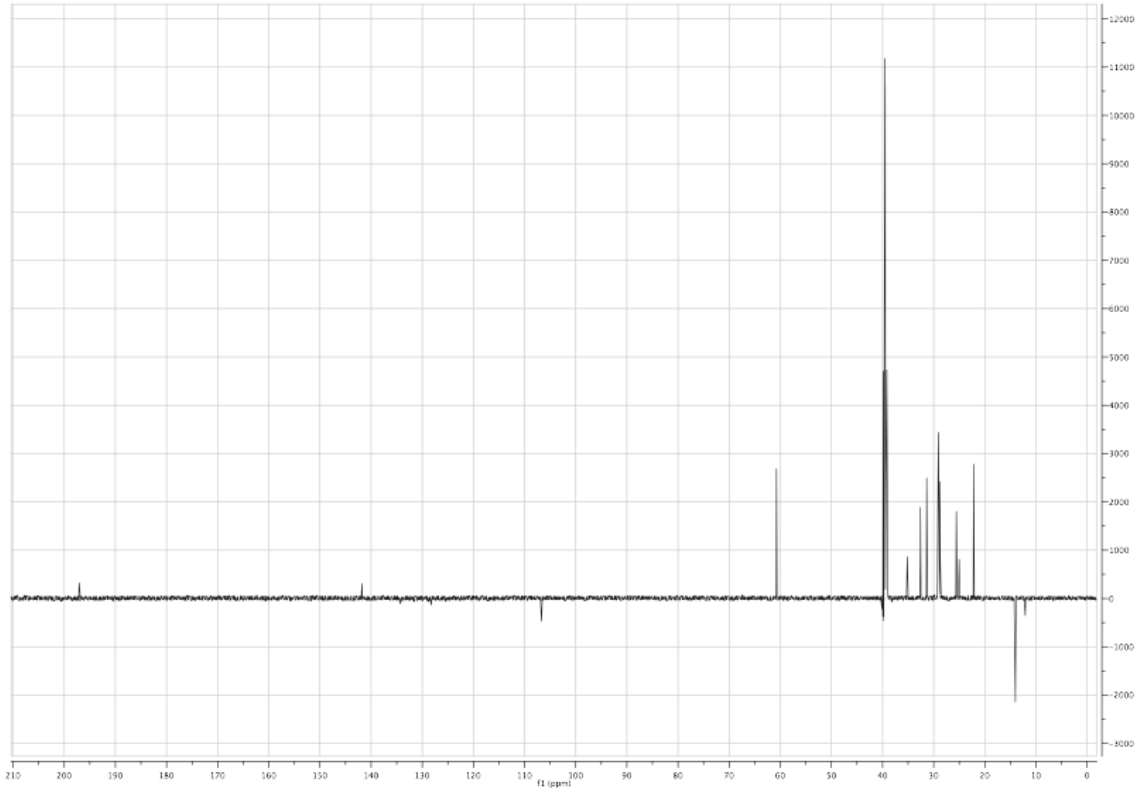
(*Z*)-3-aminotetradec-2-en-4-one, 10.



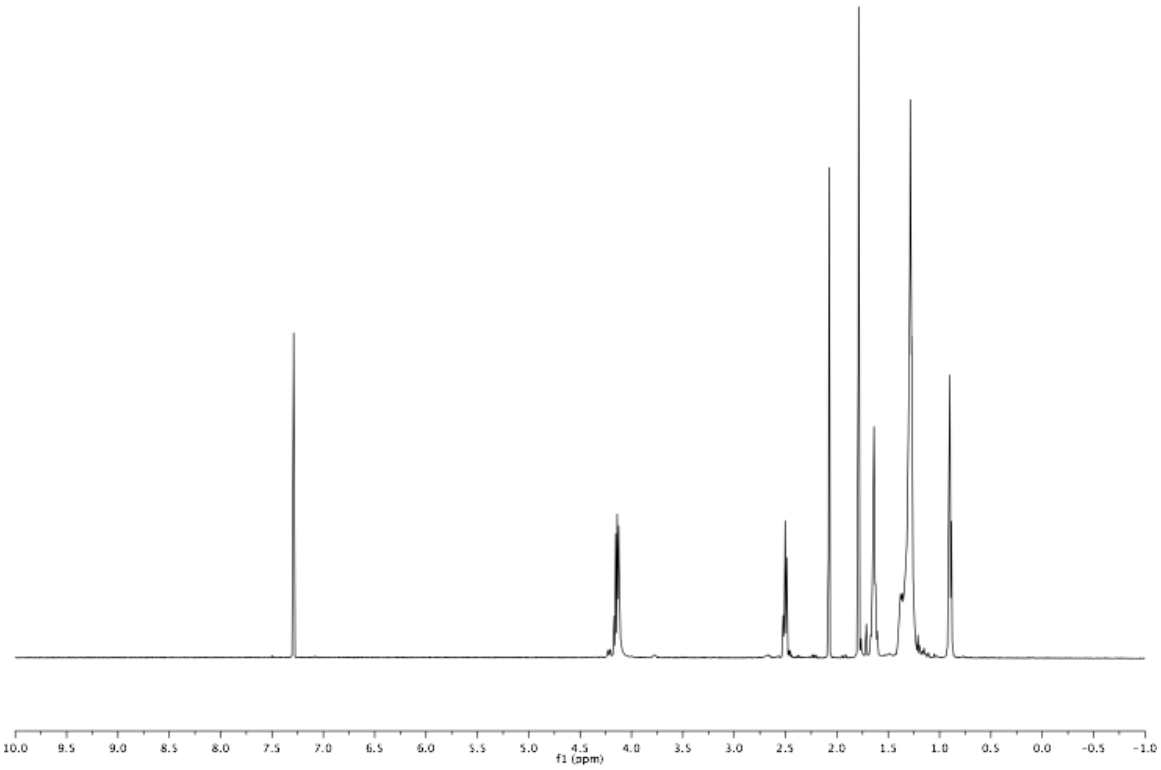


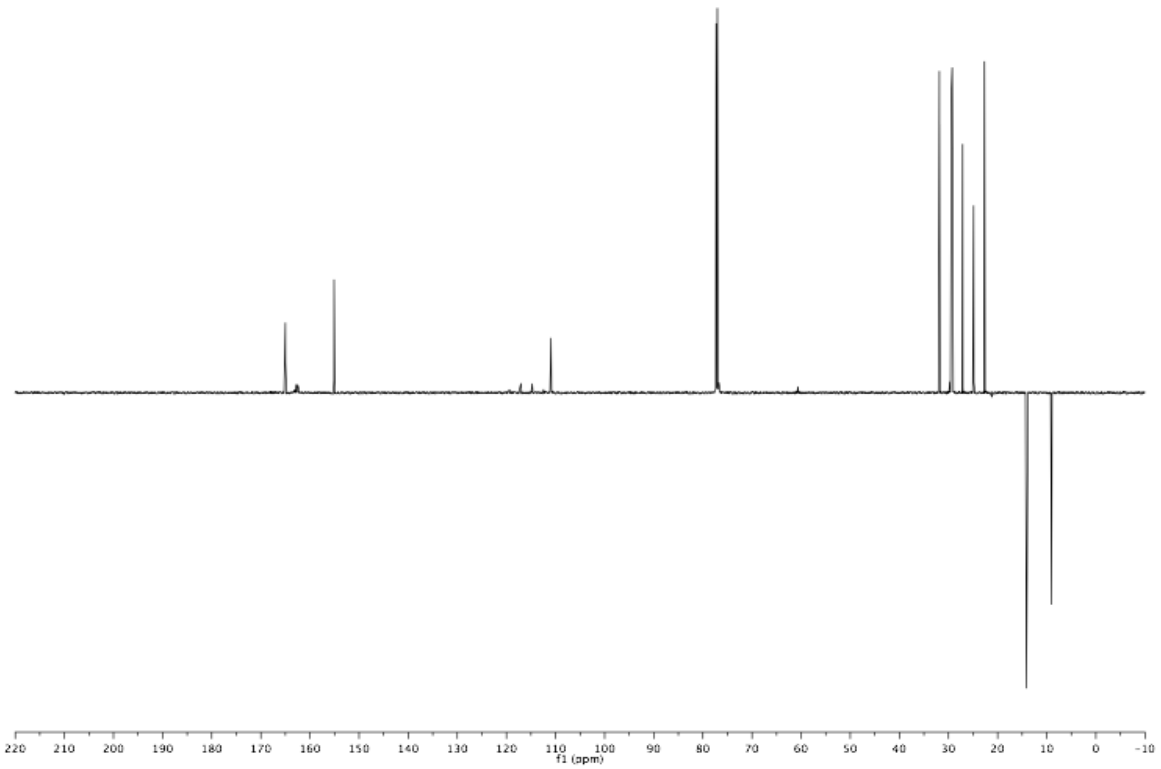
(*Z*)-3-aminohexadec-2-en-4-one, 11.



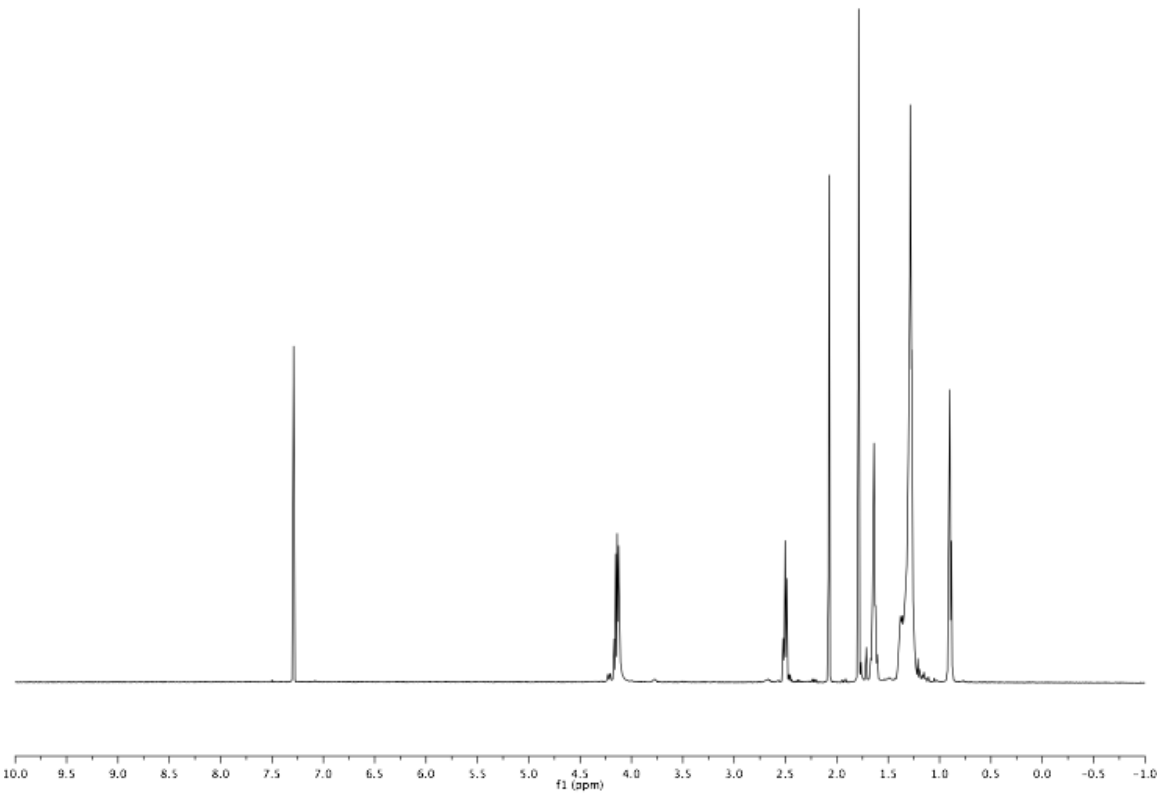


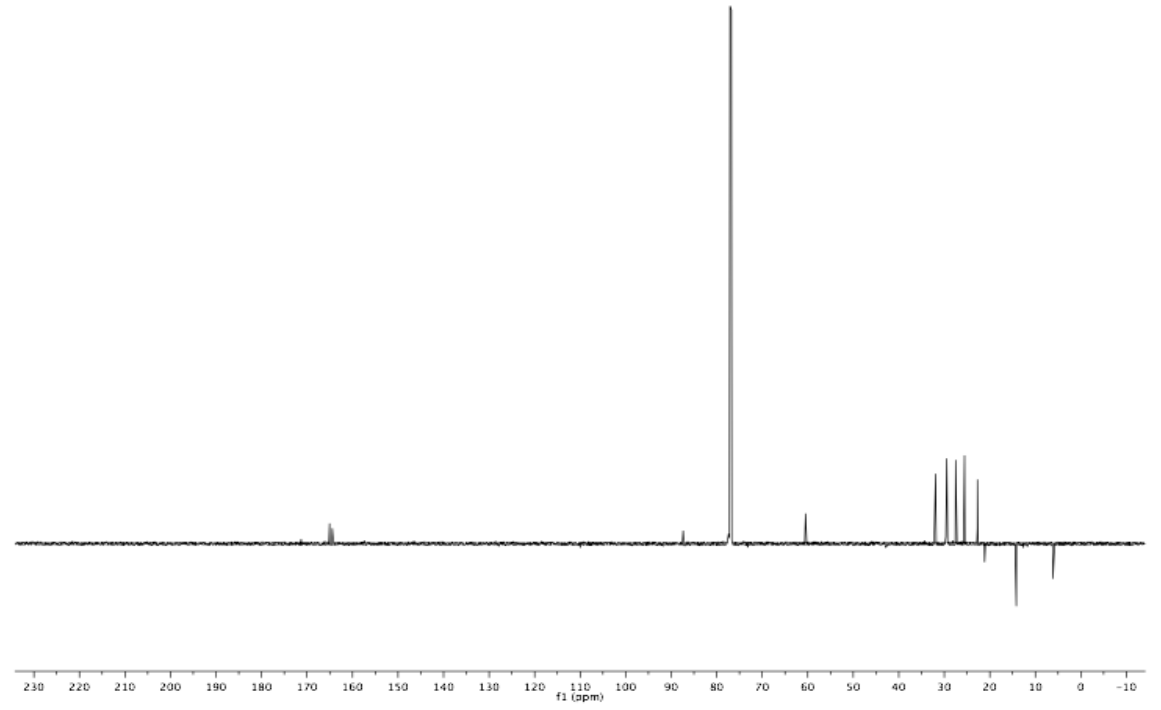
3-methyl-5-nonylisoxazol-4-amine, 15. (464)



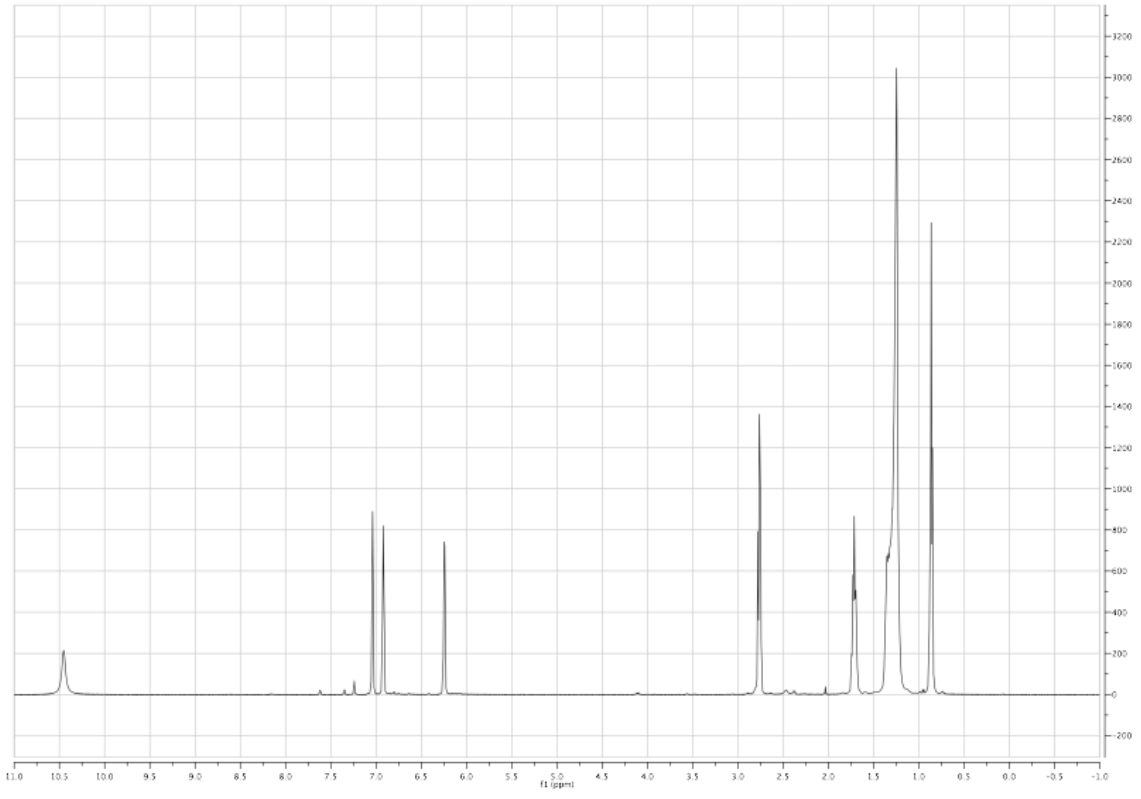


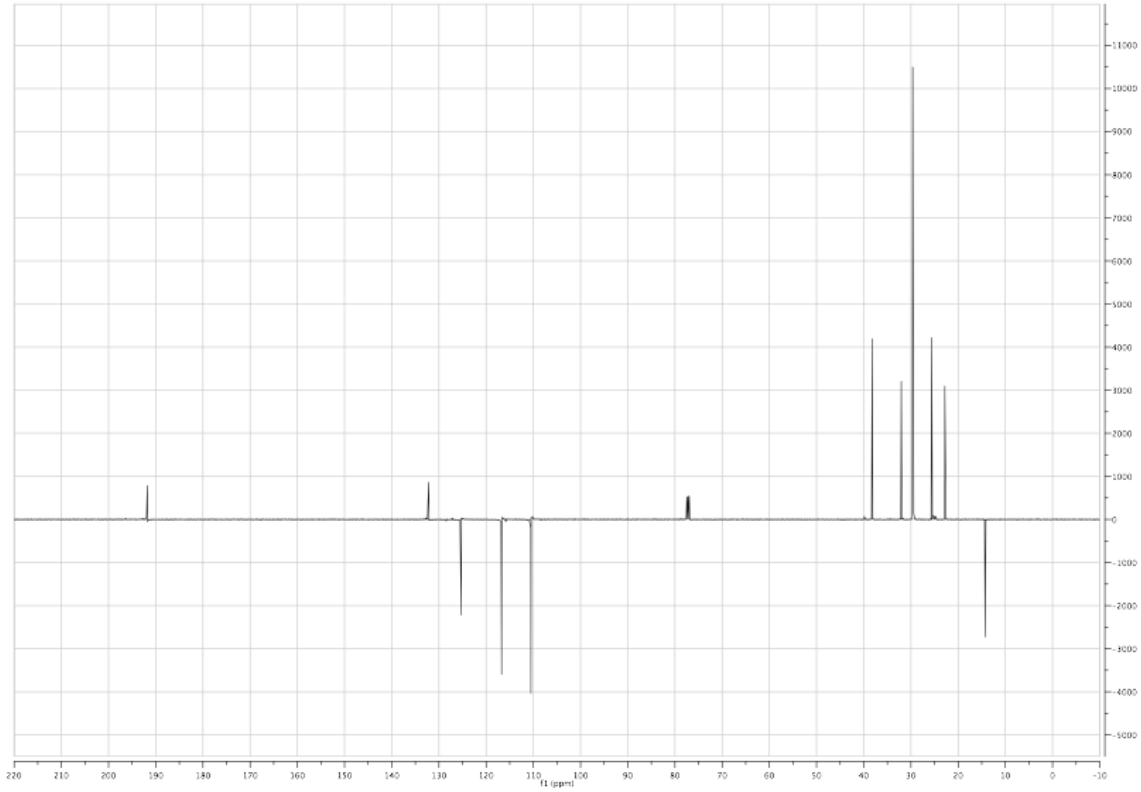
4-methyl-3-nonylisoxazol-5-amine, 16. (475)



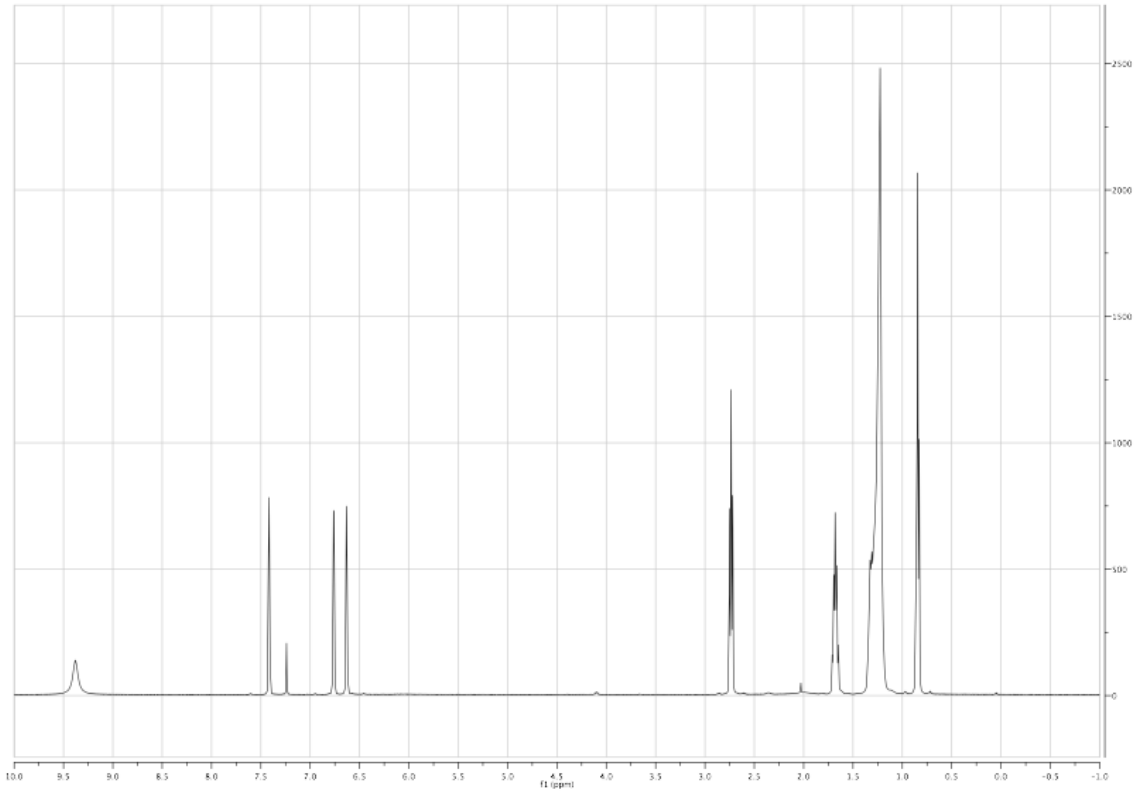


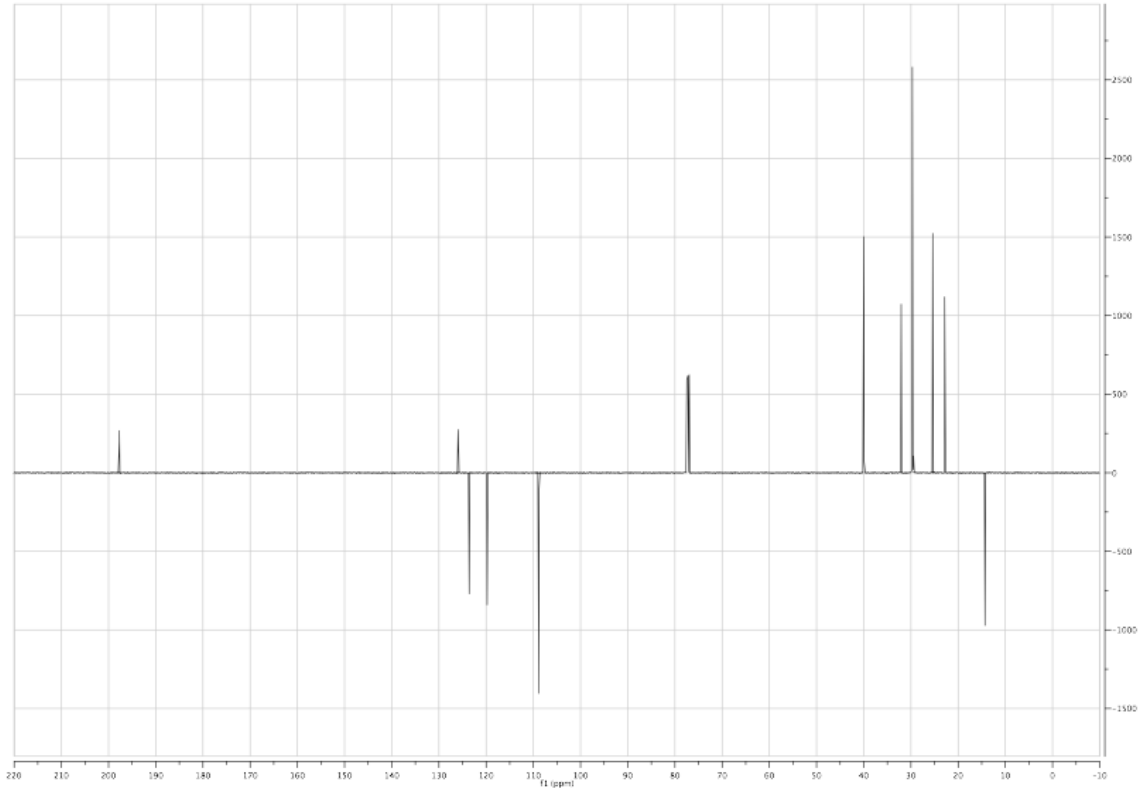
1-(1*H*-pyrrol-2-yl)decan-1-one, 17.



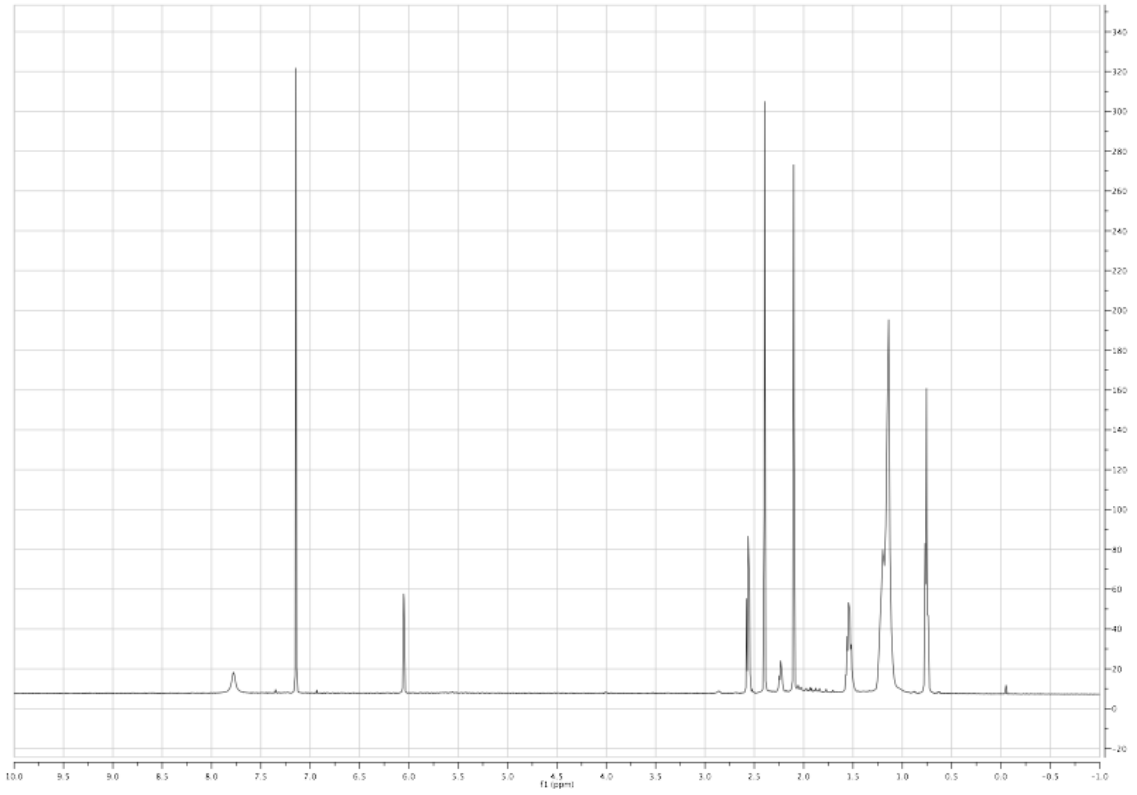


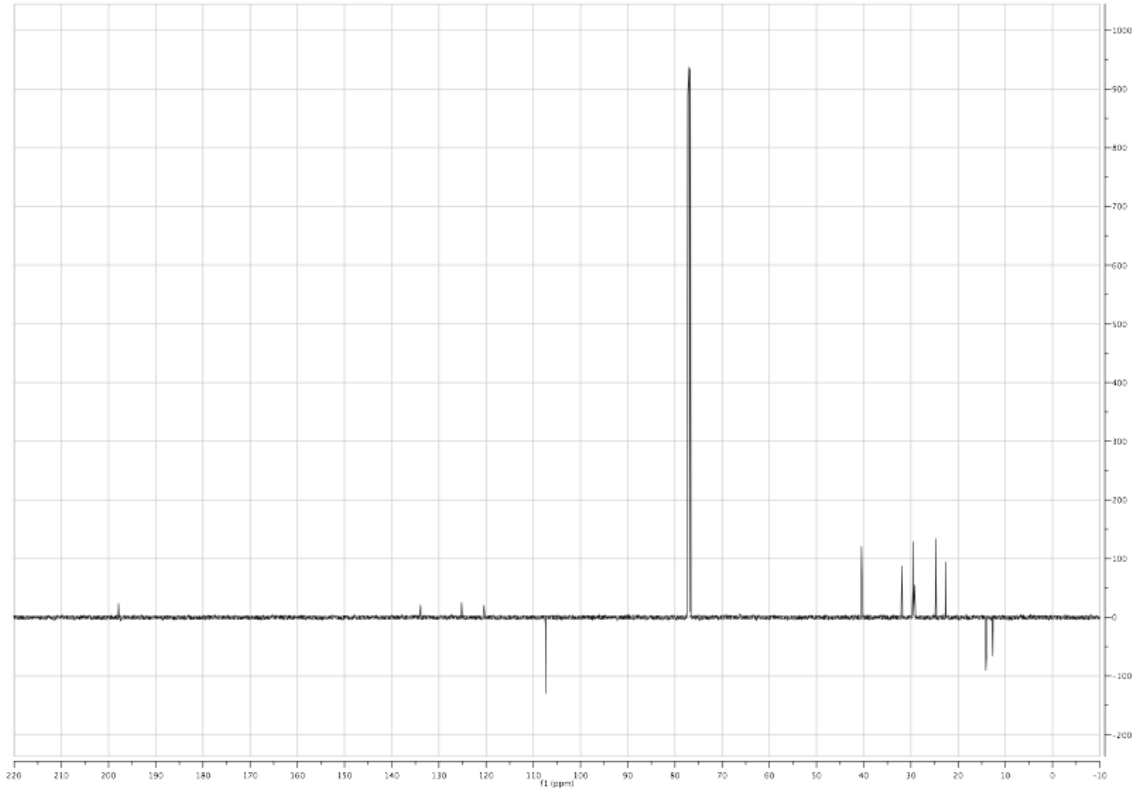
1-(1*H*-pyrrol-3-yl)decan-1-one, 18.



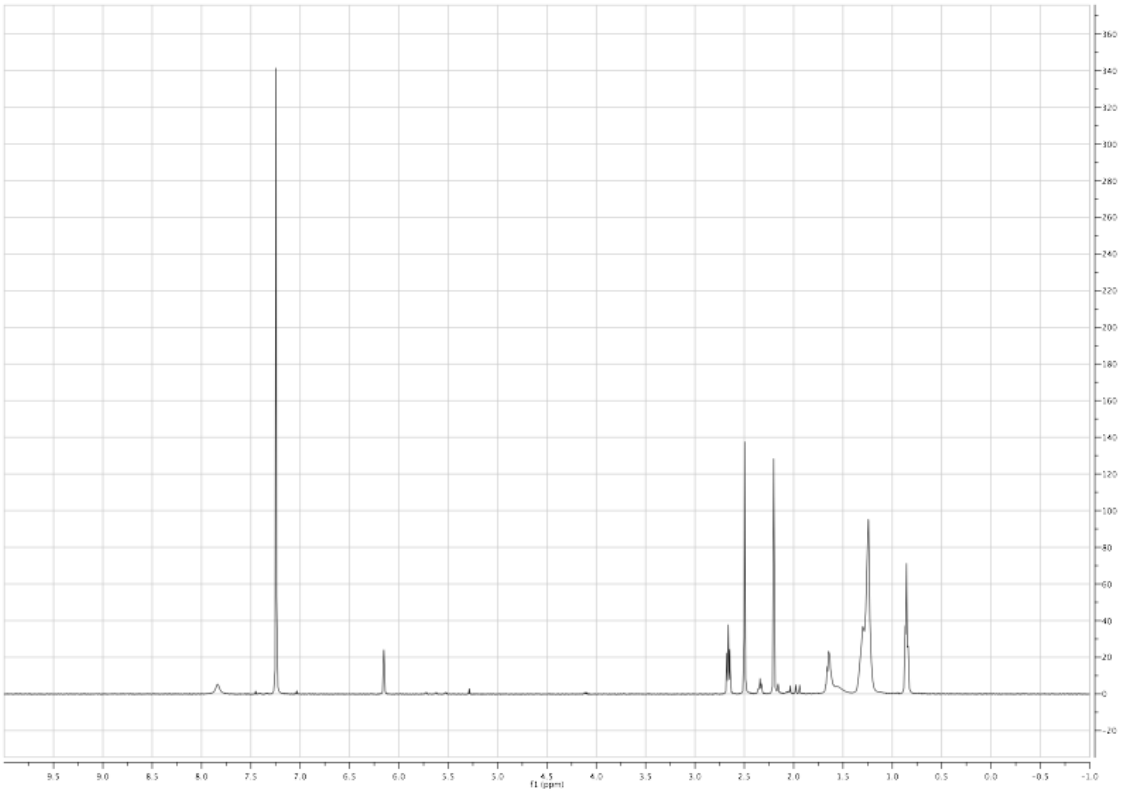


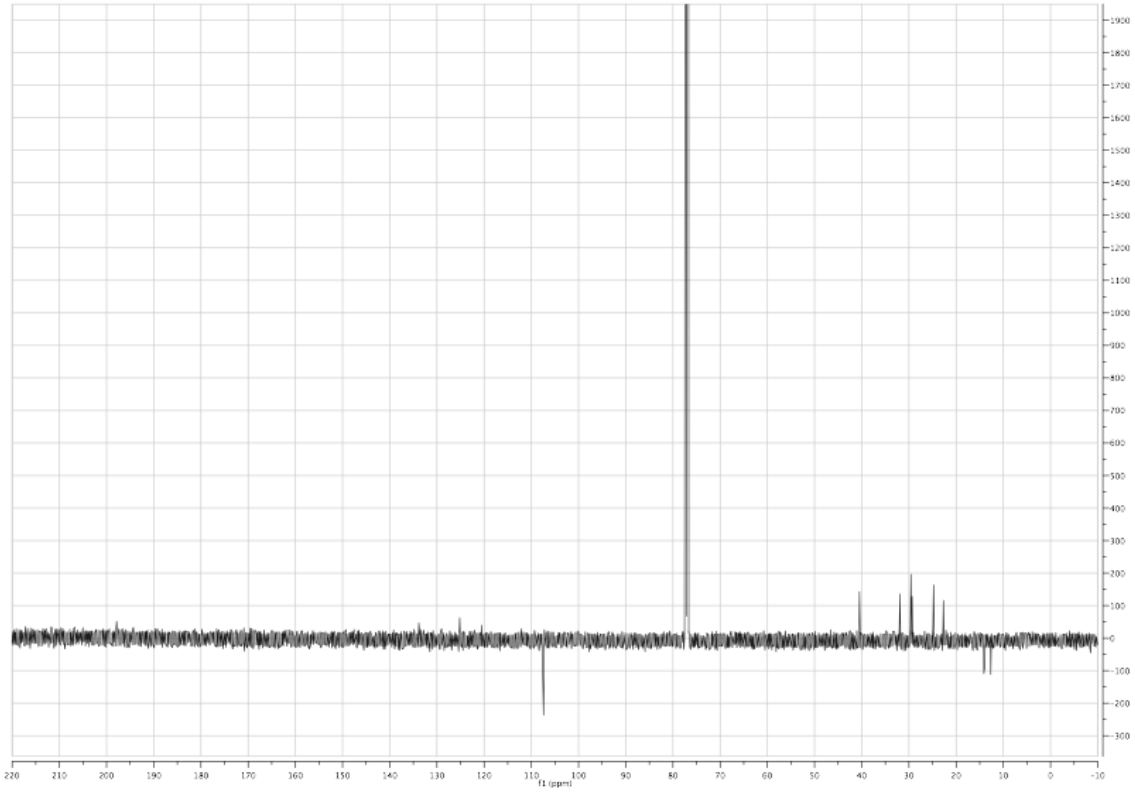
1-(2,5-dimethyl-1*H*-pyrrol-3-yl)decan-1-one, 19.



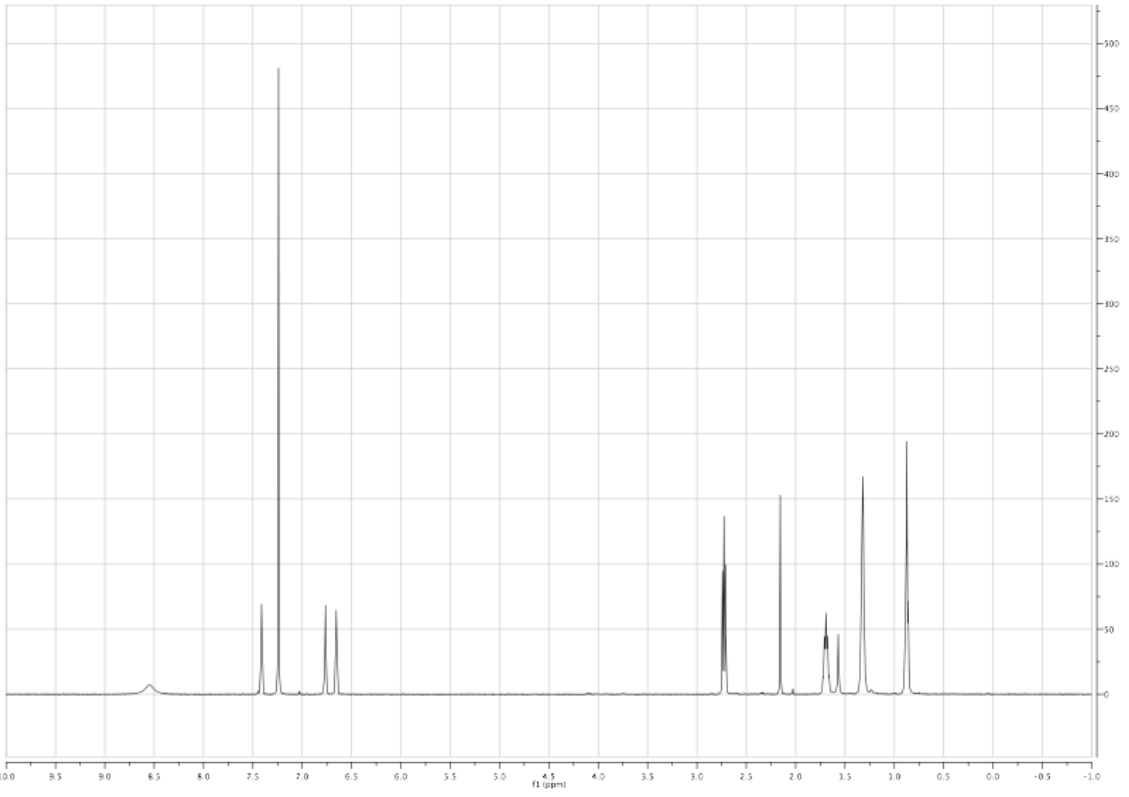


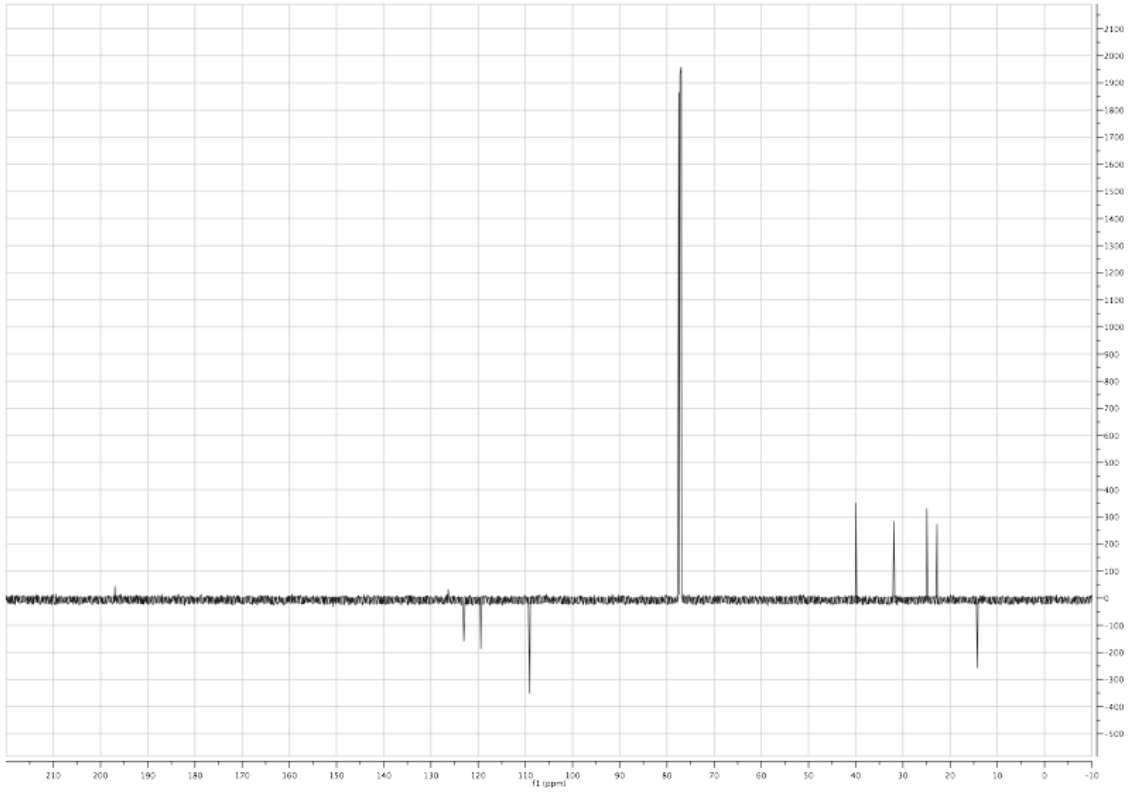
1(2,4-dimethyl-1*H*-pyrrol-3-yl)decan-1-one, 20.



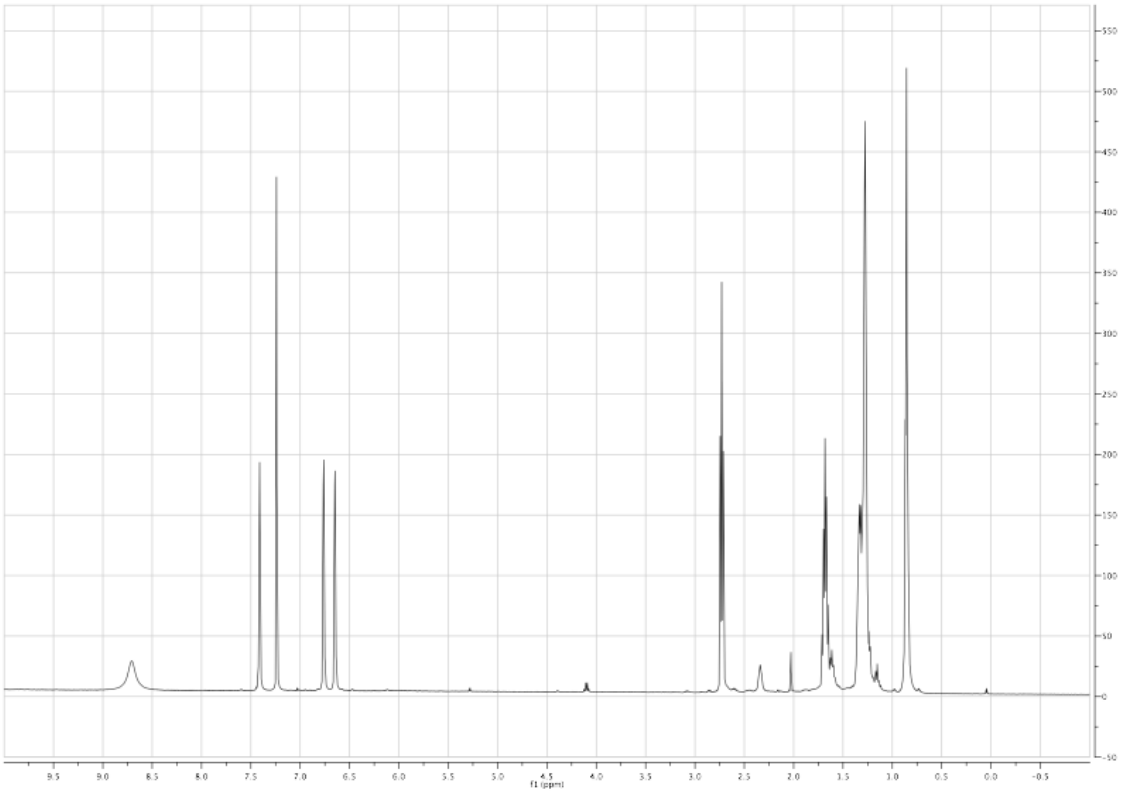


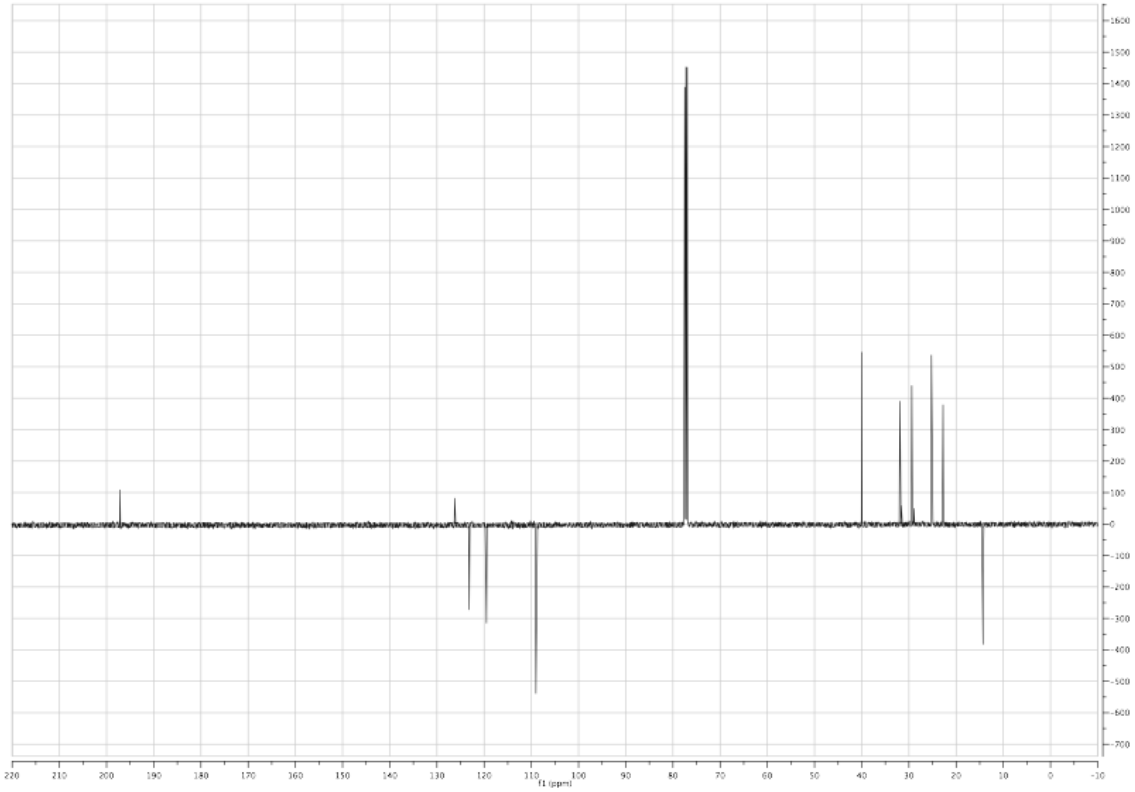
1-(1*H*-pyrrol-3-yl)hexan-1-one, 21.



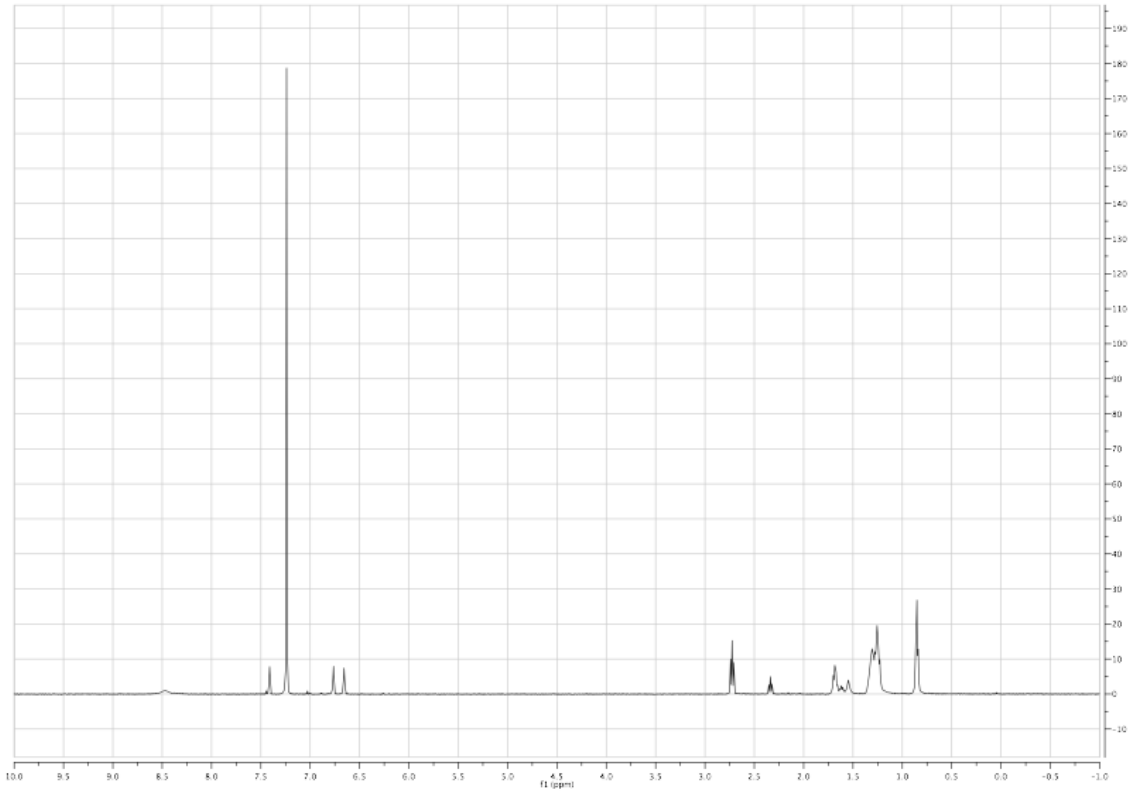


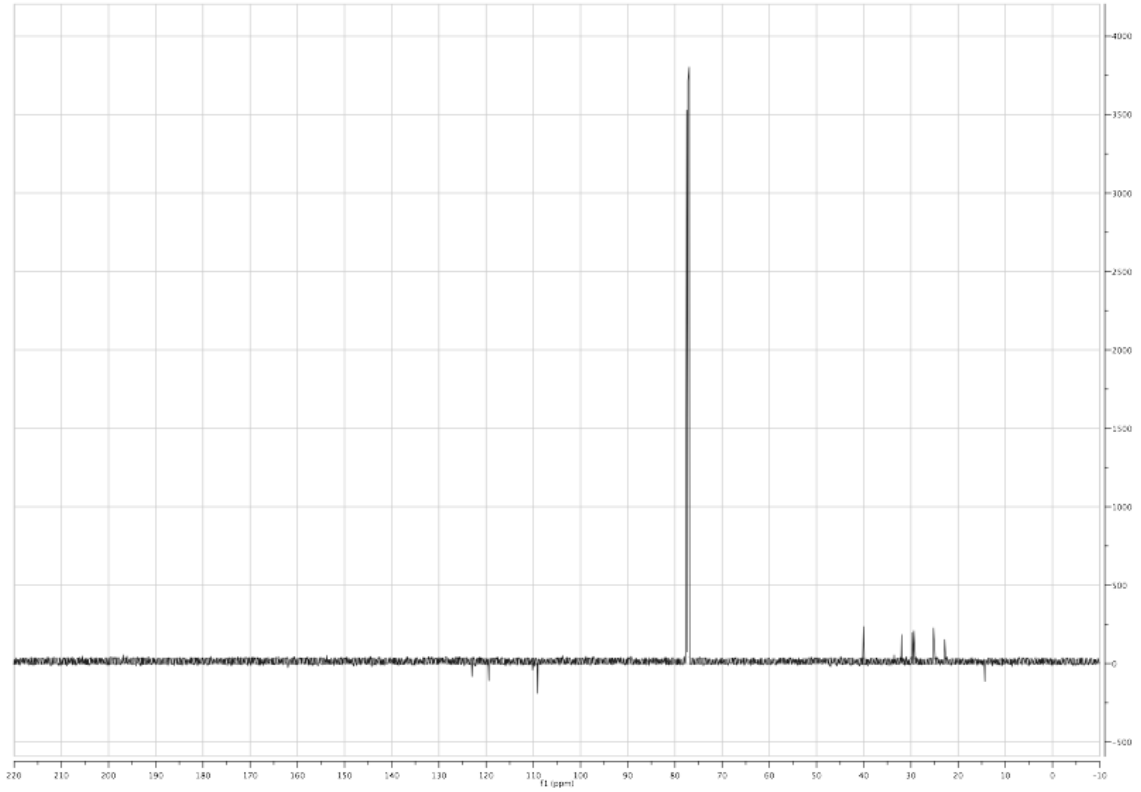
1-(1*H*-pyrrol-3-yl)heptan-1-one, 22.



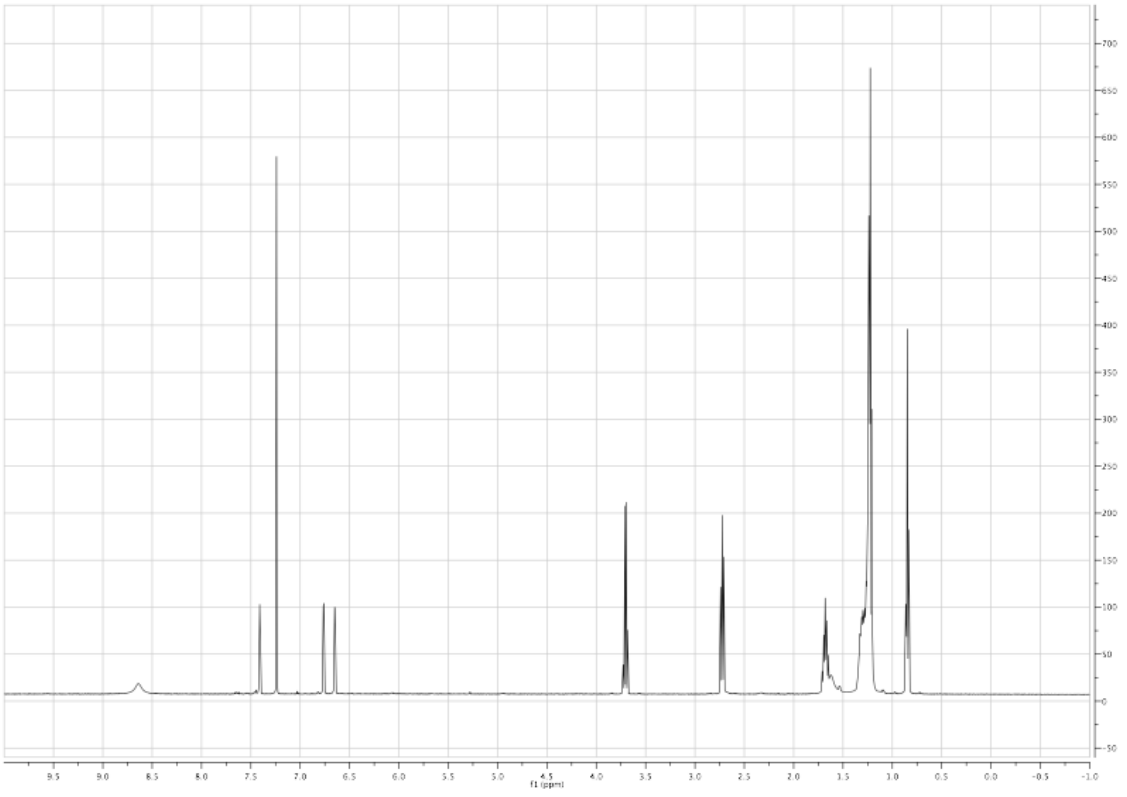


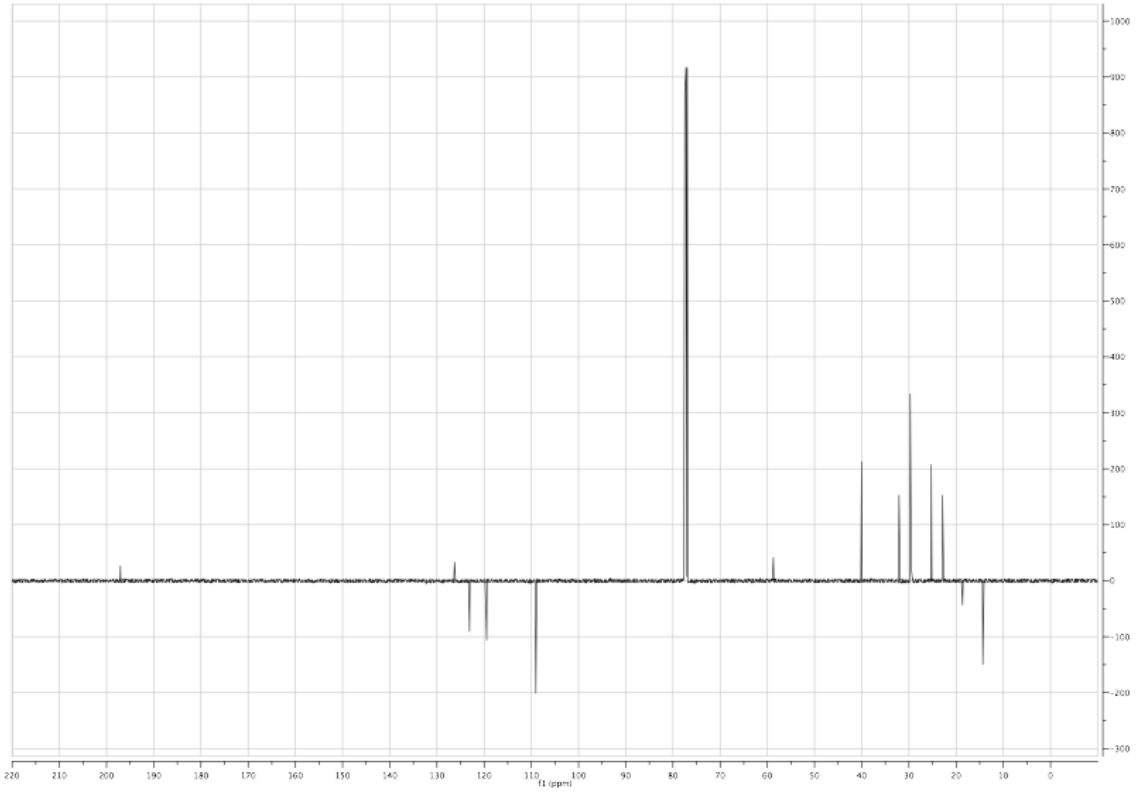
1-(1*H*-pyrrol-3-yl)octan-1-one, 23.



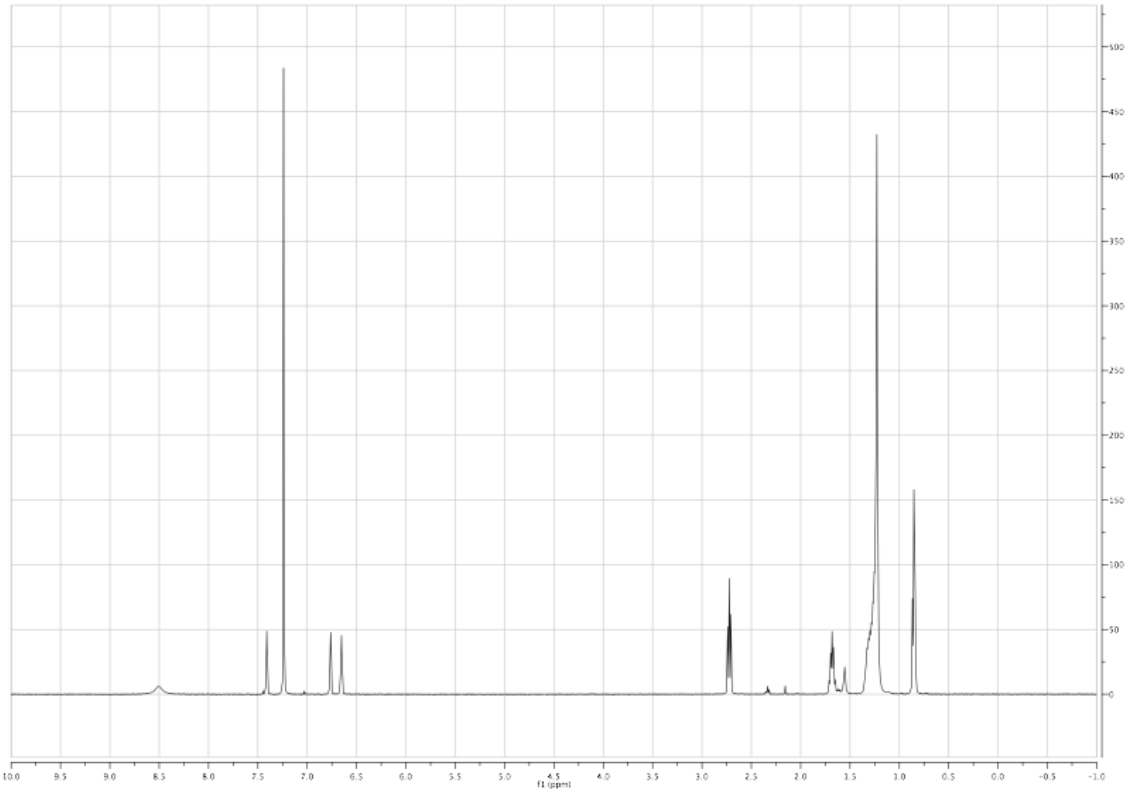


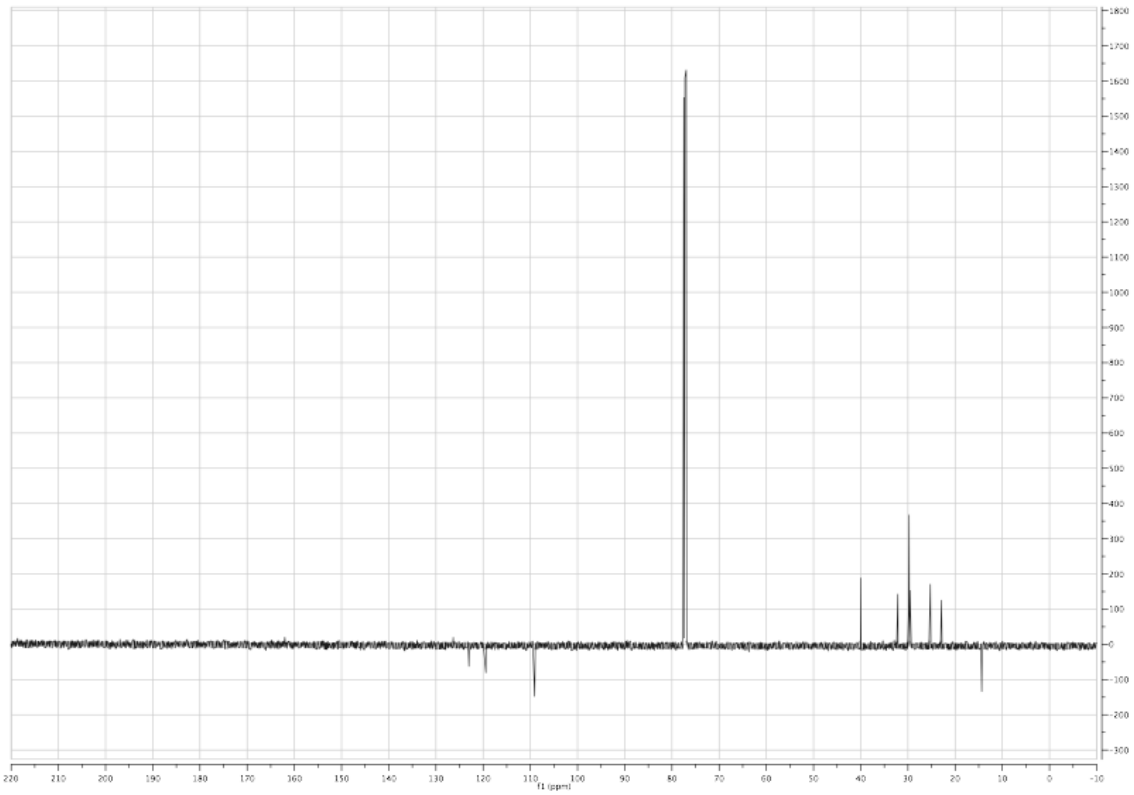
1-(1*H*-pyrrol-3-yl)nonan-1-one, 24.



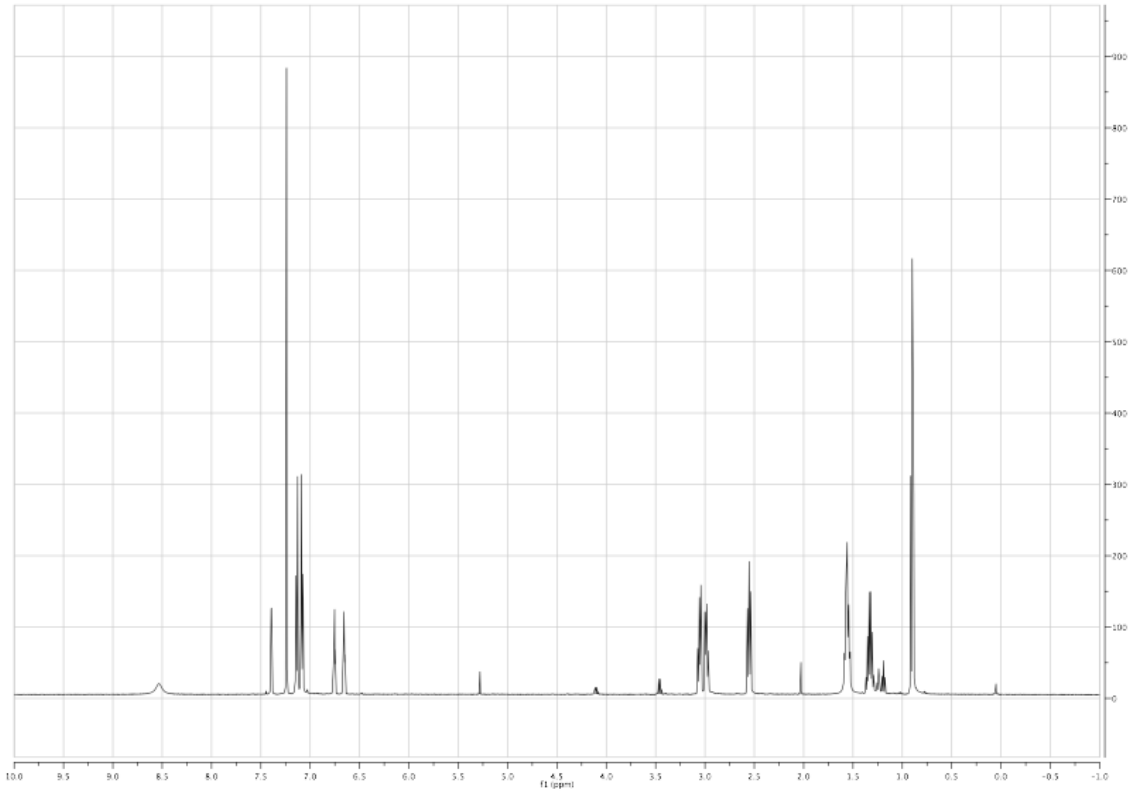


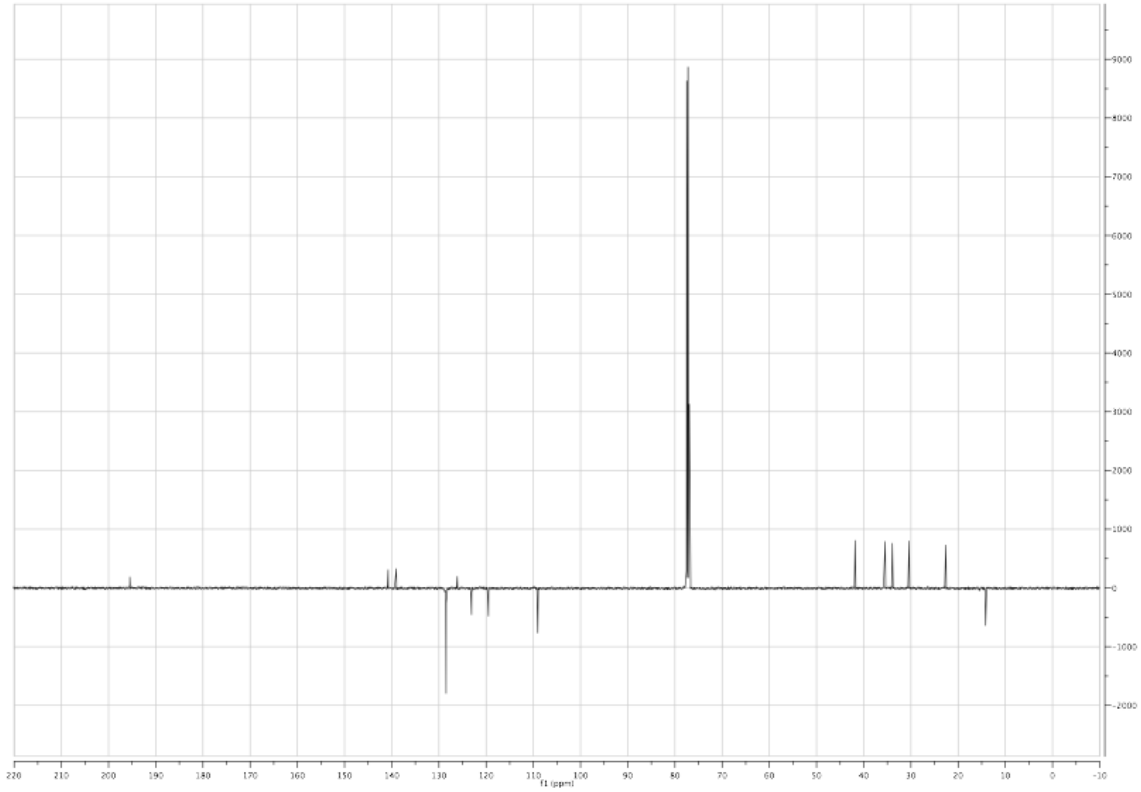
1-(1*H*-pyrrol-3-yl)dodecan-1-one, 25.



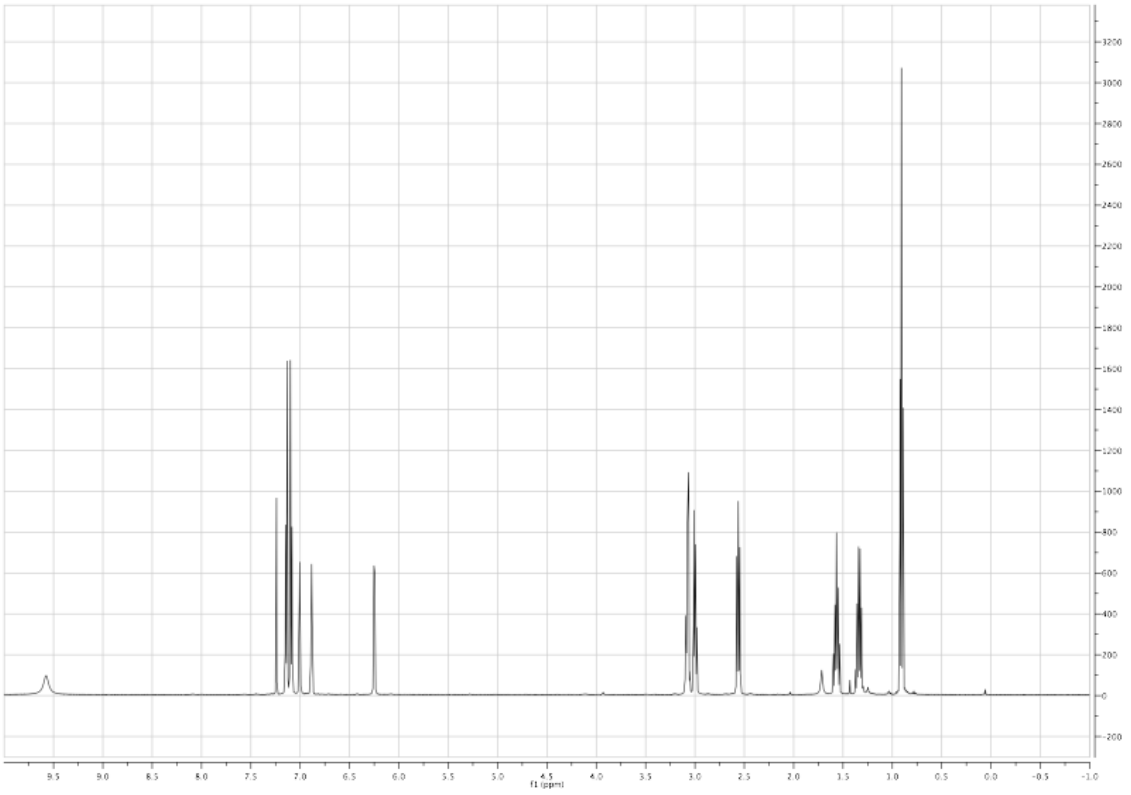


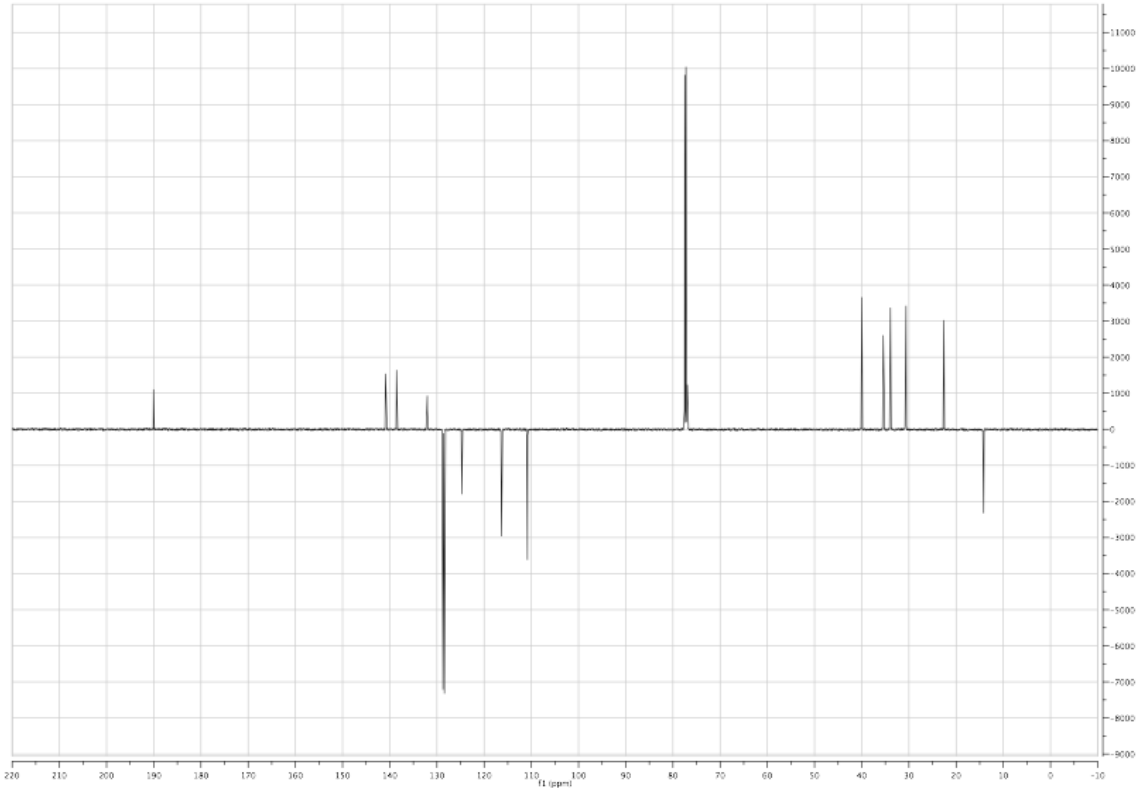
3-(4-butylphenyl)-1-(1*H*-pyrrol-3-yl)propan-1-one, 26.



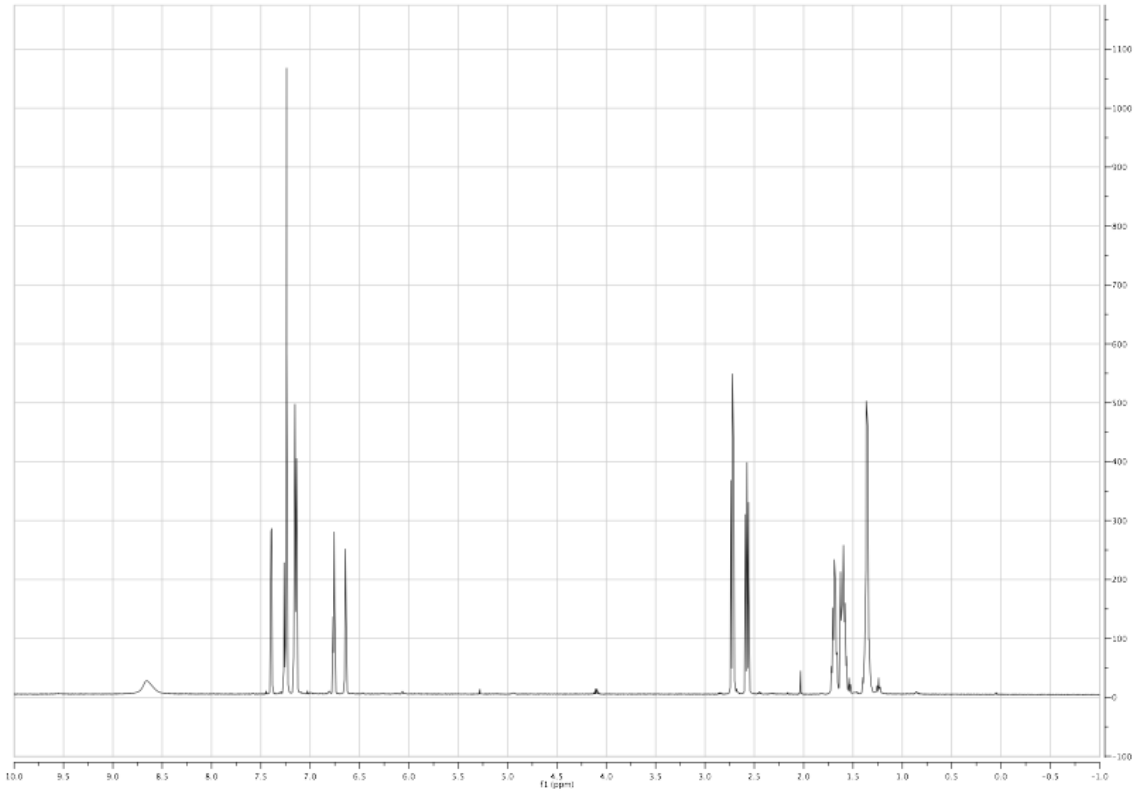


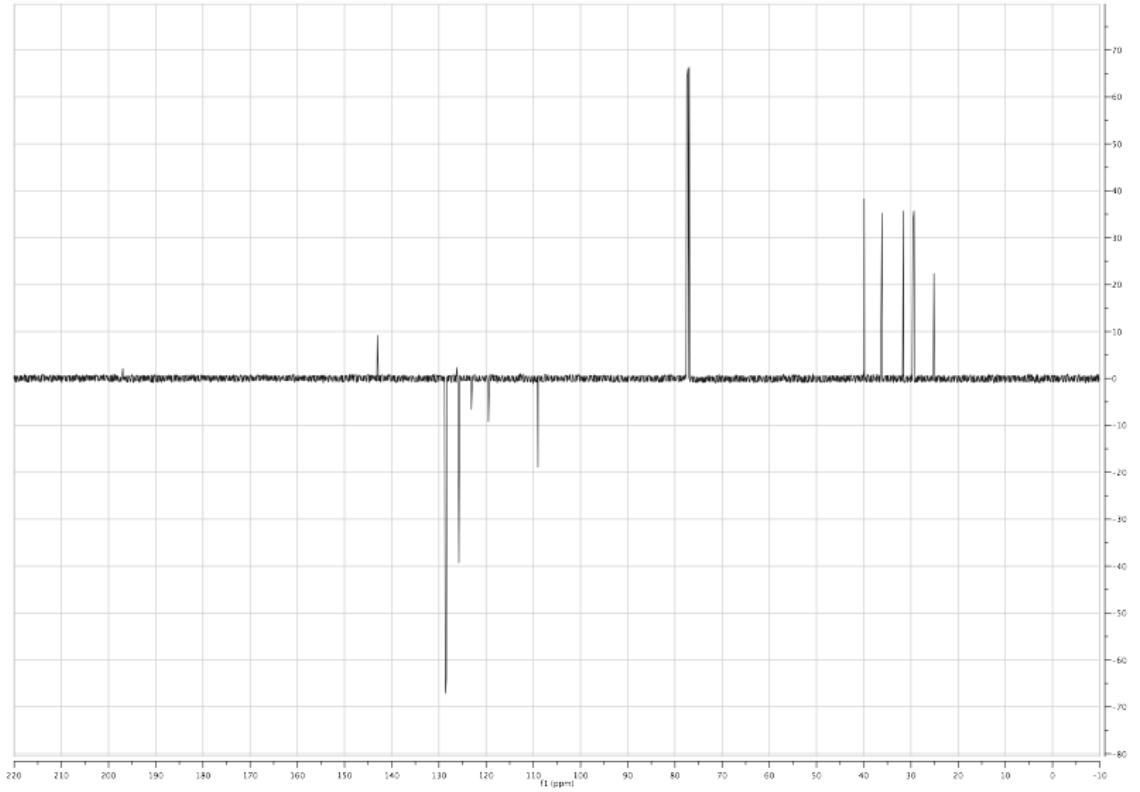
3-(4-butylphenyl)-1-(1*H*-pyrrol-2-yl)propan-1-one, 27.



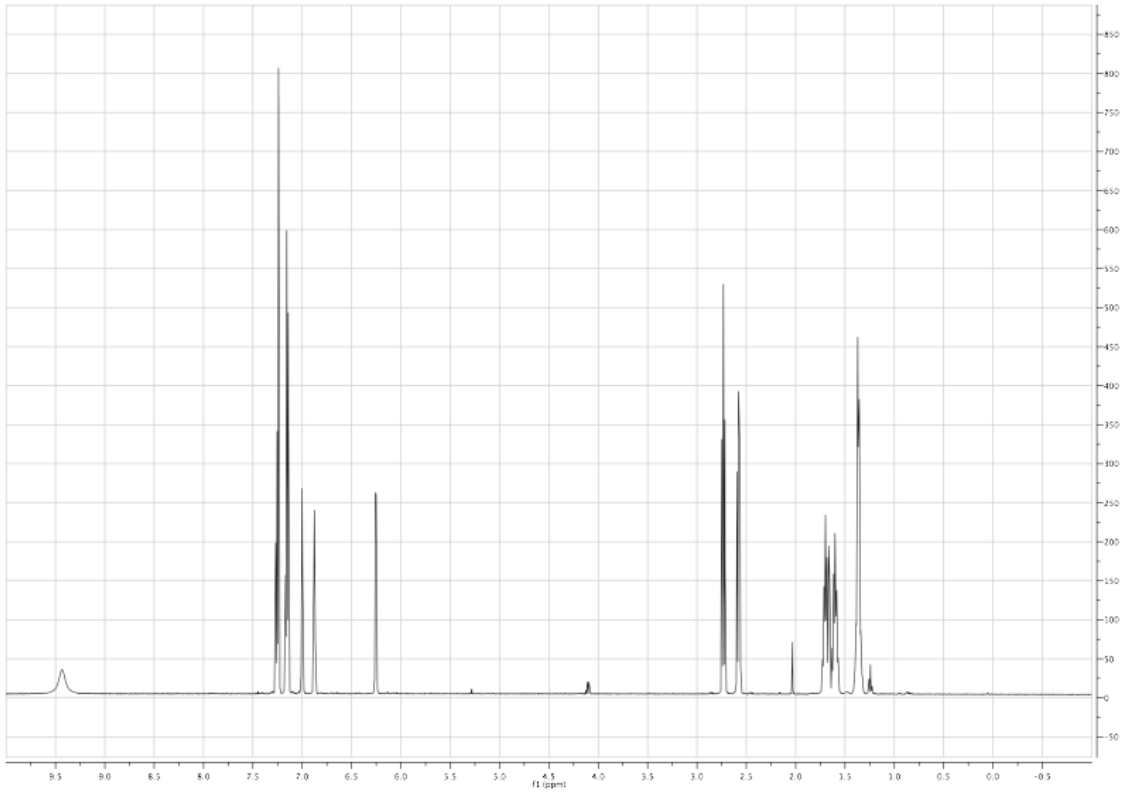


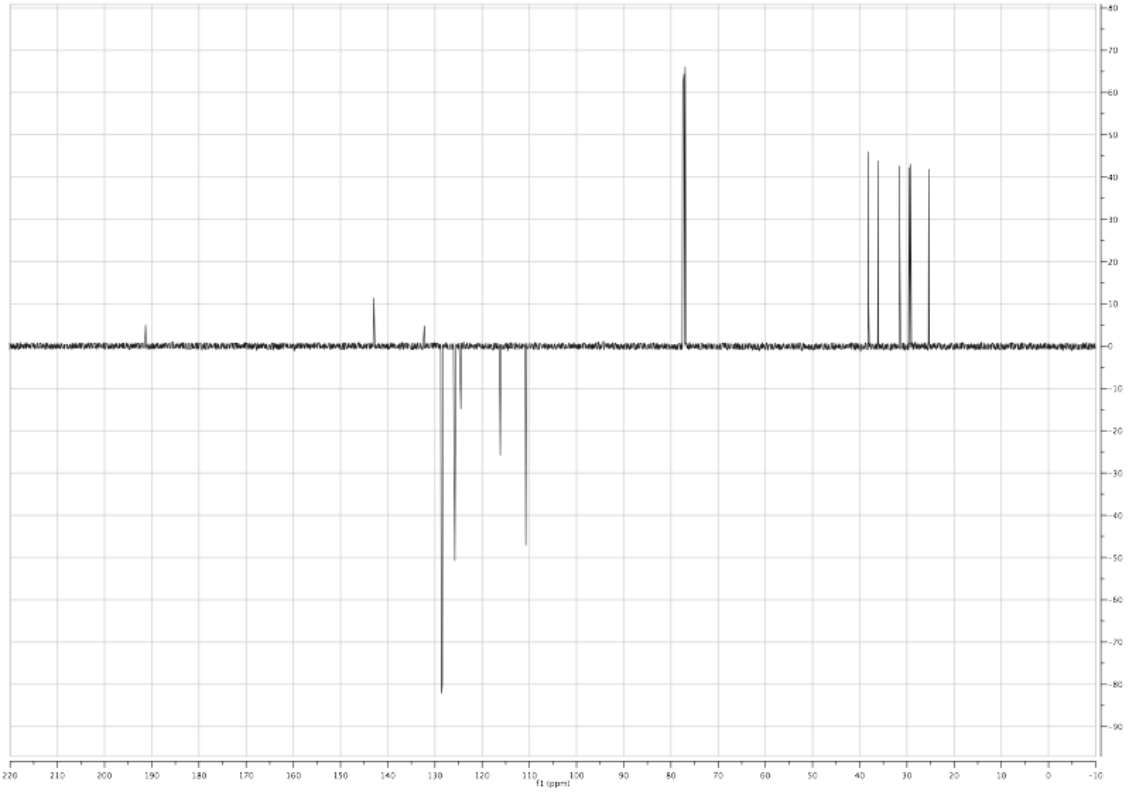
7-phenyl-1-(1*H*-pyrrol-3-yl)heptan-1-one, 28.



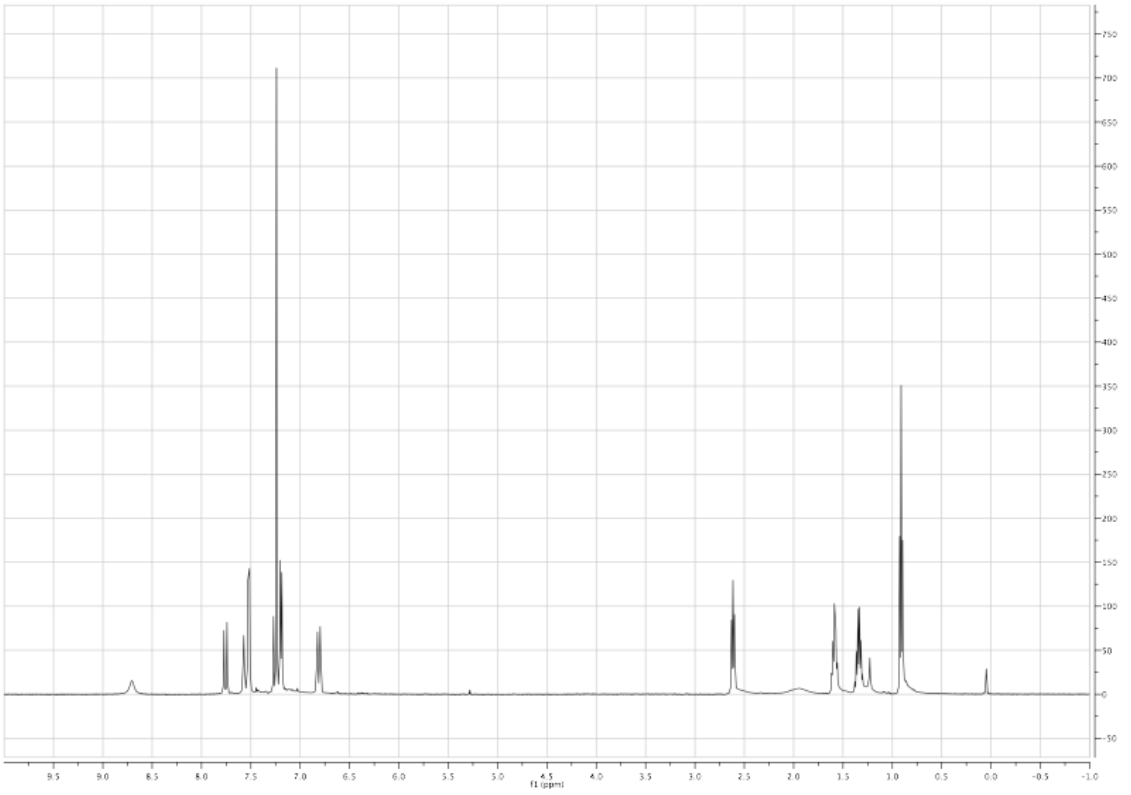


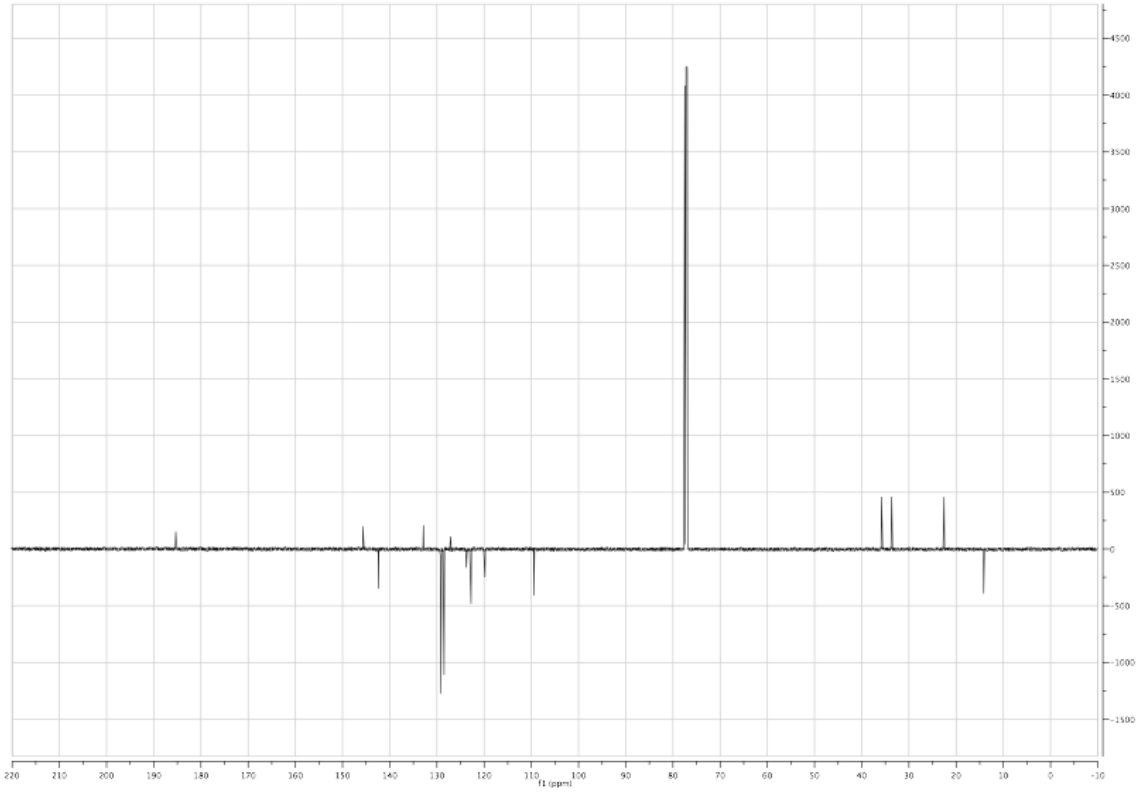
7-phenyl-1-(1*H*-pyrrol-2-yl)heptan-1-one, 29.



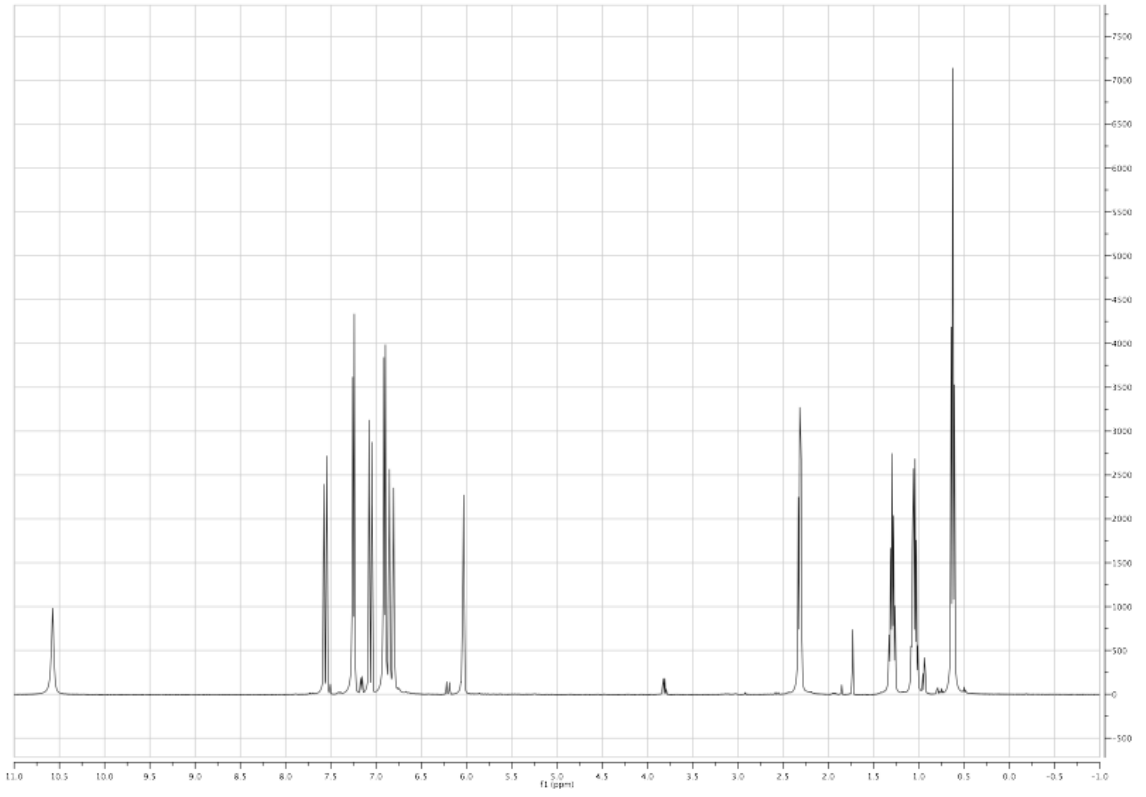


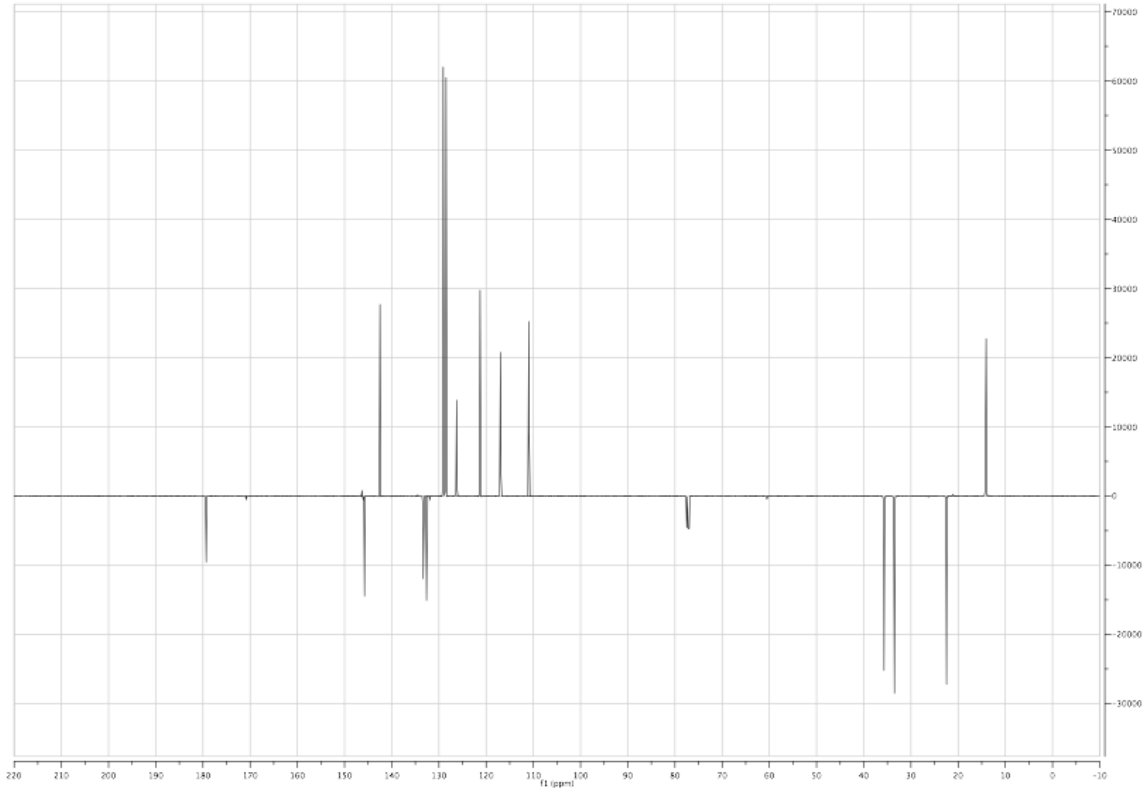
3-(4-butylphenyl)-1-(1*H*-pyrrol-3-yl)prop-2-en-1-one, 30.



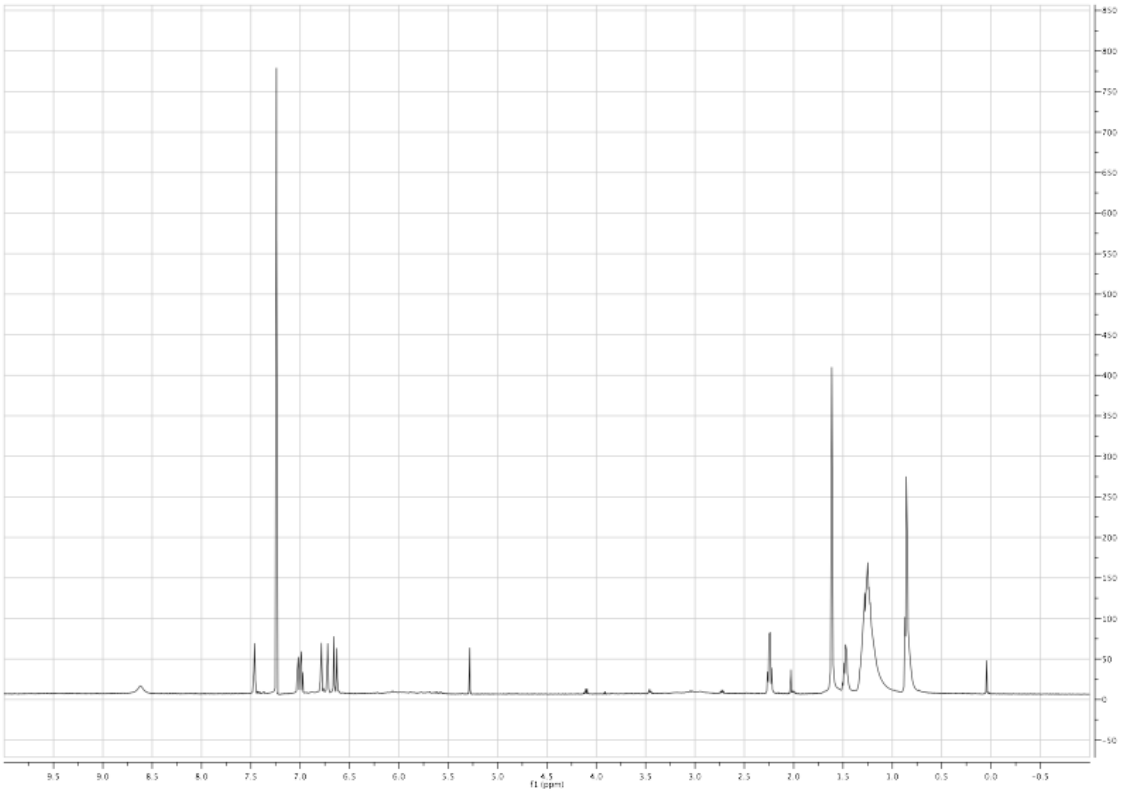


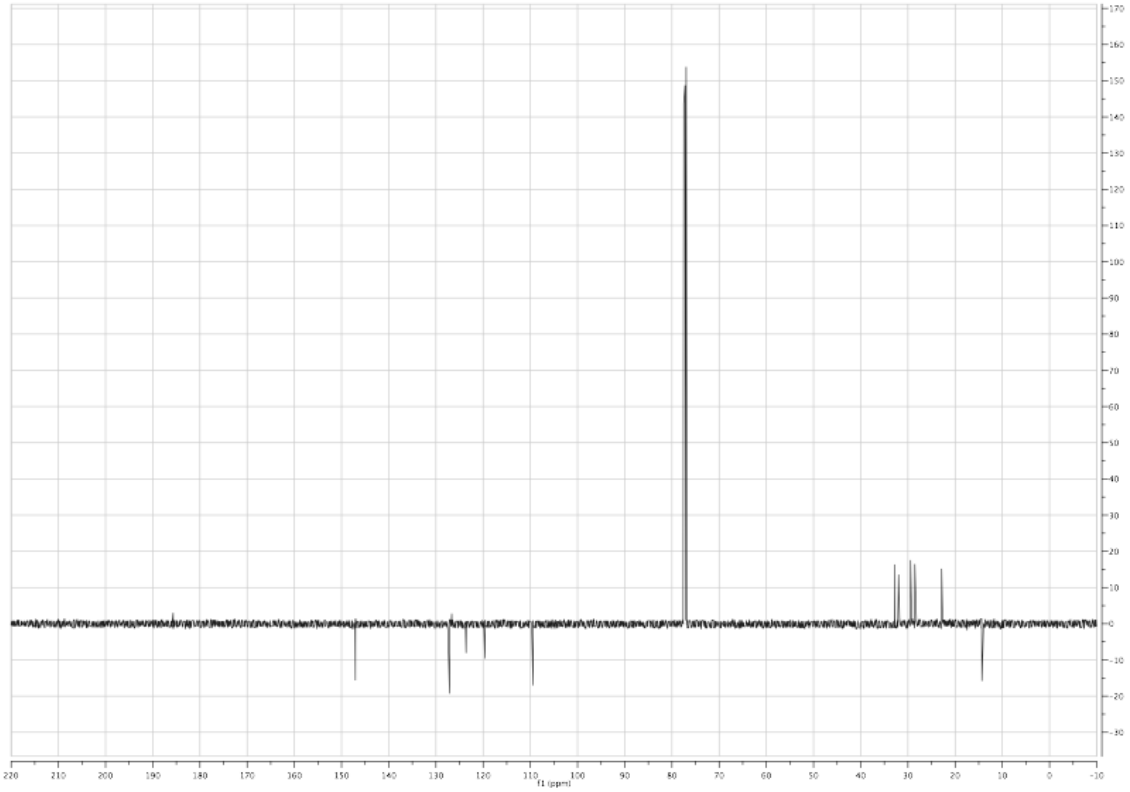
3-(4-butylphenyl)-1-(1*H*-pyrrol-2-yl)prop-2-en-1-one, 31.



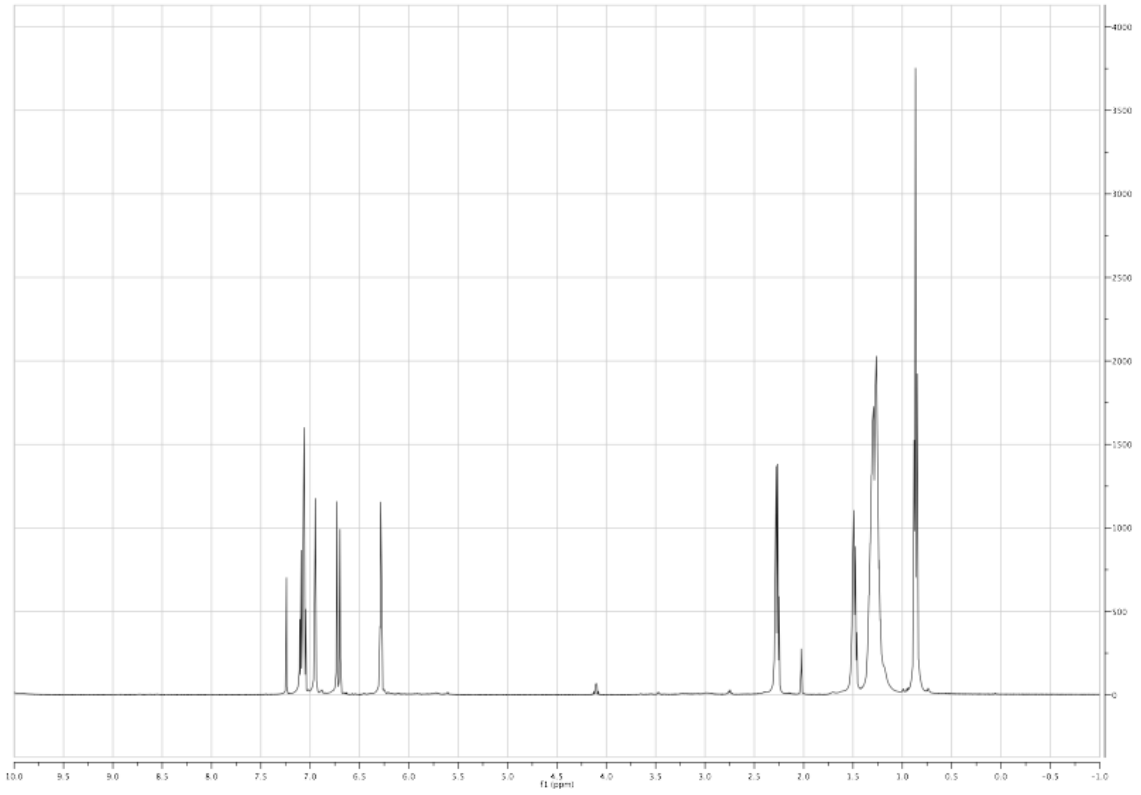


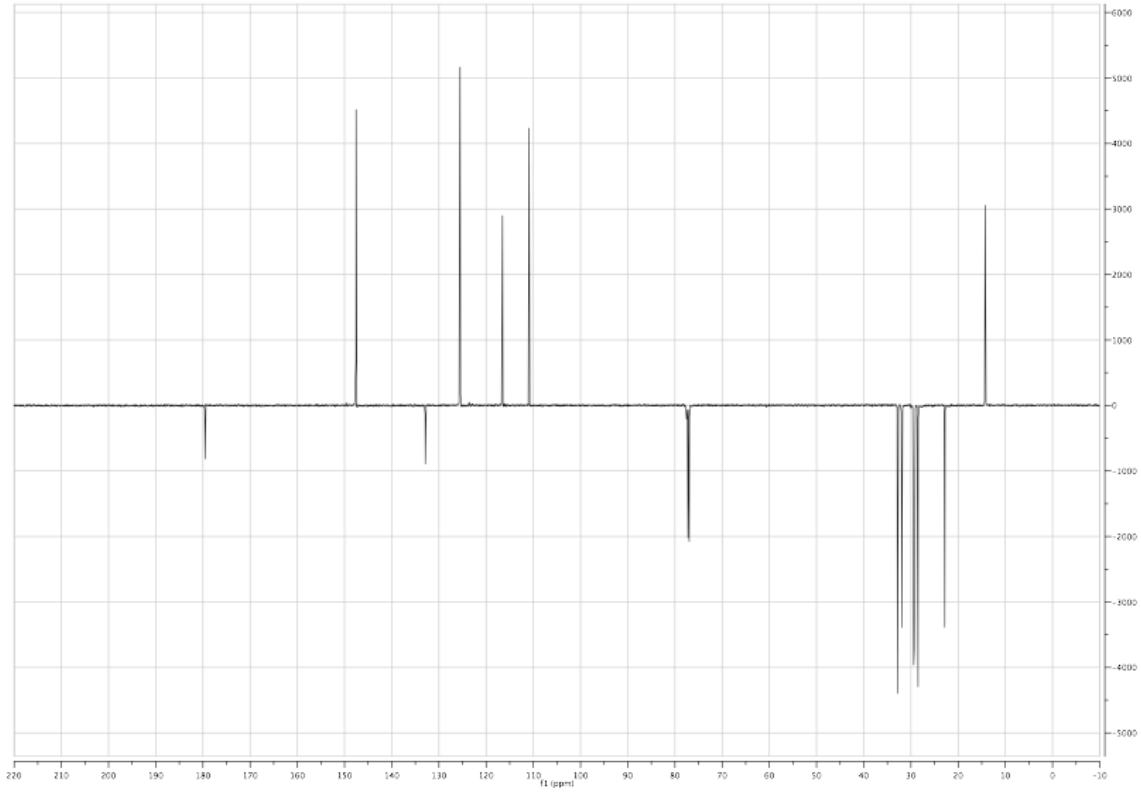
(*E*)-1-(1*H*-pyrrol-3-yl)dec-2-en-1-one, 32.



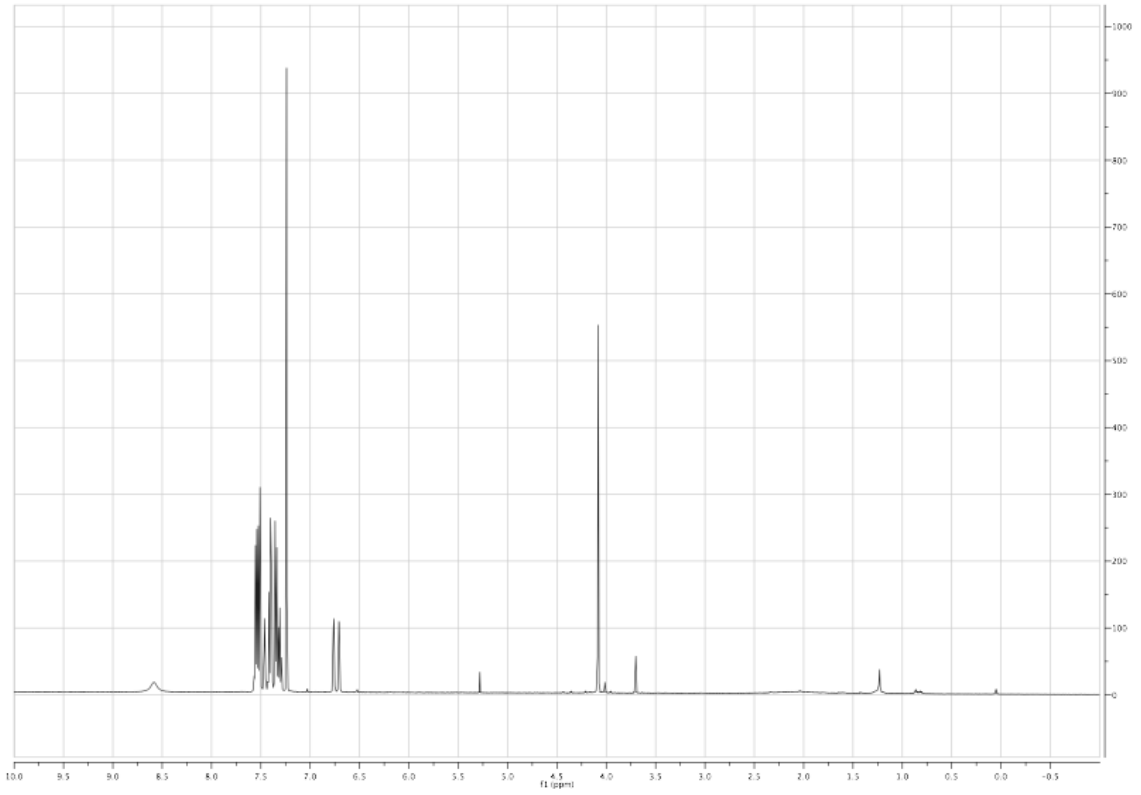


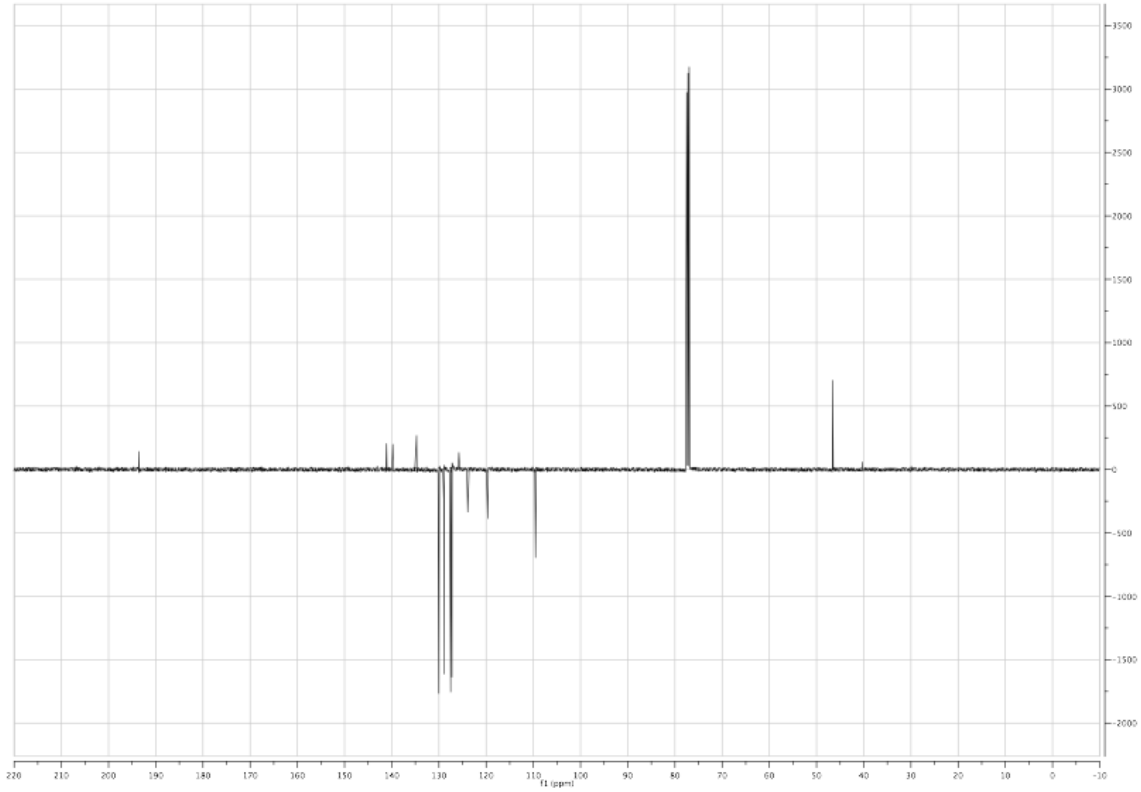
(*E*)-1-(1*H*-pyrrol-2-yl)dec-2-en-1-one, 33.





2-([1,1’-biphenyl]-4-yl)-1-(1*H*-pyrrol-3-yl)ethanone, 34.





2-([1,1’-biphenyl]-4-yl)-1-(1*H*-pyrrol-2-yl)ethanone, 35.