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Supporting Information

Harnessing a Continuous-Flow Persulfuric Acid Generator for Direct Oxidative Aldehyde Esterifications

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1. General information

All solvents and chemicals were obtained from typical commercial vendors and were used as received, without any further purification.

Column chromatographic purification was performed by using a Biotage Isolera automated flash chromatography system with cartridges packed with KP-SIL, 60 Å (32–63 µm particle size). Analytical thin-layer chromatography (TLC) was carried out using Merck silica gel 60 GF254 plates. Compounds were visualized by means of UV or by using $KMnO_4$.

^1H- and ^{13}C-NMR spectra were recorded on a Bruker Avance III 300 MHz instrument at room temperature, in $CDCl_3$ as solvent, at 300 MHz and 75 MHz, respectively. Chemical shifts (δ) are reported in ppm using TMS as internal standard. Coupling constants are given in Hz units.

Analytical HPLC measurements were carried out on a C18 reversed-phase column (150 × 4.6 mm, particle size 5 mm) at 37 °C using mobile phases A [H_2O/CH_3CN 90:10 (v/v) + 0.1% TFA] and B (CH_3CN + 0.1% TFA) at a flow rate of 1.5 mL min^{-1}. The gradient applied was as follows: linear increase from 30% solution B to 100% B in 8 min, hold at 100% solution B for 2 min.

GC-FID analysis was performed on a Shimadzu GCFID 2030 instrument equipped with a flame ionization detector, using an RTX-5MS column (30 m × 0.25 mm ID × 0.25 µm) and helium as carrier gas (40 cm s^{-1} linear velocity). The injector temperature was set to 280 °C. After 1 min at 50 °C, the temperature was increased by 25 °C min^{-1} to reach 300 °C and then kept constant at 300 °C for 3 min. The detector gases used for flame ionization were hydrogen and synthetic air (5.0 purity).

Optical rotation was measured in $CHCl_3$ (HPLC-grade) at 25 °C against the sodium D-line (λ= 589 nm) on a Perkin Elmer Polarimeter 341 using a 10-cm pathlength cell.

Equipment for the continuous flow reactions was assembled using commercially available components. Liquid streams were pumped by using Syrris® Asia syringe pumps. Flow systems were pressurized by using an adjustable backpressure regulator (BPR) from Zaiput. Reaction coils were heated by means of a conventional oil bath. Reagent feeds were either streamed directly or by using injection valves and sample loops. Sample loops and reactor coils were made by using perfluoroalkoxy alkane (PFA) tubings (1/16” OD, 0.80 mm ID).

A micro reaction calorimeter (µRC) from Thermal Hazard Technology was used to study the thermal behavior of the H_2SO_4–H_2O_2 reaction system.

Quantitative green metrics were calculated according to the literature.[S1]

CAUTION: Sulfuric acid is highly corrosive causing rapid tissue destruction and serious chemical burns. Persulfuric acid is one of the strongest oxidants known. It is unstable and potentially explosive, especially in mixtures with organic substances. Extreme care must therefore be taken when handling these substances! All equipment must be set up in a well-ventilated fume hood and personal protective equipment must be worn during experimentation. A thorough safety assessment should be made before conducting any experiments.

2. Reaction calorimetry experiments

2.1. Titration tests at different temperatures

Solution preparation:

1.0 M H_2O_2: 0.486 g 35 wt% aq. H_2O_2 was diluted to 5 mL with MeOH or *i*PrOH.
1.0 M H_2SO_4: 0.516 g 95% H_2SO_4 was diluted to 5 mL with MeOH or *i*PrOH.

NOTE: these concentrations were different from the ones used for the flow reactions.

Procedure:

The titration mode was selected and the official procedures for the calorimeter were followed. MeOH was used as the solvent for titration at 25 °C, 50 °C and 70 °C while *i*PrOH was used for titration at 80 °C. 300 µL H_2SO_4

solution was added to the sample vial and reference vial, respectively. A stirring bar was placed into the sample vial and the stirring speed was set to 200 rpm. H_2O_2 solution was loaded into a 100 μL syringe and used as titrant. After the baseline stabilized, 10 μL H_2O_2 was injected, and the power was recorded. The injection was repeated 9 times and the interval time between two injections was specified as 300 s. MeOH/*i*PrOH was also used as titrant to demonstrate the mixing process.

Results:

For the titrations at 25 °C, 50 °C and 70 °C, the detected heat was the same for the two processes, which meant that the reaction between H_2O_2 and H_2SO_4 did not happen and only the mixing heat was recorded. For the titration at 80 °C, the heat was much larger when H_2O_2 was used as titrant. This indicated the formation of persulfuric acid.

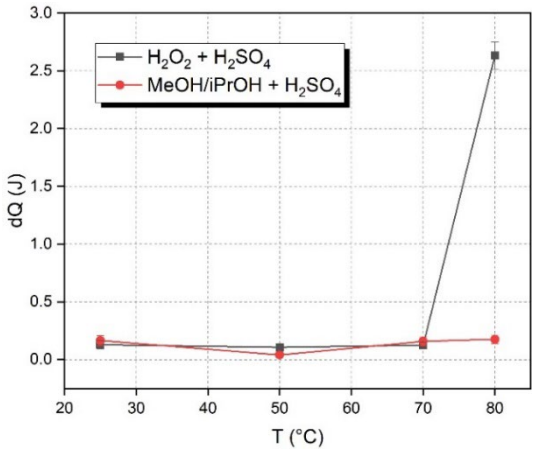


Figure S1. Detected heat of titrations at different temperatures.

2.2. Scan test

Solution preparation:

1.70 M H_2O_2: 0.826 g 35 wt% aq. H_2O_2 was diluted to 5 mL with *i*PrOH.
3.40 M H_2SO_4: 1.755 g 95% H_2SO_4 was diluted to 5 mL with *i*PrOH.

Procedure:

The scan mode was selected. 50 μL H_2O_2 solution and 50 μL H_2SO_4 solution were premixed in the sample vial at room temperature. To the reference vial, 100 μL *i*PrOH was added. A stirring bar was placed into both vials and the stirring speed was set to 200 rpm. Then the two vials were placed into the calorimeter. After the baseline stabilized, the sample was scanned from 25 °C to 150 °C at 1 °C min^{-1} and held at 150 °C for 30 min.

Results:

Only one exothermic peak, which started from around 75 °C, was observed during the scan test. As the formation of persulfuric acid cannot happen at room temperature, this peak undoubtedly included the formation heat.

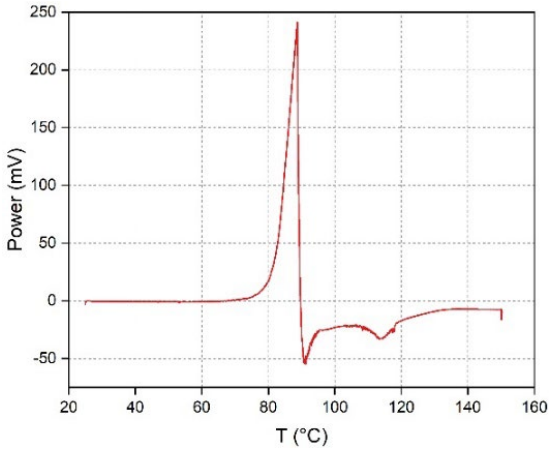


Figure S2. Sample scan from 25 °C to 150 °C at 1°C min^{-1}.

2.3. Titration test at 80 °C for reaction heat determination

Solution preparation:

8.50 M H_2O_2: 4.130 g 35 wt% aq. H_2O_2 was diluted to 5 mL with *i*PrOH.
1.89 M H_2SO_4: 0.976 g 95% H_2SO_4 was diluted to 5 mL with *i*PrOH.

Procedure:

The titration mode was selected, and the temperature was set to 80 °C. For the reaction, either 180, 270 or 360 µL H_2SO_4 solution was added to the sample vial and reference vial, respectively. A stirring bar was placed into the sample vials and the stirring speed was set to 200 rpm. H_2O_2 solution was loaded into a 100 µL syringe and used as titrant. After the baseline stabilized, either 20, 30, or 40 µL H_2O_2 was injected at once and the power was recorded. For each condition, the experiment was repeated twice in order to check the consistency. As H_2SO_4 was in excess, the calculation of reaction enthalpy was based on H_2O_2. For the mixing test, H_2O was used as the titrant. For the blank test, *i*PrOH was used as a replacement for H_2SO_4.

NOTE: The long-term exposure to high temperature does slowly cause damage to the syringe.

Results:

Table S1. Summary of reaction enthalpy.

Entry	Substrate	Titrant	dQ (J)	ΔHr (kJ mol^{-1})	Ave. ± SD (kJ mol^{-1})
1	180 µL H_2SO_4	20 µL H_2O_2	47.2	266.5	271.5 ± 10.1
2		20 µL H_2O	1.4	/	
3	270 µL H_2SO_4	30 µL H_2O_2	71.0	264.9	
4		30 µL H_2O	2.7	/	
5	360 µL H_2SO_4	40 µL H_2O_2	99.8	283.2	
6		40 µL H_2O	3.7	/	

2.4. Iodometric peroxide determination

Total peroxide concentration was measured by iodometric titration. This method was based on two major steps, as follows.

$$H_2O_2 + 2KI + H_2SO_4 \rightarrow I_2 + K_2SO_4 + 2H_2O$$

$$I_2 + 2Na_2S_2O_3 \rightarrow Na_2S_4O_6 + 2NaI$$

Solution preparation:

2 wt% KI in H_2O: 2 g KI was dissolved and diluted with H_2O to 100 mL.
$(NH_4)_6Mo_7O_{24}\times4H_2O$ solution: 9 g $(NH_4)_6Mo_7O24\times4H_2O$ was dissolved in 10 mL 25 wt% NH_4OH in H_2O. 24 g NH_4NO_3 was added, and the solution was diluted to 100 mL with H_2O.
Diluted H_2SO_4: 20 mL concentrated H_2SO_4 was diluted to 100 mL with H_2O.
0.1 M $Na_2S_2O_3$: 2.493 g $Na_2S_2O_3\times5H_2O$ was dissolved and diluted to 100 mL with H_2O.
1 wt% starch indicator: 0.1 g soluble starch was added to 100 mL hot H_2O.

Procedure:

H_2O_2 (1.70 M) and H_2SO_4 (3.40 M) solutions in the batch calorimetry scan test were used to prepare the reaction mixture. The scan mode of the calorimeter was adopted to provide the temperature for the formation of persulfuric acid. 100 µL of reaction solution was diluted with 1 mL of H_2O. 200 µL of diluted H_2SO_4 solution, then 200 µL of the KI solution were added. One drop of the $(NH_4)_6Mo_7O_{24}$ solution was added. Titration with thiosulfate (0.1 M) was performed until a pale-yellow color was reached. 20 µL of starch indicator solution was added. Further titration with 0.1 M thiosulfate was performed until a colorless solution was observed.

Results:

Table S2. Summary of iodometric titrations.

Entry	Mixture	Scan process of the calorimeter	$n_{(H2O2)}$ (mmol)
1[a]	50 µL H_2O_2 + 50 µL *i*PrOH	None	0.04900
2[a]	50 µL H_2O_2 + 50 µL H_2SO_4	Scan from 25 °C to 60 °C at 1 °C min^{-1}, held for 10 min	0.04650
3[b]	50 µL H_2O_2 + 50 µL H_2SO_4	Scan from 60 °C to 80 °C at 1 °C min^{-1}, held for 40 min	0.00075
4[a,c]	50 µL H_2O_2 + 50 µL *i*PrOH	Scan from 60 °C to 80 °C at 1 °C min^{-1}, held for 40 min	0.04710

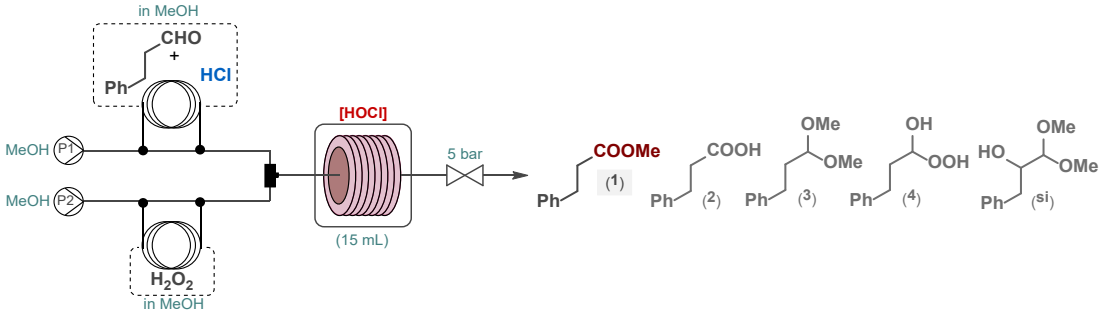
[a]Persulfuric acid was not formed. [b]Persulfuric acid was formed. [c]Blank test to prove H_2O_2 did not evaporate or decompose.

3. Description of continuous flow experiments

3.1. Oxidative esterifications with H_2O_2/HCl system

Substrate solution containing 1 equiv. of hydrocinnamaldehyde and 1.1–3.0 equiv. of HCl (added as 6 M aq. solution) in MeOH and a solution of H_2O_2 (prepared from 35 wt% aq. solution) in MeOH were pumped as separate streams (P1 and P2) by using Syrris® Asia syringe pumps equipped with two injection valves and two sample loops (5 or 8 mL, each). With MeOH serving as carrier solvent, the feeds were combined in a Y-mixer. The resulting stream was directed through a 15-mL reaction coil (15–60 min residence time) which was heated at 50, 100 or 120 °C and pressurized at 5 bar. The reactor outlet was directed into a flask containing a stirred mixture of saturated aq. $NaHCO_3$ and some MnO_2 in order to quench any excess acid and/or oxidant. After reaching steady state, approx. 20 µL aliquots of crude material were collected. The samples were diluted with 1 mL of CH_3CN/H_2O 9:1 and was analyzed by analytical HPLC directly after the flow experiments.

Table S3. Oxidative esterifications with H_2O_2/HCl system.



#	$c_{substr.}$ (M)	HCl[a] (equiv.)	H_2O_2[b] (equiv.)	T (°C)	Flow rates (µL min^{-1})	t_r (min)	Conv. (%)[c]	Chemoselectivity (%)[c]					
								1	**2**	**3**	**4**	**si**	Unid.[d]
1	0.25	1.1	1.1	100	2 × 250	30	100	42	0	14	0	44	0
2	0.25	1.5	1.5	100	2 × 250	30	100	47	0	3	0	50	0
3	0.25	3.0	3.0	100	2 × 250	30	100	55	4	0	0	41	0
4	0.25	2.0	3.0	100	2 × 250	30	100	54	4	0	0	42	0
5	0.25	3.0	2.0	100	2 × 250	30	100	54	3	0	0	43	0
6	0.25	2.0	2.0	50	2 × 250	30	48	38	0	62	0	0	0
7	0.25	2.0	2.0	50	2 × 125	60	59	54	0	46	0	0	0
8	0.25	2.0	2.0	100	2 × 500	15	100	53	0	3	0	44	0
9	0.25	2.0	2.0	120	2 × 250	20[e]	100	36	0	3	0	55	6
10	0.75	2.0	2.0	100	2 × 250	30	100	58	8	4	0	24	6

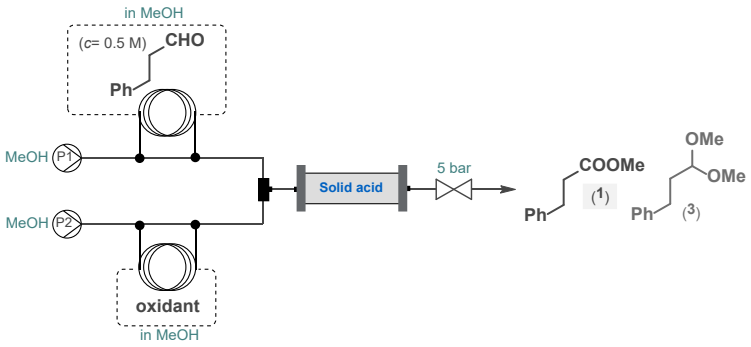
[a]Stock solution was made using 6 M aq. HCl. [b]Stock solution was made using 35 wt% aq. H_2O_2. [c]Determined by HPLC area%.
[d]Unidentified side products. [e]Gas formation occurred in the reaction coil.

In order to assign HPLC signals of side product **3** and **4**, reference samples were prepared according to a literature procedure.[S2] Hydrocinnamic acid, **2** is commercially available. Side product **si** was isolated chromatographically and characterized by ^{1}H NMR. NMR data of the compound matched the reported literature.[S3]

3.2. Oxidative esterifications in the presence of various solid acids and oxidants

Substrate solution containing 0.5 M of hydrocinnamaldehyde in MeOH and a solution of UHP or TBHP or H_2O_2 (TBHP was added as 5.5 M decane solution, H_2O_2 was added as 35 wt% aq. solution) in MeOH were pumped as separate streams (P1 and P2) by using Syrris® Asia syringe pumps equipped with two injection valves and two sample loops (6 mL, each). With MeOH serving as carrier solvent, the feeds were combined in a Y-mixer. The resulting stream was directed through an Omnifit® glass column (10 mm ID, adjustable height) containing 1.5 g of Amberlyst 15 or 5.0 g of Dowex 50WX8 as solid acid. The column was heated at 80 or 100 °C by using a Syrris® Asia column heater and was pressurized at 5 bar. The reactor outlet was directed into a flask containing a stirred mixture of some MnO_2 in MeOH in order to quench any excess oxidant. After reaching steady state, approx. 20 µL aliquots of crude material were collected. The samples were diluted with 1 mL of CH_3CN/H_2O 9:1 and was analyzed by analytical HPLC directly after the flow experiments.

Table S4. Oxidative esterifications in the presence of various solid acids and oxidants.



#	Solid acid	Oxidant			Flow rates (µL min^{-1})		*T* (°C)	t_r (min)	Conv. (%)[d]	Chemoselectivity (%)[d]		
		Name	$c_{stock.\ sol.}$ (M)	(equiv.)	P1	P2				**1**	**3**	Unid.[e]
1	Amberlyst 15	UHP	0.5	1.5	80	120	80	10	68	52	48	0
2	Dowex 50WX8	UHP	0.5	1.5	80	120	80	20	92	85	15	0
3	Dowex 50WX8	TBHP	0.5[a]	1.5	80	120	80	20	100	4	62	34
4	Dowex 50WX8	H_2O_2	0.5[b]	1.5	80	120	80	20	94	86	14	0
5	Dowex 50WX8	H_2O_2	11.6[c]	1.5	188	12	80	20	80	73	17	0
6	Dowex 50WX8	H_2O_2	0.5[b]	1.5	80	120	100	20	95	88	12	0
7	Dowex 50WX8	H_2O_2	1.5[b]	3.0	100	100	100	20	96	96	4	0
8	Dowex 50WX8	-		-	200	0	80	20	90	0	100	0

[a]Stock solution was made using 5.5 M TBHP in decane. [b]Stock solution was made using 35 wt% aq. H_2O_2. [c]35 wt% aq. H_2O_2 was pumped. [d]Determined by HPLC area%. [e]Unidentified side products.

3.3. Oxidative esterifications with in situ-generated H_2SO_5

3.3.1 Parameter screening with hydrocinnamaldehyde

Substrate solution containing 1.0, 2.0 or 3.0 M of hydrocinnamaldehyde and a 4.0 or 8.0 M solution of H_2SO_4 (prepared from cc H_2SO_4) were pumped as separate streams (P1 and P2) by using Syrris® Asia syringe pumps equipped with two injection valves and two sample loops (3, 5 or 10 mL, each). As a third stream, a 2.0 M solution of H_2O_2 in MeOH or 35 or 50 wt% aq. H_2O_2 solution (11.6 or 17.6 M) or 2.0 M UHP solution in MeOH or 2.0 M

TBHP solution in MeOH (added as 5.5 M decane solution) was pumped by using a Syrris® Asia syringe pump (P3) equipped with an injection valve and a sample loop (3 or 6 mL). With MeOH serving as carrier solvent, the substrate and H_2SO_4 feeds were combined in a Y-mixer, then the resulting stream was mixed up with the H_2O_2 feed through a second Y-mixer. The combined liquid stream was next directed through a heated reaction coil (15 or 1.5 mL, 1–20 min residence time) which was pressurized at 5 bar. The reactor outlet was directed into a flask containing a stirred mixture of saturated aq. $NaHCO_3$ and some MnO_2 in order to quench any excess acid and/or oxidant. After reaching steady state, approx. 20 µL aliquots of crude material were collected. The samples were diluted with 1 mL of CH_3CN/H_2O 9:1 and was analyzed by analytical HPLC directly after the flow experiments.

See Table 1 in the manuscript for the corresponding reaction data and also Scheme 1 for the setup.

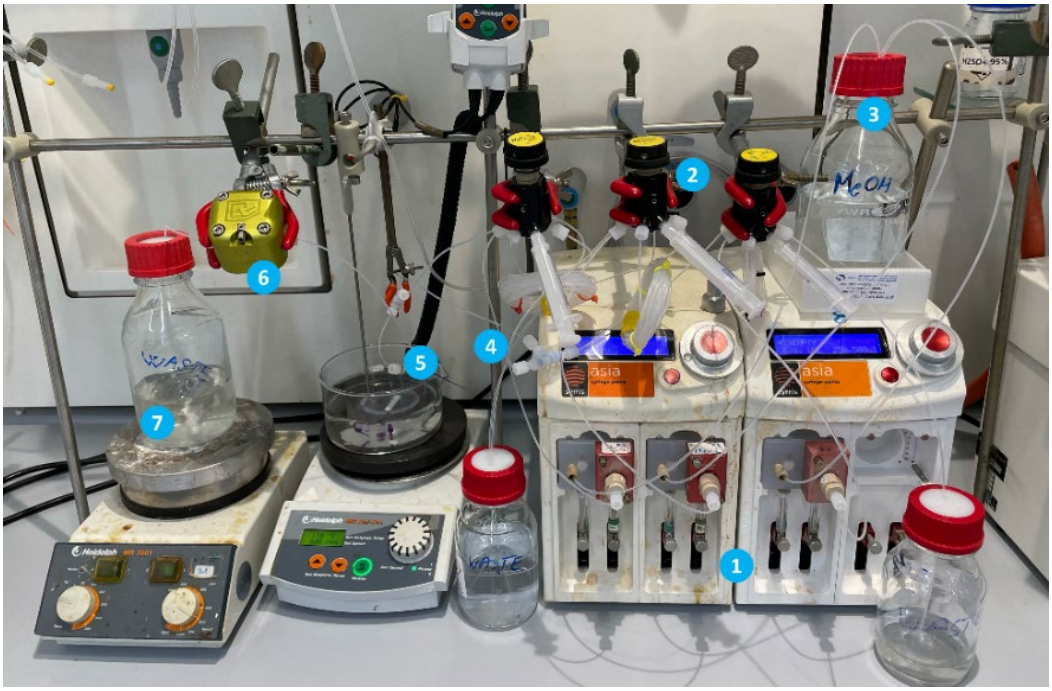


Figure S3. Photograph of the flow setup. Legend: (1) Syringe pumps (P1, P2 and P3), (2) reagent feeds with injection valves and two sample loops, (3) carrier solvent, (4) Y-mixers, (5) reaction coil in a heated oil bath, (6) adjustable BPR, (7) reactor outlet.

Table S5. Flow rates for Table 1 in the manuscript.

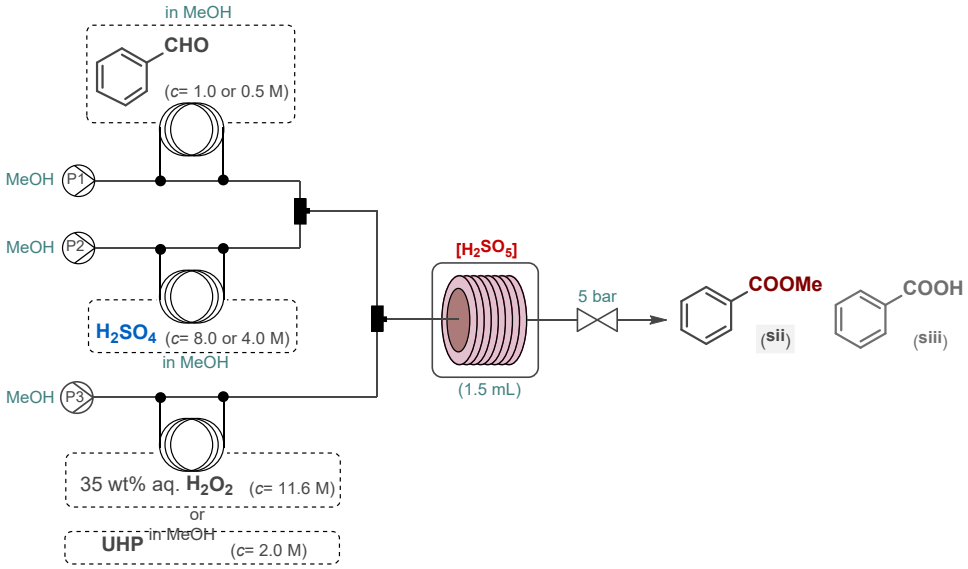
Entry in Table 1	Flow rates (µL min^{-1})		
	P1	P2	P3
1	187	187	375
2	300	150	300
3	395	119	237
4	790	237	474
5	395	237	119
6	300	270	180
7	242	73	436
8	599	90	62
9	535	161	55
10	535	161	55
11	415	249	86
12	339	305	105
13	1069	321	110
14	548	165	38
15	394	119	237
16	680	0	70

3.3.2 Additional parameter screening with benzaldehyde

Substrate solution containing 1.0 or 0.5 M of benzaldehyde and a 4.0 or 8.0 M solution of H_2SO_4 (prepared from cc H_2SO_4) were pumped as separate streams (P1 and P2) by using Syrris® Asia syringe pumps equipped with

two injection valves and two sample loops (5 or 10 mL, each). As a third stream, 35 wt% aq. H_2O_2 solution (11.6 M) or 2.0 M UHP solution in MeOH was pumped by using a Syrris® Asia syringe pump (P3) equipped with an injection valve and a sample loop (3 or 5 mL). With MeOH serving as carrier solvent, the substrate and H_2SO_4 feeds were combined in a Y-mixer, then the resulting stream was mixed up with the oxidant feed through a second Y-mixer. The combined liquid stream was next directed through a 1.5-mL reaction coil (1, 2 or 4 min residence time) which was heated at 80–140 °C and pressurized at 5 bar. The reactor outlet was directed into a flask containing a stirred mixture of saturated aq. $NaHCO_3$ and some MnO_2 in order to quench any excess acid and/or oxidant. The reactor outlet was directed into a flask containing a stirred mixture of saturated aq. $NaHCO_3$ and some MnO_2 in order to quench any excess acid and/or oxidant. After reaching steady state, approx. 20 µL aliquots of crude material were collected. The samples were diluted with 1 mL of CH_3CN/H_2O 9:1 and was analyzed by analytical HPLC directly after the flow experiments.

Table S6. Results of parameter screening with benzaldehyde.



# [a]	$c_{substr.}$ (M)	c_{H2SO4} (M)	Oxidant	Flow rates (µL min^{-1})			H_2SO_4 (equiv.)	H_2O_2 (equiv.)	t_r (min)	T (°C)	Conv. (%)[b]	Chemoselectivity (%)[b]		
				P1	P2	P3						**sii**	**siii**	Unid.[c]
1	1	8	H_2O_2	534	161	56	2.4	1.2	2	120	100	83	17	0
2	1	8	H_2O_2	534	161	56	2.4	1.2	2	80	89	82	11	7
3	1	8	H_2O_2	1068	322	112	2.4	1.2	1	120	99	84	16	0
4	1	8	H_2O_2	267	81	28	2.4	1.2	4	120	100	81	19	0
5	1	8	H_2O_2	534	161	56	2.4	1.2	2	140	95	79	21	0
6	1	8	H_2O_2	466	211	73	3.6	1.8	2	120	100	82	18	0
7	1	8	H_2O_2	466	211	73	3.6	1.8	2	90	99	88	12	0
8	1	8	H_2O_2	425	192	133	3.6	3.6	2	90	98	63	22	15
9	1	8	H_2O_2	563	128	59	1.8	1.2	2	120	100	85	15	0
10	1	8	H_2O_2	531	150	70	2.25	1.5	2	100	97	87	13	0
11	1	8	UHP	394	119	237	2.4	1.2	2	120	99	91	9	0
12	1	8	UHP	410	93	247	1.8	1.2	2	120	97	91	9	0
13	1	8	UHP	319	144	287	3.6	1.8	2	100	98	91	9	0
14	0.5	4	UHP	468	141	141	2.4	1.2	2	120	95	92	8	0
15	0.5	8	UHP	516	78	156	2.4	1.2	2	120	93	92	8	0

[a]H_2SO_4 stock solutions were made using cc. H_2SO_4. [b]Determined by HPLC area%. [c]Unidentified side products.

3.3.3 Investigation of the reaction scope

Substrate solution containing 1.0 or 0.5 M of the corresponding aldehyde and a 4.0 or 8.0 M solution of H_2SO_4 (prepared from cc H_2SO_4) were pumped as separate streams (P1 and P2) by using Syrris® Asia syringe pumps equipped with two injection valves and two sample loops (10 mL, each). As a third stream, 35 wt% aq. H_2O_2 solution (11.6 M) or 2.0 M UHP solution in MeOH was pumped by using a Syrris® Asia syringe pump (P3) equipped with an injection valve and a sample loop (3 or 6 mL). With MeOH serving as carrier solvent, the substrate and H_2SO_4 feeds were combined in a Y-mixer, then the resulting stream was mixed up with the oxidant feed through a second Y-mixer. (For some of the reactions, EtOH or *i*PrOH was used as solvent and also as carrier solvent.) The combined liquid stream was next directed through a 1.5-mL reaction coil (2 or 4 min residence time) which was heated at 120 °C and pressurized at 5 bar. The reactor outlet was directed into a flask containing a stirred mixture of saturated aq. $NaHCO_3$ and some MnO_2 in order to quench any excess acid and/or oxidant. After reaching steady state, the crude reactor outlet was collected for 2–10 min. A 20 µL aliquot of the crude material was diluted with 1 mL of CH_3CN/H_2O 9:1 and was immediately analyzed by analytical HPLC or GC-FID. The collected mixture was extracted with CH_2Cl_2, washed with brine and dried over $MgSO_4$. After evaporation, the obtained material was analyzed by ^1H and ^{13}C NMR spectroscopy. When necessary, column chromatographic purification was performed using mixtures of cyclohexane and EtOAc as eluent.

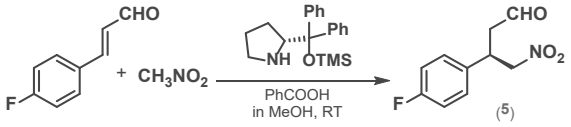
See Tables 2 and 3 in the manuscript for the corresponding reaction data and also for representation of the setup.

Table S7. Flow rates for Table 3 in the manuscript.

Entry in Table 3	Flow rates (µL min^{-1})		
	P1	P2	P3
1	534	161	56
2	394	119	237
3	534	161	56
4	534	161	56
5	534	161	56
6	534	161	56
7	534	161	56
8	534	161	56
9	197	60	119
10	394	119	237
11	394	119	237
12	394	119	237
13	234	71	71
14	394	119	237
15	197	60	119
16	394	119	237
17	234	71	71
18	468	141	141
19	534	161	56
20	534	161	56
21	394	119	237

3.3.4 Gram-scale synthesis of a key (–)-paroxetine intermediate

Preparation of γ-nitroaldehyde **5**:



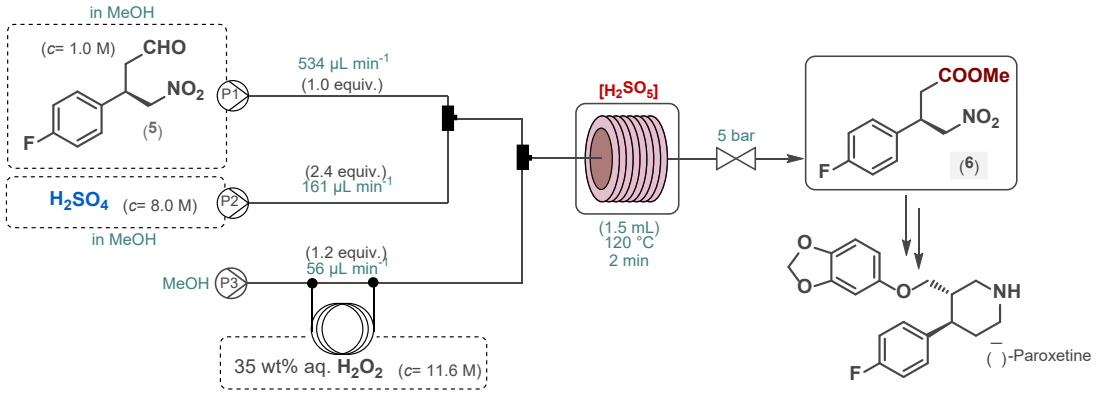
Scheme S1. Synthesis of **5**.

A mixture containing 4-fluorocinnamaldehyde (1 equiv., 0.5 M), nitromethane (3 equiv.), AcOH (0.3 equiv.) and 10 mol% of (*R*)-α,α-diphenyl-2-pyrrolidinemethanol trimethylsilyl ether as organocatalyst was stirred for 24 h at RT in MeOH as solvent. After then, the mixture was filtrated through a pad of celite, washed with CH_2Cl_2 and evaporated. The crude product was purified by means of column chromatography using a mixture of ethyl acetate/40-60 petroleum ether as eluent.

NMR data of the isolated compound matched the reported literature.[S4] $[\alpha]_D^{25}$= +15.8 (c= 1.0, $CHCl_3$).

Continuous flow oxidative esterification of **5**:

Substrate solution containing 1.0 M of γ-nitroaldehyde **5** and an 8.0 M solution of H_2SO_4 (prepared from cc H_2SO_4) were pumped directly as separate streams (P1 and P2) by using Syrris® Asia syringe pumps. As a third stream, 35 wt% aq. H_2O_2 solution (11.6 M) in MeOH was pumped by using a Syrris® Asia syringe pump (P3) equipped with an injection valve and a sample loop (15 mL). With MeOH serving as carrier solvent for the H_2O_2 stream, the substrate and H_2SO_4 feeds were combined in a Y-mixer, then the resulting stream was mixed up with the oxidant feed through a second Y-mixer. The combined liquid stream was next directed through a 1.5-mL reaction coil (2 min residence time) which was heated at 120 °C and pressurized at 5 bar. The reactor outlet was directed into a flask containing a stirred mixture of saturated aq. $NaHCO_3$ and some MnO_2 in order to quench any excess acid and/or oxidant. After reaching steady state, the crude reactor outlet was collected for 45 min. 20 μL aliquots of the crude material was diluted with 1 mL of CH_3CN/H_2O 9:1 and was immediately analyzed by analytical HPLC. The collected mixture was extracted with CH_2Cl_2, washed with brine and dried over $MgSO_4$. The obtained material was analyzed by ^1H and ^{13}C NMR spectroscopy.



Scheme S2. Flow synthesis of **6**.

3.3.5 Calculation of green metrics

E factor, process mass intensity (PMI), reaction mass efficiency (RME), atom economy (AE) and optimum efficiency (OE) were calculated using the following equations.[S1]

$$E\ factor = \frac{total\ mass\ of\ waste}{mass\ of\ product}$$

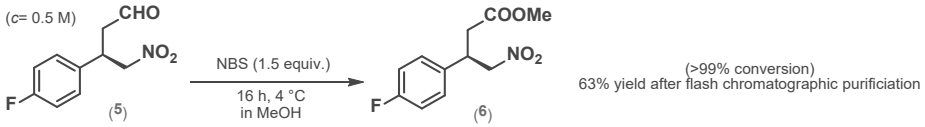
$$PMI = \frac{total\ mass\ of\ raw\ materials\ used}{mass\ of\ product}$$

$$RME = \frac{mass\ of\ isolated\ product}{total\ mass\ of\ reactants} \times 100$$

$$AE = \frac{molecular\ weight\ of\ product}{total\ molecular\ weight\ of\ reactants} \times 100$$

$$OE = \frac{RME}{AE} \times 100$$

Green metrics were calculated for the oxidative esterification of γ-nitroaldehyde **5** yielding γ-nitroester **6**. The *in situ*-generated persulfuric acid-mediated flow process (described in section 3.3.4 and also in the manuscript) was directly compared to a literature batch process utilizing *N*-bromosuccinimide (NBS)-based oxidation (Scheme S2). (See: K. L. Jensen, P. H. Poulsen, B. S. Donslund, F. Morana and K. A. Jørgensen, *Org. Lett.* **2012**, *14*, 1516-1519; *ref. 5d* in the manuscript.)



Scheme S2. NBS-mediated literature batch procedure for the oxidative esterification of **5**.

The NBS-mediated reaction was reported as a one-pot/two-step process. In the first step, Michael addition between 4-fluorocinnamaldehyde and nitromethane in the presence of a diphenylprolinol-type organocatalyst resulted γ-nitroaldehyde **5** (similarly to the reaction shown in Scheme 1). This step was reported to be quantitative and selective, thus calculation of the green metrics exclusively for the subsequent oxidative esterification step was possible.

In the NBS-mediated process, reaction conditions and yield were specified for the preparation of compound *ent*-**6** only ((*S*)-3-(4-fluorophenyl)-4-nitrobutanoate). The (*R*)-isomer (compound **6**) was prepared under identical conditions but using the opposite enantiomer of the chiral catalyst. For the calculation of green metrics, the same yield and reaction conditions were thus assumed for compound **6** as those reported for compound *ent*-**6**.

According to the NBS-mediated process, γ-nitroester **6** was isolated by means flash chromatographic purification. The exact amounts of solvents used for the purification was not reported by the authors. In case of the persulfuric acid-mediated flow process, **6** was obtained in a pure form after extractive work-up. In order that the data can be compared directly, chemicals and solvents used for work-up and purification have been excluded from the calculations.

For the calculation of the E factor, the mass of H_2O was excluded. For the calculation of PMI, the total mass used for the calculation included H_2O as well.

Table S8. Values used for the assessment of green metrics of the *in situ*-generated persulfuric acid-mediated continuous flow oxidative esterification of γ-nitroaldehyde **5**.

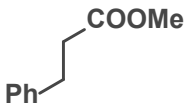
Role	Chemical	Equiv.	*n* (mmol)	Mass (g)	*V* (mL)	Mw (g mol^{-1})	*ρ* (g mL^{-1})
R E A C T I O N							
Reactant	Compound **5**	1.0	24.030	5.075		211.190	
Reactant	H_2SO_4	2.4	57.672	5.656	3.074	98.079	1.8400
Reactant	H_2O_2	1.2	28.836	0.981		34.015	
Solvent	H_2O[a]			1.822			
Solvent	MeOH			15.836 3.246	20.0[b] 4.1[c]	32.040	0.7918
P R O D U C T							
Product	Compound **6**	0.942	22.635	5.46		241.22	

[a]H_2O content of 35 wt% aq. H_2O_2 solution. (H_2O content of cc. H_2SO_4 was omitted.) [b]MeOH used for the substrate solution, approximate volume. [c]MeOH used for the H_2SO_4 solution, approximate volume.

Table S9. Values used for the assessment of green metrics of the NBS-mediated literature batch process for the oxidative esterification of γ-nitroaldehyde **5**.

Role	Chemical	Equiv.	*n* (mmol)	Mass (mg)	*V* (mL)	Mw (g mol^{-1})	*ρ* (g mL^{-1})
R E A C T I O N							
Reactant	Compound **5**	1.0	0.2	42.238		211.190	
Reactant	NBS	1.5	0.3	53.394		177.980	
Solvent	MeOH			316.72	0.4	32.040	0.7918
P R O D U C T							
Product	Compound **6**	0.63	0.126	30.394		241.22	

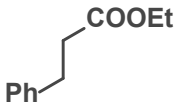
4. Characterization data



Methyl 3-phenylpropanoate

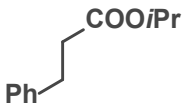
830.4 mg (95%) was isolated after extractive work-up.

^{1}H and ^{13}C NMR data of the compound matches the reported literature.[S5]



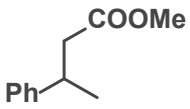
Ethyl 3-phenylpropanoate

^{1}H and ^{13}C NMR data of the compound matches the reported literature.[S5]



Ethyl 3-phenylpropanoate

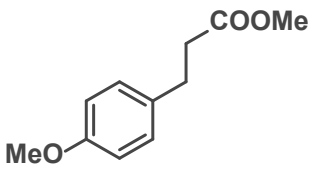
^{1}H and ^{13}C NMR data of the compound matches the reported literature.[S5]



Methyl 3-phenylbutanoate

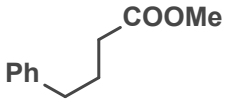
255.0 mg (89%) was isolated after extractive work-up.

^{1}H and ^{13}C NMR data of the compound matches the reported literature.[S6]



Methyl 3-(4-methoxyphenyl)propanoate

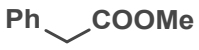
^{1}H and ^{13}C NMR data of the compound matches the reported literature.[S7]



Methyl 4-phenylbutanoate

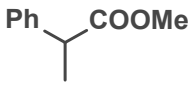
403.3 mg (85%) was isolated after column chromatographic purification (EtOAc/cyclohexane 0–50% as eluent).

^{1}H and ^{13}C NMR data of the compound matches the reported literature.[S6]



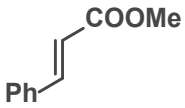
Methyl 2-phenylacetate

^{1}H and ^{13}C NMR data of the compound matches the reported literature.[S8]



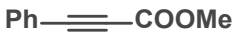
Methyl 2-phenylpropanoate

^{1}H and ^{13}C NMR data of the compound matches the reported literature.[S9]



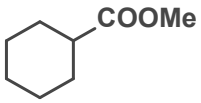
Methyl cinnamate

^{1}H and ^{13}C NMR data of the compound matches the reported literature.[S8]



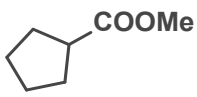
Methyl 3-phenylpropiolate

^{1}H and ^{13}C NMR data of the compound matches the reported literature.[S10]



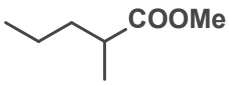
Methyl cyclohexanecarboxylate

^{1}H and ^{13}C NMR data of the compound matches the reported literature.[S8]



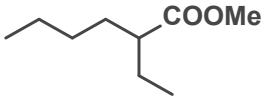
Methyl cyclopentanecarboxylate

^{1}H and ^{13}C NMR data of the compound matches the reported literature.[S11]



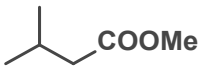
Methyl 2-methylpentanoate

^{1}H and ^{13}C NMR data of the compound matches the reported literature.[S12]



Methyl 2-ethylhexanoate

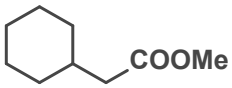
^{1}H and ^{13}C NMR data of the compound matches the reported literature.[S13]



Methyl 3-methylbutanoate

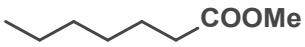
301.2 mg (97%) was isolated after extractive work-up.

^{1}H and ^{13}C NMR data of the compound matches the reported literature.[S14]



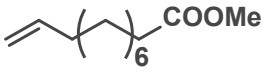
Methyl 2-cyclohexylacetate

^{1}H and ^{13}C NMR data of the compound matches the reported literature.[S15]



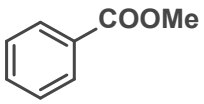
Methyl heptanoate

^{1}H and ^{13}C NMR data of the compound matches the reported literature.[S16]



Methyl undec-10-enoate

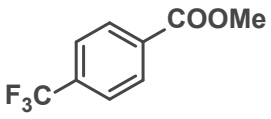
^{1}H and ^{13}C NMR data of the compound matches the reported literature.[S17]



Methyl benzoate

234.2 mg (87%) was isolated after column chromatographic purification (EtOAc/cyclohexane 0–50% as eluent).

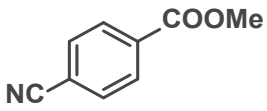
^{1}H and ^{13}C NMR data of the compound matches the reported literature.[S8]



Methyl 4-(trifluoromethyl)benzoate

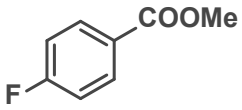
527.3 mg (97%) was isolated after extractive work-up.

^{1}H and ^{13}C NMR data of the compound matches the reported literature.[S18]



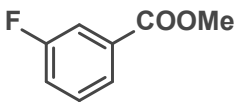
Methyl 4-cyanobenzoate

^{1}H and ^{13}C NMR data of the compound matches the reported literature.[S8]



Methyl 4-fluorobenzoate

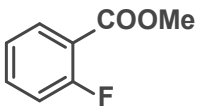
^{1}H and ^{13}C NMR data of the compound matches the reported literature.[S18]



Methyl 3-fluorobenzoate

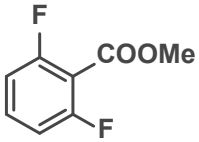
379.1 mg (92%) was isolated after extractive work-up.

^{1}H and ^{13}C NMR data of the compound matches the reported literature.[S19]



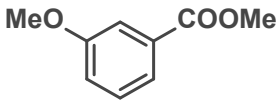
Methyl 2-fluorobenzoate

^{1}H and ^{13}C NMR data of the compound matches the reported literature.[S20]



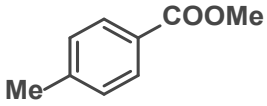
Methyl 2,6-difluorobenzoate

^{1}H and ^{13}C NMR data of the compound matches the reported literature.[S21]



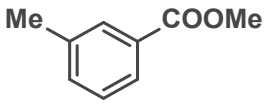
Methyl 3-methoxybenzoate

^{1}H and ^{13}C NMR data of the compound matches the reported literature.[S18]



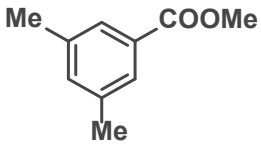
Methyl 4-methylbenzoate

^{1}H and ^{13}C NMR data of the compound matches the reported literature.[S8]



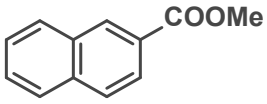
Methyl 3-methylbenzoate

^{1}H and ^{13}C NMR data of the compound matches the reported literature.[S18]



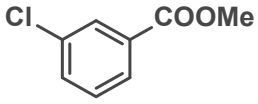
Methyl 3,5-dimethylbenzoate

^{1}H and ^{13}C NMR data of the compound matches the reported literature.[S22]



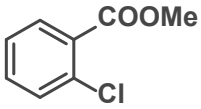
Methyl 2-naphthoate

^{1}H and ^{13}C NMR data of the compound matches the reported literature.[S8]



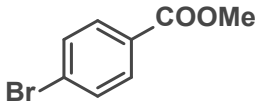
Methyl 3-chlorobenzoate

^{1}H and ^{13}C NMR data of the compound matches the reported literature.[S23]



Methyl 2-chlorobenzoate

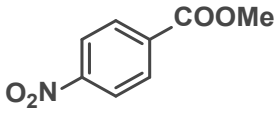
^{1}H and ^{13}C NMR data of the compound matches the reported literature.[S24]



Methyl 4-bromobenzoate

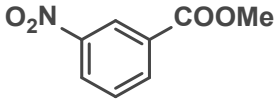
376.5 mg (89%) was isolated after extractive work-up.

^{1}H and ^{13}C NMR data of the compound matches the reported literature.[S8]



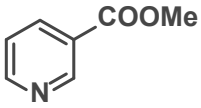
Methyl 4-nitrobenzoate

^{1}H and ^{13}C NMR data of the compound matches the reported literature.[S8]



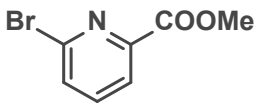
Methyl 3-nitrobenzoate

^{1}H and ^{13}C NMR data of the compound matches the reported literature.[S25]



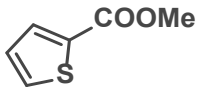
Methyl nicotinate

^{1}H and ^{13}C NMR data of the compound matches the reported literature.[S24]



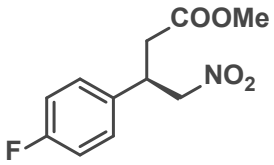
Methyl 6-bromopicolinate

^{1}H and ^{13}C NMR data of the compound matches the reported literature.[S26]



Methyl thiophene-2-carboxylate

^{1}H and ^{13}C NMR data of the compound matches the reported literature.[S18]



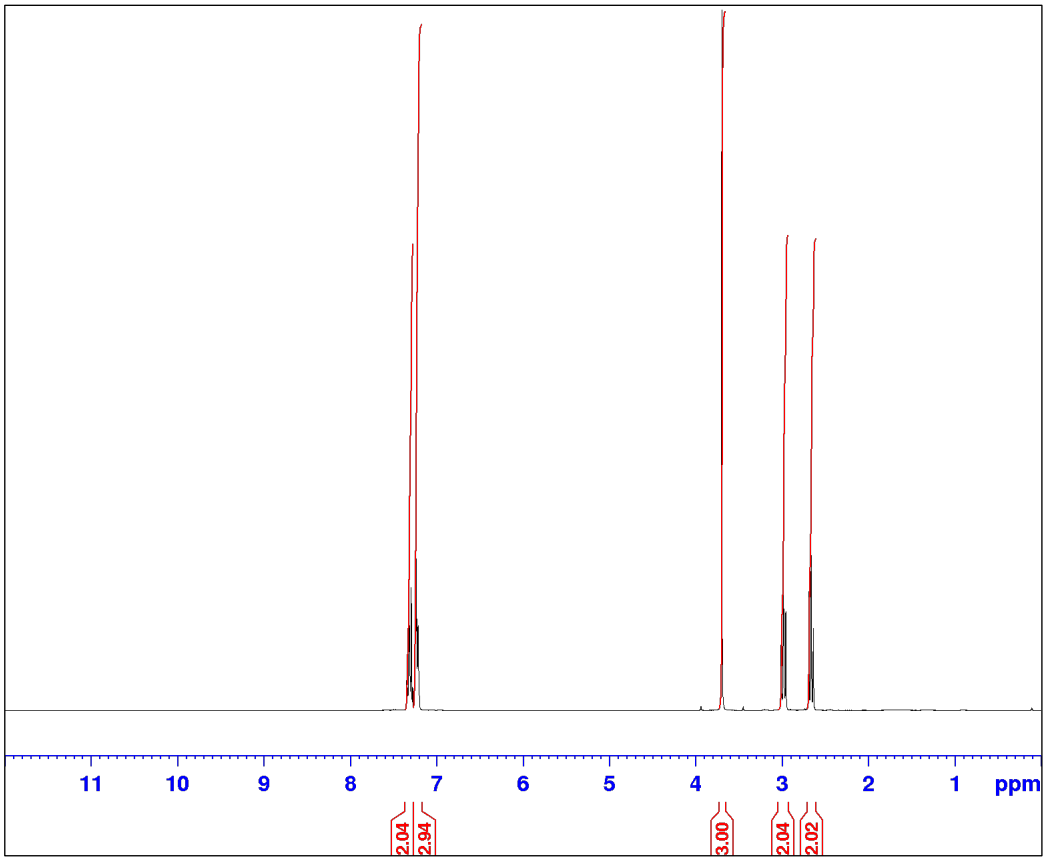
Methyl (*R*)-3-(4-fluorophenyl)-4-nitrobutanoate

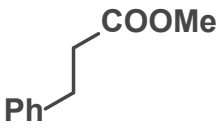
5.46 g (94%) was isolated after extractive work-up.

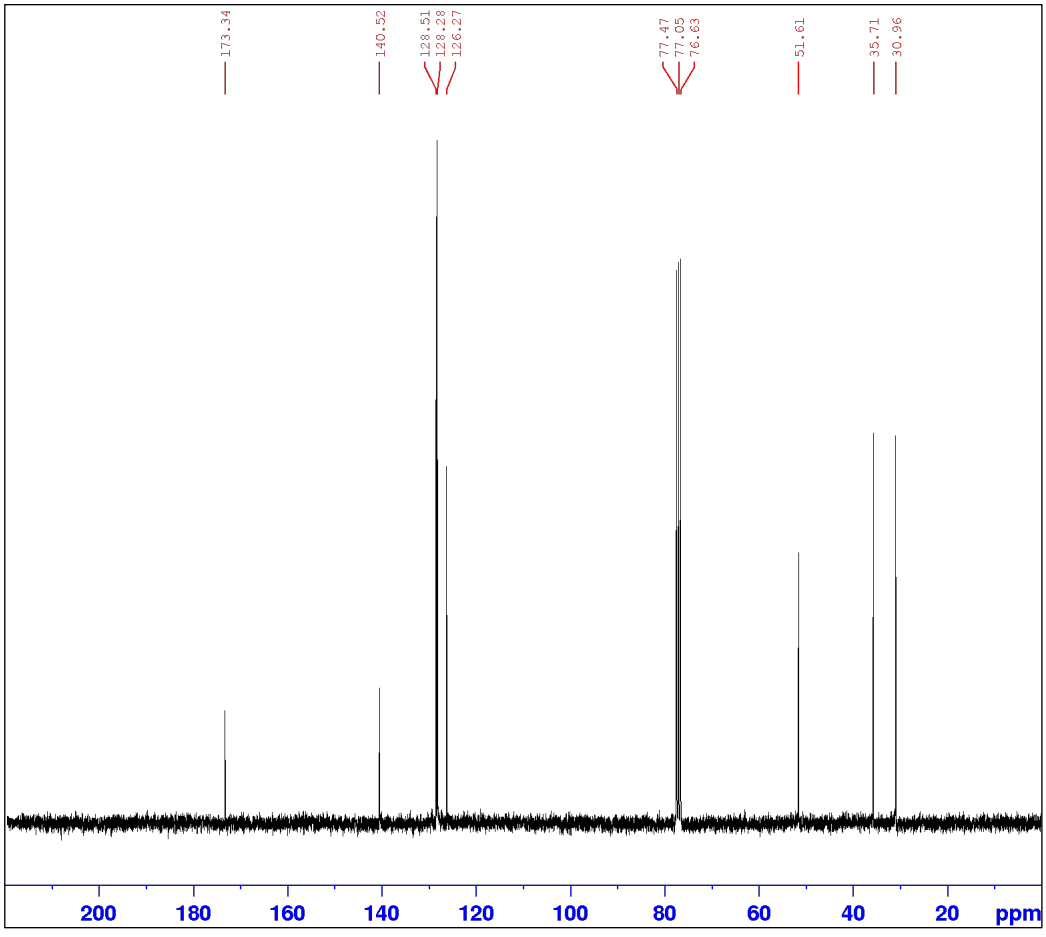
^{1}H and ^{13}C NMR data of the compound matches the reported literature.[S27] $[\alpha]_D^{25}$= +17.4 (c= 0.5, CH_2Cl_2).

5. Collection of NMR spectra

300 MHz, $CDCl_3$

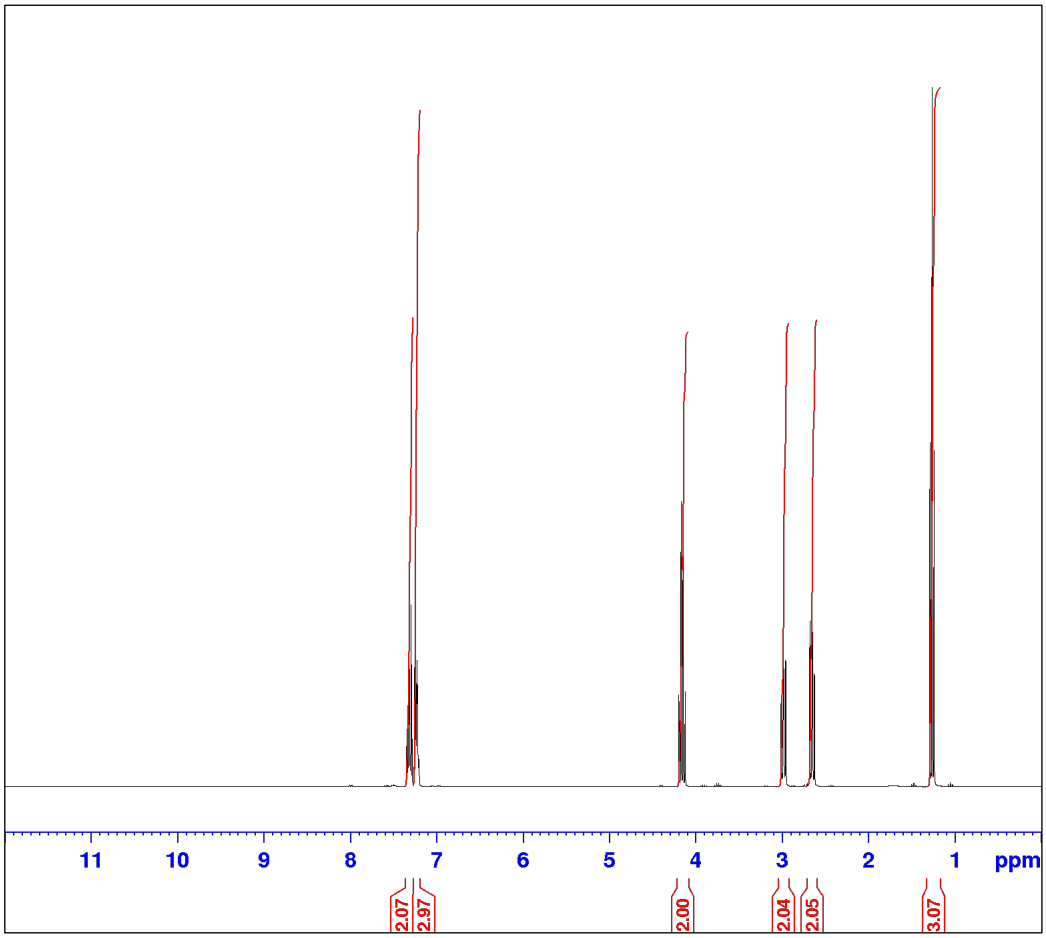


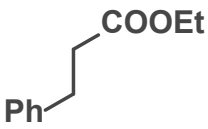


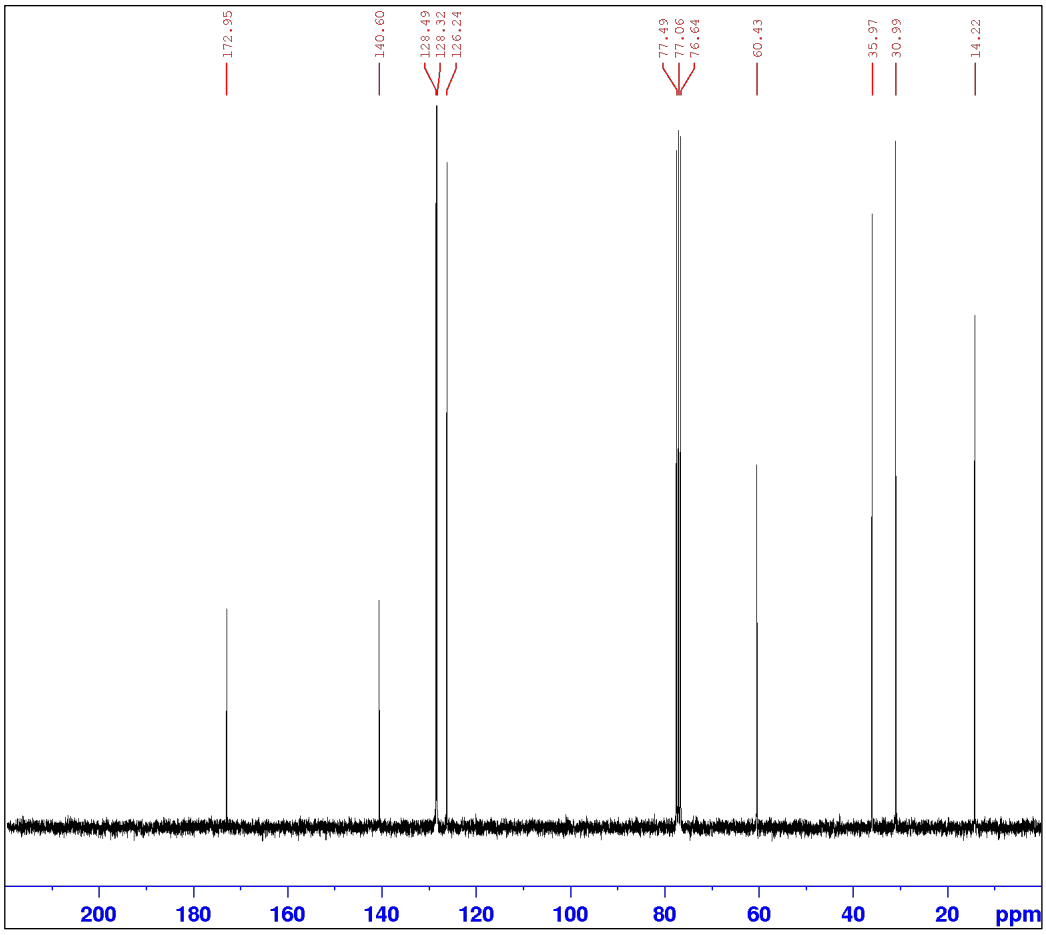


75 MHz, $CDCl_3$

300 MHz, $CDCl_3$

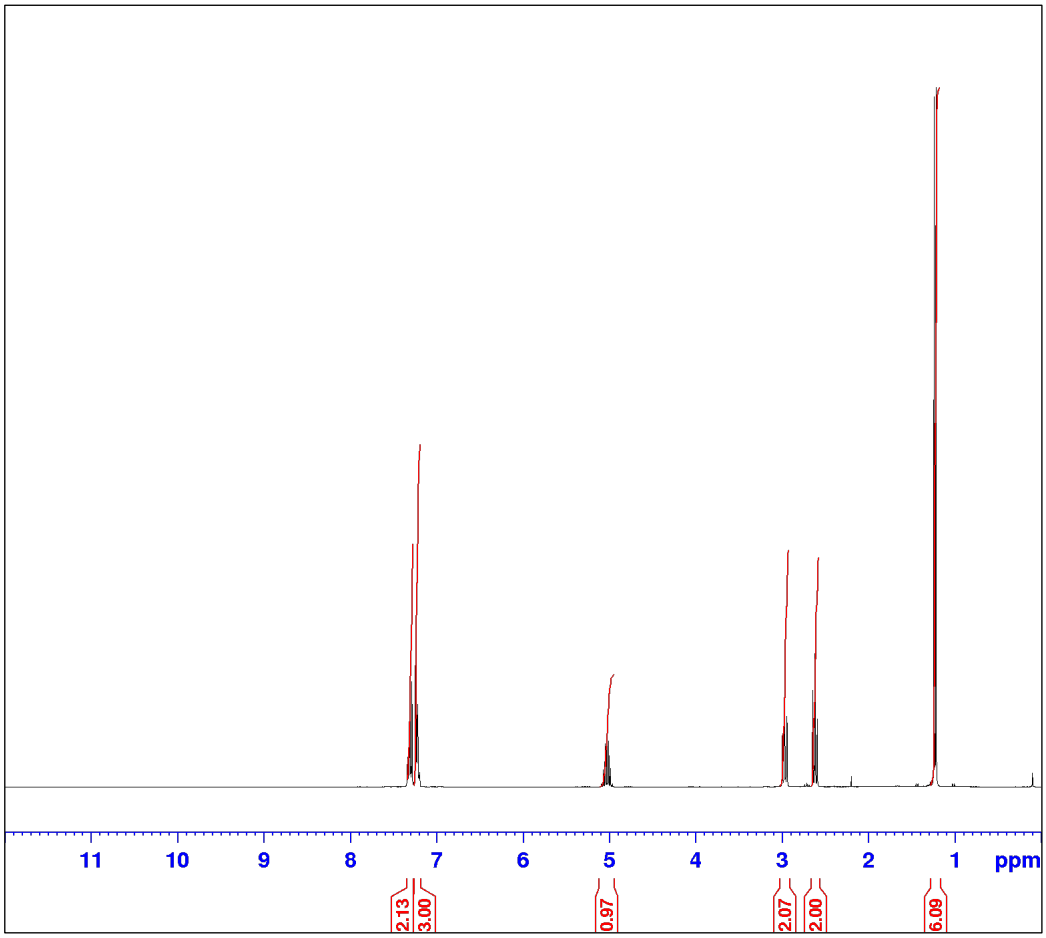


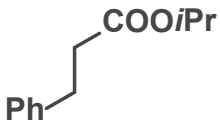


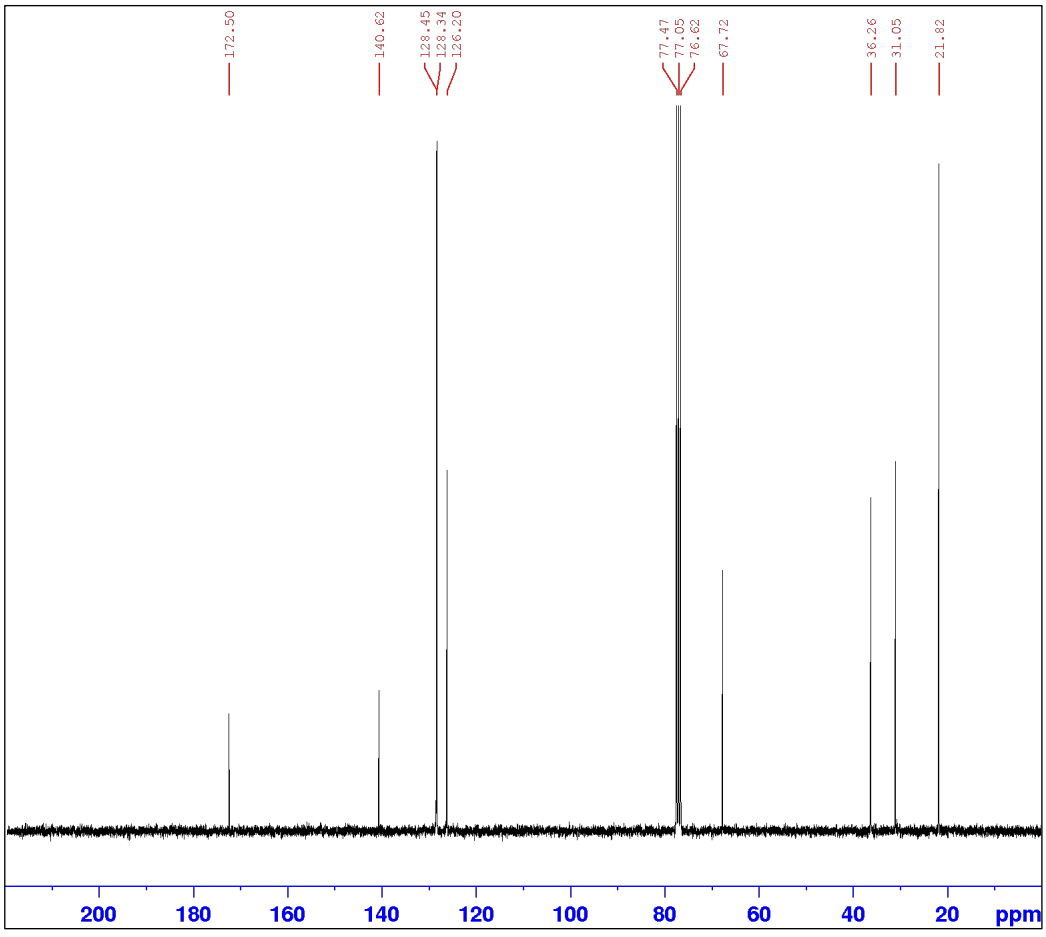


75 MHz, $CDCl_3$

300 MHz, $CDCl_3$

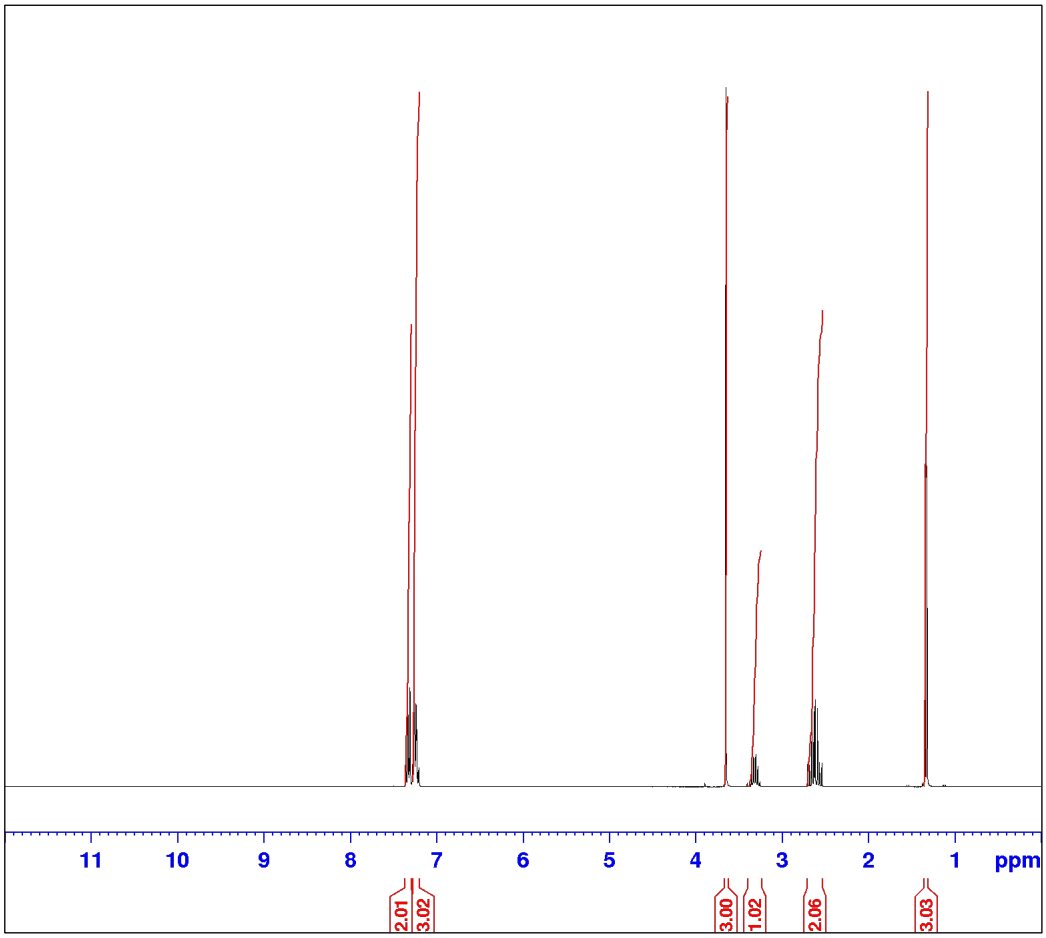


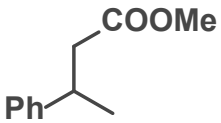


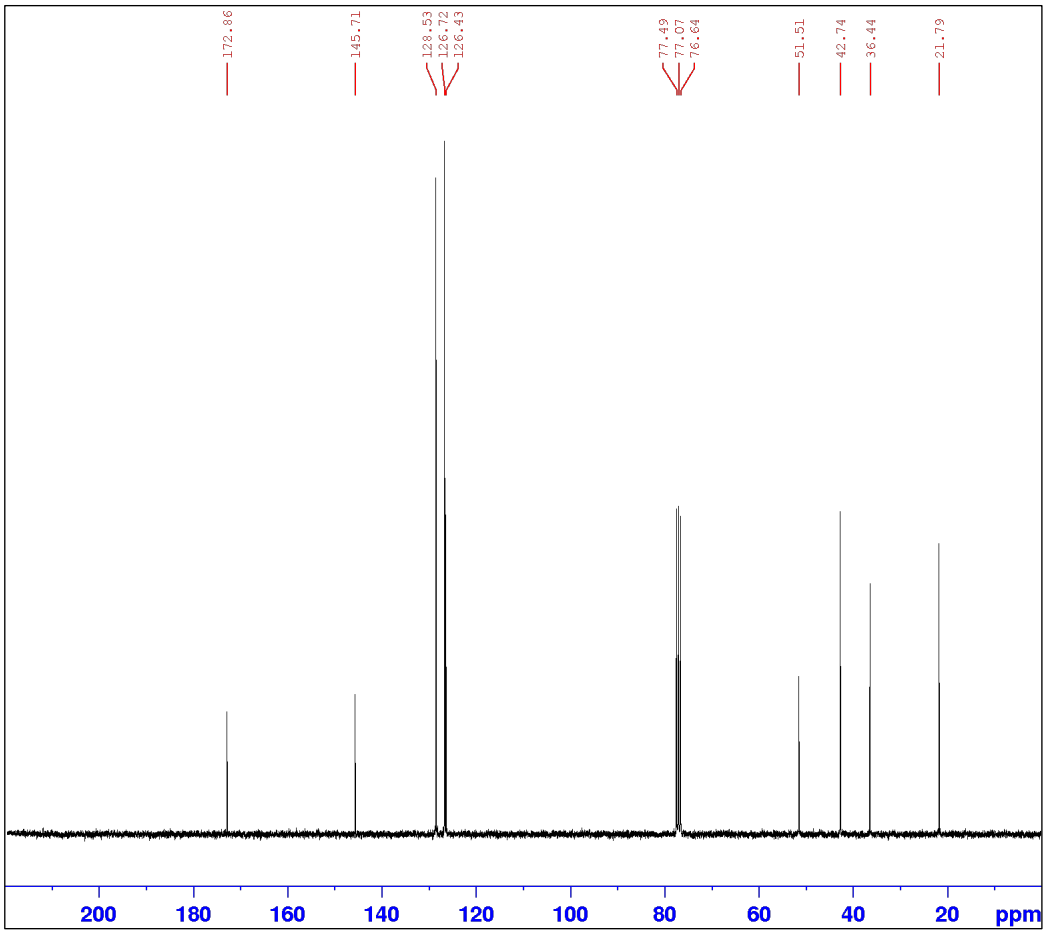


75 MHz, $CDCl_3$

300 MHz, $CDCl_3$

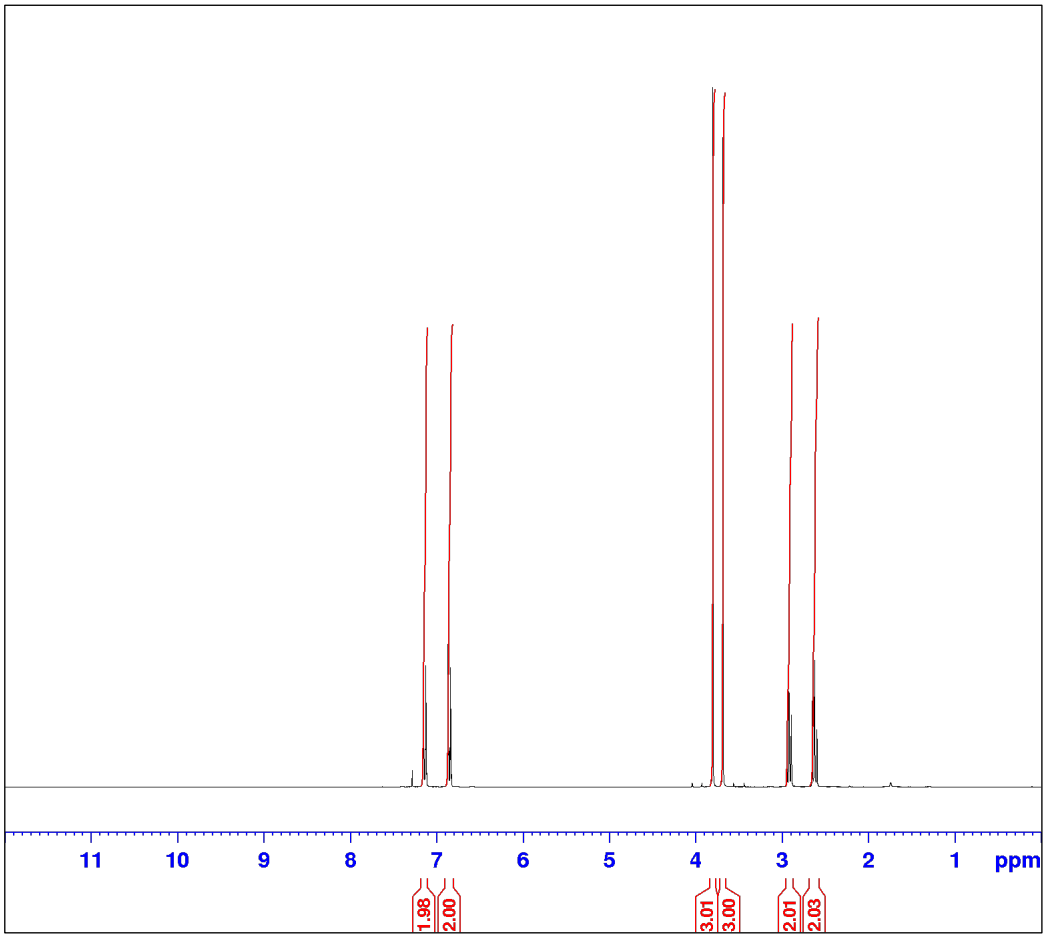


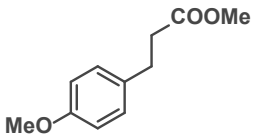


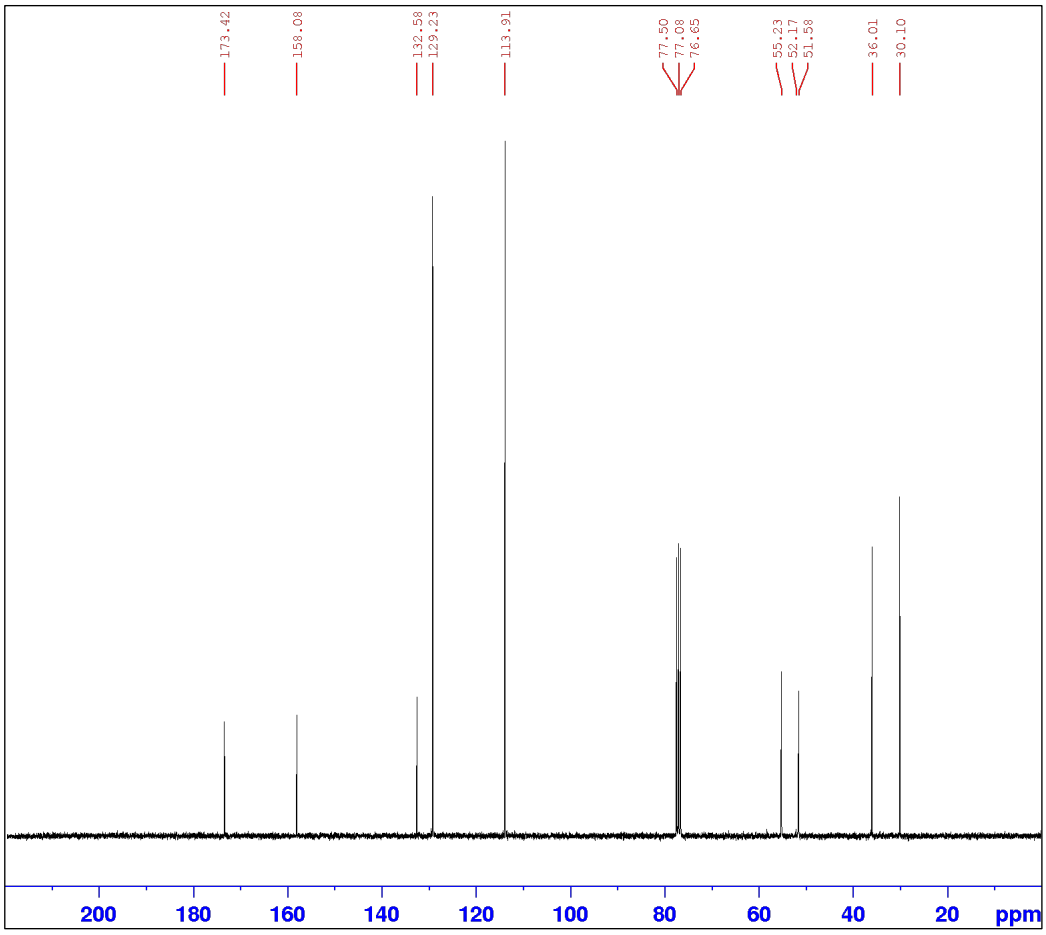


75 MHz, $CDCl_3$

300 MHz, $CDCl_3$

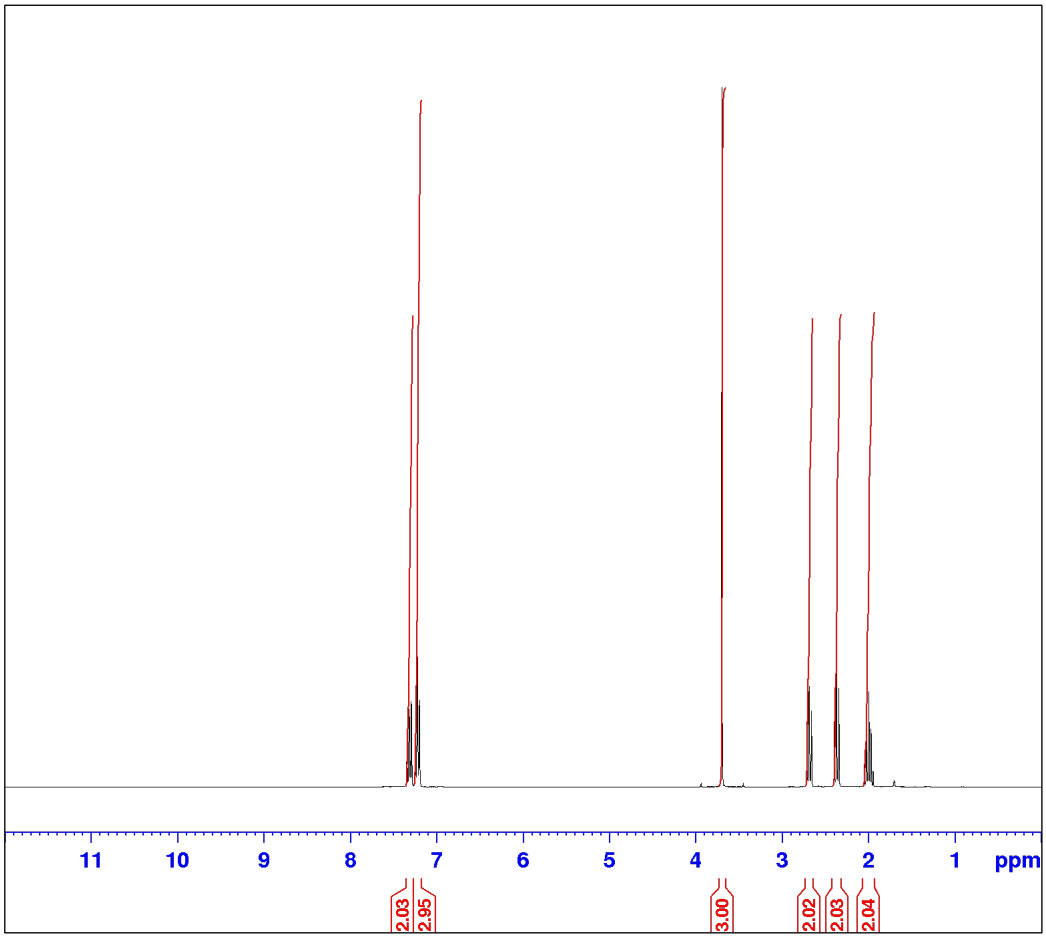


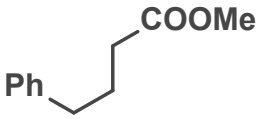


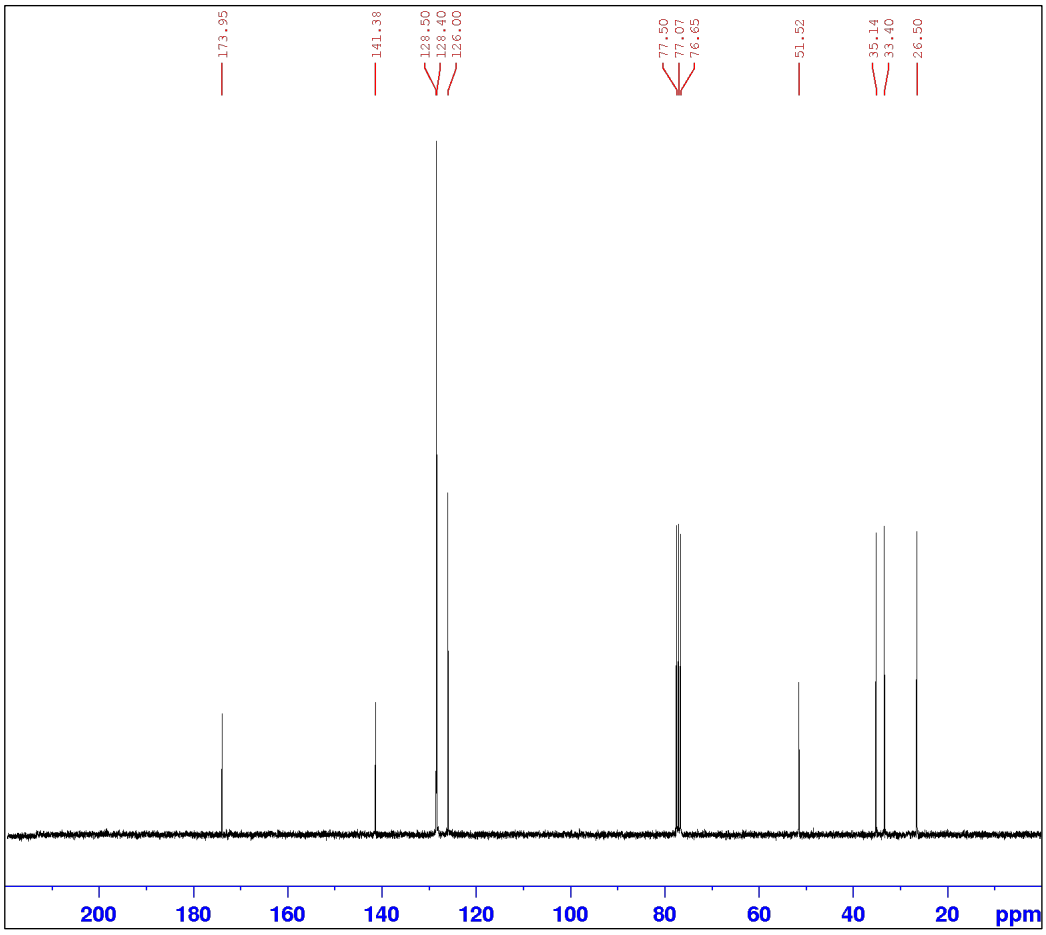


75 MHz, $CDCl_3$

300 MHz, $CDCl_3$

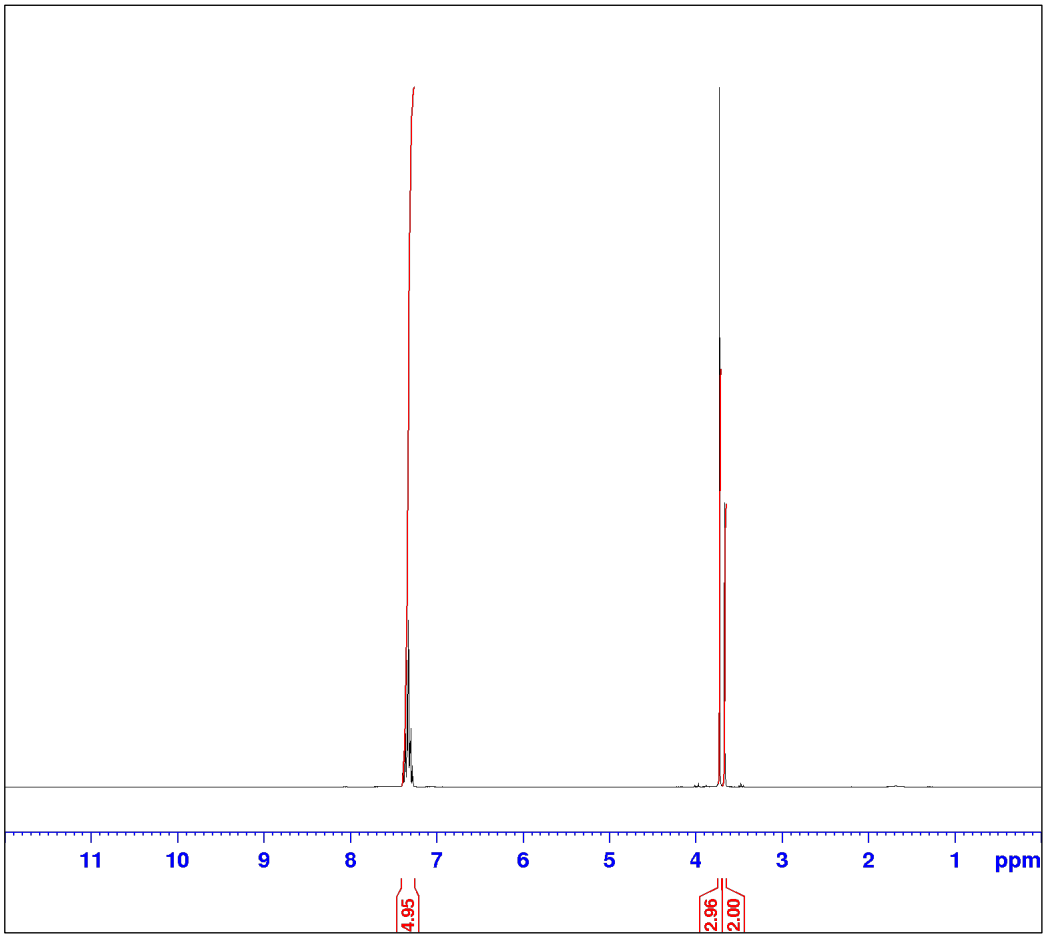




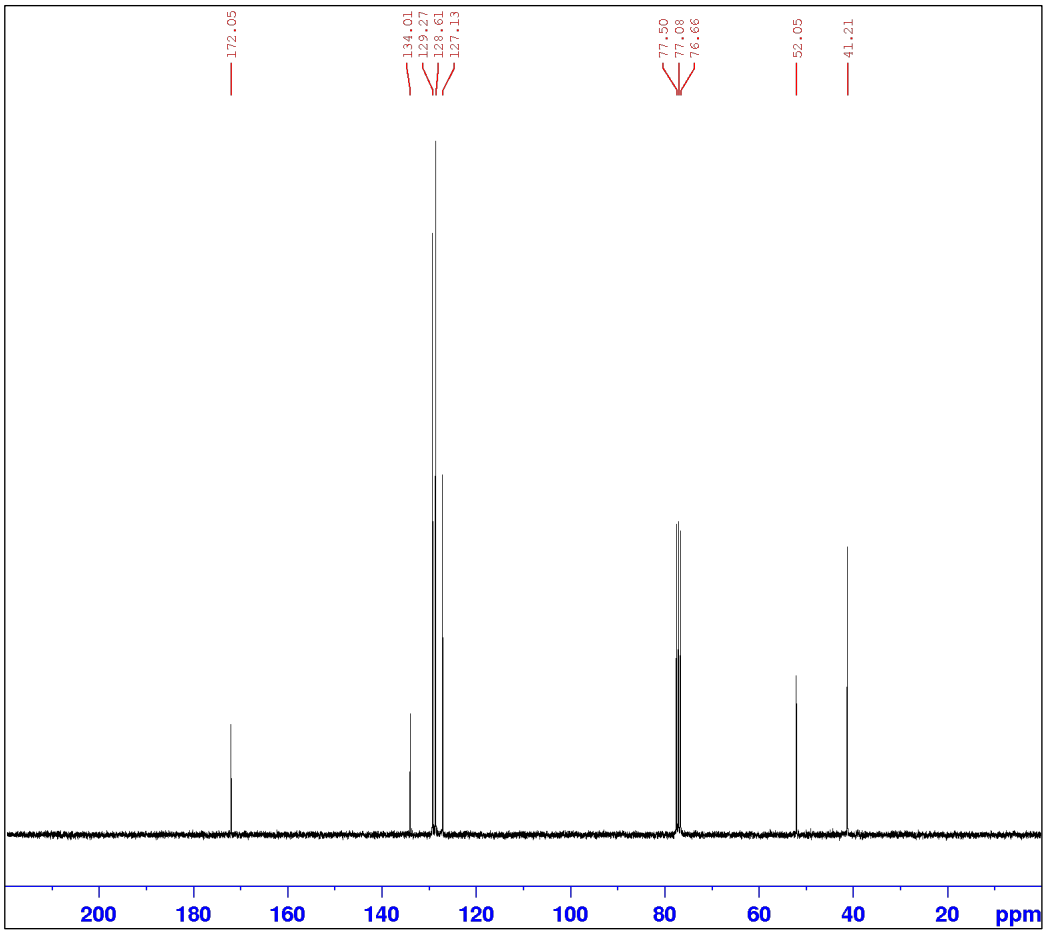


75 MHz, $CDCl_3$

300 MHz, $CDCl_3$

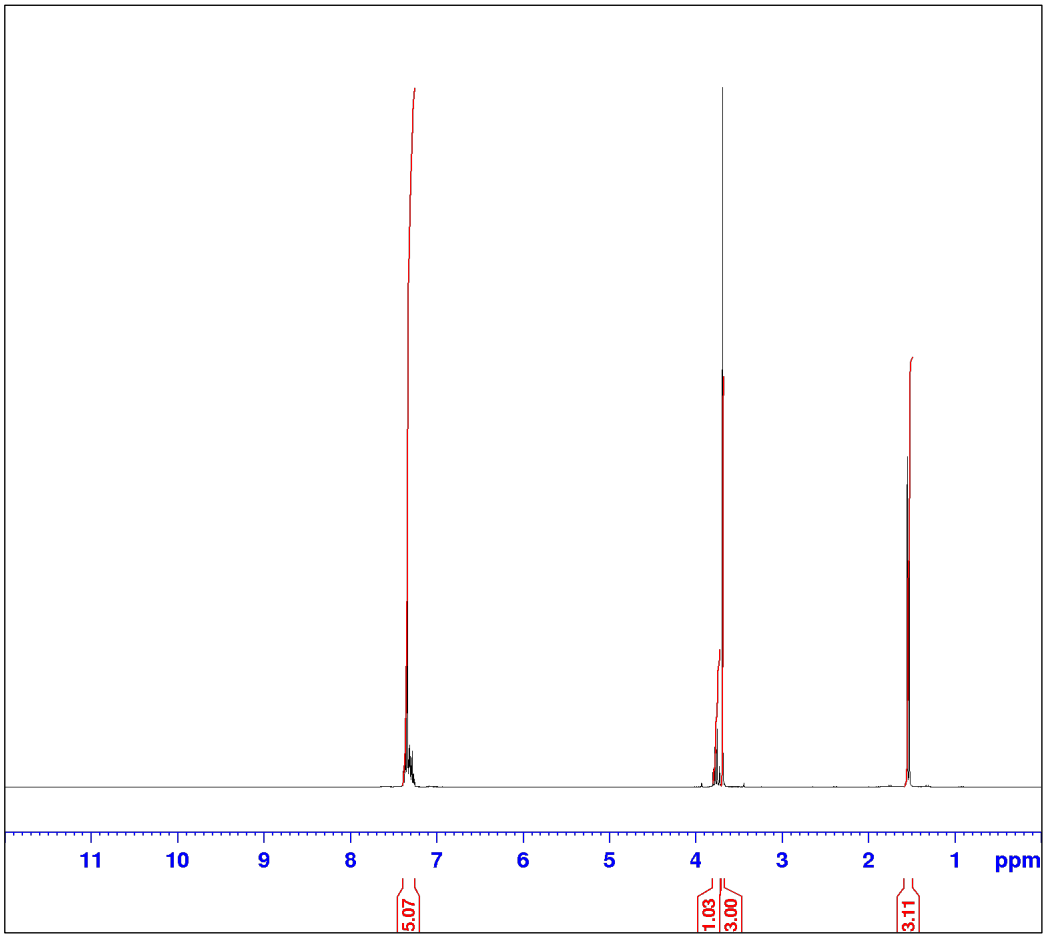


Ph COOMe



75 MHz, $CDCl_3$

300 MHz, $CDCl_3$



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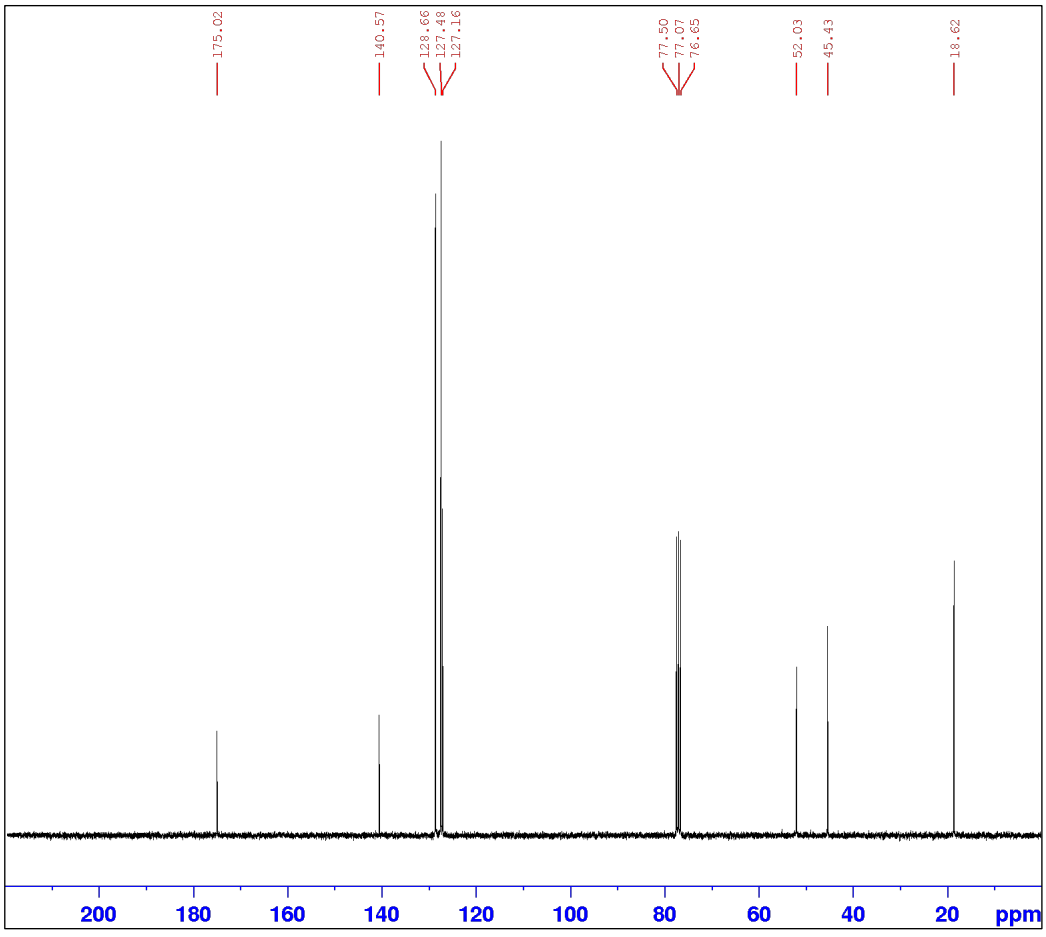
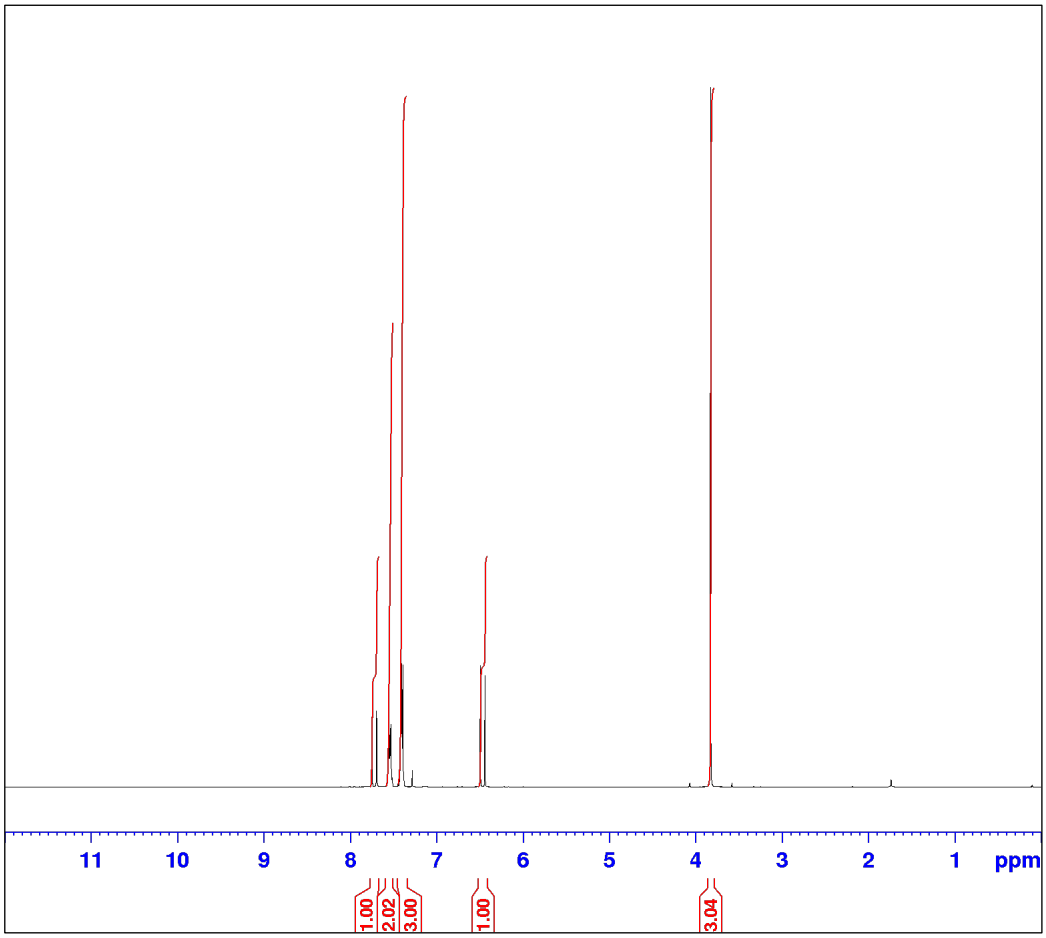
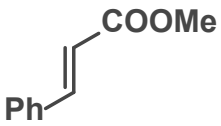
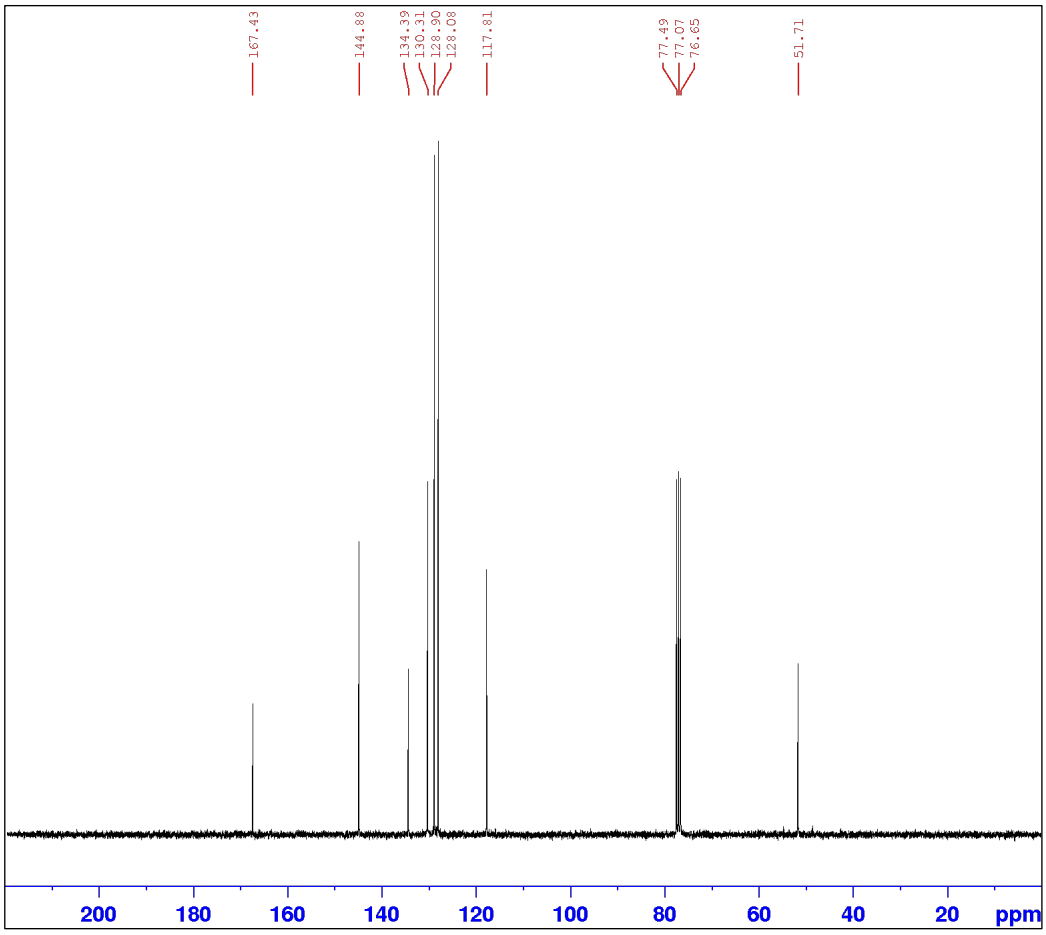


75 MHz, $CDCl_3$

300 MHz, $CDCl_3$

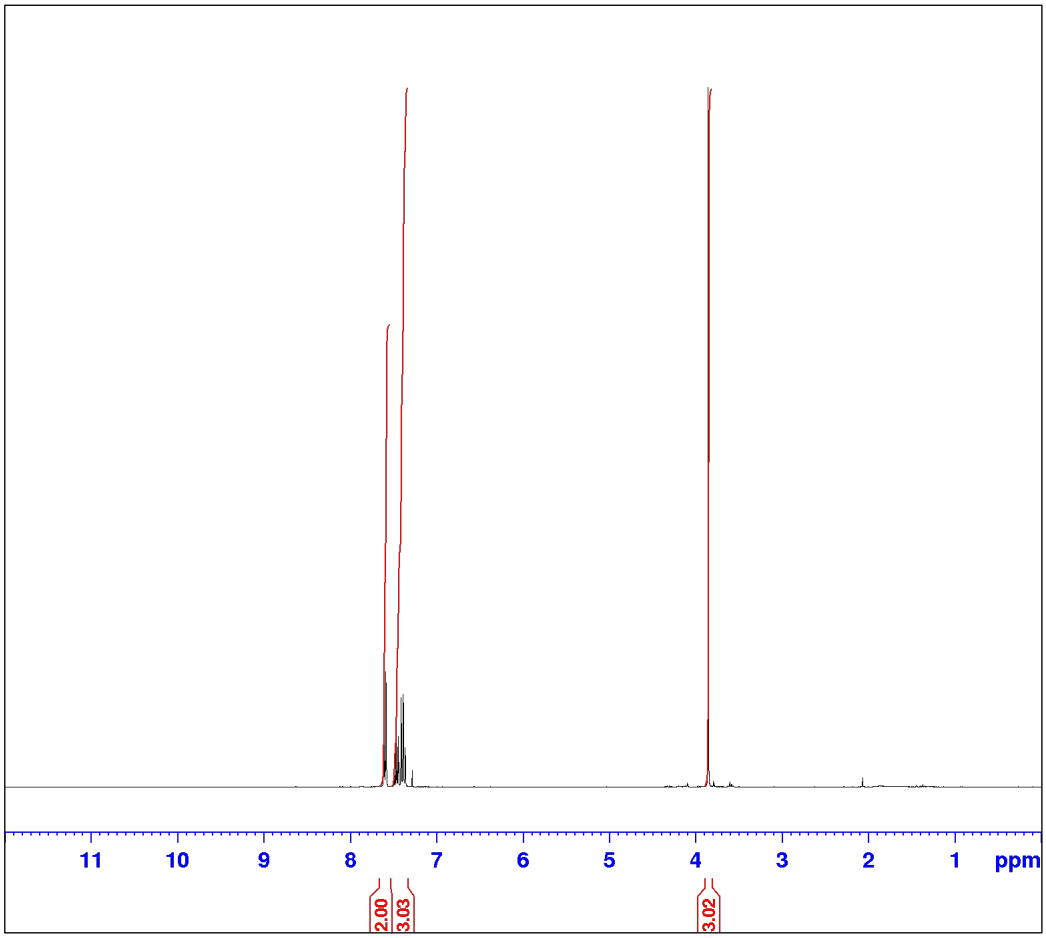




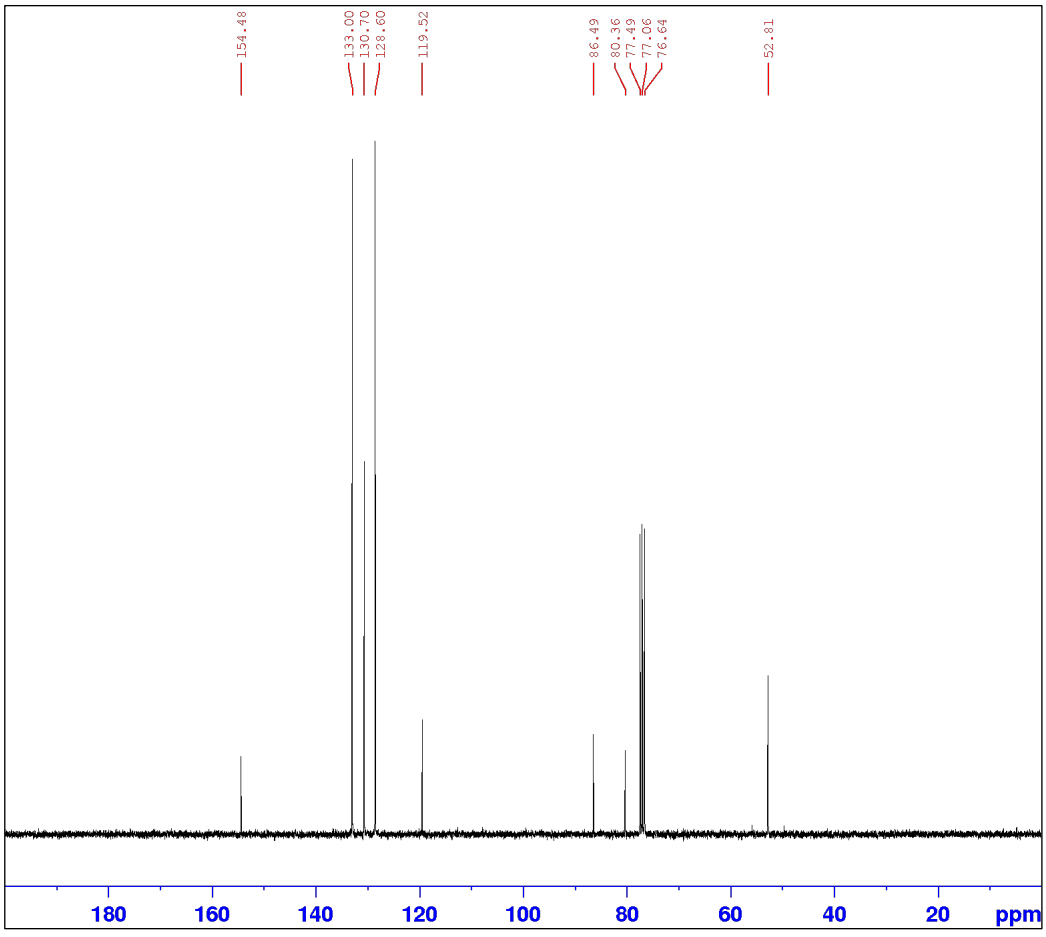


75 MHz, $CDCl_3$

300 MHz, $CDCl_3$

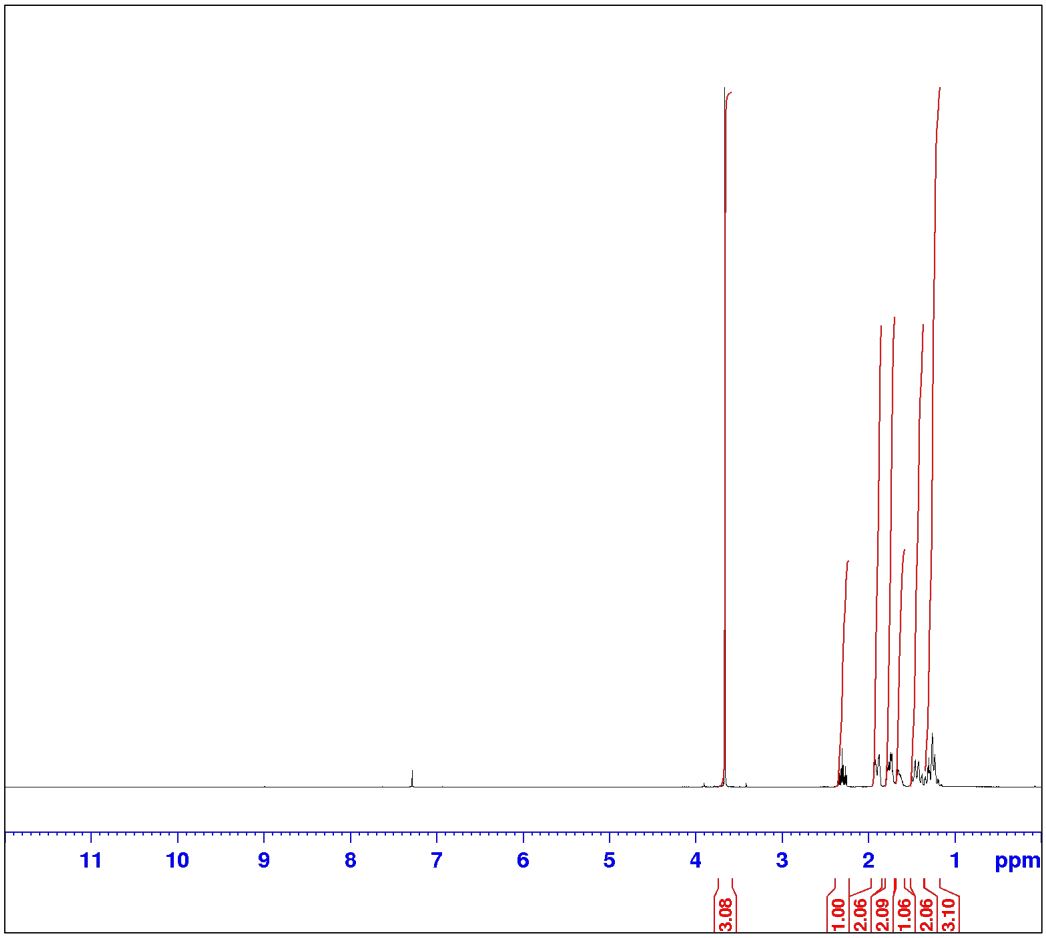


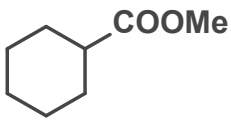
Ph—≡—COOMe

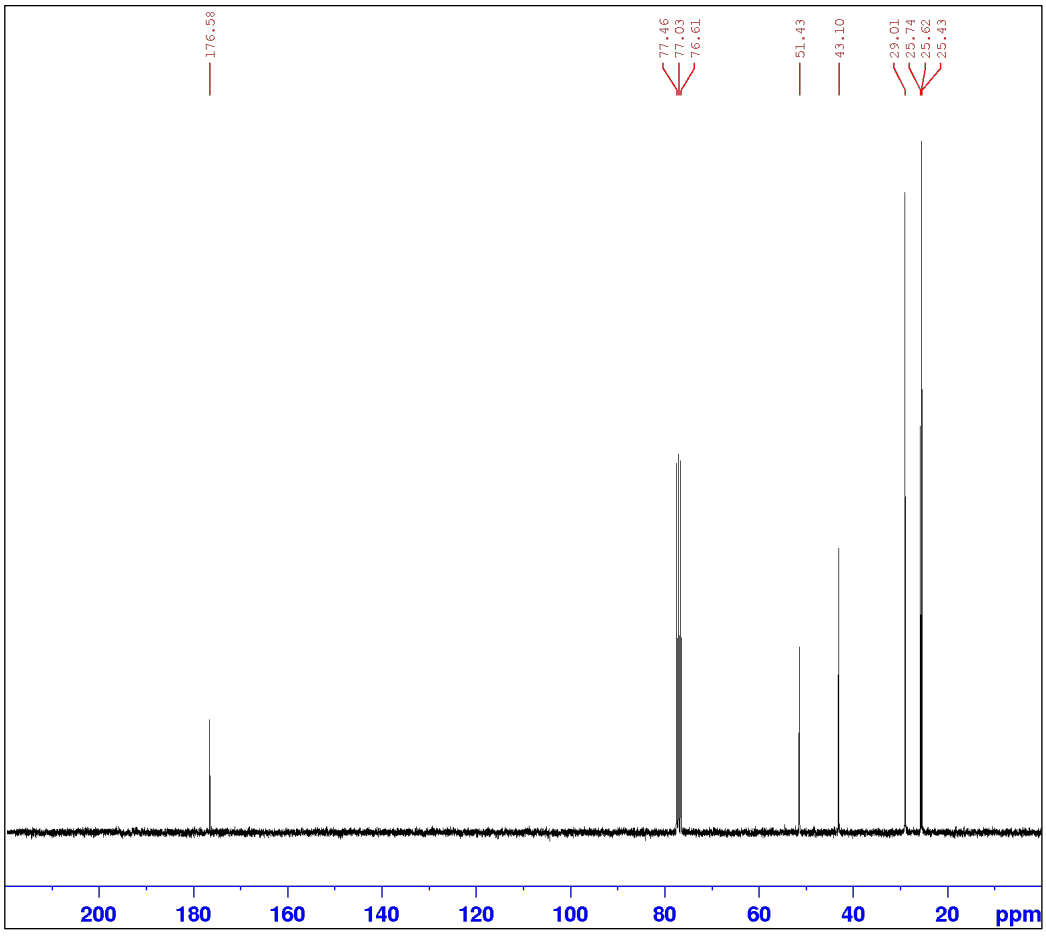


75 MHz, $CDCl_3$

300 MHz, $CDCl_3$

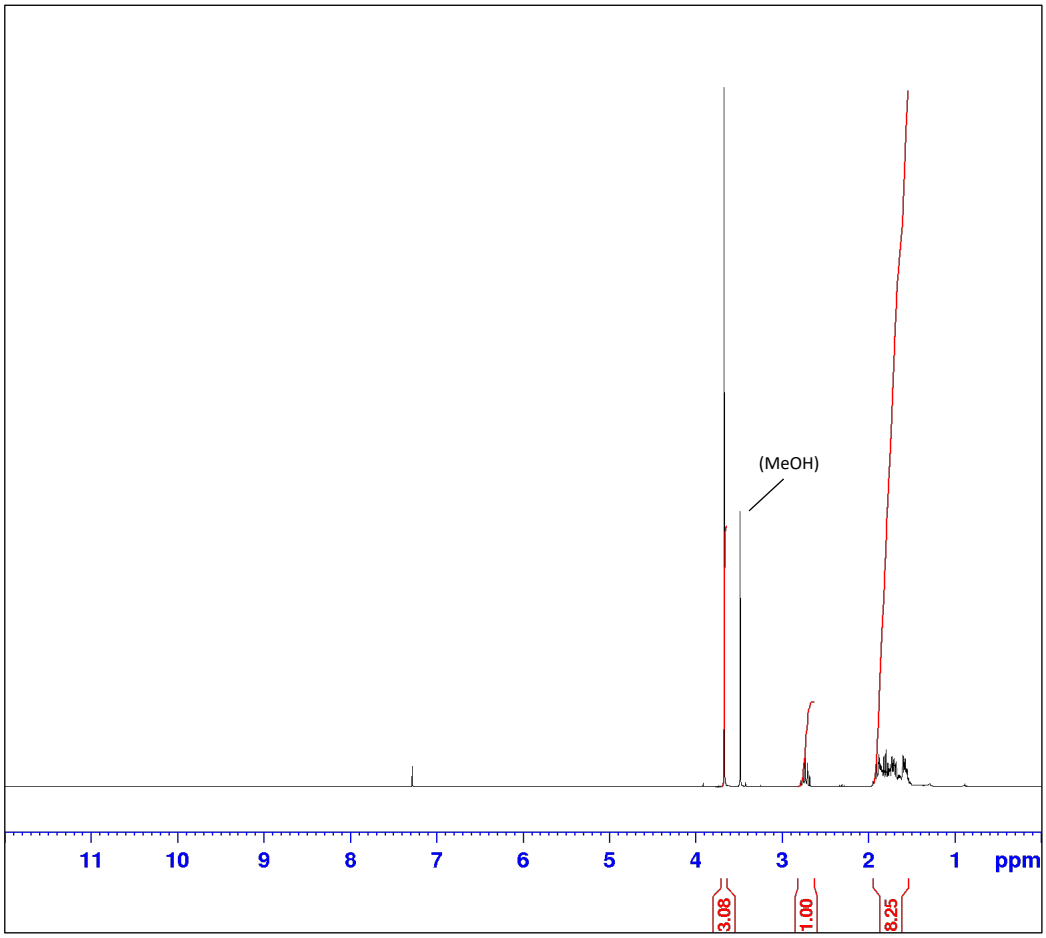


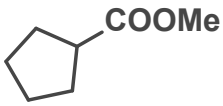


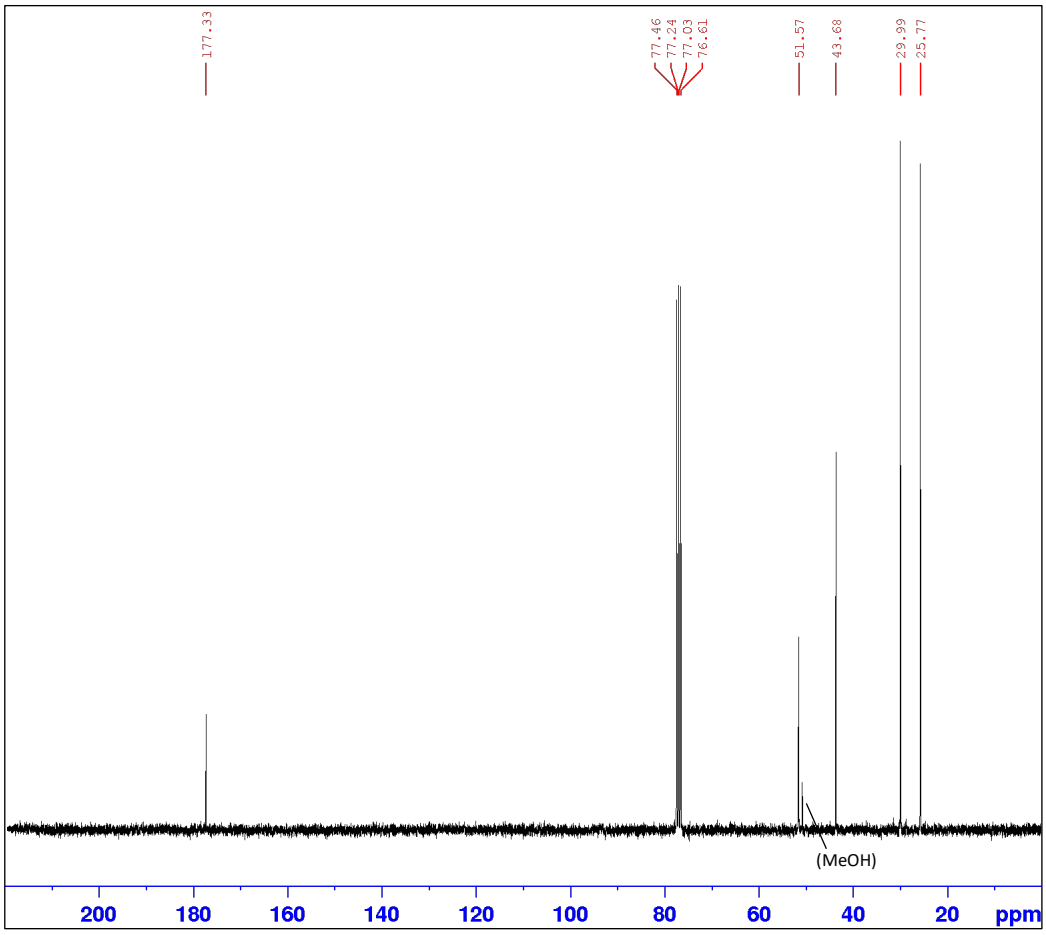


75 MHz, $CDCl_3$

300 MHz, $CDCl_3$

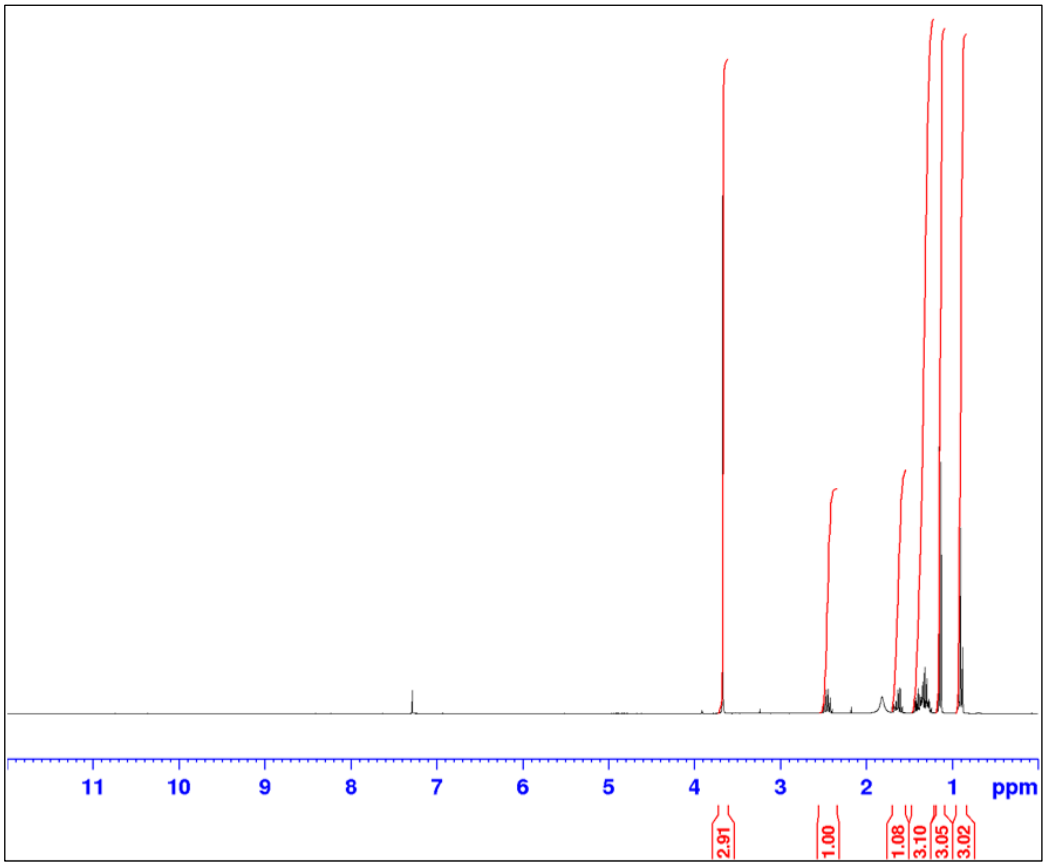


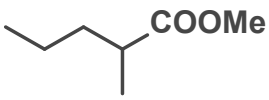


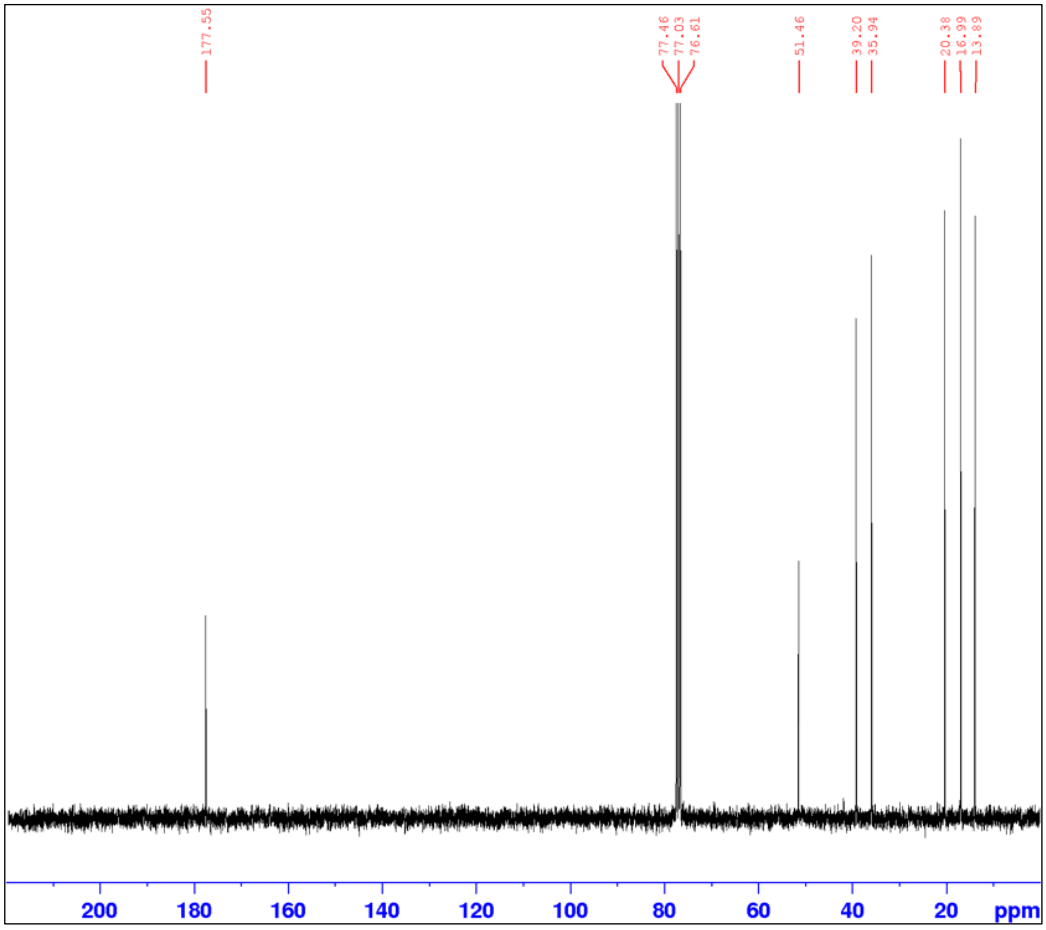


75 MHz, $CDCl_3$

300 MHz, $CDCl_3$

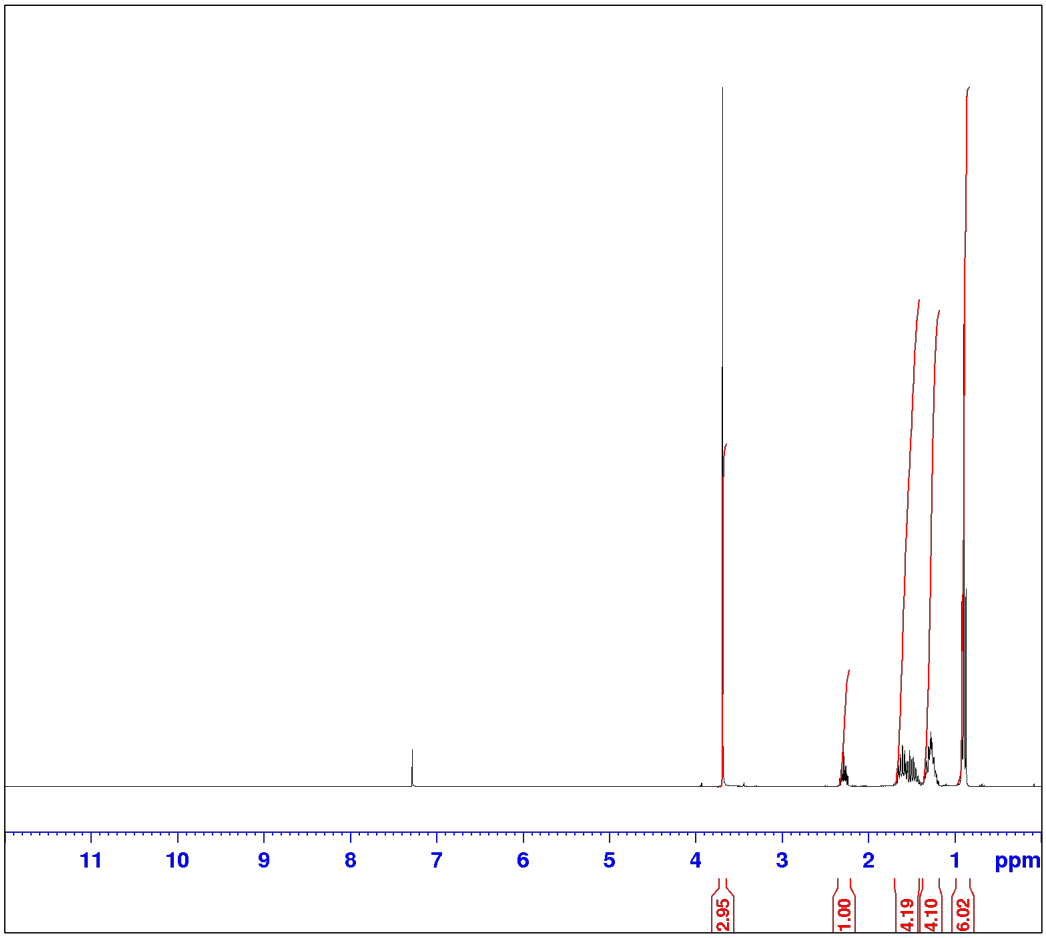


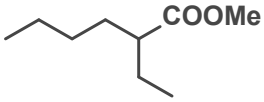


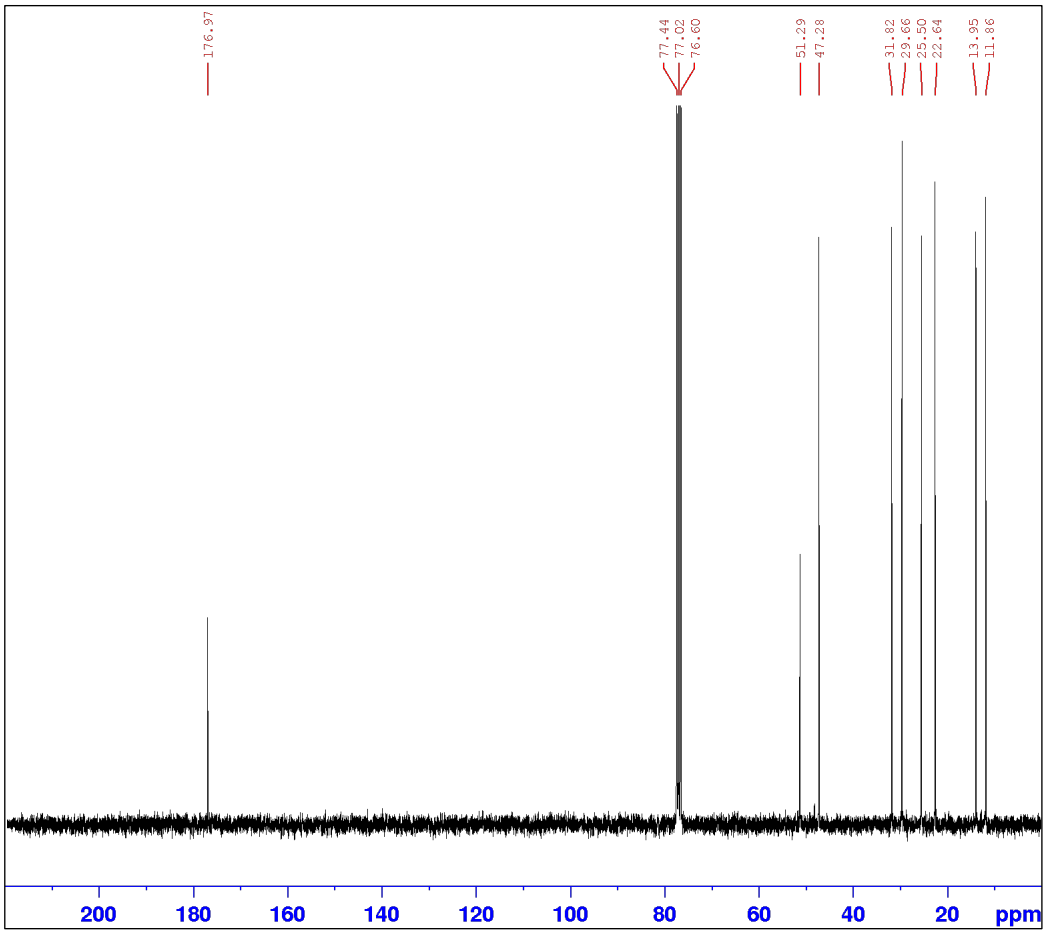


75 MHz, $CDCl_3$

300 MHz, $CDCl_3$

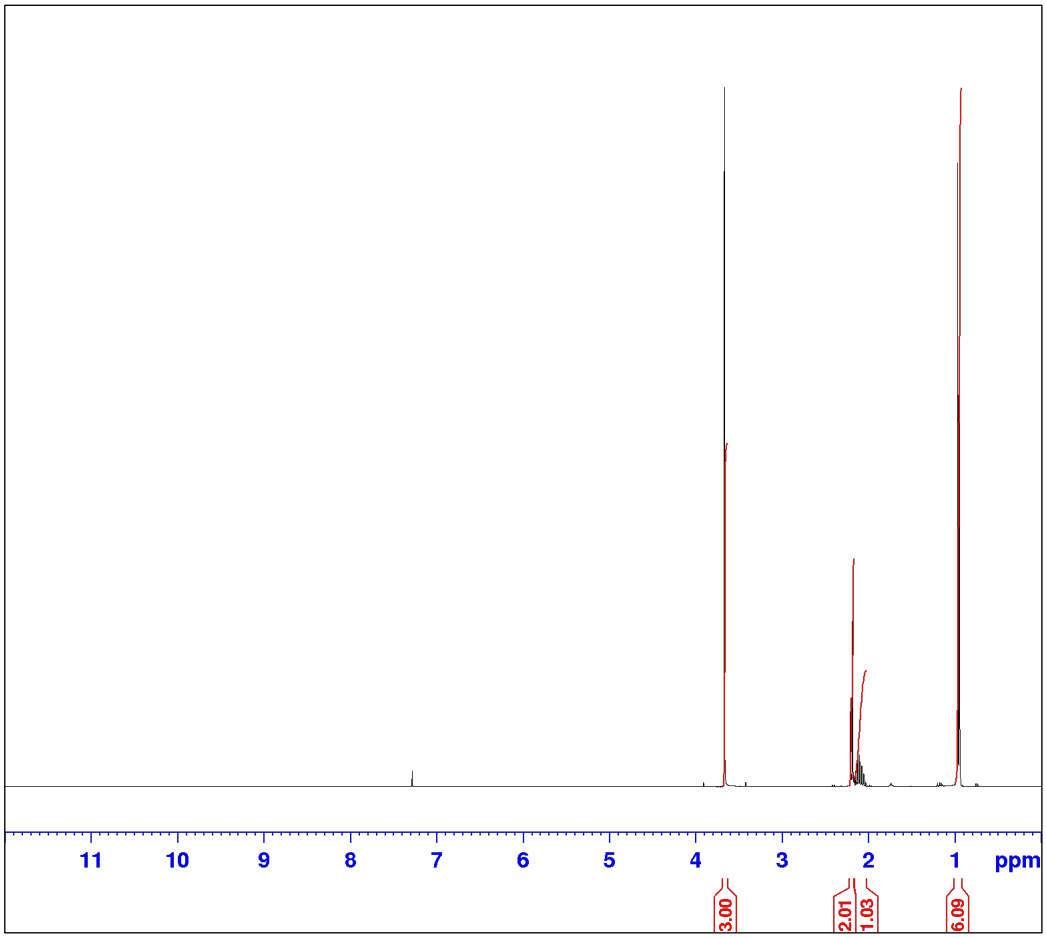


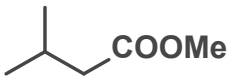


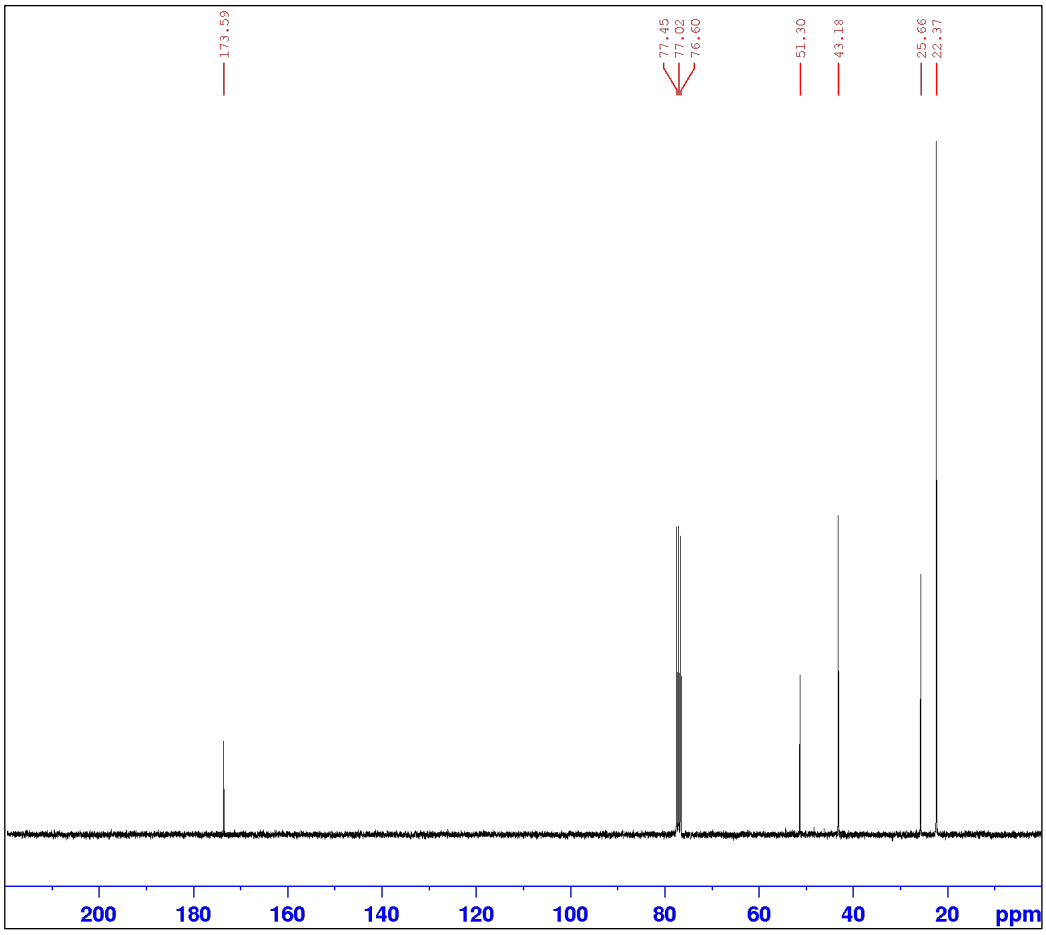


75 MHz, $CDCl_3$

300 MHz, $CDCl_3$

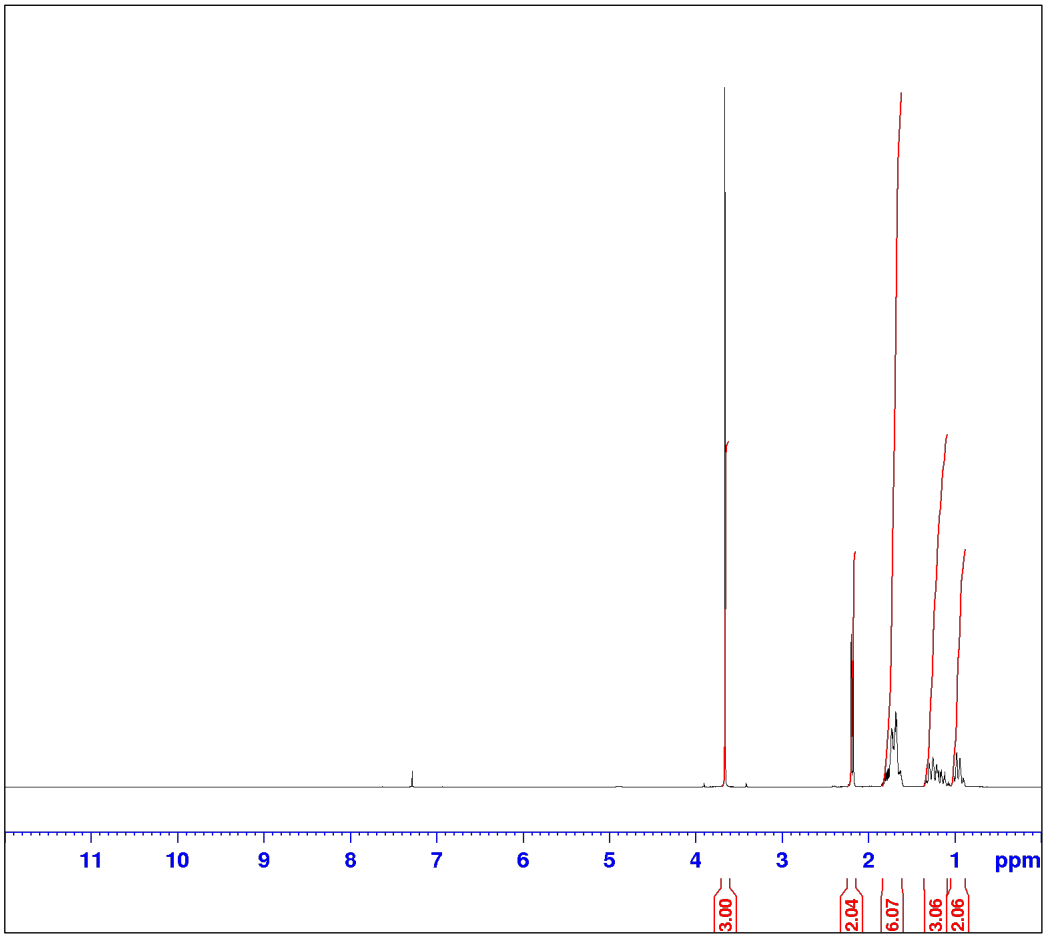


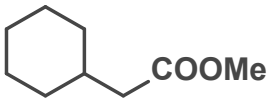


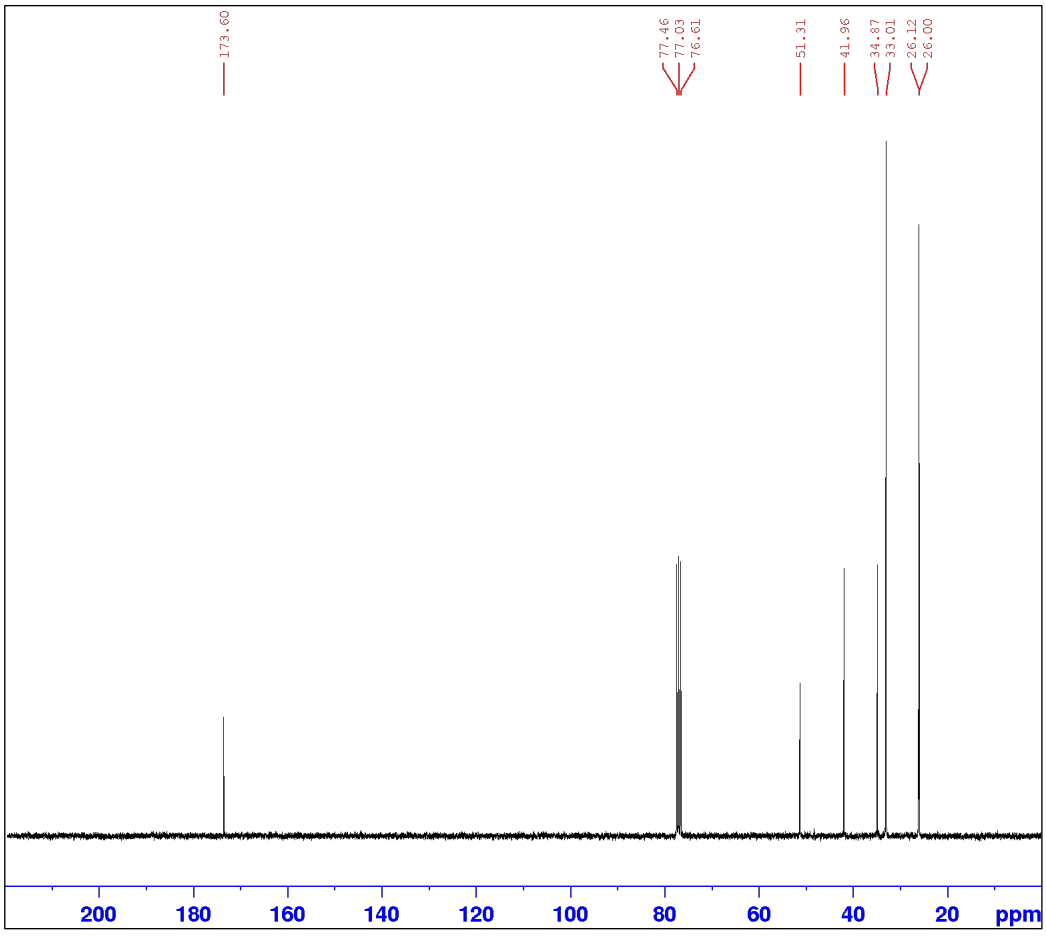


75 MHz, $CDCl_3$

300 MHz, $CDCl_3$

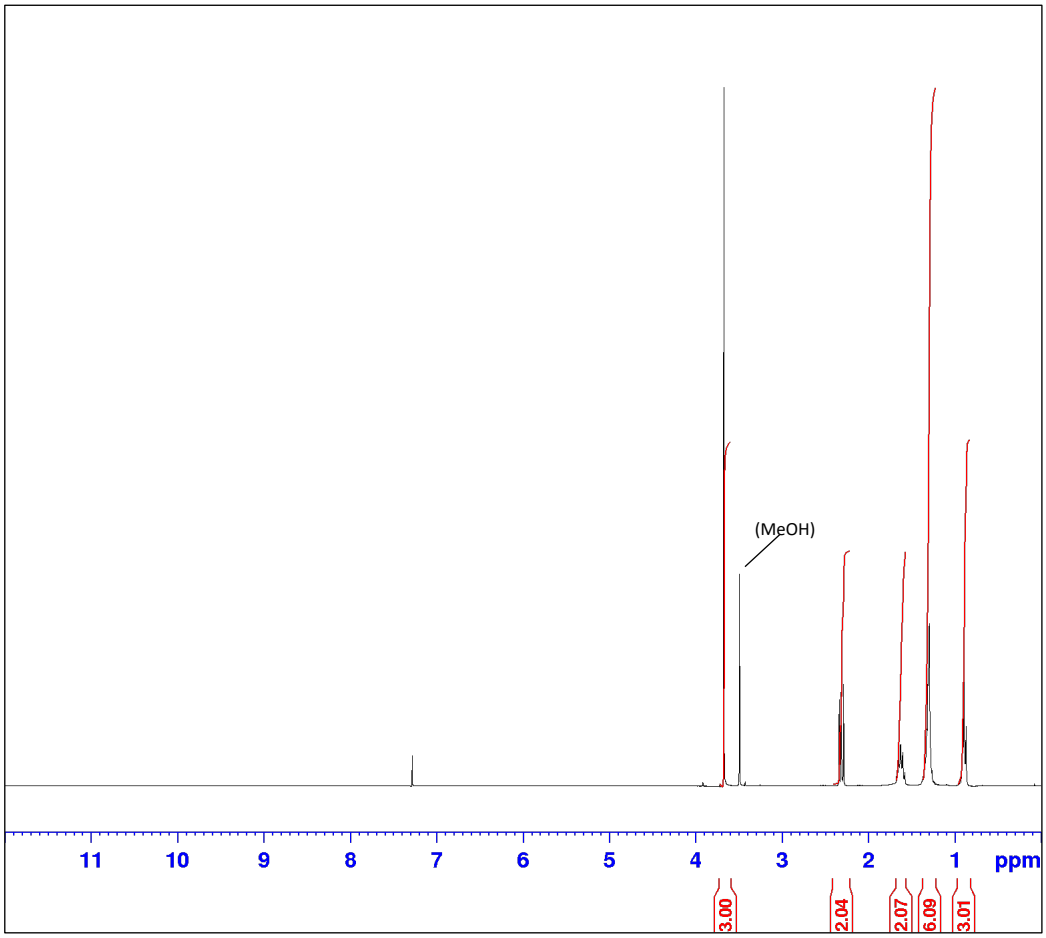


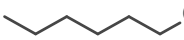


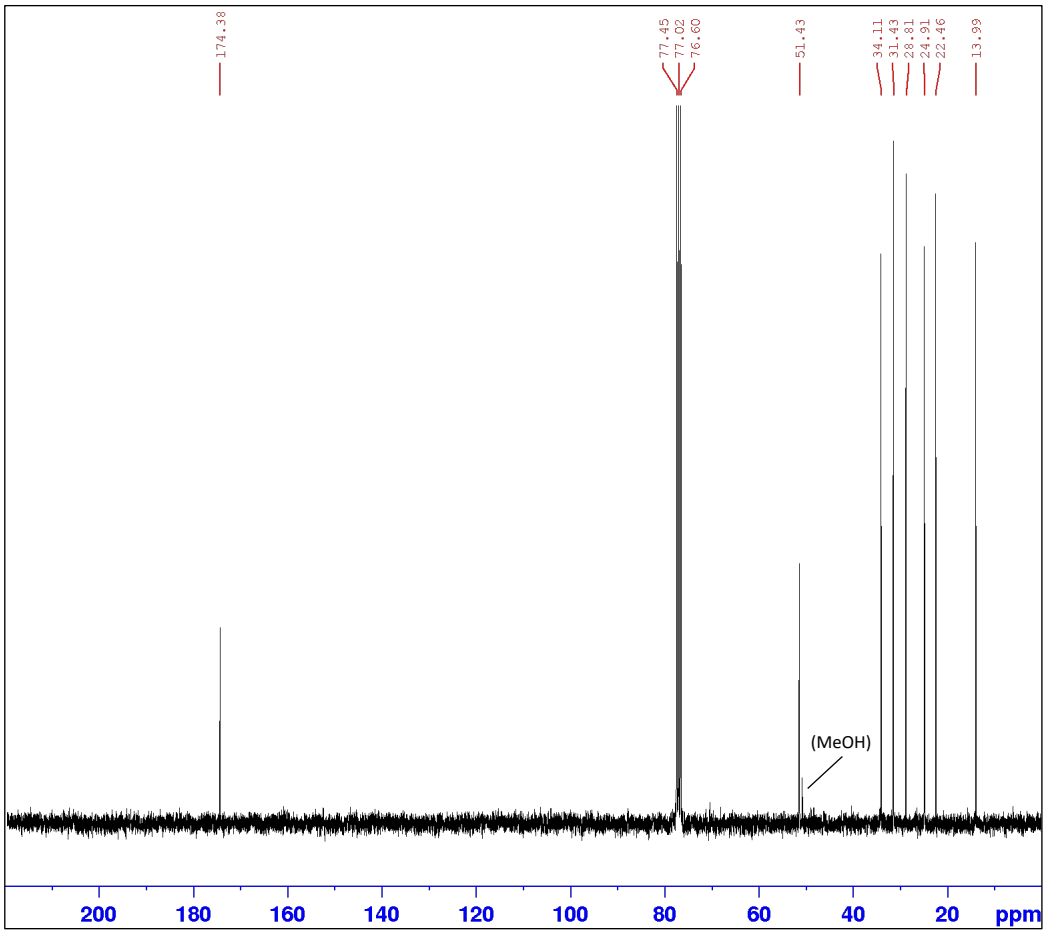


75 MHz, $CDCl_3$

300 MHz, $CDCl_3$

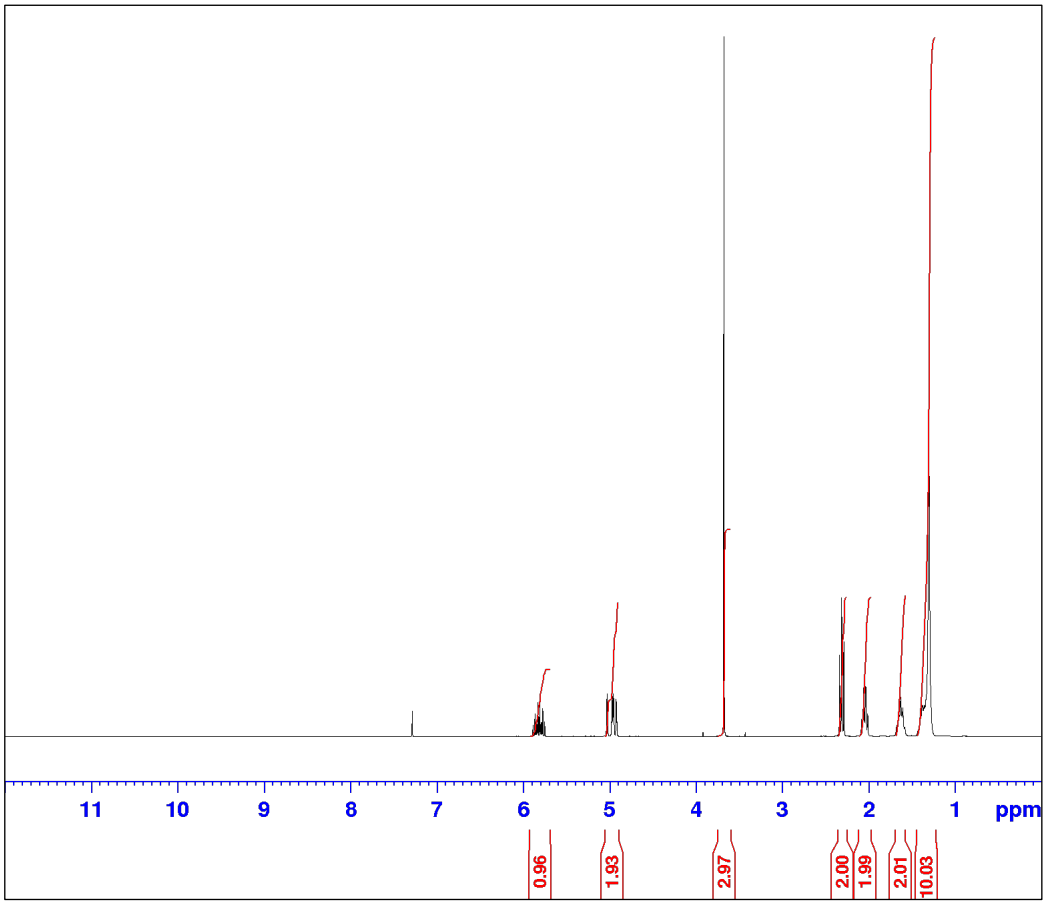


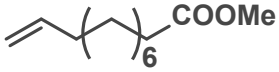


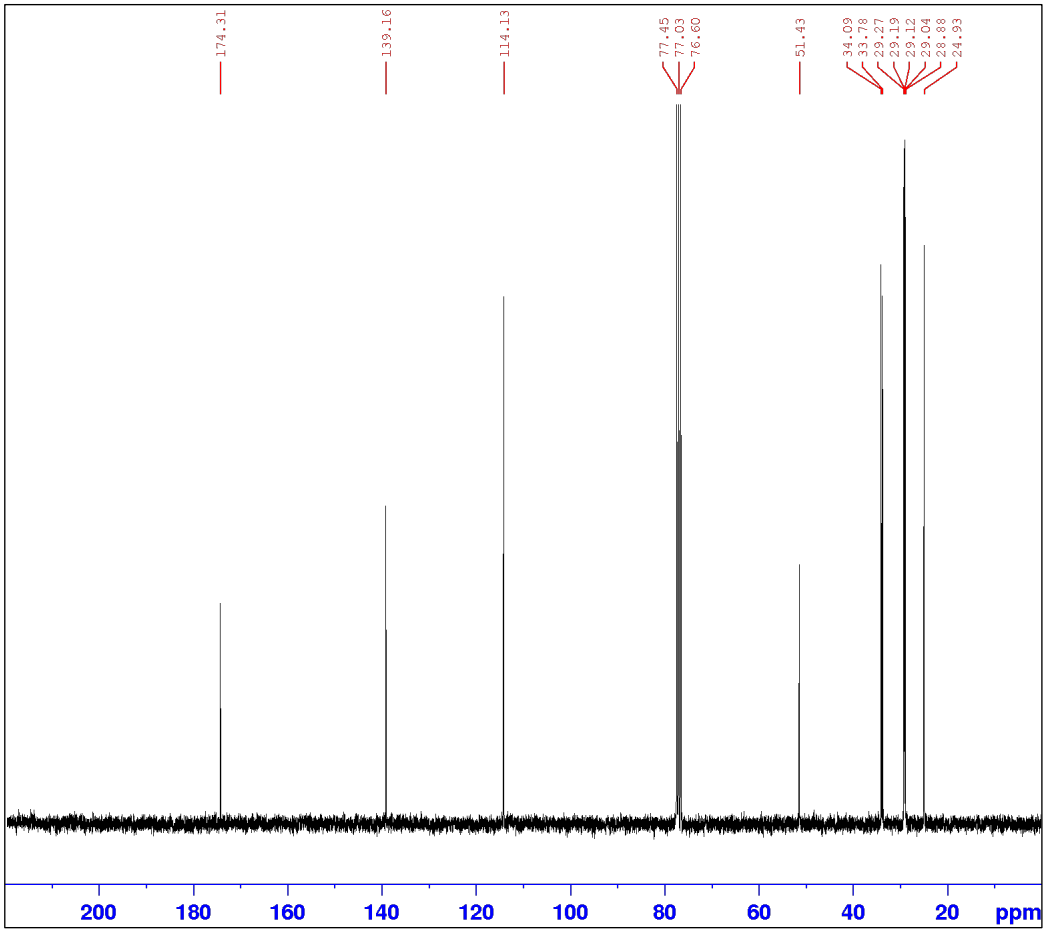


75 MHz, $CDCl_3$

300 MHz, $CDCl_3$

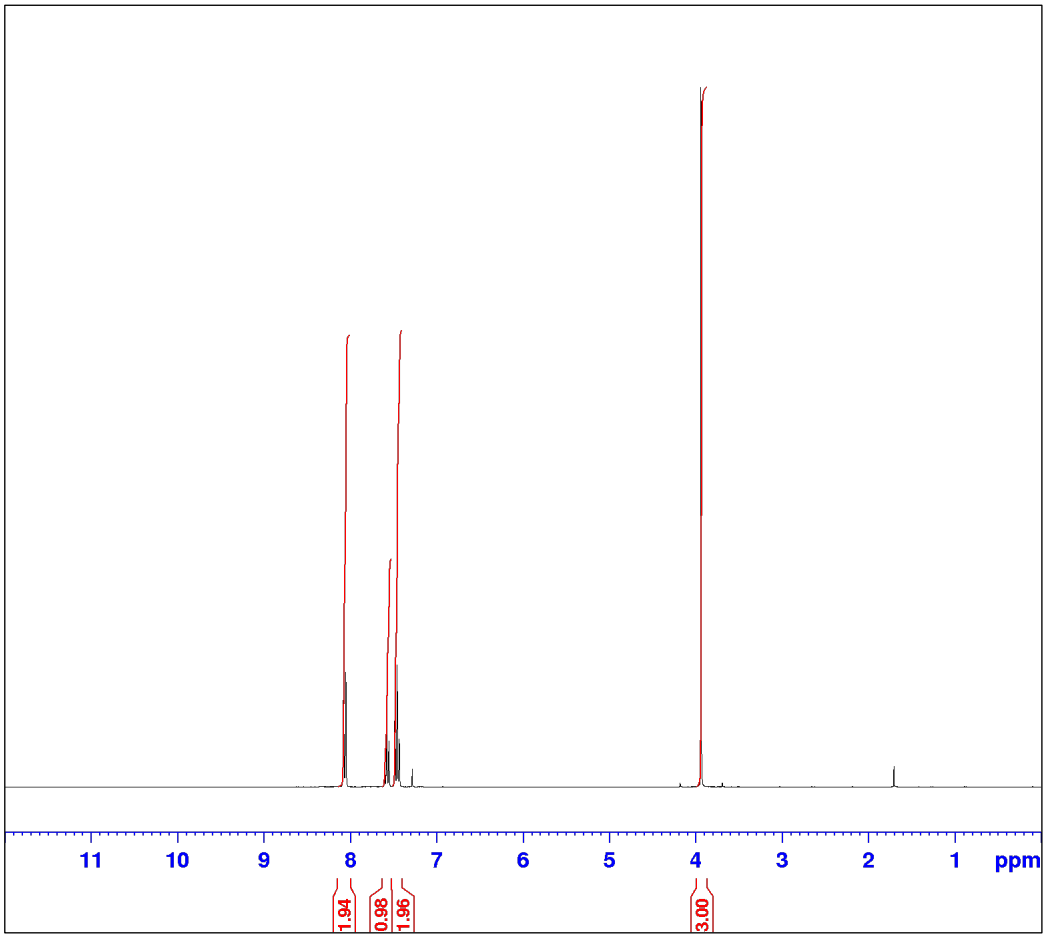


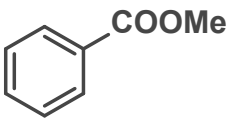


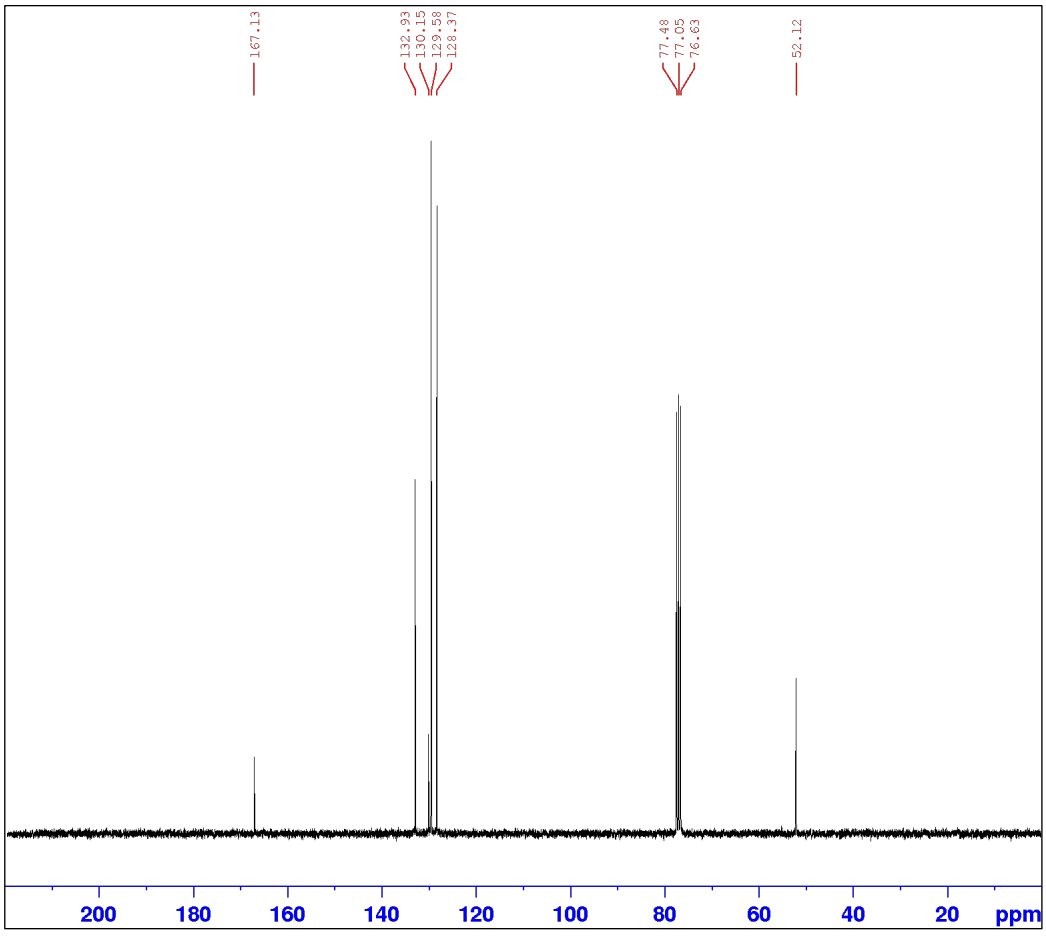


75 MHz, $CDCl_3$

300 MHz, $CDCl_3$

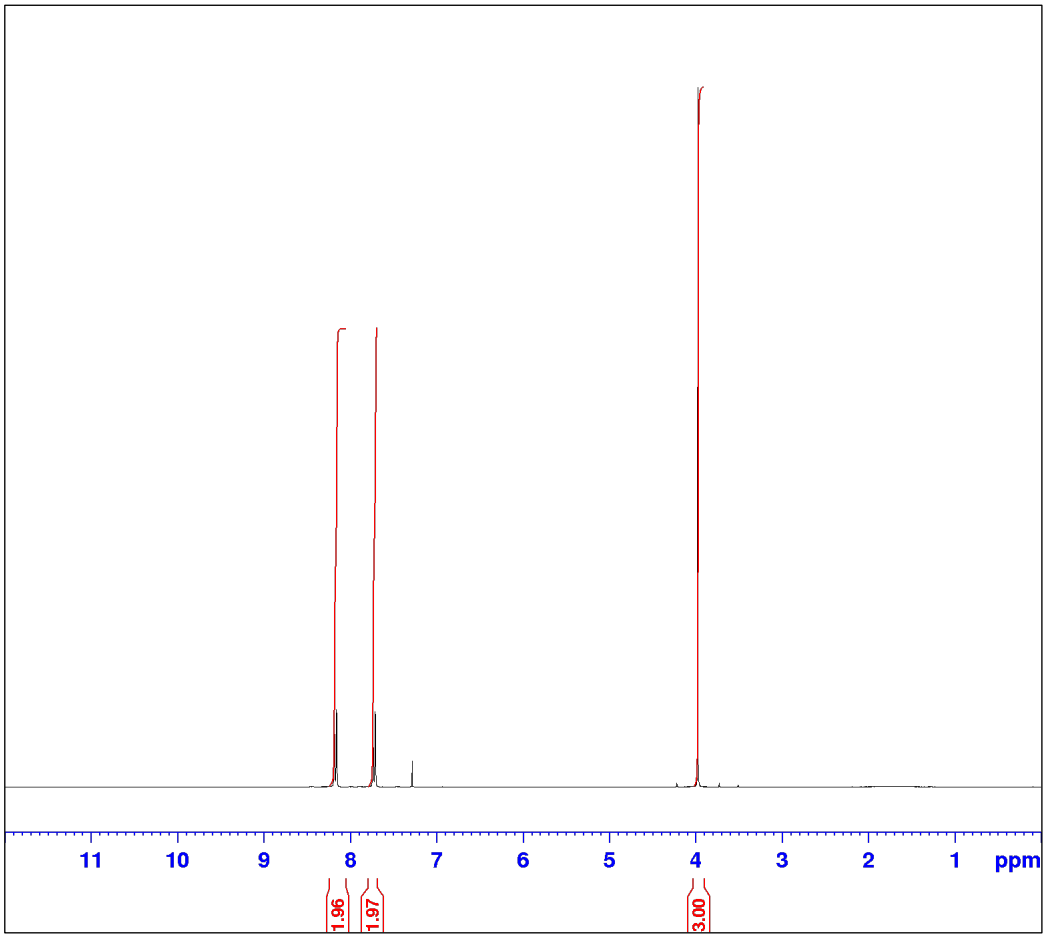


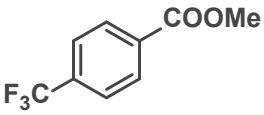


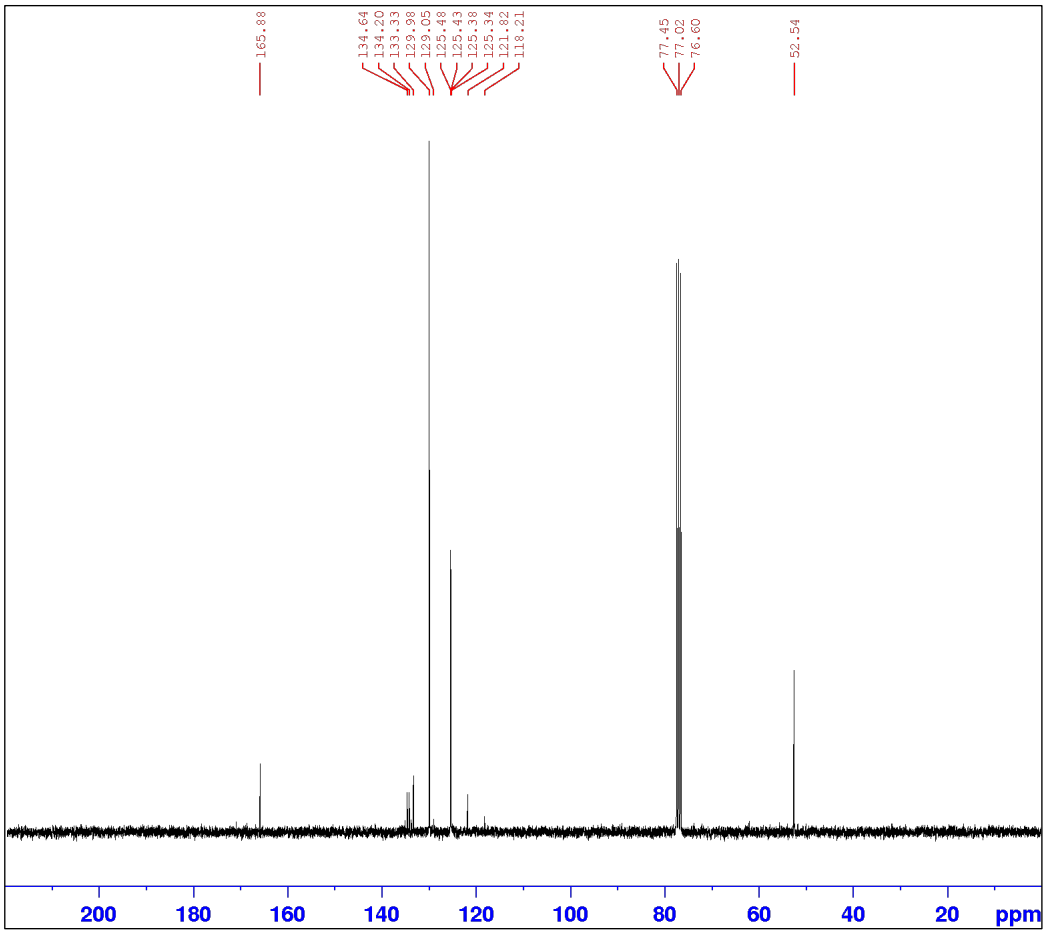


75 MHz, $CDCl_3$

300 MHz, $CDCl_3$

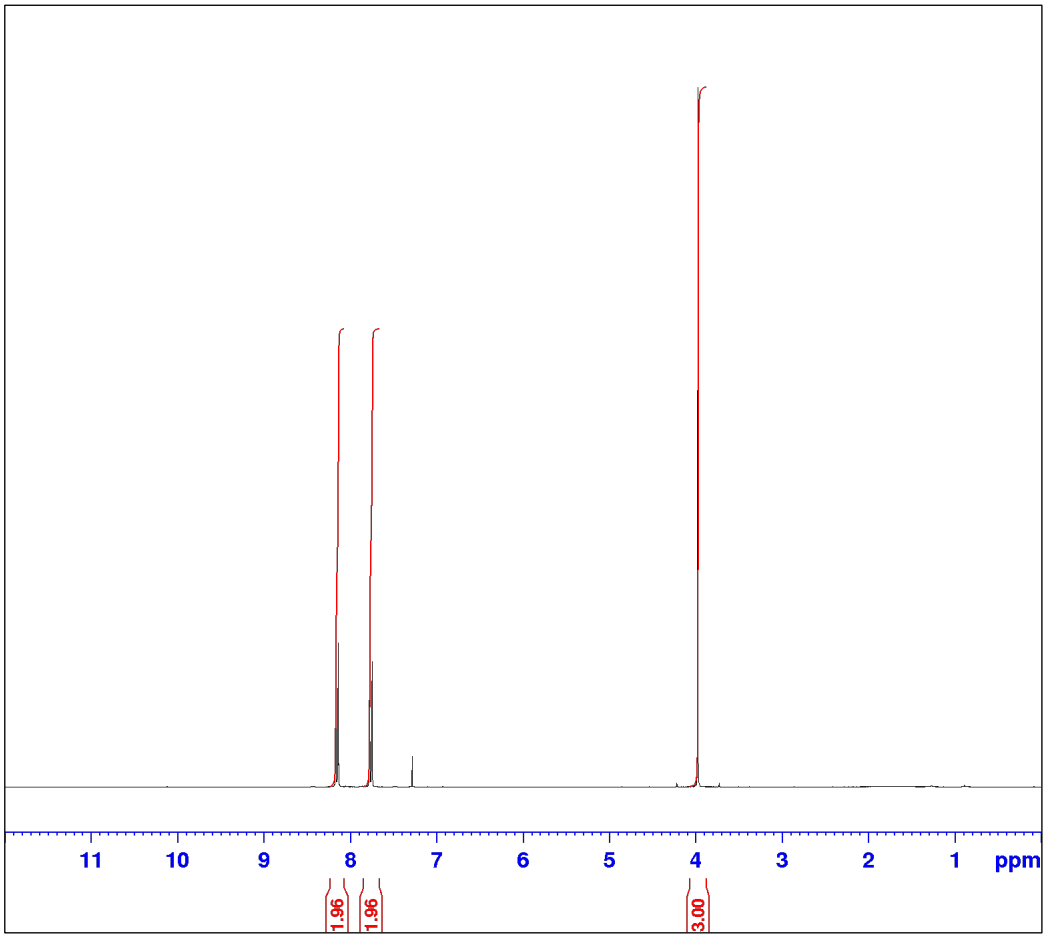


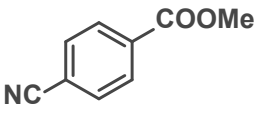


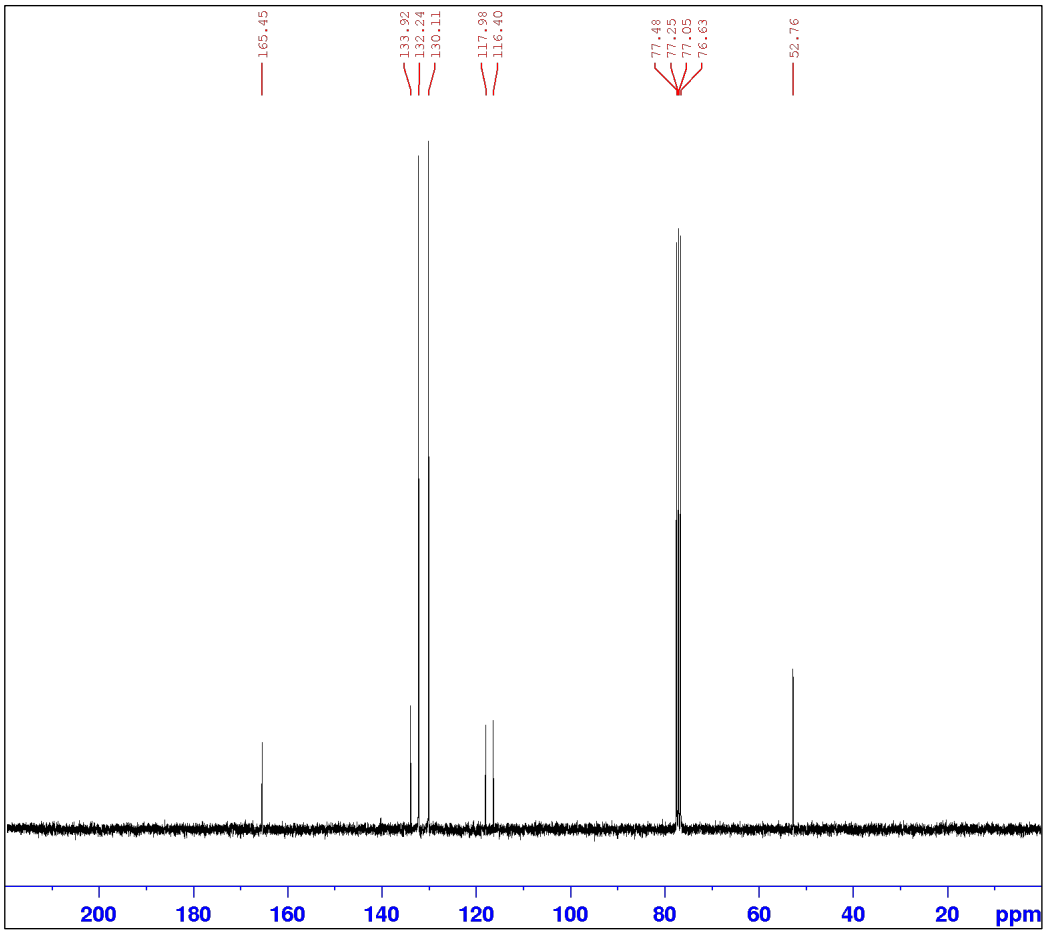


75 MHz, $CDCl_3$

300 MHz, $CDCl_3$

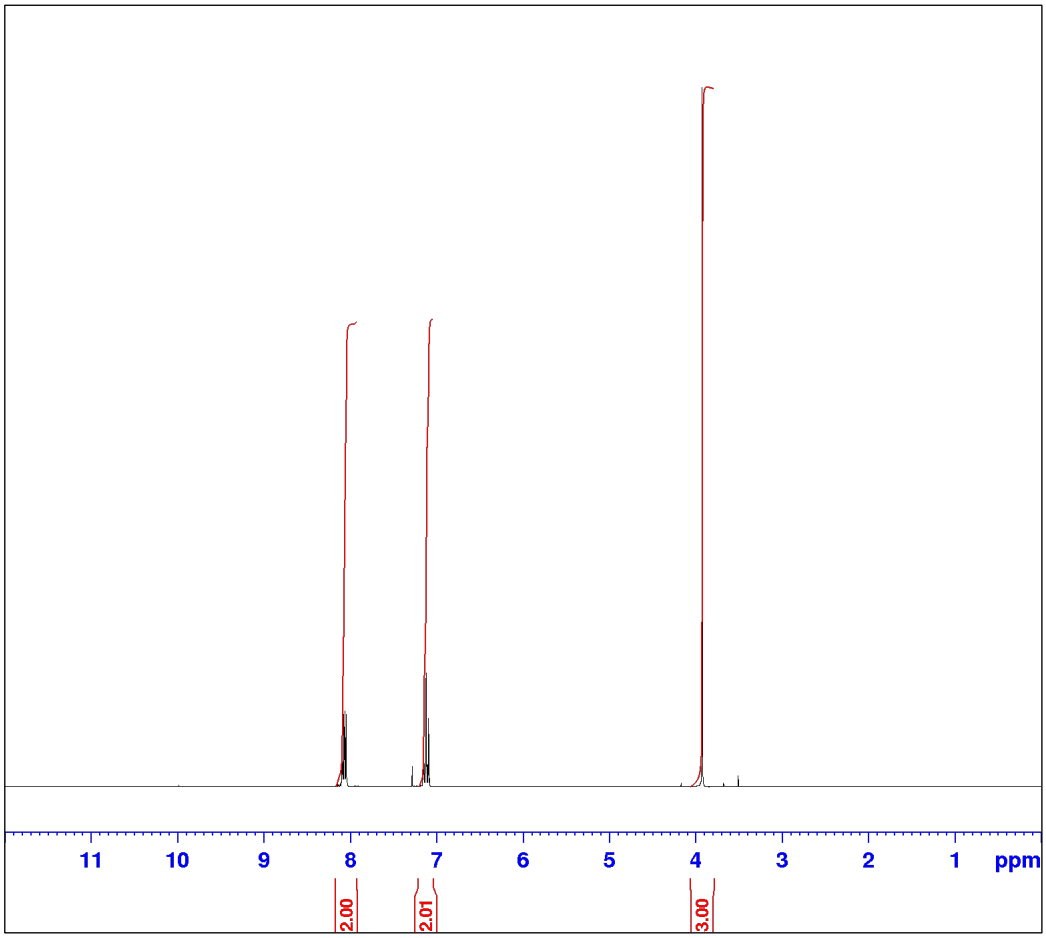


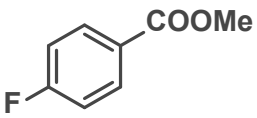


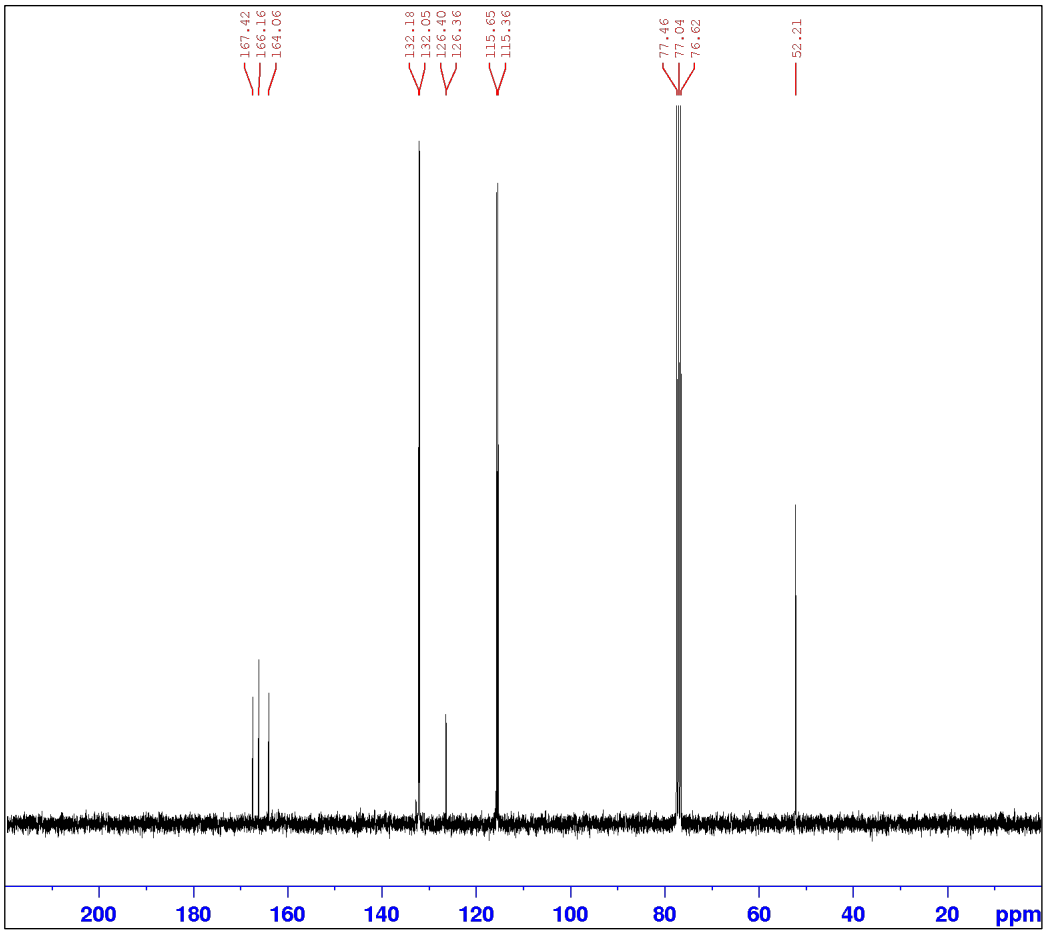


75 MHz, $CDCl_3$

300 MHz, $CDCl_3$

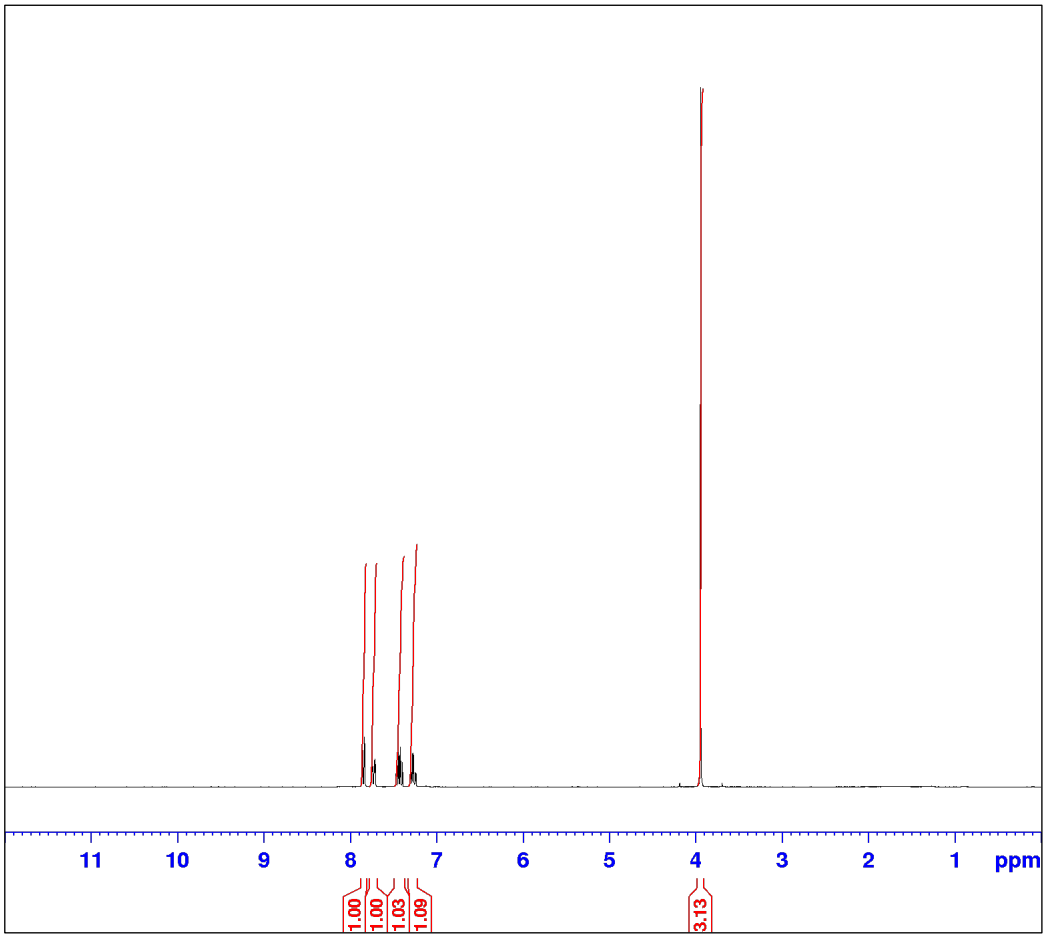


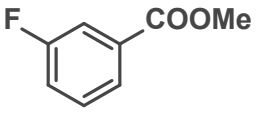


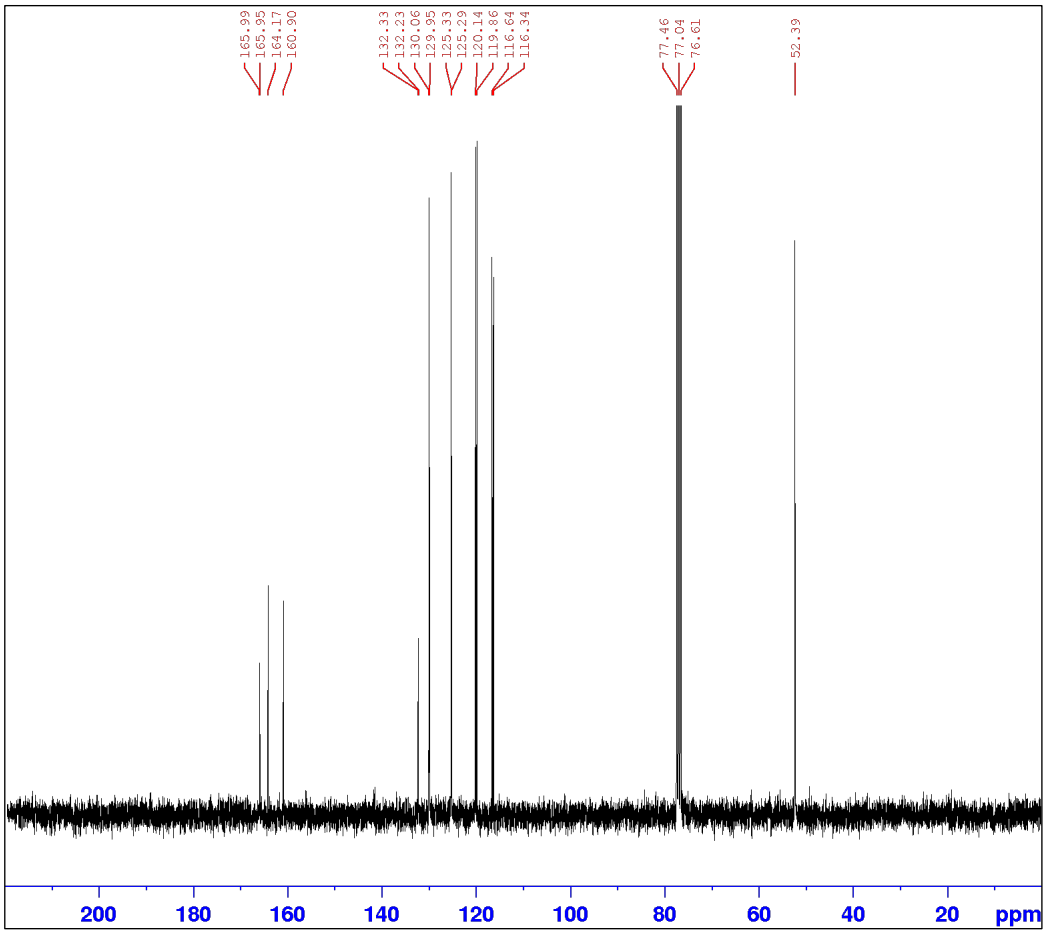


75 MHz, $CDCl_3$

300 MHz, $CDCl_3$

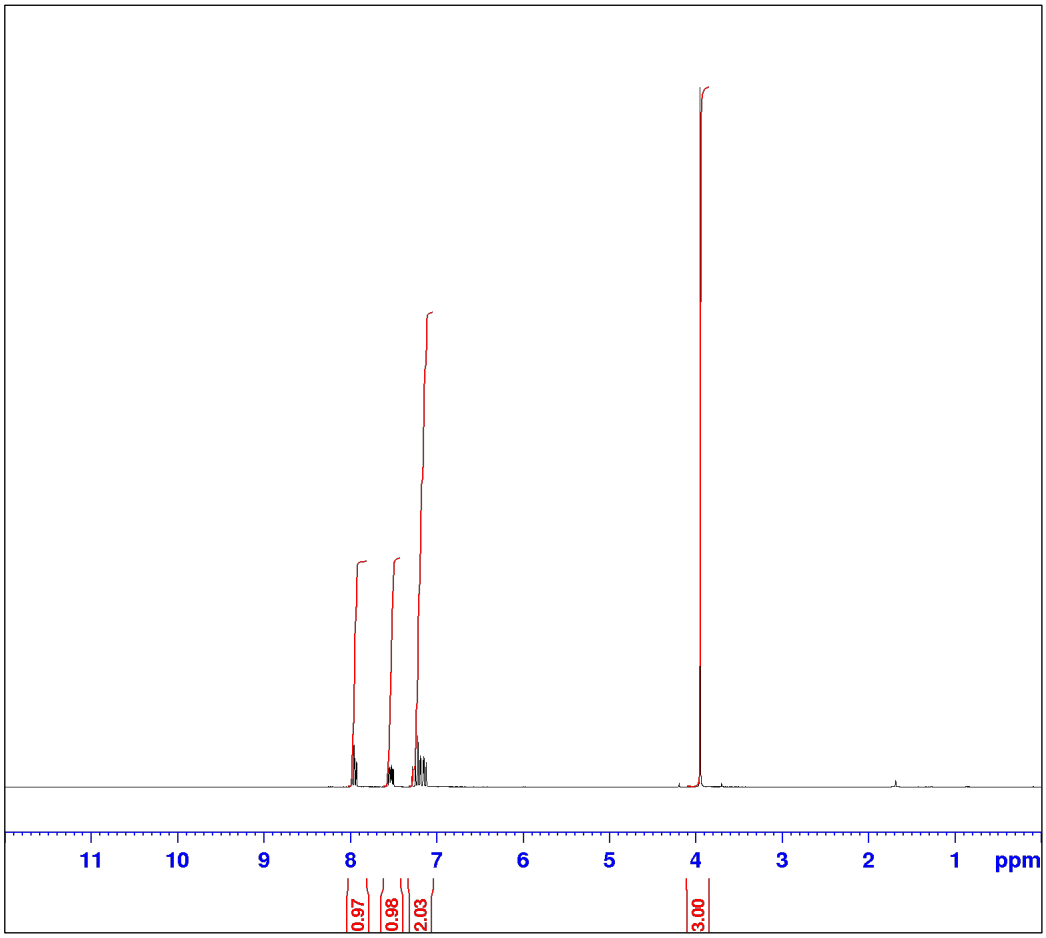


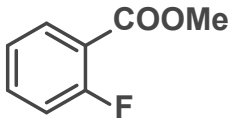


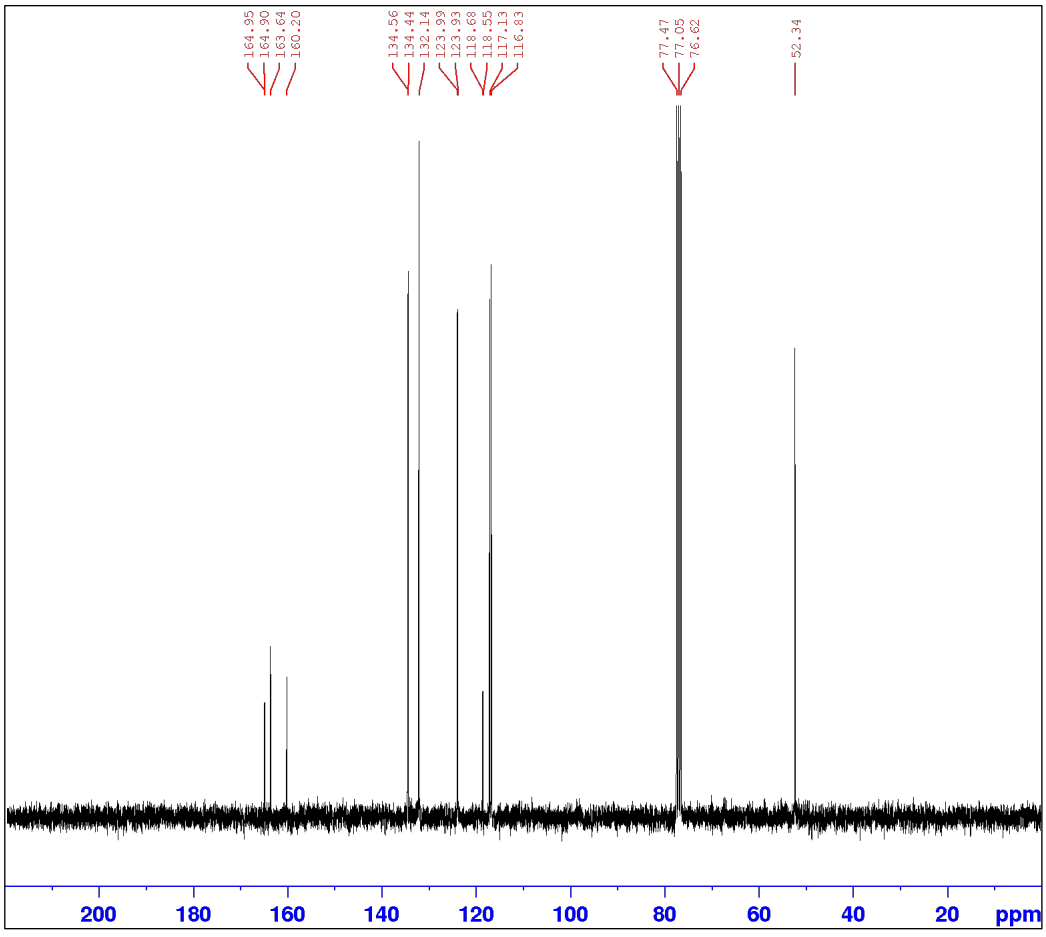


75 MHz, $CDCl_3$

300 MHz, $CDCl_3$

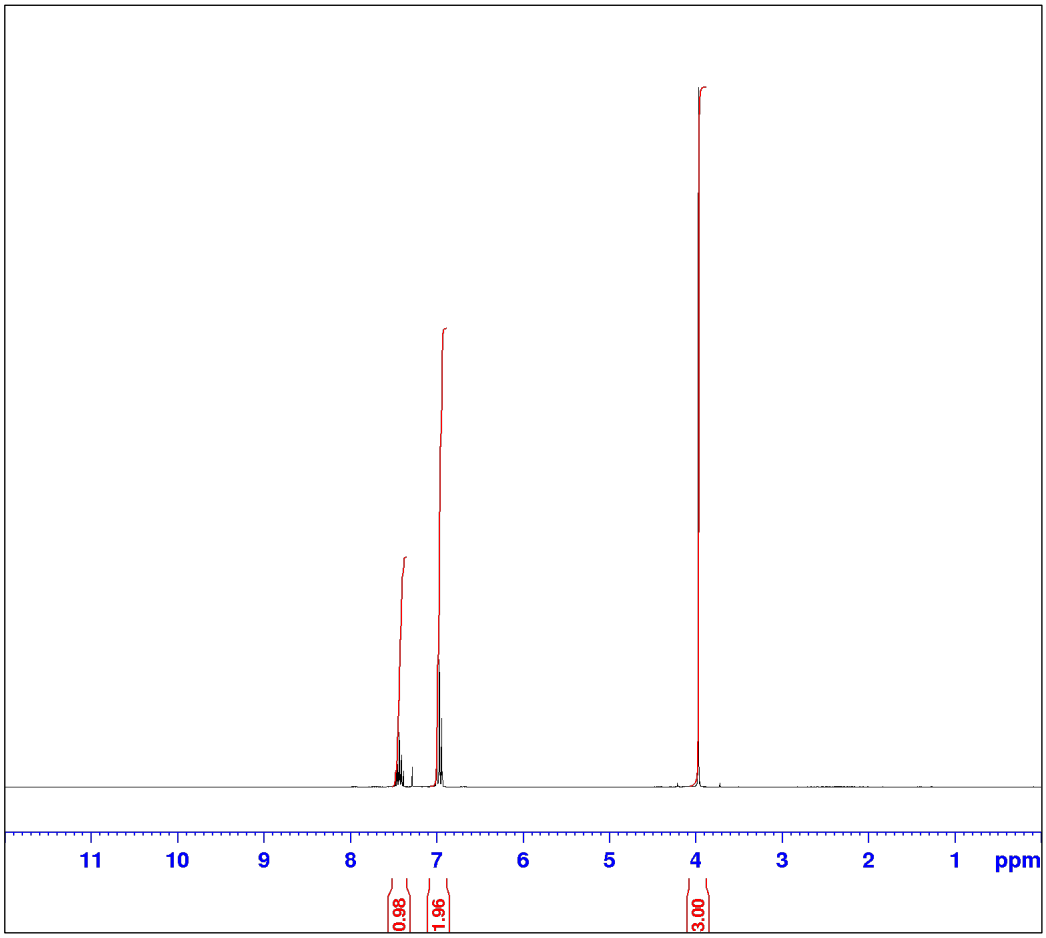


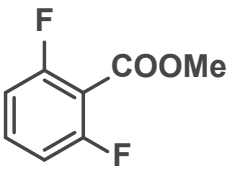


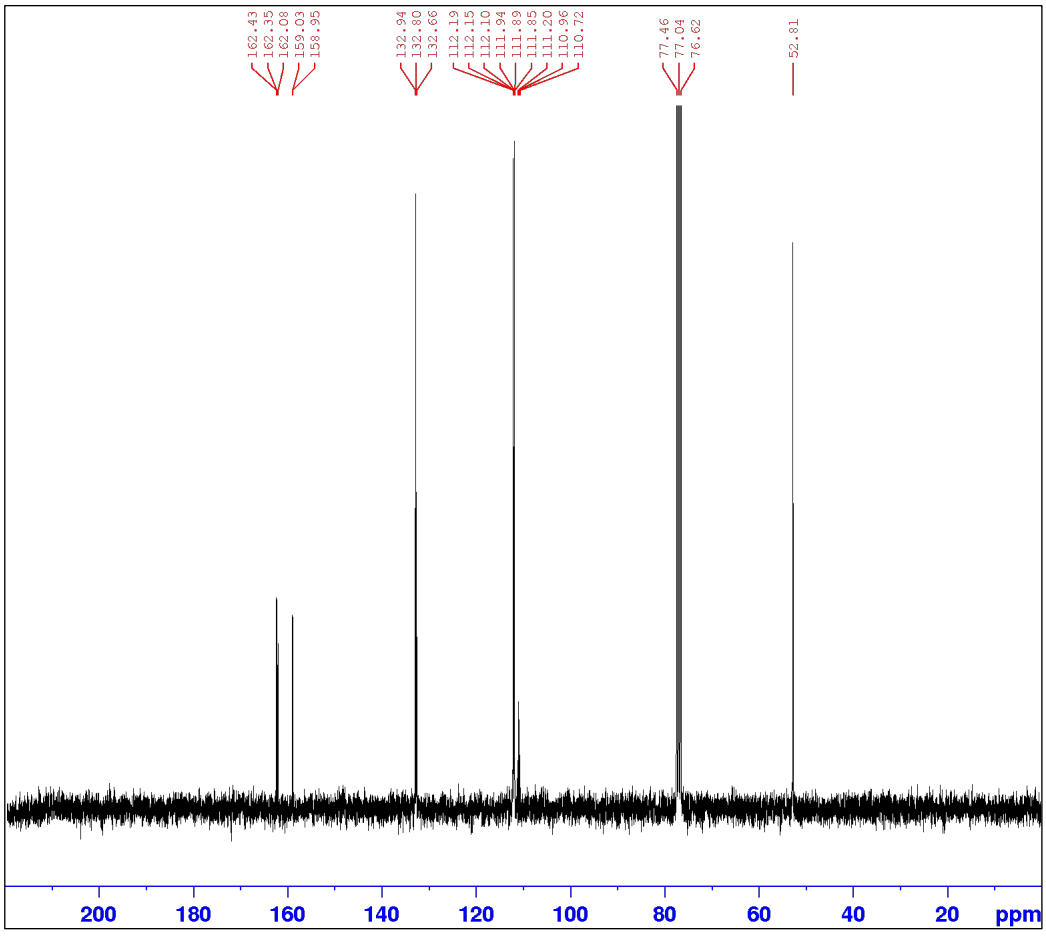


75 MHz, $CDCl_3$

300 MHz, $CDCl_3$

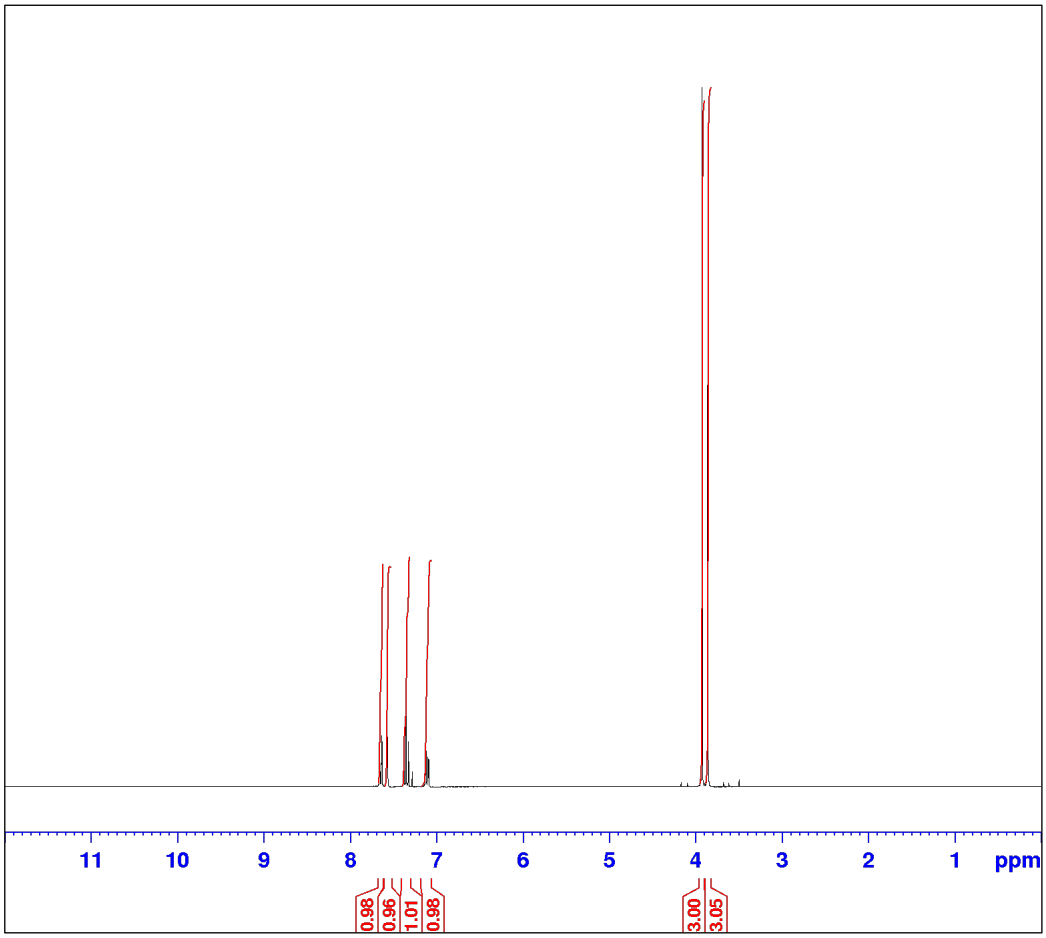


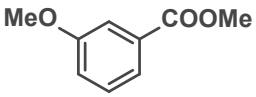


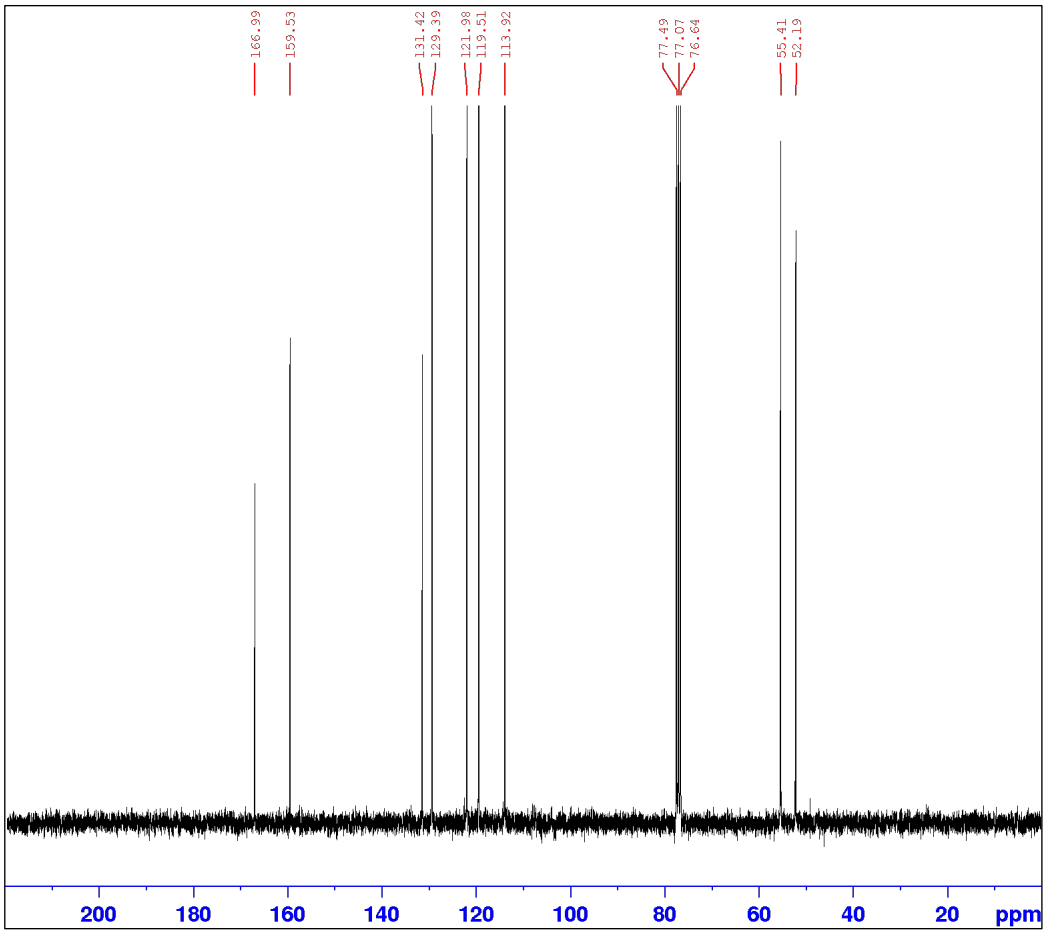


75 MHz, $CDCl_3$

300 MHz, $CDCl_3$

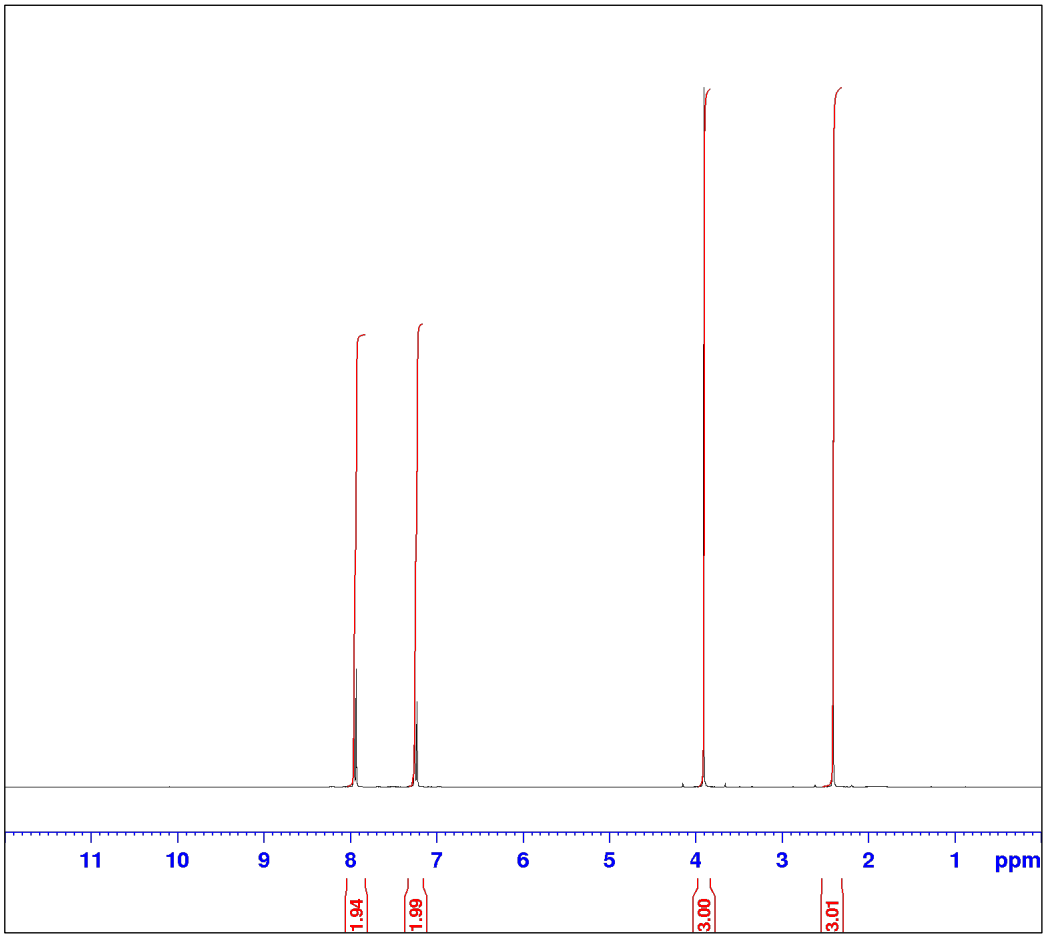


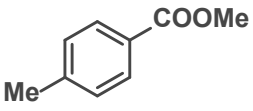


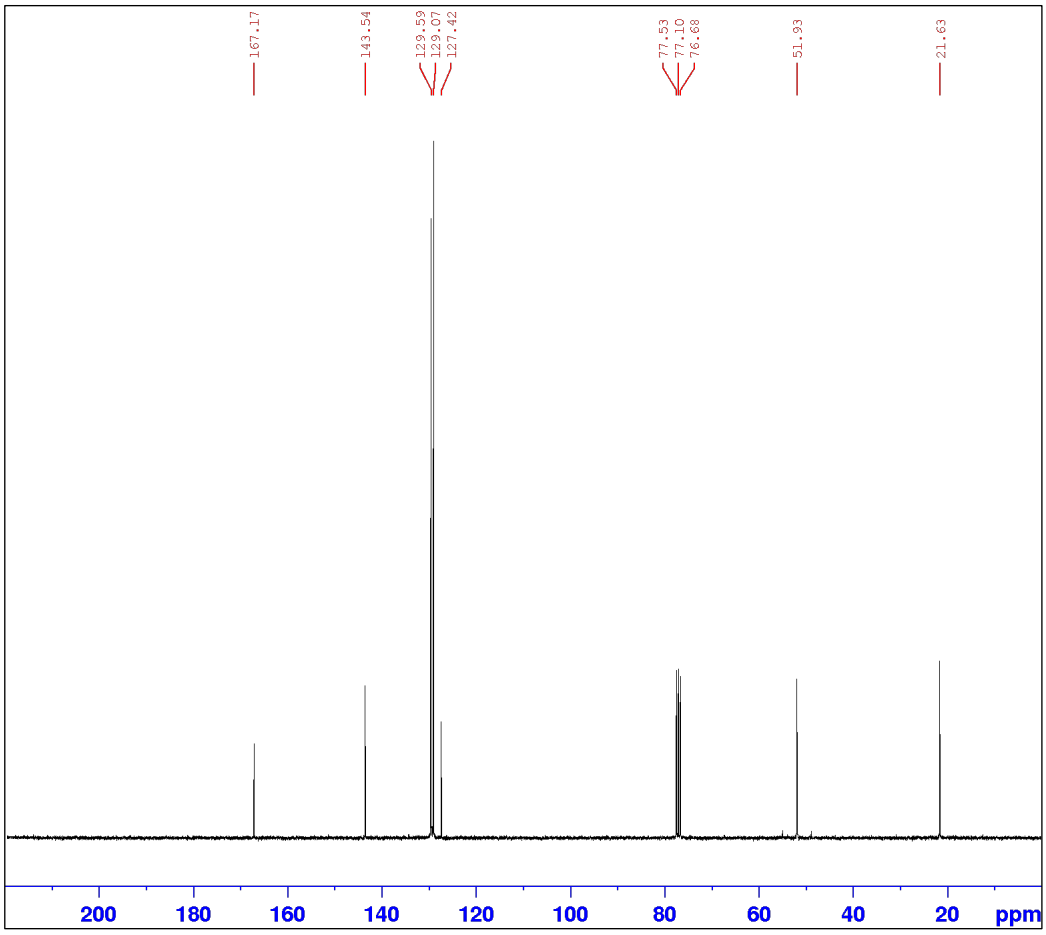


75 MHz, $CDCl_3$

300 MHz, $CDCl_3$

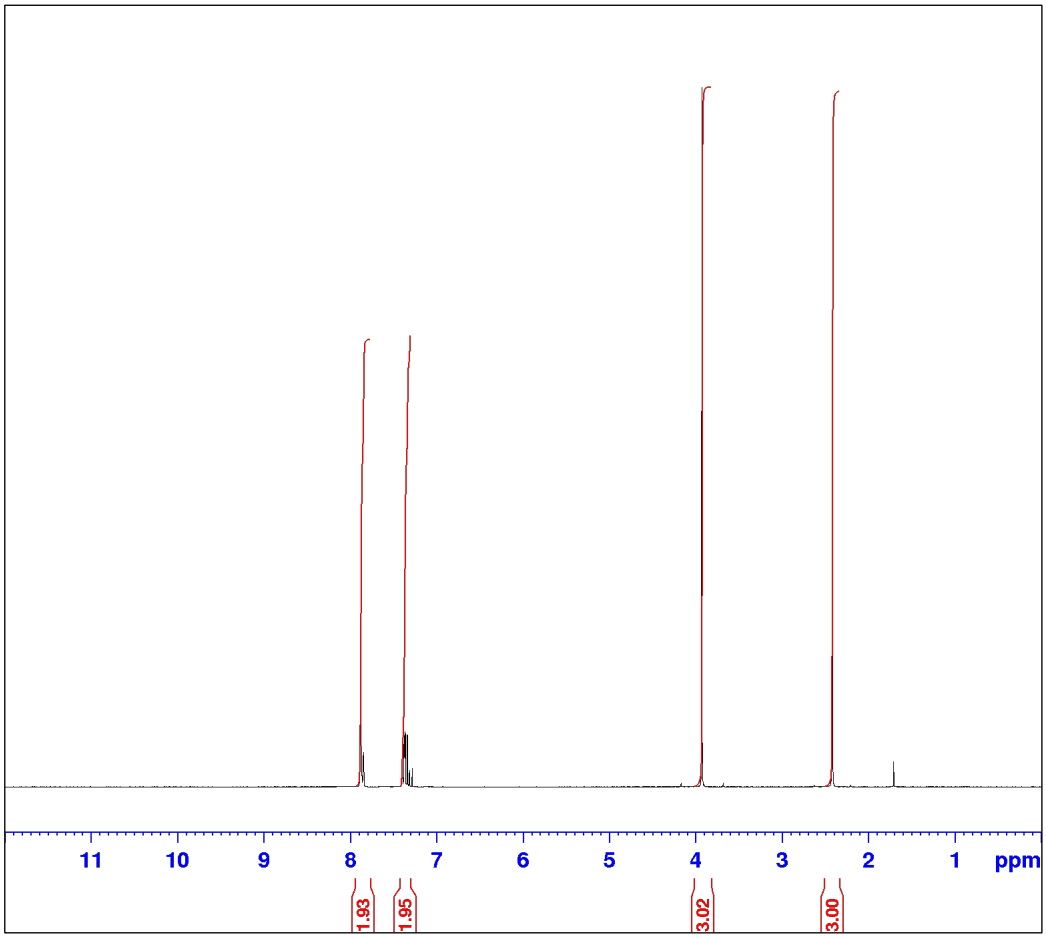


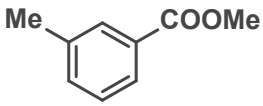


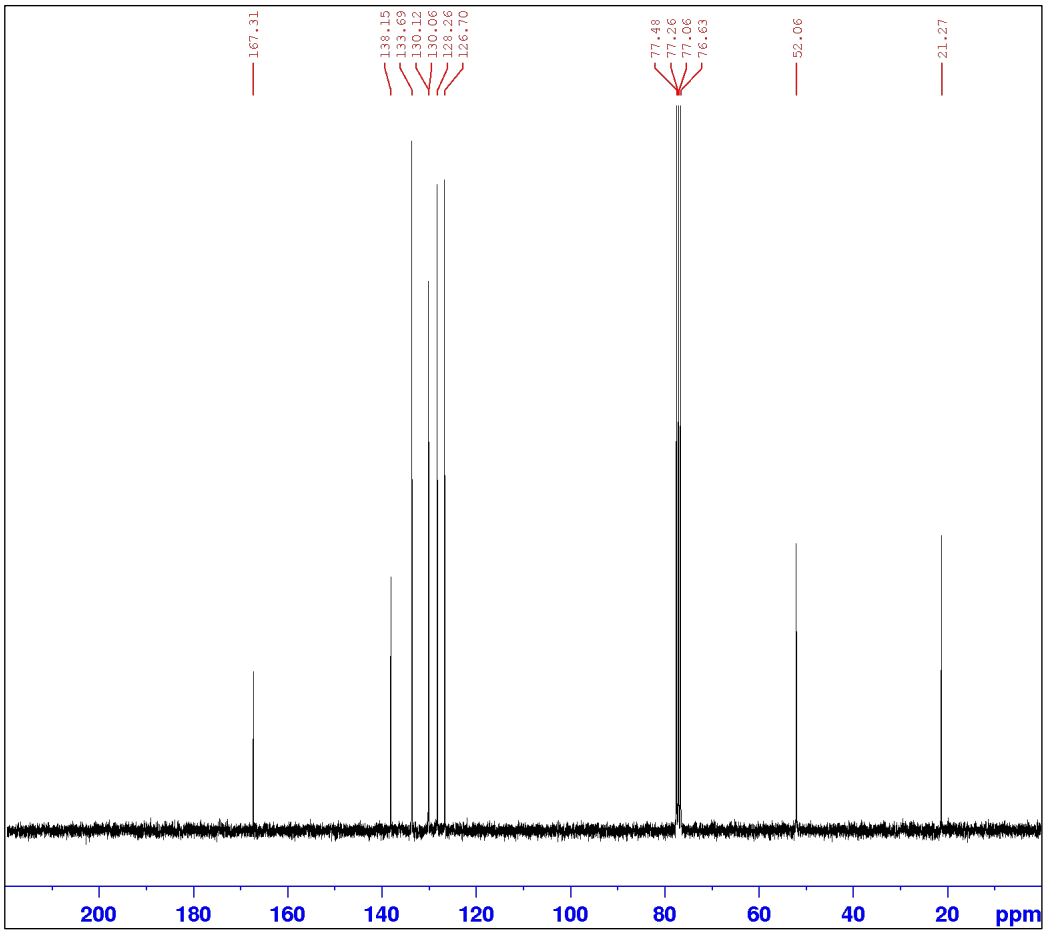


75 MHz, $CDCl_3$

300 MHz, $CDCl_3$

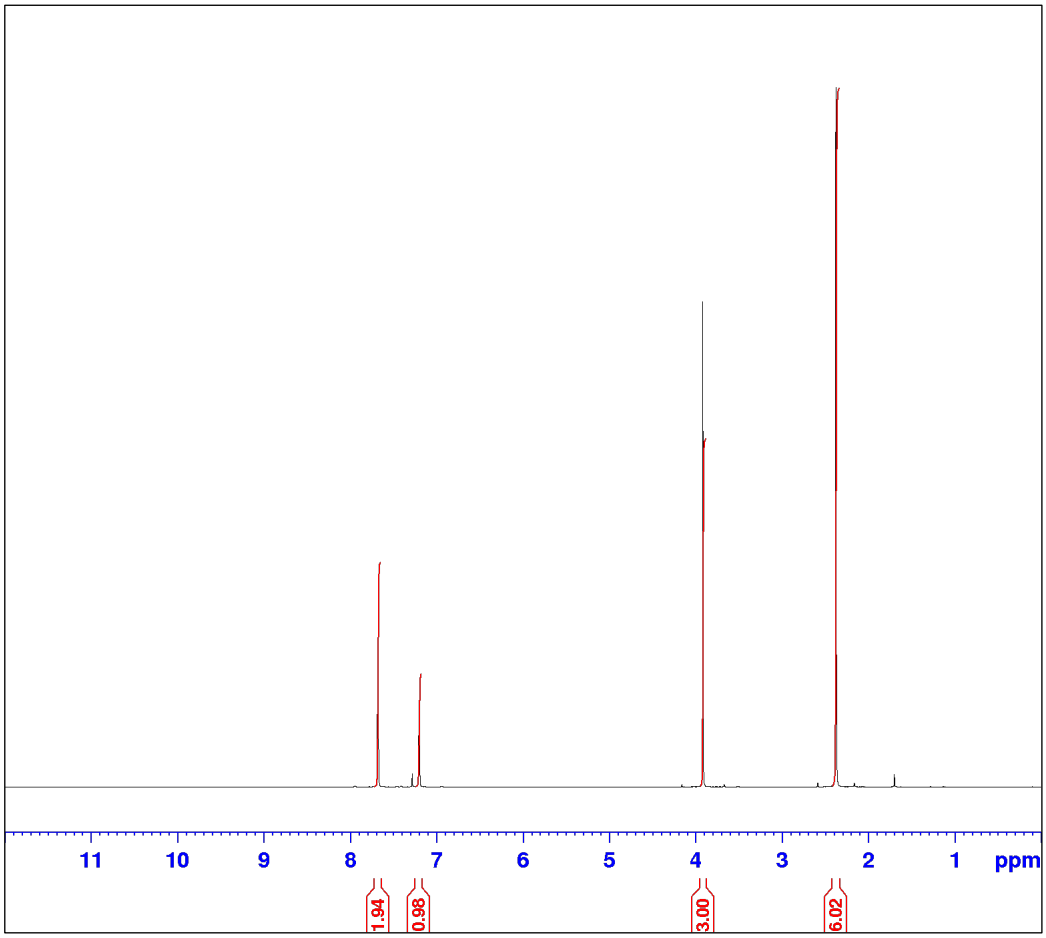


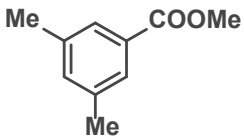


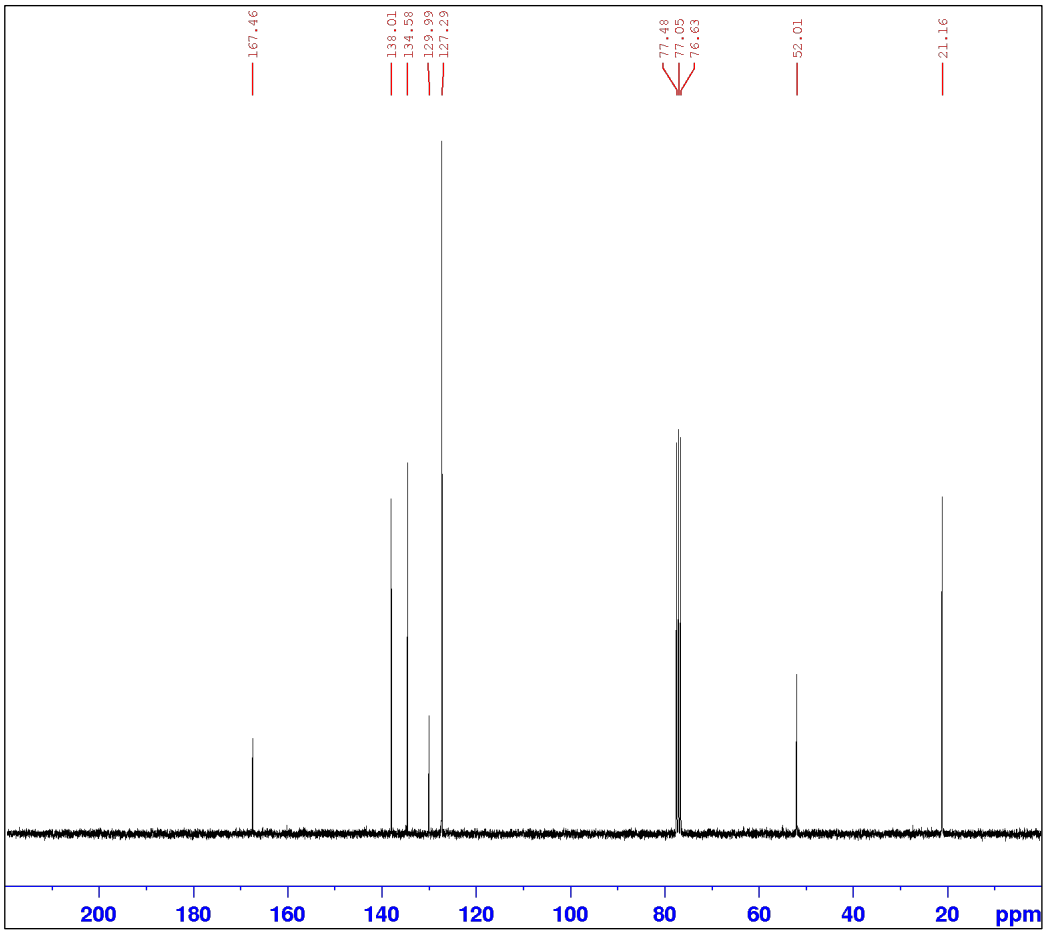


75 MHz, $CDCl_3$

300 MHz, $CDCl_3$

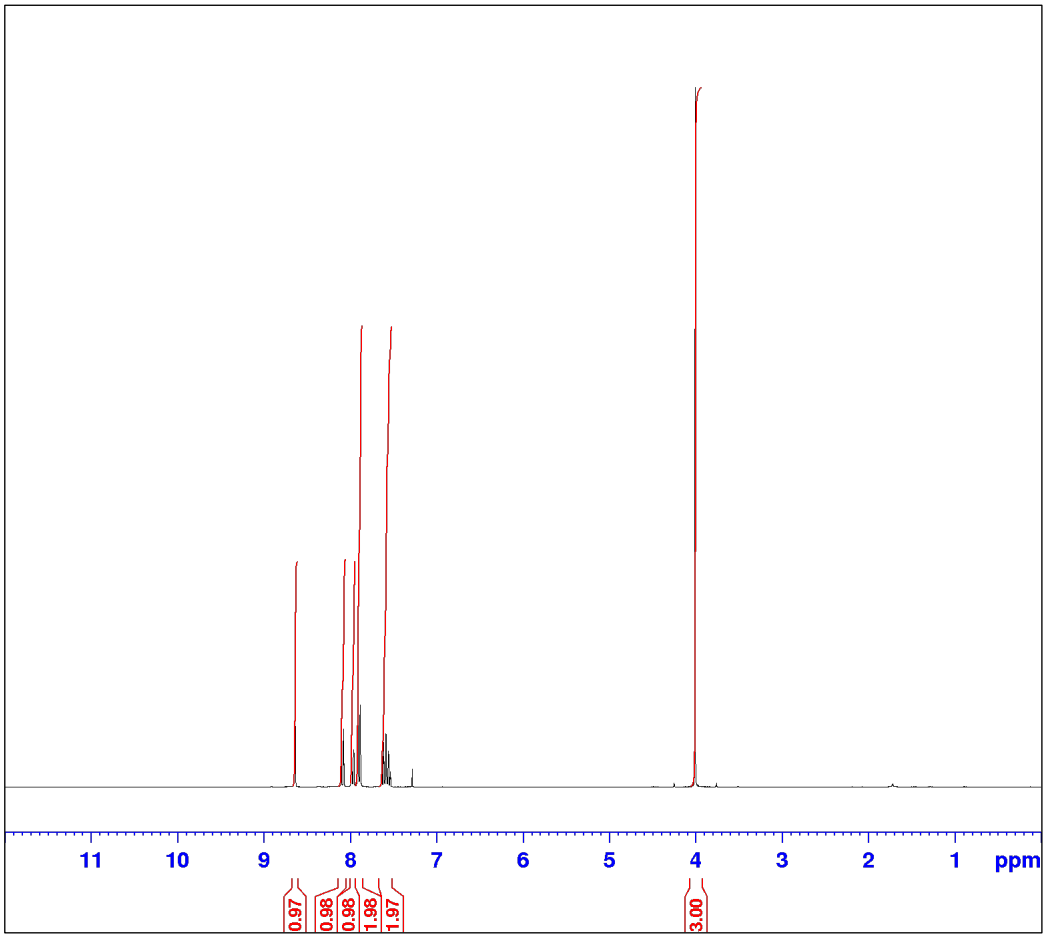


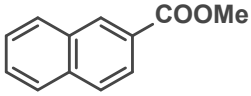


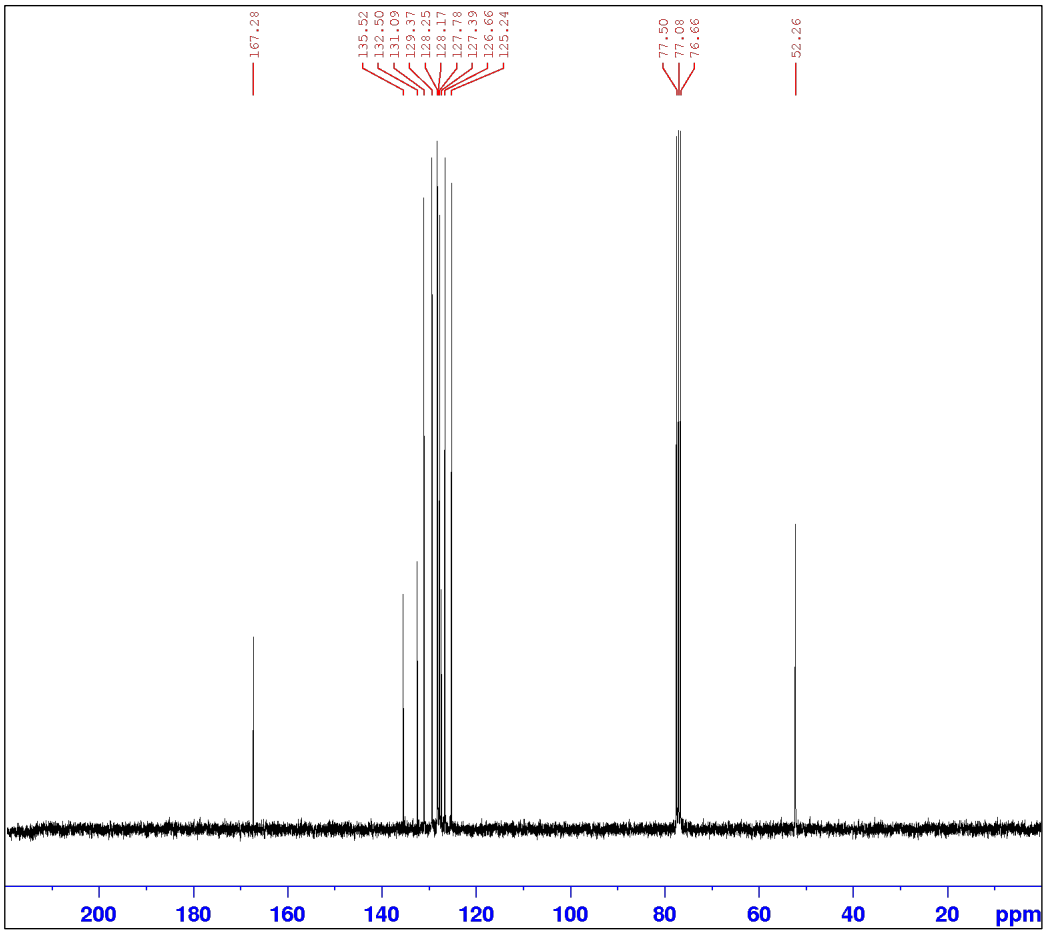


75 MHz, $CDCl_3$

300 MHz, $CDCl_3$

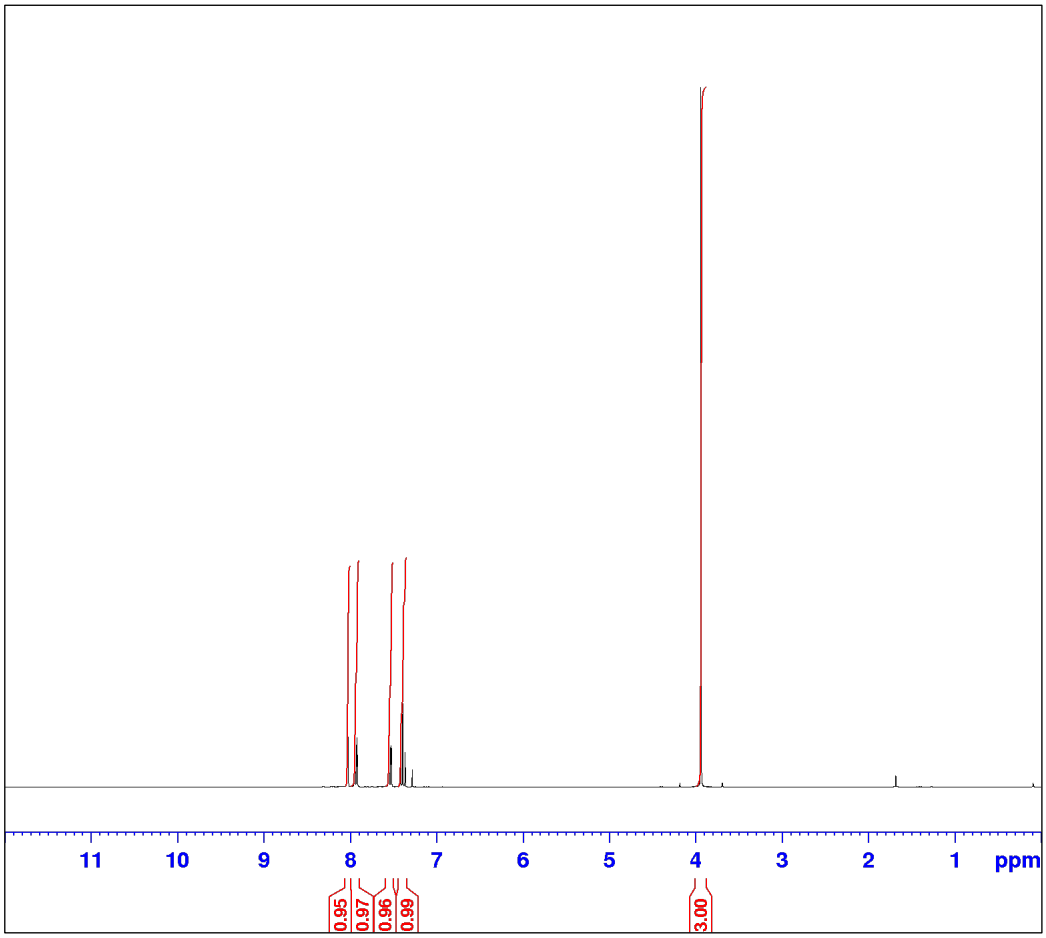


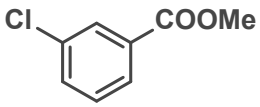


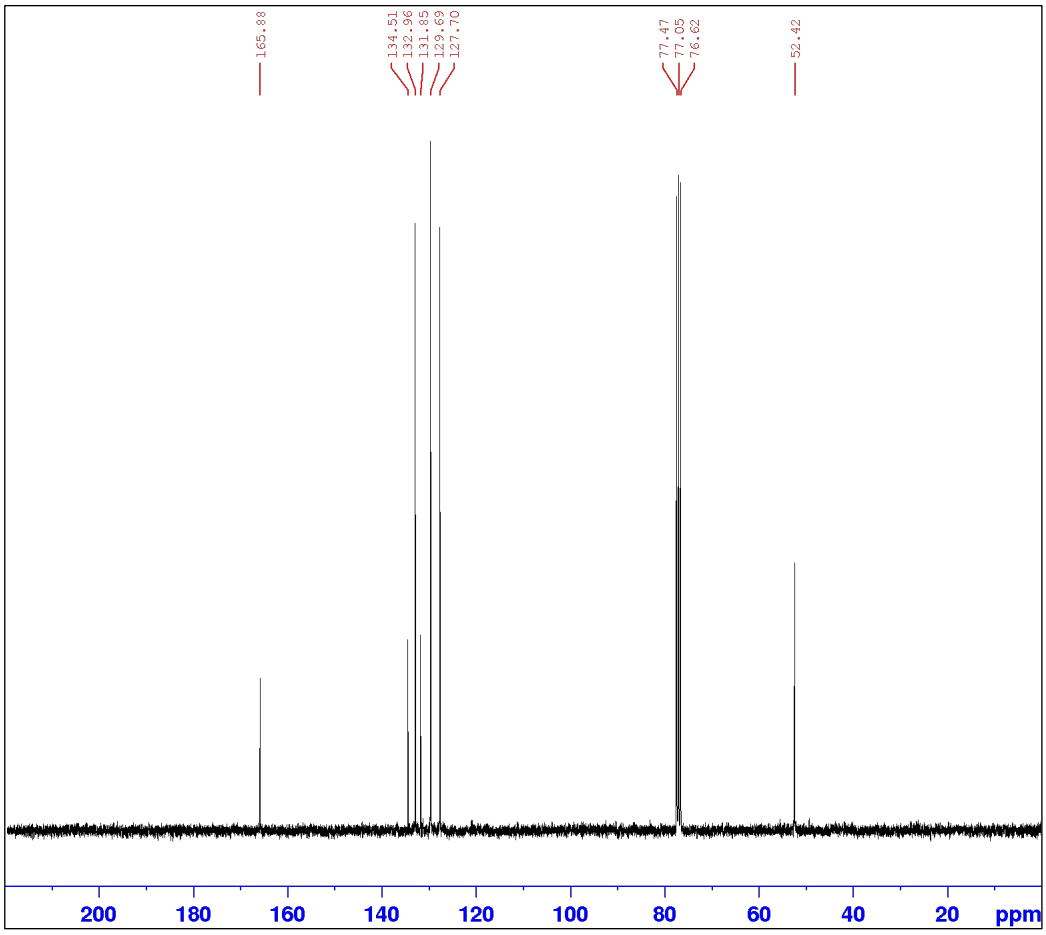


75 MHz, $CDCl_3$

300 MHz, $CDCl_3$

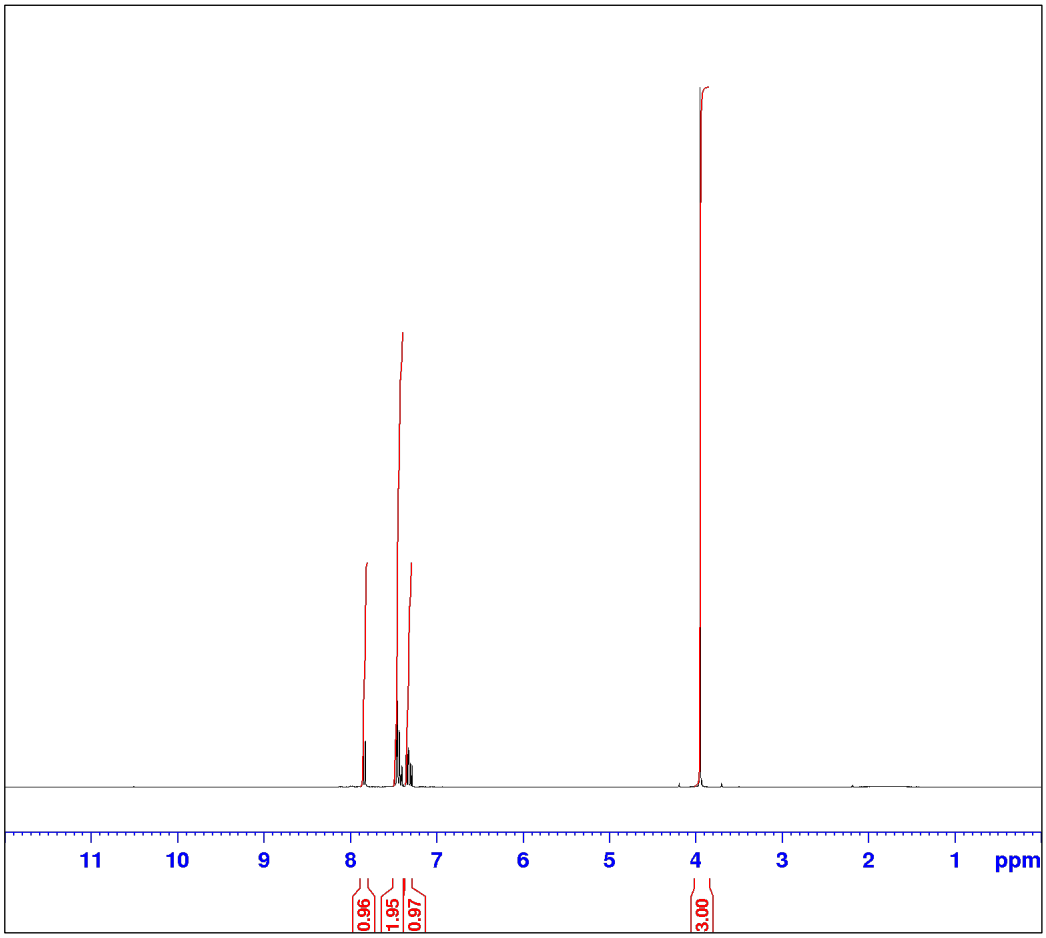


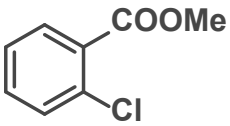


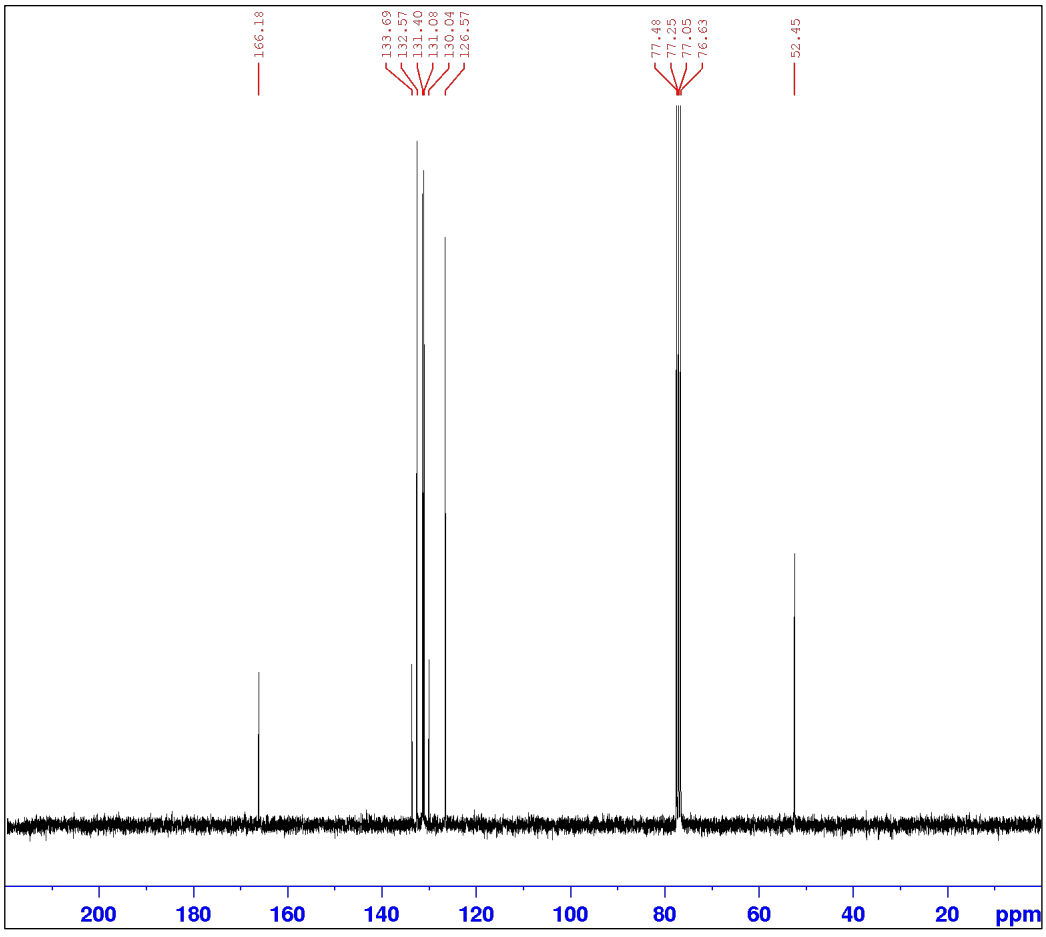


75 MHz, $CDCl_3$

300 MHz, $CDCl_3$

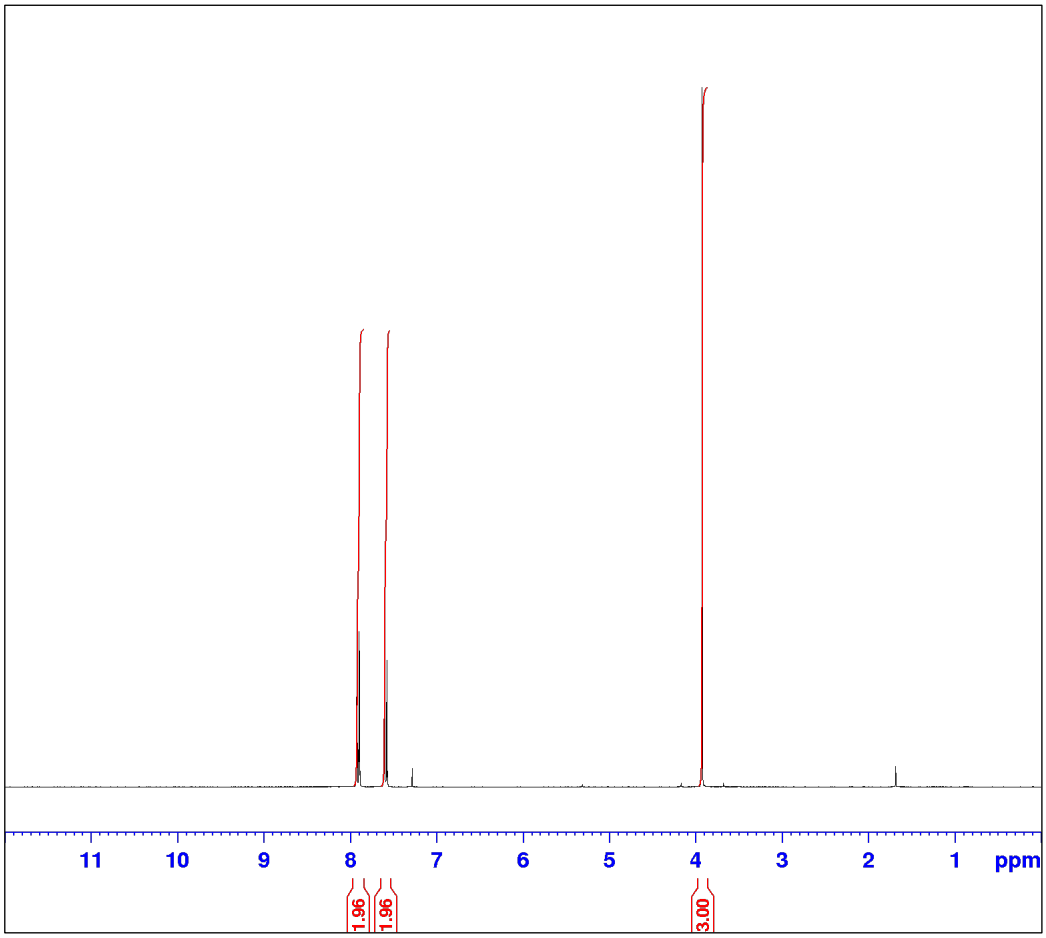


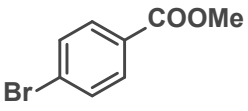


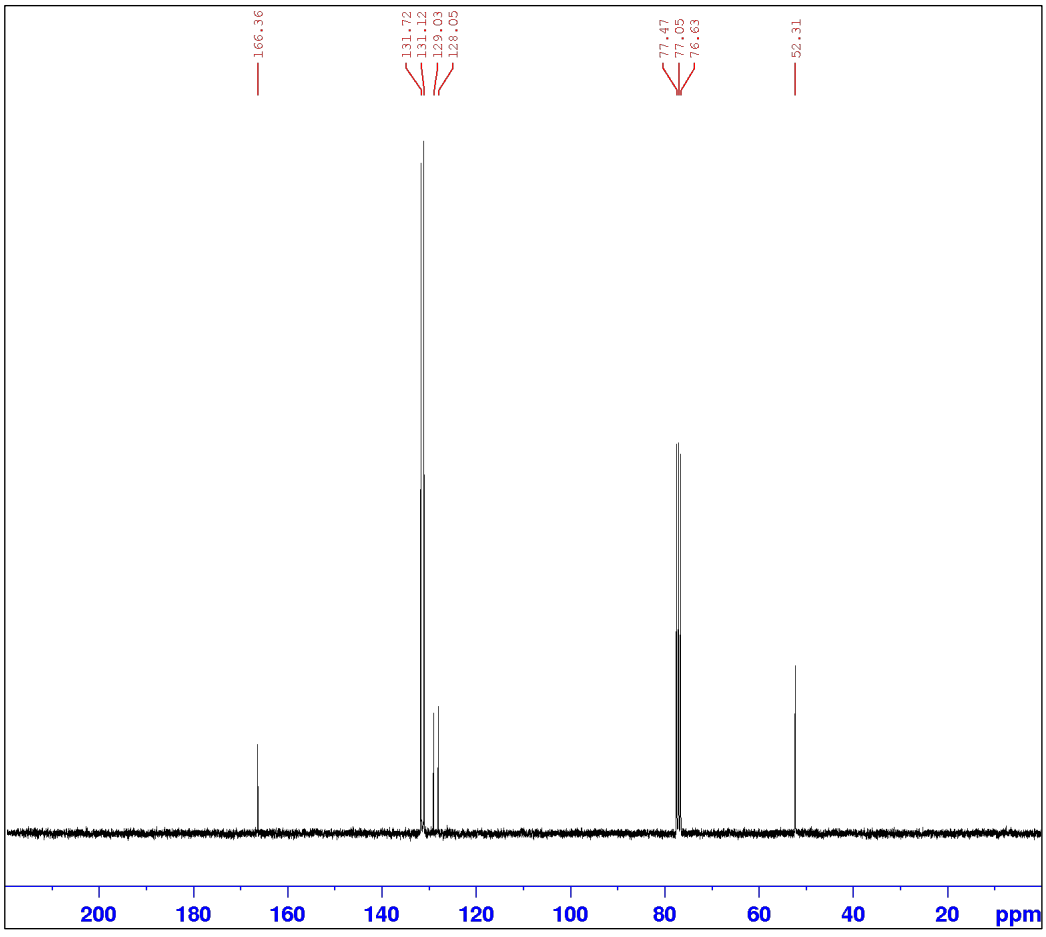


75 MHz, $CDCl_3$

300 MHz, $CDCl_3$







75 MHz, $CDCl_3$

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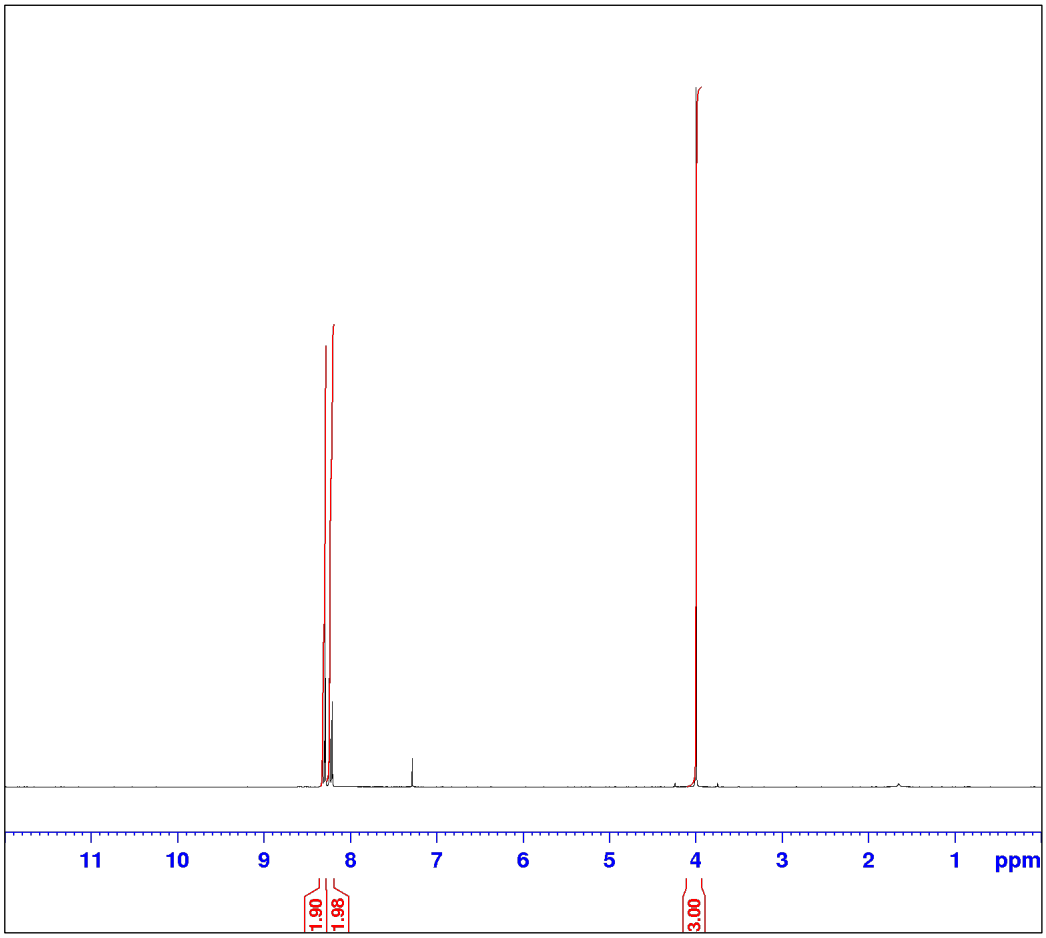

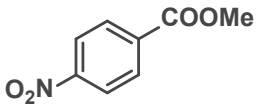

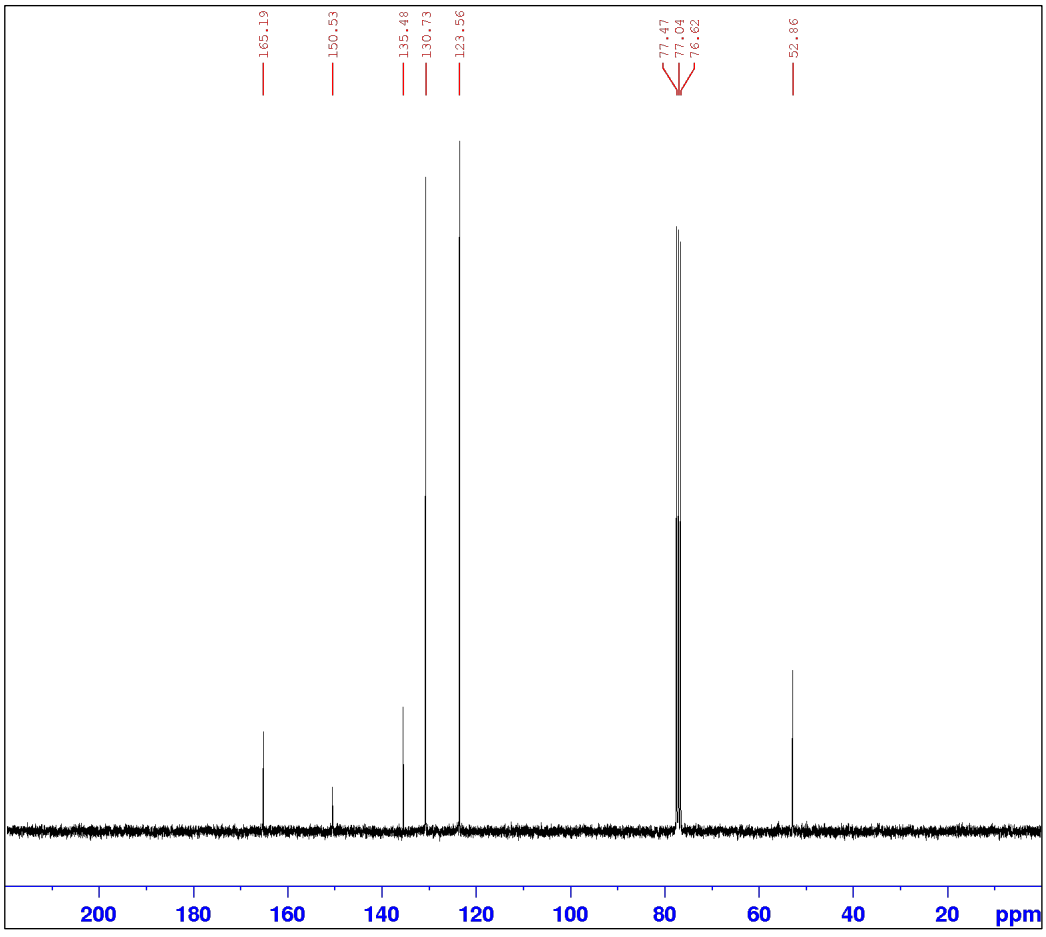

75 MHz, $CDCl_3$

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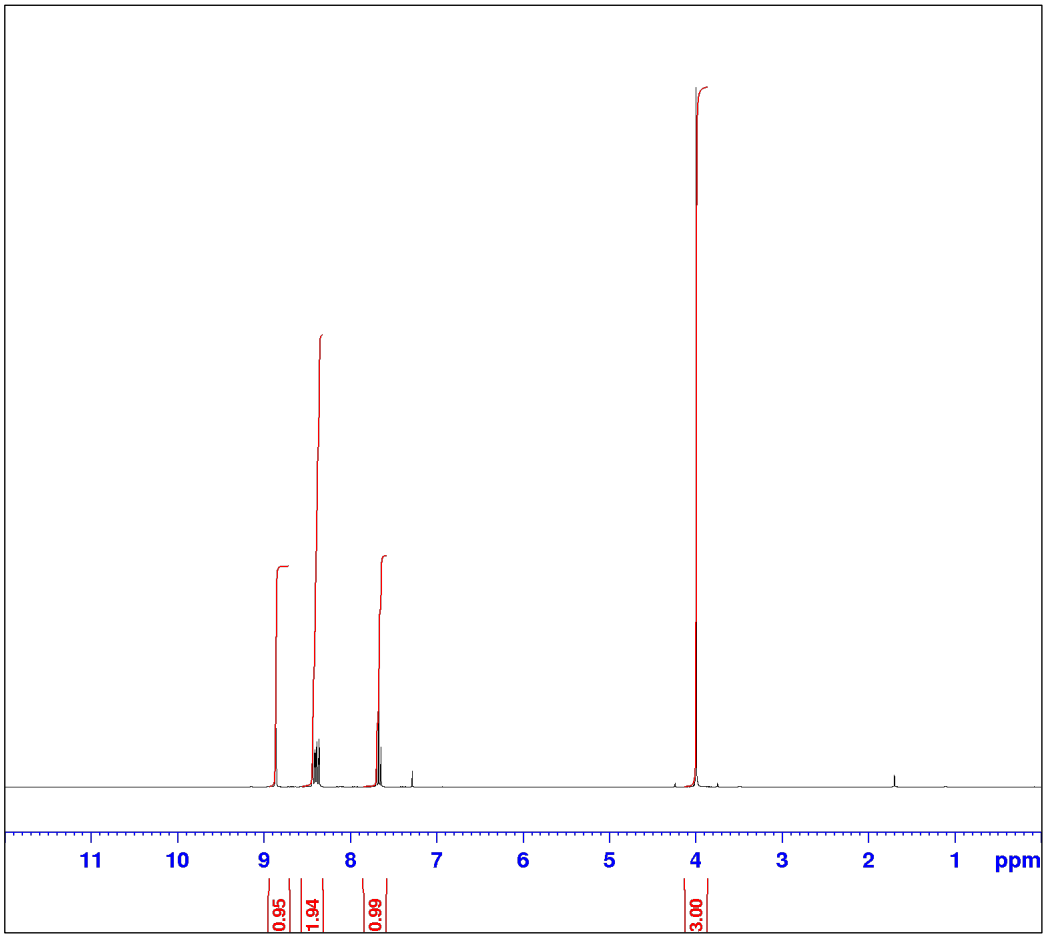

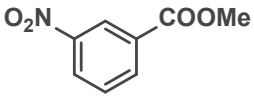

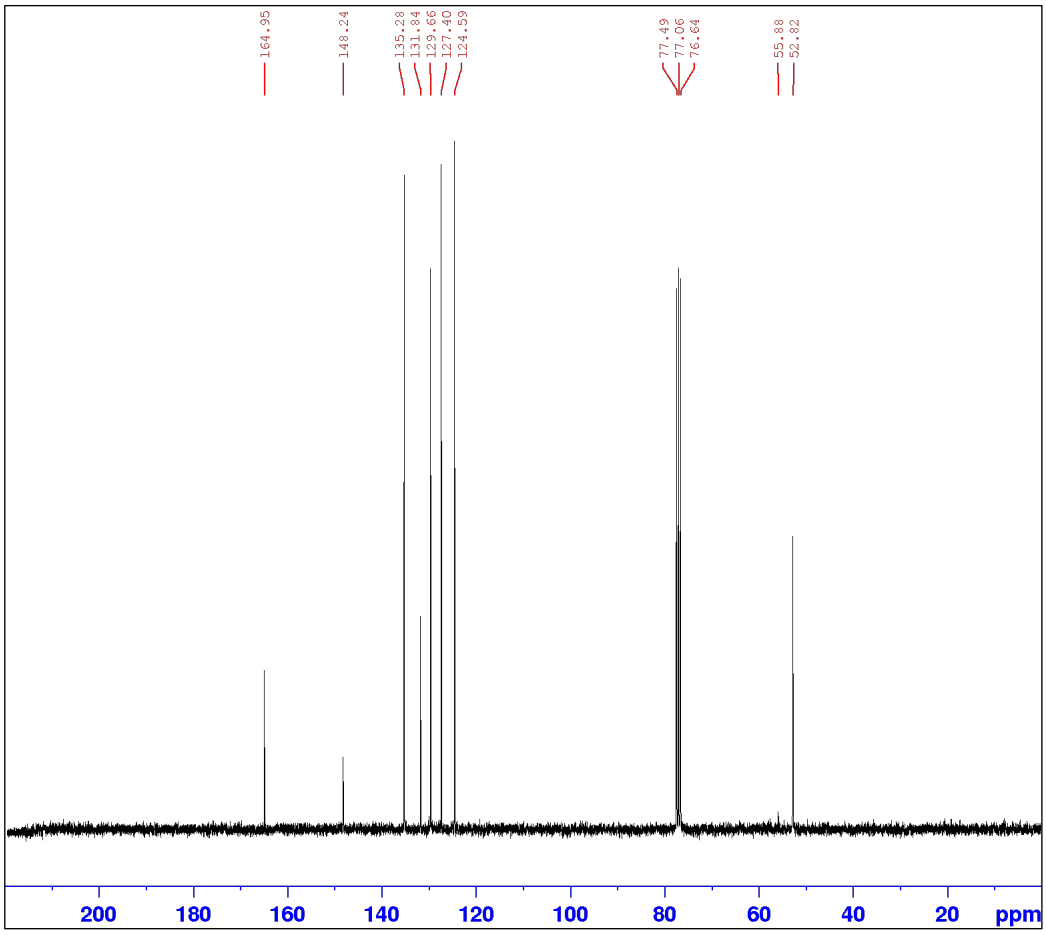

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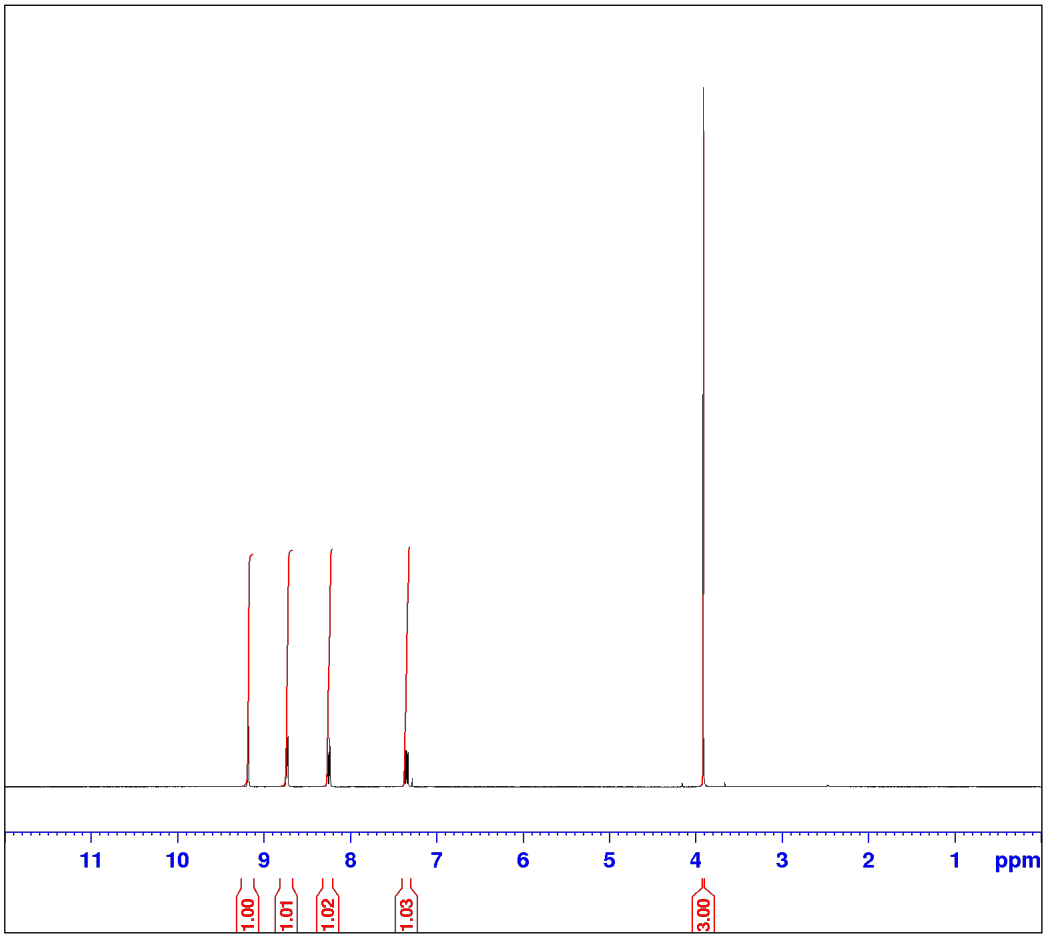

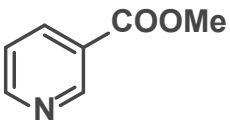

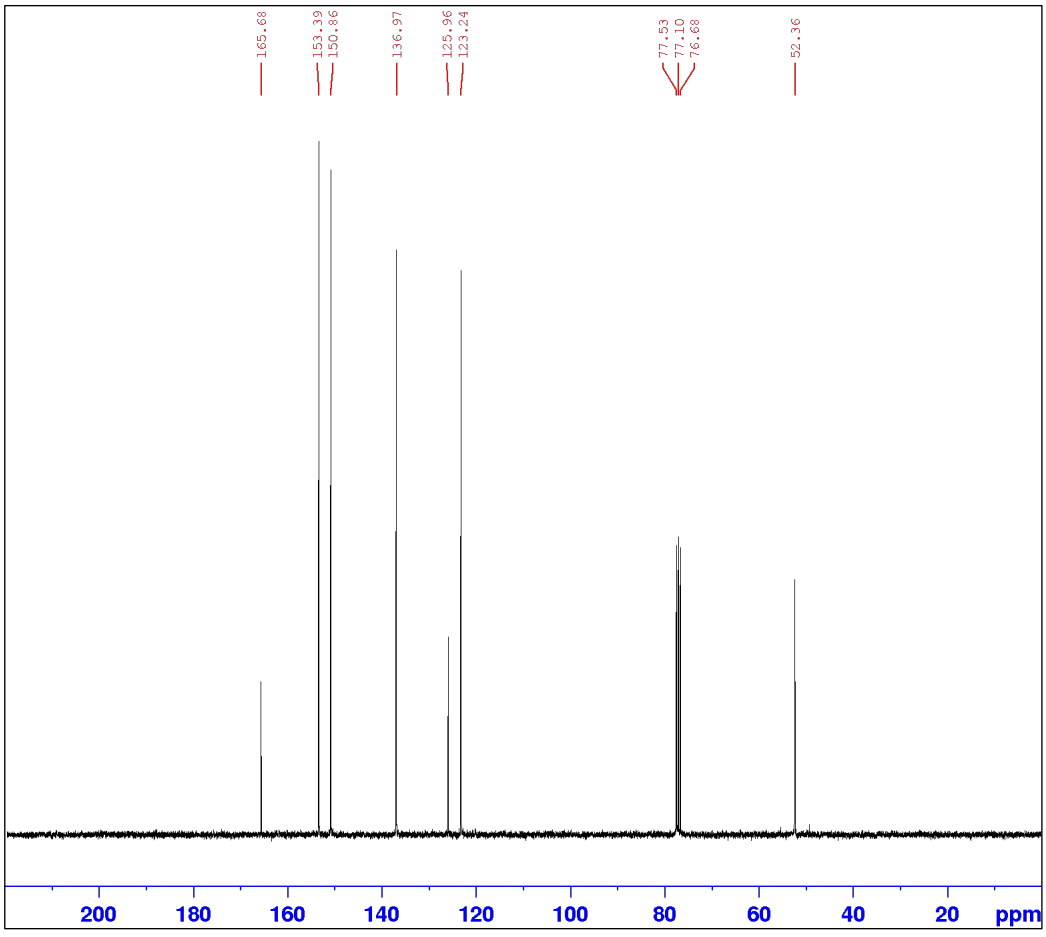

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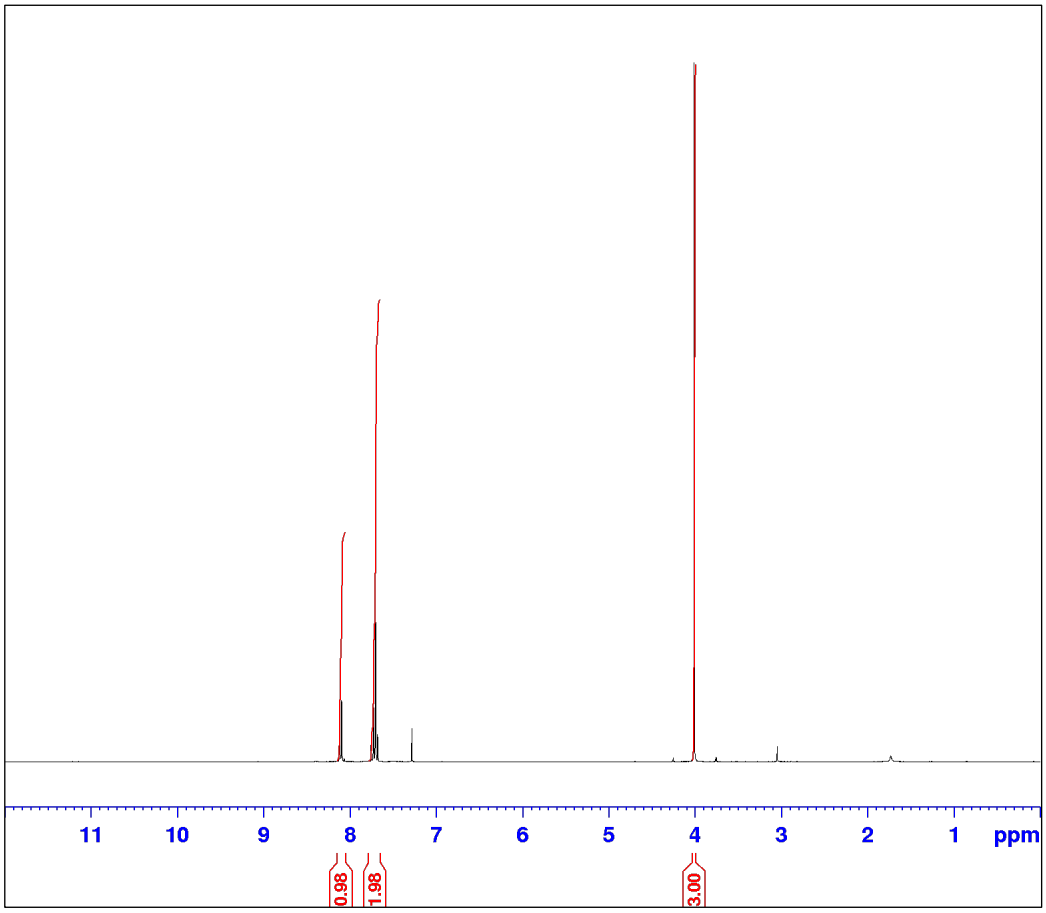

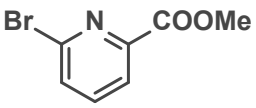

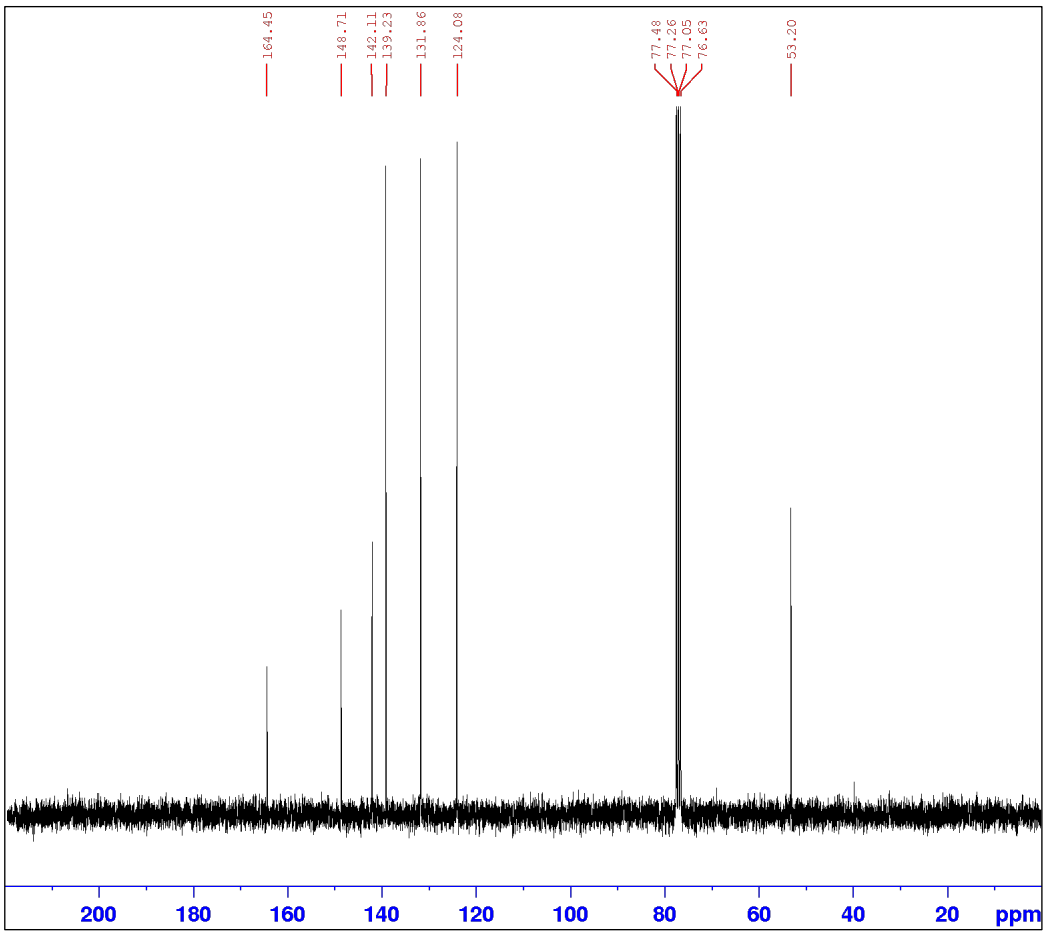

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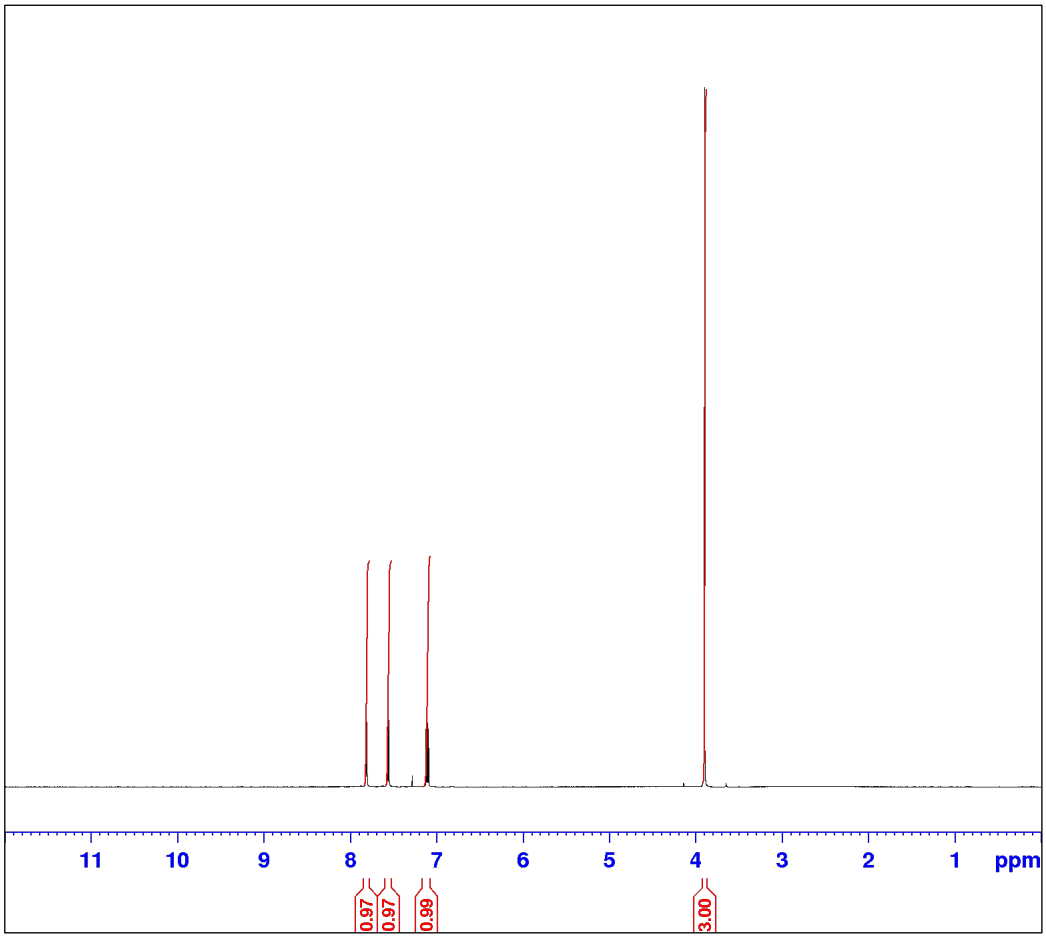
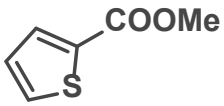
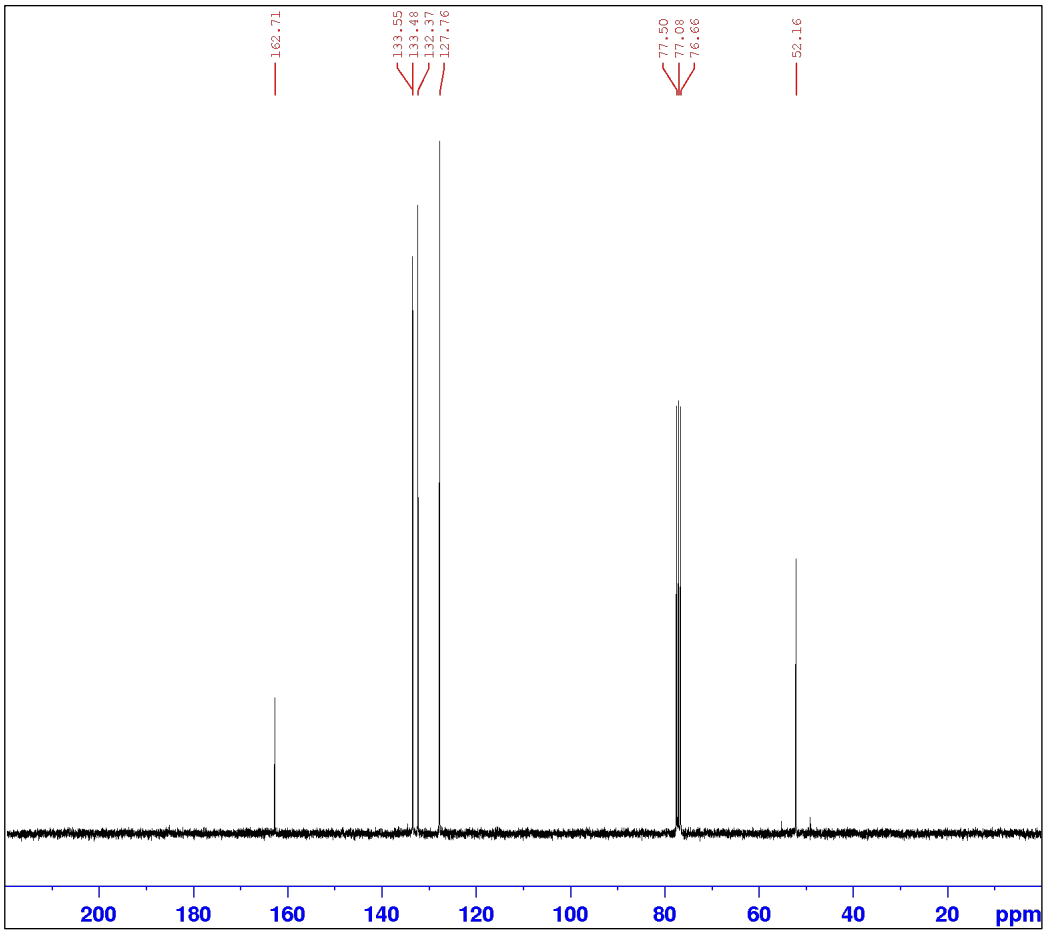
300 MHz, $CDCl_3$

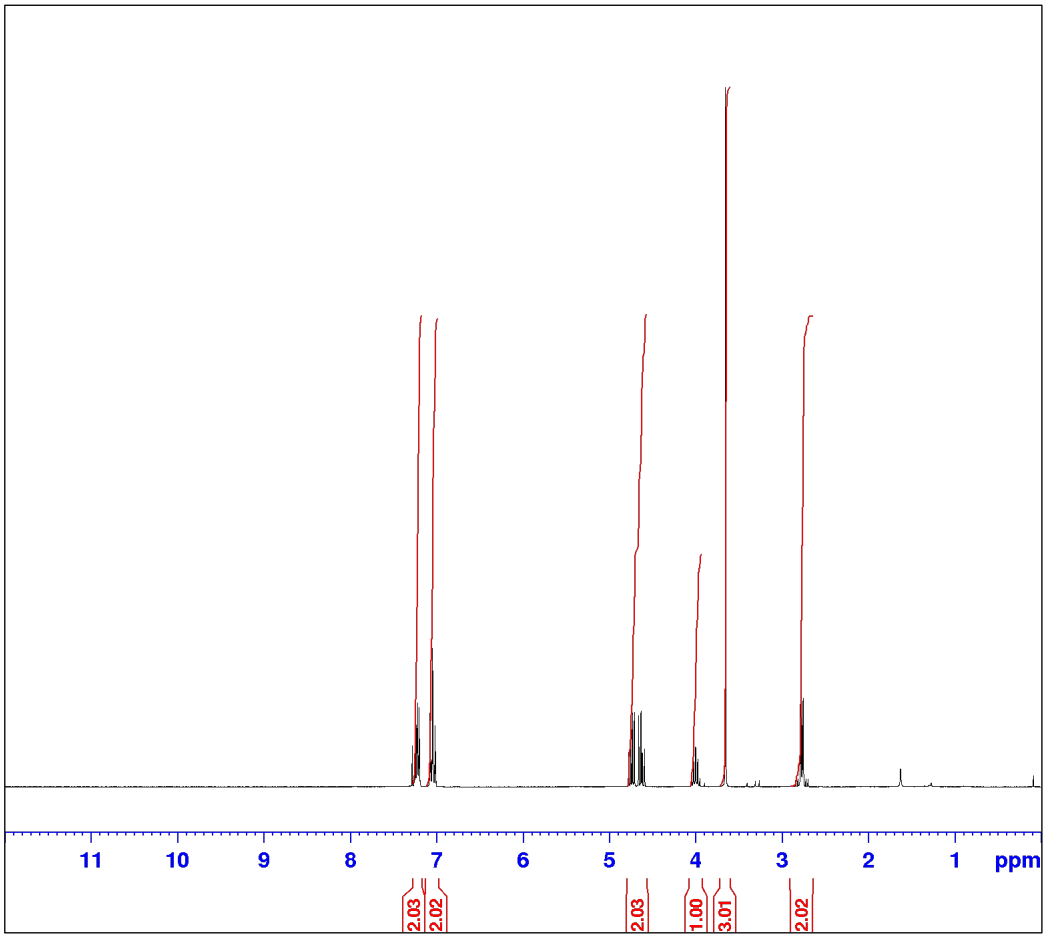


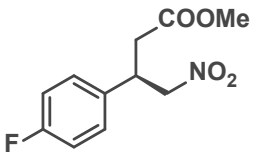


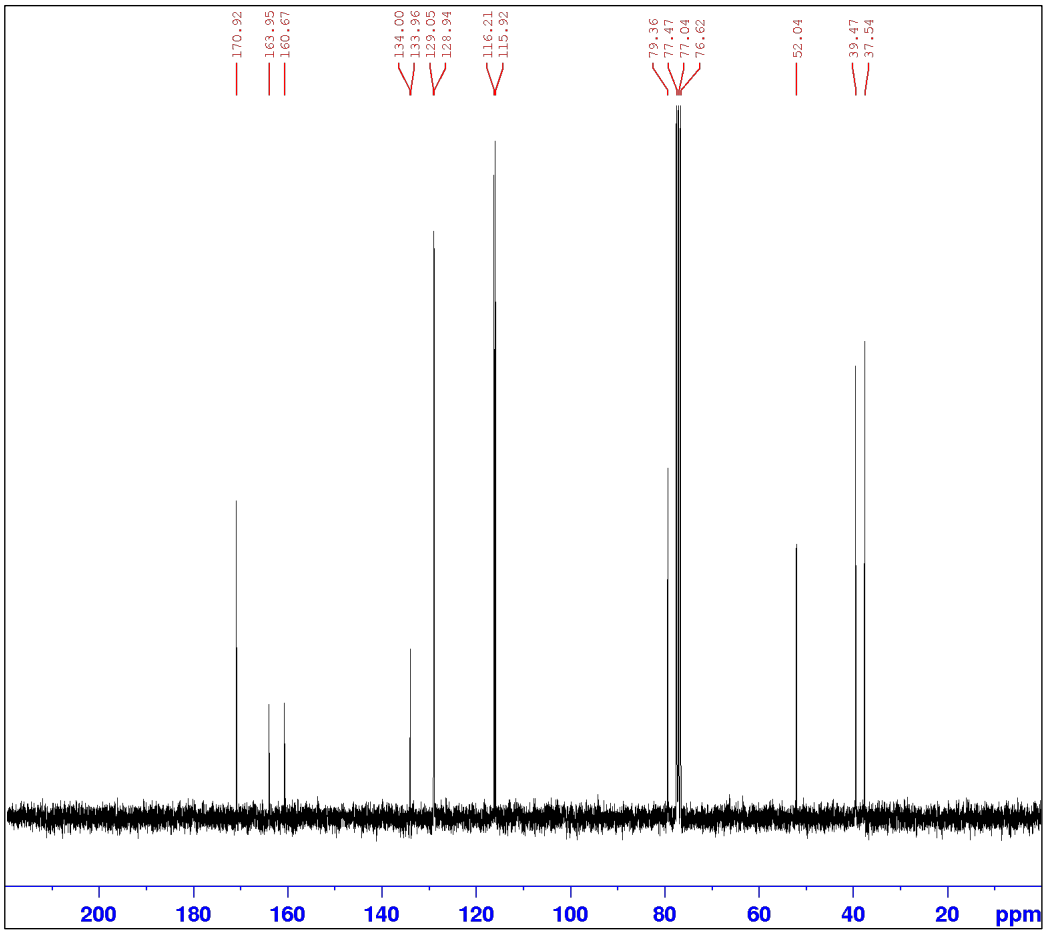


75 MHz, $CDCl_3$

300 MHz, $CDCl_3$







75 MHz, $CDCl_3$

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