Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Light-accelerated "On-Water" Hydroacylation of Dialkyl Azodicarboxylates

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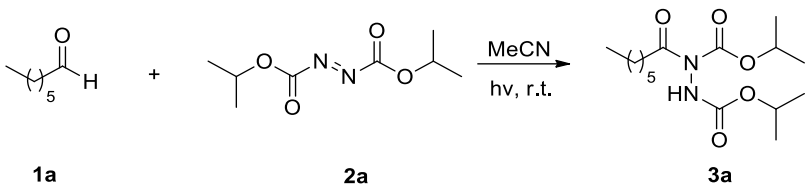
SUPPORTING INFORMATION

General Remarks

Chromatographic purification of products was accomplished using forced-flow chromatography on Merck® Kieselgel 60 F_{254} 230-400 mesh. Thin-layer chromatography (TLC) was performed on aluminum backed silica plates (0.2 mm, 60 F_{254}). Visualization of the developed chromatogram was performed by fluorescence quenching using phosphomolybdic acid, anisaldehyde or potassium permanganate stains. Melting points were determined on a Buchi® 530 hot stage apparatus and are uncorrected. Mass spectra (ESI) were recorded on a Finningan® Surveyor MSQ LC-MS spectrometer. HRMS spectra were recorded on Bruker® Maxis Impact QTOF spectrometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on an Avance III HD Brucker (400 MHz and 100 MHz, respectively) and are internally referenced to residual solvent signals. Data for ^{1}H-NMR are reported as follows: chemical shift (δ ppm), integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qu = quintet, hex = hextet, sept = septet, m = multiplet, br s = broad signal), coupling constant and assignment. Data for ^{13}C-NMR are reported in terms of chemical shift (δ ppm). Mass spectra and conversions of the reactions were also recorded on a Shimadzu® GCMS-QP2010 Plus Gas Chromatography Mass Spectrometer utilizing a MEGA® column (MEGA-5, F.T: 0.25 μm, I.D.: 0.25 mm, L: 30 m, $T_{max:}$ 350 ^{o}C, Column ID# 11475). A Varian® Cary 50 UV-Vis spectrophotometer was used for the UV-Vis absorbance studies. Kessil lamps PR160L were used as the irradiation source. For the experiments, the intensity of the Kessil lamps was controlled in the maximum level with power consumption: 370 nm (max 43W), 390 nm (max 52W), 427 nm & 440 nm (max 45W), 456 nm (max 50W) and 525 nm (max 44W).

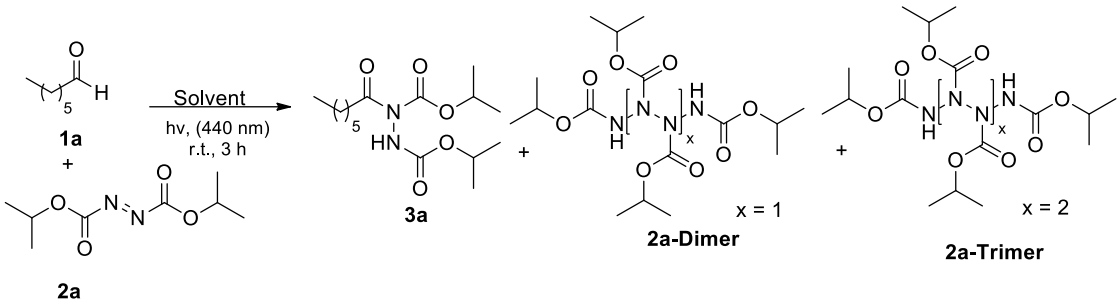
Optimization of the Reaction Conditions for the Photochemical Catalyst-free Reaction between Heptanal and Diisopropyl Azodicarboxylate



1a **2a** **3a**

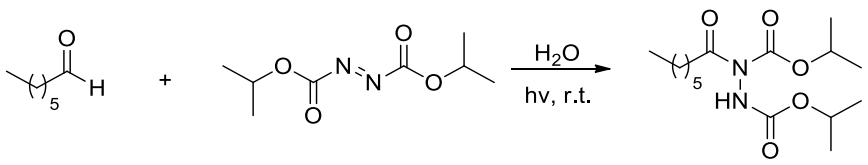
Entry	Irradiation Source (nm)	Reaction Time (h)	Conversion (%)[a]
1	370	21	100
2	**390**	**3**	**100**
3	427	5	100
4	**440**	**3**	**100**
5	456	3.5	100
6	525	24	100
7	Under Dark	3	5
8	Ambient light	3	7
9[b]	CFL lamp	3.5-4	96

[a] Conversion determined by ^{1}H-NMR. The reaction was performed with heptanal (**1a**) (114 mg, 1.00 mmol), diisopropyl azodicarboxylate (**2a**) (101 mg, 0.50 mmol) in MeCN (2 mL), under various light source irradiation. [b] Household Common Fluorescent Lamps: CFL lamps.



Entry	Irradiation Source (nm)	Solvent	Yield of 3a (%)[a]	Yield of 2a-Dimer (%)[a]	Yield of 2a-Trimer (%)[a]
1	440	MeCN	100	-	-
2	440	Et_2O	53	23	24
3	440	EtOAc	47	46	7
4	440	Toluene	46	54	-
5	440	THF	0	-	-
6	440	CH_2Cl_2	75	10	15
7	440	Pet. Eth.	23	55	2
8	440	CCl_4	46	54	-
9	440	MeOH	9	64	27
10	440	$CHCl_3$	46	48	6
11[b]	**440**	**H_2O**	**100 (87)**	**-**	**-**
12[c]	**390**	**H_2O**	**100 (92)**	**-**	**-**

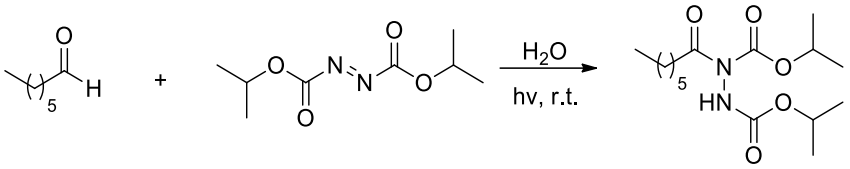
[a] Yield determined by ^{1}H-NMR. The reaction was performed with heptanal (**1a**) (114 mg, 1.00 mmol), diisopropyl azodicarboxylate (**2a**) (101 mg, 0.50 mmol) in solvent (2 mL), under irradiation. [b] The reaction was completed after 55 min. [c] The reaction was performed at 390 nm and was completed after 40 min.



1a **2a** **3a**

Entry	Heptanal:DIAD	Irradiation Source (nm)	Reaction Time	Conversion (%)[a]
1	**2:1**	**390**	**40 min**	**100 (92)**
2	**1.5:1**	**390**	**50 min**	**100 (92)**
3	1.1:1	390	110 min	100
4	1.5:1	Under dark	50 min	17
5[b]	1.5:1	390	50 min	67
6[c]	1.5:1	390	50 min	100 (92)
7	1.5:1	Ambient light	50 min	34
8	1.5:1	Sunlight	50 min	73

[a] Conversion determined by ^{1}H-NMR. The reaction was performed with heptanal (**1a**) (1.00-0.55 mmol), diisopropyl azodicarboxylate (**2a**) (101 mg, 0.50 mmol), in H_2O (2 mL), under 390 nm Kessil lamp irradiation. [b] The reaction was performed under an argon atmosphere. [c] The reaction was performed using a fan to maintain lower temperature (27^{o}C). In parenthesis, the isolated yield by column chromatography is included.

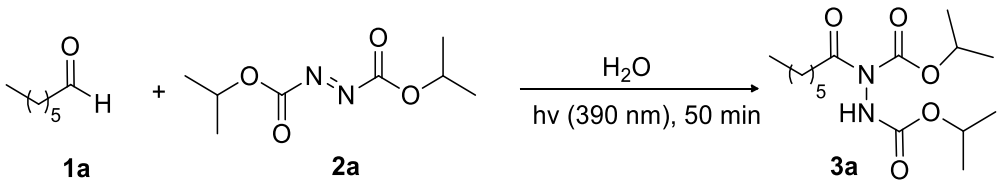


1a **2a** **3a**

Entry	Irradiation Source (nm)	Reaction Time to 100% Conversion
1	370	120 min
2	**390**	**50 min**
3	427	90 min
4	440	150 min
5	456	70 min
6	525	200 min
7	Sunlight	120 min

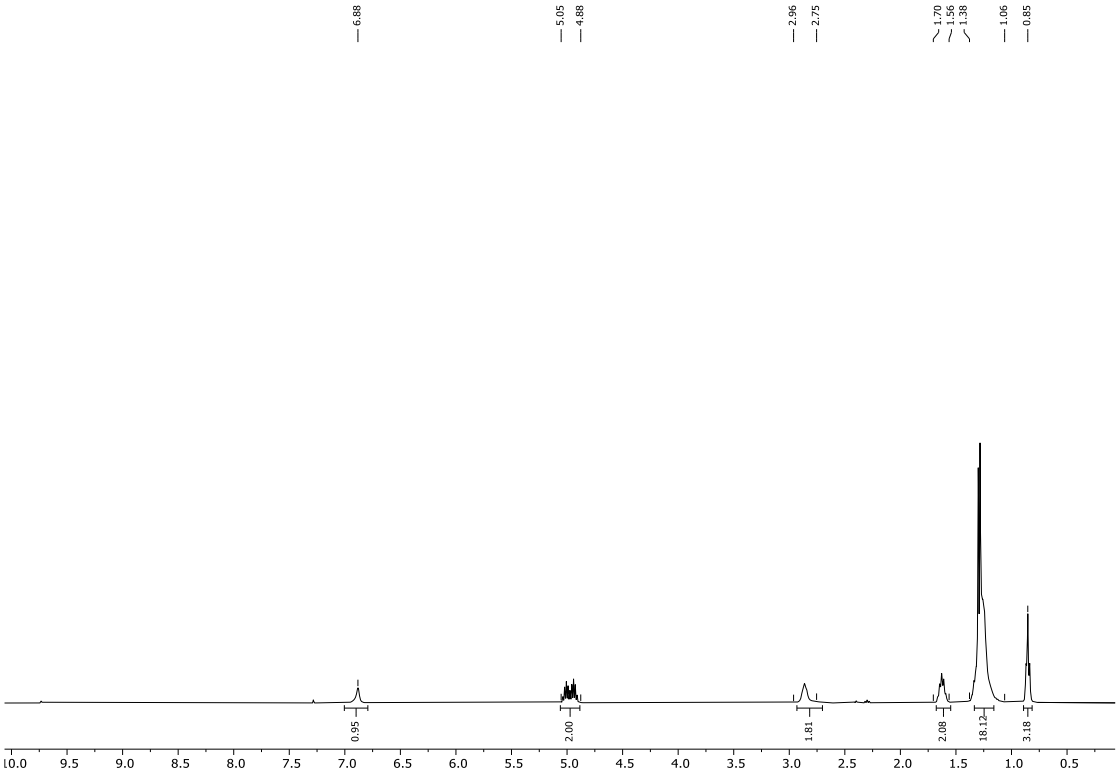
The reaction was performed with heptanal (**1a**) (0.75 mmol), diisopropyl azodicarboxylate (**2a**) (101 mg, 0.50 mmol) in H_2O (2 mL), under irradiation.

Purification by Liquid-Liquid Extraction

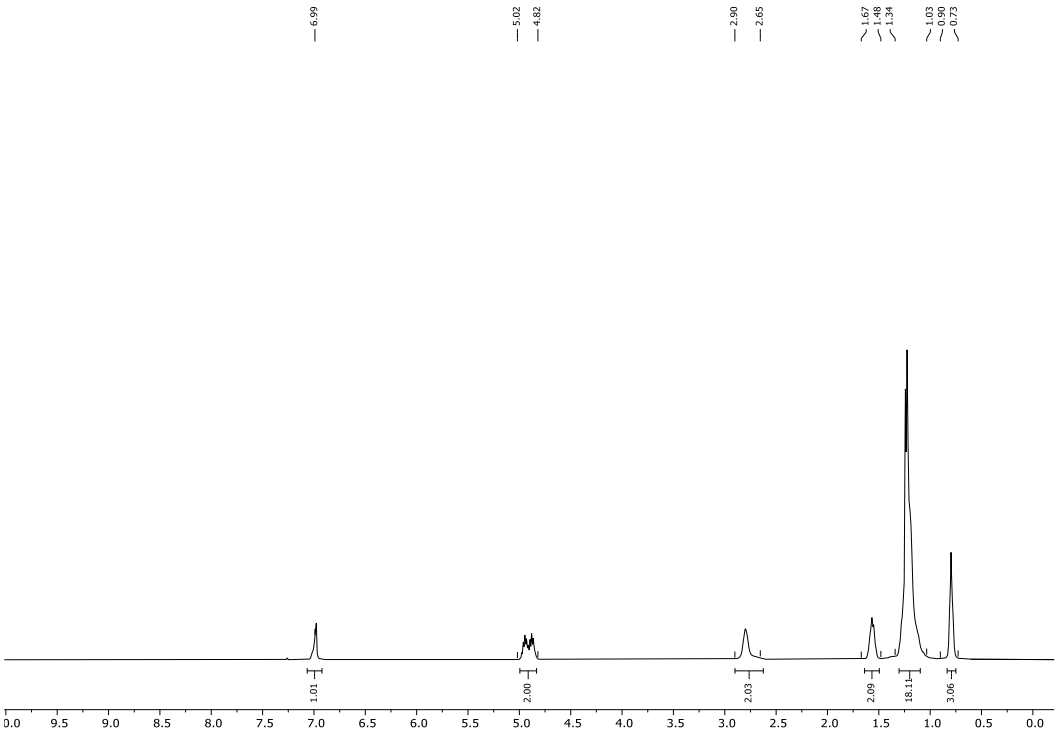


In an attempt to highlight the green and sustainable character of the method, the reaction of **1a** with **2a** was performed according to the general procedure and the isolation of the desired product **3a** was performed by a simple basic workup of the organic phase. More specifically, in a test tube, heptanal (**1a**) (86 mg, 0.75 mmol, 1.5 equiv.), diisopropylazodicarboxylate (**2a**) (101 mg, 0.50 mmol, 1.0 equiv.) and H_2O (2 mL) were added consecutively. The test tube was left stirring under Kessil lamp irradiation (390 nm) for 50 min. After reaction completion, the reaction mixture was diluted with EtOAc (10 mL) and the aqueous layer was extracted with EtOAc (2 x 5 mL). The combined organic layers were washed with aq. NaOH (1M, 10 mL), brine (10 mL) and dried with Na_2SO_4. The solvent was removed *in vacuo*. Yield: 90%.

^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of 3a, upon basic workup-extraction

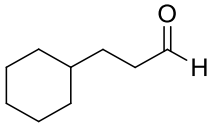


^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of 3a, after purification by column chromatography



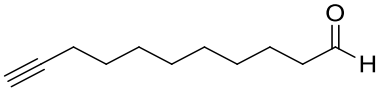
Synthesis of Starting Materials

3-Cyclohexylpropanal (1e)[1]



A flask was charged with PCC (1.30 g, 6.00 mmol, 2.0 equiv.) in dry CH_2Cl_2 (15 mL). After stirring for 10 min, 3-cyclohexyl propanol (426 mg, 3.00 mmol, 1.0 equiv.) in dry CH_2Cl_2 (15 mL) was added at 0 ºC. After the addition of the alcohol, the reaction mixture was left at the same temperature stirring for 1 h. After full conversion, silica gel (1.95 g) was added, followed by filtration through silica Celite/silica *in vacuo* (Pet. Ether/Et_2O 9:1). The product (363 mg, 2.59 mmol) was obtained after solvent evaporation as colorless oil and used without further purification. Colorless oil; 86% yield; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 9.77 (1H, s, CHO), 2.43 (2H, td, J = 7.3 and 1.9 Hz, $COCH_2$), 1.75-1.62 (5H, m, 4 x C*H*H and CH), 1.53 (2H, dt, J = 7.7 and 7.3 Hz, 2 x C*H*H), 1.30-1.07 (4H, m, 4 x C*H*H), 0.98-0.92 (2H, m, 2 x C*H*H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 203.2, 41.6, 37.3, 33.1, 29.4, 26.5, 26.3; **MS (ESI) m/z** 140 $[M]^+$

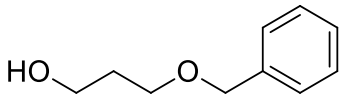
Undec-10-ynal (1f)[2]



A flask was charged with 10-undecynol (504 mg, 3.00 mmol, 1.0 equiv.) in CH_2Cl_2 (3 mL). TEMPO (47 mg, 0.30 mmol, 0.1 equiv.) was added followed by iodobenzene diacetate (1.06 g, 3.30 mmol, 1.1 equiv.). The reaction mixture was stirred at room temperature until TLC showed consumption of the alcohol (2.5 h) and then it was diluted with CH_2Cl_2 (15 mL). Saturated aqueous solution of Na_2SO_3 (15 mL) was then added and the aqueous layer was extracted with CH_2Cl_2 (3 x 8 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was further purified via column chromatography (Pet. Ether/EtOAc 9.5:0.5). The product (443 mg, 2.64 mmol) was obtained as colorless oil. Colorless oil; 88% yield; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 9.73 (1H, s, CHO), 2.39 (2H, td, J = 7.2 and 1.5 Hz, $COCH_2$), 2.14 (2H, td, J = 7.0 and 2.5 Hz, $\equiv CCH_2$), 1.90 (1H, t, J = 2.5 Hz, $\equiv CH$), 1.59 (2H, qu, J = 7.2 Hz,

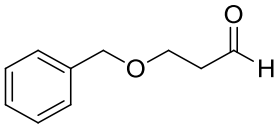
CH_2), 1.48 (2H, qu, J = 7.0 Hz, CH_2), 1.41-1.32 (2H, m, CH_2), 1.31-1.22 (6H, m, 3 x CH_2); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 202.7, 84.6, 68.1, 43.8, 29.2, 29.0, 28.8, 28.6, 28.4, 22.0, 18.3; **MS (ESI) m/z** 167 $[M+H]^+$.

3-Benzyloxypropanol (S1)[4]



A flask was charged with 1,3-propanodiol (5.70 g, 75.00 mmol, 7.5 equiv.) in dry CH_2Cl_2 (5 mL) and NaH (480 mg, 20.00 mmol, 2.0 equiv.) and benzyl bromide (1.71 g, 10.00 mmol, 1.0 equiv.). The reaction mixture was stirred at r.t. for 1 week. After full conversion, the reaction mixture was diluted with CH_2Cl_2 (15 mL) and the organic layer was washed with brine (15 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The product (1.40 g, 8.42 mmol) was used without further purification. Colorless oil; 84% yield; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.43-7.30 (5H, m, ArH), 4.54 (2H, s, OCH_2), 3.80 (2H, t, J = 5.8 Hz, OCH_2), 3.68 (2H, t, J = 5.8 Hz, OCH_2), 2.93 (1H, br s, OH), 1.89 (2H, qu, J = 5.8 Hz, CH_2); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 138.1, 128.4, 127.7, 127.7, 73.2, 69.1, 61.6, 32.1; **MS (ESI) m/z** 189 $[M+Na]^+$.

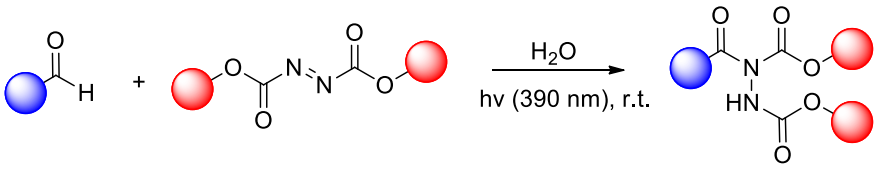
3-Benzyloxypropanal (1i)[5]



In a round bottom flask a solution of oxalyl chloride (3.00 mL, 6.00 mmol, 1.2 equiv.) was diluted with dry CH_2Cl_2 (7.8 mL). The reaction mixture was left to cool at -78 ^{o}C. Afterwards, a solution of DMSO (0.39 mL, 5.50 mmol, 1.1 equiv.) in dry CH_2Cl_2 (8.25 mL) was added dropwise. The reaction mixture was left stirring for 5 min at -78 ^{o}C. Then, a solution of 3-benzyloxypropanol (831 mg, 5.00 mmol, 1.0 equiv.) in dry CH_2Cl_2 (6.5 mL) was added dropwise as well. The reaction mixture was left to stir at -78 ^{o}C for 20 min. Then, triethylamine (3.93 mL, 25.00 mmol, 5.0 equiv.) was added and the reaction mixture was left stirring for 10 min. After full conversion, the reaction

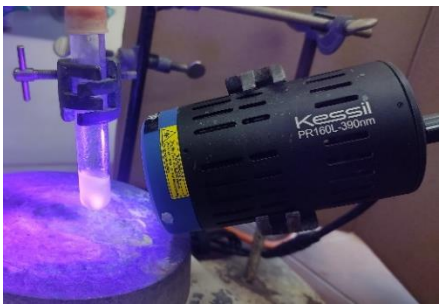
mixture was removed from cooling. The obtained crude mixture was partitioned with CH_2Cl_2 (20 mL) and ice. The organic extract was washed with a saturated aqueous solution of NH_4Cl (15 mL) and then with brine (15 mL). It was then dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was further purified by column chromatography on silica gel (Pet. Ether/EtOAc 8:2). Yellow oil; 72% yield; **^{1}H NMR** (400 MHz, $CDCl_3$) *δ:* 9.72 (1H, s, CHO), 7.30-7.16 (5H, m, ArH), 4.46 (2H, s, OCH_2Ph), 3.74 (2H, t, *J* = 6.1 Hz, OCH_2), 2.62 (2H, td, *J* = 6.1 and 1.5 Hz, $COCH_2$); **^{13}C NMR** (400 MHz, $CDCl_3$) *δ*: 201.2, 137.9, 128.4, 127.8, 127.7, 73.2, 63.8, 43.8; **MS (ESI) m/z** 165 $[M+H]^+$.

General Procedure for the Photochemical Reaction of Aldehydes with Dialkyl Azodicarboxylates



In a test tube, aldehyde (0.75-1.00 mmol, 1.5-2.0 equiv.), dialkylazodicarboxylate (0.50 mmol, 1.0 equiv.) and H_2O (2 mL) were added consecutively. The test tube was left stirring under Kessil lamp irradiation (390 nm) (see photos below) for 15-210 min, depending on the substrate, until reaction completion, determined by TLC. After reaction completion, the reaction mixture was concentrated *in vacuo*. The desired product was further purified by column chromatography.

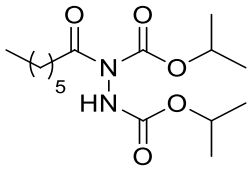
A. **B.**



C.

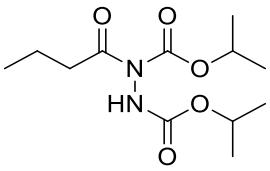
Scheme S1. A: The Kessil lamp utilized for the photochemical reaction, **B**: Beginning of the reaction, **C:** Completion of the reaction.

Diisopropyl 1-heptanoylhydrazine-1,2-dicarboxylate (3a)[6]



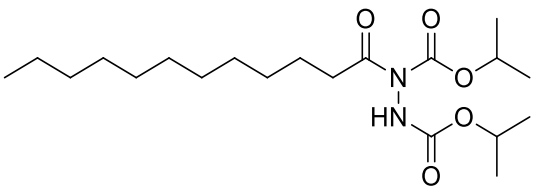
Reaction time using 1.5 equiv. of aldehyde: 50 min; 92% yield; Reaction time using 2.0 equiv. of aldehyde: 40 min; 92% yield; Colorless oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 6.99 (1H, br s, NH), 5.02-4.82 (2H, m, 2 x OCH), 2.90-2.65 (2H, m, $COCH_2$), 1.67-1.48 (2H, m, CH_2), 1.34-1.08 (18H, m, 3 x CH_2 and 4 x CH_3), 0.73 (3H, t, J = 6.7 Hz, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 173.8, 155.1, 152.6, 71.8, 70.0, 36.8, 31.4, 28.6, 24.4, 22.3, 21.7, 21.5, 13.8; **MS (ESI) m/z** 317 $[M+H]^+$.

Diisopropyl 1-butyrylhydrazine-1,2-dicarboxylate (3b)[6]



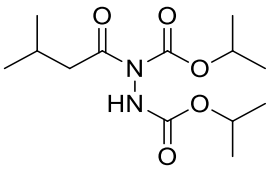
Reaction time using 1.5 equiv. of aldehyde: 45 min; 82% yield; Reaction time using 2.0 equiv. of aldehyde: 40 min; 88% yield; Colorless oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 6.91 (1H, s, NH), 4.97 (1H, sept, J = 6.5 Hz, OCH), 4.90 (1H, sept, J = 6.5 Hz, OCH), 2.92-2.59 (2H, m, $COCH_2$), 1.63 (2H, hex, J = 7.5 Hz, CH_2), 1.25 (6H, d, J = 6.5 Hz, 2 x CH_3), 1.22-1.10 (6H, m, 2 x CH_3), 0.90 (3H, t, J = 7.5 Hz, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 173.7, 155.1, 152.6, 71.9, 70.1, 38.7, 21.8, 21.6, 18.0, 13.5; **MS (ESI) m/z** 275 $[M+H]^+$.

Diisopropyl 1-dodecanoylhydrazine-1,2-dicarboxylate (3c)[7]



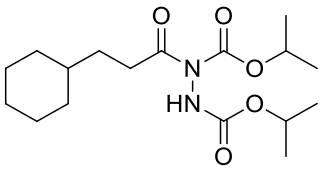
Reaction time using 1.5 equiv. of aldehyde: 25 min; 85% yield; Colorless oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 6.82 (1H, br s, NH), 5.04-4.88 (2H, m, 2 x OCH), 2.84 (2H, t, J = 7.3 Hz, $COCH_2$), 1.61 (2H, qu, J = 7.3 Hz, CH_2), 1.36-1.15 (28H, m, 8 x CH_2 and 4 x CH_3), 0.83 (3H, t, J = 6.7 Hz, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 173.9, 155.1, 152.6, 71.9, 70.1, 36.9, 31.8, 29.5, 29.4, 29.3, 29.2, 29.0, 24.5, 22.6, 21.8, 21.6, 14.0; **MS (ESI) m/z** 409 $[M+Na]^+$.

Diisopropyl 1-(3-methylbutanoyl) hydrazine-1,2-dicarboxylate (3d)[6]



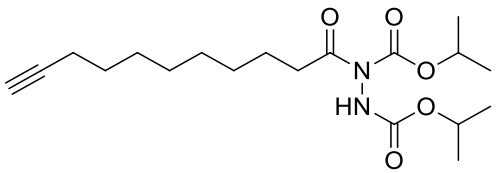
Reaction time using 1.5 equiv. of aldehyde: 40 min; 63% yield; Reaction time using 2.0 equiv. of aldehyde: 25 min; 96% yield; Colorless oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 6.74 (1H, br s, NH), 5.00 (1H, sept, J = 6.2 Hz, OCH), 4.94 (1H, sept, J = 6.2 Hz, OCH), 2.90-2.64 (2H, m, $COCH_2$), 2.23-2.09 (1H, m, CH), 1.29 (6H, d, J = 6.2 Hz, 2 x CH_3), 1.24-1.18 (6H, m, 2 x CH_3), 0.94 (6H, d, J = 6.7 Hz, 2 x CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ*:* 173.1, 155.1, 152.7, 72.0, 70.3, 45.6, 25.2, 22.5, 21.8, 21.7; **MS (ESI) m/z** 287 $[M-H]^-$.

Diisopropyl 1-(3-cyclohexylpropanoyl)hydrazine-1,2-dicarboxylate (3e)



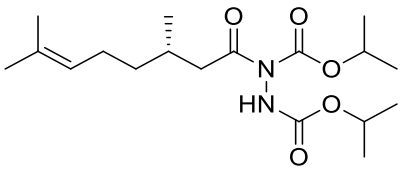
Reaction time using 1.5 equiv. of aldehyde: 120 min; 78% yield; Reaction time using 2.0 equiv. of aldehyde: 100 min; 86% yield; Colorless oil; **^{1}H NMR** (400 MHz, $CDCl_3$) *δ:* 6.66 (1H, br s, NH), 5.01 (1H, sept, *J* = 6.3 Hz, OCH), 4.95 (1H, sept, *J* = 6.3 Hz, OCH), 2.97-2.76 (2H, m, $COCH_2$), 1.71-1.60 (5H, m, 2 x CH_2 and CH), 1.56-1.51 (2H, m, CH_2), 1.30 (6H, d, *J* = 6.3 Hz, 2 x CH_3), 1.27-1.22 (6H, m, 2 x CH_3), 1.21-1.07 (4H, m, 2 x CH_2), 0.94-0.84 (2H, m, CH_2); **^{13}C NMR** (100 MHz, $CDCl_3$) *δ:* 174.2, 155.1, 152.7, 72.1, 70.3, 37.2, 34.7, 33.1, 32.0, 26.5, 26.2, 21.9, 21.7; **HRMS** exact mass calculated for $[M+H]^+$ ($C_{17}H_{31}N_2O_5^+$) requires *m/z* 343.2227, found m/z 343.2229.

Diisopropyl 1-(undec-10-ynoyl)hydrazine-1,2-dicarboxylate (3f)



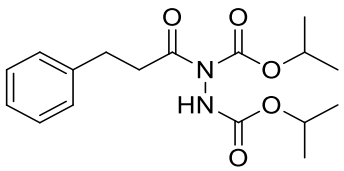
Reaction time using 1.5 equiv. of aldehyde: 100 min; 69% yield; Reaction time using 2.0 equiv. of aldehyde: 90 min; 70% yield; Colorless oil; **^{1}H NMR** (400 MHz, $CDCl_3$) *δ*: 6.66 (1H, br s, NH), 5.01 (1H, sept, *J* = 6.2 Hz, OCH), 4.95 (1H, sept, *J* = 6.2 Hz, OCH), 3.03-2.71 (2H, m, $COCH_2$), 2.15 (2H, td, *J* = 7.1 and 2.6 Hz, ≡CCH_2), 1.91 (1H, t, *J* = 2.6 Hz, ≡CH), 1.64 (2H, qu, *J* = 7.1 Hz, CH_2), 1.49 (2H, qu, *J* = 7.1 Hz, CH_2), 1.41-1.32 (4H, m, 2 x CH_2), 1.30-1.29 (10H, m, CH_3 and 2 x CH_2), 1.28-1.19 (6H, m, 2 x CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) *δ*: 173.9, 155.1, 152.7, 84.7, 72.1, 70.3, 68.1, 37.0, 29.2, 29.0, 28.9, 28.7, 28.4, 24.6, 21.9, 21.7, 18.4; **HRMS** exact mass calculated for $[M+Na]^+$ ($C_{19}H_{32}N_2NaO_5^+$) requires *m/z* 391.2203, found m/z 391.2203.

(*S*)-Diisopropyl 1-(3,7-dimethyloct-6-enoyl)hydrazine-1,2-dicarboxylate (3g)[6]



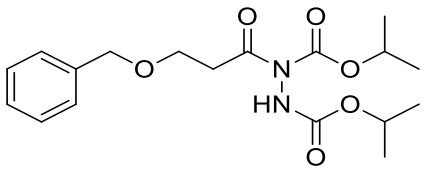
Reaction time using 1.5 equiv. of aldehyde: 30 min; 54% yield; Reaction time using 2.0 equiv. of aldehyde: 15 min; 66% yield; Colorless oil; **$[\alpha]_D$** ($CHCl_3$) = + 2.0, *c* 1; **^{1}H NMR** (400 MHz, $CDCl_3$**)** *δ:* 6.70 (1H, br s, NH), 5.09 (1H, t, *J* = 7.0 Hz, =CH), 5.06-5.00 (1H, m, OCH), 5.00-4.93 (1H, m, OCH), 3.02-2.83 (1H, m, COC*H*H), 2.79-2.65 (1H, m, COC*H*H), 2.11-1.94 (3H, m, CH and CH_2), 1.67 (3H, s, CH_3), 1.60 (3H, s, CH_3), 1.47-1.35 (1H, m, C*H*H), 1.32 (6H, d, *J* = 6.3 Hz, 2 x CH_3), 1.28-1.17 (7H, m, 2 x CH_3 and C*H*H), 0.96 (3H, d, *J* = 6.6 Hz, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$): *δ* 173.2, 155.1, 152.6, 131.3, 124.4, 72.0, 70.3, 44.0, 36.8, 29.5, 25.6, 25.4, 21.8, 21.6, 19.5, 17.6;**MS (ESI) m/z** 357 $[M+H]^+$.

Diisopropyl 1-(3-phenylpropanoyl)hydrazine-1,2-dicarboxylate (3h)[8]



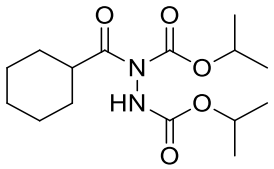
Reaction time using 1.5 equiv. of aldehyde: 30 min; 75% yield; Reaction time using 2.0 equiv. of aldehyde: 20 min; 90% yield; Colorless oil; **^{1}H NMR** (400 MHz, $CDCl_3$) *δ:* 7.31-7.13 (5H, m, ArH), 6.82 (1H, br s, NH), 5.07-4.92 (2H, m, 2 x OCH), 3.28-3.13 (2H, m, CH_2), 2.99 (2H, t, *J* = 7.5 Hz, CH_2), 1.30 (6H, d, *J* = 6.3 Hz, 2 x CH_3), 1.28-1.13 (6H, m, 2 x CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) *δ*: 173.0, 155.1, 152.6, 140.6, 128.4, 128.4, 126.1, 72.1, 70.3, 38.6, 30.6, 21.8, 21.6; **MS (ESI) m/z** 337 $[M+H]^+$.

Diisopropyl 1-(2-(benzyloxy)acetyl)hydrazine-1,2-dicarboxylate (3i)



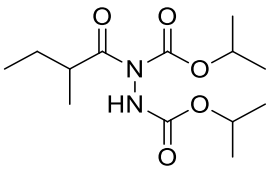
Reaction time using 1.5 equiv. of aldehyde: 40 min; 65% yield; Reaction time using 2.0 equiv. of aldehyde: 40 min; 78% yield; Colorless oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.39-7.24 (5H, m, ArH), 6.80 (1H, br s, NH), 5.10-4.92 (2H, m, 2 x OCH), 4.54 (2H, s, OCH_2Ar), 3.82 (2H, t, J = 6.4 Hz, OCH_2), 3.22 (2H, t, J = 6.4 Hz, CH_2CO), 1.31 (6H, d, J = 7.7 Hz, 2 x CH_3), 1.29-1.16 (6H, m, 2 x CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ*:* 171.5, 155.0, 152.4, 138.1, 128.3, 127.7, 127.6, 73.1, 72.2, 70.3, 65.3, 37.4, 21.8, 21.6; **HRMS** exact mass calculated for $[M+Na]^+$ ($C_{18}H_{26}N_2NaO_6^+$) requires *m/z* 389.1683, found m/z 389.1678.

Diisopropyl 1-(cyclohexanecarbonyl)hydrazine-1,2-dicarboxylate (3j)[6]



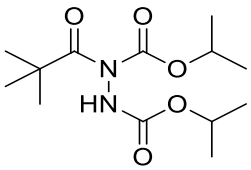
Reaction time using 1.5 equiv. of aldehyde: 30 min; 80% yield; Reaction time using 2.0 equiv. of aldehyde: 15 min; 90% yield; Colorless oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 6.77 (1H, br s, NH), 5.03 (1H, sept, J = 6.2 Hz, OCH), 4.95 (1H, sept, J = 6.2 Hz, OCH), 3.36 (1H, tt, J = 11.3 and 3.1 Hz, COCH), 1.98-1.88 (2H, m, 2 x CH*H*), 1.80-1.76 (2H, m, 2 x CH*H*), 1.70-1.63 (1H, m, C*H*H), 1.50-1.43 (2H, m, 2 x CH*H*), 1.31 (6H, d, J = 6.2 Hz, 2 x CH_3), 1.29-1.11 (9H, m, 2 x CH_3 and 3 x CH*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 177.1, 155.2, 152.7, 72.0, 70.2, 44.0, 29.4, 25.8, 25.6, 21.8, 21.7; **MS (ESI) m/z** 315 $[M+H]^+$.

Diisopropyl 1-(2-methylbutanoyl) hydrazine-1,2-dicarboxylate (3k)[6]



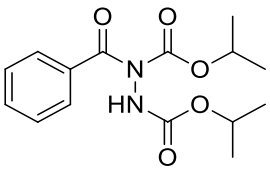
Reaction time using 1.5 equiv. of aldehyde: 60 min; 97% yield; Colorless oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 6.80 (1H, br s, NH), 5.00 (1H, d, J = 6.2 Hz, OCH), 4.93 (1H, d, J = 6.2 Hz, OCH), 3.49-3.39 (1H, m, COCH), 1.75 (1H, dqu, J = 14.2 and 7.2 Hz, CH*H*), 1.41 (1H, dqu, J = 14.2 and 7.2 Hz, CH*H*), 1.28 (6H, d, J = 6.3 Hz, 2 x CH_3), 1.24-1.17 (6H, m, 2 x CH_3), 1.14 (3H, d, J = 6.8 Hz, CH_3), 0.88 (3H, t, J = 7.2 Hz, CH_3); **^{13}C NMR** ($CDCl_3$) δ: 177.7, 155.1, 152.5, 71.9, 70.1, 40.7, 26.8, 21.7, 21.5, 16.6, 11.4; **MS (ESI) m/z** 289 $[M+H]^+$.

Diisopropyl 1-pivaloylhydrazine-1,2-dicarboxylate (3l)[6]



Reaction time using 1.5 equiv. of aldehyde: 80 min; 73% yield; Reaction time using 2.0 equiv. of aldehyde: 60 min; 90% yield; Colorless oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.00 (1H, br s, NH), 4.98 (1H, sept, J = 6.2 Hz, OCH), 4.94 (1H, sept, J = 6.2 Hz, OCH), 1.31-1.17 (21H, m, 7 x CH_3); **^{13}C NMR (**100 MHz, $CDCl_3$) δ*:* 179.6, 155.7, 153.2, 71.9, 70.2, 41.8, 27.3, 21.7, 21.5; **MS (ESI) m/z** 289 $[M+H]^+$.

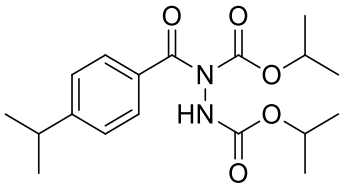
Diisopropyl 1-benzoylhydrazine-1,2-dicarboxylate (3m)[8]



Reaction time using 1.5 equiv. of aldehyde: 80 min; 66% yield; Reaction time using 2.0 equiv. of aldehyde: 60 min; 86% yield; White solid; m.p. 115-117 ^{o}C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ*:* 7.76-7.56 (2H, m, ArH), 7.49 (1H, t, J = 7.4 Hz, ArH), 7.39 (2H, t, J = 7.4 Hz, ArH), 7.29 (1H, br s, NH), 4.99 (1H, sept, J = 6.2 Hz, OCH), 4.87 (1H, sept, J = 6.2 Hz, OCH), 1.27 (6H, d, J = 6.2 Hz, 2 x CH_3), 1.10-1.00 (6H, m, 2 x CH_3); **^{13}C**

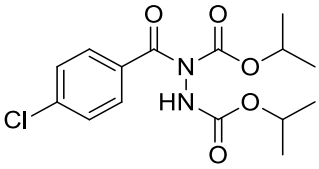
NMR (100 MHz, $CDCl_3$) δ: 171.2, 155.3, 152.9, 135.2, 131.8, 128.3, 128.0, 72.3, 70.5, 21.8, 21.2; **MS (ESI) m/z** 309 $[M+H]^+$.

Diisopropyl 1-(4-isopropylbenzoyl)hydrazine-1,2-dicarboxylate (3n)[10]



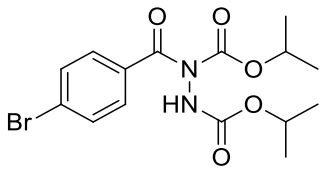
Reaction time using 1.5 equiv. of aldehyde: 70 min; 59% yield; Reaction time using 2.0 equiv. of aldehyde: 60 min; 68% yield; White solid; m.p.: 104-106 ºC; **^{1}H NMR** (400 MHz, DCl_3) δ*:* 7.69-7.55 (2H, m, ArH), 7.26 (2H, d, *J* = 7.3 Hz, ArH), 7.18 (1H, br s, NH), 5.01 (1H, sept, *J* = 6.2 Hz, OCH), 4.88 (1H, sept, *J* = 6.2 Hz, OCH), 2.95 (1H, sept, *J* = 6.9 Hz, PhCH), 1.28 (6H, d, *J* = 6.2 Hz, 2 x CH_3), 1.25 (6H, d, *J* = 6.9 Hz, 2 x CH_3), 1.13-1.01 (6H, m, 2 x CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ*:* 171.2, 155.3, 153.5, 153.1, 132.6, 128.6, 126.2, 72.3, 70.6, 34.2, 23.7, 21.9, 21.3; **MS (ESI) m/z** 351 $[M+H]^+$.

Diisopropyl 1-(4-chlorobenzoyl)hydrazine-1,2-dicarboxylate (3o)[11]



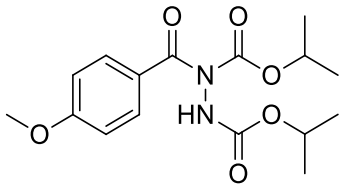
Reaction time using 1.5 equiv. of aldehyde: 40 min; 66% yield; Reaction time using 2.0 equiv. of aldehyde: 20 min; 85% yield; Colorless oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.67-7.49 (2H, m, ArH), 7.36 (2H, d, *J* = 8.3 Hz, ArH), 7.21 (1H, br s, NH), 4.97 (1H, sept, *J* = 5.9 Hz, OCH), 4.88 (1H, sept, *J* = 5.9 Hz, OCH), 1.25 (6H, d, *J* = 5.9 Hz, 2 x CH_3), 1.09 (6H, d, *J* = 5.9 Hz, 2 x CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 170.2, 155.3, 152.7, 138.1, 133.5, 129.6, 128.4, 72.6, 70.6, 21.8, 21.3; **MS (ESI) m/z** 365 $[M+Na]^+$.

Diisopropyl 1-(4-bromobenzoyl)hydrazine-1,2-dicarboxylate (3p)[8]



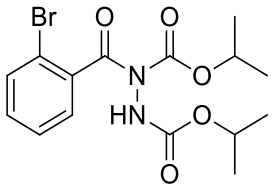
Reaction time using 1.5 equiv. of aldehyde: 40 min; 87% yield; Reaction time using 2.0 equiv. of aldehyde: 20 min; 92% yield; White solid; m.p.: 98-101 ^{o}C; **^{1}H NMR** (400 MHz, $CDCl_3$) *δ:* 7.58-7.40 (4H, m, ArH), 7.23 (1H, br s, NH), 4.97 (1H, sept, *J* = 5.9 Hz, OCH), 4.87 (1H, sept, *J* = 5.9 Hz, OCH), 1.25 (6H, d, *J* = 5.9 Hz, 2 x CH_3), 1.09 (6H, d, *J* = 5.9 Hz, 2 x CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) *δ*: 170.3, 155.2, 152.6, 133.9, 131.3, 129.6, 126.5, 72.5, 70.5, 21.8, 21.2; **MS (ESI) m/z** 387 $[M+H]^+$.

Diisopropyl 1-(4-methoxybenzoyl)hydrazine-1,2-dicarboxylate (3q)[8]



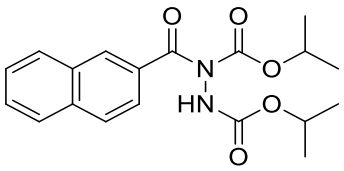
Reaction time using 1.5 equiv. of aldehyde: 210 min; 60% yield; Reaction time using 2.0 equiv. of aldehyde: 180 min; 68% yield; Yellow oil; **^{1}H NMR** (400 MHz, $CDCl_3$) *δ:* 7.76-7.56 (2H, m, ArH), 7.10 (1H, br s, NH), 6.88 (2H, d, *J* = 8.5 Hz, ArH), 4.98 (1H, sept, *J* = 5.6 Hz, OCH), 4.89 (1H, sept, *J* = 5.6 Hz, OCH), 3.83 (3H, s, OCH_3), 1.26 (6H, d, *J* = 5.6 Hz, 2 x CH_3), 1.11 (6H, d, *J* = 5.6 Hz, 2 x CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) *δ*: 170.6, 162.9, 155.4, 153.2, 131.0, 126.9, 113.4, 72.2, 70.4, 55.4, 21.9, 21.4; **MS (ESI) m/z**: 337 $[M-H]^-$.

Diisopropyl 1-(2-bromobenzoyl)hydrazine-1,2-dicarboxylate (3r)



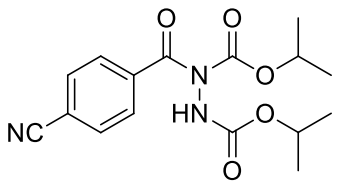
Reaction time using 1.5 equiv. of aldehyde: 50 min; 94% yield; Yellow oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.57 (1H, d, J = 7.9 Hz, ArH), 7.50-7.41 (1H, m, ArH), 7.36 (1H, t, J = 7.9 Hz, ArH), 7.29 (1H, t, J = 7.9 Hz, ArH), 7.02 (1H, br s, NH), 5.02 (1H, sept, J = 6.3 Hz, OCH), 4.90 (1H, sept, J = 6.3 Hz, OCH), 1.29 (6H, d, J = 6.3 Hz, 2 x CH_3), 1.17-1.00 (6H, m, 2 x CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 168.2, 154.9, 151.6, 138.3, 132.4, 130.9, 127.8, 127.1, 118.6, 72.6, 70.6, 21.8, 21.2; **HRMS** exact mass calculated for $[M+Na]^+$ ($C_{15}H_{19}BrN_2NaO_5^+$) requires *m/z* 409.0370/411.0350, found m/z 409.0370/411.0350.

Diisopropyl 1-(2-naphthoyl)hydrazine-1,2-dicarboxylate (3s)[8]



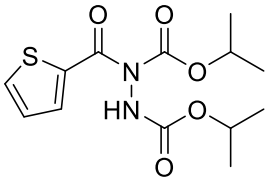
Reaction time using 1.5 equiv. of aldehyde: 70 min; 69% yield; Reaction time using 2.0 equiv. of aldehyde: 60 min; 87% yield; White solid; m.p.: 112-114 ^{o}C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.24 (1H, m, NH), 7.87 (1H, d, J = 8.0 Hz, ArH), 7.83 (2H, d, J = 8.4 Hz, ArH), 7.79-7.62 (1H, m, ArH), 7.56-7.48 (2H, m, ArH), 7.35-7.25 (1H, m, ArH), 5.02 (1H, sept, J = 6.2 Hz, OCH), 4.87 (1H, sept, J = 6.2 Hz, OCH), 1.28 (6H, d, J = 6.2 Hz, 2 x CH_3), 1.00-0.89 (6H, m, 2 x CH_3); **^{13}C NMR** 100 MHz, $CDCl_3$) δ: 171.3, 155.4, 153.0, 134.8, 132.2, 129.1, 129.0, 127.9, 127.8, 127.7, 126.7, 124.4, 72.4, 70.6, 21.9, 21.2; **MS (ESI) m/z**: 359 $[M+H]^+$.

Diisopropyl 1-(4-cyanobenzoyl)hydrazine-1,2-dicarboxylate (3t)[9]



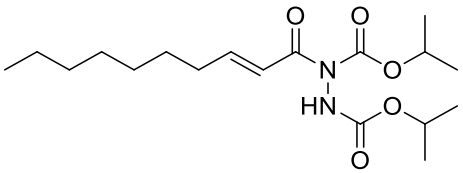
Reaction time using 1.5 equiv. of aldehyde: 95 min; 74% yield; Reaction time using 2.0 equiv. of aldehyde: 50 min.; 80% yield; White solid; m.p. 81-85 ^{o}C; **^{1}H NMR** (400 MHz, $CDCl_3$) *δ:* 7.79-7.61 (4H, m, ArH), 7.10 (1H, br s, NH), 5.03-4.94 (1H, m, OCH), 4.92-4.84 (1H, m, OCH), 1.27 (d, *J* = 6.3 Hz, 2 x CH_3), 1.11 (d, *J* = 6.3 Hz, 2 x CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) *δ*: 169.5, 155.1, 152.3, 139.4, 131.9, 128.2, 117.9, 114.9, 73.0, 70.9, 21.8, 21.3; **MS (ESI) m/z**: 334 $[M+H]^+$.

Diisopropyl 1-(thiophene-2-carbonyl)hydrazine-1,2-dicarboxylate (3u)[7]



Reaction time using 1.5 equiv. of aldehyde: 210 min; 29% yield; Reaction time using 2.0 equiv. of aldehyde: 180 min.; 50% yield; Colorless oil; **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 7.88-7.81 (1H, m, ArH), 7.62-7.58 (1H, m, ArH), 7.08-7.05 (2H, m, ArH and NH), 5.07-4.95 (2H, m, 2 x OCH), 1.35-1.07 (12H, m, 4 x CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$): *δ* 162.6, 155.4, 152.6, 135.5, 134.8, 133.6, 127.1, 72.6, 70.8, 21.8, 21.5; **MS (ESI) m/z**: 315 $[M+H]^+$.

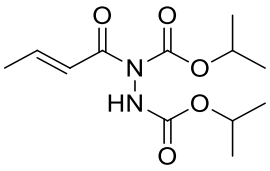
(*E*)-Diisopropyl 1-(dec-2-enoyl)hydrazine-1,2-dicarboxylate (3v)[8]



Reaction time using 1.5 equiv. of aldehyde: 120 min; 53% yield; Reaction time using 2.0 equiv. of aldehyde: 100 min; 60% yield; Colorless oil; **^{1}H NMR** (400 MHz, $CDCl_3$)

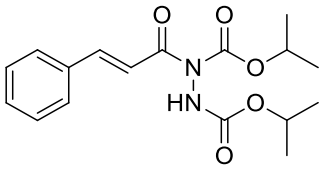
δ: 7.05 (1H, dt, J = 14.7 and 7.0 Hz, =C*H*CH_2), 6.89-6.70 (2H, m, NH and =CH), 5.05-4.89 (2H, m, 2 x OCH), 2.20 (2H, q, J = 7.0 Hz, =CHC*H*$_2$), 1.43 (2H, qu, J = 7.0 Hz, CH_2), 1.28 (6H, d, J = 6.1 Hz, 2 x CH_3), 1.25-1.13 (14H, m, 2 x CH_3 and 4 x CH_2), 0.84 (3H, t, J = 7.4 Hz, CH_3); **^{13}CNMR** (100 MHz, $CDCl_3$) δ: 166.4, 155.2, 152.8, 151.1, 121.9, 72.1, 70.2, 32.6, 31.7, 29.1, 29.0, 28.0, 22.6, 21.8, 21.6, 14.0; **MS (ESI) m/z** 357 $[M+H]^+$.

(*E*)-Diisopropyl 1-(but-2-enoyl)hydrazine-1,2-dicarboxylate (3w)[8]



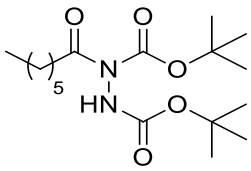
Reaction time using 1.5 equiv. of aldehyde: 150 min; 52% yield; Reaction time using 2.0 equiv. of aldehyde: 120 min; 72% yield; Colorless oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ*:* 7.14-7.05 (1H, m, =CH), 6.97-6.84 (1H, m, =CH), 6.65 (1H, br s, NH), 5.09-4.93 (2H, m, 2 x OCH), 1.93 (3H, d, J = 6.8 Hz, CH_3), 1.32 (6H, d, J = 6.2 Hz, 2 x CH_3), 1.30-1.21 (6H, m, 2 x CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 166.2, 155.1, 152.7, 145.9, 123.4, 72.0, 70.1, 21.8, 21.6, 18.3; **MS (ESI) m/z** 273 $[M+H]^+$.

Diisopropyl 1-cinnamoylhydrazine-1,2-dicarboxylate (3x)[7]



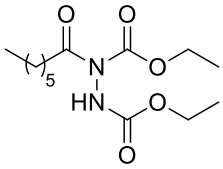
Reaction time using 1.5 equiv. of aldehyde: 70 min; 64% yield; Reaction time using 2.0 equiv. of aldehyde: 60 min; 76% yield; Yellowish oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.79 (1H, d, J = 15.7 Hz, =CH), 7.63-7.51 (3H, m, ArH), 7.42-7.34 (3H, m, ArH and =CH), 6.80 (1H, br s, NH), 5.08 (1H, hept, J = 6.2 Hz, OCH), 5.00 (1H, hept, J = 6.2 Hz, OCH), 1.34 (6H, d, J = 6.2 Hz, 2 x CH_3), 1.30-1.21 (6H, m, 2 x CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 166.6, 155.2, 152.9, 145.9, 134.8, 130.5, 128.9, 128.4, 118.9, 72.4, 70.5, 21.9, 21.8; **MS (ESI) m/z** 357 $[M+Na]^+$.

Di-*tert*-butyl 1-heptanoylhydrazine-1,2-dicarboxylate (3y)[8]



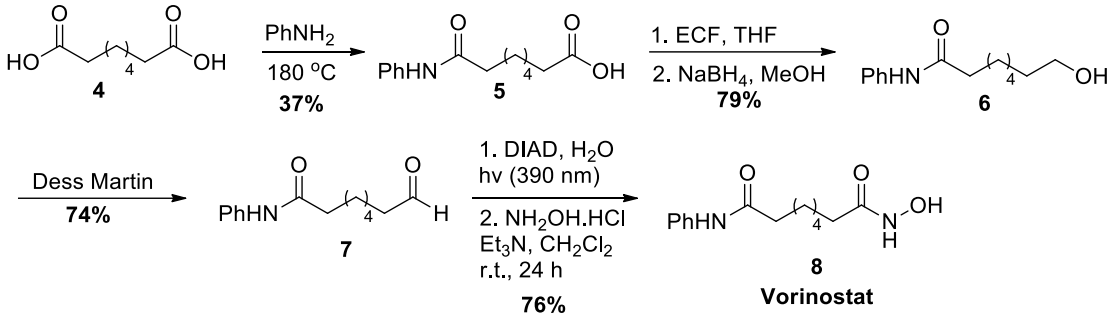
Reaction time using 1.5 equiv. of aldehyde: 110 min; 65% yield; Reaction time using 2.0 equiv. of aldehyde: 70 min; 70% yield; Colorless oil; **^{1}H NMR** (400 MHz, $CDCl_3$) *δ:* 6.61 (1H, br s, NH), 2.87-2.73 (2H, m, $COCH_2$), 1.61 (2H, qu, *J* = 6.8 Hz), 1.49 (9H, s, 3 x CH_3), 1.44 (9H, s, 3 x CH_3), 1.35-1.21 (6H, m, 3 x CH_2), 0.84 (3H, t, *J* = 6.8 Hz, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) *δ:* 174.0, 154.4, 151.7, 84.0, 81.8, 37.1, 31.5, 28.8, 28.1, 27.8, 24.6, 22.5, 14.0; **MS (ESI) m/z** 367 $[M+Na]^+$.

Diethyl 1-heptanoylhydrazine-1,2-dicarboxylate (3z)[8]

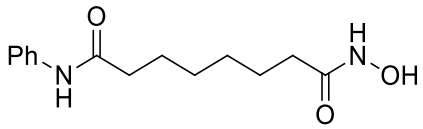


Reaction time using 1.5 equiv. of aldehyde: 20 min; 58% yield; reaction time using 2.0 equiv. of aldehyde: 20 min; 77% yield; Colorless oil; **^{1}H NMR** (400 MHz, $CDCl_3$) *δ*: 6.93 (1H, br s, NH), 4.26 (2H, q, *J* = 7.1 Hz, OCH_2), 4.17 (2H, q, *J* = 7.1 Hz, OCH_2), 2.92-2.78 (2H, m, $COCH_2$), 1.62 (2H, qu, *J* = 7.4 Hz, CH_2), 1.29 (6H, t, *J* = 7.1 Hz, 2 x CH_3), 1.27-1.16 (6H, m, 3 x CH_2), 0.84 (3H, t, *J* = 6.8 Hz, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) *δ*: 173.9, 155.6, 153.2, 63.8, 62.4, 36.9, 31.5, 28.7, 24.5, 22.4, 14.3, 14.1, 13.9; **MS (ESI) m/z** 311 $[M+Na]^+$.

Synthesis of Vorinostat



N^1-Hydroxy-N^8-phenyloctanediamide (8)[12]



Vorinostat

A mixture of suberic acid **4** (2.60 g, 15.00 mmol, 1.0 equiv.) and aniline (1.5 mL, 16.50 mmol, 1.1 equiv.) was heated under reflux at 190 °C for 20 minutes. The reaction was left to reach room temperature and then aq. KOH (1.4 M, 25 mL) was added and left stirring until dianilide was crystalized. The reaction mixture was filtrated to remove the precipitated dianilide. The filtrate was diluted with aq. HCl (1M, pH = 1) and the desired product crystalized in the reaction mixture. The reaction mixture was filtered and the solid was washed with hot water, to receive the deserved product **5** (1.38 g, 5.87 mmol, 37% yield), which was used in the next step.

To a stirred solution of acid **5** (946 mg, 3.80 mmol, 1.0 equiv.) in THF (12 mL) at -10 °C, Et_3N (0.78 mL, 5.70 mmol, 1.5 equiv.) was added, followed by ethyl chloroformate (ECF) (0.54 mL, 5.70 mmol, 1.5 equiv.). After 15 min, $NaBH_4$ (718 mg, 19.00 mmol, 8.0 equiv.) was added in one portion. MeOH (40 mL) was then added dropwise to the reaction mixture at 0 °C. The reaction mixture was stirred for 30 min and then aq. HCl (1M) was added to neutralize the mixture. The combined organic solvent was removed, and the product was extracted with EtOAc (3 x 25 mL). The organic layers were washed with aq. HCl (1M, 50 mL), water (50 mL), aq. 5% $NaHCO_3$

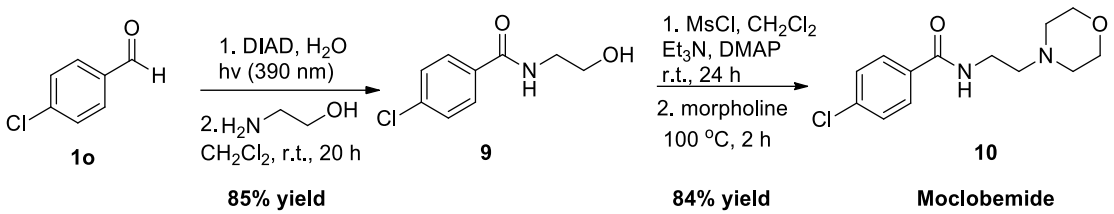
(50 mL), water (50 mL), dried over Na_2SO_4 and the mixture was concentrated *in vacuo*. The crude product **6** (701 mg, 2.98 mmol, 79% yield) was used in the next step.

A flask was charged with crude alcohol (701 mg, 2.98 mmol, 1.0 equiv.) dissolved in dry CH_2Cl_2 (8 mL) and Dess Martin periodinane (1.40 g, 3.30 mmol, 1.1 equiv.) was added. The reaction mixture was stirred at room temperature for 1 h. The organic layer was washed with aq. $NaHCO_3$ (20 mL) and brine (20 mL). The reaction mixture was dried and the solvent was evaporated *in vacuo*. Purification and data in accordance with literature.[11] (514 mg, 2.20 mmol, yield: 74%); **^{1}H NMR (400 MHz, $CDCl_3$)** δ: 9.71 (1H, br s, NH), 7.51 (2H, d, J = 8.1 Hz, ArH), 7.26 (2H, dd, J = 8.1 and 7.3 Hz, ArH), 7.05 (1H, d, J = 7.3 Hz, ArH), 2.46-2.28 (4H, m, 2 x $COCH_2$), 1.72-1.48 (4H, m, 2 x CH_2), 1.37-1.24 (4H, m, 2 x CH_2); **^{13}C NMR (100 MHz, $CDCl_3$)** δ: 203.1, 171.8, 137.9, 128.8, 124.0, 119.8, 43.6, 37.3, 28.8, 28.7, 25.2, 21.7; **MS (ESI) m/z** 234 $[M+H]^+$.

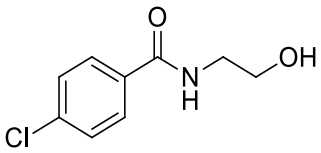
A reaction tube was charged with aldehyde **7** (117 mg, 0.50 mmol, 2.0 equiv.), diisopropyl azodicarboxylate **2a** (51 mg, 0.25 mmol, 1.0 equiv.) and water (2 mL). The reaction was left stirring under 390 nm irradiation for 40 min (until completion of the reaction). Then, EtOAc (2 mL) was added, and the aqueous layer was removed. The organic layer was concentrated *in vacuo*. The crude product was used for the next step.

A flask was charged with the crude reaction mixture, hydroxylamine hydrochloride (78 mg, 0.75 mmol, 3.0 equiv.) and triethylamine (0.11 mL, 0.75 mmol, 3.0 equiv.) in dry CH_2Cl_2 (8 mL). The reaction mixture was stirred at room temperature for 18 h. The crude product was purified using column chromatography to afford Vorinostat. White solid; m.p.: 159-161 ^{o}C; 76% yield; **^{1}H NMR** (400 MHz, DMSO) δ: 10.37 (1H, s, NH), 9.87 (1H, s, OH), 8.69 (1H, s, NH), 7.59 (2H, d, J = 7.8 Hz, ArH), 7.28 (2H, t, J = 7.8 Hz, ArH), 7.01 (1H, t, J = 7.8 Hz, ArH), 2.29 (2H, t, J = 7.4 Hz, $COCH_2$), 1.95 (2H, t, J = 7.3 Hz, $COCH_2$), 1.60-1.45 (4H, m, 2 x CH_2), 1.33-1.23 (4H, m, 2 x CH_2); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 171.9, 169.8, 139.9, 129.2, 123.5, 119.6, 36.9, 32.8, 28.9, 25.6; **MS (ESI) m/z** 263 $[M-H]^-$.

Synthesis of Moclobemide



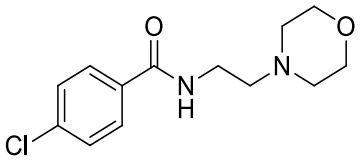
4-Chloro-*N*-(2-hydroxyethyl)benzamide (9)[13]



In a test tube, 4-chloro-benzaldehyde (**1o**) (524 mg, 4.00 mmol, 2.0 equiv.), diisopropyl azodicarboxylate (**2a**) (202 mg, 2.00 mmol, 1.0 equiv.) and H_2O (5 mL) were added consecutively. The test tube was left stirring under Kessil lamp irradiation (390 nm) for 20 min (until reaction completion). EtOAc (3 mL) was added, and the aqueous layer was removed by extraction. The organic solvent was removed *in vacuo*. The crude product was used in the next step.

Ethanolamine (0.18 mL, 3.00 mmol, 1.5 equiv.), the above crude reaction mixture and dry CH_2Cl_2 (4 mL) were added consecutively in a flask and left stirring at room temperature for 18 h. The organic solvent was concentrated *in vacuo*. The desired product was purified by column chromatography; Pale orange solid; m.p.: 68-70 °C; 85% yield; **^{1}H NMR** (400 MHz, DMSO) *δ:* 7.74 (2H, d, *J* = 8.3 Hz, ArH), 7.42 (2H, d, *J* = 8.3 Hz, ArH), 6.69 (1H, br s, NH), 3.86 (2H, t, *J* = 4.9 Hz, OCH_2), 3.64 (2H, t, *J* = 4.9 Hz, NCH_2); **^{13}C NMR** (100 MHz, DMSO) *δ*: 167.5, 138.0, 132.6, 128.9, 128.5, 62.2, 42.8; **MS (ESI) m/z** 198 $[M-H]^-$.

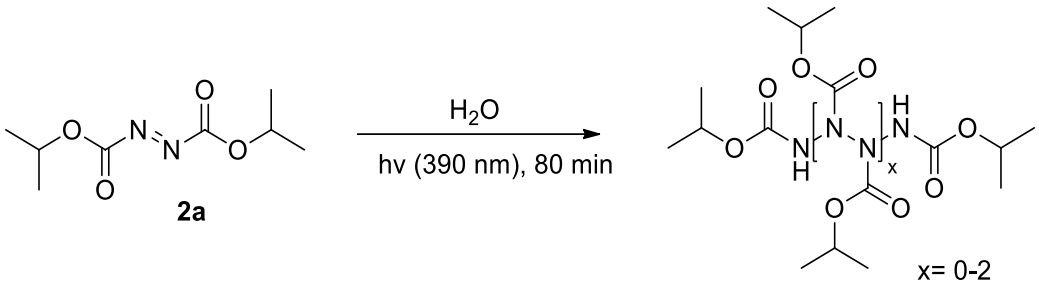
4-Chloro-*N*-(2-morpholinoethyl)benzamide (10)[13]



Moclobemide

To a stirring solution of 4-chloro-*N*-(2-hydroxyethyl)benzamide (**9**) (199 mg, 1.0 mmol, 1.0 equiv.) in dry CH_2Cl_2 (10 mL), Et_3N (0.42 mL, 3.00 mmol, 3.0 equiv.), DMAP (12 mg, 0.10 mmol, 0.1 equiv.), NaCl (175 mg, 3.00 mmol, 3.0 equiv.) and MsCl (0.23 mL, 3.00 mmol, 3.0 equiv.) were added consecutively. The reaction mixture was left stirring for 16 h at room temperature. The reaction mixture was washed with aq. 5% $NaHCO_3$ (10 mL) and brine (10 mL). The organic layer was dried and the organic solvent was evaporated *in vacuo*. Morpholine (0.70 mL, 8.00 mmol, 8.0 equiv.) was added to the crude reaction mixture and was left stirring for 2 h at 100 ^oC. The crude reaction mixture was further purified by column chromatography to afford Moclobemide. White solid; m.p.: 135-137 ^oC; 84% yield; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.68 (2H, d, J = 8.4 Hz, ArH), 7.36 (2H, d, J = 8.4 Hz, ArH), 6.91 (1H, br s, NH), 3.73-3.64 (4H, 2 x OCH_2), 3.50 (2H, t, J = 5.9 Hz, CH_2N), 2.57 (2H, t, J = 5.9 Hz, NCH_2), 2.53-2.43 (4H, m, 2 x NCH_2); **^{13}C NMR** (100 MHz, $CDCl_3$) δ*:* 166.3, 137.5, 132.9, 128.7, 128.3, 66.8, 56.8, 53.3, 36.1; **MS (ESI) m/z** 267 $[M-H]^-$.

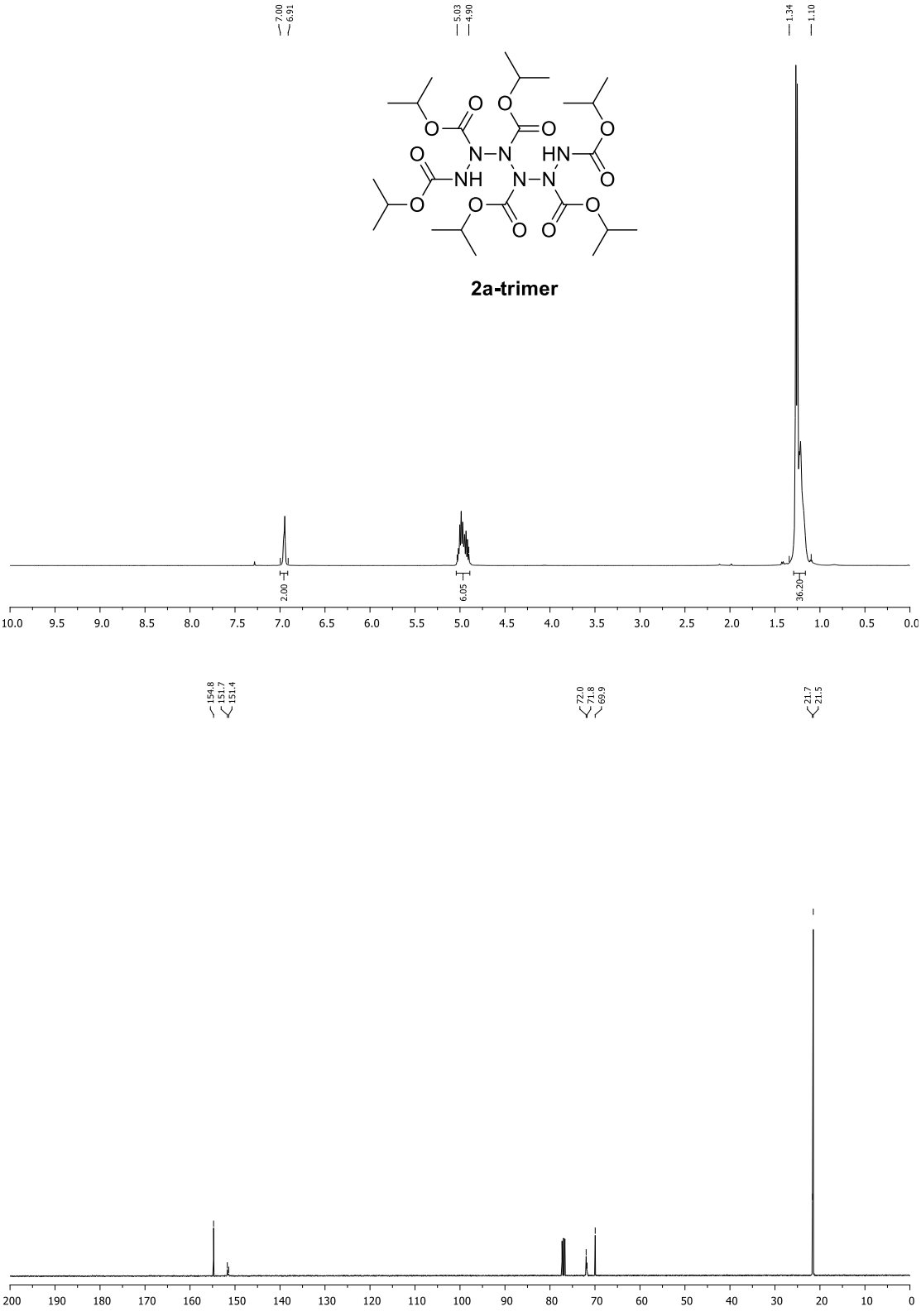
Oligomer Formation by Direct Irradiation of DIAD on Water



In a test tube, diisopropyl azodicarboxylate (**2a**) (101 mg, 0.50 mmol) and H_2O (2 mL) were added consecutively. The test tube was left stirring under Kessil lamp irradiation (330 nm) for 80 min. After reaction completion, determined by TLC, the reaction mixture was concentrated *in vacuo*. After column chromatography, several products were isolated. Among them, we managed to isolate in a pure form, 2a-trimer as the major product (44 mg, 0.07 mmol, 42% yield) and the 2a-dimer as the second major product (22 mg, 0.05 mmol, 20% yield).

Major product, **2a-trimer**:

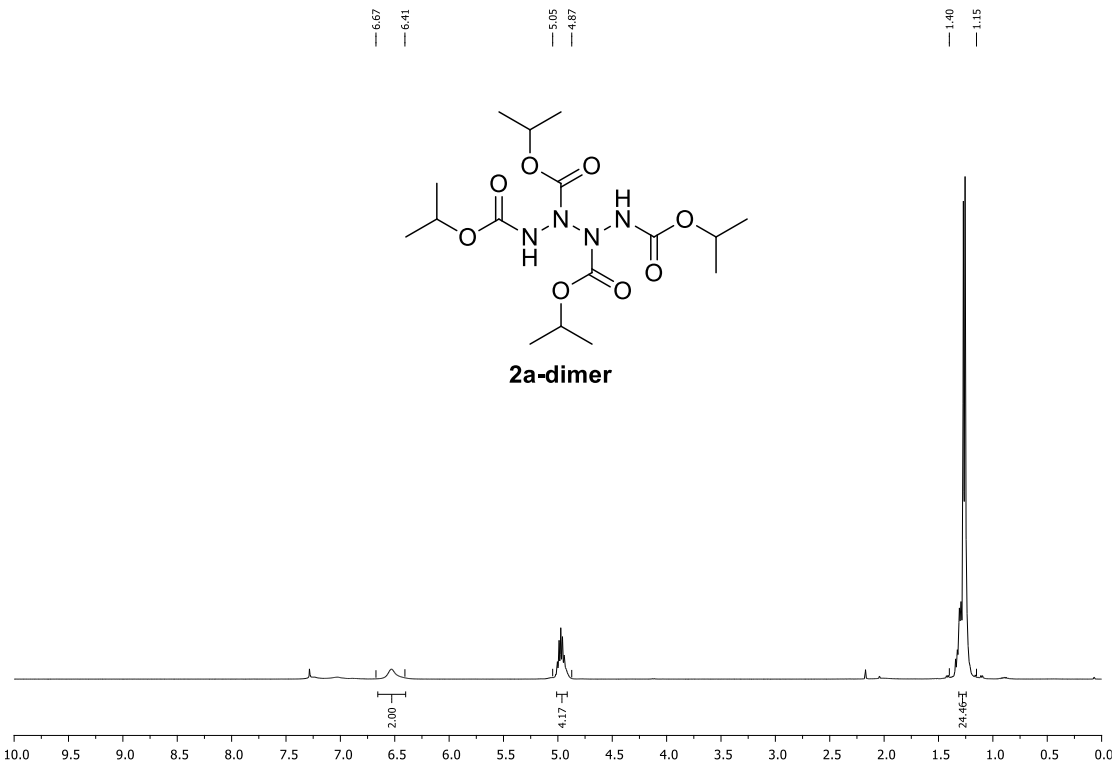
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.00-6.91 (2H, br s, 2 x NH), 5.03-4.90 (6H, m, 6 x OCH), 1.34-1.10 (36H, m, 12 x CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 154.8, 151.7, 151.4, 72.0, 71.8, 69.9, 21.7, 21.5. **HRMS** exact mass calculated for $[M+K]^+$ ($C_{24}H_{44}KN_6O_{12}^+$) requires *m/z* 647.2649, found m/z 647.2650.

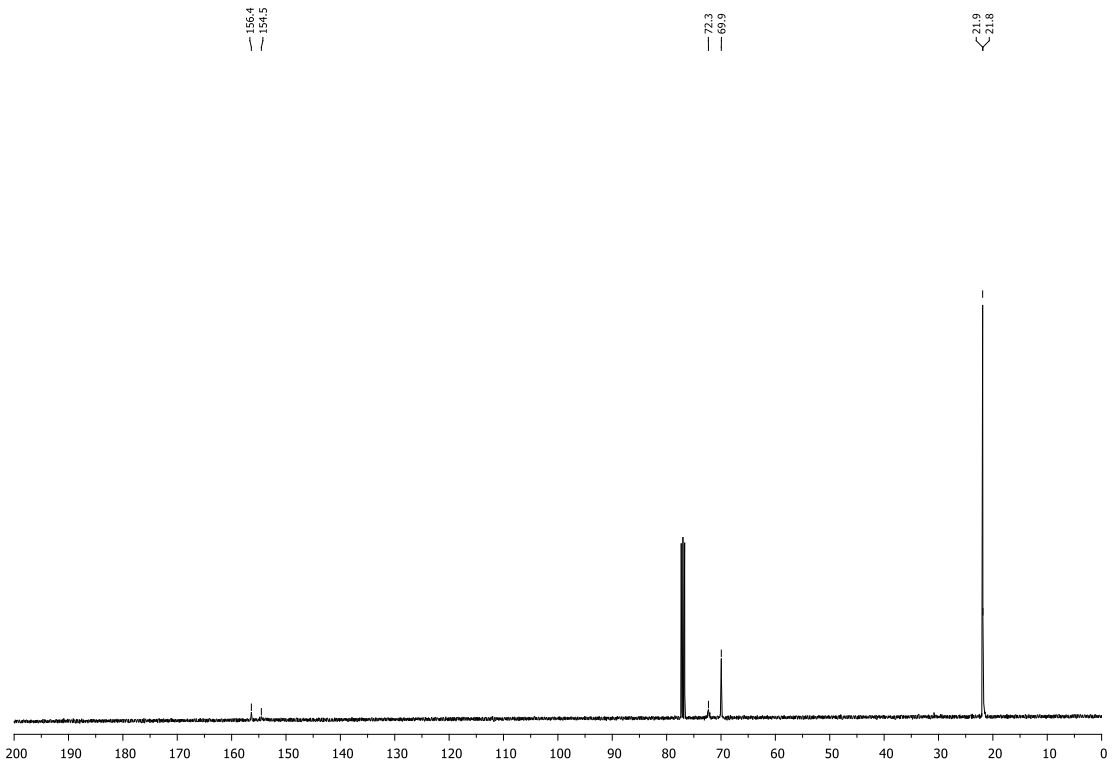


Second major product, **2a-dimer**:

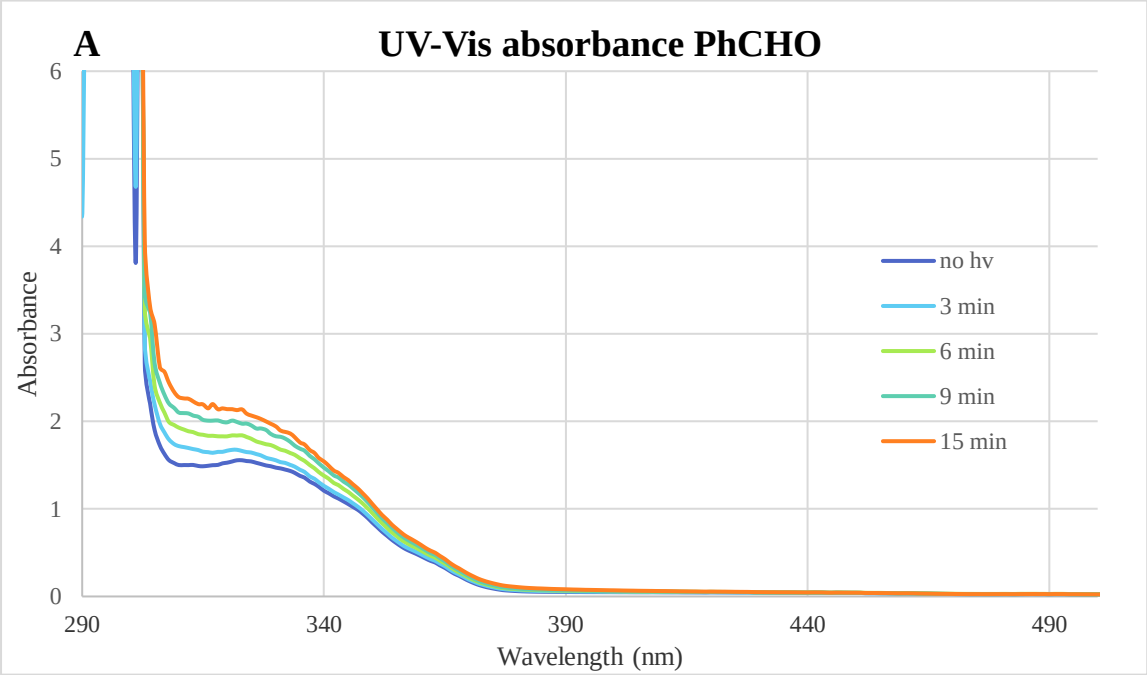
^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.67-6.41 (2H, br s, 2 x NH), 5.05-4.87 (4H, m, 4 x OCH), 1.40-1.15 (24H, m, 8 x CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 156.4, 154.5,

72.3, 69.9, 21.9, 21.8; **HRMS** exact mass calculated for $[M+K]^+$ ($C_{16}H_{30}N_4NaO_8^+$) requires *m/z* 429.1956, found m/z 429.1958.

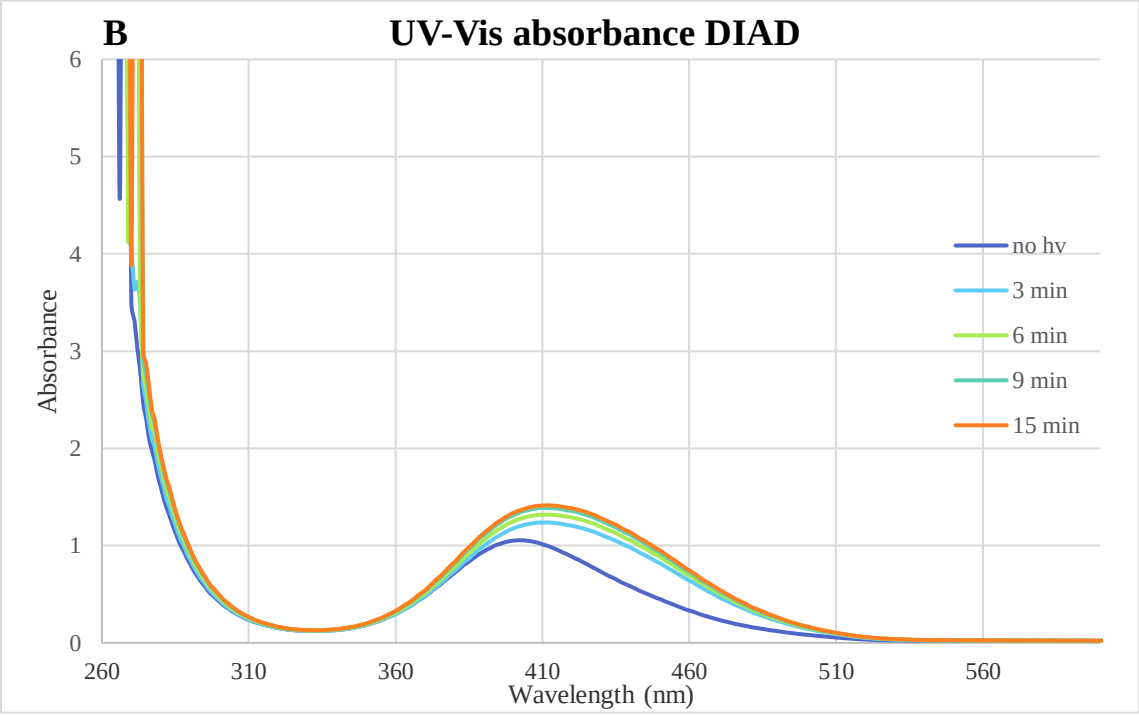




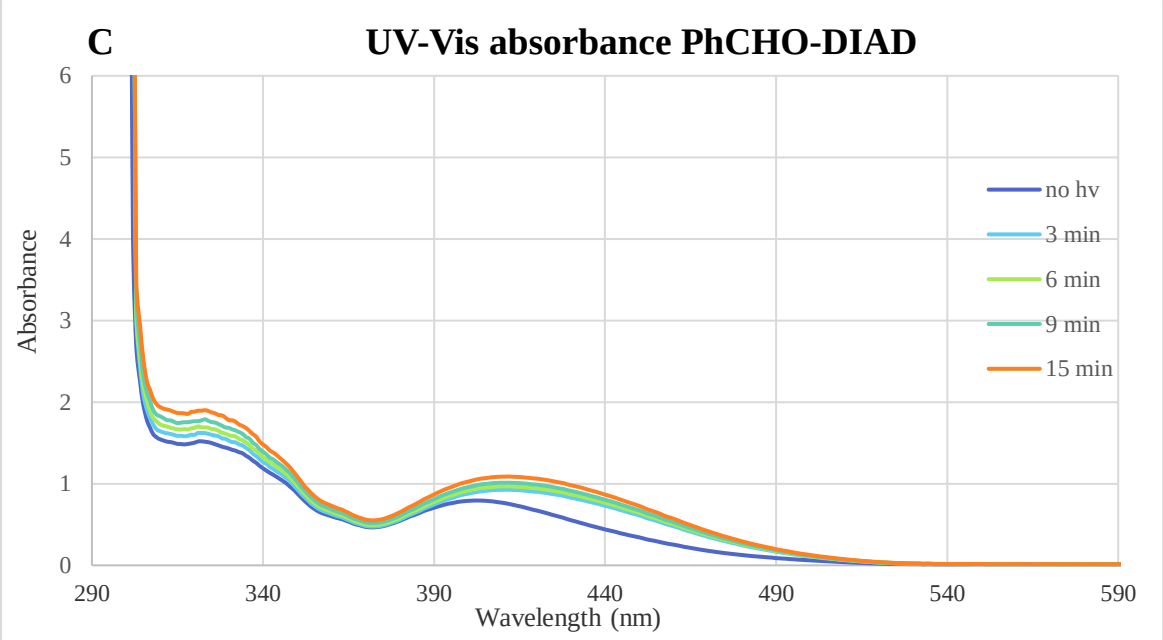
Mechanistic Investigations with UV-Vis Absorption Spectra



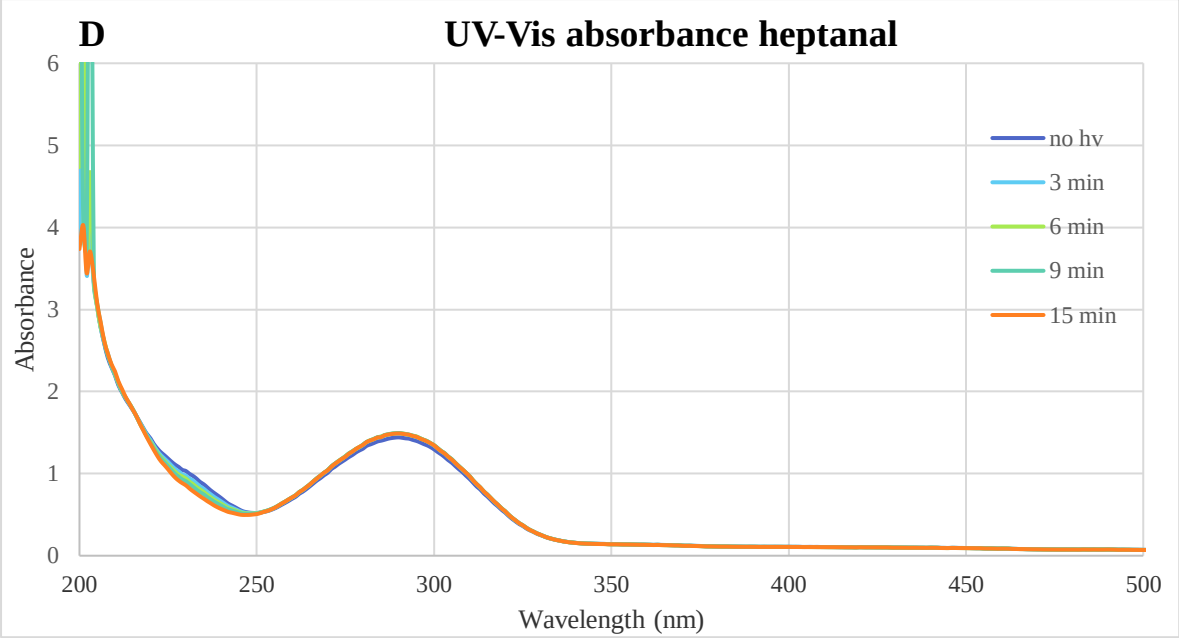
UV-Vis absorbance spectrum of benzaldehyde (**1m**) (0.06 M) in CH_3CN, after consecutive irradiation.



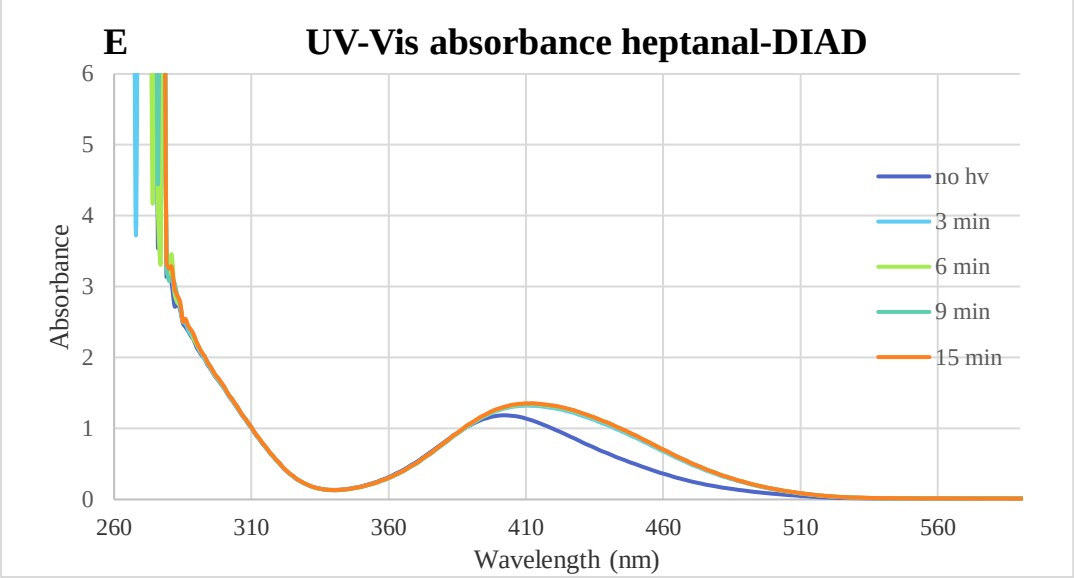
UV-Vis absorbance spectrum of DIAD (**2a**) (0.03 M) in CH_3CN, after consecutive irradiation.



UV-Vis absorbance of benzaldehyde (**1m**) (0.06M) - DIAD (**2a**) (0.03 M) mixture in CH_3CN, after consecutive irradiation.



UV-Vis absorbance of heptanal (**1a**) (0.06 M) in CH_3CN, after consecutive irradiation.



UV-Vis absorbance of heptanal (**1a**) (0.06M) - DIAD (**2a**) (0.03M) mixture in CH_3CN, after consecutive irradiation.

References

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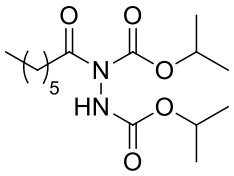
NMR Spectra



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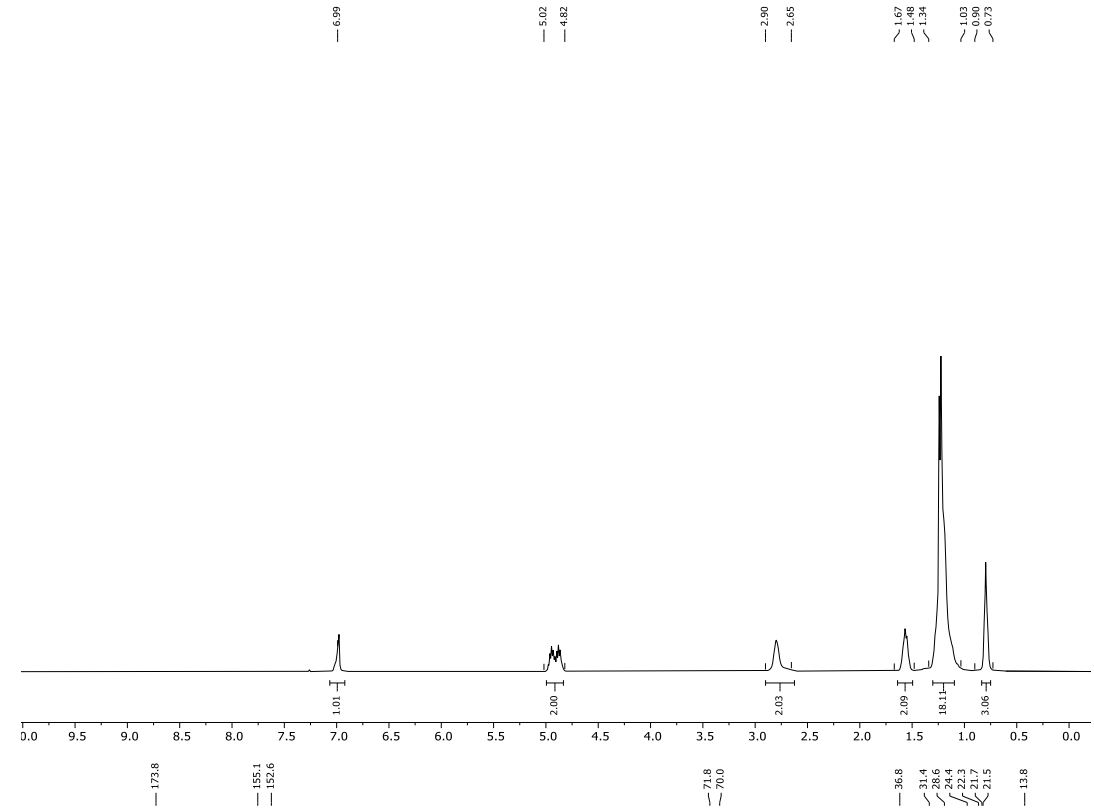

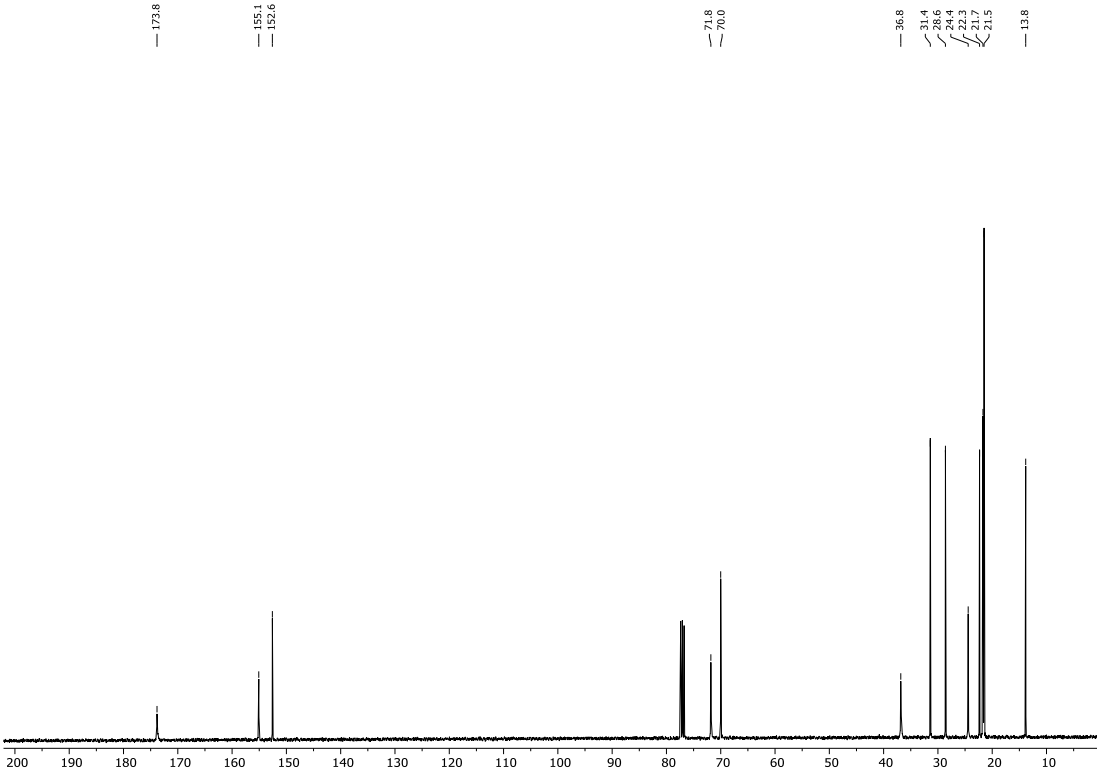

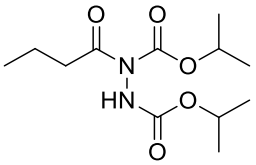

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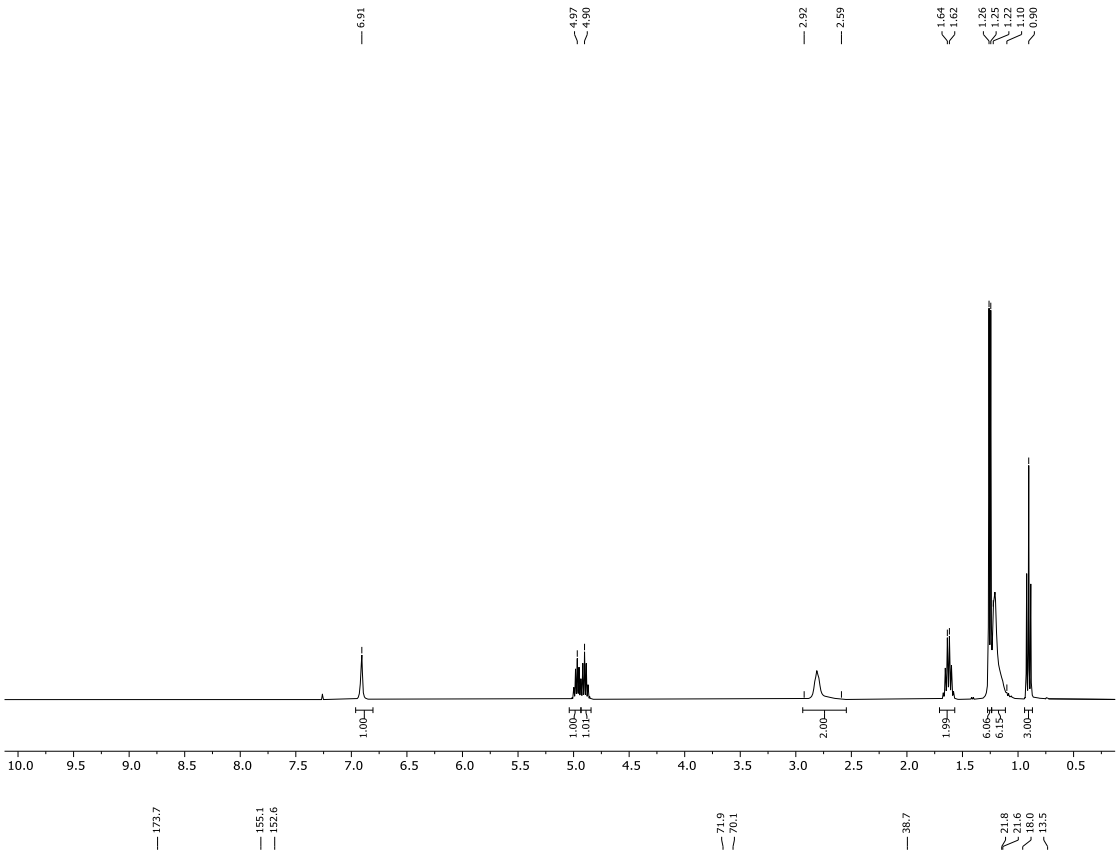
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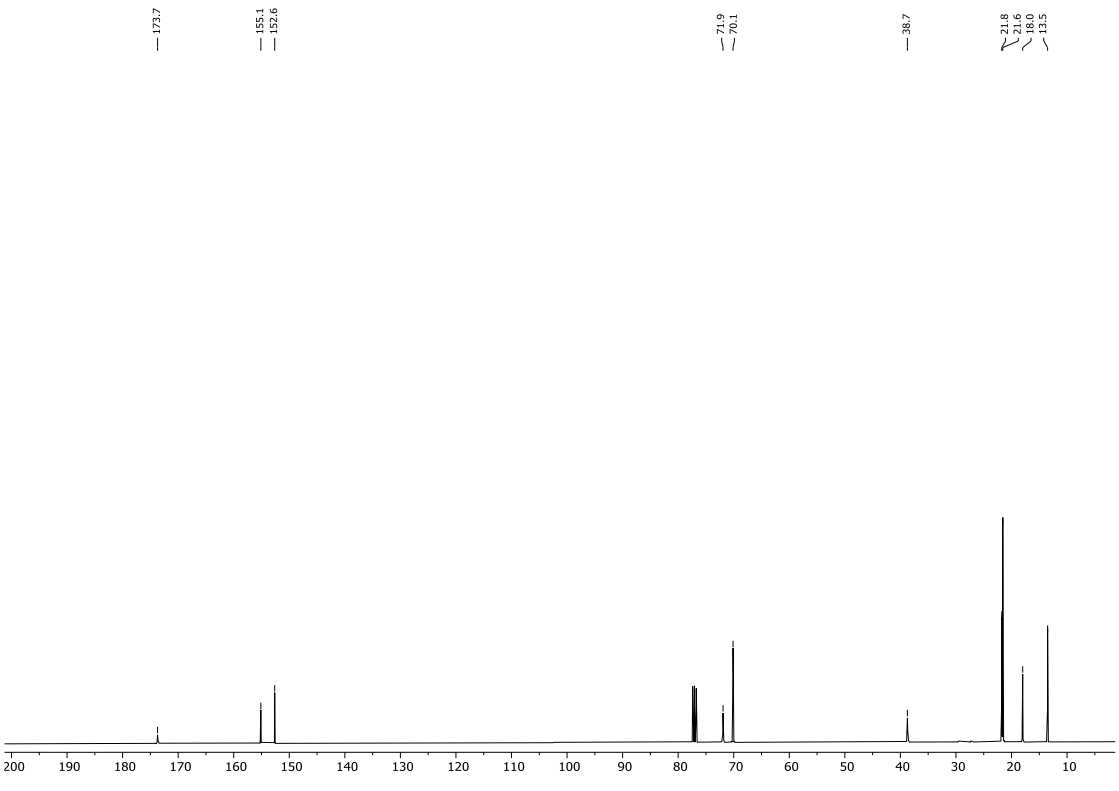
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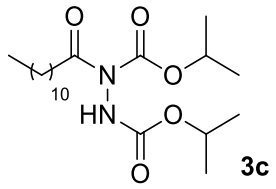
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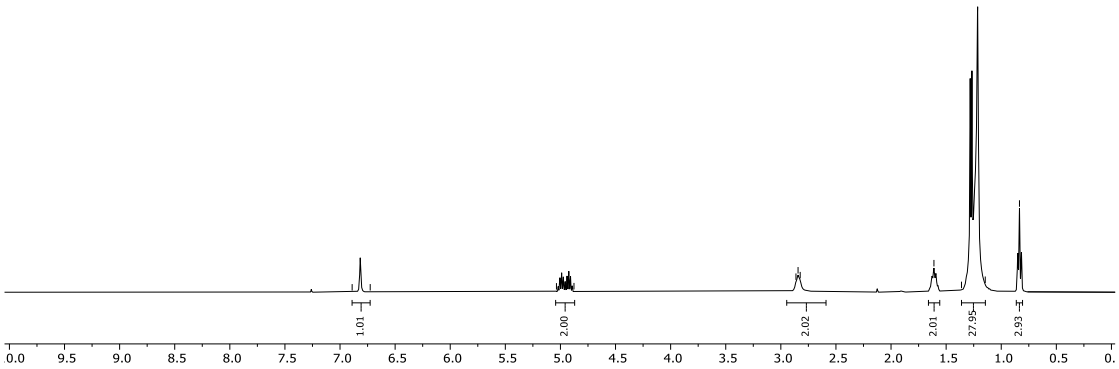
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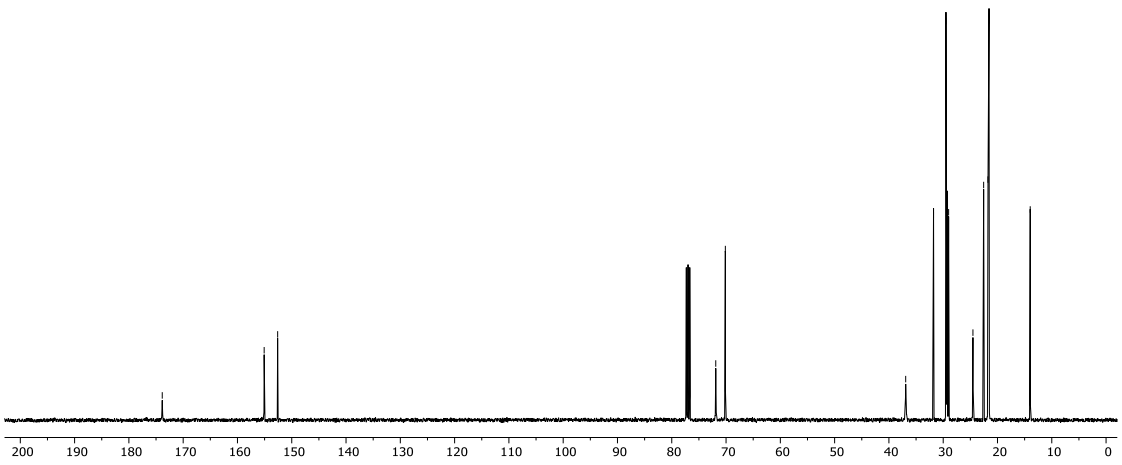
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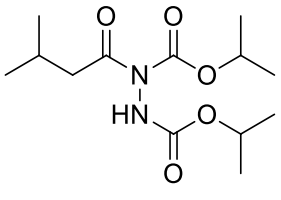

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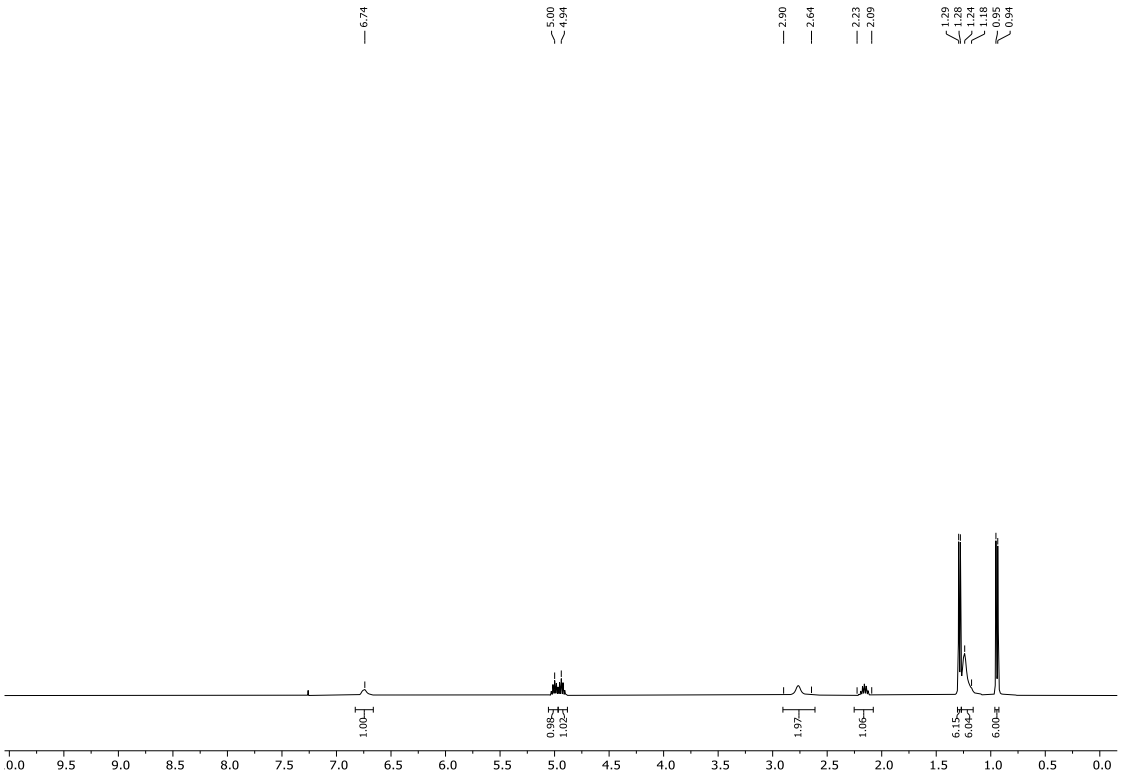
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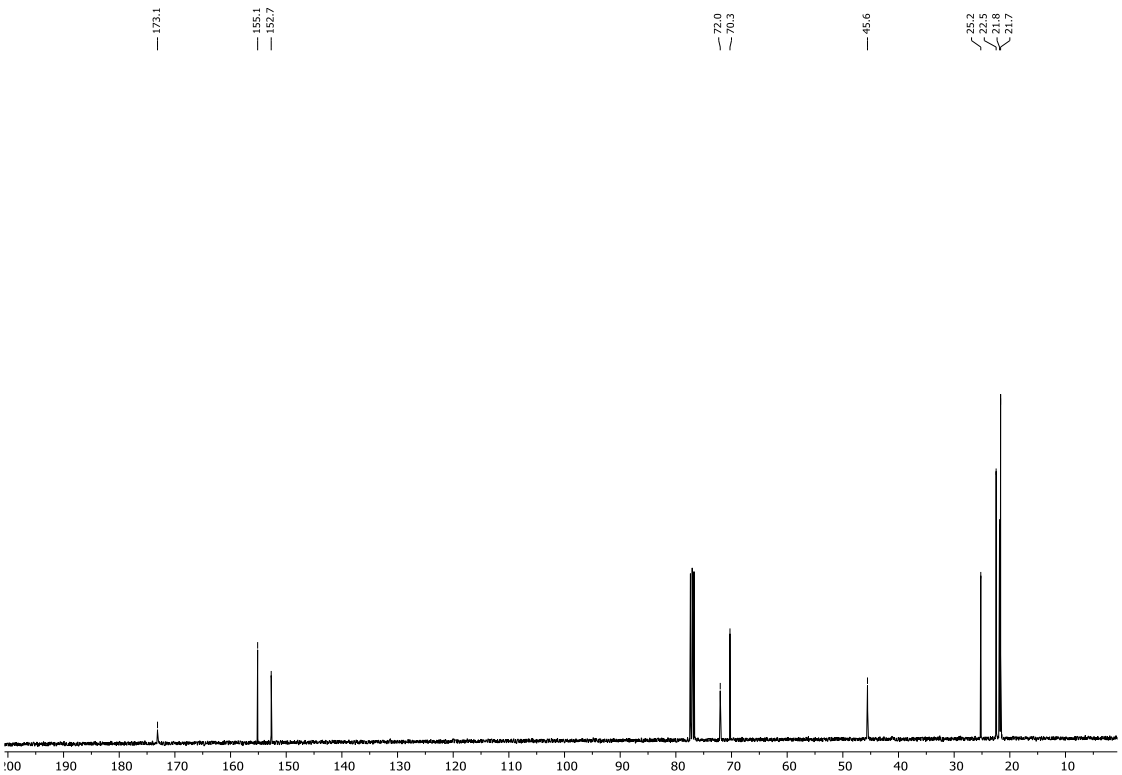
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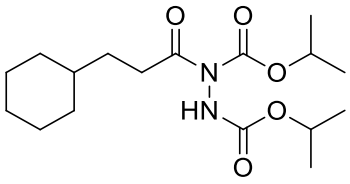

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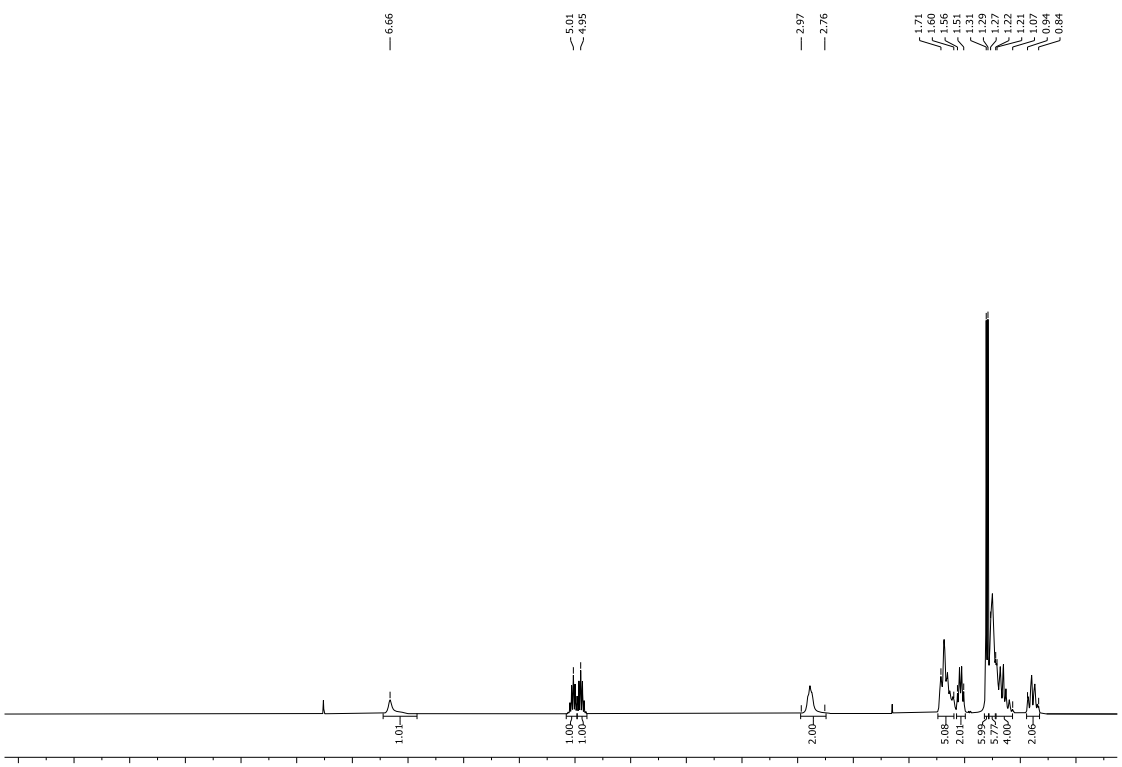
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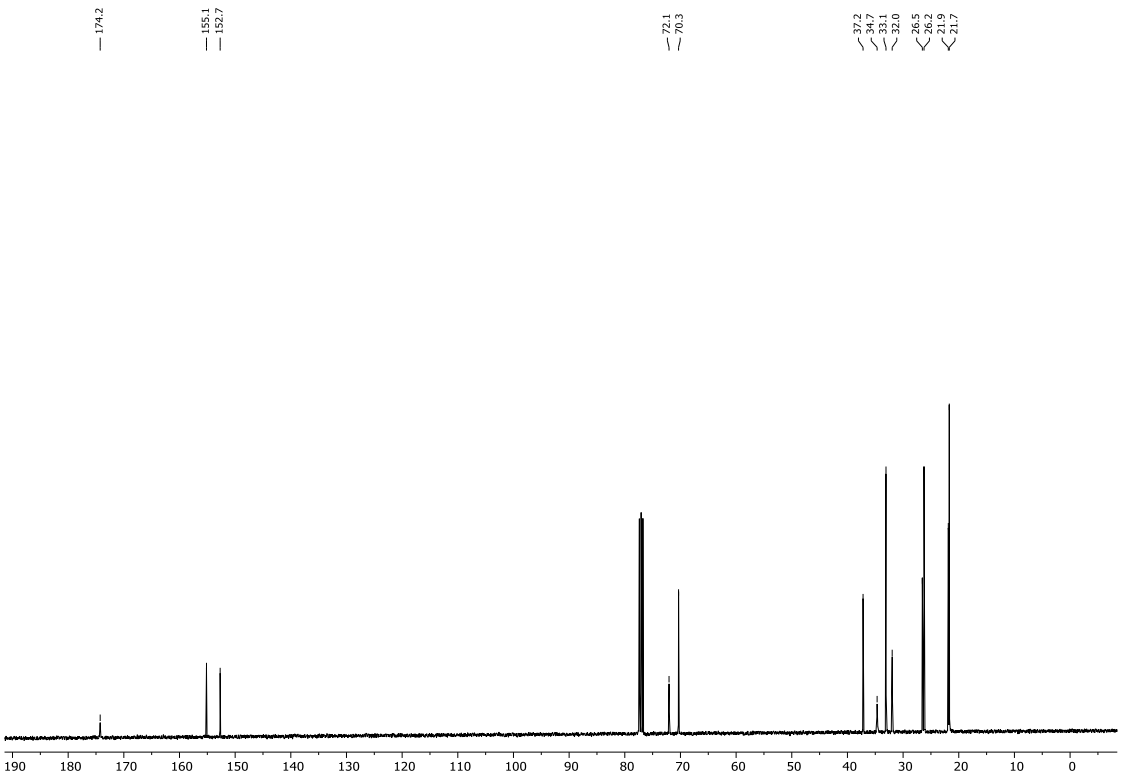
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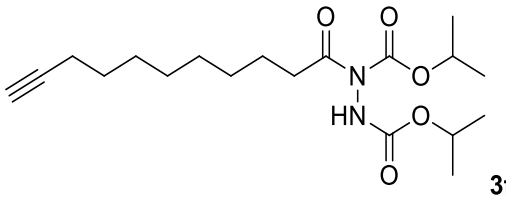
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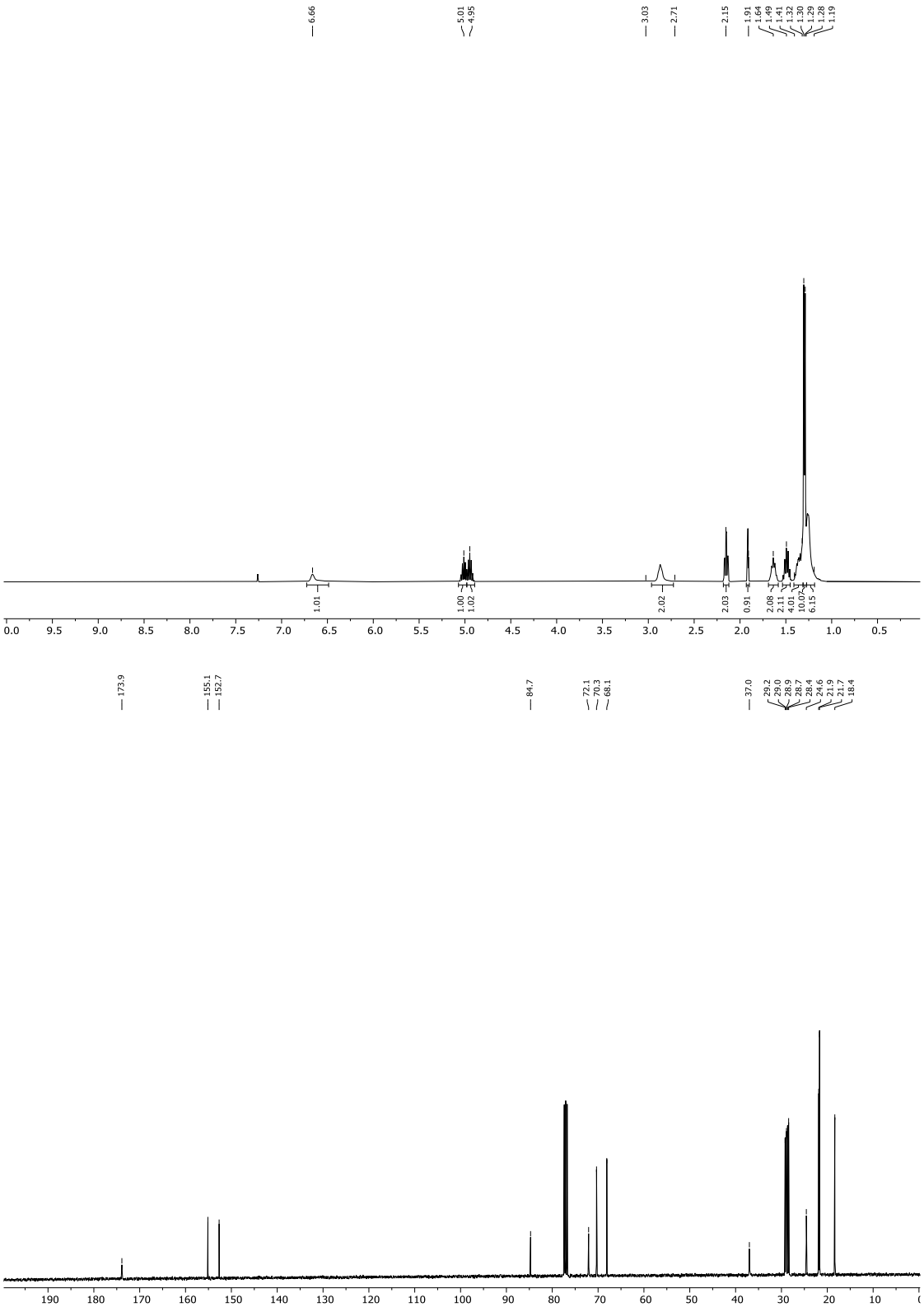
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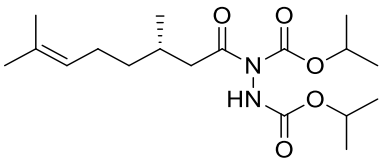
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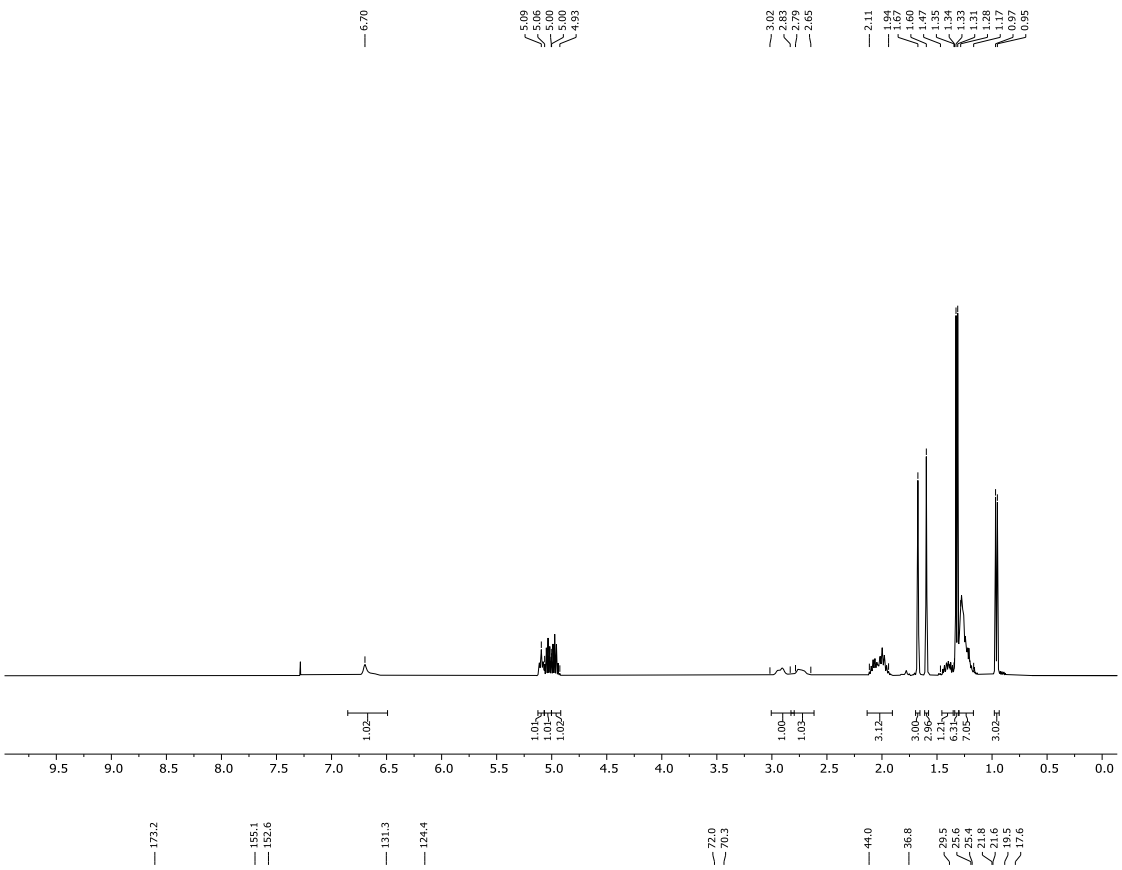
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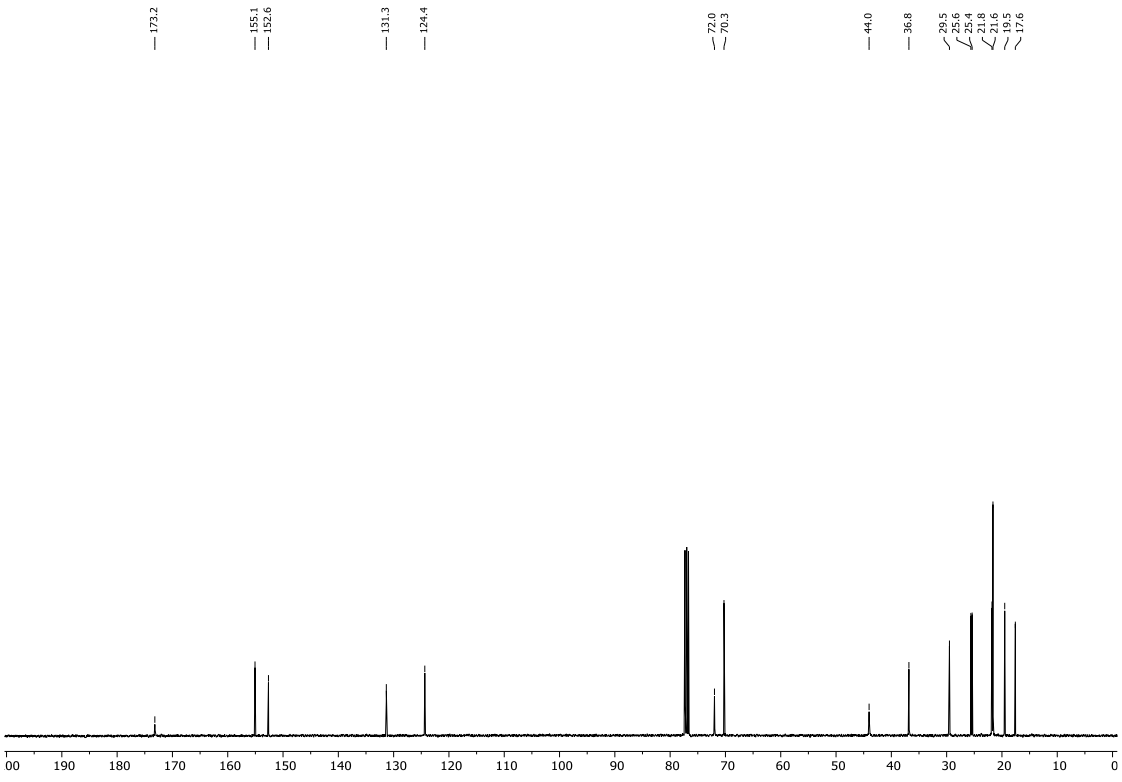
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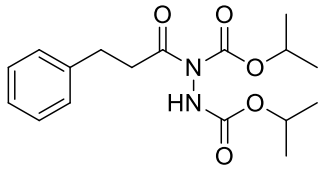

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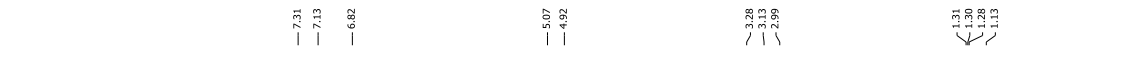
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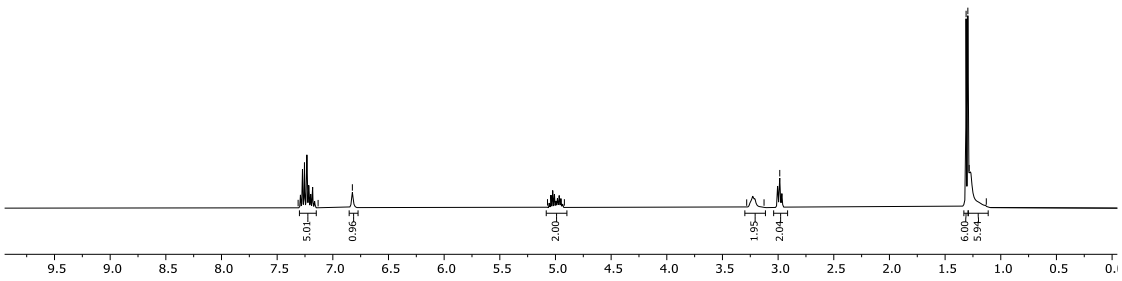
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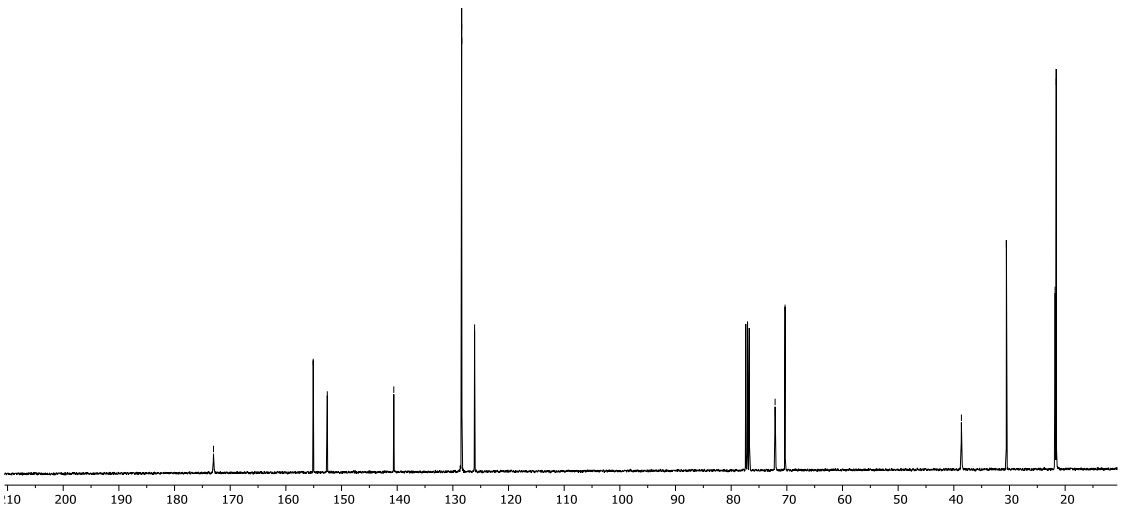

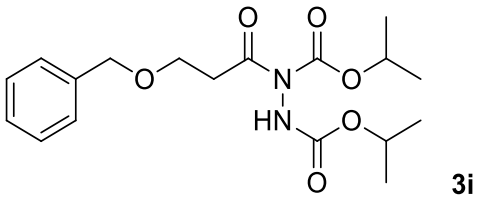

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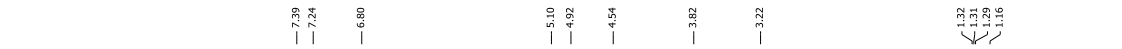
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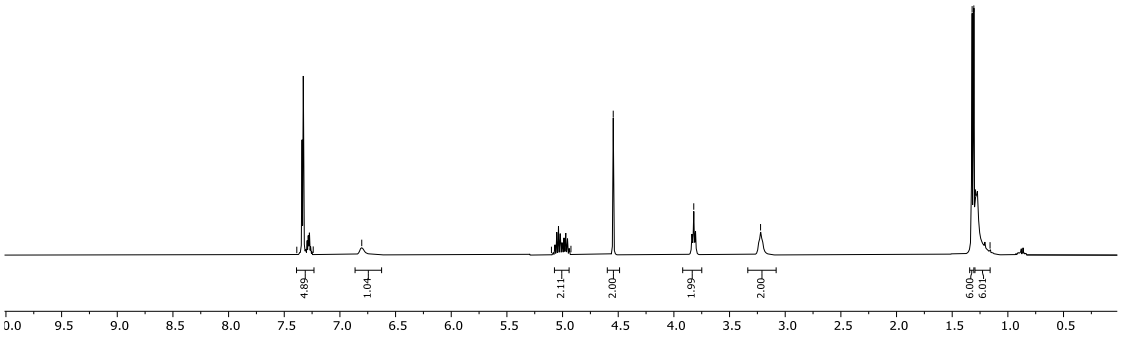
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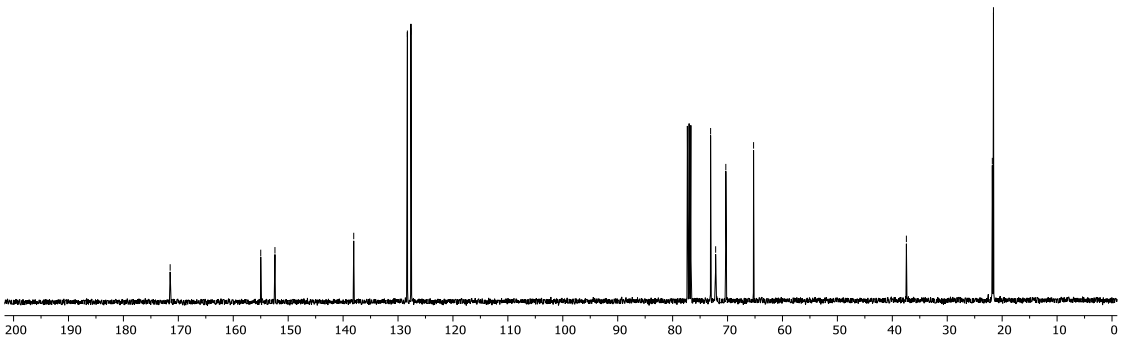

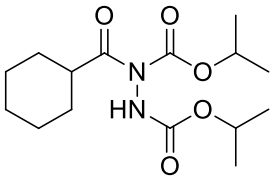

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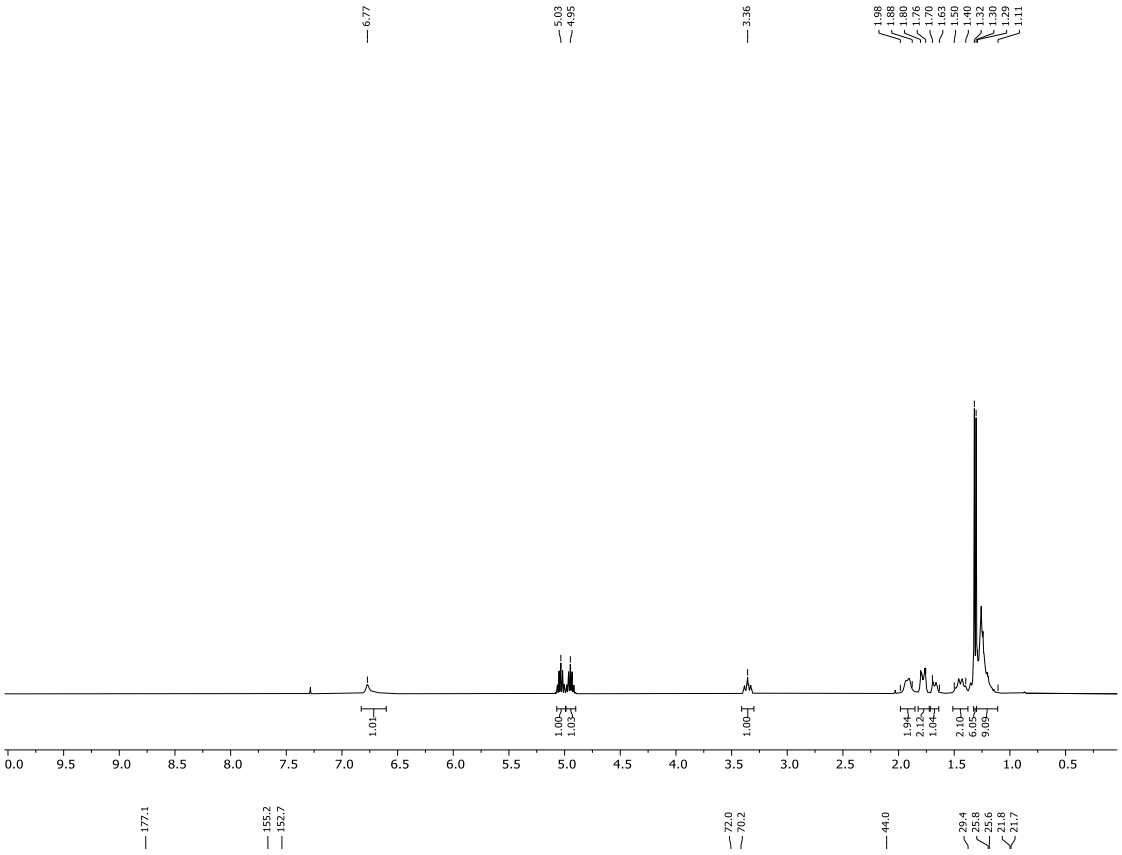
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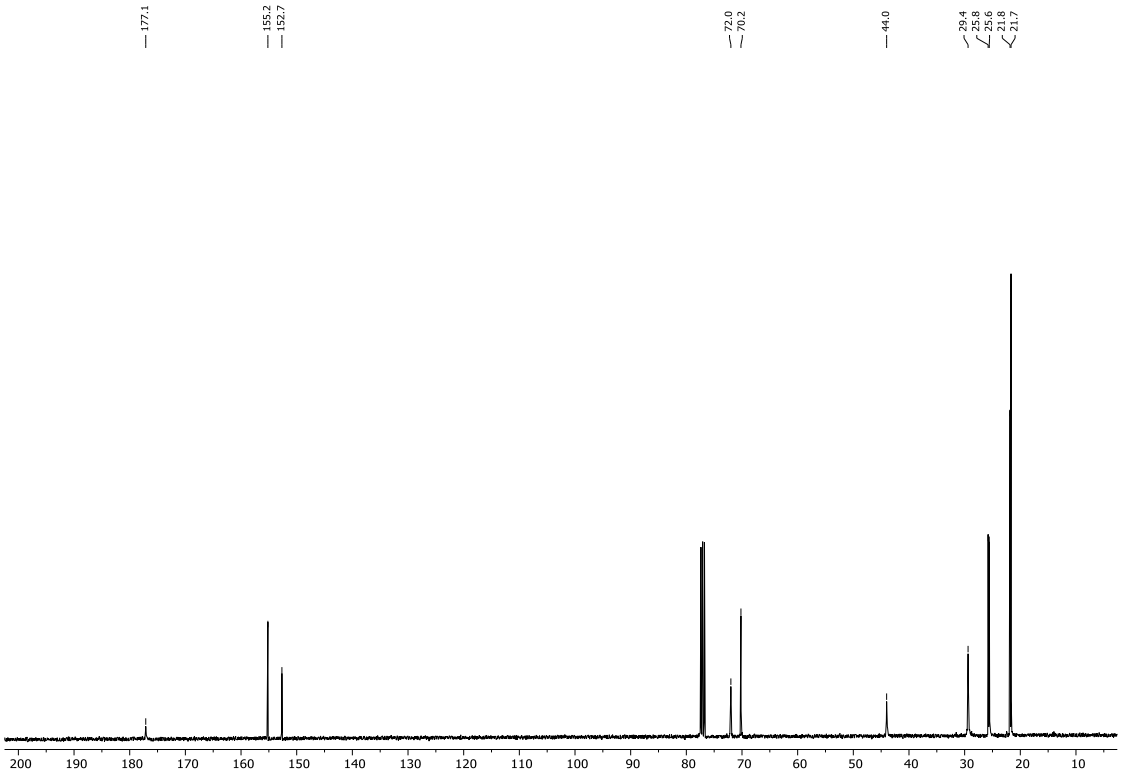
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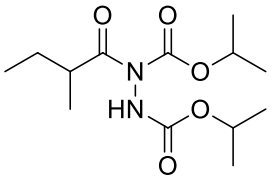

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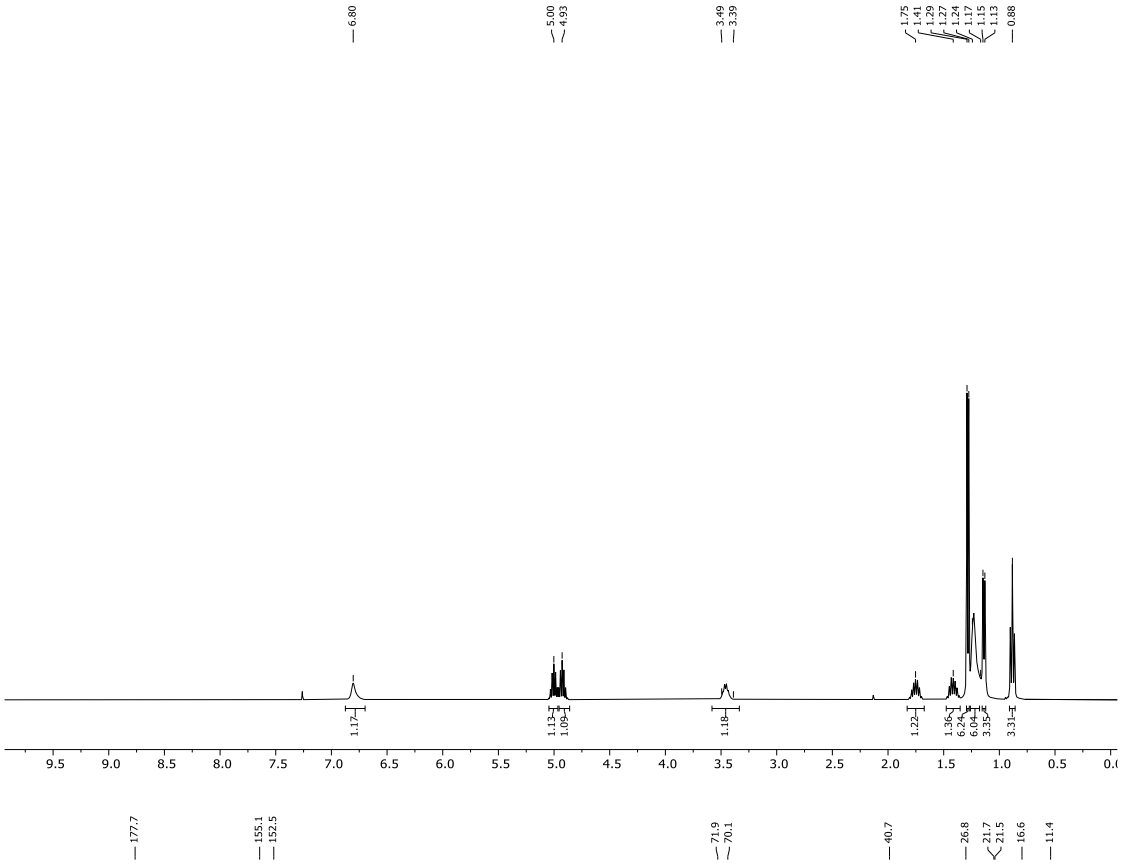

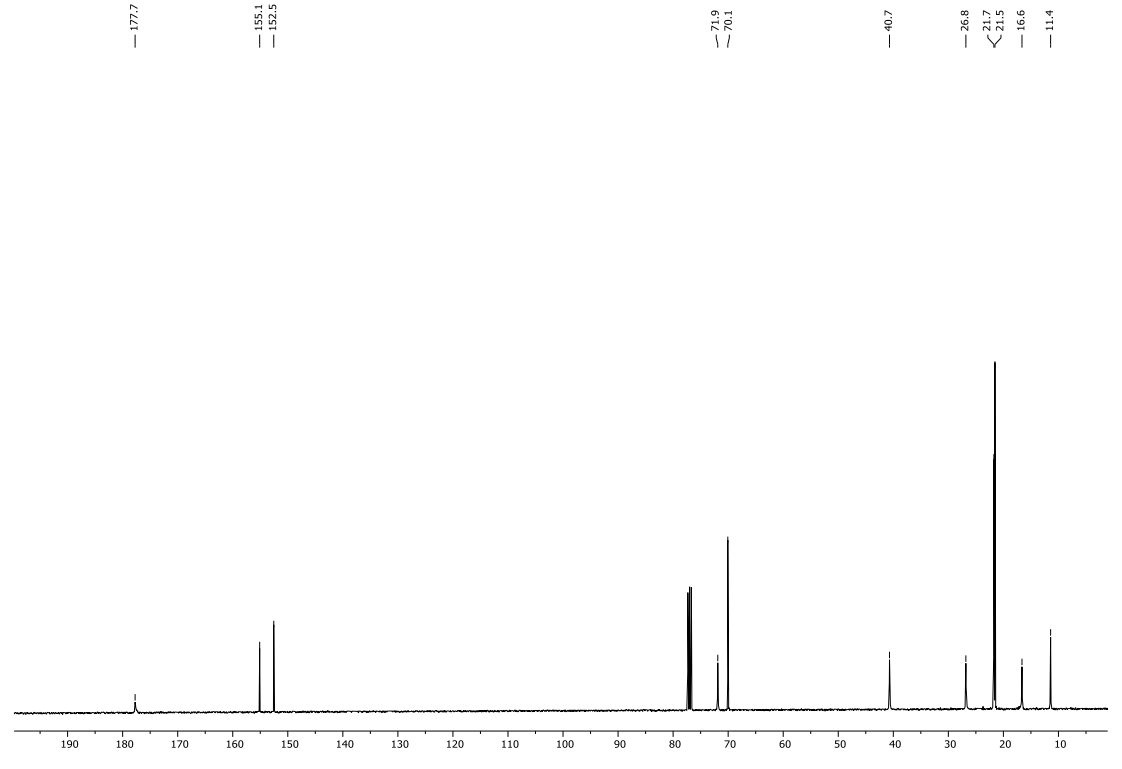

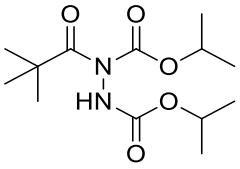

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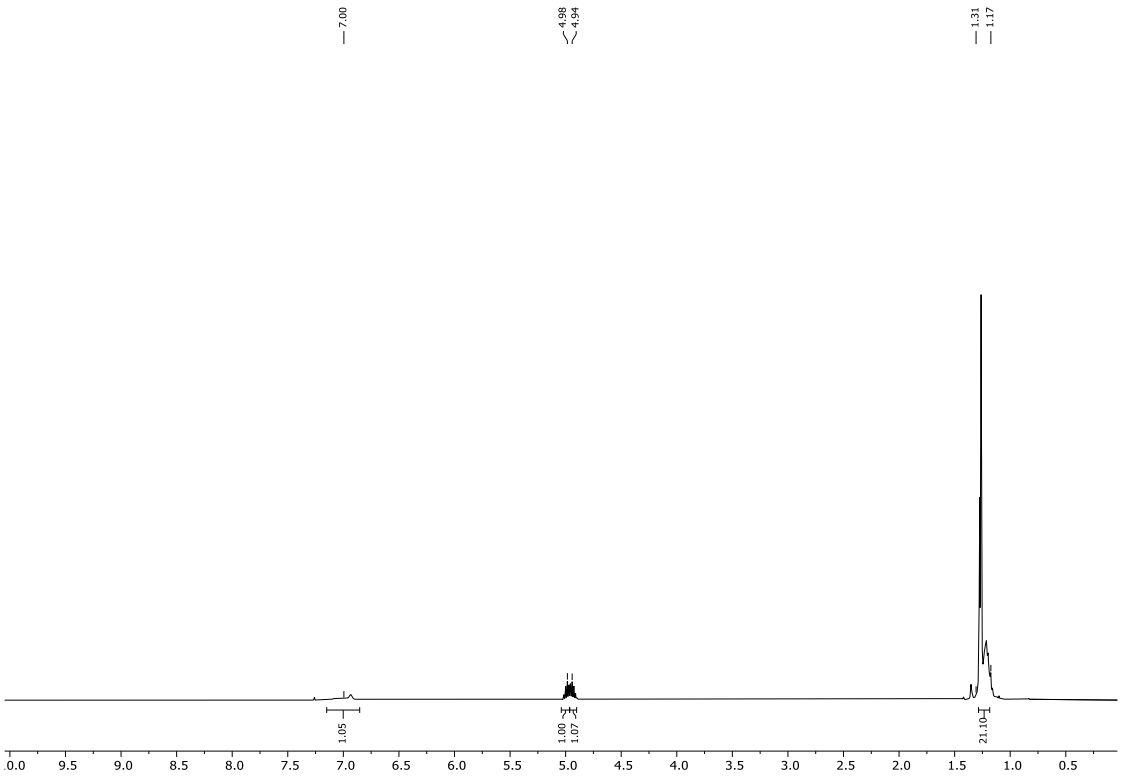
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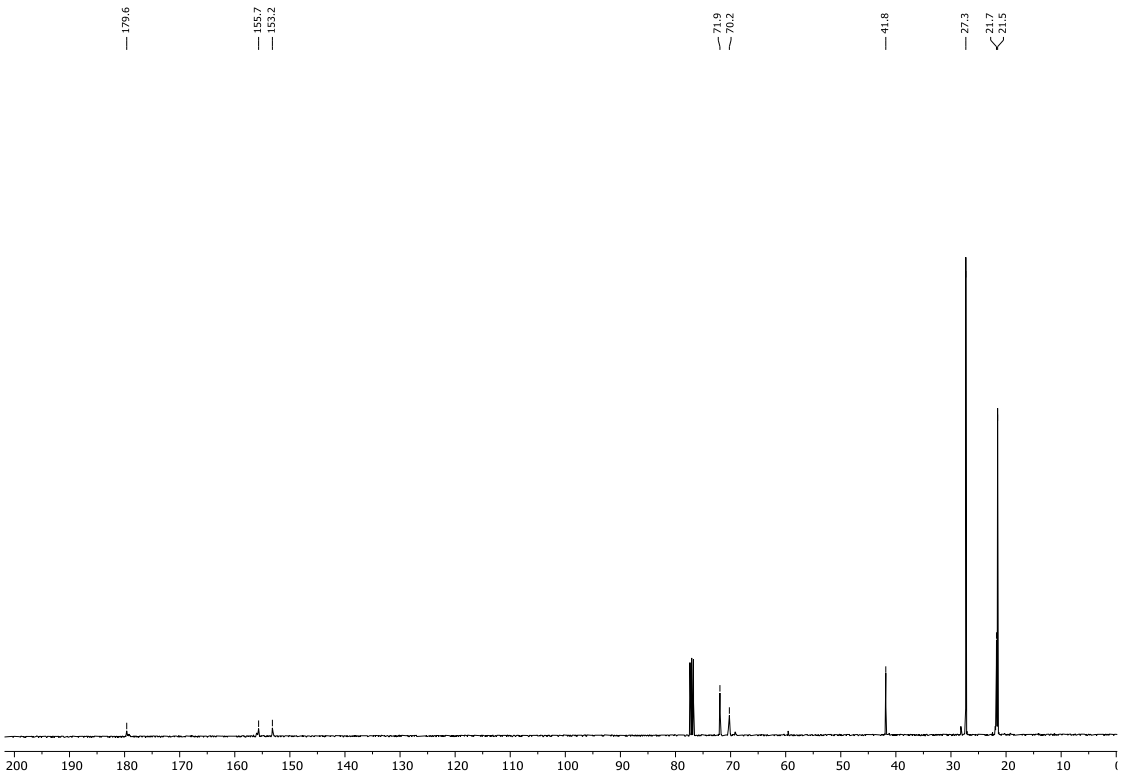
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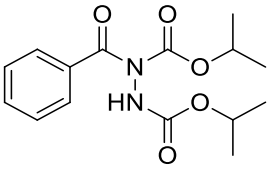
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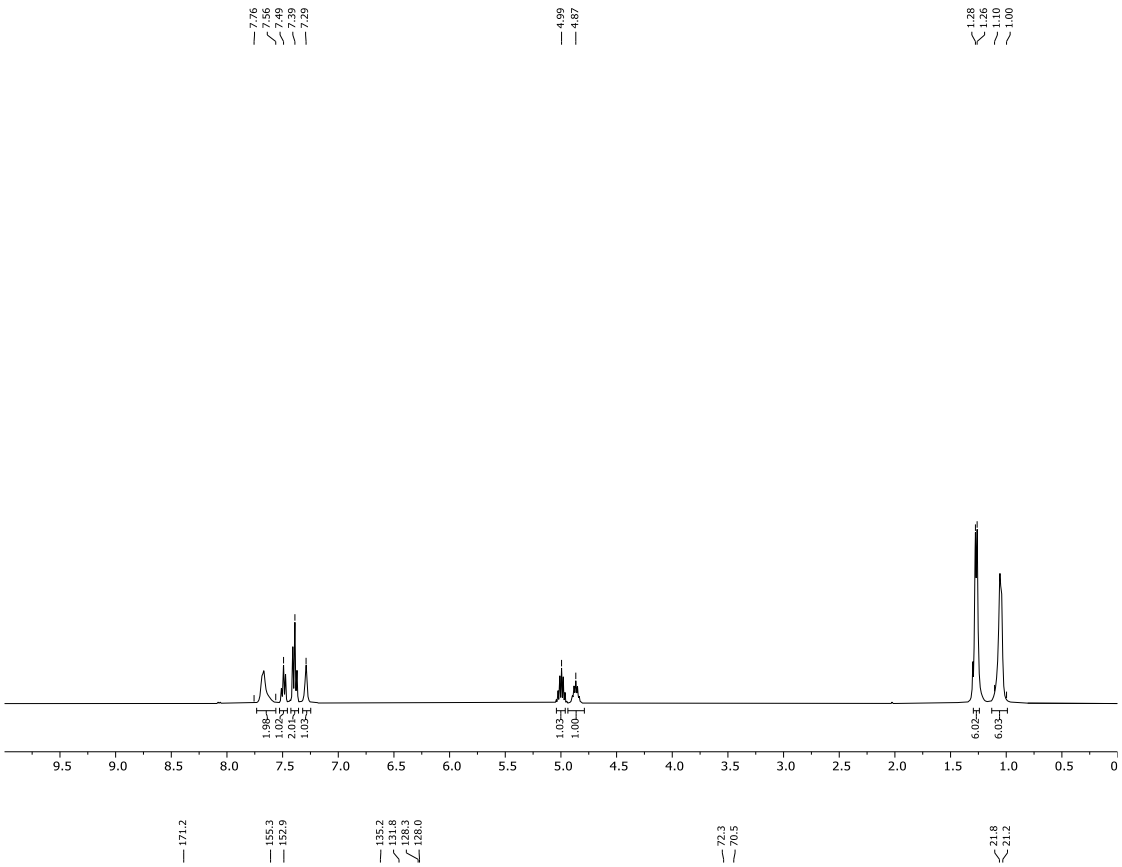
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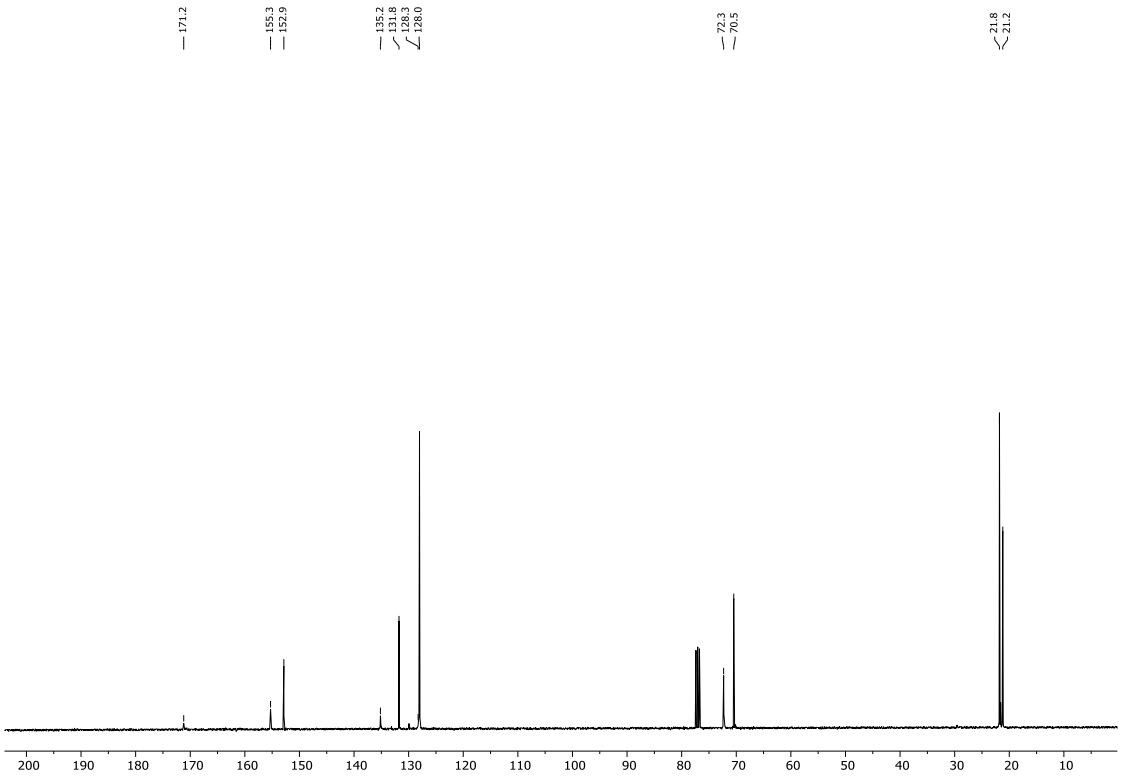
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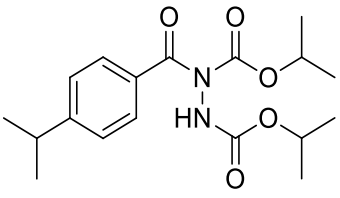
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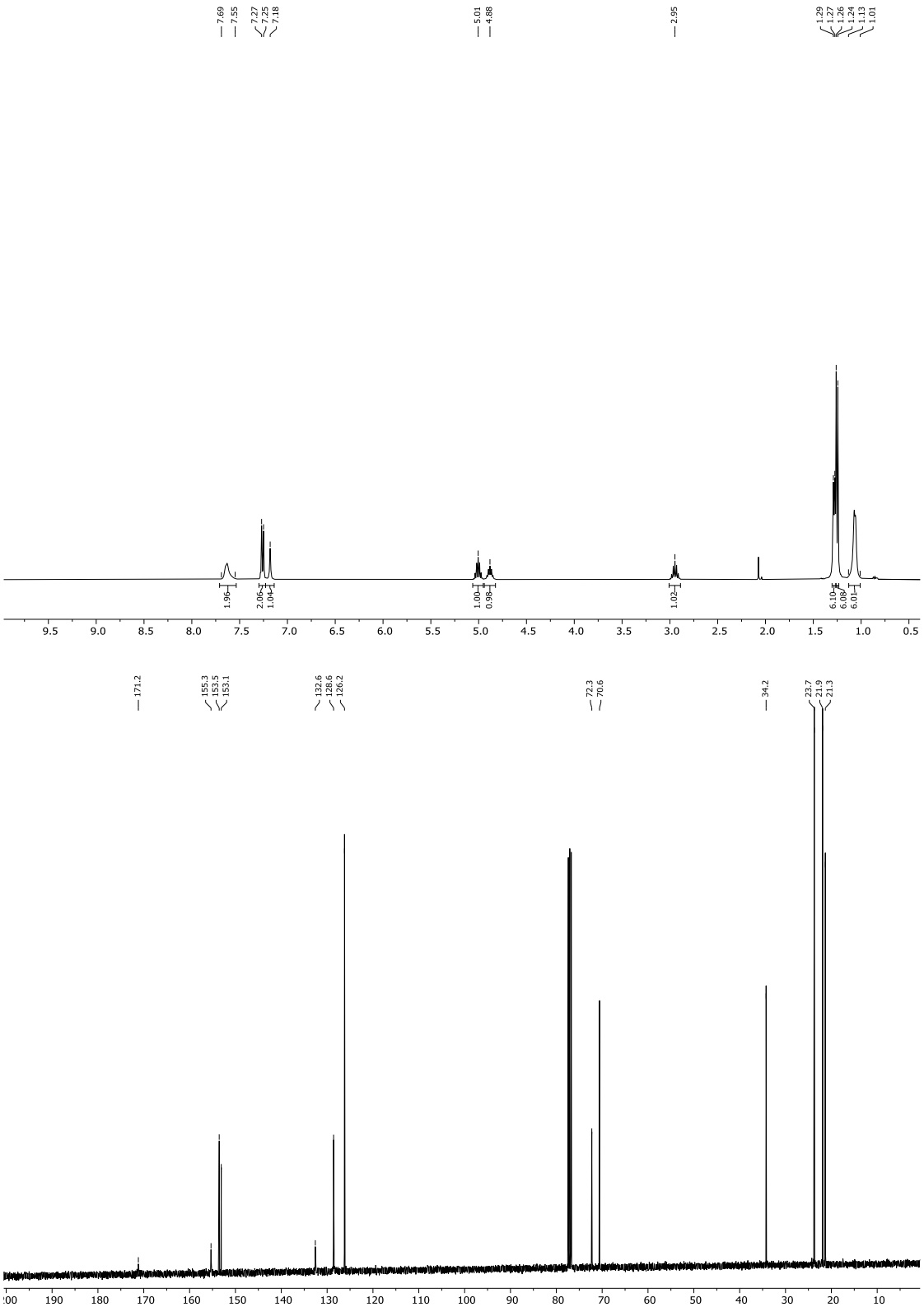
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2.06
1.04
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6.08
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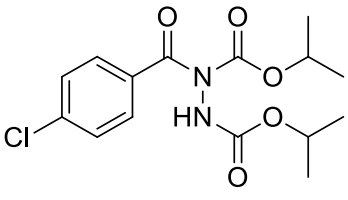
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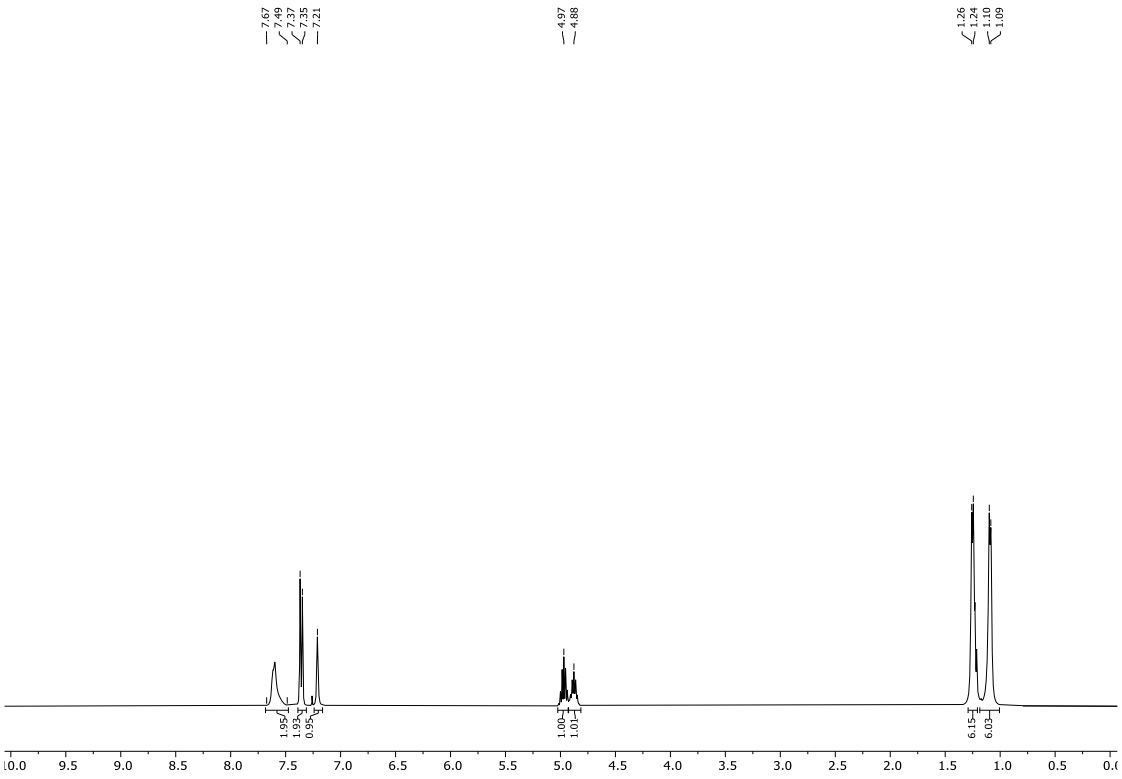
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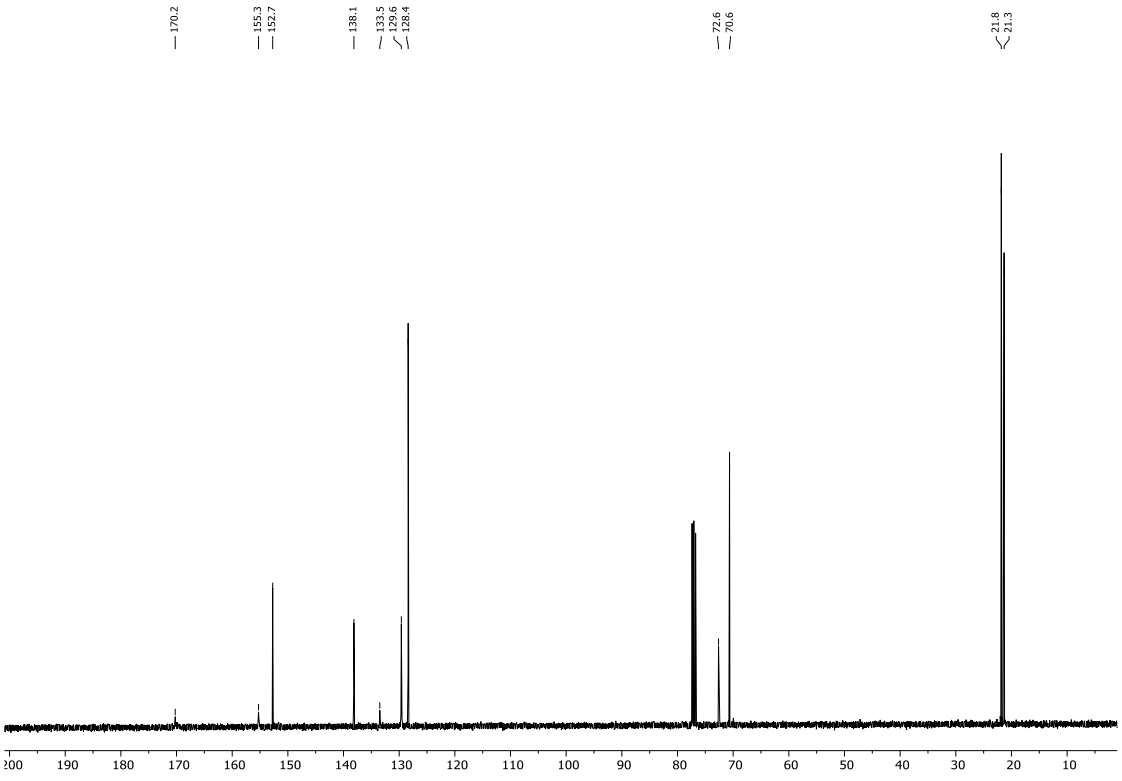
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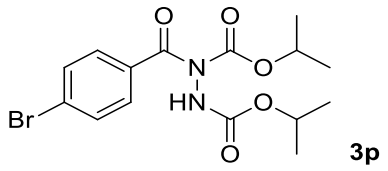
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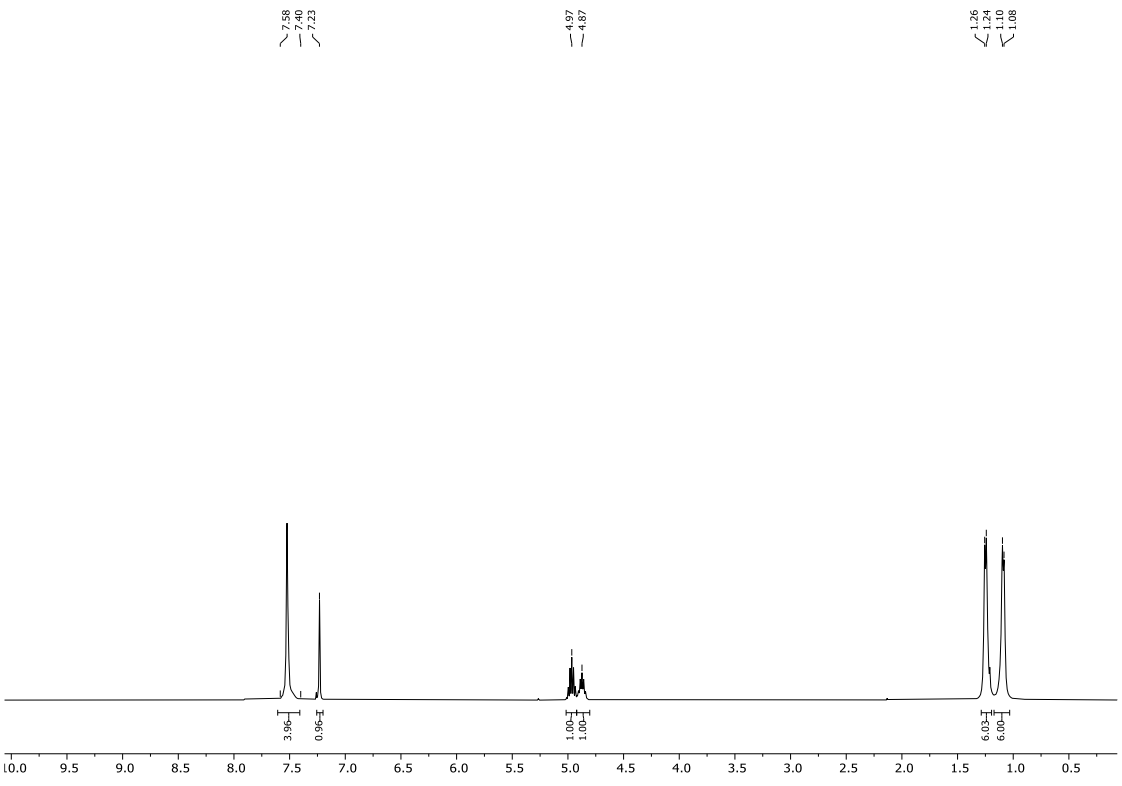
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9.5
9.0
8.5
8.0
7.5
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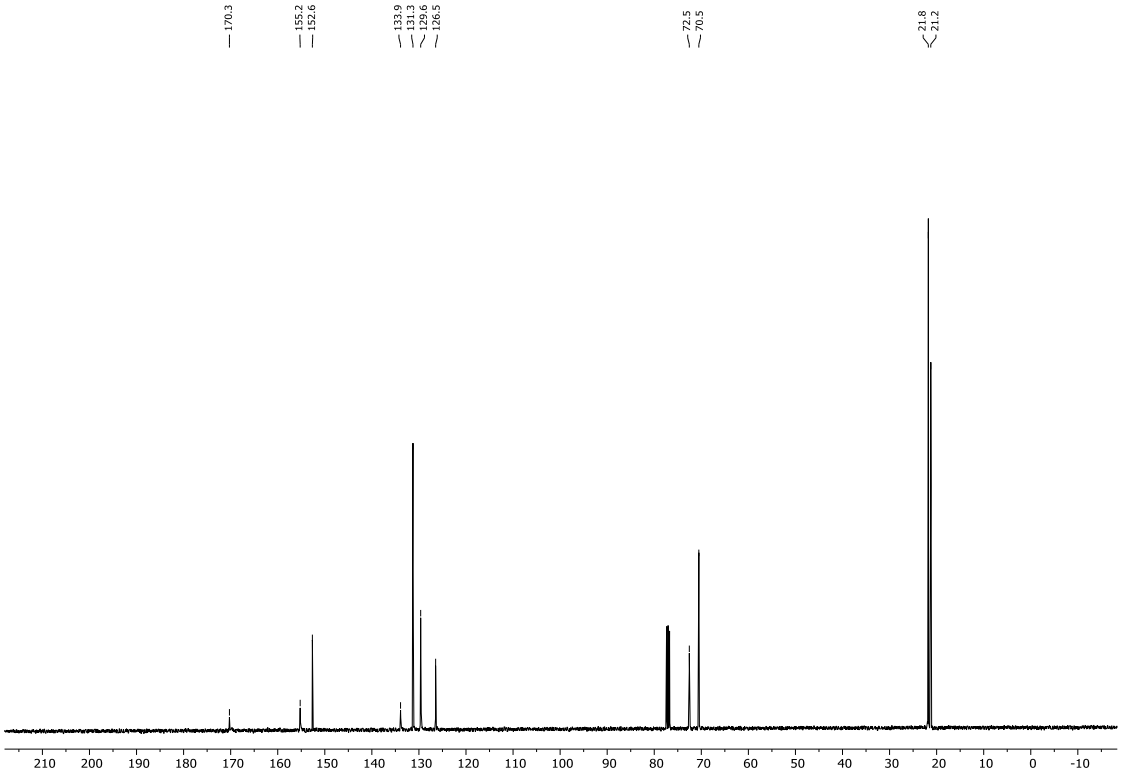
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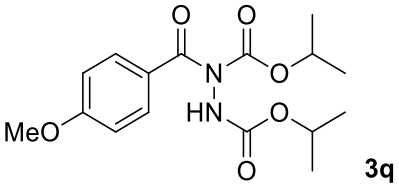
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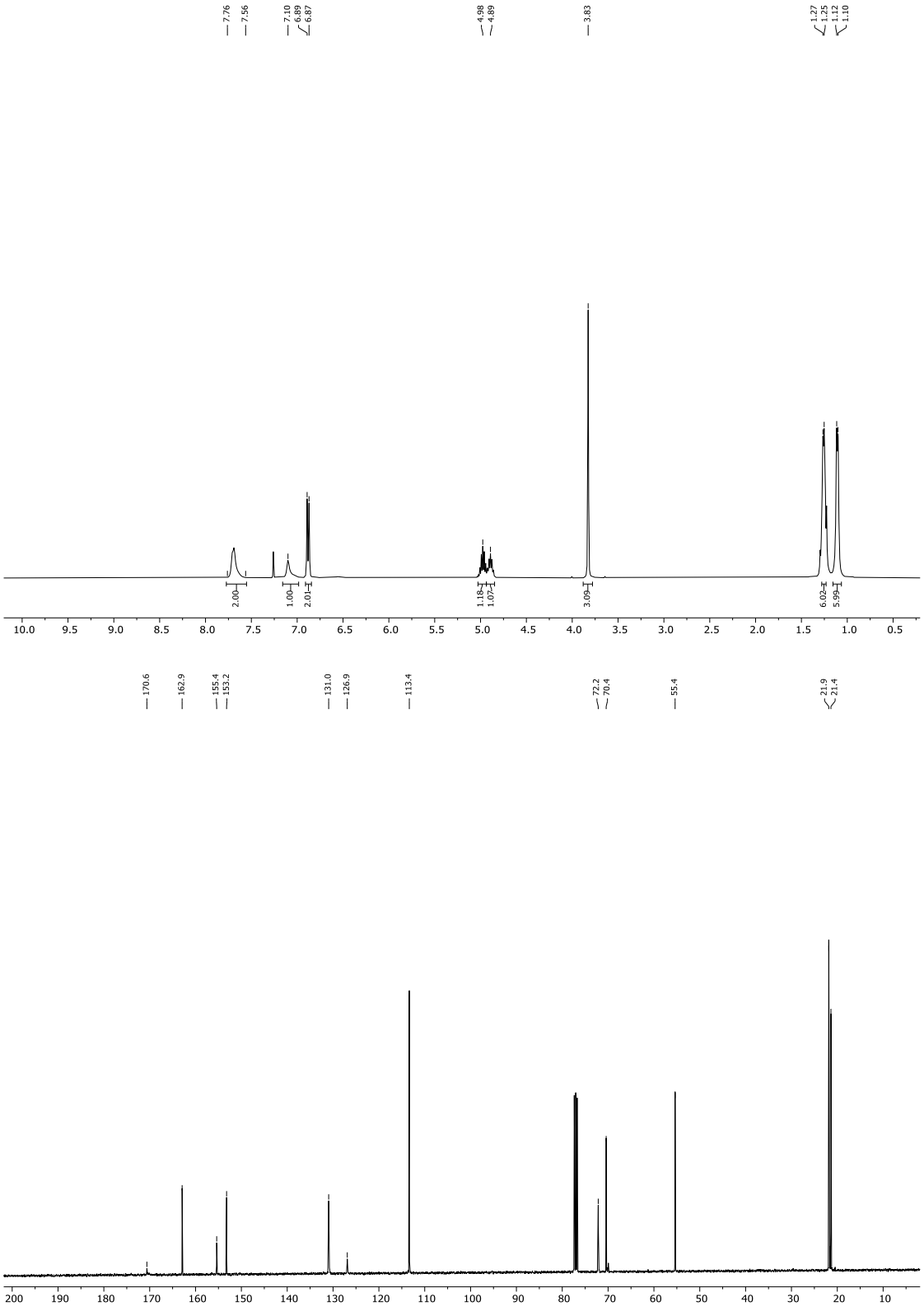
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1.07
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4.0
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3.0
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1.0
0.5
170.6
162.9
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153.2
131.0
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113.4
72.2
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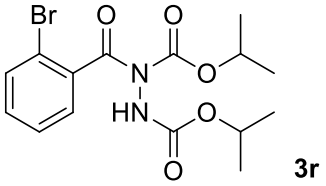
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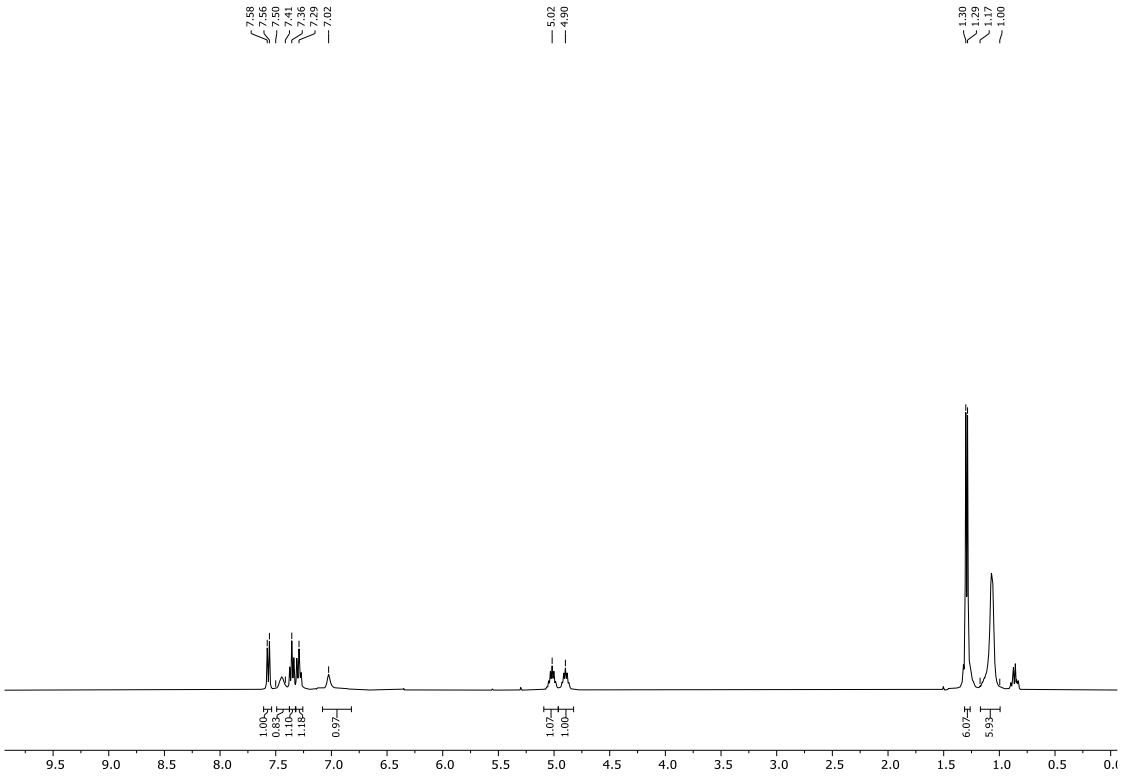
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1.00
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1.18
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1.07
1.00
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6.5
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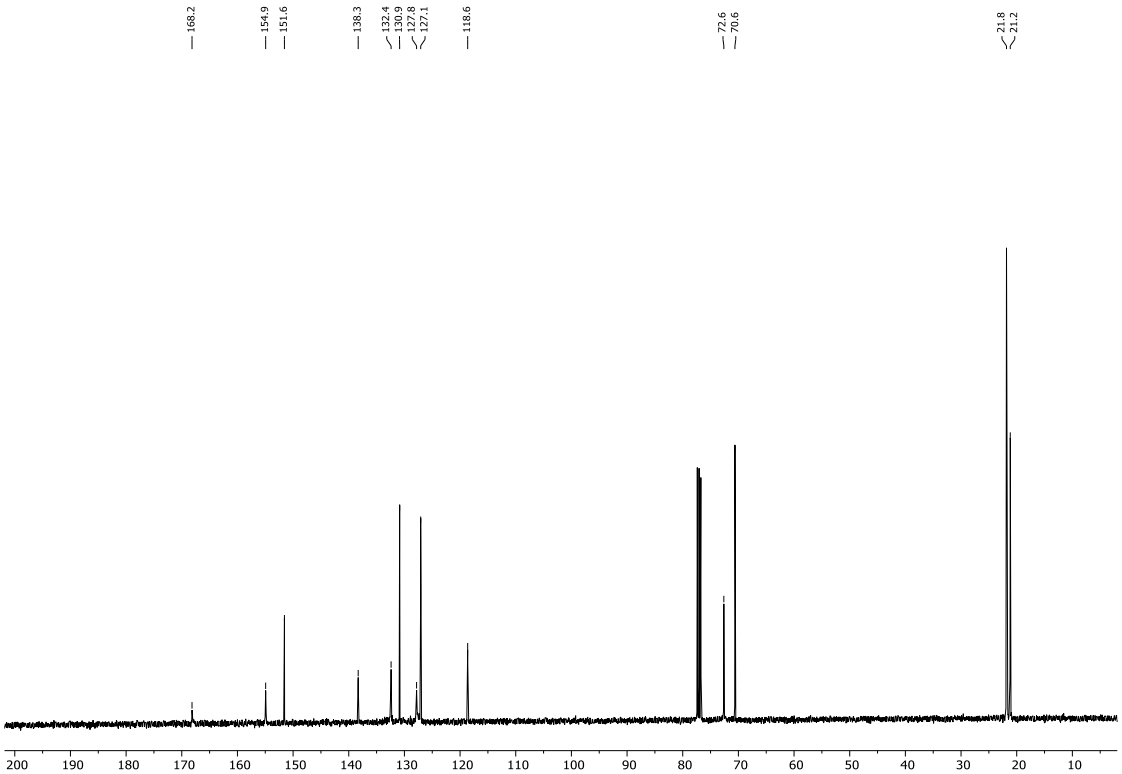
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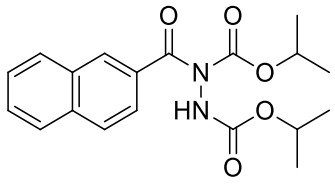

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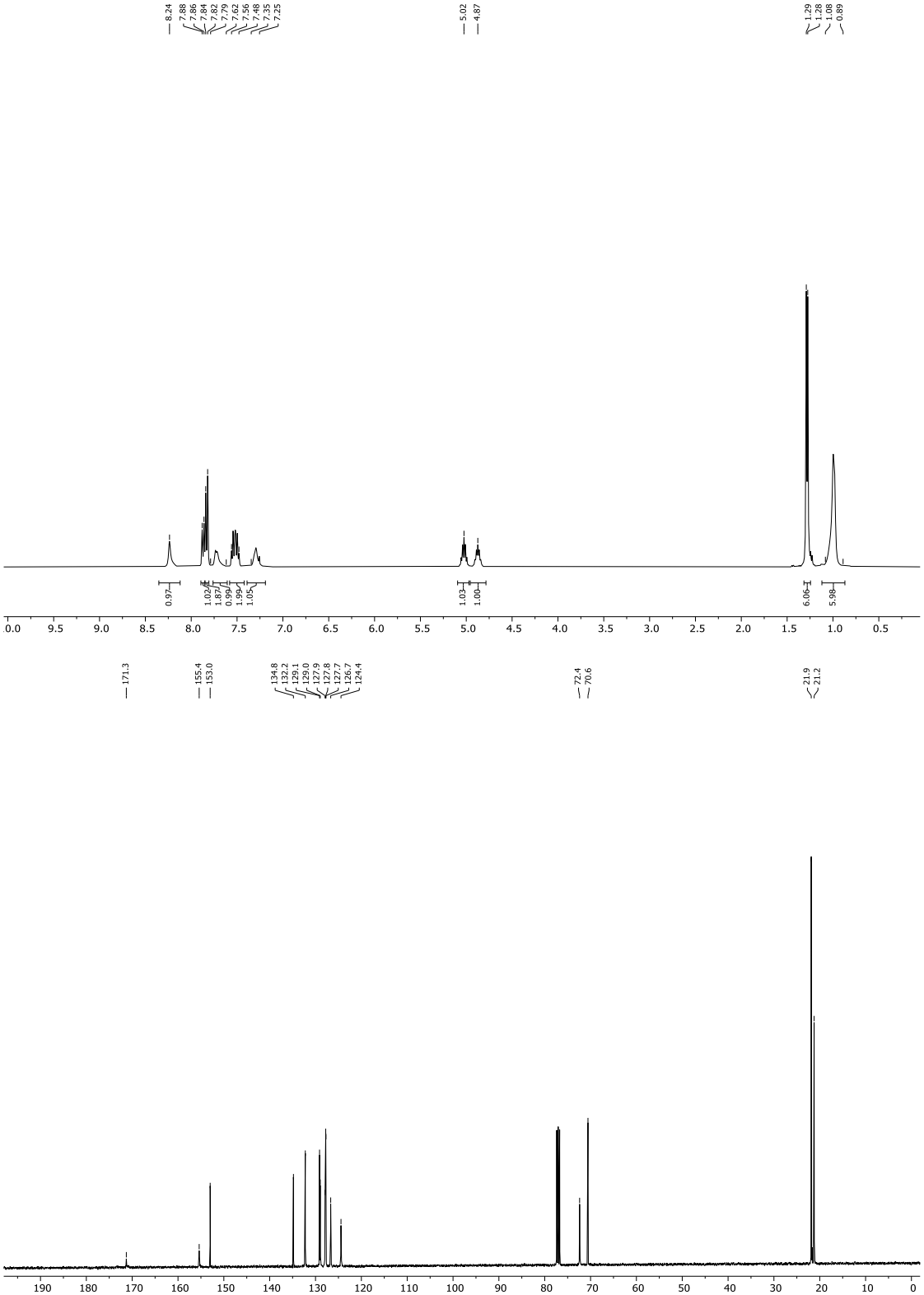
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1.28
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1.02
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0.99
1.99
1.05
1.03
1.00
6.06
5.98
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153.0
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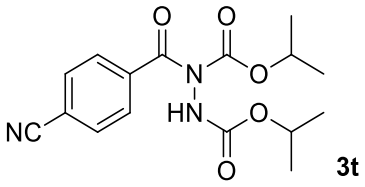
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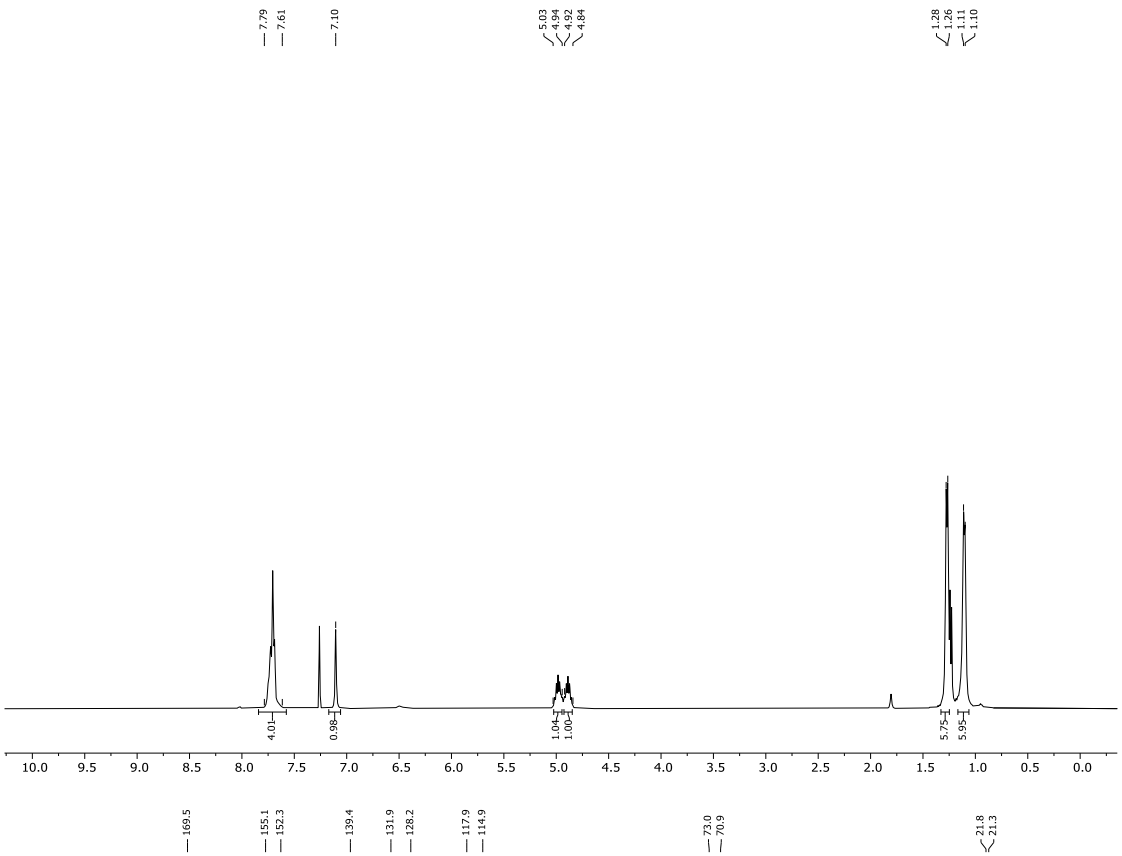
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5.95
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7.0
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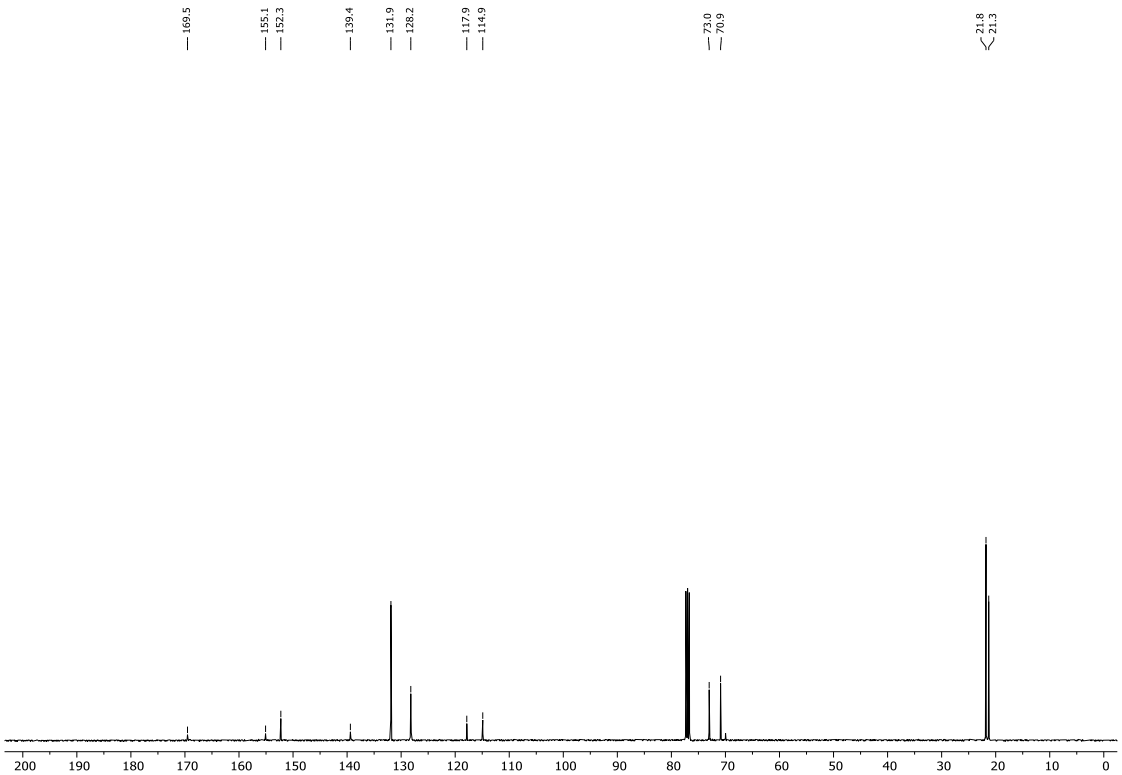
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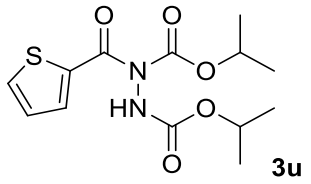
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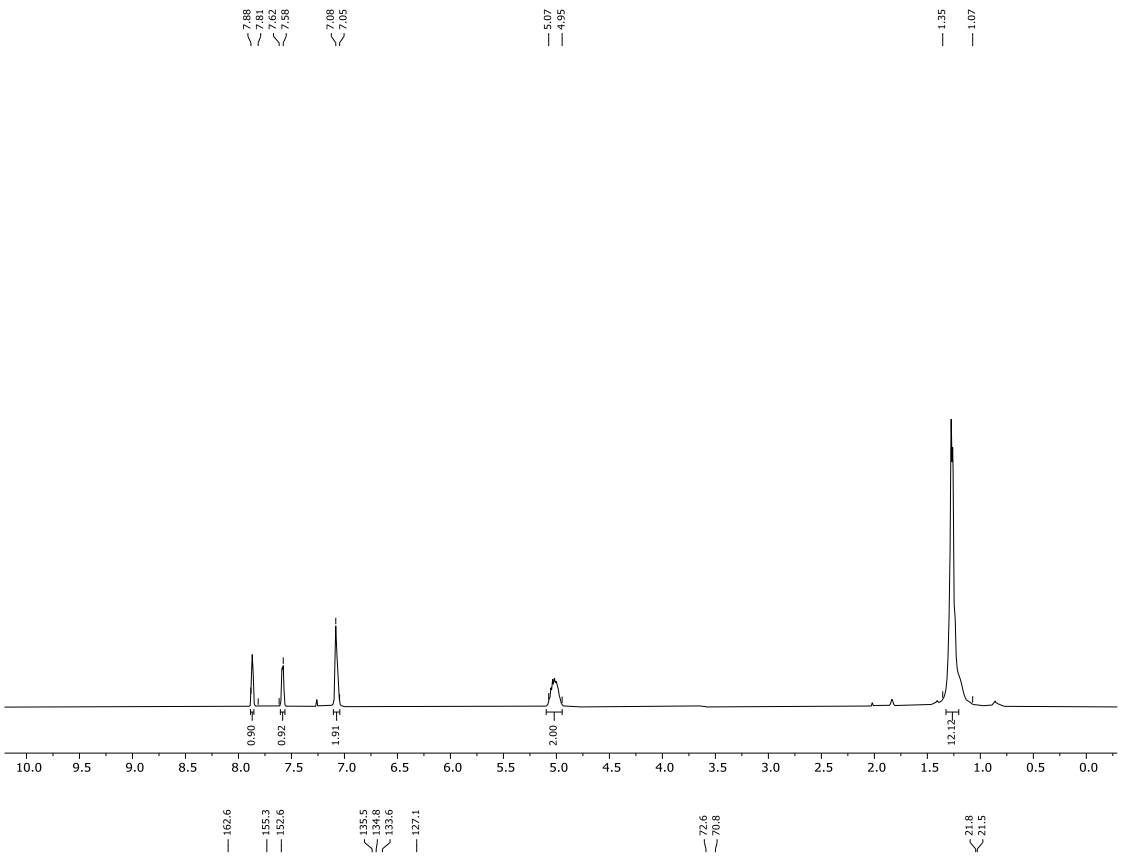
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1.91
2.00
12.12
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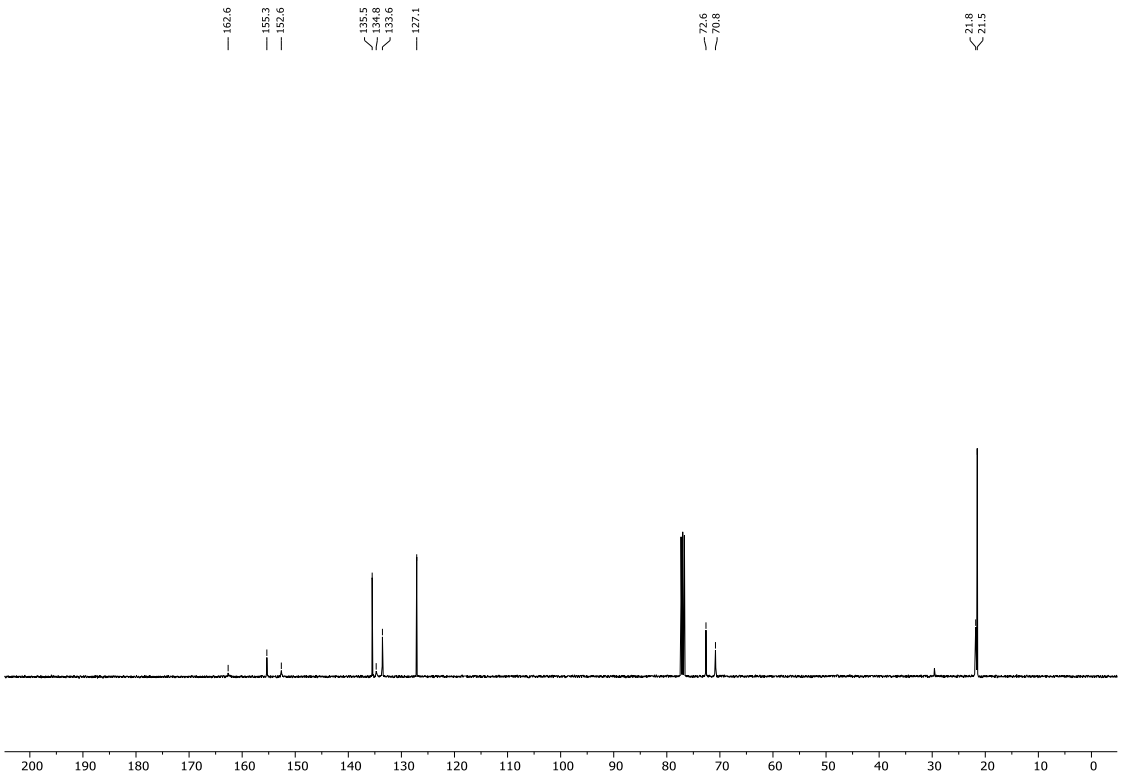
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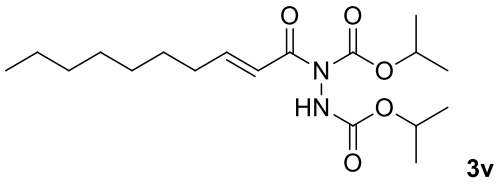

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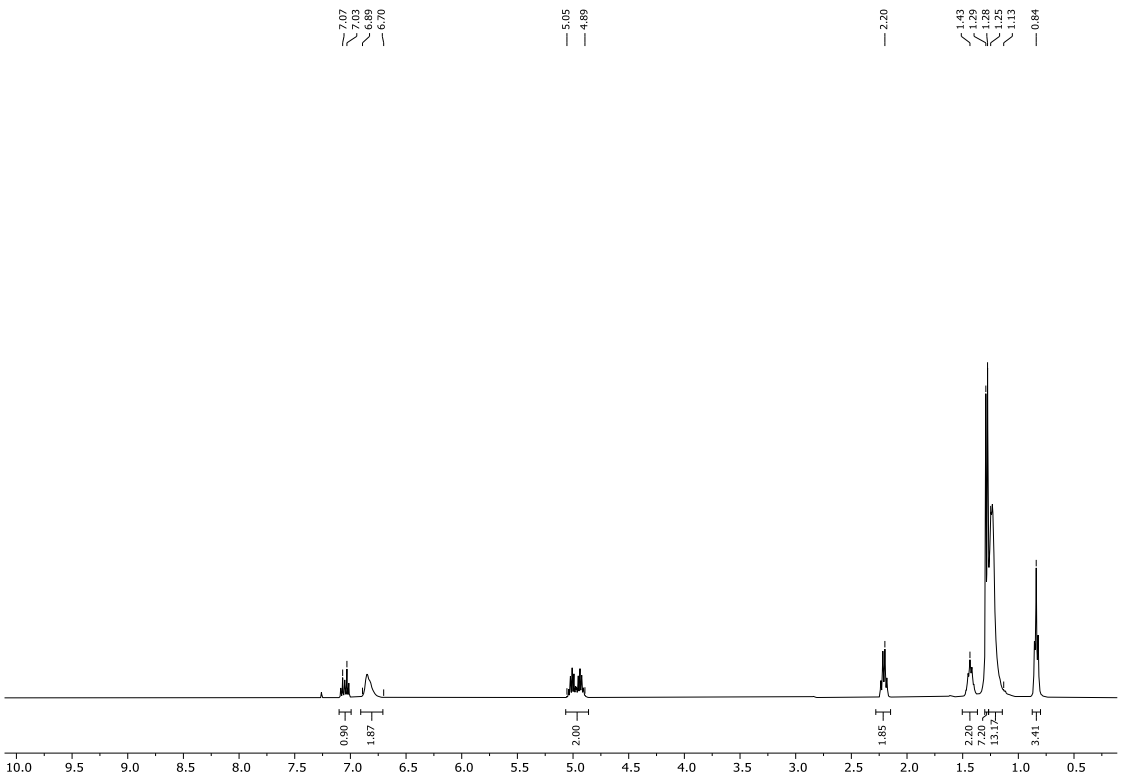
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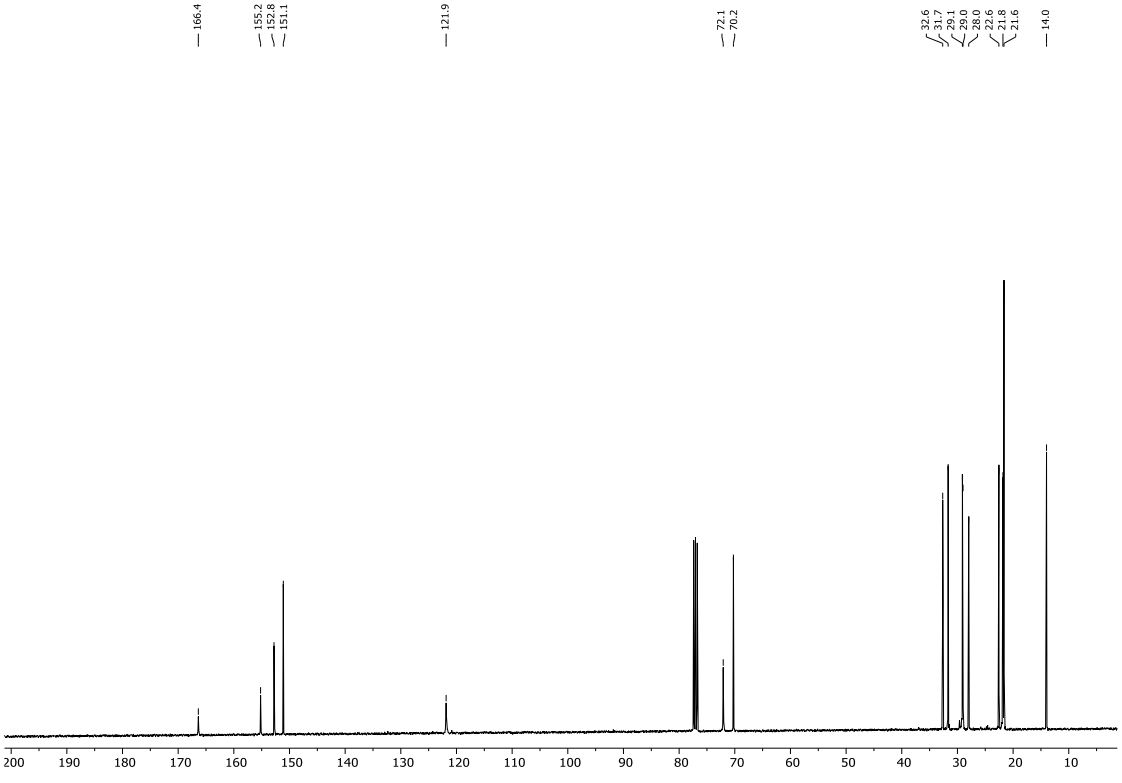
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28.0
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21.8
21.6
14.0
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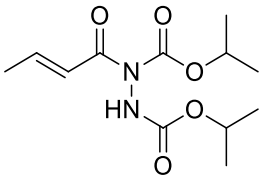

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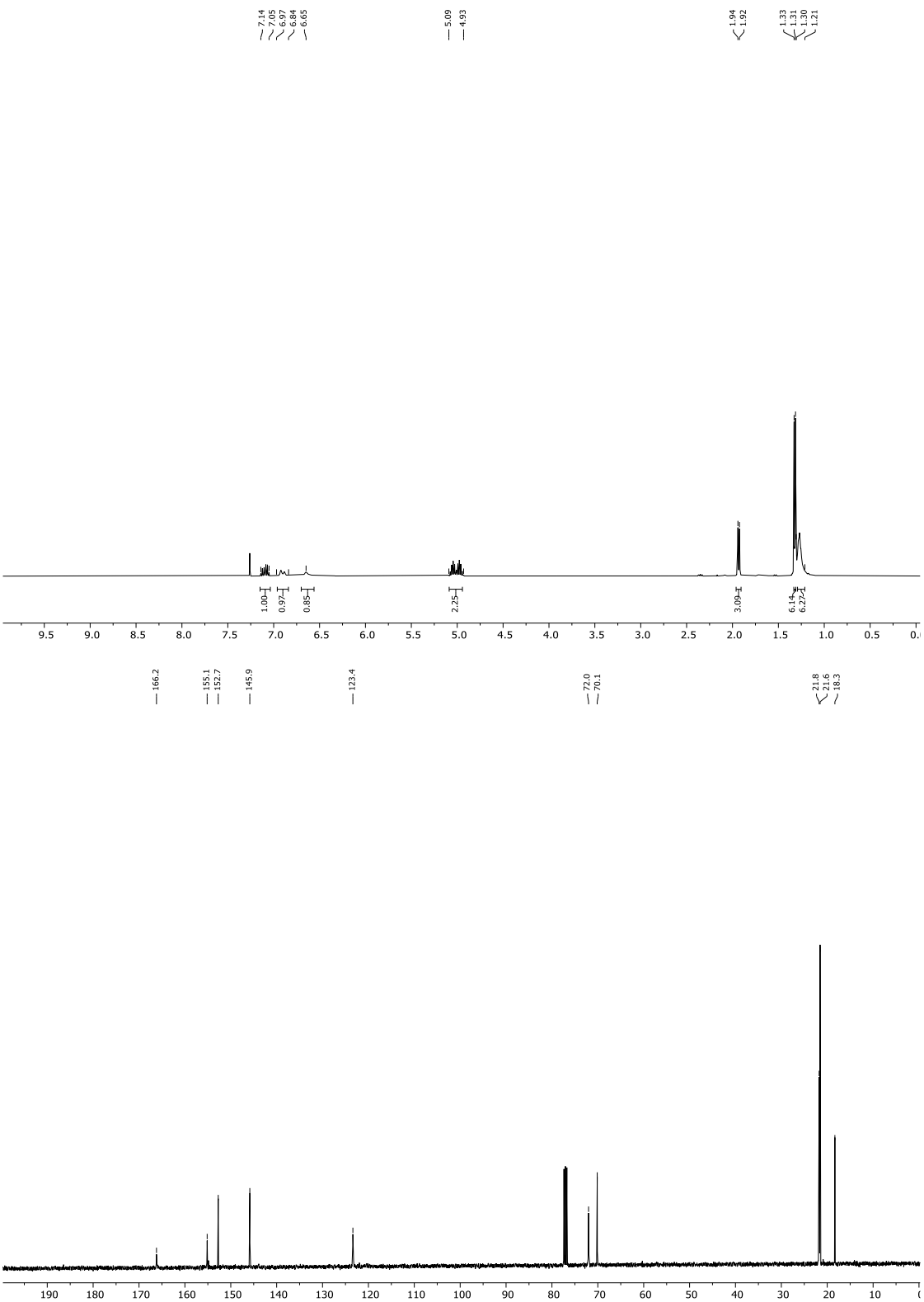
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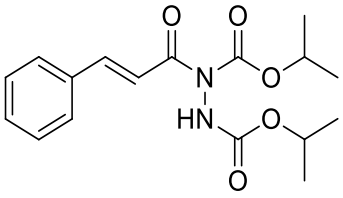
6.14
6.27
166.2
155.1
152.7
145.9
123.4
72.0
70.1
21.8
21.6
18.3



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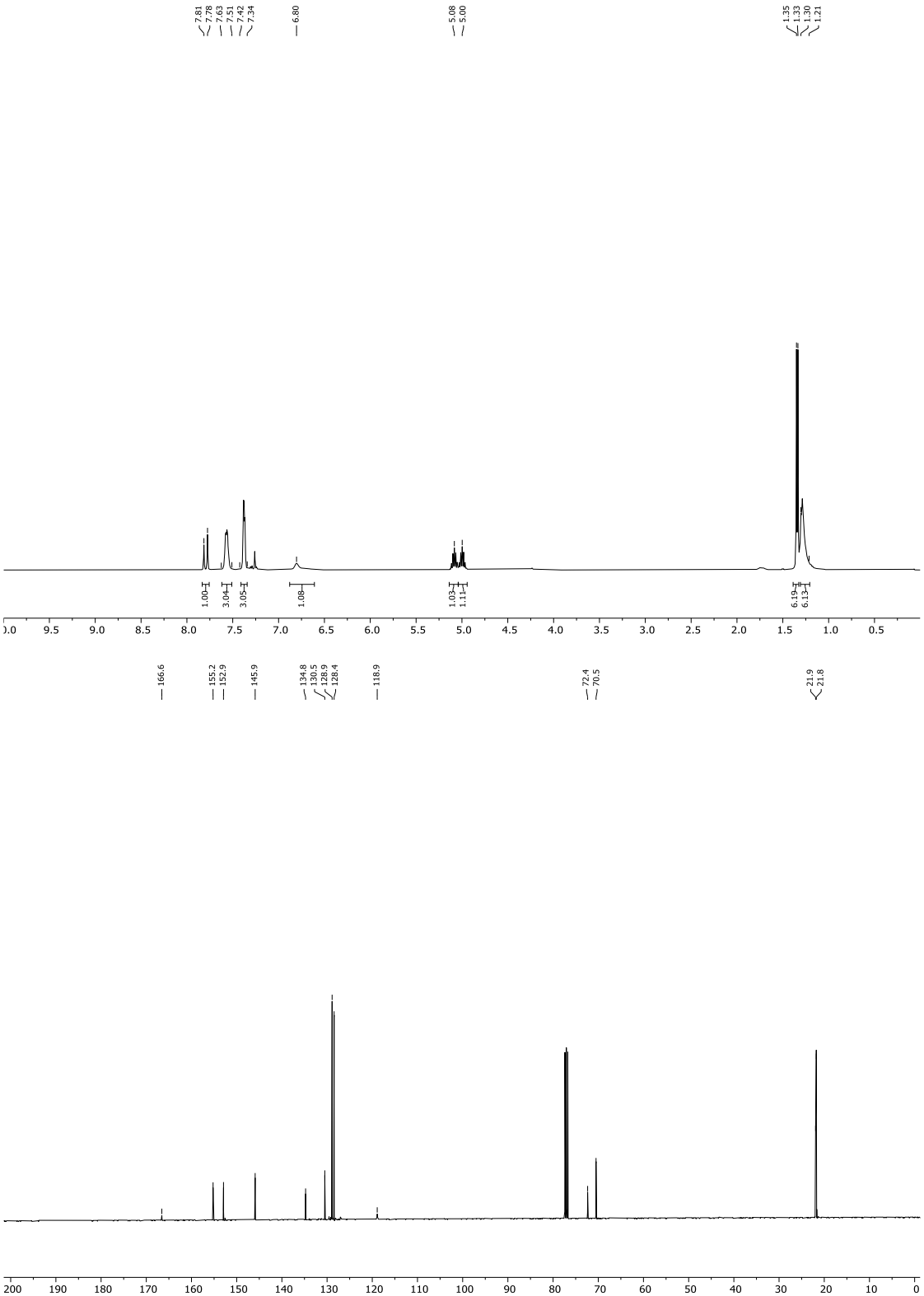
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7.78
7.63
7.51
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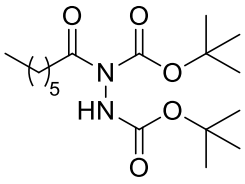
5.08
5.00
1.35
1.33
1.30
1.21
1.00
3.04
3.05
1.08
1.03
1.14
6.19
6.13
166.6
155.2
152.9
145.9
134.8
130.5
129.0
128.4
118.9
72.4
70.5
21.9
21.8



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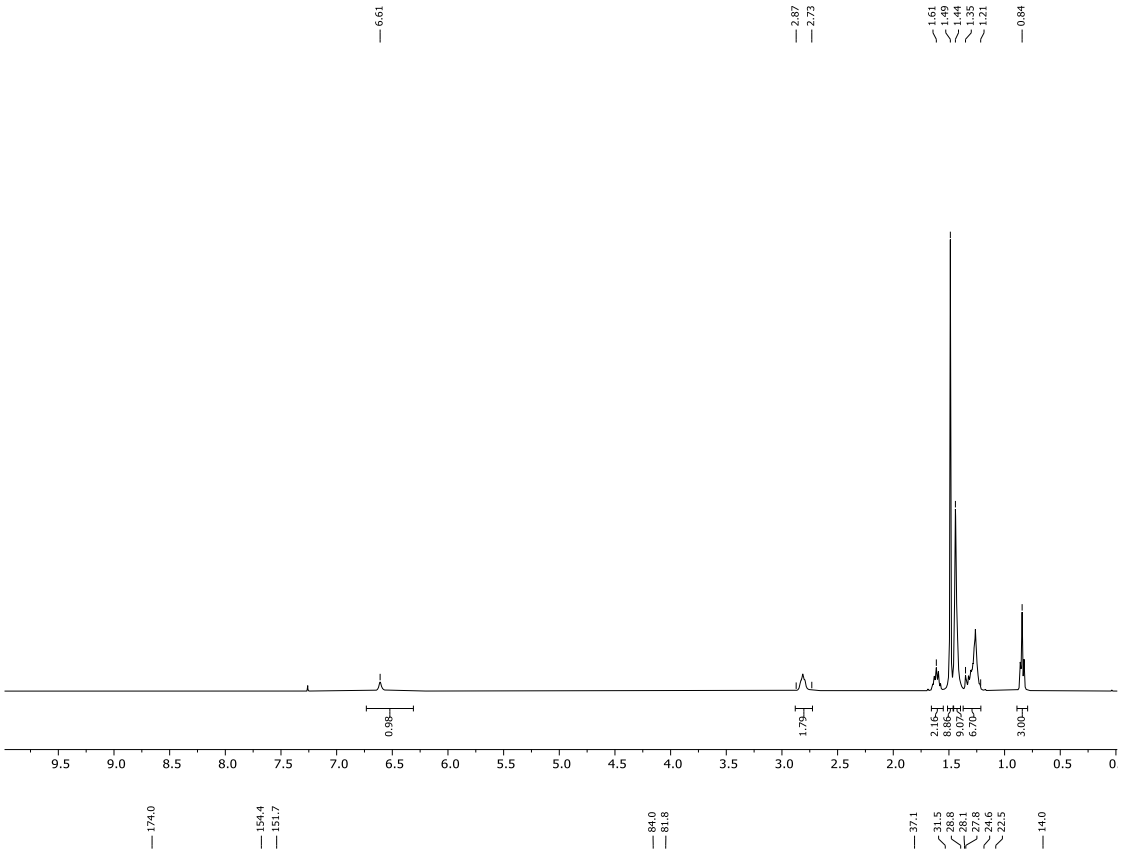
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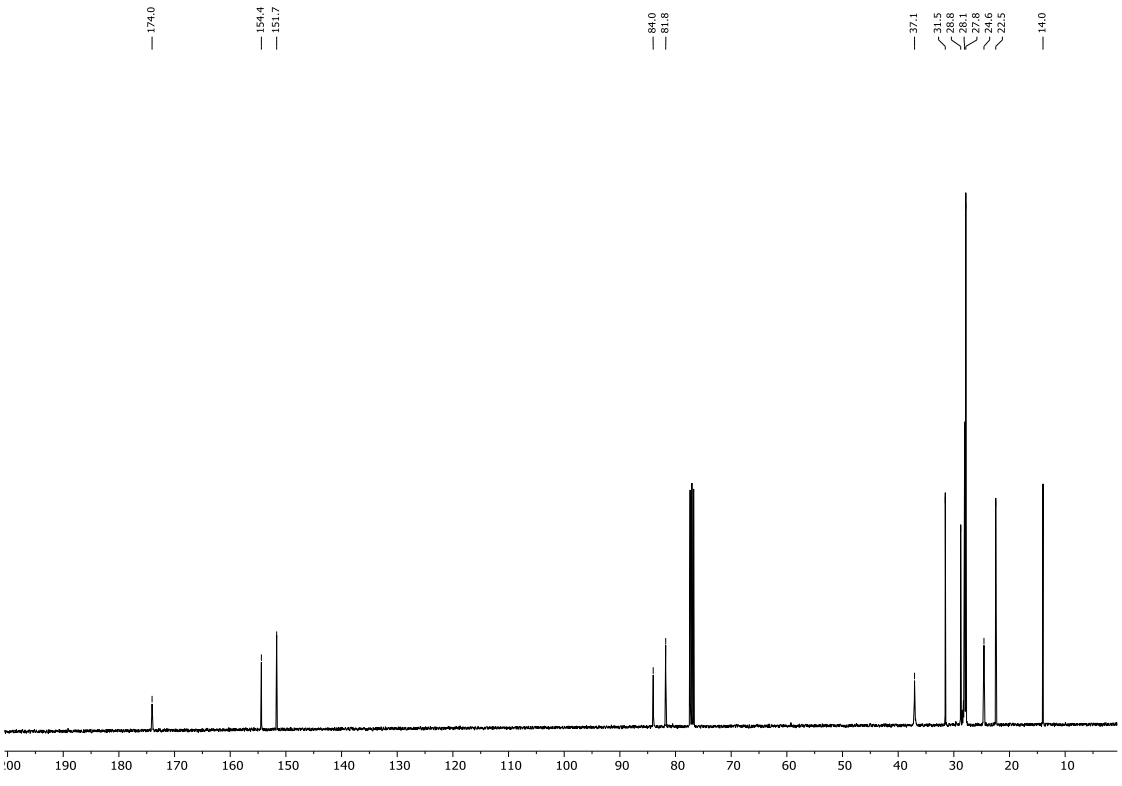
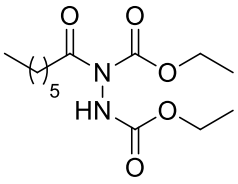
2.87
2.73
1.61
1.49
1.44
1.35
1.21
0.84
0.98
1.79
2.16
8.86
9.07
6.70
3.00


174.0
154.4
151.7
84.0
81.8
37.1
31.5
28.8
28.1
27.8
24.6
22.5
14.0



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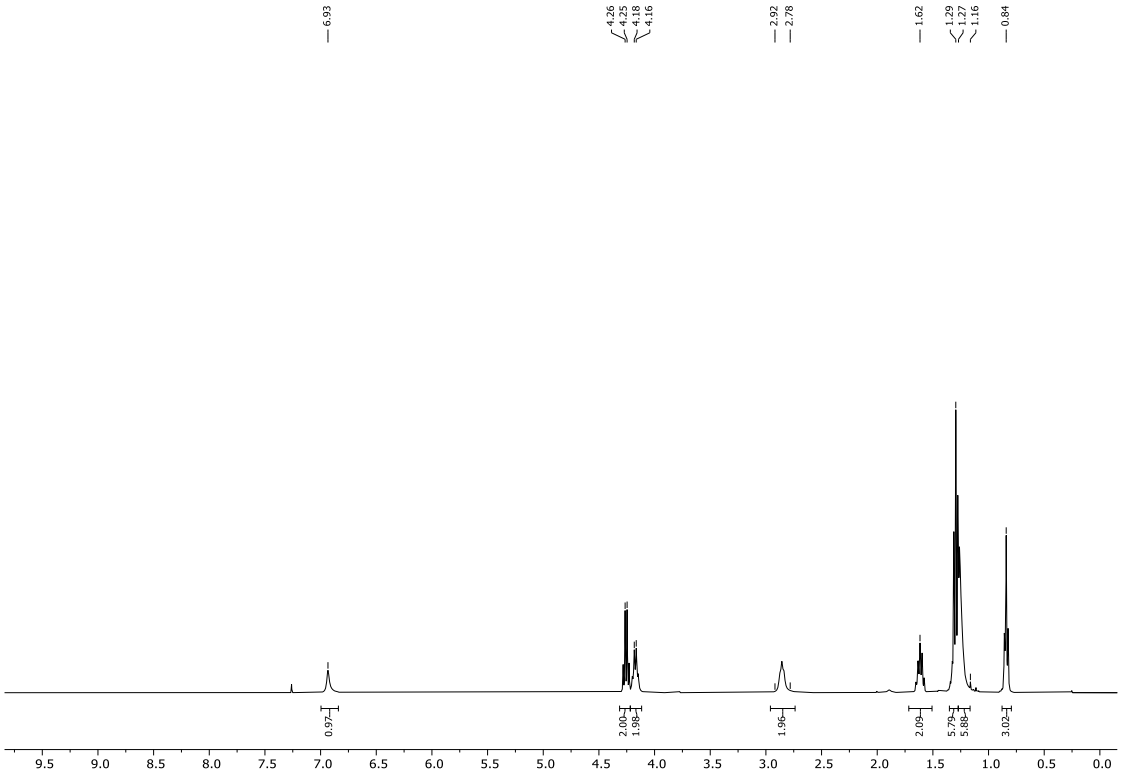
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4.18
4.16
2.92
2.78
1.62
1.29
1.27
1.16
0.84
0.97
2.00
1.98
1.96
2.09
5.79
5.88
3.02
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
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4.0
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3.0
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2.0
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1.0
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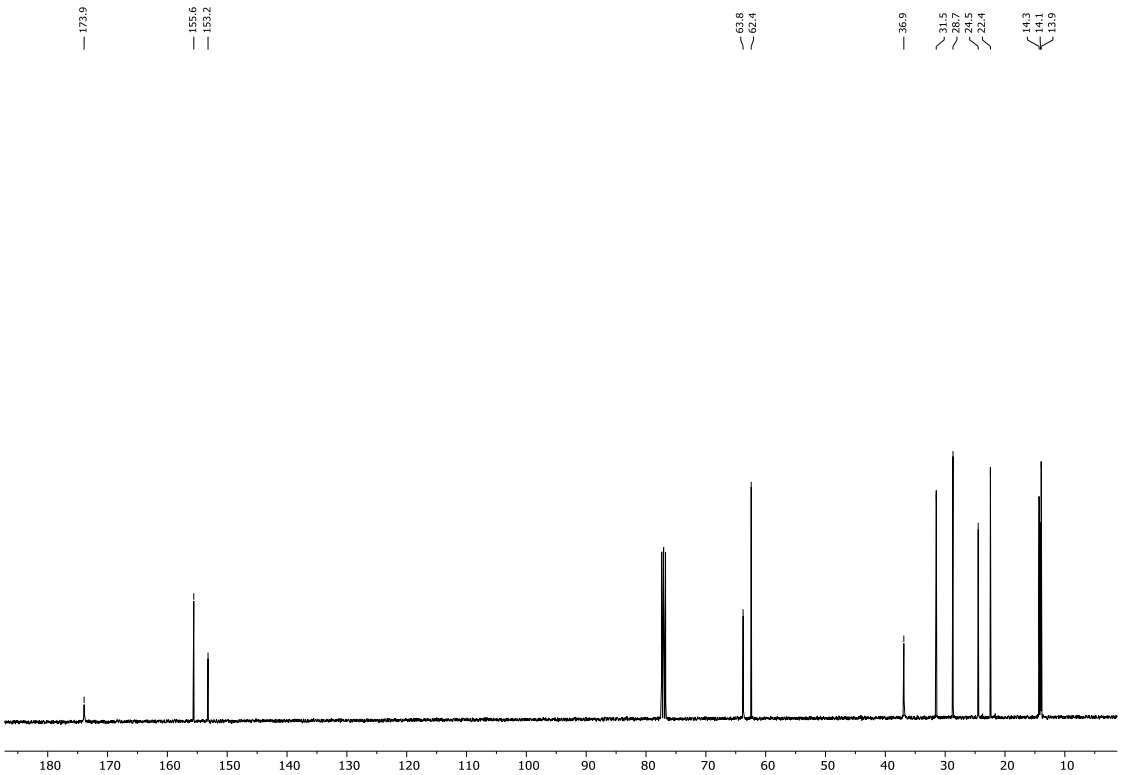
0.0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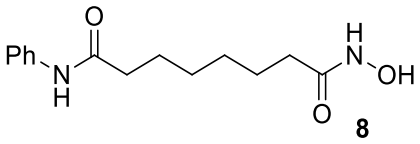
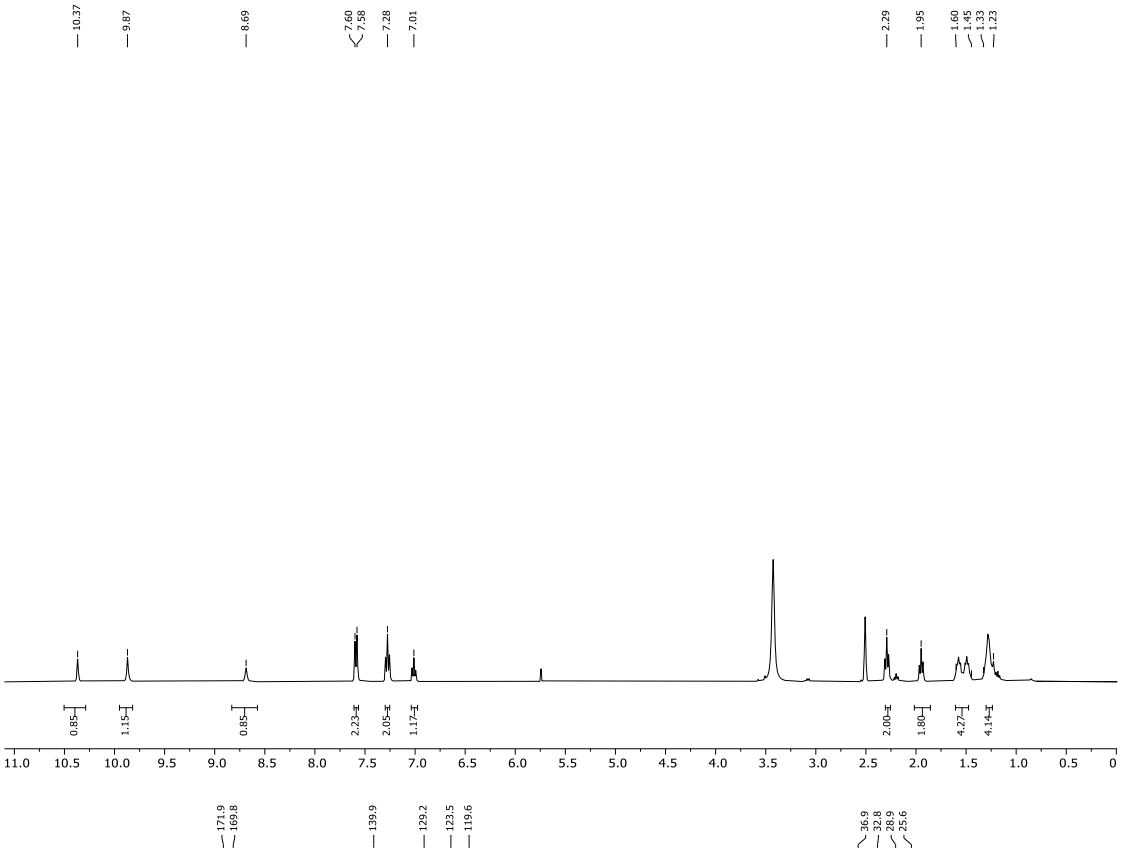
155.6
153.2
63.8
62.4
36.9
31.5
28.7
24.5
22.4
14.3
14.1
13.9
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10


O
Ph
N
H
H
N
OH
O

8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8.69
7.60
7.58
7.28
7.01
2.29
1.95
1.60
1.45
1.33
1.23
0.85
1.15
0.85
2.23
2.05
1.17
2.00
1.80
4.27
4.14
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
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2.0
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1.0
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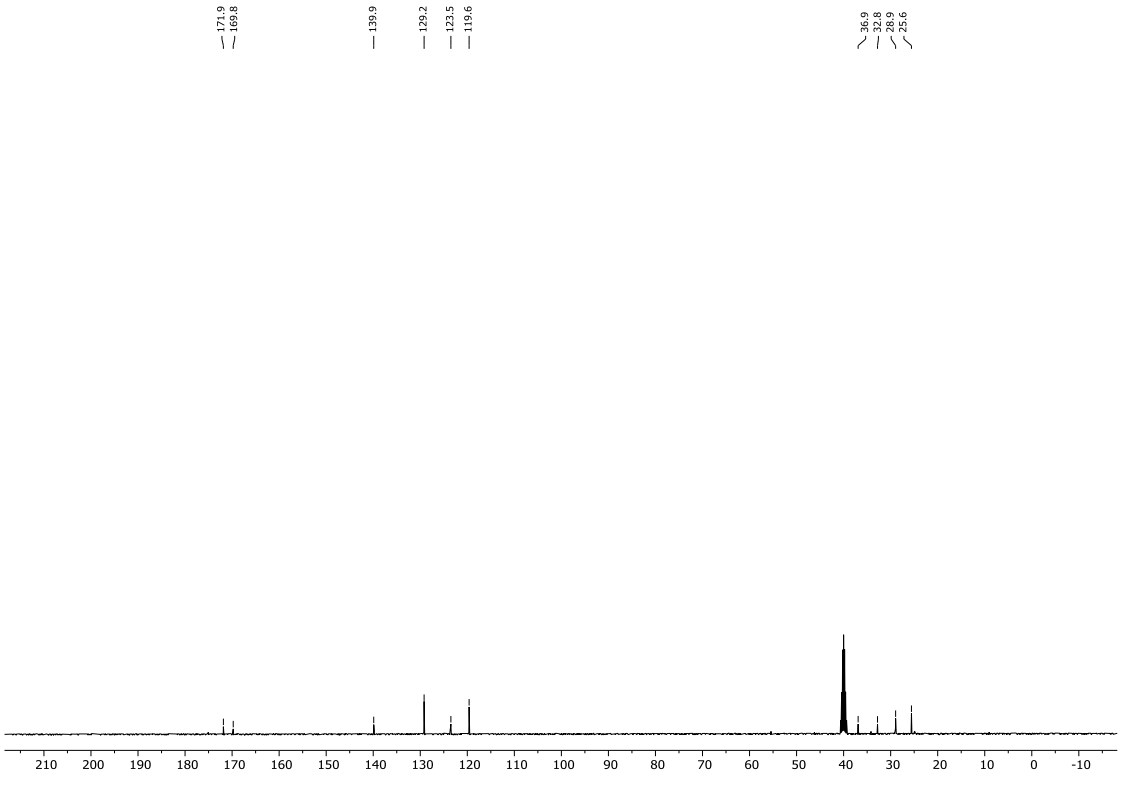
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169.8
139.9
129.2
123.5
119.6
36.9
32.8
28.9
25.6
210
200
190
180
170
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60
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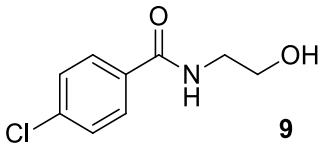
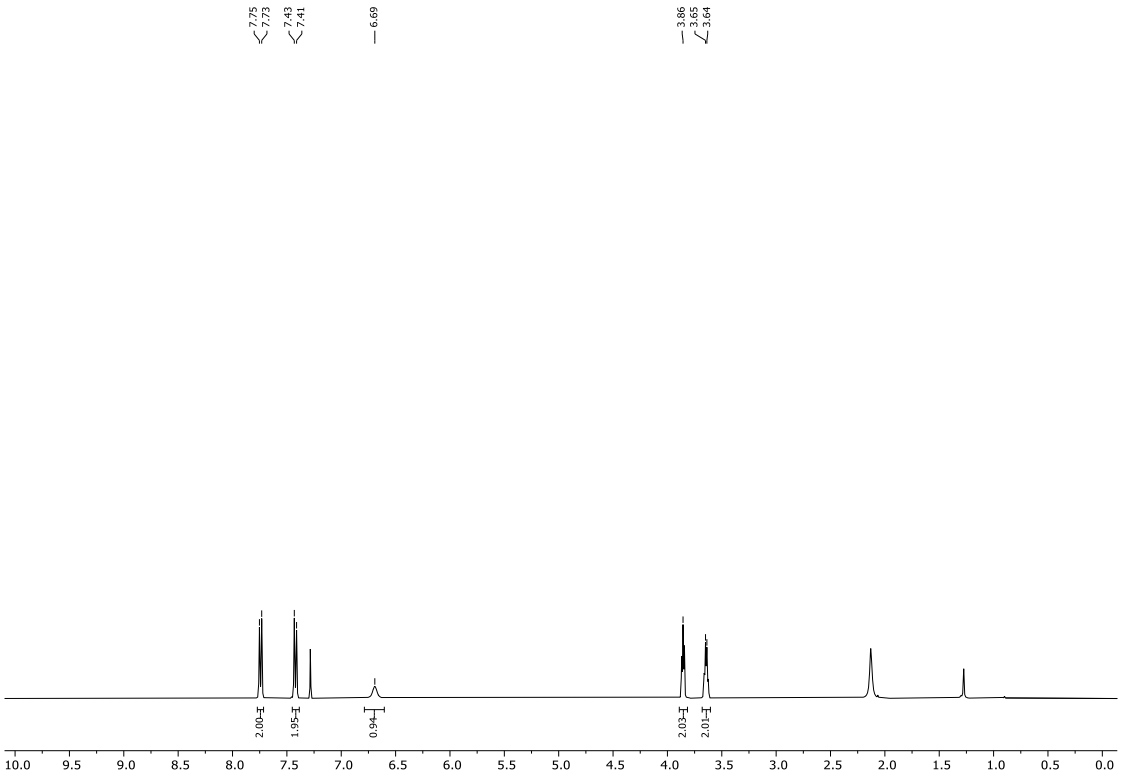
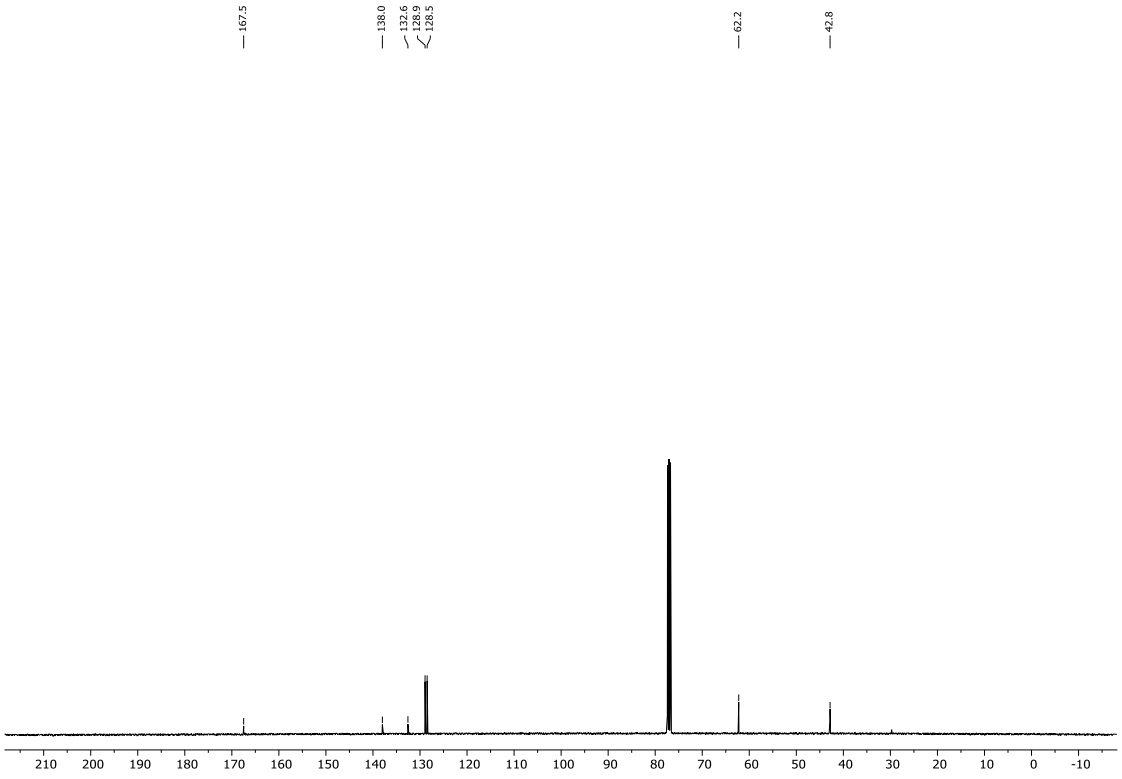
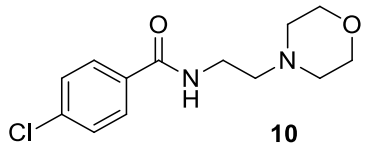
10
0
-10


O
N
H
OH
Cl

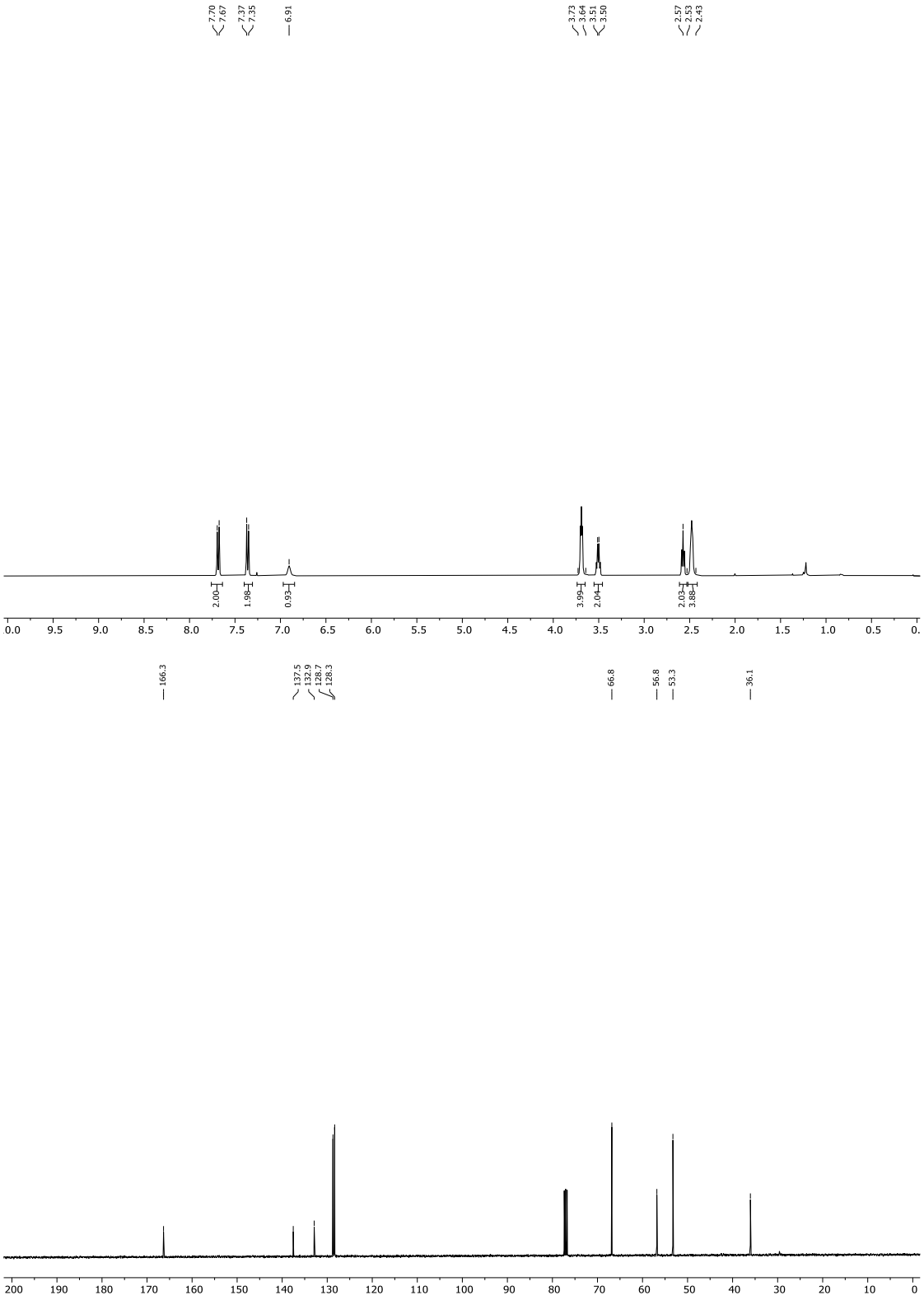
9


7.75
7.73
7.43
7.41
6.69
3.86
3.65
3.64
2.00
1.95
0.94
2.03
2.01
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0


167.5
138.0
132.6
128.9
128.5
62.2
42.8
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10


O
N
H
O
N
Cl

10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7.67
7.37
7.35
6.91
3.73
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3.51
3.50
2.57
2.53
2.43
2.00
1.98
0.93
3.99
2.04
2.03
3.88
0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.
166.3
137.5
132.9
128.7
128.3
66.8
56.8
53.3
36.1
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0