Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.
This journal is © The Royal Society of Chemistry 2020

Electronic Supplementary Information

Visible light promoted continuous flow photocyclization of 1,2-diketones

Francesco Secci,[a*] Stefania Porcu,[a,b] Alberto Luridiana,[a] Angelo Frongia,[a] Pier Carlo Ricci[b]

[a.]Dipartimento di Scienze Chimiche e Geologiche, Università degli Studi di Cagliari, S.S. 554, bivio per Sestu, 09042, Monserrato (Ca) Italy. Tel.: +39 070 675 4408. e-mail: fsecci@unica.it

[b.]Dipartimento di Scienze Fisiche, Università degli Studi di Cagliari, S.S. 554, bivio per Sestu, 09042, Monserrato (Ca) Italy.

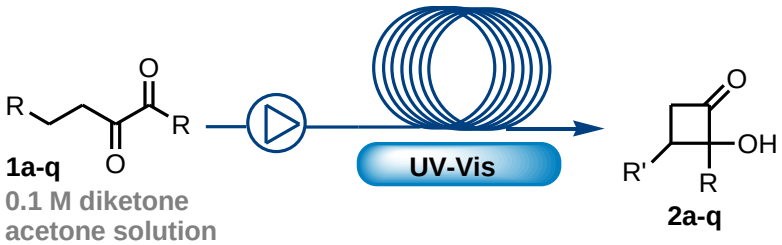


Table of Contents

1. Materials and Methods

Unless stated otherwise, respectively the synthesis of compounds **1** and **2** were performed at the reported temperatures in batch reactors or FEP flow reactors as described below. Commercially available reagents were used as received unless otherwise noted. The diones **1a-d** used in this work were purchased from Sigma Aldrich or TCI and used as received. Dione derivatives **1e-q** were prepared following the corresponding literature or by modification of previously published procedures.[1] ^{1}H NMR spectra were recorded on a 500 MHz Varian spectrometers at 25°C using $CDCl_3$ (ref. 7.26 ppm) as a solvent (or CD_3OD). ^{13}C NMR were recorded at 126 MHz (ref. $CDCl_3$ 77.00 ppm) using $CDCl_3$, (or CD_3OD) as solvent. Chemical shifts (δ) are given in ppm. Coupling constants (*J*) are reported in Hz. Infrared spectra were recorded on a FT-IR Bruker Equinox-55 spectrophotometer and are reported in wavenumbers (cm^{-1}). Low Mass Spectra Analysis were recorded on an Agilent-HP GC-MS (E.I. 70eV). High Resolution Mass Spectra (HRMS) of compounds **1**, and **2** were obtained using an High Resolution Mass Spectrometer in fast atom bombardment (FAB+) ionization mode (ESI) acquired using a Bruker micrOTF-Q II or/and Agilent Q-TOF 6520. Melting points were determined with a Büchi M-560. Analytical thin layer chromatography was performed using 0.25 mm Aldrich silica gel 60-F plates. Flash chromatography was performed using Merck 70-200 mesh silica gel. Yields refer to chromatography and/or spectroscopically pure materials. Acetone, acetonitrile, ethyl acetate were used as received (HPLC grade >99%) or distilled over 3Å MS. Diethyl carbonate was distilled using 3Å MS. THF and toluene were distilled from sodium/ benzophenone ketyl. Cyclohexane, *n*-heptane and 2-Me-THF were dried on CaH_2.

UV-vis analysis were carried out with a Agilent-Cary 5000UV-vis-NIR system. Florescence analysis were carried out with a Varian-Cary Eclipse Fluorescence spectrometer.

LED diodes (3W, 440-450 nm, royal blue and 390 nm ELE Doctor) were purchased from SUIYANR.
LED diodes (5W, 440-450 nm) were purchased from RYH. West road Shahe, Nanshan district, Shanzhen, China.
LED diodes (10W, 370 nm and 440-450 nm) were purchased from SENGI8, Unit o4, 7F bright way tower, n33, Mong Kok Rd KL, Hong Kong.

LEDs were characterized by using a power meter (Newport model 1918-C).

Table S1. Properties of employed LEDs[a]

LED power	Wavelength (nm)	Forward Voltage (V)	Forward Current (mA)	Luminoux flux (lm)	Beam Angle
3W	440-450	3.2-3.4	750	40-50	120°
3W	380-390	3.5-4.5	750	UV	120°
3W	365-370	3.9-4.5	700	UV	120°
5W	440-450	6.0-7.0	700	300-400	120°
5W	385-390	6.0-7.0	700	UV	120°
5W	370	5.0-7.0	700	UV	120°
10W	440-450	8.0-10.0	1000-1050	500-600	120°
10W	390-395	3.2-4.0	750	UV	120°
10W	370	10-12	1000	UV	120°

a) The values reported in this table have been collected from the data sheet furnished with the LEDs.

2. UV-Vis analysis of dione 1a

2.1 UV-Vis analysis of dione 1a in different solvents

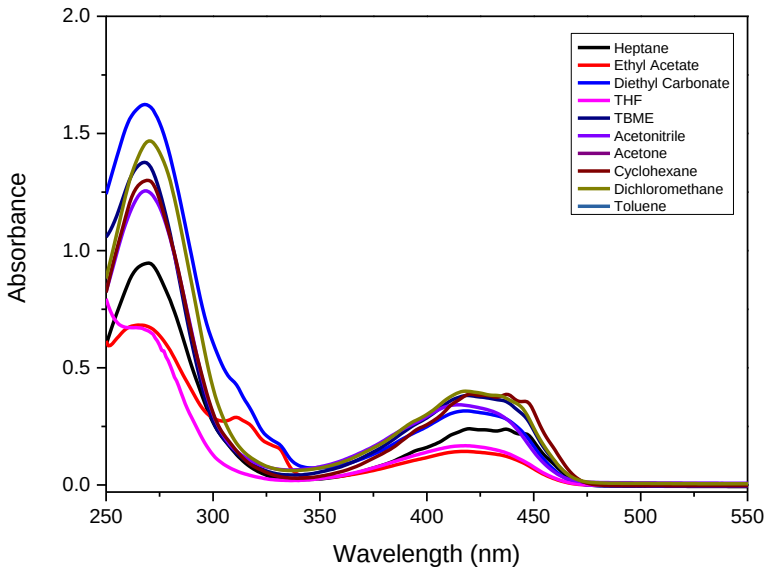


Figure S1 a) UV-Vis absorption of 2,3-pentanedione **1a** in different solvents (conc. 3.8×10^{-4}).

2.2 UV-Vis analysis of dione 1a in different solvents (350-500 nm expansion)

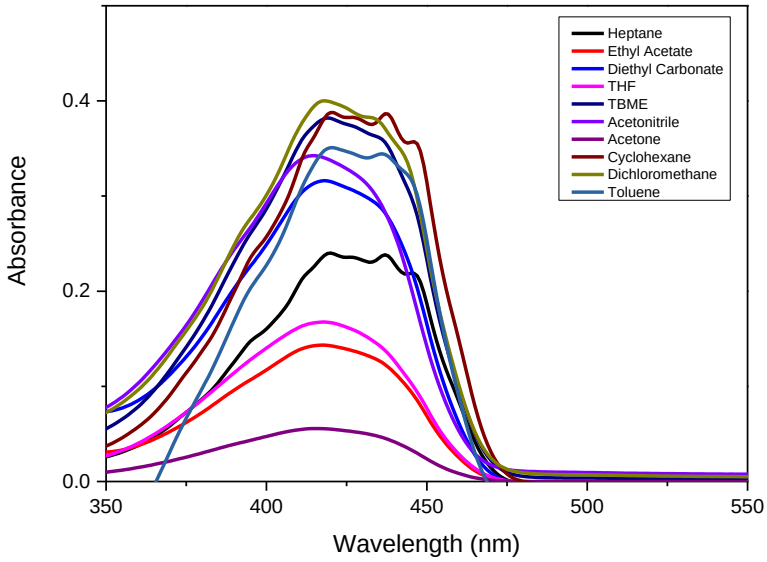


Figure S2 UV-Vis absorption of 2,3-pentanedione **1a** in different solvents (conc. 3.8x10^{-4}).

2.3 UV-Vis analysis of diones 1a-e, 1h,j,k,p in acetone

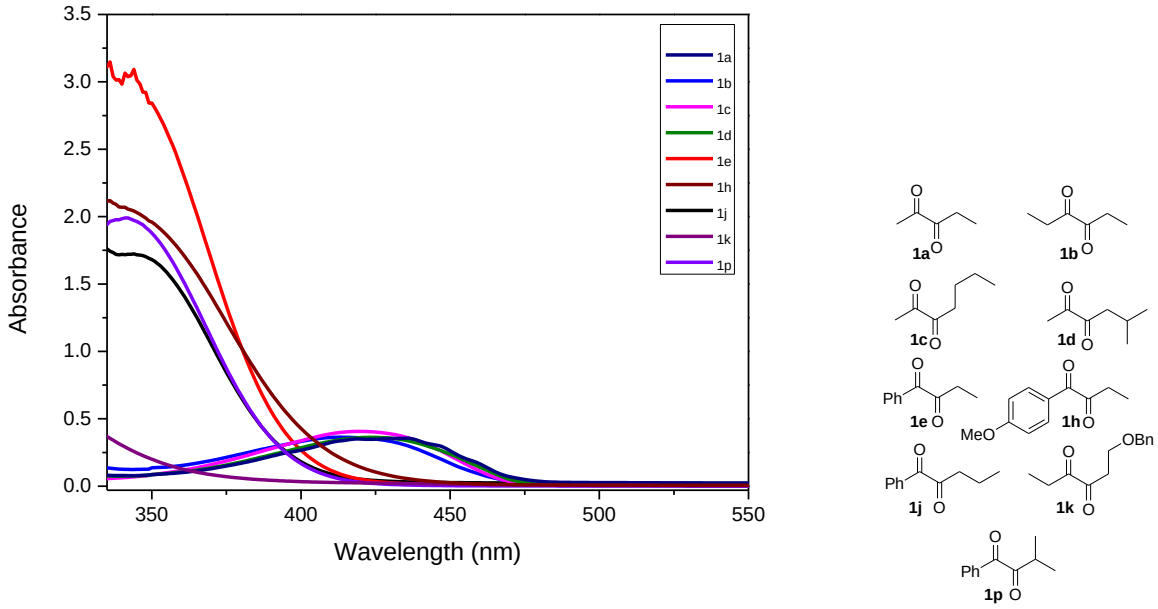


Figure S3 UV-Vis absorption of alkyl- and aryl-dione derivatives **1** (conc. 3.8x10^{-4}).

2.4 Fluorescence analysis of dione 1a in heptane, acetonitrile, acetone

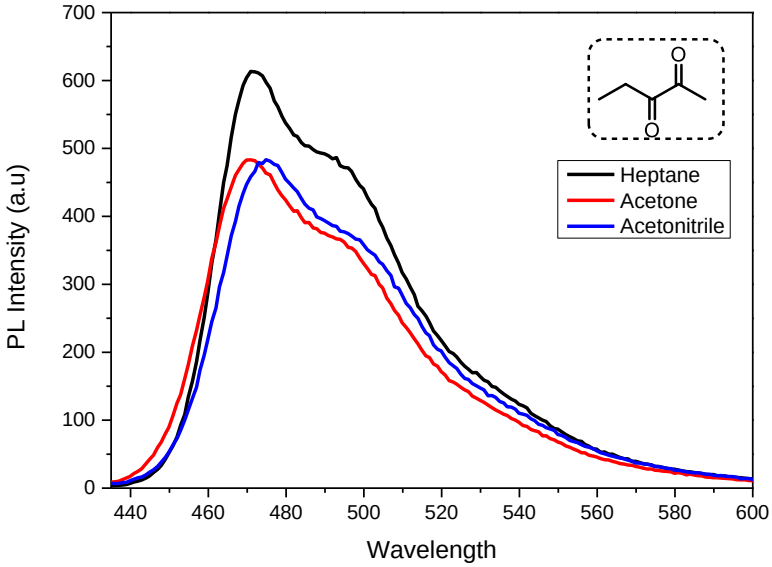


Figure S4 Fluorescence spectra of dione **1a**. (black, *n*-heptane solution $1.91x10^{-2}$; blue, acetone solution $9.57x10^{-3}$; blue, acetonitrile solution $9.57x10^{-3}$).

3. Flow experiments and apparatus optimization

3.1 Single FEP tubing layer reactor

For this optimization, a Duran-glass® tube[2] was wrapped (single layer) with a FEP-tube (10m, 0.8 mm inner diameter (i.d.), 1.6 mm outer diameter (o.d.) internal volume 5mL) and a 8x440 nm (royal blue LEDs 10W) LED system was used as a light source (figure S4). The reactor was refrigerated (24°C) by a fan coil located in the upper part of the apparatus. The so obtained system was placed on a Dewar flask as depicted in the figure S5-6. The diketone solutions were dispensed with a syringe pump (0.2-0.07 mL/min flow rate) and the resulting colourless cyclobutanone was collected in a Erlenmeyer flask.

3.2 triple FEP tubing layer reactor

For this optimization, a Duran-glass® tube[2] was wrapped (three layer) with a FEP-tube (32m, 0.8 mm inner diameter (i.d.), 1.6 mm outer diameter (o.d.) internal volume 16mL) and a 8x440 nm (royal blue LEDs 10W) LED system was used as a light source (figure S4). The reactor was refrigerated (24°C) by a fan coil located in the upper part of the apparatus (the fan coil is realized by assembling a Anima AF8 fan (80 mm with an aluminium heat exchanger radiator (BQLZR 80 Row, connected with a chiller) . The so obtained system was placed on a Dewar flask as depicted in the figure S5-6. The diketone solutions were dispensed with a syringe pump or a Hitachi-La Crom HPLC pump (0.2-2.0 mL/min flow rate) and the resulting colourless cyclobutanone was collected in an amber glass solvent tank.

Figure S4 4X10W LED rack (the thermometer probe is placed on the aluminium heat exchanger)

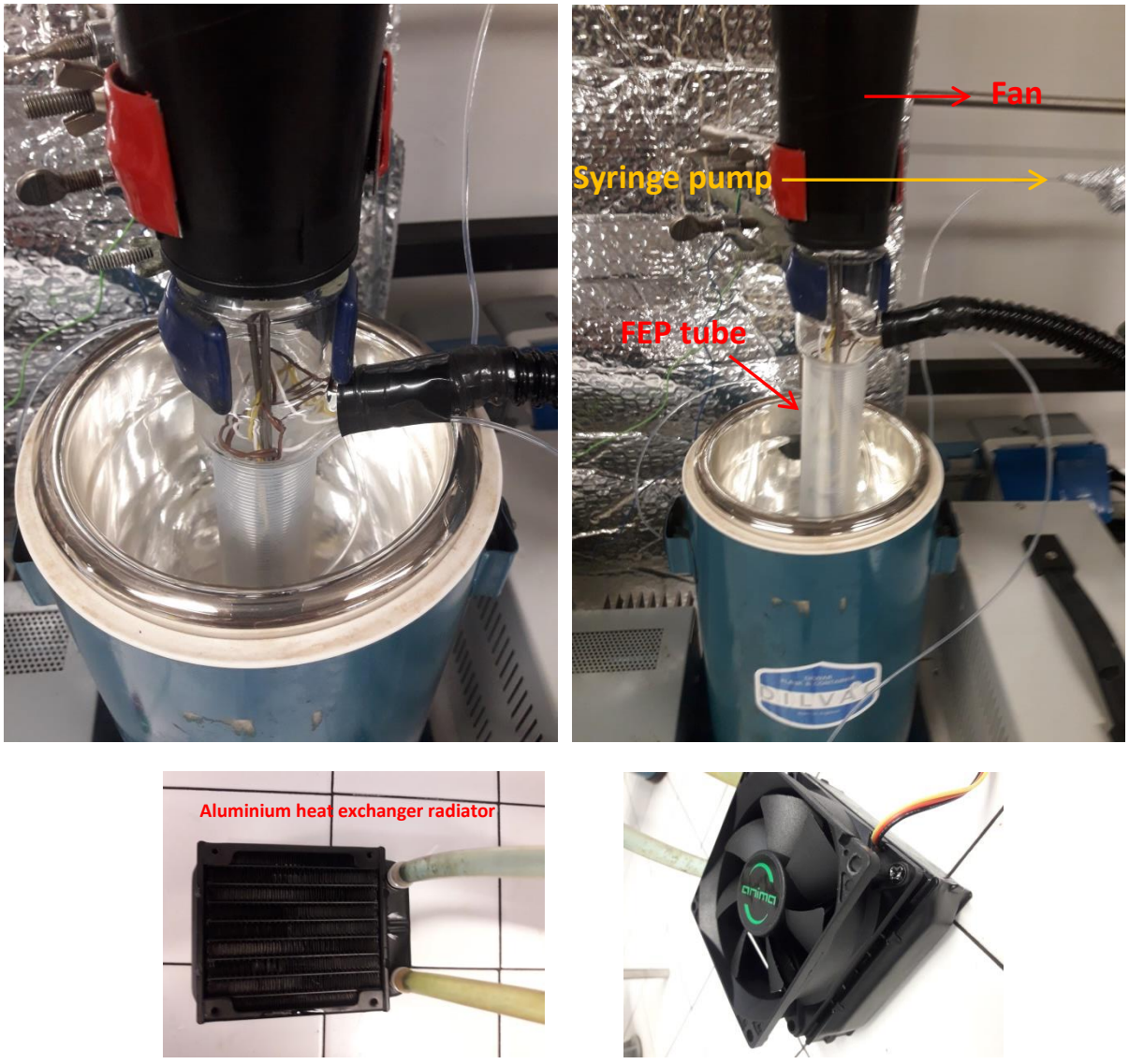


Figure S5 continuous flow reactor details

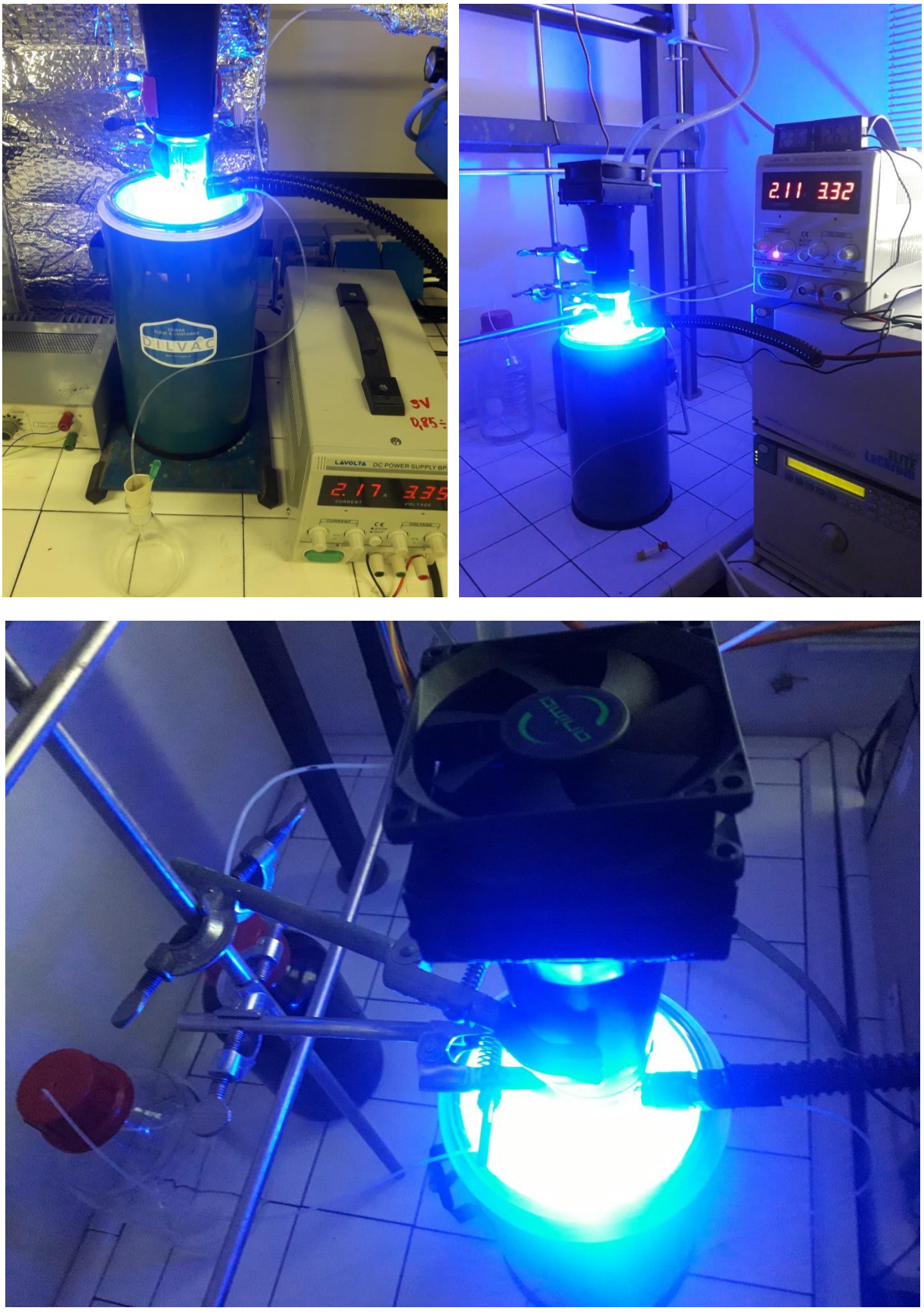


Figure S6 continuous flow reactor details

4. Quantum Yield determination[3]

A quartz cuvette was charged with a 0.1 M acetone solution of dione **1a**. The vial was fitted with a Teflon cap and the reaction mixture was irradiated by using a Stabilized laser diode Oxxius-450 (λ= 450 ± 5 nm) at room temperature for 300s and the photon flux was measured. The laser beam was expanded and then parallelized by using a telescopic arrangement of two convergent lens. The final beam dimension was set in 5.0 ± 0.2 mm in order to cover the whole solution inside a 1x10 mm quartz cuvette. The cuvette with solvent was placed in the beam (800 mw/cm^2) and the transmitted power focalized with a third convergent lens. The measurement were done using a calibrated power meter (Newport model 1918-C) placed horizontal to the cuvette. The content of the cuvette was changed to the reaction mixture and the transmitted power was measured after different times. The cyclobutanone **2a** conversion was determined by GC-MS analysis. Chemical yields were determined by weighing. The quantum yield was calculated using the following equation:

$$\phi = \frac{N_{product}}{N_{photon}} = 0.68$$

Where $N_{product}$ and N_{photon} are the number of product molecules formed and the number of photon absorbed, respectively. The QY obtained can be utilized to verify the amount of product that can be obtained in the reactor:

$$\phi = \frac{N_{product}}{N_{photon}} = \frac{hcN_A n_{product}}{\lambda P_{abs} t}$$

Where *h* is the Planck's constant in Js, c is the speed of light in m s^{-1}, λ is the wavelength of irradiation source (440 x 10^{-9} m). P_{abs} is the radiant power absorbed by the sample. Therefore, considering the P_{abs} obtained, the power emitted by the LED (about 450 mW at 440 nm) modulated for the absorbance of the sample at the same wavelength (0.4, see S1), is possible to have an estimation of the maximum molar amount of molecules created in moles ($n_{product/1\ hour}$):

$$n_{product/1h} = \frac{\phi P_{abs} t \lambda}{hcN_A} = 1.5x10^{-3} mol$$

That are equivalent to 149 milligram of cyclobutanone **2**.
The measurements were repeated with 3 acetone solutions of 1a at the same concentrations. The variations on the values found are not significant with respect to the value reported in the calculation.

5. Batch experiments and apparatus optimization

Batch reactions were carried-out in a Duran-glass tube,[2] equipped with a magnetic stirring bar and closed with a septum. This apparatus was irradiated with a LED-system realized by using 8x440 nm (or 390 nm) 10W royal blue LEDs disposed on aluminium 20x100x10mm silver bar slotted heatsink strip cooling block (see figure S7) cooled by two fan located in the front and in the rear part of the apparatus. The LEDs were placed at a distance of 1.5 cm from the reaction flask. The reaction was monitored by GC-MS.

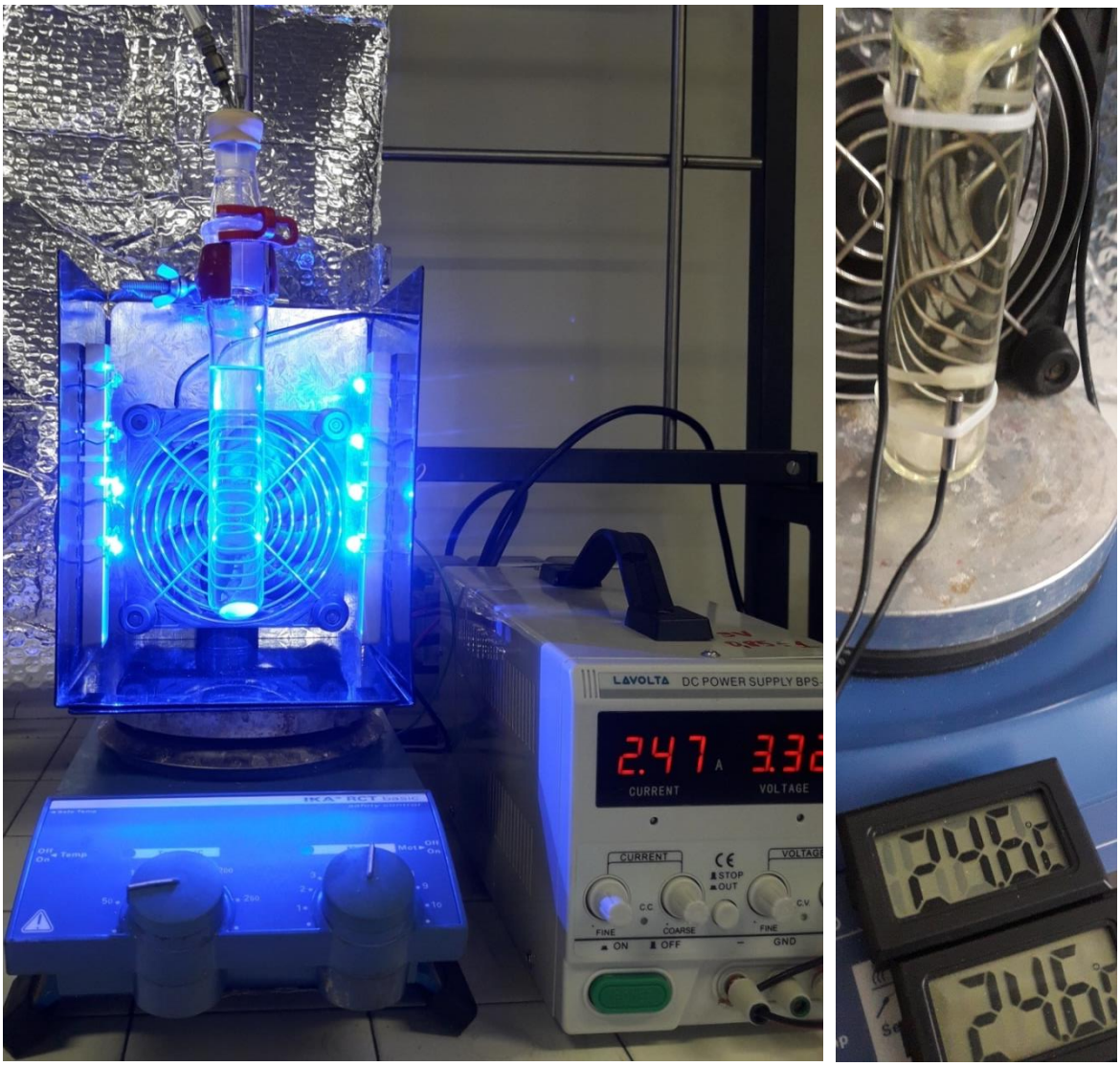


Figure S7 Batch reactor details.

Table S2 Batch initial screening studies[a]

Entry	Light-source	Solvent	Time/h	Conversion **2a**/%[b]	**2a**/**3a** *ratio*[c]	Isolated yields **2a** % (g)[d]
1	Blue LED-strip	CH_3CN	24	74	87:13	70 (245)
2	UVA lamp	CH_3CN	24	97	88:12	61 (210)
3	UVB lamp	CH_3CN	24	90	90:10 + d.p[e]	40 (140)
4	8 x 440 nm LED	CH_3CN	24	95	95:5	90 (315)
5	8 x 390 nm LED	CH_3CN	24	85	90:10	80 (280)
6	8 x 370 nm LED	CH_3CN	24	63	88:12	54 (189)
7	8 x 440 nm LED	THF	24	38	87:13 + d.p[e]	33[b] (115)
8	8 x 440 nm LED	2Me-THF	24	34	90:10 + d.p[e]	30[b] (105)
9	8 x 440 nm LED	Cyclohexane	24	80	97:3	78 (273)
10	8 x 440 nm LED	AcOEt	24	32	95:5	31 (108)
11	8 x 440 nm LED	Toluene	24	54	99:1	53 (185)
12	8 x 440 nm LED	DEC[c]	25	63	94:6	59[b] (206)
13	8 x 440 nm LED	Acetone	16	95	96:4	90 (317)
14	8 x 440 nm LED	Acetone	36	55	95:5	51[b] (178)
15	8 x 440 nm LED	Acetone	64	66	95:5	62 (217)

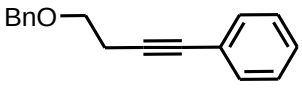
[a] Reactions Batch were performed in a Duran glass tube (internal diameter 3 cm, Vmax 50 mL) using a 0.1 M solution of **1a** (3.5 mmol, 35 mL in the appropriated solvent). [b]Reactions were followed followed by GC-MS. [c]**2a**/**3a** ratio were determined by MS-analysis. [d]Yields refer to chromatographed products. [e]d.p = decomposition products.

Table S3 Flow-rate and concentrations screening(1-3 FEP layer)[a,b]

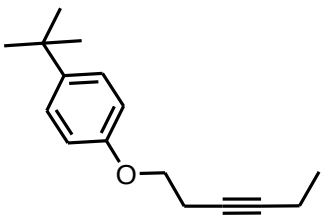
Entry	Conc. (mol/L)	Flow-rate (mL/min)	Layers of FEP	Conversion %	2a/3a *Ratio*[c]	2a Yield %[d]
1	0.05	0.5	1	80	98:2	76
2	0.1	0.2	1	>98	98:2	95
3	0.1	0.3	1	93	98:2	89
4	0.1	0.5	1	65	98:2	60
5	0.1	0.5	3	>98	98:2	97
6	0.1	1.0	3	93	98:2	91
7	0.1	1.5	3	88	>99:<1	84
8	0.1	2.0	3	53	98:2	49
9	0.2	1.0	3	71	97:3	63
10	0.3	0.5	3	38	>99:<1	31
11	0.5	0.5	3	49	>99:<1	44

[a] Reactions were performed in a FEP tube (10m, ø 0.8 x ø 1.6 mm) by using a 0.05-0.5 M solution of **1a** in acetone at the corresponding flow-rates. [b]Reactions followed by GC-MS. [c]**2a/3a** ratio were determined by MS-analysis. [d]Yields refer to chromatographed products. [e]d.p = decomposition products.

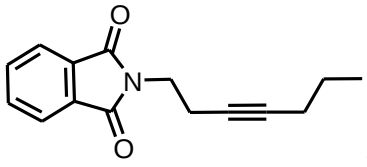
6. Synthesis of alkynes



4-Benzyloxy-1-phenyl-butyne I. Compound I was synthetized following the procedure previously reported by Cahiez and co-workers.[4a] (4-Bromo-but-3-ynyloxymethyl)-benzene (800 mg, 3.36 mmol) was reacted with a 2.0 M phenylmagnesiumchloride solution (4.03 mmol, 2.01 mL), in the presence of NMP (28 mg, 0.33 mmol) and $CuCl_2$ (13 mg, 0.011 mmol) in dry THF (6 mL) at 0°C. The reaction mixture was quenched with HCl 1.0 M solution (5 mL) and extracted with Et_2O (2x10 mL). the organic phase was dried on Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (petroleum ether/Et_2O 95:5) afforded the compound **I** as a colourless oil in 86% yield (653 mg). FTIR (film), cm^{-1} ν: 2931, 2854, 1707, 1673, 1596, 1580, 1449, 1272, 1230, 1143, 936; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.33-7.29 (m, 1H), 7.28-7.22 (m, 5H), 7.20-7.12 (m, 4H), 4.48 (s, 2H), 3.58 (t, *J* = 7.1 Hz, 2H), 2.63 (t, *J* = 7.0 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 138.1, 131.5, 128.3, 128.0, 127.6, 123.6, 86.7, 81.4, 72.8, 68.3, 20.8; HRMS (ESI): calcd for $C_{17}H_{16}O$: 236,1201 [M], found: 236,1203. Spectral data are in agreement with the literature.[4b]

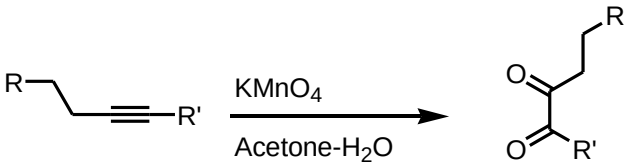


1-tert-Butyl-4-hex-3-ynyloxy-benzene II. Hex-3-yn-1-ol (1.60 g, 0.017 mol), 4-*t*-butylphenol (2.41 g, 0.016 mol), DIAD (3.25g, 0.016 mol), PPh_3 (4.23 g, 0.016 mol) were dissolved in dry THF (20 mL) and refluxed for 16h. The resulting reaction mixture was concentrated under reduced pressure and purified by flash chromatography (petroleum ether/EtOAc 90:10) without additional work-up. Yellow oil, 94% yield (3.45 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.21 (dd, *J* = 8.7, 0.9 Hz, 2H), 6.87-6.61 (m, 2H), 3.95 (td, *J* = 7.3, 1.0 Hz, 2H), 2.61-2.44 (m, 2H), 2.15-1.96 (m, 2H), 1.21 (s, 9H), 1.04 (dt, *J* = 7.7, 1.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 156.2, 143.5, 126.1, 114.1, 109.8, 83.2, 75.2, 66.6, 34.0, 31.4, 19.8, 14.1, 12.3; HRMS (ESI): calcd for $C_{16}H_{22}O$ 230,1671 [M], found: 230,1675.

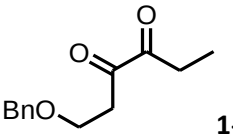


2-Hept-3-ynyl-isoindole-1,3-dione III. Hept-3-yn-1-ol (2.0 g, 0.026 mol), phtalimmide (3.47 g, 0.023 mol), DIAD (5.25 g, 0.026 mol), PPh_3 (6.19 g, 0.026 mol) were dissolved in dry THF (30 mL) and reacted for 10h. The solvent was removed under reduced pressure and the resulting slurry was crystallized in Et_2O/*n*-hexane in order to remove triphenylphosphine oxide. After concentration, the so obtained oil was purified by Flash chromatography (petroleum ether/EtOAc 90:10). Yellow solid, Mp = 48° C, 92% yield (5.01 g). FTIR (film), cm^{-1} ν: 3473, 2985, 2937, 1775, 1719, 1615, 1468, 1395, 1364, 1246, 1186, 1096, 1001; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.84 (dd, *J* = 5.3, 3.1 Hz, 2H), 7.71 (dd, *J* = 5.4, 3.0 Hz, 2H), 3.83 (t, *J* = 7.2 Hz, 2H), 2.55 (ddd, *J* = 7.2, 4.9, 2.4 Hz, 2H), 2.12-1.94 (m, 2H), 1.46-1.35 (m, 2H), 0.86 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, CDC_3) δ: 168.0, 133.8, 132.0, 123.1, 82.2, 75.9, 37.1, 22.1, 21.5, 20.5, 18.6, 13.3; HRMS (ESI): calcd for $C_{15}H_{15}NNaO_2$: 264,1000 [M+Na], found: 264,1008.

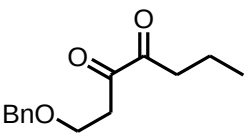
7. Synthesis of 1,2-diketones 1 (Method A)



In a 2 L Erlenmeyer flask, alkyne A (17.8 mmol) was dissolved in 670 mL of acetone and cooled to 0° C. To this vigorous stirred solution $MgSO_4$ (4.2 g, 34.4 mmol) and $NaHCO_3$ (0.9 g, 10.7 mmol) were added in water (390 mL) followed by finely grounded $KMnO_4$ (10.9 g, 69.2 mmol). After 4 h reaction, $NaNO_2$ (6.0 g, 86.9 mmol) was added portionwise. Further a H_2SO_4 water solution (50 mL, 0.1M) and 0.7 mL of H_2SO4 conc. were added. After 20 minutes, NaCl (100g) was loaded to the reaction favouring the formation of two phases which were separated in a glass funnel. The water media was further extracted with Et2O/hexane (1:1). The organic phase was washed with a NaOH solution (50 mL, 0.1M), dried on Na_2SO_4, filtered and concentrated under reduced pressure. Flash chromatography (petroleum ether/Et_2O 95:5) allowed to isolate the corresponding dione as a pure product.[5]

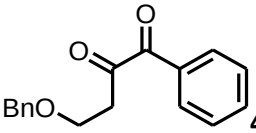


1-(benzyloxy)hexane-3,4-dione 1k. Hex-3-ynyloxymethyl-benzene (1.8 g, 10 mmol), acetone (370 mL), $MgSO_4$ (2.3 g, 19 mmol), $NaHCO_3$ (0.5 g, 6 mmol), H_2O (220 mL), $KMnO_4$ (6.1 g, 38.8 mmol), $NaNO_2$ (3.3 g, 48.8 mmol). Flash chromatography (petroleum ether/Et_2O 95:5-80:20). Yellow oil, 53% yield (1.21 g); FTIR (film), cm^{-1} ν: 2926, 1717, 1573, 1496, 1475, 1388, 1273, 1175, 1092, 1011, 819; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.47-7.17 (m, 5H), 4.50 (s, 2H), 3.78 (t, *J* = 6.1 Hz, 2H), 3.03 (t, *J* = 6.1 Hz, 1H), 2.75 (q, *J* = 7.2 Hz, 2H), 1.07 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 202.6, 200.8, 140.5, 131.0, 130.3, 130.3, 75.8, 67.3, 39.4, 32.0, 9.4; HRMS (ESI): calcd for $C_{13}H_{16}NaO_3$: 243,0997 $[M+Na]^+$, found: 243,0999. Spectral data are in agreement with the literature.[5]

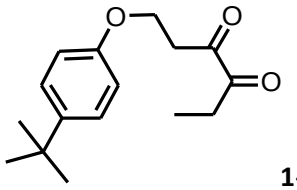


1-Benzyloxy-heptane-3,4-dione 1l. Hept-3-ynyloxymethyl-benzene (2.02 g, 10 mmol), acetone (370 mL), $MgSO_4$ (2.3 g, 19 mmol), $NaHCO_3$ (0.5 g, 6 mmol), H_2O (220 mL), $KMnO_4$ (6.1 g, 38.8 mmol), $NaNO_2$ (3.3 g, 48.8 mmol). Flash chromatography (petroleum ether/Et_2O 95:5-90:10). Yellow oil, 71% yield (1.66 g). FTIR (film), cm^{-1} ν: 3067, 3030, 2955, 2934, 2861, 1724, 1452, 1274, 1123, 1023, 757,

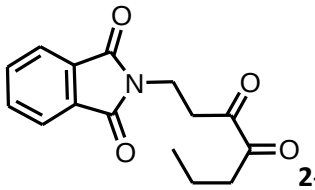
702; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.71-7.07 (m, 5H), 4.50 (s, 2H), 3.78 (t, *J* = 6.1 Hz, 2H), 3.03 (t, *J* = 6.1 Hz, 1H), 2.70 (t, *J* = 7.2 Hz, 2H), 1.60 (dd, *J* = 14.7, 7.3 Hz, 2H), 0.92 (t, *J* = 7.4 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 199.7, 198.4, 138.0, 129.7, 128.5, 127.8, 77.1, 73.3, 64.8, 37.9, 36.9, 16.5, 13.7; HRMS (ESI): calcd for $C_{14}H_{18}NaO_3$: 257,1154 $[M+Na]^+$, found: 257,1156. Spectral data are in agreement with the literature.[5]



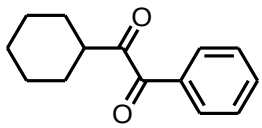
4-Benzyloxy-1-phenyl-butane-1,2-dione 1m. Alkyne **I** (371 mg, 1.57 mmol), acetone (60 mL), $MgSO_4$ (788 mg, 6.56 mmol), $NaHCO_3$ (79 mg, 0.94 mmol), H_2O (35 mL), $KMnO_4$ (964 mg, 6.10 mmol), $NaNO_2$ (404 mg, 5.85 mmol). Flash chromatography (petroleum ether/Et_2O 95:5-90:10). Yellow oil, 78% yield (328.2 mg). FTIR (film), cm^{-1} ν: 2977, 2872, 2244, 1714, 1673, 1597, 1450, 1383, 1111; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.99-7.78 (m, 2H), 7.56-7.50 (m, 1H), 7.37 (t, *J* = 7.8 Hz, 2H), 7.18 (dd, *J* = 8.7, 5.7 Hz, 3H), 7.14-7.09 (m, 2H), 4.37 (s, 2H), 3.79 (t, *J* = 6.0 Hz, 2H), 3.07 (t, *J* = 6.0 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 201.5, 191.8, 137.6, 134.4, 131.9, 130.3, 128.6, 128.3, 127.6, 127.6, 73.2, 64.7, 39.4; HRMS (ESI): calcd for $C_{17}H_{16}NaO_3$: 291,0997 [M+Na], found: 291,0998.



1-(4-tert-Butyl-phenoxy)-hexane-3,4-dione 1n. Alkyne **II** (2.12 g, 9.21 mmol), acetone (341 mL), $MgSO_4$ (4.64 g, 0.038 mol), $NaHCO_3$ (465 mg, 5.53 mmol), H_2O (205 mL), $KMnO_4$ (5.66 g, 0.035 mol), $NaNO_2$ (2.39 g, 0.034 mol). Flash chromatography (petroleum ether/Et_2O 95:5-90:10). Yellow solid Mp = 45-47° C, 88% yield (2.04 g). FTIR (film), cm^{-1} ν: 2965, 2254, 1774, 1715, 1609, 1513, 1392, 1245, 1185, 1086, 909; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.29-7.12 (m, 2H), 6.84-6.61 (m, 2H), 4.19 (t, *J* = 6.2 Hz, 2H), 3.12 (t, *J* = 6.2 Hz, 2H), 2.71 (q, *J* = 7.2 Hz, 2H), 1.21 (s, 9H), 1.02 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 199.7, 197.3, 156.0, 143.8, 126.2, 114.0, 74.3, 62.4, 36.3, 34.0, 31.4, 29.3; HRMS (ESI): calcd for $C_{16}H_{22}NaO_3$: 285,1467 [M+Na], found: 285,1471.

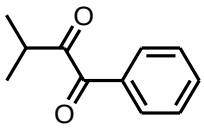


2-(3,4-Dioxo-heptyl)-isoindole-1,3-dione 1o. Alkyne **III** (3.0 g, 0.012 mol), acetone (460 mL), $MgSO_4$ (6.24 g, 0.052 mmol), $NaHCO_3$ (624 mg, 7.42 mmol), H_2O (276 mL), $KMnO_4$ (7.62 g, 0.048 mmol), $NaNO_2$ (3.21 g, 0.046 mmol). Flash chromatography (petroleum ether/Et_2O 95:5-90:10). Yellow oil, 90% yield (2.94 g). FTIR (film), cm^{-1} ν: 3459, 2966, 2254, 1774, 1712, 1444, 1400, 1370, 1188, 969; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.78-7.70 (m, 2H), 7.70-7.62 (m, 2H), 3.90 (td, *J* = 6.8, 2.4 Hz, 2H), 3.05 (td, *J* = 6.8, 1.8 Hz, 2H), 2.67 (td, *J* = 7.3, 2.4 Hz, 2H), 1.53 (ddd, *J* = 14.7, 7.3, 2.6 Hz, 2H), 0.93-0.80 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 198.5, 196.5, 185.7, 168.1, 134.0, 131.5, 123.2, 37.3, 34.9, 32.7, 16.1, 13.3; HRMS (ESI): calcd for $C_{15}H_{15}NNaO_4$: 296,0899 [M+Na], found: 296,0902.



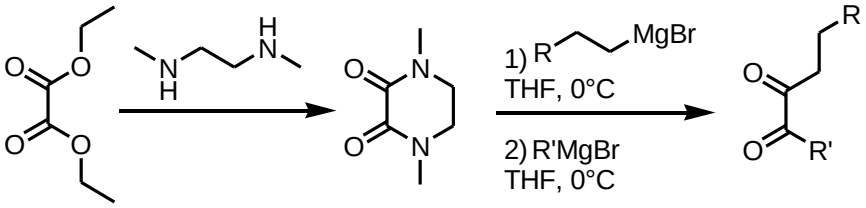
Cyclohexyl-2-phenylethane-1,2-dione 1p. Alkyne **VI** (2.57 g, 0.0138 mol), acetone (530 mL), $MgSO_4$ (7.28 g, 0.060 mmol), $NaHCO_3$ (717 mg, 8.53 mmol), H_2O (320 mL), $KMnO_4$ (8.76 g, 0.055 mmol), $NaNO_2$ (3.74 g, 0.053 mmol). Flash chromatography (petroleum ether/Et_2O 95:5-90:10). Yellow oil; Yield: 87% (2.60 g); FTIR (film), cm^{-1} ν: 2930, 2854, 1787, 1707, 1675, 1596, 1363, 1271, 1143, 1069, 916; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.92-7.70 (m, 2H), 7.66-7.46 (m, 1H), 7.41 (dd, *J* = 11.6, 4.1 Hz, 2H), 3.01 (tt, *J* = 11.2, 3.5 Hz, 1H), 2.00-1.80 (m, 2H), 1.80-1.68 (m, 2H), 1.61 (dd, *J* = 9.4, 3.4 Hz, 1H), 1.41-1.31 (m, 2H), 1.31-

1.22 (m, 2H), 1.21-1.11 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 206.0, 194.1, 134.4, 132.5, 129.8, 128.8, 45.9, 27.2, 25.7, 25.3; HRMS (ESI): calcd for $C_{14}H_{16}NaO_2$: 239,1048 [M+Na], found: 239,1053. Spectral data are in agreement with the literature.[6]



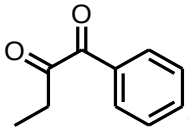
3-Methyl-1-phenyl-butane-1,2-dione 1q. Alkyne **V** (1.73 g, 0.012 mol), acetone (460 mL), $MgSO_4$ (6.24 g, 0.052 mmol), $NaHCO_3$ (624 mg, 7.42 mmol), H_2O (276 mL), $KMnO_4$ (7.62 g, 0.048 mmol), $NaNO_2$ (3.21 g, 0.046 mmol). Flash chromatography (petroleum ether/Et_2O 95:5-90:10). Yellow oil; Yield: 89% (1.88 g); FTIR (film), cm^{-1} ν: 2978, 2873, 2253, 1773, 1717, 1514, 1383, 1339, 1250, 1111, 908; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.90 (d, *J* = 7.5 Hz, 2H), 7.65 (t, *J* = 7.5 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 2H), 3.34-3.25 (m, 1H), 1.18 (s, 3H), 1.16 (s, 3H); ^{13}C NMR (126 Hz, $CDCl_3$) δ: 206.6, 194.1, 134.5, 132.5, 130.1, 129.8, 128.8, 36.5, 16.9, 16.8; HRMS (ESI): calcd for $C_{11}H_{12}NaO_2$: 199,0735 [M+Na]$^+$, found: 199,0741. Spectral data are in agreement with the literature.[7]

8. Synthesis of 1,2-diketones 1 (Method B)

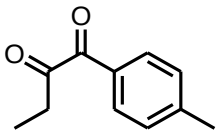


1.4-Dimethylpiperazine-2,3-dione synthesis. To a stirred solution of dimethylethylenediamine (10.3 g, 0.117 mol) in 200 mL of anhydrous ether was added diethyl oxalate (17.1 g, 0.117 mol) in one portion. After a few minutes white crystals began to precipitate. The mixture was stirred overnight. The product was filtered and washed with dry ether. Recrystallization from EtOAc produced the desired compound in 92% (g), mp 178-80 °C [8]

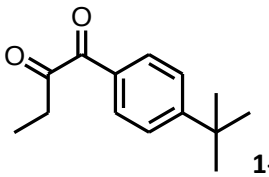
Synthesis of unsymmetrical diones from 1.4-dimethylpiperazine-2,3-dione. To a stirred THF solution (50 mL) of dimethylpiperazine-2,3-dione (1.0 g, 7.0 mmol) refrigerated to 0° C by an ice bath, the first Grignard reagent is added over 15 minutes (7.0 mmol). Then, a second Grignard reagent (7.0 mmol) is added and the resulting solution is gently warmed-up to 50° C and stirred at this temperature for 6 hours. Once cooled to rt, the reaction mixture is treated with a 1.0 M solution of HCl and extracted with Et_2O (3 x 20 mL). The resulting organic phase is dried over Na_2SO_4, filtered and concentrated under reduced pressure. Flash chromatography on silica gel hexanes-Et_2O (95:5-50:50) afforded the corresponding diketones as yellow-orange oils. [8]



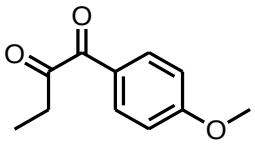
1-Phenyl-butane-1,2-dione 1e. 1.4-Dimethylpiperazine-2,3-dione (1.0 g, 7.04 mmol), THF (30 mL), EtMgCl (2.0 M, 3.5 mL, 7.04 mmol), PhMgCl (2.0 M, 3.5 mL, 7.04 mmol). Flash chromatography (petroleum ether/Et_2O 95:5-90:10). Yellow oil, 82% yield (935 mg); FTIR (film), cm^{-1} ν: 2980, 2932, 1711, 1672, 1596, 1449, 1379, 1270, 1122, 1097, 1046; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.97 (d, *J* = 8.0 Hz, 2H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.48 (t, *J* = 8.0 Hz, 2H), 2.90 (q, *J* = 7.3 Hz, 2H), 1.18 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 203.8, 192.4, 132.0, 130.0, 128.7, 32.0, 6.8. Spectral data are in agreement with the literature[5]



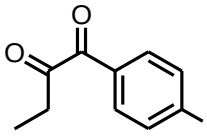
1-p-Tolyl-butane-1,2-dione 1f. 1.4-Dimethylpiperazine-2,3-dione (1.0 g, 7.04 mmol), THF (30 mL), EtMgCl (2.0 M, 3.5 mL, 7.04 mmol), *p*-MeC_6H_4MgBr (1.6 M, 4.4 mL, 7.04 mmol). Flash chromatography (petroleum ether/Et_2O 95:5-90:10). Yellow oil, 80% yield (991 mg); FTIR (film), cm^{-1} ν: 2974, 2937, 1713, 1667, 1605, 1576, 1476, 1408, 1337, 1272, 1183, 1085, 881; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.87 (t, *J* = 8.8 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 1H), 2.89 (q, *J* = 7.3 Hz, 1H), 2.43 (s, 2H), 1.19 (t, *J* = 7.3 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 204.0, 192.2, 145.7, 130.2, 129.5, 126.7, 32.0, 21.8. Spectral data are in agreement with the literature[9]



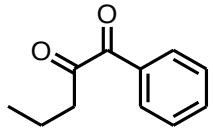
1-(4-tert-Butyl-phenyl)-butane-1,2-dione 1g. 1.4-Dimethylpiperazine-2,3-dione (1.0 g, 7.04 mmol), THF (30 mL), EtMgCl (2.0 M, 3.5 mL, 7.04 mmol), *p*-t-Bu-C_6H_4MgBr (2.3 M, 3.1 mL, 7.04 mmol). Flash chromatography (petroleum ether/Et_2O 95:5-90:10). Yellow oil, 88% yield (1.35 g); FTIR (film), cm^{-1} ν: 2986, 2254, 1774, 1711, 1670, 1602, 1460, 1273, 1105, 908; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.84 (d, *J* = 8.5 Hz, 2H), 7.43 (d, *J* = 8.5 Hz, 2H), 2.82 (q, *J* = 7.3 Hz, 2H), 1.26 (s, 9H), 1.12 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 204.0, 192.3, 158.6, 130.1, 129.4, 125.8, 35.3, 32.1, 31.0, 30.8; HRMS (ESI): calcd for $C_{14}H_{18}NaO_2$: 241,1204 $[M+Na]^+$, found: 241,1209.



1-(4-Methoxy-phenyl)-butane-1,2-dione 1h. 1.4-Dimethylpiperazine-2,3-dione (1.0 g, 7.04 mmol), THF (30 mL), EtMgCl (2.0 M, 3.5 mL, 7.04 mmol), *p*-MeO-C_6H_4MgBr (2.0 M, 3.6 mL, 7.04 mmol). Flash chromatography (petroleum ether/Et_2O 95:5-90:10). Yellow oil, 78% yield (1.05 g); FTIR (film), cm^{-1} ν: 2925, 2852, 1712, 1660, 1596, 1576, 1509, 1337, 1255, 1176, 1083, 852; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.97 (d, *J* = 8.8 Hz, 2H), 6.95 (d, *J* = 8.8 Hz, 2H), 3.88 (s, 3H), 2.89 (q, *J* = 7.3 Hz, 2H), 1.18 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 204.3, 191.1, 164.7, 132.5, 124.9, 114.1, 55.5, 32.1; HRMS (ESI): calcd for $C_{11}H_{12}NaO_3$: 215,0684 $[M+Na]^+$, found: 215,0686. Spectral data are in agreement with the literature[10]

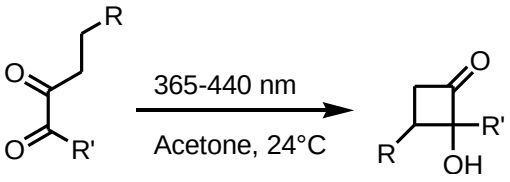


1-(4-Fluoro-phenyl)-butane-1,2-dione 1i. 1.4-Dimethylpiperazine-2,3-dione (1.0 g, 7.04 mmol), THF (30 mL), EtMgCl (2.0 M, 3.5 mL, 7.04 mmol), *p*-F-C_6H_4MgBr (1.5 M, 4.7 mL, 7.04 mmol). Flash chromatography (petroleum ether/Et_2O 95:5-90:10). Yellow oil, 81% yield (1.03 g); ^1H NMR (500 MHz, $CDCl_3$) δ: 7.97-7.94 (m, 2H), 7.06 (dd, *J* = 5.0, 15.0 Hz, 2H), 2.82 (q, *J* = 5.0 Hz, 2H), 1.09 (t, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 203.2, 190.3, 166.5 (d, *J* = 257.6 Hz), 133.0 (d, *J* = 9.7 Hz), 128.5 (d, *J* = 2.9 Hz), 117.1 (d, *J* = 22.8 Hz), 116.0 (d, *J* = 22.1 Hz), 31.9, 6.7; HRMS (ESI): calcd for $C_{10}H_9FNaO_2$: 203,0484 [M+Na], found: 203,0489.



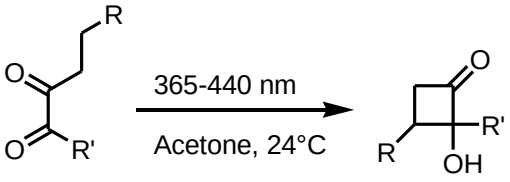
1-Phenyl-pentane-1,2-dione 1j. 1.4-Dimethylpiperazine-2,3-dione (1.0 g, 7.04 mmol), THF (30 mL), *n*-PrMgCl (2.0 M, 3.5 mL, 7.04 mmol), PhMgBr (2.0 M, 3.5 mL, 7.04 mmol). Flash chromatography (petroleum ether/Et_2O 95:5-90:10). Yellow oil, 75% yield (1.00 g); ^1H NMR (500 MHz, $CDCl_3$) δ: 7.97 (d, *J* = 6.8 Hz, 2H), 7.65-7.60 (m, 1H), 7.51-7.46 (m, 2H), 2.85 (t, *J* = 7.2 Hz, 2H), 1.77-1.68 (m, 2H), 1.00 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ: 203.4, 192.5, 134.5, 131.9, 130.1, 128.8, 40.6, 16.4, 13.6. Spectral data are in agreement with the literature.[5]

9. General procedure for the synthesis of cyclobutanones 2 (batch).



In a Duran tube equipped with a magnetic stirring bar and a rubber septum, diones **1** (3.5 mmol) were added and diluted with acetone (35 mL) under argon. The stirred solution was irradiated at 365-440 nm (UV-blue LED) for 2-24h (25° C) and followed by GC-MS until completion. The organic solutions were evaporated under reduced pressure and purified by flash chromatography (*n*-hexane/Et_2O, 10:1-5:1-3:1) without previous work-up[5]

10. General procedure for the synthesis of cyclobutanones 2 (continuous flow)

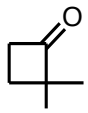


Method A

A 0.1 M solution of diketone **1** in acetone, was loaded in a 20 mL syringe wrapped with aluminium foil. The syringe is mounted on a syringe-pump apparatus calibrated so that 0.5 mL/min are dispensed constantly. The syringe outer is directly connected to a 30 m FEP-tube (ø 0.8 x ø 1.6 mm) tightly rolled to a glass Duran tube (three layers), flow direction outer→inner. The final end of the tube is inserted through a septum inside an Erlenmeyer in order to collect the reaction mixture. The solution is then concentrated under vacuum in order to eliminate the excess of unreacted reagents and the solvent. Cyclobutanone **2** is generally pure enough not to require further purification. Where needed, chromatography purification conditions have been indicated in the specific entries.

Method B

A 0.1 M solution of diketone **1** in acetone, was loaded in a 1.0 L amber glass bottle connected with an HPLC pump calibrated so that 1.0 mL/min are dispensed constantly. The HPLC outer is connected to a 30 m FEP-tube (ø 0.8 x ø 1.6 mm) tightly rolled to a glass Duran tube (three layers), flow direction outer→inner. The final end of the tube is inserted in an amber glass bottle in order to collect the reaction mixture. At the end of the reaction, the solution is concentrated under vacuum in order to eliminate the excess of unreacted reagents and the solvent.

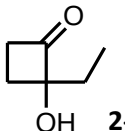


2-Hydroxy-2-methyl-cyclobutanone 2a. Compound **2a** was synthetized as described:

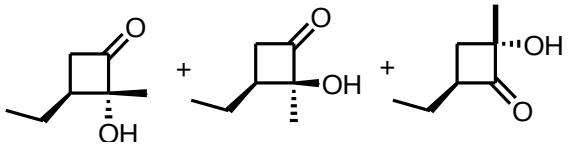
Method A (1.1h reaction). Pentane-2,3-dione **1a** (350 mg, 3.50 mmol), acetone (35 mL), flow: 0.5 mL/min. Colourless oil, 96% yield (335 mg); FTIR (film), cm^{-1} ν: 3373, 2976, 2951, 1787, 1716, 1445, 1368, 1314, 1269, 1158, 1041, 973; ^1H NMR (500 MHz, $CDCl_3$) δ: 3.39 (br. s, 1H), 3.52 (br. s, 1H), 2.99-2.83 (m, 1H), 2.83-2.71 (m, 1H), 2.18-2.07 (m, 1H), 2.07-1.98 (m, 1H), 1.44 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 211.9, 88.3, 39.3, 28.1, 22.2. Spectral data are in agreement with the literature.[11]

Method B (4h reaction). Pentane-2,3-dione **1a** (2.5 g, 0.025 mol), acetone (250 mL), flow: 1.0 mL/min. Colourless oil, 91% yield (2.18 g).

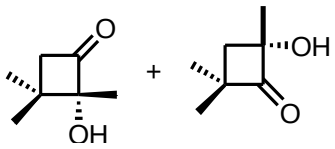
Method B (8h reaction). Pentane-2,3-dione **1a** (5.0 g, 0.050 mmol), acetone (500 mL), flow: 1.0 mL/min.. Colourless oil, 90% yield (4.35 g).



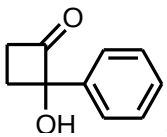
2-Ethyl-2-hydroxy-cyclobutanone 2b. Hexane-3,4-dione **1b** (1,14 g, 10.0 mmol), acetone (100 mL), flow: 0.5 mL/min. Colourless oil, 97% yield (1.10 g); FTIR (film), cm^{-1} ν: 3427, 2971, 2940, 1784, 1719, 1462, 1398, 1274, 1176, 1076, 1014, 948; ^{1}H NMR (500 MHz, $CDCl_3$) δ: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.80 (br. s, 1H), 2.78 (ddd, *J* = 17.8, 10.8, 9.6 Hz, 1H), 2.70 (ddd, *J* = 17.7, 10.5, 5.3 Hz, 1H), 2.08 (td, *J* = 11.3, 5.3 Hz, 1H), 1.98-1.88 (m, 1H), 1.68 (dt, *J* = 14.5, 7.2 Hz, 2H), 0.93 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 212.5, 91.5, 39.3, 28.3, 26.0, 7.5; HRMS (ESI): calcd for $C_6H_{11}O_2$: 115,0759 $[M+H]^+$, found: 115,0760. Spectral data are in agreement with the literature.[5]



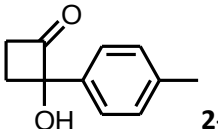
3-Ethyl-2-hydroxy-2-methyl-cyclobutanone 2c. Heptane-2,3-dione **1c** (1.28 g, 10.0 mmol), acetone (100 mL), flow: 0.5 mL/min. Flash chromatography (*n*-hexane/Et_2O, 9:1-3:1). Colourless oil, 94% yield (1.20 g), (mixture of stereo and regioisomers, ratio: 1:04,02); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.79 (br. s, 1H), 3.56 (br. s, 1H), 3.27-3.10 (m, 1H), 3.05-2.91 (m, 1H), 2.77 (ddd, *J* = 29.6, 18.7, 8.4 Hz, 2H), 2.46 (td, *J* = 16.8, 10.3 Hz, 2H), 2.36- 2.30 (m, 1H), 2.29-2.22 (m, 1H), 2.11 (m, 2H), 1.83-1.55 (m, 6H), 1.46 (ddd, *J* = 21.2, 13.6, 8.4 Hz, 3H), 1.40 (s, 1H), 1.26 (s, 3H), 0.96 (t, *J* = 6.5 Hz, 3H), 0.90 (t, *J* = 7.3 Hz, 3H), 0.87-0.81 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 211.5, 210.6, 91.0, 88.3, 85.3, 55.8, 53.2, 44.8, 44.7, 41.3, 40.7, 35.9, 35.2, 32.8, 32.8, 30.7, 25.6, 23.0, 22.9, 22.7, 22.7, 22.0, 21.9, 16.6, 13.7, 12.7, 12.7, 11.6; HRMS (ESI): calcd for $C_7H_{13}O_2$: 129,0916 $[M+H]^+$, found: 129,0933. Spectral data are in agreement with the literature.[11]



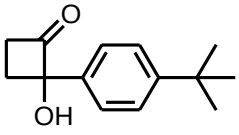
2-**Hydroxy-2,3,3-trimethyl-cyclobutanone 2d.** 5-Methyl-hexane-2,3-dione **1d** (1.28 g, 10 mmol), acetone (100 mL), flow: 0.5 mL/min. Flash chromatography (*n*-hexane/Et_2O, 9:1-3:1). Colourless oil, 94% yield (1.21 g), (mixture of regioisomers, ratio: 1:03); Minor regioisomer**,** 2-hydroxy-2,3,3-trimethyl-cyclobutanone) ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.70 (d, *J* = 16.6 Hz, 1H), 2.37 (d, *J* = 16.6 Hz, 1H), 1.30 (s, 3H), 1.22 (s, 3H), 1.07 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 211.9, 88.2, 53.3, 34.7, 23.7, 22.5, 22.1. (Major regioisomer, 2-hydroxy-2,4,4-trimethyl-cyclobutanone) ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.99 (AB q, *J* = 5.0 Hz, 2H), 1.40 (s, 3H), 1.19 (s, 3H), 1.17 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 219.5 85.2, 53.3 44.2, 34.7, 23.5, 22.1, 19.0. Spectral data are in agreement with the literature.[12]



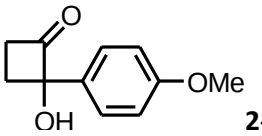
2-Hydroxy-2-phenyl-cyclobutanone 2e. 1-Phenyl-butane-1,2-dione **1e** (810 mg, 5.0 mmol), acetone (50 mL), flow: 0.5mL/min. Colourless oil, 96% yield (777 mg); FTIR (film), cm^{-1} ν: 3407, 2923, 2842, 1781, 1494, 1452, 1070, 1005, 757, 702; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.65-7.22 (m, 5H), 3.66 (s, 1H), 3.02-2.91 (m, 2H), 2.74-2.63 (m, 1H), 2.36 (dd, *J* = 22.1, 10.2 Hz, 1H); ^{13}C NMR S14 (126 MHz, $CDCl_3$) δ: 209.2, 138.8, 129.0, 128.8, 126.1, 92.6, 41.0, 28.0; HRMS (ESI): calcd for $C_{10}H_{11}O_2$: 163,0759 $[M+H]^+$, found: 163,0760. Spectral data are in agreement with the literature.[5]



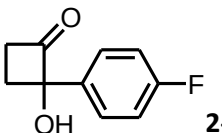
2-Hydroxy-2-p-tolyl-cyclobutanone 2f. 1-tolyl-butane-1,2-dione **1f** (880 mg, 5.0 mmol), acetone (50 mL), flow: 0.5 mL/min. Colourless oil, 91% yield (800 mg). FTIR (film), cm^{-1} ν: 3486, 2932, 2852, 1783, 1715, 1607, 1511, 1450, 1408, 1242, 1182, 1071, 1012, 917; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.34 (d, *J* = 7.8 Hz, 2H), 7.19 (d, *J* = 7.8 Hz, 2H), 2.97-2.86 (m, 2H), 2.66 (ddd, *J* = 11.8, 9.6, 6.7 Hz, 1H), 2.42 (d, *J* = 6.0 Hz, 1H), 2.34 (s, 2H), 2.39-2.25 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 209.2, 138.6, 135.6, 130.1, 129.5, 126.0, 92.1, 40.7, 27.6, 21.1; HRMS (ESI): calcd for $C_{11}H_{13}O_2$: 177,0916 $[M+H]^+$, found: 177,1261. Spectral data are in agreement with the literature.[11]



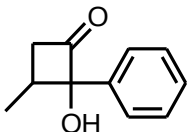
2-(4-tert-Butyl-phenyl)-2-hydroxy-cyclobutanone 2g. 1-(4-tert-Butyl-phenyl)-butane-1,2-dione **1g** (1.09 g, 5.0 mmol), acetone (50 mL), flow: 0.5 mL/min. Colourless oil, 90% yield (980 mg). FTIR (film), cm^{-1} ν: 3021, 2967, 2253, 1790, 1605, 1470, 1382, 1218, 1109, 1024, 907; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.37-7.30 (m, 2H), 2.98-2.81 (m, 2H), 2.64 (ddd, *J* = 11.8, 9.6, 6.7 Hz, 1H), 2.29 (dt, *J* = 11.8, 10.2 Hz, 1H), 1.25 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 208.6, 152.0, 135.6, 128.0, 126.0, 125.8, 92.2, 40.9, 33.1, 31.1, 27.6; HRMS (ESI): calcd for $C_{14}H_{18}NaO_2$: 241,1204 $[M+Na]^+$, found: 241,1209.



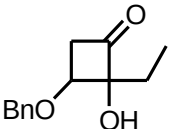
2-Hydroxy-2-(4-methoxy-phenyl)-cyclobutanone 2h. 1-(4-Methoxy-phenyl)-butane-1,2-dione **2h** (960 mg, 5.0 mmol), acetone (50 mL), flow: 0.5 mL/min. Colourless oil, 91% yield (873 mg). FTIR (film), cm^{-1} ν: 3480, 3015, 2987, 1789, 1460, 1217, 1026; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.32 (dd, *J* = 6.9, 1.9 Hz, 2H), 6.84 (dd, *J* = 6.9, 1.9 Hz, 2H), 3.74 (s, 3H), 2.87 (dd, *J* = 10.0, 8.2 Hz, 2H), 2.65-2.52 (m, 1H), 2.35-2.21 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 208.7, 160.0, 130.7, 127.6, 114.4, 92.0, 55.3, 40.7, 27.6; HRMS (ESI): calcd for $C_{11}H_{12}NaO_3$: 215,0684 $[M+Na]^+$, found: 215,0690.



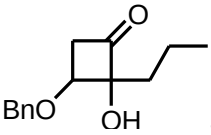
2-(4-Fluoro-phenyl)-2-hydroxy-cyclobutanone 2i. 1-(4-Fluoro-phenyl)-butane-1,2-dione **1i** (900 mg, 5.0 mmol), acetone (50 mL), flow: 0.5 mL/min. Colourless oil, 93% yield (838 mg). FTIR (film), cm^{-1} ν: 3484, 3008, 2984, 1788, 1466, 1219, 1021; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.39-7.36 (m, 2H), 7.02-6.99 (m, 2H), 3.65 (br. s, 1H), 2.95-290 (m, 2H), 2.62-2.56 (m, 1H), 2.33 (dd, *J* = 10 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 208.4, 162.9 (d, *J* = 248.5 Hz), 132.8 (d, *J* = 9.4 Hz), 128.0 (d, *J* = 8.4 Hz), 115.9 (d, *J* = 21.6 Hz), 91.9, 41.0, 28.0; HRMS (ESI): calcd for $C_{10}H_9FNaO_2$: 203,0484 $[M+Na]^+$, found: 203,0487.



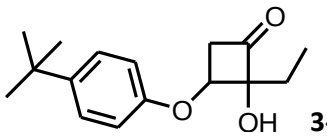
2-Hydroxy-3-methyl-2-phenyl-cyclobutanone 2j. 1-Phenyl-pentane-1,2-dione **1j** (880 mg, 5.0 mmol), acetone (50 mL). Colourless oil, 90% yield (792 mg), flow: 0.5 mL/min (Inseparable 1:0.4 mixture of diastereoisomers); Major isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.52-6.96 (m, 5H), 3.88 (br. s, 1H), 3.12 (dd, *J* = 16.6, 8.8 Hz, 1H), 2.66-2.58 (m, 1H), 2.57-2.54 (m, 1H), 0.88 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 213.7, 140.3, 131.5, 131.0, 129.3, 97.0, 51.7, 37.6, 19.5. Minor isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.52-7.00 (m, 5H), 3.88 (br. s, 1H), 3.00-2.68 (m, 1H), 2.61 (dd, *J* = 14.6, 7.1 Hz, 1H), 2.46 (dd, *J* = 14.6, 4.8 Hz, 1H), 1.27 (d, *J* = 7.1 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 212.2, 142.5, 131.5, 131.0, 128.7, 94.8, 51.6, 34.8, 16.8; HRMS (ESI): calcd for $C_{11}H_{13}O_2$: 177,0916 $[M+H]^+$, found: 177,0917. Spectral data are in agreement with the literature.[5]



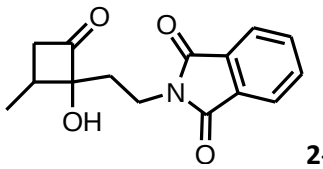
3-Benzyloxy-2-ethyl-2-hydroxy-cyclobutanone 2k. 1-Benzyloxy-hexane-3,4-dione **1k** (1.10 g, 5.0 mmol), acetone (50 mL). Overall yield 92% (1.01 g), flow: 0.5 mL/min. Flash chromatography (*n*-hexane/Et_2O, 10:1-5:1), (1:0.25 mixture of *cis/trans* diastereoisomers); Major isomer ***cis*-2k**, colourless oil, 73% yield (161 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.41-7.24 (m, 5H), 4.64 (s, 2H), 4.05 (dd, *J* = 6.5, 2.4 Hz, 1H), 3.46 (s, 1H), 3.10 (dd, *J* = 18.1, 6.5 Hz, 1H), 2.73 (dd, *J* = 18.1, 2.4 Hz, 1H), 1.84-1.58 (m, 2H), 1.02 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 210.0, 136.8, 128.5, 128.1, 127.8, 91.7, 71.9, 71.6, 47.5, 26.4, 7.4; HRMS (ESI): calcd for $C_{13}H_{17}O_3$: 221,1178 $[M+H]^+$, found: 221,1179. Minor isomer ***trans*-2k**, colourless oil, 19% yield (41 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.39-7.34 (m, 4H), 7.34-7.28 (m, 1H), 4.66 (d, *J* = 11.8 Hz, 1H), 4.59 (d, *J* = 11.7 Hz, 1H), 4.17 (t, *J* = 7.9 Hz, 1H), 2.94 (dd, *J* = 7.9, 0.9 Hz, 1H), 2.94 (dd, *J* = 7.9, 0.9 Hz, 2H), 2.03-1.86 (m, 2H), 1.04 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 209.0, 137.4, 128.3, 127.8, 127.5, 93.1, 74.4, 72.5, 46.5, 23.9, 7.7; HRMS (ESI): calcd for $C_{13}H_{17}O_3$: 221,1178 $[M+H]^+$, found: 221,1178. Spectral data are in agreement with the literature.[5]



3-Benzyloxy-2-hydroxy-2-propyl-cyclobutanone 2l. 1-Benzyloxy-heptane-3,4-dione **1l** (1.17 g, 5.0 mmol), acetone (50 mL). Overall yield 93% (1.06 mg), flow: 0.5 mL/min. Flash chromatography (*n*-hexane/Et_2O, 10:1-5:1), (partially separated 1:0.25 mixture of *cis/trans* diastereoisomers). Major isomer ***cis*-2l**, ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.53-7.15 (m, 5H), 4.63 (dd, *J* = 36.9, 11.8 Hz, 2H), 4.13 (t, *J* = 8.0 Hz, 1H), 3.10-2.80 (m, 2H), 1.89 (td, *J* = 10.9, 5.2 Hz, 2H), 1.57 (ddd, *J* = 18.2, 11.8, 5.2 Hz, 1H), 1.46-1.34 (m, 1H), 0.96 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 208.4, 137.5, 128.6, 128.1, 127.8, 93.2, 74.6, 72.8, 46.9, 46.9, 33.2, 17.0, 14.5, 14.5; HRMS (ESI): calcd for $C_{14}H_{19}O_3$: 235,1334 $[M+H]^+$, found: 235,1335. Minor isomer ***trans*-2l**, colourless oil, (extrapolated from the 80:20 mixture of *cis-/trans*-isomers), ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.49-7.22 (m, 5H), 4.66 (ABq, *J* = 12.4 Hz, 2H), 4.15 (t, *J* = 8.0 Hz, 1H), 4.07 (dd, *J* = 6.5, 2.4 Hz, 1H), 4.07 (dd, *J* = 6.5, 2.4 Hz, 1H), 3.43 (br. s, 1H), 3.14 (dd, *J* = 18.1, 6.5 Hz, 1H), 2.75 (dd, *J* = 18.1, 2.4 Hz, 1H), 1.76-1.36 (m, 4H), 0.97 (t, *J* = 7.5 Hz, 3H); HRMS (ESI): calcd for $C_{14}H_{19}O_3$: 235,1334 $[M+H]^+$, found: 235,1337. Spectral data are in agreement with the literature.[5]

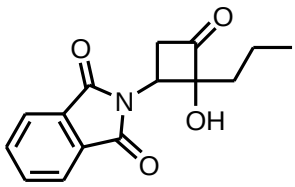


3-(4-tert-Butyl-phenoxy)-2-ethyl-2-hydroxy-cyclobutanone 2n. 1-(4-tert-Butyl-phenoxy)-hexane-3,4-dione **2n** (1.31 g, 5.0 mmol), acetone (50 mL), flow: 0.5 mL/min. Flash chromatography (*n*-hexane/Et_2O, 9:1-5:1). Pale yellow oil, 90% yield (1.16 g). FTIR (film), cm^{-1} ν: 3462, 2967, 2254, 1774, 1711, 1400, 1370, 1188, 1087, 908; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.32 (d, *J* = 8.9 Hz, 2H), 6.95 (d, *J* = 8.9 Hz, 2H), 4.73 (t, *J* = 7.9 Hz, 1H), 3.22 (d, *J* = 8.0 Hz, 2H), 2.00 (dq, *J* = 15.1, 7.6 Hz, 1H), 1.91-1.77 (m, 1H), 1.31 (s, 11H), 1.01 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 207.9, 155.5, 144.2, 126.3, 114.5, 93.4, 72.7, 47.2, 34.1, 31.4, 23.8, 7.5; HRMS (ESI): calcd for $C_{16}H_{22}NaO_3$: 285,1467 $[M+Na]^+$, found: 285,1469.



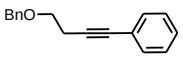
2-[2-(1-Hydroxy-2-methyl-4-oxo-cyclobutyl)-ethyl]-isoindole-1,3-dione 2o. 2-(3,4-Dioxo-heptyl)-isoindole-1,3-dione **1o** (1.36 g, 5.0 mmol), acetone (50 mL), flow: 0.5 mL/min. Flash chromatography (*n*-hexane/Et_2O, 10:1-5:1). Pale yellow oil, overall yield 88% (2;1 mixture of regioisomers, 1.19 g). Major regioisomer extrapolated from the 1:0.33 mixture of regioisomers, FTIR (film), cm^{-1} *ν*: 3438, 2955, 2918, 1770, 1609, 1582, 1514, 1461, 1392, 1360, 1243, 1189, 1132, 1078, 1020, 866; ^{1}H NMR (500

MHz, $CDCl_3$) δ: 7.77 (ddd, *J* = 4.7, 2.9, 1.4 Hz, 2H), 7.64 (dd, *J* = 5.5, 3.0 Hz, 2H), 3.97-3.83 (m, 2H), 2.85 (dd, *J* = 17.0, 9.8 Hz, 1H), 2.42 (dd, *J* = 25.6, 8.5 Hz, 1H), 2.33-2.26 (m, 1H), 2.07 (ddd, *J* = 14.7, 9.8, 7.0 Hz, 1H), 1.89 (ddd, *J* = 14.6, 6.0, 3.9 Hz, 1H), 1.16 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 208.5, 169.0, 133.9, 132.0, 123.2, 89.7, 65.7, 47.1, 33.0, 32.8, 29.1; HRMS (ESI): calcd for $C_{15}H_{15}NNaO_4$: 296,0899 $[M+Na]^+$, found: 296,0901.

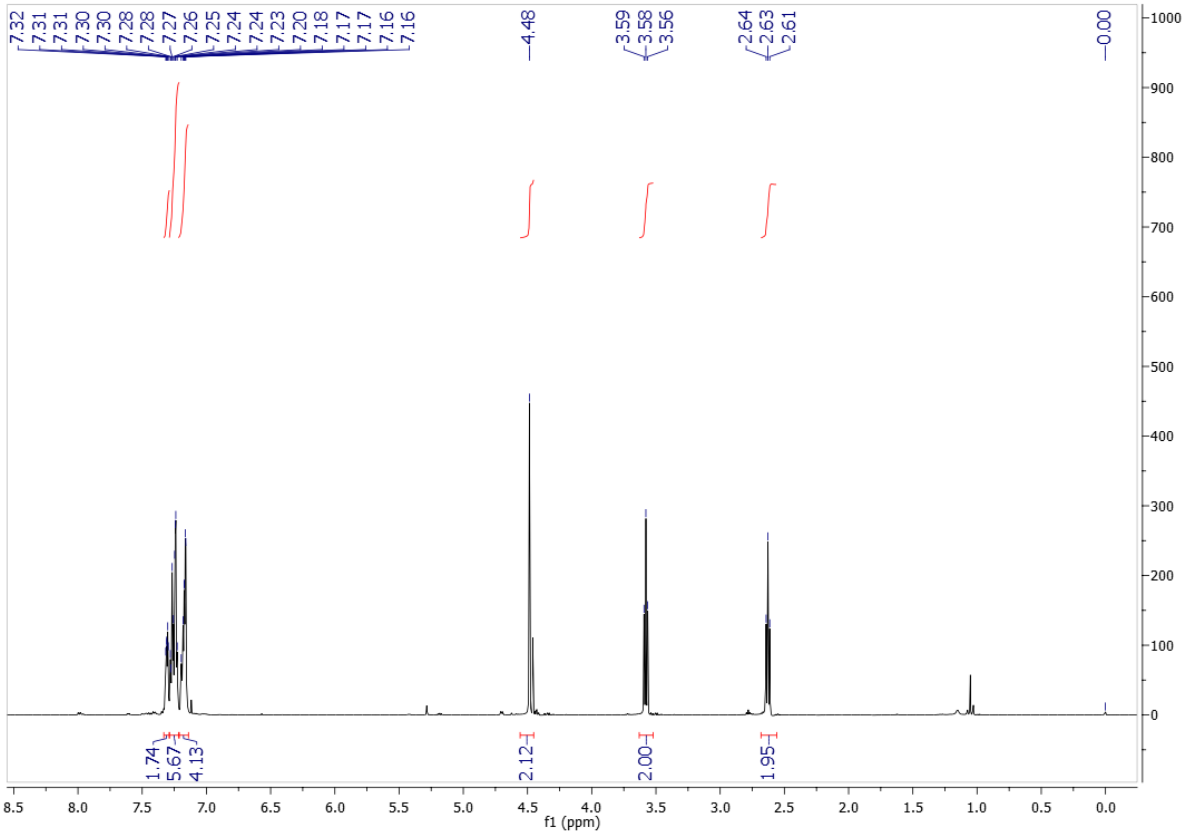


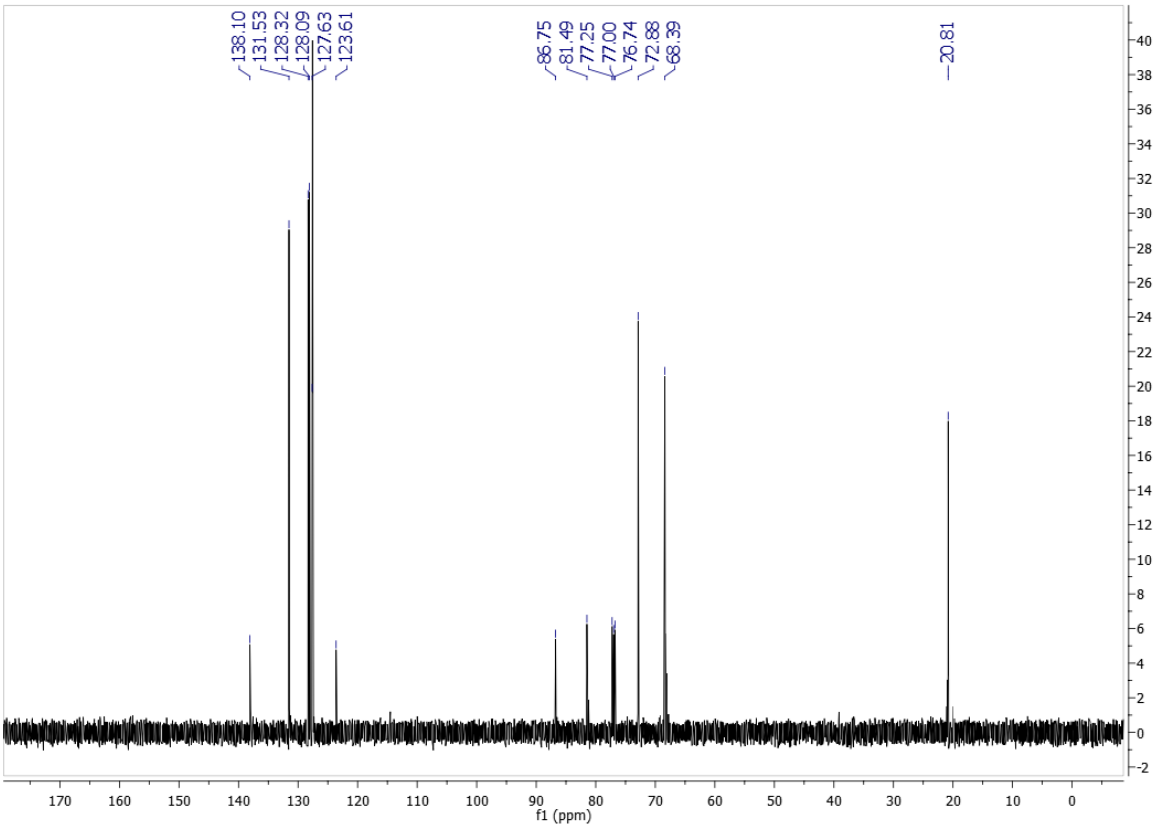
2-(2-Hydroxy-3-oxo-2-propyl-cyclobutyl)-isoindole-1,3-dione 2o' Minor regioisomer, extrapolated from the 1:0.33 mixture of regioisomers, ^1H NMR (500 MHz, $CDCl_3$) δ: δ 7.77 (ddd, *J* = 4.7, 2.9, 1.4 Hz, 2H), 7.64 (dd, *J* = 5.5, 3.0 Hz, 2H), 3.77 (m, 1H), 3.04 (dd, *J* = 16.7, 9.4 Hz, 1H), 2.71 (t, *J* = 7.4 Hz, 1H), 2.29-2.23 (m, 2H), 2.19 (ddd, *J* = 21.7, 9.9, 5.8 Hz, 1H), 2.02-1.93 (m, 1H), 1.05 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 209.2, 168.7, 167.9, 134.0, 131.9, 87.8, 47.9, 33.4, 33.0, 30.7, 14.1; HRMS (ESI): calcd for $C_{15}H_{15}NNaO_4$: 296,0899 $[M+Na]^+$, found: 296,0907.

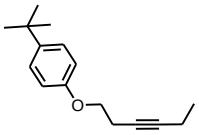
11. ^{1}H and ^{13}C NMR spectra of alkynes I-III



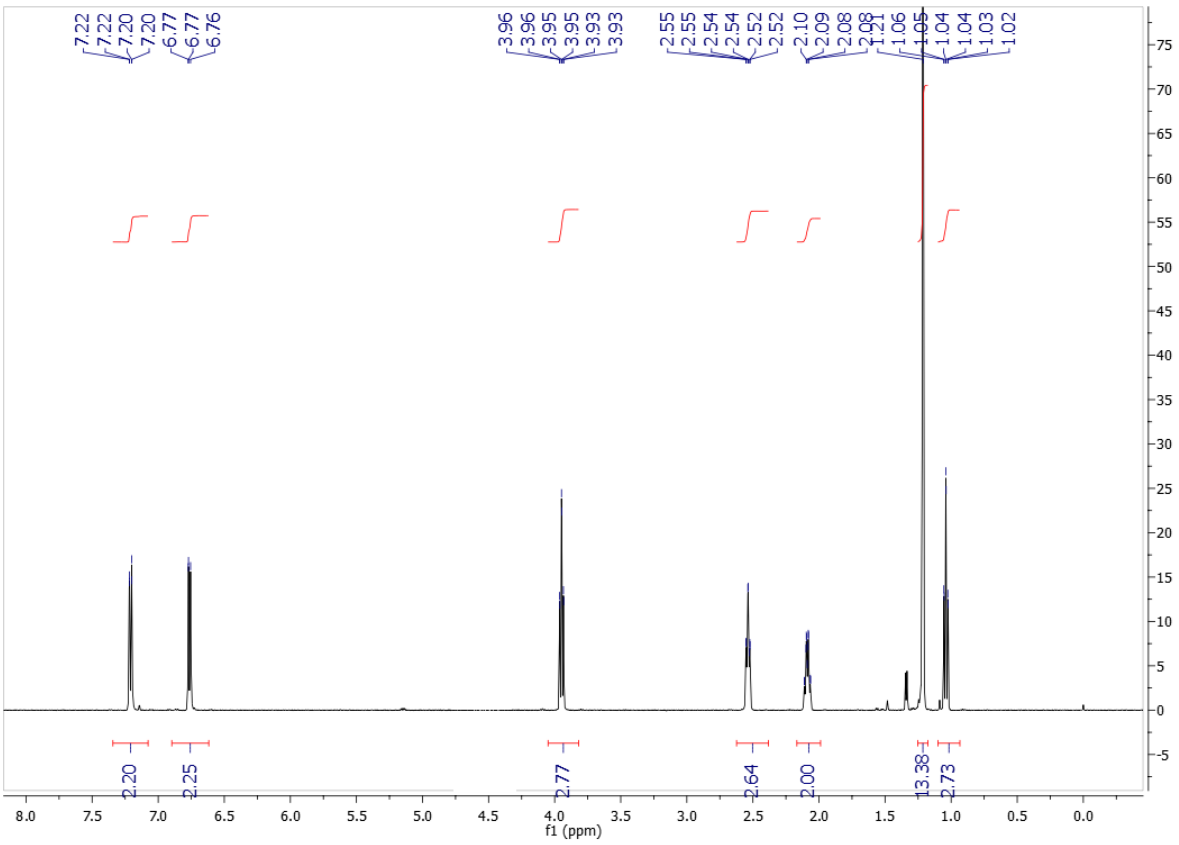
^{1}H (500 MHz) and ^{13}C (126 MHz) NMR spectra of compound **III**

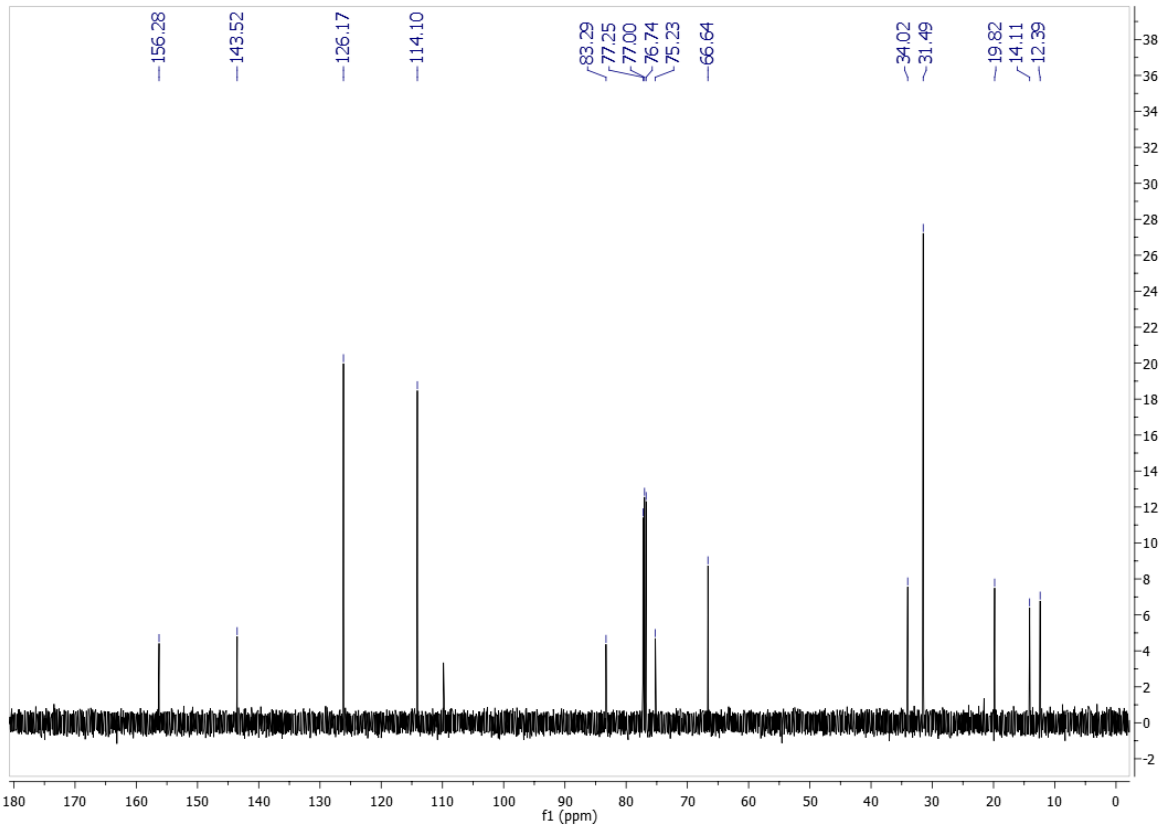


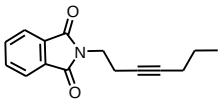




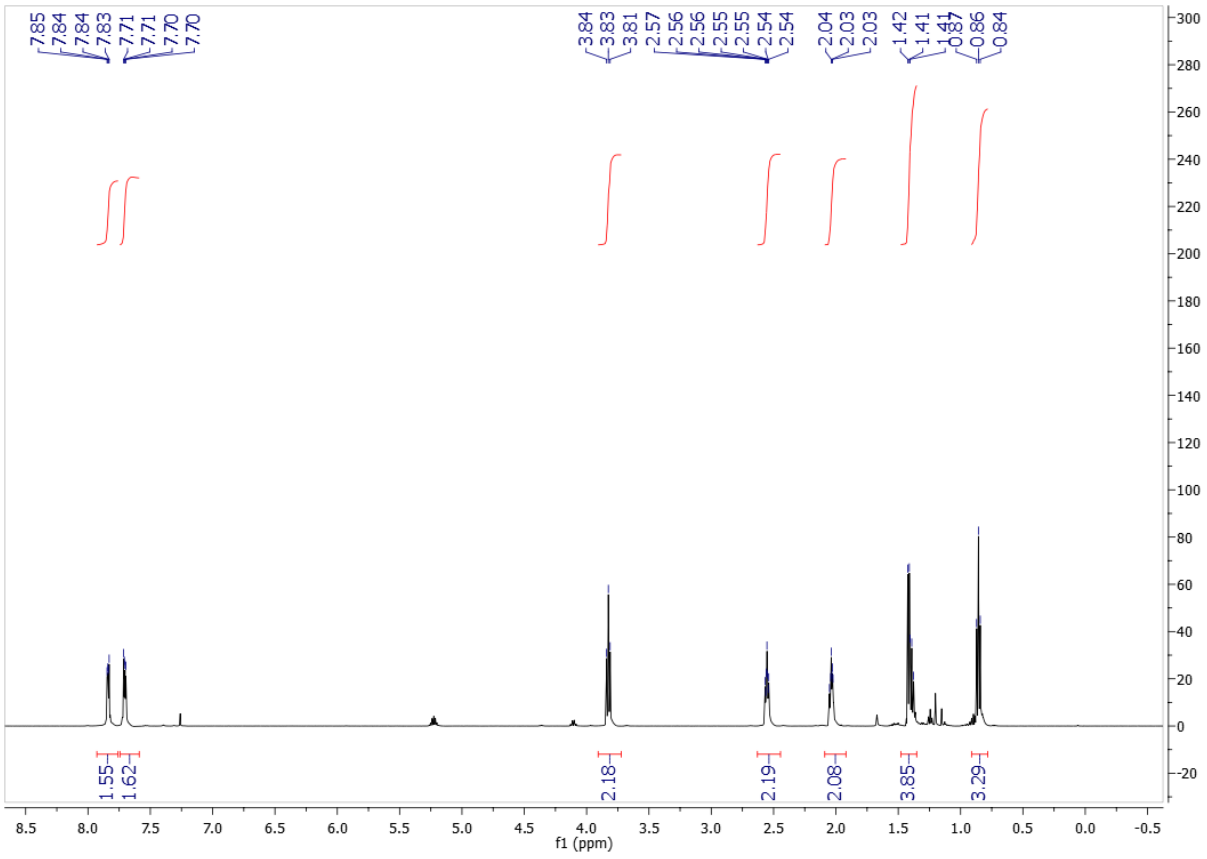
^{1}H (500 MHz) and ^{13}C (126 MHz) NMR spectra of compound **I**

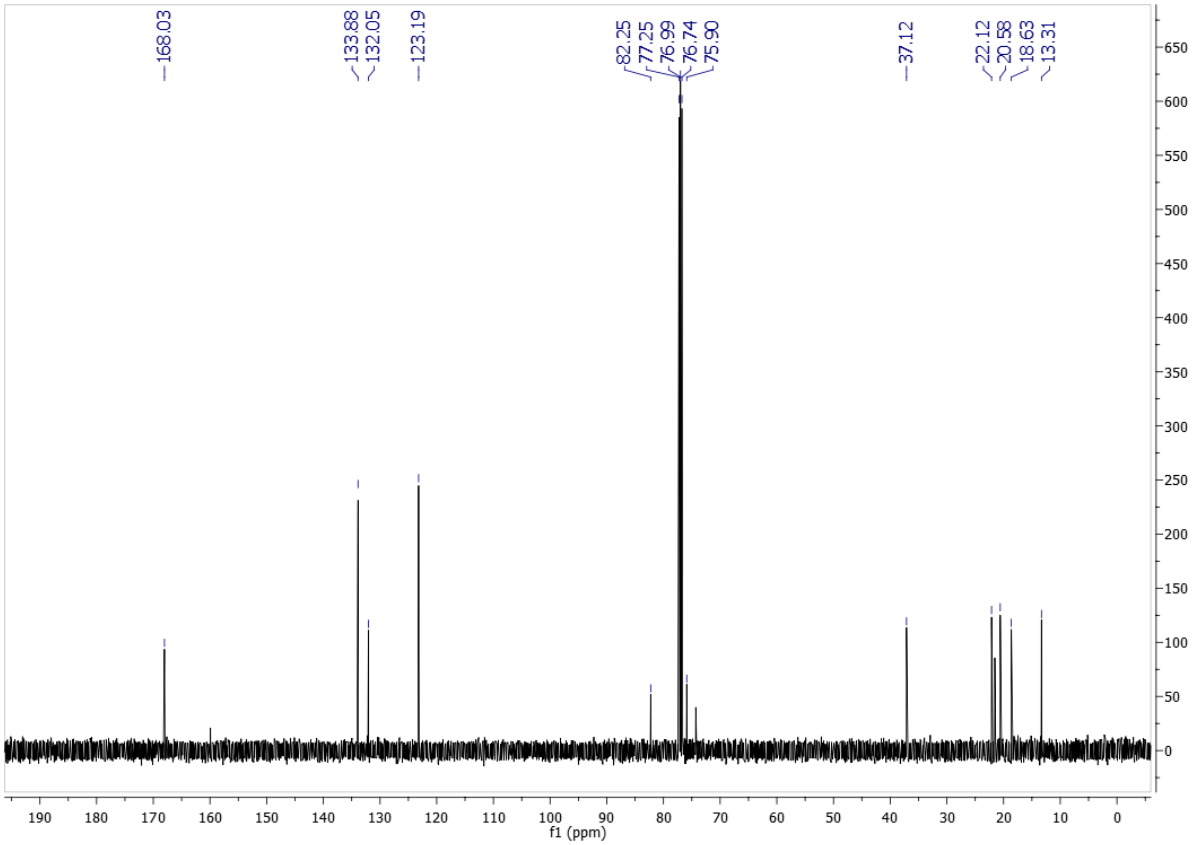




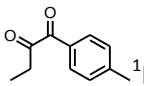


^{1}H (500 MHz) and ^{13}C (126 MHz) NMR spectra of compound **II**

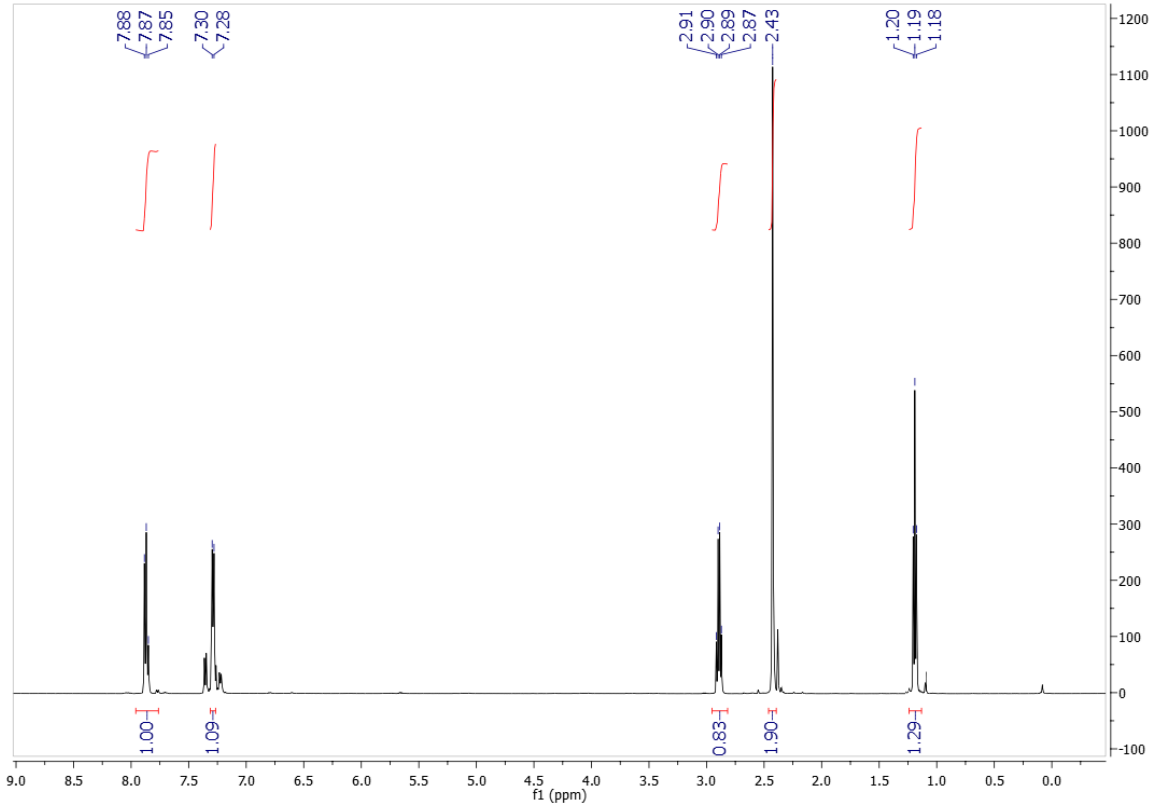


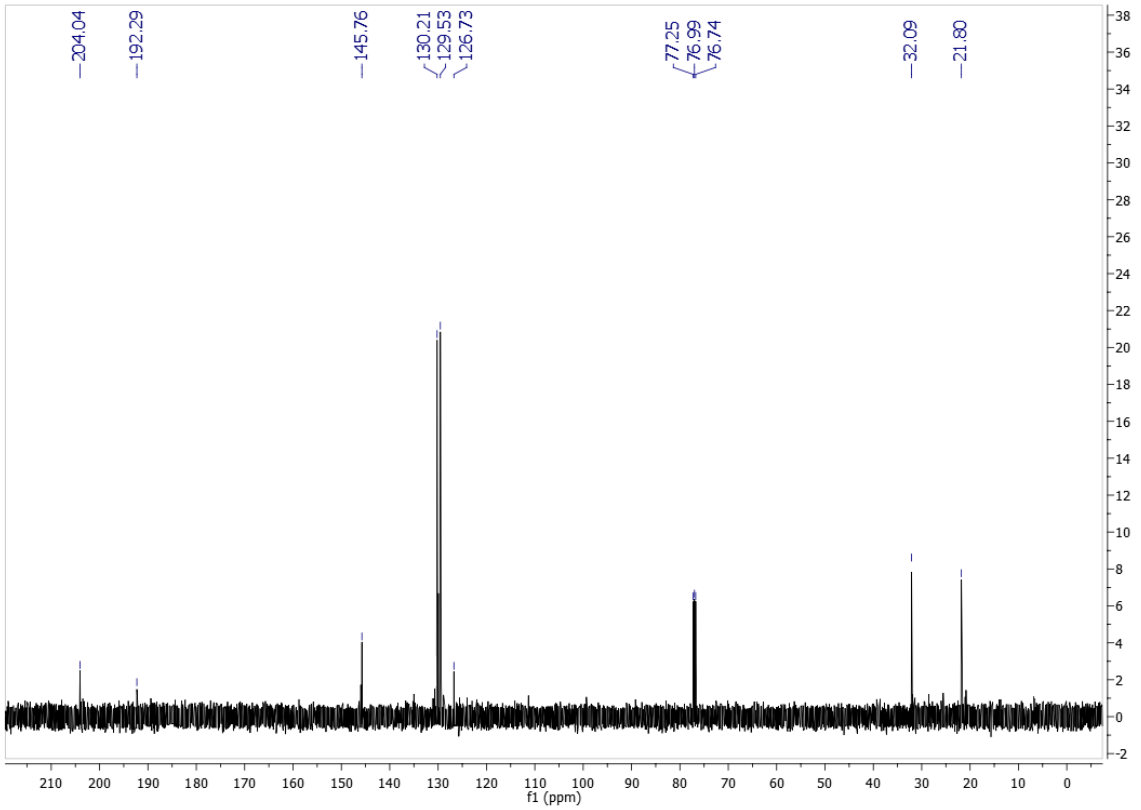


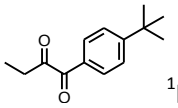
12. ^{1}H and ^{13}C NMR spectra of diones 1.



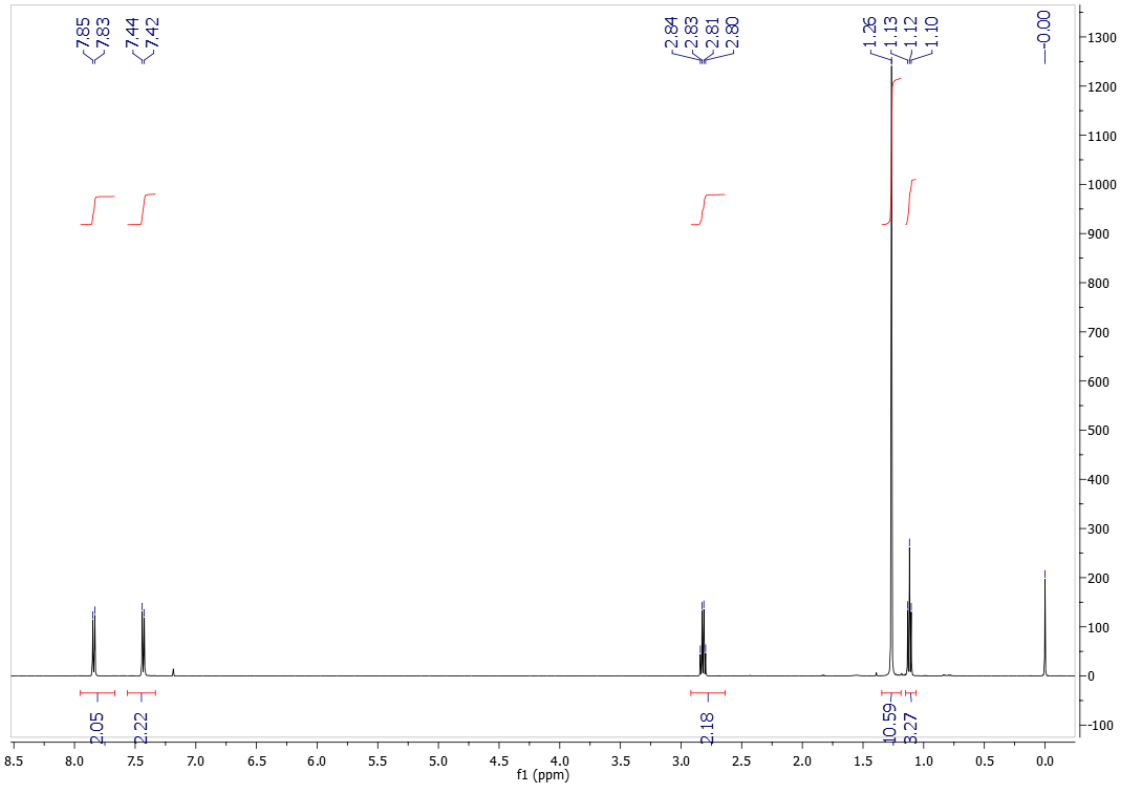
^{1}H (500 MHz) and ^{13}C (126 MHz) NMR spectra of compound **1f**

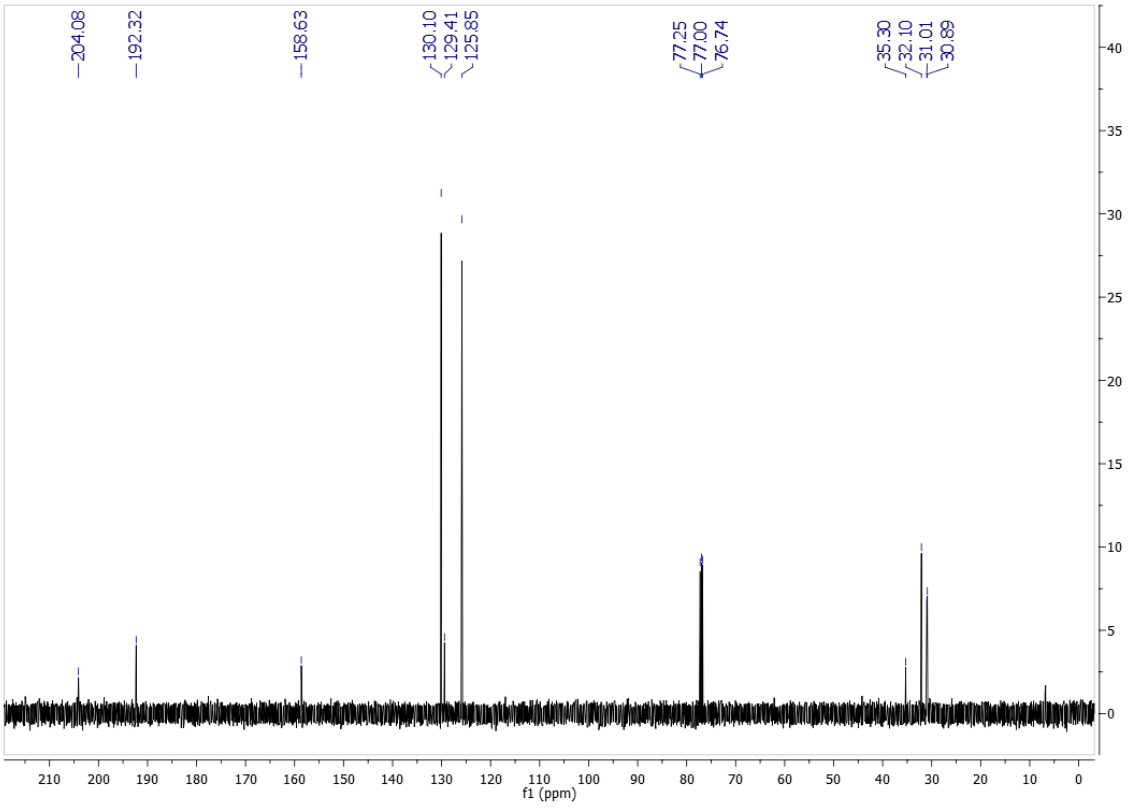


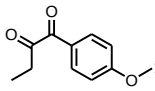




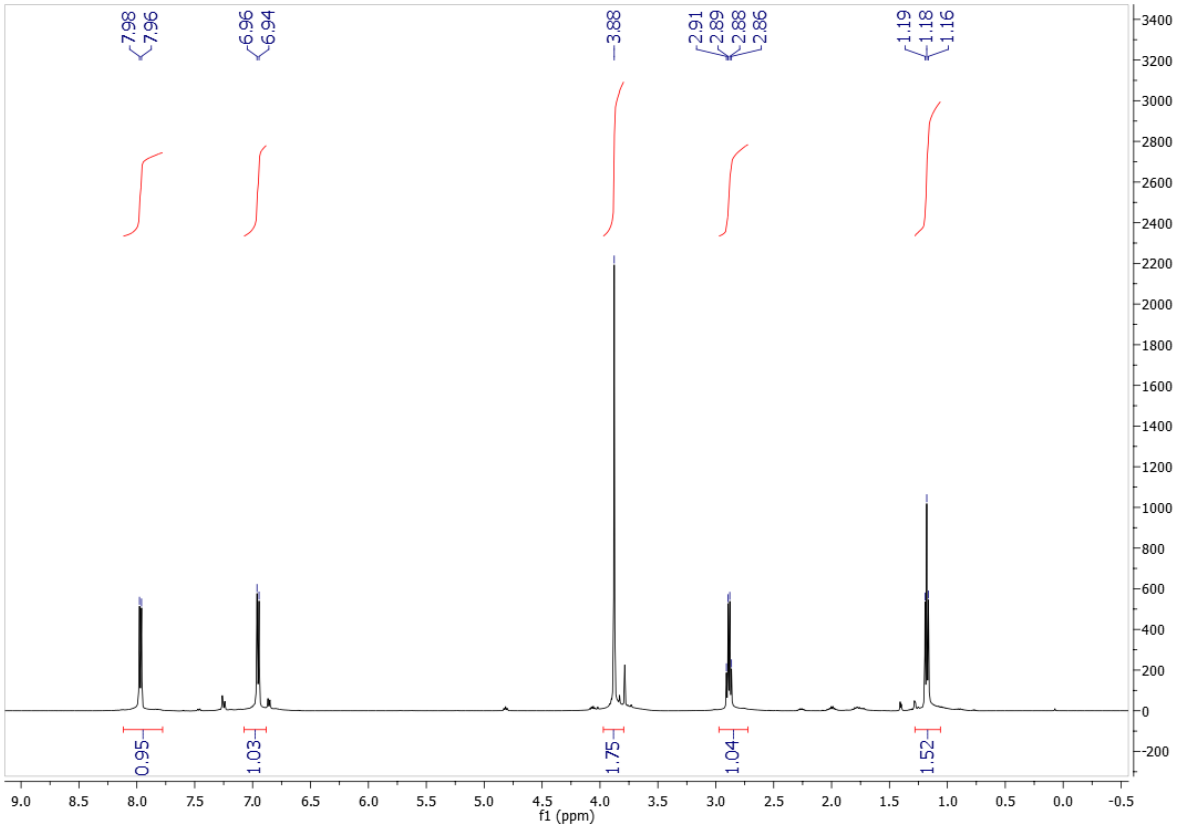
^{1}H (500 MHz) and ^{13}C (126 MHz) NMR spectra of compound **1g**

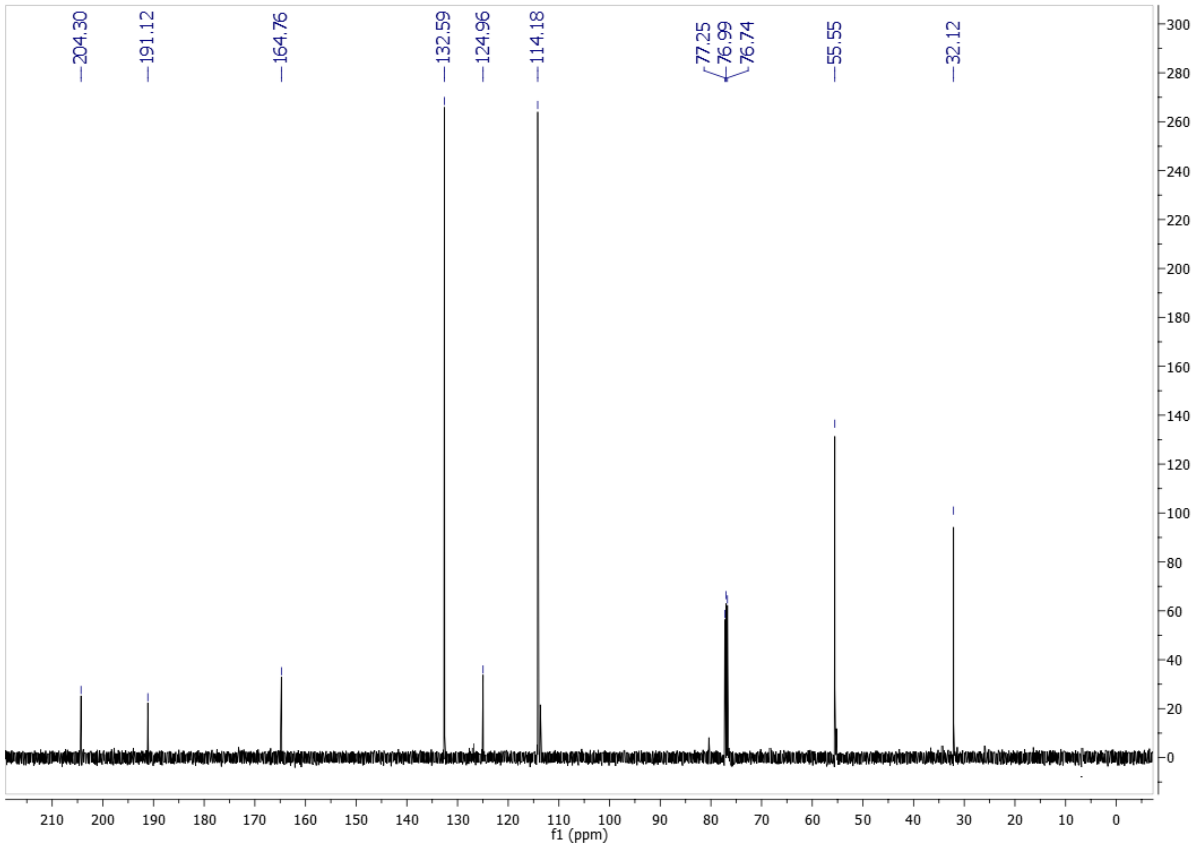


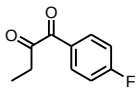




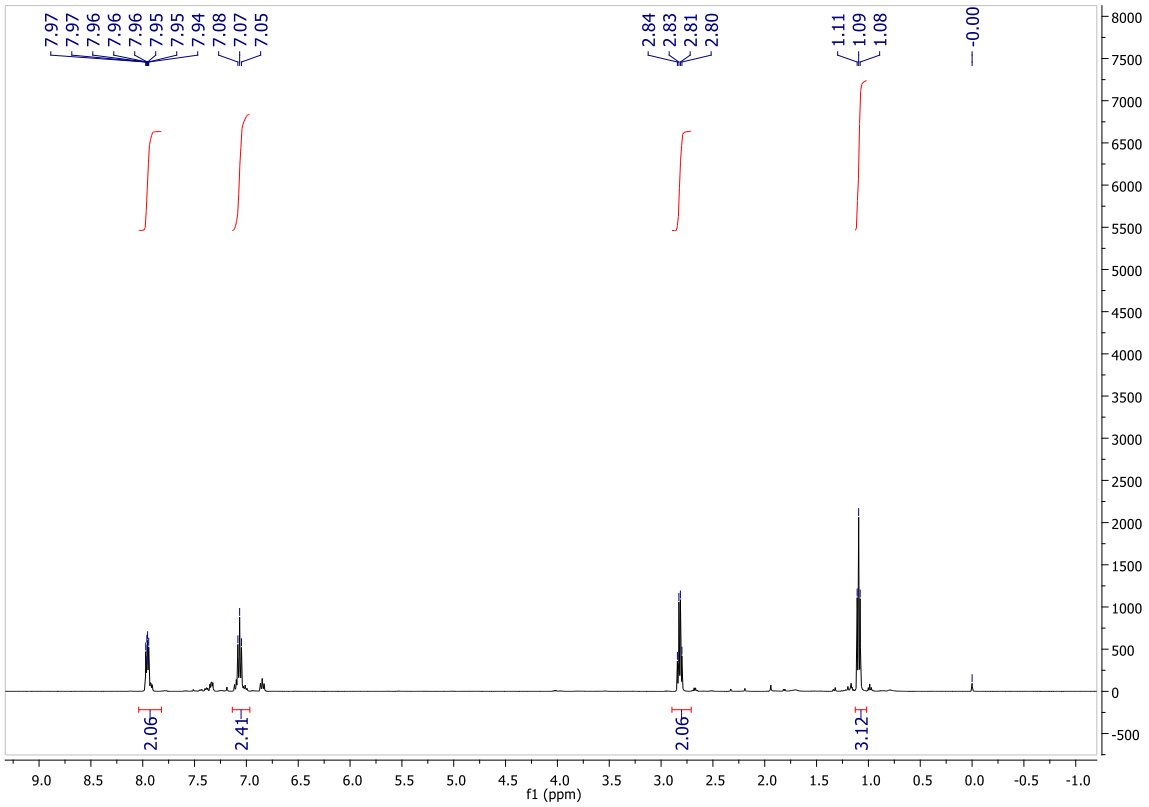
^{1}H (500 MHz) and ^{13}C (126 MHz) NMR spectra of compound **1h**

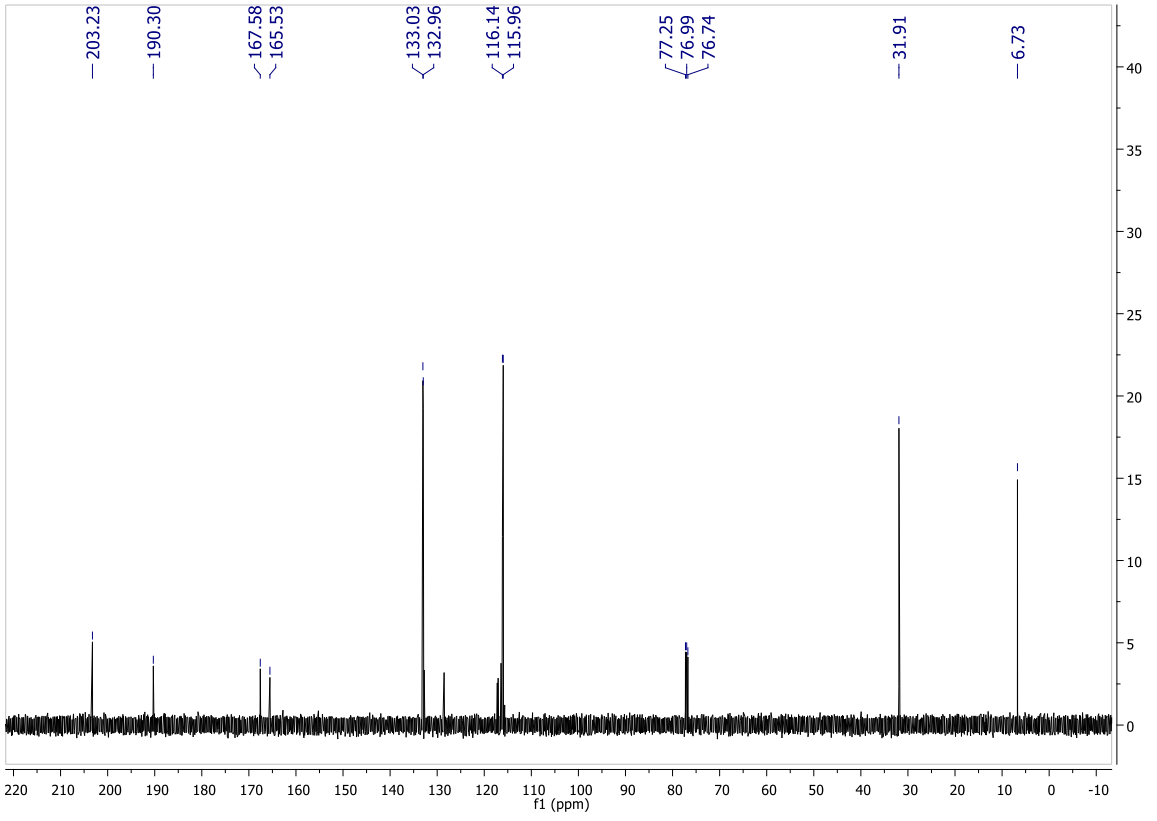


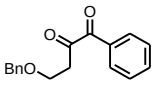




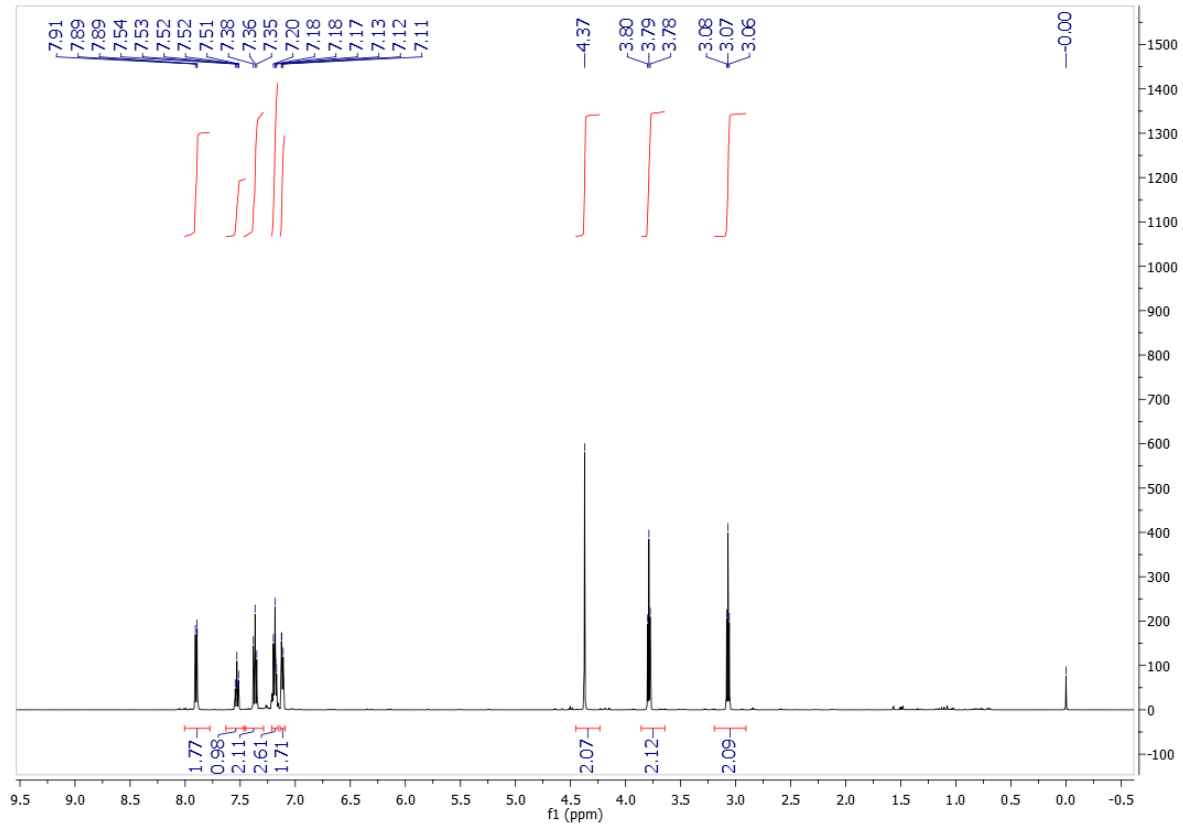
^{1}H (500 MHz) and ^{13}C (126 MHz) NMR spectra of compound **1i**

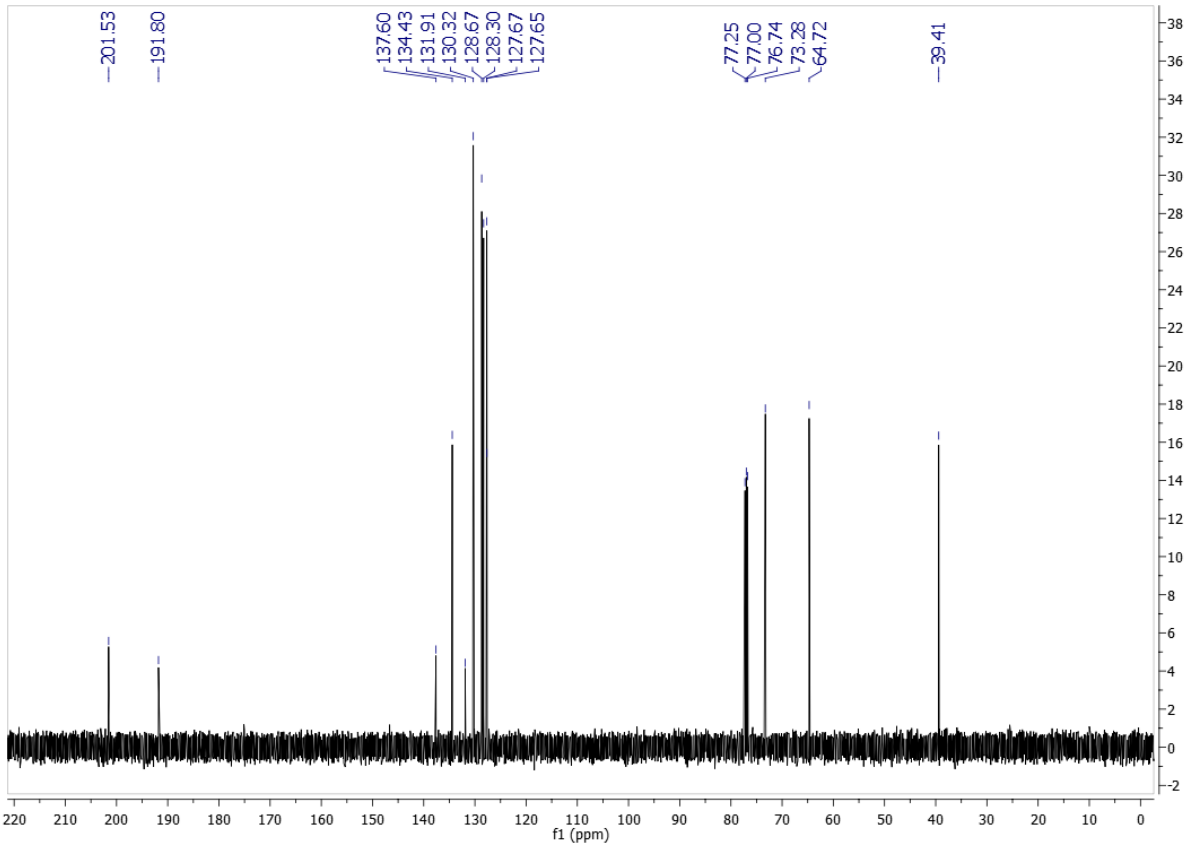


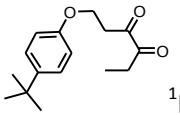




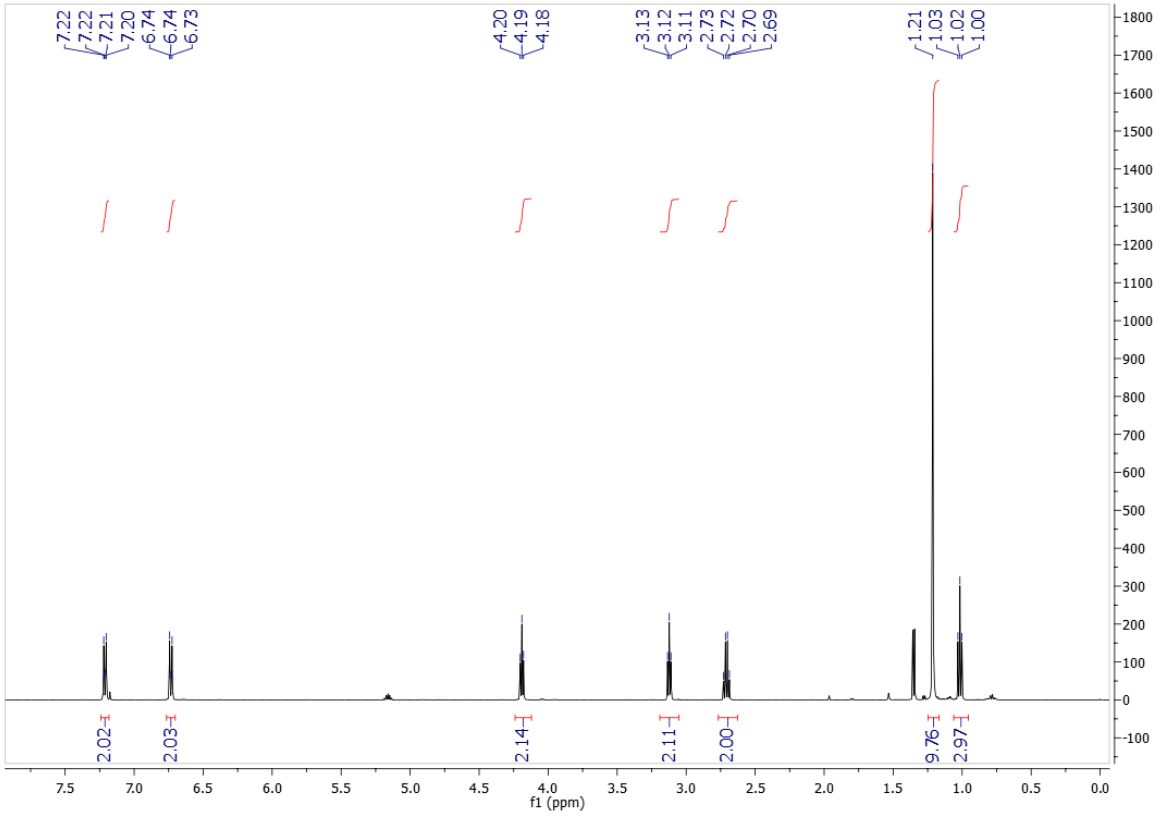
^{1}H (500 MHz) and ^{13}C (126 MHz) NMR spectra of compound **1m**

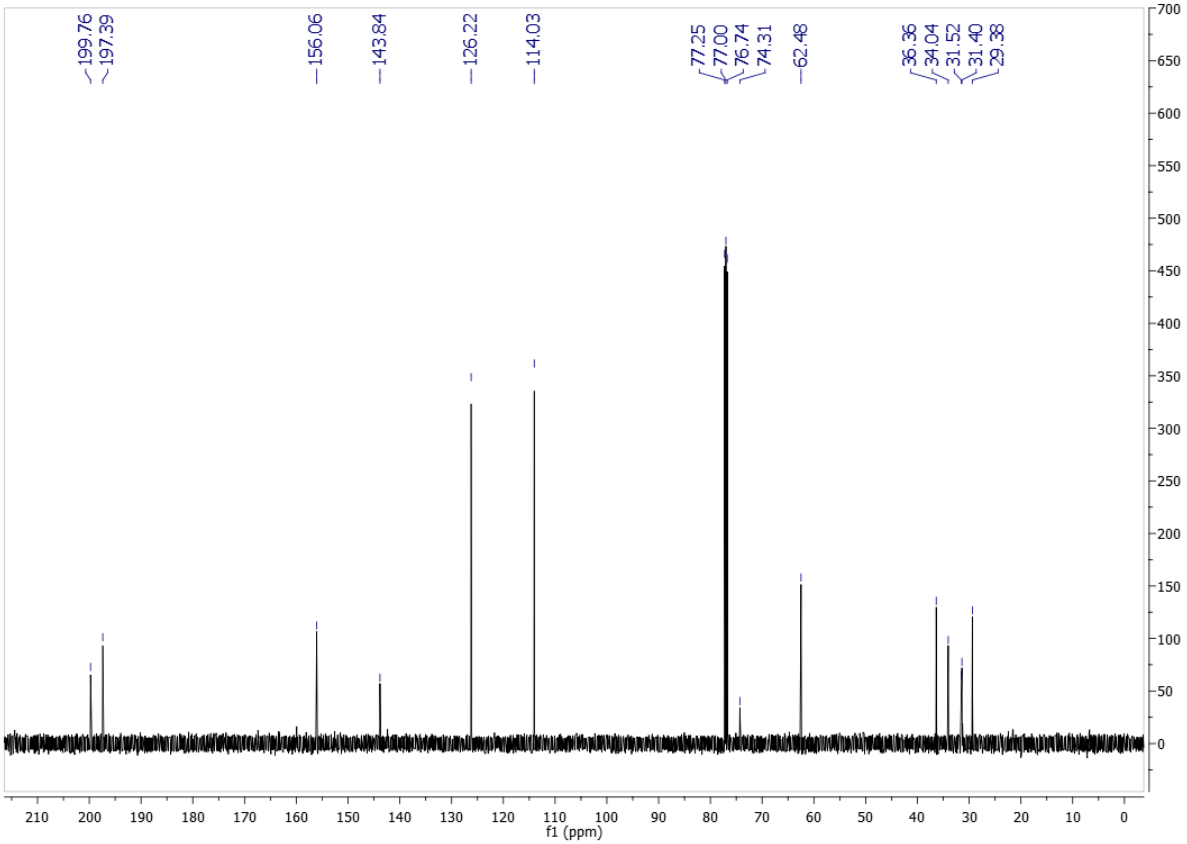


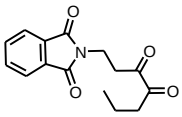




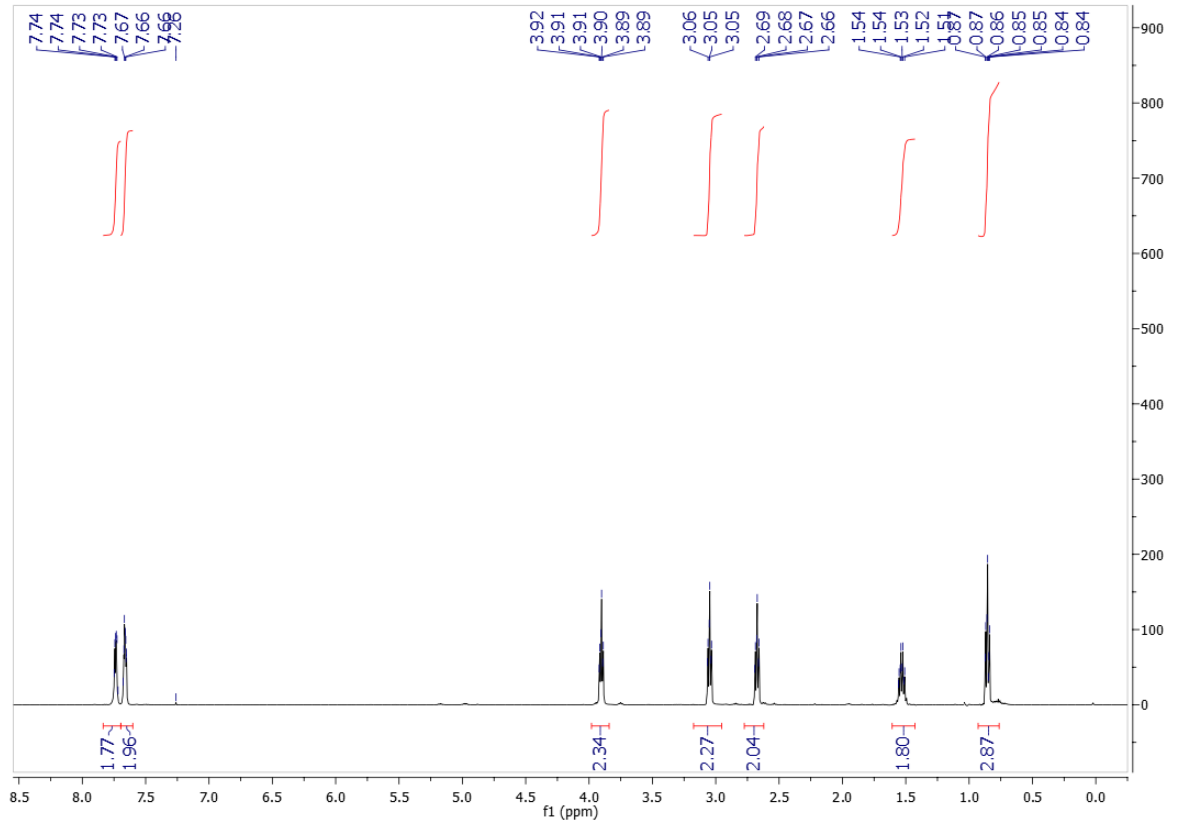
^{1}H (500 MHz) and ^{13}C (126 MHz) NMR spectra of compound **1n**

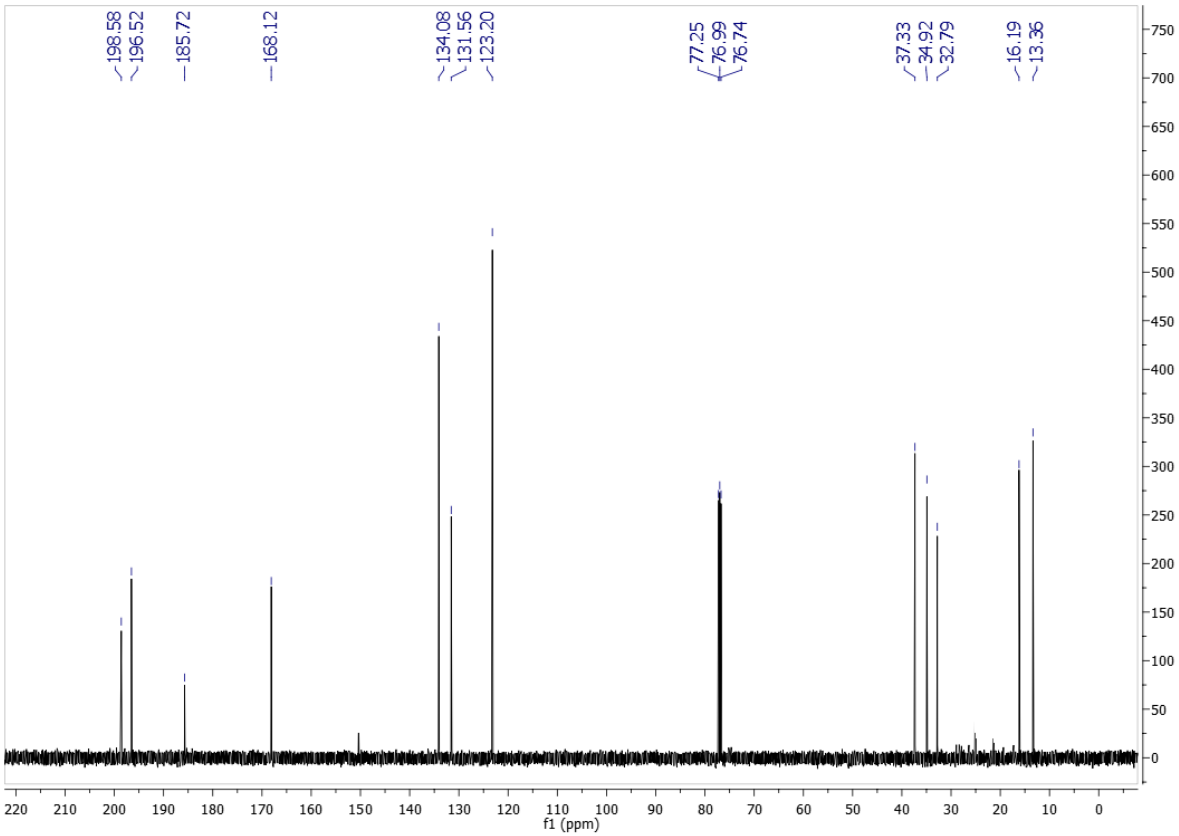


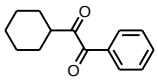




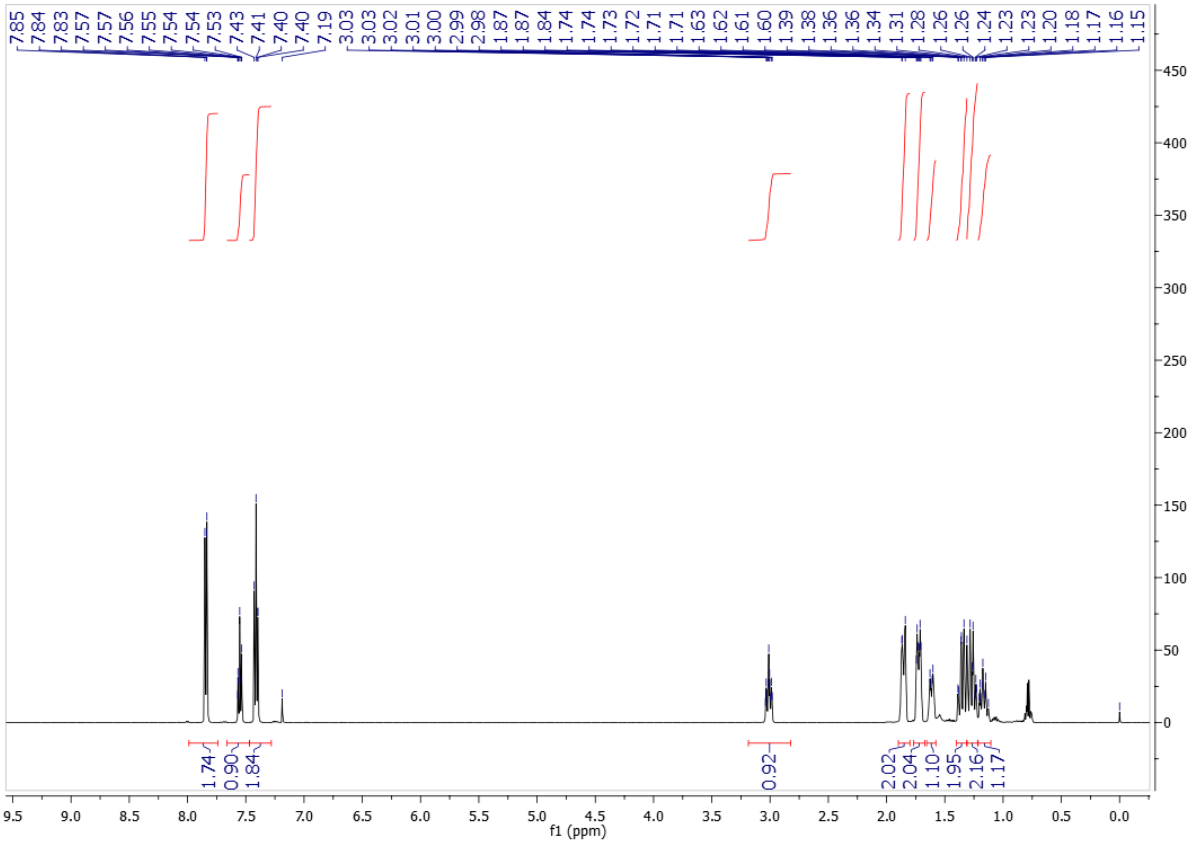
^{1}H (500 MHz) and ^{13}C (126 MHz) NMR spectra of compound **1o**

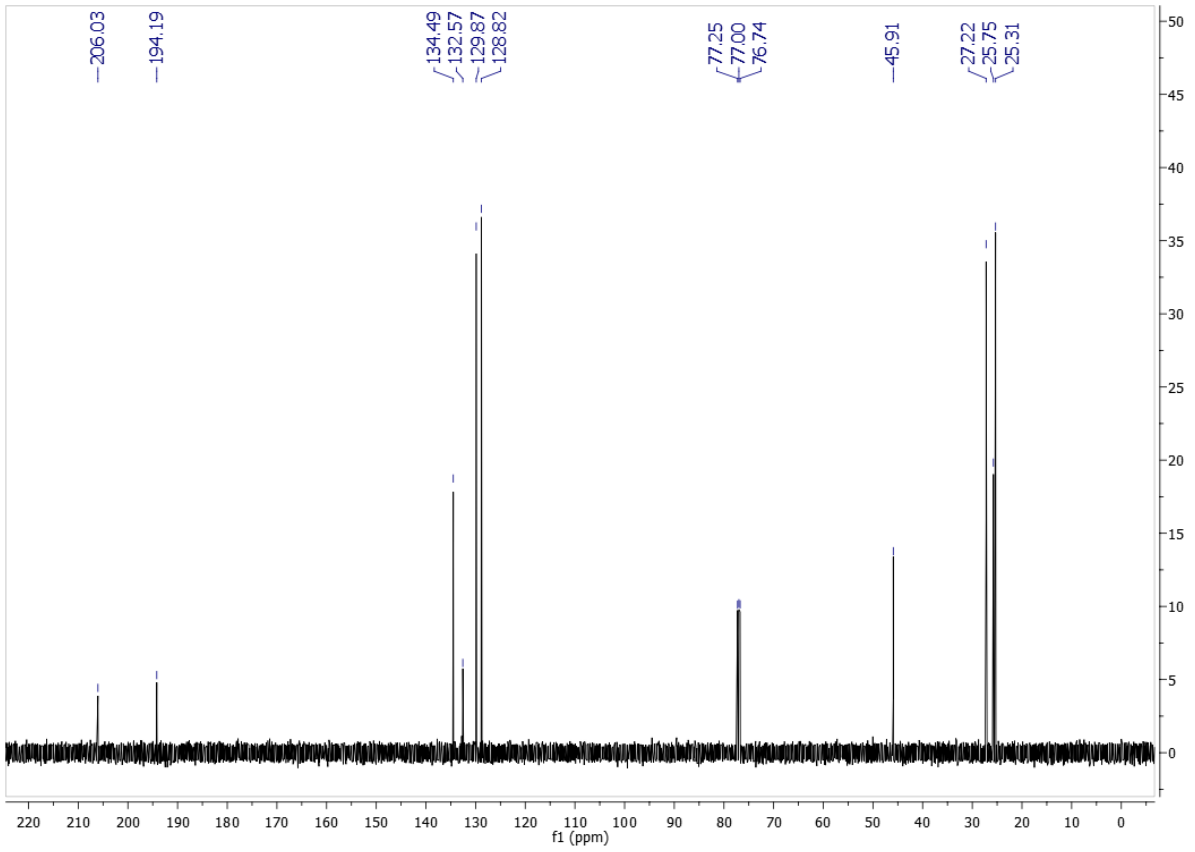






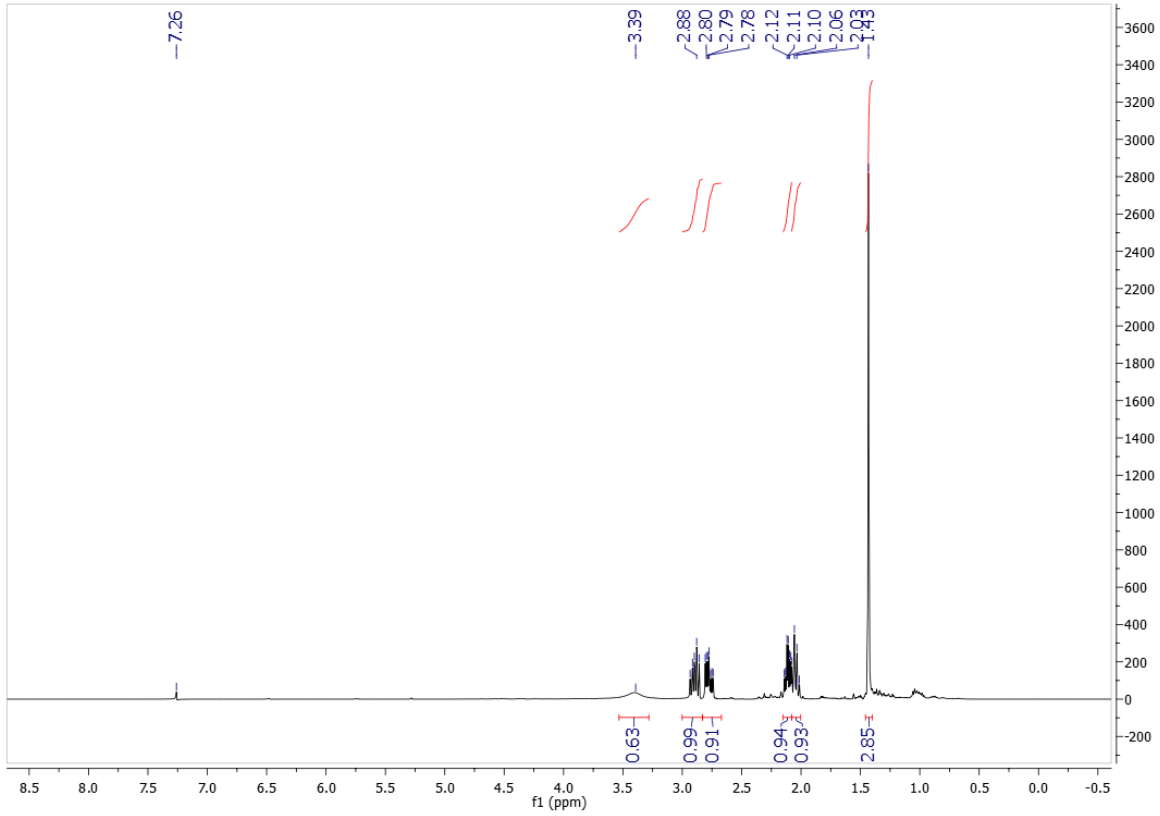
^{1}H (500 MHz) and ^{13}C (126 MHz) NMR spectra of compound **1p**

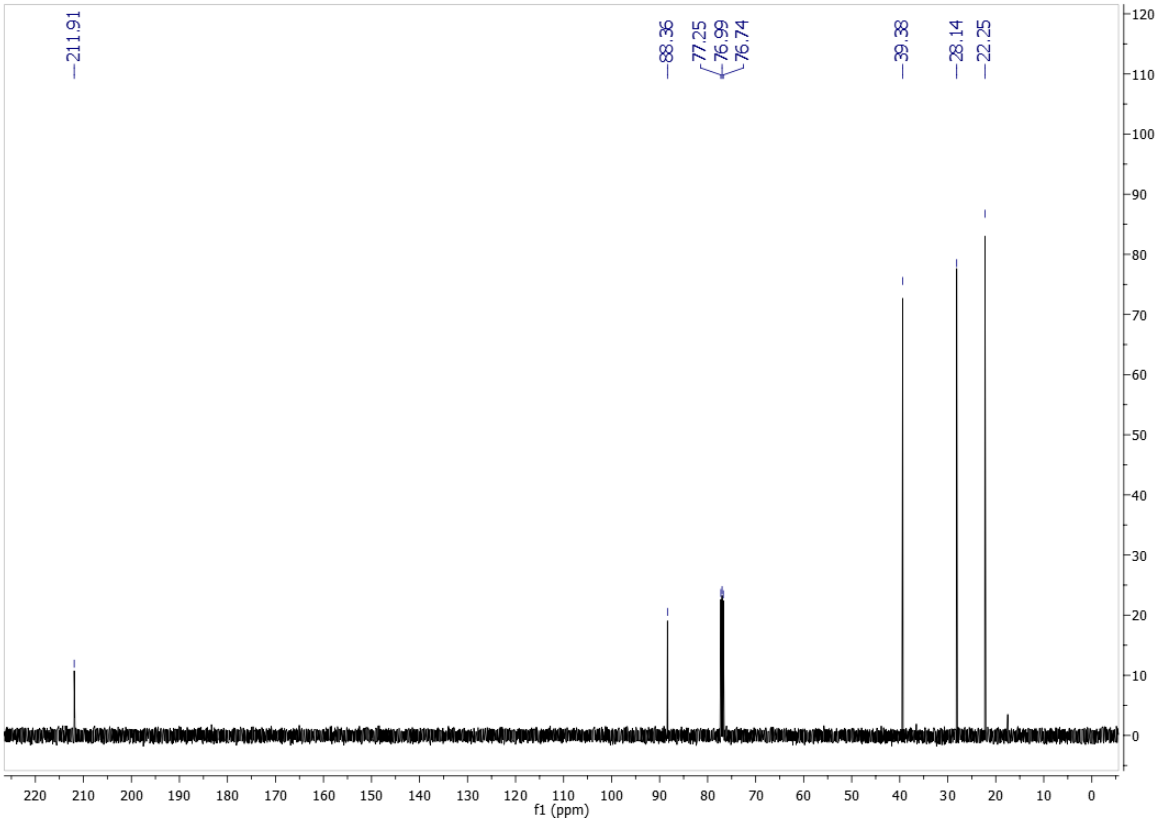


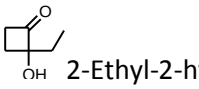


13. ^{1}H and ^{13}C NMR spectra of cyclobutanones 2.

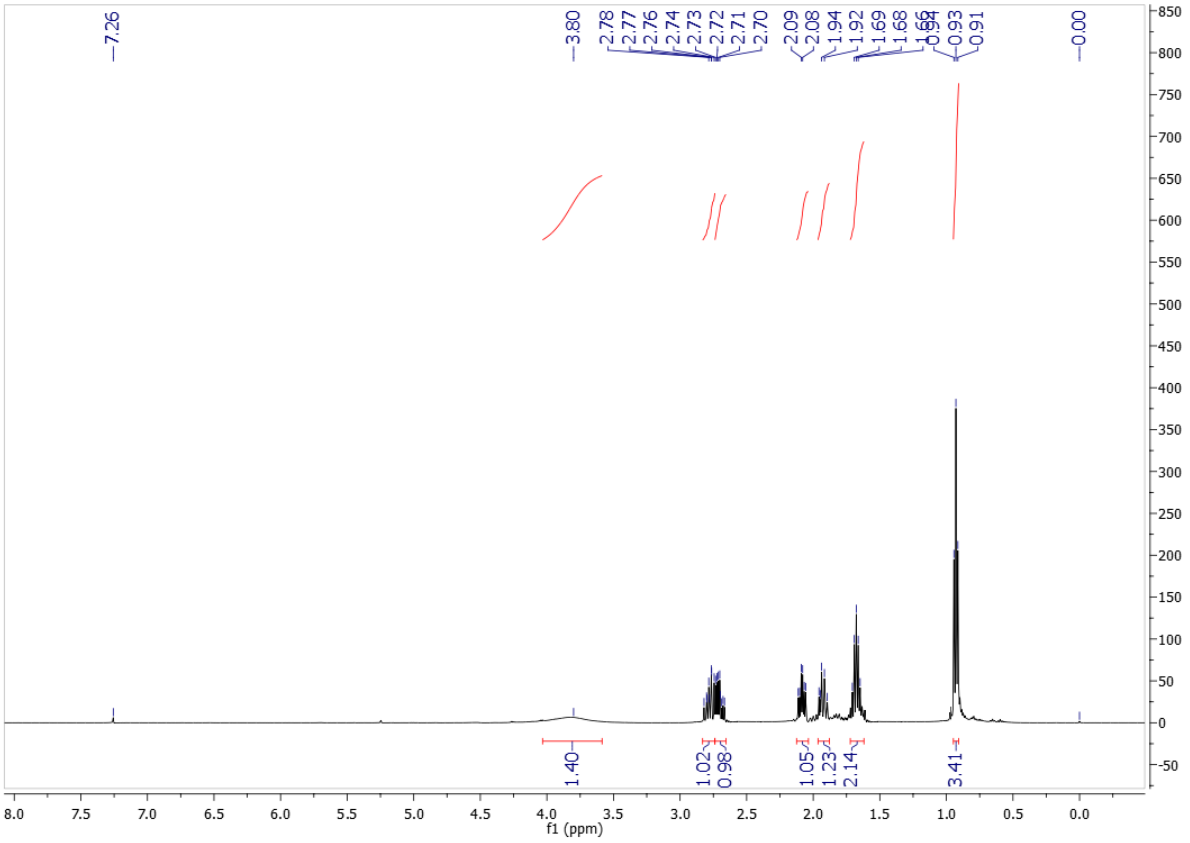
^{1}H (500 MHz) and ^{13}C (126 MHz) NMR spectra of compound **2a**

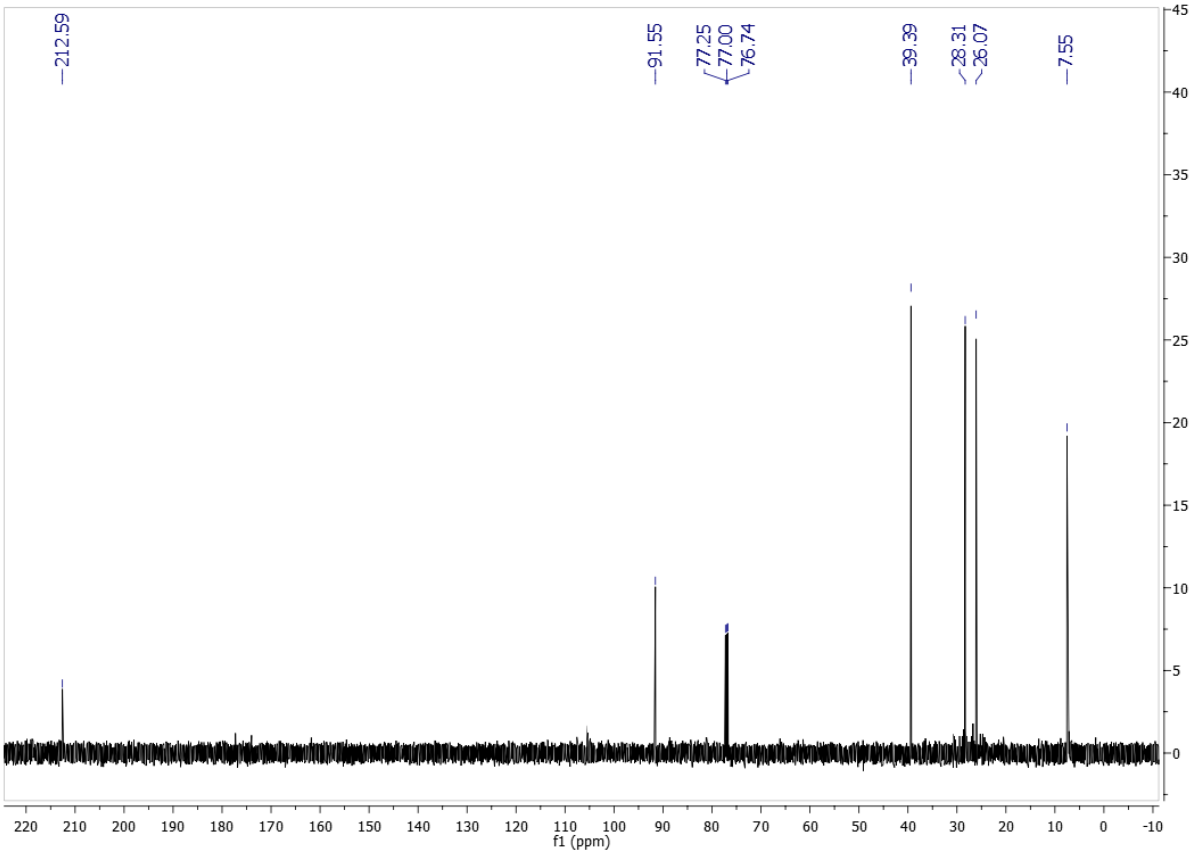


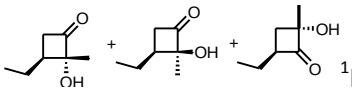




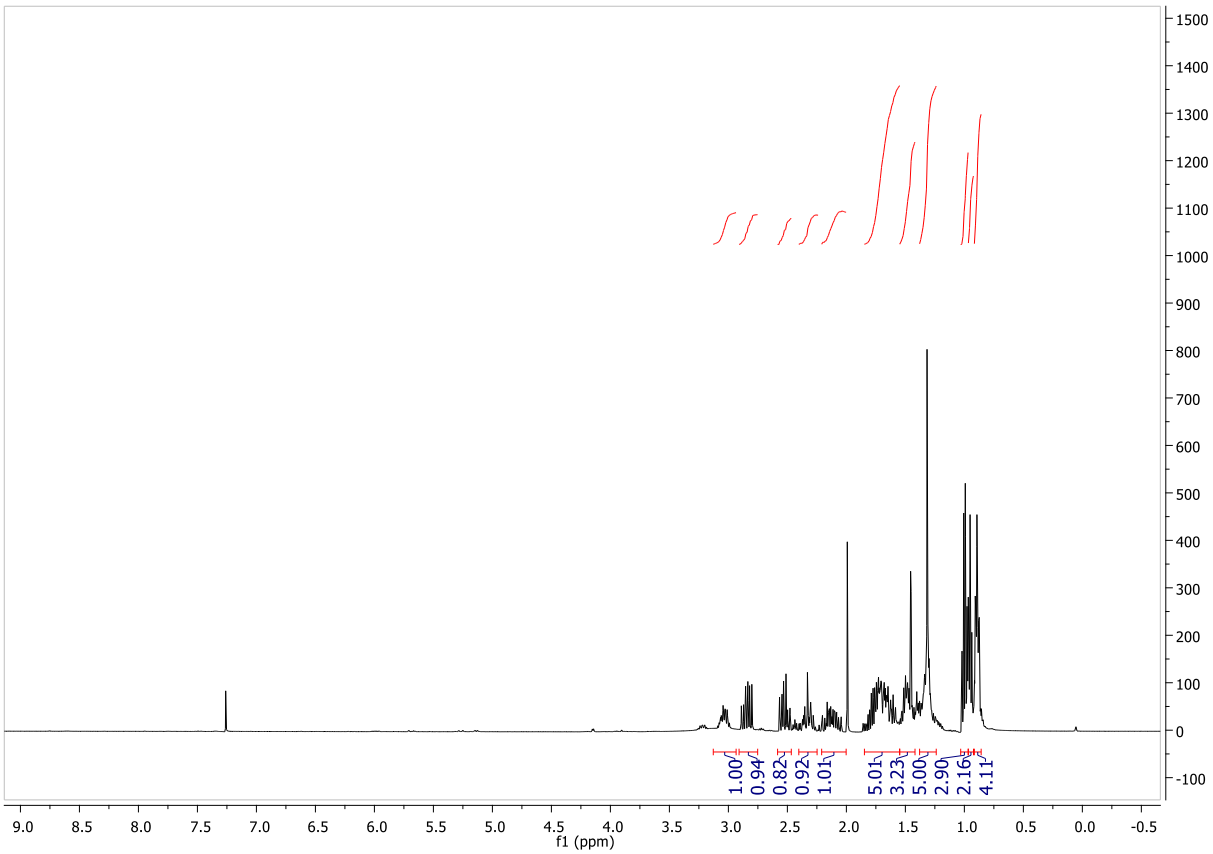
2-Ethyl-2-hydroxy-cyclobutanone **2b**

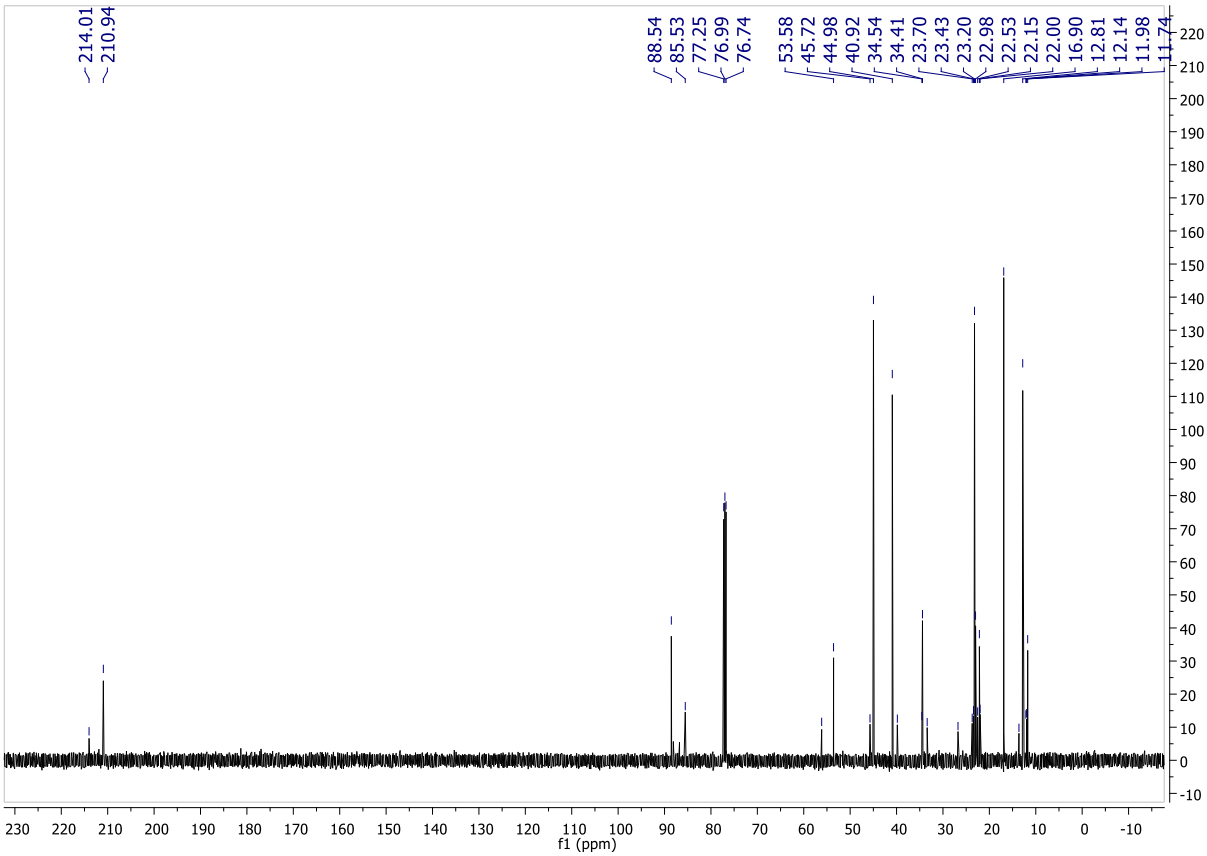


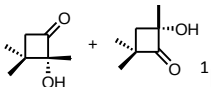




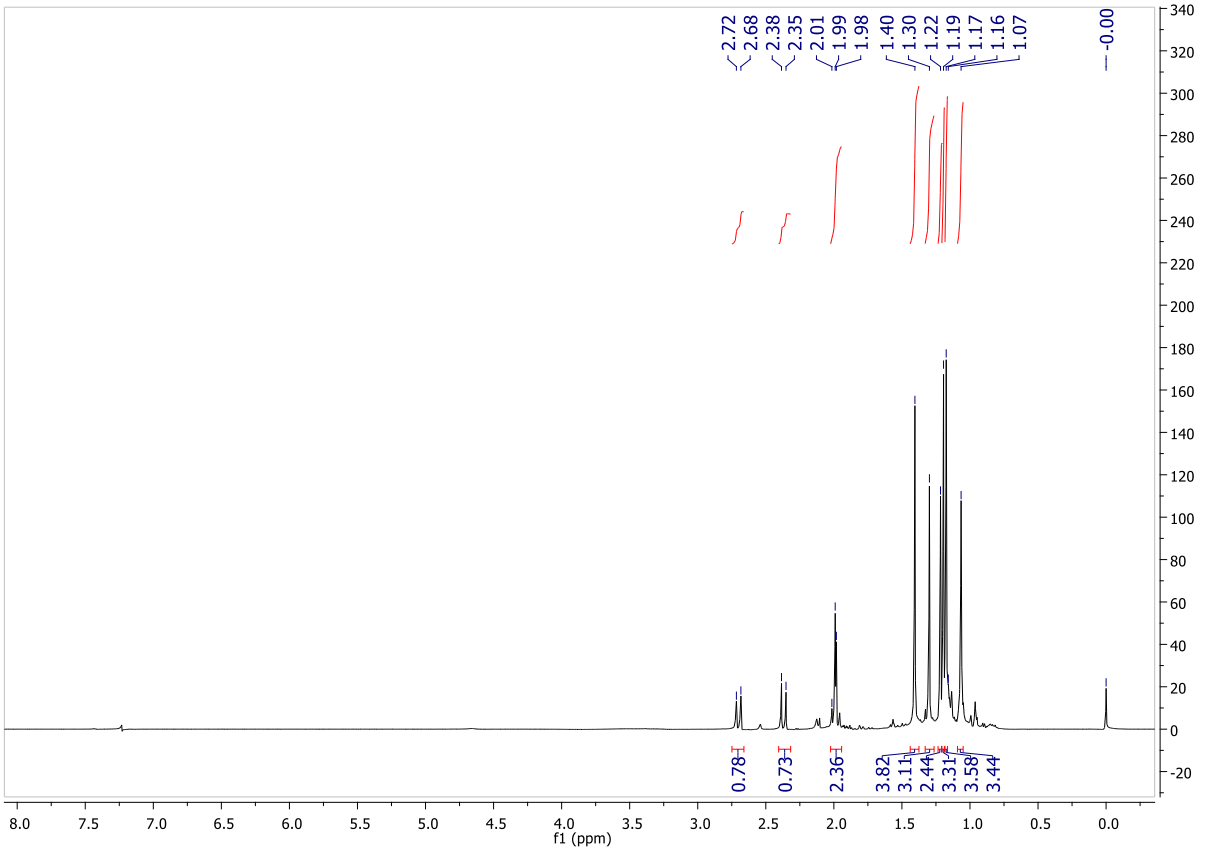
^{1}H (500 MHz) and ^{13}C (126 MHz) NMR spectra of compound **2c**

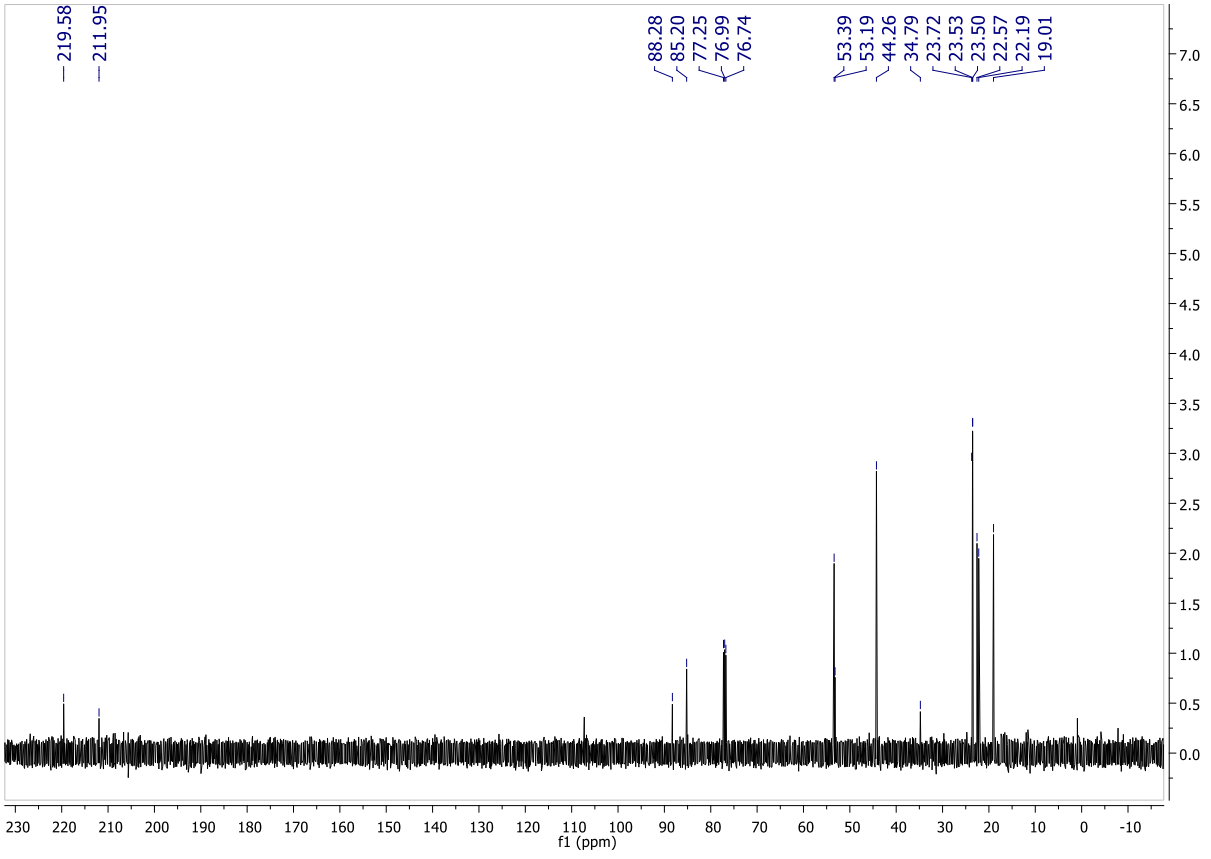


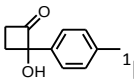




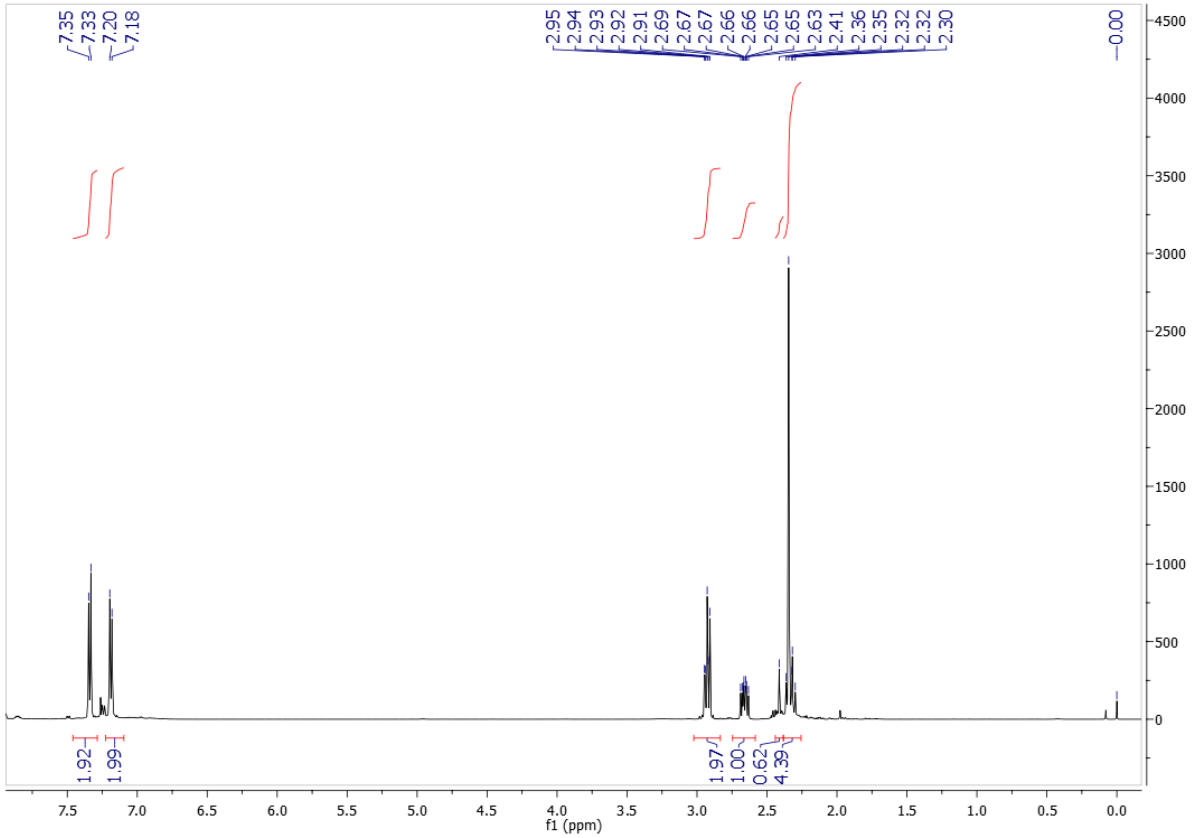
^{1}H (500 MHz) and ^{13}C (126 MHz) NMR spectra of compound **2d**

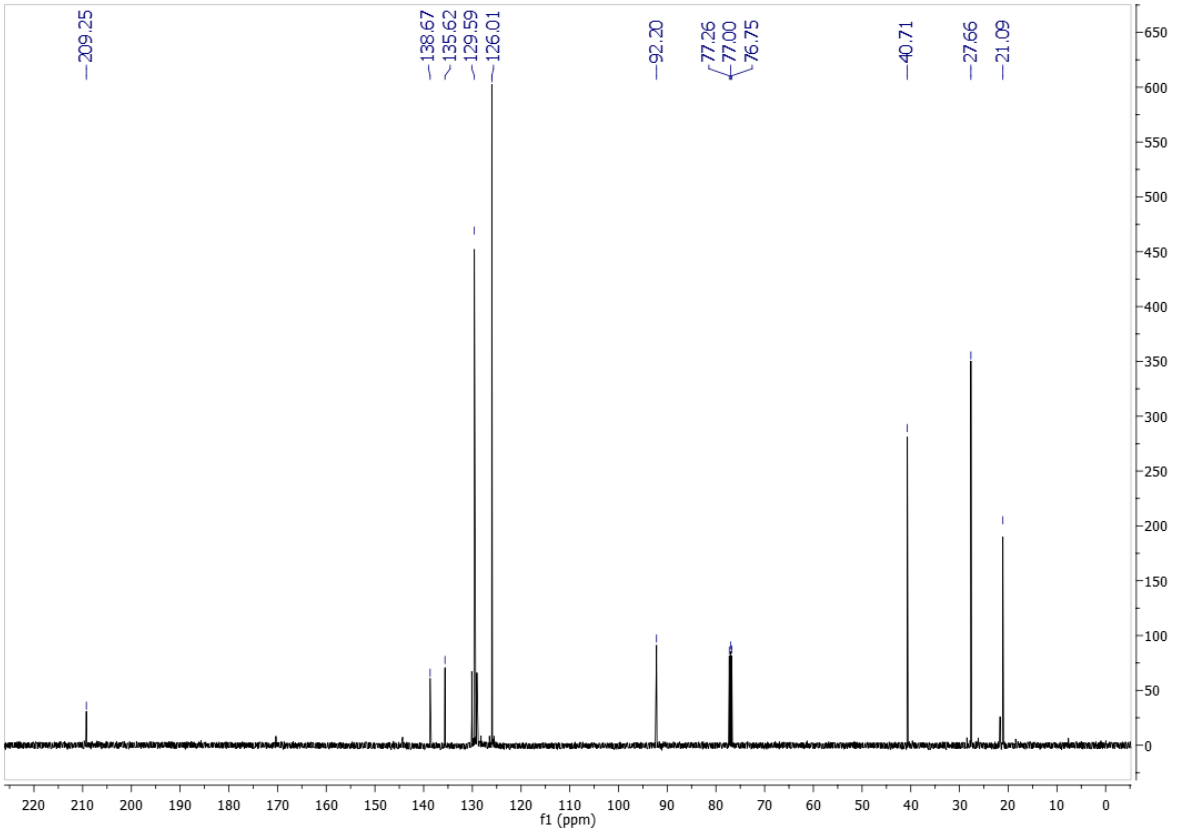


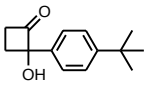




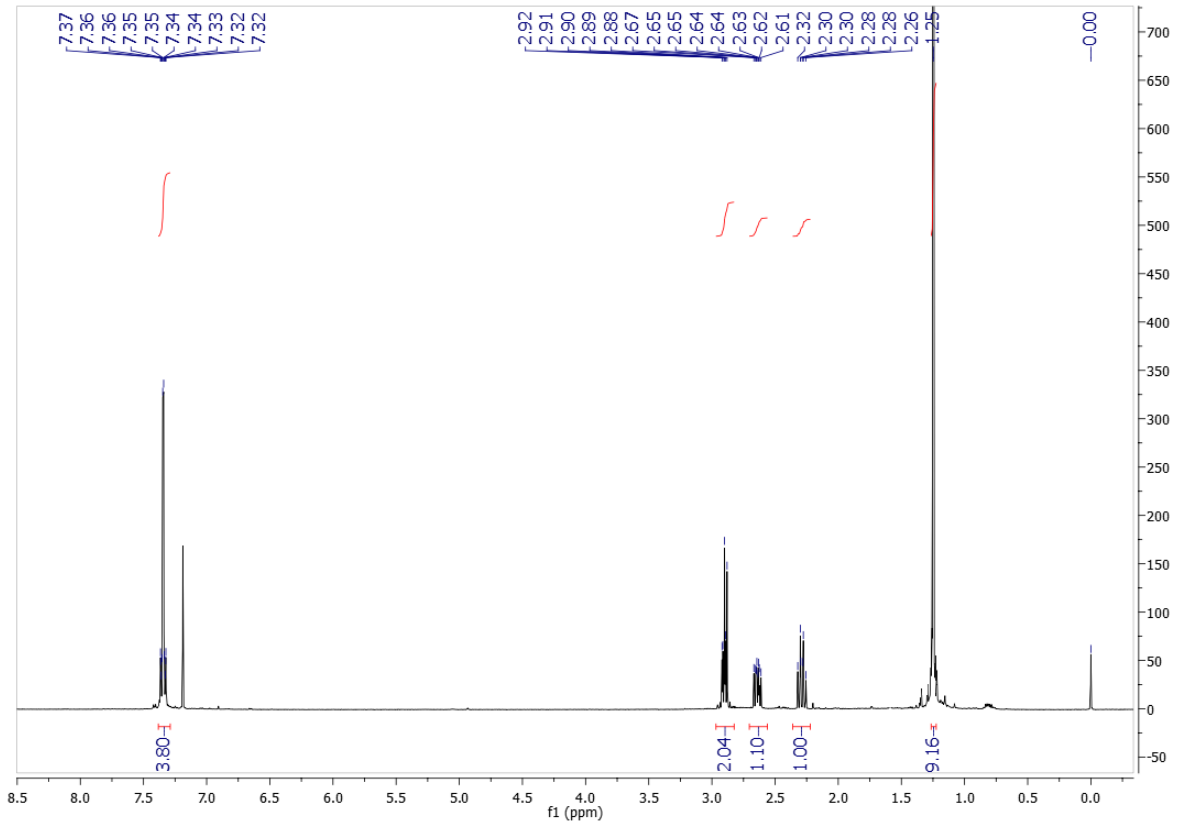
^{1}H (500 MHz) and ^{13}C (126 MHz) NMR spectra of compound **2f**

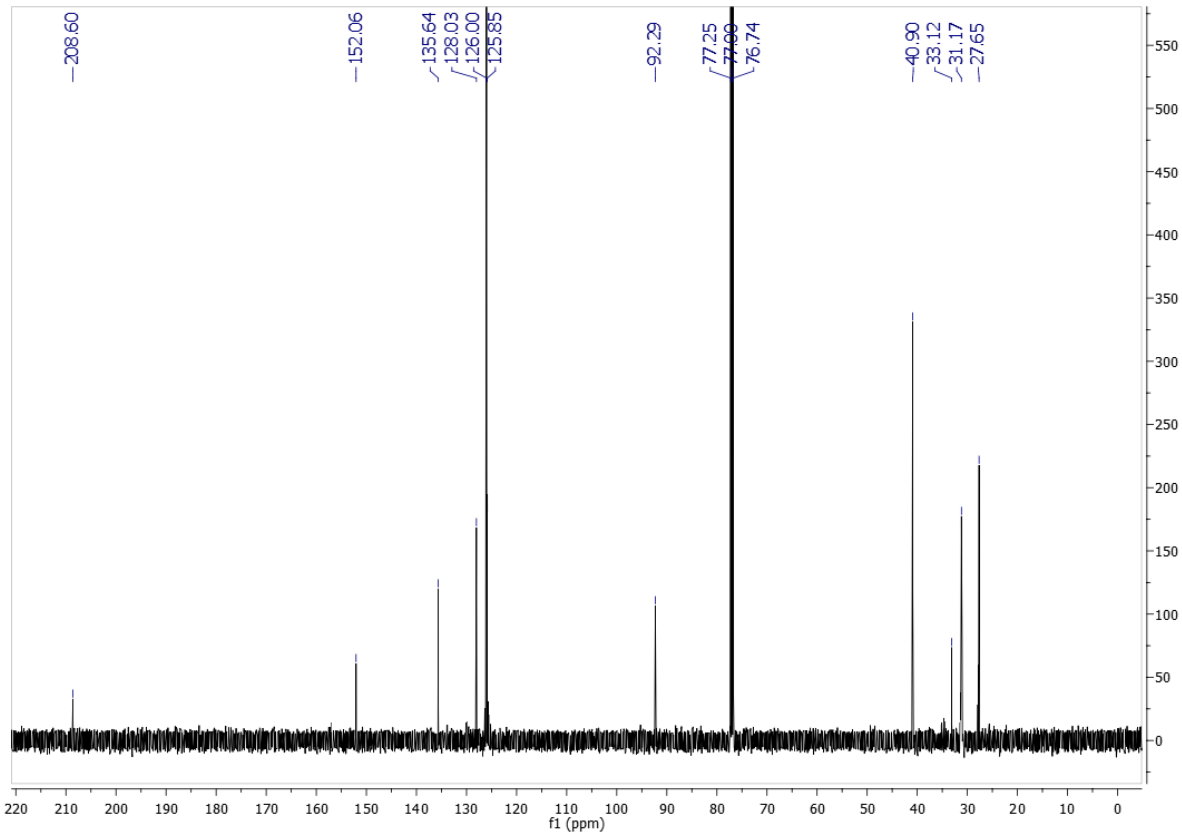


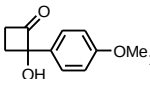




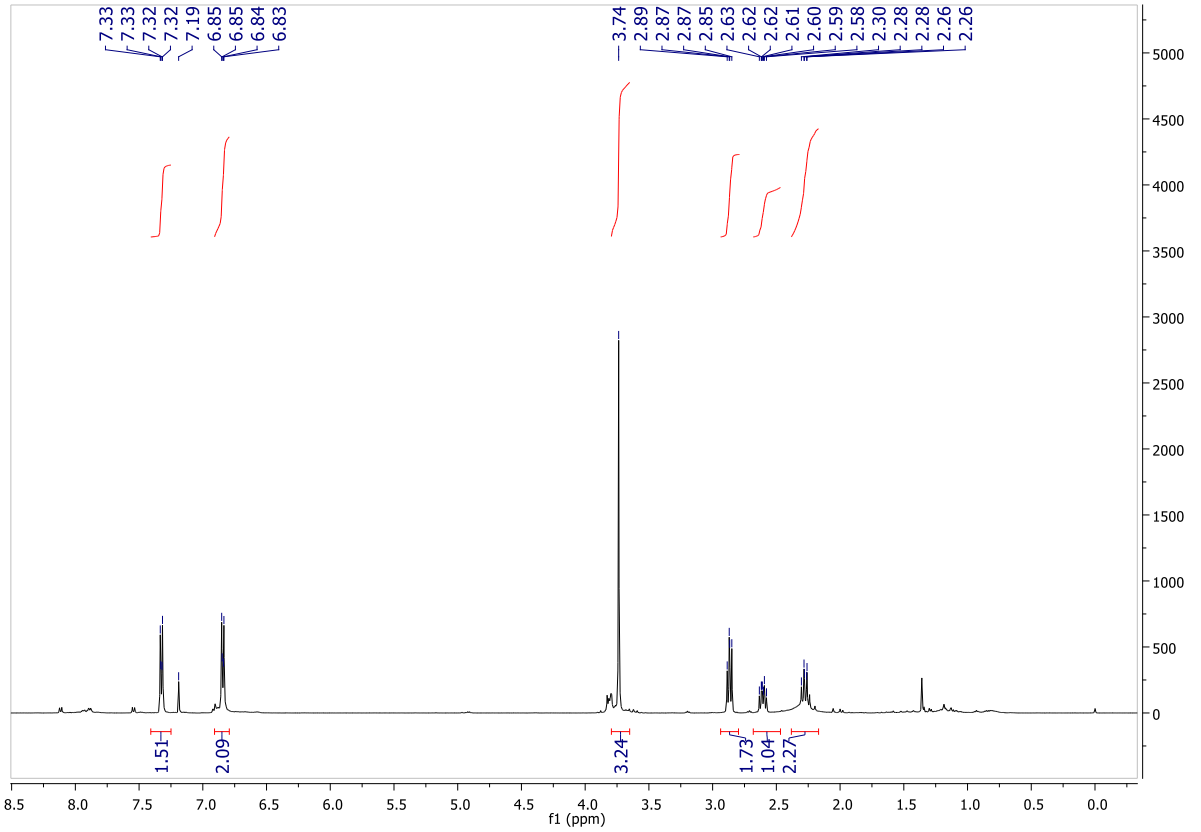
^{1}H (500 MHz) and ^{13}C (126 MHz) NMR spectra of compound **2g**

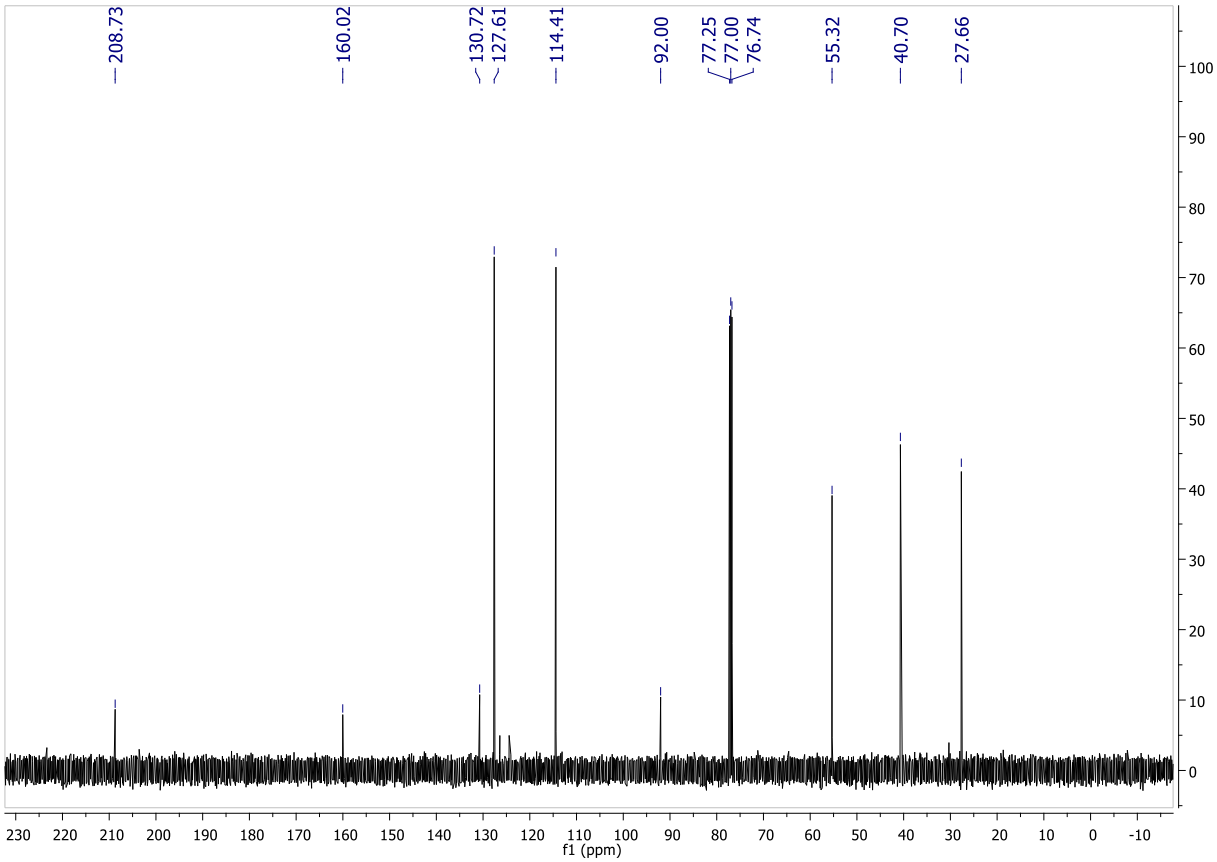


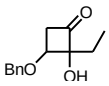




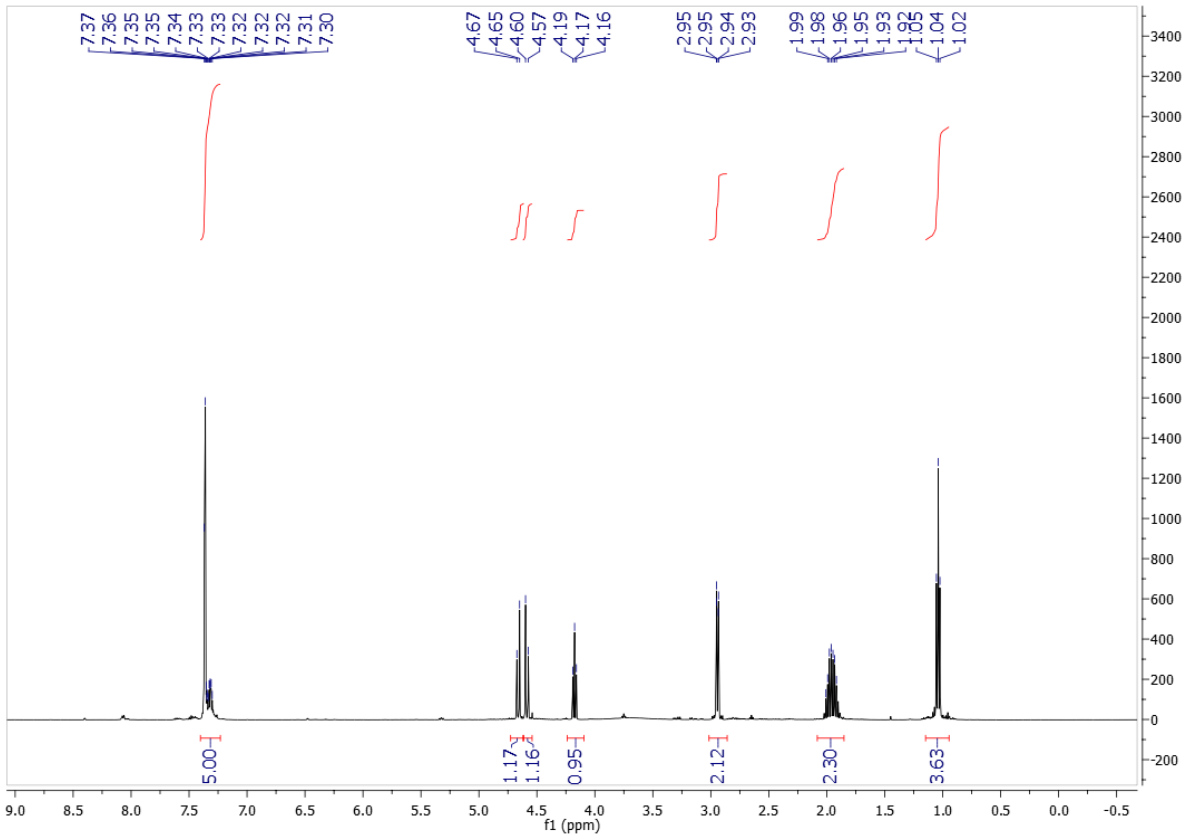
^{1}H (500 MHz) and ^{13}C (126 MHz) NMR spectra of compound **2h**

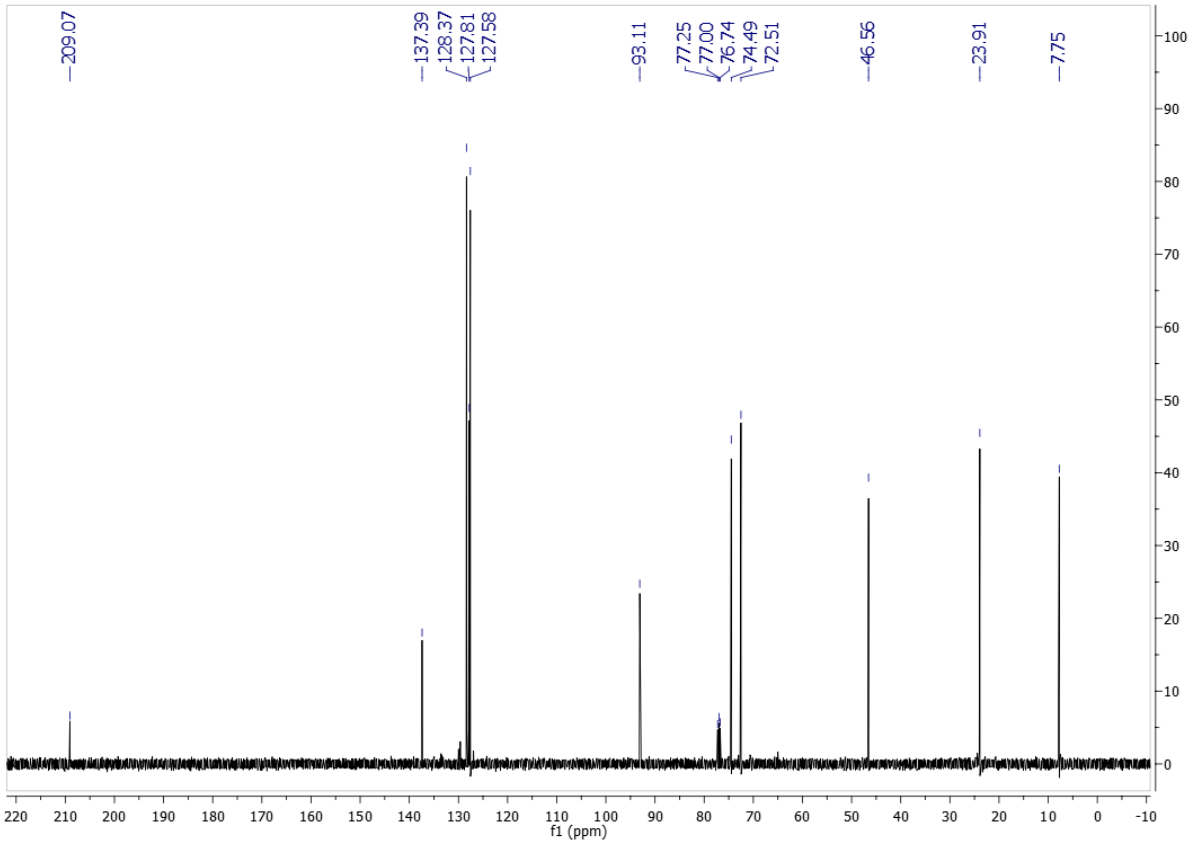


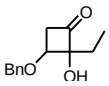




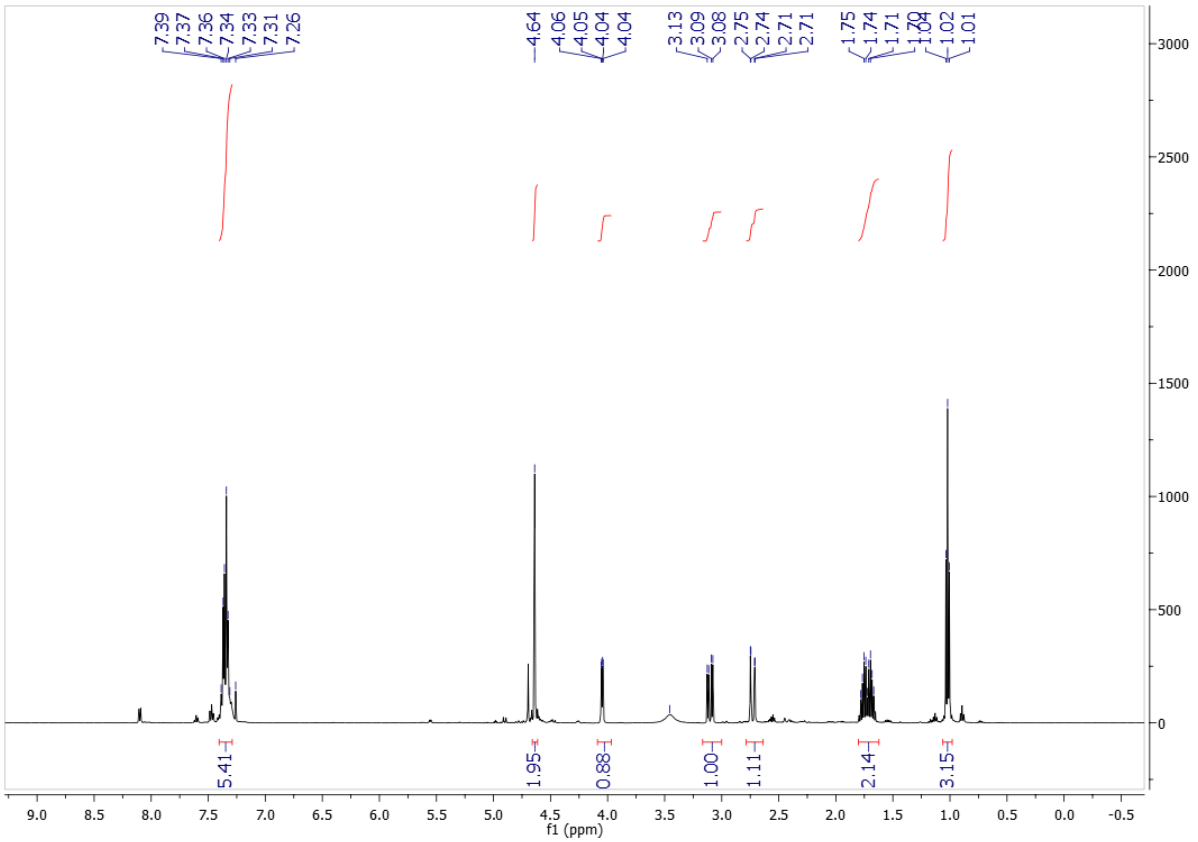
^{1}H (500 MHz) and ^{13}C (126 MHz) NMR spectra of compound ***trans*-2k**

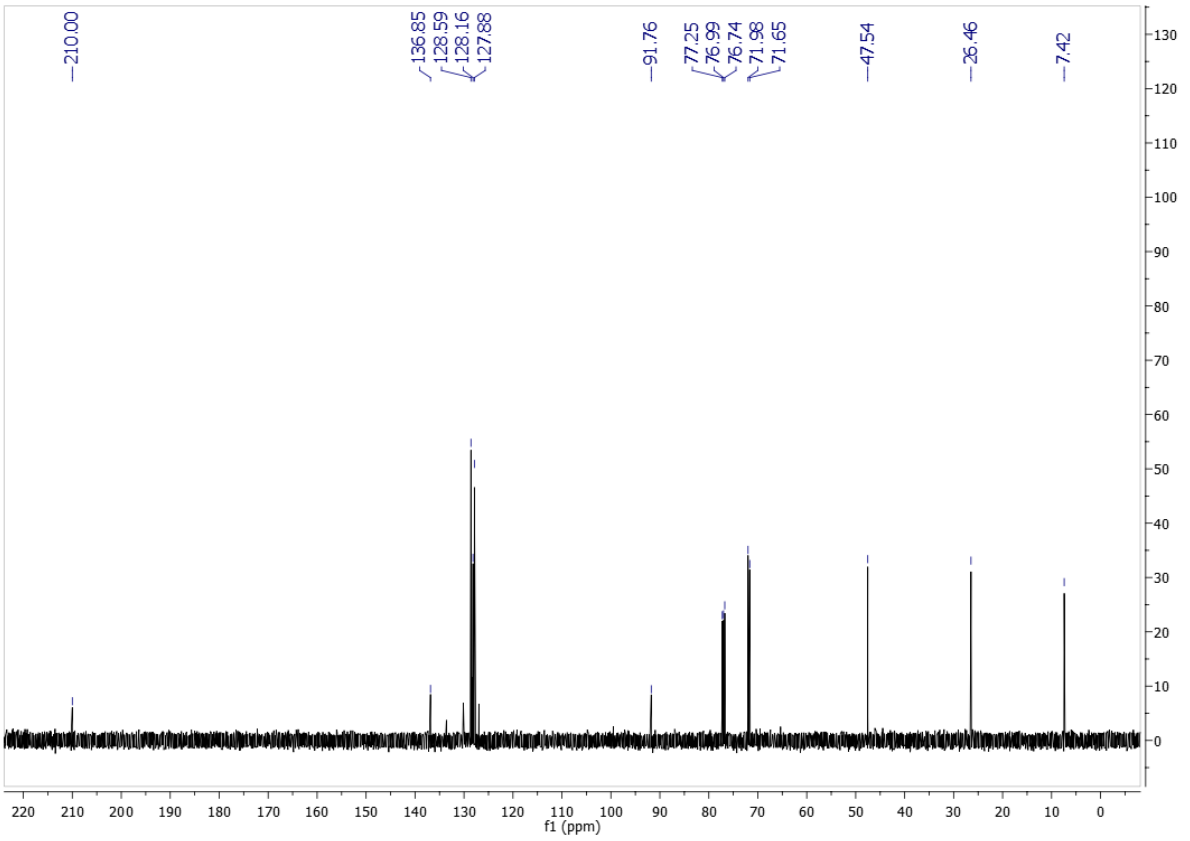


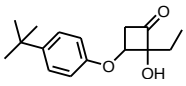




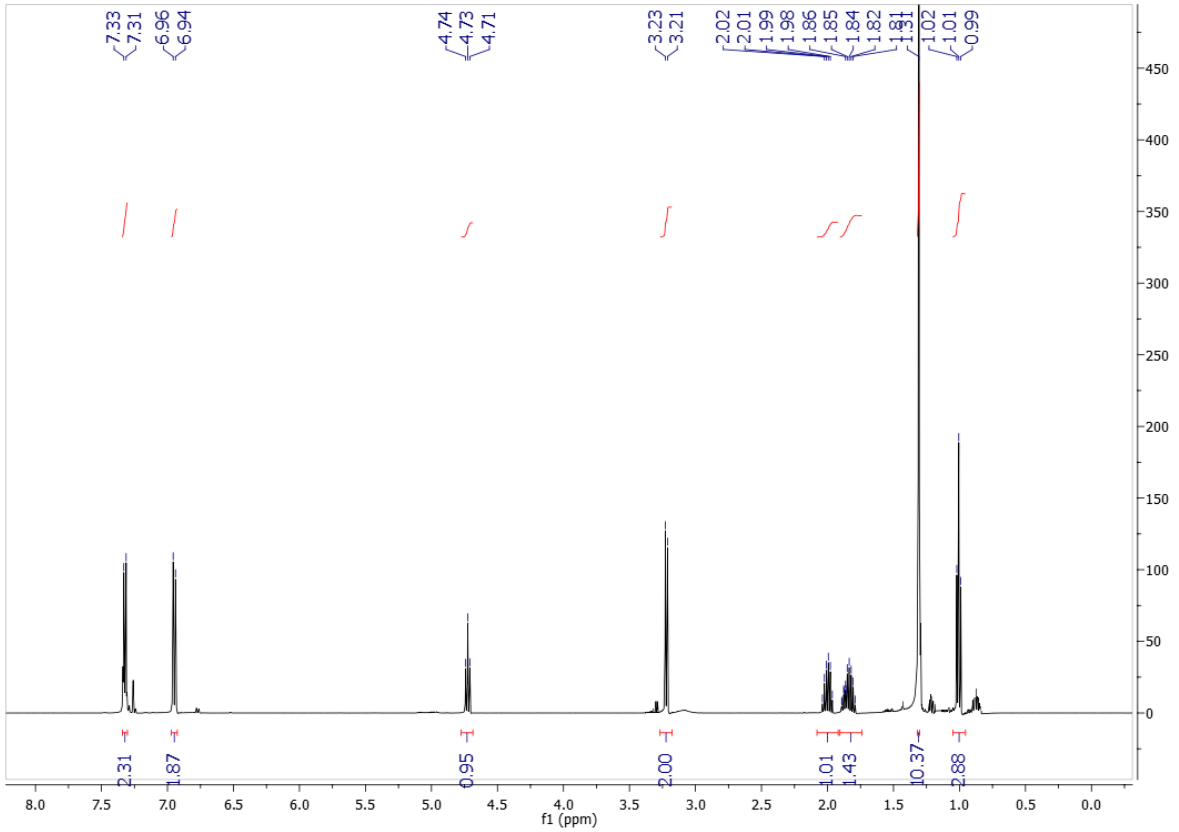
^{1}H (500 MHz) and ^{13}C (126 MHz) NMR spectra of compound ***cis*-2k**

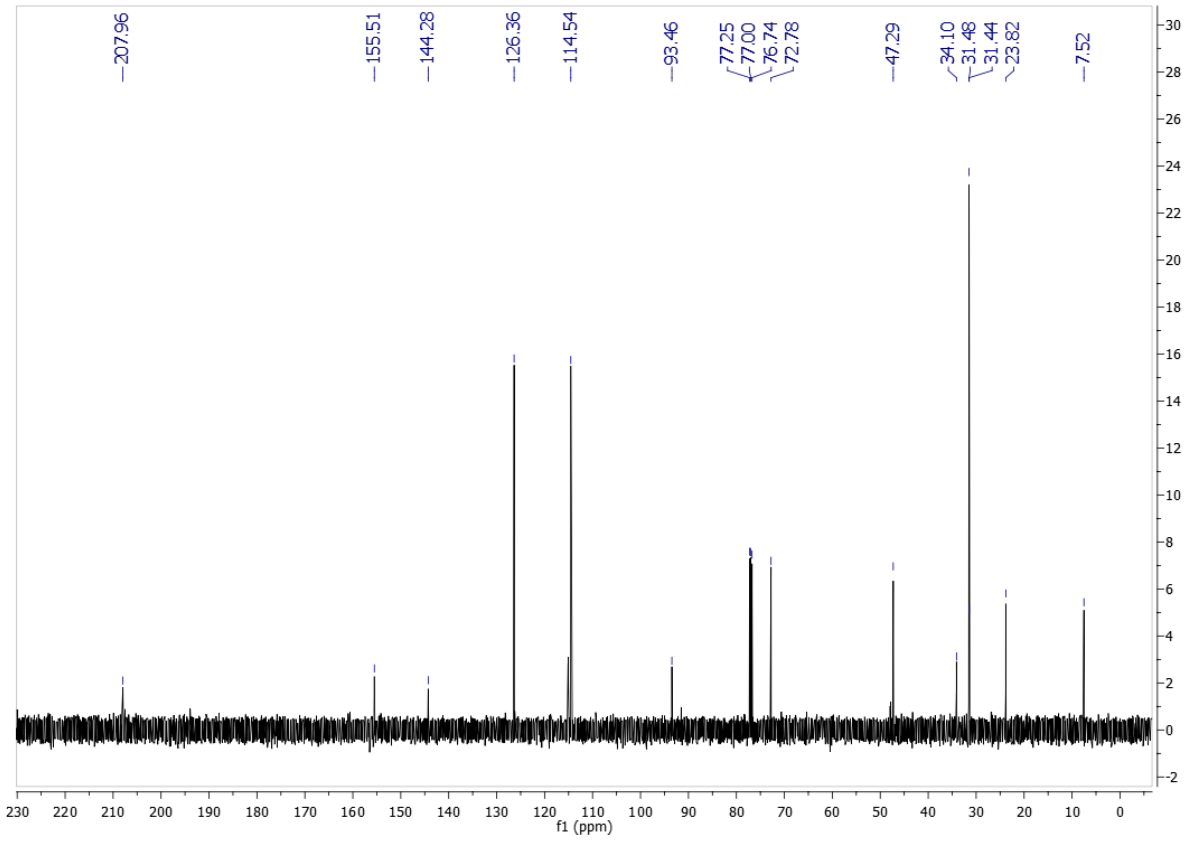


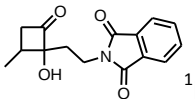




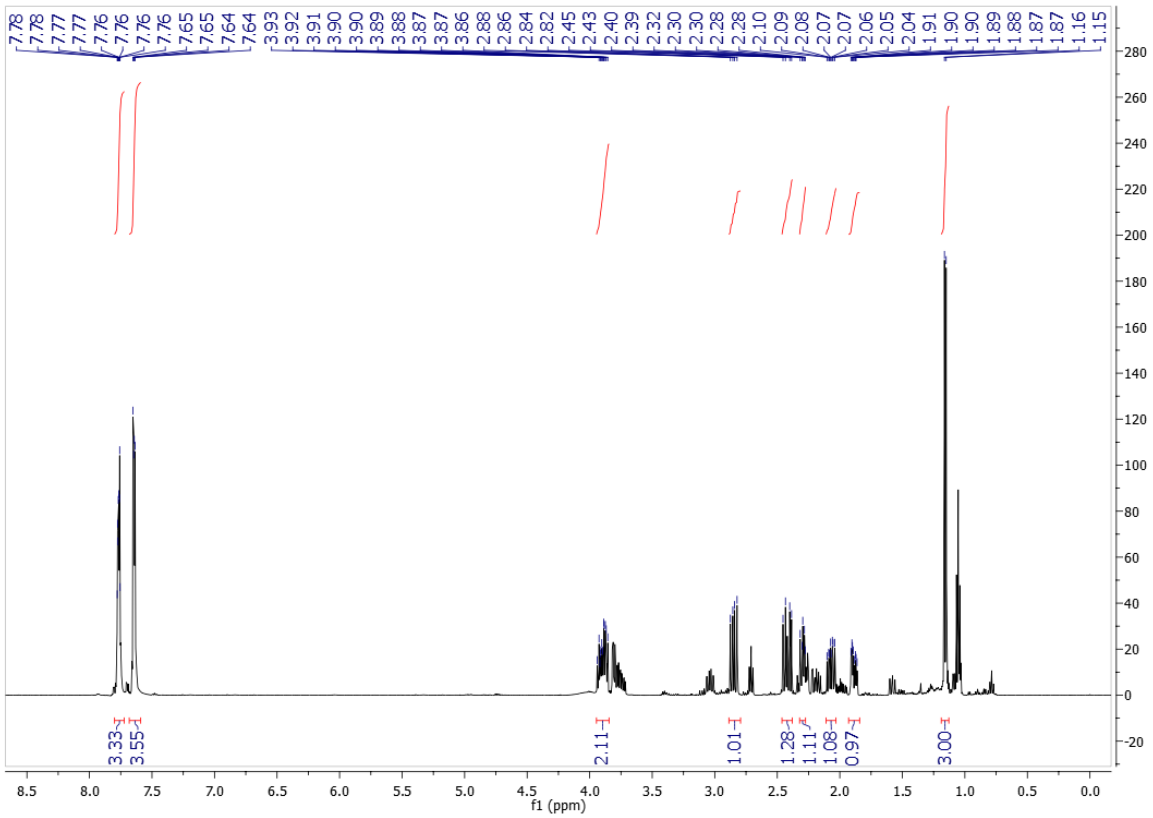
^{1}H (500 MHz) and ^{13}C (126 MHz) NMR spectra of compound **2n**

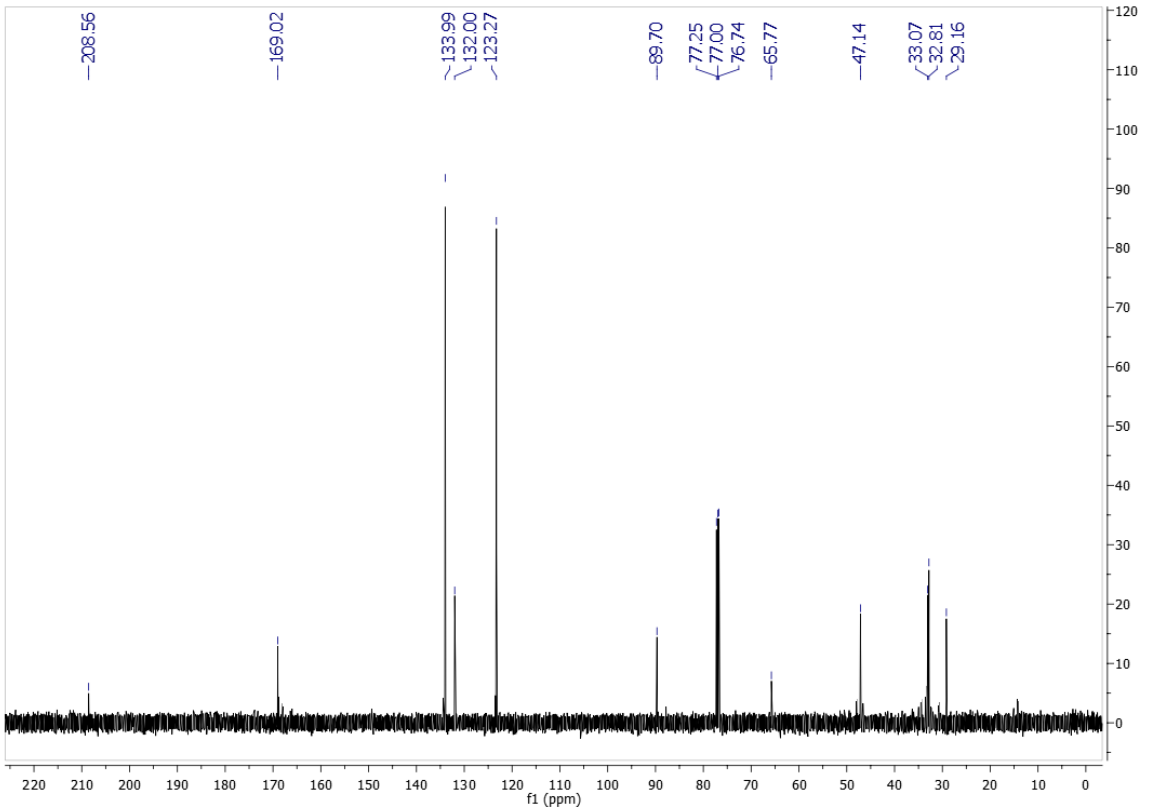






^{1}H (500 MHz) and ^{13}C (126 MHz) NMR spectra of compound **2o**





14. References and notes

1) Parkinson E. I., Hatfield M. J., Tsurkan L., Edwards H. C. C., Hicks L. D., Yan B., Potter P. M., *Bioorg. Med. Chem.,* 2011, **19**, 4635.
2) Ehrt D., The 14th conference on glass & ceramics, 24-28 Sept. 2002, Varna, Bulgaria, Proc.Vol.1, Glass, p. 152-7, Technical glass for the UV region.
3) a) A. D. McNaught, A. Wilkinson, *IUPAC Compendium of Chemical Terminology*, IUPAC, Research Triangle Park, NC, 1997; b) S. E. Braslavsky, *Glossary of terms used in photochemistry*, 3rd edition (IUPAC Recommendations 2006), *Pure Appl. Chem*., 2007, **79**, 293; c) E. Stadler, A. Eibel, D. Fast, H. Freißmuth, C. Holly, M. Wiech, N. Moszner, G. Gescheidt, *Photochem. Photobiol. Sci*., 2018, **17**, 660; d) M. Oelgemöller, N. Hoffmann, *Org. Biomol. Chem*., 2016, **14**, 7392; b)
4) a) Cahiez C.; Gager O.; Buendia J., *Angew. Chem. Int. Ed*., **2010**, *49*, 1278; b) Fuji, K.; Kakiuchi, K.; Morimoto, T.; Tsutsumi, K. *Chem. Commun*. **2005**, 3295.
5) Porcu S.; Luridiana A.; Martis A.; Frongia A.; Sarais G.; Aitken D. J.; Boddaert T.; Guillot R.; Secci F.; *Chem. Commun.*, **2018**, *54*, 13547.
6) Wei Ren Jinfeng Liu Long Chen Xiaobing Wan, Adv. Synth. Catal., 2010, 352, 1424-1428
7) a) Chang C.-L.; Kumar M. P.; Liu R.-S., *J. Org. Chem.* **2004**, *69*, 2793; b) Santoro S.; Battistelli B.; Gjoka B.; Si C.-W. S.; Testaferri L.; Tiecco M.; Santi C.; *Synlett* **2010**, 1402.
8) Mueller-Westerhoff U. T.; Zhou M., *J. Org. Chem.* **1994**, *59*, 4988.
9) Schuettler, C.; Li-Boehmer, Z.; Harms, K.; von Zezschwitz, P., *Org. Lett*., **2013**, *15*, 800.
10) Sastry D. R.; Reddy C. V.; Lal, B.; Singh, P. P.; Seshagiri R. C.; Junnarkar, A. Y.; *Indian J. Chem*., *Sec. B: Org. Chem*. **1981**, 4, 311.
11) Turnu F.; Luridiana A.; Cocco A.; Porcu S.; Frongia A.; Sarais G.; Secci F., *Org. Lett*. **2019**, *21*, 7329.
12) A) Paquette, L. A.; Hofferberth, John E., *Organic Reactions* (Hoboken, NJ, United States), **2003**; b) Urry, W. H.; Duggan, J. C.; Pai, M.-S. H.; *J. Am. Chem. Soc*., **1970**, *92*, 5785.