Linear and Macrocyclic Water Soluble Polyacylhydrazones and their Utilisation in Coatings

Alison M. Daines,[a] Hannah Robinson,[a] Mark Glenny,[b] D. Bradley G. Williams[c] and Simon F.R. Hinkley[a]*

[a] Ferrier Research Institute, Victoria University of Wellington, 69 Gracefield Road, Lower Hutt, New Zealand

[b] Resene Paints, PO Box 38242, Wellington Mail Centre, Lower Hutt, New Zealand

[c] University of Technology Sydney, School of Mathematical and Physical Sciences, PO Box 123 Broadway NSW 2007, Australia

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ABSTRACT

Water soluble polyacylhydrazones have been generated that contain a high proportion of renewable materials. The polyacylhydrazones were found to be present simultaneously as linear and macrocyclic species, the latter being favoured at higher concentrations and in certain combinations of levulinoyl ester/acyldihydrazide. Levulinoyl esters with multiple ketone reactive sites were targeted as building blocks for the backbone. Reaction of these species in aqueous media with commercially available acyldihydrazides afforded a series of high solids-content water soluble polyacylhydrazone solutions. Evaporation of the water from the solutions reproducibly generated films with differing and useful characteristics. One of the polyhydrazones was successfully formulated into two different types of resin bases of commercial coating systems, producing paint products with renewable content.

INTRODUCTION

Hydrazones and oximes have been utilised in a variety of applications ranging from the generation of combinatorial libraries[1-3] to organic polymers,[4-6] and as coatings.[7, 8] Because hydrazone formation is reversible, and since much about the equilibrium[9] and rate of reaction[10] is now understood, a certain level of control over the position of this equilibrium in solution can be achieved. The effects of pH, catalysis[11] and the nature of the parent carbonyl or hydrazide/amine containing molecule on these factors has been discussed in detail.[10, 12, 13] The reversible nature of the hydrazone formation give rise to a dynamic system in which the hydrazones can be manipulated post-preparation, giving rise to 'dynamers'.[4, 5, 14, 15]

The use of ketones in the synthesis of polyacylhydrazones is rare and in most previous studies aldehydes have been used as substrates, likely due to anticipated higher reactivity.[4, 6, 14] Polyketone species have been previously employed in the preparation of hydrogels, but

these were formed using oxime chemistry, not utilising hydrazones.[16] In the present investigation, we utilised ketones as the carbonyl functionality, with interesting outcomes, as detailed below, especially relating to the nature of the species formed in solution.

Cross-linking of polymers by formation of a hydrazone linkage, *via* the incorporation of adipic acid dihydrazide (ADH) into commercial formulations, is widely utilised in the coatings industry. Here, ketone groups are incorporated into the polymer particles of the resin by co-polymerisation of a keto-functionalised monomer such as diacetone acrylamide.[17] Evaporation of water from the waterborne coating leads to coalescence of the emulsion droplets and the formation of a film. During this process, the particles are brought into contact with the water-soluble ADH, which leads to crosslinking upon late-stage evaporation of the water and film formation. It would be valuable to the coatings industry if film-forming polyhydrazones could be directly prepared from systems that are wholly water soluble. This represents an interesting scientific challenge given the known reversibility of hydrazone formation in aqueous media. Whilst the reaction has been investigated in organic solvents, significant issues exist with the solubility of the raw materials in the organic solvents, and the process is complicated by the near-insoluble nature of the polymeric polyhydrazone material so generated, in organic solvents.[4, 6, 18, 19] We have been interested for some time in the production of waterborne coatings with improved environmental footprints over their petrochemical-derived counterparts.[20-22] Accordingly, we have chosen monomers for the present study which are not only largely renewable but also soluble in aqueous systems. Our vision was to develop sufficient understanding of the behaviour of the polyhydrazones in aqueous media to allow us to successfully incorporate them into various commercial coatings.

Here we investigate the preparation of a series acylhydrazone species from ketone functionalised monomers in reactions with dihydrazides, probing the effectiveness of di- or

tri-ketones in the formation of acylhydrazones in aqueous solution. We investigate their solution properties, film forming ability and their usefulness for incorporation into coatings.

MATERIALS AND METHODS

Materials

All commercially available chemicals were used as received unless otherwise stated. Glycerol, ethylene glycol and diethylene glycol were sourced from Sigma Aldrich, triethylene glycol was sourced from Acros Organics, and triethanolamine from Riedel-de Haën. Levulinic acid was supplied by SAFC, adipic acid dihydrazide (ADH) from Nuplex Resins Ltd and oxalyl dihydrazide, isophthalic dihydrazide and carbohydrazide from AK Scientific, Inc.

Analysis

Preparative chromatography utilised a Grace Reveleris system equipped with a pre-packed column of silica gel. All NMR spectra, including ^{1}H, ^{13}C, COSY, HSQC and HMBC experiments, were recorded on a Bruker Avance 500 spectrometer at 27 °C, in $CDCl_3$ for the monomers and in D_2O for the polymeric products, unless otherwise specified, using an inverse-detection probe. NMR spectra in $CDCl_3$ were referenced to TMS and those in D_2O to the solvent peak (δ 4.7 ppm). High temperature NMR experiments were carried out as above in D_2O at a temperature of 90 °C. Differential scanning calorimetry was completed on a Mettler DSC1 STAR^{e} system equipped with a GC200 gas controller and autosampler. Samples (0.5–1.5 mg) in pierced aluminium crucibles (40 μL, PN ME-26763) were assessed using three contiguous repeat cycles from –20 to 160 °C at a ramp rate of 5 °C.min^{-1} under a constant flow of nitrogen (30 mL.min^{-1}).

Mass spectrometric analysis was carried out on a Q-TOF Premier mass spectrometer (Micromass, UK) with the MassLynx operating system (version 4.1). Samples were dissolved in water or aqueous methanol (containing a trace amount of formic acid to assist positive-ion mode ionisation) and infused directly into the ESI source. Tandem mass experiments were carried out with an optimised collision energy and helium as the collision gas. The instrument was calibrated with an aqueous solution of sodium formate prior to accurate mass measurements.

Molecular modelling calculations were carried out in Chem 3D Pro 14.0 using the MM2 forcefield.

Preparation of ketone monomers

Monomers with multiple ketone-functionality were prepared in esterification reactions by heating (135 °C) the relevant polyol, *p*-toluenesulfonic acid (0.003 equiv.) and levulinic acid (1.4 equiv. *per* hydroxyl) under reduced pressure (10 mmHg) to remove water, in solventless reactions. Reaction completion was determined as the point where no additional water was generated (approximately 2.5 h). The reaction mixture was cooled to room temperature before being diluted with chloroform, washed with water (300 mL ×2) and the product recovered by evaporative concentration.

Dilevulinoyl ethylene glycol (**1**) (112.3g, 0.44 mol) was recovered from the reaction of ethylene glycol (30 g, 0.48 mol) in 92% yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.28 (s, 4H), 2.76 (t, *J* = 6.7 Hz, 4H), 2.60 (t, *J* = 6.7 Hz, 4H), 2.19 (s, 6H); ^{13}C NMR (125 MHz $CDCl_3$): δ 206.4, 172.5, 62.2, 37.8, 29.8, 27.8. ESI-MS: calcd for $C_{12}H_{18}O_6$ $[M + Na]^+$ 281.1001; found 281.0994.

Dilevulinoyl diethylene glycol (**2**) (411g, 1.36 mol) was prepared from diethylene glycol (180 g, 1.70 mol) and recovered as a thin, pale-yellow oil in 80% yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.23 (t, J = 4.9 Hz, 4H), 3.69 (t, J = 4.9 Hz, 4H), 2.76 (t, J = 6.5 Hz, 4H), 2.61 (t, J = 6.5 Hz, 4H), 2.19 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 206.5, 172.7, 69.0, 63.6, 37.9, 29.8, 27.9; ESI-MS: calcd for $C_{14}H_{22}O_7$ $[M + Na]^+$ 325.1263; found 325.1263.

Dilevulinoyl triethylene glycol (**3**) (12.46g, 34 mmol) was prepared from triethylene glycol (6.00 g, 38 mmol) in 90% yield.; ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.23 (t, J = 4.9 Hz, 4H), 3.70 (t, J = 4.9 Hz, 4H), 3.66 (s, 4H), 2.76 (t, J = 6.7 Hz, 4H), 2.60 (t, J = 6.7 Hz, 4H), 2.19 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 206.7, 172.6, 70.4, 68.9, 63.6, 37.8, 29.7, 27.8. ESI-MS: calcd for $C_{16}H_{26}O_8$ $[M + Na]^+$ 369.1525; found 369.1520.

Trilevulinoyl triethanolamine (**4**) (134.8 g, 0.30 mol) was prepared from triethanolamine (48.8 g, 0.33 mol) in 93% yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.12 (t, J = 6.0 Hz, 4H), 2.84 (t, J = 6.0 Hz, 4H), 2.75 (t, J = 6.7 Hz, 4H), 2.60 (t, J = 6.7 Hz, 4H), 2.19 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 206.5, 172.6, 62.8, 53.3, 37.9, 29.8, 27.9. ESI-MS: calcd for $C_{21}H_{33}O_9$ $[M + Na]^+$ 466.2053; found 466.2047.

Trilevulinoyl glycerol (**5**) (18.9g, 49 mmol) was prepared from glycerol (5.00 g, 54 mmol) in 90% yield; ^{1}H NMR ($CDCl_3$): δ 5.23–5.27 (m, 1H), 4.27 (dd, J = 11.9, 4.2 Hz, 2H), 4.18 (dd, J = 11.9, 6.0 Hz, 2H), 2.75–2.78 (m, 6H), 2.58–2.61 (m, 6H), 2.19 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 206.3 (×2), 172.2, 171.9 69.2, 62.2, 37.8, 29.7, 27.7. ESI-MS: calcd for $C_{18}H_{26}O_9$ $[M + Na]^+$ 409.1475; found 409.1468.

1,2-Dilevlinoyl-1,2-benzenedimethanol (**6**) was prepared from the reaction of 1,2-benzenedimethanol (500 mg, 3.6 mmol), levulinic acid (1.18 g, 10.2 mmol, 1.4 equiv.) and *p*-toluenesulfonic acid (6 mg). The mixture was heated for 1.5 h at 115 °C under reduced pressure. The reaction mixture was diluted with $CHCl_3$ (10 mL) and washed with water (2 ×

5 mL). The organic phase was concentrated under reduced pressure to afford **6** as a yellow oil (1.13 g, 93% containing 11% starting material): ^{1}H NMR δ (ppm) 7.31–7.41 (m, 4H), 5.20 (s, 4H), 2.76 (t, *J* = 6.7 Hz, 4H), 2.61 (t, *J* = 6.7 Hz, 4H), 2.19 (s, 6H); ^{13}C NMR δ (ppm) 206.5, 172.4, 134.4, 129.7, 128.7, 64.0, 37.9, 29.8, 27.9; ESI-HRMS found 357.1306, $C_{18}H_{22}O_6$ $[M+Na]^+$ calcd for 357.1314.

1,4-Dilevulinoyl-1,4-benzenedimethanol (**7**) was prepared in a similar fashion to **6** above by the reaction of 1,4-benzenedimethanol (500 mg, 3.6 mmol) and levulinic acid (1.04 mL, 10.2 mmol) to afford a yellow oil (810 mg, 67% containing 5% starting material): ^{1}H NMR δ (ppm) 7.34 (s, 4H), 5.11 (s, 4H), 2.76 (t, *J* = 6.7 Hz, 4H), 2.63 (t, *J* = 6.7 Hz, 4H), 2.18 (s, 6H); ^{13}C NMR δ (ppm) 206.6, 172.6, 135.9, 128.3, 66.1, 37.9, 29.8, 28.0; HRMS found 357.1310, $C_{18}H_{22}O_6$ $[M+Na]^+$ calcd for 357.1314.

Acylhydrazone test reactions

The simple acyldihydrazone test compounds were synthesised following the procedure of Zha and You.[23] ADH was added to a methanol solution containing 2–2.3 equivalents of the aldehyde or ketone. For compound **8**, glacial acetic acid was also added to the flask dropwise to achieve a pH of 4–5. The reaction mixture was heated at reflux temperature to yield a white precipitate, which was washed with methanol (2 × 5 mL) and isolated by vacuum filtration. The acyldihydrazones were soluble in DMF and DMSO. In the ^{1}H NMR data below for molecules that display rotamers in solution, we list the two signals demonstrating the rotameric forms, then their multiplicity and the *total* value for which they integrate (e.g. δ 11.14 & 11.02 (d, *J* = 5.8 Hz, *J* = 5.0 Hz, 2H)). Where one rotameric form predominates the signals for the major isomer are shown in bold type.

Compound **8** was synthesised by stirring ADH (406 mg, 2.26 mmol) and vanillin (714 mg, 4.55 mmol) in methanol (140 mL) at reflux temperature for 40 h, providing the product

as a white solid (820 mg, 1.85 mmol, 82% yield, rotamers observed in approximately 1:1 ratio). ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.14 & 11.02 (d, J = 5.8 Hz, J = 5.0 Hz, 2H), 9.45 (s, 2H), 8.05 & 7.87 (s, 2H), 7.25 & 7.22 (s, 2H), 7.08–7.00 (m, 2H), 6.84–6.76 (m, 2H), 3.81 & 3.77 (s, 6H), 2.69–2.60 (m, 2H), 2.26–2.17 (m, 2H), 1.70–1.57 (m, 4H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 173.9, 168.2, 148.8, 148.5, 148.0, 146.3, 142.9, 142.8, 125.8, 121.8, 120.8, 115.5, 115.4, 109.5, 109.3, 109.0, 55.5, 34.1, 31.8, 25.0, 24.9, 24.2, 24.0. ESI-HRMS: calcd for $C_{22}H_{26}N_4O_6$ $[M + Na]^+$ 465.1750; found 465.1752.

Compound **9** was synthesised by stirring ADH (250 mg, 1.4 mmol) and acetone/water (1:1, 10 mL) for 4.5 h, providing the product as a solid (325 mg, 1.3 mmol, 89%). ^{1}H NMR (500 MHz, DMSO-d_6): δ **9.98** and 9.79 (s, 2H), 2.54–2.52 (m, 2H), 2.50 and **2.21** (brm, 2H), **1.92** and 1.90 (s, 6H), **1.84** and 1.83 (s, 6H), 1.56-1.50 (m, 4H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 174. 5, **168. 8**, **155.5**, 150.3, **33.6**, 31. 8, 25.0, 24.9, **24.8**, 23.8, **17.4**, 16.8.

Compound **10** was synthesised by stirring ADH (201 mg, 1.10 mmol) and methyl levulinate (328 mg, 2.50 mmol) in methanol (6 mL) under reflux for 46 h, providing the product as a white solid (378 mg, 0.949 mmol, 87% yield). ^{1}H NMR (500 MHz, DMSO-d_6): δ **9.96** & 9.90 (s, 2H), 3.58 (s, 6H), 2.57–2.46 (m, 8H), 2.46–2.37 (m, 2H), 2.24–2.17 (m, 2H), 1.84 & **1.82** (s, 6H), 1.53 (s, 4H); ^{13}C NMR (126 MHz, DMSO-d_6): δ **174.5**, **172.8**, 168.3, 155.4, **150.0**, 51.2, **51.1**, 33.8, 33.0, **32.7**, **31.9**, 29.7, **29.4**, 25.0, **24.0**, 16.7, **16.3**. ESI-HRMS: calcd for $C_{18}H_{30}N_4O_6$ $[M + H]^+$ 399.2238; found 399.2230.

General method for polyacylhydrazone formation

To a solution of dilevulinoyl diethylene glycol (**2**) (316 g, 1.05 mol) in water (664 mL) was added adipic acid dihydrazide (164 g, 0.9 equiv.) with shaking. This gave a clear viscous solution of approximately 50% *w/v* solids. The resulting solution was used directly

for mass spectroscopy studies. An analogous solution prepared in D_2O was used for NMR studies.

Film formation

All film forming experiments were carried out by placing approximately 0.5 mL of a 50% *w/v* polymer solution on a glass slide then drying overnight in an oven at 60 °C. The resulting films were assessed for glass transition temperature by differential scanning calorimetry.

Coating preparation

A 50% *w/v* aqueous solution of the relevant polyhydrazone was used to substitute 30–50% of the resin component in a commercial paint coating composition. Paint formulations utilising cross-linking and non-crosslinking commercial resins were prepared. The formulation of a gloss paint with a non-crosslinking commercial resin proceeded with the preparation of a standard ‘letdown’ and ‘millbase’ and subsequent mixing, to give a final weight % composition as outlined in Table 1.

Table 1. Composition[a] and method employed to formulate a gloss paint.

Ingredient	wt %
Letdown:	
Resin	48
Defoamer, coalescent, wetting agent, *p*H modifier, water	7
Millbase:	
Water	7
MPG,[b] *p*H modifier, dispersants, defoamers, biocides, rheology modifier	6
TiO_2	26
Wetting agents, biocides, defoamers, MPG,[b] rheology modifiers, silicone emulsion	3
PROCESS	
Add millbase to letdown and wash millbase vat with water	3

[a] Proprietary composition confidential to Resene Paints Ltd.
[b] MGP = monopropylene glycol

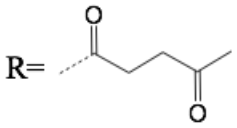
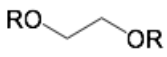
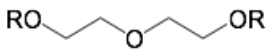
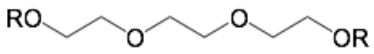
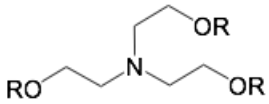
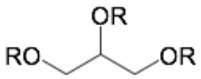
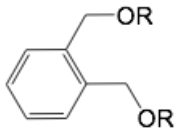
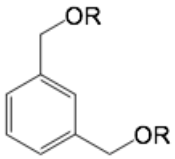
RESULTS AND DISCUSSION

Ketone containing substrates

There is already a significant body of work dealing with the preparation of levulinyl containing species such as **1**–**7**, their dioxolane derivatives and their application as renewable plasticisers,[24-27] surfactants and formulation aids.[28-30] The di- and tri-levulinyl ester monomers used in the present study were chosen to be highly renewable and readily synthesised in a one-pot chemical process. To that end esters were prepared of ethylene glycol (EG, **1**), diethylene glycol (DEG, **2**), triethyleneglycol (TEG, **3**), triethanolamine (TEA, **4**) and glycerol (**5**). The preparation of a levulinoyl ester of pegylated pentaerythritol has been described previously and utilised a carbodiimide coupling reagent.[16] Bearing the concepts of green chemistry in mind, we conducted our esterification reactions under solvent-free conditions under reduced pressure in the presence of *p*-toluenesulfonic acid, with the reaction

driven to completion by the removal of water generated. All of these monomers were oils that were water miscible in all proportions, except the trilevulinoyl glycerol which formed an emulsion in water. In the cases of triesters **4** and **5** the esterification was incomplete and small amounts of the dilevulinoyl species were also present.

Table 2. Di- and tri-ketone species used as monomers in polyhydrazone formation.

Monomer	R= 
1	
2	
3	
4	
5	
6	
7	

Simple acylhydrazides from ketones

It has been demonstrated that acyldihydrazone species exist in a number of geometric and conformational forms. To begin, we investigated simple systems generated from ADH

and ketones, specifically the levulinoyl group, before tackling the synthesis and analysis of polymeric species. The acyldihydrazones were prepared from ADH by reaction with aldehyde or ketone monomers as test species (Figure 1) and characterised through NMR spectroscopy and mass spectrometry. For acylhydrazones, (*E*/*Z*)-isomerism at the C=N double bond and conformational (*E'*/*Z'*)-isomerism from hindered rotation around the C-N amide bond can result in four different configurations (*EE'*, *EZ'*, *ZE'*, *ZZ'*; Figure 2) and has been previously reported.[31-35] Indeed, peak assignment of the NMR spectra of the acyldihydrazones prepared herein was complicated by the presence of such rotamers, as evidenced by the doubling of ^{1}H and ^{13}C signals.

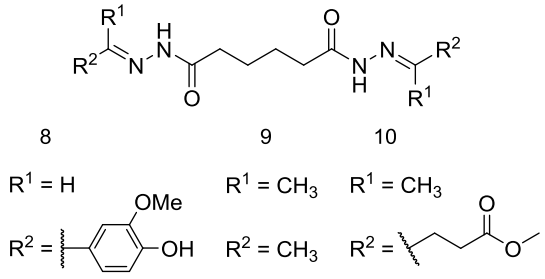


Figure 1. Acyldihydrazones synthesised from ADH and an aldehyde or ketone.

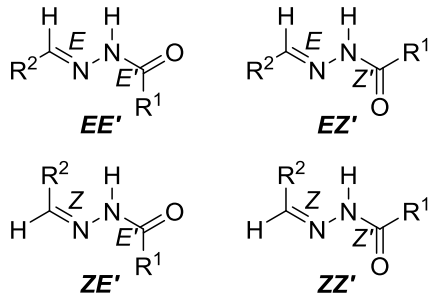


Figure 2. Possible geometric (*E*/*Z*)-isomers and (*E'*/*Z'*)-rotamers of acylhydrazones.

In regards to compound **8**, derived from an aromatic aldehyde, two signals in the ^{13}C spectrum in a ratio of ~1:1 that were assigned as the hydrazone carbonyl resonances appeared at δ 173.9 and 168.1 ppm (30 °C); these merged to a single resonance at δ 173.4 ppm when

spectra were obtained at 90 °C. Likewise, the two ^{1}H signals at δ 11.14 and 11.02 ppm for the amide N-H protons coalesced into a signal at δ 10.69 ppm at 90 °C. We attribute these signals to the (*E'*/*Z'*)-rotameric forms of the aldehyde-derived acyldihydrazone. Generally, acylhydrazones derived from aldehydes adopt the (*E*)-configuration.[32, 36] For those derived from aromatic aldehydes, this is thought to be the result of steric hindrance.[32, 33] For compound **1**, only one geometric isomer was observed, and it was assigned the (*E*)-configuration with respect to the C=N moiety. This was done by comparison with results of previous studies[34, 37-39] which utilised X-ray crystallographic and solvent effect data to confirm the configuration of the acylhydrazone products.

The preparation of compound **9** uses a symmetric ketone for acylhydrazone formation which removes any possibility for the formation of *E*/*Z* isomers about the C=N bond. Analysis of the product by NMR spectroscopy showed the presence of a major and minor isomer (approximately 1.5:1 ratio), which were attributed to *E*'/*Z*' rotamers as was the case for compound **8**. The clearest evidence for this phenomenon in the ^{1}H NMR spectrum of **9** is the presence of two separate signals at δ 2.22 and 2.51 ppm for the CH_2 adjacent to the carbonyl group, and two NH signals at δ 9.79 and 9.97 ppm, respectively, for the major and minor isomers. Peaks associated with the two methyl groups of the major and minor isomers can also be distinguished. Moreover the carbonyl region of the ^{13}C NMR contains 4 signals which are assigned as the **major** and minor isomers of the hydrazone carbonyl group (δ **168.8** and 174.5 ppm) and the C=N moiety (δ **155.5** and 150.3 ppm). Two peaks are also observed for the CH_2 carbon adjacent to the carbonyl group (δ **33.6** and 31.7 ppm) and each of the methyl groups. No evidence for the presence of the *Z* isomer was observed. The assignment of all signals was supported by homonuclear and heteronuclear correlation spectroscopy (COSY, HSQC and HMBC experiments). Heternonuclear correlation supported the assignment of the

major and minor species, where a short range correlation was observed for the CH_2 adjacent to the carbonyl group between δ ^{13}C **33.6** ppm and δ ^{1}H **2.21** ppm for the major isomer and δ ^{13}C 31.8 ppm and δ ^{1}H 2.50 ppm for the minor isomer. Similarly long range heteronuclear correlations were observed from the C=N to the methyl groups at δ ^{13}C **155.5** ppm and δ ^{1}H **1.92** and **1.84** ppm for the major isomer and δ ^{13}C 150.3 ppm and δ ^{1}H 1.90 and 1.83 ppm for the minor isomer.

Similar results to those obtained for compounds **8** and **9** were obtained for compound **10**: rotamers were observed by a doubling of ^{13}C NMR signals in a 2:1 ratio at 30 °C, and coalescence of the doubled signals was observed when spectra were recorded at 90 °C. For example, the doubled ^{13}C signals at δ 16.7 (minor) and δ **16.3** (major) ppm for the hydrazone methyl groups and δ 51.2 (minor) and δ **51.1** (major) ppm for the methoxy groups collapsed into single signals at δ 15.7 ppm and δ 50.6 ppm, respectively. Identification of the bonds involved in generating rotamers was assisted by the chemical shift difference (i.e. Δδ) in the ^{13}C NMR spectrum between the major and minor resonances attributed to rotameric forms of each carbon group, as shown in Figure 3. The Δδ value between rotamer signals was greater for signals generated by C atoms closer to the C-N amide bond, which is the bond of hindered rotation that generates rotamers (e.g. Δδ 6.2 ppm for C-3 in Figure 3). Again, only one geometric isomer was observed, and chemical shift data (in particular the alkene methyl resonance at Δδ 16.3 ppm) is consistent with the (*E*)-configuration.

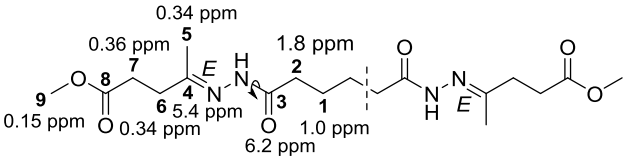


Figure 3. Δδ values between major and minor species for compound **10** (^{13}C NMR spectrum, 30 °C).

Table 3. ^{13}C NMR data for **10**.

Carbon	δ ^{13}C Major (ppm)	δ ^{13}C Minor (ppm)	Δδ ^{13}C |Major - Minor| (ppm)
1	**24.0**	25.0	1.0
2	**31.9**	33.8	1.8
3	**174.5**	168.3	6.2
4	**150.0**	155.4	5.4
5	**16.3**	16.7	0.3
6	**29.4**	29.7	0.3
7	**32.7**	33.0	0.4
8	**172.8**	-	-
9	**51.1**	51.2	0.1

Water soluble polyacylhdrazone species from polyketones

A series of diacylhydrazides were investigated for polymer formation with our levulinoyl esters, including adipic acid dihydrazide (ADH), oxalyl dihydrazide and carbohydrazide, for all of which the parent acid may be generated from renewable sources. These were added to an aqueous solution of the levulinoyl ester monomer at a level of 0.9 molar equivalents per ketone moiety, with preparations having a final overall concentration of approximately 50% *w/v* solids. The solubility of the acyl dihydrazides in the aqueous solution varies and total dissolution at high concentration occurred only upon formation of the hydrazone species. This is consistent with previous findings, including with lipophilic acyldihydrazides.[40, 41]

Whilst the levulinoyl esters **1–5** were soluble in aqueous solution, the corresponding polyhydrazones were not in some cases. The water solubility of the polyhydrazone is dependent upon the combination of ketoester and dihydrazide used (Table 4). The polyhydrazones varied between clear solutions, gels and precipitates, with some modification of the physical behaviour with time (Table 4). All of the polymer solutions were analysed by mass spectroscopy to assess the nature of the polymeric species formed. Where gels or solids had formed, the product was analysed after dissolution in methanol.

Table 4. Physical appearance of polymer solutions in reactions between acyldihydrazides and keto-esters **1-5**.

→Ketoester ↓Acyldihydrazide	**1**	**2**	**3**	**4**	**5**
ADH	Clear soln, then ppt[a]	Clear soln, then ppt[a]	Clear	Gel, then free flowing soln[a]	Gel, then syneresis
Oxalyl dihydrazide	Solid	Gel			
Carbodihydrazide	Oil	Oil	Cloudy soln[a]	Clear soln, then ppt[a]	

[a] Soln = solution; ppt = precipitate

Analysis of the hydrazone polymer systems by ^{1}H and ^{13}C NMR spectroscopy provided supporting data for the formation of polyacylhydrazone species. For the LevEG-ADH system the ^{1}H NMR showed a broadening of the methylene peaks which is consistent with the formation of a polymeric mixture. Of more interest is the carbonyl area of the ^{13}C NMR spectrum (Figure 4), which contains a series of peaks, again broadened by the formation of polymer compounds, which were fully assigned using HSQC and HMBC NMR analysis experiments. The signals at δ 154.6 and **160.9** ppm represent the C=N moieties of the rotamers of the acylhydrazone, with the corresponding signals for the hydrazone carbonyl appear at δ **172.2** and 175.3 ppm.

End group analysis to approximate the number average molecular weight is commonly performed during the characterisation of polymers but was not feasible in the present instance due to the significant overlap of groups in the ^{1}H NMR spectrum. However, mass spectrometry analysis of the resultant hydrazone products revealed the majority of the solution species to be a mixture of low molecular weight polymers, predominantly with a degree of polymerization (DP) of up to six. This finding is unexpected in light of many

examples in the polymer literature where polyacylhdrazones with DP = 129 have been prepared in organic solvents.[6, 19]

The NMR spectral data also support the notion that the product consisted of low molecular weight polymeric species. The end-group unreacted hydrazide was evidenced by a sharp carbonyl signal observed at δ 174.8 ppm (also present in this area is a broad peak at δ 174.6 ppm for the various levulinyl ester moieties), and similarly the signal of the unreacted LevEG monomer ketone is evident at δ 212.3 ppm. As is demonstrated in Figure 4, the signals in this region of the ^{13}C NMR spectrum are consistent with the formation of a set of structurally similar polymeric compounds, and similar analytical data were obtained for the other polyhydrazones. The presence of both hydrazide and ketone moieties can be attributed to the end groups of linear polyacylhydrazone polymers, with the ratio of the ketone/hydrazide to hydrazone peaks giving a measure of the average overall degree of polymerization of the mixture.

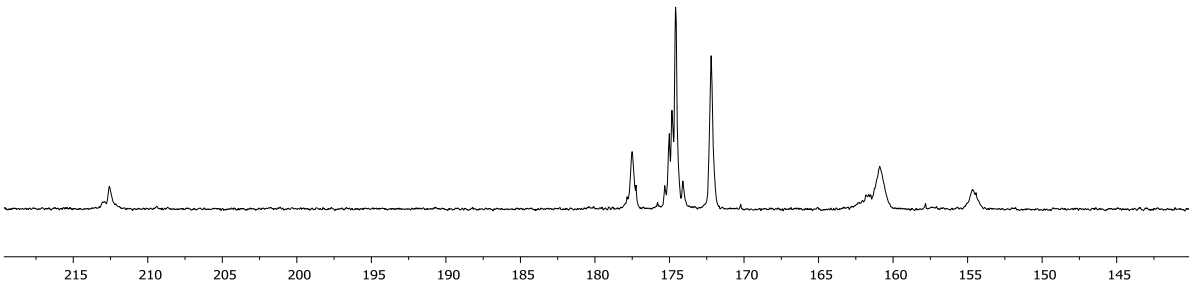


Figure 4. The carbonyl region of the ^{13}C NMR spectrum of LevEG-ADH polymer (values in ppm, 125 MHz)

Interestingly, there was also evidence in the mass spectrum for macrocyclic species. The formation of macrocyclic polyacylhydrazones has been observed in some dynamic combinatorial libraries, especially where there is a templating agent present.[42, 43] It is likely that the formation of cyclic species is favoured due to hydrogen bonding between the amide moiety of the acyl hydrazone formed and carbonyl groups of the ester species, leading to pre-organised arrangements that are predisposed to macrocyclisation (see Figure 5).[19] This would be facilitated by a very flexible backbone structure and freedom of motion imparted by the levulinoyl group, as even the more rigid 1,2- (**6**) and 1,4-dilevulinoyl benzenedimethanol (**7**) gave rise to both linear and macrocyclic compounds, upon reaction with ADH. The relative intensities of the parent ions in the mass spectrum of the polymer mixture were used to approximate a ratio of macrocycle/polymer. Reactions of diLevEG and ADH performed at higher concentrations led to increased yields of the macrocyclic product over the linear species (approximately 1.5:1 macrocycle:linear), over those performed at low concentrations (approximately 0.9:1 macrocycle:linear), based on MS analyses of the reaction mixtures. This observation supports the notion of self-assembly of the reacting partners to facilitate the macrocyclisation. This self-templating rationale has previously been postulated in support of the apparent high stability of polyhydrazone macrocycles in solution.[1] Molecular modelling (Chem 3D Pro software) using structure minimization and the MM2 forcefield on (diLevEG-ADH)$_2$ supported this notion. The computation demonstrated the presence of a number of intramolecular hydrogen bonds that are not only a stabilising feature but which arrange the molecule into a cyclic structure that would be set up for cyclisation (see Figure 5)

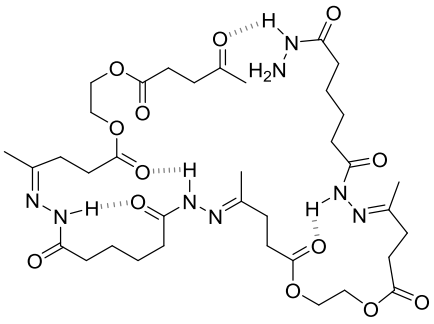


Figure 5. Hydrogen bond driven self-assembly template effect to produce macrocycle species.

Upon prolonged storage, or if a concentrated solution (>40% *w/w* polyacylhydrazone in water) was agitated, a white precipitate was generated. NMR analysis of the precipitate formed from the diLevEG-ADH system revealed no free hydrazide or ketone groups (by ^{13}C NMR spectroscopy), which is consistent with the cyclic species. MS analysis of the precipitate returned a value of *m/z* = 419.2, indicative of a dilevEG-ADH macrocycle. Similarly analysis of the precipitate from a solution of diLevDEG and ADH was shown to be predominantly the macrocycles diLevDEG-ADH, $(diLevDEG\text{-}ADH)_2$, and $(diLevDEG\text{-}ADH)_3$. The macrocycles appeared to be less soluble in aqueous solution than the corresponding linear polymers, causing precipitation thereof from the polymer solution and presumably driving the equilibrium of the dynamic system towards the formation of this thermodynamically favoured species. Literature reports indicate that these systems form dynamic equilibria,[1] with which our observations agree. The dynamic nature of the system was demonstrated by the addition of diLevEG monomer to a fully equilibrated aqueous solution of triLevTEA-ADH, which rapidly produced some diLevEG-ADH adducts (formed by an exchange reaction), as shown by MS analysis. Also observed were polymers and macrocycles containing both the triLevTEA and diLevEG monomers with ADH.

The ratios of macrocycle/linear compounds, as assessed by MS, varied greatly depending on the hydrazide used. With ADH there was little preference for one over the other, but when oxalyl dihydrazide was used linear compounds predominated with all levulinyl monomers used; conversely, with carbohydrazide the macrocycles were dominant. The exact reasons behind these phenomena are unknown but likely relate to a combination of the ability of the system to form templated arrangements that allow for macrocycle production, and the influence of kinetic/thermodynamic control under our conditions.[44]

Films from polyacylhydrazones

Given our interest in the production of renewable film-forming polymers[20-22] we investigated the properties of films of these polyhydrazone mixtures. Films were cast of all polymers that had formed clear solutions in aqueous media (Table 4), and these were dried overnight in an oven at 60 °C. The films of all polymers except triLevTEA-ADH and diLevDEG-ADH were soft and tacky to the touch. The diLevDEG-ADH film was hard and glassy while the triLevTEA-ADH film was solid yet malleable. These films were all moisture sensitive and were noted to first swell and then re-dissolve when exposed to water. A film was cast from the solution formed upon the reaction of **10** with ADH in acetonitrile and this was found to be hard and tough.

The glass transition temperatures (T_g) were measured for the films formed from polymers of diLevDEG and triLevTEA with ADH, and found to be 23 °C and 28 °C, respectively, even though these both presented as hard films. The T_g of the 1,4-dilevulinoyl dimethanolbenzene (**7**) film was 38 °C. The low T_g values presented by these polymers means that they possessed the potential to impart desirable mechanical properties (e.g. flexibility and impact resistance) to a coating. Accordingly, the ability to include them into paint formulations was pursued.

Paint coating from polyacylhydrazones

The diLevDEG-ADH and triLevTEA-ADH mixtures were taken forward as lead compounds due to their ease of preparation, good aqueous solubility characteristics and the hard yet flexible films they produced. For this work, a commercial resin capable of cross-linking and one non-crosslinking commercial resin were employed in the base paint formulation. The diLevDEG polymer solution could be incorporated into the commercial cross-linking resin at up to 50% *w/w* but the lower level of 30% *w/w* incorporation afforded improved properties in the final paint produced. The diLevDEG polymer solution could also be incorporated into the mill base of a paint (see Table 1) with a commercial non-crosslinking resin at levels of 50% *w/w*. The triLevTEA-ADH polymer could not be successfully blended into commercial paint formulations, possibly the results of its ability to form extensive cross-linked networks.

The paint compositions containing the polyhydrazone species were formed into films using industry-standard draw-down techniques. These films, once dry, demonstrated comparable hardness, gloss and adherence to standard test-cards to paints prepared from the parent paint formulations alone. Preliminary rub-tests unexpectedly indicated moderate water resistance, despite the high water solubility of the polyhydrazone species. The good compatibility of the polyhydrazone in the paint formulations, and the positive response of the paints to the industry standard tests, were pleasing and bode well for the incorporation of renewable content in petroleum-based acrylic resin formulations. We are currently investigating recoat-properties, longer term weathering and adhesion properties of the blended systems.

CONCLUSION

The reaction of structurally related levulinyl esters with a small series of acyldihydrazides in aqueous media produced dynamic systems in which substantial portions of linear and macrocyclic hydrazone products were produced. Extensive NMR experiments produced no evidence for the presence of any *Z* hydrazones, but rotamers about the C-N amide bond were clearly observed in hydrazones derived from both aldehydes and ketones. We propose that the formation of the macrocyclic structures is assisted by self-assembly that is driven by hydrogen bonding. The extent of macrocyclisation depended upon the nature of the dihydrazide used and the overall concentration of the reaction mixture; at higher concentrations formation of macrocyclic products was favoured.

High solids-content aqueous solutions (50% *w/v* solids) were capable of forming films, some of which displayed desirable properties for coatings. Accordingly, the diLevDEG-ADH polymer was successfully incorporated into a paint formulation at levels of 30–50% *w/w* with a commercial crosslinking resin, and in a second example with a non-crosslinking resin. The paints gave coatings that demonstrated good performance characteristics when subjected to a set of industry-standard tests. Further optimisation of these paint formulations and full analysis of paint properties are ongoing.

Supporting Information. Proton, carbon and 2D- NMR spectra for key di- and tri- levulinoyl esters and mono- and diacylhydrazones. This material is available free of charge via the Internet at http://pubs.acs.org.

Corresponding Author

* Dr Alison Daines, The Ferrier Research Institute, Victoria University of Wellington, 69 Gracefield Road, Lower Hutt 5010 (New Zealand)

E-mail: alison.daines@vuw.ac.nz Homepage: http://www.victoria.ac.nz/ferrier

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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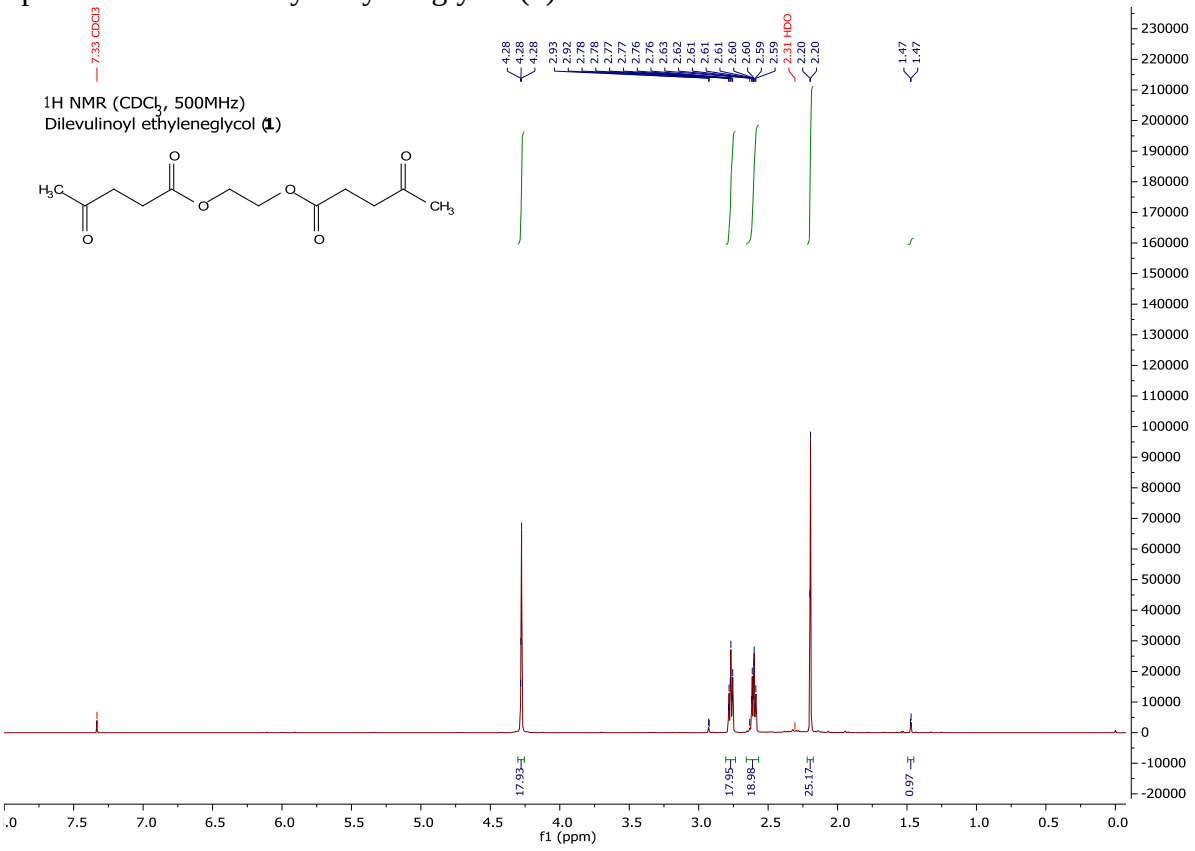
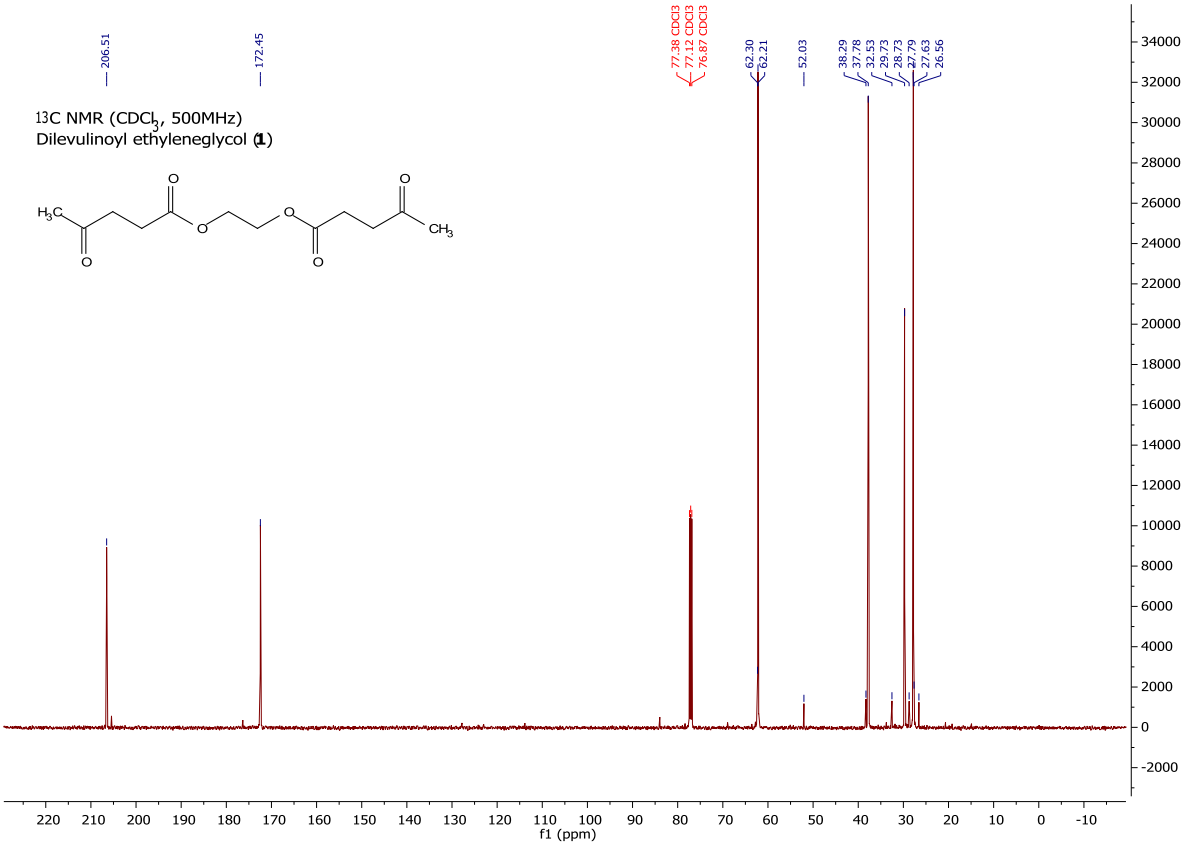
SUPPORTING INFORMATION

NMR Spectral data for compounds **1**-**10** are reported in the following supplementary information.

Spectra for Dilevulinoyl ethyleneglycol (**1**)





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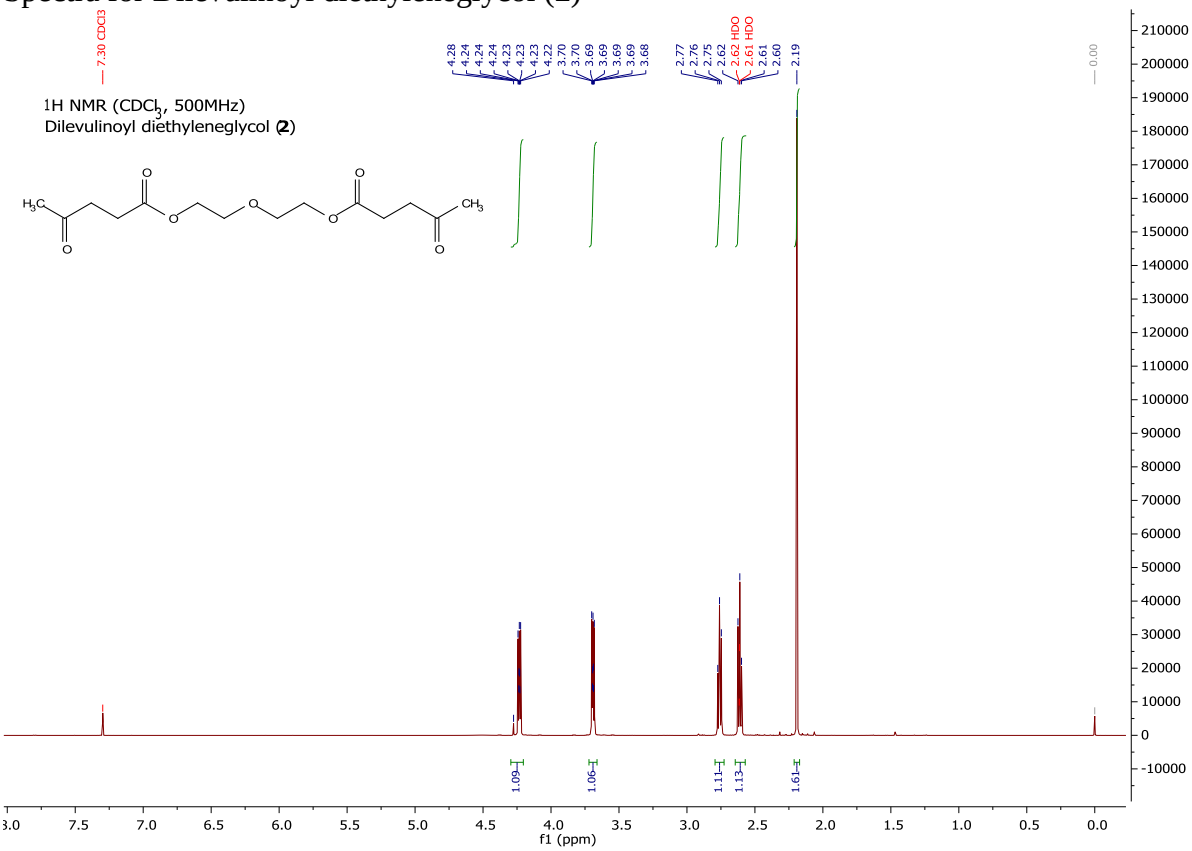
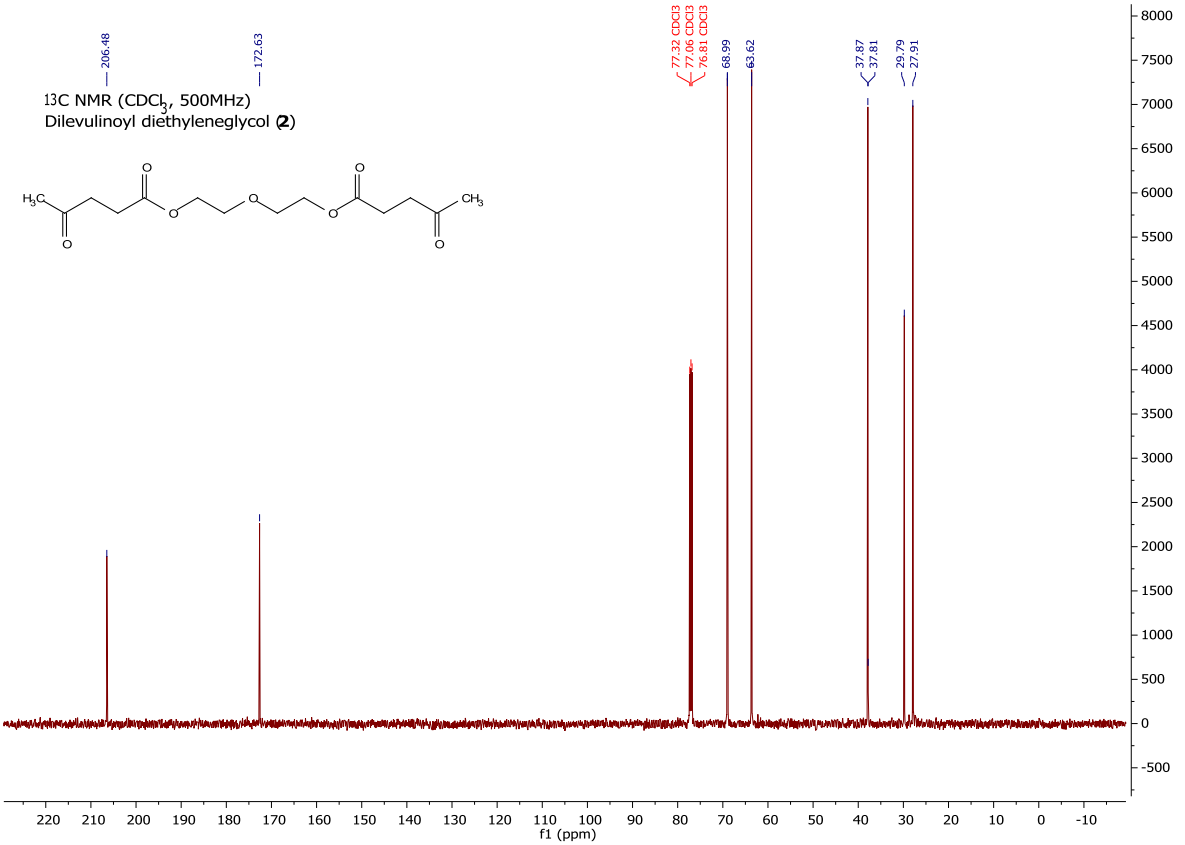
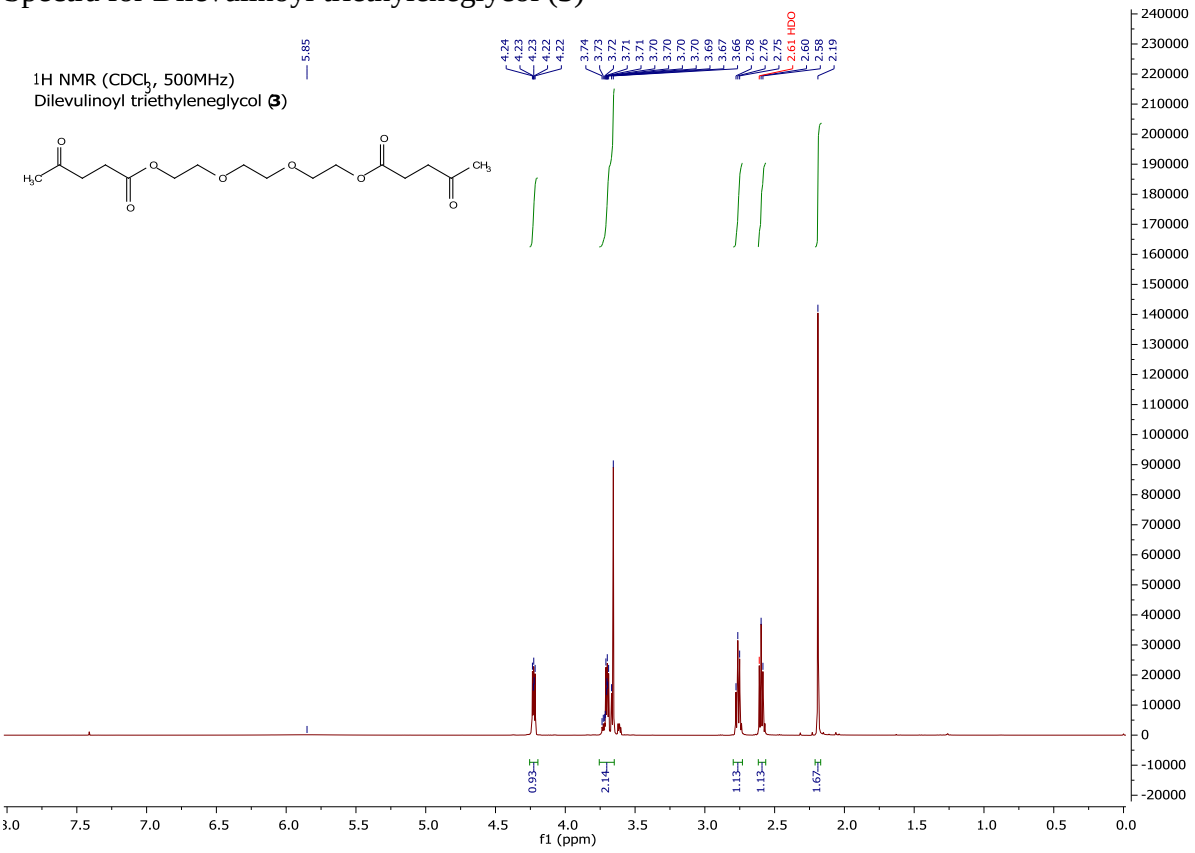
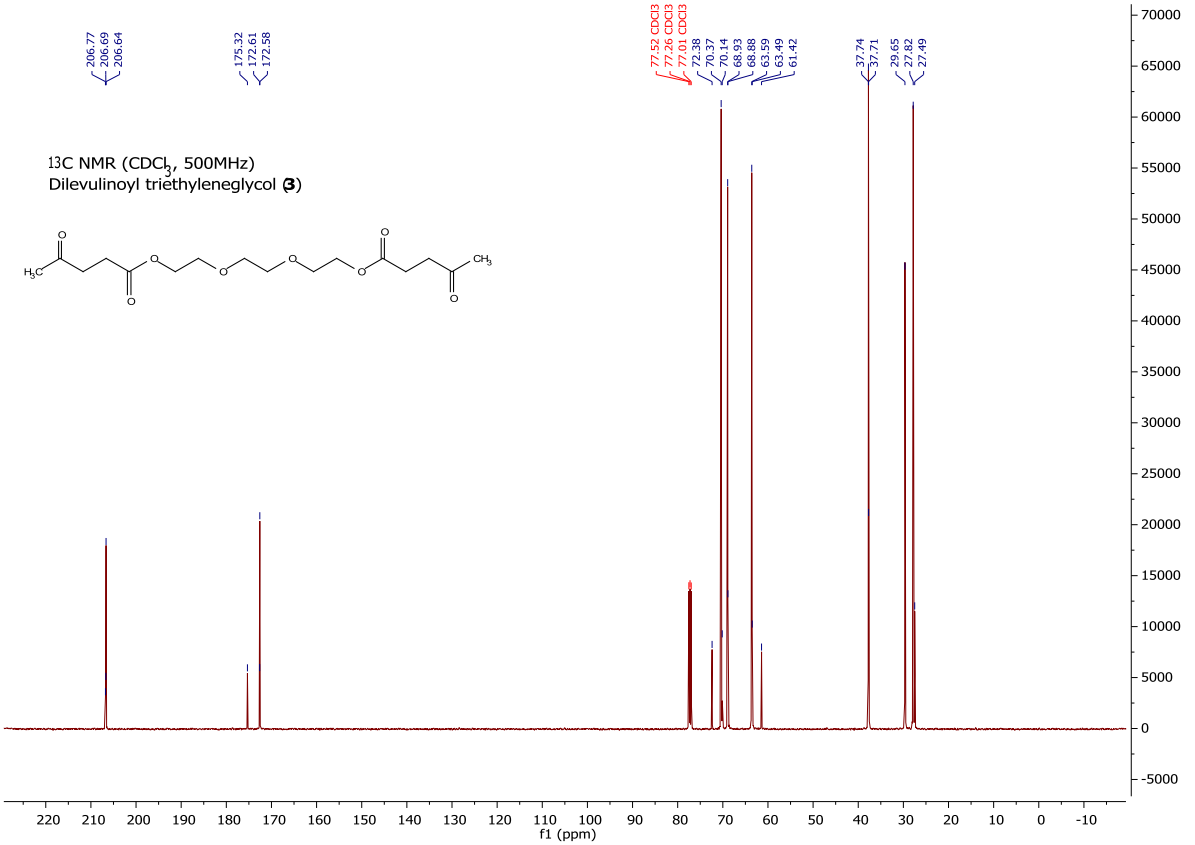


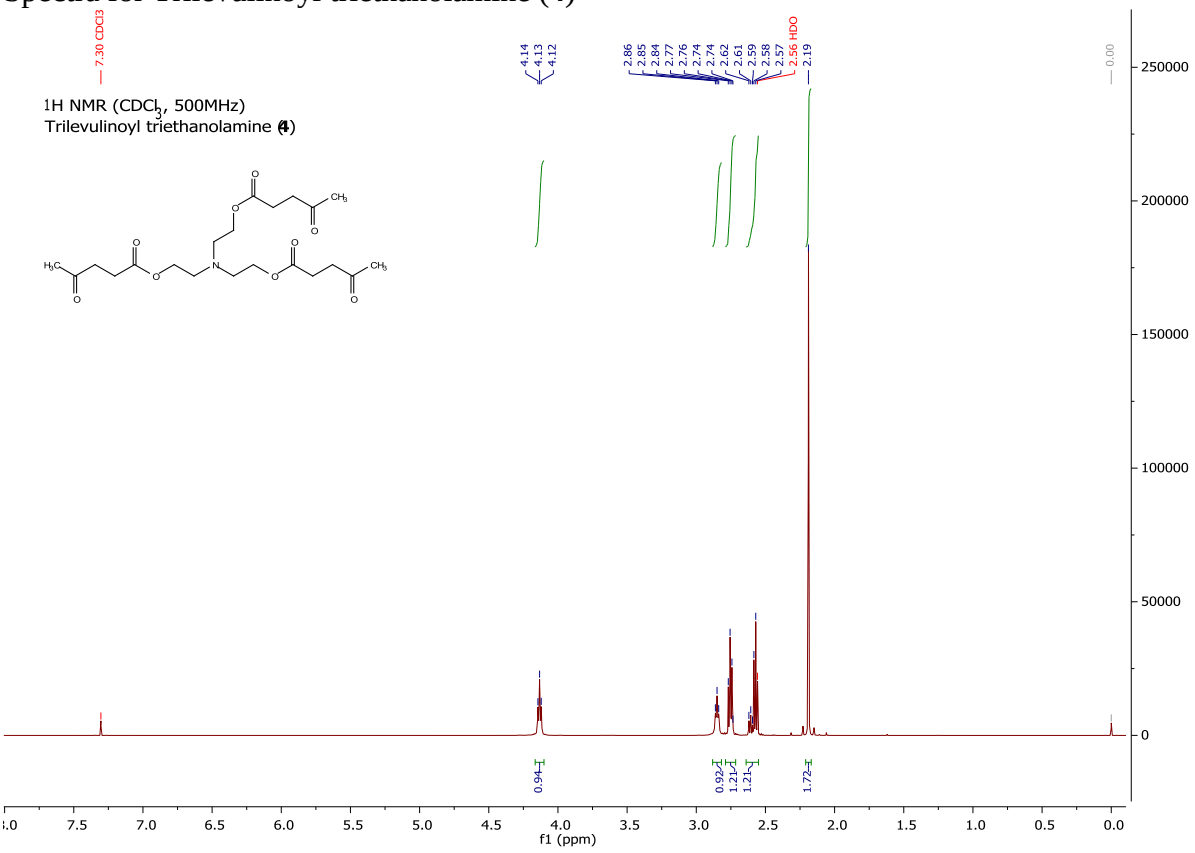


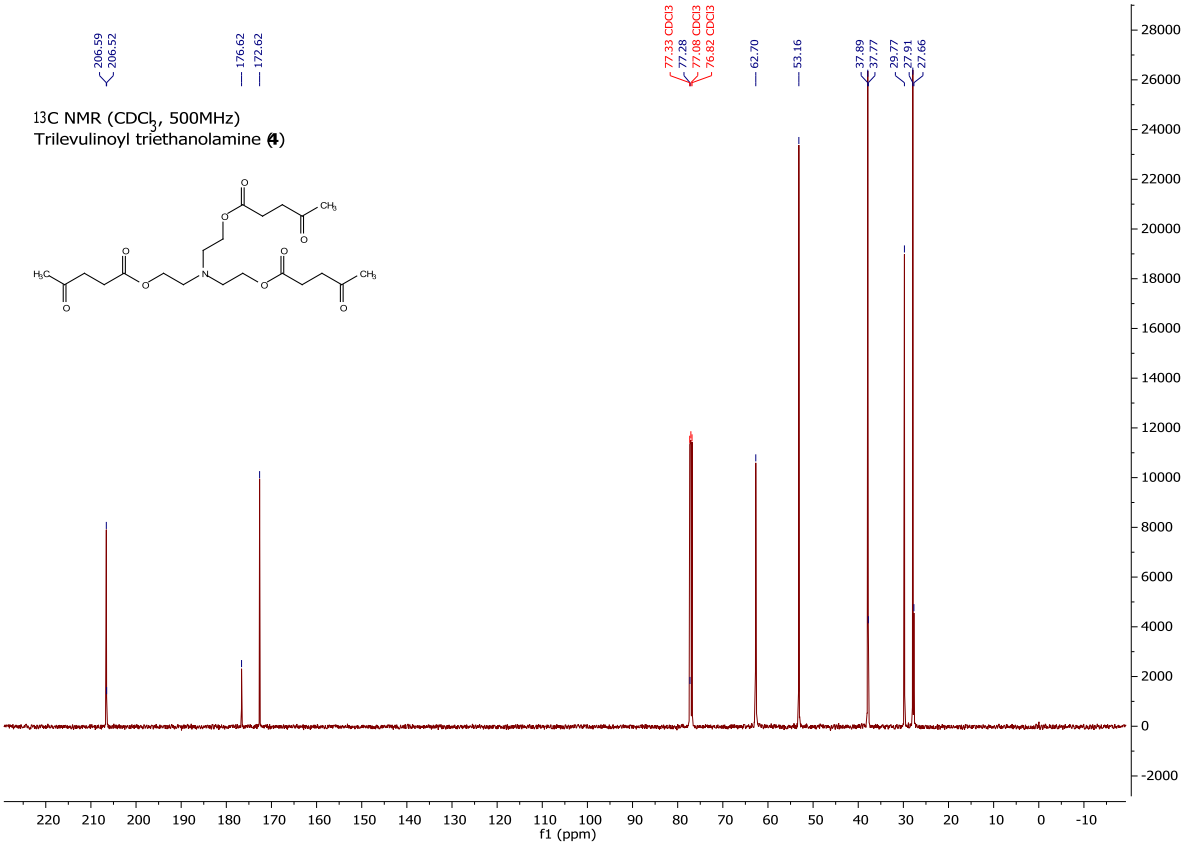
Spectra for Dilevulinoyl triethyleneglycol (**3**)



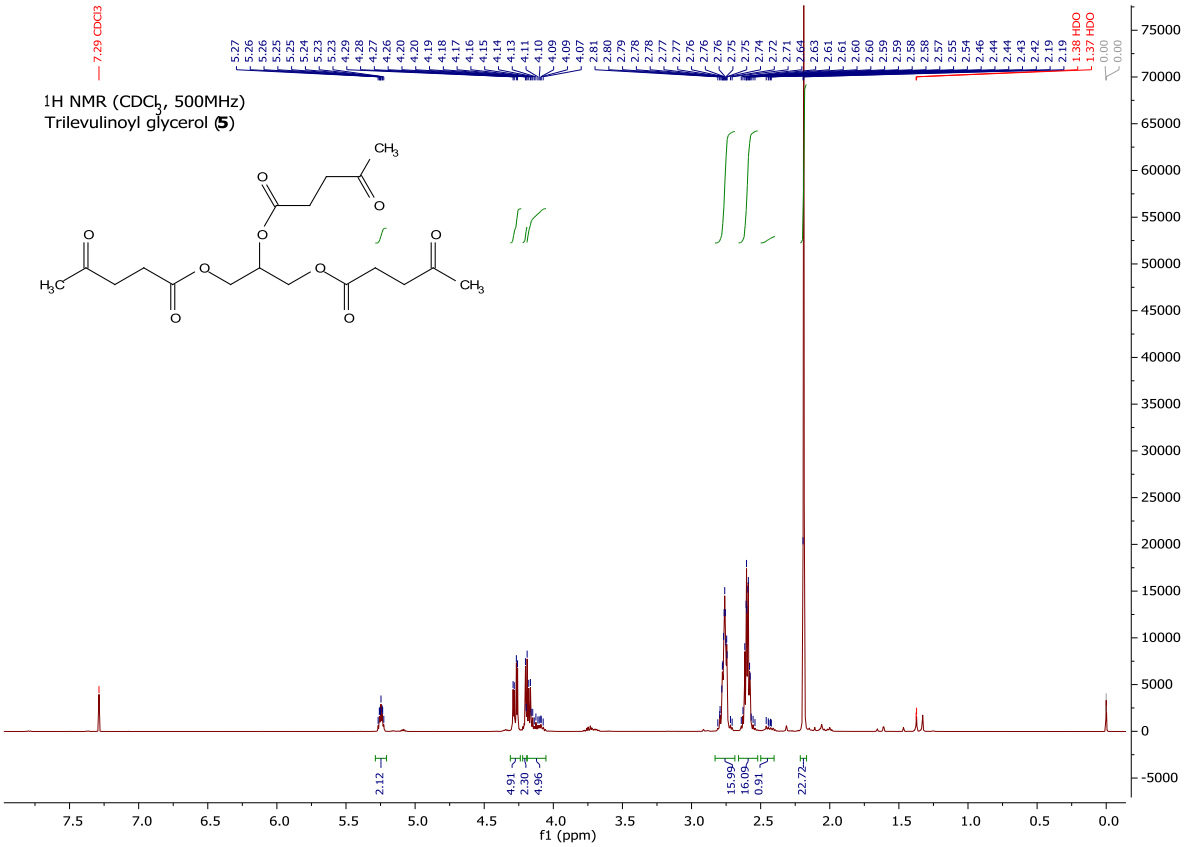


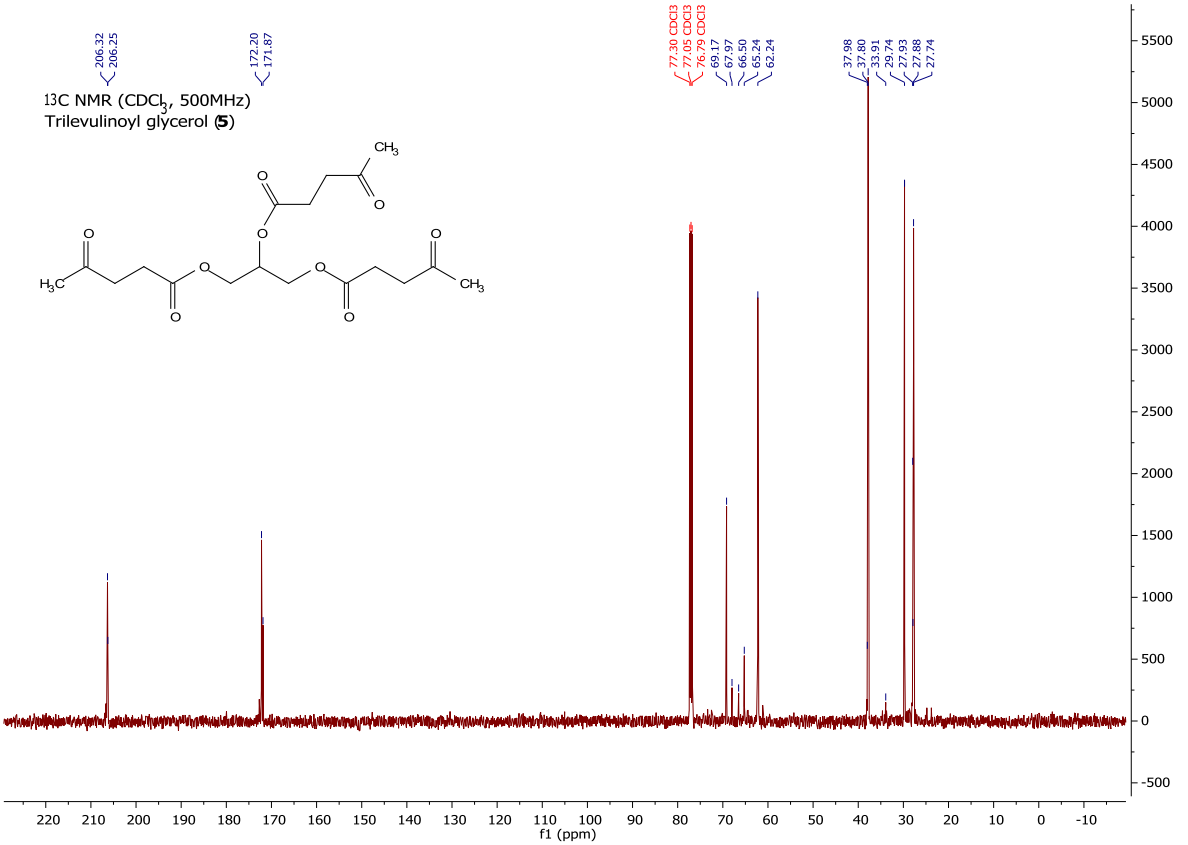
Spectra for Trilevulinoyl triethanolamine (**4**)



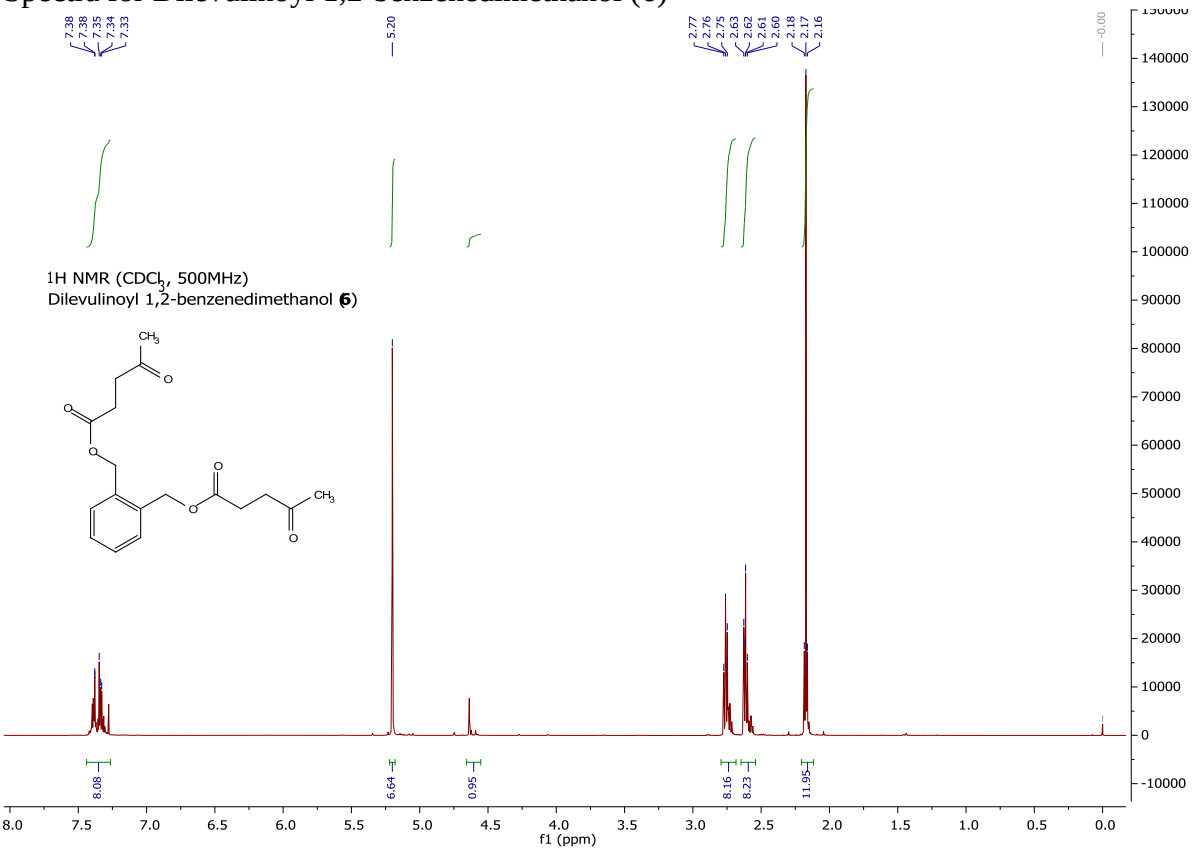


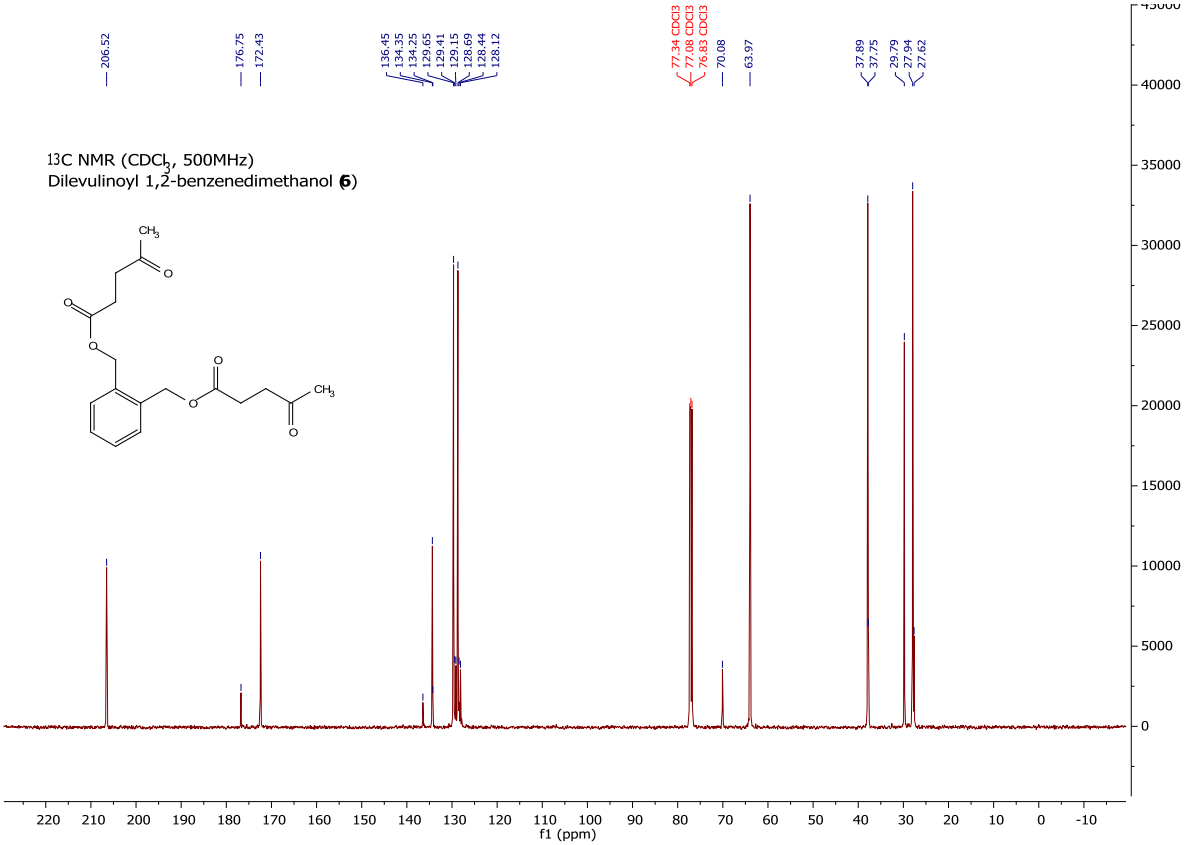
Spectra for Trilevulinoyl glycerol (**5**)



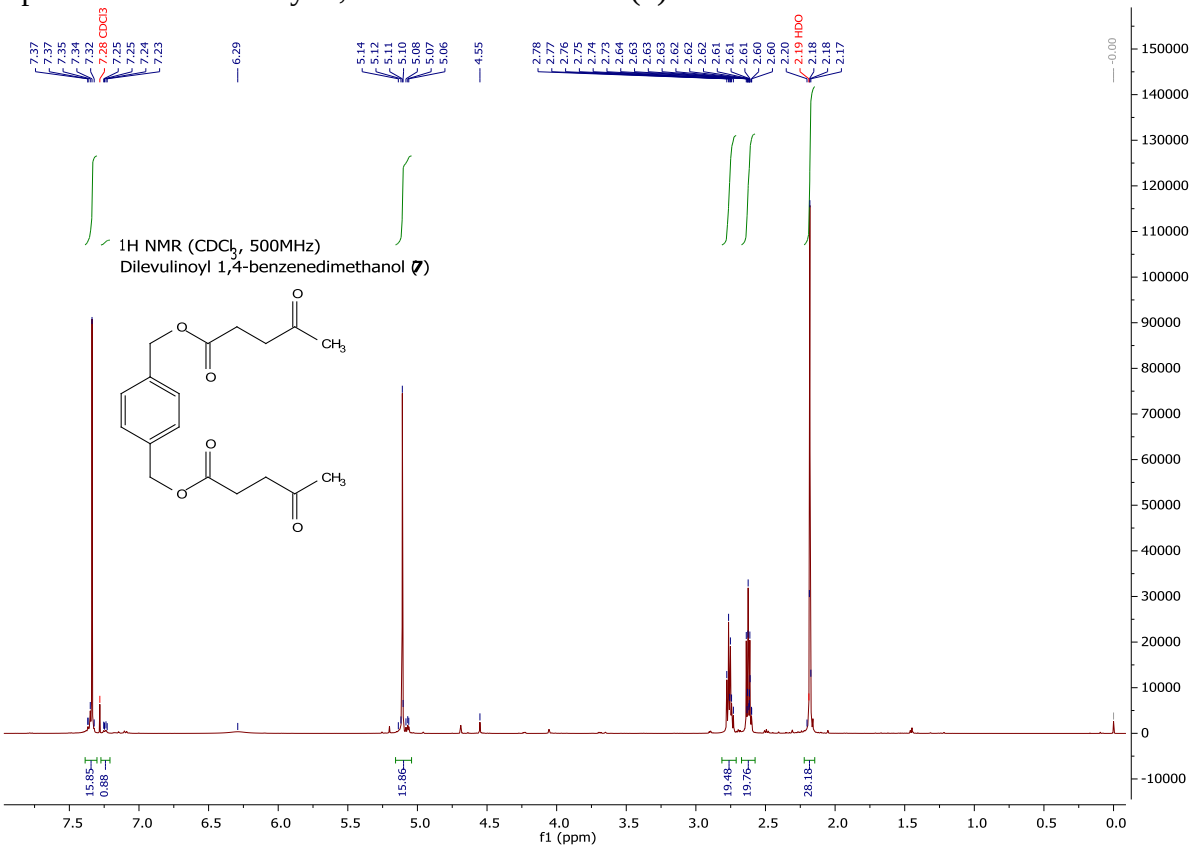


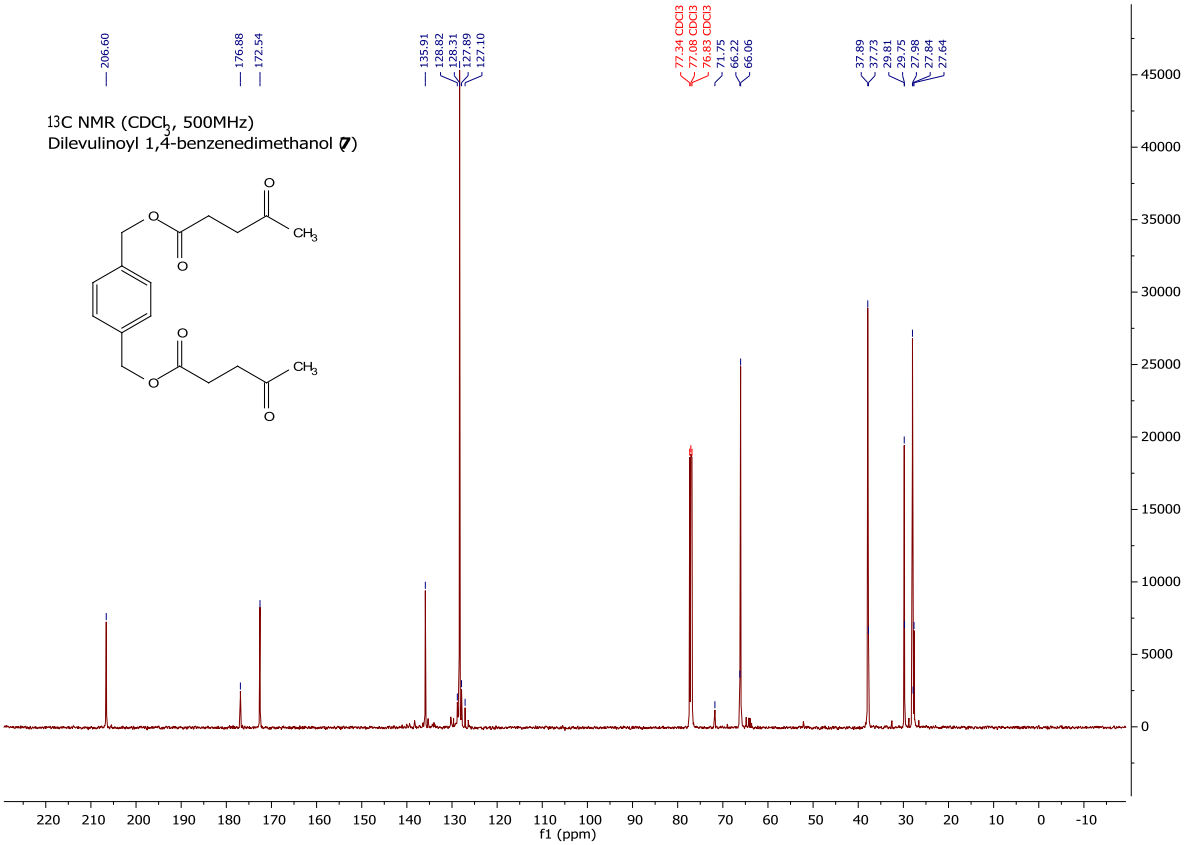
Spectra for Dilevulinoyl 1,2-benzenedimethanol (**6**)



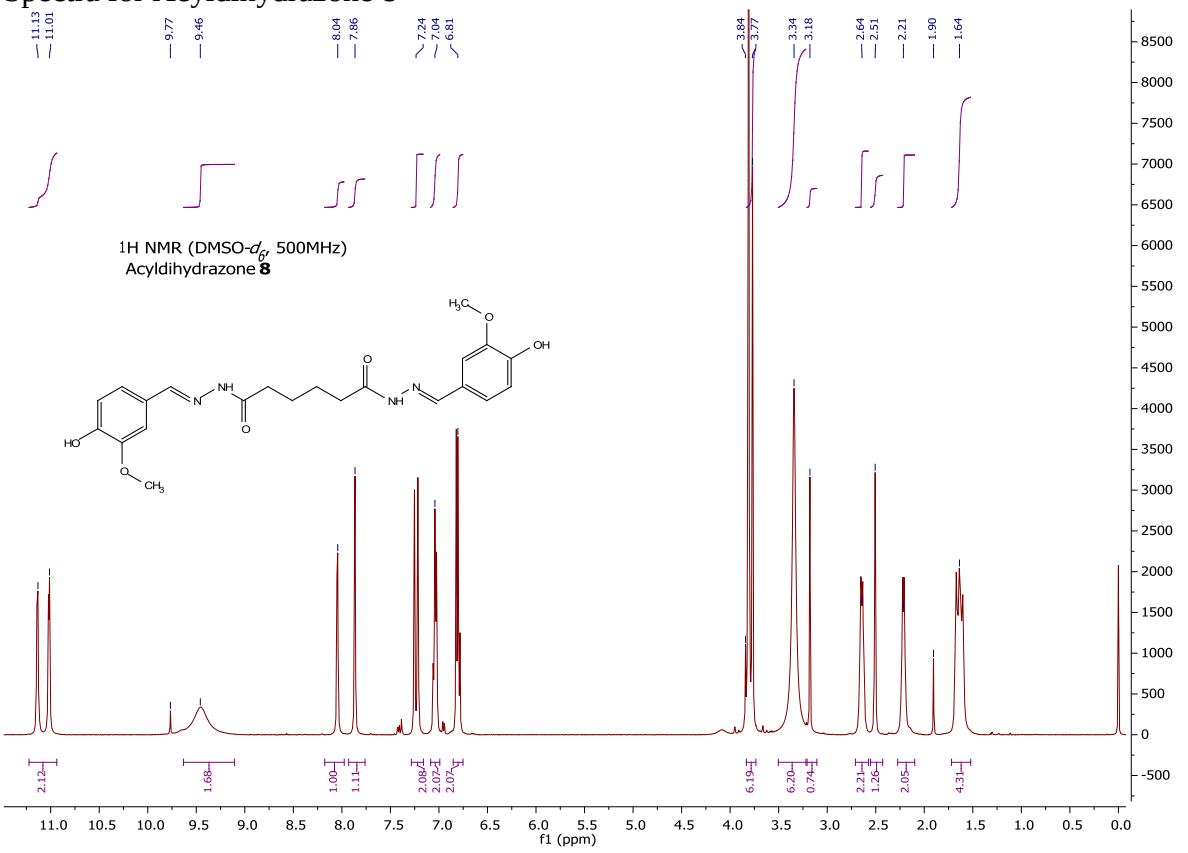


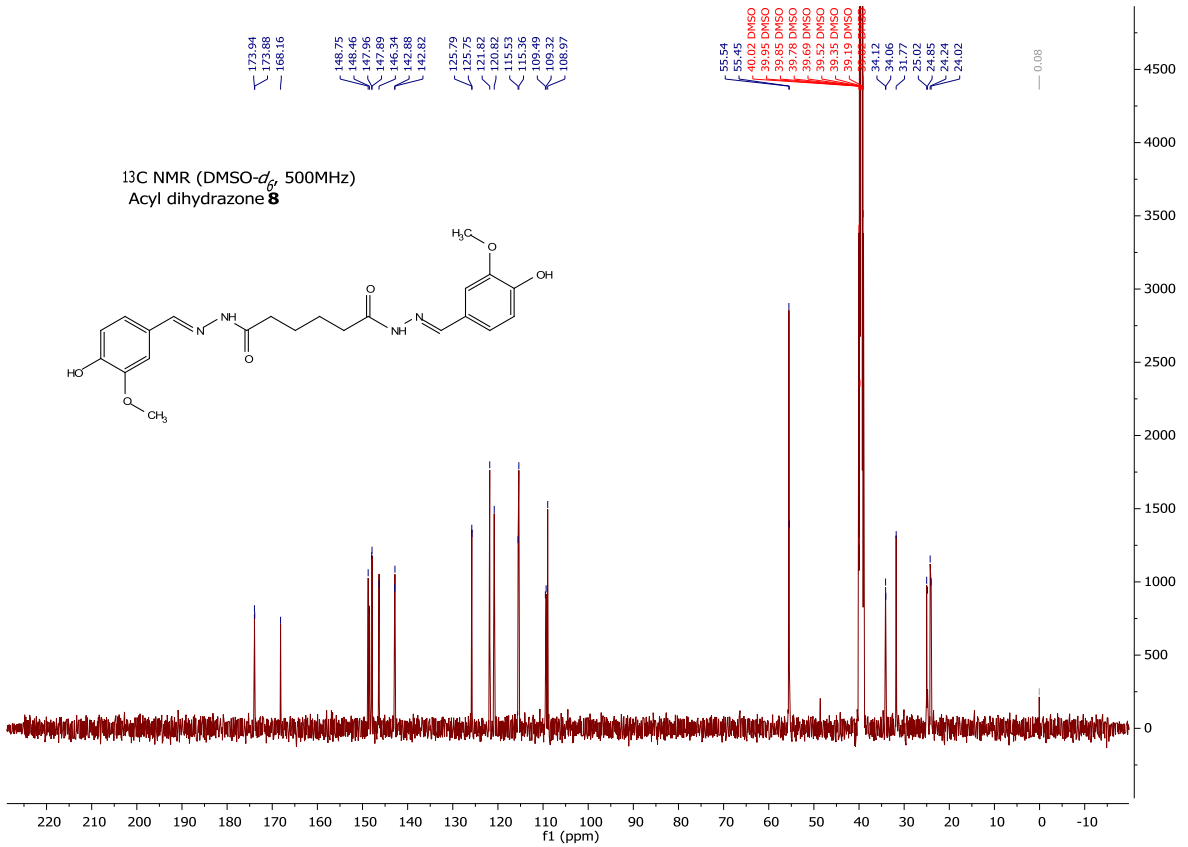
Spectra for Dilevulinoyl 1,4-benzenedimethanol (**7**)

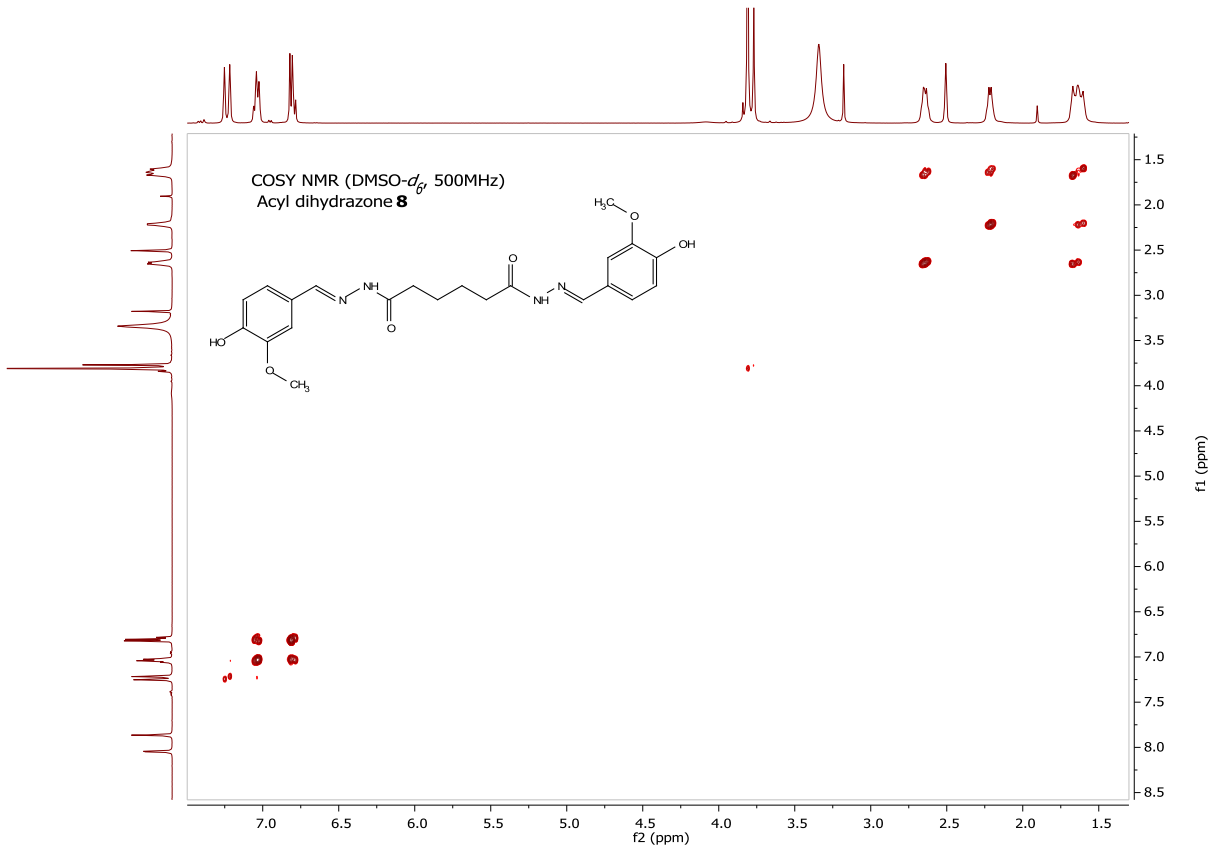


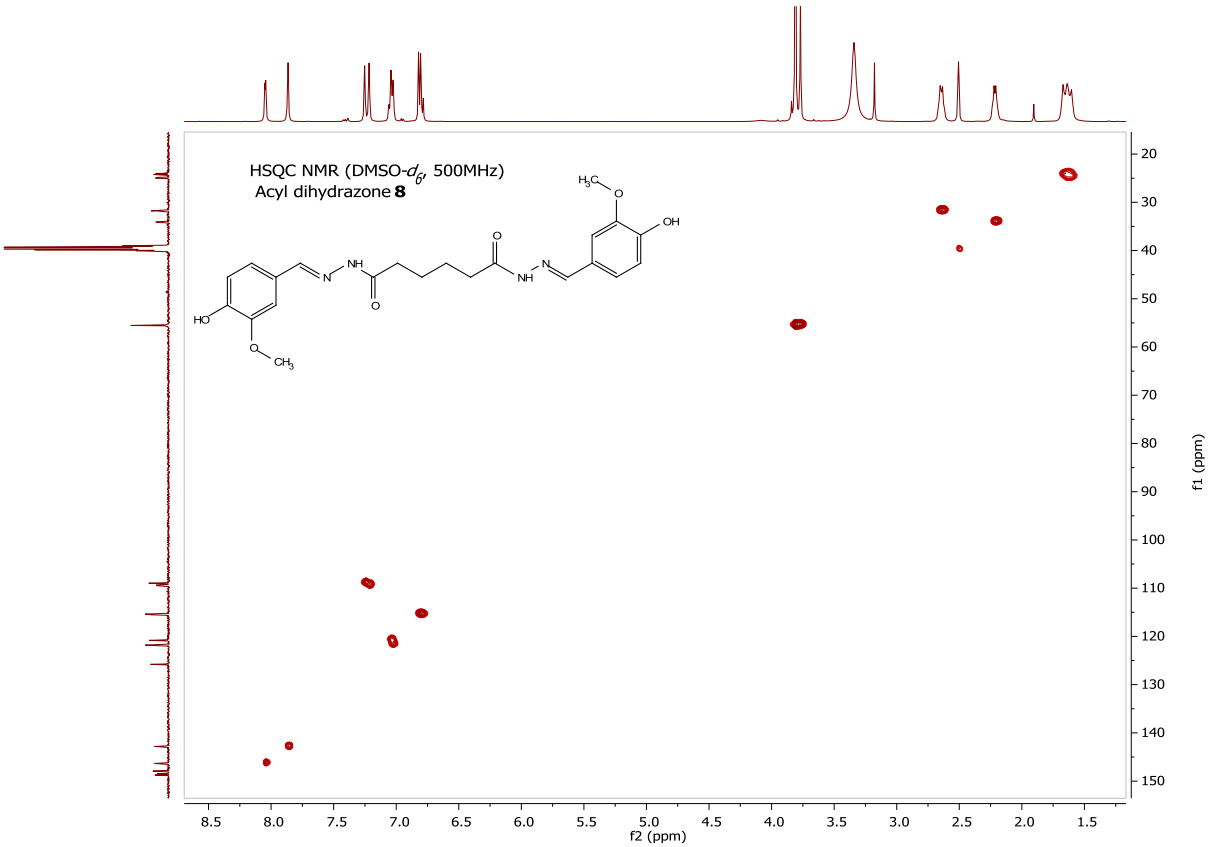


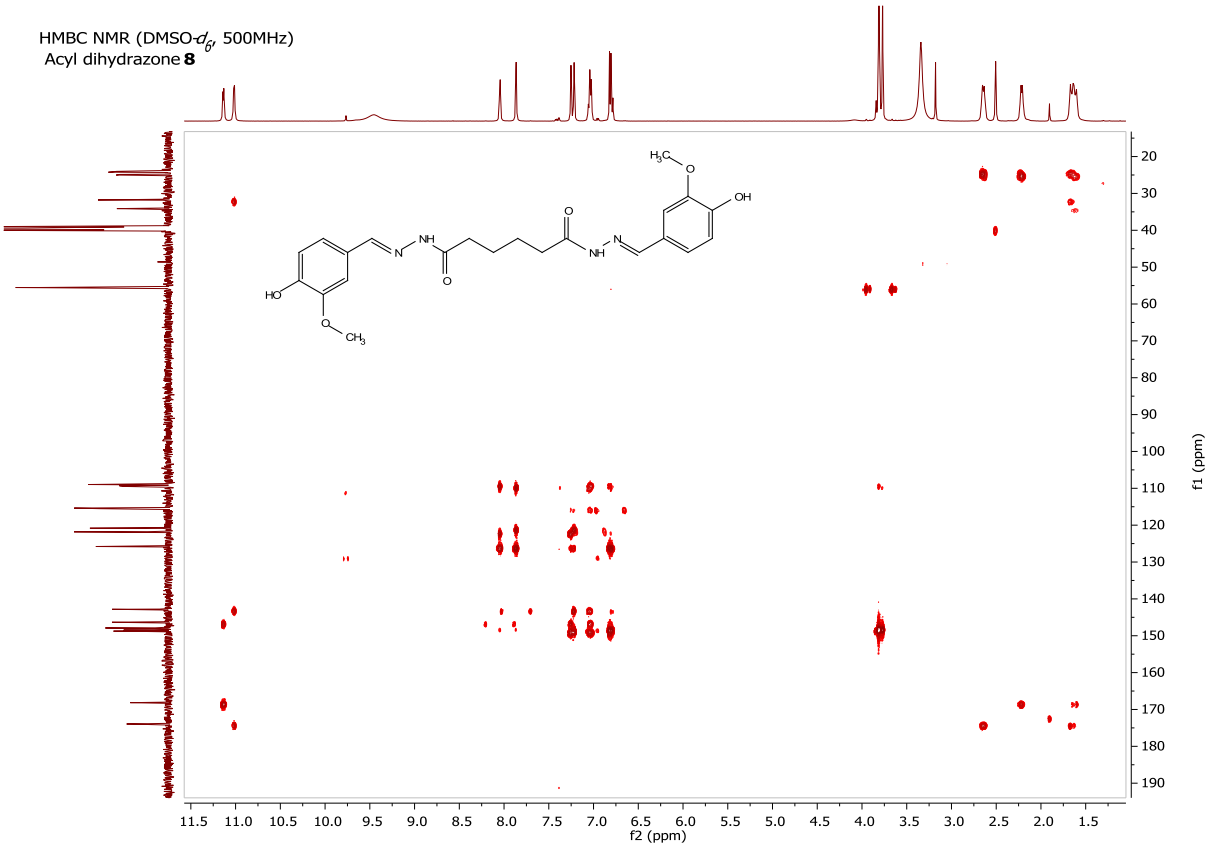
Spectra for Acyldihydrazone **8**



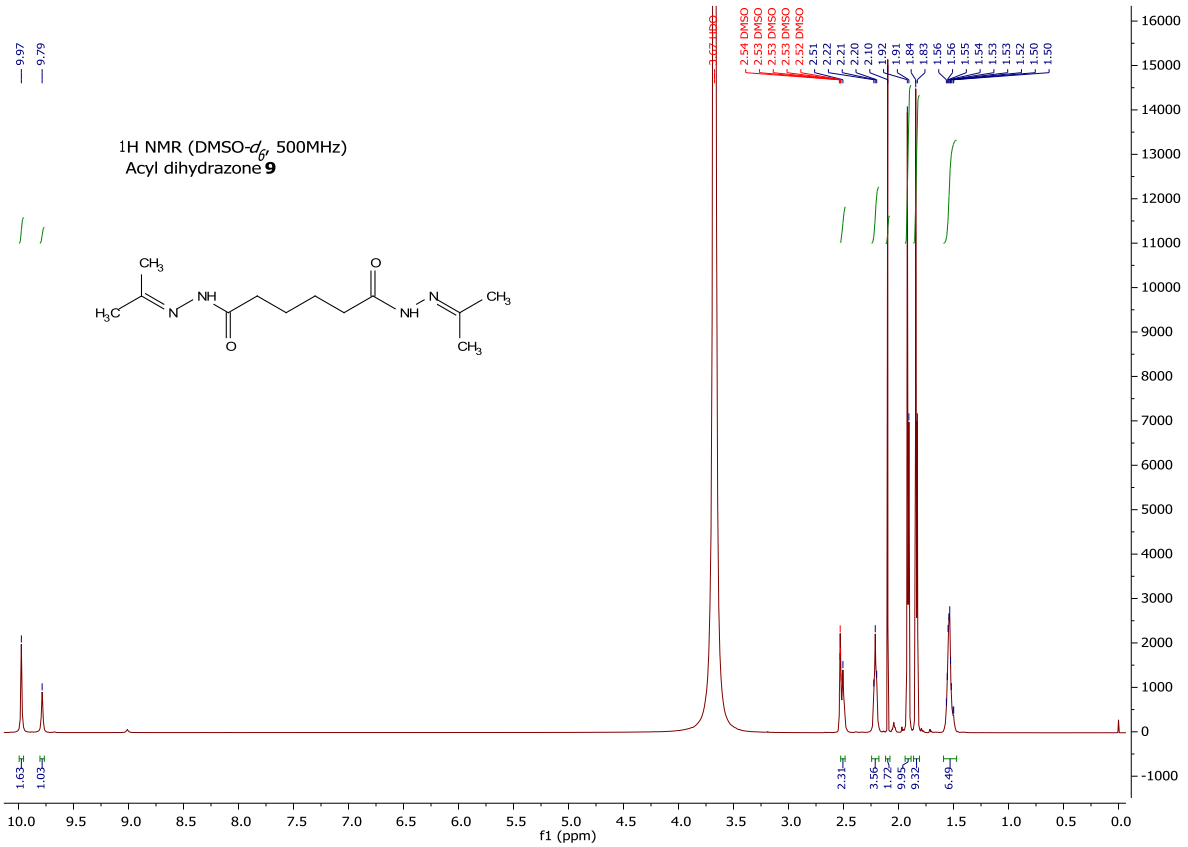

13C NMR (DMSO-d_6, 500MHz)
Acyl dihydrazone 8
f1 (ppm)

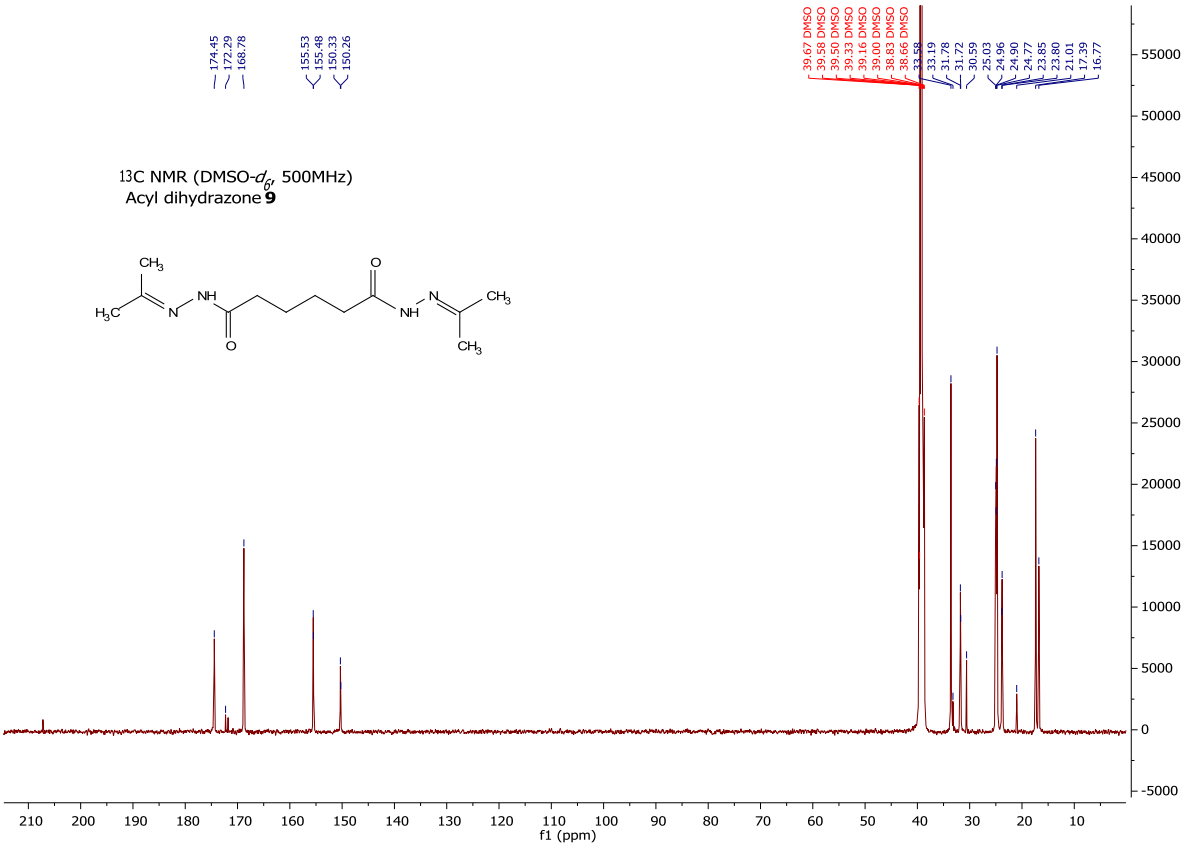

COSY NMR (DMSO-d_6, 500MHz)
Acyl dihydrazone 8
f2 (ppm)
f1 (ppm)


HSQC NMR (DMSO-d_6, 500MHz)
Acyl dihydrazone **8**
f2 (ppm)
f1 (ppm)

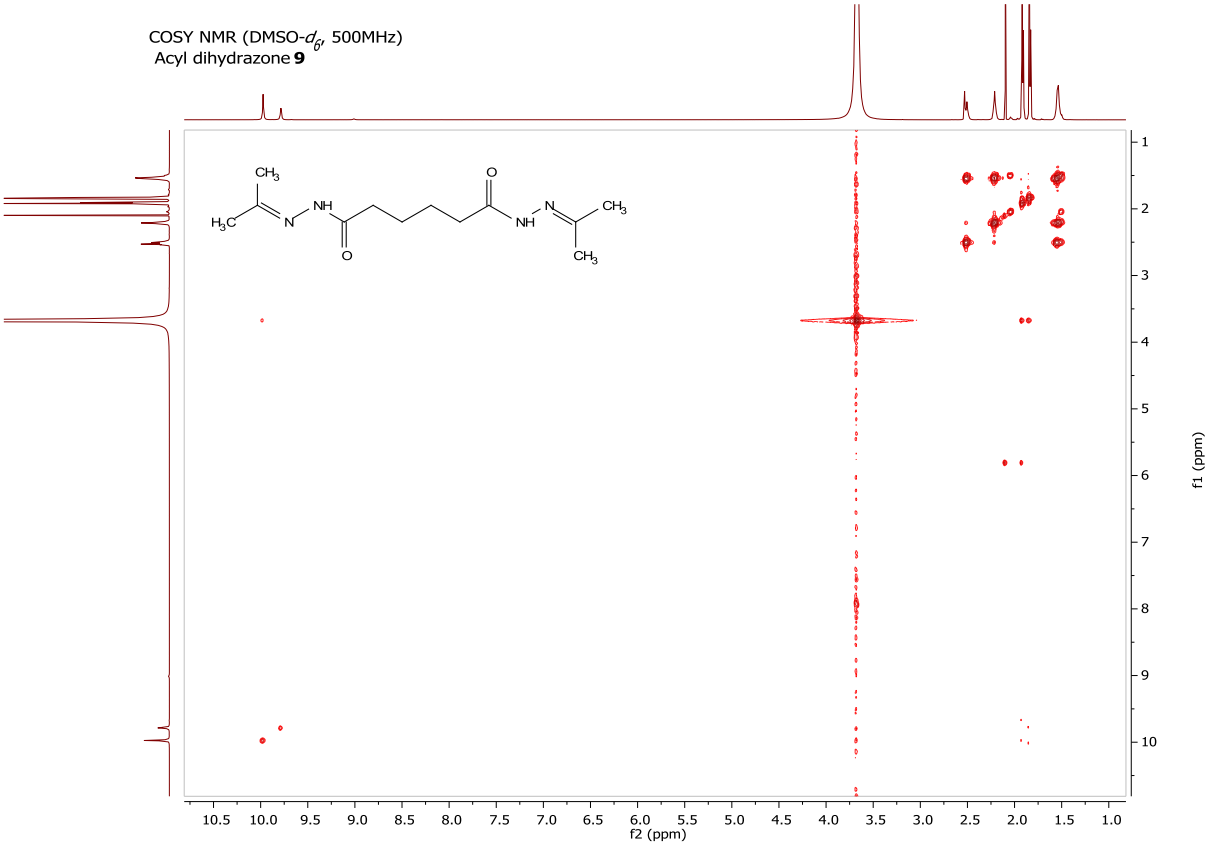

HMBC NMR (DMSO-d_6, 500MHz)
Acyl dihydrazone **8**
f2 (ppm)
f1 (ppm)

Spectra for Acyldihydrazone **9**

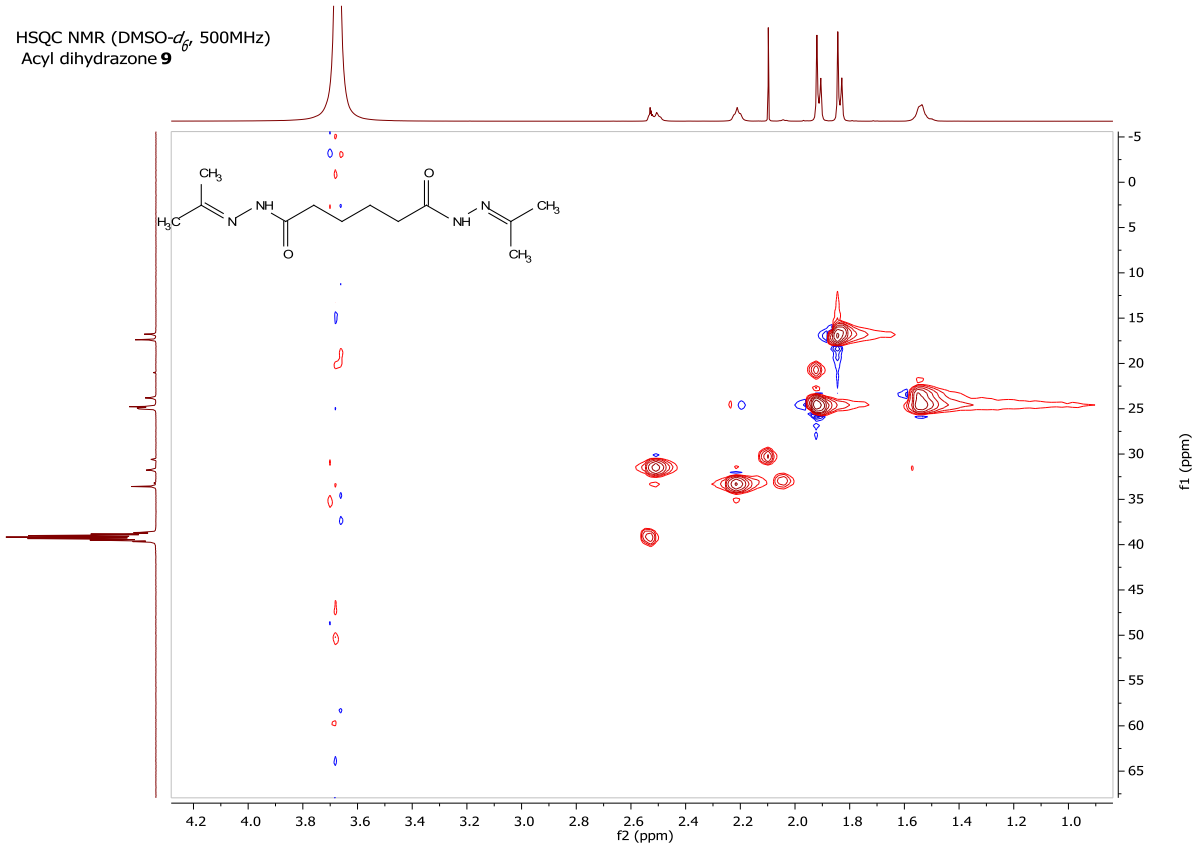


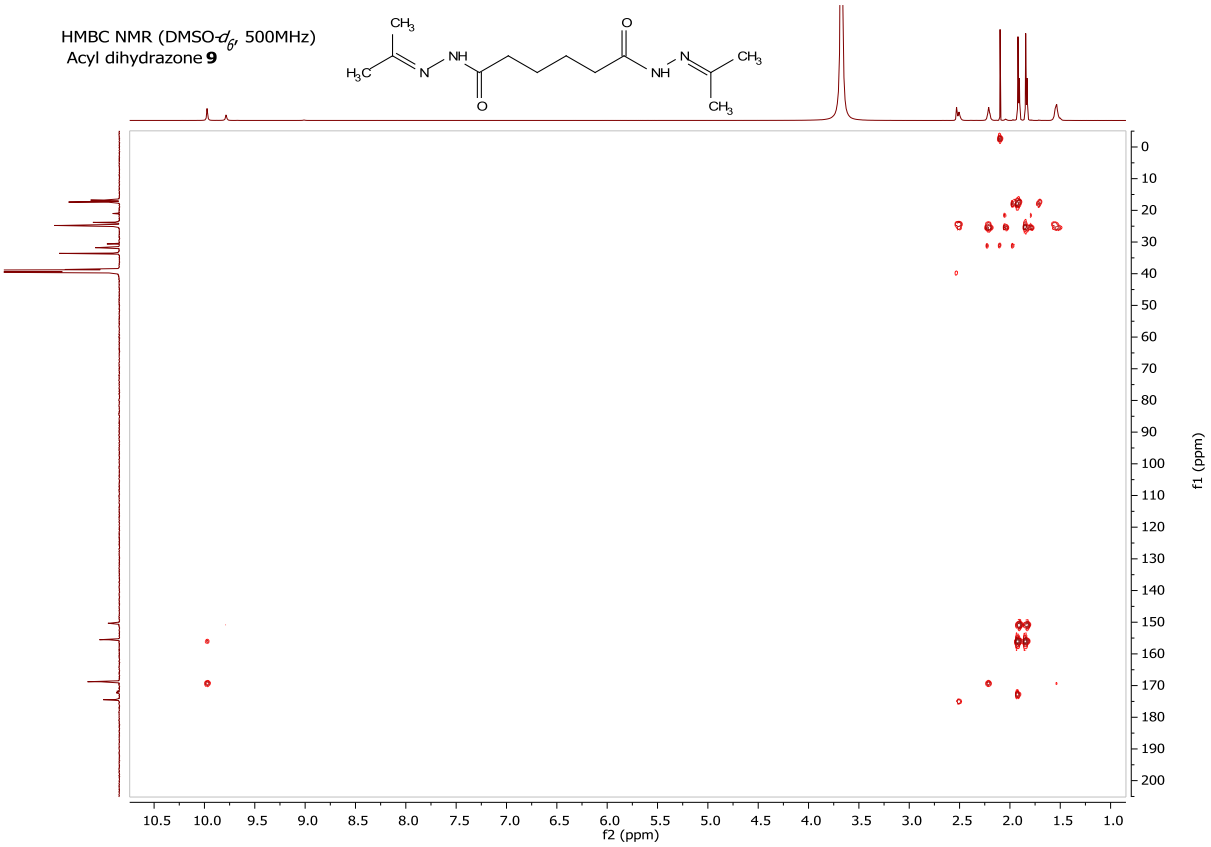


COSY NMR (DMSO-d_6, 500MHz)
Acyl dihydrazone **9**

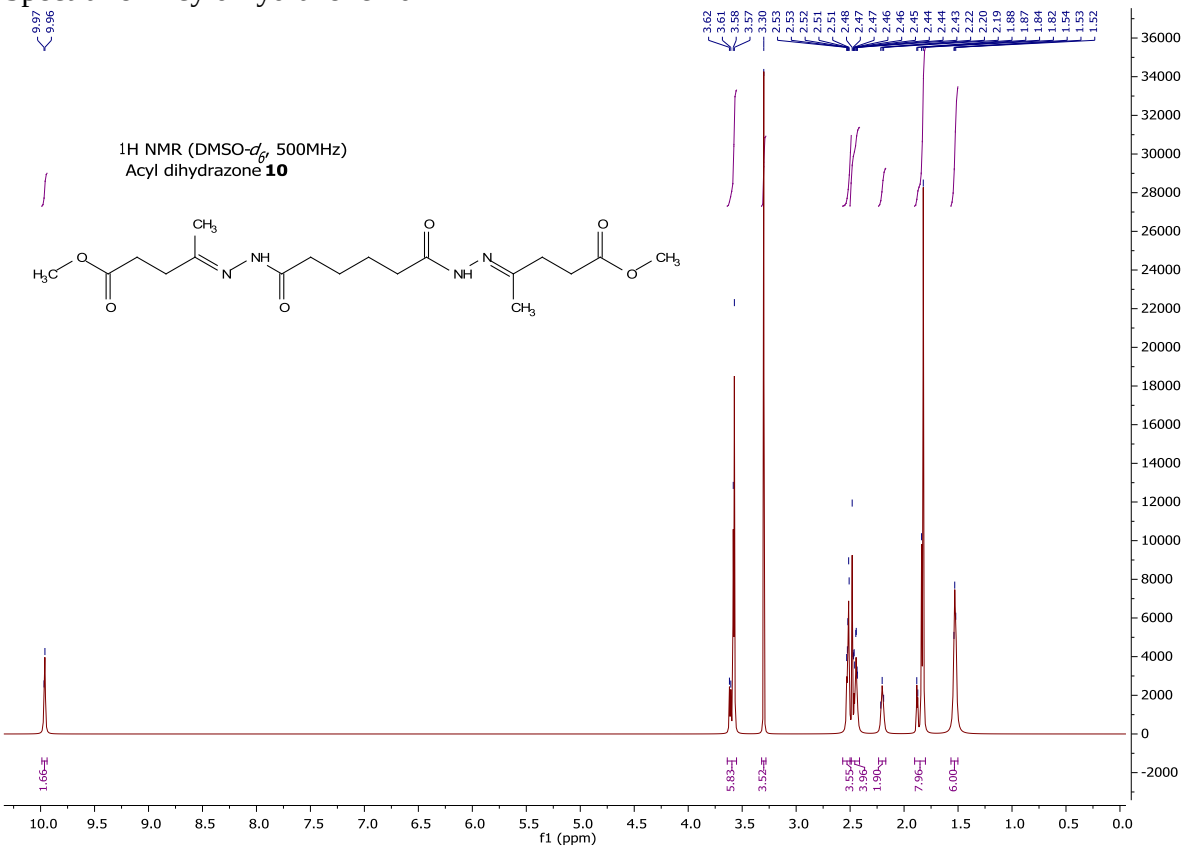


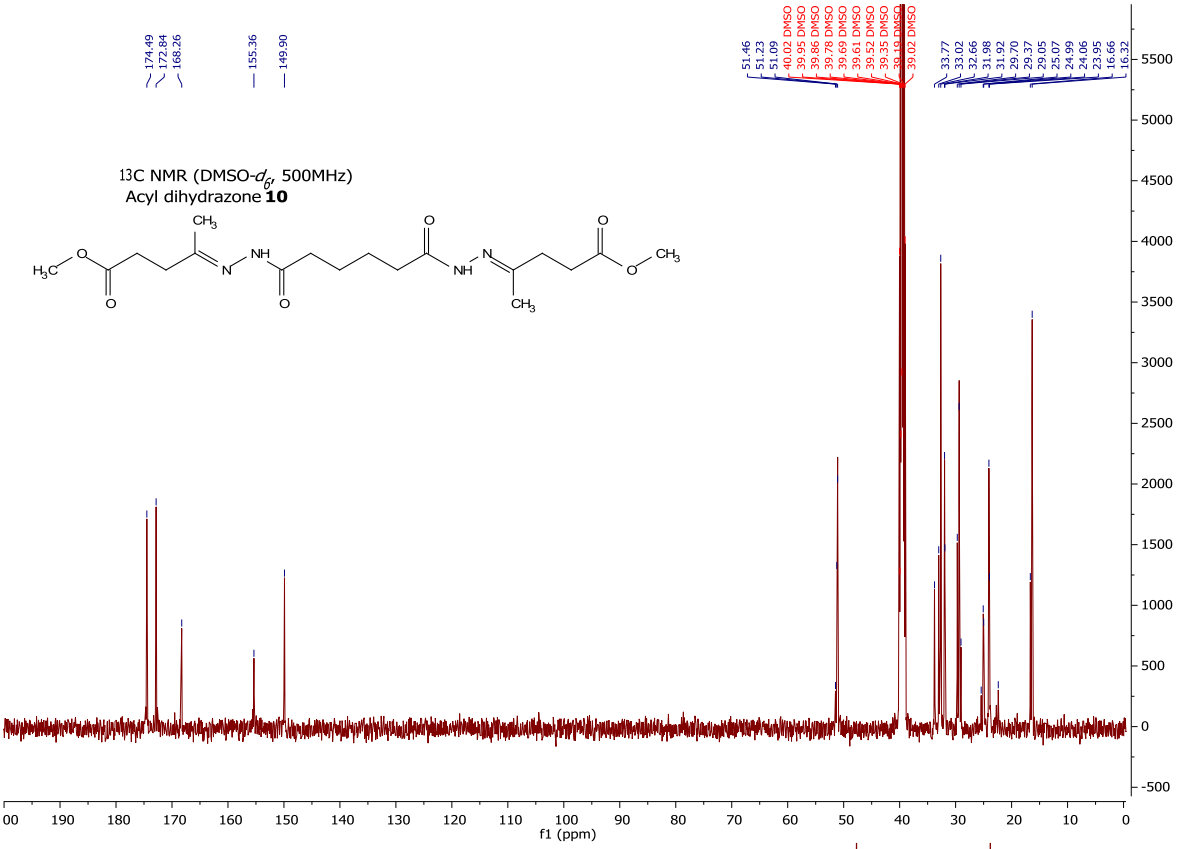
HSQC NMR (DMSO-d_6, 500MHz)
Acyl dihydrazone **9**

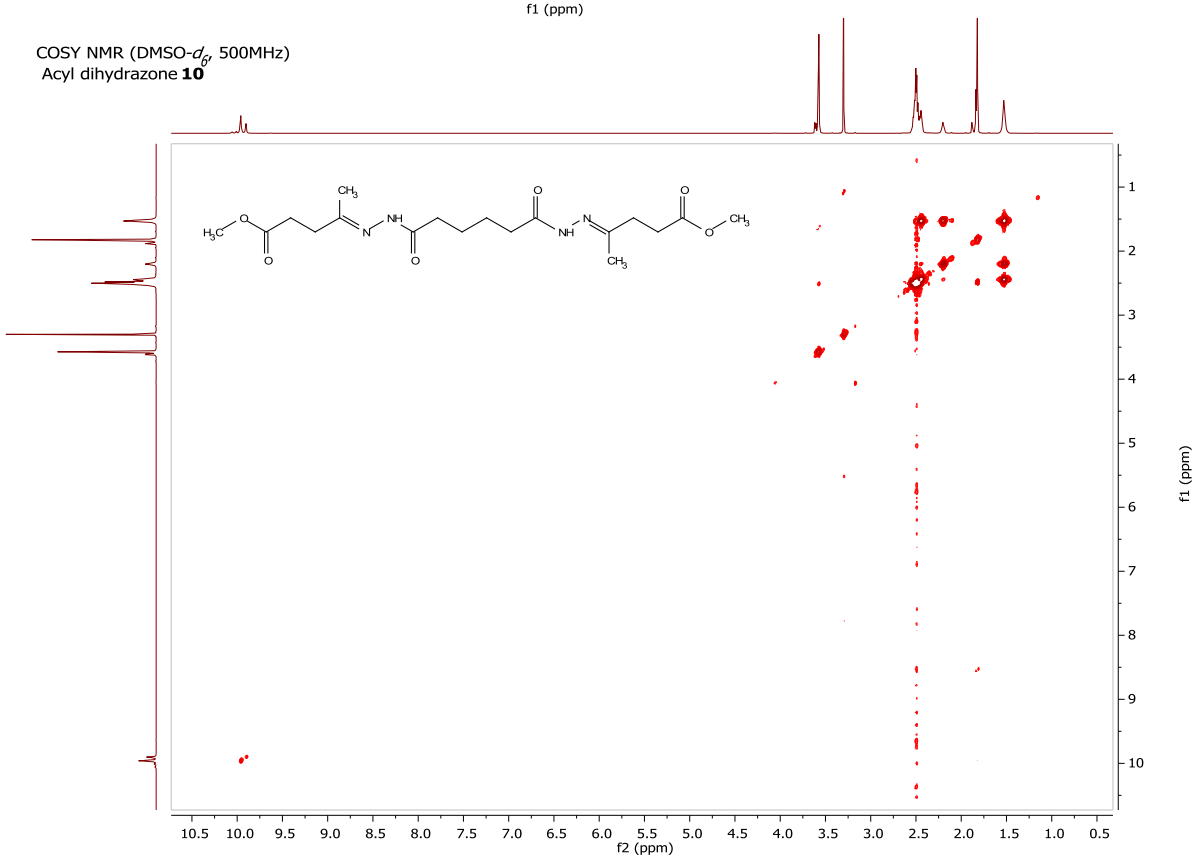




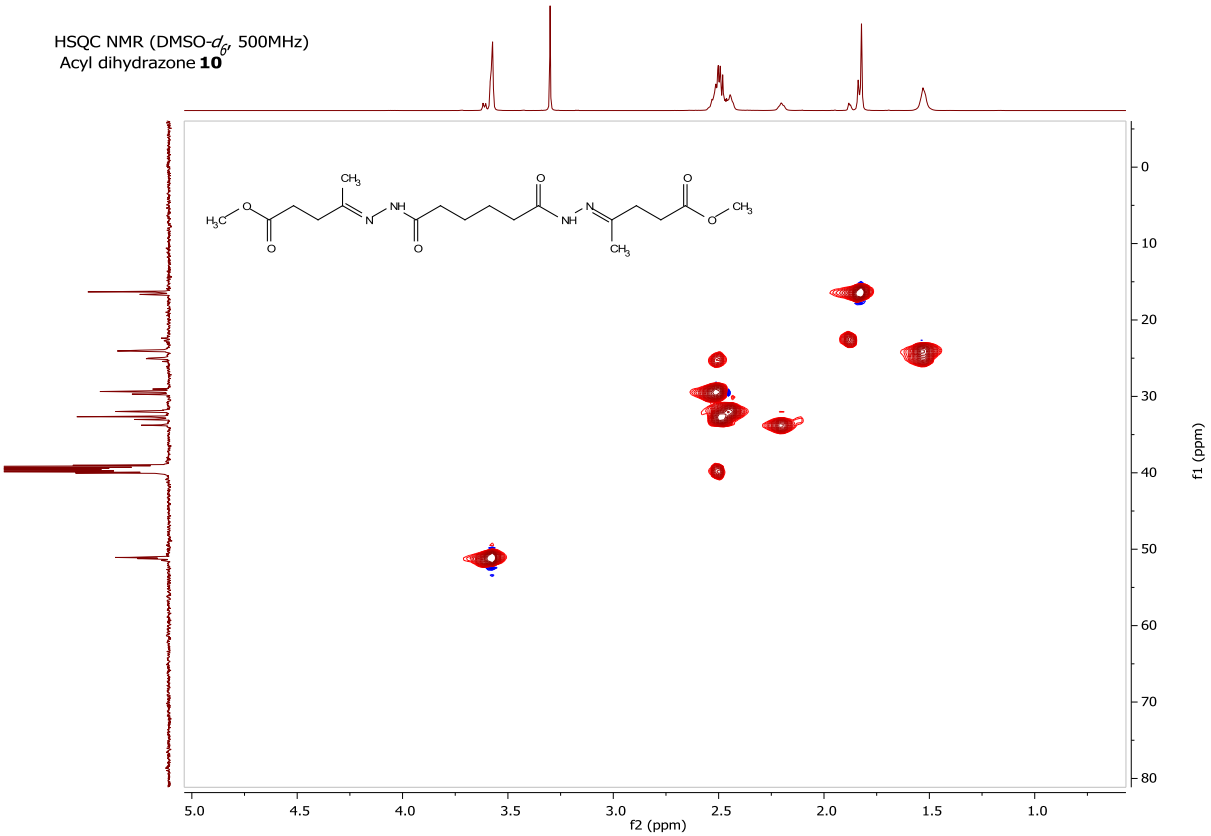
Spectra for Acyldihydrazone **10**




13C NMR (DMSO-d6, 500MHz)
Acyl dihydrazone 10
174.49
172.84
168.26
155.36
149.90
51.46
51.23
51.09
40.02 DMSO
39.95 DMSO
39.86 DMSO
39.78 DMSO
39.69 DMSO
39.61 DMSO
39.52 DMSO
39.35 DMSO
39.19 DMSO
39.02 DMSO
33.77
33.02
32.66
31.98
31.92
29.70
29.37
25.05
24.99
24.06
23.95
16.66
16.32
f1 (ppm)


COSY NMR (DMSO-d6, 500MHz)
Acyl dihydrazone 10
f2 (ppm)
f1 (ppm)

HSQC NMR (DMSO-d_6, 500MHz)
Acyl dihydrazone **10**



HMBC NMR (DMSO-d_6, 500MHz)
Acyl dihydrazone **10**