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Electronic Supporting Information

Organic synthesis by Twin Screw Extrusion (TSE): Continuous, Scalable and Solvent-Free

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1) General Aspects

All materials were purchased from Sigma Aldrich UK with >98% purity and were used as received, unless indicated. Ball mill experiments were carried out using a Retsch MM400 mixer mill or a Retsch PM100 planetary ball mill. Extrusion was carried out using a Three-Tec 12 mm, 40:1 L:D co-rotating twin screw extruder with six heating zones. NMR analysis was carried out with a Brüker Advance DPX 300 with d^6-DMSO as solvent (unless indicated). Digital Scanning Calorimetry (DSC) was carried out with a Flash DSC 1 Mettler Toledo instrument and data were analysed with STAR^{e}SW 9.10 software. Heating rates of 5, 10, 20 and 40 ^{0}C were employed (as indicated) in an atmosphere of air. DSC experiments were carried out in a sealed aluminium pan. Elemental analysis was carried out on a Perkin Elmer PE2400CHNS instrument in CHN mode.

For wettability measurements, barbituric acid powder was shaped into a disk form (15mm in diameter and 1mm thick) using a manual tablet press (Atlas Series Laboratory Hydraulic Press, GS15011). 3,4-Dimethoxybenzaldehyde and vanillin were heated to their melting points (42°C and 83°C, respectively) in a water bath. The barbituric acid disk was placed on a hot stage, and at different runs, the temperatures were set at the melting point of each chemical and at the optimal reaction temperature (approx. 160°C). A droplet of each chemical was placed on the surface of the disk and the contact angle (CA) was measured. All CA calculations were carried out using a KSV CAM 200 optical tensiometer.

a) Synthesis of 1a-c in solution

The solution reactions were carried out by dissolving 6.0 mmol of aldehyde (vanillin, veratraldehyde or 5-bromovanillin) and 6.0 mmol (0.77 g) of barbituric acid in 150 ml distilled water and stirred at room temperature. Within the first 30 minutes of the reaction, a bright yellow precipitate had formed in each experiment. Stirring was continued until 2 hours had past, and the precipitate was filtered and washed with 50 ml distilled water. The obtained yellow/orange solids were dried overnight in a desiccator.

b) Synthesis of 1a-c by ball milling

1.9 mmol of aldehyde (vanillin, veratraldehyde or 5-bromovanillin), 1.9 mmol (0.25 g) of barbituric acid and 5 *%wt* water were added to a 25 cm^3 stainless steel ball mill jar along with a 13.6 g (diameter 11 mm) stainless steel ball bearing. For each reaction, the frequency was maintained at 25 Hz, however the time was varied between 0 – 90 minutes (over 10 minute increments). A yellow/orange solid was typically obtained. Samples for ^{1}H NMR spectroscopy was prepared and analysed immediately once the experiment was finished to determine conversion to product. The NMR spectroscopy solvent used was *d*^{6}-DMSO.

Table 1: Conversion to product (1a, 1b and 1c) determined by ^{1}H NMR spectroscopy after ball milling at 25 Hz, for 30, 60 and 90 minutes,

Time (mins)	Conversion to Product (%)		
	1a	**1b**	**1c**
30	66.59	12.13	54.40
60	99.29	90.50	76.80
90	-	98.61	77.30

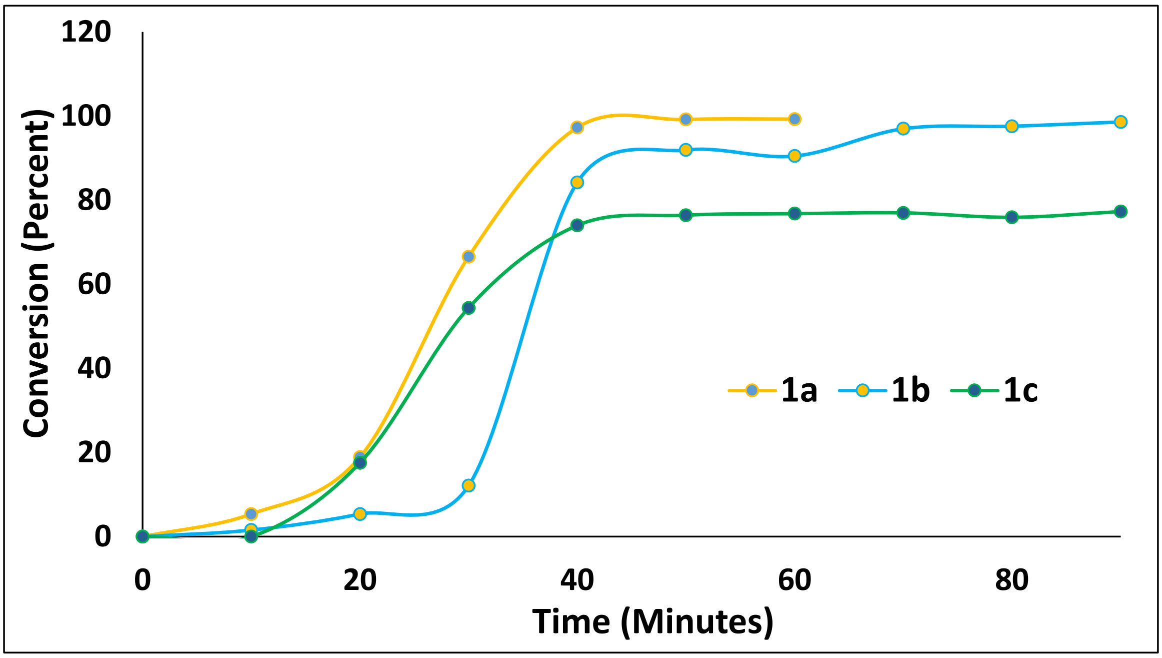

Figure 1: Conversion versus time graph for the conversion to 1a, 1b and 1c via ball milling.

c) Synthesis of 1a-c by twin screw extrusion

A mixture of aldehyde and barbituric acid were mixed by hand initially and fed into the volumetric twin screw hopper. The feed rate was set between 4 – 12 % and the reagents were fed into the twin screw extruder at 55 rpm with the extruder barrel heated to 160 ^{o}C. There was very little change in torque, and the material exited the barrel in less than 2 minutes as a bright orange powder. No further post process purification was carried out as the high temperature of the barrel removed the water by-product as steam.

Table 2: Feed and throughput rates for the synthesis of **1a**, **1b** and **1c**, including Space Time Yields (STYs) for the optimised processes.

Product	Feed Rate (kghr^{-1})	Throughput Rate (kghr^{-1})	Space Time Yield (kgm^{-3}day^{-1})
1a	0.599	0.520	258,385
1b	0.254	0.228	113,291
1c	0.433	0.398	197,942

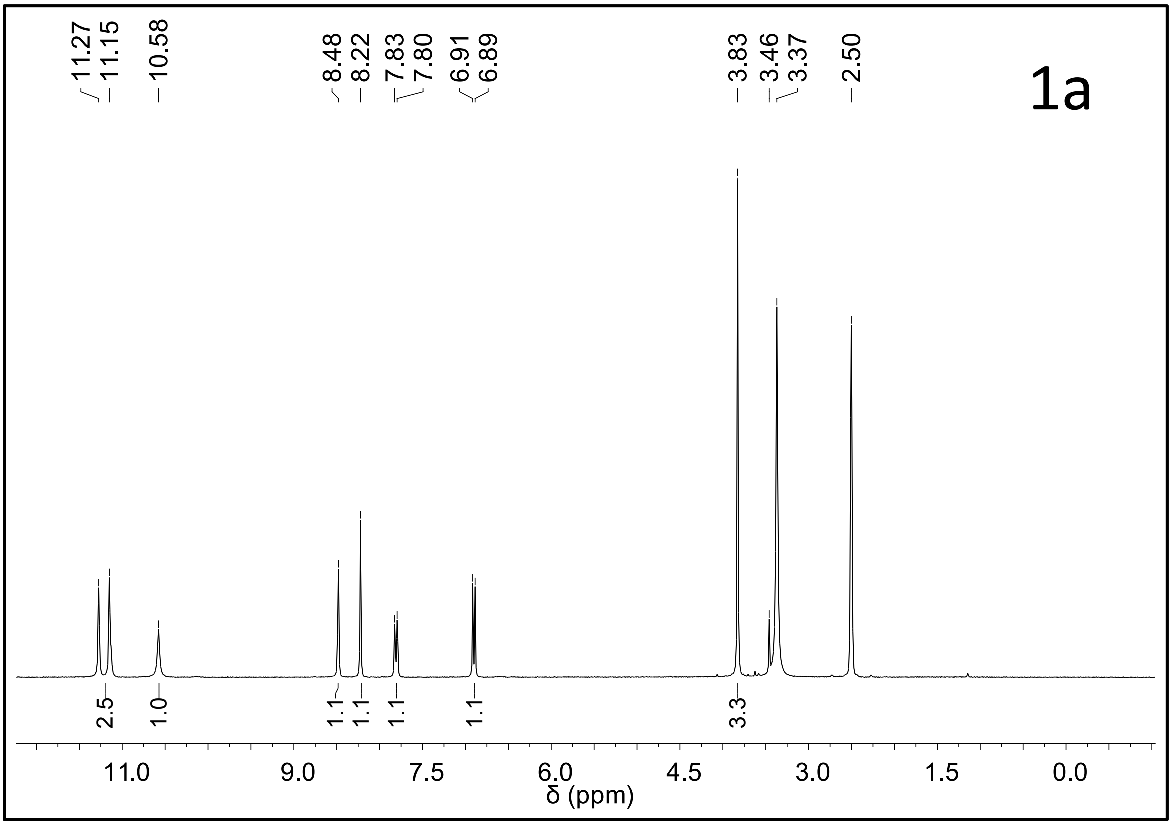

Figure 2: ^{1}H NMR spectrum in *d*^{6}-DMSO of **1a** produced by TSE.

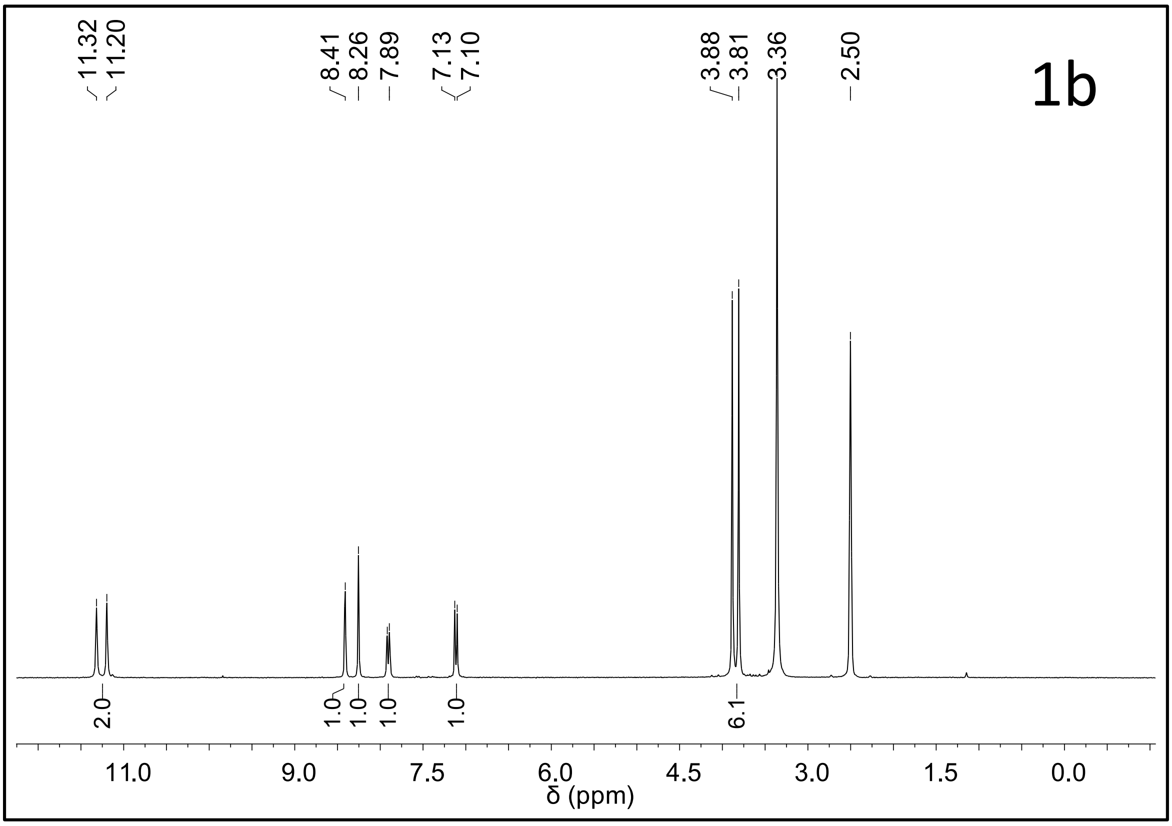

Figure 3: ^{1}H NMR spectrum in *d*^{6}-DMSO of **1b** produced by TSE.

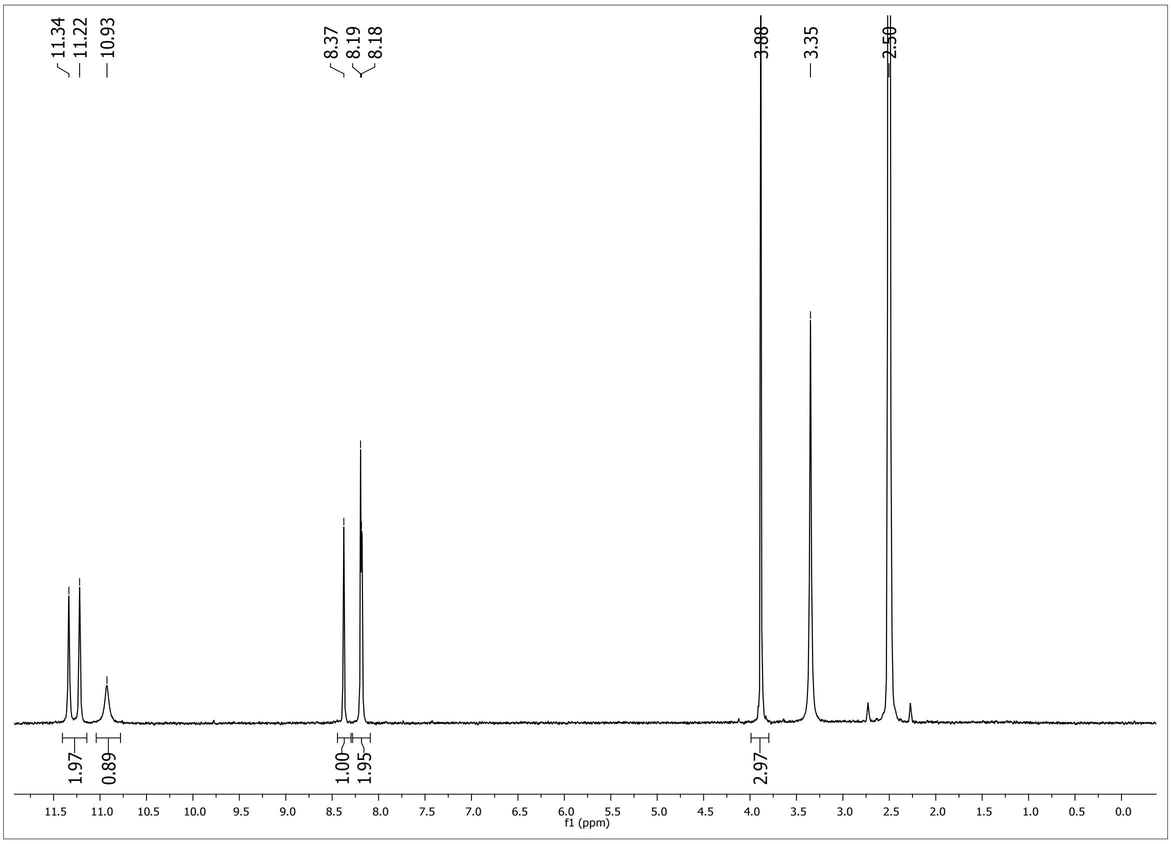

Figure 4: ^{1}H NMR spectrum in *d*^{6}-DMSO of **1c** produced by TSE.

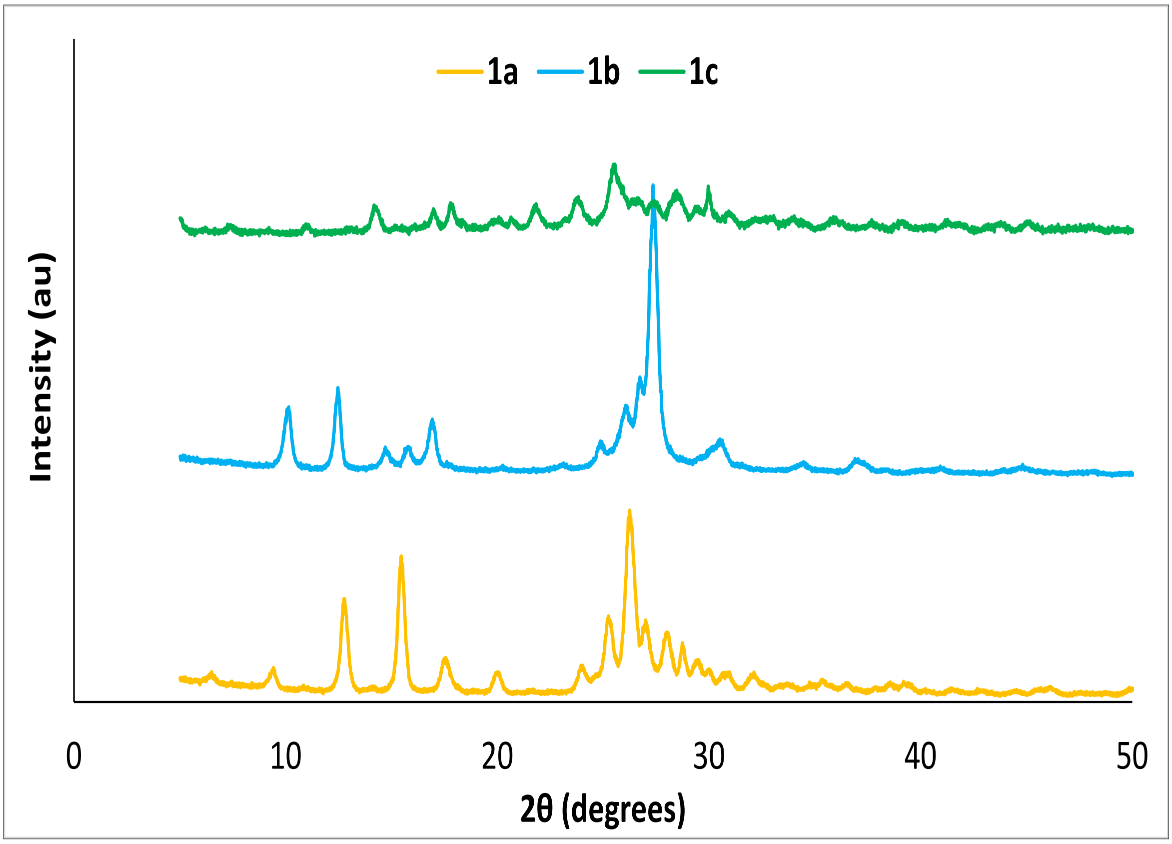

Figure 5: PXRD patterns of **1a**, **1b** and **1c** prepared by TSE.

d) ^{1}H NMR spectroscopy monitoring of the formation of 1a-c

In 1 ml of anhydrous *d*^{6}-DMSO 0.09 mmol aldehyde and 0.09 mmol of barbituric acid were dissolved to form a colourless solution. These samples were analysed by ^{1}H NMR Spectroscopy within 10 minutes and then monitored periodically over 95 days. The temperature was kept constant during this time at 18 °C. The solution gradually became a dark yellow colour as the reaction progressed.

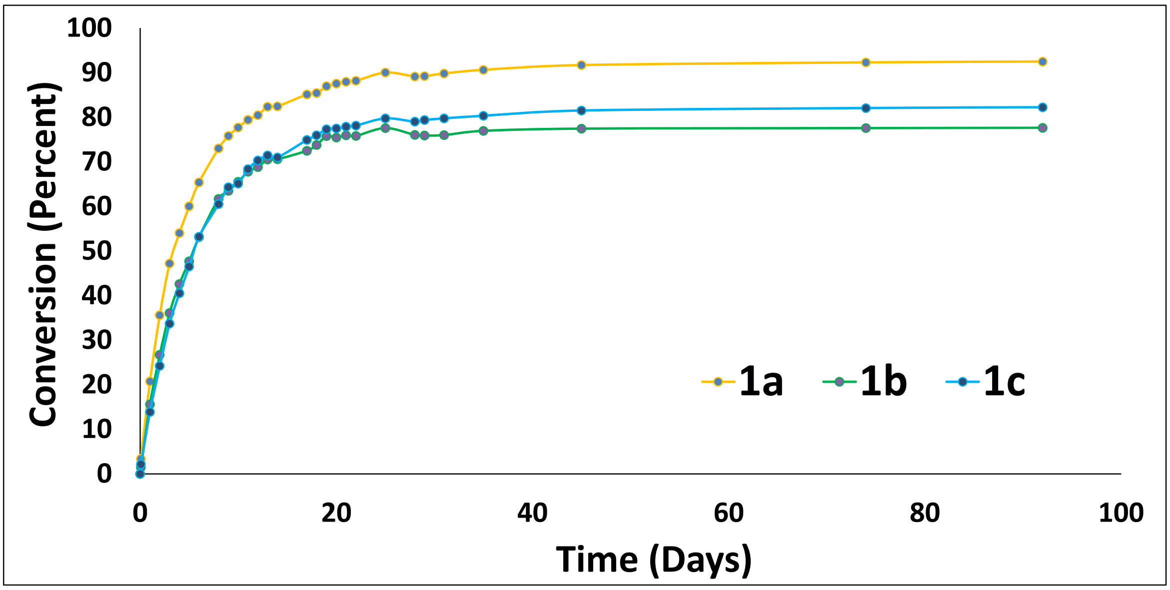

Figure 6: Conversion versus time graph for the reaction between each corresponding aldehyde with barbituric acid in *d*^{6}-DMSO.

e) DSC experiments

DSC analysis was carried out on stoichiometric mixtures of aldehyde and barbituric acid at heating rates of 10 °C per minute. DSC analysis was conducted almost immediately after mixing the solids together.

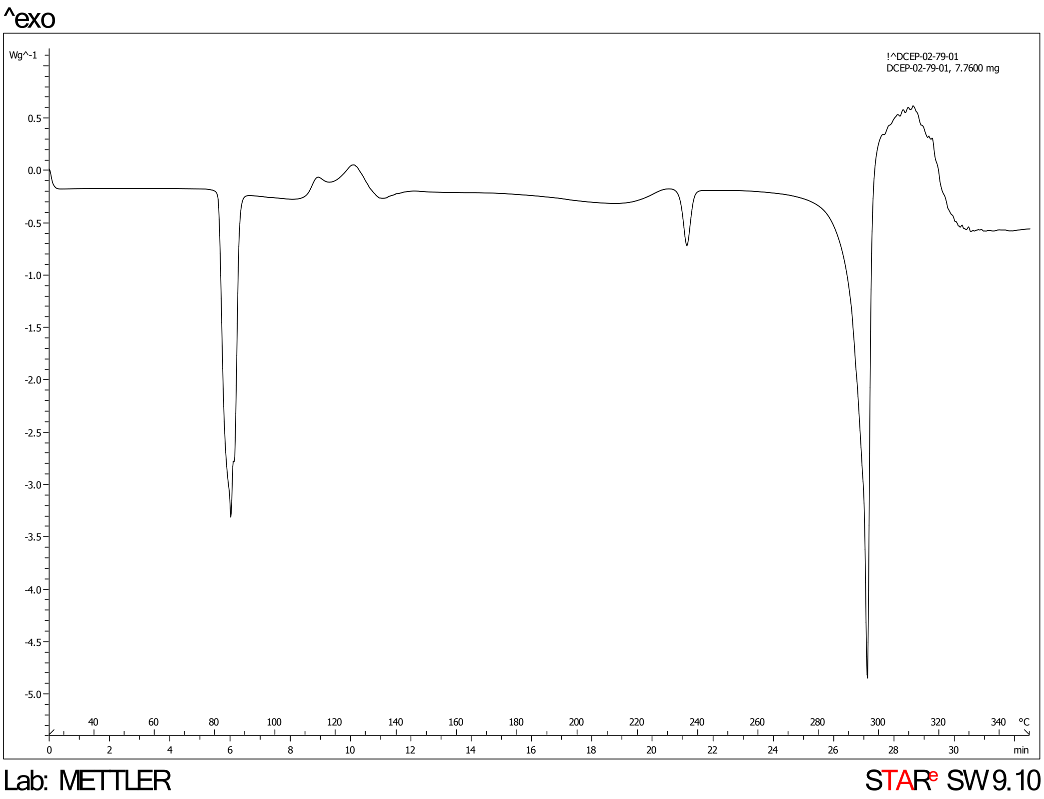

Figure 7: DSC curve obtained from analysis of vanillin and barbituric acid.

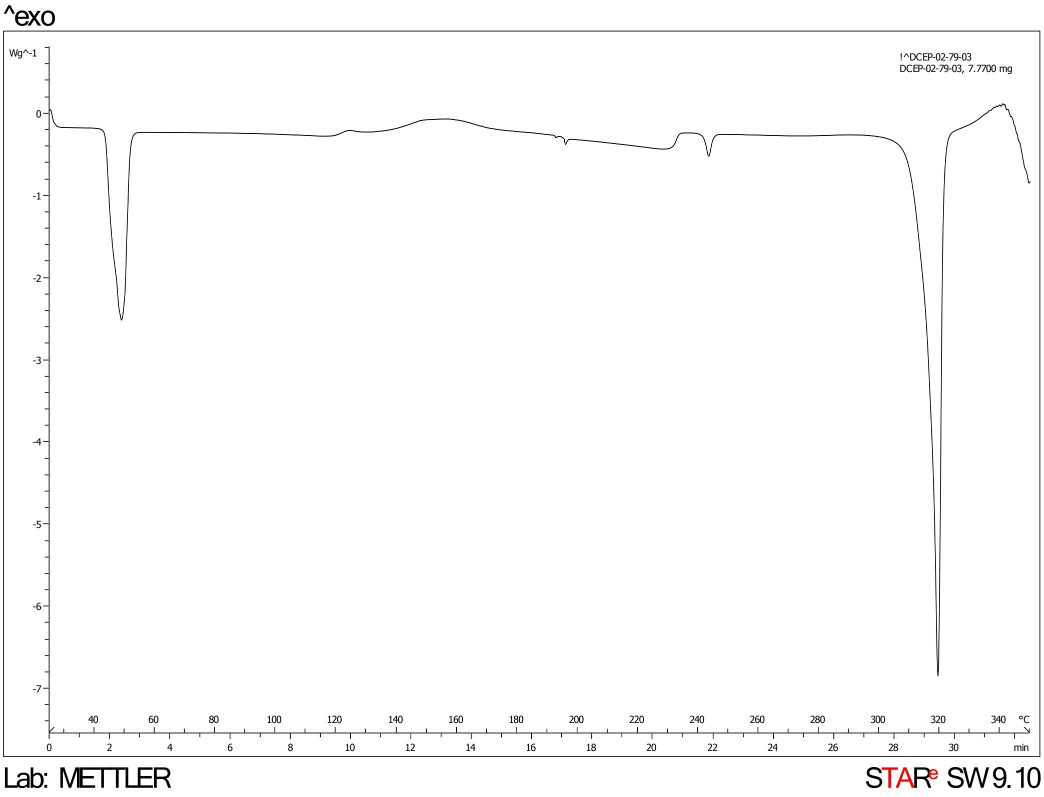

Figure 8: DSC curve obtained from analysis of veratraldehyde and barbituric acid.

Figure 9: DSC curve obtained from analysis of 5-bromovanillin and barbituric acid.

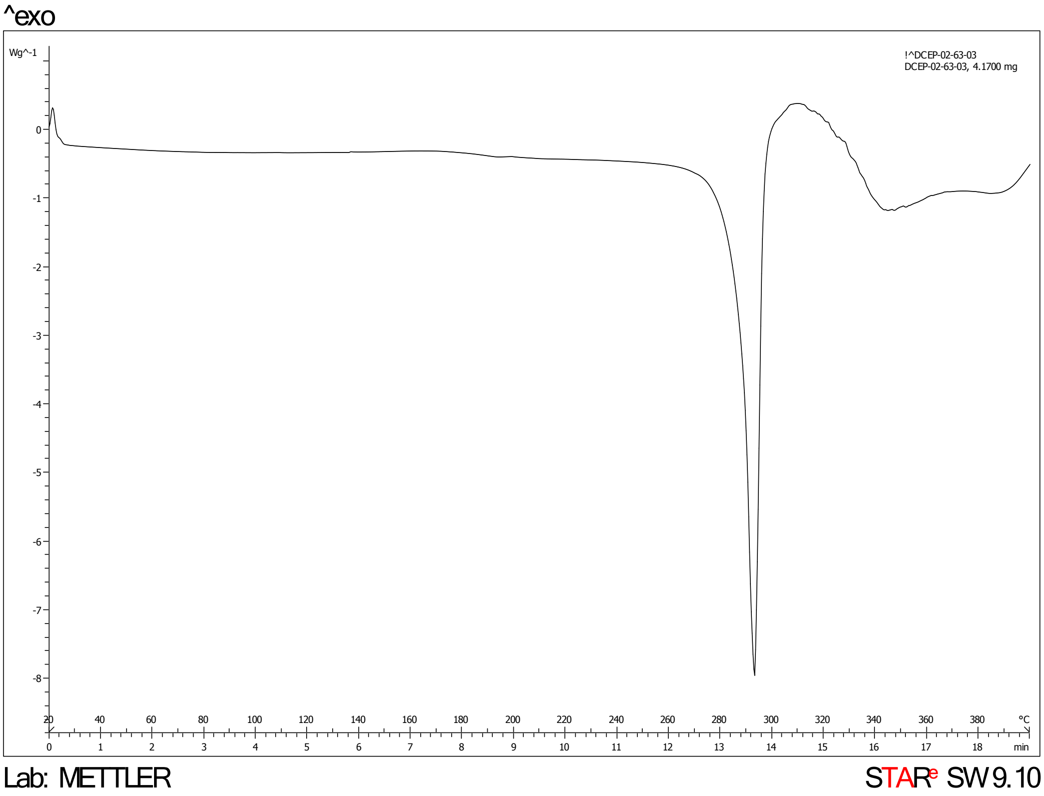

Figure 10: DSC curve obtained from analysis of **1a**.

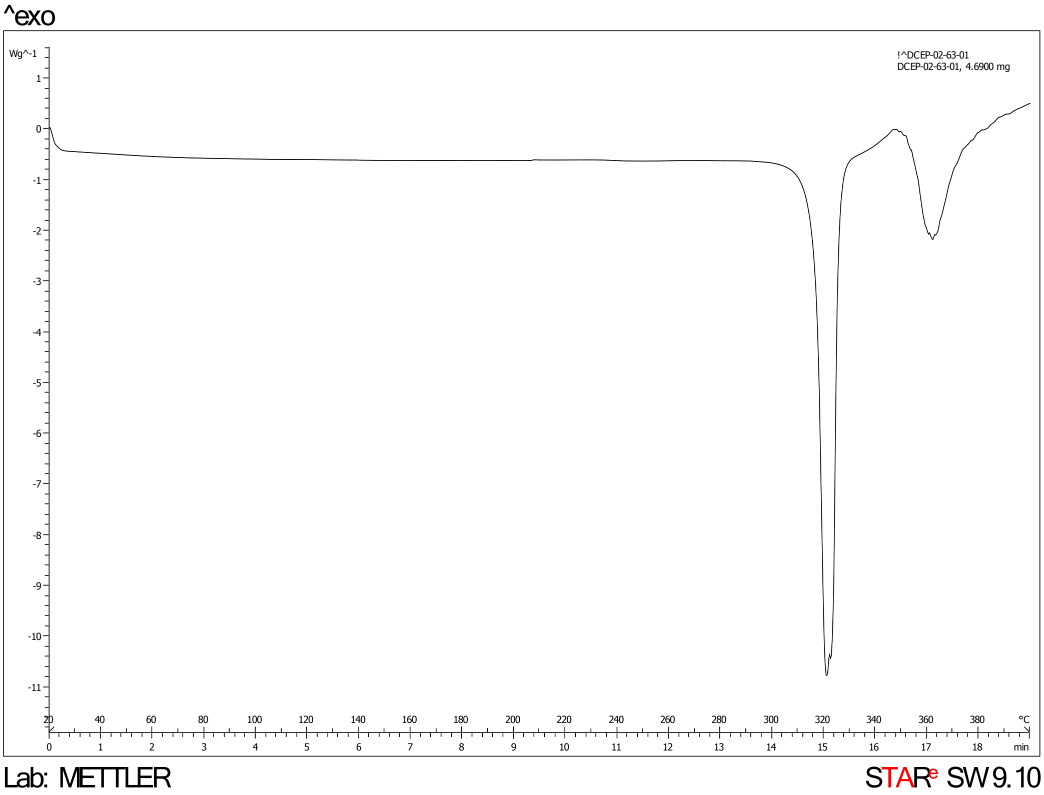

Figure 11: DSC curve obtained from analysis of **1b**.

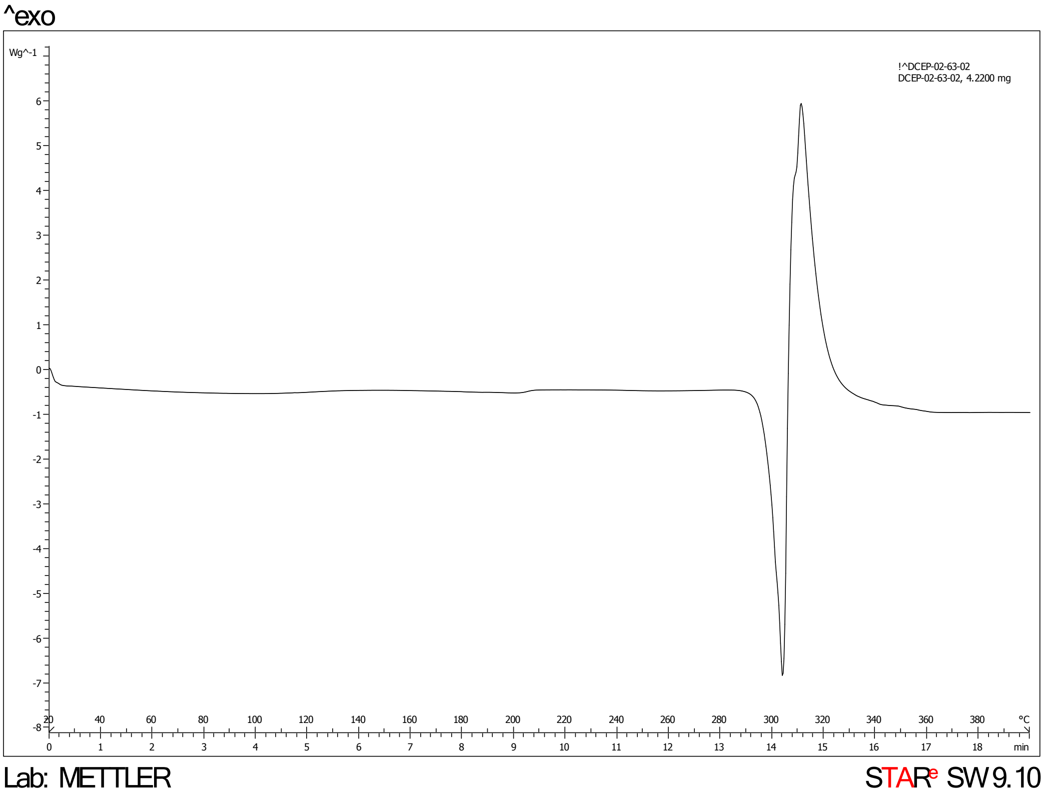

Figure 12: DSC curve obtained from analysis of **1c**.

f) **Synthesis of 2**

Synthesis of 2 in solution

To a 100 ml round bottom flask, 19 mmol vanillin (3.0 g) and 19 mmol malononitrile (1.56 g) was dissolved in 70 ml water. The reagents initially dissolved to form a yellow solution, but after a short period of time, a yellow precipitate was produced. The reaction was stirred at room temperature for 3 hours. The solid was isolated by filtration and dried in an oven for 2 hours at 120 ^{o}C to form a fine yellow powder. The ^{1}H NMR spectrum matched that in the literature.

Synthesis of 2 by twin screw extrusion

By hand, 82 mmol vanillin (12.5 g), 82 mmol malononitrile (5.4 g) and 8 mmol sodium carbonate (0.85 g), were mixed before being added to a volumetric feeder. This fed the reagents into the extruder barrel at a feed rate of 0.21 kghr^{-1} and a temperature of 120 ^{0}C was maintained throughout the length of the barrel. Screw speed was also kept constant at 55 rpm and this resulted in a throughput rate of 0.196 kghr^{-1} being achieved. The product was observed to be an orange molten liquid that solidified quickly upon cooling.

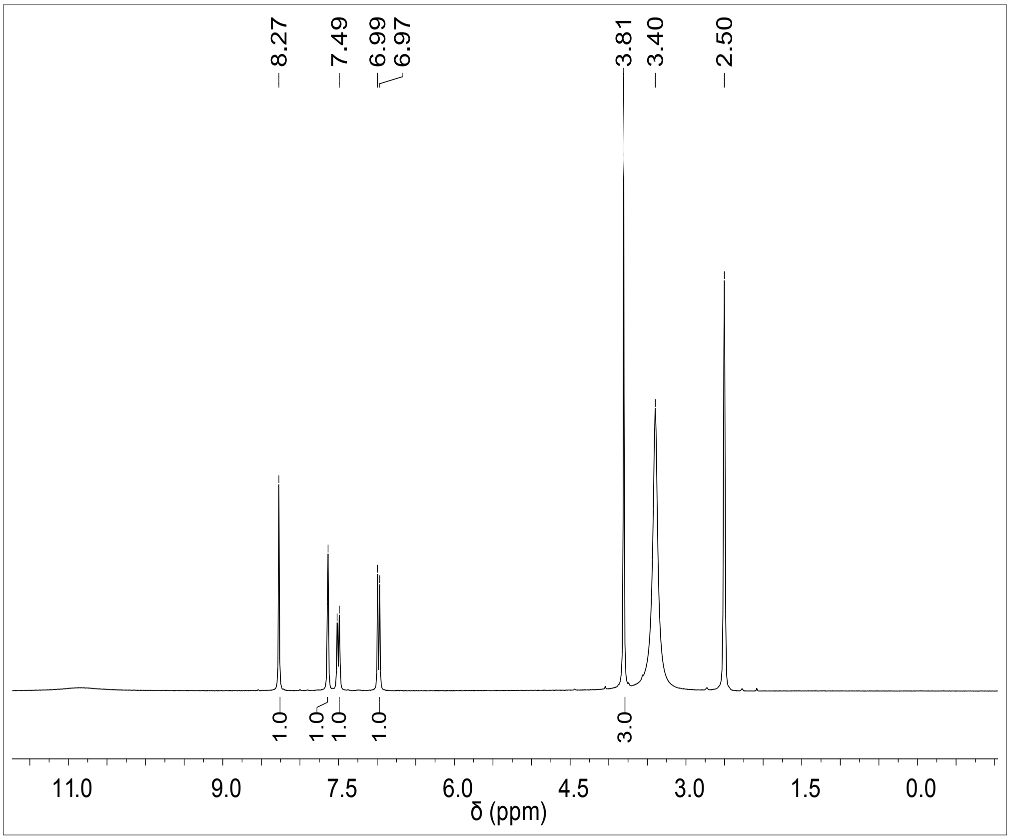

Figure 13: ^{1}H NMR spectrum of **2** in *d*^{6}-DMSO.

CHNS: Theoretical: C 66.00 %, H 4.03 %, N 13.99 %; Actual: C 63.25 %, H 3.83 %, N 13.98 %

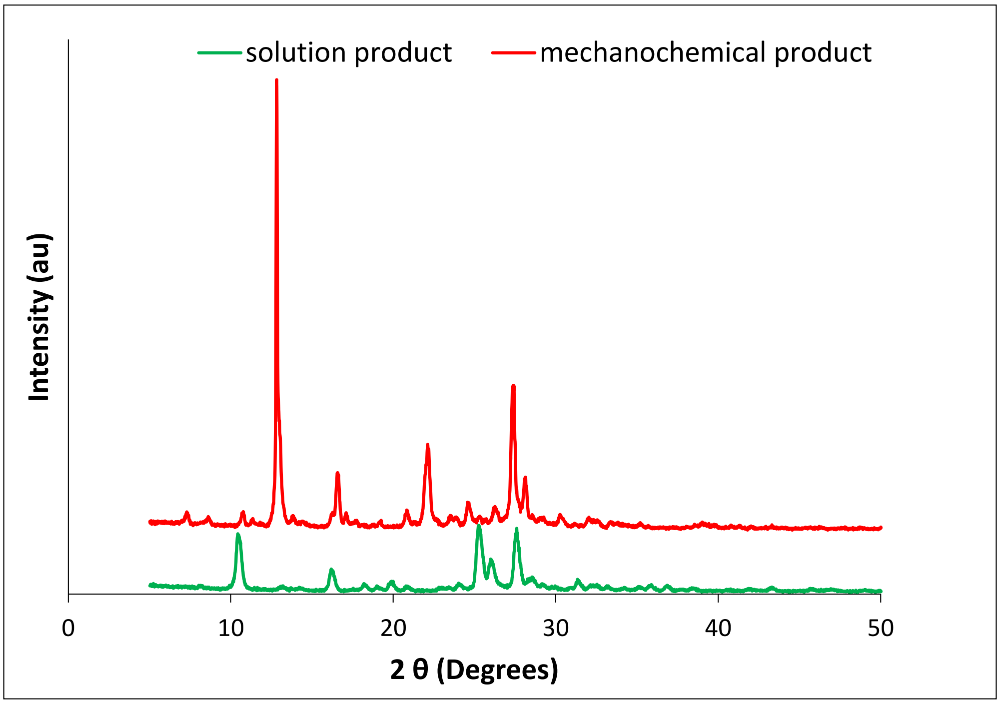

Figure 14: PXRD patterns of **2** prepared in solution, and by twin screw extrusion.

g) Synthesis of 3

Synthesis of 3 by twin screw extrusion

66 mmol vanillin (10.0 g) and 1.74 g of sodium carbonate were added to a volumetric feeder and setup up to feed into the extruder barrel at a feed rate of 2.9 gmin^{-1}. 66 mmol ethyl cyanoacetate (6.98 ml) was fed into the second port of the extruder barrel at a rate of 1.74 mlmin^{-1}. The screw speed was set at 55 rpm and the barrel was heated to 160 ^{o}C. An orange/red solid was produced with a throughput rate of 0.11 kghr^{-1}.

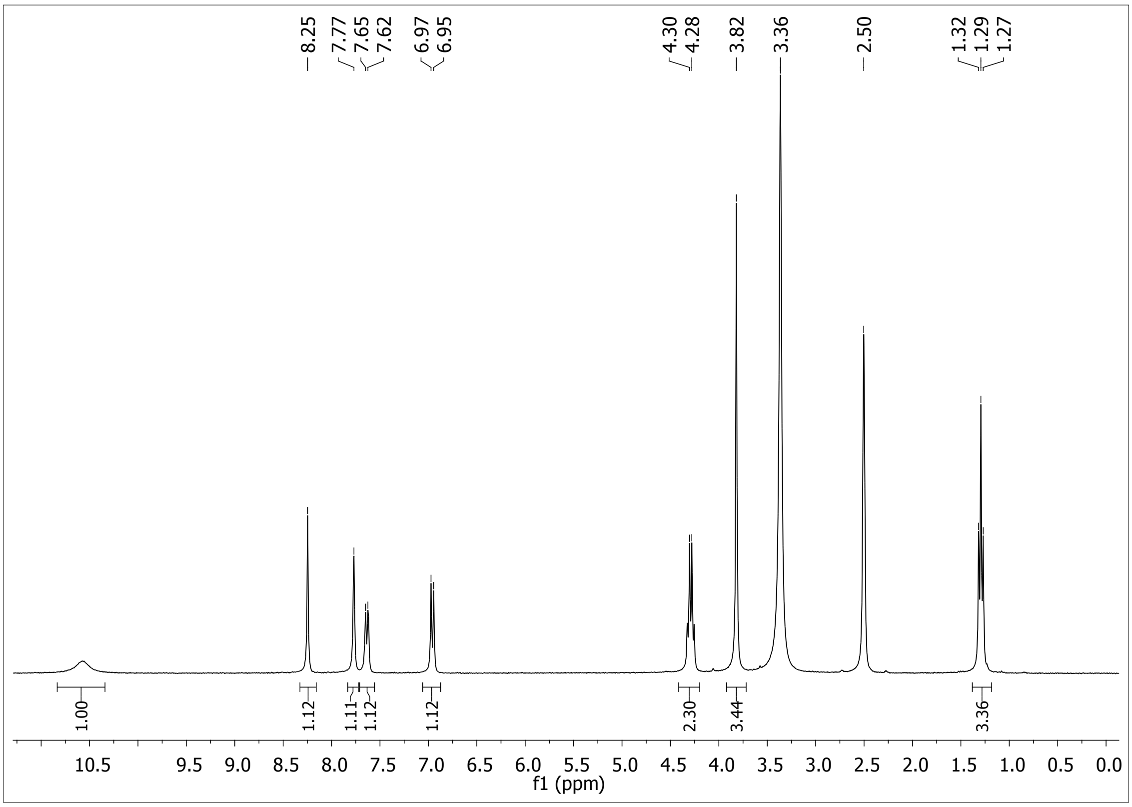

Figure 15: ^{1}H NMR spectrum of **3** in *d*^{6}-DMSO.

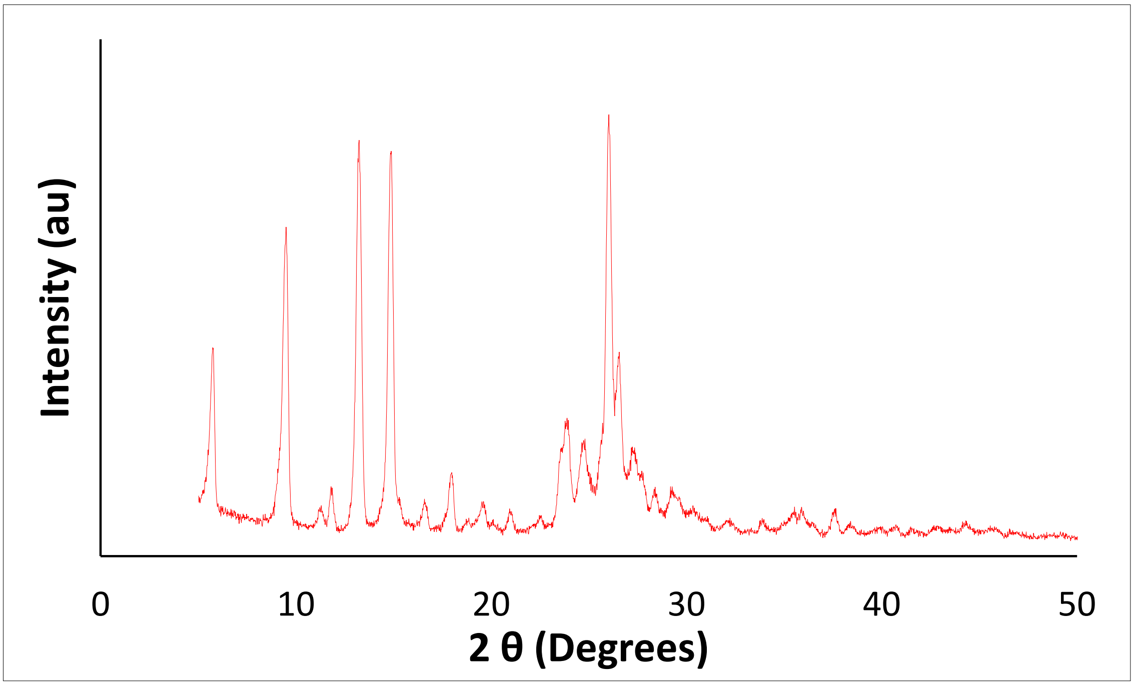

Figure 16: PXRD pattern of **3** prepared by twin screw extrusion.

CHNS: Theoretical: C 61.02 %, H 5.08 %, N 5.43 %; Actual: C 60.87 %, H 5.10 %, N 5.47 %

3) Imine Formation

Synthesis of 4 in solution

In a 250 ml round bottom flask, 20.0 mmol o-vanillin (3.0 g) and 10.0 mmol 4,4’-oxydianiline (2.0 g) was dissolved in 100 ml methanol. The reaction mixture was stirred and refluxed for 1 hour during which an orange precipitate had formed. This was isolated by filtration and washed with ice-cold methanol. Residual solvent was removed under pressure to produce a dry orange powder. NMR spectrum matched that in the literature.

CHNS: Theoretical: C 71.78 %, H 5.16 %, N 5.98 %; Actual: C 71.76 %, H 4.98 %, N 5.91 %

Synthesis of 4 by ball milling

To a 25 cm^3 stainless steel ball mill jar, equipped with a 13.6 g stainless steel ball bearing, 1.31 mmol o-vanillin (0.20 g) and 0.65 mmol 4,4’-oxydianiline (0.11 g) were added. The experiment was repeated several times at various frequencies between 15 – 25 Hz, over a period of 15 – 30 minutes (Table 3). On some occasions, 10 *%wt* methanol was also added.

The product obtained from the ball mill ranged between a fine yellow powder, an orange paste and a fine orange powder. The product was dried overnight in a desiccator. Ball milling at 25 Hz for 30 minutes was demonstrated to work best and was reproducible.

Table 3: Ball milling experiments carried out, varying frequency and time.

Frequency (Hz)	Time (Minutes)	10 %wt Methanol	Conversion (%)
15	15	Yes	74
25	15	Yes	90
25	15	No	89
25	20	No	93
25	30	No	100

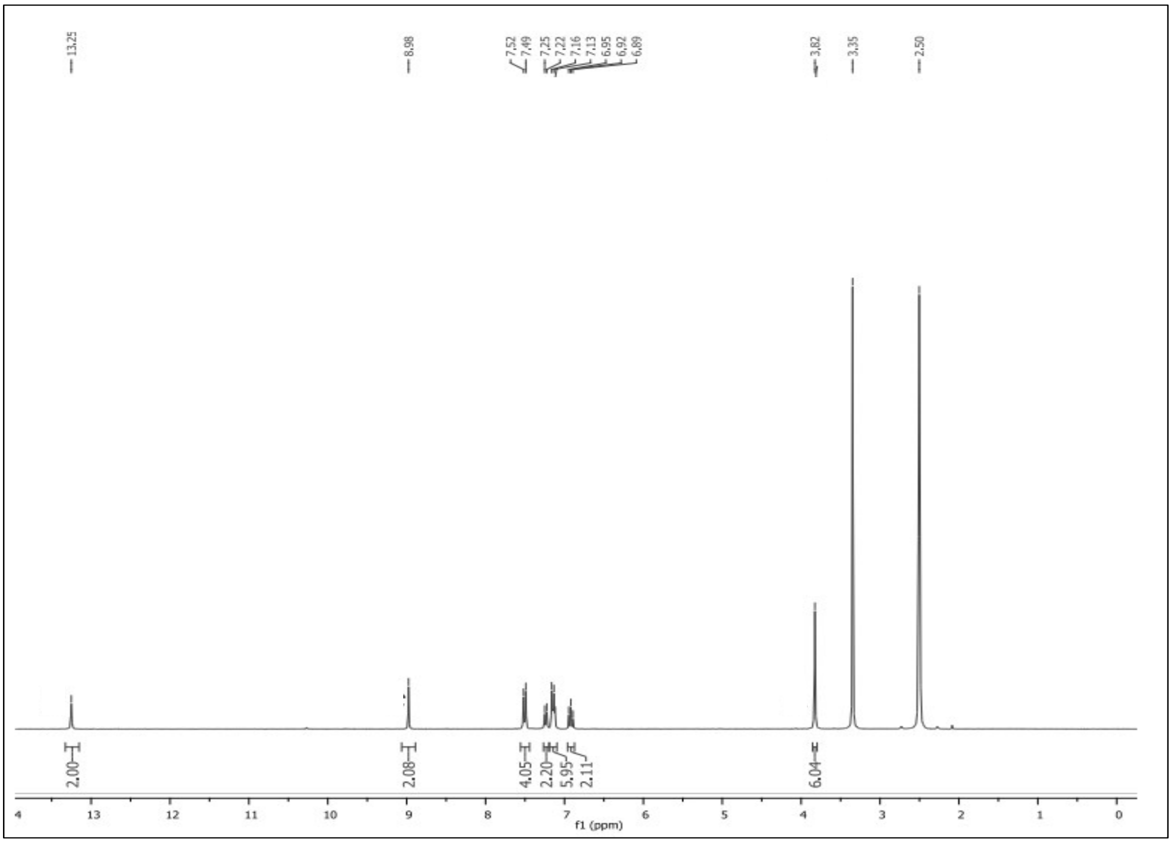

Figure 17: ^{1}H NMR spectrum of the Schiff base, **4** in *d*^{6}-DMSO.

CHNS: Theoretical: C 71.78 %, H 5.16 %, N 5.98 %; Actual: C 72.91 %, H 5.54 %, N 5.84 %

Synthesis of 4 by twin screw extrusion

By hand, 82.0 mmol o-vanillin (12.5 g) and 41.0 mmol 4,4'-oxydianiline (8.2 g), were mixed before being fed into the volumetric feeder. The reagents were then fed into the twin screw extruder at feed rates between 2 and 8 %. The extruder barrel was heated at various temperatures between room temperature and 120 ^{o}C as summarised in Table 4. Screw speeds between 30 and 250 rpm were investigated and it was identified that 55 rpm was the best candidate. Temperature and feed rates were manipulated until 100 % conversion to product was observed by ^{1}H NMR spectroscopy, which was at 55 rpm, 120 ^{o}C with a feed rate of 0.79 gmin^{-1}. A throughput rate of 30 ghr^{-1} was achieved. The product was a fine orange powder that did not require any post process purification, and the water by-product was removed as steam due to the high temperature of the extruder barrel.

Table 4: Experiments carried out to optimise extrusion process for the formation of an imine.

Temperature (^{o}C)	Screw Speed (rpm)	Feed Rate (gmin^{-1})	Conversion (%)
25	55	- [a]	0
40	55	- [a]	80
80	55	- [a]	99
80	55	0.45	0
80	55	0.73	45
80	55	0.79	70
100	55	0.79	91
120	55	0.79	100

[a] Reagents were fed manually.

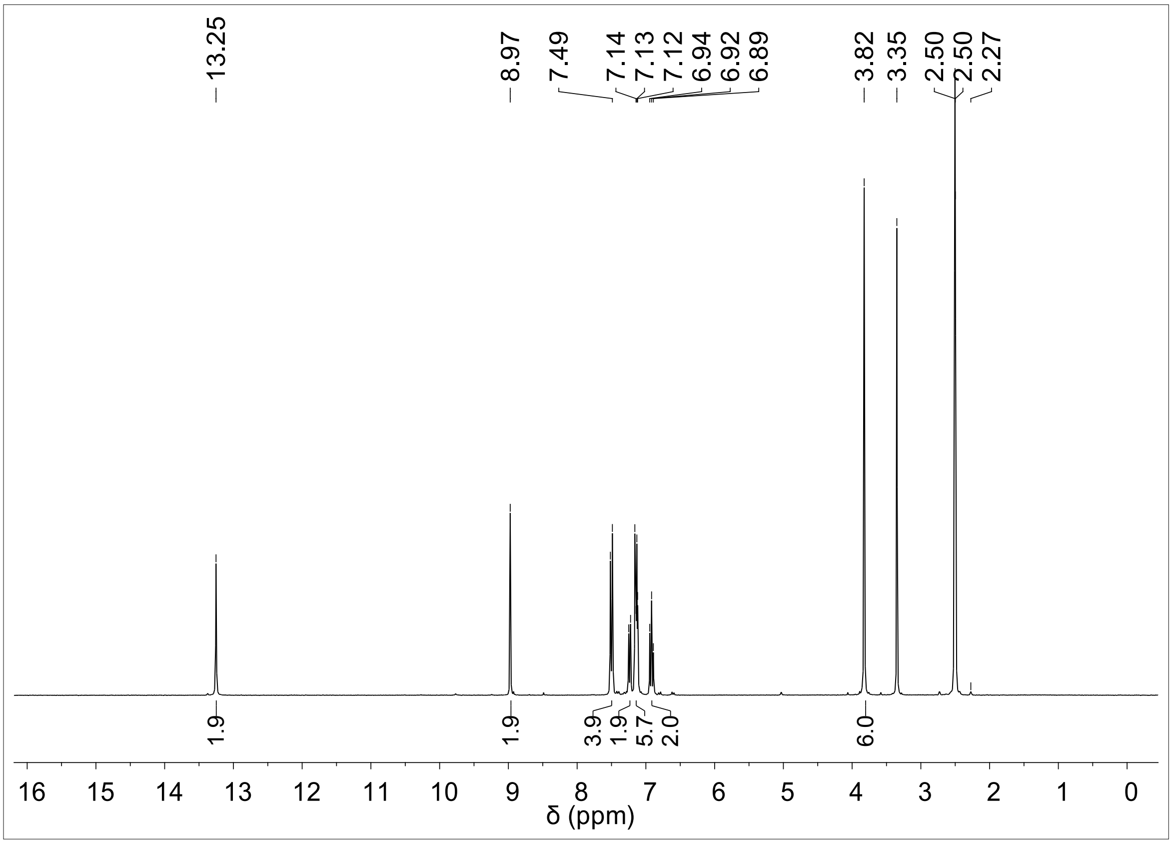

Figure 18: ^{1}H NMR spectrum of the Schiff base **4** in *d*^{6}-DMSO.

CHNS: Theoretical: C 71.78 %, H 5.16 %, N 5.98 %; Actual: C 71.48 %, H 4.69 %, N 5.97 %

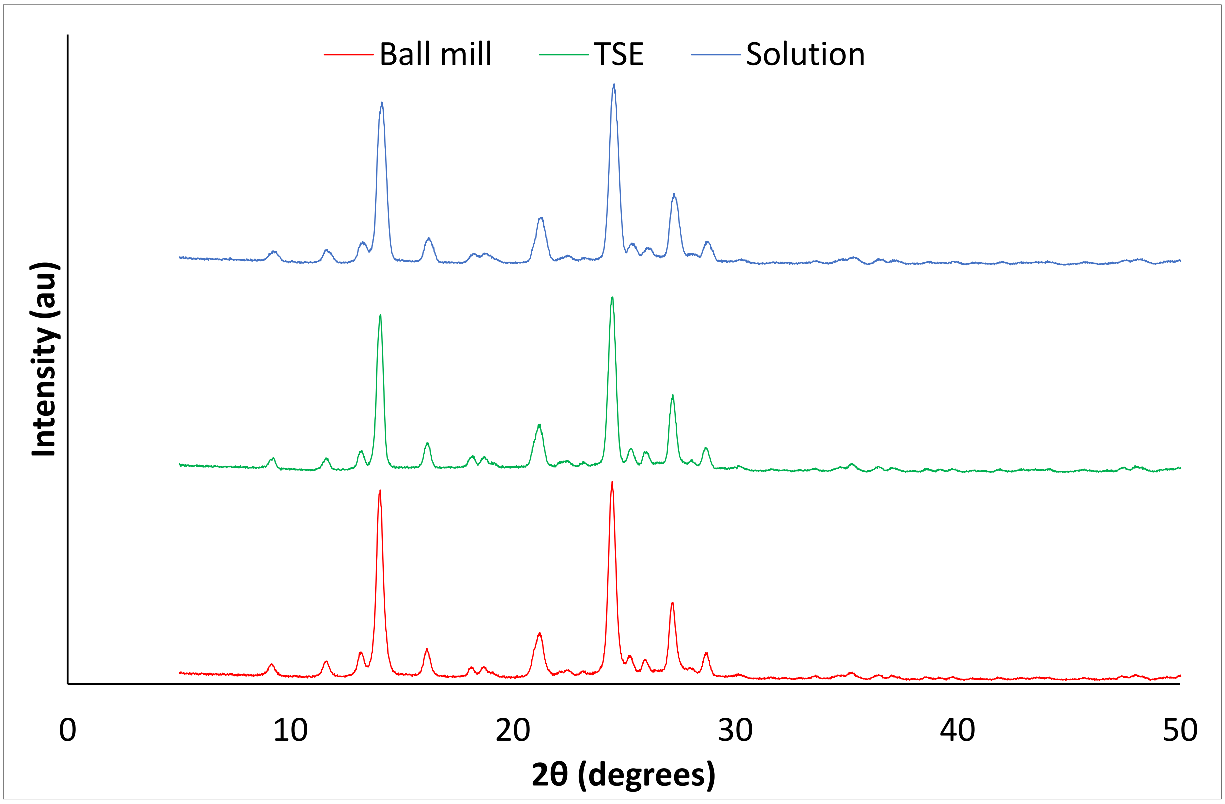

Figure 19: PXRD patterns of the Schiff base **4** prepared in solution, by ball milling and twin screw extrusion.

4) Michael Addition

Synthesis of 5 in solution

To a 250 ml round bottom flask, 3.0 mmol veratraldehyde (0.5 g), 6.0 mmol dimedone (0.84 g) and 0.3 mmol $SmBr_3.6H_2O$ (0.149 g) were suspended in 100 ml of water. After 10 minutes, all of the solid was seen to have dissolved, resulting in a pale yellow solution. This was stirred overnight at room temperature during which time a white precipitate formed. This was filtered and the product was dried overnight in a desiccator. ^1H NMR spectroscopy indicated that although there was 100 % conversion to product, there was more than one product (three identified by TLC analysis). Purification was not carried out on this sample as the goal was to prepare the product by extrusion.

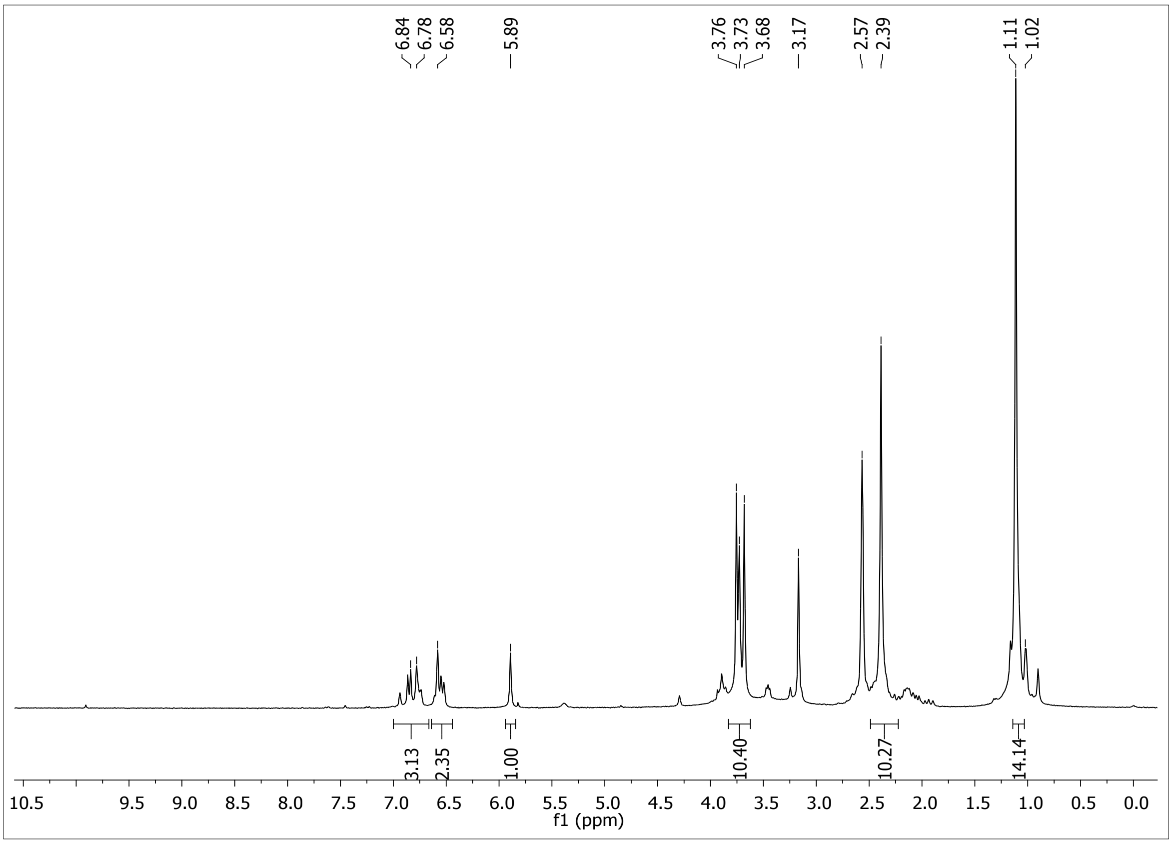

Figure 20: ^{1}H NMR spectrum of **5** (not purified) in *d*^{6}-DMSO.

Synthesis of 5 by twin screw extrusion

By hand, 60 mmol veratraldehyde (10.0 g) and 120 mmol dimedone (16.9 g), were mixed before being fed into the volumetric feeder. The reagents were then fed into the twin screw extruder at feed rates between 2 and 12 %. It must be noted that an alternative screw configuration was employed which consisted of reverse screw segments (Figure 21). The extruder barrel was heated at various temperatures between room temperature and 160 ^{o}C and screw speeds between 30 and 250 rpm were investigated. It was identified that the optimum conditions were 120 ^{o}C and 200 rpm, which in turn produced a beige fine powder. A feed rate of 0.12 kghr^{-1} was best and a throughput rate of 0.07 kghr^{-1} was achieved. ^{1}H NMR spectroscopy (in MeOD) indicated that although there was 100 % conversion to product, there was more than one product (three identified by TLC analysis). As a result, a sample was purified by column chromatography, employing an eluent system of CH_2Cl_2:EtOH 9:1. This provided an analytically pure white solid product.

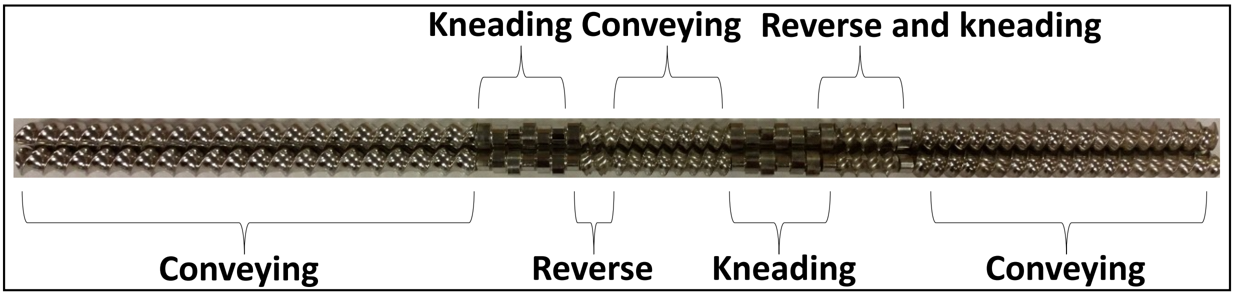

Figure 21: Alternative screw configuration employed, containing reverse conveying segments that retard the flow of material.

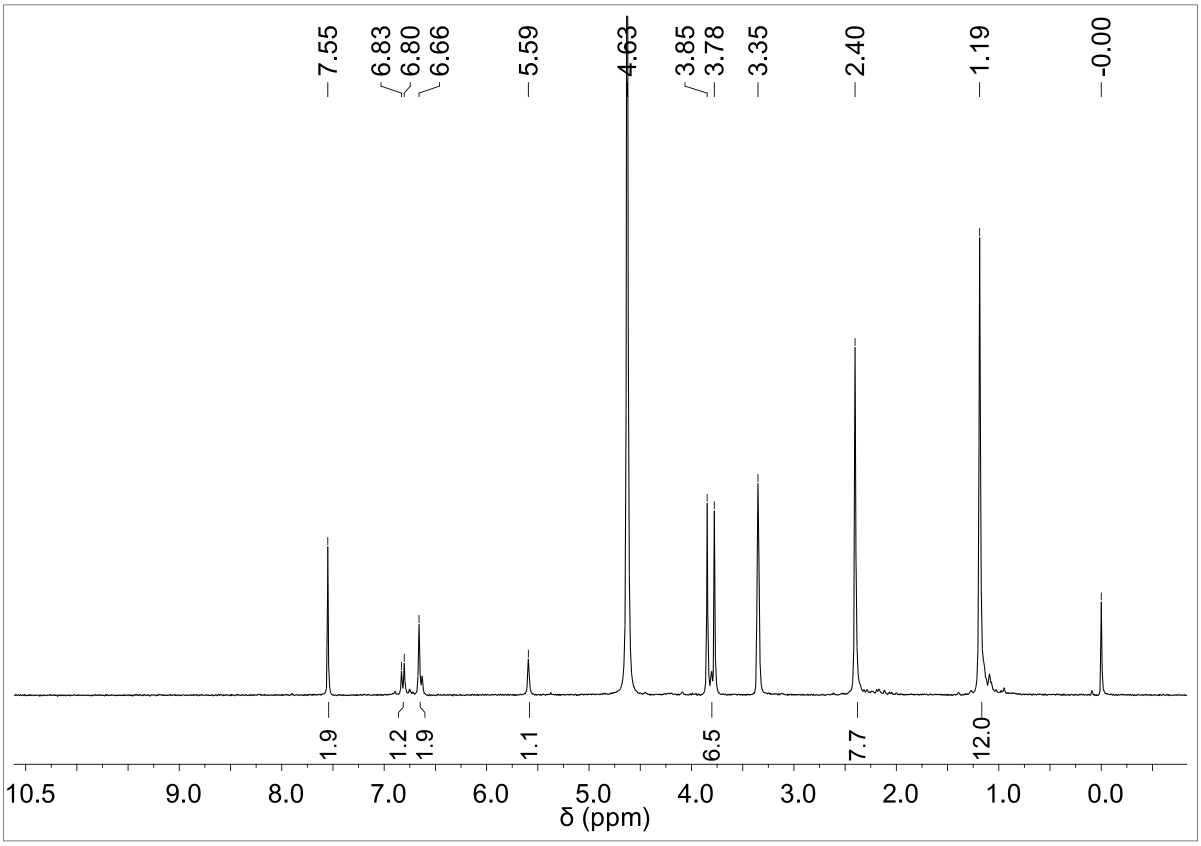

Figure 22: ^{1}H NMR Spectrum of **5** in MeOD.

CHNS: Theoretical: C 70.07 %, H 7.53 %; Actual: C 70.42 %, H 7.31 %

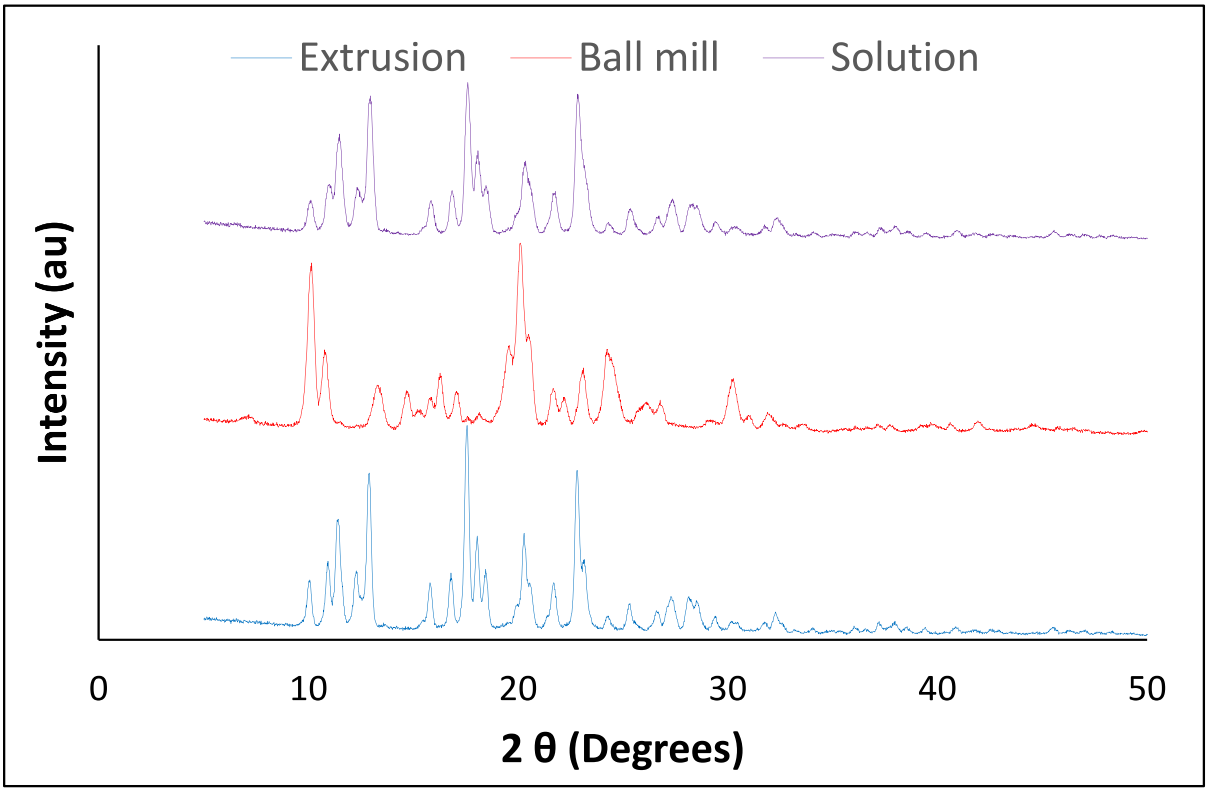

Figure 23: PXRD patterns of the **5** prepared in solution, by ball milling (unsuccessful) and twin screw extrusion.

5) Aldol Reaction

Synthesis of 6 by ball milling

To a 25 cm^3 stainless steel ball mill jar, equipped with a 13.6 g stainless steel ball bearing, 2.81 mmol ninhydrin (0.50 g), 2.81 mmol dimedone (0.39 g) and 0.023 g of sodium carbonate were added. The reaction mixture was milled at 25 Hz for 30 minutes to produce a pale yellow solid.

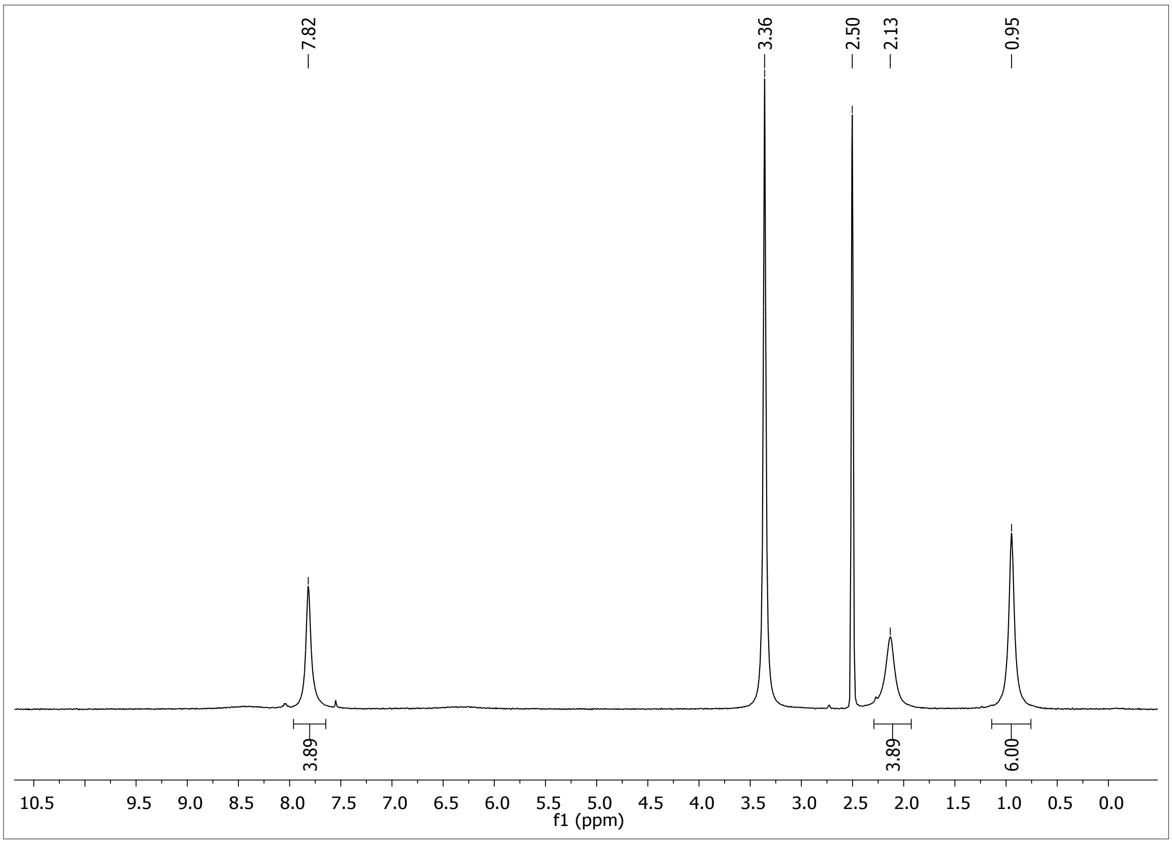

Figure 24: ^{1}H NMR spectrum of **6** prepared by ball milling, in *d*^{6}-DMSO.

Synthesis of 6 by twin screw extrusion

By hand, 57.4 mmol ninhydrin (10.0 g), 57.4 mmol dimedone (7.89 g) and 0.92 g sodium carbonate, were mixed before being fed into the volumetric feeder. The reagents were then fed into the twin screw extruder at a feed rate of 4 %. The extruder barrel was heated at 100 ^{o}C and screw speed was optimised as 55 rpm. A feed rate of 0.05 kghr^{-1} was determined and a throughput rate of 0.06 kghr^{-1} was achieved. Residence time was significantly longer at *ca.* 12 minutes, when employing the typical screw configuration.

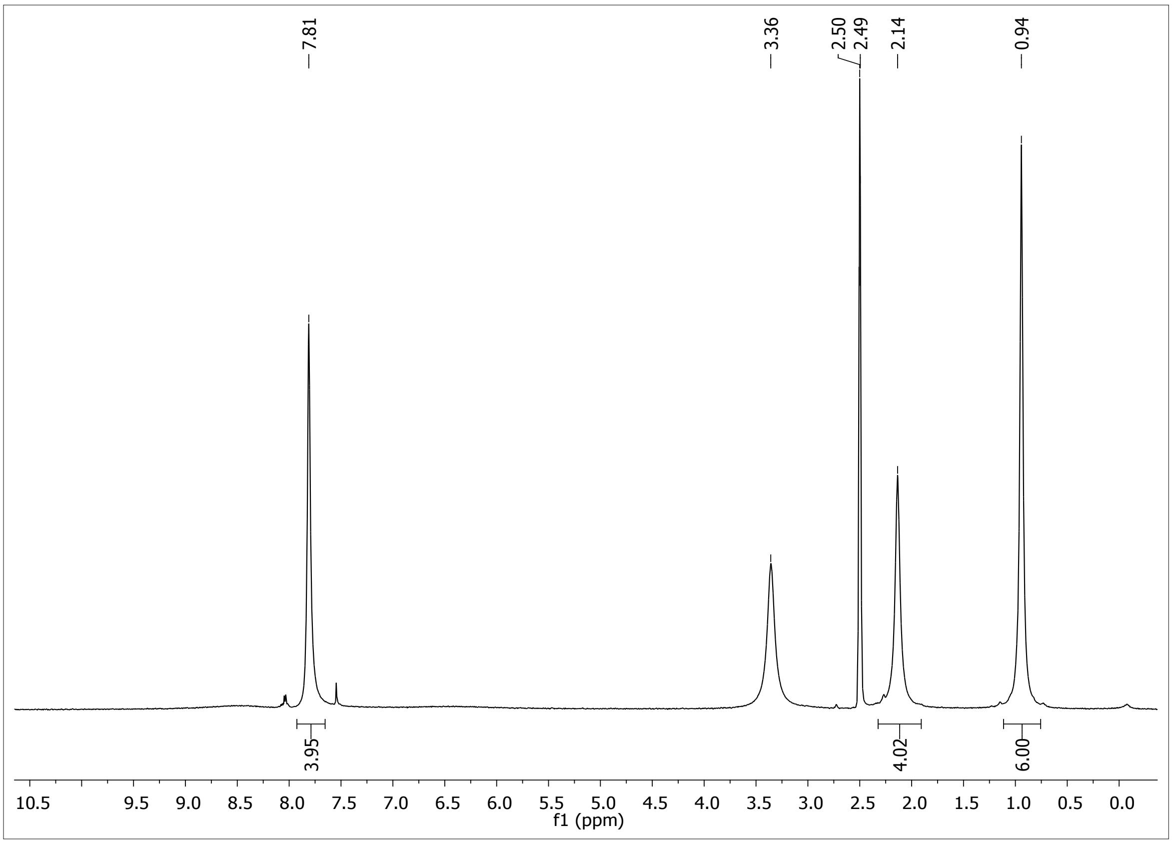

Figure 25: ^{1}H NMR spectrum of **6** prepared by twin screw extrusion, in *d*^{6}-DMSO.

CHNS: Theoretical: C 67.99 %, H 5.37 %; Actual: C 67.91 %, H 5.56 %

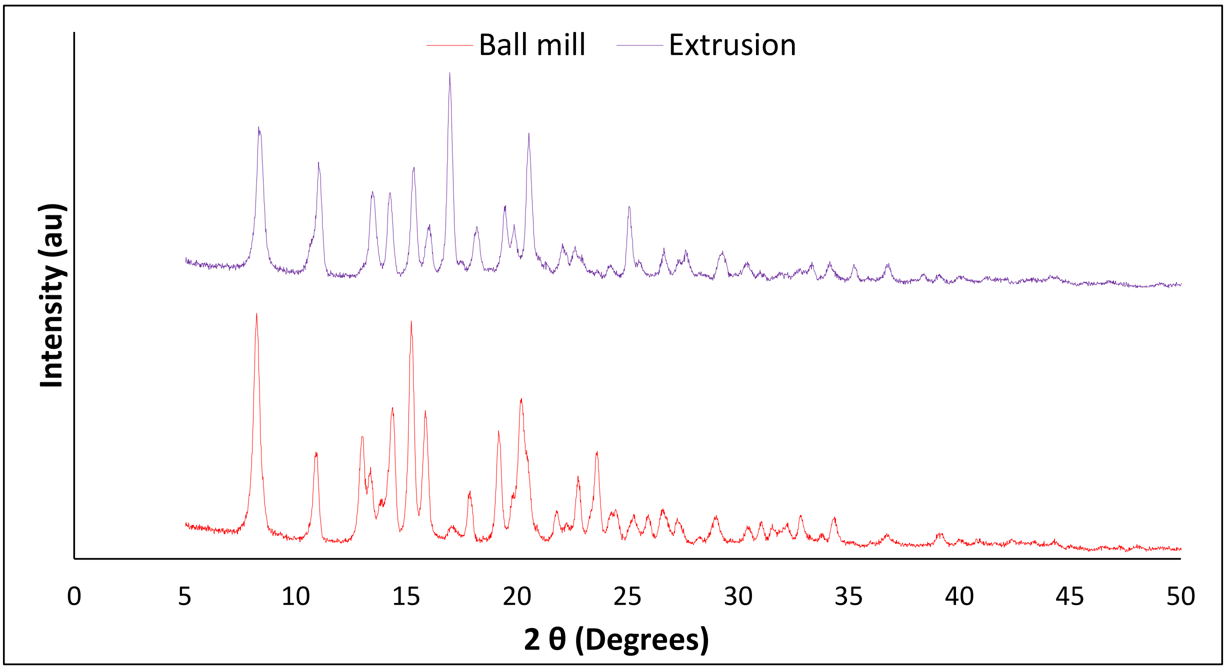

Figure 26: PXRD patterns of the ball mill and extrusion products of the aldol reaction.