SUPPORTING INFORMATION

Solvent-free, continuous synthesis of hydrazone-based active pharmaceutical ingredients by twin-screw extrusion

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36 pages, 34 Figures, 8 Tables

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General Remarks

All reagents were commercially available and used without any further purification. NMR spectra were recorded at room temperature with the appropriate deuterated solvent ($CDCl_3$ or *d*^{6}-DMSO). Chemical shifts (δ) of ^{1}H NMR and ^{13}C NMR spectra are reported in ppm relative to residual solvent signals ($CHCl_3$ in $CDCl_3$: δ = 7.27 ppm for $_1$H and $CDCl_3$: δ = 77.16 ppm for ^{13}C NMR); *J* values are given in *Hz*. ^{1}H and ^{13}C NMR spectra were registered at 300 MHz or 400 MHz. HR MAS ^{13}C NMR analyses were registered with Bruker Avance III HD 600. 600 MHz NMR spectrometer Bruker Avance III HD for high resolution spectroscopy in liquids, 5 RF channels, quadruple-resonance (^{1}H-^{31}P-^{13}C-^{15}N) inverse cryo-probe with cooled ^{1}H and ^{13}C preamplifiers, sample temperature range −40° to 80°C. The identity of analytically pure final products was assessed by comparison of their ^{1}H NMR data previously described in the literature.[1-4]

Solid State ^{13}C NMR spectra for compounds **1**-**3** were carried out at the NMR facility of Institut Charles Gerhardt in Montpellier (France) and at the Università degli Studi di Cagliari (Italy). Solid State ^{13}C NMR spectra for compounds **1 and 2** have been recorded on a 300 MHz Varian VNMRS300 spectrometer ("Wide Bore" magnet at 7,05 Tesla) using a Varian T3 Mas (Magic Angle Spinning) probe with 3.2 mm ZrO_2 rotors. Spectra have been acquired using the non-quantitative CPMAS technique (Cross Polarization Magic Angle Spinning) with ^{1}H decoupling with a recycle delay of 5 s, a π/2 pulse of 5 μs, a contact time of 1 ms and a spinning rate of 12 kHz. Adamantane was used as a secondary reference (left peak at 38.5 ppm). The width of the spectral window is 50 kHz and the line broadening is 50 Hz. Solid State ^{13}C NMR spectra for compound **3** (nitrofurantoin) were recorded on a 14.1 T Bruker Avance III HD spectrometer equipped with a 2.5 mm HX CPMAS probe. Larmor frequencies were 600.13 MHz (^{1}H), 150.92 MHz (^{13}C). Powder samples were spun at magic angle at 15 kHz in a 2.5 mm ZrO_2 rotor. Glycine was used for the Hartmann–Hahn matching procedure; ^{13}C chemical shifts were referenced to methylene resonance of adamantane at 38.48 ppm. Acquisition was performed with a standard CP pulse sequence with ramped CP scheme. A 300 ppm spectral width was used with 3.7 μs proton π/2 pulse, 2.5 ms contact time, 4 s relaxation delay and 2800 average scans. All CP data were collected using Spinal-64 proton decoupling during acquisition. All spectra were processed using 40 Hz line broadening before Fourier transform.

The ball-milling experiments were performed in a MM400 vibrational ball (Retsch GmbH, Haan, Germany) using 5 or 10 mL steel jar (with 5, 10 or 20 stainless steel balls, for each ball the weight is 0.508 g, 5 mm Ø). FT-IR analyses were registered with Perkin Elmer Spectrum 100 FT-IR Spectrometer (Attenuated Total Reflectance Infrared ATR-IR device) in reflectance mode. Measurements are performed directly on the powders. The powders were placed on the ATR-IR plate and a constant pressure (*i.e.* force gauge was kept at 19% of the scale) was applied to the powder to bring it into good contact with the ATR crystal. The application of a force uniformly distributed across the crystal allowed to obtain adequate band intensities and monitor over the time their modifications. Band positions are reported in cm^{-1}. Extrusion was carried out using a Three-Tec 12 mm, 40:1 L:D corotating twin screw extruder with six heating zones.

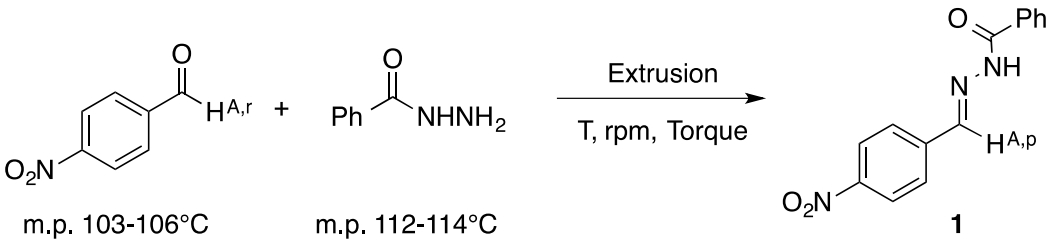
Experimental procedure for the mechanochemical preparation of *N*-acylhydrazones 1 and 2 (vibrating ball-mill).

p-Nitrophenylaldehyde (1.0 equiv, 1.324 mmol) and the relevant hydrazide (1.0 equiv, 1.324 mmol) were ball-milled in a 10 mL stainless steel milling jar with 20 stainless steel milling balls (5 mm diameter, total weight = 10.16 g) at 30 Hz for 1 h. The final product was recovered from the jar without further treatment. Target (*E*)-*N*'-(4-nitrobenzylidene)benzohydrazide **1** was obtained as a pale cream solid with a 90% yield (266 mg) after drying *in vacuo* over $MgSO_4$ overnight. The *E*-geometry was assigned on the base of previous reports.[2, 3]

Following the same procedure described above*, N*'-(4-nitrobenzylidene)benzohydrazide **2** was recovered as a white solid, with a 91 % yield (342 mg) after drying *in vacuo* over $MgSO_4$ overnight. The *E/Z*-geometry was assigned on the base of previous reports.[4]

For compound (*E*)-*N*'-(4-nitrobenzylidene)benzohydrazide **1**: ^1H NMR kinetic studies in solution (room temperature in DMSO-d_6) were performed. *Quantities: p*-nitrobenzaldehyde (10 mg, 0.066 mol), benzhydrazide (9.0 mg, 0.066 mol) in DMSO-d_6 (0.7 mL). Acquisition of ^1H NMR spectrum each *ca.* 10 minutes.

Table S1: Selected data to optimize the preparation of *N*-acylhydrazone **1** by extrusion.



Entry[a]	T (°C)	rpm	$H^{A,p}$ (*E*/*Z*)[b]	RCHO (%)	STY (%)[c]
1[e]	50	55	100/0	0	2.1 g/min
2[f]	150	55	100/0	0	0.4 g/min
3[f]	150	100	100/0	0	0.6 g/min
4[f]	150	150	100/0	0	0.5 g/min
5[f]	150	250	100/0	0	0.7 g/min

[a] Torque: 1.0 Nm, the screw profile shown in Figure 1 was used; [b] Only the *E*-isomer is formed. The *E*-geometry was assigned on the basis of previous reports[2, 3] [δ(ppm): 12.15 ppm (NH proton),[2] 8.59 ppm ($H^{A,p}C=N$)[3]]. Legend: $H^{A,r}$ and $H^{A,p}$ indicate respectively the aldehyde proton in the reactant and the *N*-acylhydrazone proton in the product **1**); [c] STY = Space Time Yield; [e] Reaction scale: *p*-nitrobenzaldehyde, RCHO (10.00 g, 0.0662 mol), benzhydrazide (9.00 g, 0.0662 mol); [f] Reaction scale: *p*-nitrobenzaldehyde, RCHO (5.0 g, 0.0331 mol), benzhydrazide (4.5 g, 0.0331 mol).

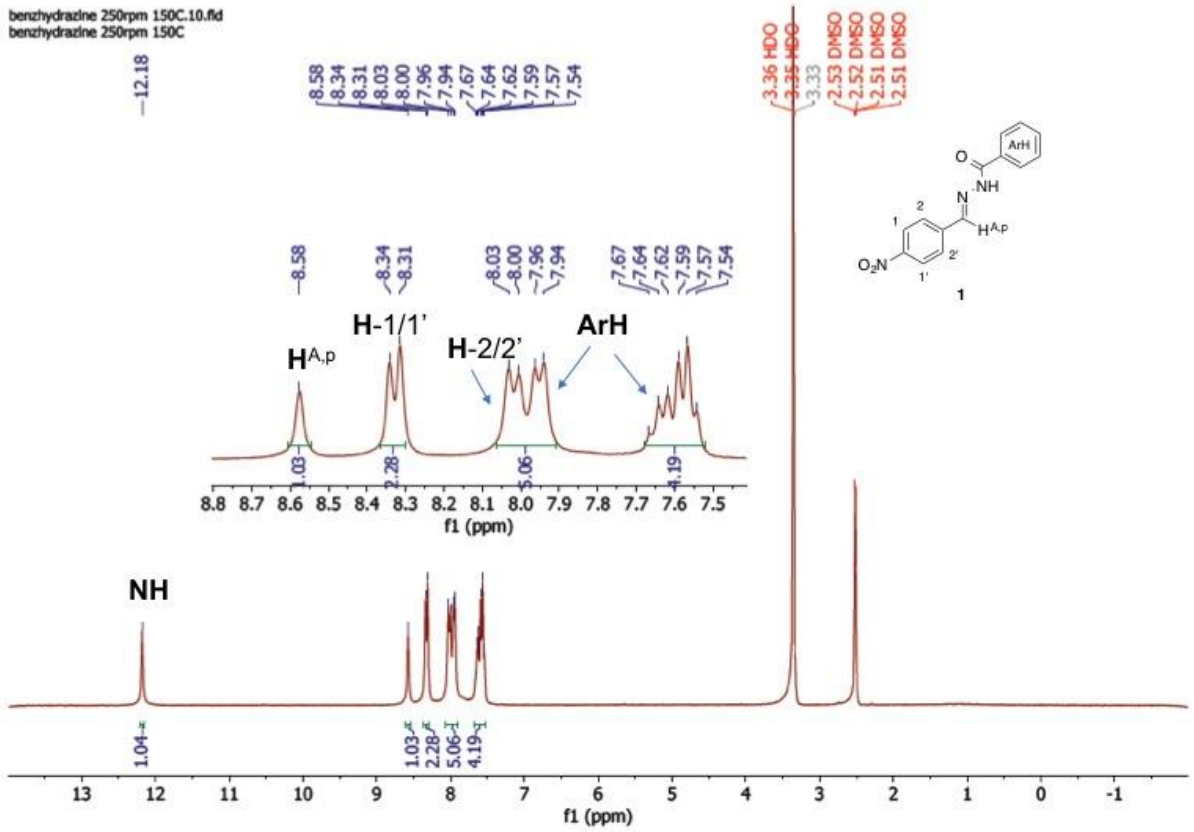


Figure S1. ^{1}H NMR spectrum of *N*-acylhydrazone **1**[2] prepared by extrusion (Table S1, entry 5).

Kinetic Studies by Solid state FT-IR (ATR device) for compound 1.

Sample preparation and analyses: each substrate was ground separately in an agate mortar. The specified quantities of solids were then gently mixed by hand in a glass tube. The background was recorded, then the powder was analyzed by FT-IR over 1 h:30 min, collecting a spectrum every 5 minutes (number of scan NS = 8). For comparison, IR spectra were recorded also for the substrates *p*-nitrobenzaldehyde (**A**) and benzhydrazide (**B**) and for the final product **1** (sample prepared by vibrating ball-mill during 1h). From the IR spectra, no reaction is observed at the solid state by contact or by applying a slight. The spectra of the starting materials and product are given in ANNEX 1.

Quantities: p-nitrobenzaldehyde (**A**, 10 mg), benzhydrazide (**B**, 9.0 mg).

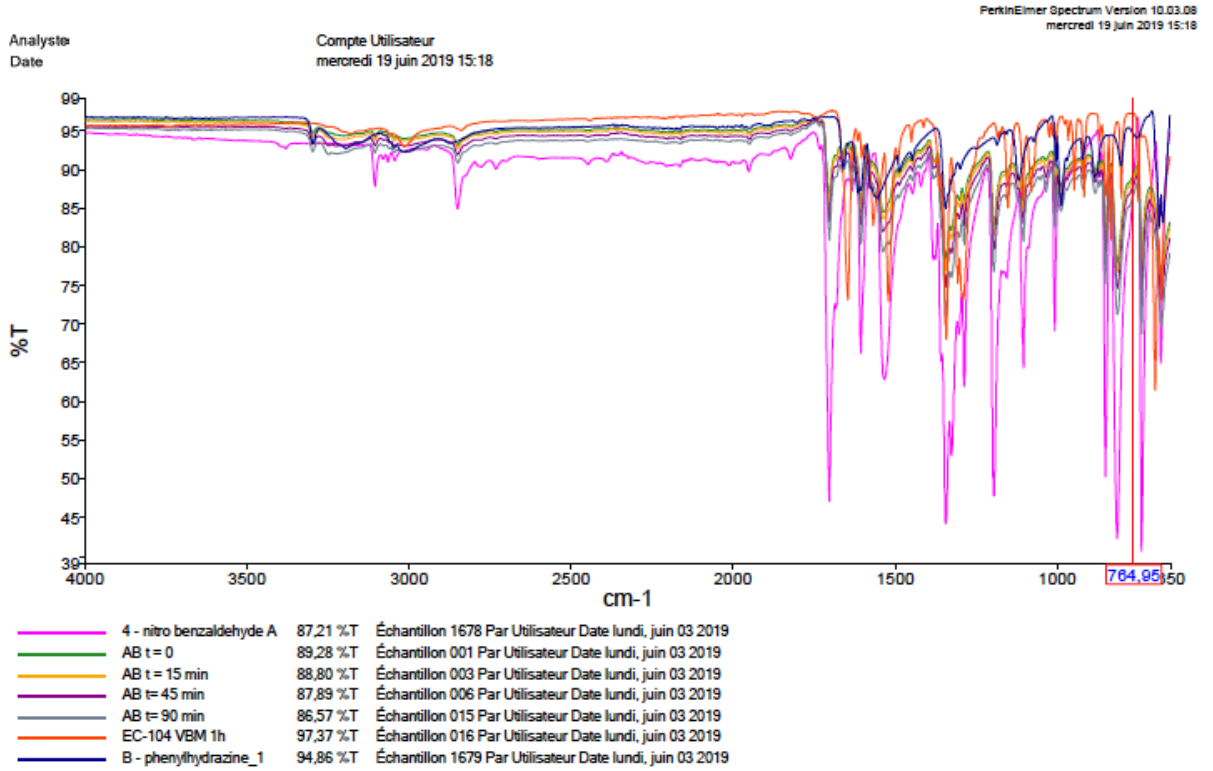


Figure S2:[5] Overlapping of selected IR spectra are here shown for visual clarity and simplicity of interpretation (Legend: **AB** refers to a stoichiometric mixture of the substrates *p*-nitrobenzaldehyde (**A**) and benzhydrazide (**B**) analysed over a period of 90 minutes; **EC-104** refers to an authentic sample of compound **1** prepared by vibrating ball mill).

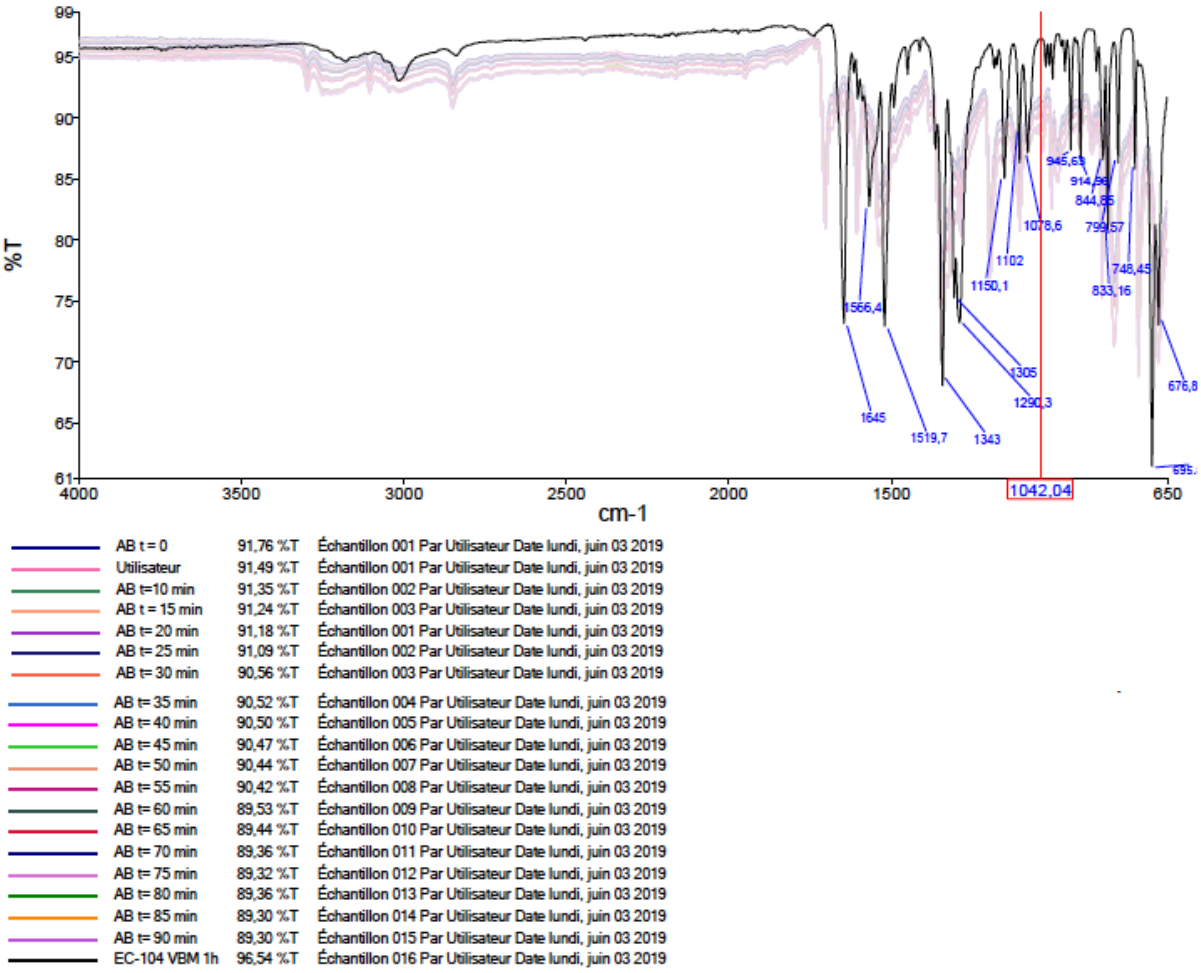
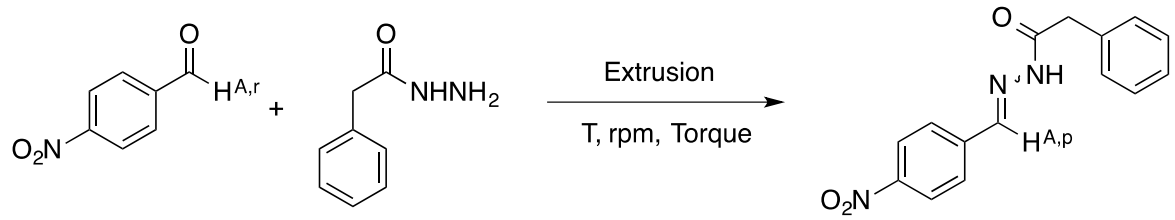


Figure S3:[5] The entire set of IR spectra recorded every 5 minutes is overlapped with the final product spectrum (used as reference). (Legend: **AB** refers to a stoichiometric mixture of the substrates *p*-nitrobenzaldehyde (**A**) and benzhydrazide (**B**) analysed over a period of 90 minutes; **EC-104** refers to an authentic sample of compound **1** prepared by vibrating ball mill).

Table S2: Selected data to optimize the preparation of *N*-acylhydrazone **2**[a,b] by extrusion.



a) Investigation of the temperature on the STY and E/Z ratio by extrusion.

Entry[a]	T (°C)	rpm	$H^{A,p}$ (*E*/*Z*)[b]	RCHO (%)[c]	STY[d,e]	$\delta(CH_2)$ (ppm) *E*/*Z*[b]
1	rt	55	41.2/58.8	90.0	n.d.	3.59/4.02
2	50	55	37.2/62.8	48.5	n.d.	3.59/4.02
3	75	55	41.0/59.0	2.1	n.d.	3.59/4.02
4	100	55	47.2/57.3	3.6	n.d.	3.59/4.02
5[f]	100	100	/	/	/	/
6	150	55	38.9/61.1	0	1.7 g/min	3.59/4.02
7	150	100	37.8/62.2	0	0.3 g/min	3.59/4.02

[a] Reaction scale: *p*-nitrobenzaldehyde, RCHO (5.00 g, 0.0331 mol), phenylacetic hydrazide (4.97 g, 0.0331 mol), the screw profile shown in Figure 1 was used; [b] The *E/Z* ratio was attributed on the basis of previous studies;[4, 6] [c] Residual amount of aldehyde was determined by comparing the ^{1}H NMR area of $H^{A,r}$C=O proton of *p*-nitrobenzaldehyde (at 10.16 ppm) to the area of protons N-NHC=O for both isomers (at 11.69 and 11.91 ppm respectively for the *E* and the *Z*-isomer). Legend: $H^{A,r}$ and $H^{A,p}$ indicate respectively the aldehyde proton in the reactant and the *N*-acylhydrazone proton in the product **2**); [d] STY = Space Time Yield, STY only really needs to be reported for the optimized process; [e] n.d. = not determined; [f] No product out of the extruder.

b) Investigation of the *N*-acylhydrazone bond formation as a function of temperature in neat conditions and in a molten phase,[7] without stirring. [a,b]

Entry[a]	T (°C)	t (h)	$H^{A,p}$ (*E*/*Z*)[b]	R-CHO (%)[c]	Yield (%)[d]	$\delta(CH_2)$ (ppm) *E*/*Z*[b]
1	100	1	37.5/62.5	84.7	n.d.	3.59/4.02
2	100	2	39.7/60.3	17.6	n.d.	3.59/4.02
3	150	1	41.2/58.8	0	n.d.	3.59/4.02
4	150	2	45.1/54.9	0	n.d.	3.59/4.02

[a] *p*-nitrobenzaldehyde (m.p. 103-106 °C), RCHO (10.0 g, 0.0662 mol) and phenylacetic hydrazide (9.94 g, 0.0662 mol, m.p. 115-116 °C) were weighed into a vial and heated in an oven without stirring; [b] The *E/Z* ratio was attributed on the basis of previously reported studies.[4,6] $H^{A,p}$ indicates the *N*-acylhydrazone proton in the product **2**); [c] Residual aldehyde (if any) determined by ^{1}H NMR spectroscopy; [c] n.d. = not determined, products were not isolated to determine yields.

c) Investigation of the *N*-acylhydrazone bond formation as a function of temperature in neat conditions and in a molten phase,[7] with stirring.[a,b]

Entry	T (°C)	t (h)	$H^{A,p}$ (*E*/*Z*)[b]	CHO (%)[c]	Yield (%)[d]	$\delta(CH_2)$ (ppm) *E*/*Z*[b]
1	100	1	40.3/59.7	10.6	n.d.	3.59/4.02
2	100	2	36.5/63.5	18	n.d.	3.59/4.02
3	150	1	41.5/58.5	3.1	n.d.	3.59/4.02
4	150	2	39.8/60.2	0	n.d.	3.59/4.02

[a] *p*-nitrobenzaldehyde, RCHO (2.5 g, 0.015 mol) and phenylacetic hydrazide (2.47 g, 0.015 mol) were weighed were weighed into a vial and heated in an oven with stirring; [b] The *E/Z* ratio was attributed on the basis of previously reported studies.[4,6] $H^{A,p}$ indicates the *N*-acylhydrazone proton in the product **2**); [c] Residual aldehyde (if any) determined by ^{1}H NMR spectroscopy; [c] n.d. = not determined, products were not isolated to determine yields.

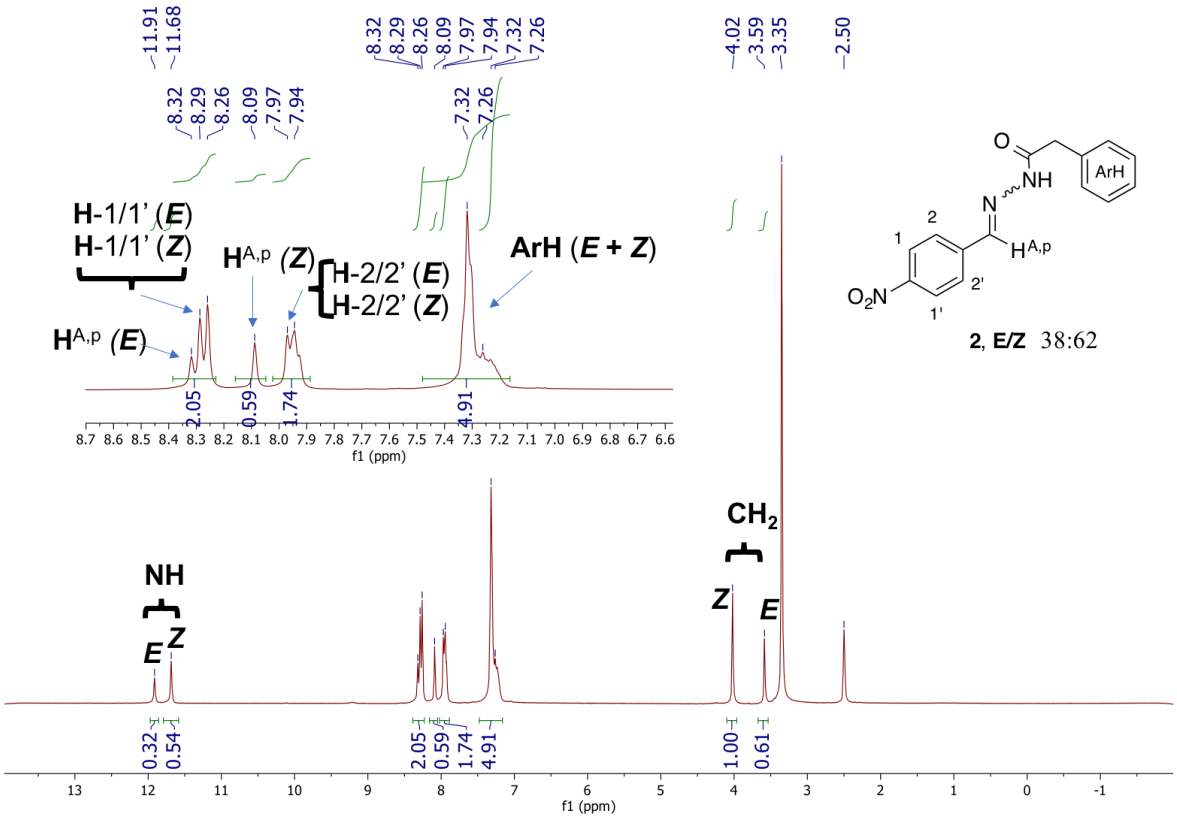


Figure S4. ^{1}H NMR spectrum of *N*-acylhydrazone **2** (E/Z mixture) prepared by extrusion (Table S2a, entry 7).

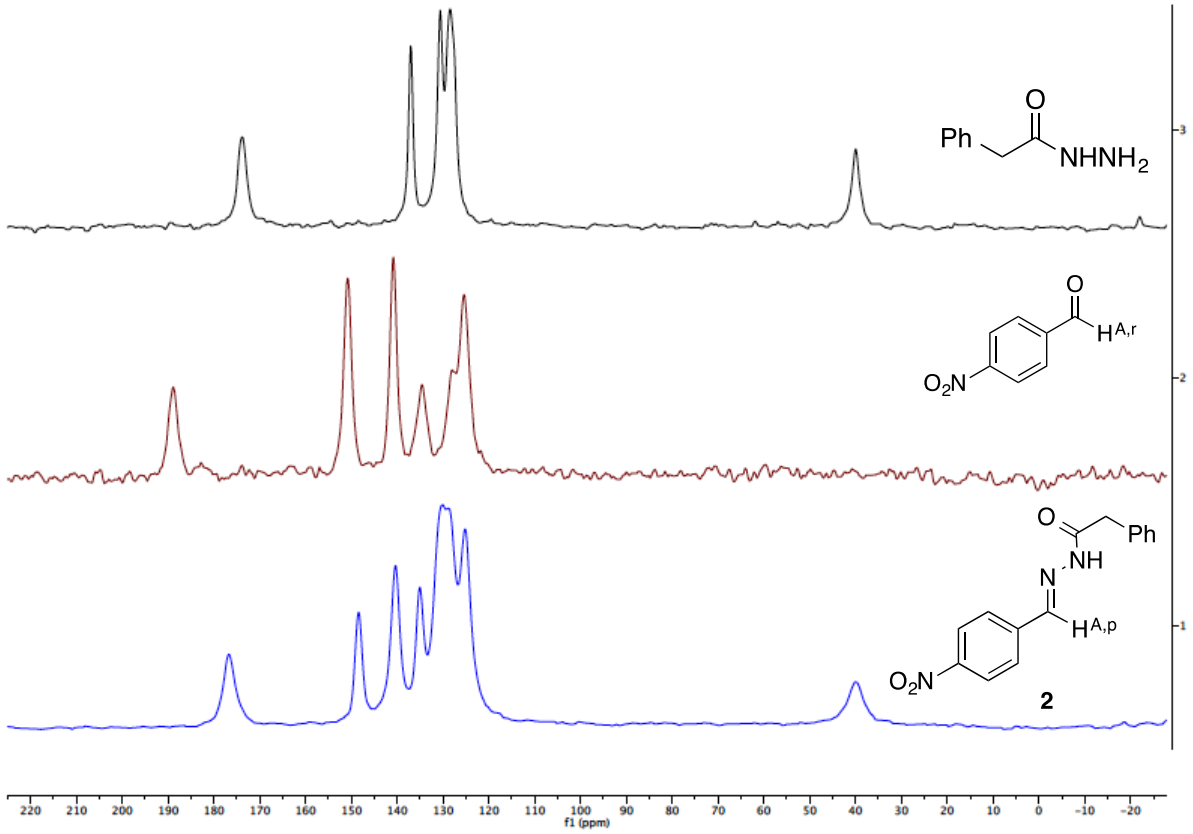
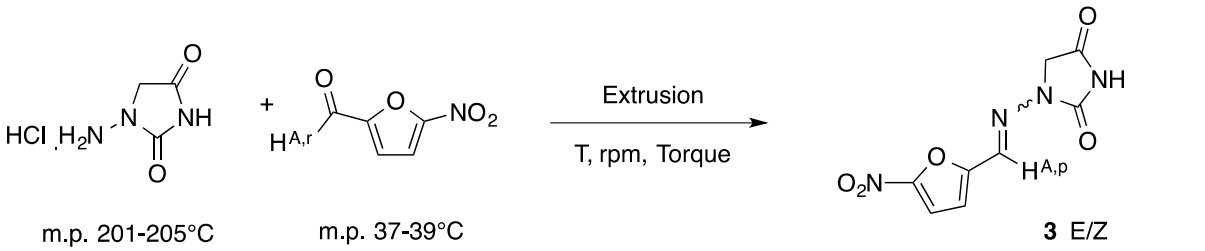


Figure S5. ^{13}C solid-state NMR spectra of reactants phenyl acetic hydrazide (black pattern), *p*-nitrobenzaldehyde (red pattern) *vs. N*-acylhydrazone **2** prepared by ball milling (blue pattern). Legend: $H^{A,r}$ and $H^{A,p}$ indicate respectively the aldehyde proton in the reactant and the *N*-acylhydrazone proton in the product **2**.

Table S3. Selected data to optimize the preparation of *N*-acylhydrazone **3**[a] (nitrofurantoin) by extrusion.



m.p. 201-205°C m.p. 37-39°C **3** E/Z

Nitrofurantoine **3** is the *E*-isomer

Entry[a,b]	**T (°C)**	**rpm**	**$H^{A,p}$ (*E*/*Z*)**[a]	**CHO (%)**	δ (NH) **(ppm) *E*[c]/Z**
1	rt	30-55[d]	100/0	0	11.43/n.d.[e]
2	rt	100	100/0	31	11.48/n.d.[e]
3	rt	250	100/0	36	11.48/n.d.[e]
4[f]	50	100	/	/	/
5[f]	50	250	/	/	/
6[f,g]	75	100	/[e]	/	/
7	100	250	50/50	0	11.44/11.24
8[h]	100	250	70/30	0	11.45/11.26

[a] Reaction scale : 1-aminohydantoin hydrochloride (5.0 g, 0.033 mol), 5-nitro-2-furaldehyde, RCHO (4,65 g, 0.033 mol). Legend: $H^{A,r}$ and $H^{A,p}$ indicate respectively the aldehyde proton in the reactant and the *N*-acylhydrazone proton in the product **3**); [b] Torque: 1.0 Nm, the screw profile (reverse screw) shown in Figure 2 was used except for Entry 1 (screw profile as in Figure 1 was used in this case); [c] The NH proton for the *E*-isomer is reported at 11.46 ppm;[1] [d] The speed was raised to 55 rpm after 1h reaction, because no product was coming out the extruder, The Space Time Yield (STY) is 0.23 g/min; [e] n.d. = not detected; [f] No product out of the extruder; [g] Sticky when feeding, dark brown powder at the end of the experiment, gaseous HCl smell; [h] Liquid-Assisted Grinding (LAG) with CH_3CN (2.5 mL).

Table S4. Additional Analyses on Entry 1, Table S3.

Entry[a,b]	Extruder segment	T (°C)	rpm	$H^{A,p}$ (*E*/*Z*)[a]	RCHO (%)	δ(NH) (ppm) *E*[c]
1	H1	rt	30-55[d]	100/0	0	11.43
2	H2	/	/	100/0	0	11.46
3	H3	/	/	100/0	0	11.47
4	H4	/	/	100/0	0	11.46
5	H5	/	/	100/0	0	11.46
6	H6	/	/	100/0	0	11.47

[a] Sampling across the barrel was done at the end of the reaction. Powders scratched out of the H2-H6 barrel sections were analyzed by ^{1}H NMR (DMSO-d_6). Reaction scale: 1-aminohydantoin hydrochloride (5.0 g, 0.033 mol), 5-nitro-2-furaldehyde, RCHO (4,65 g, 0.033 mol). Legend: $H^{A,r}$ and $H^{A,p}$ indicate respectively the aldehyde proton in the reactant and the *N*-acylhydrazone proton in the product **3**); [b] Torque: 1.0 Nm, the screw profile shown in Figure 1 was used; [c] The NH proton for the *E*-isomer is reported at 11.46 ppm;[1, 8] [d] The speed was raised to 55 rpm after 1h reaction, because no product was coming out the extruder.

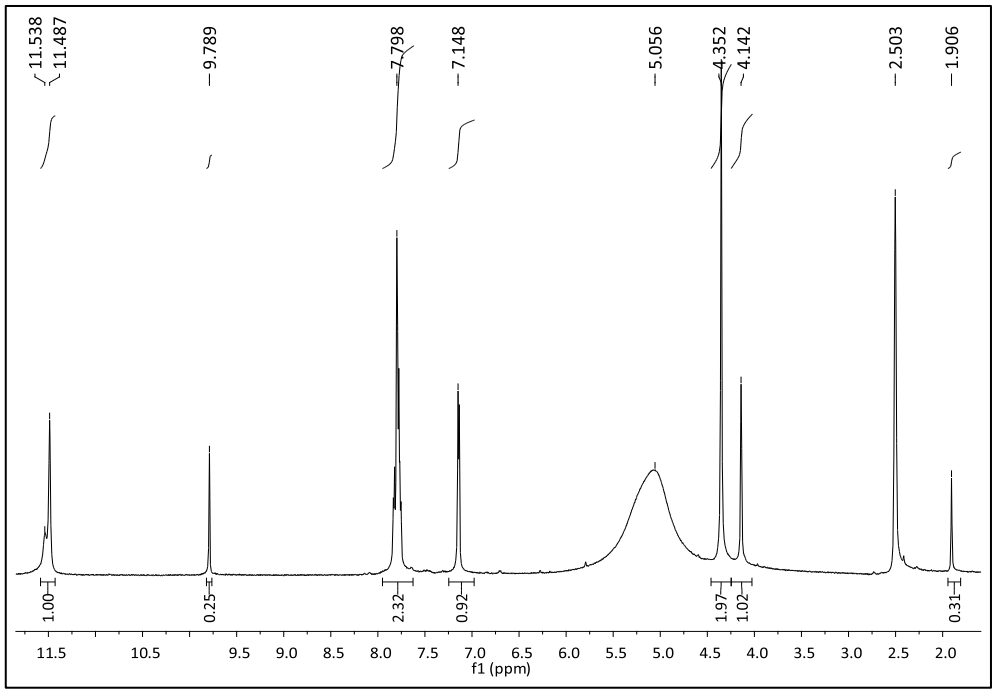


Figure S6. Investigation of the Preparation of nitrofurantoin **3** in solution, in an NMR tube.

1-aminohydantoin hydrochloride (10 mg, 0.06 mmol) and 5-nitro-2-furaldehyde, RCHO (9.3 mg, 0.06 mmol) were mixed in 0.7 mL of DMSO-d_6 and the NMR was recorder immediately after. The reaction in solution is quite fast with 34% conversion observed after ten minutes. The conversion was determined by comparing the area of the CH_2 proton of starting 1-aminohydantoin hydrochloride (at 4.14 ppm) to the corresponding protons of nitrofurantoin

3 (at 4.35 ppm).[1] However the reaction does not reach completion after 90 minutes, as further assessed by the kinetic studies reported in Table S5.

Together with the expected *E*-isomer (peak at 11.48 ppm for C=N-NH proton in nitrofurantoin, **3**),[1] the presence of a second peak was observed at 11.54 ppm, never observed when the reaction was performed in the solid state. It could possibly be the starting 1-aminohydrantoin hydrochloride (displaying a peak at 11.58 ppm in the reference spectrum) or a six-member ring structure stabilizing the *E*-isomer, due to intramolecular H-bonding between the imino hydrazone C-H group and the hydantoin C-2 carbonyl, as previously reported for similar hydrazone systems in solution[4] (Figure S7).

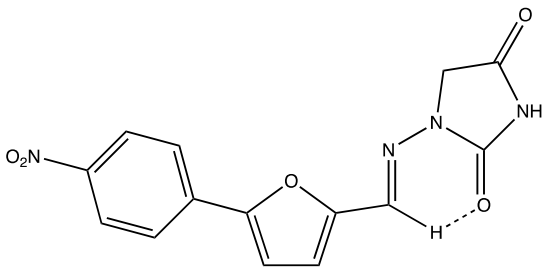


Figure S7. Hypothised six-member ring structure stabilized by intramolecular H-bonding, on the basis of previous reports.

Table S5. Kinetic studies by ^{1}H NMR in solution (DMSO-d_6, at room temperature) for nitrofurantoin **3.**

Kinetic investigation was performed during 90 minutes at room temperature. Acquisition of ^{1}H NMR spectrum each *ca.* 1.5 minutes.

Quantities: 1-aminohydantoin hydrochloride (10 mg, 0.066 mmol), 5-nitro-2-furaldehyde**,** RCHO (9.3 mg, 0.066 mmol) in DMSO-d_6 (0.7 mL).

Kinetic data extrapolated by ^{1}H NMR analyses.

Entry	t (min)	1-amino hydantoin hydrochloride (%)	RCHO (%)
1	0	13.5	9.9
2	1.5	10.6	8.2
3	3	9	7
4	4.5	7.8	6.5
5	6	6.5	5.8
6	7.5	4.7	5
7	9	4.3	5.3
8	11.5	4.3	4.7
9	13	4.3	3.4
10	14.5	3.4	4.2
11	16	2.7	2.5
12	17.5	3.6	2
13	20.5	2.7	2.5
14	23.5	2.7	2
15	26.5	2.7	1.8
16	29.5	2	1.8
17	32.5	1.5	1.8
18	38.5	1.5	1.8
19	41.5	0.5	1.8
20	53.5	0.5	1.8
21	59.5	*Ca.* 0.5	1.9
22	65.5	*Ca.* 0.5	1.8
23	71.5	*Ca.* 0.5	1.9
24	89.5	*Ca.* 0.5	1.9

The ^{1}H NMR spectra show a fast progression of the synthesis in solution, with residual traces of starting materials 1-amino hydantoin hydrochloride and aldehyde after 90 min. No isomerization reaction is observed (or detected, considering the low amount of product formed). For comparison, when using a ball mill (at 30 Hz or 450 rpm), full conversion of starting materials is always observed after 30 min (in a vibrating ball-mill) or 2h (in a planetary ball-mill or SPEX), with no isomerization (only *E*-isomer).[1]

Kinetic Studies by Solid state FT-IR (ATR device) for compound 3.

Sample preparation and analyses: each substrate was ground separately in an agate mortar. The specified quantities of solids were then gently mixed by hand in a glass tube. The background was recorded, then the powder was analyzed by FT-IR during 1 h:30 min, collecting a spectrum every 5 minutes (number of scan NS = 8). For comparison, IR spectra were recorded also for the substrates 1-aminohydantoin hydrochloride and 5-nitro-2-furaldehyde and for the final product nitrofurantoin **3** obtained as previously described by ball-milling (the sample was prepared by planetary ball-milling during 2h).[1] From the IR spectra, no reaction is observed at the solid state by contact or by applying a slight pressure. The spectra of the starting materials and product are given in ANNEX 1.

Quantities: 1-aminohydantoin hydrochloride (**D**, 10 mg, 0.066 mol), 5-nitro-2-furaldehyde, RCHO (**E**, 9.3 mg, 0.066 mol).

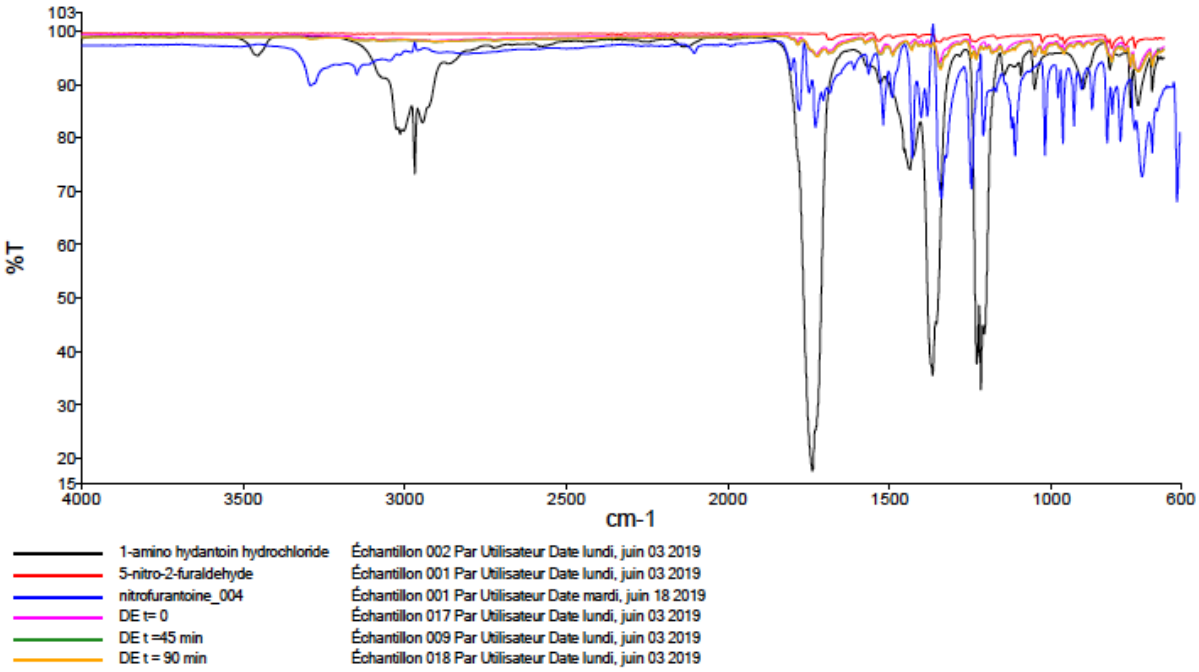


Figure S8:[5] Overlapping of selected IR spectra recorded at t = 0, 45 and 90 min, showing the substrates 1-aminohydantoin hydrochloride **D** and 5-nitro-2-furaldehyde **E**, and the product nitrofurantoin **3**. No reaction is occurring at the solid state during the kinetic study by simple contact of the reagents and by applying a constant pressure to the powders (Legend: **DE** refers to a stoichiometric mixture of the substrates 1-aminohydantoin hydrochloride **D** and 5-nitro-2-furaldehyde **E**, Nitrofurantoin refers to an authentic sample of compound **3** prepared by planetary ball mill).[1]

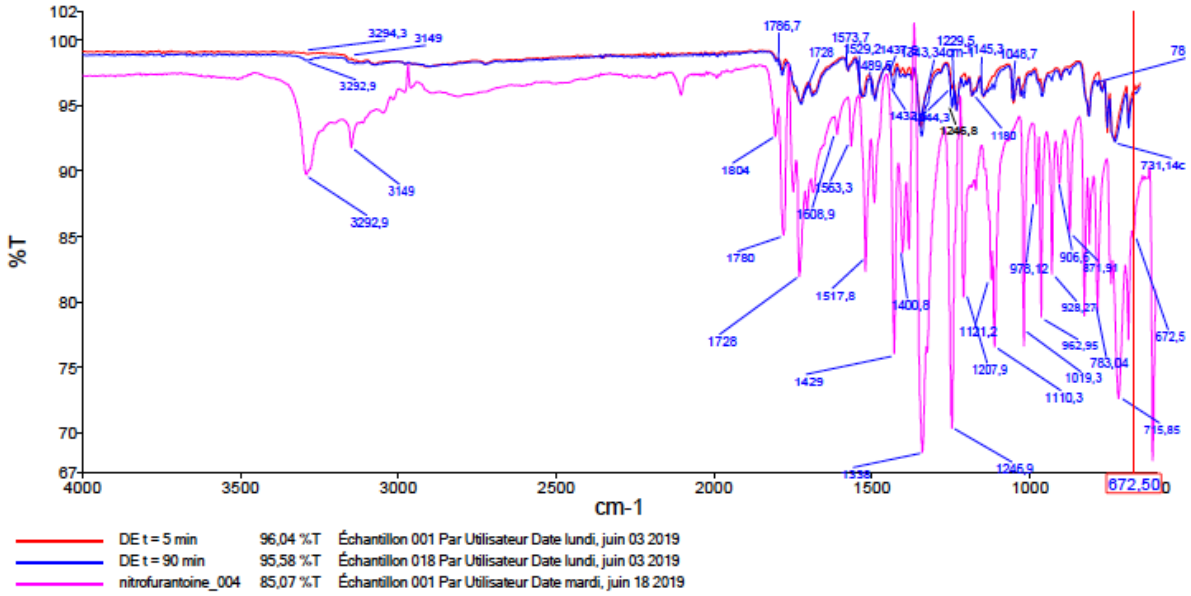


Figure S9:[5] Overlapping of selected IR spectra recorded at t = 5 min and t =90 min for the substrates 1-aminohydantoin hydrochloride **D** and 5-nitro-2-furaldehyde **E**, compared to the product nitrofurantoin **3**.[1] No reaction is occurring at the solid state during the kinetic study by simple contact of the reagents and by applying a constant pressure to the powders. (Legend: **DE** refers to a stoichiometric mixture of the substrates 1-aminohydantoin hydrochloride **D** and 5-nitro-2-furaldehyde **E**, Nitrofurantoin refers to an authentic sample of compound **3** prepared by planetary ball mill).[1]

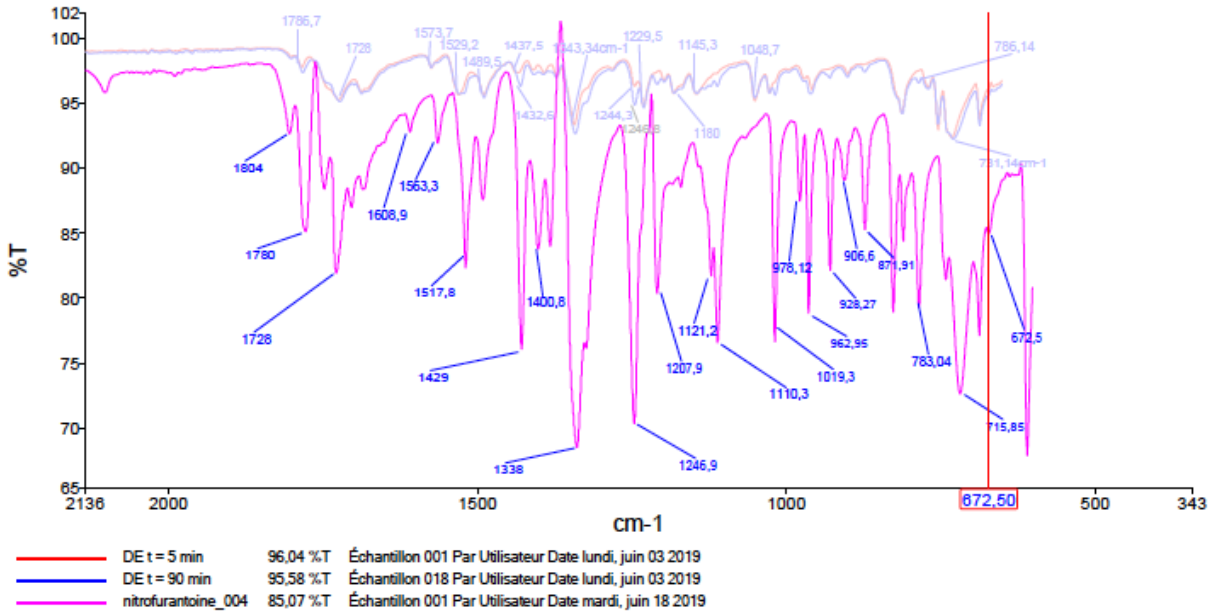


Figure S10:[5] Zoom from Figure S11 showing the overlapping of selected IR spectra recorded at t = 5 min and t =90 for the substrates 1-aminohydantoin hydrochloride **D** and 5-nitro-2-furaldehyde **E**, compared to the product nitrofurantoin **3**.[1] (Legend: **DE** (Legend: **DE** refers to a stoichiometric mixture of the substrates 1-aminohydantoin hydrochloride **D** and 5-nitro-2-furaldehyde **E**, Nitrofurantoin refers to an authentic sample of compound **3** prepared by planetary ball mill).[1]

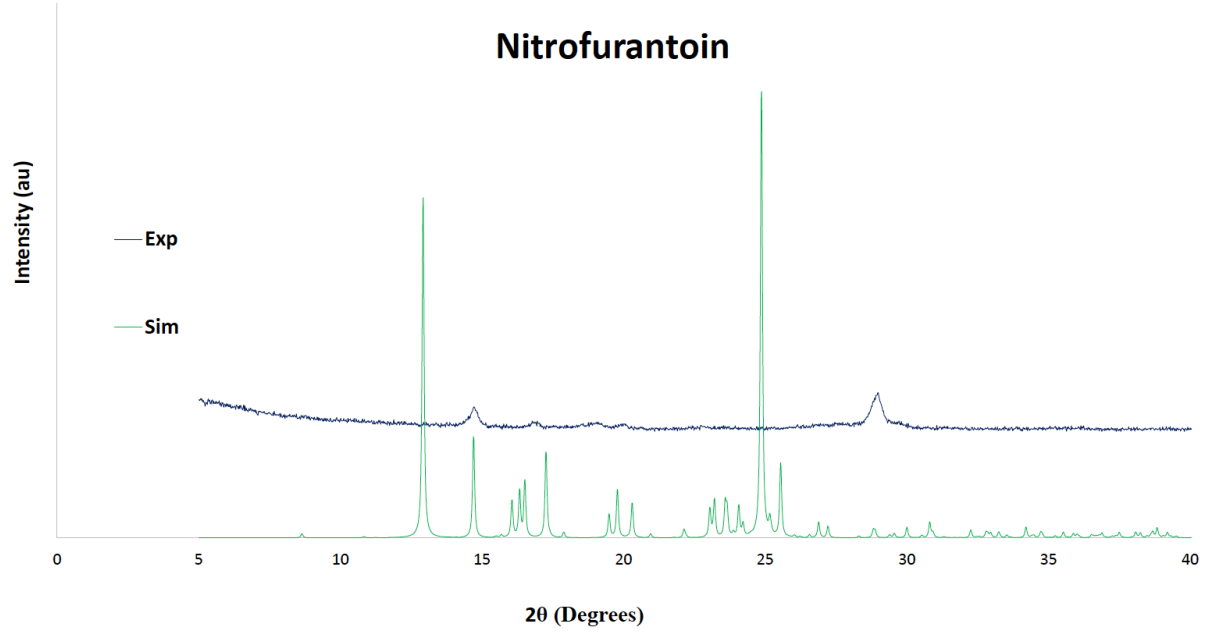


Figure S11. PXRD pattern of Nitrofurantoin **3** obtained by extrusion without post-synthetic treatment. The experimental PXRD pattern (in blue) shows that the sample is largely amorphous,[1] and no correlation is possible with the simulated pattern (LABJON, green line).

Kinetic Studies by Solid state ^{13}C NMR for compound 3.

Kinetic in the solid state at room temperature during 2h. ^{13}C NMR solid state spectra of substrates 1-aminohydantoin hydrochloride and 5-nitro-2-furaldehyde were recorded separately. A stoichiometric solid mixture of 1-aminohydantoin hydrochloride (10 mg, 0.066 mmol) and 5-nitro-2-furaldehyde (9.3 mg, 0.066 mmol) was also analysed by solid state ^{13}C NMR at room temperature after 2 h and the spectrum compared with the ^{13}C NMR (recorded in solution and used as reference)[1] of the final product nitrofurantoin **3**. No reaction occurs by simple contact of the reactants. The absence of compound **3** is also confirmed by comparison with the ^{13}C solid state NMR spectra illustrated in Figure 4.

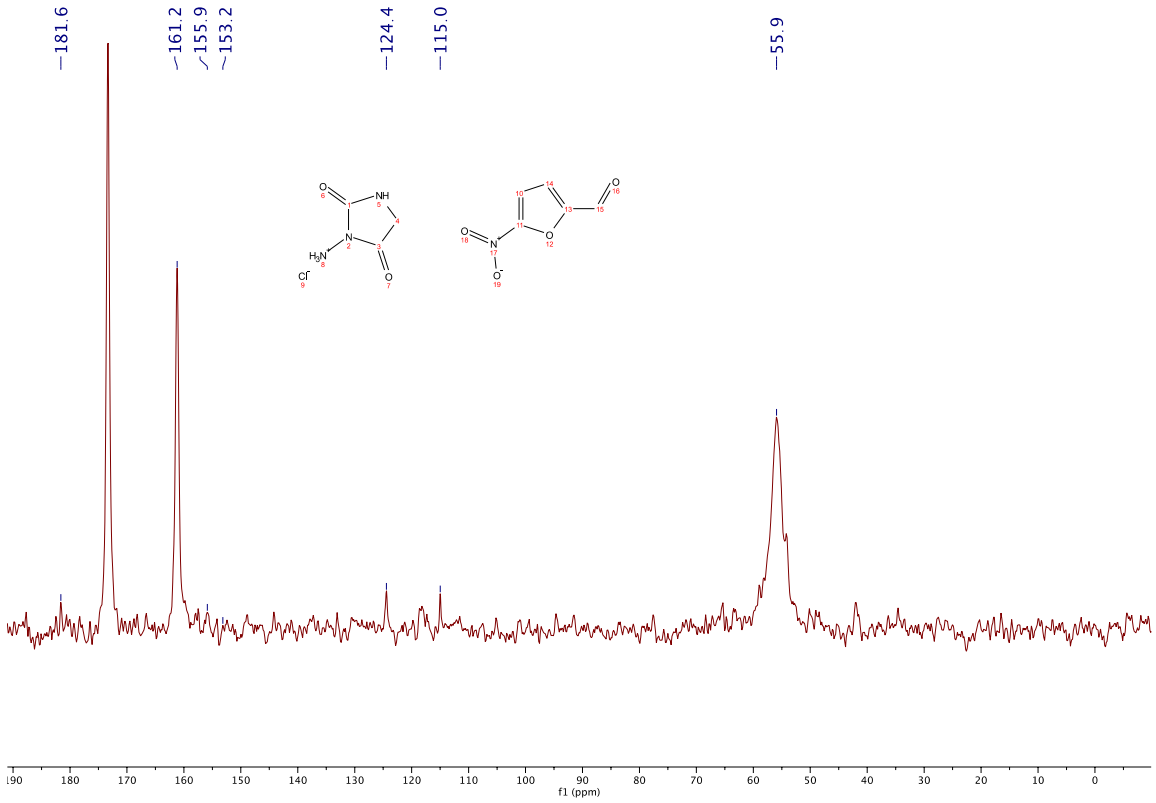
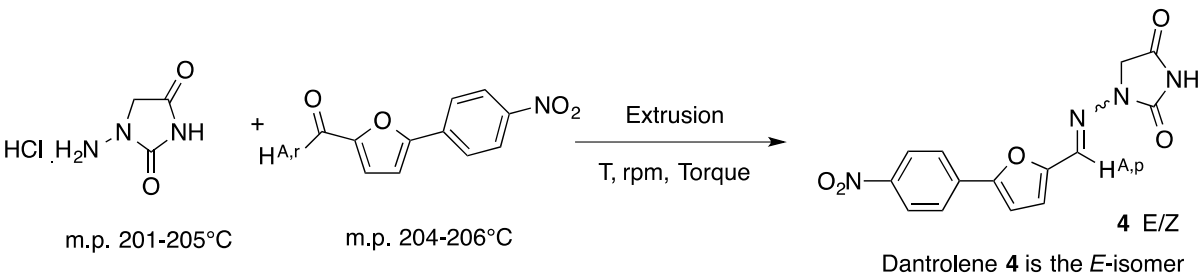


Figure S12. Solid state ^{13}C NMR of a stoichiometric mixture 1-aminohydantoin hydrochloride and 5-nitro-2-furaldehyde after 2h at room temperature.

Table S6. Selected data to optimize the preparation of *N*-acylhydrazone **4**[a] (dantrolene) by extrusion.



m.p. 201-205°C m.p. 204-206°C

Dantrolene **4** is the *E*-isomer

Entry[a,b]	T (°C)	Rpm	$H^{A,p}$ (*E/Z*)[a]	RCHO (%)	δ(C=NNH)**(ppm)** *E*[c]/*Z*
1	rt	10	100/0	16	11.33/n.d.[d]
2	rt	20	100/0	22	11.33/n.d.[d]
3	rt	30	100/0	13	11.34/n.d.[d]
4	rt	100	100/0	26	11.33/n.d.[d]
5	rt	250	43/57	48	11.33/11.14

[a] Reaction scale: 1-aminohydantoin hydrochloride (5.0 g, 0.033 mol) and 5-(4-nitrophenyl)furfural**,** RCHO (7.16 g, 0.033 mol). Legend: $H^{A,r}$ and $H^{A,p}$ indicate respectively the aldehyde proton in the reactant and the *N*-acylhydrazone proton in the product **4**); [b] Torque: 1.0 Nm, the screw profile shown in Figure 1 was used; [c] The C=NNH proton for the *E*-isomer is reported at 11.37 ppm;[1] [d] n.d. = not detected.

Table S7. Selected data to optimize the preparation of *N*-acylhydrazone **4**[a] (dantrolene) by extrusion and comparison of the ^{1}H NMR analyses of the extrudates (Figure S12) .

			δ(C=NNH) **(ppm)** (relative ratio)				
Entry[a]	**T (°C)**	**rpm**[b]	**11.05**[c]	**11.29**[c]	**11.34**[d]	**11.41**[c]	**RCHO (%)**
D10	rt	10	69.1	/	30.9	/	42.4
D30	rt	30	/	30.1	69.9	/	28.8
D60	rt	60	/	33.8	66.2	/	29.4
D100	rt	100	/	/	61.7	38.3	16.2
D150	rt	150	/	/	100	/	22.3
D250	rt	250	/	49.3	50.7	/	20.8

[a] Reaction scale : 1-aminohydantoin hydrochloride (5.0 g, 0.033 mol), 5-(4-nitrophenyl)furfural, RCHO (7.16 g, 0.033 mol); [b] Torque: 1.0 Nm, the screw profile shown in Figure 2 was used; [c] These signals were never observed during the kinetic studies in solution by NMR in DMSO-d_6. Only an "*almost invisible"* evidence of peak at 11.41 *ppm* is detected by ^{1}H NMR in DMSO-d_6 after 110 min (*c.f.* Table S8) . The presence of starting 1-aminohydantoin hydrochloride is excluded on the basis of NMR data (*c.f.* ^{1}H NMR of substrate 1-aminohydantoin hydrochloride in DMSO-d_6 in ANNEX 1); [d] This signal corresponds to the final product dantrolene **4** (*E*-geometry)[1] and it is in agreement with the data obtained when performing the kinetic studies by NMR in solution. The C=NNH proton for the *E*-isomer is reported at 11.37 ppm.[1]

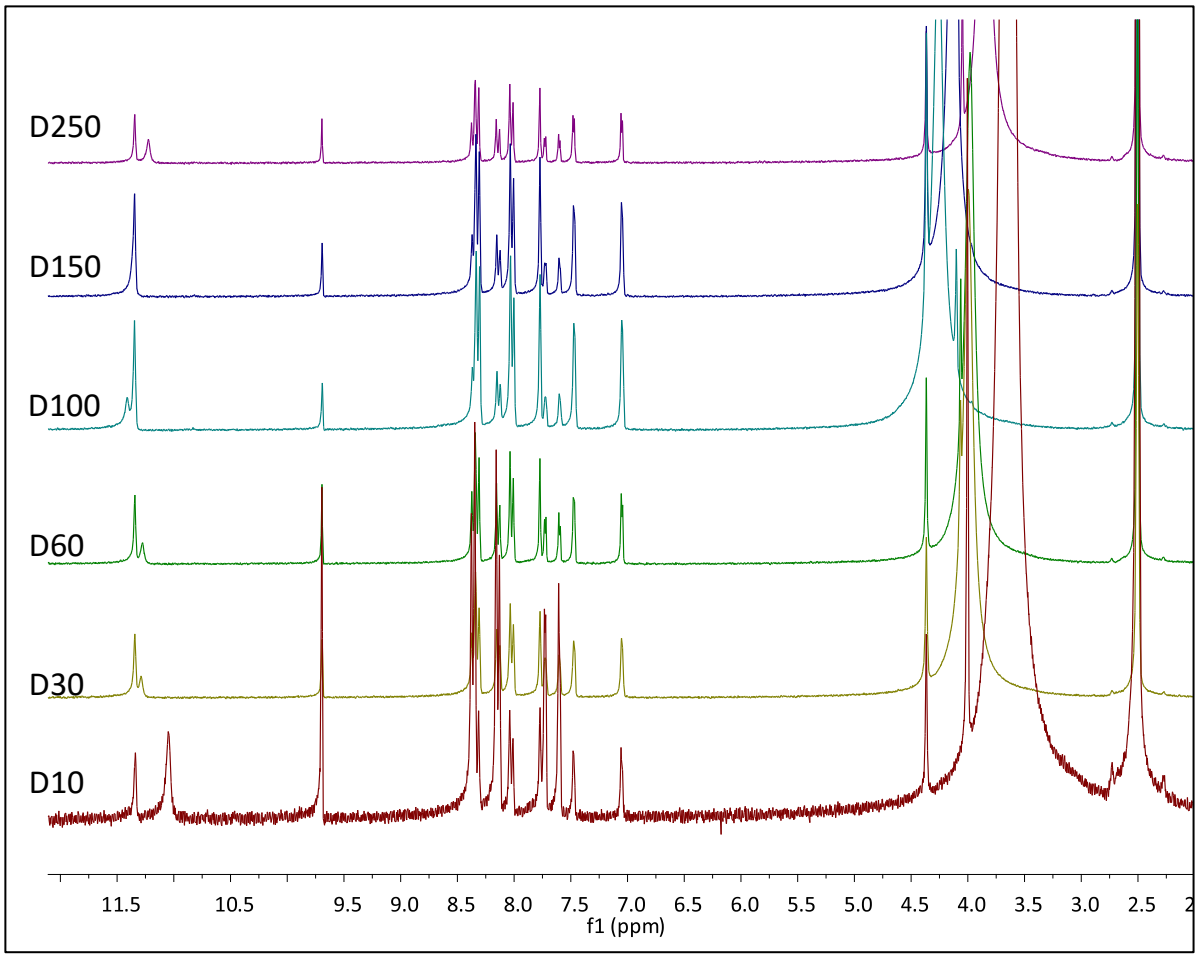


Figure S13. Comparison of the extrudates prepared in Table S7. ^{1}H NMR spectra in d^{6}-DMSO.

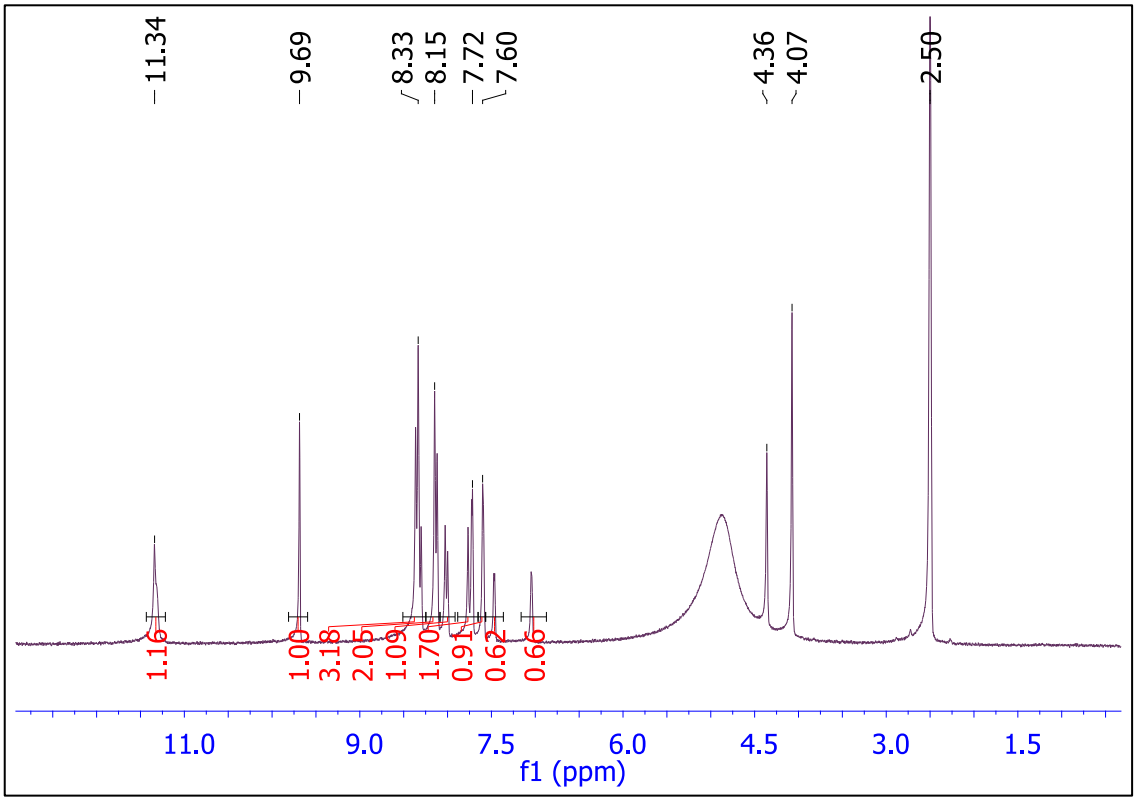


Figure S14. Preparation of *N*-acylhydrazone **4** in an NMR tube. ^{1}H NMR kinetic studies in solution (room temperature in DMSO-d_6) were performed. *Quantities:* 1-aminohydantoin hydrochloride (10 mg, 0.066 mol), and 5-(4-nitrophenyl)furfural (15.0 mg, 0.066 mol) in DMSO-d_6 (0.7 mL). Acquisition of ^{1}H NMR spectrum after *ca.* 5 minutes. The reaction in solution is quite fast and dantrolene **4** is formed almost immediately. However, the reaction does not reach completion after 90 minutes, as further assessed by the kinetic studies reported in Table S8.

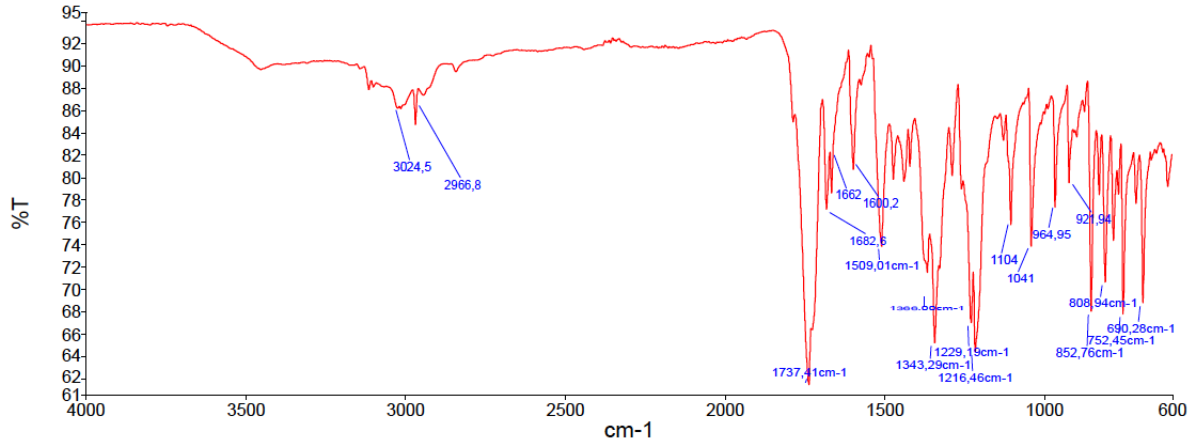


Figure S15. FT-IR of extrudate D150 (as per Table S7, for Dantrolene **4** preparation).

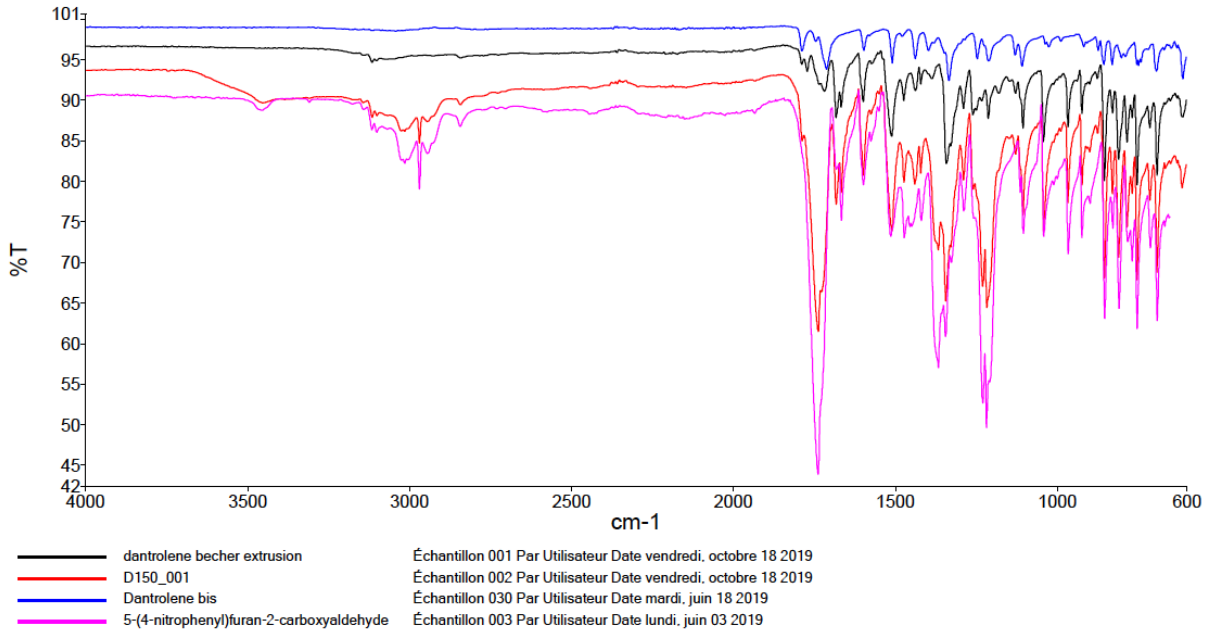


Figure S16.[5] Comparative data for Dantrolene **4**: a) collected after extrusion (black pattern), b) prepared at room temperature at 150 rpm (see Table S7, entry D150) (red pattern), c) prepared by ball-milling[1] and used as reference (blue pattern) and d) reference for starting RCHO (purple pattern).

Kinetic Studies by Solid state FT-IR (ATR device) for compound 4.

Sample preparation and analyses: each substrate was ground in an agate mortar. The specified quantities of solids were then gently mixed by hand in a glass tube. The background was recorded, then the powder was analyzed by FT-IR during 150 min, collecting a spectrum every 5 minutes (number of scan NS = 8). For comparison, FT-IR spectra were recorded also for the substrates 1-aminohydantoin hydrochloride and 5-(4-nitrophenyl)furfural and for the final product dantrolene **4**, obtained as previously described by ball-milling (the sample was prepared by planetary ball-milling during 2h).[1] EC-146-9, sample prepared by planetary ball-mill during 2h). From the IR spectra, no reaction is observed at the solid state by contact or by applying a slight pressure. The FT-IR spectra of starting materials and product are given in ANNEX 1.

Quantities: 1-aminohydantoin hydrochloride (**D,** 10 mg, 0.066 mol), 5-(4-nitrophenyl)furfural (**E,** 14.3 mg, 0.066 mol).

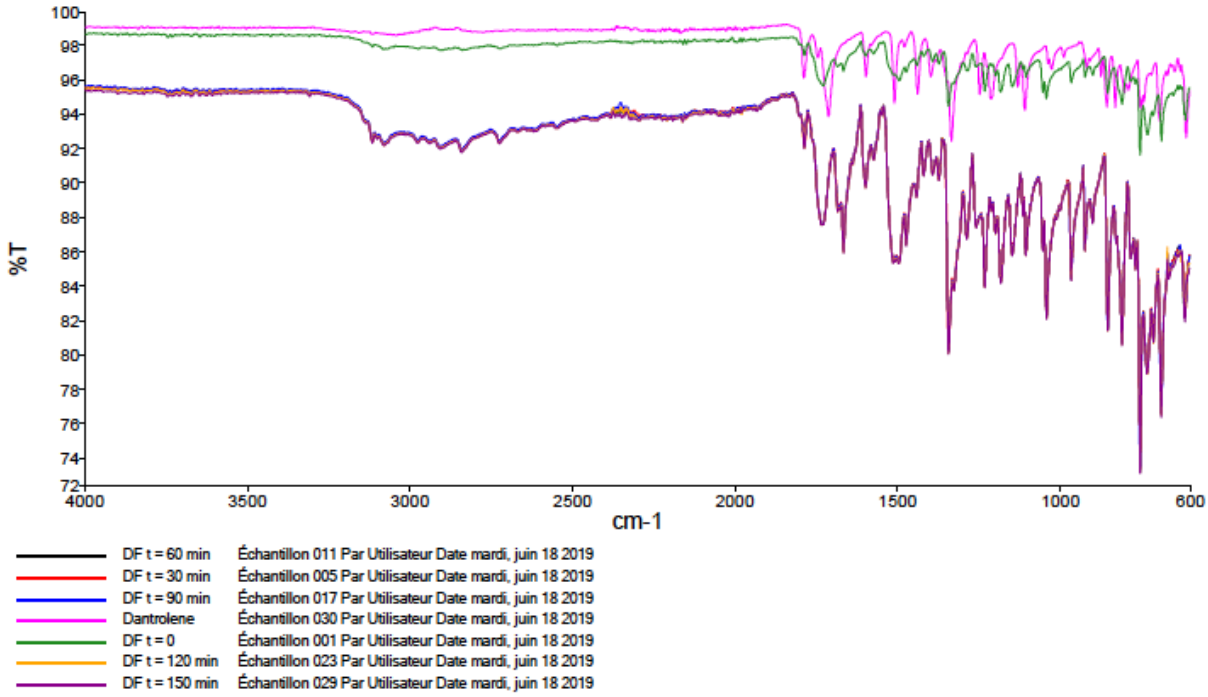
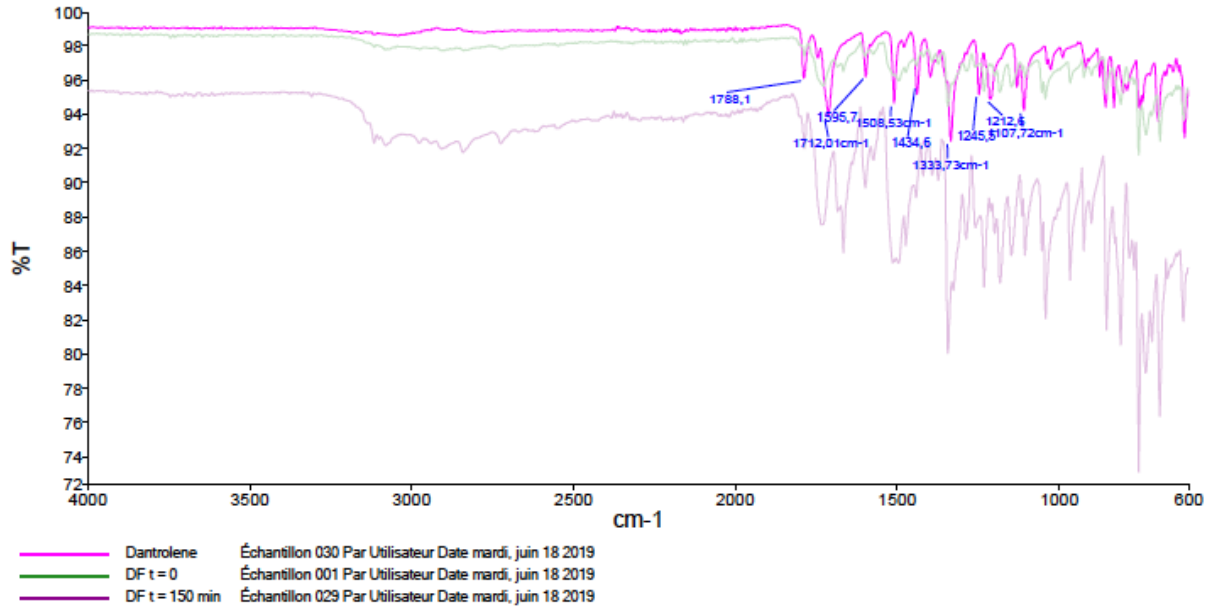


Figure S17:[5] Overlapping of selected IR spectra recorded at t = 0, 30, 60, 90, 120 and 150 min, showing the substrates 1-aminohydantoin hydrochloride (**D**) and 5-(4-nitrophenyl)furfural, (**F**) and the product dantrolene **4**. No reaction is occurring by simple contact of the reagents by applying a constant pressure. (Legend: **DF** refers to a stoichiometric mixture of the substrates 1-aminohydantoin hydrochloride (**D**) and 5-(4-nitrophenyl)furfural, (**F**) analysed over a period of 150 min; Dantrolene refers to an authentic sample of compound **4** prepared by planetary ball mill[1]).

- Full spectrum



- Zoom view in the finger print zone

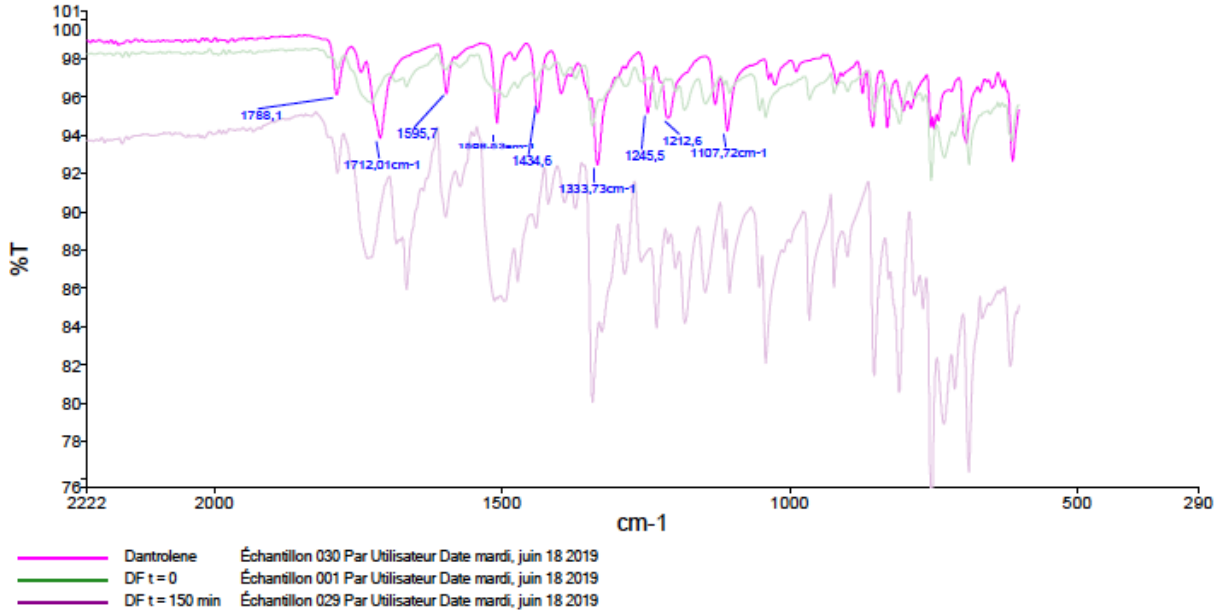


Figure S18:[5] Overlapping of selected spectra recorded at t = 0 and 150 min, showing the substrates 1-aminohydantoin hydrochloride (**D**) and 5-(4-nitrophenyl)furfural (**F**), and the product dantrolene **4**. No reaction is occurring by simple contact of the reagents by applying a constant pressure. (Legend: **DF** refers to a stoichiometric mixture of the substrates 1-aminohydantoin hydrochloride (**D**) and 5-(4-nitrophenyl)furfural, (**F**) analysed over a period of 150 min; Dantrolene refers to an authentic sample of compound **4** prepared by planetary ball mill[1]).

Table S8. Kinetic studies by ^{1}H NMR in solution (DMSO-d_6, at room temperature) for dantrolene **4.**

Kinetic investigation was performed during 150 minutes at room temperature. Acquisition of ^{1}H NMR spectrum each *ca.* 2.2 minutes.

Quantities: 1-aminohydantoin hydrochloride (10 mg, 0.066 mmol), 5-(4-nitrophenyl)furfural**,** RCHO (14.3 mg, 0.066 mmol) in DMSO-d_6 (0.7 mL).

Kinetic data extrapolated by ^{1}H NMR analyses.

Entry	t (min)	1-amino hydantoin hydrochloride (%)	RCHO
1	0	14.9	30
2	4	9	25
3	8	6.1	21
4	13	4.3	21
5	21	2.4	19
6	30	2.4	17.7
7	40	0.5	17.6
8	50	*ca.* 0.5	18
9	70	Traces	16.3
10	90	0	16.3
11	110	0	15
12	130	0	15
13	150	0	17

The ^{1}H NMR spectra show a fast progression of the synthesis in solution, with residual traces of aldehyde after 150 min. No isomerization reaction is observed (or detected, considering the low amount of product formed). For comparison, when using a ball mill (at 30 Hz or 450 rpm), full conversion of starting materials is always observed after 2h (in a planetary ball-mill or SPEX), with no isomerization (only *E*-isomer).[1]

Kinetic Studies by Solid state ^{13}C NMR for compound 4.

Kinetic in the solid state at room temperature during 2h. ^{13}C NMR solid state spectra of substrates 1-aminohydantoin hydrochloride and 5-(4-nitrophenyl)furfural were recorded separately. A stoichiometric solid mixture of 1-aminohydantoin hydrochloride (10 mg, 0.066 mmol) and 5-(4-nitrophenyl)furfural (14.3 mg, 0.066 mmol) was also analysed by solid state ^{13}C NMR at room temperature after 2 h and the spectrum compared with the ^{13}C NMR (recorded in solution and used as reference)[1] of the final product dantrolene **4**. No reaction occurs by simple contact of the reactants.

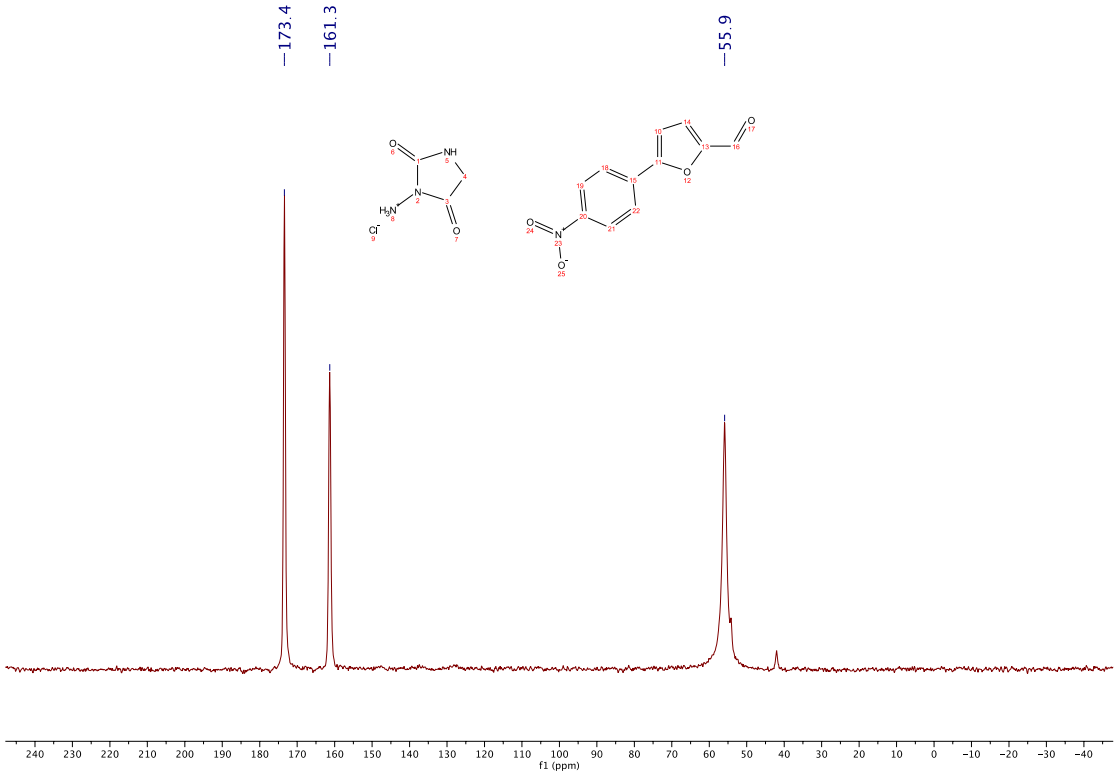


Figure S19. Solid state ^{13}C NMR of a stoichiometric mixture 1-aminohydantoin hydrochloride and 5-(4-nitrophenyl)furfural after 2h at room temperature.

ANNEX 1. FT-IR Reference spectra of starting materials and final products **1-4**.[5]

Acquisition conditions: background, then NS = 8. Powders were ground before analyses.

Figure S20. FT-IR of substrate **4-nitrobenzaldehyde.**

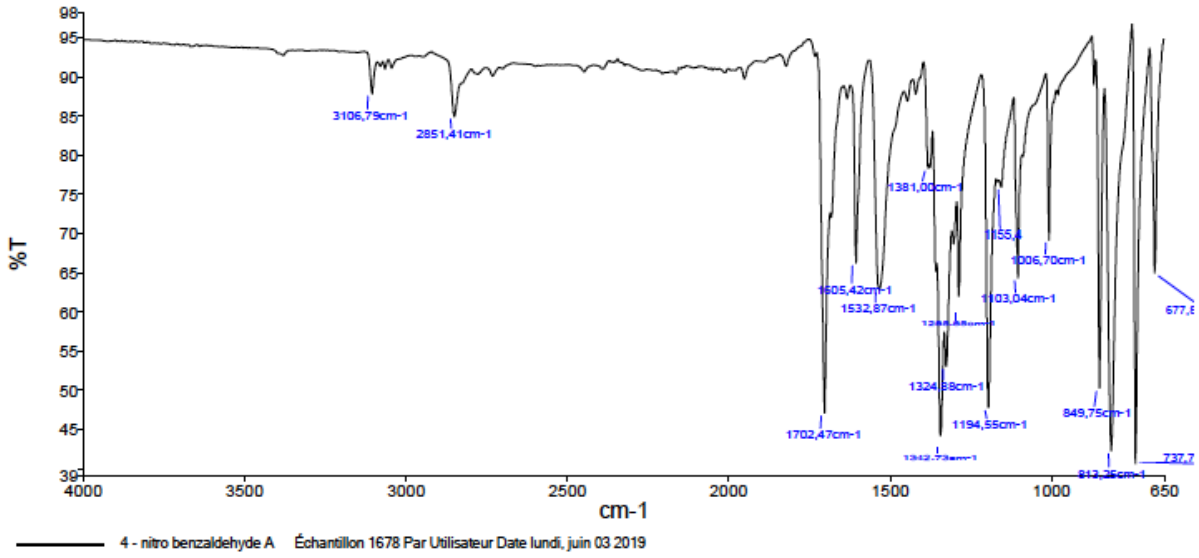


Figure S21. FT-IR of substrate: **phenylhydrazide**

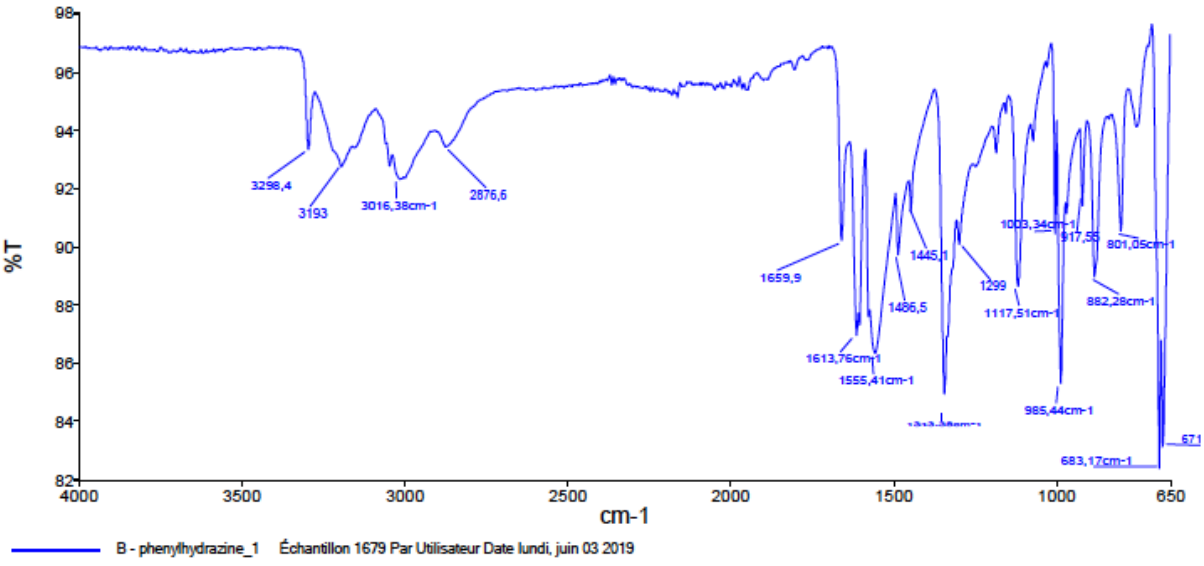


Figure S22. FT-IR of compound **1** (prepared by vibrating ball-mill).

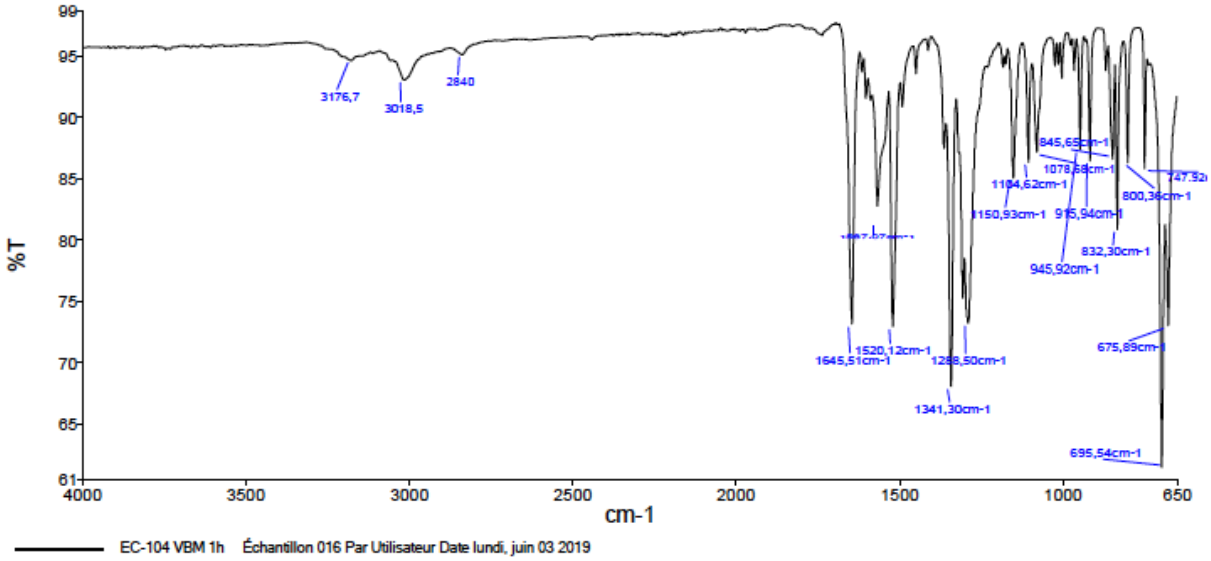


Figure S23. FT-IR of compound **2** (Legend: **AC** is referred to compound **2**).

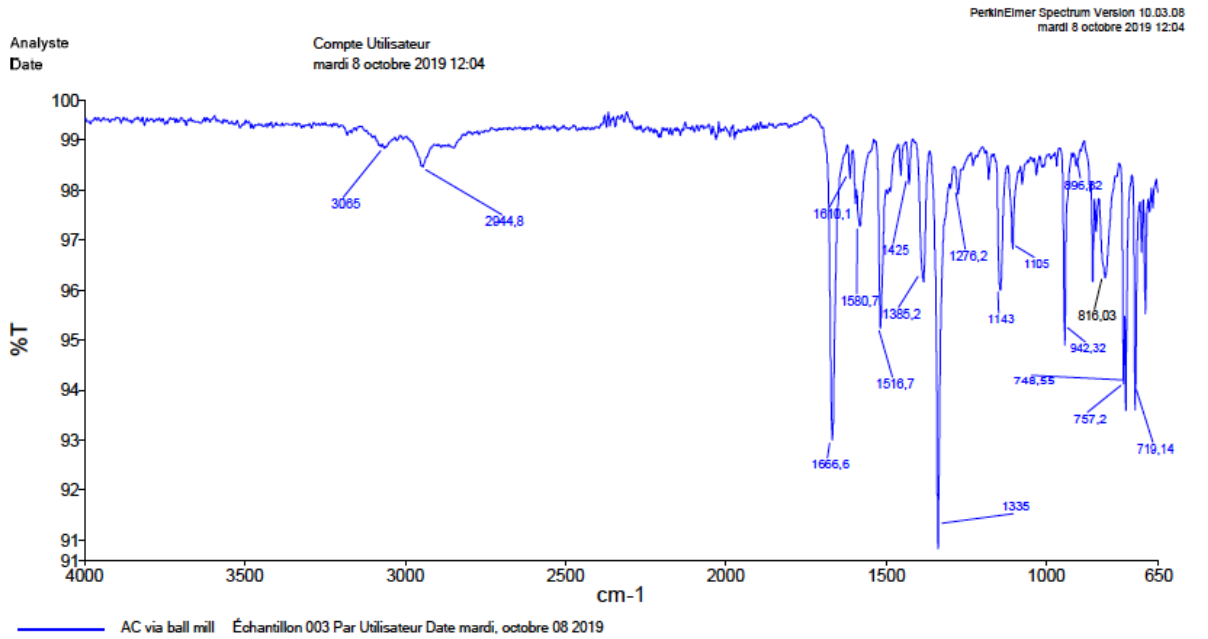


Figure S24. FT-IR of substrate **1-amino hydantoin hydrochloride.**

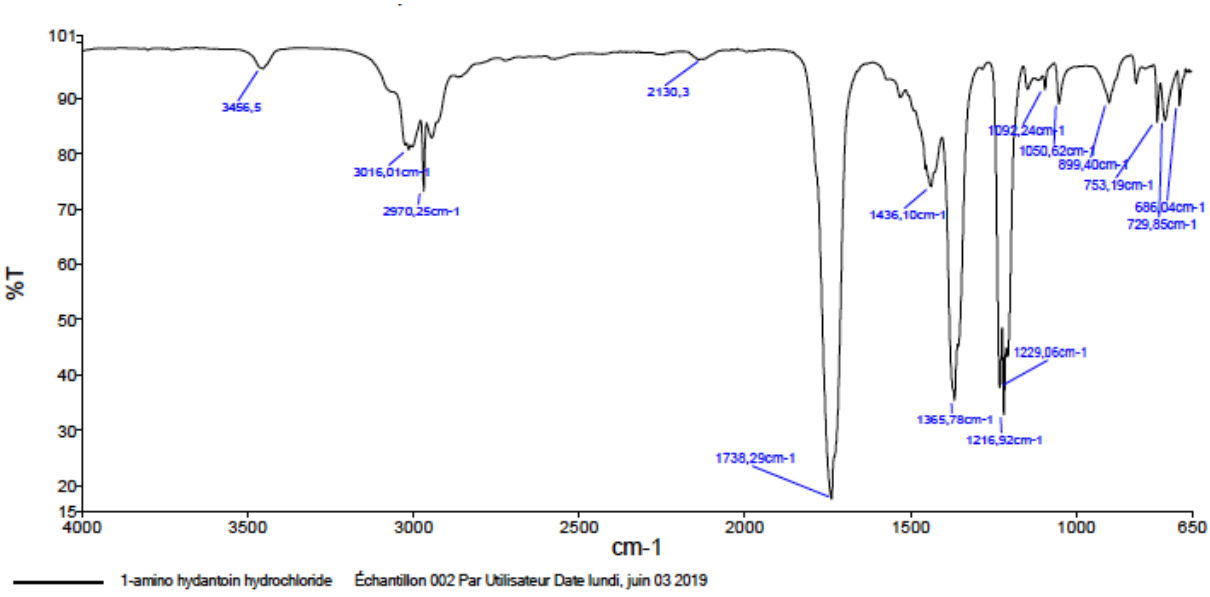


Figure S25. FT-IR of substrate **5-nitro-2-furaldehyde**

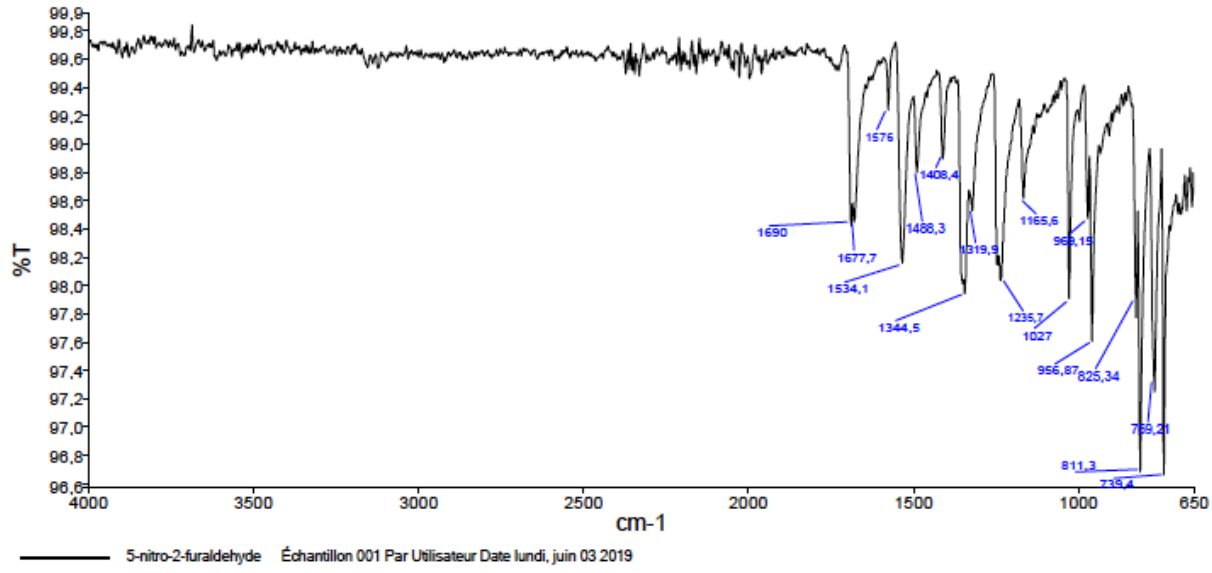


Figure S26. FT-IR of authentic sample of Nitrofurantoin 3 (prepared by planetary ball-mill).[1]

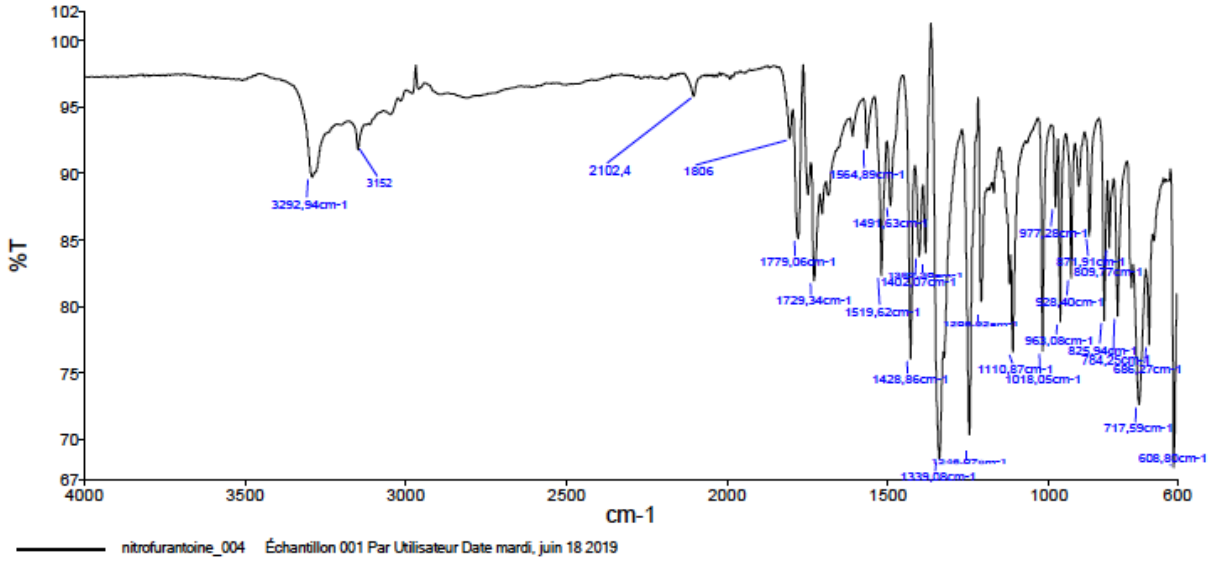


Figure S27. FT-IR of Nitrofurantoin 3 (prepared by extrusion).

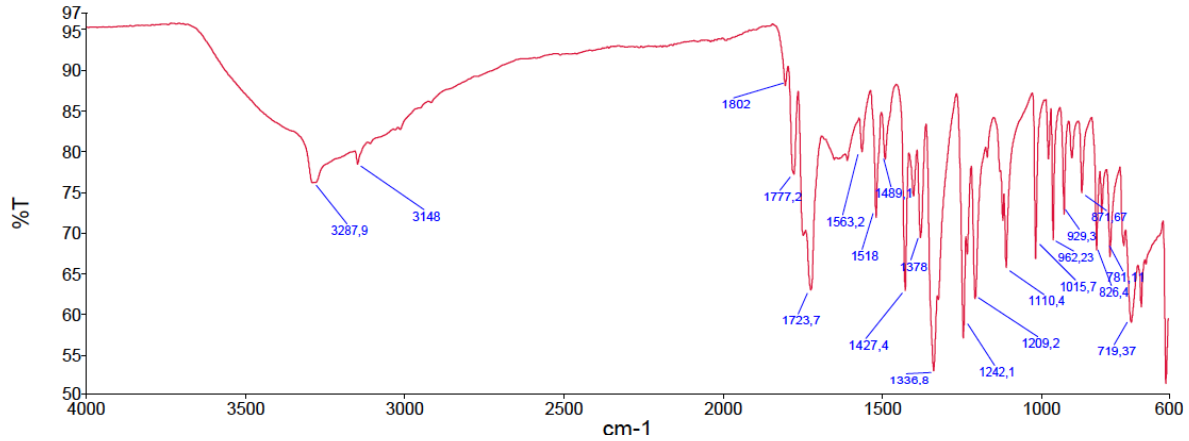


Figure S28. FT-IR of substrate **5-(4-nitrophenyl)furan-2-carboxyaldehyde.**

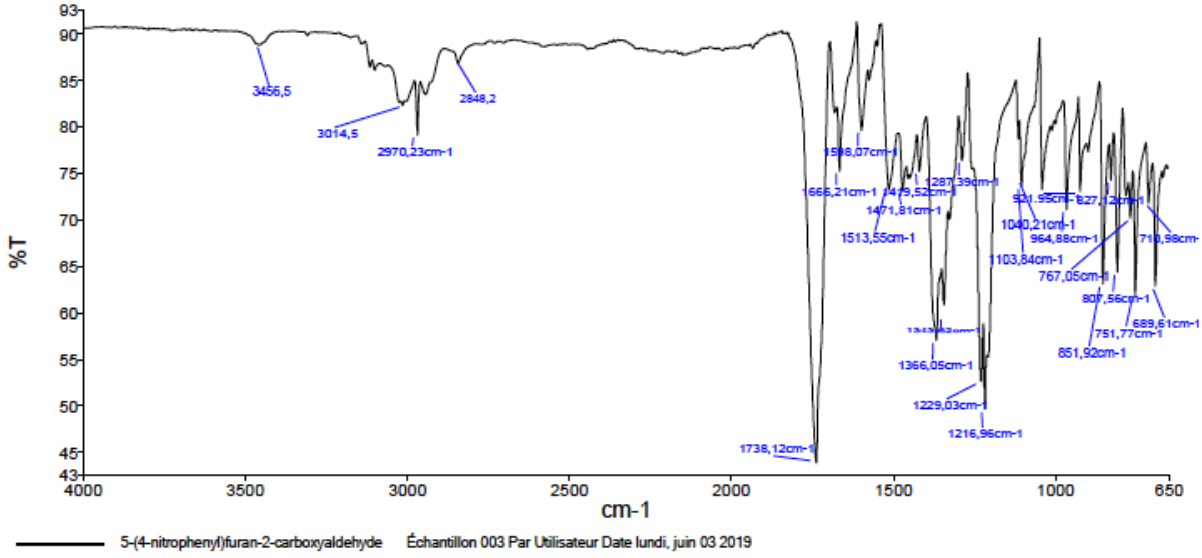
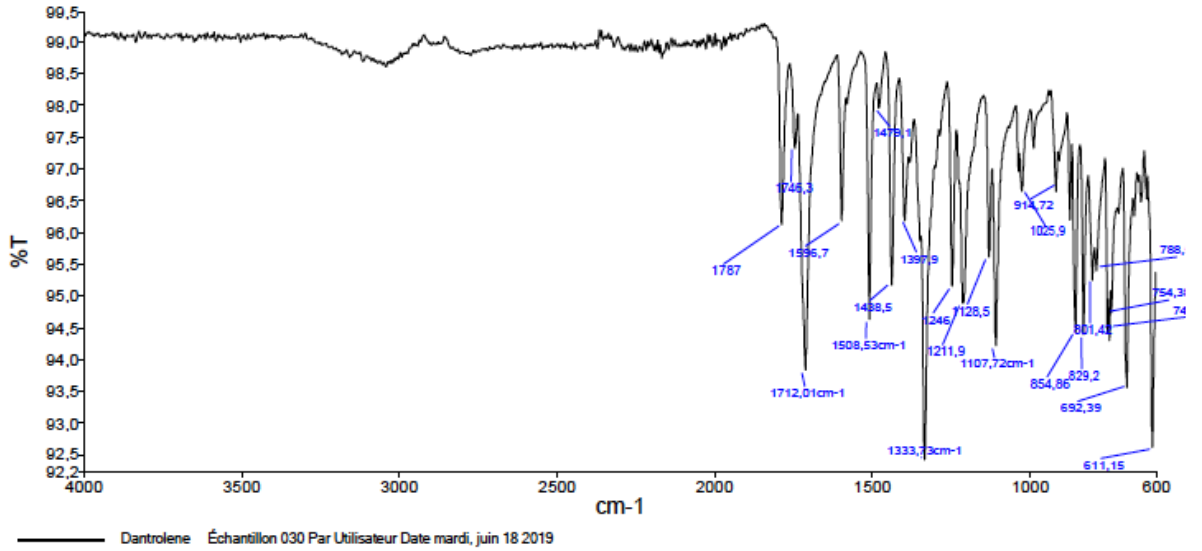


Figure S29. FT-IR of authentic sample of Dantrolene 4 (prepared by planetary ball-mill).[1]

a) Full spectrum



b) ZOOM in finger print zone.

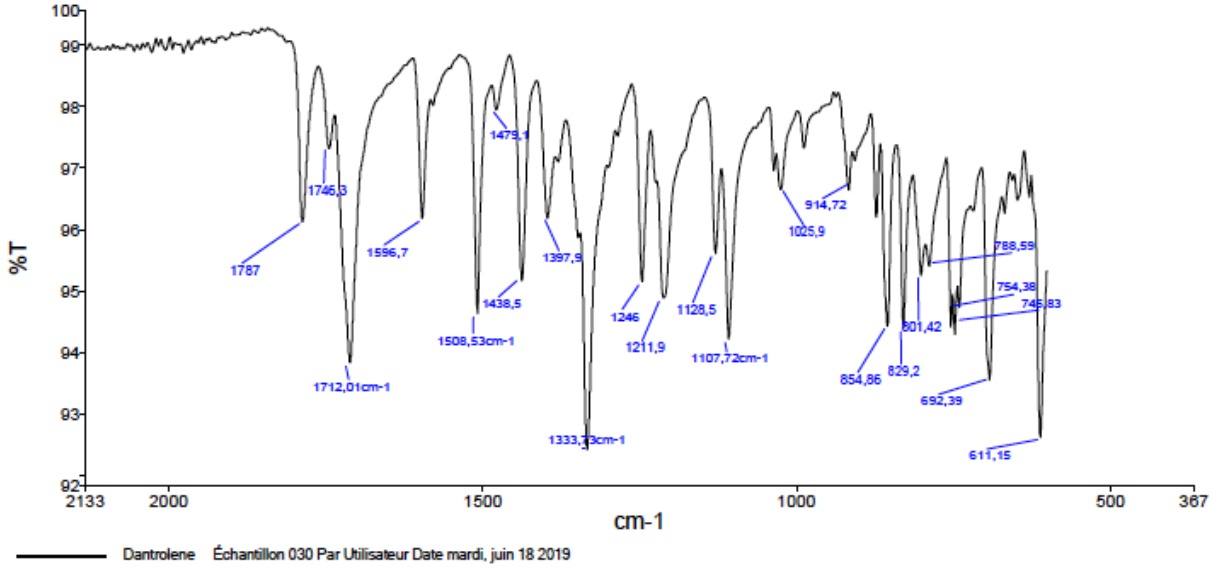


Figure S30. FT-IR of Dantrolene 4 (prepared by extrusion, 80% conversion).

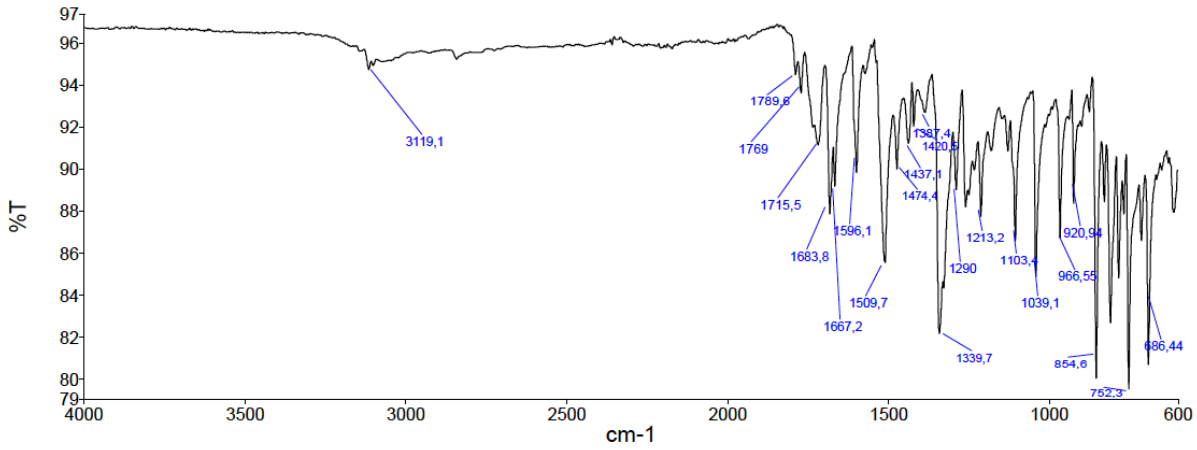


Figure S31. ^{1}H NMR of substrate 1-aminohydantoin hydrochloride in d^{6}-DMSO.

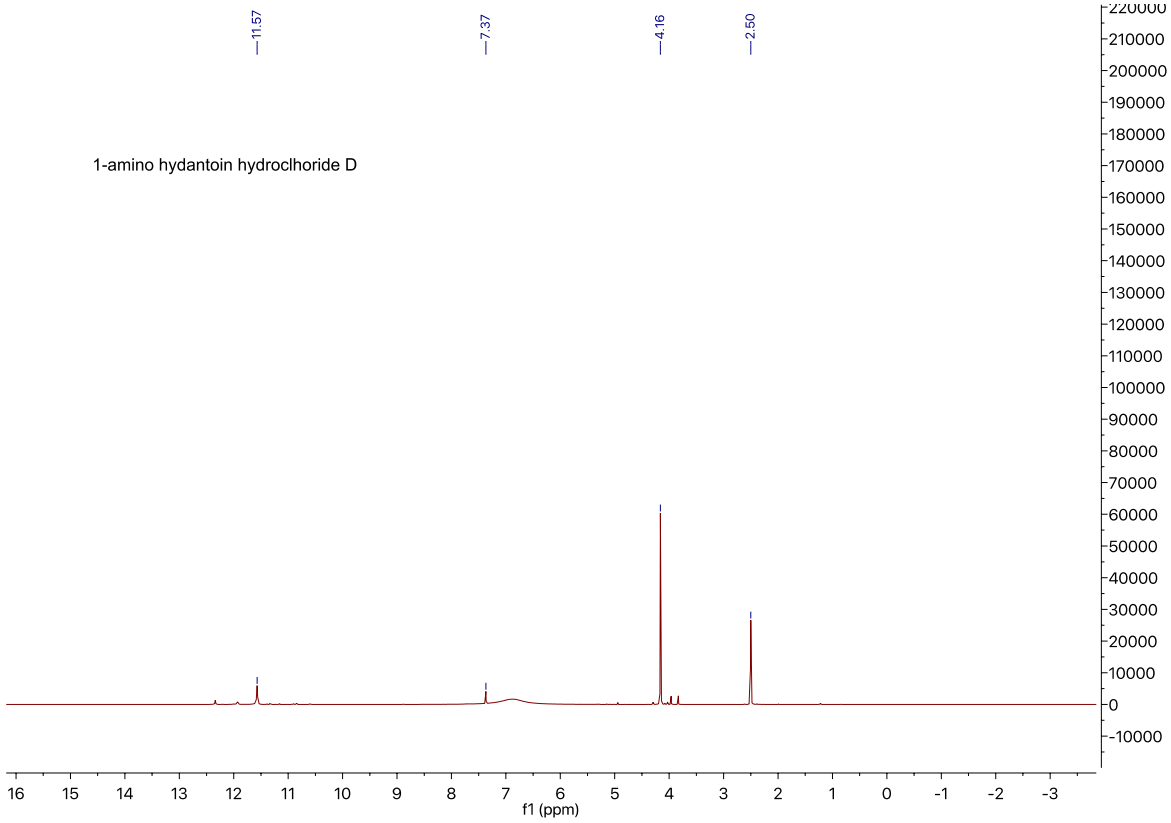


Figure S32. ^{13}C Solid state NMR of Substrate 1-aminohydantoin hydrochloride

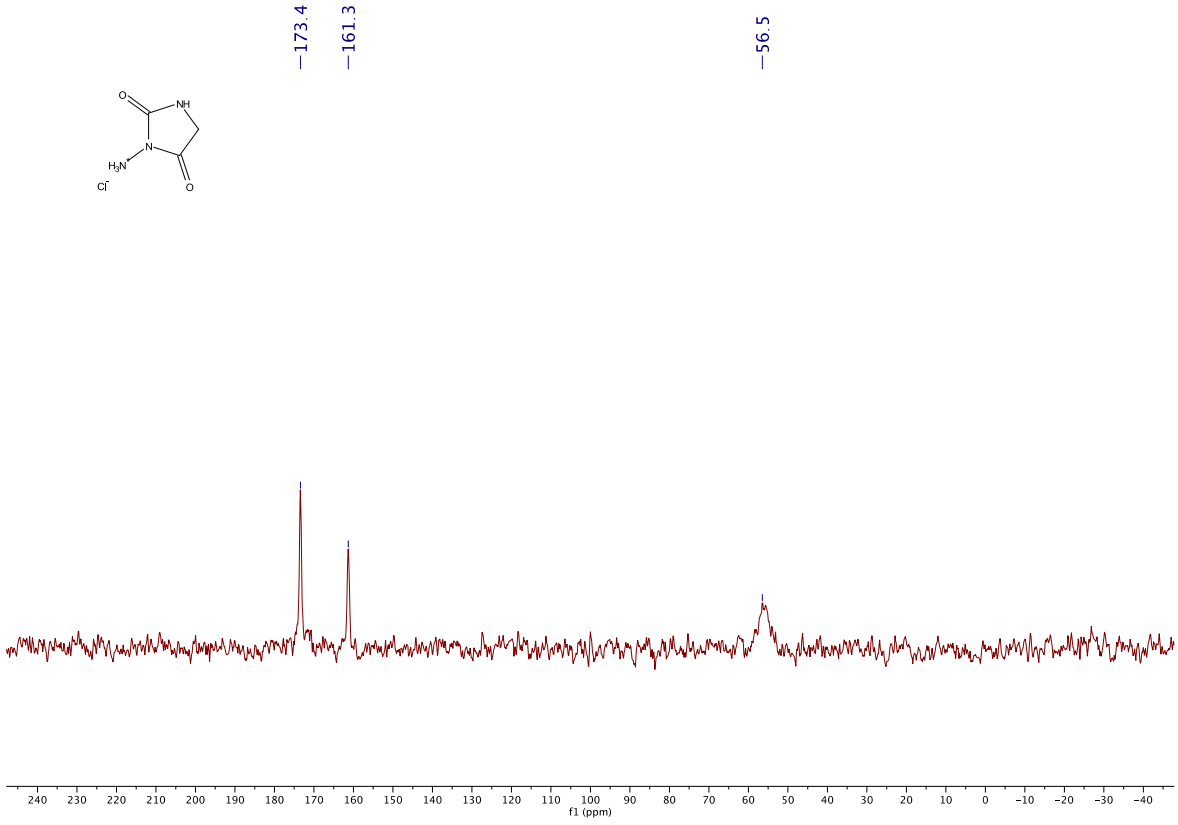


Figure S33. ^{13}C Solid state NMR of Substrate 5-nitro-2-furaldehyde

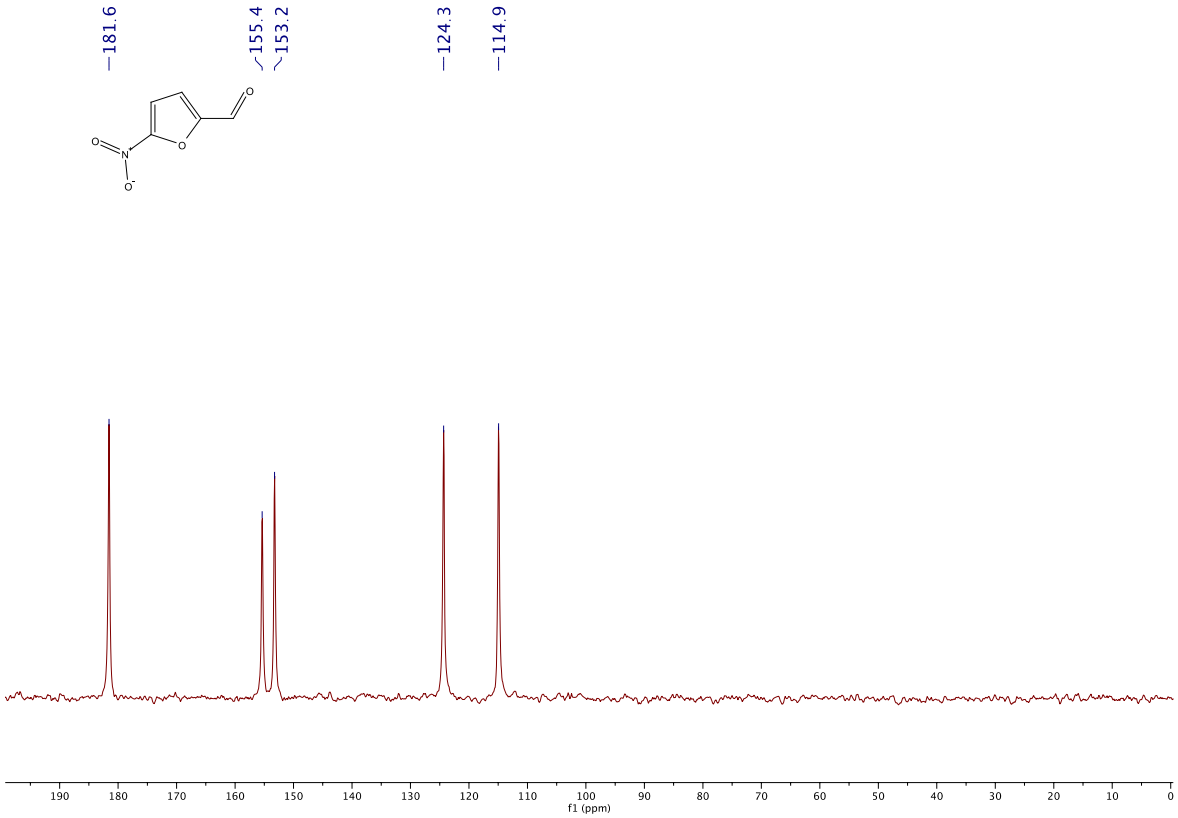
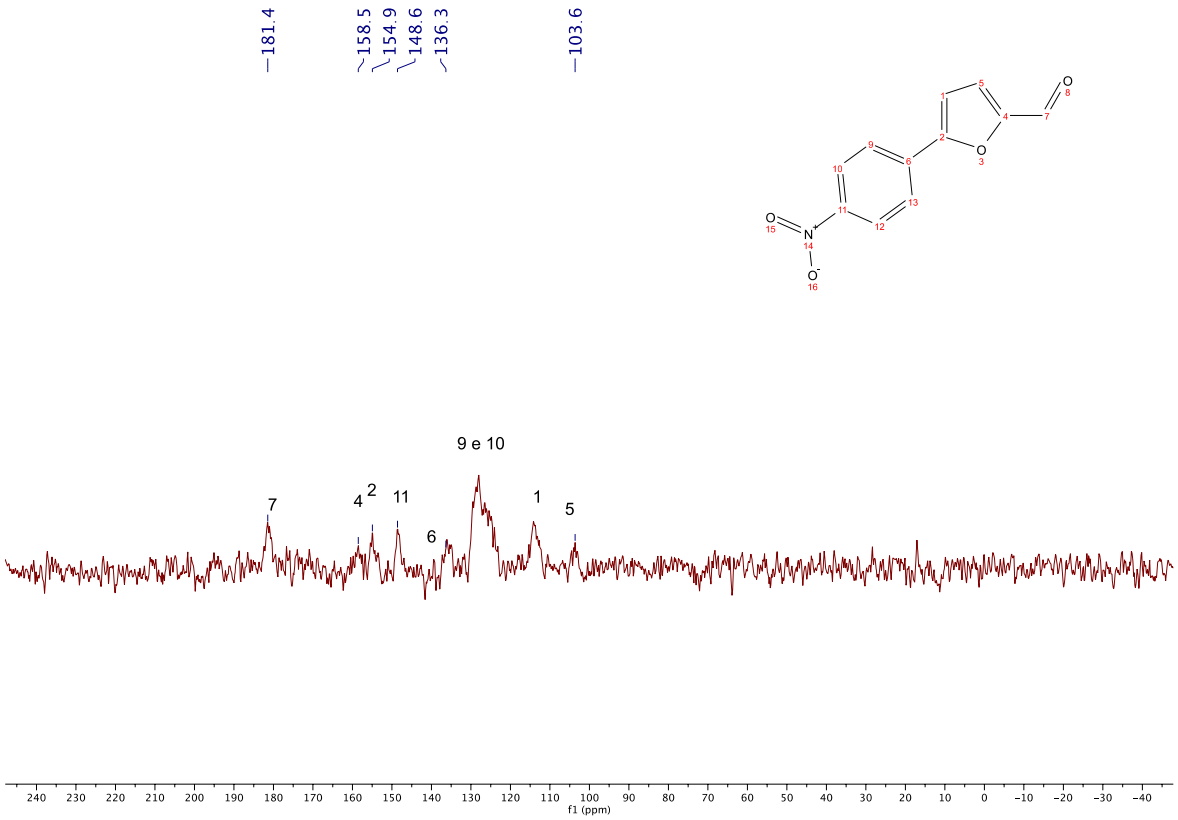


Figure S34. ^{13}C Solid state NMR of Substrate 5-(4-nitrophenyl)furfural



References.

1. E. Colacino, A. Porcheddu, I. Halasz, C. Charnay, F. Delogu, R. Guerra and J. Fullenwarth, *Green Chem.*, 2018, **20**, 2973-2977.
2. S. Morales, J. L. Aceña, J. L. García Ruano and M. B. Cid, *J. Org. Chem.*, 2016, **81**, 10016-10022.
3. S. Tumkevicius, G. Mekuskiene, V. Gefenas and P. Vainilavicius, *Chemjia*, 2005, **16**, 65-68.
4. F. Ishibashi, T. Nashima, J. Nishino, I. Kobayashi, Y. Ichihara, Y. Kitagawa, S. Sasaki, M. Yoshikawa, A. Matsuoka and K. Yamamoto, *Bull. Chem. Soc. Jpn.*, 1986, **59**, 73-76.
5. The word 'Echantillon' is the French translation for 'Sample'.
6. P. F. M. Oliveira, M. Baron, A. Chamayou, C. Andre-Barres, B. Guidetti and M. Baltas, *RSC Adv.*, 2014, **4**, 56736-56742.
7. The experiment is performed in the absence of solvent (neat). Considering the melting point of each reactants, it is assumed that the substrates melted during the experiments.
8. E. W. Pienaar, M. R. Caira and A. P. Lötter, *J. Crystallogr. Spectrosc. Res.*, 1993, **23**, 785-790.