Preprint version
Colacino, E., Porcheddu, A., Halasz, I., Charnay, C., Delogu, F., Guerra, R., & Fullenwarth, J. (2018). Mechanochemistry for "no solvent, no base" preparation of hydantoin-based active pharmaceutical ingredients: Nitrofurantoin and dantrolene. *Green Chemistry*, *20*(13), 2973–2977. https://doi.org/10.1039/C8GC01345D

Mechanochemistry for "no solvent, no base, no waste" preparation of Hydantoin-based Active Pharmaceutical Ingredients: Nitrofurantoin and Dantrolene.

Evelina Colacino,[1,*] Andrea Porcheddu,[2,*] Ivan Halasz,[3] Clarence Charnay,[4] Francesco Delogu,[5] Julien Fullenwarth.[4]

[1] Université de Montpellier, Institut des Biomolécules Max Mousseron (IBMM) UMR 5247 CNRS-UM-ENSCM, Université de Montpellier, cc1703, Place Eugène Bataillon, 34095 Montpellier Cedex 05, France. *E-mail : evelina.colacino@umontpellier.fr

[2] Dipartimento di Scienze Chimiche e Geologiche, Università degli Studi di Cagliari, Cittadella Universitaria, SS 554 bivio per Sestu, 09028 Monserrato (Ca), Italy. *E-mail: porcheddu@unica.it

[3] Ruđer Bosković Institute, Bijenicka cesta 54, Zagreb, Croatia

[4] Institut Charles Gerhardt de Montpellier (ICGM), UMR-5253 CNRS-UM, Université de Montpellier, Campus Triolet cc 1701, Place Eugène Bataillon, 34095, Montpellier Cedex 05 (France)

[5] Dipartimento di Ingegneria Meccanica, Chimica, e dei Materiali, Università degli Studi di Cagliari, via Marengo 2, 09123 Cagliari, Italy.

Keywords. Active Pharmaceutical Ingredients (API), Nitrofurantoin, Dantrolene, Hydantoins, Condensation, Hydrazones, Ball-Milling.

Abstract

The eco-compatible, energy-efficient, low environmental impact, gram scale, mechanochemical preparation of marketed drugs such as Nitrofurantoin (Furantin©, antibacterial agent), Dantrolene (Dantrium©, a muscle relaxant also used for prevention of malignant hyperthermia) and their structurally related derivatives, is herein reported. The solvent-, base- and waste-free stoichiometric ball-milling of 1-amino-hydantoin chlorohydrate and various aldehydes led to the more stable *E*-regioisomers selectively, in high yield and pure form without post-reaction work-up. Not a drop of organic solvent was used for the entire process and hydrazones were stable in the presence of water and gaseous HCl, formed during the synthesis. Comparative mechanochemical experiments were performed using diverse

milling devices and jar materials, the Active Pharmaceutical Ingredients were analyzed by PXRD and green metrics are calculated.

Introduction

"*Medicinal mechanochemistry*"[1] is an emerging field based on the use of a sustainable technology to prepare organic molecules and pharmaceutically relevant fragments and functionalities. We previously demonstrated how this approach was successfully used for the mechanochemical preparation of imidazoline-2,4-diones, or hydantoins, a scaffold of synthetic[2] and pharmaceutical interest for its many biological properties,[3] leading to clinical candidates[4-5] and marketed drugs.[6]

Several added-value hydantoin-based molecules for the industry, including Active Pharmaceutical Ingredients (API) such as Phenytoin **1**[7] and Ethotoin **2**,[8] antibacterial agents for polymer textiles **3-5**,[8-9] or the precursor **6**[10] an inhibitor of the *dihydroorodotase* enzyme, were already described by us (Figure 1). Very recently, we described the first "mechanochemical sol-gel process" to prepare silicon-based biohybrid nanomaterials containing hydantoins.[11]

With this background and aiming to still contribute to the advancement of the field of '*medicinal mechanochemistry*', we extended our investigation to the preparation of Nitrofurantoin **7** and Dantrolene **8** (Figure 1), APIs with annual global sales up to 37 UDS $ Million[12] and expected to increase in the next five years.

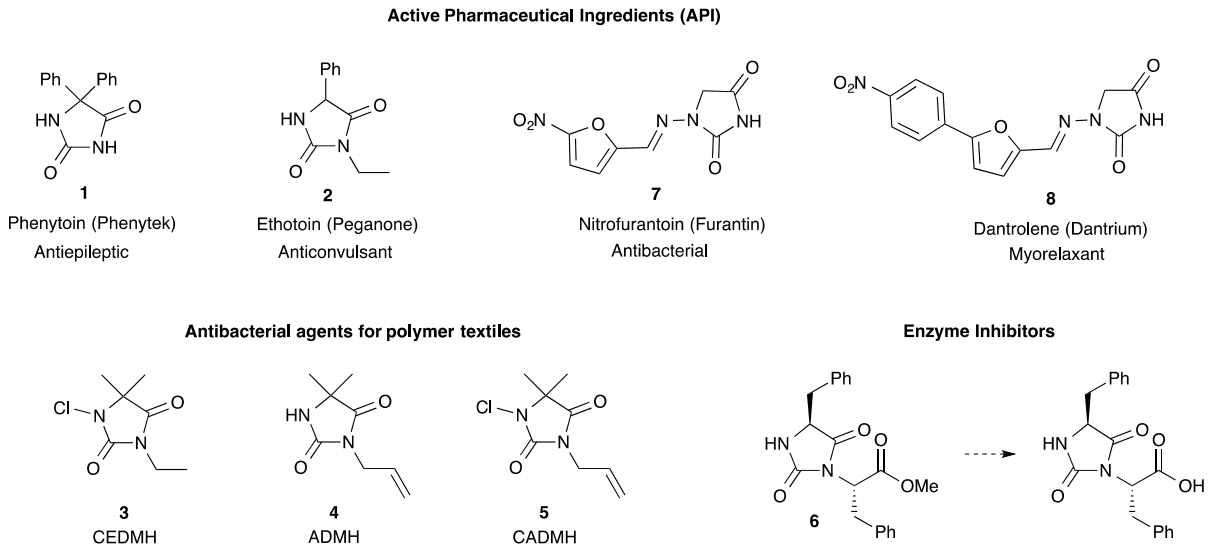


Figure 1. Industrially important hydantoin-based marketed drugs prepared by mechanochemistry.

Indeed, nitrofurantoin (Furadantin®) **7** is an antibacterial agent active against some gram positive organisms and specifically indicated for the treatement of urinary tract infections,[13] while dantrolene (Dantrium®) **8**, initially discovered as an efficient and specific skeletal muscle myorelaxant,[14] is nowadays the only clinically available agent for the treatement of malignant hyperthermia (MH)[15] and substrate for breast cancer resistant protein.[16-17]

Nitrofurantoin is usually prepared in solution via a condensation reaction between 1-aminohydantoin (up to 10 equivalents) and: 1) 5-nitro-2-furancarboxaldehyde diethyl acetal in DMF using HCl 30% in large excess upon heating at 90°C,[18] or 2) furfural, followed by an aqueous nitration reaction in a mixture of HNO_3-H_2SO_4, at -4°C.[19] The product is usually recoved after pH adjustment, by precipitation/filtration in water with yield in the range 83-92%.

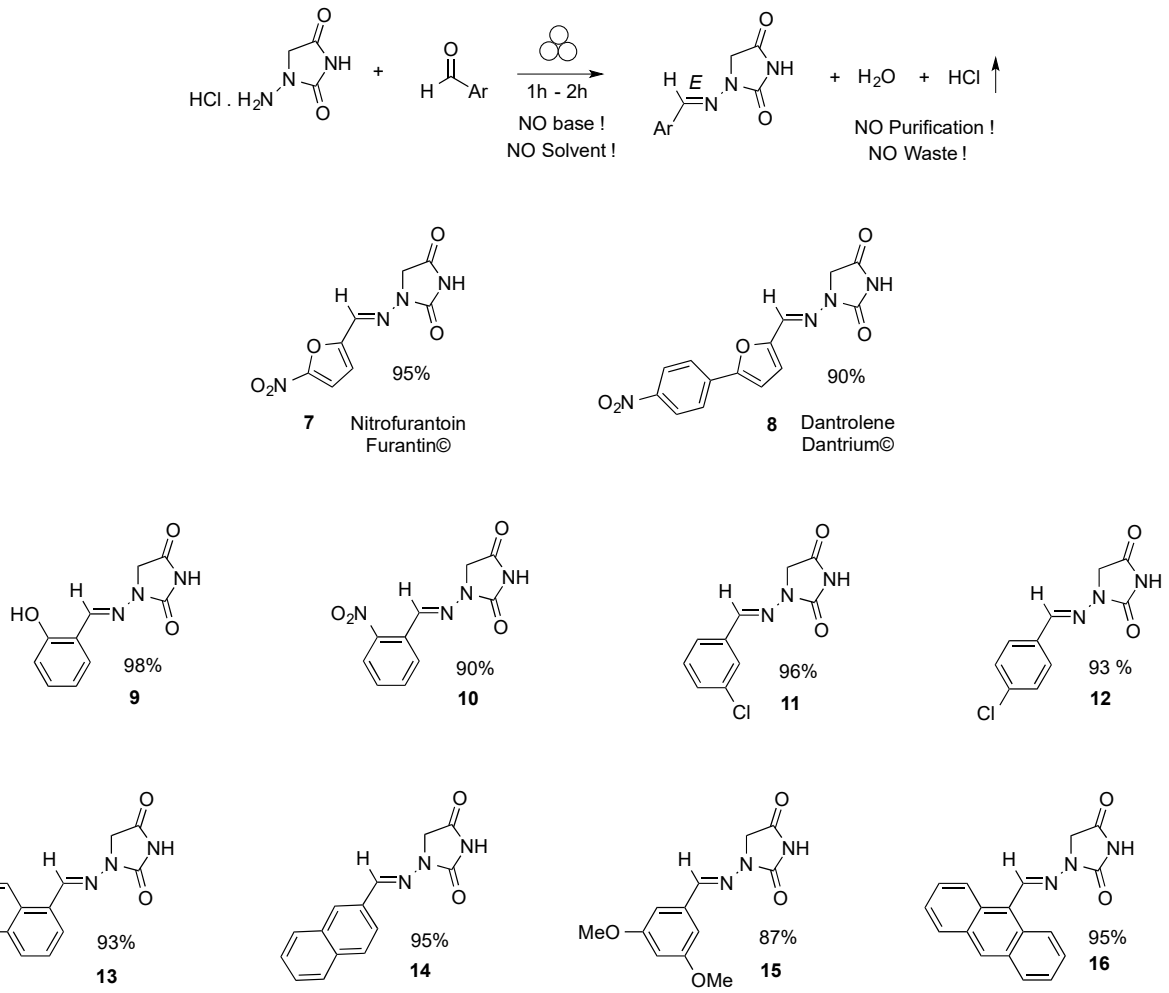
In the case of dantrolene, the condensation reaction leading to the hydrazone occurs in the presence of 5-(4-nitrophenyl)-2-furfural, in similar reaction conditions (DMF/HCl 35%[20] or in acetonitrile[21] at room temperature up to 8 hours), with yields in the range 41-96% after purification by precipitation in hexane[22] or water,[20, 23-24] or by colum chromatography.[21]

To our surprise, despite the simplicity of the preparation of arylhydrazones in solvent-free conditions by mechanochemistry, grinding in a mortar[25] or ball-milling (vibrating[26-29] or planetary[30-32]) from aryl diazonium salts in the presence of active methylene compounds[29] or more likely, by a condensation reaction,[25, 27-28, 30-31] those methodologies were never applied to the preparation of nitrofurantoin **7** or dantrolene **8**.

Thus, equimolar amounts of 1-aminohydantoin hydrochloride and 5-nitro-2-furfural were ground at 30 Hz in a 5 mL stainless steel jar (with 2 stainless steel balls, 5 mm Ø) without any special precaution. The conversion of the reactants was quantitative after 30 minutes and no other optimization studies were necessary on this first trial on small reaction scale (0.84 mmol) (Scheme 1). Nitrofurantoin **7** was recovered in 85% yields by precipitation after addition of water to the crude and drying *in vacuo* over P_2O_5, the only waste being water and hydrochloric acid.

It is worth noting that, coherently with our previous findings in other mechanochemical activated transformations,[10, 33] the strong activation provided by mechanochemical shocks avoided the use of base to generate a more nucleophilic amine. Moreover, two semi-batch large scale experiments were also performed under different mechanical stress in a planetary ball mill (13.2 mmoll) or a SPEX mill (6.6 mmol) (Table 1). Similarly to the reaction performed in a vibrating ball-mill on smaller scale (0.84 mmol), the experiment carried out in the planetary ball-mill equipped with zirconia jars and balls (25 zirconium oxide balls, 5 mm Ø) led to

nitrofurantoin **7** in 87% yield (2.73 g!) after precipitation in water, with full conversion of the reactants after two hours. However, uncomplete conversion of the substrates, even after prolonged milling (up to 6 hours), was observed when agate jars were used instead of those in zirconium oxide, confirming the importance of the hardness and density of the material in the activation process.



Scheme 1. Preparation of nitrofurantoin, dantrolene and their analogues by mechanochemistry.[34]

To our delight, much better results were obtained when using SPEX Mill 8000, characterized by an angular harmonic displacement in the vertical plane and a synchronous rotation in the equatorial plane. 1.49 g of nitrofurantoin **7** were smoothly prepared in only 15 minutes in 95% yield (Table 1). This time, the product was directly recovered as a powder from the jar without any post-synthetic treatment, except the removal of the water produced during the reaction, *in vacuo* at room temperature over P_2O_5.

Powder X-Ray Diffraction analyses (PXDR) were performed on nitrofurantoin **7** samples obtained after precipitation in water (reaction performed in the planetary ball-mill) or directly recovered from the jar without any post-synthetic work-up (reaction performed in the SPEX). In the first case, the diffraction patterns correspond to the nitrofurantoin known triclinic polymorph with at least two additional small peaks that are not accounted for suggesting there is an impurity present (Figure S1 in the supporting information). The same polymorph, but largely amorphous, is obtained on the powder directly recovered from the jar, displaying the same lower angle impurity peak as in Figure S1 (Figure S2 in the supporting information).

Table 1. Comparative results for the preparation of nitrofurantoin 7.

	Type of mill		
	Vibrating[a]	**Planetary**[b]	**SPEX**[c]
Reaction time (min)	30	120	15
Reaction scale (mol)	0.84×10^{-3}	13.2	6.6
Yield (%)	85	87	95
Quantity of **7** (g)	0.169	2.73	1.49
Jar/balls material	Stainless steel	Zirconium oxide	Zirconium oxide
Jar volume (mL)	5	12	50

Reaction conditions: 1-amino hydantoin chlorohydrate (1.0 equiv) and 5-nitro-2-furfural (1.0 equiv) were ground as follows: [a]30 Hz, 2 balls (5 mm Ø); [b] 600 rpm, 25 zirconium oxide balls (5 mm Ø); [c] 2 zirconium oxide balls (12 mm Ø).

The differences observed during the preparation of nitrofurantoin **7** in terms of reaction time (15 minutes *vs* 2 hours) and yields (95% *vs* 87%) might be due not only to the differences in reaction scale (6.6 mmol *vs* 13.2 mmol), but also to the different mechanical stress experimented by the reactants (Table 1).

To clear up any confusion, two comparative large scale experiments (6.6 mmol) were performed for the preparation of dantrolene **8** using a planetary and a SPEX mill respectively.

In both case, althought the full conversion of the reactants took longer (two hours) compared to nitrofurantoin **7** (15 minutes), almost identical yields (90%) were obtained, indipendently on the type of mill (planetary or SPEX) and the process parameters used (identical to those illustrated in Table 1). Therefore, the different reaction kinetics displayed by nitrofurantoin **7** (prepared in 15 minutes) and dantrolene **8** (prepared in two hours) could be exeplained on the base of the physical state of the reagents. Faster reaction kinetics were

possible with the low melting reagent 2-nitro-1-furfural (m.p. 37-39°C), while a melt reaction was excluded for a high melting solids such as 5-(4-nitrophenyl)-2-furfural (m.p. 204-205°C) and 1-amino hydantoin hydrochloride (m.p. 201-205°C).

Since no more optimization was necessary, in order to investigate whether this approach was of general applicability, other hydantoin-based hydrazones were prepared (Scheme 1). 1-Amino hydantoin hydrochloride reacted almost quantitatively with the different aldehydes leading to the corresponding hydrazones **7-16** upon stoichiometric milling of the components (Scheme 1). The completion of the reaction was checked by HPLC, the reactions were selective in favor of the more stable isomer *E* and the conversion was 100% in all the studied combinations, with yields approaching 100% in most of the cases, nonetheless the quantitative recovery of the powdered material from the jar was sometimes difficult. It is worth noting that resistant to hydrolysis despite the formation of water and gaseous HCl during milling. The method proved to be general (even on large scale) and the process presented the advantage of short reaction times, eco-friendliness, and ease of handling under solvent-free conditions, as no waste-producing purifying workup is necessary.

Green chemistry metrics such as the environmental factor [*E*-factor = total waste (kg)/product (kg)],[35] the Process Mass Intensity [PMI = total mass (kg) used in the process/mass of product (kg)],[36] the Atom Economy [AE = Molecular Weight of the product / Sum of the Molecular Weights of all reactants][37] and Carbon Economy [E_c = Amount of carbon in the product / total carbon present in all reactants] for both mechanochemical and solvent-based procedures were calculated for nitrofurantoin **7** and dantrolene **8** to evaluate and benchmark the more sustainable process (Table 2).

Table 2. Comparative green metrics for nitrofurantoin **7** and dantrolene **8**.

	In solution / by Mechanochemistry[a]					
	***t* (h)**	**Yield (%)**	***E*-factor**	**PMI**[b]	**AE (%)**	**E_c**[c] **(%)**
Nitrofurantoin **7**	8[38] / 0.25	95[38] / 95	16[d] / 0.29	17[d] / 1.29	81	100
Dantrolene **8**	1[24] / 2	95[24] / 90	239[e] / 0.30	240[e] / 1.30	85	100

[a] Data refer to the recovery of products without any post-synthetic work-up (reaction scale was 6.6 mmol); [b] PMI = *E*-factor + 1; [c] Carbon Ecomony (E_c); [d] Value calculated from data in Reference 38; [e] Value reported (or calculated) from data in References 24 and 20.

If metrics such as carbon economy (E_c), atom economy (AE), the nature of waste are the same and the yields comparable for both solution and ball-milling processes, the *E*–factor

and the PMI metrics were better, compared to the reactions in solution (Table 2) and no work-up was need. In addition, the preparation of nitrofurantoin **7** was faster by mechanochemistry (15 minutes instead of 8 hours).

Table 3. Comparative costs[a] for nitrofurantoin **7** and dantrolene **8**.

	Synthesis in solution	**Synthesis by Mechanochemistry**	**From commercial sources**
		Costs (€ g^{-1})[a]	
Nitrofurantoin **7**	n.d.	40.7	3.4
Dantrolene **8**	133.9[24]	54.7	498

[a] Reaction costs in euros per gram of product, excluding energetic costs. Costs are calculated considering the prices of the reagents and solvents taken from the same supplier.

Compared to solution based processes, the mechanochemical preparation of nitrofurantoin **7** and Dantrolene **8** presents several advantages: 1) to avoid the use of solvents (DMF, CAN and EtOH); 2) to avoid the use of an excess of concentrated aqueous solutions of strong bases and acids (NaOH, HCl 30%, HNO_3-H_2SO_4),[38] overcoming the problems related to corrosion and hydrolysis of the hydrazone bond; 3) to avoid the number of synthetic steps, (in the case of nitrofurantoin **7**, the aldehyde is in the form of diethyl acetal and need to be hydrolyzed *in situ*); 4) to reduce the energetic cost of the process, avoiding any heating (between 45°C and 90°C) or cooling (between -2°C and -4°C) of the reaction mixtures;[38] 5) to increase the throughput/hour of the process, due to shorter reaction times and no need of work-up procedure, being the APIs recovered as powder directly from the jar; 6) reduce the environmental footprint of the process (Table 2); 7) to reduce the costs of the synthesis leading to reduced costs for the preparation of 1 g of product (Table 3).

Conclusion

Nitrofurantoin and dantrolene were prepared without no extra-reagents (to further activate the reactants), additives, catalysts. Even if there is still much to explore in the perspective of a manufacturing process of these APIs by mechanochemistry, these syntheses are good examples and prefigure the way towards a more sustainable production of APIs at industrial level in the near future. In this regard, twin screw extrusion (TSE) technology, already applied to the preparation of co-crystals, Metal Organic Frameworks (MOFs), for organic condensation

reactions[39] and for organic light-emitting diode (OLED)[40] constitute the tool to change the way in which chemistry can be conducted.

Acknowledgements

E.C. is grateful to the Institute Charles Gerhardt (ICGM UMR 5253, France) for the access to the milling equipment. For XRD analyses, the authors are grateful to M. Bernard Fraisse (ICGM UMR 5253, France) and Dr. Francesco Torre (Università degli Studi di Cagliari, Italy).

References

1. Tan, D.; Loots, L.; Friscic, T., Towards medicinal mechanochemistry: evolution of milling from pharmaceutical solid form screening to the synthesis of active pharmaceutical ingredients (APIs). *Chem. Commun.* **2016,** *52*, 7760-7781.
2. Konnert, L.; Lamaty, F.; Martinez, J.; Colacino, E., Recent Advances in the Synthesis of Hydantoins: The State of the Art of a Valuable Scaffold. *Chem. Rev.* **2017,** *117*, 13757-13809.
3. Meusel, M.; Gütschow, M., Recent Developments in Hydantoin Chemistry. A Review. *Org. Prep. Proced. Int.* **2004,** *36*, 391-443.
4. https://clinicaltrials.gov/; (accessed April 16, 2018).
5. https://www.clinicaltrialsregister.eu/; (accessed accessed April 16, 2018).
6. U.S. Food and Drug Administration http://www.accessdata.fda.gov/scripts/cder/drugsatfda/; accessed April 16.
7. Konnert, L.; Reneaud, B.; Marcia de Figueiredo, R.; Campagne, J.-M.; Lamaty, F.; Martinez, J.; Colacino, E., Mechanochemical Preparation of Hydantoins from Amino Esters: Application to the Synthesis of the Antiepileptic Drug Phenytoin. *J. Org. Chem.* **2014,** *79*, 10132−10142.
8. Konnert, L.; Dimassi, M.; Gonnet, L.; Lamaty, F.; Martinez, J.; Colacino, E., Poly(ethylene) glycols and mechanochemistry for the preparation of bioactive 3,5-disubstituted hydantoins. *RSC Advances* **2016,** *6*, 36978–36986.
9. Mascitti, A.; Lupacchini, M.; Guerra, R.; Taydakov, I.; Tonucci, L.; d'Alessandro, N.; Lamaty, F.; Martinez, J.; Colacino, E., Poly(ethylene glycol)s as grinding additives in the mechanochemical preparation of highly functionalized 3,5-disubstituted hydantoins. *Beilstein J. Org. Chem.* **2017,** *13*, 19-25.
10. Konnert, L.; Gonnet, L.; Halasz, I.; Suppo, J.-S.; de Figueiredo, R.; Campagne, J.-M.; Lamaty, F.; Martinez, J.; Colacino, E., Mechanochemical preparation of 3,5-disubstituted

Hydantoins from Dipeptides and Unsymmetrical Ureas of Amino Acid Derivatives. *J. Org. Chem.* **2016,** *81*, 9802-9809

11. Lupacchini, M.; Mascitti, A.; Tonucci, L.; d'Alessandro, N.; Colacino, E.; Charnay, E., From Molecules to Silicon-Based Biohybrid Materials by Ball Milling. *ACS Sustainable Chem. Eng.* **2018,** *6*, 511-518.
12. https://www.pharmacompass.com/active-pharmaceutical-ingredients/nitrofurantoin (accessed accessed April 18, 2018).
13. https://www.drugbank.ca/drugs/DB00698 (accessed accessed April 16, 2018).
14. Oleinik, A. F.; Andreeva, N. I.; Syubaev, R. D.; Golovina, S. M.; Vozyakova, T. I., Synthesis and pharmacological properties of dantrolene and sodium dantrolene. *Khimiko-Farmatsevticheskii Zhurnal* **1984,** *18*, 561-3.
15. Krause, T.; Gerbershagen, M. U.; Fiege, M.; Weißhorn, R.; Wappler, F., Dantrolene – A review of its pharmacology, therapeutic use and new developments. *Anaesthesia* **2004,** *59*, 364-373.
16. Enokizono, J.; Kusuhara, H.; Ose, A.; Schinkel, A. H.; Sugiyama, Y., Quantitative investigation of the role of breast cancer resistance protein (Bcrp/Abcg2) in limiting brain and testis penetration of xenobiotic compounds. *Drug Metab. Dispos.* **2008,** *36*, 995-1002.
17. Kumata, K.; Ogawa, M.; Takei, M.; Fujinaga, M.; Yoshida, Y.; Nengaki, N.; Fukumura, T.; Suzuki, K.; Zhang, M.-R., Radiosynthesis of [^{13}N]dantrolene, a positron emission tomography probe for breast cancer resistant protein, using no-carrier-added [13N]ammonia. *Bioorg. Med. Chem.* **2012,** *20*, 305-310.
18. Li, X.; Qiu, F., *Process for preparation of nitrofurantoin crystals.* , CN 101450940 A 20090610 (2009), pp. 6.
19. Qi, X.-y.; Wu, X.-g., New technology of synthesis of nitrofurantion. *Huaxue Shijie* **2007,** *48*, 237-252.
20. Hosoya, T.; Aoyama, H.; Ikemoto, T.; Kihara, Y.; Hiramatsu, T.; Endo, M.; Suzuki, M., Dantrolene Analogues Revisited: General Synthesis and Specific Functions Capable of Discriminating Two Kinds of Ca^{2+} Release from Sarcoplasmic Reticulum of Mouse Skeletal Muscle. *Bioorg. Med. Chem.* **2003,** *11*, 663-673.
21. Crisostomo, F. P.; Martin, T.; Carrillo, R., Ascorbic Acid as an Initiator for the Direct C-H Arylation of (Hetero)arenes with Anilines Nitrosated In Situ. *Angew. Chem., Int. Ed.* **2014,** *53*, 2181-2185.
22. Jasimuddin, A.; Samaresh, C. S.; Sreejyothi, P.; Pradip, K. H.; Pavan, K. V.; Gonela, V.; Swadhin, K. M., Direct C–H Arylation of Heteroarenes with Aryl Chlorides by Using an

Abnormal N-Heterocyclic-Carbene–Palladium Catalyst. *Eur. J. Org. Chem.* **2017**, 1004-1011.

23. Zoller, J.; Fabry, D. C.; Rueping, M., Unexpected Dual Role of Titanium Dioxide in the Visible Light Heterogeneous Catalyzed C-H Arylation of Heteroarenes. *ACS Catalysis* **2015,** *5*, 3900-3904.
24. Fabry, D. C.; Ho, Y. A.; Zapf, R.; Tremel, W.; Panthoefer, M.; Rueping, M.; Rehm, T. H., Blue light mediated C-H arylation of heteroarenes using TiO_2 as an immobilized photocatalyst in a continuous-flow microreactor. *Green Chemistry* **2017,** *19*, 1911-1918.
25. Hajipour, A. R.; Mohammadpoor-Baltork, I.; Bigdeli, M., A Convenient and Mild Procedure for the Synthesis of Hydrazones and Semicarbazones from Aldehydes or Ketones under Solvent-free Conditions. *J. Chem. Res., Synop.* **1999**, 570-571.
26. Nun, P.; Martin, C.; Martinez, J.; Lamaty, F., Solvent-free synthesis of hydrazones and their subsequent N-alkylation in a Ball-mill. *Tetrahedron* **2011,** *67*, 8187-8194.
27. Magyar, T.; Miklós, F.; Lázár, L.; Fülöp, F., Application of a Ball Milling Technique for the Condensation of Anthranilic Hydrazides with Aromatic Aldehydes Towards 4-Quinazolinone Derivatives. *Chem. Heter. Comp.* **2015,** *50*, 1464-1470.
28. Oliveira, P. F. M.; Baron, M.; Chamayou, A.; André-Barrés, C.; Guidettib, B.; Baltasb, M., Solvent-free mechanochemical route for green synthesis of pharmaceutically attractive phenol-hydrazones. *RSC Advances* **2014,** *4*, 56736-56742.
29. Zhu, X.; Chen, Y.; Chen, Y.; Wang, J.; Su, W., Mechanically Activated Solid-State Synthesis of Phenylhydrazone Derivatives via High-Speed Ball Milling. *Lett. Org. Chem.* **2014,** *11*, 621-626.
30. Mokhtari, J.; Naimi-Jamal, M. R.; Hamzeali, H.; Dekamin, M. G.; Kaupp, G., Kneading Ball Milling and Stoichiometric Melts for Quantitative Derivatization of Carbonyls with Gas-Solid Recovery. *ChemSusChem* **2009,** *2*, 248-254.
31. Kaupp, G.; Schmeyers, J.; Boy, J., Iminium Salts in Solid-State Syntheses Giving 100% Yield. *J. Prakt. Chem.* **2000,** *342*, 269-280.
32. Bondock, S. E.-A., H.; Kandeel, E.-E. M.; Metwally, M. A. ; 2008, 1329, Eco-friendly solvent-free synthesis of thiazolylpyrazole derivatives. *Monatsh. Chem.* **2008,** *139*, 1329-1335.
33. Lanzillotto, M.; Konnert, L.; Lamaty, F.; Martinez, J.; Colacino, E., Mechanochemical 1,1′-Carbonyldiimidazole-Mediated Synthesis of Carbamates. *ACS Sustainable Chem. Eng.* **2015,** *3*, 2882-2889.

34. The formalism for mechanochemically activated reactions was recently proposed by Hanusa group: Rightmire, N. R.; Hanusa, T. P., *Dalton Trans.* **2016,** *45*, 2352–2362.
35. Sheldon, R.; Arends, A. I.; Hanefeld, U., *Green Chemistry and Catalysis; Wiley-VCH, Weinheim, Germany, 2007.*
36. Jimenez-Gonzalez, C.; Ponder, C. S.; Broxterman, Q. B.; Manley, J. B., Using the right green yardstick: why process mass intensity is used in the pharmaceutical industry to drive more sustainable processes. *Org. Proc. Res. Devel.* **2011,** *15*, 912-917.
37. Trost, B. M., The atom economy - a search for synthetic efficiency. *Science* **1991,** *254*, 1471-1477.
38. Li, X.; Zhang, F., Method for preparing and refining nitrofurantoin. CN 101450941 A 20071130 (2007), pp. 6.
39. Crawford, D. E.; Miskimmin, C. K. G.; Albadarin, A. B.; Walker, G.; James, S. L., Organic synthesis by Twin Screw Extrusion (TSE): continuous, scalable and solvent-free. *Green Chem.* **2017,** *19*, 1507-1518.
40. Crawford, D. E.; James, S. L.; McNally, T., Use of Batch Mixing To Investigate the Continuous Solvent-Free Mechanical Synthesis of OLED Materials by Twin-Screw Extrusion (TSE). *ACS Sustainable Chem. Eng.* **2018,** *6*, 193-201.
41. The Merck Index, 12th ed. Entry# 6696.
42. Snyder, H. R. J.; Davis, C. S.; Bickerton, R. K.; Halliday, R. P., 1-[5-Arylfurfurylidene)amino]hydantoins. A New Class of Muscle Relaxants. *J. Med. Chem.* **1967,** *10*, 807-810.

SUPPLEMENTARY INFORMATION

Mechanochemistry for "no solvent, no base, no waste" preparation of Hydantoin-based Active Pharmaceutical Ingredients: Nitrofurantoin and Dantrolene.

Evelina Colacino,[1,*] Andrea Porcheddu,[2,*] Ivan Halasz,[3] Clarence Charnay,[4] Francesco Delogu,[5] Julien Fullenwarth.[4]

[1] Université de Montpellier, Institut des Biomolécules Max Mousseron (IBMM) UMR 5247 CNRS-UM-ENSCM, Université de Montpellier, cc1703, Place Eugène Bataillon, 34095 Montpellier Cedex 05, France. *E-mail : evelina.colacino@umontpellier.fr

[2] Dipartimento di Scienze Chimiche e Geologiche, Università degli Studi di Cagliari, Cittadella Universitaria, SS 554 bivio per Sestu, 09028 Monserrato (Ca), Italy. *E-mail: porcheddu@unica.it

[3] Ruđer Bosković Institute, Bijenicka cesta 54, Zagreb, Croatia

[4] Institut Charles Gerhardt de Montpellier (ICGM), UMR-5253 CNRS-UM, Université de Montpellier, Campus Triolet cc 1701, Place Eugène Bataillon, 34095, Montpellier Cedex 05 (France)

[5] Dipartimento di Ingegneria Meccanica, Chimica, e dei Materiali, Università degli Studi di Cagliari, via Marengo 2, 09123 Cagliari, Italy.

Experimental part.

General remarks and experimental procedures

All reagents were commercially available. 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 (DMSO in DMSO-d_6: δ = 2.50 ppm for ^{1}H and DMSO-d_6: δ = 39.52 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, the samples were prepared by dissolving 10 mg of hydantoin in 0.7 mL of deuterated solvent. ^{1}H and ^{13}C NMR were recorded using 32 and 4096 scans respectively. The identity of analytically pure final product Dantrolene **8** was assessed by comparison of its spectral data previously described in the literature and by their fragmentation in LC/MS. HRMS measurements were performed on a TOF mass analyzer. Analytical high performance liquid chromatography (HPLC) was performed with a UV-detector at 214 nm using a CHROMOLITH RP18 column (50 x 4.6 mm), flow 5 mL/min, linear gradient CH_3CN in water 0-100% (+ 0.1% TFA) in 3 min. LC-MS analyses were performed by HPLC, column Onyx C_{18}, (25 x 4.6 mm), flow 3 mL/min linear gradient CH_3CN in water 0-100% (+ 0.1% HCO_2H) in 2.5 min. Melting points were measured on a Büchi Melting Point 510 apparatus and are uncorrected. The ball-milling experiments were performed in a MM400 vibrational ball mill (Retsch GmbH, Haan, Germany) using 5 mL stainless steel jar (2 stainless steel balls, 5 mm Ø), a Pulverisette P7 (Fritsch, Idar-Oberstein, Germany) using a 12 mL agate or zirconium oxide jars (8 agate balls 8 mm Ø, 25 zirconium oxide balls 5 mm Ø) or in a SPEX 8000 mill using a 50 mL zirconium oxide jar (2 zirconium oxide balls 12 mm Ø).

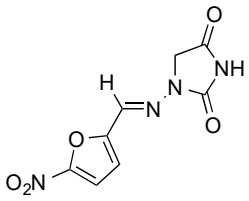
General procedure for the preparation of compounds 7-16.

1-aminohydantoin hydrochloride (1.0 equiv) and the aldehyde (1.0 equiv) were ground according to Method A, B or C as specified for each compound. The final product was recovered just scratching out the powder from the jar without further treatment (compounds **7-11** and **14**) or by precipitation in water and filtration (compounds **7**, **8**, **12**, **13**, **15**, and **16**). The crude was always dried *in vacuo* over P_2O_5 overnight.

METHOD A - Vibrating ball mill (VBM) *(only for compound 7 and **9**)*: 5 mL stainless steel jars, 2 stainless steel balls (5 mm Ø, 0.507 g for each ball) at 30 Hz for 30 min or 2 h;

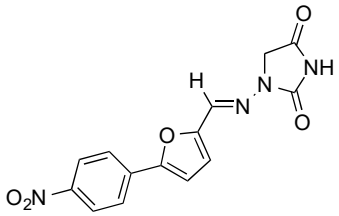
METHOD B - Planetary ball mill (PBM) (*for compounds 7, **8**, **10-16***): 12 mL zirconium oxide jars, 25 zirconium oxide balls (5 mm Ø, 0.391 g for each ball) at 600 rpm for 2 h except when differently stated for each compound;

METHOD C – SPEX *(only for compounds 7 and **8**)*: 50 mL zirconium oxide jars, 2 zirconium oxide balls (12 mm Ø, 3.3 g for each ball) for 15 min (in the case of nitrofurantoin **7**) or for 2 h (in the case of dantrolene **8**).



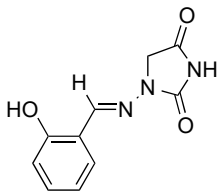
7

(*E*)-*N*-(5-nitro-2-furfurylidene)-1-aminohydantoin (7) CAS [67-20-9]. For *Method A* (30 min reaction): the reaction scale was 0.84 mmol (169 mg, 85%); for *Method B*: the reaction scale was 13.2 mmol (2.73 g, 87%). For *Method A and B* : The final product was recovered by precipitation in water. For *Method C*: the reaction scale was 6.6 mmol (1.49 g, 95%). The product was scratched out from the jar without any further work-up. Pale yellow powder; m.p. 269 - 272 °C (lit. 270-272°C with decomposition);[41] **^{1}H NMR** (300 MHz, DMSO-d_6) δ (ppm): 11.46 (s, CH=N, 1H), 7.79 (s, CH and NH, 2H), 7.14 (s, 1H, CH), 4.35 (s, 2H, CH_2); **^{13}C{1H} NMR** (75 MHz, DMSO-d_6) δ (ppm): 168.7, 153.2, 151.9, 151.7, 131.1, 114.7, 114.5, 49.1; **ESI-(+)** *m/z :* 261.2 $[M+Na]^+$, 256.2 $[M+H+H_2O]^+$, 239.1 $[M+H]^+$, 191.3, 170.1, 141.0, 131.2, 100.5 ; **HRMS ESI-(+)** calcd for $C_8H_7N_4O_5$ $[M+H]^+$ 239.0416, found 239.0415.



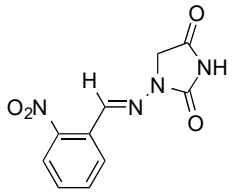
8

(*E*)-1-{[5-(4-nitrophenyl)-2-furyl]methylideneamino}-imidazolidine-2,4-dione (8) CAS [7261-97-4]. The reaction scale was 6.6 mmol. For *Method B*: the final product was recovered by precipitation in water (1.84 g, 89%). For *Method C*: the product was scratched out from the jar without any further work-up (1.87 g, 90%). Deep orange powder; m.p. 262.7 - 264.7 °C (lit. 258-260 °C);[42] **^{1}H NMR** (300 MHz, DMSO-d_6)[20] δ (ppm): 11.37 (s, CH=N, 1H), 8.35 (dd, J = 6.9 and 1.8 *Hz*, CH_{Ar}, 2H), 8.06 (dd, J = 6.9 and 1.9 *Hz*, CH_{Ar}, 2H), 7.80 (s, 1H, NH), 7.49 (d, J = 3.7 *Hz*, 1H, CH), 7.09 (d, J = 3.7 *Hz*, 1H, CH), 4.40 (s, 2H, CH_2); **^{13}C{1H} NMR** (75 MHz, DMSO-d_6)[21] δ (ppm): 169.8, 154.2, 153.1, 151.0, 147.2, 136.1, 133.6, 125.5, 125.4, 116.5, 113.4, 49.9; **ESI-(+)** *m/z :* 337.1 $[M+Na]^+$, 315.1 $[M+H]^+$, 130.2 ; **HRMS ESI-(+)** calcd for $C_{14}H_{11}N_4O_5$ $[M+H]^+$ 315.0729, found 315.0731.



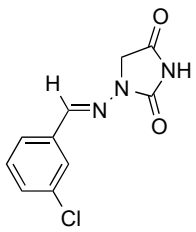
9

(*E*)-1-((2-hydroxybenzylidene)amino)imidazolidine-2,4-dione (9) The reaction scale was 1.32 mmol (*Method A*, 2 h reaction). The product was scratched out from the jar without any further work-up (284 mg, 98%). Black powder; m.p. 244.0 - 247.4 °C; **^{1}H NMR** (300 MHz, DMSO-d_6) δ (ppm): 11.35 (s, CH=N, 1H), 10.66 (s, 1H, OH), 8.02 (s, 1H, CH_{Ar}), 7.59 (s, 1H, NH), 7.30 (d, 1H, CH_{Ar}), 6.95 (s, 2H, CH_{Ar}), 4.40 (s, 2H, CH_2); **^{13}C{1H} NMR** (75 MHz, DMSO-d_6) δ (ppm): 169.8, 157.5, 154.5, 154.2, 143.5, 131.9, 129.4, 120.3, 119.8, 117.2, 49.4; **ESI-(+)** *m/z :* 220.0 $[M+H]^+$, 148.9, 130.2; **HRMS ESI-(+)** calcd for $C_{10}H_{10}N_3O_3$ $[M+H]^+$ 220.0722, found 220.0721.



10

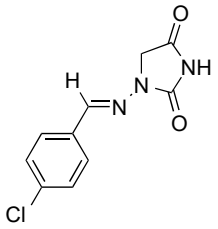
(*E*)-1-((2-nitrobenzylidene)amino)imidazolidine-2,4-dione (10). The reaction scale was 1.98 mmol (*Method B*). The product was scratched out from the jar without any further work-up (443 mg, 90%). White powder; m.p. 219.6 - 221.5 °C; **^{1}H NMR** (300 MHz, DMSO-d_6) δ (ppm): 11.41 (s, CH=N, 1H), 8.08 (dd, J = 9.0 and 3.0 Hz, 3H, NH and 2 x CH_{Ar}), 7.85 (dt, J = 9.0 and 3.0 Hz, 1H, CH_{Ar}), 7.71 (dt, J = 9.0 and 3.0 Hz, 1H, CH_{Ar}), 4.40 (s, 2H, CH_2); **^{13}C{1H} NMR** (75 MHz, DMSO-d_6) δ (ppm): 169.7, 154.4, 149.0, 139.12, 134.7, 131.5, 129.3, 129.1, 125.7, 49.8; **ESI-(+)** *m/z* : 271.1 $[M+Na]^+$, 249.1 $[M+H]^+$, 134.0, 114.0; **HRMS ESI-(+)** calcd for $C_{10}H_9N_4O_4$ $[M+H]^+$ 249.0624, found 249.0624.



11

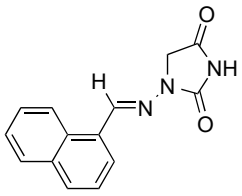
(*E*)-1-((3-chlorobenzylidene)amino)imidazolidine-2,4-dione (11) The reaction scale was 1.98 mmol (*Method B)*. The product was scratched out from the jar without any further work-up (453 mg, 96%). White powder; m.p. 256.4 - 257.4 °C; **^{1}H NMR** (300 MHz, DMSO-d_6) δ (ppm): 11.34 (s, CH=N, 1H), 7.84 (s, 1H), 7.77 (m, 1H, CH_{Ar}), 7.71-7.67 (m, 1H), 7.53-7.51 (m, 2H), 4.34 (s, 2H, CH_2); **^{13}C{1H} NMR** (75 MHz, DMSO-d_6) δ (ppm): 169.8, 154.3, 142.3, 137.5, 134.6, 131.9,

130.5, 126.9, 126.5, 49.8; **ESI-(+)** *m/z* : 240.1 / 238.1 $[M+H]^+$, 167.0, 129.9, 114.0; **HRMS ESI-(+)** calcd for $C_{10}H_9N_3O_2Cl$ $[M+H]^+$ 238.0383, found 238.0385.



12

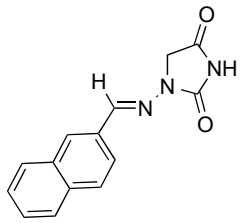
(*E*)-1-((4-chlorobenzylidene)amino)imidazolidine-2,4-dione (12) The reaction scale was 1.98 mmol (*Method B*, 3 cycles of 2h each, with 5 minutes pause in between). The final product was recovered by precipitation in water (439 mg, 93%). White powder; m.p. 240.2 (darkening), 258.7 - 260.7 °C; **^{1}H NMR** (300 MHz, DMSO-d_6) δ (ppm): 11.31 (s, CH=N, 1H), 7.84 (s, 1H, NH), 7.75 (d, J = 9 *Hz*, 2H, CH_{Ar}), 7.55 (d, J = 9 *Hz*, 2H, CH_{Ar}), 4.39 (s, 2H, CH_2); **^{13}C{1H} NMR** (75 MHz, DMSO-d_6) δ (ppm): 169.9, 154.3, 142.6, 135.1, 134.2, 129.9, 129.4, 49.8; **ESI-(+)** *m/z* : 240.1 / 238.1 $[M+H]^+$, 114.0 ; **HRMS ESI-(+)** calcd for $C_{10}H_9N_3O_2Cl$ $[M+H]^+$ 238.0383, found 238.0382.



13

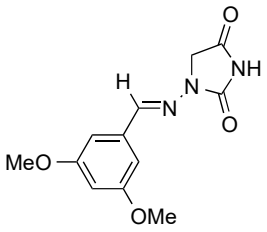
(*E*)-1-((naphthalen-1-ylmethylene)amino)imidazolidine-2,4-dione (13) The reaction scale was 1.98 mmol (*Method B*, 3 cycles of 2h each, with 5 minutes pause in between). The final product was recovered by precipitation in water (466 mg, 93%). White powder; m.p. 250.8 – 253.9 °C (darkening); **^{1}H NMR** (300 MHz, DMSO-d_6) δ (ppm): 11.35 (s, CH=N, 1H), 8.93 (dd, J = 8.4 and 1.5 *Hz*, 1H) 8.42 (s, 1H, NH), 8.06-7.98 (m, 3H), 7.71-7.60 (m, 3H), 4.57 (s, 2H, CH_2); **^{13}C{1H} NMR** (75 MHz, DMSO-d_6) δ (ppm): 170.1, 154.5, 143.3, 134.5, 131.2, 131.1, 130.7, 129.7, 128.1, 127.2, 126.5, 125.4, 49.9; **ESI-(+)** *m/z* : 276.0 $[M+Na]^+$, 254.1 $[M+H]^+$, 154.1, 114.3 ; **HRMS ESI-(+)** calcd for $C_{14}H_{12}N_3O_2$ 254.0930, found 254.0931.

(*E*)-1-((naphthalen-2-ylmethylene)amino)imidazolidine-2,4-dione (14) The reaction scale was 1.98 mmol (*Method B*, 3



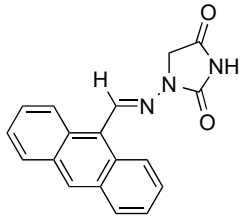
14

cycles of 2h each, with 5 minutes pause in between). The product was scratched out from the jar without any further work-up (477 mg, 95%). White powder; m.p. 251.84 °C (darkening); **^{1}H NMR** (300 MHz, DMSO-d_6) δ (ppm): 11.33 (s, CH=N, 1H), 8.17 (m, 1H), 8.04-7.95 (m, 5H), 7.63-7.58 (m, 2H), 4.46 (s, 2H, CH_2); **^{13}C{1H} NMR** (75 MHz, DMSO-d_6) δ (ppm): 169.7, 154.4, 149.1, 139.1, 134.7, 131.5, 129.3, 129.1, 125.7, 49.8; **ESI-(+)** *m/z* : 276.0 $[M+Na]^+$, 254.1 $[M+H]^+$, 113.9 ; **HRMS ESI-(+)** calcd for $C_{14}H_{12}N_3O_2$ 254.0930, found 254.0932.



15

(*E*)-1-((3,5-dimethoxybenzylidene)amino)imidazolidine-2,4-dione (15) The reaction scale was 1.98 mmol (*Method B*, 3 cycles of 2h each, with 5 minutes pause in between). The final product was recovered by precipitation in water (453 mg, 87%). Pale lila powder; m.p. 244.4 – 245.7 °C; **^{1}H NMR** (300 MHz, DMSO-d_6) δ (ppm): 11.31 (s, CH=N, 1H), 7.77 (s, 1H), 6.90 (d, J = 3.0 Hz, 2H), 6.59 (t, J = 3.0 *Hz*, 1H), 4.38 (s, 2H, CH_2), 3.82 (s, 6H, CH_3); **^{13}C{1H} NMR** (75 MHz, DMSO-d_6) δ (ppm): 169.9, 161.6, 154.4, 143.9, 137.3, 105.6, 102.9, 56.3, 49.9; **ESI-(+)** *m/z* : 327.1 $[M+Na+ACN]^+$, 286.1 $[M+Na]^+$, 264.1 $[M+H]^+$, 114.0; **HRMS ESI-(+)** calcd for $C_{12}H_{14}N_3O_4$ 264.0984, found 264.0984.



16

(*E*)-1-((anthracen-9-ylmethylene)amino)imidazolidine-2,4-dione (16) The reaction scale was 1.32 mmol (*Method B*, 3 cycles of 2h each, with 5 minutes pause in between). The final product was recovered by precipitation in water (380 mg, 95%). Yellow powder; m.p. 274.8 – 282.7 °C (darkening); **^{1}H NMR** (300 MHz, DMSO-d_6) δ (ppm): 11.36 (s, CH=N, 1H), 9.01 (s, 1H), 8.76 (s, 1H), 8.70 (s, 1H), 8.63 (d, J = 9.0 Hz, 2H), 8.14 (d, J = 6.0 *Hz*, 2H), 7.66-7.51 (m, 3H), 4.71 (s, 2H, CH_2); **^{13}C{1H} NMR** (75 MHz, DMSO-d_6) δ (ppm): 170.2, 142.2,

142.2, 131.8, 130.4, 129.9, 129.7, 127.7, 126.7, 126.5, 126.2, 49.9; **ESI-(+)** *m/z* : 629.1 $[2M+Na]^+$, 367.1 $[M+Na+ACN]^+$, 326.1 $[M+Na]^+$, 304.1 $[M+H]^+$, 205.1, 130.2 ; **HRMS ESI-(+)** calcd for $C_{18}H_{14}N_3O_2$ $[M+H]^+$ 304.1086, found 304.1084.

PXDR Analyses of Nitrofurantoin 7.

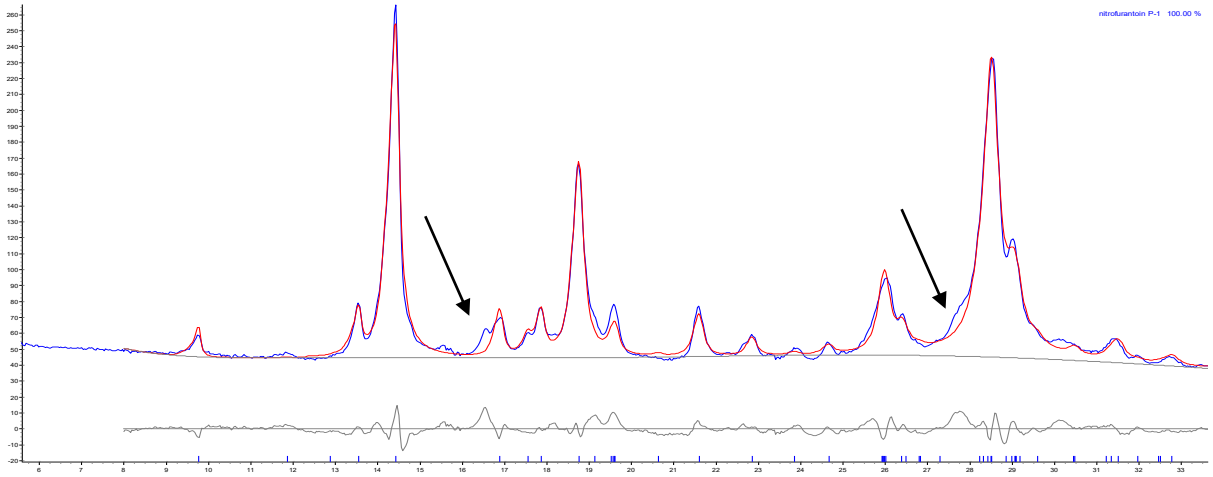


Figure S1. XRD pattern of Nitrofurantoin **7** obtained by *Method B* and recovered by precipitation in water. Rietveld fit modelled with slight preferred orientation. The sample is the triclinic polymorph of nitrofurantoine (CSD refcode LABJON01). The appears to be some impurity with peaks marked with arrows.

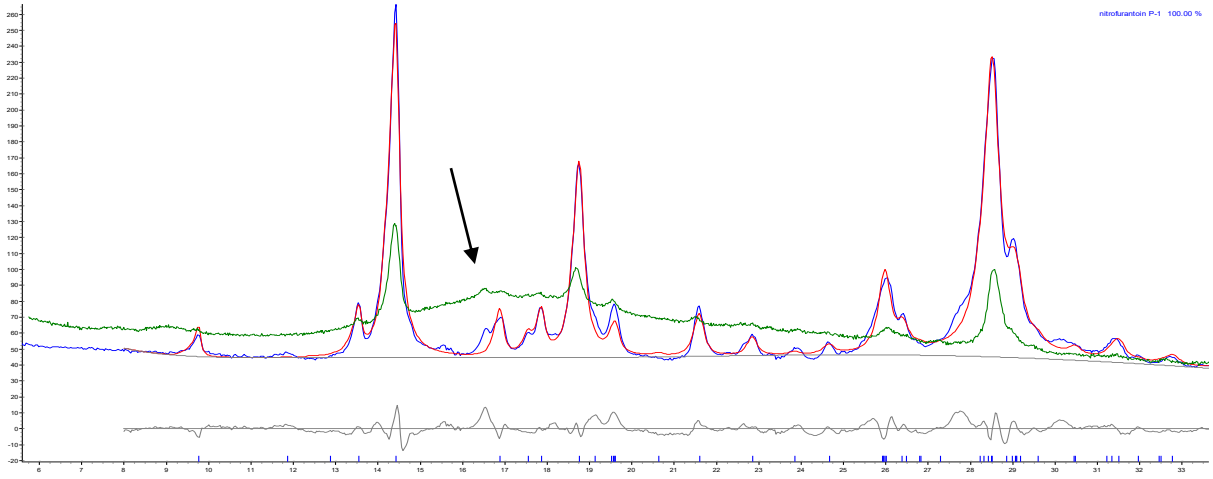


Figure S2. XRD pattern of Nitrofurantoin **7** obtained by *Method C* and directly recovered as a powder from the jar without post-synthetic treatement. **Green pattern** (overlaid with the pattern form given in Figure S1): the sample is the same polymorph of nitrofurantoin **7** as is visible from three strongest peaks. The sample seems to be very amorphous as evident from this big broad hump centered at *ca.* 17 degrees in 2θ.