

Cite this: *Chem. Sci.*, 2021, 12, 3264

All publication charges for this article have been paid for by the Royal Society of Chemistry

Mechanochemical reactivity inhibited, prohibited and reversed by liquid additives: examples from crystal-form screens†

Mihails Arhangelskis,^a Dejan-Krešimir Bučar,^{*b} Simone Bordignon,^c Michele R. Chierotti,^c Samuel A. Stratford,^d Dario Voinovich,^e William Jones^d and Dritan Hasa^{*e}

Received 12th September 2020
Accepted 28th December 2020

DOI: 10.1039/d0sc05071g

rsc.li/chemical-science

We demonstrate that liquid additives can exert inhibitive or prohibitive effects on the mechanochemical formation of multi-component molecular crystals, and report that certain additives unexpectedly prompt the dismantling of such solids into physical mixtures of their constituents. Computational methods were employed in an attempt to identify possible reasons for these previously unrecognised effects of liquid additives on mechanochemical transformations.

Introduction

Multicomponent molecular crystals,¹ such as salts and cocrystals, are highly valuable materials in pharmaceutical,^{2,3} medicinal⁴ and agrochemical^{5,6} research and development. They are also being investigated for applications in molecular electronics,⁷ energetic materials science^{8–10} and pigment chemistry.¹¹ Their functionality, and their significance to the management of patent life-cycles of specialty chemicals,^{12,13} has stimulated the development of various crystallisation and screening techniques for the rapid and thorough discovery of multicomponent molecular solids.¹⁴ Among those, mechanochemical tools¹⁵ emerged as particularly prominent as a result of their efficiency and accessibility.¹⁶

The mechanochemical preparation of salts and cocrystals—whether performed manually using a mortar and pestle, or automatically using mixer mills—is usually conducted in the presence of catalytic amounts of liquid additives to facilitate nucleation,¹⁷ to increase crystallisation rates,¹⁸ to enhance the crystallinity¹⁹ of the solid and to control polymorphism.²⁰ In

some cases, a mechanochemical reaction will not occur in the absence of such additives.^{21,22} The well-known benefits of using catalytic amounts of liquids in mechanochemical reactions, and the dearth of published reports (or even anecdotal evidence) demonstrating any detrimental effects of liquids, generally eliminates the inclination to knead materials in the absence of such additives.¹⁶ Only a small number of published reports mention such detrimental effects, and there is a pronounced shortage of comprehensive studies investigating instances wherein liquid additives have failed to facilitate cocrystal formation. The inability to mechanochemically form a multi-component crystal in the presence of a liquid additive has been, so far, associated with different phenomena. Studies by Friščić *et al.* and Shan *et al.* have attributed failed cocrystallisation attempts to the poor solubility of the cocrystal components in the liquid additive.^{17,18} A more recent study by Tumanov *et al.*, on the other hand, demonstrated that the absorption of atmospheric water by hygroscopic solids leads to the formation of viscous reaction mixtures wherein the reactant particles aggregate, thereby terminating the mechanochemical reaction.²³

Here, we describe instances wherein liquid additives unexpectedly inhibit, prohibit or reverse mechanochemical reactions. We suggest that the described inhibition and prohibition cannot merely be attributed to the poor solubility of the cocrystal components, or to the hygroscopicity and the viscosity of the reactants, but occurs through a mechanism different to those that have been earlier proposed.^{17,18,23} Our findings not only emphasise the multiplicity of roles that liquid additives can have in liquid-assisted grinding (LAG) processes, but also highlight the urgent need to adjust current protocols for highly popular liquid-assisted mechanochemical crystal-form screens, which are nowadays routinely performed in both academic and industrial settings.

^aFaculty of Chemistry, University of Warsaw, 1 Pasteura Street, Warsaw 02-093, Poland

^bDepartment of Chemistry, University College London, 20 Gordon Street, London WC1H 0AJ, UK. E-mail: d.bucar@ucl.ac.uk

^cDepartment of Chemistry and NIS Centre, University of Turin, Via Giuria 7, Torino 10125, Italy

^dDepartment of Chemistry, University of Cambridge, Lensfield Road, Cambridge CB2 1EW, UK

^eDepartment of Chemical and Pharmaceutical Sciences, University of Trieste, Piazzale Europa 1, 34127 Trieste, Italy. E-mail: dhasa@units.it

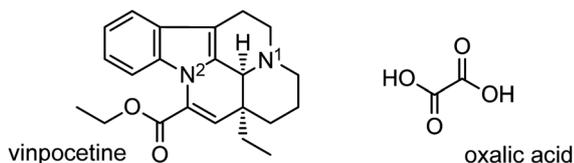
† Electronic supplementary information (ESI) available: Experimental methods, sample characterization, PXRD data, thermal analyses and DFT calculations. CCDC 2024365–2024367. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d0sc05071g



Our interest in vinpocetine²⁴ (**vin**, Scheme 1)—a synthetic vincamine derivative used in the management of cerebrovascular conditions²⁵—inspired an extensive mechanochemical salt screen of **vin** involving a range of carboxylic acids and led to the discovery of a **vin** hydrogenoxalate salt, $(\text{Hvin}^+) \cdot (\text{Hoxa}^-)$. The reactants, **vin** and oxalic acid (H_2oxa , Scheme 1), were expected to form such a salt owing to their pK_a values, which exhibit a ΔpK_a value of approximately 6.5; a value that is significantly higher than the suggested threshold for salt formation.^{26,27} We subsequently performed a polymorph screen of this salt, the main aims of which were: (1) to elucidate the role of solvent polarity and its chemical nature (protic vs. aprotic) on the polymorphism of the $(\text{Hvin}^+) \cdot (\text{Hoxa}^-)$ salt, and (2) to determine how various quantities of the liquid additive affect the polymorphic outcome of the mechanochemical reaction. The second aim was prompted by the recent discovery of the fact that both the nature and amount of the liquid used in LAG reactions (defined by the η parameter¹⁷) can significantly affect the polymorphism of a mechanochemically prepared crystal form.²⁸ Other experimental parameters, such as milling frequency or the amounts of the starting materials used, were not varied in any of the performed LAG experiments reported here. Our results revealed the unusual inhibiting and prohibiting action of liquid additives in LAG crystal-from screens.

Results and discussions

Neat grinding of **vin** and H_2oxa for 60 min (in the absence of any liquid additives, $\eta = 0 \mu\text{L mg}^{-1}$) yielded an amorphous salt (Fig. 1). The formation of this salt was established using powder X-ray diffraction, and both ^{13}C and ^{15}N CPMAS solid-state NMR spectroscopy. In particular, it was observed that the signal at 29.3 ppm, corresponding to the N^1 atom in crystalline **vin** (Scheme 1), shifted downfield to 44.8 ppm in the spectrum of the amorphous solid (Fig. 2). This signal shift is consistent with those previously reported for **vin** salts²⁴ and for other solids containing protonated aliphatic nitrogen atoms.²⁹ We further showed that a crystalline salt does not form even when small amounts of liquid additives are used ($\eta = 0.05 \mu\text{L mg}^{-1}$). The formation of amorphous and poorly crystalline solids in LAG experiments is well known in cases where small amounts of liquid additives are used, and is often attributed to the evaporation of the volatile liquid additives before or during the milling process. We note, however, that this is not the case here, since liquids that exhibit low vapour pressures, namely dimethyl sulfoxide and 2-pyrrolidone, also yielded amorphous solids at $\eta = 0.05 \mu\text{L mg}^{-1}$.



Scheme 1 Molecular structures of vinpocetine (**vin**) and oxalic acid (H_2oxa), the constituents of the vinpocetine hydrogenoxalate salt. The two basic **vin** sites are highlighted as N^1 and N^2 .

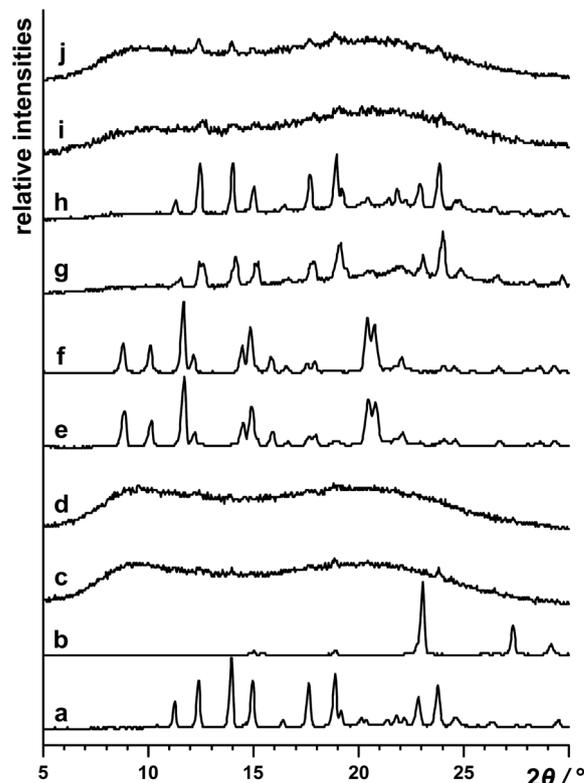


Fig. 1 Powder X-ray patterns of: (a) **vin**, (b) H_2oxa and (c) the product obtained by neat grinding for 60 min of **vin** and H_2oxa ($\eta = 0 \mu\text{L mg}^{-1}$). Diffractograms of products obtained via LAG of **vin** and H_2oxa , using various amounts of different liquid additives, are shown in: (d) ethyl acetate at $\eta = 0.05 \mu\text{L mg}^{-1}$, (e) ethyl acetate at $\eta = 0.15 \mu\text{L mg}^{-1}$, (f) ethyl acetate at $\eta = 0.30 \mu\text{L mg}^{-1}$, (g) nitromethane at $\eta = 0.15 \mu\text{L mg}^{-1}$, (h) nitromethane at $\eta = 0.30 \mu\text{L mg}^{-1}$, (i) ethanol at $\eta = 0.15 \mu\text{L mg}^{-1}$ and (j) ethanol at $\eta = 0.30 \mu\text{L mg}^{-1}$.

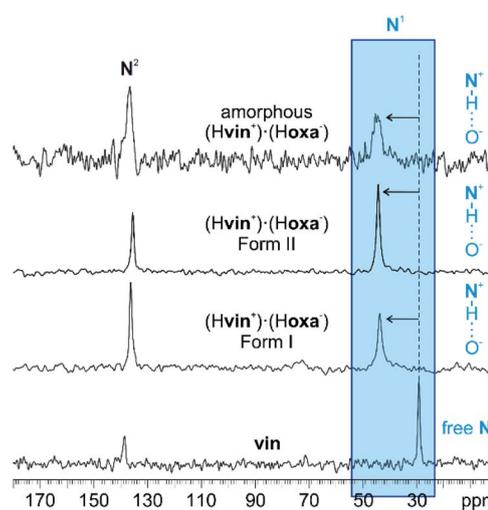


Fig. 2 ^{15}N CPMAS spectra of **vin**, crystalline $(\text{Hvin}^+) \cdot (\text{Hoxa}^-)$ forms I and II and amorphous $(\text{Hvin}^+) \cdot (\text{Hoxa}^-)$. The signal shifts, affiliated with the proton transfer from H_2oxa to **vin**, for the studied material are highlighted in blue. The ^{13}C spectra are shown in Fig. S34 in the ESI† document.



Experiments under LAG conditions, where liquid-additives were used in amounts greater than $\eta = 0.05 \mu\text{L mg}^{-1}$, resulted in three different outcomes. Based on these outcomes, we were able to classify the liquid additives in mechanochemical crystal screens of $(\text{Hvin}^+) \cdot (\text{Hoxa}^-)$ as catalytic, inhibitive and prohibitive.

The first group of liquid additives, consisting of hexane, ethyl acetate, acetone and acetonitrile, enabled the formation of two crystalline $(\text{Hvin}^+) \cdot (\text{Hoxa}^-)$ forms (see Fig. S1–S4 in the ESI† document). While hexane facilitated the formation of form I at $\eta = 0.15 \mu\text{L mg}^{-1}$ and $\eta = 0.30 \mu\text{L mg}^{-1}$, LAG experiments involving acetone, acetonitrile and ethyl acetate resulted in the formation of solvates, which swiftly undergo a complete desolvation at ambient conditions to yield a second polymorph of the salt (form II). Both crystal polymorphs were established as salts using ^{15}N CPMAS NMR spectroscopy and through the presence of the characteristic 44.3 ppm signal of the protonated $\text{N}^1(\text{vin})$ atom in the NMR spectra (Fig. 2). The formation of solvates was confirmed through thermal analyses, and in the case of the ethyl acetate solvate, also by single crystal X-ray diffraction studies. All liquid additives that enabled the formation of a crystalline $(\text{Hvin}^+) \cdot (\text{Hoxa}^-)$ salt were described as *catalytic liquid additives* (Table 1).†

The crystal structure of form I was determined using laboratory powder X-ray data. The salt crystallises in the $P2_1$ space group with one Hvin^+ cation and one Hoxa^- anion in the asymmetric unit. The Hoxa^- anions form helical molecular chains *via* C(5) O–H \cdots O $^-$ hydrogen bonds³⁰ (Fig. 3a). The helical structures are left-handed and exhibit a 7.6 Å pitch. The Hvin^+ cations link the helical tapes *via* D(2) N $^+$ –H \cdots O $^-$ hydrogen bonds³⁰ (Fig. 3a and b). The $(\text{Hvin}^+) \cdot (\text{Hoxa}^-)$ assemblies interact with each other through C–H \cdots O forces.

Form II was structurally characterised by single crystal X-ray diffraction using a crystal of an ethyl acetate salt hemisolvate, which was grown *via* slow solvent evaporation from an ethyl acetate solution and then spontaneously, rapidly and completely desolvated at ambient conditions in a single-crystal-to-single-crystal fashion.³¹ Structural analyses showed that the polymorph crystallises in the chiral space group $C2$; again, with one Hvin^+ cation and one Hoxa^- anion in the asymmetric unit.

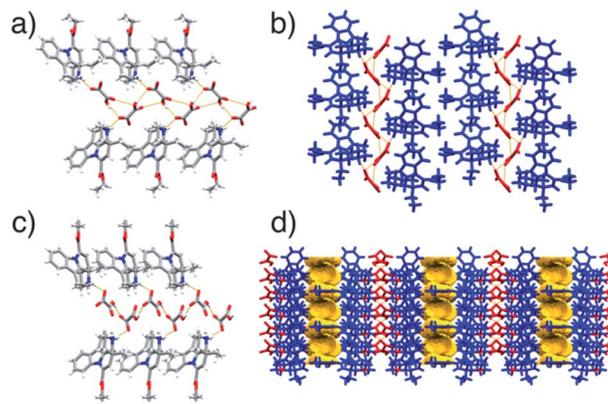


Fig. 3 Helical hydrogen-bonded $\text{Hvin}^+ \cdot \text{Hoxa}^-$ assemblies in the crystal structures of: (a) form I, viewed along the crystallographic planes (401) and (010); (b) form I, viewed along the crystallographic axis c. Crystal packing diagrams of $\text{Hvin}^+ \cdot \text{Hoxa}^-$ assemblies in: (c) form II, viewed along the crystallographic planes (103) and (010); and (d) form II, featuring voids (highlighted in yellow) and viewed along the crystallographic axis a.

The structure also features helical Hoxa^- chains that are, similarly to those seen in form I, sustained by C(5) O–H \cdots O $^-$ hydrogen bonds³⁰ and that interact with Hvin^+ cations *via* D(2) N $^+$ –H \cdots O $^-$ hydrogen bonds.³⁰ The pitch of the helical chain is, however, somewhat shorter and only 6.3 Å long (Fig. 3c). The helical assemblies interact with each other with a set of C–H \cdots O interactions that is different to that observed in form I. Notably, the crystal structure of form II exhibits sizeable voids ($V_{\text{void}} = 105 \text{ \AA}^3$ at 150 K), which are aligned along the crystallographic planes (110) and (002) (Fig. 3d). Details pertaining to the structural characterisation of forms I, II and the ethyl acetate hemisolvate are described in the ESI document (Fig. S32–S33 and Tables S1–S2†).

The relative stability of the two polymorphs was evaluated using periodic DFT-d methods and the CASTEP plane-wave code.³² The crystal structures were optimised using the Perdew–Burke–Ernzerhof (PBE) functional,³³ combined with the many-body dispersion (MBD*) correction.³⁴ The calculations revealed that form II is 14.3 kJ mol^{-1} more stable than form I.

Table 1 Summary of liquid-assisted and neat grinding experiments performed with liquid additives that vary in their chemical nature (protic vs. aprotic), polarity (ϵ) and quantities used (η)^a

Liquid additive	Protic vs. aprotic	ϵ	$\eta/\mu\text{L mg}^{-1}$			Type of liquid additive
			0.05	0.15	0.30	
Hexane	Aprotic	1.89	■ □	○ △	△	Catalytic
Ethyl acetate	Aprotic	6.02	■	▲	▲	
Acetone	Aprotic	20.7	■	▲	▲	
Acetonitrile	Aprotic	37.5	■	▲	▲	
Ethanol	Protic	24.5	■	■	■	Inhibitive
Methanol	Protic	32.7	■	■	■	
2-Pyrrolidone	Protic	23.6	■	○	○	Prohibitive
Nitromethane	Aprotic	35.9	■	○	○	
DMSO	Aprotic	47.2	■	○	○	

^a Amorphous salt: ■, physical mixture of reactants: ○, form I: △, form II: ▲.



Such relative stabilities are unexpected considering the higher density of form I, as compared to that of form II, but not unusual bearing in mind that the majority of cocrystals pack less efficiently in the crystalline state than their constituents.³⁵ We note that forms I, II and amorphous $(\text{Hvin}^+) \cdot (\text{Hoxa}^-)$ show similar *in vitro* dissolution profiles, despite their significant structural differences (Fig. S35–S37 in the ESI† document).

The second group of liquids consists of ethanol and methanol. Both liquids enabled the formation of an amorphous salt, but not the formation of a crystalline product under LAG conditions at η values higher than $0.05 \mu\text{L mg}^{-1}$ (Fig. 1 and S5–S6 in the ESI† document). Since the additives appeared to curb or slow down the crystallisation of the product, they are described as *inhibitive liquid additives* (Table 1).

Lastly, the use of a third group of liquids, involving 2-pyrrolidone, dimethyl sulfoxide and nitromethane, unexpectedly yielded only physical mixtures of the reactants upon milling for 60 min at higher η values (0.15 and $0.30 \mu\text{L mg}^{-1}$) (Fig. 1 and S7–S9 in the ESI† document). This group of liquids appeared to preclude any chemical or physical reactivity and was accordingly categorised as *prohibitive liquid additives* (Table 1).

The prohibitive action of these three liquids clearly demonstrates that, in general, the role of liquid additives is significantly more complex than being solely a lubricant that facilitates molecular diffusion between colliding particles,³⁶ or a means to lower an energy pathway to the nucleation of a crystal form.³⁷ The initially observed prohibiting action of these additives raises the obvious question of whether they are indeed prohibiting the formation of a salt, or whether they are only severely delaying the transformation of a physical mixture of reactants into a crystalline salt through a transient amorphous salt phase.

To further test the prohibitive nature of this class of additives, we performed LAG experiments that involved the milling of the amorphous and crystalline salt forms with each of the prohibitive additives (namely nitromethane, DMSO and 2-pyrrolidone) for 60 min. Remarkably, the experiments revealed the disintegration of the salt into a physical mixture of the reactants when DMSO was used as additive (Table 2), thus proving that this liquid is indeed prohibiting the formation of the target solid. Such disintegration was not observed in LAG experiments involving nitromethane or 2-pyrrolidone. This observation is particularly interesting in light of the fact that forms I and II could not be converted into a physical mixture of crystalline **vin** and H_2oxa in the absence of liquid additives. Instead, the crystalline $(\text{Hvin}^+) \cdot (\text{Hoxa}^-)$ salt was transformed into an amorphous salt when ground for 60 min without additives. The amorphous product was subsequently converted into crystalline forms I and II without difficulty using catalytic additives ethyl acetate and hexane (respectively), thereby emphasising the diversity of roles that liquid additives can play in mechanochemical crystal-form screens (Fig. 4 and S10–S12 in the ESI† document).

Further studies were focused on the role of water as inhibitor of the mechanochemical salt formation. Specifically, we aimed to elucidate whether atmospheric water suppresses the mechanochemical reactivity of **vin**: H_2oxa physical mixtures through the formation of viscous and thus unreactive solids, as previously observed by Tumanov *et al.*²³ These studies were prompted by the

Table 2 Summary of the outcomes of liquid-assisted grinding experiments involving multi-component crystals in the presence of prohibitive liquid additives^a

Crystal form	Structural changes		
	Nitromethane	DMSO	2-Pyrrolidone
$(\text{Hvin}^+) \cdot (\text{Hoxa}^-)$, form I	△	○	■
$(\text{Hvin}^+) \cdot (\text{Hoxa}^-)$, form II	■	○	■
$(\text{thp}) \cdot (23\text{diFBA})$	○	○	○
$(\text{thp}) \cdot (26\text{diFBA})$	■	○	●
$2(\text{thp}) \cdot 3(\text{ana})$	■	○	●
$(\text{ibu}) \cdot (\text{nic})$	■	■	■
$(\text{pca}) \cdot (\text{oxa})$	■	○	●
$(\text{caf}) \cdot (\text{cou})$	■	■	■

^a No structural change observed: ■, partial or full decomposition into physical mixture of reactants: ○, partial or full decomposition into physical a mixture of a reactant and a new crystal form: ●, polymorphic transformation: △.

inevitable introduction of water into **vin**: H_2oxa reaction mixtures owing to the hygroscopic nature of anhydrous H_2oxa and its fast conversion into its hydrated form. Mechanochemical experiments involving water as additive have revealed the formation of a hydrated $(\text{Hvin}^+) \cdot (\text{Hoxa}^-)$ salt, as evidenced by powder diffraction and thermogravimetric analysis. This demonstrates that the presence of atmospheric water (and water included in the crystals of H_2oxa) does not inhibit or prohibit mechanochemical reactions between **vin** and H_2oxa in any of the discussed experiments (see Fig. S25–S31 in the ESI† document).

In an effort to understand the observed effects of the selected liquid additives on the mechanochemical formation of $(\text{Hvin}^+) \cdot (\text{Hoxa}^-)$, and to identify how various solvents affect its nucleation behaviour, we employed simple and accessible DFT-d calculations to study proton transfers from H_2oxa to **vin**,

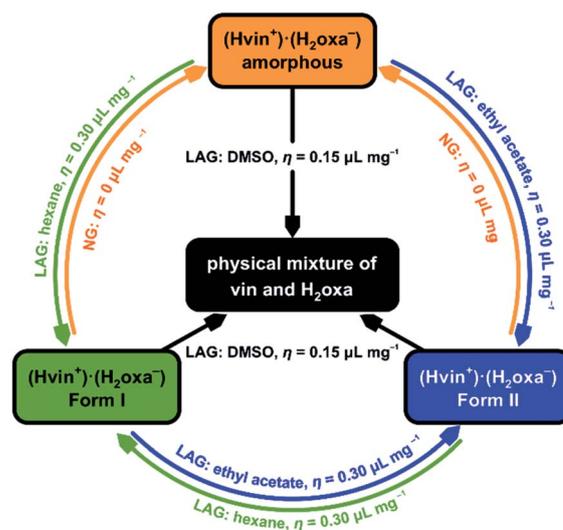


Fig. 4 Diagram summarising all interconversion LAG experiments performed and highlighting the catalytic, inhibitive and prohibitive actions of the studied liquid additives.



and the stability of $\text{Hvin}^+:\text{Hoxa}^-$ assemblies in a range of solvent environments, which were represented using a continuum SMD model (see Table S3 in the ESI† document for computational results and a brief discussion thereof).³⁸ The inability to rationalise the prohibitive, inhibitive and catalytic actions of the studied additives on the crystallisation of forms I and II using such basic DFT-d methods suggests that more elaborate computational methods need to be employed. We envision that a fundamental understanding of the described phenomena will be likely reached through the combined use of large-scale molecular dynamics simulations and DFT-d calculations. We note that molecular dynamics simulations were recently successfully employed by Ferguson *et al.* to simulate the early stages of mechanochemical cocrystallisations and to study the effects of small amounts of liquid additives on mechanochemical cocrystal formation,³⁷ while DFT-d calculations were utilised by Belenguer *et al.* to evaluate solvation and surface effects on the stabilities of mechanochemically prepared polymorphs of organic compounds.³⁹

The prohibitive action of liquid additives described herein is not an isolated case, as evidenced by other instances where the addition of a particular liquid to a solid reaction mixture precluded the formation of a cocrystal. For example, one such instance was recently discovered in our laboratories during an unrelated study of supramolecular synthons in a series of cocrystals composed of theophylline and fluorobenzoic acid isomers.⁴⁰ The cocrystallisation of theophylline (**thp**) with the fluorobenzoic acids was attempted through LAG and it was found that a cocrystal cannot be prepared using 2,3- and 2,6-difluorobenzoic acid (**23diFBA** and **26diFBA**, respectively) as cocrystal formers when nitromethane is used as liquid additive. While the cocrystallisation of the elusive cocrystals was readily achieved using ethanol as additive (Fig. S23–S24 in the ESI† document), the fact that nitromethane prohibited the formation of $(\text{Hvin}^+):(\text{Hoxa}^-)$ and the two theophylline cocrystals raised the question of whether its prohibitive action is specific only to the three studied solids, or whether nitromethane (as well as 2-pyrrolidone and DMSO) can be more generally regarded as prohibitive. Our curiosity was further heightened by a serendipitous discovery during an attempt to prepare form I of the $(\text{Hvin}^+):(\text{Hoxa}^-)$ salt. Specifically, we found that the inadvertent use of cyclohexane, instead of hexane, prevented the formation of the salt. This recalled the fact that cyclohexane precluded the formation of three different cocrystals in studies reported by Frišćić, Childs, Rizvi and Jones.^{17,18} With these examples in mind, we subjected the two **thp** cocrystals and another four arbitrarily selected cocrystals (which are based on **thp**, **H₂oxa**, **ibuprofen (ibu)**, **paracetamol (pca)**, **caffeine (caf)**, **nicotinamide (nic)**, **anthranilic acid (ana)**) to LAG in the presence of the prohibitive additives. We found a substantial number of cases in which the use of a prohibitive additive led to the decomposition of the cocrystal into a physical mixture of its constituents (Table 2 and Fig. S38–S57 in the ESI† document). The mechanistic aspects of the observed cocrystal disintegration are, so far, not understood. But keeping in mind that nitromethane, for example, is commonly and successfully used in cocrystal screens,⁴⁰ we reason that the prohibitive action of

a liquid additive is specific to certain multi-component crystal systems, rather than general and applicable to a larger group of cocrystal systems.

Conclusions

We have shown that mechanochemical reactivity can be inhibited, prohibited and reversed with the use of liquid additives. Our findings, and attempts to rationalise them, stress the current gaps in our knowledge about the role of liquid additives in mechanochemical reactions, as well as the urgent need to study and understand solvent effects in mechanochemical reactions. Our discoveries also suggest that widely accepted and commonly utilised procedures for mechanochemical crystal-form screens (wherein the use of only one solvent as liquid additive is deemed as suitable), should be revised. Specifically, we recommend the use of numerous types of liquid additives in crystal form screens in order to eliminate the possible occurrence of false negative results, which can seriously obstruct the development of marketable functional materials in industrial research and development exercises. We also speculate that liquid additives may be able to act prohibitively in other mechanochemical processes relevant to chemical and materials synthesis.^{41,42} We are therefore engaging in further studies to elucidate the mechanisms through which the reported solid-state reactions are catalysed, inhibited and prohibited. These will also include investigations into the role of (un)intentional seeding on the action of the different additive types.^{43,44}

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

M.A. thanks the National Science Center of Poland for the financial support *via* SONATA grant (2018/31/D/ST5/03619). Periodic and molecular DFT calculations were performed on the *Prometheus* supercomputer (*Cyfronet*, Krakow) to which access was granted *via* the PLGrid consortium. The UK's EPSRC is acknowledged for the funding of the crystallographic studies *via* grant EP/K03930X/1. Divya Amin is gratefully acknowledged for her help with the collection of capillary powder X-ray diffraction data. Prof. Gareth R. Williams, Sebastian Gurgul and Karolina Dziemidowicz are thanked for their help with TGA and DSC measurements. Professor Krzysztof Woźniak is gratefully acknowledged for access to the TGA/DSC instrument and Professor Damian Pocięcha for assisting with powder X-ray diffraction experiments performed at the University of Warsaw. The Reviewers are thanked for useful discussions and suggestions.

Notes and references

† We note that ethyl acetate, acetonitrile and acetone may be also suitably described as *reactants* in the mechanochemical formation of the hemisolvate of the $(\text{Hvin}^+):(\text{Hoxa}^-)$ salt. But considering that these liquids also template the formation of solvent-free and porous form II, we find that they are well suited to be described as *catalytic liquid additives*.



- 1 S. Aitipamula, R. Banerjee, A. K. Bansal, K. Biradha, M. L. Cheney, A. R. Choudhury, G. R. Desiraju, A. G. Dikundwar, R. Dubey, N. Duggirala, P. P. Ghogale, S. Ghosh, P. K. Goswami, N. R. Goud, R. R. K. R. Jetti, P. Karpinski, P. Kaushik, D. Kumar, V. Kumar, B. Moulton, A. Mukherjee, G. Mukherjee, A. S. Myerson, V. Puri, A. Ramanan, T. Rajamannar, C. M. Reddy, N. Rodriguez-Hornedo, R. D. Rogers, T. N. G. Row, P. Sanphui, N. Shan, G. Shete, A. Singh, C. C. Sun, J. A. Swift, R. Thaimattam, T. S. Thakur, R. Kumar Thaper, S. P. Thomas, S. Tothadi, V. R. Vangala, N. Variankaval, P. Vishweshwar, D. R. Weyna and M. J. Zaworotko, *Cryst. Growth Des.*, 2012, **12**, 2147–2152.
- 2 N. K. Duggirala, M. L. Perry, Ö. Almarsson and M. J. Zaworotko, *Chem. Commun.*, 2016, **52**, 640–655.
- 3 G. Bolla and A. Nangia, *Chem. Commun.*, 2016, **52**, 8342–8360.
- 4 K. Fucke, M. J. G. Peach, J. A. K. Howard and J. W. Steed, *Chem. Commun.*, 2012, **48**, 9822–9824.
- 5 B. Sandhu, A. S. Sinha, J. Desper and C. B. Aakeröy, *Chem. Commun.*, 2018, **54**, 4657–4660.
- 6 L. Casali, L. Mazzei, O. Shemchuk, L. Sharma, K. Honer, F. Grepioni, S. Ciurli, D. Braga and J. Baltrusaitis, *ACS Sustainable Chem. Eng.*, 2019, **7**, 2852–2859.
- 7 H. Jiang and W. Hu, *Angew. Chem., Int. Ed.*, 2019, **59**, 1408–1428.
- 8 H. M. Titi, M. Arhangelskis, G. P. Rachiero, T. Frišćić and R. D. Rogers, *Angew. Chem., Int. Ed.*, 2019, **131**, 18570–18575.
- 9 C. B. Aakeröy, T. K. Wijethunga and J. Desper, *Chem.–Eur. J.*, 2015, **21**, 11029–11037.
- 10 K. B. Landenberger, O. Bolton and A. J. Matzger, *J. Am. Chem. Soc.*, 2015, **137**, 5074–5079.
- 11 D.-K. Bučar, S. Filip, M. Arhangelskis, G. O. Lloyd and W. Jones, *CrystEngComm*, 2013, **15**, 6289–6291.
- 12 A. V. Trask, *Mol. Pharm.*, 2007, **4**, 301–309.
- 13 Ö. Almarsson, M. L. Peterson and M. Zaworotko, *Pharm. Pat. Anal.*, 2012, **1**, 313–327.
- 14 K. Fucke, S. A. Myz, T. P. Shakhshneider, E. V. Boldyreva and U. J. Griesser, *New J. Chem.*, 2012, **36**, 1969–1977.
- 15 S. L. James, C. J. Adams, C. Bolm, D. Braga, P. Collier, T. Frišćić, F. Grepioni, K. D. M. Harris, G. Hyett, W. Jones, A. Krebs, J. Mack, L. Maini, A. G. Orpen, I. P. Parkin, W. C. Shearouse, J. W. Steed and D. C. Waddell, *Chem. Soc. Rev.*, 2012, **41**, 413–447.
- 16 D. Hasa and W. Jones, *Adv. Drug Delivery Rev.*, 2017, **117**, 147–161.
- 17 T. Frišćić, S. L. Childs, S. A. A. Rizvi and W. Jones, *CrystEngComm*, 2009, **11**, 418–426.
- 18 N. Shan, F. Toda and W. Jones, *Chem. Commun.*, 2002, 2372–2373, DOI: 10.1039/B207369M.
- 19 K. Lien Nguyen, T. Frišćić, G. M. Day, L. F. Gladden and W. Jones, *Nat. Mater.*, 2007, **6**, 206–209.
- 20 A. V. Trask, N. Shan, W. D. S. Motherwell, W. Jones, S. Feng, R. B. H. Tan and K. J. Carpenter, *Chem. Commun.*, 2005, 880–882, DOI: 10.1039/B416980H.
- 21 D. Braga, S. L. Giaffreda, F. Grepioni, M. R. Chierotti, R. Gobetto, G. Palladino and M. Polito, *CrystEngComm*, 2007, **9**, 879–881.
- 22 E. Boldyreva, *Chem. Soc. Rev.*, 2013, **42**, 7719–7738.
- 23 I. A. Tumanov, A. A. L. Michalchuk, A. A. Politov, E. V. Boldyreva and V. V. Boldyrev, *Dokl. Chem.*, 2017, **472**, 17–19.
- 24 D. Hasa, D. Voinovich, B. Perissutti, M. Grassi, A. Bonifacio, V. Sergo, C. Cepek, M. R. Chierotti, R. Gobetto, S. Dall'Acqua and S. Invernizzi, *Pharm. Res.*, 2011, **28**, 1870–1883.
- 25 Y. Zhang, J.-d. Li and C. Yan, *Eur. J. Pharmacol.*, 2017, 819.
- 26 A. J. Cruz-Cabeza, *CrystEngComm*, 2012, **14**, 6362–6365.
- 27 M. K. Corpinot and D.-K. Bučar, *Cryst. Growth Des.*, 2019, **19**, 1426–1453.
- 28 D. Hasa, E. Miniussi and W. Jones, *Cryst. Growth Des.*, 2016, **16**, 4582–4588.
- 29 P. Cerreia Vioglio, M. R. Chierotti and R. Gobetto, *Adv. Drug Delivery Rev.*, 2017, **117**, 86–110.
- 30 M. C. Etter, J. C. MacDonald and J. Bernstein, *Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem.*, 1990, **46**, 256–262.
- 31 A. J. Cruz Cabeza, G. M. Day, W. D. S. Motherwell and W. Jones, *Chem. Commun.*, 2007, 1600–1602, DOI: 10.1039/B701299C.
- 32 S. J. Clark, M. D. Segal, C. J. Pickard, P. J. Hasnip, M. I. J. Probert, K. Refson and M. C. Payne, *Z. Kristallogr.*, 2005, **220**, 567–570.
- 33 J. P. Perdew, K. Burke and M. Ernzerhof, *Phys. Rev. Lett.*, 1996, **77**, 3865–3868.
- 34 A. Tkatchenko, R. A. DiStasio, R. Car and M. Scheffler, *Phys. Rev. Lett.*, 2012, **108**, 236402.
- 35 C. R. Taylor and G. M. Day, *Cryst. Growth Des.*, 2018, **18**, 892–904.
- 36 T. Frišćić and W. Jones, *Cryst. Growth Des.*, 2009, **9**, 1621–1637.
- 37 M. Ferguson, M. S. Moyano, G. A. Tribello, D. E. Crawford, E. M. Bringa, S. L. James, J. Kohanoff and M. G. Del Pópolo, *Chem. Sci.*, 2019, **10**, 2924–2929.
- 38 A. V. Marenich, C. J. Cramer and D. G. Truhlar, *J. Phys. Chem. B*, 2009, **113**, 6378–6396.
- 39 A. M. Belenguer, G. I. Lampronti, A. J. Cruz-Cabeza, C. A. Hunter and J. K. M. Sanders, *Chem. Sci.*, 2016, **7**, 6617–6627.
- 40 M. K. Corpinot, S. A. Stratford, M. Arhangelskis, J. Anka-Lufford, I. Halasz, N. Judaš, W. Jones and D.-K. Bučar, *CrystEngComm*, 2016, **18**, 5434–5439.
- 41 J. L. Howard, Q. Cao and D. L. Browne, *Chem. Sci.*, 2018, **9**, 3080–3094.
- 42 T. Frišćić, C. Mottillo and H. M. Titi, *Angew. Chem., Int. Ed.*, 2020, **59**, 1018–1029.
- 43 D.-K. Bučar, G. M. Day, I. Halasz, G. G. Z. Zhang, J. R. G. Sander, D. G. Reid, L. R. MacGillivray, M. J. Duer and W. Jones, *Chem. Sci.*, 2013, **4**, 4417–4425.
- 44 D. Hasa, M. Marosa, D.-K. Bučar, M. K. Corpinot, D. Amin, B. Patel and W. Jones, *Cryst. Growth Des.*, 2020, **20**, 1119–1129.



Electronic Supporting Information

Mechanochemical reactivity inhibited, prohibited and reversed by liquid additives: Examples from crystal-form screens

Mihails Arhangel'skis, Dejan-Krešimir Bučar, Simone Bordignon, Michele R. Chierotti,
Samuel A. Stratford, Dario Voinovich, William Jones and Dritan Hasa

Table of contents

1. Materials	3
2. Mechanochemical experiments	3
2.1 Experimental section	3
2.1.1 Milling experiments involving vinpocetine and oxalic acid	3
2.1.2 Milling experiments involving theophylline and fluorobenzoic acids	4
2.1.3 Powder X-ray diffraction analyses	4
2.2 Results	4
2.2.1 PXRD results of LAG experiments performed at different η values.....	4
2.2.2 Interconversion experiments.....	13
2.2.3 Effects of milling time.....	16
2.2.4 Theophylline:fluorobenzoic acid cocrystals	26
3. Probing the effect of presence of water/humidity during the grinding experiments	28
3.1 Experimental section	28
3.1.1 LAG experiments.....	28
3.1.2 PXRD analysis.....	28
3.1.3 Differential scanning calorimetry (DSC) analysis and thermogravimetric analysis (TGA).....	28
3.2 Results	29
3.2.1 LAG experiments with water	29
3.2.2 LAG experiments with dried liquid additives	31
4. Structure determination by X-ray crystallography	34
4.1 Structure determination of $(Hvin^+) \cdot (Hoxa^-)$, Form I	34
4.2 Structure determination of $(Hvin^+) \cdot (Hoxa^-)$, Form II and $(Hvin^+) \cdot (Hoxa^-) \cdot (EtOAc)_{0.16}$	35
5. Solid-state NMR analysis	38
6. DFT Calculations	39
6.1 Experimental section	39
6.2 Results and discussion	39
7. Dissolution Kinetic Tests	40
8. Liquid-assisted grinding of selected cocrystals with prohibitive liquid additives	42
8.1 Theophylline:2,3-difluorobenzoic acid and theophylline:2,6-difluorobenzoic cocrystals	42
8.2. Theophylline:anthranilic acid cocrystal	44
8.3 Ibuprofen:nicotinamide cocrystal	48
8.4 Paracetamol:oxalic acid cocrystal	51
8.5 Caffeine:p-coumaric acid cocrystal	54
9. References	57

1. Materials

Vinopoxetine (**vin**) (99%) was purchased from *Linnea SA Riazzino-Locarno*, CH. Anthranilic acid (**ana**) ($\geq 98\%$), caffeine (**caf**) (*ReagentPlus*[®]), 2,3-difluorobenzoic acid (**23diFBA**) (98%), ibuprofen ($\geq 98\%$), nicotinamide ($\geq 99.5\%$), oxalix acid (H_2 **oxa**) (99%), paracetamol (**par**) (98%), theophylline (**thp**) (99%) and all solvents ($\geq 99\%$) were obtained from *Sigma Aldrich*, Ltd. (Gillingham, UK), while 2,6-difluorobenzoic acid (**26diFBA**) (97%) was purchased from *Maybridge*.

2. Mechanochemical experiments

2.1 Experimental Section

2.1.1 Milling Experiments involving vin and H₂oxa

Neat- and liquid-assisted grinding (LAG) experiments were performed using a *Retsch MM200* mixer mill. In a typical experiment, 200 mg of equimolar physical mixture of **vin** and H_2 **oxa** (approximately 159 mg of **vin** and 41 mg of H_2 **oxa**) were added to a 15 mL steel milling jar containing two milling balls (7 mm diameter). Different amounts of liquid additives (η value in the 0.05-0.30 $\mu\text{L mg}^{-1}$ range) were also added prior to milling. The mixture was subsequently milled for 60 min at a frequency of 25 Hz. Snap-closed milling jars (*FormTech Scientific*) were used to minimise liquid evaporation.

In the case of the interconversion experiments, amorphous (H **vin**⁺)·(H **oxa**⁻) was prepared by neat grinding of a 1:1 molar mixture of **vin** and H_2 **oxa** for 60 minutes at 25 Hz, while the (H **vin**⁺)·(H **oxa**⁻) Forms I and II were prepared by LAG using ethyl acetate and hexane as liquid additives ($\eta=0.30 \mu\text{L mg}^{-1}$), respectively. The purity of the preformed products was verified by PXRD. Approximately 150 mg of preformed (H **vin**⁺)·(H **oxa**⁻) (either as crystalline Form I, Form II, or amorphous salt) were separately treated for other 60 min at 25 Hz under four different conditions: (i) neat grinding, (ii) LAG with dimethyl sulfoxide, nitromethane and 2-pyrrolidone ($\eta=0.15 \mu\text{L mg}^{-1}$), (iii) LAG using ethyl acetate ($\eta=0.15 \mu\text{L mg}^{-1}$) and LAG using hexane ($\eta=0.30 \mu\text{L mg}^{-1}$). The final products were characterised using PXRD.

In a typical *ex situ* experiment, 200 mg of an equimolar physical mixture of **vin** and H_2 **oxa** (approximately 159 mg of **vin** and 41 mg of H_2 **oxa**), together with a specific liquid (in the η range of 0.05–0.30 $\mu\text{L mg}^{-1}$) were processed for either 20, 40 or 60 min.

2.1.2 Milling experiments involving theophylline and fluorobenzoic acids

The mechanochemical cocrystal syntheses were attempted by LAG using either a *Retsch MM200* or a *FormTech Scientific FTS1000* mill. In a typical milling experiment, 200 mg of a physical mixture of equimolar amounts of thp and a FBA were added to a 15 mL stainless steel grinding jar, along with 50 μL of nitromethane ($\eta = 0.25 \mu\text{L mg}^{-1}$) and two 7 mm stainless steel milling balls. The mixer mill was operated at 30 Hz for 30 min. The obtained solids were subsequently analysed by powder X-ray diffraction.

2.1.3 Powder X-ray diffraction analyses

Unless indicated otherwise, the mechanochemically prepared solids were characterised by powder X-ray diffraction (PXRD) using a *Panalytical X'Pert Pro* diffractometer with Ni-filtered $\text{CuK}\alpha$ radiation at a wavelength of 1.5418 Å equipped with an RTMS X'celerator detector. For each experiment,

approximately 20-25 mg of mechanochemical product was gently pressed on a glass slide to give a flat surface. The data were collected in the 3–40° 2 θ range using a step size of 0.0334° and a scan speed of 0.142° s⁻¹.

2.2 Results

2.2.1 PXRD Results of LAG experiments performed at different η values

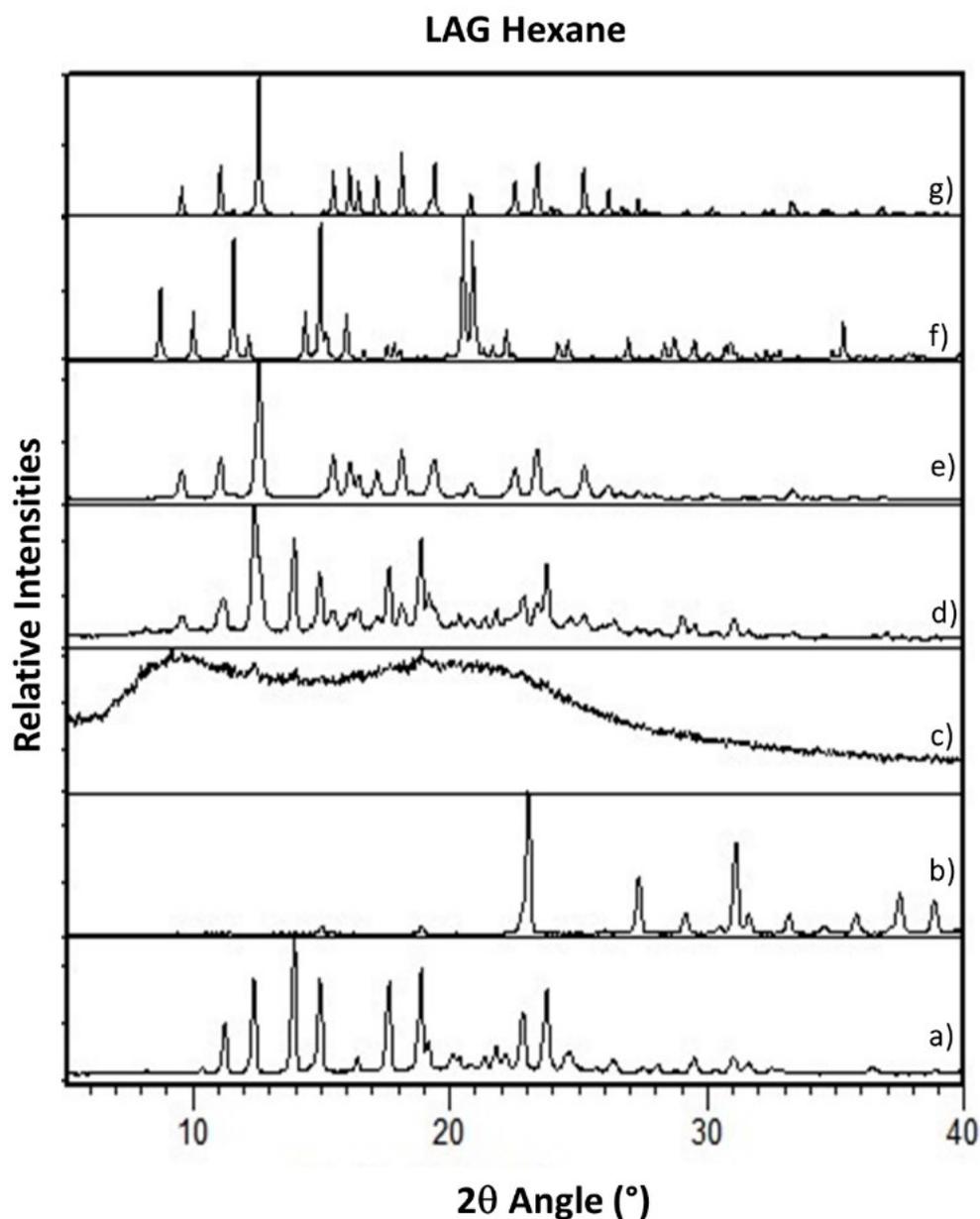


Figure S1. PXRD patterns of: (a) pure **vin**, (b) pure **H₂oxa**, (c), (d) and (e) the solid obtained through LAG of **vin** and **H₂oxa** using hexane as liquid additive at η values of 0.05 $\mu\text{L mg}^{-1}$, 0.15 $\mu\text{L mg}^{-1}$ and 0.30 $\mu\text{L mg}^{-1}$, respectively, (f) calculated pattern of Form II, (g) calculated pattern of Form I.

Ethyl Acetate

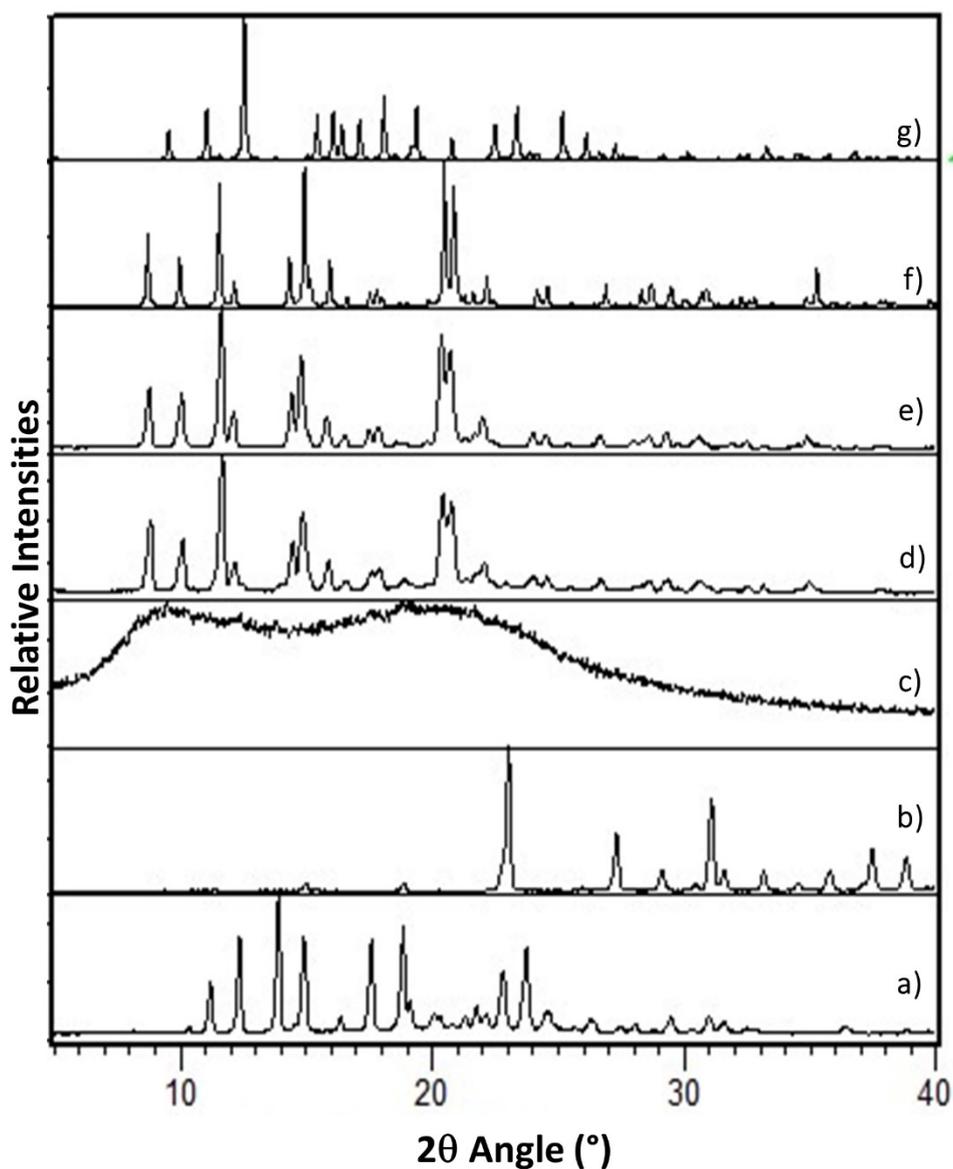


Figure S2. PXR D patterns of: (a) pure **vin**, (b) pure **H₂oxa**, (c), (d) and (e) the solid obtained through LAG of **vin** and **H₂oxa** using ethyl acetate as liquid additive at η values of $0.05 \mu\text{L mg}^{-1}$, $0.15 \mu\text{L mg}^{-1}$ and $0.30 \mu\text{L mg}^{-1}$, respectively, (f) calculated pattern of Form II, (g) calculated pattern of Form I.

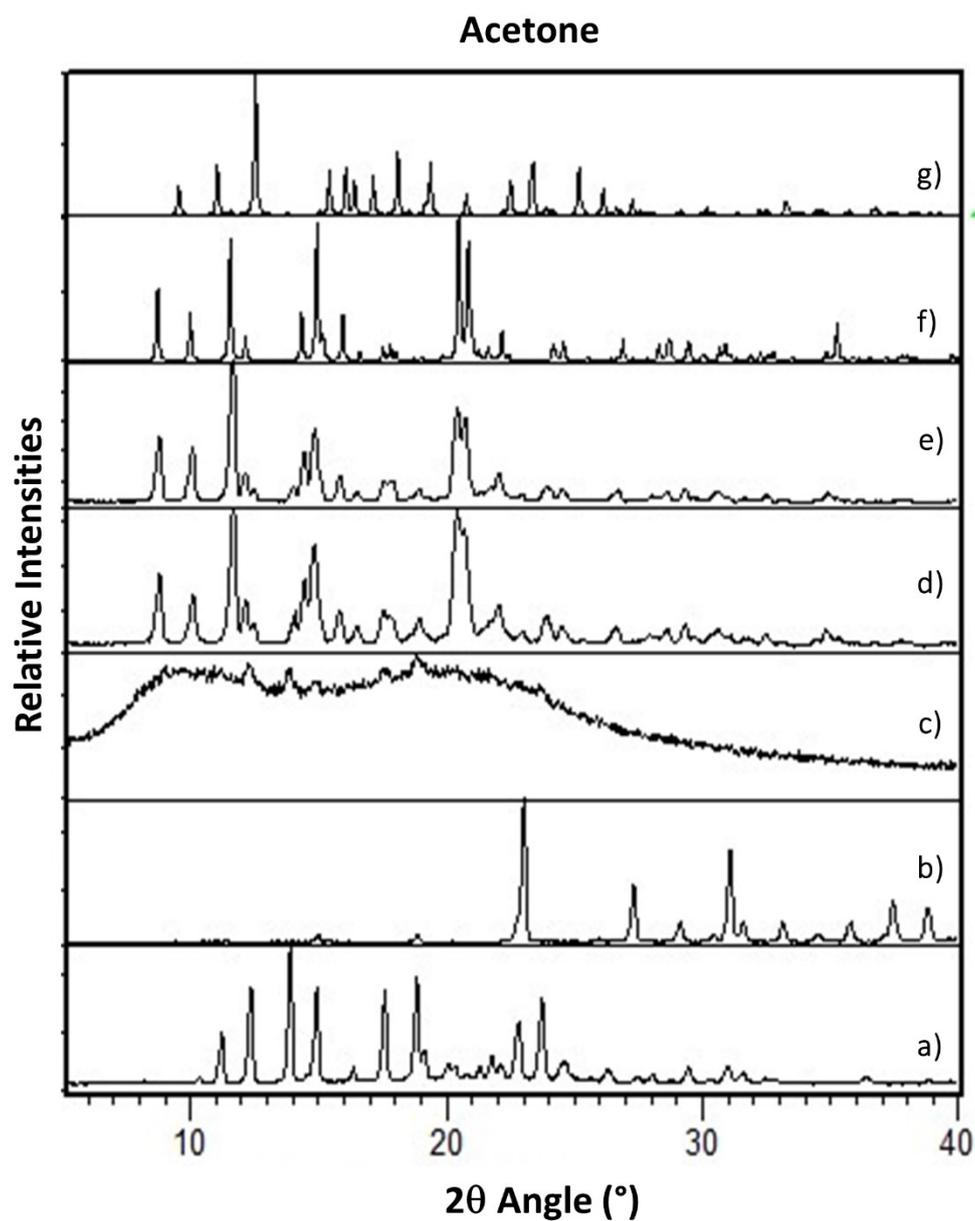


Figure S3. PXRD patterns of: (a) pure **vin**, (b) pure **H₂oxa**, (c), (d) and (e) the solid obtained through LAG of **vin** and **H₂oxa** using acetone as liquid additive at η values of $0.05 \mu\text{L mg}^{-1}$, $0.15 \mu\text{L mg}^{-1}$ and $0.30 \mu\text{L mg}^{-1}$, respectively, (f) calculated pattern of Form II, (g) calculated pattern of Form I.

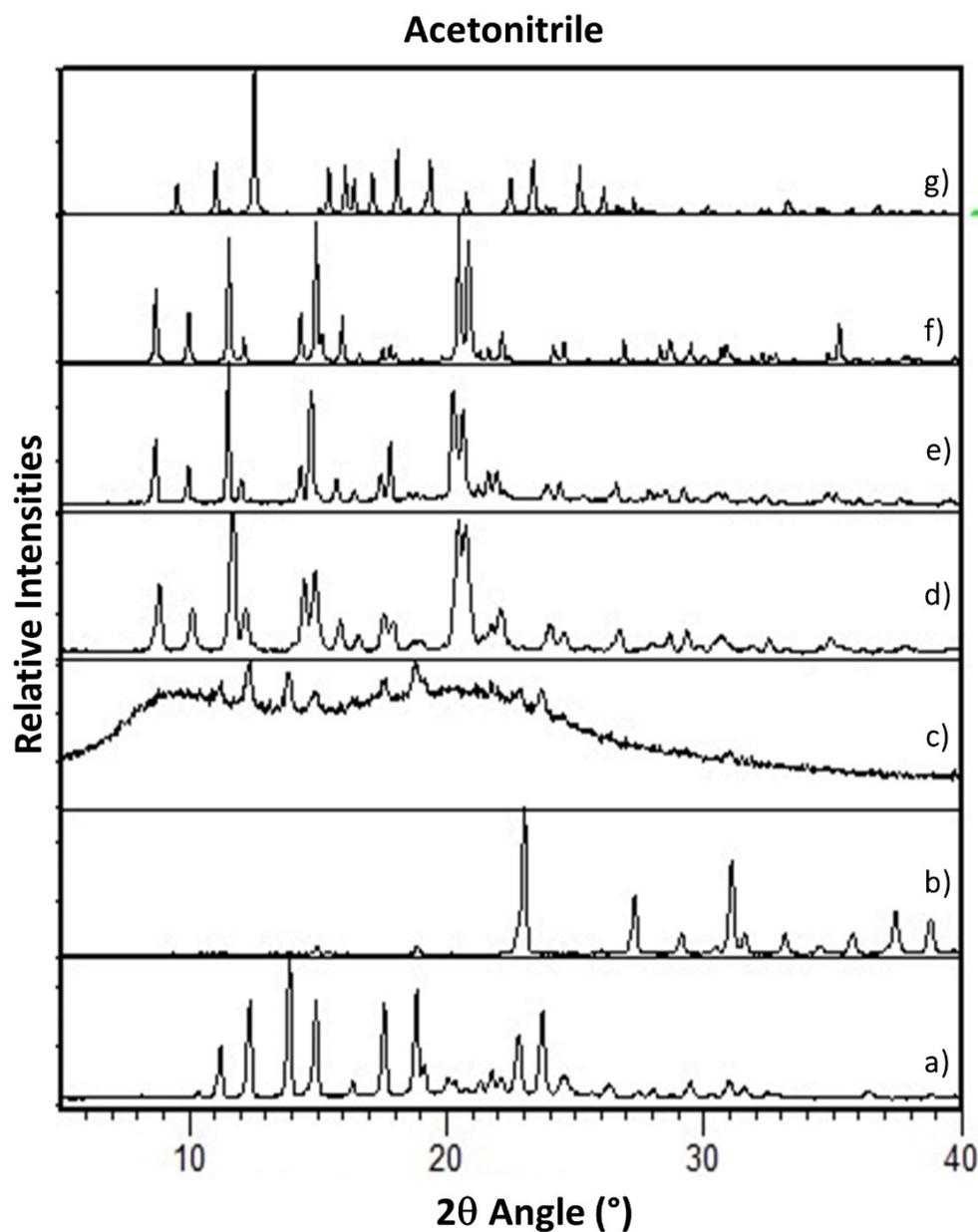


Figure S4. PXRD patterns of: (a) pure **vin**, (b) pure **H₂oxa**, (c), (d) and (e) the solid obtained through LAG of **vin** and **H₂oxa** using acetonitrile as liquid additive at η values of $0.05 \mu\text{L mg}^{-1}$, $0.15 \mu\text{L mg}^{-1}$ and $0.30 \mu\text{L mg}^{-1}$, respectively, (f) calculated pattern of Form II, (g) calculated pattern of Form I.

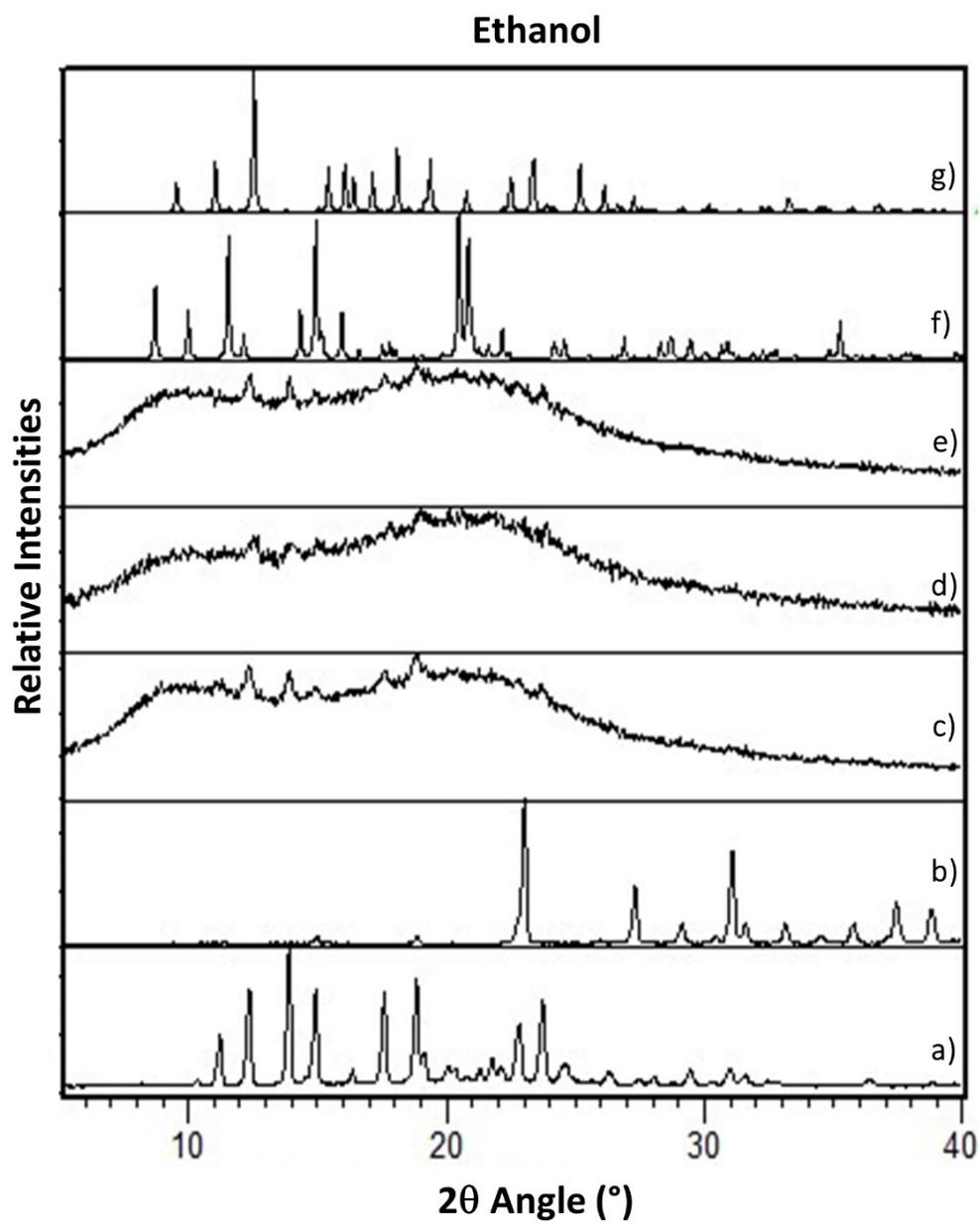


Figure S5. PXRD patterns of: (a) pure vin, (b) pure H₂oxa, (c), (d) and (e) the solid obtained through LAG of **vin** and H₂oxa using ethanol as liquid additive at η values of 0.05 $\mu\text{L mg}^{-1}$, 0.15 $\mu\text{L mg}^{-1}$ and 0.30 $\mu\text{L mg}^{-1}$, respectively, (f) calculated pattern of Form II, (g) calculated pattern of Form I.

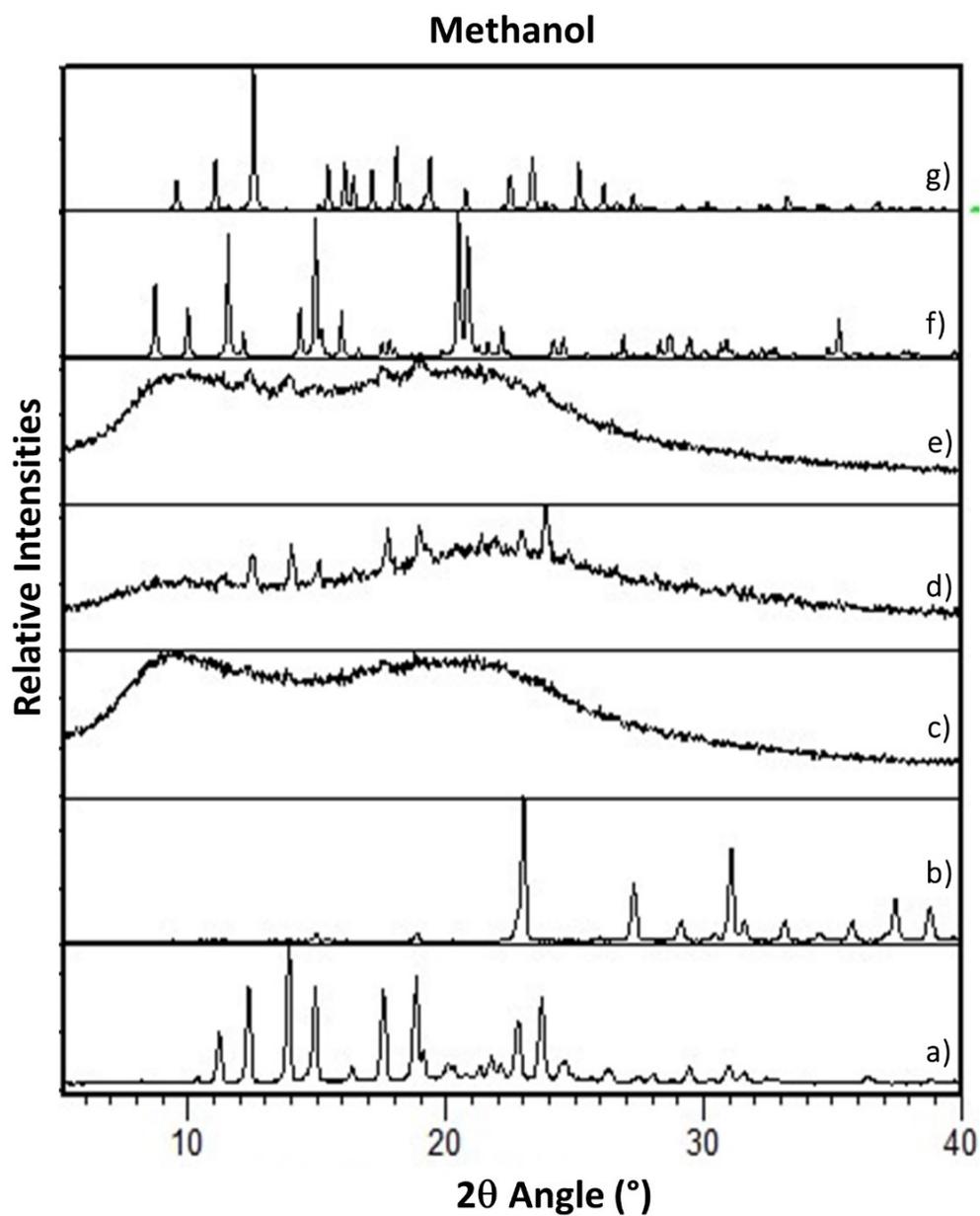


Figure S6. PXRD patterns of: (a) pure **vin**, (b) pure **H₂oxa**, (c), (d) and (e) the solid obtained through LAG of **vin** and **H₂oxa** using methanol as liquid additive at η values of 0.05 $\mu\text{L mg}^{-1}$, 0.15 $\mu\text{L mg}^{-1}$ and 0.30 $\mu\text{L mg}^{-1}$, respectively, (f) calculated pattern of Form II, (g) calculated pattern of Form I.

2-PYRROLIDONE

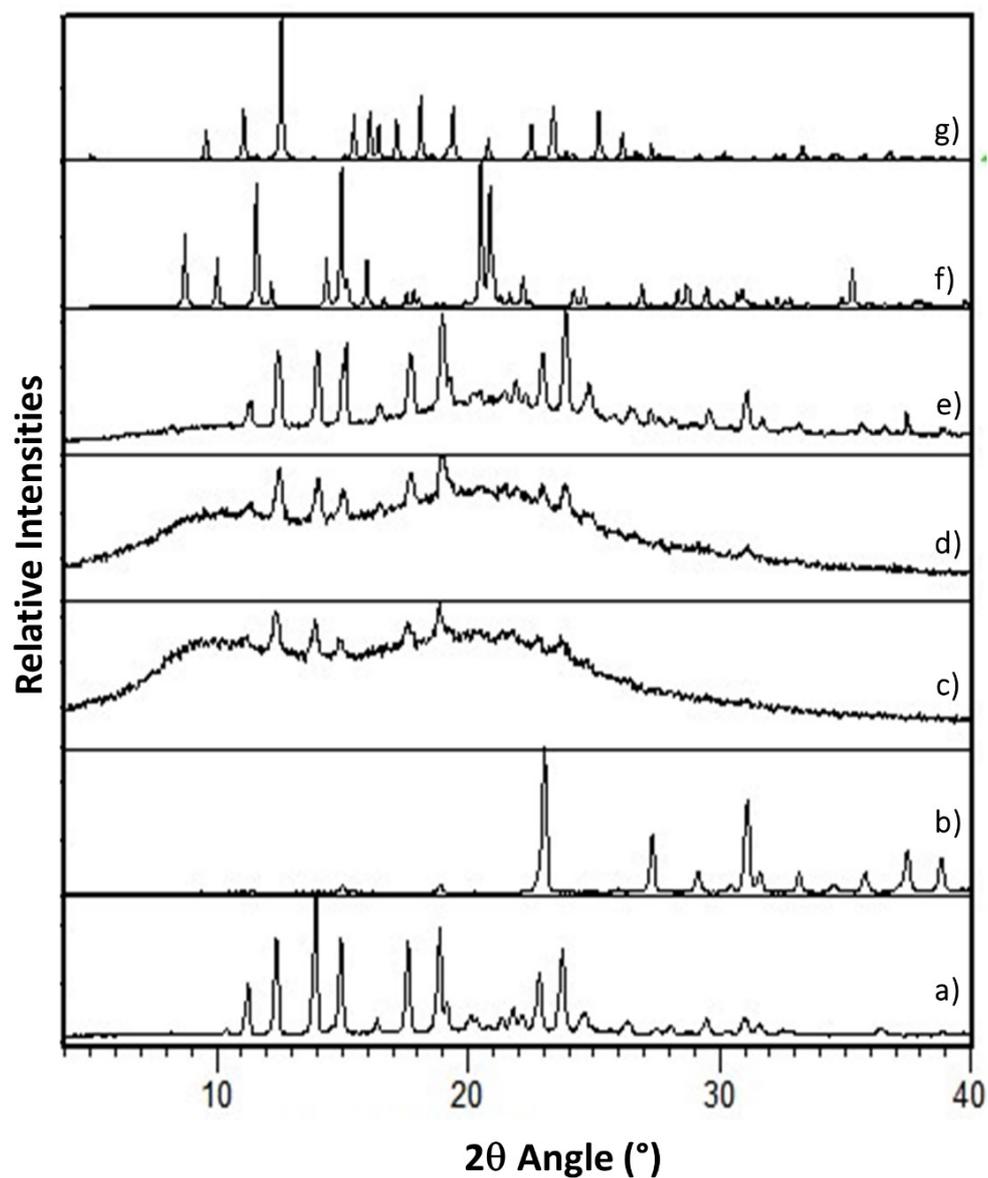


Figure S7. PXRD patterns of: (a) pure **vin**, (b) pure **H₂oxa**, (c), (d) and (e) the solid obtained through LAG of **vin** and **H₂oxa** using 2-pyrrolidone as liquid additive at η values of 0.05 $\mu\text{L mg}^{-1}$, 0.15 $\mu\text{L mg}^{-1}$ and 0.30 $\mu\text{L mg}^{-1}$, respectively, (f) calculated pattern Form II, (g) calculated pattern of Form I.

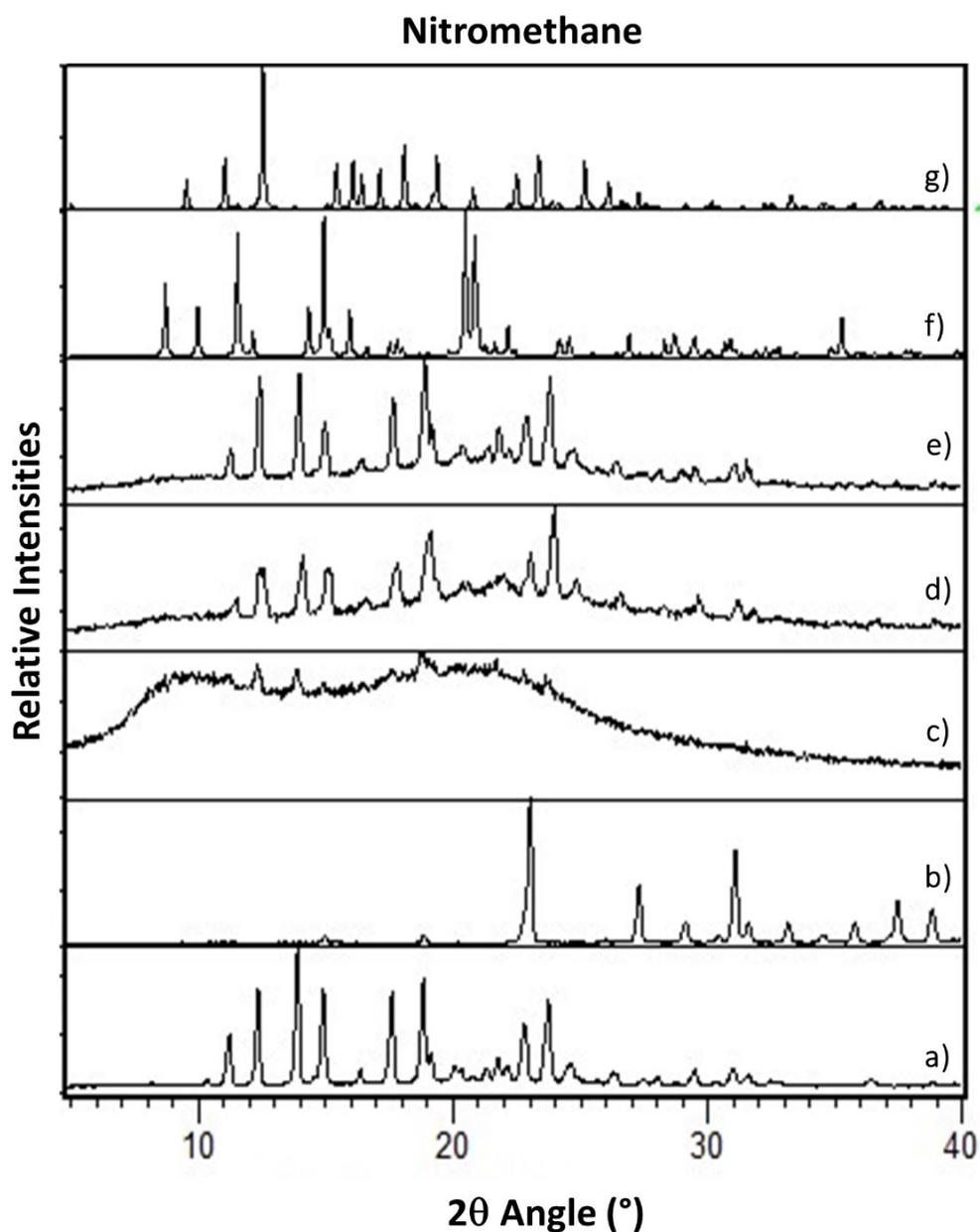


Figure S8. PXRD patterns of: (a) pure vin, (b) pure H₂oxa, (c), (d) and (e) the solid obtained through LAG of vin and H₂oxa using nitromethane as liquid additive at η values of 0.05 $\mu\text{L mg}^{-1}$, 0.15 $\mu\text{L mg}^{-1}$ and 0.30 $\mu\text{L mg}^{-1}$, respectively, (f) calculated pattern of Form II, (g) calculated pattern of Form I.

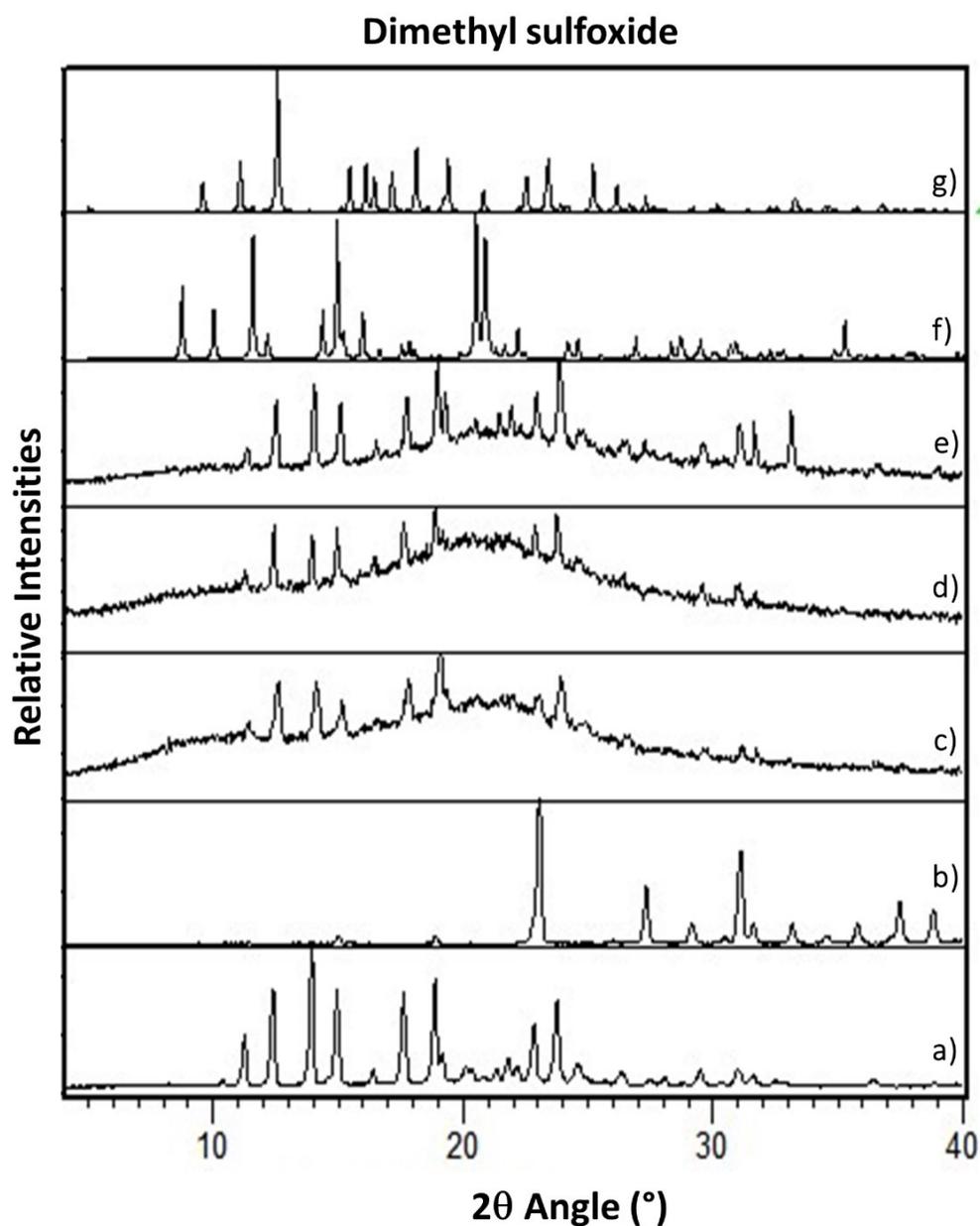


Figure S9. PXR D patterns of: (a) pure **vin**, (b) pure **H₂oxa**, (c), (d) and (e) the solid obtained through LAG of **vin** and **H₂oxa** using dimethyl sulfoxide as liquid additive at η values of $0.05 \mu\text{L mg}^{-1}$, $0.15 \mu\text{L mg}^{-1}$ and $0.30 \mu\text{L mg}^{-1}$, respectively, (f) calculated pattern of Form II, (g) calculated pattern of Form I.

2.2.2 Interconversion experiments

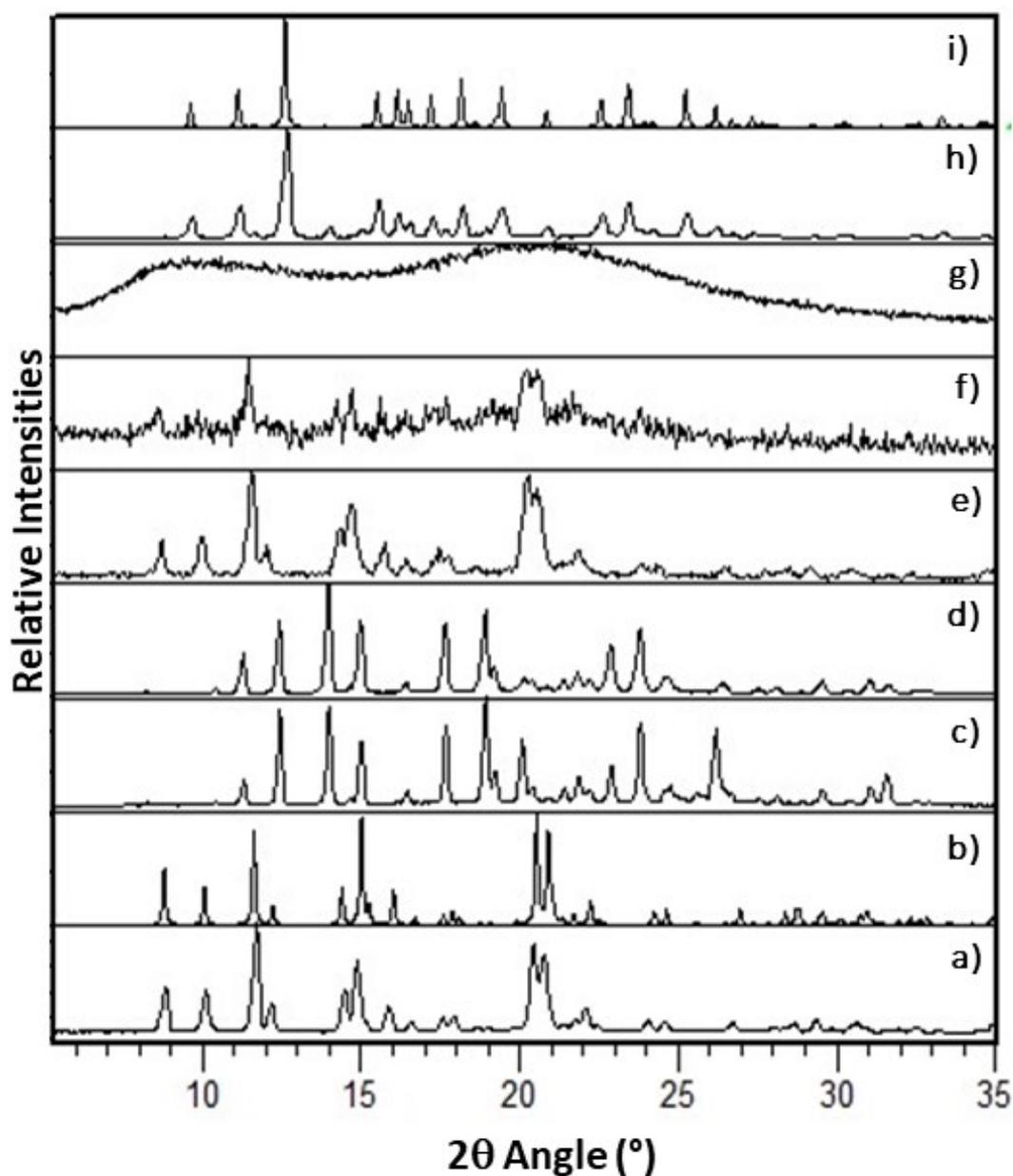


Figure S10. PXRD patterns of: (a) Form II prepared by LAG with ethyl acetate ($\eta=0.30 \mu\text{L mg}^{-1}$), (b) calculated Form II, (c), (d) pure **vin**, (e), (f) solid product obtained by LAG ($\eta=0.15 \mu\text{L mg}^{-1}$) of Form II in the presence of nitromethane, 2-pyrrolidone, respectively, (g) solid product obtained by neat grinding of Form II, (h) solid product obtained after LAG Form II with hexane ($\eta=0.30 \mu\text{L mg}^{-1}$) and (i) calculated pattern of Form I.

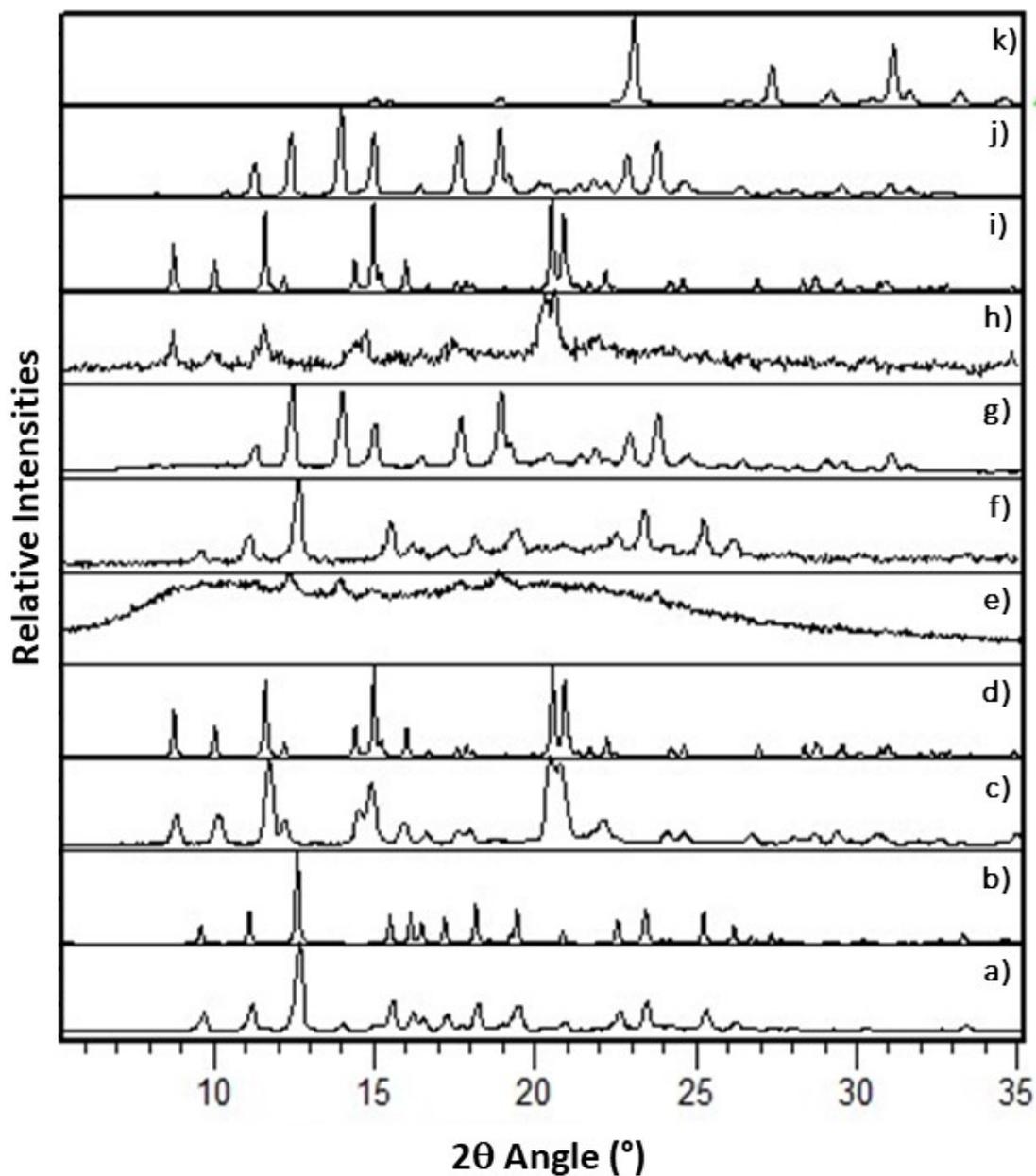


Figure S11. PXRD patterns of: (a) Form I prepared by LAG with hexane ($\eta=0.30 \mu\text{L mg}^{-1}$), (b) calculated Form I, (c) solid product obtained by LAG of Form I in the presence of ethyl acetate ($\eta=0.15 \mu\text{L mg}^{-1}$), (d) calculated Form I, (e) solid product obtained by neat grinding of Form I, (f), (g), (h) solid product obtained by LAG ($\eta=0.30 \mu\text{L mg}^{-1}$) of Form I in the presence of 2-pyrrolidone, dimethyl sulfoxide and nitromethane, respectively, (i) calculated Form II (j) pure **vin** and (k) pure **H₂oxa**.

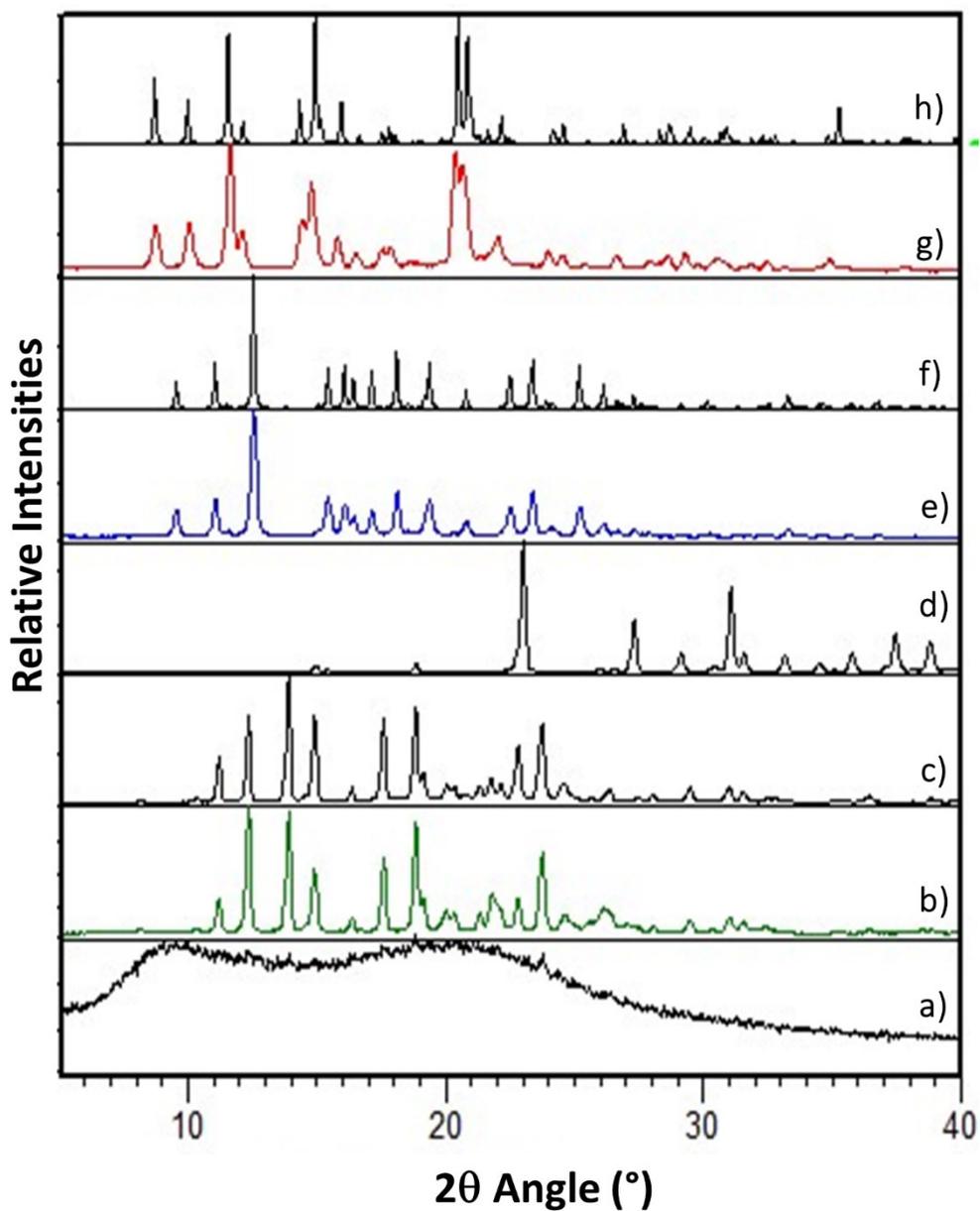


Figure S12. PXRD patterns of: (a) amorphous $(\text{Hvin}^+) \cdot (\text{Hoxa}^-)$ prepared by neat grinding, (b) product obtained through LAG of amorphous $\text{vin}:\text{oxa}$ in the presence of dimethyl sulfoxide ($\eta=0.15 \mu\text{L mg}^{-1}$), (c) pure vin , (d) pure H_2oxa , (e) product of LAG of amorphous $(\text{Hvin}^+) \cdot (\text{Hoxa}^-)$ with hexane ($\eta=0.30 \mu\text{L mg}^{-1}$), (f) calculated Form I, (g) product of LAG of amorphous $(\text{Hvin}^+) \cdot (\text{Hoxa}^-)$ with ethyl acetate ($\eta=0.15 \mu\text{L mg}^{-1}$) and (h) calculated pattern of Form II.

2.2.3 Effects of milling time

To investigate the effect of milling time on the mechanochemical formation of $(\text{Hvin}^+) \cdot (\text{Hoxa}^-)$, **vin** and H_2oxa were milled for 20, 40 and 60 min in neat or LAG conditions with ethyl acetate, hexane and methanol. The results, shown in Figures S13-S22, suggest the following:

- 1) A progressive loss of crystallinity with increasing milling times in cases where **vin** and H_2oxa were milled under neat or LAG conditions with an inhibitor liquid (e.g. methanol).
- 2) The formation of Form I appears to be more dependent on the η value than Form II.
- 3) The formation of $(\text{Hvin}^+) \cdot (\text{Hoxa}^-)$ was not observed after 20 or 40 min of milling ethyl acetate and hexane at $\eta = 0.05 \mu\text{L mg}^{-1}$, thus implying that the mechanochemical formation of crystalline $(\text{Hvin}^+) \cdot (\text{Hoxa}^-)$ dependent of the amount of (catalytic) liquid used.

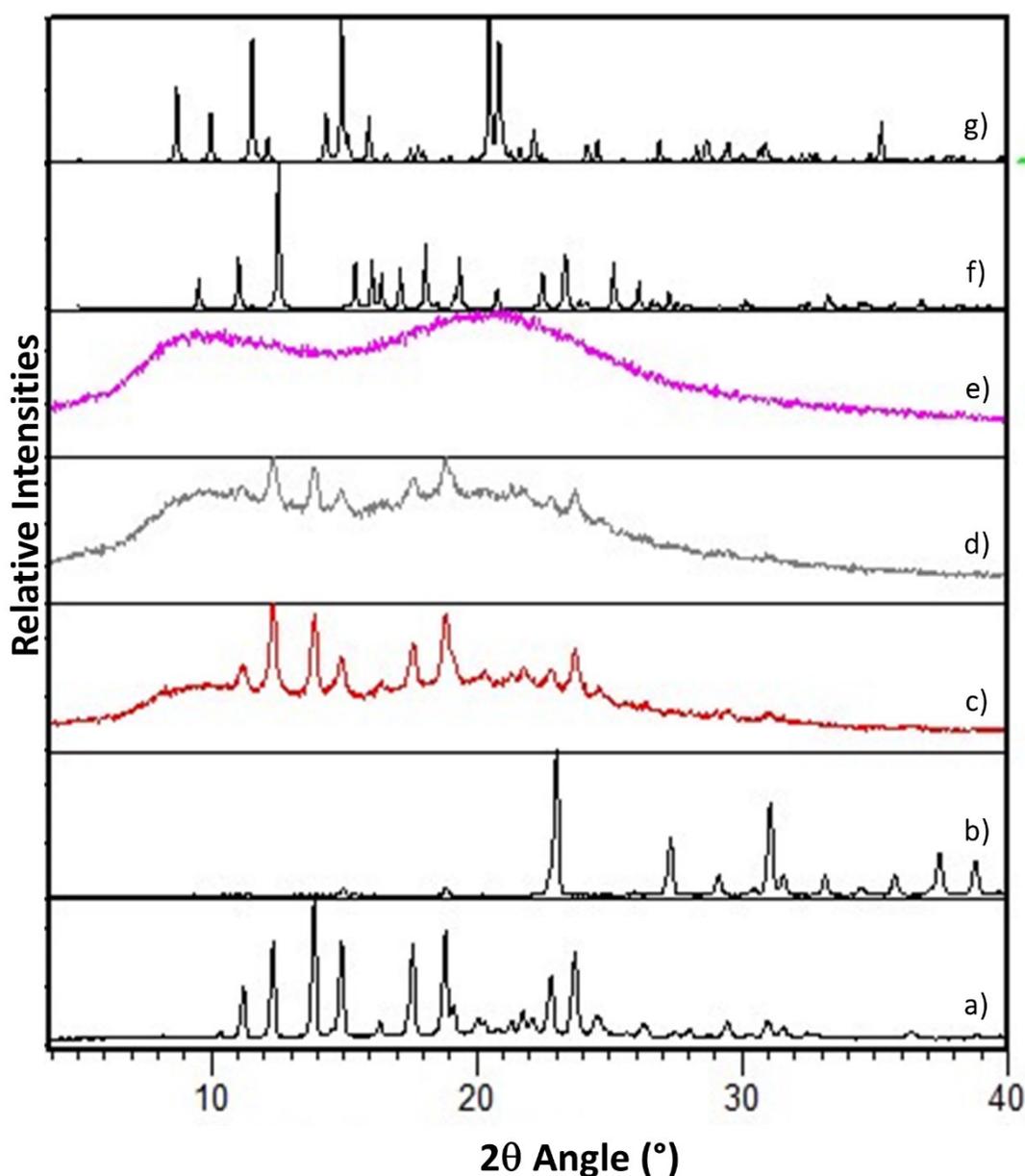


Figure S13. PXRD patterns of: (a) pure **vin**, (b) pure H_2oxa , (c), (d), (e) solids obtained through neat grinding of **vin** and H_2oxa for 20, 40 and 60 minutes respectively, (f) calculated pattern of Form I, (g) calculated pattern of Form II.

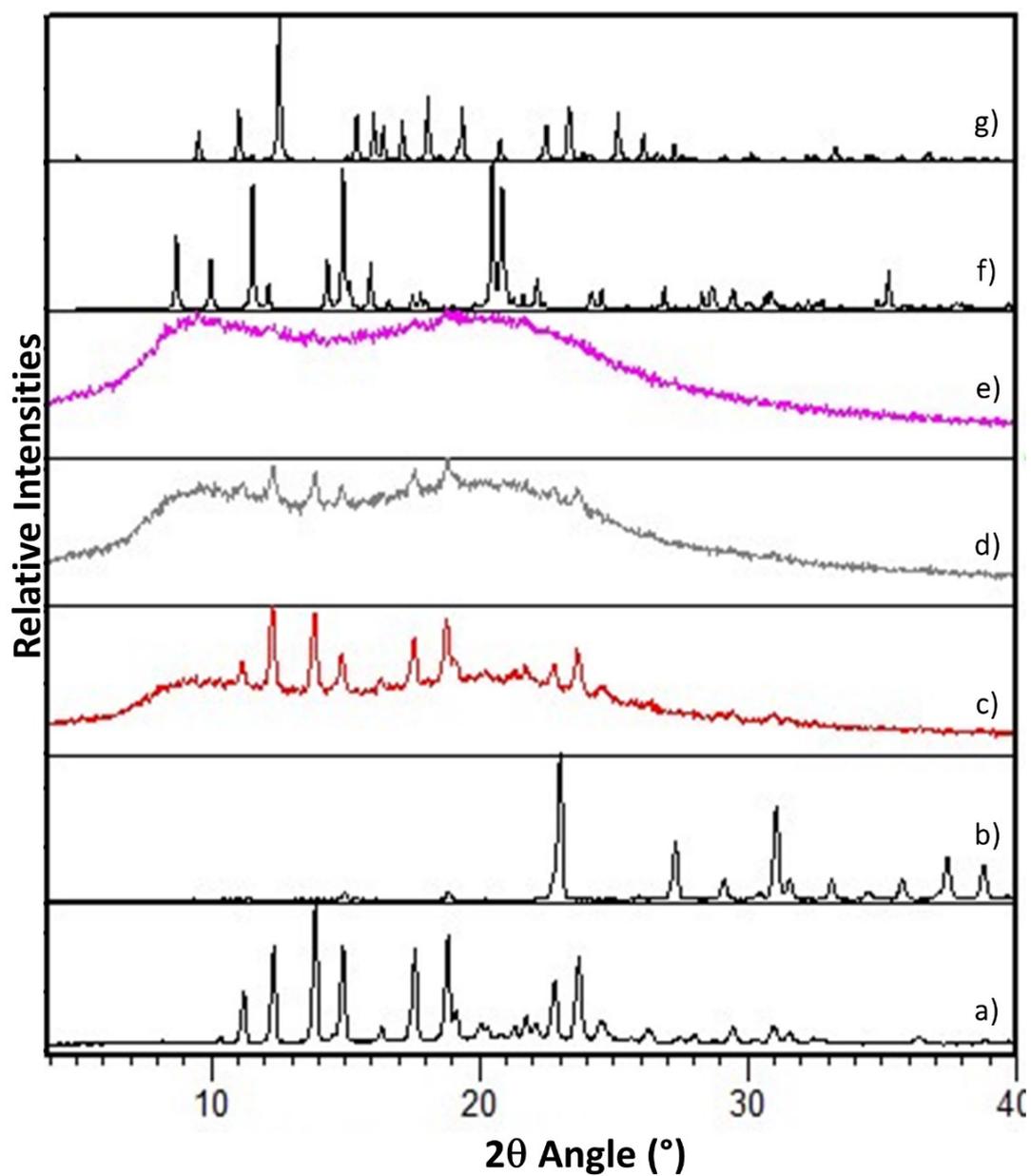


Figure S14. PXR D patterns of: (a) pure **vin**, (b) pure H_2oxa , (c), (d), (e) solids obtained through LAG of **vin** and H_2oxa in the presence of ethyl acetate ($\eta=0.05 \mu\text{L mg}^{-1}$) for 20, 40 and 60 minutes respectively, (f) calculated pattern of Form II, (g) calculated pattern of Form I.

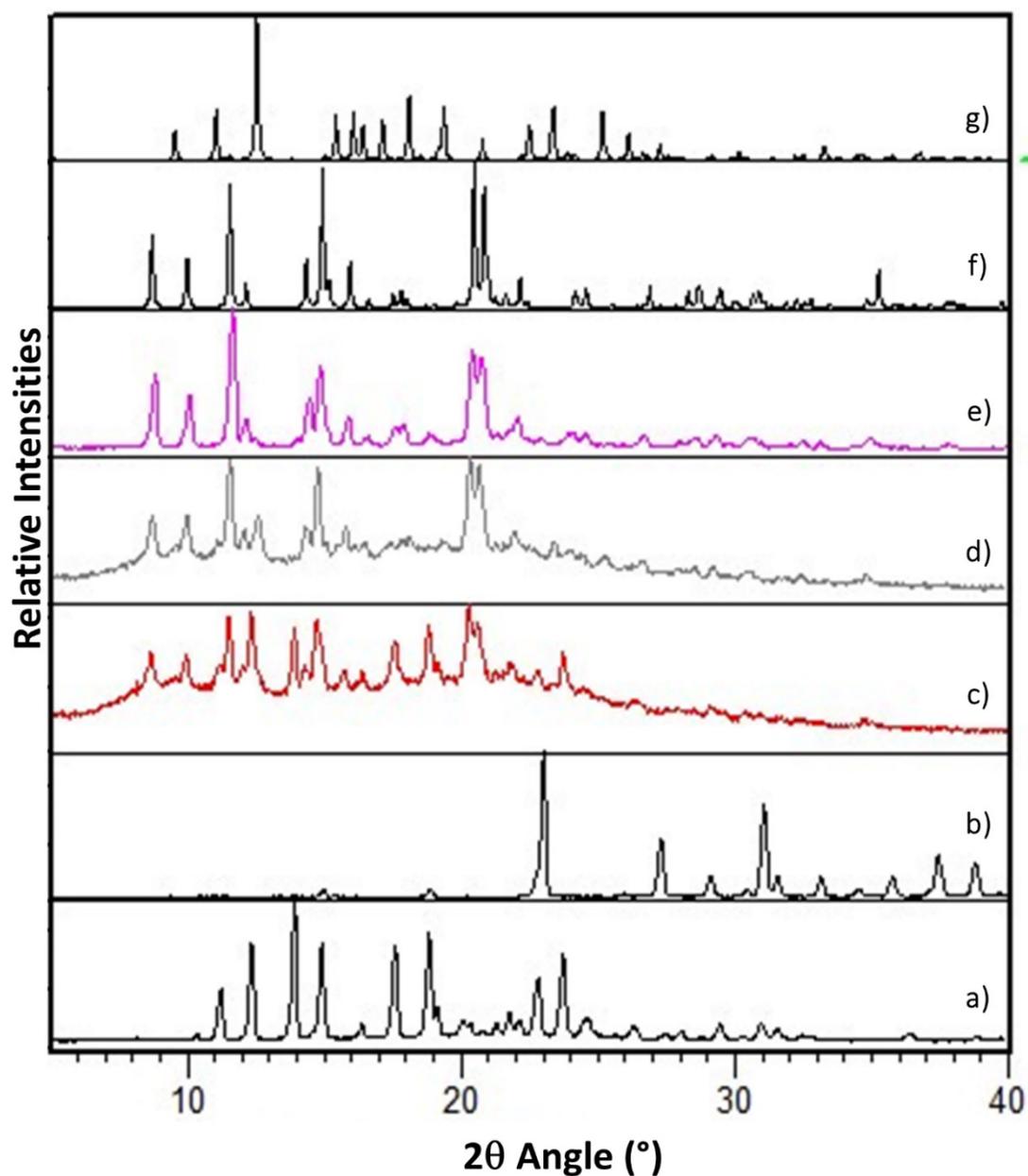


Figure S15. PXR D patterns of: (a) pure **vin**, (b) pure H_2oxa , (c), (d), (e) solids obtained through LAG of **vin** and H_2oxa in the presence of ethyl acetate ($\eta=0.15 \mu L mg^{-1}$) for 20, 40 and 60 minutes respectively, (f) calculated pattern of Form II, (g) calculated pattern of Form I.

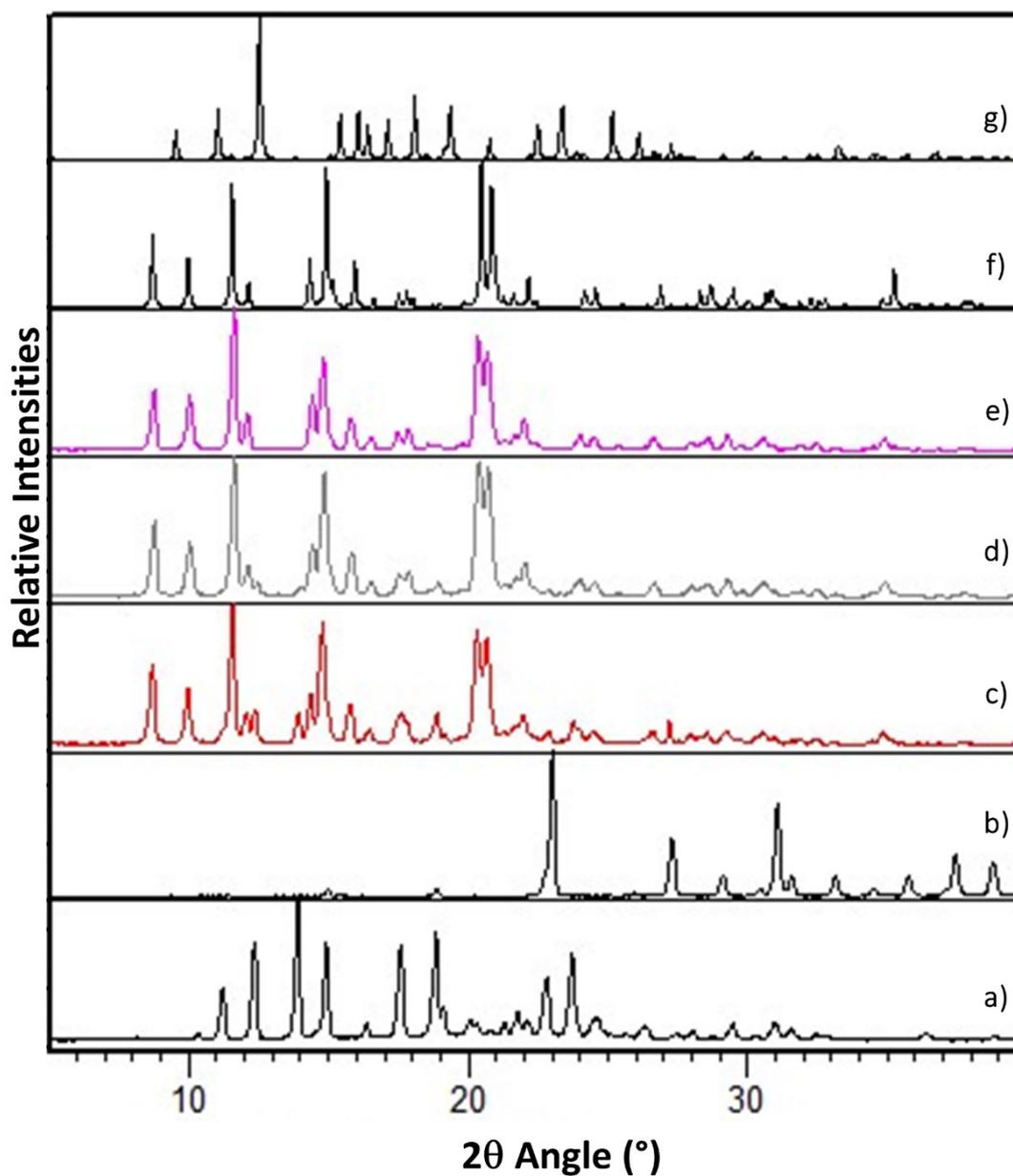


Figure S16. PXRD patterns of: (a) pure **vin**, (b) pure H_2oxa , (c), (d), (e) solids obtained through LAG of **vin** and H_2oxa in the presence of ethyl acetate ($\eta=0.30 \mu\text{L mg}^{-1}$) for 20, 40 and 60 minutes respectively, (f) calculated pattern of Form II, (g) calculated pattern of Form I.

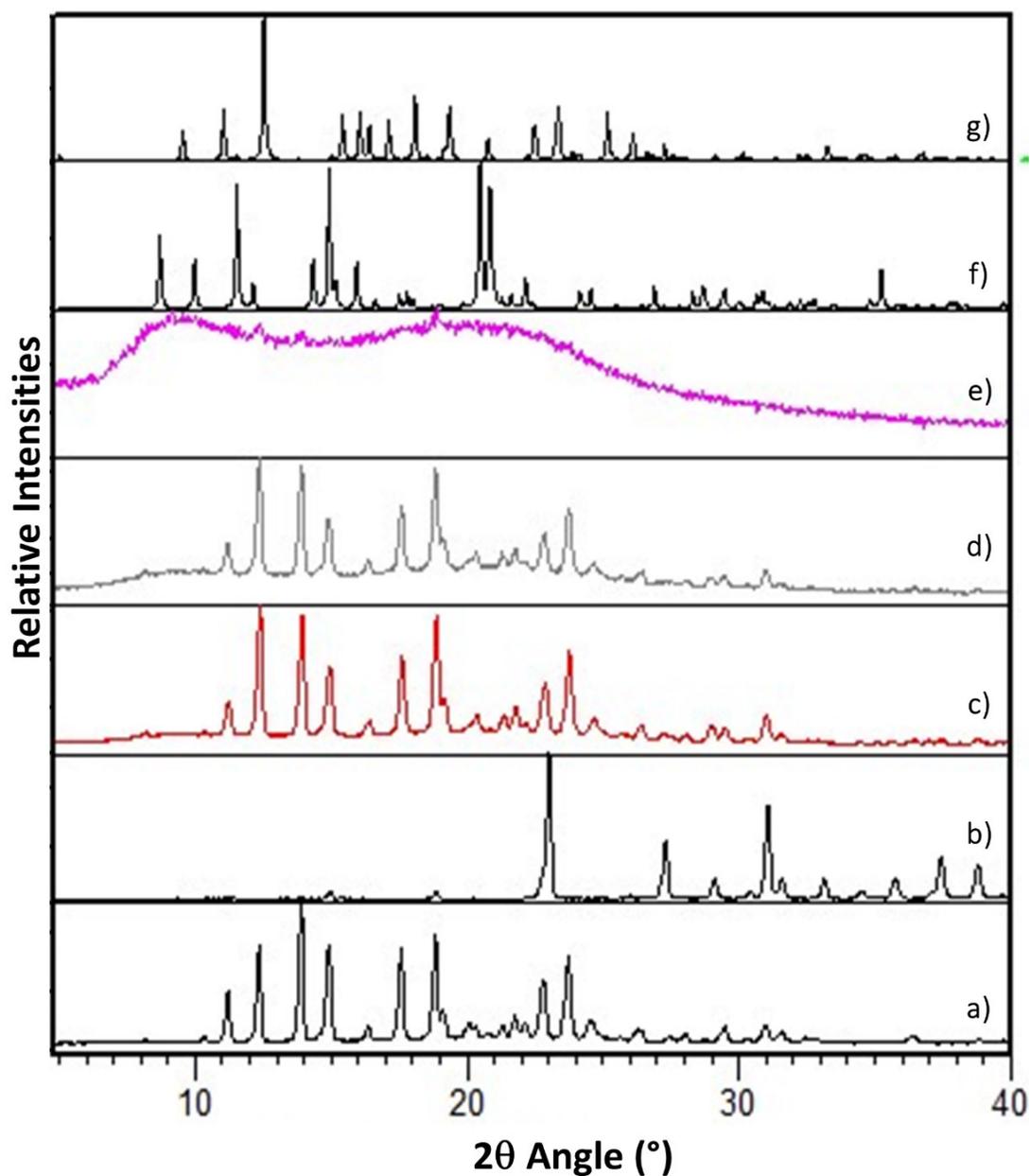


Figure S17. PXRD patterns of: (a) pure **vin**, (b) pure H_2oxa , (c), (d), (e) solids obtained through LAG of **vin** and H_2oxa in the presence of hexane ($\eta=0.05 \mu\text{L mg}^{-1}$) for 20, 40 and 60 minutes respectively, (f) calculated pattern of Form II, (g) calculated pattern of Form I.

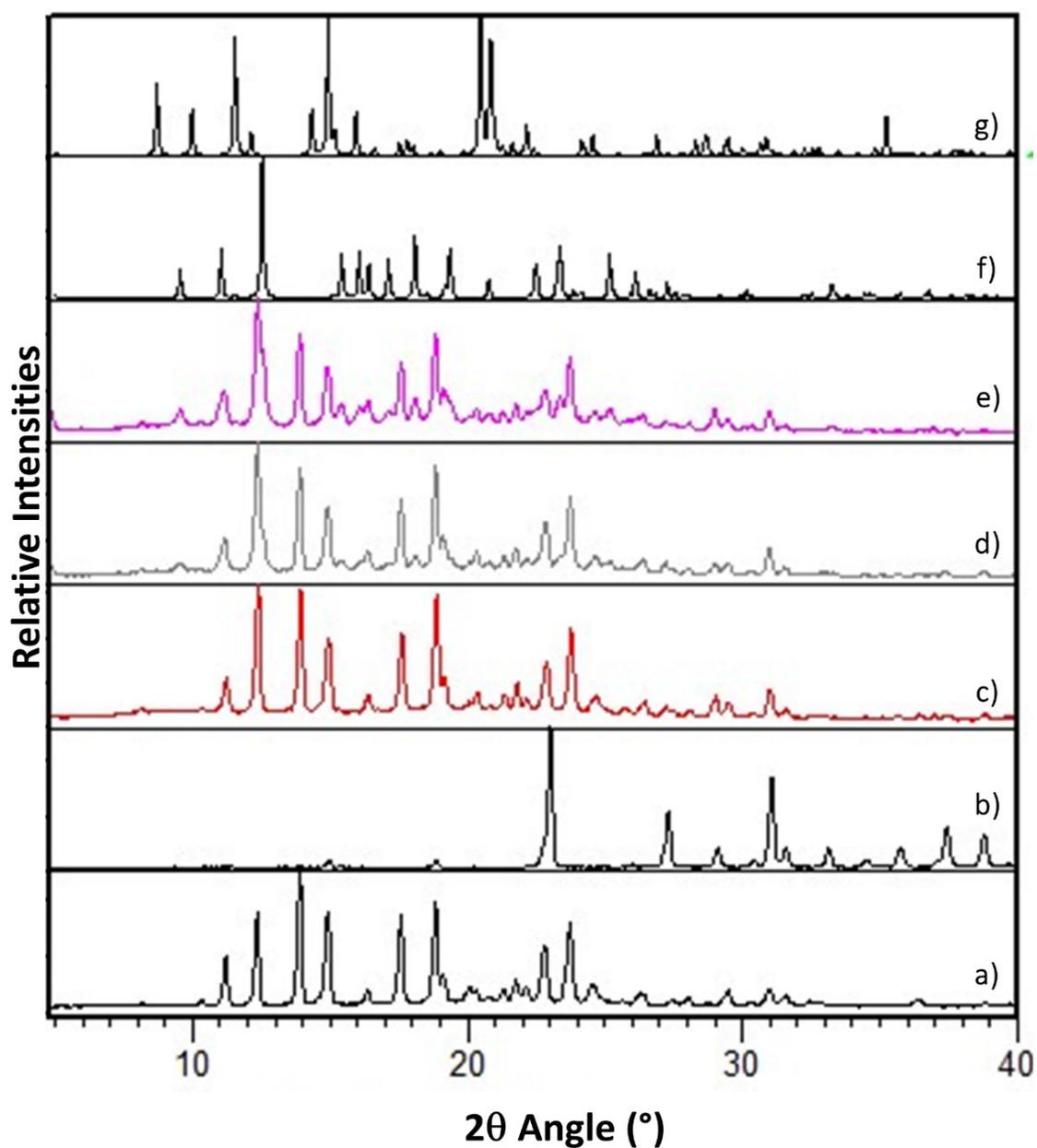


Figure S18. PXRD patterns of: (a) pure **vin**, (b) pure H_2oxa , (c), (d), (e) solids obtained through LAG of **vin** and H_2oxa in the presence of hexane ($\eta=0.15 \mu\text{L mg}^{-1}$) for 20, 40 and 60 minutes respectively, (f) calculated pattern of Form I, (g) calculated pattern of Form II.

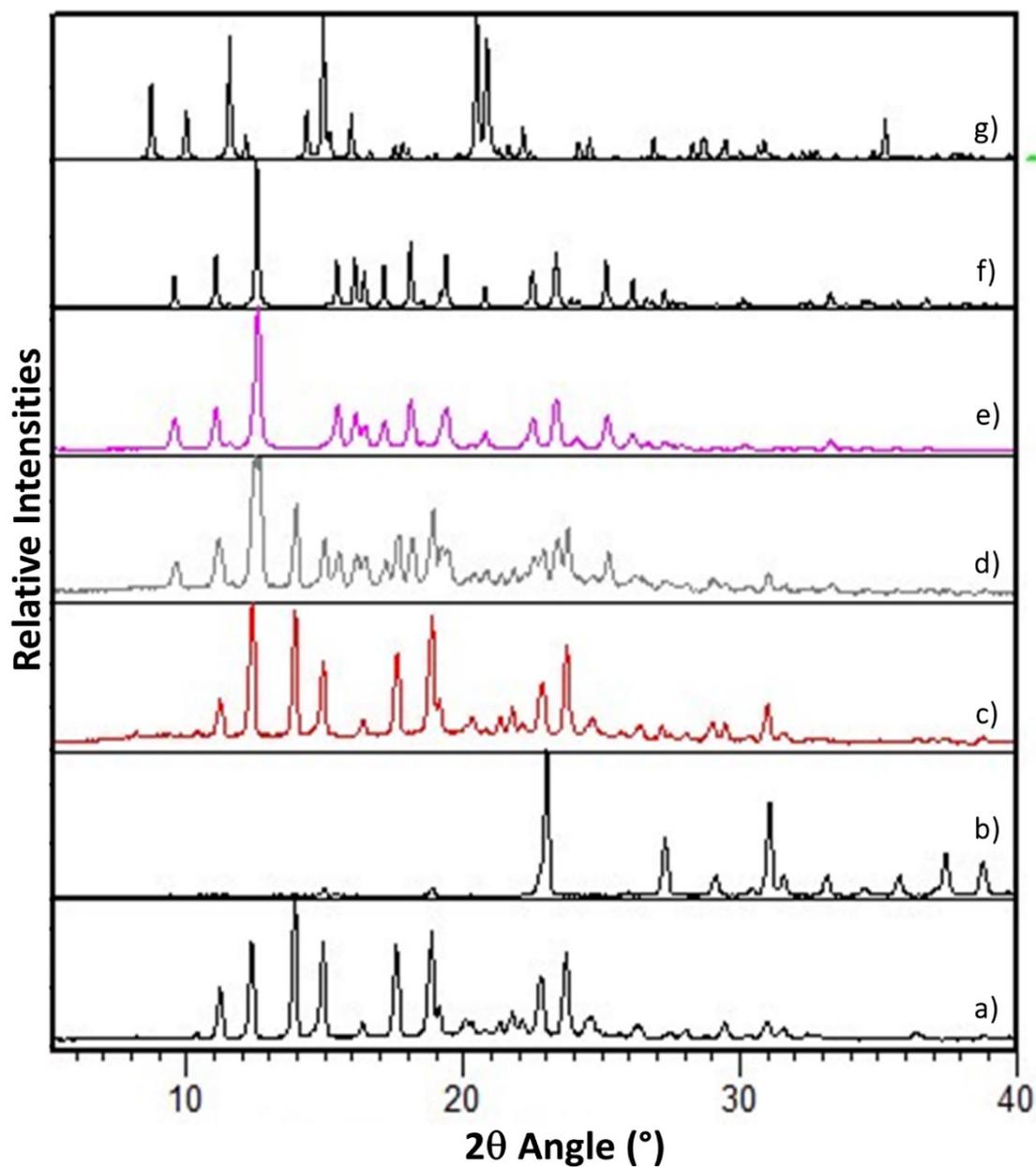


Figure S19. PXR D patterns of: (a) pure **vin**, (b) pure H_2oxa , (c), (d), (e) solids obtained through LAG of **vin** and H_2oxa in the presence of hexane ($\eta=0.30 \mu\text{L mg}^{-1}$) for 20, 40 and 60 minutes respectively, (f) calculated pattern of Form I, (g) calculated pattern of Form II.

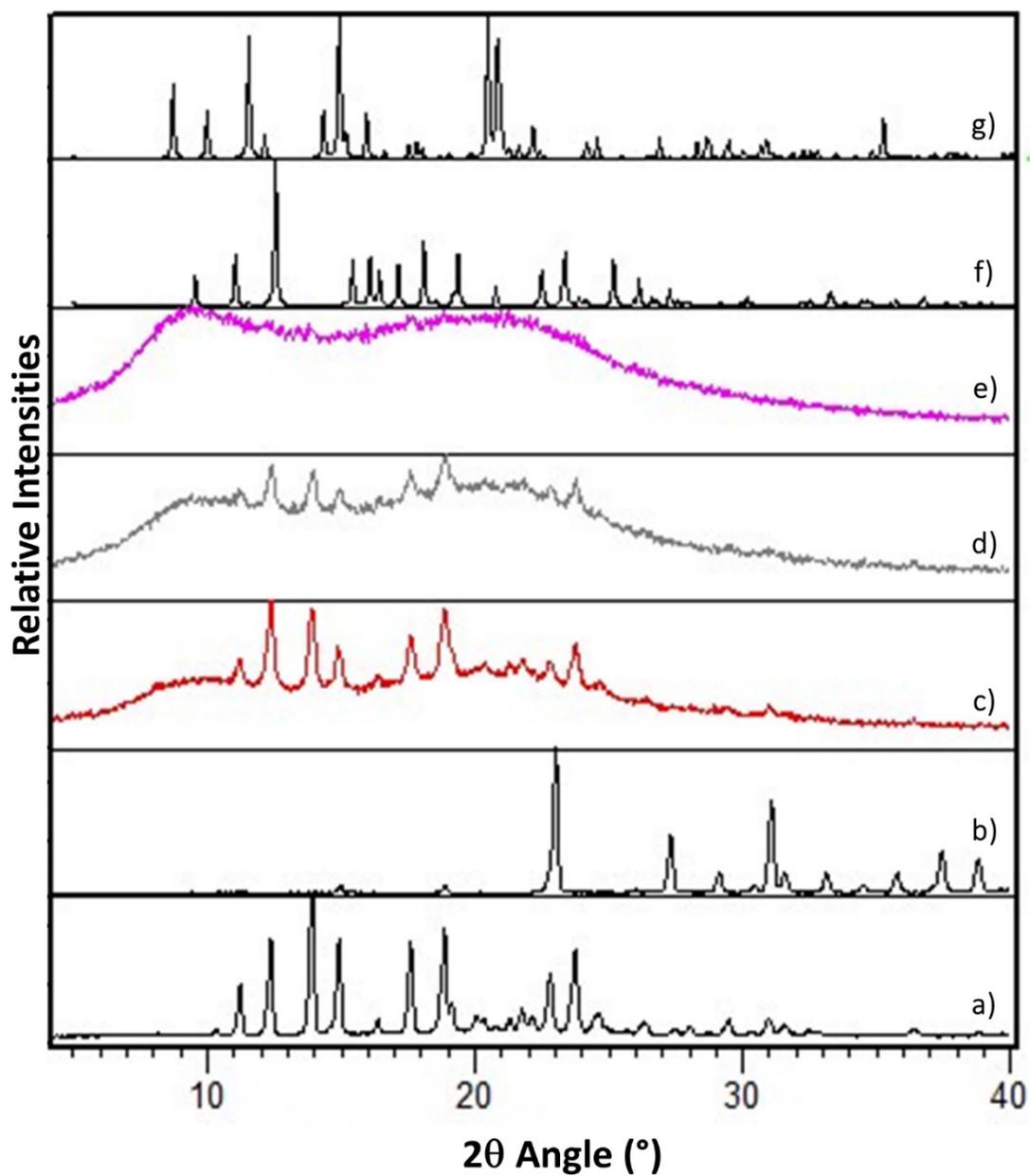


Figure S20. PXR D patterns of: (a) pure **vin**, (b) pure H_2oxa , (c), (d), (e) solids obtained through LAG of **vin** and H_2oxa in the presence of methanol ($\eta=0.05 \mu\text{L mg}^{-1}$) for 20, 40 and 60 minutes respectively, (f) calculated pattern of Form I, (g) calculated pattern of Form II.

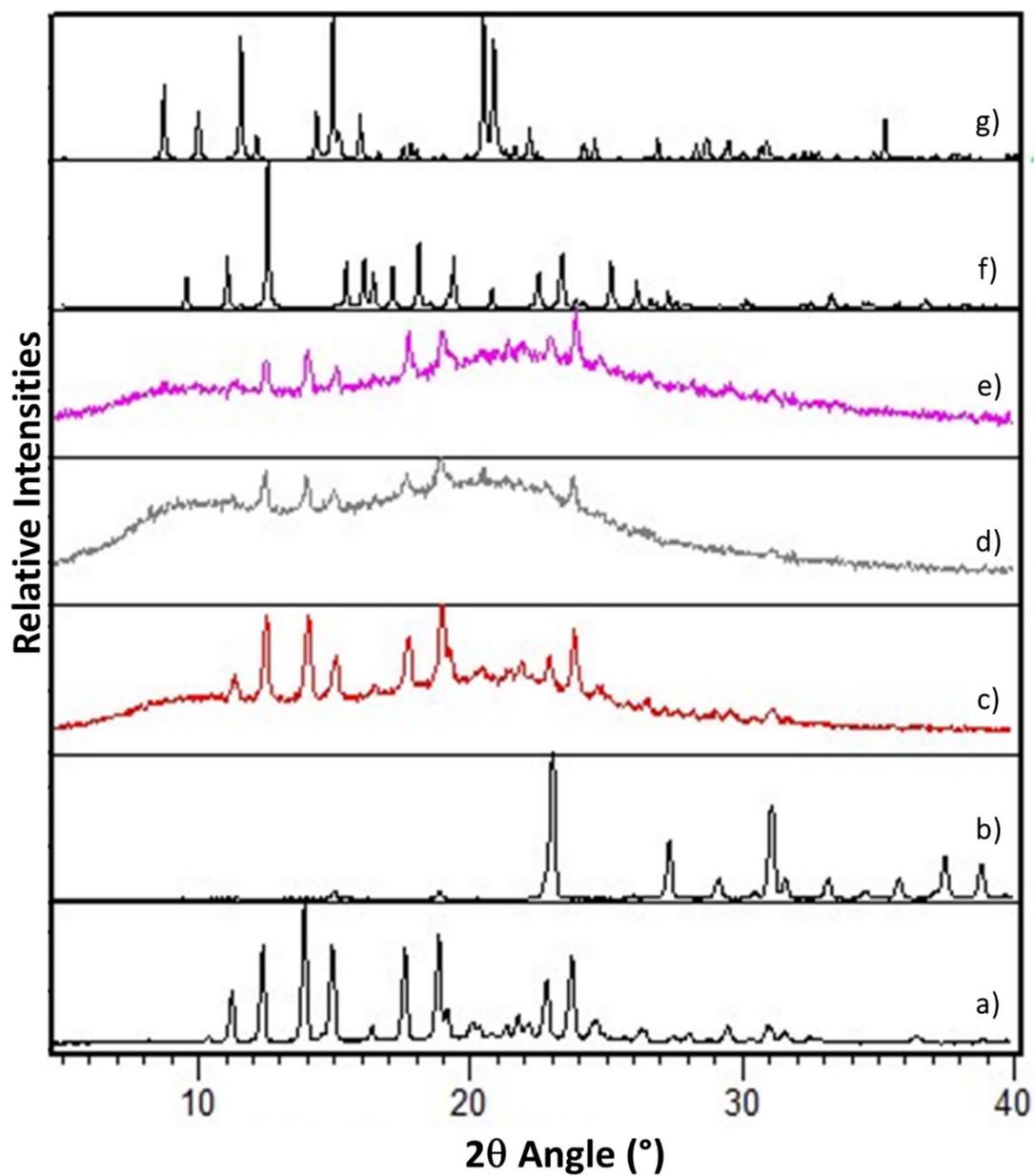


Figure S21. PXRD patterns of: (a) pure **vin**, (b) pure H₂**oxa**, (c), (d), (e) solids obtained through LAG of **vin** and H₂**oxa** in the presence of methanol ($\eta=0.15 \mu\text{L mg}^{-1}$) for 20, 40 and 60 minutes respectively, (f) calculated pattern of Form I, (g) calculated pattern of Form II.

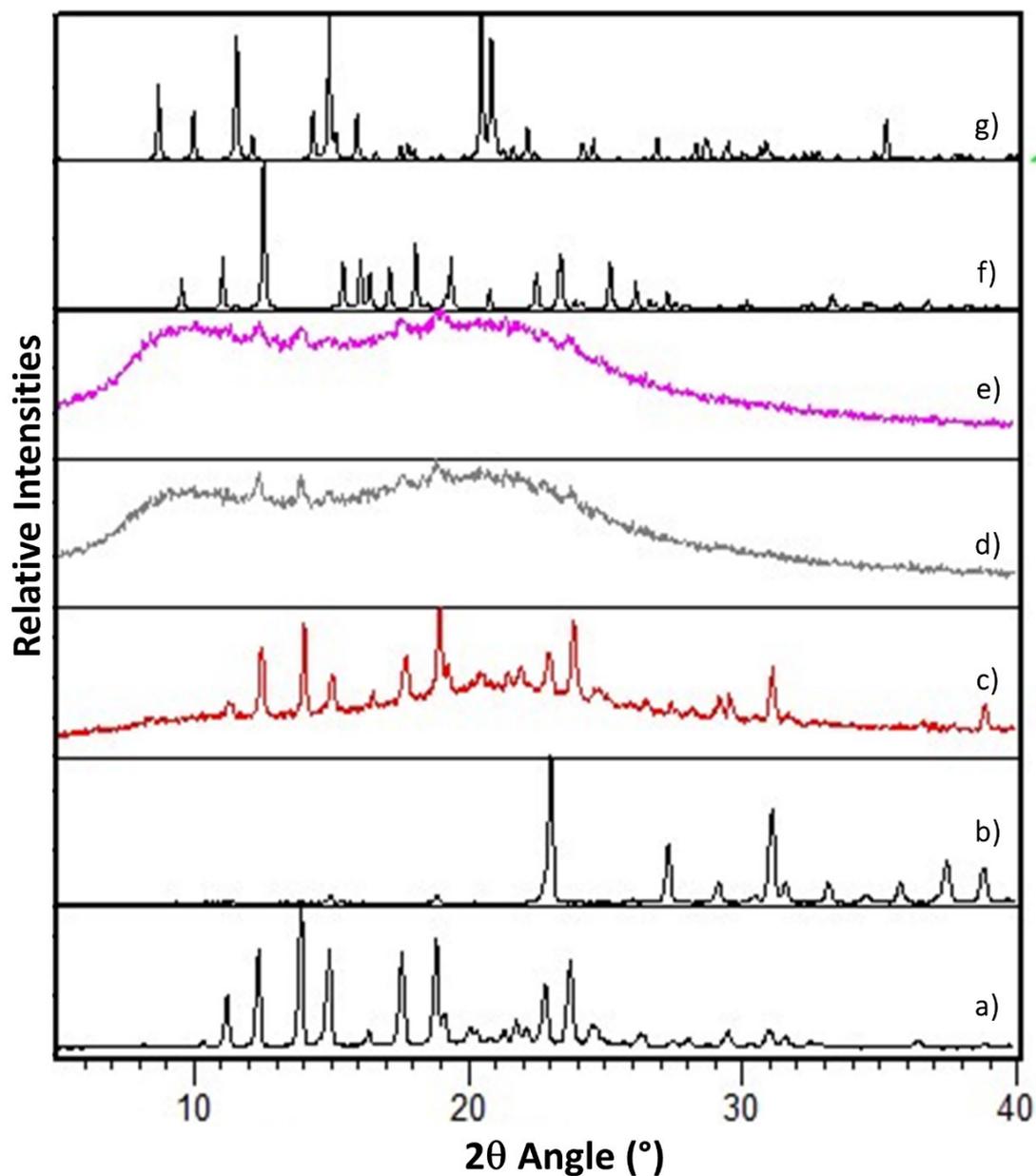


Figure S22. PXRD patterns of: (a) pure **vin**, (b) pure H₂**oxa**, (c), (d), (e) solids obtained through LAG of **vin** and H₂**oxa** in the presence of methanol ($\eta=0.30 \mu\text{L mg}^{-1}$) for 20, 40 and 60 minutes respectively, (f) calculated pattern of Form I, (g) calculated pattern of Form II.

2.2.4 Theophylline:fluorobenzoic acid cocrystals

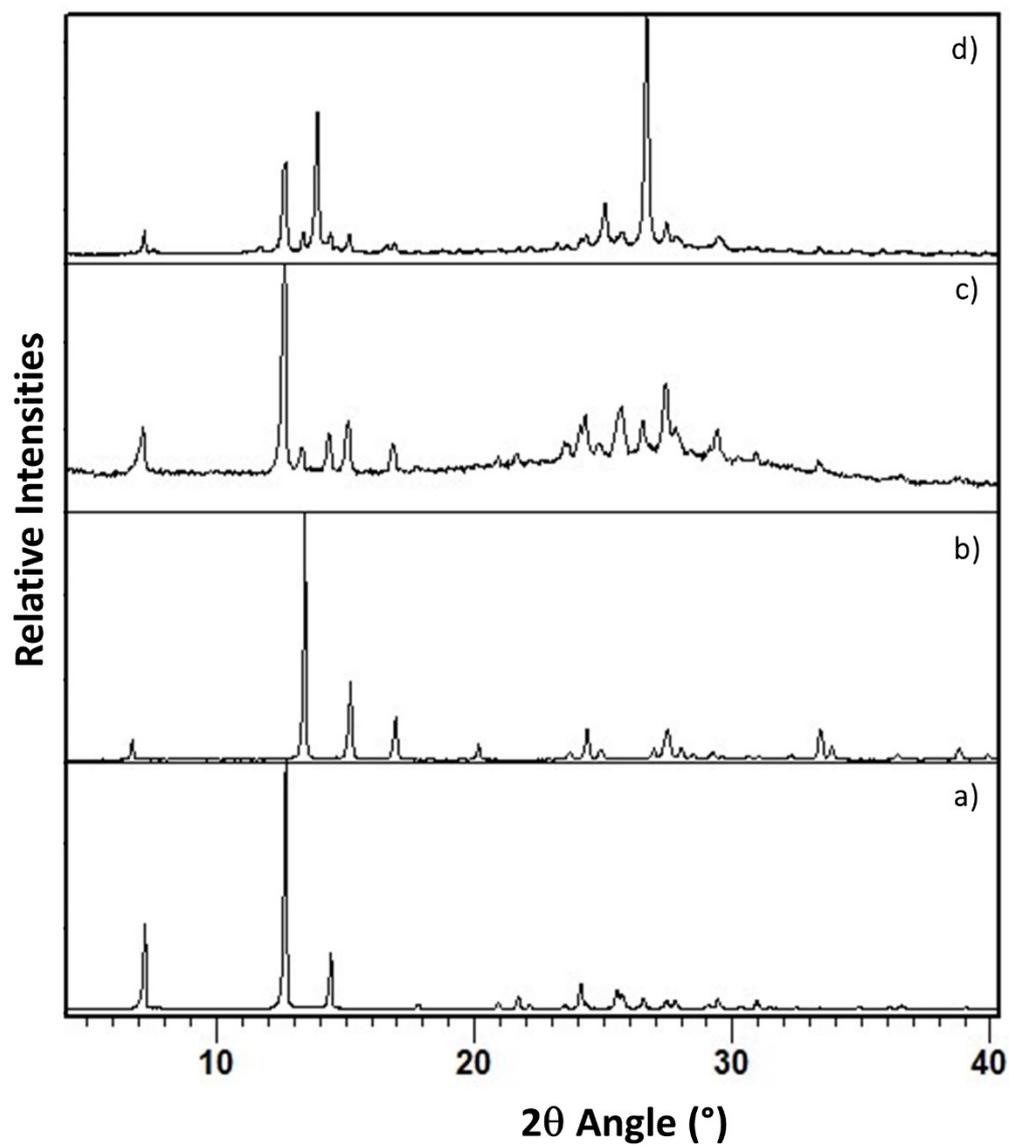


Figure S23. PXRD patterns of: (a) pure **thp**, (b) pure **23diFBA**, (c) solid product obtained after LAG of **thp** and **23diFBA** in the presence of nitromethane ($\eta=0.25 \mu\text{L mg}^{-1}$) (d) solid product obtained after LAG of **thp** and **23diFBA** acid in the presence of ethanol ($\eta=0.25 \mu\text{L mg}^{-1}$).

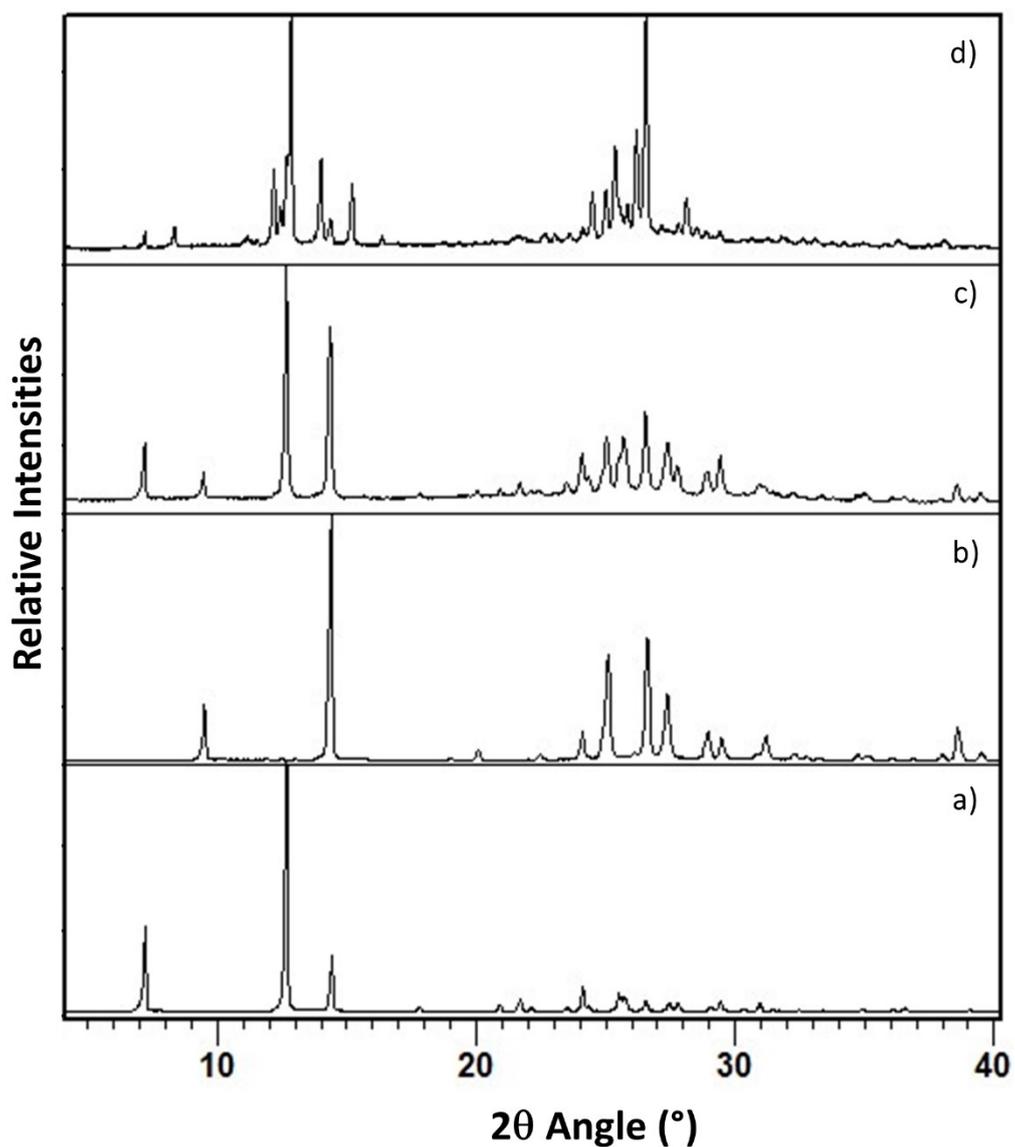


Figure S24. PXRD pattern of: (a) pure **thp**, (b) pure **26diFBA**, (c) solid product obtained through LAG of **thp** and **26diFBA** in the presence of nitromethane ($\eta=0.25 \mu\text{L mg}^{-1}$) (d) solid product obtained through LAG of **thp** and **26diFBA** in the presence of ethanol ($\eta=0.25 \mu\text{L mg}^{-1}$).

3. Probing the effect of presence of water/humidity during the grinding experiments

3.1 Experimental Section

3.1.1 LAG experiments

A series of additional milling experiments were performed to investigate the effects of trace amounts of water on the outcome of LAG reactions. Before each experiment, H₂oxa was stored in the oven at 140 °C to dehydrate H₂oxa and to remove adsorbed water traces from H₂oxa crystallites. The equimolar mixture of vin and oven-dried H₂oxa were processed for 60 min using in a *Retsch MM400* mixer mill, at 30 Hz frequency, with the addition of each of the following liquids ($\eta=0.10$ mg mL⁻¹): deionised water, hexane, ethylacetate, acetonitrile and acetone. In addition, a LAG reaction with deionised water at $\eta=0.05$ mg mL⁻¹ was also performed. All liquids, except deionised water, were dried over 3 Å molecular sieves. The other experimental conditions were kept similar to those reported in section 2.1.1. Immediately after completion of the milling reaction, the products were characterised by PXRD, TGA and DSC.

3.1.2 PXRD analysis

The reaction products were analysed on a *Bruker D8* powder diffractometer with CuK_α radiation at a wavelength of 1.5418 Å equipped with a *VANTEC2000* area detector. Three data frames, each covering a 20° 2 θ range were collected, at 300 s per frame. The frames were integrated and merged using *Bruker GADDS* software.

3.1.3 Differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA)

The TGA and DSC measurements were performed on a *Mettler Toledo TGA/DSC 2* instrument. Approximately 10 mg of each material were weighed in a 70 μ L alumina pan. The samples were heated from 30 to 300 °C temperature, with a heating rate of 10 °C min⁻¹. The measurements were accomplished under the flow of dry nitrogen gas. The TGA and DSC curves were processed using the *Mettler STARe 12.1* data evaluation software.

3.2 Results

3.2.1 LAG experiments with water

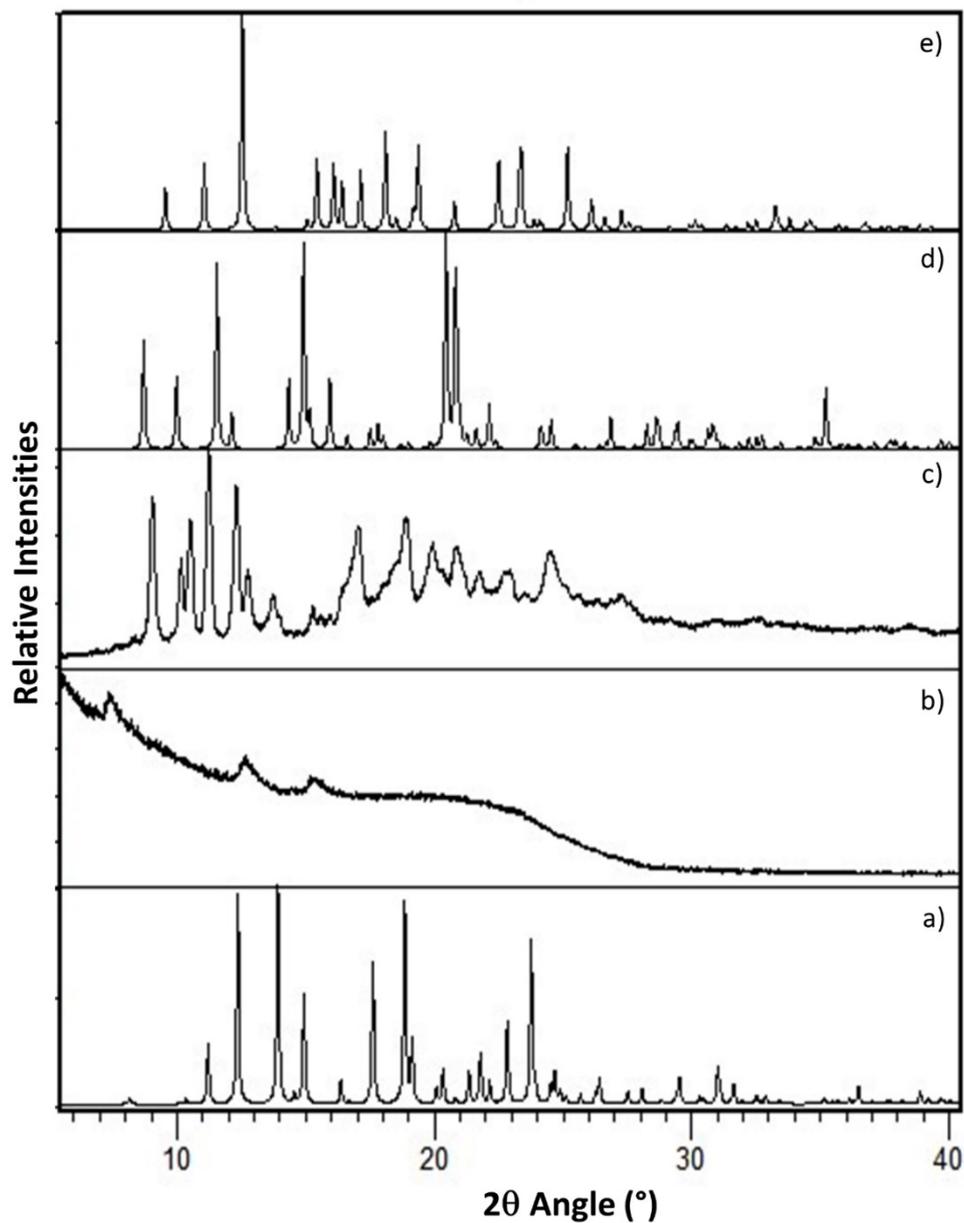


Figure S25. PXRD pattern of: (a) pure **vin**, (b), (c) solids obtained through LAG of **vin** and H_2Oxa in the presence of water ($\eta = 0.05 \mu\text{L mg}^{-1}$ and $0.10 \mu\text{L mg}^{-1}$, respectively) (d) and (e) calculated Form I and Form II, respectively.

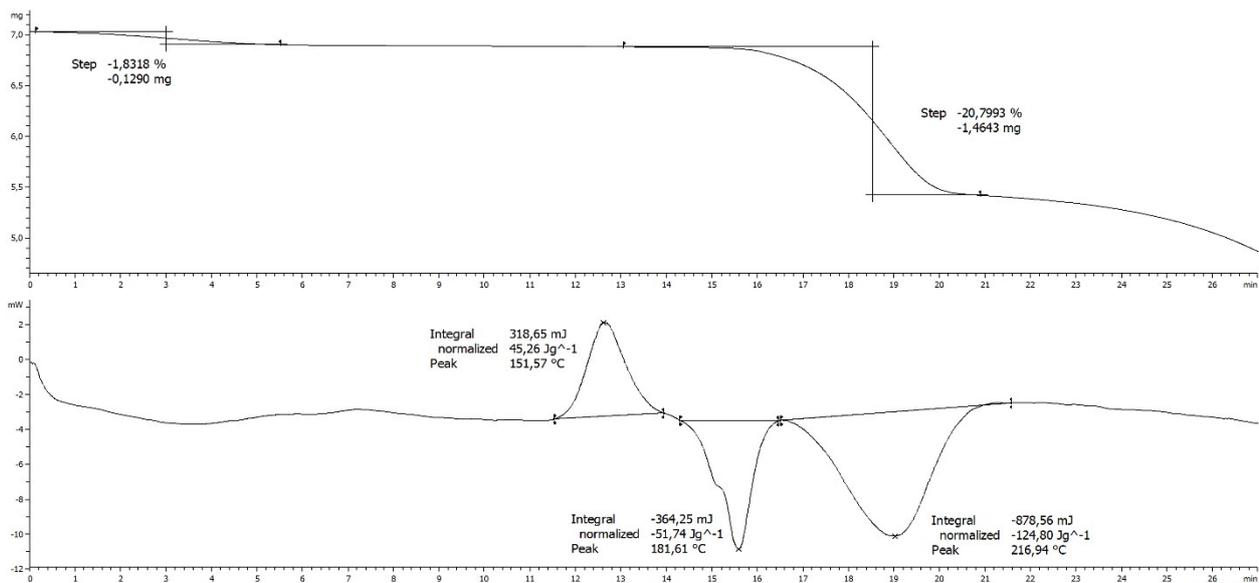


Figure S26. TGA (top) and DSC (bottom) thermograms of the solid obtained through LAG of **vin** and **H₂oxa** in the presence of water ($\eta=0.05 \mu\text{L mg}^{-1}$).

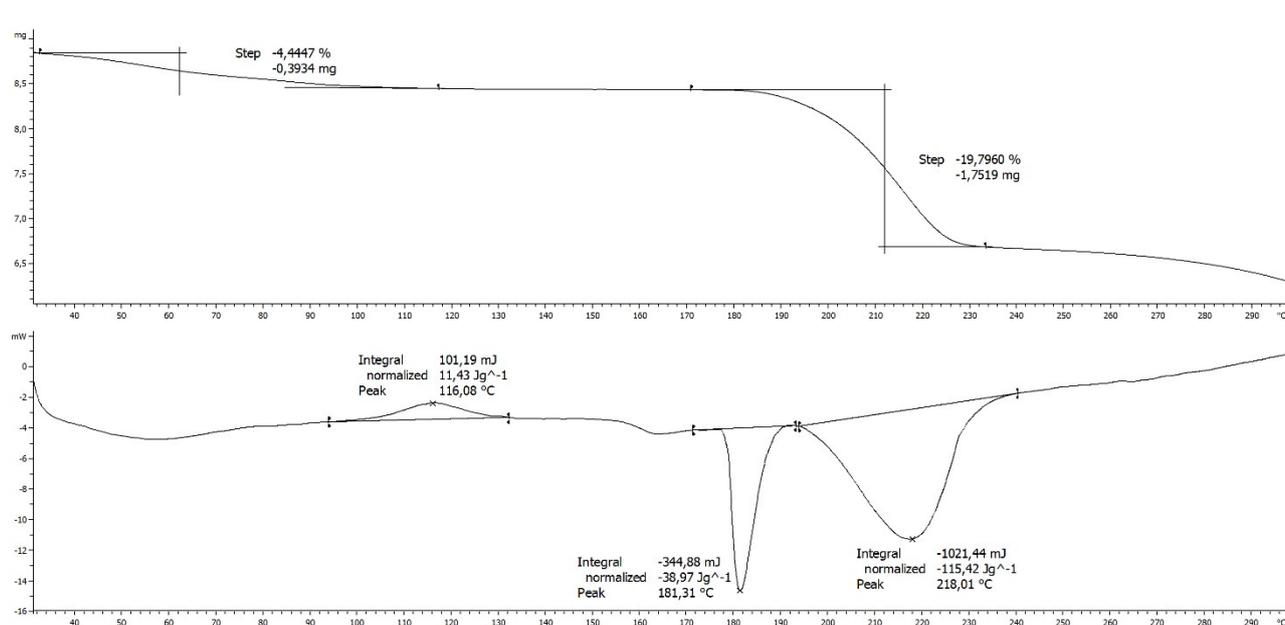


Figure S27. TGA (top) and DSC (bottom) thermograms of the solid obtained through LAG of **vin** and **H₂oxa** in the presence of water ($\eta=0.10 \mu\text{L mg}^{-1}$).

3.2.2 LAG experiments with dried liquid additives

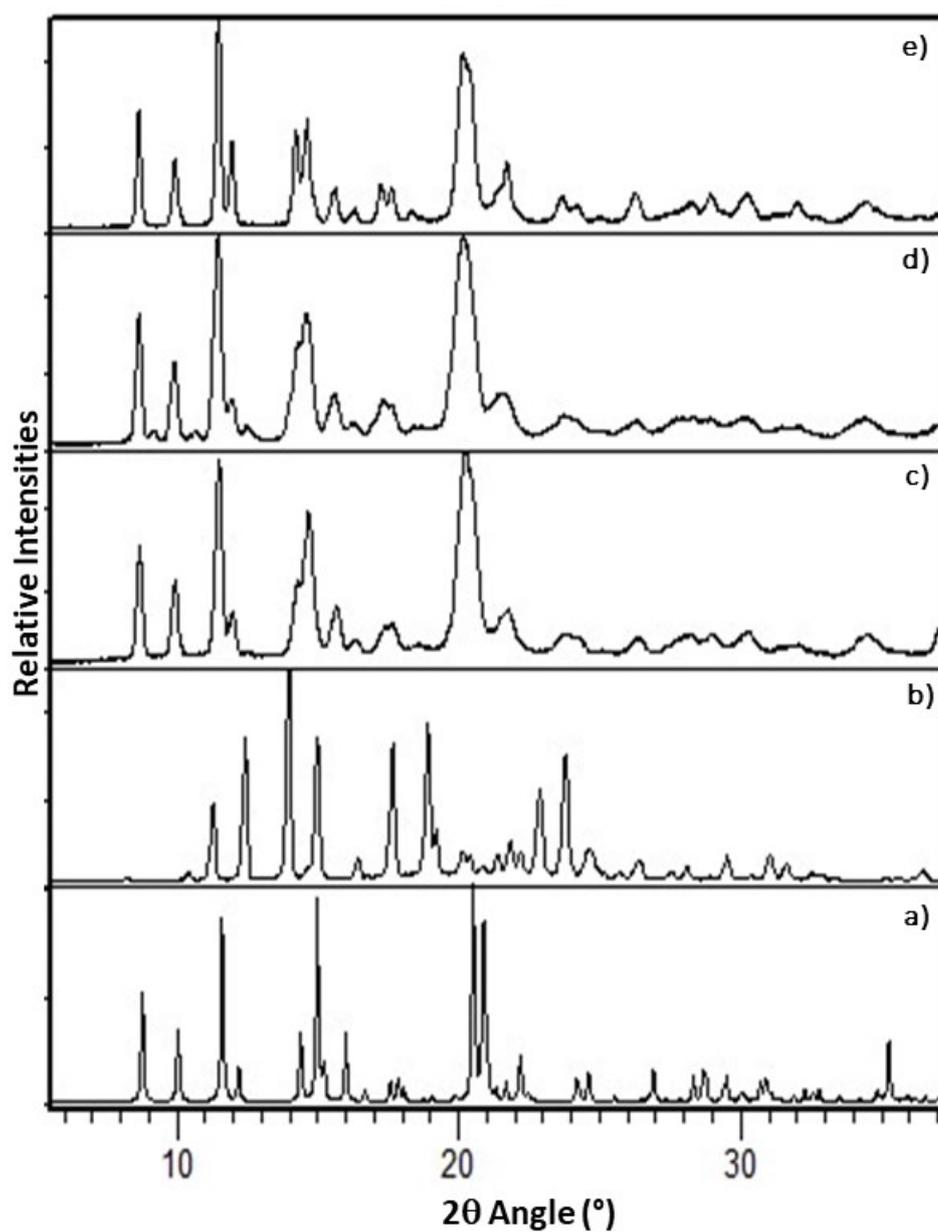


Figure S28. PXRD pattern of: (a) calculated Form II, (b) pure **vin**, (c), (d) and (e) solid products obtained after LAG of **vin** and H₂oxa with dried ethyl acetate, dried acetonitrile and dried acetone ($\eta=0.10 \mu\text{L mg}^{-1}$), respectively.

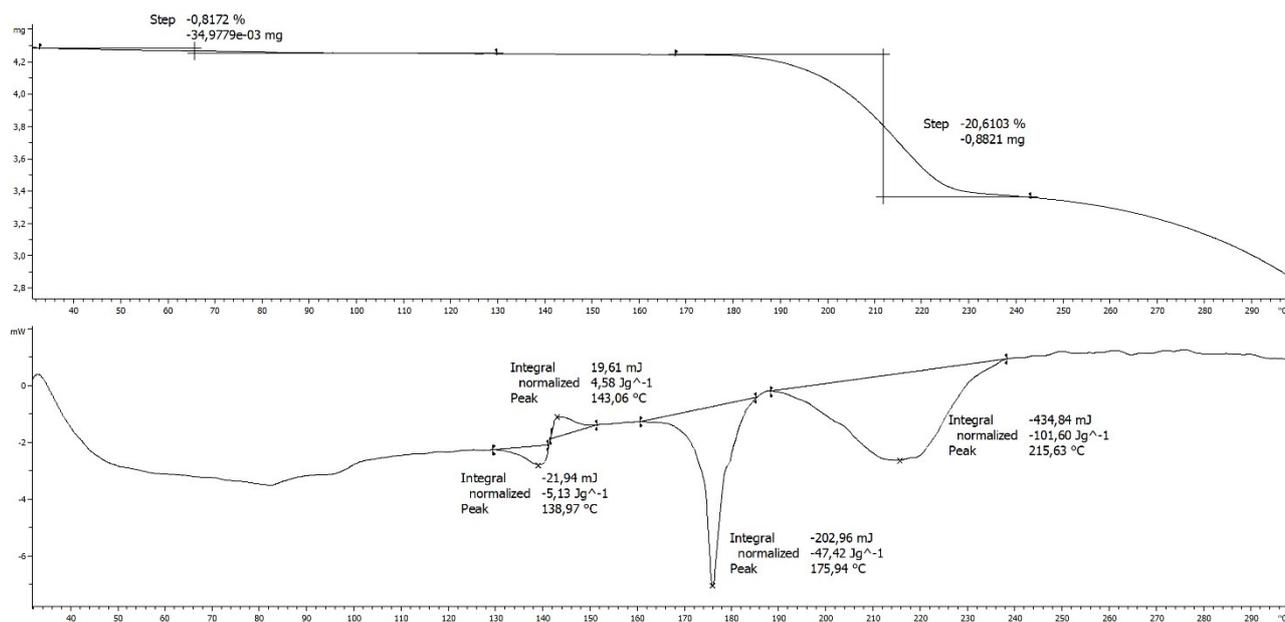


Figure S29. TGA (top) and DSC (bottom) thermograms of the solid product obtained after LAG of **vin** and **H₂oxa** with dried ethyl acetate ($\eta=0.15 \mu\text{L mg}^{-1}$).

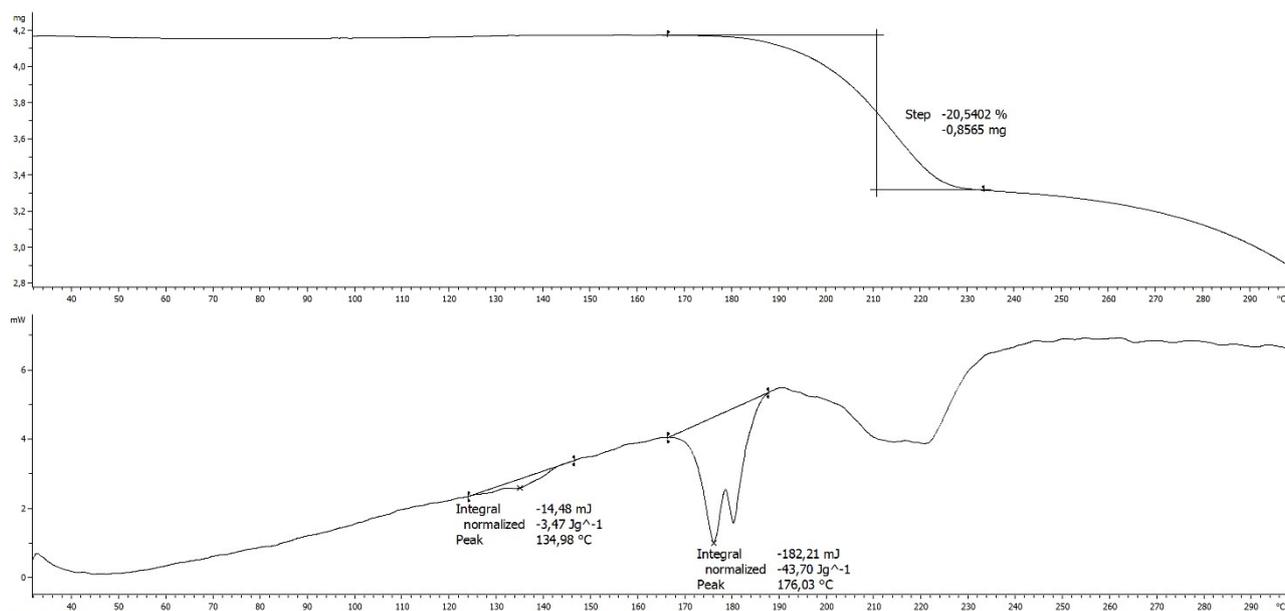


Figure S30. TGA (top) and DSC (bottom) thermograms of the solid product obtained after LAG of **vin** and **H₂oxa** with dried acetonitrile ($\eta=0.15 \mu\text{L mg}^{-1}$).

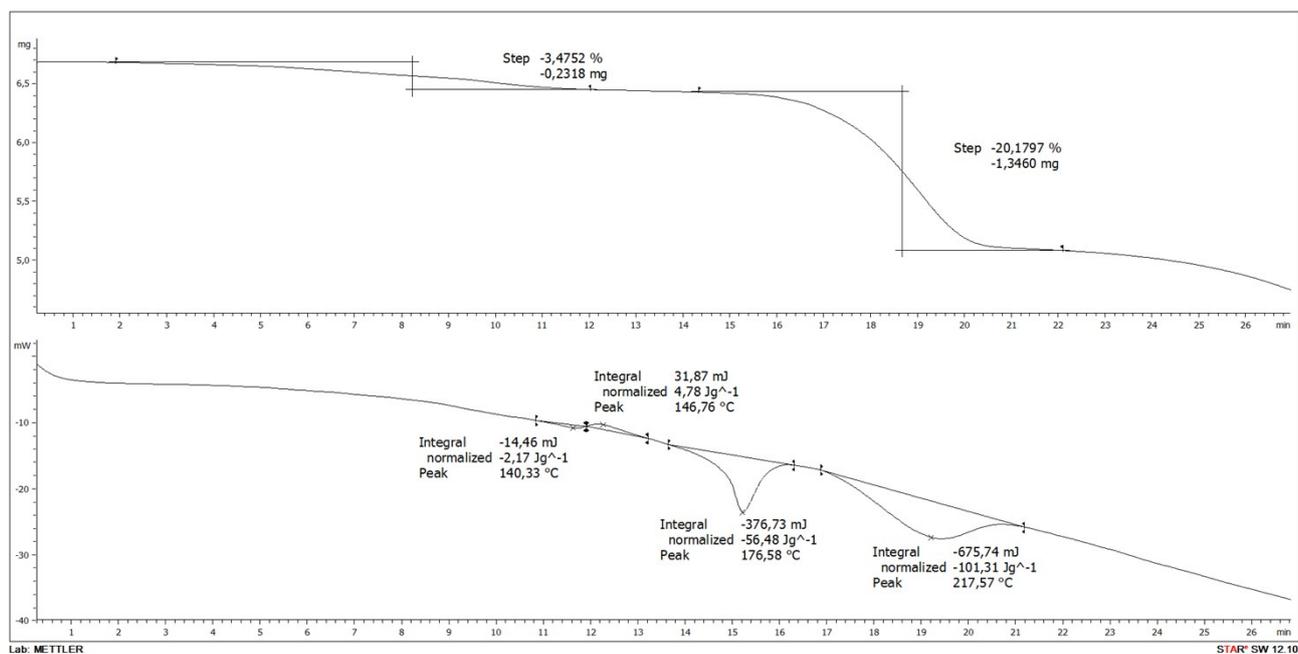


Figure S31. TGA (top) and DSC (bottom) thermograms of the solid product obtained after LAG of **vin** and H₂oxa with *dried* acetone ($\eta=0.15 \mu\text{L mg}^{-1}$).

4. Structure determination by X-ray crystallography

4.1 Structure determination of (Hvin⁺)·(Hoxa⁻), Form I

The crystal structure of Form I was solved from capillary PXRD data using a mechanochemically prepared sample of (Hvin⁺)·(Hoxa⁻) (see section 2.1.1). The diffraction data was collected at room temperature and in transmission mode using a two-axis *Stoe StadiP* diffractometer equipped with a Cu anode, a Ge(111) monochromator, a *Dectris Mythen 1K* detector and a small-aperture collimator. The CuK_{α1} X-rays ($\lambda=1.54056 \text{ \AA}$) were generated at 40 kV and 30 mA. The diffraction data was collected in the 2 to 60° 2 θ range in steps of 0.015° 2 θ with a count time of 1 s per step. The sample was placed in a flame-sealed a 0.7 mm diameter borosilicate glass capillary.

The pattern was indexed with *N-TREOR*¹ algorithm, via the interface of *EXPO2014*² software. The *EXPO2014* program was also used for space group determination and simulated annealing structure solution. Rietveld refinement was performed with *TOPAS Academic v. 6*.³ Molecular fragments of **vin** cation and H₂**oxa** anion were defined via rigid bodies, with flexible torsion angles defined for the rotatable C–C bonds. Background was modelled with a Chebyshev polynomial function and the diffraction peak shapes were defined with a pseudo-Voigt function. Atomic vibrations were modelled with a single isotropic Debye-Waller factor. The Rietveld refinement results are shown in Table S1 and Figure S32.

Table S1. Crystallographic data the structure of (Hvin⁺)·(Hoxa⁻) *Form I* determined from powder X-ray diffraction data.

	Form I
chemical formula	C ₂₄ H ₂₈ N ₂ O ₆
<i>M_r</i> / g mol ⁻¹	440.48
crystal system	monoclinic
space group	<i>C2</i>
<i>a</i> / Å	18.560(1)
<i>b</i> / Å	7.5949(4)
<i>c</i> / Å	8.0212(5)
α / °	90
β / °	96.383(5)
γ / °	90
<i>V</i> / Å ³	1123.7(1)
<i>Z</i>	2
<i>D_c</i> / gcm ⁻³	1.3019(1)
<i>F</i> (000)	468
radiation type	CuK _α
<i>T</i> / K	296(2)
<i>R</i> _{wp}	0.072
<i>R</i> _p	0.055
<i>R</i> _{Bragg}	0.037
χ^2	3.078
CCDC deposition number	2024365

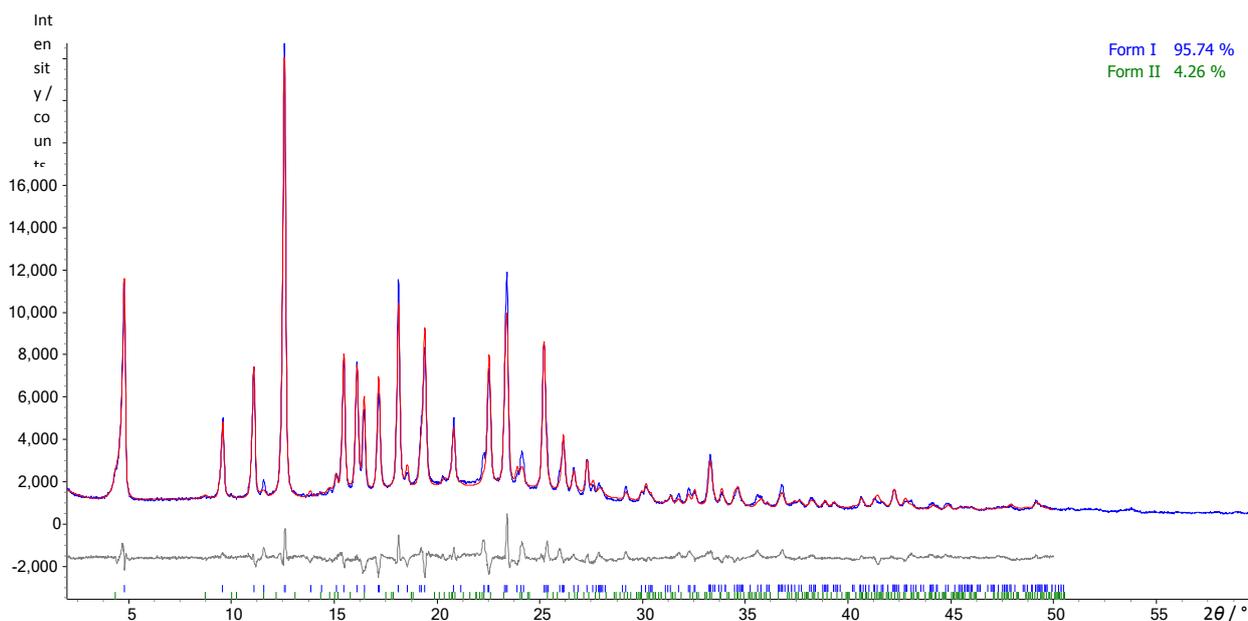


Figure S32. Rietveld refinement of $(\text{Hvin}^+) \cdot (\text{Hoxa}^-)$ Form I. The experimental diffraction profile is shown in blue, the calculated profile in red, and the difference curve is shown in grey.

4.2 Structure determination of $(\text{Hvin}^+) \cdot (\text{Hoxa}^-)$, Form II and $(\text{Hvin}^+) \cdot (\text{Hoxa}^-) \cdot (\text{EtOAc})_{0.16}$

The crystal structures of $(\text{Hvin}^+) \cdot (\text{Hoxa}^-)$ Form II and the $(\text{Hvin}^+) \cdot (\text{Hoxa}^-) \cdot (\text{EtOAc})_{0.16}$ solvate were determined using single crystal X-ray diffraction data. Single crystals of $(\text{Hvin}^+) \cdot (\text{Hoxa}^-)$ Form II were obtained by slow evaporation of a solution of mechanochemically prepared. Specifically, 0.115 mmol of **vin** and H_2oxa were transferred in a 10 mL glass vial. Subsequently, 4 mL of ethyl acetate were added and the components were dissolved through vigorous stirring using a magnetic stir bar. The obtained solution was left to evaporate slowly at room temperature. Single crystals of $(\text{Hvin}^+) \cdot (\text{Hoxa}^-)$ were obtained after 5 days and left to dry at ambient conditions for one week after they were isolated through filtration. Single crystals of $(\text{Hvin}^+) \cdot (\text{Hoxa}^-) \cdot (\text{EtOAc})_{0.16}$ were obtained from a hot and concentrated EtOAc solution of $(\text{Hvin}^+) \cdot (\text{Hoxa}^-)$, Form I. Crystals suitable for diffraction studies were obtained once the solution reached room temperature.

Single X-ray diffraction data from a colourless and prism-shaped crystals of Form II ($0.05 \times 0.19 \times 0.23 \text{ mm}^3$) and the solvate ($0.05 \times 0.11 \times 0.39 \text{ mm}^3$) were collected on a dual-source *Agilent SuperNova* single crystal X-ray diffractometer using a micro-focus Cu X-ray beam ($\lambda = 1.54184 \text{ \AA}$, generated at 50 kV and 0.8 mA) and a 135 mm *Atlas* CCD detector. The sample temperature was controlled with an *Oxford Instruments Cryojet5*. The data was acquired, processed and corrected using the *CrysAlisPro* program.⁴ Structure solution and refinement were accomplished using the *Olex2* program suite (Form II)⁵ and *SHELXL*.⁶ The structure was solved using *SHELXT*,⁷ while structure refinement was accomplished using *SHELXL*.⁸ All non-hydrogen atoms were refined anisotropically, while hydrogen atoms associated with the carbon, oxygen and nitrogen atoms were refined isotropically in geometrically constrained positions.

$(\text{Hvin}^+) \cdot (\text{Hoxa}^-) \cdot (\text{EtOAc})_{0.16}$: The geometry of the disordered ethyl group of Hvin^+ and the disordered EtOAc molecule were modelled using a range of *SHELX* restraints and constraints, namely DFIX, SADI, DELU, EADP and EXYZ.

$(\text{Hvin}^+) \cdot (\text{Hoxa}^-)$, *Form II*: The latter stages of the structure refinement suggested that the ethyl ester group is disordered over two positions. However, the crystal structure of Form II is presented without a disordered ethyl group owing to the insignificant improvement of its structural model and the resulting refinement parameters, which could only be achieved through the extensive use of *SHELX* restraints and constraints. Further structural analyses also revealed that the crystal structure exhibits sizeable voids. The solvent-mask procedure in *Olex2* was applied to determine that each void displays a size of 105 \AA^3 and an electron count of $4 e^-$. The final refinement of the reported crystal structure was accomplished *without* the use of the *Olex2 Solvent Mask* routine and a solvent-corrected hkl file, although the use of such corrected hkl file results in negligibly better refinement parameters. Such approach was justified by the insignificant electron count in each void.

The crystal structure of the ethyl acetate hemisolvate is shown in Figure S33. The crystallographic and refinement parameters for Form II and the ethyl acetate hemisolvate are shown in Table S2.

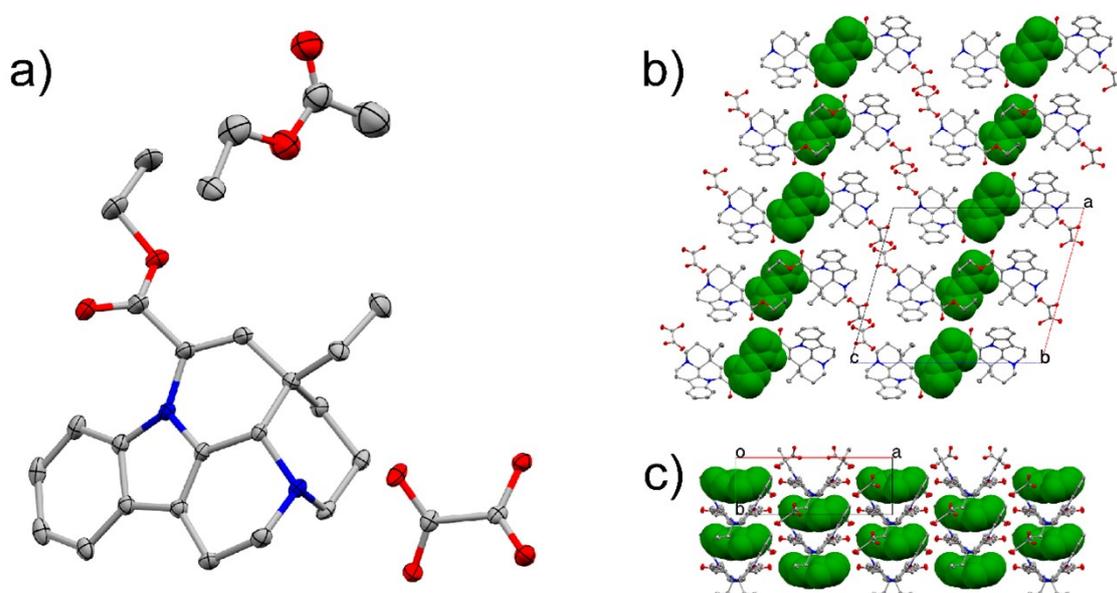


Figure S33. Perspective view of the asymmetric unit of the crystal structure of the ethylacetate hemisolvate (a). Crystal packing diagrams viewed along the crystallographic axes *b* and *c* are shown in b) and c), respectively. All disordered functional groups and hydrogen atoms are omitted for clarity. The thermal ellipsoids of all atoms are drawn at the 50% probability level. Atom colour scheme: carbon – grey, oxygen – red, nitrogen – blue. The disordered ethyl acetate molecules are shown in green using a space-fill model in b) and c).

Table S2: Crystallographic and refinement parameters for (Hvin⁺)-(Hoxa⁻) Form II and (Hvin⁺)-(Hoxa⁻)-(EtOAc)_{0.16}.

	Form II	EtOAc solvate
chemical formula	C ₂₄ H ₂₈ N ₂ O ₆	C _{24.63} H _{29.26} N ₂ O _{6.32}
$M_r / \text{g mol}^{-1}$	440.48	454.41
crystal system	monoclinic	monoclinic
space group	C2	C2
$a / \text{\AA}$	17.9007(2)	17.8855(2)
$b / \text{\AA}$	6.30220(10)	6.32180(10)
$c / \text{\AA}$	20.9554(2)	21.0313(3)
$\alpha / ^\circ$	90	90
$\beta / ^\circ$	105.3560(10)	105.3460(10)
$\gamma / ^\circ$	90	90
$V / \text{\AA}^3$	2279.66(5)	2293.19(6)
Z	4	4
D_c / gcm^{-3}	1.283	1.317
$F(000)$	936	967
$\mu(\text{CuK}\alpha) / \text{mm}^{-1}$	0.763	0.783
T / K	150.0(1)	110.0(1)
crystal size / mm ³	0.05 × 0.19 × 0.23	0.05 × 0.11 × 0.39
index range	-22 → 22 -7 → 7 -25 → 25	-22 → 22 -7 → 7 -25 → 25
collected reflections	40113	37992
unique reflections	4465	4462
R_{int}	0.0379	0.0574
reflections with $I > 2\sigma(I)$	4385	4366
no. parameters	293	366
$R(F), F > 2\sigma(F)$	0.0271	0.0336
$wR(F^2), F > 2\sigma(F)$	0.0738	0.0879
$R(F)$, all data	0.0277	0.0344
$wR(F^2)$, all data	0.0745	0.0887
Δ_r (min., max.) e \AA^{-3}	-0.185, 0.185	-0.228, 0.277
CCDC deposition number	2024366	2024367

5. Solid-state NMR analysis

Solid-state NMR spectra were acquired with a *Bruker Avance II 400 Ultra Shield* instrument, operating at 400.23, 100.63 and 40.56 MHz for ^1H , ^{13}C and ^{15}N nuclei, respectively. Powder samples were packed into cylindrical zirconia rotors with a 4 mm o.d. and a 80 μL volume and spun at 12 (^{13}C) or 9 (^{15}N) kHz. ^{13}C and ^{15}N CPMAS spectra were acquired using a ramp cross-polarisation pulse sequence with a 90° ^1H pulse of 3.60 μs , a contact time of 3 (^{13}C) or 4 (^{15}N) ms, optimised recycle delays between 1 and 2.5 s, and a number of scans in the range 850-2100 (^{13}C) or 65000-77500 (^{15}N), depending on the sample. For every spectrum, a two-pulse phase modulation (TPPM) decoupling scheme was used, with a radio frequency field of 69.4 kHz. The ^{13}C and ^{15}N chemical shift scales were calibrated through the external standard glycine (^{13}C methylenic signal at 43.7 ppm; ^{15}N peak at 33.4 ppm with respect to NH_3). Relevant NMR spectra are shown in Figure S34.

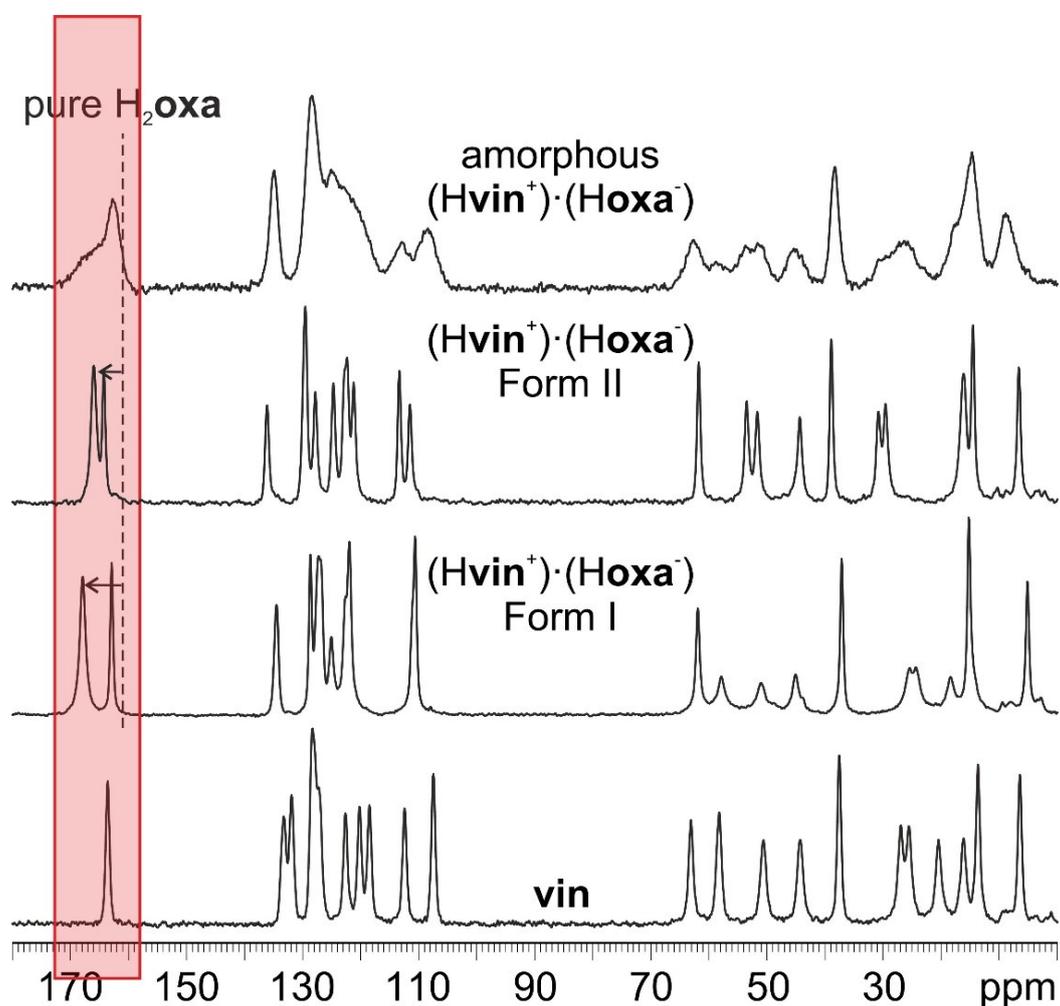


Figure S34. ^{13}C (100 MHz) CPMAS spectra of pure **vin**, Form I, Form II and amorphous $(\text{Hvin}^+) \cdot (\text{Hoxa}^-)$, acquired with a spinning speed of 12 kHz at room temperature. The dashed line represents the chemical shift of pure H_2oxa : the high-frequency shift of the signal is diagnostic of carboxylate formation.

6. DFT calculations

6.2 Experimental section

Periodic DFT calculations were performed using the plane-wave code *CASTEP 19*.⁹ Input files were prepared using the program *cif2cell*.¹⁰ Crystal structures were optimised using PBE¹¹ functional supplemented by many-body dispersion (MBD*)^{12–14} correction. The plane-wave basis set was truncated at 650 eV cutoff, and ultrasoft pseudopotentials were generated on the fly. Electronic Brillouin zone was sampled with a 0.03 Å⁻¹ Monkhorst-Pack k-point grid. Unit cell parameters and atomic coordinates were relaxed during the optimisation, subject to the space group symmetry constraints. The convergence criteria were set as follows: maximum energy change 10⁻⁵ eV atom⁻¹, maximum force on atom 0.03 eV Å⁻¹, maximum atom displacement 10⁻³ Å, maximum residual stress 0.05 GPa.

Molecular DFT calculations were performed in *Gaussian 16* version B01.¹⁵ Geometries of the **vin** and H₂**oxa** molecules, the **Hvin**⁺ and **Hoxa**⁻ ions, as well as the hydrogen-bonded (**Hvin**⁺):(Hoxa⁻) assemblies were geometry-optimised in the gas phase, as well as under SMD solvation model.⁴ Calculations accomplished using the B3LYP^{16,17} functional, combined with Grimme D2¹⁸ semiempirical dispersion corrections, and the 6-311G(d,p) basis set. Default geometric convergence criteria were used. Interaction energies were corrected for basis set superposition error (BSSE) using the counterpoise method.

6.2 Results and discussion

The energies of proton transfer between **vin** and H₂**oxa** were calculated in order to rationalise the contrasting effects of different liquid additives, as well as the energy of formation of **Hvin**⁺:**Hoxa**⁻ hydrogen-bonded dimers in solution.

Table S3. Calculated energies for dimer formation and proton transfer in different solvents and gas phase.

Liquid additive	Energy of dimer formation / kJ mol ⁻¹	Energy of proton transfer / kJ mol ⁻¹	Type of liquid additive
methanol	-93.12	-35.72	inhibitive
ethanol	-88.81	-25.64	
DMSO	-84.27	-12.23	prohibitive
nitromethane	-83.66	-10.34	
acetone	-82.71	-0.86	catalytic
acetonitrile	-82.61	-10.20	
heptane*	-74.90	200.94	
gas phase	-70.49	400.44	

* Heptane was used as the closest analogue to hexane, since the hexane parameterisation is not available within the SMD model in *Gaussian 16*.

The solvent environment was modelled with a continuum SMD model. It was found that the energy of a proton transfer is most negative with inhibitive liquids and becomes less negative in the case of prohibitive liquids such as nitromethane and DMSO. In the case of catalytic liquids, the energy of proton transfer is either close to zero or positive. Conversely, the energy of dimer formation is negative for all solvents and even in the gas phase. Although such calculations lack of explicit treatment of intermolecular solute-solvent interactions, it is notable that liquids with identical modes of action (catalytic, inhibitive or prohibitive) can be also grouped together according to the calculated energies of proton transfer and dimer formation. Indeed, favourable energies of proton transfer in inhibitive solvents allow the Hvin^+ and Hoxa^- ions to freely coexist without forming dimers, something that can occur in the amorphous $(\text{Hvin}^+) \cdot (\text{Hoxa}^-)$ salt. On the other hand, in the presence of catalytic solvents proton transfer is no longer favourable, unless the hydrogen-bonded $\text{Hvin}^+:\text{Hoxa}^-$ dimer, found in both polymorphs of crystalline $(\text{Hvin}^+) \cdot (\text{Hoxa}^-)$, is formed.

7. Dissolution Kinetic Tests

The dissolution kinetic tests (DKT) were performed under the same conditions as in a related and recent **vin** study.¹⁹ Specifically, the determination of the concentration of **vin** in $(\text{Hvin}^+) \cdot (\text{Hoxa}^-)$ products was performed by using an *in situ* fiber-optic apparatus (Hellma, Italy), connected to a spectrophotometer (Zeiss, Germany) at UV wavelength of 313 nm (Figure S35). This technique allows an *in situ* determination of the concentration of a substance without perturbing the dissolution environment and often overcomes the problem connected to drug concentration measurements in the presence of generated solid particles. About 150 cm³ of a 7.4 pH buffer (0.2 M KH_2PO_4 /0.2 M NaOH) heated at 37 °C was used as dissolution medium. In these conditions, the solubility at equilibrium of pure **vin** is 1.6 mg/L.¹⁹ In the present study, sink conditions were not maintained in order to build up the super-saturation, thus mimicking conditions in the gastrointestinal tract and to allow possible events such as nucleation, crystallisation and precipitation.²⁰ Subsequently, an amount of solid product suitable to give 5 mg of **vin** was added to the dissolution medium (maximum concentration of 33.3 mg/L) and uniformity conditions were ensured by using an impeller at a rotational speed of 200 rpm. Each DKT lasted 60 min. Additionally, since monitoring drug concentrations by using an *in situ* fiber-optic probe without proper precautions may lead to an overestimation of drug concentration due to several causes, including the Tyndall effect,²¹ the scattering effect due to the super-saturation phenomenon, occurring at every wavelength, was eliminated by a difference between the absorbance measured at 313 nm and that measured at 450 nm. The samples were tested in triplicate and the results were expressed as mean \pm S.D. The **vin** calibration curve is shown in Figures S36. The solubilisation profiles of Form I, Form II and amorphous $(\text{Hvin}^+) \cdot (\text{Hoxa}^-)$ are shown in Figure S37.

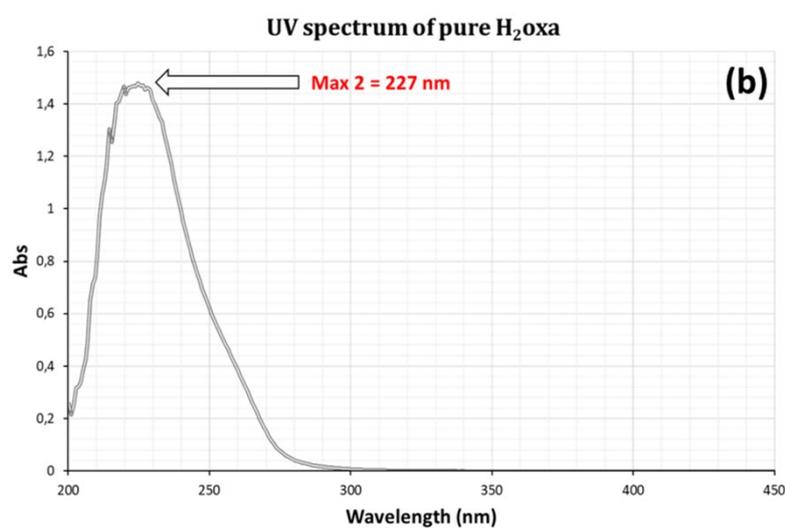
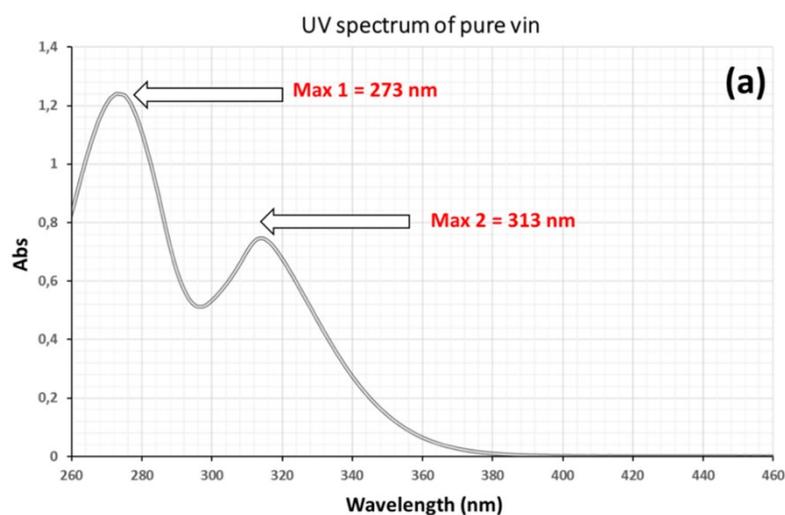


Figure S35. UV spectra of pure a) vin and b) pure H₂oxa.

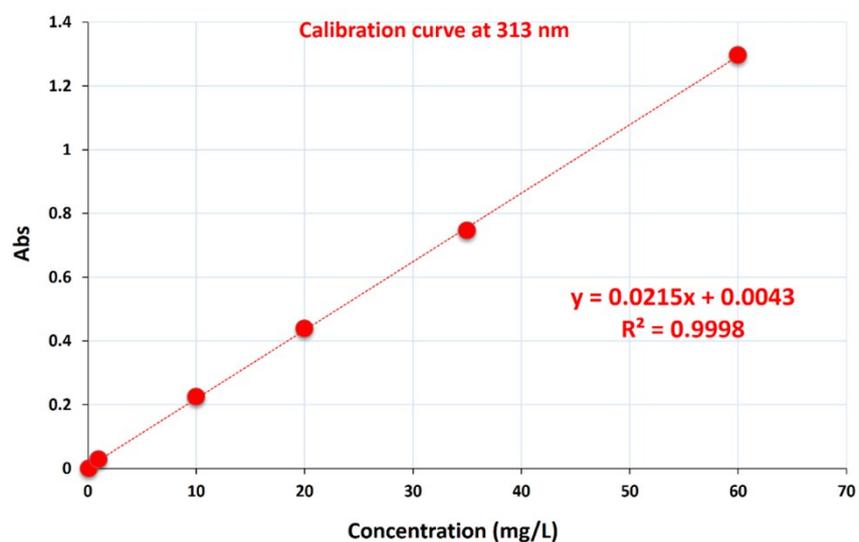


Figure S36. Calibration curve for vin at the UV wavelength of 313 nm.

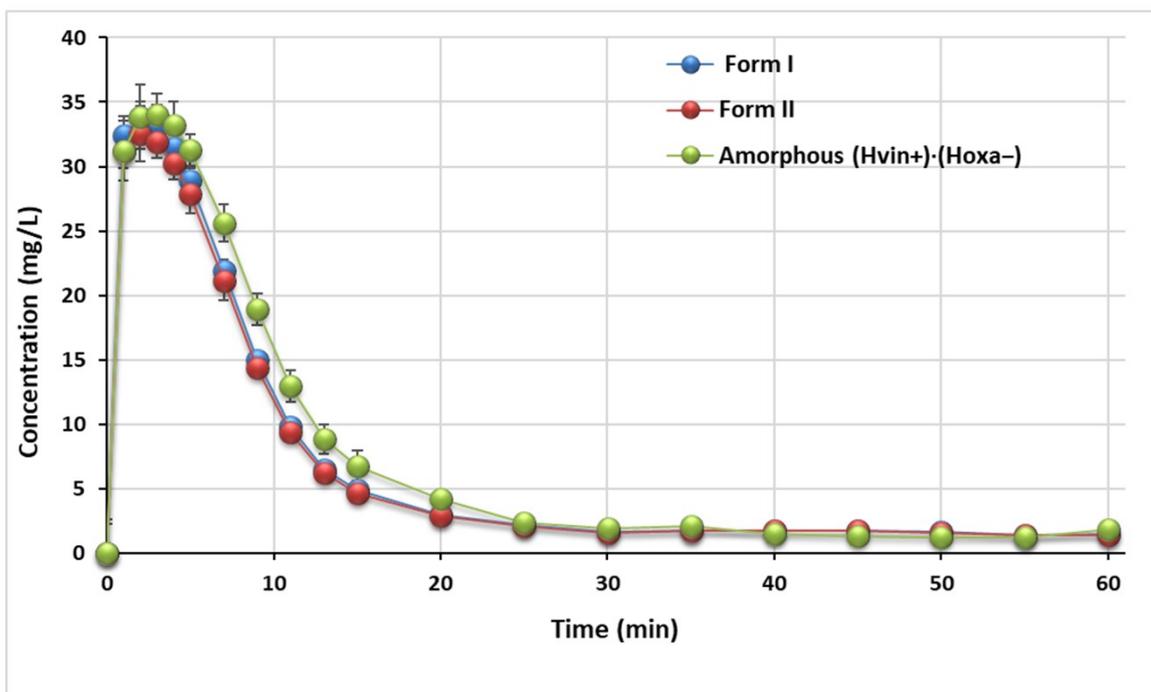


Figure S37. Dissolution profiles of the different solid forms of (Hvin⁺)·(Hoxa⁻). All solid forms show a dissolution profile typical of a protonated solid with a rapid and complete dissolution within 5 minutes of analysis, followed by precipitation of unprotonated **vin** due to supersaturation. The concentration reached a plateau at a value of 1.8 mg L⁻¹, close to the solubility at equilibrium of pure **vin** (1.6 mg L⁻¹). The dissolution profiles of Form I, Form II and amorphous (Hvin⁺)·(Hoxa⁻) are similar, suggesting that the solid form has not appreciably affected the solubilisation rate of **vin**.

8. Liquid-assisted grinding of selected cocrystals with prohibitive liquid additives

8.1 Theophylline:2,3-difluorobenzoic acid and theophylline:2,6-difluorobenzoic cocrystals

The mechanochemical syntheses of the (thp)·(23diFBA) and (thp)·(26diFBA) cocrystals was performed by LAG using a *Form-Tech Scientific FTS1000* shaker mill. Specifically, 200 mg of a physical mixture of equimolar amounts of **thp** and the fluorobenzoic acid were added to a 15 mL stainless steel grinding jar, along with 50 μL of ethanol and two 7 mm stainless steel milling balls. The mixer mill was operated at 30 Hz for 30 min. The obtained solids were subsequently analysed by powder X-ray diffraction using a *Stoe StadiP* diffractometer in transmission geometry and a monochromatic CuK_α X-ray source ($\lambda = 1.54056 \text{ \AA}$, generated at 40 kV and 30 mA). The data shown in Figures S38 and S39 was acquired in foil mode at room temperature (*ca.* 20 °C) in the 2–60° 2θ range (in continuous mode: 0.5° step, 10 s/step). The solids were characterised as cocrystals (rather than salts or solvates) using thermogravimetric analyses (TGA, DSC) and ATR-FT-IR spectroscopy. The results of these analyses will be reported elsewhere.

Each cocrystal (150 mg) was later subjected to LAG for 60 min (at 30 Hz) using nitromethane ($\eta=0.30 \text{ \mu L mg}^{-1}$), 2-pyrrolidone ($\eta=0.30 \text{ \mu L mg}^{-1}$) or DMSO ($\eta=0.30 \text{ \mu L mg}^{-1}$) as liquid additives. Figure S38

show the PXRD patterns of the resulting solids in the case of **(thp)·(23diFBA)**, which are all consistent with a partial or full decomposition of the cocrystals into a physical mixture of the cocrystal constituents. Figure S39, on the other hand, shows that the decomposition of the **(thp)·(26diFBA)** cocrystal occurred only two out of three cases; that is, in the presence of 2-pyrrolidone and dimethyl sulfoxide. The **(thp)·(26diFBA)** appears to be unaffected by LAG in the presence of nitromethane.

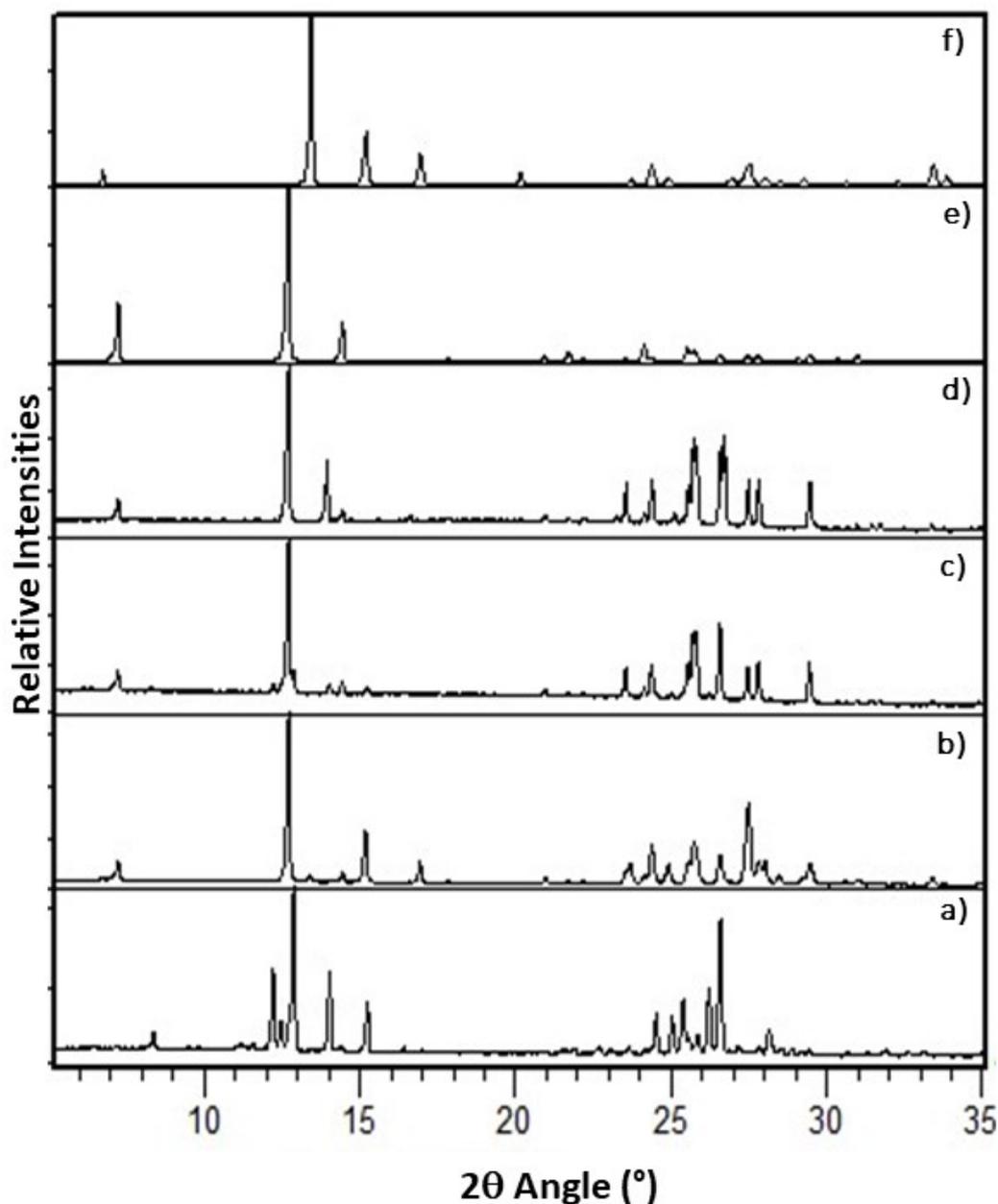


Figure S38. PXRD pattern of: (a) **(thp)·(23diFBA)** cocrystal as synthesised, (b), (c), (d) **(thp)·(23diFBA)** cocrystal subjected to LAG ($\eta=0.30 \mu\text{L mg}^{-1}$) in the presence of nitromethane, 2-pyrrolidone and dimethyl sulfoxide, respectively, (e) **thp** pure and (f) **23diFBA** pure.

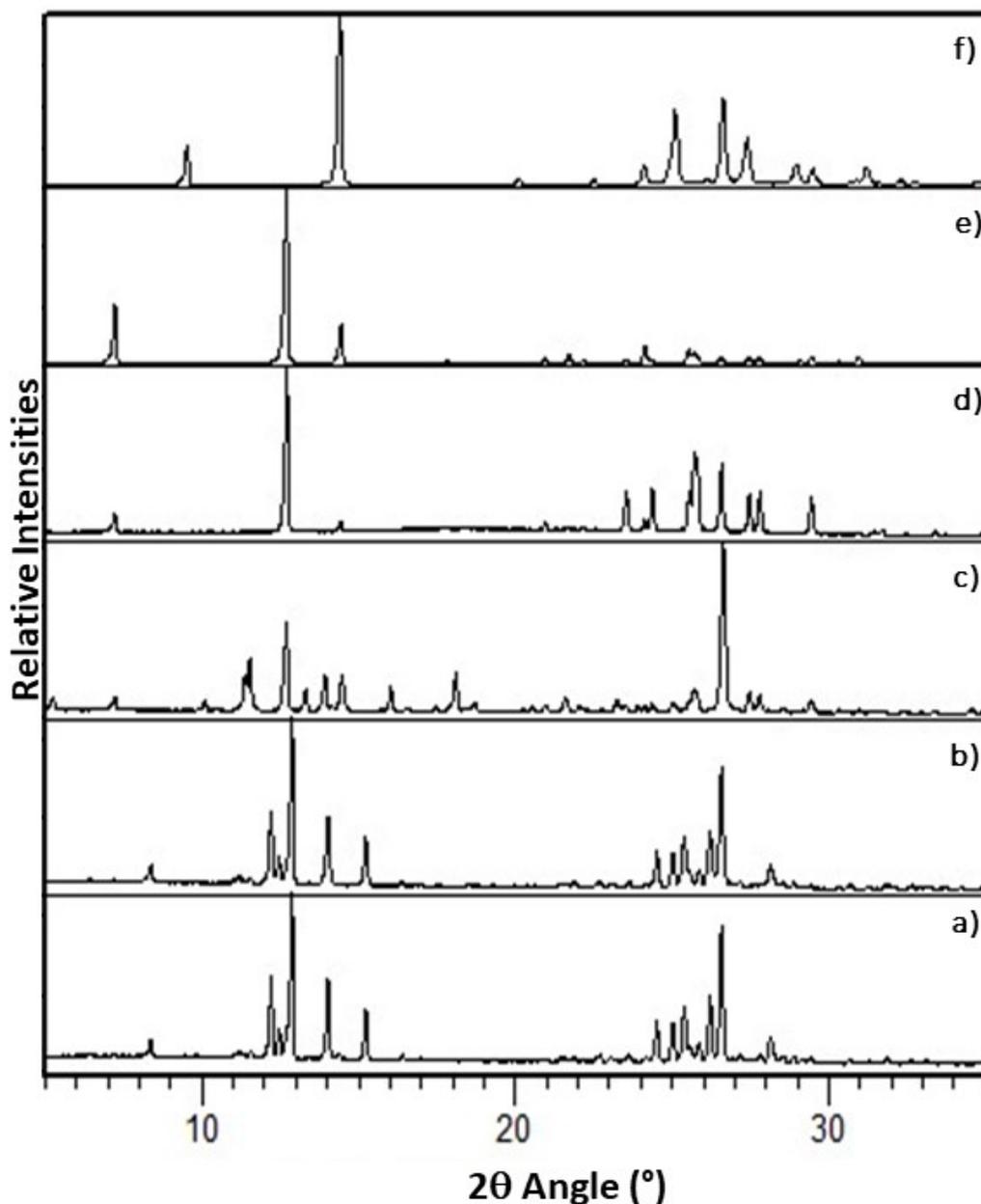


Figure S39. PXRD pattern of: (a) **(thp)·(26diFBA)** cocrystal, (b), (c), (d) **(thp)·(26diFBA)** cocrystal processed through LAG ($\eta=0.30 \mu\text{L mg}^{-1}$) using nitromethane, 2-pyrrolidone and dimethyl sulfoxide, respectively, (e) **thp** pure and (f) **26diFBA** pure.

8.2 Theophylline:anthranilic acid cocrystal

Fischer and co-authors reported that cocrystals of theophylline (**thp**) and anthranilic acid (**ana**) in 2:3 molar ratio (CSD code WUTHEA) can be obtained by LAG with ethanol using a *MM400 Retsch* ball mill.²² In the present study, **(thp)₂·(ana)₃** cocrystals were obtained mechanochemically through LAG with ethanol. Specifically, 93.4 mg of **thp** and 106.6 mg of **ana** were added to a 15 mL steel jar containing two milling balls of 7 mm diameter. The mixture was subsequently milled in the presence of ethanol ($\eta=0.30 \mu\text{L mg}^{-1}$) for 60 min at a frequency of 25 Hz. Snap-closed grinding jars (*FormTech*

Scientific) were used to minimise liquid evaporation. Such procedure was repeated four times. The purity of synthesised cocrystal was verified by Rietveld analysis (Figure S40).

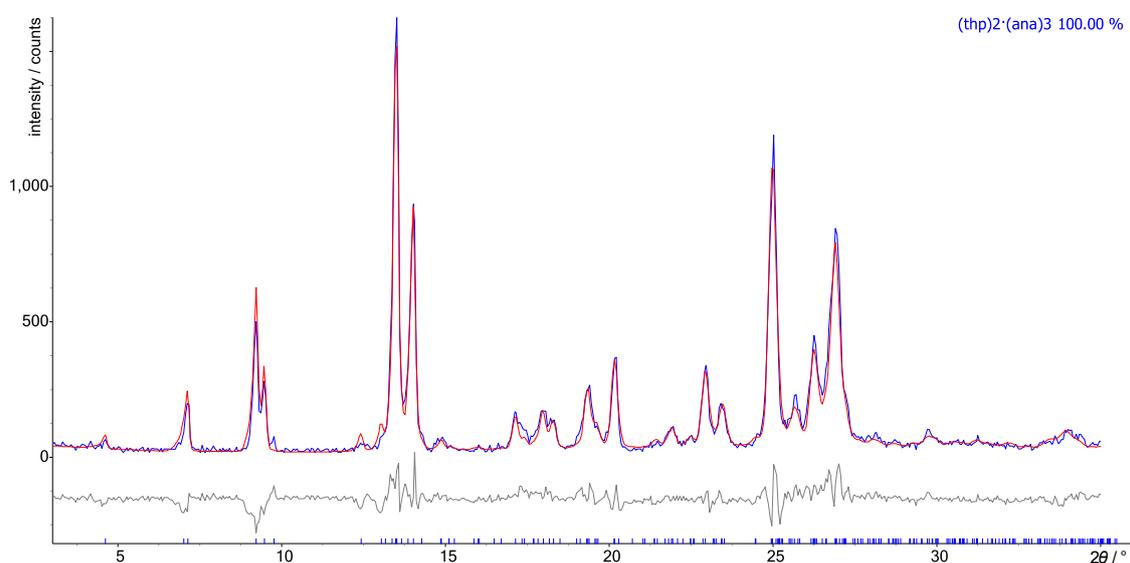


Figure S40. Rietveld refinement plot of $(\text{thp})_2 \cdot (\text{ana})_3$ prepared by LAG with ethanol ($\eta=0.30 \mu\text{L mg}^{-1}$). The calculated profile is shown in red, the experimental profile is shown in blue, and the difference curve is shown in grey.

Three samples of the synthesised $(\text{thp})_2 \cdot (\text{ana})_3$ cocrystal ($\sim 150 \text{ mg}$) were separately treated for 60 min at 25 Hz under LAG using nitromethane ($\eta=0.30 \mu\text{L mg}^{-1}$), 2-pyrrolidone ($\eta=0.30 \mu\text{L mg}^{-1}$) or DMSO ($\eta=0.30 \mu\text{L mg}^{-1}$) as liquid additives. The LAG products were characterised using PXRD (Figure S41) and each of the powder patterns was analyzed using the Rietveld refinement technique. The analyses revealed that LAG with nitromethane does not cause any significant changes to the $(\text{thp})_2 \cdot (\text{ana})_3$ cocrystal (Figures S42), while LAG with 2-pyrrolidone and DMSO caused partial dissociation of the cocrystal (Figure S43 and S44).

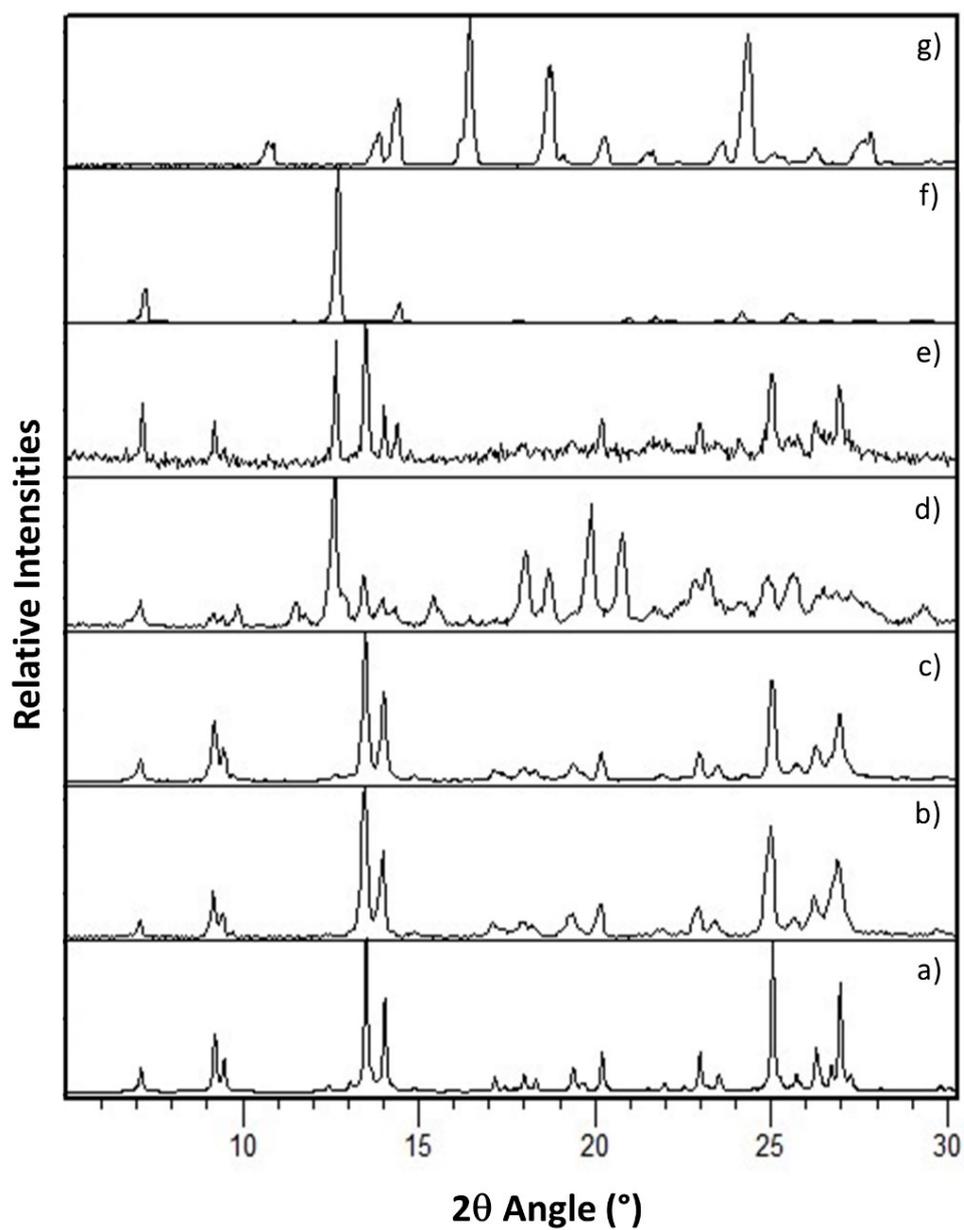


Figure S41. PXRD pattern of: (a) calculated $(\text{thp})_2 \cdot (\text{ana})_3$, (b) $(\text{thp})_2 \cdot (\text{ana})_3$ prepared by LAG with ethanol ($\eta=0.30 \mu\text{L mg}^{-1}$), (c), (d), (e) preformed $(\text{thp})_2 \cdot (\text{ana})_3$ processed by LAG ($\eta=0.30 \mu\text{L mg}^{-1}$) using nitromethane, 2-pyrrolidone and DMSO, respectively, (f) pure **theo** and (g) pure **ana**.

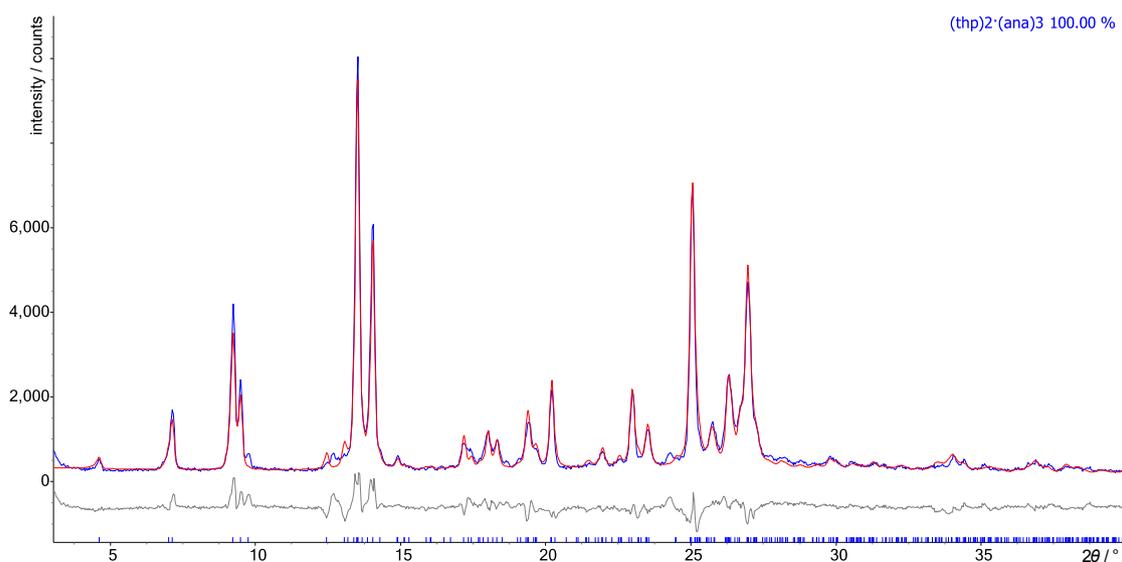


Figure S42. Rietveld refinement plot of $(\text{thp})_2 \cdot (\text{ana})_3$ processed by LAG ($\eta=0.30 \mu\text{L mg}^{-1}$) with nitromethane. The calculated profile is shown in red, the experimental profile is shown in blue, and the difference curve is shown in grey.

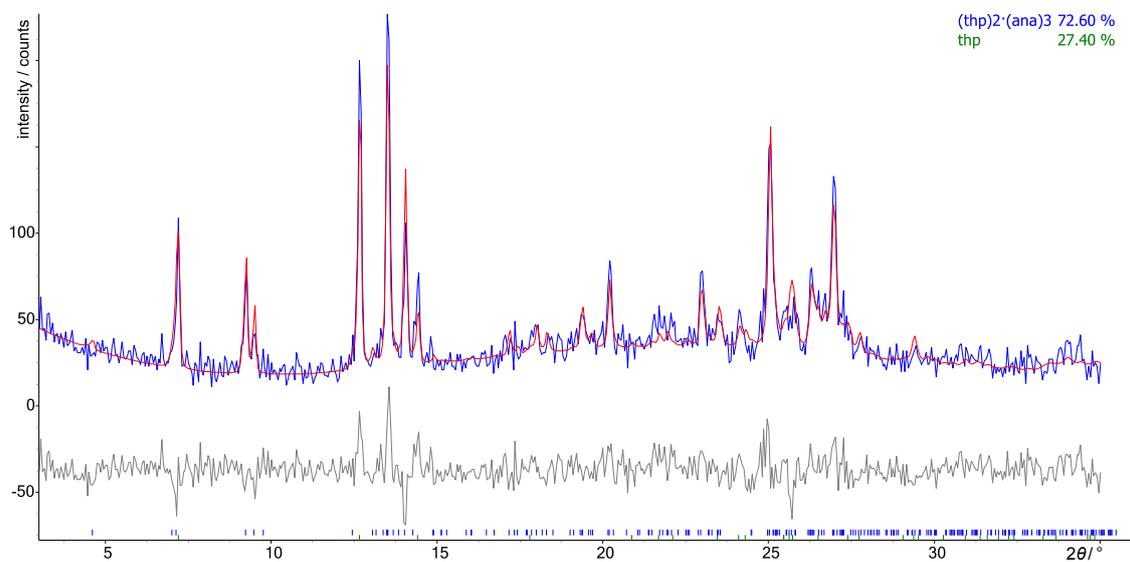


Figure S43. Rietveld refinement plot of $(\text{thp})_2 \cdot (\text{ana})_3$ processed by LAG ($\eta=0.30 \mu\text{L mg}^{-1}$) with DMSO. The calculated profile is shown in red, the experimental profile is shown in blue, and the difference curve is shown in grey.

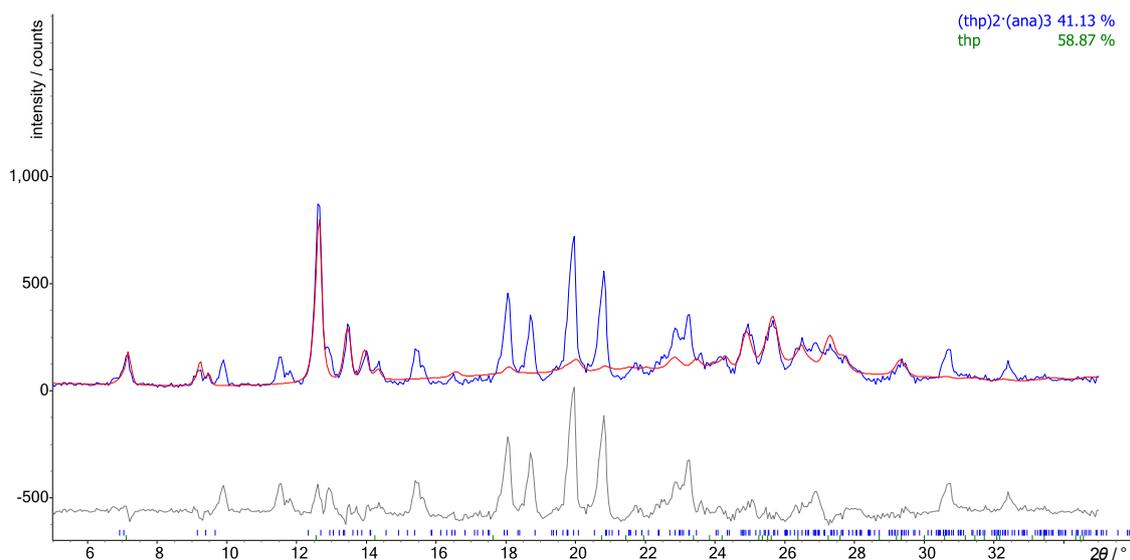


Figure S44. Rietveld refinement plot of $(\text{thp})_2 \cdot (\text{ana})_3$ processed by LAG ($\eta=0.30 \mu\text{L mg}^{-1}$) with 2-pyrrolidone. The calculated profile is shown in red, the experimental profile is shown in blue, and the difference curve is shown in grey. This experiment has resulted in the formation of a new phase with an unknown crystal structure. Due to the lack of a suitable crystal structure, the peaks corresponding to the new phase could not be modelled during Rietveld refinement.

8.3 Ibuprofen:nicotinamide cocrystal

Berry *et al.* reported the formation of a 1:1 cocrystal of racemic ibuprofen (**ibu**) and nicotinamide (**nic**) (CSD code SODDIZ) can be obtained from solutions via slow solvent evaporation.²³ In this study, racemic **(ibu)·(nic)** cocrystals were obtained mechanochemically by LAG with ethanol. Specifically, 125.7 mg of **ibu** and 74.3 mg of **nic** were added to a 15 mL steel jar containing two milling balls of 7 mm diameter. The mixture was subsequently milled in the presence of ethanol ($\eta=0.30 \mu\text{L mg}^{-1}$) for 60 min (at 25 Hz). The purity of the product was confirmed by Rietveld refinements (Figure S45).

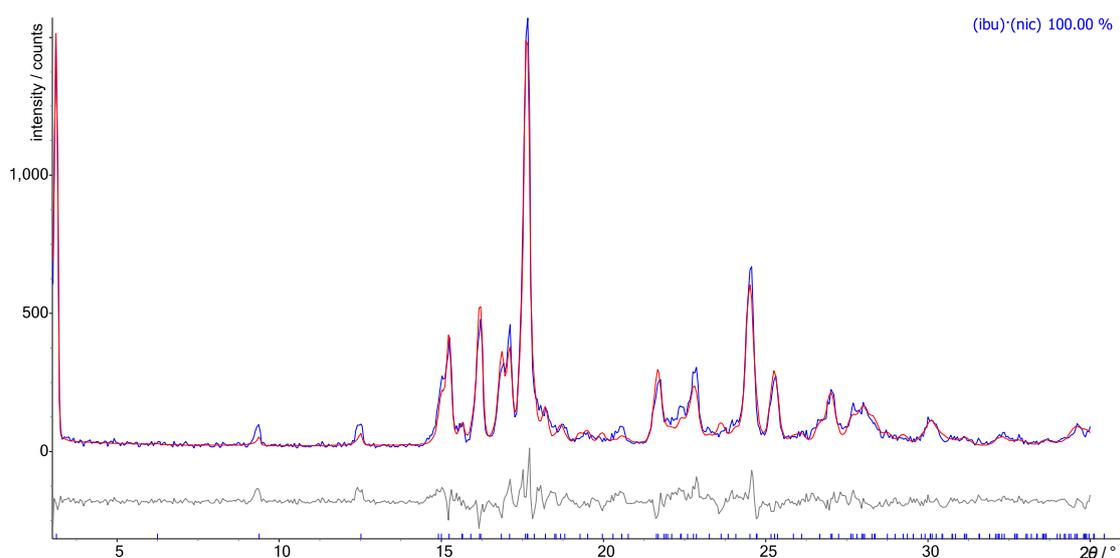


Figure S45. Rietveld refinement plot of **(ibu)·(nic)** prepared by LAG with ethanol ($\eta=0.30 \mu\text{L mg}^{-1}$). The calculated profile is shown in red, the experimental profile is shown in blue, and the difference curve is shown in grey.

Three samples of the **(ibu)·(nic)** cocrystal (~150 mg) were separately treated for 60 min at 25 Hz under LAG using nitromethane ($\eta=0.30 \mu\text{L mg}^{-1}$), 2-pyrrolidone ($\eta=0.30 \mu\text{L mg}^{-1}$) or DMSO ($\eta=0.30 \mu\text{L mg}^{-1}$) as liquid additives (Figure S46).

Approximately 150 mg of the synthesised **(ibu)·(nic)** cocrystal were then separately treated for 60 min at 25 Hz using LAG with nitromethane ($\eta=0.30 \mu\text{L mg}^{-1}$), 2-pyrrolidone ($\eta=0.30 \mu\text{L mg}^{-1}$) or DMSO ($\eta=0.30 \mu\text{L mg}^{-1}$) as liquid additives. The products were characterised using PXRD and the obtained powder patterns were analyzed using the Rietveld refinement technique. These analyses that the use of the three liquid additives did not cause any meaningful changes to the structure of the solids (Figures S47-S49).

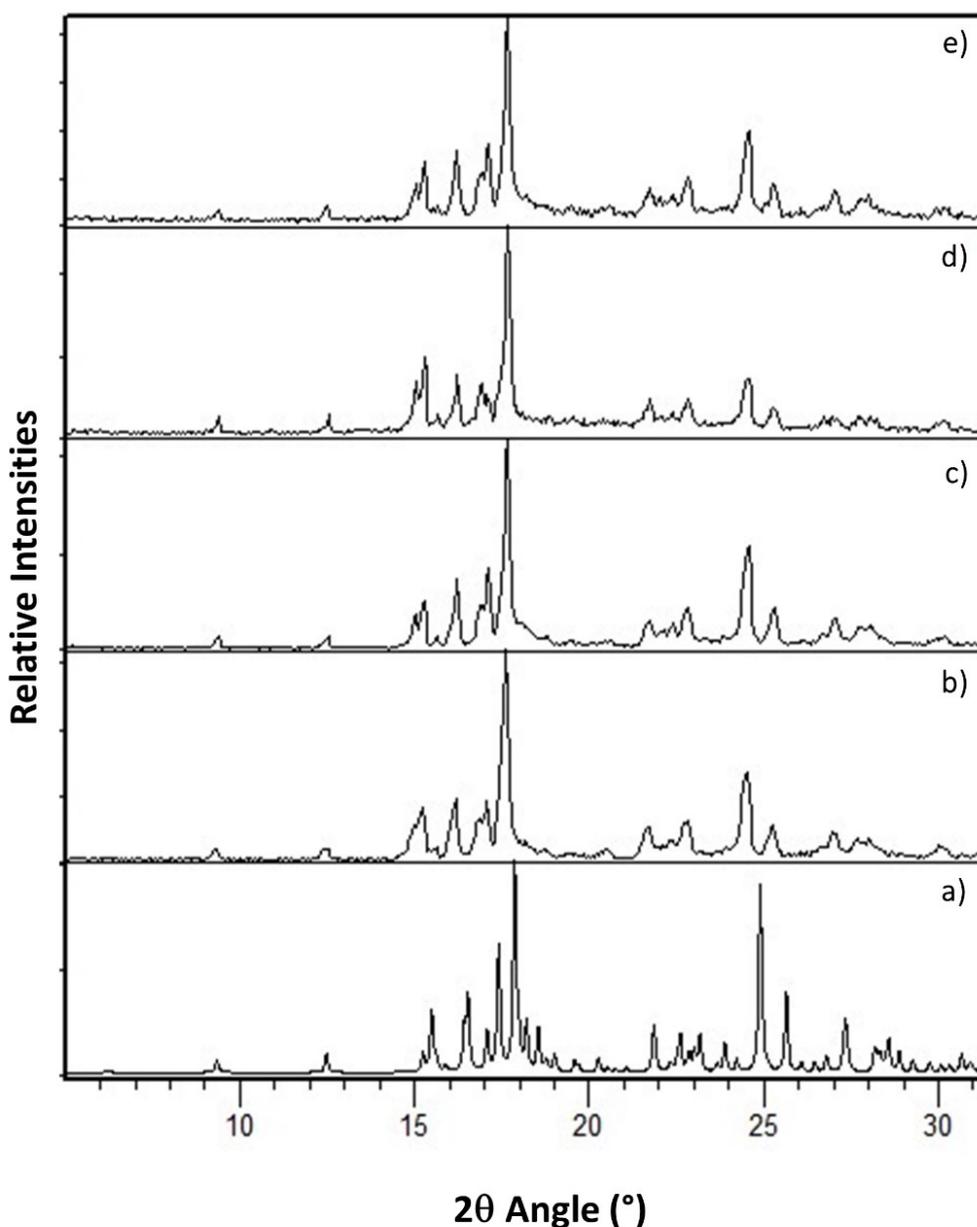


Figure S46. PXRD pattern of: (a) calculated **(ibu)·(nic)**,²³ (b) **(ibu)·(nic)** prepared by LAG with ethanol ($\eta=0.30 \mu\text{L mg}^{-1}$), (c), (d), (e) preformed **(ibu)·(nic)** processed by LAG ($\eta=0.30 \mu\text{L mg}^{-1}$) using nitromethane, 2-pyrrolidone and DMSO, respectively.

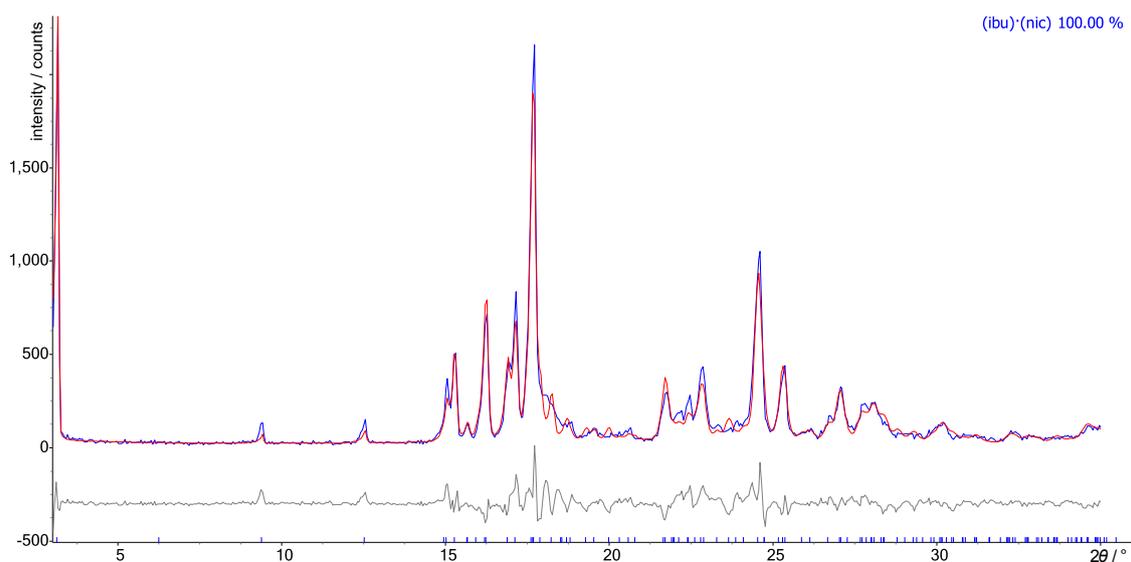


Figure S47. Rietveld refinement plot of **(ibu)·(nic)** processed by LAG ($\eta=0.30 \mu\text{L mg}^{-1}$) with nitromethane. The calculated profile is shown in red, the experimental profile is shown in blue, and the difference curve is shown in grey.

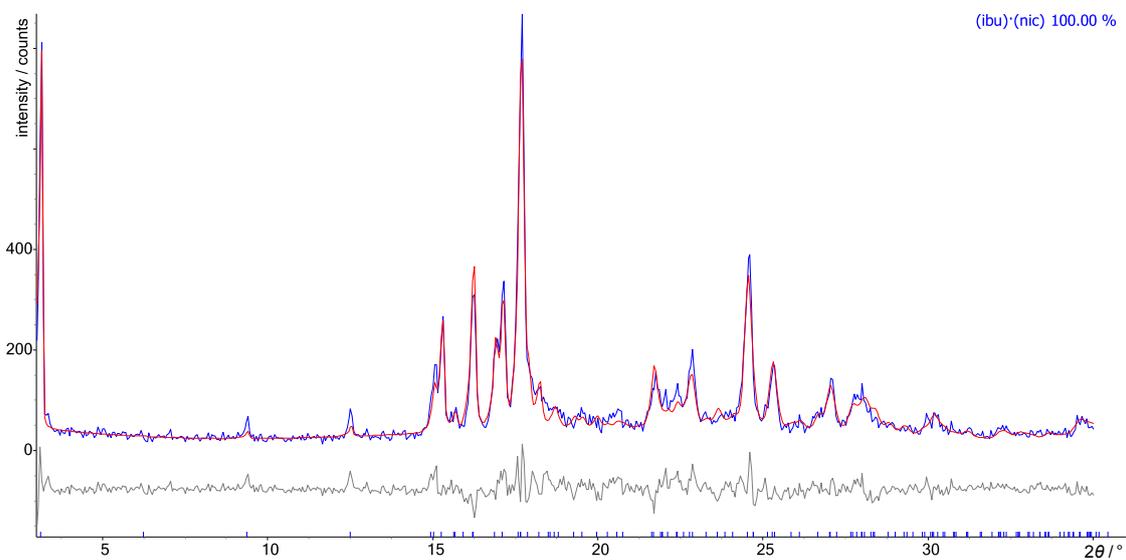


Figure S48. Rietveld refinement plot of **(ibu)·(nic)** processed by LAG ($\eta=0.30 \mu\text{L mg}^{-1}$) with DMSO. The calculated profile is shown in red, the experimental profile is shown in blue, and the difference curve is shown in grey.

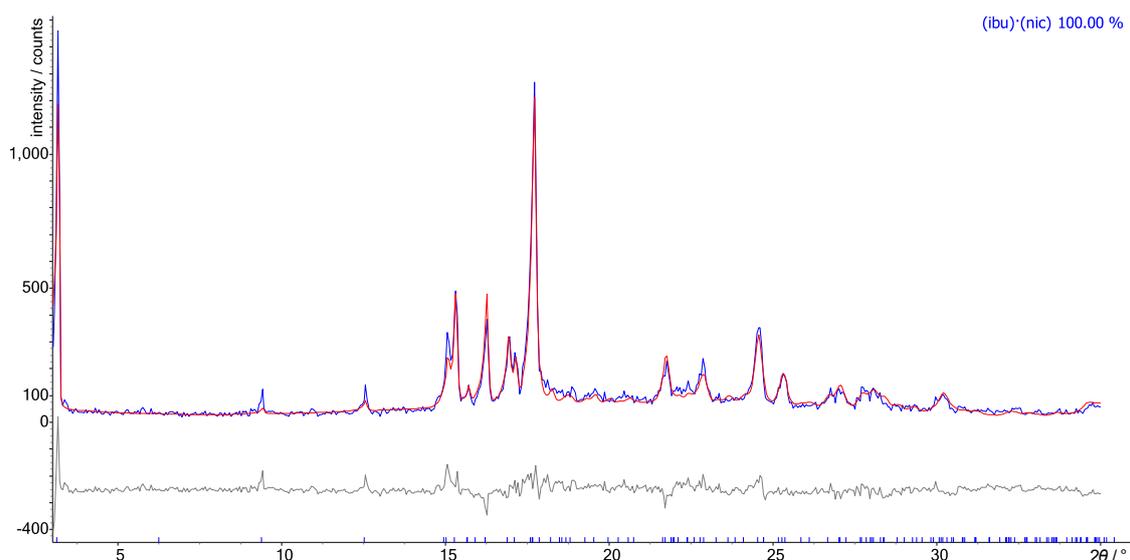


Figure S49. Rietveld refinement plot of (ibu)·(nic) processed by LAG ($\eta=0.30 \mu\text{L mg}^{-1}$) with 2-pyrrolidone. The calculated profile is shown in red, the experimental profile is shown in blue, and the difference curve is shown in grey.

8.4 Paracetamol:oxalic acid cocrystal

The 1:1 (par)·(oxa) cocrystal (CSD code LUJTAM) was prepared mechanochemically using a method reported by Karki *et al.*²⁴ Specifically, 125.4 mg of par and 74.6 mg of H₂oxa were added to a 15 mL steel jar containing two milling balls of 7 mm diameter. The mixture was subsequently milled under in the presence of methanol ($\eta=0.30 \mu\text{L mg}^{-1}$) for 60 min (at 25 Hz). The purity of synthesized was evaluated by PXRD and Rietveld refinements (Figure S50).

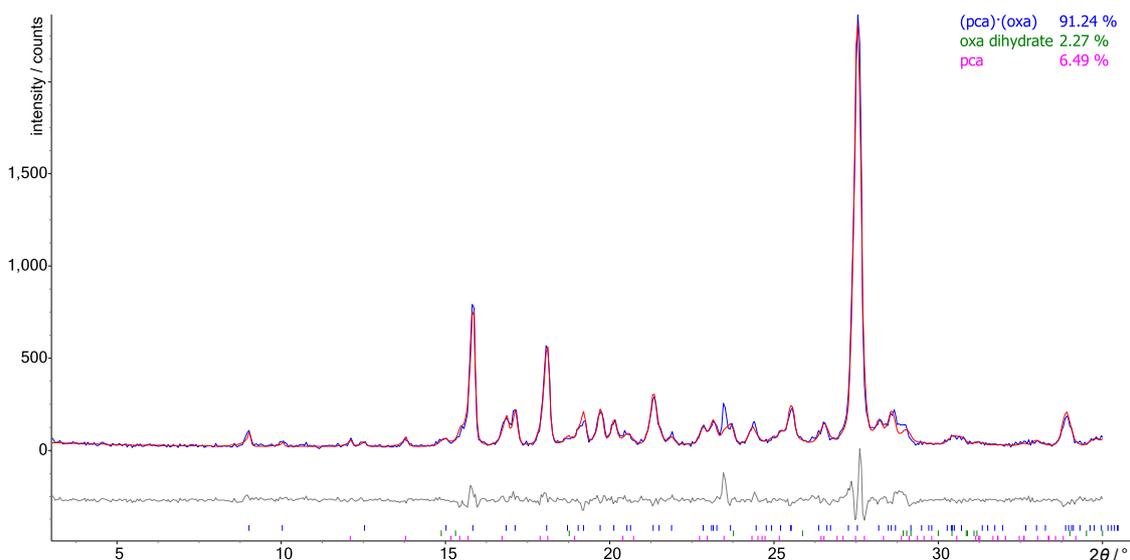


Figure S50. Rietveld refinement plot of (par)·(oxa) prepared by LAG with methanol ($\eta=0.30 \mu\text{L mg}^{-1}$). The calculated profile is shown in red, the experimental profile is shown in blue, and the difference curve is shown in grey.

Approximately 150 mg of the synthesised (**par**)·(**oxa**) cocrystal were then separately ground for 60 min at 25 Hz using nitromethane ($\eta=0.30 \mu\text{L mg}^{-1}$), 2-pyrrolidone ($\eta=0.30 \mu\text{L mg}^{-1}$) or DMSO ($\eta=0.30 \mu\text{L mg}^{-1}$) as liquid additives. The products were characterised by PXRD (Figure S51) and the obtained powder patterns were analyzed using the Rietveld refinement technique. The analyses revealed that LAG with nitromethane did not cause any changes to (**par**)·(**oxa**) (Figures S52), while LAG with 2-pyrrolidone and DMSO caused partial dissociation of the cocrystal (Figure S53 and S54).

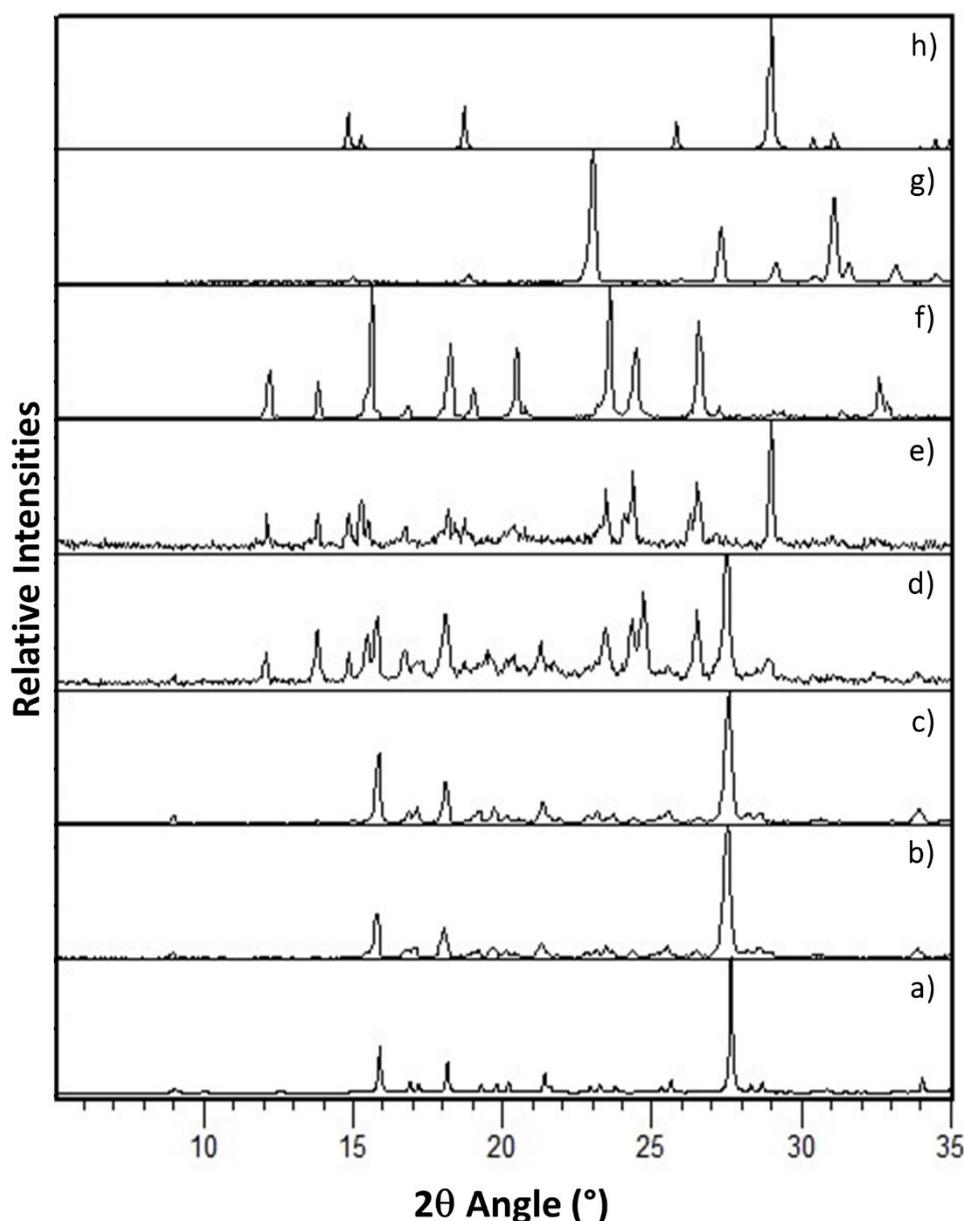


Figure S51. PXRD pattern of: (a) calculated (**par**)·(**oxa**),²⁴ (b) (**par**)·(**oxa**) prepared by LAG with methanol ($\eta=0.30 \mu\text{L mg}^{-1}$), (c), (d), (e) preformed (**par**)·(**oxa**) processed by LAG ($\eta=0.30 \mu\text{L mg}^{-1}$) using nitromethane, 2-pyrrolidone and DMSO, respectively, (f) pure **par**, (g) pure H₂**oxa** and (h) calculated H₂**oxa** dehydrate (CSD code: OXACDH04²⁶).

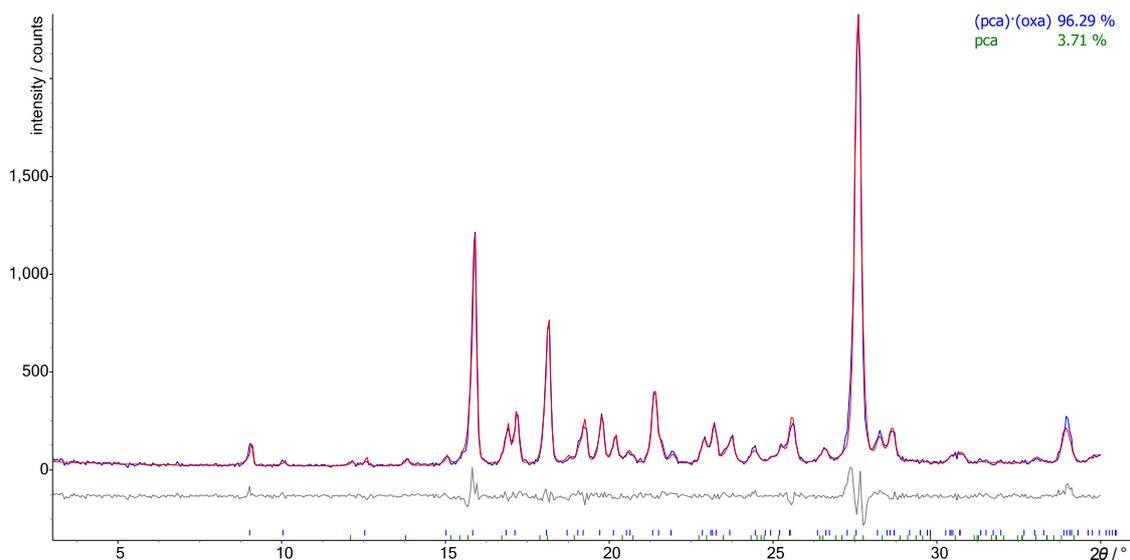


Figure S52. Rietveld refinement plot of **(par)·(oxa)** processed by LAG ($\eta=0.30 \mu\text{L mg}^{-1}$) with nitromethane. The calculated profile is shown in red, the experimental profile is shown in blue, and the difference curve is shown in grey.

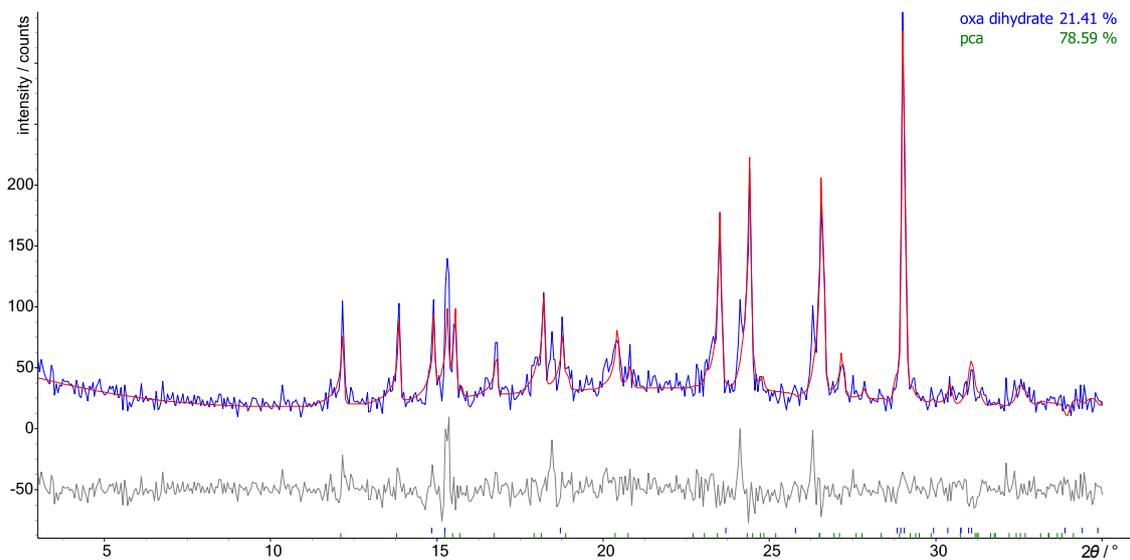


Figure S53. Rietveld refinement plot of **(par)·(oxa)** processed by LAG ($\eta=0.30 \mu\text{L mg}^{-1}$) with DMSO. The calculated profile is shown in red, the experimental profile is shown in blue, and the difference curve is shown in grey.

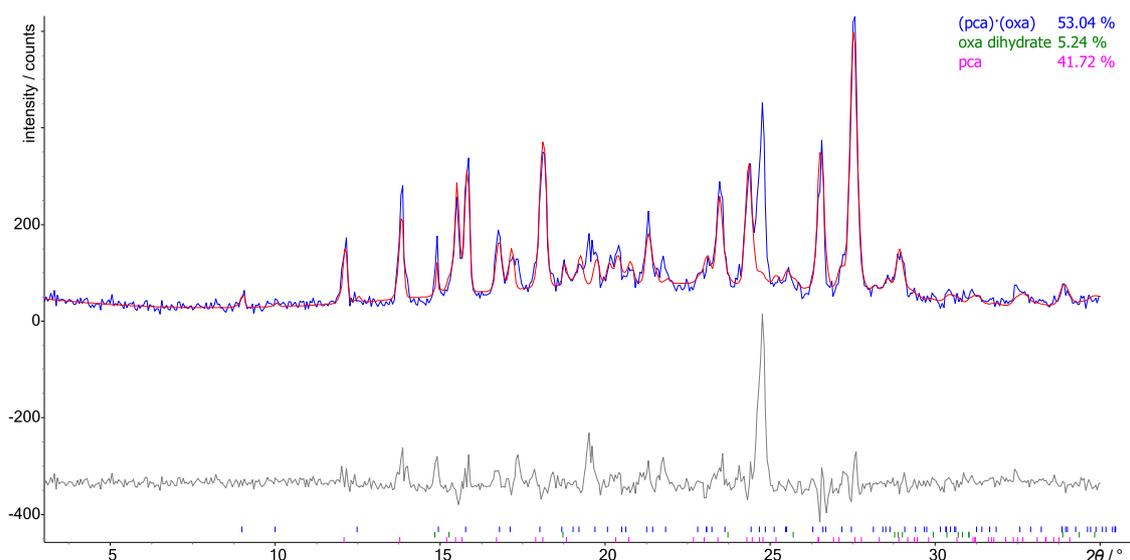


Figure S54. Rietveld refinement plot of **(par)·(oxa)** processed by LAG ($\eta=0.30 \mu\text{L mg}^{-1}$) with 2-pyrrolidone. The calculated profile is shown in red, the experimental profile is shown in blue, and the difference curve is shown in grey. LAG resulted in the formation of a new phase with an unknown crystal structure and its corresponding peaks could not be modelled during Rietveld refinement.

8.5 Caffeine:p-coumaric acid cocrystal

The 1:1 **(caf)·(cou)** cocrystal, initially reported by Schultheiss *et al.* (CSD code IJEZUT),²⁵ was prepared mechanochemically. Specifically, 108.4 mg of **caf** and 91.6 mg of **cou** were added to a 15 mL snap-closed grinding jar (*FormTech Scientific*) containing two milling balls of 7 mm diameter. The mixture was milled in the presence of acetonitrile ($\eta=0.30 \mu\text{L mg}^{-1}$) for 60 min at (at 25 Hz). Such procedure was repeated four times. Their purity of the was verified by PXRD (Figure S56).

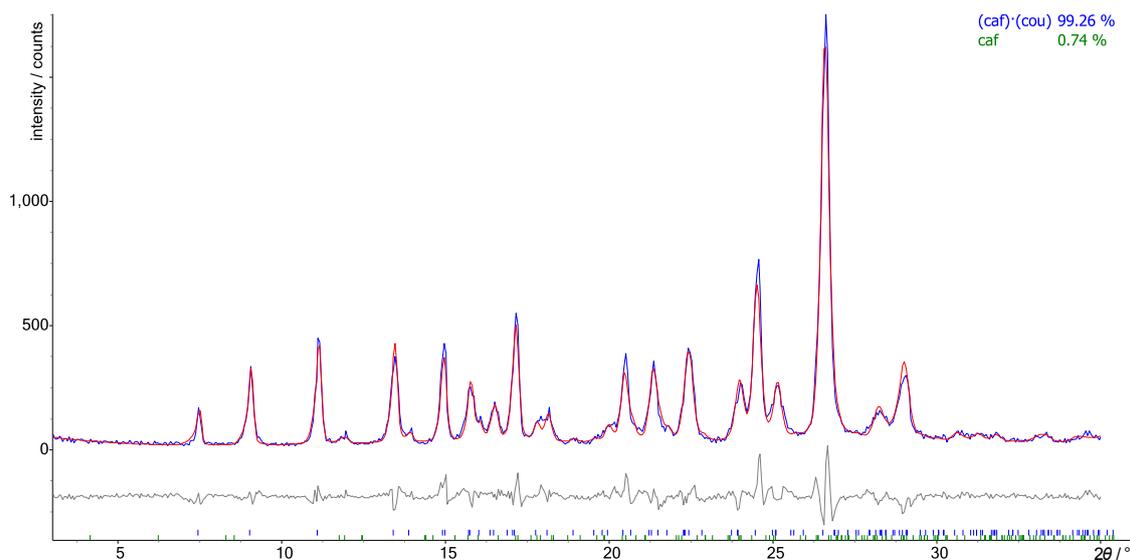


Figure S55. Rietveld refinement plot of **(caf)·(cou)** prepared by LAG with methanol ($\eta=0.30 \mu\text{L mg}^{-1}$). The calculated profile is shown in red, the experimental profile is shown in blue, and the difference curve is shown in grey.

Three batches of (**caf**)·(**cou**) (~150 mg each) were separately treated for 60 min at 25 Hz under LAG conditions using nitromethane ($\eta=0.30 \mu\text{L mg}^{-1}$), DMSO ($\eta=0.30 \mu\text{L mg}^{-1}$) and 2-pyrrolidone ($\eta=0.30 \mu\text{L mg}^{-1}$) as liquid additives. The products were characterised using PXRD (Figure S57) and the resulting powder patterns were analyzed using the Rietveld refinement method to show that the use of all three liquid additives has not resulted in any meaningful structural changes (Figures S58-S60).

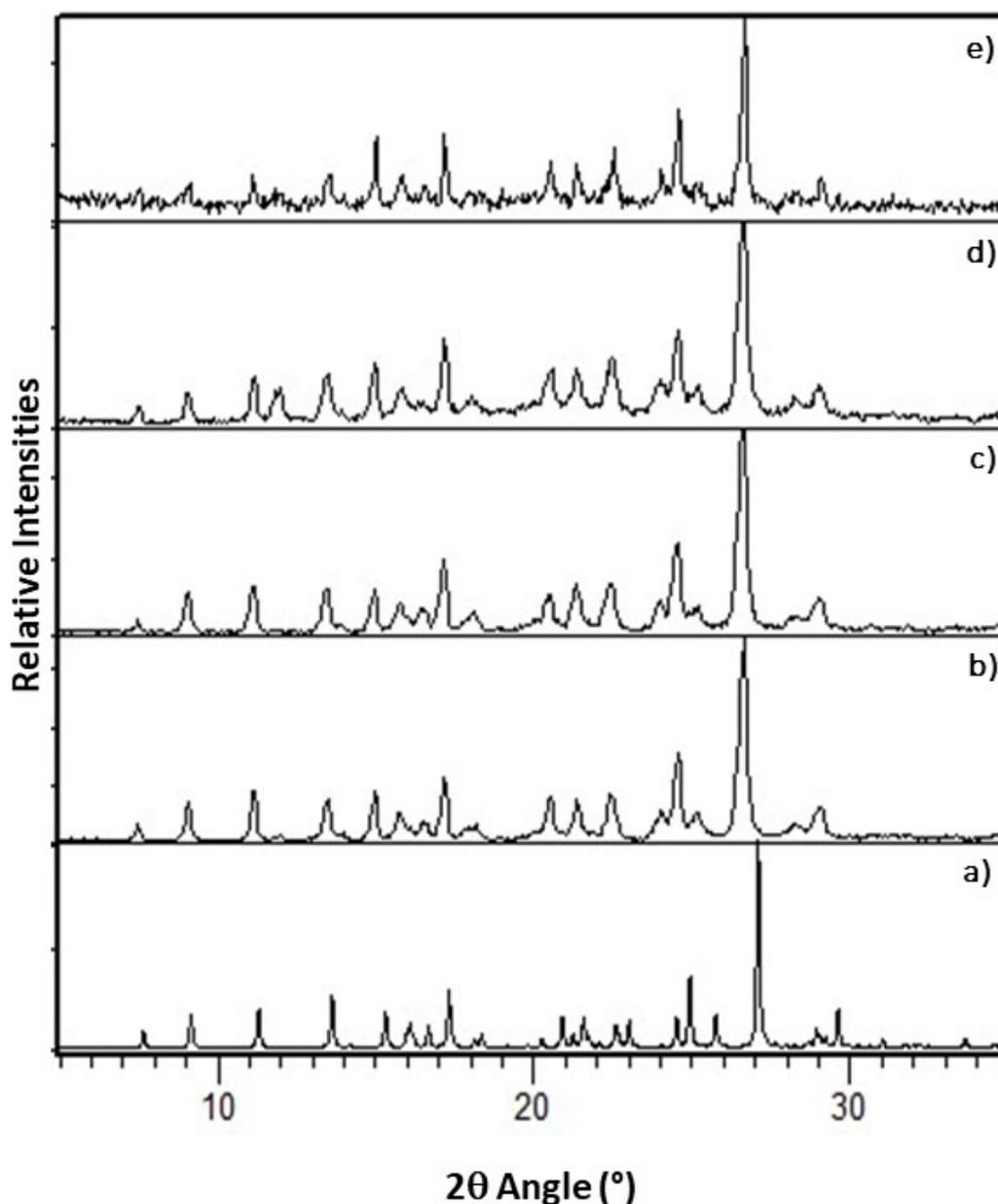


Figure S56. PXRD pattern of: (a) calculated (**caf**)·(**cou**),²⁵ (b) (**caf**)·(**cou**) prepared by LAG with methanol ($\eta=0.30 \mu\text{L mg}^{-1}$), (c), (d) and (e) preformed (**caf**)·(**cou**) processed by LAG ($\eta=0.30 \mu\text{L mg}^{-1}$) using nitromethane, 2-pyrrolidone and DMSO, respectively.

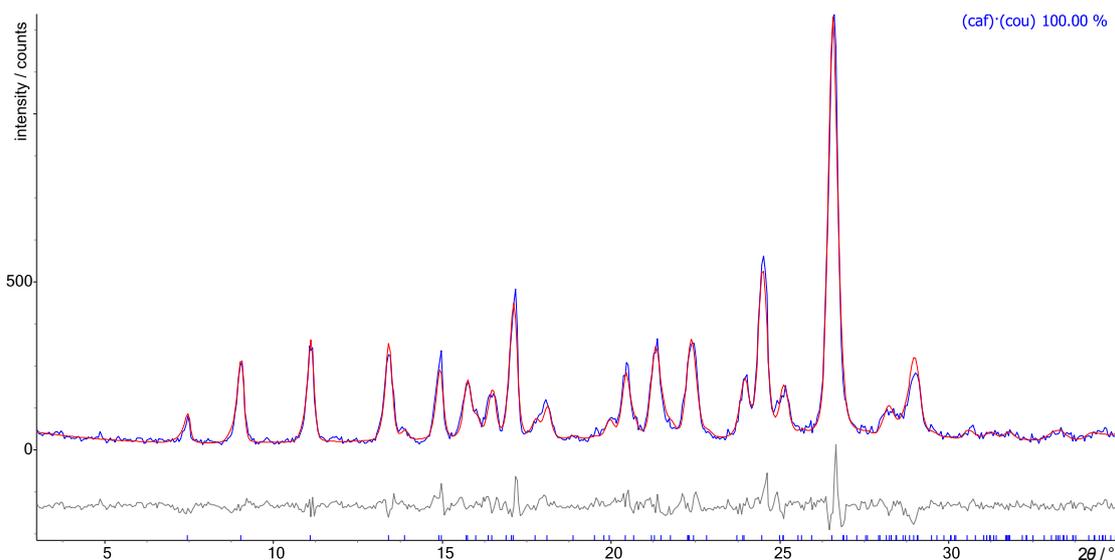


Figure S57. Rietveld refinement plot of (caf)-(cou) processed by LAG ($\eta=0.30 \mu\text{L mg}^{-1}$) with nitromethane. The calculated profile is shown in red, the experimental profile is shown in blue, and the difference curve is shown in grey.

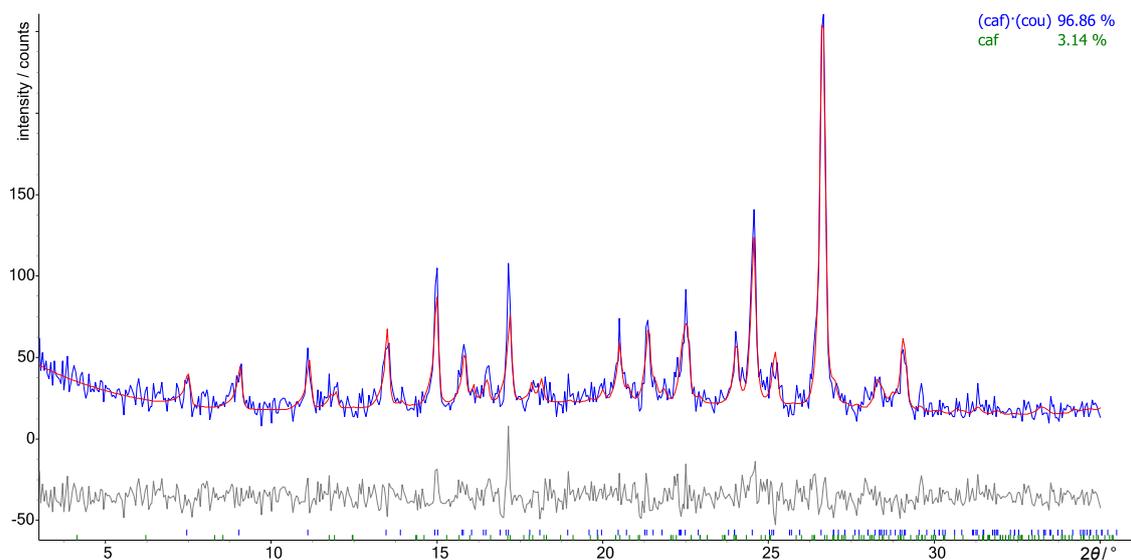


Figure S58. Rietveld refinement plot of (caf)-(cou) processed by LAG ($\eta=0.30 \mu\text{L mg}^{-1}$) with DMSO. The calculated profile is shown in red, the experimental profile is shown in blue, and the difference curve is shown in grey.

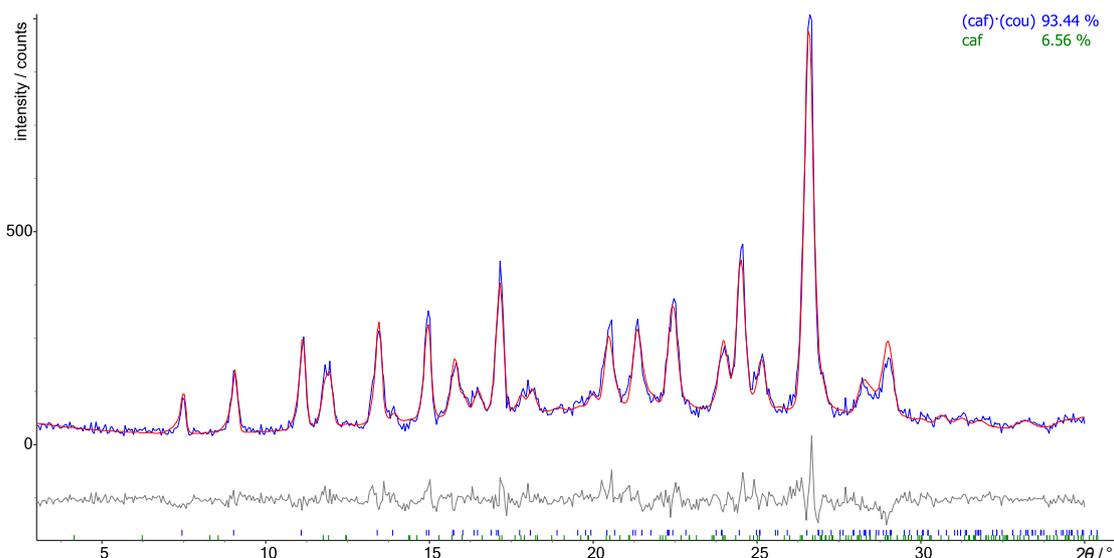


Figure S59. Rietveld refinement plot of (caf)-(cou) processed by LAG ($\eta=0.30 \mu\text{L mg}^{-1}$) with 2-pyrrolidone. The calculated profile is shown in red, the experimental profile is shown in blue, and the difference curve is shown in grey.

9. References

- (1) A. Altomare, C. Giacovazzo, A. Guagliardi, A. G. G. Moliterni, R. Rizzi, P.-E. Werner, New Techniques for Indexing: N-TREOR in EXPO. *J. Appl. Crystallogr.*, 2000, **33**, 1180–1186.
- (2) A. Altomare, C. Cuocci, C. Giacovazzo, A. Moliterni, R. Rizzi, N. Corriero, A. Falcichio, EXPO2013 : A Kit of Tools for Phasing Crystal Structures from Powder Data. *J. Appl. Crystallogr.*, 2013, **46**, 1231–1235.
- (3) A. A. Coelho, TOPAS and TOPAS-Academic : An Optimization Program Integrating Computer Algebra and Crystallographic Objects Written in C++. *J. Appl. Crystallogr.*, 2018, **51**, 210–218.
- (4) CrysAlisPro, Agilent Technologies, Version 1.171.37.34 (release 22-05-2014 CrysAlis171.NET).
- (5) O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard, H. Puschmann, OLEX2 : A Complete Structure Solution, Refinement and Analysis Program. *J. Appl. Crystallogr.*, 2009, **42**, 339–341.
- (6) C. B. Hübschle, G. M. Sheldrick, B. Dittrich, ShelXle : A Qt Graphical User Interface for SHELXL. *J. Appl. Crystallogr.*, 2011, **44**, 1281–1284.
- (7) G. M. Sheldrick, SHELXT – Integrated Space-Group and Crystal-Structure Determination. *Acta Crystallogr. A*, 2015, **71**, 3–8.
- (8) G. M. Sheldrick, Crystal Structure Refinement with SHELXL. *Acta Crystallogr.*, 2015, **71**, 3–8.
- (9) S. J. Clark, M. D. Segall, C. J. Pickard, P. J. Hasnip, M. I. J. Probert, K. Refson, M. C. Payne, First Principles Methods Using CASTEP. *Z. Kristallogr. Cryst. Mater.*, 2005, **220**, 5–6.
- (10) T. Björkman, CIF2Cell: Generating Geometries for Electronic Structure Programs. *Comput. Phys. Commun.*, 2011, **182**, 1183–1186.
- (11) J. P. Perdew, K. Burke, M. Ernzerhof, Generalized Gradient Approximation Made Simple. *Phys.*

Rev. Lett., 1996, **77**, 3865–3868.

- (12) N. V. Tkachenko, H. Lemmetyinen, J. Sonoda, K. Ohkubo, T. Sato, H. Imahori, S. Fukuzumi, Ultrafast Photodynamics of Exciplex Formation and Photoinduced Electron Transfer in Porphyrin–Fullerene Dyads Linked at Close Proximity. *J. Phys. Chem. A*, 2003, **107**, 8834–8844.
- (13) A. Ambrosetti, A. M. Reilly, R. A. DiStasio, A. Tkatchenko, Long-Range Correlation Energy Calculated from Coupled Atomic Response Functions. *J. Chem. Phys.*, 2014, **140**, 18A508.
- (14) A. M. Reilly, A. Tkatchenko, Van Der Waals Dispersion Interactions in Molecular Materials: Beyond Pairwise Additivity. *Chem. Sci.*, 2015, **6**, 3289–3301.
- (15) *Gaussian 16*, Revision B.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. V. Marenich, J. Bloino, B. G. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian, J. V. Ortiz, A. F. Izmaylov, J. L. Sonnenberg, D. Williams-Young, F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, V. G. Zakrzewski, J. Gao, N. Rega, G. Zheng, W. Liang, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. J. Bearpark, J. J. Heyd, E. N. Brothers, K. N. Kudin, V. N. Staroverov, T. A. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. P. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas, J. B. Foresman, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2016.
- (16) A. D. Becke, Density-functional Thermochemistry. III. The Role of Exact Exchange. *J. Chem. Phys.*, 1993, **9**, 5648–5652.
- (17) P. J. Stephens, F. J. Devlin, C. F. Chabalowski, M. J. Frisch, Ab Initio Calculation of Vibrational Absorption and Circular Dichroism Spectra Using Density Functional Force Fields. *J. Phys. Chem.*, 1994, **98**, 11623–11627.
- (18) S. Grimme, Semiempirical GGA-Type Density Functional Constructed with a Long-Range Dispersion Correction. *J. Comput. Chem.*, 2006, **27**, 1787–1799.
- (19) D. Hasa, D. Voinovich, B. Perissutti, M. Grassi, A. Bonifacio, V. Sergio, C. Cepek, M. R. Chierotti, R. Gobetto, S. Dall'Acqua, S. Invernizzi, Enhanced Oral Bioavailability of Vinpocetine through Mechanochemical Salt Formation: Physico-Chemical Characterization and in Vivo Studies. *Pharm. Res.*, 2011, **28**, 1870–1883.
- (20) D. D. Sun, T. R. Ju, P. I. Lee, Enhanced Kinetic Solubility Profiles of Indomethacin Amorphous Solid Dispersions in Poly(2-Hydroxyethyl Methacrylate) Hydrogels. *Eur. J. Pharm. Biopharm.*, 2012, **81**, 149–158.
- (21) B. van Eerdenbrugh, D. E. Alonzo, L. S. Taylor, Influence of Particle Size on the Ultraviolet Spectrum of Particulate-Containing Solutions: Implications for In-Situ Concentration Monitoring Using UV/Vis Fiber-Optic Probes. *Pharm. Res.*, 2011, **28**, 1643–1652.
- (22) F. Fischer, M. Joester, K. Rademann and F. Emmerling, *Chem. Eur. J.*, 2015, **21**, 14969–14974.
- (23) D. J. Berry, C. C. Seaton, W. Clegg, R. W. Harrington, S. J. Coles, P. N. Horton, M. B. Hursthouse, R. Storey, W. Jones, T. Friščić and N. Blagden, *Cryst. Growth Des.*, 2008, **8**, 1697–1712.
- (24) S. Karki, L. Fabian, T. Friščić, P. R. Laity, G. M. Day, W. Jones, L. Fabian, P. R. Laity, G. M. Day and W. Jones, *Adv. Mater.*, 2009, **21**, 3905–3909.
- (25) N. Schultheiss, M. Roe and S. X. M. Boerrigter, *CrystEngComm*, 2011, **13**, 611–619.
- (26) T.M. Sabine, G.W.Cox, B.M. Craven, *Acta Crystallogr. B*, 1969, **25**, 2437.