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From structure to crystallisation and manufacturing: the CSD in CMAC Workflows

Electronic Supporting Information

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Section A: MC and additive screening workflow document

This section is taken from the internal CMAC workflow document and provides greater detail on the experimental methods summarised in the flowcharts given in the main manuscript.

PART 1: MC Material Screening Procedure

1. Identify the most appropriate co-formers
    - *Consider supramolecular synthons and / or outputs from CCDC tools.*

Once selected, the API:co-former pairs can then be screened for multicomponent material formation by **evaporative** or **mechanochemical** crystallisation routes:

Evaporative crystallisation (Stage 1)

- Choose a solvent system for your evaporative crystallisations. Both components must be soluble in the chosen system. Solvent mixtures can be used.
- Weigh individual components for each crystallisation screen in chosen molar ratios into a vial
    - *Most often 1:1 ratio is chosen but other common ratios include 1:2 and 2:1.*
- Dissolve the components in a minimum amount of solvent and sonicate if required
    - *The amount of solvent can be informed by known solubility data, where available*
    - *Minimum solvent is preferred to prevent long evaporating times.*
- Place a thin plastic lid/parafilm over the top of the vial to prevent foreign particles from entering the vial and expediting nucleation.
- Pierce holes in the lid/parafilm to allow solvent to slowly evaporate.
- Leave vials at varying temperatures to allow the solvent to evaporate.
    - *Both elevated and low temperatures can be utilised. Temperature can affect the size, shape and quality of crystals produced*
    - *Full evaporation is favoured for analysis via PXRD*
    - *Partial evaporation to the point when crystals appear is favourable for SCXRD.*

Mechanochemical crystallisation (Stage 1a)

- Weigh individual components for each crystallisation screen in chosen molar ratios into a pestle and mortar
    - *Most often 1:1 ratio is chosen but other common ratios include 1:2 and 2:1.*
- Grind the components together for a selected period of time (between 5-15 minutes)
    - *At this stage liquid assistance can be utilised. Liquid-assisted grinding (LAG) uses a few drops of a chosen solvent to aid the grinding process*

- *The solvent choice is dependent on the system and solubility of the components. Full dissolution is not required or favoured in this method.*

- If using LAG grind until the solvent has fully evaporated again.

2. All products from mechanochemical or evaporative crystallisation routes should be analysed
   - *PXRD, then DSC measurements are generally recommended as an initial minimum*
   - *These traces should be compared to those expected for the individual starting material components, to ascertain if a new product has formed*
   - *If no new product is confirmed by PXRD and DSC, new recrystallisations should be considered, either by the alternative method, or using new co-former materials.*

3. For all suspected new multicomponent materials, a single-crystal X-ray structure is desirable
   - *For products made by mechanochemical routes, if a single-crystal structure is already known these could move on to be scaled up, for e.g. by milling methods (Stage 3a)*
   - *For products made by mechanochemical routes with unknown crystal structures, recrystallisation attempts by evaporative methods should be attempted to grow single-crystals suitable for SCXRD.*
   - *Products made via evaporative crystallisation routes should be assessed by polarised light microscopy (PLM) to determine if suitable single-crystals for SCXRD have formed*
   - *Where this is not the case, further re-crystallisations should be attempted, either using different solvents, or considering other crystallisation methods (e.g. vapour diffusion).*

   Where suitable single crystals can be obtained, SCXRD studies then be conducted to determine the full, 3D structure of the new material, according to the protocols set-out within your institution (Stage 3).

4. Once a new material and its 3D structure are confirmed, its stability should be tested (Stage 4):

   Competitive slurrying (solution stability tests)

   - Prepare a suitable portion of your multicomponent material for thermal stability testing
     - *The preparation method will be informed by prior multicomponent crystallisation screening (e.g. by mechanochemical or evaporative crystallisation methods)*
     - *You will need sufficient material for repeat analysis at regular intervals (see below).*
   - Choose a solvent system for your stability test
     - *Solvent choice will depend on the required knowledge outcomes of your experiment. Common choices are water, or water with an appropriate buffer to mimic gastric fluid (aiming to reflect stability in-vivo), or the solvent used for prior crystallisation screening experiments (for informing design of scale-up procedures).*
   - Weigh out a portion of your prepared multicomponent material for each slurry screen into a glass vial
     - *Weigh out sufficient solid to ensure you will have an excess once solvent is added*
     - *You should also consider the amounts required for regular analysis (see below).*
   - Add a small portion of solvent to produce a slurry
     - *Only add enough solvent to produce a slurry, whilst ensuring an excess of solid remains*
     - *Where available, known solubility data (of starting materials) can be used to inform the solvent amount required.*
   - Add a stirrer bar and seal the vial with an appropriate lid

- *For more volatile solvents, an additional seal of parafilm may be suitable to minimise the chances of solvent evaporation.*

- Place the vial on a hot plate / stirrer mantel or into a CRD Polar Bear set-up (depending on availability) and set the temperature and stirring rate to your required values
  - *Controlling the temperature is important to ensure a consistent environment*
  - *An elevated temperature may be required depending on the intended knowledge outcomes of the stability test (e.g. 37 °C – body temperature – for in-vivo stability)*
  - *A suitable stirring rate is usually ~500 rpm, but try to avoid agitating the solution so much that the solid is spread up the walls of the vial.*
- Leave the slurry stirring for your chosen time period and test samples at regular intervals for multicomponent material breakdown
  - *The required period for a transformation can be projected, anything from 1 day up to several weeks should be considered, depending on the feasible timescale of the study*
  - *Take samples of your slurry for analysis (PXRD is recommended) at regular intervals to assess the progress of any transformation*
  - *Ideally, continue slurrying and sampling until no further change is observed.*

Thermal stability tests

- Prepare a suitable portion of your multicomponent material for thermal stability testing
  - *The preparation method will be informed by prior multicomponent crystallisation screening (e.g. by mechanochemical or evaporative crystallisation methods)*
  - *You will need sufficient material for repeat analysis at regular intervals (see below).*
- Place your multicomponent material into an oven, at your chosen temperature, in an open glass vial or glass petri dish
  - *If room temperature stability is of interest then choose a suitable location instead*
  - *Take care to ensure the vessel you use is oven-proof at your chosen temperature and that no accidental spillage of the contents will occur.*
- Leave the sample in the oven for your chosen time period and test samples at regular intervals for multicomponent material breakdown
  - *The required period for a transformation can be projected, anything from 1 day up to several weeks should be considered, depending on the feasible timescale of the study*
  - *Take samples of your slurry for analysis (PXRD is recommended) at regular intervals to assess the progress of any transformation*
  - *Ideally, continue heating and sampling until no further change is observed.*

5. If the new multicomponent material is stable in solution by competitive slurrying tests, it may be suitable for scale-up via a crystallisation by slurrying route:

   Crystallisation by slurrying

   - Choose a solvent system for your slurrying experiment
     - *This is likely to be informed by previous evaporative crystallisation screening with your chosen API/co-former combination.*
   - Weigh out individual components for each slurry screen in chosen molar ratios into a glass vial
     - *The molar ratio is likely to be informed by prior evaporative crystallisation screening*
     - *Weigh out sufficient solid to ensure you will have an excess once solvent is added*
     - *You should also consider the amounts required for regular analysis (see below).*
   - Add a small portion of solvent to produce a slurry

- *Only add enough solvent to produce a slurry, whilst ensuring an excess of solid remains*
- *Where available, known solubility data (of starting materials) can be used to inform the solvent amount required.*

- Add a stirrer bar and seal the vial with an appropriate lid
  - *For more volatile solvents, an additional seal of parafilm may be suitable to minimise the chances of solvent evaporation.*
- Place the vial on a hot plate / stirrer mantel or into a CRD Polar Bear set-up (depending on availability) and set the temperature and stirring rate to your required values
  - *Controlling the temperature can be important to ensure a consistent environment*
  - *A suitable stirring rate is usually ~500 rpm, but try to avoid agitating the solution so much that the solid is spread up the walls of the vial.*
- Leave the slurry stirring for your chosen time period and test samples at regular intervals for multicomponent material formation
  - *The required period for a transformation can be projected, anything from 1 day up to several weeks should be considered, depending on the feasible timescale of the study*
  - *Take samples of your slurry for analysis (PXRD is recommended) at regular intervals to assess the progress of any transformation*
  - *Ideally, continue slurrying and sampling until no further change is observed.*

6. Once the stability of the new material is confirmed in solution, and a suitable quantity has been made (either by evaporative, mechanochemical or slurrying crystallisation routes), its ***solubility*** should be confirmed in all relevant solvents (Stage 6)
   - *Conduct solubility studies by referring out to the **CMAC Solubility workflow**.*

7. At this stage, the multicomponent material screening process is complete and a suitable multicomponent candidate has been selected
   - *The results of solubility studies will inform whether the new material is suitable for transfer into other crystallisation routes, (e.g. cooling, temperature cycling, antisolvent)*
   - *This workflow should then lead out to the relevant **CMAC Crystallisation workflow**, which will guide the user through appropriate scale-up procedures, with full process analytical techniques (PAT) monitoring to ensure optimisation of the bulk additive crystallisation route*
   - *The user should ensure all crystal products continue to be analysed by the methods outlined in Section 2D below, through all additive crystallisation scale up stages.*

PART 2. Additive Crystallisation Screening Procedure

(i) Inputs and Pre-requisites.

- Additive screening may be considered early-on in the primary processing stages, after Synthesis and Initial Crystallisation have been performed.
- Additive screening is most likely to be employed when it has become apparent that the crystals produced initially require optimisation to improve a key property (e.g. crystal habit/morphology, crystal particle size distribution (PSD), polymorph control etc.), **in situations where the API is only acceptably delivered in its pure form (i.e. salts or co-crystals are not acceptable).**
- The key decision that must be made before commencing an additive screening study is what crystal property/properties you wish to control, and what the criteria for success are (*e.g. a target PSD range for PSD control, etc.).* This decision will direct the analysis of your results, and also may direct your choice of additive candidates to screen, according to relevant literature.

1. Optimise non-additive API crystallisation procedure at small scale
   - *This may include a Design of Experiments (DOE) procedure, and / or may refer to a relevant **CMAC Crystallisation Workflow** (e.g. Cooling or Antisolvent Crystallisation Workflow documents)*
   - *Ideally this will involve a small, discovery scale experiment (e.g. 5 – 25 mL).*

2. (a) Identify a selection of appropriate additive candidates (ideally 6 – 10 additives per screen)
   - *Consider what crystal particle attributes / properties you wish to control?*
   - *Are these properties most influences by nucleation processes, or by crystal growth?*
   - *Would a size-matched / structurally-similar additive be suitable (consider relevant literature)? What molecules are available that are similar to your API?*
   - *Would a non-size-matched additive be suitable (e.g. polymers or surfactants, again consider relevant literature)?*
   - *An assessment of the possible intermolecular interactions your API could make with an additive may be useful, according to the functional groups present on the API*
     This can be done manually by considering supramolecular synthons, or by use of prediction tools e.g. CCDC Molecular Complementarity tool and/or CCDC Full Interaction Maps (Mercury and Isostar software)
   - *Crystal face indexing of the initial product crystals you wish to improve on (by referring out to the **CMAC Crystal Face Indexing workflow**) may also be useful, particularly for morphology control. This will help to determine the properties of the natural crystal faces and thereby choose additives to modify them.*

   (b) Choose a starting additive ratio
   - *This choice may be influenced by relevant literature*
   - *Where no guidance is available, a suggested additive-to-API ratio would be ~ 1 : 100 (i.e. ~ 1 % wt/wt of additive-to-API).*

3. Determine the API solubility and, if possible, metastable zone with (MSZW) in the presence of each additive candidate
   - *Refer out to the **CMAC Solubility workflow***

- *The presence of additives/impurities will change nature of the solution and can therefore have an effect on API solubility*
- *Where a change in solubility or MSZW occurs, this may in turn require re-evaluation of the crystallisation process parameters chosen prior to additive selection (Stage 1).*

4. Screen all additive candidates using the optimised crystallisation process at small scale
    - *Each additive screen should have identical crystallisation process parameters, excepting the change in additive candidate*
    - *Run a "control" experiment at the same time that contains no additive*
    - *These screening studies should be run at the same discovery scale (e.g. 5 – 25 mL).*

5. Analyse the product crystals by the analysis methods outlined in Section 2D below
    - *Ideally microscopy, PXRD and DSC analysis should be considered, though the choice of suitable analysis methods will be governed by the property under control.*
    - *For morphology control studies, SCXRD and crystal face indexing should also be completed (refer out to the* ***Crystal Face Indexing Workflow*** *document)*
    - *This analysis should be directed by the crystal particle property you are trying to control, thus will vary between studies*
    - *The output of this analysis should be a decision as to whether that property has been improved or not: this will likely require criteria for success to be imposed (e.g. a PSD size distribution to be reached etc.)*
    - *In the vast majority of cases, it is likely this criterion will not be reached: in this case the additive candidate should be discarded and alternatives considered.*

6. Select the best additive to control the targeted crystal particle attribute / property.

7. Vary the additive : API ratio to determine the optimal level for property control
    - *A suggested range is between 0.25 % and 10 % wt/wt of additive-to-API*
    - *Ensure all products are analysed by the methods outlines in Section 2D below.*

8. At this stage, the additive screening process is complete and a suitable additive candidate has been selected
    - *This workflow should then lead out to the* ***CMAC Additive Crystallisation workflow****, which will guide the user through appropriate scale-up procedures, with full process analytical techniques (PAT) monitoring to ensure optimisation of the bulk additive crystallisation route*
    - *The user should ensure all crystal products continue to be analysed by the methods outlined in Section 2D below, through all additive crystallisation scale up stages.*

Section B: MC Workflow Benchmarking Experiments

1. Workflow Inputs/Pre-requisites

Table ESI-1: MC material outputs from ConQuest structure search 1 (full FLU structure with explicit hydrogen atom assignments).

Co-former	CSD ref-code base	API-to-co-former ratio	No. of re-determinations	MC assignment
Sulfamethazine	DARNOC	1:1	1	Co-crystal
Nicotinamide	EXAQAW	1:1	1	Co-crystal
2-chloro-4-nitrobenzoic acid	FAQWUS	1:1	1	Co-crystal
Ethenzamide	FAQXAZ	1:1	1	Co-crystal
Tolfenamic acid	SIMDOK	0.4:0.6	2	Solid solution
Mefenamic acid	SIMFEC	0.7:0.3	1	Solid solution
Theophylline	ZIQDUA	1:1	1	Co-crystal
Pyridone	ZIQFAI	1:1	1	Co-crystal
4,4'-bipyridine	ZIQFEM	2:1	3	Co-crystal

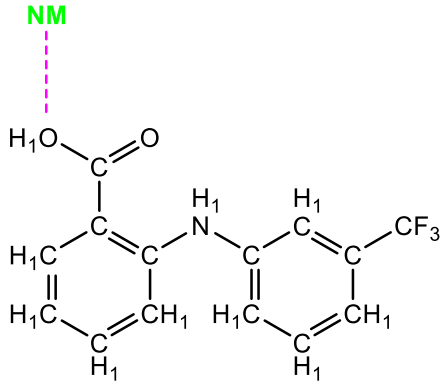

Figure ESI-1: Structure of flufenamic acid (FLU), plus an "any non-metal" query atom, used as a Add 3D structure search in ConQuest. Green indicates a defined atom label and pink dashes indicate a defined intermolecular distance, details of both are returned from the search for every hit.

Table ESI-2: Organic salt structure outputs from ConQuest structure search 3, with FLU anion (COO^-)

Cation	CSD ref-code base	Anion-cation ratio	No. of re-determinations	MC assignment
adamantan-1-aminium	SOZGAR	1:1	1	Salt
2-methylpropan-2-aminium	TEQCUQ	1:1	1	Salt
1,3-dihydroxy-2-(hydroxymethyl)propan-2-aminium	TEQYEW	1:1	1	Salt

Table ESI-3: GRAS co-former library details, for molecular complementarity screening in Mercury

Co-former	CSD ref-code
Adipic acid	ADIPAC
Benzoic acid	BENZAC
Pyridoxine	BITZAF
Citric acid	CITRAC10
DL-malic acid	DLMALC
DL-mannitol	DLMANT
Inisitol	EFURIH
Glycerol	GLCROL
D-Glucitol	GLUCIT
α-D-Glucose	GLUCSA
D-Isoascorbic acid	IASCOR10
Octanoic acid	ISENUP
L-Ascorbic acid	LASCAC01
2,4-hexadienoic acid	LEZHUT
L-Glutamic acid	LGLUAC
Nicotinic acid	NICOAC
Nicotinamide	NICOAM
Propionic acid	PRONAC
Succinic acid	SUCACB02
Sucrose	SUCROS01
L-tartaric acid	TARTAL
cis-Aconitic acid	TELZOZ
Urea	UREAXX
L-Lactic acid	YILLAG

Table ESI-4: Results of Molecular Complementarity Search 1 with FLU and GRAS library, search 1 = all descriptors

Name	CSD refcode	Outcome	Descriptor-specific Pass/Fail
Adipic acid	ADIPAC	FAIL	4 passes, M/L ratio = fail
Benzoic acid	**BENZAC**	**PASS**	**5 passed**
Pyridoxine	**BITZAF**	**PASS**	**5 passed**
Citric acid	CITRAC10	FAIL	4 passes, Fraction N,O = fail
Malic acid	DLMALC	FAIL	4 passes, Fraction N,O = fail
DL-Mannitol	DLMANT	FAIL	4 passes, Fraction N,O = fail
D-Mannitol	DMANTL	FAIL	4 passes, Fraction N,O = fail
Inisitol	EFURIH	FAIL	4 passes, Fraction N,O = fail
Glycerol	GLCROL	FAIL	4 passes, Fraction N,O = fail
Glucitol	GLUCIT	FAIL	3 passes, polarity descriptors = fail
Glucose	GLUCSA	FAIL	4 passes, Fraction N,O = fail
D-Isoascorbic acid	IASCOR10	FAIL	4 passes, Fraction N,O = fail
Octanoic acid	ISENUP	FAIL	4 passes, M/L ratio = fail
L-Ascorbic acid	LASCAC01	FAIL	3 passes, M/L ratio & Fraction N,O = fail
2,4-hexadienoic acid	**LEZHUT**	**PASS**	**5 passed**
L-glutamic acid	LGLUAC	FAIL	4 passes, Fraction N,O = fail
Nicotinic acid	**NICOAC**	**PASS**	**5 passed**
Nicotinamide	**NICOAM**	**PASS**	**5 passed**
Propionic acid	**PRONAC**	**PASS**	**5 passed**
Succinic acid	SUCACB02	FAIL	4 passes, Fraction N,O = fail
Sucrose	SUCROS01	FAIL	4 passes, Fraction N,O = fail
L-Tartaric acid	TARTAL	FAIL	4 passes, Fraction N,O = fail
cis-Aconitic acid	TELZOZ	FAIL	4 passes, Fraction N,O = fail
Urea	UREAXX	FAIL	4 passes, Fraction N,O = fail
Lactic acid	YILLAG	FAIL	4 passes, Fraction N,O = fail

Table ESI-5: Results of Molecular Complementarity Search 2 with FLU and GRAS library, search 2 = only polarity and shape descriptors

Name	CSD refcode	Outcome	Descriptor-specific Pass/Fail
Adipic acid	ADIPAC	FAIL	4 passes, M/L ratio = fail
Benzoic acid	**BENZAC**	**PASS**	**5 passed**
Pyridoxine	**BITZAF**	**PASS**	**5 passed**
Citric acid	CITRAC10	FAIL	4 passes, Fraction N,O = fail
Malic acid	DLMALC	FAIL	4 passes, Fraction N,O = fail
DL-Mannitol	DLMANT	FAIL	4 passes, Fraction N,O = fail
D-Mannitol	DMANTL	FAIL	4 passes, Fraction N,O = fail
Inisitol	EFURIH	FAIL	4 passes, Fraction N,O = fail
Glycerol	GLCROL	FAIL	4 passes, Fraction N,O = fail
Glucitol	GLUCIT	FAIL	3 passes, polarity descriptors = fail
Glucose	GLUCSA	FAIL	4 passes, Fraction N,O = fail
D-Isoascorbic acid	IASCOR10	FAIL	4 passes, Fraction N,O = fail
Octanoic acid	ISENUP	FAIL	4 passes, M/L ratio = fail
L-Ascorbic acid	LASCAC01	FAIL	3 passes, M/L ratio & Fraction N,O = fail
2,4-hexadienoic acid	**LEZHUT**	**PASS**	**5 passed**
L-glutamic acid	LGLUAC	FAIL	4 passes, Fraction N,O = fail
Nicotinic acid	**NICOAC**	**PASS**	**5 passed**
Nicotinamide	**NICOAM**	**PASS**	**5 passed**
Propionic acid	**PRONAC**	**PASS**	**5 passed**
Succinic acid	SUCACB02	FAIL	4 passes, Fraction N,O = fail
Sucrose	SUCROS01	FAIL	4 passes, Fraction N,O = fail
L-Tartaric acid	TARTAL	FAIL	4 passes, Fraction N,O = fail
cis-Aconitic acid	TELZOZ	FAIL	4 passes, Fraction N,O = fail
Urea	UREAXX	FAIL	4 passes, Fraction N,O = fail
Lactic acid	YILLAG	FAIL	4 passes, Fraction N,O = fail

Table ESI-6: Results of Molecular Complementarity Search 3 with FLU and GRAS library, search 2 = only polarity descriptors

Name	CSD refcode	Outcome	Descriptor-specific Pass/Fail
Adipic acid	**ADIPAC**	**FAIL**	**5 passed**
Benzoic acid	**BENZAC**	**PASS**	**5 passed**
Pyridoxine	**BITZAF**	**PASS**	**5 passed**
Citric acid	CITRAC10	FAIL	4 passes, Fraction N,O = fail
Malic acid	DLMALC	FAIL	4 passes, Fraction N,O = fail
DL-Mannitol	DLMANT	FAIL	4 passes, Fraction N,O = fail
D-Mannitol	DMANTL	FAIL	4 passes, Fraction N,O = fail
Inisitol	EFURIH	FAIL	4 passes, Fraction N,O = fail
Glycerol	GLCROL	FAIL	4 passes, Fraction N,O = fail
Glucitol	GLUCIT	FAIL	3 passes, polarity descriptors = fail
Glucose	GLUCSA	FAIL	4 passes, Fraction N,O = fail
D-Isoascorbic acid	IASCOR10	FAIL	4 passes, Fraction N,O = fail
Octanoic acid	**ISENUP**	**FAIL**	**5 passed**
L-Ascorbic acid	LASCAC01	FAIL	3 passes, M/L ratio & Fraction N,O = fail
2,4-hexadienoic acid	**LEZHUT**	**PASS**	**5 passed**
L-glutamic acid	LGLUAC	FAIL	4 passes, Fraction N,O = fail
Nicotinic acid	**NICOAC**	**PASS**	**5 passed**
Nicotinamide	**NICOAM**	**PASS**	**5 passed**
Propionic acid	**PRONAC**	**PASS**	**5 passed**
Succinic acid	SUCACB02	FAIL	4 passes, Fraction N,O = fail
Sucrose	SUCROS01	FAIL	4 passes, Fraction N,O = fail
L-Tartaric acid	TARTAL	FAIL	4 passes, Fraction N,O = fail
cis-Aconitic acid	TELZOZ	FAIL	4 passes, Fraction N,O = fail
Urea	UREAXX	FAIL	4 passes, Fraction N,O = fail
Lactic acid	YILLAG	FAIL	4 passes, Fraction N,O = fail

2. MC-Workflow Benchmarking Experiments

a. Evaporative crystallisation screening

For evaporative crystallisation experiments, *c.a.* 10 mg of FLU and a 1:1 stoichiometric amount of co-former were mixed in a 7 mL crystallisation vial and dissolved in the minimum volume of solvent (typically between 1 and 3 mL). In some cases, gentle warming and/or sonication were required to ensure complete dissolution of the starting materials. The crystallisation vials were then capped with polyethylene (PE) lids, into which 5 holes had been made with 0.8 mm gauge needles, to allow for slow evaporation.

The solvents were chosen in reference to initial small-scale (< 1 mg) solubility tests with the API and all 5 co-formers.

The vials were placed on a heating mantle in Asynt DrySyn reaction vial inserts, and the temperature was held at a constant 20 °C for a number of days to allow for slow evaporation.

Table ESI-7: Results of evaporative crystallisation experiments for MC material screening with FLU.

Co-former	Solvent	Stoichiometric ratio	Product?	Decision 1?
adipic acid	propan-2-ol	1:1	Y	N
benzoic acid	propan-2-ol	1:1	Y	Y
pyridoxine	propan-2-ol	1:1	Y	N
nicotinic acid	propan-2-ol	1:1	N	N
2,4-hexadienoic acid	propan-2-ol	1:1	N	N
2,2'-bipyridine	propan-2-ol	1:1	Y	N
adipic acid	propan-2-ol:water (1:1)	1:1	Y	N
benzoic acid	propan-2-ol:water (1:1)	1:1	Y	N
pyridoxine	propan-2-ol:water (1:1)	1:1	Y	N
nicotinic acid	propan-2-ol:water (1:1)	1:1	N	N
2,4-hexadienoic acid	propan-2-ol water (1:1)	1:1	N	N
2,2'-bipyridine	propan-2-ol:water (1:1)	1:1	N	N
adipic acid	ethyl acetate	1:1	N	N
benzoic acid	ethyl acetate	1:1	N	N
pyridoxine	ethyl acetate	1:1	Y	N
nicotinic acid	ethyl acetate	1:1	N	N
2,4-hexadienoic acid	ethyl acetate	1:1	Y	N
2,2'-bipyridine	ethyl acetate	1:1	Y	Y
adipic acid	acetonitrile	1:1	N	N
benzoic acid	acetonitrile	1:1	N	N
pyridoxine	acetonitrile	1:1	Y	N
nicotinic acid	acetonitrile	1:1	N	N
2,4-hexadienoic acid	acetonitrile	1:1	Y	N
2,2'-bipyridine	acetonitrile	1:1	Y	N

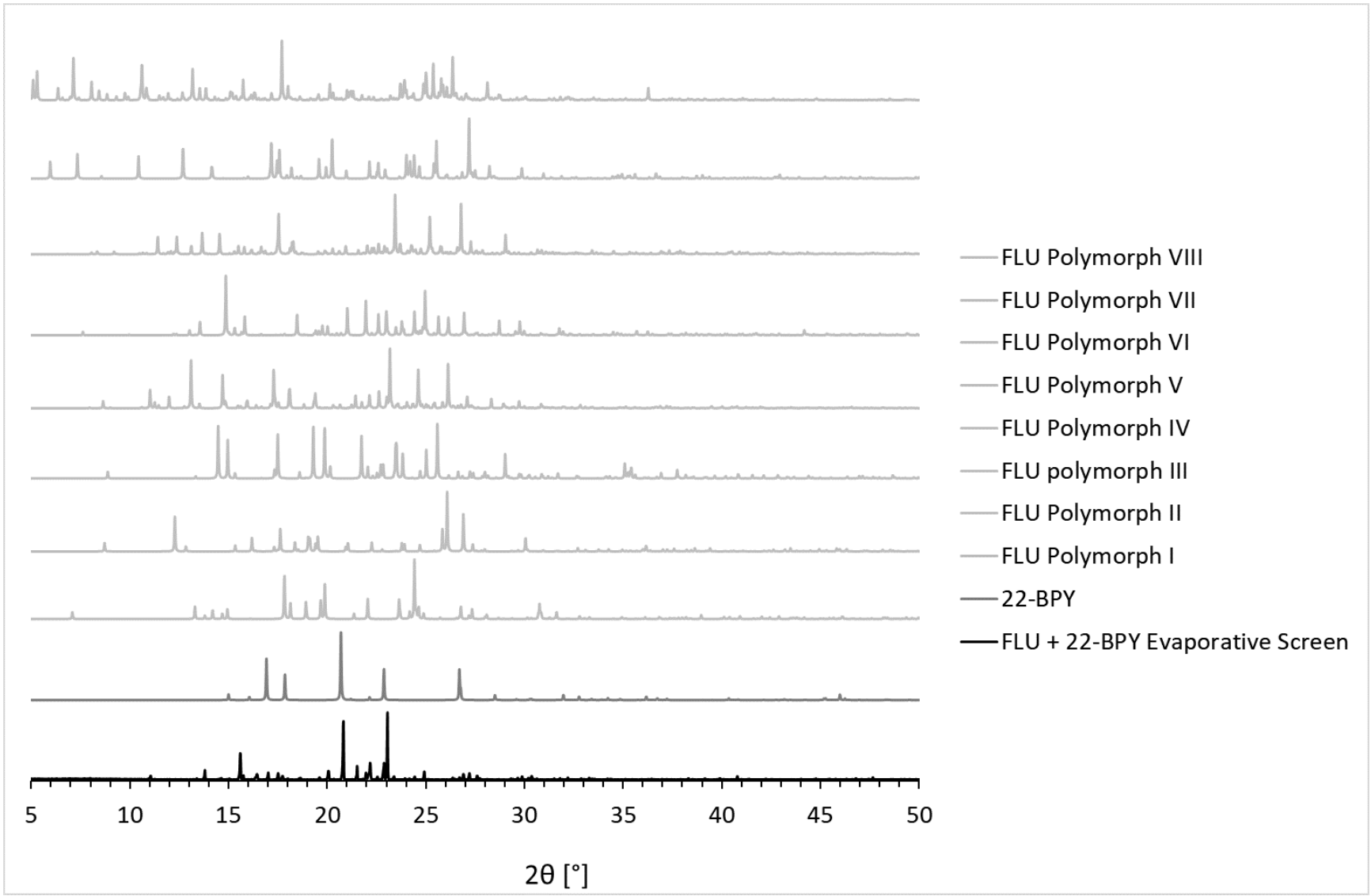

Figure ESI-2a: Comparison of experimental PXRD data for [FLU + 22-BPY] evaporative crystallisation product with predicted PXRD patterns of starting materials (all FLU polymorphs and 22-BPY) from CSD structure data.

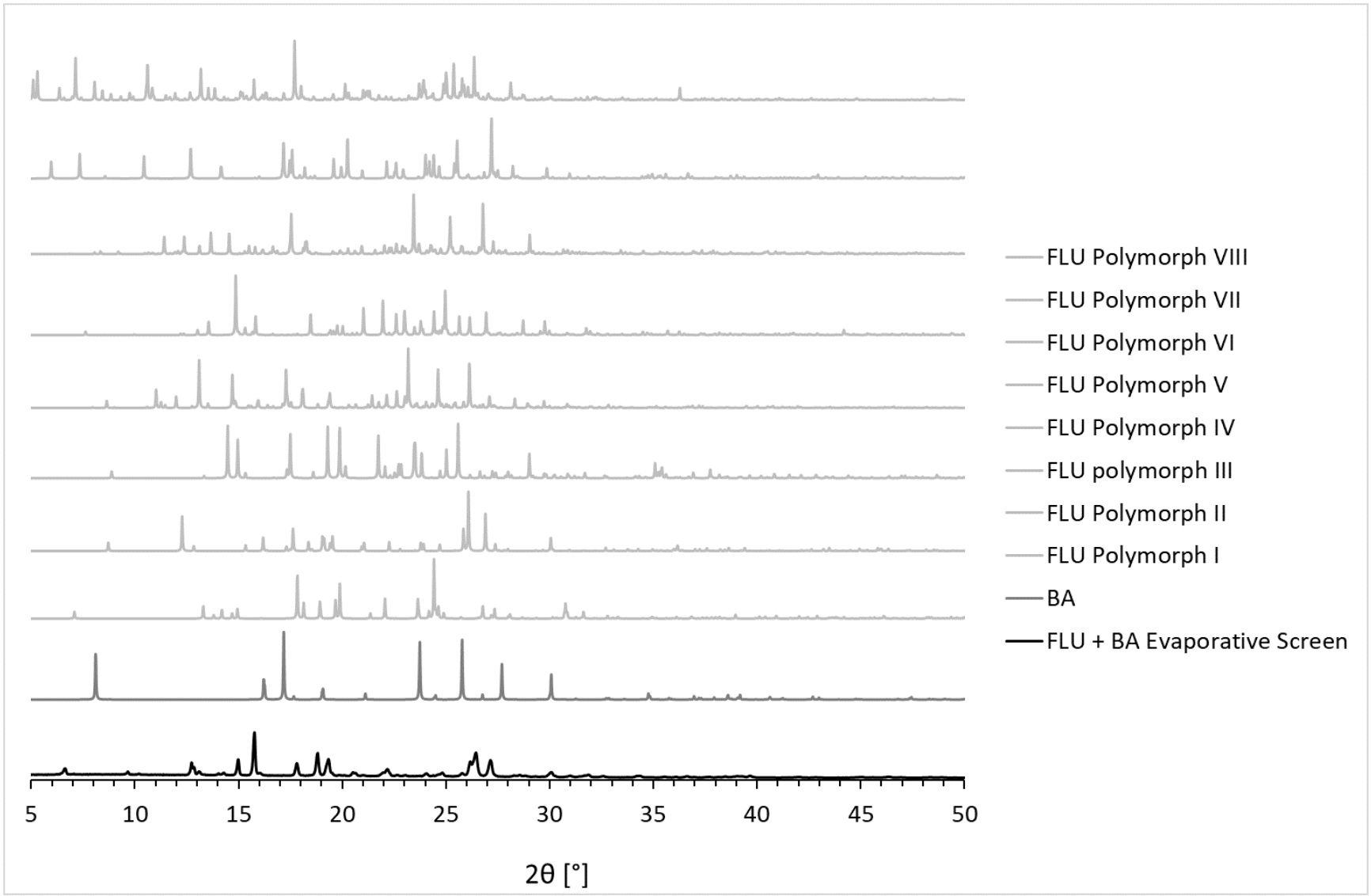

Figure ESI-2b: Comparison of experimental PXRD data for [FLU + BA] evaporative crystallisation product with predicted PXRD patterns of starting materials (all FLU polymorphs and BA) from CSD structure data.

b. FLU 22-BPY (2:1) crystal analysis

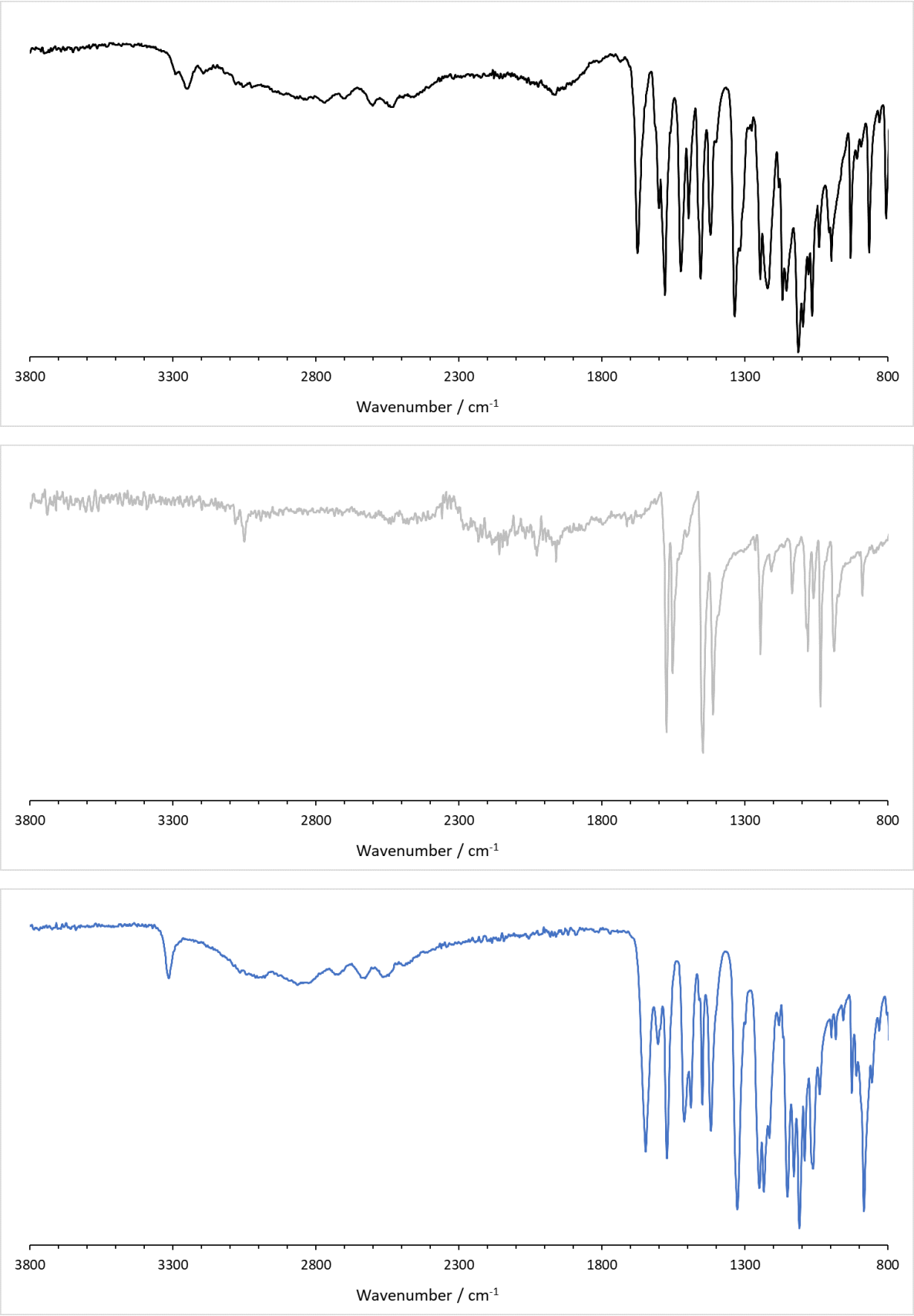

Figure ESI-3: FTIR spectra for FLU 22-BPY co-crystal and components. Black (top) = FLU 22-BPY (2:1) co-crystal, grey (centre) = 22-BPY starting material, blue (bottom) = FLU starting material.

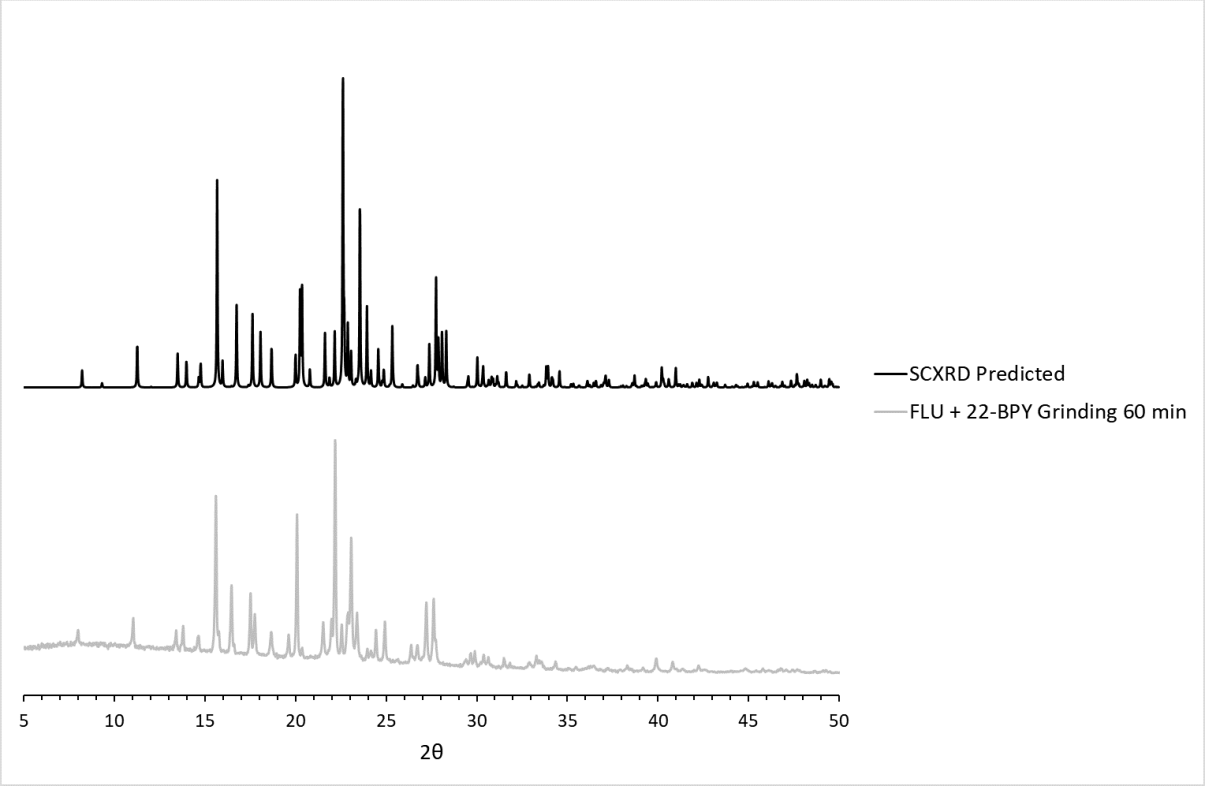

Figure ESI-4: Predicted vs. experimental PXRD data for FLU 22-BPY co-crystal. Predicted data generated from single-crystal X-ray diffraction data (Crystallographic Information File) using the CCDC software Mercury.

c. Mechanochemical crystallisation screening

For mechanochemcal crystallisation experiments, *c.a.* 15 mg of FLU and either a 1:1 or 2:1 stoichiometric amount of co-former (dependent on the number of hydrogen bond acceptors in the co-former) were mixed in a pestle and mortar and 1 drop of solvent was added. The mixture was then ground for 15 min, before the resulting solid was collected and analysed by PLM.

Only 2 solvents, ethyl acetate and acetonitrile, were used for this screening study. Other solvent systems utilised for evaporative crystallisations were tested, but these were found to exacerbate the adhesion of the solids to the mortar surface, making grinding impossible.

Table ESI-8: Results of mechanochemical crystallisation experiments for MC material screening with FLU.

Co-former	Solvent for LAG	Stoichiometric ratio (API – co-former)	Grinding time / min	Decision 1a?
adipic acid	ethyl acetate	1:1	15	N
benzoic acid	ethyl acetate	1:1	15	N
pyridoxine	ethyl acetate	1:1	15	N
nicotinic acid	ethyl acetate	1:1	15	N
2,4-hexadienoic acid	ethyl acetate	1:1	15	N
2,2'-bipyridine	ethyl acetate	2:1	15	Y
adipic acid	acetonitrile	1:1	15	N
benzoic acid	acetonitrile	1:1	15	N
pyridoxine	acetonitrile	1:1	15	N
nicotinic acid	acetonitrile	1:1	15	N
2,4-hexadienoic acid	ethyl acetate	1:1	15	N
2,2'-bipyridine	acetonitrile	2:1	15	N

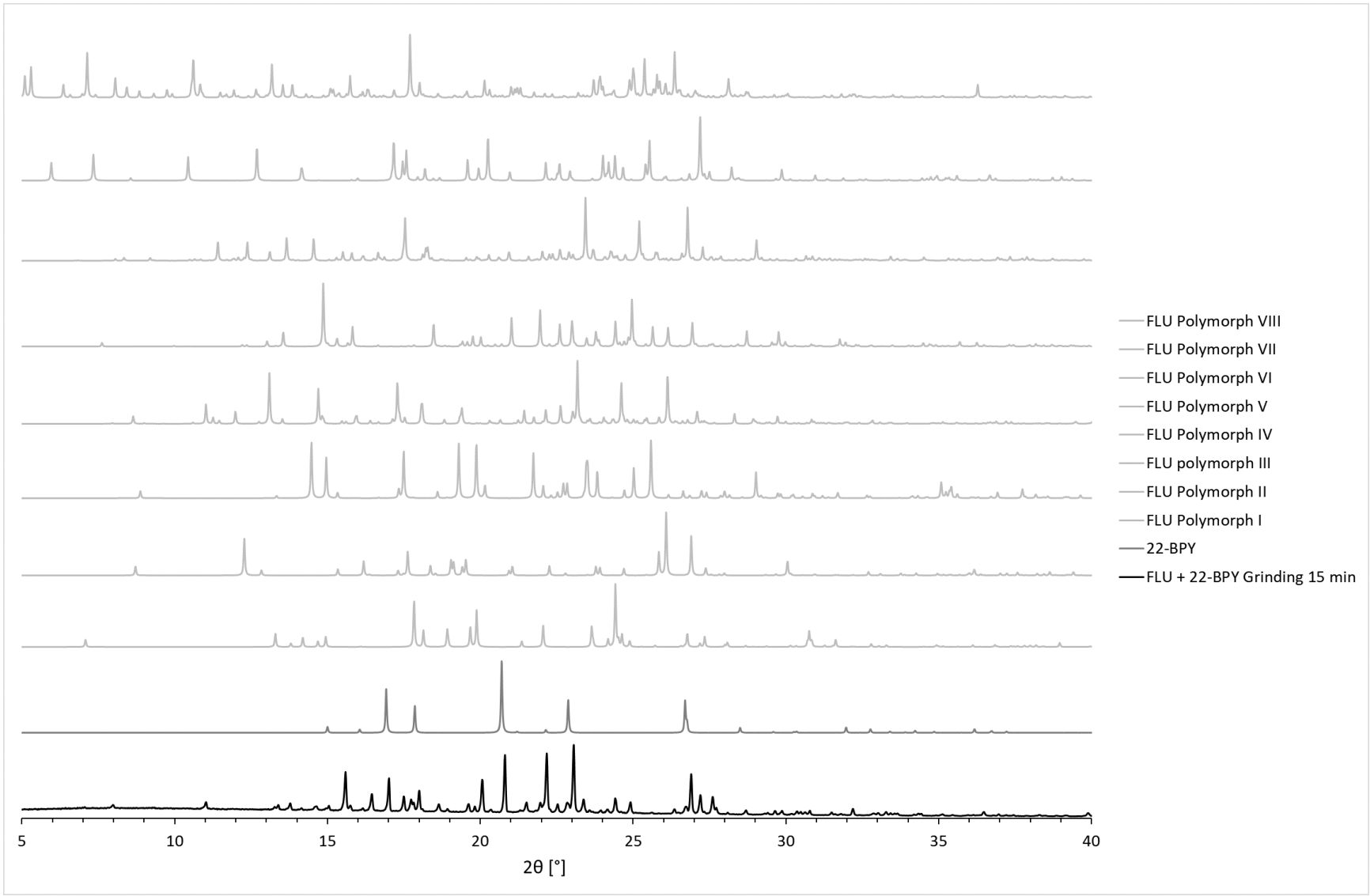

Figure ESI-5: Comparison of experimental PXRD data for [FLU + 22-BPY] mechanochemical crystallisation product with predicted PXRD patterns of starting materials (all FLU polymorphs and 22-BPY) from CSD structure data.

d. Stability testing

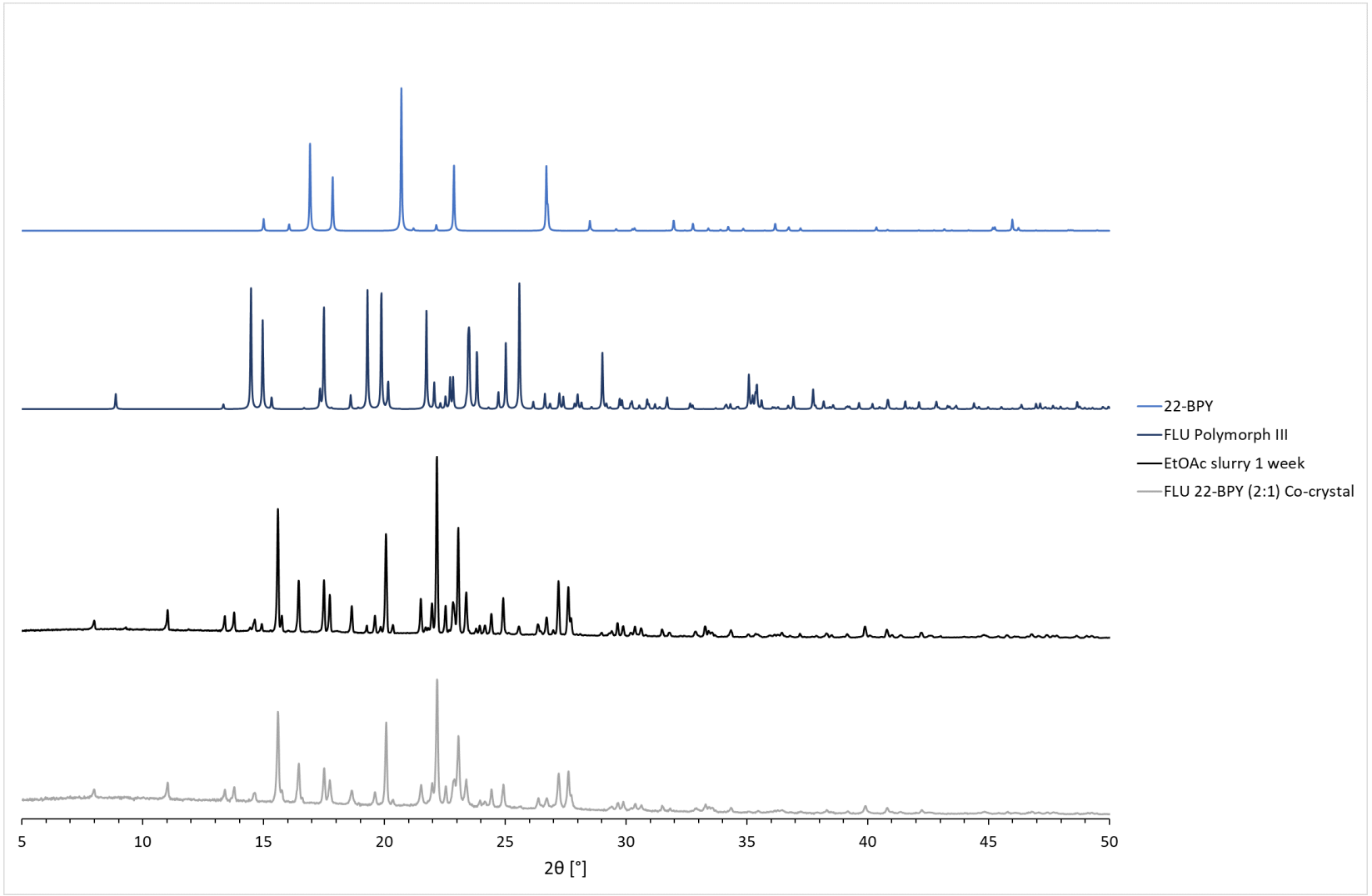

Figure ESI-6: PXRD data for FLU 22-BPY (2:1) co-crystal stability test in ethyl acetate. Material generated from competitive slurrying experiments in ethyl acetate is compared to pure co-crystal and pure starting material data.

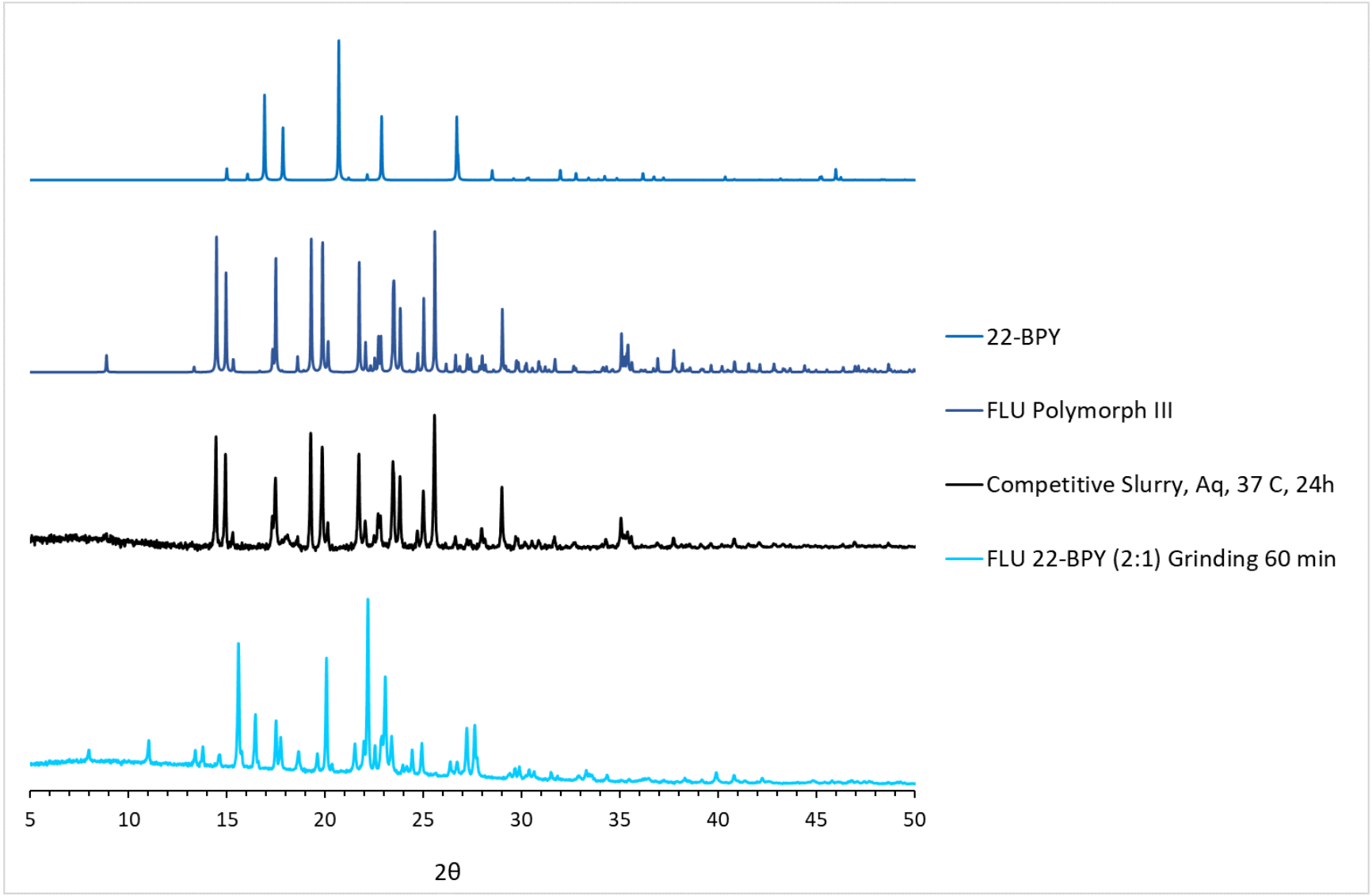

Figure ESI-7: PXRD data for FLU 22-BPY (2:1) co-crystal stability test in aqueous solution at 37 °C. Material generated from competitive slurrying experiments in water is compared to pure co-crystal and pure starting material data.

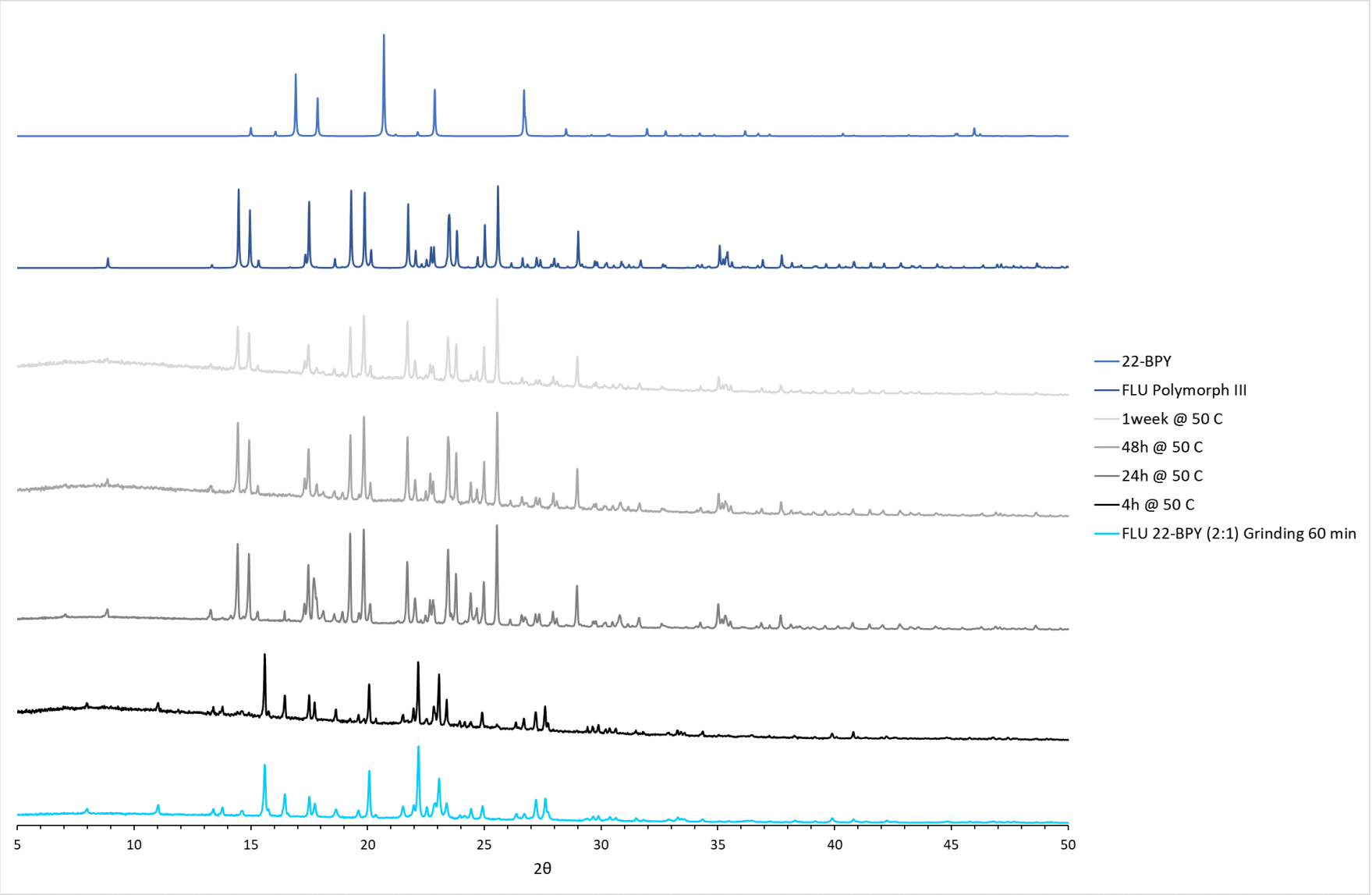

Figure ESI-8: PXRD data for FLU 22-BPY (2:1) co-crystal thermal stability test. Material heated in an oven at 50 °C is compared to pure co-crystal and pure starting material data.

e. Scale up by slurrying in ethyl acetate

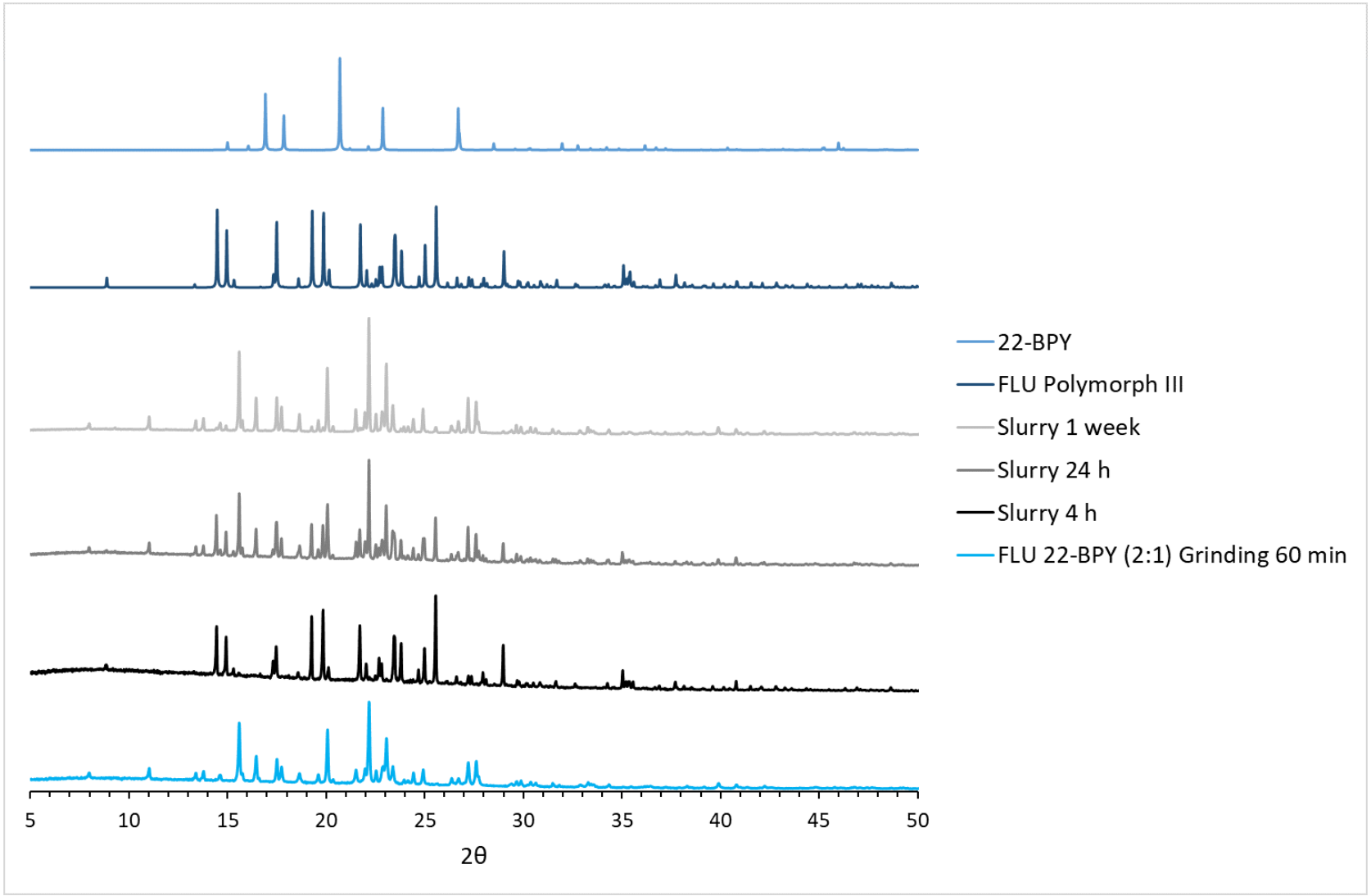

Figure ESI-9: PXRD data for FLU 22-BPY (2:1) scale-up recrystallisation by slurrying. Material generated during slurrying recrystallisation experiments in ethyl acetate is compared to pure co-crystal and pure starting material data.

Section C: Additives Workflow Benchmarking

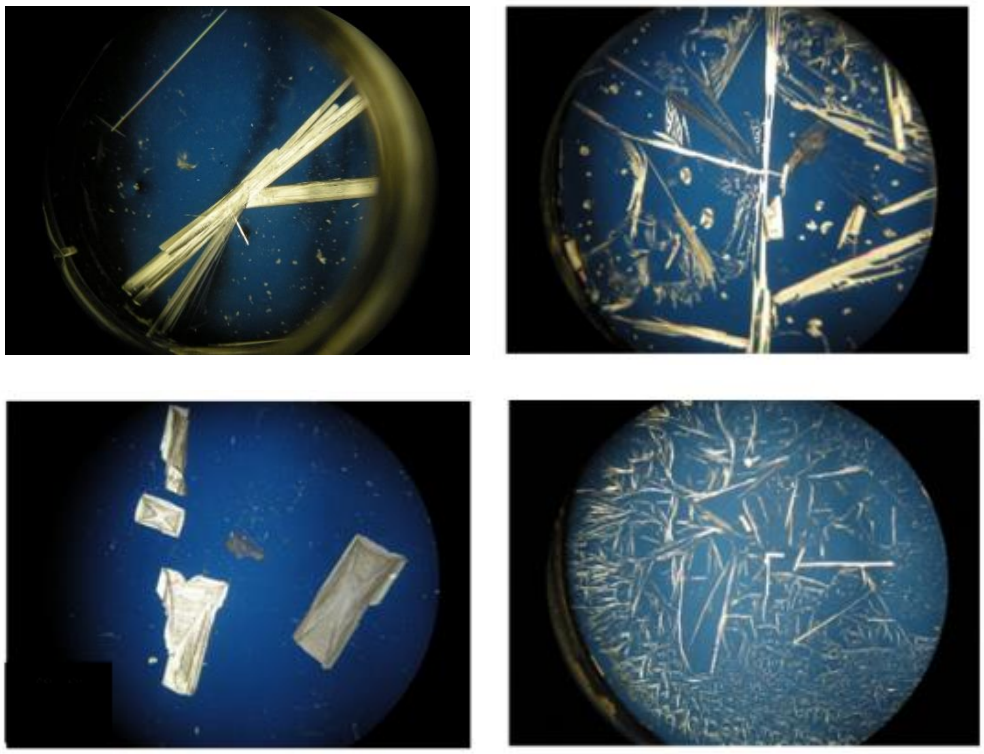

Figure ESI-10: PLM images of IZN crystals grown in Stage 1 of the additive workflow, by slow evaporation from a selection of pure solvents with no additives present. (a) distilled water, (b) ethanol, (c) propan-2-ol and (d) acetonitrile.

Table ESI-9: non-GRAS, common co-former library details, for molecular complementarity screening in Mercury. CSD ref-codes are included where used to generate the library mol2 input files. Where ref-codes are not included a suitable CSD entry could not be identified and instead mol2 files were created by modifying a related material (e.g. a hydrate or co-crystal structure) using the Edit Structure function in Mercury.

Co-former	CSD ref-code
2-bromopyridine	-
4,4'-bipyridine	-
4-acetopyridine	-
2-aminobenzoic acid	AMBACO
4-aminobenzoic acid	AMBNAC
2-aminopyridine	AMPYRD
2,3-dinitrobenzoic acid	BAQLUD
Barbituric acid	BARBAC
Benzoic acid	BENZAC
2,2'-bipyridine	BIPYRL
Benzimidazole	BZDMAZ
3,5-dinitrobenzoic acid	CUKCAM
Isonicotinamide	EHOWIH
Gallic acid	IJUMEG
Imidazole	IMAZOL
Isonicotinic acid	ISNICA
Maleic acid	MALIAC
Nicotinic acid	NICOAC
Nicotinamide	NICOAM
Oxalic acid	OXALAC
Succinic acid	SUCACB
Urea	UREAXX
3-hydroxybenzoic acid	BIDLOP
3,4-dinitrobenzoic acid	YADKOF
3-cyanobenzoic acid	-
4-cyanobenzoic acid	TAGNAR
D-Tartaric acid	TARTAC
3,4-hydroxybenzoic acid	WUYNUA
2-picoline	ZZZHKQ
Trimesic acid	-

Table ESI-10: Results of Molecular Complementarity Search with IZN and GRAS library, all 5 molecular descriptors included.

Name	CSD refcode	Outcome	Descriptor-specific Pass/Fail
Adipic acid	**ADIPAC**	**PASS**	**5 passed**
Benzoic acid	**BENZAC**	**PASS**	**5 passed**
Pyridoxine	**BITZAF**	**PASS**	**5 passed**
Citric acid	**CITRAC10**	**PASS**	**5 passed**
Malic acid	**DLMALC**	**PASS**	**5 passed**
DL-Mannitol	DLMANT	FAIL	4 passes, dipole moment = fail
D-Mannitol	**DMANTL**	**PASS**	**5 passed**
Inisitol	**EFURIH**	**PASS**	**5 passed**
Glycerol	**GLCROL**	**PASS**	**5 passed**
Glucitol	GLUCIT	FAIL	4 passes, dipole moment = fail
Glucose	**GLUCSA**	**PASS**	**5 passed**
D-Isoascorbic acid	IASCOR10	FAIL	4 passes, S/L ratio = fail
Octanoic acid	ISENUP	FAIL	4 passes, M/L ratio = fail
L-Ascorbic acid	LASCAC01	FAIL	4 passes, M/L ratio = fail
2,4-hexadienoic acid	**LEZHUT**	**PASS**	**5 passed**
L-glutamic acid	**LGLUAC**	**PASS**	**5 passed**
Nicotinic acid	**NICOAC**	**PASS**	**5 passed**
Nicotinamide	**NICOAM**	**PASS**	**5 passed**
Propionic acid	**PRONAC**	**PASS**	**5 passed**
Succinic acid	**SUCACB02**	**PASS**	**5 passed**
Sucrose	**SUCROS01**	**PASS**	**5 passed**
L-Tartaric acid	**TARTAL**	**PASS**	**5 passed**
***cis*-Aconitic acid**	**TELZOZ**	**PASS**	**5 passed**
Urea	UREAXX	FAIL	4 passes, Fraction N,O = fail
Lactic acid	YILLAG	FAIL	4 passes, S/L ratio = fail

Table ESI-11: Results of Molecular Complementarity Search with IZN and non-GRAS, common co-former library, all 5 molecular descriptors included.

Name	CSD refcode	Outcome	Descriptor-specific Pass/Fail
2-bromopyridine	**-**	**PASS**	**5 passed**
4,4'-bipyridine	**-**	**PASS**	**5 passed**
4-acetopyridine	**-**	**PASS**	**5 passed**
4-cyanobenzoic acid	**TAGNAR**	**PASS**	**5 passed**
2-aminobenzoic acid	**AMBACO**	**PASS**	**5 passed**
4-aminobenzoic acid	**AMBNAC**	**PASS**	**5 passed**
2-aminopyridine	**AMPYRD**	**PASS**	**5 passed**
2,3-dinitrobenzoic acid	**BAQLUD**	**PASS**	**5 passed**
Barbituric acid	**BARBAC**	**PASS**	**5 passed**
Benzoic acid	**BENZAC**	**PASS**	**5 passed**
3-hydroxybenzoic acid	**BIDLOP**	**PASS**	**5 passed**
3,4-dihydroxybenzoic acid	**WUYNUA**	**PASS**	**5 passed**
2,2'-bipyridine	**BIPYRL**	**PASS**	**5 passed**
Benzimidazole	**BZDMAZ**	**PASS**	**5 passed**
3,5-dinitrobenzoic acid	**CUKCAM**	**PASS**	**5 passed**
Isonicotinamide	**EHOWIH**	**PASS**	**5 passed**
Gallic acid	**IJUMEG**	**PASS**	**5 passed**
Imidazole	**IMAZOL**	**PASS**	**5 passed**
Isonicotinic acid	**ISNICA**	**PASS**	**5 passed**
3-cyanobenzoic acid	**-**	**PASS**	**5 passed**
Maleic acid	**MALIAC**	**PASS**	**5 passed**
Nicotinic acid	**NICOAC**	**PASS**	**5 passed**
Nicotinamide	**NICOAM**	**PASS**	**5 passed**
Oxalic acid	**OXALAC**	**PASS**	**5 passed**
Succinic acid	**SUCACB**	**PASS**	**5 passed**
D-Tartaric acid	TARTAC	FAIL	4 passed, S/L ratio = fail
Urea	UREAXX	FAIL	4 passed, Fraction N/O = fail
3,4-dinitrobenzoic acid	**YADKOF**	**PASS**	**5 passed**
2-picoline	**ZZZHKQ**	**PASS**	**5 passed**
Trimesic acid	**-**	**PASS**	**5 passed**

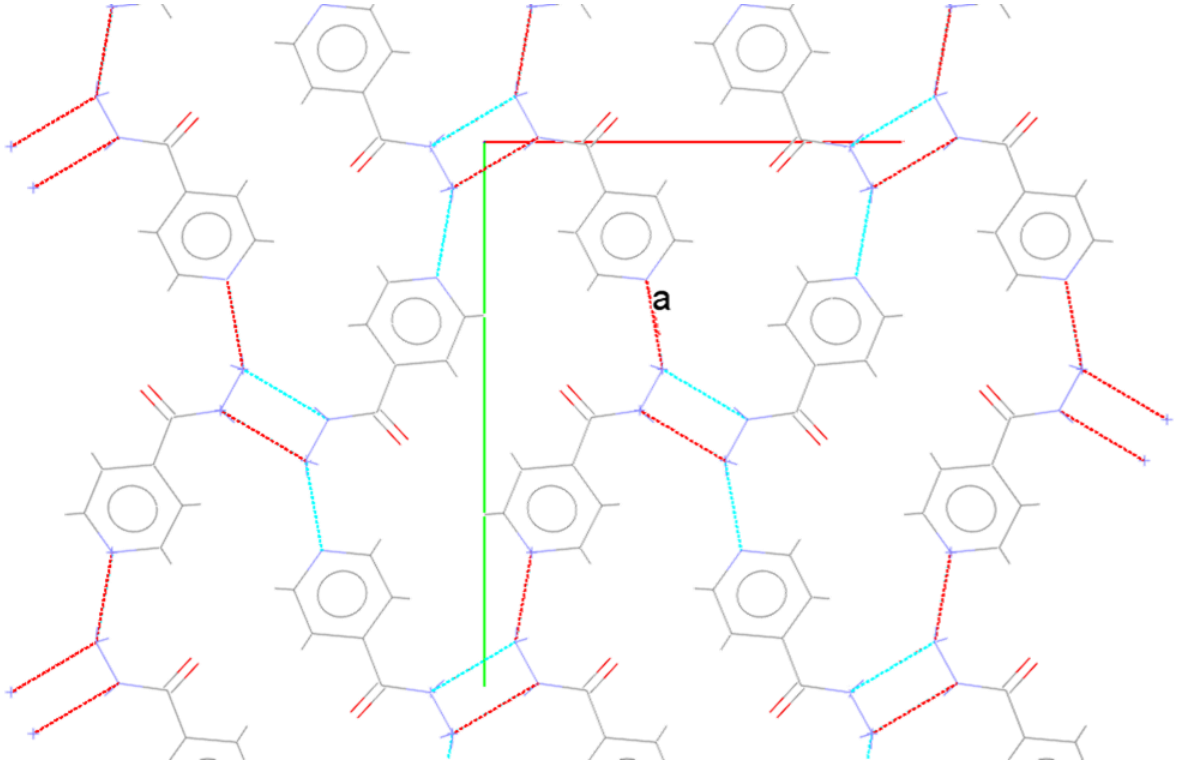

Figure ESI-11: Overlay of the crystallographic *b*-axis (green) and *a*-axis (red) with the underlying bulk IZN crystal structure in Mercury. [010] direction up and down the page. "a" represents key NH…N(py) intermolecular hydrogen bonding interactions that promote growth of 1D chains of IZN molecules along the *b*-axis, or [010] direction.

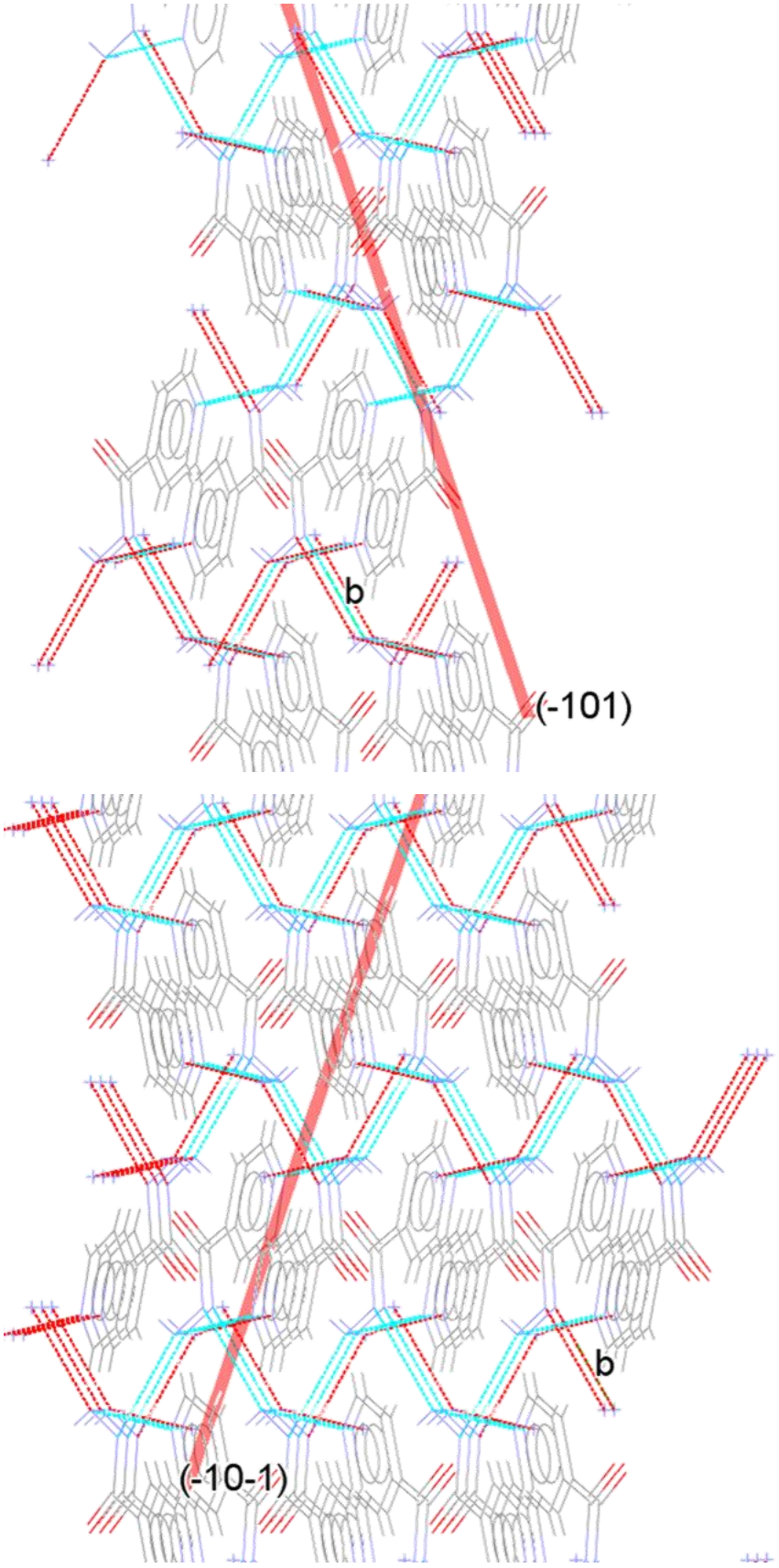

Figure ESI-12: Overlay of the key planes (red line) with the underlying bulk IZN crystal structure in Mercury. Top = (-101) plane, bottom = (-10-1) plane. "b" highlights discrete NH…N intermolecular hydrogen bonding interactions formed between adjacent hydrazine moieties, which are intersected by both planes, indicating the possible cleavage of these interactions at the real crystal faces.