

Supplementary Information

for

**Unique Supramolecular Complex of Diclofenac: Structural Robustness,
Crystal-to-Crystal Solvent Exchange, and Mechanochemical Synthesis**

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1. Experimental details

Materials

Diclofenac (**DFC**) and 4,4-dipyridyl (**4,4'-BIPY**) were purchased from Oakwood Chemical (Columbia Hwy N. Estill, SC, USA). 1,2-Bis(4-pyridyl)ethylene (**4,4'-BPE**) and 4,4'-azopyridine (**4,4'-AP**) were purchased from Sigma-Aldrich Chemical (St. Louis, MO, USA). 1,2-Bis(4-pyridyl)ethane (**4,4'-BPEth**) was purchased from Acros Organics (New Jersey, USA). Lastly, toluene and acetone were purchased from Fisher Scientific (Lenexa, KS, USA). All chemicals and solvents were used as received.

Co-crystallizations.

Co-crystals of **DFC·4,4'-BIPY** were synthesized by dissolving **DFC** (20mg, 0.068mmol) and **4,4'-BIPY** (5.3 mg, 0.034mmol) in toluene. Slow evaporation of the solution was allowed for a period of 2-3 days until single crystals were formed that were suitable for X-ray diffraction.

Co-crystals of **DFC·4,4'-BPE** synthesized by dissolving **DFC** (20mg, 0.068 mmol) and **4,4'-BPE** (6.2 mg, 0.034 mmol) in toluene. The solution was allowed to evaporate slowly over a period of 2-3 days until single crystals were formed that were suitable for X-ray diffraction.

Co-crystals of **DFC·4,4'-BPEth** synthesized by dissolving **DFC** (20mg, 0.068 mmol) and **4,4'-BPEth** (6.2 mg, 0.034 mmol) in toluene. The solution was allowed to evaporate slowly over a period of 2-3 days until single crystals were formed that were suitable for X-ray diffraction.

Co-crystals of **DFC·4,4'-AP** synthesized by dissolving **DFC** (40mg, 0.135 mmol) and **4,4'-AP** (99.5 mg, 0.540 mmol) in acetone and toluene (5 mL toluene and a few drops of acetone) or a mixture of xylenes (ca. 5 mL). The solution was allowed to evaporate slowly over a period of 2-3 days until single crystals were formed that were suitable for X-ray diffraction.

Solvent removal experiment

Co-crystals of **DFC·4,4'-AP** were placed in an oven at a variety of temperatures and heating times. A temperature of 111 °C for a period of 4 hours resulted in nearly all the solvent being removed as evidenced by ¹H NMR spectroscopy and TGA.

Mechanochemistry experiment

Co-crystals of **DFC·4,4'-AP** were synthesized by conducting mechanochemistry experiments using a FTS1000 Ball Mill purchased from Form-Tech Scientific. Experiments were conducted in 15 mL stainless steel jars with 10 mm stainless steel grinding balls. **DFC** (145 mg, 0.489 mmol), **4,4'-AP** (90 mg, 0.489 mmol), 2 drops of acetone, and 6 drops of toluene were placed in a stainless steel SmartSnap jar. The mixture was milled at 900 rpm for a period of 1 hr. The resulting solid was characterized by PXRD. For the solvent-free synthesis, the acetone and toluene were omitted from the procedure.

2. X-ray diffraction information and data tables

X-ray data for **DFC·4,4'-BIPY**, **DFC·4,4'-BPeth**, **DFC·4,4'-BPE**, and **DFC·4,4'-AP** (100 K toluene/acetone) were collected on a Bruker PLATFORM three circle diffractometer equipped with an APEX II CCD detector and operated at 1350 W (45kV, 30 mA) to generate (graphite monochromated) Mo K α radiation ($\lambda = 0.71073 \text{ \AA}$). The crystal sample in oil was mounted on a MiTiGen cryoloop and kept under a cold nitrogen stream at 100 K or 200 K throughout the experiment. Intensity data were corrected for Lorentz, polarization, and background effects using the Bruker program APEX 3. A semi-empirical correction for adsorption was applied using the program SADABS.¹ The SHELXL-2014,² series of programs was used for the solution and refinement of the crystal structure. Hydrogen atoms bound to carbon, nitrogen, and oxygen atoms were located in the difference Fourier map and were geometrically constrained using the appropriate AFIX commands.

Table S1. X-ray data for co-crystals **DFC·4,4'-BIPY**, **DFC·4,4'-BPeth**, and **DFC·4,4'-BPE**.

compound name	DFC·4,4'-BIPY	DFC·4,4'-BPeth	DFC·4,4'-BPE·toluene
chemical formula	C ₃₈ H ₃₀ C ₁₄ N ₄ O ₄	C ₂₀ H ₁₇ C ₁₂ N ₂ O ₂	C ₄₇ H ₄₀ C ₁₄ N ₄ O ₄
formula mass	748.46	388.25	535.42
crystal system	Triclinic	Orthorhombic	Monoclinic
space group	<i>P</i> $\bar{1}$	<i>Pbcn</i>	<i>C2/c</i>
a/ \AA	8.6025	27.525	19.763
b/ \AA	14.743	7.7860	7.0061
c/ \AA	15.818	16.8266	30.454
$\alpha/^\circ$	113.957°	90°	90°
$\beta/^\circ$	90.600°	90°	99.447°
$\gamma/^\circ$	105.072°	90°	90°
V/ \AA^3	1754.9	3606.1	4159.4
$\rho_{\text{calc}}/\text{g cm}^{-3}$	1.416	1.430	1.384
T/K	200	100	100
Z	2	8	4
radiation type	Mo K α	Mo K α	Mo K α
absorption coefficient, μ/mm^{-1}	0.385	0.377	0.335
no. of reflections measured	40056	22468	23563
no. of independent reflections	7844	3978	4604
no. of reflection ($I > 2\sigma(I)$)	5331	3966	3966
R_{int}	0.0311	0.0429	0.0293
R_1 ($I > 2\sigma(I)$)	0.0418	0.0333	0.0313
wR(F^2) ($I > 2\sigma(I)$)	0.1011	0.0690	0.0738
R_1 (all data)	0.0685	0.0488	0.0383
wR(F^2) (all data)	0.1155	0.0751	0.0779
Goodness-of-fit	1.040	1.026	1.027
CCDC deposition number	1909032	1909030	1909029

X-ray data for **DFC·4,4'-AP** (297 K and 100 K xylenes) were collected on a Rigaku XtaLAB Synergy-*i* Kappa diffractometer equipped with a HyPix-6000HE HPC detector and a PhotonJet-*i* X-ray source operated at 50 W (50kV, 1 mA) to generate Cu K α radiation ($\lambda = 1.54178 \text{ \AA}$). Crystals were transferred from the vial and placed on a glass slide in polyisobutylene. The crystal was glued to a M \bar{t} TiGen cryolop and transferred to the instrument where it was analyzed. The sample was optically centered with the aid of a video camera to insure that no translations were observed as the crystal was rotated through all positions. Intensity data were corrected for Lorentz, polarization, and background effects using *CrysAlis^{Pro}*.³ A numerical absorption correction was applied based on a Gaussian integration over a multifaceted crystal and followed by a semi-empirical correction for adsorption applied using the program *SCALE3 ABSPACK*.⁴ The *SHELXL-2014*² series of programs was used for the solution and refinement of the crystal structure. Hydrogen atoms bound to carbon atoms were located in the difference Fourier map and were geometrically constrained using the appropriate AFIX commands. The highly disordered toluene/acetone or xylenes molecules within all structures in Table S2 were then treated as diffuse scattering using the *SQUEEZE*⁵ routine within *PLATON*.⁶

Table S2. X-ray data for **DFC·4,4'-AP** at different temperatures and grown from different solvents.

compound name	DFC·4,4'-AP	DFC·4,4'-AP	DFC·4,4'-AP
chemical formula	C ₂₄ H ₁₉ C ₁₂ N ₅ O ₂	C ₂₄ H ₁₉ C ₁₂ N ₅ O ₂	C ₂₄ H ₁₉ C ₁₂ N ₅ O ₂
formula mass	480.34	480.34	480.34
solvent used in crystallization	toluene/acetone	toluene/acetone	xylenes
crystal system	monoclinic	monoclinic	monoclinic
space group	<i>C2/c</i>	<i>C2/c</i>	<i>C2/c</i>
a/ \AA	29.485	29.7548	29.5915
b/ \AA	4.6618	4.76130	4.67650
c/ \AA	34.442	34.8524	34.4083
α / $^\circ$	90 $^\circ$	90 $^\circ$	90 $^\circ$
β / $^\circ$	94.016 $^\circ$	94.220 $^\circ$	94.1420 $^\circ$
γ / $^\circ$	90 $^\circ$	90 $^\circ$	90 $^\circ$
V/ \AA^3	4722.6	4924.2	4749.14
P _{calc} /mg m ⁻³	1.351	1.296	1.344
T/K	100	297	100
Z	8	8	8
radiation type	Mo K α	Cu K α	Cu K α
absorption coefficient, μ/mm^{-1}	0.306	2.619	2.716
no. of reflections measured	25886	24081	26656
no. of independent reflections	5217	4986	4943
no. of reflection ($I > 2\sigma(I)$)	4140	4029	4500
R _{int}	0.0445	0.0421	0.0545
R ₁ ($I > 2\sigma(I)$)	0.0373	0.0524	0.0529
wR(F ²) ($I > 2\sigma(I)$)	0.0901	0.1590	0.1447
R ₁ (all data)	0.0511	0.0614	0.0569
wR(F ²) (all data)	0.0978	0.1695	0.1496
Goodness-of-fit	1.020	1.082	1.056
CCDC deposition number	1909031	1913839	1913840

3. Single-crystal X-ray structures

For thermal ellipsoid structures, carbon, hydrogen, oxygen, nitrogen, and chlorine atoms are represented by gray, white, red, light blue and light green ellipsoids, respectively.

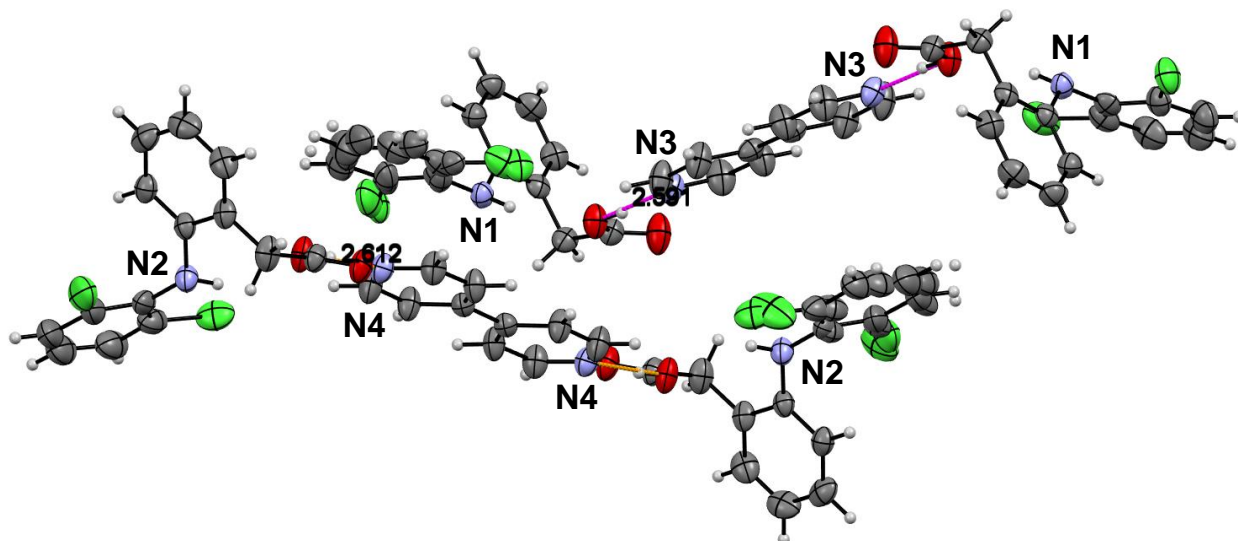


Figure S1. Crystallographically unique three-component hydrogen-bonded assemblies of **DFC·4,4'-BIPY** with thermal ellipsoids plotted at 50% probability.

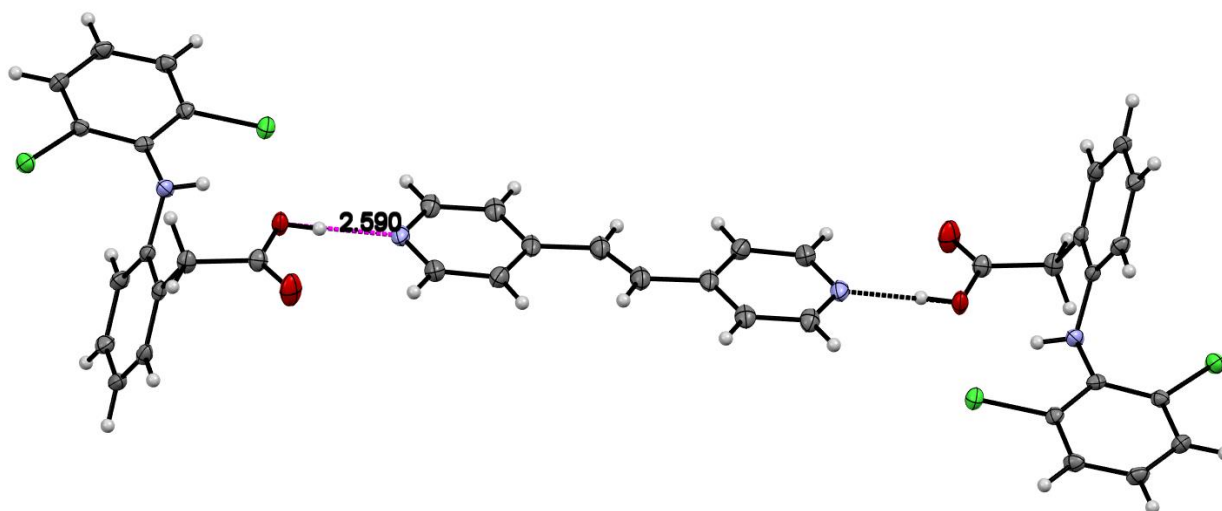


Figure S2. Three-component hydrogen-bonded assembly of **DFC·4,4'-BPE** with thermal ellipsoids plotted at 50% probability. Disordered toluene molecule is omitted for clarity.

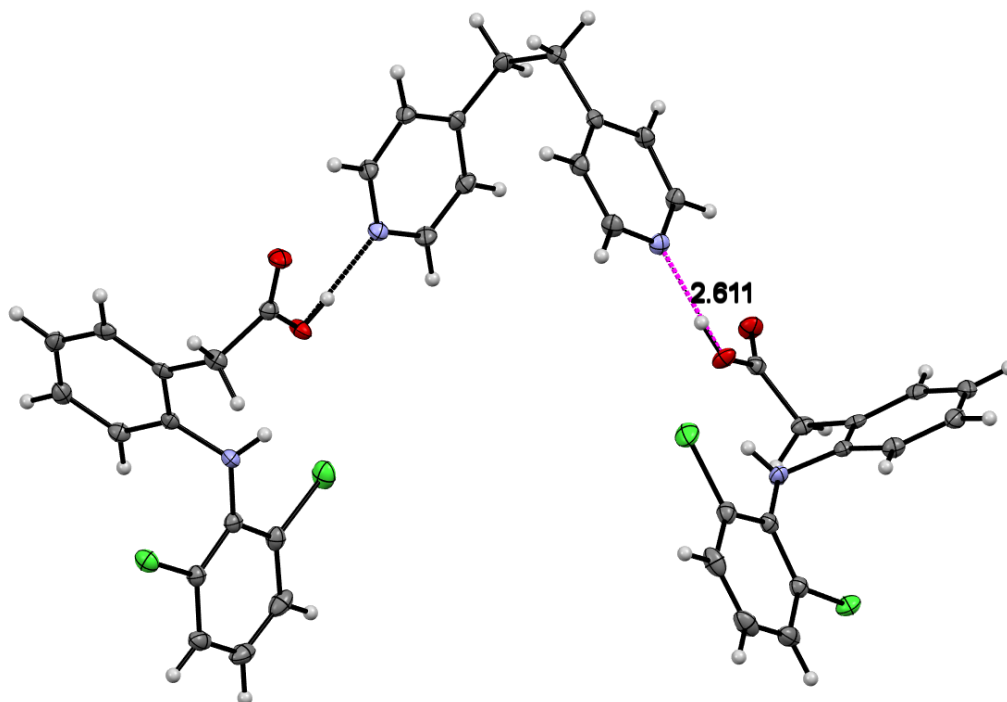


Figure S3. Three-component hydrogen-bonded assembly of **DFC·4,4'-BPeth** with thermal ellipsoids plotted at 50% probability.

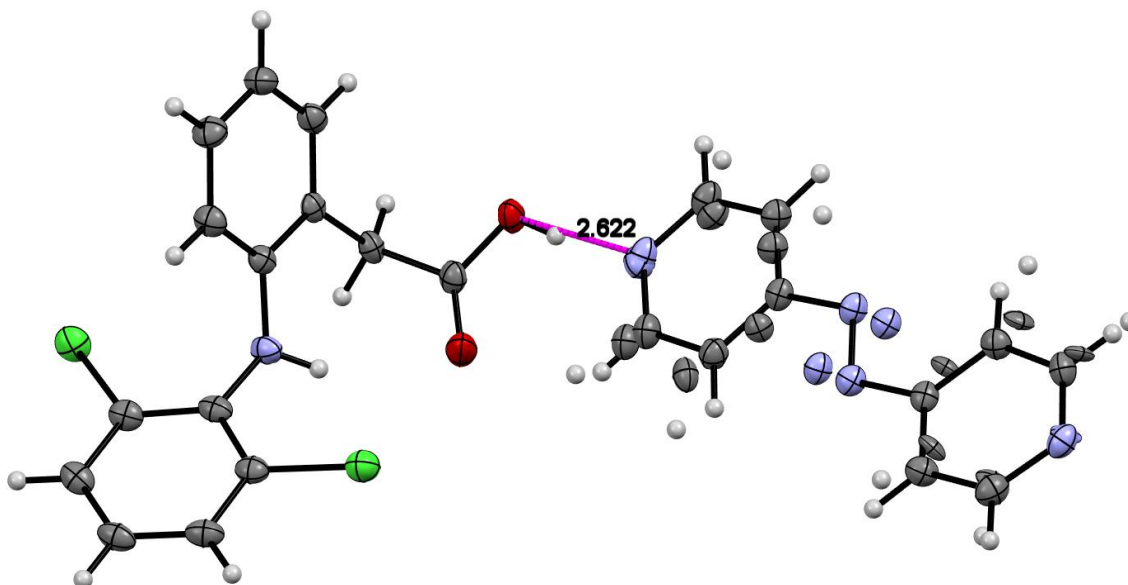


Figure S4. Asymmetric unit of **DFC·4,4'-AP** at 100 K (grown from toluene/acetone) with thermal ellipsoids plotted at 50% probability.

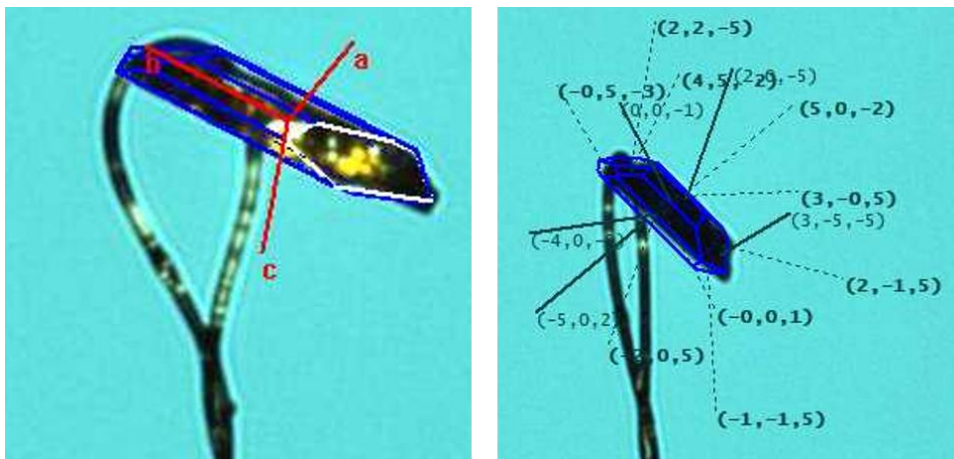


Figure S5. Face indexed images of a single crystal of **DFC·4,4'-AP**.

4. NMR data for co-crystals

Single crystals from the co-crystallization experiments were removed from the vial and dissolved in CDCl_3 or $\text{DMSO-}d_6$ for NMR experiments. NMR data was collected using a JOEL ECS 400 MHz Spectrometer with multinuclear, direct and inverse detection probes, automatic sample changer, variable temperature, and Z-gradient capabilities. The instrument was purchased with funds granted from National Science Foundation grant number CHE-1048553.

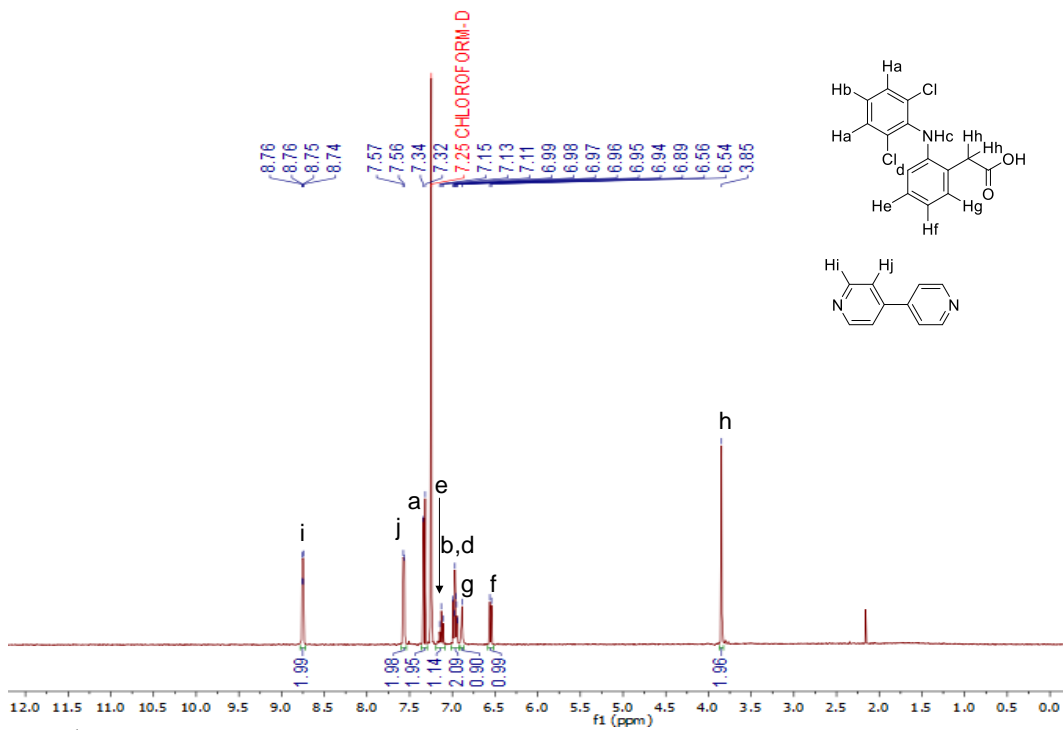


Figure S6. ^1H NMR spectrum of co-crystal $\text{DFC}\cdot 4,4'\text{-BIPY}$.

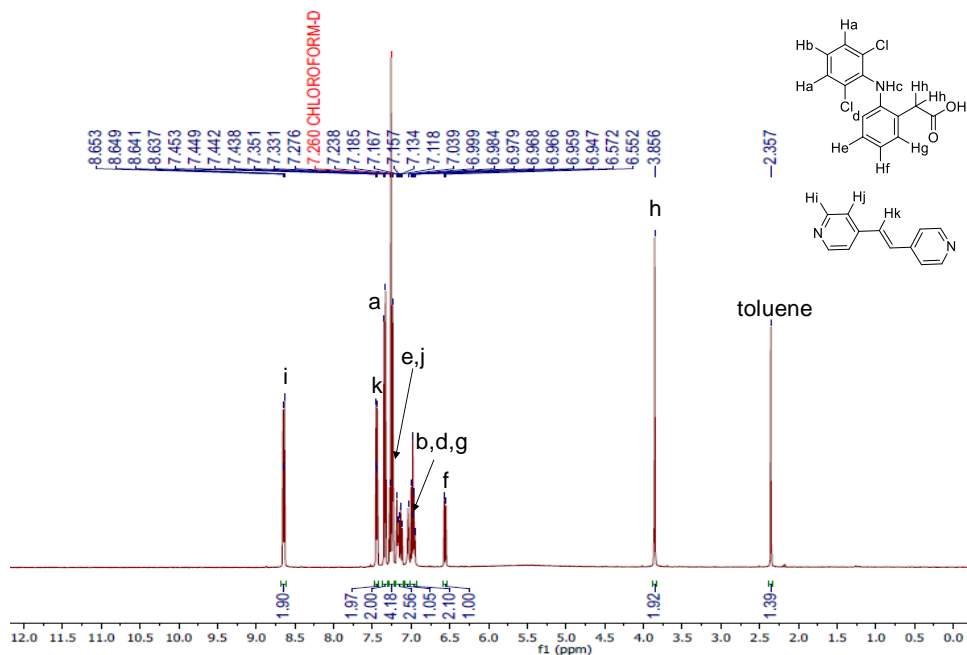


Figure S7. ^1H NMR spectrum of co-crystal **DFC·4,4'-BPE**. Additional signals in the aromatic region are from the toluene that crystallized with the components.

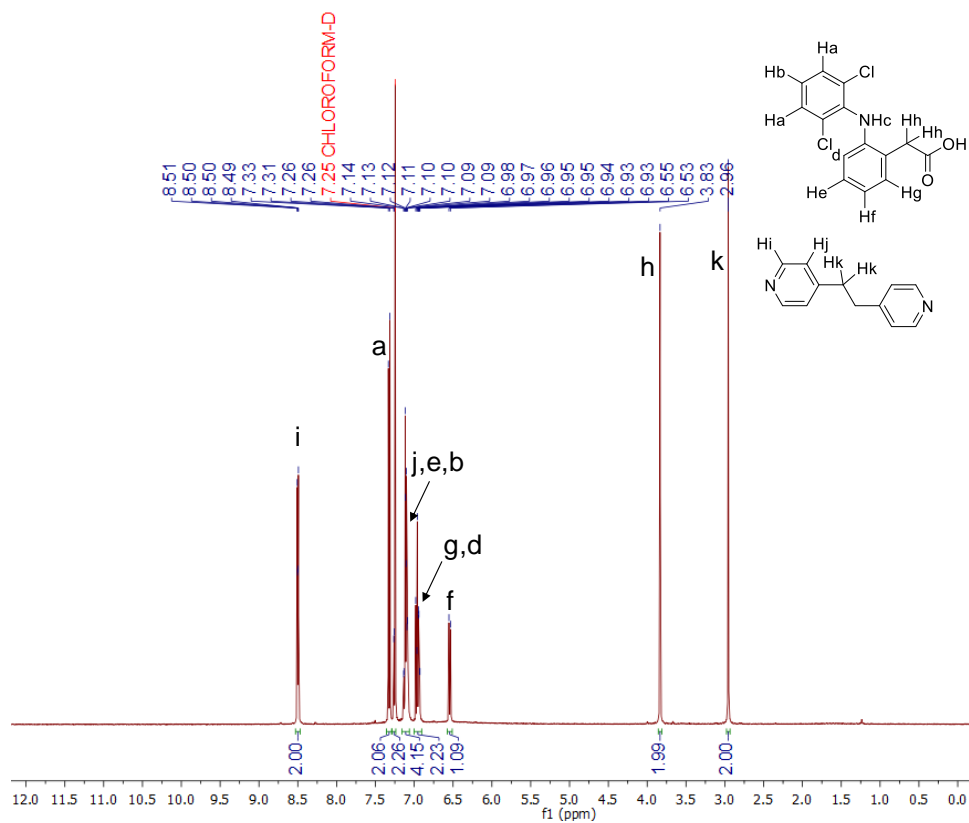


Figure S8. ^1H NMR spectrum of co-crystal **DFC·4,4'-BPEth**.

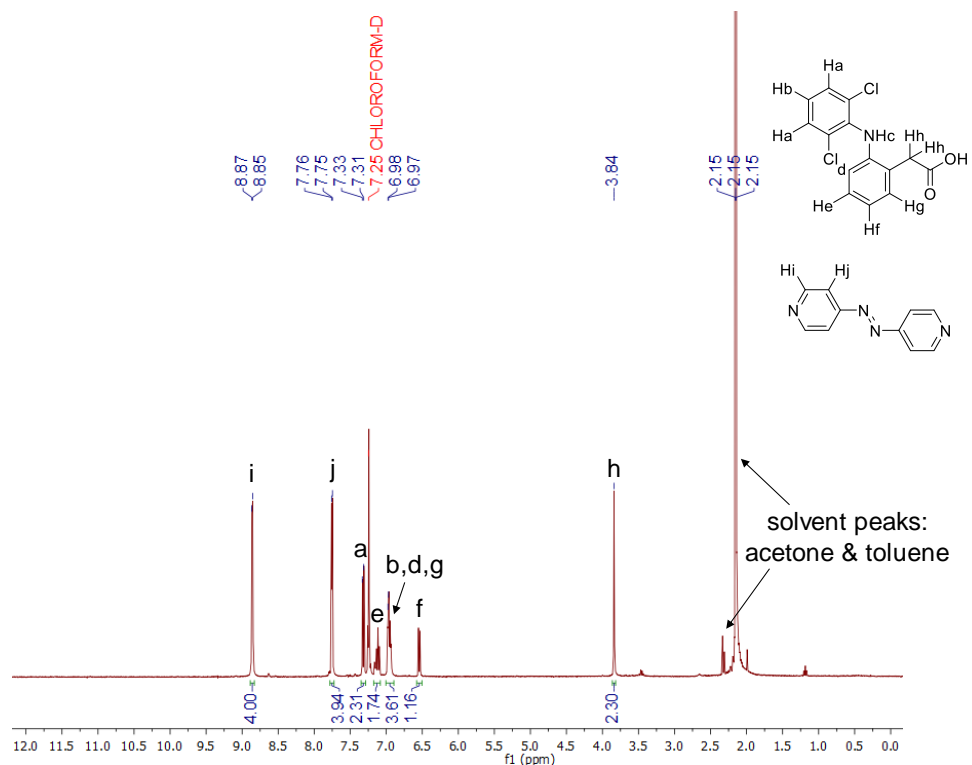


Figure S9. ¹H NMR spectrum of co-crystal DFC-4,4'-AP before solvent removal experiment. Additional signals in the aromatic region are from the toluene that crystallized with the components.

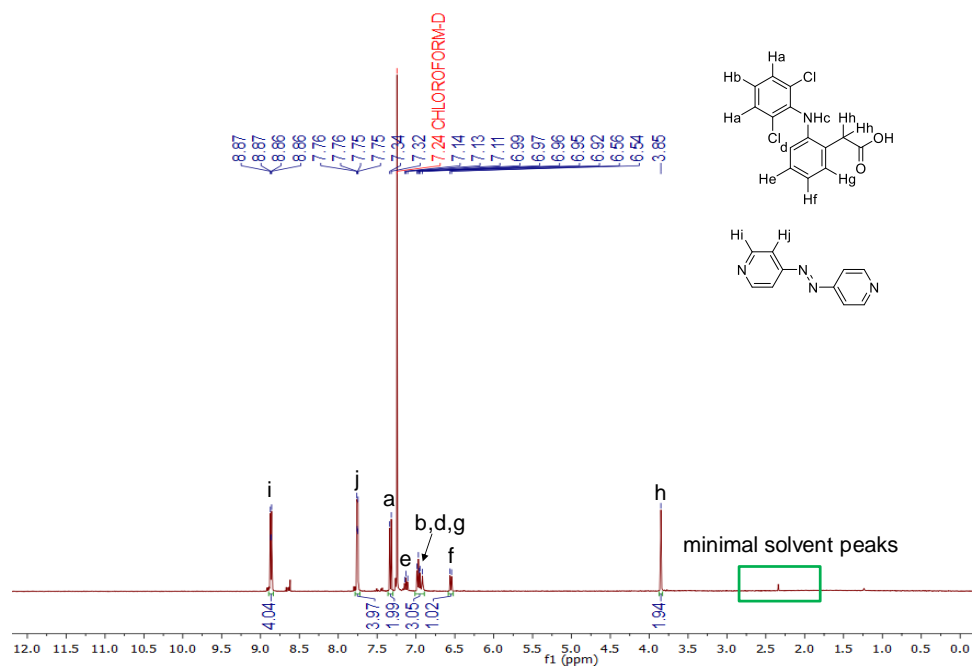


Figure S10. ¹H NMR spectrum of co-crystal DFC-4,4'-AP after solvent removal experiment at 111 °C for 4 hrs.

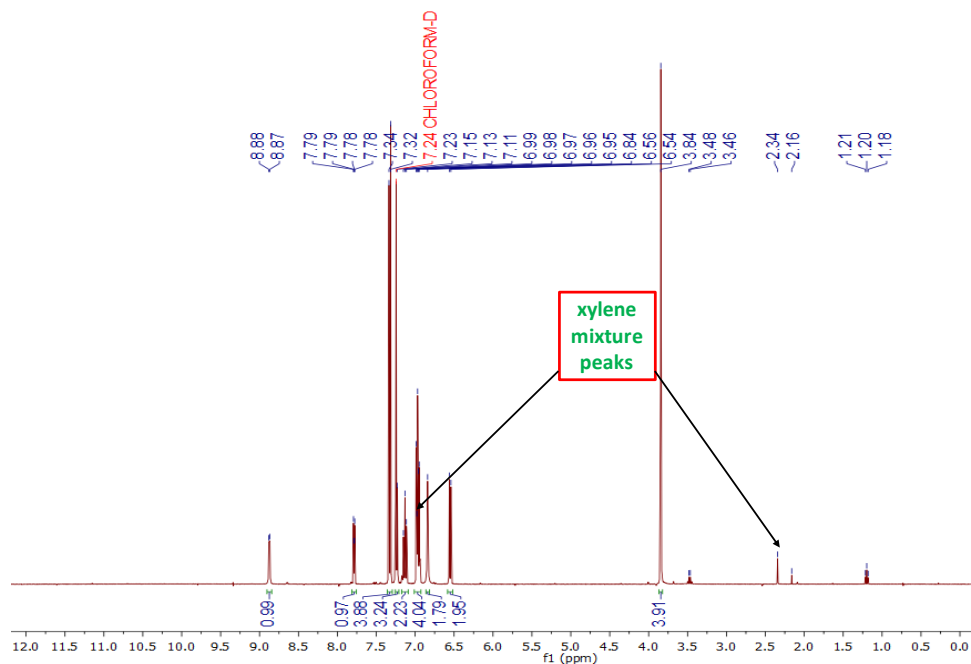


Figure S11. ^1H NMR spectrum of **DFC-4,4'-AP** following solvent exchange experiment of with xylenes in hexanes.

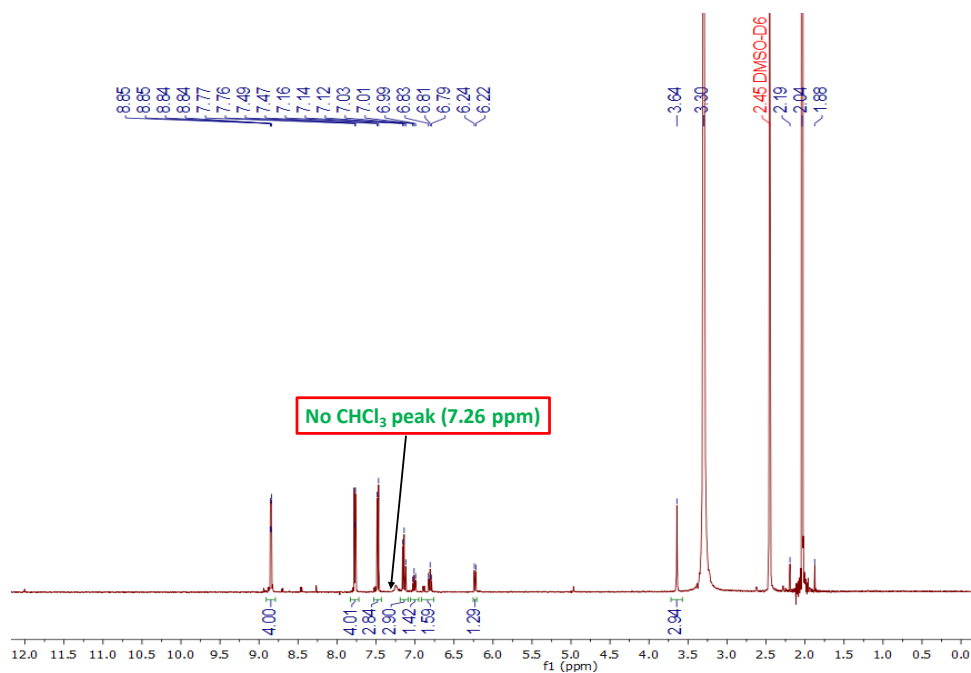


Figure S12. ^1H NMR spectrum of **DFC-4,4'-AP** following solvent exchange experiment with CHCl_3 in hexanes.

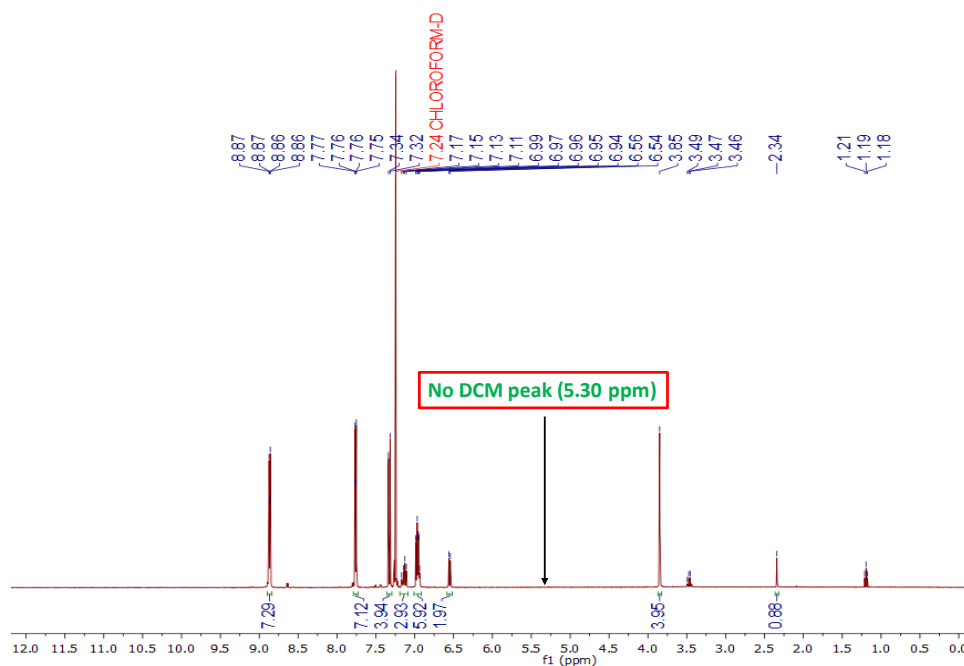


Figure S13. ^1H NMR spectrum of solvent exchange experiment of co-crystal **DFC·4,4'-AP** with DCM in hexanes.

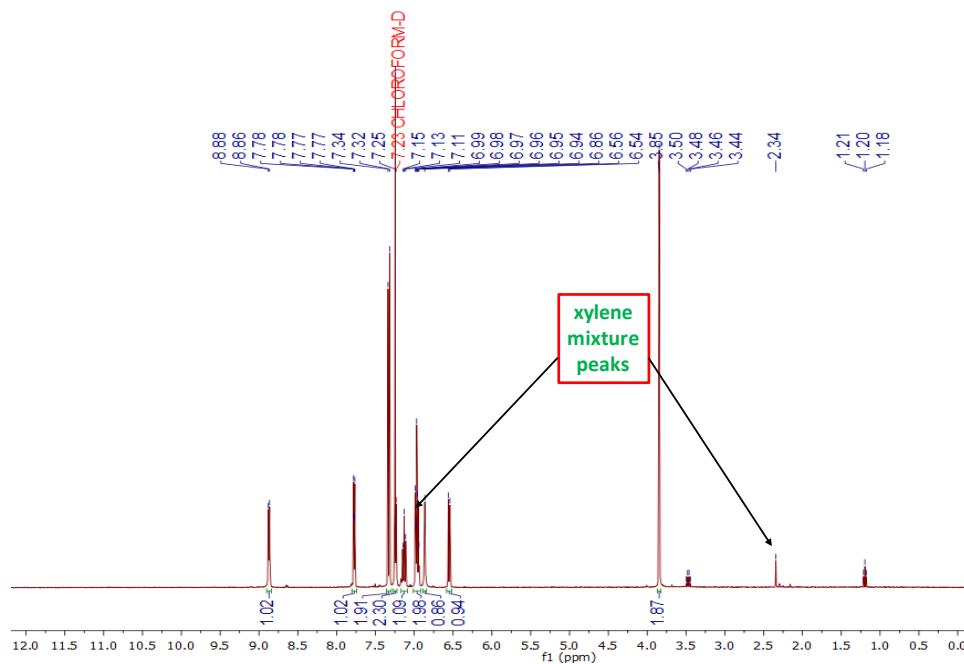


Figure S14. ^1H NMR spectrum of **DFC·4,4'-AP** following solvent exchange experiment with xylenes in H_2O .

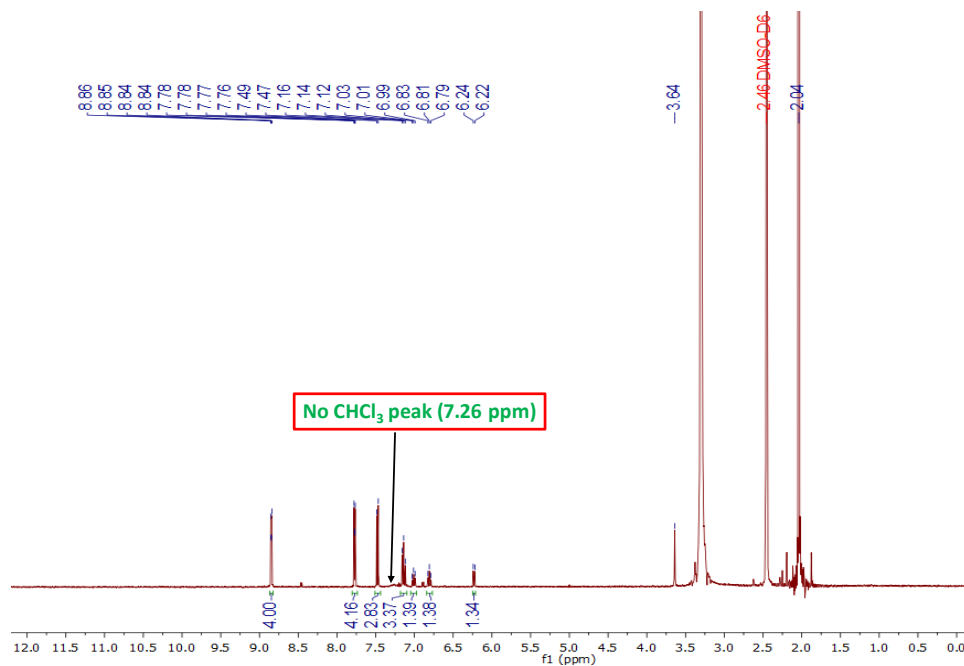


Figure S15. ^1H NMR spectrum of **DFC-4,4'-AP** following solvent exchange experiment with CHCl_3 in H_2O .

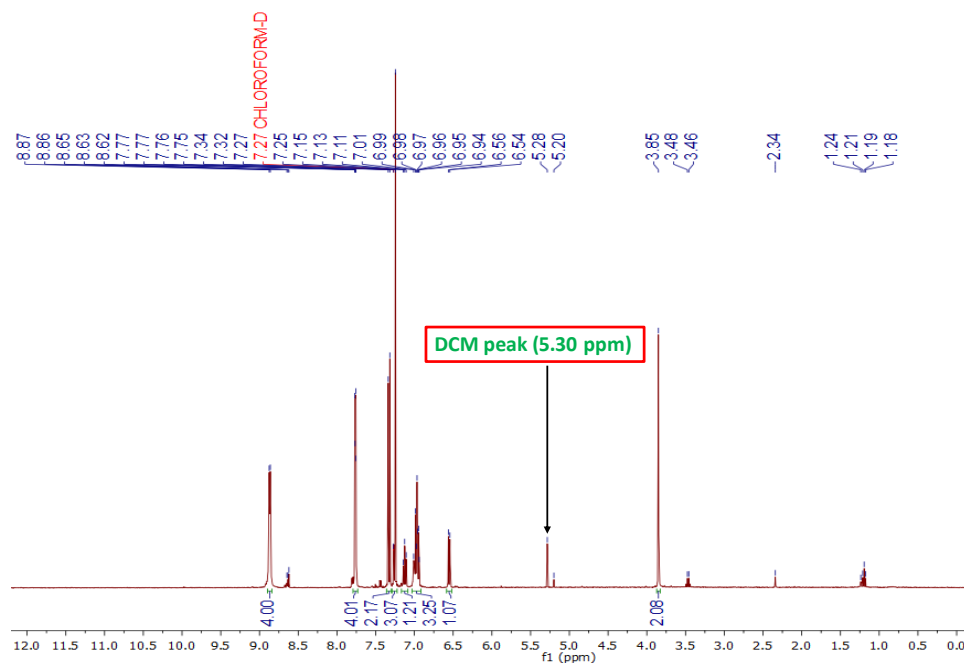


Figure S16. ^1H NMR spectrum of **DFC-4,4'-AP** following solvent exchange experiment with DCM in H_2O .

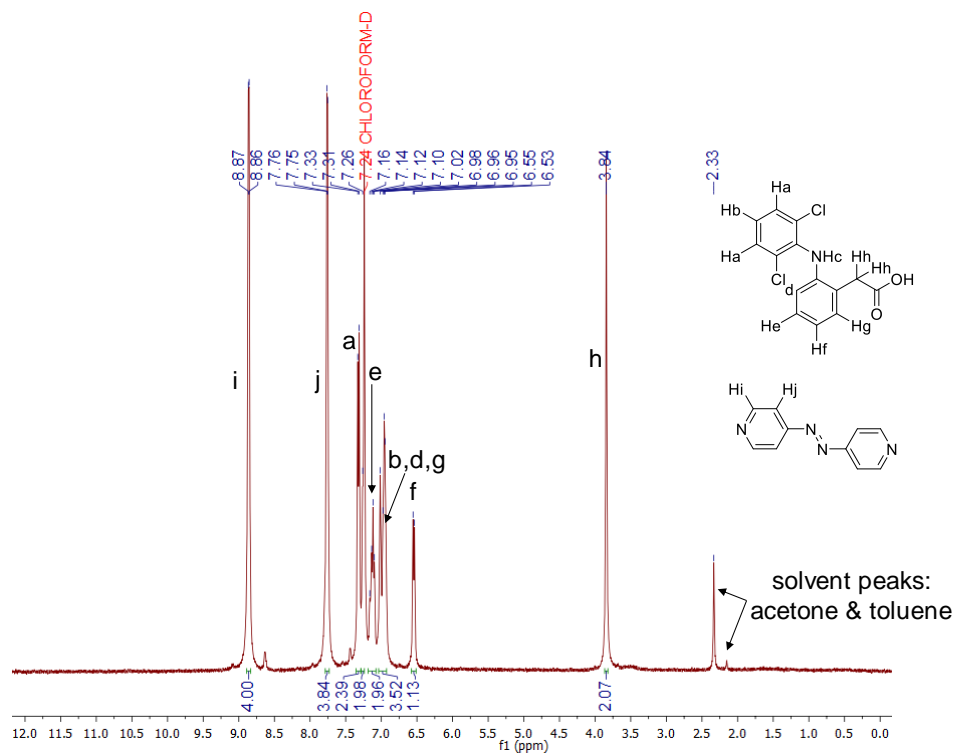


Figure S17. ^1H NMR spectrum of DFC·4,4'-AP following ball mill experiment with toluene and acetone. Additional signals in the aromatic region are from the toluene.

5. TGA data

TGA data was collected on a Mettler Toledo TGA2. A platinum cell and a nitrogen atmosphere were used. The flow rate was 25 mL/min, and the heating rate was 5 K/min.

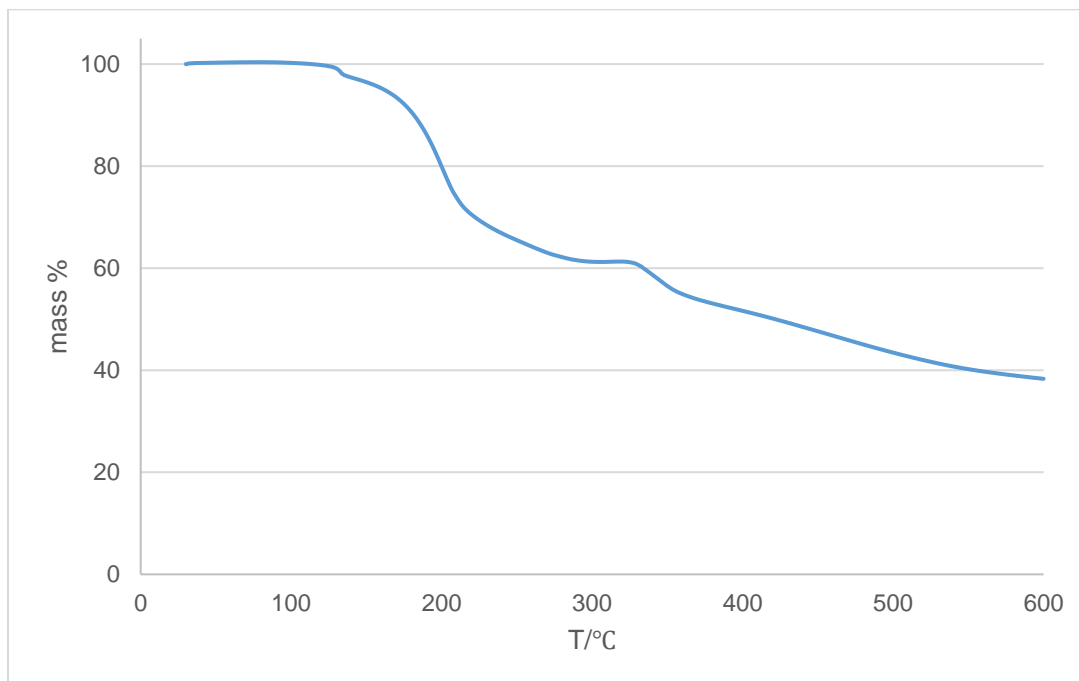


Figure S18. TGA data for solution grown **DFC·4,4'-AP** (before solvent removal). A mass loss of 2.50 % was observed at 102 °C, and crystal decomposition began at ca. 248°C.

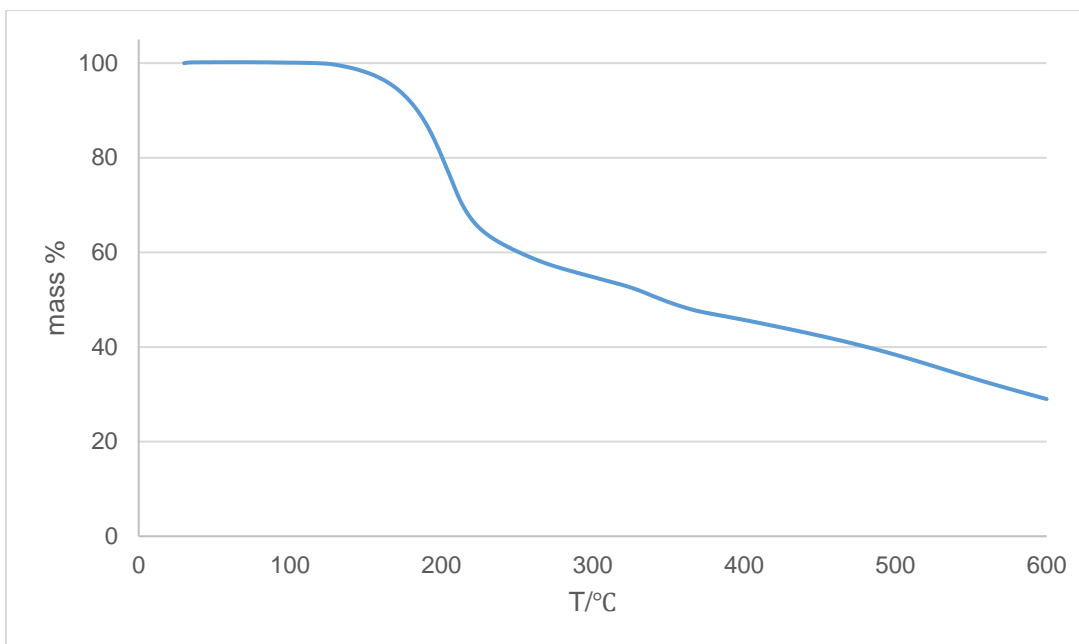


Figure S19. TGA data for **DFC·4,4'-AP** after solvent removal via oven heating.

6. PXRD patterns

The powder X-ray diffraction patterns were collected on a Rigaku Ultima III powder diffractometer. The X-ray diffraction pattern was obtained by scanning a 2θ range of $3\text{--}60^\circ$, step size = 0.02° , and scan time of 1.6 min/degree. The X-ray source was Cu K α radiation ($\lambda = 1.5418 \text{ \AA}$) with an anode voltage of 40 kV and a current of 44 mA. The beam was then discriminated by Rigaku's Cross Beam parallel beam optics to create a monochromatic parallel beam. Diffraction intensities were recorded on a scintillation detector after being filtered through a Ge monochromator. The sample was prepared as a standard powder mount and the diffractogram was processed through the software JADE v9.1.

The measured PXRD data of **DFC-4,4'-AP** repeatedly exhibited peak intensities that differed from the calculated pattern, indicating the presence of preferred orientation.⁷ The crystals also exhibit a needle morphology, and disorder of the azo component. To better compare the measured data to the calculated data, the simulated data for **DFC-4,4'-AP** was also calculated with preferred orientation. Calculated data with preferred orientation was produced with Mercury 4.1.0 using an hkl plane of 101 with a March-Dollase parameter of 0.5 (Figure S18).

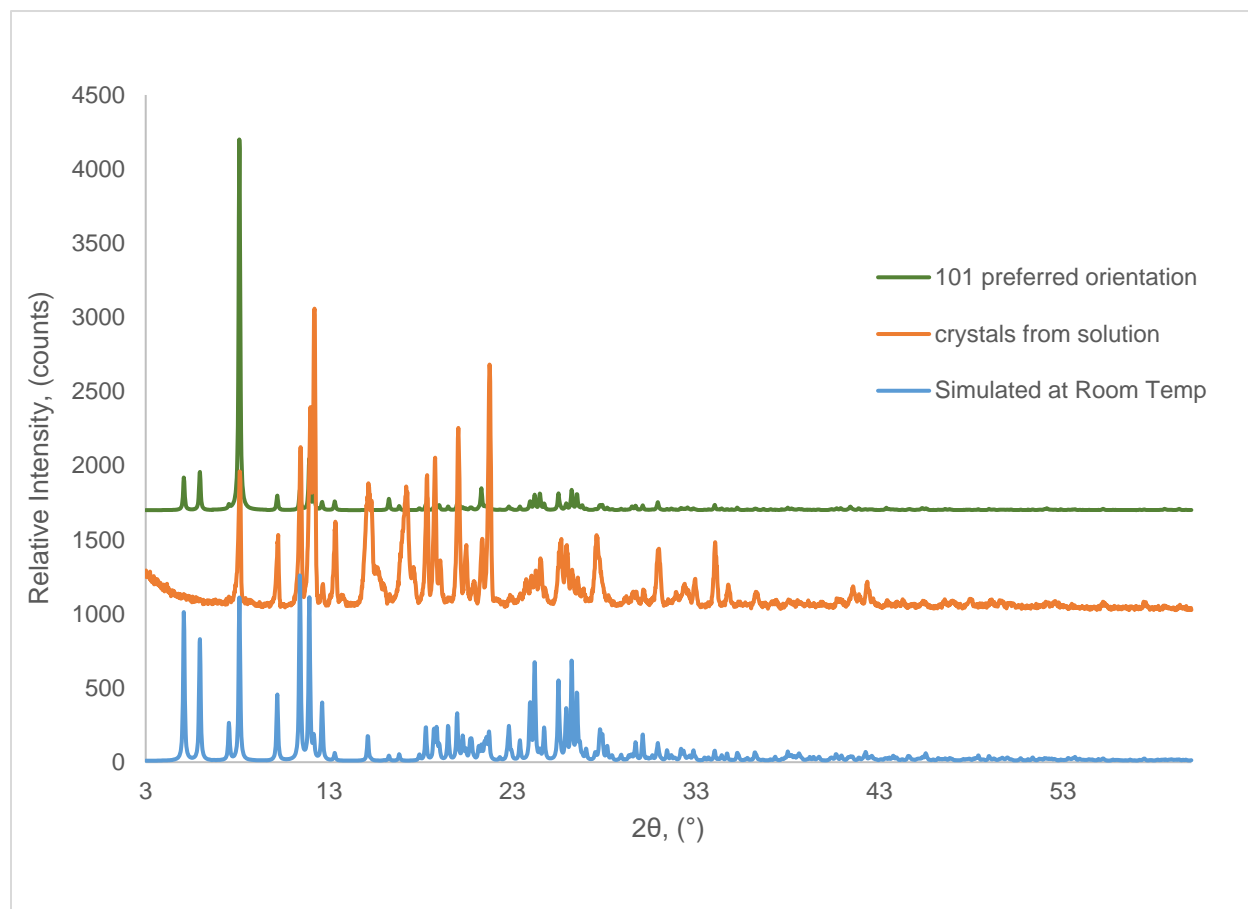


Figure S20. PXRD patterns of **DFC-4,4'-AP**: simulated from room temperature X-ray data, crystals grown from solution, and calculated with a 101 preferred orientation using a March-Dollase parameter of 0.5.

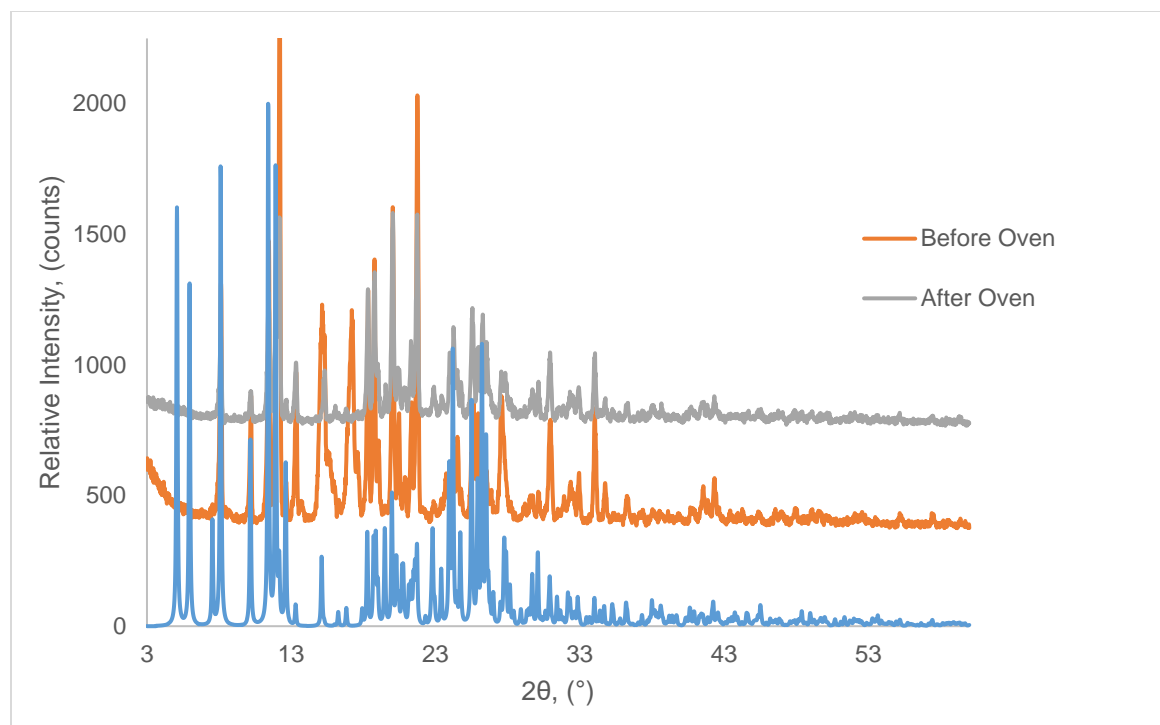


Figure S21. PXRD patterns of **DFC·4,4'-AP** grown from solution: simulated from room temperature X-ray data, before the solvent removal experiment (before oven), and following oven experiment at 111 °C for 4 hrs (after oven).

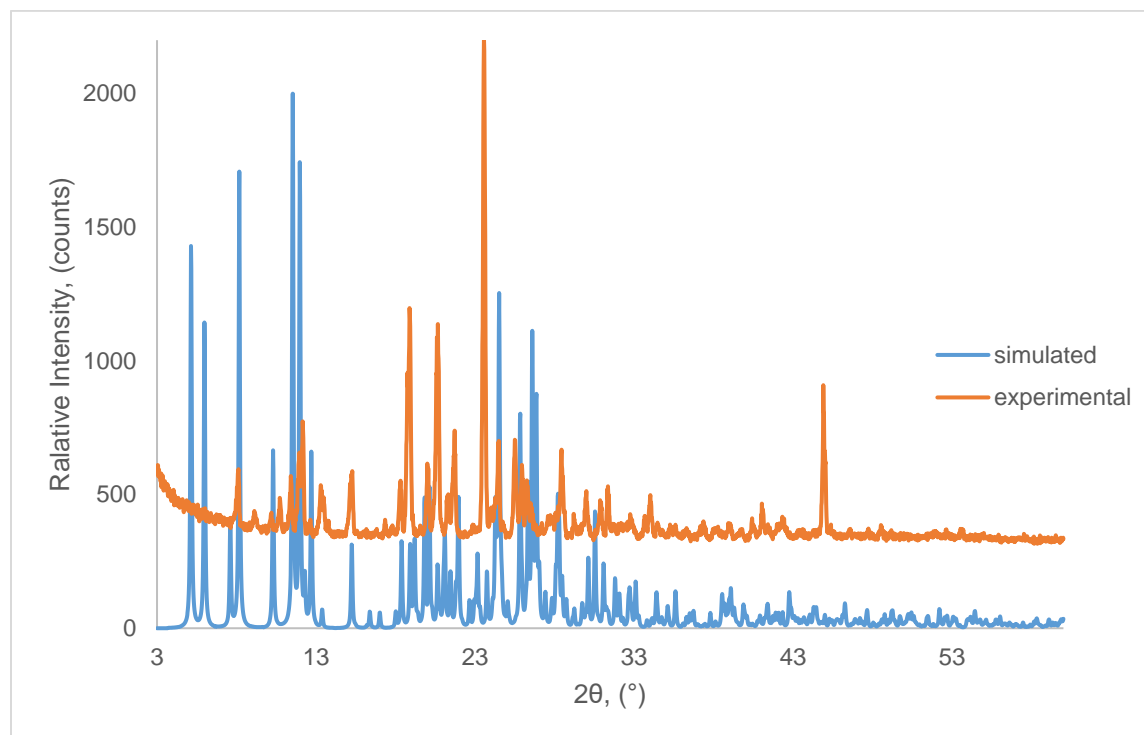


Figure S22. PXRD patterns of **DFC·4,4'-AP** following solvent exchange experiment with xylenes in H₂O (experimental). Simulated pattern is from single crystal X-ray data with xylenes as the solvent.

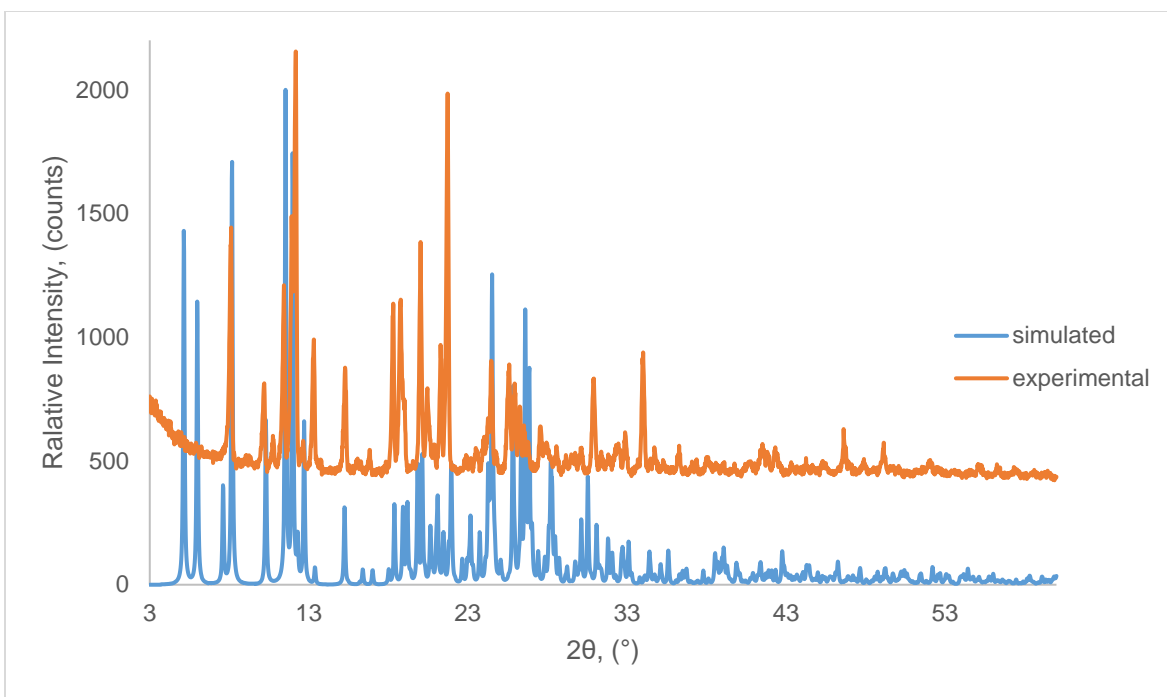


Figure S23. PXR D patterns of **DFC-4,4'-AP** following solvent exchange with xylenes in hexanes (experimental). Simulated pattern is from single crystal X-ray data with xylenes as the solvent.

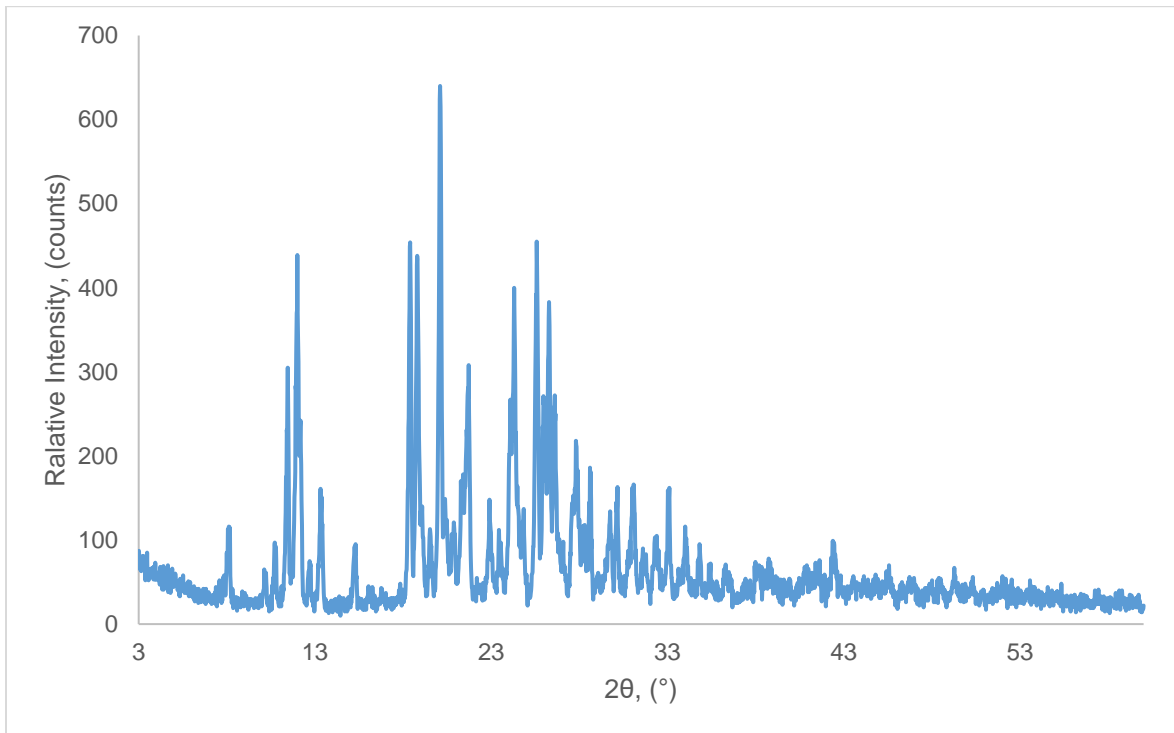


Figure S24. PXR D pattern of **DFC-4,4'-AP** following solvent exchange with DCM in H₂O.

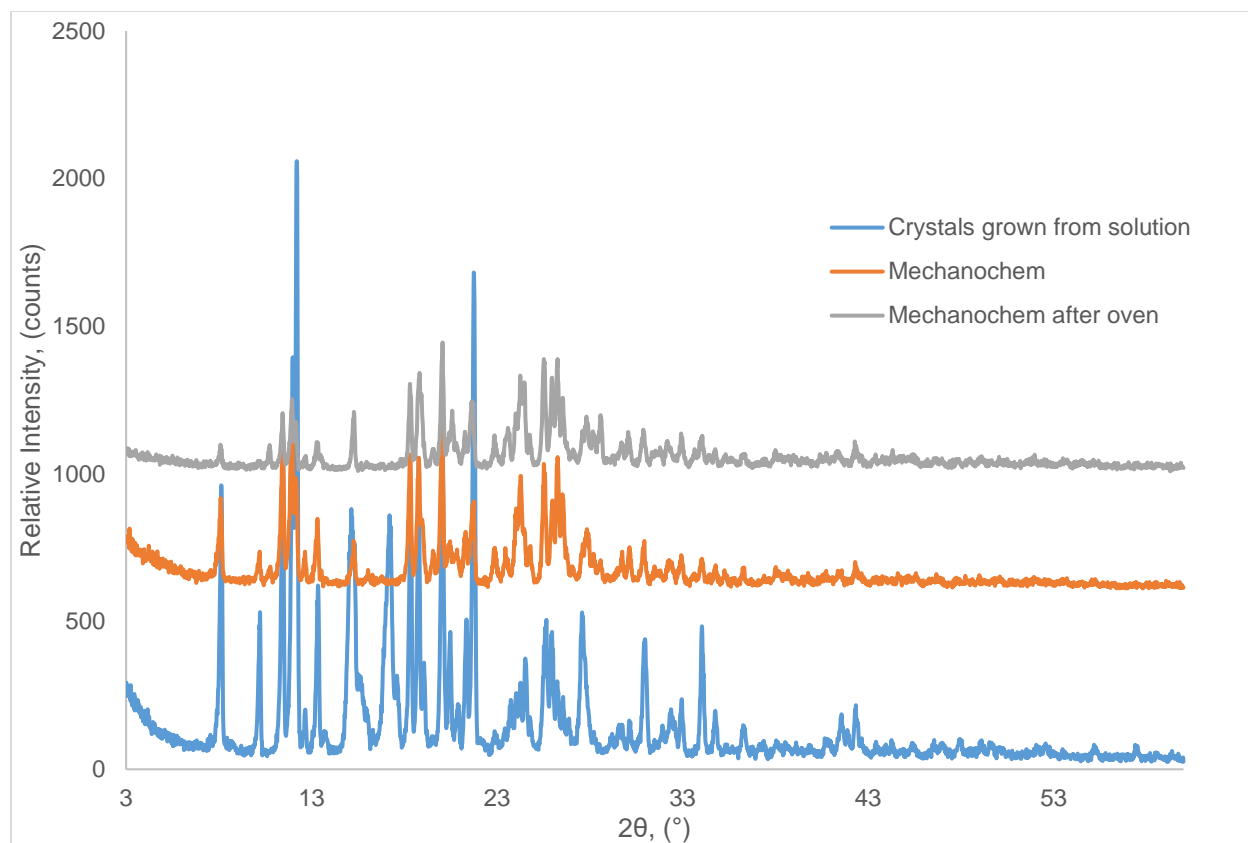


Figure S25. PXRD patterns of **DFC-4,4'-AP**: crystals grown from slow evaporation method, mechanochemistry experiment, and after heating the sample made via mechanochemistry in the oven at 111°C for 4 hours.

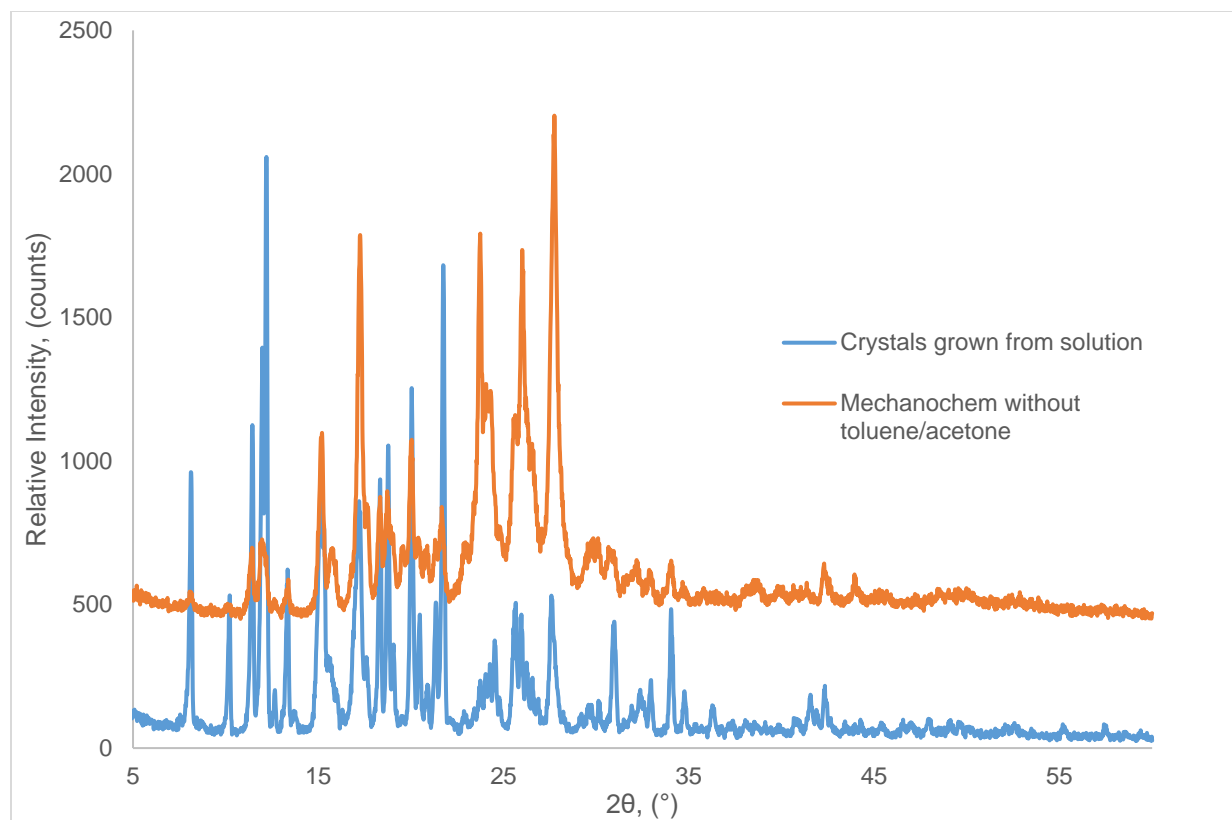


Figure S26. PXRD patterns of **DFC·4,4'-AP**: crystals grown from slow evaporation method and mechanochemistry experiment without addition of toluene/acetone.

7. Solvent exchange experiment details

Co-crystals of **DFC·4,4'-AP** were placed in solutions containing water or hexanes (ca. 4 mL) that contained a second solvent for exchange with the toluene/acetone (e.g. xylenes, chloroform, dichloromethane, ca. 1 mL). The crystals were left undisturbed for one week. The crystals were removed from solution, allowed to air dry, and placed in the oven at 35 °C for 1 hour to remove solvent on the surface of the crystals. Then, ¹H NMR spectra and PXRD data were collected.

Table S3. Results from solvent exchange experiments with **DFC·4,4'-AP**.

Experiment number	Main solvent (non-dissolving)	Solvent for exchange	Result (as evidenced by ¹ H NMR spectroscopy)
1	hexanes	xylenes	exchange
2	hexanes	CHCl ₃	no exchange
3	hexanes	CH ₂ Cl ₂	no exchange
4	hexanes	diethyl ether	no exchange
5	water	xylenes	exchange
6	water	CHCl ₃	no exchange
7	water	CH ₂ Cl ₂	exchange
8	water	diethyl ether	no exchange

References

1. Krause *et al.*, (2015) SADABS v 2016/2.
2. G. M. Sheldrick *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.*, 2015, **C71**, 3-8.
3. CrysAlis^{Pro} (2018) Oxford Diffraction Ltd.
4. SCALE3 ABSPACK (2005) Oxford Diffraction Ltd.
5. A. L. Spek, *Acta Crystallogr., Sect. D: Struct. Biol.* 2009, **D65**, 148-155.
6. A. L. Spek, *Acta Crystallogr., Sect. C: Struct. Chem.* 2015, **C71**, 9-18.
7. For detailed discussions on preferred orientations in crystalline materials and effects on signal intensities see: J. L. Crisp, S. E. Dann and C. G. Blatchford, *Eur. J. Pharm. Sci.* 2011, **42**, 568-577; A. J. Howarth, A. W. Peters, N. A. Vermeulen, T. C. Wang, J. T. Hupp and O. K. Farha, *Chem. Mater.* 2017, **29**, 26-39; S. Øien-Ødegaard, G. C. Shearer, D. S. Wragg and K. P. Lillerud, *Chem. Soc. Rev.* 2017, **46**, 4867-4876; J. Hafizovic, M. Bjørngen, U. Olsbye, P. D. C. Dietzel, S. Bordiga, C. Prestipino, C. Lamberti and K. P. Lillerud, *J. Am. Chem. Soc.* 2007, **129**, 3612-3620.