Electronic Supplementary Information (ESI)

Generation of cocrystals of Tavaborole (AN2690): opportunities for boron-containing APIs

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Supplementary Information:

SI. Experimental information

All reagents were obtained from Sigma Aldrich and used without further purification. **AN2690** (Tavaborole) was synthesized and purified using a reported literature procedure.[1]

Preparation of cocrystals: Cocrystals of composition 2(**AN2690**)·(**bpy**), 2(**AN2690**)·(**bpe**), 2(**AN2690**)·(**bpeta**), and (**AN2690**)·(**ina**) were obtained by dissolving **AN2690** (0.132 mmol) and the appropriate pyridine (0.066 mmol for **bpy**, **bpe** and **bpeta**, and 0.132 mmol for **ina**) in methanol. Slow evaporation over 2 days yielded single crystals suitable for X-ray diffraction.

S2. Single-crystal X-ray diffraction measurements

Single-crystal X-ray diffraction measurements. Single crystal XRD for the cocrystals was measured on a Nonius Kappa CCD single-crystal X-ray diffractometer using MoK_{α} radiation (λ=0.71073 Å). Structure solution and refinement were accomplished using SHELXS and SHELXL, respectively[2] within the Olex2[3] graphical user interface. All non-hydrogen atoms were refined anisotropically.

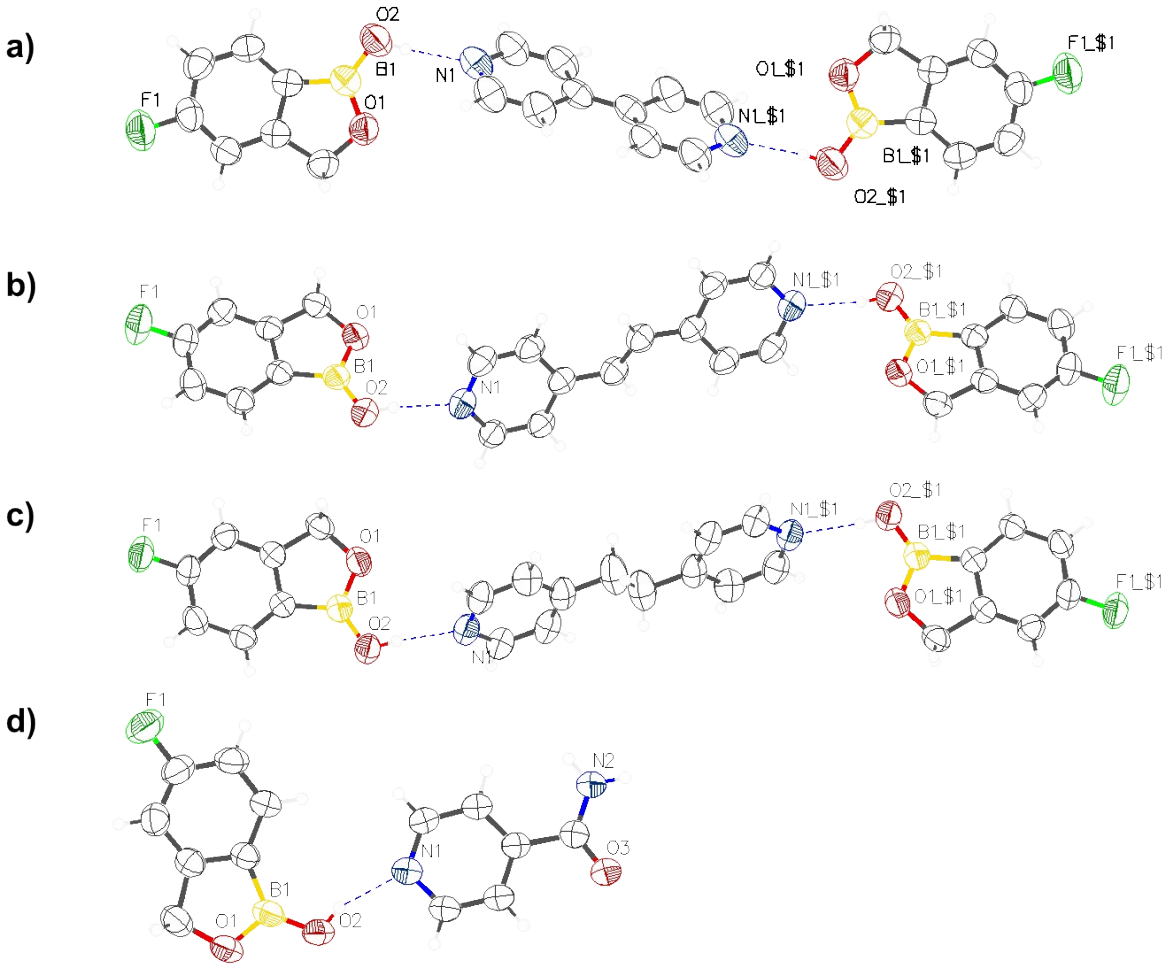

Fig. S1. ORTEP representation of a) 2(**AN2690**)·(**bpy**), b) 2(**AN2690**)·(**bpe**), c) 2(**AN2690**)·(**bpeta**) and (**AN2690**)·(**ina**) with ellipsoids drawn at the 50% probability level. [Symmetry codes (_$1): 2(**AN2690**)·(**bpe**): -x + 1, -y, -z ; 2(**AN2690**)·(**bpe**): -x, -y + 2, -z; 2(**AN2690**)·(**bpeta**): -x, -y + 2, -z].

Table S1. Crystallographic parameters for 2(**AN2690**)·(**bpy**).

Compound name	2(**AN2690**)·(**bpy**)
Empirical formula	$C_{12}H_{10}BFNO_2$
Formula weight	230.02
Temperature/K	298.15
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	14.5378(15)
b/Å	6.0517(6)
c/Å	14.4276(14)
α/°	90
β/°	118.366(5)
γ/°	90
Volume/Å^3	1116.9(2)
Z	4
ρ_{calc}g/cm^3	1.368
μ/mm^{-1}	0.103
F(000)	476.0
Crystal size/mm^3	0.26 × 0.24 × 0.18
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	6.37 to 50.75
Index ranges	$-17 \leq h \leq 17$, $-7 \leq k \leq 7$, $-17 \leq l \leq 17$
Reflections collected	6425
Independent reflections	2036 [R_{int} = 0.0279, R_{sigma} = 0.0245]
Data/restraints/parameters	2036/0/155
Goodness-of-fit on F^2	1.088
Final R indexes [I>=2σ (I)]	R_1 = 0.0413, wR_2 = 0.1033
Final R indexes [all data]	R_1 = 0.0595, wR_2 = 0.1153
Largest diff. peak/hole / e Å^{-3}	0.11/-0.14
CCDC deposition number	1531822

Table S2. Crystallographic parameters for 2(**AN2690**)·(**bpe**).

Compound name	2(**AN2690**)·(**bpe**)
Empirical formula	$C_{13}H_{11}BFNO_2$
Formula weight	243.04
Temperature/K	298.15
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	14.8742(15)
b/Å	5.9305(6)
c/Å	14.3285(14)
α/°	90
β/°	109.171(5)
γ/°	90
Volume/Å^3	1193.8(2)
Z	4
ρ_{calc}g/cm^3	1.352
μ/mm^{-1}	0.100
F(000)	504.0
Crystal size/mm^3	0.39 × 0.39 × 0.11
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	5.8 to 50.558
Index ranges	$-16 \leq h \leq 17$, $-7 \leq k \leq 7$, $-17 \leq l \leq 17$
Reflections collected	6833
Independent reflections	2162 [R_{int} = 0.0225, R_{sigma} = 0.0210]
Data/restraints/parameters	2162/0/164
Goodness-of-fit on F^2	0.999
Final R indexes [I>=2σ (I)]	R_1 = 0.0374, wR_2 = 0.1067
Final R indexes [all data]	R_1 = 0.0484, wR_2 = 0.1186
Largest diff. peak/hole / e Å^{-3}	0.14/-0.14
CCDC deposition number	1531823

Table S3. Crystallographic parameters for 2(**AN2690**)·(**bpeta**).

Compound name	2(**AN2690**)·(**bpeta**)
Empirical formula	$C_{13}H_{12}BFNO_2$

Formula weight	244.05
Temperature/K	298.15
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	15.0294(15)
b/Å	5.9476(6)
c/Å	14.5384(15)
α/°	90
β/°	110.690(5)
γ/°	90
Volume/Å^3	1215.8(2)
Z	4
ρ_{calc}g/cm^3	1.333
μ/mm^{-1}	0.099
F(000)	508.0
Crystal size/mm^3	0.34 × 0.23 × 0.14
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	5.658 to 50.734
Index ranges	$-18 \leq h \leq 18$, $-7 \leq k \leq 7$, $-17 \leq l \leq 17$
Reflections collected	6955
Independent reflections	2208 [R_{int} = 0.0200, R_{sigma} = 0.0229]
Data/restraints/parameters	2208/0/164
Goodness-of-fit on F^2	1.020
Final R indexes [I>=2σ (I)]	R_1 = 0.0467, wR_2 = 0.1319
Final R indexes [all data]	R_1 = 0.0599, wR_2 = 0.1443
Largest diff. peak/hole / e Å^{-3}	0.30/-0.27
CCDC deposition number	1531824

Table S4. Crystallographic parameters for (**AN2690**)·(**ina**).

Compound name	(**AN2690**)·(**ina**)
Empirical formula	$C_{13}H_{12}BFN_2O_3$
Formula weight	274.06
Temperature/K	298.15

Crystal system	monoclinic
Space group	$P2_1/c$

cocrystal	D-H· · · A	*d*(D-H) (Å)	*d*(H· · · A) (Å)	*d*(D· · · A) (Å)	*θ*(D-H· · · A) (deg)	symmetry code	twist angle[1] (deg)
2(**AN2690**)·(**bpy**)	O2-H2· · ·N1	0.82	1.93	2.743(2)	174		55.33(4)
	C7-H7A· · ·O2	0.97	2.49	3.422(2)	161	x, y + 1, z	
	C5-H5· · ·F1	0.93	2.63	3.434(2)	145	x - 2, -y + 1, -z + 2	
2(**AN2690**)·(**bpe**)	O2-H2· · ·N1	0.82	1.92	2.740(2)	173		56.83(3)
	C7-H7B· · ·O2	0.97	2.51	3.432(2)	158	x, y - 1, z	
	C9-H9· · ·O2	0.93	2.61	3.492(2)	158	x, - y + 5/2, z - 1/2	
	C5-H5· · ·F1	0.93	2.63	3.424(2)	144	-x + 1, -y + 1, -z + 2	
2(**AN2690**)·(**bpeta**)	O2-H2· · ·N1	0.82	1.92	2.737(2)	173		56.30(5)
	C7-H7B· · ·O2	0.97	2.51	3.435(2)	158	x, y - 1, z	
(**AN2690**)·(**ina**)	O2-H2· · ·N1	0.82	1.93	2.707(2)	158.5		1.14(0.13)

a/Å	15.8870(16)
b/Å	5.9848(6)
c/Å	13.8225(14)
α/°	90
β/°	93.469(5)
γ/°	90
Volume/Å^3	1311.8(2)
Z	4
ρ_{calc}g/cm^3	1.388
μ/mm^{-1}	0.107
F(000)	568.0
Crystal size/mm^3	0.27 × 0.26 × 0.05
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	5.138 to 50.726
Index ranges	-19 ≤ h ≤ 17, -7 ≤ k ≤ 6, -16 ≤ l ≤ 16
Reflections collected	7571
Independent reflections	2398 [R_{int} = 0.0371, R_{sigma} = 0.0342]
Data/restraints/parameters	2398/0/182
Goodness-of-fit on F^2	1.069
Final R indexes [I>=2σ (I)]	R_1 = 0.0468, wR_2 = 0.1170
Final R indexes [all data]	R_1 = 0.0794, wR_2 = 0.1346
Largest diff. peak/hole / e Å^{-3}	0.25/-0.15
CCDC deposition number	1531825

	N2-H2A· · ·O3	0.86	2.05	2.902(2)	171	-x + 1, -y + 3, -z + 1	
	N2-H2B· · ·O2	0.86	2.28	3.110(2)	162	x, -y + 3/2, z - 1/2	
	C5-H5· · ·F1	0.93	2.59	3.404(3)	147	-x + 2, -y, -z + 1	
	C7-H7B· · ·F1	0.97	2.52	3.412(3)	152	x, - y - 1/2, z + 1/2	
	C8-H8· · ·O3	0.93	2.46	3.173(2)	133	-x + 1, y -1/2, -z + 3/2	

S4. Hydrogen bond table

[1] calculated from pyridine ring plane and plane generated by atoms O2, B1, O1, C7, C2 and C1.

S4. FTIR Data

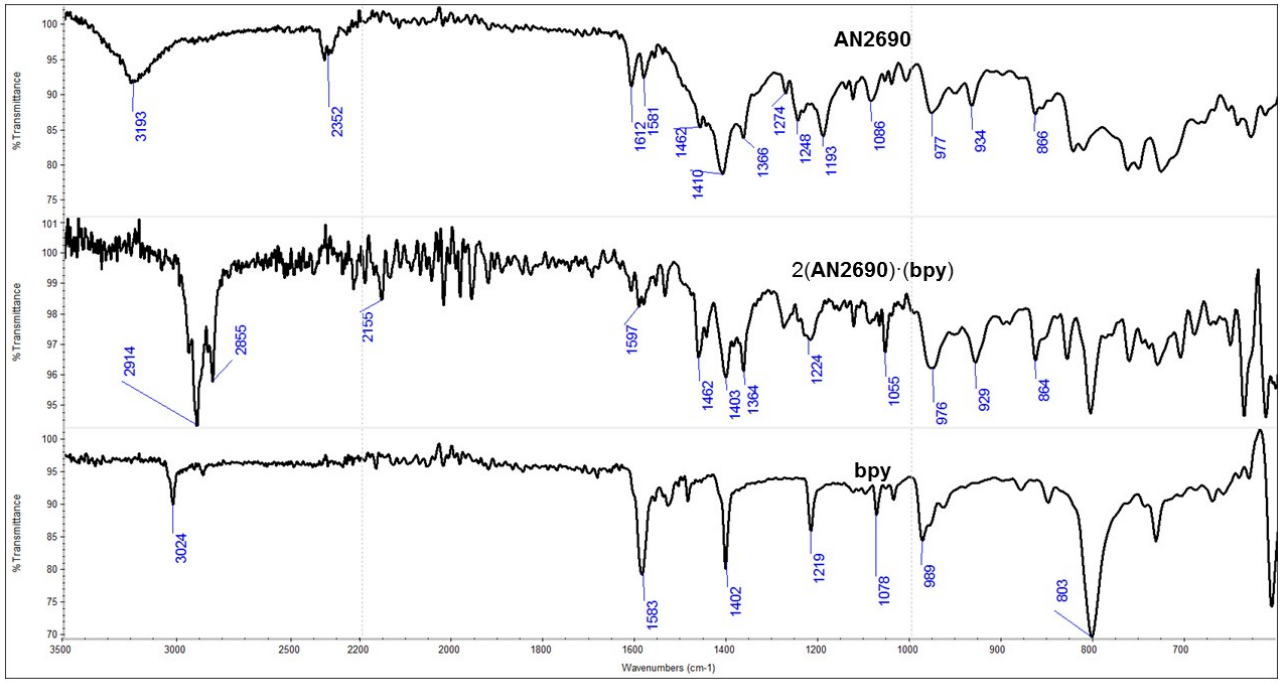

Fig. S2. FTIR spectra of cocrystal 2(**AN2690**)·(**bpy**), and starting materials.

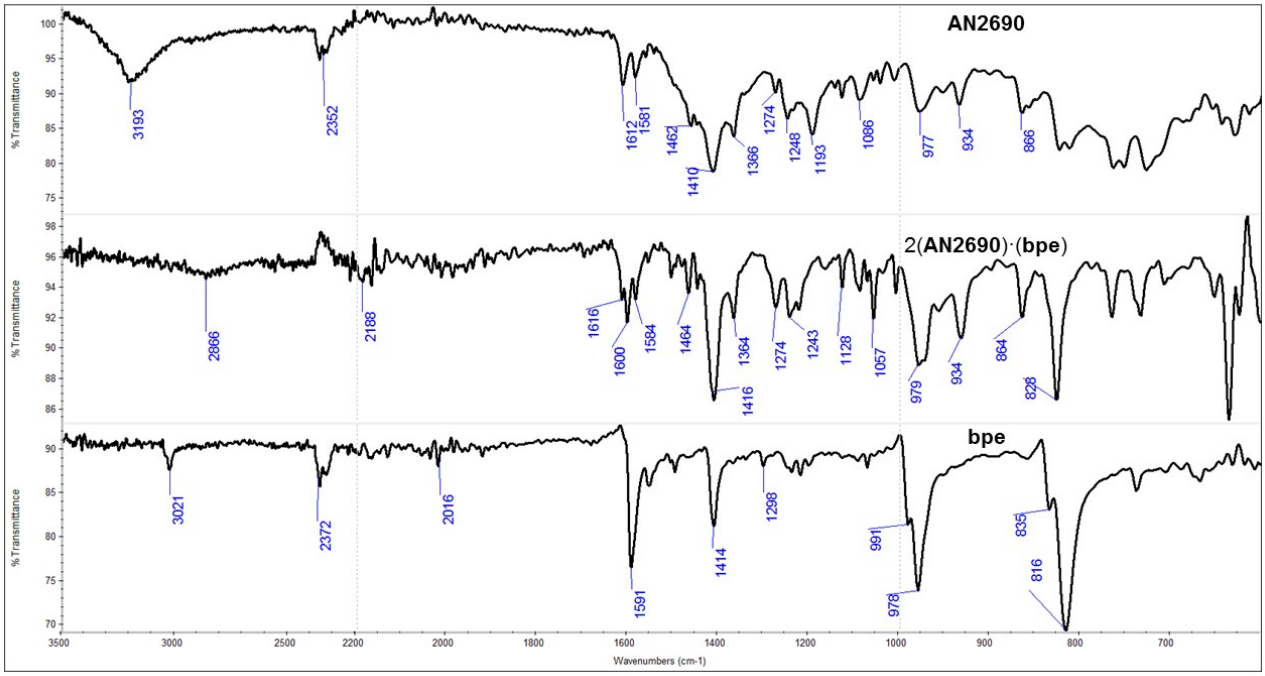

Fig. S3. FTIR spectra of cocrystal 2(**AN2690**)·(**bpe**), and starting materials.

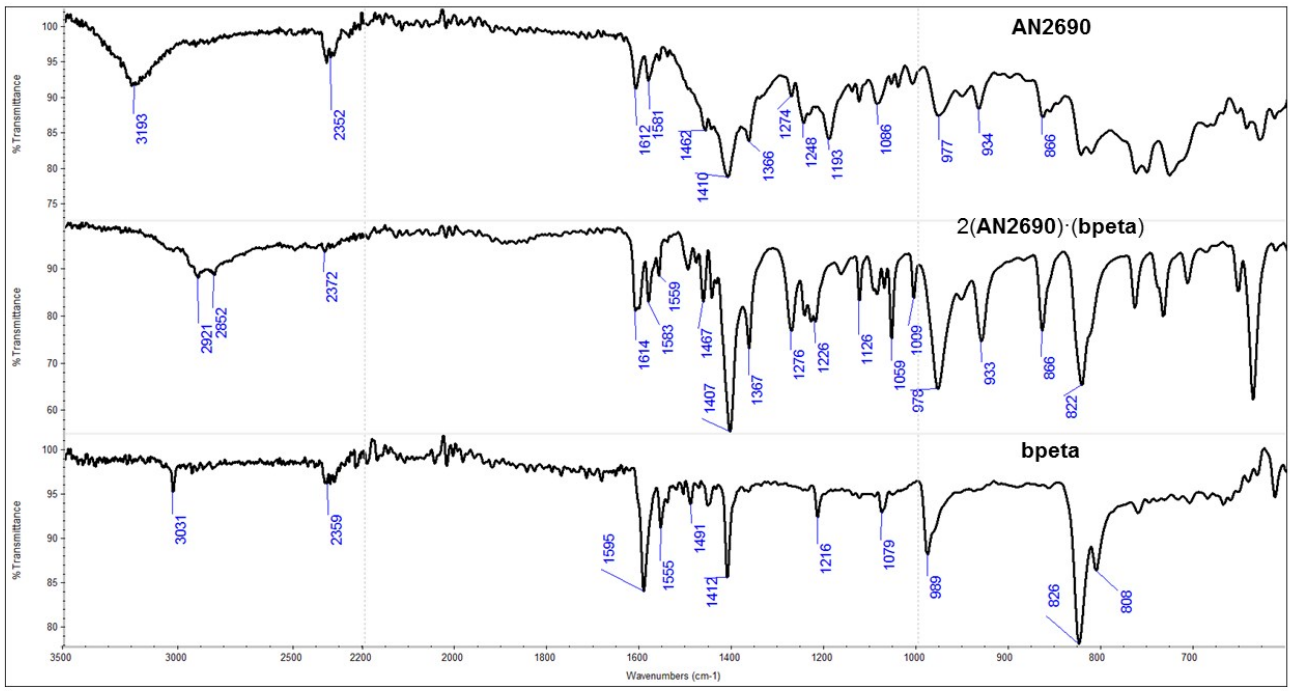

Fig. S4. FTIR spectra of cocrystal 2(**AN2690**)·(**bpeta**), and starting materials.

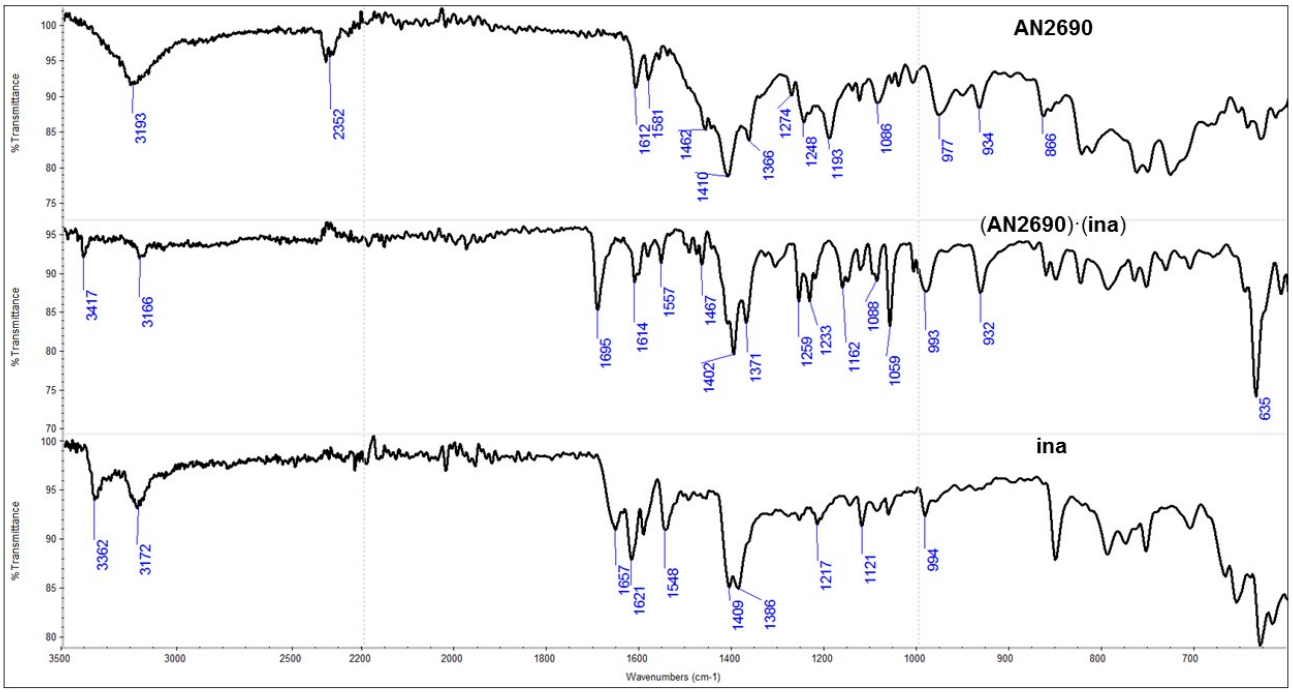

Fig. S5. FTIR spectra of cocrystal (**AN2690**)·(**ina**), and starting materials.

S5. Powder X-ray diffraction data

Powder X-ray diffraction data was collected from samples mounted on glass slides by a Siemens D5000 X-ray diffractometer using Cu $K_{\alpha}1$ radiation (λ = 1.54056 Å) between 3°- 35° two-theta (scan type: locked coupled; scan mode: continuous; step size: 0.02°).

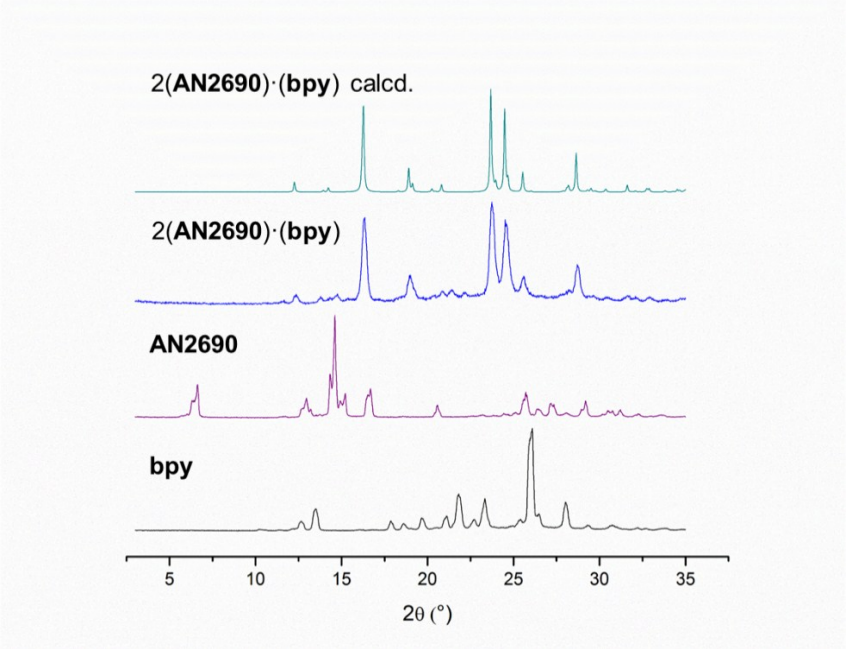

Fig. S6. PXRD analysis of the solids of cocrystal 2(**AN2690**)·(**bpy**), and starting materials.

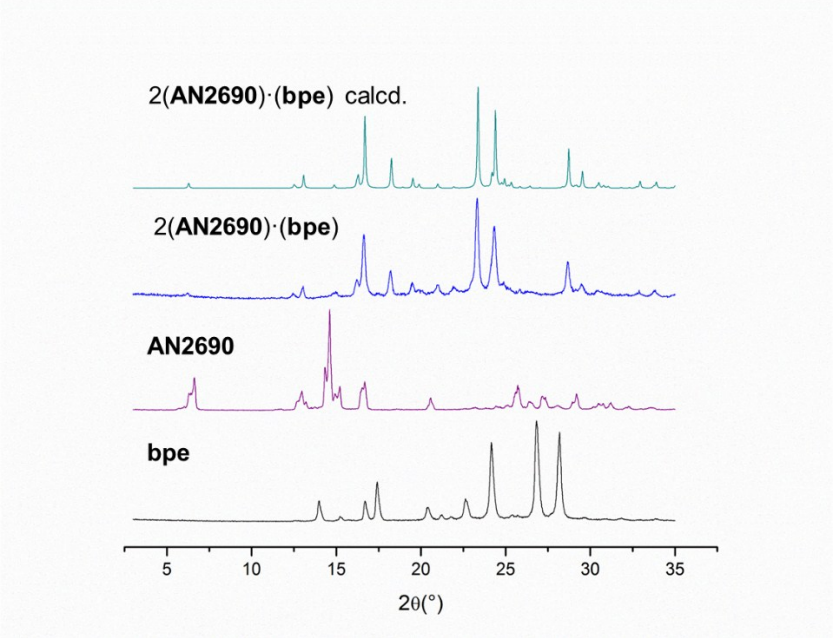

Fig. S7. PXRD analysis of the solids of cocrystal 2(**AN2690**)·(**bpe**), and starting materials.

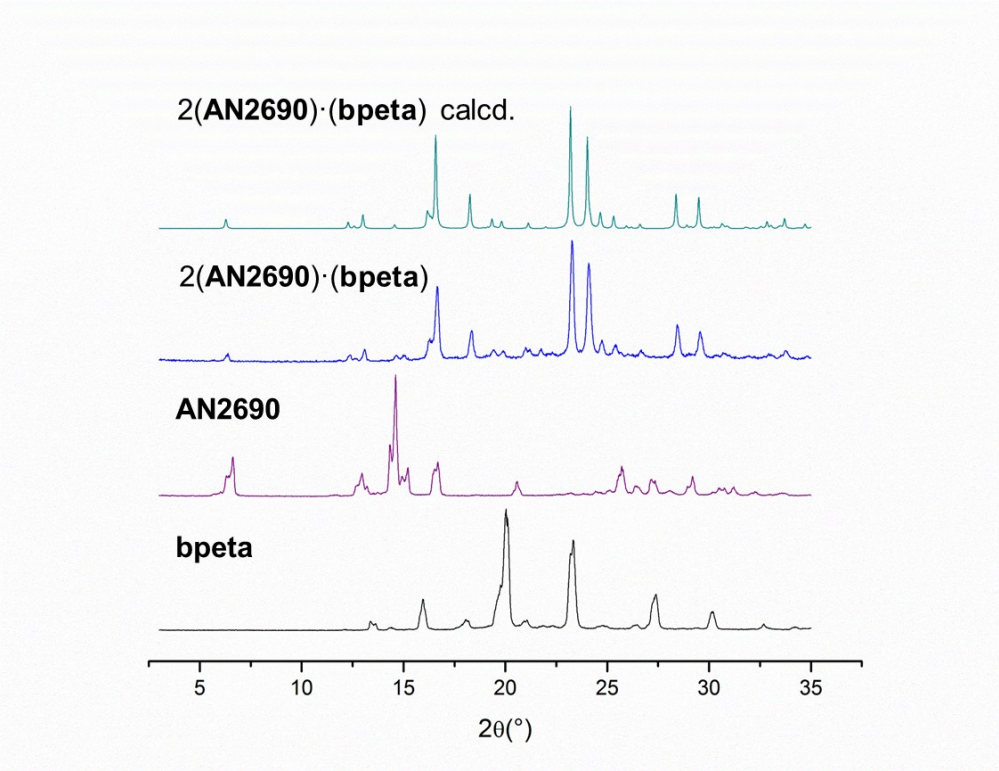

Fig. S8. PXRD analysis of the solids of cocrystal 2(**AN2690**)·(**bpeta**), and starting materials.

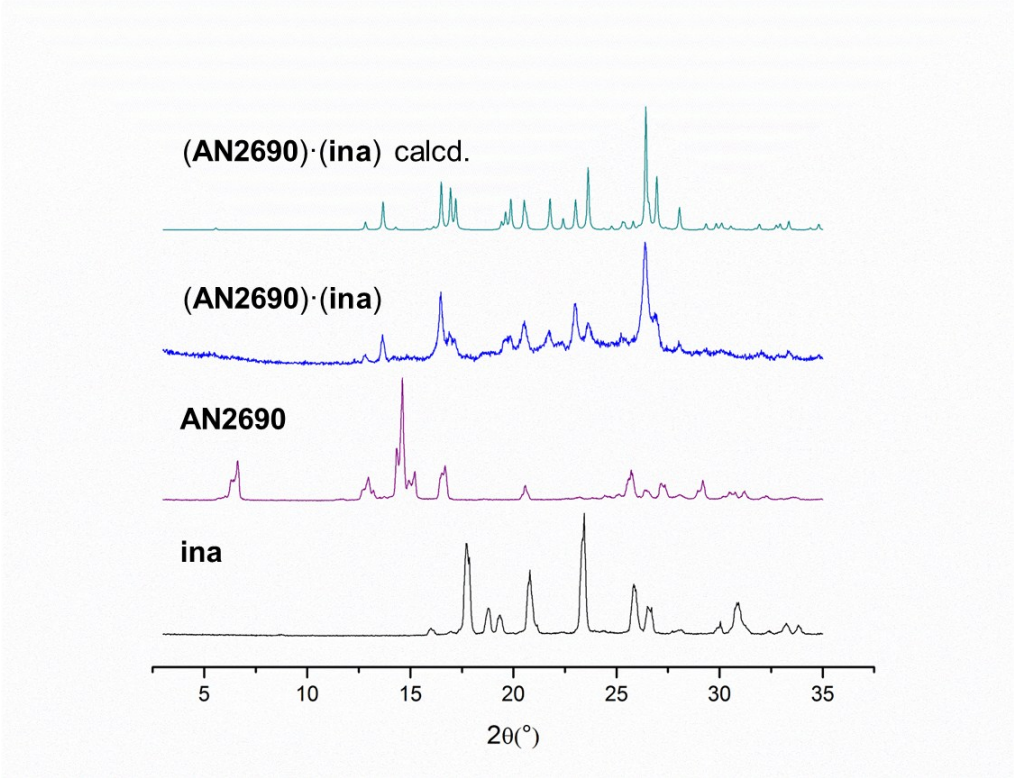

Fig. S9. PXRD analysis of the solids of cocrystal (**AN2690**)·(**ina**), and starting materials.

References

1. S. Sene, D. Berthomieu, B. Donnadieu, S. Richeter, J. Vezzani, D. Granier, S. Bégu, H. Mutin, C. Gervais and D. Laurencin, *CrystEngComm*, 2014, **16**, 4999-5011.
2. G. M. Sheldrick, *Acta Crystallogr. Sect. A: Found. Crystallogr.*, 2008, **64**, 112-122.
3. O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. Howard and H. Puschmann, *J. Appl. Crystallogr.*, 2009, **42**, 339-341.